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Functionalised organolithium compounds

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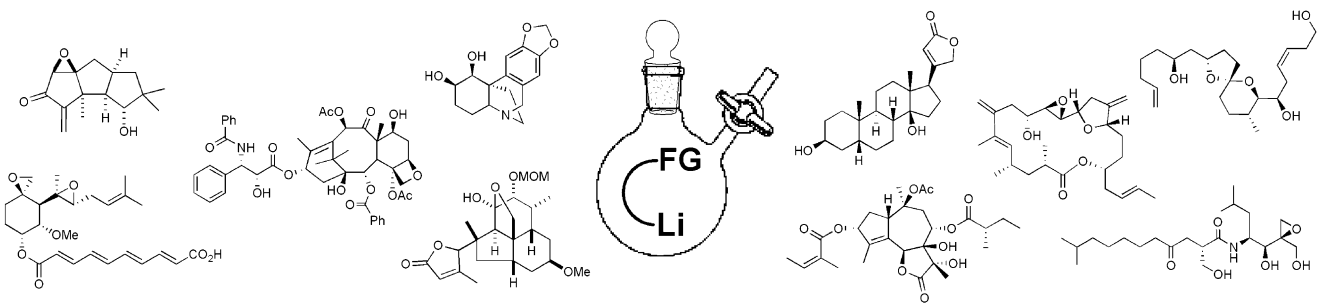
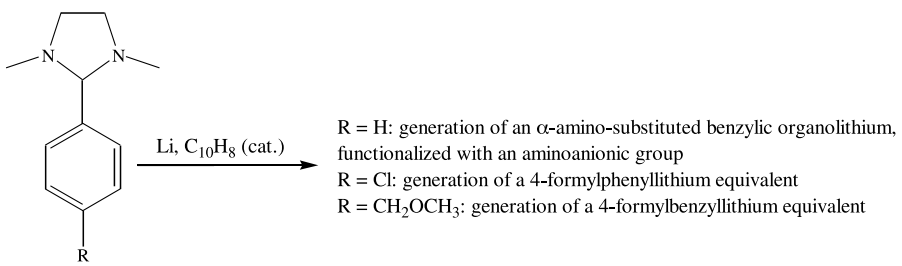
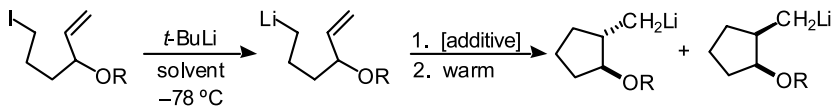
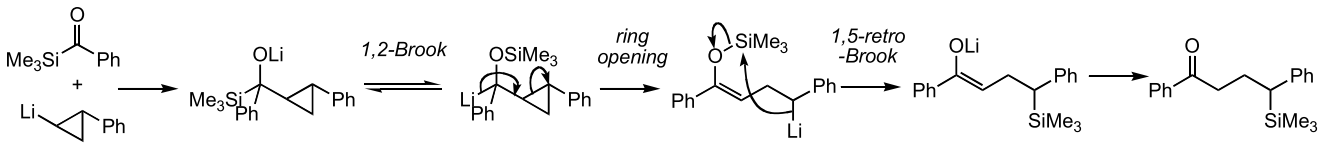
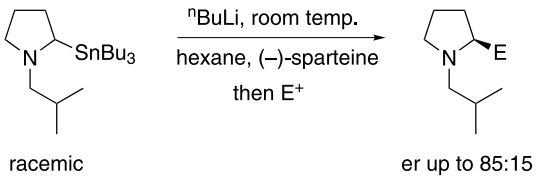
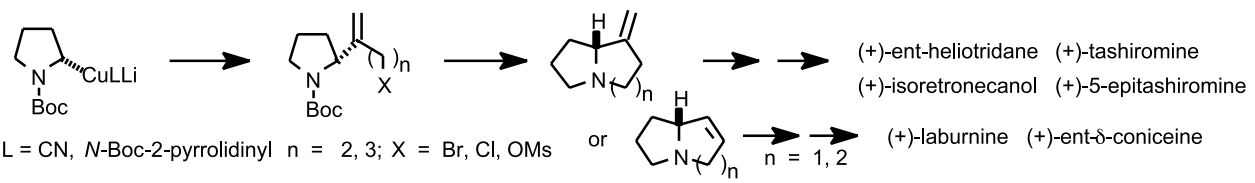


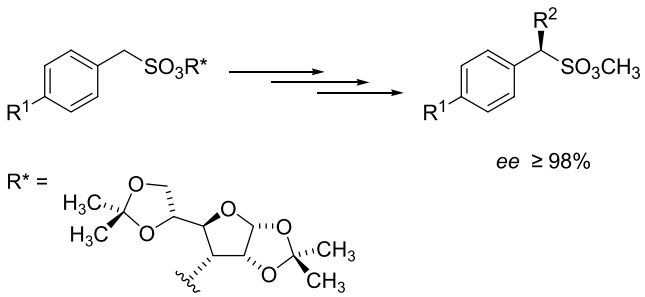


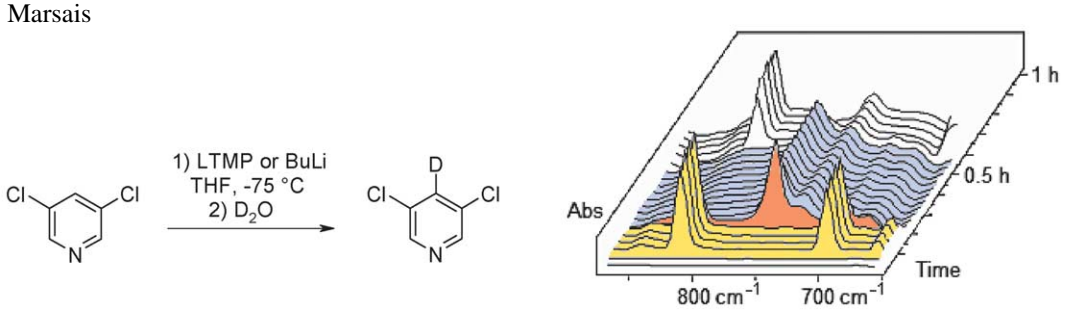


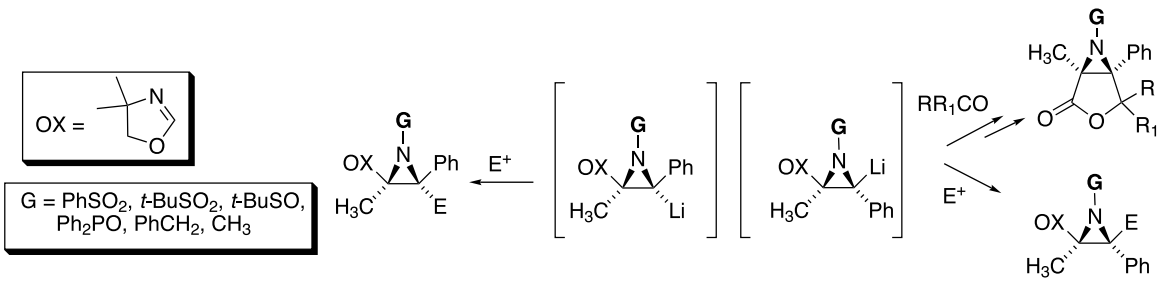


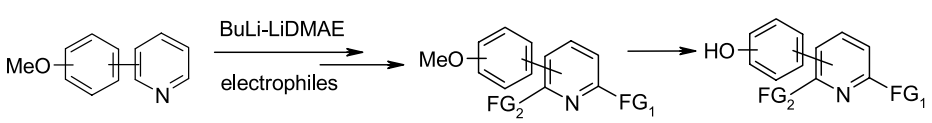


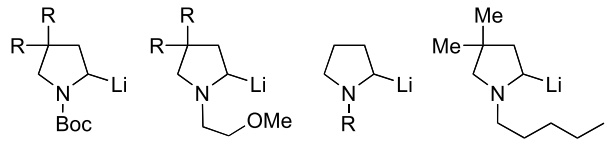




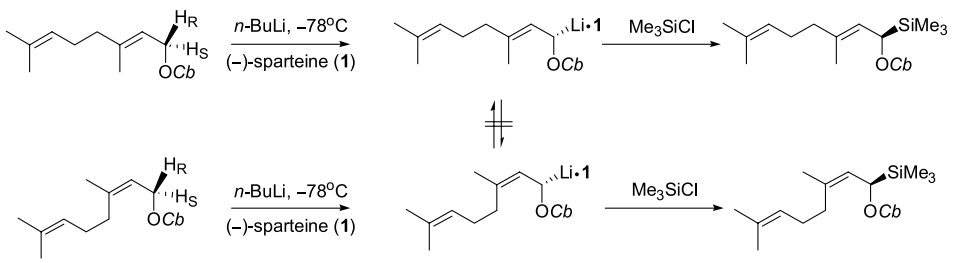


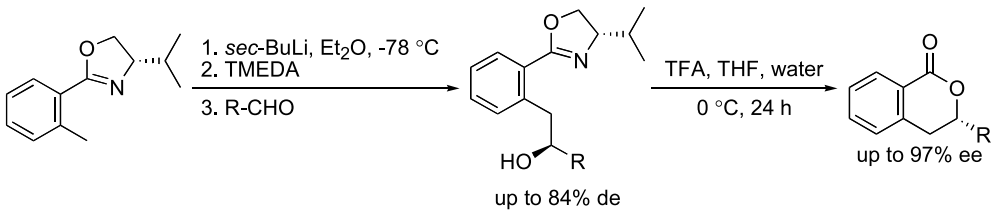


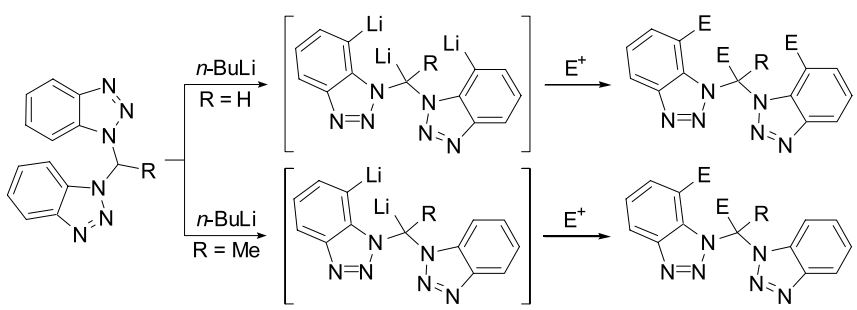


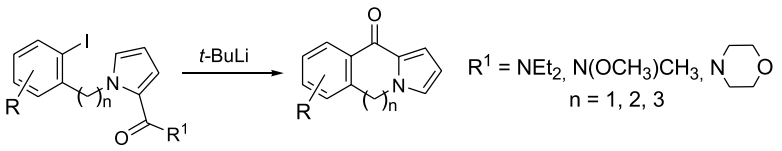


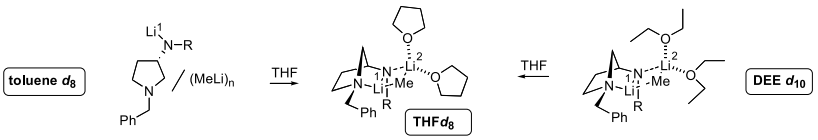
The solution structures of three structural classes of 2-lithiopyrrolidines were investigated using ^{6}Li and ^{13}C NMR. Depending on structure, enantiopurity, concentration, additives, and solvent, the structures can vary from a single predominant species to a complex mixture of interconverting aggregates.

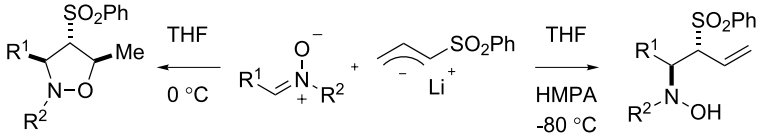


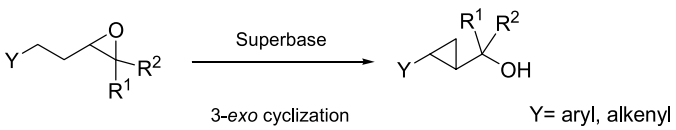


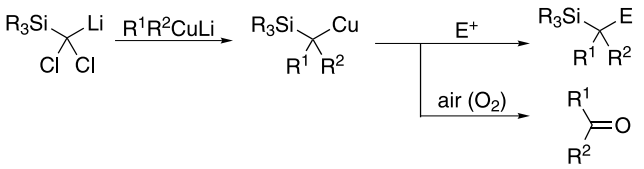


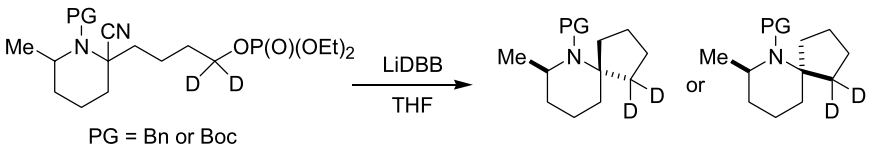


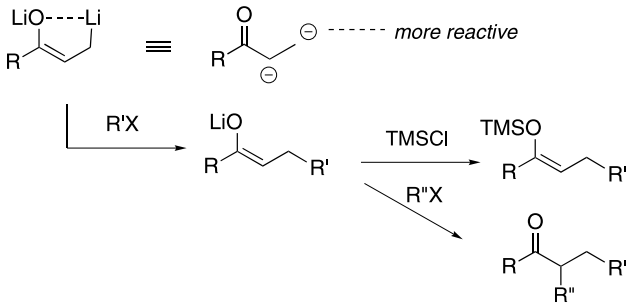


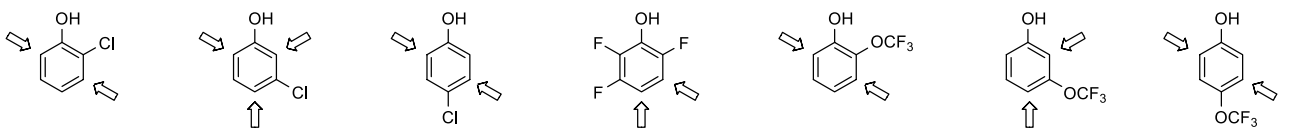


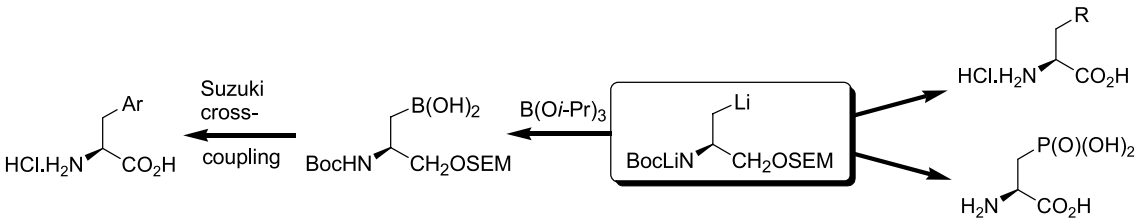


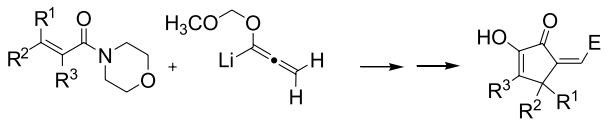


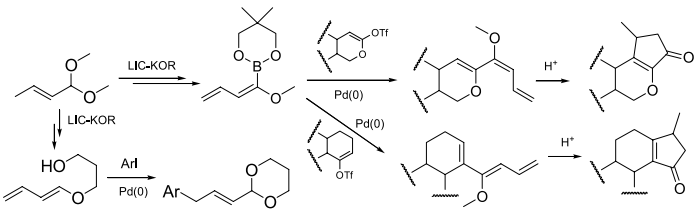




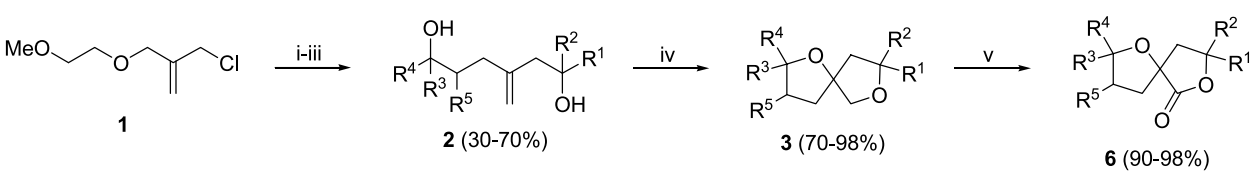








The results are grouped in two sections: (1) the Pd-catalyzed cross-coupling of alkoxydienyl-boronates with tetralone- or isochromanone-derived vinyl triflates; (2) the regio- and stereoselective Heck cross-coupling of alkoxydienes with aryl derivatives.



Reagents and conditions: (i) Li, $C_{10}H_8$ (Cat.), R^1R^2CO, THF, −78 °C; (ii) $R^3R^4C(O)CHR^5$, 0 °C; (iii) H_2O; (iv) I_2, Ag_2O, THF or dioxane–H_2O, rt; (RuO_2) (cat.), $NaIO_4$, CCl_4–H_2O, rt.

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*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The cover graphic illustrates structures of representative functionalised organolithium compounds, which have been used in different articles of this issue as intermediates in the synthesis of interesting polyfunctionalised organic molecules. *Tetrahedron* **2005**, *61*, 3125–3450.

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Preface

Functionalised organolithium compounds

Functionalised organolithium compounds have acquired great importance in synthetic organic chemistry because they behave as typical organolithium compounds, therefore being able to react with a wide series of electrophiles (such as water, deuterium oxide, alkyl and silyl halides, disulfides, carbon dioxide or carbonyl compounds) under very mild reaction conditions, transferring their own functionality to the electrophile, so polyfunctionalised molecules are easily available in only one synthetic operation. One additional advantage of such of intermediates is their ability to transmetallate with other metallic salts (specially zinc and copper derivatives), which allows the reactivity of these functionalised organolithium compounds to be extended, opening new possibilities of carbon–carbon forming process through transition metal catalysis.

Among the different contributions in this issue, a review article has been included to illustrate the use of functionalised organolithium compounds in total synthesis and demonstrate the potential of these reagents in organic synthesis.

Finally, we would like to thank Professors Richard Taylor and Harry Wasserman for the invitation to edit this special issue, the authors for their excellent contributions in the field of functionalised organolithium compounds, and the expert referees for their anonymous help. Without the cooperation of all these colleagues this issue would be just impossible.

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Functionalized organolithium compounds in total synthesis

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Contents

1. Introduction

Organolithium compounds are nowadays probably the most popular organometallics, due to their excellent nucleophilic reactivity, their importance in synthetic organic chemistry being well known.[1] Amongst them, functionalized organolithium compounds[2,3] are particularly useful as they can transfer a functionality in just a synthetic operation, although in this case the functionality must be conveniently masked to be fully compatible with the carbon–lithium bond.

This review deals with the use of functionalized organolithium compounds in the total synthesis of natural products. Although not fully comprehensive, the number of examples given is quite revealing of the importance of these species in the battlefield where the reagent must prove its real usefulness. Only the reported complete syntheses of naturally occurring compounds will be covered, reports on the preparation of relatives, intermediates or model compounds as well as synthetic approaches not being

Keywords: Organolithium compounds; Natural product; Vinyllithium.
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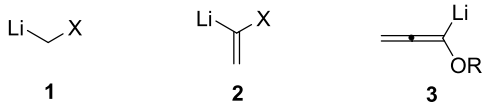
included. However, the concept of 'natural product' will be employed under a flexible stereochemical point of view, the synthesis of the racemic material or the enantiomer of the authentic natural compound also being considered.

Organolithium compounds stabilized by an electron-withdrawing group which really leaves the lithium atom bonded to a heteroatom (i.e., C=O, C=N, C≡N, RSO, RSO_2, NO_2, etc.) or by atoms such as sulphur, selenium, phosphorous or silicon, as well as acyllithium compounds, will not be considered. In addition, functionalized aryllithium compounds generated both by deprotonating[4] or non-deprotonating methods,[5] as well as heteroaryllithiums,[4–6] will not be included, as their generation and synthetic uses have been the subject of extensive and recent surveys.

The review has been divided according to the distance of the heteroatom (or the functional group) to the carbanionic center and subdivided according to its hybridization.

2. α-Functionalized organolithiums

This type of species can be considered as d^1 reagents, according to the nomenclature which considers their donor electronic characteristic and the distance between the carbanionic center and the functionality,[7] this usually being α-oxygenated or α-nitrogenated. The simplified structure of sp^3-hybridized systems **1** and their sp^2-hybridized counterparts **2**, including lithiated 1-alkoxyallenes **3**, are shown below and their applications will be discussed in this section. In the case of X=Hal, the resulting species are carbenoids and will not be considered.



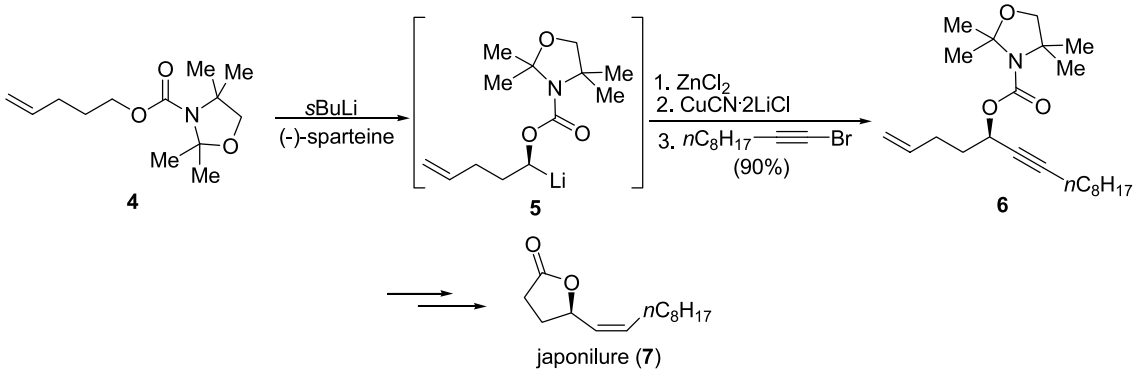
1 **2** **3**

2.1. α-Functionalized sp^3-hybridized organolithiums

Functionalized alkyllithium reagents bearing an oxygen at the α-position can be generated by halogen–lithium exchange or rapid tin–lithium transmetalation, the direct α-deprotonation being generally achieved in the case of activated allylic or benzylic systems. However, non-activated systems bearing a suitable lithium-complexing moiety have also been employed in natural product synthesis, a recent example being the generation of the chiral α-(carbamoyloxy)alkyllithium reagent **5** (Scheme 1), obtained from alkyl carbamate **4** using Hoppe's *sec*-butyllithium/(−)-sparteine methodology,[8] which can be transmetalated to the corresponding organozinc species and further to the organocopper with retention of the configuration, and reacted with decynyl bromide to give compound **6** in a synthesis of the industrially relevant pheromone japonilure (**7**).[9] This enantioselective lithiation methodology has also been applied to the allylic α-deprotonation of another carbamate in a synthesis of a diastereomer of the natural herbicide, herboxidiene.[10]

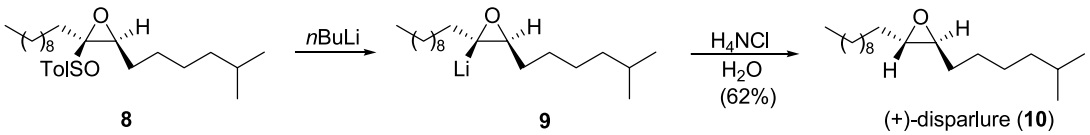
Non-stabilized oxiranyllithiums[11] have not been frequently employed in the synthesis of naturally occurring products, an example being the generation of the organolithium species **9** by desulfinylation of chiral epoxysulfoxide **8** (Tol=tolyl) (Scheme 2). Final aqueous quenching of this oxiranyllithium reagent gave rise to optically pure (+)-disparlure (**10**), the sex attractant of the female gypsy moth.[12]

The lithium–boron transmetalation has been used with α-oxygenated organolithiums in natural product synthesis. For instance, protected allyl alcohol **11** was α-lithiated to species **12** and transformed via a Brown's allylation[13] into enantiomerically enriched homoallylic alcohol **13**, which is an intermediate in the total synthesis of the acetogenin (+)-murisolin (**14**) (Scheme 3).[14] A similar enantioselective methodology starting also from an *O*-alkylated



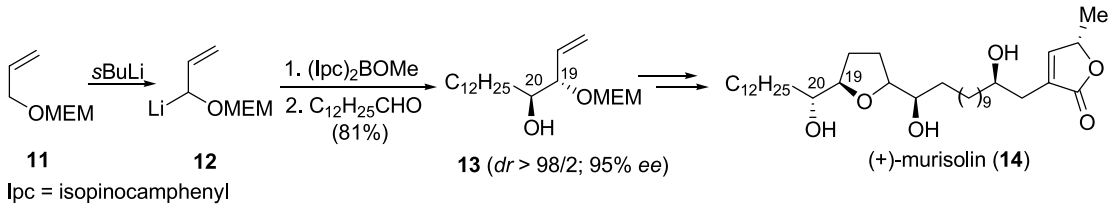
4 **5** **6**

Scheme 1.



8 **9**

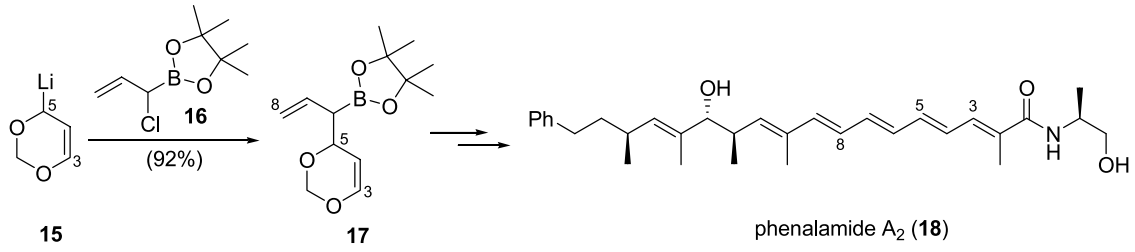
Scheme 2.



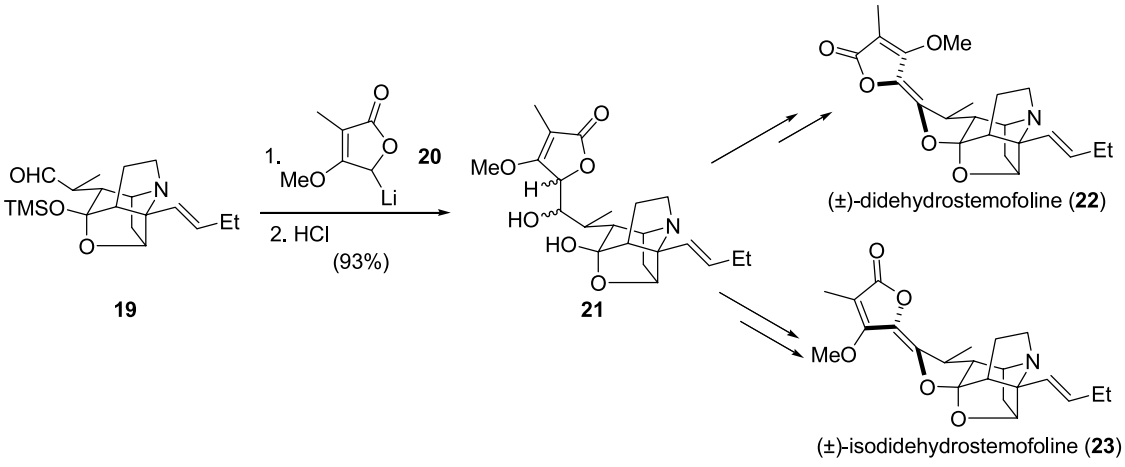
Scheme 3.

allyl alcohol has been used for the preparation of the marine sponge metabolites (+)-caliculin A and (−)-caliculin B.[15] In another example of the use of a lithium–boron-exchange, 1,3-dioxene was deprotonated with *sec*-butyllithium to generate organolithium **15** which reacted with α-chloroallyl boronate **16** to give compound **17** which has been employed in the addition to an aldehyde for the creation of the conjugated polyenic system in a synthesis of phenalamide A_2 (**18**), a natural product isolated from gliding bacteria (Scheme 4).[16]

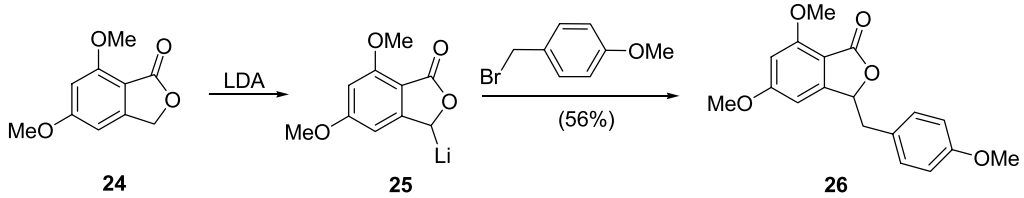
An example of the use of an α-oxygenated organolithium prepared from a heterocyclic allyl system is shown in the addition of 5-lithio-4-methoxy-3-methyl-2(5*H*)-furanone (**20**), obtained by deprotonation with *n*-butyllithium of the corresponding 2(5*H*)-furanone, to aldehyde **19**, the resulting alcohols **21** being intermediates in the total synthesis of the *Stemona* alkaloids (±)-didehydrostemofoline (asparagamine A) (**22**) and (±)-isodidehydrostemofoline (**23**) (Scheme 5).[17] In addition, an example of a heterocyclic α-oxygenated phthalide-derived benzyllithium is provided by the lithium diisopropylamide (LDA)-promoted deprotonation of 5,7-dimethoxyisobenzofuran-1(3*H*)-one (**24**), the resulting lithiated species **25** being able to react with 4-methoxybenzyl bromide to give dimethoxyphthalide **26** (Scheme 6), a metabolite of the liverwort *Frullania falciloba*.[18]



Scheme 4.



Scheme 5.

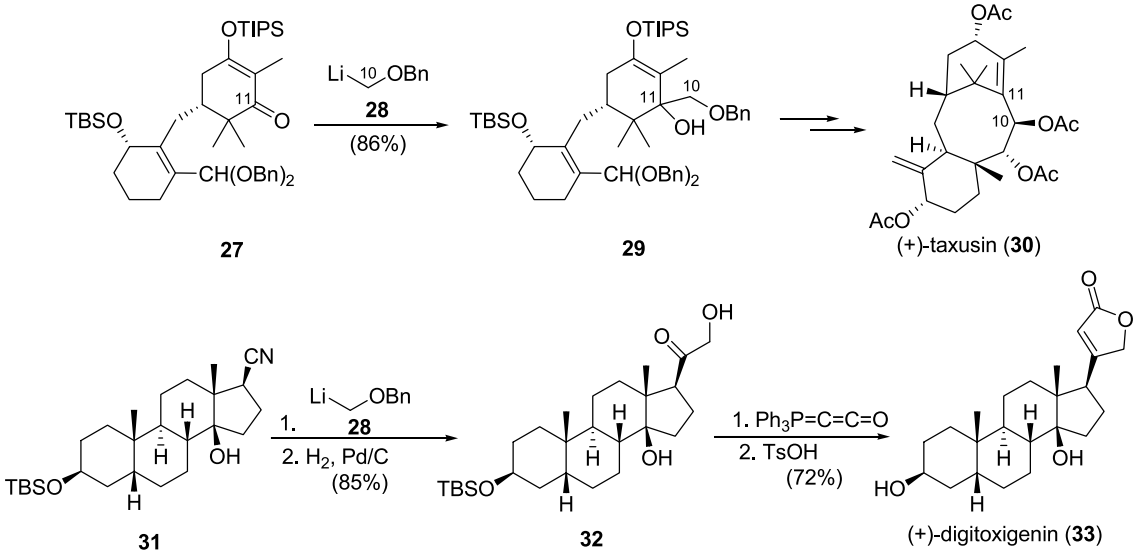


Scheme 6.

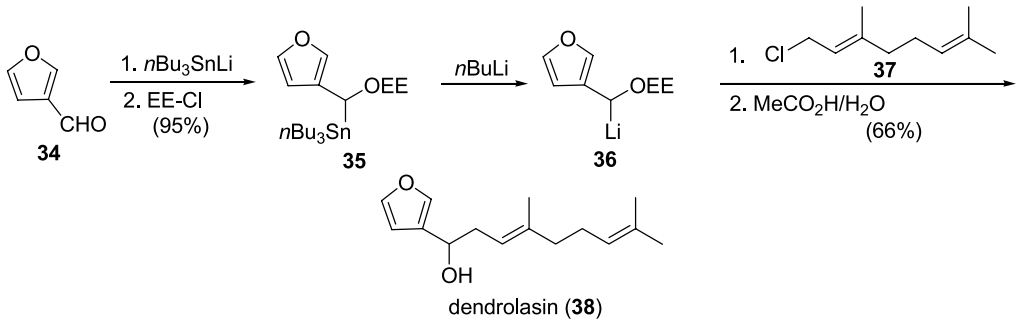
Tin–lithium transmetalation has been used as an appropriate methodology for the preparation of α-alkoxy organolithium compounds. Thus, (benzyloxy)methyllithium (**28**), which can be considered as an interesting synthetic equivalent of the 'hydroxymethylide' anion, can be generated by tin/lithium exchange from the corresponding stannane using *n*-butyllithium.[19] This α-oxygenated organolithium reagent has been used frequently in natural product syntheses, as can be seen in Scheme 7, where benzyloxymethyllithium (**28**) is added to ketone **27** to give adduct **29**, which is an intermediate in a total synthesis of (+)-taxusin (**30**).[20] Other example is shown of its addition to cyano compound **31** giving rise, after benzyl removal by hydrogenolysis, to alcohol **32** which, after treatment with triphenylphosphoranylidene ketene and silyl deprotection, afforded the cardenolide (+)-digitoxigenin (**33**), an active component of *Digitalis* extracts (Scheme 7).[21] Further examples of the use of benzyloxymethyllithium (**28**) in the total synthesis of natural products can be found in the epoxide ring opening and the addition to a lactone carbonyl for the total synthesis of the macrolides roflamycoin[22] and bryostatyn 2,[23] respectively, or in the addition to Weinreb amides employed for the preparation of the natural antifungal (+)-restricticin[24] or the antimitotic macrolide spongistatin 1.[25]

Related to this tin/lithium transmetalation procedure, the addition of trialkylstannyllithium to carbonyls allows the preparation of α-hydroxystannanes which can be *O*-protected and transmetalated via tin/lithium exchange using an alkyllithium to generate α-alkoxy organolithiums.[19] An application of this methodology is shown in the addition of tri-*n*-butylstannyllithium to furan-3-carbaldehyde (**34**) and subsequent addition of ethoxyethyl chloride (EE-Cl) to give stannane **35** (Scheme 8). Transmetalation using *n*-butyllithium to lithiated species **36**, addition of geranyl chloride (**37**) and hydrolysis afforded dendrolasin (**38**), a component of some essential oils.[19]

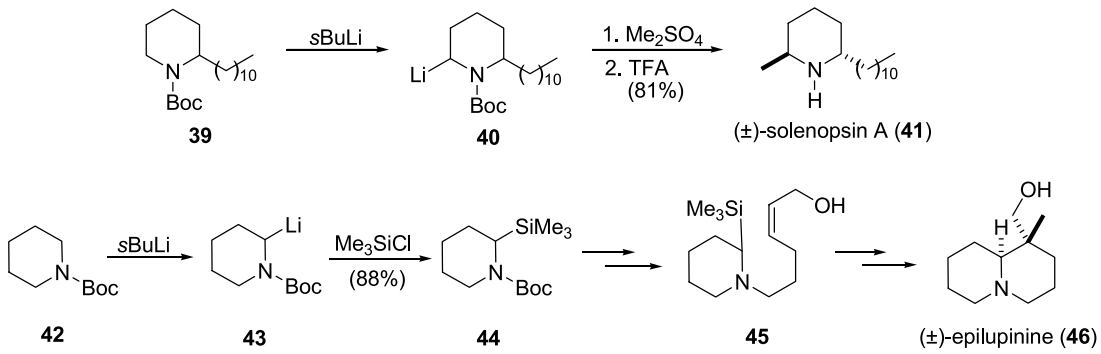
α-Aminoalkyl organolithiums can be stabilized by the close presence of a dipole such as carbamates or amides or by delocalization of the anion through an allyl or benzyl system. The most used methods for generating these organolithium compounds are deprotonation and transmetalation by tin–lithium exchange.[26] Both procedures are complementary: deprotonation can be made stereoselectively when combining the lithiation reagent with (−)-sparteine,[27] whereas tin–lithium exchange provides access to species not accessible due to a kinetic barrier. An example of the use of a dipole-stabilized deprotonating methodology is shown in Scheme 9, where *N*-Boc-piperidine **39** (Boc=*tert*-butoxycarbonyl) is treated with *sec*-butyllithium to give the lithiated species **40** which is *trans*-methylated using dimethyl sulfate affording, after Boc-deprotection using trifluoroacetic acid (TFA), the ant



Scheme 7.



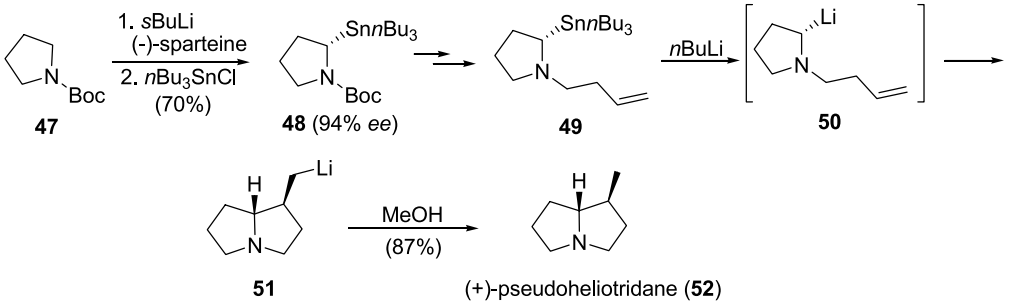
Scheme 8.



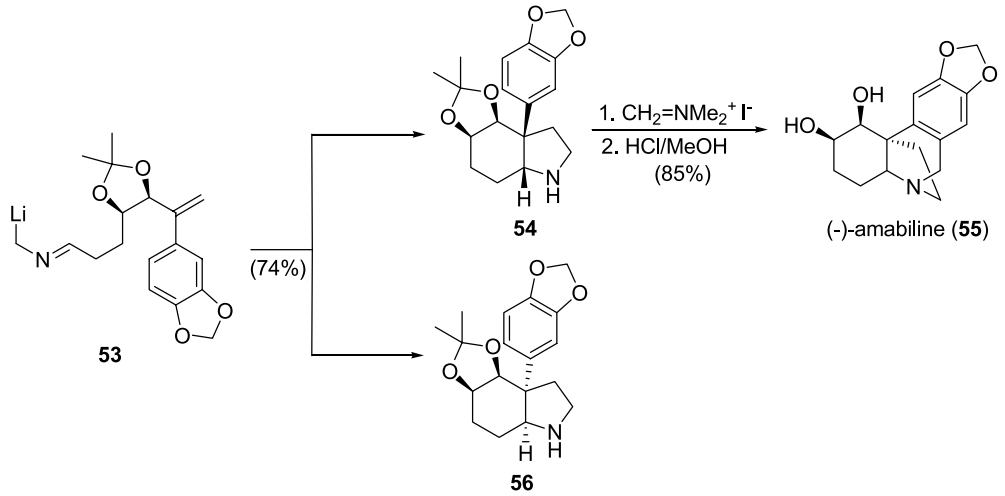
Scheme 9.

venom piperidine alkaloid (±)-solenopsin A (**41**).[28] A similar deprotonation of *N*-Boc-piperidine (**42**) to organolithium **43**, followed by reaction with trimethylsilyl chloride, gave silylated piperidine **44**, which has been transformed into olefin **45** and stereoselectively cyclized under photoinduced electron-transfer conditions, leading to the alkaloid (±)-epilupinine **46** after several steps (Scheme 9).[29]

The deprotonation of *N*-Boc-pyrrolidine (**47**), but in the presence of (−)-sparteine, gave stannylated pyrrolidine **48** in high ee after reaction with tri-*n*-butyltin chloride (Scheme 10).[27] Since metal-exchange usually proceeds with retention of the configuration, organolithiums of a known absolute configuration can be achieved. Therefore, tin/lithium transmetalation on derived compound **49** gave organolithium **50** which, after immediate stereospecific anionic cyclization, afforded the alkyllithium **51** (now a δ-nitrogenated organolithium). Final quenching with methanol afforded the alkaloid (+)-pseudoheliotridane (**52**) in 94% ee.[30] In addition, a 1,3-dipolar intramolecular cyclization has also been reported using an acyclic azaallyl lithio anion such as **53**, generated by tin/lithium exchange from the corresponding stannane after treatment with *n*-butyllithium, affording the two diastereomeric adducts **54** and **56** (5:1 ratio) (Scheme 11). Treatment of the major isomer **54** with Eschenmoser's salt followed by removal of the acetonide under acidic conditions yielded the *Amaryllidaceae* alkaloid (−)-amabiline (**55**).[31] This methodology using azaallyl organolithiums allowed also the preparation



Scheme 10.



Scheme 11.

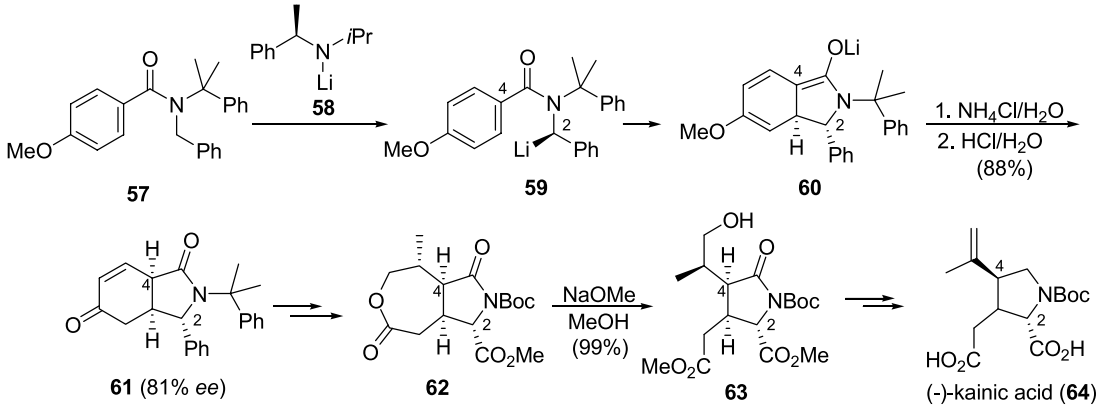
of other natural alkaloids such as (±)-crinine, (±)-6-epicrinine, (−)-augustamine,[31] (±)-lapidectine B,[32a] indolizidine 239CD[32b] and (+)-coccinine.[32c]

The generation of chiral α-nitrogenated organolithiums has also been performed, apart from the above-mentioned sparteine method, by direct deprotonation using chiral lithium amides.[33] A recent example of the use of this procedure for the synthesis of a natural product is the direct asymmetric deprotonation of benzamide **57** using chiral lithium amide **58**. The resulting chiral organolithium compound **59** cyclized to enolate **60** which gave rise to enone **61** after quenching and acidic work-up, the resulting ee of 88% being raised to 99% after recrystallization. Subsequent transformations, including a Baeyer–Villiger-promoted ring expansion afforded lactone **62** which, after hydrolysis, gave alcohol **63** which was transformed into (−)-kainic acid (**64**) after several steps (Scheme 12).[34]

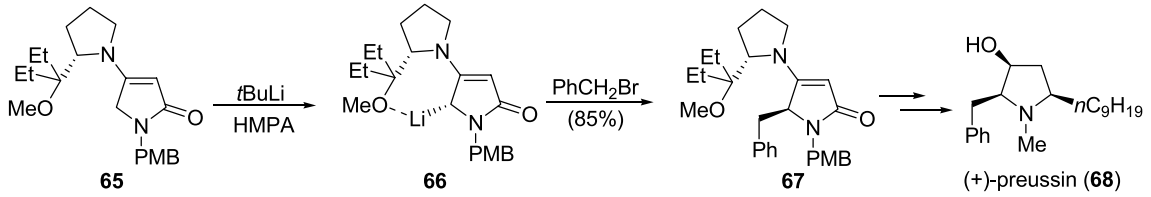
Chiral organolithiums can also be achieved by internal lithium complexation after deprotonating a suitable chiral starting material. A recent example is the *tert*-butyllithium-promoted lithiation of chiral pyrrol-2(5*H*)-one **65** (PMB = *p*-methoxybenzyl). The resulting α-nitrogenated chiral organolithium **66** was suitable for reaction with different electrophiles such as benzyl bromide to afford diastereomerically pure compound **67**, which was transformed into the pyrrolidine alkaloid (+)-preussin (**68**), a marine metabolite from the sponge *Melophlus sarassinorum* (Scheme 13).[35] In addition, aromatic ring-stabilized α-organolithiums from lactams have been employed in natural product synthesis, as in the case of 2-pivaloyl-tetrahydroisoquinolines in the total synthesis of some tetrahydroisoquinoline alkaloids,[36] or the lithium hexamethyldisilazide-promoted lithiation of azaisoindolinone **69** to the organolithium reagent **70** which was quenched with 2-iodobenzaldehyde to give alcohol **71** as a single diastereomer. After several steps, alcohol **71** was transformed into the structurally rare azaphenanthrene alkaloid eupolauramine (**72**), isolated from the relic plant *Eupomatia laurina* (Scheme 14).[37]

2.2. α-Functionalized sp^2-hybridized organolithiums

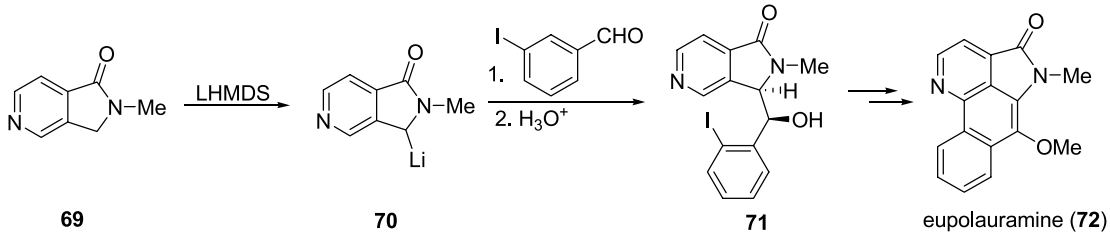
Cyclic and acyclic α-lithiated vinyl ethers can be prepared in general by deprotonation with alkyllithiums of the kinetically acidic vinyl α-hydrogen, and can be employed as acyl anion equivalents.[38] An example of the use of an acyclic vinyl ether is the deprotonation of ethyl vinyl ether with *tert*-butyllithium generating 1-ethoxyvinyllithium (**74**)



Scheme 12.



Scheme 13.



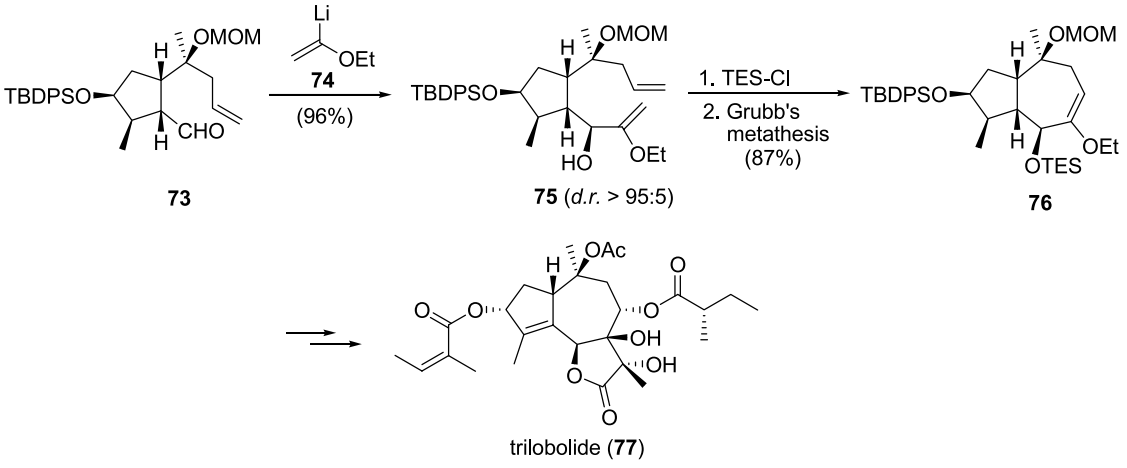
Scheme 14.

which is added diastereoselectively to aldehyde **73** to afford alcohol **75**, suitable for a metathesis closure to create the seven-membered ring of compound **76** in the total synthesis of the sesquiterpene lactone trilobolide (**77**) as well as the related nortrilobolide and thapsivillosin F, all of which are potent histamine liberators (Scheme 15).[39] 1-Ethoxyvinyllithium (**74**) has also been employed in the first steps for the total synthesis of the natural antibiotic everninomicin 13,384-1,[40] and also in the synthesis of (+)-zaragozic acid C,[41] nikkomycin B,[42] (±)-pyrenophorin,[43] some *seco*-furoeremophilanes,[44] or (±)-corydalide.[45]

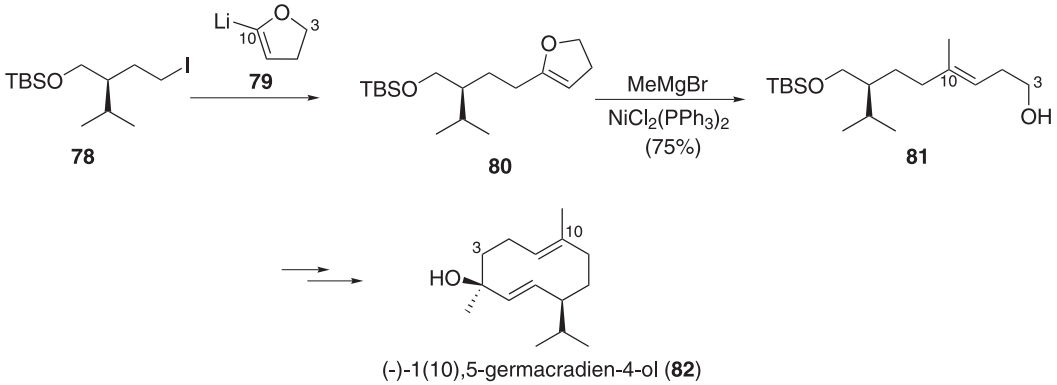
2,3-Dihydrofuran has been α-lithiated using *tert*-butyllithium, the resulting lithio derivative being used as a nucleophile and frequently transformed into homoallylic alcohols.[38] A recent example of the use of this 5-lithio-2,3-dihydrofuran (**79**) can be seen in its substitution reaction with the iodide **78**, providing the 5-substituted dihydrofuran **80**, which can be subjected to a nickel(0)-catalyzed coupling and ring opening with methylmagnesium bromide to furnish compound **81**, an intermediate in the total synthesis of (−)-1(10),5-germacradien-4-ol (**82**), a constituent of the needles of Scots pine and of the defense secretion from the larvae of the pine sawfly (Scheme 16).[46] A similar substitution-ring opening strategy has been reported for the preparation of the bioactive sesquiterpene from Caribbean marine algae (±)-dihydrohipocephalin.[47] In addition, 5-lithio-2,2-dimethyl-2,3-dihydrofuran has also been used for the introduction of the alkyl chain in the steroid 20-hydroxyecdysone, which plays a key role in the development of insects.[48] 5-Lithio-2,3-dihydrofuran (**79**) has also been used for ring opening using $(n\mathrm{Bu_3Sn})_2\mathrm{Cu(CN)Li_2}$ in an enantiocontrolled synthesis of (+)-fostriecin, an antitumor phosphate ester produced by *Streptomyces pulveraceous*.[49]

The ring opening of the 2,3-dihydrofuran moiety has also been carried out via a copper-mediated 1,2-metallate rearrangement. An application can be seen in the reaction of organolithium compound **85**, obtained by *sec*-butyllithium-promoted metalation of the corresponding dihydrofuran, with the lower order cuprate **84**, generated by lithiation of homoallylic iodide **83** and further reaction with 1-pentynylcopper, which gives rise to the high order cuprate **86** (Scheme 17). This intermediate suffers 1,2-metallate rearrangement to alkenylcuprate **87** and reacts with iodine affording alkenyl iodide **88**, an advanced intermediate in the total synthesis of sesquiterpenoid sponge metabolite manoalide (**89**).[50]

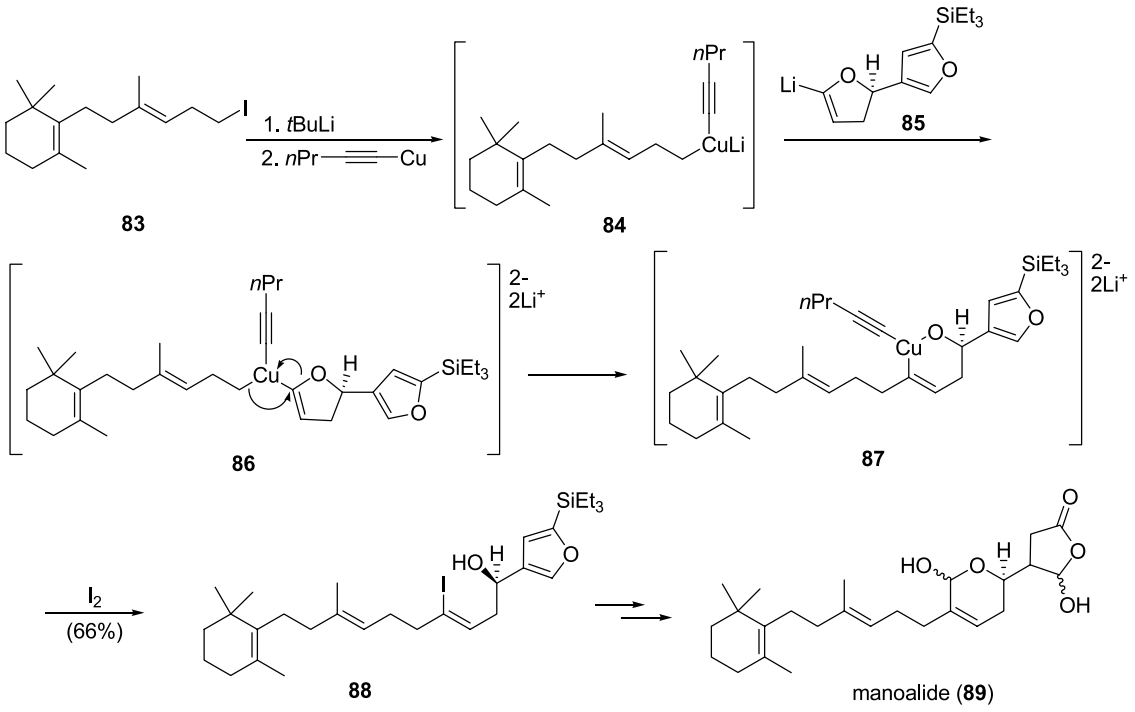
1-Alkoxyallenes can be α-lithiated using alkyllithiums and can react at the α-position with electrophiles under kinetic conditions, recent applications of these organolithiums to



Scheme 15.

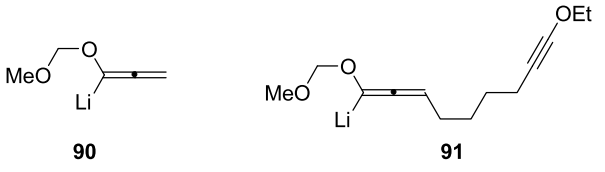


Scheme 16.



Scheme 17.

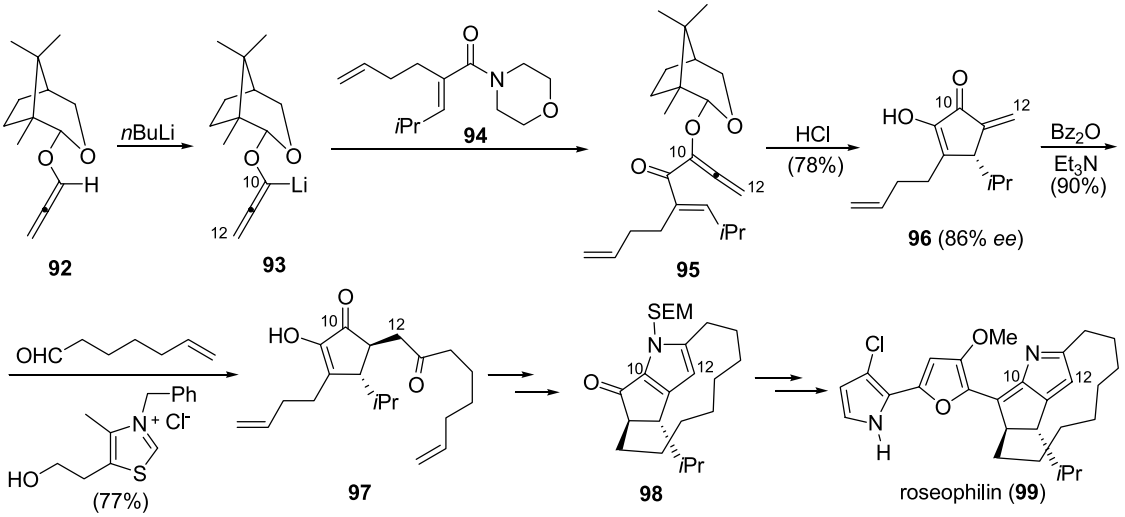
the total synthesis of natural products involving a subsequent Nazarov-type cyclization to conjugated cyclopentenones. Thus, 1-lithio-(methoxy)methoxyallene **90** has been employed in the total synthesis of the cyclopentanoid antibiotic (±)-xanthocidin,[51] whereas lithiated allene **91** has been used for the synthesis of alkylidene cyclopentenone prostaglandins.[52]



90 **91**

Recently, a (+)-camphoric acid-derived chiral lithioallene **93**, prepared by lithiation of the corresponding allene **92**, has been added to amide **94** to afford compound **95** which gives enantiomerically enriched cyclopentenone **96** after acid-promoted Nazarov cyclization. This compound can be benzoylated and subsequently transformed into the dienone **97** after treatment with 6-heptenal and 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride. Several synthetic steps, including a Grubb's metathesis, give rise to ketopyrrole **98** [SEM=2-(trimethylsilyl)ethoxymethyl], a key building block in the total synthesis of roseophilin (**99**) (Scheme 18), a compound with activity against erythroid leukaemia cells and nasopharyngeal carcinoma.[53]

Cyclic stannylated enamides derived from piperidine lactams such as **100** (Ts=*p*-toluenesulfonyl), have been obtained by palladium-catalyzed cross coupling of the corresponding enol triflates with hexamethyldistannane and

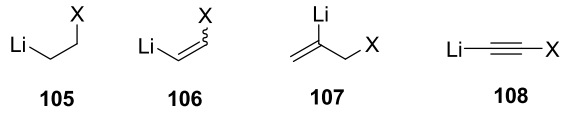


Scheme 18.

can be used for the generation of sp^2-hybridized organolithiums such as **101** after tin/lithium exchange carried out using an alkyllithium such as methyllithium. In situ lithium/magnesium exchange on lithiated species **101** using magnesium dibromide followed by addition of cyclopentanone gave rise to alcohol **102** which was converted into the spiro compound **103** after an epoxidation–silyl protection sequence followed by titanium tetrachloride-mediated ring expansion (Scheme 19).[54] Spiro compound **103** has been transformed into the marine invertebrate metabolite fasicularin (**104**), which shows DNA-damaging properties.

3. β-Functionalized organolithiums

The organolithiums with a β-functionality discussed in this report can be depicted with the general structures **105**–**108**, all of them being considered as d^2 reagents.[7] Many can be rather unstable if the possible β-elimination process cannot be avoided, both by the presence of a negative charge-containing functionality or by the formation of a highly strained cyclic system after the elimination process. Thus, sp^3-hybridized reagents of the type **105**, as well as different sp^2-hybridized species **106** or **107**, will be considered, in the case of **107** the X group being also able to be part of an acetal. Finally, the use of sp-hybridized systems **108** will be shown.

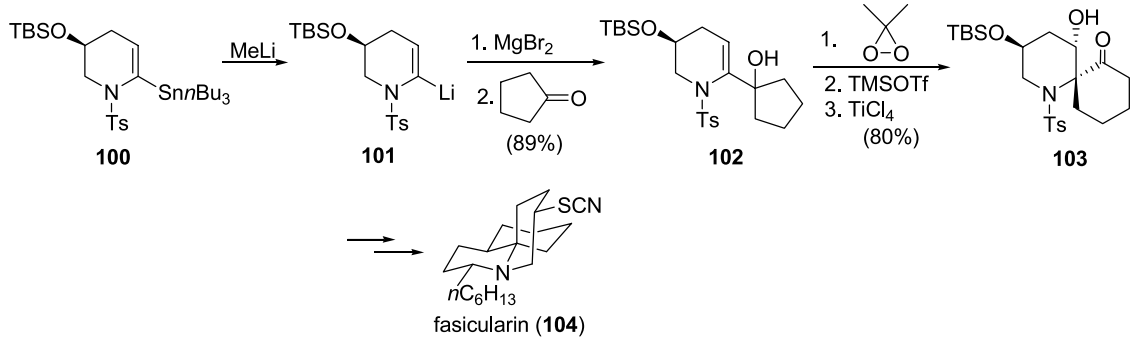


105 **106** **107** **108**

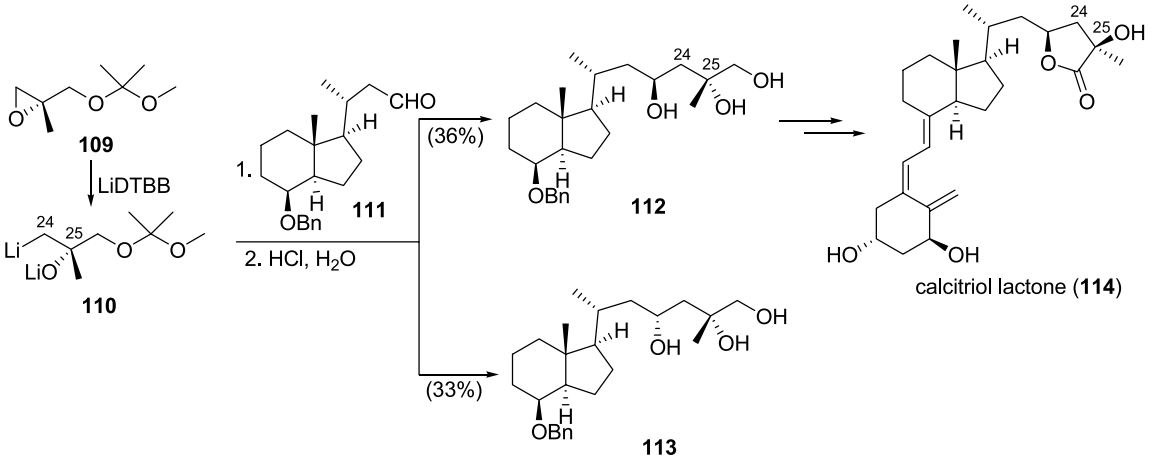
3.1. β-Functionalized sp^3-hybridized organolithiums

β-Oxido alkyllithiums in which the oxygen bears a negative charge, therefore preventing β-elimination, are usually obtained via reductive ring opening of epoxides. An example of the use of this methodology is the ring opening of chiral glycidyl ether **109** using lithium di-*tert*-butylbiphenylide (LiDTBB) to generate β-functionalized alkyllithium species **110** which reacted with aldehyde **111** to give, after acidic hydrolysis, compound **112** and its 23-epi-analogue **113**. Compound **112** is an advanced intermediate in the synthesis of calcitriol lactone (**114**) which is the major vitamin D metabolite in man and other animals (Scheme 20).[55]

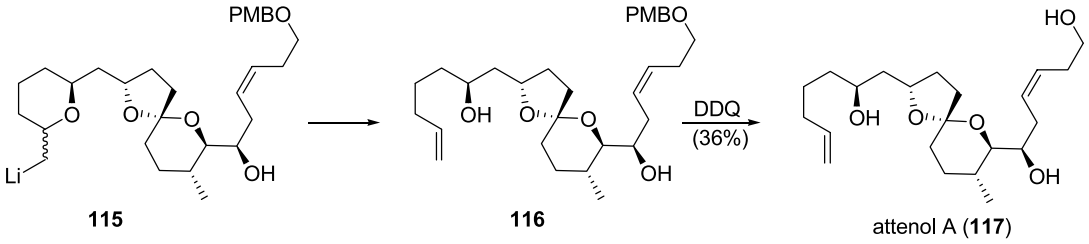
The above-mentioned β-elimination of generated β-oxido alkyllithiums can also be synthetically useful as shown in Scheme 21, where β-oxygenated organolithium **115**, generated by treatment of the corresponding iodomethylpyran with *n*-butyllithium, suffers ring opening to give alcohol **116** which can be transformed, after deprotection of the *p*-methoxybenzyl group using dichlorodicyanoquinone (DDQ), into attenol A (**117**) a metabolite of the Chinese



Scheme 19.



Scheme 20.



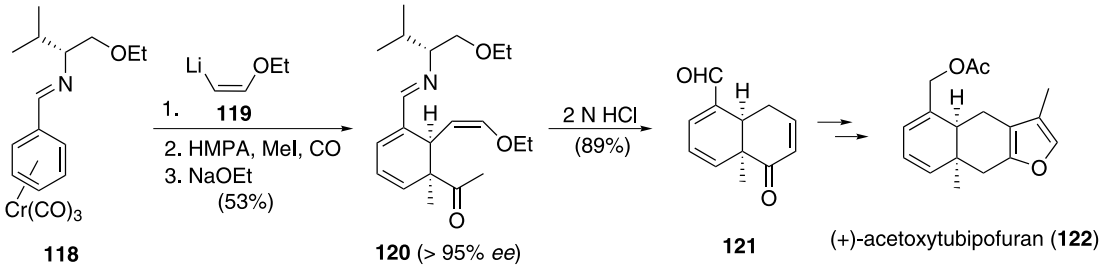
Scheme 21.

bivalve *Pinna attenuata* with moderate cytotoxicity against P388 cells.[56]

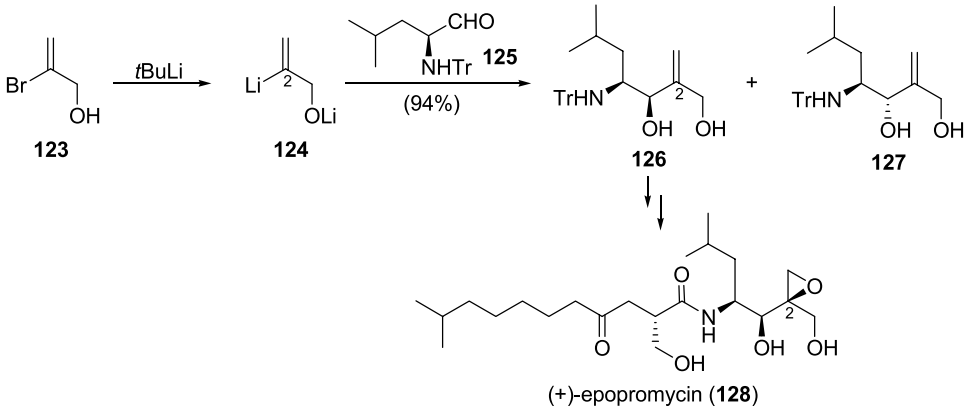
3.2. β-Functionalized sp^2-hybridized organolithiums

1-Lithio-2-alkoxyethenes, generally obtained from the corresponding brominated precursors by alkyllithium-promoted bromine/lithium exchange at low temperature, can be considered as acetaldehyde enolates, the *Z*-isomer showing much higher thermal stability than its corresponding *E* counterpart.[57] A recent example of their use in total synthesis is shown in Scheme 22, where (*Z*)-1-lithio-2-ethoxyethene (**119**) is employed in the $Cr(CO)_3$-promoted dearomatization which takes place in benzaldehyde/D-valinol-derived complex **118**. Nucleophilic addition/acylation/alkylation of complex **118** yielded enol ether **120** which was transformed into enone **121** after vinyl ether hydrolysis and intramolecular aldol condensation. This enone **121** was further converted into (+)-acetoxytubipofuran (**122**),[58] a metabolite from the Japanese stolonifer *Tubipora musica* with in vitro cytotoxicity against B-16 melanoma cells. Moreover, (*Z*)-1-lithio-2-ethoxyethene (**119**) has also been employed as a deprotonating agent in an asymmetric synthesis of (+)-gossypol, a compound from cotton seeds with oral anti-spermatogenic activity.[59]

If the starting material for the generation of the vinyllithium compound has allylic hydrogens, their removal can compete with vinyl lithiation, halogen/lithium or tin/lithium exchange being more convenient than direct deprotonation for the generation of these reagents. Thus, 2-lithioprop-2-en-1-olate (**124**) can be generated by treatment of 2-bromoprop-2-en-1-ol (**123**) (prepared by hydrobromination of the propargylic alcohol) with an alkyllithium, one example of its use being the recent synthesis of the *Streptomyces* fermentation product (+)-epopromycin B (**127**), which has shown biological activity as an inhibitor of the cell-wall synthesis of plant protoplasts. The preparation of this natural product begins with the reaction between the α-oxygenated alkenyllithium **124** with aldehyde **125** (Tr=trityl), derived from L-leucine, affording a 1:1 diastereomeric mixture of compounds **126** and **127**. From this mixture, alcohol **126** was separated and used in the preparation of the natural metabolite **128** (Scheme 23).[60] This use of 2-lithioprop-2-en-1-olate (**124**) for the introduction of a suitable moiety in order to generate



Scheme 22.

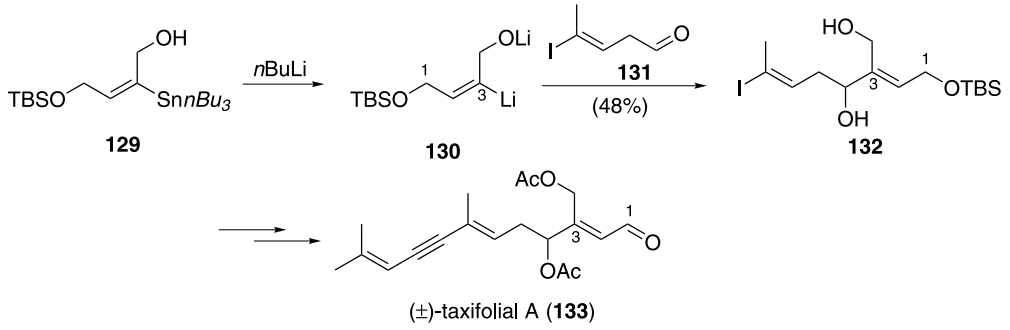


Scheme 23.

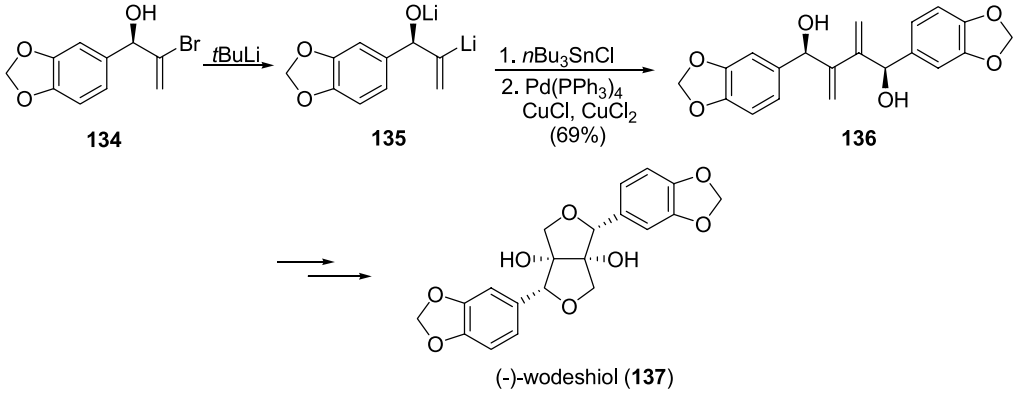
the β-hydroxy-α-epoxyketone terminus at (+)-epopromycin (**128**), has also been employed in the synthesis of the structurally similar antibiotic eponemycin.[61] In addition, 2-lithioprop-2-en-1-olate (**124**) has been transformed into a chiral sulfoxide by reaction with (−)-menthyl *p*-toluenesulfinate, the resulting chiral allylic alcohol being oxidized to a chiral acrolein for a hetero-Diels–Alder reaction in the preparation of both enantiomers of 1,7-dioxaspiro[5.5]undecane, which are pheromone components of the olive fruit-fly *Dacus oleae*.[62]

Related β-oxido vinyllithiums can also be formed by tin/lithium transmetalation. Thus, 2-lithiobut-2-en-1-olate **130**, generated by treatment of (*E*)-vinyltin reagent **129** with *n*-butyllithium, has been added to iodoaldehyde **131** to achieve diol **132**, which was transformed after several steps, including a Stille palladium-catalyzed cross-coupling reaction,[63] to the tropical green seaweed metabolite (±)-taxifolial A (**133**) (Scheme 24),[64a] as well as natural derivatives such as (±)-caulerpenyne.[64b] On the contrary, β-oxido vinyllithiums can be employed for the preparation of vinylstannanes, appropriate for palladium-catalyzed couplings, as in the case of organolithium **135**, formed by lithiation of vinyl bromide **134**, which reacted with tri-*n*-butyltin chloride and was dimerized through palladium-catalyzed homocoupling to give diol **136** which was subsequently transformed into the lignan (−)-wodeshiol (**137**) (Scheme 25).[65]

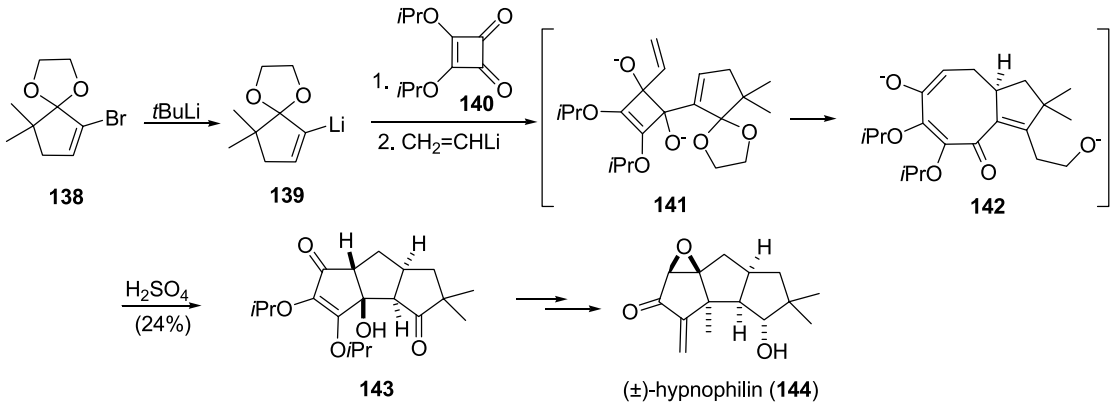
Acetalized cyclic α-bromoenones can be metalated using alkyllithiums, the resulting β-oxygenated organolithiums acting as nucleophiles, as in the application of the squarate ester cascade shown in Scheme 26, where lithiated acetal **139**, a protected α-acylvinyl anion[2c] obtained from brominated compound **138** by halogen–metal exchange using *tert*-butyllithium, reacted with diisopropyl squarate (**140**). A further addition reaction with vinyllithium gave rise to dialcoholate **141**, which evolved to intermediate **142** by charge-driven conrotatory opening–ring closure (initial *trans* stereochemistry) or dianionic oxy-Cope rearrangement (initial *cis* stereochemistry). This intermediate is capable of regioselective cyclization to give enone **143** after hydrolysis, an intermediate in the total synthesis of the sesquiterpene (±)-hypnophilin (**144**).[66] This methodology has also been used for the total synthesis of the fungal metabolite ceratopicanol starting from cyclopentenyllithium **145**.[66] In addition, related protected α-acylvinyl organolithium[2c] **146** ($R^1=R^2=H$) has been employed for the preparation of cyclopentanoid antibiotics (±)-pentenomycins,[67a] and **146** ($R^1=Me$, $R^2=H$) in the synthesis of the macrocyclic diterpene (±)-jatrophone.[67b] In addition, a similar organolithium **146** ($R^1=R^2=Me$) has been transformed into the corresponding chiral sulfoxide by using (−)-menthyl *p*-toluenesulfinate as the electrophile, being employed in a synthesis of the sesquiterpenoid (+)-asteriscanolide,[67c] whereas the cyclohexenic reagent **147** has been used in the preparation of the marine natural product nakienone B.[68] Moreover, the trisilylated cyclohexenyllithium **148** has been used in the synthesis of (+)-pericosine B.[69]



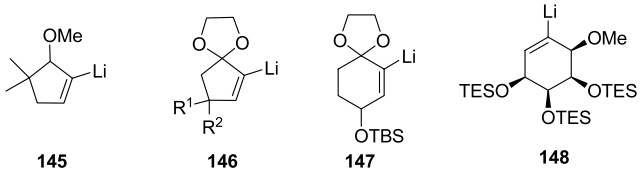
Scheme 24.



Scheme 25.

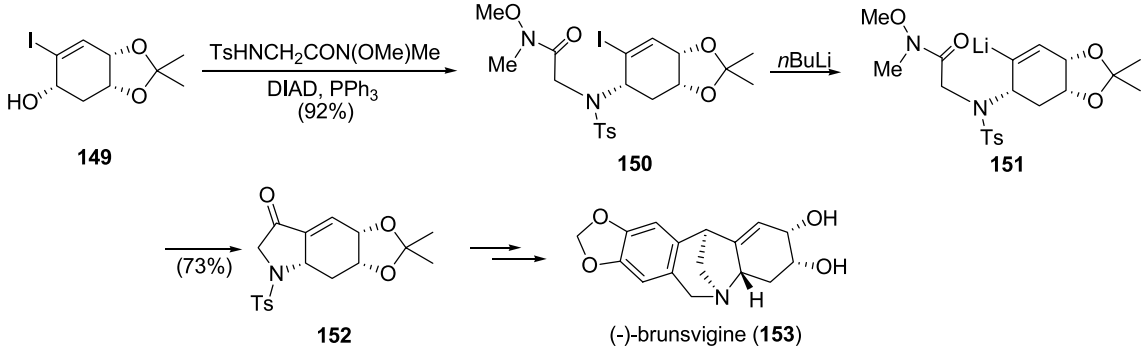


Scheme 26.

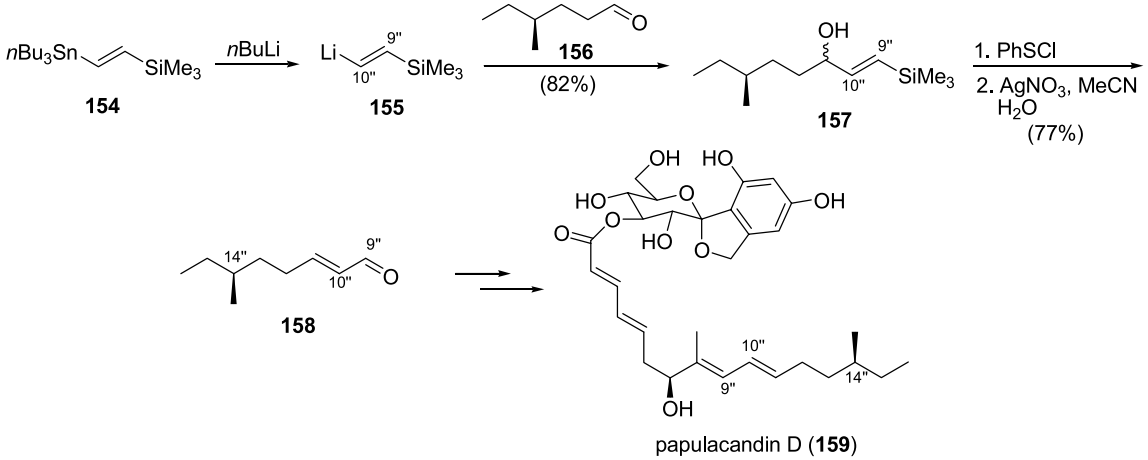


An example of the synthetic application of a β-nitrogenated alkenyllithium can be seen in Scheme 27, which shows a recent total synthesis of the *Amaryllidaceae* alkaloid (−)-brunsvigine. Thus, *N*-tosylated Weinreb amide **150**, obtained from the chiral iodoalcohol **149** through a Mitsunobu protocol, was lithiated using *n*-butyllithium, and the resulting vinyllithium species **151** cyclized to give the enone **152**. Further synthetic transformations on this enone gave rise to (−)-brunsvigine (**153**).[70]

Examples of the use of other vinyllithiums β-functionalized with other atoms can be found in the total synthesis of the antifungal agent papulacandin D, where (*E*)-β-trimethylsilylvinyllithium (**155**), generated by tin/lithium transmetalation from (*E*)-1-(tri-*n*-butylstannyl)-2-(trimethylsilyl)ethene (**154**) (Scheme 28), has been used as an acetaldehyde enolate equivalent. Thus, trimethylsilyllithium **155** was



Scheme 27.



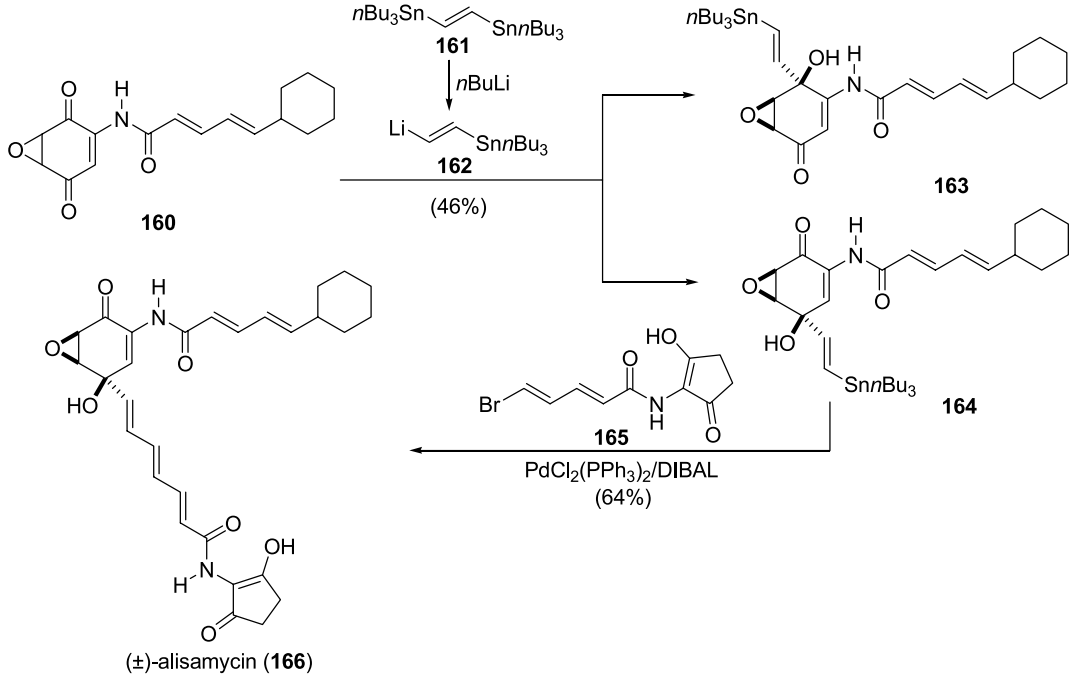
Scheme 28.

added to aldehyde **156** affording alcohol **157** which was converted into enal **158** on sequential reaction with phenylsulfenyl chloride and silver nitrate. This enal **158** was used for the introduction of the side chain of papulacandin D (**159**).[71]

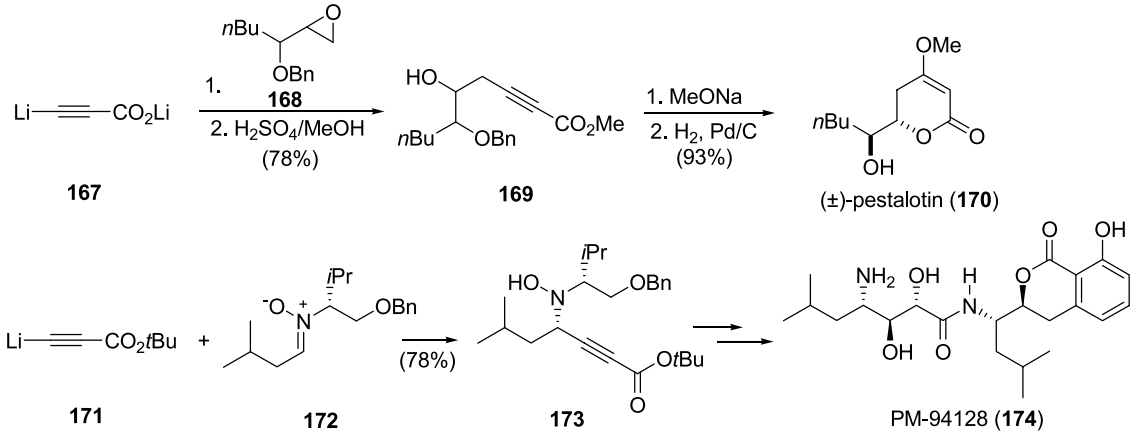
(*E*)-β-tri-*n*-butylstannylvinyllithium (**162**), which can be prepared from the corresponding di(tri-*n*-butylstannyl) ethene (**161**) via transmetalation, can be used as a nucleophile able to introduce a vinylstannyl moiety, suitable to be used as coupling partner in palladium-catalyzed Stille cross-coupling reactions, as shown in Scheme 29 in a total synthesis of alisamycin, a member of the manumycin family of antibiotics from *Streptomyces*. Thus, (*E*)-β-tri-*n*-butylstannylvinyllithium (**162**) was added to dione **160**, which afforded compounds **163** and **164** in a 1:1.3 ratio as a result of attacks on both carbonyls. Chromatographic separation of enone **164** and Stille cross-coupling to dienyl bromide **165** gave rise to (±)-alisamycin (**166**).[72] Other members of this family of antibiotics such as (±)-nisamycin,[73] (+)-manumycins A[74] and B,[75] and also the macrolide monocillin I[76] have been prepared using this stannylated vinyllithium **162**.

3.3. β-Functionalized sp-hybridized organolithiums

When propiolic acid is treated with an excess of LDA in the presence of hexamethylphosphoramide (HMPA), the propiolic acid dianion is generated, being suitable for acting as a β-functionalized lithium acetylide in reactions such as the ring opening of epoxides, which can be used for creating dihydropyrones. An example can be seen in Scheme 30, where attack of acetylide **167** on an epimeric mixture of epoxides **168** has been used, after methoxide treatment and hydrogenolysis of the resulting alcohol **169**, for the synthesis of (±)-pestalotin (**170**).[77] In addition, propiolate esters can be easily deprotonated with *n*-butyllithium to the corresponding lithium acetylides, being employed as



Scheme 29.



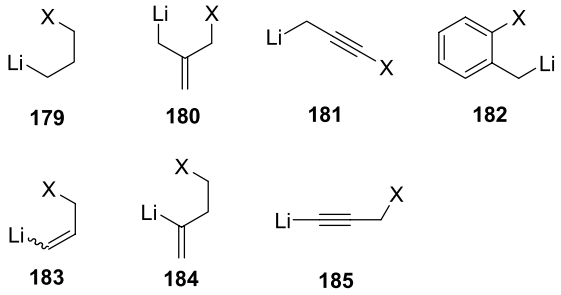
Scheme 30.

nucleophiles in substitution reactions, as in the total synthesis of the alkaloid (±)-stemoamide,[78] in addition reactions to carbonyls, as in the total syntheses of the labdane diterpene (±)-forskolin,[79] the norsesquiterpene lactone (±)-senoxepin[80] or the macrolide (±)-[81] and (+)-brefeldin A[82] or in epoxide ring opening, as in the total syntheses of lipoxins A4 and B4[83] or the ladybird alkaloid hyperaspine.[84] Moreover, these lithium acetylides have been used in addition reactions to enantiopure 2,3-dihydro-4-pyridones, as in the synthesis of the indolizidine alkaloid (+)-allopumiliotoxin 267A,[85] and also in addition reactions to nitrones, as shown in Scheme 30, where *tert*-butyl propiolate-derived lithium acetylide **171** reacts with chiral nitrone **172** to give hydroxyamine **173** as a single diastereomer. This compound has been used for the introduction of the γ-amino-α,β-dihydroxy acid fragment of the antitumor agent PM-94128 (**174**), isolated from marine sediment bacterium PhM-PHD-090.[86]

Trimethylsilylacetylene can be lithiated using an alkyllithium, the formed β-silylated lithium acetylide being considered a protected acetylide, suitable for the nucleophilic introduction of an ethynyl group after a fluoride-induced silyl removal. Many examples can be found of the use of this lithiated reagent in a total synthesis,[87] including the preparation of the neuritogenic spongean polyacetylene lembehyne A (**178**), where lithium (trimethylsilyl)acetylide (**176**) reacts with Weinreb amide **175** affording keto-alcohol **177**, which was transformed into lembehyne A (**178**) after several steps, including a final desilylation (Scheme 31).[88]

4. γ-Functionalized organolithiums

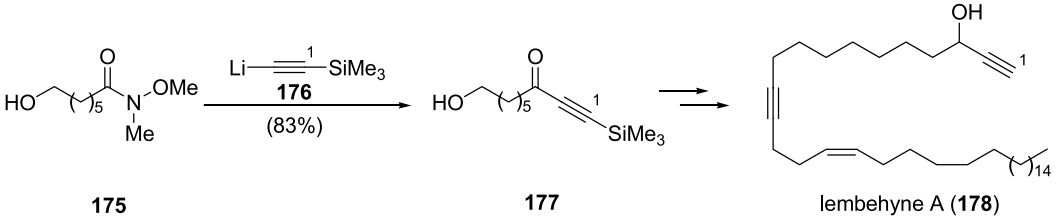
These species can be considered as d^3 reagents[7] and will also be ordered depending on the hybridization of the carbon that supports the lithium atom, their general structures following below. In this case, stabilization by internal complexation is structurally possible in many cases. When considering sp^3-hybridized systems, the synthetic examples will be presented according to the use of alkyl- (**179**), allyl- (**180**), propargyl- (**181**) as well as *o*-functionalized benzylithium regents (**182**). Afterwards, the use of sp^2-hybridized organolithiums of the general structure **183** and **184** will be described, and finally, sp-hybridized systems of type **185**. It is necessary to note that the abbreviated X functionality can also be part of an acetal or an orthoester, something that will be shown in examples using reagents of the type **179** (therefore being protected homoenolates), as well as in vinyllithiums of the type **183** and **184**.



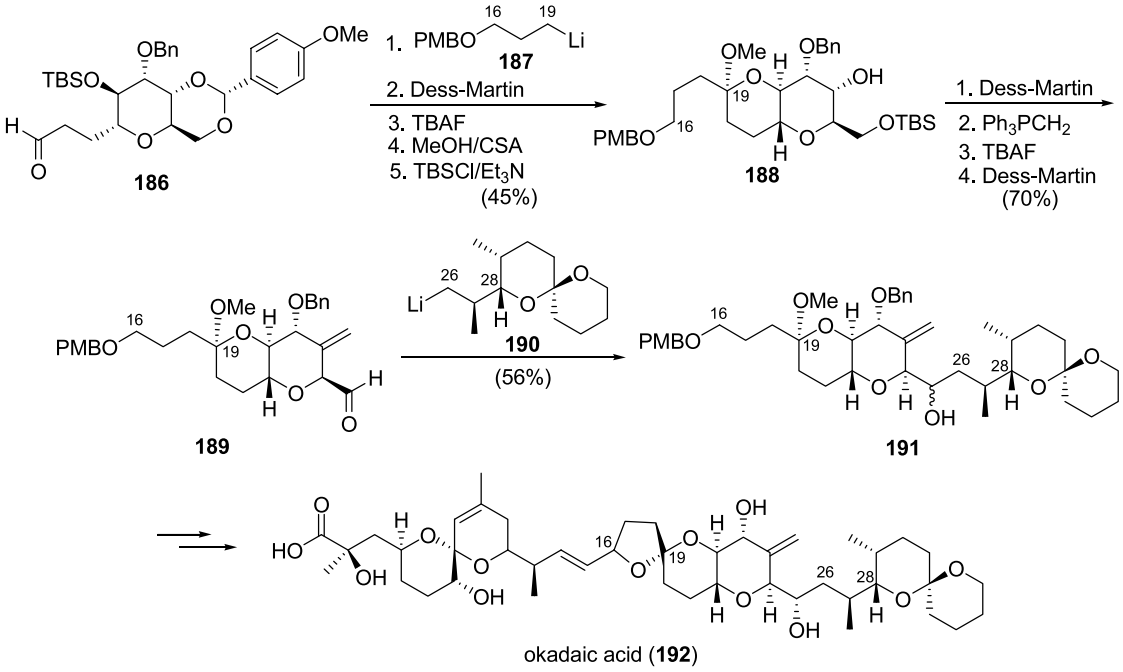
4.1. γ-Functionalized sp^3-hybridized organolithiums

There are different methods for the generation of γ-oxygenated alkyllithiums, although the simple halogen–lithium exchange is the most frequently used for the preparation of reagents applicable in total synthesis, the oxygen atom being present many times in the form of a removable ether, acetal or orthoester. Examples of the use of this type of organolithiums can be found in Scheme 32, where *p*-methoxybenzylated organolithium **187**, obtained from the corresponding bromide by treatment with *tert*-butyllithium, was added to glycosyl aldehyde **186**. Subsequent oxidation and masking of the resulting ketone as the mixed acetal gave place to alcohol **188** which was converted into aldehyde **189** after installation of an exocyclic methylene and some oxidation reactions. To this aldehyde **189** was added the chiral and thermally unstable γ-oxygenated alkyllithiums **190**, obtained from the corresponding bromide by *tert*-butyllithium-promoted halogen–lithium exchange, giving rise to a mixture of epimeric alcohols **191** which were used as intermediates in the total synthesis of okadaic acid (**192**),[89] a natural product which inhibits the protein serine/threonine phosphatases 1 (PP1) and 2A.

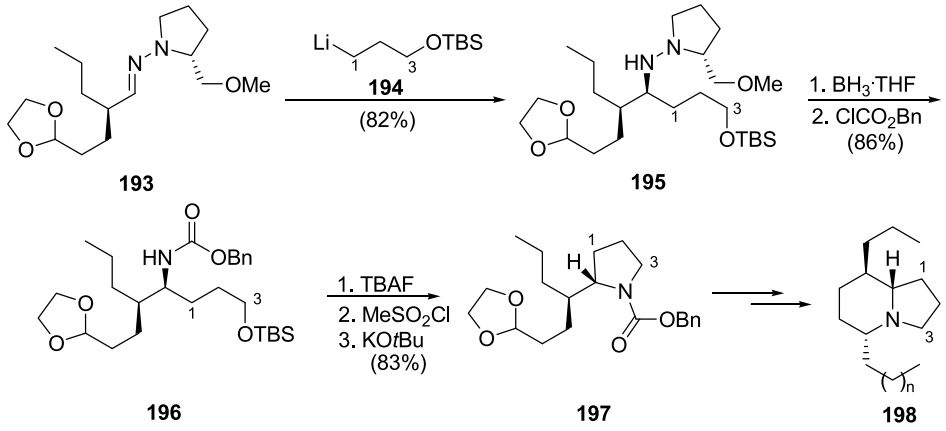
Frequently, the γ-oxygen in the functionalized organolithium belongs to a hydroxy with a silyl protecting group. An example of this type is *tert*-butyldimethylsiloxy-3-lithiopropane (**194**), which has been obtained by treatment of the corresponding iodide with *tert*-butyllithium, and employed in the total synthesis of dendrobatid indolizidine alkaloids (−)-209I and (−)-223J, isolated from the skin of a poisonous tropical frog. The synthesis includes addition of organolithium **194** to hydrazone **193** (90% *de*) affording hydrazine **195** (90% *de*) which was transformed into carbamate **196** after reductive N–N bond cleavage and protection with benzyl chloroformate (Scheme 33). Removal of the silyl group and mesylation followed by ring closure under basic conditions gave rise to pyrrolidine **197**, which was converted after several synthetic steps into



Scheme 31.

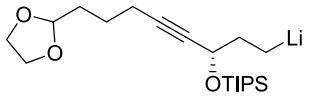


Scheme 32.



Scheme 33.

(−)-2090I (**198**, $n=1$) and (−)-223J (**198**, $n=2$).[90] In addition, the γ-silyloxy organolithium **199** has been used for the preparation of both enantiomers of the diterpenic scopadulcic acid A.[91]



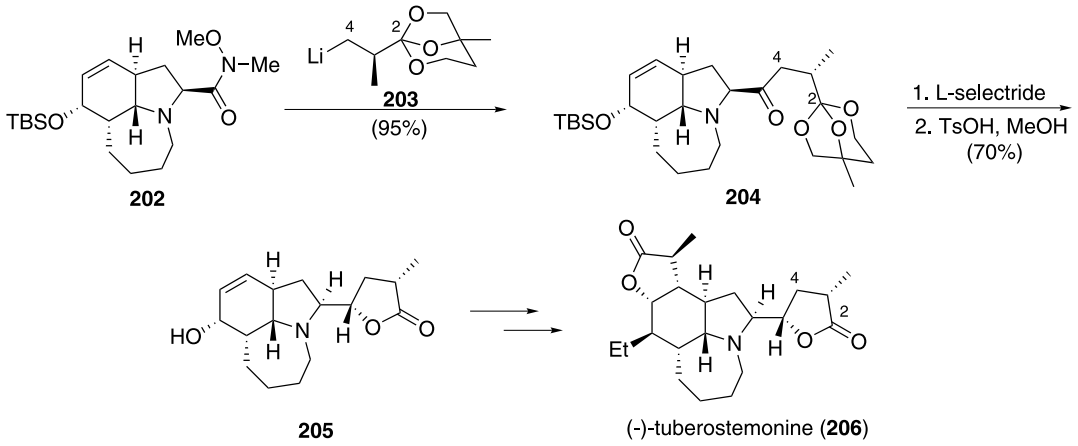
199

Enantiopure (*S*)-3-lithio-2-methyl-1-benzyloxypropane (**200**) has been generated from the corresponding iodide by *tert*-butyllithium metalation and has been employed in the total synthesis of chatancin, a tetracyclic diterpene isolated from a soft coral.[92] The lithiated acetal **201** is a well known homoenolate equivalent which has been generated from the corresponding chloride after treatment with lithium powder and a catalytic amount of an arene, and has been used for the synthesis of a natural hydroxyketone.[93]

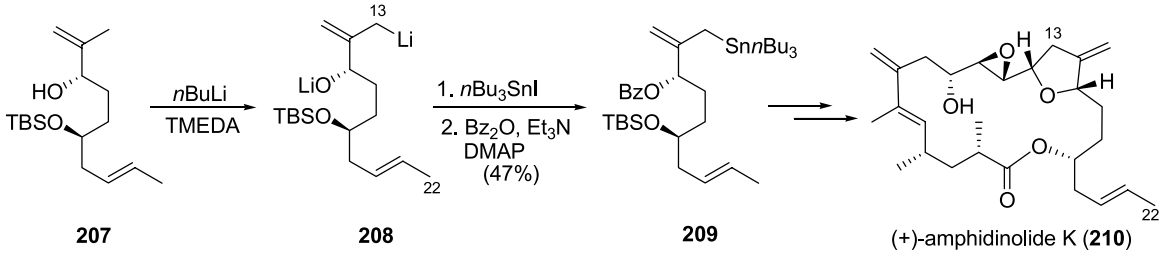
200 **201**

In addition, chiral lithiated orthoester **203** has been prepared from the corresponding bromide by LiDTBB-promoted lithiation, and employed as nucleophile in the addition reaction to Weinreb amide **202** affording ketone **204** which was transformed into lactone **205**, after a reduction/orthoester hydrolysis sequence, in the recent total synthesis of the *Stemona* alkaloid (−)-tuberostemonine (**206**) (Scheme 34).[94]

The direct deprotonation can be a suitable procedure for the generation of γ-functionalized allylithiums. An example can be seen in Scheme 35, where allylic alcohol **207** has been deprotonated with *n*-butyllithium in the presence of tetramethylethylendiamine (TMEDA) to generate organolithium reagent **208**, which was stannylated and



Scheme 34.



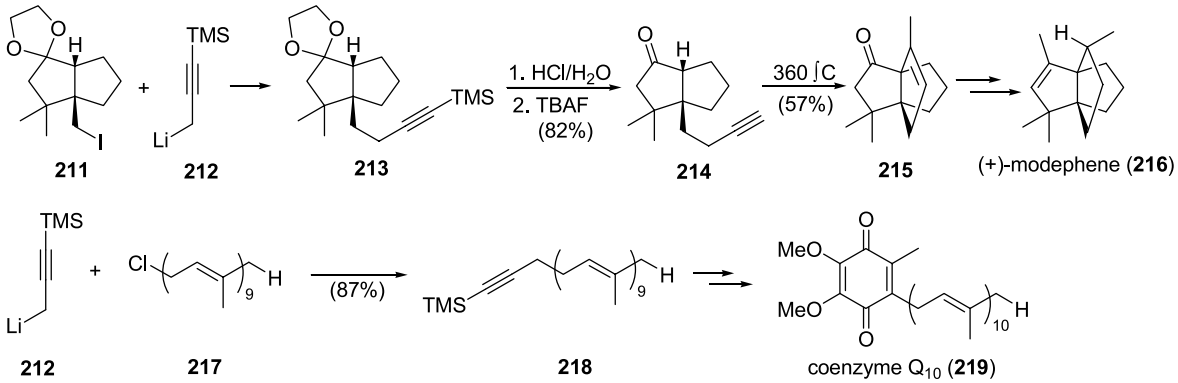
Scheme 35.

benzoylated to give stannane **209**, an intermediate able to supply the C(13)–C(22) portion of the antitumor macrolide (+)-amphidinolide K (**210**).[95]

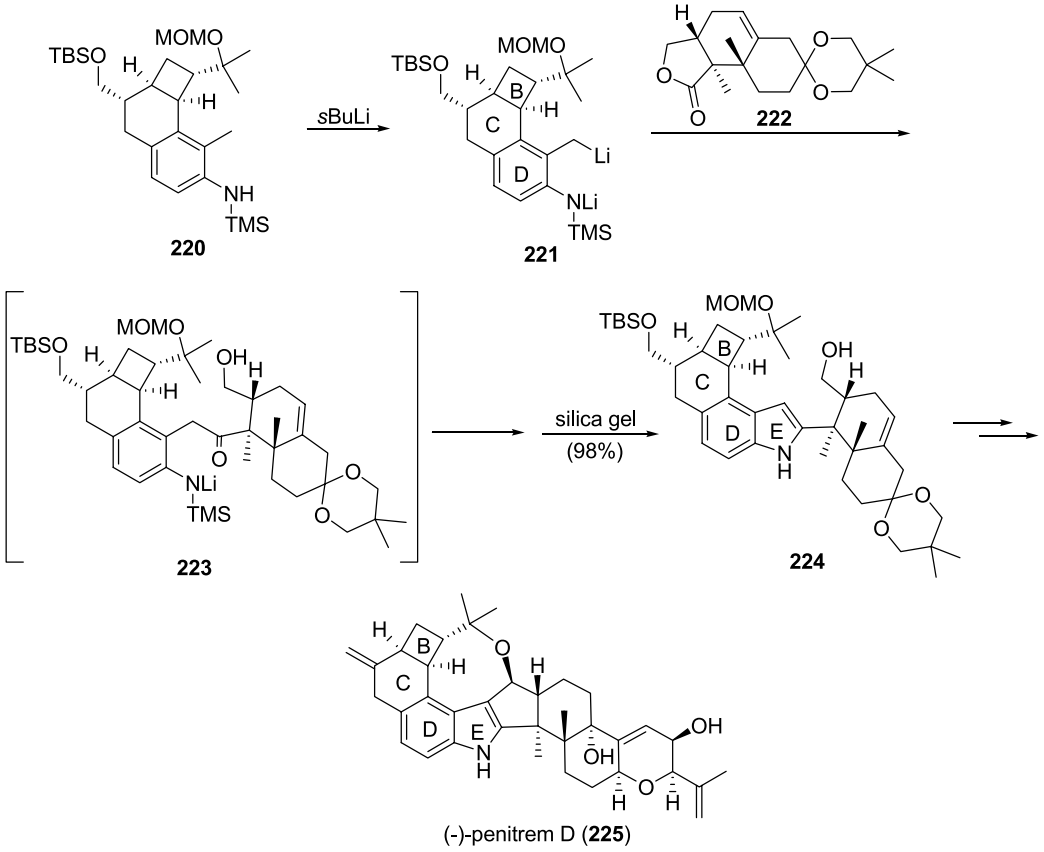
Examples of the use of a propargyllithium compound bearing a functionality at the sp-hybridized γ-position can be found in Scheme 36, where lithio-1-trimethylsilylpropyne (**212**), obtained by deprotonation of trimethyl(prop-1-ynyl)silane with *n*-butyllithium, reacted with chiral iodide **211** affording compound **213**. Subsequent hydrolysis and desilylation gave rise to ketone **214** which was converted into tricyclic compound **215** upon thermolysis, in a synthesis of the sesquiterpene (+)-modephene (**216**).[96] In addition, this organolithium reagent **212** has also been added to chloride **217** to afford silylated acetylene **218**, which was used for the introduction of the polyenic chain in a recent total synthesis of coenzyme Q_{10} (**219**) (Scheme 36).[97] Moreover, lithio-1-trimethylsilylpropyne (**212**) has also been employed in the preparation of some marine sterols such as 24,28-dehydroaplysterol, xestosterol and ostreasterol.[98]

Benzyllithiums with the functionality linked to the *ortho*-position of the aromatic ring have been generally obtained by an α-deprotonation reaction, although the halogen/-lithium exchange can also be employed. Thus, *N*-silylated aniline **220** has been treated with 2.2 equiv of *sec*-butyllithium to provide the organolithium reagent **221** which reacted with lactone **222** giving rise to intermediate **223** capable of an intramolecular Peterson olefination to furnish indole **224** after silica gel treatment, which supplied the BCDE-ring system in a recent total synthesis of tremorgenic indole alkaloid (−)-penitrem D (**225**), a component of the ergot fungi family of alkaloids (Scheme 37).[99]

Another example of the use of a benzyllithium, but which is

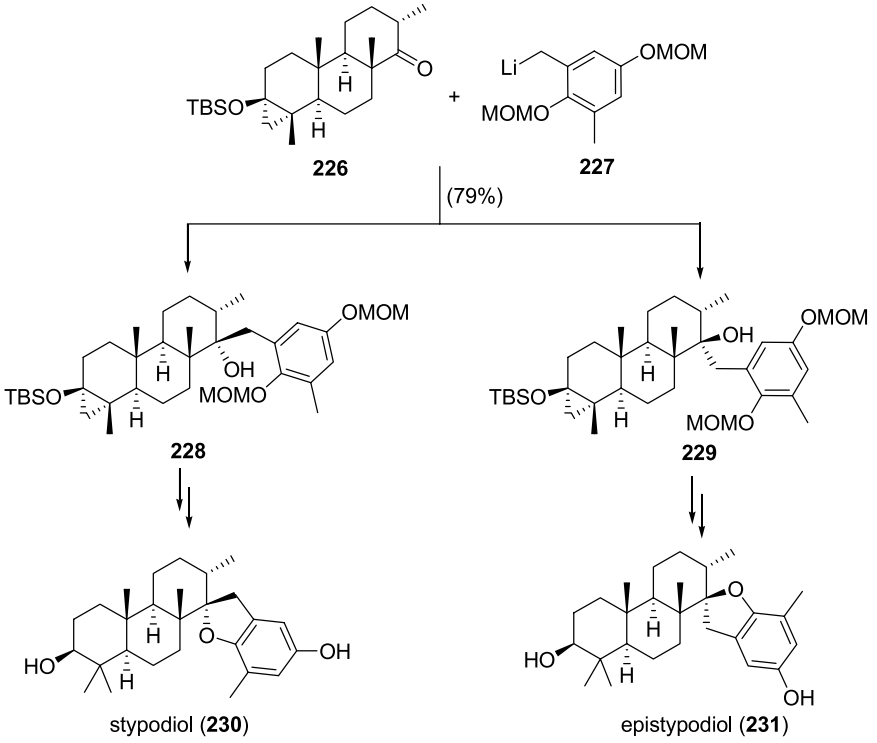


Scheme 36.



Scheme 37.

now γ-oxygenated, is the addition of reagent **227**, generated in this case by reaction of the corresponding chloride with lithium under sonication, with ketone **226**, which yielded a 3:7 mixture of the epimeric alcohols **228** and **229**. These compounds can be chromatographically separated and are precursors, respectively, of stypodiol (**230**) and epistypodiol (**231**), which are secondary diterpene metabolites excreted by the tropical algae *Stypopodium zonale* (Scheme 38).[100]



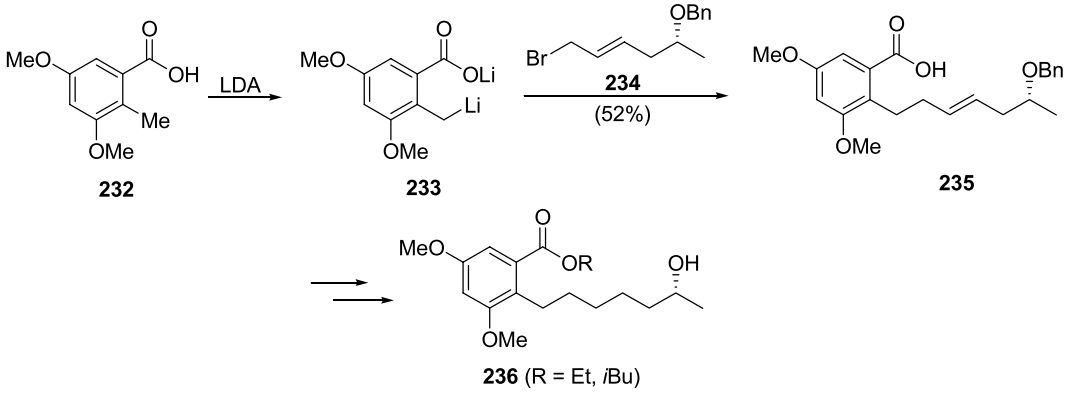
Scheme 38.

Benzyllithium **233** bearing a lithium carboxylate at the γ-position has been obtained by LDA-promoted deprotonation of the corresponding carboxylic acid **232**, being used as nucleophile in the reaction with chiral allylic bromide **234** (Scheme 39). The resulting acid **235** was used as an intermediate in the synthesis of some β-resorcylic acid derivatives **236** isolated from *Lasiodiplodia theobromae* and with potato microtuber-inducing activity.[101]

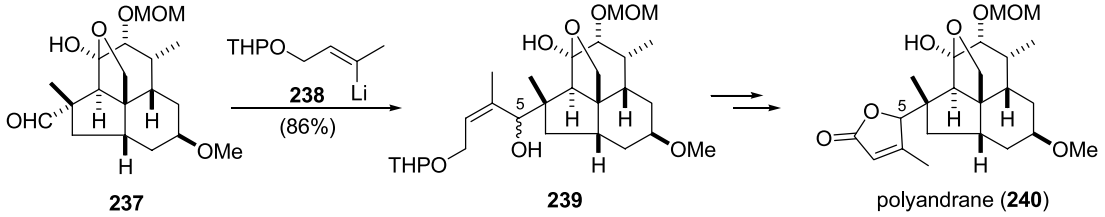
4.2. γ-Functionalized sp^2-hybridized organolithiums

As mentioned above, if the vinyllithium compound has to be prepared from an allylic hydrogen-containing starting material, the halogen/lithium or tin/lithium exchange is the usual choice for achieving a stereochemically and regiochemically defined species. An example of the use of *O*-protected γ-lithiated alcohols in the total synthesis of natural products is the vinyllithium reagent **238**, obtained by iodine/lithium exchange using *tert*-butyllithium, which was added to aldehyde **237** to give compound **239** as a 2:1 mixture of the C(5) α- and β-hydroxy epimers, respectively, which was separated by column chromatography. Further elaboration of each of these epimers allowed the synthesis of the bis-lactones (5*R*)- and (5*S*)-polyandrane (**240**), which have been isolated from *Castela texana* and *Castela polyandra*, respectively (Scheme 40).[102] Another example is the *trans*-vinyllithium orthoester **242**, a protected acylvinyllithium[2c] obtained by iodide/lithium exchange using *tert*-butyllithium, which has been employed in the ring-opening reaction of bicyclic lactone **241** affording enone **243**, an intermediate in the total synthesis of the fungal cytotoxic metabolite (+)-brefeldin A (**244**) (Scheme 41).[103]

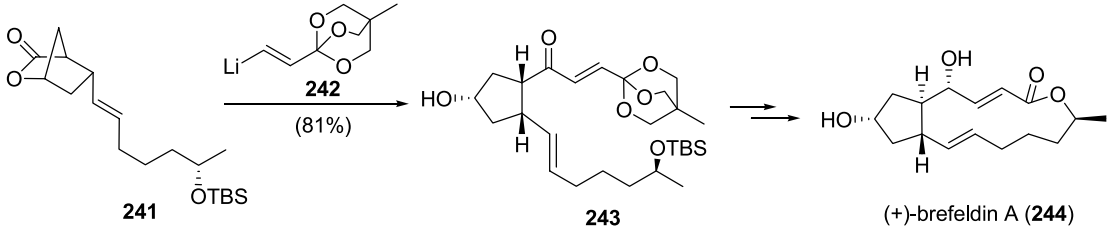
Further examples of these types of organolithium reagents are the halogen/lithium exchange-obtained dimethyl acetal acylvinylithium[2c] **245**, employed in the synthesis of the tetramic acid antibiotic (±)-tirandamycin A,[104a] as well as chiral diol-protected reagent **246**, used in the preparation of a butenolide from *Pseudomonas aureofaciens* fugomycin.[104b] In addition, dienyllithiums **247**[105] and **248**[106] have been used in the total synthesis of taxol, and chiral dioxane **249** has been transmetalated to a vinyl organocopper reagent in a synthesis of (+)-calyculin A and (−)-calyculin B.[107] Moreover, the complex organolithium **250** has also been generated by *tert*-butyllithium-induced metalation of the corresponding bromide and has been used as a key intermediate in the total synthesis of the macrolides (+)-zampanolide,[108a] enantiomer of the natural compound, as well as (+)-dactylolide.[108b]



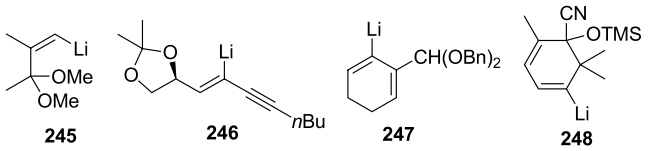
Scheme 39.

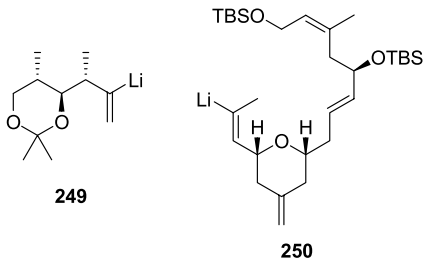


Scheme 40.



Scheme 41.





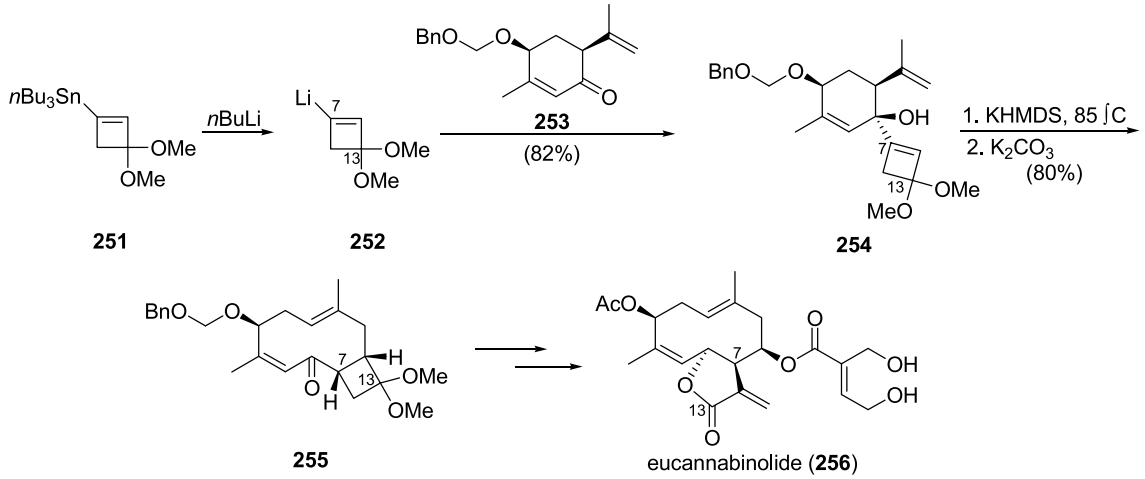
An example of the use of a γ-oxygenated vinyllithium generated by tin/lithium transmetalation is shown in Scheme 42, where acetalized cyclobutenyllithium **252**, a protected acylvinyllithium,[2c] is obtained by treating the corresponding stannane **251** with *n*-butyllithium, and is added to the (+)-carvone-derived chiral ketone **253** giving rise to alcohol **254** as a single diastereomer. Heating this alcohol in the presence of KHMDS induced an oxy-Cope rearrangement which furnished ketone **255** after equilibration under basic conditions, a product which is an intermediate in the synthesis of the cytotoxic germacranolide eucannabinolide (**256**).[109]

The *O*-protection in γ-oxygenated alkenyllithiums may frequently consist of an easily removable silyl group. Thus, γ-triethylsilyloxy vinyllithium **257** has been generated from the corresponding tri-*n*-butylstannane by *n*-butyllithium-promoted transmetalation and has been used for the addition reaction to an aldehyde in a synthesis of the marine diterpene (±)-spatol.[110] In addition, chiral reagent **258** has been prepared by iodine/lithium exchange using *n*-butyllithium and has been used in a transmetalation reaction to a cuprate for a Michael addition to a cyclopentenone in a recent total synthesis of some phytoprostanes.[111]

Organolithium **260**, generated from the corresponding bromide by reaction with *tert*-butyllithium, has been employed in the addition reaction to chiral aldehyde **259** to give an epimeric mixture of allylic alcohols **261**, which were transformed into aldehyde **262** after an oxidation–desilylation–oxidation sequence. This aldehyde **262** was employed in a synthesis of the carotenoid crassostreaxanthin B (**263**), from the edible oyster *Crassostrea gigas* (Scheme 43).[112a] Other related carotenoids such as mytiloxanthin have been prepared using this organolithium reagent **260**,[112b] whereas an identical reagent, although *O*-protected with the *tert*-butyldiphenylsilyl group, has been used in the total synthesis of the marine diterpenoid (+)-dolabellane.[113]

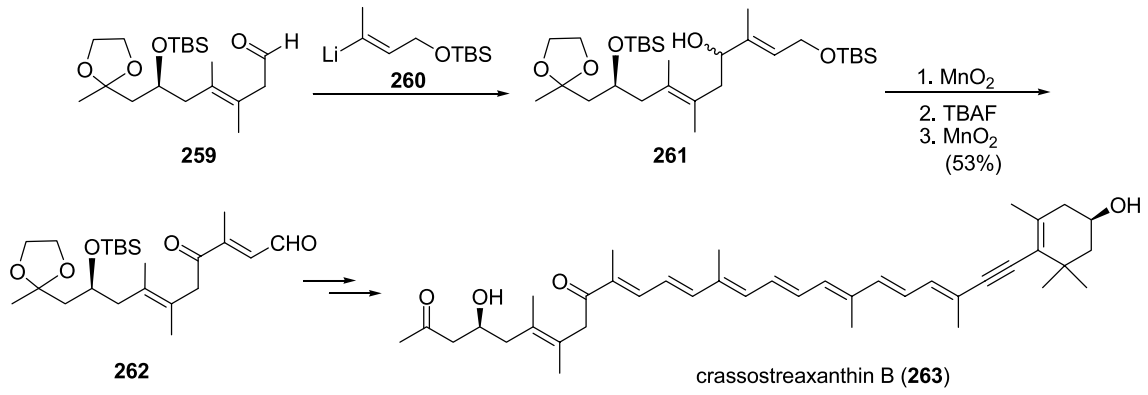
Chiral γ-oxygenated vinyllithium **264**, prepared from the corresponding iodide after treatment with *n*-butyllithium, has been used for the synthesis of vinylstannane **265** after treatment with tri-*n*-butylstannyl chloride. This organotin reagent was coupled to benzylic bromide **266** under palladium catalysis to furnish compound **267**, which has been used as an intermediate in the total synthesis of the salicylate antitumor macrodilactone lobatamide C (**268**), a metabolite of South Western Pacific tunicates (Scheme 44).[114]

An example of the use of a γ-nitrogenated alkenyllithium can be found in the generation of organolithium compound **270**, which has been prepared from bromo oxime **269** by reaction with 3 equiv of *tert*-butyllithium. This reagent has been used as nucleophile in an addition reaction to cyclopropyl ketone **271** to give the oxime **272** which, after treatment with chloramine-T, delivered the isoxazoline **273** as a single diastereomer via an intramolecular nitrile oxide cycloaddition. This heterocyclic compound was ring opened upon hydrogenation and, after dehydration of the corresponding alcohol **274**, yielded (±)-illudin C (**275**), a sesquiterpene isolated from several fungi (Scheme 45).[115] In

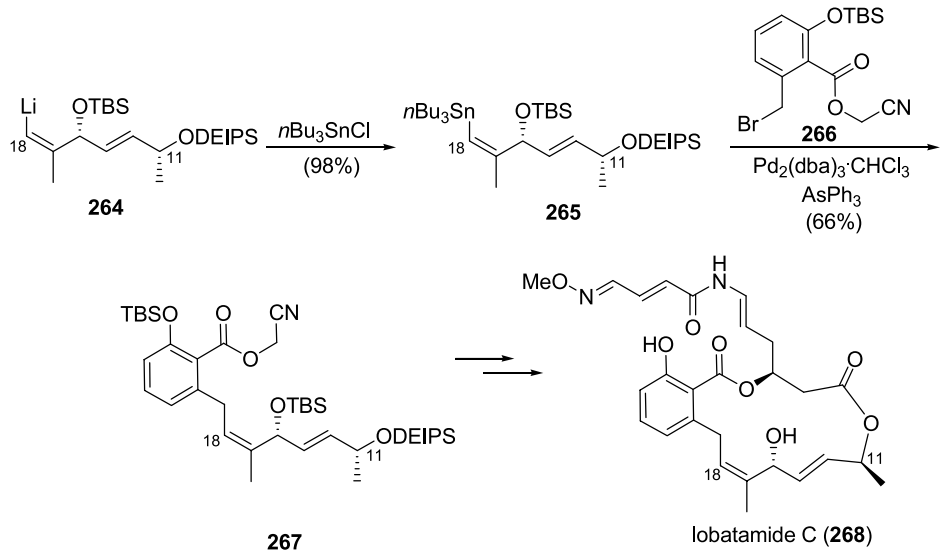


251 252 254 255 eucannabinolide (**256**)

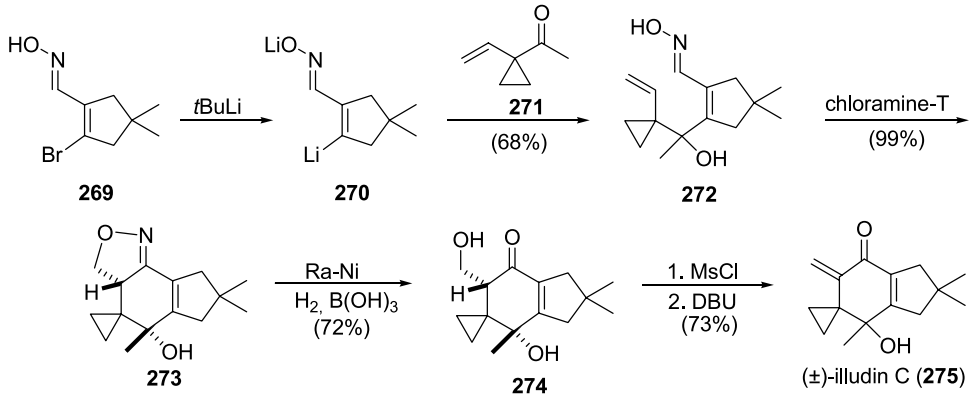
Scheme 42.



Scheme 43.



Scheme 44.

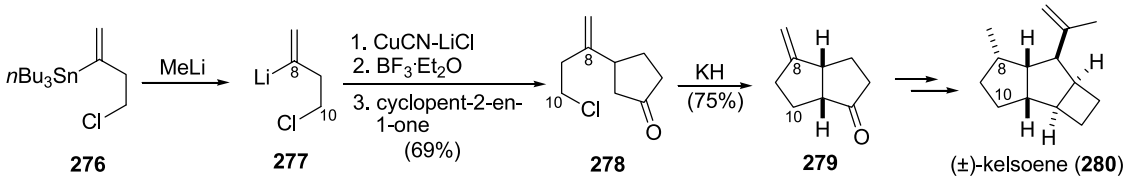


Scheme 45.

addition, Scheme 46 shows the use of a γ-halogenated alkenyllithium such as chlorinated reagent **277**, which has been obtained by tin/lithium exchange from vinylstannane **276**, and has been transmetalated to the corresponding low-order cuprate and used in the Michael addition to cyclopent-2-en-1-one to afford the conjugated addition product **278**, which was intramolecularly alkylated to the bicyclic ketone **279**, an intermediate in the total synthesis of (±)-kelsoene (**280**), a sesquiterpenoid isolated from the marine sponge *Cymbastella hooperi*.[116]

4.3. γ-Functionalized sp-hybridized organolithiums

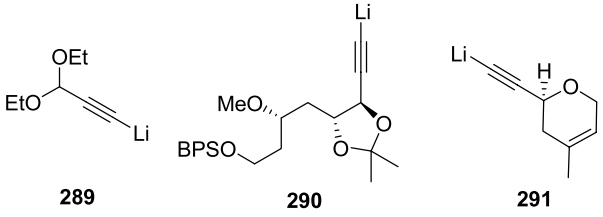
Lithiated alkynes bearing a functional group at the propargylic position are usually prepared by deprotonation with *n*-butyllithium. There are frequent examples of the use



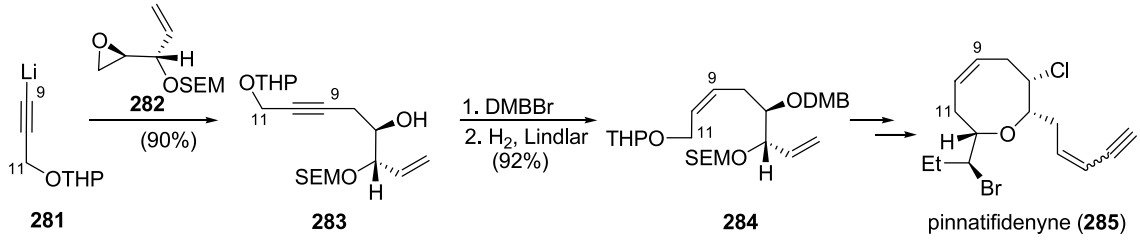
Scheme 46.

of these types of reagents, functionalized with an oxygenated function, for the total synthesis of naturally occurring compounds. Thus, the lithium acetylide of lithium 2-propyn-1-olate has been used for the total synthesis of the acetogenin diepomucaricanin,[117] although more common is the use of an *O*-protected equivalent such as the γ-tetrahydropyranyloxy-substituted organolithium reagent **281**, which has been used for the ring-opening reaction of chiral epoxide **282** to give alcohol **283** which was transformed, after alcohol dimethoxybenzylation and hydrogenation, into diene **284**, an intermediate in the synthesis of the medium-ring ether-containing marine natural products (+)-3-(*E*)- and (+)-3-(*Z*)-pinnatifidenyne (**285**) (Scheme 47).[118] Other examples of the use of this reagent **281** are the preparation of the antitumor acetogenins gigantetrocin A[119a] and asimilobin,[119b] the oxepanic diterpenoid zoapatanol,[120] the diterpenic alkaloid (−)-paspaline,[121] the macrolide haterumalide NA[122] or the polyketide (−)-callystatin A.[123] In addition, lithiated (*S*)-serinol-derived propargyl ether **286** reacted with 1,11-dibromo-undecane giving rise to the bromide **287**, which was employed for the creation of part of the alkyl chain and serinol fragment of the tunicate marine natural product (+)-didemniserinolipid B (**288**) (Scheme 48).[124]

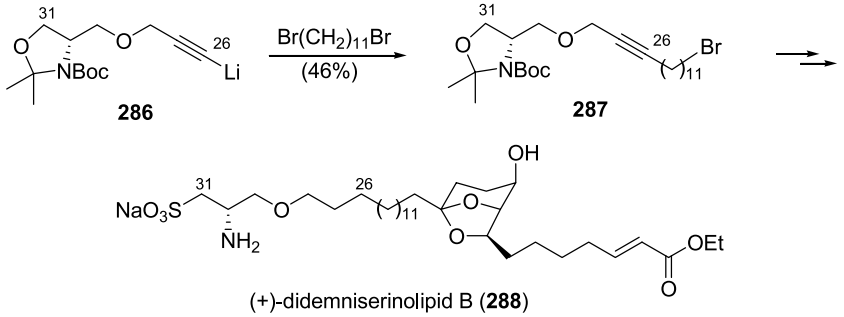
Acetalized alkynyllithium reagent **289** has been used in the recent total synthesis of the antitumor agent (−)-mucocin,[125] whereas chiral lithium acetylide **290** (BPS=*tert*-butyldiphenylsilyl) has been employed for the preparation of the marine sponge macrolide (+)-phorboxazole A.[126] Moreover, the alkynyllithium **291** was obtained by treatment of the corresponding dibromo olefin with *n*-butyllithium, being employed in the total synthesis of the microtubule-stabilizing agent (−)-laulimalide.[127]



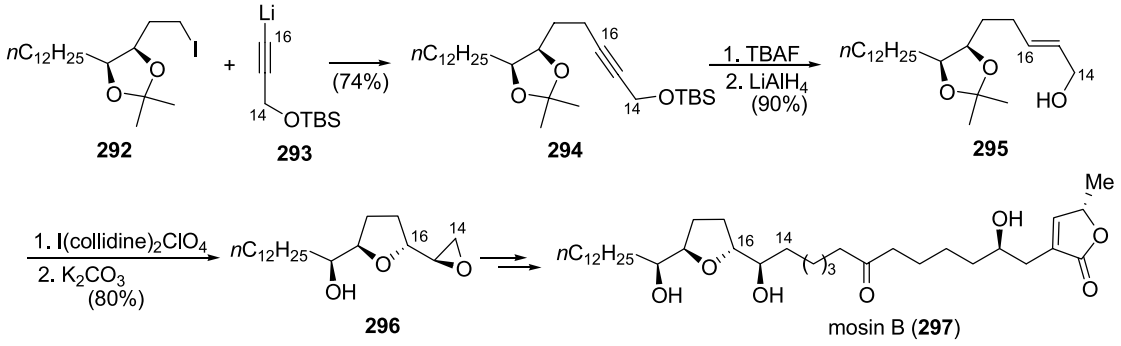
There are also frequent examples of the use of alkynyllithium reagents bearing a silyl-protected hydroxy group at the γ-position. Thus, reagent **293** has been prepared by *n*-butyllithium-promoted deprotonation of 1-*tert*-butyldimethylsilyloxy-2-propyne and reacted with iodide **292**, affording alkyne **294**, which was converted into allylic alcohol **295** after silyl deprotection and *E*-selective reduction of the triple bond. Subsequent iodoetherification gave rise, after basic treatment, to epoxide **296**, which corresponds to the THF core segment in a recent synthesis of the antitumor acetogenin mosin B (**297**) (Scheme 49).[128] In addition, this organolithium reagent **293** has also been employed in the total synthesis of other acetogenins such as (+)-parviflorin[129a] and (+)-asimicin,[129b] as well as in the



Scheme 47.



Scheme 48.



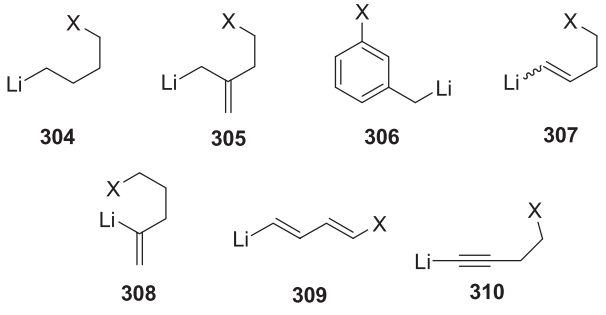
Scheme 49.

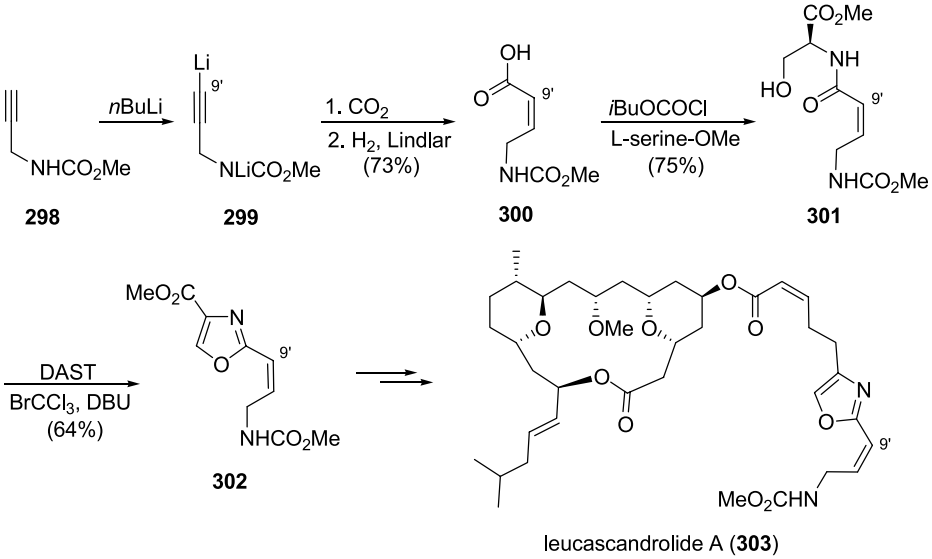
preparation of the antibiotic from *Streptomyces griseus* (±)-fredericamycin A,[130] the anticancer compound from the callus of *Panax ginseng* (+)-panaxacol[131] and also kainic acid.[132] Moreover, a similar triisopropylsilylated organolithium reagent has been employed in the synthesis of the naturally occurring compound from red algae (+)-isolaurepinnacin.[133]

An example of the use of a γ-nitrogenated alkynyllithium reagent is found in Scheme 50, which shows the double deprotonation of carbamate **298** with *n*-butyllithium to give lithiated species **299**, an organolithium compound that has been used as nucleophile in the introduction of the side chain in the total synthesis of leucascandrolide A (**303**), a cytotoxic metabolite from calcareous sponges.[134] Thus, reagent **299** reacted with carbon dioxide affording an ynoic acid, which was hydrogenated to (*Z*)-α,β-unsaturated acid **300** and subsequently amidated with L-serine methyl ester to alcohol **301** using a mixed anhydride protocol. This alcohol **301** was transformed into oxazole **302** by an in situ process consisting of dehydrative cyclization promoted by diethylaminosulfur trifluoride (DAST) and bromination/dehydrobromination achieved by bromotrichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[134a] This compound **302** was used for the introduction of the oxazole-containing side chain of leucascandrolide A (**303**).

5. δ-Functionalized organolithiums

These compounds are considered d^4 reagents,[7] allowing in many cases stabilization by internal complexation. The schematic structures of this type of reagents used in natural product synthesis are shown below, sp^3-hybridized systems **304** being mentioned first, including those where the X functionality is forming part of an acetal, thus being considered as bishomoenolate equivalents. Other sp^3-hybridized systems such as allylithiums **305** and *m*-functionalized benzyllithiums of the type **306** will be considered, as well as sp^2-hybridized organolithiums of the types **307** and **308**, including dienic systems of the type **309**. Finally, the use of acetylides of the type **310** will be included.





Scheme 50.

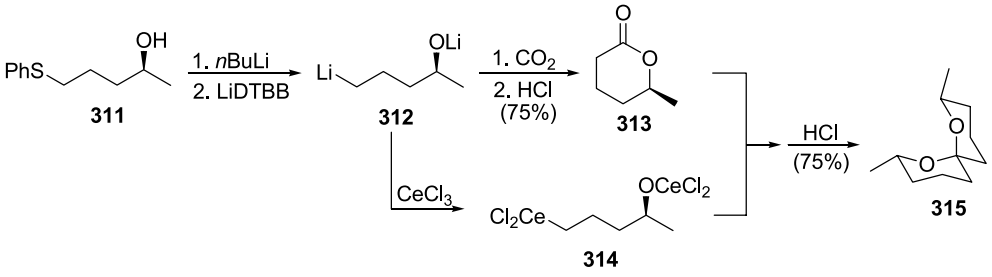
5.1. δ-Functionalized sp^3-hybridized organolithiums

4-(Phenylsulfanyl)alkanols can be used for the preparation of δ-oxido alkyllithiums. For instance, optically active alcohol **311** was deprotonated with *n*-butyllithium and was reductively lithiated with lithium di-*tert*-butylbiphenylide, affording the dilithio intermediate **312** which was carboxylated and cyclized giving the lactone **313** in one pot (Scheme 51). Another one pot reaction between the organolithium **313**, previously transformed into its corresponding organocerium compound **314**, and lactone **313** gave rise to the dioxaspiro compound **315**, which is an insect pheromone.[135a] Other naturally occurring pheromones have been prepared from this alkylithium-promoted organocerium reagent **314**.[135b]

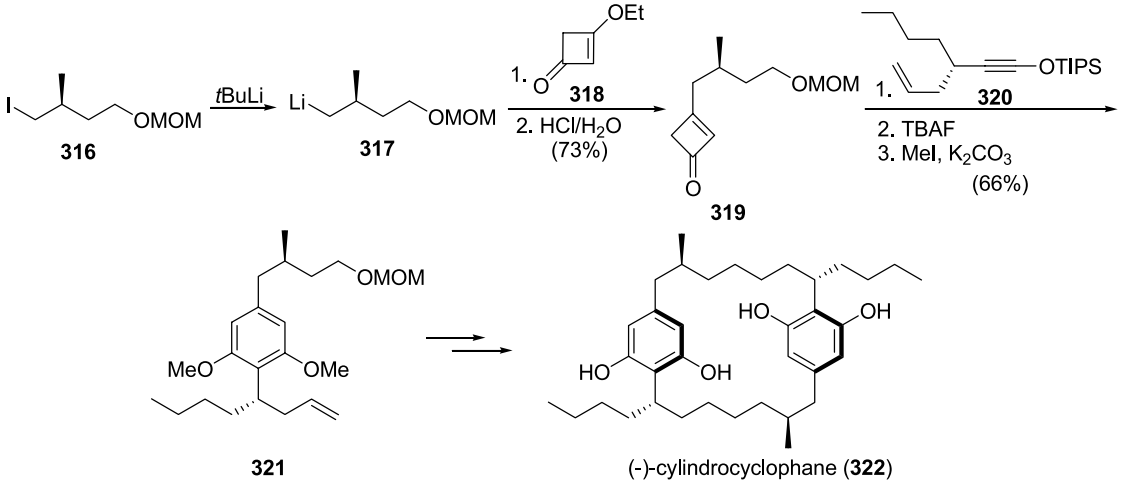
More frequently, the δ-oxygenated organolithium compounds are generated by halogen/lithium exchange, the use of *tert*-butyllithium being common in the case of iodinated reagents. Thus, chiral MOM-protected iodoalcohol **316** was converted into lithiated compound **317** after metalation using *tert*-butyllithium and reacted with β-ethoxycyclobutenone **318**, furnishing enone **319** after hydrolysis. Annulation of this compound in the presence of siloxyalkyne **320**, followed by treatment with TBAF and methylation, yielded the tetrasubstituted resorcinol-derived compound **321**, which was used as an intermediate in the synthesis of (−)-cylindrocyclophane (**322**) (Scheme 52), a cytotoxic component of strains of a terrestrian blue-green algae.[136]

Another example of the use of a δ-oxygenated organolithium generated from an iodinated system arises from 3-(1,3-dioxolan-2-yl)propyllithium (**324**), a masked bishomoenolate which has been generated from the corresponding iodide by *tert*-butyllithium-promoted lithiation, and has been used, for instance, for the synthesis of dihydroclerodin (**328**), a diterpenoid possessing the clerodane skeleton having insect-antifeedant properties. The synthesis includes the 1,2-addition reaction of the organolithium reagent **324** to ketone **323**, followed by oxidative rearrangement of the formed mixture of alcohols **325** to give rise to enone **326** (Scheme 53). Catalytic hydrogenation of compound **326** and acid-mediated aldehyde deprotection–aldol condensation afforded the decalin **327**, which was converted into dihydroclerodin (**328**) after several synthetic steps.[137] In addition, 3-(1,3-dioxolan-2-yl)propyllithium (**324**) can be generated from the corresponding chlorinated compound, which is less prone to lithiation, the metalation therefore being performed with lithium powder in the presence of a catalytic amount of an arene such as naphthalene. Using this methodology, some pheromonic brevicomins have been obtained,[138] as well as some naturally occurring δ-lactones.[139] Moreover, this organolithium reagent **324** has also been used for the synthesis of (−)-α-conhydrine.[140]

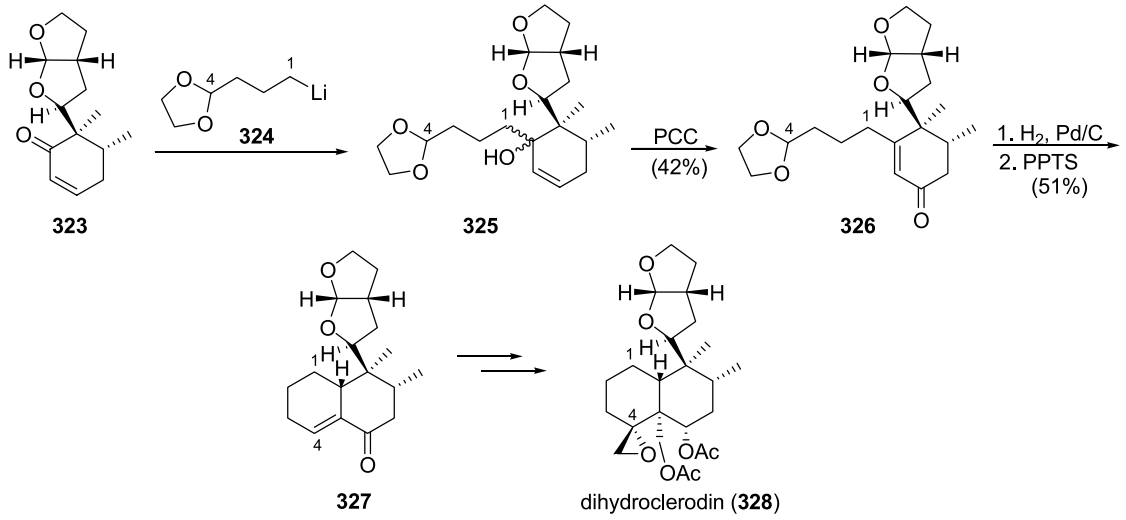
The use of another bishomoenolate equivalent is shown in Scheme 54, where the acetalized organolithium compound **329** was obtained from the γ-chloro ketone according to the above-mentioned lithium powder/catalytic naphthalene conditions.[2] Subsequent transmetalations to the corresponding organozinc and organocopper species and final quenching with cinnamoyl chloride gave rise to enone



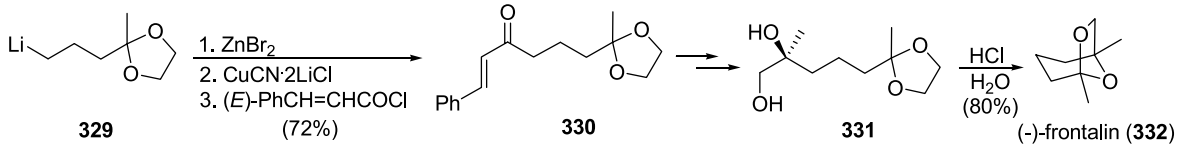
Scheme 51.



Scheme 52.



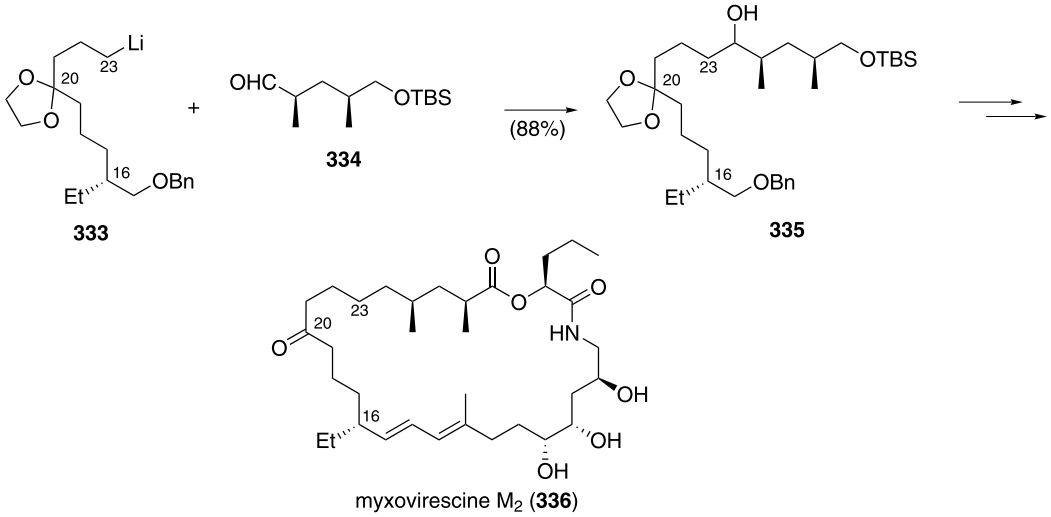
Scheme 53.



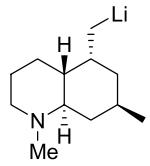
Scheme 54.

330 which was transformed into enantiomerically enriched alcohol **331** (89% *ee*) after some transformations including an enantioselective dimethylzinc addition followed by ozonolysis. Final deprotection–cyclization under aqueous acidic conditions yielded (−)-frontalin (**332**), an aggregation pheromone from pine beetles of the *Dendroctonus* family.[141] In addition, the more complex lithiated acetal **333**, obtained from the corresponding iodide after metalation with *tert*-butyllithium, reacted with chiral aldehyde **334** to give alcohol **335**, which is an intermediate in the total synthesis of the natural antibiotic myxovirescine M_2 **336** (Scheme 55).[142] In a similar way myxovirescine A_1 has been prepared.[142a,b]

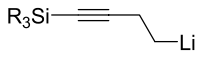
An example of a δ-nitrogenated organolithium compound being used in a total synthesis is the species **337**, obtained after *tert*-butyllithium lithiation of the corresponding iodide, which has been transmetalated to a mixed Grignard reagent in an asymmetric synthesis of the *Lycopodium* alkaloid N_a-acetyl-N_b-methylplegmarine.[143] In addition, δ-silylated alkyllithium compounds **338** have also been obtained by *tert*-butyllithium-promoted iodide/lithium exchange and have been used, for example, for the generation of cuprates in the total synthesis of the antiviral and antitumor trienamide onnamide A[144] (**338**, R=Me) and the sesterpene (−)-terpestacin (**338**, R=*i*Pr).[145]



Scheme 55.



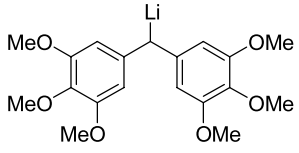
337



338

δ-Functionalized allyllithiums can be obtained by direct deprotonation using alkyllithium regents. Thus, δ-oxido organolithium compound **340** has been generated by treatment of the homoallylic alcohol **339** with 2 equiv of *n*-butyllithium. This lithiated species reacted with homoallylic iodide **341** to give an alcohol which was acylated with propionic anhydride affording compound **342**, a San Jose scale sex pheromone (Scheme 56).[146] In addition, related chiral organolithium–organopotassium reagent **344** was generated from the corresponding alcohol **343** after treatment with 2 equiv of a Lochmann–Schlosser superbase[147] (treatment with potassium *tert*-butoxide, followed by *n*-butyllithium). Subsequent substitution reaction with tosylate **345** yielded alcohol **346**, which was used in a synthesis of (−)-botryococcene (**347**), a triterpenoid from the unicellular green algae *Botryococcus braunii* (Scheme 57).[148]

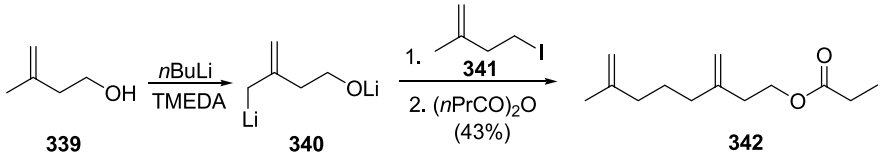
Benzyllithiums bearing a functionality at the δ-position such as **349** can be prepared from an *O*-silylated 3,5-dimethoxybenzylic alcohol by reductive lithiation (Scheme 58). Thus, the starting material **348** was treated with an excess of lithium powder and a catalytic amount of naphthalene,[2] giving rise to benzyllithium reagent **349**, which reacted with an aldehyde such as butyraldehyde furnishing alcohol **350**. Further mesylation, reduction with zinc/sodium iodide and final demethylation using hydrobromic acid gave rise to the resorcinol olivetol (**351**).[149] Some other resorcinols such as grevillol, pinosilvine, resveratrol, piceatannol and chrysotobibenzyl have been prepared following this methodology.[149] In addition, this reductive lithiation has recently been applied to 3,5-dimethoxybenzyl methyl ether, also for the synthesis of some natural resorcinols.[150] Another example of the use of these types of organolithium reagents is the dibenzyllithium compound **352**, which has been employed in the total synthesis of the secolignan (±)-peperomin.[151]



352

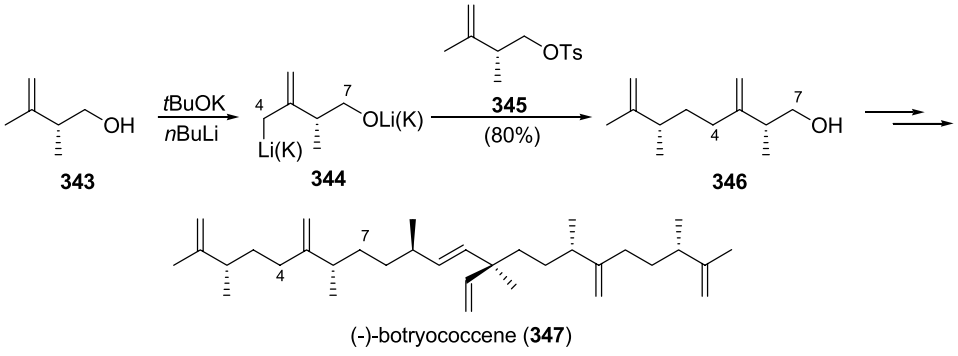
5.2. δ-Functionalized sp^2-hybridized organolithiums

As indicated above, vinyllithium compounds are usually prepared through a halogen/lithium or tin/lithium exchange



339 340 342

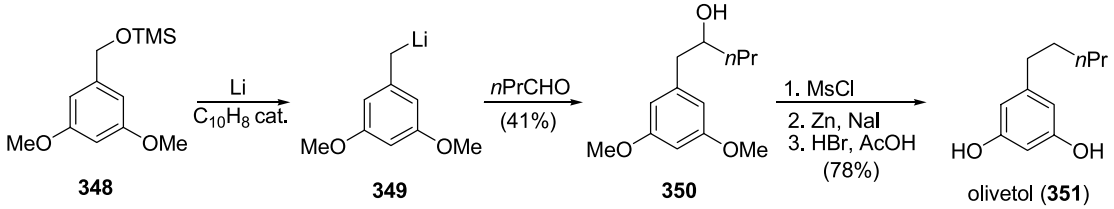
Scheme 56.



343 344 346

(-)-botryococcene (**347**)

Scheme 57.

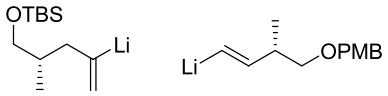


348 349 350 olivetol (**351**)

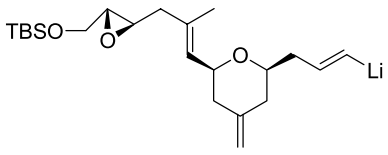
Scheme 58.

using an alkyllithium in order to avoid possible competing allylic deprotonations and therefore any loss of regio- and stereochemical integrity of the lithiated species. Thus, δ-oxygenated alkenyllithium compound **354** has been generated after treatment of the corresponding vinyl bromide with *tert*-butyllithium and has been transmetalated in the presence of copper cyanide to afford ketone **355** after Michael addition to enone **353**, which was converted, after a silyl deprotection–oxidation (tetra-*n*-propylammonium perruthenate, TPAP)-cyclization sequence, into bicyclic alcohol **356**, an intermediate in a synthesis of taxol® (**357**) (Scheme 59).[152] A similar *tert*-butyldimethylsilylated organolithium compound has also been used for the generation of an organocuprate in a synthesis of the fungitoxic sesquiterpene (±)-chokol A.[153]

The γ-methylated chiral vinyllithium **358** has been employed in a reaction to a Weinreb amide for the synthesis of the polyether antibiotic X-206.[154] In addition, chiral δ-oxygenated alkenyllithium **359**, prepared by reaction of the corresponding iodide with *tert*-butyllithium, has been used in the synthesis of vinigrol, a diterpenoid with platelet aggregation inhibitory and antihypertensive properties,[155] whereas the more complex species **360**, prepared also from its iodide although using *n*-butyllithium, is a key intermediate in a recent total synthesis of the macrolactone (−)-dactylolide.[156]

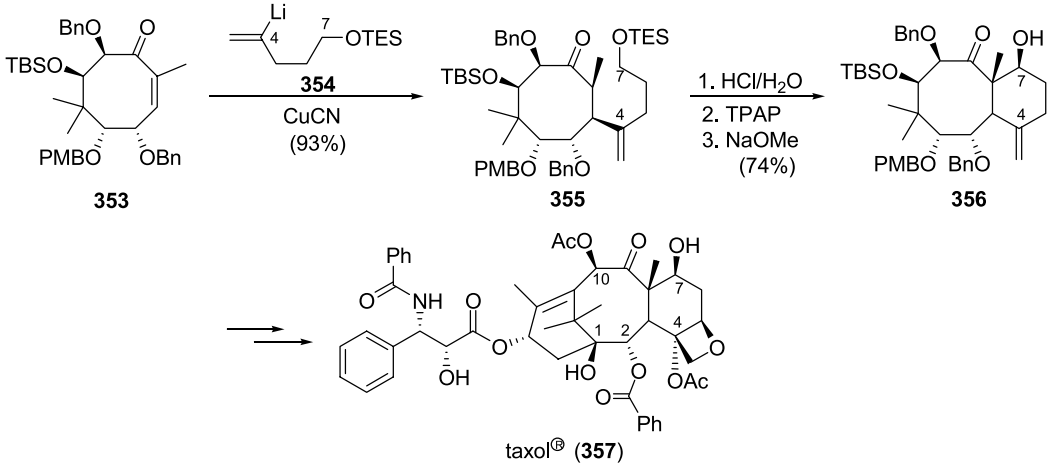


358 **359**

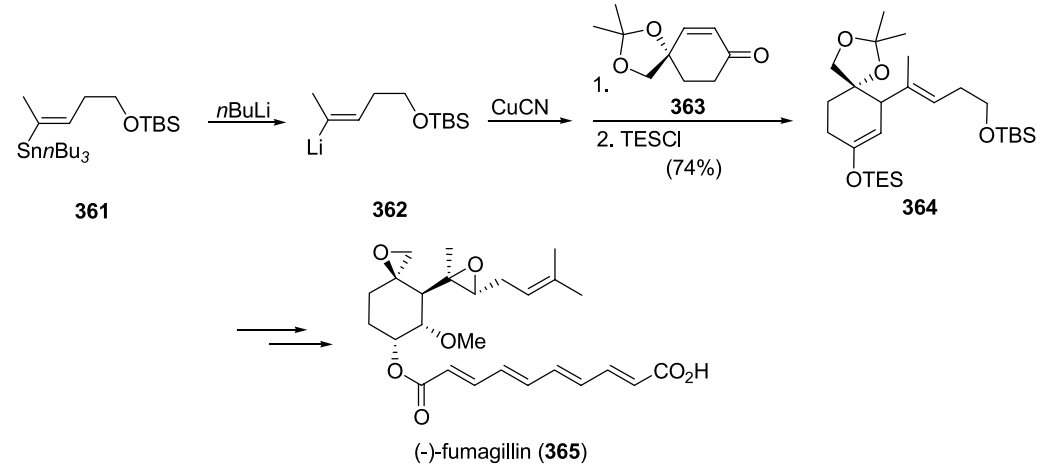


360

δ-Silyloxylated vinylstannane **361** has been used for the generation of vinyllithium reagent **362** after a tin/lithium transmetalation promoted by *n*-butyllithium. In situ reaction with copper cyanide and Michael addition reaction to chiral cyclohexenone **363** furnished the silyl enol ether **364** after trapping the formed enolate with triethylsilyl chloride (Scheme 60). This compound has been used as an

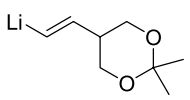


Scheme 59.



Scheme 60.

intermediate in the total synthesis of the natural angiogenesis inhibitor (−)-fumagillin (**365**).[157] In addition, alkenyllithium **366** has been obtained also by tin/lithium exchange,[158a] or even by bromo/lithium exchange,[158b] using *n*-butyllithium or *tert*-butyllithium, respectively, and has been used in a synthesis of (+)-cassiol,[158] whereas lithioacetal **367**, prepared by iodo/lithio exchange using *tert*-butyllithium, has been employed in a synthesis of retinal.[159]



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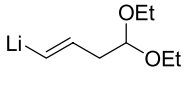


367

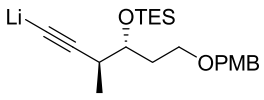
Retinal has also been prepared using the lithio dienyl ether **369** (R=Me), which was obtained from its chloro precursor **368** using the combination formed by lithium powder and a catalytic amount of an arene such as di-*tert*-butylbiphenyl. This vinyllithium reagent was used in a condensation reaction with β-cyclocitral **370** to furnish retinal (**371**) after acidic hydrolysis (Scheme 61).[160] In addition, a related dienyllithium **369** (R=H) has been prepared by tin/lithium transmetalation and, after transformation into the corresponding organomagnesium, has been coupled with polyenals in the synthesis of the polyene macrolide roflamycoin.[22]

Some δ-functionalized vinyllithiums with applications to a total synthesis have been prepared, from the corresponding ketones, by means of the Shapiro reaction, as shown in Scheme 62, where the arylhydrazone **372** (Ar=2,4,6-triisopropylbenzene) was converted into vinyllithium **373** via reaction with *n*-butyllithium. This organolithium reagent **373** reacted with the chiral aldehyde **374** to give alcohol **375** in a total synthesis of taxol® (**357**).[161]

5.3. δ-Functionalized sp-hybridized organolithiums

As mentioned above, functionalized alkynyllithiums are usually prepared by simple removal of the acetylenic proton using an alkyllithium. Thus, *O*-silylated δ-oxygenated lithium acetylide **376**, prepared by deprotonation with *n*-butyllithium, was alkylated with iodides **377** and **378**, affording acetylenes **379** and **380**, respectively (Scheme 63). These compounds were used for the introduction of the two carbon chains in a total synthesis of the macrocyclic marine alkaloid haliclamine A (**381**).[162] This reagent **376** has also been used in a synthesis of the phenolic sesquiterpene (+)-ligudentatol.[163]

An example of the use of a more complex δ-oxygenated lithium acetylide can be seen in Scheme 64, where *n*-butyllithium-generated chiral organolithium **382** (as a mixture of epimers) has been carboxylated and subsequently esterified with a chiral alcohol under Mitsunobu conditions, furnishing dienic ester **383**. This compound gave, after Grubb's metathesis and several steps, the macrolactone ring system in a recent total synthesis of the macrolide aigialomycin D (**384**).[164] In addition, alkynyllithium **385** has been prepared by deprotonation using *n*-butyllithium and employed for the coupling reaction with a Weinreb amide in the preparation of reveromycin A, a polyketide-type inhibitor of eukaryotic cell growth from *Streptomyces*,[165] whereas species **386** has been used in an addition reaction to an aldehyde in a total synthesis of the polyketide (+)-discodermolide.[166]



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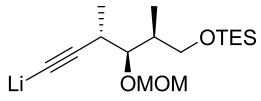
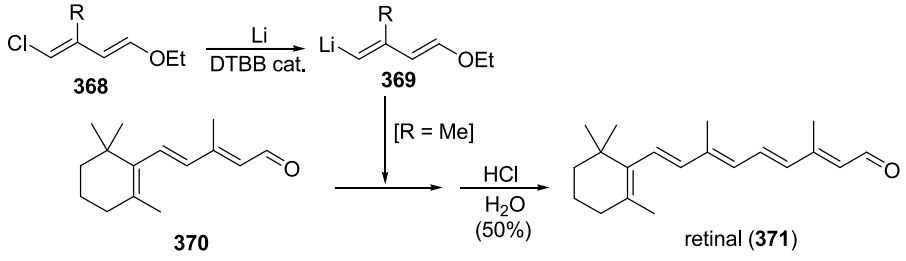
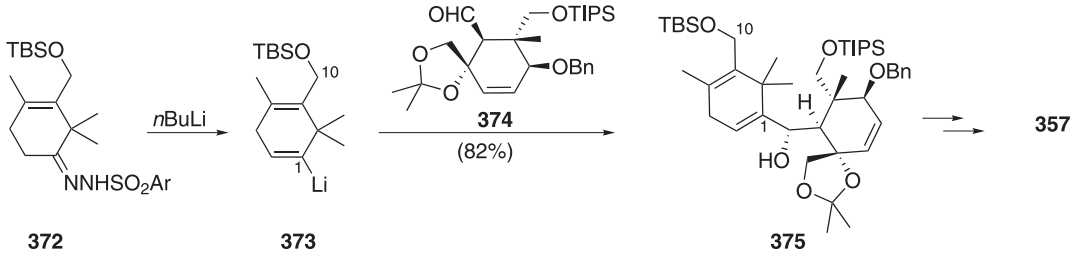


386

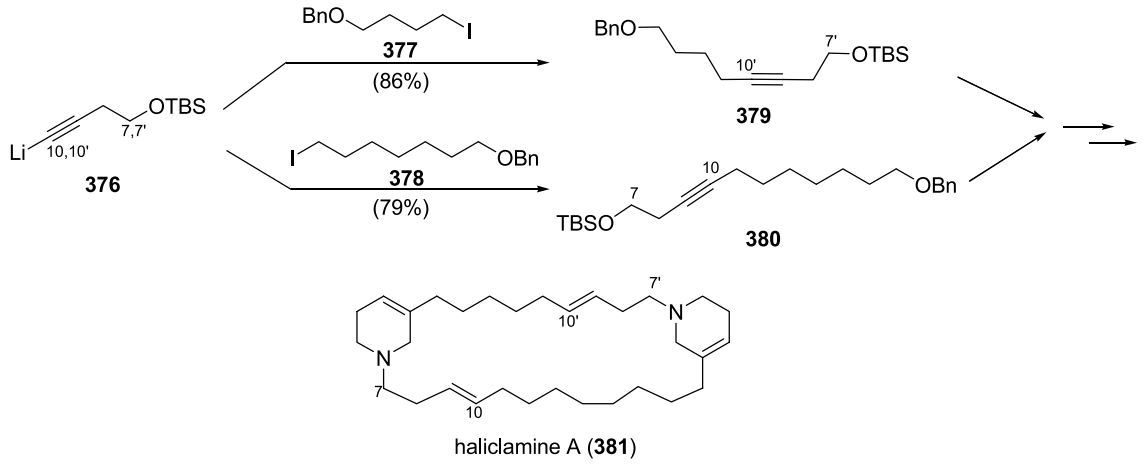
The use of δ-nitrogenated lithium acetylides in natural product synthesis is less common than that of their oxygenated counterparts. An example is shown in Scheme 65, where *N*-Boc-protected lithium butynylamide **388**, generated by deprotonation using *n*-butyllithium, was



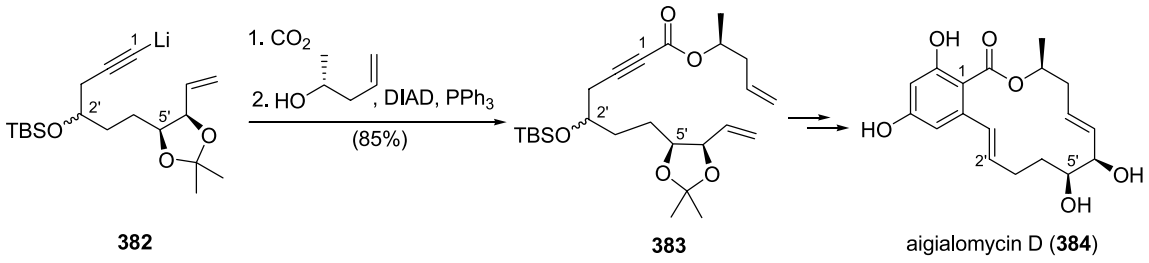
Scheme 61.



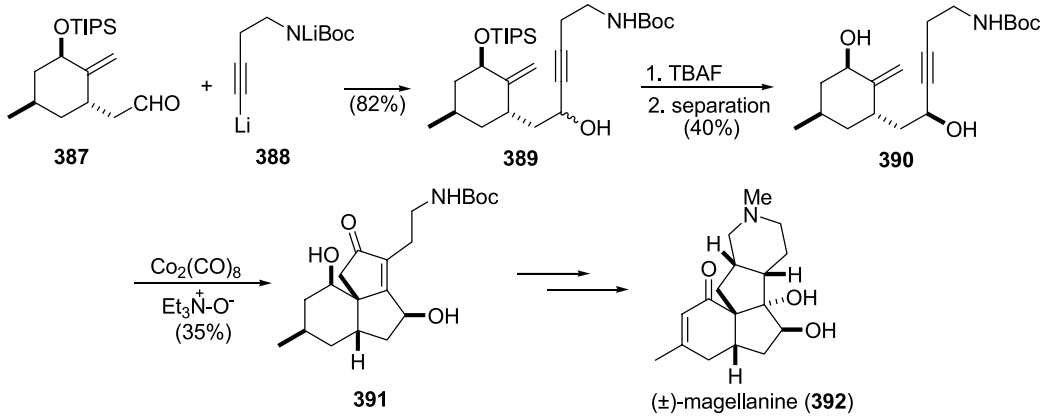
Scheme 62.



Scheme 63.



Scheme 64.



Scheme 65.

added to aldehyde **387** giving rise to a 1:1 mixture of epimers **389**, which, after silyl deprotection to the corresponding alcohols, were chromatographically separated, the isomer **390** being used in a Pauson–Khand cyclization to give tricyclic enone **391**, an intermediate in the recent synthesis of the alkaloid (±)-magellanine (**392**).[167]

6. Remote functionalized organolithiums

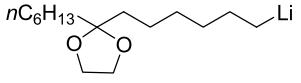
In this section, examples of the use of organolithium compounds bearing a functionality at the ε-position or more distant, therefore being considered as d^n ($n \geq 5$) reagents,[7] will be presented. In each subsection, they will be introduced according to the proximity of the functionality to the lithiation position.

6.1. Remote functionalized sp^3-hybridized organolithiums

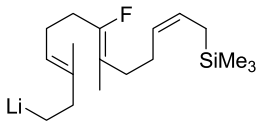
ε-Siloxy organolithium **393** has been obtained from the corresponding iodide after treatment with *tert*-butyllithium and has been used in a substitution reaction to a Weinreb amide **394** to give ketone **395**, which was transformed after several steps into urea **396**, an intermediate used for the installation of the seven-membered ring and part of the guanidinium core system of the crambescidin-derived marine alkaloid ptilomycalin A (isolated as its

hydrochloride, **397**) (Scheme 66), as well as crambescidin 657 and crambescidin 800.[168]

A recent example of the use of an sp^3-hybridized η-functionalized organolithium species is the lithiated acetal **398**, prepared from the iodide using *tert*-butyllithium, and employed in a transmetalation to the corresponding organozinc reagent for a palladium-catalyzed cross-coupling reaction with a vinyl iodide, in a synthesis of the lipid chain-containing natural antifungal (+)-sphingofungin F.[169] In addition, the similarly prepared fluorosilylated organolithium species **399** has been employed as a nucleophile in an addition reaction to an aldehyde for the synthesis of (±)-dammarenediol.[170]



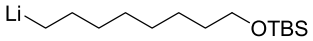
398



399

The η-silylated organolithium reagent **401** has also been generated by *tert*-butyllithium-promoted iodine/lithium exchange and reacted with chiral Cbz-protected lactam **400** (Cbz=benzyloxycarbonyl), furnishing the intermediate alcohol **402**, which was in situ exposed to boron trifluoride–acetic acid complex to provide spirocycle **404** via an *N*-acyliminium ion/allylsilane internal cyclization from species **403** (Scheme 67). This spirocyclic compound **404** was converted, after several synthetic steps, into (−)-lepadiformine (**405**), a tricyclic alkaloid from the marine ascidian *Clavelina cylindrica*.[171]

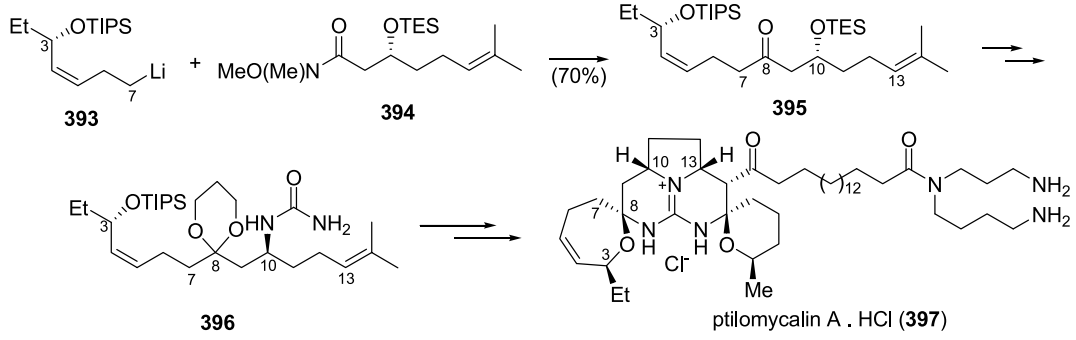
Examples of even more remotely functionalized sp^3-hybridized lithiated compounds are the *O*-protected θ-hydroxylated organolithium reagent **406**, employed in the total synthesis of the methyl ester of the metabolite of linoleic acid chromomoric acid D-I,[172] or the 10-carbon-separated lithiated acetal **407** (Scheme 68). This latter species has been generated by treatment of the corresponding bromide with lithium and has been used in a transmetalation reaction to an organocopper, followed by addition of boron trifluoride, giving rise to the alkylcopper(I)·BF_3complex **408** which was added to 2-ethoxypiperidine **409**. The resulting fully protected compound **410** was desilylated and furtherly hydrolyzed furnishing (+)-prosopinine (**411**), an alkaloid isolated from the leaves of *Prosopis africana*.[173]



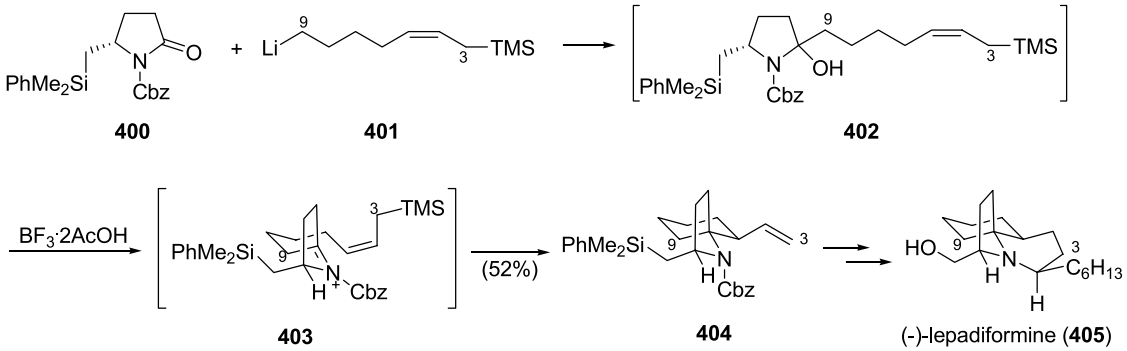
406

6.2. Remote functionalized sp^2-hybridized organolithiums

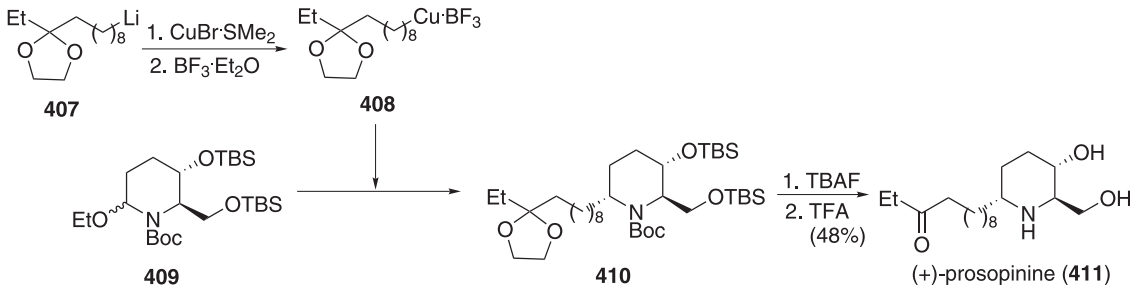
Examples of the use of remotely functionalized vinyllithium compounds in natural product synthesis can be seen in Scheme 69, which shows the reaction of lithiated ε-alcoholate **413**, prepared by treatment of the corresponding bromoalcohol with *tert*-butyllithium, with the Weinreb amide **412**, giving rise to ketone **414**, an intermediate in the synthesis of the natural neuritogenic agent (+)-epolactaene (**415**) (as a 5:1 diastereomeric mixture at C15, as with the natural product).[174] A similar, although *O*-protected, vinyllithium **417** has been prepared identically,



Scheme 66.



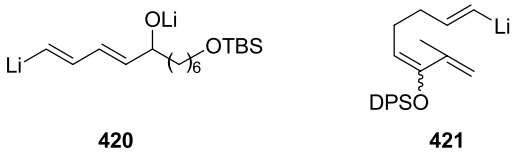
Scheme 67.



Scheme 68.

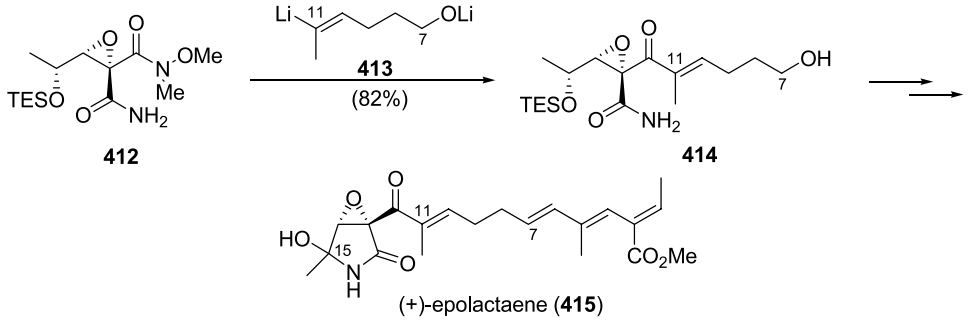
but from the corresponding vinyl iodide, and has been employed in an alkylation reaction with allylic bromide **416** to furnish diene **418**, a precursor of the trienic carbon chain in a synthesis of (−)-hennoxazole A (**419**), an antiviral natural product from a marine sponge (Scheme 70).[175]

Another example of an ε-functionalized organolithium comes from the *tert*-butyllithium-promoted bromo/lithium-exchanged dienyllithium species **420**, which has been used as nucleophile in an addition reaction to heptanal for achieving an intermediate in the total synthesis of the plant anticancer agent ostopanic acid.[176] In addition, ζ-siloxylated vinyllithium **421**, obtained by *n*-butyllithium-mediated lithiation of the corresponding vinyl iodide, was employed in the synthesis of the sesquiterpene (±)-dehydrofukinone.[177]

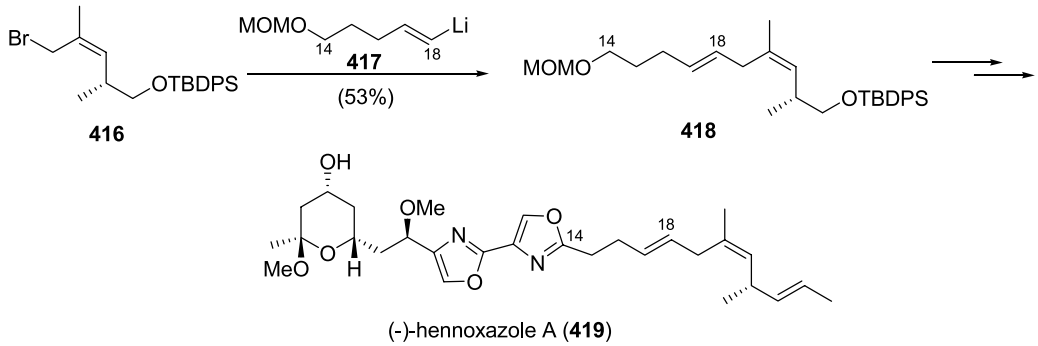


Remote functionalized alkenyllithium reagents have also been used in solid-phase synthesis. Thus, the ζ-siloxylated vinyllithium **423**, generated by iodo/lithium exchange using *tert*-butyllithium, has been used in a displacement of the chloride from the polymer-supported tin derivative **422**, leading to aldehyde **424** after silyl removal and oxidation with *N*-chlorosuccinimide (NCS) (Scheme 71). Addition of a chiral Grignard reagent **425**, followed by oxidation and deprotection, gave alcohol **426**. Further esterification with carboxylic acid **427** under Mitsunobu conditions gave rise to polymer-supported ester **428**, which was subjected to a macrolactonization via an internal Stille palladium-catalyzed cross-coupling reaction, which also allowed the cleavage from the resin. Final deprotection furnished the macrolide antibiotic (−)-zearalenone (**429**).[178]

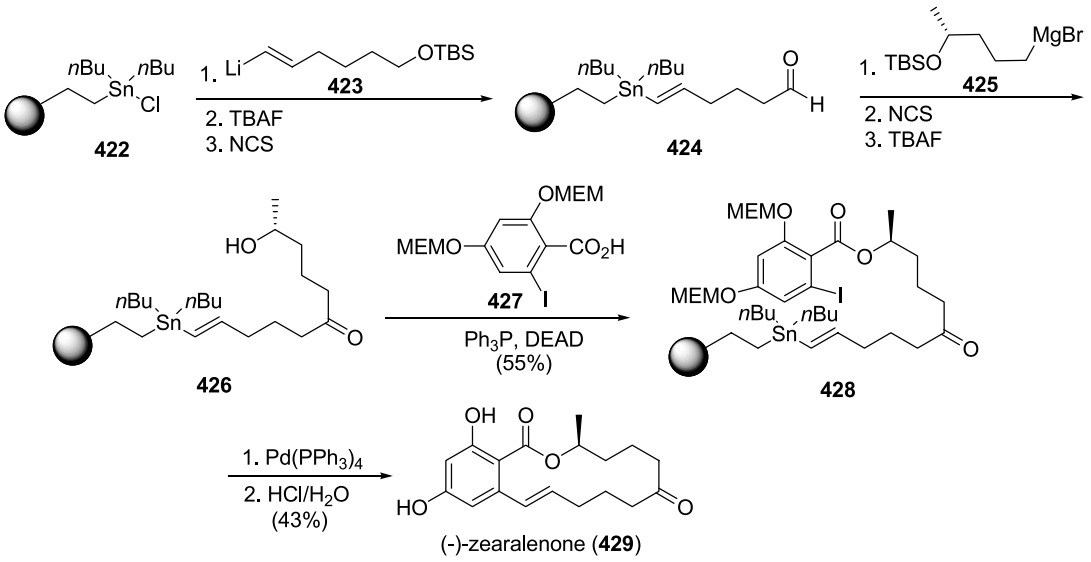
An example of an even more remotely functionalized vinyllithium is the lithiated acetalized dienyl species **430**, which has been generated from the corresponding dienyl bromide using *tert*-butyllithium, and has been used for a rather low-yielding addition reaction to the carbonyl of a bicyclic lactam to give some fungal hormones known as



Scheme 69.

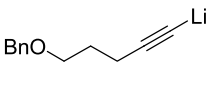


Scheme 70.

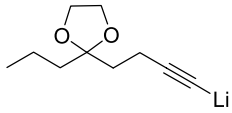


Scheme 71.

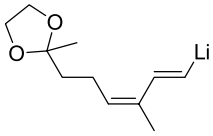
trisporic acids.[179]



431



432



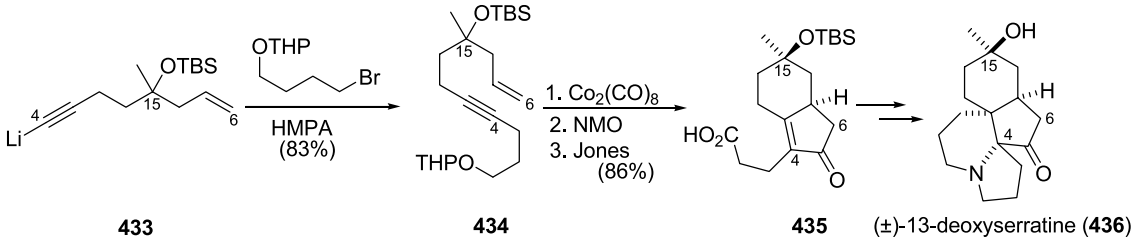
430

6.3. Remote functionalized sp-hybridized organolithiums

Different alkynyllithiums with a functionality beyond the δ-position, prepared by *n*-butyllithium-promoted deprotonation, have been used in the synthesis of natural products. Thus, metalation of the benzyl ether of pent-4-yn-1-ol gave rise to ε-functionalized species **431**, which has been used for the ring opening of (*R*)-propylene oxide in the total synthesis and structure determination of naturally occurring *iso*-cladospolide B, a hexaketide obtained from a fungal isolate from a marine sponge.[180] In addition, lithiated acetal **432** has been used for a transmetalation reaction to an organomagnesium for the incorporation of a chiral sulfoxide moiety in a recent total synthesis of the aspidosperma alkaloid (+)-aspidospermidine.[181]

The ε-oxygenated organolithium **433** has been employed in an alkynylation reaction using tetrahydropyranyl-protected 3-bromopropanol to give acetylenic compound **434**. Subsequent Pauson–Khand reaction, followed by treatment with 4-methylmorpholine *N*-oxide and further oxidation, gave rise to the carboxylic acid **435**, which is an intermediate in the total synthesis of the *Lycopodium* alkaloid (±)-13-deoxyserratine (**436**) (Scheme 72).[182]

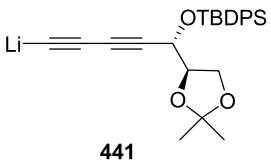
A chiral ε-oxido-functionalized lithiated diacetylene **438** has been obtained by dideprotonation of the corresponding chiral alcohol **437**, prepared by a deracemization procedure on the corresponding racemic acetyl ester using *Candida antarctica*. This organolithium reagent **438** has been used as nucleophile for the ring opening reaction of chiral epoxide **439** to furnish, after silyl deprotection, naturally occurring panaxytriol (**440**), a polyacetylenic metabolite with antitumor activity extracted from *Panax ginseng* (Scheme 73).[183] Following this procedure, its enantiomer, and also both enantiomers of the related panaxydol, have been obtained.[183] In addition, these metabolites have also been asymmetrically obtained starting from chiral acetonide-protected organolithium **441**.[184] Furthermore, more



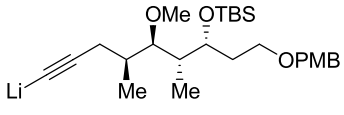
433 434 435 (±)-13-deoxyserratine (**436**)

Scheme 72.

complex chiral alkynyllithium **442** has been used in a recent total synthesis of (−)-pironetin, a δ-lactone derivative from *Streptomyces* sp.[185]



441

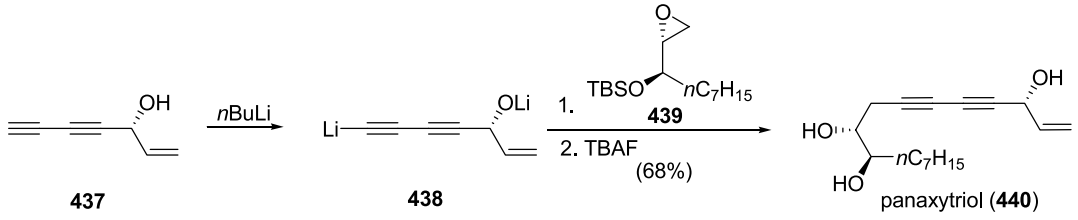


442

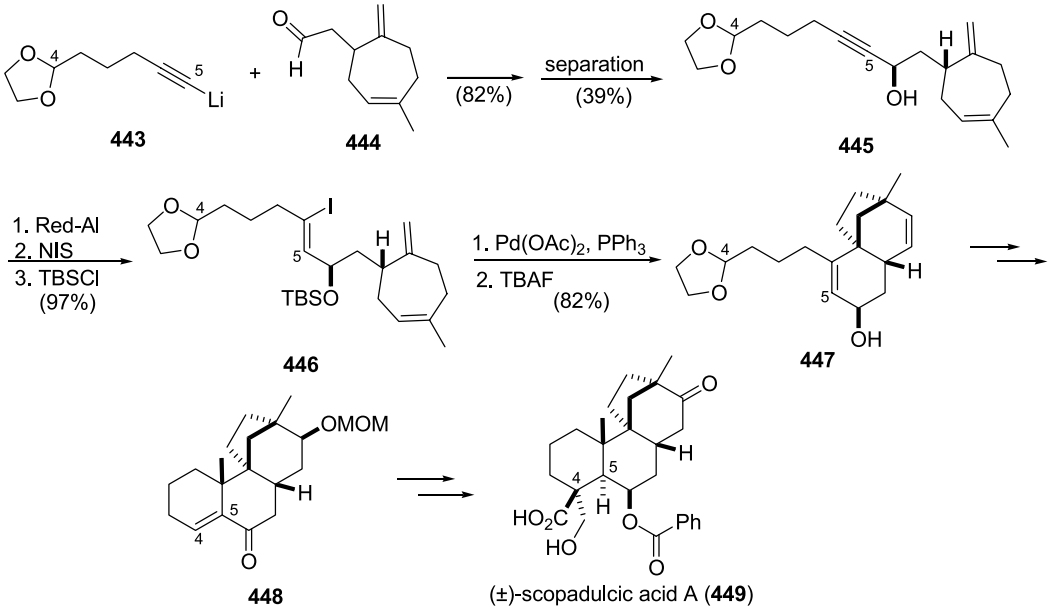
An example of the use of a ζ-functionalized alkynyllithium can be seen in Scheme 74, where 6-(ethylenedioxy)-1-hexynyllithium (**443**) reacted with aldehyde **444**, giving rise to a 1:1 mixture of propargylic alcohols from the β-OH epimer **445** was chromatographically separated and transformed into the (*Z*)- trienyl iodide **446** upon reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), followed by iodination with *N*-iodosuccinimide (NIS) and protection of the allylic alcohol. Subsequent palladium-catalyzed bis-Heck cyclization gave, after desilylation, the tricyclic compound **447**, which could be transformed into the enone **448** after several steps. This enone **448** is an intermediate in the preparation of the tetracyclic diterpene (±)-scopadulcic acid A (**449**).[186]

Another example of the use of a ζ-functionalized lithium acetylide is represented in Scheme 75, which shows the substitution reaction with propargylic bromide **451** of the organocopper generated from the lithiated ortho ester-protected derivative of 5-hexynoic acid **450**, which afforded 1,4-diyne **452**. This compound was hydrogenated using the Lindlar catalyst to the (*Z*,*Z*)-diene **453**, which is a key subunit in the synthesis of polyazamacrolide **454**, a compound isolated from the pupal defensive secretion of the ladybird beetle *Subcoccinella vigintiquatuorpunctata*.[187]

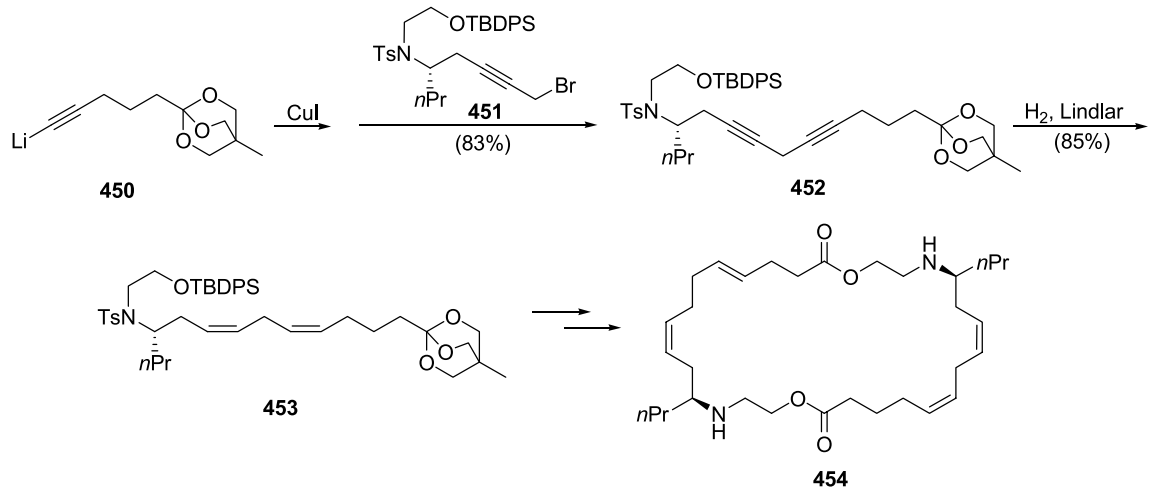
The ζ-silylated enediyne organolithium reagent **455** has been generated by deprotonation with LiHMDS and has been applied to the synthesis of the antitumor agent (±)-calicheamicinone.[188] In addition, some more-distantly functionalized alkynyllithium reagents are, for example, the lithiated diyne **456**, which has been used in a carboxylation reaction for the synthesis of the marine illudalane sesquiterpenoid alcyopterosin E,[189] as well as the *O*-silylated decynyllithium **457**, shown in Scheme 76. This latter oxygenated species has been added to the dienal **458** to give alcohol **459**, which has been used as starting material in an enantiocontrolled synthesis of some naturally occurring octadecadienoic acids such as **460**.[190] These compounds are self-defensive substances against rice blast disease.



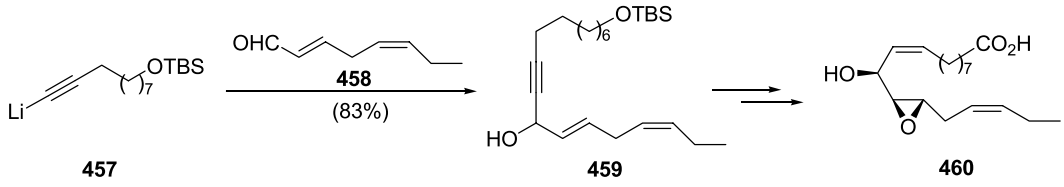
Scheme 73.



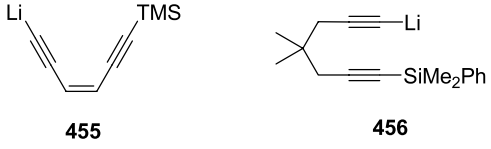
Scheme 74.



Scheme 75.



Scheme 76.



7. Conclusions

From the synthetic examples shown in this review, it is easy to conclude that the use of functionalized organolithium compounds in synthetic organic chemistry makes possible the introduction of functionalities into an organic skeleton using only one reaction step. In this process, the functionality in the nucleophilic organolithium intermediate is transferred to the electrophilic reagent, generating at the same time, in general, a new carbon–carbon bond, this synthetic operation being especially valuable when the total synthesis of an usually complex and polyfunctionalized natural product is pursued. An entire universe of naturally occurring compounds, many of them with biological and pharmacological activity, are still waiting for the organic chemists to be prepared, and there is no doubt that the functionalized organolithium reagents will continue to be an indispensable tool for confronting this challenging task.

Acknowledgements

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Biographical sketch

Rafael Chinchilla was born in Alicante and studied chemistry in the University of Alicante from which he was graduated (1985) and doctorated (1990). After a postdoctoral stay at the University of Uppsala, Sweden (1991–1992), he moved back to the University of Alicante where he was appointed Associate Professor in 1997. His current research interest includes asymmetric synthesis, amino acid and peptide synthesis and solid-supported reagents.

Carmen Nájera was born in Nájera (La Rioja) and was graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979 under the supervision of Professor J. Barluenga and M. Yus. She spent postdoctoral stays with Professor D. Seebach at the ETH (Zurich), Professor J. E. Baldwin at the Dyson Perrins Laboratory (Oxford), Professor E. J. Corey at Harvard University and Professor J.-E. Bäckvall at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and full Professor in 1993 at the University of Alicante where she is nowadays the Head of the Department of Organic Chemistry. Her current research interest is focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis, peptide coupling reagents, solid-phase synthesis, asymmetric catalysis and palladium catalysis.

Miguel Yus was born in Zaragoza in 1947. He received the BSc (1969), MSc (1971), and PhD (1973) degrees from the University of Zaragoza. After spending two years as a postdoct at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo where he became Associate Professor in 1977, being promoted to full Professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante where he is nowadays the Director of the newly created Instituto de Síntesis Orgánica (ISO). Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities at Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris VI and Strasbourg. He is member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland and United States. He is co-author of more than 300 papers mainly in the fields of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry, the use of active metals, and asymmetric catalysis. Among others, he has recently received the Spanish–French Prize (1999), the Japan Society for the Promotion of Science Prize (2000) and the Stiefvater Memorial Lectureship Award (2001). He belongs to the advisory board of the journals Tetrahedron, Tetrahedron Letters and European Journal of Organic Chemistry. Last year Professor Yus, with other members of the ISO including C. Nájera and R. Chinchilla, founded the new chemical company MEDALCHEMY, S. L. to commercialize fine chemicals.

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Reductive lithiation of 1,3-dimethyl-2-arylimidazolidines

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Abstract—Naphthalene catalyzed lithiation of 1,3-dimethyl-2-phenylimidazolidine led to cleavage of the benzylic carbon–nitrogen bond, with formation of an intermediate dianion. Under similar conditions, 1,3-dimethyl-2-(4-chlorophenyl)imidazolidine underwent regioselective cleavage of the aromatic carbon–chlorine bond, leading to a 4-formylphenyllithium equivalent, whilst 1,3-dimethyl-2-(4-methoxymethylphenyl)imidazolidine underwent regioselective cleavage of the benzylic carbon–oxygen bond, leading to a 4-formylbenzyllithium equivalent.

1. Introduction

The arene-mediated reductive lithiation of 2-aryl-substituted heterocycles is a highly effective reaction leading, through regioselective cleavage of benzylic carbon–heteroatom bonds, to the generation of a wide array of functionalized organolithium derivatives. Interesting results on this topic include, inter alia, the reductive cleavage of 4-aryl-1,3-dioxanes,[1] 2-aryl-1,3-oxazolidines,[2] benzannelated cyclic ethers[3,4] and amines,[3] phthalans,[5,6] thiophthalan,[7] *N*-isopropyl-2-phenylpyrrolidine and *N*-phenylisoindoline,[8] and styrene oxide.[9,10]

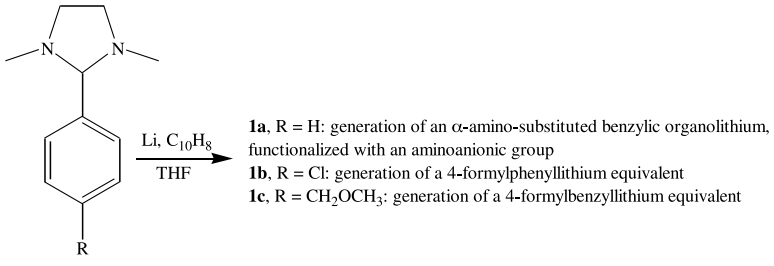
We investigated an extension of this procedure to 1,3-dimethyl-2-arylimidazolidines, and wish to report here that, notwithstanding the known relative stability of benzylic carbon–nitrogen bond to reductive metalation,[2,3,8] 1,3-dimethyl-2-phenylimidazolidine, **1a**, undergoes reductive lithiation under particularly mild reaction conditions.

Furthermore, looking for protective groups suitable to generate stable solutions of organolithium derivatives bearing masked carbonyl groups,[11] we investigated the reductive lithiation of 1,3-dimethyl-2-(4-chlorophenyl)-imidazolidine, **1b**, and 1,3-dimethyl-2-(4-methoxymethyl)-imidazolidine, **1c**, and wish to report on the generation of 4-formylphenyllithium and 4-formylbenzyllithium synthetic equivalents (Scheme 1).

2. Results and discussion

2.1. Synthesis of starting materials

1,3-Dimethyl-2-arylimidazolidines **1a–c** were synthesized by refluxing the corresponding aldehyde with *N*,*N*′-dimethylethylenediamine in dry toluene, in the presence of a catalytic amount of *p*-toluenesulfonic acid. Reductive metalations were carried out in dry tetrahydrofuran (THF)



Scheme 1. Reductive lithiation of 2-aryl-substituted-1,3-dimethylimidazolidines **1a–c**.

Keywords: Aromatic aldehydes; Lithiation; Protective groups; Reduction.
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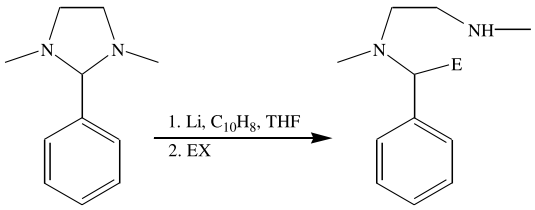


1a **2aa-2af**

Scheme 2. Reductive lithiation and reaction with electrophiles of 1,3-dimethyl-2-phenylimidazolidine, **1a**.

under Ar, with an excess of Li metal and in the presence of a catalytic amount of naphthalene ($C_{10}H_8$).

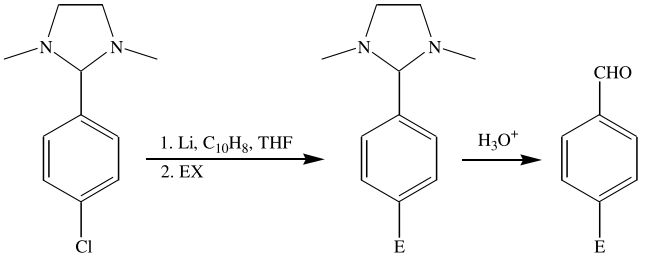
2.2. Reductive metalation of 1,3-dimethyl-2-phenyl-imidazolidine, 1a

Reductive cleavage of imidazolidine **1a** with 6 equiv of Li, in the presence of a catalytic amount of $C_{10}H_8$ (10 mol%), at −20 °C, afforded, after hydrolysis with water, *N*-benzyl-*N*,*N*′-dimethylethylenediamine, **2aa**, as the only reaction product, in variable yields, depending upon the reaction time (Scheme 2, Table 1, entries 1 and 2). Diamine **2aa** is a key intermediate in the synthesis (via alkylation or acylation, followed by hydrogenolysis) of selectively *N*-functionalized-*N*,*N*′-dimethylethylenediamines, a class of potentially biologically active compounds.[12] Therefore, we find it interesting to scale up its preparation: lithiation of 40 mmol of imidazolidine **1a**, afforded 34 mmol (85% isolated yield) of diamine **2aa** (Table 1, entry 3).

Table 1. Reductive metalation of imidazolidine **1a** and reaction with electrophiles[a]

Entry	Li equiv	*T* (°C)	*t* (h)	EX (equiv)	Product, E=	Yield (%)[b]
1	6	−20	2.5	H_2O	**2aa**, H	44[c,d]
2	6	−20	8.0	H_2O	**2aa**, H	>95[c]
3	6	−20	8.0	H_2O	**2aa**, H	85[e]
4	6	−20	8.0	D_2O	**2ab**, D	86[c]
5	12	−30	12.0	D_2O	**2ab**, D	91[c]
6	12	−30	12.0	*n*-BuBr (1.1)	**2ac**, *n*-Bu	65
7	12	−30	12.0	*i*-PrBr (1.1)	**2ad**, *i*-Pr	52
8	12	−30	12.0	$[(CH_3)_2CH]_2CO$ (1.5)	**2ae**, $[(CH_3)_2CH]_2COH$	52
9	12	−30	12.0	$(CH_3)_3CCHO$ (1.5)	**2af**, $(CH_3)_3CCHOH$[f]	56

[a] All reactions were run with 2.5 mmol of starting material, in the presence of a catalytic amount of $C_{10}H_8$ (10 mol%), unless otherwise indicated.
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^1H NMR spectroscopy.
[d] 56% starting material was detected.
[e] 40 mmol of starting material were employed.
[f] As a 77:23 mixture of diastereoisomers.



1b **1a, 2ba-2bi** **3bb-3bi**

Scheme 3. Reductive lithiation and reaction with electrophiles of 1,3-dimethyl-2-(4-chlorophenyl)imidazolidine, **1b**.

Under the conditions described in Table 1, entry 2 (6 equiv of Li, 10 mol% of $C_{10}H_8$, −20 °C, 8 h), intermediate formation of a functionalized benzylic organolithium derivative was evidenced, by quenching the reduction mixture with D_2O (Table 1, entry 4). A somewhat better result was obtained performing the reaction at −30 °C, in the presence of 12 equiv of Li, during 12 h (Table 1, entry 5). This intermediate was successfully trapped with several

Table 2. Reductive metalation of imidazolidine **1b** and reaction with electrophiles[a]

Entry	EX (*T* °C)[b]	Product, E=	Yield (%)[c]
1	H_2O (−40)	**1a**, H	>95[d]
2	D_2O (−40)	**2ba**, D	>90[d]
3	*n*-BuBr (−80)	**1a**, H	—[d,e]
4	$(CH_3)_3CCHO$ (−40)	**3bb**, $(CH_3)_3CCHOH$	72
5	PhCHO (−40)	**3bc**, PhCHOH	76
6	$[(CH_3)_2CH]_2CO$ (−80)	**3bd**, $[(CH_3)_2CH]_2COH$	64
7	$HCOOCH_3$ (−80)	**3be**, CHO	65
8	$HCOOCH_3$ (−80)[f]	**3bf**, ArCHOH[g]	54

[a] All reactions were run at −40 °C, during 3 h, in the presence of 6 equiv of Li and a catalytic amount of $C_{10}H_8$ (5 mol%).
[b] Temperature of addition of the electrophile (2 equiv, unless otherwise indicated).
[c] Isolated yield, unless otherwise indicated.
[d] As determined by ^1H NMR spectroscopy.
[e] >95% **1a** was detected.
[f] The electrophile (0.45 equiv) was added at −80 °C, then the mixture was allowed to reach −25 °C within 4 h, before aqueous work up.
[g] Ar=4-(CHO)C_6H_4.

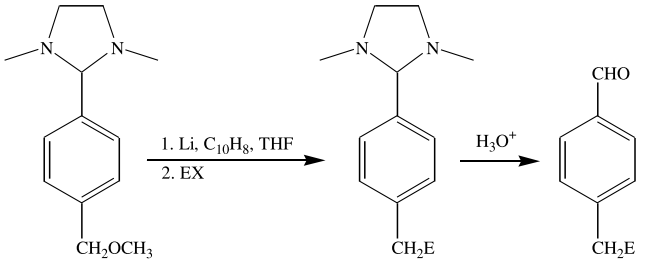
electrophiles, including primary and secondary alkyl halides, as well as enolizable and non-enolizable carbonyl derivatives, affording diamines **2ac–2af** in satisfactory yields (Table 1, entries 6–9).

2.3. Reductive metalation of 1,3-dimethyl-2-(4-chlorophenyl)imidazolidine, 1b

Application of the reductive lithiation procedure to imidazolidine **1b** allowed regioselective cleavage of the carbon–chlorine bond. Indeed, reduction of **1b** at −40 °C during 3 h, with 6 equiv of Li metal and in the presence of 5 mol% of $C_{10}H_8$, afforded quantitatively imidazolidine **1a** (Scheme 3, Table 2, entry 1). Quenching the reduction mixture with D_2O evidenced formation of an intermediate organolithium (Table 2, entry 2). However, quenching the reduction mixture with *n*-BuBr at −40 °C (not reported in Table 2) or at −80 °C (Table 2, entry 3), led to exclusive recovery of imidazolidine **1a**.

To rationalize the last result, we suggest that the organometal acts as a base towards the alkyl halide, promoting a β-elimination reaction. Support for this hypothesis was provided as follows: quenching the reduction mixture with *n*-BuBr, followed by D_2O work up of the resulting mixture, led to recovery of unlabelled **1a**, in almost quantitative yield.

More satisfactory results were obtained quenching the intermediate organolithium with aldehydes and a ketone.



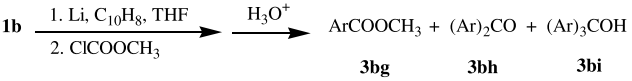
1c **2ca-2ce** **3cc-3ce**

Scheme 4. Reductive lithiation and reaction with electrophiles of 1,3-dimethyl-2-(4-methoxymethylphenyl)imidazolidine, **1c**.

The resulting products were not isolated, but directly submitted to acidic work up (2 N H_2SO_4/THF=1:1, rt, 1 h), to give the corresponding substituted benzaldehydes **3bb–3bd**, in satisfactory isolated yields (Table 2, entries 4–6).

Results obtained quenching the reduction mixture with $HCOOCH_3$, followed by acidic work up, are strongly dependent upon quenching conditions. Indeed, quenching with 2 equiv of the electrophile led to formation of terephthalaldehyde, **3be**, as the main reaction product (Table 2, entry 7), whilst quenching with 0.45 equiv of the electrophile led to alcohol **3bf**, in 54% isolated yield (Table 2, entry 8).

Relatively similar results were obtained employing $ClCOOCH_3$ as an electrophile [Eq. 1; Ar=4-(CHO)C_6H_4].



(1)

Direct quenching at −80 °C, with 1.1 equiv of the electrophile led, after acidic work up, to a mixture of ketone **3bh** and alcohol **3bi** almost in a 4:6 ratio (25 and 30% isolated yield, respectively), together with trace amounts of ester **3bg**. However, addition of the reduction mixture to 2 equiv of the electrophile, afforded a reaction mixture containing **3bg/3bh/3bi** in a 41:14:45 ratio. From this mixture, ester **3bg** was recovered in 32% isolated yield.

2.4. Reductive metalation of 1,3-dimethyl-2-(4-methoxymethylphenyl)-imidazolidine, 1c

As reported above, reductive lithiation of imidazolidine **1b** did not allow the introduction of an alkyl chain upon the aromatic ring (see above). To overcome this limitation, and taking into account the lower basicity of benzylic organometals as compared to aromatic ones,[13] we investigated the reductive lithiation of 1,3-dimethyl-2-(4-methoxymethylphenyl)imidazolidine, **1c**, as an approach to the generation of a 4-formylbenzyl-lithium equivalent (Scheme 4, Table 3).[14,15]

Table 3. Reductive metalation of imidazolidine **1c** and reaction with electrophiles[a]

Entry	Li equiv	*T* (°C)	*t* (h)	EX (equiv)	Product, E=	Yield (%)[b]
1	6[c]	−40	4.5	H_2O	**2ca**, H	>95
2	6[c]	−40	4.5	D_2O	**2ca**, H	–[d]
3	20	−50	6.0	D_2O	**2cb**, D	67
4	20	−80	12.0	D_2O	**2cb**, D	70[e]
5	30	−50	6.0	D_2O	**2cb**, D	86
6	30	−50	6.0	*n*-BuBr (1.2)	**3cc**, *n*-Bu	71[f]
7	30	−50	6.0	$Br(CH_2)_3Br$ (0.45)	**3cd**, $(CH_2)_4Ar$[g]	70[f]
8	30	−50	6.0	$Br(CH_2)_7OTHP$[h] (1.2)	**3ce**, $(CH_2)_7OTHP$	45[f]

[a] All reactions were run in the presence of a catalytic amount of $C_{10}H_8$ (10 mol%), unless otherwise indicated.
[b] As determined by ^1H NMR spectroscopy, unless otherwise indicated.
[c] In the presence of 5 mol% of $C_{10}H_8$.
[d] No deuterium incorporation was detected.
[e] 32% of **1c** was also detected.
[f] Isolated yield.
[g] Ar=4-(CHO)C_6H_4.
[h] THP=tetrahydropyranyl.

We obtained regioselective, and quantitative, reductive dealkoxylation of imidazolidine **1c** within 4.5 h, under conditions otherwise identical to those reported for imidazolidine **1b** (Table 3, entry 1); no evidence for the formation of products of carbon–nitrogen bond cleavage was obtained. However, D_2O quenching of the reduction mixture, did not show the intermediate formation of any stable organometal (Table 3, entry 2). Whilst investigating the effect of the relative amount of the metal and catalyst, as well as of reaction temperature, on the formation of an intermediate carbanion, (Table 3, entries 3 and 4), we found that reduction of imidazolidine **1c** with 30 equiv of the metal, 10 mol% of $C_{10}H_8$, at −50 °C during 6 h, followed by D_2O quenching, led to complete conversion of starting material, and recovery of 1,3-dimethyl-2-(4-deuteromethylphenyl)imidazolidine, **2cb**, with 86% isotopic purity (Table 3, entry 5).

According to our expectations, quenching of the reduction mixture with *n*-BuBr, with $Br(CH_2)_3Br$ and with a protected bromoalcohol, followed by acidic work up (see above), afforded benzaldehydes **3cc**, **3cd**, and **3ce**, respectively, in satisfactory isolated yields. Interestingly, in the last example, acidic work up allowed selective removal of the aldehyde protecting group in the presence of a tetrahydropyranyl ether.

3. Conclusions

$C_{10}H_8$-catalyzed reductive lithiation of imidazolidine **1a** represents an extension of our approach to the generation of α-amino-substituted benzyllithium derivatives via a reductive metalation procedure,[2,16,17] Interestingly, this cleavage reaction occurs under particularly mild conditions. Indeed, reductive lithiation of similar carbon–nitrogen bonds, for example, of *N*-isopropyl-2-phenylpirrolidine or *N*-phenylisoindoline, occurs at room temperature,[8] and it is worth noting that less than 10% of the literature concerning the reductive metalation of heterocycles refers to carbon–nitrogen bond cleavages.[10]

Nevertheless, the imidazolidine moiety can be employed as an efficient carbonyl protecting group in the reductive lithiation of suitably functionalized benzaldehydes. Indeed, lithiation of chlorine-substituted imidazolidine **1b** allowed regioselective cleavage of carbon–chlorine bond; interestingly, this procedure represents the first report concerning the generation of a stable solution of a synthetic equivalent of 4-formylphenyllithium, under the above reported reaction conditions.[11] Moreover, reductive metalation of methoxymethyl-substituted imidazolidine **1c** allowed the generation of a stable solution of a 4-formylbenzyllithium analogue, whose reactivity was shown to be complementary to that of the parent 4-formylphenyllithium equivalent.

4. Experimental

4.1. General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. 4-Methoxymethylbenzaldehyde was synthesized as described in Ref. 18. D_2O was 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz, in $CDCl_3$ with $SiMe_4$ as internal standard. $CDCl_3$ for recording spectra of imidazolidine-derivatives was stored over K_2CO_3 in the refrigerator. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of crude reaction mixtures, and comparing the integration of the signal corresponding to protons in the arylmethyl (**2ab**, **2cb**) or aryl (**2ba**) position with that of known signals. Flash-chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey-Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

4.2. Preparation of imidazolidines 1a–c. General procedure

A solution of the appropriate benzaldehyde (0.15 mol), *N*,*N*′-dimethylethylenediamine (0.17 mol, 14.54 g, 17.6 mL) and *p*-toluenesulfonic acid (150 mg, 0.8 mmol) in 100 mL of dry toluene, was distilled with fractionation under dry N_2, until the azeotrope toluene-H_2O was distilled away. The mixture was chilled at 0 °C and triethylamine (5 mL, 36 mmol) was added at once. The mixture was stirred at rt for 5 min, washed with saturated $NaHCO_3$ (2×20 mL), H_2O (2×20 mL), dried (K_2CO_3), and evaporated.

Crude products were purified by distillation. Imidazolidines **1a** (24.7 g, 0.14 mol, 93%)[19] and **1b** (27.4 g, 0.13 mol, 87%)[20] were characterized by comparison with literature data. Imidazolidine **1c** was characterized as follows.

4.2.1. 2-(4-Methoxymethylphenyl)-1,3-dimethylimidazolidine, 1c. 23.5 g, 0.11 mol, 73%. Colourless oil, bp 116–119 °C/1 mmHg. (Found: C, 70.95; H, 9.30; N, 12.56; $C_{13}H_{20}N_2O$ requires C, 70.87; H, 9.15; N, 12.72); δ_H 2.17 (6H, s, 2×CH_3), 2.52–2.59 (2H, m, CH–CH), 3.25 (1H, s, CH-Ar), 3.37–3.45 (2H, m, CH–CH), 3.40 (3H, s, CH_3O), 4.46 (2H, s, CH_2–O), 7.29–7.36 (2H, m, 2×ArH), 7.39–7.45 (2H, m, 2×ArH); δ_C 39.4, 53.3, 58.1, 74.5, 92.1, 127.6, 128.9, 138.4, 139.3.

4.3. Reductive cleavage of imidazolidines 1a–c, and reaction with electrophiles. General procedure

Li wire (6–12 equiv) was placed under Ar in a 50 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in THF (7 mL). A catalytic amount of $C_{10}H_8$ (5–10 mol%) was added to the suspended metal, each metal piece was cut into 2–3 smaller pieces with a spatula, and the mixture stirred until a dark green colour appeared. The mixture was chilled to the reported temperature (Tables 1–3) and a solution of the appropriate imidazolidine (2.5 mmol), dissolved in 3 mL of dry THF, was added dropwise. The mixture was stirred for the reported time (Tables 1–3), and a solution of the appropriate electrophile

in THF (2 mL) was slowly added. After stirring for 30 min, the mixture was quenched by slow dropwise addition of H_2O (10 mL, caution), the cold bath removed, and the resulting mixture extracted with Et_2O (3×10 mL). The organic phase was washed with brine (10 mL), dried (K_2CO_3) and the solvent evaporated.

D_2O quenching was performed by slow dropwise addition of 1 mL of the electrophile, dissolved in 1 mL of dry THF, followed by aqueous work up as described above.

Derivatives **2bb**–**2bi** and **2cb**–**2ce** were directly hydrolyzed to the corresponding benzaldehydes **3bb**–**3bi** and **3cb**–**3ce**, respectively, by acidic hydrolysis (THF/2 N H_2SO_4=1:1, 10 mL, 1 h, rt).

Compound **2aa**[21] was purified by distillation and characterized by comparison with literature data. Other products were purified by flash chromatography (AcOEt/petroleum ether or AcOEt/petroleum ether/Et_3N). Compounds **3bh**,[22] **2ca**,[20] and **3cc**,[23] were characterized by comparison with literature data. Compounds **3be** and **3bg** were characterized by comparison with commercially available samples. Other products were characterized as following.

4.3.1. *N*-(Phenyl)deuteromethyl-*N*,*N*′-dimethylethylenediamine, 2ab. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=7:1:3); colourless oil. (Found C, 73.56; H, 10.84; N, 15.59; $C_{11}H_{17}DN_2$ requires C, 73.69; H, 10.68; N 15.63); R_f 0.41 (AcOEt/petroleum ether/Et_3N=7:1:3); ν_{max} 3326 cm^{-1} (neat); δ_H 1.68 (1H, br s, NH), 2.18 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.53 (2H, t, J=5.7 Hz, CH_2N), 2.68 (2H, t, J=5.7 Hz, CH_2N), 3.46 (1H, br s, CHD), 7.22–7.32 (5H, m, 5×ArH); δ_C 36.5, 42.1, 49.3, 56.7, 62.3 (t, J=20 Hz), 126.9, 128.2, 128.9, 139.1.

4.3.2. 1-[Methyl-(2-methylaminoethyl)amino]-1-phenylpentane, 2ac. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=7:1:3); colourless oil. (Found C, 76.69; H, 11.27; N, 11.90; $C_{15}H_{26}N_2$ requires C, 76.87; H, 11.18; N 11.95); R_f 0.46 (AcOEt/petroleum ether/Et_3N=7:1:3); ν_{max} 3320 cm^{-1} (neat); δ_H 0.84 (3H, t, J=7.5 Hz, CH_3), 1.02–1.38 (5H, m, 2×CH_2, NH), 1.68–1.94 (2H, m, CH_2), 2.14 (3H, s, CH_3N), 2.41 (3H, s, CH_3N), 2.48–2.68 (4H, m, 2×CH_2N), 3.43 (1H, dd, J=8.7, 5.7 Hz, CHPh), 7.17–7.35 (5H, m, 5×ArH); δ_C 14.0, 22.7, 29.0, 31.9, 36.3, 37.8, 49.1, 53.0, 68.9, 126.8, 127.8, 128.7, 139.9.

4.3.3. 1-[Methyl-(2-methylaminoethyl)amino]-1-phenyl-2-methylpropane, 2ad. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=7:1:3); colourless oil. (Found C, 76.26; H, 11.04; N, 12.63; $C_{14}H_{24}N_2$ requires C, 76.31; H, 10.98; N, 12.71); R_f 0.42 (AcOEt/petroleum ether/Et_3N=7:1:31); ν_{max} 3324 cm^{-1}(neat); δ_H 0.61 (3H, d, J=6.6 Hz, CH_3), 0.99 (3H, d, J=6.6 Hz, CH_3), 2.00 (3H, s, CH_3N), 2.10–2.34 (4H, m, 2×CH, $CH(Me)_2$, NH), 2.38 (3H, s, CH_3N), 2.51–2.58 (2H, m, 2×CH), 2.96 (1H, d, J=10.2 Hz, CHPh), 7.01–7.08 (2H, m, 2×ArH), 7.13–7.27 (3H, m, 3×ArH); δ_C 20.2, 20.7, 28.4, 36.4, 36.6, 49.0, 53.2, 75.5, 126.7, 127.6, 129.2, 137.2.

4.3.4. 2,4-Dimethyl-3-[methyl-(2-methylaminoethyl)-amino]phenylmethylpentan-3-ol, 2ae. Purified by flash-chromatography (AcOEt/Et_3N=7:3); colourless oil, which solidifies upon standing, mp 95–96 °C. (Found C, 73.87; H, 11.19; N, 9.36; $C_{18}H_{32}N_2O$ requires C, 73.92; H, 11.03; N, 9.58); R_f 0.54 (AcOEt/Et_3N=7:3); ν_{max} 3308 cm^{-1} (nujol); δ_H 0.68 (3H, d, J=7.2 Hz, CH_3), 0.95 (3H, d, J=7.2 Hz, CH_3), 1.13 (3H, d, J=6.9 Hz, CH_3), 1.16 (3H, d, J=6.9 Hz, CH_3), 1.84–1.99 (2H, m, 2×CH), 2.31 (3H, s, CH_3N), 2.44 (3H, s, CH_3N), 2.46–2.74 (3H, m, 3×CH), 2.82–2.96 (1H, m, CH), 3.70 (1H, s, CH), 7.20–7.38 (3H, m, 3×ArH), 7.48–7.53 (2H, m, 2×ArH); δ_C 18.6, 18.8, 20.2, 34.2, 34.7, 36.8, 41.1, 50.2, 54.8, 70.8, 81.6, 126.5, 127.3, 131.4, 136.6.

4.3.5. 1-[Methyl-(2-methylaminoethyl)amino]-1-phenyl-3,3-dimethylbutan-2-ol, 2af. First diastereoisomer: purified by flash-chromatography (CH_2Cl_2/Et_3N=9:1); colourless oil. (Found C, 72.62; H, 10.85; N, 10.43; $C_{16}H_{28}N_2O$ requires C, 72.68; H, 10.67; N, 10.59); R_f 0.43 (CH_2Cl_2/Et_3N=9:1); ν_{max} 3316 cm^{-1} (neat); δ_H 0.74 (9H, s, 3×CH_3), 2.13 (3H, s, CH_3N), 2.20–2.60 (4H, br m, CH_2, NH, OH), 2.46 (3H, s, CH_3N), 2.64–2.79 (2H, m, CH_2), 3.56 (1H, d, J=9.9 Hz, CH), 3.78 (1H, d, J=9.9 Hz, CH), 7.15–7.18 (2H, m, 2×ArH), 7.27–7.36 (3H, m, 3×ArH); δ_C 26.9, 34.8, 36.6, 37.4, 49.3, 53.1, 68.9, 74.3, 127.5, 127.8, 129.9, 135.4; second diastereoisomer: purified by flash-chromatography (CH_2Cl_2/Et_3N=9:1); colourless oil. R_f 0.31 (CH_2Cl_2/Et_3N=9:1); δ_H 0.82 (9H, s, 3×CH_3), 2.16 (3H, s, CH_3N), 2.40 (3H, s, CH_3N), 2.46–2.54 (4H, br m, CH_2, NH, OH), 2.59–2.70 (2H, m, CH_2), 3.47 (1H, d, J=4.8 Hz, CH), 3.84 (1H, d, J=4.8 Hz, CH), 7.20–7.37 (5H, m, 5×ArH); δ_C 26.7, 34.8, 36.5, 39.4, 49.4, 54.0, 71.0, 77.7, 127.4, 127.8, 130.5, 137.2.

4.3.6. 1,3-Dimethyl-2-(4-deuterophenyl)imidazolidine, 2ba. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=7:3:1); colourless oil. (Found C, 74.32; H, 9.81; N, 15.65; $C_{11}H_{15}DN_2$ requires C, 74.53; H, 9.67; N 15.80); R_f 0.53 (AcOEt/petroleum ether/Et_3N=7:3:1); δ_H 2.18 (6H, s, 2×CH_3), 2.53–2.59 (2H, CH–CH), 3.25 (1H, s, CH), 3.38–3.44 (2H, m, CH–CH), 7.32–7.38 (2H, m, 2×ArH), 7.42–7.47 (2H, m, 2×ArH); δ_C 39.5, 53.3, 92.5, 128.1, 128.2 (t, J=18 Hz), 128.8, 139.8.

4.3.7. 4-(1-Hydroxy-2,2-dimethylpropyl)benzaldehyde, 3bb. Purified by flash-chromatography (AcOEt/petroleum ether=3:7); thick colourless oil. (Found C, 74.82; H, 8.47; $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39); R_f 0.43 (AcOEt/petroleum ether=3:7); ν_{max} 1707 cm^{-1} (nujol); δ_H 0.94 (9H, s, 3×CH_3), 2.07 (1H, br s, OH), 4.48 (1H, s, CH), 7.46–7.54 (2H, m, 2×ArH), 7.80–7.88 (2H, m, 2×ArH), 10.00 (1H, s, CHO); δ_C 25.8, 35.8, 81.9, 128.3, 129.0, 135.6, 149.1, 192.0.

4.3.8. 4-Formylbenzhydrol, 3bc. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=4:6:1); colourless oil. (Found C, 79.01; H, 5.87; $C_{14}H_{12}O_2$ requires C, 79.22; H, 5.70); R_f 0.45 (AcOEt/petroleum ether/Et_3N=4:6:1); ν_{max} 3424, 1697 cm^{-1} (neat); δ_H 2.60 (1H, br s, OH), 5.86 (1H, s, CH), 7.25–7.35 (5H, m, 5×ArH), 7.52–7.58 (2H, m, 2×ArH), 7.80–7.86 (2H, m, 2×ArH), 9.94 (1H, s, CHO); δ_C 75.8, 126.7, 126.9, 128.0, 128.7, 129.9, 135.5, 143.1, 150.5, 192.0.

4.3.9. 2,4-Dimethyl-3-(4-formylphenyl)pentan-3-ol, 3bd. Purified by flash-chromatography (AcOEt/petroleum ether/

Et_3N=2:9:1); white solid, mp 103–105 °C (Et_2O). (Found C, 76.12; H, 9.31; $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15); R_f 0.48 (AcOEt/petroleum ether/Et_3N=2:9:1); ν_{max} 3465, 1692 cm^{-1} (nujol); δ_H 0.78 (6H, d, J=6.6 Hz, 2×CH_3), 0.85 (6H, d, J=6.6 Hz, 2×CH_3), 1.62 (1H, br s, OH), 2.33 (2H, ept, J=6.6 Hz, 2×CH), 7.56–7.62 (2H, m, 2×ArH), 7.81–7.88 (2H, m, 2×ArH), 10.02 (1H, s, CHO); δ_C 16.4, 17.4, 34.1, 81.3, 127.4, 128.8, 134.7, 150.5, 192.1.

4.3.10. 4,4′-Diformylbenzhydrol, 3bf. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=7:4:1); white solid, mp 98–100 °C (triturated form petroleum ether). (Found C, 74.86; H, 5.15; $C_{15}H_{12}O_3$ requires C, 74.99; H, 5.03); R_f 0.50 (AcOEt/petroleum ether/Et_3N=7:4:1); ν_{max} 1674 cm^{-1} (nujol); δ_H 2.82 (1H, br s, OH), 5.97 (1H, s, CH), 7.52–7.60 (4H, m, 4×ArH), 7.82–7.90 (4H, m, 4×ArH), 9.98 (2H, s, 2×CHO); δ_C 75.4, 127.0, 130.1, 136.0, 149.5, 191.7.

4.3.11. 4,4′,4″-Triformyltrityl alcohol, 3bi. Purified by flash-chromatography (AcOEt/petroleum ether=4:6); thick colourless oil. (Found C, 76.59; H, 4.81; $C_{22}H_{16}O_4$ requires C, 76.73; H, 4.68); R_f 0.22 (AcOEt/petroleum ether=4:6); ν_{max} 3461, 1682 cm^{-1} (neat); δ_H 3.41 (1H, br s, OH), 7.38–7.46 (6H, m, 6×ArH), 7.74–7.84 (6H, m, 6×ArH), 9.92 (3H, s, 3×CHO); δ_C 81.7, 128.4, 129.7, 135.8, 151.5, 191.6.

4.3.12. 1,3-Dimethyl-2-(4-deuteromethylphenyl)imidazolidine, 2cb. Purified by flash-chromatography (AcOEt/petroleum ether/Et_3N=7:3:1); colourless oil; R_f 0.55 (AcOEt/petroleum ether/Et_3N=7:3:1); δ_H 2.17 (6H, s, 2×CH_3N), 2.33 (2H, t, J=2.1 Hz, CH_2D), 2.51–2.57 (2H, m, CH–CH), 3.21 (1H, s, CHAr), 3.36–3.43 (2H, m, CH–CH), 7.14–7.19 (2H, m, 2×ArH), 7.29–7.34 (2H, m, 2×ArH); δ_C 21.2 (t, J=21 Hz), 39.5, 53.3, 92.3, 128.7, 128.9, 136.7, 138.1.

4.3.13. 4-[5-(4-Formylphenyl)pentyl]benzaldehyde, 3cd. Purified by flash chromatography (AcOEt/petroleum ether=2.5:7.5); white solid, mp 75 °C (AcOEt/petroleum ether); (Found C, 81.31; H, 7.25; $C_{19}H_{20}O_2$ requires C, 81.40; H, 7.19); R_f 0.44 (AcOEt/petroleum ether=2.5:7.5); ν_{max} 1687 cm^{-1} (nujol); δ_H 1.34–1.46 (2H, m, CH_2), 1.69 (4H, quint, J=7.8 Hz, 2×CH_2), 2.69 (4H, t, J=7.8 Hz, ArCH_2), 7.30–7.36 (4H, m, 4×ArH), 7.77–7.83 (4H, m, 4×ArH), 9.97 (2H, s, CHO); δ_C 28.8, 30.8, 36.0, 129.0, 129.9, 134.5, 150.0, 191.9.

4.3.14. 4-[8-(Tetrahydropyran-2-yloxy)octyl]benzaldehyde, 3ce. Purified by flash chromatography (AcOEt/petroleum ether=1.5:8.5); colourless oil; (Found C, 75.25; H, 9.68; $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50); R_f 0.34 (AcOEt/petroleum ether=1.5:8.5); ν_{max} (neat) 1703 cm^{-1}; δ_H 1.22–1.92 (18H, m, 9×CH_2), 2.68 (2H, t, J=7.5 Hz, CH_2Ar), 3.38 (1H, dt, J=9.3, 6.6 Hz, CHO), 3.46–3.55 (1H, m, CHO), 3.73 (1H, dt, J=9.3, 6.9 Hz, CHO), 3.82–3.92 (1H, m, CHO), 4.53–4.60 (1H, m, OCHO), 7.31–7.36 (2H, m, 2×ArH), 7.76–7.82 (2H, m, 2×ArH), 9.97 (1H, s, ArCHO); δ_C 19.7, 25.5, 26.2, 29.1, 29.3, 29.7, 30.7, 30.8, 31.0, 36.2, 62.3, 67.6, 98.9, 129.0, 129.8, 134.4, 150.4, 192.0.

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Stereochemistry of the cyclization of alkoxy-substituted 5-hexenyllithiums: effect of solvent and lithium iodide on diastereoselectivity

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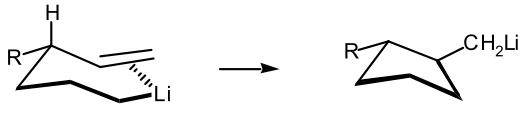
Abstract—The stereochemistry of the cyclization of 4-methoxy-5-hexenyllithium, 4-(methoxymethoxy)-5-hexenyllithium, 4-*tert*-butoxy-5-hexenyllithium, and 3-methoxy-5-hexenyllithium, each of which was generated from the corresponding iodide by low-temperature lithium–iodine exchange, has been studied in a variety of solvent systems. The results of these studies demonstrate that the stereochemical outcome of the cyclizations of alkoxy-substituted 5-hexenyllithiums may be profoundly affected by the medium in which the ring closures are conducted. The etiology of these often dramatic solvent effects is attributed to the ability of certain lithiophilic ligands to competitively complex the lithium iodide salt that is present as a co-product from the exchange reaction used to prepare the organolithiums.

1. Introduction

The cyclization of unsaturated organolithiums provides a regiospecific and highly stereoselective route to functionalized carbocyclic[1] and heterocyclic ring systems.[2] The diastereoselectivity that characterizes the 5-exo ring closure of substituted 5-hexenyllithiums is a consequence of a chair-like transition state, shown below, in which the lithium atom is intramolecularly coordinated with the remote π-bond and a substituent preferentially occupies a pseudoequatorial position.[3] It might be noted that the ground state of 5-hexenyllithium is also essentially that of a cyclohexane chair (Scheme 1).[4]



Scheme 1.

One might anticipate that the stereochemistry of the cyclization of a 5-hexenyllithium bearing a heteroatomic substituent may be more involved if the heteroatomic group is capable of intramolecular coordination to the lithium atom of the substrate.[5,6] In this connection, some time ago we reported the initial results of an investigation of the cyclization of 4-methoxy-5-hexenyllithium (**1**), which was generated from the corresponding iodide (**2**) by low-temperature lithium–iodine exchange.[7] Quite unexpectedly, the stereochemical outcome of the cyclization of this prototypical alkoxy-substituted 5-hexenyllithium was found to be dramatically dependent on the solvent system in which the isomerization was conducted. For example, as illustrated below, the ring closure of **1** is highly *trans*-selective (viz., *trans*/*cis* ratio ≈20/1) in an ether–hydrocarbon medium but it is *cis*-selective (viz., *cis*/*trans* ratio ≈4/1) when conducted in the presence of TMEDA.[7] Control experiments confirmed that these product ratios reflect the stereoselectivities of kinetically controlled cyclizations. At the time these observations were reported, it was tentatively suggested that lithiophilic Lewis base additives, such as TMEDA and THF, affect the stereochemistry of the cyclization of **1** by sequestration of the LiI generated in the course of the exchange reaction used to prepare **1**.[7] Herein, we report the results of a more detailed study of the effect of solvent on the stereochemical course of ring closure of alkoxy-substituted 5-hexenyllithiums. As detailed below, the stereochemistry of the cyclization of such 5-hexenyllithiums is highly solvent dependent and the etiology of these solvent effects appears to be related to the presence of LiI in the reaction medium (Scheme 2).

Keywords: Organolithiums; Cyclization; Stereochemistry.
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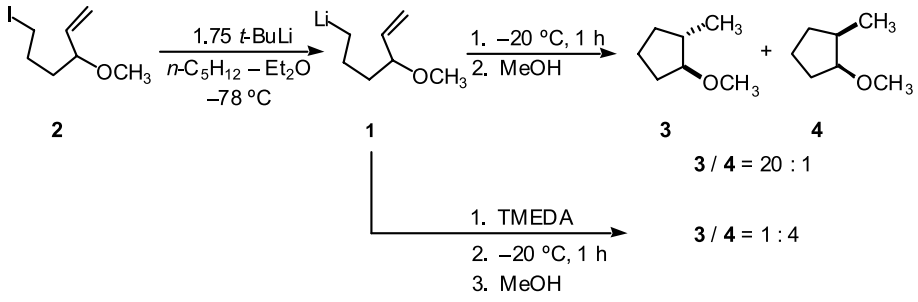


Scheme 2.

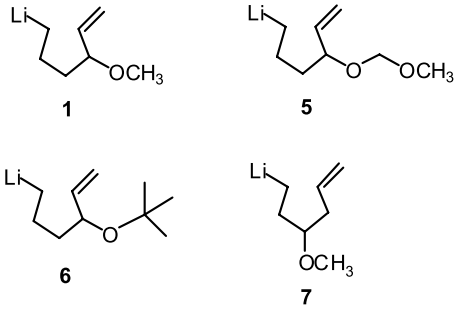
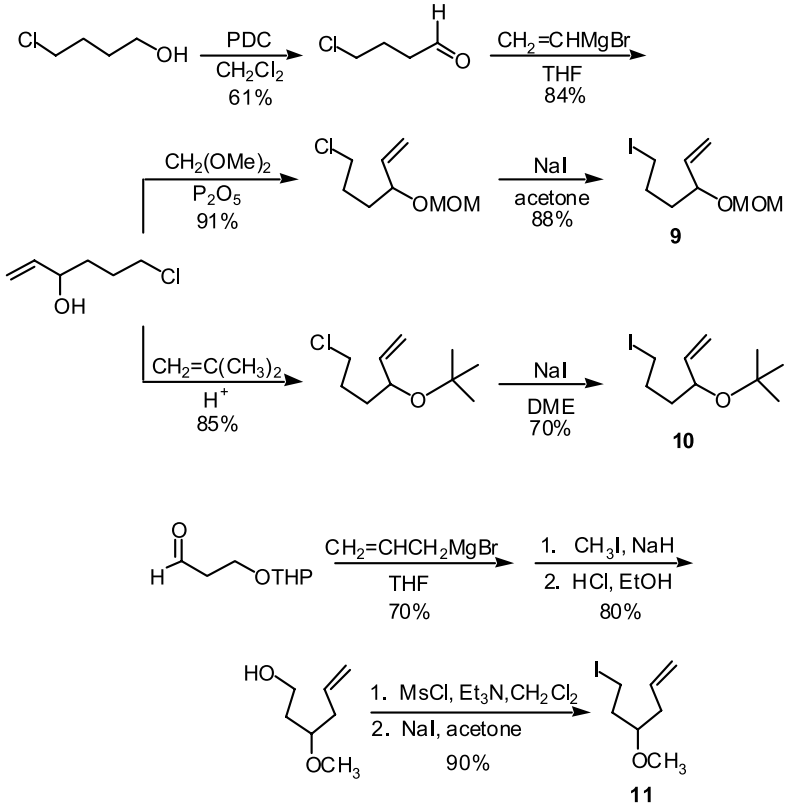


Figure 1. Substituted 5-hexenyllithiums.

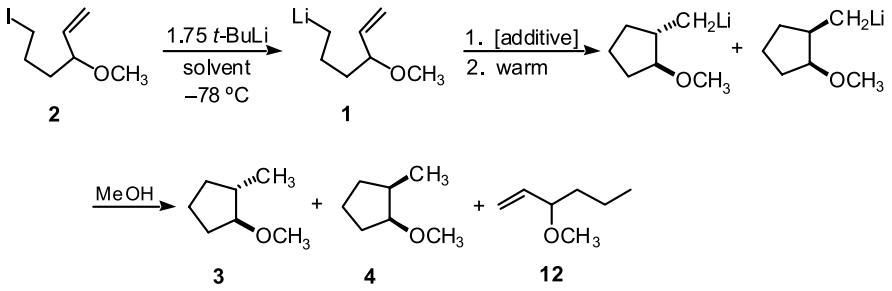
2. Results and discussion

A representative set of 5-hexenyllithiums, depicted in Figure 1,[8] bearing an ethereal oxygen substituent at the C(3) or C(4) position were selected for this exploratory investigation. No effort was made to prepare 5-hexenyllithiums bearing heteroatomic groups at the C(2) position: prior work had demonstrated that such species would undergo rapid β-elimination to give 1,5-hexadiene.[9] Similarly, placement of a heteroatomic substituent at C(5) was avoided; ring-closure of such species would invariably lead to expulsion of the heteroatomic group with formation of methylenecyclopentene.[9]

The 5-hexenyllithiums were generated, as described below, from the corresponding iodides by low-temperature lithium–iodine exchange.[10] The preparation of 6-iodo-3-methoxy-1-hexene (**2**)[7] has been previously reported; the remaining iodides were prepared as illustrated in Scheme 3 using standard synthetic routes detailed in Section 4. Authentic samples of the *trans*- and *cis*-isomers of the products expected from the cyclization of the substituted 5-hexenyllithiums (**1**, **5**–**7**) were prepared in a similar fashion from pure *trans*-2-methylcyclopentanol,[11,7] pure *cis*-2-methylcyclopentanol,[12,7] or a mixture of *trans*- and *cis*-3-methylcyclopentanol.



Scheme 3.



Scheme 4.

2.1. 4-Methoxy-5-hexenyllithium

As illustrated in Scheme 4, 4-methoxy-5-hexenyllithium (**1**) was generated by treatment of iodide **2** with 1.75 molar equiv of *t*-BuLi, rather than the full 2 molar equiv of the reagent typically employed for the exchange.[10] As we have previously noted, it is necessary to use less than an optimal quantity of *t*-BuLi in order to minimize the fairly rapid S'_N addition of excess *t*-BuLi to **1** (and other 5-hexenyllithiums such as **5** and **6** that bear a leaving group at the allylic position) leading to consumption of **1** and formation of 2,2-dimethyl-4-octene.[7] Unfortunately, when less than 2 equiv of *t*-BuLi is used, a quantity of *tert*-butyl iodide cogenerated in the exchange remains in the reaction mixture and this serves as a proton source leading to inadvertent quench of **1** to give 3-methoxy-1-hexene. As a result, the yield of **1** from the reaction of **2** with 1.75 equiv of *t*-BuLi is less than quantitative.

Be that as it may, the ring closure of **1** was investigated (Scheme 4) by allowing solutions of the organolithium, generated from **2** in diethyl ether, *n*-pentane–diethyl ether mixtures, or pure *n*-pentane, to warm and stand (normally at 0 °C) for 1 h before quench with an excess of deoxygenated MeOH. The ability to generate **1** from **2** in *n*-pentane deserves comment: pure *n*-pentane is not recommended as a generally useful solvent for the lithium–iodine exchange reaction; indeed, no exchange is observed when simple alkyl iodides are treated with *t*-BuLi at low temperature in pure hydrocarbon solution.[10] Typically, the exchange reaction is conducted in a solvent system containing an ether in which the *t*-BuLi reagent is predominantly dimeric.[10] Apparently, the CH_3O group in **2** (and in the other alkoxy-substituted substrates discussed below) serves to disaggregate the *t*-BuLi allowing a normal exchange in hydrocarbon solution.

The proportions of *trans*- and *cis*-(2-methoxycyclopentyl)-methyllithium formed upon kinetically controlled ring

Table 1. Cyclization (Scheme 4) of 4-methoxy-5-hexenyllithium (**1**)[a]

Entry	Solvent system	Temp, °C	Products, % yield[b]		
			12	**3**+**4**	*trans* (**3**)/*cis* (**4**)[c]
1	*n*-C_5H_{12}[d]	0	60.8	39.1	2.9
2	*n*-C_5H_{12}–Et_2O 49:1 by vol	0	78.1	21.9	3.1
3	19:1 by vol	0	31.0	69.0	4.3
4	9:1 by vol	0	25.1[e]	63.7	4.6
5	3:2 by vol	0	12.1	88.1	7.7
6	3:2 by vol	−20	49.0	47.8	19.8
7	1:1 by vol	0	14.6	85.4	8.2
8	Et_2O	0	36.0	65.4	11.1
9	TMEDA[f]	0	22.2	74.5	0.25
10	TMEDA[f]	20	18.3[g]	73.6	0.34
11	TMEDA[h]	18	5.9	94.1	0.18
12	1,4-dioxane[i]	0	12.2	88.0	0.43
13	*n*-C_5H_{12}–Et_2O 3:2 by vol + LiI[j]	0	<1[k]	60.0	8.5

[a] 4-Methoxy-5-hexenyllithium (**1**) was generated at −78 °C by addition of 1.75 equiv of *t*-BuLi to a solution of iodide **2** in either *n*-pentane–diethyl ether, pure diethyl ether, or pure *n*-pentane. Where indicated, TMEDA or 1,4-dioxane was added at −78 °C, the cooling bath was then removed, and the mixture was allowed to stand at the specified temperature for 1 h before the addition of an excess of oxygen-free methanol.

[b] Yields were determined by capillary GC using *n*-heptane as internal standard and correction for detector response.

[c] Ratio of *trans*- (**3**) and *cis*-1-methoxy-2-methylcyclopentane (**4**).

[d] Following the exchange, the mixture was filtered at −78 °C through a short column packed with dry, basic alumina and then allowed to warm and stand at 0 °C for 1 h; analysis of the aqueous phase for iodide following quench of the reaction mixture revealed that 5% of the original amount of LiI remained in the reaction mixture.

[e] Product mixture contained 8% of 2,2-dimethyl-4-octene.

[f] TMEDA (1.75 molar equiv) was added to a solution of **1** in *n*-C_5H_{12}–Et_2O (3:2 by vol) and the mixture was allowed to warm and stand at the specified temperature for 1 h.

[g] Product mixture contained 4% of 2,2-dimethyl-4-octene.

[h] TMEDA (1.75 molar equiv) was added to a solution of **1** in *n*-C_5H_{12}–Et_2O (3:2 by vol) at −78 °C, the mixture was filtered through a short column packed with dry, basic alumina and then allowed to warm and stand at +18 °C for 1 h; analysis of the aqueous phase for iodide following quench of the reaction mixture revealed that 7% of the original amount of LiI remained in the reaction mixture.

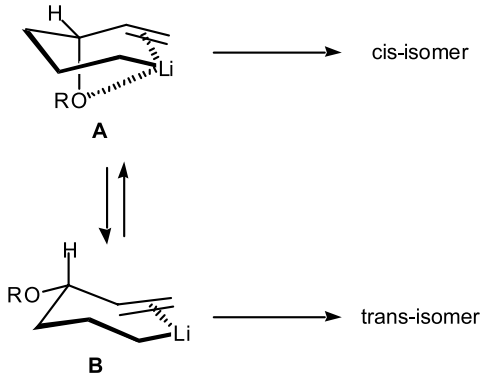
[i] 1,4-Dioxane (3.0 molar equiv) was added to a solution of **1** in *n*-C_5H_{12}–Et_2O (3:2 by vol) at −78 °C, the mixture was allowed to warm and stand at 0 °C for 1 h.

[j] LiI (4.0 molar equiv; generated by treatment *tert*-butyl iodide with *t*-BuLi at −78 °C), was added to the reaction mixture at −78 °C and the reaction mixture was then allowed to warm and stand at 0 °C for 1 h.

[k] Product mixture contained 40% of 2,2-dimethyl-4-octene.

closure of **1** were assayed as *trans*- and *cis*-1-methoxy-2-methylcyclopentane (**3** and **4**, respectively) by capillary GC using *n*-heptane as internal standard. The effect of TMEDA and 1,4-dioxane on the stereochemistry of the cyclization of **1** was investigated in a separate series of experiments in which these additives were added at −78 °C to solutions of **1** prior to warming of the organolithium. The results of these experiments are summarized in Table 1.

The data presented in Table 1, along with those presented in our initial report,[7] demonstrate that the stereochemistry of the cyclization of **1** depends rather strongly on the medium. The ring closure is *trans*-selective in *n*-pentane, in pentane–diethyl ether mixtures, and in pure diethyl ether (Table 1, entries 1–8); as noted previously,[7] this *trans*-selectivity can be substantial at lower temperatures (Table 1, entry 6). Significantly, the *trans*-selectivity increases monotonically as the proportion of diethyl ether in the solvent increases: at 0 °C, the *trans* (**3**)/*cis* (**4**) ratio, which is 2.9 in pure pentane (Table 1, entry 1), increases to 11.1 in pure ether (Table 1, entry 8). The presence of 1.75 molar equiv of TMEDA or 3.0 molar equiv of 1,4-dioxane in a reaction mixture composed primarily of *n*-pentane–diethyl ether (3:2 by vol) renders the cyclization *cis*-selective (Table 1, entries 9–12). These results are perhaps best discussed with reference to the two stereochemically distinct modes of ring closure possible for chair-like conformations of **1** (Scheme 5, R=CH_3).



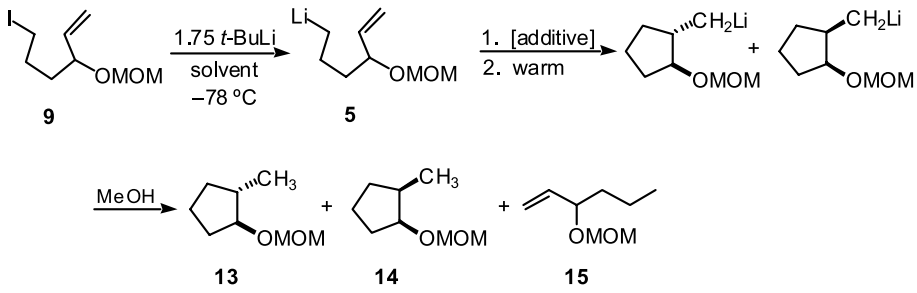
Scheme 5.

Formation of the *cis*-isomer (**4**) requires that the allylic CH_3O group occupy a pseudoaxial position and intramolecular coordination of the lithium atom with the proximal oxygen might be expected to stabilize such an arrangement (Scheme 5, **A**). The *trans*-isomer arises from cyclization of a species bearing a pseudoequatorial CH_3O group (Scheme 5, **B**). It is well known that organolithiums co-associate with lithium halides and it is likely, given the method used to prepare **1**, that it exists as an aggregate containing the co-generated LiI.[13] We have previously noted that intraaggregate coordination of the 4-OCH_3 group with LiI may disrupt the intramolecular Li–O coordination depicted in structure **A** (Scheme 5) and have suggested that Lewis base additives, such as TMEDA and 1,4-dioxane, affect the stereochemistry of the cyclization of **1** by sequestering the LiI generated in the exchange reaction.[7] In short, LiI acts as an impediment to *cis*-selective cyclization; preferential formation of a complex between LiI and a Lewis base may simply serve to remove this impediment. If this rationale is correct, addition of excess LiI to the reaction medium should result in a more *trans*-selective cyclization. Conversely, removal of LiI from the reaction mixture would favor cyclization via **A** (Scheme 5) and lead to higher proportion of the *cis*-product. The results of the experiments summarized in Table 1 are fully consistent with these expectations.

Addition of 4.0 molar equiv of LiI (generated by adding *t*-BuLi to *tert*-butyl iodide at −78 °C) to a solution of **1** in *n*-pentane–diethyl ether (3:2 by vol) followed by warming the reaction mixture to 0 °C afforded more *trans*-1-methoxy-2-methylcyclopentane (*trans* (**3**)/*cis* (**4**)=8.5) than the reaction conducted under identical conditions but in the absence of added LiI (*trans* (**3**)/*cis* (**4**)=7.7; Table 1, cf. entries 5 and 13). Removal of lithium iodide from the reaction mixture proved to be a more difficult proposition.

Various Lewis bases, such as TMEDA and 1,4-dioxane, form stable complexes with lithium halides.[14,15] Indeed, addition of TMEDA at −78 °C to solutions of **1** generated by lithium–iodine exchange in *n*-pentane–diethyl ether affords a precipitate. Thus, filtration of the reaction mixture at a low temperature (to minimize cyclization during the filtration) should serve to remove at least a portion of the LiI as the TMEDA complex and lead to a higher proportion of *cis*-isomer in the product mixture. As shown by the results summarized in Table 1 removal of the TMEDA–LiI precipitate by filtration through a pad of meticulously dry, basic alumina leads to an increase in the amount of *cis*-product (Table 1, entry 11; *trans* (**3**)/*cis* (**4**)=0.18) relative to the outcome of a similar experiment conducted without filtration (Table 1, *trans* (**3**)/*cis* (**4**)=0.34). It should be noted that the precipitate recovered by filtration of the TMEDA-containing reaction mixtures had a melting point (mp=242–243 °C) identical to that reported by White for the $[(TMEDA)LiI]_2$ complex (lit.[15] mp=242–245 °C). That such filtration was effective for removal of LiI was confirmed by analysis of the aqueous phase for iodide following quench of reaction mixtures. The Volhard method[16] was used to quantitate the amount of iodide remaining after filtration: an excess standard aqueous silver nitrate solution was added to the aqueous layer and the excess silver nitrate was titrated with standard sodium thiocyanate using iron (III) as an indicator. This analysis demonstrated that filtration of the reaction mixture to which 1.75 equiv of TMEDA had been added (Table 1, entry 11) served to remove 93% of the LiI.

Although lithium iodide has a reasonable solubility in diethyl ether, it is essentially insoluble in *n*-pentane. Thus, an increase in the pentane–ether solvent ratio should lead to a decrease in the *trans*/*cis* product ratio because the lithium iodide will be less soluble in such a solvent system. These expectations were confirmed by a series of experiments, noted above and summarized in Table 1 (entries 1–8); the *trans* (**3**)/*cis* (**4**) product ratio decreased from a high of 11.1 in pure diethyl ether (Table 1, entry 8) to a low of 2.9 in pure *n*-pentane (Table 1, entry 1). The low solubility of lithium iodide in *n*-pentane at −78 °C allowed removal of the lithium iodide by filtration of the reaction mixture (Table 1, entry 1) prior to warming to 0 °C. Quantitative analysis of the aqueous phase following quench of the reaction mixture



Scheme 6.

revealed that 95% of the lithium iodide had been removed by the filtration.

The experiments outlined above and summarized in Table 1 seem to support the hypothesis that Lewis base additives remove lithium iodide from the reaction medium. The *cis*-selectivity observed for cyclizations conducted in the presence of TMEDA and 1,4-dioxane is probably a result of both the sequestering of LiI by the Lewis base as well as stabilization of the transition state leading to the *cis*-isomer (Scheme 5, **A**).

2.2. 4-(Methoxymethoxy)-5-hexenyllithium

It was of interest to see if additional oxygen atoms in an ether group at the allylic position of 5-hexenyllithium would affect the stereochemistry of the cyclization. To this end, the cyclization of 4-(methoxymethoxy)-5-hexenyllithium (**5**) was investigated (Scheme 6). Treatment of iodide **9** with 1.75 equiv of *t*-BuLi in *n*-pentane–diethyl ether (3:2 by volume) at −78 °C, following the same procedure as that used to prepare **1**, afforded **5**; addition of deoxygenated MeOH to the cold reaction mixture gave a quantitative yield of 3-methoxymethoxy-1-hexene (**15**). When warmed to an appropriate temperature, **5** cyclizes to deliver *trans*- (**13**) and *cis*-1-(methoxymethoxy)-2-methylcyclopentane (**14**) after quench of the reaction mixture. The stereochemistry of the cyclization of **5** was investigated under a variety of experimental conditions. The results of these studies are summarized in Table 2. As was the case for the cyclization of **1**, the stereochemical outcome of isomerization of 4-(methoxymethoxy)-5-hexenyllithium (**5**) depends upon the solvent system.

Inspection of Table 2 reveals that the cyclization of **5** is less *trans*-selective in a given solvent system than is cyclization of 4-methoxy-5-hexenyllithium (**1**). A model similar to that proposed to account for the stereochemistry of the cyclization of **1** may be constructed to account for these observations (Scheme 5, R=CH_2OCH_3). The presence of two potential sites for intramolecular coordination of the Li atom with the acetal oxygens of the MOM group in the axial conformation of **5** (Scheme 5, **A**) may well provide additional stabilization relative to the analogous conformation of **1** and lead to a higher proportion of *cis*-product than is observed in the cyclization of the 4-methoxy analog. In accord with the results noted above for the 4-methoxy system, sequestration of LiI by addition of a complexing agent such as TMEDA (Table 2, entry 5) or 1,4-dioxane (Table 2, entry 6) results in a *cis*-selective cyclization of **5**.

2.3. 4-*tert*-Butoxy-5-hexenyllithium

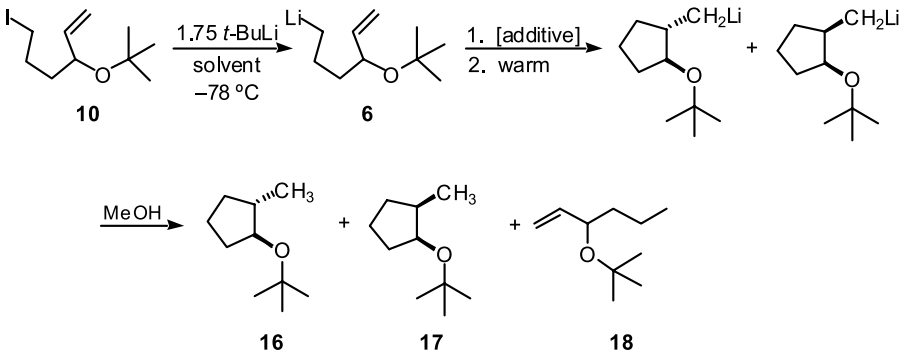
4-*tert*-Butoxy-5-hexenyllithium **6** was chosen for study in order to investigate the influence of a bulky ether group at C(4) on the stereochemistry of the cyclization. The organolithium was generated (Scheme 7) from iodide **10** and 1.75 equiv of *t*-BuLi. When allowed to warm and stand at an appropriate temperature, **6** undergoes cyclization to give *trans*- (**16**) and *cis*-1-*tert*-butoxy-2-methylcyclopentane (**17**) after quench of the reaction mixture with MeOH. Here again, as demonstrated by the data summarized in Table 3, the stereochemical outcome of the ring closure is solvent dependent.

A remarkable and quite surprising feature of the cyclization of **6** is its extraordinary diastereoselectivity: the *cis*-isomer (**17**) is the major product of the ring-closure under all

Table 2. Cyclization (Scheme 6) of 4-(methoxymethoxy)-5-hexenyllithium (**5**)[a]

Entry	Solvent system	Temp, °C	Products, % yield[b]		
			15	**13**+**14**	*trans* (**13**)/*cis* (**14**)[c]
1	*n*-C_5H_{12}	20	42.9	57.1	1.5
2	*n*-C_5H_{12}–Et_2O 3:2 by vol	22	18.3	81.6	2.1
3	3:2 by vol	−30	82.7	17.3	4.1
4	Et_2O	20	21.0	78.1	1.9
5	TMEDA[d]	23	19.9	80.0	0.20
6	1,4-dioxane[e]	23	26.3	70.2	0.60

[a] 4-(Methoxymethoxy)-5-hexenyllithium (**5**) was generated at −78 °C by addition of 1.75 equiv of *t*-BuLi to a solution of iodide **9** in either *n*-pentane–diethyl ether, pure diethyl ether, or pure *n*-pentane. Where indicated, TMEDA or 1,4-dioxane was added at −78 °C, the cooling bath was then removed, and the mixture was allowed to stand at the specified temperature for 1 h before the addition of an excess of oxygen-free methanol.
[b] Yields were determined by capillary GC using *n*-heptane as internal standard and correction for detector response.
[c] Ratio of *trans*- (**13**) and *cis*-1-(methoxymethoxy)-2-methylcyclopentane (**14**).
[d] TMEDA (1.75 molar equiv) was added to a solution of **5** in *n*-C_5H_{12}–Et_2O (3:2 by vol) and the mixture was allowed to warm and stand at 23 °C for 1 h.
[e] 1,4-Dioxane (3.0 molar equiv) was added to a solution of **5** in *n*-C_5H_{12}–Et_2O (3:2 by vol) at −78 °C, the mixture was allowed to warm and stand at 23 °C for 1 h.



Scheme 7.

Table 3. Cyclization (Scheme 7) of 4-*tert*-butoxy-5-hexenyllithium (**6**)[a]

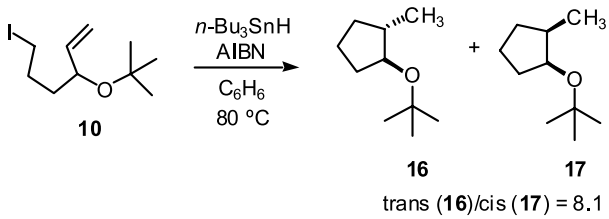
Entry	Solvent system	Temp, °C	Products, % yield[b]		
			18	**16**+**17**	*cis* (**17**)/*trans* (**16**)[c]
1	*n*-C_5H_{12}	20	40.0	60.0	1.5
2	*n*-C_5H_{12}–Et_2O 3:2 by vol	26	40.0	60.0	3.4
3	3:2 by vol	0	28.3	71.7	3.5
4	3:2 by vol	−10	30.5	69.5	2.3
5	TMEDA[d]	0	28.1	71.8	20.8
6	TMEDA[d]	−10	28.5	71.5	23.8

[a] 4-*tert*-Butoxy-5-hexenyllithium (**6**) was generated at −78 °C by addition of 1.75 equiv of *t*-BuLi to a solution of iodide **10** in either *n*-pentane–diethyl ether or pure *n*-pentane. Where indicated, TMEDA was added at −78 °C, the cooling bath was then removed, and the mixture was allowed to stand at the specified temperature for 1 h before the addition of an excess of oxygen-free methanol.
[b] Yields were determined by capillary GC using *n*-heptane as internal standard and correction for detector response.
[c] Ratio of *cis*- (**17**) and *trans*-1-*tert*-butoxy-2-methylcyclopentane (**16**).
[d] TMEDA (1.75 molar equiv) was added to a solution of **6** in *n*-C_5H_{12}–Et_2O (3:2 by vol) and the mixture was allowed to warm and stand at the specified temperature for 1 h.

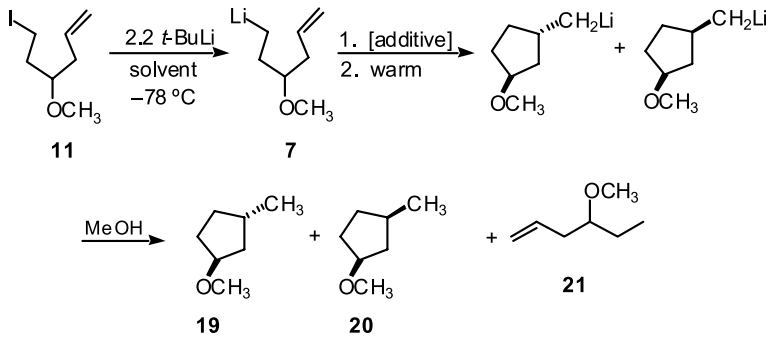
conditions investigated (Table 3). Such highly *cis*-selective cyclization of a simple, monosubstituted 5-hexenyllithium is, to our knowledge, unprecedented.[1] Addition of 1.75 molar equiv of TMEDA serves to significantly enhance the *cis*-preference (Table 3, cf. entries 3 and 5; 4 and 6). The effect of TMEDA on the stereochemistry of the cyclization of **6** is all the more dramatic when one compares the modestly *cis*-selective isomerization of 4-methoxy-5-hexenyllithium (**1**) at −20 °C in the presence of TMEDA (*cis*/*trans*=4.0)[7] with the almost exclusive production of *cis*-1-*tert*-butoxy-2-methylcyclopentane (**17**) when the cyclization of **6** is conducted at −10 °C in the presence of TMEDA (Table 3, entry 6; *cis* (**17**)/*trans* (**16**)=23.8).

If one assumes that **6** cyclizes via the chair-like transition state adopted by the parent 5-hexenyllithium, the formation of a preponderance of *cis*-1-*tert*-butoxy-2-methylcyclopentane (**17**) requires that the *tert*-butoxy group preferentially adopt a pseudoaxial position in the activated complex leading to ring closure. Given that the ground state of 5-hexenyllithium is also essentially chair-like, these results suggest that intramolecular coordination of the Li atom at C(1) with the pseudoaxial *tert*-butoxy group at C(4) in the ground state of **6** (Scheme 5, R=$C(CH_3)_3$) provides sufficient stabilization of this arrangement to more than compensate for the steric interactions that customarily dictate a pseudoequatorial orientation of the substituent. The obvious difficulty is this: why is the cyclization of **6**, with a bulky 4-*tert*-butoxy group, so much more *cis*-selective than are ring closures of seemingly analogous 4-methoxy- (**1**) and 4-MOM-5-hexenyllithium (**5**)? A simple solution to this apparent dilemma, which is consistent with the results presented above, would posit that intermolecular co-association between the alkoxy-substituted 5-hexenyllithium and the LiI present in the reaction medium is inherently less important for the large *tert*-butoxy group in **6** than it is for the smaller methoxy or MOM groups in **1** and **5**, respectively. In short, the sterically demanding *tert*-butyl group in **6** may well inhibit intermolecular association of the organolithium with LiI while having little effect on the entropically favorable intramolecular Li–O interaction that stabilizes the pseudoaxial conformation of **6**.

For comparison purposes, the radical-mediated cyclization of **10** was investigated in benzene solution at 80 °C (Scheme 8). As expected,[17] but in striking contrast to the *cis*-selective cyclization of **6**, ring-closure of the radical derived from iodide **10** gave *trans*-1-*tert*-butoxy-2-methylcyclopentane (**16**) as the major product (*trans* (**16**)/*cis* (**17**)=8.1).



Scheme 8.



Scheme 9.

2.4. 3-Methoxy-5-hexenyllithium

Intramolecular coordination of lithium with a proximate oxygen is thought to be particularly effective when it can occur via a five-membered ring.[5] To explore how such coordination might affect the stereochemistry of the cyclization of a substituted 5-hexenyllithium, the behavior of 3-methoxy-5-hexenyllithium (**7**) was studied. Organolithium **7** was generated (Scheme 9) from iodide **11** in diethyl ether, *n*-pentane–diethyl ether mixtures, or pure *n*-pentane solution at −78 °C. It should be noted that a full 2.2 molar equiv of *t*-BuLi was used to produce **7**; the nettlesome S'_N reaction that plagues the exchange reaction with substrates bearing an allylic leaving group is not a concern in this case.

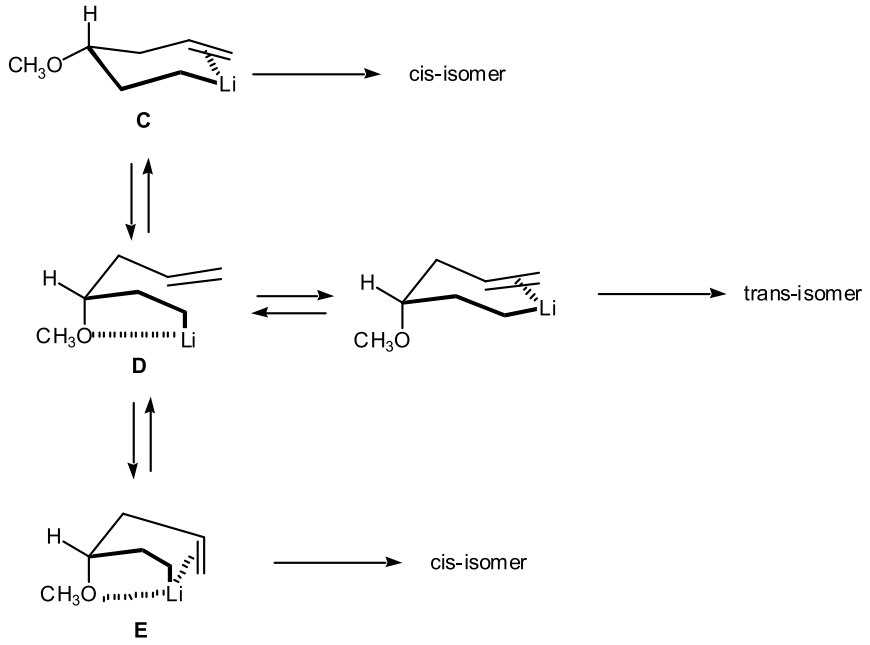
Addition of deoxygenated MeOH to solutions of **7** at −78 °C gives a quantitative yield of 4-methoxy-1-hexene (**21**). When warmed, **7** cyclizes to deliver *trans*- (**19**) and *cis*-1-methoxy-3-methylcyclopentane (**20**) after quench of the reaction mixture. However, there are two interesting features of the cyclization of **7** that were initially surprising: (1) the streochemical course of the cyclization of **7** is much less sensitive to the medium in which the reaction is conducted (Table 4) than are the cyclizations of **1**, **5**, and **6** discussed above, and; (2) the cyclization of **7** is unexpectedly slow in the absence of TMEDA. Indeed, when a solution of **7** in *n*-pentane–diethyl ether (3:2 by vol) was allowed to warm and stand at 23 °C for 1 h, only ~27% of a *cis*-rich mixture of *cis*- (**20**) and *trans*-1-methoxy-3-methylcyclopentane (**19**) was obtained (Table 4, entry 1). High yields of cyclized product (**19**+**20**) were obtained only when the isomerization of **7** was conducted in the presence of TMEDA. These cyclizations invariably gave a *cis*-rich product mixture (Table 4) but the addition of TMEDA does not substantially alter the isomeric composition of the product mixture (Table 4, cf. entries 1 and 2).

It is tempting to ascribe the modestly *cis*-selective cyclization of **7** to ring closure via a conformation having a pseudoequatorial 3-methoxy group (Scheme 10, **C**). This picture is qualitatively similar to that advanced to account for the *cis*-selective ring closures of 3-alkyl-substituted 5-hexenyllithiums.[3] However, the cyclization of **7** is considerably less stereoselective than are the seemingly analogous 3-alkyl-substituted isomerizations[3] and the model does not account for the fact that the cyclization of **7** is much slower than are cyclizations of 3-alkyl-substituted 5-hexenyllithiums.[18] Moreover, this simple rationale for the *cis*-selectivity ignores the potential effects of strong intramolecular coordination of a 3-OCH_3 group with the Li atom at C(1) via a five-membered ring. Such coordination is depicted in Scheme 10 (structures **D** and **E**). Insofar as 5-exo ring closure of a 5-hexenyllithium requires association of the Li atom with the olefinic π-bond, the simultaneous intramolecular coordination of the Li atom with both the 3-methoxy group and the olefinic moiety, which would lead to *cis*-product (**20**), resembles a boat-like

Table 4. Cyclization (Scheme 9) of 3-methoxy-5-hexenyllithium (**7**)[a]

Entry	Solvent system	Temp, °C	Products, % yield[b]		
			21	**19**+**20**	*cis* (**20**)/*trans* (**19**)[c]
1	*n*-C_5H_{12}–Et_2O 3:2 by vol	23	73.2	26.7	5.3
2	TMEDA[d]	23	2.0	98.0	2.6
3	TMEDA[d]	10	8.0	92.0	2.3
4	TMEDA[d]	0	7.4	92.6	2.3
5	TMEDA[d]	−10	11.8	88.1	2.1
6	TMEDA[d]	−20	80.7	19.3	4.0
7	Et_2O+TMEDA	21	<1	99	2.2
8	*n*-C_5H_{12}+TMEDA	0	21.0	79.0	2.4

[a] 4-Methoxy-5-hexenyllithium (**7**) was generated at −78 °C by addition of 2.20 equiv of *t*-BuLi to a solution of iodide **11** in either *n*-pentane–diethyl ether, pure diethyl ether, or in pure *n*-pentane. Where indicated, TMEDA (2.20 molar equiv) was added at −78 °C, the cooling bath was then removed, and the mixture was allowed to warm and stand at the specified temperature for 1 h before the addition of an excess of oxygen-free methanol.
[b] Yields were determined by capillary GC using *n*-heptane as internal standard and correction for detector response.
[c] Ratio of *cis*- (**20**) and *trans*-1-methoxy-3-methylcyclopentane (**19**).
[d] *n*-Pentane–diethyl ether (3:2 by vol) was used.



Scheme 10.

arrangement of atoms (Scheme 10, **E**). Moreover, this scenario nicely accounts for the sluggish nature of the isomerization of **7** since the activation energy for ring closure via a boat-like activated complex would presumably be higher than that for a chair-like transition state.

3. Conclusion

The results presented above demonstrate that the stereochemical outcome of the cyclization of 4-alkoxy substituted 5-hexenyllithiums may be profoundly affected by the medium in which the ring closures are conducted. The cyclization of 4-methoxy- (**1**) and 4-(methoxymethoxy)-5-hexenyllithium (**5**), each of which provides a *trans*-rich mixture of products when the cyclization is conducted in *n*-pentane, diethyl ether, or a pentane–ether mixture, is rendered *cis*-selective in the presence of a lithiophilic Lewis base such as TMEDA or 1,4-dioxane. The cyclization of 4-*tert*-butoxy-5-hexenyllithium (**6**), which is *cis*-selective under all conditions studied, affords a exceedingly high proportion of *cis*-1-*tert*-butoxy-2-methylcyclopentane (**17**) when conducted at −10 °C in the presence of TMEDA (*cis*/*trans*=23.8). The kinetically sluggish ring closure of 3-methoxy-5-hexenyllithium (**7**) is moderately *cis*-selective in a variety of media.

The etiology of these often dramatic solvent effects is attributed to the ability of certain Lewis bases, such as TMEDA and 1,4-dioxane, to competitively complex the lithium iodide salt generated as a co-product from the exchange reaction used to prepare the organolithiums. Sequestration of the LiI salt through preferential complexation with an added ligand is thought to favor intramolecular association of the lithium atom with a pseudoaxial 4-alkoxy substituent leading to a *cis*-selective closure.

4. Experimental

4.1. General procedures

General spectroscopic and chromatographic procedures, methods used for the purification of reagents and solvents, and precautions regarding the manipulation of organolithiums have been previously described.[3,7,19] The concentration of commercial solutions of *t*-BuLi in *n*-heptane was determined immediately prior to use by the method of Watson and Eastham.[20]

The preparations of 6-iodo-3-methoxy-1-hexene (**2**), 3-methoxy-1-hexene (**12**), *trans*-1-methoxy-2-methylcyclopentane (**3**), *cis*-1-methoxy-2-methylcyclopentane (**4**), 1-hexen-3-ol, *trans*-2-methylcyclopentanol, and *cis*-2-methylcyclopentanol have been previously described.[7] Literature procedures, incorporating some minor modifications, were followed for the preparation of 6-chloro-1-hexen-3-ol[21] and 3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-propanal.[22]

4.1.1. 6-Chloro-3-(methoxymethoxy)-1-hexene. A mixture of 2.00 g (14.8 mmol) of 6-chloro-1-hexen-3-ol[21] and 3.0 g of phosphorus pentoxide in 87 mL of dry chloroform and 87 mL of dry dimethoxymethane was stirred at room temperature for 3 h. The reaction mixture then was poured into 100 mL of cold, half-saturated, aqueous sodium carbonate and the black oil remaining in the flask was rinsed with the aqueous sodium carbonate. The aqueous layer was extracted with three 60-mL portions of diethyl ether, the ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20% Et_2O–hexanes, R_f= 0.77) to afford 2.40 g (91%) of the title compound as a colorless oil: ^{1}H NMR δ 1.66–1.73 (m, 2H), 1.79–1.90 (m,

2H), 3.34 (s, 3H), 3.54 (t, J=6.9 Hz, 2H), 3.98–4.01 (m, 1H), 4.50 and 4.67 (AB, J_{AB}=6.7 Hz, 2H), 5.16–5.23 (m, 2H), 5.58–5.65 (m, 1H); ^{13}C NMR δ 28.5, 32.6, 44.8, 55.4, 76.5, 93.8, 117.4, 137.9; HRMS calcd for $C_7H_{13}ClO$ (M^+–CH_2O) m/z 148.0655, found m/z 148.0651.

4.1.2. 6-Iodo-3-(methoxymethoxy)-1-hexene (9). A solution of 3.00 g (16.8 mmol) of 6-chloro-3-(methoxymethoxy)-1-hexene and 5.55 g (36.9 mmol) of dried sodium iodide in 60 mL of dry acetone was heated at gentle reflux overnight under an atmosphere of argon. Inorganic salts were removed by filtration, the solid was washed well with acetone, and the combined filtrate and the washings were concentrated at reduced pressure. The residue was taken up in diethyl ether and the solution was washed with 5% of aqueous sodium thiosulfate, and dried over $MgSO_4$. The solution was concentrated at reduced pressure and the residue was purified by flash chromatography on silica gel (20% Et_2O–hexanes, R_f=0.37) to afford 4.00 g (88%) of the title iodide as a colorless oil: ^{1}H NMR δ 1.60–1.69 (m, 2H), 1.86–1.94 (m, 2H), 3.18 (t, J=6.9 Hz, 2H), 3.34 (s, 3H), 3.97–4.00 (m, 1H), 4.49 and 4.66 (AB, J_{AB}=6.8 Hz, 2H), 5.15–5.22 (m, 2H), 5.57–5.68 (m, 1H); ^{13}C NMR δ 6.4, 29.4, 36.1, 55.5, 76.2, 93.8, 117.4, 137.9; IR (neat) 3077, 2939, 1641, 1436, 1226, 733 cm^{-1}; HRMS calcd for $C_7H_{13}IO$ (M^+–CH_2O) m/z 240.0011, found m/z 240.0009.

4.1.3. 3-(Methoxymethoxy)-1-hexene (15). A mixture of 1.00 g (10.0 mmol) of 1-hexen-3-ol[7] and 2.0 g of phosphorous pentoxide in 60 mL of dry chloroform and 60 mL of dry dimethoxymethane was stirred at room temperature for 3 h. The reaction mixture then was poured into 100 mL of ice-cold, half-saturated, aqueous sodium carbonate and the black oil remaining in the flask was rinsed with aqueous sodium carbonate. The aqueous layer was extracted with 30-mL portions of diethyl ether, the ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10% Et_2O–hexanes, R_f=0.70) to afford 1.30 g (90%) of the known product:[23] ^{1}H NMR δ 0.90 (t, J=7.1 Hz, 3H), 1.34–1.60 (m, 4H), 3.35 (s, 3H), 3.96–3.98 (m, 1H), 4.51 and 4.86 (AB, J_{AB}=6.7 Hz, 2H), 5.13–5.20 (m, 2H), 5.58–5.71 (m, 1H); ^{13}C NMR δ 13.9, 18.6, 37.6, 55.3, 77.2, 93.7, 116.9, 138.6.

4.1.4. *trans*-1-(methoxymethoxy)-2-methylcyclopentane (16). A mixture of 1.00 g (10 mmol) of *trans*-2-methylcyclopentanol[7,11] and 2.0 g of phosphorus pentoxide in 60 mL of dry chloroform and 60 mL of dry dimethoxymethane was stirred at room temperature for 3 h. The reaction mixture then was poured into 50 mL of ice-cold, half-saturated aqueous sodium carbonate and the black oil remaining in the flask was rinsed with aqueous sodium carbonate. The aqueous layer was extracted with 30-mL portions of diethyl ether, the ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% Et_2O–hexanes, R_f=0.65) to afford 1.10 g (77%) of the title compound as a colorless oil: ^{1}H NMR δ 1.00 (d, J=6.7 Hz, 3H), 1.68–1.77 (m, 7H), 3.32 (s, 3H), 3.82–3.84 (m, 1H), 4.54 and 4.62 (AB, J_{AB}=6.7 Hz, 2H); ^{13}C NMR δ 19.1, 22.8, 32.2, 32.8, 39.5, 56.1, 81.6, 97.0; IR (neat) 2954, 1457, 1368, 1147, 923 cm^{-1}. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.34; H, 10.81.

4.1.5. *cis*-1-(Methoxymethoxy)-2-methylcyclopentane (17). A mixture of 1.00 g (10.0 mmol) of *cis*-2-methylcyclopentanol[7,12] and 2.0 g of phosphorus pentoxide in 60 mL of dry chloroform and 60 mL of dry dimethoxymethane was stirred at room temperature for 3 h. The reaction mixture then was poured into 50 mL of ice-cold, half-saturated aqueous sodium carbonate and the black oil remaining in the flask was rinsed with aqueous sodium carbonate. The aqueous layer was extracted with 30-mL portions of diethyl ether, the ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% Et_2O–hexanes, R_f=0.74) to afford 1.30 g (88%) of the title compound as a colorless oil: ^{1}H NMR δ 0.99 (d, J=6.6 Hz, 3H), 1.67–1.76 (m, 7H), 3.34 (s, 3H), 3.91–3.93 (m, 1H), 4.57 and 4.65 (AB, J_{AB}=6.7 Hz, 2H); ^{13}C NMR δ 13.9, 21.8, 31.1, 31.4, 38.5, 55.1, 80.7, 95.2; IR (neat) 2954, 1457, 1368, 1147, 923 cm^{-1}; HRMS calcd for $C_8H_{16}O_2$ m/z 144.1150, found m/z 144.1149.

4.1.6. 3-*tert*-Butoxy-6-chloro-1-hexene. Isobutene gas was bubbled through a mixture of 9.20 g (68.0 mmol) of 6-chloro-1-hexen-3-ol[21] and 5.00 g of Amberlyst-15® in 40 mL of dry hexane. After the reaction was complete, the mixture was filtered, the filtrate washed with hexane, and 500 mg of anhydrous K_2CO_3 was added. Solvent was removed at reduced pressure and the crude product was purified by flash chromatography on silica gel (hexane, R_f=0.76) to afford 11.0 g (85%) of the title compound as a colorless oil: ^{1}H NMR δ 1.20 (s, 9H), 1.55–1.60 (m, 2H), 1.73–1.86 (m, 2H), 3.54 (t, J=6.5 Hz, 2H), 3.92–3.95 (m, 1H), 4.99–5.16 (m, 2H), 5.73–5.86 (m, 1H); ^{13}C NMR δ 28.7, 28.9, 34.5, 45.2, 72.4, 74.0, 113.9, 142.3; HRMS calcd for $C_6H_{11}ClO$ (M^+–C_4H_8) m/z 134.0498, found m/z 134.0497.

4.1.7. 3-*tert*-Butoxy-6-iodo-1-hexene (10). A solution of 1.00 g (5.25 mmol) of 3-*tert*-butoxy-6-chloro-1-hexene and 1.73 g (11.5 mmol) of dried sodium iodide in 20 mL of dry dimethoxymethane was heated at gentle reflux overnight under an atmosphere of argon. The mixture was cooled, filtered by suction, and the solid was washed with DME. The filtrate and washings were concentrated under reduced pressure and the residue was extracted with several portions of diethyl ether until it was white. The ethereal extract was washed with 5% aqueous sodium thiosulfate, dried over $MgSO_4$, and concentrated. The crude iodide was purified by flash chromatography on silica gel (5% Et_2O–hexanes, R_f=0.15) to afford 1.04 g (70%) of the title compound as a colorless oil: ^{1}H NMR δ 1.18 (s, 9H), 1.51–1.56 (m, 2H), 1.88–1.93 (m, 2H), 3.17 (t, J=6.6 Hz, 2H), 3.91–3.94 (m, 1H), 4.99–5.15 (m, 2H), 5.72–5.85 (m, 1H); ^{13}C NMR δ 7.1, 28.7, 29.8, 38.0, 72.0, 74.1, 113.9, 142.2; IR (neat) 3075, 2971, 1642, 1428, 1364, 1227, 730 cm^{-1}; HRMS calcd for $C_6H_{11}IO$ (M^+–C_4H_8) m/z 225.9855, found m/z 225.9850.

4.1.8. 3-*tert*-Butoxy-1-hexene (18). Isobutylene gas was bubbled through a mixture of 2.00 g (20.0 mmol) of 1-hexen-3-ol[7] and 2.00 g of Amberlyst-15® in 13 mL of

dry hexane. After the reaction was complete, the mixture was filtered, the filtrate washed with hexane, and 500 mg of anhydrous K_2CO_3 was added. Solvent was removed at reduced pressure and the crude product was purified by flash chromatography on silica gel (hexane, $R_f=0.39$) to afford 2.77 g (88%) of the title compound: ^{1}H NMR δ 0.88 (t, $J=$ 6.9 Hz, 3H), 1.17 (s, 9H), 1.18–1.40 (m, 4H), 3.87–3.89 (m, 1H), 4.95–5.12 (m, 2H), 5.74–5.86 (m, 1H); ^{13}C NMR δ 14.1, 18.9, 28.7, 39.6, 72.9, 73.8, 113.2, 143.0; IR (neat) 3076, 2970, 1641, 1463, 1365, 1197, 1019, 681 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.46; H, 12.55.

4.1.9. *trans*-1-*tert*-Butoxy-2-methylcyclopentane (16). Isobutylene gas was bubbled through a mixture of 0.50 g (5.0 mmol) of *trans*-2-methylcyclopentanol[7,11] and 1.00 g of Amberlyst-15® in 8.0 mL of dry hexane. After the reaction was complete, the mixture was filtered, the filtrate washed with hexane, and 500 mg of anhydrous K_2CO_3 was added. Solvent was removed at reduced pressure and the crude product was purified by flash chromatography on silica gel (hexane, $R_f=0.19$) to afford 0.66 g (85%) of the title product as a colorless oil: ^{1}H NMR δ 0.95 (d, $J=$ 6.6 Hz, 3H), 1.15 (s, 9H), 1.48–1.79 (m, 7H), 3.37–3.39 (m, 1H); ^{13}C NMR δ 17.8, 21.9, 28.7, 31.3, 34.4, 41.3, 72.7, 79.9; IR (neat) 2969, 1462, 1363, 1200, 901 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.70; H, 12.63.

4.1.10. *cis*-1-*tert*-Butoxy-2-methylcyclopentane (17). Isobutylene gas was bubbled through a mixture of 1.00 g (10.0 mmol) of *cis*-2-methylcyclopentanol[7,12] and 2.00 g of Amberlyst-15® in 8.0 mL of dry hexane. After the reaction was complete, the mixture was filtered, the filtrate washed with hexane, and 500 mg of anhydrous K_2CO_3 was added. Solvent was removed at reduced pressure and the crude product was purified by flash chromatography on silica gel (hexane, $R_f=0.60$) to afford 1.35 g (87%) of the title ether as a colorless oil: ^{1}H NMR δ 0.90 (d, $J=6.9$ Hz, 3H), 1.15 (s, 9H), 1.37–1.67 (m, 7H), 3.82–3.84 (m, 1H); ^{13}C NMR δ 14.5, 21.4, 28.5, 31.6, 33.7, 38.2, 72.6, 74.8; IR (neat) 2968, 1461,1200, 1092, 1054, 900 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.41; H, 13.09.

4.1.11. 3-Methoxy-5-hexen-1-ol. Allylmagnesium chloride in THF (48.0 mL of a 2.0 M solution, 96 mmol) was added dropwise at room temperature under an atmosphere of nitrogen to a solution of 13.0 g (82.3 mmol) of 3-[(tetrahydro-*2H*-pyran-2-yl)oxy]propanal[22] in 40 mL of dry THF. The resulting mixture was heated at gentle reflux for 1H, then cooled in an ice-bath and cautiously hydrolyzed by dropwise addition of 10 mL of water followed by 10 mL of saturated, aqueous K_2CO_3. The mixture was extracted with three 30-mL portions of Et_2O, the combined ethereal extracts were dried ($MgSO_4$), concentrated at reduced pressure, and the residue was purified by flash chromatography on silica gel (20% EtOAc–hexanes, $R_f=0.28$) to give 11.6 g (70%) of 6-[tetrahydro-*2H*-pyran-2-yl)oxy]-1-hexen-4-ol: ^{1}H NMR (two diastereomers) δ 1.49–1.77 (m, 8H), 2.19–2.24 (m, 2H), 3.09 (br s, 1H), 3.48–3.60 (m, 2H), 3.79–3.89 (m, 3H), 4.56 (t, $J=4.2$ Hz, 1H), 5.03–5.10 (m, 2H), 5.76–5.86 (m, 1H); ^{13}C NMR (two diastereomers) δ 19.3, 19.5, 25.2, 30.4, 30.6, 35.8, 35.9, 41.8, 41.8, 62.1, 62.5, 65.7, 65.9, 69.7, 70.3, 98.8, 99.0, 117.2, 117.3, 134.1, 134.9.

A stirred suspension of 3.50 g (146 mmol) of oil-free sodium hydride in 60 mL of dry THF was heated to ~50 °C and a solution of 7.70 g (38.5 mmol) of the 6-[(tetrahydro-*2H*-pyran-2-yl)oxy]-1-hexene-4-ol and 3.62 mL (58.1 mmol) of methyl iodide in 20.0 mL of dry THF was added dropwise over a 45 min period. The resulting mixture was heated at to ~50 °C for an additional 1H, then cooled in an ice-bath, and 10 mL of water was added. The resulting mixture was extracted several times with diethyl ether, the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give an oil which was purified by flash chromatography on silica gel (10% EtOAc–hexanes, $R_f=$ 0.42) to afford 7.00 g (85%) of 4-methoxy-6-[(tetrahydro-*2H*-pyran-2-yl)oxy]-1-hexene: ^{1}H NMR δ 1.47–1.81 (m, 8H), 2.24–2.28 (m, 2H), 3.31 (s, 3H), 3.34–3.39 (m, 2H), 3.77–3.84 (m, 2H), 4.54 (t, $J=5.1$ Hz, 1H), 5.01–5.08 (m, 2H), 5.73–5.83 (m, 1H); ^{13}C NMR δ 19.6, 25.5, 30.7, 33.8, 37.9, 56.6, 62.2, 64.1, 77.5, 98.7, 117.7, 134.6.

The pH of a solution of 13.0 g (65.0 mmol) of 4-methoxy-6-[(tetrahydro-*2H*-pyran-2-yl)oxy]-1-hexene in 200 mL of ethyl alcohol was adjusted to ~3 by the dropwise addition of 0.1 M aqueous hydrochloric acid. The resulting solution was heated at reflux for 50 min, allowed to cool to room temperature, and then poured into 25 mL of water and extracted with diethyl ether. The ethereal extract was dried ($MgSO_4$), concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (20% Et_2O–hexanes, $R_f=0.16$) to give 8.00 g (95%) of the title compound as a colorless oil: ^{1}H NMR δ 1.65–1.76 (m, 2H), 2.23–2.35 (m, 2H), 2.83 (br s, 1H), 3.33 (s, 3H), 3.37–3.47 (m, 1H), 3.70 (t, $J=6.1$ Hz, 2H), 5.01–5.08 (m, 2H), 5.65–5.89 (m, 1H); ^{13}C NMR δ 35.7, 37.4, 56.5, 60.5, 79.9, 117.3, 134.1; IR (neat) 3400, 3073, 2932, 1637, 1436, 1359, 1087 cm^{-1}. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.22; H, 10.66.

4.1.12. 6-Iodo-4-methoxy-1-hexene (11). Following the general procedure of Crossland and Servis,[24] 3.00 g (23.1 mmol) of 3-methoxy-5-hexene-1-ol was converted to its mesylate. The crude mesylate was added to a solution of 8.00 g (53.3 mmol) of dry sodium iodide in 80 mL of acetone and the mixture was stirred at room temperature under and atmosphere of nitrogen for 10 h and then heated at gentle reflux for 45 min. Inorganic salts were then removed by filtration, the solid was washed well with acetone, and the combined filtrate and washings were concentrated by rotary evaporation. The residue was taken up in diethyl ether and the solution was washed with 5% aqueous sodium thiosulfate solution and dried ($MgSO_4$). The solution was concentrated under reduced pressure and the residue was purified by passage through a short column of activated alumina using pentane as the eluent to give 5.00 g (90%) of the title iodide as an oil: ^{1}H NMR δ 1.89–1.97 (m, 2H), 2.23–2.30 (m, 2H), 3.24 (t, $J=7.0$ Hz, 2H), 3.36 (s, 3H), 3.28–3.34 (m, 1H), 5.03–5.11 (m, 2H), 5.68–5.81 (m, 1H); ^{13}C NMR δ 2.7, 37.1, 37.8, 57.0, 79.8, 117.5, 133.9; IR (neat) 3062, 2975, 2921, 2823, 1637, 1436, 1354, 1092, 913 cm^{-1}. Anal. Calcd for $C_7H_{13}OI$: C, 35.02; H, 5.46. Found: C, 34.76; H, 5.22.

4.1.13. 4-Methoxy-1-hexene (21). A stirred suspension of 1.50 g (62.5 mmol) of oil-free sodium hydride in 30 mL of dry THF was heated to ~50 °C under an atmosphere of nitrogen and a solution of 2.00 g (20.0 mmol) of 1-hexene-4-ol[25] and 2.0 mL (32 mmol) of methyl iodide in 10 mL of dry THF was added dropwise over a 30 min period. The resulting mixture was heated at ~50 °C for an additional 1 h. The reaction mixture was then cooled in an ice bath and hydrolyzed by addition of 10 mL of water. The resulting solution was extracted several times with diethyl ether, the combined extracts were dried ($MgSO_4$), and solvent was removed by rotary evaporation. Preparative GC on a 10-ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 100 °C afforded 2.00 g (85%) of the ether: ^{1}H NMR δ 0.86 (t, J=7.4 Hz, 3H), 1.42–1.56 (m, 2H), 2.20–2.25 (m, 2H), 3.07–3.16 (m, 1H), 3.31 (s, 3H), 4.99–5.07 (m, 2H), 5.70–5.86 (m, 1H); ^{13}C NMR δ 9.3, 25.8, 37.3, 56.4, 81.6, 116.6, 135.0. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.34; H, 12.68.

4.1.14. *trans*-(19) and *cis*-1-Methoxy-3-methylcyclopentane (20). A commercial (Aldrich) sample of *cis*- and *trans*-3-methylcyclopentanol was found to consist of 40% of the *cis*-isomer and 60% of the *trans*-isomer: the isomeric composition was determined by NMR; both ^{1}H and ^{13}C NMR of the isomers have been assigned.[26] The title ethers were prepared from this mixture. Thus, a stirred suspension of 1.50 g (62.5 mmol) of oil-free sodium hydride in 30 mL of dry THF was heated at ~50 °C under an atmosphere of nitrogen and a solution of 2.00 g (20.0 mmol) of the isomeric 2-methylcyclopentanols (*trans*/*cis*=3:2) and 2.00 mL (31.9 mmol) of methyl iodide in 15 mL of dry THF was added dropwise over a 30 min period. The resulting mixture was heated at ~50 °C for an additional 1 h. The reaction mixture was then cooled in an ice bath and hydrolyzed by addition of 3 mL of water. The resulting solution was extracted several times with diethyl ether, the combined extracts were dried ($MgSO_4$), and solvent was removed by rotary evaporation. Preparative GC on a 10-ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 100 °C afforded 2.00 g (89%) of a mixture of the *trans*- and *cis*-isomers of the ether (*trans*/*cis*=3:2): ^{1}H NMR δ 0.94 (d, J=6.7 Hz, 3H, *trans* isomer), 1.00 (d, J=6.5 Hz, 3H, *cis* isomer), 1.03–2.10 (m, 7H), 3.22 (s, 1H), 3.73–3.79 (m, 1H); ^{13}C NMR δ 20.5, 20.8, 31.9, 32.1, 32.3, 32.6, 32.9, 40.7, 41.0, 56.1, 56.4, 83.0. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.29; H, 12.40.

4.2. General procedure for the preparation of 5-hexenyllithiums by lithium–iodine exchange

The substituted 5-hexenyllithiums (**1**, **5**, **6**, and **7**) were prepared from the corresponding iodides following our general protocol.[10] Typically, a 0.1 M solution of the iodide in either *n*-pentane, diethyl ether, or an *n*-pentane–diethyl ether mixture containing an accurately weighed quantity of *n*-heptane as internal standard was cooled under an argon atmosphere to −78 °C (acetone-dry ice bath) and 2.20 molar equiv of *t*-BuLi (1.75 equiv of *t*-BuLi was used for the 4-alkoxy substituted substrates) in *n*-pentane was added dropwise via syringe over a period of 5 min. The mixture was stirred at −78 °C for 5 min, and the organolithium was used for subsequent reactions.

4.3. General procedure for the cyclization of alkoxy-substituted 5-hexenyllithiums

The organolithiums generated as described above were treated in one of the following ways. (A) *Quench at −78 °C*. Dry, deoxygenated MeOH or MeOD (1.0 mL) was added to the cold reaction mixture and the cooling bath was removed. (B) *Cyclization at elevated temperatures*. The cooling bath was removed, and the solution was allowed to warm and stand at the appropriate temperature for 1 h under a blanket of argon before the addition of 1.0 mL of dry, deoxygenated MeOH or MeOD. (C) *Cyclization in the presence of additives*. The organolithium solution was maintained at −78 °C under a blanket of argon and the dry, deoxygenated additive (typically 1.75 molar equiv of TMEDA or 3.0 equiv of 1,4-dioxane) was added by syringe. The resulting mixture was stirred for an additional 5 min at −78 °C, and then allowed to warm and stand at the appropriate temperature for 1 h under a blanket of argon prior to the addition of 1.0 mL of dry, deoxygenated MeOH or MeOD. Reaction mixtures were washed with water, dried ($MgSO_4$), and analyzed by GC on a 25-m×0.20-mm HP-1 cross-linked methyl silicone fused-silica capillary column using temperature programming (35 °C for 20 min, 30 °C/min to 250 °C) and by GC–MS on a 25-m×0.20-mm HP-5 methyl phenyl (20%) silicone fused-silica capillary column using temperature programming (35 °C for 20 min, 30 °C/min to 250 °C). Reaction products were identified by comparison of their GC retention times and mass spectra with those of authentic samples. All yields reported in the Tables were corrected for detector response under the conditions of the analysis using accurately weighed samples of pure product and standard.

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Can relief of ring-strain in a cyclopropylmethyllithium drive the Brook rearrangement?

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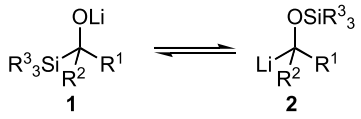
Abstract—α-Cyclopropyl-α-trialkylsilyl alkoxides were formed either by addition of cyclopropyllithiums to acylsilanes or by addition of organolithiums to a cyclopropylformylsilane. [1,2]-Brook rearrangement led to α-silyloxy organolithiums which on warming underwent cyclopropane ring opening and [1,5]-retro-Brook rearrangement to yield γ-silyl ketones. Despite the favourability of the cyclopropane ring opening, the Brook rearrangement still required the presence of an anion stabilising group to proceed. β-Silylketones were similarly formed by Brook–retro-Brook rearrangement on warming acylsilanes with a vinyllithium.

1. Introduction

The 1,2-Brook rearrangement[1] of α-silyl oxyanions to α-silyloxy anions (Scheme 1) has been studied in detail[1–7] and is typically a reversible process proceeding via a pentacoordinate silicon intermediate.[8–11] With catalytic base, the reaction can be considered an equilibrium between neutral, protonated species, and the strength of the Si–O bond (about 500–520 kJ mol^{-1}) compared with the Si–C bond (about 310–350 kJ mol^{-1}) means that, provided the anion **2** forms reasonably rapidly (some degree of stabilisation is required), Brook rearrangement (carbanion formation) is favoured over retro-Brook rearrangement (alkoxide formation). Organolithiums **2** may be present as intermediates in the catalytic Brook rearrangement, but their reactivity cannot be exploited under these conditions.

With stoichiometric organolithium bases, the reaction is an equilibrium between the alkoxide **1** and the organolithium **2**; the organolithium **2** may be formed quantitatively, and the rearrangement therefore provides a potentially very valuable synthesis of α-oxygen substituted organolithiums.[12] Stabilisation of the "carbanion" by electron-withdrawing (PhS etc.) or conjugating (vinyl, or phenyl) groups favours Brook rearrangement: formation of conjugated or α-phenylthio organolithiums by Brook rearrangement in the presence of THF or TMEDA has been widely used.[13–28]



Scheme 1. The 1,2-Brook rearrangement.

Lansbury[29] showed that cyclopropylmethyllithium **3** is unstable, and rearranges to homoallyllithium **4** in a matter of hours at −70 °C or minutes at −20 °C (Scheme 2). Ring opening reactions of cyclopropylmethyllithiums have more recently been employed in the study of the stereospecificity of the reverse reaction[30] and in the synthesis of homoallylically functionalised compounds from cyclopropanes.[31,32] With the aim of developing new methods for the synthesis of functionalised organolithiums,[12] we set out to investigate whether an equilibrium Brook rearrangement could be driven to completion by exploiting a similar loss of cyclopropyl ring strain.[†] Scheme 3 illustrates the proposed strategy. The oxy-anion **5** and silyl ether **6** should be in equilibrium, but the collapse of the strained cyclopropyl ring to form lithiated species **7** removes **6** from the equilibrium, forcing the reaction to completion and giving

Keywords: Organolithium; Cyclopropane; Silicon; Anion; Rearrangement.
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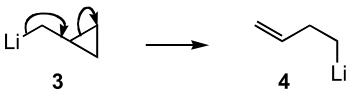
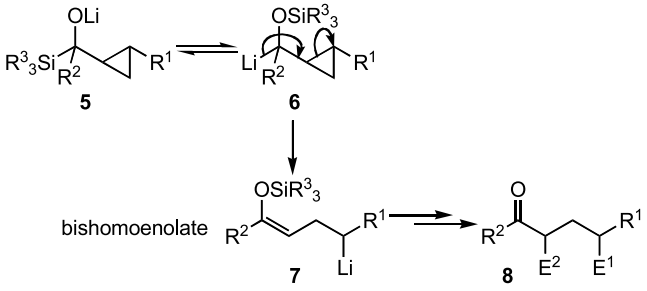
[†] Lindermann and Ghannam[8] carried out a retro-Brook rearrangement of a cyclopropyl-substituted anion without cyclopropyl ring-opening. However, the anion was kept at −15 °C for only 15 min: we hoped to use control of temperature or cyclopropane substitution to promote the ring opening. After submission of this manuscript, Takeda et al. reported a cascade Brook rearrangement–cyclopropane ring opening: see Okugawqa and Tekeda *Org. Lett.* **2004**, *6*, 2973].



Scheme 2. Ring opening of a cyclopropylmethyllithium.



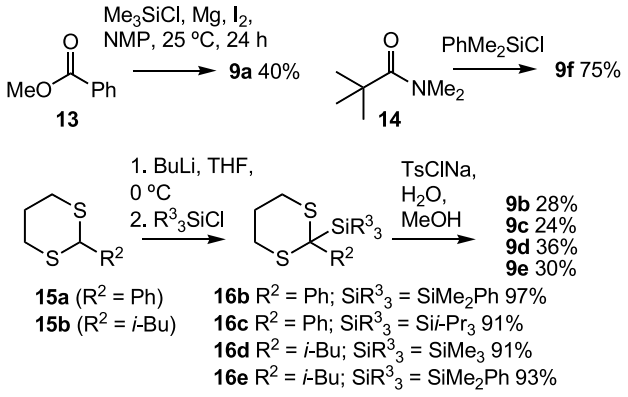
Scheme 3. Driving a Brook rearrangement.

useful organolithium products whatever the favourability or otherwise of the Brook rearrangement itself. The expected products of the reaction will be the homoallyllithium **7**, an unusual d^2+d^4 (bishomoenolate) synthon[33] of which electrophilic quench of firstly the organolithium and secondly the silyl enol ether should yield the products **8**.

The key intermediate in the route is the α-silyl oxyanion **5**. Two connective routes to **5** present themselves, represented in Scheme 4 by disconnections *a* (to acyl silanes **9** and cyclopropyllithiums **10**) and *b* (to cyclopropylformylsilane **11** and a more general family of organolithiums **12**). Each has its advantages, and we tried both, starting with disconnection *a*.‡

2. Synthesis of the starting materials

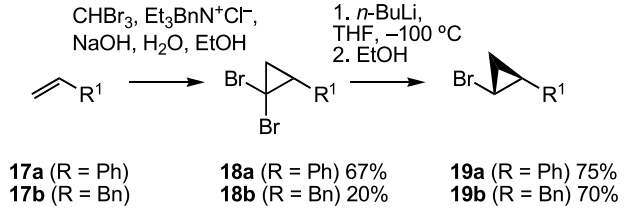
Acylsilanes **9** were prepared by three published methods (Scheme 5). Benzoylsilane **9a** was made from methyl benzoate by the method of Prakash et al.,[34] while **9b–9e** were made by silylation of the appropriate dithianes **15** followed by oxidative hydrolysis of the products **16**.[28] The



Scheme 5. Synthesis of acylsilanes.

non-enolisable **9f** was made by acylation of phenyldimethylsilyllithium with *N*,*N*-dimethylpivalamide **14**.[35]

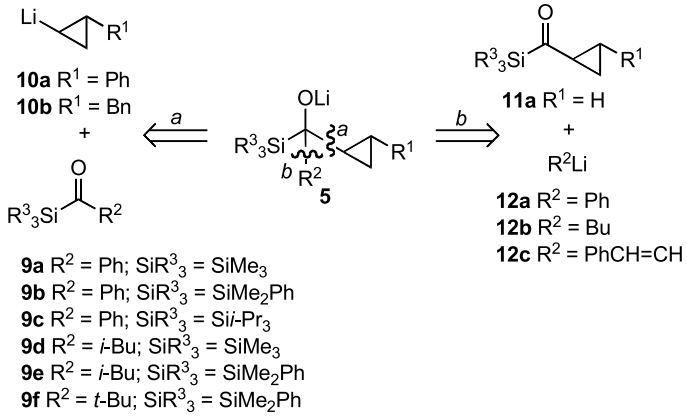
Bromocyclopropane precursors **19** of the cyclopropyllithiums **10** were prepared from styrene or allylbenzene **17a** or **17b** by cyclopropanation with dibromocarbene followed by mono-bromine-lithium exchange of the dibromocyclopropane **18a** or **18b** and protonation to yield **19a** and **19b** as single diastereoisomers (Scheme 6).[36]



Scheme 6. Synthesis of bromocyclopropanes.

3. Brook rearrangements

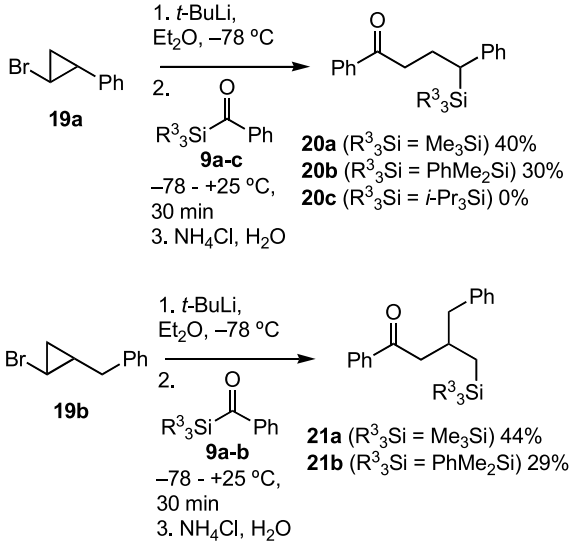
The bromocyclopropanes **19a** and **19b** were transmetallated with *t*-BuLi in ether at −78 °C to afford the cyclopropyllithiums **10a** and **10b**, and acylsilanes **9a–c** were added. The reaction mixtures were allowed to warm to room



Scheme 4. Routes to the rearrangement precursor.

‡ Reich[28] and Takeda[19–27] have demonstrated the utility of Brook rearrangements initiated by nucleophilic attack on acylsilanes.

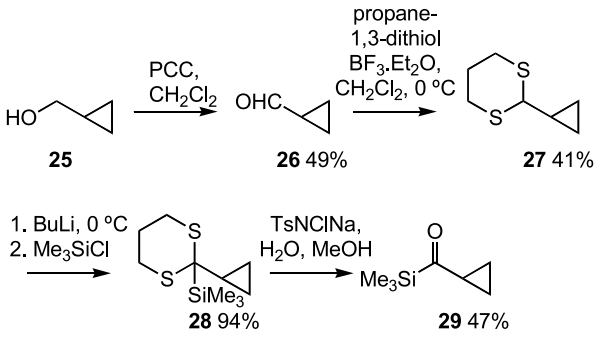
temperature over 30 min and quenched with ammonium chloride to give the ketones **20** and **21** as shown in Scheme 7.



Scheme 7. γ-Silyl ketones from acylsilanes.

The formation of **20** and **21** is clearly the result of a Brook rearrangement and cyclopropane opening as anticipated, with the regioselectivity of cyclopropane opening governed by the anion-stabilising ability of R^1. Scheme 8 shows a proposed mechanism via an intermediate represented as organolithium **6**. R^1=Ph generates benzylic organolithium **7** and R^1=Bn generates in preference the primary organolithium **23**. However, these organolithiums are unstable with respect to a second, 1,5-retro-Brook, rearrangement,[31,37] which presumably results in the formation of the C-silylated enolates **22** and **24** and thence **20** and **21**. Only with R^3=*i*-Pr was the retro-Brook rearrangement prevented, but in this case no identifiable product was obtained from the reaction. For the retro-Brook rearrangement to occur, it is necessary for the rearranging silyl enol ethers **7** and **23** to have *E* geometry: it may be that the *Z* silyl enol ethers are also formed but decompose.

Further studies of the scope and mechanism of the reaction were hindered by the need for structural variation in both acylsilane and bromocyclopropane components. We therefore decided to continue work on the rearrangement by synthesising the key intermediate **5**[38] via disconnection *b*, studying the reactions of cyclopropylformylsilane **29**. This acylsilane was synthesised from cyclopropylmethanol **25** by oxidation to the aldehyde **26**, dithiane formation, silylation and hydrolysis (Scheme 9).



Scheme 9. Synthesis of a cyclopropylformylsilane.

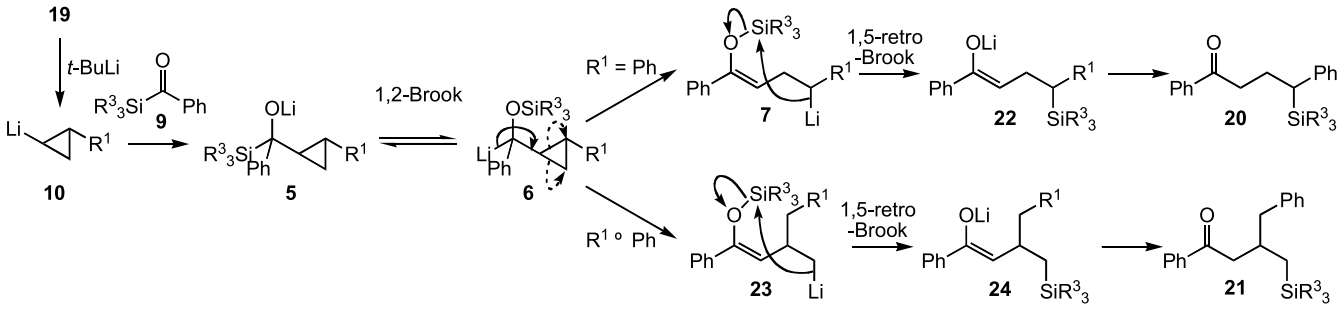
The reactions of **29** were extremely revealing with regard to the structural features and conditions required for Brook rearrangement-ring opening to succeed, and in fact showed that our original proposition—that even an unfavourable Brook rearrangement would be pushed to completion by relief of ring-strain—was flawed. Acylsilane **29** was treated with either phenyllithium or *n*-butyllithium and the reaction mixture was allowed to warm to either −30, 0. +25 or +45 °C, as shown in Table 1 and Scheme 10. In each case, one of three products **30**, **31** or **32** was obtained.

Table 1. Products of addition-rearrangement reactions of **29**

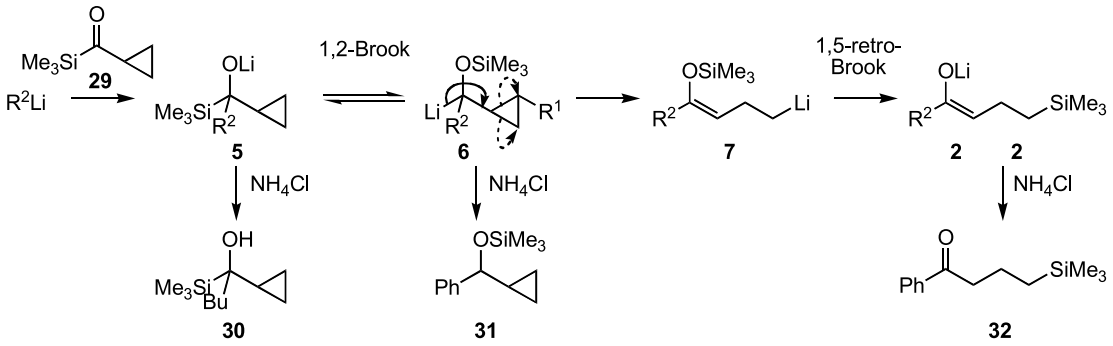
Entry	R^2=	Temperature of quench (°C)	Product	Yield (%)
1	Ph	−30	**31**	31[a]
2	Ph	0	**31**	37[b]
3	Ph	+25	**32**	48[b]
4	*n*-Bu	−30	**30**	70[a]
5	*n*-Bu	0	**30**	71[b]
6	*n*-Bu	+25	**30**	70[a]
7	*n*-Bu	+45	**30**	50[a]

[a] By NMR.
[b] Isolated yield.

With phenyllithium, the product **31** of addition and 1,2-Brook rearrangement was formed at both −30 and 0 °C (entries 1 and 2), indicating that the Ph group alone is sufficient to favour the Brook rearrangement and that the release of cyclopropyl ring strain plays only the minor role in this reaction. Only on warming to room temperature was the silane **32** resulting from cyclopropyl ring opening and



Scheme 8. Mechanism of the Brook–ring-opening–retro-Brook sequence.



Scheme 10. Addition–rearrangement reactions of **29**.

1,5-retro-Brook rearrangement observed (entry 3), showing that cyclopropane ring opening is relatively slow. With *n*-butyllithium the only product observed, even after warming the reaction mixture to 45 °C, was the alcohol **30** simply resulting from addition to the acylsilane (entries 4–7). Cyclopropyl ring opening is apparently unable to promote the Brook rearrangement when there is no anion stabilising group adjacent to the forming organolithium centre. We conclude therefore that while cyclopropyl ring-opening can provide means of transforming the products of Brook rearrangement into γ-silylated ketones, it can only do so when the Brook rearrangement is itself inherently favourable.

4. Synthesis of β-silylketones

Aiming to extend the range of substrates and products participating in the Brook rearrangement-ring opening sequence, we treated **29** with phenylvinyllithium (generated from β-bromostyrene) and allowed the mixture to warm to room temperature. We hoped to observe ring opening, followed perhaps by readdition to the alkene to complete a new annelation procedure. However, the product **36a** isolated from this reaction, in 42% yield, still contained an intact cyclopropane, and was evidently the result of 1,2-Brook rearrangement followed by 1,4-retro-Brook rearrangement, a reaction now made possible by the allylic system generated on Brook rearrangement (Scheme 11). By-products resulting from 1,4-retro-Brook rearrangement have been observed in related reactions.[28]

This reaction struck us as a potentially valuable synthesis of β-silylketones, and we therefore treated the acylsilanes **9a**, **9e** and **9f** with phenylvinyllithium under similar conditions. Acylsilane **9a**, which should generate a pentadienyllithium, gave no identifiable products, possibly because of the instability of the pentadienyllithium intermediate. However, the non-aromatic acylsilanes **9e** and **9f** did lead to formation of low to moderate yields of β-silylketones, with successful rearrangement from **9e** possibly compromised by its enolisable proton.

5. Conclusion

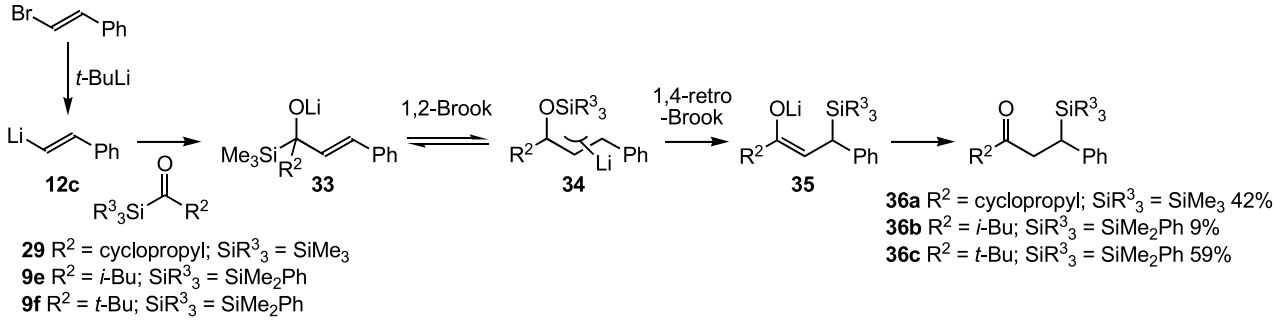
Brook rearrangement of α-silyl-α-cyclopropyl alkoxides can generate cyclopropylmethyllithiums which, on warming, undergo ring opening and 1,5-retro-Brook rearrangement to yield γ-silyl ketones. The Brook rearrangement requires the presence of an anion-stabilising group (Ph, vinyl) at the forming anionic centre to proceed: release of cyclopropyl ring strain alone is insufficient to drive the rearrangement.

6. Experimental

6.1. General methods

These have been published previously.[39]

6.1.1. Phenyltrimethylsilylmethanone 9a.[34] By the procedure of Prakash et al.,[34] magnesium powder (1.20 g, 50.0 mmol), iodine (0.20 g, 0.8 mmol), NMP (60 mL) and excess chlorotrimethylsilane (21.7 g, 0.20 mmol) were mixed and stirred for 5 min. Methyl benzoate (3.40 g, 25.0 mmol) was added drop-wise. The reaction was stirred for 18 h at room temperature and quenched with saturated aqueous ammonium chloride solution. Dilute aqueous



Scheme 11. Synthesis of β-silylketones.

hydrochloric acid (2.0 mol dm^{-3}, 50 mL) was cautiously added and the mixture was left to stir for 1 h. The layers were separated and the aqueous portion was extracted with pentane (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude product. Purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 49:1 yielded the acylsilane **9a** as a bright yellow oil (1.78 g, 40%), with spectroscopic data as reported.[34]

6.1.2. Dimethylphenyl-(2-phenyl-[1,3]dithian-2-yl)-silane 16b.[40] By a modification of the procedure of Reich et al.,[28] 2-phenyl-1,3-dithiane (5.04 g, 25.7 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. *n*-Butyllithium (13.8 mL, 2.13 M solution in pentane, 28.1 mmol) was added drop-wise over 45 min. The solution turned deep yellow-orange. After 2 h chlorodimethylphenylsilane (5.00 g, 29.3 mmol) was added. Water (75 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3×50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to yield the silane **16b** as white needles (8.20 g, 97%), mp 74–76 °C; spectroscopic data as reported.[40]

6.1.3. Triisopropyl-(1-phenyl-[1,3]dithian-2-yl)-silane 16c. In a similar way, 2-phenyl-1,3-dithiane (4.47 g, 22.8 mmol), chlorotriisopropylsilane (5.00 g, 25.93 mmol), *n*-butyllithium (11.53 mL, 2.13 M solution in pentane, 24.6 mmol) and THF (50 mL) gave the silane **16c** as a white crystalline solid (7.30 g, 91%), mp 34–36 °C; R_f (petrol–ethyl acetate, 49:1) 0.75; ν_{max} (film)/cm^{-1} 2946, 2904, 2867 (C–H), 1273 and 883 (C–Si); δ_H (300 MHz; $CDCl_3$) 8.12–7.18 (5H, m, Ar*H*), 2.81 (2H, dt, J=13.5, 2.5 Hz, $SCH_{2A}CH_2$), 2.39 (2H, td, J=14.0, 4.0 Hz, $SCH_{2B}CH_2$), 2.12–1.84 (2H, m, SCH_2CH_2), 1.42–1.31 (3H, m, $CH(CH_3)_2$×3) and 1.16 (18H, d, J=7.0 Hz, $CH(CH_3)_2$×3); δ_C (75 MHz; $CDCl_3$) 141.6, 130.9, 128.5, 125.5 (Aromatic), 25.9, 25.7, 25.5, 20.0 and 12.2; *m*/*z* 353 (100%, $M+H^+$); Found M^+, 352.1708. $C_{19}H_{32}S_2Si$ requires *M* 352.1715.

6.1.4. (2-Isobutyl-[1,3]dithian-2-yl)-trimethylsilane 16d. In a similar way, 2-isobutyl-1,3-dithiane (5.00 g, 30.7 mmol), chlorophenyldimethylsilane (5.97 g, 35.04 mmol), *n*-butyllithium (14.6 mL, 2.27 M solution in pentane, 33.2 mmol) and THF (50 mL) gave the silane **16d** as a colourless oil (6.94 g, 91%); R_f (petrol–ethyl acetate, 49:1) 0.79; ν_{max} (film)/cm^{-1} 2952, 2910, 2865 (C–H), 1251 and 818 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.78–7.37 (5H, m, Ar*H*), 3.00 (2H, ddd, J=14.5, 11, 3.5 Hz, $SCH_{2A}CH_2$), 2.51 (2H, ddd, J=14.5, 5.5, 3.5 Hz, $SCH_{2B}CH_2$), 2.06 (2H, d, J=7.0 Hz, CH_2-2), 2.04–1.82 (3H, m, SCH_2CH_2), 0.97 (6H, d, J=6.5 Hz, $(CH_3)_2CHCH_2$-2) and 0.60 (6H, s, $Si(CH_3)_2$); δ_C (75 MHz; $CDCl_3$) 136.5, 135.3, 129.9, 127.9 (Aromatic), 46.1, 39.8, 27.4, 25.3, 24.6, 1.3 and −3.1; *m*/*z* 311 (15%, $M+H^+$); Found M^+, 310.1239. $C_{16}H_{26}S_2Si$ requires *M* 310.1245.

6.1.5. (2-Isobutyl-[1,3]dithian-2-yl)-dimethylphenylsilane 16e. In a similar way, 2-isobutyl-1,3-dithiane (2.51 g, 15.46 mmol), chlorotrimethylsilane (1.84 g, 17.0 mmol), *n*-butyllithium (7.34 mL, 2.27 M solution in pentane, 16.6 mmol) and THF (20 mL) gave the silane **16e** as a colourless oil (4.46 g, 93%); R_f (petrol–ethyl acetate, 49:1) 0.83; ν_{max} (film)/cm^{-1} 2954, 2910, 2867 (C–H), 1249 and 844 (Si–C); δ_H (300 MHz; $CDCl_3$) 3.07 (2H, tq, J=12.0, 1.5 Hz, $SCH_{2A}CH$), 2.52 (2H, double septuplet, J=14.5, 1.5 Hz, $SCH_{2B}CH_2$), 2.18 (2H, td, J=5.0, 1.5 Hz, CH_2-2), 2.12–1.84 (3H, m, SCH_2CH_2 and $CHCH_2$-2), 1.08 (6H, td, J=6.5, 1.0 Hz, $(CH_3)_2CHCH_2-2$) and 0.25 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 45.7, 39.3, 27.4, 25.3, 25.1, 24.0 and −2.0; *m*/*z* 249 (100%, $M+H^+$); Found M^+, 249.1167. $C_{11}H_{24}S_2Si$ requires *MH* 249.1162.

6.1.6. (Dimethylphenylsilyl)phenylmethanone 9b.[41] By a modification of the method of Reich et al.,[28] a stirred solution of **16b** (8.00 g, 24.2 mmol) in methanol (84 mL) and water (23 mL) at 0 °C was treated with chloramine-T hydrate (33.87 g, 0.12 mol) in portions over 45 min. After an additional 30 min the mixture was allowed to warm to room temperature and allowed to stir at this temperature for 45 min. Water (10 mL) was added, and the mixture was extracted with pentane (7×30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 29:1 yielded the acylsilane **9b** as a yellow oil (1.63 g, 28%); spectroscopic data as reported.[41]

6.1.7. Phenyltriisopropylsilylmethanone 9c.[42] In a similar manner, **15c** (7.16 g, 20.33 mmol), chloramine-T hydrate (29.6 g, 0.11 mol), methanol (84 mL) and water (20 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 99:1, the acylsilane **9c** as a yellow oil (1.28 g, 24%); R_f (petrol–ethyl acetate, 49:1) 0.58; ν_{max} (film)/cm^{-1} 2945, 2890, 2867 (C–H), 1611 (C=O), 1204 and 882 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.84–7.48 (5H, m, Ar*H*), 1.54 (3H, septuplet, J=7.5 Hz, $CH(CH_3)_2$×3) and 1.17 (18H, d, J=7.5 Hz, $CH(CH_3)_2$×3); δ_C (75 MHz; $CDCl_3$) 236.4 (*C*=O), 143.7, 132.6, 128.8, 127.3 (Aromatic), 19.1 and 12.6.

6.1.8. 3-Methyltrimethylsilylbutan-1-one 9d.[43] In a similar way, **16d** (6.50 g, 26.20 mmol), chloramine-T hydrate (37.3 g, 0.16 mol), methanol (100 mL) and water (25 mL) gave, after distillation [100–105 °C (2 mmHg)], the acylsilane **9d** as colourless oil (1.5 g, 36%); spectroscopic data as reported.[43]

6.1.9. 1-(Dimethylphenylsilyl)-3-methylbutan-1-one 9e.[44] In a similar way, **16e** (4.00 g, 12.90 mmol), chloramine-T hydrate (18.28 g, 80.29 mmol), methanol (50 mL) and water (13 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 49:1, the acylsilane **9e** as a colourless oil (0.85 g, 30%); spectroscopic data as reported.[44]

6.1.10. 2,2,*N*,*N*-Tetramethylpropionamide 14.[45] To a stirred solution of *N*,*N*-dimethylamine hydrochloride (10.83 g, 132.7 mmol) in toluene (50 mL) were added triethylamine (16.78, 165.8 mmol) and pivaloyl chloride (4.00 g, 33.17 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h, cooled to 0 °C, quenched by the addition of dilute aqueous hydrochloric acid (1.0 mol dm^{-3}, 4 mL) at the same temperature. Water (50 mL) was then

added and the mixture was extracted with ethyl acetate (3× 50 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography eluting with petrol–ethyl acetate 3:1 yielded the amide **14** as a colourless oil (292 mg, 45%); R_f (petrol–ethyl acetate, 8:2) 0.41; ν_{max} (film)/cm^{-1} 2963, 2931, 2876 (C–H), 1630 (C=O), 1398 and 1364 ($C(CH_3)_3$); δ_H (300 MHz; $CDCl_3$) 3.03 (6H, s, $N(CH_3)_2$) and 1.21 (9H, s, $C(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 177.9 (*C*=O), 38.9, 38.5 and 28.4.

6.1.11. 1-(Dimethylphenylsilyl)-2,2-dimethylpropan-1-one 9f.[35] Dimethylphenylsilyl chloride (1.19 g, 7.00 mmol) was stirred with lithium (147 mg, 21.0 mmol) in THF (19 mL) at −8 °C for 36 h. The solution turned red. For calibration, an aliquot (1 mL) was injected into water and the alkaline solution was titrated against dilute aqueous hydrochloric acid (2.0 mol dm^{-3}). Dimethylphenylsilyllithium (17.99 mL, 0.32 M solution in THF, 5.76 mmol) was added drop-wise to a stirred solution of 2,2,*N*,*N*-tetramethylpropionamide **14** (619.0 mg, 4.80 mmol), in dry THF (20 mL) under nitrogen, at −78 °C, and the mixture was kept for 1.5 h at −78 °C. Saturated aqueous ammonium chloride (25 mL) was added to the mixture followed by water (25 mL). The mixture was extracted with ether (3× 50 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography (SiO_2) eluting with petrol–ether 95:5 yielded the acylsilane **9f** as a pale yellow oil (792.5 mg, 75%); spectroscopic data as reported.[35]

6.1.12. (2,2-Dibromocyclopropyl)-benzene 18a.[46] By the method of de Land et al.,[36] styrene (13.88 g, 0.13 mol), bromoform (50.0 g, 0.20 mol) and triethylbenzylammonium chloride (0.4 g, 1.76 mmol) were stirred vigorously. A solution of sodium hydroxide (20.8 g, 0.52 mol) in water (21 mL) was then added in small portions, at such a rate that the temperature of the mixture remained below 50 °C. When all the sodium hydroxide had been added and the exothermic reaction had subsided, the reaction mixture was stirred for an additional 2 h at 60 °C after which time water (80 mL) was added. After extraction with dichloromethane (3×100 mL), the combined organic fractions were washed with water (100 mL), dried ($MgSO_4$) and the solvents were removed under reduced pressure. Distillation [120 °C (12 mmHg)] of the residue afforded the dibromide **18a** as a colourless oil (24.0 g, 67%); spectroscopic data as reported.[35]

6.1.13. (2,2-Dibromocyclopropylmethyl)-benzene 18b.[46] In similar way, allylbenzene (6.31 g, 53.4 mmol), bromoform (20.26 g, 80.16 mmol), triethylbenzylammonium chloride (200 mg, 0.88 mmol), sodium hydroxide (20.0 g, 0.5 mol), water (20 mL) and ethanol (0.32 mL) gave, after distillation of the crude product [120 °C (1 mmHg)], the dibromide **18b** as a pale brown oil (3.10 g, 20%); R_f (petrol–ethyl acetate, 49:1) 0.83; ν_{max} (film)/cm^{-1} 3062, 3028, 2915 (C–H) and 735 (C–Br); δ_H (300 MHz; $CDCl_3$) 7.43–7.28 (5H, m, Ar*H*), 3.09 (1H, dd, J=15.5, 4.0 Hz, $PhCH_AH_B$), 2.83 (1H, dd, J=15.5, 6.5 Hz, $PhCH_ACH_B$), 2.10–1.95 (1H, m, $PhCH_2CH$), 1.91 (1H, dd, J=10.5, 6.0 Hz, $CBr_2CH_ACH_B$) and 1.45 (1H, dd, J=6.0, 6.0 Hz, $CBr_2CH_ACH_B$); δ_C (75 MHz; $CDCl_3$) 139.5, 128.9, 128.6, 126.8 (Aroamtic), 38.5, 32.2, 29.3 and 28.7.

6.1.14. (2-Bromocyclopropyl)benzene 19a.[36] By the method of de Lang et al.[36], a three-necked, round-bottomed flask was charged with lithium bromide (5.12 g, 59.0 mmol) in THF (40 mL) and ether (40 mL). The air in the flask was replaced by nitrogen and *n*-butyllithium (30.0 mL of 2.0 M solution in hexane, 60.0 mmol) was added with cooling below 0 °C. Subsequently a solution of (2,2-dibromocyclopropyl)-benzene (**18a**) (15.0 g, 54.0 mmol) in THF (16 mL) was added over a period of 1 h while the temperature of the reaction mixture was kept carefully between −100 and −110 °C. The thick white suspension was stirred for 1 h at −100 °C, after which, under continuous cooling, it was cautiously quenched with ethanol (10 mL). After the exothermic reaction had subsided, water (20 mL) was added and the mixture was extracted with hexane (3×30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was distilled [105 °C (12 mmHg)] to yield the bromide **19a** as a colourless oil (7.94 g, 75%); spectroscopic data as reported.[35]

6.1.15. (2-Bromocyclopropylmethyl)-benzene 19b.[47] In a similar way, **18b** (2.98 g, 10.3 mmol), lithium bromide (0.98 g, 11.3 mmol), *n*-butyllithium (4.52 mL of 2.5 M solution in hexane, 11.3 mmol), THF (32 mL) and ether (14 mL) gave, after purification by kugelrohr distillation [200 °C (1 mmHg)], the bromide **19b** as a pale yellow oil (1.5 g, 70%); R_f (petrol–ether, 49:1) 0.91; ν_{max} (film)/cm^{-1} 3061, 3027, 2919 (C–H) and 736 (C–Br); δ_H (300 MHz; $CDCl_3$) 7.37–7.21 (5H, m, Ar*H*), 2.78 (1H, dd, J=15.0, 5.5 Hz, $PhCH_AH_B$), 2.74 (1H, dd, J=6.5, 4.0 Hz, C*H*Br), 2.63 (1H, dd, J=15.0, 7.0 Hz, $PhCH_AH_B$), 1.62–1.51 (1H, m, C*H*CHBr), 1.24–1.12 (1H, m, $CHBrCH_AH_B$) and 0.98–0.87 (1H, m, $CHBrCH_AH_B$); δ_C (75 MHz; $CDCl_3$) 140.0, 128.7, 128.6, 126.6 (Aromatic), 38.4, 23.2, 19.9 and 15.9.

6.1.16. 1,4-Diphenyl-4-trimethylsilylbutan-1-one 20a. To a stirred solution of **19a** (196.2 mg, 0.84 mmol) in ether (10 mL) was added *t*-butyllithium (1.01 mL of 1.66 M solution in hexane, 1.68 mmol) drop-wise at 0 °C, and the mixture was left to stir at this temperature for 1 h. The reaction was cooled to −80 °C and a solution of **9a** (150 mg, 0.84 mmol) in THF (15 mL) was added drop-wise over 10 min. After the addition was complete the reaction was allowed to warm to −30 °C over 30 min. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL). The solvents were removed under reduced pressure and water (15 mL) was added. The aqueous phase was extracted with ether (3× 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 19:1 yielded the title compound **20a** as a pale yellow oil (99.1 mg, 40%); R_f (petrol–ethyl acetate, 49:1) 0.33; ν_{max} (film)/cm^{-1} 2953, 2895 (C–H), 1685 (C=O), 1248 an 838 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.87–7.05 (10H, m, Ar*H*), 3.01–2.80 (2H, m, CH_2-2), 2.28–2.16 (2H, m, CH_2-3), 2.10 (1H, dd, J=10.0, 5.0 Hz, C*H*-4)

and −0.01 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 200.9 (*C*=O), 142.9, 137.1, 133.0, 128.6, 128.4, 128.1, 127.8, 124.7 (Aromatic), 38.3, 36.7, 24.0 and −2.9; *m/z* 297 (80%, M+H$^+$), 314 (50%, M+NH_4^+); Found MH$^+$, 297.1670. $C_{19}H_{24}OSi$ requires *M* 297.1674).

6.1.17. 4-(Dimethylphenylsilanyl)-1,4-diphenylbutan-1-one 20b. In a similar way, **9b** (150 mg, 0.63 mmol), **19a** (147 mg, 0.75 mmol), *t*-butyllithium (0.98 mL, 1.25 M solution in ether, 1.23 mmol), ether (15 mL), THF (15 mL) and saturated ammonium chloride solution (3 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 99:1, the title compound **20b** as a pale yellow oil (80 mg, 35%); R_f (petrol–ethyl acetate, 24:1) 0.20; ν_{max} (film)/cm^{-1} 3064, 3023, 2955, 2894 (C–H), 1684 (C=O), 1251 and 832 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.84–6.86 (15H, m, Ar*H*), 2.92 (1H, ddd, *J*=17.5, 8.5, 6.0 Hz, CH_AH$_B$−2), 2.81 (1H, ddd, *J*=17.5, 8.0, 6.5 Hz, CH$_A$$H_B$-2), 2.36 (1H, dd, *J*=12.0, 4.0 Hz, C*H*−4), 2.31–2.18 (2H, m, CH_AH$_B$-3 and CH$_A$$H_B$-3), 0.33 (3H, s, SiC$H_{3A}$) and 0.26 (3H, SiC$H_{3B}$); δ_C (75 MHz; $CDCl_3$) 200.9 (*C*=O), 142.4, 142.2, 137.2, 134.4, 133.1, 129.4, 128.7, 128.5, 128.3, 128.2, 127.9, 125.1 (Aromatic), 38.4, 36.5, 24.3, −3.7 and −5.9; *m/z* 281 (100%, M-Ph), 376 (10%, M+NH_4^+); Found MNH_4^+, 376.2089. $C_{24}H_{26}OSi$ requires *MNH4* 376.2097.

6.1.18. 1,4-Diphenyl-3-trimethylsilylmethylbutan-1-one 21a. In a similar way, **19b** (177 mg, 0.84 mmol), **9a** (150 mg, 0.84 mmol), *t*-butyllithium (0.91 mL, 1.85 M solution in ether, 1.68 mmol), ether (15 mL), THF (15 mL) and saturated aqueous ammonium chloride solution (3 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 19:1, the title compound **21a** as a pale yellow oil (115 mg, 44%); R_f (petrol–ethyl acetate, 49:1) 0.85; ν_{max} (film)/cm^{-1} 3026, 2952, 2896 (C–H), 1684 (C=O), 1248 and 839 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.85–7.18 (10H, m, Ar*H*), 2.99 (1H, dd, *J*=16.5, 5.0 Hz, CH_AH$_B$-2), 2.84–2.72 (2H, m, CH$_A$$H_B$-2 and C$H_AH_B$-4), 2.61–2.51 (2H, m, CH$_A$$H_B$−4 and C*H*-3), 0.75 (1H, dd, *J*=15.0, 5.5 Hz, CH_AH$_B$CH-3), 0.67 (1H, dd, *J*=15.0, 7.0 Hz, CH$_A$$H_B$CH-3) and 0.02 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 200.4 (*C*=O), 140.9, 137.6, 133.0, 129.5, 128.7, 128.5, 128.2, 126.3, 126.3 (Aromatic), 45.6, 43.8, 33.4, 22.4 and −0.4; *m/z* 311 (80%, M+H$^+$), 328 (30%, M+NH_4^+); Found MH$^+$, 311.1830. $C_{20}H_{26}OSi$ requires *MH* 311.1831.

6.1.19. 3-[(Dimethylphenylsilyl)methyl]-1,4-diphenylbutan-1-one 21b. In a similar way, **19b** (186 mg, 0.88 mmol), **9b** (176 mg, 0.73 mmol), *t*-butyllithium (1.07 mL, 1.37 M solution in ether, 1.47 mmol), ether (15 mL), THF (15 mL) and saturated aqueous ammonium chloride solution (3 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate, the title compound **21b** as colourless plates (79 mg, 29%), mp 32–33 °C 99:1; R_f (petrol–ethyl acetate, 49:1) 0.23; ν_{max} (film)/cm^{-1} 3064, 3025, 2955 (C–H), 1683 (C=O), 1250 and 832 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.75–7.08 (15H, m, Ar*H*), 2.91 (1H, dd, *J*=16.0, 5.5 Hz, CH_AH$_B$−2), 2.75 (1H, dd, *J*=16.0, 6.5 Hz, CH$_A$$H_B$-2), 2.71–2.51 (3H, m, C$H_AH_B$-4, C$H_AH_B$-4 and C*H*−3), 1.01 (1H, dd, *J*=15.0, 6.0 Hz, SiCH_AH$_B$C-3), 0.99 (1H, dd, *J*=15.0, 7.0 Hz, SiCH$_A$$H_B$C-3) and 0.32 (6H, s, Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 200.3, 140.8, 139.5, 137.4, 133.8, 132.9, 129.5, 129.1, 128.6, 128.5, 128.2, 128.1, 126.2 (Aromatic), 45.5, 43.7, 27.1, 21.4, −1.8 and −2.0; *m/z* 390 (30%, M+NH_4^+); Found M$^+$, 372.1900. $C_{25}H_{28}OSi$ requires *M* 372.1909.

6.1.20. Cyclopropanecarbaldehyde 26.[48] By the procedure of Heck et al.,[49] cyclopropylmethanol (22.1 g, 0.31 mol) dissolved in dichloromethane (20 mL) was added rapidly to a stirred solution of pyridinium chlorochromate (100.0 g, 0.46 mol) in dichloromethane (100 mL) at room temperature. After stirring for 3 h the mixture was passed through a short column of silica. The black residue was rinsed with ether and the washings were also put through the column. The combined eluates were concentrated under reduced pressure to afford the aldehyde **26** as a green oil (10.5 g, 49%); spectroscopic data as reported.[48]

6.1.21. 2-Cyclopropyl-[1,3]dithiane 27. By a modification of the procedure of Moran et al.,[50] boron trifluoride diethyl etherate (85.2 g, 0.60 mol) was added slowly to a stirred solution of aldehyde **26** (10.5 g, 0.15 mol), 1,3-propanedithiol (16.7 g, 0.15 mol) in dichloromethane (300 mL) and molecular sieves (4 Å) (150 g) at 0 °C. The solution was stirred for 2 h at 0 °C and warmed to room temperature and was stirred for another 15 h. A saturated aqueous solution of sodium bicarbonate (200 mL) was then cautiously added and the aqueous phase was extracted with chloroform (3× 200 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was distilled [80 °C (1 mmHg)] to yield the dithiane **27** as a colourless oil (9.8 g, 41%); R_f (petrol–ethyl acetate, 49:1) 0.25; ν_{max} (film)/cm^{-1} 3003, 2935, 2897 and 2826 (C–H); δ_H (300 MHz; $CDCl_3$) 3.41 (1H, d, *J*=10.0 Hz, C*H*S$_2$), 2.90–2.78 (4H, m, SCH_{2A} and SCH_{2B}), 2.16–2.06 (1H, m, SCH$_2$CH_AH$_B$), 1.93–1.78 (1H, m, SCH$_2$CH$_A$$H_B$), 1.12–1.00 (1H, m, C*H*CS$_2$), 0.72–0.60 (2H, m, CHCH_{2A}) and 0.49–0.43 (2H, m, CHCH_{2B}); δ_C (75 MHz; $CDCl_3$) 52.5 (CS_2), 31.0, 26.2, 16.1 and 5.9; *m/z* 161 (90%, M+H$^+$); Found M$^+$, 160.0369. $C_7H_{12}S_2$ requires *M* 160.0380.

6.1.22. (2-Cyclopropyl-[1,3]dithian-2-yl)-trimethylsilane 28. By the method used for **16b**, **27** (9.80 g, 66.2 mmol), chlorotrimethylsilane (8.24 g, 75.9 mmol), *n*-butyllithium (29.9 mL, 2.4 M solution in pentane, 71.8 mmol) and THF (100 mL) gave the silane **28** as a colourless oil (14.4 g, 94%); R_f (petrol–ethyl acetate, 49:1) 0.68; ν_{max} (film)/cm^{-1} 3002, 2954, 2913 (C–H), 1247 and 845 (Si–C); δ_H (300 MHz; $CDCl_3$) 2.83 (2H, t, *J*=13.0 Hz, SCH_{2A}CH$_2$), 2.30–2.25 (2H, m, SCH_{2B}CH$_2$), 1.90–1.85 (1H, m, SCH$_2$-CH_AH$_B$), 1.73–1.61 (1H, m, SCH$_2$CH$_A$$H_B$), 1.16–1.12 (1H, m, C*H*CH$_2$), 0.39–0.32 (4H, m, CHCH_{2A} and CHCH_{2B}) and 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz; $CDCl_3$) 67.8 (CS_2Si), 25.0, 24.5, 20.4, 2.8, −3.1; *m/z* 233 (90%, M+H$^+$); Found M$^+$, 232.0769. $C_{10}H_{20}S_2Si$ requires *M* 232.0776.

6.1.23. Cyclopropyltrimethylsilylmethanone 29. By the method used for **9b**, **28** (13.1 g, 60.0 mmol), chloramine-T hydrate (87.5 g, 0.31 mol), methanol (150 mL), water (38 mL) gave a crude product. During work-up, the solvent from the combined organic fractions was removed by distillation through a vigreux column at atmospheric

pressure (Care! Product has a low boiling point) to afford the title compound **29** as pale yellow oil (3.69 g, 47%); R_f (petrol–ethyl acetate, 49:1) 0.28; ν_{max} (film)/cm^{-1} 3005, 2959, 2901 (C–H), 1625 (C=O), 1249 and 864 (Si–C); δ_H (300 MHz; $CDCl_3$) 2.49 (1H, tt, $J=8.0$, 4.5 Hz, C*H*CO), 1.05–1.01 (2H, m, CH_{2A}), 0.84–0.79 (2H, m, CH_{2B}), 0.23 (9H, s, Si(CH_3)$_3$; δ_C (75 MHz; $CDCl_3$) 142.2 (*C*=O), 25.3, 11.4 and −2.99.

6.1.24. 1-Cyclopropyl-1-trimethylsilylpentan-1-ol 30. *n*-Butyllithium (0.43 mL, 2.45 M solution in pentane, 1.05 mmol) was added drop-wise to THF (15 mL) at −78 °C with stirring. A solution of **29** (150 mg, 1.06 mmol) in THF (15 mL) was added drop-wise. The reaction mixture was allowed to warm to 0 °C over 40 min, and was quenched by the addition of saturated aqueous solution ammonium chloride (3 mL). The solvents were removed using a rotary evaporator and water (15 mL) was added. The mixture was extracted with ether (3×15 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated to afford a crude oil. Purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 29:1 yielded the title compound **30** as a colourless oil (151 mg, 71%); R_f (petrol–ethyl acetate, 29:1) 0.24; ν_{max} (film)/cm^{-1} 3494 (O–H), 3002, 2933, 2903 (C–H), 1248 and 837 (Si–C); δ_H (300 MHz; $CDCl_3$) 1.55 (2H, t, $J=$ 7.5 Hz, CH_2-2), 1.42–1.30 (4H, m, CH_2−3 and CH_2-4), 0.93 (3H, t, $J=7.0$ Hz, CH_3−5), 0.85 (1H, m, C*H*C-1), 0.53 (1H, s, O*H*), 0.42–0.27 (4H, m, CHCH_{2A} and CHCH_{2B}) and 0.09 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 65.7 (COH), 39.8, 26.2, 23.9, 16.9, 14.4, 0.5, −1.6 and −2.8; *m*/*z* 200 (45%, M+H$^+$); Found M$^+$, 199.1505. $C_{11}H_{23}OSi$ requires *M* 199.1513.

6.1.25. (Cyclopropylphenylmethoxy)trimethylsilane 31.[51] In a similar way, **29** (150 mg, 1.06 mmol), phenyllithium (0.75 mL, 1.41 M solution in ether) and THF (15 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 49:1, the title compound **31** as a colourless oil (86 mg, 37%); R_f (petrol–ethyl acetate, 49:1) 0.81; ν_{max} (film)/cm^{-1} 3006, 2957, 2861 (C–H), 1250 and 840 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.41–7.27 (5H, m, Ar*H*), 4.12 (1H, d, $J=7.0$ Hz, C*H*Ph), 1.23–1.12 (1H, m, C*H*CPh), 0.61–0.32 (4H, m, PhCHCHCH_{2A} and PhCHCHCH_{2B}) and 0.08 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 145.4, 128.3, 127.2, 126.2 (Aromatic), 78.4, 20.2, 3.9, 3.1 and 0.5.

6.1.26. Trimethylsilylbutan-1-one 32.[52] In a similar way, after stirring at −78 °C for 5 min the reaction mixture was warmed to room temperature over 40 min, and quenched by the addition of saturated aqueous ammonium chloride solution at this temperature. Quantities used were **29** (150 mg, 1.06 mmol), phenyllithium (0.75 mL, 1.41 M solution in ether, 1.06 mmol), THF (15 mL). Purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 49:1 yielded the title compound **32** as a colourless oil (182 mg, 78%); R_f (petrol–ethyl acetate, 49:1) 0.37; ν_{max} (film)/cm^{-1} 2952, 2892 (C–H), 1687 (C=O), 1248 and 838 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.99–7.36 (5H, m, Ar*H*), 3.01 (3H, t, $J=7.5$ Hz, CH_2-2), 1.83–1.72 (2H, m, CH_2−3), 0.60 (2H, t, $J=8.5$ Hz, CH_2-4) and 0.02 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 200.7 (*C*=O), 137.2, 132.9, 128.6, 128.1 (Aromatic), 42.4, 19.2, 16.7 and −1.7.

6.1.27. 1-Cyclopropyl-3-phenyl-3-trimethylsilylpropan-1-one 36a. By the method used for **20a**, cyclopropyltrimethylsilylmethanone (**29**) (150.0 mg, 1.06 mmol), β-bromostyrene (252.2 mg, 1.34 mmol), *t*-butyllithium (1.66 mL, 1.28 M solution in ether, 2.12 mmol), ether (15 mL), THF (15 mL) and saturated aqueous ammonium chloride solution (3 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 49:1, the title compound **36a** as a colourless oil (110 mg, 42%); R_f (petrol–ethyl acetate, 49:1) 0.18; ν_{max} (film)/cm^{-1} 3024, 2955, 2897 (C–H), 1698 (C=O), 1249 and 840 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.29–7.40 (5H, m, Ar*H*), 3.10 (1H, dd, $J=16.5$, 10.5 Hz, CH_AH$_B$−2), 2.91 (1H, dd, $J=16.5$, 5.0 Hz, CH$_A$$H_B$-2), 2.75 (1H, dd, $J=10.5$, 5.0 Hz, C*H*−3), 1.92 (1H, tt, $J=7.5$, 4.5 Hz, C*H*CH$_{2A}$-CH$_{2B}$), 0.89–0.84 (2H, m, CHCH_{2A}CH$_{2B}$), 0.79–0.73 (2H, m, CHCH$_{2A}$CH_{2B}) and −0.01 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 210.4 (*C*=O), 143.3, 128.3, 127.6, 124.8 (Aromatic), 44.2, 31.8, 20.7, 11.0, 10.7 and −2.8; *m*/*z* 247 (90%, M+H$^+$), 264 (30%, M+NH$_4^+$); Found MH$^+$, 247.1509. $C_{15}H_{22}OSi$ requires *MH* 247.1518.

6.1.28. 1-(Dimethylphenylsilyl)-5-methyl-1-phenylhexan-3-one 36b. Similarly, β-bromostyrene (324.5 mg, 1.78 mmol), **9e** (300.0 mg, 1.36 mmol), *t*-butyllithium (2.13 mL, 1.28 M solution in ether, 2.72 mmol), ether (15 mL), THF (15 mL) and water (3 mL) gave, after purification by flash column chromatography (SiO_2) eluting with petrol–ethyl acetate 49:1, the title compound **36b** as a yellow oil (40 mg, 9%); R_f (petrol–ethyl acetate, 49:1) 0.75; ν_{max} (film)/cm^{-1} 3066, 3023, 2956 (C–H), 1602 (C=O), 1251 and 832 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.48–6.94 (10H, m Ar*H*), 2.95 (1H, dd, $J=11$, 23.5 Hz, CH_AH$_B$-2), 2.92 (1H, dd, $J=11$, 11 Hz, C*H*−1), 2.63 (1H, dd, $J=11$, 23.5 Hz, CH$_A$$H_B$-2), 2.14 (2H, d, $J=6.5$ Hz, CH_2−4), 2.01 (1H, t quintet, $J=6.5$, 6.5 Hz, C*H*-5), 0.80 (3H, d, $J=$ 6.5 Hz, CH_{3A}CH$_{3B}$CH-5), 0.76 (3H, d, $J=6.5$ Hz, CH$_{3A}$-CH_{3B}CH-5), 0.29 (3H, s, SiCH_{3A}) and 0.26 (3H, s, SiCH_{3B}); δ_C (75 MHz; $CDCl_3$) 210.1, (*C*=O), 142.5, 137.0, 134.4, 129.6, 128.4, 128.0, 127.9, 125.1 (Aromatic), 52.2, 43.9, 31.4, 24.5, 22.8, 22.6, −3.7 and −5.0; *m*/*z* 247 (100%, M−Ph), 342 (10%, M+NH$_4^+$); Found MNH$_4^+$, 342.2252. $C_{21}H_{28}OSi$ requires *MNH*$_4$ 342.2253.

6.1.29. 1-(Dimethylphenylsilyl)-4,4-dimethyl-1-phenylpentan-3-one 36c.[53] Similarly, 1-(dimethylphenylsilyl)-2,2-dimethylpropan-1-one **9f** (150 mg, 0.68 mmol), β-bromostyrene (162.29 mg, 0.89 mmol), *t*-butyllithium (1.01 mL, 1.35 M solution in ether, 1.36 mmol), THF (15 mL), ether (15 mL) and saturated aqueous ammonium chloride solution (3 mL) gave, after purification by flash column chromatography (SiO_2), eluting with petrol–ethyl acetate 49:1, the title compound **36c** as colourless plates (130 mg, 59%), mp 42–44 °C; R_f (petrol–ethyl acetate, 49:1) 0.29; ν_{max} (film)/cm^{-1} 2963 (C–H), 1705 (C=O), 1250 and 816 (Si–C); δ_H (300 MHz; $CDCl_3$) 7.51–7.00 (5H, m, Ar*H*), 3.17(1H, dd, $J=17.0$, 9.5 Hz, CH_AH$_B$−2), 3.07 (1H, dd, $J=9.5$, 3.0 Hz, C*H*-1), 2.73 (1H, dd, $J=17.0$, 3.0 Hz, CH$_A$$H_B$−2), 1.06 (9H, s, C(C$H_3$)$_3$), 0.32 (3H, s, Si(C$H_3$)$_A$) and 0.28 (3H, s, Si(C$H_3$)$_B$); δ_C (75 MHz; $CDCl_3$)

214.3 (*C*=O), 143.2, 137.3, 134.4, 129.5, 128.3, 128.1, 128.0, 124.9 (Aromatic), 44.2, 37.4, 30.3, 26.6, −3.4 and −4.7; *m/z* 247 (100%, M−Ph), 342 (30%, $M+NH_4^+$); Found M^+, 342.2248. $C_{21}H_{28}OSi$ requires MNH_4 324.1909.

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Dynamic resolution of *N*-alkyl-2-lithiopyrrolidines with the chiral ligand (−)-sparteine

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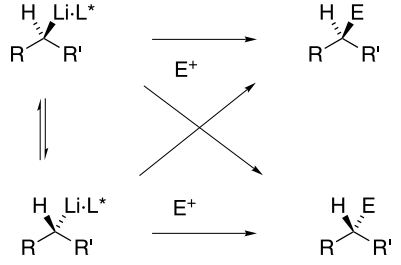
Abstract—A selection of 2-lithiopyrrolidines with different *N*-alkyl-substituents were prepared and tested for their dynamic resolution in the presence of the chiral ligand (−)-sparteine. Good yields of the electrophile-quenched products were obtained with enantiomer ratios up to 85:15 using branched *N*-alkyl derivatives. The major product was shown to have the opposite absolute configuration compared with that obtained in the asymmetric deprotonation of *N*-Boc-pyrrolidine with (−)-sparteine. The enantioselectivity arises from a dynamic thermodynamic resolution in which the minor diastereomeric complex reacts faster with the electrophile.

1. Introduction

Organolithium compounds are amongst the most well used reagents and intermediates in synthetic chemistry. When the lithium is attached to a stereogenic carbon center, the resulting chiral organolithium species can be used in asymmetric synthesis. There has been tremendous growth in such chemistry over the last decade, with impressive levels of enantioselectivity achieved for a range of substrates and electrophiles.[1–6] The stereoselectivity arises from an enantioenriched organolithium species, typically formed at low temperature by either a stereospecific tin–lithium exchange from an enantioenriched organostannane or by an asymmetric deprotonation with a chiral base. Alternatively an asymmetric substitution of the organolithium species in the presence of a chiral ligand can be used. Success in these processes depends crucially on the rate at which the organolithium species undergoes enantiomerization and in addition depends on the stereochemical course of the electrophilic substitution.

In an asymmetric substitution reaction, the chiral organolithium species is prepared as a racemate and this can be achieved by any of the known methods for organolithium formation. Addition of a chiral ligand (L*) that co-ordinates to the lithium leads to the formation of two diastereomeric complexes (Scheme 1). Ideally, these can interconvert at the carbanion center, such that a dynamic process allows high yields of the substitution product (formed either by retention or inversion of configuration). The enantioselectivity arises by one (or a mixture) of two processes: a dynamic thermodynamic resolution can proceed, in which the enantiomer ratio of the products reflects the ratio of the two diastereomeric organolithium chiral ligand complexes (which are normally interconverting slowly in comparison with electrophilic quench);[7] alternatively a dynamic kinetic resolution can take place, in which the enantiomer ratio derives from the faster reaction of one of the two diastereomeric complexes (which are normally interconverting rapidly) with the electrophile.



Scheme 1. Dynamic resolution and substitution of chiral organolithium compounds.

Examples of the asymmetric substitution of chiral organolithium compounds typically involve benzylic or allylic substrates. The simplest of these, 1-phenyl-ethyllithium, formed from ethylbenzene and *n*-BuLi in the presence of the chiral ligand (−)-sparteine, was reported by Nozaki and

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co-workers over 30 years ago, although low selectivities were obtained after electrophilic quench.[8] High selectivities have, however, been obtained using (−)-sparteine as the chiral ligand with other benzylic substrates.[9] Likewise, good selectivities can be achieved in the asymmetric substitution of benzylic or allylic organolithium compounds bearing an alkoxy, arylthio, or amino group in the α-position.[10] In contrast, the only reported examples, as far as we are aware, of dynamic resolution with alkyllithium (non-mesomerically stabilized) substrates involve α-thio- or α-seleno-alkyllithium compounds.[11] A requirement for efficient dynamic resolution is that the organolithium species undergoes racemization at a temperature at which the organolithium species is chemically stable. As benzylic, allylic and α-thio/seleno organolithium compounds are configurationally labile at low temperatures, they are ideal for such chemistry. Compounds such as α-alkoxy- and α-amino-alkyllithium compounds are configurationally stable at low temperature.[12,13] However, our work on chiral α-amino-organolithium compounds has shown that at room temperature racemization does take place, and we were therefore intrigued to determine if dynamic resolution could be carried out with such compounds at ambient temperature.

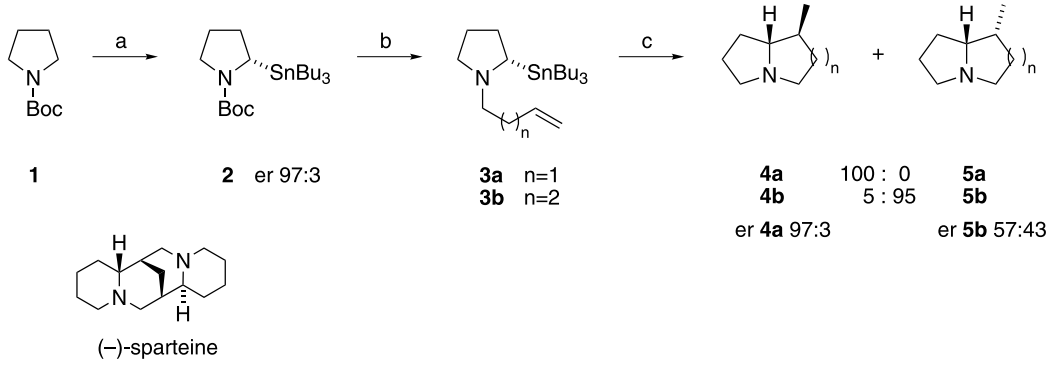
During our work on the intramolecular carbolithiation of α-amino-organolithium compounds, we studied the stereoselectivity using a chiral organolithium species.[14] This was made possible using the stannane **2**, prepared with high selectivity by an asymmetric deprotonation of *N*-Boc-pyrrolidine **1** using *sec*-BuLi and (−)-sparteine followed by electrophilic quench with tributyltin chloride (Scheme 2).[15] The *N*-Boc group of **2** can be deprotected using *B*-bromocatecholborane and converted to *N*-alkyl derivatives by acylation and reduction (or by reductive amination). Best results for the transmetalation–cyclization of the stannane **3a** were achieved with *n*-BuLi in hexane–Et_2O at room temperature and gave the pyrrolizidine **4a**. Despite the relatively high temperature a single diastereomer was formed with no loss of enantiopurity, corresponding to cyclization with retention of configuration. Presumably, the rate of cyclization is sufficiently fast that no observable racemization takes place. In contrast, transmetalation of the homolog **3b** resulted in the indolizidines **4b** and **5b**, with the major product being **5b**, formed with low enantioselectivity.[16] The rate of cyclization to the 6-membered ring was determined ($k=1.2\times10^{-4}\ s^{-1}$) and this was used to calculate the rate of enantiomerization ($k=3.4\times10^{-4}\ s^{-1}$). Clearly, the organolithium species derived from **3b** racemizes at a rate that is competitive with cyclization.

The high yields achieved in these cyclization reactions indicate that *N*-alkyl-2-lithiopyrrolidines have good chemical stability at room temperature in the non-polar solvent hexane–Et_2O. In addition, the loss of enantiopurity in the formation of the indolizidine **5b** indicates that *N*-alkyl-2-lithiopyrrolidines are configurationally labile at room temperature in the non-polar solvent hexane–Et_2O. The calculated rate of enantiomerization equates to a half-life of about 30 min at room temperature in this solvent system. This rate is similar to that found for the simple *N*-ethyl derivative but slower than that for the corresponding *N*-Boc or *N*-methoxyethyl derivatives.[17] This contrasts with the known configurational stability of such compounds at low temperature in THF or Et_2O and suggests that dynamic resolution should be feasible at room temperature.

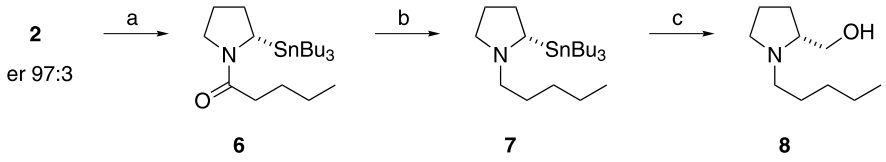
2. Results and discussion

To study the dynamic resolution of *N*-alkyl-2-lithiopyrrolidines, we prepared initially the stannane **3b** in racemic form and treated it as in Scheme 2 with *n*-BuLi and with added chiral ligand (−)-sparteine. Unfortunately, only protodestannylated product and no cyclization products **4b** or **5b** were isolated from the reaction mixture and it appears that complexation to (−)-sparteine prevents cyclization. We therefore turned to intermolecular quench of the complexed organolithium compounds.

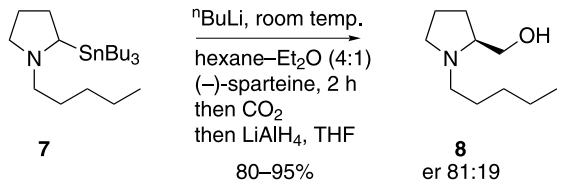
The most obvious first attempt at dynamic resolution involved the use of the analog **7**, lacking the alkene functional group. This was prepared from the stannane **2** (racemic or enantioenriched) in the same way as the compounds **3a** and **3b** (by deprotection with *B*-bromocatecholborane, acylation to give the amide **6** and reduction) or by deprotection and reductive amination.[18] Two experiments were then conducted to confirm the expected configurational stability/lability of the resulting organolithium compound. First, treatment of enantioenriched stannane **7** (er 97:3) with *n*-BuLi in THF at −40 °C followed by quenching with CO_2 and reduction gave



Scheme 2. Enantioselective intramolecular carbolithiation of 2-lithiopyrrolidines. (a) *sec*-BuLi, (−)-sparteine, Et_2O then Bu_3SnCl, 83%; (b) (i) *B*-bromocatecholborane, CH_2Cl_2, room temperature, then $CH_2{=}CH(CH_2)_nCOCl$, $NaOH_{(aq)}$, $n=1$ 65%, $n=2$ 65%, (ii) AlH_3 or $LiAlH_4$, Et_2O, $n=1$ 89%, $n=2$ 90%; (c) *n*-BuLi, hexane–Et_2O (10:1 or 4:1), room temperature, 6 h, then MeOH, $n=1$ 90%, enantiomer ratio (er) **4a** 97:3, $n=2$ 80%, er **5b** 57:43.



Scheme 3. Configurational stability studies of *N*-pentyl-2-lithiopyrrolidine. a) *B*-bromocatecholborane, CH_2Cl_2, room temperature, then C_4H_9COCl, $NaOH_{(aq)}$, 52%; b) $LiAlH_4$, Et_2O, 89%; c) *n*-BuLi, THF, –40 °C, 1 h, then CO_2 then $LiAlH_4$, THF, 40 °C, 92%, er **8** 97:3; or *n*-BuLi, hexane-Et_2O (4:1), room temperature, 1 h, then CO_2 then $LiAlH_4$, THF, 40 °C, 63%, er **8** 50:50.



Scheme 4. Dynamic resolution of *N*-pentyl-2-lithiopyrrolidine.

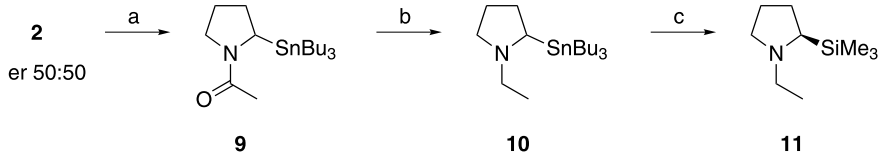
N-pentyl-prolinol **8** with no loss in enantiopurity, as determined by ^{1}H NMR spectroscopic studies in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Scheme 3). This result follows that expected based on the known stability (chemical and configurational) of *N*-methyl-2-lithiopyrrolidine at low temperature in THF (although in our case there was no need for the additive TMEDA) and that quench with CO_2 occurs with complete retention of configuration.[13] Secondly, transmetalation of enantioenriched stannane **7** (er 97:3) with *n*-BuLi in the non-polar solvent hexane–Et_2O (4:1) at room temperature followed by quenching with CO_2 and reduction gave *N*-pentyl-prolinol **8** as a racemic mixture. This confirmed the anticipated configurational lability of this organolithium compound, as desired for efficient dynamic resolution.

Addition of the chiral ligand (−)-sparteine to the organolithium species derived from transmetalation of the racemic stannane **7** with *n*-BuLi in hexane–Et_2O (4:1) at room temperature should allow the formation of two interconverting diastereomeric complexes and hence a potential dynamic resolution. We were pleased to find that, after quenching with CO_2 and reduction, the product **8** was formed in high yield (Scheme 4). Analysis by ^{1}H NMR spectroscopy revealed a good enantiomer ratio (er 81:19), confirming the dynamic process and indicating the potential of this chemistry as a method for the asymmetric synthesis of chiral 2-substituted pyrrolidines.

The major enantiomer in this dynamic resolution, (*S*)-*N*-pentyl-prolinol **8**, was opposite from that obtained when using the enantioenriched stannane (*S*)-**7** in THF at low temperature. Hence this chemistry provides access to either major enantiomer of the quenched product with the asymmetry arising from the same chiral ligand (−)-sparteine. The opposite selectivity is a consequence of the method of asymmetric induction, either by a dynamic resolution process at room temperature or by a configurationally stable organolithium species at low temperature (prepared originally by asymmetric deprotonation).

Very similar results (er 80:20–81:19 of the product **8**) in the dynamic resolution with (−)-sparteine were obtained by transmetalation of the racemic stannane **7** with *n*-BuLi at room temperature in hexane, cyclohexane, cumene or Et_2O as the solvent. The enantiomer ratio was determined by comparing the integration of the signals corresponding to the methyl triplet in the ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. This method was satisfactory but not always successful, so we decided to continue optimization studies on the related *N*-ethyl derivative.

The substrate **10** was prepared in the same way as above and was treated with *n*-BuLi (1.2 equiv) in hexane and



Scheme 5. Dynamic resolution of *N*-ethyl-2-lithiopyrrolidine. (a) *B*-bromocatecholborane, CH_2Cl_2, room temperature, then MeCOCl, $NaOH_{(aq)}$, 65%; (b) $LiAlH_4$, Et_2O, 78%; (c) 1.2 equiv *n*-BuLi, hexane (0.2 M except for entry 6, Table 1), (−)-sparteine, 20 °C, 30 min, then TMSCl.

Table 1. Different conditions for the dynamic resolution of *N*-ethyl-2-lithiopyrrolidine

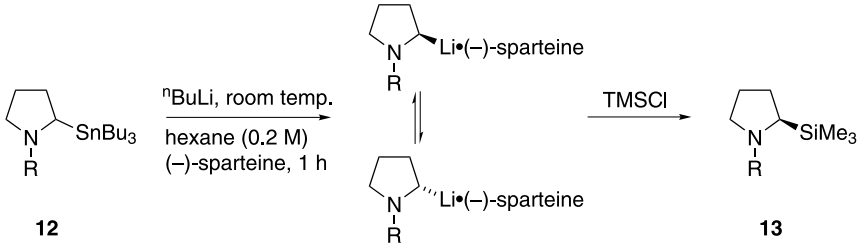
Entry	Equivalents of (−)-sparteine	Temperature of quench (°C)	Yield **11** (%)	er **11** (*R*/*S*)
1	1.5	20	69	71:29
2	1.5	45	56	63:37
3	1.5	-78	58	75:25
4	3	20	45	74:26
5	0.5	20	66	53:47
6[a]	1.5	20	81	73:27

[a] Concentration 0.8 M (others 0.2 M).

(−)-sparteine. After 30 min, the electrophile trimethylsilyl chloride (TMSCl) was added and the enantiomer ratio of the product **11** was determined by ^{1}H NMR spectroscopy in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Scheme 5, Table 1). In this case, the product **11** was formed with slightly lower selectivity in comparison with that achieved using the *N*-pentyl derivative **7**. The major product had the (*R*)-configuration, as determined by comparison with an authentic sample, prepared from the stannane (*S*)-**2** by transmetalation at low temperature and quench with TMSCl,[15] followed by removal of the *N*-Boc group, acylation and reduction. Similar levels of enantioselectivity (er 72:28) were also obtained using the electrophile CO_2 (followed by reduction to the prolinol) or by leaving the organolithium (−)-sparteine complex for longer time periods before quenching with TMSCl. By quenching at higher temperature (entry 2) the product **11** was formed with lower enantioselectivity, although a slight improvement was obtained by quenching at −78 °C (entry 3) or on addition of excess (−)-sparteine (entry 4). However, attempted use of less than one equivalent of the chiral ligand resulted in low selectivity (entry 5). Increasing the concentration from 0.2 M to 0.8 M had a beneficial effect, particularly on the yield of the product **11** (entry 6).

It is apparent that the nature of the *N*-substituent plays some role in the selectivity of the dynamic resolution. We therefore screened a selection of *N*-substituted 2-lithiopyrrolidines with the chiral ligand (−)-sparteine (Scheme 6, Table 2).[19] The enantiomer ratios of the products **13** were determined by ^{1}H NMR spectroscopy in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol or (*S*)-mandelic acid. Increasing the steric bulk of the *N*-substituent gave a slight increase in the selectivity of the dynamic resolution. Best results were obtained using the *N*-pentyl (entry 3) and *N*-isobutyl (entries 5 and 6) derivatives. The substrates with the bulky *N*-cyclohexylmethyl (entry 8) and *N*-*tert*-butylmethyl (entry 9) substituents were sluggish to transmetalate and tetrabutyltin was isolated in low yield from these reactions. Using the substrates **12**, R = Boc or methoxyethyl (entries 10, 11) gave racemic product under all temperatures studied (yields were low at higher temperature but the product **13** was still racemic). Increasing the concentration of the reaction to 1.0 M using the *N*-isobutyl derivative **12**, R = ^{i}Bu (entry 6) improved the selectivity slightly (er 85:15). Other variations in the concentration, solvent, amount of (−)-sparteine, time and temperature gave similar or reduced selectivities.

There are two modes of asymmetric induction in such asymmetric substitution reactions, namely dynamic thermodynamic resolution and dynamic kinetic resolution.[7] To distinguish between these a number of experiments were performed using both the *N*-ethyl and the *N*-isobutyl derivatives. Firstly, as can be seen from Table 1 (entry 3), the 75:25 ratio of enantiomers persists after cooling to −78 °C and quenching. Likewise, a similar enantiomer ratio of the product **13c** is obtained if the mixture is cooled to −78 °C prior to quenching with TMSCl. If the same reactions are carried out with transmetalation at room temperature using hexane–Et_2O (4:1) (some Et_2O is required to allow transmetalation in the absence of (−)-sparteine) followed by cooling to −78 °C, with the addition of (−)-sparteine after cooling, then racemic product (**11** or **13c**) is formed. There is therefore no dynamic resolution at low temperature. These results imply that, at room temperature in the presence of the chiral ligand there is an



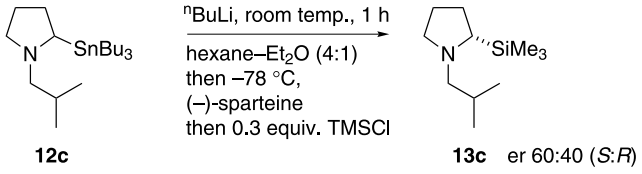
Scheme 6. Dynamic resolution of *N*-substituted-2-lithiopyrrolidines.

Table 2. Different *N*-substituents for the dynamic resolution

Entry	R	Product	Yield (%)	er (*R*/*S*)
1	Et	**11**	69	71:29
2	$CH_2CH_2CH_2CH_3$	**13a**	74	74:26
3[a]	$(CH_2)_4CH_3$	**8**	95	81:19
4	$(CH_2)_7CH_3$	**13b**	50	75:25
5	$CH_2CH(CH_3)_2$	**13c**	68	82:18
6[b]	$CH_2CH(CH_3)_2$	**13c**	78	85:15
7	$CH_2CH_2CH(CH_3)_2$	**13d**	64	77:23
8	$CH_2(^cC_6H_{11})$	**13e**	35	82:18
9	$CH_2C(CH_3)_3$	**13f**	30	80:20
10[c]	$CO_2C(CH_3)_3$	**13g**	80	50:50
11[d]	$CH_2CH_2OCH_3$	**13h**	83	50:50

[a] Quench with CO_2 then $LiAlH_4$ (see Scheme 4).
[b] Concentration 1.0 M, all other entries 0.1 or 0.2 M.
[c] At 0 °C.
[d] At −20 °C.

unequal ratio of the two diastereomeric organolithium complexes. This would indicate that a dynamic thermodynamic resolution is operating and this was confirmed by the addition of a sub-stoichiometric amount of the electrophile as shown in Scheme 7. In this experiment the chiral ligand is added after cooling to −78 °C, so a 1:1 ratio of the two complexes is produced. The product **13c** was formed (42% yield based on the electrophile) as a mixture of enantiomers, with the (*S*)-enantiomer predominating to a small extent. The presence of some selectivity shows that (−)-sparteine can complex to the organolithium species at low temperature. The fact that the ratio of enantiomers of the product **13c** is different from that obtained by adding (−)-sparteine at room temperature (Table 2, entry 5) argues against a dynamic kinetic resolution. There is however a kinetic component, as the predominant enantiomer in this sub-stoichiometric quench experiment has the opposite absolute configuration (in comparison with the same experiment conducted by adding (−)-sparteine at room temperature). The results can therefore be rationalized by proposing (at room temperature, Scheme 6) a dynamic thermodynamic resolution in which there is a ratio of the two diastereomeric complexes of approximately 80:20, but that the activation barrier to reaction with the electrophile is slightly lower for the minor diastereomeric complex.

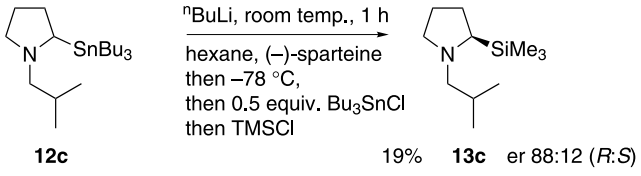


Scheme 7. Evidence for dynamic thermodynamic resolution.

The major enantiomer (er ~80:20) of the 2-trimethylsilylpyrrolidines in these dynamic resolution reactions has the (*R*) absolute configuration. At low temperature in THF *N*-alkyl-2-tributylstannylpyrrolidines undergo tin–lithium exchange and electrophilic quench with TMSCl (or CO_2) with overall retention of configuration and this is thought to involve retention in both the metal exchange and the quench.[13] Assuming that the electrophilic quench in hexane at room temperature occurs with retention of configuration, then the major diastereomer of the organolithium (−)-sparteine complex has the (*R*) configuration at the carbanion center.

Density functional theory calculations were performed on the two diastereomeric *N*-methyl-2-lithiopyrrolidine (−)-sparteine complexes (geometry optimized with B3LYP/6-31G*). The model system used monomeric organolithium species in which the lithium atom bridges the nitrogen and carbon atoms and is co-ordinated to the two nitrogen atoms of a (−)-sparteine molecule. The calculations indicated that the (*S*) enantiomer complexed to (−)-sparteine was more stable than the (*R*) enantiomer by about 1.4 kcal/mol. This is in contrast to the expected preference for the (*R*) enantiomer based on our knowledge that the selectivity arises from a dynamic thermodynamic resolution and that reaction with electrophiles such as TMSCl should occur with retention of configuration. It could be that our calculated model is insufficient and maybe that a different complex is formed, such as a dimeric organolithium in hexane-(−)-sparteine,[20] although we have not attempted to model higher aggregates. Alternatively, we could have the (*R*) enantiomer and electrophilic quench could be taking place with inversion of configuration. However, preparation of the enantioenriched organolithium species by transmetalation of (*S*)-**10** (er 97:3) at room temperature in hexane–Et_2O (4:1) for only 15 min (to avoid complete racemization) followed by cooling to −78 °C, addition of (−)-sparteine then electrophilic quench with TMSCl gave predominantly the (*S*) enantiomer of the product **11** (er 82:18). The ligand (−)-sparteine should complex under these conditions (compare with Scheme 7 which used racemic organostannane); this result suggests therefore that the organolithium (−)-sparteine complex quenches with retention of configuration. The reasonable level of enantioselectivity obtained in this reaction is in line with that expected based on the slow rate of enantiomerization of *N*-ethyl-2-lithiopyrrolidine;[17] it also indicates that enantiomerization (epimerization) is faster when the organolithium species is complexed to (−)-sparteine than in hexane–Et_2O alone since the thermodynamic ratio of complexes was formed within 30 min (see Scheme 5).

We have established that the mode of asymmetric induction in these reactions is by a dynamic thermodynamic resolution in which the minor diastereomeric complex reacts at a faster rate with the electrophile. We therefore attempted to improve the enantiomer ratio of the product by use of a sacrificial electrophile, which should remove the faster reacting minor complex. If the reaction mixture is cooled to prevent equilibration of the complexes then on subsequent quench with the desired electrophile an improvement in the enantiomer ratio should ensue, although at the expense of the yield. Addition of MeOH (0.3 equiv) to the cooled diastereomeric complexes generated from the stannane **12c** followed by addition of TMSCl gave the desired silane **13c** with essentially the same enantiomer ratio (er 86:14) (compare with Table 2, entry 6). The use of tributyltin chloride (0.5 equiv) as the sacrificial electrophile, followed by TMSCl gave the silane **13c** with only a slight improvement in the enantiomer ratio (er 88:12) (Scheme 8). We were not able therefore to improve significantly the enantiomer ratio of the desired product under these conditions.



Scheme 8. Use of a sacrificial electrophile.

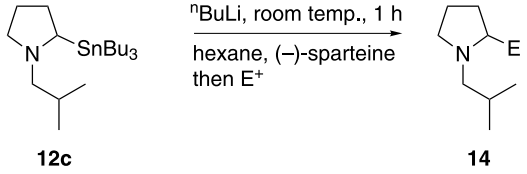
To probe the generality of this chemistry, the *N*-isobutyl compound **12c** was treated with butyllithium under our optimized conditions using a 1.0 M solution in hexane with 1.5 equiv of (−)-sparteine, allowing 1 h for transmetalation and equilibration before addition of a variety of electrophiles (Scheme 9). The yields and enantiomer ratios of the products are shown in Table 3. In each case the racemic product was also prepared by tin–lithium exchange in the

Table 3. Different electrophilic quenches in the dynamic resolution

Entry	E^+	E	Product	Yield (%)	er (*R*/*S*)
1	TMSCl	$SiMe_3$	**13c**	78	85:15
2	Bu_3SnCl	$SnBu_3$	**12c**	80	83:17[a]
3	PhNCO	CONHPh	**14a**	57	18:82
4	$Me_2C{=}O$	$C(OH)Me_2$	**14b**	57	16:84
5	$Ph_2C{=}O$	$C(OH)Ph_2$	**14c**	80	50:50
6	$PhCH_2Cl$	CH_2Ph	**14d**	50	53:47[a]
7	$PhCH_2CH_2CH_2Br$	$CH_2CH_2CH_2Ph$	**14e**	46	46:54
8	$CH_2{=}CHSiPh_2Me$	$CH_2CH_2SiPh_2Me$	**14f**	66	42:58[b]

[a] Ratio estimated from specific rotations (see text and Section 4).
[b] Or (*R*:*S*) 58:42.

absence of (−)-sparteine; the enantiomers were resolved by chiral HPLC (**14a**, **c**, **e**, **f**) or by ^{1}H NMR spectroscopy in the presence of a chiral solvating agent (**13c**, **14b**), except for **12c** and **14d** which were not resolvable under a variety of conditions and the enantiomer ratios were estimated from the specific rotation.

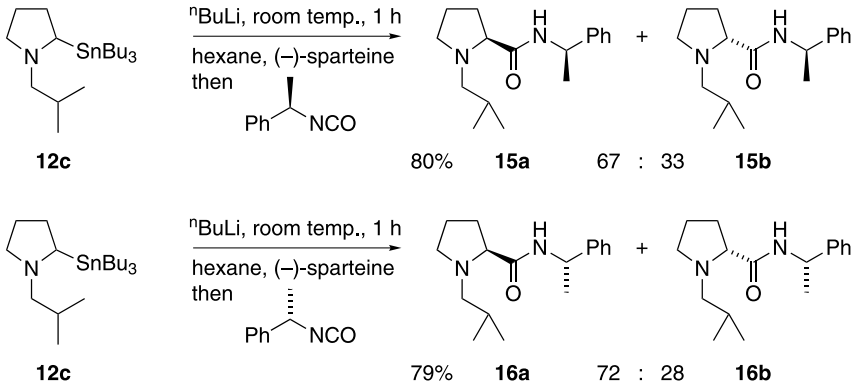


Scheme 9. Variation of the electrophile.

The absolute configurations of the substituted products were determined by comparison of the sign of optical rotation to that of an authentic sample, prepared by low temperature tin–lithium exchange of the enantioenriched organostannane **12c** (er 97:3) in THF. Using this method the sign of rotation was always opposite to that obtained from the dynamic resolution. The electrophilic quench of enantioenriched *N*-methyl-2-lithiopyrrolidine is reported to proceed with retention of configuration for the electrophiles Bu_3SnCl and acetone, racemization for the electrophile benzophenone and partial inversion of configuration for the electrophiles benzyl chloride and 3-bromo-1-phenylpropane.[21] We have found independently that electrophilic quench of *N*-alkyl-2-lithiopyrrolidines with TMSCl and PhNCO occurs with retention of configuration.

Table 3, entries 1–4 shows that good enantiomer ratios are obtained using the electrophiles TMSCl, Bu_3SnCl, PhNCO and acetone. These ratios (82–85:15–18) are probably a reflection of the thermodynamic ratio of the diastereomeric organolithium (−)-sparteine complexes that are quenched stereospecifically with retention of configuration. The reaction mixture after addition of the electrophile benzophenone turned a deep blue colour and racemic product **14c** was obtained. This result indicates that a single electron transfer (SET) process takes place.[13b] The electrophile benzyl chloride gave the product **14d** with a low specific rotation, $[\alpha]_D^{25} = +6.5$ (1.1, $CHCl_3$). We were not able to determine the enantiomer ratio by chiral HPLC or NMR spectroscopic analysis, but the low temperature quench of the enantioenriched organolithium, generated from the stannane (*S*)-**12c** (er 97:3) gave the product **14d** with specific rotation, $[\alpha]_D^{25} = -14.1$ (1.2, $CHCl_3$). The corresponding *N*-methyl organolithium (94% ee) has been reported to quench with benzyl chloride in THF to give *N*-methyl-2-benzylpyrrolidine with 15% ee.[21] Assuming that the *N*-isobutyl compound also quenches with a similar low level of selectivity, then the specific rotation obtained for the product **14d** after dynamic resolution corresponds to product with low enantiomer ratio (estimated to be approximately 53:47). This would be in favour of the (*R*) enantiomer, as expected from a slight preference for inversion of configuration. A similar level of selectivity was obtained for the quench with 3-bromo-1-phenylpropane, again with a slight preference for inversion at the carbanion center. This result was disappointing in comparison with the reported significant extent of inversion of configuration in the formation of *N*-methyl-2-(3′-phenylpropyl)pyrrolidine (formed with 51% ee from stannane of 94% ee).[21] To probe this, we carried out the electrophilic quench of (*S*)-**12c** (er 97:3) in THF at −78 °C followed by quench with 3-bromo-1-phenylpropane to give the product **14e**. Under these conditions we obtained the same enantiomer ratio (er 54:46) as that obtained in the dynamic resolution (although the major enantiomer had opposite absolute configuration). Therefore with this substrate the electrophilic quench with 3-bromo-1-phenylpropane was poorly stereoselective. Electrophilic quench with methyldiphenylvinylsilane gave a low enantiomer ratio of the product **14f** (Table 3, entry 8). It is not known if this electrophile quenches with predominant retention or inversion of configuration.

Finally, we have investigated the electrophilic quench of the organolithium (−)-sparteine complex with the chiral electrophiles (*R*)- and (*S*)-1-phenylethyl isocyanate (Scheme 10). We anticipated that these electrophiles would quench with retention of configuration at the carbanion center and hence (assuming that the major organolithium (−)-sparteine complex has the (*R*)-stereochemistry at the carbanion center) the major products would have the stereochemistry shown for **15a** and **16a**. In the absence of (−)-sparteine (racemic organolithium species), electrophilic quench using (*R*)-1-phenylethyl isocyanate occurred to give a 1:1 mixture of the two diastereomeric products **15a** and **15b**. In the presence of (−)-sparteine the products **15a** and **15b** were formed with low selectivity (in comparison with the 82:18 ratio of enantiomers as found for **14a**, Table 3). This may be a consequence of a preference for the minor diastereomeric organolithium (−)-sparteine complex to react with this electrophile (possible mismatched case); however, no improvement in the selectivity was obtained with (*S*)-1-phenylethyl isocyanate, leading to



Scheme 10. Electrophilic quench with 1-phenylethyl isocyanate.

the products **16a** and **16b** (possibly as the minor complex is still more reactive, as discussed earlier).

3. Conclusions

In summary, we have demonstrated that dynamic resolution of *N*-alkyl-2-lithiopyrrolidines takes place at ambient temperature and that good levels of selectivity arise using the chiral ligand (−)-sparteine. The highest enantiomer ratios were obtained with branched *N*-alkyl derivatives and the asymmetric induction is a result of a dynamic thermodynamic resolution. Further examples with other chiral ligands and with other chiral α-amino-organolithium species are in progress and will be reported shortly.

4. Experimental

4.1. General

All experiments were carried out under an inert atmosphere of argon or nitrogen. Diethyl ether (Et_2O) and THF were distilled from sodium/benzophenone. (−)-Sparteine was distilled from calcium hydride prior to use. Optical rotations were recorded on an AA-1000 polarimeter using either a 0.5 or 0.1 dm path-length cell. Infrared spectra were recorded on a Nicolet Magna 550 FT-IR spectrometer. ^{1}H nuclear magnetic resonance (NMR) spectra were run on a Brucker AM250 (250 MHz), AC300 (300 MHz) or DRX400 (400 MHz) instrument. Chemical shifts are reported in parts per million (ppm) relative to solvent signals and coupling constants, *J*, are given in Hz (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). ^{13}C NMR were run on the above instruments at either 62.5, 75 or 100 MHz. Mass spectra were run on a Micromass GCT instrument or at the EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea. Low resolution mass spectra were recorded using a Thermoquest CE Trace GCMS2000 series instrument fitted with a Restek RTX-5MS (Cross bond 5% diphenyl–95% dimethyl polysiloxane 15 m column) with helium as the carrier gas using either EI or CI mode. Microanalysis was performed on a Carlo Erba 1110 instrument. Chiral HPLC was performed using a Gilson 231 XL fitted with a Chiralpak AD, Chiralcel OD, OJ, or ChiroV column (250×4.6 mm i.d.) with visualisation by a Gilson UV detector, or using a HP1050 LC fitted with a Chiralpak AD column (250×4.6 mm i.d.) with visualisation by a Varian RI4 refractive index detector, or using a Thermo Separation Products Spectra Series AS300 fitted with either a Chiralpak AD, Chiralcel OD or OJ column (250×4.6 mm i.d.) with visualisation by a Spectra Series UV100 detector.

4.1.1. 1-(2-Tributylstannyl-pyrrolidin-1-yl)-pentan-1-one 6. *B*-Bromocatecholborane (20 mL, 12 mmol, 0.6 M in CH_2Cl_2) was added to the stannane **2** (5.0 g, 11 mmol) in CH_2Cl_2 (100 mL) at room temperature under argon. After 10 min, $NaOH_{(aq)}$ (80 mL, 2 M) and *n*-pentanoyl chloride (4.7 mL, 40 mmol) were added. After 18 Hz, the two layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), to give the amide (±)-**6** (2.5 g, 52%) as an oil; R_f 0.48 [petrol–EtOAc (9:1)]; ν_{max} (film)/cm^{-1} 2955, 2920, 2870 (C–H), 1620 (C=O); δ_H (300 MHz, $CDCl_3$) 3.54–3.44 (1H, m, NCH), 3.39–3.30 (2H, m, 2×NCH), 2.25 (2H, t, J=7.0 Hz, $COCH_2$), 2.21–2.10 (1H, m, CH), 2.01–1.82 (3H, m, $CHCH_2$), 1.70–1.54 (2H, m, CH_2), 1.49–1.45 [14H, m, CH_2, $Sn(CH_2CH_2CH_2)_3$], 0.94–0.76 [18H, m, CH_3, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 170.1, 47.2, 46.8, 34.6, 29.6, 29.2, 27.65, 27.6, 27.5, 22.8, 13.9, 13.8, 10.2; HRMS (ES) found: MH^+, 446.2442. $C_{21}H_{44}NO^{120}Sn$ requires MH^+, 446.2445; MS *m/z* (ES) 446 (36%, MH^+), 388 (100).

4.1.2. *N*-Pentyl-2-tributylstannyl-pyrrolidine 7. The amide **6** (2.5 g, 5.7 mmol) in Et_2O (10 mL) was added to a suspension of $LiAlH_4$ (0.57 g, 15.0 mmol) in dry Et_2O (20 mL) under nitrogen at 0 °C. After 1 Hz, the mixture was quenched with MeOH (4 mL) and pre-absorbed on basic alumina. Purification by column chromatography on basic alumina, eluting with petrol–EtOAc (98:2), gave the pyrrolidine **7** (2.2 g, 89%) as an oil; R_f 0.6 [petrol–EtOAc (9:1)]; ν_{max} (film)/cm^{-1} 2955, 2920, 2870, 2775 (C–H); δ_H (300 MHz, $CDCl_3$) 2.98–2.84 (1H, m, NCH), 2.78–2.64 (1H, m, NCH), 2.50–2.42 (1H, m, NCH), 2.10–1.72 (6H, m, NCH_2, 2×CH_2), 1.56–1.43 (8H, m, 4×CH_2), 1.38–1.24 (12H, m, 6×CH_2), 0.94–0.84 [18H, m, CH_3, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 57.9, 57.2, 54.1, 29.9, 29.3, 27.9, 27.6, 24.4, 22.6, 14.1, 13.7, 9.3; HRMS (ES) found: MH^+, 432.2643. $C_{21}H_{46}N^{120}Sn$ requires MH^+, 432.2652; GC–MS *m/z* (CI) 432 (54%, MH^+), 430 (43), 140 (100).

4.1.3. *N*-Pentyl-prolinol 8. *n*-BuLi (0.13 mL, 2.5 M in hexanes, 0.33 mmol) was added to the stannane **7** (100 mg, 0.23 mmol) in hexane–Et_2O (2 mL, 4:1) and (−)-sparteine (0.08 mL, 0.33 mmol) at room temperature. After 1 h, CO_2 gas was bubbled through the mixture. The mixture was then added to a suspension of $LiAlH_4$ (38 mg, 1.0 mmol) in dry THF (3 mL) and was heated to 40 °C for 4 h. MeOH (3 mL) was added, the solvents were evaporated and the mixture was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9:1), to give the alcohol (*S*)-**11** (37 mg, 95%) as an oil; $[\alpha]_D^{22} = -31.2$ (0.8, $CHCl_3$); R_f 0.4 [CH_2Cl_2–MeOH (4:1)]; ν_{max} (film)/cm^{-1} 3360 (OH), 2930, 2860 (CH); δ_H (300 MHz, $CDCl_3$) 3.62 (1H, dd, $J=11$, 4 Hz, CH^AH^BOH), 3.37 (1H, dd, $J=11$, 2 Hz, CH^AH^BOH), 3.20–3.12 (1H, m, NCH), 2.69 (1H, dt, $J=11.5$, 8 Hz, NCH), 2.58–2.47 (1H, m, NCH), 2.28–2.17 (2H, m, NCH_2), 1.88–1.20 (10H, m, $5\times CH_2$), 0.92 (3H, t, $J=7$ Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 64.7, 61.7, 54.4, 54.1, 29.6, 28.7, 27.7, 23.6, 22.6, 14.1; HRMS (ES) found: MH^+, 172.1703. $C_{10}H_{22}NO$ requires MH, 172.1701; *m/z* (ES) 172 (100%, MH^+). The enantiomeric excess of (*S*)-**8** was determined to be 62% ee by inducing non-equivalence in the ^1H NMR spectrum for the CH_3 triplet by use of *R*-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (19 mg) as a chiral solvating agent with the pyrrolidine (*S*)-**8** (6.5 mg) in $CDCl_3$ (0.8 mL).

Alternatively, *n*-BuLi (0.16 mL, 2.5 M in hexanes, 0.4 mmol) was added to the stannane (*S*)-**7**[18] (116 mg, 0.27 mmol, er 95:5) in THF (2 mL) at −78 °C. After 10 min, CO_2 gas was bubbled through the mixture. The mixture was then added to a suspension of $LiAlH_4$ (38 mg, 1.0 mmol) in dry THF (2 mL) and was heated as above to give, after purification as above, the alcohol (*R*)-**8** (38 mg, 83%) as an oil; $[\alpha]_D^{22} = +45.2$ (0.9, $CHCl_3$); other data as above.

4.1.4. *N*-Acetyl-2-tributylstannyl-pyrrolidine 9. In the same way as the amide **6**, *B*-bromocatecholborane (15.7 mL, 4.4 mmol, 0.3 M in CH_2Cl_2), the stannane **2** (2.0 g, 4.3 mmol), $NaOH_{(aq)}$ (50 mL, 2 M) and acetyl chloride (0.95 mL, 13 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the amide **9** (1.3 g, 65%) as an oil; R_f 0.27 [petrol–EtOAc (4:1)]; ν_{max} (film)/cm^{-1} 1630 (C=O); δ_H (400 MHz, $CDCl_3$) 3.48–3.42 (1H, m, NCH), 3.33–3.25 (2H, m, $2\times$NCH), 2.17–2.03 (1H, m, CH), 1.89 (3H, s, $COCH_3$), 1.88–1.79 (3H, m, $CHCH_2$), 1.54–1.36 [6H, m, $Sn(CH_2CH_2)_3$], 1.31–1.21 [6H, m, $(CH_3CH_2)_3$], 0.86–0.78 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 167.3, 47.9, 46.7, 29.8, 29.1, 27.6, 21.9, 13.7, 10.3; HRMS (EI) found: M^+, 403.1895. $C_{18}H_{37}NO^{120}Sn$ requires M, 403.1897; *m/z* (EI) 403 (10%, M^+), 346 (100); Found: C, 53.62; H, 9.60; N, 3.27. $C_{18}H_{37}NOSn$ requires C, 53.75; H, 9.27; N, 3.48%.

4.1.5. *N*-Ethyl-2-tributylstannyl-pyrrolidine 10. To a suspension of $LiAlH_4$ (419 mg, 11 mmol) in Et_2O (14 mL) at 0 °C was added the amide **9** (2.1 g, 5.2 mmol) in Et_2O (4 mL). After 20 min, MeOH (1 mL) was added dropwise and the mixture was absorbed onto basic alumina. Chromatography on basic alumina, eluting with petrol then petrol–EtOAc (9:1), gave the stannane **10** (1.6 g, 78%) as an oil; R_f 0.26 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2950–2770 (CH); δ_H (400 MHz, $CDCl_3$) 2.92–2.69 (2H, m, NCH_2), 2.40–2.30 (1H, m, NCH), 2.14–1.68 (6H, m, $NCH_2CH_2CH_2$), 1.56–1.39 [6H, m, $Sn(CH_2CH_2)_3$], 1.36–1.24 [6H, m, $(CH_3CH_2)_3$], 1.18 (3H, t, $J=7.8$ Hz, CH_3CH_2N), 0.90–0.79 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 57.8, 53.7, 50.8, 29.4, 29.2, 27.2, 24.3, 14.2, 13.7, 9.1; HRMS (CI) found: MH^+, 390.2168. $C_{18}H_{40}N^{120}Sn$ requires MH, 390.2183; *m/z* (CI) 390 (7%, MH^+), 98 (100); Found: C, 55.60; H, 10.44; N, 3.50. $C_{18}H_{39}NSn$ requires C, 55.69; H, 10.12; N, 3.61%.

4.1.6. *N*-Ethyl-2-trimethylsilyl-pyrrolidine 11. *n*-BuLi (0.276 mL, 2.5 M in cyclohexane, 0.69 mmol) was added to the amine **10** (185 mg, 0.48 mmol) in THF (2.5 mL) at −78 °C. After 30 min TMSCl (0.091 mL, 0.71 mmol) was added. After a further 30 min, the solvents were evaporated and the mixture was purified by distillation under reduced pressure (70 °C, 25 mm of Hg) to give the pyrrolidine **11** (47 mg, 57%) as an oil; R_f 0.15 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:4:0.5)]; ν_{max} (film)/cm^{-1} 2950 (CH); δ_H (400 MHz, $CDCl_3$) 3.22–3.18 (1H, m, NCHSi), 2.93–2.88 (1H, m, NCH), 2.15–2.07 (1H, m, NCH), 1.91–1.81 (2H, m, NCHC*H*C*H*), 1.75–1.63 (4H, m, NCHC*H*C*H*C*H*$_2$), 1.10 (3H, t, $J=7.0$ Hz, NCH_2CH_3), 0.04 [9H, s, $Si(CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 56.3, 55.3, 50.7, 27.4, 23.8, 13.8, 2.5; HRMS (CI) found: MH^+, 172.1519. $C_9H_{21}NSi$ requires MH, 172.1516; *m/z* (CI) 172 (41%, MH^+), 114 (100), 98 (56, $M^+ - SiMe_3$).

n-BuLi (0.192 mL, 2.5 M in cyclohexane, 0.48 mmol) was added to the stannane **10** (155 mg, 0.40 mmol) in hexane (0.5 mL) and (−)-sparteine (0.138 mL, 0.60 mmol) at room temperature. After 30 min TMSCl (0.086 mL, 0.68 mmol) was added at 0 °C. After a further 30 min, MeOH (0.4 mL) was added, the solvents were evaporated and the mixture was purified by distillation under reduced pressure (70 °C, 25 mm of Hg) to give the pyrrolidine (*R*)-**11** (55 mg, 81%) as an oil; $[\alpha]_D^{22} = -38.0$ (1.1, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**11** was determined to be 46% ee by inducing non-equivalence in the ^1H NMR spectrum for the CH_3 triplet by use of *R*-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (12.0 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**11** (2.5 mg) in $CDCl_3$ (0.5 mL).

4.1.7. *N*-Butyl-2-tributylstannyl-pyrrolidine 12a. *B*-Bromocatecholborane (16.5 mL, 20.6 mmol, 1.25 M in CH_2Cl_2) was added to the stannane (±)-**2** (7.9 g, 17.2 mmol) in CH_2Cl_2 (200 mL) at 10 °C under argon. After 30 min, the mixture was washed with 2 M $NaOH_{(aq)}$ (3×60 mL) and the CH_2Cl_2 layer was dried (Na_2SO_4) and filtered. Immediately the mixture was cooled to −50 °C and triethylamine (14.1 mL, 85.8 mmol) was added followed by the dropwise addition of *n*-butanoyl chloride (2.7 mL, 25.7 mmol). After 1 h, the mixture was warmed to room temperature for 4 h. The mixture was washed with saturated $NaHCO_{3(aq)}$ (100 mL), dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel, eluting with petrol–EtOAc (10:1), gave the amide 1-(2-tributylstannyl-pyrrolidin-1-yl)-pentan-1-one (6.81 g, 92%) as an oil; R_f 0.38 [petrol–EtOAc (4:1)]; ν_{max} (film)/cm^{-1} 2960, 2925, 2870 (C–H), 1625 (C=O); δ_H (400 MHz, $CDCl_3$) 3.50–3.46 (1H, m, NCH), 3.37–3.33 (2H, m,

2×NCH), 2.22 (2H, t, J=7.0 Hz, $COCH_2$), 2.20–1.96 (1H, m, CH), 2.00–1.81 (3H, m, $CHCH_2$), 1.69–1.67 (2H, m, CH_2), 1.49–1.45 (6H, m, 3×CH_2), 1.32–1.27 (6H, m, 3×CH_2), 0.96 (3H, t, J=7.5 Hz, CH_3), 0.90–0.82 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 169.9, 47.2, 46.8, 36.8, 29.4, 28.1, 27.5, 27.4, 18.8, 14.2, 13.8, 10.3; HRMS (EI) found: M^+, 431.2209. $C_{20}H_{41}NO^{120}Sn$ requires M^+, 431.2210; GC–MS m/z (CI) 431 (100%, M^+); Found: C, 55.34; H, 9.78; N, 3.50. $C_{20}H_{41}NOSn$ requires C, 55.83; H, 9.60; N, 3.26%.

This amide (3.5 g, 8.1 mmol) in Et_2O (40 mL) was added to a suspension of $LiAlH_4$ (0.62 g, 16.3 mmol) in dry Et_2O (40 mL) under nitrogen at −10 °C. After 30 min, the mixture was quenched with H_2O (0.6 mL), 2 M $NaOH_{(aq)}$ (1.2 mL) and H_2O (1.2 mL). The mixture was filtered, dried (Na_2SO_4) and evaporated. Purification by column chromatography on basic alumina, eluting with petrol–EtOAc (98:2), gave the pyrrolidine **12a** (2.37 g, 70%) as an oil; R_f 0.51 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2955, 2780 (C–H); δ_H (400 MHz, $CDCl_3$) 2.88–2.82 (1H, m, NCH), 2.73–2.64 (1H, m, NCH), 2.48–2.44 (1H, m, NCH), 2.10–1.90 (3H, m, NCH, CH_2), 1.89–1.81 (1H, m, NCH), 1.78–1.76 (2H, m, CH_2), 1.53–1.46 (8H, m, 4×CH_2), 1.36–1.29 (8H, m, 4×CH_2), 0.94–0.86 [18H, m, CH_3, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 57.9, 56.9, 54.1, 29.2, 27.9, 27.7, 26.8, 24.6, 20.9, 14.1, 13.7, 9.4; HRMS (CI) found: MH^+, 418.2482. $C_{20}H_{44}N^{120}Sn$ requires MH^+, 418.2496; GC–MS m/z (CI) 418 (100%, MH^+).

4.1.8. *N*-Octyl-2-tributylstannyl-pyrrolidine 12b. In the same way as the stannane **12a**, the stannane **2** (2.0 g, 4.4 mmol), CH_2Cl_2 (20 mL), *B*-bromocatecholborane (16 mL, 0.3 M, 4.8 mmol), $NaOH_{(aq)}$ (27 mL, 2 M) and octanoyl chloride (2.25 mL, 13.0 mmol) gave after purification by column chromatography on silica gel, eluting with petrol then petrol–EtOAc (9:1), the amide 1-(2-tributylstannyl-pyrrolidin-1-yl)-octan-1-one (1.2 g, 57%) as an oil; R_f 0.47 [petrol–EtOAc (9:1)]; ν_{max} (film)/cm^{-1} 1625 (C=O); δ_H (300 MHz, $CDCl_3$) 3.49–3.45 (1H, m, NCH), 3.35–3.31 (2H, m, 2×NCH), 2.25–1.81 (6H, m, 3×CH_2), 1.68–1.37 (8H, m, 4×CH_2), 1.32–1.23 (14H, m, 7×CH_2), 0.90–0.80 [18H, m, $Sn(CH_2CH_2CH_2CH_3)_3$ and CH_3CH_2]; δ_C(75 MHz, $CDCl_3$) 170.2, 47.4, 46.9, 35.0, 31.9, 29.9, 29.8, 29.5, 29.4, 29.3, 27.8, 25.6, 22.8, 14.2, 13.9, 10.4; HRMS (CI) found: MH^+, 488.2914. $C_{24}H_{50}NO^{120}Sn$ requires MH, 488.2915; m/z (CI) 488 (4%, MH^+), 430 (100%, $M^+-C_4H_9$).

In the same way as the amine **10**, this amide (1.0 g, 2.0 mmol) and $LiAlH_4$ (164 mg, 4.3 mmol) gave, after purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (9:1), the stannane **12b** (591 mg, 61%) as an oil; R_f 0.51 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2965–2770 (CH); δ_H (400 MHz, C_6D_6) 3.13 (1H, td, J=6.0, 3.5 Hz, NCH), 3.04–3.00 (1H, m, NCH), 2.56 (1H, dd, J=8.5, 7.5 Hz, NCHSn), 2.28–2.17 (1H, m, NCH), 2.11–1.92 (3H, m, NCH and CH_2), 1.90–1.34 [26H, m, 7×CH_2 and $Sn(CH_2CH_2CH_2CH_3)_3$], 1.15–0.90 [18H, m, $Sn(CH_2CH_2CH_2CH_3)_3$ and CH_3]; δ_C(100 MHz, C_6D_6) 58.1, 57.4, 54.2, 32.3, 30.2, 30.0, 29.9, 29.8, 29.7, 28.2, 28.7, 25.1, 23.2, 14.1, 13.9, 9.5; HRMS (CI) found: MH^+, 474.3136. $C_{24}H_{52}N^{120}Sn$ requires MH, 474.3121; m/z (CI) 474 (2%, MH^+), 182 (100, MH^+-Bu_3Sn-H).

4.1.9. *N*-(2-Methylpropyl)-2-tributylstannyl-pyrrolidine 12c. *B*-Bromocatecholborane (20.9 mL, 20.9 mmol, 1.0 M in CH_2Cl_2) was added to the stannane **2** (8.0 g, 17.4 mmol) in CH_2Cl_2 (170 mL). After 30 min, the mixture was washed with 2 M $NaOH_{(aq)}$ (3×60 mL) and the CH_2Cl_2 layer was dried (Na_2SO_4) and filtered. The mixture was cooled to −50 °C under argon and triethylamine (24.2 mL, 174 mmol) was added followed by a dropwise addition of isobutyryl chloride (2.8 mL, 26.1 mmol). The mixture was maintained at −50 °C for 1 h, and then at room temperature for 4 h. The mixture was washed with saturated $NaHCO_{3(aq)}$ (100 mL), dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (10:1), gave the amide 2-methyl-1-(2-tributylstannyl-pyrrolidin-1-yl)-propan-1-one (6.95 g, 93%) as an oil; R_f 0.40 [petrol–EtOAc (10:1)]; ν_{max} (film)/cm^{-1} 2960 (C–H), 1620 (C=O); δ_H (400 MHz, $CDCl_3$) 3.53–3.50 (1H, m, NCH), 3.40–3.35 (2H, m, NCH, NCHSn), 2.65–2.61 [1H, septet, J=7.0 Hz, $CH(CH_3)_2$], 2.18–2.12 (1H, m, CH), 1.94–1.90 (3H, m, $CHCH_2$), 1.47–1.45 (6H, m, 3×CH_2), 1.31–1.25 (6H, m, 3×CH_2), 1.11–1.09 [6H, m, $CH(CH_3)_2$], 0.89–0.80 (15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$); δ_C(100 MHz, $CDCl_3$) 173.7, 46.9, 46.8, 32.3, 29.4, 29.3, 27.6, 27.3, 19.2, 13.8, 10.0; HRMS (ES) found: MH^+, 432.2289. $C_{20}H_{42}NO^{120}Sn$ requires MH^+, 432.2288; GC–MS m/z (CI) 432 (100%, MH^+); Found: C, 56.12; H, 9.64; N, 3.05. $C_{20}H_{41}NOSn$ requires C, 55.83; H, 9.60; N, 3.26%.

In the same way as the amine **12a**, this amide (4.0 g, 9.3 mmol) and $LiAlH_4$ (0.71 g, 18.6 mmol) gave, after purification by column chromatography on basic alumina, eluting with petrol–EtOAc (95:5), the stannane **12c** (3.14 g, 81%) as an oil; R_f 0.65 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2955, 2925, 2870 (C–H); δ_H (400 MHz, C_6D_6) 3.03–2.99 (1H, m, NCH), 2.59 (1H, m, NCH), 2.54 (1H, m, NCHSn), 2.12 (1H, m, NCH), 2.09–1.95 (2H, m, CH_2), 1.91–1.68 [10H, m, NCH, $CH(CH_3)_2$, 4×CH_2), 1.52–1.48 (6H, m, 3×CH_2), 1.18 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 1.13–1.08 (6H, m, 3×CH_2), 1.05 (9H, m, 3×CH_3), 1.01 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$]; δ_C(100 MHz, $CDCl_3$) 65.7, 58.0, 53.9, 29.7, 29.6, 27.9, 27.7, 24.9, 21.5, 20.5, 13.7, 9.3; HRMS (ES) found: MH^+, 418.2497. $C_{20}H_{44}N^{120}Sn$ requires MH^+, 418.2495; GC–MS m/z (CI) 418 (100%, MH^+).

Enantioenriched pyrrolidine **12c** was also prepared by dynamic resolution (Table 3): *n*-BuLi (0.58 mL, 1.44 mmol, 2.5 M in cyclohexane) was added to the stannane (±)-**12c** (500 mg, 1.20 mmol) and (−)-sparteine (422 mg, 1.80 mmol) in dry hexane (1.2 mL) under nitrogen at room temperature. After 1 h, the mixture was cooled to −20 °C and Bu_3SnCl (0.55 mL, 2.04 mmol) was added. After 30 min saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with Et_2O (3×40 mL), dried (Na_2SO_4), and evaporated. Purification as above gave the stannane (*R*)-**12c** (399 mg, 80%) as an oil; $[\alpha]_D^{24}=-59.9$ (2.4, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**12c** was determined to be 65% ee by comparison of its specific rotation to the specific rotation of the stannane (*S*)-**12c**, $[\alpha]_D^{24}=+86.2$ (2.4,

$CHCl_3$), prepared from the *N*-Boc stannane (*S*)-**2** (94% ee).[15]

4.1.10. *N*-(3-Methylbutyl)-2-tributylstannyl-pyrrolidine 12d. In the same way as the amide **6**, the stannane **2** (2.0 g, 4.4 mmol), *B*-bromocatecholborane (16 mL, 0.3 M, 4.8 mmol) and 3-methyl-butyryl chloride (1.6 mL, 13 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol then petrol–EtOAc (9:1), the amide 3-methyl-1-(2-tributylstannyl-pyrrolidin-1-yl)-butan-1-one (1.2 g, 65%) as an oil; R_f 0.43 [petrol–EtOAc (9:1)]; ν_{max} (film)/cm^{-1} 1620 (C=O), 2955–2860 (CH); δ_H (300 MHz, $CDCl_3$) 3.51–3.46 (1H, m, NCH), 3.38–3.32 (2H, m, NCHSn and NCH), 2.16 (3H, m, $NC(O)CH_2$, CH), 1.86–1.71 (3H, m, CH_2CH), 1.42–1.27 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.21–1.13 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 0.85–0.69 [22H, m, $Sn(CH_2CH_2CH_2CH_3)_3$ and $(CH_3)_2CH$]; δ_C(75 MHz, $CDCl_3$) 169.7, 47.6, 47.0, 43.9, 29.8, 29.4, 27.7, 25.8, 23.1, 23.0, 14.3, 10.4; HRMS (CI) found: MH^+, 446.2445. $C_{21}H_{46}NO^{120}Sn$ requires MH, 446.2446; *m/z* (CI) 446 (3%, MH^+), 388 (100, $M^+-C_4H_9$).

In the same way as the amine **10**, this amide (2.0 g, 4.5 mmol) and $LiAlH_4$ (359 mg, 9.5 mmol) gave, after purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (9:1), the stannane **12d** (1.0 g, 52%) as an oil; R_f 0.43 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2950–2780 (CH); δ_H (400 MHz, C_6D_6) 3.04–2.86 (2H, m, 2×NCH), 2.47–2.42 (1H, m, NCHSn), 2.15–2.05 (1H, m, NCH), 2.02–1.77 (3H, m, NCH and CH_2), 1.75–1.60 [9H, m, CH, CH_2 and $Sn(CH_2CH_2CH_2CH_3)_3$], 1.48–1.34 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.10–0.90 [23H, m, $Sn(CH_2CH_2CH_2CH_3)_3$, $(CH_3)_2CH$ and CH_2]; δ_C(100 MHz, C_6D_6) 58.1, 55.6, 54.2, 38.8, 29.9, 29.8, 28.0, 26.9, 25.1, 23.2, 23.0, 14.0, 9.5; HRMS (CI) found: MH^+, 432.2668. $C_{21}H_{46}N^{120}Sn$ requires MH, 432.2652; *m/z* (CI) 432 (11%, MH^+), 374 (8, $M^+-C_4H_9$), 140 (100, M^+-Bu_3Sn-H).

4.1.11. *N*-(Cyclohexylmethyl)-2-tributylstannyl-pyrrolidine 12e. In the same way as the amide **6**, the stannane **2** (2.0 g, 4.4 mmol), *B*-bromocatecholborane (8 mL, 0.6 M, 5 mmol) and cyclohexanecarbonyl chloride (0.9 mL, 6.5 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol then petrol–EtOAc (9:1), the amide cyclohexyl-(2-tributylstannyl-pyrrolidin-1-yl)-methanone (665 mg, 66%) as an oil; R_f 0.63 [petrol–EtOAc (4:1)]; ν_{max} (film)/cm^{-1} 2920–2855 (CH), 1615 (C=O); δ_H (400 MHz, $CDCl_3$) 3.54–3.50 (1H, m, NCH), 3.40–3.33 (2H, m, NCHSn and NCH), 2.32 (1H, m, CH), 2.15–2.09 (1H, m, CH), 1.97–1.82 (3H, m, $CHCH_2$), 1.85–1.25 [22H, m, $Sn(CH_2CH_2CH_2CH_3)_3$ and $(CH_2)_5$], 0.89–0.80 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 172.8, 46.9, 46.8, 42.9, 29.4, 29.2, 29.1, 27.6, 27.5, 27.3, 26.0, 25.9, 25.7, 13.8, 10.0; HRMS (ES) found: M^+, 471.2520. $C_{23}H_{45}NO^{120}Sn$ requires M, 471.2523; *m/z* (ES) 471 (11%, M^+), 413 (100, $M^+-C_4H_9$-H); Found: C, 58.66; H, 9.90; N, 2.89. $C_{23}H_{45}NOSn$ requires C, 58.61; H, 9.62; N, 2.97%.

In the same way as the amine **10**, this amide (590 mg, 1.3 mmol) and $LiAlH_4$ (100 mg, 2.6 mmol) gave, after purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (19:1), the stannane **12e** (930 mg, 77%) as an oil; R_f 0.56 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2950–2780 (CH); δ_H (400 MHz, $CDCl_3$) 3.88–3.80 (1H, m, NCH), 2.50–2.37 (2H, m, NCH and NCHSn), 2.02–1.58 (13H, m, NCH_2, CH and 5×CH_2), 1.49–1.46 [6H, m, $(CH_3CH_2)_3$], 1.36–1.16 [10H, m, CH_2CH_2 and $(CH_3CH_2CH_2)_3$], 0.98–0.78 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 64.7, 58.5, 54.6, 37.7, 32.7, 32.1, 29.7, 29.6, 27.9, 27.3, 26.7, 26.5, 24.9, 13.7, 9.2; HRMS (CI) found: MH^+, 458.2792. $C_{23}H_{48}N^{120}Sn$ requires MH, 458.2809; *m/z* (CI) 458 (2%, MH^+), 166 (100, M^+-Bu_3Sn); Found: C, 60.82; H, 10.79; N, 3.08. $C_{23}H_{47}NSn$ requires C, 60.54; H, 10.38; N, 3.07%.

4.1.12. *N*-(2,2-Dimethylpropyl)-2-tributylstannyl-pyrrolidine 12f. In the same way as the amide **6**, the stannane **2** (1.0 g, 2.2 mmol), *B*-bromocatecholborane (3.8 mL, 0.6 M, 2.28 mmol) and 2,2-dimethylpropionyl chloride (0.8 mL, 6.5 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol then petrol–EtOAc (9:1), the amide 2,2-dimethyl-1-(2-tributylstannyl-pyrrolidin-1-yl)-propan-1-one (793 mg, 80%) as an oil; R_f 0.60 [petrol–EtOAc (4:1)]; ν_{max} (film)/cm^{-1} 1630 (C=O); δ_H (400 MHz, $CDCl_3$) 3.71–3.65 (1H, m, NCH), 3:50–3.44 (2H, m, NCH and NCHSn), 2.05–2.02 (1H, m, CH), 1.96–1.77 (3H, m, $CHCH_2$), 1.57–1.37 [6H, m, $Sn(CH_2CH_2)_3$], 1.34–1.23 [15H, m, $(CH_3CH_2)_3$ and $(CH_3)_3C$], 0.89–0.78 [15H, m, $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 174.2, 50.1, 48.0, 38.7, 29.3, 28.0, 27.9, 27.8, 27.7, 13.7, 9.9; HRMS (FI) found: M^+, 445.2357. $C_{21}H_{43}NO^{120}Sn$ requires M, 445.2367; *m/z* (FI) 445 (11%, M^+), 388 (100, $M^+-C_4H_9$); Found: C, 56.52; H, 9.92; N, 2.98. $C_{21}H_{43}NOSn$ requires C, 56.64; H, 9.73; N, 3.14%.

In the same way as the amine **10**, this amide (1.3 g, 2.7 mmol) and $LiAlH_4$ (220 mg, 5.8 mmol) gave, after purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (19:1), the stannane **12f** (982 mg, 78%) as an oil; R_f 0.47 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2960–2860 (CH); δ_H (400 MHz, $CDCl_3$) 2.92–2.84 (1H, m, NCH), 2.72–2.66 (1H, m, NCHSn), 2.46 (1H, d, $J=15.0$ Hz, NCH), 2.13 (1H, q, $J=8.0$ Hz, CH), 1.96 (2H, m, 2×NCH), 1.78–1.68 (3H, m, CH_2CH), 1.56–1.43 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.38–1.22 [6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$], 0.96–0.82 [24H, m, $(CH_3CH_2CH_2CH_2)_3Sn$ and $(CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 70.2, 60.9, 56.9, 32.6, 29.7, 29.6, 29.3, 28.0, 25.9, 14.1, 9.8; HRMS (CI) found: MH^+, 432.2647. $C_{21}H_{46}N^{120}Sn$ requires MH, 432.2652; *m/z* (CI) 432 (5%, MH^+), 140 (100, M^+-Bu_3Sn-H); Found: C, 58.47; H, 11.00; N, 3.26. $C_{21}H_{45}NSn$ requires C, 58.62; H, 10.54; N, 3.25%.

4.1.13. *N*-Butyl-2-trimethylsilyl-pyrrolidine 13a. *n*-BuLi (0.23 mL, 0.57 mmol, 2.5 M in cyclohexane) was added to the stannane **12a** (200 mg, 0.48 mmol) in dry Et_2O (5 mL) under nitrogen at room temperature. After 1 h, Me_3SiCl (0.10 mL, 0.81 mmol) was added. After 10 min saturated $NaHCO_{3(aq)}$ (10 mL) was added. The mixture was extracted with Et_2O (3×20 mL), the combined Et_2O extracts were dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel, eluting with

CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1), gave the pyrrolidine (±)-**13a** (66 mg, 0.33 mmol, 69%) as an oil; R_f 0.36 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2960, 2870, 2780 (C–H); δ_H (400 MHz, $CDCl_3$) 3.16–3.12 (1H, m, NCH), 2.82–2.75 (1H, m, NCH), 2.04–2.02 (1H, m, NCH), 1.85–1.30 (10H, m, NCH, NCHSi, 4×CH_2), 0.93 (3H, t, J=7.0 Hz, CH_2CH_3), 0.03 [9H, s, $Si(CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 59.4, 58.7, 58.2, 33.5, 29.8, 26.6, 23.3, 16.6, 0.0; HRMS (CI) found: MH^+, 200.1827. $C_{11}H_{26}NSi$ requires MH^+, 200.1835; GC–MS *m/z* (CI) 200 (100%, MH^+), 126 [85, $M^+ - Si(CH_3)_3$].

n-BuLi (0.23 mL, 0.57 mmol, 2.5 M in cyclohexane) was added to the stannane (±)-**12a** (200 mg, 0.48 mmol) and (−)-sparteine (169 mg, 0.72 mmol) in dry hexane (5 mL) under nitrogen at room temperature. After 1 h, Me_3SiCl (0.10 mL, 0.81 mmol) was added. After 10 min saturated $NaHCO_{3(aq)}$ (10 mL) was added. The mixture was extracted with Et_2O (3×20 mL), the combined Et_2O extracts were dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1), gave the pyrrolidine (*R*)-**13a** (71 mg, 74%) as an oil; $[\alpha]_D^{25} = -48.5$ (1.2, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**13a** was determined to be 48% ee by inducing non-equivalence in the ^1H NMR spectrum for the CH_2CH_3 triplet by use of *R*-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (30 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**13a** (3 mg) in $CDCl_3$.

4.1.14. *N*-Octyl-2-trimethylsilyl-pyrrolidine 13b. In the same way as the pyrrolidine **11**, *n*-BuLi (0.41 mL, 2.5 M in cyclohexane, 1.0 mmol), the stannane **12b** (193 mg, 0.41 mmol) in THF (1.5 mL) and TMSCl (0.14 mL, 1.1 mmol) gave, after purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:0.3:0.1), the pyrrolidine (±)-**13b** (99 mg, 95%) as an oil; R_f 0.54 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2950–2705 (CH), 830 (Si–C); δ_H (400 MHz, $CDCl_3$) 3.30–3.04 (1H, m, NCH), 2.92–2.72 (1H, m, NCH), 2.15–2.01 (1H, m, NCH), 1.85–1.22 (21H, m, 8×CH_2, NCH_2 and CH_3), 0.04 [9H, s, $Si(CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 59.5, 58.9, 58.1, 34.2, 31.9, 31.7, 30.0, 29.7, 26.4, 25.0, 24.9, 16.5, 0.1; HRMS (CI) found: MH^+, 256.2472. $C_{15}H_{34}NSi$ requires MH, 256.2460; *m/z* (CI) 256 (25%, MH^+), 182 (100, $M^+ - SiMe_3$).

In the same way as the pyrrolidine **11**, *n*-BuLi (0.20 mL, 0.50 mmol, 2.5 M in cyclohexane), the stannane **12b** (197 mg, 0.42 mmol), (−)-sparteine (0.144 mL, 0.62 mmol) and TMSCl (0.09 mL, 0.71 mmol) gave, after purification as above the pyrrolidine (*R*)-**13b** (53 mg, 50%) as an oil; $[\alpha]_D^{25} = -29.7$ (1.2, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**13b** was determined to be 50% ee by inducing non-equivalence in the ^1H NMR spectrum for the $Si(CH_3)_3$ singlet by use of *R*-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (36.0 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**13b** (3.8 mg) in $CDCl_3$.

4.1.15. *N*-(2-Methylpropyl)-2-trimethylsilyl-pyrrolidine 13c. *n*-BuLi (0.46 mL, 1.15 mmol, 2.5 M in cyclohexane) was added to the stannane (±)-**12c** (400 mg, 0.96 mmol) in dry Et_2O (1.0 mL) under nitrogen at room temperature. After 1 h, Me_3SiCl (0.20 mL, 1.6 mmol) was added. After 10 min water (15 mL) was added. The mixture was acidified to pH ~3 with 2 M $HCl_{(aq)}$ (2 mL) and the aqueous layer was washed with Et_2O (2×25 mL). The aqueous layer was basified to pH ~12 with 2 M $NaOH_{(aq)}$ (4 mL) and the mixture was extracted with Et_2O (3×25 mL). The latter combined Et_2O extracts were dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1), gave the pyrrolidine (±)-**13c** (145 mg, 76%) as an oil; R_f 0.77 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2955, 2900, 2870, 2780 (C–H); δ_H (400 MHz, C_6D_6) 3.17–3.13 (1H, m, NCH), 2.55–2.49 (1H, m, NCH), 2.10–2.07 (1H, m, NCH), 1.89–1.66 (7H, m, NCH, NCHSi, $CHMe_2$, CH_2CH_2), 1.16 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 0.95 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 0.18 [9H, s, $Si(CH_3)_3$]; δ_C(100 MHz, C_6D_6) 66.0, 55.8, 55.7, 28.1, 27.4, 24.8, 21.4, 20.5, −2.6; HRMS (CI) found: M^+, 199.1753. $C_{11}H_{25}NSi$ requires M^+, 199.1756; GC–MS *m/z* (CI) 200 (100%, MH^+), 126 [58, $M^+ - Si(CH_3)_3$]; Found: C, 66.26; H, 12.80; N, 6.63. $C_{11}H_{25}NSi$ requires C, 66.25; H, 12.64; N, 7.02%.

In the same way as the pyrrolidine **11**, *n*-BuLi (0.46 mL, 1.15 mmol, 2.5 M in cyclohexane), the stannane **12c** (400 mg, 0.96 mmol) in dry hexane (1.0 mL), (−)-sparteine (338 mg, 1.44 mmol) and TMSCl (0.20 mL, 1.62 mmol) gave, after purification as above the pyrrolidine (*R*)-**13c** (149 mg, 78%) as an oil; $[\alpha]_D^{25} = -77.8$ (1.0, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**13c** was determined to be 70% ee by inducing non-equivalence in the ^1H NMR spectrum for the $Si(CH_3)_3$ singlet by use of (*S*)-(+)-mandelic acid (8 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**13c** (5 mg) in C_6D_6.

4.1.16. *N*-(3-Methylbutyl)-2-trimethylsilyl-pyrrolidine 13d. In the same way as the pyrrolidine **11**, the stannane **12d** (184 mg, 0.42 mmol) in THF (1.5 mL), *n*-BuLi (0.43 mL, 1.06 mmol, 2.5 M in cyclohexane) and TMSCl (0.147 mL, 1.15 mmol) gave, after purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:0.3:0.1), the pyrrolidine **13d** (73 mg, 80%) as an oil; R_f 0.50 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2930–2705 (CH), 830 (Si–C); δ_H (400 MHz, $CDCl_3$) 3.30–3.19 (1H, m, NCH), 3.08–2.88 (1H, m, NCH), 2.19–1.22 (10H, m, CH, 4×CH_2 and NCH), 0.89 (6H, d, J=6.5 Hz, 2×CH_3), 0.06 [9H, s, $Si(CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 56.9, 55.6, 55.2, 27.4, 27.3, 26.6, 24.0, 22.8, 22.7, 2.3; HRMS (CI) found: MH^+, 214.1967. $C_{12}H_{28}NSi$ requires MH, 214.1991; *m/z* (CI) 213 (18%, M^+), 141 (100, $M^+ - SiMe_3$).

In the same way as the pyrrolidine **11**, *n*-BuLi (0.21 mL, 0.52 mmol, 2.5 M in cyclohexane), the stannane **12d** (187 mg, 0.43 mmol), (−)-sparteine (0.15 mL, 0.65 mmol) and TMSCl (0.09 mL, 0.74 mmol) gave, after purification as above the pyrrolidine (*R*)-**13d** (60 mg, 64%) as an oil; $[\alpha]_D^{22} = -22.6$ (1.2, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**13d** was determined to be 53% ee by inducing non-equivalence in the ^1H NMR spectrum for the $Si(CH_3)_3$ singlet by use of *S*-(+)-

mandelic acid (3.5 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**13d** (4 mg) in C_6D_6.

4.1.17. *N*-(Cyclohexylmethyl)-2-trimethylsilyl-pyrrolidine 13e. *n*-BuLi (0.525 mL, 1.36 mmol, 2.5 M in cyclohexane) was added to the stannane **12e** (250 mg, 0.55 mmol) in hexane–Et_2O [(4:1), 2.5 mL] at room temperature. After 30 min TMSCl (0.187 mL, 1.47 mmol) was added. After a further 30 min, the mixture was absorbed on alumina. Purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (9:1), gave a mixture of the product and the starting material. The mixture was purified by distillation under reduced pressure (150 °C, 25 mm of Hg) to give the pyrrolidine **13e** (19 mg, 14%) as an oil; R_f 0.61 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2915–2695 (CH), 835 (Si-C); δ_H (400 MHz, $CDCl_3$) 3.12–3.07 (1H, m, NCH), 2.48 (1H, d, J=11.0 Hz, NCH), 2.12–2.04 (1H, m, NCH), 2.08–2.03 (1H, m, NCH), 1.92–1.13 (16H, m, NCH, CH and 7×CH_2), 0.02 [9H, m, $(CH_3)_3Si$]; δ_C(100 MHz, $CDCl_3$) 64.7, 56.2, 56.1, 37.5, 32.4, 31.8, 29.3, 27.4, 26.3, 24.5, 22.9, −2.4; HRMS (CI) found: MH^+, 240.2153. $C_{14}H_{30}NSi$ requires MH, 240.2148; *m*/*z* (CI) 240 (37%, MH^+), 167 [100, $MH^+ - Si(Me)_3$]; Found: C, 70.22; H, 12.52; N, 5.70. $C_{14}H_{29}NSi$ requires C, 70.22; H, 12.20; N, 5.85%.

n-BuLi (0.197 mL, 0.49 mmol, 2.5 M in cyclohexane) was added to the stannane **12e** (188 mg, 0.41 mmol) and (−)-sparteine (0.142 mL, 0.61 mmol) in hexane (2 mL) at room temperature. After 30 min TMSCl (0.09 mL, 0.69 mmol) was added at 0 °C. After a further 30 min, the mixture was absorbed on alumina and purified as described above to give the pyrrolidine (*R*)-**13e** (34 mg, 35%) as an oil; $[\alpha]_D^{25} = -22.7$ (1.0 in $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**13e** was determined to be 64% ee by inducing non-equivalence in the ^{1}H NMR spectrum for the $Si(CH_3)_3$ singlet by use of *S*-(+)-mandelic acid (11.2 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**224** (3.8 mg) in C_6D_6.

4.1.18. *N*-(2,2-Dimethylpropyl)-2-trimethylsilyl-pyrrolidine 13f. In the same way as the pyrrolidine **13e**, the stannane **12f** (164 mg, 0.38 mmol), *n*-BuLi (0.38 mL, 0.96 mmol, 2.5 M in cyclohexane) and TMSCl (0.13 mL, 1.0 mmol) gave, after purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (9:1), followed by distillation under reduced pressure (110 °C, 25 mm of Hg) the pyrrolidine **13f** (20 mg, 25%) as an oil; R_f 0.47 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2940–2710 (CH), 835 (Si–C); δ_H (400 MHz, $CDCl_3$) 3.25–3.15 (1H, m, NCH), 2.54 (1H, d, J=15.0 Hz, NCH), 2.04–1.50 (7H, m, NCH and NCH_2-CH_2CH_2), 1.90 [9H, s, $(CH_3)_3C$], 0.02 [9H, m, $(CH_3)_3Si$]; δ_C(100 MHz, $CDCl_3$) 70.3, 58.9, 58.8, 32.7, 29.2, 27.0, 25.4, 2.3; HRMS (CI) found: MH^+, 214.1997. $C_{14}H_{30}NSi$ requires MH, 214.1992; *m*/*z* (CI) 214 (22%, MH^+), 141 [100, $MH^+ - Si(Me)_3$].

In the same way as the pyrrolidine **13e**, the stannane **12f** (166 mg, 0.39 mmol), (−)-sparteine (0.13 mL, 0.58 mmol), *n*-BuLi (0.185 mL, 0.46 mmol, 2.5 M) and TMSCl (0.084 mL, 0.66 mmol) gave, after purification as above the pyrrolidine (*R*)-**13f** (25 mg, 30%) as an oil; $[\alpha]_D^{25} = -31.7$ (1.1 in $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*R*)-**13f** was determined to be 60% ee by inducing non-equivalence in the ^{1}H NMR spectrum for the $Si(CH_3)_3$ singlet by use of *R*-(−)-mandelic acid (10.2 mg) as a chiral solvating agent with the pyrrolidine (*R*)-**13f** (4.0 mg) in C_6D_6.

4.1.19. *N*-(2-Methylpropyl)-pyrrolidine-2-carboxylic acid phenylamide 14a. *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane) was added to the stannane (±)-**12c** (1.0 g, 2.4 mmol) in dry Et_2O (2.4 mL) under nitrogen at room temperature. After 1 h, phenylisocyanate (0.44 mL, 4.1 mmol) was added. After 30 min, water (1 mL) was added. The mixture was acidified to pH ~3 with 10% aqueous citric acid solution (15 mL) and the aqueous layer was washed with Et_2O (2×25 mL). The aqueous layer was basified to pH ~9 with 10% $NaHCO_{3(aq)}$ (30 mL) and the mixture was extracted with Et_2O (3×25 mL). The latter combined Et_2O extracts were dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:3), gave the amide (±)-**14a** (0.36 g, 60%). A small portion was recrystallised from hot EtOAc to give the amide (±)-**14a** as plates; mp 88–90 °C; R_f 0.27 [petrol–EtOAc (4:1)]; ν_{max} (KBr)/cm^{-1} 3280 (N–H), 2950, 2870 (C–H), 1675 (C=O), 1600, 1520 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 9.50 (1H, broad s, NH), 7.60–7.57 (2H, m, Ar), 7.35–7.31 (2H, m, Ar), 7.11–7.07 (1H, m, Ar), 3.27–3.24 (1H, m, NCH), 3.15 (1H, m, NCH), 2.39–2.28 (4H, m, NCH, NCH_2, CH), 2.05–1.95 (1H, m, CH), 1.84–1.74 (3H, m, CH_2, C*H*Me_2), 1.08 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 0.92 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$]; δ_C(100 MHz, $CDCl_3$) 173.2, 138.0, 129.0, 123.9, 118.9, 68.9, 64.5, 53.6, 30.4, 27.5, 24.5, 21.1, 20.5; HRMS (ES) found: MH^+, 247.1810. $C_{15}H_{23}N_2O$ requires MH^+, 247.1810; GC–MS *m*/*z* (CI) 247 (100%, MH^+); 126 (54, $M^+ - C_7H_6NO$); Found: C, 73.13; H, 9.21; N, 11.16. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00; N, 11.37%.

In the same way as the enantioenriched stannane (*R*)-**12c**, the stannane (±)-**12c** (1.00 g, 2.40 mmol), (−)-sparteine (844 mg, 3.60 mmol), *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane) and phenyl isocyanate (0.44 mL, 4.08 mmol) gave, after purification by acidifying to pH ~3 with 10% aqueous citric acid solution (15 mL) and washing with Et_2O (2×25 mL) then basifying to pH ~9 with 10% aqueous $NaHCO_3$ (30 mL) and extracting with Et_2O (3×25 mL), drying (Na_2SO_4), evaporating and column chromatography on silica gel, eluting with petrol–EtOAc (7:3), the amide (*S*)-**14a** (337 mg, 57%) as plates; $[\alpha]_D^{24} = -96.5$ (1.7, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*S*)-**14a** was determined to be 64% ee by chiral HPLC. Resolution between the enantiomers of the pyrrolidine **14a** was achieved using a Gilson 231 XL system fitted with a Chiralpak AD column (250 mm×4.6 mm i.d.) as the stationary phase with hexane–EtOH (90:10 v/v) as the mobile phase at a flow rate of 1.0 mL min^{-1}; ambient temperature, detection by UV absorbance at 235 nm. Injection volume 20 μL of the sample prepared in a 1 mg mL^{-1} solution of EtOH. Under these conditions, the faster running component and slower running component were eluted at 6.7 min (minor) and 10.4 min (major), respectively.

An authentic sample of (*R*)-**14a** was prepared from (*S*)-*N*-Boc-2-tributylstannyl-pyrrolidine, lit.[15] $[\alpha]_D^{23} = +132.2$ (2.9, $CHCl_3$) quoted as 94% ee, our sample $[\alpha]_D^{24} = +136.4$ (4.9, $CHCl_3$), by replacing the *N*-Boc group with *N*-isobutyl (using *B*-bromocatecholborane, then *i*PrCOCl, then $LiAlH_4$) to give (*S*)-**12c**, then treating with *n*-BuLi in THF at −78 °C and adding PhNCO to give (*R*)-**14a**, $[\alpha]_D^{20} = +135.0$ (1.0, $CHCl_3$).

4.1.20. 2-(1-Hydroxy-1-methylethyl)-*N*-(2-methylpropyl)-pyrrolidine 14b. In the same way as the silane (±)-**13c**, the stannane (±)-**12c** (1.0 g, 2.4 mmol) in Et_2O (2.4 mL), *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane) and acetone (0.30 mL, 4.08 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:1), the pyrrolidine (±)-**14b** (0.28 g, 62%) as an oil; R_f 0.40 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 3450 (O–H), 2960, 2870, 2795 (C–H); δ_H (400 MHz, C_6D_6) 2.96–2.93 (1H, m, NCH), 2.52–2.48 (1H, m, NCH), 2.48–2.42 (1H, m, NCH), 2.34–2.31 (1H, m, NCH), 2.20–2.15 (1H, m, NCH), 1.70–1.62 (5H, m, CH_2CH_2, C*H*Me_2), 1.27 [3H, s, $COH(CH_3)^A(CH_3)^B$], 1.21 [3H, s, $COH(CH_3)^A(CH_3)^B$], 1.06 [3H, d, $J=7.0$ Hz, $CH(CH_3)^C(CH_3)^D$], 0.87 [3H, d, $J=7.0$ Hz, $CH(CH_3)^C(CH_3)^D$]; δ_C(100 MHz, C_6D_6) 73.9, 72.3, 68.0, 55.2, 28.4, 28.3, 27.2, 25.5, 25.2, 21.0, 20.1; HRMS (ES) found: MH^+, 186.1861. $C_{11}H_{24}NO$ requires MH^+, 186.1858; GC–MS *m/z* (CI) 186 (100%, MH^+), 126 (52, $M^+ - C_3H_7O$).

In the same way as the pyrrolidine **11**, *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane), the stannane (±)-**12c** (1.00 g, 2.40 mmol) in dry hexane (2.4 mL), (−)-sparteine (0.84 g, 3.60 mmol) and acetone (0.30 mL, 4.08 mmol) gave, after purification as above the pyrrolidine (*S*)-**14b** (254 mg, 57%) as an oil; $[\alpha]_D^{22} = -20.2$ (1.2, $CHCl_3$); other spectroscopic data as above. The enantiomeric excess of (*S*)-**14b** was determined to be 68% ee by inducing non-equivalence in the ^1H NMR spectrum for the two diastereotopic $CH(CH_3)_2$ doublets by use of *R*-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (30 mg) as a chiral solvating agent with the pyrrolidine (*S*)-**14b** (4 mg) in $CDCl_3$.

An authentic sample of (*R*)-**14b** was prepared from (*S*)-*N*-Boc-2-tributylstannyl-pyrrolidine, which was converted as described for **14a** above to the stannane (*S*)-**12c**, which (500 mg, 1.2 mmol) was treated with *n*-BuLi (0.62 mL, 1.56 mmol, 2.5 M in cyclohexane) in THF (12 mL) and TMEDA (0.24 mL, 1.56 mmol) at −78 °C followed by acetone (0.15 mL, 2.04 mmol) to give, after purification as above, the pyrrolidine (*R*)-**14b** (91 mg, 41%) as an oil; $[\alpha]_D^{24} = +27.9$ (2.1, $CHCl_3$).

4.1.21. 2-(Diphenylhydroxymethyl)-*N*-(2-methylpropyl)-pyrrolidine 14c. In the same way as the pyrrolidine **13c**, the stannane (±)-**12c** (1.0 g, 2.4 mmol) in Et_2O (2.4 mL), *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane) and benzophenone (0.74 g, 4.1 mmol) gave, after purification by column chromatography on silica gel, eluting with CH_2Cl_2–EtOAc (10:1), the pyrrolidine (±)-**14c** (0.60 g, 81%). A portion was recrystallised from hot hexane to give the pyrrolidine (±)-**14c** as cubes; mp 85.5–90 °C; R_f 0.34 [CH_2Cl_2–EtOAc (10:1)]; ν_{max} (KBr)/cm^{-1} 3335 (O–H), 2960, 2805 (C–H); δ_H (400 MHz, $CDCl_3$) 7.65–7.63 (2H, m, Ar), 7.57–7.54 (2H, m, Ar), 7.30–7.26 (4H, m, Ar), 7.15–7.13 (2H, m, Ar), 5.01 (1H, broad s, OH), 3.82–3.79 (1H, m, NCH), 3.23–3.18 (1H, m, NCH), 2.32–2.30 (1H, m, NCH), 2.06–2.03 (1H, m, NCH), 1.94–1.85 (1H, m, CH), 1.71–1.66 (3H, m, $CHCH_2$), 1.59–1.52 [2H, m, NCH, C*H*$(CH_3)_2$], 0.63 [3H, d, $J=6.5$ Hz, $CH(CH_3)^A(CH_3)^B$], 0.55 [3H, d, $J=6.5$ Hz, $CH(CH_3)^A(CH_3)^B$]; δ_C(100 MHz, $CDCl_3$) 148.1, 146.9, 128.0, 127.9, 126.1, 125.9, 125.5, 77.7, 71.7, 64.7, 55.4, 29.5, 27.7, 24.4, 21.0, 19.7; HRMS (ES) found: MH^+, 310.2165. $C_{21}H_{28}NO$ requires MH^+, 310.2171; GC–MS *m/z* (CI) 310 (99%, MH^+), 183 (100, $C_{13}H_{10}OH^+$), 126 (94, $M^+ - C_{13}H_{10}OH$); Found: C, 81.07; H, 9.10; N, 4.22. $C_{21}H_{27}NO$ requires C, 81.51; H, 8.79; N, 4.53%. Resolution between the enantiomers of the pyrrolidine **14c** was achieved using a Gilson 231 XL system fitted with a Chiralpak AD column (250 mm×4.6 mm i.d.) as the stationary phase with hexane–EtOH (95:5 v/v) as the mobile phase at a flow rate of 1.0 mL min^{-1}; ambient temperature, detection by UV absorbance at 215 nm. Injection volume 20 μL of the sample prepared in a 1 mg mL^{-1} solution of EtOH. Under these conditions, the faster running component and slower running component were eluted at 10.8 and 11.0 min, respectively.

4.1.22. 2-Benzyl-*N*-(2-methylpropyl)-pyrrolidine 14d. In the same way as the pyrrolidine **13c**, the stannane (±)-**12c** (1.0 g, 2.4 mmol) in Et_2O (2.4 mL), *n*-BuLi (1.15, 2.88 mmol, 2.5 M in cyclohexane) and benzyl chloride (0.47 mL, 4.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:1), the pyrrolidine (±)-**14d** (0.29 g, 60%) as an oil; R_f 0.32 [petrol–EtOAc (1:1)]; δ_H (400 MHz, C_6D_6) 7.29–7.18 (5H, m, Ar), 3.17–3.12 (1H, m, NCH), 3.04–3.02 (1H, m, CH), 2.56–2.52 (3H, m, CH, 2×NCH), 2.14–2.10 (1H, m, NCH), 2.08–2.04 (1H, m, NCH), 1.85–1.80 (1H, m, C*H*Me_2), 1.70–1.60 (2H, m, CH_2), 1.60–1.50 (2H, m, CH_2), 1.14 [3H, d, $J=6.0$ Hz, $CH(CH_3)^A(CH_3)^B$], 1.00 [3H, d, $J=6.0$ Hz, $CH(CH_3)^A(CH_3)^B$]; δ_C(100 MHz, C_6D_6) 140.4, 129.5, 128.2, 125.9, 66.5, 63.4, 54.3, 41.3, 30.4, 27.8, 22.5, 21.3, 20.6; HRMS (ES) found: MH^+, 218.1909. $C_{15}H_{24}N$ requires MH^+, 218.1908; GC–MS *m/z* (CI) 218 (100%, MH^+), 126 (84, $M^+ - C_7H_7$). Attempts at inducing non-equivalence in the ^1H NMR spectrum to resolve the enantiomers of (±)-**14d** using a variety of chiral solvating reagents in a range of deuterated solvents proved unsuccessful. Also, attempts to resolve the enantiomers of (±)-**14d** by chiral HPLC using a variety of column types with a range of solvents were also unsuccessful.

In the same way as the pyrrolidine **11**, *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane), the stannane (±)-**12c** (1.00 g, 2.40 mmol) in dry hexane (2.4 mL), (−)-sparteine (0.84 g, 3.60 mmol) and benzyl chloride (0.47 mL, 4.1 mmol) gave, after purification as above, the pyrrolidine (*R*)-**14d** (263 mg, 50%) as an oil; $[\alpha]_D^{25} = +6.5$ (1.1, $CHCl_3$); other spectroscopic data as above for (±)-**14d**. The major enantiomer was assumed to have the (*R*) stereochemistry on the basis that the corresponding *N*-methyl compound in THF is known to quench with partial inversion of configuration with benzyl chloride as the electrophile.[21] The extent of inversion reported for the *N*-methyl compound (15% ee (*S*) product from (*S*) stannane

of 94% ee) was correlated with that obtained in the analogous experiment conducted with *N*-isobutyl-2-lithiopyrrolidine.

n-BuLi (1.25 mL, 3.12 mmol, 2.5 M in cyclohexane) was added, using the method by Gawley,[21] to the stannane (*S*)-**12c** (94% ee) (1.0 g, 2.4 mmol) and TMEDA (0.47 mL, 3.12 mmol) in dry THF (24 mL) under nitrogen at −78 °C. After 30 min, benzyl chloride (0.47 mL, 4.1 mmol) was added and the mixture was maintained at −78 °C for a further 1 h before warming to room temperature. After evaporation, the mixture was acidified to ~pH 3 with 2 M aqueous HCl (2 mL) and the aqueous layer was washed with Et_2O (2×25 mL). The aqueous layer was basified to pH ~12 with 2 M aqueous NaOH (4 mL) and the mixture was extracted with Et_2O (3×25 mL). The latter combined Et_2O extracts were dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography as above, gave the pyrrolidine **14d** (213 mg, 41%) as an oil; $[\alpha]_D^{24} = -14.1$ (1.2, $CHCl_3$). Assuming that this specific rotation corresponds to 15% ee of the (*S*)-enantiomer (inversion of configuration) then the dynamic resolution experiment with (−)-sparteine as the chiral ligand (described above) resulted in the (*R*)-enantiomer of approximately 7% ee. Caution must be taken with this assumption as the specific rotation for the experiment in THF may not correspond to 15% ee of the inverted compound using this *N*-isobutyl derivative.

4.1.23. *N*-(2-Methylpropyl)-2-(3-phenylpropyl)-pyrrolidine 14e. In the same way as the pyrrolidine **13c**, the stannane (±)-**12c** (500 mg, 1.20 mmol) in Et_2O (1.2 mL), *n*-BuLi (0.58 mL, 1.44 mmol, 2.5 M in cyclohexane) and 1-bromo-3-phenylpropane (0.31 mL, 2.04 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:1), the pyrrolidine (±)-**14e** (82 mg, 28%) as an oil; R_f 0.68 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (10:1:0.1)]; ν_{max} (film)/cm^{-1} 2955, 2870, 2790 (C–H); δ_H (400 MHz, C_6D_6) 7.29–7.15 (5H, m, Ar), 3.17–3.13 (1H, m, NCH), 2.62–2.60 (2H, m, CH_2Ph), 2.45–2.40 (1H, m, NCH), 2.25–2.17 (1H, m, NCH), 2.04–1.99 (2H, m, 2× NCH), 1.80–1.51 (7H, m, 3×CH_2, CH), 1.49–1.35 (2H, m, CH_2), 1.11 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 0.99 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$]; δ_C(100 MHz, C_6D_6) 142.8, 128.5, 128.4, 128.0, 127.8, 125.8, 64.8, 63.3, 54.3, 36.5, 34.0, 30.3, 28.0, 27.8, 22.6, 21.4, 20.6; HRMS (EI) found: M^+, 245.2151. $C_{17}H_{27}N$ requires M^+, 245.2144; GC–MS *m/z* (CI) 246 (100%, MH^+), 126 (54, $M^+ - C_9H_{11}$).

In the same way as the pyrrolidine **11**, *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane), the stannane (±)-**12c** (1.00 g, 2.40 mmol) in dry hexane (2.4 mL), (−)-sparteine (0.84 g, 3.60 mmol) and 1-bromo-3-phenylpropane (0.62 mL, 4.08 mmol) gave, after purification as above, the pyrrolidine (*S*)-**14e** (274 mg, 46%) as an oil; $[\alpha]_D^{23} = +6.4$ (1.1, $CHCl_3$); other spectroscopic data as above for (±)-**14e**. The major enantiomer was assumed to have the (*S*) stereochemistry on the basis that the corresponding *N*-methyl compound in THF is known to quench with partial inversion of configuration with 1-bromo-3-phenylpropane as the electrophile.[21] The enantiomeric excess of (*S*)-**14e** was determined to be 7% ee by chiral HPLC. Resolution between the enantiomers of the pyrrolidine **14e** was achieved using a Gilson 231 XL system fitted with a ChiroV column (250 mm×4.6 mm i.d.) as the stationary phase with MeOH–Et_3N–HOAc (100:0.01:0.01 v/v) as the mobile phase at a flow rate of 0.5 mL min^{-1}; ambient temperature, detection by UV absorbance at 265 nm. Injection volume 20 μL of the sample prepared in a 1 mg mL^{-1} solution of EtOH. Under these conditions, the faster running component and slower running component are eluted at 37.1 min (major) and 38.6 min (minor), respectively.

The pyrrolidine **14e** was also prepared by the method by Gawley,[21] using *n*-BuLi (1.25 mL, 3.12 mmol, 2.5 M in cyclohexane), the stannane (*S*)-**12c** (94% ee) (1.0 g, 2.4 mmol), TMEDA (0.47 mL, 3.12 mmol) in dry THF (24 mL) and 1-bromo-3-phenylpropane (0.62 mL, 4.1 mmol) which gave, after purification as above, the pyrrolidine **14e** (176 mg, 30%) as an oil; $[\alpha]_D^{24} = -7.9$ (1.4, $CHCl_3$).

4.1.24. 2-[2-(Methyldiphenylsilyl)ethyl]-*N*-(2-methylpropyl)-pyrrolidine 14f. In the same way as the pyrrolidine **13c**, the stannane (±)-**12c** (1.00 g, 2.40 mmol) in Et_2O (2.4 mL), *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane) and methyldiphenylvinylsilane (0.92 g, 4.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:1), the pyrrolidine (±)-**14f** (0.66 g, 78%) as an oil; R_f 0.32 [CH_2Cl_2–MeOH–$NH_{3(aq)}$ (20:1:0.1)]; ν_{max} (film)/cm^{-1} 2955, 2870, 2785 (C–H); δ_H (400 MHz, C_6D_6) 7.57–7.54 (4H, m, Ar), 7.20–7.16 (6H, m, Ar), 3.09–3.04 (1H, m, NCH), 2.30–2.24 (1H, m, NCH), 2.24–2.20 (1H, m, NCH), 1.96–1.90 (2H, m, 2× NCH), 1.70–1.66 (4H, m, 4×CH), 1.55–1.48 (3H, m, 3× CH), 1.25–1.20 (1H, m, CHSi), 1.05 (1H, m, CHSi), 0.98 [3H, d, J=6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 0.83 [3H, d, J= 6.5 Hz, $CH(CH_3)^A(CH_3)^B$], 0.52 (3H, s, $SiCH_3$); δ_C(100 MHz, C_6D_6) 137.5, 134.7, 129.2, 127.6, 66.8, 63.3, 54.5, 29.5, 27.8, 27.6, 22.7, 21.3, 20.6, 9.1, −4.4; HRMS (ES) found: MH^+, 352.2456. $C_{23}H_{34}NSi$ requires MH^+, 352.2460; GC–MS *m/z* (CI) 352 (93%, MH^+), 126 (100, $M^+ - C_{15}H_{17}Si$); Found: C, 78.48; H, 9.86; N, 3.76. $C_{23}H_{33}NSi$ requires C, 78.57; H, 9.46; N, 3.98%.

In the same way as the pyrrolidine **11**, *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in cyclohexane), the stannane (±)-**12c** (1.00 g, 2.40 mmol) in dry hexane (2.4 mL), (−)-sparteine (0.84 g, 3.60 mmol) and methyldiphenylvinylsilane (0.92 g, 4.1 mmol) gave, after purification as above, the pyrrolidine **14f** (641 mg, 76%) as an oil; $[\alpha]_D^{24} = -14.4$ (1.2, $CHCl_3$); other spectroscopic data as above for (±)-**14f**. If the electrophilic quench proceeds with retention of configuration then the major enantiomer will have the (*S*) stereochemistry. The enantiomeric excess of **14f** was determined to be 15% ee by chiral HPLC. Resolution between the enantiomers of the pyrrolidine **14f** was achieved using a Gilson 231 XL system fitted with a ChiroV column (250 mm×4.6 mm i.d.) as the stationary phase with MeOH–Et_3N–HOAc (100:0.01:0.01 v/v) as the mobile phase at a flow rate of 0.5 mL min^{-1}; ambient temperature, detection by UV absorbance at 265 nm. Injection volume 20 μL of the sample prepared in a 1 mg mL^{-1} solution of EtOH. Under these conditions, the

faster running component and slower running component are eluted at 30.9 min (minor) and 32.5 min (major), respectively.

The pyrrolidine **14f** was also prepared by the method by Gawley,[21] using *n*-BuLi (1.3 mL, 3.12 mmol, 2.5 M in cyclohexane), the stannane (*S*)-**12c** (94% ee) (1.0 g, 2.4 mmol), TMEDA (0.47 mL, 3.12 mmol) in dry THF (24 mL) and methyldiphenylvinylsilane (0.92 mL, 4.1 mmol) which gave, after purification as above, the pyrrolidine **14f** (135 mg, 16%) as an oil; $[\alpha]_D^{22} = +93.6$ (0.9, $CHCl_3$). It is not known if this electrophile quenches with retention or inversion of configuration, but it is clear from the above data that at low temperature the reaction is stereoselective, but under the conditions of the dynamic resolution with (−)-sparteine low selectivity (of opposite absolute sense) is obtained.

4.1.25. *N*-(2-Methylpropyl)-pyrrolidine-2-carboxylic acid 1-phenylethylamide 15a,b and 16a,b. *n*-BuLi (0.58 mL, 1.44 mmol, 2.5 M in cyclohexane) was added to the stannane (±)-**12c** (500 mg, 1.20 mmol) in dry Et_2O (1.2 mL) under nitrogen at room temperature. After 1 h, *R*-(+)-phenylethyl isocyanate (0.25 mL, 1.80 mmol) was added. After 20 min water (1 mL) was added. The mixture was acidified to pH ~3 with 10% aqueous citric acid solution (15 mL) and the aqueous layer was washed with Et_2O (2×25 mL). The aqueous layer was basified to pH ~9 with 10% aqueous $NaHCO_3$ (30 mL) and the mixture was extracted with Et_2O (3×25 mL). The latter combined Et_2O extracts were dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:1), gave the pyrrolidines (*SR*,*R*)-**15a**,**b** (257 mg, 78%) as an inseparable (1:1) mixture of diastereomers. A small portion was recrystallised from hot EtOAc to give plates; mp 67–70 °C; R_f 0.25 [petrol–EtOAc (1:1)]; ν_{max} (KBr)/cm^{-1} 3335 (N–H), 2960, 2870, 2795 (C–H), 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 7.75 (0.5H, m, NH), 7.65 (0.5H, m, NH), 7.33–7.24 (5H, m, Ar), 5.13–5.05 (1H, m, CH), 3.15–3.12 (1H, m, NCH), 3.03–2.96 (1H, m, NCH), 2.32–2.30 (1H, m, NCH), 2.22–2.13 (3H, m, 2×NCH, CH), 1.78–1.73 (4H, m, CH, CH_2, C*H*Me_2), 1.48–1.46 [3H, m, NHCH(CH_3)], 0.98 [1.5H, d, J=6.5 Hz, CH(CH_3)$_2$], 0.91 [1.5H, d, J=6.5 Hz, CH(CH_3)$_2$], 0.75 [1.5H, d, J=6.5 Hz, CH(CH_3)$_2$], 0.71 [1.5H, d, J=6.5 Hz, CH(CH_3)$_2$]; δ_C(100 MHz, $CDCl_3$) 174.0, 173.9, 143.7, 143.2, 128.6, 128.5, 127.3, 127.1, 126.3, 125.8, 68.4, 68.4, 64.7, 64.4, 53.6, 53.4, 48.0, 47.7, 30.4, 30.3, 27.5, 27.4, 24.4, 24.3, 22.4, 21.7, 21.2, 21.1, 20.6, 20.0; HRMS (ES) found: MH^+, 275.2121. $C_{17}H_{27}N_2O$ requires MH^+, 275.2123; GC–MS *m*/*z* (CI) 275 (100%, MH^+), 126 (32, $M^+ - C_9H_{10}NO$); Found: C, 74.38; H, 9.82; N, 10.14. $C_{17}H_{26}N_2O$ requires C, 74.41; H, 9.55; N, 10.21%.

n-BuLi (0.58 mL, 1.44 mmol, 2.5 M in cyclohexane) was added to the stannane (±)-**12c** (500 mg, 1.20 mmol) and (−)-sparteine (422 mg, 1.80 mmol) in dry hexane (1.2 mL) under nitrogen at room temperature. After 1 h, the mixture was cooled to −20 °C and *R*-(+)-phenylethyl isocyanate (0.25 mL, 1.80 mmol) was added. After 30 min, water (1 mL) was added. Purification as above gave the pyrrolidines (*SR*,*R*)-**15a**,**b** (263 mg, 80%), as an inseparable (2:1) mixture of diastereomers; spectroscopic data as above. The diastereomeric excess was determined to be 34% de by GC–MS. Resolution between the diastereomers of pyrrolidine **15a**,**b** was achieved using a Thermoquest CE Trace GC–MS2000 system. The faster running diastereomer and slower running diastereomer were eluted at 18.15 min (minor) and 18.3 min (major), respectively.

In the same way as the pyrrolidines (*SR*,*R*)-**15a**,**b**, the stannane (±)-**12c** (500 mg, 1.20 mmol), (−)-sparteine (422 mg, 1.80 mmol), *n*-BuLi (0.58 mL, 1.44 mmol, 2.5 M in cyclohexane) and *S*-(−)-phenylethyl isocyanate (0.25 mL, 1.80 mmol) gave, after purification as above, the pyrrolidines (*SR*,*S*)-**16a**,**b** (260 mg, 79%) as an inseparable (3:1) mixture of diastereomers; spectroscopic data as above. The diastereomeric excess was determined to be 44% de by GC–MS as described above with the diastereomers eluting at 18.15 min (major) and 18.3 min (minor).

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Copper mediated scalemic organolithium reagents in alkaloid syntheses

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Dedicated to Professor Amos B. Smith, III on the occasion of his 60th birthday

Abstract—Scalemic 2-pyrrolidinylcuprates generated via asymmetric deprotonation of *N*-Boc-pyrrolidine followed by treatment with THF soluble CuCN·2LiCl react with ω-functionalized vinyl halides to afford 2-alkenyl-*N*-Boc-pyrrolidines. *N*-Boc deprotection and cyclization via intramolecular *N*-alkylation generates the pyrrolizidine or indolizidine skeletons. Subsequent functional group manipulation affords enantioenriched (+)-heliotridane, (+)-isoretronecanol, a formal synthesis of (+)-laburnine, (+)-(*R*)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine, (*R*)-1,2,3,5,6,8a-hexahydroindolizine, (+)-*ent*-δ-coniceine, (+)-tashiromine and (+)-5-epitashiromine.

1. Introduction

The pyrrolizidine (1-azabicyclo[3,3]octanes)[1] and indolizidine (1-azabicyclo[4,3]nonanes)[2] alkaloids are found in a wide variety of plants. Pyrrolizidine alkaloids are generally found in the genus *Senecio* (>1000 species) of the Compositae family and often consist of esters between an alkanolamine (i.e., necine base) and a necic acid.[1d] Although the pyrrolizidine alkaloids function as insect anti-feedents and insecticides, some insects sequester them for biological purposes.[1b–c] Both series of alkaloids display toxicity to mammals.[3–4] Plants containing pyrrolizidine alkaloids are the most common source of animal poisoning and pyrrolizidine macrocyclic diesters exhibit the more potent genotoxicity and tumorigenicity.[3a] The polyhydroxy indolizidine alkaloids swainsonine and castanospermine were shown to be agents of toxicity to grazing animals and the isolation of these causative agents led to the discovery of the aza sugars as glycosidase inhibitors.[4b]

Simple members of the two classes have been the subject of frequent total syntheses often serving as a testing ground for new synthetic methodology.[1a,d,2] Asymmetric syntheses abound[5–14] and enantioenriched pyrrolizidines **1–3** and indolizidines **6–8** have all been synthesized, while pyrrolizine **4**[15] and indolizine **5**[16] have only been prepared in racemic form. Of the nearly 50 asymmetric syntheses involving (−)-heliotridane,[5,7e–f,h] (+)-*ent*-heliotridane (**1**),[6] (−)-isoretronecanol,[7] (+)-isoretronecanol (**2**),[8] (+)-laburnine (**3**)[7a–c,n,9] and its enantiomer (−)-trachelanthamidine,[7d,i–k,m,10] (−)-coniceine,[11] (+)-coniceine,[12] (+)-tashiromine (**7**),[7b,13,14b] (−)-tashiromine[14] and (+)-5-epitashiromine (**8**) [or its (−) isomer][13b,17] all but six have involved the use of chiral auxiliaries[11d,f–h,12d] or molecules from the chiral pool [e.g., (*S*)-proline,[7d,f,h,i,k,m,11a,c,e] (*S*)-α-methylbenzylamine,[7b,g] α-D-glucosamine,[7l] (*R*)-phenylglycinol,[12d] L-glutamic acid,[14a] (+)-carvone,[5] (*S*)-pyroglutaminol,[11b] (*S*)-ethyl pyroglutamate,[7e] and (−)-4-hydroxy-L-proline[7n]] containing one or more of the stereocenters to be incorporated into the target molecules. The reported asymmetric syntheses involving enzymatic kinetic resolution,[12a] or asymmetric transformations [e.g., dihydroxylation,[12b] Heck,[12b] catalytic desymmetrization,[7c] and iminium ion cyclization[9b]] are also limited by scale, length of the synthetic route, or the enantioselectivity achieved. An elegant asymmetric catalyzed conjugate addition of a pyrrole moiety intramolecularly to a Michael acceptor was recently employed in an asymmetric synthesis of (−)-tashiromine.[14a]

A potentially rapid strategy for the synthesis of enantioenriched pyrrolizidines **1–2**, as well as indolizidines **7** and **8** (Fig. 1), could involve stereo- and regiocontrolled functional group manipulation of exo-cyclic alkenes **11a** and

Keywords: Alkaloid syntheses; α-(*N*-Carbamoyl)alkylcuprates; Stereogenic cuprates; (+)-Heliotridane; (+)-Isoretronecanol; (+)-(*R*)-2,3,5,7a-Tetrahydro-1*H*-pyrrolizine; (*R*)-1,2,3,5,6,8a-hexahydroindolizine; (+)-*ent*-δ-Coniceine; (+)-Tashiromine; (+)-5-Epitashiromine.
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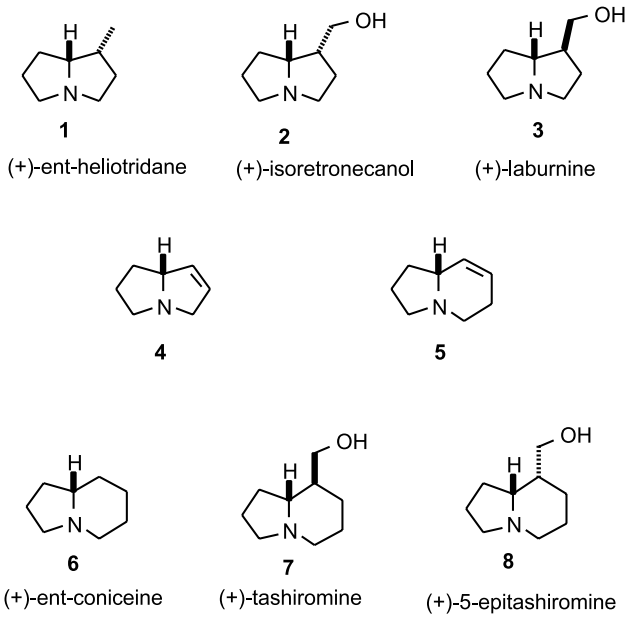
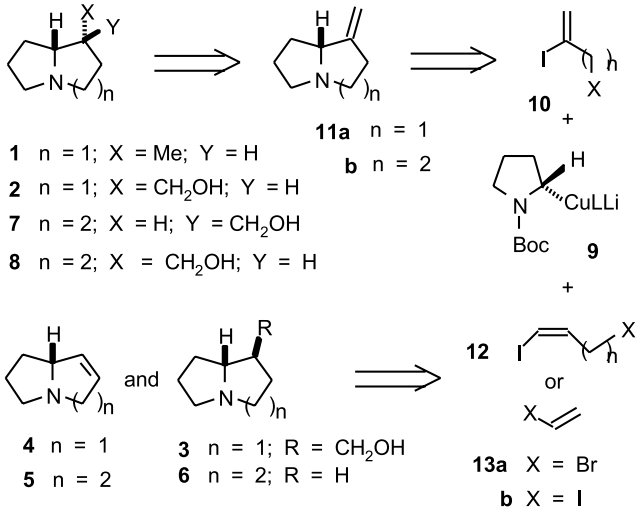


Figure 1. Pyrrolizidine and indolizidine synthetic targets.

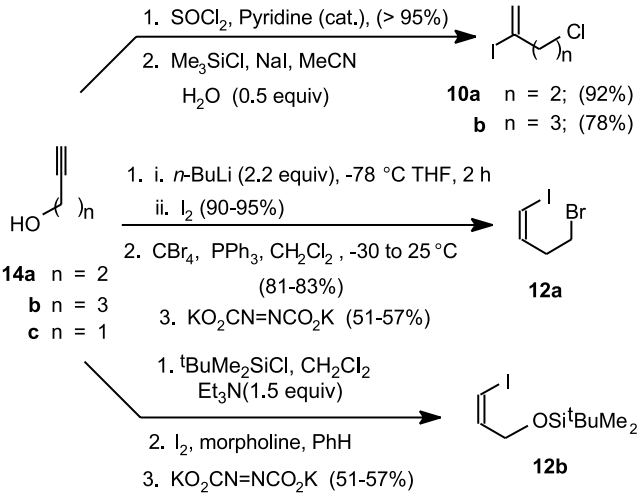
11b, respectively, which in turn could be constructed by sequential vinylation of cuprate **9**, generated from the scalemic stereogenic α-lithio carbamate,[18] followed by ring annulation (Scheme 1).[19] Extension of the strategy to pyrrolizine **4**, indolizine **5**, and indolizidine **6** would utilize 1-halo-1-alkenes **12a–b** with good leaving groups in the 3- or 4-positions for subsequent cyclization onto the *N*-atom. Variations on the strategy involving vinyl halides **13a–b** require subsequent radical cyclization of *N*-(2-iodo-1-oxoethyl)-2-vinylpyrrolidine to afford, after functional group manipulation, pyrrolizidine **3**. The success of this versatile asymmetric synthetic strategy relies upon the stereocontrolled formation of scalemic α-lithio and α-cuprio *N*-Boc-pyrrolidine and coupling of the cuprate reagent with vinyl halides in a highly enantioselective fashion. In this full report, we detail the rapid and efficient asymmetric syntheses of pyrrolizidines **1–3**, pyrrolizine **4**, indolizine **5**, and indolizidines **6–8**.



Scheme 1.

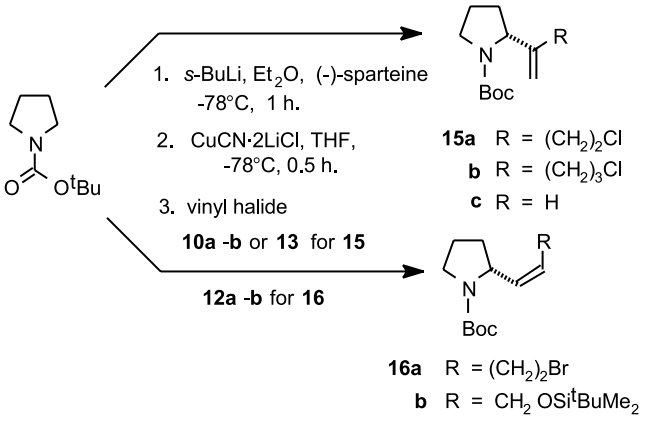
2. Results and discussion

The requisite 1- or 2-halo-1-alkenes containing ω-functionalization were readily prepared from commercially available 1-alkynes (Scheme 2). Conversion of alcohol **14a** into the alkyl chloride[20] followed by addition of in situ generated HI[21] to the chloro alkyne afforded vinyl iodide **10a**. Similar addition of HI to commercially available 5-chloro-1-pentyne (**14b**) afforded vinyl iodide **10b**. *cis*-Vinyl iodide **12a** was prepared by iodination of alkyne **14a**,[22] followed by conversion of the alcohol to the alkyl bromide[23] and diimide reduction[24] of the triple bond. Silylation of alkynyl alcohol **14c** followed by 1-alkynyl iodination and diimide reduction gave vinyl iodide **12b** in good overall yield.[25] Coupling of these readily prepared ω-functionalized vinyl iodides with metallated *N*-Boc-pyrrolidine provides all of the carbon atoms of the alkaloid skeletons (Scheme 3).



Scheme 2.

The key synthetic step involves the generation of scalemic *N*-Boc-2-pyrrolidinylcuprates and coupling with the vinyl iodides **10a–b** and **12a–b** or vinyl halides **13a–b** (Scheme 3). Asymmetric deprotonation of *N*-Boc-pyrrolidine according to Beak's procedure[26] followed by treatment with THF soluble CuCN·2LiCl afforded either the alkyl(cyano)cuprate (i.e., RCuCNLi) or dialkylcuprate (i.e., R_2CuLi) reagent depending upon the equivalents of CuCN employed.



Scheme 3.

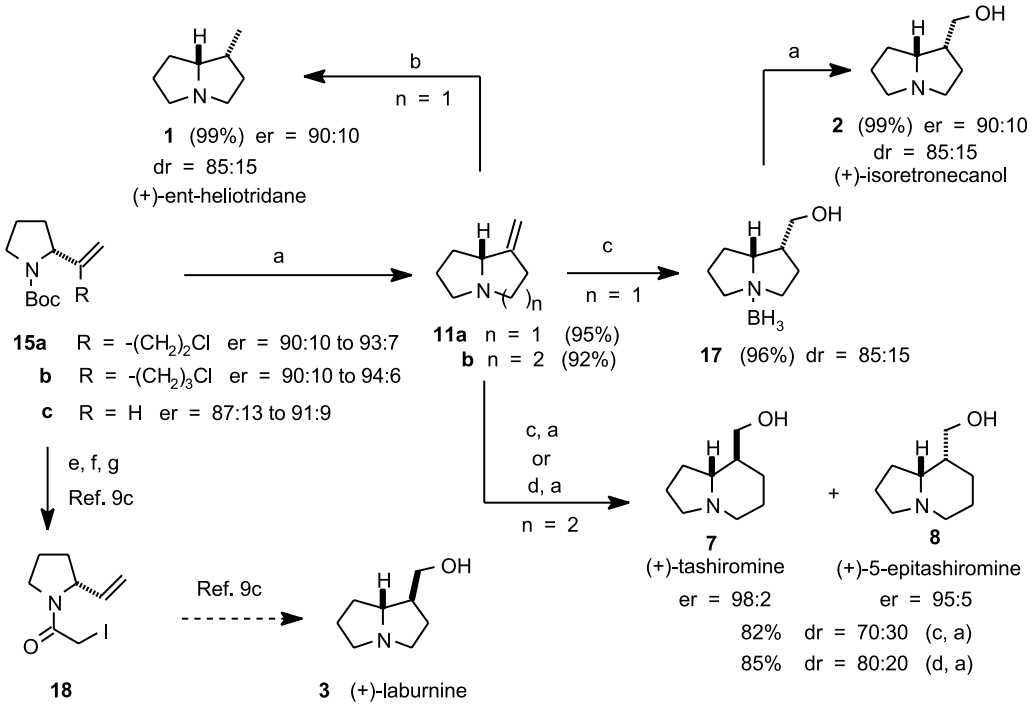
Table 1. Asymmetric deprotonation of *N*-Boc-pyrrolidine followed by cuprate formation and cuprate vinylation

Entry	Vinyl halide	CuCN·2LiCl (equiv)[a]	Product	% Yield[b]	er[c]
1	**10a**	1.0	**15a**	71–75	87:13–90:10
2	**10a**	0.5	**15a**	73–81	93:7–95:5
3	**10b**	1.0	**15b**	79	85:15–91:9
4	**10b**	0.5	**15b**	83	94:6–95:5
5	**12a**	1.0	**16a**	64–69	60:40–70:30
6	**12a**	0.5	**16a**	51–57	90:10–93:7
7	**12b**	1.0	**16b**	81	86:14
8	**12b**	0.5	**16b**	83	90:10
9	**13a**	0.5	**15c**	61–67	87:13
10	**13b**	0.5	**15c**	73	91:9

[a] Deprotonation of *N*-Boc-pyrrolidine [(i) *s*-BuLi, Et_2O, (−)-sparteine, −78 °C, 1 h; (ii) CuCN·2LiCl, 1.0 equiv=RCuCNLi, 0.5 equiv=R_2CuLi].
[b] Based upon isolated products purified by column chromatography.
[c] Enantiomeric ratio determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel].

As previously established,[26,27] high enantioselectivities require deprotonation of *N*-Boc-pyrrolidine in diethyl ether and formation of the cuprate reagents at low temperatures. This can be achieved by addition of a THF solution of CuCN·2LiCl to the cold solution of *N*-Boc-(*S*)-2-lithiopyrrolidine affording the scalemic cuprate reagent in a THF/Et_2O (1:1) solvent mixture. These reaction conditions afforded the *N*-Boc-2-alkenylpyrrolidines in modest to good chemical yields and with very good to excellent enantiomeric ratios as determined by chiral stationary phase HPLC (Table 1). In all instances the two reagents gave comparable chemical yields while the dialkylcuprate reagent gave higher enantiomeric ratios than the alkylcyanocuprate reagent. These very good to excellent enantiomeric ratios could be achieved on 1.0 mmol and on 10 mmol scale reactions. From previous studies, it had been established that the Li to Cu transmetallation as well as the vinylation reactions proceeded with retention of configuration.[27] It should be noted that in principle the opposite absolute configuration can be achieved by use of a (+)-sparteine analogue developed by O'Brien.[28]

N-Boc deprotection and cyclization of **15a–b** afforded **11a–b** as key intermediates for the preparation of the pyrrolizidine (i.e., **1** and **2**) and indolizidine (i.e., **7** and **8**) alkaloids (Scheme 4). Although the one-pot transformation could be achieved with either trimethylsilyl triflate (TMSOTf) or with TMSCl/NaI/MeCN, the most convenient procedure involved deprotection of **15a–b** with TMSCl/MeOH followed by neutralization with $NaHCO_3$ to effect cyclization. Simple hydrogenation of **11a** afforded (+)-*ent*-heliotridane (**1**) and its diastereomer (dr=85:15) while hydroboration–oxidation of **11a** afforded the amine–borane complex **17** after aqueous workup. The amine–borane complex **17** and its diastereomer (dr=85:15) were readily purified by column chromatography and gave ^1H and ^{13}C



Scheme 4. Reagents and conditions: (a) (i) Me_3SiCl, MeOH, 12 h, 25 °C; (ii) $NaHCO_3$. (b) H_2, Pd/C (10%), CH_2Cl_2, 12 h. (c) (i) BH_3·THF (2.2 equiv), THF, 0–25 °C, 1 h, then 60 °C, 1 h; (ii) 10 M NaOH (3 equiv), H_2O_2 (30%, 5 equiv), 0–25 °C, 12 h, (96%). (d) (i) BH_3·THF, THF, 0–25 °C, 1 h; (ii) 9-BBN (1.0 equiv), THF, 60 °C, 1 h; (iii) 10 M NaOH (3 equiv), H_2O_2 (30%, 5 equiv), 0–25 °C, 12 h. (e) CF_3COOH (20 equiv), CH_2Cl_2 (100%). (f) $ClCH_2COCl$, CH_2Cl_2, Et_3N (72%). (g) NaI, CH_3CN (95%).

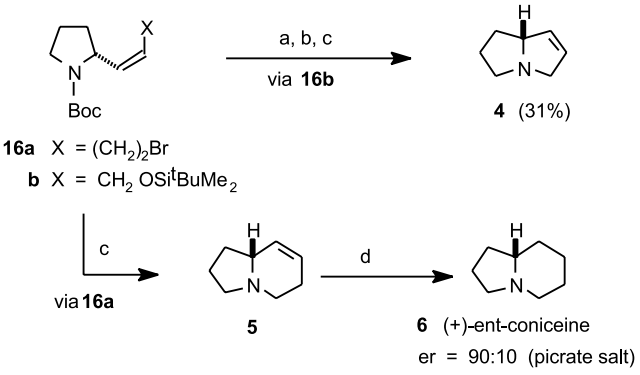
NMR spectra strikingly similar to isoretronecanol.[29] A broad absorption peak between δ 1.60 and 2.10 characteristic of the BH_3-protons was observed in the ^1H NMR spectrum. (+)-Isoretronecanol and its diastereomer (+)-laburnine (**3**) were obtained as an 85:15 mixture of diastereomers by treatment of **16** with TMSCl/MeOH. Previous reports on the hydroboration–oxidation of the lactam analogues of **11a** have not mentioned formation of diastereomeric mixtures of hydroxy lactams, although reported yields were low.[7e,h,29] Interestingly, hydrogenation of **11a** affords the same diastereomeric ratio as the hydroboration reaction, consistent with the 80:20 dr observed for hydrogenation of a lactam analogue of **11a**.[30]

Given that **1** and pseudoheliotridane are prepared from the same intermediate (i.e., **11a**) under the same reaction conditions, the er for each diastereomer is assumed to be the same. The specific rotation of the synthetic mixture of **1** [$[\alpha]_D^{25}=+57$ (*c* 0.5, EtOH)] and pseudoheliotridane when compared to reported values for pure **1** [(+)-heliotridane, $[\alpha]_D^{25}=+86$ (*c* 0.5, EtOH)][6a] and pure pseudoheliotridane ($[\alpha]_D^{25}=+7.0$ (*c* 0.5, EtOH))[6b] corresponds to an er= 88.4:11.6 taking into account the 85:15 diastereomeric ratios. The er is calculated from the expression $0.85\ [ax+(1-a)(-x)]+0.15\ [ay+(1-a)(-y)]=+57$ where *a* is the fraction of the major enantiomer, *x* is the specific rotation for pure heliotridane and *y* is the specific rotation for pure pseudoheliotridane obtained from the literature. Calculation of the optical purity from measured $[\alpha]_{mixture}$/theoretical $[\alpha]_{mixture}$ gave an optical purity of 77% (i.e., an er=88.5:11.5) where Theoretical $[\alpha]_{mixture}=(+86)(0.85)+(+7.0)(0.15)$. Since the specific rotation can be non-linear with concentration, the specific rotation of the synthetic mixture of diastereomers was determined at three different concentrations ($[\alpha]_D^{25}=+57.9$ (*c* 1.0, EtOH), +57.0 (*c* 0.5, EtOH) and +54.2 (*c* 0.25, EtOH)] over a four-fold range of concentrations and showed a small non-linearity.[31] Similarly, the specific rotation of the synthetic mixture of **2** and **3** ($[\alpha]_D^{25}=+60$ (*c* 0.5, EtOH)) when compared to the reported values for **2** ($[\alpha]_D^{25}=+70.2$ (*c* 5, EtOH))[7n] and **3** ($[\alpha]_D{}^{25}=+14.6$ (*c* 3.2, EtOH))[7n] corresponds to an er=95:5 when taking into account the 85:15 mixture of diastereomers. Consequently, within the limits of the method, no epimerization of the stereogenic center appears to occur during *N*-Boc deprotection, cyclization or subsequent functional group manipulations.

Execution of the same sequence with **15b** afforded **11b** which gave (+)-tashiromine (**7**) and (+)-5-epitashiromine (**8**) in a 70:30 ratio after sequential hydroboration–oxidation on the amine–BH_3 complex with BH_3–THF followed by cleavage of the BH_3-complex with TMSCl/MeOH. The two diastereomers could be separated by flash column chromatography and the measured optical rotations corresponded to an er=98:2 for **7** and an er=95:5 for **8**. The differences between the two values most likely reflect errors in measurement and/or some loss of the minor enantiomer during sequential operations and purifications. 5-Epitashiromine displayed a dextrorotatory rotation after initial isolation which changed to a levorotatory rotation after additional passage through a plug of silica gel as previously observed.[13b] Reaction of **11b** with 9-BBN followed by oxidation gave a low yield of organic material upon extraction with CH_2Cl_2, while 9-BBN hydroboration–oxidation of **11b**–BH_3 complex at reflux temperatures in THF gives an 80:20 ratio of **7**:**8** after BH_3 decomplexation with TMSCl/MeOH. Efforts to increase the diastereoselectivity with low temperature hydroboration or with more sterically hindered boranes were not pursued. Control experiments with one equivalent of BH_3-THF did show that amine complexation occurs before olefin hydroboration. The BH_3 complex thus facilitates isolation and purification of these highly water soluble amino alcohols.

This synthetic strategy also provides a synthetic route to (+)-laburnine (Scheme 4). Carbamate cleavage of **15c** followed by amide formation with α-chloroacetyl chloride and Finkelstein conversion of the α-chloroamide to the α-iodoamide afforded **18**.[9c] The enantiomer of **18** has been converted into (−)-trachelanthamidine which is the enantiomer of (+)-laburnine.[9c] The synthesis of **18** thus constitutes a formal total synthesis of (+)-laburnine.

Scalemic 2-alkenyl pyrrolidines **16a–b** are also readily converted to pyrrolizine **4** and indolizine **5**. Sequential silyl ether cleavage of **16b** with H_2SiF_6, mesylation of the alcohol and subsequent treatment of the mesyloxy carbamate with methanolic HCl followed by neutralization with $NaHCO_3$ yields pyrrolizine **4**. The low yield was a result of the volatility of the compound. Similar deprotection of carbamate **16a** and cyclization upon neutralization afforded **5**. Hydrogenation of the indolizine **5** affords (+)-δ-coniceine (**6**) (Scheme 5).



Scheme 5. Reagents and conditions. (a) H_2SiF_6, THF (79%). (b) MsCl, Et_3N, CH_2Cl_2 (87%). (c) (i) Me_3SiCl, MeOH, 12 h, 25 °C; (ii) $NaHCO_3$. (d) MeOH, $Pd(OH)_2$, H_2, 15 h.

3. Summary

In summary, *N*-Boc-2-pyrrolidinylcuprate chemistry offers a rapid entry into the pyrrolizidine and indolizidine carbon skeletons via a two pot process of cuprate coupling with a functionalized vinyl halide followed by a tandem *N*-Boc deprotection–cyclization sequence. The efficient asymmetric syntheses of (+)-*ent*-heliotridane, (+)-isoretronecanol, (+)-laburnine, (+)-**4**, (+)-**5**, (+)-*ent*-δ-coniceine, (+)-tashiromine and (+)-5-epitashiromine illustrate the synthetic power of scalemic α-(*N*-carbamoyl)alkylcuprate methodology and of the enantioenriched 2-lithiocarbamates from which they are derived. Scalemic α-lithiocarbamate methodology is thus significantly extended by copper mediated transformations. Although this strategy for

pyrrolizidine and indolizidine synthesis, as executed, required manipulation of functionality for elaboration and functional group substitution patterns of the natural products subsequent to the generation of the tertiary bridgehead amine, these transformations can in principle be conducted before *N*-Boc deprotection and cyclization. These strongly basic, nucleophilic and easily oxidized tertiary bridgehead nitrogen centers can be problematic in subsequent functional group manipulations. This difficulty can be circumvented if the nitrogen can be protected as the amine–borane or amine–BF_3 complexes.

These asymmetric syntheses employing scalemic stereogenic *N*-Boc-2-pyrrolidinyl metals represent one of the most efficient synthetic routes to these alkaloids to date and illustrates the synthetic power and potential of scalemic stereogenic organometallic reagents in organic synthesis.

4. Experimental

4.1. General

4.1.1. 4-Chloro-2-iodo-but-1-ene (10a). NaI (3.5 g, 23 mmol) was completely dissolved in dry acetonitrile (20 mL). To this solution was added chlorotrimethylsilane (TMSCl, 2.5 g, 23 mmol) which resulted in a cloudy white, fine suspension. After 5 min, water (0.20 g, 11.5 mmol) was added to generate anhydrous HI in situ. The mixture was stirred another 10 min and 4-chloro-1-butyne (2.0 g, 23 mmol) was added neat by syringe. The reaction mixture was stirred for 1 h at room temperature. Then *n*-pentane (40 mL) was added along with aqueous $NaHCO_3$ (saturated). After vigorous shaking, the layers were separated. The top organic layer was washed with sodium thiosulfate ($Na_2S_2O_3$, saturated aqueous), dried ($MgSO_4$) and concentrated in vacuo to give **10a** as a clear liquid (4.5 g, 92%), which was used without further purification: IR (neat) 3003, 1645, 875, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (t, J= 6.6 Hz, 2H), 3.62 (t, J=6.5 Hz, 2H), 5.83 (m, 1H), 6.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 42.9, 47.7, 104.2, 125.7; mass spectrum, *m/z* (rel. intensity) 218 (12, M^++2), 216 (40, M^+), 127 (48), 89 (48), 53 (100).

4.1.2. 5-Chloro-2-iodo-pent-1-ene (10b). Following the procedure described above for **10a** with 5-chloro-1-pentyne on a 5.0 mmol scale, gave **10b** as a clear liquid (0.90 g, 78%) that was used without further purification: IR (neat) 2956, 1612, 1432, 897, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (quint, J=6.5 Hz, 2H), 2.55 (t, J=6.9 Hz, 2H), 3.51 (t, J= 6.8 Hz, 2H), 5.74 (m, 1H), 6.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 31.43, 42.10, 43.09, 109.60, 127.03; mass spectrum, *m/z* (rel. intensity) 232 (21, M^+ +2), 230 (56, M^+), 168 (16), 127 (15), 103 (20), 67 (100).

4.1.3. *cis* 4-Bromo-1-iodo-1-butene (12a). To a solution of 1.88 g of **14a** (26.8 mmol) in 80 mL THF at −78 °C was added 20 mL of 2.00 M *n*-BuLi (54.0 mmol). The thick suspension was vigorously stirred at −78 °C and then allowed to warm up to room temperature over 2 h. Then the suspension was again cooled to −78 °C and to it was added 6.70 g (52.0 mmol) I_2 in 40 mL of THF. After warming to room temperature overnight, the mixture was quenched with saturated aqueous NaCl (3×20 mL), washed with H_2O (2× 20 mL), and dried over anhydrous Na_2SO_4. A yellowish oil (4.72 g, 90% yield) was obtained. The crude product was used for the next reaction without further purification. 4-Hydroxy-1-iodo-1-butyne: IR (neat) 3341 (br), 2931, 1906 (vw), 1051, 683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 1H), 2.61 (t, J=6.3 Hz, 2H), 3.70 (t, J=6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.05, 60.94, 91.05, 100.03; mass spectrum *m/z* (rel. intensity) EI 196 (100, M^+), 166 (68), 127 (33).

To a solution of 1.96 g of 4-hydroxy-1-iodo-1-butyne (10 mmol) in 30 mL of dry CH_2Cl_2 was added 3.97 g of CBr_4 (12 mmol) at −30 °C. The mixture was stirred vigorously, and a solution of PPh_3 (2.70 g, 10 mmol) in 10 mL of dry CH_2Cl_2 was added. The solution was stirred for 2 h at −30 °C, warmed to 0 °C, and then stirred another hour. The crude mixture was filtered through a thin layer of silica gel, and concentrated in vacuo. After column chromatography (100% Petroleum ether), 4-bromo-1-iodo-1-butyne (2.10 g, 81% yield) was obtained: IR (neat) 2100 (vw), 1430, 1322, 1268 (vs), 1208 (vs), 1142, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (t, J=7.2 Hz, 2H), 3.41 (t, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.12, 28.98, 91.70, 100.06; mass spectrum *m/z* (rel. intensity) EI 260 (100, M^++1), 258 (100, M^+−1), 179 (38), 165 (34), 127 (13), 51 (48).

Dipotassium azodicarboxylate was prepared by adding 9.0 g (77 mmol) of azodicarbonamide to a vigorously stirred 40% aqueous potassium hydroxide solution (30 mL), cooled by an ice water bath. After the addition was completed, the mixture was stirred for an additional 45 min at 0 °C and then filtered and the solid was washed with 100 mL of cold methanol. The solid potassium salt was placed in a 500 mL flask with 200 mL of methanol and 10 g (48 mmol) of 4-bromo-1-iodo-1-butyne was added. The mixture was stirred vigorously while a solution of 35 mL of acetic acid in 100 mL of methanol was added via a constant pressure addition funnel at such a rate as to cause gentle boiling. After the addition, the cloudy mixture turned colorless. The reaction mixture was transferred to a separatory funnel containing 500 mL of water and extracted with three 100 mL portions of pentane. The pentane fractions were combined, washed with two 100 mL portions of water, dried over anhydrous sodium sulfate, and filtered. The pentane was removed under reduced pressure to afford 7.14 g (57.0%) of **12a**: IR (neat) 3049, 1640 (w), 1614, 1444, 1282 (s), 1256 (vs), 703, 617; ^1H NMR ($CDCl_3$) δ 2.68–2.74 (m, 2H), 3.41 (t, J=6.9 Hz, 2H), 6.24–6.31 (m, 1H), 6.38–6.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 30.28, 37.70, 85.20, 137.88; mass spectrum *m/z* (relative intensity) EI 262 (20, M^++2), 260 (20, M^+), 167 (20), 135 (89), 133 (90), 53 (100).

4.1.4. *cis* 3-Dimethyl(1,1-dimethylethyl)silyloxy-1-iodo-1-propene (12b). Iodination and diimide reduction of the *tert*-butyldimethylsilyl ether of propargyl alcohol as described above for **12a** gave **12b** in 51% yield: IR (neat) 3420, 2996, 1642, 1455, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (dt, J=14.3, 4.4 Hz, 1H), 6.27 (dt, J=14.5, 1.8 Hz, 1H), 4.28 (dd, J=4.8, 1.8 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.3, 25.8, 66.8, 79.9, 142.0; mass spectrum *m/z* (relative intensity) 241 (100, M^+), 185 (65), 85 (90), 73 (55).

4.2. General procedure A: asymmetric vinylation of *N*-Boc-pyrrolidine for R_2CuLi

N-Boc-pyrrolidine (1.71 g, 10 mmol) was dissolved in freshly distilled ether (30 mL) along with (−)-sparteine (2.69 g, 11 mmol). The reaction mixture was cooled to −78 °C under an argon atmosphere and *sec*-BuLi (6.9 mL, 1.6 M, 11 mmol) was added dropwise by syringe. The resultant solution was stirred at −78 °C for 1 h. Then a solution containing CuCN (450 mg, 5 mmol) and LiCl (450 mg, 11 mmol) in THF (30 mL) was added portion-wise by syringe. The mixture was allowed to stir at −78 °C for 30 min before the vinyl iodide (11 mmol) was added neat. The reaction mixture was then allowed to warm to room temperature overnight. It was diluted with Et_2O (20 mL) and quenched with 5% aqueous HCl (15 mL). After shaking vigorously, the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oil which was purified by column chromatography on silica gel.

4.2.1. 1,1-Dimethylethyl (2*R*)-2-(3-chloro-1-methylene-propyl)-1-pyrrolidinecarboxylate (15a). Following general procedure A on a 10 mmol scale, carbamate **15a** was isolated [R_f 0.75, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (2.11 g, 81%): IR (neat) 2964 (s), 1703 (vs), 1658 (s), 1436 (m), 892, 888 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.60–1.75 (m, 1H), 1.75–1.95 (m, 2H), 1.95–2.15 (m, 1H), 2.30–2.55 (m, 2H), 3.35–3.55 (m, 2H), 3.55–3.70 (m, 2H), 4.10–4.25 (m, 1H), 4.83 (br s with shoulder, 2H); ^{13}C NMR ($CDCl_3$) δ 22.6 (23.3), 28.4, (30.6) 31.3, 36.2, 42.6, 46.6, 61.1, 79.3, 110.2, 146.3, 154.3 (rotamers); mass spectrum, *m*/*z* (rel. intensity) 261 (0.1, $M^+ +2$), 259 (0.5, M^+), 203 (14), 186 (14), 167 (30), 114 (49), 70 (45), 57 (100).

The enantiomeric purity of **15a** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 95:5 (1 mmol scale) to 90–10 (10 mmol scale) er [hexane/^{i}PrOH, 99:1 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 15.98 min followed by the (*S*)-isomer (minor) at 18.19 min.

4.2.2. 1,1-Dimethylethyl (2*R*)-2-(4-chloro-1-methylene-butyl)-1-pyrrolidinecarboxylate (15b). Following general procedure A on a 10 mmol scale, carbamate **15b** was isolated [silica gel, R_f 0.70, petroleum ether/Et_2O, 50;50, v/v] as a clear colorless oil (2.28 g, 83%): IR (neat) 2965 (s), 1702 (vs), 1680 (m), 1440 (m), 890 (s), 882 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.60–1.75 (m, 1H), 1.75–1.90 (m, 2H), 1.90–2.10 (m, 3H), 2.10–2.25 (m, 2H), 3.35–3.50 (br s, 2H), 3.55 (t, J=6.2 Hz, 2H), 4.15–4.35 (m, 1H), 4.77 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 23.4, 28.4, 32.8, 33.2, 36.1, 41.9, 47.6, 61.9, 79.8, 108.9, 146.5, 155.1; mass spectrum, *m*/*z* (rel. intensity) 275 (0.1, $M^+ +2$), 273 (0.4, M^+), 238 (0.1), 217 (15), 200 (14), 181 (28), 154 (32), 114 (56), 70 (57), 57 (100).

The enantiomeric purity of **15b** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 95:5 (1 mmol scale) to 90:10 (10 mol scale) er [hexane/^{i}PrOH, 99:1 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 14.57 min followed by the (*S*)-isomer (minor) at 17.17 min.

4.2.3. 1,1-Dimethylethyl (2*R*)-2-ethenyl-1-pyrrolidine-carboxylate (15c). Following general procedure A on a 2 mmol scale, carbamate **15c** was isolated [R_f 0.65, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (288 mg, 73%): IR (neat) 3049, 1690, 1660, 1340, 990, 892 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.56–2.10 (m, 4H), 3.12–3.37 (m, 2H), 4.10–4.30 (m, 1H), 4.85–5.10 (m, 2H), 5.62–5.80 (m, 1H);^{13}C NMR δ 23.1 (br s), 28.3, 31.2 (br s), 46.2, 58.7, 78.9, 113.7, 149.0, 154.4; mass spectrum *m*/*z* (rel. intensity) EI 197 (0.5, M^+), 141 (33), 124 (12), 96 (27).

The enantiomeric purity of **15c** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 91:9 er [hexane/^{i}PrOH, 99.5:0.5 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 9.68 min followed by the (*S*)-isomer (minor) at 10.15 min.

4.2.4. 1,1-Dimethylethyl (2*R*)-2-[1-[(*Z*)-4-bromo-1-butenyl]]-1-pyrrolidinecarboxylate 16a. Following general procedure A on a 2 mmol scale, carbamate **16a** was isolated [R_f 0.70, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (0.420 g, 69%); IR (neat) 2967, 2873, 1703 (vs), 1651, 1385 (vs), 1169; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.55–1.70 (m, 2H), 1.70–1.95 (m, 2H), 2.55–2.81 (m, 2H), 3.25–3.52 (m, 4H), 4.34–4.69 (m, 1H), 5.22–5.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.80, 28.54, 30.88, 31.50, 32.41, 46.46, 54.21, 79.16, 126.10, 134.40, 154.40.

The enantiomeric purity of **16a** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 90:10 er [hexane/^{i}PrOH, 99.5:0.5 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 13.59 min followed by the (*S*)-isomer (minor) at 14.92 min.

4.2.5. 1,1-Dimethylethyl (2*R*)-2-[1-[(*Z*)-3-[dimethyl(1,1-dimethylethyl)silyloxy]-1-propenyl]]-1-pyrrolidinecarboxylate (16b). Following general procedure A on a 2 mmol scale, carbamate **16b** was isolated [R_f 0.75, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (0.566 g, 83%): IR (neat) 2967, 1688 (vs), 1376 (vs), 1253, 1161, 1100, 843, 770; ^1H NMR ($CDCl_3$) δ −0.8 (s, 6H), 0.81 (s, 9H), 1.35 (s, 9H), 1.50–1.61 (m, 1H), 1.65–1.87 (m, 2H), 1.92–2.06 (m, 1H), 3.22–3.42 (m, 2H), 4.23 (br s, 2H), 4.39 (br s, 1H), 5.21–5.32 (m, 1H), 5.34–5.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.90, 18.15, 23.59, 25.83, 28.42, 33.33, 46.26, 54.33, 59.30, 76.72, 128.60, 132.50, 154.35; mass spectrum *m*/*z* (rel. intensity) 341 (1, M^+), 268 (7), 228 (48), 184 (46), 153 (74), 110 (100), 75 (59), 57 (81).

The enantiomeric purity of **16b** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]

to be a 90:10 er [hexane/^{i}PrOH, 99:1 (v/v), flow rate) 0.5 mL/min, detection at $\lambda=210$ nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 9.17 min followed by the (*S*)-isomer (minor) at 10.58 min.

4.2.6. (*R*)-Hexahydro-1-methylene-1*H*-pyrrolizine (11a). Carbamate **15a** (259 mg, 1.0 mmol) was dissolved in methanol (5.0 mL) at 25 °C, and trimethylsilylchloride (TMSCl, 540 mg, 5.0 mmol) was added dropwise by syringe. The mixture was stirred at room temperature overnight then quenched with saturated aqueous $NaHCO_3$ until pH>8. The mixture was diluted with methylene chloride, two layers were separated, and the organic layer was extracted three times with methylene chloride, and dried ($MgSO_4$). Concentration in vacuo afforded a clear yellow oil which was purified by Kugelrohr distillation (100 °C, 20 mm Hg) to give **11a** as a clear, colorless liquid (0.113 g, 92%): $[\alpha]_D^{22}=+53$ (*c* 1.0, $HCCl_3$); IR (neat) 3400 (vs), 2950 (m), 1660 (m), 1642, 1420 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–1.60 (m, 1H), 1.60–1.80 (m, 2H), 1.90–2.15 (m, 1H), 2.35–2.50 (m, 2H), 2.50–2.60 (m, 2H), 2.80–3.10 (m, 2H), 3.77 (t, $J=6.6$ Hz, 1H), 4.75 (dd, $J=1.5$, 2.0 Hz, 1H), 4.87 (dd, $J=1.5$, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5, 32.2, 32.5, 52.6, 54.1, 67.4, 104.6, 154.5; mass spectrum, *m/z* (rel. intensity) 123 (28, M^+), 122 (44), 108 (5), 95 (100), 80 (15), 67 (22), 55 (19).

4.2.7. (+)-*ent*-Heliotridane (1). Alkene **11a** (123 mg, 1 mmol) was dissolved in methylene chloride (10 mL) and 10% palladium on carbon (30 mg) was added. The round bottom flask (50 mL) was capped with a rubber septum, and sealed with parafilm. A balloon filled with hydrogen gas was attached via a syringe and the reaction mixture was stirred overnight at room temperature. Afterwards, the catalyst was removed by filtration through a thin layer of celite, and methylene chloride removed in vacuo to give a light brown oil which was purified by Kugelrohr distillation (100 °C, 20 mm Hg) to give (+)-*ent*-heliotridane (**1**) and its epimer (+)-pseudoheliotridane as a mixture of diastereomers (85:15, 99%): $[\alpha]_D^{25}=+57$ (*c* 0.5, EtOH), [lit.:[6a] (+)-heliotridane, $[\alpha]_D^{25}=+86$ (*c* 0.5, EtOH); lit.[6b] epimer (+)-pseudoheliotridane, $[\alpha]_D^{25}=+7.0$ (*c* 0.5, EtOH); calculated $[\alpha]_{mixture}=(+86)(0.85)+(+7.0)(0.15)=+74$ corresponding to an ee=77% or an er=88.5:11.5 assuming both diastereomers have the same er]; IR (neat) 3408 (vs), 2936 (m), 1642 (w), 1461 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, $J=6.8$ Hz, 3H), 1.55–1.80 (m, 2H), 1.80–2.20 (m, 4H), 2.40–2.55 (m, 1H), 2.65–2.75 (m, 1H), 2.90–3.10 (m, 1H), 3.50–3.70 (m, 1H), 3.80–4.00 (m, 1H), 4.15–4.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 25.7, 25.9, 30.7, 34.7, 53.6, 56.5, 69.9; mass spectrum, *m/z* (rel. intensity) 125 (19, M^+), 108 (4), 97 (10), 83 (100), 55 (52). Pseudoheliotridane: ^{13}C NMR δ 16.5, 24.9, 29.1, 34.1, 39.8, 54.51, 54.54, 72.9.

Heliotridane–BH_3 complex. ^{13}C NMR ($CDCl_3$) δ 13.80, 24.92, 27.40, 31.40, 34.76, 63.60, 65.02, 76.91 [lit.[1e] ^{13}C NMR δ 13.76, 24.88, 27.36, 31.37, 34.74, 63.54, 64.97, 76.88]. *Pseudoheliotridane–BH_3 complex.* ^{13}C NMR ($CDCl_3$) δ 17.63, 24.46, 30.99, 33.03, 41.60, 63.76, 65.02, 80.18 [lit.:[1e] ^{13}C NMR δ 17.60, 24.43, 30.07, 33.01, 41.60, 63.73, 64.27, 80.18].

4.2.8. (+)-Isoretronecanol (2). Alkene **11a** (123 mg, 1 mmol) was dissolved in THF (3 mL) and cooled to 0 °C under an inert argon atmosphere. Then a 1.0 M solution of $BH_3\cdot$THF in THF (1 mL, 1 mmol) was added and the reaction mixture was allowed to slowly warm to room temperature over 1 h. 9-BBN (2.0 mL, 1.0 mmol) was added dropwise. The reaction mixture was then heated at reflux for 1 h, cooled to 0 °C, and treated with 10 M NaOH (1.0 mL). H_2O_2 (1.0 mL, 30% aq) was added and stirring continued for 1 h while allowing the reaction mixture to warm to room temperature. The crude mixture was then diluted with Et_2O and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography on silica gel (petroleum ether/ether, 80:20, v/v) afforded the amine–borane complexes **17** as a 85:15 mixture of diastereomers: IR (neat) 3415 (s), 2976 (s), 2881 (s), 2365 (vs), 2314 (vs), 2271 (vs), 1634 (w), 1453 (s), 1170 (vs), 1015 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–2.10 (vbr s, BH_3, 3H), 1.50–1.65 (m, 2H), 1.70–1.90 (m, 2H), 1.90–2.05 (m, 3H), 2.62–2.78 (m, 2H), 2.90–2.98 (m, 1H), 3.10–3.21 (m, 1H), 3.30–3.40 (m, 1H), 3.58–3.75 (m, 3H); ^{13}C NMR ($CDCl_3$). *Major diastereomer*: δ 24.4, 26.3, 26.6, 42.6, 61.6, 62.7, 64.1, 74.6. *Minor diastereomer*: δ 24.6, 28.0, 31.8, 49.0, 63.1, 64.0, 65.6, 76.2; mass spectrum, *m/z* (rel. intensity) 141 (28, M^+), 124 (14), 110 (9), 97 (3), 83 (100), 70 (10), 55 (48).

Decomposition of the amine–borane complexes **17** with methanolic HCl (chlortrimethylsilane in methanol) afforded **2** and its epimer (+)-laburnine (**3**) as a mixture of diastereomers (85:15, 80%): $[\alpha]_D^{25}=+60$ (*c* 0.5, EtOH), [lit.[7n] (+)-isoretronecanol $[\alpha]_D^{25}=+70.2$ (*c* 5, EtOH) and its epimer (+)-laburnine $[\alpha]_D^{25}=+14.6$ (*c* 3.2, EtOH);[7n] calculated $[\alpha]_{mixture}=(+70.2)(0.85)+(+14.6)(0.15)=+62$ corresponding to an ee=90% or an er=95:5 assuming both diastereomers have the same er]; ^1H NMR ($CDCl_3$) 1.35–1.55 (m, 2H), 1.55–2.20 (m, 6H), 2.40–2.75 (m, 2H), 3.00–3.15 (m, 1H), 3.15–3.30 (m, 1H), 3.59 (d, $J=7.4$ Hz, 2H), 5.25–6.50 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.4, 27.0, 44.1, 53.8, 55.5, 62.8, 66.5. *(+)-Laburnine*. ^{13}C NMR δ 25.6, 29.5, 31.7, 47.9, 54.4, 54.7, 64.5, 68.0; [lit.[7n] ^{13}C NMR ($CDCl_3$) δ 24.9, 30.0, 31.9, 48.3, 52.5, 54.6, 64.9, 67.5 and for the enantiomer (−)-trachelanthamide[13b] δ 25.7, 29.8, 31.8, 48.1, 54.5, 54.8, 65.6, 68.0].

4.2.9. 2,3,5,7a-Tetrahydro-1*H*-pyrrolizine (4). To the solution of **16b** (341 mg, 1.0 mmol) in THF (10 mL) was added H_2SiF_6 (1.0 mL, 2.2 mmol) under an Argon atmosphere. After addition was complete, the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with Et_2O (20 mL) and quenched with brine (15 mL). After shaking vigorously, the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil (179 mg, 79%) which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70:30, v/v) to give pure *N*-Boc-2-(*Z*)-3-hydroxy-1-propenyl)pyrrolidine: IR (neat) 3360 (br), 1688 (vs), 1460 (s), 992, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.63–1.76 (m, 1H), 1.76–1.98 (m, 2H), 2.08–2.22 (m, 1H), 3.29–3.53 (m, 2H), 4.05–4.16 (m, 1H), 4.32 (br s, 1H), 4.50–5.61 (m, 1H), 5.49–5.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.86, 28.51, 32.99, 39.34, 46.48, 53.80, 79.51, 124.76, 136.57, 154.46.

Treatment of the alcohol (0.114 g, 0.5 mmol) with triethylamine (0.076 g, 0.75 mmol) and mesyl chloride (0.069 g, 0.60 mmol) in dry CH_2Cl_2 at −30 °C for 2 h followed by the $NaHCO_3$ work up afforded crude mesylate (0.133 g, 87%) which was used without further purification. The crude mesylate was dissolved in methanol (3 mL) and TMSCl (0.295 g, 2.5 mmol) was added slowly at room temperature and the mixture was stirred for 6 h followed by $NaHCO_3$ workup. The crude product was distilled under low pressure (30 mm Hg, 50 °C) to afford **4** (0.049 g, 31%): $[\alpha]_D^{25} = +2.1$ (*c* 1.5, $CHCl_3$); IR (neat) 3058 (vs), 1649 (w), 685 (br) cm^{-1}; ^1H NMR 1.75–2.04 (m, 4H), 2.10–2.29 (m, 2H), 2.87–2.98 (m, 1H), 3.61 (m, 2H), 4.40 (m, 1H), 4.83–4.93 (m, 1H); ^{13}C NMR 24.6, 29.9, 56.9, 61.4, 73.4, 124.3, 129.0; mass spectrum *m/z* (rel. intensity), EI 110 (5, $M^+ + 1$), 109 (49, M^+), 108 (42), 107 (25), 106 (42), 94 (5), 81 (100), 80 (94), 79 (18), 67 (11), 54 (28).

4.2.10. (+)-Coniceine (6). Carbamate **16a** (0.304 g, 1.0 mmol) was dissolved in methanol (5 mL) and TMSCl (0.540 g, 5.0 mmol) was added slowly at room temperature. The reaction mixture was stirred for 6 h followed by the addition of $NaHCO_3$ until pH > 8, stirred for another 2 h at room temperature. The crude material was extracted three times with 15 mL CH_2Cl_2, the combined organic phase was dried over Na_2SO_4, and concentrated in vacuo to afford (*R*)-**5** (0.106 g, 86%): IR (neat) 3073 (vs), 2995, 2315, 1639 (w), 1434; ^1H NMR ($CDCl_3$) δ 1.44–1.56 (m, 1H), 1.75–1.86 (m, 2H), 1.96–2.03 (m, 2H), 2.19–2.32 (m, 1H), 2.72–2.81 (m, 2H), 2.85–2.95 (m, 2H), 3.31–3.42 (m, 1H), 5.62–5.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.23, 22.74, 29.50, 46.07, 51.40, 59.26, 124.77, 128.38; mass spectrum *m/z* (rel. intensity) EI 123 (M^+, 51), 122 (100), 95 (47), 80 (24), 67 (27).

A suspension of (*R*)-**5** (123 mg, 1.0 mmol) and palladium hydroxide (35 mg) in methanol (5.0 mL) was stirred under a hydrogen atmosphere (50 psi) for 15 h. The catalyst was removed through Celite by filtration. After conc. HCl (0.20 mL) was added to the filtrate, the organic solvent was evaporated to yield a hydrochloride salt. The salt was treated with 10% K_2CO_3, and the mixture was extracted with diethyl ether twice. The combined ether extract was washed with brine, and dried over Na_2SO_4. After the solvent was removed, picric acid in EtOH was added. After slight heating, the mixture was cooled to room temperature and the solid was precipitated to yield the picrate salt (315 mg, 89%) of (+)-coniceine (**6**): $[\alpha]_D^{25} = +1.60$ (*c* 0.1, EtOH) for the picrate salt corresponding to an 80% ee or an er = 90:10, [lit.[11f] −2.0 (*c* 0.35, EtOH) for the enantiomer]; ^1H NMR ($CDC1_3$) δ 1.38–2.15 (10H, m), 2.50–2.67 (2H, m), 3.75–3.95 (3H, m), 10.38 (br s 2H), 10.88 (br s 1H); ^{13}C NMR ($CDC1_3$) δ 19.8, 22.9, 23.0, 27.3, 28.3, 53.7, 69.1, 126.6, 129.4, 142.3, 161.9; [lit.[12b] ^{13}C NMR δ 19.8, 23.0, 23.1, 27.3, 28.1, 53.6, 68.6, 126.8, 128.3, 141.8, 162.1]; mass spectrum (neat) *m/z* (rel. intensity) EI 125 (M^+, 51), 124 (100), 97 (94), 96 (96), 83 (61), 69 (67).

4.2.11. (*R*)-8-Methyleneoctahydroindolizine (11b). Carbamate **15b** (259 mg, 1.0 mmol) was dissolved in methanol (5 mL) at 25 °C and trimethylsilylchloride (TMSCl, 540 mg, 5.0 mmol) was added dropwise by syringe. The mixture was stirred at room temperature overnight and then quenched with saturated aqueous $NaHCO_3$ until pH > 8. The mixture was diluted with methylene chloride, two layers were separated and the organic layer extracted three times with methylene chloride, and dried ($MgSO_4$). Concentration in vacuo afforded a clear yellow oil which was purified by Kugelrohr distillation (100 °C, 20 mm Hg) to give **11b** as a clear colorless liquid (116 mg, 85%): $[\alpha]_D^{22} = +79$ (*c* 0.30, $HCCl_3$); IR (neat) 3395 (vs), 2955 (m), 1655 (m), 1644 (m), 1410 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53–1.80 (m, 6H), 1.96 (td, *J* = 5.2, 14.8 Hz, 1H), 2.00–2.20 (m, 2H), 2.20–2.30 (m, 1H), 2.30–2.45 (m, 1H), 3.08–3.20 (m, 2H), 4.68 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.72 (dd, *J* = 1.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 26.0, 26.7, 33.3, 52.7, 54.6, 66.6, 106.0, 147.1; mass spectrum, *m/z* (rel. intensity) 137 (58, M^+), 136 (96), 122 (100), 109 (98), 94 (23), 81 (44), 67 (28), 54 (28).

4.2.12. (+)-Tashiromine (7) and (+)-5-epitashiromine (8). Indolizidine olefin **11b** (137 mg, 1 mmol) was dissolved in THF (5 mL) and a 0.5 M solution of 9-BBN in THF (2.0 mL, 1.0 mmol) was added. The mixture was heated for 1 h at 60 °C and then cooled to room temperature before the addition of $BH_3 \cdot THF$ (1.0 mL, 1.0 mmol). After stirring for 30 min, the mixture was cooled to 0 °C and treated with 10 M NaOH (1.0 mL). Then H_2O_2 (35% aq, 1.0 mL) was added dropwise and allowed to stir for 1 h. The white cloudy reaction mixture was diluted with Et_2O, the combined ether phase was washed with $NaHCO_3$ twice, the combined organic phase was dried over Na_2SO_4, and concentrated in vacuo to afford a mixture of the BH_3-complexes of (+)-tashiromine and (+)-5-epitashiromine. Flash column chromatography (R_f 0.5, diethyl ether, 100%) gave a mixture of the BH_3-complexes. (+)-Tashiromine–BH_3 complex: ^{13}C NMR ($CDCl_3$) δ 18.74, 19.99, 20.92, 21.75, 35.43, 52.04, 64.28, 65.23, 66.82. (+)-epitashiromine–BH_3-complex: ^{13}C NMR ($CDCl_3$) δ 19.05, 20.44, 24.38, 28.11, 38.65, 55.30, 56.77, 64.69, 66.70.

Treatment of the BH_3 complexes of **7** and **8** with methanolic HCl (chlortrimethylsilane in methanol) afforded (+)-tashiromine (**7**) and its epimer (+)-5-epitashiromine (**8**) as a mixture of diastereomers (70:30, 85%). The two diastereomers were separated by column chromatography (flash silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:4.75:0.25). (+)-Tashiromine (**7**): $[\alpha]_D^{22} = +41.9$ (*c* 1.1, EtOH) [lit.[13b] ($[\alpha]_D^{20} = +42.9$ (*c* 1.1, EtOH)]; IR (neat) 3560 (br), 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.48 (dd, *J* = 10.8, 6.1 Hz, 1H); 3.15–3.02 (m, 2H), 2.09–2.01 (m, 1H), 2.05–1.80 (m, 3H), 1.74–1.37 (m, 7H), 1.23–1.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 24.9, 27.4, 28.9, 44.3, 52.6, 53.5, 65.6, 65.6; [lit.[1e] ^{13}C NMR δ 20.2, 24.6, 27.1, 28.5, 44.1, 52.1, 53.6, 65.0, 65.8].

(+)-5-Epitashiromine (**8**). $[\alpha]_D^{22} = +1.48$ (*c* 1.5, EtOH) [lit. $[\alpha]_D^{20} = +1.1$ (EtOH),[13b] $[\alpha]_D = -0.96$ (*c* 0.31, EtOH);[14a] IR (neat) 3450, 2952 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.15 (dd, *J* = 10.9, 4.1 Hz, 1H), 3.71 (br d, *J* = 9.7 Hz, 1H), 3.11–3.05 (m, 1H), 3.03–2.91 (m, 1H), 2.36–2.24 (m, 1H), 2.12–1.93 (m, 3H), 1.90–1.61 (m, 6H), 1.60–1.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 23.2, 25.7, 30.5, 35.3, 54.0, 54.4, 66.5, 66.8; [lit.[1e] ^{13}C NMR δ 20.8, 23.3, 25.8, 30.6, 35.3, 53.5, 54.5, 65.7, 66.8]. A sample of **8** taken from the column chromatography gave $[\alpha]_D^{22} = +1.48$ (*c* 1.5, EtOH) and this sample upon passage through a pipette with a small

amount of silica gel gave $[\alpha]_D^{22} = -0.87$ (*c* 1.5, EtOH). This change in the sign of rotation as a function of sample history was previously noted.[13b]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.094. General experimental information, description of materials and ^1H and ^{13}C NMR spectra for compounds **1**–**5**, **7**–**8**, **2**–BH_3 (i.e., **17**)/**3**–BH_3, **7**–BH_3/**8**–BH_3, **11a**–**b**, **15a**–**c**, and **16a**–**b** are available.

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31. The specific rotation can vary with concentration, temperature, solvent and the presence of soluble impurities in the sample. The optical and enantiomeric purities may be nonequivalent (Horeau effect), although this is generally a small effect observed in weakly polar solvents that disappears in polar solvents. All these effects must be kept in mind when attempting to determine optical purity by polarimetry and rotations should be measured at the same concentration, temperature and in the same solvent when making comparisons with literature values. The 85:15 mixture of **1** (*c* 0.45) and pseudoheliotridane (*c* 0.07) were measured at $c=0.5$ (EtOH) giving the concentrations shown in parentheses for each species. Thus the concentration of **1** is close to the reported literature concentration of $c=0.5$ and pseudoheliotridane is at 1/6th the concentration of the reported value (i.e., *c* 0.5). See: Eliel, E. L.; Whilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 217–221 and 1071–1080.

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Efficient asymmetric synthesis of α-alkylated benzylic methyl sulfonates

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Abstract—The first highly efficient auxiliary-controlled synthesis of various α-substituted sulfonic acid derivatives is described. Alkyl or aryl halides were reacted with lithiated benzylic sulfonic esters bearing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as a removable enantiopure alcohol auxiliary to give the alkylated products in excellent diastereomeric excesses. The racemization-free cleavage conditions provided highly enantioenriched sulfonic acid derivatives (ee≥98%).

1. Introduction

Enantiopure α-substituted sulfonic acids as well as their various derivatives are important building blocks and precursors of biologically interesting compounds. A number of these compounds has been isolated, synthesized, and tested for their biological activity. 6-Gingesulfonic acid **1**, for example, which has been isolated from *Zingiberis rhizoma*, shows potent anti-ulcer activity.[1] The natural products echinosulfonic acid A, B, and C (**2**, R=Et, Me, H, respectively) have been isolated from the southern Australian marine sponge *Echinodictyum* and have antibacterial activity.[2] The semisynthetic penicillin **3**, namely α-sulfobenzylpenicillin, has been reported to show potent antibacterial activity against *Pseudomonas aeruginosa*.[3,4] Cefsulodin, a representative compound of the semisynthetic cephalosporins, exhibits in vivo antipseudomonal activity.[5] Moreover, the synthetic α-phosphono sulfonates **4** are potent squalene synthase inhibitors (Fig. 1).[6,7]

In general, enantiopure α-substituted sulfonic acids are obtained from the corresponding racemates by resolution

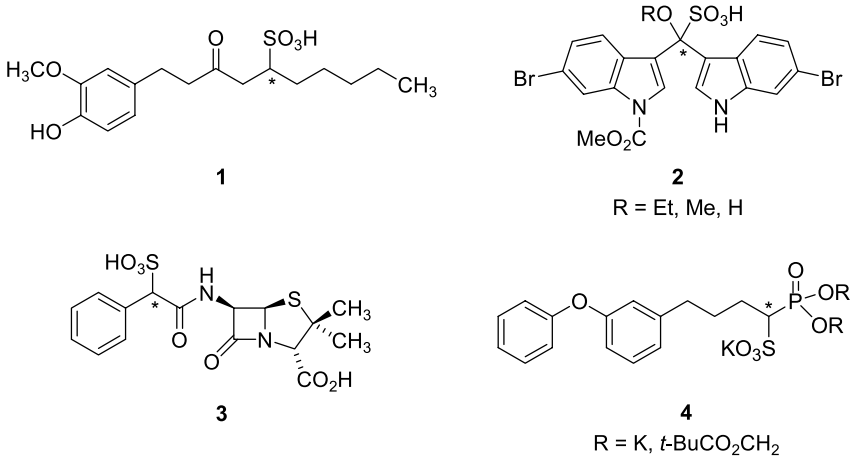

Figure 1. Biologically active α-substituted sulfonic acid derivatives.

Keywords: Asymmetric synthesis; Alkylation; Sulfonates; Sugar auxiliary.
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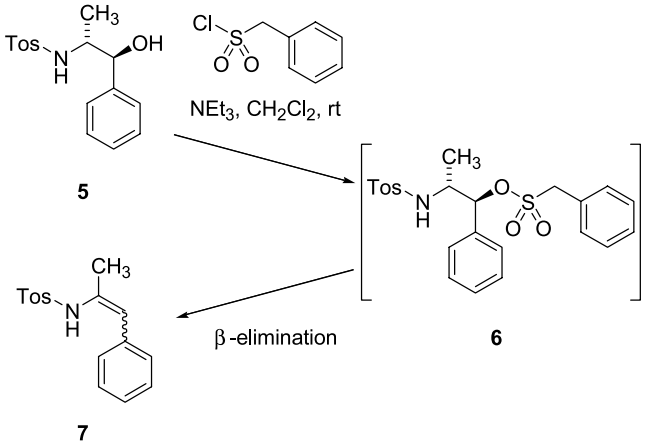
techniques with chiral amines.[8] To the best of our knowledge, only two stereoselective methods for the asymmetric synthesis of α-substituted sulfonic acids have been reported so far. Enantiopure (*R*)-1-phenylethanol, obtained by catalytic asymmetric reduction of methyl phenyl ketone, could be transformed into (*S*)-(−)-1-phenylethane sulfonic acid [(−)-PES] in a two step sequence.[9] In the synthesis of the squalene synthase inhibitor **4**, asymmetric α-alkylation of an α-phosphono sulfonate bearing the chirality information within the phosphono moiety was employed.[10]

In contrast, no efficient method has been reported for asymmetric α-alkylations of metalated sulfonic acid esters derived from enantiopure alcohols as auxiliaries.[11] As a potential drawback we considered β-elimination or substitution reactions during metalation of the sulfonates. However, by choosing a suitable auxiliary system these obstacles should be overcome. In preceding communications,[12–16] we have described the asymmetric synthesis of several α-substituted sulfonic acid derivatives by reacting electrophiles with metalated sulfonic esters which possess a chiral alcohol as auxiliary. Herein, we present in detail the development of this methodology.

2. Results and discussion

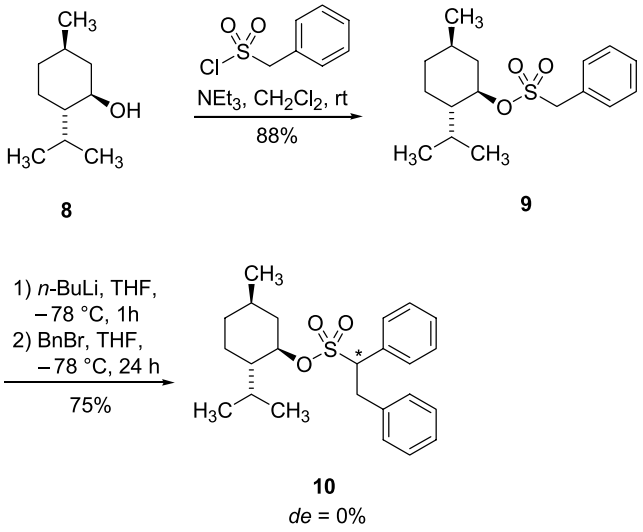
The aim of our project was to develop a practical methodology for an auxiliary controlled asymmetric synthesis of α-alkylated sulfonic acids. The initial concept was to use chiral amines as auxiliaries in order to perform alkylations of the corresponding sulfonamides. Due to the stability of the sulfur–nitrogen-bond, acidic hydrolysis of the sulfonamides did not give the desired sulfonic acids but instead enantioenriched sulfonamides.[17,18] To circumvent this dilemma we had to find a suitable alcohol as chiral auxiliary to provide sulfonic acid esters which are more readily cleaved and would be stable during α-lithiation to be trapped in a stereocontrolled fashion with electrophiles.

The first alcohol we tested was the tosylated norephedrine derivative **5**.[19] Unfortunately, the reaction did not proceed to the desired benzyl sulfonate **6** due to decomposition of the intermediate ester by β-elimination to form the *N*-tosyl enamine **7** (Scheme 1).



Scheme 1. Attempted synthesis of the sulfonate **6** from the norephedrine derivative **5**.

This led us to employ a cyclic auxiliary alcohol where β-elimination is less favourable. Thus, menthol **8** could be easily converted into the corresponding sulfonate **9** in 88% yield under standard conditions. In addition, the deprotonation with *n*-butyllithium and subsequent alkylation with benzyl bromide to form the sulfonate **10** worked well but without any diastereoselectivity (Scheme 2).

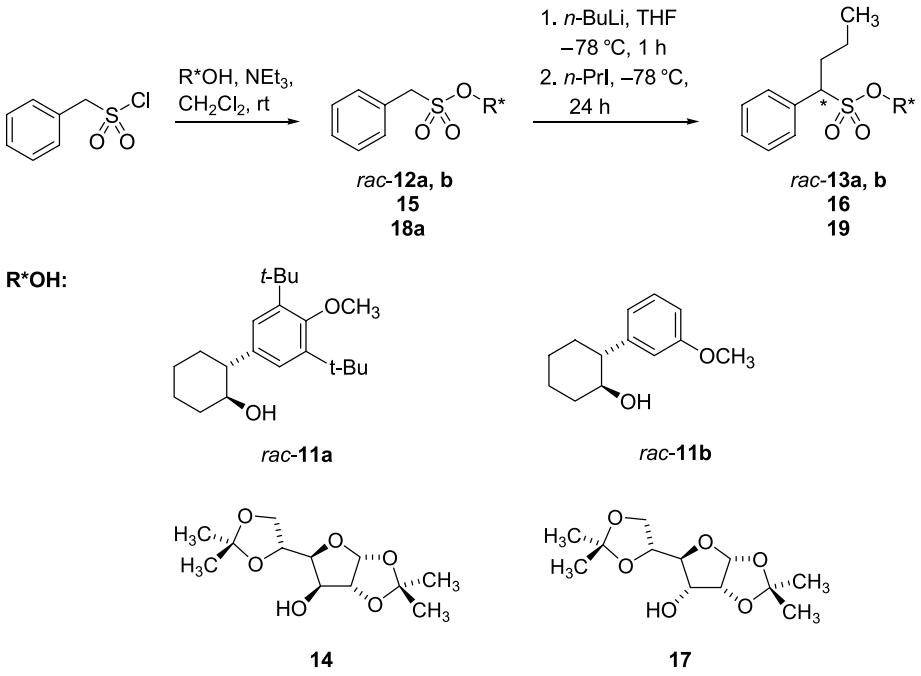


Scheme 2. Menthol as the chiral auxiliary.

The synthetically encouraging results with menthol led us to a screening of different cyclic alcohols (Scheme 3, Table 1). First, two racemic auxiliary alcohols *rac*-**11a**, **b** were synthesized according to a literature procedure[20] by reaction of different aryl Grignard reagents with cyclohexene oxide. These were converted into the corresponding benzyl sulfonates *rac*-**12a**, **b**, lithiated with *n*-butyllithium and trapped with *n*-propyl iodide at −78 °C to afford the alkylated esters **13a**, **b** (entries 1 and 2). Remarkably, the sterically less demanding methoxyphenyl side chain in *rac*-**12b** resulted in a similar diastereomeric excess as the alkylation of the sterically hindered sulfonate *rac*-**12a**.

Thus, we envisioned the methoxy group as a chelating moiety in the lithiated system supporting the asymmetric induction. This led us to use oxygen-rich alcohols like diacetone-D-glucose **14**. The corresponding sulfonate **15** was lithiated and alkylated with *n*-propyl iodide in the presence of hexamethylphosphoric acid triamide (HMPA) to give the alkylated sulfonate **16**. This sugar-auxiliary provided similar inductions as compared to the reactions with the esters *rac*-**12a**, **b** (de=59%, entry 3).

Although the induction was the same, we continued our investigations on the sugar system as a potential auxiliary group. We assumed that inversion of the hydroxy group would provide a species where the reaction center is exposed to better coordination by the rigid dioxolane moiety. We, therefore, inverted the hydroxy group by a simple epimerization procedure to get the new auxiliary.[21] Allowing this 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose



Scheme 3. Screening of different alcohols *rac*-**11a**, *rac*-**11b**, **14**, **17**.

Table 1. Screening of different alcohols *rac*-**11a**, *rac*-**11b**, **14**, **17**

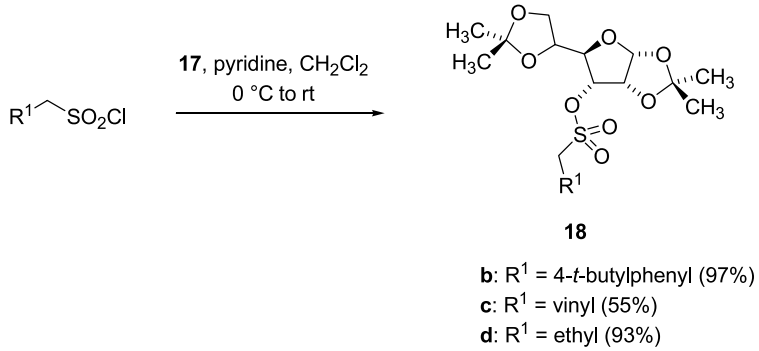
Entry	Alcohol	Substrate/yield (%)	Product/yield (%)	de (%)[a]
1	*rac*-**11a**	*rac*-**12a**/78	*rac*-**13a**/55	60
2	*rac*-**11b**	*rac*-**12b**/62	*rac*-**13b**/71	59
3	**14**	**15**/81	**16**[b]/73	59
4	**17**	**18a**/91	**19**[b]/69	78

[a] Determined by ^{13}C NMR.
[b] The reaction was performed in the presence of HMPA.

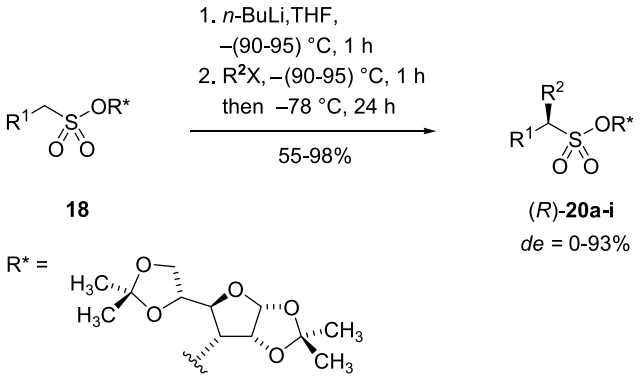
(**17**) to react with benzylsulfonyl chloride provided the epimeric sulfonate **18a**. Following the already known procedure, sulfonate **18a** could be easily alkylated with *n*-propyl iodide under BuLi/HMPA-conditions to afford the alkylated product **19** with an improved diastereomeric excess of de=78% (entry 4).

The co-solvent HMPA, which was essential for the alkylation, could be avoided by using electrophiles that have a higher reactivity than *n*-propyl iodide. Gratifyingly, when using methyl iodide as an electrophile the methylated product (*R*)-**20a** was obtained in high yield and a diastereomeric excess of de=91%. To further explore the scope of the reaction different sulfonates **18b–d** were prepared by treatment of the allofuranose derivative **17** with sulfonyl chlorides, which were commercially available or could be easily obtained from the corresponding sodium sulfonates (Scheme 4).[22–24]

The enantiopure sulfonates **18a**,**b** were lithiated with 1 equiv of *n*-butyllithium in THF at −(90–95) °C and then reacted with different reactive electrophiles at −(90–95) °C for 1 h and at −78 °C for 24 h. After work up and purification, the α-substituted sulfonates **20a–g** were obtained in excellent yields (90–98%) and high diastereoselectivities (Scheme 5, Table 2). In all cases, the



Scheme 4. Different sulfonates possessing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose moiety.



Scheme 5. α-Alkylation of the sulfonates **18**.

diastereomerically pure sulfonates could be obtained by recrystallization from 2-propanol (de≥98%).

In order to explore further the scope of the reaction a series of experiments with different sulfonate residues were conducted. Whereas benzylic carbanions lead to very high asymmetric inductions, the allylic lithiosulfonate gave **20 h** with only a de-value of 50% and aliphatic group showed virtually no diastereoselectivity of product **20i**. Thus, at present the methodology seems to be limited to benzylic type of sulfonates.

The configuration of the newly formed stereogenic centre was determined to be *R* by single crystal Röntgen structure analysis in the case of product (*R*)-**20f**.[12] Since we can postulate a uniform reaction mechanism, all described α-alkylated sulfonates should possess the same configuration.

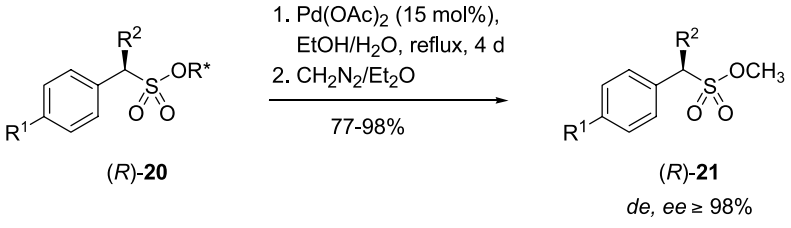
Finally, various procedures were screened for an efficient racemization-free cleavage of the auxiliary, which turned out to be more difficult than expected. Several procedures under basic conditions were unsuccessful. The analysis of the recovered starting material showed a decrease of diastereomeric excess. In addition, the cleavage was attempted by refluxing the sulfonate in aqueous ethanol in order to eliminate the sulfonic acid by nucleophilic substitution or to reach a transesterification or saponification with removal of the sugar alcohol auxiliary. Unfortunately, the protocol was unsuccesfull and obviously the high steric demand blocked the planned cleavage processes.

We assumed that a preceding mild acetonide deprotection would decrease the steric strain and thus allow substitution with a protic solvent, such as water or ethanol, to provide the desired sulfonic acid. Furthermore, this could give rise to an intramolecular substitution reaction with one of the hydroxy groups formed to give a stable bicyclic system. Thus, a mild cleavage method for the removal of the acetal protection

Table 2. α-Alkylation of the sulfonates **18a–d** affording the sulfonates (*R*)-**20a–i**

(*R*)-**20**	R^1	R^2	Yield (%)	de (%)[a,b]
(*R*)-**20a**	Phenyl	Methyl	95	91 (≥98)
(*R*)-**20b**	Phenyl	Allyl	93	90 (≥98)
(*R*)-**20c**	Phenyl	Benzyl	94	89 (≥98)
(*R*)-**20d**	Phenyl	4-Bromophenyl	90	90 (≥98)
(*R*)-**20e**	Phenyl	(2-Naphthyl)methyl	96	91 (≥98)
(*R*)-**20f**	4-*t*-Butylphenyl	Benzyl	95	91 (≥98)
(*R*)-**20g**	4-*t*-Butylphenyl	(2-Naphthyl)methyl	98	93 (≥98)
(*R*)-**20h**	Vinyl	Methyl	55	50
(*R*)-**20i**	Ethyl	Methyl	87	0

[a] In brackets after recrystallization from 2-propanol.
[b] Determined by ^{13}C NMR.



Scheme 6. Removal of the auxiliary to give the α-alkylated methyl sulfonates (*R*)-**21**.

Table 3. Removal of the sugar auxiliary to give the α-alkylated methyl sulfonates (*R*)-**21**

(*R*)-**21**	R^1	R^2	Yield (%)	ee [%][a]	$[\alpha]_D^{rt}$[b]
(*R*)-**21a**	H	Methyl	98	≥98	+25.6
(*R*)-**21b**	H	Allyl	90	≥98	−6.3
(*R*)-**21c**	H	Benzyl	94	≥98	−77.4
(*R*)-**21d**	H	4-Bromophenyl	77	≥98	−93.4
(*R*)-**21e**	H	(2-Naphthyl)methyl	96	≥98	−89.5
(*R*)-**21f**	*t*-Bu	Benzyl	90	≥98	−92.8
(*R*)-**21g**	*t*-Bu	(2-Naphthyl)methyl	87	≥98	−108.2

[a] Determined by HPLC using a chiral stationary phase.
[b] All optical rotations were measured in Uvasol grade $CHCl_3$ with concentrations of 1.0 at rt.

groups based on a protocol reported by Lipshutz et al.[25] was utilized by refluxing the sulfonates **20** in an EtOH/H_2O solution containing a catalytic amount of $Pd(OAc)_2$. To isolate the final products in a more accessible form, the intermediate sulfonic acids were directly converted with diazomethane to the corresponding methyl sulfonates (*R*)-**21** in very good yields and as pure stereoisomers (Scheme 6, Table 3).

In order to provide evidence for the assumptions made concerning the mechanism of the sulfonate cleavage we investigated more closely the by-products of the reaction. The TLC of the reaction mixture indicated besides the desired sulfonic acids two less polar products, which were anticipated to be residues of the sugar moiety. Thus, the reaction was repeated on larger scale in order to isolate and analyse these interesting fragments. The products were identified as intramolecularly cyclized derivatives **22a** and **22b** with yields of 25 and 37%, respectively. A single crystal Röntgen-structure analysis was carried out with compound **22b** proving the structure unambiguously as shown in Figure 2. On the other hand, compound **22a** is a viscous oil, whose structure could be determined as the corresponding α-anomer by NOE-measurements.

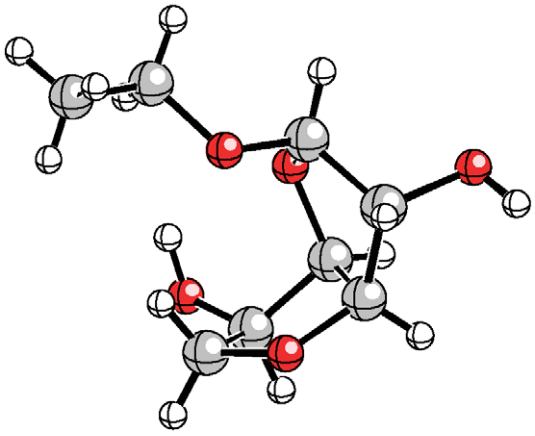
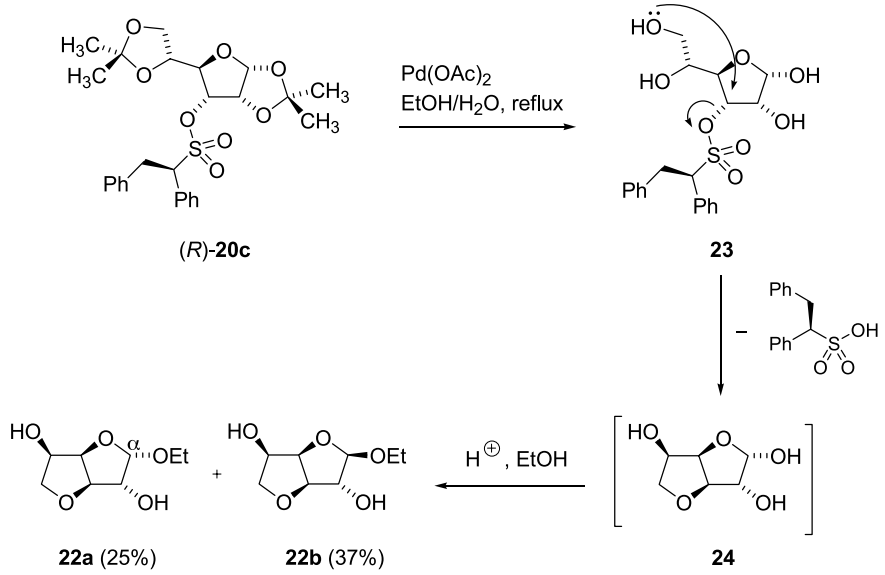


Figure 2. Röntgen crystal structure of compound **22b**.

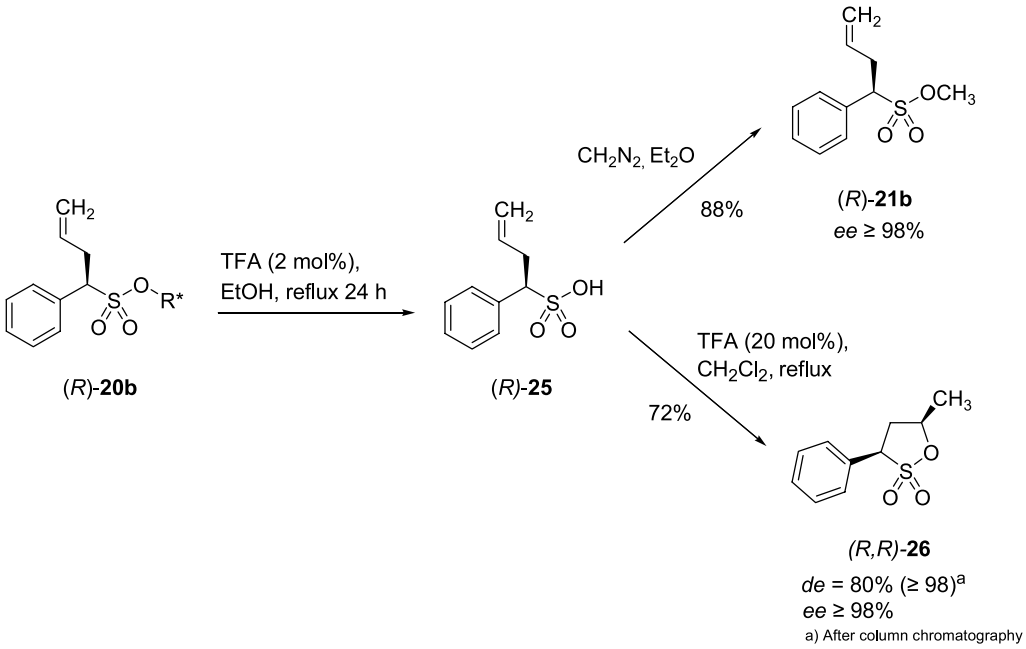
Based on the Röntgen-structure of the residual sugar fragment, the following cleavage mechanism can be proposed as depicted in Scheme 7. First, the acetal groups are cleaved to provide the tetraol **23**. This sets the stage for an intramolecular substitution reaction to afford the desired enantioenriched sulfonic acid derivatives and the intermediate **24**. The bicyclic compound **24** reacts further in the acidic media with the solvent (ethanol) to give the glycosides **22** roughly as a 1:1 mixture of the anomers **22a** and **22b** as witnessed via NMR spectroscopy.

Thus, the removal of the auxiliary depends on the deprotection of the sugar moiety, which allows the intramolecular nucleophilic substitution of the sulfonyl-moiety to provide the desired α-alkylated sulfonic acids without racemization. As the deprotection of the acetals is sufficient for the sulfonic acid formation, the cleavage should also be possible by using trifluoroacetic acid (TFA). This seemed to be more convenient than to use the expensive $Pd(OAc)_2$. The allyl substituted sulfonate (*R*)-**20b** was cleaved with TFA (2 mol%) in ethanol. By trapping the resulting sulfonic acid (*R*)-**25** with diazomethane, the sulfonate (*R*)-**21b** could be obtained with excellent enantiomeric excess. Furthermore, it was found that the intermediate allylic sulfonic acid (*R*)-**25** can also be cyclized to afford enantiopure sultones.[14,15] Refluxing in dichloromethane in the presence of 20% TFA provided the enantioenriched sultone (*R*,*R*)-**26** in good yield and excellent enantiomeric excess with satisfactory diastereoselectivity (Scheme 8).

Moreover, we have expanded this methodology to provide a great variety of different sulfonic acid derivatives as illustrated in Scheme 9. The asymmetric Michael addition of the sulfonate **18a** with nitroalkenes leads to either the



Scheme 7. Proposed reaction sequence of the cleavage reaction.



Scheme 8. TFA cleavage of the sulfonate **20b** to give either the methyl sulfonate (*R*)-**21b** or the γ-sultone (*R*,*R*)-**26**.

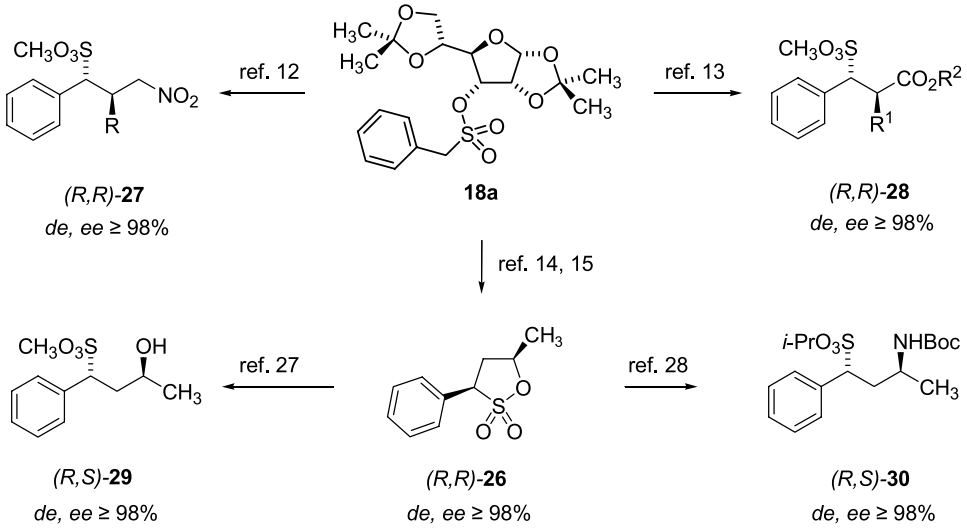
γ-nitro sulfonates (*R*,*R*)-**27** or β-alkoxycarbonyl sulfonates (*R*,*R*)-**28** depending on the conditions used for the cleavage of the chiral auxiliary.[12,13] Further functional groups could be easily introduced by performing diastereoselective ring opening reactions on α,γ-substituted γ-sultones to give enantiopure α,γ-substituted γ-alkoxy,[26] γ-hydroxy[27] (*R*,*S*)-**29** and γ-amino sulfonates (*R*,*S*)-**30**.[28]

In summary, the proper choice of a sugar auxiliary led to the breakthrough in the first asymmetric synthesis of α-substituted sulfonic acid esters. High asymmetric inductions were obtained with the inexpensive and readily available 1,2:5,6-di-*O*-isopropyliden-α-D-allofuranose as auxiliary group which can be cleaved off racemization-free under mild conditions.

3. Experimental

3.1. General

Starting materials and reagents were purchased from commercial suppliers without further purification. Asymmetric alkylations were carried out under Ar in dry solvents. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium-lead alloy under Ar. *n*-Butyllithium (1.6 M in hexane) was purchased from Merck, Darmstadt. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC: silica gel 60 F_{254} plates from Merck, Darmstadt. Optical rotation values were measured on a Perkin–Elmer P241 polarimeter.



Scheme 9. Asymmetric synthesis of enantioenriched sulfonic acid derivatives.

Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 (EI 70 eV) spectrometer. High-resolution mass spectra were recorded on a Finnigan MAT95 spectrometer. IR spectra were taken on a Perkin–Elmer FT-IR 1760. ^{1}H and ^{13}C spectra were recorded on Varian Gemini 300 or Inova 400 spectrometers with tetramethylsilane as internal standard. δ of the minor diastereomers are indicated in brackets. Melting points were determined on a Tottoli melting point apparatus and are uncorrected.

3.1.1. *rac-trans*-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-cyclohexanol (*rac*-11a). To magnesium (1.7 g, 69.0 mmol) in THF (50 mL) was added a solution of 5-bromo-3,5-di-*tert*-butyl-4-methoxybenzene (21.2 g, 71.0 mmol) in THF (50 mL) over 1 h. The resulting mixture was stirred for 0.5 h and then CuI (1.3 g, 7.0 mmol) was added and the mixture was cooled to −30 °C. Cyclohexene oxide (4.6 g, 47.6 mmol) was then added dropwise. After the addition was complete, the mixture was stirred for 3 h and then quenched by pouring into cold saturated NH_4Cl (30 mL). The mixture was partitioned between CH_2Cl_2 and the aqueous layer further extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, pentane/diethyl ether 6:1) to give *rac*-**11a** (12.0 g, 80%) as a colorless solid; mp = 101 °C. IR (KBr): 3381, 2953, 2920, 2852, 1597, 1449, 1415, 1393, 1361, 1305, 1262, 1224, 1118, 1065, 1015, 993, 857 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–2.20 (m, 8H), 1.43 (s, 18H), 2.35 (m, 1H), 3.59 (m, 1H), 3.69 (s, 3H), 7.09 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 26.1, 32.1, 34.1, 35.7, 35.8, 53.0, 63.9, 74.4, 125.6, 136.3, 143.4, 157.9. MS (EI, 70 eV): *m/z* (%) 318 (100) [M^+], 303 (85) [$M^+ - CH_3$], 247 (8), 187 (15), 57 (40). HRMS: *m/z* calcd for $C_{21}H_{34}O_2$ (M^+) 318.2559; found 318.2557.

3.1.2. *rac-trans*-2-(3-Methoxyphenyl)-cyclohexanol (*rac*-11b). To magnesium (1.7 g, 69.0 mmol) in THF (30 mL) was added a solution of 3-bromo anisole (13.3 g, 71.0 mmol) in THF (30 mL) over 1 h. The resulting mixture was stirred for 0.5 h and then CuI (1.3 g, 7.0 mmol) was added and the mixture was cooled to −30 °C. Cyclohexene oxide (4.6 g, 47.6 mmol) was then added dropwise. After the addition was complete, the mixture was stirred for 3 h and then quenched by pouring into cold saturated NH_4Cl (30 mL). The mixture was partitioned between CH_2Cl_2 and the aqueous layer further extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, pentane/diethyl ether 4:1) to afford *rac*-**11b** (6.9 g, 71%) as a colorless oil. IR (film): 3419, 2929, 2856, 1602, 1584, 1487, 1464, 1449, 1345, 1323, 1285, 1260, 1228, 1200, 1157, 1122, 1049, 854, 780, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–2.10 (m, 8H), 2.39 (m, 1H), 3.62 (m, 1H), 3.78 (s, 3H), 6.70–7.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 26.0, 33.2, 34.3, 53.2, 55.1, 74.2, 111.8, 113.5, 120.0, 129.5, 144.8, 159.6. MS (EI, 70 eV): *m/z* (%) 206 (74) [M^+], 178 (12) [$M^+ - C_2H_4$], 135 (43), 122 (100), 91 (19) [$C_7H_7^+$]. HRMS: *m/z* calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307; found 206.1308.

3.2. General procedure for the synthesis of the substrate sulfonates (GP 1)

A solution of the alcohol (1.0 equiv) and NEt_3 or pyridine (3.0 equiv) in CH_2Cl_2 (10 mL/mmol) was cooled to 0 °C. After adding the sulfonyl chloride (1.1 equiv), the solution was stirred at rt for 24 h. The mixture was then washed with brine and the aqueous layer extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, pentane/diethyl ether).

3.2.1. Compound 9. According to GP 1 (−)-menthol (**8**) (0.8 g, 5.0 mmol) was reacted with 1.1 g phenyl-methanesulfonyl chloride (5.5 mmol) in the presence of 1.5 g triethyl amine (15.0 mmol) to give **9** (1.4 g, 88%) as a colorless solid; mp = 72 °C; $[\alpha]_D^{29} = +53.4$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2961, 2943, 2866, 1499, 1456, 1350, 1330, 1275, 1203, 1171, 1160, 1142, 942, 919, 891, 826, 701, 615 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (d, $J = 7.1$ Hz, 3H), 0.86 (d, $J = 4.9$ Hz, 3H), 0.88 (d, $J = 4.9$ Hz, 3H), 0.90–2.00 (m, 9H), 4.32 (s, 2H), 4.53 (dt, $J = 4.7$, 11.0 Hz, 1H), 7.3–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 20.8, 21.8, 23.0, 25.5, 31.6, 33.7, 42.0, 47.5, 57.8, 83.2, 128.7, 128.8, 130.8, 134.5. MS (EI, 70 eV): *m/z* (%) 310 (2) [M^+], 138 (100) [$M^+ - C_7H_7SO_2OH$], 97 (12), 95 (22), 91 (73), 83 (57). Anal. Calcd for $C_{17}H_{26}O_3S$ (310.45): C, 65.77; H, 8.44, found: C, 65.82; H, 8.64.

3.2.2. Compound *rac*-12a. According to GP 1 the alcohol *rac*-**11a** (0.8 g, 2.5 mmol) was reacted with phenyl-methanesulfonyl chloride (0.52 g, 2.8 mmol) in the presence of triethyl amine (0.8 g, 7.5 mmol) to give *rac*-**12a** (0.9 g, 78%) as a colorless solid; mp = 147 °C. IR (KBr): 2952, 2863, 1600, 1455, 1414, 1359, 1332, 1267, 1226, 1171, 1145, 1016, 953, 916, 900, 886, 829, 813, 769, 699, 620, 540 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–2.30 (m, 8H), 1.43 (s, 18H), 2.71 (m, 1H), 3.13 (d, $J = 13.7$ Hz, 1H), 3.26 (d, $J = 13.7$ Hz, 1H), 3.49 (s, 3H), 4.73 (m, 1H), 7.00–7.30 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 25.3, 32.1, 33.6, 34.5, 35.8, 49.8, 56.0, 64.2, 87.3, 125.9, 128.5, 130.2, 127.6, 136.3, 143.7, 158.4. MS (EI, 70 eV): *m/z* (%) 472 (10) [M^+], 300 (100) [$M^+ - C_7H_7SO_3H$], 217 (2), 285 (26), 243 (17), 91 (12) [$C_7H_7^+$]. Anal. Calcd for $C_{28}H_{40}O_4S$ (472.68): C, 71.15; H, 8.53, found: C, 71.01; H, 8.42.

3.2.3. Compound *rac*-12b. According to GP 1 the alcohol *rac*-**11b** (5.7 g, 36.0 mmol) was reacted with phenyl-methanesulfonyl chloride (7.5 g, 39.6 mmol) in the presence of triethyl amine (10.0 g, 100.0 mmol) to give *rac*-**12b** (8.0 g, 62%) as a colorless solid; mp = 150 °C. IR (KBr): 2952, 2863, 1600, 1455, 1414, 1359, 1332, 1267, 1226, 1171, 1145, 1016, 953, 916, 900, 886, 829, 813, 769, 699, 620, 540 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–2.35 (m, 8H), 2.73 (m, 1H), 3.39 (d, $J = 13.7$ Hz, 1H), 3.55 (d, $J = 13.7$ Hz, 1H), 3.81 (s, 3H), 4.79 (m, 1H), 6.78–7.35 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 25.7, 34.3, 34.8, 50.5, 55.6, 56.9, 86.7, 112.7, 114.1, 120.4, 128.8, 129.9, 130.7, 128.1, 144.5, 160.1. MS (EI, 70 eV): *m/z* (%) 360 (16) [M^+], 188 (100) [$M^+ - C_7H_7SO_2OH$], 217 (2),

159 (9), 134 (14), 91 (12) [$C_7H_7^+$]. HRMS: *m/z* calcd for $C_{20}H_{24}O_4S$ (M^+) 360.1395, found 360.1399.

3.2.4. Compound 15. According to GP 1 the alcohol **14** (2.0 g, 8.0 mmol) was reacted with phenyl-methanesulfonyl chloride (1.8 g, 8.8 mmol) in the presence of triethyl amine (2.4 g, 24.0 mmol) to give **15** (2.7 g, 81%) as a colorless oil; $[\alpha]_D^{27} = -42.2$ ($c=1.0$; $CHCl_3$). IR ($CHCl_3$): 2979, 1496, 1456, 1368, 1317, 1265, 1225, 1167, 1162, 1123, 1084, 1043, 1010, 873, 854, 829, 699, 644, 622, 562 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.35 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 4.01 (dd, $J=4.4$, 8.8 Hz, 1H), 4.12 (dd, $J=5.8$, 8.8 Hz, 1H), 4.16 (dd, $J=3.0$, 8.5 Hz, 1H), 4.23 (ddd, $J=8.5$, 6.0, 4.4 Hz), 4.40 (d, $J=14.0$ Hz, 1H), 4.49 (d, $J=14.0$ Hz, 1H), 4.56 (d, $J=3.6$ Hz, 1H), 5.04 (d, $J=3.0$ Hz, 1H), 5.84 (d, $J=3.6$ Hz), 7.30–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.1, 26.5, 26.9, 57.2, 67.2, 71.9, 79.7, 82.4, 83.3, 104.9, 109.5, 112.4, 128.8, 129.0, 130.6, 127.2. MS (EI, 70 eV): *m/z* (%) 414 (9) [M^+], 399 (100) [M^+-CH_3], 385 (11), 113 (23), 91 (44) [$C_7H_7^+$]. Anal. Calcd for $C_{19}H_{26}O_8S$ (414.47): C, 55.06; H, 6.32, found: C, 55.11; H, 6.35.

3.2.5. Compound 18a. According to GP 1 the alcohol **17** (2.6 g, 10.0 mmol) was reacted with phenyl-methanesulfonyl chloride (2.0 g, 11.0 mmol) in the presence of triethyl amine (3.0 g, 30.0 mmol) to give **18a** (3.8 g, 91%) as a colorless solid; mp = 130 °C; $[\alpha]_D^{27} = +59.1$ ($c=1.0$; $CHCl_3$). IR (KBr): 2982, 1496, 1458, 1368, 1317, 1266, 1222, 1177, 1162, 1123, 1084, 1043, 1016, 873, 854, 829, 700, 646, 619, 559 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.60 (s, 3H, 3.84 (dd, $J=6.3$, 8.5 Hz, 1H), 4.01 (dd, $J=6.9$, 8.5 Hz, 1H), 4.15 (dd, $J=4.1$, 8.5 Hz, 1H), 4.26 (ddd, $J=6.6$, 6.3, 4.1 Hz, 1H), 4.44 (d, $J=14.0$ Hz, 1H), 4.53 (d, $J=14.0$ Hz, 1H), 4.56 (dd, $J=4.1$, 4.6 Hz, 1H), 4.76 (dd, $J=4.7$, 8.5 Hz, 1H), 5.77 (d, $J=3.9$ Hz), 7.37–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 26.18, 3.7, 26.7, 57.6, 65.2, 74.6, 76.8, 77.0, 77.8, 103.6, 110.0, 113.6, 128.9, 129.2, 130.9, 127.41. MS (EI, 70 eV): *m/z* (%) 399 (36) [M^+-CH_3], 113 (47), 101 (60), 91 (100) [$C_7H_7^+$]. Anal. Calcd for $C_{19}H_{26}O_8S$ (414.47): C, 55.06; H, 6.32, found: C, 54.81; H, 6.47.

3.2.6. Compound 18b. According to GP 1 the alcohol **17** (0.5 g, 2.0 mmol) was reacted with (4-*tert*-butylphenyl)-methanesulfonyl chloride (0.6 g, 2.2 mmol) in the presence of pyridine (0.4 g, 6.0 mmol) to give **18b** (0.9 g, 97%) as a colorless solid; mp = 97 °C; $[\alpha]_D^{28} = +49.5$ ($c=1.0$; $CHCl_3$). IR (KBr): 2980, 2881, 1515, 1497, 1373, 1316, 1265, 1241, 1213, 1179, 1121, 1078, 1042, 1016, 975, 873, 839, 609, 585, 545, 527 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 1.36 (s, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.60 (s, 3H), 3.85 (dd, $J=6.3$, 8.5 Hz, 1H), 4.01 (dd, $J=6.9$, 8.5 Hz, 1H), 4.16 (dd, $J=4.1$, 8.5 Hz, 1H), 4.28 (m, 1H), 4.41 (d, $J=14.0$ Hz, 1H), 4.51 (d, $J=14.0$ Hz, 1H), 4.62 (dd, $J=3.9$, 4.7 Hz, 1H), 4.77 (dd, $J=4.7$, 8.5 Hz, 1H), 5.77 (d, $J=3.8$ Hz, 1H), 7.30–7.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.2, 26.7, 26.7, 31.2, 34.7, 57.3, 65.3, 74.7, 76.9, 77.1, 77.9, 103.8, 110.1, 113.7, 125.9, 130.5, 124.3, 152.3. MS (EI, 70 eV): *m/z* (%) 470 (1) [M^+], 455 (40) [M^+-CH_3], 147 (100) [$C_{11}H_{15}^+$], 113 (35), 101 (48). Anal. Calcd for $C_{23}H_{34}O_8S$ (470.58): C, 58.71; H, 7.28, found: C, 58.71; H, 7.18.

3.2.7. Compound 18c. According to GP 1 the alcohol **17** (0.5 g, 2.0 mmol) was reacted with prop-2-ene-1-sulfonyl chloride (0.3 g, 2.2 mmol) in the presence of pyridine (0.5 g, 6.0 mmol) to give **18c** (0.8 g, 55%) as a colorless solid; mp = 64 °C; $[\alpha]_D^{25} = +75.15$ ($c=1.0$; $CHCl_3$). IR (KBr): 2979, 2933, 1384, 1372, 1344, 1216, 1261, 1217, 1171, 1118, 1082, 1051, 1017, 999, 942, 928, 910, 882, 861, 849, 835, 792, 647, 612, 574, 547 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 6H), 1.49 (s, 3H), 1.58 (s, 3H), 3.93 (dd, $J=6.0$, 8.8 Hz, 1H), 3.96 (m, 2H), 4.09 (dd, $J=4.1$, 8.2 Hz, 1H), 4.33 (m, 1H), 4.76–4.85 (m, 2H), 5.82 (d, $J=3.6$ Hz, 1H), 5.47–5.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 26.2, 26.7, 26.7, 55.9, 65.4, 74.6, 76.9, 77.0, 77.9, 103.8, 110.0, 113.6, 123.9, 124.7. MS (EI, 70 eV): *m/z* (%) 349 (100) [M^+-CH_3], 167 (11), 127 (16), 113 (57), 101 (71). Anal. Calcd for $C_{15}H_{24}O_8S$ (364.41): C, 49.44; H, 6.64, found: C, 49.45; H, 49.45.

3.2.8. Compound 18d. According to GP 1 the alcohol **17** (2.0 g, 8.0 mmol) was reacted with propane-1-sulfonyl chloride (1.2 g, 8.8 mmol) in the presence of pyridine (1.8 g, 24.0 mmol) to give **18d** (2.7 g, 93%) as a colorless oil; $[\alpha]_D^{27} = +81.0$ ($c=1.0$; $CHCl_3$). IR ($CHCl_3$): 2986, 2938, 2885, 1458, 1372, 1257, 1218, 1168, 1121, 1045, 1021, 932, 873, 839, 522 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, $J=7.4$ Hz, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.96 (m, 2H), 3.20 (m, 2H), 3.93 (dd, $J=6.0$, 8.5 Hz, 1H), 4.09 (dd, $J=6.9$, 8.5 Hz, 1H), 4.15 (dd, $J=4.1$, 7.7 Hz, 1H), 4.33 (m, 1H), 4.80 (m, 2H), 5.82 (d, $J=3.6$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 17.1, 25.1, 26.2, 26.6, 26.7, 53.3, 65.5, 74.7, 76.3, 77.3, 77.9, 103.8, 110.0, 113.5. MS (EI, 70 eV): *m/z* (%) 351 (57) [M^+-CH_3], 127 (17), 113 (75), 101 (100). Anal. Calcd for $C_{15}H_{26}O_8S$ (366.43): C, 49.17; H, 7.15, found: C, 49.07; H, 7.08.

3.3. General procedure for the α-alkylation of chiral sulfonates (GP 2)

The enantiopure sulfonate (1.0 mmol) was dissolved in dry THF (20 mL) and the solution cooled to −(90–95) °C. After 30 min *n*-BuLi (1.0 equiv) was added dropwise. The solution was stirred for an additional hour after which the electrophile (1.5 equiv) was added dropwise. The mixture was stirred for 1 h at −(90–95) °C, then at −78 °C. After 24 h the reaction was quenched by adding pH 7 buffer (2 mL). The mixture was partitioned between CH_2Cl_2 and the aqueous layer further extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, pentane/diethyl ether).

3.3.1. Compound 10. According to GP 2 the sulfonate **9** (310 mg, 1.0 mmol) was reacted with benzylbromide (190 mg, 1.1 mmol) to give **10** (300 mg, 75%) as a colorless solid; de = 75% (^{13}C NMR); mp = 122 °C. IR (KBr): 2960, 2936, 2870, 1496, 1454, 1353, 1326, 1165, 1073, 940, 913, 870, 845, 823, 696, 643, 632, 596, 566, 552, 478 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87–2.10 (m, 17H), 3.40 (m, 1H), 3.77 (dd, $J=3.6$, 13.7 Hz, 1H), 4.35 (m, 1H), 4.52 (m, 1H), 6.98–7.40 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5 [15.3], 20.9, 21.8 [20.8, 21.8], 23.0 [22.8], 25.6 [25.2], 31.6, 33.7, 36.5 [36.4], 41.3 [42.3], 47.6 [47.5], 69.7 [69.3],

83.5 [82.6], 126.6, 128.2, 128.3, 128.6, 128.8, 129.7, 132.0, 136.5. MS (EI, 70 eV): *m/z* (%) 181 (100) [CH(Ph)CH_2-Ph^+], 138 (2) [$M^+ - C_{14}H_{13}SO_2OH$]). Anal. Calcd for $C_{24}H_{32}O_3S$ (400.575): C, 71.96; H, 8.05, found: C, 71.79; H, 7.91.

3.3.2. Compound 13a. According to GP 2 the sulfonate *rac*-**12a** (470 mg, 1.0 mmol) was reacted with *n*-propyl iodide (180 mg, 1.1 mmol) to give **13a** (280 mg, 55%) as a colorless solid; de=60% (^{13}C NMR); mp=72 °C. IR (KBr): 2960, 2869, 1601, 1496, 1455, 1415, 1394, 1359, 1337, 1264, 1223, 1168, 1117, 1070, 1053, 1013, 960, 922, 899, 870, 829, 806, 698, 634 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 [0.66] (t, J=7.4 Hz, 3H), 1.20–2.40 (m, 12H), 1.47 [1.46] (s, 18H), 2.60 [2.68] (m, 1H), 3.61 [3.55] (dd, J=3.9, 11.3 Hz, 1H), 3.69 (s, 3H), 4.97 [4.89] (m, 1H), 7.140–7.30 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 19.6 [19.5], 24.7, 25.4, 31.0 [31.2], 32.2, 34.0 [34.4], 35.2 [35.7], 35.8, 49.9 [50.0], 64.1 [64.0], 67.4 [67.6], 83.7 [84.7], 125.3, 128.3, 128.4, 129.4 [129.5], 132.3 [132.1], 136.4 [136.5], 143.2 [143.3], 157.9 [158.0]; MS (EI, 70 eV): *m/z* (%) 514 (13) [M^+], 300 (100) [$M^+ - C_{10}H_{13}SO_2OH$], 217 (2), 285 (16), 91 (20) [$C_7H_7^+$]. HRMS: *m/z* calcd for $C_{31}H_{46}O_4S$ (M^+) 514.3117, found 514.3114.

3.3.3. Compound 13b. According to GP 2 the sulfonate *rac*-**12b** (310 mg, 1.0 mmol) was reacted with *n*-propyl iodide (180 mg, 1.1 mmol) to give **13b** (250 mg, 71%) as a colorless solid; de=59% (^{13}C NMR); mp=74 °C. IR (KBr): 2936, 2866, 1607, 1585, 1493, 1454, 1344, 1290, 1265, 1214, 1168, 1101, 1048, 998, 939, 905, 884, 863, 828, 803, 785, 698, 577 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 [0.70] (t, J=7.2 Hz, 3H), 1.20–2.50 (m, 12H), 2.74 [2.63] (m, 1H), 3.39 (dd, J=7.4, 1H), 3.81 [3.82] (s, 3H), 4.86 [4.84] (m, 1H), 6.70–7.35 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.53 [13.19], 19.63 [19.60], 24.74 [24.66], 25.31 [25.34], 31.56 [31.25], 34.41 [34.35], 34.58 [34.50], 55.01 [55.08], 50.28 [50.08], 67.73 [67.51], 85.73 [84.32], 112.05 [112.09], 113.51 [113.44], 119.70 [119.76], 128.23, 128.34 [128.40], 129.21 [129.27], 129.50 [129.33], 132.06 [132.25], 144.46 [144.12], 159.60 [159.55]. MS (EI, 70 eV): *m/z* (%): 402 (8) [M^+], 188 (100) [$M^+ - C_{10}H_{13}SO_2OH$], 133 (18), 121 (23), 91 (76) [$C_7H_7^+$]. Anal. Calcd for $C_{23}H_{30}O_4S$ (402.55): C, 68.63; H, 7.51, found: C, 68.67; H, 7.40.

3.3.4. Compound 16. According to GP 2 the sulfonate **15** (410 mg, 1.0 mmol) was reacted with *n*-propyl iodide (180 mg, 1.1 mmol) in the presence of 1.1 equiv of HMPA (0.19 mL, 1.1 mmol) to give **16** (330 mg, 73%) as a colorless solid; de=59% (^{13}C NMR); mp=93 °C. IR (KBr): 2981, 2960, 2937, 2876, 1456, 1373, 1255, 1210, 1169, 1076, 1047, 1026, 979, 955, 897, 882, 858, 843, 752, 698, 620, 615, 566 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 [0.90] (t, J=7.4 Hz, 3H), 1.19 [1.28] (s, 3H), 1.38 [1.35] (s, 3H), 1.44 [1.45] (s, 3H), 1.49 [1.48] (s, 3H), 1.25 [1.22] (m, 2H), 2.17 [2.23] (m, 1H), 2.38 [2.32] (m, 1H), 33.90–4.20 (m, 5H), 4.27 [4.30] (dd, J=3.9, 11.5 Hz, 1H), 4.96 [4.97] (d, J=2.3 Hz, 1H), 5.62 [5.88] (d, J=3.6 Hz, 1H), 7.38–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4 [13.6], 19.9 [19.8], 25.2, 25.9, 26.5 [26.6], 26.9, 31.6, 67.0 [67.1], 68.2 [67.8], 71.9 [72.0], 79.8, 81.9 [82.1], 82.6 [83.4], 104.7, 109.4, 112.1 [112.3], 128.7, 129.0, 129.4, 132.3 [131.5]. MS (EI, 70 eV): *m/z* (%) 441 (12) [$M^+ - CH_3$], 133 (100) [$C_{10}H_{13}^+$], 113 (66), 101 (40), 91 (96) [C_7H_7]. Anal. Calcd for $C_{22}H_{32}O_8S$ (456.55): C, 57.88; H, 7.06, found: C, 57.74; H, 7.20.

3.3.5. Compound 19. According to GP 2 the sulfonate **18a** (410 mg, 1.0 mmol) was reacted with *n*-propyl iodide (180 mg, 1.1 mmol) in the presence of 1.1 equiv of HMPA (0.19 mL, 1.1 mmol) to give **19** (310 mg, 69%) as a colorless solid; de=78% (^{13}C NMR); mp=124 °C. IR (KBr): 2976, 2955, 2934, 2890, 1638, 1498, 1471, 1457, 1372, 1353, 1312, 1296, 1259, 1233, 1216, 1173, 1116, 1053, 1041, 1018, 999, 932, 880, 867, 837, 804, 734, 697, 659, 630 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J=7.4 Hz, 3H), 1.33 (s, 3H), 1.38 [1.36] (s, 3H), 1.48 [1.43] (s, 3H), 1.56 (s, 3H), 1.25 (m, 2H), 2.20 (m, 1H), 2.41 (m, 1H), 3.89 [3.6] (dd, J=6.6. 8.5 Hz, 1H), 4.04 (dd, J=6.6. 8.5 Hz, 1H), 4.14 (dd, J=3.8, 8.5 Hz, 1H), 4.22 (dd, J=4.1, 4.7 Hz, 1H), 4.33 (m, 2H), 4.66 [4.69] (dd, J=4.7, 8.5 Hz, 1H), 5.71 [5.8] (d, J=3.6 Hz, 1H), 7.36–7.55 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4 [13.5], 19.8, 25.3, 26.2 [26.3], 26.6, 26.7, 31.9 [31.5], 65.2 [64.9], 68.2 [67.8], 74.6, 76.8, 77.0, 77.5, 103.7 [103.8], 110.1, 113.5, 128.8, 129.1, 129.9 [129.7], 131.9. MS (EI, 70 eV): *m/z* (%) 441 (10) [$M^+ - CH_3$], 133 (97) [$C_{10}H_{13}^+$], 113 (43), 101 (48), 91 (100) [$C_7H_7^+$]. Anal. Calcd for $C_{22}H_{32}O_8S$ (456.55): C, 57.88; H, 7.06, found: C, 58.08; H, 7.07.

3.3.6. (*R*)-1-Phenyl-ethanesulfonate (*R*)-20a. According to GP 2 the sulfonate **18a** (410 mg, 1.0 mmol) was reacted with methyl iodide (200 mg, 1.5 mmol) to give (*R*)-**20a** (410 mg, 95%) as a colorless solid; de=91% (^{13}C NMR); de≥98 (after recrystallization from 2-propanol); mp=103.4 °C; $[\alpha]_D^{25} = +91.3$ (c=1.0, $CHCl_3$). IR (KBr): 2980, 2934, 2908, 1496, 1456, 1383, 1366, 1351, 1314, 1267, 1237, 1216, 1173, 1117, 1096, 1078, 1048, 1015, 1000, 931, 890, 873, 831, 695, 628, 614, 563, 506 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.56 (s, 3H), 1.87 (d, J=7.2 Hz, 3H), 3.86 (dd, J=6.6, 8.5 Hz, 1H), 4.01 (dd, J=6.6, 8.5 Hz, 1H), 4.14 (dd, J=4.1, 8.5 Hz, 1H), 4.27 (ddd, J=3.9, 4.1, 6.6 Hz, 1H), 4.35 (dd, J=3.8, 4.7 Hz, 1H), 4.49 (q, J=7.2 Hz, 1H), 4.64 (dd, J=4.7, 8.5 Hz, 1H), 5.72 (d, J=3.9 Hz, 1H), 7.30–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 25.1, 25.2, 26.2, 26.6, 63.1, 65.2, 74.6, 76.8, 77.5, 77.8, 103.6, 109.9, 113.3, 128.5, 129.0, 128.2, 129.2, 130.7, 133.2. MS (EI, 70 eV): *m/z* (%) 413 (62) [$M^+ - CH_3$], 113 (29), 105 (100) [$(CH_3)(C_6H_5)CH^+$], 101 (33). Anal. Calcd for $C_{20}H_{28}O_8S$ (428.50): C, 56.06; H, 6.59, found: C, 55.92; H, 6.76.

3.3.7. (*R*)-1-Phenyl-but-3-ene-1-sulfonate (*R*)-20b. According to GP 2 the sulfonate **18a** (410 mg, 1.0 mmol) was reacted with allyl bromide (180 mg, 1.5 mmol) to give (*R*)-**20b** (420 mg, 93%) as a colorless solid; de=90% (^{13}C NMR); de≥98 (after recryst. from 2-propanol); mp=149.2 °C; $[\alpha]_D^{24} = +77.0$ (c=1.0, $CHCl_3$). IR (KBr): 2978, 2934, 1497, 1457, 1370, 1355, 1313, 1255, 1220, 1172, 1115, 1054, 1038, 1015, 1001, 933, 880, 864, 840, 810, 698, 627, 571, 503 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.56 (s, 3H), 2.98 (m, 1H), 3.21 (m, 1H), 3.89 (dd, J=6.6, 8.5 Hz, 1H), 4.04 (dd, J=6.9, 8.5 Hz, 1H), 4.14 (dd, J=3.9, 8.5 Hz, 1H), 4.26–4.32 (m, 2H), 4.37 (dd, J=4.1, 11.3 Hz, 1H), 4.68 (dd, J=4.7,

8.8 Hz, 1H), 5.01 (d, J=9.9 Hz, 1H), 5.08 (d, J=17.0 Hz, 1H), 5.54 (m, 1H), 5.72 (d, J=3.9 Hz, 1H), 7.30–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.2, 26.6, 26.6, 34.3, 65.2, 67.8, 74.6, 76.8, 77.19, 103.6, 110.0, 113.4, 118.5, 128.6, 129.1, 129.8, 131.1, 132.4. MS (EI, 70 eV): m/z (%) 439 (78) [M^+-CH_3], 131 (100) [$(C_3H_5)(C_6H_5)CH^+$], 113 (30), 101 (32). Anal. Calcd for $C_{22}H_{30}O_8S$ (454.53): C, 58.13; H, 6.65, found: C, 57.78; H, 6.61.

3.3.8. (*R*)-1,2-Diphenyl-ethanesulfonate (*R*)-20c. According to GP 2 the sulfonate **18a** (410 mg, 1.0 mmol) was reacted with benzyl bromide (260 mg, 1.5 mmol) to give (*R*)-**20c** (470 mg, 94%) as a colorless solid; de=89% (^{13}C NMR); de≥98 (after recryst. from 2-propanol); mp=143 °C; $[\alpha]_D^{24}=+34.4$ (c=1.1, $CHCl_3$). IR (KBr): 2979, 2932, 1498, 1456, 1369, 1315, 1259, 1246, 1218, 1167, 1118, 1049, 1015, 998, 876, 857, 824, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 3.41 (dd, J=11.5, 13.7 Hz, 1H), 3.81 (dd, J=3.6, 13.7 Hz, 1H), 3.92 (dd, J=6.6, 8.5 Hz, 1H), 4.06 (dd, J=6.9, 8.5 Hz, 1H), 4.16 (dd, J=3.9, 8.8 Hz, 1H), 4.30–4.37 (m, 2H), 4.57 (dd, J=3.6, 11.5 Hz, 1H), 4.77 (dd, J=4.7, 8.8 Hz, 1H), 5.74 (d, J=3.6 Hz, 1H), 6.9–7.5 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 26.2, 26.6, 26.7, 36.5, 65.2, 69.8, 74.5, 76.7, 77.2, 77.4, 103.6, 110.0, 113.5, 128.2, 128.5, 128.7, 128.8, 129.0, 129.8, 131.0, 136.1. MS (EI, 70 eV): m/z (%) 489 (48, M^+-CH_3), 245 (2), 181 (100) [$(C_7H_7)(C_6H_5)CH^+$], 113 (25), 101 (30). Anal. Calcd for $C_{26}H_{32}O_8S$ (504.59): C, 61.89; H, 6.39, found: C, 61.60; H, 6.33.

3.3.9. (*R*)-2-(4-Bromophenyl)-1-phenyl-ethanesulfonate (*R*)-20d. According to GP 2 the sulfonate **18a** (410 mg, 1.0 mmol) was reacted with 1-bromo-4-bromomethyl-benzene (380 mg, 1.5 mmol) to give the (*R*)-**20d** (520 mg, 90%) as a colorless solid; de=90% (^{13}C NMR); de≥98 (after recryst. from 2-propanol); mp=143 °C; $[\alpha]_D^{25}=+17.8$ (c=0.8, $CHCl_3$). IR (KBr): 2985, 2939, 2900, 1491, 1457, 1372, 1312, 1260, 1217, 1177, 1164, 1115, 1073, 1053, 1040, 1015, 929, 876, 835, 810, 698, 642, 569, 528, 514 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 3.36 (dd, J=11.5, 13.7 Hz, 1H), 3.78 (dd, J=3.6, 13.7 Hz, 1H), 3.90 (dd, J=6.6, 8.8 Hz, 1H), 4.05 (dd, J=6.6, 8.8 Hz, 1H), 4.15 (dd, J=4.1, 8.8 Hz, 1H), 4.30–4.40 (m, 2H), 4.50 (dd, J=3.6, 11.5 Hz, 1H), 4.76 (dd, J=4.7, 8.8 Hz, 1H), 5.74 (d, J=3.6 Hz, 1H), 6.90–7.40 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 26.2, 26.7, 26.7, 36.0, 65.2, 69.5, 74.5, 76.6, 76.9, 77.4, 103.6, 110.1, 113.5, 120.7, 130.7, 135.1, 128.6, 129.2, 129.7, 130.5, 131.3. MS (EI, 70 eV): m/z (%) 569 (77) [$M^+(Br^{81})-CH_3$], 567 (65) [$M^+(Br^{79})-CH_3$], 261 (89) [$(Br^{81}C_7H_6)(C_6H_5)CH^+$], 259 (100) [$(Br^{79}C_7H_6)(C_6H_5)CH^+$], 180 (73), 165 (14), 113 (69), 101 (9). Anal. Calcd for $C_{26}H_{31}O_8SBr$ (583.50): C, 53.52; H, 5.35, found: C, 53.64; H, 5.38.

3.3.10. (*R*)-2-Naphtalen-2-yl-1-phenyl-ethanesulfonate (*R*)-20e. According to GP 2 the sulfonate **18a** (410 mg, 1.0 mmol) was reacted with 2-bromomethyl-naphthalene (330 mg, 1.5 mmol) to give (*R*)-**20e** (530 mg, 96%) as a colorless solid; de=91% (^{13}C NMR); de≥98 (after recryst. from 2-propanol); mp=136 °C; $[\alpha]_D^{26}=+17.3$ (c=1.0, $CHCl_3$). IR (KBr): 2987, 2937, 2899, 2185, 1637, 1602, 1457, 1373, 1218, 1168, 1121, 1019, 930, 872, 843, 822, 752, 699, 570 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 1.59 (s, 3H), 3.57 (dd, J=11.5, 13.7 Hz, 1H), 3.89 (dd, J=6.6, 8.5 Hz, 1H), 3.97–4.05 (m, 2H), 4.16 (dd, J=3.8, 8.8 Hz, 1H), 4.32 (ddd, J=3.8, 6.6, 6.6 Hz, 1H), 4.68 (dd, J=3.6, 4.7 Hz, 1H), 4.68 (dd, J=3.6, 11.5 Hz, 1H), 4.73 (dd, J=4.7, 8.5 Hz, 1H), 5.74 (d, J=3.6 Hz, 1H), 7.10–7.90 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 26.2, 26.7, 26.7, 36.7, 65.1, 69.7, 74.5, 76.9, 77.2, 77.4, 103.6, 110.0, 113.5, 125.6, 126.0, 126.8, 127.3, 127.4, 127.7, 127.9, 131.0, 132.0, 133.1, 133.6. MS (EI, 70 eV): m/z (%) 554 (14) [M^+], 539 (23) [M^+-CH_3], 312 (21), 231 (100) [$(C_{11}H_9)(C_6H_5)CH^+$], 215 (8), 153 (35), 141 (39), 101 (17). Anal. Calcd for $C_{30}H_{34}O_8S$ (554.65): C, 64.96; H, 6.18, found: C, 64.83; H, 6.34.

3.3.11. (*R*)-1-(4-*tert*-Butylphenyl)-2-phenyl-ethanesulfonate (*R*)-20f. According to GP 2 the sulfonate **18b** (470 mg, 1.0 mmol) was reacted with benzyl bromide (260 mg, 1.5 mmol) to give (*R*)-**20f** (530 mg, 95%) as a colorless solid; de=91% (^{13}C NMR); de≥98 (after recryst. from 2-propanol); mp=143 °C; $[\alpha]_D^{26}=+22.6$ (c=1.0, $CHCl_3$). IR (KBr): 2903, 1606, 1455, 1370, 1313, 1246, 1215, 1177, 1165, 1117, 1083, 1057, 1043, 1019, 877, 859, 834, 745, 699, 672, 615, 576, 557, 521 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H), 1.34 (s, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 3.41 (dd, J=11.3, 14.0 Hz, 1H), 3.81 (dd, J=3.6, 14.0 Hz, 1H), 3.90 (dd, J=6.6, 8.5 Hz, 1H), 4.04 (dd, J=6.6, 8.5 Hz, 1H), 4.14 (dd, J=3.9, 8.8 Hz, 1H), 4.27 (dd, J=3.8, 4.7 Hz, 1H), 4.32 (ddd, J=3.9, 6.6, 6.6 Hz, 1H), 4.55 (dd, J=3.6, 11.3 Hz, 1H), 4.73 (dd, J=4.7, 8.8 Hz, 1H), 5.72 (d, J=3.9 Hz, 1H), 6.90–7.40 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 26.2, 26.7, 26.7, 31.2, 34.6, 36.4, 65.1, 69.4, 74.6), 76.7, 77.4, 77.6, 103.5, 110.0, 113.4, 125.5, 126.6, 128.2, 128.8, 129.4, 127.8, 136.4, 152.1. MS (EI, 70 eV): m/z (%) 545 (15) [M^+-CH_3], 237 (100), 113 (4), 101 (7), 91 (20) [$C_7H_7^+$]. Anal. Calcd for $C_{30}H_{40}O_8S$ (560.70): C, 64.26; H, 7.19, found: C, 64.29; H, 7.20.

3.3.12. (*R*)-1-(4-*tert*-Butylphenyl)-2-naphtalen-2-yl-ethanesulfonate (*R*)-20g. According to GP 2 the sulfonate **18b** (470 mg, 1.0 mmol) was reacted with 2-bromomethyl-naphthalene (330 mg, 1.5 mmol) to give (*R*)-**20g** (600 mg, 98%) as a colorless solid; de=93% (^{13}C NMR); de≥98 (after recryst. from 2-propanol); mp=139 °C; $[\alpha]_D^{26}=+3.8$ (c=1.0., $CHCl_3$). IR (KBr): 2978, 2903, 1602, 1510, 1454, 1370, 1318, 1258, 1217, 1166, 1122, 1018, 933, 893, 878, 839, 819, 795, 746, 625, 607 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.26 (s, 9H), 1.36 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 1.59 (s, 3H), 3.57 (dd, J=11.3, 14.0 Hz, 2H), 3.88 (dd, J=6.6, 8.5 Hz, 1H), 3.95–4.03 (m, 2H), 4.15 (dd, J=3.6, 8.5 Hz, 1H), 4.29–4.36 (m, 2H), 4.67 (dd, J=3.6, 11.3 Hz, 1H), 4.76 (dd, J=4.7, 8.5 Hz, 1H), 5.73 (d, J=3.9 Hz, 1H), 7.10–7.80 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 26.2, 26.7, 26.7, 31.2, 34.6, 36.6, 65.1, 69.3, 74.5, 76.7, 77.2, 77.2, 77.4, 103.6, 110.0, 113.5, 125.5, 125.9, 126.8, 127.3, 127.4, 127.7, 127.8, 127.8, 129.4, 132.0, 133.1, 133.8, 152.1. MS (EI, 70 eV): m/z (%) 595 (4) [M^+-CH_3], 287 (100), 141 (16) [$C_{11}H_9^+$], 101 (7). Anal. Calcd for $C_{34}H_{42}O_8S$ (610.76): C, 66.86; H, 6.93, found: C, 67.12; H, 6.86.

3.3.13. Compound 20h. According to GP 2 the sulfonate **18c** (360 mg, 1.0 mmol) was reacted with methyl iodide (200 mg, 1.5 mmol) to give **20h** (210 mg, 55%) as a colorless oil; de = 50% (^{13}C NMR). IR (film): 2987, 2939, 2900, 1640, 1457, 1373, 1360, 1217, 1167, 1121, 1020, 934, 873, 832, 751, 657 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.49 (s, 3H), 1.60 (s, 3H), 1.62 (s, 3H), 1.62 [1.61] (d, J = 6.9 Hz, 3H), 3.80–4.35 (m, 4H), 4.77–4.83 (m, 2H), 5.47–5.54 (m, 2H), 5.82 (d, J = 3.6 Hz, 1H), 6.00 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 [14.4], 25.1, 26.2, 26.6, 26.7, 55.9, 65.4 [65.5], 74.65, 76.6, 76.9, 77.9 [77.8], 103.7 [103.7], 110.0, 113.5, 121.9 [121.7], 130.0 [130.3]. MS (EI, 70 eV): *m/z* (%) 363 (100) [$M^+ - CH_3$], 167 (7), 127 (14), 113 (49), 101 (70). Anal. Calcd for $C_{16}H_{26}O_8S$ (378.44): C, 50.78; H, 6.92, found: C, 50.41; H, 7.12.

3.3.14. Compound 20i. According to GP 2 the sulfonate **18d** (370 mg, 1.0 mmol) was reacted with methyl iodide (200 mg, 1.5 mmol) to give **20i** (330 mg, 87%) as a colorless oil; de = 0% (^{13}C NMR). IR (film): 2987, 2940, 2884, 1458, 1373, 1218, 1175, 1121, 1021, 931, 872, 829, 793, 757, 599, 524 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 [1.06] (t, J = 7.4 Hz, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 1.57 (s, 3H), 1.46 (d, J = 7.4 Hz, 3H), 1.65 [2.17] (m, 2H), 3.19 (m, 1H), 3.92 (dd, J = 6.9, 8.5 Hz, 1H), 4.09 (dd, J = 6.9, 8.5 Hz, 1H), 4.14–4.19 (m, 1H), 4.32 (m, 1H), 4.78 (m, 2H), 5.82 (d, J = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.9 [11.0], 13.3 [13.4], 23.4 [23.5], 25.2, 26.2, 26.7, 26.7, 58.9 [59.0], 65.4 [65.5], 74.7 [74.8], 76.1, 78.0, 78.0, 103.8, 110.0, 113.4. MS (EI, 70 eV): *m/z* (%) 363 (100) [$M^+ - CH_3$], 167 (7), 127 (14), 113 (49), 101 (70). Anal. Calcd for $C_{16}H_{28}O_8S$ (380.45): C, 50.51; H, 7.42, found: C, 50.36; H, 7.67.

3.4. General procedure for the removal of the chiral auxiliary to form the α-alkylated methyl sulfonates (*R*)-21a–g (GP 3)

The sulfonate (*R*)-**20** (0.6 mmol) was dissolved in an EtOH/H_2O-solution (19:1 mL). To the solution was added $Pd(OAc)_2$ (15 mol%, 20 mg) and the mixture was refluxed for 4 d (TLC control). The palladium residues were removed by filtration and washed twice with EtOH. The filtrate was treated with an ethereal solution of diazomethane until the yellow color persisted. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography (SiO_2, pentane/diethyl ether, 1:6) to afford the methyl sulfonate (*R*)-**21**.

3.4.1. Methyl (*R*)-1-phenylethane sulfonate (*R*)-21a. The sulfonate (*R*)-**20a** (260 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21a** (120 mg, 98%) as a colorless oil; ee ≥ 98% (HPLC, Daicel OJ); $[\alpha]_D^{26} = +25.6$ (c = 1.0; $CHCl_3$). IR ($CHCl_3$): 2992, 2960, 1496, 1455, 1353, 1304, 1168, 1056, 1030, 991, 802, 781, 767, 699, 624, 566 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (d, J = 7.1 Hz, 3H), 3.66 (s, 3H), 4.40 (q, J = 7.1 Hz, 1H), 7.37–7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 56.7, 61.8, 128.6, 128.9, 128.9, 133.5. MS (EI, 70 eV): *m/z* (%) 200 (5) [M^+], 105 (100) [$M^+ - SO_3CH_3$), 103 (8), 79 (9). HRMS: *m/z* calcd for $C_9H_{12}O_3S$ (M^+) 200.0507, found 200.0507.

3.4.2. Methyl (*R*)-1-phenyl-3-butene sulfonate (*R*)-21b. The sulfonate (*R*)-**20b** (270 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21b** (130 mg, 90%) as a colorless solid; mp = 58 °C; ee ≥ 98% (HPLC, (*S*,*S*)-Whelk-O1); $[\alpha]_D^{28} = -6.3$ (c = 1.0; $CHCl_3$). IR (KBr): 2959, 2944, 2922, 1643, 1456, 1350, 1320, 1228, 1163, 993, 939, 835, 767, 734, 700, 654 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (m, 1H), 3.13 (m, 1H), 3.64 (s, 3H), 4.26 (dd, J = 4.7, 11.0 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 5.10 (d, J = 17.0 Hz, 1H), 5.57 (m, 1H), 7.36–7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.0, 56.8, 66.7, 118.6, 128.7, 129.0, 129.5, 132.3, 132.7. MS (EI, 70 eV): *m/z* (%) 181 (100) [$M^+ - SO_3CH_3$], 103 (5), 91 (28) [$C_7H_7^+$]. Anal. Calcd for $C_{11}H_{14}O_3S$ (226.29): C, 58.39; H, 6.24, found: C, 58.30; H, 6.32.

3.4.3. Methyl (*R*)-1,2-diphenylethane sulfonate (*R*)-21c. The sulfonate (*R*)-**20c** (300 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21c** (160 mg, 94%) as a colorless solid; mp = 67 °C; ee ≥ 98% (HPLC, Daicel OD); $[\alpha]_D^{27} = -77.4$ (c = 1.0; $CHCl_3$). IR (KBr): 3032, 2964, 2935, 1497, 1454, 1347, 1329, 1158, 984, 848, 818, 767, 755, 724, 697, 628, 582, 556 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (dd, J = 11.0, 13.7 Hz, 1H), 3.63 (s, 3H), 3.73 (dd, J = 3.6, 13.7 Hz, 1H), 4.44 (dd, J = 3.6, 11.0 Hz, 1H), 6.98–7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.3, 56.9, 68.6, 126.9, 128.5, 128.8, 129.0, 129.2, 129.7, 131.7, 136.4. MS (EI, 70 eV): *m/z* (%) 276 (3) [M^+], 181 (100) [$M^+ - SO_3CH_3$], 166 (18), 115 (1), 103 (14), 91 (19) [$C_7H_7^+$]. Anal. Calcd for $C_{15}H_{16}O_3S$ (276.35): C, 65.19; H, 5.84, found: C, 65.00; H, 5.83.

3.4.4. Methyl (*R*)-2-(4-bromophenyl)-1-phenylethane sulfonate (*R*)-21d. The sulfonate (*R*)-**20d** (350 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21d** (160 mg, 77%) as a colorless solid; mp = 82 °C; ee ≥ 98% (HPLC, (*S*,*S*)-Whelk-O1); $[\alpha]_D^{32} = -93.4$ (c = 1.0; $CHCl_3$). IR (KBr): 3037, 2967, 1490, 1454, 1439, 1489, 1455, 1439, 1347, 1164, 1075, 1048, 1017, 981, 921, 856, 820, 809, 775, 731, 701, 638, 608, 569, 545, 509, 482, 462 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (dd, J = 11.3, 14.0 Hz, 1H), 3.63 (s, 3H), 3.68 (dd, J = 3.9, 14.0 Hz, 1H), 4.38 (dd, J = 3.9, 11.3 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.33–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.7, 56.9, 68.6, 128.7, 129.1, 129.4, 130.5, 131.4, 120.7, 131.2, 135.1 (Aryl-C). MS (EI, 70 eV): *m/z* (%) 356 (10) [$M^+(Br^{81})$], 354 (11) [$M^+(Br^{79})$], 261 (47) [$M^+(Br^{81}) - SO_3CH_3$)], 259 (73) [$M^+(Br^{79}) - SO_3CH_3$], 180 (100), 169 (4), 89 (36). Anal. Calcd for $C_{15}H_{15}O_3SBr$ (355.25): C, 50.72; H, 4.26, found: C, 50.40; H, 4.51.

3.4.5. Methyl (*R*)-2-naphtalen-2-yl-1-phenylethane sulfonate (*R*)-21e. The sulfonate (*R*)-**20e** (330 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21e** (190 mg, 96%) as a colorless solid; mp = 67 °C, ee ≥ 98% (HPLC, Daicel OD); $[\alpha]_D^{31} = -89.5$ (c = 1.0; $CHCl_3$). IR (KBr): 3056, 2959, 1602, 1455, 1356, 1327, 1180, 1167, 1081, 990, 863, 821, 784, 767, 696, 610, 577, 483 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (dd, J = 11.3, 14.0 Hz, 1H), 3.65 (s, 3H), 3.90 (dd, J = 3.8, 14.0 Hz, 1H), 4.38 (dd, J = 3.9, 11.3 Hz, 1H), 7.20–7.80 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.5, 56.8, 68.5, 125.6, 125.9, 126.7, 127.4, 127.4, 127.7, 128.0, 128.6, 129.0, 129.5, 131.5, 132.0, 133.1, 133.7. MS (EI, 70 eV): *m/z* (%) 326 (27) [M^+], 230

(40), 215 (18), 153 (58), 141 (42) [$C_{11}H_9^+$], 172 (9) [$C_{10}H_7^+$], 115 (31). Anal. Calcd for $C_{19}H_{18}O_3S$ (326.41): C, 69.91; H, 5.56, found: C, 69.75; H, 5.77.

3.4.6. Methyl (*R*)-1-(4-*tert*-butylphenyl)-2-phenylethane sulfonate (*R*)-21f. The sulfonate (*R*)-**20f** (340 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21f** (180 mg, 90%) as a colorless oil; ee≥98% (HPLC, Daicel AD); $[\alpha]_D^{26}=-92.8$ ($c=1.0$; $CHCl_3$). IR (film) 3031, 3005, 2961, 2906, 2870, 1604, 1512, 1497, 1456, 1416, 1357, 1166, 989, 861, 829, 794, 756, 727, 699, 673, 611, 576 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 3.41 (dd, $J=$ 10.7, 14.0 Hz, 1H), 3.62 (s, 3H), 3.71 (dd, $J=4.1$, 14.0 Hz, 1H), 4.42 (dd, $J=4.1$, 10.7 Hz, 1H), 7.00–7.40 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 34.7, 36.5, 56.8, 68.5, 125.6, 125.9, 126.7, 127.4, 127.4, 127.7, 128.0, 128.6, 129.0, 129.5, 131.5, 132.1, 133.1, 133.7. MS (EI, 70 eV): *m/z* (%) 332 (2) [M^+], 237 (2) [$M^+-SO_3CH_3$], 172 (9) [$C_{10}H_7^+$], 115 (2), 91 (22) [$C_7H_7^+$], 57 (74). HRMS: *m/z* calcd for $C_{19}H_{24}O_3S$ (M^+) 332.1446, found 332.1446.

3.4.7. Methyl (*R*)-1-(4-*tert*-butylphenyl)-2-naphtalen-2-yl-ethane sulfonate (*R*)-21g. The sulfonate (*R*)-**20g** (340 mg, 0.6 mmol) was reacted according to GP 3 to give (*R*)-**21g** (200 mg, 87%) as a colorless solid; mp= 94 °C; ee≥98% (HPLC, Daicel AD); $[\alpha]_D^{28}=-108.2$ ($c=$ 1.0; $CHCl_3$). IR (KBr) 2962, 1599, 1560, 1508, 1351, 1162, 994, 960, 859, 827, 809, 777, 765, 749, 673, 623, 603, 518, 484, 474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 3.58 (dd, $J=11.0$, 14.0 Hz, 1H), 3.63 (s, 3H), 3.88 (dd, $J=3.9$, 14.0 Hz, 1H), 4.53 (dd, $J=3.9$, 10.7 Hz, 1H), 7.10–8.00 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=31.2$, 34.6, 36.5, 56.8, 68.1, 125.8, 126.0, 126.1, 127.0, 127.6, 127.6, 127.9, 128.1, 129.4, 128.5, 132.3, 133.3, 134.1, 152.3. MS (EI, 70 eV): *m/z* (%) 382 (39) [M^+], 287 (100) [$M^+-SO_3CH_3$], 231 (12), 153 (16), 141 (22) [$C_{11}H_9^+$], 122 (26), 57 (88). Anal. Calcd for $C_{23}H_{26}O_3S$ (382.52): C, 72.22; H, 6.85, found: C, 71.84; H, 6.71.

3.5. Investigations on the cleavage mechanism

The sulfonate (*R*)-**20c** (1.7 g, 4.0 mmol) was dissolved in an EtOH/H_2O solution (80:5 mL). To the solution was added $Pd(OAc)_2$ (15 mol%, 150 mg) and the mixture was refluxed for 4 d (TLC control). The palladium residues were removed by filtration and washed twice with EtOH. The filtrate was treated with an ethereal solution of diazomethane until the yellow color persisted. The solvent was evaporated under reduced pressure and the compounds **22a** and **22b** were isolated by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 30:1).

3.5.1. Compound 22a. 25% yield (190 mg); colorless oil; $[\alpha]_D^{25}=+137.8$ ($c=1.15$; $CHCl_3$). IR ($CHCl_3$): 3414, 2975, 2898, 1725, 1642, 1445, 1404, 1376, 1355, 1111, 1085, 1054, 1006, 976, 947, 889, 839, 756, 700, 667, 648, 592 cm^{-1}. ^1H NMR (400 MHz, C_5D_5N): δ 1.09 (t, $J=$ 7.1 Hz, 3H), 3.49 (dq, $J=7.1$, 9.6 Hz, 1H), 3.81 (dt, $J=7.1$, 9.6 Hz, 1H), 3.86 (dd, $J=8.2$, 8.5 Hz, 1H), 4.05 (dd, $J=6.1$, 8.5 Hz, 1H), 4.38 (m, 1H), 4.53 (t, $J=3.9$ Hz, 1H), 4.76 (dd, $J=5.4$, 5.5 Hz, 1H), 4.86 (dd, $J=3.6$, 5.5 Hz, 1H), 5.29 (d, $J=4.1$ Hz, 1H). ^{13}C NMR (100 MHz, C_5D_5N): $\delta=15.5$, 64.0, 71.4, 72.3, 78.6, 79.9, 88.8, 105.0. MS (EI, 70 eV): *m/z* (%)=192 (9) [M^++2], 191 (100) [M^++1], 173 (10) [$(M^++1)-H_2O$], 145 (61, [$(M^++1)-C_2H_5O$], 130 (4), 103 (2), 85 (4), 73 (1). Anal. Calcd for $C_8H_{14}O_5$ (190.20): C, 50.52; H, 7.42, found: C, 50.50; H, 7.31.

3.5.2. Compound 22b. 37% yield (280 mg); colorless solid; mp=79 °C; $[\alpha]_D^{24}=-46.3$ ($c=1.0$; $CHCl_3$). IR (KBr): 3414, 2975, 2899, 1725, 1640, 1445, 1404, 1376, 1360, 1111, 1085, 1054, 1001, 972, 947, 889, 839, 756, 700, 660, 648, 590 cm^{-1}. ^1H NMR (400 MHz, C_5D_5N): δ 1.10 (t, $J=$ 7.1 Hz, 3H), 3.47 (dq, $J=7.1$, 9.3 Hz, 1H), 4.02 (dq, $J=7.1$, 9.3 Hz, 1H), 4.08 (t, $J=7.1$ Hz, 1H), 4.17 (t, $J=8.5$ Hz, 1H), 4.47 (m, 1H), 4.66 (s, 1H), 4.81 (d, $J=4.7$ Hz), 5.04 (dd, $J=4.7$, 5.0 Hz, 1H), 5.50 (s, 1H). ^{13}C NMR (100 MHz, C_5D_5N): $\delta=15.3$, 63.79, 71.8, 72.9, 81.4, 84.6, 88.7, 111.5. MS (EI, 70 eV): *m/z* (%)=192 (9) [M^++2], 191 (100) [M^++1], 173 (12) [$(M^++1)-H_2O$], 145 (61, [$(M^++1)-C_2H_5O$], 130 (4), 103 (2), 85 (6), 73 (2). Anal. Calcd for $C_8H_{14}O_5$ (190.20): C, 50.52; H, 7.42, found: C, 50.49; H, 7.35.

Röntgen crystal structure determination of **22b**. Single crystals were obtained by recrystallization from a *n*-heptane/CH_2Cl_2 mixture (10:1). A single crystal (colorless, transparent parallelepiped with dimensions $0.18\times0.35\times0.70$ mm^3) was measured on a SIEMENS SMART diffractometer at a temperature of about −130 °C. The substance ($C_8H_{14}O_5$ $M_r=190.19$) crystallized in the orthorhombic space group $P2_12_12_1$, $a=5.3014$ (6) Å, $b=7.0086$ (11) Å, $c=24.599$ (3) Å, $V=914.0$ (2) $Å^3$, $Z=4$, $\rho_{calcd}=1.382$ g/cm^3. Repeatedly measured reflections remained stable. A numerical absorption correction using six indexed crystal faces gave a transmission factor between 0.943 and 0.980. Equivalent reflections were averaged. Friedel opposites were not averaged. $R(I)_{int}=0.025$. The structure was determined by direct methods using program SHELXS. The H atoms were taken from a difference Fourier synthesis and were refined with isotropic thermal parameters. The structure was refined on F^2 values using program SHELXL-97. The final difference density was between −0.17 and +0.31 $e/Å^{-3}$. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-248428. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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On the deprotonation of 3,5-dichloropyridine using lithium bases: in situ infrared spectroscopic studies

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Abstract—Deprotonation of 3,5-dichloropyridine using LTMP and BuLi was monitored in real time by infrared spectroscopy. It appeared that the substrate was rapidly deprotonated. Transient structures between the substrate and the lithio derivative were detected. The absorbances recorded for the lithio derivative showed that the structures obtained using LTMP and BuLi were similar. When BuLi was used to deprotonate, a complete deuteration of the lithio derivative was noted upon quenching with D_2O. The latter did not allow the quantification of the lithio derivative when LTMP was used, since only partial deuteration was observed.

1. Introduction

Interest in π-deficient heteroaromatics (pyridine, quinoline, diazines etc.) either for pharmaceuticals or as building blocks for various applications within materials science and supramolecular chemistry has led to extensive efforts devoted to a variety of synthetic methodologies.[1] Notably, the uses of organolithium compounds formed through deprotonation allow many functionalizations.[2] Yet, due to uncertainties related to aggregation states and the structures of the reactive species, reaction sequences that proceed via organolithium species are among the most difficult to characterize.[3] Over the last years, only some studies of metallations by in situ infrared spectroscopy were developed,[4] often concerning aliphatic substrates. For IR spectroscopy monitorings, a strongly absorbing group (typically, a C=O group) is often preferred. Nevertheless, in order to extend the use of this technique, we have attempted the real time monitoring of commercial aromatic substrates deprotonations.

In this paper, we provide an investigation into the kinetics and mechanism of the 3,5-dichloropyridine deprotonation using LTMP (thermodynamic or kinetic control) and BuLi (kinetic control).

2. Results and discussion

Metallation of 3,5-dichloropyridine at C4 with LDA is known to be facile in THF.[2b] For IR monitorings, we used LTMP and BuLi. The spectra were recorded with a ReactIR™ 4000 fitted with an immersible DiComp ATR probe.[5] The experiments were conducted as follows: (1) THF was introduced and cooled to −75 °C; (2) the spectral baseline was reset to zero and the spectra recording was started; (3) the substrate was introduced; (4) the base was added dropwise; and (5) the deuteriolysis was effected after complete deprotonation.

The absorption bands associated with 3,5-dichloropyridine (695, 811, 884, 1011, 1108, 1208, 1305, 1401, 1420, 1559, 3046 and 3123 cm^{-1}; Fig. 1) instantly decreased upon addition of the base as 3,5-dichloropyridine was consumed. They were rapidly replaced by the absorbance associated with the aryllithium species. By comparing the absorbance bands obtained using LTMP (Fig. 1(a)) and BuLi (Fig. 1(b)), one can realize that two values (753 and 1007 cm^{-1}) out of the three attributed unambiguously to 3,5-dichloro-4-pyridyllithium are identical, the third (1139 cm^{-1} using LTMP and 1143 cm^{-1} using BuLi) differing little. This slight difference between both structures could be due to different ligands on lithium (THF, 2,2,6,6-tetramethylpiperidine or LTMP); the presence of the ring nitrogen could complicate even more things.[6]

The profiles obtained for the consumption of 3,5-dichloropyridine versus time showed that 1.25 equiv of LTMP were

Keywords: Metallation; Pyridines; In situ IR; Mechanism; Deuteration.
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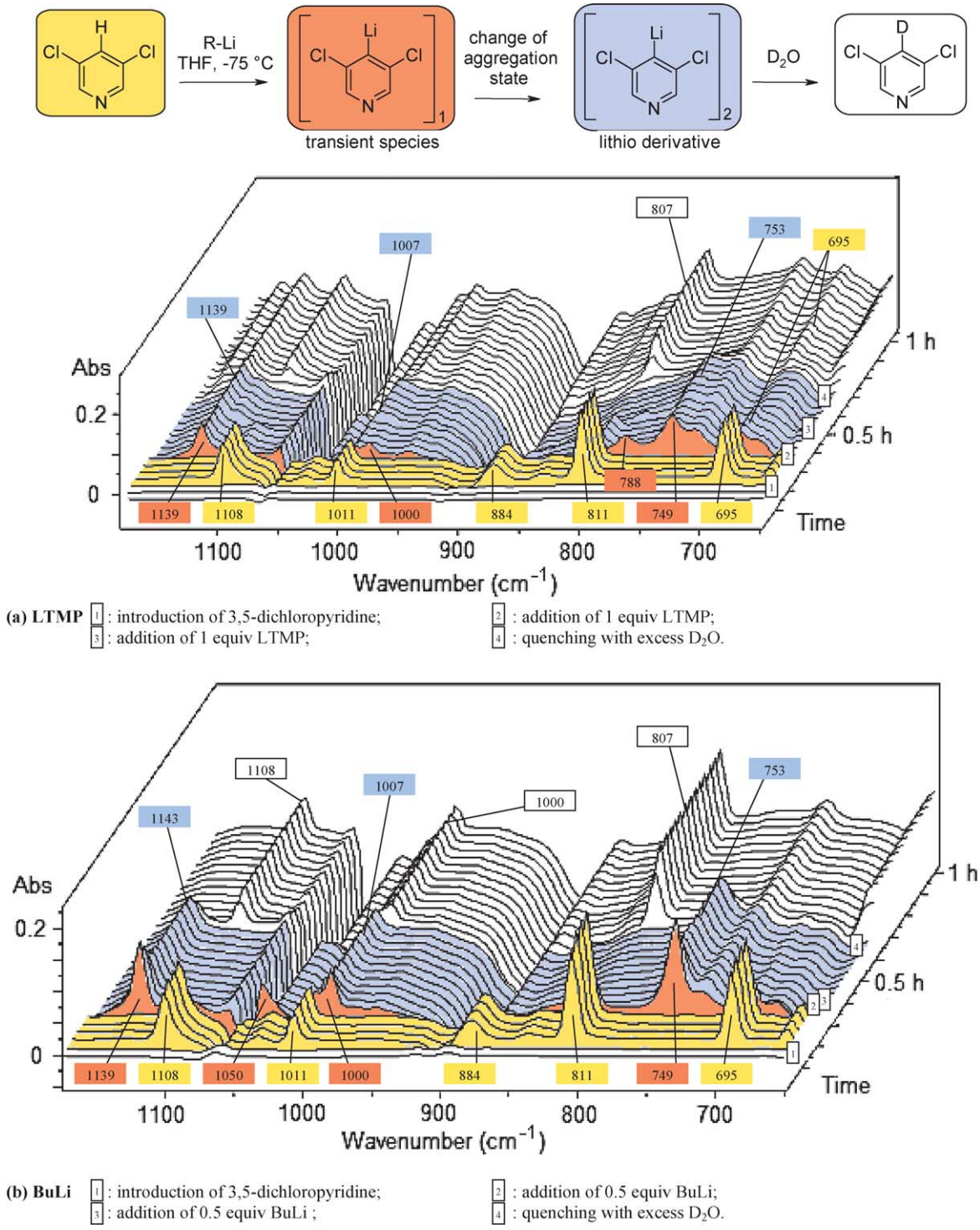


Figure 1. Progression of the reaction between 3,5-dichloropyridine and (a) LTMP or (b) BuLi, and subsequent deuteriolysis.

required to allow a complete deprotonation (Fig. 2(a)), which was ensured using 1 equiv of BuLi (Fig. 2(b)). A competitive formation of a complex between the aryllithium generated and LTMP could be responsible for this observation.[7,8]

Other peaks are of particular interest (749, 788, 1000, 1139 and 1532 cm^{-1} using LTMP (Figs. 1(a) and 3), and 749, 1000, 1050 and 1139 cm^{-1} using BuLi (Fig. 1(b))): they initially grew upon addition of the base, but immediately disappeared to be replaced by the absorbance associated with the aryllithium species.

Since various examples demonstrate dominance of a complex-induced proximity effect (CIPE)[9] process in the metallation reactions with alkyllithiums and, rarely, with lithium dialkylamides, we wondered if such transient structures could consist of prelithiation complexes (formed through interaction between the substrate and the lithium of the base before deprotonation).[4c] This possibility could be

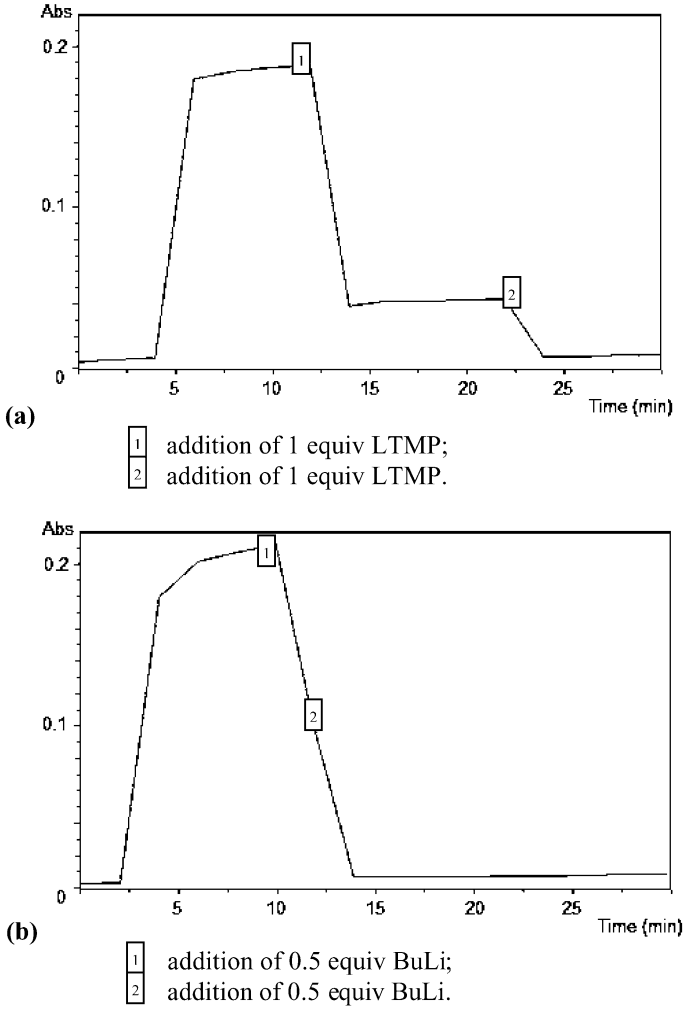


Figure 2. Consumption of 3,5-dichloropyridine versus time using (a) LTMP or (b) BuLi at 811 cm^{-1}.

discarded since a careful analysis of the spectra showed 2,2,6,6-tetramethylpiperidine (N–H at 3316 cm^{-1}) appeared at the same time as the transient structure, when LTMP was used.

The formation of a transient 2-lithiopyridine was next considered.[10] In this case, deprotonation of 4-deuterated 3,5-dichloropyridine would have afforded some 2-deuterated derivative. This possibility can also be ruled out since

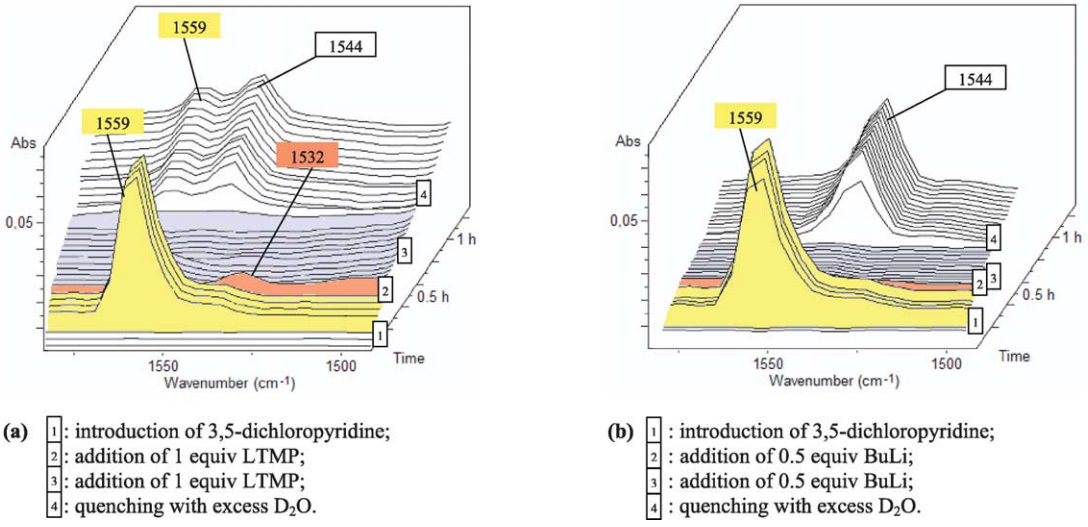
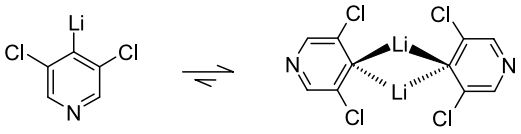


Figure 3. Progression of the reaction between 3,5-dichloropyridine and (a) LTMP or (b) BuLi, and subsequent deuteriolysis.

treating the 4-deuterated substrate successively with LTMP or BuLi and 3,4,5-trimethoxybenzaldehyde did not afford the 2-deuterated compounds. A product functionalized at C4 without deuterium at C2 was obtained using BuLi.

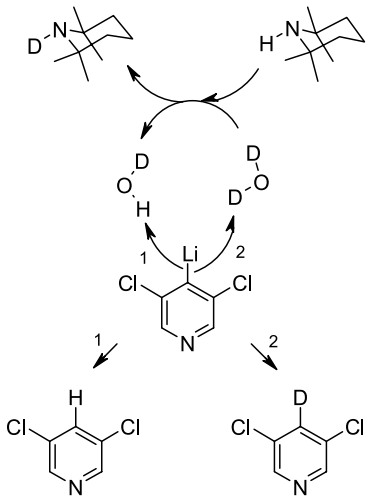
The existence of identical absorption values for the transient structures detected using LTMP and BuLi (749, 1000 and 1139 cm^{-1}), as well as wavenumbers close to those of the lithio derivatives, suggest a rapid change in the aggregation state from a transient monomer to a dimer structure. It is known that phenyllithium is a mixture of dimer and monomer in THF;[11] concerning pyridyllithiums, such studies were not reported (Scheme 1).



Scheme 1.

The deuteriolysis was effected after complete deprotonation. Nevertheless, when LTMP (2 equiv) was used, the IR monitoring of the trapping step evidenced the formation of both 3,5-dichloropyridine (1559 cm^{-1}) and 3,5-dichloro-4-deuteriopyridine (1544 cm^{-1}). This was confirmed by NMR analysis, which showed that the product obtained incorporated only 70% of deuterium. On the other hand, the reaction carried out with BuLi (1 equiv) afforded the completely 4-deuterated compound (Fig. 3). A similar observation was described by Brandsma, when deprotonating quinoline or isoquinoline with equimolar quantities of potassium *tert*-butoxide and LDA in THF-hexane with HMPA as a co-solvent.[12] A H-bonded complex between the lithio derivative and 2,2,6,6-tetramethylpiperidine (Scheme 2) could be envisaged as responsible for the partial deuteration observed, analogous to that observed several years ago by Seebach between lithium enolates and secondary amines.[13]

Nevertheless, chelation between the aryllithium and 2,2,6,6-tetramethylpiperidine is unlikely and a more plausible explanation can be claimed. Trost proposed a competition between the hydrogen–deuterium exchange of the N–H and the organolithium trapping during deuteriolysis.[14] In our case, the IR spectra showed the disappearance of the N–H band at 3316 cm^{-1} associated with 2,2,6,6-tetramethylpiperidine upon addition of D_2O. It results that HOD obtained in this way could compete with D_2O in the quenching of the pyridyllithium (Scheme 3).



Scheme 3.

3. Conclusion

It is worth noting that even in the absence of a strongly absorbing group, deprotonation reactions can be monitored by in situ infrared spectroscopy. When treated with LTMP or BuLi, it appeared that 3,5-dichloropyridine was instantly deprotonated. Without monitoring, reaction conditions (time, temperature, number of equivalents) are often overestimated, which can be a source of degradation and/or competitive reactions.

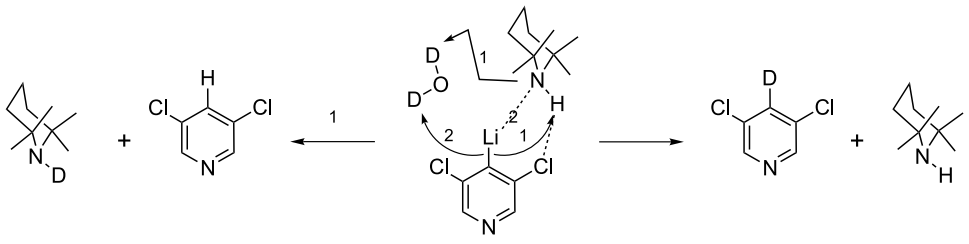
In addition, the monitoring furnished information on the contents of the reaction mixture. Transient structures between the substrate and the lithio derivative were detected and attributed to a monomeric pyridyllithium structure. The absorbances recorded for the lithio derivative showed similar structures obtained using LTMP and BuLi.

Finally, we gained in knowledge about the trapping step. When BuLi was used to deprotonate, a complete deuteration of the lithio derivative was noted. On the other hand, D_2O proved to react with HTMP giving HOD, since only partial deuteration was observed.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer. THF was distilled from



Scheme 2. To simplify matters, 3,5-dichloro-4-pyridyllithium was shown as a monomer.

benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[15] Metallation reactions were carried out under dry nitrogen. Deuterium incorporation was determined from the ^{1}H NMR integration values. After the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvents were evaporated under reduced pressure, and unless otherwise noted, the crude compound was chromatographed on a silica gel column (the eluent is given in the product description).

4.2. IR spectroscopic analyses, typical procedure

Samples were recorded using a ReactIR™ 4000 from ASI Applied Systems fitted with an immersible DiComp ATR probe optimized for maximum sensitivity. The spectra were acquired in 64 scans per spectrum at a gain of 1 and a resolution of 8 using system ReactIR™ 2.21 software. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical adjustable-volume ReactIR™ microcell[16] fitted with a magnetic stir bar under N_2 atmosphere. The flask was charged with THF (4 mL) and cooled at −75 °C before the recording of a background spectrum (1024 scans). IR spectra were collected at 2 min intervals over the course of the reaction. 3,5-Dichloropyridine (0.25 g, 1.7 mmol) was introduced after two acquisitions. BuLi was added after the sixth (0.85 mmol) and the seventh (0.85 mmol) acquisition at the same temperature. The mixture was quenched by an excess of D_2O (0.5 mL) after the 18th acquisition.

4.3. α-(3,4,5-Trimethoxyphenyl)-3,5-dichloro-4-pyridinemethanol

A solution of 4-deuterio-3,5-dichloropyridine (0.26 g, 1.7 mmol) in THF (4 mL) was cooled at −75 °C and treated with BuLi (1.7 mmol). After 1 h at −75 °C, the mixture was quenched with 3,4,5-trimethoxybenzaldehyde. Addition of water saturated with NH_4Cl (0.5 mL) was effected after 1 h to give 0.23 g (39%) of α-(3,4,5-trimethoxyphenyl)-3,5-dichloro-4-pyridinemethanol (eluent: CH_2Cl_2): white solid, mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (broad s, 1H), 3.78 (s, 6H), 3.82 (s, 3H), 6.48 (d, 1H, J=6.8 Hz), 6.53 (s, 2H), 8.49 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0 (2C, p), 60.8 (p), 71.3 (t), 102.7 (2C, t), 131.8 (q), 135.2 (q), 137.3 (q), 145.8 (q), 148.5 (t), 153.1 (q); IR (KBr) ν 3413, 3000, 2939, 2837, 2249, 1593, 1507, 1462, 1417, 1394, 1329, 1235, 1128, 1099, 1004, 732, 711, 641. Anal. calcd for $C_{15}H_{15}Cl_2NO_4$ (344.20): C, 52.34; H, 4.39; N, 4.07. Found: C, 51.95; H, 4.02; N, 3.84%.

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Synthesis and lithiation of oxazolinylaziridines: the *N*-substituent effect

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Abstract—The preparation of *N*-substituted oxazolinylaziridines and their deprotonation to afford the corresponding aziridinyllithiums is described. The chemical and configurational stability of the lithiated species depends on the *N*-substituent on the aziridine ring. The trapping with carbonyl compounds of (*R**,*S**) configurated oxazolinylaziridines is an interesting route for the preparation of functionalised α,β-aziridino-γ-lactones.

1. Introduction

Aziridines are versatile synthetic intermediates. The interest in these types of compounds has led organic chemists to develop several synthetic procedures[1–4] including those based on cyclisation of a pre-existing C–C–N chain as in the thermolysis of β-haloamines[5] and those involving addition of nitrogen reagents to an alkene[6,7] or carbon nucleophiles to an imino (C=N) linkage.[8–13]

The use of aziridinyl anions as reactive intermediates for the preparation of functionalised aziridines has been neglected for years probably because of the difficulty that can be encountered in their generation and trapping with electrophiles. Desulfinylation of sulfinyl aziridines, desilylation of silyl aziridines and transmetalation methodologies have been used to generate nonstabilised aziridinyl anions.[13,14] Stabilised aziridinyl anions are usually made by deprotonation. Such a procedure is usually restricted to those aziridines bearing an electron-withdrawing group on the aziridine ring,[15] while the deprotonation of unsubstituted aziridines has been made possible by Lewis acid activation.[16] Among the electron-withdrawing groups which have been used to facilitate the metalation of aziridines, the oxazolinyl group is promising. Indeed, in previous papers, we have reported that oxazolinylaziridines can be α- or β-lithiated and trapped with electrophiles.[17]

Keywords: Aziridinyllithiums; Oxazolinylaziridines; Aziridino-γ-lactones; Lithiation.
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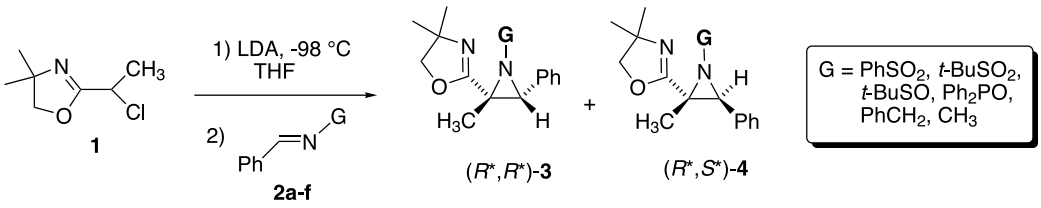
2. Results and discussion

In the present paper we describe the preparation of *N*-substituted oxazolinylaziridines, lithiation β to the oxazolinyl ring and trapping of the resulting lithiated species with electrophiles. Particular attention has been addressed to the influence of the *N*-substituent on the synthesis of the diastereomeric aziridines as well as on the stability (chemical and configurational) of the lithiated aziridines. The study was confined to some electron-withdrawing groups ($PhSO_2$, *t*-$BuSO_2$, *t*-BuSO and $POPh_2$) and alkyl groups (Me, Bn). The required aziridines **3** and **4** were prepared by the Darzens reaction of lithiated 2-(1-chloroethyl)oxazoline **1** with imines **2a–f**.[18] It is worth noting that the use of imines with an alkyl group as the *N*-substituent led to the formation of (*R**,*S**) aziridines exclusively or prevalently, while (*R**,*R**) aziridines predominated with imines bearing an electron-withdrawing group on the nitrogen (Table 1).[19]

As previously reported,[17b] lithiated aziridine **3a**-**Li**, derived from **3a**, is sufficiently stable (chemically and configurationally) at low temperature (−98 °C) (the stabilisation is likely provided by the phenylsulfonyl and phenyl groups), and could be trapped with electrophiles (Scheme 1).

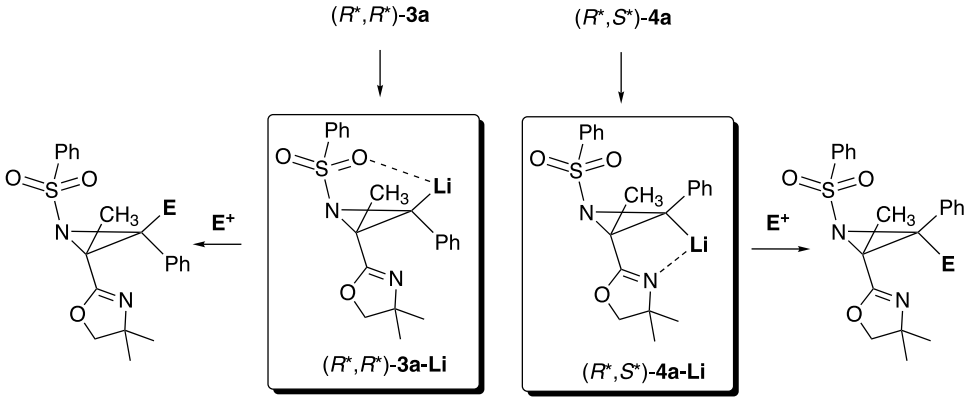
The aziridine *N*-lone pair participation to the stabilisation of the lithiated intermediate can be excluded in this case as it is *trans* to the C–Li bond and epimerisation does not occur (the configurational stability at the aziridine nitrogen is well documented).[20]

Table 1. Preparation of oxazolinylaziridines



G	Imine	Aziridine (*R**,*R**)-**3** (yield %)[a]	Aziridine (*R**,*S**)-**4** (yield %)[a]	dr (*R**,*R**)-**3**/(*R**,*S**)-**4**
$PhSO_2$	**2a**	**3a** (67)	**4a** (33)	67/33
Ph_2PO	**2b**	**3b** (66)	**4b** (6)	90/10
t-BuSO	**2c**	**3c** (60)	–	—[b]
t-$BuSO_2$	**2d**	**3d** (64)	–	>99/1
CH_3	**2e**	**3e** (12)	**4e** (71)	15/85
$PhCH_2$	**2f**	**3f** (7)	**4f** (63)	10/90

[a] Isolated yields.
[b] A diastereomeric mixture 62/25/13 of three inseparable isomers formed: the major one, **3c**, could be obtained by crystallisation.



Scheme 1.

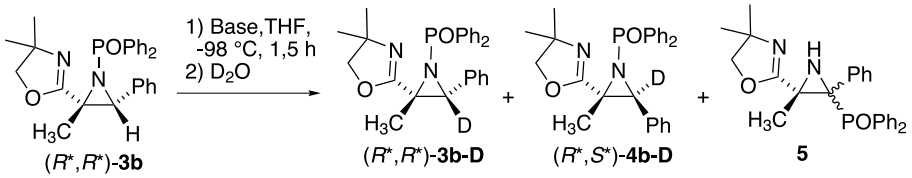
Lithiated oxazolinylaziridine (*R**,*S**)-**4a**-**Li**, derived from **4a**, proved to be equally stable (chemically and configurationally) at low temperature, the stabilisation being provided mainly by the lone pair of the aza atom of the oxazoline ring.[21] The generation of (*R**,*S**)-**4a**-**Li** could be proved by its trapping with electrophiles (Scheme 1).

With both the aziridines (*R**,*R**)-**3a** and (*R**,*S**)-**4a**, lithiation in the aziridine ring competed with the *ortho*-lithiation of the phenylsulfonyl group and trapping of (*R**,*R**)-**3a**-**Li** and (*R**,*S**)-**4a**-**Li** with carbonyl compounds took place in poor yields, whatever the experimental conditions. Therefore, we investigated other *N*-substituents.

Thus, we studied the lithiation of *N*-diphenylphosphinoyl oxazolinylaziridine (*R**,*R**)-**3b** and the capture of the resulting lithiated intermediate with D_2O (Table 2).

Using *s*-BuLi, with or without TMEDA, a complete deuterium incorporation was observed together with a 10–15% of epimerisation to give (*R**,*R**)-**3b**-**D** and (*R**,*S**)-**4b**-**D**. Epimerisation highly predominated when

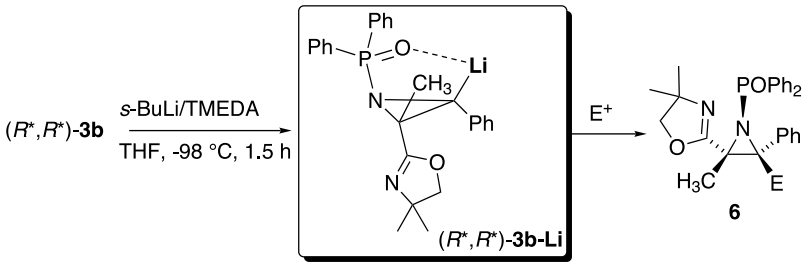
Table 2. Lithiation–deuteration sequence on oxazolinylaziridine **3b**



Base	(*R**,*R**)-**3b**-**D**, % yield[a] (%D)	(*R**,*S**)-**4b**-**D**, % yield[a] (% D)	**5**, % yield
s-BuLi/TMEDA	90 (>98%)	10 (>98%)	—
s-BuLi	85 (> 98%)	15 (> 98%)	—
LDA	10 (80%)	60 (85%)	25

[a] Isolated yields.

Table 3. Lithiation of oxazolinylaziridine **3b** and trapping with electrophiles



E^+	Oxazolinylaziridine **6** (% yield)[a]
CH_3I	**6a** (50)[b]
$PhCH_2Br$	**6b** (58)
$CH_2{=}CHCH_2Br$	**6c** (30)
Cyclohexanone/TMSCl	**6d** (40)[c]
PhCHO/TMSCl or BF_3	**6e** (24)[c]

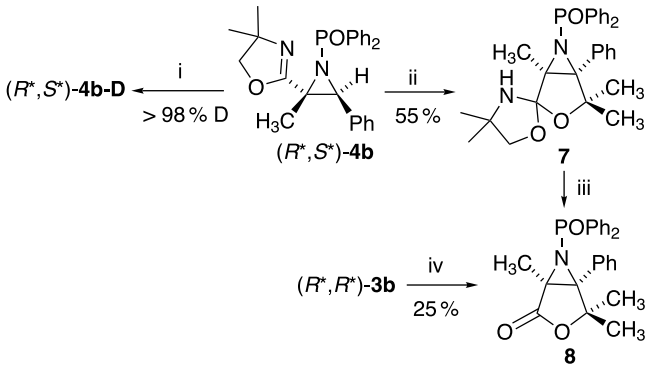
[a] Isolated yields.
[b] In this case a dimethylated (39%) aziridine with one of the two phenyl ring of the phosphinoyl group *o*-methyl-substituted was also isolated.
[c] The activation of the carbonyl group was needed; only one diastereoisomer was isolated.

LDA was used to give mainly aziridine (*R**,*S**)-**4b-D**. In this experiment the formation of compound **5** was also observed: probably a nitrogen to carbon migration of the phosphinoyl group in the lithiated intermediate takes place.[22]

Lithiated oxazolinylaziridine (*R**,*R**)-**3b-Li**, generated from (*R**,*R**)-**3b** by using *s*-BuLi/TMEDA,[23] reacted stereospecifically with a series of electrophiles to give compounds **6a-e** (Table 3).[24]

The yields were not so high and, in all cases, some starting material was recovered unreacted. With carbonyl compounds, the reaction needed an activating agent, such as TMSCl or BF_3, to occur.

Deprotonation of (*R**,*R**)-**3b** with LDA and re-protonation furnished the diastereomeric oxazolinylaziridine (*R**,*S**)-**4b** (60% yield). Aziridine (*R**,*S**)-**4b** was then deprotonated with *s*-BuLi/TMEDA and the resulting lithiated intermediate trapped with D_2O to give deuterated aziridine (*R**,*S**)-**4b-D** with complete retention of configuration. Moreover, the reaction of (*R**,*S**)-**4b** with *s*-BuLi/TMEDA in THF and then with acetone produced the spirocyclic compound **7**, which could be easily hydrolysed to the aziridino-γ-lactone **8** (55% yield) (Scheme 2).



Scheme 2. Conditions: (i) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h; (b) D_2O. (ii) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h; (b) Acetone. (iii) H_2O/H^+. (iv) (a) LDA, THF, −98 °C, 1.5 h; (b) Acetone; (c) H_2O/H^+.

Starting from oxazolinylaziridine (*R**,*R**)-**3b**, under the epimerising conditions above (LDA), the trapping with acetone and acidic hydrolysis gave the expected aziridino-γ-lactone **8** but with lower yield (25%) (Scheme 2).

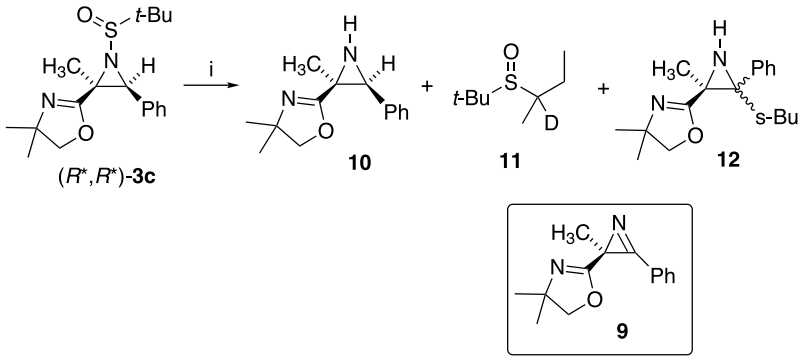
Next, the *N*-*tert*-butylsulfinyl oxazolinylaziridine (*R**,*R**)-**3c** was investigated. Deprotonation (*s*-BuLi/TMEDA, THF, −98 °C) and trapping with D_2O of the resulting (*R**,*R**)-**3c-Li** gave mainly compound **10**,[25] the desulfinylation product. Compounds **11** and **12** were also detected by GC-MS analysis: they likely resulted from the desulfinylation of (*R**,*R**)-**3c** and addition of *s*-BuLi to the azirine **9**, presumably originated from (*R**,*R**)-**3c** via *tert*-butyl sulfinic acid elimination (Scheme 3).[26]

We also investigated the lithiation reaction of the *N*-*tert*-butylsulfonyl oxazolinylaziridine (*R**,*R**)-**3d**. Deprotonation and trapping with D_2O gave the deuterated oxazolinylaziridine (*R**,*R**)-**3d-D** (>95% D) quantitatively with complete retention of configuration (Scheme 4). In the deprotonation/deuteration sequence performed with LDA and in the absence of TMEDA, azirine **9** (63% yield) formed together with the deuterated aziridine (*R**,*R**)-**3d-D** (37% yield, >98% D) thus indicating that TMEDA contributes to stabilize the lithiated intermediate.

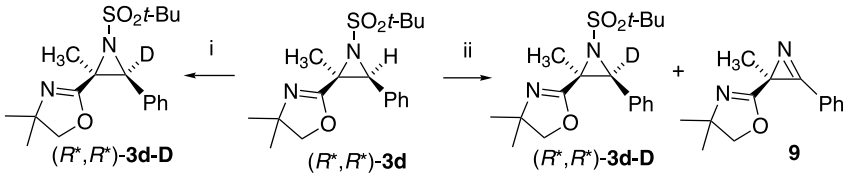
Lithiation of the *N*-*tert*-butylsulfonyl oxazolinylaziridine (*R**,*R**)-**3d** with *s*-BuLi/TMEDA and trapping with PhCHO and MeI gave products **13** (40% yields) and **14** (35% yields), respectively, together with aziridines **12** (55% yields) and **15** (45% yields), the latter likely formed by the addition of *s*-BuLi to **9** (Scheme 5). A similar behaviour has been already reported for *N*-tosyl aziridines.[14f]

We then studied the lithiation reaction of *N*-alkyl-substituted aziridines (Table 4).[27]

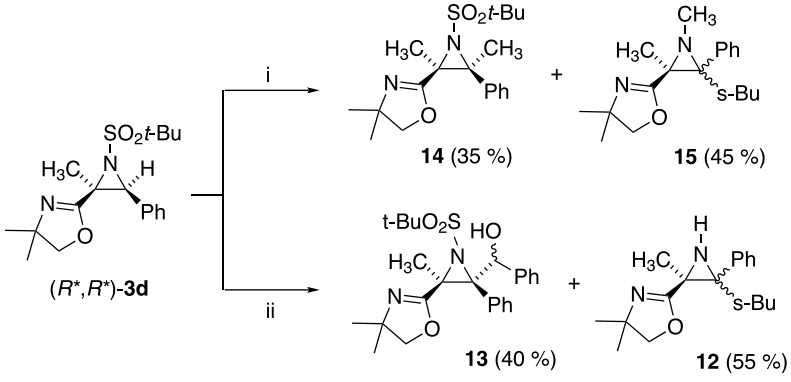
Aziridine (*R**,*S**)-**4e** could be easily deprotonated and the corresponding aziridinyllithium trapped with D_2O. The best



Scheme 3. Conditions: (i) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h; (b) D_2O.

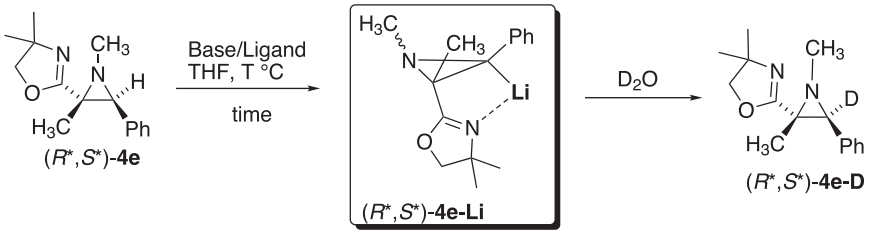


Scheme 4. Conditions: (i) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h; (b) D_2O. (ii) (a) LDA, THF, −98 °C, 1.5 h; (b) D_2O.

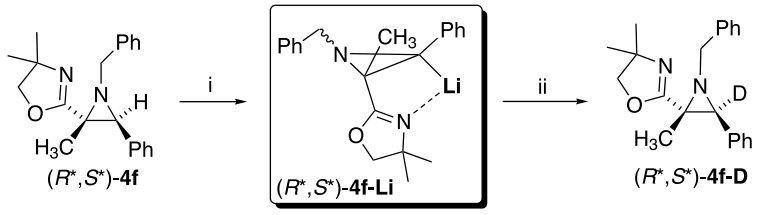


Scheme 5. Conditions: (i) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h; (b) MeI. (ii) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h; (b) PhCHO; (c) H_2O/H^+.

Table 4. Lithiation–deuteration sequence on *N*-alkyl-substituted oxazolinylaziridine **4e**

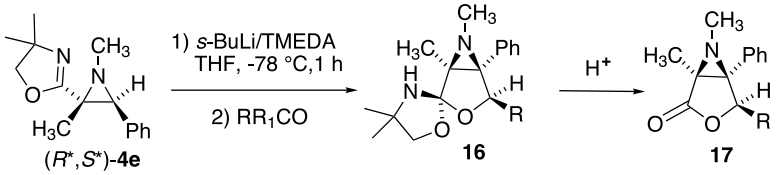


Base (equiv)	Ligand	*T* (°C)	Time (h)	% D
s-BuLi (1.5)	TMEDA	−98	1.5	50
s-BuLi (1.5)	TMEDA	−98	3.0	55
s-BuLi (2.0)	TMEDA	−98	3.0	90
s-BuLi (2.0)	TMEDA	−78	3.0	98
s-BuLi (2.0)	TMEDA	−78	1.5	98
s-BuLi (2.0)	None	−78	1.0	98



Scheme 6. Conditions: (i) (a) *s*-BuLi/TMEDA, THF, −98 °C, 1.5 h. (ii) D_2O.

Table 5. Synthesis of aziridino-γ-lactones



RCHO	Spirocyclic **16** (yield %)[a]	Aziridinolactone **17** (yield %)[b]	dr[c]
PhCHO	**16a** (68)	**17a** (98)	>98/2
*p*ClC$_6$H$_4$CHO	**16b** (48)	**17b** (98)[d]	80/20[e]
CH$_3$CHO	−[d]	**17c** (75)	64/36[e]

[a] Isolated yields.
[b] Overall yields for the diastereomeric mixture.
[c] Diastereomeric ratio determined by GC and GC-MS analyses.
[d] The spirocyclic compound was not isolated and the crude reaction mixture was directly hydrolysed to give **17c**.
[e] The two diastereomeric lactones could be easily separated by flash chromatography.

conditions for the lithiation-trapping sequence are summarised in Table 4. The ^{1}H NMR analysis of the crude reaction mixture showed that the deuteration takes place smoothly and with complete retention of configuration to give (*R**,*S**)-**4e**-**D**. (*R**,*S**)-**4e**-**Li** proved to be chemically stable: the stabilisation has to be ascribed mainly to the intramolecular chelation involving the oxazoline ring.

Similar results were obtained in the deprotonation reaction (under the same conditions used for (*R**,*S**)-**4e**) of the *N*-benzyloxazolinylaziridine (*R**,*S**)-**4f** (Scheme 6). The addition of D_2O to (*R**,*S**)-**4f**-**Li** afforded aziridine (*R**,*S**)-**4f**-**D** quantitatively deuterated.

(*R**,*S**)-**4e**-**Li** and (*R**,*S**)-**4f**-**Li** proved to be quite stable at −78 °C: also in this case the stability has to be ascribed mainly to the coordinative stabilizing effect of the oxazoline moiety.[21] Reaction of (*R**,*S**)-**4e**-**Li** with carbonyl compounds led to spirocyclic compound **16**[28] and, upon hydrolysis, to aziridino-γ-lactone **17**[28] in very good yields and excellent to acceptable diastereoselectivity (Table 5).

3. Conclusion

All the results presented above leads us to the conclusion that the nature of the *N*-substituent of the aziridine moiety plays an important role in the deprotonation reaction of oxazolinylaziridines. When an electron-withdrawing group with coordinative ability is present on the aziridine nitrogen, an enhancement of the kinetic acidity of the proton to be removed results in the case of both the geometric isomers but, at the same time, side reactions compete (e.g. epimerisation, desulfinylation, intramolecular nucleophilic addition, elimination, *ortho*-lithiation). On the other hand, an electron-donating group (e.g. alkyl or arylalkyl) seems to be the *N*-substituent of choice when the oxazoline moiety has a *cis*-relationship with respect to the proton to be removed. The high stability of the resulting aziridinyllithium can be likely ascribed to the coordinative effect of the oxazoline ring[21] thus making such intermediates promising for synthetic purposes (e.g. stereoselective preparation of aziridinolactones). The synthetic application of lithiated oxazolinylaziridines is now underway and results will be reported in due course.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere over sodium/-benzophenone ketyl *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) was distilled over finely powdered calcium hydride. Oxazolinylaziridines **3a**–**f**, **4a**,**b** and **4e**,**f** were prepared following a reported procedure.[18] All other chemicals were of commercial grade and used without further purification. Petroleum ether refers to the 40–60 °C boiling fraction. Commercial solutions of *n*-BuLi (2.5 M hexanes solution) and *s*-BuLi (1.3 M cyclohexane solution) were titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[29] For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR 300, 500 MHz; ^{13}C NMR 75.4, 125 MHz), $CDCl_3$ was used as the solvent. GC-MS spectrometry analyses were performed on a gas chromatograph HP 6890 plus (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a 5973 mass selective detector operating at 70 eV (EI). MS-ESI analyses

were performed on Agilent 1100 LC/MSD trap system VL. Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm) or by exposing to I_2 vapours. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

4.1.1. (2*R,3*R**)-2-(1-Diphenylphosphinoyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (3b).** (66%); white solid; mp 198 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.96 (s, 3H), 1.02 (s, 3H), 1.77 (s, 3H), 3.61 (d, J=8.0 Hz, 1H), 3.66 (d, J=8.0 Hz, 1H), 4.07 (d, J=15.7 Hz, 1H), 7.10–7.60 (m, 11H), 7.90–8.05 (m, 2H), 8.25–8.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.8 (qdd, J_{CH}=126.5, 2.9 Hz, $^3J_{CP}$=6.7 Hz), 27.9, 46.9 (d, J_{CP}=5.7 Hz), 47.6 (d, J_{CP}=6.7 Hz), 67.3, 78.9, 127–135 (Ar*C*), 162.2; MS *m*/*z* (%): 430 [M^+] (6), 229 (100), 201 (75), 104 (17); FT-IR cm^{-1}: 2966, 1652,1440, 1206, 1122, 696. Anal. Calcd for $C_{26}H_{27}N_2O_2P$; C, 72.54;H, 6.32; N, 6.51. Found C, 72.47,H, 6.28; N, 6.47.

4.1.2. (2*R,3*R**)-4,4-Dimethyl-2-(1-*tert*-butylsulfinyl-2-methyl-3-phenylaziridin-2-yl)-4,5-dihydrooxazole (3c).** (60%); colorless solid; mp 117–118 °C (hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.92 (s, 3H), 1.10 (s, 3H), 1.23 (s, 9H), 1.83 (s, 3H), 3.61–3.68 (m, 2H), 3.73 (s, 1H), 7.22–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.5 (qd, J_{CH}=129.7, 3.8 Hz), 23.0, 28.3, 28.35, 42.5, 46.6, 57.7, 67.6, 79.1, 127.9, 128.0, 128.1, 134.6, 162.4; ESI/MS 335 [M−H^+], (96) 230 [M−H^+-tBuSO] (100); FT-IR cm^{-1}: 2970, 1659, 1462, 1362, 1190, 1078, 879, 765. Anal. Calcd for $C_{18}H_{26}N_2O_2S$; C, 64.64;H, 7.84; N, 8.38. Found C, 64.51,H, 7.54; N, 8.22.

4.1.3. (2*R,3*R**)-4,4-Dimethyl-2-(1-*tert*-butylsulfonyl-2-methyl-3-phenylaziridin-2-yl)-4,5-dihydrooxazole (3d).** (64%); white solid; mp 74–75 °C (hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.84 (s, 3H), 1.10 (s, 3H), 1.47 (s, 9H), 2.02 (s, 3H), 3.66 (d, J=7.9 Hz, 1H), 3.73 (d, J=7.9 Hz, 1H), 3.92 (s, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 18.5 (qd, J_{CH}=130.7, 3.7 Hz),, 23.8, 28.3, 50.6, 52.6, 60.4, 67.3, 78.9, 126.9, 128.0, 128.1, 132.8, 161.0; ESI-MS 351 [M−H^+] (100), 230 [M−H^+-t$BuSO_2$] (55); FT-IR cm^{-1}: 2985, 1670, 1458, 1311, 1130, 901, 701.

4.1.4. (2*R,3*R**)-2-(1,2-Dimethyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (3e).** (12%); orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.91 (s, 3H), 0.95 (s, 3H), 1.58 (s, 3H), 2.55 (s, 1H), 2.61 (s, 3H), 3.44–3.55 (m, 2H), 7.48–7.65 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.4 (qd, $^3J_{CH}$=3.8 Hz), 27.9, 27.9$_4$, 39.1, 44.1, 54.2, 66.7, 78.6, 126.7, 127.3, 127.4, 136.5, 163.9. MS *m*/*z* (%): 244 [M^+] (4), 189 (24), 188 (32), 112 (37), 56 (100); FT-IR cm^{-1}: 2969, 1650, 1648, 1452, 1141, 749, 699.

4.1.5. (2*R,3*R**)-2-(1-Benzyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (3f).** (7%); yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.97 (s, 3H), 0.99 (s, 3H), 1.68 (s, 3H), 2.82 (s, 1H), 3.54 (d, J=7.9 Hz, 1H), 3.59 (d, J=7.9 Hz, 1H), 3.84 (d, J=14.7 Hz, 1H), 4.09 (d, J=14.7 Hz, 1H), 7.12–7.29 (m, 6H), 7.30–7.38 (m, 2H), 7.43–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.9, 27.9, 28.0, 44.8, 53.0, 56.0, 65.8, 78.6, 126.6, 126.7, 127.4, 127.5$_1$, 127.5$_2$, 128.1, 136.4, 138.9, 164.0; MS *m*/*z* (%): 320 [M^+] (24), 305 (21), 217 (36), 202 (65), 194 (100); FT-IR: 698, 735, 970, 1132, 1364, 1454, 1667, 2968 cm^{-1}.

4.1.6. (2*R,3*S**)-2-(1-Diphenylphosphinoyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (4b).** (6%); colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (s, 3H), 1.27 (s, 3H), 1.35 (s, 3H), 3.79 (d, J=8.0 Hz, 1H), 3.90 (d, J=8 Hz, 1H), 4.64 (d, J=16.4 Hz. 1H), 7.20–7.60 (m, 11H), 7.80–8.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.1 (qd, J_{CH}=128.7 Hz, J_{CP}=3.8 Hz), 27.7, 45.4 (d, J_{CP}=8.5 Hz), 45.9 (d, J_{CP}=5.7 Hz), 67.3, 79.2, 127–135 (Ar*C*), 162.7; GC-MS *m*/*z* (%) 430 [M^+] (10), 229 (100), 201 (79), 174 (25), 104 (25); FT-IR cm^{-1}: 1969, 1667, 1439, 1206, 1126, 729, 697.

4.1.7. (2*R)(3*S**)-2-(1,2-Dimethyl-3-phenyl-aziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (4e).** (71%); yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.11 (s, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 2.57 (s, 3H), 3.34 (s, 1H), 3.93 (d, J=8 Hz, 1H), 3.98 (d, J=8 Hz, 1H), 7.25–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.5, 29.0, 39.0, 40.0, 52.0, 67.8, 79.2, 127.1, 128.2, 137.5, 164.0. GC-MS *m*/*z* (%): 244 [M^+], (6), 189 (31), 188 (42), 112 (46), 56 (100); FT-IR cm^{-1}: 2969, 2892, 1646, 1452, 1040, 701, 621.

4.1.8. (2*R,3*S**)-2-(1-Benzyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (4f).** (63%); yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.17 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 3.63 (s, 1H), 3.85 (d, J=14.0 Hz, 1H), 3.80–3.88 (m, 2H), 4.01 (d, J=14.0 Hz, 1H), 7.18–7.34 (m, 8H), 7.35–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.8, 28.4, 28.6, 43.2, 50.9, 56.4, 67.5, 78.8, 126.8, 126.9, 127.8, 127.9$_1$, 127.9$_2$, 128.2, 136.7, 139.6, 163.5; GC-MS *m*/*z* (%): 320 [M^+] (42), 305 (36), 217 (48), 202 (77), 194 (100); FT-IR cm^{-1}: 2969, 1651, 1604, 1453, 1190, 1118, 733, 698.

4.2. General procedure for the lithiation of oxazolinylaziridines (*R**,*R**)-3b–d and (*R**,*S**)-4b and reaction with electrophiles

A solution of the oxazolinylaziridine **3** (or **4**) (0.40 mmol) and TMEDA (0.8 mmol) in 8 mL of dry THF at −98 °C (methanol/liquid nitrogen bath) under N_2 was reacted with *s*-BuLi (0.80 mmol, 1.2 M in cyclohexane). The resulting orange mixture was stirred for 1.5 h at −98 °C. (In the deprotonation reaction with LDA oxazolinylaziridines (0.4 mmol) were added to a solution of the base (0.6 mmol) at −98 °C and stirred for 1.5 h before to add the electrophile.) Then, the solution was treated at −98 °C with the electrophile (0.60 mmol), added at once, neat if liquid or as solution in 2 mL of THF if solid. The resulting reaction mixture was allowed to warm up to room temperture and finally quenched with saturated aqueous NH_4Cl, poured into 20 mL of saturated brine, extracted with AcOEt (3×10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt) to give the substituted aziridines showing the following data:

4.2.1. 2-(3-Diphenylphosphinoyl-2-methyl-3-phenylaziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (5). (25%); yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.17 (s, 3H), 1.28 (s, 3H), 1.33 (s, 3H), 3.04 (d, J=15.2 Hz, 1H, exchange with D_2O), 4.03 (s, 2H), 6.92–7.16 (m, 5H), 7.24–7.32 (m, 4H), 7.40–7.44 (m, 3H), 7.50–7.56 (m, 1H), 7.82–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.1,28.0, 28.2, 43.8, 49.1 (d, J_{CP}=89 Hz), 68.2, 79.6, 127–135 (Ar*C*), 165.0. ESI/MS: 431 [M−H$^+$]. FT-IR cm^{-1}: 3248 1672, 1440, 1190, 761, 703, 556.

4.2.2. (2*R,3*R**)-2-(1-Diphenylphosphinoyl-2,3-dimethyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (6a).** (50%); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (s, 3H), 0.92 (s, 3H), 1.85 (s, 3H), 2.04 (s, 3H), 3.32 (d, J=7.8 Hz, 1H), 3.57 (d, J=7.8 Hz, 1H), 7.10–7.60 (m, 11H), 7.95–8.05 (m, 2H), 8.22–8.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.8, 19.8, 28.0, 48.6 (d, J_{CP}= 5.7 Hz), 54.1 (d, J_{CP}=6.8 Hz), 67.3, 79.0, 126–142 (Ar*C*), 164.1; GC-MS *m*/*z* (%) 444 [M$^+$] (6), 270 (6), 243 (53), 201 (100), 171 (17), 103 (33).;FT-IR cm^{-1}: 2967, 1675, 1439, 1205, 1103, 697.

4.2.3. (2*R,3*R**)-2-(3-Benzyl-1-diphenylphosphinoyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (6b).** (58%); white solid; mp 171–172 °C (hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.89 (s, 3H), 1.04 (s, 3H), 1.96 (s, 3H), 3.24 (d, J=7.9 Hz, 1H), 3.57 (d, J=14.6 Hz, 1H), 3.61 (d, J=7.9 Hz, 1H), 3.93 (d, 14.6 Hz, 1H), 6.74–6.78 (m, 2H), 6.86–6.90 (m, 2H), 6.95–7.08 (m, 6H), 7.36–7.52 (m, 6H), 8.06–8.12 (m, 2H), 8.22–8.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.2, 26.6, 26.8, 38.2 (d, J_{CP}=5.7 Hz), 46.9 (d, J_{CP}=5.7 Hz), 66.1, 78.0, 125–139 (Ar*C*), 163.4; ESI/MS: 521 [M−H$^+$]; FT-IR cm^{-1} 2959, 2922, 1675, 1440, 1206, 1112, 727, 699.

4.2.4. (2*R,3*R**)-2-(3-Allyl-1-diphenylphosphinoyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (6c).** (30%); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (s, 3H), 1.01 (s, 3H), 1.83 (s, 3H), 3.10–3.35 (m, 2H), 3.28 (d, J=7.96 Hz, 1H). 3.61 (d, J=7.96 Hz, 1H), 4.85 (dd, J=1 0, 0.9 Hz, 1H), 5.00 (d, J=17 Hz, 1H), 5.42–5.58 (m, 1H), 7.03–7.20 (m, 5H), 7.35–7.52 (m, 6H), 8.05–8.15 (m, 2H), 8.22–8.32 (m,2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.39, 27.7, 27.8, 37.2, 47.8 (d, J_{CP}=6.7 Hz), 57.3 (d, J_{CP}=6.7 Hz), 67.1, 78.8, 118.6, 126–135 (Ar*C*), 139.1, 164.1; ESI/MS: 471 [M−H$^+$]; FT-IR cm^{-1}: 1671, 1650, 1439, 1385, 1202, 1093, 729, 698, 521.

4.2.5. (2*R,3*R**)-1-[3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-1-diphenylphosphinoyl-3-methyl-2-phenylaziridin-2-yl]cyclohexanol (6d).** (40%); white solid; mp 145 °C (hexane) dec; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.38 (s, 3H), 1.02 (s, 3H), 1.20–1.48 (m, 4H), 1.56 (s, 3H), 1.62–1.79 (m, 2H), 2.01–2.16 (m, 2H), 2.35–2.58 (m, 2H), 3.47–3.59 (2× d, AB system, J=7.9 Hz, 2H), 5.26 (s, 1H, exchange with D_2O), 7.00–7.29 (m, 3H), 7.30–7.47 (m, 8H), 7.84–7.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.8, 22.1, 22.2, 24.5, 27.1, 27.9, 30.1, 41.3, 55.8, 65.8, 79.6, 126–140 (Ar*C*), 65.9; ESI/MS: 551 [M−Na$^+$]; FT-IR cm^{-1} 3420, 3269, 2930, 1662, 1447, 1230, 1109, 699, 535.

4.2.6. (2*R,3*R**)-2-[1-Diphenylphosphinoyl-3-hydroxyphenylmethyl-2-methyl-3-phenylaziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (6e).** (24%); white solid; mp 218 °C (hexane) dec; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.87 (s, 3H), 1.09 (s, 3H), 1.93 (s, 3H), 3.21 (d, J=7.93 Hz, 1H), 3.62 (d, J=7.93 Hz, 2H), 5.18 (br s, 1H, exchange with D_2O), 5.84 (s, 1H), 6.72–7.02 (m, 7H), 7.04–7.12 (m, 3H), 7.30–7.38 (m, 2H), 7.40–7.50 (m, 4H), 8.08–8.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.8, 27.6, 27.8, 48.1 (d, J_{CP}=5.7 Hz), 62.3 (d, J_{CP}=7.6 Hz), 67.2, 74.6, 78.9, 126–141 (Ar*C*), 164.5; ESI/MS: 537 [M−H$^+$]; FT-IR cm^{-1}: 3347, 1676, 1439, 1191, 1090, 695, 668, 523. Anal. Calcd for $C_{33}H_{33}N_2O_3P$; C, 73.86;H, 6.20; N, 5.22. Found C, 73.91,H, 6.18; N, 5.13.

4.2.7. (8*R,9*R**)-8,9-*N*-Diphenylphosphinoylaziridino-3,3,7,7,9-pentamethyl-8-phenyl-1,6-dioxa-4-aza-spiro-[4.4]nonane (7).** (25%); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.92 (s, 3H), 0.99 (s, 3H), 1.26 (s, 3H), 1.31 (s, 3H), 1.56 (s, 3H), 3.55 (d, J=7.7 Hz, 1H), 3.72 (d, J= 7.7 Hz, 1H), 6.96–7.03 (m, 2H), 7.18–7.34 (m, 3H), 7.36–7.55 (m, 6H), 8.04–8.16 (m, 4H).^{13}C NMR ($CDCl_3$, 75 MHz) δ: 9.6, 21.4, 24.0, 26.1, 53.6 (d, J_{CP}=6.3 Hz), 54.5, 61.3 (d, J_{CP}=7.5 Hz), 78.4, 117.7, 125–134 (Ar*C*); ESI/MS: 489 [M−H$^+$]; FT-IR cm^{-1}: 2974, 1439, 1205, 1105, 727, 700.

4.2.8. (1*R,5*S**)-6-Diphenylphosphinoyl-1,4,4-trimethyl-5-phenyl-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (8).** (85%); yellow solid; mp 160 °C (hexane) dec. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.08 (s, 3H), 1.45 (s, 3H), 1.70 (s, 3H), 6.99–7.08 (m, 2H), 7.24–7.60 (m, 9H), 7.85–8.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 10.4, 21.7, 26.2, 49.4 (d, J_{CP}=5.7 Hz), 62.4 (d, J_{CP}=7.6 Hz), 85.5, 128–134 (Ar*C*), 172.8, GC-MS *m*/*z* (%) 417 [M$^+$] (1), 270 (9), 219 (27), 201 (100), 171 (92), 131 (38); FT-IR cm^{-1}: 1765, 1218, 1111. Anal. Calcd for $C_{25}H_{24}NO_3P$; C, 71.93;H, 5.80; N, 3.36. Found C, 71.84,H, 5.76; N, 3.28.

4.2.9. 2-(3-*sec*-Butyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (12). (55%, mixture of diasteroisomers dr: 1/1, unknown configuration); yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.79–0.88 (m, 3×CH_3, 9H), 0.96 (d, J=7.3 Hz, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.30–1.45 (m, 3H), 1.55–1.67 (m, 3H), 1,70–1.90 (s br, 1H), 3.98–4.04 (AB system, 2H), 4.00 (d, J=7.9 Hz, 1H), 4.06 (d, J= 7.9 Hz, 1H), 7.07–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 11.9$_1$, 11.9$_2$, 15.8, 17.5, 26.7, 27.1, 27.9, 28.0, 28.1, 28.3, 40.0, 40.3, 40.5, 42.1, 56.4, 56.8, 67.1, 79.8$_1$, 79.8$_2$; 126.7, 127.9 (br), 129.1 (br), 130.3 (br), 136.7, 165.8. GC-MS (fisrt eluted) *m*/*z* (%) 286 [M$^+$] (4), 285 (4), 271 (8), 229 (100), 158 (98); GC-MS (second eluted) *m*/*z* (%) 286 [M$^+$] (4), 285 (5), 271 (9), 229 (95), 158 (100); FT-IR cm^{-1}: 3275, 2964, 1659, 1446, 1136, 705.

4.2.10. 2-(1-*tert*-Butylsulfonyl-3-hydroxyphenylmethyl-2-methyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (13). (40%, unseparable mixture of diasteroisomers dr 60/40); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.84 (s, 3H, minor), 0.99 (s, 3H, minor), 1.01 (s, 3H, major), 1.20 (s, 3H, major), 1.44 (s, 9H, major), 1.60 (s, 9H, minor), 1.76 (s, 3H, major), 2.24 (s, 3H, minor), 3.18 (d, J= 8.0 Hz, 1H, minor), 3.53 (d, J=8.0 Hz, 1H, minor), 4.00 (d,

J=8.1 Hz, 1H, major), 4.11 (d, J=8.1 Hz, 1H, major), 4.49 (d, J=2.4 Hz, 1H, minor), 4.77 (s, 1H, major,), 5.02 (s, 1H, major), 5.60 (d, J=2.4 Hz, 1H, minor), 6.80–7.41 (m, 20H, major+minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.3, 23.8, 24.5, 27.5, 27.7, 28.1, 60.4, 60.9, 61.0, 61.8, 65.3, 66.9, 67.4, 70.2, 72.3, 79.0, 80.3, 126.3, 126.4, 126.9, 127.2, 127.5, 127.6, 127.8, 127.9, 128.5, 129.6, 130.0, 132.6, 133.5, 134.5, 138.6, 140.1, 164.8; ESI/MS 479 [M−Na^+]; FT-IR cm^{-1} 3464, 3321, 2967, 1661, 1454, 1313, 1260, 1123, 1024, 804, 699.

4.2.11. (2*R,3*R**)-2-(1-*tert*-Butylsulfonyl-2,3-Dimethyl-3-phenylaziridin-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (14).** (35%); yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.81 (s, 3H), 0.92 (s, 3H), 1.57 (s, 9H), 1.94 (s, 3H), 1.98 (s, 3H), 3.28 (d, J=9.7 Hz, 1H), 3.53 (d, J=9.7 Hz, 1H), 7.05–7.30 (m, 3H), 7.35–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.7, 18.4, 23.9, 27.9, 53.2, 54.8, 61.1, 67.2, 78.8, 126.7, 127.7, 129.5, 140.1, 162.9; ESI/MS: 387 [M−H^+]; FT-IR cm^{-1}: 2970, 1672, 1448, 1365, 1309, 1128, 1098, 700.

4.3. General procedure for the lithiation of oxazolinyl-aziridines (*R**,*S**)-4e: preparation of spirocyclic compounds 16a,b

A solution of the oxazolinylaziridine **4e** (0.40 mmol) and TMEDA (0.8 mmol) in 8 mL of dry THF at −78 °C under N_2 was reacted with *s*-BuLi (0.80 mmol, 1.2 M in cyclohexane). The resulting orange mixture was stirred for 1.5 h at −78 °C. Then, the solution was treated at −78 °C with the electrophile (0.60 mmol), added at once, neat if liquid or as solution in 2 mL of THF if solid. The resulting reaction mixture was allowed to warm up to room temperture and finally quenched with saturated aqueous NH_4Cl, poured into 20 mL of saturated brine, extracted with AcOEt (3×10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt) to give compounds **17a**,**b** showing the following data:

4.3.1. (5*R,7*R**,8*R**,9*S**)-8,9-*N*-Methylaziridino-3,3,9-trimethyl-7,8-diphenyl-1,6-dioxa-4-azaspiro[4.4]nonane (16a).** (68%); white solid, mp: 121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), two invertomers at the nitrogen can be seen δ: 1.28 (s, 3H), 1.37 (s, 6H), 2.13 (br s, CH_3N, 3H), 2.33 (br s, CH_3N, 3H), 3.75 (d, J=6.0 Hz, 1H), 3.83 (d, J=6.0 Hz, 1H), 4.70 (br s, 1H), 6.80–7.10 (m, 2H), 7.10–7.30 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.0, 29.2, 34.8, 51.0, 56.9, 57.1, 82.4, 120.1, 127.9, 128.0, 128.2, 128.6, 131.2, 137.3; Esi/Ms 351 [M−H^+]. FT-IR cm^{-1}: 3381, 2971, 2871, 1604, 1080, 965, 705. Anal. Calcd for $C_{22}H_{26}N_2O_2$; C, 75.40;H, 7.48; N, 7.99. Found C, 75.38,H, 7.35; N, 7.89.

4.3.2. (5*R,7*R**,8*R**,9*S**)-8,9-*N*-Methylaziridino-3,3,9-trimethyl-8-phenyl-7-(4-chlorophenyl)-1,6-dioxa-4-azaspiro[4.4]nonane (16b).**[28] (48%); white solid, mp: 122–123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), two invertomers at the nitrogen can be seen δ: 1.27 (s, 3H), 1.36 (s, 6H), 2.16 (br s, CH_3N, 3H), 2.4 0 (br s, CH_3N, 3H), 3.74–3.83 (2×d, AB system, J=7.6 Hz, 2H), 4.66 (br s, 1H), 6.90–7.00 (m, 2H), 7.15–7.37 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 6.1, 27.0, 29.1, 34.8, 51.1, 57.1, 81.9, 121.0, 128.1, 128.2, 128.7, 129.6, 131.2, 133.8, 135.9; Esi/Ms: 385 [M−H^+]. FT-IR cm^{-1}: 3361, 2970, 2927, 2870, 1488, 1467, 1404, 1381, 1182, 1078, 966. Calcd for $C_{22}H_{25}N_2O_2Cl$; C, 68.65;H, 6.55; N, 7.28. Found C, 68.51,H, 6.38; N, 7.18.

4.4. General procedure for the hydrolisys of spirocyclic compounds 17a-c: preparation of α,β-aziridino-γ-lactones 17a-c

To a stirred solution of the spirocyclic compound **17** (0.5 mmol) in dioxane/water (5 mL, 4:1) at room temperature is added a catalytic amount of CF_3COOH (20–25 μL). The resulting solution is stirred for 4–6 h until complete conversion of the starting material (TLC, GC). Then, 20 mL of $NaHCO_3$ (10%) were added, extracted with AcOEt (3× 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt) to give compounds **18a–c** showing the following data:

4.4.1. (1*R,4*S**,5*S**)-1,6-Dimethyl,-4,5-diphenyl-3-oxa-6-aza-bicyclo[3.1.0]hexan-2-one (17a).** (98%); white solid; mp 144–145 °C. ^{1}H NMR ($CDCl_3$, T=275 °K, 500 MHz), two invertomers (dr 2:1), δ: 1.19 (s, 3H, major) 1.55 (s, 3H minor), 2.08 (s, CH_3N, 3H minor) 2.39 (s, CH_3N, 3H major), 5.21 (s, 1H minor), 6.25 (s, 1H major), 6.88–7.60 (m, 10H major+minor). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.5, 24.7, 35.0, 51.5, 56.9, 60.4, 70.5, 125.9, 127.6, 127.9, 128.2, 129.0, 130.0, 139.7, 173.0. GC-MS *m*/*z* (%) 279 [M^+], (7), 251 (16), 236 (39), 220 (26), 174 (68), 118 (18), 77 (17), 56 (100); FT-IR cm^{-1}:1775, 1129, 1100, 703. Calcd for $C_{18}H_{17}NO_2$; C, 77.40;H, 6.13; N, 5.01. Found C, 77.28,H, 6.08; N, 4.89.

4.4.2. 1,6-Dimethyl,-4-(4-chlorophenyl)-5-phenyl-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (17b). (98% overall yield for two separable diastereomers dr 80:20); Major (1*R**,4*S**,5*S**): white solid, mp 144–145 °C. ^{1}H NMR (DMSO, T=295 °K, 500 MHz), two invertomers, dr 6:4 δ: 1.04 (s, 3H minor), 1.43 (s, 3H major), 2.07 (s, CH_3N, 3H major), 2.28 (s, CH_3N, 3H minor), 5.29 (s, 1H major), 6.43 (s, 1H minor), 6.90–7.80 (m, 9H). GC-MS *m*/*z* (%) 313 [M^+], (7), 270 (16), 236 (39), 220 (26), 174 (68), 118 (18), 77 (17), 56 (100). FT-IR (KBr) cm^{-1}: 1775, 1129, 1100, 703. Minor (1*R**,4*R**,5*S**): colorless oil. ^{1}H NMR ($CDCl_3$, T=295 °K, 300 MHz), two invertomers, dr 85:15 δ: 1.29 (s, 3H, major), 1.54 (s, 3H, minor), 2.23 (s, 3H, minor), 2.79 (s, 3H, major), 5.39, (s, 1H, major), 5.51 (s, 1H, minor), 6.60–6.90 (m, 4H major+minor) 7.01–7.35 (m, 5H, major+minor). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.0, 33.4, 48.0, 61.3, 78.0, 127.8, 128.3, 128.8, 129.7, 132.8, 134.7, 173.3. GC-MS *m*/*z* (%) 313 [M^+], (7), 270 (16), 236 (39), 220 (26), 174 (68), 118 (18), 77 (17), 56 (100). FT-IR (film) cm^{-1}: 2928, 1767, 1449, 1088, 818.

4.4.3. 1,4,6-Trimethyl,-5-phenyl-3-oxa-6-azabicyclo-[3.1.0]hexan-2-one (17c).[28] (75% overall yield for two diastereoisomers dr 64:36). Major (1*R**,4*S**,5*S**): white solid, mp 99–101 °C. ^{1}H NMR ($CDCl_3$, T=275 °K, 500 MHz), two invertomers (dr ≈1:1), δ: 1.15 (br s, 3H), 1.42 (d, J=6.7 Hz, 3H), 2.24 (br s, CH_3N), 2.78 (br s, CH_3N), 4.35 (br s, C*H*), 4.35 (br s, C*H*), 7.15–7.55 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 5.8, 11.4, 13.8, 29.7, 34.6, 35.7, 46.7, 50.0, 56.5, 73.7, 80.5, 128.1, 128.5, 130.3, 172.8,

175.9. GC-MS *m/z* (%) 217 [M^+], (9), 174 (85), 158 (25), 115 (21), 56 (100). FT-IR cm^{-1}: 2927, 1768, 1136, 1060. Minor (1*R**,4*R**,5*S**): oil. ^1H NMR ($CDCl_3$, $T=275$ °K, 500 MHz), two invertomers (dr 8:2), δ: 0.97 (d, $J=6.7$ Hz, 3H minor), 1.25 (s, 3H minor), 1.26 (d, $J=6.7$ Hz, 3H major), 1.29 (s, 3H major), 2.14 (s, CH_3N minor), 2.62 (s, CH_3N major), 4.55 (q, $J=6.7$ Hz, 1H major), 4.70 (q, $J=6.7$ Hz, 1H minor), 7.21–7.45 (m, 5H minor+5H major). ^{13}C NMR ($CDCl_3$, $T=275$ °K, 125 MHz) 2 invertomers (dr 8:2), δ: 6.4, 13.0, 19.1, 19.6, 29.6, 33.0, 34.3, 46.3, 48.2, 57.8, 59.7, 73.7, 80.1, 128.6, 129.3, 133.3, 172.8, 175.5. GC-MS *m/z* (%) 217 [M^+], (6), 174 (66), 158 (19), 115 (17), 56 (100). FT-IR cm^{-1}: 2927, 1757, 1433, 1335, 1060.

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24. The configuration of aziridines **6** (*R**,*R**) was assigned on the basis of the chemical shift of the Me (to the oxazolinyl ring either by analogy to similar trisubstituted oxazolinylaziridines, as reported in Ref.17a, or by analogy to compounds **3b**-**D** and **4b**-**D**. A Ph group in a *cis* relationship with a Me group (*R**,*R** isomers) was found to induce a high field displacement on it (chemical shift range: 1.30–1.40 (δ); in the case of a *trans* relationship (*R**,*S** isomers) the Me group was always downfield shifted (chemical shift range: 1.70–1.80 (δ).
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28. An X-ray analysis confirmed the structure of the spirocyclic compounds **16b** and aziridino-γ-lactone **17c** (major isomer). Crystallographic data (excluding structure factors) for **16b** (CCDC 249588) and **17c** (CCDC 249587) have been deposited to the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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Pyridino-directed lithiation of anisylpyridines: new access to functional pyridylphenols

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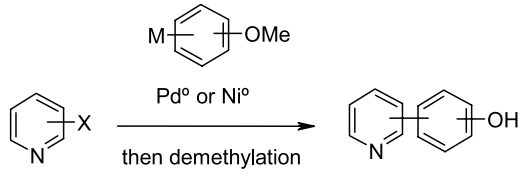
Abstract—The lithiation of nine anisylpyridines has been studied. While usual reagents did not react or gave addition products on pyridine ring, the BuLi-LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) superbase induced exclusive pyridino directed metallation. The usefulness of this new reaction allowed the efficient preparation of a range of alpha functional pyridylphenols. A successful subsequent cyclisation of an appropriate isomer into corresponding benzofuropyridine was also performed.

1. Introduction

Pyridylphenols constitute key structures for biologically active molecules (e.g., adrenergic receptor ligands),[1] metal ligands for asymmetric synthesis[2] or building blocks for supramolecular architectures.[3] They are generally prepared from halogenated heterocycles by Pd-catalyzed Suzuki[3] or Ni-catalyzed Corriu–Kumada–Tamao[4] cross-couplings followed by a demethylation step (Scheme 1).

This methodology however suffers from limitations when functional pyridyl derivatives have to be coupled since substituents can display steric hindrance, reactivity towards the organometallic species (e.g., carbonyl moieties towards Grignards) or act as poisons or competing ligands for the catalyst (e.g., sulfides or phosphines). Thus, methodologies allowing the selective functionalization of parent methoxyphenylpyridines are a valuable alternative to couplings for the preparation of functional pyridylphenols. Our laboratory has recently reported the selective C-2 pyridine ring lithiation of phenylpyridines using the BuLi-containing aggregates BuLi-LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$)[5] which thus could be of great interest for introduction of functionalities in the methoxy-phenylpyridine series.[6] At the beginning of this work a paper by Quéguiner and coworkers[4b] appeared dealing with lithiation of some methoxyphenylpyridines with LiTMP as basic reagent. The aim was to metallate the pyridine ring using the remote directing ability of the methoxy group. From this work it appeared that lithiation of the pyridine ring was strongly substrate dependent. Only 2-(2-methoxy-phenyl)pyridine **1** underwent lithiation with subsequent introduction of electrophiles at the C-6 position but not at the expected C-3 one! This latter selectivity could be attributed to an internal cooperating lithium complexation by both the pyridine nitrogen and methoxy group. This kind of concomitant chelation effect was already observed in our recent works on lithiation of phenylchloropyridine with *t*-BuLi[7] (Fig. 1).



Scheme 1. Usual synthetic route to pyridylphenols.

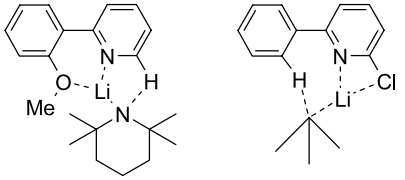


Figure 1. Proposed models for cooperative internal chelations in substituted phenylpyridines.

Keywords: Selective lithiation; Pyridino-direction; Anisylpyridines; Cyclization.
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On the other hand lithiation did not occur with isomers bearing a methoxy group more distant from nitrogen. Indeed, **4** was found unreactive and **7** led to a dimer. Consequently lithiation of these isomers could be achieved using a reagent bringing an external lithium chelating agent and the BuLi-LiDMAE superbase could be the ideal candidate for such task due to its affinity for the pyridine nitrogen[5] (Fig. 2).

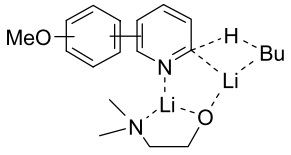


Figure 2. Expected external chelation by lithium aggregates.

Herein we report a new process for the clean pyridino-directed lithiation of methoxyphenylpyridines with high selectivity regardless of the position of the methoxyphenyl group on pyridine.

2. Results and discussion

A series of nine isomers was first prepared in acceptable to good yields by Corriu–Kumada–Tamao couplings between the appropriate anisylmagnesium bromides and bromopyridines except for derivatives **7–9** for which 4-chloropyridine was used (Scheme 2).

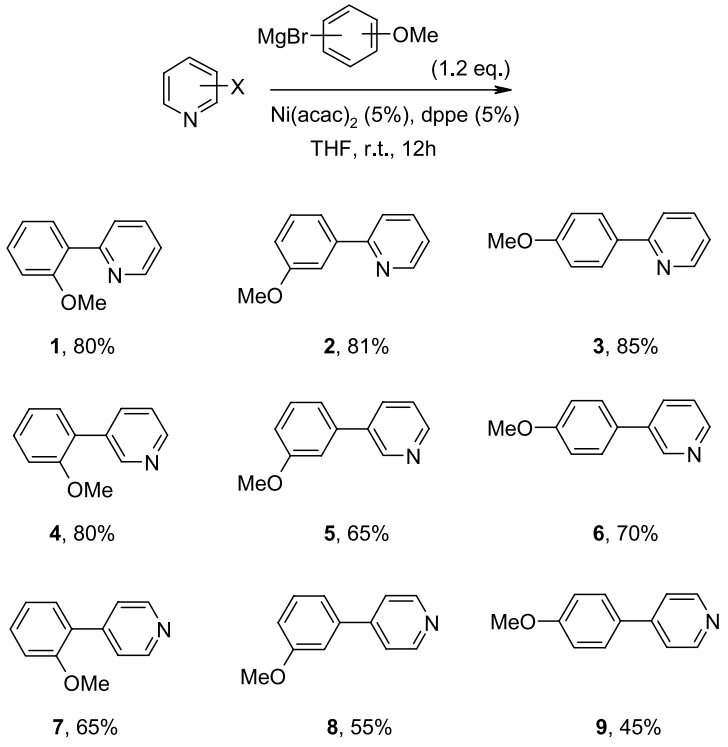
The first lithiation experiments were carried out with *n*-BuLi, *t*-BuLi, *n*-BuLi-TMEDA and BuLi-*t*-BuOK under various conditions. Sluggish reactions generally occurred with all substrates leading to nucleophilic addition products on the pyridine ring. Then we turned to lithiation with the BuLi-LiDMAE reagent, which was expected to display lower nucleophilicity.[5]

2.1. Lithiation of 2-anisylpyridines

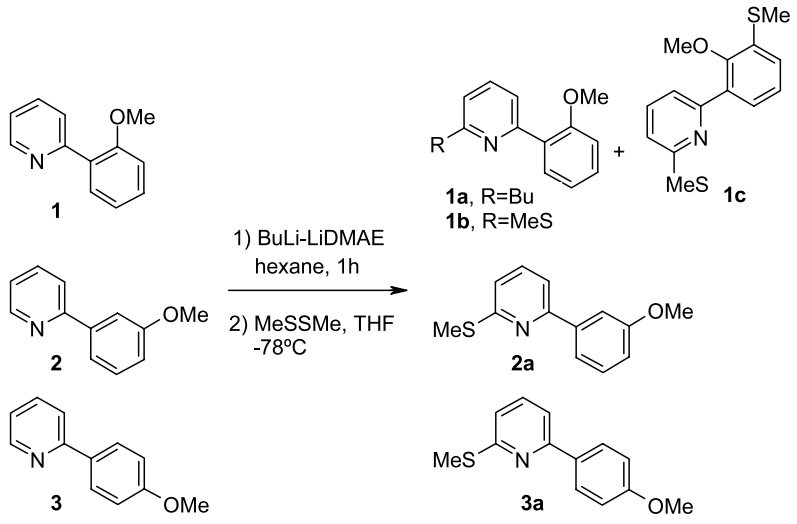
2-Anisylpyridines **1–3** were first reacted with BuLi-LiDMAE under usual conditions in hexane at various temperatures (Scheme 3, Table 1). All substrates led to efficient lithiation α to nitrogen. With **1**, the selectivity was in agreement with those observed by Quéguiner and co-workers.[4b] However the lithiation of this isomer was found highly temperature-sensitive since lithiation conducted at 0 °C led, besides nucleophilic addition product **1a**, to the derivative **1c** resulting from a bis-sulfuration of both the pyridine and phenyl ring (*ortho* to methoxy) (run 1). The temperature had to be decreased to −40 °C to ensure selective monolithiation and good conversion (runs 3–5). An increase of base amount and substitution of toluene to hexane in the metallation step to improve the solubility of **1** in the reaction medium were also beneficial. This was not necessary with **2–3** which were soluble in hexane. Moreover, no temperature effect was observed and **2a–3a** were obtained in good yields after metallation at 0 °C with 3 equiv of the reagent (runs 6–7).

These different behaviours are in good agreement with the relative heat of formation of potential carbanions in substrates as depicted in Figure 3.[8]

As shown, the carbanion *ortho* to methoxy in **1** is thermodynamically more stable than those α to nitrogen. Deprotonation on pyridine ring is obtained as a single reaction at low temperature (−40 °C) and is thus assumed



Scheme 2. Preparation of methoxyphenylpyridine **1–9**.



Scheme 3. Lithiation of **1–3** with BuLi-LiDMAE.

Table 1. Study of pyridino lithiation in **1–3**[a]

Entry	Substrate	Base (equiv)	*T* (°C)	Products (yield,%)[b]	Isolated yield (%)
1	**1**	3	0	**1a** (18) +**1b** (36) +**1c** (20)	—
2	**1**	3	−78	**1b** (15)	—
3	**1**	3	−40	**1b** (73)	—
4	**1**	4	−40	**1b** (80)	70
5	**1**	4	−40	**1b** (91)	85[c]
6	**2**	3	0	**2a** (92)	85
7	**3**	3	0	**3a** (85)	76

[a] All reactions performed on 2 mmol of substrate.
[b] GC yield.
[c] Metallation performed in toluene.

to be under kinetic control. On the other hand dilithiation at both α to nitrogen and *ortho* to methoxy was observed only at higher temperature (0 °C) rather under thermodynamic conditions. With the two other isomers **2–3**, the carbanion α to nitrogen is always the most stable explaining exclusive lithiation at this position even at 0 °C. The inertness of these latter substrates towards LTMP could be explained by the insufficient basicity of such reagent to abstract both the phenyl and pyridine protons. With BuLi-LiDMAE, chelation by the pyridine nitrogen and higher basicity allowed the deprotonation of the pyridinic site.

These selective lithiations were subsequently exploited for introduction of functionalities on the pyridine ring. Substrates **1–3** were then lithiated under the best conditions reported in Table 1 and reacted with various electrophiles (Table 2).

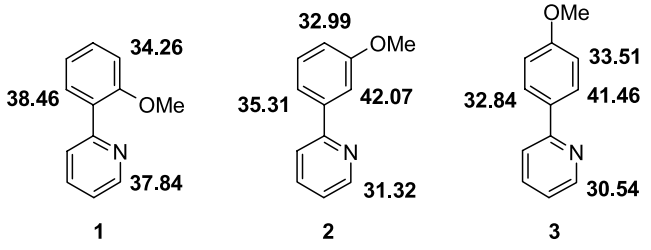


Figure 3. Calculated relative heats of formation (kcal/mol) of potential carbanions in **1–3**.

Several functional derivatives were prepared efficiently, especially alcohol **3d** and ketone **2d** not easy to obtain via classical couplings and the new P,N,O ligand **1f**. Note that **1** again behaved differently from **2** and **3** since it was not fully deuterated indicating that incomplete lithiation may be due to competitive chelation of lithium aggregates by the methoxy group thus partially impeding lithiation α to nitrogen.

2.2. Lithiation of 3- and 4-anisylpyridines

Then, we turned to the lithiation of isomers **4–9** displaying two available protons α to the pyridine nitrogen thus offering possibility for new selectivities (Fig. 4).

We first studied substrates **4** and **7** with a methoxy group at the *ortho* position on the phenyl ring which was expected to induce directing effects on pyridine (Scheme 4). As already observed with derivative **1**, **4** was poorly soluble in hexane and best results were obtained when metallation was performed in toluene at −20 °C. The lithiation occurred exclusively at C-6 and not at C-2 as could be expected from the directing power of the methoxy and a potential cooperative effect. This selectivity could be attributed to steric hindrance generated by the methoxyphenyl group at the C-2 position preventing the formation of aggregates. Note that such a compound was found inert towards LTMP supporting the need for external chelation to ensure pyridine lithiation and the role of steric hindrance. The reaction

Table 2. Preparation of functional methoxyphenylpyridines from **1–3**

Substrate	Electrophile	Product	Yield (%)[a]
1	D_2O	E=D, **1d**	80 (d%=75)[b]
1	C_2Cl_6	E=Cl, **1e**	82
1	$ClPPh_2$	E=PPh_2, **1f**	50
2	D_2O	E=D, **2b**	75 (d%>95)[b]
2	CBr_4	E=Br, **2c**	74
2	$PhCONMe_2$	E=COPh, **2d**	78
3	D_2O	E=D, **3b**	80 (d%>98)[b]
3	C_2Cl_6	E=Cl, **3c**	90
3	PhCHO	E=CH(OH)Ph, **3d**	75

[a] Isolated yield after column chromatography.
[b] Determined by ^1H NMR.

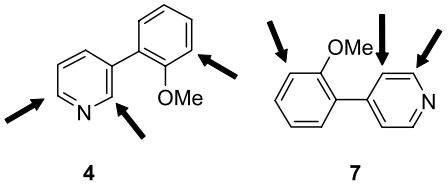
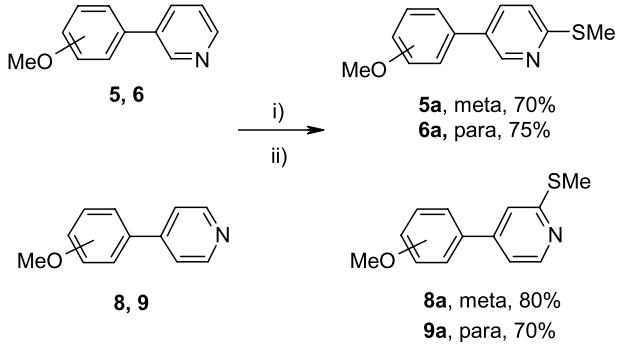


Figure 4. Potential deprotonation sites in **4** and **7**.

conditions were then applied to isomer **7**. As shown, lithiation also occurred selectively α to nitrogen. Interestingly, **7** did not lead to the radical induced dimerisation product[9] as was observed with LTMP indicating actual formation of the lithio intermediate (supported by a deuteration experiment) and subsequent stabilisation by lithium aggregates. A number of functionalities were further introduced efficiently leading to a range of new derivatives.

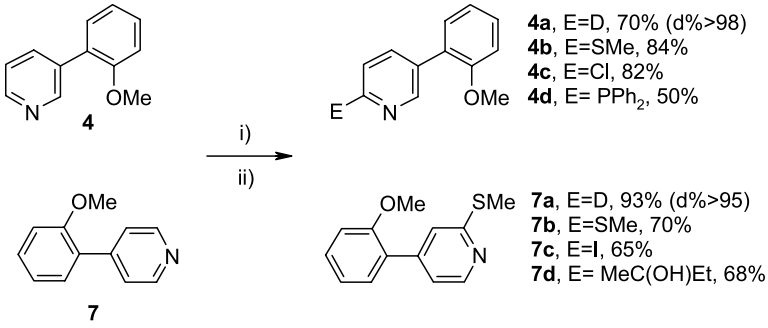
We then studied the remaining isomers **5**, **6**, **8** and **9** (Scheme 5). These compounds were lithiated under the above determined conditions. The reaction was also selectively pyridino directed at the α position. Note that



Scheme 5. Lithiation of **5**, **6**, **8**, **9**. For conditions see Scheme 4.

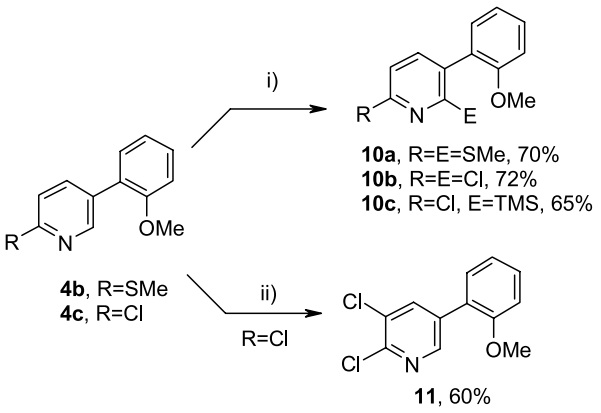
substrates **5**, **6** and **9** were soluble in hexane and the reaction proceeded as well in this solvent.

We next focused on the use of this new reaction for preparation of bifunctional derivatives via iterative lithiations. Then, compounds **4b** and **4c** bearing synthetically useful and base compatible substituents were first subjected



Scheme 4. Lithiation of **4** and **7**. Conditions: (i) BuLi-LiDMAE (3 equiv), toluene, −20 °C, 1 h. (ii) MeOD or MeSSMe or C_2Cl_6 or $ClPPh_2$ (3.2 equiv), THF, −78 °C to rt, 1 h.

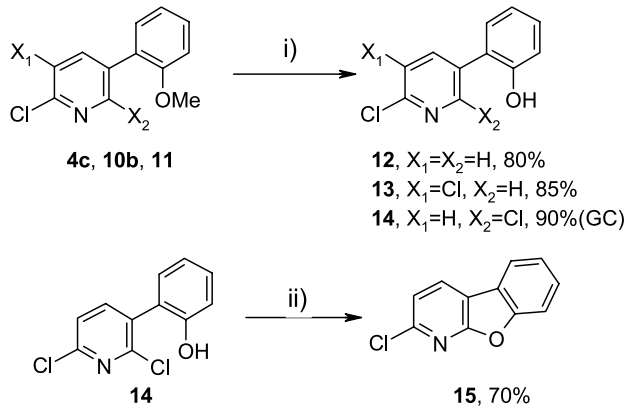
to reaction with BuLi-LiDMAE in order to check the ability of the available α proton to be abstracted (Scheme 6).



Scheme 6. Sequential lithiations. Conditions: (i) (1) BuLi-LiDMAE (3 equiv), toluene, −20 °C, 1 h. (2) MeSSMe or C_2Cl_6 or $ClSiMe_3$ (3.2 equiv), THF, −78 °C to −20 °C, 1 h. (ii) (1) LTMP (3.2 equiv), THF, −20 °C, 1 h. (2) C_2Cl_6 (3.5 equiv), THF, −20 °C 1 h.

As shown, the C-2 position was lithiated in slightly lower yield than was the C-6 one in **4**, presumably due to the previously proposed steric effects. However bifunctional derivatives **10a–c** were obtained in good overall yields (typically 60% from **4**). Reaction of **4c** with LTMP yielded exclusively the 2,3-dichloro derivative in 60% yield indicating the poor remote directing power of the methoxy group compared to those of chlorine on pyridine.

In order to demonstrate the usefulness of our methodology for the synthesis of functional pyridylphenols we examined the demethylation of some of the prepared derivatives (Scheme 7). We chose chlorinated compounds, which are useful precursors for further introduction of diversity. A clean demethylation was obtained by reaction of **4c**, **10b** and **11** with BBr_3 solutions in CH_2Cl_2 at room temperature furnishing the expected phenols in high yields. Finally, crude phenol **14** was not purified and involved as such in cyclisation under basic conditions leading to chlorinated benzofuropyridine **15** in good yield (70%).



Scheme 7. (i) BBr_3 (5 equiv),CH_2Cl_2, −78 °C then rt overnight. (ii) K_2CO_3 (3 equiv), CH_3CN, reflux, 5 h.

3. Conclusion

We have developed an efficient methodology for the functionalisation of nine methoxyphenylpyridines. The BuLi-LiDMAE superbase effected a selective pyridino directed lithiation α to nitrogen. The obtained functional derivatives were smoothly deprotected under mild conditions and converted into the corresponding phenols. Work is now in progress to extend such reactions to the preparation of various functional benzofuropyridines such as **15** and fused polyheterocyclic compounds.

4. Experimental

4.1. General

Et_2O, THF, and hexane were distilled and stored over sodium wire before use. 2-Dimethylaminoethanol was distilled under nitrogen and stored on molecular sieves. *n*-BuLi was used as a 1.6 M solution in hexanes. All other reagents were commercially available and used as such. ^1H and ^{13}C and ^{31}P NMR were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker AC400 instrument at 400, 100 and 162 MHz respectively. GC experiments were performed on a Shimadzu chromatograph fitted with a 15 m capillary column. GC/MS (EI) were obtained on HP5971 spectrometer.

4.2. Preparation of starting anisylpyridines

To a mixture of appropriate bromo or chloropyridine (9 mmol), $Ni(acac)_2$ (120 mg, 0.45 mmol) and dppe (180 mg, 0.45 mmol) in THF (30 mL) was added dropwise the appropriate anisylmagnesium bromide (10 mmol) (prepared by dropwise addition of the anisyl bromide (10 mmol) to a refluxing suspension of Mg turnings (240 mg, 10 mmol) in THF). The mixture was then stirred for 18 h at room temperature before hydrolysis with water (20 mL). The aqueous layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. The crude products were then purified by column chromatography on silica gel.

4.2.1. 2-(2-Methoxyphenyl)pyridine 1. Column chromatography (80% hexanes/AcOEt) afforded **1** (1.33 g, 80%) as a pale yellow oil. Spectrocopic data consistent with that reported in the literature.[10]

4.2.2. 2-(3-Methoxyphenyl)pyridine 2.[11] Column chromatography (80% hexanes/AcOEt) afforded **2** (1.35 g, 81%) as a pale yellow oil. δ_H 3.89 (s, 3H), 6.96 (d, J=9.0 Hz, 1H), 7.22–7.24 (m, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.52 (t, J=1.4 Hz, 1H), 7.52–7.60 (m, 1H), 7.71–7.75 (m, 2H), 8.68 (d, J=4.8 Hz, 1H). δ_C 55.6, 112.3, 115.4, 119.6, 120.9, 122.5, 130.0, 137, 141.2, 149.9, 157.5, 160.4. *m/z* (EI) 185 (M, 100), 154 (M−31, 100), 140 (M−45, 22), 126 (M−59, 8), 114 (M−71, 9), 89 (M−96, 4), 63 (M−122, 4%).

4.2.3. 2-(4-Methoxyphenyl)pyridine 3.[12] Column chromatography (80% hexanes/AcOEt) afforded **3** (1.41 g, 85%) as a white solid. Mp 54–55 °C [Lit[10a] 53–55 °C]. δ_H 3.89 (s, 3H), 7.02 (d, J=8.9 Hz, 2H), 7.18 (dd, J=3.4, 1.4 Hz, 1H),

7.68–7.75 (m, 2H), 7.97 (d, J=9.0 Hz, 2H), 8.67 (d, J=5.3 Hz, 1H). δ_C 55.7, 114.5, 120.2, 121.8, 128.5, 137, 149.9. m/z (EI) 185 (M, 100), 170 (M−15, 42), 142 (M−43, 74), 141 (M−44, 56), 115 (M−70, 21), 89 (M−96, 17),78 (M−107, 9), 63 (M−122, 21), 51 (M−134, 14%).

4.2.4. 3-(2-Methoxyphenyl)pyridine 4. Column chromatography (80% hexanes/AcOEt) afforded **4** (1.33 g, 80%) as a colourless oil. Spectrocopic data consistent with that reported in the literature.[10a,13]

4.2.5. 3-(3-Methoxyphenyl)pyridine 5. Column chromatography (80% hexanes/AcOEt) afforded **5** (1.08 g, 65%) as a pale yellow oil. Spectrocopic data consistent with that reported in the literature.[14]

4.2.6. 3-(4-Methoxyphenyl)pyridine 6. Column chromatography (70% hexanes/AcOEt) afforded **6** (1.16 g, 70%) as a white solid. Mp 59–60 °C [Lit[10a] 60–61 °C]. δ_H 3.85 (s, 3H), 6.99 (d, J=8.4 Hz, 2H), 7.32 (dd, J=7.8, 4.8 Hz, 1H), 7.51 (d, J=8.5 Hz, 2H), 7.82 (d, J=7.9 Hz, 1H), 8.55 (s, 1H), 8.82 (s, 1H). δ_C 55.5, 114.7, 123.7, 128.4, 130.4, 134.0, 148.0, 148.4, 159.9. m/z (EI) 185 (M, 100), 170 (M−15, 40), 142 (M−43, 32), 115 (M−70, 16), 89 (M−96, 10), 63 (M−122, 10%).

4.2.7. 4-(2-Methoxyphenyl)pyridine 7. 4-Chloropyridine was used as halopyridine. Column chromatography (70% hexanes/AcOEt) afforded **7** (1.08 g, 65%) as a white solid. Mp 63–64 °C [Lit[10a] 63–65 °C]. Spectrocopic data consistent with that reported in the literature.[15]

4.2.8. 4-(3-Methoxyphenyl)pyridine 8.[15] 4-Chloropyridine was used as halopyridine. Column chromatography (50% hexanes/AcOEt) afforded **8** (0.92 g, 55%) as a pale yellow oil. Spectrocopic data consistent with that reported in the literature.[15]

4.2.9. 4-(4-Methoxyphenyl)pyridine 9. 4-Chloropyridine was used as halopyridine. Column chromatography (50% hexanes/AcOEt) afforded **9** (0.75 g, 45%) as a white solid. Mp 94–96 °C [Lit[10a] 95–96 °C]. δ_H 3.88 (s, 3H), 7.03 (d, J=8.7 Hz, 2H), 7.48 (d, J=5.9 Hz, 2H), 7.62 (d, J=8.6 Hz, 2H), 8.64 (d, J=5.5 Hz, 2H). δ_C 55.8, 114.9, 121.5, 128.5, 150.6. MS (EI) m/z: 185 (M, 100), 170 (M−15, 26), 142 (M−43, 34), 115 (M−70, 24), 89 (M−96, 10), 63 (M−122, 10%).

4.3. Procedure for lithiation of anisylpyridines

A solution of 2-dimethylaminoethanol (0.8 mL, 8 mmol) in hexane or toluene (10 mL) was cooled at 0 °C and treated dropwise with n-BuLi (10 mL, 16 mmol). After 30 min at 0 °C, a solution of the anisylpyridine (2 mmol for 4 equiv of n-BuLi LiDMAE or 2.66 mmol for 3 equiv) in hexane or toluene (5 mL) was added dropwise. After 1 h at appropriate temperature, the red brown reaction mixture was cooled to −78 °C and treated with a solution of appropriate electrophile in THF (20 mL). After 30 min at −78 °C, the temperature was allowed to raise the room temperature. The hydrolysis was then performed at 0 °C with H_2O. The aqueous layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. The crude products were then purified by column chromatography with hexane/AcOEt mixture as eluent.

4.3.1. Compound 1b. (522 mg, 85%) was obtained as a yellow viscous oil after column chromatography (90% hexanes/AcOEt) as eluents. δ_H 2.59 (s, 3H), 3.80 (s, 3H), 6.9 (d, J=8.2 Hz, 1H), 7.0 (d, J=3.0 Hz, 1H), 7.1 (d, J=3.0 Hz, 1H), 7.33 (d, J=7.2 Hz, 1H), 7.44 (d, J=7.9 Hz, 1H), 7.6 (d, J=7.9 Hz, 1H), 7.94 (m, 1H). δ_C 13.4, 55.8, 111.7, 119.7, 120.7, 121.2, 128.9, 130.2, 131.4, 135.9, 155.4, 157.4, 158.9. m/z (EI) 231 (M, 100), 230 (M−1, 42), 200 (M−31, 48), 198 (M−33, 92), 180 (M−51, 28), 170 (M−61, 40), 154 (M−77, 42), 140 (M−91, 28), 115 (M−116, 31%). Anal. Calcd for $C_{13}H_{13}NOS$: C%, 67.50; H%, 5.66; N%, 6.06. Found C%, 67.35; H%, 5.53; N%, 5.84.

4.3.2. Compound 1d.[4b] (396 mg, 80%, d%>75) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.83 (s, 3H), 6.99 (d, J=8.3 Hz, 1H), 7.07 (dt, J=7.3, 0.7 Hz, 1H), 7.17 (d, J=7.5 Hz, 2H), 7.36 (dt, J=7.8, 2.1 Hz, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.81 (dd, J=7.8, 1.0 Hz, 1H). δ_C 55.9, 111.7, 125.5, 125.7, 128.6, 128.9, [129.2, 129.4, 129.6], 131.05, 135.9, 149.8, 156.3, 157.3. m/z (EI) 186 (M, 73), 185 (M−1, 100), 156 (M−30, 66), 155 (M−31, 100), 142 (M−44, 12), 128 (M−58, 17), 116 (M−70, 13), 81 (M−105, 58),63 (M−123, 21%).

4.3.3. Compound 1e. (478 mg, 82%) was obtained as a pale yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.88 (s, 3H), 7.01 (d, J=8.4 Hz, 1H), 7.10 (dt, J=7.3, 1.0 Hz, 1H), 7.24 (d, J=7.8 Hz, 1H), 7.40 (dt, J=8.0, 2.1 Hz, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.84 (dd, J=7.6, 0.8 Hz, 1H), 7.88 (dd, J=7.8, 1.8 Hz, 1H). δ_C 55.9, 111.7, 121.5, 122.4, 123.9, 127.7, 130.9, 131.7, 138.7, 151.1, 156.8, 157.4. MS (EI) m/z: 219 (M, 72), 218 (M−1, 100), 189 (M−30, 28), 154 (M−65, 36), 140 (M−79, 13), 127 (M−92, 15), 114 (M−105, 32%).

4.3.4. Compound 1f. (491 mg, 50%) was obtained as a white solid after recrystallisation in MeOH. Mp 166–168 °C. δ_H 3.83 (s, 3H), 6.99 (m, 3H), 7.3–7.5 (m, 11H), 7.55 (dd, J=7.8, 2.0 Hz, 1H), 7.77 (dd, J=5.2, 1.8 Hz, 2H). δ_C 55.7, 111.5, 121.2, 123.8, 125.9, 128.8, 128.6, 129.0, 130.1, 131.8, 134.2, 136.6. δ_P −3.30. Anal. Calcd for $C_{24}H_{20}NOP$: C%, 78.04; H%, 5.46; N%, 3.79. Found C%, 78.15; H%, 5.43; N%, 3.80.

4.3.5. Compound 2a. (522 mg, 85%) was obtained as a yellow oil after column chromatography using (90% hexanes/AcOEt). δ_H 2.66 (s, 3H), 3.88 (s, 3H), 6.9 (dd, J=6.5, 2.4 Hz, 1H), 7.1 (d, J=7.5 Hz, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.42 (d, J=4.0 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.62–7.67 (m, 2H). δ_C 13.5, 55.6, 112.7, 114.9, 115.9, 119.5, 130.0, 136.7, 140.9, 159.6, 160.7. m/z (EI) 231 (M, 100), 230 (M−1, 62), 185 (M−46, 13), 170 (M−61, 8), 154 (M−77, 9), 142 (M−89, 20), 140 (M−91, 9), 115 (M−116, 10%).

4.3.6. Compound 2b. (371 mg, 75%, d%>98) was obtained as a yellow viscous oil after column chromatography (90% hexanes/AcOEt). δ_H 3.89 (s, 3H), 6.96 (d, J=9.0 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 7.38 (d, J=8.0 Hz,

1H), 7.52 (d, J=1.4 Hz, 1H), 7.50–7.68 (m, 3H). δ_C 55.6, 117.3, 120.9, [122.5, 122.8, 123.1], 126.7, 130.7, 133.3, 134.9, 150.1, 158.4, 162.8. *m/z* (EI) 186 (M, 100), 171 (M−15, 35), 143 (M−43, 57), 116 (M−70, 15), 90 (M−96, 11), 63 (M−123, 17%).

4.3.7. Compound 2c. (519 mg, 74%) was obtained as a light brown oil after column chromatography using (90% hexanes/AcOEt). δ_H 3.89 (s, 3H), 6.96 (d, J=9.0 Hz, 1H), 7.39 (dd, J=7.6, 3.1 Hz, 2H), 7.52 (s, 1H), 7.52–7.57 (m, 2H), 7.65 (d, J=7.2 Hz, 1H). δ_C 55.7, 112.6, 115.8, 119.4, 119.6, 126.7, 130.0, 139.1, 142.3, 160.4. *m/z* (EI) 264 (M, 100), 233 (M−31, 32), 184 (M−80, 7), 169 (M−95, 24), 154 (M−110, 73), 140 (M−124, 67), 127 (M−137, 34), 114 (M−150, 40), 92 (M−172, 32), 77 (M−187, 32), 63 (M−201, 57%), 51 (M−213, 30%). Anal. Calcd for $C_{12}H_{10}BrNO$: C%, 54.57; H%, 3.82; N%, 5.30. Found C%, 54.85; H%, 3.76; N%, 5.06.

4.3.8. Compound 2d. (600 mg, 78%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.84 (s, 3H), 6.97 (dd, J=5.6, 2.7 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.51 (d, J=7.6 Hz, 2H), 7.57–7.66 (m, 3H), 7.96 (d, J=5.5 Hz, 2H), 8.02 (d, J=4.1 Hz, 1H), 8.22 (dd, J=7.0, 1.7 Hz, 2H). δ_C 55.5, 112.4, 115.7, 122.8, 123.2, 128.2, 130.1, 131.6, 133.0, 136.7, 138.1, 154.8, 160.4. *m/z* (EI) 288 (M−1, 100), 260 (M−29, 80), 230 (M−59, 14), 105 (M−184, 25), 77 (M−112, 28%). Anal. Calcd for $C_{19}H_{15}NO_2$: C%, 78.87; H%, 5.23; N%, 4.84. Found C%, 78.75; H%, 5.35; N%, 4.96.

4.3.9. Compound 3a. (467 mg, 76%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.66 (s, 3H), 3.87 (s, 3H), 6.99 (d, J=8.6 Hz, 2H), 7.07 (d, J=7.9 Hz, 1H), 7.36 (d, J=8.6 Hz, 1H), 7.51 (d, J=7.5 Hz, 1H), 8.01 (d, J=9 Hz, 2H). δ_C 13.3, 55.5, 114.2, 114.9, 119.4, 128.2, 131.8, 136.6, 156.4, 159.2, 160.7. *m/z* (EI) 231 (M, 100), 230 (M−1, 62), 185 (M−46, 17), 170 (M−61, 34), 140 (M−91, 11), 115 (M−116, 12%).

4.3.10. Compound 3b. (396 mg, 80%, d%>98) was obtained as a yellow oil after column chromatography (80% hexanes/AcOEt). δ_H 3.85 (s, 3H), 7.01 (d, J=9.0 Hz, 2H), 7.16 (d, J=6.8 Hz, 1H), 7.65–7.70 (m, 2H), 7.97 (d, J=9.0 Hz, 2H). δ_C 55.7, 114.5, 120.2, [121.8, 122.2, 122.6], 128.5, 137, 149.9. *m/z* (EI) 187 (M+1, 36), 186 (M, 100), 171 (M−15, 35), 143 (M−43, 57), 116 (M−70, 15), 90 (M−96, 11), 63 (M−123, 17%).

4.3.11. Compound 3c. (553 mg, 90%) was obtained as a white solid after column chromatography (90% hexanes/AcOEt). Mp 77–79 °C. δ_H 3.83 (s, 3H), 6.95 (d, J=8.9 Hz, 2H), 7.14 (dd, J=7.1, 1.0 Hz, 1H), 7.53 (dd, J=8.9, 1.0 Hz, 1H), 7.59 (d, J=7.5 Hz), 7.93 (d, J=9.0 Hz, 2H). δ_C 55.5, 114.4, 117.9, 121.8, 128.6, 139.3, 142.9, 151.4, 157.9, 161.1. *m/z* (EI) 221 (M+2, 33), 219 (M, 100), 204 (M−15, 17), 176 (M−43, 25), 141 (M−78, 18%). Anal. Calcd for $C_{12}H_{10}ClNO$: C%, 65.61; H%, 4.59; N%, 6.38. Found C%, 65.50; H%, 4.60; N%, 6.26.

4.3.12. Compound 3d. (580 mg, 75%) was obtained as a yellow viscous oil after column chromatography (90% hexanes/AcOEt). δ_H 3.89 (s, 3H), 4.69 (d, J=5.0 Hz, 1H), 5.82 (d, J=3.5 Hz, 1H), 6.96 (d, J=7.5 Hz, 1H), 7.02 (d, J=8.9 Hz, 2H), 7.28–7.37 (m, 3H), 7.41 (d, J=7 Hz, 2H), 7.57 (d, J=7.6 Hz, 1H), 7.63 (d, J=7.8 Hz, 1H), 8.02 (d, J=7.0 Hz, 2H). δ_C 55.5, 74.9, 114.3, 118.4, 119.2, 127.1, 127.4, 128.0, 128.4, 128.7, 137.8, 143.5, 155.2, 160.4, 160.9. *m/z* (EI) 291 (M, 100), 214 (M−77, 72), 185 (M−106, 37), 170 (M−121, 24%).

4.3.13. Compound 4a. (346 mg, 70%, d%>98) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.84 (s, 3H), 7.03 (d, J=8.3 Hz, 1H), 7.08 (dt, J=7.6, 0.8 Hz, 1H), 7.34 (dd, J=7.8, 1.5 Hz, 2H), 7.39 (dt, J=7.8, 1.8 Hz, 1H), 7.88 (dd, J=8.0, 2.3 Hz, 1H), 8.79 (d, J=1.7 Hz, 1H). δ_C 55.9, 111.6, 121.4, 123.1, [127.4, 127.7, 128.0], 129.9, 131.0, 134.6, 137.2, 150.6, 157.0. *m/z* (EI) 186 (M, 100), 171 (M−15, 51), 116 (M−70, 30%).

4.3.14. Compound 4b. (516 mg, 84%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.81 (s, 3H), 6.98 (dd, J=8.0, 0.7 Hz, 1H), 7.0 (td, J=8.0, 1.1 Hz, 1H), 7.21 (dd, J=8.0, 1.1 Hz, 1H), 7.30 (dd, J=7.0, 1.9 Hz, 1H), 7.34 (dt, J=7.0, 1.9 Hz, 1H), 7.69 (dd, J=6.1, 2.3 Hz, 1H), 8.61 (d, J=2.3 Hz, 1H). δ_C 13.8, 55.9, 111.7, 121.0, 121.5, 127.2, 129.6, 130.7, 137.3, 150.1, 158.5. *m/z* (EI) 230 (M−1, 100), 198 (M−33, 16), 185 (M−46, 13), 169 (M−62, 8), 115 (M−116, 9%).

4.3.15. Compound 4c. (478 mg, 82%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.80 (s, 3H), 7.01–7.07 (m, 2H), 7.25–7.41 (m, 3H), 7.82 (dd, J=8.3, 2.4 Hz, 1H), 8.51 (d, J=2.4 Hz, 1H). δ_C 55.6, 111.5, 121.3, 123.6, 125.7, 130.1, 130.5, 133.3, 139.8, 149.7, 150.1, 156.6. *m/z* (EI) 221 (M+2, 33), 219 (M, 100), 204 (M−15, 25), 169 (M−50, 20), 168 (M−51, 29), 140 (M−79, 27%).

4.3.16. Compound 4d. (535 mg, 50%) was obtained as a white solid after column chromatography using 80:20 hexanes–AcOEt as eluents. Mp 150–151 °C. δ_H 3.81 (s, 3H), 6.97–7.07 (m, 2H), 7.12 (d, J=8.3 Hz, 1H), 7.30–7.50 (m, 12H), 7.74 (dd, J=6.3, 1.7 Hz, 1H), 8.9 (d, J=2.1 Hz, 1H). δ_C 55.5, 111.5, 121.3, 126.9, 127.5, 128.7, 128.9, 129.3, 129.9, 130.9, 134.7, 136.59, 136,65, 151.12, 161.7, 161.9. δ_P −3.69. Anal. Calcd for $C_{24}H_{20}NOP$: C%, 78.04; H%, 5.46; N%, 3.79. Found C%, 78.16; H%, 5.44; N%, 3.83.

4.3.17. Compound 5a. (430 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.85 (s, 3H), 6.91 (dd, J=8.2, 2.4 Hz, 1H), 7.06 (s, 1H), 7.12 (d, J=7.6 Hz, 1H), 7.23 (d, J=8.2 Hz, 1H), 7.37 (d, J=7.8 Hz, 1H), 7.68 (dd, J=8.3, 2.4 Hz, 1H), 8.58 (d, J=4.8 Hz, 1H), 8.67 (s, 1H). δ_C 13.5, 55.4, 112.7, 113.2, 119.3, 121.4, 130.3, 132.2, 134.5, 139.2, 147.8, 159.1, 160.2. *m/z* (EI) 231 (M, 100), 198 (M−33, 27), 185 (M−46, 19), 115 (M−116, 21), 63 (M−168, 12%). Anal. Calcd for $C_{13}H_{13}NOS$: C%, 67.50; H%, 5.66; N%, 6.06. Found C%, 67.34; H%, 5.68; N%, 6.09.

4.3.18. Compound 6a. (460 mg, 75%) was obtained as a

yellow oil after column chromatography (90% hexanes/AcOEt). Spectrocopic data consistent with that reported in the literature.[8a,16]

4.3.19. Compound 7a. (346 mg, 93%, d%>95) was obtained as a yellow oil after column chromatography (80% hexanes/AcOEt). δ_H 3.83 (s, 3H), 7.04 (dd, J=8.3, 5.5 Hz, 2H), 7.26–7.43 (m, 3H), 7.47 (s, 1H), 8.62 (d, J=3 Hz, 1H). δ_C 55.7, 111.6, 121.2, 124.4, 127.8, [129.7, 130.2, 130.7], 146.5, 149.7, 156.7. *m/z* (EI) 186 (M, 100), 171 (M−15, 30), 157 (M−29, 15), 116 (M−70, 38), 63 (M−123, 17%).

4.3.20. Compound 7b. (323 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.57 (s, 3H), 3.79 (s, 3H), 6.94–7.05 (m, 2H), 7.14 (dd, J=5.5, 1.7 Hz, 1H), 7.26–7.39 (m, 3H), 8.43 (dd, J=5.5, 0.7 Hz, 1H). δ_C 12.8, 55.7, 111.6, 113.1, 121.5, 124.5, 127.8, 130.3, 130.6, 146.4, 149.7, 156.7, 170.2. *m/z* (EI) 231 (M, 100), 198 (M−33, 25), 185 (M−46, 31), 115 (M−116, 33).

4.3.21. Compound 7c. (404 mg, 65%) was obtained as an orange oil after column chromatography (80% hexanes/AcOEt). δ_H 3.84 (s, 3H), 6.98–7.09 (m, 2H), 7.01 (dd, J=7.5, 1.7 Hz, 2H), 7.44 (dd, J=3.8, 1.4 Hz, 1H), 7.89 (s, 1H), 8.34 (d, J=5.2 Hz, 1H). δ_C 55.8, 111.7, 114.3, 121.3, 123.7, 130.5, 130.9, 135.3, 150.3. *m/z* (EI) 311 (M, 75), 184 (M−127, 74), 169 (M−142, 100), 140 (M−171, 16). Anal. Calcd for $C_{12}H_{10}INO$: C%, 46.33; H%, 3.24; N%, 4.50. Found C%, 46.52; H%, 3.29; N%, 4.40.

4.3.22. Compound 7d. (349 mg, 68%) was obtained as an orange oil after column chromatography (80% hexanes/AcOEt). δ_H 0.82 (t, 3H, J=7.3 Hz, 1H), 1.56 (s, 3H), 1.81–1.92 (m, 2H), 5.03 (s, 1H), 3.85 (s, 3H), 7.03 (d, J=8.3 Hz, 1H), 7.09 (d, J=7.6 Hz, 1H), 7.36–7.44 (m, 3H), 7.49 (s, 1H), 8.54 (d, J=5 Hz, 1H). δ_C 8.53, 29.30, 36.49, 55.95, 74.36, 111.85, 120.27, 121.47, 122.97, 130.59, 130.92, 147.17, 147.70, 156.9, 160.87, 164.89. *m/z* (EI) 257 (M, 2), 242 (M−15, 15), 228 (M−29, 100), 212 (M−45, 15), 185 (M−72, 10), 170 (M−87, 10), 115 (M−142, 9).

4.3.23. Compound 8a. (370 mg, 80%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.84 (s, 3H), 6.95 (dd, J=8.2, 2.5 Hz, 1H), 7.10 (d, J=1.7 Hz, 1H), 7.16 (dd, J=5.3, 1.8 Hz, 2H), 7.32–7.35 (m, 2H), 8.46 (d, J=5.3 Hz, 1H). δ_C 13.7, 55.7, 113.2, 114.8, 118.0, 119.6, 119.8, 130.5, 139.9, 148.6, 150.1, 160.5, 160.9. *m/z* (EI) 231 (M, 100), 185 (M−46, 37), 115 (M−116, 18%). Anal. Calcd for $C_{13}H_{13}NOS$: C%, 67.50; H%, 5.66; N%, 6.06. Found C%, 67.39; H%, 5.59; N%, 6.07.

4.3.24. Compound 9a.[15] (324 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.84 (s, 3H), 6.97 (d, J=8.0 Hz, 2H), 7.15 (d, J=5.3 Hz, 1H), 7.35 (s, 1H), 7.55 (d, J=7.7 Hz, 2H), 8.43 (d, J=5.3 Hz, 1H). δ_C 13.8, 55.8, 114.9, 117.5, 118.9, 128.6, 130.6, 148.2, 150.0, 160.7, 161.0. *m/z* (EI) 231 (M, 100), 230 (M−1, 63), 185 (M−46, 42), 170 (M−61, 14), 115 (M−116, 22%).

4.3.25. Compound 10a. (516 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.51 (s, 3H), 2.62 (s, 3H), 3.75 (s, 3H), 6.93 (d, J=7.9 Hz, 1H), 6.97 (d, J=8.6 Hz, 1H), 7.01 (d, J=7.4 Hz, 1H), 7.19 (d, J=7.8 Hz, 2H), 7.37 (dt, J=8.2, 1.6 Hz, 1H). δ_C 13.7, 13.9, 56.0, 89.3, 111.7, 116.5, 120.9, 126.9, 128.3, 130.2, 131.7, 137.5, 154.4, 157.7, 158.4. *m/z* (EI) 277 (M, 80), 246 (M−31, 100), 230 (M−47, 75), 212 (M−65, 32).

4.3.26. Compound 10b. (484 mg, 72%) was obtained as a yellow viscous oil after column chromatography using 90:10 hexanes–AcOEt as eluents. δ_H 3.79 (s, 3H), 6.99 (d, J=8.4 Hz, 1H), 7.03 (t, J=7.5 Hz, 1H), 7.18 (dd, J=7.5, 1.7 Hz, 1H), 7.31 (d, J=7.8 Hz, 1H), 7.42 (dd, J=8.4, 1.8 Hz, 3H), 7.59 (d, J=7.9 Hz, 1H). δ_C 55.9, 111.5, 120.9, 123.0, 125.7, 130.8, 131.0, 133.3, 142.8, 149.2, 150.1, 156.9. *m/z* (EI) 255 (M+2, 40), 253 (M, 63), 218 (M−35, 100), 203 (M−50, 72), 140 (M−113, 19%).

4.3.27. Compound 10c. (503 mg, 65%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 0.30 (s, 9H), 3.73 (s, 3H), 6.91–6.99 (m, 2H), 7.06 (dt, J=7.5, 2.0 Hz, 1H), 7.21 (d, J=8.2 Hz, 1H), 7.35–7.42 (m, 2H). δ_C −0.69, 55.3, 110.6, 120.2, 129.8, 131.5, 139.2, 150.2, 157.1. *m/z* (EI) 291 (M, 20), 276 (M−15, 61), 261 (M−30, 55), 256 (M−35, 90), 246 (M−45,100), 73 (M−218, 71%).

4.3.28. Preparation of 11 by lithiation of 4c with LTMP. To a solution of TMP (0.58 mL, 3.4 mmol) in THF (5 mL) cooled at −30 °C was added dropwise *n*-BuLi (2 mL, 3.2 mmol). The medium was then allowed to warm at 0 °C for 30 min and cooled at −20 °C. A solution of **4c** (219 mg, 1 mmol) in THF (2 mL) was then added drowpise. The red solution was stirred for 1 h at the same temperature and cooled at −78 °C. A solution of C_2Cl_6 (830 mg, 3.5 mmol) in THF (10 mL) was then added dropwise. The reaction medium was then allowed to warm to 0 °C and hydrolysed with H_2O (5 mL). The aqueous layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. Column chromatography (90% hexanes/AcOEt) yielded **11** (538 mg, 80%) as a white solid. Mp 81 °C. δ_H 3.84 (s, 3H), 7.00 (d, J=8.3 Hz, 1H), 7.06 (t, J=7.4 Hz, 1H), 7.29 (dd, J=7.6, 1.6 Hz, 1H), 7.40 (dt, J=8.1, 1.6 Hz, 1H), 7.97 (d, J=2.1 Hz, 1H), 8.43 (d, J=2.1 Hz, 1H). δ_C 55.9, 111.7, 121.6, 124.5, 130.7, 130.8, 134.9, 139.8, 140.2, 147.9, 156.8, 160.1. *m/z* (EI) 255 (M+2, 66), 253 (M, 100), 238 (M−15, 13), 203 (M−50, 53), 174 (M−79, 20), 140 (M−113, 16), 63 (M−190, 15%). Anal. Calcd for $C_{12}H_9Cl_2NO$: C%, 56.72; H%, 3.57; N%, 5.51. Found C%, 56.83; H%, 3.47; N%, 5.43.

4.4. Procedure for demethylation anisylpyridines

To a solution of appropriate anisylpyridine (1 mmol) in dry dichloromethane at −78 °C was added dropwise a solution of boron tribromide (5 mmol, 5 mL of a 1 M solution in dichloromethane). After addition the mixture was stirred overnight at room temperature, then treated with water and extracted with ethyl acetate. The organic layer was then dried over anhydrous $MgSO_4$, and evaporated under vacuum.

4.4.1. Compound 12. (165 mg, 80%) was obtained as a white solid after recrystallisation in dichloromethane. Mp 171–173 °C. δ_H 7.01–7.09 (m, 2H), 7.34 (t, $J=7.4$ Hz, 1H), 7.43 (d, $J=7.4$ Hz, 1H), 7.64 (d, $J=8.3$ Hz, 1H), 8.12 (d, $J=8.3$ Hz, 1H), 8.67 (s, 1H), 9.99 (s, 1H). δ_C 114.6, 118.2, 121.3, 122.3, 128.2, 128.6, 131.9, 138.4, 146.6, 148.0, 152.9. *m/z* (EI) 207 (M+2, 32), 205 (M, 100), 170 (M−35, 34), 115 (M−90, 22%). Anal. Calcd for $C_{11}H_8ClNO$: C%, 64.25; H%, 3.92; N%, 6.81. Found C%, 64.43; H%, 3.83; N%, 6.77.

4.4.2. Compound 13. (200 mg, 84%) was obtained as a white solid after recrystallisation in dichloromethane. Mp 162–164 °C. δ_H 7.02–7.11 (m, 2H), 7.37 (t, $J=7.6$ Hz, 1H), 7.50 (d, $J=7.5$ Hz, 1H), 8.39 (s, 1H), 8.68 (s, 1H), 10.14 (s, 1H). δ_C 114.7, 118.3, 119.9, 126.9, 128.8, 133.5, 137.8, 143.7, 146.2, 149.5, 153.1. *m/z* (EI) 241 (M+2, 58), 239 (M, 100), 204 (M−35, 19), 140 (M−99, 14). Anal. Calcd for $C_{11}H_8Cl_2NO$: C%, 55.03; H%, 2.94; N%, 5.83. Found C%, 55.21; H%, 2.83; N%, 5.87.

4.4.3. Compound 15. The title compound was prepared as above described in 90% yield (GC) and dissolved as such in acetonitrile (10 mL), potassium carbonate was then added (410 mg, 3 mmol) and the mixture was refluxed for 5 h. After removal of solvent, the residue was treated with water and extracted with chloroform. The organic layer was dried over anhydrous $MgSO_4$, and evaporated under vacuum. Column chromatography (90% hexanes–AcOEt) yielded **15** (142 mg, 70%) as a white solid. Mp 155–156 °C [Lit.[17] 150–157 °C]. δ_H 7.40–7.45 (m, 2H), 7.54 (dt, $J=7.2$, 1.4 Hz, 1H), 7.64 (d, $J=7.2$ Hz, 1H), 7.92 (dd, $J=8.6$, 2.5 Hz, 1H), 8.20 (d, $J=7.9$ Hz, 1H). δ_C 111.48, 112.7, 119.8, 120.7, 122.2, 124.2, 128.2, 128.9, 131.9. *m/z* (EI) 205 (M+2, 34), 203 (M, 100), 168 (M−35, 21%), 140 (M−63, 24%). Anal. Calcd for $C_{11}H_6ClNO$: C%, 64.88; H%, 2.97; N%, 6.88. Found C%, 64.69; H%, 3.01; N%, 6.77.

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Structural studies of {^{6}Li} 2-lithiopyrrolidines using NMR spectroscopy

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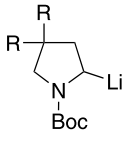
Abstract—A selection of *N*-substituted 2-lithiopyrrolidines were prepared and their structures were investigated by ^{6}Li and ^{13}C NMR spectroscopy. Evidence is presented for aggregation and dynamic solvation effects, depending on the nature of the *N*-substituent and substituents on the pyrrolidine ring. Studies were performed with *N*-Boc (coordinating carbonyl group), *N*-methoxyethyl (coordinating methoxy group) and *N*-alkyl (no coordinating group) heterocycles to represent three different classes of organolithiums: dipole-stabilized, unstabilized and chelated, and unstabilized.

1. Introduction

In addition to this Symposium-In-Print, three recent review monographs on organolithium chemistry attest to the importance of organolithium species in organic synthesis.[1] One of the more versatile such classes is α-aminoorganolithium compounds, which often carry a stereogenic carbon attached to the lithium.[2] When a chiral organolithium is enantioenriched either by deprotonation, transmetalation of scalemic stannanes, or by dynamic resolution, excellent enantioselectivities may be achieved. If chiral organolithium species are to find use in asymmetric synthesis then the organolithium species must either be generated enantioselectively and not lose its configurational stability (and must quench stereoselectively with retention or inversion of configuration) or it must be amenable to resolution (preferably dynamic) in the presence of a chiral ligand. In both cases, it is important to have knowledge of the rate of racemization of the organolithium species in question. This will be influenced by a number of factors, including its structure, the solvent and the temperature. In addition, the relative rate of reaction with the electrophile can influence the selectivity.

One class of compounds that have found use in asymmetric synthesis is 2-lithiopyrrolidines, which readily undergo electrophilic substitutions,[3,4] transition metal transmetalation and coupling,[5] sigmatropic rearrangements,[6] anionic cyclizations,[7–9] and dynamic resolutions.[10] The mechanism and steric course of these processes depend to some degree on the rate of racemization and on the solution structure.



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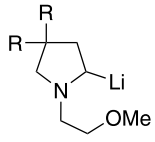
1b, R = Me



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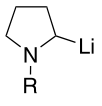
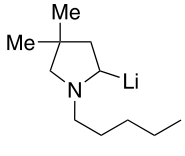


3a, R = Me
3b, R = Et



4

In a preliminary communication, the solution structure of ^{6}Li-**3a** was deduced using ^{6}Li and ^{13}C NMR spectroscopy.[11] After transmetalation of 2-(tributylstannyl)-*N*-methylpyrrolidine with Bu^{6}Li, a single peak was observed in the ^{6}Li NMR spectrum and a pentet ($\delta = 66.3$, $^1J = 6.8$ Hz) was observed in the ^{13}C NMR spectrum, the latter corresponding

Keywords: Organolithium; Lithiation; Tin–lithium exchange; Lithiopyrrolidine; NMR spectroscopy.
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to the carbanionic carbon atom. When the pyrrolidine was enriched with ^{13}C at C-2, a triplet was observed in the ^{6}Li spectrum. These results show that two lithium atoms are attached to the carbanionic carbon atom, and conversely, that two carbon atoms are attached to the lithium atoms. Figure 1 shows the partial ^{13}C and full ^{6}Li spectrum of unlabelled *rac*-**3a** and the ^{6}Li NMR spectrum of (*S*)-**3a** enriched at C2 in ^{13}C.

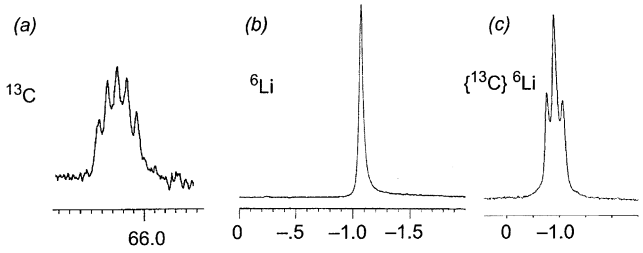
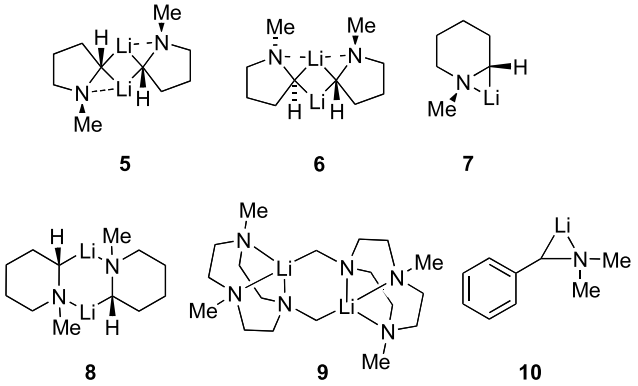
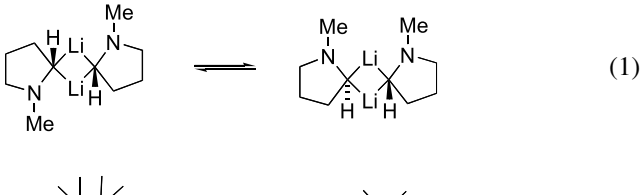


Figure 1. (a) Partial ^{13}C NMR and (b) ^{6}Li spectra of *rac*-^{6}Li-**3a**, 0.39 M in THF; (c) ^{6}Li spectrum of {^{13}C, ^{6}Li} (*S*)-**3a** (90:10 er, 0.39 M in THF; a ~0.05 M solution showed similar splitting). Temperature −100 °C.

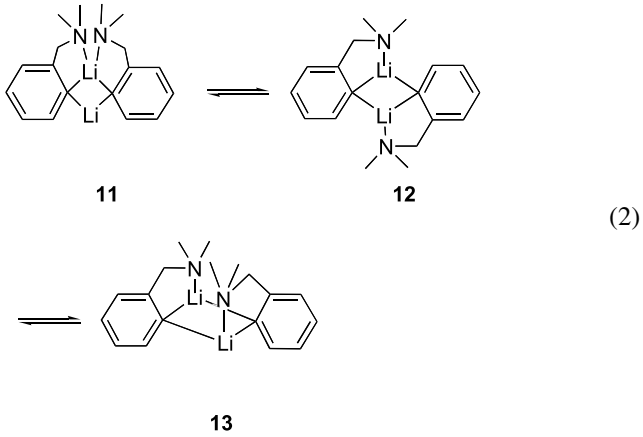
These data do not distinguish between a homochiral and a heterochiral dimer, but do indicate that, unless signals for the two dimers are coincidentally isochronous in both ^{13}C and ^{6}Li, both cannot be present (see below). If both heterochiral and homochiral dimers were energetically viable, a partly enantioenriched sample would show both. When the spectrum of ^{6}Li-**3a** of 90:10 er was recorded, only one ^{6}Li signal and one carbanionic carbon (a pentet) were observed. We therefore concluded that the dimer must be homochiral.[11] There are two possible homochiral dimeric structures that can be imagined for **3a**, namely **5** and **6**. Both have C_2 symmetry, and each should exhibit only one signal for the carbanionic carbon. However, since the two lithiums of **6** are nonequivalent, the conclusion was that **5** is the correct structure.[11] Note that the dashed lines between the lithiums and nitrogens indicate bonding that was not explicitly proven for **3a**, but was demonstrated in the homolog, 2-lithio-*N*-methylpiperidine **7**, which, we concluded, is monomeric. More recently, we found that the *N*-ethyl pyrrolidine **3b** may exist as a mixture of monomer and dimer.[12]



A referee has suggested that another structure for 2-lithio-*N*-methylpiperidine, that is also consistent with the observed ^{6}Li couplings to ^{13}C and ^{15}N, is **8**. Such a cyclic dimer is known in the solid state (**9**),[13] but this appears to be a rather special case where a triazacyclononane acts as a tridentate ligand and effectively competes with bridging of the lithium to the α-nitrogen. A more relevant example may be **10**, which shows lithium bridging to the nitrogen in the solid state.[14] Furthermore, note that the nitrogen atoms in both **7** and **8** are stereogenic. In the former, only one stereoisomer is possible due to the constraints of the 3/6 ring fusion. In the latter, four possible stereoisomers exist (epimeric at nitrogen only, not carbon), and one might reasonably expect to see more than one. However, only one set of signals was observed in the ^{6}Li, ^{15}N, and ^{13}C spectra, so we believe the conclusion is valid. The referee also noted that signals in the ^{13}C and ^{6}Li spectra of **5** and **6** might be coincidentally isochronous, or perhaps in equilibrium. Such an equilibrium might exist in the absence of Li–N bridging, by rotation of one heterocycle around the C···C axis of the C–Li–C–Li ring, as shown in Eq. 1. Such rotations are precedented.[15] A nitrogen-chelated example is shown in Eq. 2. Compound **11** has two nonequivalent lithiums, while in **12** and **13**, the two lithiums are equivalent. In this system, all three species could be observed in the ^{6}Li NMR spectrum at −135 °C. By −55 °C, all three had coalesced into a broad singlet. The *N*-ethyl analogs showed similar coalescence at temperatures around −100 °C. Note that the equilibrium between **12** and **13** involves loss of a solvent molecule (not shown), but rotation does not require breaking the N–Li bond. In contrast, if the lithium in **3a** is bridged to nitrogen as tentatively illustrated in **5**, such rotation would be expected to have a high barrier because it would entail breaking two N–Li bonds. Since we do not yet have evidence of lithium–nitrogen coordination in **3a**, structures such as those in Eq. 1 cannot be ruled out. At present, we are working under the hypothesis that **5** is the correct solution structure for **3a**. As we show below, unstabilized lithiopyrrolidines such as **3b** and **4** have much more complex solution behavior than does **3a**.



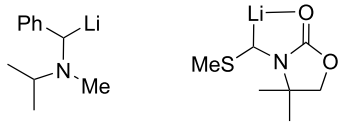
(1)



(2)

There are a number of methods by which configurational stability can be determined. These include using variable temperature NMR spectroscopy (with analysis of the coalescence of diastereotopic signals), using the Hoffmann test (as a qualitative measure by quenching with a chiral electrophile), or using electrophilic quench and analysis of

the enantiomer ratio of the products over different reaction times. In terms of gaining the most structural information, the use of NMR spectroscopy has considerable appeal. For example, benzylic α-aminoorganolithium **14** was studied by Ahlbrecht et al., and dipole stabilized organolithium **15** by Gaul et al.[16,17] Coalescence of the diastereotopic methyl groups of **14** occurred around 190 K and this equated to a barrier to inversion of about 9.0 kcal/mol at 190 K. This barrier increased slightly (to 10.0 or 10.5 kcal/mol) in the presence of the additives TMEDA or pentamethyldiethylenetriamine (PMDTA).[16] Line shape analysis of the coalescence of the H-5 signals of the lithiated *S*,*N*-acetal **15**, revealed activation parameters of $\Delta H^{\ddagger}=8.9\pm0.2$ kcal/mol and $\Delta S^{\ddagger}=-8.9\pm4.2$ cal/mol K ($\Delta G^{\ddagger}=10.8$ kcal/mol).[17]



14 **15**

It is clear from this discussion that some isolated information is known about the structures and the configurational stabilities of a few chiral α-amino-organolithium species. The importance of 2-lithiopyrrolidines in synthesis and our own studies in this area prompted us to compare a selection of *N*-substituted derivatives and to investigate their structures and relative stabilities. The *gem*-dimethyl compounds **1b**, **2b**, and **4** were prepared in the hope that DNMR could be used to evaluate their enantiomerization barriers. This was a reasonable expectation, since, in hexane–ether solvent mixtures, at least some *N*-alkyl lithiopyrrolidines are chemically stable at or near room temperature,[6,7] and dynamic resolution in the presence of a chiral ligand is possible at these temperatures.[10] However, such was not the case, and configurational stability had to be studied by aging, chemical trapping, and kinetic analysis of enantiomerization of **1a**, **2a**, and **3b**.[12] Herein we report details of our NMR spectral studies of three classes of ^{6}Li-labelled pyrrolidines: dipole stabilized **1a/b**, unstabilized and presumably chelated **2a/b**, and unstabilized **3b** and **4**.

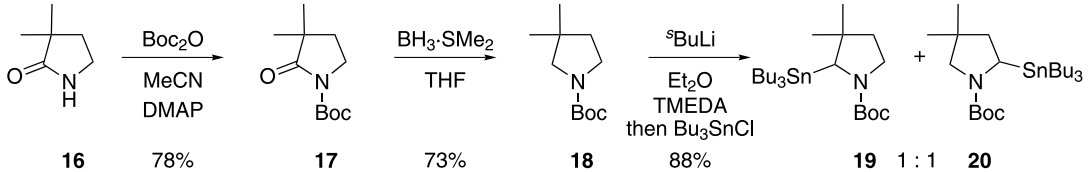
2. Results and discussion

We chose to study the structures of various *N*-substituted 2-lithiopyrrolidines by NMR spectroscopy. The *N*-substituted compounds **1**–**4** were selected to represent the different types of such compounds, containing coordinating carbonyl (**1**) or methoxy (**2**) groups, or non coordinating *n*-alkyl (**3**,**4**) groups.

In order to study these organolithiums by NMR, tin-lithium exchange from the corresponding 2-(tributylstannyl)-pyrrolidines was employed for their generation. These stannanes are typically prepared by deprotonation of *N*-Boc-pyrrolidine, addition of tributyltin chloride and replacement of the *N*-Boc substituent with another *N*-substituent as desired. We were interested to determine if this approach could be applied to the *gem*-dimethyl analog **18** (Scheme 1). This compound could undergo deprotonation with *sec*-BuLi at C-2 or at C-5 to give different regioisomeric products. The pyrrolidine **18** was prepared from the known lactam **16**.[18] Addition of Boc_2O gave imide **17**, which was reduced selectively to the pyrrolidine **18** using borane. No selectivity was obtained in the deprotonation of this compound under standard conditions (*sec*-BuLi, TMEDA) and an inseparable mixture of the stannylated products **19** and **20** was obtained. This lack of regioselectivity may be due to rotational restriction, and lithiation *syn* to the Boc carbonyl, as has been observed before.[19]

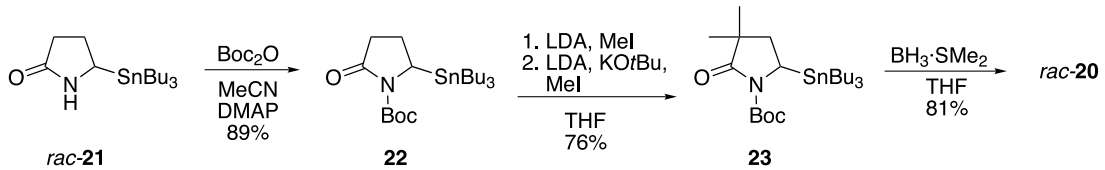
We therefore turned to an alternative route for the preparation of the dimethylpyrrolidines **1b**, **2b**, and **4**. The known lactam *rac*-**21**[20] was protected to give **22** and alkylated twice with iodomethane to give the lactam **23** (Scheme 2). The intermediate mono-methylated compound was used directly in the second methylation, which was found to be low-yielding using LDA but successful in the presence of potassium *tert*-butoxide (which is thought to give the base KDA[21]). Reduction of the lactam **23** with borane gave the desired pyrrolidine *rac*-**20**.

Deprotonation of the lactam **21** with sodium hydride and *N*-alkylation with bromopentane gave lactam **24** (Scheme 3). The base LDA was successful for both subsequent *C*-alkylations with iodomethane. The



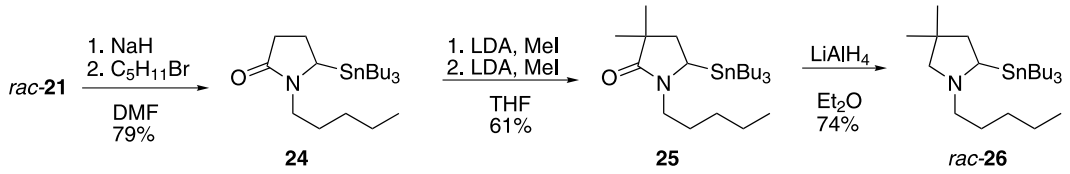
16 78% **17** 73% **18** 88% **19** 1 : 1 **20**

Scheme 1.



rac-**21** **22** **23**

Scheme 2.

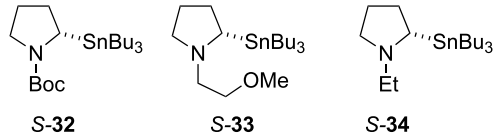


Scheme 3.

intermediate mono-methylated compound was found to be a single diastereomer and is likely to be the *trans* stereoisomer on the basis of related examples.[8,20,22] Reduction of the dialkylated lactam **25** to the pyrrolidine **26** was achieved using lithium aluminium hydride.

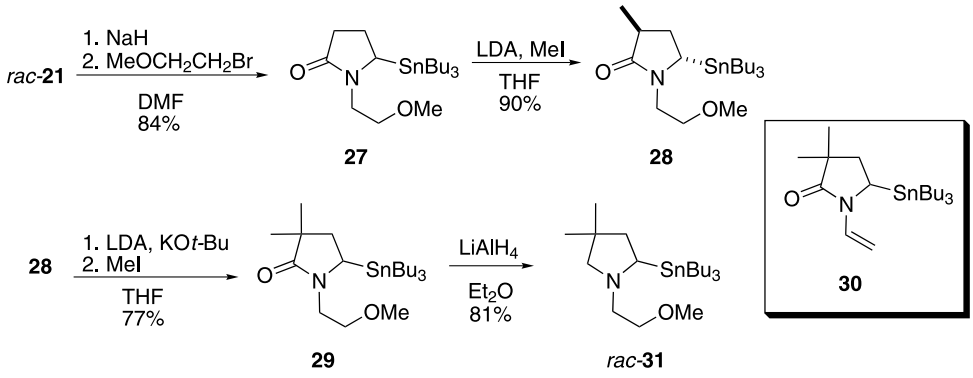
Alkylation of lactam **21** with bromoethyl methyl ether gave lactam **27** (Scheme 4). Mono-methylation gave **28** as a single diastereomer. Use of LDA as the base for the second methylation resulted in a mixture of products, including the desired compound **29** together with products such as **30**, resulting from deprotonation on the chain α- to the nitrogen atom and elimination of methanol. The base KDA however provided a good yield of the desired *gem*-dimethyl lactam **29** (together with **30**, 18%). Reduction of the lactam **29** gave the pyrrolidine **31**.

We now had the stannanes **20**, **26** and **31**, as well as the unsubstituted analogs that have previously been reported, *S*-**32**,[4] *S*-**33**,[23] and *S*-**34**[12] as precursors to the desired organolithium compounds **1**–**4**. The stannanes were treated with substoichiometric amounts of Bu^{6}Li in THF-d_8 at −80 °C in an NMR tube to give the organolithium species **1**–**4**.



2.1. Dipole-stabilized lithiopyrrolidines 1a,b (*N*-Boc)

The ^{6}Li and ^{13}C NMR spectra of the organolithium *S*-**1a** (95:5 er) in THF are shown in Figure 2. The lithium spectrum shows a single broad peak indicative of a species undergoing dynamic exchange of some sort. The carbon spectrum revealed only a single signal for the carbanionic carbon, but no coupling to ^{6}Li could be observed. The enantiomerization of **1a** is first order in organolithium, with a free energy barrier ($\Delta G^{\ddagger}$) of ~19–20 kcal/mol in ether and 4:1 hexane/ether solvent; in ether, $\Delta H^{\ddagger} = 19 \pm 3$ kcal/mol and $\Delta S^{\ddagger} = 40 \pm 8$ cal/mol K.[12] The proton NMR spectrum of lithiodimethylpyrrolidine **1b** is shown in Figure 3. At −20 °C, all the protons can be assigned, and there is no evidence of dynamic exchange of the *gem*-dimethyls. However, note that the broad AB quartet due to the H-5 protons at 2.72 ppm separates into a pair of doublets upon



Scheme 4.

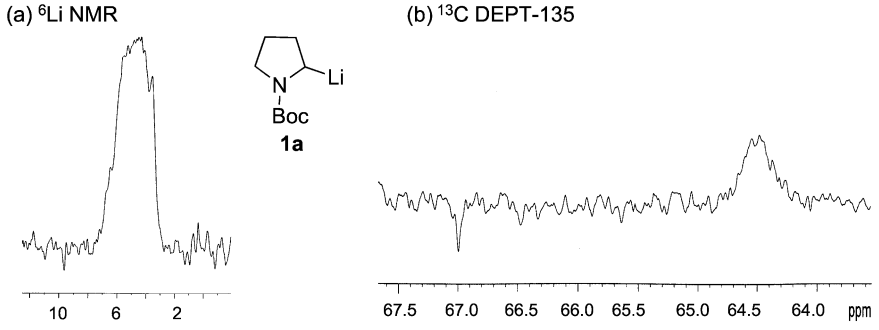


Figure 2. ^{6}Li and partial ^{13}C NMR spectra of *S*-**1a** in THF at −70 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal.

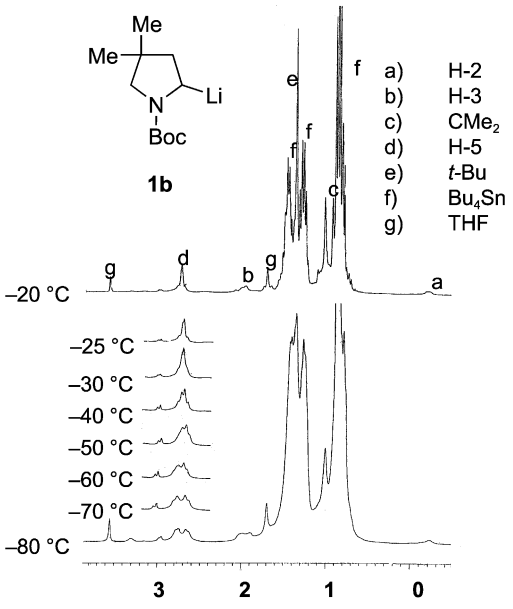


Figure 3. 300 MHz ^{1}H spectra of *rac*-**1b** in THF at varying temperatures.

cooling. At these temperatures, this dynamic phenomenon cannot be due to rotamers ($\Delta G^{\ddagger} \geq 15$ kcal/mol) or enantiomerization ($\Delta G^{\ddagger} = 20 \pm 3$ kcal/mol at -33 °C in ether or 4:1 hexane/ether[12]) as both would be slow on the NMR time scale. Instead, this may be an equilibrium between different aggregation states or, more probably, a solvation–desolvation phenomenon. The latter seems a more likely explanation since different aggregation states would be expected to show separate ^{6}Li signals at this temperature (see below). Although the ^{6}Li spectrum of **1b** was not recorded, the ^{6}Li spectrum of **1a** did show broadening indicative of a dynamic phenomenon, possibly of the same type as that observed in the proton spectrum **1b**. If this dynamic phenomenon is solvent exchange, it could be responsible for the large positive $\Delta S^{\ddagger}$ for enantiomerization of **1a**. Interestingly, Beak has reported that TMEDA accelerates the racemization of *S*-**1a** in ether, which could be due to a solvent/TMEDA exchange.[4,24]

2.2. Unstabilized, chelated lithiopyrrolidines 2a,b (*N*-methoxyethyl)

N-Methoxyethyl-2-lithiopyrrolidine *S*-**2a** ($\geq$95:5 er) showed one peak in its ^{6}Li spectrum, and a single signal in the carbanion region of the ^{13}C spectrum (Fig. 4). In the

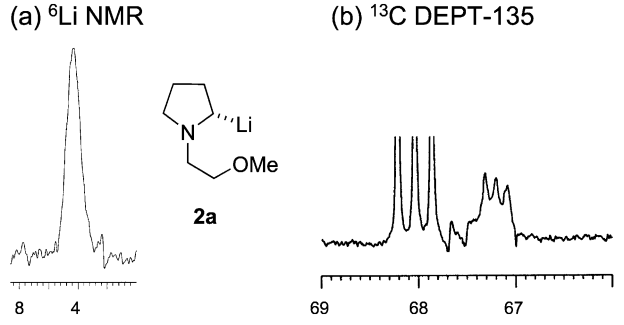


Figure 4. ^{6}Li and partial ^{13}C spectra of *S*-**2a** at -75 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal. The 1:1:1 triplet at 68.0 ppm is THF-d_7.

^{13}C spectrum, the signal is a 1:1:1 triplet, $\delta = 67.2$, $^{1}J\{^{13}C–^{6}Li\} = 14.4$ Hz, indicating a monomeric structure.[25] We did not anticipate observing coalescence due to enantiomerization on the NMR timescale, as *S*-**2a** is known to undergo racemization only slowly at -40 °C ($\Delta G^{\ddagger} = 20 \pm 3$ kcal/mol at 0 °C in THF or 4:1 hexane/ether).[12,23] The NMR spectrum of *rac*-**2b** showed one major peak in the ^{6}Li NMR spectrum, together with some minor signals, indicating that predominantly one species was present. The ^{13}C NMR spectrum of *rac*-**2b** did, however, give some useful information, revealing a triplet at $\delta = 68.2$, $^{1}J\{^{13}C–^{6}Li\} = 13.6$ Hz, corresponding to the carbon atom attached to the lithium atom (Fig. 5). In an experiment with a longer acquisition time, this signal lost its coupling information and appeared as an unresolved peak. No other signals were evident in this region. We infer that the major *rac*-**2b** species has only one lithium atom attached to the carbanionic carbon atom and is therefore likely to be a monomer in THF.[25] However, note that there are three possible monomeric structures that are consistent with this observation (**35**–**37**).

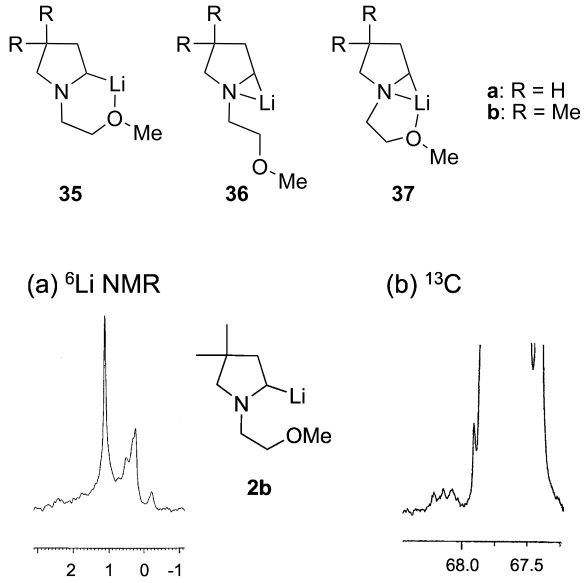


Figure 5. ^{6}Li and partial ^{13}C spectra of *rac*-**2b** at -80 °C in THF-d_8.

2.3. Unstabilized lithiopyrrolidines 3b, 4 (*N*-alkyl)

As reported elsewhere,[12] on one occasion we recorded a spectrum of *N*-ethyl-2-lithiopyrrolidine *S*-^{6}Li-**3b** in THF ($\geq$95:5 er) revealing two species in THF solution, one with a single attached lithium and one with two, probably monomeric and dimeric structures. At higher concentration (0.67 vs 0.27 M), as shown in Figure 6, four signals are discernable in the ^{6}Li NMR of *S*-**3b** ($\geq$95:5 er), as are four carbanionic carbons at 63.0, 64.1, 64.4, and 65.4 ppm. At this higher concentration, no monomer was detected. The signals at 63.0 and 64.1 ppm are clearly pentets indicative of dimers $^{1}J\{^{13}C–^{6}Li\} = 6.4$ and 6.8 Hz, respectively,[25] while the other two signals do not show resolved coupling. Also shown in Figure 6 are ^{6}Li and ^{13}C spectra of *S*-**3b** in the presence of one and two molar equivalents of PMDTA. Three of the four ^{6}Li signals appear to coalesce or merge, while a new 1:1:1 triplet appears near 69 ppm ($^{1}J\{^{13}C–^{6}Li\} = 14.2$ Hz), indicative of a monomer.[25]

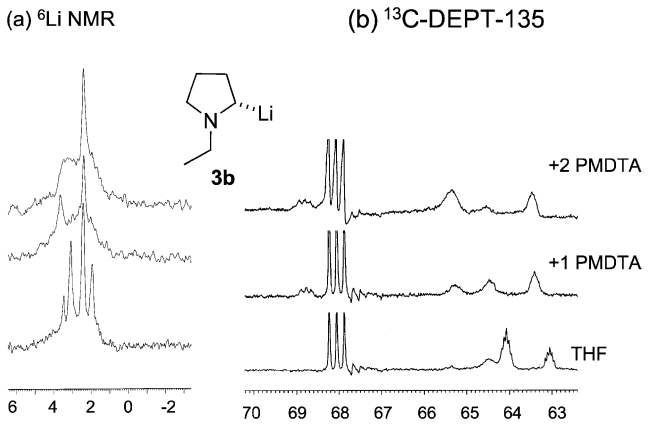
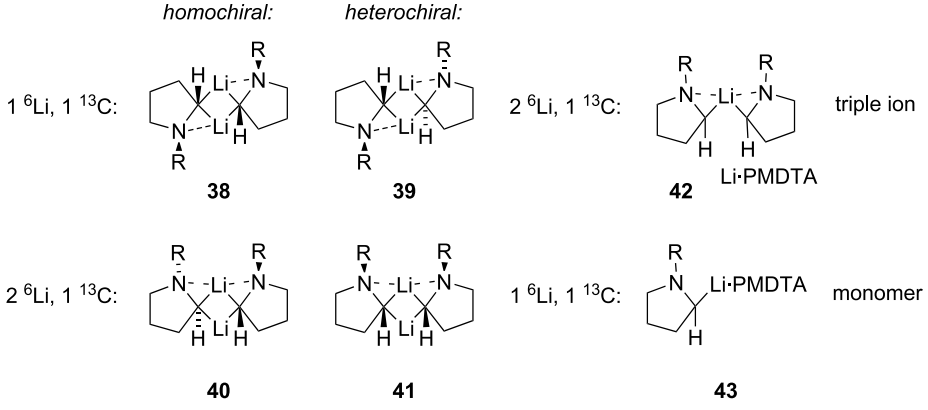


Figure 6. ^{6}Li and partial ^{13}C spectra of *S*-**3b** in the absence and presence of PMDTA at −75 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal. The 1:1:1 triplet at 68.0 ppm is THF-d_7.

Evident in the spectra recorded in the presence of PMDTA is a change in the relative ratios of the carbanionic species. In particular, the pentet at 64.1 ppm diminishes, while a peak at 65.0–65.2 ppm increases. Also, the upfield peak at 63.0 ppm loses its coupling information in the presence of PMDTA.

carbons, a pentet at $\delta = 65.4$, $^{1}J\{^{13}C–^{6}Li\} = 6.6$ Hz, and an unresolved peak at 63.7 of approximate equal intensity (Fig. 7). Thus, **4** exists in THF as a mixture of species, one of which is a dimer.

The unstabilized *N*-alkyl-2-lithiopyrrolidines show the greatest tendency toward structural diversity among the compounds studied. *N*-Methyl pyrrolidine *S*-**3a** or *rac*-**3a** appear to be homochiral dimers at 0.31–0.39 M in THF.[11] In contrast, *N*-ethyl pyrrolidine **3b** can exist as both a monomer and a dimer at 0.27 M. At higher concentrations, there is no evidence of monomeric *S*-**3b**, rather two distinct dimers and two other species are observed. Racemic **4** shows a dimeric structure as well as a second species. Structures **38**–**43** are possible monomers and dimeric aggregates. The dashed lines represent possible Li–N coordination. The number of lithium and carbon signals for each is indicated. For *S*-**3a**, the solution structure was established as **38** (R = Me; see also **5**), as described in Section 1.[11] Based on the similarity of chemical shifts, it is reasonable to assign a similar structure **38** (R = Et) to the *S*-**3b** dimer resonating at 63.0 or 64.1 ppm in the ^{13}C spectrum (Fig. 6). The other *S*-**3b** dimeric species (resonating at 63.0 or 64.1 ppm) may be **40** (R = Et). Together, these species would account for three of the four ^{6}Li resonances observed for **3b** (Fig. 6). In the



Transmetalation of the *N*-pentyl pyrrolidinylstannane *rac*-**26** with Bu^{6}Li in THF-d_8 gave the unstabilized organolithium *rac*-^{6}Li-**4**. The ^{6}Li NMR spectrum showed two large and several smaller signals, indicating several species in solution. The ^{13}C NMR spectrum showed two carbanionic

presence of PMDTA, a new signal appears at 69 ppm, in which only one ^{6}Li is in contact with the carbanionic carbon. In principle, this could be either triple ion **42** or monomer **43**, but since PMDTA is tridentate,[26] we assign it to monomer **43**. The unresolved resonance of **4** at 63.7 ppm

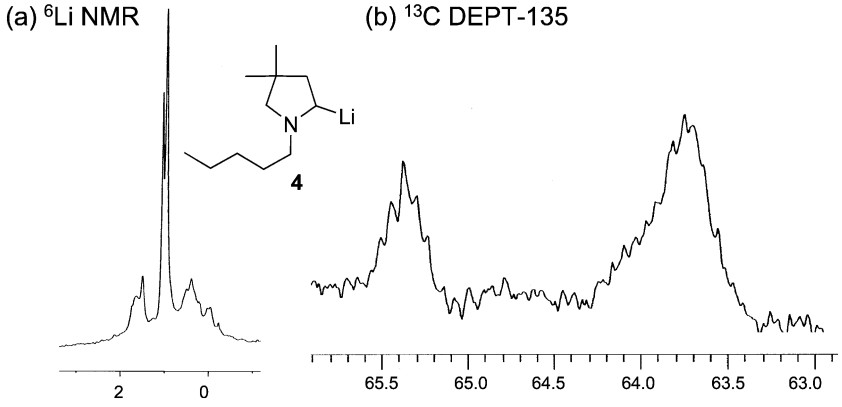


Figure 7. ^{6}Li and partial ^{13}C spectrum of *rac*-**4** at −75 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal.

(Fig. 7) has a chemical shift similar to the homochiral dimer of **3a**, so we assign it a similar structure, **38** (R=pentyl; dimethyls not shown). Based on the fact that there is only one other major ^{6}Li signal (Fig. 7), the signal resonating at 65.7 ppm is assigned to heterochiral dimer **39** (R=pentyl; dimethyls not shown).

In summary, we have shown that the solution structure of *N*-substituted-2-lithiopyrrolidines can vary from a single predominant species to a complex mixture of interconverting aggregates whose structure is influenced by a variety of effects, including chelation, enantiomer ratio, and concentration. It is interesting to note that, of the three structural types studied here and in a related work on the barrier to enantiomerization,[12] the class of lithiopyrrolidines with the most complex solution structure and the highest barrier to enantiomerization is also the only one that has been shown to undergo dynamic resolution in the presence of a chiral ligand.[10]

3. Experimental

3.1. General

NMR spectroscopy experiments with the organolithium species **1**–**4** were performed on 300, 400, or 500 MHz instruments. All manipulations were carried out under an argon atmosphere. Bu^{6}Li was prepared according to the procedure of Hilmersson and Davidsson,[27] as follows: ^{6}Li chunks (325 mg, 54.2 mmol) were cleaned with paper tissue, weighed, flattened between filter papers with a mallet, cut into thin strips, and contained under argon in a thick-walled tube with a rubber septum. Isopropanol (10 mL) was added and when the metal surface was clean, the solvent was removed by syringe. The lithium metal was washed four times with dry hexane, and then dry hexane (10 mL) was added followed by chlorobutane (2.83 mL, 27.1 mmol). The mixture was allowed to stand for 30 min, and then sonicated for 1 h. The mixture was allowed to stand overnight to settle. The clear solution of Bu^{6}Li was transferred by cannula to a flame-dried vacuum flask equipped with a vacuum tap and a magnetic stirrer bar. The solvent was removed carefully under high vacuum with vigorous stirring to give neat Bu^{6}Li as a viscous liquid determined to be ~8 M by titration. Samples in THF-d_8 were prepared either by addition of the neat Bu^{6}Li to a solution of the substrate in the NMR tube (the Bu^{6}Li solidified on the side of the tube and was carefully dissolved by intermittent removal of the tube from the cooling bath (−78 °C) and vigorous shaking for a few seconds), or by preparing the Bu^{6}Li solution in the NMR tube at low temperature in half of the solvent prior to addition of the substrate in the remainder of the solvent.

3.1.1. 1-*t*-Butoxycarbonyl-3,3-dimethyl-2-pyrrolidinone 17. To a solution of 3,3-dimethyl-2-pyrrolidinone **16**[18] (150 mg, 1.33 mmol) and Boc_2O (320 mg, 1.46 mmol) in MeCN (3.5 mL) was added 4-dimethylaminopyridine (DMAP) (7 mg, 0.06 mmol) at room temperature. After 16 h water (3 mL) and Et_2O (5 mL) were added and the organic phase was dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (50:1 to 10:1) gave the lactam **17** (222 mg, 78%) as an oil; R_f (petrol–EtOAc, 9:1) 0.15; ν_{max}(neat)/cm^{-1} 2975–2870 (C–H), 1780, 1750 and 1715 (C=O); δ_H(300 MHz, $CDCl_3$) 3.62 (2H, t, J=7 Hz, NCH_2), 1.81 (2H, t, J=7 Hz, NCH_2CH_2), 1.49 [9H, s, $C(CH_3)_3$], 1.15 [6H, s, $C(CH_3)_2$]; δ_C(75 MHz, $CDCl_3$) 179.0, 150.6, 82.7, 42.7, 42.2, 32.8, 28.0, 24.3; Found (ES) $[M+NH_4]^+$, 231.1710, $C_{11}H_{23}N_2O_3$ requires 231.1709; *m*/*z* (CI) 231 ($[M+NH_4]^+$, 5%), 175 (67), 131 (100) and 114 (92).

3.1.2. 1-*t*-Butoxycarbonyl-3,3-dimethyl-pyrrolidine 18. To a solution of the pyrrolidinone **17** (339 mg, 1.59 mmol) in THF (3 mL) was added $BH_3\cdot SMe_2$ (6.2 mL, 12.3 mmol, 2 M in THF) at room temperature. After 18 h MeOH (1 mL) was added dropwise with cooling, followed by water (3 mL) and $CHCl_3$ (10 mL). The aqueous phase was extracted with $CHCl_3$ (2×10 mL) and the organic phases were dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 10:1) gave the pyrrolidine **18** (232 mg, 73%) as an oil; R_f (petrol–EtOAc, 1:1) 0.70; ν_{max}(neat)/cm^{-1} 2965–2870 (C–H) and 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 3.36 and 3.30 (2×1H, t, J=7 Hz, NCH_2CH_2, rotamers), 3.02 and 2.96 (2×1H, s, NCH_2C, rotamers), 1.60–1.50 (2H, m, NCH_2CH_2), 1.40 [9H, s, $C(CH_3)_3$], 0.99 [6H, s, $C(CH_3)_2$]; δ_C (75 MHz, $CDCl_3$) 154.6, 154.5, 78.8, 78.7, 58.8, 58.2, 45.1, 44.8, 39.3, 38.5, 38.2, 37.4, 28.5, 26.1; Found (EI) M^+, 199.1571, $C_{11}H_{21}NO_2$ requires 199.1572; *m*/*z* (EI) 199 (M^+, 9%) and 57 (100).

3.1.3. 1-*t*-Butoxycarbonyl-4,4-dimethyl-2-tributylstannyl-pyrrolidine and 1-*t*-Butoxycarbonyl-3,3-dimethyl-2-tributylstannyl-pyrrolidine, 19 and 20. To a solution of TMEDA (0.21 mL, 1.40 mmol) and the pyrrolidine **12** (232 mg, 1.17 mmol) in Et_2O (10 mL) at −78 °C was added ^{s}BuLi (1.08 mL, 1.40 mmol, 1.3 M in cyclohexane). After 6 h Bu_3SnCl (0.48 mL, 1.8 mmol) was added and the mixture was allowed to warm to room temperature. Water (5 mL) and petrol (10 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 20:1) gave stannanes **19** and **20** (503 mg, 88%) as an inseparable mixture (1:1), as an oil; R_f (petrol–EtOAc, 9:1) 0.55; ν_{max}(neat)/cm^{-1} 2965–2855 (C–H) and 1685 (C=O); δ_H(400 MHz, $CDCl_3$) 3.62–3.51 (0.6H, m, NCH), 3.46–3.35 (1.8H, m, NCH), 3.30–3.20 (1H, m, NCH), 3.16–3.09 (1.6H, m, NCH), 2.89 (1H, d, J=10.5 Hz, NCH), 1.78–1.20 [46H, m, $NCH(Sn)CH_2$, NCH_2CH_2, $C(CH_3)_3$ and $Sn(CH_2CH_2CH_2)_3$], 1.14–0.75 [42H, m, $CH_2C(CH_3)_2$ and $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 154.4, 154.3, 78.4, 78.3, 60.3, 59.4, 45.5, 45.2, 44.3, 41.5, 41.4, 39.0, 29.2, 28.6, 28.5, 27.7, 27.6, 26.7, 26.5, 26.1, 25.7, 13.8, 13.7, 11.7, 10.1.

3.1.4. 1-*t*-Butoxycarbonyl-5-tributylstannyl-2-pyrrolidinone 22. To a solution of 5-tributylstannyl-2-pyrrolidinone **21**[20] (368 mg, 0.98 mmol) and Boc_2O (235 mg, 1.08 mmol) in MeCN (2.5 mL) and CH_2Cl_2 (0.5 mL) was added DMAP (6 mg, 0.05 mmol) at room temperature. After 16 h water (3 mL) and petrol (5 mL) were added and the organic phase was dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc

(50:1 to 20:1) gave the stannane **22** (413 mg, 89%) as an oil; R_f (petrol–EtOAc, 9:1) 0.40; ν_{max}(neat)/cm^{-1} 2960–2860 (C–H), 1755 and 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 3.84 (1H, dd, J=8.5, 7 Hz, NCH), 2.60–2.20 (3H, m, CH^AH^{B}CH_2CO), 2.09–1.96 (1H, m, CH^AH^BCH$_2$CO), 1.60–1.38 [15H, m, C$(CH_3)_3$ and Sn$(CH_2CH_2CH_2)_3$], 1.31 [6H, sextet, J=7 Hz, Sn$(CH_2CH_2CH_2)_3$], 1.02–0.80 [15H, m, Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 174.3, 151.6, 82.7, 47.8, 35.0, 29.0, 28.1, 27.5, 23.5, 13.7, 9.8; Found (ES) [M+H]$^+$, 476.2183, $C_{21}H_{42}NO_3^{120}Sn$ requires 476.2186; *m/z* (ES) 476 ([M+H]$^+$, 12%), 498 ([M+Na]$^+$, 100).

3.1.5. 1-*t*-Butoxycarbonyl-3,3-dimethyl-5-tributylstannyl-2-pyrrolidinone 23. To a solution of ^{i}Pr$_2$NH (89 μL, 0.74 mmol) in THF (1.5 mL) at 0 °C was added ^{n}BuLi (0.3 mL, 0.74 mmol, 2.5 M in hexanes). After 30 min the mixture was cooled to −78 °C and transferred via cannula to a −78 °C solution of lactam **22** (270 mg, 0.57 mmol) in THF (1.5 mL). After 20 min, MeI (0.1 mL, 1.6 mmol) was added and stirring was continued for 1 h at −78 °C. After warming to room temperature, water (2 mL) and hexane (10 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 10:1) gave the mono-methylated lactam (230 mg, 83%) as an oil, which was used directly in the second methylation:

To a solution of ^{i}Pr$_2$NH (75 μL, 0.63 mmol) and KO^{t}Bu (72 mg, 0.63 mmol) in THF (2 mL) at −78 °C was added ^{n}BuLi (0.25 mL, 0.63 mmol, 2.5 M in hexanes). After 10 min the mixture was transferred via cannula to a precooled (−78 °C) solution of the mono-methylated lactam (230 mg, 0.47 mmol) in THF (2 mL). After 10 min, MeI (0.25 mL, 4.0 mmol) was added and the mixture was allowed to warm to room temperature over 1 h. Water (5 mL) and petrol (40 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 50:1) gave the lactam **23** (215 mg, 91%) as an oil; R_f (petrol–EtOAc, 9:1) 0.42; ν_{max}(neat)/cm^{-1} 2965–2860 (C–H), 1755 and 1695 (C=O); δ_H (300 MHz, $CDCl_3$) 3.62 (1H, dd, J=10.5, 7.5 Hz, NCH), 2.03–1.83 (2H, m, NCHCH_2), 1.60–1.38 [15H, m, C$(CH_3)_3$ and Sn$(CH_2CH_2CH_2)_3$], 1.31 [6H, sx, J=7 Hz, Sn$(CH_2CH_2CH_2)_3$], 1.17 (3H, s, CH_3CCO), 1.15 (3H, s, CH_3CCO), 1.00–0.78 [15H, m, Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 179.3, 152.2, 82.7, 43.3, 42.6, 38.4, 29.1, 28.0, 27.5, 24.8, 23.5, 13.7, 10.0; Found (ES) [M+H]$^+$, 504.2490, $C_{23}H_{46}NO_3^{120}Sn$ requires 504.2499; *m/z* (ES) 504 ([M+H]$^+$, 17%), 526 ([M+Na]$^+$, 60) and 549 ([M+2Na]$^+$, 100).

3.1.6. 1-*t*-Butoxycarbonyl-4,4-dimethyl-2-tributylstannyl-pyrrolidine 20. In the same way as lactam **17**, the lactam **23** (100 mg, 0.20 mmol) and BH_3·DMS (0.40 mL, 0.80 mmol, 2 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (50:1) the pyrrolidine **20** (79 mg, 81%) as an oil; R_f (petrol–EtOAc, 9:1) 0.55; ν_{max}(neat)/cm^{-1} 2960–2855 (C–H), 1680 (C=O); δ_H(300 MHz, $CDCl_3$) 3.43 (1H, dd, J=11, 8 Hz, NCHSn), 3.12 (1H, d, J=10.5 Hz NCH^AH^B), 2.88 (1H, d, J=10.5 Hz, NCH^AH^B), 1.80–1.62 [2H, m, NCH(Sn)CH_2], 1.60–1.37 [15H, m, C$(CH_3)_3$ and Sn$(CH_2CH_2CH_2)_3$], 1.29 [6H, sextet, J=7 Hz, Sn$(CH_2CH_2CH_2)_3$], 1.08 (3H, s, NCH_2CCH_3), 1.01 (3H, s, NCH_2CCH_3), 0.96–0.74 [15H, m, Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 154.3, 78.4, 59.4, 45.2, 44.3, 39.0, 29.2, 28.6, 28.5, 27.6, 26.5, 25.7, 13.8, 10.1; Found (FI) M$^+$, 489.2626, $C_{23}H_{47}NO_2^{120}Sn$ requires 489.2629; *m/z* (FI) 489 (M$^+$, 64%), 432 (100).

3.1.7. 1-Pentyl-5-tributylstannyl-2-pyrrolidinone 24. To a solution of lactam **21**[20] (430 mg, 1.15 mmol) in DMF (4 mL) at room temperature was added NaH (93 mg, 2.3 mmol, 60% in mineral oil) in one portion, and after 30 min, bromopentane (435 mg, 0.36 mL, 2.9 mmol) was added. After 2 h water (2 mL) and hexane (10 mL) were added and the organic phase was separated, washed with water (4×2 mL), dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 4:1) gave the lactam **24** (402 mg, 79%) as an oil; R_f (petrol–EtOAc, 1:1) 0.80; ν_{max}(neat)/cm^{-1} 2965–2855 (C–H), 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 3.86 (1H, ddd, J=13.5, 8.5, 7.5 Hz, NCH^AH^B), 3.66 (1H, dd, J=8.0, 5.5 Hz, NCHSn), 2.54 (1H, ddd, J=13.5, 8.5, 4.5 Hz, NCH^AH^B), 2.44–2.24 (3H, m, NCOCH_2CH^CH^D), 2.08–2.01 (1H, m, NCOCH$_2$CH^CH^D), 1.65–1.20 [18H, m, NCH$_2$CH_2CH_2CH_2 and Sn$(CH_2CH_2CH_2)_3$], 0.99–0.84 [18H, m, N$(CH_2)_4CH_3$ and Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 174.1, 48.2, 43.1, 32.3, 29.1, 29.0, 27.5, 27.2, 24.0, 22.5, 14.0, 13.6, 9.2; Found (ES) [M+H]$^+$, 446.2441, $C_{21}H_{44}NO^{120}Sn$ requires 446.2445; *m/z* (CI) 446 ([M+H]$^+$, 9%), 154 (100).

3.1.8. 1-Pentyl-3,3-dimethyl-5-tributylstannyl-2-pyrrolidinone 25. In the same way as lactam **23**, ^{i}Pr$_2$NH (0.14 mL, 1.14 mmol), BuLi (1.0 mL, 1.14 mmol, 1.15 M in hexanes), the lactam **24** (338 mg, 0.76 mmol) and MeI (0.12 mL, 1.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 4:1), the mono-methylated lactam (427 mg, 82%) as an oil; R_f (petrol–EtOAc, 1:1) 0.72; ν_{max}(neat)/cm^{-1} 2970–2860 (C–H), 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 3.86 (1H, dt, J=13.5, 8.5 Hz, NCH^AH^B), 3.59 (1H, dd, J=9.5, 3.5 Hz, NCHSn), 2.54 (1H, ddd, J=13.5, 8.5, 4.5 Hz, NCH^AH^B), 2.36–2.24 [2H, m, NCOCH(CH$_3$)CH^CH^D], 1.98–1.90 [1H, m, NCOCH(CH$_3$)CH^CH^D], 1.55–1.38 [8H, m, NCH$_2$CH_2 and Sn$(CH_2CH_2CH_2)_3$], 1.38–1.22 [10H, m, NCH$_2$CH$_2$CH_2CH_2 and Sn$(CH_2CH_2CH_2)_3$], 1.20 (3H, d, J=6.5 Hz, NCOCHCH_3), 0.98–0.82 [18H, m, N$(CH_2)_4CH_3$ and Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 175.9, 46.0, 43.0, 37.7, 33.0, 29.1, 29.0, 27.5, 27.1, 22.4, 16.0, 14.0, 13.7, 9.4; Found (ES) [M+H]$^+$, 460.2604, $C_{22}H_{46}NO^{120}Sn$ requires 460.2601; *m/z* (CI) 460 ([M+H]$^+$, 8%), 168 (100), which was used in the second methylation:

In the same way as above, the mono-methylated lactam (155 mg, 0.34 mmol), ^{i}Pr$_2$NH (61 μL, 0.51 mmol), ^{n}BuLi (0.20 mL, 0.51 mmol, 2.5 M in hexanes) and MeI (50 μL, 0.80 mmol) gave the lactam **25** (119 mg, 74%) as an oil; R_f (petrol–EtOAc, 1:1) 0.67; ν_{max}(neat)/cm^{-1} 2960–2860 (C–H), 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 3.88 (1H, ddd, J=13.5, 9, 7.5 Hz, NCH^AH^B), 3.57 (1H, dd, J=10, 7 Hz, NCHSn), 2.57 (1H, ddd, J=13.5, 9, 5 Hz, NCH^AH^B),

2.08–1.89 [2H, m, NCH(Sn)CH_2], 1.58–1.20 [18H, m, NCH_2CH_2CH_2CH_2 and Sn(CH_2CH_2CH_2)$_3$], 1.15 (3H, s, NCOCCH_3), 1.09 (3H, s, NCOCCH_3), 1.00–0.84 [18H, m, N(CH_2)$_4$CH_3 and Sn(CH_2CH_2CH_2CH_3)$_3$]; δ_C(100 MHz, $CDCl_3$) 179.3, 43.7, 43.6, 40.8, 39.9, 29.2, 28.9, 27.4, 27.0, 25.0, 23.6, 22.4, 14.0, 13.6, 9.0; Found (ES) $[M+H]^+$, 474.2753, $C_{23}H_{48}NO^{120}Sn$ requires 474.2758; *m/z* (CI) 474 ($[M+H]^+$, 8%), 182 (100).

3.1.9. 1-Pentyl-4,4-dimethyl-2-tributylstannyl-pyrrolidine 26. To a suspension of $LiAlH_4$ (15 mg, 0.39 mmol) in Et_2O (0.5 mL) at 0 °C was added the lactam **25** (45 mg, 0.10 mmol) in Et_2O (1 mL). The mixture was warmed to room temperature, and after 1 h, re-cooled to 0 °C, quenched with MeOH (1 mL) and absorbed onto basic alumina. Purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (100:1 to 20:1) gave the pyrrolidine **26** (33 mg, 74%) as an oil; R_f (petrol–EtOAc, 1:1) 0.25; ν_{max}(neat)/cm^{-1} 2970–2780 (C–H); δ_H(400 MHz, C_6D_6) 2.97–2.88 (2H, m, NCH^AH^{B}CH$_2$ and NCH^CH^{D}CCH$_3$), 2.74 (1H, dd, J=10.5, 8.5 Hz, NCHSn), 2.17 (1H, ddd, J=12, 8.5, 4.5 Hz, NCH^AH^BCH$_2$), 1.94–1.38 [21H, m, NCH^CH^DC(CH$_3$)CH_2, NCH$_2$CH_2CH_2-CH_2 and Sn(CH$_2$CH_2CH_2)$_3$], 1.26 (3H, s, CCH$_3$), 1.17–0.98 [21H, m, CCH$_3$, N(CH$_2$)$_4$CH_3 and Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(100 MHz, C_6D_6) 69.1, 58.0, 57.1, 45.8, 38.6, 30.6, 30.0, 29.6, 29.0, 28.8, 27.8, 22.9, 14.1, 13.7, 9.2; Found (ES) $[M+H]^+$, 460.2966, $C_{23}H_{50}N^{120}Sn$ requires 460.2965; *m/z* (CI) 460 ($[M+H]^+$, 1%), 170 (100).

3.1.10. 1-(2-Methoxy-ethyl)-5-tributylstannyl-2-pyrrolidinone 27. In the same way as lactam **24**, lactam **21** (1.40 g, 3.74 mmol), DMF (13 mL), NaH (302 mg, 7.48 mmol, 60% in mineral oil) and bromoethylmethylether (1.3 g, 0.88 mL, 9.4 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 1:1) the lactam **27** (1.36 g, 84%) as an oil; R_f (EtOAc) 0.45; ν_{max}(neat)/cm^{-1} 2965–2855 (C–H), 1685 (C=O); δ_H(300 MHz, C_6D_6) 4.02 (1H, dt, J=14.5, 6.0 Hz, CH), 3.77 (1H, t, J=6.5 Hz, CH), 3.56–3.40 (2H, m, 2×CH), 3.30 (3H, s, OCH$_3$), 2.80–2.70 (1H, m, CH), 2.45–2.00 (4H, m, CH$_2$CH$_2$CO), 1.56–1.40 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.30 [6H, sextet, J=7.5 Hz, Sn(CH$_2$CH$_2$CH_2)$_3$], 0.98–0.79 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(75 MHz, C_6D_6) 173.6, 71.4, 58.4, 50.0, 43.5, 32.0, 29.5, 27.8, 24.5, 13.8, 9.5; Found (FI) M^+, 433.1997, $C_{19}H_{39}NO_2^{120}Sn$ requires 433.2003; *m/z* (FI) 433 (M^+, 100%).

3.1.11. 1-(2-Methoxy-ethyl)-3-methyl-5-tributylstannyl-2-pyrrolidinone 28. In the same way as lactam **23**, the lactam **27** (170 mg, 0.39 mmol), ^{i}Pr$_2$NH (68 μL, 0.57 mmol), ^{n}BuLi (0.49 mL, 0.57 mmol, 1.15 M in hexanes) and MeI (60 μL, 0.96 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (10:1 to 4:1), the lactam **28** (158 mg, 90%) as an oil; R_f (petrol–EtOAc, 1:1) 0.55; ν_{max}(neat)/cm^{-1} 2960–2855 (C–H), 1685 (C=O); δ_H(300 MHz, C_6D_6) 4.25–4.10 (1H, dt, J=14, 5 Hz, CH), 3.74 (1H, dd, J=9, 3 Hz, NCHSn), 3.38–3.21 (2H, m, 2×CH), 3.01 (3H, s, OCH$_3$), 2.75 (1H, ddd, J=14.5, 7, 4 Hz, CH), 2.34–2.21 (2H, m, NCHCH^AH^{B}CH), 1.92–1.76 (1H, m, NCHCH^AH^BCH), 1.55–1.34 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.29 [6H, sextet, J=7.5 Hz, Sn(CH$_2$CH$_2$CH_2)$_3$], 1.18 (3H, d, J=6.5 Hz, NCOCHCH_3), 1.00–0.78 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(75 MHz, C_6D_6) 175.6, 71.8, 58.5, 48.2, 43.6, 37.6, 33.7, 29.6, 27.9, 16.3, 14.0, 9.9; Found (CI) $[M+H]^+$, 448.2234, $C_{20}H_{42}NO_2^{120}Sn$ requires 448.2238; *m/z* (CI) 448 ($[M+H]^+$, 24%), 156 (100).

3.1.12. 1-(2-Methoxy-ethyl)-3,3-dimethyl-5-tributylstannyl-2-pyrrolidinone 29 and 3,3-dimethyl-5-tributylstannyl-1-vinyl-2-pyrrolidinone 30. To a solution of ^{i}Pr$_2$NH (81 μL, 0.68 mmol) and KO^{t}Bu (77 mg, 0.68 mmol) in THF (3 mL) at −78 °C was added ^{n}BuLi (0.27 mL, 0.68 mmol, 2.5 M in hexanes). After 10 min a precooled (−78 °C) solution of the lactam **28** (200 mg, 0.45 mmol) in THF (3 mL) was added dropwise via cannula. The mixture was warmed to −40 °C and after 1 h, MeI (0.10 mL, 1.6 mmol) was added and the mixture was allowed to warm to room temperature. Water (5 mL) and petrol (20 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 4:1) gave the lactam **29** (159 mg, 77%) as an oil, R_f (petrol–EtOAc, 1:1) 0.65; ν_{max}(neat)/cm^{-1} 2960–2860 (C–H), 1685 (C=O); δ_H(300 MHz, C_6D_6) 4.26 (1H, dt, J=14, 5 Hz, CH), 3.76 (1H, t, J=8.5 Hz, NCHSn), 3.45–3.28 (2H, m, 2×CH), 3.08 (3H, s, OCH$_3$), 2.84 (1H, ddd, J=12, 7, 5 Hz, CH), 2.04–1.85 [2H, m, NCH(Sn)CH_2], 1.72–1.49 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.41 [6H, sextet, J=7.5 Hz, Sn(CH$_2$CH$_2$-CH_2)$_3$], 1.33 (3H, s, COCCH$_3$), 1.20 (3H, s, COCCH$_3$), 1.06–0.92 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(75 MHz, C_6D_6) 179.1, 71.1, 58.5, 45.8, 44.2, 40.9, 40.7, 29.6, 28.0, 25.5, 23.9, 14.0, 9.4; Found (CI) $[M+H]^+$, 462.2392, $C_{21}H_{44}NO_2^{120}Sn$ requires 462.2394; *m/z* (CI) 462 ($[M+H]^+$, 19%), 170 (100); and the lactam **30** (35 mg, 18%) as an oil; R_f (petrol–EtOAc, 9:1) 0.38; ν_{max}(neat)/cm^{-1} 2965–2860 (C–H), 1705 (C=O), 1625 (C=C); δ_H(400 MHz, C_6D_6) 7.49 (1H, dd, J=15.5, 8.5 Hz, NCH=), 4.30 (1H, d, J=8.5 Hz, NCH=CH^AH^B), 4.17 (1H, d, J=15.5 Hz, NCH=CH^AH^B), 3.37 (1H, dd, J=8, 7 Hz, NCHSn), 1.95–1.80 [2H, m, NCH(Sn)CH_2], 1.57–1.45 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.33 [6H, sextet, J=7 Hz, Sn(CH$_2$CH$_2$-CH_2)$_3$], 1.15 (3H, s, NCOCCH$_3$), 1.09 (3H, s, NCOCCH$_3$), 0.98–0.85 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(100 MHz, C_6D_6) 177.3, 130.7, 93.2, 41.8, 40.8, 38.3, 29.2, 27.6, 25.2, 24.5, 13.6, 10.4; Found (CI) $[M+H]^+$, 430.2134, $C_{20}H_{40}NO^{120}Sn$ requires 430.2132; *m/z* (CI) 430 ($[M+H]^+$, 100%).

3.1.13. 1-(2-Methoxy-ethyl)-4,4-dimethyl-2-tributylstannylpyrrolidine 31. To a suspension of $LiAlH_4$ (35 mg, 0.91 mmol) in Et_2O (1 mL) at 0 °C was added the lactam **29** (75 mg, 0.16 mmol) in Et_2O (1 mL). After 40 min at 0 °C MeOH (1 mL) was added and the mixture was absorbed onto basic alumina. Purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (50:1 to 10:1) gave the pyrrolidine **31** (58 mg, 81%) as an oil; R_f (petrol–EtOAc, 1:1) 0.20; ν_{max}(neat)/cm^{-1} 2960–2770 (C–H); δ_H(400 MHz, C_6D_6) 3.44 (2H, t, J=6 Hz, OCH$_2$), 3.17 (3H, s, OCH$_3$), 3.11 (1H, dt, J=12, 6 Hz, NCH^AH^{B}CH$_2$), 2.87 (1H, d, J=8.5 Hz, NCH^CH^{D}CCH$_3$), 2.67 (1H, dd, J=9.5, 8 Hz, NCHSn), 2.38 (1H, dt, J=12, 6 Hz, NCH^AH^BCH$_2$), 1.82–1.59 [9H, m, NCH^CH^DC(CH$_3$)-CH_2 and Sn(CH$_2$CH_2)$_3$], 1.43 [6H, sx, J=7 Hz, Sn(CH$_2$-CH$_2$CH_2)$_3$], 1.18 (3H, s, CCH$_3$) 1.08–1.03 [9H, m, CCH$_3$

and $Sn(CH_2)_3$], 0.96 [9H, t, $J=7$ Hz, $Sn(CH_2(CH_2)_2CH_3)_3$]; δ_C(100 MHz, C_6D_6) 72.6, 70.4, 58.8, 58.4, 56.8, 46.0, 39.4, 30.9, 30.0, 29.1, 28.2, 14.2, 9.5; Found (CI) $[M+H]^+$, 448.2611, $C_{21}H_{46}NO^{120}Sn$ requires 448.2601; *m/z* (CI) 448 ($[M+H]^+$, 4%), 156 (100).

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Enantioselective, (−)-sparteine-mediated deprotonation of geranyl and neryl *N*,*N*-diisopropylcarbamate: configurational stability of the intermediate lithium compounds

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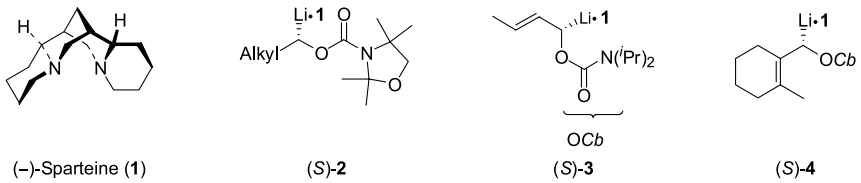
Abstract—(*E*)/(*Z*)-Isomeric allylic carbamate esters were deprotonated by *n*-butyllithium/(−)-sparteine in toluene. Trapping experiments with chlorotrimethylsilane afforded the α-substitution products, with (*R*)-configuration, revealing that the *pro-S* proton is removed predominantly to form the corresponding (*S*)-lithium·(−)-sparteine derivatives; $k_S/k_R > 15{:}1$ and $>7{:}1$, respectively. A slow (*S*)→(*R*)-epimerization occurs at −78 °C ($T_{1/2} > 60$ min). The allylic double bond is stable to (*Z*)–(*E*) isomerization under these conditions.

1. Introduction

Chiral carbanionic species play an important role in modern stereoselective synthesis.[1] In particular, the (−)-sparteine-mediated deprotonation of suitable substrates provides an efficient, rapid access to enantioenriched lithium intermediates.[2] As we found several years ago, *O*-alkyl-,[3] *O*-2-alkenyl-,[4] *O*-benzyl-,[5] and *O*-2-alkynyl[6] carbamates react with *n*-butyl- or *s*-butyllithium/(−)-sparteine (**1**) with preferential abstraction of the *pro-S*-proton (Fig. 1). The method was extended by Beak et al. to several *N*-carbamates[7] and benzylic compounds.[2b] The lithium complexes (*S*)-**2**, formed from alkyl carbamates at −78 °C with selectivities (*S*)/(*R*) between 50 to 100:1, are configurationally stable below −70 °C and react with all electrophiles with complete retention of the configuration.[3] However, the epimeric ion pairs (*S*) and (*R*)-**3** of the lithiated crotyl carbamate turned out to be configurationally unstable even in pentane solution at −78 °C. In the presence of cyclohexane, a selective crystallization of complex (*S*)-**3** takes place. As a consequence of the dynamic thermodynamic resolution[8] nearly all of the material is converted into (*S*)-**3**.[4] It can be transformed stereospecifically via metal exchange with complete stereoinversion to the corresponding tris(isopropoxy)-titanium intermediate. On the other hand, the trisubstituted cyclic allyllithium derivative (*S*)-**4** undergoes epimerization only very slowly ($T_{1/2} > 10$ h at −78 °C), rendering (*S*)-**4** and related lithium intermediates synthetically very useful.[9]

Although the mechanism of the epimerization is not known yet, it became clear that a high degree of substitution at the allylic moiety and, usually, a secondary carbanionic center support high configurational stability. Further information on the configurational behaviour of the lithiated 2-alkenyl carbamates is required. Unfortunately, the system is not suitable for NMR investigation at low temperature, although these (−)-sparteine complexes are monomeric even in the



(–)-Sparteine (**1**) (*S*)-**2** (*S*)-**3** (*S*)-**4**

Figure 1.

Keywords: (−)-Sparteine; Allyllithium; Asymmetric deprotonation; Stereoselectivity.
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† X-ray structure analysis.

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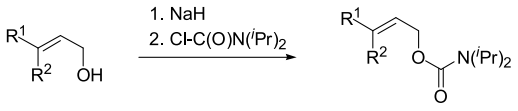
solid (for a representative X-ray structure analysis see Ref. 10), line broadenings and splittings of the *N*,*N*-diisopropylcarbamoyl group, due to slow rotation and diastereotopicity, hamper NMR investigation severely.[11]

We have now studied the *E*/*Z*-isomers geranyl- and neryl *N*,*N*-diisopropylcarbamate [(*E*)- and (*Z*)-**6**], which both were prepared by our standard procedure from the pure alcohols (*E*)- and (*Z*)-**5** (Scheme 1), by applying lithiation and trapping experiments. The results are presented herein.



(*E*)-**5**, (*E*)-**6**: R^1=$(CH_3)_2CCH(CH_2)_2$-, R^2=CH_3, yield: 76%
(*Z*)-**5**, (*Z*)-**6**: R^1=CH_3, R^2=$(CH_3)_2CCH(CH_2)_2$-, yield: 76%

Scheme 1.

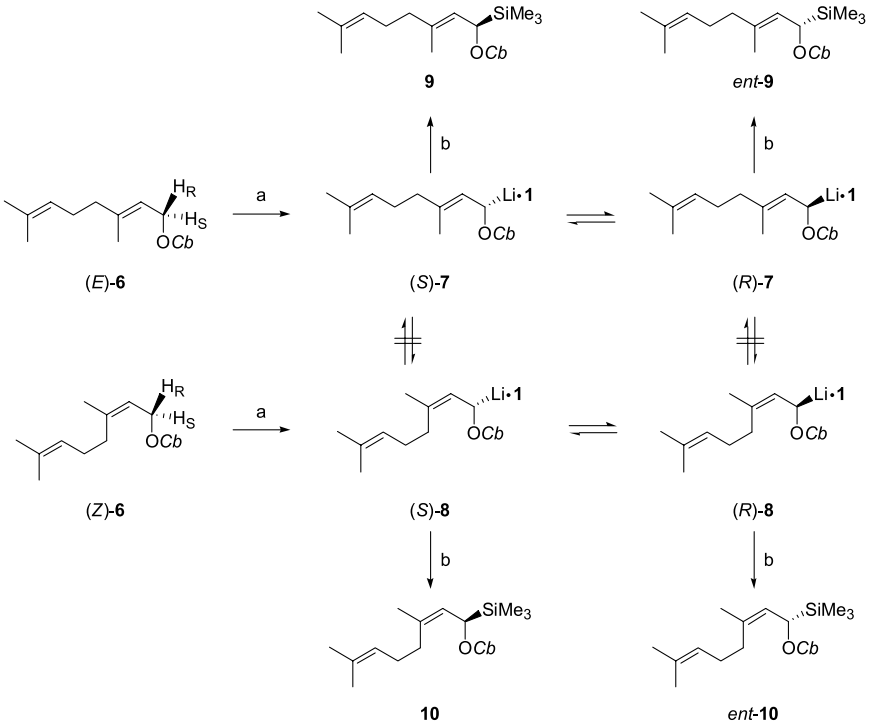
2. Results and discussion

The following questions were addressed (Scheme 2):

(1) What is the direction and magnitude of enantiotopos-differentiating deprotonation of (*E*)- and (*Z*)-**6** in the presence of (−)-sparteine?
(2) How rapidly do the intermediate diastereomer pairs (*R*)- and (*S*)-**7**, (*R*)- and (*S*)-**8** epimerize under the reaction conditions?
(3) Is there an interconversion of **7** and **8** occurring by *E*–*Z* isomerization of the allylic double bond as we have observed for an α-silyl-substituted derivative?[12]

For question (1) we used an in situ experiment[13] by deprotonating either (*E*)- or (*Z*)-**6** in toluene at −78 °C with *n*-butyllithium/(−)-sparteine (**1**) (each 1.5 equiv) in the presence of excess chlorotrimethylsilane (entry 1 and 6, Table 1). The silylation of the carbanionic intermediates (*S*)/(*R*)-**7** or **8** is highly α-selective and proceeds with strict inversion of the configuration[11a,14] producing the α-silyl-alkenyl carbamates (*S*)/(*R*)-**9** and (*S*)/(*R*)-**10**, respectively. The ratios of enantiomers were determined by ^{1}H NMR shift experiments in the presence of (+)-Eu(hfc)$_3$. The *R*/*S*-ratio expresses the minimum of kinetically controlled enantiotopic differentiation in the deprotonation step. In principle, errors might arise by a renewed deprotonation of silanes **9** or **10**. These could be excluded by control experiments: Firstly, *n*-butyllithium/**1** is not able to deprotonate **9** and **10** under the reaction condition. Secondly, the lithium compounds, derived from silanes **9** and **10**, undergo only very slow epimerization. Enantiomeric ratios up to 93.5:6.5 (87% ee) for (*S*)-**9**, starting from (*E*)-**6**, and up to 87.5:12.5 (75% ee) for (*S*)-**10** from (*Z*)-**6** could be obtained. Using pentane as a solvent under the same conditions (entry 1 and 6, Table 2) these selectivities are diminished: 72% ee from (*E*)-**6** and 61% ee from (*Z*)-**6**.

For finding an answer to question (2), the reaction mixture was allowed defined times for deprotonation before the trapping agent Me_3SiCl was added. Whereas the yields increased (due to a higher degree of deprotonation), the er decreased, giving evidence for configurational lability of the lithium compounds in toluene at −78 °C. After 30 min, the er of (*R*)/(*S*)-**9** was 84.5:15.5 (69% ee, Table 1, entry 4), and after 240 min (entry 5), the ratio 55.5:44.5 (11% ee) presumably closely reflects the thermodynamically determined ratio of the epimers (*S*)- and (*R*)-**7**. Applying a lower



Scheme 2. Reagents: (a) **1**, *n*-BuLi, −78 °C. (b) $ClSiMe_3$; MeOH.

Table 1. Enantioselective deprotonation and silylation of (*E*)- and (*Z*)-**6** in toluene

Entry	Starting material	Conditions	Time (min)	Product(s)	Yield (%)	Ratio (*R*)/(*S*)	% ee
1	(*E*)-**6**	In situ[a], −78 °C	(360)[b]	**9**	76	88.5:11.5	77
2	(*E*)-**6**	In situ[a], −78 °C	(90)[b]	**9**	37	93.5:6.5	87
3	(*E*)-**6**	−78 °C	15	**9**	47	86.5:13.5	73
4	(*E*)-**6**	−78 °C	30	**9**	59	84.5:15.5	69
5	(*E*)-**6**	−78 °C	240	**9**	85	55.5:44.5	11
6	(*E*)-**6**	In situ[a], −95 °C	(90)[b]	**9**	30	87.5:12.5	75
7	(*Z*)-**6**	In situ[a], −78 °C	(180)[b]	**10**	43	87.5:12.5	75
8	(*Z*)-**6**	−78 °C	15	**10**	75	84.5:15.5	69
9	(*Z*)-**6**	−78 °C	120	**10**	84	72.0:28.0	44
10	(*Z*)-**6**	−78 °C	240	**10**	87	56.0:44.0	12
11	(*Z*)-**6**	−78 °C	360	**10**	87	52.0:48.0	4
12	(*Z*)-**6**	−78 °C	480	**10**	88	50.5:49.5	1
13	(*Z*)-**6**	In situ[a], −95 °C	(90)[b]	**10**	31	90.5:9.5	81

[a] Deprotonation was carried out in the presence of Me_3SiCl.
[b] The reaction time is not identical with the standing time of **7** or **8**.

Table 2. Enantioselective deprotonation and silylation of (*E*)- and (*Z*)-**6** in pentane at −78 °C

Entry	Starting material	Conditions	Product(s)	Yield (%)	Ratio (*R*)/(*S*)	% ee
1	(*E*)-**6**	In situ[a], (90)[b]	**9**	49	86.0:14.0	72
2	(*E*)-**6**	5 min	**9**	52	87.0:13.0	74
3	(*E*)-**6**	15 min	**9**	59	94.5:5.5	89[c]
4	(*E*)-**6**	30 min	**9**	54	79.5:20.5	59
5	(*E*)-**6**	60 min	**9**	61	78.0:22.0	56
6	(*Z*)-**6**	In situ[a], (90)[b]	**10**	44	80.5:19.5	61
7	(*Z*)-**6**	5 min	**10**	66	80.0:20.0	60
8	(*Z*)-**6**	15 min	**10**	70	75.0:25.0	50
9	(*Z*)-**6**	60 min	**10**	79	68.0:32.0	36
10	(*Z*)-**6**	120 min	**10**	81	63.0:37.0	26

[a] *n*-Butyllithium was added to a solution of **6** and **1**.
[b] Reaction time does not represent the standing time of the lithium compound.
[c] A crystallization was observed which disappeared after 30 min.

temperature −95 °C (entry 6), both rates of deprotonation and epimerization are diminished.

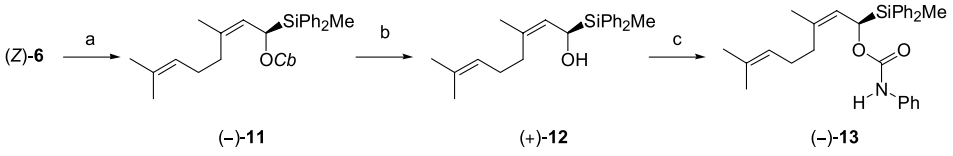
The situation is similar for the experiments with (*Z*)-**6** (entries 7–13), but the level of kinetically controlled stereoselection (entry 7) of 87.5:12.5 (75% ee) is somewhat lower. A kinetic resolution during the silylation step could be excluded by the following experiment: neryl carbamate (*Z*)-**6** was deprotonated in toluene by *sec*-butyllithium at −78 °C in the absence of any diamine, and later, (−)-sparteine (1.5 equiv) was added before the chlorosilane was introduced. The enantiomeric ratio (*R*/*S*) of silane **10** was 51:49 (59% yield). This result demonstrates that only a very slow interconversion of the epimers **8** and *epi*-**8** takes place.

A surprising result applying (*E*)-**6** was obtained, when the same series of experiments were carried out in *n*-pentane (Table 2). The er of (*S*)-**9** (94.5:5.5, 89% ee) after 15 min reaction time (entry 3) exceeded the kinetically controlled ratio (entry 1), 86:14 (72% ee); but it dropped again after prolonged reaction times (entry 4 and 5). After 15 min, a precipitate was observed in the reaction mixture, which subsequently dissolved again. We have no sound explanation for the phenomenon. Certainly, a dynamic thermodynamic resolution of the diastereomers occurred,[8] but the nature of the precipitating associate remains unknown.[15]

Concerning the question (3) of double bond (*Z*)–(*E*) isomerization in the lithium compounds **7** and **8**, we carefully investigated the reaction mixture by GC. In no case, more than 2% of the opposite silane **9** or **10**, respectively, was found. So, at −78 °C, the 2,3-double bond is perfectly stable against isomerization. This also turned out for the corresponding lithium–TMEDA complexes in toluene, pentane, and ether. Usually, substituted allyllithium compounds undergo facile isomerization of the 2,3-double bond.[16,17] Here again, the five-membered chelate complex, accomplishing a strong contact of the lithium cation with the α-carbon atom, causes an improved configurational stability both of the stereogenic α-carbon atom and the adjacent double bond.

2.1. Determination of the absolute configuration

All attempts to convert the optically active silanes (+)-**9** or (−)-**10** into crystalline derivates, suitable for X-ray analysis with anomalous dispersion, failed. Finally, the neryl carbamate (*Z*)-**6** was transformed with *n*-butyllithium/**1** and chloromethyldiphenylsilane to (−)-**11** (Scheme 3), followed by DIBAL-H-mediated decarbamoylation,[18] and, subsequently, the α-silyl alcohol (+)-**12** was added to phenyl isocyanate to furnish the crystalline *N*-phenylurethane (−)-**13**. The X-ray structure analysis with anomalous dispersion of (−)-**13** (Fig. 2) clearly shows the (*R*)-configuration of the major enantiomer.[19]



Scheme 3. Reagents: (a) $ClSiPh_2Me$, **1**, *n*-BuLi (in situ procedure); 70%. (b) DIBAL-H in hexane (8 equiv), THF, 6 h, rt, 78%. (*c*) PhN=C=O, toluene, pyridine, 70 °C, 4d, 77%.

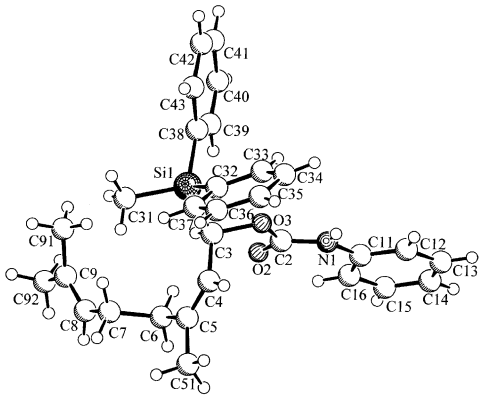
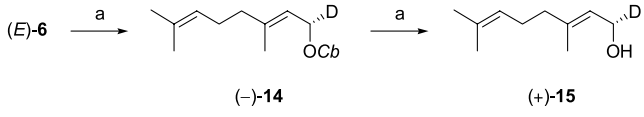


Figure 2. X-ray crystal structure analysis of (−)-**13**.[19]

Since all reported silylations of lithiated allyl carbamates[14,2c] are known to proceed with inversion of the configuration, the major epimer of lithium compounds **8** is likely to have the (*S*) configuration.

The similar reaction sequence applied to (*E*)-**6** did not lead to crystalline urethanes. However, (*S*)-1D-geraniol [(+)-**15**] (Scheme 4) is a known compound.[20,21] Hence, (*E*)-**6b** was deprotonated by means of *n*-butyllithium/(−)-sparteine (Scheme 4), and addition of MeOD yielded the α-deuterated carbamate (−)-**14**, followed by reductive cleavage with DIBAL-H reduction to form (*S*)-1D-geraniol (+)-**15**.[18] The specific rotation of the sample ($[\alpha]_D^{20} = +0.97$, $c = 1.75$ in cyclopentane) matches well with the reported data +0.44 ($c = 1.23$)[21] and +1.38 ($c = 1.70$).[20] Since all known protonation reactions of lithiated carbamates proceed with retention, it is very likely that the major intermediate of **7** has the (*S*)-configuration.



Scheme 4. Reagents: (a) *n*-BuLi, **1**; MeOD at −78 °C, 92%. (b) DIBAL-H in hexane (8 equiv), THF, 8 h, rt, 78%.

3. Conclusion

The kinetically controlled deprotonation of geranyl and neryl carbamate (*E*)- and (*Z*)-**6** by *n*-butyllithium/(−)-sparteine removes preferentially the *pro-S* proton, leading to the lithium intermediates (*S*)-**7** and (*S*)-**8**, respectively. These epimerize only slowly and have been employed in synthetically useful enantioselective homoaldol reactions.[22]

4. Experimental

4.1. General

All organometallic reactions were performed under argon at −78 °C with exclusion of air and moisture. Toluene was distilled from sodium benzophenone ketyl before use and THF was dried by refluxing over potassium/benzophenone. Pentane was dried over CaH_2 by refluxing overnight, distilled, and stored over 4 Å molecular sieves under an argon atmosphere; (−)-sparteine and TMEDA were dried over CaH_2 prior to use. LC separations were carried out at 0.5–1.5 bar on silica gel 40–63 μm (Merck, Darmstadt) with petroleum ether (PE)/Et_2O. Melting point: Gallenkamp melting point apparatus MFB-595; value uncorrected. Optical rotations: Perkin-Elmer 341 polarimeter. IR: Nicolet 5 DXC. Infrared spectra were recorded on a Fourier transform spectrometer and data were reported in wave numbers (cm^{-1}). NMR: Bruker ARX 300, AM 360, or AMX 400. All NMR spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^1H at 7.24 ppm and ^{13}C at 77.0 ppm). The ^1H NMR shift experiments were performed by addition of (+)-Eu(hfc)$_3$ to a solution of enantioenriched product (20 mg) in $CDCl_3$ (0.7 mL). Elemental analyses: Elementar Analysensysteme Vario EL III. All new compounds gave satisfactory elemental analyses (C, H ±0.3%).

4.1.1. (*Z*)-3,7-Dimethylocta-2,6-dienyl *N*,*N*-diisopropylcarbamate (*Z*)-6. A solution of nerol (12.6 g, 81.7 mmol) in THF (100 mL) was added to a suspension of NaH (3.9 g, 60% in mineral oil) in THF (40 mL) under an argon atmosphere. After refluxing for 2.5 h, *Cb*Cl (15.5 g, 1.17 equiv) in THF (40 mL) was added dropwise and the mixture was refluxed for 17 h. Cooled with ice (50 g), diluted with diethyl ether (60 mL), quenched with 2 N HCl (15 mL), the reaction mixture was extracted with diethyl ether. The combined organic layers were washed by saturated $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation of the solvents gave the crude product which was purified by distillation under reduced pressure to yield (*Z*)-**6** (17.5 g, 76%) as colourless oil. bp 112 °C (0.2 torr). IR (film) ν 2973, 2933, 2882, 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 12H, *Cb*-CH_3, $^3J_{2',1'} = 6.8$ Hz), 1.60, 1.67, 1.76 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.04–2.12 (m, 4H, 4-H_2, 5-H_2), 3.68–3.91 (m, 2H, *Cb*-CH), 4.58 (d, 2H, 1-H, $J = 6.8$ Hz), 5.08–5.14 (m, 1H, 6-H), 5.38 (t, 1H, 2-H, $J = 6.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 18.0, 26.0, 23.8, 27.1, 32.6, 46.1, 61.6, 120.8, 124.1, 132.3, 141.2, 156.2. ESI-MS (*m*/*e*) 304.4 [M^+ + Na]. $C_{17}H_{31}NO_2$ calcd. C 72.55 H 11.10 N 4.98; found C 72.55 H 11.42 N 4.83.

4.1.2. (*E*)-3,7-Dimethylocta-2,6-dienyl *N*,*N*-diisopropylcarbamate (*E*)-6. The carbamate (*E*)-**6** (18.8 g, 76%) was

obtained from geraniol (12.9 g, 83.8 mmol) and *Cb*Cl (17.5 g, 1.27 equiv) according to the procedure for (*Z*)-**6**. Colourless oil; bp 100 °C (0.1 torr). IR (film) ν 2950, 2910, 1685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 12 H, *Cb*-CH_3, $^3J_{2',1'}=6.9$ Hz), 1.60, 1.67, 1.70 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.05–2.13 (m, 4H, 4-H_2, 5-H_2), 3.70–3.91 (m, 2H, *Cb*-CH), 4.60 (d, 2H, 1-H, $J=6.9$ Hz), 5.07–5.13 (m, 1H, 6-H), 5.38 (t, 1H, 2-H, $J=6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 19.9, 24.5, 25.2, 38.4, 44.6, 60.3, 118.5, 122.8, 130.4, 139.6, 154.8. ESI-MS (*m/e*) 304.3 [M^++Na]. $C_{17}H_{31}NO_2$ calcd. C 72.55 H 11.10 N 4.98; found C 72.60 H 11.14 N 4.86.

4.2. General procedure for the lithiation and silylation of (*E*)- or (*Z*)-6

n-Butyllithium (1.5 equiv) was added dropwise with vigorous stirring to a solution of allyl carbamate **6** (1.0 mmol) and diamine (1.5 equiv) in toluene (5 mL) at −78 °C under an argon atmosphere. After this had been stirred for a given time (Tables 1 and 2) at the same temperature, the electrophile (1.5 equiv) was added. The mixture was stirred for a given time (see Tables 1 and 2) at −78 °C, after which it was quenched with MeOH (1 mL) at the same temperature, and saturated NH_4Cl solution (10 mL) was added. The aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuum. The residues were purified by silica gel flash column chromatography.

4.3. General procedure for the in situ lithiation and silylation of (*E*)- or (*Z*)-6

To a pre-dried one-necked round bottomed flask under argon atmosphere, was added allyl carbamate **6** (1.0 mmol), (−)-sparteine (1.5 equiv), toluene (5 mL), and the chlorosilane (1.5 equiv). After the reaction mixture was cooled to −78 °C, 1.6 M *n*-BuLi (1.5 equiv) was added slowly while stirring. Stirring was continued for a given time (Tables 1 and 2), the reaction was quenched with methanol (1 mL) at −78 °C. Saturated NH_4Cl solution was added to the reaction mixture. The aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and then concentrated in vacuum; the crude product was purified by silica gel flash column chromatography.

4.3.1. (1*R*,2*E*)-3,7-Dimethyl-1-(trimethylsilyl)-octa-2,6-dienyl *N*,*N*-diisopropylcarbamate (9).

As described under Section 4.3, the solution of (*E*)-**6** (281 mg, 1.0 mmol), TMSCl (162 mg, 1.5 equiv), and (−)-sparteine (351 mg, 1.5 mmol) was treated with *n*-BuLi (0.94 mL, 1.5 mmol, 1.6 M solution in hexane) at −78 °C. The reaction mixture was stirring for 90 min at −78 °C then quenched with MeOH. The described work-up procedure and a subsequent purification of the crude product by flash chromatography on silica gel (PE/E 20:1) furnished **9** (130 mg, 37%); colourless oil; $[\alpha]_D^{20}=+16.9$ (*c* 0.90 in MeOH); shift experiment: er=93.5:6.5 (87% ee), 17.9 mol % (+)-Eu(hfc)$_3$. R_f (PE/Et_2O, 8:1)=0.47. IR (film) ν 2967, 2931, 2883,1692. ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H, Si–CH_3), 1.20 (d, 12H, *Cb*-CH_3, $^3J_{2',1'}=6.9$ Hz), 1.59, 1.66, 1.68 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.00–2.05 (m, 4H, 4-H_2, 5-H_2), 3.69–3.91 (m, 2H, *Cb*-CH), 5.06–5.10 (m, 1H, 1-H), 5.14–5.18 (m, 1H, 6-H), 5.35 (d, 1H, 2-H, $J=10.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.6, 16.9, 17.6, 21.2, 25.7, 27.1, 39.9, 45.6, 67.4, 122.7, 126.3, 131.3, 135.7, 156.3. EI-MS (*m/e*) 353.2 [M^+], 338.2 [M^+−Me], 216.1 [M^+−*Cb*], 128.1 [Cb^+], 73.0 [$SiMe_3^+$]. $C_{20}H_{39}NO_2Si$ calcd. C 67.93 H 11.12 N 3.96; found C 68.21 H 11.14 N 4.24.

4.3.2. (1*R*,2*Z*)-3,7-Dimethyl-1-(trimethylsilyl)-octa-2,6-dienyl *N*,*N*-diisopropylcarbamate (10).

As described under Section 4.3, the solution of (*Z*)-**6** (281 mg, 1.0 mmol), TMSCl (162 mg, 1.5 mmol), and (−)-sparteine (351 mg, 1.5 mmol) was treated with *n*-BuLi (0.94 mL, 1.5 mmol, 1.6 M solution in hexane) at −78 °C. The reaction mixture was stirred for 180 min at −78 °C, and then quenched with MeOH. The described work-up procedure and a subsequent purification of the crude product by flash chromatography on silica gel (PE/E 15:1) furnished **10** (153 mg, 43%); colourless oil; $[\alpha]_D^{20}=-15.0$ (*c* 0.85 in MeOH); shift experiment: er=87.5:12.5 (75% ee), 23.5 mol % (+)-Eu(hfc)$_3$. R_f (PE/Et_2O, 8:1)=0.66. IR (film) ν 2968, 2933, 2871, 1708. ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H, Si–CH_3), 1.21 (d, 12H, *Cb*-CH_3, $^3J_{2',1'}=6.8$ Hz), 1.61, 1.68, 1.74 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.10–2.20 (m, 4H, 4-H_2, 5-H_2), 3.68–3.89 (m, 2H, *Cb*-CH), 5.15–5.20 (m, 2H, 6-H, 1-H), 5.36 (d, 1H, 2-H, $J=11.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.4, 17.5, 21.1, 23.4, 25.5, 26.7, 32.4, 45.2, 66.8, 124.4, 122.2, 131.2, 137.3, 156.0. ESI-MS (*m/e*) 376.4 [M^++Na], 729.7 [$2M^+$+Na]. $C_{20}H_{39}NO_2Si$ calcd. C 67.93 H 11.12 N 3.96; found C 67.78 H 11.23 N 3.75.

4.3.3. (1*R*,2*Z*)-3,7-Dimethyl-1-(methyldiphenylsilyl)-octa-2,6-dienyl *N*,*N*-diisopropylcarbamate (11).

As described under Section 4.3, the solution of (*Z*)-**6** (562 mg, 2.0 mmol), chloromethyldiphenylsilane (1.420 g, 2.0 equiv), and (−)-sparteine (701 mg, 1.5 mmol) was treated with *n*-BuLi (1.87 mL, 3.0 mmol, 1.6 M solution in hexane) at −78 °C. The reaction mixture was stirred for 210 min at −78 °C, and then quenched with MeOH. The described work-up procedure and a subsequent purification of the crude product by flash chromatography on silica gel (PE/E 15:1) furnished **11** (920 mg, 70%); colourless oil; $[\alpha]_D^{20}=-10.7$ (*c* 1.04 in MeOH). R_f (PE/Et_2O, 8:1)=0.57. Determination of the enantiomeric excess failed by using (+)-Eu(hfc)$_3$ or (+)-Pr(hfc)$_3$ in $CDCl_3$. IR (film) ν 2973, 2934, 2874, 1690. ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3H, Si–CH_3), 1.21 (d, 12H, *Cb*-CH_3, $^3J_{2',1'}=6.9$ Hz), 1.51, 1.63, 1.68 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.00–2.05 (m, 4H, 4-H_2, 5-H_2), 3.70–3.90 (m, 2H, *Cb*-CH), 5.00–5.05 (m, 1H, 6-H), 5.30 (d, 1H, 1-H, $J=10.8$ Hz), 5.98 (d, 1H, 2-H, $J=10.8$ Hz), 7.18–7.40 (m, 10H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, 17.7, 21.0, 23.4, 25.5, 26.3, 32.4, 45.7, 65.9, 121.9, 124.6, 127.6, 127.9, 129.3, 129.9, 131.1, 134.0, 134.3, 155.4. ESI-MS (*m/e*) 537.7 [M^++Na+K], 500.6 [M^++Na]. $C_{30}H_{43}NO_2Si$ calcd. C 75.42 H 9.07 N 2.93; found C 75.24 H 9.12 N 2.91.

4.3.4. (1*R*,2*Z*)-3,7-Dimethyl-1-(methyldiphenylsilyl)-octa-2,6-dien-1-ol (12).

DIBAL-H (1.0 M in hexane, 12.0 mL) was added dropwise to a solution of the carbamate

(*R*)-**11** (826 mg, 1.89 mmol) in anhydrous THF (14 mL) at 0 °C. The reaction mixtures were stirred for 6 h at room temperature. After it had been again cooled to 0 °C, MeOH (20 mL) was added, followed by saturated solution of NH_4Cl (30 mL). The aqueous phase was extracted with Et_2O (3×30 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$. Purification of the crude product by flash chromatography on silica gel (PE/E, 4:1) yielded alcohol (*R*)-**12** (515 mg, 78%) as a colourless liquid. $[\alpha]_D^{20}=+31.5$ (*c* 1.08 in MeOH). R_f (PE/Et_2O, 2:1) =0.43. Attempts to determine the ee failed by using (+)-Eu(hfc)$_3$ or (+)-Pr(hfc)$_3$ in $CDCl_3$. IR (film) ν 3384, 2965, 2929, 2833, 1602. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.52 (s, 3H, Si–CH_3), 1.56, 1.69, 1.73 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 1.96–2.04 (m, 4H, 4-H_2, 5-H_2), 4.66 (d, 1H, 1-H, J= 10.8 Hz), 5.00–5.06 (m, 1H, 6-H), 5.37 (d, 1H, 2-H, J= 10.8 Hz), 7.25–7.40 (m, 10H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ −6.4, 15.2, 17.6, 23.4, 25.6, 49.5, 66.8, 124.0, 125.3, 127.3, 127.7, 128.8, 129.7, 131.9, 134.0. EI-MS (*m*/*e*) 350.3 [M^+], 335.2 [M^+-CH_3], 268.2 [$M^+-C_6H_{10}$], 197.1 [$SiPh_2Me^+$], 121.1 [$SiPhMe^+$], 69.1 [$C_5H_9^+$]. $C_{23}H_{30}OSi$ calcd. C 78.80 H 8.63; found C 78.78 H 8.75.

4.3.5. (1*R*,2*Z*)-3,7-Dimethyl-1-(methyldiphenylsilyl)-octa-2,6-dienyl *N*-phenylcarbamate (13). Under argon, a solution of methyldiphenylsilyl alcohol (*R*)-**12** (158 mg, 0.45 mmol), phenyl isocyanate (126 mg, 1.06 mmol, 2.35 equiv) and pyridine (21 mg, 0.60 equiv) in toluene (1 mL) was stirred for 4 days at 70 °C. The solution was poured into a mixture of Et_2O (10 mL) and 2 N aq HCl (3 mL). The aqueous phase was extracted with Et_2O (3× 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuum. Flash chromatography (PE/Et_2O, 5:1) of the crude product gave (*R*)-**13** (163 mg, 77%) as a white solid. mp 105–106 °C (PE/Et_2O). $[\alpha]_D^{20}=-21.3$ (*c* 1.20 in MeOH). R_f (PE/Et_2O, 8:1)=0.27. IR (KBr) ν 3352, 2962, 2926, 2852, 1695, 1604, 1535. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H, Si–CH_3), 1.75, 1.82, 1.87 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.20–2.25 (m, 4H, 4-H_2, 5-H_2), 4.95–4.99 (m, 1H, 6-H), 5.19 (d, 1H, 1-H, J= 10.8 Hz), 5.87 (d, 1H, 2-H, J=10.8 Hz), 6.36 (s, 1H, N–H), 7.34–7.49 (m, 15H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.8, 17.6, 22.6, 23.5, 26.4 (C-5), 39.8, 66.0, 118.8, 121.0, 123.2, 124.3, 127.8, 129.6, 131.4, 133.8, 134.4, 135.0, 138.1, 153.6. ESI-MS (*m*/*e*) 469.3 [M^+], 400.2 [$M^+-C_5H_9$], 256.1 [M^+-CH_3–$SiPh_2Me$], 197.1 [$SiPh_2Me^+$], 136.1 [$OCNHPh^+$], 69.1 [$C_5H_9^+$]. $C_{27}H_{37}NO_2Si$ calcd. C 76.71 H 7.51 N 2.98; found C 76.51 H 7.50 N 2.85.

4.3.6. (1*S*,2*E*)-1-Deuterio-3,7-dimethylocta-2,6-dienyl *N*,*N*-diisopropylcarbamate (14). As described under Section 4.1.1, the solution of (*E*)-**6** (281 mg, 1.0 mmol) and (−)-sparteine (351 mg, 1.5 mmol) was treated with *n*-BuLi (0.94 mL, 1.5 mmol, 1.6 M solution in hexane) at −78 °C. The reaction mixture was stirring for 30 min at −78 °C. MeOD (0.06 mL, 50 mg) was added to the solution and the mixture was stirred for 1 h. The usual work-up was done and a subsequent purification of the crude product by flash chromatography on silica gel (PE/E 10:1) furnished **15** (260 mg, 92%); deuterium content was >99% (mass spectral analysis); colourless liquid. $[\alpha]_D^{20}=-0.45$ (*c* 1.34 in MeOH). R_f (PE/Et_2O, 8:1)=0.47. IR (film) ν 2967, 2930, 2882, 1695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 12 H, *Cb*-CH_3, $^3J_{2',1'}$=6.9 Hz), 1.60, 1.67, 1.69 (each s, 9H, 3-CH_3, 7-CH_3, 8-H_3), 2.03–2.10 (m, 4H, 4-H_2, 5-H_2), 3.70–3.92 (m, 2H, *Cb*-CH), 4.57 (d, 1H, 1-H, J=6.9 Hz), 5.05–5.09 (m, 1H, 6-H), 5.36 (d, 1H, 2-H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 21.4, 26.0, 26.7, 29.4, 39.9, 45.6, 61.8, 120.0, 124.3, 132.0, 141.1, 156.3. EI-MS (*m*/*e*) 282.3 [M^+], 213.2 [$M^+-C_5H_9$], 128.1 [Cb^+], 94.1 [$C_7H_{10}^+$], 86.1 [$C_4H_9NO^+$], 69.1 [$C_5H_9^+$]. $C_{17}H_{30}DNO_2$ calcd. C 72.29 H 11.42 N 4.96; found C 72.66 H 11.29 N 4.84.

4.3.7. (1*S*,2*E*)-1-Deuterio-3,7-dimethyl-octa-2,6-dien-1-ol (15). As described for (*R*)-**12**, DIBAL-H (1.0 M in hexane, 5.4 mL) was added dropwise to a solution of the carbamate (*S*)-**14** (190 mg, 0.67 mmol) in anhydrous THF (4 mL) at 0 °C. The reaction mixture was stirred for 8 h at room temperature. After it had been cooled to 0 °C, methanol (2 mL) was added, followed by saturated solution of NH_4Cl. The usual work-up was done and a subsequent purification of the crude product by flash chromatography on silica gel (PE/E 5:1) furnished **15** (81 mg, 78%) as a colourless liquid. Deuterium content was >99% (mass spectral analysis); $[\alpha]_D^{20}=+0.97$ (*c* 1.75 in cyclopentane). Other spectral data correspond to Refs. 20, 21.

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Asymmetric synthesis of 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes followed by diastereomer-selective lactonization

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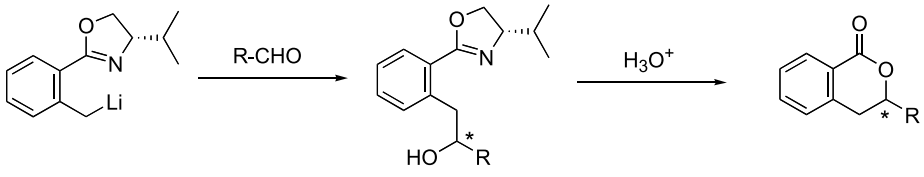
Abstract—Lateral lithiation of (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline in diethyl ether followed by the reaction with aldehydes in the presence of TMEDA produced the addition products with stereoselectivities up to 84% de. Utilization of TMEDA as a ligand is essential for the good selectivity. Rationale for the stereoselectivity is proposed based on ab initio calculation of the lateral lithio species. The major (*S*,*S*)-products lactonized faster than the minor (*S*,*R*)-products to the corresponding 3,4-dihydroisocoumarins under acidic conditions. Thus, (3*S*)-3,4-dihydroisocoumarins were obtained in good optical purities up to 97% ee by sequential application of these matched stereoselective reactions.

1. Introduction

A number of functional groups promote *ortho*-lithiation to produce relatively stable functionalized aryl- and heteroaryllithiums.[1] Such functional groups also assist lateral lithiation at the benzylic position of the *ortho*-alkyl substituent.[2] These directed lithiations have been extensively studied to produce a variety of regiospecifically substituted aromatic and heteroaromatic compounds. Utilization of the oxazoline ring as a directing group in aromatic lithiation was demonstrated by both Gschwend and Meyers in 1975.[3] Recently, we reinvestigated the lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazolines and discovered that the regioselectivity (*ortho* or lateral) can be simply controlled by the presence or absence of TMEDA.[4] The selectivity has been rationalized by steric interaction between TMEDA and C-4 substituents on the oxazoline ring in the transition states of deprotonation. This interesting and unique reactivity has been successfully applied to an efficient synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins including the natural products (±)-hydrangenol and (±)-phyllodulcin.[5] As an extension of these studies, we planned to investigate an asymmetric synthesis of optically enriched 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes followed by acid-catalyzed lactonization (Scheme 1). Asymmetric syntheses of 3-substituted 3,4-dihydroisocoumarins[6] have been achieved by using several



Scheme 1.

Keywords: 2-(*o*-Tolyl)oxazoline; Lateral lithiation; Asymmetric synthesis; 3,4-Dihydroisocoumarin; Ab initio calculation.
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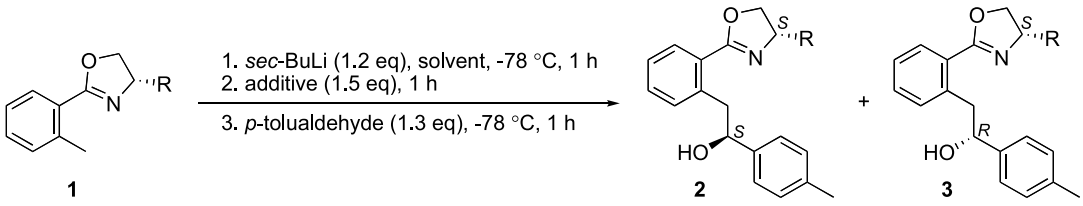
Table 1. Stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines **1** to *p*-tolualdehyde



Entry	1	R	Solvent	Additive	Adduct	Yield (%)[a]	dr (**2**:**3**)[b]
1	**1a**	*i*-Pr	Et_2O	None	**2a**, **3a**	93	1.5:1
2	**1a**	*i*-Pr	THF	None	**2a**, **3a**	93	2.7:1
3	**1a**	*i*-Pr	Et_2O	TMEDA	**2a**, **3a**	99	7.6:1
4	**1a**	*i*-Pr	Et_2O	PMDTA	**2a**, **3a**	66	1.8:1
5	**1a**	*i*-Pr	Et_2O	$MgBr_2$	**2a**, **3a**	93	1:1.5
6	**1a**	*i*-Pr	Et_2O	$MgBr_2$+TMEDA	**2a**, **3a**	90	1.2:1
7	**1b**	Me	Et_2O	TMEDA	**2b**, **3b**	91	6.1:1
8	**1c**	Bn	Et_2O	TMEDA	**2c**, **3c**	82	4.0:1
9	**1d**	*t*-Bu	Et_2O	TMEDA	**2d**, **3d**	97	5.4:1

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).

different types of key reactions, such as (1) ring-opening of chiral epoxides with metallated aromatics,[6a–c] (2) asymmetric dihydroxylation of olefinic side-chain of aromatic substrates,[6d–f] (3) CBS reduction of aryl *o*-carbamoylbenzyl ketones,[6g] (4) stereoselective addition of laterally metallated *o*-toluates to chiral aldehydes[6h–j] or to prochiral aldehydes in the presence of chiral ligands.[6k,l] Our approach using chiral 2-(*o*-tolyl)oxazolines as the chiral *o*-toluate equivalents has not been reported so far.[7]

2. Results and discussion

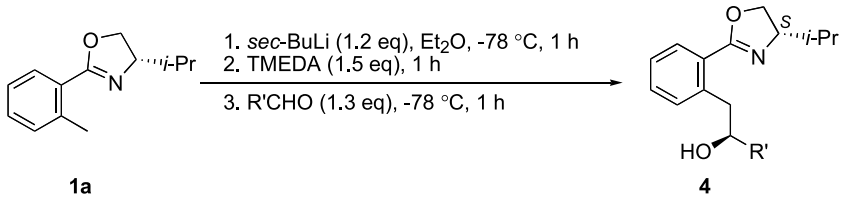
2.1. Stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes

Initially, we examined the addition of the lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline (**1a**) to *p*-tolualdehyde under a variety of conditions. Thus, (*S*)-4-isopropyl-2-(*o*-tolyl)-oxazoline (**1a**) was lithiated regioselectively at the lateral methyl group in diethyl ether or THF by treatment with 1.2 equiv of *sec*-BuLi at −78 °C for 1 h.[4] After injection of an appropriate additive, the lithiated species[8] was reacted with *p*-tolualdehyde at −78 °C for 1 h. A diastereomeric mixture of the addition products, **2a** and **3a**, was readily isolated by column chromatography in good yields. The diastereomer ratio was estimated by HPLC analysis. The results are summarized in Table 1. When diethyl ether was used as a solvent without additive, the diastereomer ratio was found to be only 1.5:1 (entry 1). The ratio was somewhat improved by using THF as a solvent (entry 2). To our surprise, when the addition was carried out in diethyl ether in the presence of TMEDA, the selectivity was dramatically improved to 7.6:1 (entry 3). These results suggested that utilization of solvents or ligands possessing high coordinating ability are advantageous for the stereoselective addition. Therefore, we tested tridentate PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) as an additive. In this case, however, both the diastereomer ratio and the chemical yield decreased considerably (entry 4). The characteristic deep purple color of the anion did not fade under these conditions indicating the poor reactivity of the PMDTA complex towards the aldehyde. Next, we examined the metal exchange of lithium to the more Lewis acidic magnesium. However, the results were disappointing even in the presence of TMEDA (entries 5 and 6). Finally, effects of an alkyl substituent on the oxazoline 4-position were inspected under the diethyl ether–TMEDA conditions. Although we tested easily synthesized methyl-, benzyl-, and *tert*-butyloxazolines **1b–d**, all of these substrates were less selectively reacted with *p*-tolualdehyde than **1a** (entries 7–9). Thus, we conclude the stereoselective addition of the laterally lithiated **1** can be most satisfactorily achieved by using the isopropyl oxazoline as an auxiliary group, diethyl ether as a solvent, and TMEDA as an additive.

Following these preliminary experiments, we surveyed the scope and limitations of this stereoselective addition using a variety of aldehydes (Table 2). Common aromatic aldehydes including cinnamaldehyde reacted with the lithiated **1a** in the presence of TMEDA in excellent yields to give adducts **4** in over 70% de (entries 1–3, 5–6). The stereoselectivity, however, decreased in the reactions with electron-deficient *p*-chlorobenzaldehyde (entry 4). An aliphatic and bulky pivalaldehyde was reacted in high stereoselectivity (entry 8). On the other hand, linear octylaldehyde gave a disappointing result (entry 9).

It is quite interesting that the transfer of chirality from the oxazoline to the prochiral aldehydes can be effected via the lateral lithio species only in the presence of TMEDA. Thus, we tried to reveal the structures of the lithio species by means of ab initio calculations. All calculations were performed by the DFT method implemented in the Gaussian 98 program package.[9] Geometry optimizations were carried out at the B3LYP/6-31G(d) level. The optimized structures of the parent oxazoline **5**, the laterally lithiated oxazoline **6**, and the laterally lithiated oxazoline coordinated with two ammonia molecules **7** as a model of the TMEDA complex are shown in Figure 1. It has been presumed that the lateral litho species generated from *o*-toluic acid derivatives

Table 2. Stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazoline **1a** to aldehydes



1a **4**

Entry	Aldehyde	Adduct[a]	R′	Yield (%)[b]	dr[c,d]	% de
1	Benzaldehyde	**4a**	Phenyl	94	8.2:1	78
2	*p*-Tolualdehyde	**4b**	*p*-Tolyl	99	7.6:1	77
3	*p*-Anisaldehyde	**4c**	*p*-Methoxyphenyl	95	6.2:1	72
4	*p*-Chlorobenzaldehyde	**4d**	*p*-Chlorophenyl	97	3.2:1	53
5	Veratraldehyde	**4e**	3,4-Dimethoxyphenyl	97	5.7:1	70
6	1-Naphthaldehyde	**4f**	1-Naphthyl	95	5.7:1	70
7	Cinnamaldehyde	**4g**	(*E*)-Styryl	87	7.1:1	75
8	Pivalaldehyde	**4h**	*t*-Butyl	91	11.8:1	84
9	Octylaldehyde	**4i**	Heptyl	75	2.1:1[e]	35

[a] Diastereomeric mixture.
[b] Isolated yield.
[c] Diastereomer ratio of (*S*,*S*)- to (*S*,*R*)-isomer unless otherwise mentioned.
[d] Determined by HPLC analysis (Daicel Chiralpak AD).
[e] Diastereomer ratio of (*S*,*R*)- to (*S*,*S*)-isomer.

possess *o*-quinodimethane (extended enolate) structures.[10] Comparison of the relative bond lengths (C_1–C_2, C_2–C_3, C_3–C_4, C_4–N) of our calculated models **5**, **6**, and **7** clearly indicated that the lithiated oxazolines, especially when lithium is coordinated with ammonia, are nicely represented as the *N*-lithio-*o*-quinodimethane structures. The other characteristic features of the lithiated species are as follows. The aromatic and oxazoline rings are twisted with each other by about 20° in both **6** and **7**. The lithium in **6** exists essentially in the same plane of the oxazoline ring, whereas the lithium in **7** bends upward about 25° from the oxazoline plane.

Next, we examined the structures of the TMEDA complex. For simplification, the calculations were performed on a complex derived from the (*S*)-4-methyl-2-(*o*-tolyl)oxazoline. The complex can exists as an *anti*- or a *syn*-isomer with respect to 4-methyl and *N*-Li-TMEDA. The optimized structures of the *anti*-isomer **8a** and the *syn*-isomer **8b** are shown in Figure 2. The calculation indicated the *anti*-isomer

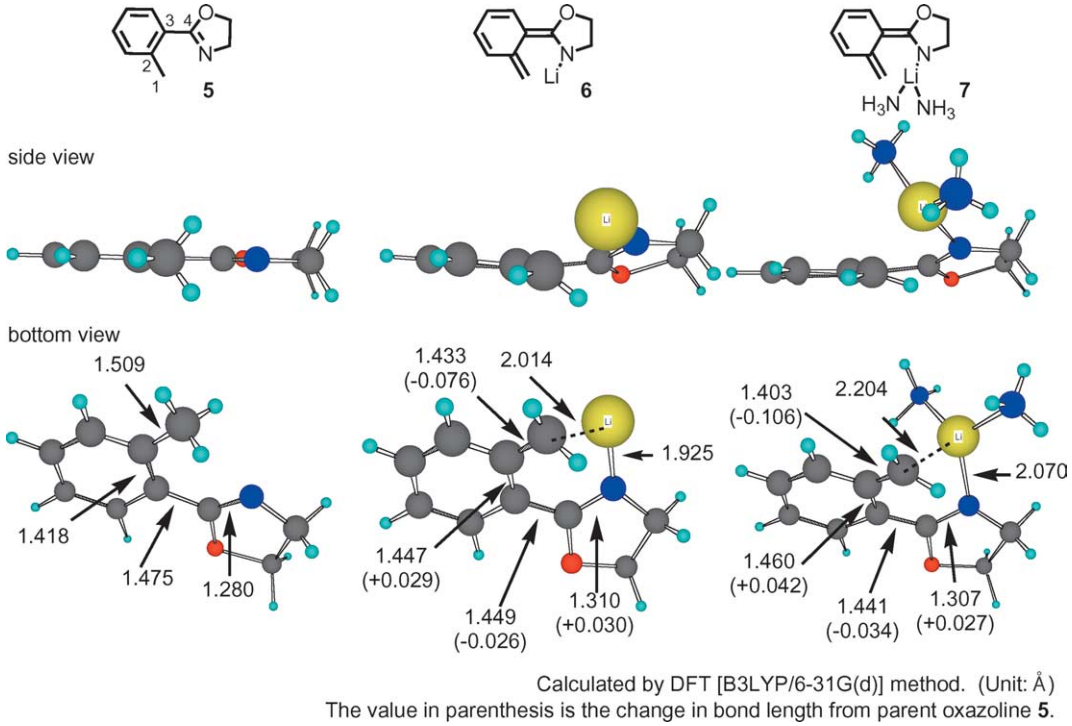


Figure 1. The optimized structures of **5**, **6** and **7**.

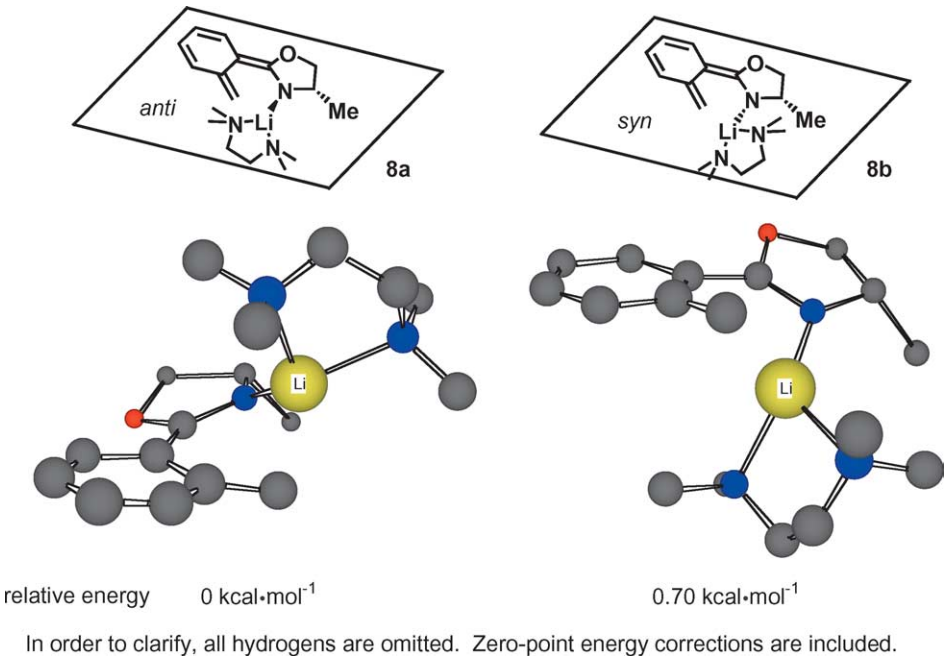
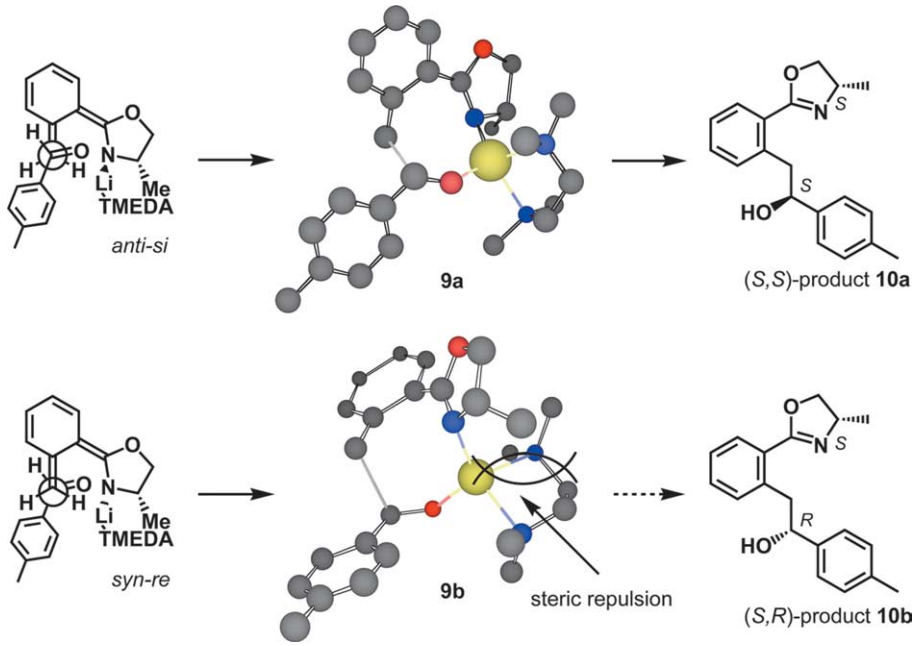


Figure 2. The TMEDA complexes of lithiated chiral oxazoline **1b**.

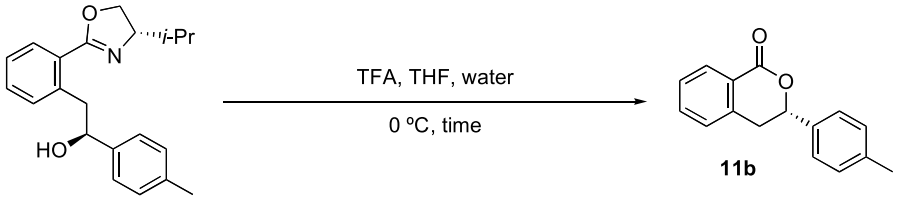
8a is more stable than the *syn*-isomer **8b** by 0.70 kcal mol^{-1} apparently due to unfavorable steric interactions between the 4-methyl group and TMEDA.[11]

By considering the computer-generated models **8a** and **8b**, a plausible mechanism for the stereoselective addition to *p*-tolualdehyde is proposed (Scheme 2). The stereoselectivity can be rationalized by assuming eight-membered ring transition states, **9a** and **9b**, in which the lithium is chelated to the carbonyl oxygen. The more stable *anti*-quinodimethane **8a** may attack the *si*-face of the aldehyde preferentially to give the (*S*,*S*)-product **10a** via the transition state **9a** in which unfavorable steric interactions between the quinodimethane ring and the aromatic ring of the aldehyde are minimized. The less stable *syn*-quinodimethane **8b** may attack the *re*-face preferentially to give (*S*,*R*)-product **10b** via a similar chelation-controlled mechanism. In this case, however, severe steric repulsion between TMEDA and the substituent of the oxazoline ring must be generated in the transition state **9b**. Thus, the (*S*,*S*)-isomer **10a** is formed as a major product through the energetically favorable transition state **9a**. The loss of the stereoselectivity in the presence of



Scheme 2. Plausible addition mechanism.

Table 3. Acid-catalyzed lactonization of the addition product **4b**



4b (77% de)

Entry	Time (h)	3,4-Dihydroisocoumarin **11b**		Unreacted **4b**	
		Yield (%)[a]	% ee[b]	Yield (%)[a]	% de[b]
1	1	11	95	86	74
2	2	15	95	84	73
3	4	28	94	66	70
4	6	37	94	62	66
5	12	63	93	36	52
6	24	77	91	19	25
7	48	89	88	9	−34
8[c]	48	99	77	0	—

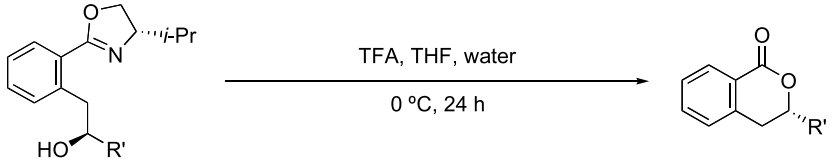
[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).
[c] Reaction at room temperature.

tridentate PMDTA strongly supports this chelation-controlled mechanism. The effects of alkyl substituent on the C-4 position of the oxazoline ring cannot be clearly understood at the present stage. We suppose, however, the transition states described above are rather tight and sensitive to the steric effects. Thus, a very large substituent such as *t*-butyl group may exert some unfavorable steric effects even in the transition state of type **9a** and consequently induce the decrease of stereoselectivity.

2.2. Diastereomer-selective lactonization of the addition products

Lactonization of the addition product **4b** (77% de sample) to the corresponding 3,4-dihydroisocoumarin **11b** was carried out carefully at 0 °C in aqueous THF in the presence of trifluoroacetic acid (TFA). The reaction was stopped after appropriate time and the 3,4-dihydroisocoumarin **11b** and the unreacted **4b** were isolated by flash chromatography. The yields of **11b** and **4b** and their ee or de in each reaction are summarized in Table 3. The reaction is rather slow under these conditions, and, to our surprise, the optical purity of the 3,4-dihydroisocoumarin **11b** isolated was found to be much higher than that expected from the de of the starting material. For example, a 95% ee sample of **11b** was isolated in 11% yield after 1 h (entry 1). With the elapse of the reaction time, yield of **11b** increased and its optical purity decreased gradually. These results clearly indicated that the lactonization rate of the major (*S*,*S*)-diastereomer is faster than that of the minor (*S*,*R*)-diastereomer. The cyclization

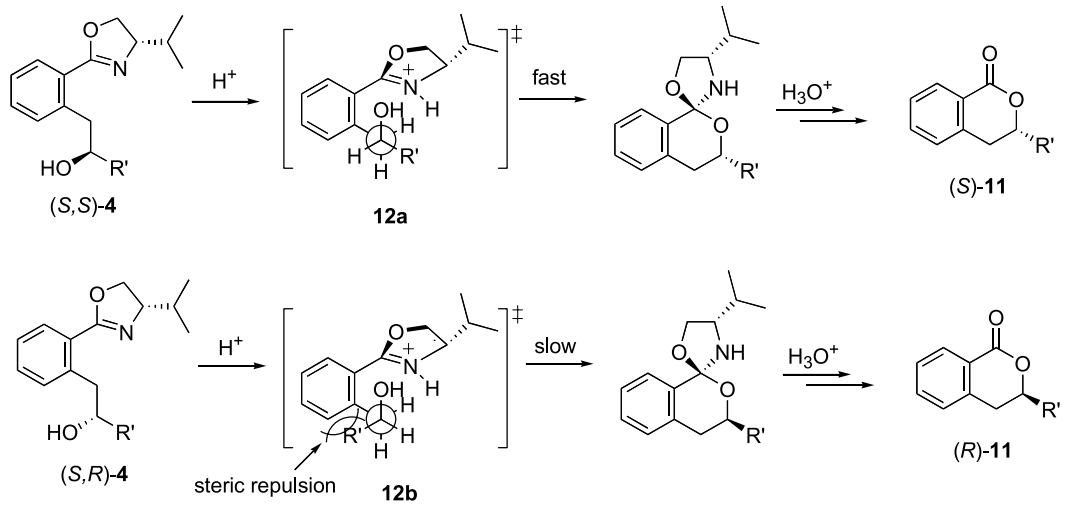
Table 4. Synthesis of optically enriched 3,4-dihydroisocoumarins **11** via diastereomer-selective lactonization



4 **11**

Entry	Addition product			3,4-Dihydroisocoumarin		
	4	R′	% de	**11**	Yield (%)[a]	% ee
1	**4a**	Phenyl	78	**11a**	84	89[b]
2	**4b**	*p*-Tolyl	77	**11b**	77	91[b]
3	**4c**	*p*-Methoxyphenyl	72	**11c**	72	86[b]
4	**4d**	*p*-Chlorophenyl	53	**11d**	83	73[b]
5	**4e**	3,4-Dimethoxyphenyl	70	**11e**	57	82[c]
6	**4f**	1-naphthyl	70	**11f**	72	92[b]
7	**4g**	(*E*)-styryl	75	**11g**	67	88[c]
8	**4h**	*t*-Butyl	84	**11h**	56	97[c]
9	**4i**	Heptyl	35	**11i**	43	79[b]

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).
[c] Determined by HPLC analysis (Daicel Chiralpak AS).



Scheme 3. Rationale for diastereomer-selective lactonization.

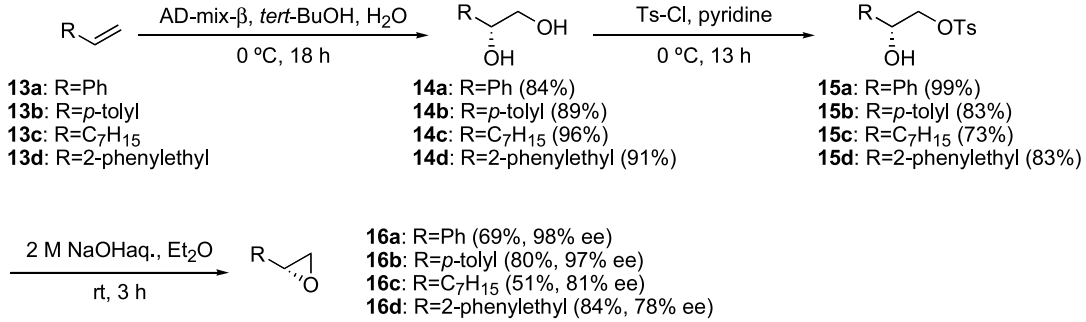
rates of both diastereomers fit to the first-order kinetics and the relative rate [$k(S,S)/k(S,R)$] is estimated to be approximately 5 from the data shown in Table 3.

The generality of this diastereomer-selective lactonization was tested using a variety of adducts **4a–i**. The reactions were carried out at 0 °C for 24 h. As shown in Table 4, the selective cyclization was observed in all cases under these restricted conditions and the optically enriched (3*S*)-3,4-dihydroisocoumarins **11a–i** were isolated in 69–97% ee.

The preferential lactonization of (*S*,*S*)-**4** can be explained as follows. The cyclization may proceed via initial and rate-determining addition of the hydroxy group to the C=N bond of the protonated oxazoline. It is reasonable to assume that the addition proceeds most readily when the oxazoline ring takes near-perpendicular conformations against the benzene ring due to deconjugation between oxazoline C=N and aromatic π-systems. In such conformations, the hydroxy group attacks the less hindered *re*-face of the oxazoline preferentially in order to avoid unfavorable steric interactions between isopropyl and lateral substituents. In such mode of cyclization, the transition state **12a** is expected to be more stable in energy than the transition state **12b** in which the *gauche* interaction between the aromatic ring and the substituent R′ is unfavorable. Thus, (*S*,*S*)-**4** cyclizes faster than (*S*,*R*)-**4** (Scheme 3).

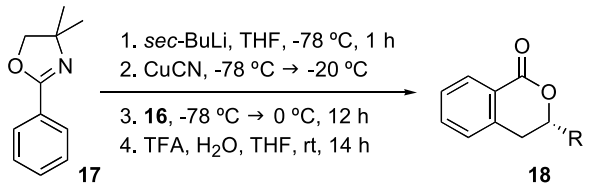
2.3. Determination of the absolute configurations

The absolute configurations of the 3-substituted 3,4-dihydroisocoumarins were determined by unequivocal syntheses. The chiral epoxides **16a–d** were synthesized using the established procedures (Scheme 4).[6j,12,13] Thus, the olefins **13a–d** were converted to the chiral diols **14a–d** using AD-mix-β.[12] The diols were transformed to the (*R*)-epoxides **16a–d** via the tosylate intermediates **15a–d**.[13] The optical purities of the epoxides varied from 78 to 98% ee depending on the substituent R. The oxazoline **17** was *ortho*-lithiated with *sec*-BuLi and, after conversion to the cyanocuprate, reacted with the epoxides **16a–d**. The crude products were treated with TFA in aq THF to give *S* (R=Ph, *p*-Tol) or *R* (R=2-phenylethyl, *n*-heptyl) dihydroisocoumarins **18a–d** in modest yields (Table 5). The absolute configurations of the 3,4-dihydroisocoumarins **11a**,**b**,**i** are shown to be identical with the authentic samples **18a–c**, respectively, by comparison of their specific rotations and HPLC profiles. The configuration of **11g** is correlated to **18d** after hydrogenation of its styryl side chain (Scheme 5). The absolute configurations of other dihydroisocoumarins **11c–f**,**h** were determined



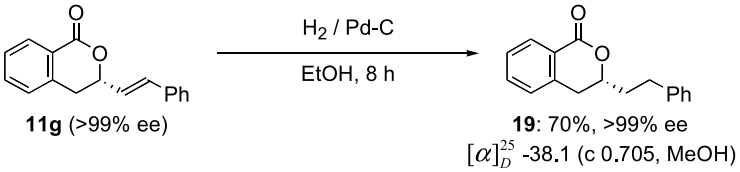
Scheme 4. Synthesis of chiral epoxides **16a–d**.

Table 5. Synthesis of chiral 3,4-dihydroisocoumarins **18a–d**



Entry	Epoxide	18	R	Yield (%)[a]	% ee	$[\alpha]_D^{25}$
1	**16a**	**18a**	Phenyl	27	98 (*S*)[b]	−151 (*c* 1.53, MeOH)
2	**16b**	**18b**	*p*-Tolyl	26	98 (*S*)[b]	−124 (*c* 1.46, MeOH)
3	**16c**	**18c**	C_7H_{15}	38	84 (*R*)[b]	−51.9 (*c* 1.00, MeOH)
4	**16d**	**18d**	2-Phenylethyl	62	79 (*R*)[c]	−30.4 (*c* 1.00, MeOH)

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).
[c] Determined by HPLC analysis (Daicel Chiralpak AS).



Scheme 5.

by comparison of their CD spectra with those of **11a**,**b**,**i** (Figs. 3 and 4).

3. Conclusion

We have discovered that the stereoselective addition of the laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes proceeds in diethyl ether in the presence of TMEDA. The stereoselectivity has been rationalized by chelation-controlled addition of the TMEDA complexes, which are nicely represented as *N*-lithio-*o*-quinodimethane structures by ab initio calculations. We have also discovered that the major addition products lactonize much faster than the minor adducts under acidic conditions to give optically enriched 3,4-dihydroisocoumarins. The procedure presented herein is simple and practically useful to produce a variety of optically active 3-substituted 3,4-dihydroisocoumarins.

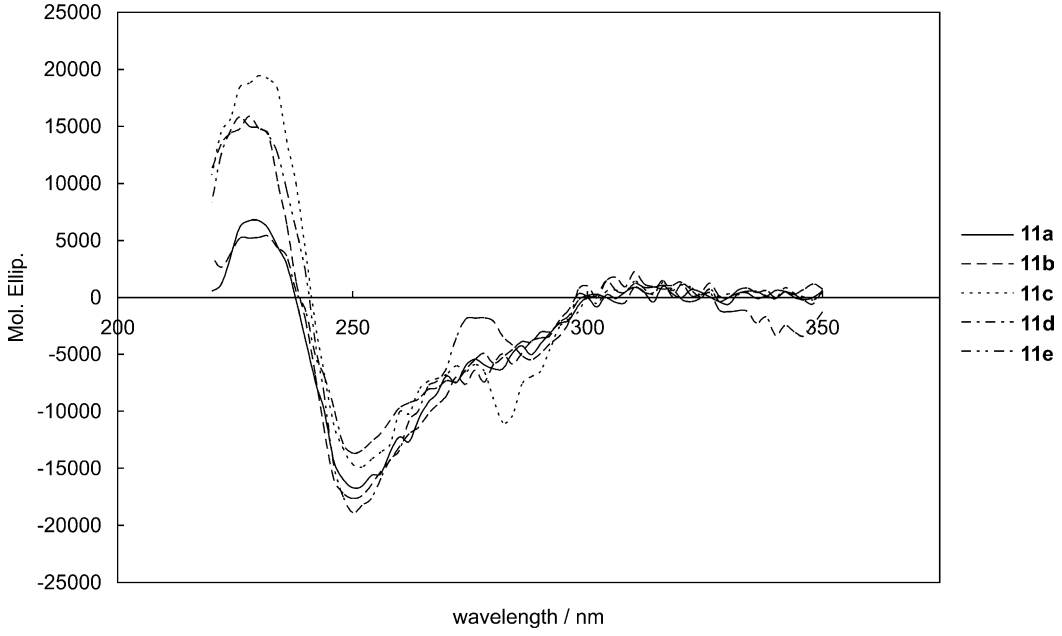


Figure 3. CD spectra of 3,4-dihydroisocoumarins **11a–e**.

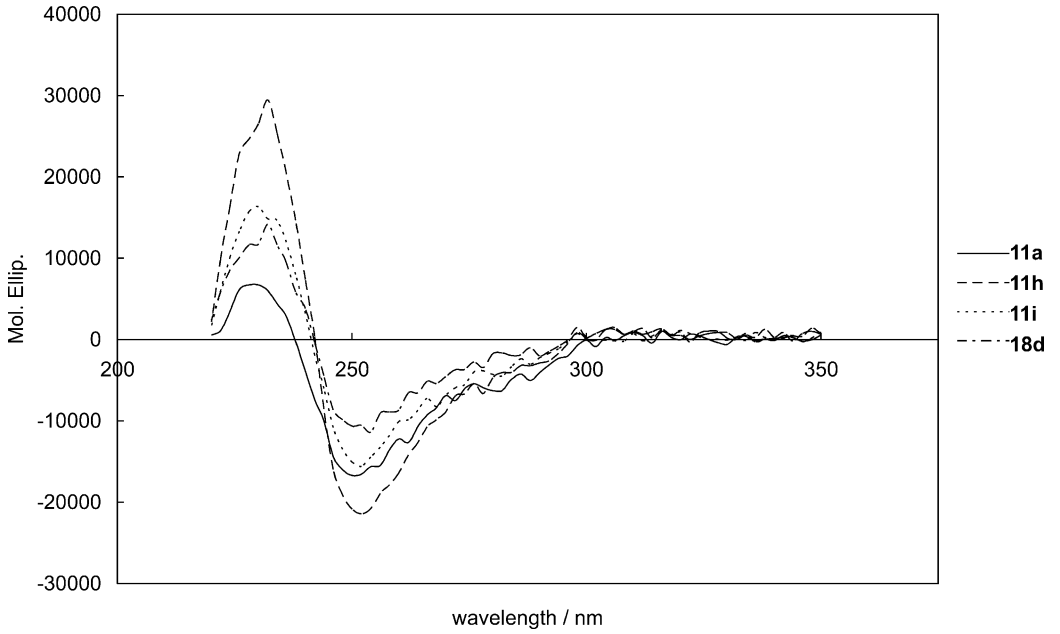


Figure 4. CD spectra of 3,4-dihydroisocoumarins **11a**, **11h**, **11i** and **18d**.

4. Experimental

4.1. General

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer System 2000 instrument. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini-300 instrument using TMS as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz on a JEOL JNM-AL400 instrument using TMS as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-DX303 spectrometer. HPLC analyses were performed on a Shimadzu LC-6A apparatus. Optical rotations were measured on a JASCO DPI-1000 digital polarimeter at ambient temperature. Flash chromatography was conducted on Silica Gel 60N, 40–50 μm (Kanto Chemical Co., Inc.). Column chromatography was conducted on Silica Gel 60N, 63–210 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd). *sec*-BuLi was purchased from Kanto Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol. AD-mix-β was purchased from Aldrich Chemical Co., Inc. Diethyl ether and THF were dried over Na-benzophenone ketyl under Ar and distilled immediately before use. Dichloromethane was distilled from CaH_2.

4.2. Synthesis of (*S*)-4-alkyl-2-(*o*-tolyl)oxazoline 1. General procedure

A solution of *o*-toluoyl chloride (4.90 mL, 38 mmol) in THF (46 mL) was added dropwise to a mixed solution of (*S*)-2-amino-2-alkylethanol (34 mmol) and triethylamine (5.6 mL, 40 mmol) in THF (46 mL) at 0 °C. After being stirred for 1 h, saturated aqueous $NaHCO_3$ was added and the mixture was evaporated. The residue was extracted with dichloromethane and the extract was washed with brine, dried over Na_2SO_4, and evaporated. The residual solid was dried in vacuo to give the intermediate *o*-toluamide. Thionyl chloride (21.5 mL, 295 mmol) was added dropwise to the amide at 0 °C and mixture was stirred for 1 h. Methanol (21.5 mL) was added 0 °C to decompose excess of thionyl chloride. When gas evolution ceased, the solution was made basic with 10% aqueous KOH. After stirring for 30 min at room temperature, the mixture was extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residual oil was purified by bulb-to-bulb distillation to give the oxazoline **1**.

4.2.1. (*S*)-4-Isopropyl-2-(*o*-tolyl)-4,5-dihydrooxazole (1a). According to the general procedure, (*S*)-2-amino-3-methyl-1-butanol (3.50 g, 34 mmol) was reacted to give **1a** as colorless oil (6.02 g, 87%). Bp 90 °C (1.6 mmHg, bulb-to-bulb); IR (neat): 2960, 1646, 1576, 1493, 1456, 1385, 1348, 1307, 1274, 1246, 1053, 972, 904, 775, 728, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, J=6.8 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H), 1.80–1.93 (m, 1H), 2.58 (s, 3H), 4.05–4.18 (m, 2H), 4.30–4.42 (m, 1H), 7.17–7.35 (m, 3H), 7.76 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.20, 18.81, 21.58, 32.86, 69.34, 72.91, 125.33, 127.37, 129.57, 130.15, 130.91, 138.42, 163.63; $[\alpha]_D^{26}=-76.2$ (*c* 1.03, MeOH). HREIMS *m*/*z*. Calcd for $C_{13}H_{17}NO$ (M^+): 203.1310. Found: 203.1349.

4.2.2. (*S*)-4-Methyl-2-(*o*-tolyl)-4,5-dihydrooxazole (1b). According to the general procedure, (*S*)-2-amino-1-propanol (1.31 g, 17 mmol) was reacted to give **1b** as colorless oil (2.22 g, 72%). Bp 105 °C (2.0 mmHg, bulb-to-bulb); IR (neat): 3064, 3027, 2967, 2926, 2894, 1644, 1603, 1574, 1492, 1475, 1454, 1374, 1353, 1337, 1304, 1287, 1248, 1205, 1163, 1140, 1124, 1106, 1065, 1038, 974, 931, 888, 851, 776, 729, 683, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, J=6.7 Hz, 3H), 2.57 (s, 3H), 3.92 (t,

J=6.7 Hz, 1H), 4.32–4.50 (m, 2H), 7.17–7.36 (m, 3H), 7.77 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.54, 21.63, 62.20, 73.31, 125.36, 127.22, 129.63, 130.26, 130.93, 138.40, 163.82; $[\alpha]_D^{27}=-64.9$ (c 1.00, MeOH). HREIMS m/z. Calcd for $C_{11}H_{13}NO$ (M^+): 175.0997. Found: 175.0984.

4.2.3. (*S*)-4-Benzyl-2-(*o*-tolyl)-4,5-dihydrooxazole (1c). According to the general procedure, (*S*)-2-amino-3-phenyl-1-propanol (709 mg, 4.7 mmol) was reacted to give **1c** as colorless oil (753 mg, 64%). Bp 160 °C (1.0 mmHg, bulb-to-bulb); IR (neat): 3062, 3027, 2963, 2924, 1770, 1651, 1644, 1604, 1574, 1552, 1494, 1473, 1454, 1383, 1352, 1310, 1270, 1250, 1203, 1178, 1163, 1133, 1123, 1075, 1050, 1031, 970, 916, 776, 753, 728, 700, 682, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 2.76 (dd, J=8.4, 13.7 Hz, 1H), 3.22 (dd, J=5.2, 13.7 Hz, 1H), 4.11 (dd, J=7.3, 8.4 Hz, 1H), 4.30 (dd, J=8.4, 9.2 Hz, 1H), 4.55–4.69 (m, 1H), 7.17–7.36 (m, 8H), 7.76 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.66, 41.82, 68.11, 70.91, 125.36, 126.30, 127.06, 128.32, 129.17, 129.63, 130.33, 130.97, 137.85, 138.53, 164.27; $[\alpha]_D^{27}=-15.2$ (c 1.00, MeOH). HREIMS m/z. Calcd for $C_{17}H_{17}NO$ (M^+): 251.1310. Found: 251.1297.

4.2.4. (*S*)-4-(*t*-Butyl)-2-(*o*-tolyl)-4,5-dihydrooxazole (1d). According to the general procedure, (*S*)-2-amino-3,3-dimethyl-1-butanol (1.00 g, 8.5 mmol) was reacted to give **1d** as colorless oil (1.72 g, 93%). Bp 120 °C (1.0 mmHg, bulb-to-bulb); IR (neat): 3063, 3028, 2957, 2903, 2869, 1651, 1604, 1575, 1493, 1478, 1456, 1393, 1383, 1364, 1352, 1334, 1306, 1288, 1248, 1209, 1194, 1162, 1123, 1070, 1049, 1025, 992, 971, 931, 901, 775, 731, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 9H), 2.59 (s, 3H), 4.08 (dd, J=8.0, 10.2 Hz, 1H), 4.18 (t, J=8.0 Hz, 1H), 4.30 (dd, J=8.0, 10.2 Hz, 1H), 7.17–7.35 (m, 3H), 7.75 (d, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.60, 25.88, 33.90, 67.88, 76.60, 125.33, 127.40, 129.54, 130.11, 130.90, 138.46, 163.53; $[\alpha]_D^{27}=-76.1$ (c 1.00, MeOH). HREIMS m/z. Calcd for $C_{14}H_{19}NO$ (M^+): 217.1467. Found: 217.1482.

4.3. Stereoselective addition of laterally lithiated (*S*)-4-alkyl-2-(*o*-tolyl)oxazolines 1 to *p*-tolualdehyde (Table 1). General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (12 mmol) was added dropwise to a solution of the oxazoline **1** (10 mmol) in diethyl ether or THF (50 mL) at −78 °C. After being stirred for 1 h, an appropriate additive (15 mmol) was added as a neat liquid or diethyl ether solution and the mixture was stirred for 1 h at −78 °C. A solution of *p*-tolualdehyde (1.53 mL, 13 mmol) in diethyl ether or THF (10 mL) was added and the solution was stirred for an additional 1 h at −78 °C. The reaction mixture was quenched with H_2O at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N using the following eluents: hexane–ethyl acetate=10:1 containing 1% triethylamine for **2a**, **3a** and **2d**, **3d**; hexane–ethyl acetate=3:1 containing 1% triethylamine for **2b**, **3b** and **2c**, **3c**. The diastereoselectivity was determined by HPLC analysis (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1).

4.3.1. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2a, 3a). According to the general procedure, **1a** (2.03 g, 10 mmol) was reacted under the conditions shown in Table 1, entry 3, to give a 7.6:1 mixture of **2a** and **3a** as colorless semisolid (3.21 g, 99%). IR (KBr): 2965, 1645, 1513, 1492, 1358, 1252, 1064, 958, 853, 806, 747, 557 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=6.7 Hz, 3H, both isomers), 1.08 (d, J=6.7 Hz, 3H, both isomers), 1.84–1.98 (m, 1H, both isomers), 2.34 (s, 0.35H, minor isomer), 2.36 (s, 2.65H, major isomer), 3.06–3.20 (m, 1H, both isomers), 3.47 (dd, J=9.4, 13.3 Hz, 0.12H, minor isomer), 3.58 (t, J=9.8, 13.3 Hz, 0.88H, major isomer), 4.10–4.30 (m, 2H, both isomers), 4.36–4.51 (m, 1H, both isomers), 4.95 (br d, J=9.1 Hz, 1H, both isomers), 7.10–7.44 (m, 7H, both isomers), 7.73–7.80 (m, 1H, both isomers). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.68; H, 8.04; N, 4.09.

4.3.2. (*S*)- and (*R*)-2-{2-[(*S*)-4-Methyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2b, 3b). According to the general procedure, **1b** (175 mg, 1.0 mmol) was reacted under the conditions shown in Table 1, entry 7, to give a 6.1:1 mixture of **2b** and **3b** as colorless oil (268 mg, 91%). IR (neat): 3224, 3057, 3022, 2968, 2924, 2867, 1726, 1644, 1600, 1575, 1513, 1493, 1446, 1376, 1358, 1342, 1307, 1252, 1199, 1177, 1127, 1104, 1055, 966, 893, 851, 807, 776, 738, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, J=6.6 Hz, 0.42H, minor isomer), 1.44 (d, J=6.3 Hz, 2.58H, major isomer), 2.35 (s, 2.58H, major isomer), 2.38 (s, 0.42H, minor isomer), 3.02 (dd, J=2.9, 16.3 Hz, 0.14H, minor isomer), 3.09 (dd, J=3.4, 13.3 Hz, 0.86H, major isomer), 3.43–3.62 (m, 1H, both isomers), 3.97–4.20 (m, 1H, both isomers), 4.42–4.60 (m, 2H, both isomers), 4.88–4.99 (m, 1H, both isomers), 7.12–7.44 (m, 7H, both isomers), 7.71–7.80 (m, 1H, both isomers). HREIMS m/z. Calcd for $C_{19}H_{21}NO_2$ (M^+): 295.1572. Found: 295.1554.

4.3.3. (*S*)- and (*R*)-2-{2-[(*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2c, 3c). According to the general procedure, **1c** (251 mg, 1.0 mmol) was reacted under the conditions shown in Table 1, entry 8, to give a 4.0:1 mixture of **2c** and **3c** as colorless oil (306 mg, 82%). IR (neat): 3238, 3061, 3027, 2922, 1726, 1644, 1603, 1575, 1514, 1494, 1454, 1358, 1309, 1274, 1225, 1178, 1118, 1063, 1031, 1001, 967, 914, 878, 852, 808, 776, 737, 700, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 2.40H, major isomer), 2.37 (s, 0.60H, minor isomer), 2.76–2.98 (m, 1H, both isomers), 3.00–3.20 (m, 1H, both isomers), 3.31 (dd, J=5.3, 13.7 Hz, 0.80H, major isomer), 3.41 (dd, J=9.5, 13.3 Hz, 0.20H, minor isomer), 3.50–3.68 (m, 1H, both isomers), 4.14–4.22 (m, 1H, both isomers), 4.41 (t, J=9.1 Hz, 0.80H, major isomer), 4.46 (t, J=8.9 Hz, 0.20H, minor isomer), 4.61–4.80 (m, 1H, both isomers), 4.85–4.98 (m, 1H, both isomers), 7.00–7.50 (m, 12H, both isomers), 7.68–7.80 (m, 1H, both isomers). HREIMS m/z. Calcd for $C_{25}H_{25}NO_2$ (M^+): 371.1885. Found: 371.1884.

4.3.4. (*S*)- and (*R*)-2-{2-[(*S*)-4-(*t*-Butyl)-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2d, 3d). According to the general procedure, **1d** (217 mg, 1.0 mmol) was reacted under the conditions shown in Table 1, entry 9, to give a 5.4:1 mixture of **2d** and **3d** as colorless solid (326 mg, 97%). Mp 79–85 °C; IR (KBr): 3224, 3060, 3021, 2959, 2868, 1645, 1600, 1576, 1513, 1494, 1478, 1445,1396, 1358, 1340, 1309, 1252, 1210, 1196, 1176, 1128, 1074, 1056, 997, 966, 911, 854, 806, 773, 740, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H, both isomers), 2.36 (s, 3H, both isomers), 3.10 (dd, J=2.7, 13.5 Hz, 0.84H, major isomer), 3.20 (dd, J=3.7, 13.3 Hz, 0.16H, minor isomer), 3.44 (dd, J=9.2, 13.3 Hz, 0.16H, minor isomer), 3.63 (dd, J=9.9, 13.5 Hz, 0.84H, major isomer), 4.15–4.30 (m, 2H, both isomers), 4.35–4.48 (m, 1H, both isomers), 4.90–5.01 (m, 1H, both isomers), 7.12–7.48 (m, 7H, both isomers), 7.72–7.81 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{22}H_{27}NO_2$ (M^+): 337.2042. Found: 337.2027.

4.4. Stereoselective addition of laterally lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline (1a) to aldehydes (Table 2). General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (2.4 mmol) was added dropwise to a solution of **1a** (2.0 mmol) in diethyl ether (10 mL) at −78 °C. After being stirred for 1 h, TMEDA (452 μL, 3.0 mmol) was added as a neat liquid and the mixture was stirred for 1 h at −78 °C. A solution of an appropriate aldehyde (2.6 mmol) in diethyl ether (2.0 mL) was added and the reaction mixture was stirred for an additional 1 h at −78 °C. The reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography to give **4** as a diastereomeric mixture.

4.4.1. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-phenylethanol (4a). According to the general procedure, **1a** (407 mg, 2.0 mmol) and benzaldehyde (264 μL, 2.6 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate =20:1), **4a** was obtained as colorless powder (584 mg, 94%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 78% de. Mp 105–110 °C; IR (KBr): 3199, 2959, 1647, 1491, 1452, 1358, 1248, 1201, 1164, 1087, 1062, 998, 960, 758, 703, 556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=6.6 Hz, 3H, both isomers), 1.09 (d, J=6.6 Hz, 2.67H, major isomer), 1.12 (d, J=6.7 Hz, 0.33H, minor isomer), 1.82–2.00 (m, 1H, both isomers), 3.11–3.23 (m, 1H, both isomers), 3.47 (dd, J=9.3, 13.5 Hz, 0.11H, minor isomer), 3.57 (dd, J=9.6, 13.5 Hz, 0.89H, major isomer), 4.13–4.28 (m, 2H, both isomers), 4.45–4.51 (m, 1H, both isomers), 4.96–5.02 (m, 1H, both isomers), 7.15–7.52 (m, 8H, both isomers), 7.76–7.80 (m, 1H, both isomers). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.57; H, 7.58; N, 4.48.

4.4.2. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(4-methoxyphenyl)ethanol (4c). According to the general procedure, **1a** (609 mg, 3.0 mmol) and *p*-anisaldehyde (531 mg, 3.9 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate=5:1 containing 1% triethylamine), **4c** was obtained as colorless oil (966 mg, 95%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 72% de. IR (neat): 3213, 2961, 1733, 1652, 1646, 1616, 1586, 1516, 1464, 1362, 1247, 1172, 1065, 965, 825, 777, 741, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, J=6.9 Hz, 3H, both isomers), 1.09 (d, J=6.9 Hz, 2.58H, major isomer), 1.11 (d, J=7.1 Hz, 0.42H, minor isomer), 1.84–1.98 (m, 1H, both isomers), 3.11–3.23 (m, 1H, both isomers), 3.44 (dd, J=9.0, 13.3 Hz, 0.14H, minor isomer), 3.54 (dd, J=9.3, 13.5 Hz, 0.86H, major isomer), 3.82 (s, 3H, both isomers), 4.05–4.30 (m, 2H, both isomers), 4.45–4.51 (m, 1H, both isomers), 4.90–5.00 (m, 1H, both isomers), 6.85–6.95 (m, 2H, both isomers), 7.23–7.45 (m, 5H, both isomers), 7.75–7.79 (m, 1H, both isomers). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.24; H, 7.51; N, 4.04.

4.4.3. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(4-chlorophenyl)ethanol (4d). According to the general procedure, **1a** (203 mg, 1.0 mmol) and *p*-chlorobenzaldehyde (182 mg, 1.3 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate=20:1 containing 1% triethylamine), **4d** was obtained as colorless semisolid (334 mg, 97%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 53% de. IR (KBr): 1641, 1490, 1065, 972, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=6.7 Hz, 2.30H, major isomer), 1.02 (d, J=6.9 Hz, 0.70H, minor isomer), 1.07 (d, J=6.7 Hz, 2.30H, major isomer), 1.11 (d, J=6.9 Hz, 0.70H, minor isomer), 1.82–1.98 (m, 1H, both isomers), 3.16–3.27 (m, 1H, both isomers), 3.37 (dd, J=8.5, 13.5 Hz, 0.23H, minor isomer), 3.47 (dd, J=9.1, 13.5 Hz, 0.77H, major isomer), 4.14–4.27 (m, 2H, both isomers), 4.46–4.52 (m, 1H, both isomers), 4.99 (br d, J=7.4 Hz, 1H, both isomers), 7.08 (dd, J=1.1, 6.6 Hz, 0.23H, minor isomer), 7.15 (dd, J=1.1, 7.7 Hz, 0.77H, major isomer), 7.25–7.42 (m, 6H, both isomers), 7.55–7.66 (m, 1H, both isomers), 7.75–7.79 (m, 1H, both isomers). Anal. Calcd for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.75; H, 6.64; N, 4.08.

4.4.4. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(3,4-dimethoxyphenyl)ethanol (4e). According to the general procedure, **1a** (203 mg, 1.0 mmol) and veratraldehyde (216 mg, 1.3 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate=2:1 containing 1% triethylamine), **4e** was obtained as colorless oil (358 mg, 97%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 70% de. IR (neat): 3208, 2960, 1726, 1652, 1593, 1516, 1464, 1418, 1362, 1265, 1139, 1029, 963, 911, 862, 808, 761, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, J=6.7 Hz, 3H, both isomers), 1.11 (d, J=6.7 Hz, 2.55H, major isomer), 1.13 (d, J=5.6 Hz, 0.45H, minor isomer), 1.81–1.97 (m, 1H, both isomers), 3.17 (dd, J=3.0, 13.4 Hz, 0.85H, major isomer), 3.27 (dd, J=3.8, 13.5 Hz, 0.15H, minor isomer), 3.41 (dd, J=8.7, 13.5 Hz, 0.15H, minor isomer), 3.54 (dd, J=9.3, 13.4 Hz, 0.85H, major isomer), 3.86 (s, 0.45H, minor isomer), 3.88 (s, 2.55H, major isomer), 3.89 (s, 3H, both isomers), 4.10–4.28 (m, 2H, both isomers), 4.42–4.55 (m, 1H, both isomers), 4.91–5.01

(m, 1H, both isomers), 6.83–7.12 (m, 3H, both isomers), 7.17–7.49 (m, 4H, both isomers), 7.75–7.80 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{22}H_{27}NO_4$ (M^+): 369.1940. Found: 369.1940.

4.4.5. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(1-naphthyl)ethanol (4f). According to the general procedure, **1a** (203 mg, 1.0 mmol) and 1-naphthaldehyde (203 mg, 1.3 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate = 10:1 containing 1% triethylamine), **4f** was obtained as colorless oil (341 mg, 95%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 1:1): 70% de. IR (neat): 3202, 2961, 1728, 1645, 1598, 1578, 1494, 1467, 1360, 1254, 1064, 965, 799, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J = 6.7 Hz, 2.55H, major isomer), 1.09 (d, J = 6.6 Hz, 0.45H, minor isomer), 1.11 (d, J = 6.7 Hz, 2.55H, major isomer), 1.18 (d, J = 6.6 Hz, 0.45H, minor isomer), 1.85–2.00 (m, 1H, both isomers), 3.37–3.47 (m, 1H, both isomers), 3.55 (dd, J = 8.6, 13.6 Hz, 0.15H, minor isomer), 3.65 (dd, J = 9.2, 13.6 Hz, 0.85H, major isomer), 4.15–4.33 (m, 2H, both isomers), 4.47–4.54 (m, 1H, both isomers), 5.77–5.87 (m, 1H, both isomers), 7.08–7.62 (m, 6H, both isomers), 7.67–7.93 (m, 4H, both isomers), 8.21–8.28 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{24}H_{25}NO_2$ (M^+): 359.1885. Found: 359.1883.

4.4.6. (2*S*,3*E*)- and (2*R*,3*E*)-1-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-4-phenyl-3-buten-2-ol (4g). According to the general procedure, **1a** (609 mg, 3.0 mmol) and cinnamaldehyde (515 mg, 3.9 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate = 5:1), **4g** was obtained as colorless solid (877 mg, 87%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 1:1): 75% de. Mp 69–72 °C; IR (KBr): 3211, 2961, 1647, 1600, 1577, 1494, 1446, 1356, 1250, 1104, 1065, 965, 747, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, J = 6.6 Hz, 0.37H, minor isomer), 1.00 (d, J = 6.9 Hz, 2.63H, major isomer), 1.08 (d, J = 6.9 Hz, 3H, both isomers), 1.75–1.90 (m, 1H, both isomers), 3.15 (dd, J = 3.6, 13.3 Hz, 1H, both isomers), 3.38 (dd, J = 9.1, 13.3 Hz, 1H, both isomers), 4.10–4.21 (m, 2H, both isomers), 4.44–4.53 (m, 1H, both isomers), 4.53–4.65 (m, 1H, both isomers), 6.38 (dd, J = 5.6, 15.8 Hz, 0.12H, minor isomer), 6.39 (dd, J = 5.5, 15.8 Hz, 0.88H, major isomer), 6.68 (d, J = 15.8 Hz, 0.12H, minor isomer), 6.72 (dd, J = 0.8, 15.8 Hz, 0.88H, major isomer), 7.19–7.47 (m, 8H, both isomers), 7.76 (dd, J = 1.2, 7.8 Hz, 1H, both isomers). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.59; H, 7.59; N, 4.03.

4.4.7. (*S*)- and (*R*)-1-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-3,3-dimethylbutan-2-ol (4h). According to the general procedure, **1a** (203 mg, 1.0 mmol) and pivalaldehyde (149 μL, 1.3 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate = 20:1), **4h** was obtained as colorless semisolid (262 mg, 91%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 9:1): 84% de. IR (KBr): 3267, 2959, 1648, 1480, 1359, 1247, 1065, 965, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, J = 6.8 Hz, 3H, both isomers), 1.00 (s, 0.70H, minor isomer), 1.02 (s, 8.30H, major isomer), 1.03 (d, J = 6.8 Hz, 3H, both isomers), 1.84–1.98 (m, 1H, both isomers), 2.71–2.83 (m, 1H, both isomers), 3.33–3.45 (m, 2H, both isomers), 4.08–4.27 (m, 2H, both isomers), 4.38–4.45 (m, 1H, both isomers), 6.42 (br s, 1H, both isomers), 7.21–7.32 (m, 2H, both isomers), 7.37–7.45 (m, 1H, both isomers), 7.68–7.76 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{18}H_{27}NO_2$ (M^+): 289.2042. Found 289.2018.

4.4.8. (*R*)- and (*S*)-1-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}nonane-2-ol (4i). According to the general procedure, **1a** (203 mg, 1.0 mmol) and octylaldehyde (203 μL, 1.3 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate = 20:1), **4i** was obtained as colorless oil (247 mg, 75%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 9:1): 35% de; IR (neat): 3273, 2927, 1733, 1646, 1601, 1576, 1493, 1467, 1355, 1308, 1249, 1115, 1065, 967, 909, 776, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.77–1.02 (m, 9H, both isomers), 1.16–1.58 (m, 12H, both isomers), 1.68–1.83 (m, 1H, both isomers), 2.87 (dd, J = 3.2, 13.2 Hz, 0.68H, major isomer), 2.98 (dd, J = 3.8, 13.3 Hz, 0.32H, minor isomer), 3.08 (dd, J = 7.8, 13.3 Hz, 0.32H, minor isomer), 3.19 (dd, J = 9.1, 13.2 Hz, 0.68H, major isomer), 3.75 (br s, 1H, both isomers), 4.00–4.13 (m, 2H, both isomers), 4.30–4.42 (m, 1H, both isomers), 6.30 (br s, 1H, both isomers), 7.14–7.25 (m, 2H, both isomers), 7.33 (dt, J = 1.3, 7.4 Hz, 1H, both isomers), 7.66 (dd, J = 1.1, 7.7 Hz, 1H, both isomers). Anal. Calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.94; H, 10.22; N, 4.19.

4.5. Acid-catalyzed lactonization of the addition product 4b (Table 3)

The 77% de sample of **4b** (100 mg, 0.309 mmol) was dissolved in 4.0 mL of a mixed solvent (THF–H_2O–TFA = 10:1.5:0.5) at 0 °C. After being stirred for an appropriate reaction time, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The product **11b** and the unreacted **4b** were separated by column chromatography over Silica Gel 60N using hexane–ethyl acetate = 20:1 containing 1% triethylamine as an eluent. Both ee of **11b** and de of **4b** were determined by HPLC analyses (Daicel Chiralpak AD: hexane–*i*-PrOH = 7:3 for **11b**, hexane–*i*-PrOH = 1:1 for **4b**). The results are in Table 3.

4.6. Synthesis of optically enriched 3,4-dihydroisocoumarins 11 via diastereomer-selective lactonization (Table 4). General procedure

The addition product **4** (1.6 mmol) was dissolved in 20 mL of a mixed solvent (THF–H_2O–TFA = 10:1.5:0.5) at 0 °C. After being stirred for 24 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using the following eluents: toluene–ethyl acetate = 20:1 for **11a**, **11d**, **11f**, **11g**, **11h** and **11i**; hexane–ethyl acetate = 10:1 for **11c**; toluene–ethyl acetate = 5:1 for

11e. Recrystallizations of **11a**, **11b**, **11f**, **11g** and **11h** afforded the optically pure samples (>99% ee).

4.6.1. (*S*)-3-Phenyl-3,4-dihydroisocoumarin (11a). According to the general procedure, **4a** (500 mg, 1.6 mmol) was reacted to give **11a** as colorless solid (304 mg, 84%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 89% ee. Recrystallization from diethyl ether–hexane gave an optically pure sample as colorless needles. Mp 76.5–77.0 °C; IR (KBr): 1717, 1604, 1488, 1458, 1349, 1278, 1226, 1117, 1090, 1072, 1031, 999, 923, 802, 762, 748, 701, 640, 575, 511, 433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.14 (dd, J=3.3, 16.5 Hz, 1H), 3.35 (dd, J=12.0, 16.5 Hz, 1H), 5.56 (dd, J=3.3, 12.0 Hz, 1H), 7.29 (d, J=7.4 Hz, 1H), 7.33–7.52 (m, 6H), 7.57 (dt, J=1.4, 7.6 Hz, 1H), 8.16 (dd, J=1.1, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.51, 79.84, 124.93, 125.94, 127.20, 127.69, 128.46, 128.50, 130.21, 133.74, 138.36, 138.75, 165.10; $[\alpha]_D^{26}=-158$ (*c* 0.990, MeOH, >99% ee) {lit.[6g] $[\alpha]_D=+89$ [*c* 1, $CHCl_3$, ca. 45% ee, (*R*)-isomer]}. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.10; H, 5.33.

4.6.2. (*S*)-3-(*o*-Tolyl)-3,4-dihydroisocoumarin (11b). According to the general procedure, **4b** (102 mg, 0.32 mmol) was reacted to give **11b** as colorless solid (57.9 mg, 77%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 91% ee. Recrystallization from diethyl ether–hexane gave an optically pure sample as colorless needles. Mp 98.0–98.5 °C; IR (KBr): 1719, 1604, 1516, 1464, 1344, 1276, 1226, 1121, 1083, 1066, 1029, 1006, 913, 820, 747, 692, 530, 508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.11 (dd, J=3.2, 16.5 Hz, 1H), 3.34 (dd, J=12.0, 16.5 Hz, 1H), 5.53 (dd, J=3.2, 12.0 Hz, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.43 (t, J=7.6 Hz, 1H), 7.57 (dt, J=1.4, 7.6 Hz, 1H), 8.15 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.15, 35.48, 79.80, 125.01, 125.93, 127.19, 127.63, 129.14, 130.20, 133.67, 135.43, 138.28, 138.86, 165.18; $[\alpha]_D^{26}=-132$ (*c* 1.02, MeOH, >99% ee). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.41; H, 5.95.

4.6.3. (*S*)-3-(4-Methoxyphenyl)-3,4-dihydroisocoumarin (11c). According to the general procedure, **4c** (729 mg, 2.1 mmol) was reacted to give **11c** as colorless solid (393 mg, 72%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 86% ee. Mp 84.0–86.0 °C; IR (KBr): 1717,1612, 1516, 1460, 1279, 1249, 1181, 1119, 1072, 1027, 999, 828, 742, 687, 615, 523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.09 (dd, J=3.0, 16.4 Hz, 1H), 3.35 (dd, J=12.0, 16.4 Hz, 1H), 3.82 (s, 3H), 5.50 (dd, J=3.0, 12.0 Hz, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.28 (d, J=7.5 Hz, 1H), 7.40 (d, J=8.7 Hz, 2H), 7.42 (t, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 1H), 8.14 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.37, 55.24, 79.71, 113.85, 124.98, 127.20, 127.48, 127.63, 130.18, 130.46, 133.68, 138.90, 159.62, 165.25; $[\alpha]_D^{26}=-93.8$ (*c* 1.02, MeOH, 86% ee). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.53; H, 5.57.

4.6.4. (*S*)-3-(4-Chlorophenyl)-3,4-dihydroisocoumarin (11d). According to the general procedure, **4d** (138 mg, 0.40 mmol) was reacted to give **11d** as colorless solid (85.5 mg, 83%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 73% ee. Mp 74.5–75.0 °C; IR (KBr): 3071, 2907, 1725, 1606, 1495, 1461, 1418, 1346, 1271, 1225, 1116, 1084, 1031, 1016, 914, 894, 817, 744, 704, 686, 646, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.12 (dd, J=3.3, 16.4 Hz, 1H), 3.30 (dd, J=11.8, 16.4 Hz, 1H), 5.54 (dd, J=3.3, 11.8 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.36–7.43 (m, 4H), 7.44 (t, J=7.5 Hz, 1H), 7.58 (dt, J=1.3, 7.5 Hz, 1H), 8.15 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.47, 79.04, 124.80, 127.20, 127.32, 127.83, 128.72, 130.28, 133.86, 134.28, 136.93, 138.42, 164.81; $[\alpha]_D^{26}=-91.3$ (*c* 1.01, MeOH, 73% ee). Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.72; H, 4.72.

4.6.5. (*S*)-3-(3,4-Dimethoxyphenyl)-3,4-dihydroisocoumarin (11e). According to the general procedure, **4e** (148 mg, 0.40 mmol) was reacted to give **11e** as colorless solid (64.8 mg, 57%). HPLC (Daicel Chiralpak AS, hexane–EtOH=3:7): 82% ee. Mp 73.5–74.5 °C; IR (KBr): 2941, 1716, 1607, 1518, 1461, 1427, 1388, 1348, 1278, 1240, 1157, 1142, 1123, 1075, 1024, 996, 909, 866, 822, 734, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.11 (dd, J=3.0, 16.4 Hz, 1H), 3.37 (dd, J=12.1, 16.4 Hz, 1H), 3.91 (s, 3H), 3.92 (s, 3H), 5.51 (dd, J=3.0, 12.1 Hz, 1H), 6.88 (d, J=8.2 Hz, 1H), 6.99 (dd, J=1.9, 8.2 Hz, 1H), 7.04 (d, J=1.9 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 1H), 7.58 (dt, J=1.4, 7.5 Hz, 1H), 8.16 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.53, 55.88, 55.91, 79.85, 109.26, 110.83, 118.55, 124.96, 127.19, 127.67, 130.23, 130.94, 133.72, 138.86, 148.96, 149.11, 165.22; $[\alpha]_D^{26}=-85.1$ (*c* 0.995, MeOH, 82% ee). HREIMS *m*/*z*. Calcd for $C_{17}H_{16}O_4$ (M^+): 284.1048. Found: 284.1066.

4.6.6. (*S*)-3-(1-Naphthyl)-3,4-dihydroisocoumarin (11f). According to the general procedure, **4f** (100 mg, 0.28 mmol) was reacted to give **11f** as colorless solid (54.6 mg, 72%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 92% ee. Recrystallization from CH_2Cl_2–hexane gave an optically pure sample as colorless needles. Mp 189.0–189.5 °C; IR (KBr): 3041, 1711, 1602, 1514, 1459, 1431, 1343, 1287, 1238, 1123, 1098, 1087, 1032, 1008, 995, 967, 921, 909, 777, 738, 729, 693, 640, 534, 498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.33 (dd, J=3.2, 16.6 Hz, 1H), 3.48 (dd, J=11.9, 16.6 Hz, 1H), 6.33 (dd, J=3.2, 11.9 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.48 (t, J=7.6 Hz, 1H), 7.51–7.58 (m, 3H), 7.61 (dt, J=1.4, 7.6 Hz, 1H), 7.82 (d, J=7.1 Hz, 1H), 7.88 (d, J=8.2 Hz, 1H), 7.90–7.94 (m, 1H), 7.97–8.10 (m, 1H), 8.22 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.06, 77.09, 122.30, 123.79, 125.01, 125.25, 125.65, 126.46, 127.20, 127.80, 128.97, 129.82, 130.37, 133.57, 133.80, 139.01, 165.30; $[\alpha]_D^{26}=-178$ (*c* 0.100, MeOH, >99% ee); $[\alpha]_D^{26}=-252$ (*c* 1.00, $CHCl_3$, >99% ee). HREIMS *m*/*z*. Calcd for $C_{19}H_{14}O_2$ (M^+): 274.0994. Found 274.0994.

4.6.7. (*S*)-3-[(*E*)-Styryl]-3,4-dihydroisocoumarin (11g). According to the general procedure, **4g** (700 mg, 2.1 mmol) was reacted to give **11g** as colorless solid (351 mg, 67%). HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=1:1): 88% ee. Recrystallization from diethyl ether gave an optically pure sample as colorless needles. Mp 92.0–92.5 °C; IR (KBr): 1707, 1605, 1460, 1378, 1278, 1256, 1223, 1138, 1105, 1084, 995, 971, 914, 804, 762, 747, 696, 589, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.11

(dd, J=4.1, 16.2 Hz, 1H), 3.19 (dd, J=9.9, 16.2 Hz, 1H), 5.16–5.26 (m, 1H), 6.34 (dd, J=6.4, 16.1 Hz, 1H), 6.79 (d, J=16.1 Hz, 1H), 7.27–7.44 (m, 7H), 7.56 (dt, J=1.2, 7.6 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.71, 78.54, 124.99, 125.68, 126.55, 127.29, 127.66, 128.17, 128.51, 130.17, 133.12, 133.68, 135.64, 138.43, 164.89; $[\alpha]_D^{25}=-53.3$ (c 1.03, MeOH, >99% ee). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.38; H, 5.64.

4.6.8. (*S*)-3-(*t*-Butyl)-3,4-dihydroisocoumarin (11h). According to the general procedure, **4h** (200 mg, 0.69 mmol) was reacted to give **11h** as colorless solid (79.7 mg, 56%). HPLC (Daicel Chiralpak AS, hexane–EtOH=9:1): 97% ee. Recrystallization from diethyl ether–hexane gave an optically pure sample as colorless needles. Mp 82.5–83.5 °C (diethyl ether); IR (KBr): 2967, 1716, 1608, 1459, 1346, 1281, 1237, 1121, 1085, 998, 909, 746, 694, 639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (s, 9H), 2.84 (dd, J=2.7 and 16.1 Hz, 1H), 3.02 (dd, J=12.6, 16.1 Hz, 1H), 4.17 (dd, J=2.7, 12.6 Hz, 1H), 7.26 (d, J=7.4 Hz, 1H), 7.38 (t, J=7.4 Hz, 1H), 7.53 (t, J=7.4 Hz, 1H), 8.09 (d, J=7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.60, 28.41, 33.99, 86.05, 125.09, 127.33, 127.35, 130.01, 133.38, 139.53, 165.81; $[\alpha]_D^{26}=-107$ (c 1.04, MeOH, >99% ee). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.10; H, 8.28.

4.6.9. (*R*)-3-Heptyl-3,4-dihydroisocoumarin (11i). According to the general procedure, **4i** (161 mg, 0.49 mmol) was reacted to give **11i** as colorless oil (51.8 mg, 43%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=9:1): 79% ee. IR (neat): 2927, 2857, 1733, 1609, 1461, 1359, 1277, 1116, 1086, 1031, 914, 802, 745, 716, 694, 604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=6.7 Hz, 3H), 1.24–1.62 (m, 10H), 1.66–1.78 (m, 1H), 1.82–1.96 (m, 1H), 2.90 (dd, J=4.1, 16.2 Hz, 1H), 2.99 (dd, J=10.6, 16.2 Hz, 1H), 4.47–4.58 (m, 1H), 7.24 (d, J=7.6 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.53 (dt, J=1.3, 7.6 Hz, 1H), 8.09 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.07, 22.60, 24.89, 29.11, 29.32, 31.72, 33.18, 34.94, 78.68, 125.09, 127.19, 127.40, 130.06, 133.45, 139.06, 165.49; $[\alpha]_D^{25}=-50.4$ (c 1.01, MeOH, 79% ee). HREIMS m/z. Calcd for $C_{16}H_{22}O_2$ (M^+): 246.1620. Found 246.1624.

4.7. Synthesis of chiral epoxides 16. General procedure

AD-mix-β (14 g) was dissolved in a mixture of *tert*-butyl alcohol (50 mL) and water (50 mL). The olefin **13** (10 mmol) was added dropwise to this mixture at 0 °C. After being stirred for 18 h at 0 °C, Na_2SO_3 (15 g, 119 mmol) was added to the mixture. The mixture was extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using hexane–ethyl acetate=1:1 as an eluent. Yields of the diol intermediates **14** after chromatography are shown in Scheme 4.

p-Toluenesulfonyl chloride (1.29 g, 6.76 mmol) was added portionwise to a solution of diol **14** (6.14 mmol) in pyridine (5 mL) at 0 °C. After being stirred for 13 h at 0 °C, the mixture was quenched with water and the product was extracted with diethyl ether. The extract was washed successively with 2 M aqueous HCl, water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using the following eluents: hexane–ethyl acetate=3:1 for **15a**, **15b** and **15d**; hexane–ethyl acetate=5:1 for **15c**. Yields of the tosylate intermediates **15** after chromatography are shown in Scheme 4.

To a solution of the tosylate **15** (3.9 mmol) in diethyl ether (20 mL) was added 2 M aqueous NaOH (10 mL) at room temperature. After being stirred for 3 h, the mixture was extracted with diethyl ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by distillation. Yields of the epoxides **16** after distillation are shown in Scheme 4.

4.7.1. (*R*)-Phenyloxirane (16a). Bp 85–120 °C (24 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (dd, J=2.5, 5.5 Hz, 1H), 3.15 (dd, J=4.0, 5.5 Hz, 1H), 3.86 (dd, J=2.5, 4.0 Hz, 1H), 7.23–7.40 (m, 5H); HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=30:1): 98% ee; $[\alpha]_D^{26}=+45.9$ (c 0.652, benzene), {lit.[13] $[\alpha]_D^{22}=-44.5$ (c 1.15, benzene): (*S*)-isomer (99% ee)}.

4.7.2. (*R*)-(*p*-Tolyl)oxirane (16b). Bp 105–120 °C (10 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.80 (dd, J=2.0, 6.0 Hz, 1H), 3.12 (dd, J=4.0, 6.0 Hz, 1H), 3.83 (dd, J=2.0, 4.0 Hz, 1H), 7.17 (s, 4H); HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=30:1): 97% ee; $[\alpha]_D^{26}=+26.7$ (c 1.12, benzene), {lit.[13] $[\alpha]_D^{22}=-25.9$ (c 1.02, benzene): (*S*)-isomer (97% ee)}.

4.7.3. (*R*)-Heptyloxirane (16c). Bp 40–50 °C (1.0 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J=6.0 Hz, 3H), 1.20–1.60 (m, 12H), 2.46 (dd, J=3.5, 6.0 Hz, 1H), 2.75 (t, J=6.0 Hz, 1H), 2.85–2.95 (m, 1H); $[\alpha]_D^{24}=+7.21$ (c 1.01, $CHCl_3$), {lit.[14] $[\alpha]_D^{24}=-8.9$ (c 1.14, $CHCl_3$): (*S*)-isomer (>97% ee)}. Optical purity of **16c** was estimated to be 81% ee from the lit. $[\alpha]_D$.

4.7.4. (*R*)-(2-Phenylethyl)oxirane (16d). Bp 90–110 °C (7.0 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76–1.93 (m, 2H), 2.47 (dd, J=3.5, 5.0 Hz, 1H), 2.65–2.90 (m, 3H), 2.90–3.00 (m, 1H), 7.12–7.36 (m, 5H); HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH=9:1): 78% ee; $[\alpha]_D^{26}=+15.8$ (c 1.24, acetone), {lit.[15] $[\alpha]_D^{23}=+16.4$ (c 1.4, acetone): (*R*)-isomer (96% ee)}.

4.8. Synthesis of chiral 3,4-dihydroisocoumarins 18. General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (3.1 mmol) was added dropwise to a solution of oxazoline **17** (491 mg, 2.8 mmol) in THF (5.0 mL) at −78 °C. After being stirred for 1 h, the reaction mixture was added dropwise to a suspension of copper cyanide (125 mg, 1.4 mmol) at −78 °C. The mixture was gradually warmed to −20 °C over 3 h, and then cooled to −78 °C. The epoxide **16** in THF (2.0 mL) was added to the mixture at −78 °C. The mixture was gradually warmed to 0 °C over

4 h and then stirred for additional 12 h at 0 °C. The reaction mixture was quenched with a mixture of 28% aqueous NH_3 (10 mL) and saturated aqueous NH_4Cl (15 mL) and the product was extracted with diethyl ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in 36 mL of a mixed solvent (THF–H_2O–TFA=10:1.5:0.5) at room temperature. After being stirred for 14 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using the following eluents: hexane–ethyl acetate=10:1 for **18a** and **18b**; hexane–ethyl acetate=5:1 for **18c** and **18d**.

4.8.1. (*S*)-3-Phenyl-3,4-dihydroisocoumarin (18a). According to the general procedure, **16a** (120 mg, 1.0 mmol) was reacted to give **18a** as colorless solid (58.4 mg, 27%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 98% ee. Mp 73.0–75.0 °C; $[\alpha]_D^{25}=-151$ (*c* 1.53, MeOH). Other spectroscopic data are identical with those of **11a**.

4.8.2. (*S*)-3-(*p*-Tolyl)-3,4-dihydroisocoumarin (18b). According to the general procedure, **16b** (134 mg, 1.0 mmol) was reacted to give **18b** as colorless solid (62.4 mg, 26%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 98% ee. Mp 88.0–90.0 °C; $[\alpha]_D^{25}=-124$ (*c* 1.46, MeOH). Other spectroscopic data are identical with those of **11b**.

4.8.3. (*R*)-3-Heptyl-3,4-dihydroisocoumarin (18c). According to the general procedure, **16c** (142 mg, 1.0 mmol) was reacted to give **18c** as colorless oil (94.8 mg, 38%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=9:1): 84% ee. $[\alpha]_D^{25}=-51.9$ (*c* 1.00, MeOH). Other spectroscopic data are identical with those of **11i**.

4.8.4. (*R*)-3-(2-Phenylethyl)-3,4-dihydroisocoumarin (18d). According to the general procedure, **16d** (148 mg, 1.0 mmol) was reacted to give **18d** as colorless oil (157 mg, 62%). HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=7:3): 79% ee. IR (neat): 3063, 3028, 2948, 1722, 1606, 1496, 1456, 1362, 1280, 1159, 1123, 1030, 942, 913, 803, 745, 701, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.96–2.08 (m, 1H), 2.16–2.29 (m, 1H), 2.79–3.07 (m, 4H), 4.47–4.56 (m, 1H), 7.16–7.33 (m, 6H), 7.38 (t, J=7.6 Hz, 1H), 7.52 (dt, J=1.4, 7.6 Hz, 1H), 8.10 (dd, J=1.1, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.98, 33.21, 36.57, 77.49, 124.95, 125.95, 127.17, 127.45, 128.31, 128.35, 130.07, 133.51, 138.85, 140.71, 165.32; $[\alpha]_D^{25}=-30.4$ (*c* 1.00, MeOH). HREIMS *m*/*z*. Calcd for $C_{17}H_{16}O_2$ (M^+): 252.1150. Found 252.1056.

4.9. Catalytic hydrogenation of 11g

Under a hydrogen atmosphere, a mixture of 3,4-dihydroisocoumarin **11g** (>99% ee) (20.0 mg, 0.0799 mmol), 5% palladium carbon (2.0 mg), and ethanol (2.0 mL) was vigorously stirred at room temperature for 8 h. The mixture was passed through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–ethyl acetate=10:1) to give **19** (14.1 mg, 70%). HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=7:3): >99% ee. $[\alpha]_D^{25}=-38.1$ (*c* 0.705, MeOH). Other spectroscopic data are identical with those of **18d**.

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Generation and reactivity of polyanions derived from 1-[1-(benzotriazol-1-yl)alkyl]-1*H*-benzotriazoles

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Abstract—1-[1-(Benzotriazol-1-yl)alkyl]-1*H*-benzotriazoles undergo deprotonation with *n*-BuLi at the α-position of the *N*-substituent and at the 7-position of benzotriazole to afford polyanions. Treatment of these polyanions with electrophiles allows the preparation of highly functionalized benzotriazole derivatives.

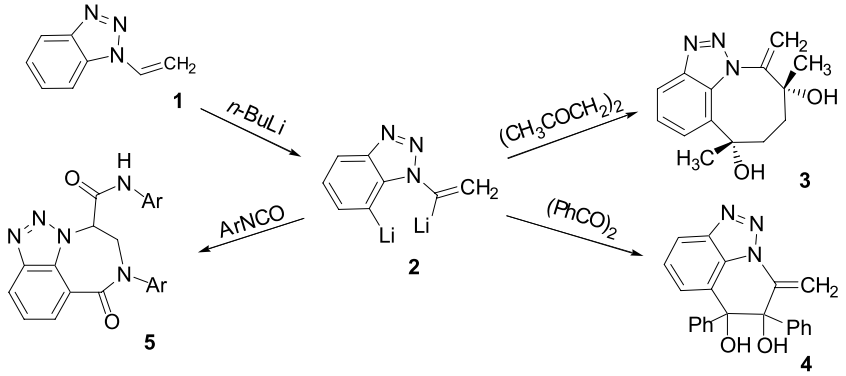
1. Introduction

Reactions of di- and polyanions with electrophiles are of great importance in synthetic organic chemistry. Although such reactions frequently involve only the most nucleophilic center of the polyanion, reactions of dianions as dinucleophiles with electrophiles have also been studied.[1] Previously, we[2] and Knight et al.[3] reported that certain N-substituted benzotriazoles can be dilithiated by deprotonation both at the α-position of *N*-substituent and at the 7-position of benzotriazole. Recently, we studied the reactions of dianion of the 1-vinylbenzotriazole **1** with electrophiles, which gave the new heterocyclic ring systems **3**, **4** and **5** (Scheme 1).[4]

Continuing our efforts to develop new routes to heterocycles and to investigate the reactivity of polyanions toward electrophiles, we have now studied the generation of polyanions **7** and **15** from dibenzotriazolylmethane **6** and 1,1-dibenzotriazolylethane **14**, respectively, and their reactions with a variety of mono-, di- and trielectrophiles (Schemes 2 and 3). Upon reactions with electrophiles, we found that the formation of **7** and **15** occurs giving the corresponding products of addition or substitution. In one case, the heterocyclization took place to give product **20**.

2. Results and discussion

Compound **6** was treated with excess of *n*-BuLi (4.1 equiv) in THF at −78 °C for a period of 12 h to give polyanion **7**, which was treated with 4 equiv of methyl iodide at the same



Scheme 1.

Keywords: Polyanions; Functionalization; Benzotriazole; Deprotonation; Electrophiles.
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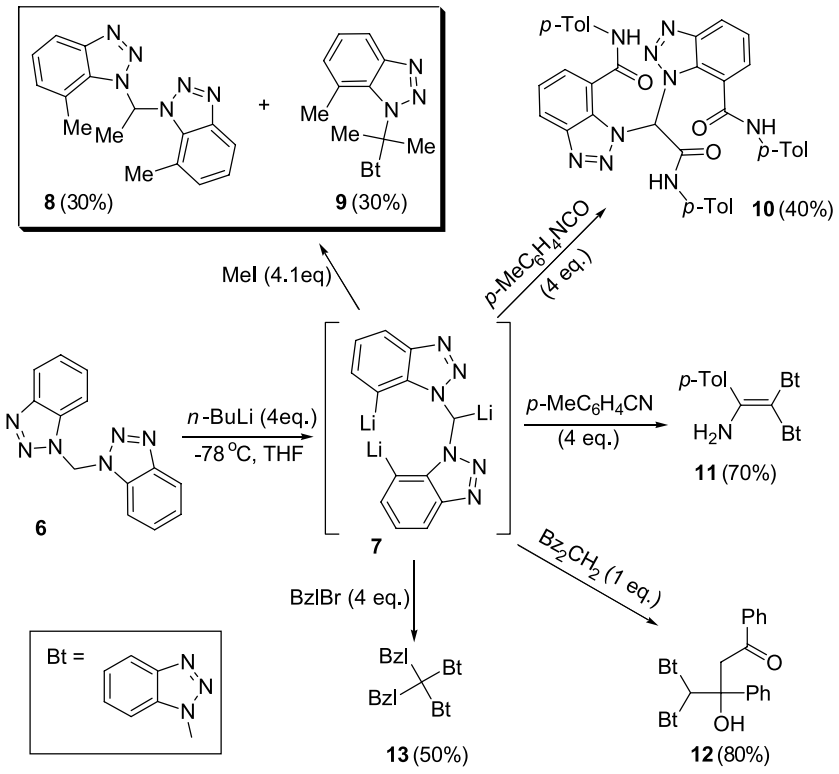
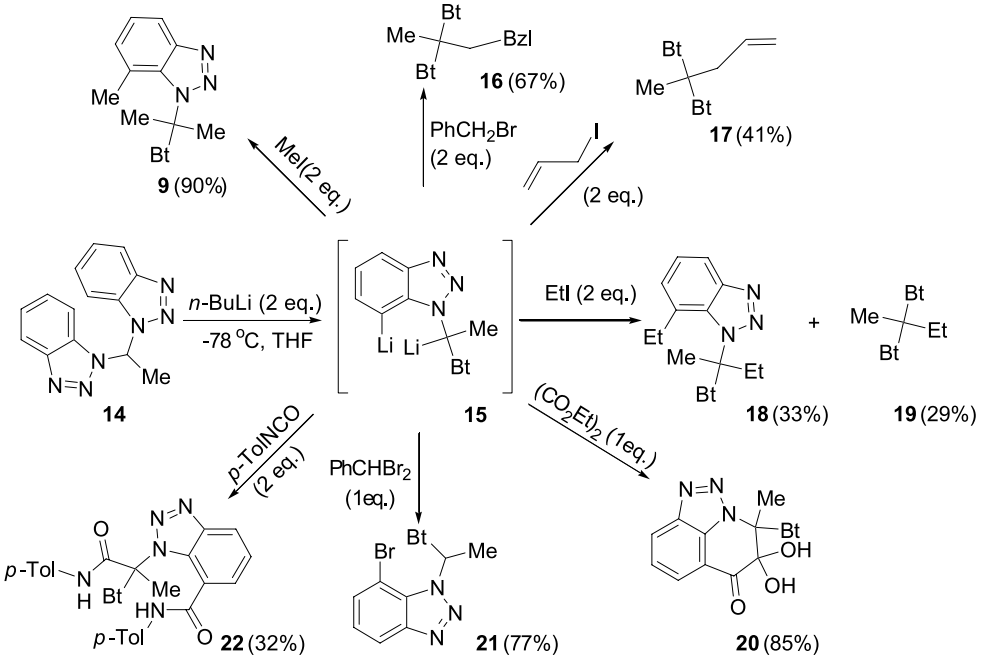


Scheme 2.

temperature for 1 h to furnish products **8** and **9** (Scheme 2). The reaction of **7** with *p*-tolyl isocyanate (4 equiv) gave the corresponding amide **10** in 40% yield. Treatment of polyanion **7** with 4-methylbenzonitrile (4 equiv) gave only enamine **11** in 70% yield as a result of single addition–tautomerization.[5] Reaction of **7** with dibenzoylmethane gave only the product of single addition **12** in 80% yield probably due to the high acidity of the methylene protons of the diketone. Unlike the reaction of **7** with methyl iodide, treatment with benzyl bromide produced a single product **13**; no products involving the reaction of the 7-position of the benzotriazole rings in **7** were observed. Attempts to trap polyanion **7** with di- and tri-electrophiles, such as benzotrichloride, diethyl oxalate, diphenylethanedione, hexachloroethane and 1,2-diiodoethane gave complex mixtures of products.

To determine the threshold of lithiation, compound **14** was



Scheme 3.

treated with excess of *n*-BuLi (4.0 equiv) in THF at −78 °C for a period of 12 h to give a polyanion, which was then trapped with methyl iodide (4 equiv) at the same temperature (Scheme 3). This resulted in the formation of single compound **9** in 65% yield. Assuming that lithiation produces only the dianion **15**, compound **14** was treated with 2 equiv of *n*-BuLi in THF at −78 °C for a period of 12 h and then reacted with 2 equiv of methyl iodide to give **9** in 90% yield. The electron-donor inductive effect of the α-methyl group in **14** may decrease the acidity of the C-7 protons in the benzotriazolyl groups and thus preclude lithiation of the second benzotriazolyl group in **15**. Having established efficient conditions for the generation of dianion **15** we tested its reactivity with a range of electrophiles (Scheme 3).

Reaction of **15** with benzyl bromide (2 equiv) gave only product **16** of due to addition at the α-carbon adjacent to the benzotriazole group in 67% yield. The addition of the propenyl group at the α-carbon was also found in the reaction of **15** with 3-iodopropene, which gave **17** in 41% yield. The reaction of iodoethane (2 equiv) with **15** produced a mixture of products: (i) from addition at the α-carbon and the 7-position of the benzotriazole ring **18**, and (ii) from addition at the α-carbon **19**; compounds **18** and **19** were isolated in 33 and 29% yields, respectively. The reaction of **15** with *p*-tolyl isocyanate (2 equiv) gave amide **22** in 32% yield. Significantly, the formation of triazoloquinolinone **20** in 85% yield was effected by reaction of dianion **15** with diethyl oxalate. The attempted reaction of **15** with benzylidene bromide gave lithium–bromine exchange resulting in the formation of the 7-bromo derivative **21** in 77% yield.

Unlike the reaction of **7** with 1,3-diphenylpropane-1,3-dione, attempted trapping of dianion **15** with diethyl malonate and diethyl phenylmalonate failed, perhaps due to the acidity of the methylene protons in these 1,3-dielectrophiles and the sufficient basisity of anion **15**. Only lithium–hydrogen exchange was observed together with the corresponding starting materials. The treatment of **15** with diethyl 2,2-diethylmalonate gave a complex mixture of products and no product of substitution was isolated.

The structure of the products was confirmed by ^{1}H, and ^{13}C NMR data (see Section 3). Significantly, the recently reported ^{1}H, and ^{13}C NMR data for related compounds were supported by X-ray analysis.[5] The analysis of the ^{1}H NMR data for **9**, **11**, **13**, **16**, **18**–**20** and **22** shows the absence of signals for the protons at the α-carbon of *N*-substituents and for **9**, **18**, **20** and **22** the absence of a signal for the proton assigned to the 7-position of the benzotriazole ring. The ^{13}C NMR of **9**, **11**, **12**, **18** and **20**–**22** show twelve signals of the carbon atoms corresponding to two unsymmetrical benzotriazolyl groups and for **9**, **18** and **20**–**22** the lack of a signal around 110 ppm, typical of the 7-unsubstituted benzotriazole ring of starting compounds **6** or **14**. In contrast, the ^{13}C NMR of compounds **8**, **10**, **13**, **16**, **17** and **19** show only six carbon resonance signals atoms characteristic of two symmetrical benzotriazolyl groups and for **8** and **10** the lack of signal of the carbon atoms around 110 ppm. The ^{1}H NMR spectra of **8** and **21** show that the protons of the methyl group and the proton at the α-carbon of the *N*-substituents resonate as doublets and quartets, respectively.

In summary, we have extended the scope of our previously reported reactions of lithiated α-benzotriazolyl derivatives. We have also investigated the reactivity of the resulting polyanions derived from 1-[1-(benzotriazol-1-yl)alkyl]-1*H*-benzotriazoles with a range of electrophiles. As a result of these reactions both the functionalization of the 7-position of benzotriazole and the α-carbon of *N*-substituent has been demonstrated.

3. Experimental

3.1. General

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, acetone-d_6 or DMSO-d_6 with TMS as the internal standard for ^{1}H (300 MHz) or a solvent as the internal standard for ^{13}C (75 MHz). Microanalyses were performed on an EA-1108 elemental analyzer. THF was dried over sodium/benzophenone and used freshly distilled. Column chromatography was conducted on silica gel 200–425 meshes.

The dibenzotriazolylmethane[6] **6** and 1,1-dibenzotriazolylethane[7] **14** were prepared according to published procedures.

3.1.1. Procedure for preparation of polyanion (7) solution. A stirred solution of dibenzotriazolylmethane 6 (1 g, 4.00 mmol) in THF (50 mL) was cooled to −78 °C, and a solution of *n*-BuLi (10 mL, 15.5 mmol, 1.6 M in hexane) was added dropwise. The reaction mixture was stirred at this temperature for 12 h and then treated with an appropriate electrophile at the same temperature.

3.1.2. Procedure for the preparation of 8 and 9. A solution of methyl iodide (2.3 g, 16.0 mmol) in THF (15 mL) was added dropwise to a stirred solution of polyanion **7** (4.00 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and then water (10 mL) was added and the product was extracted with diethyl ether (3×30 mL). The extract was washed with water (40 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexanes/EtOAc to give **8** and **9**.

3.1.2.1. 7-Methyl-1-[1-(7-methyl-1*H*-benzotriazol-1-yl)ethyl]-1*H*-benzotriazole (8). Microcrystals from acetone (30%); mp 180–181 °C; ^{1}H NMR ($CDCl_3$): δ 8.04 (q, J=6.6 Hz, 1H), 7.90 (d, J=7.9 Hz, 2H), 7.30–7.16 (m, 4H), 2.59 (d, J=6.6 Hz, 3H), 2.57 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 147.0, 131.5, 129.9, 124.6, 119.9, 118.2, 69.8, 22.6, 18.7. Anal. Calcd for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52; N, 28.75. Found: C, 65.57; H, 5.59; N, 29.07.

3.1.2.2. 1-[1-(1*H*-Benzotriazol-1-yl)-1-methylethyl]-7-methyl-1*H*-benzotriazole (9). Microcrystals from acetone (30%); mp 146–147 °C; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J= 8.3 Hz, 1H), 8.00 (d, J=8.3 Hz, 1H), 7.30–7.20 (m, 2H),

7.17–7.00 (m, 2H), 6.24 (d, $J=8.3$ Hz, 1H), 2.68 (s, 6H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 148.2, 146.9, 131.9, 131.5, 130.9, 128.2, 124.7, 124.4, 121.2, 120.2, 118.3, 110.2, 79.8, 30.0, 20.0. Anal. Calcd for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52; N, 28.75. Found: C, 65.45; H, 5.56; N, 29.15.

3.1.3. General procedure for the preparation of compounds 10–13. A solution of corresponding electrophile (16.0 mmol) in THF (15 mL) was added dropwise to a stirred solution of polyanion **7** (4.00 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and then water (10 mL) was added and the product was extracted with diethyl ether (3×30 mL). The extract was washed with water (30 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexanes/EtOAc to give **10–13**.

3.1.3.1. *N*-(4-Methylphenyl)-1-(2-(4-methylphenylamino)-1-{7-[(4-methylphenylamino)carbonyl]-1*H*-benzotriazol-1-yl}-2-oxoethyl)-1*H*-benzotriazole-7-carboxamide (10). Microcrystals (40%); mp 172–174 °C; ^{1}H NMR (DMSO-d_6): δ 10.75 (s, 1H), 10.38 (s, 2H), 9.24 (s, 1H), 8.29 (d, $J=8.2$ Hz, 2H), 8.00 (d, $J=7.1$ Hz, 2H), 7.56–7.51 (m, 2H), 7.44 (d, $J=8.3$ Hz, 4H), 7.35 (d, $J=8.4$ Hz, 2H), 7.02 (d, $J=8.4$ Hz, 2H), 6.97 (d, $J=8.3$ Hz, 4H), 2.22 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 163.9, 161.2, 146.9, 136.0, 135.9, 132.7, 132.5, 130.8, 128.9, 128.7, 128.2, 123.8, 122.6, 121.8, 120.4, 119.6, 75.4, 20.5, 20.4. Anal. Calcd for $C_{37}H_{31}N_9O_3$: C, 68.40; H, 4.81; N, 19.40. Found: C, 68.26; H, 5.07; N, 19.31.

3.1.3.2. 2,2-Di-(1*H*-benzotriazol-1-yl)-1-(4-methylphenyl)-1-ethylenamine (11). Microcrystals (70%); mp 202–204 °C; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, $J=8.3$ Hz, 1H), 7.88 (d, $J=8.2$ Hz, 1H), 7.87 (d, $J=8.4$ Hz, 1H), 7.72 (d, $J=8.2$ Hz, 1H), 7.52–7.46 (m, 1H), 7.43–7.30 (m, 4H), 7.26–7.21 (m, 1H), 6.97 (d, $J=7.8$ Hz, 2H), 4.67 (s, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 148.9, 145.5, 144.9, 140.3, 134.6, 133.1, 130.1, 129.2, 128.5, 128.2, 127.4, 124.5, 124.0, 119.7, 119.6, 110.9, 110.2, 97.9, 21.1. Anal. Calcd for $C_{21}H_{17}N_7$: C, 68.65; H, 4.66; N, 26.69. Found: C, 68.68; H, 4.66; N, 26.88.

3.1.3.3. 4,4-Di-(1*H*-benzotriazol-1-yl)-3-hydroxy-1,3-diphenyl-1-butanone (12). Microcrystals (95%); mp 183–184 °C; ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H), 8.00 (d, $J=8.2$ Hz, 1H), 7.96–7.89 (m, 2H), 7.81–7.74 (m, 3H), 7.58–7.26 (m, 9H), 7.15–7.04 (m, 3H), 5.95 (s, 1H), 4.18 (d, $J=17.3$ Hz, 1H), 3.71 (d, $J=17.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.6, 145.9, 145.1, 140.6, 136.4, 133.8, 133.1, 132.8, 128.6, 128.5, 128.4, 128.1, 128.0, 125.3, 124.7, 124.5, 120.0, 119.8, 111.8, 110.2, 79.7, 76.0, 45.6. Anal. Calcd for $C_{28}H_{22}N_6O_2$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.81; H, 4.61; N, 17.77.

3.1.3.4. 1-[1-(1*H*-Benzotriazol-1-yl)-1-benzyl-2-phenylethyl]-1*H*-benzotriazole (13). Microcrystals (46%); mp 121–122 °C; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, $J=8.4$ Hz, 2H), 7.26–7.20 (m, 2H), 7.16–7.11 (m, 2H), 7.06–6.96 (m, 6H), 6.52 (d, $J=7.3$ Hz, 4H), 6.14 (d, $J=8.4$ Hz, 2H), 4.45 (s, 4H); ^{13}C NMR ($CDCl_3$): δ 146.5, 132.7, 132.5, 130.4, 128.3, 128.1, 127.7, 124.4, 120.3, 110.3, 84.6, 42.5. Anal. Calcd for $C_{27}H_{22}N_6$: C, 75.33; H, 5.15; N, 19.52. Found: C, 75.55; H, 5.40; N, 19.25.

3.1.4. Procedure for preparation of dianion (15) solution. A stirred solution of 1,1-dibenzotriazolylethane 14 (1 g, 3.79 mmol) in THF (50 mL) was cooled to −78 °C, and a solution of *n*-BuLi (4.9 mL, 7.58 mmol, 1.6 M in hexane) was added dropwise. The reaction mixture was stirred at this temperature for 12 h and then treated with an appropriate electrophile at the same temperature.

3.1.5. Procedure for the preparation of (9) from dianion (15). A solution of methyl iodide (1.07 g, 7.58 mmol) in THF (15 mL) was added dropwise to a stirred solution of dianion 15 (3.79 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and then water (10 mL) was added and the product was extracted with diethyl ether (3×30 mL). The extract was washed with water (30 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexanes/EtOAc to give 9 as microcrystals (90%).

3.1.6. General procedure for the preparation of compounds 16–22. A solution of corresponding electrophile (8.00 mmol) in THF (15 mL) was added dropwise to a stirred solution of dianion **15** (3.79 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and then water was added and the product was extracted with diethyl ether (3×30 mL). The extract was washed with water (30 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexanes/EtOAc to give **16–22**.

3.1.6.1. 1-[1-(1*H*-Benzotriazol-1-yl)-1-methyl-2-phenylethyl]-1*H*-benzotriazole (16). White microcrystals (67%); mp 139–141 °C; ^{1}H NMR ($CDCl_3$): δ 8.08 (d, $J=8.3$ Hz, 2H), 7.08–7.31 (m, 7H), 6.63 (d, $J=8.4$ Hz, 2H), 6.53 (d, $J=7.3$ Hz, 2H), 4.59 (s, 2H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.8, 132.7, 131.6, 130.1, 128.4, 128.3, 127.8, 124.6, 120.5, 110.1, 81.5, 43.9, 25.0. Anal. Calcd for $C_{21}H_{18}N_6$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.42; H, 5.08; N, 23.84.

3.1.6.2. 1-[1-(1*H*-Benzotriazol-1-yl)-1-methyl-3-butenyl]-1*H*-benzotriazole (17). White microcrystals (41%), mp 91–92 °C; ^{1}H NMR δ 8.04–8.07 (m, 2H), 7.14–7.29 (m, 4H), 6.68–6.71 (m, 2H), 5.49–5.58 (m, 1H), 5.06–5.12 (m, 2H), 4.02 (d, $J=7.0$ Hz, 2H), 2.68 (s, 3H); ^{13}C NMR δ 146.7, 131.2, 129.1, 128.1, 124.4, 121.7, 120.2, 110.0, 80.6, 42.9, 24.9. Anal. Calcd for $C_{17}H_{16}N_6$: C, 67.09; H, 5.30; N, 27.61. Found: C, 67.15; H, 5.29; N, 27.61.

3.1.6.3. 1-[1-(1*H*-Benzotriazol-1-yl)-1-methylethyl]-7-ethyl-1*H*-benzotriazole (18). White microcrystals (33%); mp 93–95 °C; ^{1}H NMR ($CDCl_3$): δ 8.04–8.07 (m, 1H), 8.02 (d, $J=8.2$ Hz, 1H), 7.24–7.34 (m, 2H), 7.10–7.18 (m, 2H), 6.30 (d, $J=8.5$ Hz, 1H), 3.30–3.41 (m, 1H), 3.13–3.26 (m, 1H), 2.62 (s, 3H), 2.05 (q, $J=7.0$ Hz, 2H), 0.78 (t, $J=7.0$ Hz, 3H), 0.56 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 148.1, 146.8, 131.8, 131.4,, 128.6, 128.1, 127.8, 124.8, 124.4, 120.2, 118.0, 110.3, 83.0, 34.0, 26.5, 24.5, 14.8, 7.9.

Anal. Calcd for $C_{18}H_{20}N_6$: C, 67.48; H, 6.29; N, 26.23. Found: C, 67.64; H, 6.35; N, 26.33.

3.1.6.4. 1-[1-(1*H*-Benzotriazol-1-yl)-1-methylpropyl]-1*H*-benzotriazole (19). White microcrystals (29%); mp 93–94 °C; ^{1}H NMR ($CDCl_3$): δ 8.03–8.07 (m, 2H), 7.12–7.28 (m, 4H), 6.63–6.66 (m, 2H), 3.32 (q, J=7.4 Hz, 2H), 2.67 (s, 3H), 0.91 (t, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 146.9, 131.4, 128.1, 124.5, 120.3, 110.2, 82.2, 31.8, 24.3, 7.7. Anal. Calcd for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52; N, 28.75. Found: C, 66.11; H, 5.58; N, 28.65.

3.1.6.5. 4-(1*H*-Benzotriazol-1-yl)-5,5-dihydroxy-4-methyl-4,5-dihydro-6*H*-[1,2,3]triazolo[4,5,1-*ij*]quinolin-6-one (20). Plates (78%); mp 182–186 °C; ^{1}H NMR (DMSO-d_6): δ 8.50 (d, J=8.2 Hz, 1H), 8.25 (s, 1H), 8.22 (d, J=7.1 Hz, 1H), 8.16 (d, J=8.5 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.80 (s, 1H), 7.75–7.70 (m, 1H), 7.68–7.62 (m, 1H), 7.48–7.42 (m, 1H), 3.03 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 186.9, 145.2, 143.9, 134.2, 132.1, 128.6, 125.8, 125.5, 125.3, 124.5, 119.6, 117.1, 113.0, 95.1, 83.7, 16.5. Anal. Calcd for $C_{16}H_{12}N_6O_3$: C, 57.14; H, 3.60; N, 24.99. Found: C, 56.90; H, 3.94; N, 25.03.

3.1.6.6. 1-[1-(1*H*-Benzotriazol-1-yl)ethyl]-7-bromo-1*H*-benzotriazole (21). Microcrystals (77%); mp 165–166 °C; ^{1}H NMR ($CDCl_3$): δ 8.72 (q, J=6.9 Hz, 1H), 8.06–8.01 (m, 2H), 7.82 (d, J=8.4 Hz, 1H), 7.70–7.63 (m, 1H), 7.48–7.40 (m, 1H), 7.38–7.31 (m, 1H), 7.28–7.20 (m, 1H), 2.67 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 147.2, 146.6, 132.8, 131.1, 130.7, 128.0, 125.7, 124.3, 120.1, 119.6, 110.8, 102.2, 67.8, 20.3. Anal. Calcd for $C_{14}H_{11}BrN_6$: C, 49.00; H, 3.23; N, 24.49. Found: C, 49.00; H, 3.15; N, 24.32.

3.1.6.7. 1-[1-(1*H*-Benzotriazol-1-yl)-1-methyl-2-(4-methylphenylamino)-2-oxoethyl]-*N*- (4-methylphenyl)-1*H*-benzotriazole-7-carboxamide (22). Microcrystals (32%); mp 203–204 °C; ^{1}H NMR ($CDCl_3$): δ 10.6 (s, 1H), 8.28 (d, J=8.5 Hz, 1H), 7.92 (d, J=8.4 Hz, 1H), 7.59–7.55 (m, 2H), 7.41–7.36 (m, 1H), 7.26–7.20 (m, 3H), 7.15–7.10 (m, 1H), 6.95 (d, J=8.2 Hz, 2H), 6.86 (d, J=8.3 Hz, 2H), 6.82 (d, J=8.2 Hz, 2H), 5.93 (d, J=6.4 Hz, 1H), 2.95 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.5, 163.4, 147.9, 145.8, 134.7, 134.4, 134.3, 133.8, 132.3, 130.2, 129.1, 129.0, 128.8, 127.7, 124.6, 124.2, 123.4, 123.3, 120.3, 120.2, 119.2, 110.7, 84.0, 29.9, 20.8. Anal. Calcd for $C_{30}H_{26}N_8O_2$: C, 67.91; H, 4.94; N, 21.12. Found: C, 67.70; H, 5.13; N, 21.08.

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An efficient entry to pyrrolo[1,2-*b*]isoquinolines and related systems through Parham cyclisation

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Abstract—Aryllithiums generated by lithium–iodine exchange undergo intramolecular cyclisation to give pyrrolo[1,2-*b*]isoquinolines, in high yields. The best results were obtained when Weinreb or morpholine amides were used as internal electrophiles. The procedure has been extended to the preparation of seven and eight membered rings, opening a route to benzazepine and benzazocine skeletons.

1. Introduction

Aryl and heteroaryllithium compounds[1] are interesting building blocks in synthetic organic chemistry because by reaction with carbon electrophiles they produce, together with the formation of a carbon–carbon bond, the transference of functionality to the electrophilic reagent, so polyfunctionalised molecules can be prepared in one step. Lithium–halogen exchange, though mechanistically controversial,[2] is a particularly useful tactic for the metalation of aromatic substrates, because metal–halogen exchange can effectively compete with the organolithium reaction with internal electrophiles.[3] Once generated, the aryllithiums may react with internal or external electrophiles and give rise to cyclisation reactions.

The intramolecular cyclisations that employ aryllithiums generated by lithium–halogen exchange are known as Parham cyclisations. Thus, the aromatic metalation–cyclisation sequence has become a valuable protocol for the regiospecific construction of carbocyclic and heterocyclic systems.[4] When the internal electrophile is a carboxylate, this anionic cyclisation could be considered as an anionic Friedel–Crafts equivalent, with the advantage that it lacks the electronic requirements of the classical reaction. The complementary character of the anionic and classical cyclisations is exemplified by the synthesis of azafluorenone alkaloids.[5] Acid derivatives, such as amides and carbamates constitute even more effectively used internal electrophiles than the carboxylates in Parham-type cycliacylations.[6] For instance, Avendaño[7] has applied this protocol to the synthesis of 1,8-diazanthracene-9,10-diones using a tandem directed *ortho*-metalation/metal–halogen exchange reactions. Various amides can be used for these reactions and, in some cases, it has been reported that there is an influence of the nature of the susbstituents at nitrogen in the course of the cyclisation reaction. Thus, Quallich[8] has prepared azatetralones starting from 3-bromopyridines with a *N*,*N*-dialkylaminocarbonylpropyl substituent at C-2. Although three different amides (dimethyl, diisopropyl, and pyrrolidine) were tested as substrates for this carbanionic ring annelation, best results were obtained with the *N*,*N*-dimethyl derivative. However, when Wu et al.[9] applied a similar Parham cyclisation protocol to the synthesis of dibenzocycloheptenone derivatives, they found no significant influence of the nitrogen substitution pattern in the cyclisation yields.

On the other hand, Weinreb[10] amides have been widely used in synthesis, although their use in Parham cyclisations is scarce. Thus, aryl and heteroaryllithium compounds have been generated in the presence of this group to give access to benzocyclobutenones,[11] thieno[2,3-*b*]thiophenes,[12] or methylideneindanones.[13] Weinreb amides have also been successfully used as internal electrophiles in cyclisation reactions of organolithiums derived from alkyl iodides, accessing cyclic ketones,[14] or vinyl iodides, in the synthesis of (−)-Brunsvigine,[15] or the hexahydrobenzofuran subunit of Avermeticin.[16]

In connection with our interest in aromatic lithiation,[17] we decided to develop an anionic cyclisation approach toward

Keywords: Lithiation; Lithium–halogen exchange; Parham cyclisation; Pyrrolo[1,2-*b*]isoquinoline.
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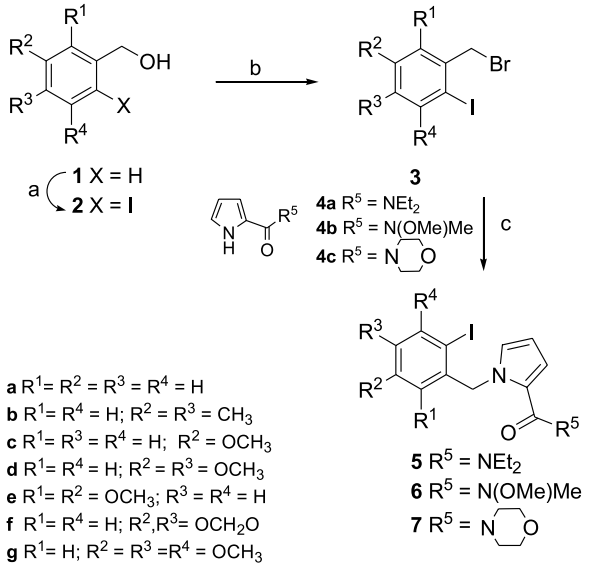
the construction of the pyrrolo[1,2-*b*]isoquinolone core present in some natural products such as the lycorine class of *Amaryllidaceae* alkaloids[18] and the phenanthroindolizidine alkaloids.[19] In the planned synthetic strategy, an aryllithium would be generated from a *N*-(*o*-halobenzyl)-pyrrole-2-carboxamide, that is expected to undergo a 6-*exo*-trig cyclisation onto the amide carbonyl of the pyrrole ring to provide the target heterocycle. A key feature of this synthetic approach is the ability of the amide moiety to intercept the aryllithium in an intramolecular fashion. Therefore, in order to study the influence of the nature of the substituents at the amide nitrogen atom on Parham-type cyclisations, this metalation–cyclisation sequence would be tested using different types of amides (*N*,*N*-dialkyl, Weinreb amides and morpholine amides) as internal electrophiles. It should be pointed out that, although morpholine amides are expected to be good electrophiles, and have been used in acylation reaction with organometallic reagents,[20] they have not been used in Parham-type cyclisations. However, the low cost of the morpholine, compared to the MeONHMe·HCl that is needed to make the Weinreb amides, led us to test the morpholine amides as internal electrophiles. Herein, we provide the full account of our investigations in this area,[21] including the extension of this strategy to the construction of seven and eight membered rings.



Scheme 1. Synthesis of *N*-benzylpyrroles **5**–**7**. Reagents: (a) I_2, CF_3CO_2Ag, $CHCl_3$, rt; (b) PBr_3, rt or HBr (45%), 0 °C; (c) KOH, DMSO, rt.

2. Results

2.1. Synthesis of *N*-benzylpyrroles

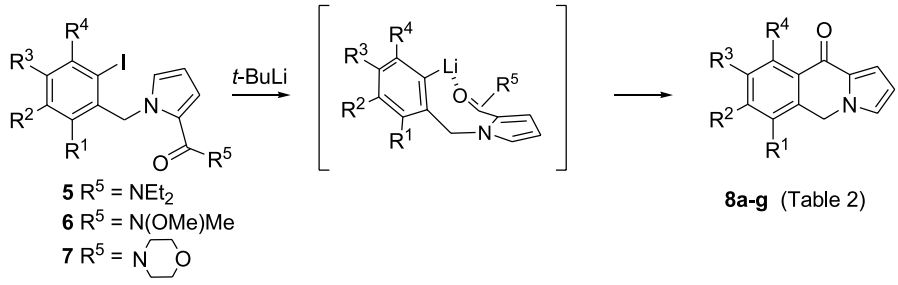
The study started with the synthesis of the substrates **5**–**7** with different substituents at the aromatic ring to prove the generality of the approach. Thus, *N*-(*o*-iodobenzyl)pyrroles were prepared by alkylation of the corresponding pyrrole-2-carboxamide **4a**–**c** under standard conditions (Scheme 1, Table 1). Iodobenzyl bromides **3a**–**g** were obtained from the corresponding benzylic alcohols **1** in two steps. Aromatic iodination of benzylic alcohols **1b**–**g** with I_2/CF_3CO_2Ag in $CHCl_3$ afforded alcohols **2b**–**g** in good yields (64–94%). In all cases the reaction was completely regioselective, except in **e**, where a minor amount of the 5-iodo regioisomer was obtained (see Section 3). Subsequent treatment with PBr_3 for cases **a**–**f**, or with HBr for **g** afforded bromides **3a**–**g** (86–99%).

2.2. Parham cyclisation of *N*-benzylpyrroles

We started studying the *N*,*N*-diethylcarbamoyl group as an internal electrophile. The metalation–cyclisation sequence was carried out under several conditions, using *t*-BuLi (2.2 equiv). Cyclisation conditions had to be optimised for each substrate **5a**–**g**, and minor amounts of deiodinated *N*-benzylpyrroles **9a**–**g** were always isolated together with the pyrrolisoquinolines **8**. For instance, when benzylpyrrole **5d** was treated with *t*-BuLi (2.2 equiv) at −78 °C for 3 h, and the reaction was quenched at 0 °C, pyrrolosoquinoline **8d** was obtained in 49% yield, together with **9d** (24%) (Fig. 1). However, if the reaction mixture was allowed to reach rt, and stirred for 3 h, the pyrroloisoquinoline **8d** was obtained in 79% yield (Table 2, entry 4). Thus, iodine–lithium exchange took place efficiently at −78 °C, but higher temperature was required for cyclisation. As shown in Table 2, some of the substrates required even longer periods at room temperature (entry 6), or the use of *n*-BuLi as metalating agent (entry 2). Thus, when **5f** or **5b** were treated with *t*-BuLi under the standard conditions (Method A), the corresponding deiodinated benzylpyrroles **9f** or **9b** were obtained (39 and 33% respectively). Under all conditions tested, no cyclisation product was obtained from **5g** which, under standard conditions gave only deiodinated product **9g** (81%, entry 7). In general, only moderate yields of pyrroloisoquinolines were obtained when the aromatic ring is activated by donor groups. Although in related Parham-type cyclisations no influence of the aromatic ring substitution pattern has been observed,[22] it seems that, once the iodine–lithium exchange

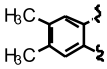
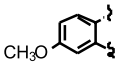
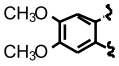
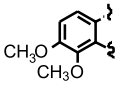
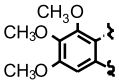
Table 1. Synthesis of benzylpyrroles **5**, **6**, and **7** by alkylation of **4**

Entry	$R^5=NEt_2$		$R^5=N(OMe)Me$		$R^5=N\square O$	
	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
1	**5a**	60	**6a**	90	**7a**	63
2	**5b**	83	**6b**	78	**7b**	98
3	**5c**	94	**6c**	83	**7c**	86
4	**5d**	73	**6d**	95	**7d**	93
5	**5e**	25	**6e**	61	**7e**	50
6	**5f**	84	**6f**	77	**7f**	68
7	**5g**	56	**6g**	73	**7g**	40



Scheme 2. Parham cyclisation of benzylpyrroles **5**–**7**.

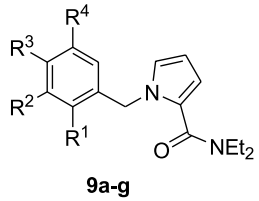
Table 2. Synthesis of pyrrolo[1,2-*b*]isoquinolines

Entry	Product		$R^5=NEt_2$	$R^5=N(OMe)Me$		$R^5=N\square O$	
			Method A[a], yield (%)	Method A[a], yield (%)	Method B[b], yield (%)	Method A[a], yield (%)	Method B[b], yield (%)
1	**8a**		28[c]	83	87	73	63
2	**8b**		10[c]	60	80	60	98
3	**8c**		54	77	69	81	77
4	**8d**		79	70	86	60	88
5	**8e**		40	24	62	40	76
6	**8f**		34[d]	62	73	60	63
7	**8g**		[e]	15	68	—	59

[a] Method A: *t*-BuLi (2.2 equiv), −78 °C, 3 h; →rt, 4 h.
[b] Method B: *t*-BuLi (2.2 equiv), −78 °C, 3 h.
[c] *n*-BuLi (3 equiv), −78 °C, 3 h; →rt, 4 h.
[d] *t*-BuLi (2.2 equiv), −78 °C, 3 h; →rt, 16 h.
[e] 81% of deiodinated benzylpyrrole **9g** was obtained.

has occurred, the more reactive aryllithium compounds lead to better yields of pyrroloisoquinolines **8** (Scheme 2).

We next focused our attention on the metalation–cyclisation sequence using Weinreb amides **6** and morpholine amides **7**. As shown in Table 2, both types of amides gave moderate to good yields of pyrroloisoquinolines **8** under Method A conditions, except when the aromatic ring bears methoxy groups on C-6 or C-3 (entries 5 and 7). However, when the reactions were quenched at −78 °C (Method B), yields of pyrroloisoquinolines **8** were consistently improved. Most significant is the improvement of the yield of pyrroloisoquinolines **8e** (24% vs. 62% from **6e** and 40% vs. 76% from **7e**) and **8g** (15% vs. 68% from **6g** and 0% vs. 59% from **7g**) (Table 2, entries 5 and 7). In these cases, the poor results obtained when the reactions are quenched at room temperature might be due to an equilibration of the intermediate organolithium prior to cyclisation. Thus, as shown in Table 2, in all cases the use of Weinreb amides or morpholine amides as internal electrophiles clearly improved the results obtained with diethyl amides. The most significant results would be the synthesis of pyrroloisoquinolines **8a**, **8b**, or **8g**.



a $R^1=R^2=R^3=R^4=H$
b $R^1=R^4=H$; $R^2=R^3=CH_3$
c $R^1=R^3=R^4=H$; $R^2=OCH_3$
d $R^1=R^4=H$; $R^2=R^3=OCH_3$
e $R^1=R^2=OCH_3$; $R^3=R^4=H$
f $R^1=R^4=H$; $R^2,R^3=OCH_2O$
g $R^1=H$; $R^2=R^3=R^4=OCH_3$

Figure 1. Deiodinated *N*-benzylpyrroles **9a**–**g**.

Amides are generally useful electrophiles in Parham cyclisations due to a complex induced proximity effect (CIPE).[23,24] Thus, lithium–iodine exchange could be favoured first by coordination of the organolithium to the

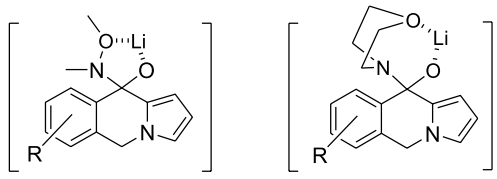
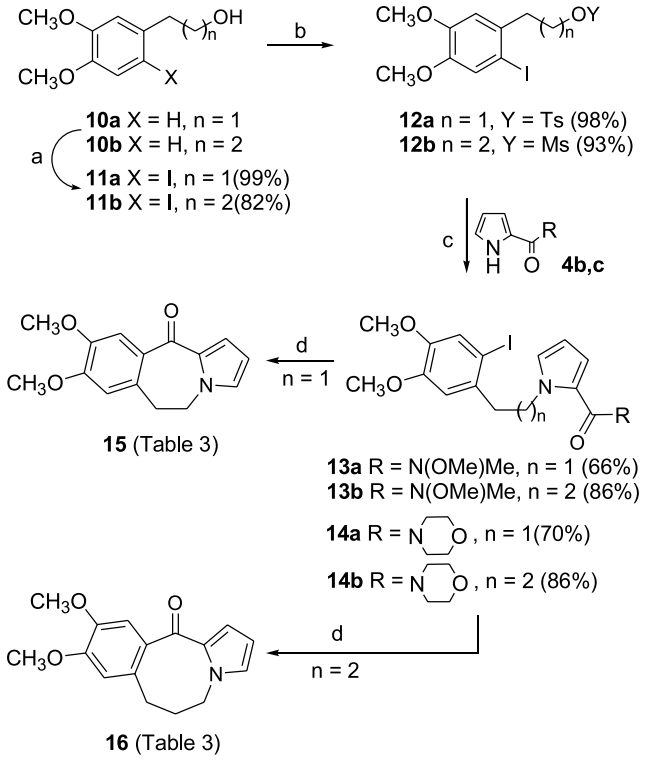


Figure 2.

amide group, and second, by stabilisation of the resulting aryllithium. Although there is no significant difference in the efficiency of Weinreb amides and morpholine amides as internal electrophiles, the better behaviour of both compared to *N*,*N*-diethyl amides could be attributed to the extra stabilisation of the intermediate generated after cyclisation by formation of an internal chelate, as depicted in Figure 2.

2.3. Parham cyclisation of *N*-phenethyl- and *N*-phenylpropylpyrroles

In view of the excellent results obtained in the formation of pyrrolosoquinoline ring system with Weinreb amides or morpholine amides, we decided to investigate the feasibility of using this type of Parham cyclisation to construct a seven or an eight-membered ring, opening a new access to the pyrrolobenzoazepine and pyrrolobenzoazocine skeletons. The pyrrolobenzoazepine core is present in *Cephalotaxus* alkaloids,[25] and some pyrrolobenzoazepines have muscle relaxant, antihypertensive or antipsychotic properties.[26] Thus, the required pyrrole-2-carboxamides **13** and **14** and were obtained from 3,4-dimethoxyphenethyl alcohol **10a** and 3,4-dimethoxyphenylpropan-1-ol **10b** in three steps, as described in Scheme 3. Parham cyclisation was carried out



Scheme 3. Parham cyclisation of *N*-phenethyl and *N*-phenylpropylpyrroles. Reagents: (a) I_2, CF_3CO_2Ag, $CHCl_3$, rt; (b) TsCl or MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) KOH, DMSO, rt; (d) *t*-BuLi, −78 °C, 3 h.

Table 3. Synthesis of **15** and **16**

Substrate	Method[a]	Product	Yield, %
13a	B	**15**	59
14a	B	**15**	58
13b	B	**16**	55
14b	B	**16**	57

[a] Method B: *t*-BuLi (2.2 equiv), −78 °C, 3 h.

using 2.2 equiv of *t*-BuLi at −78 °C. As shown in Table 3, moderate to good yields of the pyrrolo[1,2-*a*]benzo[*d*]-azepine-11-one **15** and pyrrolo[1,2-*a*]benzo[*d*]azozin-12-one **16** were obtained when the reaction was quenched at low temperature.

In summary, it has been shown that *N*-(*o*-iodobenzyl)-pyrrole-2-carboxamides tolerate lithium–iodine exchange reaction conditions, allowing the efficient synthesis of the pyrrolo[1,2-*b*]isoquinoline nucleus. The *N*-methoxy-*N*-methyl and morpholine amides behave as excellent internal electrophiles, improving the results obtained with *N*,*N*-diethyl amides. This procedure has also been extended to the construction of fused seven and eight membered rings, opening also new routes to other heterocyclic systems (pyrrolo[1,2-*a*]benzazepines and pyrrolo[1,2-*a*]benzo-azocines) with potential pharmacological properties that could compete with previously reported strategies.[27]

3. Experimental

3.1. Iodination reactions. General procedure

A solution of I_2 (250 mg, 1 mmol) in dry $CHCl_3$ (30 mL) was added over a suspension of CF_3COOAg (220 mg, 1 mmol) and alcohols **1b–g**, or **10a**,**b** (1 mmol) in $CHCl_3$ (5 mL). The reaction mixture was stirred at rt during 30 min, the resulting AgI precipitate was filtered, and the resulting solution was washed with saturated $Na_2S_2O_3$. Evaporation of the solvent afforded iodinated alcohols **2b–g**, or **11a**,**b**, which were crystallised from Et_2O.

3.1.1. 2-Iodo-4,5-dimethylbenzyl alcohol (2b). According to the general procedure, alcohol **1b** (136 mg, 1 mmol) was treated with I_2 (250 mg, 1 mmol) and CF_3COOAg (220 mg, 1 mmol) in $CHCl_3$ (30 mL). After work-up, alcohol **2b** was recrystallised from Et_2O (183 mg, 70%): mp (Et_2O) 110–112 °C; IR (KBr) 3260 cm^{-1}; ^1H NMR ($CDCl_3$) 2.20 (s, 3H), 2.21 (s, 3H), 4.58 (s, 2H), 7.17 (s, 1H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$) 18.9, 19.3, 68.9, 93.8, 129.8, 137.1, 138.2, 139.7, 139.8. MS (EI) *m*/*z* (rel intensity) 262 (M^+, 78), 245 (11), 135 (30), 133 (21), 107 (84), 106 (31), 105 (37), 103 (17), 92 (33), 91 (100), 85 (28), 83 (42), 79 (32), 78 (14), 77 (35), 65 (20), 63 (17), 53 (11), 51 (23). Anal. Calcd for $C_9H_{11}IO$: C, 41.24; H, 4.23. Found: C, 41.59; H, 3.94.

3.1.2. 2-Iodo-5-methoxybenzyl alcohol (2c).[28] According to the general procedure, alcohol **1c** (136 mg, 1 mmol) was treated with I_2 (250 mg, 1 mmol) and CF_3COOAg (220 mg, 1 mmol) in $CHCl_3$ (30 mL). After work-up, alcohol **2c** was recrystallised from Et_2O (167 mg, 64%): mp (Et_2O) 64–65 °C; IR (KBr) 3260 cm^{-1}; ^1H NMR ($CDCl_3$) 3.10 (s, 1H), 3.75 (s, 3H), 4.54 (s, 2H), 6.54 (dd, J=8.7, 2.8 Hz, 1H),

7.01 (d, $J=2.8$ Hz, 1H), 7.60 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 55.2, 68.7, 85.1, 113.8, 115.0, 139.3, 143.4, 159.9. The rest of the spectroscopic and physical data are consistent with those described in the literature.[28]

3.1.3. 2-Iodo-4,5-dimethoxybenzyl alcohol (2d).[29] According to the general procedure, alcohol **1d** (168 mg, 1 mmol) was treated with I_2 (250 mg, 1 mmol) and CF_3COOAg (220 mg, 1 mmol) in $CHCl_3$ (30 mL). After work-up, alcohol **2d** was recrystallised from Et_2O (188 mg, 64%): mp (Et_2O) 83–85 °C; IR (KBr) 3270 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.40 (s, 1H), 3.84 (s, 6H), 4.56 (s, 2H), 6.97 (s, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$) 55.8, 56.1, 68.9, 85.2, 111.4, 121.3, 135.1, 148.7, 149.3. The rest of the spectroscopic and physical data are consistent with those described in the literature.[29]

3.1.4. 6-Iodo-2,3-dimethoxybenzyl alcohol (2e) and 5-iodo-2,3-dimethoxybenzyl alcohol (2e′). According to the general procedure, alcohol **1d** (168 mg, 1 mmol) was treated with I_2 (250 mg, 1 mmol) and CF_3COOAg (220 mg, 1 mmol) in $CHCl_3$ (30 mL). After work-up, flash column chromatography afforded a mixture of **2e** and **2e′** in a 3:1 ratio, that could not be separated. Data of the mixture is given (178 mg, 73 and 83% conversion); IR (neat) 3422 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.42 (s, 1H, both isomers), 3.71 (s, 3H, minor), 3.73 (s, 3H, both isomers), 3.77 (s, 3H, major), 4.51 (s, 2H, minor), 4.68 (s, 2H, major), 6.53 (d, $J=$ 8.7 Hz, 1H, major), 7.03 (d, $J=2.0$ Hz, 1H, minor), 7.22 (d, $J=2.0$ Hz, 1H, minor), 7.40 (d, $J=8.7$ Hz, 1H, major); ^{13}C NMR ($CDCl_3$) 55.7 (major), 55.8 (minor), 59.6 (minor), 60.6 (minor), 61.5 (major), 64.2 (major), 86.8, 88.5 (major, minor), 113.9 (major), 120.7, 129.0 (minor), 134.3 (major), 136.3 (major), 136.5 (minor), 146.2 (minor), 147.9 (major), 152.7 (minor), 152.9 (major). MS (EI) *m/z* (rel intensity) 295 ($M^+ +1$, 10), 294 (M^+, 100), 279 (13), 152 (19), 139 (24), 124 (39), 109 (30), 108 (12), 106 (10), 85 (11), 83 (17), 81 (19), 79 (13), 78 (11), 77 (19), 65 (11), 63 (17), 53 (23), 52 (10), 51 (20).

3.1.5. 2-Iodo-4,5-methylendioxybenzyl alcohol (2f).[30] According to the general procedure, alcohol **1f** (152 mg, 1 mmol) was treated with I_2 (250 mg, 1 mmol) and CF_3COOAg (220 mg, 1 mmol) in $CHCl_3$ (30 mL). After work-up, alcohol **2f** was recrystallised from Et_2O (211 mg, 76%): mp (Et_2O) 107–109 °C; IR (KBr) 3200 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.31 (s, 1H), 4.55 (s, 2H), 5.96 (s, 2H), 6.96 (s, 1H), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$) 69.1, 85.3, 101.6, 109.0, 118.4, 136.1, 147.8, 148.5. The rest of the spectroscopic and physical data are consistent with those described in the literature.[30]

3.1.6. 2-Iodo-3,4,5-trimethoxybenzyl alcohol (2g).[31] According to the general procedure, alcohol **1g** (198 mg, 1 mmol) was treated with I_2 (250 mg, 1 mmol) and CF_3COOAg (220 mg, 1 mmol) in $CHCl_3$ (30 mL). After work-up, alcohol **2g** was recrystallised from Et_2O (305 mg, 94%): mp (Et_2O) 52–54 °C; IR (neat) 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.75 (s, 1H), 3.83 (s, 6H), 3.84 (s, 3H), 4.59 (s, 2H), 6.89 (s, 1H); ^{13}C NMR ($CDCl_3$) 56.0, 60.7, 60.9, 69.1, 84.2, 107.6, 138.3, 141.0, 152.7, 153.7. The rest of the spectroscopic and physical data are consistent with those described in the literature.[31]

3.1.7. 2-(2-Iodo-4,5-dimethoxyphenyl)ethanol (11a).[32] According to the general procedure, alcohol **10a** (1 g, 6 mmol) was treated with I_2 (1.5 g, 6 mmol) and CF_3COOAg (1.33 g, 6 mmol) in $CHCl_3$ (100 mL). After work-up, alcohol **11a** was recrystallised from Et_2O (1.8 g, 99%): mp (Et_2O) 53–54 °C; IR (neat) 3580 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.27 (s, 1H), 2.87 (t, $J=6.7$ Hz, 2H,), 3.75 (t, $J=$ 6.7 Hz, 2H), 3.78(s, 3H), 3.79 (s, 3H), 6.73 (s, 1H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$) 43.1, 55,8, 56.0, 62.2, 88.1, 112.9, 121.5, 133.3, 147.9, 149.0. The rest of the spectroscopic and physical data are consistent with those described in the literature.[32]

3.1.8. 3-(2-Iodo-4,5-dimethoxyphenyl)propan-1-ol (11b). According to the general procedure, alcohol **10b** (6.3 g, 32 mmol) was treated with I_2 (8.2 g, 32 mmol) and CF_3COOAg (7.14 g, 32 mmol) in $CHCl_3$ (100 mL). After work-up, alcohol **11a** was recrystallised from Et_2O (8.5 g, 82%): mp (Et_2O) 107–108 °C; IR (neat) 3381 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.52 (s, 1H), 1.79–1.90 (m, 2H), 2.75 (t, $J=$ 7.8 Hz, 2H), 3.71 (t, $J=6.3$ Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.75 (s, 1H), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$) 33.2, 36.5, 55.8, 56.0, 61.8, 87.8, 112.1, 121.5, 136.7, 147.6, 149.2. MS (EI) *m/z* (rel intensity) 322 (M^+, 64), 277(36), 167(16), 152(12), 151(100).

3.2. Synthesis of bromides 3a–g. General procedure

PBr_3 (0.19 mL, 2 mmol) was added over a solution of alcohols **2a–g** (1 mmol) in dry CH_2Cl_2 (10 mL), and the reaction mixture was stirred at rt for 16 h. Solvent was evaporated, and the resulting oil was treated with saturated $NaHCO_3$. The resulting aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, yielding bromides **3a–g**, which were crystallised from Et_2O.

3.2.1. 2-Iodobenzyl bromide (3a).[33] According to the general procedure, alcohol **2a** (234 mg, 1 mmol) was treated with PBr_3 (0.19 mL, 2 mmol) in dry CH_2Cl_2 (10 mL). After work-up, bromide **3a** was recrystallised from Et_2O (291 mg, 98%): mp (Et_2O) 56–58 °C; ^{1}H NMR ($CDCl_3$) 4.60 (s, 2H), 6.98 (td, $J=7.7$, 1.5 Hz, 1H), 7.34 (td, $J=7.5$, 0.9 Hz, 1H), 7.47 (dd, $J=7.6$, 1.5 Hz, 1H), 7.86 (d, $J=7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 38.8, 100.1, 128.8, 130.1, 130.4, 140.0, 140.1. The rest of the spectroscopic and physical data are consistent with those described in the literature.[33]

3.2.2. 2-Iodo-4,5-dimethylbenzyl bromide (3b). According to the general procedure, alcohol **2b** (262 mg, 1 mmol) was treated with PBr_3 (0.19 mL, 2 mmol) in dry CH_2Cl_2 (10 mL). After work-up, bromide **3b** was recrystallised from Et_2O (325 mg, 99%): mp (Et_2O) 76–78 °C; IR (KBr) 3260 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.21 (s, 6H), 4.56 (s, 2H), 7.24 (s, 1H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) 19.0, 19.3, 38.9, 96.3, 131.4, 137.3, 137.5, 139.4, 140.5. MS (EI) *m/z* (rel intensity) 326 ($M^+ +2$, 10), 324 (M^+, 9), 246 (10), 245 (100), 118 (41), 117 (24), 115 (15), 91 (14), 85 (30), 83 (46), 51 (12).

3.2.3. 2-Iodo-5-methoxybenzyl bromide (3c).[34] According to the general procedure, alcohol **2c** (264 mg, 1 mmol) was treated with PBr_3 (0.19 mL, 2 mmol) in dry CH_2Cl_2

(10 mL). After work-up, bromide **3c** was recrystallised from Et_2O (280 mg, 86%): mp (Et_2O) 111–113 °C; ^1H NMR ($CDCl_3$) 3.80 (s, 3H), 4.54 (s, 2H), 6.59 (dd, $J=8.7$, 2.8 Hz, 1H), 7.03 (d, $J=2.8$ Hz, 1H), 7.70 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 38.7, 55.4, 88.3, 116.0, 116.3, 140.4, 140.9, 160.0. The rest of the spectroscopic and physical data are consistent with those described in the literature.[34]

3.2.4. 2-Iodo-4,5-dimethoxybenzyl bromide (3d).[33] According to the general procedure, alcohol **2d** (294 mg, 1 mmol) was treated with PBr_3 (0.19 mL, 2 mmol) in dry CH_2Cl_2 (10 mL). After work-up, bromide **3d** was recrystallised from Et_2O (339 mg, 95%): mp (Et_2O) 74–75 °C; ^1H NMR ($CDCl_3$) 3.86 (s, 3H), 3.87 (s, 3H), 4.58 (s, 2H), 6.96 (s, 1H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) 39.4, 56.0, 56.2, 88.5, 112.7, 121.8, 132.5, 149.6. The rest of the spectroscopic and physical data are consistent with those described in the literature.[33]

3.2.5. 6-Iodo-2,3-dimethoxybenzyl bromide (3e) and 5-iodo-2,3-dimethoxybenzyl bromide (3e′). According to the general procedure, a mixture of alcohols **2e/2e′** in a 3:1 ratio (294 mg, 1 mmol) was treated with PBr_3 (0.19 mL, 2 mmol) in dry CH_2Cl_2 (10 mL). After work-up, a mixture of bromides **3e/3e′** in a 3:1 ratio was obtained, that could not be separated by chromatographic methods (332 mg, 93%). Data of the mixture are given: ^1H NMR ($CDCl_3$) 3.84 (s, 3H both isomers), 3.92 (s, 3H minor), 3.95 (s, 3H, major), 4.44 (s, 2H, minor), 4.70 (s, 2H, major), 6.64 (d, $J=8.7$ Hz, 1H, major), 7.13 (d, $J=2.0$ Hz, 1H, minor), 7.28 (d, $J=2$ Hz, 1H, minor), 7.51 (d, $J=8.7$ Hz, 1H, major); ^{13}C NMR ($CDCl_3$) 26.6 (minor), 33.5 (major), 55.8, 61.0 (major), 56.0, 60.8 (minor), 86.4 (minor), 89.1 (major), 114.5 (major), 121.9, 131.1 (minor), 133.6, 134.2 (major, minor), 134.5 (major), 147.3 (minor), 148.1, 153.1 (major), 153.3 (minor). MS (EI) *m/z* (rel intensity) 358 ($M^+ +2$, 16), 356 (M^+, 15), 277 (80), 262 (58), 232 (10), 92 (17), 90 (24), 87 (12), 85 (68), 83 (100), 77 (15), 64 (22), 63 (20).

3.2.6. 2-Iodo-4,5-methylendioxybenzyl bromide (3f).[30] According to the general procedure, alcohol **2f** (278 mg, 1 mmol) was treated with PBr_3 (0.19 mL, 2 mmol) in dry CH_2Cl_2 (10 mL). After work-up, bromide **3f** was recrystallised from Et_2O (310 mg, 91%): mp (Et_2O) dec.; ^1H NMR ($CDCl_3$) 4.55 (s, 2H), 5.99 (s, 2H), 6.96 (s, 1H), 7.24 (s, 1H); ^{13}C NMR ($CDCl_3$) 39.5, 88.8, 102.0, 110.0, 119.0, 133.3, 148.6. The rest of the spectroscopic and physical data are consistent with those described in the literature.[30]

3.2.7. 2-Iodo-3,4,5-trimethoxybenzyl bromide (3g). Alcohol **2g** (324 mg, 1 mmol) was treated with HBr (45%) (10 mL) at −10 °C under argon for 48 h. The precipitate obtained was filtered and washed with H_2O. The resulting bromide **3g** was recrystallised from Et_2O (298 mg, 77%): mp (Et_2O) 78–80 °C; ^1H NMR ($CDCl_3$) 3.86 (s, 9H), 4.62 (s, 2H), 6.88 (s, 1H); ^{13}C NMR ($CDCl_3$) 39.5, 56.1, 60.7, 60.9, 88.3, 109.5, 135.3, 142.0, 153.4, 153.6. MS (EI) *m/z* (rel intensity) 388 ($M^+ +2$, 4), 386 (M^+, 4), 165 (21), 135 (11), 90 (13), 79 (16), 77 (11), 66 (10), 63 (12), 53 (10), 51 (25).

3.2.8. 2-(2-Iodo-4,5-dimethoxyphenyl)ethyl *p*-toluensulfonate (12a). Et_3N (4.6 mL, 32.9 mmol) and tosyl chloride (6.3 g, 32.9 mmol) were added over a solution of alcohol **11a** (8.45 g, 27.4 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C, and the reaction mixture was stirred at rt for 30 min. The reaction mixture was washed with HCl (5 M, 5 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, yielding **12a**, which was crystallised from Et_2O (12.5 g, 98%): mp (Et_2O) 109–110 °C; ^1H NMR ($CDCl_3$) 2.42 (s, 3H), 3.01 (t, $J=6.9$ Hz, 2H), 3.81, 3.83 (s, 3H), 4.20 (t, $J=6.9$ Hz, 2H), 6.67 (s, 1H), 7.11 (s, 1H), 7.27 (d, $J=7.9$ Hz, 2H), 7.68 (d, $J=7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 21.3, 39.2, 55.6, 55.8, 69.0, 87.6, 112.8, 121.2, 127.4, 129.5, 130.9, 132.5, 144.4, 148.2, 148.9. MS (EI) *m/z* (rel intensity) 462 (M^+, 27), 291 (11), 290 (100), 277 (26), 151 (14), 91 (25), 65 (10).

3.2.9. 3-(2-Iodo-4,5-dimethoxyphenyl)propyl methanesulfonate (12b). Et_3N (1.9 mL, 13.6 mmol) and mesyl chloride (1.06 mL, 13.6 mmol) were added over a solution of alcohol **11b** (3.66 g, 11.4 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C, and the reaction mixture was stirred at rt for 30 min. The reaction mixture was washed with saturated $NaHCO_3$ (15 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, yielding **12b** (4.1 g, 93%); ^1H NMR ($CDCl_3$) 1.79–1.90 (m, 2H), 2.75 (t, $J=7.8$ Hz, 2H), 2.91 (s, 3H), 3.71 (t, $J=6.3$ Hz, 2H), 3.84, 3.85 (s, 3H), 6.75 (s, 1H), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$) 33.2, 36.5, 37.1, 55.8, 56.0, 65.8, 87.8, 112.1, 121.5, 136.7, 147.6, 149.2. MS (EI) *m/z* (rel intensity) 400 (M^+, 100), 304 (22), 289 (10), 277 (92), 177 (39), 151 (31), 146 (22), 91 (18).

3.3. Alkylation reactions. General procedure for the synthesis of *N*-benzyl-, *N*-phenethyl-, and *N*-phenylpropylpyrroles 5–7, 13, and 14

Pyrrole-2-carboxamide **4a**, **4b** or **4c** (1 mmol) was added over a suspension of powdered KOH (224 mg, 4 mmol) in DMSO (5 mL). The mixture was stirred at rt for 2 h, bromide **3a–g**, tosylate **12a**, or mesylate **12b** (2 mmol) was added, and the reaction mixture was stirred for 3 h. H_2O (10 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silicagel) afforded *N*-benzylpyrroles **5**, **6**, and **7**, *N*-phenethylpyrroles or *N*-phenylpropylpyrroles **13** or **14**.

3.3.1. 1-(2-Iodobenzyl)pyrrole-2-carboxylic acid diethyl amide (5a). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (165 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3a** (595 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **5a** as a colourless oil (227 mg, 60%); IR ($CHCl_3$) 1616 cm^{-1}; ^1H NMR ($CDCl_3$) 1.10 (t, $J=7.1$ Hz, 6H), 3.43 (q, $J=7.1$ Hz, 4H), 5.32 (s, 2H), 6.13 (dd, $J=3.7$, 2.6 Hz, 1H), 6.38 (dd, $J=3.7$, 1.7 Hz, 1H), 6.69 (dd, $J=7.7$, 1.3 Hz, 1H), 6.74 (dd, $J=2.6$, 1.7 Hz, 1H), 6.91 (td, $J=7.7$, 1.4 Hz, 1H), 7.21 (td, $J=7.7$, 1.3 Hz, 1H), 7.79 (dd, $J=7.7$, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 41.4, 56.2, 97.5, 107.2, 111.0,

125.1, 126.2, 128.2, 128.3, 128.9, 139.1, 140.8, 163.4. MS (EI) *m/z* (rel intensity) 383 ($M^+ + 1$, 8), 382 (M^+, 39), 282 (15), 256 (13), 255 (70), 217 (28), 184 (25), 183 (100), 182 (42), 156 (29), 155 (19), 154 (22), 127 (13), 100 (16), 91 (12), 90 (37), 89 (17), 72 (34). Anal. Calcd for $C_{16}H_{19}IN_2O$: C, 50.28; H, 5.01; N, 7.33. Found: C, 49.99; H, 5.10; N, 7.29.

3.3.2. 1-(2-Iodo-4,5-dimethylbenzyl)pyrrole-2-carboxylic acid diethyl amide (5b). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (260 mg, 1.6 mmol) was treated with KOH (340 mg, 6.1 mmol) in DMSO (6 mL), and bromide **3b** (1.03 g, 3.2 mmol). After work-up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **5b** as a colourless oil (530 mg, 83%); IR ($CHCl_3$) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 1.11 (t, $J=7.1$ Hz, 6H), 2.09 (s, 3H), 2.13 (s, 3H), 3.45 (q, $J=7.1$ Hz, 4H), 5.25 (s, 2H), 6.09 (dd, $J=4.0$, 2.8 Hz, 1H), 6.35 (dd, $J=4.0$, 2.0 Hz, 1H), 6.59 (s, 1H), 6.72 (dd, $J=2.8$, 2.0 Hz, 1H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.5, 18.8, 19.4, 41.3, 55.6, 94.4, 107.0, 110.9, 124.9, 126.1, 129.9, 139.8, 136.9, 137.9, 163.6. MS (EI) *m/z* (rel intensity) 410 (M^+, 17), 284 (23), 283 (100), 245 (31), 212 (17), 211 (57), 210 (44), 196 (17), 190 (17), 184 (19), 183 (13), 168 (12), 119 (10), 118 (23), 117 (17), 115 (13), 100 (17), 91 (12), 85 (10), 83 (16), 72 (29). Anal. Calcd for $C_{18}H_{23}IN_2O$: C, 52.69; H, 5.65; N, 6.83. Found: C, 52.44; H, 5.21; N, 7.02.

3.3.3. 1-(2-Iodo-5-methoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (5c). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (150 mg, 0.9 mmol) was treated with KOH (250 mg, 4.4 mmol) in DMSO (5 mL), and bromide **3c** (610 mg, 1.9 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **5c** as a colourless oil (350 mg, 94%); IR ($CHCl_3$) 1617 cm^{-1}; ^1H NMR ($CDCl_3$) 1.10 (t, $J=7.1$ Hz, 6H), 3.45 (q, $J=7.1$ Hz, 4H), 3.64 (s, 3H), 5.27 (s, 2H), 6.12 (dd, $J=3.6$, 2.8 Hz, 1H), 6.26 (d, $J=2.8$ Hz, 1H), 6.38 (dd, $J=3.6$, 1.6 Hz, 1H), 6.50–6.52 (m, 1H), 6.73 (dd, $J=2.8$, 1.6 Hz, 1H), 7.63 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 41.3, 55.1, 56.1, 85.8, 107.2, 111.1, 114.5, 125.1, 126.1, 139.5, 141.9, 160.0, 163.3. MS (EI) *m/z* (rel intensity) 412 (M^+, 3), 286 (24), 285 (100), 214 (14), 213 (41), 212 (23), 192 (23), 186 (13), 170 (17), 120 (15), 100 (14), 85 (23), 83 (39), 72 (20). Anal. Calcd for $C_{17}H_{21}IN_2O_2$: C, 49.52; H, 5.13; N, 6.79. Found: C, 49.23; H, 5.41; N, 6.59.

3.3.4. 1-(2-Iodo-4,5-dimethoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (5d). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (884 mg, 2.0 mmol) was treated with KOH (448 mg, 8.0 mmol) in DMSO (20 mL), and bromide **3d** (1.5 g, 4.2 mmol). After work-up, flash column chromatography (silicagel, 40% hexane/AcOEt) afforded **5d** as a colourless oil (1.72 mg, 73%); IR ($CHCl_3$) 1616 cm^{-1}; ^1H NMR ($CDCl_3$) 1.11 (t, $J=7.1$ Hz, 6H), 3.44 (q, $J=7.1$ Hz, 4H), 3.68 (s, 3H), 3.80 (s, 3H), 5.24 (s, 2H), 6.08–6.09 (m, 1H), 6.34 (dd, $J=3.6$, 1.5 Hz, 1H), 6.44 (s, 1H), 6.72 (dd, $J=2.5$, 1.5 Hz, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.5, 41.2, 55.6, 55.6, 56.0, 86.1, 107.1, 111.0, 111.9, 121.3, 124.8, 126.2, 133.2, 148.7, 149.4, 163.5. MS (EI) *m/z* (rel intensity) 442 (M^+, 2), 316 (21), 315 (100), 277 (62), 244 (22), 243 (22), 242 (33), 222 (29), 200 (12), 150 (18), 107 (15), 100 (36), 94 (11), 92 (15), 85 (10), 83 (13), 79 (10), 77 (20), 72 (56), 64 (14), 63 (13), 56 (14), 51 (12). Anal. Calcd for $C_{18}H_{23}IN_2O_3$: C, 48.88; H, 5.24; N, 6.33. Found: C, 48.60; H, 5.36; N, 6.24.

3.3.5. 1-(6-Iodo-2,3-dimethoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (5e). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (600 mg, 3.6 mmol) was treated with KOH (780 mg, 13.9 mmol) in DMSO (15 mL), and a mixture of bromides **3e/3e′** in a 2:1 ratio (2.5 g, 7 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **5e** as a colourless oil (400 mg, 25%); IR ($CHCl_3$) 1613 cm^{-1}; ^1H NMR ($CDCl_3$) 1.23 (t, $J=7.1$ Hz, 6H), 3.57 (q, $J=7.1$ Hz, 4H), 3.68 (s, 3H), 3.81 (s, 3H), 5.39 (s, 2H), 5.97 (dd, $J=4.0$, 2.8 Hz, 1H), 6.29 (dd, $J=4.0$, 1.6 Hz, 1H), 6.49 (dd, $J=2.8$, 1.6 Hz, 1H), 6.64 (d, $J=8.7$ Hz, 1H), 7.51 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.5, 41.9, 50.5, 55.7, 60.8, 89.6, 106.6, 110.0, 114.1, 123.1, 126.7, 133.5, 134.5, 148.6, 153.1, 164.0. MS (EI) *m/z* (rel intensity) 442 (M^+, 16), 262 (15), 87 (11), 85 (64), 83 (100), 72 (13). Anal. Calcd for $C_{18}H_{23}IN_2O_3$: C, 48.88; H, 5.24; N, 6.33. Found: C, 49.03; H, 4.89; N, 5.90.

3.3.6. 1-(2-Iodo-4,5-methylendioxybenzyl)pyrrole-2-carboxylic acid diethyl amide (5f). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (710 mg, 4.3 mmol) was treated with KOH (1.05 g, 18.7 mmol) in DMSO (6 mL), and bromide **3f** (2.9 g, 8.6 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **5f** as a colourless oil (1.53 mg, 84%); IR ($CHCl_3$) 1615 cm^{-1}; ^1H NMR ($CDCl_3$) 1.14 (t, $J=7.1$ Hz, 6H), 3.46 (q, $J=7.1$ Hz, 4H), 5.22 (s, 2H), 5.89 (s, 2H), 6.10 (dd, $J=4.0$, 2.8 Hz, 1H), 6.34 (s, 1H), 6.36 (dd, $J=4.0$, 1.6 Hz, 1H), 6.73 (dd, $J=2.8$, 1.6 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.2, 41.0, 55.7, 85.4, 101.3, 107.0, 108.5, 110.8, 118.0, 124.6, 125.7, 134.0, 147.3, 148.3, 163.1. MS (EI) *m/z* (rel intensity) 426 (M^+, 2), 299 (45), 261 (23), 227 (15), 226 (16), 206 (9), 100 (9), 87 (13), 85 (69), 83 (100), 76 (11), 72 (13). Anal. Calcd for $C_{17}H_{19}IN_2O_3$: C, 47.90; H, 4.49; N, 6.57. Found: C, 48.01; H, 4.65; N, 6.12.

3.3.7. 1-(2-Iodo-3,4,5-trimethoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (5g). According to the general procedure, *N*,*N*-diethyl-pyrrole-2-carboxamide **4a** (150 mg, 0.9 mmol) was treated with KOH (240 mg, 4.3 mmol) in DMSO (6 mL), and bromide **3g** (700 mg, 1.8 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **5g** as a colourless oil (240 mg, 56%); IR ($CHCl_3$) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 1.09 (t, $J=7.1$ Hz, 6H), 3.43 (q, $J=7.1$ Hz, 4H), 3.63 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 5.27 (s, 2H), 6.08–6.10 (m, 1H), 6.15 (s, 1H), 6.34–6.36 (m, 1H), 6.73 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 41.4, 55.7, 56.2, 60.6, 60.7, 85.4, 107.1, 107.8, 111.0, 125.0, 126.1, 136.4, 141.0, 152.6, 153.6, 163.2. MS (EI) *m/z* (rel intensity) 346 (12), 345 (38), 307 (16), 252 (48), 181 (24), 100 (18), 87 (12), 85 (72), 83 (100), 72 (25). Anal. Calcd for $C_{19}H_{25}IN_2O_4$: C, 48.32; H, 5.33; N, 5.93. Found: C, 48.17; H, 5.01; N, 5.12.

3.3.8. 1-(2-Iodobenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6a). According to the general

procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3a** (594 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **6a** as a colourless oil, that was crystallised from Et_2O (333 mg, 90%): mp (Et_2O) 100–102 °C; IR ($CHCl_3$) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) 3.27 (s, 3H), 3.66 (s, 3H), 5.52 (s, 2H), 6.23(dd, $J=4.0$, 2.8 Hz, 1H), 6.48 (dd, $J=7.9$, 1.2 Hz, 1H,), 6.79 (dd, $J=2.8$, 1.8 Hz), 6.90–6.93 (m, 1H), 7.02 (dd, $J=4.0$, 1.8 Hz, 1H), 7.18–7.24 (m, 1H), 7.82 (dd, $J=7.9$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.5, 57.3, 60.8, 96.9, 108.2, 116.6, 123.1, 127.1, 127.5, 128.3, 128.6, 138.9, 161.8. MS (EI) *m/z* (rel intensity) 370 (M^+, 5), 311 (7), 310 (51), 217 (15), 184 (12), 183 (10), 182 (10), 154 (10), 127 (5), 90 (14), 89 (7). Anal. Calcd for $C_{14}H_{15}IN_2O_2$: C, 45.42; H, 4.08; N, 7.57. Found: C, 45.42; H, 4.27; N, 7.25.

3.3.9. 1-(2-Iodo-4,5-dimethylbenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6b). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3b** (645 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 10% hexane/AcOEt) afforded **6b** as a colourless oil, that was crystallised from Et_2O (310 mg, 78%): mp (Et_2O) 76–79 °C; IR ($CHCl_3$) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 2.08 (s, 3H), 2.16 (s, 3H), 3.30 (s, 3H), 3.66 (s, 3H,), 5.46 (s, 2H), 6.19 (dd, $J=4.0$, 2.4 Hz, 1H), 6.38 (s, 1H), 6.76 (dd, $J=2.4$, 1.8 Hz, 1H), 6.99 (dd, $J=4.0$, 1.8 Hz, 1H), 7.59(s, 1H); ^{13}C NMR ($CDCl_3$) 18.8, 19.5, 33.7, 56.8, 60.9, 93.7, 108.8, 116.5; 123.3, 127.3, 128.9; 137.1, 137.8, 138.3, 139.8, 162.1. MS (EI) *m/z* (rel intensity) 398 (M^+, 1), 338 (25), 245 (19), 241 (8), 221 (18), 211 (100), 210 (7), 196 (24), 168 (6), 118 (15), 117 (11), 115 (8), 91 (7), 83 (6).

3.3.10. 1-(2-Iodo-5-methoxybenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6c). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3c** (654 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **6b** as a colourless oil, that was crystallised from Et_2O (332 mg, 83%): mp (Et_2O) 84–85 °C; IR ($CHCl_3$) 1663 cm^{-1}; ^1H NMR ($CDCl_3$) 3.28 (s, 3H), 3.64 (s, 3H), 3.66 (s, 3H,), 5.48 (s, 2H), 6.07 (d, $J=3.0$ Hz, 1H), 6.22 (dd, $J=4.0$, 2.6 Hz, 1H), 6.53 (dd, $J=8.7$, 3.0 Hz, 1H), 6.80 (dd, $J=2.6$, 1.8 Hz, 1H), 7.02 (dd, $J=4.0$, 1.8 Hz, 1H), 7.67 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.7, 55.1, 57.3, 61.0, 85.3, 108.3, 113.8, 114.3, 116.8, 123.3, 127.7, 139.5, 142.5, 160.2, 162.0. MS (EI) *m/z* (rel intensity) 400 (M^+, 2), 340 (21), 273 (6), 247 (6), 214 (15), 213 (100), 212 (9), 182 (5), 170 (11), 120 (6), 93 (5), 77 (5). Anal. Calcd for $C_{15}H_{17}IN_2O_3$: C, 45.02; H, 4.28; N, 7.00. Found: C, 44.73; H, 4.20; N, 6.94.

3.3.11. 1-(2-Iodo-4,5-dimethoxybenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6d). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3d** (714 mg, 2 mmol) after work-up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **6d** as a colourless oil, that was crystallised from pentane (409 g, 95%); IR ($CHCl_3$) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) 3.30 (s, 3H), 3.65 (s, 3H), 3.67 (s, 3H), 3.84 (s, 3H), 5.46 (s, 2H), 6.19 (dd, $J=4.0$, 2.8 Hz, 1H), 6.28 (s, 1H), 6.82 (dd, $J=2.8$, 1.8 Hz, 1H), 6.97 (dd, $J=4.0$, 1.8 Hz, 1H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) 33.7, 55.6, 56.1, 56.6, 60.9, 85.6, 108.1, 111.1, 116.6, 121.3, 123.2, 127.4, 133.6, 148.6, 149.5, 162.2. MS (EI) *m/z* (rel intensity) 430 (M^+, 6), 370 (22), 243 (100), 83 (29). Anal. Calcd for $C_{16}H_{19}IN_2O_4$: C, 44.67; H, 4.45; N, 6.51. Found: C, 45.12; H, 4.44; N, 5.96.

3.3.12. 1-(6-Iodo-2,3-dimethoxybenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6e). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and a mixture of bromides **3e/3e′** in a 3:1 ratio (714 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **6e** as a colourless oil, that was crystallised from pentane (262 mg, 61%): mp (pentane) 94–96 °C; IR (KBr) 1622 cm^{-1}; ^1H NMR ($CDCl_3$) 3.39 (s, 3H), 3.70 (s, 3H), 3.72 (s, 3H), 3.84 (s, 3H), 5.62 (s, 2H), 6.03 (dd, $J=4.0$, 2.6 Hz, 1H), 6.52 (dd, $J=2.6$, 1.8 Hz, 1H), 6.68 (d, $J=8.7$ Hz, 1H), 6.86 (dd, $J=4.0$, 1.8 Hz, 1H), 7.56 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 34.1, 51.2, 56.7, 60.8, 60.9, 89.9, 107.3, 114.2, 115.5, 123.9, 125.0, 133.5, 134.5, 148.7, 153.1, 162.7. MS (EI) *m/z* (rel intensity) 430 (M^+,1), 370 (25), 262 (14), 244 (16), 243 (100), 228 (17), 212 (25), 200 (7), 108 (8), 92 (7), 90 (8). Anal. Calcd for $C_{16}H_{19}IN_2O_4$: C, 44.67; H, 4.45; N, 6.51. Found: C, 44.55; H, 4.46; N, 6.34.

3.3.13. 1-(2-Iodo-4,5-methylendioxybenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6f). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3f** (682 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **6f** as a colourless oil (319 mg, 77%); IR (KBr) 1624 cm^{-1}; ^1H NMR ($CDCl_3$) 3.30 (s, 3H), 3.67 (s, 3H), 5.43 (s, 2H), 5.90 (s, 2H), 6.10 (s, 1H), 6.21 (dd, $J=4.0$, 2.8 Hz, 1H), 6.78 (dd, $J=2.8$, 1.6 Hz, 1H), 7.01 (dd, $J=4.0$, 1.6 Hz, 1H), 7.23 (s, 1H); ^{13}C NMR ($CDCl_3$) 33.6, 57.2, 61.0, 84.8, 101.5, 107.9, 108.4, 116.8, 118.3, 123.1, 127.4, 134.8, 147.5, 148.7, 161.3. MS (EI) *m/z* (rel intensity) 414 (M^+, 2), 354 (21), 287 (11), 261 (15), 227 (100), 134 (6), 76 (8). Anal. Calcd for $C_{15}H_{15}IN_2O_4$: C, 43.50; H, 3.65; N, 6.76. Found: C, 43.53; H, 3.69; N, 6.54.

3.3.14. 1-(2-Iodo-3,4,5-trimethoxybenzyl)pyrrole-2-carboxylic acid methoxy methyl amide (6g). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **4b** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **3g** (756 mg, 2 mmol). After work-up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **6g** as a colourless oil, that was crystallised from pentane (336 mg, 73%): mp (pentane) 80–82 °C; IR (KBr) 1624 cm^{-1}; ^1H NMR ($CDCl_3$) 3.30 (s, 3H), 3.63 (s, 3H), 3.67 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 5.50 (s, 2H), 5.98 (s, 2H), 6.22 (dd, $J=4.0$, 2.6 Hz, 1H), 6.82 (dd, $J=2.6$, 1.8 Hz, 1H), 7.00 (dd, $J=4.0$, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.4, 55.5, 57.1,

60.4, 60.6, 60.7, 84.5, 106.8, 108.0, 116.4, 123.0, 127.5, 140.7, 156.8, 152.5, 153.7, 161.8. MS (EI) *m/z* (rel intensity) 460 (M^+,1), 400 (12), 334 (8), 333 (39), 307 (21), 274 (17), 273 (100), 272 (6), 259 (13), 258 (83), 240 (22), 230 (7), 227 (12), 210 (8), 165 (6). Anal. Calcd for $C_{17}H_{21}IN_2O_5$: C, 44.36; H, 4.60; N, 6.09. Found: C, 45.13; H, 4.64; N, 5.71.

3.3.15. 1-(2-Iodobenzyl)pyrrole-2-carboxylic acid morpholine amide (7a). According to the general procedure, pyrrole-2-carboxamide **4c** (1.34 g, 7.4 mmol) was treated with KOH (1.66 g, 29.7 mmol) in DMSO (35 mL), and bromide **3a** (4.41 g, 14.8 mmol) after work-up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **7a** as a colourless oil, that was crystallised from ethyl ether (2.00 g, 63%): mp (Et_2O) 96–98 °C; IR ($CHCl_3$) 1619 cm^{-1}; ^1H NMR ($CDCl_3$) 3.54–3.58 (m, 4H), 3.67–3.71 (m, 4H), 5.35 (s, 2H), 6.16 (dd, J=3.8, 2.8 Hz, 1H), 6.37 (dd, J=3.8, 1.6 Hz, 1H), 6.68 (dd, J=7.9, 1.2 Hz, 1H), 6.97 (dd, J=2.8, 1.6 Hz, 1H), 6.95 (td, J=7.9, 1.2 Hz, 1H), 7.22 (td, J=7.5, 1.2 Hz, 1H), 7.82 (dd, J=7.5, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 45.5, 56.3, 66.8, 97.6, 107.5, 112.0, 124.8, 125.9, 128.2, 128.4, 129.1, 139.3, 140.7, 162.7. MS (EI) *m/z* (rel intensity) 397 (M^++1, 10), 396 (M^+, 55), 282 (15), 269 (70), 217 (23), 184 (24), 183 (100), 182 (42), 155 (15), 154 (17), 90 (31), 70 (17). Anal. Calcd for $C_{16}H_{17}IN_2O_2$: C, 48.50; H, 4.32; N, 7.07. Found: C, 48.21; H, 4.43; N, 6.72.

3.3.16. 1-(2-Iodo-4,5-dimethylbenzyl)pyrrole-2-carboxylic acid morpholine amide (7b). According to the general procedure, pyrrole-2-carboxamide **4c** (118 mg, 0.65 mmol) was treated with KOH (147 mg, 2.6 mmol) in DMSO (10 mL), and bromide **3b** (425 mg, 1.31 mmol). After work-up, flash column chromatography (silicagel, 40% hexane/AcOEt) afforded **7b** as a colourless oil (271 mg, 95%); IR ($CHCl_3$) 1621 cm^{-1}; ^1H NMR ($CDCl_3$) 2.09 (s, 3H), 2.14 (s, 3H), 3.52–3.56 (m, 4H), 3.66–3.69 (m, 4H), 5.26 (s, 2H), 6.10 (dd, J=3.6, 2.7 Hz, 1H), 6.32 (dd, J=3.6, 1.6 Hz, 1H), 6.54 (s, 1H), 6.75 (dd, J=2.7, 1.6 Hz, 1H), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$) 18.6, 19.3, 45.4, 55.4, 66.6, 94.2, 107.1, 112.5, 124.6, 125.6, 129.6, 136.8, 137.6, 137.9, 139.7, 162.7. MS (EI) *m/z* (rel intensity) 424 (M^+, 9), 298 (21), 297 (100), 245 (21), 212 (11), 211 (46), 210 (29), 204 (21), 196 (11), 118 (11), 70 (9). Anal. Calcd for $C_{18}H_{21}IN_2O_2$: C, 50.96; H, 4.99; N, 6.60. Found: C, 50.87; H, 4.63; N, 6.72.

3.3.17. 1-(2-Iodo-5-methoxybenzyl)pyrrole-2-carboxylic acid morpholine amide (7c). According to the general procedure, pyrrole-2-carboxamide **4c** (597 mg, 3.3 mmol) was treated with KOH (744 mg, 13.2 mmol) in DMSO (15 mL), and bromide **3c** (2.17 g, 6.6 mmol). After work-up, flash column chromatography (silicagel, 40% hexane/AcOEt) afforded **7c** as a white solid, that was crystallised from ethyl ether (1.22 g, 86%): mp (Et_2O) 96–98 °C; IR (KBr) 1619 cm^{-1}; ^1H NMR ($CDCl_3$) 3.49–3.53 (m, 4H), 3.62 (s, 3H), 3.64–3.67 (m, 4H), 5.27 (s, 2H), 6.11 (dd, J=3.7, 2.8 Hz, 1H), 6.22 (d, J=2.8 Hz, 1H), 6.32 (dd, J=3.7, 1.6 Hz, 1H), 6.51 (dd, J=8.7, 2.8 Hz, 1H), 6.76 (dd, J=2.8, 1.6 Hz, 1H), 7.63 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 45.7, 55.3, 56.3, 67.0, 85.8, 107.4, 112.9, 114.3, 114.9, 124.7, 125.9, 139.7, 141.8, 160.1, 162.7. MS (EI) *m/z* (rel intensity) 426 (M^+, 11), 299 (100), 214 (11), 213 (37), 212 (16), 206 (25), 170 (11), 120 (10), 114 (10), 70 (13). Anal. Calcd for $C_{17}H_{19}IN_2O_3$: C, 47.90; H, 4.49; N, 6.57. Found: C, 47.81; H, 4.42; N, 6.45.

3.3.18. 1-(2-Iodo-4,5-dimethoxybenzyl)pyrrole-2-carboxylic acid morpholine amide (7d). According to the general procedure, pyrrole-2-carboxamide **4c** (446 mg, 2.5 mmol) was treated with KOH (560 mg, 9.9 mmol) in DMSO (5 mL), and bromide **3d** (1.77 g, 4.9 mmol) after work-up, flash column chromatography (silicagel, 70% hexane/AcOEt) afforded **7d** as a colourless oil (1.05 g, 93%); IR ($CHCl_3$) 1619 cm^{-1}; ^1H NMR ($CDCl_3$) 3.42–3.43 (m, 4H), 3.52–3.54 (m, 4H), 3.55 (s, 3H), 3.67 (s, 3H), 5.13 (s, 2H), 5.97 (dd, J=3.6, 2.8 Hz, 1H), 6.19 (dd, J=3.6, 1.6 Hz, 1H), 6.34 (s, 1H), 6.66 (dd, J=2.8, 1.6 Hz, 1H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$) 45.0, 55.1, 55.2, 55.6, 66.3, 85.8, 106.9, 111.6, 112.3, 120.9, 124.3, 125.3, 132.5, 148.4, 148.9, 162.3. MS (EI) *m/z* (rel intensity) 456 (M^+, 3), 330 (19), 329 (100), 277 (52), 243 (17), 242 (16), 236 (26), 150 (10), 114 (11), 70 (14).

3.3.19. 1-(6-Iodo-2,3-dimethoxybenzyl)pyrrole-2-carboxylic acid morpholine amide (7e). According to the general procedure, pyrrole-2-carboxamide **4c** (321 mg, 1.8 mmol) was treated with KOH (400 mg, 7.1 mmol) in DMSO (10 mL), and a mixture of bromides **3e/3e′** in a 2.2/1 ratio (1.27 g, 3.5 mmol). After work-up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **7e** as a white solid that was crystallised from pentane. (413 mg, 50%): mp (pentane) 148–150 °C; IR (KBr) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 3.68 (s, 3H), 3.68–3.70 (m, 4H), 3.75–3.77 (m, 4H), 3.79 (s, 3H), 5.42 (s, 2H), 5.97 (dd, J=3.6, 2.4 Hz, 1H), 6.23 (dd, J=3.6, 1.6 Hz, 1H), 6.59 (dd, J=2.4, 1.6 Hz, 1H), 6.63 (d, J=8.7 Hz, 1H), 7.50 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 45.8, 50.4, 55.8, 60.9, 66.9, 89.5, 107.1, 112.1, 114.3, 124.1, 125.4, 133.6, 134.7, 148.8, 153.2, 163.5. MS (EI) *m/z* (rel intensity) 456 (M^+, 6), 330 (22), 391 (100), 262 (10), 243 (13), 236 (24), 114 (11), 70 (15).

3.3.20. 1-(2-Iodo-4,5-methylendioxybenzyl)pyrrole-2-carboxylic acid morpholine amide (7f). According to the general procedure, pyrrole-2-carboxamide **4c** (53 mg, 0.3 mmol) was treated with KOH (66 mg, 1.2 mmol) in DMSO (5 mL), and bromide **3f** (200 mg, 0.6 mmol). After work-up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **7f** as a colourless oil that was crystallised from diethyl ether (90 mg, 68%): mp (Et_2O) 134–138 °C; IR ($CHCl_3$) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 3.58–3.62 (m, 4H), 3.70–3.73 (m, 4H), 5.25 (s, 2H), 5.91 (s, 2H), 6.13 (dd, J=3.8, 2.8 Hz, $1H_l$), 6.31 (s, 1H), 6.33 (dd, J=3.8, 1.6 Hz, 1H), 6.77 (dd, J=2.8, 1.6 Hz, 1H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) 45.5, 55.9, 66.8, 85.6, 101.6, 107.5, 108.6, 112.9, 118.4, 124.6, 125.7, 134.1, 147.7, 148.6, 162.7. MS (EI) *m/z* (rel intensity) 440 (M^+, 2), 314 (21), 313 (100), 261 (44), 227 (31), 226 (22), 220 (23), 134 (12), 114 (12), 76 (15), 70 (15). Anal. Calcd for $C_{17}H_{17}IN_2O_4$: C, 46.38; H, 3.89; N, 6.36. Found: C, 46.02; H, 3.74; N, 5.96.

3.3.21. 1-(2-Iodo-3,4,5-trimethoxybenzyl)pyrrole-2-carboxylic acid morpholine amide (7g). According to the general procedure, pyrrole-2-carboxamide **4c** (354 mg, 1.9 mmol) was treated with KOH (441 mg, 7.8 mmol) in

DMSO (10 mL), and bromide **3g** (1.52 mg, 3.9 mmol). After work-up, flash column chromatography (silicagel, 60% hexane/AcOEt) afforded **7g** as a colourless oil (374 mg, 40%); IR ($CHCl_3$) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) 3.57–3.61 (m, 4H), 3.67 (s, 3H), 3.68–3.72 (m, 4H), 3.83 (s, 3H), 3.86 (s, 3H), 5.31 (s, 2H), 6.14 (dd, J= 4.0, 2.8 Hz, 1H), 6.21 (s, 1H), 6.35 (dd, J=4.0, 1.6 Hz, 1H, H), 6.78 (dd, J=2.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 45.6, 55.9, 56.3, 60.7, 60.9, 66.8, 85.6, 107.5, 108.2, 113.0, 124.9, 126.0, 136.3, 141.3, 152.9, 153.8, 162.8. MS (EI) *m/z* (rel intensity) 486 (M^+, 3), 360 (23), 359 (100), 307 (17), 273 (6), 267 (9), 266 (55), 114 (7), 70 (8).

3.3.22. 1-[2-(2-Iodo-4,5-dimethoxyphenyl)ethyl]-pyrrole-2-carboxylic acid methoxy methyl amide (13a). According to the general procedure, pyrrole-2-carboxamide **4b** (150 mg, 1 mmol) was treated with KOH (220 mg, 4 mmol) in DMSO (10 mL), and tosylate **12a** (440 mg, 1 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **13a** as a colourless oil (290 mg, 67%); IR ($CHCl_3$) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) 3.13 (t, J=6.9 Hz, 2H), 3.33 (s, 3H), 3.68 (s, 3H), 3.72 (s, 3H), 3.83 (s, 3H), 4.46 (t, J=6.9 Hz, 2H), 6.04 (dd, J=4.0, 2.6 Hz, 1H), 6.45 (s, 1H), 6.57 (dd, J=2.6, 1.8 Hz, 1H), 6.91 (dd, J=4.0, 1.8 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) 33.7, 42.1, 49.2, 55.6, 55.9, 60.8, 87.8, 107.1, 112.7, 116.5, 121.0, 122.1, 127.8, 133.6, 147.9, 148.9, 162.3. MS (EI) *m/z* (rel intensity) 444 (M^+, 1), 317 (54), 286 (10), 257 (100), 230 (10), 191 (15), 164 (6).

3.3.23. 1-[3-(2-Iodo-4,5-dimethoxyphenyl)-propyl]-pyrrole-2-carboxylic acid methoxy methyl amide (13b). According to the general procedure, pyrrole-2-carboxamide **4b** (440 mg, 2.8 mmol) was treated with KOH (650 mg, 11.5 mmol) in DMSO (10 mL), and mesylate **12b** (1.15 mg, 2.8 mmol). After work-up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **13b** as a colourless oil (1.14 g, 86%); IR ($CHCl_3$) 1622 cm^{-1}; ^1H NMR ($CDCl_3$) 1.95–2.11 (m, 2H), 2.64 (t, J=7.4 Hz, 2H), 3.31 (s, 3H), 3.69 (s, 3H), 3.81, 3.84 (s, 3H), 4.38 (t, J=6.3 Hz, 2H), 6.11 (dd, J=4.0, 2.6 Hz, 1H), 6.71 (s, 1H), 6.81 (dd, J=2.6, 1.8 Hz, 1H), 6.91 (dd, J=4.0, 1.8 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) 32.5, 34.0, 37.6, 48.8, 55.9, 56.1, 61.0, 87.9, 107.5, 112.0, 116.5, 121.6, 122.6, 127.3, 136.4, 147.8, 149.3, 162.6. MS (EI) *m/z* (rel intensity) 458 (M^+, 13), 427 (13), 370 (13), 331 (27), 272 (20), 271 (100), 243 (21), 199 (11), 176 (22), 120 (10), 109 (12), 108 (14), 106 (13), 80 (61).

3.3.24. 1-[2-(2-Iodo-4,5-dimethoxyphenyl)-ethyl]-pyrrole-2-carboxylic acid morpholine amide (14a). According to the general procedure, pyrrole-2-carboxamide **4c** (480 mg, 2.7 mmol) was treated with KOH (600 mg, 10.7 mmol) in DMSO (10 mL), and tosylate **12a** (1.06 g, 2.7 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **14a** as a colourless oil (880 mg, 70%); IR ($CHCl_3$) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 3.12 (t, J=6.9 Hz, 2H), 3.69–3.73 (m, 8H), 3.73 (s, 3H), 3.84 (s, 3H), 4.34 (t, J=6.9 Hz, 2H), 6.03 (dd, J=4.0, 2.6 Hz, 1H), 6.27 (dd, J=4.0, 1.6 Hz, 1H), 6.45 (s, 1H), 6.61 (dd, J=2.6, 1.6 Hz, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$) 42.4, 45.6, 48.0, 55.8, 56.0, 66.9, 87.9, 107.0, 112.8, 113.0, 121.2, 124.0, 125.7, 133.5, 148.1, 149.1, 162.9. MS (EI) *m/z* (rel intensity) 470 (M^+, 1), 344 (18), 343 (75), 290 (16), 256 (27), 114 (20), 97 (14), 85 (20), 83 (21), 71 (20), 70 (33), 69 (12).

3.3.25. 1-[3-(2-Iodo-4,5-dimethoxyphenyl)-propyl]-pyrrole-2-carboxylic acid morpholine amide (14b). According to the general procedure, pyrrole-2-carboxamide **4c** (900 mg, 5 mmol) was treated with KOH (1.22 mg, 20 mmol) in DMSO (20 mL), and mesylate **12b** (2.0 g, 5 mmol). After work-up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **14b** as a colourless oil (1.94 g, 86%); IR ($CHCl_3$) 1616 cm^{-1}; ^1H NMR ($CDCl_3$) 1.85–2.05 (m, 2H), 2.67 (t, J=7.4 Hz, 2H), 3.61–3.68 (m, 4H), 3.71–3.80 (m, 4H), 3.86 (s, 3H), 3.88 (s, 3H), 4.25 (t, J=6.3 Hz, 2H), 6.09 (dd, J=4.0, 2.6 Hz, 1H), 6.31 (dd, J=4.0, 1.6 Hz, 1H), 6.66 (s, 1H), 6.80 (dd, J=2.6, 1.6 Hz, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$) 32.3, 37.7, 45.6, 47.6, 55.9, 56.1, 67.1, 87.8, 107.1, 112.0, 113.0, 121.7, 124.1, 125.3, 136.2, 147.9, 149.4, 163.2. MS (EI) *m/z* (rel intensity) 484 (M^+, 7), 370 (8), 358 (24), 357 (100), 271 (18), 270 (39), 243 (10), 207 (10), 177 (25), 151 (10), 120 (11), 114 (71), 108 (13), 80 (19), 70 (16).

3.4. Parham cyclisation reactions. General procedure

Method A. To a solution of iodinated pyrrole-2-carboxamides **5**–**7**, **13** or **14** (1 mmol) in dry THF (15 mL), *t*-BuLi (2.2 mmol) was added at −78 °C, and the resulting mixture was stirred at this temperature for 3 h, allowed to reach rt, and stirred for 4 h. The reaction was quenched by the addition of sat. NH_4Cl (10 mL). Et_2O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography afforded **8a**–**g**, **15** or **16**.

Method B. To a solution of iodinated pyrrole-2-carboxamides **5**–**7**, **13** or **14** (1 mmol) in dry THF (15 mL), *t*-BuLi (2.2 mmol) was added at −78 °C, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by the addition of sat. NH_4Cl (10 mL). Et_2O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography afforded pyrroloisoquinolones **8a**–**g**, **15** or **16**.

3.4.1. 5*H*-Pyrrolo[1,2-*b*]isoquinolin-10-one (8a). According to the general procedure B pyrrole-2-carboxamide **6a** (288 mg, 0.78 mmol) was treated with *t*-BuLi (1.07 mL of a 1.6 M solution in pentane, 1.72 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **8a** as a colourless oil (125 mg, 87%); IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) 5.38 (s, 2H), 6.44 (dd, J= 4.0, 2.4 Hz, 1H), 7.08–7.09 (m, 1H,), 7.20 (dd, J=4.0, 1.5 Hz, 1H), 7.33 (dd, J=7.6, 0.9 Hz, 1H), 7.47 (td, J=7.3, 0.9 Hz, 1H), 7.56 (td, J=7.3, 1.4 Hz, 1H), 8.30 (dd, J=7.6, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 46.9, 111.6, 113.6, 125.6, 127.1, 127.8, 129.6, 130.5, 132.4, 135.6, 174.7. MS (EI) *m/z* (rel intensity) 183 (M^+, 100), 182 (58), 155 (11), 154 (51), 128 (12), 127 (30), 89 (16), 77 (20), 63 (20), 51 (13). Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.88; H, 4.82; N, 7.54.

3.4.2. 7,8-Dimethyl-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (8b). According to the general procedure B pyrrole-2-carboxamide **7b** (122 mg, 0.29 mmol) was treated with *t*-BuLi (0.72 mL of a 1.05 M solution in pentane, 0.81 mmol). After work up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **8b** as a colourless oil (63 mg, 98%); IR (neat) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) 2.35 (s, 6H), 5.33 (s, 2H), 6.43 (dd, $J=4.0$, 2.8 Hz, 1H), 7.06 (dd, $J=2.8$, 1.6 Hz, 1H), 7.10 (s, 1H), 7.18 (dd, $J=4.0$, 1.6 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) 19.5, 20.1, 46.6, 111.4, 113.2, 125.3, 126.6, 127.6, 128.3, 129.7, 133.2, 136.6, 142.2, 175.1. MS (EI) *m/z* (rel intensity) 211 (M^+, 100), 210 (28), 197 (12), 196 (80), 168 (13), 167 (15). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.51; H, 6.17; N, 6.51.

3.4.3. 7-Methoxy-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (8c). According to the general procedure A pyrrole-2-carboxamide **7c** (261 mg, 0.61 mmol) was treated with *t*-BuLi (1.68 mL of a 0.8 M solution in pentane, 1.3 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **8c** as a colourless oil (105 mg, 81%); IR (neat) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) 3.88 (s, 3H), 5.34 (s, 2H), 6.41 (dd, $J=4.0$, 2.4 Hz, 1H), 6.78 (dd, $J=2.4$, 1.2 Hz, 1H), 6.98 (dd, $J=8.7$, 2.4 Hz, 1H), 7.04 (dd, $J=2.4$, 1.6 Hz, 1H), 7.16 (dd, $J=4.0$, 1.2 Hz, 1H), 8.25 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 47.0, 55.5, 110.1, 111.4, 113.1, 114.0, 123.9, 125.2, 129.4, 129.6, 137.9, 162.8, 174.3. MS (EI) *m/z* (rel intensity) 213 (M^+, 100), 182 (24), 170 (41), 169 (14), 142 (13), 141 (13), 115 (10), 87 (14), 85 (66), 83 (94). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.14; H, 5.27; N, 6.41.

3.4.4. 7,8-Dimethoxy-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (8d). According to the general procedure B pyrrole-2-carboxamide **7d** (425 mg, 0.93 mmol) was treated with *t*-BuLi (2.0 mL of a 1.3 M solution in pentane, 2.61 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **8d** as a colourless oil (199 mg, 88%); IR (neat) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 3.90 (s, 3H), 3.92 (s, 3H), 5.17 (s, 2H), 6.35 (dd, $J=4.0$, 2.4 Hz, 1H), 6.64 (s, 1H), 6.95–6.97 (m, 1H), 7.08 (dd, $J=4.0$, 1.5 Hz, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) 46.4, 56.0, 56.0, 107.1, 107.9, 111.1, 112.7, 123.7, 125.2, 129.2, 129.7, 148.7, 152.8, 174.1. MS (EI) *m/z* (rel intensity) 243 (M^+, 100), 242 (22), 228 (21), 212 (28), 200 (13), 199 (13). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.24; H, 5.41; N, 5.84.

3.4.5. 6,7-Dimethoxy-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (8e). According to the general procedure B pyrrole-2-carboxamide **7e** (140 mg, 0.31 mmol) was treated with *t*-BuLi (0.77 mL of a 1.12 M solution in pentane, 0.86 mmol). After work up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **8e** as a white powder, that was crystallised from Et_2O (53 mg, 76%): mp(Et_2O) 177–179 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 3.94 (s, 3H), 3.97 (s, 3H), 5.37 (s, 2H), 6.43 (dd, $J=4.0$, 2.4 Hz, 1H), 7.05 (d, $J=8.7$ Hz, 1H), 7.10 (dd, $J=2.4$, 1.6 Hz, 1H), 7.17 (dd, $J=4.0$, 1.6 Hz, 1H), 8.09 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 43.4, 55.9, 60.3, 111.5, 113.1, 123.9, 124.1, 125.7, 129.3, 129.9, 143.8, 155.6, 174.2. MS (EI) *m/z* (rel intensity) 243 (M^+, 100), 242 (12), 213 (16), 212 (63), 198 (10), 185 (16), 157 (16). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.79; H, 5.48; N, 5.72.

3.4.6. 7,8-Methylenedioxy-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (8f). According to the general procedure B pyrrole-2-carboxamide **6f** (159 mg, 0.38 mmol) was treated with *t*-BuLi (0.52 mL of a 1.6 M solution in pentane, 0.84 mmol). After work up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **8f** as a white powder, that was crystallised from Et_2O (163 mg, 73%): mp(Et_2O) 181–183 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 5.24 (s, 2H), 6.03 (s, 2H), 6.38 (dd, $J=4.0$, 2.8 Hz, 1H), 6.69 (s, 1H), 7.02 (broad s, 1H), 7.10 (dd, $J=4.0$, 1.2 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$) 46.9, 101.9, 105.0, 105.9, 111.3, 112.9, 125.2, 129.2, 131.7, 147.8, 151.5, 173.8. MS (EI) *m/z* (rel intensity) 227 (M^+, 66), 226 (M^+-1, 26), 169 (17), 141 (14), 87 (14), 85 (72), 83 (100). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.28; H, 3.86; N, 5.94.

3.4.7. 7,8,9-Trimethoxy-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (8g). According to the general procedure B pyrrole-2-carboxamide **6g** (202 mg, 0.43 mmol) was treated with *t*-BuLi (0.59 mL of a 1.6 M solution in pentane, 0.95 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **8g** as a colourless oil that was crystallised from Et_2O (80 mg, 68%): mp(Et_2O) 144–145 °C; IR (neat) 1639 cm^{-1}; ^1H NMR ($CDCl_3$) 3.91 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 5.30 (s, 2H), 6.38 (dd, $J=4.0$, 2.4 Hz, 1H), 6.60 (s, 1H), 6.97 (dd, $J=2.4$, 1.6 Hz, 1H), 7.10 (dd, $J=4.0$, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 47.0, 56.0, 61.2, 61.7, 104.3, 111.1, 112.7, 118.4, 124.0, 130.4, 133.8, 142.6, 155.5, 156.6, 174.0. MS (EI) *m/z* (rel intensity) 273 (M^+, 76), 272 (6), 259 (14), 258 (100), 256 (12), 240 (9), 230 (11), 228 (8), 227 (14), 215 (17), 213 (6), 212 (14), 207 (9), 198 (8), 197 (6), 184 (6), 170 (6), 137 (17), 94 (15), 85 (7), 83 (8), 51 (7). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 66.17; H, 5.65; N, 5.12.

3.4.8. 8,9-Dimethoxy-5,6-dihydropyrrolo[1,2-*a*]benzo-[*d*]azepin-11-one (15). According to the general procedure B pyrrole-2-carboxamide **14a** (108 mg, 0.23 mmol) was treated with *t*-BuLi (0.57 mL of a 1.0 M solution in pentane, 0.57 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **15** as a colourless oil that was crystallised from pentane (23 mg, 58%): mp (pentane) 122–124 °C; IR (neat) 1639 cm^{-1}; ^1H NMR ($CDCl_3$) 3.24–3.28 (m, 2H), 3.93 (s, 6H), 4.30–4.34 (m, 2H), 6.20 (dd, $J=4.0$, 2.4 Hz, 1H), 6.63 (s, 1H), 6.82 (dd, $J=2.4$, 2.0 Hz, 1H), 7.36 (dd, $J=4.0$, 2.0 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$) 35.6, 50.0, 56.0, 109.4, 111.7, 113.6, 121.0, 127.9, 129.5, 133.5, 133.6, 147.9, 151.9, 179.4. MS (EI) *m/z* (rel intensity) 258 ($M^+ +1$; 18), 257 (M^+, 100), 256 (15), 242 (10), 191 (35), 164 (12). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 69.98; H, 5.43; N, 5.37.

3.4.9. 9,10-Dimethoxy-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]-benzo[*d*]azocin-12-one (16). According to the general procedure B pyrrole-2-carboxamide **13b** (269 mg, 0.59 mmol) was treated with *t*-BuLi (1.36 mL of a 1.08 M

solution in pentane, 1.47 mmol). After work up, flash column chromatography (silicagel, 40% hexane/AcOEt) afforded **16** as a colourless oil (88 mg, 55%); IR (neat) 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 1.85–2.01 (m, 2H), 2.66 (t, $J=7.4$ Hz, 2H), 3.31 (s, 3H), 3.69 (s, 3H), 3.81, 3.84 (s, 3H), 4.38 (t, $J=6.3$ Hz, 2H), 6.22 (dd, $J=4.0$, 2.6 Hz, 1H), 6.57 (s, 1H), 6.76 (dd, $J=2.6$, 1.8 Hz, 1H), 7.24 (dd, $J=4.0$, 1.8 Hz, 1H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$) 29.6, 32.8, 45.6, 55.9, 109.4, 111.1, 112.6, 119.3, 128.0, 131.2, 132.4, 135.7, 147.6, 152,0, 183.1. MS (EI) *m/z* (rel intensity) 271 (M^+, 100), 254 (10), 243 (27), 242 (15), 228 (17), 212 (17), 191 (30), 163 (12), 106 (12). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.53; H, 6.20; N, 5.22.

3.4.10. 1-Benzylpyrrole-2-carboxylic acid diethyl amide (9a). Obtained as a by-product (14 mg, 13%) when, according to the general procedure A, pyrrole-2-carboxamide **5a** (160 mg, 0.4 mmol) was treated with *t*-BuLi (0.6 mL of a 1.6 M solution in pentane, 0.9 mmol); IR (neat) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 1.02 (t, $J=7.1$ Hz, 6H), 3.32 (q, $J=7.1$ Hz, 4H), 5.31 (s, 1H), 6.10 (dd, $J=3.6$, 2.4 Hz, 1H), 6.33 (dd, $J=3.6$, 1.6 Hz, 1H), 6.81 (dd, $J=2.4$, 1.6 Hz, 1H), 7.06–7.10 (m, 2H), 7.17–7.29 (m, 3H); ^{13}C NMR ($CDCl_3$) 13.5, 42.1, 51.5, 106.6, 111.1, 124.9, 125.9, 127.1, 127.3, 128.3, 138.5, 163.8. MS (EI) *m/z* (rel intensity) 256 (M^+, 15), 184 (38), 183 (14), 156 (25), 91 (100), 72 (16), 65 (26).

3.4.11. 1-(3,4-Dimethylbenzyl)pyrrole-2-carboxylic acid diethyl amide (9b). Obtained as a by-product (10 mg, 18%) when, according to the general procedure A, pyrrole-2-carboxamide **5b** (80 mg, 0.2 mmol) was treated with *t*-BuLi (0.4 mL of a 1.0 M solution in pentane, 0.4 mmol); IR (neat) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 1.04 (t, $J=7.1$ Hz, 6H), 2.19 (s, 3H), 2.20 (s, 3H), 3.35 (q, $J=7.1$ Hz, 4H), 5.23 (s, 2H), 6.08 (dd, $J=4.0$, 2.8 Hz, 1H), 6.32 (dd, $J=4.0$, 1.6 Hz, 1H), 6.78–6.84 (m, 2H), 6.89 (s, 1H), 7.01 (d, $J=8.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 19.4, 19.7, 41.4, 51.3, 106.6, 111.0, 124.8, 125.9, 128.7, 129.6, 135.6, 135.9, 136.5, 164.0. MS (EI) *m/z* (rel intensity) 284 (M^+, 18), 212 (25), 211 (24), 196 (16), 184 (21), 120 (12), 119 (100), 91 (23), 77 (11), 72 (20).

3.4.12. 1-(3-Methoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (9c). Obtained as a by-product (13 mg, 39%) when, according to the general procedure A, pyrrole-2-carboxamide **5c** (48 mg, 0.1 mmol) was treated with *t*-BuLi (0.2 mL of a 1.0 M solution in pentane, 0.2 mmol); IR (neat) 1604 cm^{-1}; ^1H NMR ($CDCl_3$) 1.04 (t, $J=7.1$ Hz, 6H), 3.35 (c, $J=7.1$ Hz, 4H), 3.74 (s, 3H), 5.28 (s, 2H), 6.10 (dd, $J=3.6$, 2.8 Hz, 1H), 6.33 (dd, $J=3.6$, 1.6 Hz, 1H), 6.62–6.80 (m, 4H), 7.17 (t, $J=7.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 40.5, 51.5, 55.1, 106.8, 111.2, 112.7, 112.8, 119.4, 125.0, 126.0, 129.4, 140.2, 159.7, 163.9 (CO). MS (EI) *m/z* (rel intensity) 286 (M^+, 61), 215 (16), 214 (86), 213 (51), 187 (26), 186 (41), 170 (11), 122 (15), 121 (100), 94 (10), 91 (34), 78 (18), 77 (16), 72 (24), 65 (12).

3.4.13. 1-(3,4-Dimethoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (9d). Obtained as a by-product (30 mg, 24%) when, according to the general procedure A, pyrrole-2-carboxamide **5d** (176 mg, 0.4 mmol) was treated with *t*-BuLi (0.5 mL of a 1.6 M solution in pentane, 0.8 mmol); IR (neat) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 (t, $J=7.1$ Hz, 6H), 3.34 (q, $J=7.1$ Hz, 4H), 3.78 (s, 3H), 3.81 (s, 3H), 5.22 (s, 2H), 6.07 (dd, $J=3.6$, 2.8 Hz, 1H), 6.31 (dd, $J=3.6$, 1.6 Hz, 1H), 6.62–6.66 (m, 2H), 6.72–6.75 (m, 1H), 6.78 (dd, $J=2.8$, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 42.0, 51.3, 55.7, 55.8, 106.6, 110.5, 110.9, 119.6, 124.7, 125.8, 131.1, 148.2, 148.8, 163.9. MS (EI) *m/z* (rel intensity) 316 (M^+, 18), 244 (6), 243 (18), 216 (8), 152 (12), 151 (100), 107 (11), 72 (9). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.64; N, 8.85. Found: C, 68.54; H, 7.46; N, 8.77.

3.4.14. 1-(2,3-Dimethoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (9e). Obtained as a by-product (41 mg, 35%) when, according to the general procedure A, pyrrole-2-carboxamide **5e** (162 mg, 0.4 mmol) was treated with *t*-BuLi (0.5 mL of a 1.6 M solution in pentane, 0.8 mmol); IR (neat) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) 1.09 (t, $J=7.1$ Hz, 6H), 3.42 (q, $J=7.1$ Hz, 4H), 3.76 (s, 3H), 3.83 (s, 3H), 5.34 (s, 2H), 6.07 (dd, $J=4.0$, 2.8 Hz, 1H), 6.31 (dd, $J=4.0$, 1.6 Hz, 1H), 6.52 (d, $J=7.9$ Hz, 1H), 6.79 (dd, $J=2.8$, 1.6 Hz, 1H), 6.82 (s, 1H), 6.93 (t, $J=7.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 46.5, 55.7, 60.4, 106.6, 110.8, 111.7, 120.7, 123.8, 125.2, 126.0, 132.3, 146.6, 152.4, 164.0. MS (EI) *m/z* (rel intensity) 316 (M^+, 56), 285 (21), 245 (10), 244 (57), 243 (15), 229 (10), 228 (39), 216 (16), 214 (17), 212 (16), 186 (13), 165 (10), 152 (11), 151 (76), 137 (13), 136 (100), 135 (11), 122 (16), 106 (13), 100 (13), 94 (14), 91 (58), 80 (11), 78 (11), 77 (11), 72 (29), 65 (22).

3.4.15. 1-(3,4-Methylendioxybenzyl)pyrrole-2-carboxylic acid diethyl amide (9f). Obtained as a by-product (11 mg, 14%) when, according to the general procedure A, pyrrole-2-carboxamide **5f** (112 mg, 0.3 mmol) was treated with *t*-BuLi (0.4 mL of a 1.6 M solution in pentane, 0.6 mmol); ^1H NMR ($CDCl_3$) 1.08 (t, $J=7.1$ Hz, 6H), 3.37 (q, $J=7.1$ Hz, 4H), 5.20 (s, 2H), 5.90 (s, 2H), 6.08 (dd, $J=4.0$, 2.4 Hz, 1H), 6.32 (dd, $J=4.0$, 1.6 Hz, 1H), 6.61–6.69 (m, 2H), 6.71–6.74 (m, 1H), 6.78 (dd, $J=2.4$, 1.6 Hz, 1H).

3.4.16. 1-(3,4,5-Trimethoxybenzyl)pyrrole-2-carboxylic acid diethyl amide (9g). According to the general procedure A pyrrole-2-carboxamide **5g** (140 mg, 0.3 mmol) was treated with *t*-BuLi (0.7 mL of a 1.0 M solution in pentane, 0.7 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **9g** as a colourless oil (83 mg, 81%); IR (neat) 1616 cm^{-1}; ^1H NMR ($CDCl_3$) 1.02 (t, $J=7.1$ Hz, 6H), 3.35 (q, $J=7.1$ Hz, 4H), 3.75 (s, 6H), 3.77 (s, 3H), 5.24 (s, 2H), 6.09 (dd, $J=3.6$, 2.8 Hz, 1H), 6.29 (s, 2H), 6.33 (dd, $J=3.6$, 1.6 Hz, 1H), 6.80 (dd, $J=2.4$, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 40.9, 51.7, 55.9, 60.7, 104.0, 106.7, 111.4, 125.0, 125.8, 134.3, 153.1, 163.7. MS (EI) *m/z* (rel intensity) 346 (M^+, 39), 273 (11), 242 (38), 182 (16), 181 (100), 137 (11), 83 (14).

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Solvent effects on the mixed aggregates of chiral 3-aminopyrrolidine lithium amides and alkyllithiums

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Abstract—The condensation of *n*-butyllithium on *o*-tolualdehyde in the presence of a chiral 3-aminopyrrolidine lithium amide led to the expected alcohol with ee strongly dependent on the solvent (THF, diethylether and toluene). A NMR and theoretical study of this effect was undertaken to rationalize these results. The addition of two equivalents of methyllithium to a 3-aminopyrrolidine [benzhydryl-(1-benzylpyrrolidin-3-yl)-amine] led, in THF-d_8 and at −90 °C, to an *exo* aza-norbornyl-type mixed aggregate, similar to that characterized previously between the lithium amide and *n*-butyllithium in the same solvent. In diethyl ether, a non-covalent complex presenting a comparable *exo* topology was obtained despite a ∼1 ppm high-field drift of the chemical shift of one of its two ^{6}Li nuclei (Li^2). The progressive addition of THF to the medium brought the Li^2 signal back to its original value, suggesting that this atom could also be the target of the incoming aldehyde. When reacting the same aminopyrrolidine with MeLi and BuLi in toluene, the expected lithium amide was recovered, apparently under two forms, which did not aggregate with the excess MeLi or BuLi until THF was added to the medium. Reacting the aminopyrrolidine with *n*-butyllithium, which is more soluble in toluene, led to a comparable complex. Finally, a discussion on the interaction between a mixed aggregate and the aldehyde, based on a theoretical analysis of the solvation energies of the two lithium atoms by three different ethers, is proposed.

1. Introduction

Condensing a nucleophilic organometallic reagent onto a carbonyl compound is doubtlessly one of the simplest ways to create a carbon–carbon bond, explaining why an efficient asymmetric version of this reaction has been a central challenge to organic chemists for more than two decades. An almost countless number of chiral auxiliaries have been designed in this prospect. Aminoalcohols for instance have had a remarkably large success when used as chiral ligands for organozinc reagents.[1] The exact structure of the aggregates formed between these species has been investigated in several cases and catalytic cycles have been proposed to justify both the efficiency and the enantioselectivities of these reactions. By contrast, organolithium reagents enjoy an exceptional popularity as nucleophiles but have been seldom used in the asymmetric alkylation of carbonyl compounds. This void is probably related to the very large exothermicity of alkyllithium condensation on most electrophiles that tends to diminish the influence of the relatively small energy differences between diastereomeric transition states. Nevertheless, among the few examples reported in the literature, high enantiomeric excesses (ee) have been obtained in the alkylation of aldehydes associating alkyllithium reagents and chiral diamines,[2] aminoalcohols,[3] or chiral lithium amides.[4] With the latter, it has even been shown, generally by NMR, that non-covalent complexes associating lithium amides to alkyllithium compounds can be formed,[5] at the expenses of the eventual homogeneous $(RLi)_n$ and multiple $(R_2NLi)_n$ aggregates.[6] The enantioselectivity has been suggested as being directly related to the structure of these mixed aggregates that seem to display a reactivity superior to that of the homo aggregates.[7]

We have been interested in the use of 3-aminopyrrolidine (3-AP) lithium amides as chiral auxiliaries in the asymmetric nucleophilic alkylation of aromatic aldehydes by alkyllithium derivatives.[8] When used in conjunction with butyl, methyl or phenyllithium, these amides give access to the expected alcohols **2** in good yields and satisfying ee at −78 °C in THF (Scheme 1).

Keywords: 3-Aminopyrrolidine lithium amides; Alkyllithiums; Solvation; Multinuclear NMR; DFT calculations.
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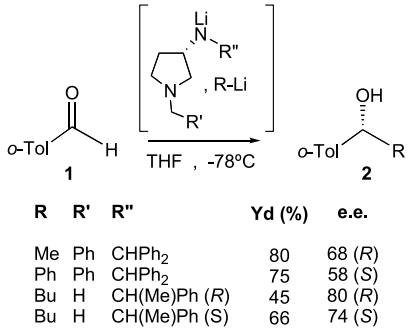


R	R'	R"	Yd (%)	e.e.
Me	Ph	$CHPh_2$	80	68 (*R*)
Ph	Ph	$CHPh_2$	75	58 (*S*)
Bu	H	CH(Me)Ph (*R*)	45	80 (*R*)
Bu	H	CH(Me)Ph (S)	66	74 (*S*)

Scheme 1.

Simultaneously, theoretical[8e,9] and multinuclear (^{1}H, ^{6}Li, ^{13}C, ^{15}N) NMR studies[8b,e] have revealed the existence in solution, in THF-d_8, of non-covalent robust 1:1 complexes between *n*-butyl- or methyllithium and the 3-AP lithium amides (Fig. 1).

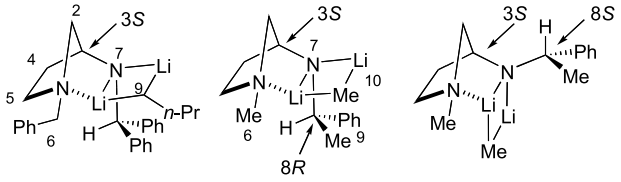
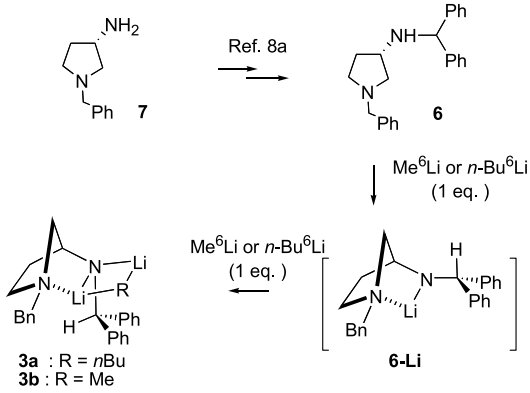


Figure 1. *Exo* and *endo* topologies of mixed aggregates **3a**, **4** and **5**.

In all the cases considered, these species adopt an aza-norbornyl-like topology due to the chelation of the lithium cation by the pyrrolidine ring nitrogen. We have also shown that the precise arrangement adopted by the aggregate depends on the relative configuration of the lateral chain: while the (3*S*,8*R*) diastereomer **4** leads to an *exo* complex, its (3*S*,8*S*) epimer **5** adopts an *endo* conformation.[8e]

We present here results detailing and comparing: (i) the solvent effect on the enantioselectivity of the reaction in Scheme 1 (with R=*n*-Bu, R′=Ph and R″=$CHPh_2$); (ii) the structure of complexes **3a** or **3b** (Scheme 2) in deuterated THF, diethyl ether and toluene; (iii) a computational study on the solvation energies of complex **4** by three discrete solvent molecules.



Scheme 2.

2. Experimental results

Amine **6** was synthesized from commercially available *N*-benzyl-3-aminopyrrolidine **7** (Scheme 2).[8a] The nucleophilic alkylation of *o*-tolualdehyde by *n*-butyllithium (salt-free in hexanes), according to a protocol described before,[8c] was repeated in three usual solvents, viz. THF, diethylether and toluene plus one solvent mixture (Table 1).

Table 1. Solvent effects on the reaction of Scheme 1 (R′=Ph and R″=$CHPh_2$)

Solvent	R	Yd (%)	ee[a] (conf.)
THF	Me	80	68 (*R*)[b]
THF	*n*-Bu	81	70 (*R*)[b]
Et_2O	*n*-Bu	96	50 (*R*)
DME+Et_2O (1:1)	*n*-Bu	92	3 (*R*)
Toluene	*n*-Bu	99	21 (*R*)

[a] Configuration and ee of **2** determined by ^{1}H NMR shift analysis using $Eu(hfc)_3$ in $CDCl_3$.
[b] Values from Ref. 8d.

The data confirm that THF is, by far, the best solvent in terms of enantioselectivity. In diethylether (DEE) a significant decrease was observed while the ee plummeted in a DME–DEE (1:1) mixture. In toluene, the induction was poor. Note that the sense of the induction remains the same in all cases.

These puzzling differences prompted us to characterize the species present in these various media.

3. Spectroscopic results

The structure of aggregate **3a** in THF had been determined in a previous study.[8b] We chose to focus here on methyllithium complexes **3b** (Scheme 2) because: (i) MeLi NMR characteristics make it a very convenient probe in the reaction mixture; (ii) the level and the sense of the induction measured with *n*-BuLi and MeLi complexes are similar (see Table 1 and Ref. 8c,d). Salt-free solutions of $Me^{6}Li$ were prepared, stored and handled safely in ether solvents.[8e,10] All the NMR samples studied during this work were in the 0.15–0.30 M range.

3.1. Structure of 3b in THF

The complex **3b** between **6-Li** lithium amide and methyllithium was prepared, as described previously, directly in the NMR tube, adding two equivalents of $Me^{6}Li$ in freshly distilled THF-d_8 to dry amine **6** in solution in the same solvent at −78 °C (Scheme 2).

The arrangement of **3b** were determined by the same set of NMR experiments used in our previous studies. All one-dimensional spectra displayed the expected features for this complex, that is: (i) a singlet at −1.76 ppm (corresponding to the methyl group of methyllithium, Figure 2(A)) in the ^{1}H spectrum; (ii) a quintet at −12.36 ppm (assigned to the same Me coupled to two ^{6}Li nuclei with $^{1}J_{CLi}=8.41$ Hz, Figure 2(B)) in the ^{13}C spectrum;[11] (iii) two singlets at 2.75

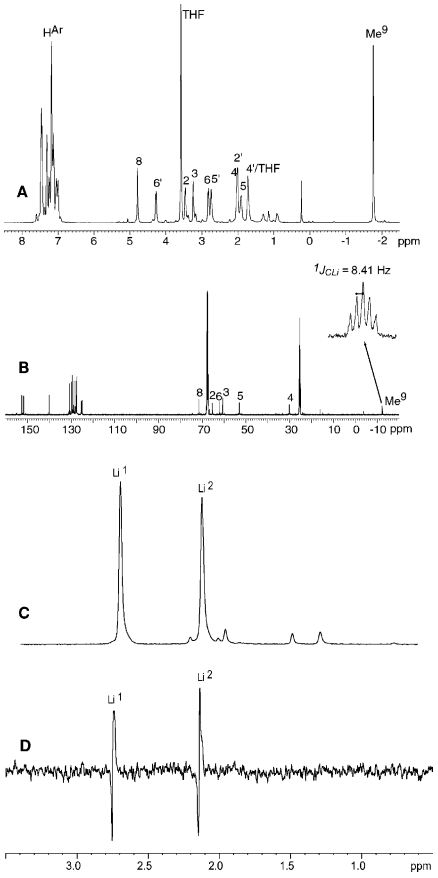


Figure 2. ^{1}H, ^{13}C, ^{6}Li monodimensional standard (A, B and C) and INADEQUATE (D) spectra of complex **3b** in THF-d_8 at −78 °C.

and 2.13 ppm (corresponding to Li^1 and Li^2, respectively, Figure 2(C)) in the ^{6}Li spectra.

Complementary, a ^{6}Li one-dimensional INADEQUATE[12] spectrum demonstrated that the two lithium nuclei are coupled and belong to the same complex (Fig. 2(D)).

The most important information regarding the conformation of **3b** was given here by the two-dimensional $^{1}H,^{1}H$ NOESY and $^{1}H,^{6}Li$ HOESY (Fig. 3). These spectra display correlations between methyl Me^9 (Fig. 3(A)) or Li^1 (Fig. 3(B)) and H^2, H^6 and some H^{Ar} as well as correlations between Li^2 and H^2 and H^{Ar} that are fully consistent with the proposed *exo* structure. A similar conformation had for instance been described in the case of **6-Li/***n*BuLi mixed aggregate **3a** in comparable experimental conditions.[8] A complementary EXSY experiment (data not shown) exhibited a correlation between the lithiums, suggesting a possible intra-molecular exchange between these nuclei.

This first part of the study indicates that the topology of the complex is not very sensitive to the chain structure, at least for primary alkyllithiums, as both methyl and *n*-butyl residues lead to the same *exo* arrangement.

3.2. Structure of 3b in diethyl ether

We then repeated these experiments in distilled deuteriated diethylether (DEE-d_{10}). We first tried to get an insight onto

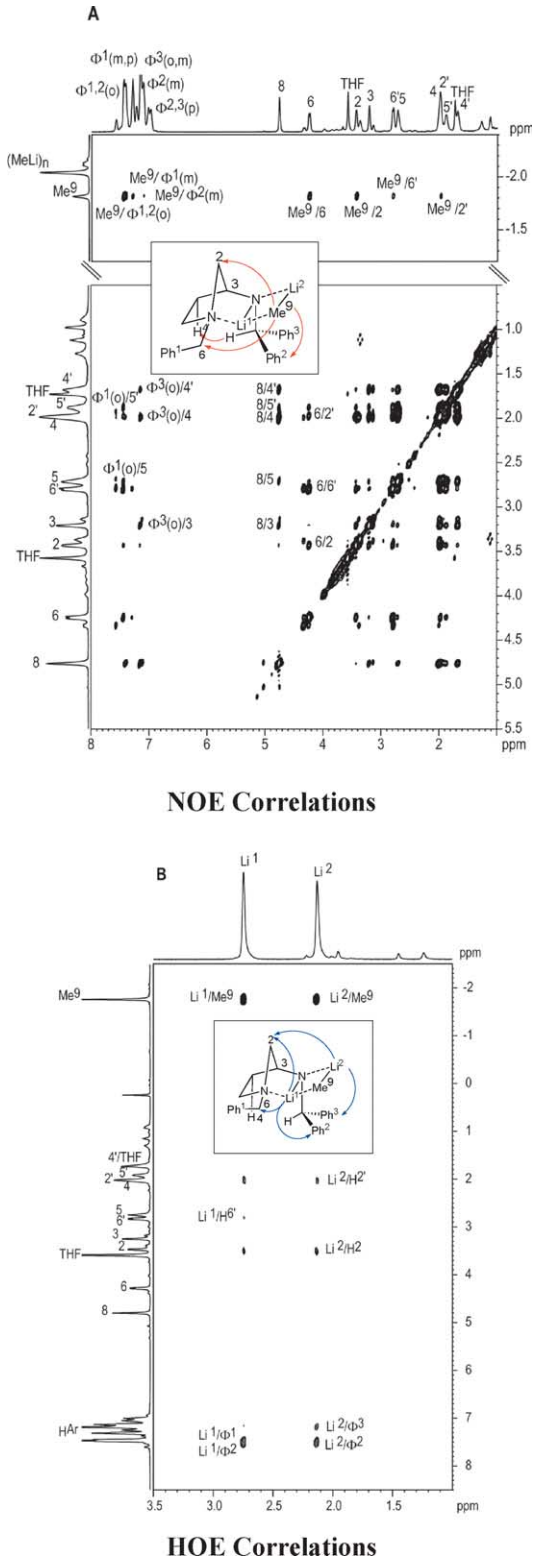


Figure 3. NOE (A) and HOE (B) spectra on **3b** in THF-d_8 at −78 °C.

amide **6-Li** structure adding one equivalent of Me^6Li to the solution of **6**. However, a complex ^{6}Li spectrum was recorded, typical of a mixture of oligomers. Thus, this lithium amide behaves differently in DEE and THF in which it gave a well-defined bridged (monomeric?) species.[8b]

Adding a second equivalent of methyllithium provided the

expected complex **3b** of which NMR spectra were very alike those obtained in THF, leading to analogous conclusions about its conformation. The two-dimensional data show similar correlations between nuclei (Fig. 4). However, a swap between ^{6}Li nuclei chemical shifts is worthy of note: the HOESY spectrum (Fig. 4(B)) clearly indicates that Li^1 is now at higher field (2.63 ppm) than Li^2 (2.96 ppm).

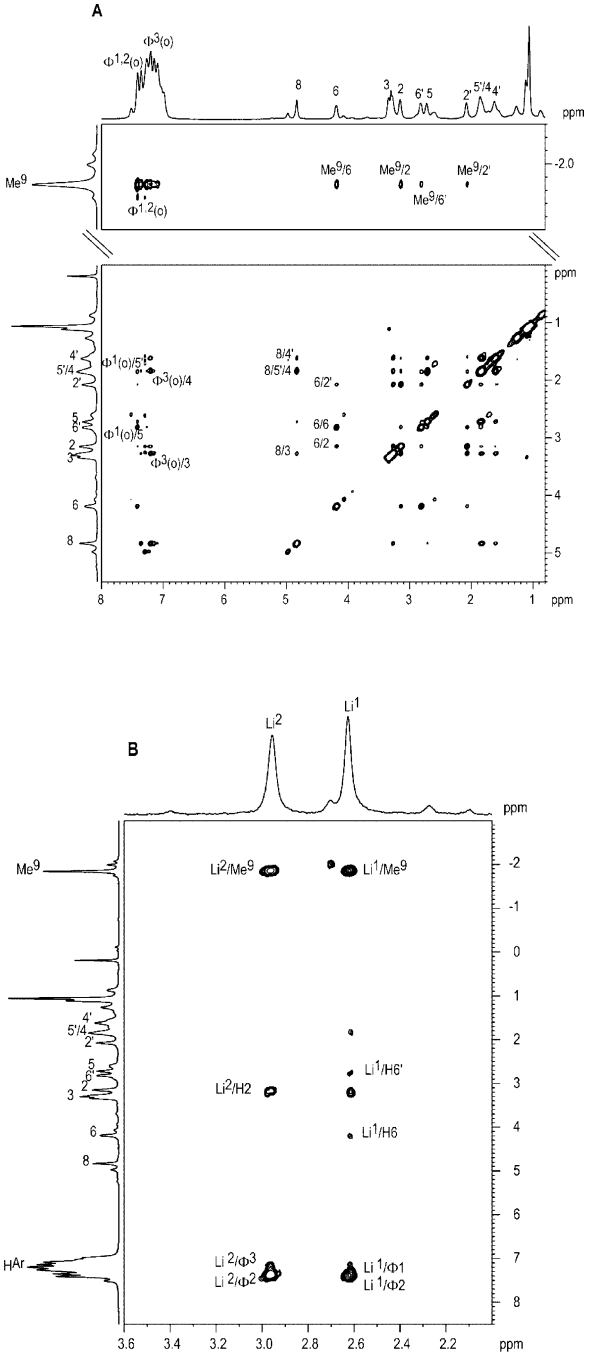


Figure 4. NOE (A) and HOE (B) spectra on **3b** in DEE-d_{10} at −78 °C.

This latter observation was checked adding aliquots of THF-d_8 to the DEE-d_{10} solution and recording the corresponding set of ^{6}Li NMR spectra (Fig. 5).

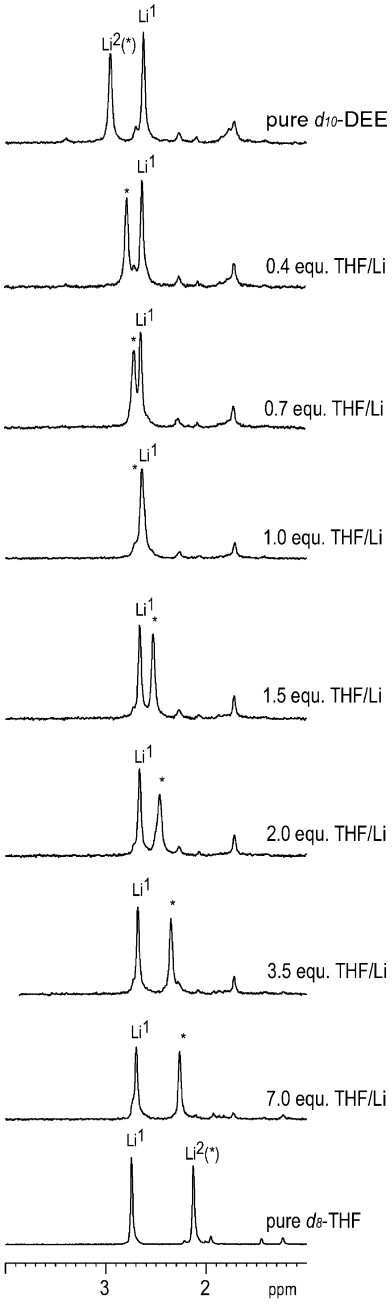


Figure 5. ^{6}Li spectra of complex **3b** in DEE-d_{10} upon progressive addition of THF-d_8 at −78 °C.

A progressive drift to high field of the Li^2 signal was observed, that ended up at 2.27 ppm upon addition of 7 equiv of THF. By contrast, the Li^1 signal stood almost perfectly still. This phenomenon will be discussed below.

3.3. Structures of 3b then 3a in toluene

This study was designed to understand the origin of the ee drop observed in this solvent. In our experimental study, the mixed aggregate was prepared in pure toluene at ∼20 °C (1/2 h) then cooled to −78 °C before adding the aldehyde in the same solvent. The NMR study was thus conducted in distilled deuteriated toluene, first with methyllithium, which is poorly soluble in this solvent, then *n*-butyllithium. Figure 6(A) shows key-portions of the ^{1}H spectrum (H^8

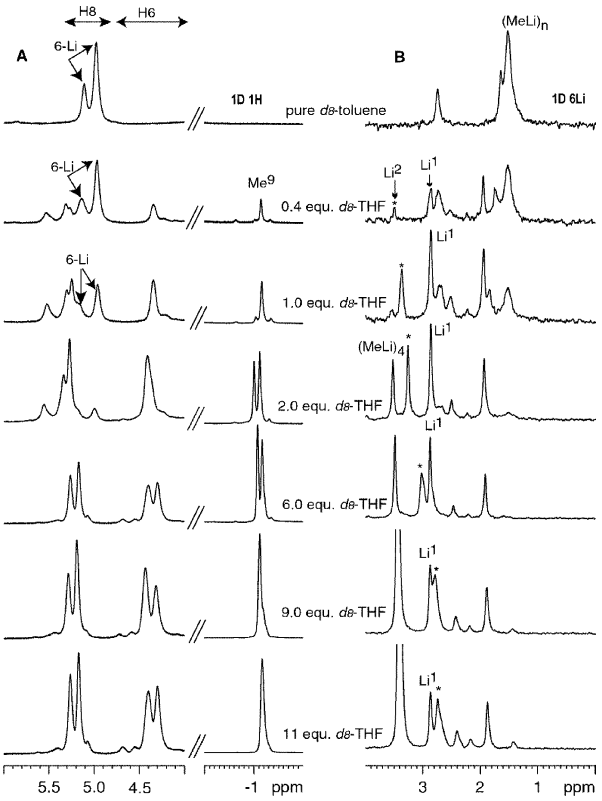


Figure 6. ^{1}H (A) and ^{6}Li (B) spectra recorded during the formation of complex **3b** from amide **6-Li** in toluene-d_8 upon addition of THF-d_8 at −78 °C.

around 5 ppm, H^6 around 4.3 ppm and Me^9 in the −1 ppm region) and the whole ^{6}Li spectrum after addition of a MeLi suspension to a solution of **6** in pure toluene-d_8. The NMR spectra recorded during the addition showed that a large excess of methyllithium is needed for a complete deprotonation of the amine. At this point, the ^{1}H spectrum remained simple and exhibited two signals between 5.0 and 5.4 ppm assigned to lithium amide **6-Li** (monomer+dimer?). Note that the −1 ppm region does not show any methyl signal, suggesting that no mixed aggregate is formed. By contrast, a large oligomeric methyllithium signal appeared in the ^{6}Li spectrum. This difference can be due to fast transverse relaxation of the $(MeLi)_n$ protons broadening their signal to an undetectable bump. A small peak at 2.71 and a shoulder at 1.61 ppm appear also on the ^{6}Li spectrum, possibly corresponding to the two forms of amide **6-Li**.

Interesting observations could then be made upon progressive introduction of THF aliquots. After the addition of 0.4 equiv of THF-d_8 (with respect to **6**), both spectra became more complex. In the ^{1}H spectrum, the main peaks remained that of amide **6-Li** at 4.98 and 5.14 ppm. In addition, several little peaks appeared at low field (between 5.26 and 5.53 ppm), probably due to complexes between **6-Li** and THF. Also, signals at 5.21, 4.34 and −1.14 ppm showed up, characteristic of H^8, H^6 and Me^9, respectively, in **3b**. Simultaneously, a tiny signal corresponding to Li^2 in **3b** was observed at 3.49 ppm on the ^{6}Li spectrum, together with the complementary Li^1 peak buried in the multiplet at 2.80 ppm. The ^{1}H and ^{6}Li signals of **3b** kept increasing when THF was further added, while the proportions between the unidentified solvates of lithium amide **6-Li** by THF changed and the amine ^{1}H signal decreased constantly. Although, the ^{6}Li spectrum is difficult to analyze probably because of the multiple aggregates in the medium, a decrease of the oligomeric methyllithium more or less parallel to that of amide **6-Li** to the benefit of mixed aggregate **3b** is easily followed. Actually, the chemical shifts of Li^2 in **3b**, that is larger than that of Li^1 in the presence of small amounts of THF, broadens progressively until the signals merge when between 6 and 9 equiv of THF were added. Finally, at higher THF concentrations, Li^2 signal appears at higher field than Li^1. Let us also mention that when approximately 1 equiv of THF was added to the sample, the residual solid methyllithium in suspension progressively came into solution (as a hexamer or a tetramer)[13] as observed from both the ^{1}H and ^{6}Li spectra. From there, its ^{1}H and ^{6}Li signals kept increasing with the THF concentration, the former merging with Me^9 singlet after 6–9 equiv THF were introduced. However, the doubling of the ^{1}H signals and the multiple ^{6}Li peaks observed at high THF loadings suggests that **3b** adopts more than one conformation (the *endo* and *exo* arrangements of **3b** are found almost isoenergetic at the DFT/B3P86 level)[14] or is involved in higher order aggregates.

We did not pursue our efforts to understand the behavior of the lithiated entities in this heterogeneous medium and switched to [^{6}Li]-*n*-butyllithium which is much more soluble in toluene. The above experiments were thus repeated by adding 3–5 equiv of *n*-Bu^{6}Li (prepared as described previously),[8b] to a solution of **6** in pure toluene-d_8 at −78 °C. Both the ^{1}H and ^{6}Li spectra (Fig. 7) suggest that the amide **6-Li** adopts the same two forms mentioned above.

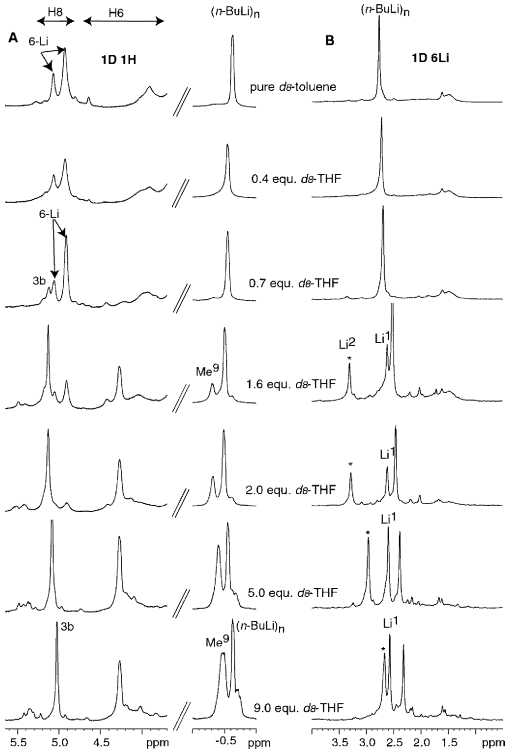


Figure 7. ^{1}H (A) and ^{6}Li (B) spectra recorded during the formation of complex **3a** from amide **6-Li** in toluene-d_8 upon addition of THF-d_8 at −78 °C.

Beside the large singlet observed in the ^{6}Li at 2.76 ppm due to the oligomeric *n*-BuLi, two tiny signals appeared at the same chemical shifts (2.71 and 1.61 ppm) as in Figure 6 top spectrum. No other significant peak arose until about 1.5 equiv of THF-d_8 was added (Fig. 7). From there, two singlets at 3.31 and 2.62 ppm showed up that were assigned, as before, to Li^1 and Li^2 in complex **3a**. These peaks increased simultaneously (with respect to the *n*-BuLi signal) upon addition of THF, suggesting that the aggregate **3a**, which does not seem to form in pure toluene, requires THF to build up. Interestingly, the drift of Li^2 chemical shift mentioned above was also observed here, the $\delta(Li^2)$–$\delta(Li^1)$ value getting from 0.69 (1.6 equiv THF) to 0.09 ppm (9 equiv THF). We did not add more than 9 equiv of this solvent to the sample and, therefore, did not record a signal crossover as for complex **3b** in the DEE/THF couple studied above.

Correspondingly, the proton spectra showed, upon addition of THF, a progressive fading of one of the H^8 signal of **6-Li** (at 5.07 ppm) to the benefit of the other (monomeric?) form of the same amide **6-Li** (at 4.98 ppm), then of **3a** (at 5.13 ppm). This latter complex is also characterized by the parallel appearance of a singlet at 4.27 ppm, associated to one of its H^6. At high field, the original singlet at −0.63 ppm due to the CH_2Li methylene in $(n\text{BuLi})_n$ is progressively associated to another signal drifting from −0.31 ppm when 1.6 equiv THF were added to −0.47 ppm upon addition of 9 equiv of the same solvent (Fig. 7).

The comparison of the ^{1}H and ^{6}Li NMR spectra suggests that the structure of complexes **3b** and **3a** obtained with MeLi and *n*-BuLi, respectively, in toluene after addition of an excess of THF is very similar to those obtained in pure THF. By contrast, the results suggest that the mixed-aggregates hardly form in pure toluene, probably leaving the homogeneous oligomers of alkyllithium unaltered. This could explain why the ee drops in this solvent. Note, however, that our NMR samples are between two and four fold more concentrated than the experimental medium (0.15–0.30 versus 0.07 M) and the influence of this parameter has not been evaluated.

4. Theoretical study of the aggregate solvation

We thought a theoretical evaluation of the energies associated to the solvation of Li^1 and Li^2 separately could help to analyze the above results. However, a fine description of the interaction between a mixed aggregate such as **3** and various solvents was requiring a relatively sophisticated level of computation. The B3P86 functional and 6-31G** basis set, which behaved satisfactorily in our previous studies, were thus retained. All the calculations have been performed using the Jaguar 4.1 software.[15] The somewhat simpler model **4** (Figs. 1 and 8) was considered in this part of the work since: (i) the aggregates **3** are relatively large (32 and 29 'heavy' atoms in **3a** and **3b**, respectively, vs 18 for **4**); (ii) it has been shown[8e] that **4** adopts an *exo* arrangement very similar to **3**, provided the (3*S*,8*R*) diastereomer is considered. We also limited our computations to the oxygenated solvents.

The modeling of the solvent by the DELPHI[16] continuum technique was first considered to describe the aldehyde/aggregate interactions. However, this approximation led to a structure in which the docking of the aldehyde takes place more or less coplanar to the N–Li–C–Li quadrilateral, a situation unrealistic in the eventuality of a tetrahedral surrounding of the lithiums. We thus preferred to incorporate discrete solvent molecules to simulate the first solvation shell. The number of molecules to be taken into account required a preliminary set of calculations. An increasing number of dimethyl ether, the smallest solvent considered were thus progressively added to aggregate **4**. A fully solvated structure was obtained in which one and two Me_2O were bound to Li^1 and Li^2, respectively, placing the two lithium cations in pseudo-tetrahedral surroundings. The identification of the three ether molecules, labeled a^2 (pseudo-axial) and e^2 (pseudo-equatorial) on Li^2, and a^1 (on Li^1), is reported on Figure 8 while the fully optimized structures appear on Figure 9.

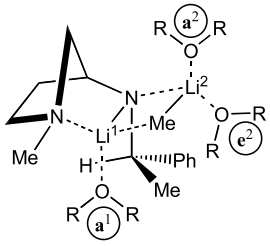


Figure 8. Solvent tags on aggregate **4**.

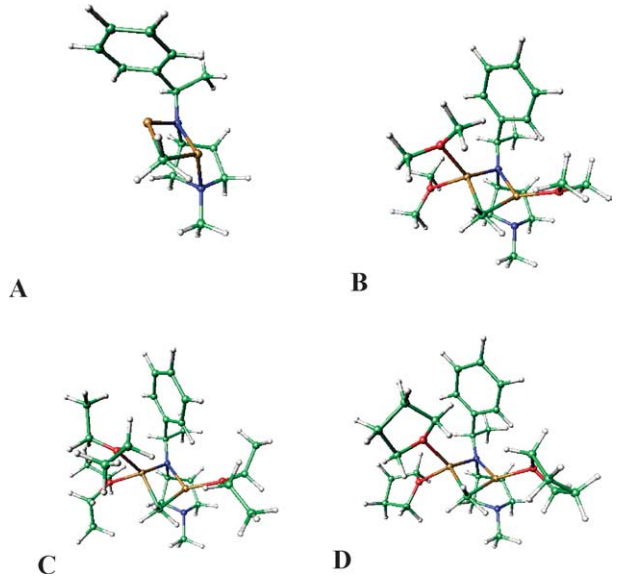


Figure 9. Optimized structures of aggregate **4** in vacuo (A) or solvated by three molecules of Me_2O (B), Et_2O (C) or THF (D).

The relative energies associated to the selective solvation of Li^1 and Li^2 in **4** by dimethylether, diethylether and THF were computed by optimizing the tri-solvated aggregates, removing one solvent molecule and re-computing the energy of this partially desolvated entity without optimizing its structure. The specific solvation energy was taken as the difference between the energy of the tri-solvated complex

Table 2. Total and partial solvation energies of aggregate **4** in Me_2O, Et_2O and THF

Entries	Solv.	Fig	Solvation[a] (q_{Li1}/q_{Li2})[b]	$\Delta E/\delta E$[c]
1	None	9A	None (0.84/0.86)	–
2	Me_2O	9B	$a^1+a^2+e^2$ (0.84/0.86)	$\Delta E=-21.1$
3	Me_2O		a^2+e^2 (0.86/0.86)	$\delta E=-10.2$
4	Me_2O		a^1+e^2 (0.83/0.88)	$\delta E=-8.4$
5	Me_2O		a^1+a^2 (0.84/0.88)	$\delta E=-8.3$
6	Et_2O	9C	$a^1+a^2+e^2$ (0.84/0.88)	$\Delta E=-18.1$
7	Et_2O		a^2+e^2 (0.86/0.87)	$\delta E=-9.8$
8	Et_2O		a^1+e^2 (0.84/0.89)	$\delta E=-7.1$
9	Et_2O		a^1+a^2 (0.84/0.89)	$\delta E=-6.3$
10	THF	9D	$a^1+a^2+e^2$ (0.85/0.87)	$\Delta E=-21.4$
11	THF		a^2+e^2 (0.86/0.86)	$\delta E=-10.4$
12	THF		a^1+e^2 (0.84/0.88)	$\delta E=-7.2$
13	THF		a^1+a^2 (0.84/0.88)	$\delta E=-8.4$

[a] Labeling of the solvents as on Figure 8(A).
[b] NBO charges calculated on Li^1 and Li^2.
[c] Values in kcal mol^{-1}. Total solvation energy $\Delta E=E$(trisolv.)–E(unsolv.)–3E(solvent). Partial solvation energy $\delta E=E$(trisolv.)–E(disolv.)–E(solvent).

and the sum of the energies of the di-solvated complex plus one isolated solvent molecule. The values obtained are gathered in Table 2, together with the Natural Bonding Orbital (NBO) partial charges on Li^1 and Li^2.

These data suggest that: (i) THF and dimethyl ether are better solvents for the aggregate (by $\sim$3 kcal mol^{-1}) than diethyl ether (entries 2, 6 and 10). This latter solvent is probably handicapped by the floppiness of its alkyl chains; (ii) Li^1 is more difficult to desolvate (by more than 1.8 kcal mol^{-1}), whatever the solvent (entries 3, 7 and 11); (iii) the energy differences between the a^2 and e^2 sites are relatively limited and depend on the solvent.

The calculated NBO charges for the two lithium differ by insignificant amounts. The solvation scheme we have retained (two solvents on Li^2 and one on Li^1) keeps Li^2 slightly more positive (and therefore, more attractive to the incoming aldehyde) than Li^1 (entries 2, 6 and 10). Note that the removal of one solvent is associated with a minor ($\leq$0.02 e) charge increase on the desolvated lithium.

Actually, the large solvation energy δE calculated for Li^1 in aggregate **4** seems in contradiction with the iso-shielding of this same cation measured for **3** in DEE and THF, which suggests that this cation could be unsolvated. This discrepancy could very well stem from the structural differences between **3** and **4**. In particular, one could imagine that the aromatic ring of the benzyl group borne by the cyclic nitrogen in **3** come as a supplementary π-ligand to Li^1, preventing its solvation, by contrast with the tiny *N*-methyl group in **4** which would leave free access to the solvent. This hypothesis, in accord with both the HOESY and NOESY experiments on **3b** which suggest a close proximity between Li^1 and the benzyl phenyl ring Ph^1 in both THF and ether (Figs. 3(B) and 4(B)), is not supported by the results of DFT calculations. If the Ph^1 ring faces the Li^1 in both the unsolvated[14] and fully solvated aggregate **3b** (by 3 THF, Fig. 10 left), the interaction energies computed for this complex suggest that the contribution of the intramolecular Ph^1–Li^1 contact is limited to 2.1 kcal mol^{-1} while the extra intermolecular THF coordination on Li^1 brings about 9.8 kcal mol^{-1} (Table 3, entry 3). However, this latter figure is probably overestimated by about

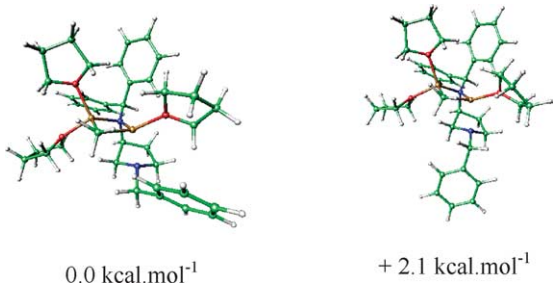


Figure 10. Optimized local minima of **3b** solvated by 3 THF with (left) and without (right) a Ph^1–Li^1 interaction.

3 kcal mol^{-1} due to the neglect of THF–THF interactions in our calculation.

The relative solvation energies (δE) and the charges borne by each lithium in **3b** are relatively similar to those given for **4** in Table 2, THF a^2 remaining the more labile one. However, the differences between the δE and between q_{Li1}/q_{Li2} are much less pronounced (Table 3).

Table 3. Total and partial solvation energies of aggregate **3b** in THF

Entry	Solvation[a] (q_{Li1}/q_{Li2})[b]	$\Delta E/\delta E$[c]
1	None (0.86/0.86)	$\Delta E=0.0$
2	$a^1+a^2+e^2$ (0.86/0.86)	$\Delta E=-22.4$
3	a^2+e^2 (0.86/0.88)	$\delta E=-9.8$
4	a^1+e^2 (0.85/0.87)	$\delta E=-9.4$
5	a^1+a^2 (0.86/0.88)	$\delta E=-9.5$

[a] Labeling of the solvents as on Figure 8(A).
[b] NBO charges calculated on Li^1 and Li^2.
[c] Values in kcal mol^{-1}. ΔE and δE as in Table 2.

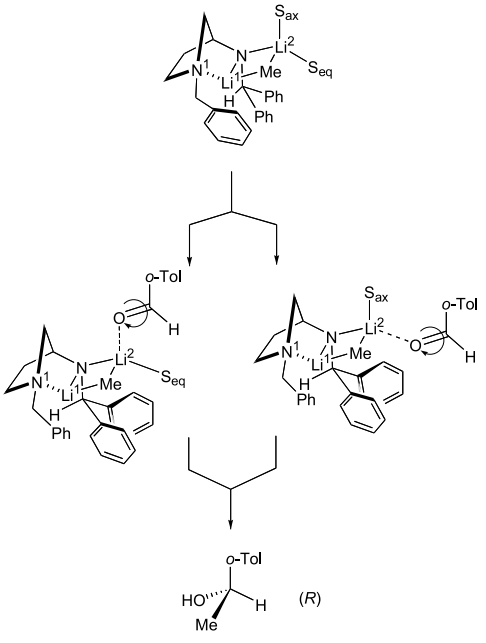
5. Discussion of the solvation

We have seen in the experimental part above that pure toluene does not favor the aggregation while similar complexes are observed in THF and DEE. These results are of interest with respect to the ee values reported in Table 1. In toluene, large amounts of uncomplexed butyllithium remain available for the uncontrolled alkylation of the aldehyde in this solvent. The difference between the induction levels measured in THF and DEE is more difficult to explain. It can derive from (i) the stability of the

aggregate that could be lesser in DEE; (ii) the solvation/desolvation phenomena, expected to be significantly different in THF and DEE on the basis of the calculated energies; (iii) a change in the docking site of the aldehyde (unlikely from the calculated values). At this stage, the relative importance of these contributions is difficult to establish.

Regarding the problem at the origin of this study, the connection between the topology of the aggregates **3**–**5** and the induction remains to be established. However, in all cases studied to date, a swap from an *exo* to an *endo* arrangement is associated with a reversal of the sense of the induction on alcohol **2**.[8c,e] Getting a spectroscopic insight on the interaction between the incoming aldehyde and this type of complex is not easy. McGarrity, Ogle and their colleagues could establish, through a rapid-injection NMR study published in 1985,[17] that the condensation of butyllithium dimers on benzaldehyde is extremely fast in THF and, therefore, very difficult to follow by NMR. The mixed aggregates, we are dealing with are probably more reactive than *n*-butyllithium oligomers in THF. Thus a direct spectroscopic approach to this problem, at least with potent electrophiles such as aldehydes, is hardly conceivable at the moment.

Previous theoretical studies[7,18] have led to the conclusion that the interaction between an aldehyde and an organolithium compound begins with the complexation of the lithium cation by one of the electron lone pairs of the carbonyl oxygen, the metal acting as a Lewis acid towards the aldehyde (Scheme 3). For the reaction to take place, the incoming aldehyde has probably to access the first coordination sphere of the metal and to displace at least one solvent molecule. Thus, the exchanges between DEE or toluene and a more nucleophilic Lewis base such as THF can be regarded, in a first approximation, as a rough simulation of the organolithium/aldehyde encounter in the reaction medium and thus as fair models for the docking phenomena on complexes **3**. In this case, the relative consistency of Li^1 chemical shift with respect to the driftings observed for Li^2 signals upon THF addition suggests that Li^1, buried at the heart of the complex, is hardly influenced by incoming ligands, making peripheral Li^2 a prime target for electrophiles. If this scenario holds for *o*-tolualdehyde, two cases can still be considered, the data in Table 3 suggesting that the 'axial' as well as the 'equatorial' solvent could be chased from Li^2 surroundings (Scheme 3). The molecular models hint that one orientation of the aldehyde should be preferred in each case. When the aldehyde docks along the axial position, the proton of the CHO group is likely to be directed towards the portion of space crowded by the complex, orienting the aromatic ring 'anti' to the O–Li coordination direction. From there, a gentle rotation around the C=O axis brings the *Re* face of the carbonyl to a reacting distance of the nucleophilic methyl group, yielding the R alcohol. If the aldehyde enters along the equatorial direction, the proton of the CHO will again points toward the region crowded by the two phenyl nuclei of the $CHPh_2$ benzhydryl group. Also in this case the tolyl residue will be oriented toward the outer part of the complex. Finally, the same rotation exposes the same *Re* face of the aldehyde, leading again to the R alcohol.



Scheme 3.

Therefore, if it seems that the aldehyde should bind to Li^2, it is difficult, from simple molecular models, to decide along which face of the N–Li–C–Li quadrilateral its approach should occur since both directions are expected to provide the same enantiomer, which is, incidentally, the one obtained experimentally. A DFT theoretical study of the docking of *o*-tolualdehyde on a model of aggregate **4** exploring these various possibilities will be presented in a forthcoming paper.[19]

6. Conclusions

We have shown in this work that adding 2 equiv of methyllithium to 3-aminopyrrolidine **6** leads, in THF-d_8 and at −90 °C, to an *exo* aza-norbornyl-type aggregate similar to that characterized previously between lithium amide **6**-**Li** and *n*-butyllithium in the same solvent. In diethyl ether, a complex presenting a comparable *exo* topology was obtained. However, the chemical shift of the Li^2 nucleus was shifted to low field, while $\delta(Li^1)$ remained unchanged. The progressive addition of THF to the medium led to a drift of the Li^2 signal back to its original value, suggesting that this cation is much more accessible to the solvents.

The aggregation experiment was next repeated in toluene-d_8, with MeLi then *n*-BuLi. In this solvent, the lithium amide **6**-**Li** was obtained, apparently under two forms, which did not seem to aggregate with MeLi or BuLi until THF was added to the medium. At higher THF loadings, complex **3b** became the single entity and a drift of its Li^2 signal similar to that described above was recorded. These results clearly point out that ether solvents are required for the mixed-aggregation phenomenon considered here to take place.

Overall, this work further supports the idea that mixed aggregates can become useful tools in asymmetric synthesis. The tight non-covalent association of a chiral entity to a very reactive nucleophile can indeed constitute a perfect couple provided the chelation[20] and solvation phenomena are attuned to the task.

7. Experimental

7.1. Spectral data

7.1.1. Compound 3a. The titled compound in THF-d_8 at −70 °C: ^{1}H NMR (500.13 MHz): δ 7.43–6.96 (m, 15H^{Ar}), 4.77 (s, 1H^8), 4.23 (d, 1H^6, $J_{6-6'}$=10.7 Hz), 3.22 (d, 1H^2, $J_{2-2'}$=7.7 Hz), 3.19 (s, 1H^3), 2.79 (d, 1H^6, $J_{6-6'}$=10.7 Hz), 2.68 (s, 1H^5), 1.99 (s, 1H^5, 1H^2), 1.82 (m, 1H^4), 1.67 (s, 2H$^\beta$), 1.60 (s, 1H^4), 1.26 (m, 2H$^\gamma$), 0.81 (m, 2Hδ), −0.72 (m, 1H$^\alpha$), −0.81 (m, 1H$^\alpha$); ^{13}C NMR (125.75 MHz): δ 152.20, 151.60, 140.00 (C$^{Ar(IV)}$), 130.60, 129.70, 129.20, 128.80, 127.90, 127.70, 125.40, 125.20 (C$^{Ar(III)}$), 71.60 (C^8), 65.80 (C^2), 62.40 (C^6), 60.50 (C^3), 53.30 (C^5), 31.10 (C^4), 37.30 (C$^{\gamma \text{ or } \beta}$), 35.90 (C$^{\beta \text{ or } \gamma}$), 15.10 (C$\delta$), 13.40 (qt, C$^\alpha$, J_{C-Li}=7.90 Hz); ^{6}Li NMR (73.59 MHz): δ 2.57 (s, Li^1), 2.19 (s, Li^2).

7.1.2. Compound 3b. The titled compound in THF-d_8 at −78 °C: ^{1}H NMR (500.13 MHz): δ 7.65–6.88 (m, 15H^{Ar}), 4.80 (s, 1H^8), 4.28 (d, 1H^6, $J_{6-6'}$=10.7 Hz), 3.47 (s, 1H^2), 3.25 (s, 1H^3), 2.83 (d, 1H^6, $J_{6-6'}$=10.7 Hz), 2.75 (s, 1H^5), 2.02 (s, 1H^4, 1H^2), 1.91 (s, 1H^5), 1.73 (s, 1H^4), −1.76 (s, 3H^9); ^{13}C NMR (125.75 MHz): δ 152.44, 151.56, 140.02 (C$^{Ar(IV)}$), 130.57, 129.75, 129.41, 128.57, 127.8, 127.72, 127.33, 125.28, 124.97 (C$^{Ar(III)}$), 71.45 (C^8), 65.35 (C^2), 62.15 (C^6), 60.65 (C^3), 53.04 (C^5), 30.17 (C^4), −12.35 (qt, C^9, J_{C-Li}=8.41 Hz); ^{6}Li NMR (73.59 MHz): δ 2.75 (s, Li^1), 2.13 (s, Li^2).

7.1.3. Compound 3b. The titled compound in DEE-d_{10} at −78 °C: ^{1}H NMR (500.13 MHz,): δ 7.62–6.78 (m, 15H^{Ar}), 4.83 (s, 1H^8), 4.19 (s, 1H^6), 3.32 (s,1H^3), 3.16 (s, 1H^2), 2.83 (s, 1H^6), 2.72 (s,1H^5), 2.08 (s, 1H^2), 1.85 (s, 1H^5, 1H^4), 1.61 (s, 1H^4), −1.84 (s, 3H^9); ^{13}C NMR (125.75 MHz): δ 151.49, 150.70, 139.04 (C$^{Ar(IV)}$), 130.13, 128.66, 128.14, 127.54, 127.44, 127.72, 127.30, 125.07, 124.94 (C$^{Ar(III)}$), 72.03 (C^8), 65.83 (C^2), 61.56 (C^6), 60.15 (C^3), 52.32 (C^5), 29.54 (C^4), −13.58 (qt, C^9, J_{C-Li}=7.65 Hz); ^{6}Li NMR (73.59 MHz): δ 2.96 (s, Li^2), 2.63 (s, Li^1).

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Nucleophilic additions of lithiated allylphenylsulfone to nitrones: experimental and theoretical investigations

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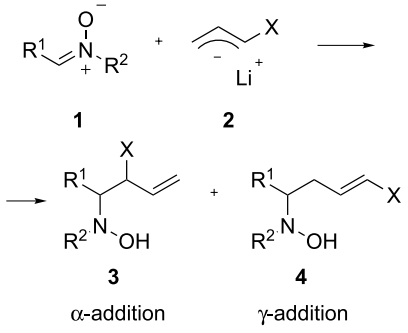
Abstract—The nucleophilic addition of lithiated allylphenylsulfone to nitrones at −80 °C proceeds exclusively α to the phenylsulfonyl group affording *anti* adducts in high yield. At 0 °C isoxazolidines are obtained with complete all-*trans* selectivity. The formation of these compounds involves isomerization of the allylsulphonyl moiety to give a transient vinylsulfone that then undergoes a subsequent intramolecular Michael addition. The addition to several nitrones has been studied and theoretical calculations have been refined to accurately explain the selectivity of the allylation reaction.

1. Introduction

Allylmetalations of imines and related compounds have proven to be of a great importance for the efficient synthesis of acyclic and cyclic amine derivatives.[1] Although the reaction of several allylic metals, including allyllithium derivatives, with imines has been extensively investigated,[2] little attention has been directed toward the allylation of nitrones Wuts and Jung[3] have reported the reaction of allylsilanes and nitrones with trimethylsilyl-triflate as a catalyst. Similarly, Trombini and co-workers[4] found that the same catalyst served to promote the condensation of allyltributylstannane with nitrones. The same authors[5] have also described the reaction of allylic magnesium and zinc reagents with nitrones to form homoallylic hydroxylamines. More recently, allylation of nitrones in aqueous media have been reported using indium[6] and samarium[7] allylic derivatives.

To date, no general studies have appeared in the literature concerning allyllithiation of nitrones **1**. A particular example has been described by Trombini and co-workers regarding the addition of a substituted lithiated derivative **2** (X=OSiMe$_2^t$Bu); however, it was reported that low chemical yields were obtained (Scheme 1).[8]

The introduction of a functional group into the allylic moiety (leading to functionalized allyllithiums **2**) would allow the preparation of hydroxyamino-containing subunits **3** or **4**, depending on the type of addition (α vs γ). In particular, α-substituted homoallylic hydroxylamines **3** should find use as important fundamental building blocks in many biologically active compounds. In extending our previous investigations on nucleophilic additions to nitrones[9] we now focus on the allylsulfonylation of nitrones. Allylic carbanions formed from the corresponding allylsulfones (X=SO$_2$R) have been widely used in organic synthesis.[10] The presence of the sulfonyl group in **3** strongly increases the synthetic potential of these compounds to be used as building blocks.[11]



Scheme 1.

In this paper, we describe reaction of the lithiated allylphenylsulfone **2** (X=SO$_2$Ph) with nitrones **1** and the dependence of the reaction on the reaction conditions and on the substrate. The nitrones were subjected to several allylsulfonylation conditions with the purpose of finding reaction conditions suitable for the preparation of allylation

Keywords: Nitrones; Allylation; Hydroxylamines; Isoxazolidines; Allyllithium.
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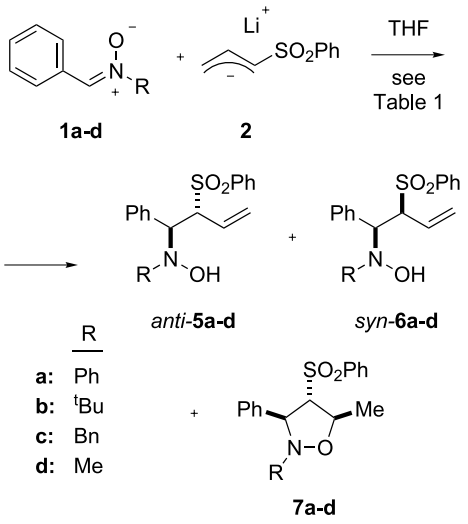


Scheme 2.

products in good regio- and stereoselective ways. Furthermore, we also describe herein a theoretical study of the possible reaction pathways associated with the addition of allylic anions to nitrones.

2. Results and discussion

For our initial studies we selected C-phenyl nitrones **1a–d** (Scheme 2) as the substrates and varied both the reaction conditions and the nature of the N-substituent. Some pertinent data are collected in Table 1.

As illustrated, the reaction of lithiated allylphenylsulfone **2** with nitrone **1a** at −80 °C and in THF as a solvent (entry 1) afforded a 54:46 mixture of products consisting of the expected hydroxylamine **5a**, coming from a α-addition to the allylic moiety and the unexpected isoxazolidine **7a**. Each compound was obtained as one stereoisomer possessing the indicated relative configuration and no traces of γ-addition were detected in the reaction mixture.[12] Compound **7** can be seen as the product of a formal [3+2] cycloaddition between the nitrone and a propenyl sulfone; however, it is possible to explain its formation in terms of a nucleophilic addition as discussed below. The addition of pre-complexing agents of the nitrone such as Et_2AlCl (entry 2) or $BF_3\cdot Et_2O$ (entry 3) did not affect the selectivity of the reaction but lower yields were obtained.

On the other hand, when the reaction was performed in the presence of a lithium coordinating agent (entries 4 and 5) the amount of isoxazolidine decreased considerably. Indeed, in the presence of HMPA the hydroxylamine **5a** was the only product of the reaction. Again, only one diastereoisomer could be detected. Interestingly, when the reaction was carried out at 0 °C only the cyclic compound **7a** was obtained (entries 6 and 7) in a complete regio- and stereoselective manner. The isoxazolidine **7a** was obtained in almost quantitative chemical yield in the absence of any additive. Replacement of the *N*-phenyl group by a *tert*-butyl group led to similar results although considerably lower chemical yields were observed (entries 8 and 9). In the case of the *N*-benzyl nitrone **1c** only one compound having an *anti* configuration was obtained at −80 °C (entry 10); at 0 °C (entry 11) a mixture of three compounds was isolated from the reaction mixture. Even though the isoxazolidine **7c** was the major product; the *anti*/*syn* selectivity was only 3:2. A similar result was observed with *N*-methyl nitrone **1d** (entries 12 and 13). Whereas the reaction at low temperature afforded a 4:1 mixture of hydroxylamines **5d** and **6d**, respectively, the reaction at 0 °C gave isoxazolidine **7d** preferentially, the hydroxylamines being obtained in a non-stereoselective way.

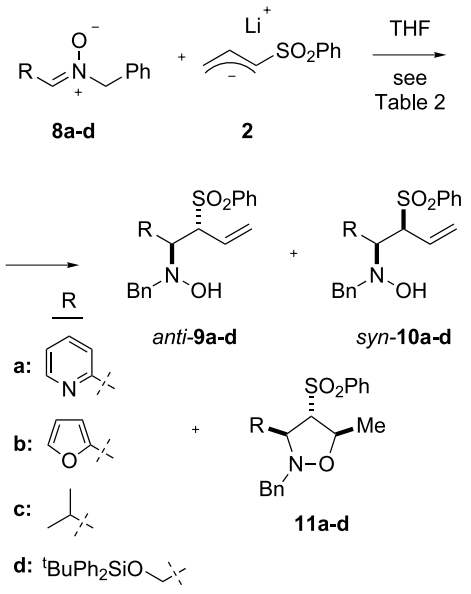
In order to establish the range of application of the allylsulfonylation of nitrones, the addition of lithiated allylphenylsulfone to other C-substituted nitrones was investigated (Scheme 3, Table 2). We chose the benzyl group for N-substitution because it can be easily eliminated by hydrogenation methods during further elaborations with synthetic purposes.

As in the case of C-phenyl nitrones **1a–d** the reaction at −80 °C in the presence of HMPA afforded exclusively hydroxylamines having an *anti* relative configuration (entries 1, 3, 5 and 7). With non-aromatic C-substituents (entries 5 and 7) lower *anti*/*syn* selectivity was observed.

Table 1. Addition of lithiated allylphenylsulfone to nitrones **1a–d**[a]

Entry	Nitrone	*T* (°C)	Additive[b]	(**5**+**6**):**7**[c]	**5**:**6**[c]	Yield (%)[d]
1	**1a**	−80	None	54:46	>20:1	80
2	**1a**	−80	Et_2AlCl[e]	40:60	>20:1	53
3	**1a**	−80	$BF_3\cdot Et_2O$[e]	55:45	>20:1	55
4	**1a**	−80	TMEDA	80:20	>20:1	63
5	**1a**	−80	HMPA	100:0	>20:1	80
6	**1a**	0	None	0:100	—	98
7	**1a**	0	HMPA	0:100	—	70
8	**1b**	−80	HMPA	100:0	>20:1	52
9	**1b**	0	None	0:100	—	46
10	**1c**	−80	HMPA	100:0	>20:1	88
11	**1c**	0	None	30:70	3:2	91
12	**1d**	−80	HMPA	100:0	4:1	80
13	**1d**	0	None	30:70	1:1	91

[a] The reaction was performed with 1.2 equiv of lithiated allylphenylsulfone, formed from 1.2 equiv of BuLi and 1.2 equiv of allylphenylsulphone, in THF.
[b] 1.0 equiv with respect to allylphenylsulfone was added unless otherwise indicated.
[c] Measured by ^{1}H NMR from the isolated reaction mixture.
[d] Referred to the isolated reaction mixture.
[e] 1.0 equiv with respect to the nitrone was added.



Scheme 3.

in a complete agreement with previous nucleophilic additions of organometallic reagents to **12**.[9b]

The formation of isoxazolidines **7**, **11** and **14** can be explained in terms of equilibrium between the hydroxyamino anion **15**, immediately formed after the addition, and the corresponding vinylsulfone **17** as displayed in Scheme 5. The isomerization between allyl and vinyl sulfones in a basic medium is well-known[13] and it has been evidenced in tandem sequences involving intramolecular Michael additions.[14]

According to the reaction pathway shown in Scheme 5, at low temperature (−80 °C) the initially formed adduct **15** is stable enough to afford the corresponding hydroxylamine after aqueous work-up. At 0 °C the equilibrium takes place and the reaction proceeds via the anionic intermediate **17** which ultimately produces **18** through an intramolecular Michael addition.[15] The presence of HMPA is crucial for avoiding isomerization of **15** even at −80 °C (compare entries 1 and 5 in Table 1). Presumably, the coordinating capabilities of HMPA block the equilibration between **15**

Table 2. Addition of lithiated allylphenylsulfone to nitrones **8a–d**[a]

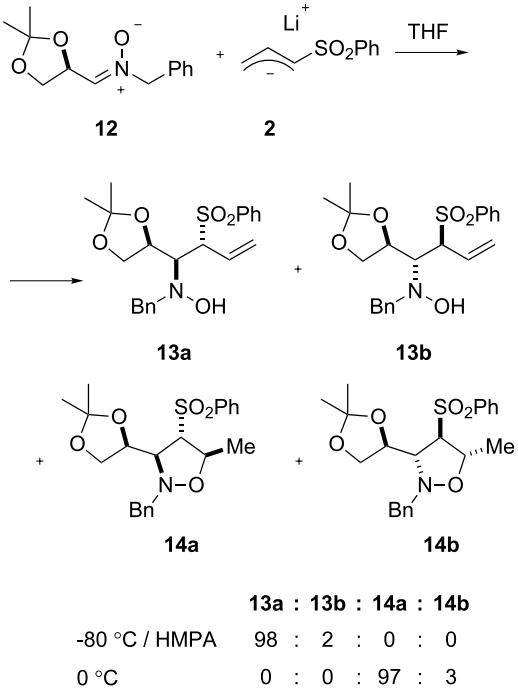
Entry	Nitrone	*T* (°C)	Additive[b]	(**9**+**10**):**11**[c]	**9**:**10**[c]	Yield (%)[d]
1	**8a**	−80	HMPA	100:0	>20:1	86
2	**8a**	0	None	15:85	2:1	87
3	**8b**	−80	HMPA	100:0	>20:1	80
4	**8b**	0	None	20:80	2:1	74
5	**8c**	−80	HMPA	100:0	6:1	69
6	**8c**	0	None	30:70	2:1	73
7	**8d**	−80	HMPA	100:0	>20:1	72
8	**8d**	0	None	0:100	—	69

[a] The reaction was performed with 1.2 equiv of lithiated allylphenylsulfone, formed from 1.2 equiv of BuLi and 1.2 equiv of allylphenylsulphone, in THF.
[b] 1.0 equiv with respect to allylphenylsulfone was added unless otherwise indicated.
[c] Measured by ^{1}H NMR from the isolated reaction mixture.
[d] Referred to the isolated reaction mixture.

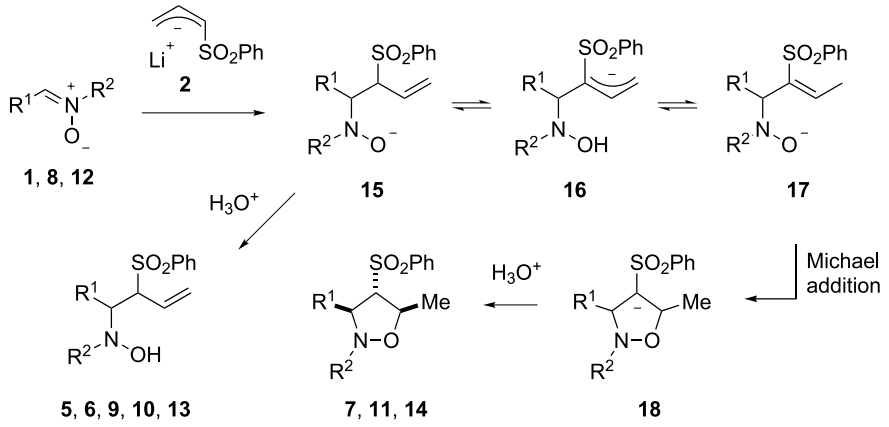
Following the same trend that nitrones **1a–d**, the reaction at 0 °C, in the absence of HMPA, gave rise to isoxazolidines **11** as major products (entries 2, 4, 6 and 8). The modest *anti*/*syn* selectivity observed for hydroxylamines **9** and **10** under these conditions was probably due to the higher temperature. Only in the case of nitrone **8d** the corresponding isoxazolidine **11d** was obtained as the only product of the reaction. It is noteworthy that in all cases only one stereoisomer of isoxazolidines **7** and **11** was obtained thus showing a complete stereoselectivity in the formation of such compounds.

Finally, we decided to explore the reactivity of a chiral substrate. For this purpose nitrone **12**, derived from D-glyceraldehyde and widely used in our laboratory,[9b] was chosen. As expected (Scheme 4), the allylsulfonylation of **12** at −80 °C afforded hydroxylamine **13a** as the main product of the reaction. At 0 °C only isoxazolidines **14a** and **14b** were obtained. The diastereofacial selectivity was also excellent; the *syn* adducts (with respect to the dioxolane ring being obtained with high levels of diastereoselectivity. Indeed, stereoisomers **13b** and **14b** were detected in minor amounts (2–3%).

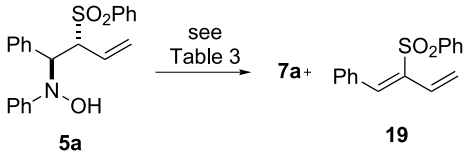
The diastereofacial selectivity observed in the reaction was



Scheme 4.



Scheme 5.



Scheme 6.

although some elimination product **19** was obtained. This product corresponds to the elimination of the *N*-benzyl hydroxyamino moiety. An excess of BuLi (entry 4) dramatically increased the amount of elimination product.

On the other hand, when hydroxylamine **5a** was treated with 1.0 equiv of potassium *tert*-butoxide (entry 5) only a minor amount of **19** was obtained, the main product of the reaction being the isoxazolidine **7a**. This behavior was also observed for other hydroxylamines. Under elimination conditions, compounds **20**–**23** were preferentially obtained and fully characterized (Chart 1). The geometry of the alkene group was established in all cases by NOESY experiments which showed cross-peaks between the terminal vinyl group and the vinylic proton of the trisubstituted alkene. In a similar way to **5a**, deprotonation with 1.0 equiv of either BuLi in the presence of 1.0 equiv of HMPA or potassium *tert*-butoxide at 0 °C afforded the corresponding

Table 3. Deprotonation of **5a**[a]

Entry	*T* (°C)	Base	Equiv[b]	**19**:**7a**[c]	Yield (%)[d]
1	−80	BuLi	1.0	—[e]	—[e]
2	−80	BuLi	1.5	—[f]	—[f]
3	0	BuLi	1.0	8:92	77
4	0	BuLi	1.5	90:10	90
5	0	^{t}BuOK[g]	1.0	4:96	85

[a] The reaction was carried out in THF in the presence of 1.0 equiv of HMPA unless otherwise indicated.
[b] With respect to **5a**.
[c] Measured by ^{1}H NMR from the isolated reaction mixture.
[d] Referred to the isolated reaction mixture.
[e] Pure hydroxylamine **5a** was recovered.
[f] A mixture of *anti* and *syn* hydroxylamines were recovered.
[g] The reaction was conducted without HMPA.

and **17** at low temperature. At 0 °C it has no effect since formation of isoxazolidine is observed anyway (Table 1, entry 7). The formation of isoxazolidines through a concerted cycloaddition reaction between the nitrone and a propenyl sulfone is not very likely since in a basic medium the latter is not present but exists as the corresponding allylic anion.[16]

In order to assess the mechanistic proposal illustrated in Scheme 5 we decided to study the deprotonation of hydroxylamine **5a** (Scheme 6, Table 3). Treatment of **5a** with 1.0 equiv of BuLi in THF at −80 °C in the presence of 1.0 equiv of HMPA, stirring for 2 h and then aqueous work-up afforded the starting compound without traces of any other stereoisomer or isoxazolidine (entry 1). This experiment clearly demonstrates the stability of **5a** at low temperature. The same experiment carried out with 1.5 equiv of BuLi (entry 2) afforded a mixture of *anti*/*syn* diastereomers proving that although a second deprotonation takes place at the α-phenylsulfonyl carbon atom no isomerization to **17** is produced. When the reaction was carried out at 0 °C (entry 3) cyclization to **7a** was observed

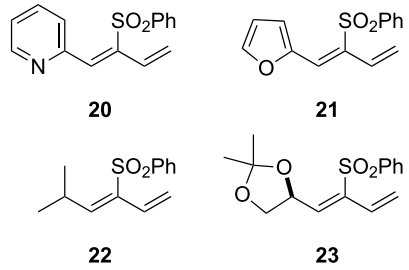


Chart 1.

Table 4. Selected coupling constants for **5a–d**, **6a–d**, **9a–c** and **10a–c**

Entry	R^1	R^2	*anti*	*syn*	$^3J_{H,H}$ (*anti*)	$^3J_{H,H}$ (*syn*)
1	Ph	Ph	**5a**	**6a**	10.0	—[a]
2	Ph	Bn	**5b**	**6b**	9.9	9.1
3	Ph	Me	**5c**	**6c**	9.8	8.5
4	Ph	^{t}Bu	**5d**	**6d**	10.0	—[a]
5	Py[b]	Bn	**9a**	**10a**	9.1	9.6
6	Fu[c]	Bn	**9b**	**10b**	10.1	9.1
7	^{i}Pr	Bn	**9c**	**10c**	10.0	8.8

[a] Not obtained.
[b] 2-Pyridyl.
[c] 2-Furyl.

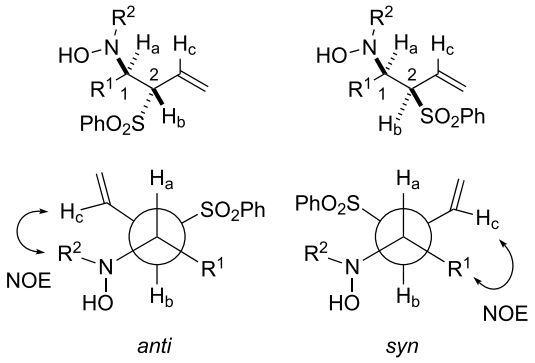


Figure 1. Preferred conformations for compounds **5a–d**, **6a–d**, **9a–c** and **10a–c**.

isoxazolidines thus confirming the mechanism outlined in Scheme 5.

The observed geometry of the newly generated double bond is in agreement with a stereospecific *syn* elimination following a concerted path for the loss of the alkylhydroxyamino unit. Such a reaction represents a retro-Michael addition of a hydroxylamine. Indeed, the corresponding direct reaction has been demonstrated to be a concerted process by Ortuño and co-workers.[17]

3. Determination of configuration

The stereochemical assignments of hydroxylamines **5a–d**, **6a–d**, **9a–c** and **10a–c** were based on NMR evidence In all cases the $^3J_{H,H}$ coupling constants between H_a and H_b (Table 4, Fig. 1) were in the range of 8.5–10.1 Hz. Those values are in agreement with the depicted *anti* and *syn* arrangements in which protons H_a and H_b adopt an antiperiplanar disposition.

Support for that conformation was secured upon cooling to −40 and −80 °C, no significant changes being observed for the ^{1}H NMR coupling patterns. This observation indicated that the solution contained almost exclusively, one single conformer with respect to the C1–C2 bond. Indeed, semiempirical calculations[18] also supported the conformational disposition shown in Figure 1 for *anti* and *syn* isomers. These observations, coupled with the 2D NOESY spectra, which showed strong NOE between the vinylic protons H_c and groups R^2 (Ph, Me, ^{t}Bu, Bn) for *anti* adducts, and between the same proton (H_c) and groups R^1 (Ph, 2-Py, 2-Fu, ^{i}Pr) for *syn* adducts indicated the assigned setereochemistry. In the case of α-alkoxyhydroxylamines **9d**, **13a** and **13b** the observed coupling constants were 4.0, 3.3 and 2.8 Hz, respectively. For these compounds the assigned relative configurations were deduced from 2D COSY, NOESY and HMQC experimental data.

Even though these assignments cannot be considered unambiguous, they are in accordance with earlier reports by Hassner and co-workers[13,19] concerning allylsulfonylation of imines and are also further supported by theoretical calculations (see below).

The *cis*/*trans* relative configuration of isoxazolidines was assigned by NOE experiments (Fig. 2). Irradiation of H_a for all obtained compounds, only produced enhancement of H_c (5–7%) and irradiation of H_b in the same experiment, produced enhancement of the methyl group (8–11%). Irradiation of the methyl group produced enhancements of H_b (8–10%) and, as expected, of H_c (15–17%). These relationships were confirmed by 2D NOESY experiments in which no interesting cross-peaks were detected between H_a and H_b, and H_b and H_c.

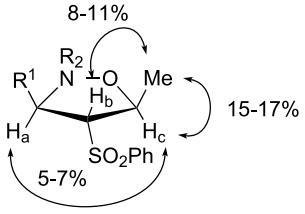


Figure 2. Selected NOE observed for **7a–d**, **11a–d** and **14** (η_{obs} is given as percent of η_{max}).

The observed pattern for the described NOE is in agreement with previous observations for substituted isoxazolidines.[20]

The structures of **7c** and **14a** were confirmed by single-crystal X ray structure determination (Fig. 3).[21] This crystallographic analysis also served to assign unambiguously the absolute configuration of both **13a** and **14a** thus confirming the *syn* diastereofacial preference in the addition to nitrone **12**

4. Theoretical study

In order to evaluate the importance of electronic and steric

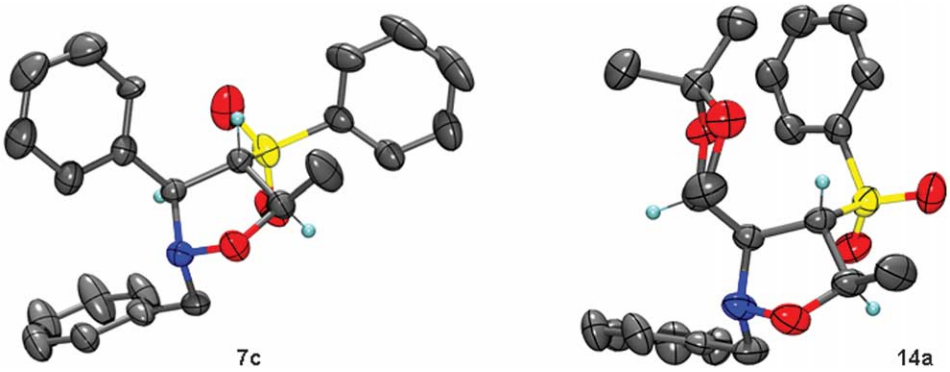
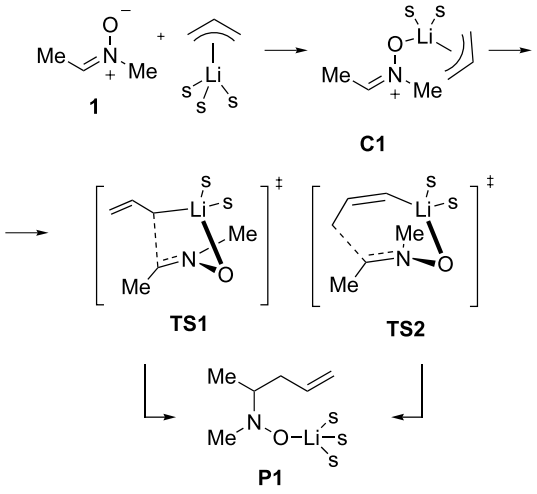


Figure 3. Perspective views (ORTEP) of **7c** and **14a**. Non-hydrogen atoms are drawn as 50% thermal ellipsoids while hydrogens are drawn at an arbitrary size. Only the atoms refined with anisotropic thermal parameters are drawn with the principal axes indicated; the isotropic atoms are represented as simple circles. Some hydrogens have been omitted for clarity.

effects in the outcome of the allylation reactions of nitrones **1** and **8** with lithiated allylphenylsulfone **2**, the reaction has been studied by ab initio molecular orbital calculations We aimed to clarify what is the preferred attack to the substituted allylic metal (α vs γ) and to rationalize the experimentally observed differences in *anti*/*syn* selectivities.

Geometry optimizations of the stationery points (reactants, transition structures and products) were carried out by using ab initio Hartree–Fock calculations with the 6-31G(d) basis set.[22] All transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all HF/6-31G(d) optimized structures and used unscaled, to compute ZPVE and activation energies. The transition states reported were shown to belong to the studied reaction by intrinsic reaction coordinate (IRC). All calculations were performed using the Gaussian 03 revision B.05 suite of programs.[23]

We began our study by examining the reaction profile for the nucleophilic addition of unsubstituted allylic lithium to nitrone **1** ($R^1=R^2=Me$). In order to simulate the presence of solvent, water molecules were added when needed. The reaction proceeds through the initial formation of a starting complex without energy barrier. The formation of stable complexes without energy barriers prior to the addition step has been proposed and demonstrated previously for nucleophilic additions to nitrones[24] and carbonyls.[25] After the formation of the complex, the two possible pathways illustrated in Scheme 7 and corresponding to α and γ attacks should be considered. Thus, the reaction is expected to proceed through 'closed' transition states in which the lithium atom is transferred to the nitrone oxygen concomitant with C–C bond formation.



Scheme 7.

We found two minima corresponding to the starting complex **C1** and the product **P1**. Two transition states **TS1** and **TS2**, corresponding to α and γ attacks, respectively, connecting **C1** with **P1** were also located. The calculated free energies for reactants, complex, transition states and product are collected in Table 5, and the geometry of **TS1** and **TS2** is given in Figure 4. As shown by the energy barrier values (Table 5) the preferred transition state corresponds to the γ attack. Based upon these simplified calculations it is obvious that the presence of the sulfonyl group must be considered in order to achieve valid conclusions.

Table 5. Calculated free energies (HF/6-31G(d)) and relative free energies for the stationery points of the allylation of **1**

	Total energy[a]	Relative energy[b]
Nitrone	−246.812390	
Allyllithium·$3H_2O$	−351.913262	
C1	−522.722565	−1.43[c,d]
TS1	−522.693904	17.99[d,e]
TS2	−522.707354	9.55[d,e]
P1	−598.793418	−42.52[e]

[a] Hartrees.
[b] kcal/mol.
[c] Referred to nitrone + allyllithium·$3H_2O$.
[d] The energy corresponding to a molecule of water (−76.005368 au) has been included for comparison of relative energies.
[e] Referred to complex **C1**.

Anders and co-workers[26] have studied the structure of sulfur-stabilized allyllithium derivatives, including lithiated allylphenylsulfone **2**. These authors found three possible structures in the range of 1 kcal/mol as the more stable for **2**. Such structures correspond to the expected η^1 C_α–Li **A** and

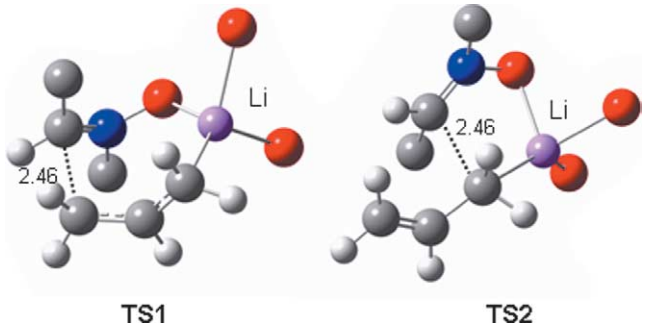


Figure 4. Optimized geometries at HF/6-31G(d) level for the transition structures **TS1** and **TS2**. Some hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms.

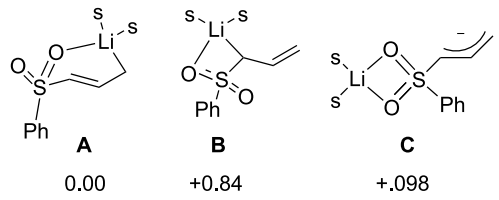


Figure 5. Energetically stable conformers found for lithiated allylphenylsulfone **2**. Relative energies are given in kcal/mol. (Data taken from Ref. 26).

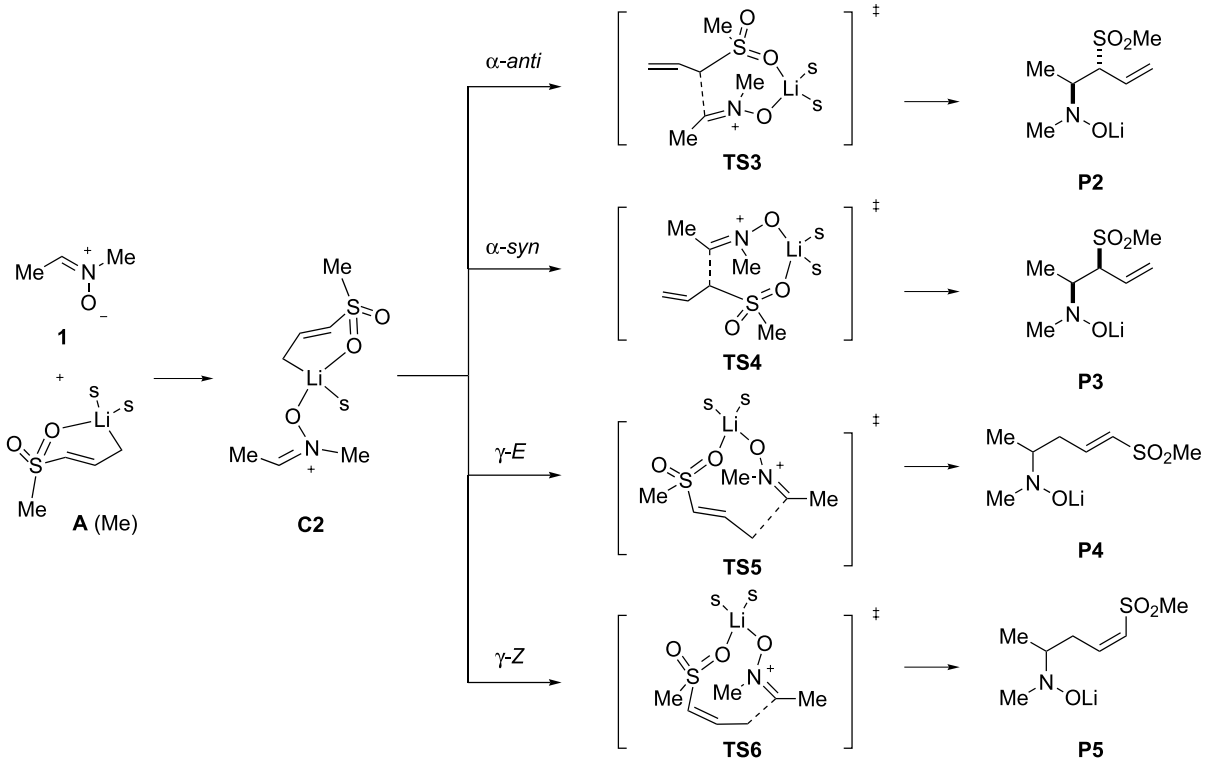
η^1C_γ–Li **B** contacted ion pairs (Fig. 5) and, in addition, an intramolecular OLiO scissor contact ion pair **C** that is defined by the authors as a 'naked' allyl anion.

We initially use in our studies structure **A** as the nucleophile to be added to **1**.[27] The calculated reaction paths are depicted in Scheme 8. The total and relative free energies are summarized in Table 6.

The first step corresponds to the formation of a stable complex **C2** (6.97 kcal/mol below the reactants) through the displacement of a molecule of solvent by the nitrone. This complex can then evolve in two ways: (i) to give an α addition affording *anti* and *syn* diastereomers **P2** and **P3**, respectively, and (ii) to give a γ addition which, in principle, could led to *E* and *Z* isomers **P4** and **P5**, respectively. The geometries of the corresponding transition structures **TS3**, **TS4**, **TS5** and **TS6** are given in Figure 6.

Contrary to the obtained data for unsubstituted allyllithium and in an excellent agreement with experimental results, the most stable transition structure corresponds to the α attack. Moreover, calculations correctly predict the preferential formation of the corresponding *anti* adduct since **TS3** presented the lowest free activation energy (13.01 kcal/mol). The calculated energy differences between α and γ attacks (**TS3** is 5.52 kcal/mol lower in energy than **TS5**) as well as the differences between *anti* and *syn* approaches (**TS3** is 8.79 kcal/mol lower in energy than **TS4**) for the α attack justify the obtention of only one isomer. The final products are lower in energy than complex **C2**, indicating an exothermic transformation.

The geometries of the transition states are similar regardless of the approach. It is noteworthy that although we started from the most stable isomer of lithiated methylsulfone (**A**, Fig. 5), all transition states present a geometry (Fig. 6) nearest to the 'naked' anion defined by Anders and coworkers[25] (**C**, Fig. 5) thus evidencing the crucial role of the



Scheme 8.

Table 6. Calculated free energies and relative free energies (HF/6-31G(d)) for the stationery points of the allylphenylsulfonylation of **1**

	Total energy[a]	Relative energy[b]
Nitrone	−246.812390	
A (Me)	−862.118716	
C2	−1032.936849	−6.97[c,d]
TS3	−1108.921484	13.010154[d,e]
TS4	−1108.907476	21.800308[d,e]
TS5	−1108.914279	17.531360[d,e]
TS6	−1108.911434	19.316625[d,e]
P2	−1108.945702	−2.18687[e]
P3	−1108.950959	−5.485688[e]
P4	−1108.954456	−7.680089[e]
P5	−1108.948299	−3.816513[e]

[a] Hartrees.
[b] kcal/mol.
[c] Referred to nitrone + lithiated allylmethylsulfone **A**·$3H_2O$.
[d] The energy corresponding to a molecule of water (−76.005368 au) has been included for comparison of relative energies.
[e] Referred to complex **C2**.

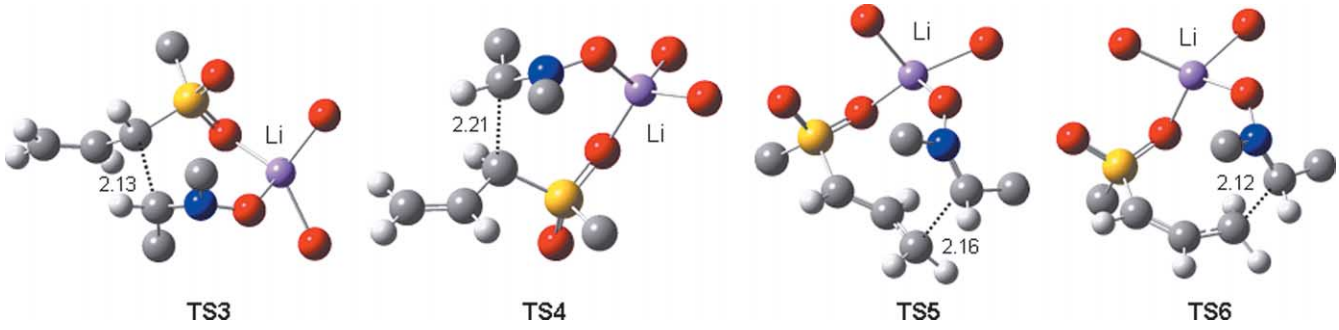


Figure 6. Optimized geometries at HF/6-31G(d) level for the transition structures **TS3**, **TS4**, **TS5** and **TS6**. Some hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms.

phenylsulfonyl group in favoring the α-addition. The bond lengths of the C–C forming bonds do not change significantly, whether the approach is α-*anti* (**TS3**, 2.13 Å), γ-*E* (**TS5**, 2.16 Å), or γ-*Z* (**TS6**, 2.12 Å). Only a slightly longer forming bond is found for the α-*syn* approach (**TS4**, 2.21 Å).

5. Conclusions

In conclusion, we have studied in detail the nucleophilic addition of lithiated allylphenylsulfone **2** to nitrones The reaction only leads to α-adducts. Thus α-sulfonyl homoallyl hydroxylamines having an *anti* relative configuration are exclusively obtained when the reaction is carried out at −80 °C and in the presence of HMPA. These products are stable, but upon treatment with BuLi at 0 °C they cyclized to isoxazolidines in a process involving isomerization of the double bond and an intramolecular Michael addition. Indeed, it is possible to obtain such isoxazolidines by carrying out the addition of **2** at 0 °C. On the contrary, an excess of base favors a side reaction consisting of elimination of the hydroxyamino group, giving rise to 2-phenylsulfonyl dienes. The observed regio- and stereochemical results are well explained by means of computational methods, which correctly predict both the α-attack and the preferential *anti* selectivity.

6. Experimental

6.1. General

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid and iodine Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA) and with solvents that were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5–1.5 mL min^{-1}. Melting points were uncorrected. IR spectra were recorded on a Perkin–Elmer FT IR instrument in $CHCl_3$. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 instrument in $CDCl_3$. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ ($\delta=7.26$) in $CDCl_3$. Optical rotations were taken at 25 °C on a Perkin–Elmer 241 polarimeter. Elemental analysis were performed on a Perkin–Elmer 240B microanalyzer. Nitrones **1**, **8** and **12** were prepared from the corresponding aldehydes as described.[28]

6.2. General procedure for the allylphenylsulfonylation of nitrones at −80 °C. Synthesis of homoallyl hydroxylamines

To a cooled (−80 °C) solution of *n*-BuLi (1.33 mL of a 1.6 M solution in hexanes, 1.2 mmol) in anhydrous THF (5 mL) a solution of allylphenylsulfone (0.218 g, 1.2 mmol) and HMPA (0.215 g, 1.2 mmol) in THF (5 mL) was added dropwise. After 30 min a solution of nitrone (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at −80 °C for 2 h at which time the reaction was quenched by adding saturated aq NH_4Cl (1 mL). The reaction mixture was extracted with EtOAc (3×30 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated. The crude material was purified by radial chromatography using 4:1 hexane/ethyl acetate as an eluent.

6.2.1. (3*R,4*S**)-4-Phenyl-4-(*N*-phenylhydroxyamino)-3-(phenylsulfonyl)-1-butene 5a.** Oil; δ_H (400 MHz, $CDCl_3$) 4.70 (dd, 1H, $J=9.4$, 10.0 Hz), 4.81 (d, 1H, $J=11.0$ Hz), 4.89 (d, 1H, $J=17.0$ Hz), 5.03 (d, 1H, $J=10.0$ Hz), 5.52 (ddd, 1H, $J=9.4$, 11.0, 17.0 Hz), 5.90 (bs, 1H, ex. D_2O), 6.80 (m, 1H), 6.84 (m, 2H), 7.10 (m, 7H), 7.56 (m, 2H), 7.62 (m, 1H), 7.98 (m, 2H); δ_C (100 MHz, $CDCl_3$) 69.3, 71.4, 116.8, 121.8 (2C), 125.4, 127.9 (2C), 128.1, 128.4, 128.5 (2C), 128.8 (2C), 129.3 (4C), 133.8, 134.2, 138.3, 149.7. IR ν 1140, 1230, 1300 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_3S$ (379.47): C, 69.63; H, 5.58; N, 3.69. Found: C 69.45, H, 5.80, N, 3.70.

6.2.2. (3*R,4*S**)-4-(*N*-*tert*-Butylhydroxyamino)-4-phenyl-3-(phenylsulfonyl)-1-butene 5b.** Oil; δ_H (400 MHz, $CDCl_3$) 1.12 (s, 9H), 4.02 (d, 1H, $J=10.0$ Hz), 4.52 (t, 1H, $J=9.9$ Hz), 4.68 (d, 1H, $J=17.0$ Hz), 5.00 (d, 1H, $J=10.1$ Hz), 5.20 (bs, 1H, ex. D_2O), 5.25 (dt, 1H, $J=$ 10.0, 17.0 Hz), 7.29 (m, 5H), 7.58 (m, 2H), 7.70 (m, 1H), 7.88 (m, 2H); δ_C (100 MHz, $CDCl_3$) 25.4, 59.6, 70.5, 71.5, 122.1, 128.2, 128.3 (2C), 128.5 (2C), 129.0 (2C), 128.9, 129.9 (2C), 132.1, 133.0, 139.3. IR ν 1135, 1220, 1290 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3S$ (359.48): C, 66.82; H, 7.01; N, 3.90. Found: C 66.70, H, 7.16, N, 3.77.

6.2.3. (3*R,4*S**)-4-(*N*-Benzylhydroxyamino)-4-phenyl-3-(phenylsulfonyl)-1-butene 5c.** Oil; δ_H (400 MHz, $CDCl_3$) 3.57 (s, 2H), 4.28 (d, 1H, $J=9.9$ Hz), 4.51 (t, 1H, $J=$ 9.9 Hz), 4.64 (d, 1H, $J=16.9$ Hz), 4.83 (d, 1H, $J=10.4$ Hz), 5.37 (dt, 1H, $J=9.9$, 16.9 Hz), 5.55 (bs, 1H, ex. D_2O), 7.30 (m, 10H), 7.45 (m, 2H), 7.59 (m, 1H), 7.84 (m, 2H); δ_C (100 MHz, $CDCl_3$) 61.0, 69.5, 71.9, 124.7, 128.1, 128.2 (2C), 128.3 (2C), 128.7 (2C), 128.9, 129.0 (2C), 129.1 (2C), 130.0 (2C), 133.2, 134.8, 137.5, 138.7, 138.9. IR ν 1145, 1230, 1310 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_3S$ (393.50): C, 70.20; H, 5.89; N, 3.56. Found: C 70.33, H, 5.91, N, 3.38.

6.2.4. (3*S,4*S**)-4-(*N*-Benzylhydroxyamino)-4-phenyl-3-(phenylsulfonyl)-1-butene 6c.** Oil; δ_H (400 MHz, $CDCl_3$) 3.53 (d, 1H, $J=14.2$ Hz), 3.57 (d, 1H, $J=14.2$ Hz), 4.13 (dd, 1H, $J=9.1$, 10.1 Hz), 4.51 (d, 1H, $J=9.1$ Hz), 4.87 (d, 1H, $J=17.0$ Hz), 4.90 (bs, 1H, ex. D_2O), 5.25 (dd, 1H, $J=$ 1.3, 10.1 Hz), 6.11 (dt, 1H, $J=10.1$, 17.0 Hz), 7.25 (m, 10H), 7.46 (m, 2H), 7.60 (m, 1H), 7.78 (m, 2H); δ_C (100 MHz, $CDCl_3$) 61.2, 69.1, 70.5, 123.7, 128.2 (2C), 128.3, 128.4 (2C), 128.5, 128.6 (2C), 128.9, 129.0 (2C), 129.1, 129.7, 129.9, 133.2 (2C), 137.9, 138.5, 138.9. IR ν 1145, 1225, 1290 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_3S$ (393.50): C, 70.20; H, 5.89; N, 3.56. Found: C 70.45, H, 5.68, N, 3.49.

6.2.5. (3*R,4*S**)-4-(*N*-Methylhydroxyamino)-4-phenyl-3-(phenylsulfonyl)-1-butene 5d.** White solid; mp 115–116 °C; δ_H (400 MHz, $CDCl_3$) 2.43 (s, 3H), 4.14 (d, 1H, $J=$ 9.8 Hz), 4.53 (t, 1H, $J=9.8$ Hz), 4.75 (d, 1H, $J=16.8$ Hz), 4.94 (d, 1H, $J=10.2$ Hz), 5.46 (dt, 1H, $J=10.2$, 16.8 Hz), 5.83 (bs, 1H, ex. D_2O), 7.31 (m, 5H), 7.54 (m, 2H), 7.62 (m, 1H), 7.92 (m, 2H); δ_C (100 MHz, $CDCl_3$) 44.7, 71.1, 71.8, 123.8, 128.1 (2C), 128.2, 128.6 (2C), 129.2 (2C), 129.9, 130.4 (2C), 133.2, 133.6, 138.7. IR ν 1140, 1235, 1310 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_3S$ (317.40): C, 64.33; H, 6.03; N, 4.41. Found: C 64.42, H, 5.87, N, 4.63.

6.2.6. (3*S,4*S**)-4-(*N*-Methylhydroxyamino)-4-phenyl-3-(phenylsulfonyl)-1-butene 6d.** Oil; δ_H (400 MHz, $CDCl_3$) 2.38 (s, 3H), 4.06 (dd, 1H, $J=8.6$, 10.1 Hz), 4.31 (d, 1H, $J=8.6$ Hz), 4.84 (d, 1H, $J=17.2$ Hz), 5.1 (bs, 1H, ex. D_2O), 5.25 (dd, 1H, $J=1.3$, 10.1 Hz), 6.07 (dt, 1H, $J=10.1$, 17.2 Hz), 7.21 (m, 5H), 7.34 (m, 2H), 7.46 (m, 1H), 7.63 (m, 2H); δ_C (100 MHz, $CDCl_3$) 45.7, 71.3, 74.4, 124.1, 128.1 (2C), 128.4, 128.6 (2C), 128.9 (2C), 129.4, 129.9 (2C), 133.3, 135.3, 138.8. IR ν 1145, 1230, 1290 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_3S$ (317.40): C, 64.33; H, 6.03; N, 4.41. Found: C 64.51, H, 6.23, N, 4.70.

6.2.7. (3*R,4*S**)-4-(*N*-Benzylhydroxyamino)-4-(2-pyridyl)-3-(phenylsulfonyl)-1-butene 9a.** Oil; δ_H (400 MHz, $CDCl_3$) 3.55, (d, 1H, $J=13.6$ Hz), 3.69 (d, 1H, $J=13.6$ Hz), 4.48 (d, 1H, $J=9.1$ Hz), 4.70 (t, 1H, $J=9.3$ Hz), 4.80 (d, 1H, $J=16.9$ Hz), 4.89 (dd, 1H, $J=1.1$, 10.3 Hz), 5.39 (dt, 1H, $J=10.3$, 16.9 Hz), 6.67 (bs, 1H, ex. D_2O), 7.30 (m, 7H), 7.51 (m, 2H), 7.60 (m, 1H), 7.83 (m, 2H), 7.90 (m, 1H), 8.45 (m, 1H). δ_C (100 MHz, $CDCl_3$) 57.4, 69.3, 70.8, 123.1, 123.5, 123.7, 128.2 (2C), 128.5, 128.6 (2C), 129.4 (2C), 129.6 (2C), 133.4, 136.4, 136.5, 137.4, 138.3, 148.6, 156.2. IR ν 1135, 1235, 1285 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_3S$ (359.48): C, 66.98; H, 5.62; N, 7.10. Found: C 66.81, H, 5.44, N, 7.32.

6.2.8. (3*S,4*S**)-4-(*N*-Benzylhydroxyamino)-4-(2-pyridyl)-3-(phenylsulfonyl)-1-butene 10a.** Oil; δ_H (400 MHz, $CDCl_3$) 3.44 (d, 1H, $J=13.4$ Hz), 3.75 (d, 1H, $J=13.4$ Hz), 4.51 (d, 1H, $J=9.6$ Hz), 4.67 (t, 1H, $J=9.9$ Hz), 4.94 (d, 1H, $J=17.2$ Hz), 5.21 (dd, 1H, $J=1.2$, 10.1 Hz), 6.01 (dt, 1H, $J=10.1$, 17.2 Hz), 6.70 (bs, 1H, ex. D_2O), 7.29 (m, 7H), 7.48 (m, 2H), 7.58 (m, 1H), 7.81 (m, 2H), 7.90 (m, 1H), 8.44 (m, 1H).; δ_C (100 MHz, $CDCl_3$) 61.0, 66.6, 72.1, 123.2, 123.6, 123.7, 128.2, 128.3 (2C), 128.6 (2C), 128.9 (2C), 129.0 (2C), 133.8, 136.4 (2C), 137.6, 138.2, 148.7, 156.1. IR ν 1145, 1235, 1310 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_3S$ (359.48): C, 66.98; H, 5.62; N, 7.10. Found: C 66.79, H, 5.83, N, 7.25.

6.2.9. (3*R,4*S**)-4-(*N*-Benzylhydroxyamino)-4-(2-furyl)-3-(phenylsulfonyl)-1-butene 9b.** Oil; δ_H (400 MHz, $CDCl_3$) 3.64 (d, 1H, $J=13.6$ Hz), 3.69 (d, 1H, $J=$ 13.6 Hz), 4.37 (d, 1H, $J=10.1$ Hz), 4.50 (t, 1H, $J=$ 9.8 Hz), 4.81 (d, 1H, $J=17.2$ Hz), 4.94 (dd, 1H, $J=0.9$, 10.1 Hz), 5.46 (dt, 1H, $J=9.9$, 17.2 Hz), 5.50 (bs, 1H, ex. D_2O), 6.27 (dd, 1H, $J=0.8$, 3.2 Hz), 6.30 (dd, 1H, $J=1.8$, 3.2 Hz), 7.30 (m, 5H), 7.32 (dd, 1H, $J=0.8$, 1.8 Hz), 7.40 (m, 2H), 7.51 (m, 1H), 7.79 (m, 2H); δ_C (100 MHz, $CDCl_3$) 60.9, 63.1, 70.5, 110.2, 111.1, 124.4, 127.3 (2C), 128.3 (2C), 128.4, 128.7 (2C), 129.1 (2C), 129.2, 133.5, 137.1, 138.7, 142.6, 148.8. IR ν 1130, 1245, 1310 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4S$ (383.46): C, 65.78; H, 5.52; N, 3.65. Found: C 65.59, H, 5.78, N, 3.44.

6.2.10. (3*S,4*S**)-4-(*N*-Benzylhydroxyamino)-4-(2-furyl)-3-(phenylsulfonyl)-1-butene 10b.** Oil; δ_H (400 MHz, $CDCl_3$) 3.60 (s, 2H), 4.30 (dd, 1H, $J=9.1$, 9.9 Hz), 4.56 (d, 1H, $J=9.1$ Hz), 4.70 (bs, 1H, ex. D_2O), 5.02 (d, 1H, $J=16.8$ Hz), 5.27 (dd, 1H, $J=1.1$, 10.1 Hz), 6.02 (dt, 1H, $J=10.1$, 16.8 Hz), 6.24 (dd, 1H, $J=1.8$, 3.2 Hz), 6.26 (dd, 1H, $J=0.8$, 3.2 Hz), 7.30 (m, 5H), 7.33 (dd, 1H, $J=0.8$, 1.8 Hz), 7.43 (m, 2H), 7.55 (m, 1H), 7.72

(m, 2H); δ_C (100 MHz, $CDCl_3$) 61.1, 61.4, 72.3, 110.6, 111.1, 123.7, 127.5 (2C), 128.4 (2C), 128.7 (2C), 129.0, 129.2 (2C), 129.6, 133.4, 137.1, 138.4, 142.4, 148.5. IR ν 1125, 1240, 1310 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4S$ (383.46): C, 65.78; H, 5.52; N, 3.65. Found: C 65.84, H, 5.41, N, 3.89.

6.2.11. (3*R,4*S**)-4-(*N*-Benzylhydroxyamino)-5-methyl-3-(phenylsulfonyl)-1-hexene 9c.** Oil; δ_H (400 MHz, $CDCl_3$) 0.98 (d, 6H, J=7.0 Hz), 1.80 (m, 1H), 3.52 (t, 1H, J=10.0 Hz), 3.56 (d, 1H, J=13.4 Hz), 3.61 (d, 1H, J=13.4 Hz), 4.30 (t, 1H, J=9.4 Hz), 4.88 (d, 1H, J=16.9 Hz), 5.20 (d, 1H, J=10.1 Hz), 5.40 (bs, 1H, ex. D_2O), 5.47 (dt, 1H, J=10.1, 16.9 Hz), 7.28 (m, 5H), 7.40 (m, 2H), 7.58 (m, 1H), 7.80 (m, 2H); δ_C (100 MHz, $CDCl_3$) 20.1 (2C), 26.1, 61.4, 63.2, 72.1, 123.6, 127.9, 128.6 (2C), 128.8 (2C), 129.0 (2C), 129.4 (2C), 130.1, 133.6, 133.8, 138.2. IR ν 1135, 1240, 1285 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3S$ (359.48): C, 66.82; H, 7.01; N, 3.90. Found: C 66.69, H, 7.17, N, 3.83.

6.2.12. (3*S,4*S**)-4-(*N*-Benzylhydroxyamino)-5-methyl-3-(phenylsulfonyl)-1-hexene 10c.** Oil; δ_H (400 MHz, $CDCl_3$) 1.00 (d, 6H, J=6.8 Hz), 1.72 (m, 1H), 3.58 (dd, 1H, J=8.8, 10.0 Hz), 3.60 (s, 2H), 4.47 (dd, 1H, J=4.8, 8.8 Hz), 4.92 (d, 1H, J=17.2 Hz), 5.30 (d, 1H, J=10.4 Hz), 5.62 (bs, 1H, ex. D_2O), 5.94 (dt, 1H, J=10.4, 17.2 Hz), 7.25 (m, 5H), 7.43 (m, 2H), 7.61 (m, 1H), 7.84 (m, 2H); δ_C (100 MHz, $CDCl_3$) 19.8 (2C), 25.2, 61.6, 62.9, 72.4, 123.8, 128.2, 128.4 (2C), 128.7 (2C), 128.9 (2C), 129.3 (2C), 132.4, 133.4, 133.9, 138.4. IR ν 1130, 1220, 1320 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3S$ (359.48): C, 66.82; H, 7.01; N, 3.90. Found: C 66.70, H, 6.88, N, 3.95.

6.2.13. (2*S,3*R**)-2-(*N*-Benzylhydroxyamino)-1-*O*-(*tert*-butyldiphenylsilyl)-3-(phenylsulfonyl)-4-penten-1-ol 9d.** Oil; δ_H (400 MHz, $CDCl_3$) 1.00 (s, 9H), 3.78 (d, 1H, J=13.6 Hz), 3.82 (m, 2H), 3.90 (dd, 1H, J=4.0, 10.4 Hz), 3.95 (d, 1H, J=13.6 Hz), 4.12 (dd, 1H, J=4.3, 9.6 Hz), 4.60 (bs, 1H, ex. D2O), 4.77 (d, 1H, J=17.2 Hz), 5.17 (dd, 1H, J=1.2, 10.1 Hz), 6.02 (dt, 1H, J=10.1, 17.2 Hz), 7.35 (m, 12H), 7.53 (m, 2H), 7.60 (m, 4H), 7.75 (m, 2H); δ_C (100 MHz, $CDCl_3$) 19.2, 26.8 (3C), 59.4, 62.3, 65.3, 71.3, 124.3, 127.6, 127.8 (2C), 127.9 (2C), 128.0, 128.3 (2C), 128.6 (2C), 129.0 (2C), 129.1, 129.9, 130.0, 130.1, 133.4, 135.3, 135.6, 135.7 (4C), 137.8, 138.2. IR ν 1145, 1240, 1315 cm^{-1}. Anal. Calcd for $C_{34}H_{39}NO_4SSi$ (585.83): C, 69.71; H, 6.71; N, 2.39. Found: C 69.93, H, 6.90, N, 2.51.

6.2.14. (2*S*,3*S*,4*R*)-3-(*N*-Benzylhydroxyamino)-1,2-di-*O*-isopropylidene-4-(phenylsulfonyl)-5-hexen-1,2-diol 13a. Oil; $[\alpha]_D^{20}$ = +35 (*c* 0.45, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.31 (s, 3H), 1.39 (s, 3H), 3.59 (dd, 1H, J=3.3, 10.1 Hz), 3.70 (dd, 1H, J=7.3, 8.6 Hz), 3.91 (dd, 1H, J=6.7, 8.6 Hz), 3.96 (dd, 1H, J=3.3, 7.1 Hz), 4.04 (d, 1H, J=13.9 Hz), 4.27 (d, 1H, J=13.9 Hz), 4.61 (pseudo q, 1H, J=7.1 Hz), 4.72 (bs, 1H, ex. D_2O), 4.82 (d, 1H, J=16.9 Hz), 5.22 (dd, 1H, J=1.0, 10.1 Hz), 6.13 (dt, 1H, J=10.1, 16.9 Hz), 7.29 (m, 3H), 7.34 (m, 2H), 7.41 (m, 2H), 7.53 (m, 1H), 7.74 (m, 2H); δ_C (100 MHz, $CDCl_3$) 25.3, 26.8, 63.7, 65.2, 66.6, 71.0, 73.2, 109.1, 124.6, 127.3, 128.3 (2C), 128.7 (2C), 129.2 (2C), 129.4 (2C), 133.5, 138.3 (2C), 143.3. IR ν 1135, 1240, 1300 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5S$ (417.52): C, 63.29; H, 6.52; N, 3.35. Found: C 63.05, H, 6.36, N, 3.49.

6.2.15. (2*S*,3*S*,4*S*)-3-(*N*-Benzylhydroxyamino)-1,2-di-*O*-isopropylidene-4-(phenylsulfonyl)-5-hexen-1,2-diol 13b. Oil; $[\alpha]_D^{20}$ = −8 (*c* 0.32, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.26 (s, 3H), 1.34 (s, 3H), 3.70 (dd, 1H, J=2.8, 8.4 Hz), 3.89 (d, 1H, J=13.6 Hz), 3.95 (dd, 1H, J=6.6, 8.6 Hz), 4.03 (d, 1H, J=13.6 Hz), 4.07 (dd, 1H, J=6.3, 8.6 Hz), 4.32 (m, 2H), 4.65 (bs, 1H, ex. D_2O), 5.00 (dd, 1H, J=1.2, 17.2 Hz), 5.22 (dd, 1H, J=1.3, 10.1 Hz), 5.97 (dt, 1H, J=10.1, 17.2 Hz), 7.32 (m, 5H), 7.41 (m, 2H), 7.53 (m, 1H), 7.74 (m, 2H); δ_C (100 MHz, $CDCl_3$) 25.5, 26.3, 63.9, 68.2, 69.0, 70.2, 71.3, 109.5, 124.3, 127.4, 128.5 (2C), 128.8 (2C), 129.0 (2C), 129.7 (2C), 133.4, 138.5 (2C), 142.0. IR ν 1140, 1210, 1280 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5S$ (417.52): C, 63.29; H, 6.52; N, 3.35. Found: C 63.11, H, 6.67, N, 3.52.

6.3. General procedure for the allylphenylsulfonylation of nitrones at 0 °C. Synthesis of isoxazolidines

To a cooled (−80 °C) solution of *n*-BuLi (1.33 mL of a 1.6 M solution in hexanes, 1.2 mmol) in anhydrous THF (5 mL) a solution of allylphenylsulfone (0.218 g, 1.2 mmol) in THF (5 mL) was added dropwise. After 30 min the resulting mixture was warmed to 0 °C and a solution of nitrone (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h at which time the reaction was quenched by adding saturated aq NH_4Cl (1 mL). The reaction mixture was extracted with EtOAc (3×30 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated. The crude material was purified by radial chromatography.

6.3.1. (3*S,4*S**,5*R**)-2,3-Diphenyl-4-(phenylsulfonyl)-5-methylisoxazolidine 7a.** Oil; δ_H (400 MHz, $CDCl_3$) 1.34 (d, 3H, J=6.1 Hz), 3.96 (t, 1H, J=5.9 Hz), 4.54 (d, 1H, J=5.6 Hz), 4.80 (pseudo quintuplet, 1H, J=6. 5 Hz), 6.94 (m, 3H), 7.29 (m, 5H), 7.50 (m, 4H), 7.61 (m, 1H), 7.82 (m, 2H); δ_C (100 MHz, $CDCl_3$) 18.4, 71.0, 75.8, 83.2, 114.3 (2C), 122.1, 126.4 (2C), 127.8, 128.8 (2C), 128.9 (2C), 129.0 (2C), 129.5 (2C), 134.3, 137.4, 140.7, 149.8. IR ν 1130, 1240, 1310 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_3S$ (379.47): C, 69.63; H, 5.58; N, 3.69. Found: C 69.76, H, 5.72, N, 3.40.

6.3.2. (3*S,4*S**,5*R**)-2-*tert*-Butyl-3-phenyl-4-(phenylsulfonyl)-5-methylisoxazolidine 7b.** Oil; δ_H (400 MHz, $CDCl_3$) 1.01 (s, 9H), 1.32 (d, 3H, J=6.4 Hz), 3.50 (dd, 1H, J=5.5, 6.8 Hz), 4.00 (d, 1H, J=6.8 Hz), 4.10 (dq, 1H, J=5.5, 6.4 Hz), 7.33 (m, 5H), 7.55 (m, 2H), 7.62 (m, 1H), 7.81 (m, 2H); δ_C (100 MHz, $CDCl_3$) 20.4, 26.9 (3C), 59.0, 74.1, 74.8, 82.3, 127.9, 128.2 (2C), 128.5 (2C), 128.8 (2C), 129.1 (2C), 135.2, 137.9, 139.5. IR ν 1140, 1230, 1305 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3S$ (359.5): C, 66.82; H, 7.01; N, 3.90. Found: C 66.75, H, 7.24, N, 4.10.

6.3.3. (3*S,4*S**,5*R**)-2-Benzyl-3-phenyl-4-(phenylsulfonyl)-5-methylisoxazolidine 7c.** White solid; mp 89–90 °C; δ_H (400 MHz, $CDCl_3$) 1.30 (d, 3H, J=6.4 Hz), 3.74 (t, 1H, J=5.9 Hz), 4.05 (d, 1H, J=13.5 Hz), 4.13 (d, 1H, J=13.5 Hz), 4.44 (d, 1H, J=5.9 Hz), 4.85 (pseudo quintuplet, 1H, J=6.4 Hz), 7.20 (m, 10H), 7.52 (m, 2H), 7.65 (m, 1H), 7.88 (m, 2H); δ_C (100 MHz, $CDCl_3$) 20.3, 59.1, 70.7, 74.8, 81.9, 127.2 (2C), 127.3, 127.9, 128.3 (4C), 128.5 (2C), 128.7 (2C), 129.5 (2C), 134.2, 137.0, 138.2, 139.1. IR ν 1135, 1240, 1310 cm^{-1}. Anal. Calcd for

$C_{23}H_{23}NO_3S$ (393.5): C, 70.20; H, 5.89; N, 3.56. Found: C 70.00, H, 5.96, N, 3.39.

6.3.4. (3*S,4*S**,5*R**)-2,5-Dimethyl-3-phenyl-4-(phenylsulfonyl) isoxazolidine 7d.** White solid; mp 68–69 °C; δ_H (400 MHz, $CDCl_3$) 1.36 (d, 3H, $J=6.3$ Hz), 2.62 (s, 3H), 3.75 (dd, 1H, $J=5.1$, 7.0 Hz), 4.02 (d, 1H, $J=7.0$ Hz), 4.75 (dq, 1H, $J=5.1$, 6.3 Hz), 7.28 (m, 5H), 7.54 (m, 2H), 7.65 (m, 1H), 7.84 (m, 2H); δ_C (100 MHz, $CDCl_3$) 20.7, 42.8, 73.7, 73.9, 81.6, 127.7, 128.1 (2C), 128.4 (2C), 128.5 (2C), 129.4 (2C), 134.1, 137.7, 138.2. IR ν 1125, 1250, 1275 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_3S$ (317.4): C, 64.33; H, 6.03; N, 4.41. Found: C 64.29, H, 6.28, N, 4.22.

6.3.5. (3*S,4*S**,5*R**)-2-Benzyl-3-(2-pyridyl)-4-(phenylsulfonyl)-5-methylisoxazolidine 11a.** Oil; δ_H (400 MHz, $CDCl_3$) 1.17 (d, 3H, $J=6.1$ Hz), 4.20 (d, 1H, $J=13.5$ Hz), 4.33 (d, 1H, $J=13.5$ Hz), 4.60 (d, 1H, $J=4.6$ Hz), 4.64 (dd, 1H, $J=4.6$, 7.1 Hz), 4.90 (dq, 1H, $J=6.1$, 7.1 Hz), 6.98 (m, 1H), 7.13 (m, 1H), 7.21 (m, 1H), 7.27 (m, 2H), 7.45 (m, 5H), 7.50 (m, 1H), 7.87 (m, 2H), 8.26 (m, 1H); δ_C (100 MHz, $CDCl_3$) 19.12, 59.8, 70.39, 75.2, 77.7, 122.5, 122.7, 127.6, 128.5 (2C), 128.6 (2C), 129.3 (2C), 129.6 (2C), 133.9, 136.5, 138.7, 138.9, 148.8, 157.8. IR ν 1145, 1250, 1300 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_3S$ (394.5): C, 66.98; H, 5.62; N, 7.10. Found: C 67.12, H, 5.78, N, 6.89.

6.3.6. (3*S,4*S**,5*R**)-2-Benzyl-3-(2-furyl)-4-(phenylsulfonyl)-5-methylisoxazolidine 11b.** Oil; δ_H (400 MHz, $CDCl_3$) 1.24 (d, 3H, $J=6.1$ Hz), 3.62 (dd, 1H, $J=4.9$, 6.8 Hz), 4.40 (d, 1H, $J=13.6$ Hz), 4.51 (d, 1H, $J=13.6$ Hz), 4.77 (d, 1H, $J=4.9$ Hz), 4.98 (pseudo quintuplet, 1H, $J=$ 6.5 Hz), 6.25 (dd, 1H, $J=1.7$, 3.2 Hz), 6.28 (dd, 1H, $J=0.9$, 3.2 Hz), 7.30 (m, 5H), 7.34 (dd, 1H, $J=0.9$, 1.7 Hz), 7.49 (m, 2H), 7.60 (m, 1H), 7.82 (m, 2H); δ_C (100 MHz, $CDCl_3$) 21.2, 60.2, 63.6, 75.2, 81.4, 110.4, 111.3, 127.2, 127.7 (2C), 128.1 (2C), 128.9 (2C), 129.1 (2C), 133.2, 137.3, 138.5, 140.3, 149.0. IR ν 1140, 1240, 1275 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4S$ (383.5): C, 65.78; H, 5.52; N, 3.65. Found: C 65.62, H, 5.36, N, 3.81.

6.3.7. (3*S,4*S**,5*R**)-2-Benzyl-3-(isopropyl)-4-(phenylsulfonyl)-5-methylisoxazolidine 11c.** Oil; δ_H (400 MHz, $CDCl_3$) 0.55 (d, 3H, $J=6.8$ Hz), 0.70 (d, 3H, $J=6.6$ Hz), 0.95 (d, 3H, $J=6.1$ Hz), 2.70 (m, 1H), 3.28 (dd, 1H, $J=3.8$, 7.8 Hz), 3.36 (dd, 1H, $J=3.8$, 6.4 Hz), 4.10 (d, 1H, $J=$ 13.2 Hz), 4.15 (d, 1H, $J=13.2$ Hz), 4.70 (dq, 1H, $J=6.1$, 7.8 Hz), 7.32 (m, 5H), 7.55 (m, 2H), 7.64 (m, 1H), 7.80 (m, 2H); δ_C (100 MHz, $CDCl_3$) 19.8 (2C), 20.5, 27.3, 59.6, 61.7, 75.8, 80.9, 127.4, 127.5 (2C), 128.3 (2C), 128.5 (2C), 129.2 (2C), 134.1, 138.1, 138.6. IR ν 1160, 1240, 1305 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3S$ (359.48): C, 66.82; H, 7.01; N, 3.90. Found: C 66.65, H, 7.25, N, 4.11.

6.3.8. (3*S,4*S**,5*R**)-2-Benzyl-3-(*tert*-butyldiphenylsiloxymethyl)-4-(phenylsulfonyl)-5-methylisoxazolidine 11d.** Oil; δ_H (400 MHz, $CDCl_3$) 0.93 (s, 9H), 0.95 (d, 3H, $J=6.2$ Hz), 3.36 (dd, 1H, $J=6.1$, 10.6 Hz), 3.52 (dd, 1H, $J=6.2$, 10.6 Hz), 3.55 (dd, 1H, $J=4.3$, 7.4 Hz), 3.70 (dt, 1H, $J=4.3$, 6.1 Hz), 3.99 (d, 1H, $J=13.2$ Hz), 4.12 (d, 1H, $J=13.2$ Hz), 4.66 (dq, 1H, $J=6.2$, 7.4 Hz), 7.25 (m, 7H), 7.33 (m, 4H), 7.45 (m, 6H), 7.59 (m, 1H), 7.80 (m, 2H); δ_C (100 MHz, $CDCl_3$) 18.7, 26.9 (3C), 29.7, 64.8, 67.5, 74.3, 75.5, 79.1, 127.5, 127.8 (2C), 128.4 (4C), 129.1 (2C), 129.5 (2C), 129.6 (2C), 129.8 (2C), 133.9, 134.1 (2C), 135.6 (4C), 136.7, 139.2. IR ν 1145, 1250, 1310 cm^{-1}. Anal. Calcd for $C_{34}H_{39}NO_4SSi$ (585.8): C, 69.71; H, 6.71; N, 2.39. Found: C 69.98, H, 6.83, N, 2.12.

6.3.9. (3*S*,4*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(phenylsulfonyl)-5-methylisoxazolidine 14a. White solid; mp 109–110 °C; $[\alpha]_D^{20}=+10$ (*c* 0.32, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (s, 3H), 1.07 (s, 3H), 1.10 (d, 3H, $J=6.1$ Hz), 3.15 (m, 1H), 3.42 (dd, 1H, $J=2.8$, 8.6 Hz), 3.66 (dd, 1H, $J=2.8$, 7.8 Hz), 3.82 (m, 2H), 4.11 (s, 2H), 4.78 (dq, 1H, $J=6.1$, 7.8 Hz), 7.28 (m, 3H), 7.33 (m, 2H), 7.54 (m, 2H), 7.61 (m, 1H), 7.86 (m, 2H); δ_C (100 MHz, $CDCl_3$) 18.9, 25.1, 26.3, 60.0, 68.4, 69.0, 75.4, 77.0 (2C), 109.9, 128.1, 128.8 (2C), 128.9 (2C), 129.9 (2C), 130.2 (2C), 134.5, 137.1, 139.3. IR ν 1130, 1225, 1285 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5S$ (417.5): C, 63.29; H, 6.52; N, 3.35. Found: C 63.17, H, 6.74, N, 3.49.

6.3.10. (3*R*,4*R*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(phenylsulfonyl)-5-methylisoxazolidine 14b. Oil; $[\alpha]_D^{20}=-22$ (*c* 0.32, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.01 (d, 3H, $J=6.1$ Hz), 1.05 (s, 3H), 1.09 (s, 3H), 3.41 (dd, 1H, $J=3.8$, 8.1 Hz), 3.66 (dd, 1H, $J=5.8$, 8.8 Hz), 3.72 (dd, 1H, $J=3.8$, 5.8 Hz), 3.79 (dd, 1H, $J=6.8$, 8.8 Hz), 3.93 (pseudoq, 1H, $J=5.8$ Hz), 4.11 (s, 2H), 4.74 (dq, 1H, $J=6.1$, 8.1 Hz), 7.25 (m, 3H), 7.34 (m, 2H), 7.52 (m, 2H), 7.63 (m, 1H), 7.82 (m, 2H); δ_C (100 MHz, $CDCl_3$) 16.7, 23.8, 25.1, 59.4, 64.8, 66.3, 74.1, 74.7, 75.5, 108.4, 126.8, 127.6 (2C), 127.9 (2C), 128.8 (2C), 128.9 (2C), 133.5, 136.0, 137.8. IR ν 1135, 1225, 1310 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5S$ (417.5): C, 63.29; H, 6.52; N, 3.35. Found: C 63.15, H, 6.39, N, 3.56.

6.4. General procedure for the conversion of hydroxylamines into isoxazolidines

To a cooled (0 °C) solution hydroxylamine (0.5 mmol) in THF (5 mL) *n*-BuLi (0.8 mL of a 1.6 M solution in hexanes, 0.5 mmol) was added dropwise. After 1 h the reaction was quenched by adding saturated aq NH_4Cl (1 mL). The reaction mixture was extracted with EtOAc (3×15 mL). The combined organic extract was washed with brine, dried ($MgSO_4$), concentrated and examined by ^1H NMR. The crude material was purified by radial chromatography.

To obtain elimination products preferentially the reaction was repeated using 1.5 equiv of BuLi (0.47 mL of a 1.6 M solution in hexanes, 0.75 mmol).

6.4.1. (*Z*)-4-Phenyl-3-(phenylsulfonyl)-1,3-butadiene 19. Oil; δ_H (400 MHz, $CDCl_3$) 5.40 (dt, 1H, $J=1.2$, 11.0 Hz), 5.83 (dd, 1H, $J=1.2$, 17.8 Hz), 6.31 (ddd, 1H, $J=1.2$, 11.0, 17.8 Hz), 7.32 (m, 3H), 7.44 (m, 4H), 7.51 (m, 1H), 7.82 (m, 3H), 7.81 (s, 1H); δ_C (100 MHz, $CDCl_3$) 123.9, 126.5, 128.1 (2C), 128.7 (2C), 129.0 (2C), 130.0 (2C), 130.5 (2C), 133.2, 133.4, 138.2, 138.7. IR ν 1125, 1210, 1270 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_2S$ (270.4): C, 71.08; H, 5.22. Found: C 71.17, H, 5.40.

6.4.2. (*Z*)-4-(2-Pyridyl)-3-(phenylsulfonyl)-1,3-butadiene 20. Oil; δ_H (400 MHz, $CDCl_3$) 5.36 (dt, 1H, $J=1.1$,

11.6 Hz), 5.71 (dd, 1H, J=1.0, 17.4 Hz), 6.50 (ddd, 1H, J=1.1, 11.6, 17.4 Hz), 7.40 (m, 3H), 7.54 (m, 1H), 7.80 (m, 3H), 8.3 (s, 1H), 8.6 (m, 1H); δ_C (100 MHz, $CDCl_3$) 123.8, 124.5, 128.6 (2C), 129.4 (2C), 130.0, 130.6, 132.9, 133.1, 133.3, 138.5, 139.1, 148.3, 150.2. IR ν 1115, 1200, 1275 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_2S$ (271.33): C, 66.40; H, 4.83; N, 5.16. Found: C, 66.72; H, 4.56; N, 5.37.

6.4.3. (*Z*)-4-(2-Furyl)-3-(phenylsulfonyl)-1,3-butadiene 21. Oil; δ_H (400 MHz, $CDCl_3$) 5.40 (dt, 1H, J=1.0, 12.1 Hz), 5.90 (dd, 1H, J=1.0, 17.9 Hz), 6.46 (dd, 1H, J=2.0, 3.5 Hz), 6.74 (bd, 1H, J=3.5 Hz), 6.83 (ddd, 1H, J=1.2, 12.1, 17.9 Hz), 7.41 (m, 3H), 7.53 (m, 1H), 7.80 (m, 2H), 8.08 (s, 1H); δ_C (100 MHz, $CDCl_3$) 110.1, 122.9, 123.6, 128.5 (2C), 129.6 (2C), 130.2, 131.9, 134.3, 137.9, 139.6, 139.7, 143.0. IR ν 1135, 1225, 1250 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_3S$ (260.31): C, 64.60; H, 4.65. Found: C 64.71, H, 4.80.

6.4.4. (*Z*)-5-Methyl-3-(phenylsulfonyl)-1,3-hexadiene 22. Oil; δ_H (400 MHz, $CDCl_3$) 1.03 (d, 6H, J=6.6 Hz), 2.70 (dh, 1H, J=6.6, 10.1 Hz), 5.32 (dt, 1H, J=1.0, 11.6 Hz), 5.45 (dd, 1H, J=1.0, 17.9 Hz), 6.18 (ddd, 1H, J=1.0, 11.6, 17.9 Hz), 6.80 (d, 1H, J=10.1 Hz), 7.43 (m, 2H), 7.51 (m, 1H), 7.76 (m, 2H); δ_C (100 MHz, $CDCl_3$) 22.0 (2C), 28.1, 123.1, 125.5, 127.8 (2C), 128.9 (2C), 129.0, 133.1, 140.0, 149.4. IR ν 1110, 1220, 1260 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2S$ (236.33): C, 66.07; H, 6.82. Found: C 65.84, H, 6.99.

6.4.5. (*Z*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(phenylsulfonyl)-1,3-butadiene 23. Oil; $[\alpha]_D^{20}=+28$ (*c* 0.26, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.41 (s, 3H), 1.50 (s, 3H), 3.78 (dd, 1H, J=6.9, 8.4 Hz), 4.16 (dd, 1H, J=6.4, 8.4 Hz), 4.83 (td, 1H, J=6.6, 8.3 Hz), 5.50 (m, 2H), 6.28 (dd, 1H, J=11.1, 17.9 Hz), 6.96 (d, 1H, J=8.3 Hz), 7.50 (m, 2H), 7.63 (m, 1H), 7.86 (m, 2H); δ_C (100 MHz, $CDCl_3$) 25.7, 26.6, 69.1, 72.1, 110.6, 125.1, 125.4, 128.2 (2C), 129.1 (2C), 133.4, 138.7, 139.2, 143.2. IR ν 1130, 1235, 1280 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_4S$ (294.4): C, 61.20; H, 6.16. Found: C 61.08, H, 6.30.

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21. The authors have deposited the atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. CCDC 250314 and CCDC 250315 contain the supplementary crystallographic data for compounds **7c** and **14a**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. The graphic views shown in Figure 3 were made with ORTEP3 software. Copyright by Farrugia, L. J., University of Glasgow, 1997–2000.
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Superbase-promoted rearrangement of oxiranes to cyclopropanes

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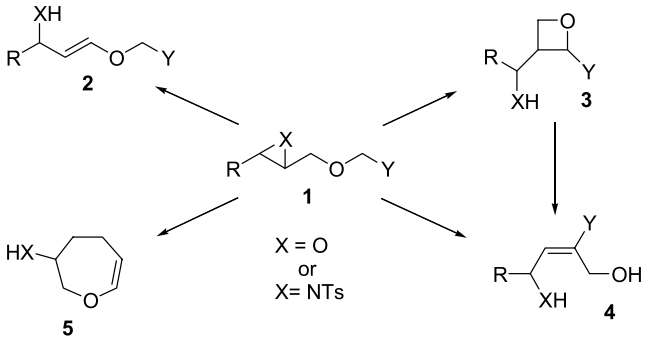
Dedicated to Prof. Manfred Schlosser on the occasion of his 70th birthday

Abstract—Aryl- and alkenyl substituted oxiranes, when submitted to treatment with superbasic reagents, undergo a highly regio- and stereoselective rearrangement leading to cyclopropylmethanol derivatives. The process can also be applied to mono- and dihydroxy substituted substrates thus leading to polyhydroxylated cyclopropanes.

1. Introduction

The usefulness of superbasic reagents[1,2] in promoting small ring heterocycle rearrangements has been clearly shown in recent years. We have indeed demonstrated that alkoxyalkyl oxiranyl-**1** (X=O) and aziridinyl ethers **1** (X=NTs) are efficiently converted into the isomeric hydroxy-[3–7] **2** (X=O) or amino vinylethers **2** (X=NTs),[8,9] respectively. In addition we have shown that benzyl-**1** (X=O, Y=aryl), allyl-**1** (X=O, Y=alkenyl) and propargyl **1** (X=O, Y=alkynyl) oxiranyl ethers can be conveniently rearranged to the corresponding di- or trisubstituted oxetanes **3** (X=O)[10–14] usually with very high regio- and stereoselectivity. Both the benzyl oxiranyl ethers **1** (X=O, Y=C_6H_5) and the rearranged phenyl substituted oxetanes **3** (X=O, Y=C_6H_5) can also be further isomerized to unsaturated 1,4-diols **4** with perfect *Z*-stereocontrol.[13,15] More recently, we have also reported that monosubstituted oxiranyl allyl ethers **1** (X=O, Y=alkenyl, R=H) are regio- and stereoselectively converted into the isomeric disubstituted tetrahydrooxepines **5** (X=O, R=H).[16] All these transformations have been carried out making use of superbases[1,2] and in particular the equimolar mixtures butyllithium/potassium *tert*-butoxide (Schlosser's base, LICKOR)[1] and butyllithium/diisopropylamine/potassium *tert*-butoxide (LIDAKOR)[17] (Scheme 1).

These results clearly show that superbasic reagents are very efficient in promoting 4-*exo* and 7-*endo* ring forming reactions from substituted oxiranyl ethers and this encouraged us to investigate additional possible intramolecular cyclization processes induced by formation of carbanions suitably positioned in oxirane derivatives.



Scheme 1.

In this paper, we describe our results on the synthesis of cyclopropanes **7** through a 3-*exo* cyclization process performed on alkenyl- or phenyl substituted oxiranes **6** (Y=alkenyl or phenyl) (Scheme 2).

2. Results and discussion

It is well known that cyclopropanes can be obtained from oxiranes through 3-*exo* cyclizations induced by carbanions. Usually the formation of the carbanionic species is

Keywords: Superbase; Cyclopropanes; Rearrangement; 3-*exo* Cyclization.
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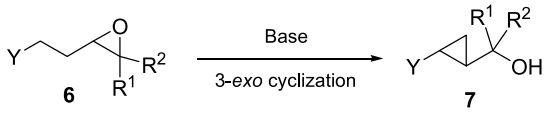


Scheme 2.

performed on substrates possessing good activating groups (nitriles,[18–20] esters,[21,22] amides,[23] ketones,[24] sulfones,[25–27] sulfides[28]) while very little is known on similar processes performed on oxiranes without a heterosubstituent able to stabilize the carbanionic intermediates. The only known results in this field date back to the 1970s when it was first reported[29,30] that lithium amides in the presence of HMPT as a cosolvent were able to convert a few 1-aryl- and 1-alkenyl-3,4-epoxyalkanes into the corresponding cyclopropanes. Drawbacks of this reaction are the use of the highly toxic HMPT, the low stereoselectivity and the quite limited number of examples. Thus, we decided to see if the use of the superbasic mixtures, LIDAKOR and LICKOR, could positively affect the outcome of the 3-*exo* cyclization reaction on a variety of suitably substituted oxiranes. For this purpose, we synthesized a series of arylethyl oxiranes and we submitted them to reaction with superbasic reagents. The simplest substrate in the series, the 1,2-epoxy-4-phenylbutane **8** easily obtained by epoxidation of 4-phenyl-1-butene, served as a test for finding the best organometallic base and reaction conditions. When **8** was treated with an excess of TMEDA-activated *sec*-butyllithium or with the superbasic mixture LICKOR, it gave no 3-*exo* cyclization products but instead the two olefins **9** and **10**, respectively as the only detected products (Scheme 3).

Such results can be explained by assuming that an initial α-metalation of the oxirane ring is then followed by isomerization to a carbene species which then adds a second organometallic reagent and eventually leads to the olefin via lithium oxide elimination (Scheme 4).[31,32]

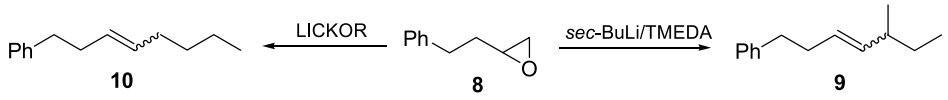
The use of stoichiometric amounts of the base resulted only in recovery of starting material and a decrease of the amount of olefin formed.

On the other hand, the use of the less nucleophilic reagent LIDAKOR, gave only the expected phenyl cyclopropyl methanol **11** in good yields and very good stereoselectivity, the *trans*-cyclopropane being the only detectable product (Scheme 5).

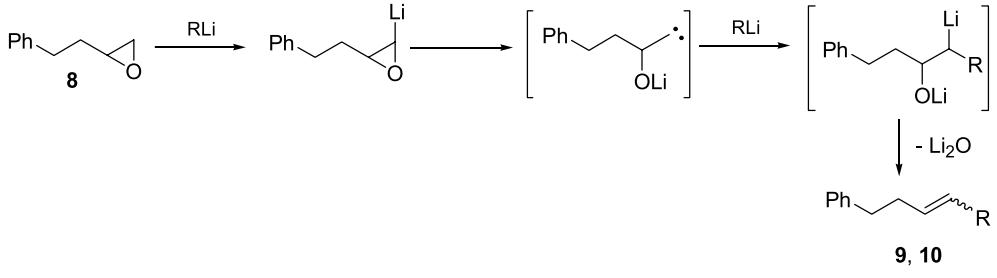
A similar behaviour was observed also with a representative series of di- and trisubstituted oxiranes which were prepared by epoxidation of the corresponding olefins, all synthesized by Wittig olefination. A 67:33 mixture of *cis* and *trans*-3,4-epoxy-2-methyl-6-phenylhexane **12** gave the corresponding cyclopropane **15** in 64% yield as a 67:33 *anti*:*syn* mixture by treatment with 2 equiv LIDAKOR in THF at −50 °C; no *cis* cyclopropanes were detected in the reaction mixture. When the oxirane ring has a methyl substituent as in the 2,3-epoxy-5-phenylpentane **13** and in the 2,3-epoxy-2-methyl-5-phenylpentane **14** cases, treatment with LIDAKOR afforded again the desired *trans*-cyclopropyl derivatives **16** and **17**, respectively in good yields but contaminated by the allylic alcohols **18** and **19**. Their formation is clearly due to a β-elimination process induced by deprotonation of the methyl groups. Interestingly such pathway became exclusive when LICKOR was used, showing the higher efficiency of the metal amide base towards the deprotonation of benzylic positions (Scheme 6).

The LIDAKOR promoted rearrangement leading to cyclopropanes works well even when the intermediate metallic species is of the allylic type.[33] Thus, 5,6-epoxy-1-hexene **20** was converted into *trans*-vinyl cyclopropylmethanol **21** in 75% yield with LIDAKOR in THF at −50 °C (Scheme 7).

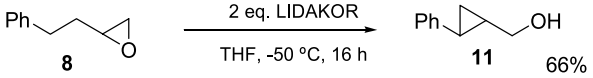
In order to extend the scope of the described 3-*exo* cyclization process we then turned our attention to



Scheme 3.

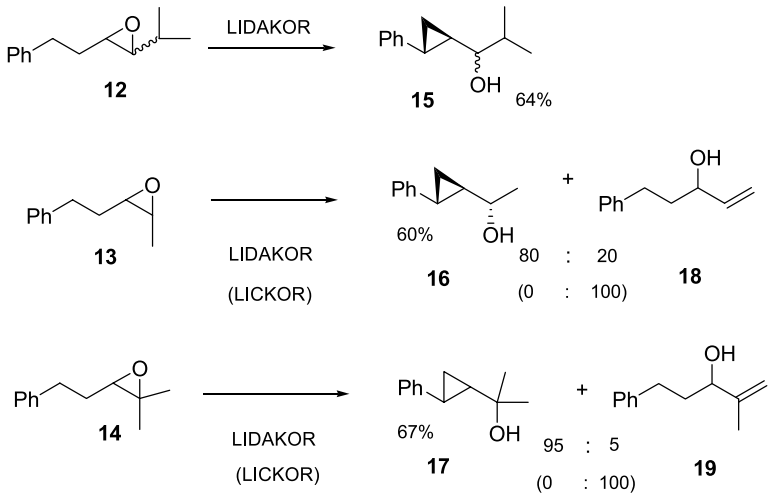


Scheme 4.

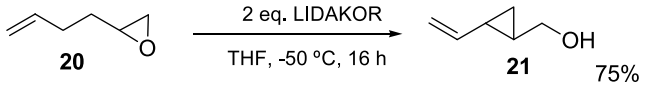


Scheme 5.

functionalized 1-aryl-3,4-epoxy substrates. Methoxy substituted compounds **22**, **23** and **24** derived from the corresponding allylic alcohols via *m*-CPBA epoxidation, were first selected to test their reaction with superbases. The position of the methoxy group is clearly crucial in driving

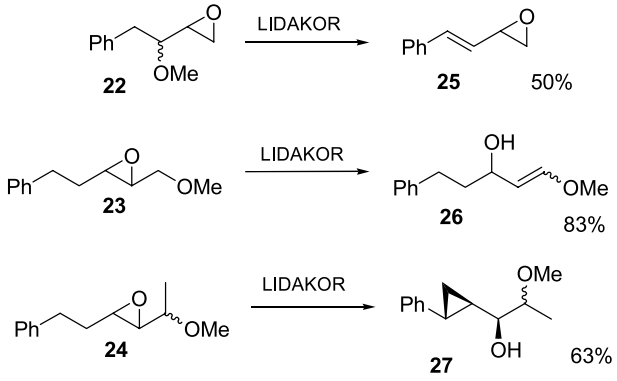


Scheme 6. Reaction conditions: 2 equiv LIDAKOR, THF, −50°C, 16 h; 2 equiv LICKOR, pentane, 25°C, 16 h.



Scheme 7.

the base-promoted reaction. Oxirane **22** was in fact converted into the vinyl oxirane **25** via benzylic metalation followed by elimination of the methoxy group. When the substituent is instead located on the other side of the oxirane



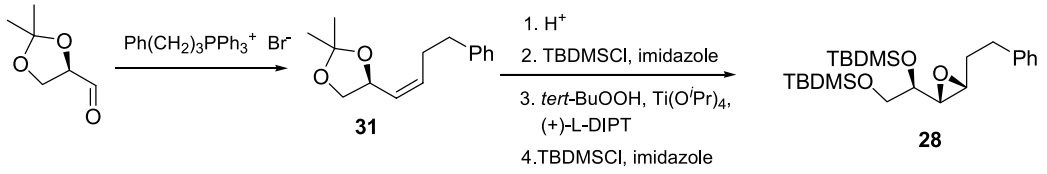
Scheme 8. Reaction conditions: 2 equiv LIDAKOR, THF, −50°C, 16 h.

ring as in **23**, treatment with a superbase produced a ring-opened product **26** derived from deprotonation at the methylene α to the oxirane ring and the methoxy group, followed by β-elimination. No 3-*exo* ring-closure compounds could be detected in both cases while the cyclopropyl derivative **27** became the only observed reaction product when oxirane **24**, derived from a secondary allylic alcohol, was treated with LIDAKOR. In this case the benzylic deprotonation again becomes the predominant pathway due to the decreased availability of the methine proton, and then follows the 3-*exo* cyclization pathway to the cyclopropyl derivative (Scheme 8).

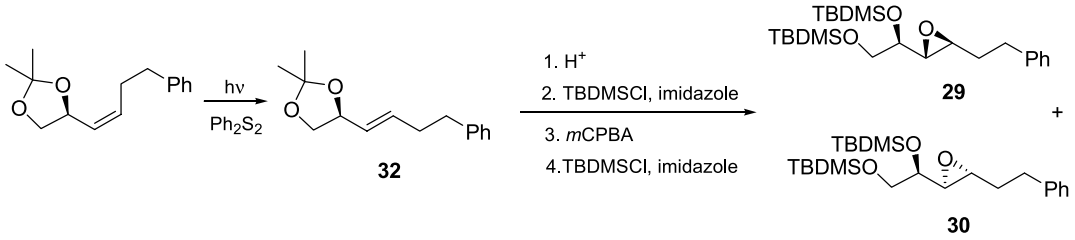
The reaction is again highly stereoselective leading to the *trans*-stereoisomer only, and shows that this can be a convenient way to access cyclopropyl diols or polyols starting from oxiranyl ethers derived from secondary allylic alcohols. In order to further prove this finding and to study in more details the stereochemical outcome of the isomerization reaction, we synthesized the 1,2-di-*tert*-butyldimethylsilyloxy-3,4-epoxy-6-phenylhexane in its diastereomeric forms *syn*,*cis* (**28**, *R*,*R*,*R*), *syn*,*trans* (**29**, *R*,*R*,*S*) and *anti*,*trans* (**30**, *R*,*S*,*R*). Compound **28** was prepared by diastereoselective epoxidation with *tert*-butylhydroperoxide, titanium isopropoxide and (+)-L-diethyl tartrate of the corresponding *cis*-olefin **31** which in turn has been prepared by Wittig olefination of the 2,3-isopropylidene-D-glyceraldehyde[34] with phenylpropyl triphenylphosphonium bromide (Scheme 9).

The two oxiranes **29** and **30** were obtained as a 50:50 mixture by *m*-CPBA epoxidation of the corresponding *trans*-olefin **32** which was prepared by the same Wittig olefination as described above, followed by a photochemically induced isomerization of the double bond in the presence of diphenyl disulfide.[34] The two diastereomers **29** and **30** were separated and then used, together with **28**, in the base-promoted rearrangements (Scheme 10).

Treatment of compounds **28**–**30** with the superbasic reagent LIDAKOR, gave the same result: all diastereoisomers were



Scheme 9.



Scheme 10.

converted into the corresponding *trans*-cyclopropanes **33–35a**,**b** with a perfect stereocontrol thus showing that changes in the configuration of the oxirane ring or in the relative stereochemistry of the silyloxy substituent did not affect the outcome of the rearrangement process.

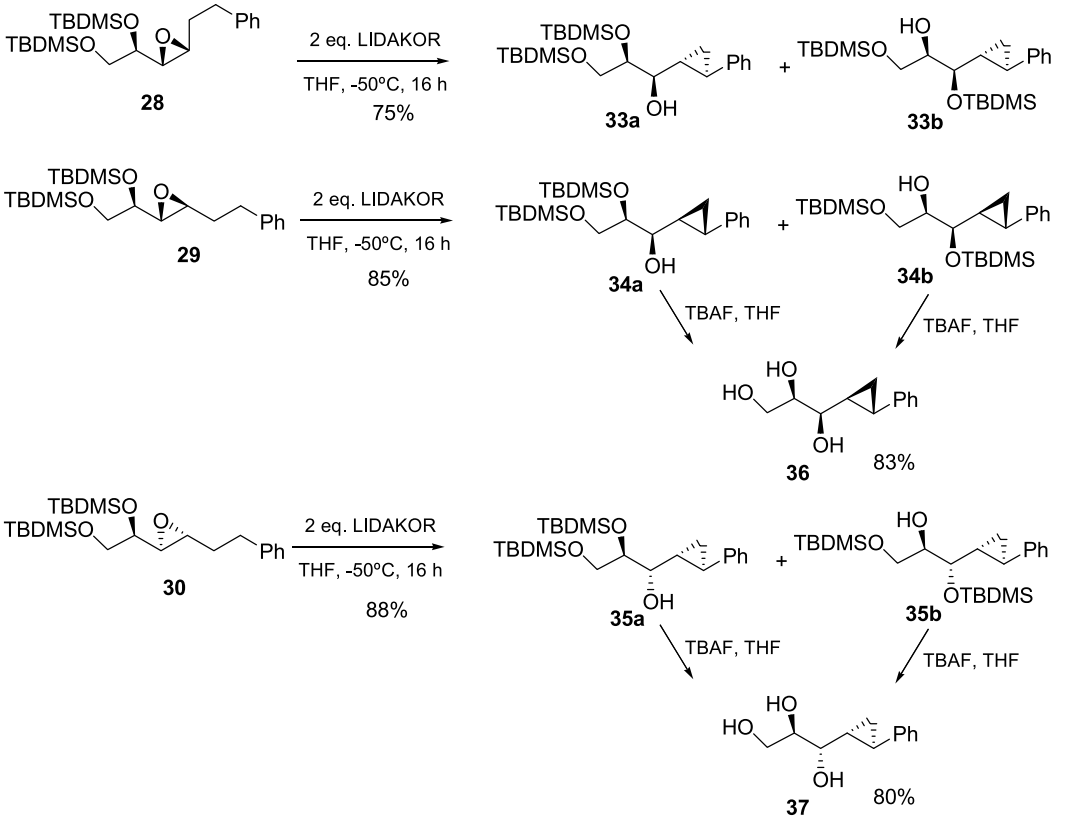
In all cases the reaction mixture contained actually two isomers which, upon a careful NMR investigation, turned out to be those deriving from a *tert*-butyldimethylsilyl group migration from one oxygen to the neighbouring one during the isomerization process. This was then further demonstrated for the cyclopropane derivatives **34a**,**b** and **35a**,**b** which by fluoride deprotection of all the silylated hydroxy groups afforded the triols **36** and **37**, respectively (Scheme 11).

In conclusion, we have found that superbasic mixtures can be conveniently used for the 3-*exo* cyclization of suitably substituted oxiranes lacking strong electron withdrawing substituents. The reaction is highly stereoselective and seems to be of a general applicability allowing the synthesis of functionalized cyclopropanes.

3. Experimental

3.1. General procedures

Air- and moisture-sensitive compounds were stored in Schlenk tubes or in Schlenk burettes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ethereal extracts were dried with sodium sulfate. Purifications by flash column chromatography[35] were performed using glass columns (10–50 mm wide); silica gel 230–400 mesh was chosen as stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic resonance spectra of hydrogen nuclei were recorded at 200 or 400 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Coupling constants (*J*) are measured in Hz. Coupling patterns are



Scheme 11.

described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of a doublet), m (multiplet), bs (broad singlet), app (apparent). Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 or 100 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). Mass spectra were obtained at a 70 eV ionization potential.

3.2. Materials

Starting materials were commercially available unless otherwise stated. All commercial reagents were used without further purification except diisopropyl amine, which was distilled over calcium hydride. Tetrahydrofuran was obtained anhydrous by distillation over sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl[36] was found to persist. Pentane was stored over lithium aluminum hydride. Methylene chloride was dried over calcium chloride and stored over 4 Å molecular sieves. Petroleum ether, unless specified, was the 40–70 °C boiling fraction.

3.3. Preparation of oxiranes

3.3.1. 1,2-Epoxy-4-phenylbutane 8.[37] *m*-CPBA (1. 035 g, 6.0 mmol, 2 equiv) was added to a cooled (0 °C) solution of the 4-phenyl-1-butene (400 mg, 3.0 mmol, 1 equiv) in 30 mL CH_2Cl_2. The mixture was allowed to reach room temperature and then stirred overnight. The reaction mixture was cooled to −20 °C, and the *m*-chlorobenzoic acid was filtered on Celite. The organic layer was washed twice with satd $Na_2S_2O_3$, once with satd $NaHCO_3$ and dried over Na_2SO_4. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate 10:1) giving 173 mg (39% yield) of oxirane **8** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.38–7.18 (5H, m); 3.05–2.94 (1H, m); 2.93–2.71 (3H, m); 2.51 (1H, dd, J=4.8, 2.6 Hz); 1.95–1.80 (2H, m).

3.3.2. Preparation of *cis*,*trans*-3,4-epoxy-2-methyl-6-phenylhexane 12.[38] *(Z,E)-2-Methyl-6-phenyl-3-hexene*. To a stirred suspension of isobutyltriphenylphosphonium bromide (1.26 g, 1.05 equiv, 3.15 mmol) in 8 mL of dry THF a 1.6 M hexane solution of BuLi (1.96 mL, 1.0 equiv, 3.00 mmol) was added dropwise under N_2 at −78 °C until the mixture became homogeneous and deep red coloured. After 2 h, 3-phenylpropionaldehyde (0.40 mL, 1.0 equiv, 3.00 mmol) was added dropwise. The mixture was allowed to reach room temperature and then stirred for 6 h. Petroleum ether was added and the triphenylphosphine oxide was filtered on Celite. After evaporation of the solvent, 0.52 g (99% yield) of a 67:33 mixture of (*Z*,*E*)-2-methyl-6-phenyl-3-hexene was obtained and used in the next step without any further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ *Z*: 7.37–7.20 (5H, m); 5.48–5.18 (2H, m); 2.95–2.67 (4H, m); 2.46–2.35 (1H, appq, J=6.4 Hz); 0.93 (6H, d, J=6.6 Hz). *E*: 7.37–7.20 (5H, m); 5.48–5.18 (2H, m); 2.95–2.67 (4H, m); 2.65–2.47 (1H, m); 1.00 (6H, d, J=7.0 Hz).

cis,trans-3,4-Epoxy-2-methyl-6-phenylhexane **12**. *m*-CPBA (0.69 g, 4.0 mmol, 2 equiv) was added to a cooled (0 °C) solution of the (*E*,*Z*)-2-methyl-6-phenyl-3-hexene (350 mg, 2.0 mmol, 1 equiv) in 20 mL CH_2Cl_2. The mixture was allowed to reach room temperature and then stirred overnight. The reaction mixture was cooled to −20 °C, and the *m*-chlorobenzoic acid was filtered on Celite. The organic layer was washed twice with satd $Na_2S_2O_3$, once with satd $NaHCO_3$ and dried over Na_2SO_4. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate 10:1) giving 215 mg (49% yield) of **12** as a colourless oil in a 67:33 *cis*/*trans* mixture. ^{1}H NMR ($CDCl_3$, 200 MHz) δ *cis*: 7.32–7.17 (5H, m); 3.07–2.96 (1H, m); 2.92–2.70 (2H, m); 2.63 (1H, dd, J=9.2, 4.2 Hz); 1.98–1.69 (2H, m); 1.63–1.38 (1H, m); 1.13 (3H, d, J=6.6 Hz); 0.94 (3H, d, J=6.6 Hz). *trans*: 7.32–7.17 (5H, m); 3.07–2.96 (1H, m); 2.92–2.70 (2H, m); 2.47 (1H, dd, J=6.6, 1.9 Hz); 1.98–1.69 (2H, m); 1.63–1.38 (1H, m); 1.01 (3H, d, J=6.4 Hz); 0.91 (3H, d, J=6.6 Hz).

3.3.3. Preparation of *cis*-2,3-epoxy-5-phenylpentane 13.[37] *(Z)-5-Phenylpent-2-ene*. A solution 1.6 M of BuLi (3.2 mL, 1.0 equiv, 5.1 mmol) in hexane was added, at −78 °C under N_2, to a solution of triphenylethylphosphonium bromide (2.00 g, 1.05 equiv, 5.4 mmol) in 15 mL of dry THF. The mixture was stirred at −78 °C for 2 h and then 3-phenylpropionaldehyde (0.76 mL, 1.13 equiv, 5.8 mmol) was added. The mixture was allowed to reach room temperature and then stirred for 12 h. Petroleum ether was added and the triphenylphosphinoxide was filtered on Celite. After evaporation of the solvent the residue was purified by flash chromatography (petroleum ether:ethyl acetate 10:1) to give 296 mg of (*Z*)-5-phenylpent-2-ene (40% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.39–7.17 (5H, m); 5.49 (2H, appd, J=5.4 Hz); 2.83–2.58 (2H, m); 2.46–2.32 (2H, m); 1.60 (3H, d, J=4.4 Hz).

cis-2,3-Epoxy-5-phenylpentane **13**. *m*-CPBA (0.35 g, 2.0 mmol, 2 equiv) was added to a cooled (0 °C) solution of the (*Z*)-5-phenylpent-2-ene (146 mg, 1.0 mmol, 1 equiv) in 10 mL CH_2Cl_2. The mixture was allowed to reach room temperature and then stirred overnight. The reaction mixture was cooled to −20 °C, and the *m*-chlorobenzoic acid was filtered on Celite. The organic layer was washed twice with satd $Na_2S_2O_3$, once with satd $NaHCO_3$ and dried over Na_2SO_4. After the solvent was evaporated 162 mg (100% yield) of the crude epoxide **13** were obtained and used in the next step without any further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.35–7.17 (5H, m); 3.11–2.65 (4H, m); 1.86 (2H, appquint); 1.21 (3H, d, J=5.6 Hz).

3.3.4. Preparation of 2,3-epoxy-2-methyl-5-phenylpentane 14.[37] *2-Methyl-5-phenylpent-2-ene*. Isopropyltriphenylphosphonium bromide/sodium amide mixture (3.60 g, 8.3 mmol, 1.0 equiv) was poured, under N_2, in 20 mL of dry THF. After 30 min, 3-phenylpropionaldehyde (1.32 mL, 10.0 mmol, 1.2 equiv) was added and the mixture stirred at 40 °C under N_2 overnight. Petroleum ether was then added and the precipitate was filtered on silica. After evaporation of the solvent, 1.55 g (97% yield) of 2-methyl-5-phenylpent-2-ene was obtained as a dark yellow oil and used in the next step without any further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.42–7.18 (5H, m); 5.23 (1H, t, J=6.7 Hz); 2.80–2.62 (2H, m); 2.34 (2H, dt, J=8.8, 6.7 Hz); 1.74 (3H, s); 1.62 (3H, s).

2,3-Epoxy-2-methyl-5-phenylpentane **14**. *m*-CPBA (1.72 g, 10.0 mmol, 2 equiv) was added to a cooled (0 °C) solution of the 2-methyl-5-phenylpent-2-ene (1.60 g, 5.0 mmol, 1 equiv) in 40 mL CH_2Cl_2. The mixture was allowed to reach room temperature and then stirred overnight. The reaction mixture was cooled to −20 °C, and the *m*-chlorobenzoic acid was filtered on Celite. The organic layer was washed twice with satd $Na_2S_2O_3$, once with satd $NaHCO_3$ and dried over Na_2SO_4. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate 10:1) giving 436 mg (50% yield) of **14** as a colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.32–7.10 (5H, m); 2.98–2.61 (3H, m); 1.99–1.65 (2H, m); 1.27 (3H, s); 1.12 (3H, s).

3.3.5. Preparation of *syn,anti*-3,4-epoxy-2-methoxy-1-phenylbutane 22. *1-Phenylbut-3-en-2-ol*. Vinylmagnesium bromide (22.5 mL, 22.5 mmol, 1.5 equiv) was added, at 0 °C under N_2, to a solution of phenylacetaldehyde (1.95 mL, 15 mmol, 1.0 equiv) in 30 mL of dry THF. After the addition was complete the temperature was allowed to reach 25 °C and the mixture was stirred for 2.5 h and then cooled to 0 °C. HCl (10 mL of a 1.0 M solution) was then added and, after 30 min, the precipitate was filtered through Celite. The aqueous layer was extracted with Et_2O, and the organic layer washed with brine and dried over Na_2SO_4. After the solvent was evaporated 2.20 g (100% yield) of 1-phenylbut-3-en-2-ol were obtained. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.42–7.05 (5H, m); 5.94 (1H, ddd, J=17.0, 10.3, 5.8 Hz); 5.34–4.95 (2H, m); 4.62–4.57 (1H, m); 2.87–2.60 (2H, m); 2.40 (1H, bs).

syn,anti-3,4-Epoxy-1-phenyl-2-butanol. *m*-CPBA (1.72 g, 10.0 mmol, 2 equiv) was added to a cooled (0 °C) solution of the 1-phenylbut-3-en-2-ol (740 mg, 5.0 mmol, 1 equiv) in 40 mL CH_2Cl_2. The mixture was allowed to reach room temperature and then stirred overnight. The reaction mixture was cooled to −20 °C, and the *m*-chlorobenzoic acid was filtered on Celite. The organic layer was washed twice with satd $Na_2S_2O_3$, once with satd $NaHCO_3$ and dried over Na_2SO_4. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate 4:1) giving 295 mg (36% yield) of a 1:1 *syn*:*anti* mixture of 3,4-epoxy-1-phenyl-2-butanol as a yellow oil. *First diastereoisomer*: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.17 (5H, m); 4.07–3.95 (1H, m); 3.08–3.00 (1H, m); 2.99–2.85 (2H, m); 2.83–2.71 (1H, m); 2.61 (1H, dd, J=4.8, 2.6 Hz); 2.48 (1H, bs). *Second diastereoisomer*: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.17 (5H, m); 3.71 (1H, td, J=6.8, 4.8 Hz); 3.08–3.00 (1H, m); 2.99–2.85 (2H, m); 2.83–2.71 (1H, m); 2.61 (1H, dd, J=4.8, 2.6 Hz); 2.48 (1H, bs).

syn,anti-3,4-Epoxy-2-methoxy-1-phenylbutane **22**. NaH (29 mg, 1.2 mmol, 1.2 equiv) in a 60% dispersion in mineral oil, was suspended in dry THF (1 mL) under N_2 at 0 °C. Then a 0.5 M THF solution of the *syn,anti*-3,4-epoxy-1-phenyl-2-butanol (164 mg, 1.0 mmol, 1.0 equiv) was added and the mixture stirred at 0 °C under N_2 for 45 min. The temperature was allowed to rise to room temperature and methyl iodide (170 mg, 1.2 mmol, 1.2 equiv) was then added. After stirring for 6 h, ice and Et_2O were added and the aqueous layer extracted with Et_2O; the organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate 4:1) giving 112 mg (52% yield) of a 1:1 *syn*:*anti* diastereomeric mixture of **22** as a yellow oil. First diastereoisomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.41–7.19 (5H, m); 3.49 (3H, s); 3.32–3.20 (1H, m); 3.18–2.73 (4H, m); 2.66 (1H, app t, J=4.4 Hz). Second diastereoisomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.41–7.19 (5H, m); 3.36 (3H, s); 3.32–3.20 (1H, m); 3.18–2.73 (4H, m); 2.25 (1H, dd, J=4.7, 2.5 Hz). MS (*m*/*z*, %): 178 (0.2, M^+); 148 (14); 146 (34, M^+ −OMe− 1); 135 (7); 119 (14); 115 (18); 103 (19); 91 (54); 88 (55); 87 (100); 77 (18); 65 (28); 57 (34).

3.3.6. Preparation of *trans*-2,3-epoxy-1-methoxy-5-phenylpentane 23.[39] *Ethyl 5-phenyl-(E)-2-pentenoate*. NaH (600 mg, 1.15 equiv, 17.2 mmol) in a 60% dispersion in mineral oil, was suspended in 25 mL under N_2 and the mixture was cooled to 0 °C. A solution of diisopropyl-(ethoxycarbonylmethyl)phosphonate (4.1 mL, 1.1 equiv, 16.5 mmol) in 10 mL of dry THF was added slowly; after stirring at room temperature for 30 min, the mixture was cooled to 0 °C and 3-phenylpropionaldehyde (1.98 mL, 1.0 equiv, 15 mmol) in 15 mL of THF was added. After stirring at 0 °C for 1 h, satd NH_4Cl was added and the organic layer was washed twice with satd $NaHCO_3$ and brine, then dried over Na_2SO_4. After the solvent was evaporated 3.0 g (98% yield) of the crude ethyl 5-phenyl-(*E*)-2-pentenoate were obtained as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.20 (5H, m); 7.07 (1H, dt, J=15.8, 6.8 Hz); 5.91 (1H, dt, J=15.8, 1.7 Hz); 4.24 (2H, q, J=7.1 Hz); 2.84 (2H, t, J=8.4 Hz); 2.58 (2H, tdd, J=8.4, 6.8, 1.7 Hz); 1.34 (3H, t, J=7.1 Hz).

(2E)-5-Phenylpent-2-en-1-ol. A solution of 3.06 g (1.0 equiv, 15 mmol) of 5-phenyl-(*E*)-2-pentenoate in 35 mL of dry CH_2Cl_2 was cooled to −78 °C; 37 mL (2.5 equiv, 37 mmol) of DIBAL-H 1.0 M in CH_2Cl_2 was added and the mixture was stirred under N_2 for 1 h; then 10 mL of H_2O was added and the organic layer was washed twice with a 10% sodium tartrate solution, once with brine, and then dried over Na_2SO_4. Evaporation of the solvent afforded 2.03 g (83% yield) of the crude (2*E*)-5-phenylpent-2-en-1-ol as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.42–7.19 (5H, m); 5.76 (2H, m); 4.13 (2H, bs); 2.77 (2H, t, J=7.4 Hz); 2.50–2.40 (2H, m); 1.77 (1H, bs).

trans-2,3-Epoxy-5-phenylpentan-1-ol.[39] *m*-CPBA (3.44 g, 20.0 mmol, 2 equiv) was added to a cooled (0 °C) solution of the (2*E*)-5-phenylpent-2-en-1-ol (1.62 g, 10.0 mmol, 1 equiv) in 80 mL CH_2Cl_2. The mixture was allowed to reach room temperature and then stirred overnight. The reaction mixture was cooled to −20 °C, and the *m*-chlorobenzoic acid was filtered on Celite. The organic layer was washed twice with satd $Na_2S_2O_3$, once with satd $NaHCO_3$ and dried over Na_2SO_4. After the solvent was evaporated, 1.48 g (83% yield) of the crude colourless oil *trans*-2,3-epoxy-5-phenylpentan-1-ol were obtained and used in the next step without any further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.41–7.18 (5H, m); 3.90 (1H, dd, J=12.6, 2.5 Hz); 3.61 (1H, dd, J=12.6, 4.3 Hz); 3.33 (1H, bs); 3.05 (1H, td, J=5.8, 2.5 Hz); 2.95–2.63 (3H, m); 2.00–1.85 (2H, m).

trans-2,3-Epoxy-1-methoxy-5-phenylpentane **23**. NaH (58 mg, 2.4 mmol, 1.2 equiv) in a 60% dispersion in mineral oil, was suspended in dry THF (2 mL) under N_2 at 0 °C.

Then a 0.5 M THF solution of the *trans*-2,3-epoxy-5-phenylpentan-1-ol (356 mg, 2.0 mmol, 1.0 equiv) was added and the mixture stirred at 0 °C under N_2 for 45 min. The temperature was allowed to rise to room temperature and methyl iodide (340 mg, 2.4 mmol, 1.2 equiv) was then added. After stirring for 6 h, ice and Et_2O were added and the aqueous layer extracted with Et_2O; the organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 213 mg (55% yield) of the crude **23** as a colourless oil that was used in the next step without any further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.34–7.15 (5H, m); 3.58 (^{1}H, dd, J=11.4, 2.8 Hz); 3.67 (3H, s); 3.31 (1H, dd, J=11.4, 5.3 Hz); 2.91–2.61 (4H, m); 1.89 (2H, td, J=7.7, 5.3 Hz).

3.3.7. Preparation of *syn,anti-trans*-3,4-epoxy-2-methoxy-6-phenylhexane 24. *trans-2,3-Epoxy-5-phenylpentanal*. *trans*-2,3-Epoxy-5-phenylpentan-1-ol (270 mg, 1.0 equiv, 1.5 mmol) was dissolved in 15 mL of dry CH_2Cl_2, and Dess Martin periodinane (950 mg, 1.5 equiv, 2.3 mmol) was added at room temperature under N_2. After 1 h and 30 min Et_2O (5 mL) and satd $Na_2S_2O_3$ (5 mL) were added and the aqueous layer was extracted with Et_2O. The organic layers were washed with satd $NaHCO_3$ and brine, then dried over Na_2SO_4. Evaporation of the solvent gave 260 mg (98% yield) of the crude *trans*-2,3-epoxy-5-phenylpentanal as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 9.02 (1H, d, J=6.2 Hz); 7.39–7.20 (5H, m); 3.29 (1H, td, J=5.5, 1.9 Hz); 3.15 (1H, dd, J=6.2, 1.9 Hz); 2.95–2.77 (2H, m); 2.10–1.92 (2H, m).

syn,anti-trans-3,4-Epoxy-2-hydroxy-6-phenylhexane. *trans*-2,3-Epoxy-5-phenylpentanal (350 mg, 1.0 equiv, 2.0 mmol) was dissolved in 4 mL of dry THF and then cooled to 0 °C. A 3.0 M THF solution of methylmagnesium chloride (0.7 mL, 1.05 equiv, 2.1 mmol) was added and the mixture stirred at 0 °C under N_2 for 1.5 h and for other 45 min at room temperature. 1 M HCl (4 mL) and Et_2O (4 mL) were added and the organic layer was washed with water and brine, then dried over Na_2SO_4. After evaporation of the solvent, 252 mg (65% yield) of the crude *syn,anti-trans*-3,4-epoxy-2-hydroxy-6-phenylhexane were obtained as a yellow oil in a 62:38 *syn*:*anti* ratio. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: *syn*: 7.35–7.15 (5H, m); 3.55 (1H, appquint, J=5.5 Hz); 2.91 (1H, td, J=5.7, 2.3 Hz); 2.84–2.62 (3H, m); 2.11–2.01 (1H, bs); 2.00–1.81 (2H, m); 1.16 (3H, d, J=6.4 Hz) *anti*: 7.35–7.15 (5H, m); 3.94–3.79 (1H, m); 3.00 (1H, td, J=5.6, 2.2 Hz); 2.84–2.62 (3H, m); 2.11–2.01 (1H, bs); 2.00–1.81 (2H, m); 1.14 (3H, d, J=5.9 Hz).

syn,anti-trans-3,4-Epoxy-2-methoxy-6-phenylhexane **24**. NaH (44 mg, 1.8 mmol, 1.2 equiv) in a 60% dispersion in mineral oil, was suspended in dry THF (1.5 mL) under N_2 at 0 °C. Then a 0.5 M THF solution of the *syn,anti-trans*-3,4-epoxy-2-hydroxy-6-phenylhexane (288 mg, 1.5 mmol, 1.0 equiv) was added and the mixture stirred at 0 °C under N_2 for 45 min. Methyl iodide (255 mg, 1.8 mmol, 1.2 equiv) was then added and the temperature was allowed to rise to room temperature. After stirring for 6 h, ice and Et_2O were added and the aqueous layer extracted with Et_2O; the organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate 4:1) giving 110 mg (36% yield) of a 64:36 *syn*:*anti* diastereomeric mixture as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: *syn*: 7.38–7.18 (5H, m); 3.46 (3H, s); 3.08 (1H, appquint, J=6.6 Hz); 3.01–2.67 (4H, m); 1.92 (2H, td, J=7.0, 6.5 Hz); 1.16 (3H, d, J=6.6 Hz). *anti*: 7.38–7.18 (5H, m); 3.38 (3H, s); 3.20 (1H, appquint, J=6.2 Hz); 3.01–2.67 (4H, m); 1.92 (2H, td, J=7.0, 6.5 Hz); 1.24 (3H, d, J=6.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: *syn*: 140.9, 128.3, 128.2, 126.0, 77.5, 61.8, 57.0, 53.8, 33.2, 32.1, 16.7. *anti*: 141.0, 128.3, 128.2, 125.9, 76.1, 60.4, 56.9, 56.8, 33.4, 32.0, 17.0. MS (*m*/*z*, %): 187 (1); 175 (2, M^+-OMe); 173 (6); 147 (8); 129 (9); 128 (13); 117 (91); 103 (35); 91 (100); 77 (23); 58 (100).

3.4. Preparation of oxiranyl ethers from mannitol

3.4.1. Preparation of 2,3-isopropylidene-D-glyceraldehyde.[34] 1,2:5,6-Diisopropylidene-D-mannitol (787 mg, 3 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2 (7 mL) and a saturated solution of $NaHCO_3$ (0.4 mL); $NaIO_4$ (963 mg, 4.5 mmol, 1.5 equiv) was then slowly added and the mixture stirred at room temperature. After 5 h, Na_2SO_4 was added with vigorous stirring. The resulting suspension was filtered and the filtrate washed with CH_2Cl_2. The organic layers were evaporated to give 709 mg (91% yield) of the crude 2,3-isopropylidene-D-glyceraldehyde as a colourless oil which was immediately used in the next reaction. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.72 (1H, d, J=1.9 Hz); 4.38 (1H, ddd, J=7.4, 4.7, 1.9 Hz); 4.17 (1H, dd, J=8.8, 7.4 Hz); 4.10 (1H, dd, J=8.8, 4.7 Hz); 1.49 (3H, s); 1.42 (3H, s).

3.4.2. Preparation of *syn*-(3,4-*cis*)-(2*R*,3*R*,4*R*)-1,2-di(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexane 28. *(3Z)-(2S)-1,2-Isopropyliden-6-phenylhex-3-enyl-1,2-diol* **31**.[34] To a stirred suspension of 1-phenylpropyltriphenylphosphonium bromide (1.45 g, 3.15 mmol, 1.05 equiv) in 8 mL of dry THF, a 1.6 M hexane solution of BuLi (1.96 mL, 3.00 mmol, 1.0 equiv) was added dropwise, under N_2 at −78 °C, until the mixture became homogeneous and deep red coloured. After 1 h, a solution of 2,3-isopropylidene-D-glyceraldehyde (390 mg, 3.0 mmol, 1.0 equiv) in 2 mL of dry THF was added and the mixture stirred at room temperature, under N_2 overnight. Petroleum ether was added, the precipitate filtered through Celite and the filtrate was washed with petroleum ether. The organic layer was evaporated to give 366 mg (56% yield) of **31** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.34–7.12 (5H, m); 5.67 (1H, dt, J=11.0, 7.4 Hz); 5.41 (1H, dd, J=11.0, 8.5 Hz); 4.70 (1H, ddd, J=8.5, 8.0, 6.0 Hz); 3.77 (1H, dd, J=8.0, 6.0 Hz); 3.35 (1H, appt, J=8.0 Hz); 2.82–2.34 (4H, m); 1.40 (3H, s); 1.36 (3H, s).

(3Z)-(2S)-6-Phenylhex-3-enyl-1,2-diol. To a solution of **31** (349 mg, 1.50 mmol, 1 equiv) in 8.5 mL of THF, 2 mL of 10% HCl were added and the mixture stirred at room temperature overnight. Solid $NaHCO_3$ was then added until CO_2 evolution finished; the mixture was dried over Na_2SO_4. After evaporation of the solvent 218 mg (75% yield) of (3*Z*)-(2*S*)-6-phenylhex-3-enyl-1,2-diol as a white solid were obtained. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.37–7.10 (5H, m); 5.68–5.54 (1H, m); 5.36 (1H, td, J=8.8, 2.2 Hz); 4.37–4.27 (1H, m); 3.36 (2H, d, J=5.9 Hz); 2.70 (2H, td, J=6.6, 2.2 Hz); 2.43 (2H, t, J=6.6 Hz); 1.76 (2H, bs).

(3Z)-(2R)-1-(tert-Butyldimethylsilyloxy)-6-phenylhex-3-en-2-ol. To a stirred solution of (3*Z*)-(2*S*)-6-phenylhex-3-enyl-1,2-diol (200 mg, 1.04 mmol, 1 equiv) in 2 mL of dry CH_2Cl_2, *tert*-butyldimethylsilyl chloride (165 mg, 1.09 mmol, 1.05 equiv) and imidazole (177 mg, 2.6 mmol, 2.5 equiv) were added, under N_2, and the mixture stirred for 5 h. The reaction was quenched with H_2O; the aqueous layer washed with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 320 mg of the crude product that was purified by flash chromatography (petroleum ether:ethyl acetate 5:1) to give 151 mg (47% yield) of pure (3*Z*)-(2*R*)-1-(*tert*-butyldimethylsilyloxy)-6-phenylhex-3-en-2-ol as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.10–7.33 (5H, m); 5.68–5.54 (1H, m); 5.35 (1H, td, $J=8.1$, 1.5 Hz); 4.43–4.33 (1H, m); 3.42–3.26 (2H, m); 2.77–2.62 (2H, m); 2.52–2.30 (2H, m); 1.67 (1H, bs); 0.91 (9H, s); 0.07 (6H, s).

syn-(3,4-cis)-(2S)-1-(tert-Butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexan-2-ol. (+)-L-Diethyl tartrate (80 μL, 1 equiv, 0.46 mmol), titanium (IV) isopropoxide (140 μL, 1 equiv, 0.46 mmol) and (3*Z*)-(2*S*)-1-(*tert*-butyldimethylsilyloxy)-6-phenylhex-3-en-2-ol (140 mg, 1 equiv, 0.46 mmol) were sequentially added to a cooled (−20 °C) suspension of activated 4 Å powdered molecular sieves in 2 mL of dry CH_2Cl_2. After stirring at −20 °C for 15 min, *tert*-butylhydroperoxide (170 μL, 2 equiv, 0.92 mmol), previously dried on activated 4 Å molecular sieves, was added dropwise. After the mixture was stirred for 15 h under N_2 at −20 °C, the reaction was quenched by adding a solution of 400 mg of citric acid and 1.32 g of $FeSO_4 \cdot 7H_2O$ in 4 mL of H_2O at 0 °C. After 10 min the aqueous layer was extracted twice with Et_2O and the combined organic layers were poured into 4 mL of a precooled (0 °C) solution of 30% NaOH (w/v) in saturated brine and stirred for 1 h. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine and dried over Na_2SO_4. After the solvent was evaporated 169 mg of the crude product were obtained. Purification by flash chromatography (petroleum ether:ethyl acetate 5:1) led to 80 mg (54% yield) of the pure (3,4-*cis*)-(2*R*)-1-(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexan-2-ol as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33–7.19 (5H, m); 3.61 (2H, appt, $J=5.1$ Hz); 3.58–3.53 (1H, m); 3.06 (1H, dt, $J=7.8$, 4.4 Hz); 3.00 (1H, dd, $J=6.6$, 4.4 Hz); 2.89 (1H, ddd, $J=14.4$, 8.9, 5.9 Hz); 2.77 (1H, ddd, $J=13.9$, 8.9, 7.22 Hz); 2.42 (1H, bs); 2.00 (1H, dddd, $J=14.0$, 12.1, 7.4, 4.7 Hz); 1.94–1.85 (1H, m); 0.94 (9H, s); 0.11 (6H, s).

syn-(3,4-cis)-(2R,3R,4R)-1,2-di(tert-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexane **28**. To a stirred solution of -(3,4-*cis*)-(2*S*)-1-(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexan-2-ol (161 mg, 0.5 mmol, 1 equiv) in 1 mL of dry CH_2Cl_2, *tert*-butyldimethylsilyl chloride (113 mg, 0.75 mmol, 1.05 equiv) and imidazole (85 mg, 1.25 mmol, 2.5 equiv) were added, under N_2, and the mixture stirred for 5 h. The reaction was quenched with H_2O; the aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 204 mg (94%, yield) of **28** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.37–7.20 (5H, m); 3.69–3.52 (3H, m); 3.10–3.00 (1H, m); 2.97–2.73 (3H, m); 2.15–1.97 (1H, m); 1.81–1.60 (1H, m); 0.94 (9H, s); 0.91 (9H, m); 0.16 (3H, s); 0.11 (3H, s); 0.08 (3H, s); 0.07 (3H, s).

3.4.3. Preparation of *syn*-(3,4-*trans*)-(2*R*,3*R*,4*S*)-1,2-di(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexane 29 and *anti*-(3,4-*trans*)-(2*R*,3*S*,4*R*)-1,2-di(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexane 30. *(3E)-(2S)-6-Phenylhex-3-enyl-1,2-diol*[34] To a stirred solution of **31** (835 mg, 3.6 mmol, 1.0 equiv) in 18 mL of dry cyclohexane, diphenyl sulfide (786 mg, 3.6 mmol, 1.0 equiv) was added under N_2. The solution was irradiated by a water-cooled high-pressure mercury lamp for 11 h at room temperature. The reaction mixture was then concentrated to give 1.6 g of the residue containing **31** and **32** in a 9:91 ratio (by ^{1}H NMR analysis). ^{1}H NMR ($CDCl_3$, 200 MHz) δ, **32**: 7.30–7.10 (5H, m); 5.79 (1H, dt, $J=15.4$, 6.6 Hz); 5.43 (1H, ddt, $J=15.3$, 7.8, 1.4 Hz); 4.42 (1H, ddd, $J=8.0$, 7.8, 6.2 Hz); 4.01 (1H, dd, $J=8.1$, 6.1 Hz); 3.49 (1H, appt, $J=8.0$ Hz); 2.72–2.62 (2H, m); 2.40–2.26 (2H, m); 1.38 (3H, s); 1.34 (3H, s). The crude was dissolved in a solution of 18 mL of THF and 4.5 mL of 10% HCl and the mixture was stirred at room temperature overnight. Solid $NaHCO_3$ was added until CO_2 evolution finished; then the mixture was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether:ethyl acetate 1:1–1:2) to give 421 mg (61% yield) of (3*E*)-(2*S*)-6-phenylhex-3-enyl-1,2-diol as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.34–7.13 (5H, m); 5.81 (1H, dtd, $J=15.5$, 6.7, 1.1 Hz); 5.44 (1H, ddt, $J=15.5$, 6.3, 1.4 Hz); 4.18 (1H, ddd, $J=7.0$, 6.3, 3.6 Hz); 3.59 (1H, dd, $J=11.1$, 3.6 Hz); 3.45 (1H, dd, $J=11.1$, 7.0 Hz); 2.76–2.26 (2H, m); 2.45–2.31 (2H, m); 1.98 (1H, bs); 1.81 (1H, bs). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.5; 133.1; 129.3; 128.4; 128.3; 125.9; 73.0; 66.5; 35.4; 34.0.

(3E)-(2S)-1-(tert-Butyldimethylsilyloxy)-6-phenylhex-3-en-2-ol. To a stirred solution of (3*E*)-(2*S*)-6-phenylhex-3-enyl-1,2-diol (421 mg, 2.2 mmol, 1 equiv) in 8 mL of dry CH_2Cl_2, *tert*-butyldimethylsilyl chloride (332 mg, 2.2 mmol, 1.0 equiv) and imidazole (373 mg, 5.5 mmol, 2.5 equiv) were added, under N_2, and the mixture stirred at room temperature for 6 h. The reaction was quenched with H_2O; the aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 629 mg (93% yield) of (3*E*)-(2*S*)-1-(*tert*-butyldimethylsilyloxy)-6-phenylhex-3-en-2-ol as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.30–7.13 (5H, m); 5.81 (1H, dtd, $J=15.5$, 6.6, 1.0 Hz); 5.42 (1H, ddt, $J=15.5$, 6.6, 1.4 Hz); 4.16–4.05 (1H, m); 3.59 (1H, dd, $J=10.0$, 3.6 Hz); 3.38 (1H, dd, $J=10.0$, 8.0 Hz); 2.75–2.64 (2H, m); 2.43–2.28 (2H, m); 1.67 (1H, bs); 0.91 (9H, s); 0.07 (6H, s); ^{13}C–NMR ($CDCl_3$, 50 MHz) δ: 141.7; 132.8; 128.8; 128.4; 128.3; 125.8; 72.8; 67.3; 35.5; 34.2; 25.9; 18.3; −5.3.

syn- and anti-(3,4-trans)-(2R)-1-(tert-Butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexan-2-ol. *m*-CPBA (740 mg, 3.0 mmol, 1.5 equiv) was added to a cooled (0 °C) solution of (3*E*)-(2*S*)-1-(*tert*-butyldimethylsilyloxy)-6-phenylhex-3-en-2-ol (610 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2. The mixture was allowed to reach room temperature and then

stirred overnight. The mixture was diluted with CH_2Cl_2, washed twice with satd $Na_2S_2O_3$, twice with 1 M NaOH solution and dried over Na_2SO_4. The crude was purified by flash chromatography (petroleum ether: dichloromethane 1:1), to afford 231 mg (36% yield) of the *syn*-epoxide and 215 mg (33% yield) of the *anti*-epoxide both white solids. *syn*-Epoxide: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.34–7.16 (5H, m); 3.76–3.69 (1H, A part of ABX spin system); 3.69–3.61 (1H, B part of ABX spin system); 3.57–3.44 (1H, m); 3.00 (1H, ddd, J=6.3, 5.1, 2.2 Hz); 2.85–2.69 (2H,m); 2.81 (1H, dd, J=5.3, 2.2 Hz); 2.35 (1H, bs); 2.01–1.79 (2H, m); 0.90 (9H, s); 0.09 (3H, s); 0.08 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.1; 128.5; 128.4; 126.1; 71.0; 64.3; 58.2; 56.1; 33.5; 32.2; 25.8; 18.3; −5.4. *anti*-Epoxide: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.32–7.17 (5H, m); 3.65–3.54 (3H, m); 2.99 (1H, ddd, J=5.8, 5.8, 2.3 Hz); 2.87–2.68 (2H, m); 2.82 (1H, dd, J=3.6, 2.3 Hz); 2.21 (1H, d, J=5.7 Hz); 1.93–1.84 (2H, m); 0.90 (9H, s); 0.07 (6H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.1; 128.5; 128.4; 126.1; 70.5; 64.5; 58.9; 54.9; 33.4; 32.2; 25.8; 18.2; −5.4, −5.4.

syn-(3,4-trans)-(2R,3R,4S)-1,2-Di(tert-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexane **29**. To a stirred solution of *syn*-(3,4-*trans*)-(2*R*)-1-(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexan-2-ol (231 mg, 0.72 mmol, 1 equiv) in 7 mL of dry CH_2Cl_2, *tert*-butyldimethylsilyl chloride (163 mg, 1.08 mmol, 1.5 equiv) and imidazole (123 mg, 1.8 mmol, 2.5 equiv) were added, under N_2, and the mixture stirred at room temperature for 2 h. The reaction was quenched with H_2O; the aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 325 mg (100% yield) of **29** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31–7.16 (5H, m); 3.69 (1H, ddd, J=5.6, 5.4, 3.8 Hz); 3.61 (1H, dd, J=10.2, 5.4 Hz); 3.56 (1H, dd, J=10.2, 5.6 Hz); 2.97 (1H, ddd, J=6.7, 4.8, 2.2 Hz); 2.85 (1H, dd, J=3.8, 2.2 Hz); 2.83–2.67 (2H, m); 1.95–1.75 (2H, m); 0.89 (9H, s); 0.87 (9H, s); 0.05 (9H, s); 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.3; 128.4; 128.3; 125.9; 71.7; 65.8; 59.1; 54.9; 33.7; 32.3; 25.9; 25.8; 18.4; 18.2; −4.6; −4.7; −5.3; −5.4.

anti-(3,4-trans)-(2R,3S,4R)-1,2-Di(tert-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexane **30**. To a stirred solution of *anti*-(3,4-*trans*)-(2*R*)-1-(*tert*-butyldimethylsilyloxy)-3,4-epoxy-6-phenylhexan-2-ol (215 mg, 0.67 mmol, 1 equiv) in 7 mL of dry CH_2Cl_2, *tert*-butyldimethylsilyl chloride (152 mg, 1.01 mmol, 1.5 equiv) and imidazole (114 mg, 1.68 mmol, 2.5 equiv) were added, under N_2, and the mixture stirred at room temperature for 2 h. The reaction was quenched with H_2O; the aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 300 mg (100% yield) of **30** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30–7.15 (5H, m); 3.55 (2H, d, J=6.5 Hz); 3.40 (1H, td, J=6.5, 6.0 Hz); 2.93 (1H, ddd, J=6.7, 4.5, 2.2 Hz); 2.80 (1H, dd, J=6.0, 2.2 Hz); 2.77–2.67 (2H, m); 1.96–1.76 (2H, m); 0.89 (9H, s); 0.88 (9H, s); 0.09 (3H, s); 0.06 (3H, s); 0.05 (3H, s); 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.3; 128.4; 128.3; 126.0; 74.2; 65.1; 60.8; 55.6; 33.7; 32.2; 25.9; 25.8; 18.3; 18.2; −4.7; −4.8; −5.4; −5.4.

3.5. Isomerization of oxiranes with LIDAKOR and LICKOR

3.5.1. General procedure. Hexane was stripped off from a solution of BuLi (0.74 mL of a 1.5 M solution, 2 equiv, 1.00 mmol both for LIDAKOR and LICKOR), and precooled THF (1.0 mL) was added at −78 °C under N_2, followed by diisopropylamine (112 mg, 2 equiv, 1.00 mmol for LIDAKOR) and potassium *tert*-butoxide (124 mg, 2 equiv, 1.00 mmol for LIDAKOR, 124 mg, 2 equiv, 1.00 mmol for LICKOR). The mixture was stirred at −78 °C for 45 min and the oxirane (1 equiv, 0.50 mmol) was added and allowed to react at −50 °C; after 15 h the reaction mixture was warmed up to room temperature, quenched with H_2O and extracted twice with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent the residue was purified.

3.5.2. (*trans*-2-Phenylcyclopropyl)methanol 11.[30] The procedure with 2.2 equiv of LIDAKOR was used on the epoxide **8** obtaining 76 mg of the crude product which was purified by flash chromatography (petroleum ether:ethyl acetate 2:1) giving 60 mg (66% yield) of **11** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.25–6.95 (5H, m); 3.58 (2H, d, J=6.8 Hz); 1.92 (1H, bs); 1.79 (1H, appdt, J=8.0, 5.2 Hz); 1.51–1.33 (1H, m); 0.99–0.85 (2H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.3; 128.2; 125.7; 125.5; 66.4; 25.2; 21.2;13.8.

3.5.3. 1-(*trans*-2-Phenylcyclopropyl)-2-methylpropan-1-ol 15.[40] The procedure with 2.2 equiv of LIDAKOR was used on the 67:33 *cis:trans* diasteromeric mixture of epoxide **12** obtaining, after purification by flash chromatography (eluent: CH_2Cl_2), 64 mg (64% yield) of the *anti*-**15** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.34–7.07 (5H, m); 2.95 (1H, appt, J=6.2 Hz); 1.98–1.80 (2H, m); 1.51 (1H, bs); 1.35–1.20 (1H, m); 1.04–0.96 (2H, m); 1.03 (6H, d, J=6.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.7; 128.3; 125.8; 125.5; 80.5; 34.3; 27.5; 20.3; 18.7; 18.0; 14.4. MS (*m/z*, %): 190 (7, M^+); 173 (1, M^+−OH); 147 (8); 129 (54); 127 (71); 117 (61); 115 (76); 102 (100); 91 (45); 89 (59); 77 (84).

3.5.4. 1-(*trans*-2-Phenylcyclopropyl)ethan-1-ol 16.[41] The procedure with 2.2 equiv of LIDAKOR was used on the epoxide **13** obtaining 97 mg of the crude product which was purified by flash chromatography (petroleum ether:ethyl acetate 5:2) giving 51 mg (60% yield) of **16** as a yellow oil and 13 mg (15% yield) of **18** as a pale yellow oil. **16**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.36–7.08 (5H, m); 3.41 (1H, dq, J=7.4, 6.3 Hz); 2.00–1.87 (1H, m); 1.84 (1H, bs); 1.35 (3H, d, J=6.3 Hz); 1.34–1.24 (1H, m); 1.00–0.88 (2H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.6; 128.3; 125.7; 125.5; 71.6; 30.7; 22.3; 21.2; 13.3.

3.5.5. 5-Phenylpent-1-en-3-ol 18. The procedure with 2.2 equiv of LICKOR was used on the epoxide **13** obtaining 62 mg of the crude product which was purified by flash chromatography (petroleum ether:ethyl acetate 3:1) giving 42 mg (52% yield) of **18** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.38–7.21 (5H, m); 5.95 (1H, ddd, J=17.2, 10.4 Hz); 5.28 (1H, appdt, J=17.2, 1.4 Hz); 5.18 (1H,

appdt, $J=10.4$, 1.4 Hz); 4.24–4.10 (1H, m); 2.76 (2H, td, $J=7.9$, 3.5 Hz); 1.97–1.83 (2H, m); 1.61 (1H, d, $J=$ 4.1 Hz).

3.5.6. 2-(*trans*-2-Phenylcyclopropyl)propan-2-ol 17.[42] The procedure with 2.2 equiv of LIDAKOR was used on the epoxide **14** obtaining 136 mg of the crude product which was purified by flash chromatography (petroleum ether:-ethyl acetate 3:1) giving 105 mg (67% yield) of **17** and 12 mg (7% yield) of **19** both as yellow oils. **17**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.45–7.20 (5H, m); 2.09 (1H, appdt, $J=8.9$, 5.1 Hz); 1.61 (1H, bs); 1.43 (6H, s); 1.42–1.34 (1H, m); 1.19 (1H, ddd, $J=8.9$, 6.0, 5.1 Hz); 0.99 (1H, appdt, $J=$ 8.9, 5.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.1; 128.2; 125.9; 125.3; 69.4; 34.1; 29.1; 28.9; 19.2; 11.7.

3.5.7. 5-Phenyl-2-methylpent-1-en-3-ol 19. The procedure with 2.2 equiv of LICKOR was used on the epoxide 14 obtaining 59 mg of the crude product which was purified by flash chromatography (petroleum ether:ethyl acetate 3:1) giving 46 mg (57% yield) of **19** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.27–7.05 (5H, m); 4.97 (1H, br s); 4.88 (1H, br s); 4.09 (1H, br t, $J=6.4$ Hz); 2.69 (2H, appq, $J=7.6$ Hz); 1.89 (2H, appquint, $J=7.6$ Hz); 1.74 (1H, bs); 1.29 (3H, s).

3.5.8. (*trans*-2-Vinylcyclopropyl)methanol 21.[30] The procedure with 2.2 equiv of LIDAKOR was used on the commercially available epoxide obtaining 186 mg of the crude product which was purified by flash chromatography (petroleum ether:ethyl acetate 2:1) giving 150 mg (75% yield) of **21** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.41 (1H, ddd, $J=17.2$, 10.1, 8.4 Hz); 5.06 (1H, ddd, $J=$ 17.2, 1.8, 0.5 Hz); 4.88 (1H, ddd, $J=10.1$, 1.8, 0.4 Hz); 3.51 (2H, d, $J=6.8$ Hz); 1.49 (1H, bs); 1.41–1.26 (1H, m); 1.25–1.09 (1H, m); 0.72–0.63 (2H, m).

3.5.9. (*E*)-1-Phenyl-3,4-epoxybut-1-en 25. The procedure with 2.2 equiv of LIDAKOR was used on the 1:1 *syn*:*anti* diasteromeric mixture of epoxide **22** obtaining, after purification by flash chromatography (petroleum ether:ethyl acetate 4:1), 40 mg (50% yield) of **25** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.39–7.18 (5H, m); 6.85 (1H, d, $J=16.0$ Hz); 5.90 (1H, dd, $J=16.0$, 8.0 Hz); 3.12–3.02 (1H, m); 2.88–2.74 (2H, m). MS (*m*/*z*, %): 146 (32, M^+); 117 (100); 115 (76); 102 (11); 90 (48); 50 (16).

3.5.10. (*E*,*Z*)-5-Phenyl-1-methoxypent-1-en-3-ol 26. The procedure with 2.2 equiv of LIDAKOR was used on the epoxide **23** obtaining 88 mg (83% yield) of a 20:80 *Z*/*E* diastereomeric mixture of **26** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: *Z*-**26**: 7.44–7.12 (5H, m); 6.08 (1H, d, $J=5.3$ Hz); 4.73–4.58 (2H, m); 3.50 (3H, s); 2.79 (2H, appt, $J=7.8$ Hz); 2.18–1.82 (3H, m); *E*-**26**: 7.44–7.12 (5H, m); 6.63 (1H, d, $J=12.7$ Hz); 4.93 (1H, dd, $J=12.7$, 8.5 Hz); 4.15 (1H, dt, $J=8.5$, 6.6 Hz); 3.64 (3H, s); 2.79 (2H, appt, $J=7.8$ Hz); 2.18–1.82 (3H, m).

3.5.11. 1-(*trans*-2-Phenylcyclopropyl)-2-methoxypropan-1-ol 27. The procedure with 2.2 equiv of LIDAKOR was used on the 64:36 diasteromeric mixture of epoxide **24** obtaining, after purification by flash chromatography (petroleum ether:ethyl acetate 2:1), 66 mg (63% yield) of a *syn*/*anti* diasteromeric mixture of **27** as a pale yellow oil. Major isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.38–7.04 (5H, m); 3.42 (3H, s); 3.38–3.25 (1H, m); 3.09–2.90 (1H, m); 2.44 (1H, d, $J=4.1$ Hz); 1.98–1.81 (1H, m); 1.24 (3H, bs); 1.18–0.82 (3H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.2; 128.3; 125.6; 125.5; 79.6; 78.1; 56.5; 25.7; 21.1; 14.9; 12.8. MS (*m*/*z*, %): 206 (1, M^+); 188 (5); 175 (10); 147 (21); 131 (52); 129 (100); 118 (72); 103 (69); 91 (100); 77 (84); 59 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.59; H, 8.78. Minor isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.38–7.04 (5H, m); 3.41 (3H, s); 3.38–3.25 (1H, m); 3.09–2.90 (1H, m); 2.56 (1H, d, $J=$ 3.4 Hz); 1.98–1.81 (1H, m); 1.21 (3H, bs); 1.18–0.82 (3H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.3; 128.2; 125.7; 125.4; 81.1; 76.2; 56.5; 24.4; 20.7; 13.6; 13.2.

3.5.12. (1*R*,2*R*,1′*R*,2′*R*)-1-(*trans*-2-Phenylcyclopropyl)-2,3-di-*tert*-butyldimethylsilyloxy-propan-1-ol 33a and 1-(*trans*-2-phenylcyclopropyl)-1,3-di-*tert*-butyldimethylsilyloxypropan-2-ol 33b. The procedure with 2.0 equiv of LIDAKOR was used on the *syn*-epoxide **28** (76 mg, 0.17 mmol) obtaining 66 mg of the crude product which was purified by flash chromatography (petroleum ether:-ethyl acetate 3:1) giving 57 mg (75% yield) of a mixture of **33a** and **33b** as a yellow oil in a 67/33 ratio. **33a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.21 (2H, m); 7.16–7.10 (1H, m); 7.09–7.03 (2H, m); 3.78 (1H, ddd, $J=7.5$, 4.8, 2.7 Hz); 3.70 (1H, dd, $J=9.7$, 7.5 Hz); 3.56 (1H, dd, $J=9.7$, 4.8 Hz); 3.20 (1H, ddd, $J=8.3$, 7.9, 2.7 Hz); 2.53 (1H, d, $J=8.3$ Hz); 2.03 (1H, ddd, $J=8.4$, 5.2, 4.4 Hz); 1.38–1.30 (1H, m); 0.94–0.84 (2H, m); 0.91 (9H, s); 0.89 (9H, s); 0.12 (3H, s); 0.11 (3H, s); 0.09 (6H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.0; 128.2; 125.8; 125.4; 75.1; 74.9; 62.2; 26.3; 25.9; 25.8; 21.5; 18.3; 18.1; 13.1; −4.3; −4.8; −5.4; −5.5. Anal. Calcd for $C_{24}H_{44}O_3Si_2$: C, 66.00; H, 10.15. Found: C, 66.19; H, 10.08. **33b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.21 (2H, m); 7.16–7.10 (1H, m); 7.09–7.03 (2H, m); 3.68–3.55 (3H, m); 3.47 (1H, dd, $J=7.4$; 2.6 Hz); 2.50 (1H, d, $J=6.8$ Hz); 1.88 (1H, ddd, $J=8.6$, 5.2, 4.8 Hz); 1.48 (1H, m); 0.94–0.84 (2H, m); 0.88 (9H, s); 0.87 (9H, s); 0.06 (3H, s); 0.05 (3H, s); 0.04 (3H, s); 0.03 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.7; 128.2; 125.7; 125.4; 74.8; 74.4; 63.4; 26.0; 25.9; 25.8; 22.1; 18.2; 18.1; 13.2; −4.0; −4.7; −5.3; −5.4.

3.5.13. (1*R*,2*R*,1′*S*,2′*S*)-1-(*trans*-2-Phenylcyclopropyl)-2,3-di-*tert*-butyldimethylsilyloxy-propan-1-ol 34a and 1-(*trans*-2-phenylcyclopropyl)-1,3-di-*tert*-butyldimethylsilyloxypropan-2-ol 34b. The procedure with 2.0 equiv of LIDAKOR was used on the *syn*-epoxide **29** (87 mg, 0.2 mmol) obtaining 79 mg of the crude product which was purified by flash chromatography (petroleum ether:-ethyl acetate 3:1) giving 50 mg (57% yield) of **34a** and 24 mg (28% yield) of **34b** both as yellow oils. **34a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27–7.22 (2H, m); 7.17–7.11 (1H, m); 7.07–7.03 (2H, m); 3.75 (1H, ddd, $J=6.7$, 5.4, 4.4 Hz); 3.68 (1H, d, $J=5.4$ Hz); 3.68 (1H, d, $J=6.7$ Hz); 3.45 (1H, bdd, $J=6.8$, 4.4 Hz); 2.88 (1H, bs); 1.94 (1H, ddd, $J=8.8$, 5.1, 5.0 Hz); 1.37 (1H, m); 1.11 (1H, ddd, $J=8.8$, 5.6, 4.9 Hz); 0.94–0.89 (1H, m); 0.88 (9H, s); 0.87 (9H, s); 0.08 (3H, s); 0.07 (3H, s); 0.04 (3H, s); 0.03 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.9; 128.3; 125.8; 125.4; 76.3; 75.0; 65.5; 25.9; 25.8; 24.4; 20.3; 18.2; 18.1; 12.7; −4.4; −4.8;

−5.4; −5.5. MS (*m*/*z*, %): 247 (8); 155 (18); 147 (20); 129 (24); 117 (19); 101 (19); 91 (18); 89 (30); 75 (43); 73 (100); 59 (14). Anal. Calcd for $C_{24}H_{44}O_3Si_2$: C, 66.00; H, 10.15. Found: C, 66.11; H, 10.19. **34b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27–7.22 (2H, m); 7.17–7.11 (1H, m); 7.07–7.04 (2H, m); 3.78–3.70 (2H, m); 3.67–3.60 (1H, m); 3.46 (1H, dd, J=7.2; 4.0 Hz); 2.51 (1H, bs); 1.91 (1H, ddd, J=8.1, 5.9, 4.6 Hz); 1.31 (1H, m); 0.98–0.87 (2H, m); 0.92 (9H, s); 0.89 (9H, s); 0.14 (3H, s); 0.09 (3H, s); 0.05 (3H, s); 0.04 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.5; 128.2; 125.7; 125.5; 75.6; 75.5; 63.7; 25.9; 25.9; 25.3; 20.4; 18.3; 18.2; 13.3; −4.0; −4.4; −5.3; −5.3. MS (*m*/*z*, %): 287 (2, M^+-H_2O -OTBDMS); 261 (18); 247 (7); 155 (15); 129 (21); 117 (27); 91 (16); 89 (34); 75 (52); 73 (100); 59 (15).

3.5.14. (1*R*,2*R*,1′*S*,2′*S*)-1-(*trans*-2-Phenylcyclopropyl)-1,2,3-propantriol 36. To a stirred solution of **34a** (26 mg, 0.06 mmol, 1.0 equiv) in THF (1.0 mL), TBAF·3H_2O (57 mg, 0.18 mmol, 3.0 equiv) and 20 μL of water were added. After 12 h at room temperature, evaporation of the solvent gave 30 mg of the crude product that was purified by flash chromatography (ethyl acetate:methanol 10:1) to give 10 mg (80% yield) of pure **36** as a colorless solid. $[\alpha]_D=-98.2°$ (c=0.22; methanol) ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.24–7.19 (2H, m); 7.12–7.06 (3H, m); 3.72 (1H, dd, J=10.3, 4.2 Hz); 3.68 (1H, ddd, J=6.2, 4.8, 4.2 Hz); 3.57 (1H, dd, J=10.3, 6.2 Hz); 3.23 (1H, dd, J=7.8, 4.8 Hz); 1.89 (1H, ddd, J=8.7, 5.0, 4.9 Hz); 1.35 (1H, m); 1.01 (1H, ddd, J=8.7, 5.5, 4.8 Hz); 0.91 (1H, ddd, J=8.7, 5.5, 4.9 Hz). ^{13}C NMR (CD_3OD, 100 MHz) δ: 144.1; 129.3; 126.8; 126.5; 76.5; 76.4; 64.6; 26.1; 21.9; 13.2. MS (*m*/*z*, %): 190 (8, M^+-H_2O); 159 (8); 147 (12); 129 (88); 117 (67); 115 (36); 104 (64); 91 (100, $C_7H_7^+$); 77 (20); 65 (23); 61 (45); 51 (21). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.11; H, 7.82.

To a stirred solution of **34b** (13 mg, 0.03 mmol, 1.0 equiv) in THF (0.5 mL), TBAF·3H_2O (28 mg, 0.09 mmol, 3.0 equiv) and 10 μL of water were added. After 12h at room temperature, evaporation of the solvent gave 20 mg of the crude product that was purified by flash chromatography (ethyl acetate:methanol 10:1) to give 5 mg (80% yield) of pure **36**, identical to that described above.

3.5.15. (1*S*,2*R*,1′*R*,2′*R*)-1-(*trans*-2-Phenylcyclopropyl)-2,3-di-*tert*-butyldimethylsilyloxy-propan-1-ol 35a and 1-(*trans*-2-phenylcyclopropyl)-1,3-di-*tert*-butyldimethylsilyloxypropan-2-ol 35b. The procedure with 2.0 equiv of LIDAKOR was used on the *anti*-epoxide **30** (87 mg, 0.2 mmol) obtaining 82 mg of the crude product which was purified by flash chromatography (petroleum ether:-ethyl acetate 3:1) giving 52 mg (59% yield) of **35a** and 25 mg (29% yield) of **35b** both as yellow oils. **35a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.21 (2H, m); 7.16–7.11 (1H, m); 7.05–7.01 (2H, m); 3.77 (1H, ddd, J=7.3, 4.8, 2.7 Hz); 3.69 (1H, dd, J=9.7, 7.3 Hz); 3.55 (1H, dd, J=9.7, 4.8 Hz); 3.27 (1H, ddd, J=7.9, 7.7, 2.7 Hz); 2.62 (1H, d, J=7.9 Hz); 1.81 (1H, ddd, J=8.7, 5.0, 4.3 Hz); 1.30 (1H, m); 1.14 (1H, ddd, J=8.7, 5.3, 5.3 Hz); 1.02 (1H, ddd, J=8.4, 5.3, 5.0 Hz); 0.89 (9H, s); 0.86 (9H, s); 0.05 (3H, s); 0.04 (3H, s); 0.03 (3H, s); −0.08 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.6; 128.2; 125.5; 125.4; 75.3; 74.3; 64.2; 26.5; 25.9; 25.8; 20.1; 18.3; 18.0; 14.0; −4.3; −5.1; −5.4; −5.5. Anal. Calcd for $C_{24}H_{44}O_3Si_2$: C, 66.00; H, 10.15. Found: C, 66.03; H, 10.10. **35b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.22 (2H, m); 7.17–7.11 (1H, m); 7.07–7.03 (2H, m); 3.65–3.55 (3H, m); 3.43 (1H, dd, J=7.8, 2.9 Hz); 2.51 (1H, d, J=5.9 Hz); 1.81 (1H, ddd, J=7.1, 6.8, 4.9 Hz); 1.39 (1H, m); 1.00 (2H, appt, J=7.1 Hz); 0.93 (9H, s); 0.88 (9H, s); 0.15 (3H, s); 0.10 (3H, s); 0.05 (3H, s); 0.04 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.3; 128.3; 125.9; 125.6; 75.1; 74.9; 63.4; 26.1; 25.9; 25.8; 20.4; 18.2; 18.2; 14.9; −3.8; −4.7; −5.3; −5.4.

3.5.16. (1*S*,2*R*,1′*R*,2′*R*)-1-(*trans*-2-Phenylcyclopropyl)-1,2,3-propantriol 37. To a stirred solution of **35a** (13 mg, 0.03 mmol, 1.0 equiv) in THF (0.5 mL), TBAF·3H_2O (28 mg, 0.09 mmol, 3.0 equiv) and 10 μL of water were added. After 12 h at room temperature, evaporation of the solvent gave 25 mg of the crude product that was purified by flash chromatography (ethyl acetate:methanol 10:1) to give 5 mg (80% yield) of pure **37** as a colourless solid. $[\alpha]_D$ +52.6° (c=0.48; methanol) ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.24–7.19 (2H, m); 7.13–7.06 (3H, m); 3.68 (1H, dd, J=10.1, 3.7 Hz); 3.61 (1H, ddd, J=6.0, 4.8, 3.7 Hz); 3.57 (1H, dd, J=10.1, 6.0 Hz); 3.11 (1H, dd, J=8.4, 4.8 Hz); 1.87 (1H, ddd, J=8.7, 5.1, 4.9 Hz); 1.31 (1H, m); 1.06 (1H, ddd, J=8.7, 5.5, 4.9 Hz); 0.98 (1H, ddd, J=8.5, 5.1, 4.9 Hz). ^{13}C NMR (CD_3OD, 100 MHz) δ: 143.9; 129.3; 126.8; 126.5; 76.6; 76.4; 64.4; 27.3; 21.9; 14.4. MS (*m*/*z*, %): 190 (1, M^+-H_2O); 159 (10); 147 (8); 129 (100); 128 (25); 118 (37); 117 (68); 115 (35); 104 (76); 91 (98, $C_7H_7^+$); 84 (17); 77 (26); 65 (20); 61 (49); 51 (26). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.32; H, 7.69.

To a stirred solution of **35b** (13 mg, 0.03 mmol, 1.0 equiv) in THF (0.5 mL), TBAF·3H_2O (28 mg, 0.09 mmol, 3.0 equiv) and 10 μL of water were added. After 12 h at room temperature, evaporation of the solvent gave 26 mg of the crude product that was purified by flash chromatography (ethyl acetate:methanol 10:1) to give 4 mg (64% yield) of pure **37**, identical to that described above.

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Preparation of α-silyl- or α,α-bis(silyl)-substituted alkylcopper reagents and their synthetic use

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Abstract—Treatment of chlorobis(methyldiphenylsilyl)methyllithium with various alkyl and aryl Grignard reagents and CuCN·2LiCl afforded 1,1-disilylalkylcopper species. The aerobic oxidation of the resulting copper reagents provided a variety of acylsilanes in good yields. Meanwhile, treatment of dichloro(methyldiphenylsilyl)methyllithum with $Bu_2CuLi·LiCN$ provided 1-cyano-1-silylalkylcopper species via consecutive double 1,2-migration of alkyl and cyano groups.

1. Introduction

Organocuprates and organocoppers are highly important tools for organic synthesis, and numerous reports have been published on the preparative methods and reactions.[1] There are several types of copper reagents, such as the classical Gilman cuprates, cyanocuprates, hetero-cuprates, alkylcopper borontrifluoride complexes, and so on.[2] Most of them are prepared according to two approaches: (1) transmetalation from organolithium or magnesium compounds with copper salts and (2) direct metalation of organic halides with active copper.

1,2-Migration of an alkyl group on the metal center in metal carbenoid reagents is a typical reaction of an organometallic complex.[3] This process has been successfully utilized in alkylation of α-haloalkylmetals (metal=Zn, B, Al, Cu, Mn, etc.) and allows facile introduction of an alkyl group to the organometallic reagents.[4] The method would provide us with a facile route to a wide variety of metal reagents from relatively simple and easily accessible organometallics.

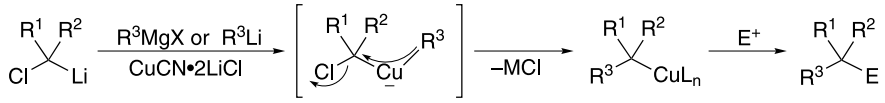
In this context, we have chosen the combination of lithium carbenoid, copper cyanide, and Grignard reagents/organolithium compounds (Scheme 1).

Here we wish to report the 1,2-migration reaction of the alkyl group from copper to the adjacent carbon bearing a chlorine atom in copper carbenoid reagents.[5] We also describe the reaction protocol in which organocuprates enable sequential introduction of two different groups into α,α-dichlorosilylmethyllithium.[6]

2. Results and discussion

2.1. Preparation of 1,1-disilylalkylcoppers and their conversion into various acylsilanes via aerobic oxidation

An addition of *n*-BuLi to a THF solution of $(Ph_2MeSi)_2CCl_2$ (**1**)[7] at −78 °C provided chlorodisilylmethyllithium **2** quantitatively via chlorine–lithium exchange in 10 min. Then, lithium carbenoid **2** was then treated with *n*-BuMgBr



Scheme 1.

Keywords: Carbenoids; 1,2-Migration; Organocopper reagents; Halogen–lithium exchange; Grignard reagents.
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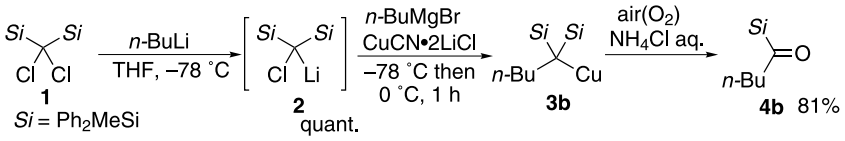


Scheme 2.

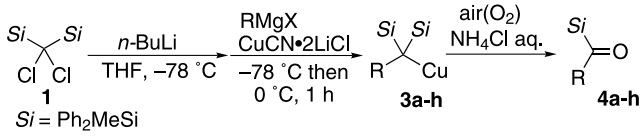
(1.2 equiv in THF) and CuCN·2LiCl (1.2 equiv in THF), and the mixture was stirred at 0 °C. After 1 h stirring in the presence of a copper salt, the requisite organocopper species **3b** was generated via a 1,2-alkyl migration (Scheme 2).[8] Hexane (5 mL) and NH_4Cl aq (10 mL) were added, and the mixture was exposed to air with stirring for 0.5 h. During this period, the aqueous layer turned blue, indicating that copper(I) was oxidized to copper(II). Extractive workup followed by purification afforded acylsilane **4b** in 81% yield.

Oxidation of the α,α-disilylalkylcopper species **3a–h** with air provided the corresponding acylsilanes in good yields (Table 1). Several features of this reaction are noteworthy. Various primary and secondary Grignard reagents can be employed in the reaction. Interestingly, the reaction with crotylmagnesium chloride yielded 3-pentenoylsilane **4h** without contamination of 2-methyl-3-butenoylsilane (entry 8). Unfortunately, these intermediary copper species did not react with electrophiles such as either alkyl halides or acyl chlorides. Aerobic oxidation of organocoppers often results in the Ullmann coupling reaction.[9] In these cases, however, the Ullmann-type coupling products were not observed at all: no dimerization reaction of the disilylalkyl group nor coupling between the disilylalkyl group and the cyano group proceeded. We presume that the reasons for the selective formation of acylsilanes would be the bulkiness of the disilylalkyl moiety and the absence of a cyano ligand on the copper(I) center in copper species **3**.

Furthermore, we found that various aromatic Grignard reagents can be employed favorably in this reaction protocol (Table 2). Unfortunately, disilylphenylmethylcopper under the standard conditions caused considerable hydrolysis due to the increased reactivity of the benzylic copper (entry 1).[10] In this case, however, oxidation of the intermediary copper species in the presence of 4 equiv of pyridine to yield benzoylsilane **6a** in 84% yield. Additionally, several features deserve to be pointed out. As shown in entries 2 and 3, *p*-FC_6H_4MgBr and C_6F_5MgBr, which are electron-deficient and less nucleophilic arylmagnesiums, can be efficiently employed. Interestingly, 2-thienyllithium which usually acts as a non-transferable or dummy ligand[1,11] in mixed homocuprates or mixed higher order cyanocuprates, provided none of acylsilanes. However, an addition of magnesium bromide to 2-thienyllithium resulted in the formation of the corresponding acylsilane **6d** in good yields (Table 2, entries 4 and 5). Furthermore, this reaction procedure can be applied to the synthesis of various aroylsilanes in entries 6–10. It enables to introduce silyl carbonyl groups into large π-conjugated system such as tolan, naphthalene, and phenanthrene.

Further application of (silyldichloromethyl)disilane **8** to the procedure described above worked well to yield benzoyldisilane **10** selectively in 51% yield (Scheme 3). Curiously, the diphenylmethylsilyl group was cleaved selectively and benzoylsilane **6a** was not obtained at all.

Table 1. Preparation of 1,1-disilylalkylcoppers and their aerobic oxidation



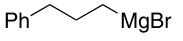
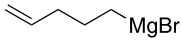
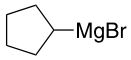
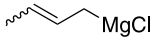
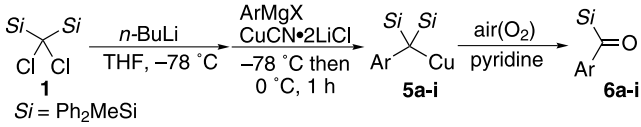
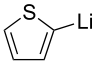
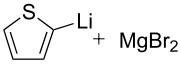
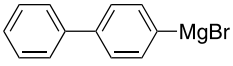
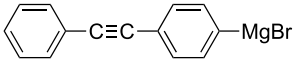
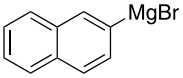
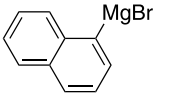
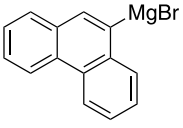
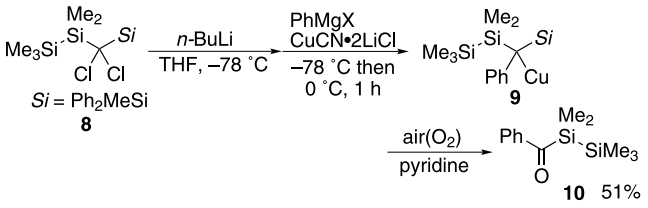
Entry	RMgX	**4** Yield/%
1	EtMgBr	**4a** 75
2	*n*-BuMgBr	**4b** 81
3		**4c** 75
4		**4d** 65
5	*i*-PrMgBr	**4e** 88
6		**4f** 84
7	MeMgBr	**4g** 47
8		**4h** 47

Table 2. Synthesis of aroylsilanes via aerobic oxidation



Entry	ArMgX	**6** Yield/%
1	PhMgBr	**6a** 84
2	*p*-FC_6H_4MgBr	**6b** 72
3	C_6F_5MgBr	**6c** 76
4		—[a]
5		**6d** 75
6		**6e** 80
7		**6f** 85
8		**6g** 82
9		**6h** 41
10		**6i** 73

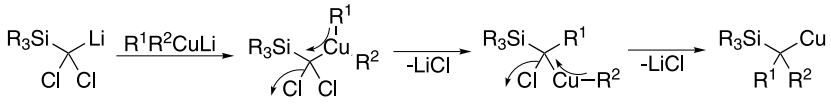
[a] Disilylacetonitrile **7** instead of silyl(2-thienyl)ketone **6d** was obtained in 81% yield.



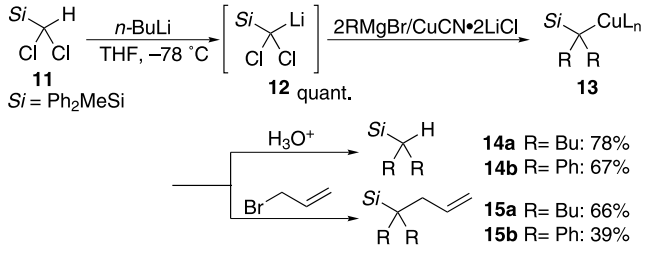
Scheme 3.

of the intermediary coppers **13** with allyl bromide proceeded successfully to furnish the allylated compounds **15a** and **15b**.

Next, we attempted double butylation of **11** by utilizing $Bu_2CuLi\cdot LiCN$ which is widely known as a cyano-Gilman cuprate. Contrary to our expectations, it turned out to provide butylation–cyanation product **16a** in good yield



Scheme 4.



Scheme 5.

2.2. Consecutive double alkylation of α,α-dichlorosilylmethyllithium by organocopper reagents

We next contemplated introduction of two different alkyl groups into dihalo carbenoids via double 1,2-migration (Scheme 4).

An addition of *n*-BuLi to a solution of dichloromethylsilane **11**[12] in THF at −78 °C resulted in the quantitative deprotonation to yield silyldichloromethyllithium **12**. Then, this dihalo-lithium carbenoid was added to organocopper reagents derived from copper cyanide. As expected from Scheme 1, the use of the copper reagent prepared by premixing butylmagnesium bromide with CuCN in a 2:1 ratio at 0 °C yielded the dibutylated product **14a** via the consecutive migration in good yield after aqueous workup (Scheme 5).[13] The use of phenylmagnesium bromide instead of BuMgBr also afforded the diphenylated product **14b** in 67% yield. The addition of allyl bromide before quenching resulted in trapping of the intermediary copper species to provide **15a** and **15b**. The nucleophilic trapping

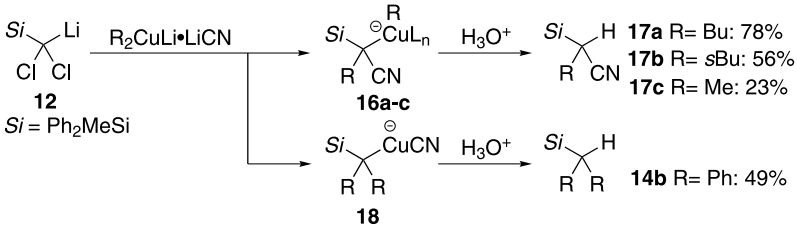
without the formation of dibutylated silane **14a** (Scheme 6). The reaction with $sBu_2CuLi\cdot LiCN$ and $Me_2CuLi\cdot LiCN$ also furnished α-cyano silanes **17b** in 56% yield and **17c** in 23% yield, respectively. Furthermore, in the case of $Ph_2CuLi\cdot LiCN$, the reaction fashion was reversed to obtain the diphenylated product **14b** in a moderate yield.

The intermediary copper species **16a** reacted with a variety of electrophiles such as allyl bromide, methyl iodide, acyl chlorides, and aldehydes.[14] Table 3 summarizes the trapping experiment of the α-cyanoalkylcopper species. The reaction with aldehydes provided α,β-unsaturated nitriles **19e** and **19f/19f′** via the Peterson elimination of the initial adducts.[15] In entry 7, aerobic oxidation of this copper reagent in the presence of pyridine afforded pentanoyl cyanide (**19g**) in a moderate yield.

In addition to alkylation–cyanation, consecutive butylation–phenylation was accomplished by sequential treatment of dichloromethyllithium **12** with BuCu and PhMgBr. The employment of BuCu derived from BuLi and copper iodide worked nicely to provide the desired butylation–phenylation product **21**. The resulting copper compound **20** can be coupled with allyl bromide and acetyl chloride to give the corresponding adducts in moderate yields. The use of a combination of BuLi and CuCN for butylation of **12** resulted in a formation of significant amount of the alkylation–cyanation product (Scheme 7).

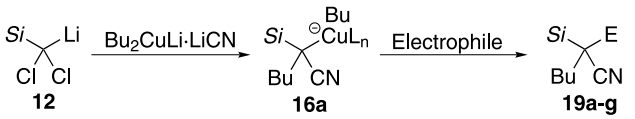
3. Conclusion

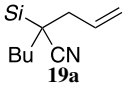
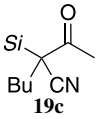
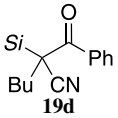
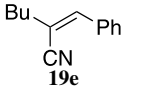
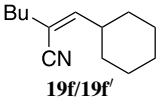
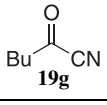
We have developed an easy and simple procedure which enables us to synthesize various kinds of acylsilanes from dichlorodisilylmethane and the corresponding Grignard



Scheme 6.

Table 3. Consecutive butylation–cyanation followed by C–C bond formation



Entry	Electrophile	Product	Yield/%
1	CH_2=$CHCH_2Br$	 **19a**	71
2	MeI	 **19b**	70
3	CH_3COCl	 **19c**	54
4	PhCOCl	 **19d**	57
5	PhCHO[a]	 **19e**	75 ($Z/E \geq 99/1$)
6	$cC_6H_{11}CHO$[b]	 **19f/19f'**	57 (Z/E=54/45)
7	air(O_2)[c]	 **19g**	51

[a] Conditions: $Bu_2CuLi \cdot LiCN$ (1.1 equiv), electrophile (2.0 equiv) were employed.
[b] $Bu_2CuLi \cdot LiCN$ (1.1 equiv), RCHO (3.0 equiv), Me_3SiCl (4.5 equiv) were employed. Me_3SiCl was used as a Lewis acid.
[c] The resultant copper reagent was exposed to air in the presence of 2 equiv pyridine at 0 °C for 30 min.

reagents. Treatment of chlorodisilylmethyllithium with various Grignard reagents and CuCN·2LiCl efficiently affords 1,1-disilylalkylcopper species. The aerobic oxidation of the resulting organocoppers provides a variety of acylsilanes in good yields. In a second part, we have also demonstrated a very different reactivity between two types of cyanocuprates prepared from CuCN and either Grignard reagents or lithium reagents. Treatment of silyldichloromethyllithium with the copper species prepared from BuMgBr and CuCN (2BuMgBr/CuCN) provides dibutylation products. On the other hand, $Bu_2CuLi \cdot LiCN$ (cyano-Gilman cuprate) yields butylation–cyanation products.

4. Experimental

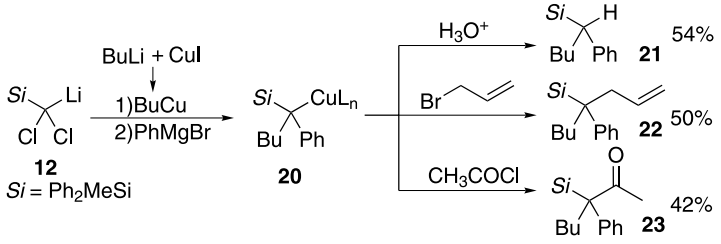
4.1. General information

Melting points were obtained a Yanako MP-50929 melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz), ^{13}C NMR (75.3 MHz) and ^{19}F NMR (282.5 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as a solvent, and chemical shifts were given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL JMS-700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merk Silica gel $60F_{254}$. Column chromatography was done with silica gel (Wakogel 200 mesh). The analyses were carried out at the Elemental Analysis Center of Kyoto University. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl before use. Grignard reagents were prepared from the corresponding alkyl halide and Mg turning (Nacalai tesque, INC). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

4.1.1. Preparation of dichlorobis(methyldiphenylsilyl)-methane (1). *n*-BuLi (21 mL, 1.6 M solution in hexane, 33 mmol) was added to a solution of diisopropylamine (4.9 mL, 35 mmol) in THF (20 mL) dropwise at 0 °C, and the mixture was stirred for 0.5 h. To a pre-cooled solution of dichloromethane (0.96 mL, 15 mmol) and (chloro)methyldiphenylsilane (6.3 mL, 30 mmol) in THF (30 mL) was added the resultant solution dropwise at −78 °C via a cannula. After the mixture was stirred for 0.5 h, the cooling bath was removed. After stirring for 0.5 h at room temperature, the mixture was poured into 1 M HCl and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Recrystallization of the residual white solid from hexane/ethyl acetate provided dichlorobis(methyldiphenylsilyl)methane (**1**, 6.1 g, 12.8 mmol) in 85% yield: Mp 138 °C; IR (nujol) 1427, 1254, 1107, 843, 802, 723, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6H), 7.34 (dd, J= 7.5, 8.1 Hz, 8H), 7.43 (t, J=7.5 Hz, 4H), 7.72 (d, J= 8.1 Hz, 8H); ^{13}C NMR ($CDCl_3$) δ −4.0, 71.4, 127.7, 130.1, 133.2, 136.3. Found: C, 67.91; H, 5.40%. Calcd for $C_{27}H_{26}Cl_2Si_2$: C, 67.90; H, 5.49%.

4.2. General procedure for the preparation of acylsilanes (4a) from dichlorodisilylmethane

Under argon atmosphere, to a solution of dichlorobis-(methyldiphenylsilyl)methane (**1**, 239 mg, 0.5 mmol) in



Scheme 7.

THF (3 mL) was added butyllithium (0.31 mL, 1.6 M solution in hexane, 0.5 mmol) dropwise at −78 °C and the solution was stirred for 5 min. Ethylmagnesium bromide (0.6 mL, 1.0 M solution in THF, 0.6 mmol) and CuCN·2LiCl (0.6 mL, 1.0 M solution in THF, 0.6 mmol) were added successively at −78 °C. After stirring for 1 h at 0 °C, saturated aqueous NH_4Cl (10 mL) and hexane (5 mL) were added. The mixture was stirred vigorously for 0.5 h under air at room temperature and then extracted with hexane. The organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided 1-(methyldiphenylsilyl)-1-propanone (**4b**, 95 mg, 0.37 mmol) in 75% yield as colorless oil. Spectral data for this compound were identical with those reported in the literature.[16]

4.2.1. 1-(Methyldiphenylsilyl)-1-pentanone (4b). R_f=0.58 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 3474, 2932, 1722, 1643, 1429, 1254, 1113, 793, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.79 (t, J=7.5 Hz, 3H), 1.18 (tq, J=7.5, 7.5 Hz, 2H), 1.44 (tt, J=7.5, 7.5 Hz, 2H), 2.65 (t, J=7.5 Hz, 2H), 7.34–7.47 (m, 6H), 7.55–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.4, 13.7, 22.2, 24.1, 46.4, 128.3, 130.2, 133.0, 135.1, 245.1. Found: C, 76.79; H, 7.86%. Calcd for $C_{18}H_{22}OSi$: C, 76.54; H, 7.85%.

4.2.2. 1-(Methyldiphenylsilyl)-4-phenyl-1-butanone (4c, known compound). Spectral data for this compound were identical with those reported in the literature.[17]

4.2.3. 1-(Methyldiphenylsilyl)-5-hexen-1-one (4d). R_f=0.45 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 3071, 2936, 1643, 1429, 1254, 1113, 997, 912, 793, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 1.58 (tt, J=6.9, 7.2 Hz, 2H), 1.94 (dt, J=6.6, 6.9 Hz, 2H), 2.66 (t, J=7.2 Hz, 2H), 4.89 (d, J=11.1 Hz, 1H), 4.90 (d, J=16.2 Hz, 1H), 5.58–5.74 (m, 1H), 7.35–7.48 (m, 6H), 7.55–7.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.3, 21.2, 33.0, 48.8, 115.0, 128.2, 130.1, 132.8, 135.0, 138.1, 244.4. Found: C, 77.43; H, 7.40%. Calcd for $C_{19}H_{22}OSi$: C, 77.50; H, 7.53%.

4.2.4. 2-Methyl-1-(methyldiphenylsilyl)-1-propanone (4e). R_f=0.58 (hexane/ethyl acetate=10/1); colorless oil; a paleIR (neat) 2968, 1639, 1429, 1254, 1113, 986, 793, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H), 0.91 (d, J=6.9 Hz, 6H), 3.02 (sept, J=6.9 Hz, 1H), 7.34–7.47 (m, 6H), 7.56–7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.7, 16.5, 45.8, 128.1, 130.0, 133.2, 135.0, 247.1. Found: C, 76.16; H, 7.55%. Calcd for $C_{17}H_{20}OSi$: C, 76.07; H, 7.51%.

4.2.5. Cyclopentyl methyldiphenylsilyl ketone (4f). R_f=0.45 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 2957, 2866, 1638, 1429, 1254, 1111, 793, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H), 1.40–1.53 (m, 6H), 1.60–1.77 (m, 2H), 3.24–3.36 (m, 1H), 7.30–7.47 (m, 6H), 7.56–7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.8, 26.0, 26.9, 56.9, 128.1, 129.9, 133.2, 135.0, 245.1. Found: C, 77.43; H, 7.53%. Calcd for $C_{19}H_{22}OSi$: C, 77.50; H, 7.53%.

4.2.6. Acetylmethyldiphenylsilane (4g, known compound). R_f=0.34 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 1643, 1429, 1340, 1254, 1113, 791, 731, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 2.32 (s, 3H), 7.36–7.48 (m, 6H), 7.59 (dd, J=1.5, 8.1 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ −5.6, 36.9, 128.3, 130.3, 132.7, 135.1, 243.9. Found: C, 74.71; H, 6.79%. Calcd for $C_{15}H_{16}OSi$: C, 74.95; H, 6.71%. Spectral data for this compound were identical with those reported in the literature.[18]

4.2.7. 1-(Methyldiphenylsilyl)-3-penten-1-one (*E*/*Z*=60/40) (4h). R_f=0.46 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 1645, 1429, 1254, 1113, 996, 793, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 1.8H), 0.76 (s, 1.2H), 1.45 (d, J=6.6 Hz, 1.2H), 1.60 (d, J=4.8 Hz, 1.8H), 3.32 (dd, J=1.2, 5.4 Hz, 1.2H), 3.40 (d, J=6.9 Hz, 0.8H), 5.25–5.42 (m, 1.2H), 5.37–5.50 (m, 0.4H), 5.54–5.67 (m, 0.4H), 7.35–7.50 (m, 6H), 7.55–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.2, −5.1, 13.1, 18.1, 48.0, 53.2, 120.7, 121.9, 128.1, 128.1, 128.2, 130.1, 130.1, 130.2, 132.6, 132.7, 135.0, 241.5, 242.1. HRMS (*m*/*z*) Found: 128.1270. Calcd for $C_{18}H_{20}OSi$: 280.1283.

4.2.8. Benzoylmethyldiphenylsilane (6a, known compound). Under argon atomosphere, to a solution of dichlorobis(methyldiphenylsilyl)methane (**1**, 239 mg, 0.5 mmol) in THF (3 mL) was added butyllithium (0.31 mL, 1.6 M solution in hexane, 0.5 mmol) dropwise at −78 °C and the solution was stirred for 5 min. Phenylmagnesium bromide (0.6 mL, 1.0 M solution in THF, 0.6 mmol) and CuCN·2LiCl (0.6 mL, 1.0 M solution in THF, 0.6 mmol) were added successively at −78 °C. After stirring for 1 h at 0 °C, pyridine (0.16 mL, 2.0 mmol) was added. The mixture was stirred for 1 h under air at 0 °C and then extracted with hexane. The organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided benzoylmethyldiphenylsilane (**6a**, 127 mg, 0.42 mmol) in 84% yield as clear, yellow oil. Spectral data for this compound were identical with those reported in the literature.[19] R_f=0.44 (hexane/ethyl acetate=10/1); IR (neat) 1612, 1589, 1576, 1447, 1429, 1252, 1209, 1173, 1111, 794, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3H), 7.31–7.50 (m, 9H), 7.60 (dd, J=1.5, 7.5 Hz, 4H), 7.77 (dd, J=1.5, 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −3.3, 128.2, 128.2, 128.5, 130.0, 132.9, 133.7, 135.1, 141.7, 232.0. Found: C, 79.68; H, 6.06%. Calcd for $C_{20}H_{18}OSi$: C, 79.43; H, 6.00%.

4.2.9. 4-Fluorobenzoylmethyldiphenylsilane (6b). R_f=0.44 (hexane/ethyl acetate=10/1); pale yellow oil; IR (neat) 3071, 1614, 1583, 1500, 1429, 1406, 1225, 1151, 1113, 843, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3H), 7.02 (t, J=9.0 Hz, 2H), 7.36–7.48 (m, 6H), 7.57–7.62 (m, 4H), 7.80 (dd, J=5.4, 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −3.2, (115.4, 115.7), 128.2, 130.0, (130.6, 130.7), 133.4, 134.9, (138.1, 138.7), (163.5, 166.9), 229.5; ^{19}F NMR ($CDCl_3$) δ −105.3. Found: C, 75.11; H, 5.42%. Calcd for $C_{20}H_{17}FOSi$: C, 74.97; H, 5.35%.

4.2.10. 2,3,4,5,6-Pentafluorobenzoylmethyldiphenylsilane (6c). R_f=0.56 (hexane/ethyl acetate=10/1); yellow oil; IR (neat) 3074, 1649, 1518, 1489, 1429, 1306, 1117, 974, 731, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3H), 7.36–7.50 (m, 6H), 7.54–7.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.5, 128.3, 130.6, 130.8, 135.0, 136.3, 138.2, 141.2, 141.6, 143.2, 143.7, 229.2; ^{19}F NMR ($CDCl_3$) δ −160.1,

−150.4, −142.9. Found: C, 61.21; H, 3.36%. Calcd for $C_{20}H_{13}F_5OSi$: C, 61.22; H, 3.34%.

4.2.11. Methyldiphenylsilyl 2-thienyl ketone (6d). R_f=0.53 (hexane/ethyl acetate=5/1); yellow oil; IR (KBr) 3068, 1570, 1512, 1428, 1406, 1230, 1113, 1051, 788, 731, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3H), 6.97 (t, J=4.5 Hz, 1H), 7.34 (d, J=4.5 Hz, 1H), 7.38–7.48 (m, 6H), 7.59 (d, J=4.5 Hz, 1H), 7.61–7.65 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −3.8, 128.2, 130.2, 133.2, 133.6, 134.6, 135.2, 151.2, 221.0. Found: C, 70.10; H, 5.33%. Calcd for $C_{18}H_{16}OSSi$: C, 70.09; H, 5.23%.

4.2.12. (4-Phenylbenzoyl)methyldiphenylsilane (6e). R_f=0.50 (hexane/ethyl acetate=5/1); yellow oil; IR (neat) 3069, 1593, 1556, 1429, 1217, 1177, 847, 486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3H), 7.34–7.49 (m, 6H), 7.55–7.61 (m, 4H), 7.62–7.67 (m, 4H), 7.86 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −3.1, 127.0, 127.1, 128.0, 128.1, 128.6, 128.7, 129.9, 133.6, 135.0, 139.7, 140.2, 145.3, 230.8. Found: C, 82.56; H, 5.99%. Calcd for $C_{26}H_{22}OSi$: C, 82.50; H, 5.86%.

4.2.13. [4-(Phenylethynyl)benzoyl]diphenylsilane (6f). R_f=0.35 (hexane/ethyl acetate=10/1); yellow oil; IR (neat) 3071, 2957, 1589, 1427, 1209, 1111, 756, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H), 7.19–7.33 (m, 9H), 7.35–7.42 (m, 4H), 7.59–7.64 (m, 4H), 7.76 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −3.3, 128.2, 128.2, 128.5, 130.0, 132.9, 133.7, 135.1, 141.7, 232.0. Found: C, 83.70; H, 5.41%. Calcd for $C_{28}H_{22}OSi$: C, 83.54; H, 5.51%.

4.2.14. 2-Naphthalene(methyldiphenylsilyl)methanone (6g). R_f=0.59 (hexane/ethyl acetate=5/1); yellow oil; IR (neat) 3069, 2959, 1595, 1429, 1252, 1177, 1113, 727, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 7.37–7.50 (m, 7H), 7.52–7.59 (m, 1H), 7.63–7.70 (m, 5H), 7.82 (d, J=8.1 Hz, 2H), 7.91 (dd, J=1.8, 8.1 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.1, 122.4, 126.4, 127.6, 128.1, 128.3, 128.4, 129.6, 129.9, 132.3, 132.3, 133.8, 135.0, 135.3, 139.1, 231.2. Found: C, 81.50; H, 5.96%. Calcd for $C_{20}H_{18}OSi$: C, 81.77; H, 5.72%.

4.2.15. 1-Naphthalene(methyldiphenylsilyl)methanone (6h). R_f=0.60 (hexane/ethyl acetate=5/1); yellow oil; IR (KBr) 3028, 1612, 1589, 1576, 1447, 1429, 1252, 1209, 1173, 1111, 794, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 3H), 7.30–7.46 (m, 7H), 7.48–7.59 (m, 2H), 7.62–7.66 (m, 4H), 7.75 (d, J=7.5 Hz, 1H), 7.85 (d, J=7.5 Hz, 1H), 7.91 (d, J=8.1 Hz, 1H), 8.70 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −3.1, 124.1, 125.7, 126.4, 128.1, 128.2, 128.2, 128.7, 129.9, 131.3, 132.5, 133.8, 135.0, 139.1, 236.8. Found: C, 81.63; H, 5.86%. Calcd for $C_{24}H_{20}OSi$: C, 81.77; H, 5.72%.

4.2.16. 9-Phenanthrene(methyldiphenylsilyl)methanone (6i). R_f=0.42 (hexane/ethyl acetate=5/1); yellow oil; IR (KBr) 3021, 1591, 1428, 1245, 1112, 892, 788, 722, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3H), 7.37–7.49 (m, 6H), 7.52 (d, J=3.9 Hz, 2H), 7.58–7.62 (m, 1H), 7.63–7.66 (m, 1H), 7.67–7.71 (m, 4H), 7.71–7.74 (m, 1H), 8.00 (s, 1H), 8.63 (d, J=8.1 Hz, 1H), 8.68 (d, J=8.1 Hz, 1H), 8.75 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −3.5, 122.6, 122.7, 126.7, 126.9, 127.2, 127.5, 127.7, 127.9, 128.3, 129.0, 130.1, 130.8, 131.8, 134.0, 134.6, 135.1, 138.2, 236.7. HRMS (m/z) Found: 402.1438. Calcd for $C_{28}H_{22}OSi$: 402.1440.

4.2.17. Bis(methyldiphenylsilyl)acetonitrile (7). R_f=0.35 (hexane/ethyl acetate=5/1); white solid; IR (neat) 2208, 1429, 1165, 1009, 816, 725, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.32 (s, 6H), 2.32 (s, 1H), 7.27–7.45 (m, 16H), 7.56–7.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −3.9, 5.1, 71.8, 128.1, 128.2, 130.1, 130.2, 134.0, 134.7. Found: C, 77.81; H, 6.32; N, 3.17%. Calcd for $C_{28}H_{27}NSi_2$: C, 77.54; H, 6.28; N, 3.23%.

4.2.18. 1-[Dichloro-(methyldiphenylsilyl)methyl]-1,1,2,2,2-pentamethyldisilane (8). R_f=0.60 (hexane/ethyl acetate=30/1); colorless oil; IR (neat) 3072, 2953, 1429, 1400, 1248, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.06 (s, 6H), 0.15 (s, 9H), 0.84 (s, 6H), 0.32 (s, 3H), 7.35–7.48 (m, 6H), 7.80–7.87 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −3.2, −3.0, −0.7, 74.4, 127.7, 130.1, 133.5, 136.1. Found: C, 55.22; H, 6.93. Calcd for $C_{19}H_{28}Cl_2Si_3$: C, 55.44; H, 6.86%.

4.2.19. General procedure for the preparation of 1-benzoyl-1,1,2,2,2-pentamethyldisilane (10) from dichlorosilylmethyldisilane 8. Under argon atmosphere, to a solution of (dichlorosilylmethyl)disilane (**8**, 206 mg, 0.5 mmol) in THF (3 mL) was added butyllithium (0.31 mL, 1.6 M solution in hexane, 0.5 mmol) dropwise at −78 °C and the solution was stirred for 5 min. Phenylmagnesium bromide (0.6 mL, 1.0 M solution in THF, 0.6 mmol) and CuCN·2LiCl (0.6 mL, 1.0 M solution in THF, 0.6 mmol) were added successively at −78 °C. After stirring for 1 h at 0 °C, pyridine (0.16 mL, 2.0 mmol) was added. The mixture was stirred for 1 h under air at 0 °C and then extracted with hexane. The organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided 1-benzoyl-1,1,2,2,2-pentamethyldisilane (**10**, 61 mg, 0.27 mmol) in 51% yield. R_f=0.38 (hexane/ethyl acetate=20/1); IR (neat) 2955, 1614, 1591, 1576, 1447, 1429, 1113, 1055, 831, 799, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 9H), 0.43 (s, 6H), 7.45–7.57 (m, 3H), 7.78 (dd, J=2.0, 13.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −3.8, −1.8, 128.1, 132.5, 133.8, 141.9, 236.2.

4.2.20. General procedure for the preparation of 5-(methyldiphenylsilyl)nonane (14a). n-BuLi (0.31 mL, 1.6 M solution in hexane, 0.50 mmol) was added to a solution of $Ph_2MeSiCHCl_2$ (**11**, 141 mg, 0.50 mmol) in THF (5 mL) at −78 °C, and the mixture was stirred for 30 min. Then $nBu_2CuCN(MgBr)_2$ in THF, which was prepared from n-BuMgBr (1.25 mL, 1.0 M solution in THF, 1.25 mmol) and CuCN·2LiCl (0.55 mL, 1.0 M solution in THF, 0.55 mmol) at 0 °C, was added to the resulting solution at −78 °C. After stirring for 5 min, the mixture was allowed to warm gradually to 0 °C. After stirring the mixture for 1 h at 0 °C, the reaction was quenched with diluted aqueous HCl (20 mL). The mixture was extracted with hexane (10 mL×3), and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided 5-(methyldiphenylsilyl)nonane (**14a**, 127 mg, 0.39 mmol) in 78% yield as colorless oil: R_f=0.78

(hexane/ethyl acetate=10/1); IR (neat) 3069, 2856, 1952, 1880, 1817, 1466, 1252, 1111, 787, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (s, 3H), 0.81 (t, J=7.2 Hz, 6H), 1.12–1.44 (m, 12H), 1.48–1.62 (m, 1H), 7.31–7.42 (m, 6H), 7.51–7.59 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.06, 14.10, 23.02, 23.61, 29.65, 31.77, 127.54, 128.76, 134.63, 137.26. Found: C, 81.19; H, 9.71%. Calcd for $C_{22}H_{32}Si$: C, 81.41; H, 9.94%.

4.2.21. 4-Butyl-4-(methyldiphenylsilyl)-1-octene (15a). R_f=0.66 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 2957, 2858, 1636, 1427, 1254, 1105, 999, 910, 784, 737, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 3H), 0.78 (t, J=6.9 Hz, 6H), 1.06–1.24 (m, 8H), 1.44–1.60 (m, 4H), 3.32 (d, J=7.5 Hz, 2H), 4.88–4.98 (m, 2H), 5.75 (ddt, J=9.3, 16.5, 7.5 Hz, 1H), 7.30–7.38 (m, 6H), 7.60–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −3.21, 13.83, 23.56, 26.64, 29.14, 35.75, 40.74, 116.69, 127.59, 128.78, 135.53, 136.21, 137.63. Found: C, 82.13; H, 9.72%. Calcd for $C_{25}H_{36}Si$: C, 82.35; H, 9.95%. HRMS (*m/z*) Found: 364.2571. Calcd for $C_{25}H_{36}Si$: 364.2586.

4.2.22. (Methyldiphenylsilyl)diphenylmethane (14b). R_f=0.59 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 3024, 1958, 1886, 1821, 1597, 1493, 1427, 1254, 1111, 999, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.53 (s, 3H), 4.14 (s, 1H), 7.0–7.21 (m, 10H), 7.24–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −3.58, 44.31, 125.23, 127.51, 128.06, 129.18, 129.26, 135.21, 135.62, 141.78. Found: C, 85.39; H, 6.77%. Calcd for $C_{26}H_{24}Si$: C, 85.66; H, 6.64%.

4.2.23. 1-(Methyldiphenylsilyl)-1,1-diphenyl-3-butene (15b). R_f=0.67 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 3053, 2957, 1599, 1493, 1427, 1254, 1105, 912, 791, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.46 (s, 3H), 3.24 (d, J=6.6 Hz, 2H), 4.89 (dd, J=2.1, 10.5 Hz, 1H), 4.95 (dd, J=2.1, 17.1 Hz, 1H), 5.58 (ddt, J=10.5, 17.1, 6.6 Hz, 1H), 7.11–7.23 (m, 10H), 7.23–7.28 (m, 4H), 7.28–7.41 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −3.12, 40.63, 45.66, 117.11, 125.22, 127.39, 127.45, 127.51, 128.05, 128.98, 129.17, 129.25, 129.93, 134.87, 135.20, 135.85, 135.94, 141.77, 143.42. HRMS (*m/z*) Found: 404.1954. Calcd for $C_{29}H_{28}Si$: 404.1960.

4.2.24. General procedure for the preparation of 2-(methyldiphenylsilyl)hexanenitrile (17a). *n*-BuLi (0.31 mL, 1.6 M solution in hexane, 0.50 mmol) was added to a solution of $Ph_2MeSiCHCl_2$ (**8**, 141 mg, 0.50 mmol) in THF (5 mL) dropwise at −78 °C, and the mixture was stirred for 30 min. Then $nBu_2CuLi\cdot LiCN$ in THF, which was prepared from *n*-BuLi (0.78 mL, 1.6 M solution in THF, 1.25 mmol) and $CuCN\cdot 2LiCl$ (0.55 mL, 1.0 M solution in THF, 0.55 mmol) at 0 °C, was added to the resulting solution at −78 °C. After stirring for 5 min, the mixture was allowed to warm gradually to 0 °C. And after stirring the mixture for 1 h at 0 °C, the reaction was quenched with dilute aqueous HCl (20 mL). The mixture was extracted with ethyl acetate (10 mL ×3), and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided 2-(methyldiphenylsilyl)hexanenitrile (**17a**, 116 mg, 0.39 mmol) in 79% yield as colorless oil: R_f=0.38 (hexane/ethyl acetate=10/1); IR (neat) 3072, 2932, 2860, 2222, 1429, 1258, 1115, 793, 729, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 0.85 (t, J=7.2 Hz, 3H), 1.12–1.72 (m, 6H), 2.30 (dd, J=4.2, 10.8 Hz, 1H), 7.38–7.51 (m, 6H), 7.56–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.46, 13.90, 17.84, 22.01, 26.87, 32.01, 121.88, 128.06, 128.10, 130.16, 132.21, 132.50, 134.55. Found: C, 77.78; H, 7.80%. Calcd for $C_{19}H_{23}NSi$: C, 77.76; H, 7.90%.

4.2.25. 2-(Methyldiphenylsilyl)-3-methylpentanenitrile (17b). R_f=0.37 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 2964, 2220, 1429, 1115, 793, 732, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (t, J=7.4 Hz, 3H), 0.80 (s, 3H), 0.81 (s, 3H), 0.86 (t, J=7.4 Hz, 3H), 0.93 (d, J=6.6 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.20–1.77 (m, 6H), 2.38 (d, J=4.5 Hz, 1H), 2.53 (d, J=3.0 Hz, 1H), 7.36–7.51 (m, 12H), 7.56–7.62 (m,4H), 7.63–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.41, −4.11, 11.70, 11.76, 18.12, 20.31, 23.60, 26.03, 27.78, 30.88, 33.21, 33.36, 120.33, 120.79, 128.07, 128.11, 128.14, 130.07, 130.12, 130.15, 132.65, 132.84, 133.39, 133.52, 134.50, 134.55. Found: C, 77.87; H, 8.08%. Calcd for $C_{19}H_{23}NSi$: C, 77.76; H, 7.90%.

4.2.26. 2-(Methyldiphenylsilyl)propanenitrile (17c). R_f=0.31 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 3072, 2224, 1429, 1261, 1114, 794, 731, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3H), 1.33 (d, J=7.5 Hz, 3H), 2.38 (q, J=7.5 Hz, 1H), 7.40–7.52 (m, 6H), 7.59–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −6.11, 10.62, 12.49, 122.82, 128.19, 128.22, 130.31, 132.11, 132.36, 134.70. Found: C, 76.19; H, 6.90%. Calcd for $C_{16}H_{17}NSi$: C, 76.44; H, 6.82%.

4.2.27. 2-Butyl-2-(methyldiphenylsilyl)-pent-4-enenitrile (19a). R_f=0.41 (hexane/ethylacetate=10/1); colorless oil; IR (neat) 2936, 2214, 1962, 1890, 1827, 1639, 1429, 1259, 1113, 922, 793, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3H), 0.80 (t, J=7.2 Hz, 3H), 1.13–1.30 (m, 2H), 1.30–1.50 (m, 2H), 1.50–1.72 (m, 2H), 2.29 (dd, J=7.2, 14.1 Hz, 1H), 2.48 (dd, J=7.2, 14.1 Hz, 1H), 5.02 (d, J=16.8 Hz, 1H), 5.08 (d, J=9.9 Hz, 1H), 5.82 (ddt, J=9.9, 16.8, 7.2 Hz, 1H), 7.38–7.49 (m, 6H), 7.70–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.96, 13.82, 22.92, 27.39, 28.50, 32.71, 38.03, 118.74, 123.94, 128.03, 130.07, 132.50, 133.42, 134.61, 135.15, 135.19. Found: C, 79.34; H, 8.35%. Calcd for $C_{22}H_{27}NSi$: C, 79.22; H, 8.16%.

4.2.28. 2-Methyl-2-(methyldiphenylsilyl)hexanenitrile (19b). R_f=0.48 (hexane/ethyl acetate=5/1); colorless oil; IR (neat) 2936, 2214, 1429, 1259, 1113, 793, 729, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 0.86 (t, J=7.2 Hz, 3H), 1.33 (s, 3H), 1.19–1.36 (m, 3H), 1.42–1.54 (m, 2H), 1.68–1.81 (m, 1H), 7.38–7.49 (m, 6H), 7.70–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −6.27, 13.98, 19.28, 22.12, 22.83, 27.36, 34.08, 125.36, 128.03, 130.09, 132.11, 132.14, 135.22, 135.24. Found: C, 77.82; H, 8.22%. Calcd for $C_{20}H_{25}NSi$: C, 78.12; H, 8.19%.

4.2.29. 2-Acetyl-2-(methyldiphenylsilyl)hexanenitrile (19c). R_f=0.52 (hexane/ethyl acetate=5/1); colorless oil; IR (neat) 2930, 2205, 1632, 1429, 1286, 1121, 797, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (s, 3H), 0.89 (t, J=7.2 Hz, 3H), 1.24–1.38 (m, 3H), 1.39–1.51 (m, 2H), 2.02 (s, 3H), 2.21 (t, J=7.5 Hz, 2H), 7.40–7.47 (m, 6H), 7.55–7.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −1.49, 13.90, 18.92, 22.07,

22.23, 26.55, 30.26, 120.65, 128.11, 130.21, 130.50, 133.91, 134.17, 134.62, 162.85. HRMS (*m/z*) Found: 335.1702. Calcd for $C_{21}H_{25}NOSi$: 335.1705.

4.2.30. 2-Benzoyl-2-(methyldiphenylsilyl)hexanenitrile (19d). R_f=0.41 (hexane/ethyl acetate=5/1); colorless oil; IR (neat) 2959, 2206, 1746, 1429, 1258, 1115, 795, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.40 (s, 3H), 0.88 (t, J= 7.2 Hz, 3H), 1.23–1.36 (m, 2H), 1.38–1.51 (m, 2H), 2.29 (dd, J=7.5, 8.1 Hz, 2H), 7.32–7.38 (m, 6H), 7.43–7.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −2.06, 13.91, 22.32, 27.80, 30.18, 97.32, 120.08. HRMS (*m/z*) Found: 397.1860. Calcd for $C_{26}H_{27}NOSi$: 397.1862.

4.2.31. (*Z*)-2-Butyl-3-phenyl-acrylonitrile (determined by NOESY) (19e). R_f=0.54 (hexane/ethyl acetate= 10/1); colorless oil; IR (neat) 2959, 2208, 1730, 1448, 926, 750, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, J=7.2 Hz, 3H), 1.33–1.47 (m, 2H), 1.65 (quint, J=7.8 Hz, 2H), 2.41 (t, J=7.8 Hz, 2H), 6.93 (s, 1H), 7.34–7.46 (m, 3H), 7.68–7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.85, 21.92, 30.41, 36.04, 111.54, 118.75, 128.41, 128.66, 129.69, 133.72, 143.09. Found: C, 84.06; H, 8.20%. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16%. NOE (^1H difference spectrum, 300 MHz, $CDCl_3$) irradiation of δ 2.41 (CH_2)—enhancement of signals at δ 6.93 (CH, 1.6%); irradiation of δ 6.93 (CH)—enhancement of signals at δ 2.41 (CH_2, 0.9%), δ 7.68–7.78 (Ph, 0.7%)

4.2.32. (*Z*)-2-Butyl-3-cyclohexyl-acrylonitrile (*Z*/*E*= 55/45) (19f). R_f=0.62 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 2855, 2214, 1591, 1429, 1259, 1124, 858, 796, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.5 Hz 3H), 1.20–1.24 (m, 4H), 1.24–1.42 (m, 4H), 1.45–1.55 (m, 2H), 1.62–1.78 (m, 6H), 2.18 (dt, J=1.5, 6.9 Hz, 2H), 2.44–2.60 (m, 1H), 5.95 (d, J=9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.80, 21.77, 25.36, 25.71, 30.23, 32.28, 33.92, 40.72, 112.34, 117.84, 152.73. HRMS (*m/z*) Found: 191.1677. Calcd for $C_{13}H_{21}N$: 191.1674. NOE (^1H difference spectrum, 300 MHz, $CDCl_3$) irradiation of δ 2.18 (CH_2)—enhancement of signals at δ 5.95 (CH, 1.2%); irradiation of δ 5.95 (CH)—enhancement of signals at δ 2.18 (CH_2, 0.8%)

4.2.33. (*E*)-2-Butyl-3-cyclohexyl-acrylonitrile (*Z*/*E*= 55/45) (19f′). R_f=0.55 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 2855, 2214, 1591, 1429, 1259, 1124, 858, 797, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J=7.2 Hz, 3H), 1.04–1.43 (m, 8H), 1.43–1.80 (m, 8H), 2.19 (dt, J=1.2, 7.2 Hz, 2H), 2.24–2.39 (m, 1H), 6.14 (d, J=10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.87, 22.09, 25.39, 25.66, 28.39, 30.44, 31.98, 37.64, 113.12, 120.27, 152.78. HRMS (*m/z*) Found: 191.1680. Calcd for $C_{13}H_{21}N$: 191.1674. NOE (^1H difference spectrum, 300 MHz, $CDCl_3$) irradiation of δ 6.14 (CH_2)—no enhancement of signals at δ 2.19 (CH_2, 0.9%).

4.2.34. 2-Oxo-hexanenitrile (19g, known compound). Spectral data for this compound were identical with those reported in the literature.[20]

4.2.35. Preparation of 1-(methyldiphenylsilyl)-1-phenylpentane (21). *n*-BuLi (0.31 mL, 1.6 M solution in hexane, 0.50 mmol) was added to a solution of $Ph_2MeSiCHCl_2$ (**8**, 141 mg, 0.50 mmol) in THF (5 mL) dropwise at −78 °C, and the mixture was stirred for 30 min. Then *n*-BuCu in THF, which was prepared with *n*-BuLi (0.34 mL, 1.6 M solution in THF, 0.55 mmol) and CuI·LiI (0.55 mL, 1.0 M solution in THF, 0.55 mmol) at −78 °C, was added to the resultant solution at −78 °C. After stirring for 10 min., and addition of PhMgBr (0.75 mL, 1.0 M solution in THF, 0.75 mmmol), the mixture was allowed to warm gradually to −10 °C. And then the reaction was quenched with diluted aqueous HCl (20 mL). The mixture was extracted with ethyl acetate (10 mL×3), and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided 1-(methyldiphenylsilyl)-1-phenylpentane (**21**, 93 mg, 0.27 mmol) in 54% yield as colorless oil: R_f=0.72 (hexane/ethyl acetate=10/1); IR (neat) 2957, 1956, 1882, 1818, 1599, 1427, 1252, 1111, 789, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.42 (s, 3H), 0.77 (t, J=6.6 Hz, 3H), 1.06–1.34 (m, 4H), 1.76–1.87 (m, 2H), 2.65 (dd, J=5.1, 10.5 Hz, 1H), 6.86–6.92 (m, 2H), 7.04–7.19 (m, 4H), 7.24–7.49 (m, 6H), 7.50–7.58 (m, 3H); ^{13}C NMR ($CDCl_3$) δ −5.22, 14.02, 22.45, 29.78, 31.43, 35.02, 124.48, 127.06, 127.43, 127.59, 127.78, 127.96, 128.36, 128.64, 128.91, 129.16, 134.54, 134.77, 135.16, 136.21, 142.34. HRMS (*m/z*) Found: 344.1963. Calcd for $C_{24}H_{28}Si$: 344.1960.

4.2.36. 4-(Methyldiphenylsilyl)-4-phenyl-1-octene (22). R_f=0.68 (hexane/ethyl acetate=20/1); colorless oil; IR (neat) 2957, 1427, 1254, 1107, 784, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.59 (s, 3H), 0.81 (t, J=7.2 Hz, 3H), 1.16–1.33 (m, 4H), 1.94–2.14 (m, 2H), 2.73–2.90 (m, 2H), 4.93 (dd, J=1.5, 10.2 Hz, 1H), 5.03 (dd, J=1.5, 17.1 Hz, 1H), 5.65–5.81 (m, 1H), 6.88–6.94 (m, 2H), 7.06–7.18 (m, 3H), 7.22–7.31 (m, 4H), 7.32–7.42 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −4.42, 14.12, 23.69, 25.94, 33.53, 36.34, 38.48, 116.52, 124.35, 127.25, 128.15, 128.88, 135.36, 135.58, 136.10, 143.95. HRMS (*m/z*) Found: 384.2258. Calcd for $C_{27}H_{32}Si$: 384.2273.

4.2.37. 3-(Methyldiphenylsilyl)-3-phenyl-heptan-2-one (23). R_f=0.48 (hexane/ethyl acetate=10/1); colorless oil; IR (neat) 2957, 1659, 1429, 1217, 1119, 986, 793, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.56 (s, 3H), 0.80 (t, J=7.2 Hz, 3H), 1.13–1.37 (m, 6H), 1.99 (s, 3H), 6.84–6.90 (m, 2H), 7.13–7.19 (m, 3H), 7.22–7.36 (m, 5H), 7.37–7.42 (m, 3H), 7.56–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −3.49, 13.85, 23.65, 28.05, 33.46, 59.01, 125.75, 127.23, 127.37, 127.66, 128.62, 129.02, 134.78, 135.47, 135.89, 136.01, 139.61, 212.33. HRMS (*m/z*) Found: 386.2071. Calcd for $C_{26}H_{30}OSi$: 386.2066.

Acknowledgements

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13. The structure of copper species derived from Grignard reagents and CuCN has not been well elucidated. We here describe the reagent as 2RMgBr/CuCN to indicate stoichiometry.
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Stereochemical course of the reductive spiroannulations of *N*-Boc and *N*-benzyl 2-cyanopiperidines

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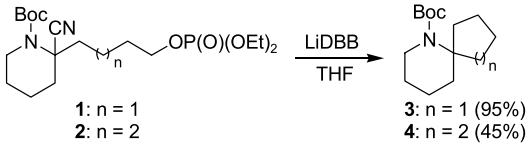
Abstract—The stereochemical outcome of spiroannulations of *N*-protected 2-lithiopiperidines (generated by lithium di-*tert*-butyl biphenylide (LiDBB) mediated reductive lithiation of 2-cyanopiperidines) was investigated using deuterium labeled side-chains containing phosphate leaving groups. High stereoselectivity was observed when benzyl (Bn) protected 2-cyanopiperidines were employed, while *tert*-butoxycarbonyl (Boc) protected 2-cyanopiperidines afforded lower selectivity. Models are proposed to rationalize the results of this study.

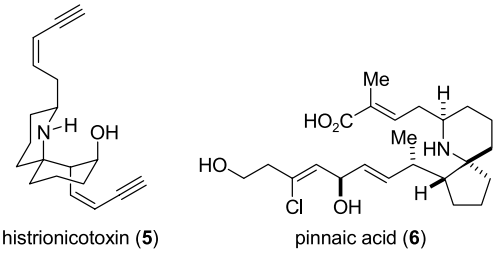
1. Introduction

Sequential nitrile alkylation and reductive decyanation/lithiation with subsequent intramolecular electrophile displacement ('reductive annulation') represents a powerful method for the synthesis of carbocyclic molecules.[1] Work in our laboratory has demonstrated the utility of this strategy in the stereoselective synthesis of complex spirocyclic tetrahydrofuran derivatives[2] and in an enantioselective synthesis of cyclopentane rings.[3] This approach is convergent and possesses the potential for the stereoselective generation of quaternary centers. As an extension of this chemistry, we have also applied this sequence towards 2-cyanopiperidines (Scheme 1).[4,5] The resulting 2-spiropiperidine ring systems can be found in a small but structurally and biologically interesting selection of naturally-occurring alkaloids such as histrionicotoxin[6] (**5**) and pinnaic acid[7] (**6**) (Fig. 1).



Scheme 1. Reductive spiroannulation approach to 2-spiropiperidines.

The efficiency of these spiroannulations, especially in forming the five-membered ring product **3**, encouraged further development of this approach in the context of the 2-spiropiperidine alkaloids. New stereocenters are not generated in the simple examples in Scheme 1. We chose to probe the stereoinduction imparted by additional stereocenters on the piperidine ring. At the onset of these studies, we recognized that the protecting group on nitrogen could have a profound effect in directing the resulting stereochemistry of the quaternary spiro center. For example, Husson[8] has shown that *N*-benzyl (benzyl = Bn) 2-cyanopiperidine **7** undergoes highly stereoselective reductive decyanation under dissolving metal conditions to produce **8** as a single diastereomer while Nagasaka[9] has revealed that under similar conditions, the related *N*-carbethoxy compound **9** produces decyanated products **10** and **11** with low stereoselectivity (Scheme 2).



histrionicotoxin (**5**) pinnaic acid (**6**)

Figure 1. Naturally-occurring 2-spiropiperidine alkaloids.

For our studies, we targeted *N*-benzyl and *N*-*tert*-butoxycarbonyl (Boc) protected cyanopiperidines **12** and **13**. Alkylation with deuterium labeled iodide **14** and reductive spiroannulation should produce the diastereomeric products *N*-benzyl *trans*/*cis*-**17** and *N*-Boc *trans*/*cis*-**18** (Scheme 3). The relative configuration of the generated quaternary spiro centers could then be determined using nuclear Overhauser effect (NOE) studies to establish the position of the

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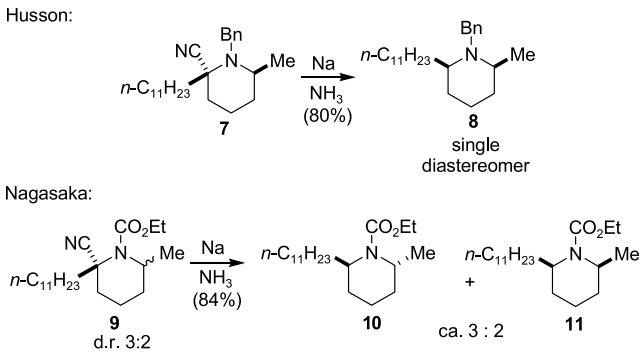
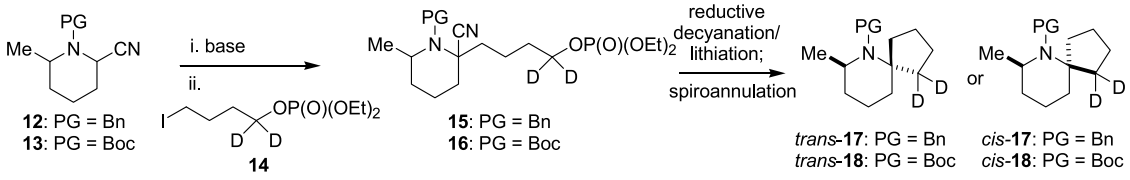


Scheme 2. Representative reductive decyanations.

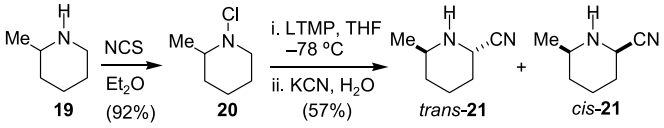
diastereomers following chromatographic purification. For ease of characterization, typically only *trans*-**21** was carried forward, although the relative stereochemistry at this stage was ultimately irrelevant.

Protection of the relatively unreactive 2-cyanopiperidines was accomplished by treatment with BnBr/KI/Na_2CO_3 in refluxing acetone or with neat di-*tert*-butyl dicarbonate (Boc_2O) at 60 °C for several hours to afford *N*-benzyl derivative *trans*-**12** and *N*-Boc derivative *trans*-**13**, respectively (Scheme 5).

The 2-cyanopiperidines *trans*-**12** and *trans*-**13** are readily alkylated by treatment with lithium diisopropylamide



Scheme 3. Proposed deuterium-labelled spiroannulations.



Scheme 4. Synthesis of unprotected 2-cyanopiperidines.

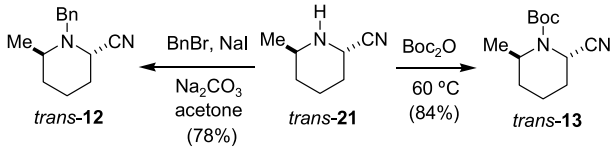
deuterium labels. This study would provide information regarding the stereoselectivity of the reductive lithiations and would indicate the most appropriate protecting group for more complex spiroannulations leading to the 2-spiropiperidine cores of histrionicotoxin and pinnaic acid.

2. Results and discussion

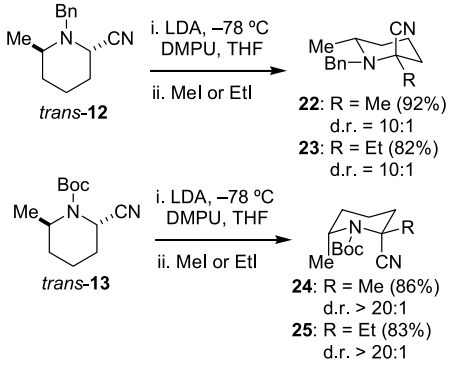
2.1. Synthesis of substrates

A flexible approach to either *N*-benzyl or *N*-Boc cyanopiperidines was desired. Our attention was drawn to work by Davis, who showed that imine formation by base-induced elimination of cyclic *N*-chloro amines could be rendered regioselective by choice of base.[10] Trapping of these cyclic imines with a nucleophilic cyanide source would produce the unprotected 2-cyanopiperidines.[11,12] Starting with 2-methylpiperidine (**19**), *N*-chlorination using *N*-chlorosuccinimide (NCS) produced *N*-chloro-2-methylpiperidine (**20**), which was reacted in unpurified form in a regioselective elimination mediated by lithium 2,2,6,6-tetramethylpiperidide (LTMP) (Scheme 4). Direct addition of an aqueous solution of KCN and gradual warming to room temperature produces diastereomeric 2-cyanopiperidines *trans*- and *cis*-**21** in 52% overall yield from **19**. Analysis of the crude products by ^{1}H NMR indicates a diastereomer ratio of ca. 3:1 *trans*/*cis* (relative stereochemistry assigned by NOE studies), however facile epimerization on silica gel produces ratios on the order of 9:1 of the separable

(LDA) at −78 °C in the presence of *N*,*N*-dimethylpropyleneurea (DMPU) followed by addition of an alkyl iodide electrophile (Scheme 6). Alkylation of *N*-benzyl derivative *trans*-**12** with MeI or EtI affords axial nitriles **22** and **23** along with their minor diastereomers in a ratio of ca. 10:1. Relative configuration of the major diastereomer was



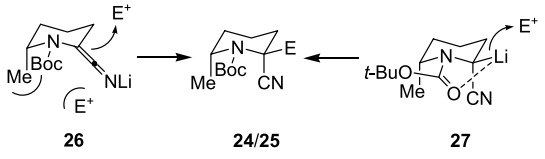
Scheme 5. Protection of 2-cyanopiperidine **21**.



Scheme 6. Alkylation of *N*-protected 2-cyanopiperidines.

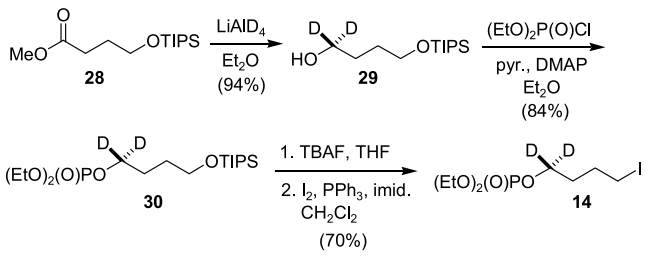
assigned based on the known anomeric-type effect in 2-cyanopiperidines.[13] *N*-Benzyl 2-alkyl-2-cyanopiperidines such as **22** and **23** are rather labile compounds and decompose in the presence of acid and on silica gel, presumably due to facile iminium ion formation and ensuing side reactions. Purification is best performed on basic alumina and long-term storage (>6 months) can be accomplished at low-temperature (−20 °C) in the presence of small amounts of triethylamine as an acid scavenger. Alkylation of *N*-Boc 2-cyanopiperidine *trans*-**13** under similar conditions produces single detectable diastereomers **24** and **25**. The relative configuration of **24** was assigned by X-ray crystallography and products from similar alkylations were assigned by analogy. In contrast to the *N*-benzyl compounds, *N*-Boc 2-alkyl-2-cyanopiperidines are very stable compounds, readily purified by silica gel chromatography and storable at room temperature for extended periods of time (>1 year).

The highly stereoselective alkylation of *N*-Boc 2-cyanopiperidine *trans*-**13** is a useful demonstration of a stereocontrol element found in amide and carbamate protected piperidines. The presence of such carbonyl groups on nitrogen forces substituents at the 2- or 6-positions to adopt axial dispositions to relieve severe $A^{1,3}$-strain.[14] This effect has been elegantly exploited by Beak in stereoselective lithiations of *N*-Boc piperidines.[15] While we are unsure of the precise nature of the intermediate involved in the *N*-Boc 2-cyanopiperidine alkylations, reasonable possibilities include 1) *N*-lithiated ketene iminate[16] **26**, where equatorial electrophile incorporation results due to blocking of the bottom face by the axial methyl group or 2) *C*-lithiated nitrile[17] **27**, stabilized by Boc–Li coordination, which undergoes electrophilic substitution with retention of configuration to afford equatorial products **24** and **25** (Scheme 7).



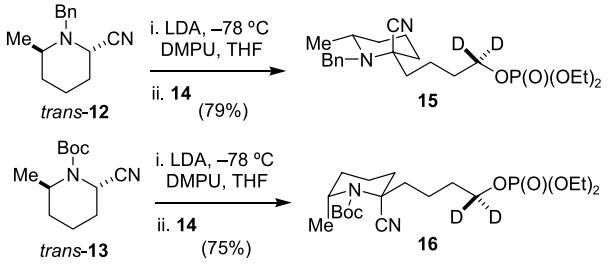
Scheme 7. Possible rationales for stereoselective nitrile alkylations.

The deuterium labeled bis-electrophile **14** was prepared starting with $LiAlD_4$ reduction of ester **28**. Phosphorylation, TIPS removal and iodination produced **14** in good overall yield (Scheme 8). Alkylation of *trans*-**12** and *trans*-**13** as described previously for **22**–**25** afforded the deuterium labeled cyclization precursors **15** (dr=ca. 9:1) and **16**



Scheme 8. Synthesis of deuterated bis-electrophile **14**.

(single diastereomer) without evidence of competing phosphate displacement (Scheme 9).

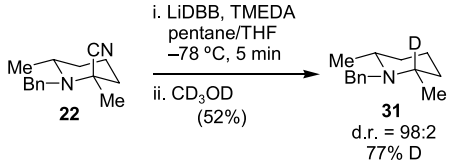


Scheme 9. Preparation of deuterium-labeled cyclization precursors.

2.2. Preliminary reductive lithiations

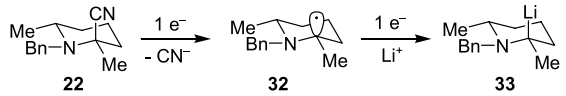
Prior to exploring the reductive spiroannulations of **15** and **16**, we conducted some preliminary reductive decyanation/lithiations on *N*-benzyl 2-cyanopiperidine **22** and *N*-Boc 2-cyanopiperidine **24** in order to explore the stereoselectivity of reductive lithiation in these simpler systems. The intermediate α-aminoorganolithiums were typically generated by addition of the cyanopiperidines to solutions of lithium di-*tert*-butylbiphenylide (LiDBB) in THF at low temperature. After a given time period, CD_3OD was added and the reaction was worked up and crude mixtures were analyzed by GC to determine diastereomer ratios and ^1H NMR (for **22**) or GC–MS (for **24**) to determine deuterium incorporation.

The reductive lithiations of *N*-benzyl 2-cyanopiperidine **22** were problematic, with low crude yields and the presence of small amounts of several unidentified by-products. Additionally, deuterium incorporation was often low despite extensive efforts to exclude proton sources. These results are indicative of the high basicity of the α-aminoorganolithium derived from **22**, where THF is likely acting as a proton donor.[18] Efforts to utilize Cohen's THF-free conditions[19] (lithium 1-(dimethylamino)naphthalenide (LDMAN), Me_2O, −78 °C) produced no reduced product. Reasonably useful yields and deuterium incorporations were ultimately achieved using *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA) as an additive[20] in a pentane/THF (1:1) solvent system (Scheme 10). The reductive lithiations of **22** occur with high stereoselectivity (≥95:5) to produce *cis* piperidine **31**.[21] While higher temperatures are not conducive to the chemical stability of the intermediate α-aminoorganolithiums, they appear to be configurationally stable at −78 °C for at least 60 min.



Scheme 10. Reductive lithiation/deuteriation of **22**.

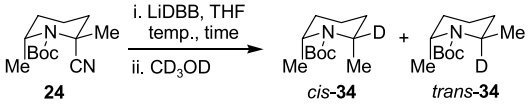
In accord with Husson's work, the major stereoisomer isolated from these reactions displays axial incorporation of the proton or electrophile. We interpret these results with the following explanation: (1) single-electron transfer to **22**



Scheme 11. Rationale for stereoselective reductive lithiation.

diastereomers *trans*/*cis*-**35** (Scheme 12).[24] These are presumed to be in rapid equilibrium due to a low-lying barrier to radical inversion.[22] A cursory inspection of the radical diastereomers suggests that a strong thermodynamic preference does not exist. Unlike the *N*-benzyl derivative,

Table 1. Reductive lithiation/deuteriation of **22**

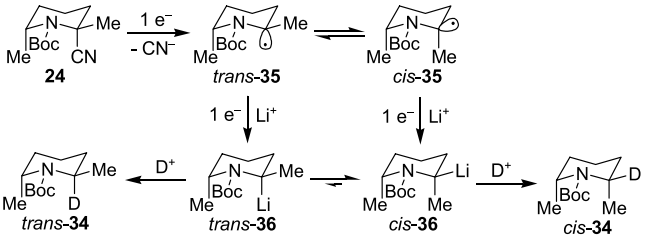


Entry	Reduction temperature (°C)	Time	Ratio (*cis*-**34**: *trans*-**34**)	Total yield (%)
1	−78	5 min	62 (91% D): 38 (89% D)	88
2	−78	12.5 h	78 (92% D): 22 (79% D)	83
3	−40	5 min	94 (84% D): 6 (72% D)	67

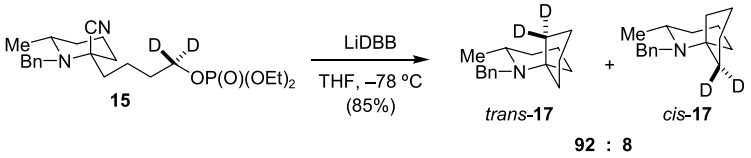
leads to carbon–CN bond cleavage, predominantly generating anomerically-stabilized axial radical[22] **32**; (2) subsequent single-electron transfer occurs with retention of configuration, leading to formally axial 2-lithiopiperidine **33**, which reacts with CD_3OD with retention of configuration to produce **31** (Scheme 11). Attempts to utilize electrophiles other than D^+ (*i*-PrCHO, PhCHO, MeI and Me_2SO_4) produced complex reaction mixtures. While our work with this class (*N*-benzyl) of α-aminoorganolithiums has not demonstrated broad synthetic utility in intermolecular reactions with electrophiles, this route does provide a means of accessing axial 2-lithiopiperidines. Gawley has reported failed Sn–Li exchange in attempted generation of an axial *N*-methyl 2-lithiopiperidine from the corresponding axial 2-stannylpiperidine.[23]

Reductive lithiations of *N*-Boc 2-cyanopiperidine **24** initially proved to be less stereoselective than those of the *N*-benzyl derivative. However, several features of these reductive lithiations are noteworthy. The α-aminoorganolithiums derived from **24** were far more robust than the α-aminoorganolithium derived from **22**, as evidenced by generally high yields and levels of deuterium incorporation (Table 1). While rapid (<1 h) CD_3OD quenches afforded low ratios of diastereomeric products *cis*/*trans*-**34** (entry 1), maintaining a solution of the α-aminoorganolithiums derived from **24** at −78 °C for extended time periods demonstrated slow equilibration of the intermediate diastereomeric organolithiums (entry 2). Conducting the reductive lithation at −40 °C provided superior diastereomer ratios, albeit at the expense of yield and deuterium incorporation (entry 3).

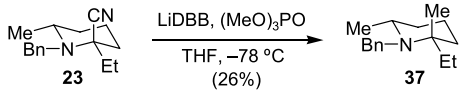
To account for these results, we suggest the following possibilities. Single-electron transfer produces radical anomeric stabilization of an axially disposed radical (*trans*-**35**) would be expected to be diminished due to significant delocalization of the nitrogen lone pair into the carbonyl moiety. Additionally, $A^{1,3}$-strain between the Boc group and the equatorial methyl group in *trans*-**35** serves to destabilize this conformation.[15] Further single-electron reduction of the diastereomeric radical intermediates leads to α-aminoorganolithiums *trans*/*cis*-**36**. *trans*-**36** is destabilized by the axial disposition of the carbon–lithium bond, a manifestation of an anti-anomeric (HOMO–HOMO) effect,[25] and by $A^{1,3}$-strain arising from interactions between the Boc group and the equatorial methyl group. This stereoelectronic interaction is absent in *cis*-**36**, which may also benefit from coordinative stabilization between the Boc group and the equatorial lithium.[15] These factors appear to override the 1,3-diaxial (Me–Me) interactions in *cis*-**36**.[15c] Deuterium incorporation with retention of configuration produces the observed products, *trans*/*cis*-**34**. Despite the presumed thermodynamic preference for *cis*-**36**, a substantial energy barrier still exists, resulting in slow equilibration at −78 °C. Computational work by Haeffner, Brandt and Gawley suggests an inversion barrier of ca. 16 kcal/mol for related *N*-Boc 2-lithiopyrrolidines.[26] At



Scheme 12. Possible rationale for stereoselectivity in reductive lithiation of **24**.



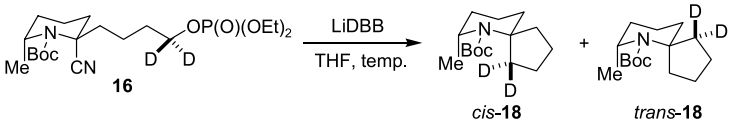
Scheme 13. Reductive spiroannulation of **15**.



Scheme 14. Intermolecular addition of a phosphate electrophile.

below). The cyclization of *N*-benzyl derivative **15** is presumably rapid enough to outcompete the side reactions which plagued the intermolecular reactions of **22**, leading to high yields of the spirocyclic products. From these results, we conclude that reductive lithiation generated a predominantly axially lithiated α-aminoorganolithium intermediate corresponding to **33** (Scheme 11). Cyclization with retention of configuration then produces the major diastereomer *trans*-**17**. Further evidence for retentive electrophilic addition was shown by conducting reductive lithiation on *N*-benzyl 2-cyanopiperidine **23** in the presence of a large excess (20 equiv) of trimethyl phosphate (Scheme 14). The sole detectable isomer (**37**) by GC–MS again displays axial incorporation of the electrophile as determined by NOESY.

Table 2. Reductive spiroannulation of **16**



Entry	Reduction temperature (°C)	Ratio (*cis*-**34**: *trans*-**34**)	Total yield (%)
1	−78	72:28	85
2	−40	74:26	90

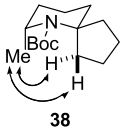
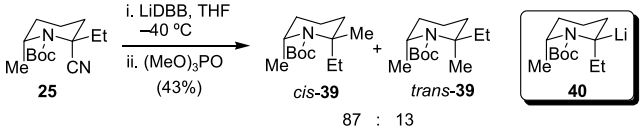


Figure 2. Relevant NOESY signals.



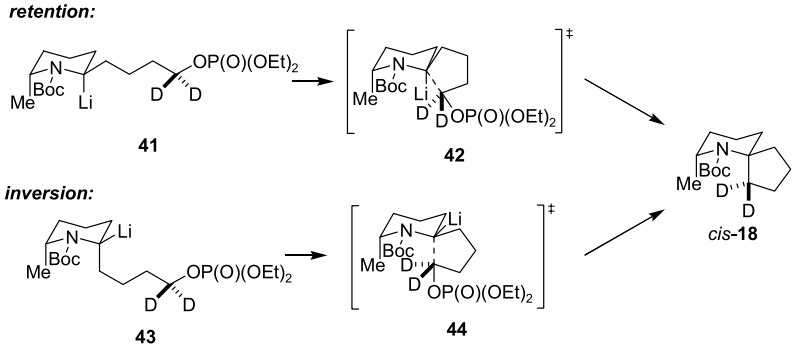
Scheme 15. Intermolecular addition of a phosphate electrophile to **25**.

−40 °C, we may be observing faster equilibration of these species, however the lower yield may indicate selective decomposition of the axially lithiated *trans*-**36**.

2.3. Reductive spiroannulations

With the above information in hand, cyclization precursors **15** and **16** were subjected to LiDBB in THF at −78 °C. As anticipated from our preliminary studies, the reductive spiroannulation of **15** was highly stereoselective producing *trans*/*cis*-**17** in a ratio of 92:8 (Scheme 13). Relative configurations of the diastereomeric products were assigned by conversion to the corresponding *N*-Boc compounds (see

As we had previously observed with *N*-Boc 2-cyanopiperidine **24**, reductive spiroannulation of **16** was not highly stereoselective (Table 2). Proton assignments of the non-deuterated compound **38** were assigned using COSY, HMQC and NOESY experiments (Fig. 2) and relative stereochemistry and diastereomeric ratios of the deuterated compounds *cis*/*trans*-**18** were made using ^{1}H NMR. We also observed that spiroannulation stereoselectivity was independent of temperature, providing nearly identical results at −78 °C (entry 1) or −40 °C (entry 2). Whereas the major diastereomer from reductive lithiation/deuteration of **24** displayed equatorial electrophile incorporation (Table 1), the major spirocycle diastereomer (*cis*-**18**) results from axial electrophile incorporation. Subjecting *N*-Boc 2-cyanopiperidine **25** to reductive lithiation conditions at −40 °C, at which temperature the equatorially lithiated α-aminoorganolithium (**40**) is presumed to be present in excess, followed by addition of trimethyl phosphate affords *cis*/*trans*-**39** in a ratio of 87:13 (Scheme 15). As with CD_3OD, the phosphate electrophile is predominantly



Scheme 16. Possible raation pathways leading to *cis*-**18**.

incorporated equatorially, resulting in major diastereomer *cis*-**39**.

An explanation for the disparity in stereoselection between the reductive spiroannulations of *N*-Boc 2-cyanopiperidine **16** and the intermolecular reactions of **24** and **25** is not readily apparent. Fast deuterium quenches (Table 1, entry 1) indicate that a mixture of equatorially and axially lithiated intermediates are initially produced following single electron reduction of the radical intermediates. If the diastereomer ratios of *cis*/*trans*-**34** are representative of the diastereomer ratios of the lithiated intermediates through a retentive electrophilic addition pathway, an equatorially lithiated intermediate such as **43** would be expected to predominate. This scenario in the reductive spiroannulation of **16** would lead to *trans*-**18** as the major diastereomer, which is not the observed result. The major diastereomer, *cis*-**18**, may arise through retentive cyclization of an axially lithiated intermediate (**41**) or through an invertive cyclization of an equatorially lithiated intermediate (**43**) (Scheme 16). While retentive electrophilic addition occurs in the intermolecular cases, competing invertive electrophilic addition of the presumed major equatorially lithiated **43** may be responsible for the generation of *cis*-**18** as the major diastereomer. The constrained transition states that must be operative in these cyclizations (e.g., **42** and **44**) would appear to include a different set of interactions when compared to the intermolecular reactions.

3. Conclusion

Clearly, the missing piece of the puzzle in these reductive lithiations remains the exact structure and stereochemistry of the α-aminoorganolithium intermediates. Nevertheless, we have demonstrated several interesting features associated with this chemistry. As Gawley has reported with secondary *N*-methyl 2-lithiopiperidines, tertiary *N*-benzyl 2-lithiopiperidines such as **33** possess high configurational stability.[20,27] While chemical lability remains an issue for intermolecular reactions, the methods reported herein allow for their stereoselective generation and use in intramolecular electrophilic additions. The *N*-Boc 2-lithiopiperidines present an unresolved synthetic dichotomy. They possess superior chemical stability when compared to the *N*-benzyl derivatives. However, their generation in stereochemically homogenous form and understanding the stereoselectivity of their reactions with electrophiles require further study. Exploration of the fascinating chemistry and synthetic potential of these reactive intermediates will continue in our laboratory.[28]

4. Experimental

4.1. General experimental details

Unless otherwise noted, all reactions were carried out under positive argon pressure in flame- or oven-dried glassware using standard syringe/septum techniques. THF, Et_2O and CH_2Cl_2 were degassed with argon and dried by vacuum filtration through activated alumina columns purchased from GlassContour, Laguna Beach, CA.[29] *n*-Butyllithium was used from freshly opened bottles following the indicated molarity or was titrated using *N*-benyzlbenzamide.[30] Diisopropylamine and 2,2,6,6-tetramethylpiperidine was distilled from CaH_2. DMPU was distilled from CaH_2 and stored over microwave-activated 4 Å molecular sieves. d_4-Methanol was utilized from freshly opened (<1 week old) bottles. Iodomethane and iodoethane were filtered through oven-dried basic alumina prior to use. Trimethylphosphate was vacuum-distilled from CaH_2 onto microwave-activated 4 Å molecular sieves. LiDBB was prepared as described previously.[4] All other reagents were used as received from commercial suppliers. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV (0.25 mm) plates. Flash chromatography was performed using the indicated solvent system on Sorbent Technologies 230–400 mesh silica gel. Melting points were determined using an Electrothermal apparatus and are reported uncorrected. Infrared spectra were recorded on a MIDAC Prospect FT-IR. NMR spectra were recorded on Bruker instruments. ^{1}H NMR spectra are reported in ppm relative to tetramethylsilane or residual solvent ($CDCl_3$: δ 7.26 ppm; C_6D_6: δ 7.16 ppm). Data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, br=broad), coupling constant(s) in Hertz (Hz), and integration. ^{13}C NMR spectra were reported in ppm relative to the solvent signal ($CDCl_3$: 77.2 ppm; C_6D_6: δ 128.0 ppm). Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument with a 30 m X 0.25 μM Alltech EC-5 (SE-54) or Restek RTX-1701 capillary column equipped with a flame ionization detector. Mass spectral data was obtained on a MicroMass Autospec E spectrometer or a MicroMass LCT Electrospray spectrometer. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

4.1.1. *trans*/*cis*-6-Methyl-piperidine-2-carbonitrile (21). To a 0 °C suspension of *N*-chlorosuccinimide (14.8 g, 111 mmol) in Et_2O (100 mL) was added 2-methylpiperidine (11.8 mL, 101 mmol) over 5 min. After 1.5 h, the reaction was diluted with hexanes (250 mL), washed with water (3x50 mL), satd aq NaCl (50 mL), dried ($MgSO_4$) and concentrated to afford 1-chloro-2-methylpiperidine[10] (12.5 g, 92%) as a pale yellow oil that was dissolved in THF (200 mL) and cooled to −78 °C. To a 0 °C solution of 2,2,6,6-tetramethylpiperidine (22.5 g, 159 mmol) in THF (100 mL) was added *n*-BuLi (2.50 M, 58.4 mL, 146 mmol) over 30 min. The cooling bath was removed and the orange solution was allowed to warm to room temperature at which time it was added to the 1-chloro-2-methylpiperidine solution via cannula over 1 h. After 30 min, a solution of KCN (17.3 g, 266 mmol) in MeOH (100 mL)/water (30 mL) was added over 10 min. The reaction was stirred for 14 h with gradual warming to room temperature. Water (500 mL) was added and the mixture was extracted with EtOAc (3×100 mL) and CH_2Cl_2 (3×100 mL). The combined organic phases were washed with satd aq NaCl (50 mL), dried (Na_2SO_4) and concentrated. ^{1}H NMR revealed a diastereomeric ratio of ca. 5.5 *trans*-**21**: 1 *cis*-**21**. Flash chromatography (30–50% EtOAc/hexanes) afforded less polar cyanopiperidine *cis*-**21** (1.01 g, 6%) and more polar cyanopiperidine *trans*-**21** (8.43 g, 51%) as pale yellow oils.

Analytical data for cis-**21**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (dd, $J=11.6$, 2.6 Hz, 1H), 2.62 (dqd, $J=12.4$, 6.2, 2.5 Hz, 1H), 1.96 (m, 1H), 1.86 (m, 1H), 1.68–1.60 (m, 3H), 1.37 (qt, $J=13.2$, 3.8 Hz, 1H), 1.08 (d, $J=6.2$ Hz, 3H), 1.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.6, 52.4, 47.5, 33.2, 30.3, 23.9, 22.7.

Analytical data for trans-**21**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (m, 1H), 3.02 (dqd, $J=12.4$, 6.2, 2.5 Hz, 1H), 1.87–1.64 (m, 6H), 1.12 (m, 1H), 1.06 (d, $J=6.2$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.4, 48.2, 46.9, 33.4, 28.2, 22.7, 21.2; IR (thin film) 3332, 2223 cm^{-1}; MS (CI) *m/z* 125 (M+H, 100%).

4.1.2. *trans*-1-Benzyl-6-methyl-piperidine-2-carbonitrile (*trans*-12). To a solution of *trans*-**21** (4.88 g, 39.3 mmol) in acetone (50 mL) was added NaI (5.89 g, 39.3 mmol) and K_2CO_3 (8.15 g, 59.0 mmol). Benzyl bromide (5.6 mL, 47 mmol) was added over 2 min and the mixture was heated at 50 °C for 9 h. The reaction was cooled to room temperature, diluted with water (250 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were washed with satd aq NaCl (25 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (3% EtOAc/hexanes) afforded cyanopiperidine *trans*-**12** (6.70 g, 78%) as an orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 4.25 (d, $J=13.3$ Hz, 1H), 3.65 (m, 1H), 3.21 (d, $J=13.3$ Hz, 1H), 2.66 (dqd, $J=12.1$, 6.0, 2.5 Hz, 1H), 1.81–1.59 (m, 5H), 1.34 (m, 1H), 1.22 (d, $J=6.1$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 129.2, 128.8, 127.6, 117.5, 55.5, 53.6, 51.5, 34.7, 28.9, 21.3, 21.3; IR (thin film) 2937, 1454 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}N_2$ $[M+H]^+$ 215.1548, found 215.1553.

4.1.3. *trans*/*cis*-2-Cyano-6-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (*trans*/*cis*-13). A mixture of diastereomers **21** (5.14 g, 41.4 mmol) and Boc_2O (9.03 g, 41.4 mmol) was heated at 60 °C for 10 h. Flash chromatography (10% to 15% to 20% EtOAc/hexanes) afforded inseparable cyanopiperidines *trans*/*cis*-**13** (7.78 g, 84%) as a pale yellow oil.

Analytical data for cis diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (m, 1H), 4.33 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.71–1.61 (m, 4H), 1.48 (s, 9H), 1.33 (d, $J=7.0$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 120.5, 81.5, 47.1, 40.8, 29.4, 28.7, 28.5, 17.5, 15.3.

Analytical data for trans diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (app t, $J=4.2$ Hz, 1H), 4.00 (m, 1H), 2.10 (m, 1H), 2.04–2.00 (m, 2H), 1.88–1.73 (m, 2H), 1.64–1.57 (m, 1H), 1.48 (s, 9H), 1.24 (d, $J=6.7$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 119.8, 81.4, 48.3, 42.7, 28.5, 27.1, 25.7, 20.8, 14.6; IR (thin film) 1704 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}N_2O_2Na$ $[M+Na]^+$ 247.1420, found 247.1420.

4.1.4. *cis*-1-Benzyl-2,6-dimethyl-piperidine-2-carbonitrile (22). To a −78 °C solution of diisopropylamine (6.2 mL, 44 mmol) in THF (50 mL) was added *n*-BuLi (2.31 M, 16.2 mL, 37.4 mmol) over 10 min. After 30 min, DMPU (7.5 mL, 62 mmol) was added followed by dropwise addition of a solution of **12** (6.69 g, 31.2 mmol) in THF (15 mL) over 15 min. After 30 min, iodomethane (3.9 mL, 62 mmol) was added over 5 min and the solution was stirred for 1 h. Buffer solution (pH 7.0, 50 mL) was added and the reaction was warmed to room temperature and extracted with EtOAc (3×50 mL). The combined organic phases were washed with satd aq NaCl (50 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (10% triethylamine/hexanes to 5% EtOAc/10% triethylamine/85% hexanes) afforded cyanopiperidine **22** (6.56 g, 92%) as an orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J=7.3$ Hz, 2H), 7.30 (t, $J=7.7$ Hz, 2H), 7.20 (t, $J=7.3$ Hz, 1H), 3.95 (d, $J=17.7$ Hz, 1H), 3.77 (d, $J=17.7$ Hz, 1H), 2.72 (m, 1H), 1.95 (m, 1H), 1.76–1.56 (m, 5H), 1.40 (s, 3H), 1.35 (m, 1H), 0.99 (d, $J=6.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.4, 126.8, 126.5, 120.9, 60.1, 56.8, 55.1, 38.9, 35.0, 28.1, 22.5, 21.7; IR (thin film) 2216 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}N$ $[M-CN]^+$ 202.1596, found 202.1591. Additional purification could be performed using flash chromatography on basic Al_2O_3 (30% CH_2Cl_2/hexanes). Long term storage (>24 h) was conducted by concentrating the cyanopiperidine down from Al_2O_3-filtered NEt_3 several times and low-temperature (−20 °C) storage under argon.

4.1.5. *cis*-1-Benzyl-2-ethyl-6-methyl-piperidine-2-carbonitrile (23). To a −78 °C solution of diisopropylamine (0.657 mL, 4.69 mmol) in THF (15.0 mL) was added *n*-BuLi (1.46 M, 2.98 mL, 4.36 mmol) over 5 min. After 15 min, DMPU (0.810 mL, 6.70 mmol) was added followed by dropwise addition of a solution of **12** (0.718 g, 3.35 mmol) in THF (3.0 mL) over 5 min. After 1 h, iodoethane (0.804 mL, 6.70 mmol) was added over 2 min and the solution was stirred for 1 h. Water (50 mL) was added and the reaction was warmed to room temperature and extracted with EtOAc (3×20 mL). The combined organic phases were washed with satd aq NaCl (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (basic Al_2O_3, 30% CH_2Cl_2/hexanes) afforded cyanopiperidine **23** (0.667 g, 82%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, $J=7.2$ Hz, 2H), 7.29 (t, $J=7.6$ Hz, 2H), 7.19 (t, $J=7.3$ Hz, 1H), 3.98 (d, $J=18.0$ Hz, 1H), 3.75 (d, $J=18.0$ Hz, 1H), 2.73 (dqd, $J=12.2$, 6.12, 2.74 Hz, 1H), 2.07 (ddd, $J=13.3$, 5.6, 3.1 Hz, 1H), 1.86 (dq, $J=14.9$, 7.5 Hz, 1H), 1.77–1.62 (m, 3H), 1.55–1.48 (m, 2H), 1.32 (m, 1H), 0.99 (d, $J=6.1$ Hz, 3H), 0.94 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 128.3, 126.8, 126.4, 120.3, 65.2, 57.2, 55.3, 35.0, 34.7, 32.6, 22.8, 21.3, 8.8; IR (thin film) 2216 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}N$ $[M-CN]^+$ 216.1752, found 216.1761. Long term storage (>24 h) was effected by concentrating the cyanopiperidine down from Al_2O_3-filtered NEt_3 several times and low-temperature (−20 °C) storage under argon.

4.1.6. *trans*-2-Cyano-2,6-dimethyl-piperidine-1-carboxylic acid *tert*-butyl ester (24). To a −78 °C solution of diisopropylamine (8.6 mL, 61 mmol) in THF (200 mL) was added *n*-BuLi (1.6 M, 35.6 mL, 57 mmol) over 10 min. After 30 min, DMPU (10.6 mL, 88 mmol) was added followed by dropwise addition of a solution of **13** (9.82 g, 43.8 mmol) in THF (50 mL) over 20 min. After 1.5 h, iodomethane (8.2 mL, 131 mmol) was added over 5 min and the solution was stirred for 1.5 h. Half-saturated NH_4Cl solution (500 mL) was added and the reaction was warmed

to room temperature and extracted with Et_2O (3×150 mL). The combined organic phases were washed with satd aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded cyanopiperidine **24** (9.03 g, 86%) as a pale yellow solid. Low-temperature (−20 °C) recrystallization from EtOH/MeOH/H_2O provided crystals (colorless cubes) suitable for X-ray diffraction. Mp 38–40 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (m, 1H), 4.00 (m, 1H), 2.21 (m, 1H), 1.94–1.84 (m, 1H), 1.81 (s, 3H), 1.79–1.59 (m, 5H), 1.52 (s, 9H), 1.24 (d, J=6.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 122.8, 81.7, 49.8, 49.7, 38.9, 29.3, 29.0, 28.5, 18.8, 15.3; IR (thin film) 1708 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{22}N_2O_2Na$ $[M+Na]^+$ 261.1579, found 261.1580; Anal. calcd for $C_{13}H_{22}N_2O_2$: C 65.51, H 9.30, N 11.75; found C 65.70, H 9.23, N 11.93.

4.1.7. *trans*-2-Cyano-2-ethyl-6-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (25). To a −78 °C solution of diisopropylamine (0.240 mL, 1.72 mmol) in THF (10.0 mL) was added *n*-BuLi (1.46 M, 1.09 mL, 1.59 mmol) over 5 min. After 15 min, DMPU (0.297 mL, 2.46 mmol) was added followed by dropwise addition of a solution of **13** (0.275 g, 1.23 mmol) in THF (1.0 mL +0.5 mL rinse) over 5 min. After 2 h, iodoethane (0.295 mL, 3.69 mmol) was added over 2 min and the solution was stirred for 2 h. Half-saturated NH_4Cl solution (40 mL) was added and the reaction was warmed to room temperature and extracted with EtOAc (3×15 mL). The combined organic phases were washed with satd aq NaCl (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded cyanopiperidine **25** (0.257 g, 83%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (m, 1H), 2.28 (dq, J=14.7, 7.4 Hz, 1H), 2.16–2.06 (m, 2H), 1.92–1.82 (m, 2H), 1.76–1.60 (m, 3H), 1.52 (s, 9H), 1.30 (d, J=6.9 Hz, 3H), 0.94 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 122.4, 81.5, 53.9, 49.4, 33.6, 32.2, 28.6, 28.5, 19.5, 14.6, 8.5; IR (thin film) 1708 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{24}N_2O_2Na$ $[M+Na]^+$ 275.1736, found 275.1725.

4.1.8. 4-(Triisopropylsiloxy)butyric acid methyl ester (28). To a solution of γ-hydroxybutyric acid methyl ester (4.30 g, 36.4 mmol (contaminated with 2.21 g of γ-butyrolactone)) in DMF (20 mL) was added imidazole (2.98 g, 43.7 mmol) followed by dropwise addition of TIPS-Cl (9.4 mL, 44 mmol) over 5 min. After 24 h, water (200 mL) was added and the mixture was extracted with Et_2O (4×50 mL) and the combined organic phases were washed with satd aq NaCl (3×50 mL), dried ($MgSO_4$)- and concentrated. Flash chromatography (10% Et_2O/hexanes) afforded ester **28** (9.99 g, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (t, J=6.1 Hz, 2H), 3.66 (s, 3H), 2.43 (t, J=7.5 Hz, 2H), 1.85 (p, J=6.9 Hz, 2H), 1.03 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 62.1, 51.4, 30.4, 28.0, 17.9, 11.8; IR (thin film) 1743 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{15}H_{30}O_3Si$ $[M+H]^+$ 275.2042, found 275.2054.

4.1.9. 1,1-Dideuterio-4-triisopropylsilanyloxybutan-1-ol (29). To a 0 °C suspension of $LiAlD_4$ (0.576 g, 13.7 mmol) in Et_2O (40 mL) was added a solution of ester **28** (5.02 g, 18.3 mmol) in Et_2O (10 mL) over 15 min. After 30 min, satd aq NaCl (ca. 10 mL) was added dropwise and the resulting mixture was stirred vigorously for 15 min and then filtered through a thin Celite pad, washing with Et_2O (ca. 200 mL). Concentration of the filtrate and flash chromatography (30% EtOAc/hexanes) afforded alcohol **29** (4.27 g, 94%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, J=4.5 Hz, 2H), 2.55 (br s, 1H), 1.66 (m, 4H), 1.09 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.8, 30.3, 30.2, 18.4, 12.4; IR (thin film) 3337 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{14}H_{28}D_2O_2Si$ $[M+H]^+$ 249.2217, found 249.2222.

4.1.10. Phosphoric acid diethyl ester 1,1-dideuterio-4-triisopropylsilanyloxy-butyl ester (30). To a 0 °C solution of alcohol **29** (2.01 g, 8.09 mmol) in Et_2O (30 mL) was added pyridine (0.98 mL, 12 mmol) followed by dropwise addition of diethyl chlorophosphate (1.40 mL, 9.71 mmol) over 5 min. A catalytic amount of DMAP (5 crystals) was added and the reaction was allowed to stir at room temperature for 24 h. Water (100 mL) was added, the mixture was stirred for 15 min and the layers were separated. The aqueous phase was extracted with Et_2O (2×30 mL) and the combined organic phases were washed with satd aq NaCl (3×20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (gradient elution: 10 to 50% EtOAc/hexanes) afforded phosphate **30** (2.60 g, 84%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (dp, J=7.2, 1.4 Hz, 4H), 3.70 (dt, J=6.2, 1.2 Hz, 2H), 1.74 (t, J=8.0 Hz, 2H), 1.60 (m, 2H), 1.32 (t, J=7.0 Hz, 6H), 1.04 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.0 (J=5.8 Hz), 63.2, 29.3, 27.2 (J=7.0 Hz), 18.4, 16.6 (J=6.8 Hz), 12.4; IR (thin film) 1281, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{37}D_2O_5PSiNa$ $[M+Na]^+$ 407.2326, found 407.2308.

4.1.11. Phosphoric acid diethyl ester 1,1-dideuterio-4-iodo-butyl ester (14). To a chilled (0 °C) flask containing phosphate **30** (1.96 g, 5.10 mmol) was added TBAF solution (1.0 M in THF, 5.6 mL, 5.6 mmol) and the solution was stirred for 30 min. The cooling bath was removed and the reaction was allowed to stir for an additional 30 min. Solvent was removed by rotary evaporation and the resulting pale brown oil was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Imidazole (2.28 g, 33.5 mmol) was added followed by PPh_3 (8.00 g, 30.5 mmol) and the mixture was stirred until dissolution at which time iodine (7.74 g, 30.5 mmol) was added in portions over 5 min. After 1 h, Et_2O (50 mL) was added and the mixture was washed with 1 M aq HCl (2×10 mL), satd aq $NaHCO_3$ (2×10 mL) and 10% aq $Na_2S_2O_3$ (2×10 mL). The combined aqueous phases were extracted with Et_2O (3×10 mL) and the combined organic phases were then washed with satd aq NaCl (10 mL), dried (Mg_2SO_4) and concentrated. Flash chromatography (Et_2O) afforded iodide **14** (1.21 g, 70% over 2 steps) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (m, 4H), 3.22 (t, J=6.8 Hz, 2H), 1.94 (m, 2H), 1.78 (t, J=8.1 Hz, 2H), 1.34 (dt, J=7.1, 0.95 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.2 (J=5.8 Hz), 31.3 (J=6.9 Hz), 29.8, 16.6 (J=6.6 Hz), 6.3; IR (thin film) 1267, 1030 cm^{-1}; HRMS (CI/NH_3) calcd for $C_8H_{16}D_2IO_4P$ 338.0111, found 338.0110. Comparison to the corresponding non-deuterated compound[4] confirmed the position of the deuterium labels. Deuterium incorporation was quantitative within the limits of ^{1}H NMR.

4.1.12. Phosphoric acid 3-(*cis*-1-benzyl-2-cyano-6-methyl-piperidin-2-yl)-1,1-dideuterio-propyl ester diethyl ester (15). To a −78 °C solution of diisopropylamine (0.297 mL, 2.12 mmol) in THF (5.0 mL) was added *n*-BuLi (1.38 M, 1.42 mL, 1.96 mmol) over 2 min. After 15 min, DMPU (0.394 mL, 3.26 mmol) was added followed by dropwise addition of a solution of *trans*-**12** (0.350 g, 1.63 mmol) in THF (2.0 mL +0.5 mL flask rinse) over 10 min. After 1.5 h, a solution of **14** (0.552 g, 1.63 mmol) in THF (1.5 mL +0.5 mL rinse) was added over 2 min. After 1.5 h, water (15 mL) was added and the mixture was warmed to room temperature and extracted with EtOAc (3×8 mL). The combined organic extracts were washed with satd aq NaCl (2×5 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (basic Al_2O_3, CH_2Cl_2 to 10% Et_2O/CH_2Cl-$_2$ to Et_2O to 10% MeOH/Et_2O) afforded cyanopiperidine **15** (0.550 g, 79%) as a pale yellow oil. Additional chromatography (basic Al_2O_3, 50% EtOAc/hexanes to EtOAc) afforded an analytical sample: ^{1}H NMR (500 MHz, C_6D_6) δ 7.22 (d, J=7.6 Hz, 2H), 7.16 (m, 2H), 7.05 (t, J=7.2 Hz, 1H), 3.94 (m, 4H), 3.89 (d, J=17.9 Hz, 1H), 3.55 (d, J=17.9 Hz, 1H), 2.58 (m, 1H), 1.65–1.49 (m, 4H), 1.36–1.27 (m, 5H), 1.24–1.09 (m, 3H), 1.05 (t, J=7.0 Hz, 6H), 1.00–0.92 (m, 2H), 0.78 (d, J=6.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.6, 128.6, 127.0, 126.6, 119.9, 64.2, 63.4 (d, J=5.5 Hz), 57.0, 55.5, 39.0, 35.0, 34.8, 30.0 (d, J=6.7 Hz), 22.7, 21.4, 20.3, 16.2 (d, J=6.4 Hz); IR (thin film) 1275, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{33}D_2NO_4P$ $[M-CN]^+$ 398.2215, found 398.2208. Long term storage (>24 h) was effected by concentrating the cyanopiperidine down from Al_2O_3-filtered NEt_3 several times and low-temperature (−20 °C) storage under argon.

4.1.13. *trans*-2-Cyano-2-[4-(diethoxy-phosphoryloxy)-4,4-dideuterio-butyl]-6-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (16). To a −78 °C solution of diisopropylamine (0.195 mL, 1.39 mmol) in THF (5.0 mL) was added *n*-BuLi (1.52 M, 0.845 mL, 1.28 mmol) over 2 min. After 15 min, DMPU (0.259 mL, 2.14 mmol) was added followed by dropwise addition of a solution of **13** (0.264 g, 1.18 mmol) in THF (1.0 mL) over 5 min. After 1 h, a solution of **14** (0.362 g, 1.07 mmol) in THF (1.0 mL) was added over 3 min. After 3 h, half-saturated aq NH_4Cl (25 mL) was added and the mixture was warmed to room temperature and extracted with EtOAc (3×10 mL). The combined organic phases were washed with satd $Na_2S_2O_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (25% hexanes/EtOAc) afforded cyanopiperidine **16** (0.349 g, 75%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (m, 1H), 4.11 (m, 4H), 2.31 (td, J=12.5, 5.1 Hz, 1H), 2.17–2.12 (m, 1H), 2.04 (td, J=12.7, 4.3 Hz, 1H), 1.92–1.81 (m, 2H), 1.75–1.59 (m, 5H), 1.51 (s, 9H), 1.39 (m, 1H), 1.34 (m, 6H), 1.30 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 122.2, 81.6, 63.9 (d, J=6.2 Hz), 53.2, 49.5, 38.6, 34.4, 30.1 (d, J=6.8 Hz), 28.6, 28.5, 20.2, 19.4, 16.4 (d, J=6.7 Hz), 14.7; IR (thin film) 1705 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{36}N_2O_6PD_2$ $[M+H]^+$ 435.2595, found 435.2606.

4.1.14. *cis*-1-Benzyl-2,6-dimethyl-piperidine (31). To a −78 °C solution of **22** (0.0972 g, 0.426 mmol) in THF (0.5 mL)/pentane (0.5 mL) was added 3 drops of *n*-BuLi/hex. This solution was transferred over 15 s via cannula down the chilled wall of a flask containing a solution of LiDBB (1.05 mmol) and TMEDA (0.141 mL, 0.936 mmol) in THF (2.0 mL)/pentane (2.0 mL). After 5 min, CD_3OD (0.3 mL) was added down the flask wall over 15 s. After 15 min, water (10 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic phases were washed with satd aq NaCl solution (3 mL), dried (Na_2SO_4) and concentrated. GC analysis of the crude reaction mixture indicated a dr of 98:2 *cis*/*trans*. Flash chromatography (10% *i*-PrOH/CH_2Cl_2) afforded piperidine **31** (0.0457 g, 52%) as a pale brown oil. ^{1}H NMR was consistent with literature data[21] and indicated 77% D.

4.1.15. Representative reductive lithiation/deuterium quench (inverse addition). To a −40 °C solution of **24** (0.0534 g, 0.224 mmol) and 1,10-phenanthroline (1 crystal) in THF (5.0 mL) was added *n*-BuLi/hexanes (2 drops) followed by addition of LiDBB solution (ca. 0.50 M, 0.986 mL, 0.493 mmol) over 15 s. After 5 min, CD_3OD (0.3 mL) was added and the reaction was stirred for 5 min. Half-saturated NH_4Cl (20 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with satd aq NaCl (3 mL), dried (Na_2SO_4). A sample was analyzed by GC, indicating a dr of 94:6 *cis*-**34**/*trans*-**34**. GC–MS (EI) analysis of a sample indicated deuterium incorporations of 84% D (*cis*-**34**) and 72% D (*trans*-**34**). Flash chromatography (20% CH_2Cl_2/hexanes to 10% Et_2O/hexanes) afforded an inseparable mixture of *cis*/*trans*-**34** (0.0321 g, 67%) as a colorless oil. ^{1}H NMR was consistent with literature data.[15b,31]

4.1.16. *trans*/*cis*-Dideuterio-6-benzyl-7-methyl-6-aza-spiro[4.5]decane (*trans*/*cis*-17). To a 0 °C solution of **15** (0.0140 g, 0.0330 mmol) and 1,10-phenanthroline (1 crystal) in THF (0.25 mL) was added *n*-BuLi/hexanes (1 drop). This solution was added via syringe down the chilled flask wall over 1 min to a −78 °C solution of LiDBB solution (ca. 0.50 M, 0.165 mL, 0.0824 mmol) in THF (2.0 mL) followed by a syringe/flask rinse of THF (0.25 mL). After 1.5 h, MeOH (0.1 mL) was added followed by water (6 mL) and the mixture was warmed to room temperature and extracted with EtOAc (3×2 mL). The combined organic phases were washed with satd aq NaCl (1 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (20% CH_2Cl_2/hexanes to 7.5% EtOAc/hexanes) afforded spirocycles *trans*/*cis*-**17** (0.0063 g, 85%) as a pale yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.42 (d, J=7.2 Hz, 2H), 7.27 (m, 2H), 7.15 (t, J=7.3 Hz, 1H), 3.79 (d, J=17.1 Hz, 1H), 3.50 (d, J=17.1 Hz, 1H), 2.75 (dqd, J=9.6, 6.5, 3.1 Hz, 1H), 1.71–1.19 (m, 12H), 0.81 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 145.4, 128.1, 127.2, 125.9, 67.9, 55.0, 51.5, 39.5, 36.7, 32.9, 25.6, 25.1, 22.0, 21.4; IR (thin film) 2930, 1453 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}D_2N$ $[M+H]^+$ 246.2189, found 246.2175. For correlation purposes, the product from a larger scale experiment (ca. 0.300 g) was transformed without purification to the corresponding *N*-Boc compounds (*cis*/*trans*-**18**) through the following sequence: (1) LiDBB, THF, −78 °C; (2) $Pd(OH)_2$/C, H_2 (1 atm), 1 N HCl/MeOH, 6 h and (3) Boc_2O, 60 °C, 48 h (34% yield, 3 steps). ^{1}H NMR indicated a dr of 92:8 *trans*/*cis*-**18**.

4.1.17. *cis*-1-Benzyl-2-ethyl-2,6-dimethyl-piperidine (37). To a −78 °C solution of **23** (0.0799 g, 0.330 mmol), trimethyl phosphate (0.777 mL, 6.60 mmol) and 1,10-phenanthroline (1 crystal) in THF (1.0 mL) was added *n*-BuLi/hexanes (3 drops). This solution was transferred via cannula over 5 min down the chilled flask wall of an LiDBB solution (ca. 0.50 M, 2.64 mL, 1.32 mmol) in THF (4.0 mL) at −78 °C. The reaction was stirred for 15 h with gradual warming to room temperature at which time it was diluted with Et_2O (25 mL) and extracted with 1 N HCl (3× 7.5 mL). The combined acidic aqueous phases were washed with Et_2O (3×5 mL), basified to pH=12 with solid KOH and extracted with Et_2O (3×5 mL). The combined organic phases were washed with satd aq NaCl (3 mL), dried (K_2CO_3) and concentrated. GC analysis of a sample indicated the presence of a single major component with several minor components. GC–MS (CI) confirmed the identity of the major component as **37** but failed to detect the minor components. Flash chromatography (5% EtOAc/hexanes) afforded **37** (0.0203 g, 26%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J=7.7 Hz, 2H), 7.25 (t, J=7.6 Hz, 2H), 7.14 (t, J=7.3 Hz, 1H), 3.99 (d, J=17.4 Hz, 1H), 3.34 (d, J=17.4 Hz, 1H), 2.69 (dqd, J=12.5, 6.2, 2.3 Hz, 1H), 1.59–1.43 (m, 8H), 1.26 (m, 2H), 0.99 (s, 3H), 0.81–0.78 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 127.9, 127.2, 125.7, 57.6, 54.5, 52.5, 36.6, 36.1, 35.4, 23.5, 20.4, 15.6, 8.7; IR (thin film) 2929, 1459 cm^{-1}; MS (CI) *m/z* 232 (M+H, 100%).

4.1.18. *cis/trans*-Dideuterio-7-methyl-6-aza-spiro[4.5]-decane-6-carboxylic acid *tert*-butyl ester (*cis/trans*-18). To a −78 °C solution of **16** (0.0522 g, 0.120 mmol) and 1,10-phenanthroline (1 crystal) in THF (0.5 mL) was added *n*-BuLi/hex (1 drop) to form a brown solution. This solution was transferred via syringe to a −78 °C solution of LiDBB solution (ca. 0.50 M in THF, 0.529 mL, 0.264 mmol) in THF (2.0 mL) down the chilled flask wall over 3 min followed by a flask/syringe rinse with THF (0.25 mL). After 2.5 h, half-saturated NH_4Cl (10 mL) was added and the mixture was warmed to room temperature and extracted with EtOAc (3×4 mL). The combined organic phases were washed with satd aq NaCl (3 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (20% CH_2Cl_2/hexanes to 5% Et_2O/hexanes) afforded diastereomers *cis/trans*-**18** (0.0236 mg, 77%) as a colorless oil. ^{1}H NMR indicated a dr of 72:28 *cis/trans*-**18**; HRMS (ESI) calcd for $C_{15}H_{25}D_2NO_2Na$ $[M+Na]^+$ 278.2063, found 278.2061.

Analytical data for non-deuterated compound. ^{1}H NMR (500 MHz, C_6D_6) δ 4.38 (m, 1H), 2.75 (ddd, J=13.0, 8.9, 4.6 Hz, 1H), 2.28–2.15 (m, 2H), 1.94 (dtt, J=11.1, 7.0, 3.4 Hz, 1H), 1.59–1.48 (m, 4H), 1.44 (s, 9H), 1.43–1.35 (m, 3H), 1.31–1.17 (m, 3H), 1.08 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.9, 78.8, 64.8, 49.2, 41.0, 39.8, 38.7, 30.1, 29.0, 27.3, 26.2, 21.5, 16.4; IR (thin film) 1698 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{27}NO_2Na$ $[M+Na]^+$ 276.1939, found 276.1949.

4.1.19. *cis/trans*-2-Ethyl-2,6-dimethyl-piperidine-1-carboxylic acid *tert*-butyl ester (*cis/trans*-39). To a −40 °C solution of **25** (0.104 g, 0.412 mmol) and 1,10-phenanthroline (1 crystal) in THF (5.0 mL) was added *n*-BuLi/hex (3 drops) to form a brown solution. To this solution was added LiDBB solution (ca. 0.50 M, 1.81 mL, 0.907 mmol) rapidly via syringe. After 5 min, the solution was cooled to −78 °C and trimethyl phosphate (0.970 mL, 8.24 mmol) was added over 2 min. The solution was allowed to stir for 15 h with gradual warming to room temperature. Satd aq NH_4Cl (15 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic phases were washed with satd aq NaCl (3 mL), dried (Na_2SO_4) and concentrated. GC analysis indicated a diastereomeric ratio of 87:13 *cis/trans*. Flash chromatography (20% CH_2Cl_2/hexanes to 2.5% EtOAc/hexanes) afforded a mixture of *cis/trans*-**39** (0.0370 mg, 37%) as a colorless oil.

Analytical data for cis-**39**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (m, 1H), 2.16 (dq, J=15.0, 7.5 Hz, 1H), 2.03 (ddd, J=14.3, 9.6, 6.9 Hz, 1H), 1.86 (m, 1H), 1.73–1.40 (m, 4H), 1.46 (s, 9H), 1.37 (s, 3H), 1.20 (m, 1H), 1.18 (d, J=7.0 Hz, 3H), 0.78 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 79.0, 57.0, 47.9, 33.1, 33.0, 28.8, 27.3, 26.9, 22.2, 14.2, 9.1; IR (thin film) 1688 cm^{-1}; MS (CI) *m/z* 242 (M+H, 100%).

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Generation of ketone dilithio α,β-dianions and their reactions with electrophiles

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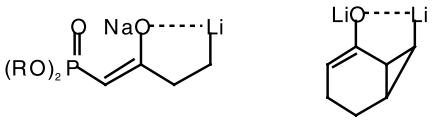
Abstract—Ketone dilithio α,β- and α,β′-dianions can be generated by a tin–lithium exchange reaction of the lithium enolate of β-tributyltin substituted ketones. A chelation-aided approach, which employs β-dichlorobutyltin substituted ketones and *n*-BuLi, is also useful for the generation of ketone α,β-dianions having the *Z*-geometry at the alkene. The generated dianions can be transformed into substituted ketones by reaction with various carbon electrophiles.

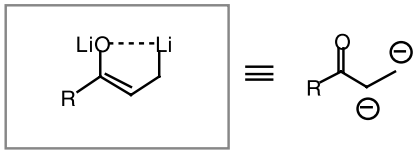
1. Introduction

One of the distinct advantages of carbanion chemistry[1] over radical and cation chemistry is the relatively facile generation and control of carbon species having doubly reactive centers.[2] We have been interested in the behavior of dianionic species of ketones, and in particular lithium enolate species containing an additional carbon–lithium center. Initial work on ketone dianion chemistry involving the generation and reactions of ketone α,α′- and α,α-dianion species were reported by Harris[3] and Kowalski[4] and their co-workers, respectively. In terms of ketone α,β′-dianions, the Goswami group reported α-diethylphosphoryl dianionic species **A**,[5] in which the cationic counterions were sodium and lithium. Subsequently, the Cohen group reported the first dilithio species of α,β′-dianionic species **B**, characteristically bearing a cyclopropyllithium moiety.[6]

Stimulated by this earlier work, we became interested in the preparation and reaction of the simple dilithio species **C**. Thus, we previously reported a two-step method for its generation from β-tributylstannyl ketones via conversion to the corresponding lithium enolates and subsequent tin–lithium exchange reactions.[7] Very recently we also reported a one-step method, starting from β-dichlorobutylstannyl ketones and using 4 equiv of BuLi, which was found to be particularly useful for the regio- and stereo-controlled



A **B**



C *this work*

synthesis of ketone α,β-dianions.[8,9] In the reactions of these ketone α,β-dianions with alkyl halides, two anionic centers are available for reaction. We found that the dianions exhibited higher reactivity at the allylic lithium moiety rather than lithium enolate moiety toward a variety of carbon electrophiles.[10] In this article, we would like to report on the full scope of the generation of ketone α,β-dianions using tin–lithium exchange reactions and their reactions with electrophilic reagents.

2. Results and discussion

2.1. Generation of ketone α,β-dianions from β-tributylstannyl ketones

In order to generate ketone dilithio α,β-dianions, we

Keywords: Dianion; Electrophiles; Enolate; Tin–lithium exchange reaction; *Z* geometry.
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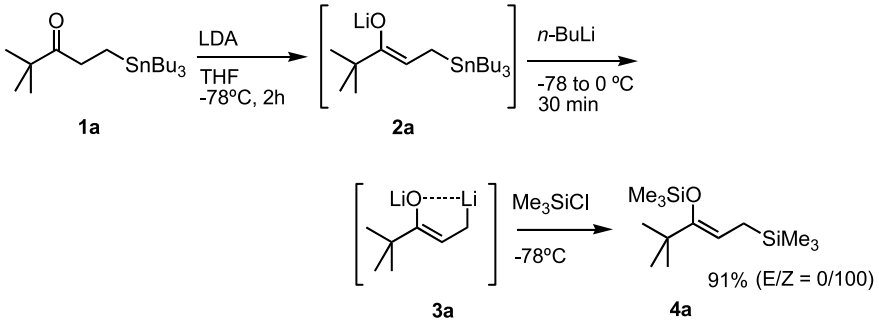


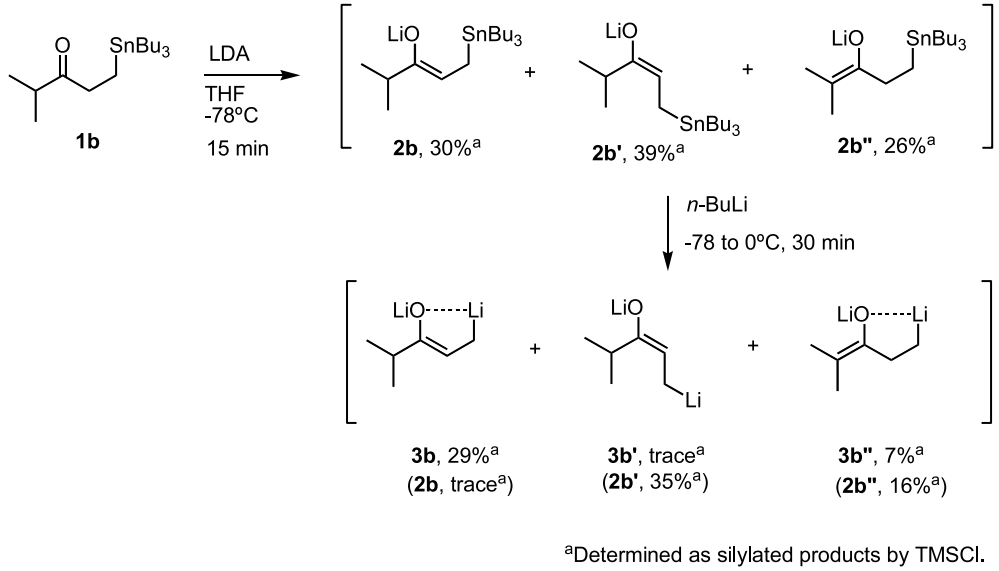
Scheme 1.

initially attempted a two-step method using β-tributylstannyl ketones **1** as the substrates. The β-tributylstannyl ketones **1**, were conveniently prepared by the chemoselective alkylation at the Sn atom of the corresponding β-trichlorostannyl ketones, readily available from the ring opening reaction of siloxycyclopropanes with tin tetrachloride[11] or hydrotrichlorostannylation of enones,[12] using 3 equiv of *n*-BuMgBr. Treatment of *tert*-butyl β-(tributylstannyl)ethyl ketone (**1a**) with lithium diisopropylamide (LDA) in THF at −78 °C gave the corresponding lithium enolate **2a** having a *Z* geometry selectively. The resulting lithium enolate was then treated with *n*-BuLi at −78 to 0 °C for 30 min to give the expected lithium ketone dilithio α,β-dianion **3a**, which was trapped as its silyl ether **4a** (Scheme 1).

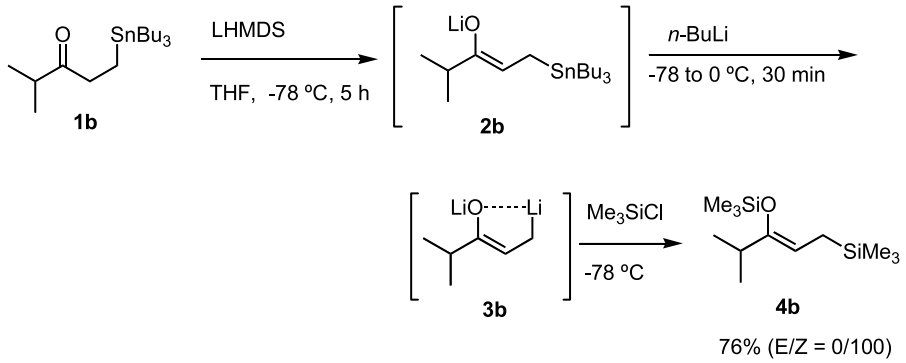
To determine the ease of the tin–lithium exchange reaction, we examined the reaction of stereo- and regioisomeric mixtures of lithium enolates derived from isopropyl β-tributylstannyl ketone **1b** (Scheme 2). Deprotonation of **1b** by LDA gave a mixture of three isomeric lithium enolates, **2b** (allyl-*Z*, 30%), **2b′** (allyl-*E*, 39%), and **2b″** (homoallyl, 26%). Li–Sn exchange reactions of this mixture of the enolates with *n*-butyllithium at −78 to 0 °C for 30 min, followed by TMSCl trapping, gave bis-silylated products **3b** (allyl-*Z*, 29%), **3b′** (allyl-*E*, trace), and **3b″** (homoallyl, 7%) along with the silylated products of the unreacted enolates (**2b**, trace; **2b′**, 35%; and **2b″**, 16%). These results suggested that (i) Li–Sn exchange proceeds in a stereospecific manner, (ii) the ease of Li–Sn exchange decreases in the order: **2b** (allyl-*Z*) > **2b″** (homoallyl) ≫ **2b′** (allyl-*E*), and (iii) the inefficient Li–Sn exchange of *E*-enolate **2b′** may be due to the lack of stabilization by internal coordination of the lithioxy group on the resulting lithium dianionic species.

Although the use of LDA gave a mixture of enolates in the above case, lithium hexamethyldisilazide (LHMDS), a bulkier base, was able to generate *Z*-allyl anion **2b** from **1b** selectively, which then underwent a selective conversion to dianion **3b** (Scheme 3).

Table 1 summarizes examples of the present two-step procedure for the generation of ketone dianions **3** from **1**. Thus, **1c–f** were smoothly converted into the corresponding *Z*-allyl dianions (runs 1–4). On the other hand, the reactions of **1g–i**, underwent H-abstractions of the less hindered C–H bonds generating dianions **3g–i** having homoallyllithium structures (runs 5–7). Consistent with the observation in the experiment of **2b″** in Scheme 2, the Sn-Li exchange reaction required a prolonged reaction time (3 h at −78 to 0 °C).

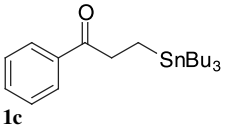
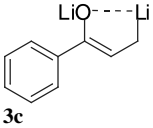
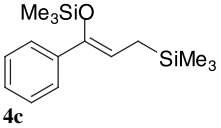
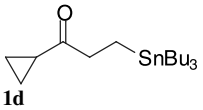
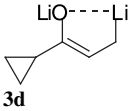
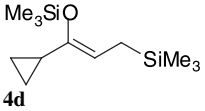
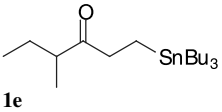
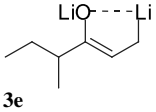
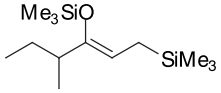
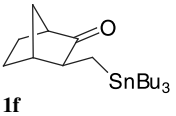
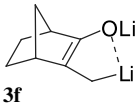
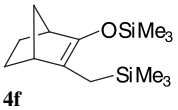
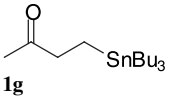
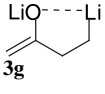
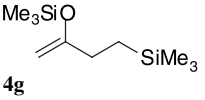
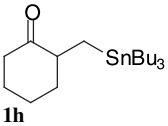
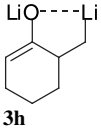
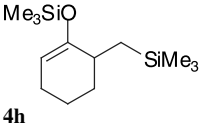
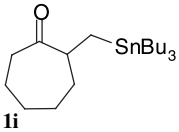
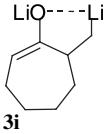
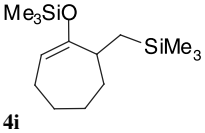


Scheme 2. Tin–Li exchange of lithium enolates derived from **1b**.



Scheme 3.

Table 1. Generation of dianions **3** from β-tributylstannyl ketones **1**[a]

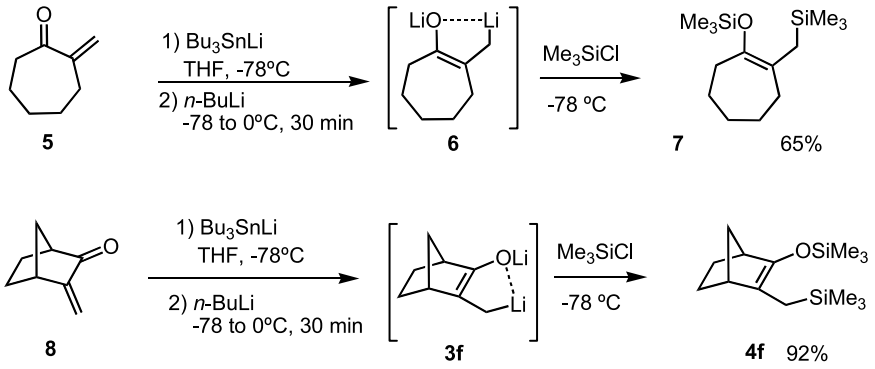
Run	Substrate **1**	Conditions[b]	Dianions **3**	Silylated product **4**	Yield(%)[c]
1	 **1c**	A	 **3c**	 **4c**	70 (*E*/*Z*=0/100)
2	 **1d**	B	 **3d**	 **4d**	79 (*E*/*Z*=0/100)
3	 **1e**	B	 **3e**	 **4e**	85 (*E*/*Z*=0/100)
4	 **1f**	A	 **3f**	 **4f**	75[d]
5	 **1g**	C	 **3g**	 **4g**	72 (95)[e]
6	 **1h**	C	 **3h**	 **4h**	76 (98)[e]
7	 **1i**	C	 **3i**	 **4i**	72 (99)[e]

[a] Carried out on 1 mmol scale in THF (5 mL),for details, see Section 4.
[b] Conditions A: LDA, −78 °C, 2 h/−78 to 0 °C, 30 min. Conditions B: LHMDS, −78 °C, 5 h/−78 to 0 °C, 30 min. Conditions C: LDA, −78 °C, 15 min/−78 to 0 °C, 3 h.
[c] Isolated by flash chromatography.
[d] GC yield.
[e] Regioisomeric purity (%).

We also attempted the Michael addition reaction of Bu_3SnLi with enones to generate lithium enolates of β-tributylstannyl ketones (Scheme 4). Treatment of **5** with tributyltinlithium in THF at −78 °C for 30 min, followed by addition of *n*-butyllithium (1.2 equiv, −78 to 0 °C, 30 min), gave the expected dianion **6**, which was transformed to silyl ether **7** (Scheme 4). Thus, with these two methods, it is possible to prepare regioisomers **6** and **3i**, respectively. Dianion **3f** was also generated from **8** by this Michael addition/Sn-Li exchange protocol.

2.2. Regio- and stereocontrolled generation of dianions from coordinated β-butyldichlorostannyl ketones

It seems likely that the α-protons of β-trichloro- or β-butyl(dichloro)stannyl ketones are more acidic than those of



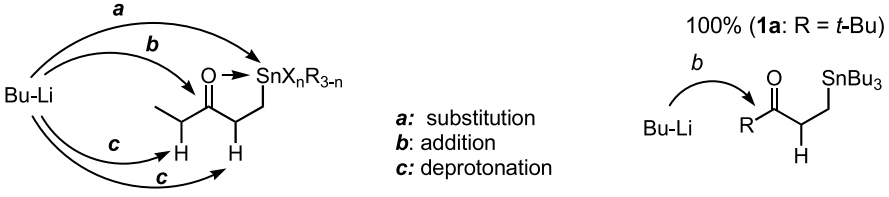
Scheme 4. Michael addition route to ketone α,β-dianions.

β-tributylstannyl ketones due to the intramolecular coordination and/or the inductive effect of the chlorostannyl group.[12] Seeking a convenient approach for stereo- and regioselective dianion formation, we became interested in the utility of such coordinated species. As outlined in Scheme 5, in principle the reaction of β-halostannyl ketones with organolithium reagents can proceed through three different pathways: **a**, substitution at Sn; **b**, addition to the carbonyl; and **c**, abstraction of the α and/or α′-proton. Although the chelation-free substrate, **1a**, undergoes exclusive nucleophilic attack on the carbonyl group in the presence of *n*-BuLi, we envisioned that in the case of a coordinated species, α-deprotonation to form a *Z* enolate would be more rapid than nucleophilic attack on the carbonyl, which would permit a straightforward method for the generation of ketone dianions.

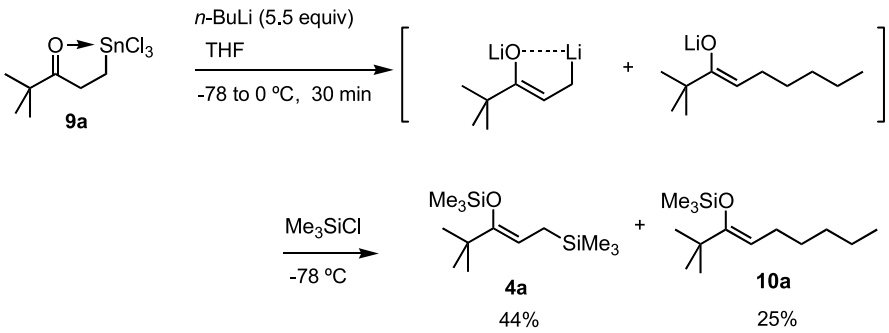
With this working hypothesis, we initially examined the reaction of β-trichlorostannyl ketone **9a** with *n*-BuLi (5.5 equiv) in THF, followed by trapping with TMSCl (Scheme 6). The reaction did indeed give bis-silylated product **4a** via silylation of the expected ketone α,β-dianion **3a** in 44%, together with the formation of enol silyl ether **10a**. This side-reaction involves dehydrostannylation to give *tert*-butyl vinyl ketone, followed by the Michael addition of *n*-BuLi.

Consequently, we found that the selective generation of the desired dianion could be achieved using β-dichlorobutylstannyl ketones as substrates, with which no such side-reaction was observed. For example, when **11a** was treated with *n*-BuLi (4 equiv) in THF at −78 to 0 °C for 30 min, a clean reaction took place to give the desired dianion **3a**, which was transformed to the disilylated product **4a** in 90% yield by trapping with TMSCl (Scheme 7). Treatment of **11a** with 3 equiv of *n*-BuLi at −78 °C and then subsequent quenching with TMSCl at that temperature gave the *Z*-enol silyl ether **12** of the corresponding β-tributylstannyl ketone in 72% yield, supporting the intermediacy of **2a** as a precursor to the dianion **3a**. Thus abstraction of an α-proton by *n*-BuLi precedes the second alkylation at the Sn atom.

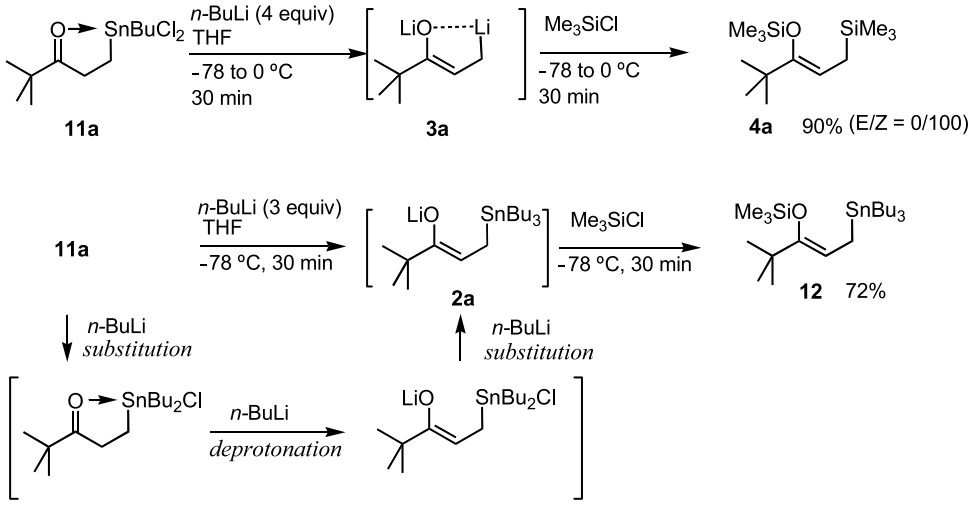
Results of this 'one operation' method are also summarized in Table 2. In each case dianion formation was conducted by simply adding 4 equiv of *n*-BuLi to a THF solution of β-dichlorobutylstannyl ketone **11** at −78 °C and warming up



Scheme 5. Possible reaction courses for the reaction of β-Sn ketones with BuLi.



Scheme 6.



Scheme 7. Generation of dianion **3a** from β-dichlorobutylstannyl ketone **11a** and *n*-BuLi.

Table 2. Generation of ketone α,β-dianions from β-dichlorobutylstannyl ketones[a]

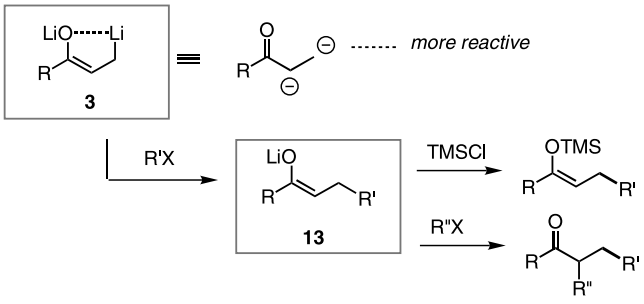
Run	Substrate	Dianions	Product	Yield (%)[b]
1	**11a**	**3a**	**4a**	90 (*E*/*Z*=0/100)
2	**11b**	**3b**	**4b**	84 (*E*/*Z*=0/100)
3	**11c**	**3c**	**4c**	78 (*E*/*Z*=0/100)
4	**11e**	**3e**	**4e**	81 (*E*/*Z*=0/100)
5	**11j**	**3j**	**4j**	76 (*E*/*Z*=0/100)

[a] Carried out on 1 mmol scale in THF (5 mL), for details, see Section 4.
[b] Isolated by flash chromatography.

to 0 °C and the regio- and the stereochemical outcomes of the dianion **3** were confirmed by derivatization to **4**. It is noteworthy that the deprotonation of substrates **11b** and **11e** with α-methylene and α′-methine groups occurred with high α-regio- and *Z*-stereoselectivity. Although the regioselective deprotonation of substrates having two methylene groups α and α′ to the carbonyl is particularly difficult to achieve, it is significant that the α-selective deprotonation was achieved with **11j**. It should be noted that this 'one operation' route has an advantage over the β-tributylstannyl ketone route, vide supra, since it is amine-free, which allows for a clean transmetallation.[9]

2.3. Reactions of ketone α,β-dianions with carbon electrophiles

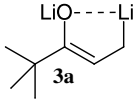
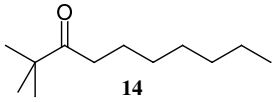
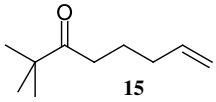
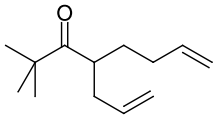
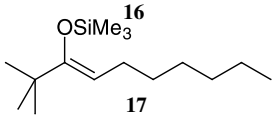
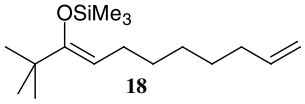
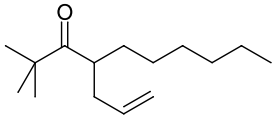
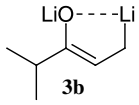
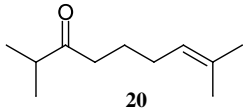
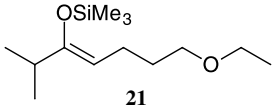
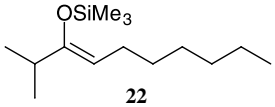
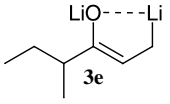
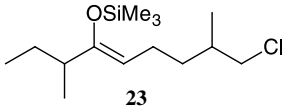
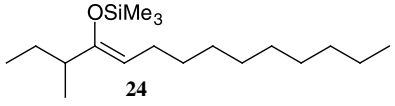
If alkylation of dilithio species **3** were to occur at the carbonyl β-position preferentially, this would provide straightforward access to lithium enolates **13** having a *Z*-geometry (Scheme 8).



Scheme 8. Dianions **3** as a precursor for (*Z*)-form enolates.

As outlined in Scheme 8, the alkylation of dianions **3** with alkyl bromides took place more rapidly at the β-position than at the α-position under controlled conditions, allowing

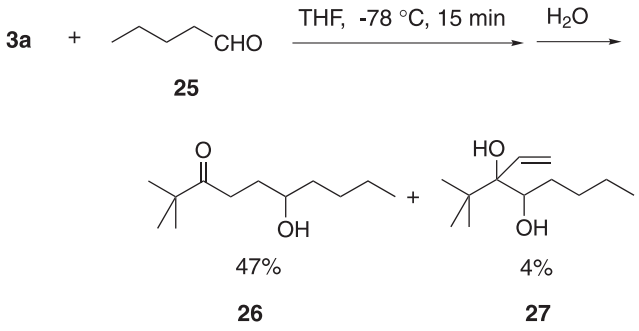
Table 3. Reactions of ketone α,β-dianions **3** with electrophiles[a]

Run	Dianions[b]	Electrophiles (equiv) conditions	Product	Yield (%)[c]
1	 **3a**	1) *n*-$C_5H_{11}Br$ (3) −78 to −20 °C, 1 h 2) H_2O	 **14**	71
2	**3a**	1) CH_2=$CHCH_2Br$ (3) −78 °C, 15 min 2) H_2O	 **15**	62
3	**3a**	CH_2=$CHCH_2Br$ (5)[d] −78 to −20 °C, 1 h	 **16**	74
4	**3a**	1) *n*-$C_5H_{11}Br$ (3) −78 to −20 °C, 1 h 2) Me_3SiCl (2) −78 °C, 15 min	 **17**	70[e]
5	**3a**	1) CH_2=$CH(CH_2)_4Br$ (3) −78 to −20 °C, 1 h 2) Me_3SiCl (2) −78 °C, 15 min	 **18**	69[e]
6	**3a**	1) *n*-$C_5H_{11}Br$ (2) −78 to −20 °C, 1 h 2) CH_2=$CHCH_2Br$ (3)[d] −78 to −25 °C, 1 h	 **19**	70
7	 **3b**	1) Me_2C=$CHCH_2Br$ (3) −78 °C, 15 min 2) H_2O	 **20**	53
8	**3b**	1) $EtO(CH_2)_2Br$ (3) −78 to −20 °C, 1 h 2) Me_3SiCl (2) −78 °C, 15 min	 **21**	72[e]
9	**3b**	1) *n*-$C_5H_{11}Br$ (3) −78 to −20 °C, 1 h 2) Me_3SiCl (2) −78 °C, 15 min	 **22**	68[e]
10	 **3e**	1) $BrCH_2CH(Me)CH_2Cl$ (3) −78 to −20 °C, 1 h 2) Me_3SiCl (2) −78 °C, 15 min	 **23**	68[e]
11	**3e**	1) *n*-$C_8H_{17}Br$ (3) −78 to −20 °C, 1 h 2) Me_3SiCl (2) −78 °C, 15 min	 **24**	81[e]

[a] Carried out on 1 mmol scale in THF(5 mL), for details, see Section 4.
[b] Generated from β-tributylstannyl ketones.
[c] Isolated by flash chromatography.
[d] HMPA (0.5 mL) was added.
[e] *E*/*Z*=0/100.

the conversion to *Z* lithium enolates **13**. Table 3 summarizes the results of the reactions of dianions **3** with electrophiles. For example, treatment of **3a** with *n*-pentyl bromide (3 equiv) at −78 to −20 °C for 1 h followed by proton quenching gave the β-alkylated ketone **14** in 71% yield (run 1). Similarly, β-allylated ketone **15** was prepared by the treatment with allyl bromide (−78 °C, 15 min) followed by proton quenching in 62% yield (run 2). The use of excesses of allyl bromide and HMPA as a co-solvent led to the formation of diallylated product **16** in 74% yield, which could be useful as a substrate for Grubbs' ring closing olefin metathesis leading to cyclohexene derivatives.[13] Needless to say, the β-alkylated enolates can undergo a number of useful transformations developed for metal enolates.[14] Treatment with TMSCl after β-alkylation of **3** provided β-alkylated enol silyl ethers having *Z* geometry in good yields (runs 4, 5, 8, 9, 10 and 11), which are important compounds in synthesis.[15] The β-alkylation/α-allylation sequence leading to **19** was also successful (run 6).

The reaction of dianion **3a** with valeraldehyde **25** followed by proton quenching gave 47% of the desired homoaldol product **26** (Scheme 9).[16] However, optimization of the yields seems rather difficult, because of the large number of byproducts presumably resulting from competing rapid aldol reactions. Interestingly, however, a small amount of 1,2-diol **27** was isolated as a byproduct, which demonstrates the ambident character of the ketone α,β-dianions.[17]



Scheme 9.

3. Conclusions

In summary, we have shown that ketone α,β- and α,β′-dianions can be generated by a Sn-Li exchange reaction of the lithium enolate of β-tributyltin substituted ketones using *n*-BuLi. A chelation-aided approach, which employs β-dichlorobutyltin substituted ketones and *n*-BuLi, was particularly useful for the straightforward generation of ketone α,β-dianions having *Z*/allyl-type structures. The thus generated dianions can be transformed into ketones by sequential reaction at the β and α positions with a variety of carbon electrophiles.

4. Experimental

4.1. General remarks

All reactions were carried out in oven-dried glassware and under an atmosphere of argon. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. Diisopropylamine, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and other reagents were distilled prior to use. β-Tributylstannyl ketones, β-dichlorobutylstannyl ketones, and β-trichlorostannyl ketones were prepared by reported procedure.[9,10] For column chromatography, silica gel 60 (230–400 mesh ASTM, E. Merck) was used. GLC analysis was carried out with a Shimadzu GC-12A apparatus using Hicap-CBP-M25-025 (OV-1 type) column. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX-270 (270 MHz), a JEOL JNM-GSX-400 (400 MHz), or Bruker AM 600 (600 MHz) spectrometer in $CDCl_3$. ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-270 (68 MHz) spectrometer in $CDCl_3$. IR spectra were obtained from a Perkin–Elmer 1610 FTIR spectrometer. Mass spectra (EIMS) and high-resolution mass spectra (HRMS) were recorded on JEOL JMS-DX303 HF spectrometer using electronical ionization (EI) mass spectrometry. Elemental analyses were performed by the Analytical Center, Faculty of Engineering, Osaka University.

4.2. General procedure for the generation of ketone dilithio α,β-dianions 3 from β-tributylstannyl ketones 1 and then trapping with TMSCl

The preparation of (*Z*)-4,4-dimethyl-3-(trimethylsiloxy)-1-(trimethylsilyl)-2-pentene (**4a**) is described as a typical example. *tert*-Butyl (β-tributylstannyl)ethyl ketone **1a** (0.432 g, 1.0 mmol) was added to a cooled solution (−78 °C) of LDA (prepared from diisopropylamine (0.184 mL, 1.3 mmol) and *n*-BuLi (1.58 M hexane solution, 0.76 mL, 1.2 mmol)) in THF (5 mL). After stirring for 2 h at −78 °C, *n*-BuLi (1.58 mL, 2.5 mmol) was added slowly. The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. After cooling to −78 °C, the mixture was quenched with Me_3SiCl (0.271 g, 3.0 mmol). The quenched mixture was diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (SiO_2) using pentane as eluent to yield (*Z*)-4,4-dimethyl-3-(trimethylsiloxy)-1-(trimethylsilyl)-2-pentene (**4a**) (0.235 g, 91%). For **4d** and **4e**, HMDS was used instead of diisopropylamine. The spectral data of β-silyl enol silyl ether **4a–i** are as follows.

4.2.1. (*Z*)-4,4-Dimethyl-3-(trimethylsiloxy)-1-(trimethylsilyl)-2-pentene (4a). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.02 (s, 9H), 0.22 (s, 9H), 1.03 (s, 9H), 1.29 (d, J=8.2 Hz, 2H), 4.51 (t, J=8.2 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.79, 1.19, 15.68, 28.73, 36.31, 98.81, 157.02. IR (NaCl) 1656 cm^{-1} (C=C). MS (EI) 258 (M^+). Anal. Calcd for $C_{13}H_{30}OSi_2$: C, 60.37; H, 11.71. Found: C, 60.36; H, 11.71.

4.2.2. (*Z*)-4-Methyl-3-(trimethylsiloxy)-1-(trimethylsilyl)-2-pentene (4b). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.19 (s, 9H), 1.02 (d, J=6.7 Hz, 6H), 1.31 (d, J=8.6 Hz, 2H), 2.16 (m, 1H), 4.43 (dt, J=0.6, 8.6 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.69, 0.86, 14.99, 21.04, 34.49, 100.24, 154.72. IR (NaCl) 1664 cm^{-1} (C=C). MS (EI) 244 (M^+). HRMS calcd for

$C_{12}H_{28}OSi_2$ 244.1678, found 244.1694. Anal. Calcd for $C_{12}H_{28}OSi_2$: C, 58.92; H, 11.56. Found: C, 58.55; H, 11.51.

4.2.3. (*Z*)-1-Phenyl-1-(trimethylsiloxy)-3-(trimethylsilyl)-1-propene (4c). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.13 (s, 9H), 1.57 (d, J=8.2 Hz, 2H), 5.26 (t, J=8.2 Hz, 1H), 7.19–7.45 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.48, 0.77, 16.89, 107.29, 125.11, 126.82, 127.95, 139.67, 147.91. IR (NaCl) 1638 cm^{-1} (C=C). MS (EI) 278 (M^+). Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.66; H, 9.42. Found: C, 64.47; H, 9.65.

4.2.4. (*Z*)-1-Cyclopropyl-1-(trimethylsiloxy)-3-(trimethylsilyl)-1-propene (4d). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.02 (s, 9H), 0.20 (s, 9H), 0.45–0.57 (m, 4H), 1.26–1.35 (m, 1H), 1.31 (d, J=7.9 Hz, 2H), 4.41 (t, J=7.9 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.66, 0.97, 5.48, 14.98, 15.81, 101.17, 150.08. IR (NaCl) 1664 cm^{-1} (C=C). MS (EI) 242 (M^+). HRMS calcd for $C_{12}H_{26}OSi_2$ 242.1522, found 242.1548.

4.2.5. (*Z*)-4-Methyl-3-(trimethylsiloxy)-1-(trimethylsilyl)-2-hexene (4e). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.19 (s, 9H), 0.86 (t, J=7.4 Hz, 3H), 1.00 (d, J=6.7 Hz, 3H), 1.18–1.37 (m, 1H), 1.32 (d, J=8.0 Hz, 2H), 1.40–1.58 (m, 1H), 1.87–2.03 (m, 1H), 4.41 (t, J=8.0 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.64, 0.97, 11.68, 15.19, 18.48, 27.42, 41.66, 101.43, 153.05. IR (NaCl) 1663 cm^{-1} (C=C). MS (EI) 258 (M^+). HRMS calcd for $C_{13}H_{30}OSi_2$ 258.1835, found 258.1898.

4.2.6. 2-(Trimethylsiloxy)-3-(trimethylsilylmethyl)bicyclo[2.2.1]hept-2-ene (4f). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.19 (s, 9H), 1.07–1.64 (m, 8H), 2.51 (s, 1H), 2.58 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −0.98, 0.64, 14.27, 26.21, 26.26, 45.29, 45.39, 45.61, 118.04, 150.22. IR (NaCl) 1656 cm^{-1} (C=C). MS (EI) 268 (M^+). HRMS calcd for $C_{14}H_{28}OSi_2$ 268.1678, found 268.1679.

4.2.7. 2-(Trimethylsiloxy)-4-(trimethylsilyl)-1-butene (4g). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.19 (s, 9H), 0.61–0.70 (m, 2H), 1.93–2.02 (m, 2H), 4.00 (s, 1H), 4.07 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.81, 0.12, 13.99, 30.72, 88.63, 161.90. IR (NaCl) 1635 cm^{-1} (C=C). MS (EI) 216 (M^+). HRMS calcd for $C_{10}H_{24}OSi_2$ 216.1365, found 216.1376.

4.2.8. 1-(Trimethylsiloxy)-6-(trimethylsilylmethyl)-1-cyclohexene (4h). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.17 (s, 9H), 0.43 (dd, J=10.7, 15.0 Hz, 1H), 0.38–0.47 (m, 1H), 1.06 (dd, J=3.3, 15.0 Hz, 1H), 1.18–1.52 (m, 2H), 1.74–1.99 (m, 1H), 1.89–2.03 (m, 2H), 2.04–2.17 (m, 1H), 4.75 (t, J=3.7 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −0.71, 0.37, 19.96, 20.28, 24.22, 31.29, 35.05, 102.88, 154.91. IR (NaCl) 1711 cm^{-1} (C=C). MS (EI) 256 (M^+). HRMS calcd for $C_{13}H_{28}OSi_2$ 256.1678, found 256.1672.

4.2.9. 1-(Trimethylsiloxy)-6-(trimethylsilylmethyl)-1-cycloheptene (4i). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.17 (s, 9H), 0.67 (dd, J=8.8, 14.6 Hz, 1H), 0.89 (m, 1H), 0.96 (dd, J=6.1, 14.6 Hz, 1H), 1.43–1.78 (m, 5H), 1.94–2.05 (m, 2H), 2.32–2.36 (m, 1H), 4.85 (t, J=7.0 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −0.86, 0.40, 18.99, 24.05, 26.08, 28.03, 31.85, 41.03, 106.24, 159.48. IR (NaCl) 1658 cm^{-1} (C=C). MS (EI) 270 (M^+).

4.3. Generation of ketone dilithio α,β-dianions 3 from α,β-unsaturated ketones via Michael addition of Bu_3SnLi

The preparation of 1-(trimethylsiloxy)-2-(trimethylsilylmethyl)-1-cycloheptene (**7**) is described as a typical example. 2-Methylenecycloheptanone (0.124 g, 1.0 mmol) was added to a cooled solution (−78 °C) of Bu_3SnLi (prepared from Bu_3SnH (0.466 g, 1.6 mmol) and LDA (1.2 mmol)) in THF (5 mL). After stirring for 30 min at −78 °C, *n*-BuLi (1.5 M hexane solution, 1.67 mL, 2.5 mmol) was added. The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. After re-cooling to −78 °C, the mixture was quenched with Me_3SiCl (0.271 g, 3.0 mmol). The quenched mixture was diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (SiO_2) using pentane as eluent to yield 1-(trimethylsiloxy)-2-(trimethylsilylmethyl)-1-cycloheptene (**7**) (0.176 g, 65%).

4.3.1. 1-(Trimethylsiloxy)-2-(trimethylsilylmethyl)-1-cycloheptene (7). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.16 (s, 9H), 1.43 (s, 2H), 1.46–1.58 (m, 4H), 1.60–1.74 (m, 2H), 1.98 (t, J=5.4 Hz, 2H), 2.26 (t, J=5.3 Hz, 2H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −0.64, 0.95, 23.48, 25.73, 26.91, 31.81, 33.40, 34.99, 117.74, 145.82. IR (NaCl) 1655 cm^{-1} (C=C). MS (EI) 270 (M^+). Anal. Calcd for $C_{14}H_{30}OSi_2$: C, 62.16; H, 11.18. Found: C, 61.90; H, 11.24.

4.4. General procedure for the generation of ketone dilithio α,β-dianions 3 from β-dichlorobutylstannyl ketones 11 and the trapping with TMSCl

(*Z*)-3-(Trimethylsiloxy)-1-(trimethylsilyl)-2-nonene (**4j**) is described as a typical example. A solution of β-dichlorobutylstannyl ketone **11j** (0.365 g, 0.94 mmol) in THF (10 mL) was treated with *n*-BuLi (1.66 M hexane solution, 2.40 mL, 3.95 mmol) at −78 °C. The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. After cooling to −78 °C, the mixture was quenched with Me_3SiCl (0.253 g, 2.35 mmol). The quenched mixture was diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (SiO_2) using pentane as eluent to yield (*Z*)-3-(trimethylsiloxy)-1-(trimethylsilyl)-2-nonene (**4j**) (0.204 g, 76%). Regioisometic purity, >99% (GC analysis of the crude products).

4.4.1. (*Z*)-3-(Trimethylsiloxy)-1-(trimethylsilyl)-2-nonene (4j). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.17 (s, 9H), 0.85–0.90 (m, 3H), 1.22–1.33 (m, 8H), 1.35–1.48 (m, 2H), 1.99 (t, J=7.3 Hz, 2H), 4.41 (t, J=8.0 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ −1.63, 0.81, 14.07, 14.96, 22.67, 27.24, 28.83, 31.73, 36.60, 103.11,

149.02. IR (NaCl) 1669 cm^{-1} (C═C). MS (EI) 286 (M^+). Anal. Calcd for $C_{15}H_{34}OSi_2$: C, 62.84; H, 11.97. Found: C, 62.89; H, 12.16.

4.5. General procedure for the bond formation at the β-position of ketone dilithio α,β-dianions 3 with alkyl bromides

The preparation of 2,2-dimethyl-3-decanone (**14**) is described as a typical example. β-Tributylstannyl ketone **1a** (0.403 g, 1.0 mmol) was added to a cooled solution of LDA (prepared from diisopropyl amine (0.184 mL, 1.3 mmol) and *n*-BuLi (1.58 M hexane solution, 0.76 mL, 1.2 mmol)) in THF (5 mL). After stirring for 2 h at −78 °C, *n*-BuLi (1.58 M hexane solution, 1.58 mL, 2.5 mmol) was added. The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. After re-cooling to −78 °C, *n*-pentyl bromide (0.453 g, 3.0 mmol) was added. The mixture was allowed to warm to −20 °C and stirred for 1 h. Dilution with ether followed by washing with water, concentration, and flash chromatography (SiO_2, 10% ether in pentane) gave 2,2-dimethyl-3-decanone (**14**) (0.130 g, 71%).

4.5.1. 2,2-Dimethyl-3-decanone (14). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, J=6.7 Hz, 3H), 1.13 (s, 9H), 1.27 (m, 8H), 1.57 (m, 2H), 2.46 (t, J=7.3 Hz, 2H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.05, 22.59, 23.94, 26.39, 29.15, 29.29, 31.71, 36.42, 44.07, 216.10. IR (NaCl) 1707 cm^{-1} (C═C). MS (EI) 184 (M^+). HRMS calcd for $C_{12}H_{24}O$ 184.1827, found 184.1819.

4.5.2. 2,2-Dimethyl-7-octen-3-one (15). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.63 (t, J=7.3 Hz, 2H), 2.00 (m, 2H), 2.46 (t, J=7.3 Hz, 2H), 4.92–5.01 (m, 2H), 5.69–5.79 (m, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.86, 26.35, 33.08, 35.48, 44.04, 114.95, 138.17, 215.73. IR (NaCl) 1645 cm^{-1} (C═C), 1703 cm^{-1} (C═O). MS (EI) 154 (M^+). HRMS calcd for $C_{10}H_{18}O$ 154.1357, found 154.1376.

4.5.3. 2,2-Dimethyl-4-(3-propenyl)-7-octen-3-one (16). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.41–1.54 (m, 1H), 1.61–1.74 (m, 1H), 1.94–2.15 (m, 3H), 2.25–2.35 (m, 1H), 2.95–3.04 (m, 1H), 4.94–5.04 (m, 4H), 5.62–5.83 (m, 2H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.36, 31.19, 31.55, 36.73, 44.44, 44.56, 114.98, 116.74, 135.97, 138.10, 217.91. IR (NaCl) 1640 cm^{-1} (C═C), 1702 cm^{-1} (C═O). MS (EI) 194 (M^+). HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1707. Anal. Calcd for $C_{13}H_{22}O$: C, 80.33; H, 11.43. Found: C, 80.11; H, 11.23.

4.5.4. (*Z*)-2,2-Dimethyl-3-(trimethylsiloxy)-3-decene (17). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.22 (s, 9H), 0.80–0.90 (m, 3H), 1.03 (s, 9H), 1.21–1.36 (m, 8H), 1.89–2.00 (m, 2H), 4.50 (t, J=6.7 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.08, 22.64, 26.27, 28.64, 29.19, 29.99, 31.82, 36.18, 104.27, 157.95. IR (NaCl) 1660 cm^{-1} (C═C). MS (EI) 256 (M^+). HRMS calcd for $C_{15}H_{32}OSi$ 256.2222, found 256.2218. Anal. Calcd for $C_{15}H_{32}OSi$: C, 70.12; H, 12.59. Found: C, 70.04; H, 12.76.

4.5.5. (*Z*)-2,2-Dimethyl-3-(trimethylsiloxy)-3,10-undecadiene (18). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.21 (S, 9H), 1.03 (s, 9H), 1.25–1.43 (m, 6H), 1.88–2.10 (m, 4H), 4.49 (t, J=6.8 Hz, 1H), 4.90–5.02 (m, 2H), 5.73–5.88 (m, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 1.05, 26.16, 28.62, 28.82, 28.96, 29.83, 33.75, 36.18, 104.15, 114.11, 139.17, 158.01. IR (NaCl) 1660 cm^{-1} (C═C). MS (EI) 268 (M^+). HRMS calcd for $C_{16}H_{32}OSi$ 268.2222, found 268.2241. Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.54; H, 12.03. Found: C, 71.75; H, 12.14.

4.5.6. 2,8-Dimethyl-7-nonen-3-one (20). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (d, J=7.0 Hz, 6H), 1.57 (s, 3H), 1.58 (m, 2H), 1.67 (s, 3H), 1.96 (m, 2H), 2.41 (t, J=7.3 Hz, 2H), 2.57 (m, 1H), 5.06 (t, J=7.0 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.74, 18.32, 23.95, 25.74, 27.52, 39.79, 40.85, 123.95, 132.26, 214.93. IR (NaCl) 1674 cm^{-1} (C═C), 1712 cm^{-1} (C═O). MS (EI) 168 (M^+). HRMS calcd for $C_{11}H_{20}O$ 168.1514, found 168.1517.

4.5.7. (*Z*)-2-Methyl-7-ethoxy-3-(trimethylsiloxy)-3-heptene (21). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.02 (d, J=6.8 Hz, 6H), 1.19 (t, J=8.5 Hz, 3H), 1.23–1.45 (m, 2H), 1.99–2.05 (m, 2H), 2.11–2.17 (m, 1H), 3.40 (t, J=6.8 Hz, 2H), 3.46 (q, J=6.8 Hz, 2H), 4.27 (m, 1H). IR (NaCl) 1669 cm^{-1} (C═C). MS (EI) 244 (M^+). HRMS calcd for $C_{13}H_{28}O_2Si$ 244.1858, found 244.1853. Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.85; H, 11.56. Found: C, 63.90; H, 11.48.

4.5.8. (*Z*)-2-Methyl-3-(trimethylsiloxy)-3-decene (22). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.19 (s, 9H), 0.88 (t, J=6.9 Hz, 3H), 1.03 (d, J=6.7 Hz, 6H), 1.27–1.30 (m, 8H), 1.96–1.98 (m, 2H), 2.12–2.17 (m, 1H), 4.45 (dt, J=0.6, 6.9 Hz, 1H). IR (neat) 1669 cm^{-1} (C═C). MS (EI) 242 (M^+). HRMS calcd for $C_{14}H_{30}OSi$ 242.2066, found 242.2043. Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.32, H, 12.49. Found: C, 69.00; H, 12.58.

4.5.9. (*Z*)-9-Chloro-3,8-dimethyl-4-(trimethylsiloxy)-4-nonene (23). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.18 (s, 9H), 0.99 (d, J=6.8 Hz, 3H), 1.00 (d, J=6.3 Hz, 3H), 1.17–1.34 (m, 2H), 1.43–1.57 (m, 2H), 1.78–2.10 (m, 4H), 3.37–3.53 (m, 2H), 4.39 (t, J=7.0 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.78, 11.60, 17.69, 18.11, 22.81, 27.11, 34.04, 35.07, 41.38, 51.17, 105.91, 154.71. IR (NaCl) 1668 cm^{-1} (C═C). MS (EI) 276 (M^+). HRMS calcd for $C_{14}H_{29}OSiCl$ 276.1676, found 276.1685. Anal. Calcd for $C_{14}H_{29}OSiCl$: C, 60.70; H, 10.57. Found: C, 60.83; H, 10.74.

4.5.10. (*Z*)-3-Methyl-4-(trimethylsiloxy)-4-tetradecene (24). A colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.18 (s, 9H), 0.78–0.94 (m, 6H), 0.99 (d, J=6.7 Hz, 3H), 1.18–1.36 (m, 14H), 1.44–1.61 (m, 2H), 1.91–2.01 (m, 3H), 4.42 (t, J=6.8 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.80, 11.63, 14.10, 18.14, 22.70, 25.59, 27.19, 29.35, 29.49, 29.59, 29.63, 30.04, 31.94, 41.52, 106.82, 154.06. IR (NaCl) 1669 cm^{-1} (C═C). MS (EI) 298 (M^+). HRMS calcd for $C_{18}H_{38}OSi$ 298.2692, found 298.2696.

4.5.11. 2,2-Dimethyl-4-(propenyl)-3-decanone (19). A solution of lithium enolate of β-lithio ketone **3a** (1.0 mmol) in THF (5 mL) was cooled to −78 °C, and pentyl bromide (0.302 g, 2 mmol) was added. The reaction

mixture was stirred at −20 °C for 1 h. After cooling to −78 °C, HMPA (0.5 mL) and allyl bromide (0.360 g, 3 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was worked up as described in the general procedure. Flash chromatography (SiO_2) gave 2,2-dimethyl-4-(2-propenyl)-3-decanone (**19**) (0.158 g, 70%) as a colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (t, J=6.5 Hz, 3H), 1.12 (s 9H), 1.23–1.58 (m, 10H), 2.03–2.33 (m, 2H), 2.90–2.97 (m, 1H), 4.95–5.03 (m, 2H), 5.61–5.74 (m, 1H) ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.04, 22.59, 26.37, 27.63, 29.49, 31.69, 32.30, 36.93, 44.38, 45.37, 116.48, 136.30, 218.34. IR (NaCl) 1640 cm^{-1} (C=C), 1703 cm^{-} (C=O). MS (EI) 224 (M^+). HRMS calcd for $C_{15}H_{28}O$ (M^+) 224.2140, found 224.2150.

4.6. Reaction of ketone dilithio α,β-dianion 3a with valeraldehyde

To a solution of β-lithio ketone enolate **3a** generated from β-tributylstannyl ketone **1a** (1 mmol) in THF (5 mL) at −78 °C was added valeraldehyde (**25**) (0.086 g, 1 mmol) in one portion. After the mixture was stirred at −78 °C for 15 min, water was added. The aqueous layer was extracted with ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified PTLC (SiO_2, ethyl acetate/hexane (1:5)) to give aldol product **26** (94 mg, 47%) and diol **27** (8 mg, 4%).

4.6.1. 2,2-Dimethyl-6-hydroxydecane-3-one (26). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87–0.95 (m, 3H), 1.15 (s, 9H), 1.25–1.67 (m, 8H), 1.74–1.86 (m, 1H), 2.65 (t, J=6.8 Hz, 2H), 3.55 (bs, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.04, 22.69, 26.47, 27.84, 31.08, 32.99, 37.58, 44.22, 71.59, 217.04. IR (NaCl) 1703 cm^{-1} (C=O), 3429 cm^{-1} (OH). MS (EI) 200 (M^+). HRMS calcd for $C_{12}H_{22}O$ (M^+-H_2O) 182.1670, found 182.1670.

4.6.2. 2,2-Dimethyl-3-vinyl-3,4-octanediol (27). A colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87–0.95 (m, 3H), 0.97 (s, 9H), 1.20–1.81 (m, 7H), 3.73 (bs, 2H), 5.22 (dd, J= 2.0, 11.0 Hz, 1H), 5.33 (dd, J=2.0, 17.0 Hz, 1H), 5.90 (dd, J=11.0, 17.0 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.06, 25.11, 26.51, 28.71, 33.80, 46.50, 73.55, 80.28, 114.69, 137.96. IR (NaCl) 3425 cm^{-1} (OH). HRMS calcd for $C_{12}H_{24}O_2$ 200.1776, found 200.1771.

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The site-selective functionalization of halogen-bearing phenols: an exercise in diversity-oriented organometallic synthesis

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Abstract—The organometallic approach to diversity-oriented organic synthesis was subjected to a further test, this time in the phenol series. The model compounds selected were 2,3,6-trifluorophenol, the three isomers of (trifluoromethoxy)phenol and the three isomers of chlorophenol. A combination of optionally site selective metalations and protective group-controlled metalations enabled the selective generation of several isomeric intermediates in each case and their subsequent conversion into functionalized derivatives, in particular hydroxybenzoic acids.

1. Introduction

Phenols as a class of compounds do presently not attract much attention. This happened to be different at the dawn of organic chemistry. In these days they played a prominent role as both targets and intermediates of structural elaboration. In fact, they rapidly became one of the cornerstones supporting the progress in a frenetically developing area. The names of the researchers involved in this process reads like an almanac of chemical nobility: Baeyer, Bucherer, Claisen, Fries, Kolbe, Pechmann, Reimer, Schmitt, Simonis, Tiemann, Ullmann and Vilsmeier.

Some of the classical phenol reactions give rise to mainly *ortho*-substituted derivatives as they benefit from neighboring group assistance provided by the neutral or deprotonated hydroxyl group or proceed in a concerted fashion, in particular as a [3.3]-sigmatropic rearrangement. Others favor, for steric and electronic reasons, the *para* isomers. By and large, however, electrophilic substitutions of phenols tend to give mixtures of *ortho* and *para* isomers, *meta* isomers being formed only in trace amounts, if at all.

The only rigorous way to secure regiochemical predictability and fidelity in phenol reactions is to transit organometallic species wherein the nucleophilically active center is unequivocally defined. To realize this idea in a most simple fashion, one needs only to select the appropriate bromophenol, treat it with two equivalents of an organometallic agent such as butyllithium or *tert*-butyllithium and trap the generated (lithiooxy)phenyllithium with a suitable electrophile. Such sequences have been successfully carried out in several cases indeed.[1] The yields, in general moderate to good, can still be improved if the phenolic hydroxyl group is protected as a methoxymethoxy or 2-tetrahydropyranyloxy unit prior to the crucial halogen/metal permutation step.[1]

This scheme nevertheless suffers from a serious drawback. Only the most simple bromophenols are commercially available and even those are rarely inexpensive. Thus, the access to the required starting material will often constitute a major obstacle. It would be more straightforward and economic to start from a bromine-free (or iodine-free) phenol and to subject it to a permutational hydrogen/metal rather than halogen/metal interconversion. Unfortunately, the direct 'metalation' of halogen-devoid phenols has only been accomplished with phenol itself[2] and with 2-naphthol[3,4] as the substrates (at the 2- and 3-position, respectively). 1-Naphthol was found to be attacked concomitantly at the 2- and 8-position.[4] Alkoxy- and aroxy-substituted phenols[5–7] also tend to produce regioisomeric mixtures despite poor yields, unless they dispose of no more than one vacant position.[8]

We wondered whether halogen-substituents would not considerably facilitate the metalation of phenol-derived acetals and, moreover, comprise an option on more regioflexibility. This was anticipated on the basis of

Keywords: Butyllithium; Carboxylation; Halogens; Metalation; Phenols; Superbases; Trialkylsilyl groups.
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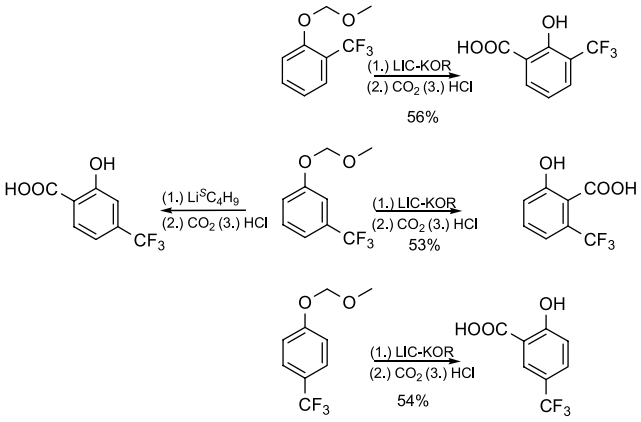
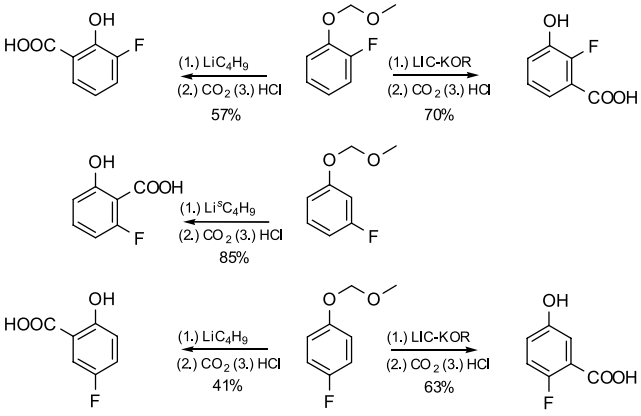
optionally site selective metalations we had previously carried out with a variety of halogenated substrates, in particular fluorotoluenes,[9,10] fluoroanisoles,[11] fluoroanilines,[12] chlorofluorobenzenes,[13] bromofluorobenzenes,[13] (trifluoromethyl)toluenes,[9] (trifluoromethyl)anilines,[12] fluorobenzotrifluorides,[14] chlorobenzotrifluorides,[14] bromobenzotrifluorides[14] and bis- or tris(trifluoromethyl)benzenes.[15,16] Our first endeavors in this direction proved to be quite encouraging.

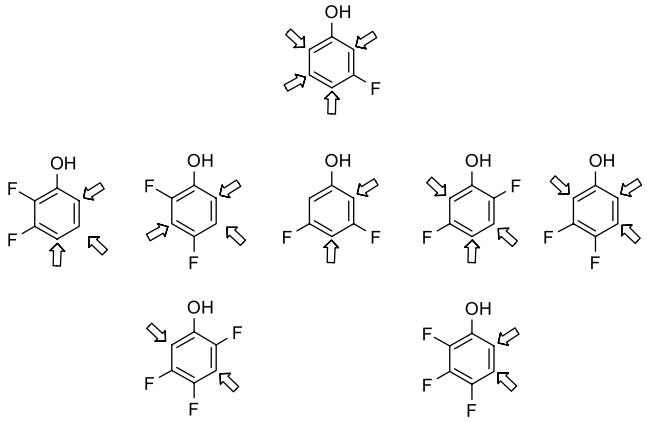
The *O*-methoxymethyl protected 2- and 4-(trifluoromethyl)-phenols reacted with the mixture of butyllithium and potassium *tert*-butoxide ('LIC-KOR' superbase) under proton abstraction from the oxygen-adjacent positions to provide the corresponding hydroxybenzoic acids in 56 and 54% yield.[17] The *meta* isomer featured another example of optional site selectivity by undergoing metalation with LIC-KOR at the 2-position flanked by both substituents and at the coordinatively assisted 6-position with *sec*-butyllithium, affording the corresponding hydroxybenzoic acids in 53 and 93% yield, respectively.[17]



The metalation of the three fluoro(methoxymethoxy)benzenes with butyllithium or *sec*-butyllithium at the position next to the oxygen substituent having already been reported, we were still able to improve the yields of the isolated fluorohydroxybenzoic acids (to 69–93%).[17] At the same time we installed optional site selectivity in the metalation of the *ortho* and *para* isomers, which were deprotonated and subsequently carboxylated (84 and 80% of the acids) at the fluorine-adjacent positions when LIC-KOR was employed as the base.[17]

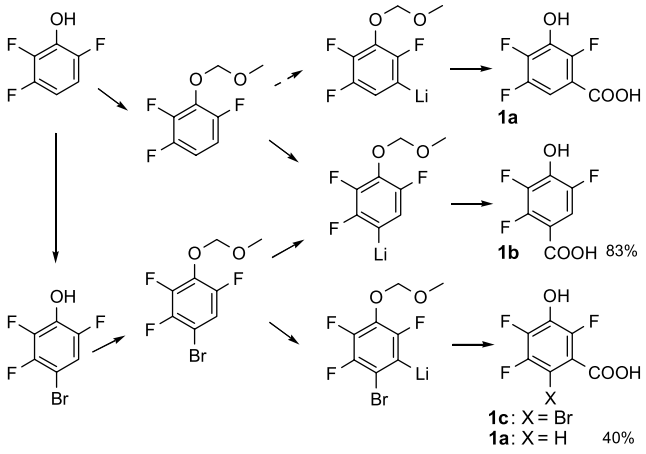


Work of this kind contributes to the prospects of diversity-oriented synthesis.[18] Meanwhile the toolbox approach[19,20] has been conceived to extend and perfect such opportunities. By virtue of sophisticated organometallic protocols any vacant position in an aromatic or heterocyclic substrate can be selectively metalated and subsequently functionalized. To demonstrate the validity of the concept, several model substrates were converted into all possible isomeric derivatives by carrying out regioisomerically exhaustive metalations and functionalizations. Mono-, di- and trifluorophenols belong to the noteworthy examples in this respect.[21,22]



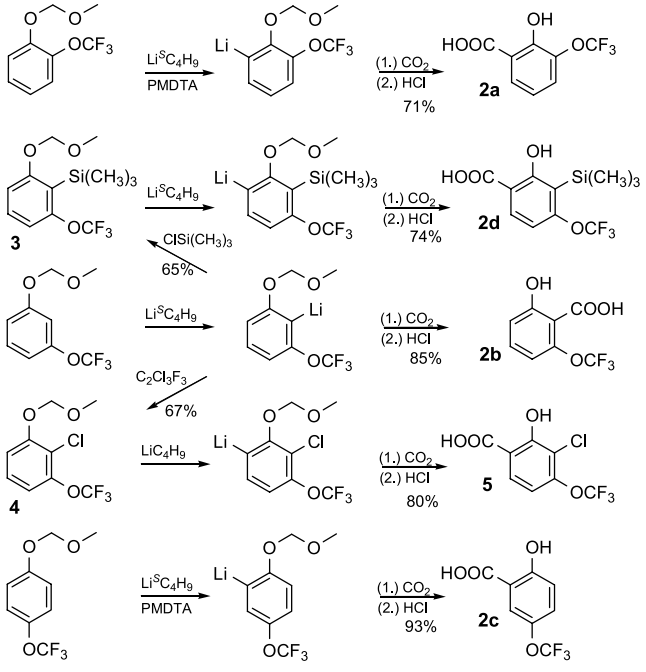
2. Results and discussion

We wanted to complement our study of trifluorophenols by including the 2,3,6-trifluoro isomer into the investigations. This model compound represents a challenge. Although there are only two vacant positions left, both of them are activated in an almost identical manner each having a fluorine atom as a direct neighbor. Actually, the metalation of either the *O*-methoxymethyl or *O*-triisopropylsilyl protected 2,3,6-trifluorophenol gave more or less random mixtures of organolithium species, the latter being eventually trapped as the hydroxybenzoic acid **1a** and **1b**. The highest regioselectivity of 5:95 was achieved when the acetal was treated with lithium diisopropylamide (LIDA) in tetrahydrofuran. The problem could be easily circumvented by bromination of the phenol at the *para* position. Halogen/metal permutation accomplished with butyllithium in tetrahydrofuran afforded the acid **1b** in 83% yield. The isomeric acid **1a** (40%) was prepared in a one-pot procedure by consecutive deprotonation of the acetal with lithium diisopropylamide, reaction with dry ice and debromination of the intermediate with zinc powder in alkaline medium.

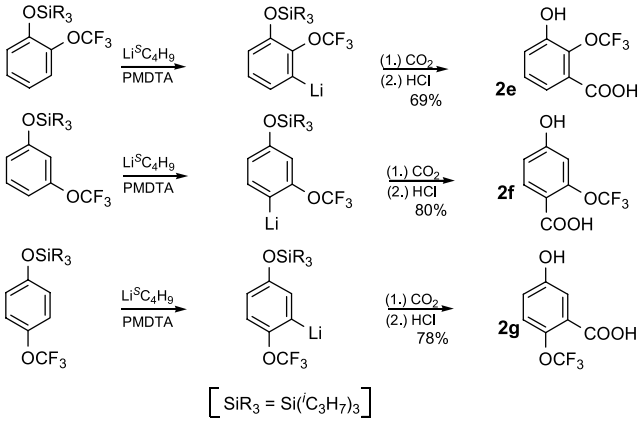


The (trifluoromethoxy)phenols, the next selection of model substrates, are quite expensive starting materials. Therefore, we contented ourselves to make only seven rather than all ten of the corresponding carboxylic acids. Optional site selectivity was this time not achieved by reagent matching[18] but rather by an appropriate choice of the *O*-protecting entity.

1-Methoxymethoxy-2- and -4-(trifluoromethoxy)benzene reacted smoothly at the acetal-adjacent sites thus leading to the acids **2a** (71%) and **2c** (93%). The *meta* isomer underwent metalation at the doubly activated position flanked by the two substituents thus providing the acid **2b** (85%) after carboxylation and neutralization. When, instead of the carboxy function, a trimethylsilyl group or a chlorine atom was introduced in the lithiated 2-position (to give the silane **3** or the chloroarene **4**), the next metalation took place at the methoxymethoxy-neighboring 6-position. This opened an entry to the acids **2d** (74%; after protodesilylation using tetrabutylammonium fluoride hydrate ['TBAF']) and **5** (80%).

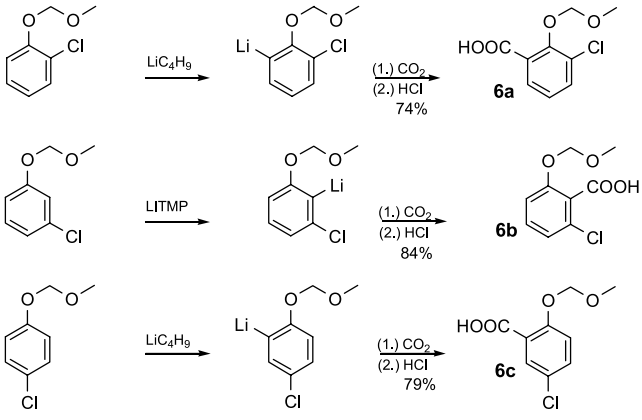


On the other hand, the bulky triisopropylsilyl group sterically shields its immediate vicinity. Therefore, metalation with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine ('PMDTA') was deflected to the remote OCF_3-adjacent position. Carboxylation and deprotection afforded the hydroxy(trifluoromethoxy)-benzoic acids **2e**–**2g** (in 69, 80 and 78% yield).



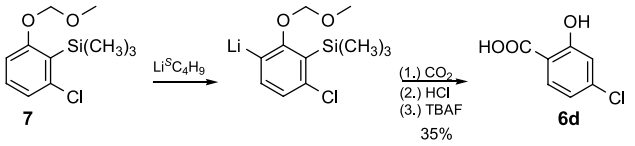
Trifluoromethoxy groups resemble chloro substituents in several respects[23] even if the latter are a bit less effective in activating *ortho*-position toward metalation.[24] For sake of comparison, the three chlorophenols were protected as methoxymethyl and triisopropylsilyl ethers before being metalated with butyllithium and *sec*-butyllithium, respectively.

In analogy with the behaviour of the corresponding (trifluoromethoxy)phenol derivatives, proton abstraction from the chloro(methoxymethoxy)benzenes occurred exclusively from oxygen-adjacent positions. The hydroxybenzoic acids **6a**, **6b** and **6c** were isolated in 74, 84 and 79% yield. The metalation of 1-chloro-2-(methoxymethoxy)benzene has been reported previously.[25]

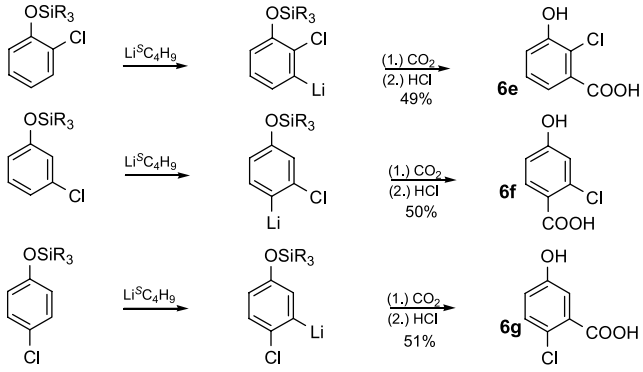


The weaker base[26] lithium 2,2,6,6-tetramethylpiperidide (LITMP) had to be employed with the *meta*-substituted substrate as both butyllithium and *sec*-butyllithium provided a mixture of the acid **6b** and its isomer **6d**. The latter compound was selectively prepared in 35% yield by treating the silane **7**, obtained after mixing 1-chloro-3-

(methoxymethoxy)benzene with LITMP and chlorotrimethylsilane, consecutively with *sec*-butyllithium, dry ice, hydrochloric acid and TBAF.



The *O*-triisopropylsilyl protected chlorophenols also followed the previously encountered pattern. *sec*-Butyllithium attacked solely the chlorine-adjacent positions remote from the silyloxy entity. After trapping with dry ice the hydroxybenzoic acids **6e**, **6f** and **6g** were obtained in 49, 50 and 51% yield.



Carboxylation is presumably the most common way to characterize an organometallic intermediate by derivatization. Despite its popularity, carbon dioxide remains just one out of dozens if not hundreds of eligible electrophiles. The metalation reactions disclosed above thus do not simply open a route leading to rare benzoic acids but may be used to access numerous classes of otherwise functionalized compounds.

3. Experimental

3.1. Generalities

Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[27–29] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, samples having been dissolved in $CDCl_3$ or, if marked by an asterisk (*), in acetone-d_6. Mass spectra were obtained by the chemical ionization technique (c.i.) in an ammonia atmosphere at 100 °C source temperature. To avoid redundancy, only the [^{35}Cl] and [^{79}Br] fragments, and not the [^{37}Cl] or [^{81}Br] isotopomers, are listed in all cases. Whenever possible and appropriate, yields and purities of products were determined, prior to isolation, by gas chromatographic comparison of their peak areas with that of a known amount of a reference substance ('internal standard') and correction of the ratios thus obtained by means of separately established calibration factors. The stationary phases employed are encoded as DB-23 (silicone type) and DB-WAX (polyethylene glycol type).

3.2. Derivatives of 2,3,6-trifluorophenol

3.2.1. 4-Bromo-2,3,6-trifluorophenol. A solution containing 2,3,6-trifluorophenol (15 g, 0.10 mol) and *N*-bromosuccinimide (18 g, 0.10 mol) in chloroform (0.20 L) was kept 2 h at 0 °C. After the addition of a saturated aqueous solution (0.10 L) of sodium thiosulfate, the reaction mixture was extracted with dichloromethane (3×0.10 L). The organic layer was evaporated and the residue crystallized from hexanes as colorless platelets; mp 44–45 °C; yield: 19.8 g (87%). ^{1}H NMR: δ=7.16 (ddd, J=9.7, 5.8, 2.6 Hz, 1H), 5.38 (broad s, 1H) ppm; ^{13}C NMR: δ=148.0 (td, J=243, 4 Hz), 145.9 (ddd, J=245, 12, 4 Hz), 141.7 (ddd, J=248, 17, 6 Hz), 134.1 (ddd, J=15, 13, 2 Hz), 114.3 (dd, J=23, 4 Hz), 98.8 (dd, J=20, 11 Hz) ppm; MS (c.i.): m/z (%)=244 (0) [M^++NH_4], 229 (39) [M^++3], 228 (99) [M^++2], 227 (28) [M^++1], 226 (61) [M^+], 99 (100).

3.2.2. 1-Bromo-2,3,5-trifluoro-4-(methoxymethoxy)benzene. Prepared at 0 °C, a solution of 4-bromo-2,3,6-trifluorophenol (17 g, 75 mmol), chloromethyl methyl ether[30] (9.1 mL, 9.7 g, 90 mmol) and *N*-ethyldiisopropylamine (14 mL, 12 g, 90 mmol) in dichloromethane (75 mL) was kept at 25 °C for 2 h. The mixture was poured into a 3.0 M aqueous solution (0.15 L) of sodium hydroxide, extracted with dichloromethane (2×75 mL) and distilled; colorless liquid; bp 59–61 °C/3 mmHg; n_D^{20}=1.4902; yield: 17.9 g (88%). ^{1}H NMR: δ=7.16 (ddd, J=9.9, 6.1, 2.9 Hz, 1H), 5.20 (s, 2H), 3.61 (s, 3H) ppm; ^{13}C NMR: δ=152.2 (td, J=248, 4 Hz), 146.0 (ddd, J=254, 15, 6 Hz), 145.9 (ddd, J=249, 13, 4 Hz), 133.9 (ddd, J=16, 12, 2 Hz), 114.6 (dd, J=24, 4 Hz), 103.2 (ddd, J=29, 11, 2 Hz), 99.0 (t, J=4 Hz), 57.6 ppm; MS (c.i.): m/z (%)=288 (0) [M^++NH_4], 272 (2) [M^++2], 270 (3) [M^+], 228 (62), 99 (100); $C_8H_6BrF_3O_2$ (271.03): calcd C 35.45, H 2.23; found C 35.61, H 2.41.

3.2.3. 2,4,5-Trifluoro-3-hydroxybenzoic acid (1a). 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol), potassium *tert*-butoxide (2.8 g, 25 mmol), *N*,*N*,*N*′,*N*″,*N*″-pentamethylethylenediamine (5.2 mL, 4.3 g, 25 mmol) and 1-bromo-2,3,5-trifluoro-4-(methoxymethoxy)benzene (6.8 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (32 mL) and hexanes (16 mL) kept at −125 °C. After 45 min, the reaction mixture was poured onto freshly crushed dry ice and evaporated. The residue was partitioned between water (25 mL) and diethyl ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3×50 mL). After evaporation of the solvents, the residue was dissolved in a 3.0 M aqueous solution (25 mL) of sodium hydroxide and stirred with zinc powder (4.9 g, 75 mmol) for 2 h at 25 °C. The reaction mixture was acidified to pH 1 with concentrated hydrochloric acid and extracted with diethyl ether (3×25 mL). After evaporation of the solvents, the residue was crystallized from chloroform; colorless needles; mp 143–144 °C; yield: 1.92 g (40%). ^{1}H NMR*: δ=7.35 (ddd, J=10.6, 8.3, 5.8 Hz, 1H) ppm; ^{13}C NMR*: δ=163.5 (m), 149.3 (ddd, J=254, 5, 3 Hz), 147.0 (ddd, J=242, 11, 3 Hz), 141.1 (ddd, J=251, 16, 5 Hz), 136.7 (ddd, J=18, 12, 3 Hz), 114.7 (ddd, J=17, 7, 4 Hz), 108.1 (d, J=21 Hz) ppm; MS (c.i.): m/z

(%)=210 (0) [$M^+ + NH_4$], 194 (8) [$M^+ + 2$], 193 (55) [$M^+ + 1$], 192 (76) [M^+], 175 (100); $C_7H_3F_3O_3$ (192.09): calcd C 43.77, H 1.57; found C 43.94, H 1.54.

3.2.4. 2,3,5-Trifluoro-4-hydroxybenzoic acid (1b). 1-Bromo-2,3,5-trifluoro-4-(methoxymethoxy)-benzene (6.8 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in hexanes (17 mL) and tetrahydrofuran (33 mL) kept in a dry ice/methanol bath. After 15 min at −75 °C, the reaction mixture was poured onto freshly crushed dry ice. After addition of water (25 mL) and washing with diethyl ether (2×25 mL), the aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3×50 mL). Evaporation of the solvents and crystallization from toluene afforded colorless needles; mp 154–156 °C; yield: 3.99 g (83%). ^{1}H NMR*: δ=7.53 (ddd, J=10.6, 6.7, 2.2 Hz, 1H) ppm; ^{13}C NMR*: δ=163.3 (m), 148.7 (ddd, J=258, 12, 4 Hz), 147.8 (dt, J=241, 4 Hz), 141.8 (ddd, J=243, 16, 6 Hz), 140.1 (ddd, J=17, 13, 5 Hz), 112.7 (symm. m), 109.8 (t, J=8 Hz) ppm; MS (c.i.): m/z (%)=210 (0) [$M^+ + NH_4$], 194 (5) [$M^+ + 2$], 193 (12) [$M^+ + 1$], 192 [M^+], 175 (100); $C_7H_3F_3O_3$ (192.09): calcd C 43.77, H 1.57; found C 43.58, H 1.49.

3.2.5. 1,2,4-Trifluoro-3-(methoxymethoxy)benzene. Prepared analogously as 1-bromo-2,3,5-trifluoro-4-(methoxymethoxy)benzene (see above) from 2,3,6-trifluorophenol (15 g, 0.10 mol), colorless liquid; bp 33–39 °C/3 mmHg; n_D^{20}=1.4429; yield: 16.7 g (87%).^{1}H NMR: δ=6.87 (m, 2H), 5.20 (s, 2H), 3.63 (s, 3H) ppm; ^{13}C NMR: δ=152.8 (td, J=244, 3 Hz), 148.1 (ddd, J=235, 11, 3 Hz), 145.6 (ddd, J=246, 15, 6 Hz), 134.8 (ddd, J=14, 12, 2 Hz), 111.2 (dd, J=20, 9 Hz), 110.7 (ddd, J=22, 8 Hz), 99.3 (t, J=4 Hz), 57.5 ppm; MS (c.i.): m/z (%)=200 (0) [$M^+ + NH_4$], 192 (100) [M^+], 141 (32), 82 (43); $C_8H_7F_3O_2$ (192.14): calcd C 50.01, H 3.67; found C 50.08, H 3.52. Upon reaction of the acetal with butyllithium or lithium diisopropylamide in tetrahydrofuran followed by carboxylation, a mixture of the acids **1a** and **1b** was obtained in the ratios of 40:60 (61%) and 5:95 (83%) respectively, as determined by gas chromatographic analysis of the crude product after esterification with ethereal diazomethane [30 m, DB-WAX, 150 °C; 30 m, DB-23, 150 °C].

3.2.6. Triisopropyl(2,3,6-trifluorophenoxy)silane. 2,3,6-Trifluorophenol (15 g, 0.10 mol), chlorotriisopropylsilane (22 mL, 20 g, 0.10 mol) and imidazole (6.8 g, 0.10 mol) were dissolved in *N*,*N*-dimethylformamide (50 mL). After 20 h at 25 °C, the mixture was poured into water (100 mL) and extracted with dichloromethane (3×50 mL). Distillation under reduced pressure gave a colorless liquid; bp 101–102 °C/3 mmHg; n_D^{20}=1.4695; yield: 25.0 g (82%). ^{1}H NMR: δ=6.76 (dddd, J=11.8, 9.6, 7.4, 2.2 Hz, 2H), 6.68 (symm. m, 1H), 1.30 (hept., J=7.4 Hz, 3H), 1.09 (d, J=7.4, 18 Hz) ppm; ^{13}C NMR: δ=151.4 (dt, J=241, 3 Hz), 148.2 (ddd, J=245, 12, 3 Hz), 144.2 (ddd, J=247, 15, 5 Hz), 135.2 (ddd, J=15, 12, 3 Hz), 110.0 (ddd, J=21, 8, 3 Hz), 107.5 (dd, J=20, 8 Hz), 18.0 (3 C), 13.2 (6 C) ppm; MS (c.i.): m/z (%)=322 (0) [$M^+ + NH_4$], 305 (4) [$M^+ + 1$], 304 (4) [M^+], 262 (100); $C_{15}H_{23}F_3OSi$ (304.42): calcd C 59.18, H 7.62; found C 59.16, H 7.79. Consecutive treatment of the silyl ether with lithium 2,2,6,6-tetramethylpiperidide in diethyl ether, dry ice and hydrochloric acid afforded a 10:90 mixture (80%) of the acids **1a** and **1b** as determined by gas chromatographic analysis of the crude product after esterification with ethereal diazomethane [30 m, DB-WAX, 150 °C; 30 m, DB-23, 150 °C].

3.3. Derivatives of (trifluoromethoxy)phenols

3.3.1. 1-(Methoxymethoxy)-2-(trifluoromethoxy)benzene. Prepared at 0 °C, a solution of 2-(trifluoromethoxy)-phenol (18 g, 0.10 mol), *N*-ethyldiisopropylamine (18 mL, 16 g, 0.12 mol) and chloromethyl methyl ether[30] (9 mL, 10 g, 0.12 mol) in dichloromethane (80 mL) was kept for 2 h at 25 °C, before being poured into a 3.0 M aqueous solution (0.20 L) of sodium hydroxide. Extraction with dichloromethane (2×0.10 L) and distillation gave a colorless liquid; bp 51–52 °C/6 mmHg; n_D^{20}=1.4320; yield: 16.2 g (73%). ^{1}H NMR: δ=7.22 (symm. m, 3H), 7.0 (m, 1H), 5.25 (s, 2H), 3.51 (s, 3H) ppm. ^{13}C NMR: δ=150.1, 139.2, 128.3, 123.5, 122.4, 121.1 (q, J=256 Hz), 117.3, 95.4, 56.5 ppm. MS (c.i.): m/z (%)=240 (0) [$M^+ + NH_4$], 222 (0) [M^+], 202 (86), 184 (51), 132 (26), 107 (100). $C_9H_9F_3O_3$ (222.16): calcd C 48.66, H 4.08; found C 48.73, H 4.11.

3.3.2. 1-(Methoxymethoxy)-3-(trifluoromethoxy)benzene. Prepared analogously from 3-(trifluoromethoxy)-phenol (18 g, 0.10 mol); colorless liquid, bp 42–43 °C/4 mmHg; n_D^{20}=1.4304; yield: 19.3 g (87%). ^{1}H NMR: δ=7.26 (t, J=8.3 Hz, 1H), 6.96 (ddd, J=8.3, 2.2, 0.6 Hz, 1H), 6.92 (broad s, 1H), 6.83 (dm, J=8.3 Hz, 1H), 5.14 (s, 2H), 3.45 (s, 3H) ppm. ^{13}C NMR: δ=158.7, 150.4 (q, J=2 Hz), 130.5, 120.9 (q, J=257 Hz), 114.8, 114.3, 109.9, 94.9, 56.4 ppm. MS (c.i.): m/z (%)=240 (0) [$M^+ + NH_4$], 223 (37) [$M^+ + 1$], 222 (100) [M^+], 191 (22), 161 (29). $C_9H_9F_3O_3$ (222.16): calcd C 48.66, H 4.08; found C 48.77, H 3.88.

3.3.3. 1-(Methoxymethoxy)-4-(trifluoromethoxy)benzene. Prepared analogously from 4-(trifluoromethoxy)-phenol (18 g, 0.10 mol); colorless liquid, bp 47–49 °C/5 mmHg; n_D^{20}=1.4295; yield: 14.2 g (64%). ^{1}H NMR: δ=7.18 (d, J=9.2 Hz, 2H), 7.07 (d, J=9.2 Hz, 2H), 5.18 (s, 2H), 3.50 (s, 3H) ppm. ^{13}C NMR: δ=156.2, 144.0 (q, J=2 Hz), 122.7 (2 C), 121.0 (q, J=257 Hz), 117.5 (2 C), 95.0, 56.2 ppm. MS (c.i.): m/z (%)=240 (0) [$M^+ + NH_4$], 223 (48) [$M^+ + 1$], 222 (63) [M^+], 192 (81), 137 (100). $C_9H_9F_3O_3$ (222.16): calcd C 48.66, H 4.08; found C 48.41, H 4.22.

3.3.4. Triisopropyl[2-(trifluoromethoxy)phenoxy]silane. 2-(Trifluoromethoxy)phenol (8.9 g, 50 mmol), chlorotriisopropylsilane (11 mL, 10 g, 50 mmol) and imidazole (3.4 g, 50 mmol) were dissolved in *N*,*N*-dimethylformamide (25 mL). After 20 h at 25 °C, the mixture was poured into water (50 mL) and extracted with dichloromethane (3×25 mL). Upon distillation under reduced pressure a colorless liquid was collected; bp 92–94 °C/7 mmHg; n_D^{20}=1.4582; yield: 12.9 g (77%). ^{1}H NMR: δ=7.24 (dm, J=8.0 Hz, 1H), 7.17 (ddd, J=8.9, 7.4, 1.6 Hz, 1H), 6.95 (dd, J=8.0, 1.6 Hz, 1H), 6.9 (m, 1H), 1.30 (sept, J=7.4 Hz, 3H), 1.13 (d, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=149.0, 140.5, 127.9, 123.2, 121.4, 121.2 (q, J=257 Hz), 121.2, 18.1 (3 C), 13.2 (6 C) ppm. MS (c.i.): m/z (%)=352 (0) [$M^+ + NH_4$],

334 (5) [M^+], 291 (14), 139 (100). $C_{16}H_{25}F_3O_2Si$ (334.45): calcd C 57.46, H 7.53; found C 57.55, H 7.35.

3.3.5. Triisopropyl[3-(trifluoromethoxy)phenoxy]silane. Prepared analogously from 3-(trifluoromethoxy)phenol (8.9 g, 50 mmol); colorless liquid; bp 82–83 °C/4 mmHg; $n_D^{20}=1.4549$; yield: 15.0 g (90%). ^{1}H NMR: $\delta=7.24$ (t, $J=8.3$ Hz, 1H), 6.9 (m, 2H), 6.79 (broad s, 1H), 1.31 (sept, $J=7.4$ Hz, 3H), 1.14 (t, $J=7.4$ Hz, 18H) ppm. ^{13}C NMR: $\delta=157.6$, 150.4 (q, $J=2$ Hz), 130.3, 120.9 (q, $J=257$ Hz), 118.8, 113.7, 113.4, 18.2 (3 C), 13.0 (6 C) ppm. MS (c.i.): *m/z* (%)=352 (0) [$M^+ + NH_4$], 335 (8) [$M^+ + 1$], 334 (1) [M^+], 293 (18), 292 (100). $C_{16}H_{25}F_3O_2Si$ (334.45): calcd C 57.46, H 7.53; found C 57.47, H 7.54.

3.3.6. Triisopropyl[4-(trifluoromethoxy)phenoxy]silane. Prepared analogously from 4-(trifluoromethoxy)phenol (8.9 g, 50 mmol); colorless liquid; bp 126–127 °C/5 mmHg; $n_D^{20}=1.4551$; yield: 14.4 g (86%). ^{1}H NMR: $\delta=7.13$ (d, $J=8.6$ Hz, 2H), 6.91 (dd, $J=8.9$, 1.6 Hz, 2H), 1.30 (sept, $J=7.4$ Hz, 3H), 1.14 (d, $J=7.4$ Hz, 18H) ppm. ^{13}C NMR: $\delta=155.1$, 143.4 (q, $J=2$ Hz), 122.6 (2 C), 121.0 (q, $J=254$ Hz), 121.0 (2 C), 18.2 (3 C), 13.0 (6 C) ppm. MS (c.i.): *m/z* (%)=352 (0) [$M^+ + NH_4$], 336 (28) [$M^+ + 2$], 335 (47) [$M^+ + 1$], 334 (81) [M^+], 236 (100). $C_{16}H_{25}F_3O_2Si$ (334.45): calcd C 57.46, H 7.53; found C 57.50, H 7.58.

3.3.7. 2-Hydroxy-3-(trifluoromethoxy)benzoic acid (2a). 1-(Methoxymethoxy)-2-(trifluoromethoxy)benzene (5.6 g, 25 mmol) was added to a solution of *sec*-butyllithium and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (5.2 mL, 4.3 g, 25 mmol) in tetrahydrofuran (30 mL) and cyclohexane (20 mL), cooled in a dry ice/methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was partitioned between water (25 mL) and diethyl ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with diethyl ether (3×25 mL). After evaporation of the combined organic layers, the residue was crystallized from hexanes; colorless needles; mp 132–133 °C; yield: 3.94 g (71%). ^{1}H NMR*: $\delta=7.94$ (dd, $J=8.1$, 1.5 Hz, 1H), 7.57 (dm, $J=8.1$ Hz, 1H), 7.06 (t, $J=8.0$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=172.0$, 155.8, 137.8 (q, $J=2$ Hz), 130.3, 129.9, 121.7 (q, $J=256$ Hz), 119.6, 115.6 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (4) [$M^+ + 1$], 222 (29) [M^+], 205 (13), 204 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.19, H 2.29.

3.3.8. 2-Hydroxy-5-(trifluoromethoxy)benzoic acid (2c). Prepared analogously from 1-(methoxymethoxy)-4-(trifluoromethoxy)benzene (5.6 g, 25 mmol); colorless stars (from toluene); mp 133–134 °C (lit.[31]: mp 128–129 °C); yield: 5.16 g (93%). ^{1}H NMR*: $\delta=7.80$ (dd, $J=2.9$, 1.0 Hz, 1H), 7.55 (ddd, $J=9.0$, 2.9, 0.6 Hz, 1H), 7.08 (d, $J=9.0$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=171.1$, 161.3, 140.9 (q, $J=2$ Hz), 129.7, 123.0, 121.0 (q, $J=254$ Hz), 119.4, 113.2 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (12) [$M^+ + 1$], 222 (16) [M^+], 205 (16), 204 (30), 107 (100).

3.3.9. 2-Hydroxy-6-(trifluoromethoxy)benzoic acid (2b). Prepared analogously from 1-(methoxymethoxy)-3-(trifluoromethoxy)benzene (5.6 g, 25 mmol) using *sec*-butyllithium alone; colorless needles (from chloroform); mp 119–120 °C yield: 4.72 g (85%). ^{1}H NMR*: $\delta=7.57$ (t, $J=8.6$ Hz, 1H), 7.06 (d, $J=8.6$ Hz, 1H), 6.92 (d, $J=7.4$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=170.5$, 163.7, 148.7 (q, $J=2$ Hz), 135.4, 121.1 (q, $J=256$ Hz), 117.3, 113.6, 108.2 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (25) [$M^+ + 1$], 222 (36) [M^+], 205 (53), 204 (88), 107 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.28, H 2.17.

3.3.10. [2-Methoxymethoxy-6-(trifluoromethoxy)-phenyl]trimethylsilane (3). The metalation was carried out as described for the preparation of the acid **2b**, but the reactant dry ice was replaced by chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol). Upon distillation, a colorless liquid was collected; bp 75–76 °C/5 mmHg; $n_D^{20}=1.4514$; yield: 4.78 g (65%). ^{1}H NMR: $\delta=7.30$ (t, $J=8.3$ Hz, 1H), 7.01 (d, $J=8.3$ Hz, 1H), 6.89 (dm, $J=8.3$ Hz, 1H), 5.18 (s, 2H), 3.45 (s, 3H), 0.34 (s, 9H) ppm. ^{13}C NMR: $\delta=163.5$, 154.8 (q, $J=2$ Hz), 131.8, 121.1 (q, $J=257$ Hz), 121.0, 113.5, 111.6, 94.6, 56.4, 1.3 ppm. MS (c.i.): *m/z* (%)=314 (0) [$M^+ + NH_4$], 296 (15) [$M^+ + 2$], 295 (24) [$M^+ + 1$], 294 (61) [M^+], 279 (70), 105 (100). $C_{12}H_{17}F_3O_3Si$ (294.32): calcd C 48.67, H 5.82; found C 48.66, H 5.99.

3.3.11. 2-Hydroxy-4-(trifluoromethoxy)benzoic acid (2d). [1-(Methoxymethoxy)-6-(trifluoromethoxy)phenyl]-trimethylsilane (**3**, 2.9 g, 10 mmol) in tetrahydrofuran (14 mL) was treated with *sec*-butyllithium in cyclohexane (6 mL) at −75 °C for 6 h before being poured on dry ice. The residue was neutralized with ethereal hydrogen chloride and dissolved in diethyl ether (10 mL) containing tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol). After 2 h at 25 °C, a 10% aqueous solution (10 mL) of hydrochloric acid was added and the reaction mixture was extracted with diethyl ether (3×15 mL). The combined organic layers were dried and evaporated; colorless needles (from toluene); mp 122–123 °C; yield: 1.62 g (73%). ^{1}H NMR: $\delta=7.59$ (d, $J=8.6$ Hz, 1H), 6.5 (m, 1H), 6.40 (dm, $J=8.6$ Hz, 1H) ppm. ^{13}C NMR: $\delta=174.2$, 164.0, 155.8 (q, $J=2$ Hz), 133.2, 120.6 (q, $J=260$ Hz), 111.9, 109.9, 109.3 ppm. MS (c.i.): *m/z* (%)=240 (4) [$M^+ + NH_4$], 223 (5) [$M^+ + 1$], 222 (41) [M^+], 176 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.27, H 2.15. When *sec*-butyllithium was replaced by butyllithium as the metalating agent, the yield dropped to 47%.

3.3.12. 1-Chloro-2-(methoxymethoxy)-6-(trifluoromethoxy)benzene (4). Prepared analogously as the silane **3** but replacing the reactant chlorotrimethylsilane by 1,1,2-trichloro-1,2,2-trifluoroethane (3.1 mL, 4.8 g, 25 mmol). Direct distillation of the reaction mixture afforded a colorless liquid; bp 61–63 °C/4 mmHg; $n_D^{20}=1.4554$; yield: 4.29 g (67%). ^{1}H NMR: $\delta=7.20$ (t, $J=8.1$ Hz, 1H), 7.13 (dd, $J=8.1$, 1.8 Hz, 1H), 7.00 (dm, $J=8.2$ Hz, 1H), 5.26 (s, 2H), 3.49 (s, 3H) ppm. ^{13}C NMR: $\delta=154.9$, 146.7 (q, $J=2$ Hz), 127.6, 120.8 (q, $J=256$ Hz), 118.0, 115.7, 114.5, 95.7, 56.8 ppm. MS (c.i.): *m/z* (%)=274 (14) [$M^+ + NH_4$], 258 (20) [$M^+ + 2$], 257 (8) [$M^+ + 1$], 256 (100) [M^+]. $C_9H_8ClF_3O_3$ (256.61): calcd C 42.13, H 3.14; found C 42.25, H 3.11.

3.3.13. 3-Chloro-2-hydroxy-4-(trifluoromethoxy)benzoic acid (5). The chloroarene **4** (2.6 g, 10 mmol) in tetrahydrofuran (14 mL) was treated with butyllithium (10 mmol) in hexanes (6 mL) at −75 °C for 6 h before being poured onto an excess of freshly crushed dry ice. Acidification with concentrated hydrochloric acid, extraction with diethyl ether (3×15 mL) and crystallization from toluene afforded colorless tiny needles; mp 186–187 °C; yield: 2.05 g (80%). ^{1}H NMR*: δ=8.01 (d, J=8.9 Hz, 1H), 7.11 (dm, J=8.9 Hz, 1H), ppm. ^{13}C NMR*: δ=171.3, 160.9, 150.2 (q, J=2 Hz), 130.0, 120.7 (q, J=259 Hz), 115.1, 112.9, 112.1 (q, J=2 Hz) ppm. MS (c.i.): *m/z* (%)=274 (0) [$M^+ + NH_4$], 257 (3) [$M^+ + 1$], 256 (30) [M^+], 240 (31), 238 (100). $C_8H_4ClF_3O_4$ (256.56): calcd C 37.45, H 1.57; found C 37.23, H 1.43.

3.3.14. 3-Hydroxy-2-(trifluoromethoxy)benzoic acid (2e). Triisopropyl[2-(trifluoromethoxy)-phenoxy]silane (3.4 g, 10 mmol) was added to a solution of *sec*-butyllithium (10 mmol) and *N*,*N*,*N*′,*N*″,*N*‴-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol) in tetrahydrofuran (12 mL) and cyclohexane (8 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. Acidification with a 1.0 M aqueous solution (10 mL) of citric acid, extraction with diethyl ether (3×15 mL) and evaporation of the solvents afforded a residue which was treated with tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol) in diethyl ether (10 mL). After 2 h at 25 °C, the mixture was evaporated to dryness. The residue crystallized from toluene as colorless platelets; mp 152–153 °C; yield: 1.53 g (69%). ^{1}H NMR*: δ=7.42 (dd, J=7.4, 1.9 Hz, 1H), 7.3 (m, 2H) ppm. ^{13}C NMR*: δ=165.5, 151.4, 135.3, 128.4, 122.3, 121.6 (2 C), 121.2 (q, J=257 Hz) ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (3) [$M^+ + 1$], 222 (62) [M^+], 202 (47), 136 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.52, H 2.19.

3.3.15. 4-Hydroxy-2-(trifluoromethoxy)benzoic acid (2f). Prepared analogously from triisopropyl[3-(trifluoromethoxy)phenoxy]silane (3.4 g, 10 mmol); colorless needles (from chloroform); mp 129–130 °C; yield: 1.73 g (78%). ^{1}H NMR*: δ=7.99 (d, J=8.6 Hz, 1H), 6.98 (dd, J=8.6, 2.2 Hz, 1H), 6.87 (symm. m, 2H) ppm. ^{13}C NMR*: δ=164.9, 162.7, 149.8, (q, J=2 Hz), 134.5, 120.8 (q, J=257 Hz), 116.3, 114.6, 110.2 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (77) [$M^+ + 1$], 222 (100) [M^+], 206 (66), 205 (90). $C_8H_5F_3O_4$ (222.12): calcd C 48.66, H 4.08; found C 48.77, H 3.88.

3.3.16. 5-Hydroxy-2-(trifluoromethoxy)benzoic acid (2g). Prepared analogously as described above for the acid **2e** from triisopropyl[4-(trifluoromethoxy)phenoxy]silane (3.4 g, 10 mmol); colorless tiny needles (from dichloromethane); mp 201–202 °C; yield: 1.78 g (80%). ^{1}H NMR*: δ=7.45 (d, J=3.2 Hz, 1H), 7.28 (dm, J=9.0 Hz, 1H), 7.14 (dd, J=9.0, 3.2 Hz, 1H) ppm. ^{13}C NMR*: δ=165.0, 156.6, 140.4 (q, J=2 Hz), 126.9, 124.8, 121.0 (q, J=255 Hz), 120.4, 118.3 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (22) [$M^+ + 1$], 222 (100) [M^+], 205 (18), 136 (31). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.57; found C 43.52, H 1.99.

3.4. Derivatives of chlorophenols

3.4.1. 1-Chloro-3-(methoxymethoxy)benzene. Mixed at 0 °C, a solution of 2-chlorophenol (13 g, 10 mL, 0.10 mol), chloromethyl methyl ether[30] (9.1 mL, 9.7 g, 0.12 mol) and *N*-ethyldiisopropylamine (18 mL, 16 g, 0.12 mol) in dichloromethane (80 mL) was kept at 25 °C for 2 h. The mixture was then poured into a 3.0 M aqueous solution (0.20 L) of sodium hydroxide. Extraction with diethyl ether (2×100 mL) and distillation gave a colorless liquid; bp 59–61 °C/5 mmHg; n_D^{20}=1.5209; yield: 9.4 g (55%). ^{1}H NMR: δ=7.20 (t, J=8.3 Hz, 1H), 7.06 (tm, J=2.2 Hz, 1H), 6.99 (dm, J=8.0 Hz, 1H), 6.92 (dm, J=8.3 Hz, 1H), 5.16 (s, 2H), 3.53 (s, 3H) ppm. ^{13}C NMR: δ=158.4, 135.2, 130.6, 122.4, 117.2, 115.0, 94.8, 56.4 ppm. MS (c.i.): *m/z* (%)=190 (0) [$M^+ + NH_4$], 174 (3) [$M^+ + 2$], 173 (97) [$M^+ + 1$], 172 (100) [M^+]. $C_8H_9ClO_2$ (172.61): calcd C 55.67, H 5.26; found C 55.75, H 5.19.

3.4.2. (2-Chlorophenoxy)triisopropylsilane. 2-Chlorophenol (6.4 g, 5.1 mL, 50 mmol), chlorotriisopropylsilane (11 mL, 10 g, 50 mmol) and imidazole (3.4 g, 50 mmol) were dissolved in *N*,*N*-dimethylformamide (25 mL). After 20 h at 25 °C, the mixture was poured into water (50 mL) and extracted with dichloromethane (3×25 mL). Distillation under reduced pressure gave a colorless liquid; bp 108–109 °C/5 mmHg; n_D^{20}=1.5216; yield: 12.3 g (83%). ^{1}H NMR: δ=7.34 (dd, J=8.0, 1.3 Hz, 1H), 7.11 (td, J=8.0, 1.3 Hz, 1H), 6.93 (dd, J=8.0, 1.3 Hz, 1H), 6.86 (t, J=8.0 Hz, 1H), 1.33 (sept, J=7.4 Hz, 3H), 1.18 (d, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=152.4, 130.7, 127.8, 125.7, 122.0, 120.5, 18.3 (3 C), 13.3 (6 C) ppm. MS (c.i.): *m/z* (%)=302 (0) [$M^+ + NH_4$], 287 (1) [$M^+ + 3$], 284 (0) [M^+], 241 (100). $C_{15}H_{25}ClOSi$ (284.90): calcd C 63.24, H 8.84; found C 63.18, H 8.94.

3.4.3. (3-Chlorophenoxy)triisopropylsilane. Prepared analogously from 3-chlorophenol (6.4 g, 5.1 mL, 50 mmol); colorless liquid; bp 110–112 °C/6 mmHg; n_D^{20}=1.4968; yield: 6.43 g (45%). ^{1}H NMR: δ=7.13 (t, J=8.0 Hz, 1H), 6.93 (ddd, J=8.0, 1.9, 0.6 Hz, 1H), 6.88 (t, J=2.2 Hz, 1H), 6.75 (ddd, J=8.0, 2.0, 0.6 Hz, 1H), 1.24 (sept, J=7.4 Hz, 3H), 1.08 (t, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=157.3, 135.0, 130.4, 121.7, 120.8, 118.6, 18.3 (3 C), 13.1 (6 C) ppm. MS (c.i.): *m/z* (%)=302 (0) [$M^+ + NH_4$], 286 (25) [$M^+ + 2$], 285 (31) [$M^+ + 1$], 284 (15) [M^+], 157 (100). $C_{15}H_{25}ClOSi$ (284.90): calcd C 63.24, H 8.84; found C 63.43, H 8.62.

3.4.4. (4-Chlorophenoxy)triisopropylsilane. Prepared analogously from 4-chlorophenol (6.4 g, 4.9 mL, 50 mmol); colorless liquid; bp 91–93 °C/5 mmHg; n_D^{20}=1.5031; yield: 13.6 g (96%). ^{1}H NMR: δ=7.18 (t, J=8.9 Hz, 2H), 6.82 (d, J=8.9 Hz, 2H), 1.3 (m, 3H), 1.12 (d, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=155.1, 129.7 (2 C), 126.3, 121.5 (2 C), 18.3 (3 C), 13.0 (6 C) ppm. MS (c.i.): *m/z* (%)=302 (0) [$M^+ + NH_4$], 286 (9) [$M^+ + 2$], 285 (17) [$M^+ + 1$], 284 (15) [M^+], 185 (100). $C_{15}H_{25}ClOSi$ (284.90): calcd C 63.24, H 8.84; found C 63.25, H 8.86.

3.4.5. 3-Chloro-2-hydroxybenzoic acid (6a). 1-Chloro-2-(methoxymethoxy)benzene[25,32] (4.3 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in tetrahydrofuran

(35 mL) and hexanes (15 mL), cooled in a dry ice/methanol bath. After 6 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was taken up in water (25 mL) and washed with diethyl ether (2×15 mL). The aqueous phase was acidified to pH 1 and extracted with diethyl ether (3×25 mL). After evaporation of the combined and dried organic layers, the residue was crystallized from toluene; colorless needles; mp 176–178 °C (lit.[33]: mp 183–183.5 °C); yield: 3.19 g (74%). ^{1}H NMR: δ=7.89 (dd, J=8.0, 1.6 Hz, 1H), 7.67 (dd, J=8.0, 1.6 Hz, 1H), 6.96 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR: δ=172.0, 158.2, 136.2, 129.5, 121.9, 119.7, 114.2 ppm. MS (c.i.): m/z (%)=192 (0) [M^++NH_4], 174 (6) [M^++2], 173 (3) [M^++1], 172 (26) [M^+], 154 (100).

3.4.6. 5-Chloro-2-hydroxybenzoic acid (6c). Prepared analogously from 1-chloro-4-(methoxymethoxy)benzene[25,32] (4.3 g, 25 mmol); colorless needles (from toluene); mp 173–175 °C (lit.[34]: mp 172 °C); yield: 3.41 g (79%). ^{1}H NMR: δ=7.85 (d, J=2.9 Hz, 1H), 7.54 (dd, J=9.0, 2.9 Hz, 2H), 6.99 (d, J=9.0 Hz, 1H) ppm. ^{13}C NMR: δ=171.5, 161.7, 136.5, 130.3, 124.1, 120.1, 114.4 ppm. MS (c.i.): m/z (%)=190 (0) [M^++NH_4], 173 (13) [M^++1], 172 (0) [M^+], 154 (100).

3.4.7. 6-Chloro-2-hydroxybenzoic acid (6b). 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and 1-chloro-3-(methoxymethoxy)benzene (4.3 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (34 mL) and hexanes (16 mL) kept in a dry ice/ methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After addition of water (25 mL) and washing with diethyl ether (2×30 mL), the aqueous phase was acidified to pH 1 with concentrated hydrochloric acid, extracted with dichloromethane (3×25 mL), dried and evaporated under reduced pressure, crystallization of the residue from toluene afforded colorless needles; mp 169–170 °C (lit.[35]: mp 171.5–172.5 °C); yield: 3.62 g (84%). ^{1}H NMR: δ=7.37 (d, J=8.0 Hz, 1H), 7.01 (dd, J=8.0, 1.0 Hz, 1H), 6.91 (dd, J=8.3, 1.3 Hz, 1H) ppm. ^{13}C NMR: δ=169.5, 161.1, 133.6 (2 C), 122.0, 116.2, 116.3 ppm. MS (c.i.): m/z (%)=192 (0) [M^++NH_4], 174 (7) [M^++2], 173 (7) [M^++1], 172 (24) [M^+], 154 (100). When butyllithium was used instead of lithium 2,2,6,6-tetramethylpiperidide in otherwise identical conditions, a mixture of 6-chloro-2-hydroxybenzoic acid and 4-chloro-2-hydroxybenzoic acid was obtained in the ratio 60:40 (89%) according to gas chromatographic analysis (30 m, DB-WAX, 150 °C; 30 m, DB-23, 150 °C).

3.4.8. [2-Chloro-6-(methoxymethoxy)phenyl]trimethylsilane (7). 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol), 1-chloro-3-(methoxymethoxy)benzene (4.3 g, 25 mmol) and chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. Upon distillation, a colorless liquid was collected; bp 82–85 °C/4 mmHg; n_D^{20}=1.5062; yield: 4.03 g (66%). ^{1}H NMR: δ=7.26 (t, J=8.3 Hz, 1H), 7.05 (d, J=8.3 Hz, 2H), 5.21 (s, 2H), 3.54 (s, 3H), 0.50 (s, 9H) ppm. ^{13}C NMR: δ=163.4, 141.6, 131.5, 127.1, 124.1, 111.9, 94.6, 56.5, 2.6 ppm. MS (c.i.): m/z (%)=262 (22) [M^++NH_4], 246 (11) [M^++2], 245 (2) [M^++1], 244 (16) [M^+], 199 (100). $C_{11}H_{17}ClO_2Si$ (244.18): calcd C 53.97, H 7.00; found C 54.38, H 7.41.

3.4.9. 2-Hydroxy-4-chlorobenzoic acid (6d). [2-(Chloro)-6-(methoxymethoxy)phenyl]trimethylsilane (**7**, 2.4 g, 10 mmol) in tetrahydrofuran (15 mL) was treated with *sec*-butyllithium in cyclohexane (6 mL) at −75 °C for 6 h before being poured on dry ice. After evaporation of the solvents, the residue was partitioned between water (10 mL) and diethyl ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with diethyl ether (3×15 mL). After evaporation of the combined organic layers, the residue was dissolved in *N*,*N*-dimethylformamide (10 mL) containing tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol) and heated to 100 °C for 48 h. A 10% aqueous solution (20 mL) of hydrochloric acid was then added. The product was isolated by extraction with diethyl ether (3×15 mL); colorless stars (from dichloromethane); mp 206–208 °C (lit.[36]: mp 207 °C); yield: 0.60 g (35%). ^{1}H NMR*: δ=7.92 (d, J=8.6 Hz, 1H), 7.02 (d, J=1.9 Hz, 1H), 7.00 (dd, J=8.6, 1.9 Hz, 1H) ppm. ^{13}C NMR*: δ=171.6, 163.1, 141.2, 132.2, 120.0, 117.5, 111.7 ppm. MS (c.i.): m/z (%)=190 (0) [M^++NH_4], 174 (12) [M^++2], 173 (6) [M^++1], 172 (34) [M^+], 156 (34), 154 (100).

3.4.10. 2-Chloro-3-hydroxybenzoic acid (6e). (2-Chlorophenoxy)triisopropylsilane (2.8 g, 10 mmol) was added to a solution of *sec*-butyllithium in tetrahydrofuran (12 mL) and cyclohexane (8 mL) kept at −100 °C. After 6 h at this temperature, the reaction mixture was poured onto an excess of freshly crushed dry ice. After acidification with 1.0 M aqueous solution (10 mL) of citric acid and extraction with diethyl ether (3×15 mL), the combined organic layers were reduced to a volume of 10 mL and tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol) was added. After standing for 2 h at 25 °C, the solvents were evaporated and the product crystallized from toluene to give colorless platelets; mp 157–158 °C (lit.[37]: mp 157.5–158.5 °C); yield: 0.85 g (49%). ^{1}H NMR: δ=7.34 (dd, J=7.7, 1.9 Hz, 1H), 7.25 (t, J=8.0 Hz, 1H), 7.16 (dd, J=8.0, 1.6 Hz, 1H) ppm. ^{13}C NMR: δ=166.6, 154.2, 132.9, 127.8, 122.1, 119.5, 119.4 ppm. MS (c.i.): m/z (%)=190 (0) [M^++NH_4], 174 (41) [M^++2], 173 (16) [M^++1], 172 (98) [M^+], 155 (100).

3.4.11. 2-Chloro-4-hydroxybenzoic acid (6f). Prepared analogously from (3-chlorophenoxy)triisopropylsilane (2.8 g, 10 mmol); colorless tiny needles (from dichloromethane); mp 192–193 °C (lit.[38]: mp 159 °C); yield: 0.86 g (50%). ^{1}H NMR: δ=7.92 (d, J=8.6 Hz, 1H), 6.95 (d, J=2.6 Hz, 1H), 6.89 (dd, J=8.6, 2.6 Hz, 1H) ppm. ^{13}C NMR: δ=166.2, 162.0, 136.2, 134.8, 121.5, 118.6, 114.9 ppm. MS (c.i.): m/z (%)=192 (0) [M^++NH_4], 174 (18) [M^++2], 173 (11) [M^++1], 172 (66) [M^+], 155 (100).

3.4.12. 2-Chloro-5-hydroxybenzoic acid (6g). Prepared analogously from (4-chlorophenoxy)triisopropylsilane (2.8 g, 10 mmol); colorless needles (from toluene); mp 167–168 °C (lit.[37]: mp 168–169 °C); yield: 0.87 g (51%). ^{1}H NMR: δ=7.36 (d, J=3.2 Hz, 1H), 7.34 (d, J=8.6 Hz, 2H),

7.04 (dd, $J=8.6$, 2.9 Hz, 1H) ppm. ^{13}C NMR: $\delta=166.2$, 156.5, 132.1, 131.9, 120.1, 118.2, 118.1 ppm. MS (c.i.): *m/z* (%)=190 (0) [$M^+ + NH_4$], 174 (27) [$M^+ + 2$], 173 (16) [$M^+ + 1$], 172 (81) [M^+], 155 (100).

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Highly functionalised organolithium and organoboron reagents for the preparation of enantiomerically pure α-amino acids

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Abstract—Homochiral, highly functionalised organolithium reagents derived from L-serine have been generated and reacted with electrophiles. The novel enantiomerically pure adducts thus obtained were then converted, through β-amino alcohols, into novel non-proteinogenic α-amino acids. The methodology also made available a novel boronic acid which was then employed as a Suzuki cross-coupling partner, elaborating a new pathway to phenylalanine analogues.

Nucleophilic alanine equivalents have attracted a great deal of attention in recent years.[1–6] These reagents are particularly useful for the preparation of enantiopure proteinogenic and non-proteinogenic α-amino acids,[1] as well as enantiopure α-amino alcohols, and other related 'chiral building blocks' used in natural product synthesis. Prominent examples of these reagents include aspartate-derived anion **1**,[2] related sulfonyl reagent **2**,[3] Wittig reagents **3**[4] and **4**,[5] and the organonickel reagent **5**.[6] Although ground-breaking and potentially valuable, these reagents have not been widely employed in organic synthesis, possibly due to the difficulty of preparation, the additional steps needed to remove the anion-stabilising/activating group or to readjust the oxidation level and, in the case of reagent **5**, its low reactivity.

The organozinc reagent **6** designed and prepared by Jackson and his group,[7] has proved particularly versatile and has been successfully adopted by other researchers for preparation of a number of natural products and medicinally active compounds.[8] This reagent can be employed in a variety of coupling procedures (e.g., to aryl halides and acyl halides[7a]), and its copper derivative also undergoes allylation or conjugate additions.[7b] Unfortunately, due to its low nucleophilicity, reaction with simple aldehydes/ketones is not possible (Fig. 1).

During synthetic efforts towards the synthesis of scyphostatin[9a] and aranorosin,[9b] we required a highly reactive organometallic reagent, i.e. **7**, capable of 1,2-addition to cyclic ketones. In this paper we describe the successful

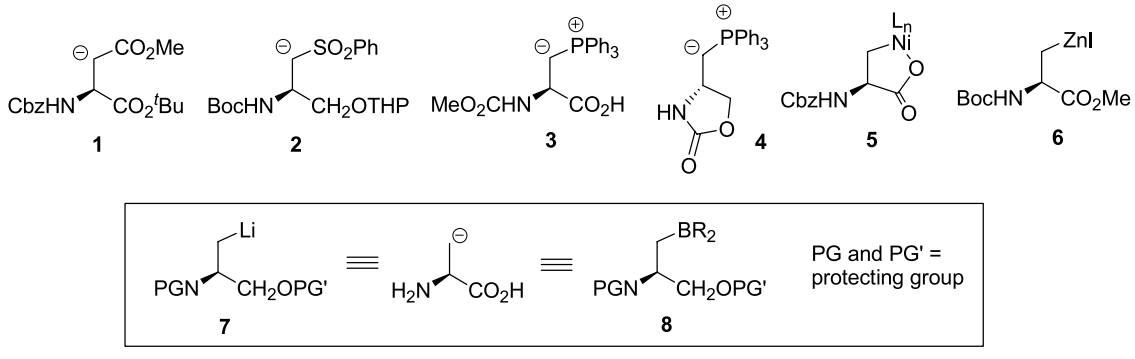

Figure 1. Alanine anion equivalents.

Keywords: Cross-coupling; α-Amino acids; Organolithium; Suzuki; Alanine anions.
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development and application of such highly functionalised organolithium reagents **7**.[10] The novel homochiral adducts are then manipulated into proteinogenic and non-proteinogenic α-amino acids. We also outline the synthesis of a new alkylboron reagent **8**,[11] which is employed in Suzuki cross-coupling reactions. Thus, two new alanine anion equivalents are described.

1. Preparation and application of functionalised organolithium reagents (7)

We first embarked on a program to explore the preparation of organolithium reagents **7** commencing from a readily available proteinogenic α-amino acid (Scheme 1).[12] Standard conditions were employed to convert L-serine via ester **9**[13] into chloro-alcohol **10**. Protection of alcohol **10** was undertaken using a number of different groups, giving the key lithiation precursors **11a–d**.

With precursors **10** and **11a–d** in hand we were able to investigate the generation of organolithium reagents **12a–e** (Scheme 1). Due to the required anion **7** having a β-heteroatom it was obviously crucial to generate a dianionic species in order to impede β-elimination. We therefore employed the *n*-butyllithium/lithium naphthalenide (LiNp) combination pioneered by Yus et al. for β-chloroamide lithiation.[14] This protocol was employed with the unprotected alcohol **10** and with the protected derivatives **11a–d**, the reaction mixture was then quenched with cyclohexanone with the aim of assessing the procedure in terms of the yield of adducts **13a–e** (Table 1).

Table 1. Metallation-trapping of **11a–d** and **10**[a]

Entry	Precursor	Product[b]
i	**11a**, P=TBS	**13a**, P=TBS, 0%
ii	**11b**, P=THP	**13b**, P=THP, 57%
iii	**11c**, P=MOM	**13c**, P=MOM, 82%
iv	**11d**, P=SEM	**13d**, P=SEM, 82%
v[c]	**10**	**13e**, P=H, 0%

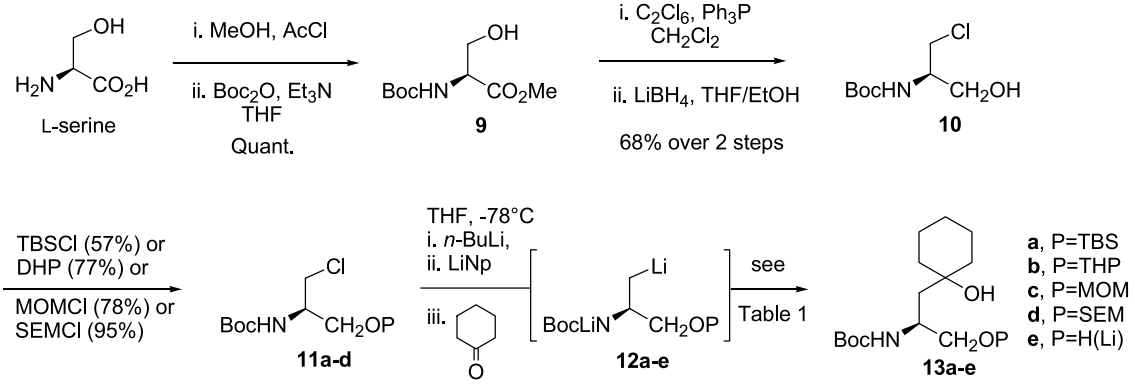
[a] THF, −78 °C: (i) *n*-BuLi (1.1 equiv), (ii) LiNp (2.5–3.0 equiv), (iii) E^+ (1.5–2.5 equiv).
[b] Isolated yields.
[c] 2.1 equiv of *n*-BuLi was employed.

We were encouraged by the promising results with THP, MOM and SEM protecting groups (Table 1, entries ii–iv), indicating the possibility that an additional coordinating site in the protecting group might be advantageous. The unprotected alcohol **10** gave no product, nor did the TBS ether **11a**. The failure of silyl-protected **11a** was presumably due to susceptibility to intramolecular Brook-type rearrangement, although this could not be verified by analysis of the crude product mixture. No further work was carried out with the THP-protected **11b** in view of the diastereomeric nature of the adducts.

As might be anticipated,[15] preliminary deprotection studies showed the SEM ether **13d** could be deprotected more easily than MOM ether **13c**, although many standard methods[15] led to decomposition. *N*-Br-Catecholborane cleanly converted MOM-protected **13c** into alcohol **13e**, but only in a disappointing 58% yield. It should be pointed out that deprotection of the SEM ether employing TBAF (in THF[16] and DMPU[17]) failed at room temperature, and decomposition ensued on heating at elevated temperatures. Fortunately, deprotection of SEM ether **13d** could be performed cleanly using 0.1 M HCl in MeOH[18] over 3 h at room temperature, delivering **13e** (P=H) in an excellent 79% yield. Unfortunately, this reaction time (3 h) led to incomplete conversion, and so starting material was recovered (see Table 2 footnote). Extended reaction times led to substantial cleavage of the Boc group.

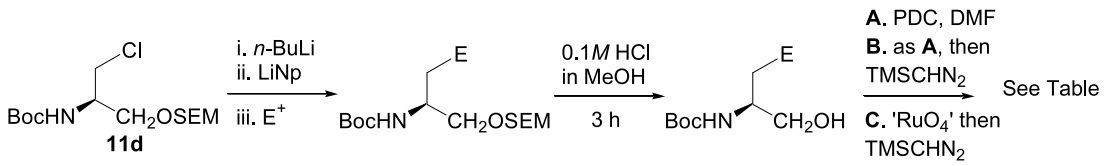
Due to the success of the SEM group in the deprotection studies, it was therefore chosen for further investigation and a range of electrophiles were used to trap the organolithium reagent **12d** (Table 2). Thus, in addition to cyclohexanone (entry i), cyclobutanone, benzaldehyde, Weinreb amides, carbon dioxide, trimethylsilyl chloride, CD_3OD and tributyltin chloride were all successfully employed as electrophilic trapping agents delivering adducts **15**, **18**, **21**, **23**, **25**, **27**, **30** and **33**, respectively, in yields ranging from 51 to 98% (entries ii–viii).

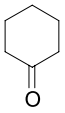
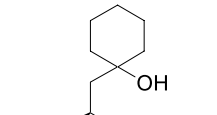
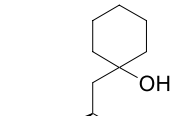
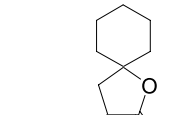
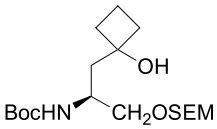
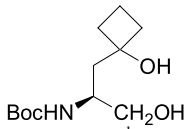
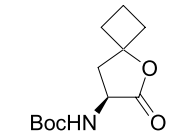
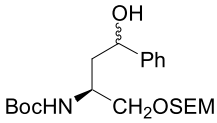
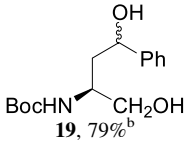
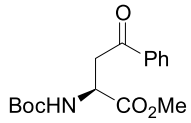
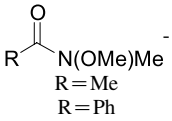
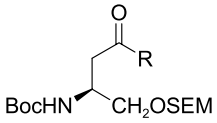
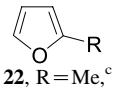
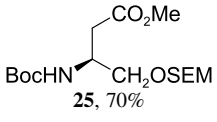
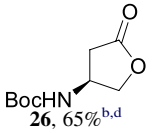
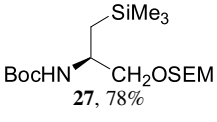
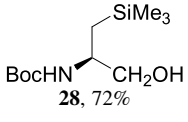
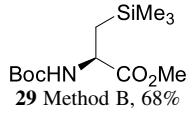
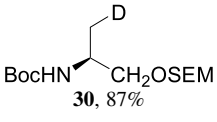
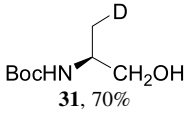
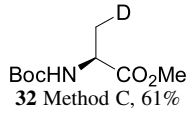
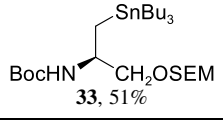
Cleavage of the SEM-protecting groups proceeded smoothly, in most cases, delivering alcohols **13e**, **16**, **19**, **28** and **31** in unoptimised but reasonable yields (entries i–iii, vi–vii). The main exceptions (entry iv) involved methanolysis of ketone adducts **21** and **23** where the only observed products were the furans **22** and **24**, respectively, resulting from a cyclocondensation–aromatisation sequence. In addition (entry v), the alcohol resulting from deprotection of ester **25** underwent partial lactonisation, and a second



Scheme 1. Initial studies.

Table 2. Metallation-trapping–methanolysis–oxidation of **11d**[a]

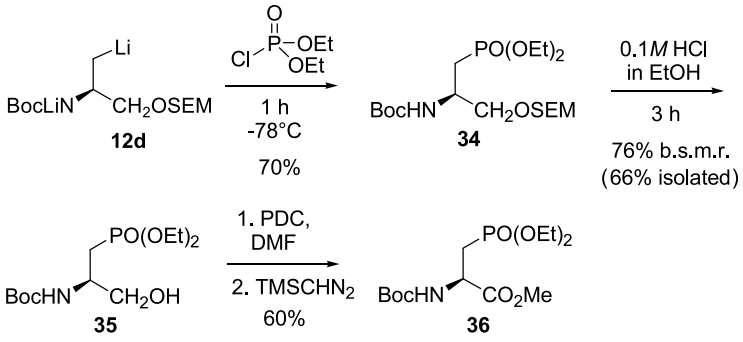


	Electrophile (E^+)	Adduct	Methanolysis product	Oxidation product
i		 **13d**, 82%	 **13e**, 88%[b]	 **14** Method A, 69%
ii		 **15**, 81%	 **16**, 76%[b]	 **17** Method A, 74%
iii	PhCHO	 **18**, 98% (3:2) ratio	 **19**, 79%[b]	 **20** Method B, 47%, Method C, 44%
iv	 R = Me R = Ph	 **21** R = Me, 82%, **23** R = Ph, 80%	 **22**, R = Me,[c] **24**, R = Ph[c]	—
v	CO_2, then $TMSCHN_2$	 **25**, 70%	 **26**, 65%[b,d]	—
vi	Me_3SiCl	 **27**, 78%	 **28**, 72%	 **29** Method B, 68%
vii	CD_3OD	 **30**, 87%	 **31**, 70%	 **32** Method C, 61%
viii	Bu_3SnCl	 **33**, 51%	—	—

[a] Trapping of **12d** using the electrophile indicated; deprotection using 0.1 M HCl in MeOH for 3 h; oxidation/esterification using Method A: PDC, DMF, Method B: (i) PDC, DMF, (ii) $TMSCHN_2$ or Method C: (i) $RuCl_3$ (cat.), $NaIO_4$, $CCl_4/H_2O/CH_3CN$, (ii) $TMSCHN_2$; isolated yields are shown.
[b] Based on recovered starting material (isolated yields were **13e**, 79%; **16**, 65%; **19**, 64%; **26**, 50%).
[c] The desired deprotected product was not observed. Due to the volatility of **22** and **24** isolated yields were not obtained; these were the only products observed by TLC and ^1H NMR spectroscopy.
[d] Lactonisation to give **26** was completed by treatment with CSA in PhH.[19]

treatment of the crude material with CSA in benzene[19a] completed lactonisation to give the known γ-lactone **26**.[19] The standard deprotection method failed to effect clean removal of the SEM from the tributyltin adduct **33** (entry viii).

The Boc-protected β-amino alcohol derivatives obtained by SEM-deprotection were then oxidised to the corresponding Boc-protected α-amino acids which were converted into their methyl esters using trimethylsilyl diazomethane. Thus, fully protected α-amino acids **20**,[20] **29** and **32** were obtained

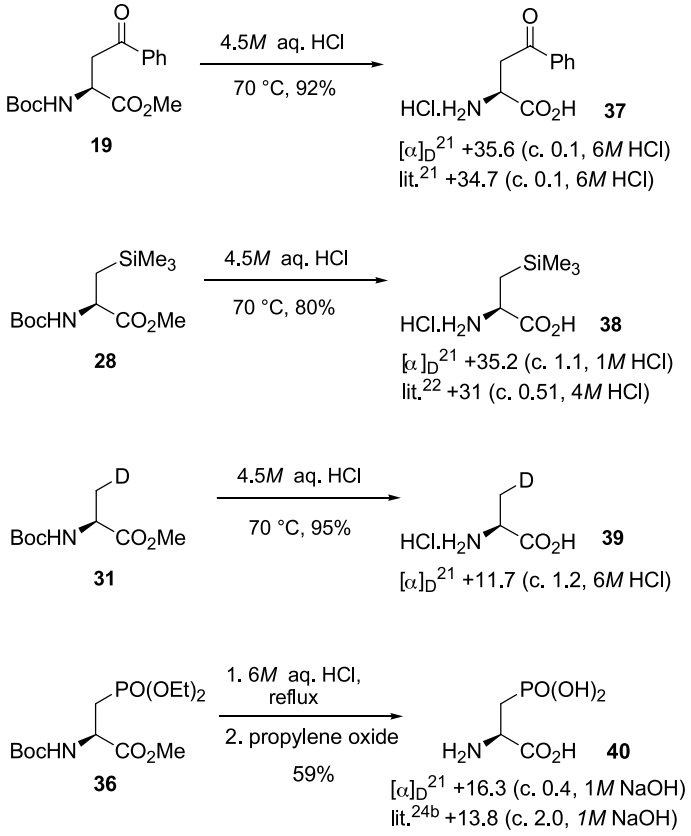


Scheme 2. Preparation of phosphonate α-amino acid **36**.

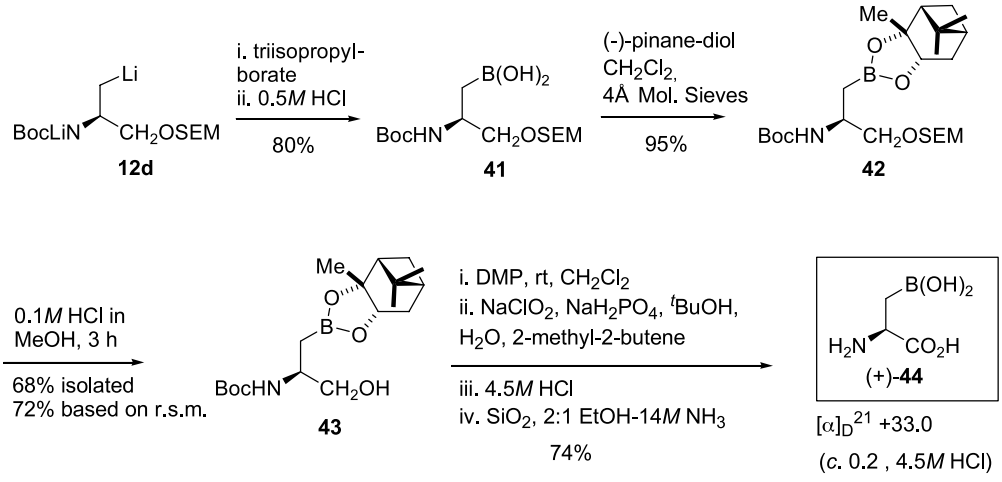
in reasonable yields (entries iii and vi–vii). Oxidation of 1°/3° diols **13e** and **16** under these PDC oxidation conditions gave the spirocyclic lactones **14** and **17**, respectively, by in situ lactonisation (entries i and ii). It should be noted that the problems with methanolysis of the SEM–ketone adducts, such as **21** and **23**, were overcome by double oxidation of the deprotected benzaldehyde adduct **19**, therefore allowing the synthesis of β-keto-α-amino acid **20** (entry iii).[20]

A more demanding electrophile such as diethyl chlorophosphate could also be employed. Reaction of organolithium **12d** with diethyl chlorophosphate delivered a good yield of the phosphonate **34** (Scheme 2), although reduced reaction times were required to minimise side reactions. SEM-deprotection was then carried out efficiently by means of 0.1 M ethanolic HCl, avoiding trans-esterification problems. The subsequent alcohol **35** was converted into the protected α-amino acid **36** in the manner described above.

Hydrolysis of the protected amino acids **19**, **28** and **31** was straightforward (Scheme 3). Thus, treatment of the *N*-Boc amino ester **19** with 4.5 M HCl at 70 °C for 3 h gave the hydrochloride salt **37** in 92% yield. The optical rotation was in good agreement with the published value $\{[\alpha]_D^{21} = +35.6$ (c 0.1, 6 M HCl); lit.[21] +34.7 (c 0.1, 6 M HCl)$\}$. Similarly, trimethylsilylalanine was obtained as its hydrochloride salt **38** from **28** in 80% yield $\{[\alpha]_D^{21} = +35.2$ (c 1.1, 1 M HCl); lit.[22] +31 (c 0.51, 4 M HCl)$\}$. The deutero-alanine HCl salt **39** was obtained in 95% yield from **31** in the same manner $\{[\alpha]_D^{21} = +11.7$ (c 1.2, 6 M HCl)$\}$. This labelled amino acid has been observed in the reaction of alanine with hydroxyl radicals,[23] but has never been isolated and characterised.



Scheme 3. Preparation of (+)-α-amino acids.



Scheme 4. Preparation of aspartic acid mimic (+)-**44**.

Future employment of this deuterated amino acid (+)-**39** could be envisaged in biological studies.

L-2-Amino-3-phosphonopropionic acid **40** has been shown to be an antagonist of the metabotropic glutamate receptor.[24a] This can lead to inhibition of phosphoserine phosphatase, which catalyses the final step in the major pathway of L-serine biosynthesis in the brain. The synthesis of phosphonic acid **40** was achieved through global deprotection of the phosphonate **36** in 6 M HCl under reflux, followed by treatment with propylene oxide (Scheme 3).[24b] The optical rotation value $\{[\alpha]_D^{21} = +16.3$ (*c* 0.4, 1 M NaOH)} of amino acid **40** was in good agreement with that reported by Smith et al. {lit.[24b] +13.8 (*c* 2, 1 M NaOH)}.

We also employed this novel methodology to complete the first asymmetric synthesis of the aspartic acid mimic (+)-**44**, in which the β-carboxylic acid has been substituted by a boronic acid (Scheme 4). This compound has already been synthesised as a racemate,[25,26] and in one case resolution was performed by separation of a dipeptide derivative.[26] It is a member of the increasing number of biomolecules which synthetic chemists have altered by incorporation of boron-containing moieties.[27]

Reaction of the functionalised organolithium reagent **12d** with triisopropylborate followed by treatment with mild acid delivered the boronic acid **41** in 80% yield (Scheme 4). In order to manipulate the boronic acid adduct **41**, protection as the (−)-pinane-diol boronate ester was undertaken. This was followed by methanolysis of the SEM ether **42**, giving the alcohol **43** in reasonable yield. The oxidation of alcohol **43** was found to be sensitive to the reagent used, for example, both PDC/DMF and 'RuO_4' oxidations led to decomposition. Fortunately, sequential Dess–Martin periodinane/sodium chlorite oxidations gave the crude carboxylic acid[28] which was directly deprotected using 4.5 M HCl. The crude hydrogen chloride salt of the amino acid could then be purified on silica gel eluting with 2:1 EtOH–14 M NH_3[29] to deliver the aspartic acid mimic (+)-**44**, $\{[\alpha]_D^{21} = +33.0$ (*c* 0.2, 4.5 M HCl)}.[30] This constitutes the first asymmetric synthesis of the aspartic acid mimic (+)-**44**, increasing its potential in future biological studies.

2. Preparation and application of functionalised organoboron reagents (8)

Recently, we have explored the use of complex alkyl-borane Suzuki cross-coupling partners derived from readily available chiral-pool starting materials. The homoalanine and bis-homoalanine alkyl-organoboranes **45** and **46**,[12] obtained by hydroboration of alkenyl-precursors, were employed in cross-coupling reactions delivering a variety of novel non-proteinogenic α-amino acids (Fig. 2). Attempts to synthesise alanine-organoborane derivatives (**47**, BR_2=9-BBN) had previously been made, but unfortunately hydroboration of the dehydro-amino acid derivatives failed.[31] The synthesis of boronic acid **41** (Scheme 4) raises the possibility of its application as the lower homologue of **45** and **46**. Application of this lower homologue to Suzuki cross-coupling would expand the scope of the methodology. An added benefit is that boronic acid **41** is stable and presumably has a low level of toxicity,[32] compared to the organoboranes **45** and **46**,[12] both of which need to be prepared immediately before use.

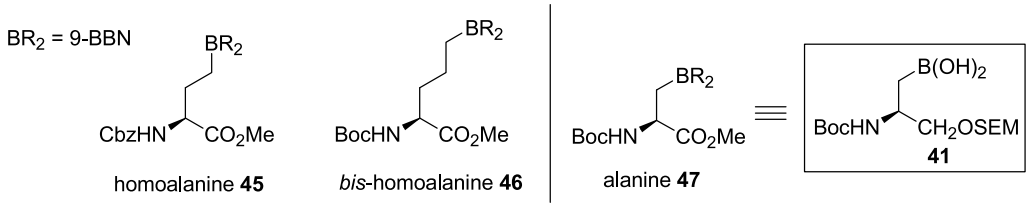


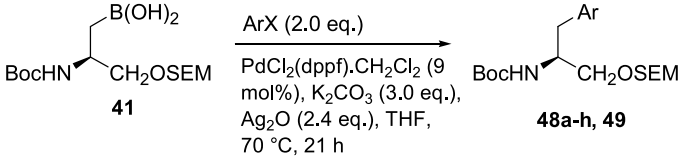
Figure 2. Suzuki cross-coupling substrates.

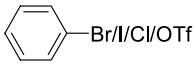
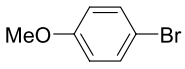
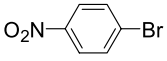
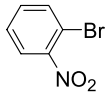
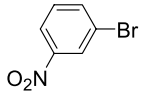
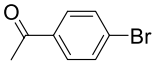
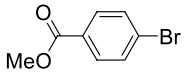
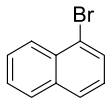
Traditionally, Suzuki cross-coupling reactions with alkyl boronic acids were thought to be non-viable, due to their low nucleophilicity and tendency for β-hydride elimination after transmetallation.[32] Over recent years this has been proved to be wrong with pioneering work by Falck,[33] Molander[34] and Fu,[35] who have shown that, by judicious choice of catalyst and conditions, clean Suzuki cross-coupling of alkyl-boronic acids is possible.

We first wished to discover if our highly functionalised boronic acid **41** was applicable to Suzuki cross-coupling with aryl halides, and whether we could then transform the adducts into phenylalanine analogues. Through optimisation[11] we were able to devise conditions delivering good yields of the coupled products **48a–h** and **49** (Table 3). Employment of modified Falck[33] conditions ($Pd^{II}Cl_2(dppf).CH_2Cl_2/K_2CO_3/Ag_2O$/THF) gave a clean conversion into the coupled products **48a–h**, **49** at 70 °C over 21 h. It should be pointed out that the maximum yield of coupled products from boronic acid **41** is 82%, due to 18% of the starting alkyl boronic acid being lost during reduction of the Pd^{II} precatalyst to Pd^0. A variety of aryl halides were found to react smoothly in the coupling procedure, from electron-rich *p*-bromoanisole (entry ii) to the electron-deficient *o*, *m* and *p*-nitrobromobenzenes (entries iii–v). Unsurprisingly iodobenzene also reacted well, but chlorobenzene failed to react. Rather unexpectedly, phenyl trifluoromethanesulfonate (PhOTf) failed, despite these conditions previously being employed effectively with triflates.[33] The presence of carbonyl groups in the aryl halide was found to be tolerated (entries vi and vii). A doubly coupled product **49** was isolated in a modest 35% yield by reaction of the boronic acid with 0.5 equiv of 1,4-diiodobenzene (entry ix).

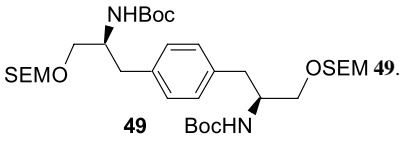
The bromobenzene and *p*-bromonitrobenzene systems were

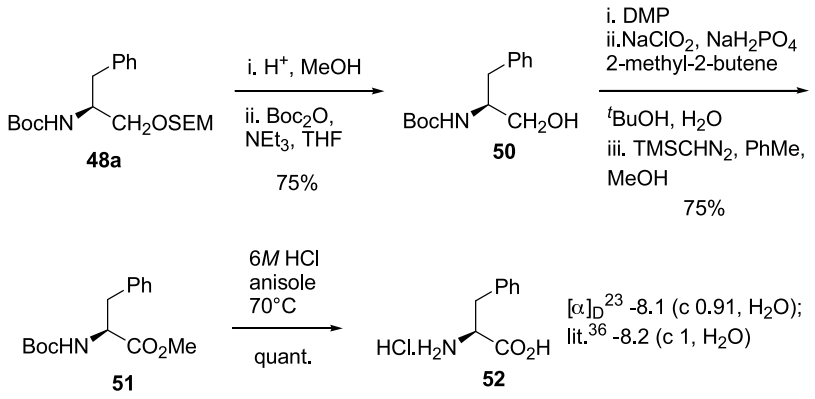
Table 3. Suzuki cross-coupling of alkyl boronic acid **35** with aryl halides[a]



Entry	ArX	Yield (%)[b]	Product
i		72/73/0/0	**48a**
ii		65	**48b**
iii		65	**48c**
iv		70	**48d**
v		67	**48e**
vi		68	**48f**
vii		52	**48g**
viii		73	**48h**
ix		35[c]	**49**

[a] All performed on 0.10–0.13 mmol scale at ca. 0.1 mol L^{-1} concentration.
[b] Yields are based on boronic acid **41**.
[c] 0.5 equiv of dihalide used; doubly coupled product **49** formed:





Scheme 5. Preparation of (−)-phenylalanine hydrochloride **52**.

demonstrated to be amenable to a modest scale-up (ca. 0.5 mmol), giving a reasonable 63% yield of **48a** and a better 71% yield of **48c**, respectively. No problems are foreseen in further scale-ups.

To demonstrate the synthetic utility of these adducts and to prove that no racemisation occurred during the coupling process we transformed the phenyl adduct **48a** into (−)-phenylalanine **52** (Scheme 5). A two-step deprotection procedure was used, whereby both SEM and Boc groups were removed to deliver the β-amino alcohol, which was reprotected with Boc, giving **50**. A two-step Dess–Martin periodinane/sodium chlorite oxidation was then employed to deliver the amino acid, which was again protected as a methyl ester, producing the fully protected phenylalanine **51**. This was then globally deprotected as before with 6 M HCl, this time including anisole as a cation trap. The optical rotation of the so-obtained HCl salt, **52**, matched the known data {$[\alpha]_D^{23} = -8.1$ (*c* 0.91, H_2O); [lit.[36] $[\alpha]_D^{23} = -8.2$ (*c* 1, H_2O)]}.

In summary, we have prepared a number of highly functionalised organolithium reagents from L-serine using the Yus procedure in the key lithiation step and established that they can be employed as alaninol/alanine anion equivalents. The optimum SEM-protected reagent **11d** has been used to prepare a range of novel adducts which were hydrolysed to give alaninol derivatives and then oxidised to give known and novel non-proteinogenic amino acids as their protected derivatives. A selection of these compounds was converted into the amino acid hydrochloride salts. We were also able to undertake the first asymmetric synthesis of the aspartic acid mimic (+)-**44**. In addition, the alkyl boronic acid **41** was employed as a β-alanine anion equivalent in Suzuki cross-coupling reactions with aryl halides. One of the cross-coupled adducts was then manipulated into (−)-phenylalanine hydrochloride **52**.

3. Experimental

3.1. General experimental

NMR spectra were recorded on a Jeol EX-270 or Jeol EX-400 instrument (specified below); chemical shifts are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent. An external sample of $BF_3 \cdot OEt_2$ was used to calibrate ^{11}B NMR spectra. Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer with NaCl plates. Optical rotation values were measured on a JASCO DIP-370 digital polarimeter using a sodium lamp. Low-resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high-resolution mass spectra were recorded on a Micromass Autospec spectrometer. Melting points were recorded on Gallenkamp apparatus and are uncorrected. Thin layer chromatography was performed on aluminium plates coated with Merck silica gel 60 F_{254}. Flash column chromatography was carried out using Fluka flash silica gel 60 and the eluent is specified. Where necessary, ether and THF were distilled from sodium benzophenone ketyl immediately before use and CH_2Cl_2 distilled from calcium hydride. Except where specified, all reagents were purchased from commercial sources and used without further purification.

3.2. Synthesis of (*R*)-[2-chloro-1-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester (11d)

3.2.1. 2-(*R*)-*tert*-Butoxycarbonylamino-3-chloro-propionic acid methyl ester. A solution of triphenylphosphine (19.2 g, 73.2 mmol) and hexachloroethane (17.3 g, 73.2 mmol) in dichloromethane (50 mL) was added in one portion to a solution of *N*-Boc-serine methyl ester **9**[12] (14.6 g, 66.5 mmol) in dichloromethane (250 mL) under an atmosphere of argon. The reaction was stirred at room temperature for 2 h, then quenched with a saturated solution of sodium hydrogen carbonate (50 mL). The organic phase was separated and washed with brine (100 mL), dried ($MgSO_4$), evaporated then triturated with Et_2O (300 mL). After filtration and evaporation the subsequent residue was purified on silica gel, eluting with petrol(40–60)–EtOAc 5:1, delivering 2-*tert*-butoxycarbonylamino-3-chloro-propionic acid methyl ester (13.2 g, 84%) as a white solid, mp 62–64 °C; R_f 0.31 (4:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3362 (NH), 2982 (CH), 1721 (CO); $[\alpha]_D^{21} = +37.8$ (*c* 1.5, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.37 (1H, brd, J= 7.5 Hz), 4.65 (1H, m), 3.90 (1H, dd, J=3 Hz, 11.5), 3.78 (1H, dd, J=3.5, 11.5 Hz), 3.73 (3H, s), 1.40 (9H, s); δ_C (100 MHz; $CDCl_3$) 169.6, 154.9, 80.5, 54.4, 52.9, 45.5,

28.2. (Found: MNH_4^+, 255.1110. $C_8H_{16}NO_4^{35}Cl$ requires MNH_4, 255.1112 (0.8 ppm)).

3.2.2. (2-(*R*)-Chloro-1-hydroxymethyl-ethyl)-carbamic acid *tert*-butyl ester 10. Lithium borohydride (1.18 g, 54.1 mmol) was added in portions to a stirred solution of the above ester (12.9 g, 54.1 mmol) in ethanol–THF 9:1 (700 mL) at 0 °C under an atmosphere of argon. The reaction was stirred for 18 h at room temperature then quenched with a saturated solution of ammonium chloride (10 mL). The organics were then evaporated and the residue partitioned between water (300 mL) and Et_2O (300 mL). After separation, the aqueous was further extracted with Et_2O (300 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a gummy residue which was purified on silica gel, eluting with petrol(40–60)–Et_2O 2:1, giving the alcohol **10** (8.1 g, 81%) as a gum; R_f 0.42 (1:2, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3353 (OH), 2978 (CH), 1689 (CO); $[\alpha]_D^{21} = -4.6$ (*c* 0.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.94 (1H, br s), 3.86 (1H, br s), 3.8–3.55 (4H, m), 1.42 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.6, 80.2, 62.0, 52.5, 44.2, 28.3. (Found: MH^+, 210.0889. $C_8H_{16}NO_3^{35}Cl$ requires MH, 210.0897 (4.0 ppm)).

3.2.3. [2-(*R*)-Chloro-1-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 11d. SEMCl (1.27 mL, 7.2 mmol) was added dropwise to a stirred solution of alcohol **10** (1.58 g, 7.57 mmol) and Hunig's base (1.44 mL, 8.29 mmol) in dichloromethane (20 mL) at 0 °C under an atmosphere of argon. The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was evaporated and partitioned between Et_2O (50 mL) and water (30 mL). After separation, further extraction with Et_2O (2×40 mL), the combined organics were dried ($MgSO_4$) and evaporated. The subsequent crude residue was purified on silica gel, eluting with petrol(40–60)–Et_2O 4:1, giving the ether **11d** (2.31 g, 95%) as a colourless oil; R_f 0.30 (4:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3346 (NH), 2955, 2932, 2893 (CH), 1719 (CO); $[\alpha]_D^{21} = +12.4$ (*c* 0.4, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.03 (1H, br d, *J*=8.0 Hz), 4.67 (2H, s), 4.01 (1H, br s), 3.80 (1H, dd, *J*=4, 10 Hz), 3.71 (1H, dd, *J*=4, 11 Hz), 3.6–3.5 (4H, m), 1.44 (9H, s), 0.95 (2H, t, *J*=9 Hz), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.4, 95.4, 80.2, 66.4, 65.8, 51.1, 44.3, 28.7, 18.4, −1.1. (Found: MH^+, 340.1711. $C_{14}H_{30}NO_4^{35}ClSi$ requires MH, 340.1711 (0.0 ppm)).

3.3. General lithiation procedure

n-BuLi (0.21 mL, 0.42 mmol, 1.98 M solution in hexanes, 1.1 equiv) was added dropwise to a stirred solution of chloride **11d** (128 mg, 0.38 mmol, 1.0 equiv) in THF (5 mL, ~12 mL/mmol) at −78 °C under an atmosphere of argon. Stirring was continued for 15 min, followed by the dropwise addition of LiNp[14] (2.2 mL, 1.1 mmol, 0.5 M solution in THF, 2.5–3.0 equiv) over 5 min. The dark solution was stirred at −78 °C for 2 h. Subsequently electrophile (1.1 mmol, 1.5–3.0 equiv) was added dropwise to the solution causing decolourisation. The reaction mixture was kept cold (ca. −78 to −40 °C) overnight then quenched with a saturated solution of ammonium chloride (~1 mL) and allowed to warm to room temperature. The reaction was diluted with ether (20 mL) and saturated ammonium chloride (20 mL). The layers were separated and the aqueous layer was extracted with ether (2×10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash column chromatography on silica gel, eluting with diethyl ether–petrol ether (40–60) to give the product.

3.3.1. [2-(1-Hydroxy-cyclohexyl)-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 13d. 149 mg, 82%. Colourless oil; R_f 0.10 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3448 (OH), 2932, 2867 (CH), 1691 (CO); $[\alpha]_D^{21} = -5.0$ (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.13 (1H, br s), 4.65 (2H, s), 3.95 (1H, br s), 3.6–3.5 (4H, m), 2.98 (1H, br s), 1.65–1.2 (21H, m), 0.94 (2H, t, *J*=8.5 Hz), 0.01 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.3, 95.3, 79.8, 71.9, 70.4, 65.5, 46.8, 44.6, 38.5, 37.9, 29.5, 26.0, 22.4, 22.3, 18.2, −1.3. (Found: MH^+, 404.2831. $C_{20}H_{41}NO_5Si$ requires MH, 404.2832 (0.4 ppm)).

3.3.2. [2-(1-Hydroxy-cyclobutyl)-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 15. 204 mg, 81%. Colourless oil; R_f 0.18 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3397 (OH), 2977, 2953, 2934 (CH), 1686 (CO); $[\alpha]_D^{21} = -1.6$ (*c* 0.2, $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 5.19 (1H, br d, *J*=8 Hz), 4.68 (2H, s), 4.41 (1H, br s), 3.97 (1H, br m), 3.7–3.6 (4H, m), 2.2–1.8 (6H, m), 1.7–1.5 (2H, m), 1.44 (9H, s), 0.96 (2H, t, *J*=8.5 Hz), 0.03 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.3, 95.3, 80.1, 73.3, 71.6, 65.4, 47.3, 42.5, 35.9, 35.6, 28.4, 18.1, 13.0, −1.5. (Found: MH^+, 376.2521. $C_{18}H_{37}NO_5Si$ requires MH, 376.2519 (−0.4 ppm)).

3.3.3. [3-(*RS*)-Hydroxy-3-phenyl-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-propyl]-carbamic acid *tert*-butyl ester 18. 162 mg, 98%. Crude ratio 3:2.

Diastereomer 1. Colourless oil; R_f 0.25 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3422 (OH), 2954, 2894 (CH), 1689 (CO); $[\alpha]_D^{21} = -0.3$ (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.5–7.2 (5H, m), 5.29 (1H, br d, *J*=8 Hz), 4.8–4.6 (3H, m), 4.46 (1H, d, *J*=3.5 Hz), 4.10 (1H, br s), 3.7–3.5 (4H, m), 1.93 (1H, m), 1.75 (1H, m), 1.48 (9H, s), 0.93 (2H, t, *J*=8.5 Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.3, 144.1, 128.2, 127.0, 125.5, 95.2, 80.1, 70.8, 69.9, 65.4, 47.5, 43.3, 28.3, 18.0, −1.5. (Found: MH^+, 412.2519. $C_{21}H_{37}NO_5Si$ requires MH, 412.2519 (0.0 ppm)).

Diastereomer 2. Colourless oil; R_f 0.12 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3373 (OH), 2953, 2893 (CH), 1696 (CO); $[\alpha]_D^{21} = +17.0$ (*c* 0.3, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.4–7.2 (5H, m), 5.10 (1H, br d), 4.78 (1H, t, *J*=6.5 Hz), 4.65 (2H, s), 3.89 (1H, br s), 3.7–3.5 (4H, m), 3.26 (1H, br s), 1.97 (2H, t, *J*=6.5 Hz) 1.43 (9H, s), 0.93 (2H, t, *J*=8.5 Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.8, 144.6, 128.4, 127.4, 125.7, 95.1, 79.5, 72.0, 70.2, 65.4, 48.6, 42.0, 28.4, 18.0, −1.5.

3.3.4. [3-Oxo-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-butyl]-carbamic acid *tert*-butyl ester 21. 170 mg, 82%. Colourless oil; R_f 0.09 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3348 (NH), 2954 (CH), 1715 (CO); $[\alpha]_D^{21} = -2.3$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.15 (1H, br d, *J*=7 Hz), 4.63 (2H, s), 4.11 (1H, br m), 3.7–3.5

(4H, m), 2.8–2.65 (2H, m), 2.15 (3H, s), 1.42 (9H, s), 0.93 (2H, t, $J=8.5$ Hz), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 207.5, 155.4, 95.3, 79.6, 69.2, 65.5, 47.1, 44.9, 30.5, 28.5, 18.2, −1.3. (Found: MH^+, 348.2201. $C_{16}H_{33}NO_5Si$ requires MH, 348.2206 (1.4 ppm)).

3.3.5. [3-Oxo-3-phenyl-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-propyl]-carbamic acid *tert*-butyl ester 23. 214 mg, 80%. Colourless oil; R_f 0.39 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3356 (NH), 2954 (CH), 1715, 1688 (2×CO); $[\alpha]_D^{21}=+6.6$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.96 (2H, d, $J=7.5$ Hz), 7.56 (1H, t, $J=7.5$ Hz), 7.45 (2H, t, $J=7.5$ Hz), 5.32 (1H, br d, $J=7.5$ Hz), 4.63 (2H, s), 4.28 (1H, br m), 3.75 (1H, dd, $J=4$, 9.5 Hz), 3.64 (1H, dd, $J=5$, 9.5 Hz), 3.54 (2H, t, $J=8.5$ Hz), 3.36 (1H, br m), 3.23 (1H, dd, $J=7$, 16.5 Hz), 1.42 (9H, s) 0.89 (2H, t, $J=8.5$ Hz), −0.03 (9H, s); δ_C (100 MHz; $CDCl_3$) 199.0, 155.6, 137.2, 133.6, 129.0, 128.4, 95.5, 79.7, 69.3, 65.7, 47.7, 39.9, 28.7, 18.4, −1.1. (Found: MH^+, 410.2362. $C_{21}H_{35}NO_5Si$ requires MH, 410.2363 (0.3 ppm)).

3.3.6. 3-(*S*)-*tert*-Butoxycarbonylamino-4-(2-trimethylsilanyl-ethoxymethoxy)-butyric acid methyl ester 25. An excess of $TMSCHN_2$ (~1.2 equiv, 2 M in ether) was added to the crude carboxylic acid in MeOH–PhMe at 0 °C. The reaction was then evaporated delivering the crude ester, which was purified on silica gel.
102 mg, 70%. Colourless oil; R_f 0.16 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3356 (NH), 2954 (CH), 1741, 1718 (2×CO); $[\alpha]_D^{21}=-2.2$ (*c* 0.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.19 (1H, br d, $J=8$ Hz), 4.65 (2H, s), 4.13 (1H, br s), 3.67 (3H, s), 3.65–3.5 (4H, m), 2.7–2.5 (2H, m), 1.43 (9H, s), 0.93 (2H, t, $J=8.5$ Hz), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 172.0, 155.3, 95.3, 79.6, 69.1, 65.5, 51.8, 47.4, 36.2, 28.5, 18.2, −1.3. (Found: MH^+, 364.2154. $C_{16}H_{33}NO_6Si$ requires MH, 364.2155 (0.4 ppm)).

3.3.7. [2-Trimethylsilanyl-1-(*R*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 27. 158 mg, 78%. Colourless oil; R_f 0.11 (6:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3360 (NH), 2954, 2897 (CH), 1716 (CO); $[\alpha]_D^{21}=-11.6$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.7–4.65 (3H, m), 3.88 (1H, br s), 3.61 (2H, m), 3.55–3.4 (2H, m), 1.43 (9H, s), 0.94 (2H, m), 0.85 (2H, d, $J=7$ Hz), 0.04 (9H, s), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.0, 95.1, 79.0, 72.5, 65.2, 47.7, 28.5, 20.6, 18.1, −1.0, −1.4. (Found: MH^+, 378.2497. $C_{17}H_{39}NO_4Si_2$ requires MH, 378.2496 (−0.4 ppm)).

3.3.8. [1-(*S*)-Deuteromethyl-2-(2-trimethylsilanyl-ethoxymethoxy)-ethyl]-carbamic acid *tert*-butyl ester 30. 101 mg, 87%. Colourless oil; R_f 0.40 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3351 (NH), 2954 (CH), 1715 (CO); $[\alpha]_D^{21}=-13.6$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.78 (1H, br s), 4.65 (2H, s), 3.91 (1H, br s), 3.60 (2H, t, $J=8.5$ Hz), 3.48 (2H, m), 1.42 (9H, s), 1.15 (2H, m), 0.93 (2H, t, $J=8.5$ Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.5, 92.2, 79.2, 71.4, 65.3, 46.3, 28.5, 18.2, 17.8 (t, $J=19.8$ Hz, CH_2D), −1.3. (Found: MH^+, 307.2162. $C_{14}H_{31}NDO_4Si$ requires MH, 307.2163 (0.5 ppm)).

3.3.9. [2-Tributylstannanyl-1-(*R*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 33. 174 mg, 51%. Colourless oil; R_f 0.31 (9:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3350 (NH), 2954, 2914 (CH), 1716 (CO); $[\alpha]_D^{21}=-8.6$ (*c* 0.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.66–4.62 (3H, m), 3.92 (1H, bs), 3.63–3.59 (2H, m), 3.49–3.41 (2H, m), 1.60–1.25 (22H, m), 0.96–0.83 (19H, m), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.1, 95.2, 79.1, 72.8, 65.3, 49.6, 29.3, 28.6, 27.5, 18.2, 13.8, 13.4, 9.4, −1.3. (Found: MH^+, 592.3141. $C_{26}H_{57}NO_4Si^{116}Sn$ requires MH, 592.3153 (1.9 ppm)).

3.3.10. [2-(*R*)-(*tert*-Butoxycarbonylamino-3-(2-trimethylsilanyl-ethoxymethoxy)-propyl]-phosphonic acid diethyl ester 34. 136 mg, 70%. Colourless oil; R_f 0.32 (2:1, EtOAc–petrol(40–60)); ν_{max}(film)/cm^{-1} 3298 (NH), 2978, 2955, 2931 (CH), 1714 (CO), 1249 (P=O), 1174 (PO); $[\alpha]_D^{21}=-8.8$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.23 (1H, br d, $J=6.0$ Hz), 4.64 (2H, s), 4.10–4.05 (5H, m), 3.69 (1H, dd, $J=4.0$, 10.0 Hz), 3.67–3.54 (3H, m), 2.08 (2H, dd, $J=6.0$, 18.0 Hz), 1.40 (9H, s), 1.29 (6H, t, $J=7.0$ Hz), 0.95 (2H, t, $J=8.5$ Hz) 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.1, 95.3, 79.5, 69.7 (d, $^3J_{C,P}=7.5$ Hz), 65.5, 61.9 (d, $^2J_{C,P}=7.0$ Hz), 61.8 (d, $^2J_{C,P}=6.0$ Hz), 46.4, 27.8 (d, $^1J_{C,P}=131.0$ Hz), 18.1, 16.5 (d, $^3J_{C,P}=6.0$ Hz) −1.3. (Found: MH^+, 442.2386. $C_{19}H_{40}NO_7SiP$ requires MH, 442.2390 (0.9 ppm)).

3.4. General SEM deprotection procedure

0.1 M HCl[18] in methanol (2 mL, ~6 mL/mmol) was added to a SEM-ether (0.28 mmol). The subsequent reaction mixture was stirred at room temperature for 3 h. Excess triethylamine (~0.1 mL) was then added and the volatiles were removed under reduced pressure to deliver a crude mixture, this was then purified by flash column chromatography on silica gel, eluting with diethyl ether to give the product.

3.4.1. [2-(1-Hydroxy-cyclohexyl)-1-(*S*)-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester 13e. 62 mg, 79%, 9% s.m. recovered, 88% b.s.m.r. Colourless oil; R_f 0.20 (Et_2O); ν_{max}(film)/cm^{-1} 3348 (OH), 2933, 2861 (CH), 1689 (CO); $[\alpha]_D^{21}=-5.8$ (*c* 0.8, $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 5.31 (1H, br s), 3.83 (1H, br m), 3.66 (1H, dd, $J=5$, 11 Hz), 3.58 (1H, dd, $J=4$, 11 Hz), 1.7–1.35 (21H, m); δ_C (67.5 MHz; $CDCl_3$) 156.2, 79.8, 71.1, 66.4, 49.2, 43.1, 38.0, 37.8, 28.4, 25.6, 22.2, 22.1. (Found: MH^+, 274.2016. $C_{14}H_{27}NO_4$ requires MH, 274.2018 (0.8 ppm)).

3.4.2. [2-(1-Hydroxy-cyclobutyl)-1-(*S*)-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester 16. 86 mg, 65%, 11% s.m. recovered, 76% b.s.m.r. Colourless oil; R_f 0.20 (Et_2O); ν_{max}(film)/cm^{-1} 3339 (OH), 2980, 2935 (CH), 1682 (CO); $[\alpha]_D^{21}=-0.5$ (*c* 0.4, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.22 (1H, br s), 4.27 (1H, br s), 3.81 (1H, br m), 3.51 (2H, br m), 3.45 (1H, br s), 2.15–2.05 (2H, m), 1.89 (1H, dd, $J=9$, 14 Hz), 1.85–1.7 (2H, m), 1.58 (1H, m), 1.42 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.8, 80.0, 73.9, 65.7, 49.4, 41.2, 36.2, 35.8, 28.4, 12.7. (Found: MH^+, 246.1703. $C_{12}H_{23}NO_4$ requires MH, 246.1705 (0.9 ppm)).

3.4.3. (3-(*RS*)-Hydroxy-1-(*S*)-hydroxymethyl-3-phenyl-propyl)-carbamic acid *tert*-butyl ester 19. 87 mg, 64%, 15% s.m. recovered, 79% b.s.m.r.

Diastereomer 1. Colourless oil; R_f 0.29 (Et_2O); ν_{max}(film)/cm^{-1} 3382 (NH, OH), 2978, 2932 (CH), 1683 (CO); $[\alpha]_D^{21} = -7.5$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.4–7.2 (5H, m), 5.18 (1H, br d, $J=7.5$ Hz), 4.73 (1H, br d, $J=8.5$ Hz), 4.11 (1H, br s), 3.95 (1H, br m), 3.72 (1H, br d, $J=8.5$ Hz), 3.63 (1H, dd, $J=4$, 10.5 Hz), 2.60 (1H, br s), 1.82 (2H, m), 1.46 (9H, s); δ_C (100 MHz; $CDCl_3$) 157.3, 144.1, 128.4, 127.3, 125.5, 80.2, 70.4, 65.4, 49.7, 42.3, 28.3. (Found: MH^+, 282.1711. $C_{15}H_{24}NO_4$ requires MH, 282.1705 (−1.8 ppm)).

Diastereomer 2. Colourless oil; R_f 0.17 (Et_2O); ν_{max}(film)/cm^{-1} 3358 (NH, OH), 2976, 2931 (CH), 1686 (CO); $[\alpha]_D^{21} = +33.8$ (*c* 0.8, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.35–7.25 (5H, m), 5.25 (1H, br s), 4.84 (1H, br d, $J=7$ Hz), 3.78 (1H, br s), 3.67 (2H, br s), 3.30 (1H, br s), 2.03 (1H, ddd, $J=4.6$, 15 Hz), 1.92 (1H, ddd, $J=6.5$, 9, 15 Hz), 1.45 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.5, 144.4, 128.8, 127.9, 125.8, 79.9, 71.9, 65.9, 51.0, 41.3, 28.5. (Found: MH^+, 282.1700. $C_{15}H_{24}NO_4$ requires MH, 282.1705 (2.0 ppm)).

3.4.4. (*S*)-(5-Oxo-tetrahydro-furan-3-yl)-carbamic acid *tert*-butyl ester 26. Crude mixture was treated with CSA (~10 mol%) in benzene at 80 °C overnight. Evaporation and purification on silica gel, eluting with Et_2O–petrol(40–60) 1:2, gave the product (27 mg, 50%, 15% s.m. recovered, 65% b.s.m.r.). Colourless blades, mp 109–110 °C (Et_2O), (lit.[19b] 113–114 °C); ν_{max}(film)/cm^{-1} 3317 (NH), 1767, 1687 (CO); $[\alpha]_D^{21} = -64.2$ (*c* 0.5, $CHCl_3$); ^1H NMR was identical to that reported in the literature.[19b]

3.4.5. (1-(*R*)-Hydroxymethyl-2-trimethylsilanyl-ethyl)-carbamic acid *tert*-butyl ester 28. 71 mg, 72%. Colourless oil; R_f 0.48 (Et_2O); ν_{max}(film)/cm^{-1} 3256 (OH), 2954 (CH), 1695 (CO); $[\alpha]_D^{21} = -14.6$ (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.51 (1H, br s), 3.79 (1H, br s), 3.63 (1H, br d, $J=9$ Hz), 3.44 (1H, dd, $J=6.5$, 10.5 Hz), 2.47 (1H, br s), 1.44 (9H, s), 0.74 (2H, m), 0.05 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.6, 80.0, 69.1, 50.6, 28.8, 20.1, −0.72. (Found: MH^+, 248.1679. $C_{11}H_{25}NO_3Si$ requires MH, 248.1682 (1.2 ppm)).

3.4.6. (2-Hydroxy-1-(*S*)-deuteromethyl-ethyl)-carbamic acid *tert*-butyl ester 31. 34 mg, 70%. Colourless oil; R_f 0.42 (Et_2O); ν_{max}(film)/cm^{-1} 3361 (OH), 2978, 2936 (CH), 1690 (CO); $[\alpha]_D^{21} = -12.6$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.71 (1H, br s), 3.68 (1H, br s), 3.55 (1H, m), 3.43 (1H, dd, $J=6.0$, 10.5 Hz), 3.00 (1H, br s), 1.38 (9H, s), 1.07 (2H, m); δ_C (100 MHz; $CDCl_3$) 156.6, 79.8, 67.4, 48.6, 28.5, 17.2 (t, $J=19$ Hz, CH_2D). (Found: MH^+, 177.1353. $C_8H_{17}NDO_3$ requires MH, 177.1350 (2.2 ppm)).

3.4.7. (2-(*R*)-*tert*-Butoxycarbonylamino-3-hydroxy-propyl)-phosphonic acid diethyl ester 35. 0.1 M HCl in ethanol was employed in this deprotection using the general procedure described above. (54 mg, 66%, 10% s.m. recovered, 76% b.s.m.r.). Colourless oil; R_f 0.30 (9:1, EtOAc–MeOH); ν_{max}(film)/cm^{-1} 3358 (OH, NH), 2978, 2933 (CH), 1713 (CO), 1249 (P=O), 1172 (PO); $[\alpha]_D^{21} = +14.9$ (*c* 0.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.23 (1H, br d, $J=8.0$ Hz), 4.11–4.07 (4H, m), 3.94–3.89 (1H, m), 3.78 (1H, dd, $J=4.0$, 11.5 Hz), 3.66 (1H, dd, $J=4.0$, 11.5 Hz), 2.21–2.01 (2H, m), 1.41 (9H, s), 1.31 (6H, t, $J=7.0$ Hz); δ_C (100 MHz; $CDCl_3$) 155.7, 79.7, 64.8 (d, $^3J_{C,P}=6.0$ Hz), 62.1 (d, $^2J_{C,P}=5.0$ Hz), 62.1 (d, $^2J_{C,P}=5.0$ Hz), 48.3, 28.5, 27.8 (d, $^1J_{C,P}=133.5$ Hz), 16.5 (d, $^3J_{C,P}=6.0$ Hz). (Found: MH^+, 312.1576. $C_{12}H_{26}NO_6P$ requires MH, 312.1576 (0.0 ppm)).

3.5. General oxidation procedures

3.5.1. Method A. PDC (1.1 mmol, 6 equiv) was added to a stirred solution of the diol (0.18 mmol, 1 equiv) in anhydrous dimethylformamide (1.5 mL, ~8 mL/mmol). The reaction mixture was stirred for 6 h, then water (5 mL) was added and the mixture was extracted with dichloromethane (2×15 mL). The combined extracts were then washed with water (2×20 mL) and brine (20 mL), then dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue was purified on silica gel, eluting with petrol(40–60)–Et_2O 1:1, delivering the product.

3.5.1.1. (*S*)-(2-Oxo-1-oxa-spiro[4.5]dec-4-yl)-carbamic acid *tert*-butyl ester 14. Method A (34 mg, 69%) white foam; R_f 0.20 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3365 (NH), 2937, 2863 (CH), 1778, 1697 (2×CO); $[\alpha]_D^{21} = +17.7$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.05 (1H, br s), 4.51 (1H, br s), 2.73 (1H, br t, $J=10$ Hz), 1.8–1.4 (20H, m); δ_C (100 MHz; $CDCl_3$) 175.0, 155.8, 84.9, 80.8, 51.0, 41.4, 38.6, 36.1, 28.6, 25.2, 22.9, 22.8. (Found: MNH_4^+, 287.1977. $C_{14}H_{23}NO_4$ requires MNH_4, 287.1971 (−2.1 ppm)).

3.5.1.2. (*S*)-(6-Oxo-5-oxa-spiro[3.4]oct-7-yl)-carbamic acid *tert*-butyl ester 17. Method A (63 mg, 74%) amorphous solid; ν_{max}(film)/cm^{-1} 3321 (NH), 2976, 2945 (CH), 1761, 1712 (2×CO); $[\alpha]_D^{21} = +1.2$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.06 (1H, br s), 4.41 (1H, br m), 2.95 (1H, br m), 2.63 (1H, q, $J=10$ Hz), 2.36 (1H, q, $J=10$ Hz), 2.25–1.95 (3H, m), 1.88 (1H, m), 1.67 (1H, m), 1.45 (9H, s); δ_C (100 MHz; $CDCl_3$) 174.8, 155.8, 83.2, 80.9, 50.9, 41.5, 34.6, 28.7, 28.3, 12.7. (Found: MH^+, 242.1398. $C_{12}H_{19}NO_4$ requires MH, 242.1392 (−2.3 ppm)).

3.5.2. Method B. PDC (1.2 mmol, 6 equiv) was added to a stirred solution of alcohol (0.29 mmol, 1 equiv) in anhydrous dimethylformamide (3 mL, ~8 mL/mmol). The reaction mixture was stirred for 18 h, then quenched with water (5 mL) and extracted with EtOAc (2×20 mL). The combined extracts were then washed with water (2×20 mL) and brine (20 mL), then dried ($MgSO_4$) and evaporated under reduced pressure to deliver the crude carboxylic acid. This was then dissolved in MeOH–toluene (3 mL, 1:1) and treated with $TMSCHN_2$ (0.29 mL, 0.58 mmol, 2.0 M solution in hexanes) at 0 °C. The reaction was stirred for 1 h then all volatiles were removed under reduced pressure to deliver a crude mixture, which was then purified by flash column chromatography on silica gel, eluting with Et_2O–petrol(40–60) 1:2 to give the product.

3.5.2.1. 2-(*S*)-*tert*-Butoxycarbonylamino-4-oxo-4-phenyl-butyric acid methyl ester 20. Method B (36 mg, 47%) colourless oil; R_f 0.25 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3383 (NH), 2979, 2932 (CH), 1748, 1714 (2×CO); $[\alpha]_D^{21} = +59.9$ (*c* 1.1, DCM); ^1H NMR spectrum identical to literature.[20] *m/z* 308 (10, M^+), 252 (40, M−*t*Bu), 208 (100, M−Boc).

3.5.2.2. 2-(*R*)-*tert*-Butoxycarbonylamino-3-trimethylsilanyl-propionic acid methyl ester 29. Method B (54 mg, 68%) colourless waxy solid, mp 40–42 °C; R_f 0.34 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3373 (NH), 2977, 2955 (CH), 1745, 1715 (2×CO); $[\alpha]_D^{21}=+10.8$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.84 (1H, br s), 4.28 (1H, br m), 3.67 (3H, s), 1.37 (9H, s), 1.05 (1H, dd, *J*=6, 9.5 Hz), 0.88 (1H, dd, *J*=9.5, 14.5 Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 174.3, 154.9, 79.8, 52.1, 50.6, 28.4, 21.4, −1.3. (Found: MH$^+$, 276.1633. $C_{12}H_{25}NO_4Si$ requires MH, 276.1631 (−0.6 ppm)).

3.5.2.3. 2-(*R*)-*tert*-Butoxycarbonylamino-3-(diethoxyphosphoryl)-propionic acid methyl ester 36. Method B (61 mg, 60%) colourless oil, R_f 0.50 (9:1, EtOAc–MeOH); ν_{max}(film)/cm^{-1} 3371 (NH), 2982, 2929 (CH), 1751 (CO), 1716 (CO), 1249 (P=O), 1166 (PO); $[\alpha]_D^{21}=+12.8$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.68 (1H, br d, *J*=7.5 Hz), 4.58–4.46 (1H, m), 4.10–4.03 (4H, m), 3.73 (3H, s), 2.34–2.27 (2H, m), 1.41 (9H, s), 1.29 (6H, t, *J*=7.0 Hz); δ_C (100 MHz; $CDCl_3$) 171.5 (d, $^3J_{C,P}$=8.0 Hz), 155.3, 80.2, 62.1 (d, $^2J_{C,P}$=4.0 Hz), 62.1 (d, $^2J_{C,P}$=3.0 Hz), 52.7, 49.2 (d, $^2J_{C,P}$=5.0 Hz), 28.4, 28.0 (d, $^1J_{C,P}$=141.5 Hz), 16.5 (d, $^3J_{C,P}$=2.0 Hz), 16.4 (d, $^3J_{C,P}$=2.0 Hz). (Found: MH$^+$, 340.1523. $C_{13}H_{26}NO_7P$ requires MH, 340.1525 (0.6 ppm)).

3.5.3. Method C.

3.5.3.1. (*S*)-*N*-Boc-deuteroalanine methyl ester 32. Ruthenium chloride (4 mg, 21 μmol, 5 mol%) was added to a stirred suspension of alcohol **31** (75 mg, 0.43 mmol) and sodium periodate (273 mg, 1.28 mmol) in CH_3CN–H_2O–CCl_4 (3 mL, 2:3:2) at room temperature. The reaction mixture went dark after 30 min. Stirring was continued for 12 h in total then the reaction was diluted with a saturated solution of ammonium chloride (10 mL) and EtOAc (10 mL). After separation the aqueous was extracted again with EtOAc (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to deliver the crude carboxylic acid. This was then dissolved in MeOH–toluene (2 mL, 1:1) and treated with $TMSCHN_2$ (0.42 mL, 0.85 mmol, 2.0 M solution in hexanes) at 0 °C. The reaction was stirred for 1 h then all volatiles were removed under reduced pressure to deliver a crude mixture, which was then purified by flash column chromatography on silica gel, eluting with Et_2O–petrol(40–60) 1:2 to give the protected amino acid **32** (53 mg, 61%) as a colourless oil; R_f 0.20 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3382 (NH), 2980 (CH), 1748, 1716 (2×CO); $[\alpha]_D^{21}=-43.5$ (*c* 1.4, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.03 (1H, br s), 4.31 (1H, br m), 3.74 (3H, s), 1.44 (9H, s), 1.36 (2H, br d, *J*=7.5 Hz); δ_C (100 MHz; $CDCl_3$) 174.0, 155.2, 80.0, 52.3, 49.2, 28.5, 18.6 (t, *J*=20 Hz, *C*H_2D). (Found: MH$^+$, 205.1296. $C_9H_{17}NDO_4$ requires MH, 205.1299 (1.3 ppm)).

3.6. General amino acid deprotection procedure

The protected amino acid (~50 mg, 0.25 mmol) was heated at 70 °C with 4.5 M HCl (~2 mL) for 3 h. After cooling, the aqueous phase was diluted with water (10 mL) and washed with diethyl ether (10 mL). The aqueous phase was then evaporated under reduced pressure delivering a solid which was triturated with diethyl ether. After decanting and drying, the product was obtained.

3.6.1. 2-(*S*)-Amino-4-oxo-4-phenyl-butyric acid hydrochloride 37. 24 mg, 92%. White powder, mp ~200 °C decomposed (lit.[21] mp 207–209 °C decomposed); $[\alpha]_D^{21}=+35.6$ (*c* 0.104, 6 M HCl), lit.[21] $[\alpha]_D=+34.7$ (*c* 0.098, 6 M HCl); ^{1}H NMR spectrum identical to literature.[21]

3.6.2. (*R*)-Trimethylsilanylalanine hydrochloride 38. 31 mg, 80%. White solid, mp ~180 °C decomposed; $[\alpha]_D^{22}=+35.2$ (*c* 1.1, 1 M HCl), lit.[23] $[\alpha]_D=+31$ (*c* 0.51, 4 M HCl); δ_H (400 MHz; D_2O) 4.01 (1H, dd, *J*=5.5, 10.5 Hz), 1.22 (1H, dd, *J*=10.5, 14.5 Hz), 1.16 (1H, dd, *J*=5.5, 14.5 Hz), 0.08 (9H, s); δ_C (100 MHz; D_2O) 17.3, 51.7, 19.3, −2.3; *m/z* (ESI) 176 (100%, M$^+$), 162 (35%, M−Cl).

3.6.3. (*S*)-Deuteroalanine hydrochloride 39. 31 mg, 95%. Off-white wax; $[\alpha]_D^{21}=+11.7$ (*c* 1.2, 6 M HCl); δ_H (400 MHz, D_2O) 4.09 (1H, t, *J*=7.5 Hz), 1.50 (2H, d, *J*=7.5 Hz); δ_C (100 MHz; D_2O) 172.8, 48.7, 15.0 (t, *J*=20 Hz, *C*H_2D). (Found: M−Cl$^+$, 91.0620. $C_3H_7NClO_2D$ requires M−Cl, 91.0618 (1.9 ppm)).

3.6.4. 2-(*S*)-Amino-3-phosphono-propionic acid 40. The protected amino acid **36** (61 mg, 0.18 mmol) was heated with 6 M HCl (~3 mL) under reflux for 21 h. After cooling, the aqueous phase was diluted with water (5 mL) and washed with ethyl acetate (2×5 mL). The aqueous phase was then evaporated under reduced pressure delivering an off-white solid which was triturated with diethyl ether. After decanting and drying, the salt was obtained as an off-white solid. Propylene oxide (~1 mL) was added dropwise to a suspension of the salt in EtOH (~1 mL) at 0 °C and the resulting mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure delivering a white solid. Recrystallisation from 50% EtOH/H_2O followed by trituration with EtOH gave the phosphate **40** (18 mg, 59%) as a white solid, mp ~225 °C decomposed, lit.[24b] 224–226 °C decomposed; $[\alpha]_D^{21}=+16.3$ (*c* 0.4, 1 M NaOH), lit.[24b] $[\alpha]_D^{24}=+13.8$ (*c* 2, 1 M NaOH); δ_H (400 MHz; D_2O) 4.17–4.12 (1H, m), 2.36–2.26 (1H, m), 2.14–2.04 (1H, m); δ_C (100 MHz; D_2O) 172.1 (d, $^3J_{C,P}$=13.0 Hz), 49.9 (d, $^2J_{C,P}$=4.5 Hz), 28.2 (d, $^1J_{C,P}$=131.0 Hz); *m/z* ESI (−ve) 168 ([M−H$^+$]$^-$, 100%).

3.7. Synthesis of aspartic acid mimic 44

3.7.1. [2-Borono-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 41. *n*-BuLi (0.48 mL, 0.95 mmol, 1.97 M solution in hexanes) was added dropwise to a stirred solution of chloride **11d** (291 mg, 0.89 mmol) in THF (5 mL) at −78 °C under an atmosphere of argon. Stirring was continued for 15 min, followed by the dropwise addition of LiNp (5.7 mL, 2.83 mmol, 0.5 M solution in THF) over 5 min. The dark solution was stirred at −78 °C for 2 h. Subsequently triisopropylborate (0.5 mL, 2.15 mmol) was added dropwise to the solution. The reaction mixture was kept cold (ca. −78 to −40 °C) overnight then quenched with a saturated solution of ammonium chloride (1 mL), then allowed to warm to room temperature. To the mixture was then added an aqueous solution of 0.5 M HCl (5 mL, saturated with NaCl), and stirring was continued for 30 min. The solution was then extracted with petrol(40–60) (3× 20 mL). The combined organics were then extracted with

2 M NaOH (3×15 mL). These extracts were combined and acidified (~pH 1–2) with 4.5 M HCl, then extracted again with Et_2O (3×30 mL). The final combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the boronic acid **41** (238 mg, 80%) as a light yellow oil. δ_H (400 MHz; acetone-d^6) 6.95–6.8 (1H, br), 6.55–6.45 (1H, br), 5.88 (1H, br s), 4.63 (2H, s), 3.88 (1H, br m), 3.63 (2H, m), 3.53 (1H, dd, J=5.5, 9.5 Hz), 3.47 (1H, dd, J=5.5, 9.5 Hz), 1.5–1.35 (9H, several singlets), 1.07 (1H, dd, J=6, 16 Hz), 1.00 (2H, m), 0.05–0.00 (9H, several singlets). Due to the many possible solution structures of the boronic acid, the compound was better characterised as the boronate ester **42**.

3.7.2. [2-(−)-Pinaneboronate-1-(*S*)-(2-trimethylsilanylethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 42. (−)-Pinane diol (47 mg, 0.28 mmol) was added to a stirred solution of **41** (88 mg, 0.25 mmol) and powdered 4 Å molecular sieves (~100 mg) in dry dichloromethane (3 mL) under an atmosphere of argon. The reaction mixture was stirred for 18 h then filtered and evaporated. The subsequent residue was purified on silica gel, eluting with petrol(40–60)–Et_2O 3:1, delivering boronate ester **42** (113 mg, 95%) as a colourless oil; R_f 0.26 (3:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 2926 (CH), 1718 (CO); $[\alpha]_D^{21}=-200$ (c 0.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.06 (1H, br d, J=7 Hz), 4.65 (2H, s), 4.25 (1H, dd, J=2, 9 Hz), 4.01 (1H, br s), 3.60 (2H, t, J=8.5 Hz), 3.53 (2H, d, J=4.5 Hz), 2.32 (1H, m), 2.20 (1H, m), 2.03 (1H, t, J=5 Hz), 1.9–1.8 (2H, m), 1.43 (9H, s), 1.37 (3H, s), 1.28 (3H, s), 1.2–1.05 (2H, m), 0.93 (2H, t, J=8.5 Hz), 0.9–0.8 (4H, m), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.4, 95.1, 85.8, 77.8, 71.5, 65.3, 51.4, 39.6, 38.3, 36.2, 35.6, 29.2, 28.7, 28.6, 27.2, 26.6, 24.2, 22.8, 18.2, −1.3. (Found: MH^+, 484.3271. $C_{24}H_{46}NBO_6Si$ requires MH, 484.3266 (−1.1 ppm)).

3.7.3. (2-(−)-Pinaneboronate-1-(*S*)-hydroxymethylethyl)-carbamic acid *tert*-butyl ester 43. 0.1 M HCl in methanol (2 mL, ~6 mL/mmol) was added to SEM-ether **42** (99 mg, 0.21 mmol). The subsequent reaction mixture was stirred at room temperature for 3 h. Excess triethylamine (~0.1 mL) was then added and the volatiles were removed under reduced pressure to deliver a crude mixture, which was then purified by flash column chromatography on silica gel, eluting with petrol(40–60)–Et_2O 1:2 to give starting material (4 mg, 4%) and the alcohol **43** (49 mg, 68%) as a colourless oil; R_f 0.51 (Et_2O); ν_{max}(film)/cm^{-1} 3420 (OH), 2975, 2929, 2872 (CH), 1694 (CO); $[\alpha]_D^{21}=-148$ (c 0.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.01 (1H, br s), 4.24 (1H, d, J=2, 9 Hz), 3.89 (1H, br s), 3.60 (1H, br d, J=10.5 Hz), 3.51 (1H, m), 2.31 (1H, m), 2.19 (1H, m), 2.02 (1H, m), 1.95–1.75 (2H, m), 1.41 (9H, s), 1.35 (3H, s), 1.26 (3H, s), 1.25 (1H, m), 1.15–1.0 (2H, m), 0.81 (3H, s). (Found: MH^+, 354.2452. $C_{18}H_{32}NBO_5$ requires MH, 354.2452 (−0.2 ppm)).

3.7.4. 2-(*S*)-Amino-3-boronopropionic acid 44. Dess–Martin periodinane (78 mg, 0.18 mmol) was added to a stirred solution of **43** (54 mg, 0.15 mmol) in dichloromethane (2 mL) under an atmosphere of argon. After 2 h, 1 M sodium sulfite (5 mL) was added and the mixture was extracted with Et_2O (2×10 mL). The combined organic extracts were washed with 1 M sodium hydrogen carbonate (10 mL), dried (Na_2SO_4) and evaporated. The crude mixture was then dissolved in *t*-butanol (3 mL) and treated with a solution of 2-methyl-2-butene (1.5 mL, 3.1 mmol, 2 M in THF). A solution of NaH_2PO_4 (167 mg, 1.07 mmol) and $NaClO_2$ (125 mg, 1.38 mmol) in water (2 mL) was added and the reaction was stirred for 1 h. The *t*-butanol was evaporated in vacuo and the residue was partitioned between 0.5 M HCl (5 mL) and EtOAc (10 mL). After separation and further extraction (EtOAc 2×5 mL), the combined extracts were dried ($MgSO_4$) and evaporated. The subsequent residue was heated at 70 °C with 4.5 M HCl (3 mL) for 3 h. After cooling the aqueous solution was washed with dichloromethane (2×2 mL). The aqueous solution was then evaporated in vacuo. The crude residue was purified on silica gel, eluting with 2:1 EtOH–14 M NH_3, delivering the 2-amino-3-boronopropionic acid **44** (15 mg, 74%) as a white solid. After trituration with acetone the product was obtained as a white powder, mp >290 °C decomposed. δ_H (400 MHz; D_2O) 3.94 (1H, br t, J=9.5 Hz), 1.08 (1H, br dd, J=9.5, 13 Hz), 0.79 (1H, br dd, J=10.5, 12 Hz); δ_C (100 MHz; D_2O) 178.0, 53.4, 20.4 (br); δ_B[11] (160 MHz; D_2O) 16.38; m/z ESI (-ve) 160 ($[M-H^+]^-$, 75%), 343 ($(2[M-H^+]+Na^+)^-$, 100%). HCl salt[30] $[\alpha]_D^{21}=+33.0$ (c 0.2, 4.5 M HCl); δ_H (400 MHz, D_2O) 4.15 (1H, dd, J=7, 10 Hz), 1.35 (1H, dd, J=7, 15 Hz), 1.19 (1H, dd, J=10, 15 Hz); δ_C (125 MHz; D_2O) 175.3, 52.4, 18.6 (br); δ_B[11] (160 MHz; D_2O) 24.85.

3.8. General procedure for Suzuki coupling of boronic acid 41

The boronic acid **41** (ca. 0.12 mmol), K_2CO_3 (3.0 equiv), $PdCl_2$(dppf).CH_2Cl_2 (0.09 equiv) and Ag_2O (2.4 equiv) were placed under Ar. Tetrahydrofuran (1.0 mL) and the aryl halide (2 equiv) were added and the resulting mixture was refluxed for 21 h. The reaction mixture was filtered through a 0.5 cm pad of Celite™ and eluted with diethyl ether (40 mL). The filtrate was concentrated to afford an oil. Subjection of this material to flash chromatography on silica gel and concentration of the appropriate fractions provided the coupled product.

3.8.1. [1-(*S*)-2-Phenyl-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48a). 72%. Colourless oil; R_f 0.25 (4:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3352, 2953, 1714, 1497; $[\alpha]_D^{20}=-14.4$ (c 1.1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 7.31–7.18 (complex m, 5H), 4.95 (1H, broad d, J=7 Hz), 4.67 (2H, m), 3.94 (1H, br m), 3.63 (2H, m), 3.49 (1H, dd, J=10, 4 Hz) 3.45 (1H, dd, J=10, 4 Hz), 2.91 (1H, br dd, J=13.5, 5 Hz), 2.82 (1H, dd, J=13.5, 8 Hz), 1.41 (9H, s), 0.94 (2H, m), 0.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.5, 138.3, 129.5, 128.5, 126.5, 95.4, 79.4, 68.6, 65.5, 51.8, 38.1, 28.5, 18.2, −1.3. (Found (CI^+) MH^+, 382.2413. $C_{20}H_{36}NO_4Si$ requires MH^+, 382.2414 (0.0 ppm)).

3.8.2. [1-(*S*)-2-(4-Methoxyphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48b). 65%. Pale yellow oil; R_f 0.18 (3:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3359, 2953, 1714, 1613, 1513, 1248, 1173; $[\alpha]_D^{20}=-13.1$ (c 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.13 (2H, d, J=8 Hz), 6.82 (2H, d, J=8 Hz), 4.92 (1H, br d, J=8.0 Hz), 4.68 (2H, m), 3.89

(1H, br m), 3.78 (3H, s), 3.63 (2H, m), 3.46 (2H, m), 2.86 (1H, dd, $J=13$, 5 Hz), 2.75 (1H, dd, $J=13$, 8 Hz), 1.42 (9H, s), 0.95 (2H, m), 0.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 158.3, 155.5, 130.5, 130.3, 114.0, 95.4, 79.3, 68.6, 65.5, 55.4, 51.9, 37.1, 28.5, 18.2, −1.3. (Found (CI^+): 412.2520. $C_{21}H_{38}NO_5Si$ requires (MH^+): 412.2519 (0.1 ppm)).

3.8.3. [1-(*S*)-2-(4-Nitrophenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48c). 65%. Colourless oil; R_f 0.30 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3412, 2953, 2894, 1714, 1604, 1522, 1346; $[\alpha]_D^{20}=-34.2$ (c 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 8.14 (2H, d, $J=8.5$ Hz), 7.39 (2H, d, $J=8.5$ Hz), 5.04 (1H, br d, $J=8$ Hz), 4.67 (2H, m), 3.97 (1H, br m), 3.63 (2H, m), 3.50 (2H, d, $J=4$ Hz), 3.02–2.92 (2H, complex m), 1.38 (9H, s), 0.94 (2H, m), 0.02 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.4, 146.8, 146.4, 130.3, 123.7, 95.5, 79.7, 68.9, 65.7, 51.5, 38.2, 28.4, 18.2, −1.3. (Found (CI^+): 427.2266. $C_{20}H_{35}N_2O_6Si$ requires (MH^+): 427.2264 (0.5 ppm)).

3.8.4. [1-(*S*)-2-(2-Nitrophenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48d). 70%. Pale yellow oil; R_f 0.17 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3351, 2954, 2892, 1713, 1610, 1528, 1453; $[\alpha]_D^{20}=-22.9$ (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.91 (1H, d, $J=8$ Hz), 7.52 (1H, dd, $J=8$ Hz, 7.5), 7.42–7.34 (2H, complex m), 5.03 (1H, br d, $J=9$ Hz), 4.68 (2H, m), 4.14 (1H, br m), 3.66–3.58 (4H, complex m), 3.22 (1H, dd, $J=13.5$, 5 Hz), 3.09 (1H, dd, $J=13.5$, 9.5 Hz), 1.30 (9H, s), 0.95 (2H, m), 0.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.3, 150.1, 133.8, 132.9, 127.6, 124.9, 95.4, 79.3, 70.1, 65.6, 51.3, 35.4, 28.4, 18.2, −1.3 (one C obscured). (Found (CI^+): 427.2264. $C_{20}H_{35}N_2O_6Si$ requires (MH^+): 427.2264 (0.0 ppm)).

3.8.5. [1-(*S*)-2-(3-Nitrophenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48e). 67%. Colourless oil; R_f 0.21 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3346, 2954, 2930, 2894, 1714, 1531, 1504, 1453; $[\alpha]_D^{20}=-19.8$ (c 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 8.09–8.07 (2H, complex m), 7.59 (1H, d, $J=7.3$ Hz), 7.46 (1H, m), 5.04 (1H, broad d, $J=8.2$ Hz), 4.68 (2H, m), 3.97 (1H, br m), 3.64 (2H, m), 3.51 (2H, m), 2.97 (2H, m), 1.37 (9H, s), 0.95 (2H, m), 0.02 (9H, s); δ_C(100 MHz, $CDCl_3$) 155.4, 148.4, 140.3, 135.8, 129.4, 124.4, 121.7, 95.5, 79.7, 68.9, 65.7, 51.6, 38.0, 28.4, 18.2, −1.3. (Found (CI^+): 427.2268. $C_{20}H_{35}N_2O_6Si$ requires (MH^+): 427.2264 (0.9 ppm)).

3.8.6. [1-(*S*)-2-(4-Acetylphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48f). 68%. Colourless oil; R_f 0.21 (2:3, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3352, 2954, 1712, 1681, 1607, 1517; $[\alpha]_D^{20}=-19.7$ (c 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.88 (2H, d, $J=8$ Hz), 7.32 (2H, d, $J=8$ Hz), 5.00 (1H, br d, $J=8$ Hz), 4.68 (1H, d, $J=10.5$ Hz), 4.65 (1H, d, $J=10.5$ Hz), 3.96 (1H, br s), 3.63 (2H, m), 3.47 (2H, d, $J=3.5$ Hz), 2.98 (1H, dd, $J=13$, 6.5 Hz), 2.90 (1H, dd, $J=13$, 8 Hz), 2.58 (3H, s), 1.40 (9H s), 0.94 (2H, m), 0.03 (9H, s); δ_C(100 MHz, $CDCl_3$) 198.0, 155.4, 144.2, 135.6, 129.7, 128.6, 95.4, 79.5, 68.7, 65.6, 51.6, 38.2, 28.4, 26.7, 18.2, −1.3. (Found (CI^+): 424.2536. $C_{22}H_{38}NO_5Si$ requires (MH^+): 424.2519 (3.9 ppm)).

3.8.7. [1-(*S*)-2-(4-Carbomethoxyphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48g). 52%. Colourless oil; R_f 0.26 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3365, 2953, 1723, 1612, 1504, 1280; $[\alpha]_D^{20}=-16.5$ (c 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.95 (2H, d, $J=8$ Hz), 7.29 (2H, d, $J=8$ Hz), 4.99 (1H, br d, $J=8$ Hz), 4.67 (1H, d, $J=10.5$ Hz), 4.65 (1H, d, $J=10.5$ Hz), 3.96 (1H, br m), 3.90 (3H, s), 3.62 (2H, m), 3.46 (2H, d, $J=3.5$ Hz), 2.96 (1H, dd, $J=13$, 6.5 Hz), 2.89 (1H, dd, $J=13$, 8 Hz), 1.40 (9H, s), 0.94 (2H, m), 0.02 (9H, s); δ_C (68.5 MHz, $CDCl_3$) 167.2, 155.4, 143.9, 129.8, 129.6, 128.5, 95.5, 79.5, 68.7, 65.6, 52.1, 51.6, 38.1, 28.5, 18.2, −1.3. (Found (CI^+): 440.2468. $C_{22}H_{38}NO_6Si$ requires (MH^+): 440.2468 (0.0 ppm)).

3.8.8. [1-(*S*)-2-(Naphthalen-1-yl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48h). 73%. Colourless oil; R_f 0.25 (4:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3451, 3351, 2953, 2893, 1713, 1495; $[\alpha]_D^{20}=-34.1$ (c 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 8.39–8.09 (1H, br m), 7.85 (1H, d, $J=8$ Hz), 7.74 (1H, d, $J=8.5$ Hz), 7.57 (1H, m), 7.48 (1H, m), 7.41–7.35 (2H, complex m), 5.17 (1H, br d, $J=7.5$ Hz), 4.72–4.65 (2H, complex m), 4.13 (1H, br m), 3.73–3.62 (2H, complex m), 3.54–3.18 (4H, complex m), 1.50–1.23 (9H, m), 0.96 (2H, m), 0.04 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.4, 134.6, 134.0, 132.5, 128.7, 127.8, 127.4, 126.4, 125.7, 125.5, 124.3, 95.6, 79.3, 68.6, 65.7, 51.1, 35.3, 28.5, 18.2, −1.3. (Found (CI^+): 432.2575. $C_{24}H_{38}NO_4Si$ requires (MH^+): 432.2570 (1.0 ppm)).

3.8.9. 1,4-Bis-[2-(*S*)-2′-(*S*)-2-(*tert*-butoxycarbonylamino)-3-(2-trimethylsilanylethoxymethoxy)propyl]-benzene (49). 35%. Colourless oil; R_f 0.09 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3350, 2952, 2894, 1713, 1514, 1503; $[\alpha]_D^{20}=-16.4$ (c 0.7, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) δ 7.13 (4H, s), 4.94 (2H, br d, $J=8$ Hz), 4.66 (4H, m), 3.90 (2H, br m), 3.63 (4H, m), 3.46 (4H, d, $J=3.5$ Hz), 2.86 (2H, partially obscured dd, $J=13.5$, 6.5 Hz), 2.78 (2H, dd, $J=13.5$, 8 Hz), 1.41 (18H, s), 0.94 (4H, m), 0.03 (18H, s); δ_C (100 MHz, $CDCl_3$) 155.5, 136.3, 129.6, 95.4, 79.3, 68.6, 65.5, 51.7, 37.6, 28.5, 18.2, −1.2. (Found (CI^+): 707.4103. $C_{34}H_{64}N_2O_8Si_2Na$ requires ($M+Na^+$): 707.4099 (0.6 ppm)).

3.9. Synthesis of phenylalanine hydrochloride 52

3.9.1. Deprotection of 48a.

3.9.1.1. [1-(*S*)-2-Phenyl-1-(hydroxymethyl)ethyl]carbamic acid *tert*-butyl ester (50). The SEM-protected phenylalaninol **48a** (54 mg, 0.14 mmol) was treated with a 0.1 M solution of HCl in MeOH (1.4 mL). After 8 h stirring under N_2 at room temperature, the reaction mixture was concentrated under reduced pressure to a white solid. To this residue was added THF (0.70 mL), triethylamine (0.060 mL, 0.43 mmol) and di-*tert*-butyldicarbonate (43 mg, 0.20 mmol) and the resulting mixture was stirred under N_2 at room temperature for 16 h. Water (10 mL) was added and the aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic phases were washed with

brine (10 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (2:1, Et_2O–petroleum(40–60) elution) provided the title compound as a white solid (27 mg, 75%), mp 94–95 °C (lit.[37] mp 94.5–95.5 °C); R_f 0.25 (1:2, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3352, 2961, 2937, 1683, 1526; $[\alpha]_D^{20}=-22.0$ (*c* 1.0, $CHCl_3$), lit.[38] $[\alpha]_D^{20}=-24.0$ (*c* 1, $CHCl_3$)]; δ_H (270 MHz, $CDCl_3$) δ 7.34–7.19 (5H, complex m), 4.71 (1H, br s), 3.87 (1H, br m), 3.66 (1H, m), 3.55 (1H, m), 2.84 (2H, d, $J=7.5$ Hz), 2.23 (1H, br s), 1.41 (9H, s); δ_C (68.5 MHz, $CDCl_3$) 156.2, 138.0, 129.4, 128.6, 126.6, 79.8, 64.0, 53.8, 37.5, 28.4. (Found (CI^+): 252.1603. $C_{14}H_{22}NO_3$ requires (MH^+): 252.1600 (1.3 ppm)).

3.9.2. Oxidation of 50.

3.9.2.1. Methyl 2-(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate (51). A solution of phenyl alaninol **50** (36 mg, 0.14 mmol) in dichloromethane (1.5 mL) under N_2 at room temperature was treated with Dess–Martin periodinane (67 mg, 0.16 mmol). After 1.5 h the cloudy suspension was treated sequentially with saturated aqueous $NaHCO_3$ solution (3 mL), 1 M aqueous NaS_2O_3 solution (10 mL) and Et_2O (10 mL). The biphasic mixture was stirred for 15 min, then partitioned. The aqueous layer was re-extracted with Et_2O (2×10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a white solid. This residue was dissolved in *t*-BuOH (3.0 mL), and a 2 M solution of 2-methyl-2-butene in THF (1.40 mL, 2.80 mmol) was added. A solution of sodium chlorite (117 mg, 1.29 mmol) and sodium dihydrogen orthophosphate (165 mg, 1.06 mmol) in water (1.40 mL) was cautiously added dropwise. After 1.5 h, the reaction mixture was concentrated and saturated aqueous $NaHCO_3$ solution (10 mL) was added. The aqueous layer was washed with EtOAc (10 mL) and then acidified to pH 1 with 10% HCl solution. The resulting acidic aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless oil. This crude carboxylic acid was dissolved in toluene (0.7 mL) and MeOH (0.7 mL) and cooled to 0 °C under an atmosphere of N_2, before being treated with a 2 M ethereal solution of (trimethylsilyl)diazomethane (0.14 mL, 0.28 mmol). The reaction mixture was maintained at 0 °C for 40 min, and then was concentrated to afford a colourless oil. This oil was subjected to flash chromatography (1:3, Et_2O–petrol(40–60) elution) to provide the title compound as a colourless oil (30 mg, 75%); R_f 0.22 (1:2, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3365, 3030, 2978, 1746, 1714, 1502, 1454; $[\alpha]_D^{20}=+43.6$ (*c* 2.9, CH_2Cl_2) lit.[39] $[\alpha]_D^{20}=+46.9$ (*c* 3.43, CH_2Cl_2); δ_H (270 MHz, $CDCl_3$) δ 7.35–7.23 (3H, complex m), 7.14 (2H, d, $J=6.5$ Hz), 4.99 (1H, br d, $J=7.5$ Hz), 4.61 (1H, dt, $J=7.5$, 6 Hz), 3.73 (3H, s), 3.14 (1H, dd, $J=13.5$, 6 Hz), 3.06 (1H, dd, $J=13.5$, 6 Hz), 1.43 (9H, s); δ_C(100 MHz, $CDCl_3$) 172.5, 155.2, 136.1, 129.4, 128.7, 127.1, 80.0, 54.5, 52.3, 38.5, 28.4.

3.9.3. Deprotection of 51.

3.9.3.1. (*S*)-Phenylalanine hydrochloride (52). The ester **51** (31 mg, 0.11 mmol), anisole (0.020 mL, 0.18 mmol) and a 6 M aqueous HCl solution (2.0 mL) were mixed and heated at 70 °C for 5 h. The resulting mixture was then cooled to room temperature and treated with water (15 mL). The aqueous phase was washed with EtOAc (2×15 mL) and the separated aqueous layer was concentrated under reduced pressure to a white solid (22 mg, 100%), mp (dec.) 215–216 °C [lit.[36] mp 241–243 °C]. ν_{max}/cm^{-1} (thin film) 3385, 2947, 2616, 1731, 1605, 1485; $[\alpha]_D^{20}=-8.1$ (*c* 0.91, H_2O) [lit.[36] $[\alpha]_D^{20}=-8.2$ (*c* 1, H_2O)]; δ_H (400 MHz, $CDCl_3$) δ 7.42–7.32 (3H, complex m), 7.30 (2H, d, $J=7.5$ Hz), 4.25 (1H, dd, $J=7.5$, 5.5 Hz), 3.32 (1H, dd, $J=14.5$, 5.5 Hz), 3.18 (1H, dd, $J=14.5$, 7.5 Hz); δ_C(100 MHz, $CDCl_3$) 171.8, 134.3, 129.5, 129.3, 128.0, 55.4, 35.8.

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Tandem alkylation–cyclization process via an *O*,*C*-dianion

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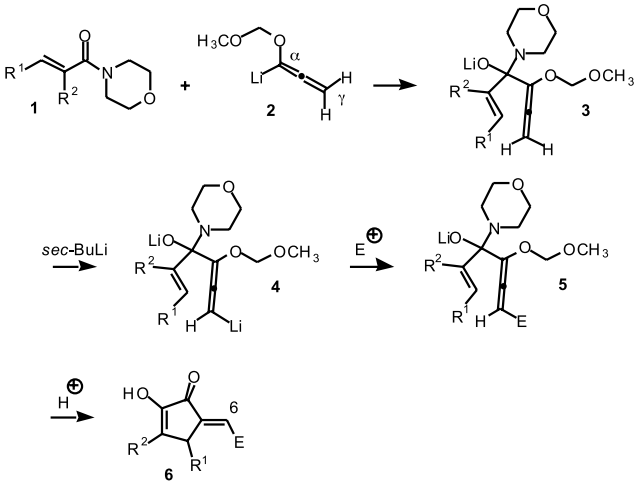
Abstract—A general protocol for preparing densely functionalized cyclopentenones through a tandem nucleophilic addition–deprotonation–alkylation–cyclization process is described. Addition of lithioallene **2** to enamides **1** generates tetrahedral intermediate **3**. Deprotonation of the γ carbon atom of the allene function in situ, followed by trapping by a suitable electrophile and cyclization during workup leads to C6 substituted cyclopentenones **6**.

1. Introduction

In a preliminary communication we described the triply convergent process whereby morpholino enamide **1** (Eq. 1) is first combined with lithio allene **2** to give tetrahedral intermediate **3**.[1] The acidity of the allenic protons in **3** makes it possible to deprotonate **3** by exposure to a strong base. Lithio allene **4** is a good nucleophile, and can be trapped by a number of different types of electrophiles to produce **5**, which is cyclized upon workup with acid to give cross conjugated cyclopentenone **6** bearing a substituent on exocyclic carbon atom C6. This strategy makes it possible to combine three large fragments, the allene, the enamide and the electrophile, and for this reason we have described the process as being 'triply' convergent.

2. Discussion

There are several advantages inherent to this approach in addition to the high degree of convergency. The alternative approach to structures such as **6** is by means of a lithioallene analogous to **2**, but bearing a substituent at the γ carbon atom. Whereas the preparation of **2** is completely straightforward, the preparation of homologs of **2** requires several additional steps, and is not always efficient.[2] Some allene substituents may interfere with the generation of the lithioallene, or may inhibit the clean addition of the morpholino enamide. These problems are avoided by following the protocol that is summarized in Eq. 1.



(1)

There are some potential difficulties in implementing such a process efficiently. Whenever a number of sequential processes is attempted in a single operation, it is important that each step proceed to completion (if possible) and that each step not be plagued by the creation of undesired side products. Whereas these shortcomings might be tolerable in a reaction that proceeds in a single step, it is clear that in a process that encompasses a series of linked steps this would result in a low yield of product, and in the generation of complex product mixtures.

In our preliminary communication we described the reactions of a single morpholino enamide derived from

Keywords: Allene; Nazarov; Cyclization.
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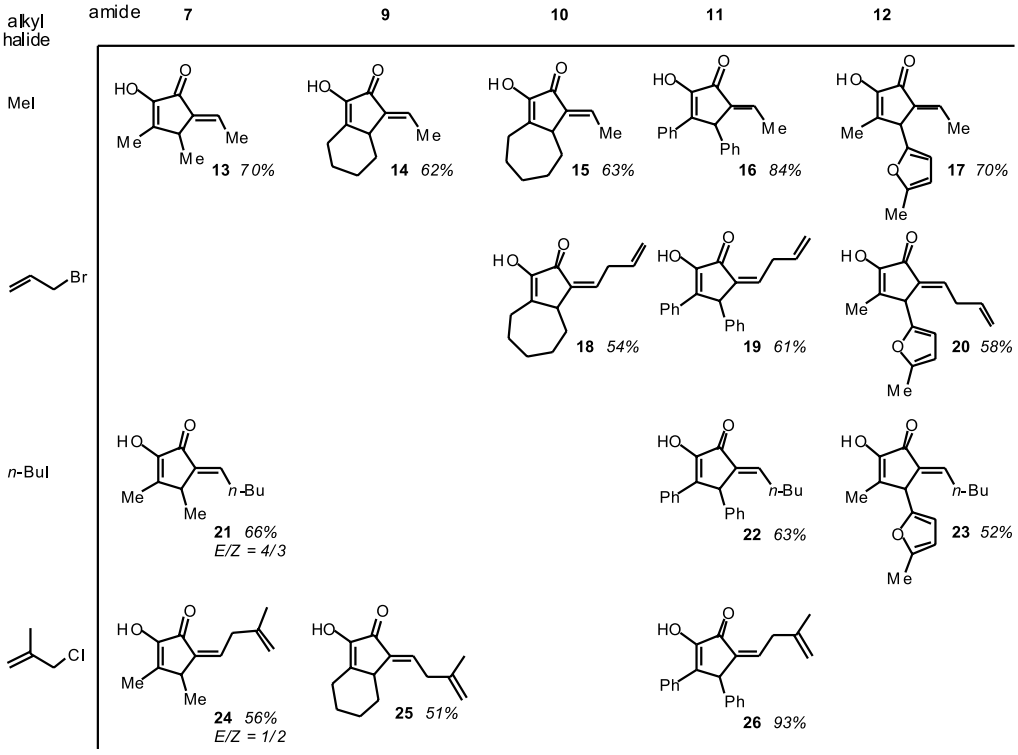
Table 1. Alkyl halide electrophiles



commercially available *trans*-α-methylcinnamic acid with a representative panel of electrophiles. The question we wished to answer with the work described herein is whether the method can be applied to other morpholino enamides and to other electrophiles. In addition, we hoped to be able to define optimum conditions for the process. Our results with enamides **7**–**12** and an expanded panel of electrophiles are summarized in Tables 1–3.

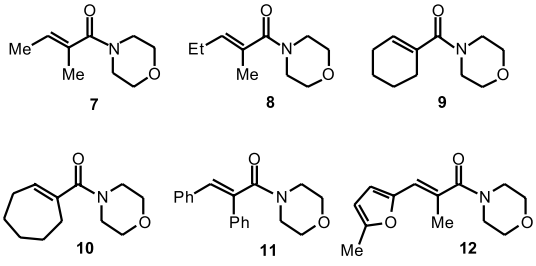


Table 2. Ketone electrophiles

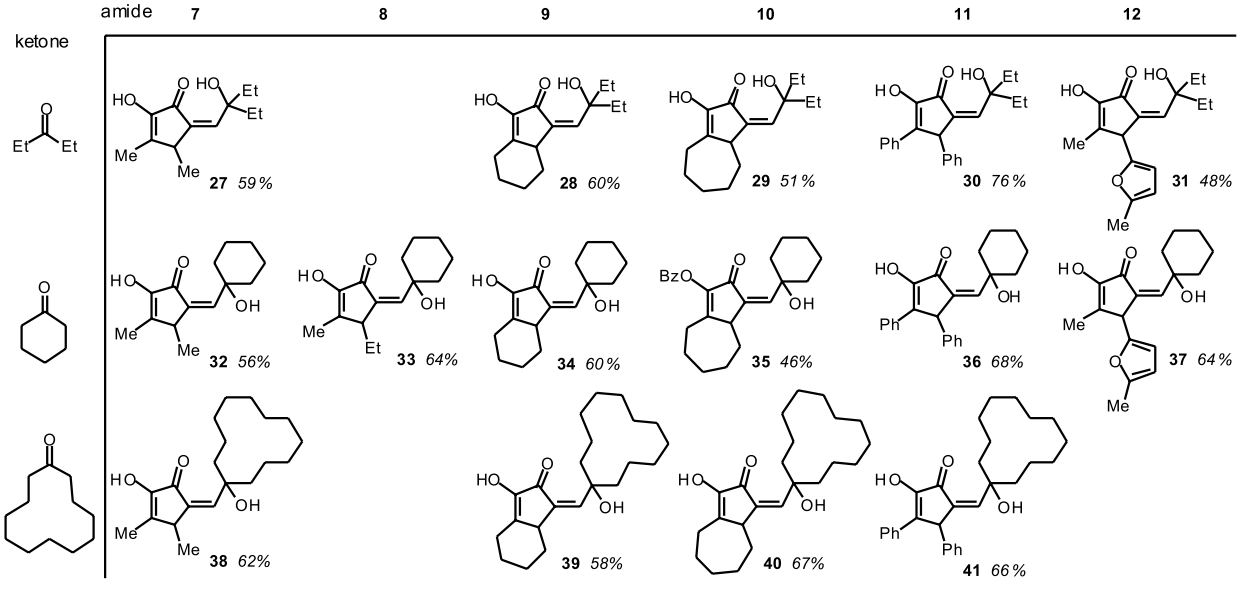
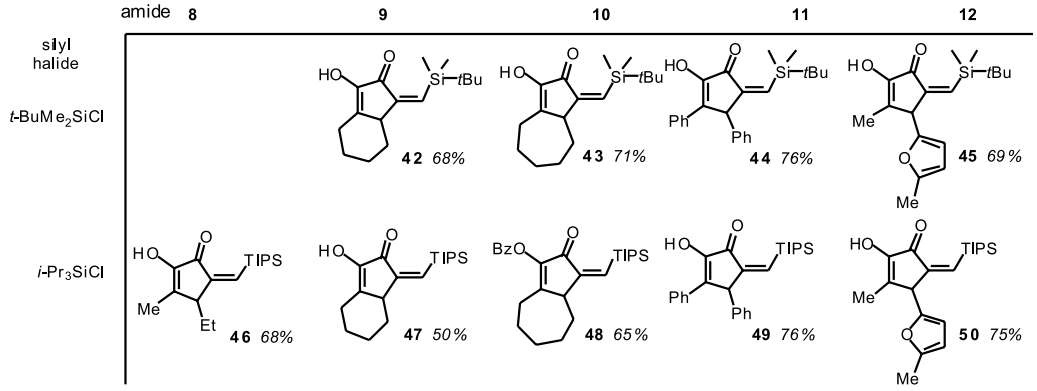


Table 3. Trialkylsilyl chloride electrophiles



Morpholino enamides **7**, **8**, and **11** were prepared from the commercially available carboxylic acids in two steps. Exposure to oxalyl chloride and catalytic DMF led to the acid chlorides that were treated with morpholine and pyridine to give the amides. Amides **9** and **10** were prepared from cyclohexanone and cycloheptanone, respectively. The ketones were first converted to the corresponding cyanohydrins with potassium cyanide and acetic acid, then dehydrated with phosphorus oxychloride according to the published procedure.[3] The resulting α,β-unsaturated nitriles were hydrolyzed to the corresponding carboxylic acids by exposure to aqueous ethanolic sodium hydroxide at reflux, in the presence of catalytic tetra-*n*-butylammonium hydrogen sulfate. The carboxylic acids were converted to enamides in the same way as **7**, **8** and **11**. Enamide **12** was prepared in two steps from commercially available 5-methylfurfural. Horner–Emmons reaction with triethyl 2-phosphonopropionate led to the expected enoate as a single geometrical isomer. Exposure of the ester to morpholine and trimethylaluminum gave enamide **12**.[4]

In all reactions that proceed by means of carbanion intermediates it is critical to take pains to exclude adventitious proton sources. In the present case, it is necessary that conversion of tetrahedral intermediate **3** to lithioallene **4** be complete, and that the electrophile be dry and acid free. If either of these two conditions is not met, the reaction mixture at the end of the process will be derived from cyclization of a mixture of **3** and **5**, resulting in a mixture of the desired product **6** and of the corresponding protio compound (**6**, E=H). Another way in which this byproduct can be formed is if the kinetics for the alkylation step (Eq. 1, **4**→**5**) are slow. In this case, premature quenching of the mixture of **4** and **5** again leads to the same product mixture. Separation of the byproduct by means of flash column chromatography is tedious.

During the course of the execution of this research we made a number of observations that have an important bearing on the outcome of these reactions. In all cases the amides were dried by azeotropic distillation with benzene, then stored in THF over 4 Å molecular sieves prior to use. Best results were obtained when a fresh solution of *sec*-butyllithium was used for the generation of *O*,*C*-dianion **4**. The use of aged solutions invariably led to erosion of the yield of product. This was not due to any uncertainty regarding the titer of alkyllithium, since the *sec*-butyllithium solution had been titrated immediately prior to its use. There are apparently two reasons to which the low product yields may be attributed. First, when the titer of the *sec*-butyllithium falls much below 1 M, the volume of the solution that must be added increase, as does the proportion of hydrocarbon solvent (cyclohexane) in the reaction medium (THF). This may have an effect on the kinetics of the subsequent steps leading to **6**. Second, the reduction in the observed *sec*-butyllithium titer is probably caused by introduction of small amounts of air through leaks in the septum closure. This suggests the presence of hydroperoxides in aged *sec*-butyllithium solutions that may be able to degrade *O*,*C*-dianion **4** through oxidative processes. The progress of the reactions was not monitored by TLC so as to avoid introducing moisture.

In all cases the quality of the allene that is used for the preparation of **2** is important. The allene undergoes some discoloration upon standing. Discolored samples of allene should be distilled before use. The allene is prepared from the isomerization of methoxymethyl propargyl ether with freshly sublimed potassium *tert*-butoxide,[5] a procedure that can result in contamination of the allene by variable amounts of *tert*-butanol. Distilling the allene from potassium hydride leads to dry, alcohol-free material.

The critical alkylation step (Eq. 1, **4**→**5**) must be performed at −78 °C. The solution of the electrophile was cooled and transferred rapidly by cannula to the solution of *O*,*C*-dianion **4**.

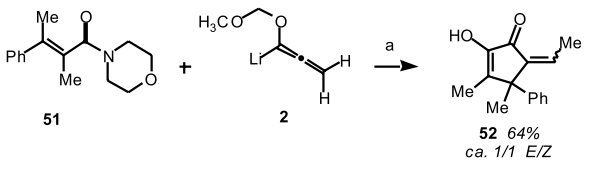
There is some variation allowed in the conditions for the cyclization step. The conditions on which we have converged call for transferring the solution of **5** to 5% HCl in ethanol, stirring for no more than 5–10 min at rt, and neutralizing the solution with pH 7 phosphate buffer. Contact with ethanolic HCl for times longer than 10 min often resulted in diminished yields of product. It is important that addition of the solution of **5** to the acid be performed as rapidly as possible, otherwise the yield of product was lower.

What emerges from the discussion above is a protocol that is sensitive to essentially all of the reaction parameters. While it is true that the procedure is quite unforgiving of

inattention to experimental detail, if the precautions that have been delineated above are followed, it is easy to reproduce. Table 1 shows that there is some variability in the yields, but that in all cases they are within the synthetically useful range. The reactions with allyl bromide, methallyl chloride and *n*-butyl iodide were surprisingly sluggish compared to the reaction with iodomethane. The addition of HMPA, and of several equivalents of LiI in the case of allyl bromide and methallyl chloride was necessary in order to achieve the results that are reported in Table 1. The alkyl halides were distilled and passed through a short column of basic alumina prior to use. The liquid ketones, 3-pentanone and cyclohexanone, were distilled and dried over 4 Å molecular sieves prior to use, whereas no such precaution was necessary in the case of cyclododecanone, a crystalline solid. *tert*-Butyldimethylsilyl chloride was sublimed, then treated with anhydrous potassium carbonate as a solution in THF, followed by 4 Å molecular sieves prior to use. Triisopropylsilyl chloride was used as received from Acros.

For reasons that we have discussed in earlier work,[6,7] the kinetic products of cyclization are the *Z* isomers at the exocyclic double bond. Longer contact times with acid during cyclization can lead to isomerization to the *E* isomer, when that isomer is thermodynamically favored. For example, most of the cyclopentenones shown in Table 1 were isolated as the *E* isomer. When the substituent at C6 has a large steric requirement, the *Z* isomer is often thermodynamically, as well as kinetically favored. For example, as shown in Table 2, cyclopentenones **27**–**41** that bear a tertiary group at C6 were all isolated as the *Z* isomer. The situation is the same in the case of trialkylsilyl cyclopentenones **42**–**50** (Table 3). It is noteworthy that cyclopentenones **18**–**20** and **24**–**26** (Table 1) were isolated as skipped dienes. Conjugation of the terminal double bond on the side chain did not take place to any large extent. This testifies to the mildness of the reaction conditions. Products **35** and **48** were converted to the corresponding benzoate esters for ease of purification. In both cases the reported yield is of the benzoate derivative. All reaction products were fairly stable to storage under neutral conditions, however, some decomposition took place on standing at rt.

Amides **7**–**12** bear a single substituent at the β carbon atom. Limited work with β-disubstituted morpholino enamides suggested that the tandem alkylation–cyclization process would take place with this class of substrates, however, the efficiency of such a process was open to question.[8] In the few examples that we examined, yields for the simple cyclization had been modest. Part of the reason for this appears to be related to the fact that addition of the allene nucleophile to β-disubstituted enamides is much slower, a fact that we had not fully appreciated. Although the slow kinetics for the addition can be easily accommodated by a longer reaction time in a process that takes place in a single step, it was less clear that it would be practical to do so in the tandem process.



(2)

Eq. 2 summarizes our results with a single tetrasubstituted enamide. Addition of lithioallene **2** to enamide **51** took place during 1.5 h at −5 °C. The solution was cooled to −78 °C, deprotonated to generate the *O*,*C*-dianion, and exposed to excess iodomethane. Cyclization led to cyclopentenone **52** in 64% yield as a ca. 1/1 mixture of geometrical isomers. These were separated with difficulty by means of column chromatography on silica gel.

3. Conclusions

The scope of a tandem alkylation–cyclization process for preparing highly substituted cyclopentenones has been expanded. The structures of the products that are shown in Tables 1–3 would be challenging to prepare by other means, and would require several discrete steps. A large degree of molecular complexity can be created in a single step. On the basis of the results that are summarized in (Eq. 2) it appears likely that the synthesis of cyclopentenones such as **52** bearing a quaternary ring carbon atom is also amenable through this method. Applications to natural products total synthesis as well as to diversity-oriented synthesis can be anticipated.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Mercury Plus 300 operating at 300 MHz (^{1}H) or 75 MHz (^{13}C) or on a Varian Unity Inova 500 operating at 500 MHz (^{1}H) or 126 MHz (^{13}C). Infrared spectra were recorded on a Perkin–Elmer IR 1430 spectrometer. Electron impact mass spectra were recorded on a VG-70SE mass spectrometer. Thin-layer chromatography (TLC) was performed on Sigma-Aldrich TLC plates, 250 μm, particle size 5–17 μm, pore size 60 Å. Flash column chromatography was performed on Natland International Corporation silica gel, 200–400 mesh and Sorbent Technologies silica gel, premium R_f, 60 Å, 40–75 μm. Anhydrous THF was taken from a solvent purification system from GlassContour (www.glasscontour.com). Reagents were purified as described in text or were used as received. All moisture sensitive reactions were performed under a static nitrogen or argon atmosphere in oven-dried or flame-dried glassware.

A general method for the preparation of compounds **13**–**17** is described in section 4.1.1, compounds **18**–**26** is described in section 4.1.6, compounds **27**–**41** is described in section 4.1.15, compounds **42**–**45** is described in section 4.1.30, compounds **46**–**50** is described in section 4.1.34.

4.1.1. (5*E*)-5-Ethylidene-2-hydroxy-3,4-diphenylcyclopent-2-enone 16. A solution of allenyllithium **2** was prepared in 3 mL THF at −78 °C from 43 mg (0.43 mmol) of allene and 155 μL *n*-BuLi (2.91 M in hexanes, 0.45 mmol). After 45 min, a solution of amide **11** (105 mg, 0.36 mmol) in 2 mL THF was added at −78 °C via cannula. After 10 min at −78 °C, the reaction mixture was warmed from −78 to −30 °C over 30 min, and stirred

further for 30 min at −30 °C. *sec*-BuLi (415 μL, 1.35 M in cyclohexane, 0.56 mmol) was added dropwise at −78 °C. After 45 min, MeI (110 μL, 1.77 mmol) in 2 mL THF was added at −78 °C via cannula. The reaction mixture was warmed from −78 to −30 °C over 15 min, and stirred further for 1 h at −30 °C; then quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in EtOH (7 mL). After 10 min, it was neutralized with pH 7 buffer, and extracted with EtOAc (3×). The combined organic extracts were washed with brine (2×) and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (10% EtOAc in hexanes) gave cyclopentenone **16** as a white crystalline solid (83 mg, 84% yield): mp 196–198 °C; R_f=0.32 (20% EtOAc in hexanes). IR (film): 3222 (br), 3018, 1683, 1655, 1401 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ=7.90–7.82 (m, 2H), 7.36–7.10 (m, 8H), 6.98 (bs, 1H), 6.80 (qd, J=7.3, 1.3 Hz, 1H), 4.93 (d, J=1.3 Hz, 1H), 1.71 (d, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.0, 150.7, 140.6, 138.3, 135.5, 132.7, 132.4, 128.9 (2), 128.6 (2), 128.4 (2), 128.1 (2), 126.9 (2), 45.8, 14.2. MS: *m/z* (%)=276 (M^+, 100), 261 (2), 258 (13), 232 (3), 199 (3). HREIMS calcd for $C_{19}H_{16}O_2$ 276.1150, found 276.1179.

Compounds **13**, **14**, **15** and **17** were prepared according to the general procedure described above for **16**.

4.1.2. (5*E*)-5-Ethylidene-2-hydroxy-3,4-dimethylcyclopent-2-enone 13. Isolated as a white crystalline solid (106 mg, 69% yield): mp 132–134 °C. IR (film): 3270 (br), 1675, 1630, 1405 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ=7.86 (bs, 1H), 6.57 (qd, J=7.2, 1.5 Hz, 1H), 2.54 (bq, J=6.9 Hz, 1H), 1.69 (s, 3H), 1.34 (d, J=7.2 Hz, 3H), 0.77 (d, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ=189.8, 151.3, 142.5, 139.7, 129.6, 36.7, 17.3, 14.3, 11.5. MS: *m/z* (%)=152 (M^+, 100), 137 (65), 109 (60). HREIMS calcd for $C_9H_{12}O_2$ 152.0837, 152.0868.

4.1.3. (3*E*)-3-Ethylidene-3a,4,5,6-tetrahydro-1-hydroxy-1*H*-inden-2(4*H*)-one 14. Isolated as a white amorphous solid (111 mg, 62% yield): mp 132 °C. IR (film): 3300 (br), 2935, 2856, 1682, 1630, 1444, 1399, 1202, 1119, 1050, 972 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.64 (dq, J=7.2, 4.2 Hz, 1H), 5.95 (bs, 1H), 3.01 (dd, J=12.0, 4.5 Hz, 2H), 2.41–2.35 (dm, 1H), 2.12–1.83 (m, 6H), 1.52 (qt, J=13.2, 3.3 Hz, 1H), 1.34 (qt, J=12.6, 3.3 Hz, 1H), 1.04 (qd, J=12.9, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.4, 107.0, 144.4, 137.5, 130.8, 39.5, 32.7, 26.2 (2), 25.2, 14.6. MS: *m/z* (%)=178 (M^+, 96), 160 (21), 149 (17), 135 (100), 79 (58). HREIMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0996.

4.1.4. (3*E*)-3-Ethylidene-3a,4,5,6,7,8-hexahydro-1-hydroxyazulen-2(1*H*)-one 15. Isolated as a white crystalline solid (61 mg, 63% yield): decomposition at 73 °C. IR (film): 3292 (br), 2927, 1671, 1626, 1404, 953 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ=7.45 (bs, 1H), 6.59 (q, J=7.3 Hz, 1H), 2.74 (d, J=9.9 Hz, 1H), 2.70–2.44 (m, 2H), 1.89–1.78 (m, 1H), 1.60–1.44 (m, 2H), 1.35 (d, J=7.3, 3H), 1.30–0.76 (m, 5H). ^{13}C NMR (75 MHz, C_6D_6): δ=188.9, 150.5, 147.2, 139.3, 128.6, 41.4, 34.3, 30.3, 29.5, 28.1, 25.5, 14.0. MS: *m/z* (%)=192 (M^+, 100), 174 (20), 164 (10), 149 (85), 135 (20), 107 (20). HREIMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1166.

4.1.5. (5*E*)-5-Ethylidene-2-hydroxy-3-methyl-4-(5-methylfuran-2-yl)cyclopent-2-enone 17. Isolated as a white crystalline solid (97 mg, 70% yield): mp 188 °C. IR (film): 3243, 2980, 1678 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.67 (qd, J=8.0, 1.8 Hz, 1H), 5.95 (d, J=3.0 Hz, 1H), 5.85 (dt, J=3.0, 0.9 Hz, 1H), 4.30 (bs, 1H), 2.19 (d, J=0.9 Hz, 3H), 1.88 (s, 3H), 1.75 (d, J=8.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.3, 153.8, 150.6, 150.4, 149.9, 145.7, 137.2, 132.6, 101.1, 43.8, 14.0, 13.2, 11.9. HREIMS calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0943.

4.1.6. (5*Z*)-2-Hydroxy-5-(3-methylbut-3-enylidene)-3,4-diphenylcyclopent-2-enone 26. A solution of allenyllithium **2** was prepared in 3 mL THF at −78 °C from 40 mg (0.40 mmol) of allene and 140 μL *n*-BuLi (2.91 M in hexanes, 0.41 mmol). After 45 min, a solution of amide **11** (97 mg, 0.33 mmol) in 2 mL THF was added at −78 °C via cannula. After 10 min at −78 °C, the reaction mixture was warmed from −78 to −30 °C over 30 min and stirred further for 30 min at −30 °C. *sec*-BuLi (380 μL, 1.35 M in cyclohexane, 0.51 mmol) was added dropwise at −78 °C. After 45 min, a solution of methallyl chloride (165 μL, 1.67 mmol), LiI (225 mg, 1.68 mmol), and HMPA (115 μL, 0.66 mmol) in 3 mL THF was added at −78 °C via cannula. The reaction mixture was warmed from −78 to −30 °C over 15 min and stirred further for 2 h at −30 °C; then quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in EtOH (7 mL). After 10 min, it was neutralized with pH 7 buffer and extracted with EtOAc (3×). The combined organic extracts were washed with brine (2×) and dried over $MgSO_4$. Purification by crystallization of the crude in 3% EtOAc in hexanes gave cyclopentenone **26** as a yellow crystalline solid (97 mg, 93% yield): mp 164–166 °C; R_f=0.58 (20% EtOAc in hexanes).

^1H NMR (300 MHz, $CDCl_3$): δ=7.90–7.82 (m, 2H), 7.35–7.14 (m, 8H), 6.61 (bs, 1H), 5.95 (t, J=7.9 Hz, 1H), 4.79 (s, 1H), 4.70 (s, 1H), 4.54 (s, 1H), 3.62 (dd, J=15.9, 8.1 Hz, 1H), 3.46 (dd, J=15.9, 7.8 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.4, 151.6, 143.6, 141.7, 141.2, 136.8, 132.8, 132.4, 129.2 (2), 128.9 (2), 128.4 (2), 127.4 (2), 127.0 (2), 111.3, 47.6, 35.9, 22.8. MS: *m/z* (%)=316 (M^+, 100), 301 (30), 298 (7), 287 (4), 259 (3). HREIMS calcd for C_{22} $H_{20}O_2$ 316.1463, found 316.1477.

Compounds **18**–**25** were prepared according to the general procedure described above for **26**.

4.1.7. (3*Z*)-3-(But-3-enylidene)-3a,4,5,6,7,8-hexahydro-1-hydroxyazulen-2(1*H*)-one 18. Isolated as a white amorphous solid (75 mg, 68% yield). IR (neat): 3584, 3383 (br), 2924, 1670, 1613, 1407, 1078 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ=5.60–5.45 (m, 1H), 5.33 (t, J=7.6 Hz, 1H), 4.84–4.68 (m, 2H) 3.54–3.32 (m, 2H), 2.40–2.32 (m, 1H) 2.18–2.10 (m, 2H), 1.45–1.34 (m, 1H), 1.34–1.90 (m, 3H), 0.96–0.55 (m, 5H). ^{13}C NMR (75 MHz, C_6D_6): δ=190.1, 151.3, 146.2, 137.2, 136.2, 136.2, 115.9, 43.8, 35.1, 32.0, 30.7, 29.8, 28.1, 25.9. MS: *m/z* (%)=218

(M^+, 25), 105 (10), 91 (10), 84 (100), 70 (10). HREIMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1297.

4.1.8. (5*Z*)-5-(But-3-enylidene)-2-hydroxy-3,4-diphenylcyclopent-2-enone 19. Isolated as a yellow crystalline solid (65 mg, 61% yield): mp 158–160 °C. IR (film): 3248 (br), 2915, 1668, 1398 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ= 7.90–7.82 (m, 2H), 7.40–7.10 (m, 8H), 6.77 (bs, 1H), 5.93 (t, J=7.5 Hz, 1H), 5.80 (m, 1H), 5.00 (s, 1H), 4.95 (m, 1H), 4.78 (s, 1H), 3.82–3.62 (m, 1H), 3.52–3.34 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.4, 151.6, 141.6, 140.7, 136.4, 135.2, 133.0, 132.4, 129.2 (2), 128.9 (2), 128.4 (2), 127.4 (2), 127.0 (2), 116.1, 47.5, 32.1. MS: *m*/*z* (%)=302 (M^+, 100), 273 (6), 284 (10), 245 (5). HREIMS calcd for $C_{21}H_{18}O_2$ 302.1307, found 302.1337.

4.1.9. (5*E*)-5-(But-3-enylidene)-2-hydroxy-3-methyl-4-(5-methylfuran-2-yl)cyclopent-2-enone 20. Isolated as a yellow oil (80 mg, 58% yield). IR (film): 3280, 1673, 1490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.64 (m, 1H), 6.05 (dt, J=3.0, 0.9 Hz, 1H), 5.87 (d, 0.9 Hz, 1H), 5.70–5.59 (m, 1H), 5.31 (bs, 1H), 4.98 (d, J=10.0 Hz, 1H), 4.89 (d, J=17.0 Hz, 1H), 4.35 (bs, 1H), 2.91–2.80 (m, 2H), 2.24 (d, J=0.9 Hz, 3H), 1.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.9, 161.3, 153.2, 152.5, 150.2, 146.8, 138.4, 134.8, 116.0, 112.1, 108.2, 44.8, 31.0, 13.7, 12.9. HREIMS calcd for $C_{15}H_{16}O_3$ 244.1099 found 244.1089.

4.1.10. (5*E*)-2-Hydroxy-3,4-dimethyl-5-pentylidenecyclopent-2-enone 21. Isolated as a pale amber oil (57 mg, 29% yield). The *Z* isomer was isolated as an amorphous solid (67 mg, 37% yield). IR *Z* isomer: (neat) 3310 (br), 2960, 2930, 2870, 1770, 1680, 1625 cm^{-1}; *E* isomer: (neat) 3310 (br), 2960, 2930, 2870, 1680, 1625, 1410 cm^{-1}. ^1H NMR (300 MHz, C_6D_6). *Z* isomer: δ=7.12 (s, 1H), 5.62 (td, J=7.8, 0.9 Hz, 1H), 2.93 (m, 2H), 2.52 (bq, J=7.0 Hz, 1H), 1.64 (s, 3H), 1.28 (m, 4H), 1.25 (t, J= 6.9 Hz, 3H), 0.86 (d, J=7.0 Hz, 3H); *E* isomer: δ=6.61 (td, J=8.1, 1.5 Hz, 1H), 2.63 (bq, J=6.9 Hz, 1H), 1.89 (m, 2H), 1.68 (s, 3H), 1.13 (m, 4H), 0.83 (d, J=6.9 Hz, 3H), 0.80 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *Z* isomer: δ=190.5, 151.7, 139.8, 139.7, 137.2, 38.4, 31.8, 27.5, 22.6, 17.6, 14.2, 11.1; *E* isomer: δ=189.4, 150.7, 141.6, 138.2, 134.6, 36.5, 30.9, 28.4, 22.6, 17.3, 13.9, 11.0. *Z* isomer HREIMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1297. *E* isomer HREIMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1250.

4.1.11. (5*E*)-2-Hydroxy-5-pentylidene-3,4-diphenylcyclopent-2-enone 22. Isolated as a yellow crystalline solid (74 mg, 63% yield): mp 200–202 °C. IR (film): 3208 (br), 2958, 1655, 1401 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.82 (d, J=7.3 Hz, 2H), 7.40–7.10 (m, 8H), 6.82 (bs, 1H), 6.71 (t, J=7.9 Hz, 1H), 4.93 (s, 1H), 2.25–1.95 (m, 2H), 1.30–0.90 (m, 4H), 0.76 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.5, 150.9, 141.2, 138.3, 137.4, 135.6, 132.7, 129.2 (2), 128.9 (2), 128.6 (2), 128.4 (2), 127.1 (2), 46.1, 30.3, 28.5, 22.6, 14.0. MS: *m*/*z* (%)=318 (M^+, 100), 300 (13), 289 (10). HREIMS calcd for C_{22} $H_{22}O_2$ 318.1620, found 318.1589.

4.1.12. (5*E*)-2-Hydroxy-3-methyl-4-(5-methylfuran-2-yl)-5-pentylidenecyclopent-2-enone 23. Isolated as a pale yellow wax (65 mg, 52% yield). IR (neat): 3300, 2960, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.57 (td, J= 8.1, 1.8 Hz, 1H), 5.92 (d, J=3.0 Hz, 1H), 5.80 (dt, J=3.0, 0.9 Hz, 1H), 4.24 (bs, 1H), 2.15 (d, J=0.9 Hz, 3H), 1.92–2.06 (m, 2H), 1.82 (s, 3H), 1.04–1.65 (m, 4H), 0.75 (t, J= 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=188.5, 153.2, 151.5, 150.4, 149.9, 141.4, 138.5, 131.1, 106.1, 42.2, 30.3, 28.2, 22.3, 13.8, 13.5, 11.8. HREIMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1415.

4.1.13. (5*Z*)-2-Hydroxy-3,4-dimethyl-5-(3-methylbut-3-enylidene)cyclopent-2-enone 24. Isolated as an oil (114 mg, 59% yield). IR (neat): 3314, 2967, 2932, 2871, 1679, 1626, 1650, 1409, 1357 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.02 (td, J=7.8, 1.2 Hz, 1H), 4.72 (s, 1H), 4.76 (s, 1H), 3.54 (d, J=7.8 Hz, 2H), 3.02 (q, J=7.2 Hz, 1H), 1.96 (d, J=1.2 Hz, 3H), 1.75 (s, 3H), 1.20 (d, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.5, 150.9, 148.9, 144.3, 141.0, 137.1, 111.3, 38.6, 35.8, 22.9, 17.9, 11.7. HREIMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1146.

4.1.14. (3*Z*)-3a,4,5,6-Tetrahydro-1-hydroxy-3-(3-methylbut-3-enylidene)-1*H*-inden-2(4*H*)-one 25. Isolated as an oil (104 mg, 51% yield). IR (film): 3315, 2933, 2855, 1687, 1623, 1445, 1400, 1361.2 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.35 (bs, 1H), 5.99 (t, J=7.8 Hz, 1H), 4.76 (s, 1H), 4.70 (s, 1H) 3.53 (d, J=7.8 Hz, 2H), 2.97 (dd, J= 13.8, 4.2 Hz, 1H), 2.82 (dd, J=11.7, 5.4 Hz, 1H) 2.26–2.14 (m, 1H), 2.10–1.80 (m, 3H), 1.74 (s, 3H), 1.56–1.38 (m, 1H), 1.36–1.15 (m, 1H), 1.15–0.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.9, 148.1, 144.3, 142.9, 136.8, 136.5, 111.3, 40.9, 35.7, 33.2, 25.5, 25.2, 25.1, 22.9. HREIMS calcd for $C_{14}H_{18}O_2$ 218.2915, found 260.1334.

4.1.15. (5*Z*)-2-Hydroxy-5-((1-hydroxycyclohexyl)methylene)-3,4-diphenylcyclopent-2-enone 36. A solution of allenyllithium **2** was prepared in 3 mL THF at −78 °C from 44 mg (0.44 mmol) of allene and 160 μL *n*-BuLi (2.91 M in hexanes, 0.47 mmol). After 45 min a solution of amide **11** (108 mg, 0.37 mmol) in 2 mL THF was added at −78 °C via cannula. After 10 min at −78 °C, the reaction mixture was warmed from −78 to −30 °C over 30 min and stirred further for 30 min at −30 °C. *sec*-BuLi (430 μL, 1.35 M in cyclohexane, 0.58 mmol) was added dropwise at −78 °C. After 45 min, a solution of cyclohexanone (170 μL, 1.64 mmol) in 2 mL THF was added at −78 °C via cannula. The reaction mixture was warmed from −78 to −30 °C over 15 min, and stirred further for 1 h at −30 °C; then quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in EtOH (7 mL). After 10 min, it was neutralized with pH 7 buffer, and extracted with EtOAc (3×). The combined organic extracts were washed with brine (2×) and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (10% EtOAc in hexanes) gave cyclopentenone **36** as a yellow, crystalline solid (90 mg, 68% yield): mp 184–186 °C; R_f=0.18 (20% EtOAc in hexanes).

IR (film): 3372 (br), 2938, 1651, 1451 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.84–7.74 (m, 2H), 7.40–7.00 (m, 8H), 6.47 (bs, 1H), 6.12 (bs, 1H), 6.04 (s, 1H), 4.75 (s, 1H), 1.84–1.10 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.6, 153.1, 151.7, 141.0, 136.1, 135.7, 132.1, 129.5 (2), 129.0 (2), 128.4 (2), 127.4 (2), 127.2 (2), 71.9, 47.8, 37.5, 37.2,

25.3, 21.9, 21.8. MS: *m/z* (%)=360 (M^+, 100), 342 (57), 248 (47). HREIMS calcd for $C_{24}H_{24}O_3$ 360.1726, found 360.1685.

Compounds **27–35** and **37–41** were prepared according to the general procedure described above for **36**.

4.1.16. (5*Z*)-2-Hydroxy-5-(2-hydroxy-2-ethylbutylidene)-3,4-dimethylcyclopent-2-enone 27. Isolated as a pale yellow oil (70 mg, 59% yield). IR (film): 3306 (br), 2966, 1661, 1616, 797 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ=7.11 (bs, 1H), 5.75 (s, 1H), 5.65 (bs, 1H), 2.45–2.32 (m, 1H), 1.86–1.70 (m, 2H), 1.66–1.52 (m, 2H), 1.50 (d, *J*=1.2 Hz, 3H), 1.12–0.96 (m, 6H), 0.67 (d, *J*=7.2 Hz, 3H) ^{13}C NMR (75 MHz, C_6D_6): δ=190.8, 151.7, 147.6, 143.5, 138.0, 77.0, 38.9, 34.4, 17.5, 11.5, 8.7. HREIMS calcd for $C_{13}H_{20}O_3$ 224.2961, found 224.1416.

4.1.17. (3*Z*)-3a,4,5,6-Tetrahydro-1-hydroxy-3-(2-hydroxy-2-ethylbutylidene)-1*H*-inden-2(4*H*)-one 28. Isolated as a pale yellow crystalline solid (150 mg, 60% yield): mp 90–93 °C. IR (film): 3294 (br), 2934, 1664, 1616, 1457, 1403, 1255, 1204, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.59 (s, 1H), 6.05 (s, 1H), 3.01–2.95 (m, 1H), 2.87 (dd, *J*=12.0, 5.1 Hz, 1H), 2.21 (m, 1H), 2.24–1.86 (m, 4H), 1.74–1.41 (m, 5H), 1.28 (qt, *J*=12.9, 3.9 Hz, 1H), 1.06 (qd, *J*=12.9, 3.3 Hz, 1H), 0.92 (t, *J*=7.5 Hz, 3H), 0.90 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.8, 147.7, 147.6, 145.5, 136.1, 76.7, 41.2, 33.8, 33.8, 33.0, 25.2, 25.1, 24.8, 8.3, 8.2. MS: *m/z* (%)=250 (M^+, 2), 222 (13), 221 (100), 193 (17). HREIMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1565.

4.1.18. (3*Z*)-3a,4,5,6,7,8-Hexahydro-1-hydroxy-3-(2-hydroxy-2-ethylbutylidene)azulen-2(1*H*)-one 29. Isolated as a white crystalline solid (135 mg, 51% yield): mp 140–142 °C. IR (neat): 3310, 2960, 1715, 1666, 1610, 1457, 1415, 1359 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.71 (s, 1H), 6.09 (s, 1H), 3.19 (dd, *J*=10.2, 1.8 Hz, 1H), 2.82–2.58 (m, 2H), 2.10 (dd, *J*=14.0, 2.7 Hz, 1H), 2.00–1.80 (m, 3H), 1.76–1.40 (m, 6H), 1.38–1.20 (m, 2H), 0.90 (t, *J*=7.5 Hz, 3H), 0.91 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.0, 150.3, 149.9, 148.5, 137.2, 44.8, 35.6 (2), 34.2, 34.1, 30.8, 29.9, 28.5, 25.9, 8.5 (2). MS: *m/z* (%)=264 (M^+, 2), 246 (9), 235 (100). HREIMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1742.

4.1.19. (5*Z*)-2-Hydroxy-5-(2-hydroxy-2-ethylbutylidene)-3,4-diphenylcyclopent-2-enone 30. Isolated as a yellow crystalline solid (98 mg, 76% yield): mp 144–145 °C. IR (film): 3321 (br), 2939, 1644, 1405 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.90–7.76 (m, 2H), 7.40–7.10 (m, 8H), 6.88 (bs, 1H), 6.53 (bs, 1H), 5.94 (s, 1H), 4.78 (s, 1H), 1.80–1.38 (m, 4H), 0.94 (t, *J*=7.5 Hz, 3H), 0.57 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.9, 153.0, 151.6, 141.2, 136.7, 135.8, 132.0, 129.5 (2), 129.0 (2), 128.4 (2), 127.4 (2), 127.2 (2), 77.2, 48.0, 34.0, 33.8, 8.3, 8.0. HREIMS calcd for $C_{23}H_{24}O_3$ 348.1725, found 348.1738.

4.1.20. (5*Z*)-2-Hydroxy-5-(2-hydroxy-2-ethylbutylidene)-3-methyl-4-(5-methylfuran-2-yl)cyclopent-2-enone 31. Isolated as a clear oil (77 mg, 48% yield). IR (neat): 3312, 1676, 1482 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.43 (d, *J*=1.8 Hz, 1H), 6.05 (d, *J*=3.0 Hz, 1H), 5.86 (dt, *J*=3.0, 0.9 Hz, 1H), 4.69 (bs, 1H), 4.22 (bs, 1H), 2.20 (d, *J*=0.9 Hz, 3H), 1.95 (s, 3H), 1.41–1.72 (m, 4H), 1.11 (t, *J*=7.4 Hz, 3H), 0.80 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.9, 154.0, 152.1, 151.8, 150.7, 139.2, 118.1, 106.6, 104.3, 55.9, 46.2, 38.0, 33.4, 13.6, 12.7, 8.1, 8.0. HREIMS calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1522.

4.1.21. (5*Z*)-2-Hydroxy-5-((1-hydroxycyclohexyl)methylene)-3,4-dimethylcyclopent-2-enone 32. Isolated as a colorless oil (123 mg, 56% yield). IR (film): 3300, 2932, 2855, 1659, 1613, 1446, 1403, 1350 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ=6.64 (bs, 1H), 6.14 (bs, 1H), 5.89 (s, 1H), 3.24–3.16 (m, 1H), 3.14–3.06 (m, 1H), 2.42–2.30 (m, 1H), 2.08–1.90 (m, 3H), 1.52 (s, 3H), 1.50–1.38 (m, 3H), 1.18–1.15 (m, 2H), 0.69 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.3, 150.8, 148.9, 144.2, 136.6, 71.7, 38.9, 37.9, 37.8, 25.6, 25.4, 22.3, 17.8, 12.0. HREIMS calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1440.

4.1.22. (5*Z*)-4-Ethyl-2-hydroxy-5-((1-hydroxycyclohexyl)methylene)-3-methylcyclopent-2-enone 33. Isolated as a clear oil (107 mg, 64% yield). IR (film): 3329 (br), 2933, 1753, 1659, 1612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.76 (s, 1H), 5.92 (d, *J*=0.9 Hz, 1H), 2.52 (m, 1H), 1.93–2.06 (m, 4H), 1.54 (d, *J*=1.5 Hz, 3H), 1.53–1.20 (m, 8H), 0.41 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.1, 152.8, 147.9, 141.8, 134.2, 71.8, 43.7, 38.1, 37.9, 25.9, 22.9, 22.3 (2), 11.5, 7.3. HREIMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1600.

4.1.23. (3*Z*)-3a,4,5,6-Tetrahydro-1-hydroxy-3-((1-hydroxycyclohexyl)methylene)-1*H*-inden-2(4*H*)-one 34. Isolated as a white crystalline solid (157 mg, 60% yield): mp 281–282 °C. IR (neat): 3300, 2932, 2855, 1659, 1613, 1446, 1403, 1350 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.23 (d, *J*=3.0 Hz, 1H), 5.70 (bs, 1H), 3.05–2.92 (m, 1H), 2.83 (dd, *J*=12.0, 5.4 Hz, 1H), 2.26–1.05 (m, 17H), 1.05 (qd, *J*=12.6, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.7, 148.6, 147.9, 146.2, 135.3, 71.8, 41.1, 37.9 (2), 33.0, 25.6, 25.4 (2), 25.1, 22.3 (2). MS: *m/z* (%)=262 (M^+, 100), 244 (56), 150 (79). HREIMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1572.

4.1.24. (1*Z*)-1,2,4,5,6,7,8,8a-Octahydro-1-((1-hydroxycyclohexyl)methylene)-2-oxoazulen-3-yl benzoate 35. Isolated as a clear oil (88 mg, 46% yield). IR (film): 3442 (br), 2931, 1745, 1681, 1633, 707 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ=8.19 (d, *J*=8.3 Hz, 2H), 7.30–6.95 (m, 3H), 6.72 (bs, 1H), 6.25 (s, 1H), 2.67 (d, *J*=7.5 Hz, 1H), 2.37–2.16 (m, 2H), 2.10–1.90 (m, 4H), 1.74–0.80 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=188.8, 164.5, 163.0, 150.8, 147.4, 139.6, 136.2, 133.6, 132.9, 130.2, 128.5, 126.0, 71.3, 45.1, 38.1, 37.9, 34.6, 30.2, 29.5, 28.4, 25.9, 25.2, 22.2, 20.5. HREIMS calcd for $C_{24}H_{28}O_4$ 380.1988, found 380.1961.

4.1.25. (5*Z*)-2-Hydroxy-5-((1-hydroxycyclohexyl)methylene)-3-methyl-4-(5-methylfuran-2-yl)cyclopent-2-enone 37. Isolated as a clear oil (143 mg, 64% yield). IR (film): 3316, 1678 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=6.15 (d, *J*=1.8 Hz, 1H), 6.02 (d, *J*=3.0 Hz, 1H), 5.88 (dt, *J*=3.0,

0.9 Hz, 1H), 5.40 (bs, 1H), 4.31 (d, J=1.8 Hz, 1H), 2.23 (d, J=0.8 Hz, 3H), 1.96 (s, 3H), 1.82–1.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.2, 153.4, 152.1, 151.4, 150.2, 138.7, 118.2, 108.0, 106.1, 57.0, 43.4, 33.4, 25.3, 25.2, 20.9, 18.5, 13.2, 11.7. HREIMS calcd for $C_{18}H_{22}O_4$ 302.1518 found 302.1537.

4.1.26. (5*Z*)-2-Hydroxy-5-((1-hydroxycyclododecyl)-methylene)-3,4-dimethylcyclopent-2-enone 38. Isolated as a white crystalline solid (198 mg, 62% yield): mp 149–151 °C. IR (film): 3340 (br), 2930, 2860, 1680, 1660, 1615, 1110 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): δ=6.80 (s, 1H), 6.50 (bs, 1H), 5.96 (bs, 1H), 2.42 (q, J=7.0 Hz, 1H), 2.05–1.80 (m, 4H), 1.57 (d, J=0.6 Hz, 3H), 1.50–1.30 (m, 18H), 0.75 (d, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ= 190.3, 151.6, 148.6, 143.1, 136.2, 75.2, 38.6, 35.4, 35.3, 26.8, 26.4, 22.8, 22.3, 20.3, 20.1, 17.3, 11.3. HREIMS calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2390.

4.1.27. (3*Z*)-3a,4,5,6-Tetrahydro-1-hydroxy-3-((1-hydroxycyclododecyl)methylene)-1*H*-inden-2(4*H*)-one 39. Isolated as a white crystalline solid. (119 mg, 58% yield): mp 154–156 °C. IR (neat): 3310, 2960, 1714, 1665, 1610, 1457, 1414, 1359 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.39 (bs, 1H), 6.19 (s, 1H), 3.05–2.90 (m, 1H), 2.81 (dd, J=11.7, 5.4 Hz, 1H), 2.24–0.80 (m, 29H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.7, 148.8, 147.9, 146.2, 134.9, 75.4, 41.2, 35.1, 35.0, 33.1, 26.6, 26.3, 25.4 (2), 25.1 (2), 22.7 (2), 22.3 (2), 20.2, 19.9. MS: m/z (%)=346 (M^+, 100), 328 (51), 150 (86). HREIMS calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2487.

4.1.28. (3*Z*)-3a,4,5,6,7,8-Hexahydro-1-hydroxy-3-((1-hydroxycyclododecyl)methylene)azulen-2(1*H*)-one 40. Isolated as a white crystalline solid (120 mg, 67% yield): mp 160–162 °C. IR (neat): 3345, 2927, 2850, 1667, 1610, 1470, 1419 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.43 (bs, 1H), 6.24 (s, 1H), 5.65 (bs, 1H), 3.14 (d, J=9.9 Hz, 1H), 2.82–2.58 (m, 2H), 2.08 (d, J=11.7 Hz, 1H), 2.00–1.71 (m, 5H), 1.70–1.57 (m, 3H) 1.50–1.20 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.5, 150.2, 149.9, 149.1, 135.5, 75.1, 44.3, 35.1, 34.9, 34.8 (2), 30.6, 29.7, 28.3, 26.4 (2), 26.0, 25.6, 22.5 (2), 22.0, 19.9, 19.8. HREIMS calcd for $C_{23}H_{36}O_3$ 360.2664, found 360.2700.

4.1.29. (5*Z*)-2-Hydroxy-5-((1-hydroxycyclododecyl)-methylene)-3,4-diphenylcyclopent-2-enone 41. Isolated as a yellow crystalline solid (106 mg, 66% yield): mp 200–202 °C. IR (film): 3417 (br), 2939, 1665, 1405 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.90–7.76 (m, 2H), 7.40–7.10 (m, 8H), 6.79 (bs, 1H), 6.25 (bs, 1H), 6.08 (s, 1H), 4.73 (s, 1H), 1.90–0.80 (m, 22H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.5, 153.6, 151.6, 141.0, 135.0, 135.1, 132.1, 129.5 (2), 129.0 (2), 128.5 (2), 127.4 (2), 127.2 (2), 75.5, 47.8, 34.8, 34.7, 26.3, 26.3, 26.0, 22.4 (2), 22.0, 21.9, 19.5 (2). HREIMS calcd for $C_{30}H_{36}O_3$ 444.2664, found 444.2687.

4.1.30. (5*Z*)-5-((*tert*-Butyldimethylsilyl)methylene)-2-hydroxy-3,4-diphenylcyclopent-2-enone 44. A solution of allenyllithium **2** was prepared in 3 mL THF at −78 °C from 44 mg (0.44 mmol) of allene and 155 μL *n*-BuLi (2.91 M in hexanes, 0.45 mmol). After 45 min a solution of amide **11** (106 mg, 0.36 mmol) in 2 mL THF was added at −78 °C via cannula. After 10 min at −78 °C, the reaction mixture was warmed from −78 to −30 °C over 30 min and stirred further for 30 min at −30 °C. *sec*-BuLi (420 μL, 1.35 M in cyclohexane, 0.57 mmol) was added dropwise at −78 °C. After 45 min, a solution of freshly sublimed *tert*-butyldimethylsilyl chloride (218 mg, 1.45 mmol) in 2 mL THF was added at −78 °C via cannula. The reaction mixture was warmed from −78 to −30 °C, stirred further for 1.5 h at −30 °C; then quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in EtOH (7 mL). After 10 min, it was neutralized with pH 7 buffer, and extracted with EtOAc (3×). The combined organic extracts were washed with brine (2×) and dried over $MgSO_4$. Purification by flash column chromatography on silica (1% EtOAc in hexanes) gave cyclopentenone **44** as a yellow crystalline solid (107 mg, 79% yield): mp 136–138 °C.

IR (film): 3272 (br), 2927, 1668, 1398 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.84–7.74 (m, 2H), 7.40–7.10 (m, 8H), 6.18 (s, 1H), 4.76 (s, 1H), 0.83 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.2, 152.1, 151.8, 141.6, 140.9, 133.9, 132.6, 129.4 (2), 128.8 (2), 128.5 (2), 128.4 (2), 127.5 (2), 49.4, 26.4 (3), 17.2, −5.6, −5.9. MS: m/z (%)=361 (M^+–CH_3, 3), 343 (1), 319 (100). HREIMS calcd for $C_{24}H_{28}O_2Si$ (M^+–CH_3) 361.1624, found 361.1604.

Compounds **42**, **43** and **45** were prepared according to the general procedure described above for **44**.

4.1.31. (3*Z*)-3-((*tert*-Butyldimethylsilyl)methylene)-3a,4,5,6-tetrahydro-1-hydroxy-1*H*-inden-2(4*H*)-one 42. Isolated as a white crystalline solid (140 mg, 50% yield): mp 118–121 °C. IR (film): 3326 (br), 2930, 2855, 1686, 1657, 1607, 1401, 1250, 1087, 1070, 860, 825, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.16 (d, J=0.9 Hz, 1H), 6.06 (bs, 1H), 2.98 (dm, J=14.2 Hz, 1H), 2.82 (dd, J=11.8, 5.3 Hz, 1H), 2.27–2.21 (m, 1H), 2.11–1.86 (m, 3H), 1.48 (qt, J=13.2, 3.0 Hz, 1H), 1.29 (qt, J=12.0, 3.6 Hz, 1H), 1.01 (qd, J=9.6, 3.0 Hz, 1H), 0.92 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.8, 152.3, 148.0, 143.7, 135.7, 42.3, 32.6, 26.4 (3), 25.3, 25.1, 24.9, 17.0, −5.8, −5.9. MS: m/z (%)=221 (M^+–C_4H_9, 100), 75 (23). HREIMS calcd for $C_{16}H_{26}O_2Si$ (–C_4H_9) 221.0998, found 221.0999.

4.1.32. (3*Z*)-3-((*tert*-Butyldimethylsilyl)methylene)-3a,4,5,6,7,8-hexahydro-1-hydroxyazulen-2(1*H*)-one 43. Isolated as a white crystalline solid (86 mg, 65% yield): mp 128–133 °C. IR (film): 3339, 2923, 1671, 1601, 1407, 825 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): δ=6.83 (s, 1H), 6.14 (s, 1H), 2.73–2.69 (m, 1H), 2.54–2.49 (m, 2H), 1.92–1.82 (m, 1H), 1.62–1.40 (m, 3H), 1.24–1.14 (m, 2H), 1.12 (s, 9H), 1.00–0.80 (m, 2H), 0.51 (s, 3H), 0.50 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ=189.6, 154.3, 151.9, 148.7, 134.9, 45.5, 35.1, 30.7, 30.1, 28.4, 26.7 (3), 25.8, 17.4, −5.3 (2). HREIMS calcd for $C_{17}H_{28}O_2Si$ 292.18586, found 292.1875.

4.1.33. (5*Z*)-5-((*tert*-Butyldimethylsilyl)methylene)-2-hydroxy-3-methyl-4-(5-methylfuran-2-yl)cyclopent-2-enone 45. Isolated as an amorphous solid (95 mg, 75% yield): mp 140–142 °C. IR (film): 3400, 1680, 1410 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.21 (d, J=1.2 Hz, 1H),

5.98 (d, J=3.0 Hz, 1H), 5.87 (dt, J=3.0, 1.2 Hz, 1H), 5.51 (s, 1H), 4.23 (bs, 1H), 2.22 (d, J=0.9 Hz, 3H), 1.93 (d, J=1.2 Hz, 3H), 0.83 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.3, 151.9, 151.8, 151.0, 149.0, 138.2, 107.9, 106.1, 94.7, 45.9, 26.3 (3), 17.2, 13.5, 12.1, −5.6, −5.8. HREIMS calcd for $C_{18}H_{26}O_3Si$ 318.1651, found 318.1642.

4.1.34. (1*Z*)-1,2,4,5,6,7,8,8a-Octahydro-1-((triisopropylsilyl)methylene)-2-oxoazulen-3-yl benzoate 48. To a solution of methoxymethyl allene ether (76 mg, 0.76 mmol) in 2 mL of THF at −78 °C was added *n*-BuLi (0.31 mL, 2.49 M in hexanes, 0.78 mmol). After 30 min, a solution of amide **10** (99 mg, 0.47 mmol) in 2 mL THF was added at −78 °C via cannula and the reaction mixture was allowed to warm from −78 to −30 °C over 1 h, added with *sec*-BuLi (0.57 mL, 1.68 M in cyclohexane, 0.95 mmol) and was stirred at −78 °C for an additional 30 min. TIPSCl (0.30 mL, 1.40 mmol) in 1 mL THF was then added at −78 °C via cannula and the reaction was allowed to warm from −78 to −30 °C over 1 h, was quenched with 5% HCl in EtOH, allowed to warm to rt over 20–30 min and was then neutralized with pH 7 buffer. The mixture was extracted with EtOAc (3×) and the combined organic extracts were washed with brine, dried over $MgSO_4$. The crude mixture was dissolved into 2 mL of DCM and was followed by the addition of Hünig's base (0.25 mL, 1.42 mmol). The mixture was cooled to 0 °C, added with benzoyl chloride (0.06 mL, 0.52 mmol) dropwise, stirred at rt for 1 h, was quenched with $NaHCO_3$(aq), washed with brine and was isolated via flash column chromatography on silica gel (1% EtOAc in hexanes) to yield a pale yellow oil (112 mg, 71% yield): R_f=0.39 (3% EtOAc in hexanes).

IR (film): 2929, 1747, 1702, 1608, 1257, 882, 706 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): δ=8.13 (d, J=8.1 Hz, 2H), 7.13–6.95 (m, 3H), 6.10 (s, 1H), 2.88 (brd, J=9.0 Hz, 1H), 2.36–2.28 (m, 2H), 1.99–1.89 (m, 1H), 1.70–1.23 (m, 6H), 1.23–1.14 (m, 20H), 1.14–0.84 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6): δ=186.7, 163.0, 162.0, 154.6, 148.2, 133.4, 133.3, 130.5, 129.3, 128.6, 46.7, 35.1, 30.4, 29.7, 28.3, 25.5, 19.5, 12.6. HREIMS calcd for $C_{27}H_{38}O_3Si$ (M^+ − C_3H_8) 395.2042, found 395.2040.

Compounds **46**, **47**, **49** and **50** were prepared according to the general procedure described above for **48**.

4.1.35. (5*Z*)-4-Ethyl-2-hydroxy-5-((triisopropylsilyl)methylene)-3-methylcyclopent-2-enone 46. Isolated as a white crystalline solid (150 mg, 68% yield): mp 83–85 °C. IR (neat): 3316 (br), 2939, 2864, 1684, 1656, 1606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.08 (d, J=1.2 Hz, 1H), 5.98 (s, 1H), 3.16 (m, 1H), 1.95 (d, J=1.2 Hz, 3H), 1.71–1.92 (m, 2H), 1.43 (m, 2H), 1.04[†] (d, J=7.4 Hz, 9H), 1.04 (d, J=7.4 Hz, 9H), 0.64 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.7, 151.7 (2), 139.4, 133.9, 45.4, 22.7, 19.1 (2),[†] 12.3, 11.5, 7.7. HREIMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1590.

4.1.36. (3*Z*)-3a,4,5,6-Tetrahydro-1-hydroxy-3-((triisopropylsilyl)methylene)-1*H*-inden-2(4*H*)-one 47. Isolated as a white amorphous solid (142 mg, 50% yield): mp 118–121 °C. IR (neat): 3373 (br), 2934, 1681, 1402 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.07 (d, J=0.9 Hz, 1H), 5.70 (bs, 1H), 3.00–2.94 (m, 1H), 2.87 (dd, J=11.7, 5.5 Hz, 1H), 2.28 (m, 1H), 2.09 (ddd, J=12.7, 5.5, 1.5 Hz, 1H), 1.98–1.86 (m, 2H), 1.53–1.47 (m, 1H), 1.45–1.36 (m, 3H), 1.34–1.25 (m, 2H), 1.05 (d, J=3.3 Hz, 12H), 1.02 (d, J=3.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.6, 153.2, 147.9, 143.0, 134.3, 42.8, 33.2, 25.5, 25.4, 25.1, 19.3, 12.4. MS *m/z*: 277 (M^+, –C_3H_7, 100), 145 (14), 117 (11), 115 (10), 74 (10), 68 (3). HREIMS calcd for $C_{19}H_{32}O_2Si$ (M^+–C_3H_7) 277.1624, found 277.1618.

4.1.37. (5*Z*)-2-Hydroxy-5-((triisopropylsilyl)methylene)-3,4-diphenylcyclopent-2-enone 49. Isolated as a low melting solid (118 mg, 76% yield). IR (film): 3273 (br), 2948, 1667, 1402 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.96–7.88 (m, 2H), 7.40–7.10 (m, 8H), 6.10 (bs, 1H), 6.05 (s, 1H), 4.83 (s, 1H), 1.56–1.36 (m, 3H), 1.20–0.90 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.6, 152.9, 141.9, 139.9, 134.7, 132.7, 129.4 (2), 129.0 (2), 128.7 (2), 128.3 (2), 127.3 (2), 126.8, 49.6, 18.5 (6), 17.6 (3). HREIMS calcd $C_{24}H_{27}O_2Si$ (M^+–C_3H_8) 375.1780, found 375.1761.

4.1.38. (5*Z*)-2-Hydroxy-5-((triisopropylsilyl)methylene)-3-methyl-4-(5-methylfuran-2-yl)cyclopent-2-enone 50. Isolated as a colorless oil (123 mg, 75% yield). IR (neat): 3315, 2935, 1681, 1652 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.10 (d, J=1.5 Hz, 1H), 6.01 (d, J=2.7 Hz, 1H), 5.86 (dt, J=3.0, 0.9 Hz, 1H), 4.75 (bs, 1H), 2.20 (d, J=0.9 Hz, 3H), 1.94 (s, 3H), 1.38 (m, 3H), 1.03–1.89 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.3, 151.9, 151.7, 151.1, 149.6, 137.8, 108.1, 105.9, 94.4, 45.9, 18.9 (6), 17.7 (3), 13.5, 12.8. HREIMS calcd for $C_{21}H_{32}O_3Si$ 360.2121, found 360.2134.

4.1.39. (5*Z*)-5-Ethylidene-2-hydroxy-3,4-dimethyl-4-phenylcyclopent-2-enone 52. To a solution of methoxymethyl allene ether (88 mg, 0.88 mmol) in 2 mL of THF at −78 °C was added *n*-BuLi (0.30 mL, 2.78 M in hexanes, 0.83 mmol). After 20 min, a solution of amide **51** (108 mg, 0.44 mmol) in 1 mL THF was added at −78 °C via syringe and the reaction mixture warmed to −5 °C and maintained for 90 min. The reaction was then recooled to −78 °C, *sec*-BuLi (0.70 mL, 1.33 M in cyclohexane, 0.92 mmol) added and stirred at −78 °C for an additional 20 min. MeI (373 mg, 2.6 mmol) in 3 mL THF was then added at −78 °C via cannula and the reaction stirred at −78 °C for 30 min and −30 °C for 30 min and followed by quench with 5% HCl in EtOH at −5 °C. The reaction mixture was allowed to warm to rt over 7 min and was then neutralized with pH 7 buffer. The mixture was extracted with EtOAc (3×) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified via flash column chromatography on silica gel (10–25% Et_2O in hexanes) to provide **52**

[†] For this substrate the methyl groups of the isopropyl group displayed unusual asymmetry in the ^{1}H NMR at 300 and 500 MHz and the ^{13}C NMR at 125 MHz. For this compound, at these field strengths, there are exactly two types of isopropyl methyls. Thus, in the ^{1}H NMR there are two doublets of equal intensity and in the ^{13}C NMR there are two signals for the methyl carbons. It had been anticipiated that methyl groups on a given isopropyl group would be equivalent and if there was any asymmetry, it would give rise to different types of isopropyl group rather than different types of methyl groups. This, however, was not the case.

(*Z* isomer) as a clear oil and **52** (*E* isomer) as a white crystalline solid (33 mg of *Z* isomer, 26 mg of *E* isomer, 5 mg of a mixture, 64% yield): mp (*E* isomer) 134–136 °C; R_f=0.42 (*Z*), 0.31 (*E*) (25% Et_2O in hexanes).

IR *Z* isomer: (neat) 3310 (br), 2969, 2932, 1676, 1627 cm^{-1}; *E* isomer: (neat) 3292 (br), 2922, 1679, 1630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) *Z* isomer: δ=7.18–7.32 (m, 5H), 5.84 (q, *J*=7.4 Hz, 1H), 2.19 (d, *J*=7.4, 3H), 1.69 (s, 3H), 1.63 (s, 3H); *E* isomer: δ=7.18–7.34 (m, 5H), 6.62 (q, *J*=7.4 Hz, 1H), 5.85 (s, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.48 (d, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *Z* isomer: δ=191.2, 150.6, 143.7, 143.1, 142.8, 136.7, 128.4, 126.5, 126.5, 48.9, 23.2, 14.3, 9.4; *E* isomer: δ=189.8, 149.3, 146.4, 143.5, 142.4, 130.7, 128.4, 126.6 (2), 48.2, 21.2, 13.9, 8.9. HREIMS calcd for $C_{15}H_{16}O_2$ 228.1150 (*E* isomer), found 228.1132.

Acknowledgements

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LIC-KOR promoted formation of conjugated dienes as useful building blocks for palladium-catalyzed syntheses

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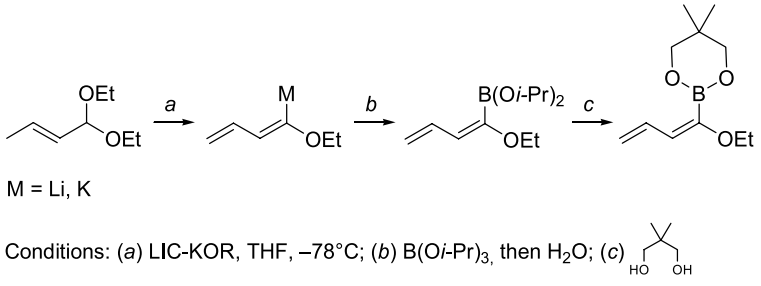
Abstract—It is demonstrated that α,β-unsaturated acetals can be considered a synthetic tool for transforming carbonyl derivatives into cheap and easily accessible starting materials for the construction of various and more complex structures. The lithium–potassium mixed superbase LIC-KOR induces a conjugate elimination reaction that converts α,β-unsaturated acetals into 1*E*-1-alkoxybuta-1,3-dienes. These derivatives can be readily metalated in situ and functionalized by reaction with electrophiles. The results can be grouped in two sections: (1) the palladium-catalyzed cross-coupling reaction between alkoxydienylboronates and tetralone- or isochromanone-derived vinyl triflates; (2) the regio- and stereoselective cross coupling reaction with aryl derivatives in the presence of a palladium catalyst (Heck conditions).

1. Introduction

A few years ago, we reported that in the presence of Schlosser's superbase LIC-KOR[1] (LIC: butyllithium, KOR: potassium *tert*-butoxide), α,β-unsaturated acetals selectively yield 1-alkoxybuta-1,3-dienes.[2] The product derives from a stereoselective conjugate elimination that is initiated by the metalation reaction at the γ-allylic position of the unsaturated substrate. Moreover, butadienyl derivatives can be further functionalized at their α-position by conducting the former elimination reaction in the presence of at least two equivalents of the LIC-KOR base: the excess reagent selectively deprotonates the elimination product at the 1-alkenyl site, giving a nucleophile that can be quenched with various electrophiles, yielding substitution or addition products.[3] By resorting to this procedure, we have described different functionalized unsaturated systems.[4] More recently, the reactivity of α-metalated alkoxydienes in the presence of trialkylboranes[5] and trialkylborates[6] as electrophiles has also been described (Scheme 1). The arylation of α,β-unsaturated carbonyl compounds by an Heck reaction has also been reported.[7]

In this paper we provide the details of our work on two



Scheme 1. Synthesis of trialkylborates starting from α,β-unsaturated acetals, in the presence of LIC-KOR superbase.

Keywords: Unsaturated acetals; Mixed superbases; Pd-catalyzed reactions; Suzuki reaction; Heck reaction; Nazarov reaction.
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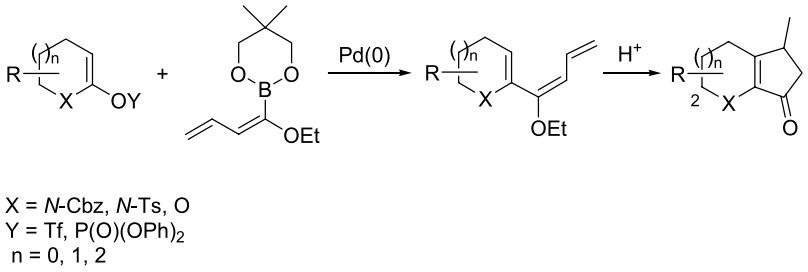


Scheme 2. Pd-catalyzed cross-coupling reaction of lactam- and lactone derived triflates or phosphates with 2-(1-ethoxybuta-1,3-dienyl)-5,5-dimethyl-[1,3,2]-dioxaborinane, and subsequent Amberlyst-15® catalyzed cyclization.

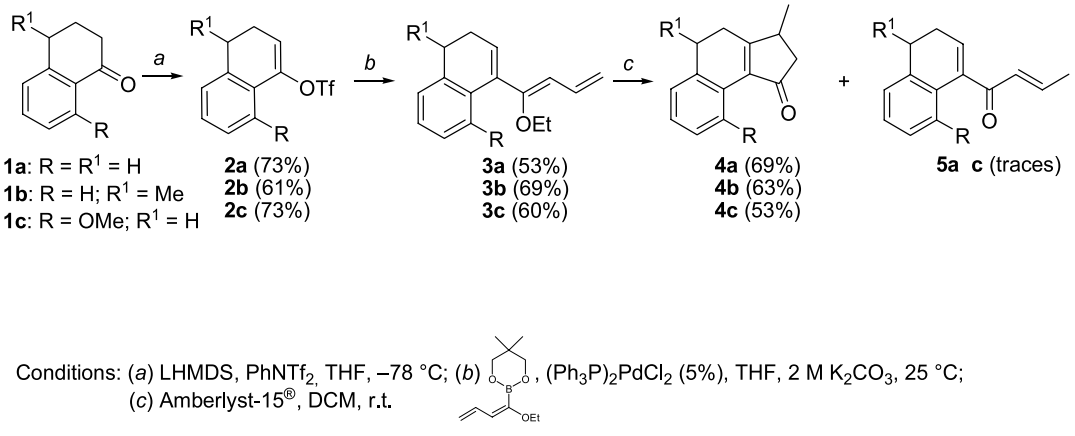
different uses of alkoxydienyl derivatives in synthesis: (1) the Pd-catalyzed cross-coupling reaction with tetralone- or isochromanone-derived vinyl triflates or phosphates, and (2) the Heck coupling with diazonium salts.

1.1. Pd-catalyzed cross-coupling reaction with lactam- and lactone-derived vinyl triflates or phosphates

We have recently found that conjugated ethoxytrienes obtained by the Pd-catalyzed cross-coupling reaction of lactam- and lactone- derived triflates or phosphates with ethoxydienylboronates (Scheme 2) undergo cyclization in the presence of the acidic resin Amberlyst-15® to give byciclic fused [3.3.0], [4.3.0], and [5.3.0] systems.[8] A Nazarov-type electrocyclization can explain the cyclization reaction.[9] This process has been extended here to the synthesis of tricarbocyclic derivatives by exploiting commercially available α-tetralones with different patterns of substitution.

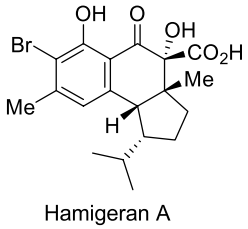
Commercially available α-tetralones **1a–c** (Scheme 3) were converted into the corresponding triflates **2a–c** by treatment with LHMDS at −78 °C and by trapping the enolates with *N*-phenyl triflimide. The triflates thus obtained proved to be stable enough to be purified by flash chromatography and successively coupled with 2-(1-ethoxybuta-1,3-dienyl)-5,5,-dimethyl-[1,3,2]-dioxaborinane.[6] The reaction was performed with $(Ph_3P)_2PdCl_2$ (5%) as a catalyst in THF and 2 M K_2CO_3 as a base at room temperature and was complete in 1 h. Chromatography of the crude reaction mixture afforded pure ethoxytrienes **3a–c** in good yields that were used for the subsequent intramolecular cyclization. In our previous studies we have already shown that hydrolysis conditions strongly affect the reaction outcome. As a matter of fact the mechanism could be driven towards the synthesis of α,β-unsaturated ketone (**5**) or towards the Nazarov adducts (**4**) by choosing the appropriate acidic catalyst and solvent. In 0.02 M HCl MeOH–H_2O as a solvent, the open chain ketone was recovered as the main product and could be successively transformed into the Nazarov adduct by treatment with pure TFA at room temperature, while the acidic sulfonic resin Amberlyst-15® promoted the electrocyclic process. Ethoxytrienes **3a–c** have been hydrolyzed under inert atmosphere using Amberlyst-15® as a catalyst and anhydrous CH_2Cl_2 as a solvent. In all examples products **4a–c** were obtained in good yields, while open chain ketones **5a–c** were merely obtained in traces. In particular, **4b** was recovered as a 1:1 mixture of *cis* and *trans* diastereomers. We were not surprised to find a lack of diastereocontrol in the electrocyclization of **3b**. In our studies on the torquoselectivity of the Nazarov reaction performed on ethoxytrienes in which one double bond is embedded in a heterocyclic structure, we have found that, while substituents in 2- or 4-position of the heterocyclic moiety could affect the diastereoselection, a substituent at position 3 exerted a low remote stereocontrol.[8] In compound **3b** the methyl group in position 3 is too far from the reacting centers to affect the sense of electrocyclic conrotation so that the two faces of the endocyclic double bond are not differentiated and both modes of conrotation are thus possible.[10]

The here described synthetic sequence could be applicable to the construction of new derivatives structurally connected



Scheme 3. Pd-catalyzed cross-coupling reaction of α-tetralones derived triflates with 2-(1-ethoxybuta-1,3-dienyl)-5,5,-dimethyl-[1,3,2]-dioxaborinane, and subsequent Amberlyst-15® catalyzed cyclization.

to some attractive natural products, in particular to biologically active substances endowed with a ring system in which a substituted aromatic nucleus is fused to a hydrindane framework,[11] as in the core of the hamigerans (Fig. 1). Hamigerans are a small group natural products that were isolated from the marine sponge *Hamigera tarangaensis*.[12] The biological activity profile of hamigerans is quite interesting: in particular, for hamigeran B3 has been found a 100% in vitro inhibition against both herpes and polio viruses.[13] The absolute configuration of hamigeran A1 has been determined by X-ray crystallographic analysis.[14] Because of their biological properties and novel structural features, the synthesis of hamigerans represents an important synthetic target.[15] For the synthesis of an analogue of hamigerans containing an heteroatom in the [4.3.0] bicyclic moiety, the same synthetic sequence was applied to the aromatic lactone 3-isochroman-2-one **1d** (Scheme 4). Triflate **2d** was coupled with 2-(1-ethoxybuta-1,3-dienyl)-5,5,-dimethyl-[1,3,2]-dioxaborinane under the usual conditions [$(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C] giving triene **3d**. The hydrolysis of **3d** with Amberlyst-15® afforded cyclic ketone **4d** along with the open chain isomer **5d** that, in this case, was unexpectedly isolated in significant yield. However, it could be easily converted into **4d** by treatment with pure TFA at 25 °C.



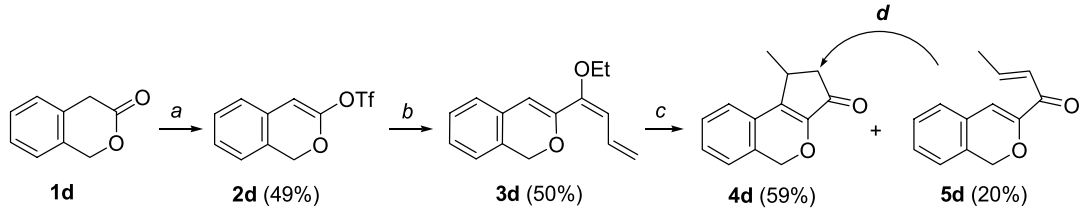
Hamigeran A

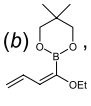
Figure 1.

1.2. Heck coupling with diazonium salts

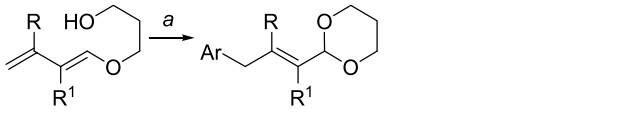
Substituted dienes and other unsaturated structures are very attractive as precursors of dyes, UV screens, and drugs.[16] Although arylation of two-carbon vinyl fragments might sometimes result in scarcely regioselective reactions,[17,18] highly regioselective α-arylation and α-vinylation procedures have been reported under specific experimental conditions.[19] In particular, 100% regioselective α-functionalization of vinyl ethers can be achieved by favoring the coordination of the Pd complex to the carbon–carbon double bond via dissociation of the anion ligand. Such a mechanism can be promoted by using triflate as a leaving group or adding a sequestering agent of halide anions.[20] Otherwise, a mixture of isomers is obtained when the coordination-insertion process proceeds via dissociation of one neutral ligand. Moreover, regioselective β-arylation of vinyl ethers has been achieved when the olefinic substrate contains groups that control the palladium catalyzed reaction through chelation. Such a procedure has been reported as a useful access to arylethylamines or arylacetic acids of significant pharmaceutical value.[21] On the other hand, the Pd-catalyzed arylation of conjugate dienes would be expected to produce arylated dienes. However, some differences and perhaps complications could be expected since π-allylic palladium species are involved in the reactions. Particularly stable π-allylic complexes in the presence of tertiary amines are formed, while the use of secondary amines leads to mixtures of polyenes and allylic amines.[22] Thus, low yields and/or low selectivity are encountered when the diene does not have a carbonyl or phenyl group and the synthesis of linear conjugated polyenes remains to be improved. Recently we reported a regioselective γ-arylation of α,β-unsaturated carbonyl compounds from aryl iodides and alkoxydienes by an Heck reaction.[7] We observed the stereoselective formation of γ-arylated α,β-unsaturated acetals in good yields working in DMSO at 80 °C, and using K_2CO_3 as a base and $Pd(OAc)_2$ as a catalyst (Scheme 5(A)). A possible mechanism has been also suggested: first, the arylpalladium intermediate adds to the terminal double bond of the diene, then this intermediate arranges to the π-allylic complex and an iodide ion-acetate ligand exchange takes place. Finally, attack of the hydroxy group upon the complex displaces the palladium complex and gives the cyclic acetal.

In this paper we wish to report the results obtained studying the Pd-catalyzed cross coupling reaction of 1-alkoxy-1,3-butadienes with arendiazonium salts. The Heck reaction with these substrates is mild and fast. Moreover, the use of these compounds is synthetically more convenient than the use of aryl halides, since many of them, especially iodides, are prepared from diazonium salts. Interestingly, no



Conditions: (*a*) LHMDS, $PhNTf_2$, THF, –78 °C; (*b*)  , $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C;
(*c*) Amberlyst-15®, DCM, r.t.
(*d*) TFA

Scheme 4. Pd-catalyzed cross-coupling reaction of 3-isochroman-2-one derived triflate with 2-(1-ethoxybuta-1,3-dienyl)-5,5,-dimethyl-[1,3,2]-dioxaborinane, and subsequent Amberlyst-15® catalyzed cyclization.



6a: R = R^1 = H
6b: R = Me; R^1 = H
6c: R = H; R^1 = Me

7a: R = H, R^1 = H, Ar = *p*-$MeOC_6H_4$ (30%)
7b: R = H, R^1 = H, Ar = *m*-$MeOC_6H_4$ (37%)
7c: R = H, R^1 = H, Ar = *p*-IC_6H_4 (34%)
7d: R = H, R^1 = H, Ar = *p*-ClC_6H_4 (34%)
7e: R = Me, R^1 = H, Ar = *p*-IC_6H_4 (27%)
7f: R = Me, R^1 = H, Ar = *p*-ClC_6H_4 (25%)
7g: R = H, R^1 =Me, Ar = *p*-IC_6H_4 (30%)

A: (*a*) ArI, K_2CO_3, 80 °C, AcO_2Pd, DMSO

B: (a) ArN_2^+ BF_4^-, AcONa, 25 °C, $Pd(OAc)_2$, MeCN

Scheme 5. Heck reaction on 1-(3-hydropropoxy)buta-1,3-dienes.

difference in reactivity in relation to the electronic nature of the diazonium compound is observed.[23] Moreover it seems that for this type of Heck reaction, contrary to the reactions of aryl chlorides or bromides, the insertion of the palladium catalyst is not the rate determining step.[24] Unfortunately, the process is rather inefficient as the loading of Pd precatalyst required is usually no less than 1–2 mol%. Most probably this is associated with an inefficient preactivation of the catalyst.

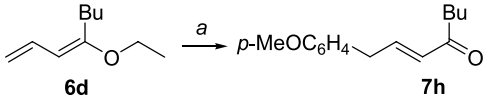
The use of bases and strongly coordinating ligands in reactions with arendiazonium salts is usually detrimental as a consequence of dediazotation:[25] unfortunately, basic conditions are required since the starting alkoxydienes and products are acid sensitive and the formation of acids caused by β-H-elimination can be problematic.[26] In fact, some tests carried out without addition of base did not give the expected arylated compound in appreciable amount.

The results of the cross coupling reaction are reported in Scheme 5(B). These data have been obtained working in anhydrous MeCN (alcoholic solvents turned out inadequate) at room temperature in the presence of NaOAc as a base and of $Pd(OAc)_2$ as a catalyst.

First of all, we focused our attention on halo-substituted diazonium salts because of the interest towards differential Pd-catalyzed reaction in the synthesis of unsymmetrical substituted teraryls and oligoarylenesvinylenes considering their medicinal and NLO properties.[27]

The reactions are regio- and stereoselective, and the aryl group adds, as expected, to the unsubstituted CH_2 site of the conjugate system. Unfortunately, the coupling yields are modest: probably they are affected by the stability of whether the diazonium salts or the dienes under the reaction conditions.

When the cross-coupling reaction was carried out on (*E*)-4-ethoxyocta-1,3-diene **6d** the corresponding (2*E*)-γ-arylated α,β-unsaturated ketone **7h** was recovered (Scheme 6). The formation of the conjugate ketone can be most likely attributed to the presence of water molecules that may be present in the diazonium salt or in the base.



6d **7h**

Conditions: (*a*) *p*-$MeOC_6H_4N_2^+$ BF_4^-, AcONa, r.t., $Pd(OAc)_2$, MeCN

Scheme 6. Heck reaction on (*E*)-4-ethoxyocta-1,3-diene.

2. Conclusions

In summary, we have developed new synthetic routes that allow the acetal group of α,β-unsaturated acetals to be considered not simply a protective function but also a useful synthetic tool. In particular, we have shown that Suzuki coupling of ethoxydienylboronates with vinyl triflates or phosphates derived from aromatic ketones or lactones is a tactically suitable strategy for the synthesis of cyclopenta-fused polycyclic systems that are present in many natural products. Moreover, when 1-alkoxybuta-1,3-dienes cross couple under Heck conditions with arendiazonium derivatives, the final outcome of the process formally corresponds to the direct γ-arylation of starting α,β-unsaturated acetals.

3. Experimental

3.1. General

Flasks and all equipments used for the generation and reaction of moisture-sensitive compounds are flame dried under Argon. Anhydrous CH_3CN was purchased by Fluka. All aromatic substrates, palladium(II) acetate, palladium bistriphenylphosphinobichloride, NaOAc and K_2CO_3 are commercially available and are used as received. All the acetals and ethoxydienes were prepared as previously described.[4] The arenediazonium tetrafluoborates were prepared from commercial aromatic amines according to reported procedures.[28] Purification of products was carried out by preparative column chromatography on Merck Silica gel 60 with light petroleum ether (distillation range 40–60 °C)-Et_2O as eluent. ^{1}H NMR spectra were recorded at 200 or 400 MHz in $CDCl_3$, using TMS as internal standard. Coupling constants (*J*) are given in Hz and coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), br s (broad singlet). ^{13}C NMR spectra are recorded at 50 and 100.4 MHz in $CDCl_3$, and chemical shifts are determined relative to the residual solvent peak (77.36). GC–MS spectra are obtained on a mass selective detector HP 5970 B instrument operating at an ionizing voltage of 70 eV connected to a HP 5890 GC, cross linked methyl silicone capillary column (25 m×0.2 mm×0.33 μm film thickness).

3.1.1. Trifluoromethanesulfonic acid 3,4-dihydro-naphthalen-1-yl ester (2a). Typical procedure. To a solution of KHMDS (8 mL of a 0.5 M solution in toluene, 4 mmol) in THF (12 mL), cooled at −78 °C and under nitrogen atmosphere, was added a solution of 3,4-dihydro-2*H*-naphthalen-1-one (440 mg, 3 mmol) in THF (4 mL) and the resulting mixture was stirred for 1.5 h. Afterward a solution of $PhNTf_2$ (964 mg, 2.7 mmol) in THF (2 mL) was quickly added, leaving under stirring for 1 h at −78 °C

before allowing the temperature to rise to 0 °C. Then, a 10% NaOH solution (20 mL) was added, the mixture was extracted with Et_2O (3×20 mL), washed with H_2O (2× 10 mL), and dried (K_2CO_3). After filtration and evaporation of the solvent, crude vinyl triflate **1** was obtained as a yellowish oil and purified by flash chromatography (petroleum ether: Et_2O 4:1, 610 mg, 73%): 200 MHz ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3 (m, 4H), 6.05 (t, J=2.9 Hz, 1H), 2.90 (t, J=6.5 Hz, 2H), 2.5 (m, 2H).

3.1.2. Trifluoromethanesulfonic acid 4-methyl-3,4-dihydro-naphthalen-1-yl ester (2b). Flash chromatography (Et_2O–petroleum ether 1:4, 0.5% Et_3N) gave pure **2b** (531 mg, 61%, R_f 0.75) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.2 (m, 4H), 6.01 (t, J=2.9 Hz, 1H), 3.01 (hex, J=6.5 Hz, 1H), 2.75 (ddd, J=13.0, 6.5, 2.9 Hz, 1H), 2.29 (dd, J=13.0, 2.9 Hz, 1H), 1.35 (d, J=6.5 Hz, 3H).

3.1.3. Trifluoromethanesulfonic acid 5-methoxy-3,4-dihydro-naphthalen-1-yl ester (2c). Flash chromatography (Et_2O–petroleum ether 1:4, 0.5% Et_3N) gave pure **2c** (678 mg, 73%, R_f 0.76) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (t, J=5.9 Hz, 1H), 7.18 (d, J= 5.9 Hz, 1H), 6.97 (d, J=5.9 Hz, 1H), 6.04 (t, J=2.9 Hz, 1H), 3.95 (s, 3H), 2.95 (t, J=5.5 Hz, 2H), 2.65 (m, 1H), 2.5 (m, 1H).

3.1.4. Trifluoromethanesulfonic acid 1H-isochromen-3-yl ester (2d). Flash chromatography (Et_2O–petroleum ether 3:7, 0.5% Et_3N) gave pure **2d** (414 mg, 49%, R_f 0.74) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.2 (m, 4H), 5.81 (s, 1H), 5.37 (s, 2H).

3.1.5. *E*-4-(1-Ethoxy-buta-1,3-dienyl)-1,2-dihydro-naphthalene (3a). Typical procedure. To a solution of crude **2a** (417 mg, 1.5 mmol) in THF (4 mL) were added, under a nitrogen atmosphere, $(Ph_3P)_2PdCl_2$ (57 mg, 0.075 mmol), 2-(1-ethoxybuta-1,3-dienyl)-5,5,-dimethyl-[1,3,2]-dioxaborinane (315 mg, 1.5 mmol), and a 2 M aqueous K_2CO_3 solution (1.5 mL). The mixture was stirred for 2.5 h at 25 °C. H_2O (10 mL) was then added, the mixture extracted with diethyl ether (3×20 mL) and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow oil that was purified by flash chromatography (petroleum ether–Et_2O 4:1, 0.5% Et_3N, R_f 0.7) to give **4a** (180 mg, 53%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.09 (s, 4H), 6.38 (dt, J=15.0, 10.5 Hz, 1H), 6.10 (t, J=2.9 Hz, 1H), 5.65 (d, J=10.5 Hz, 1H), 5.06 (dd, J=15.0, 1.8 Hz, 1H), 4.81 (dd, J=10.5, 1.8 Hz, 1H), 3.84 (q, J=7.5 Hz, 2H), 2.82 (t, J=6.5 Hz, 2H), 2.42 (m, 2H), 1.27 (t, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.6, 143.6, 137.5, 136.4, 135.4, 134.0, 133.1, 130.4, 129.4, 128.0, 125.8, 119.2, 69.8, 42.6, 29.3, 19.5; MS *m*/*z* 226 (M^+, 100), 197 (35), 181 (37), 115 (23). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.79; H, 8.72.

3.1.6. 4-(1-Ethoxy-buta-1,3-dienyl)-1-methyl-1,2-dihydro-naphthalene (3b). Flash chromatography (Et_2O–petroleum ether 1:9, 0.5% Et_3N) gave pure **3b** (165 mg, 69%, R_f=0.85) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.3 (m, 4H), 6.30 (dt, J=15.0, 10.5 Hz, 1H), 6.06 (t, J=2.9 Hz, 1H), 5.66 (d, J=10.5 Hz, 1H), 5.06 (dd, J=15.0, 1.8 Hz, 1H), 4.81 (dd, J=10.5, 1.8 Hz, 1H), 3.87 (q, J=7.5 Hz, 2H), 2.97 (hex, J=6.5 Hz, 1H), 2.45 (ddd, J=15.0, 6.5, 2.9 Hz, 1H), 2.20 (dd, J=15.0, 2.9 Hz, 1H), 1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.39, 143.20, 130.83, 130.26, 130.13, 129.65, 129.01, 128.90, 128.30, 127.55, 113.92, 108.06, 65.82, 34.08, 33.85, 22.77, 17.93; MS *m*/*z* 240 (M^+, 100), 211 (16), 193 (13), 129 (15). Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.12; H, 8.09.

3.1.7. 4-(1-Ethoxy-buta-1,3-dienyl)-8-methoxy-1,2-dihydro-naphthalene (3c). Flash chromatography (Et_2O–petroleum ether 2:8, 0.5% Et_3N) gave pure **3c** (154 mg, 60%, R_f=0.80) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.01 (t, J=5.5 Hz, 1H), 6.96 (d, J=5.5 Hz, 1H), 6.85 (d, J=5.5 Hz, 1H), 6.72 (dt, J=15.0, 10.5 Hz, 1H), 6.11 (t, J=3.0 Hz, 1H), 5.66 (d, J=10.5 Hz, 1H), 5.09 (dd, J=15.0, 1.8 Hz, 1H), 4.85 (dd, J=10.5, 1.8 Hz, 1H), 3.86 (q, J=7.5 Hz, 2H), 3.84 (s, 3H), 2.83 (t, J=5.2 Hz, 2H), 2.36 (m, 2H), 1.33 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.65, 158.66, 136.84, 136.16, 134.52, 129.17, 127.52, 120.26, 113.82, 112.52, 107.78, 103.31, 67.02, 58.18, 25.14, 21.99, 18.23; MS *m*/*z* 256 (M^+, 100), 225 (22), 211 (32), 199 (20), 165 (23). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.21; H, 7.19.

3.1.8. 3-(1-Ethoxy-buta-1,3-dienyl)-1*H*-isochromene (3d). Flash chromatography (Et_2O–petroleum ether 2:8, 0.5% Et_3N) gave pure **3d** (115 mg, 50%, R_f=0.85) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.2 (m, 5H), 6.34 (s, 1H), 5.68 (d, J=10.5 Hz, 1H), 5.14 (s, 2H), 5.10 (dd, J=15.0, 1.8 Hz, 1H), 4.95 (dd, J=10.5, 1.8 Hz, 1H), 3.88 (q, J=7.5 Hz, 2H), 1.33 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.58, 153.59, 135.73, 133.70, 130.80, 129.58, 127.91, 126.63, 126.35, 117.26, 111.42, 108.59, 71.12, 66.80, 18.23; MS *m*/*z* 228 (M^+, 89), 199 (39), 155 (34), 128 (95), 77 (100). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.41; H, 7.89.

3.1.9. 3-Methyl-2,3,4,5-tetrahydro-cyclopenta[*a*]-naphthalen-1-one (4a). Typical procedure. To a solution of **3a** (180 mg, 0.80 mmol) in anhydrous DCM (7 mL) under argon atmosphere, Amberlyst-15® (2.3 mequiv/g, 18 mg) was added and the resulting mixture was stirred at 25 °C. The reaction was monitored by TLC: after 2 h the resin was filtered off through a short pad of K_2CO_3 and concentrated under vacuum. Crude products were purified by flash chromatography (petroleum ether–Et_2O 1:1, 0.5% Et_3N, R_f 0.4) to give pure **4a** (110 mg, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, J=6.2 Hz, 1H), 7.24 (m, 3H), 2.95 (br s, 3H), 2.81 (dd, J=19.4, 5.5 Hz, 1H), 2.69 (m, 1H), 2.58 (m, 1H), 2.16 (d, J=19.4 Hz, 1H), 1.35 (d, J= 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.60, 178.91, 134.46, 134.17, 129.21, 127.90, 127.57, 126.85, 124.26, 44.85, 35.39, 27.79, 24.80, 18.74; MS *m*/*z* 198 (M^+, 100), 183 (42), 170 (53), 155 (60). Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.21; H, 7.88.

3.1.10. 3,5-Dimethyl-2,3,4,5-tetrahydro-cyclopenta[*a*]-naphthalen-1-one (4b). Flash chromatography (Et_2O–petroleum ether 1:1, 0.5% Et_3N) gave pure **4b** as 1:1 mixture of diastereoisomers. (110 mg, 63%, R_f=0.35) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (d,

J=6.2 Hz, 2H *cis*+*trans*), 7.23 (m, 6H, *cis*+*trans*), 3.1 (m, 2H, *cis*+*trans*), 2.8 (m, 2H, *cis*+*trans*), 2.82 (dd, J=17.9, 5.1 Hz, 1H *trans*), 2.80 (dd, J=18.3, 7.5 Hz, 2H *cis*+*trans*), 2.67 (dd, J=17.9, 5.0 Hz, 1H *cis*), 2.48 (dd, J=17.9, 6.6 Hz, 1H *cis*), 2.33 (dd, J=17.9, 6.0 Hz, 1H *trans*), 2.17 (d, J=18.3 Hz, 2H, *cis*+*trans*), 1.25 (d, J=6.2 Hz, 3H), 1.24 (d, J=6.2 Hz, 3H), 1.23 (d, J=6.2 Hz, 3H), 1.22 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.60, 205.33, 177.72, 177.60, 139.80, 139.62, 128.20, 126.72, 126.62, 126.32, 124.43, 44.90, 44.79, 32.74, 32.68, 32.60, 32.48, 21.68, 20.91, 19.26, 18.51; MS *m/z* 212 (M^+, 97), 197 (47), 184 (22), 155 (100). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.21; H, 7.88.

3.1.11. 6-Methoxy-3-methyl-2,3,4,5-tetrahydro-cyclopenta[*a*]naphthalen-1-one (4c). Flash chromatography (Et_2O–petroleum ether 3:7, 0.5% Et_3N) gave pure **4c** (120 mg, 53%, R_f=0.4) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.21 (d, J=5.5 Hz, 1H), 7.24 (t, J=5.5 Hz, 1H), 6.85 (d, J=5.5 Hz, 1H), 3.83 (s, 3H), 2.95 (m, 3H), 2.78 (dd, J=19.4, 5.5 Hz, 1H), 2.6 (m, 2H), 2.15 (d, J=19.4 Hz, 1H), 1.35 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 205.45, 178.22, 156.09, 127.10, 126.30, 125.51, 116.94, 110.36, 109.65, 55.44, 44.72, 35.19, 24.16, 19.82, 15.22; MS *m/z* 228 (M^+, 100), 200 (40), 185 (34), 115 (28). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.25; H, 7.88.

3.1.12. 3-Methyl-2,3-dihydro-5*H*-cyclopenta[*c*]isochromen-1-one (4d). Flash chromatography (Et_2O–petroleum ether 45:55, 0.5% Et_3N) gave pure **4d** (118 mg, 59%, R_f=0.4) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.3 (m, 4H), 5.32 (d, J=8.5 Hz, 2H), 3.28 (m, 1H), 2.78 (dd, J=19.3, 5.5 Hz, 1H), 2.18 (d, J=19.4 Hz, 1H), 1.37 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.89, 144.44, 128.58, 128.28, 126.70, 126.43, 126.20, 122.70, 120.42, 67.79, 40.44, 25.70, 18.86; MS *m/z* 200 (M^+, 100), 200 (40), 185 (32), 158 (21), 115 (56), 64 (25). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.55; H, 6.04.

3.1.13. 1-(1*H*-Isochromen-3-yl)-but-2-en-1-one (5d). (40 mg, 20%, R_f=0.75) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.2 (m, 4H), 7.17 (dq, J=15.5, 6.5 Hz, 1H), 7.05 (s, 1H), 6.84 (d, J=15.5 Hz, 1H), 5.19 (s, 2H), 1.97 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 185.14, 151.59, 145.00, 129.96, 129.65, 129.35, 128.68, 125.96, 125.84, 124.24, 111.96, 68.94, 18.77; MS *m/z* 200 (M^+, 23), 103 (26), 77(17), 69 (100). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.15; H, 6.84.

3.2. General procedure for the arylation of ethoxydienes (6a–c)

Ethoxydiene (2 mmol) was added to a mixture of the corresponding arendiazonium tetrafluoborate (1 mmol), $Pd(OAc)_2$ (0.05 mmol), K_2CO_3 or NaOAc (1 mmol) in anhydrous CH_3CN (6 mL) degassed with argon for 10 min. The reaction mixture was stirred under argon in a sealed tube for 15–30 min. Samples were periodically taken and tested with β-naphtol. After complete consumption of the starting tetrafluoborate, H_2O (10 mL) was added. All reactions were worked up by extraction with Et_2O (3× 20 mL) and the organic phases were washed with brine (3× 10 mL). The products were purified by column chromatography on SiO_2 deactivated with 1% of Et_3N. Eluent: petroleum ether/Et_2O.

3.2.1. (*E*)-2-[03-(4-Methoxyphenyl)prop-1-enyl]-1,3-dioxane (7a). 70 mg, (30%) as a colorless oil (70/30). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02 (d, J=8.6 Hz, 2H), 6.75 (d, J=8.6 Hz, 2H), 5.97 (dt, J=16.4, 6.9 Hz, 1H), 5.42 (ddt, J=16.4, 5.2, 1.5 Hz, 1H), 4.95 (d, J=5.2 Hz, 1H), 4.05 (m, 2H), 3.77 (m, 5H), 3.28 (d, J=6.9 Hz, 2H), 2.0 (m, 1H), 1.3 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.01, 134.48, 129.66, 127.94, 113.84, 100.86, 66.88, 55.23, 34.48, 25.64; *m/z* (EI, 70 eV rel. Int.) 234 (M^+, 38), 147 (37), 113 (100), 87 (92), 55 (31). ν_{max} (neat)/cm^{-1} 3050, 1650, 1635, 1251, 823, 808. (Found: C, 71.00%; H 7.93%. Calcd for $C_{14}H_{18}O_3$: C, 71.77%; H, 7.74%).

3.2.2. (*E*)-2-[3-(3-Methoxyphenyl)prop-1-enyl]-1,3-dioxane (7b). 86 mg, (37% yield) as a colorless oil (70/30). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (m, 2H), 6.7 (m, 2H), 6.05 (dt, J=16.0, 6.6 Hz, 1H), 5.55 (dm, J=16.0 Hz, 1H), 4.95 (d, J=5.6 Hz, 1H), 4.10 (m, 2H), 3.80 (m, 5H), 3.38 (d, J=6.6 Hz, 2H), 1.5 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.70, 140.89, 133.83, 129.38, 128.33, 121.12, 114.40, 111.58, 100.78, 66.90, 55.14, 38.44, 25.67; *m/z* (EI, 70 eV rel. Int.) 234 (M^+, 21), 158 (38), 147 (17), 113 (100), 83 (23). ν_{max} (neat)/cm^{-1} 3010, 2853, 1599, 1454, 1259, 1078, 993, 773. (Found: C, 71.90%; H 7.02%. Calcd for $C_{14}H_{18}O_3$: C, 71.77%; H, 7.74%).

3.2.3. (*E*)-2-[3-(4-Iodophenyl)prop-1-enyl]-1,3-dioxane (7c). 112 mg, (34% yield) as a colorless oil (70/30). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, J=7.4 Hz, 2H), 6.95 (d, J=7.4 Hz, 2H), 6.05 (dt, J=15.4, 6.2 Hz, 1H), 5.50 (dbd, J=15.4, 6.2 Hz, 1H), 4.95 (d, J=6.2 Hz, 1H), 4.15 (m, 2H), 3.80 (m, 2H), 3.30 (d, J=6.5 Hz, 2H), 2.1 (m, 1H), 1.3 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.20, 137.42, 133.12, 130.79, 128.73, 100.53, 91.30, 66.85, 37.77, 25.61; *m/z* (EI, 70 eV rel. Int.) 330 (M^+, 5), 144 (15), 113 (100), 100 (36), 55 (29). ν_{max} (neat)/cm^{-1} 3050, 2851, 1279, 1078, 930, 800. (Found: C, 47.85%; H 4.99%. Calcd for $C_{13}H_{15}IO_2$: C, 47.29%; H, 4.58%).

3.2.4. (*E*)-2-[3-(4-Chlorophenyl)prop-1-enyl]-1,3-dioxane (7d). 81 mg, (34% yield) as a colorless oil (90/10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, J=7.0 Hz, 2H), 7.05 (d, J=7.0 Hz, 2H), 6.20 (dt, J=14.9, 6.0 Hz, 1H), 5.55 (dbd, J=14.9, 5.8 Hz, 1H), 4.95 (d, J=5.8 Hz, 1H), 4.15 (m, 2H), 3.85 (m, 2H), 3.35 (d, J=6.0 Hz, 2H), 1.6 (m, 1H), 1.3 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.33, 132.05, 130.06, 129.50, 128.67, 128.51, 100.55, 66.88, 37.65, 25.61; *m/z* (EI, 70 eV rel. Int.) 238 (M^+, 56), 180 (46), 145 (100), 115 (50), 68 (40), 55 (50). ν_{max} (neat)/cm^{-1} 3080, 1599, 1259, 1078, 993, 773. (Found: C, 66.05%; H 6.65%. Calcd for $C_{13}H_{15}ClO_2$: C, 65.41%; H, 6.33%).

3.2.5. (*E*)-2-[3-(4-Iodophenyl)-2-methylprop-1-enyl)-5,5-dimethyl-1,3-dioxane (7e). 100 mg, (27% yield) as a colorless oil (90/10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, J=8.0 Hz, 2H), 6.94 (d, J=8.0 Hz, 2H), 5.11 (bd, J=6.3 Hz, 1H), 5.08 (d, J=6.3 Hz, 1H), 3.65 (m, 2H), 3.51 (m, 2H), 3.23 (s, 2H), 1.68 (s, 3H), 1.23 (s, 3H), 0.75 (s, 3H); ^{13}C

NMR (50 MHz, $CDCl_3$) δ 141.44, 139.31, 138.42, 137.98, 137.41, 131.23, 124.27, 98.75, 45.12, 30.02, 22.97, 21.95, 17.03; *m/z* (EI, 70 eV rel. Int.) 372 (M^+, 3), 155 (86), 128 (14), 115 (15), 69 (100). (Found: C, 49.20%; H 5.15%. Calcd for $C_{14}H_{17}IO_2$: C, 48.85%; H, 4.98%).

3.2.6. (*E*)-2-[3-(4-Chlorophenyl)-2-methylprop-1-enyl)-1,3-dioxane (7f). 63 mg, (25% yield) as a colorless oil (90/10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (d, J=8.6 Hz, 2H), 7.05 (d, J=8.6 Hz, 2H), 5.25 (d, J=6.2 Hz, 1H), 5.15 (d, J=6.2 Hz, 1H), 4.15 (m, 2H), 3.80 (m, 2H), 3.25 (s, 2H), 2.3 (m, 1H), 1.65 (s, 3H), 1.2 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.25, 137.16, 130.42, 128.42, 124.53, 98.75, 66.90, 44.88, 25.58, 16.98; *m/z* (EI, 70 eV rel. Int.) 252 (M^+, 2), 127 (100), 87 (13), 69 (42), 41 (16). ν_{max} (neat)/cm^{-1} 3050, 1490, 1376, 1138, 1086, 994, 787. (Found: C, 67.00%; H 7.10%. Calcd for $C_{14}H_{17}ClO_2$: C, 66.53%; H, 6.78%).

3.2.7. (*E*)-2-[3-(4-Iodophenyl)-1-methylprop-1-enyl)-1,3-dioxane (7g). 103 mg, (30% yield) as a colorless oil (90/10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (d, J=7.0 Hz, 2H), 6.95 (d, J=7.0 Hz, 2H), 5.75 (bt, J=6.6 Hz, 1H), 4.82 (s, 1H), 4.10 (m, 2H), 3.82 (m, 2H), 3.15 (d, J=6.8 Hz, 2H), 2.1 (m, 1H), 1.80 (s, 3H), 1.1 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.89, 137.42, 130.54, 126.99, 104.50, 91.00, 67.02, 33.14, 25.72, 15.00; *m/z* (EI, 70 eV rel. Int.) 344 (M^+, 7), 127 (100), 87 (57), 69 (33), 59 (15). ν_{max} (neat)/cm^{-1} 3050, 1483, 1377, 1151, 1107, 958, 801. (Found: C, 49.15%; H 4.75%. Calcd for $C_{14}H_{17}IO_2$: C, 48.85%; H, 4.98%).

3.2.8. (*E*)-1-(4-Methoxyphenyl)-ott-2-en-4-one (8). 50 mg, (22% yield) as a colorless oil (90/10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02 (d, J=7.2 Hz, 2H), 6.9 (m, 3H), 6.05 (bd, J=15.0 Hz, 1H), 3.80 (s, 3H), 3.45 (bd, J=6.2 Hz, 2H), 2.55 (t, J=6.1 Hz, 2H), 1.55 (pent, J=6.0 Hz, 2H), 1.32 (sext, J=6.0 Hz, 2H), 0.9 (t, J=6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.66, 158.32, 145.40, 130.76, 129.66, 114.00, 55.14, 39.71, 37.74, 26.17, 22.28, 13.76; *m/z* (EI, 70 eV rel. Int.) 232 (M^+, 66), 160 (44), 175 (34), 147 (100), 121 (29). ν_{max} (neat)/cm^{-1} 3030, 1672, 1626, 1458, 1246, 1033, 733. (Found: C, 78.05%; H 8.20%. Calcd for $C_{15}H_{20}O_2$: C, 77.55%; H, 8.68%).

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Regioselective synthesis of 1,7-dioxaspiro[4.4]nonanes from a trimethylenemethane dianion synthon

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Dedicated to the memory of Dr. Juan Carlos del Amo who died in the horrific terrorist attack of the 11th of March 2004 in Madrid.

Abstract—2-Chloromethyl-3-(2-methoxyethoxy)prop-1-ene behaves as a versatile trimethylenemethane dianion synthon, precursor of a variety of methylidenic diols obtained by DTBB-catalysed lithiation in the presence of a carbonyl compound ($E^1=R^1R^2CO$) in THF at −78 to 0 °C, followed by the addition of an epoxide [$E^2=R^3R^4C(O)CHR^5$] at 0 to 20 °C and final hydrolysis. These diols undergo double intramolecular iodoetherification in the presence of iodine and silver(I) oxide in THF or dioxane–water, to give the corresponding 1,7-dioxaspiro[4.4]nonanes, which can be easily oxidised to a variety of 1,7-dioxaspiro[4.4]nonan-6-ones. These skeletons are present in a wide series of natural products.

1. Introduction

1,7-Dioxaspiro[4.4]nonanes and its derived lactones are substructures present in a variety of natural products, some of them with important biological activities. These types of compounds are especially abundant within the family of the labdane diterpenoids, some representatives of which are prehispanolone (**I**) (a specific platelet activating factor receptor antagonist, isolated from the Chinese herbal medicine *Leonurus heterophyllus*),[1,2] leopersin J (**II**) (from *Leonurus persicus*),[3] otostegins (from *Otostegia fruticosa*),[4] or marrubiglobosin (from *Marrubium globosum*).[5] Some other naturally occurring compounds containing the mentioned skeletons are sphydrofuran (**III**) (a secondary metabolite produced by Actinomycetes),[6] cinatrin A (**IV**) (a potent inhibitor of rat platelet phospholipase A_2, from the fermentation broth of the microorganism *Circinotrichum falcatisporum*),[7] longianone (**V**) (from *Xylaria longiana*),[8,9] hyperolactone A (**VI**) (from *Hypericum chinense* L.),[10] or syringolides 1 and 2,[11] and secosyrins 1 and 2 (**VII**) (all from *Pseudomonas syringae*).[12] 1,7-Dioxaspiro[4.4]nonanes have also been used as valuable polycyclic scaffolds in the synthesis of natural products (e.g., **VIII**, in zaragozic acid synthesis)[13,14] or have been obtained as a result of carbohydrate modification (**IX**, **X**)[15–18] (Chart 1).

The unique structural nature of these spirocyclic compounds has attracted the interest of many synthetic organic chemists.[19–21] However, most of the research has focused on the synthesis of spirocyclic γ-mono- and bislactones, less attention being dedicated to the 1,7-dioxaspiro[4.4]nonane itself as a polycyclic ether. The methodologies described in the literature normally involve the intramolecular cyclisation of a moiety attached to a preformed γ-lactone or tetrahydrofuran ring. As representative examples we can mention: (a) the intramolecular Michael addition of a 3-hydroxyalkyl group to a 2-butenolide ring;[19] (b) Reformatsky-type reaction on a tetrahydrofuran-3-one, followed by lactonisation;[22] (c) lactonisation of 2-hydroxyalkyl-γ-lactone acids and related compounds;[23,24] (d) radical cyclisation of a 4-(3-butynyloxy)-2,5-dihydro-2-furanone;[25] or (e) intramolecular ketalisation from a 2,2-disubstituted tetrahydrofuran.[26]

On the other hand, in recent years we have shown an increasing interest in the synthesis of bicyclic[27–31] and spirocyclic[32,33] polyether skeletons as constituents of

Keywords: 1,7-Dioxaspiro[4.4]nonanes; Arene-catalysed lithiation; Spirolactones; Spirocyclisation.
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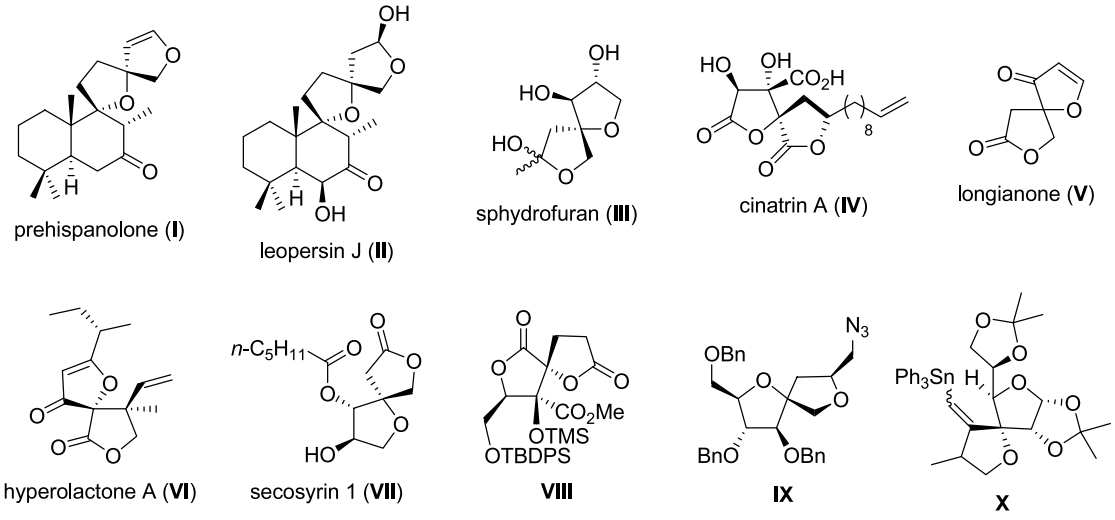
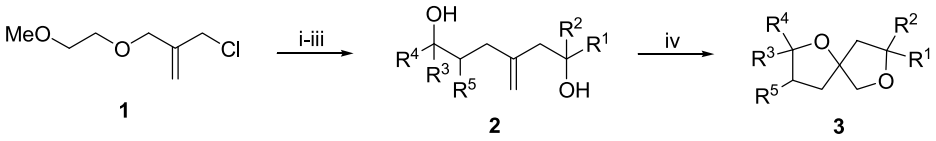


Chart 1.



Scheme 1. (i) Reagents and conditions: (i), Li, DTBB (2.5 mol%), R^1R^2CO, THF, −78 to 0 °C, 3.5 h; (ii), $R^3R^4C(O)CHR^5$, 0 to 20 °C, overnight; (iii), H_2O; (iv), I_2, Ag_2O, THF or dioxane–H_2O (7:1), 20 °C, overnight.

Table 1. Obtention of 1,7-dioxaspiro[4,4]nonanes from diols **2**

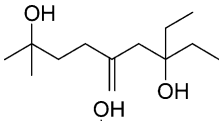
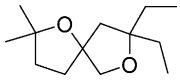
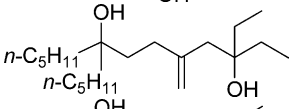
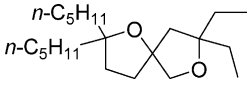
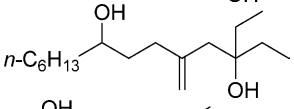
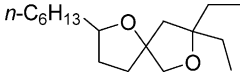
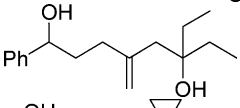
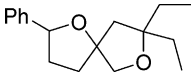
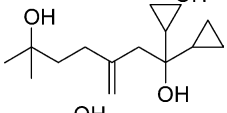
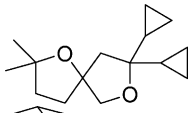
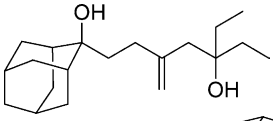
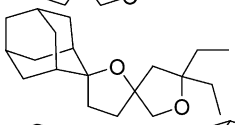
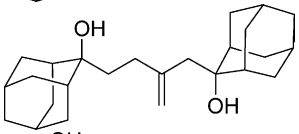
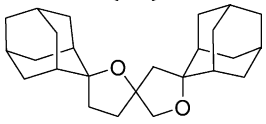
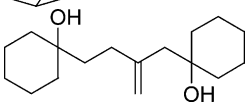
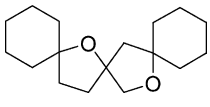
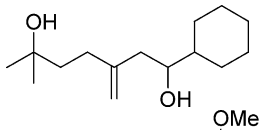
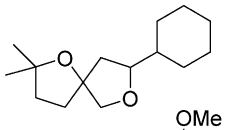
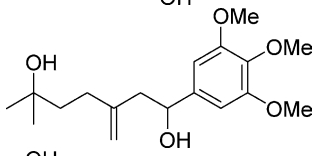
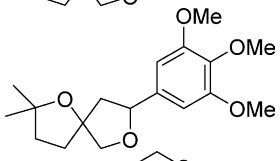
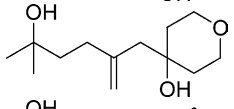
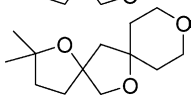
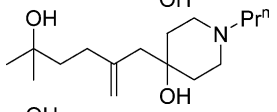
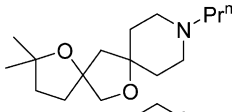
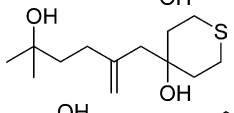
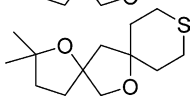
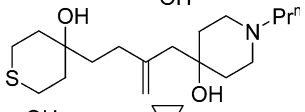
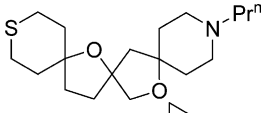
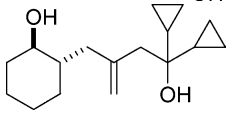
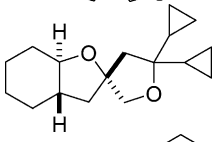
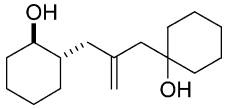
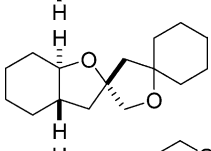
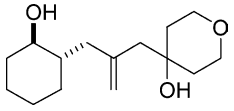
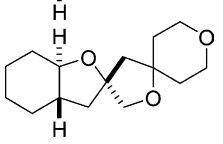
Entry	Product **2**[a]			Product **3**[a]		
	No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
1	**2a**		70	**3a**		98
2	**2b**		43	**3b**		96
3	**2c**		55	**3c**		97[d]
4	**2d**		68	**3d**		88[e]
5	**2e**		57	**3e**		99
6	**2f**		41	**3f**		96
7	**2g**		33	**3g**		70[f]
8	**2h**		54	**3h**		92

Table 1 (*continued*)

Entry	Product **2**[a]			Product **3**[a]		
	No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
9	**2i**		41	**3i**		–[g]
10	**2j**		30	**3j**		89[h]
11	**2k**		50	**3k**		91
12	**2l**		51	**3l**		89
13	**2m**		59	**3m**		90
14	**2n**		40	**3n**		92
15	**2o**		41	**3o**		90[i]
16	**2p**		43	**3p**		93[j]
17	**2q**		40	**3q**		92[k]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc or EtOAc/MeOH) based on the starting chloroether **1**.
[c] Yield of pure **3** from the reaction crude (unless stated otherwise) based on the starting diol **2**.
[d] Obtained as a 3.5:1 mixture of diastereoisomers (56% d.e.) (^{13}C NMR).
[e] Obtained as a 1:1 mixture of diastereoisomers (^{1}H and ^{13}C NMR).
[f] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the corresponding diol **2g**.
[g] Cyclisation of **2i** proved to be difficult and led to the corresponding iodohydrin **4i** in 97% yield, apparently, as a single diastereoisomer.
[h] Obtained as a 12:1 mixture of diastereoisomers (85% d.e.) (GLC).
[i] Obtained as a 3:1 mixture of diastereoisomers (50% d.e.) (^{1}H NMR), the major diastereoisomer is shown.
[j] Obtained as a 12:1 mixture of diastereoisomers (85% d.e.) (^{1}H NMR), the major diastereoisomer is shown.
[k] Obtained as a 13:1 mixture of diastereoisomers (86% d.e.) (GLC and ^{1}H NMR), the major diastereoisomer is shown.

important biologically active compounds. In particular, and in connection with the title topic, we reported the two-step synthesis of 1,6-dioxaspiro[3.4]octanes from 3-chloro-2-(chloromethyl)prop-1-ene[32] and 1,5-dioxaspiro[2.4]heptanes from 2,3-dichloroprop-1-ene.[33] In both cases an arene-catalysed lithiation[34–36] under Barbier conditions[37,38] and an iodine-mediated double intramolecular cyclisation were utilised as the key reaction steps. We want to demonstrate herein that the above mentioned methodology also allows a straight and ready access to the synthesis of 1,7-dioxaspiro[4.4]nonanes using 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**1**) as starting material. This compound undergoes a selective lithiation catalysed by DTBB (4,4′-di-*tert*-butylbiphenyl) with concomitant one-pot incorporation of two different electrophilic fragments, derived from a carbonyl compound and an epoxide, respectively. The resulting methylidenic diols (**2**) can be regioselectively cyclised in the presence of iodine and silver(I) oxide, affording the expected 1,7-dioxaspiro[4.4]nonanes (**3**) in high yields. In addition, these compounds can be easily oxidised to the corresponding 1,7-dioxaspiro[4.4]nonan-6-ones **6**.[39] The present study covers the scope and limitations of this methodology in the synthesis of the title compounds including a wide range of electrophiles and discusses in some detail the spirocyclisation reaction mechanism as well as the stereoselectivity

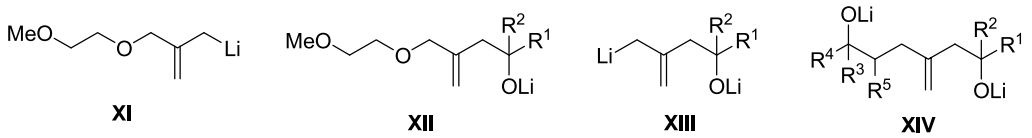


Chart 2.

observed. In addition, the structure of these compounds has been confirmed by X-ray diffraction analysis carried out for compound **3g**.

2. Results and discussion

The reaction of 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**1**) with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) (1:0.1 molar ratio, 2.5 mol%), in the presence of different carbonyl compounds ($E^1=R^1R^2CO$; 1:0.95 molar ratio) in THF, at temperatures ranging from −78 to 0 °C for ca. 3.5 h, led to a reaction mixture, which was treated with an excess of an epoxide as a second electrophile [$E^2=R^3R^4C(O)CHR^5$; 1:3 molar ratio] at 0 to 20 °C overnight giving, after hydrolysis with water, the corresponding methylidenic diols **2a–q** (Scheme 1 and Table 1). A wide variety of carbonyl compounds were utilised as the first electrophiles, including acyclic, cyclic, and heterocyclic ketones, as well as two aldehydes, whereas monosubstituted, 1,1-disubstituted, spirocyclic, and bicyclic oxiranes were used as the second electrophiles. In spite of the fact that the yields of diols **2** are moderate, this methodology is very advantageous since it allows the introduction of two different electrophiles in a one-pot sequence. It is noteworthy that even styrene oxide, which is prone to undergo reductive ring opening under the reaction conditions, could be introduced as a second electrophile in good yield (entry 4, Table 1). In the case of using cyclohexene oxide as the second electrophile, only the corresponding *trans*-diastereomeric products were obtained (entries 15–17, Table 1).

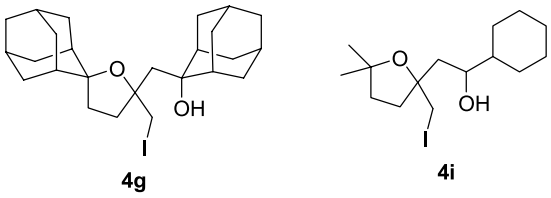
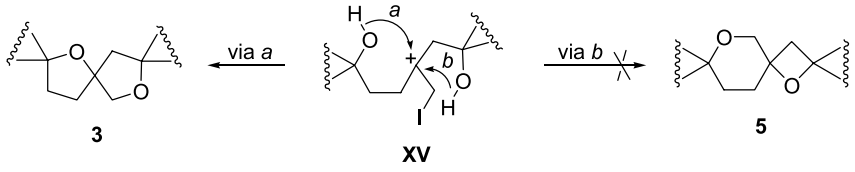
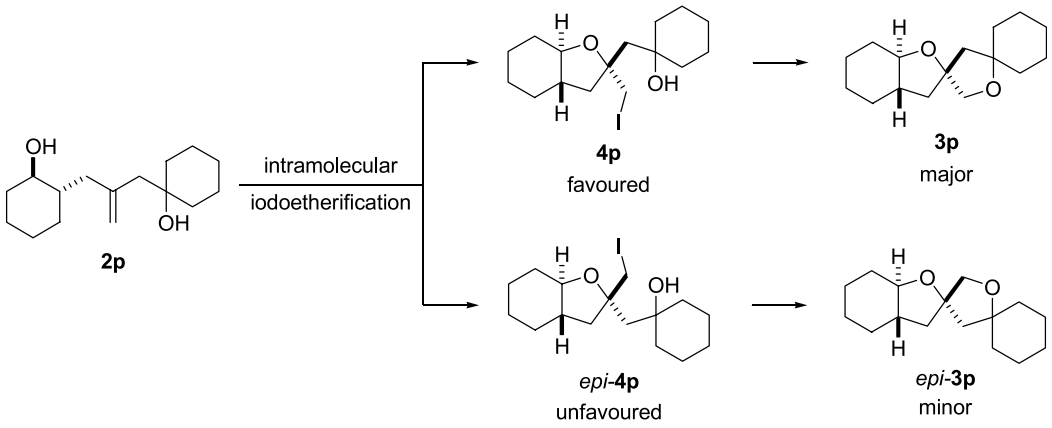


Chart 3.

This sequential incorporation of two electrophilic fragments arises from the different reactivity of the carbon–chlorine and carbon–oxygen bonds in arene-catalysed lithiations.[28–31] Thus, after the first chlorine–lithium exchange, a functionalised organolithium intermediate **XI** is formed,[40–42] which by reaction with a carbonyl compound (E^1) gives the expected alkoxide **XII**. This species can be lithiated at higher temperatures to yield a new dilithiated compound **XIII**, which by final reaction with an epoxide (E^2) affords the dialkoxide **XIV**, precursor of the diol formed **2** (Chart 2). The mediocre yield observed for some of the diols **2** (Table 1) was mainly due to competitive proton capture of carbanion **XIII** from the reaction medium instead of reaction with the corresponding epoxide.

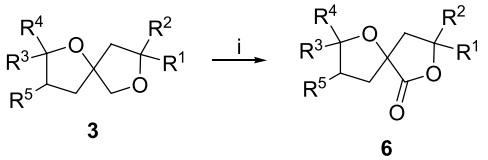


Scheme 2.



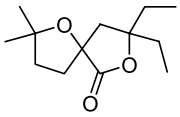
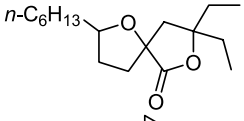
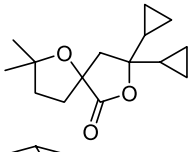
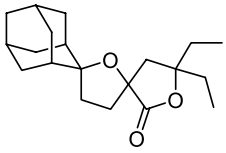
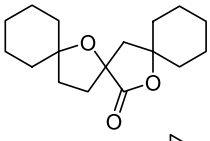
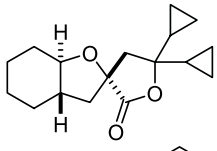
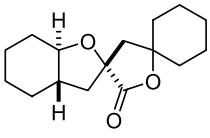
Scheme 3.

The isolated diols **2** were subjected to intramolecular cyclisation by treatment with iodine (1.5 equiv) and silver(I) oxide (1.5 equiv) in THF or a 7:1 mixture of dioxane–water at room temperature overnight, affording the corresponding 1,7-dioxaspiro[4.4]nonanes **3** in excellent yields and with such a high purity that they did not need any further purification (Scheme 1 and Table 1). Entries 1–5 in Table 1 show several monospirocyclic products. It is worth of note that chiral racemic diols where obtained when 1-octene and styrene oxides where used as second electrophiles (Table 1, entries 3 and 4), and consequently some asymmetric induction could be expected in the formation of the new spirocyclic stereocentre. Spirocyclisation of diol **2d** gave a disappointing 1:1 diastereomeric ratio, whereas a 3.5:1 ratio was observed for diol **2c**. Polyspirocyclic structures were easily obtained by the incorporation of cyclic ketones and spirocyclic epoxides in the starting diol (Table 1, entries 6–8). Symmetrically substituted dispirocyclic products **3g** and **3h** were readily prepared by using a cyclic carbonyl compound and its derived epoxide (Table 1, entries 7 and 8). In particular, compound **3g** was a solid and was subjected to X-ray diffraction analysis in order to provide more evidence about the presence of the 1,7-dioxaspiro[4.4]nonane skeleton in all products **3** (see Section 3). Unfortunately, cyclisation of diol **2i**, derived from cyclohexanecarboxaldehyde and isobutylene oxide, stopped at the iodohydrin stage, which however was apparently obtained as a single diastereoisomer (GLC, ^{1}H and ^{13}C NMR) (entry 9, Table 1). On the other hand, diol **2j** could be nicely cyclised to afford product **3j** as a 12:1 diastereomeric mixture. NOESY experiments carried out on compound **3j** did not provide any information about the relative stereochemistry of the major diasteroisomer. The heteroatom content in the whole structure of compounds **3** could be increased by choosing appropriate heteroatom-containing electrophiles. Thus,



Scheme 4. Reagents and conditions: (i) RuO_2 (0.15 equiv), $NaIO_4$ (4.88 equiv), CCl_4–H_2O 1:1, 20 °C.

Table 2. Oxidation of 1,7-dioxaspiro[4,4]nonanes **3** to lactones **6**

Entry	Starting compound	Product **6**[a]		
		No.	Structure	Yield (%)[b]
1	**3a**	**6a**		98
2	**3c**	**6c**		95
3	**3e**	**6e**		98
4	**3f**	**6f**		97
5	**3h**	**6h**		91
6	**3o**	**6o**		90[c]
7	**3p**	**6p**		93[d]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Yield of pure **6** from the reaction crude based on the starting compound **3**.
[c] Obtained as a 3.5:1 mixture of diastereoisomers (56% d.e.) (^{13}C NMR), the major diastereoisomer is shown.
[d] Obtained as a 12:1 mixture of diastereoisomers (85% d.e.) (^{13}C NMR), the major diastereoisomer is shown.

dispirocyclic compounds **3k–m** derived from tetrahydro-2*H*-pyran-4-one, *N*-propylpiperidin-4-one, and tetrahydrothio-2*H*-pyran-4-one with isobutylene oxide, were obtained in high yields (entries 11–13, Table 1). Even more interesting is the trispiro compound **3n**, derived from *N*-propylpiperidin-4-one and 1-oxa-6-thiaspiro[2.5]octane, which contains three different heteroatoms, oxygen, nitrogen and sulfur (entry 14, Table 1). The versatility of the methodology was also demonstrated in the synthesis of spirobicyclic ethers derived from an acyclic or cyclic ketone and cyclohexene oxide. In this case, cyclisation of the chiral racemic diols **2o–q** exhibited some diastereoselectivity, which was relatively high for compounds **3p** and **3q** [12:1 (85% d.e. and 13:1 (86% d.e.), respectively]. The structure of the major diasteroisomers of **3o–q** shown in Table 1 was determined by NOESY experiments (see Section 5). This result can be promising in the synthesis of chiral non-racemic 1,7-dioxaspiro[4.4]nonanes by utilising enantiomerically pure epoxides as second electrophiles.

It must be mentioned that spirocyclisation of the diol **2g** (entry 7, Table 1) could not be driven to completion, this explaines the lower yield observed in the formation of **3g** (70%) compared to the rest of compounds **3**. However, this reaction allowed the isolation of the corresponding iodohydrin intermediate **4g** (15%) (Chart 3). This fact, together with the isolation of the iodohydrin **4i** derived from diol **2i** gave us firm proofs about the mechanism of the spirocyclisation reaction (Chart 3). From compounds **4g**,**i** it can be inferred that the first cyclisation involves the nucleophilic attack of the epoxide derived hydroxylic moiety onto the iodonium ion (**XV**) in a 5-*exo* mode, followed by a nucleophilic displacement of iodide by the ketone derived hydroxylic moiety (Scheme 2, route a). The alternative cyclisation route involving 4-*exo* attack of the ketone derived hydroxylic moiety and nucleophilic displacement of iodide by the epoxide derived hydroxylic moiety did not occur at all (Scheme 2, route b). Therefore, the formation of 1,7-dioxaspiro[4.4]nonanes **3** is highly regioselective to the detriment of the less favoured 1,6-dioxaspiro[3.5]nonanes **5** (Scheme 2).

With a mechanism of spirocyclisation in hand, we tried to rationalize the diastereoselectivity observed in the cyclisation of compounds **2o–q** by using **2p** as a model compound. Thus, the geometry and the heats of formation of the diasteromeric intermediate iodohydrins were calculated and optimised with the semiempirical method PM3.[43] As a result, iodohydrin **4p** was found to be 4.7 kcal/mol more stable than the corresponding diastereoisomer *epi*-**4p**, which is in fair agreement with the 85% d.e. observed for compound **3p** (Scheme 3).

We believed that the spirocyclic compounds synthesized **3** could be used as adequate precursors of 1,7-dioxaspiro[4.4]nonan-6-ones **6**, which are also present as substructures in many natural products (see Chart 1). This transformation was successfully accomplished with the system composed of catalytic ruthenium(IV) oxide and sodium periodate,[44] leading to the corresponding lactones **6** in remarkable yields and without any further purification (Scheme 4, Table 2).

3. X-ray diffraction studies of compound 3g

Different attempts to crystallise compound **3g** led to very small and irregular crystals which were not good enough to be analysed by the single-crystal X-ray diffraction technique. On the other hand, the crystal structure determination of organic compounds by means of X-ray powder diffraction has been developed in recent years.[45] The data collected by this technique, in contrast to the single-crystal technique, have the inconvenience of peak overlapping. This limitation increases for most of the organic molecules composed of light atoms because of the decreasing of the peak intensity at high scattering angles. We used conventional X-ray powder diffractometers because, in contrast with the synchrotron radiation, are easily available and not expensive.

We could not use conventional direct methods for the structure solution because we were working with low quality data. However, we could work with initial organic structures as starting solutions and the support of other experimental techniques (IR, ^{1}H and ^{13}C NMR, MS and HRMS). We located such starting solutions on an indexed unit cell and refined it from the experimental diffraction data. We report herein the best solution found, which is in agreement with the structure proposed from other experimental techniques presented.

The samples were measured on a Siemens D5005 diffractometer with Bragg–Brentano geometry and with twin Göbel mirrors[46] as optical setup. A Cu sealed tube [λ(Kα1)=1.5406 Å] was used operating at 40 kV and 30 mA. The pattern was collected in the $4<2\theta<45$ range with a step size of 0.02° and counting time of 40 s per step. The sample was spun during the data acquisition in order to get the best peak profile and minimise the preferred orientation effect.

Once the data were collected with the greatest possible quality, the pattern was indexed using the program suite Crysfire.[47] The accepted solution was suggested by the programs *DICVOL91*[48] and *LZONv6.23b*,[49] based on the position of the 20 first peaks. The cell parameters, the zero point, the background and the peak shape (pseudo-Voigt function) were refined using the program Bruker AXS Topas.[50] The refined cell parameters were $a=6.4422(15)$, $b=10.9992(26)$, $c=28.3696(7)$, and $\beta=99.627(28)$. The systematic extinctions were consistent with the suggested monoclinic space group *P21/c*. This solution was also coherent with the expected values of density for the supposed molecule ($C_{25}H_{36}O_2$), since with

Table 3

	Cell refinement	Structural refinement
r_exp	3.00	3.75
r_exp_dash	2.94	3.46
r_wp	27.44	37.81
r_wp_dash	26.92	34.90
r_p	15.63	22.51
r_p_dash	15.45	21.87
weighted_Durbin_Watson	0.61	0.53
gof	9.15	10.07

$V=1981.92(10)$ Å^3 we obtained $Z=4$. In Table 3 it is shown the agreement factors of the cell refinement.

CHEM 3D[51] was used for the chemical modelling. We used different configurations in agreement with the other experimental analyses in order to test them with the diffraction data. Firstly, we located the different molecular solutions into the refined unit cell calculated with the F.O.X. program[52] from the experimental diffraction data. The best positioning obtained corresponds to the parameters Chi2=41534.562, GoF=26.78, RwP=0.54, Rp=0.36. The Rietveld method was used for the refinement of the positions of non H atoms with isotropic thermal factors using the Bruker AXS Topas program. Due to the low quality of the experimental data (because of the high overlapping and low intensity of the high angle peaks), we released the non hydrogen atomic positions within a box of 0.005 Å for each cycle. Once the new values of the atomic positions were calculated, the hydrogen positions were constrained to idealised positions with the WinGx program[53] at the end of each cycle. In the Figure 1 it is shown the variation of the atomic positions of the first cycle (F.O.X. solution) with respect to the last one (in green).

The agreement factors of the last cycle of the refinement are shown in Table 3, where 514 reflections were used. The experimental pattern (in black), calculated (in red) and the difference (in red) are shown in the Figure 2.

The resulting molecule was optimised by comparison with other models in which the oxygen atoms were located at different positions of the 1,7-dioxaspiro[4.4]nonane skeleton, a clear worsening of the obtained adjustments being observed. Therefore, it is possible to conclude that the technique of structural resolution by powder diffraction data is sensitive to changes of the atomic positions or the nature of atoms of the starting molecule, and that this technique has allowed the confirmation of the structure of compound **3g** (Fig. 3) as it was suggested by means of spectroscopic techniques.

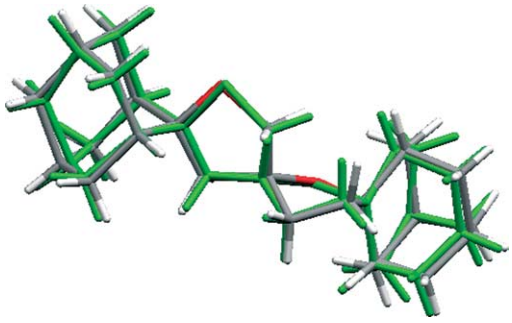


Figure 1.

4. Conclusions

We have described herein a methodology that gives a straight access to the synthesis of 1,7-dioxaspiro[4.4]-nonanes and 1,7-dioxaspiro[4.4]nonan-6-ones from 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene. This starting material behaves as a versatile trimethylenemethane dianion synthon under arene-catalyzed lithiation conditions,

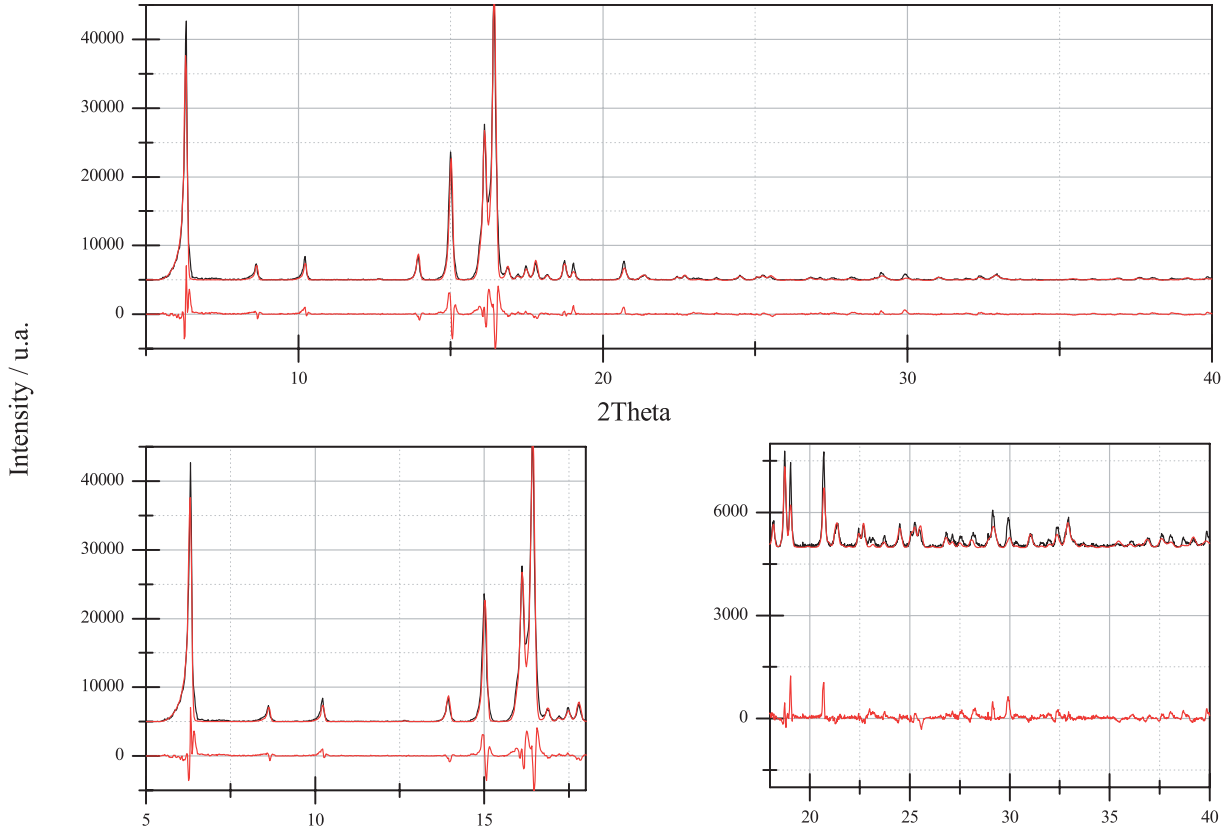


Figure 2.

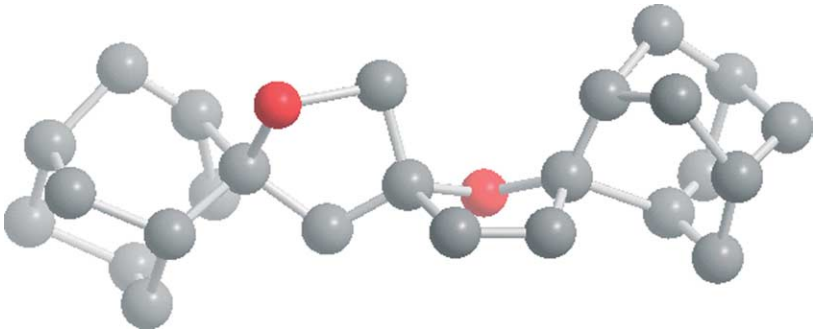


Figure 3.

allowing the one-pot incorporation of two different electrophilic fragments derived from a carbonyl compound and an epoxide. Iodine-promoted double intramolecular cyclisation of the resulting diols provides the expected spirocyclic ethers, which are easily oxidised to the corresponding lactones, all in excellent yields as well as in a regio- and stereoselective manner.

5. Experimental

5.1. General

Melting points were obtained with a Reichert Thermovar apparatus. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 and Agilent 5973 spectrometers, fragment ions in m/z with relative intensities (%) in parenthesis. HRMS analyses were carried out on a Finnigan MAT95S spectrometer. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 elemental analyser. The purity of volatile and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and a 12 m capillary column (0.2 mm diametre, 0.33 mm film thickness), using nitrogen (2 ml/min) as carrier gas, $T_{injector}$=275 °C, T_{column}=60 °C (3 min) and 60–270 °C (15 °C/min); retention times (t_r) are given under these conditions. Column chromatography was performed using silica gel 60 of 40–60 microns. Thin layer chromatography was carried out on TLC plastic sheets with silica gel 60 F_{254} (Merck). THF was directly used without any purification (Acros, 99.9%). Lithium powder was commercially available (MEDALCHEMY S. L.). For the preparation of 2-chloromethyl-3-(2-methoxyethoxy)propene, see Ref. 30. Isobutylene, octene, styrene and cyclohexene oxides were commercially available. The other starting epoxides (α-methylstyrene, 2-pentylheptene, 2-methylideneadamantane, methylidenecyclohexane, 4-methylideneoxacyclohexane, and 4-methylidenethiacyclohexane oxides) were prepared from the corresponding ketones by reaction with the ylide derived from trimethylsulfoxonium iodide.[54]

5.2. General procedure for the preparation of diols 2

A solution of 2-chloromethyl-3-(2-methoxyethoxy)propene (164 mg, 1 mmol) and the corresponding carbonyl compound (0.95 mmol) in THF (3 ml), was added over 1.5 h to a green suspension of lithium powder (50 mg, 7 mmol) and DTBB (27 mg, 0.1 mmol) in THF (3 ml) at −78 °C. The mixture was allowed to reach 0 °C and then a solution of the corresponding epoxide (3 mmol) in THF (3 ml) was added over 1.5 h continuing the stirring for 8 h at room temperature. The reaction mixture was hydrolysed with water (5 ml), extracted with ethyl acetate (3×10 ml), and the organic phase was dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane/EtOAc; EtOAc/MeOH was used for compounds **2k–n,q**) to yield compounds **2**. Compounds **2c,d,f,h,p** were previously described by us.[31] The physical and spectroscopic data of new compounds follow:

5.2.1. 7-Ethyl-2-methyl-5-methylenenonane-2,7-diol (2a). Colourless oil; t_r 11.04; R_f 0.33 (hexane/EtOAc 8:2); ν (film) 3388 (OH), 1639 (C=CH), 1133 cm^{-1} (CO); δ_H 0.87 (6H, t, J=7.4 Hz, 4×CH_3CH$_2$), 1.23 (6H, s, 2×CH$_3$C), 1.47 (4H, q, J=7.4 Hz, 2×CH_2CH$_3$), 1.60–1.66 (2H, m, CH$_2$CH_2COH), 1.97 (2H, s, 2×OH), 2.20–2.25 (4H, m, 2×CH_2C=CH$_2$), 4.79, 4.94 (2H, 2s, H$_2$C=C); δ_C 8.0 (2×CH$_3$CH$_2$), 29.2 (2×CH$_2$CH$_3$), 30.8 (2×CCH$_3$), 32.3 (CH$_2$CH$_2$COH), 42.0 (CH$_2$$CH_2$COH), 44.4 (C$CH_2$C), 70.8, 74.7, (2×COH), 113.4 (H$_2$$C$=C), 147.1 ($C$=CH$_2$); m/z 181 (M$^+$−33, 1%), 110 (13), 109 (16), 95 (74), 87 (85), 81 (14), 69 (21), 68 (27), 67 (14), 59 (25), 57 (88), 55 (19), 45 (98), 43 (100), 41 (41). HRMS calcd for $C_{13}H_{26}O_2$ 214.1933, (M$^+$−H$_2$O) 196.1827, found 196.1823.

5.2.2. 7-Ethyl-5-methylene-8-pentyltridecane-3,8-diol (2b). Colourless oil; t_r 15.76; R_f 0.38 (hexane/EtOAc 8:2); ν (film) 3361 (OH), 1640 (C=CH), 1030 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH$_3$), 1.25–1.60 (24H, m, 11×CH_2CH$_2$, 2×OH), 2.05–2.20 (4H, m, 2×CH_2C=CH$_2$), 4.79, 4.94 (2H, 2s, H$_2$C=C); δ_C 7.9, 8.1 (4×CH$_3$), 29.3, 29.4, 29.7, 31.0, 31.6, 31.7, 44.5 (12×CH$_2$CH$_2$, CH$_2$C=CH$_2$), 74.4, 74.6 (2×COH), 113.4 (H$_2$$C$=C), 147.4 ($C$=CH$_2$); m/z 290 (M$^+$−36, 5%), 261 (24), 233 (15), 219 (48), 207 (43), 165 (15), 163 (16), 151 (18), 149 (20), 137 (22), 136 (11), 135 (54), 124 (21), 123 (52), 122 (13), 121 (26), 111 (11), 110 (20), 109 (45), 108 (11), 107 (56), 105 (14), 99 (13), 97 (17), 95 (62), 94 (12), 93 (52), 91 (29), 87 (47), 83 (23), 81 (68), 79 (38), 77 (18), 71 (20), 69 (53), 68 (12), 67 (51), 57 (48), 56 (11), 55 (100), 53 (15). HRMS calcd for $C_{21}H_{42}O_2$ 326.3185, found 326.3191.

5.2.3. 1,1-Dicyclopropyl-6-methyl-3-methyleneheptane-1,6-diol (2e). Colourless oil; t_r 12.82; R_f 0.23 (hexane/EtOAc 8:2); ν (film) 3355 (OH), 3051 (cyclopropyl C–H), 1642 (C=C), 1030 cm^{-1} (CO); δ_H 0.30–0.45 (8H, m, 4×CH_2CH), 0.75–0.85 (2H, m, 2×CH), 1.24 (6H, s, 2×CH_3), 1.62–1.68 (2H, m, CH_2CH_2COH), 2.29–2.35 (6H, m, 2×CH_2C=CH_2, 2×OH), 4.84, 4.93 (2H, 2s, H_2C=C); δ_C −0.3, 1.0 (4×CH_2CH), 19.1 (2×CH), 29.2 (2×CH_3), 32.3 (CH_2CH_2COH), 42.0 (CH_2CH_2COH), 48.2 (CCH_2C), 70.2, 71.0 (2×COH), 113.2 (H_2C=C), 147.2 (C=CH_2); *m/z* 220 (M^+−18, 1%), 117 (14), 111 (100), 105 (11), 95 (12), 91 (17), 69 (98), 59 (18), 55 (23), 53 (11), 43 (54), 41 (99). HRMS calcd for $C_{15}H_{26}O_2$ 238.1933, (M^+−H_2O) 220.1827, found 220.1804.

5.2.4. 2-[3-(2-Hydroxy-2-adamantylmethyl)-3-butenyl]-adamantan-2-ol (2g). Colourless solid; R_f 0.53 (hexane/EtOAc 8:2); mp 69–70 °C; ν (film) 3340 (OH), 1639 (C=CH), 1028 cm^{-1} (CO); δ_H 1.45–2.25 (34H, m, 8×CH, 13×CH_2), 2.47 (2H, s, 2×OH), 4.83, 4.97 (2H, 2s, H_2C=C); δ_C 27.0, 27.2, 27.4, 29.6, 36.9, 37.5, 38.4, 40.7 (8×CH), 30.6, 32.9, 33.1, 33.9, 34.6, 34.8, 35.0, 36.1, 37.0, 37.8, 38.3 (10×CH_2CH, CH_2CH_2CO), 41.1 (CH_2CH_2CO) 47.9 (CCH_2C), 74.3, 74.8 (2×CO), 114.0 (H_2C=C), 147.9 (C=CH_2); *m/z* 352 (M^+−18, >1%), 152 (11), 151 (100), 150 (36), 148 (16), 116 (11), 107 (13), 105 (10), 93 (17), 91 (27), 81 (25), 80 (28), 79 (42), 77 (15), 67 (14), 55 (18), 53 (10). Anal. calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34, found C, 80.95; H, 10.35.

5.2.5. 1-Cyclohexyl-6-methyl-3-methylideneheptane-1,6-diol (2i). Colourless oil; t_r 13.65; R_f 0.40 (hexane/EtOAc 8:2); ν (film) 3378 (OH), 1641 (C=CH), 1133 cm^{-1} (CO); δ_H 1.00–1.80 [13H, m, CHCHOH, $(CH_2)_5$, CH_2COH], 1.24 (6H, s, 2×CH_3), 1.85 (br s, 2×OH), 2.00–2.20 (3H, m, CH_2CH_2C=CH_2, CHC$H_A$$H_B$C), 2.31 (1H, d, J=12.0 Hz, CHC$H_A$$H_B$C), 3.48 (1H, ddd, J=10.2, 5.6, 2.8 Hz, CHO), 4.86, 4.93 (2H, 2s, H_2C=C); δ_C 26.2, 26.3, 26.5, 28.2, 29.1, 29.2 [$(CH_2)_5$, CH_2CH_2COH], 30.3 (2×CH_3), 41.5 (CH_2-CH_2COH), 41.6 (CHCOH), 43.5 (CCH_2CH), 70.9 (COH), 72.8 (CHOH), 112.2 (H_2C=C), 147.5 (C=CH_2); *m/z* 222 (M^+−18, <1%), 113 (11), 110 (21), 95 (100), 83 (12), 81 (15), 69 (14), 68 (29), 67 (21), 59 (30), 55 (48), 53 (11), 43 (48), 41 (64). HRMS calcd for $C_{15}H_{28}O_2$ 240.2089, (M^+−H_2O) 222.1984, found 222.1987.

5.2.6. 6-Methyl-3-methylene-1-(3,4,5-trimethoxyphenyl)heptane-1,6-diol (2j). Colourless oil; t_r 17.63; R_f 0.33 (MeOH/EtOAc 1:1); ν (film) 3394 (OH), 1595, 1507, 1630 (C=CH), 1127 cm^{-1} (CO); δ_H 1.25 (6H, s, 2×CH_3), 1.60–1.70 (2H, m, CH_2COH), 1.90–2.20 (6H, m, 2×OH, 2×CH_2C=CH_2), 3.83, 3.88 (9H, 2s, 3×CH_3O), 4.75–4.85 (1H, m, CHO), 4.94, 4.97 (2H, 2s, CH_2=C), 6.61 (2H, s, 2×ArH); δ_C 29.3 (2×CH_3), 30.4 (CH_2CH_2COH), 41.5 (CH_2CH), 46.9 (CH_2COH), 56.1, 60.8 (3×CH_3O), 70.9 (COH), 72.0 (CHOH), 102.7, 103.6 (2×ArCH), 112.7 (H_2C=C), 139.7, 139.8, 153.2 (4×ArC), 146.6 (C=CH_2); *m/z* 324 (M^+, <1%), 198 (11), 197 (100), 196 (25), 181 (10), 169 (44), 154 (16), 138 (17). HRMS calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1928.

5.2.7. 5-(4-Hydroxytetrahydro-2*H*-4-pyranylmethyl)-2-methyl-5-hexen-2-ol (2k). Colourless oil; t_r 12.65; R_f 0.43 (EtOAc); ν (film) 3396 (OH), 1639 (C=CH), 1097 cm^{-1} (CO); δ_H 1.23 (6H, m, 2×CH_3), 1.45–1.80 (6H, m, CH_2CH_2COH, 2×CH_2CH_2O), 2.03 (2H, br s, 2×OH), 2.18–2.25 (4H, m, 2×CH_2C=CH_2), 3.73–3.77 (4H, m, 2×CH_2CH_2O), 4.82, 4.98 (2H, 2s, H_2C=C); δ_C 29.3 (2×CH_3), 32.5 (CH_2CH_2COH), 38.0 (2×CH_2CH_2O), 41.7 (CH_2CH_2COH), 48.9 (CCH_2C), 63.8 (2×CH_2CH_2O), 68.5, 70.8 (2×COH), 114.1 (H_2C=C), 145.9 (C=CH_2); *m/z* 210 (M^+−18, <1%), 119 (12), 110 (32), 101 (46), 96 (10), 95 (100), 81 (13), 71 (28), 68 (23). HRMS calcd for $C_{13}H_{24}O_2$ 228.1725, found 228.1723.

5.2.8. 5-(4-Hydroxy-1-propyl-4-piperidylmethyl)-2-methyl-5-hexen-2-ol (2l). Colourless oil; t_r 14.55; R_f 0.30 (MeOH/EtOAc 1:1); ν (film) 3373 (OH), 1638 (C=CH), 1134 cm^{-1} (CO); δ_H 0.91 (3H, t, J=7.3 Hz, CH_3CH_2), 1.23 (6H, m, 2×CH_3C), 1.45–1.85 (8H, m, CH_2CH_2COH, 2×CH_2CH_2N, CH_2CH_3), 2.03 (2H, s, 2×OH), 2.15–2.23 (4H, m, 2×CH_2C=CH_2), 2.35–2.45, 2.75–2.85 (6H, 2m, 3×CH_2N), 4.82, 4.97 (2H, 2s, H_2C=C); δ_C 11.9 (CH_3CH_2), 19.5 (CH_2CH_3), 29.3 (2×CH_3), 32.5 (CH_2CH_2COH), 36.8 (2×CH_2CH_2N), 41.8 (CH_2CH_2OH), 49.1 (CCH_2C), 60.2 (3×CH_2N), 68.8, 70.8 (2×COH), 114.0 (H_2C=C), 146.2 (C=CH_2); *m/z* 269 (M^+, 2%), 240 (23), 222 (21), 142 (17), 140 (61), 124 (12), 112 (25), 98 (13), 72 (20), 70 (16), 59 (18), 57 (14), 56 (25), 55 (22), 44 (21), 43 (85), 42 (100), 41 (50). HRMS calcd for $C_{16}H_{31}NO_2$ 269.2355, found 269.2321.

5.2.9. 5-(4-Hydroxytetrahydro-2*H*-4-thiopyranylmethyl)-2-methyl-5-hexen-2-ol (2m). Colourless oil; t_r 14.53; R_f 0.45 (hexane/EtOAc 1:1); ν (film) 3385 (OH), 1637 (C=CH), 1127 cm^{-1} (CO); δ_H 1.24 (6H, m, 2×CH_3), 1.58–1.95 (6H, m, CH_2CH_2COH, 2×CH_2CH_2S), 1.95 (2H, br s, 2×OH), 2.18–2.22 (4H, m, 2×CH_2C=CH_2), 2.40, 2.44, (2H, 2m, 2×CH_2C$H_A$$H_B$S), 2.98 (2H, m, 2×$CH_2CH_A$$H_B$S), 4.80, 4.98 (2H, 2s, H_2C=C); δ_C 24.2 (2×CH_2S), 29.3 (2×CH_3), 32.7 (CH_2CH_2COH), 38.6 (2×CH_2CH_2S), 41.8 (CH_2CH_2COH), 49.2 (CCH_2C), 69.6, 70.9 (2×COH), 114.3 (H_2C=C), 145.8 (C=CH_2); *m/z* 244 (M^+, 1%), 110 (31), 99 (23), 95 (86), 88 (19), 87 (10), 83 (29), 81 (15), 79 (10), 71 (17), 69 (16), 68 (39), 67 (19), 61 (22), 60 (14), 59 (48), 55 (69), 53 (26), 47 (24), 46 (13), 45 (27), 44 (14), 43 (100), 42 (12), 41 (67), 40 (15). HRMS calcd for $C_{13}H_{24}O_2S$ 244.1497, found 244.1492.

5.2.10. 4-[2-(4-Hydroxytetrahydro-2*H*-4-thiopyranyl)-ethyl]allyl-1-propylpiperidin-4-ol (2n). Colourless oil; t_r 20.18; R_f 0.38 (MeOH/EtOAc 1:1); ν (film) 3385 (OH), 1638 cm^{-1} (C=CH); δ_H 0.90 (3H, t, J=7.3 Hz, CH_3CH_2,), 1.45–1.90 (12H, m, CH_2CH_2COH, 3×CH_2CH_2N, 2×CH_2CH_2S), 2.05 (2H, s, 2×OH), 2.18–2.23 (4H, m, 2×CH_2C=CH_2), 2.37–2.47 (2H, br dt, 2×C$H_A$$H_B$S), 2.25–2.35, 2.65–2.75 (6H, 2m, 3×CH_2N), 2.90–3.00 (2H, td, J=12.5, 2.8 Hz, 2×C$H_A$$H_B$S), 4.81, 4.96 (2H, 2s, H_2C=C); δ_C 12.0 (CH_3CH_2), 20.0 (CH_2CH_3), 24.3 (2×CH_2S), 30.6 (CCH_2CH_2COH), 37.2, 38.3 (2×CH_2CH_2N, 2×CH_2CH_2S), 41.4 (CCH_2CH_2COH), 49.5 (CCH_2C), 60.4, 60.7 (3×CH_2N), 69.3, 69.9 (2×COH), 114.3 (H_2C=C), 146.0 (C=CH_2); *m/z* 327 (M^+, 7%), 299 (20), 298 (99), 281 (37), 210 (10), 142 (20), 141 (15), 140 (100), 124 (12), 112 (27). HRMS calcd for $C_{18}H_{33}NO_2S$ 327.2232, found 327.2230.

5.2.11. 1,1-Dicyclopropyl-3-[(1*R,2*S**)-2-hydroxycyclohexylmethyl)]-3-buten-1-ol (2o).** Colourless oil; t_r 14.95; R_f 0.40 (hexane/EtOAc 8:2); ν (film) 3360 (OH), 3083 (cyclopropyl C–H), 1638 (C=CH), 1024 cm^{-1} (CO); δ_H 0.25–0.50 (8H, m, 4×cyclopropyl CH_2), 0.75–0.95 (2H, m, 2×cyclopropyl CH), 1.15–2.10 [12H, m, 2×OH, C*H*$_2$-CHCHOH, $(CH_2)_4$], 2.30, 2.39 (2H, AB system, J= 13.6 Hz, CCH_2C), 2.74 (1H, dd, J=13.9, 4.2 Hz, C*H*CHOH), 3.25 (1H, td, J=5.5, 4.2 Hz, CHOH), 4.87, 4.93 (2H, 2s, H_2C=C); δ_C −0.3, −0.2, 0.9, 1.0 (4× cyclopropyl CH_2), 18.9, 19.1 (2×cyclopropyl CH), 24.8, 25.5, 30.8, 35.5, 41.5 [$(CH_2)_4$, C*C*H$_2$CH], 43.7 (*C*HCOH), 47.6 (C*C*H$_2$C), 70.8 (COH), 75.2 (CHOH), 115.3 (H$_2$*C*=C), 146.1 (*C*=CH$_2$); *m/z* 246 (M^+−18, 1%), 160 (16), 145 (22), 120 (36), 119 (12), 117 (22), 111 (12), 105 (36), 92 (10), 91 (39), 79 (24), 77 (20), 69 (22), 67 (14), 65 (13), 57 (18), 55 (25), 53 (19), 51 (10), 43 (23), 41 (100), 40 (11). HRMS calcd for $C_{17}H_{28}O_2$ 264.2089, (M^+−H_2O) 246.1984, found 246.1980.

5.2.12. 4-[2-(1*R,2*S**)-(2-Hydroxycyclohexylmethyl)-allyl]tetrahydro-2*H*-pyran-4-ol (2q).** Colourless oil; t_r 15.68; R_f 0.30 (EtOAc); ν (film) 3441 (OH), 1641 (C=CH), 1106 cm^{-1} (CO); δ_H 1.15–2.05 (14H, m, $(CH_2)_4$, C*H*$_2$CHCHOH, 2×C*H*$_2$CH$_2$O), 2.22, 2.27 (2H, AB system, J=13.6 Hz, CC*H*$_2$C), 2.32 (2H, br s, 2×OH), 2.69 (1H, dd, J=13.9, 4.2 Hz, C*H*CHOH), 3.24 (1H, td, J= 5.5, 4.2 Hz, CHOH), 3.73–3.80 (4H, m, 2×CH_2O), 4.85–4.97 (2H, 2s, CH_2=C); δ_C 24.9, 25.5, 30.9, 35.7, 37.7, 38.6, 41.8 [C*C*H$_2$CH, 2×*C*H$_2$CH$_2$O, $(CH_2)_4$], 43.4 (*C*HCHOH), 48.3 (C*C*H$_2$C), 64.0 (2×CH_2O), 68.7 (COH), 75.3 (CHOH), 115.8 (H$_2$*C*=C), 144.7 (*C*=CH$_2$); *m/z* 236 (M^+−18, <1%), 136 (23), 121 (68), 107 (21), 101 (48), 99 (11), 98 (85), 95 (14), 94 (37), 93 (35), 91 (13), 83 (21), 81 (68), 80 (28), 79 (37), 77 (13), 71 (45), 69 (11), 68 (11), 67 (30), 57 (21), 55 (52), 54 (10), 53 (52), 43 (80), 42 (22), 41 (100). HRMS calcd for $C_{15}H_{26}O_3$ 254.1882, (M^+−H_2O) 236.1776, found 236.1786.

5.3. General procedure for the preparation of 1,7-dioxaspiro[4.4]nonanes 3. Isolation of iodohydrins 4g and 4i

Iodine (0.382 g, 1.5 mmol) was added to a solution of the corresponding diol **2** (1 mmol) in THF (20 ml) (dioxane/H_2O 7:1 was used for diols **2l**–**n**). The mixture was stirred for 5 min at room temperature and then Ag_2O (0.346 g, 1.5 mmol) was added with additional stirring for 24 h. The resulting suspension was filtered and water (10 ml) was added to the filtrate, followed by extraction with ethyl acetate (3×10 ml). The organic phase was successively washed with a saturated solution of Na_2SO_3 (2×10 ml) and water (2×10 ml), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure (15 Torr) to furnish pure compounds **3**. Compound **3g** needed purification by column chromatography (silica gel, hexane/EtOAc).

5.3.1. 8,8-Diethyl-2,2-dimethyl-1,7-dioxaspiro[4.4]nonane (3a). Colourless oil; t_r 9.34; R_f 0.50 (hexane/EtOAc 8:2); ν (film) 1461, 1056 cm^{-1} (CO); δ_H 0.80–0.88 (6H, m, 2×C*H*$_3$CH$_2$), 1.20–1.30 (10H, m, 2×C*H*$_2$CH$_3$, 2×CCH$_3$), 1.35–2.15 (4H, CH_2CH_2), 1.75, 1.98 (2H, AB system, J= 13.2 Hz, CCH_2C), 3.64, 3.73 (2H, AB system, J=9.0 Hz, CH_2O); δ_C 8.4, 8.5 (2×*C*H$_3$CH$_2$), 28.9, 29.1, (2×*C*H$_3$C), 29.6, 30.0 (2×*C*H$_2$CH$_3$), 37.0, 38.8, (CH_2CH_2), 48.7 (C*C*H$_2$C), 76.6 (CH_2O), 80.7, 85.7, 89.5 (3×C); *m/z* 183 (M^+−29, 57%), 165 (10), 153 (32), 109 (57), 101 (12), 97 (17), 93 (25), 84 (15), 83 (21), 73 (18), 71 (11), 70 (29), 69 (43), 67 (12), 57 (100), 56 (29), 55 (66), 53 (13), 43 (81), 42 (15), 41 (85). HRMS calcd for $C_{13}H_{24}O_2$ 183.1385, found 183.1381.

5.3.2. 8,8-Diethyl-2,2-dipentyl-1,7-dioxaspiro[4.4]nonane (3b). Colourless oil; t_r 15.07; R_f 0.59 (hexane/EtOAc 8:2); ν (film) 1453, 1060 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH_3), 1.20–2.10 (24H, m, 4×C*H*$_2$CH$_3$, 8×C*H*$_2$CH$_2$), 1.74, 1.99 (2H, AB system, J=13.1 Hz, CCH_2C), 3.61, 3.72 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 8.5, 14.0 (4×CH_3), 22.6, 24.0, 24.1, 29.4, 29.6, 30.1, 32.5, 32.6, 35.5, 36.9, 39.2, 39.5 (4×*C*H$_2$CH$_3$, 8×*C*H$_2$CH$_2$), 48.4 (C*C*H$_2$C), 77.2 (CH_2O), 85.5, 85.7, 89.1 (3×C); *m/z* 295 (M^+−29, 22%), 253 (29), 139 (21), 121 (45), 109 (21), 101 (21), 99 (11), 97 (19), 95 (14), 83 (20), 81 (13), 71 (20), 69 (29), 67 (15), 57 (100), 56 (18), 55 (77), 43 (94), 42 (10), 41 (84). HRMS calcd for $C_{21}H_{40}O_2$ 324.3028, (M^+−C_2H_5) 295.2637, found 295.2638.

5.3.3. (2*R,5*R**) and (2*R**,5*S**)-8,8-Diethyl-2-hexyl-1,7-dioxaspiro[4.4]nonane (3c).** Colourless oil; t_r 13.38; R_f 0.50 (hexane/EtOAc 8:2); ν (film) 1459, 1060 cm^{-1} (CO); δ_H 0.75–1.00 (18H, m, 6×CH_3), 1.15–2.10 (40H, m, 6×C*H*$_2$CH$_3$, 12×C*H*$_2$CH$_2$, 2×CCH$_2$C), 3.40–3.45 (1H, m, CH minor diastereoisomer), 3.61, 3.76 (2H, AB system, J= 9.1 Hz, CH_2O minor diastereoisomer), 3.63, 3.80 (2H, AB system, J=9.1 Hz, CH_2O major diastereoisomer), 3.75–3.90 (1H, m, CH major diastereoisomer); δ_C 8.5, 13.4 (6×CH_3), 22.5, 26.0, 29.3, 29.4, 29.7, 29.8, 30.0, 31.3, 31.6, 31.7, 34.9, 36.2, 36.3 (6×*C*H$_2$CH$_3$, 12×*C*H$_2$CH$_2$), 47.4, 48.1 (2×C*C*H$_2$C), 76.0, 76.6 (2×CH), 78.8, 79.0 (2×CH_2O), 85.9, 86.0, 89.4 (4×C); *m/z* 239 (M^+−29, 33%), 221 (10), 109 (11), 83 (20), 69 (12), 57 (90), 55 (63), 43 (72), 41 (100). HRMS calcd for $C_{17}H_{32}O_2$ 268.2402, (M^+−C_2H_5) 239.2011, found 239.1992.

5.3.4. (2*R,5*R**) and (2*R**,5*S**)-8,8-Diethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane (3d).** Colourless oil; t_r 14.08, 14.40; R_f 0.61, 0.63 (hexane/EtOAc 8:2); ν (film) 1459, 1060 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH_3), 1.20–2.40 (20H, m, 4×C*H*$_2$CH$_3$, 2×CH_2CH_2, 2×CCH$_2$C), 3.70, 3.93 (2H, AB system, J=9.1 Hz, CH_2O), 3.75, 3.98 (2H, AB system, J= 9.5 Hz, CH_2O), 4.20, 4.93 (2H, 2t, J=8.9 Hz, CHPh), 7.20–7.40 (10H, m, 10×ArH); δ_C 8.5, 8.55, 8.6, 8.65 (4×CH_3), 29.7, 29.8, 29.9, 35.0, 35.1, 42.8, 45.0, 46.0 (4×*C*H$_2$CH$_3$, 2×CH_2CH_2), 48.4 (2×C*C*H$_2$C), 77.2 (2×CH_2O), 80.4 (2×CHO), 86.3, 86.7, 90.5, 90.8 (4×C); *m/z* (t_r 14.08) 231 (M^+−29, 52%), 129 (10), 109 (28), 105 (17), 104 (65), 91 (21), 77 (10), 57 (100), 55 (33), 53 (10), 43 (24), 41 (28), 40 (11); *m/z* (t_r 14.40) 231 (M^+−29, 30%), 91 (16), 83 (20), 57 (100), 55 (24), 43 (12), 41 (15). HRMS calcd for $C_{17}H_{24}O_2$ 260.1776, (M^+−C_2H_5) 231.3102, found 231.3100.

5.3.5. 8,8-Dicyclopropyl-2,2-dimethyl-1,7-dioxaspiro-[4.4]nonane (3e). Colourless oil; t_r 15.07; R_f 0.65 (hexane/EtOAc 8:2); ν (film) 3060 (cyclopropyl C–H), 1054 cm^{-1} (CO); δ_H 0.30–0.50 (8H, m, 4×C*H*$_2$CH), 0.80–0.95, 1.00–1.15 (2H, 2m, 2×CH), 1.20, 1.24 (6H, 2s,

2×CH_3), 1.70–1.85, 1.95–2.15 (4H, 2m, CH_2CH_2), 1.76, 1.98 (2H, AB system, J=13.3 Hz, CCH_2C), 3.60, 3.73 (2H, AB system, J=8.7 Hz, CH_2O); δ_C 0.5, 0.6, 1.3, 1.5 (4×CH_2CH), 18.8, 19.1 (2×CH), 28.9, 29.1 (2×CH_3), 36.7, 38.8 (CH_2CH_2), 48.1 (CCH_2C), 77.7 (CH_2O), 80.7, 83.4, 89.1 (3×C); *m/z* 236 (M^+, <1%), 195 (67), 121 (13), 109 (12), 93 (10), 79 (13), 69 (65), 67 (14), 55 (40), 43 (90), 41 (100). HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, ($M^+-C_3H_5$) 195.1395, found 195.1404.

5.3.6. 2″,2‴-Diethyldispiro[adamantane-2,2′-tetrahydrofuran-5′,4‴-tetrahydrofuran] (3f). Colourless oil; t_r 16.28; R_f 0.75 (hexane/EtOAc 8:2); ν (film) 1460, 1061 cm^{-1} (CO); δ_H 0.70–0.85 (6H, m, 2×CH_3), 1.15–2.10 (24H, m, 2×CH_2CH_3, CCH_2C, CCH_2CH_2C, 4×C$H$$CH_2$, 5×C$H_2$CH), 3.62, 3.74 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 8.6, 8.7 (2×CH_3), 27.2, 27.4, 36.1, 37.8, (4×CH), 31.3, 32.9, 33.2, 33.3, 34.4, 35.3, 35.9, 37.0, 37.7 (5×CH_2CH, CH_2CH_2, 2×CH_2CH_3), 49.5 (CCH_2C), 75.7 (CH_2O), 85.9, 86.2, 89.2 (3×C); *m/z* 304 (M^+, <1%), 276 (13), 275 (71), 203 (34), 190 (11), 175 (12), 166 (11), 135 (99), 151 (41), 149 (16), 148 (15), 135 (38), 133 (10), 121 (11), 105 (14), 97 (10), 95 (11), 93 (24), 92 (13), 91 (38), 81 (19), 80 (12), 79 (44), 77 (17), 69 (21), 67 (32), 65 (10), 57 (84), 55 (100), 53 (22), 43 (44), 42 (11), 41 (95). HRMS calcd for $C_{20}H_{32}O_2$ 304.2402, ($M^+-C_2H_5$) 275.2011, found 275.2015.

5.3.7. Dispiro[adamantane-2,2′-tetrahydrofuran-5′,4″-tetrahydrofuran-2″,2‴-adamantane] (3g). Colourless solid; R_f 0.67 (hexane/EtOAc 8:2); mp 48–49 °C; ν (film) 1469, 1065 cm^{-1} (CO); δ_H 1.40–2.28 (34H, m, 8×CH, 10×CH_2CH, CH_2CH_2, CCH_2C), 3.66, 3.77 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 26.8, 27.1, 27.2, 27.3, 35.7, 38.0, 38.3, 38.8 (8×CH), 33.0, 33.4, 33.5, 33.7, 35.2, 35.5, 35.7, 35.8, 35.9, 36.3, 37.8, 37.9 (10×CH_2CH, CH_2CH_2), 49.7 (CCH_2C), 76.5 (CH_2O), 86.3, 86.6, 88.7 (3×C); *m/z* 368 (M^+, 2%), 338 (10), 206 (15), 205 (100), 204 (11), 165 (28), 151 (15), 91 (12), 79 (15). HRMS calcd for $C_{25}H_{36}O_2$ 368.2715, found 368.2711.

5.3.8. Trispiro[cyclohexane-1,2′-tetrahydrofuran-5′,4″-tetrahydrofuran-2″,1‴-cyclohexane] (3h). Colourless oil; t_r 14.45; R_f 0.45 (hexane/EtOAc 8:2); ν (film) 1459, 1061 cm^{-1} (CO); δ_H 1.20–2.10 (24H, m, 12×CH_2CH_2), 1.72, 2.01 (2H, AB system, J=12.8 Hz, CCH_2C), 3.65, 3.76 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 23.5, 23.8, 23.9, 25.5, 25.6, 35.9, 36.1, 37.9, 38.3, 38.7 (12×CH_2CH_2), 50.3 (CCH_2C), 76.3 (CH_2O), 82.6, 82.8, 88.6 (3×C); *m/z* 264 (M^+, 14%), 221 (12), 165 (11), 155 (14), 152 (25), 151 (14), 133 (15), 125 (13), 113 (71), 109 (12), 97 (20), 96 (14), 95 (33), 94 (19), 91 (12), 81 (36), 79 (27), 69 (17), 67 (50), 57 (10), 55 (81), 54 (24), 53 (22), 43 (40), 42 (22), 41 (100), 40 (18). HRMS calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2122.

5.3.9. 2,2-Dimethyl-8-(3,4,5-trimethoxyphenyl)-1,7-dioxaspiro[4.4]nonane (3j) (major diastereoisomer). Colourless oil; t_r 17.21; R_f 0.55 (EtOAc); ν (film) 1591, 1506 (C=CH), 1127 cm^{-1} (CO); δ_H 1.27, 1.31 (6H, 2s, 2×CH_3), 1.70–2.20 (6H, m, CH_2CH_2, CH_2CH), 3.83, 3.86 (9H, 2s, 3×CH_3O), 3.84, 3.87 (2H, AB system, J=9.0 Hz, CH_2O), 5.04 (1H, dd, J=10.1, 5.9 Hz, CHO), 6.57 (2H, s, 2×ArH); δ_C 29.1 (2×CH_3), 35.0, 37.7 (CH_2CH_2), 48.8 (CH_2CH), 56.1, 60.8 (3×CH_3O), 77.2 (CH_2O), 79.5, 80.8 (2×C), 89.7 (CHO), 102.6 (2×ArCH), 138.1, 153.3 (4×ArC); *m/z* 322 (M^+, 85%), 251 (15), 221 (12), 211 (16), 195 (60), 194 (23), 182 (13), 181 (100), 179 (27). HRMS calcd for $C_{18}H_{26}O_5$ 322.1780, found 322.1767.

5.3.10. 2,2-Dimethyldispiro[tetrahydrofuran-5,4′-tetrahydrofuran-2′,4″-tetrahydro-2*H*-pyran] (3k). Colourless oil; t_r 11.48; R_f 0.34 (hexane/EtOAc 1:1); ν (film) 1051 cm^{-1} (CO); δ_H 1.22, 1.24 (6H, 2s, 2×CH_3), 1.60–2.10 (8H, m, 2×CH_2CH_2O, CCH_2CH_2C), 1.77, 2.08 (2H, AB system, J=13.0 Hz, CCH_2C), 3.56–3.65, 3.77–3.86 (4H, 2m, 2×CH_2CH_2O), 3.61, 3.72 (2H, AB system, J=9.2 Hz, CH_2O); δ_C 29.0, 29.1 (2×CH_3), 36.3, 37.2, 37.9, 38.7 (2×CH_2CH_2O, CCH_2CH_2C), 51.0 (CCH_2C), 65.1, 65.2 (2×CH_2CH_2O), 77.2 (CCH_2O), 79.4, 81.1, 89.2 (3×C); *m/z* 226 (M^+, 10%), 140 (15), 125 (14), 122 (28), 115 (52), 112 (17), 97 (12), 95 (13), 83 (53), 81 (13), 70 (40), 69 (25), 68 (16), 67 (22), 57 (14), 56 (33), 55 (45), 53 (27), 43 (100), 42 (27), 41 (91), 40 (23). HRMS calcd for $C_{13}H_{22}O_3$ 295.1569, found 226.1571.

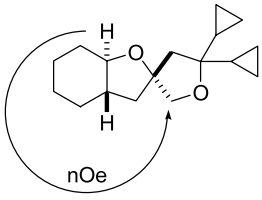
5.3.11. 2″,2‴-Dimethyl-1-propyldispiro[piperidine-4,2′-tetrahydrofuran-4′,5‴-tetrahydrofuran] (3l). Colourless oil; t_r 14.01; R_f 0.25 (EtOAc/MeOH 1:1); ν (film) 1057 (CO); δ_H 0.92 (3H, t, J=7.4 Hz, CH_3CH_2), 1.20, 1.22 (6H, 2s, 2×CCH_3), 1.40–2.10 (10H, m, CCH_2CH_2C, 2×CH_2CH_2N, CH_2CH_3), 1.73, 2.07 (2H, AB system, J=13.0 Hz, CCH_2C), 2.35–2.45, 2.70–2.80 (6H, 2m, 3×CH_2N), 3.63, 3.75 (2H, AB system, J=9.2 Hz, CH_2O); δ_C 12.1 (CH_3CH_2), 19.4 (CH_2CH_3), 28.7, 29.0 (2×CH_3C), 35.5, 36.1, 37.3, 37.5 (2×CH_2CH_2N, CCH_2CH_2C), 43.8 ($NCH_2CH_2CH_3$), 51.3 (CCH_2C), 60.1, 60.2 (2×NCH_2CH_2-C), 77.0 (CH_2O), 80.0, 81.1, 81.9 (3×C); *m/z* 267 (M^+, 3%), 239 (17), 238 (100), 110 (10). HRMS calcd for $C_{16}H_{29}NO_2$ 267.2198, found 267.2198.

5.3.12. 2,2-Dimethyldispiro[tetrahydrofuran-5,4′-tetrahydrofuran-2′,4″-tetrahydro-2*H*-thiopyran] (3m). Colourless oil; t_r 13.46; R_f 0.35 (hexane/EtOAc 7:3); ν (film) 1021 cm^{-1} (CO); δ_H 1.22, 1.26 (6H, 2s, 2×CH_3), 1.60–2.10 (8H, m, 2×CH_2CH_2S, CCH_2CH_2C), 1.78, 2.07 (2H, AB system, J=13.6 Hz, CCH_2C), 2.25–2.50, 2.75–2.90 (4H, 2m, 2×CH_2CH_2S), 3.69, 3.79 (2H, AB system, J=9.2 Hz, CH_2O); δ_C 25.4, 26.2 (2×CH_2CH_2S), 29.0, 29.1 (2×CH_3), 35.7, 38.7, 42.5, 42.6 (2×CH_2CH_2S, CCH_2CH_2-C), 52.5 (CCH_2C), 77.2 (CH_2O), 79.0, 81.4, 89.3 (3×C); *m/z* 242 (M^+, <1%), 227 (10), 209 (11), 140 (21), 125 (15), 110 (35), 99 (45), 98 (43), 97 (41), 83 (51), 81 (11), 70 (41), 67 (22), 57 (14), 53 (12), 44 (10), 43 (100), 42 (17). HRMS calcd for $C_{13}H_{22}O_2S$ 242.1341, (M^+-CH_3) 227.1106, found 227.1104.

5.3.13. 1-Propyltrispiro[piperidine-4,2′-tetrahydrofuran-4′,2″-tetrahydrofuran-5″,4‴-tetrahydro-2*H*-thyopyran] (3n). Colourless oil; t_r 18.51; R_f 0.10 (EtOAc); ν (film) 1045 cm^{-1} (CO); δ_H 0.87 (3H, t, J=7.4 Hz, CH_3CH_2), 1.40–2.10 (14H, m, CH_2CH_3, 2×CH_2CH_2N, 2×CH_2CH_2S, CCH_2CH_2C), 1.70, 2.05 (2H, AB system, J=12.8 Hz, CCH_2C) 2.20–2.75 (10H, 2×CH_2S, 3×CH_2N), 3.60, 3.73 (2H, AB system, J=9.3 Hz, CH_2O);δ_C 11.8 (CH_3CH_2), 22.5 (CH_2CH_3), 24.1, 24.3 (2×CH_2S), 33.3, 35.2, 37.1, 37.5, 38.0, 38.1 (CCH_2CH_2C, 2×CH_2CH_2N, 2×CH_2CH_2S), 49.9, 50.8 ($NCH_2CH_2CH_3$,

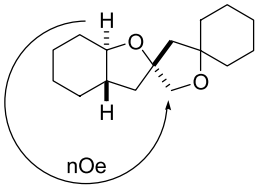
C*C*H$_2$C), 58.3, 59.0 (2×N*C*H$_2$CH$_2$C), 76.8 (CH$_2$O), 82.2, 82.4, 84.3 (3×C); *m/z* 325 (M$^+$, <1%), 296 (100), 282 (30), 142 (12), 141 (70), 140 (12), 124 (23), 123 (10), 112 (29), 44 (36), 43 (20), 42 (20), 41 (11). HRMS calcd for $C_{18}H_{31}NO_2S$ 325.2075, found 325.2070.

5.3.14. (2*R,3a*S**,7a*R**) and (2*R**,3a*R**,7a*S**)-2′,2′-Dicyclopropylspiro[perhydrobenzo[*b*]furan-2,4′-tetrahydrofuran] (3o).** Colourless oil; t_r 14.65; R_f 0.40 (hexane/EtOAc 8:2); *ν* (film) 3053 (cyclopropyl C–H), 1063 cm^{-1} (CO); δ_H 0.25–0.50 (16H, m, 8×cyclopropyl C*H*$_2$CH), 0.75–1.00 (4H, m, 4×cyclopropyl CH), 1.05–2.20 [26H, m, 2×(CH$_2$)$_4$, 2×CC*H*$_2$CH, 2×C*H*CHO, 2×CCH$_2$C], 3.00 (1H, td, *J*=10.0, 3.8 Hz, CHO major diastereoisomer), 3.05–3.15 (1H, m, CHO minor diastereoisomer), 3.48, 3.76 (2H, AB system, *J*=8.9 Hz, CH$_2$O minor diastereoisomer), 3.59, 3.87 (2H, AB system, *J*=9.2 Hz, CH$_2$O major diastereoisomer); δ_C −0.4, 0.1, 0.3, 0.6, 1.0, 1.2, 1.3, 1.4 (8×cyclopropyl *C*H$_2$CH), 18.5, 18.8, 19.0, 19.3 (4×cyclopropyl CH), 24.3, 25.4, 25.8, 28.8, 29.0, 29.4, 31.4, 31.5, 40.0, 40.6 [2×(CH$_2$)$_4$, 2×C*C*H$_2$CH], 45.4, 45.7 (2×*C*HCHO), 48.3, 48.9 (2×C*C*H$_2$C), 78.1, 78.4 (2×CH$_2$O), 82.8, 83.2 (2×CHO), 84.1, 84.3, 87.9, 88.2 (4×C); *m/z* 262 (M$^+$, <1%), 222 (15), 221 (100), 121 (11), 95 (10), 81 (11), 79 (13), 69 (14), 67 (11), 57 (17), 55 (55), 54 (25), 53 (35), 44 (10), 43 (79), 42 (27), 41 (100), 40 (27). HRMS calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1931.

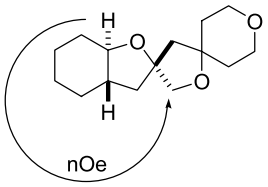


major diastereoisomer

5.3.15. (2″*R,3a″*S**,7a″*R**)-Dispiro[cyclohexane-1,2′-tetrahydrofuran-4′,2″-perhydrobenzo[*b*]furan] (3p).** Colourless oil; t_r 14.33; R_f 0.43 (hexane/EtOAc 8:2); *ν* (film) 1447, 1064 cm^{-1} (CO); δ_H 1.20–2.10 (21H, m, 9×C*H*$_2$CH$_2$, CC*H*$_2$CH, C*H*CHO), 1.76, 2.03 (2H, AB system, *J*=13.2 Hz, CCH$_2$C), 3.02 (1H, td, *J*=10.1, 3.6 Hz, CHO), 3.64, 3.90 (2H, AB system, *J*=9.4 Hz, CH$_2$O); δ_C 23.7, 23.8, 24.3, 25.4, 25.7, 29.0, 31.6, 37.3, 37.7, 40.6 (9×*C*H$_2$CH$_2$, C*C*H$_2$CH), 45.4 (*C*HCHO), 51.3 (C*C*H$_2$C), 76.2 (CH$_2$O), 83.1 (CHO), 83.2, 88.4 (2×C); *m/z* 250 (M$^+$, 16%), 221 (15), 207 (37), 155 (24), 154 (18), 152 (30), 119 (16), 113 (12), 107 (22), 96 (10), 95 (24), 82 (15), 81 (57), 80 (14), 79 (22), 69 (11), 68 (10), 67 (47), 57 (11), 55 (74), 54 (20), 53 (27), 43 (37), 42 (19), 41 (100), 40 (16). HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1963.



5.3.16. (2*R,3a*S**,7a*R**)-Dispiro[perhydrobenzo[*b*]-furan-2,4′-tetrahydrofuran-2′,4″-tetrahydro-2*H*-pyran] (3q).** Colourless oil; t_r 14.59; R_f 0.34 (hexane/EtOAc 1:1); *ν* (film) 1055 cm^{-1} (CO); δ_H 1.00–2.20 [15H, m, 2×C*H*$_2$CH$_2$CO, (CH$_2$)$_4$, CC*H*$_2$CH, C*H*CHO], 1.80, 2.07 (2H, AB system, *J*=13.3 Hz, CCH$_2$C), 3.04 (1H, td, *J*=10.1, 3.7 Hz, CHO), 3.60–3.90 (4H, m, 2×CH$_2$C*H*$_2$O), 3.67, 3.93 (2H, AB system, *J*=9.5 Hz, CH$_2$O); δ_C 24.2, 25.6, 28.9, 31.1, 31.5, 37.9, 40.0 [(CH$_2$)$_4$, C*C*H$_2$CH, *C*H$_2$CH$_2$O], 45.3 (*C*HCHO), 51.6 (C*C*H$_2$C), 65.1, 67.3 (CH$_2$*C*H$_2$O), 76.4 (CH$_2$O), 79.9, 88.2 (2×C), 83.3 (CHO); *m/z* (t_r 14.59) 252 (M$^+$, 4%), 208 (10), 155 (12), 154 (13), 122 (14), 107 (21), 115 (17), 108 (17), 99 (17), 98 (14), 97 (11), 96 (19), 95 (23), 94 (12), 83 (34), 82 (16), 81 (43), 80 (10), 79 (20), 70 (12), 69 (14), 68 (24), 67 (58), 57 (14), 55 (53), 54 (22), 53 (33), 43 (49), 42 (24), 41 (100), 40 (25). HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1724.



5.3.17. 5′-(2-Hydroxy-2-adamantylmethyl)-5′-iodomethylspiro[adamantane-2,2′-tetrahydrofuran] (4g). Colourless oil; R_f 0.60 (hexane/EtOAc 8:2); *ν* (film) 3444 (OH), 1100 cm^{-1} (CO); δ_H 1.20–2.20 (35H, m, 8×CH, 10×C*H*$_2$CH, OH, CCH$_2$CH$_2$C, CCH$_2$C), 3.33, 3.51 (2H, AB system, *J*=9.8 Hz, CH$_2$I); δ_C 15.1 (CH$_2$I), 26.2, 26.3, 27.3, 27.4, 29.4, 36.3, 37.4, 39.1 (8×CH), 31.0, 31.7, 31.8, 32.4, 32.9, 33.0, 33.3, 33.5, 34.4, 34.7, 38.4, 40.0, 42.5 (10×*C*H$_2$CH, C*C*H$_2$C, CC*H*$_2$*C*H$_2$C), 74.0, 78.1, 82.5 (3×C); *m/z* 368 (M$^+$−128, <1%), 338 (10), 206 (10), 205 (100), 151 (10), 79 (11), 127 (25), 126 (45), 43 (22), 42 (13). HRMS calcd for $C_{25}H_{37}IO_2$ 496.1838, (M$^+$−HI) 368.2715, found 368.2701.

5.3.18. 1-Cyclohexyl-2-(2-iodomethyl-5,5-dimethyltetrahydro-2-furanyl)ethan-1-ol (4i). Colourless oil; t_r 12.52; R_f 0.62 (hexane/EtOAc 8:2); *ν* (film) 3380 (OH), 1050 cm^{-1} (CO); δ_H 0.98–2.00 [16H, m, (CH$_2$)$_5$, CCH$_2$CH$_2$C, CHC*H*$_A$-H$_B$C, OH], 1.25, 1.28 (6H, 2s, 2×CH$_3$), 2.23–2.35 (2H, 2m, CHCH$_A$*H*$_B$C, C*H*CHOH), 3.19, 3.40 (2H, AB system, *J*=10.2 Hz, CH$_2$I,), 3.55–3.60 (1H, m, C*H*OH); δ_C 12.4 (CH$_2$I), 26.2, 26.3, 26.6, 28.4, 28.6 [(CH$_2$)$_5$], 29.0, 29.5 (2×CH$_3$), 37.5, 38.1 (CC*H*$_2$*C*H$_2$C), 41.1 (CH*C*H$_2$C), 44.0 (*C*HCHOH), 72.3 (CHOH), 84.3, 85.5 (2×C); *m/z* 238 (M$^+$−128, <1%), 155 (49), 127 (25), 126 (45), 125 (47), 113 (21), 97 (11), 95 (36), 93 (11), 83 (11), 81 (24), 70 (15), 69 (25), 67 (22), 57 (11), 56 (18), 55 (84), 54 (10), 53 (16), 43 (83), 42 (12), 41 (100). HRMS calcd for $C_{15}H_{27}IO_2$ 366.1056, (M$^+$−HI) 238.1933, found 238.1911.

5.4. General procedure for the oxidation of 1,7-dioxaspiro[4.4]nonanes 3 to lactones 6

A suspension of RuO_2 (21 mg, 0.16 mmol) and $NaIO_4$ (1.04 g, 4.88 mmol) in H_2O (5 ml) was added to a solution of the corresponding 1,7-dioxaspiro[4.4]nonane **3** (1.0 mmol) in CCl_4 (5 ml) at room temperature. After stirring the reaction for 24 h, Pr^{i}OH (3 ml) was added, the resulting mixture being extracted with CCl_4 (2×5 ml). The

organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The resulting residue was passed through a pad containing celite, in order to eliminate the remaining ruthenium compounds, yielding the corresponding pure lactones **6**, which did not require any further purification.

5.4.1. 8,8-Diethyl-2,2-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one (6a). Colourless oil; t_r 11.05; R_f 0.31 (hexane/EtOAc 8:2); ν (film) 1770 (C=O), 1050 cm^{-1} (CO); δ_H 0.80–0.95 (6H, m, 2×CH_3CH$_2$), 1.21–1.29 (6H, m, 2×CH_3C), 1.35–1.40 (4H, m, 2×CH_2CH$_3$), 1.35–2.25 (4H, m, CH$_2$CH$_2$), 2.05, 2.24 (2H, AB system, J=13.7 Hz, CCH$_2$C); δ_C 7.7, 7.8 (2×CH$_3$CH$_2$), 28.3, 28.9 (2×CH$_2$CH$_3$), 30.6, 30.7 (2×CH$_3$C), 37.2, 38.5 (CH$_2$CH$_2$), 45.1 (CCH$_2$C), 83.8, 84.1, 86.4 (3×C), 178.0 (C=O); *m/z* 211 (M^+−15, 1%), 169 (34), 154 (10), 153 (71), 139 (16), 101 (12), 97 (35), 95 (10), 91 (11), 83 (37), 70 (31), 69 (47), 67 (10), 57 (78), 56 (41), 55 (50), 53 (15), 43 (100), 42 (18), 41 (76), 40 (12). HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, (M^+−CH$_3$) 211.1334, found 211.1339.

5.4.2. (2*R,5*R**) and (2*R**,5*S**)-8,8-Diethyl-2-hexyl-1,7-dioxaspiro[4.4]nonan-6-one (6c).** Colourless oil; t_r 14.86; R_f 0.32 (hexane/EtOAc 8:2); ν (film) 1774 (C=O), 1030 cm^{-1} (CO); δ_H 0.80–1.00 (18H, m, 6×CH$_3$), 1.20–2.50 (36H, m, 12×CH_2CH$_2$, 6×CH_2CH$_3$) 2.07, 2.25 (4H, AB system, J=14.0 Hz, 2×CCH$_2$C), 3.50–3.83 (2H, 2m, 2×CH); δ_C 7.6, 7.7, 14.0, 14.05 (6×CH$_3$), 22.4, 22.5, 23.7, 28.1, 28.8, 30.5, 30.6, 31.4, 31.5, 31.7, 35.6, 35.7, 35.8, 37.7, 42.8 (12×CH$_2$CH$_2$, 6×CH$_2$CH$_3$), 44.3, 46.6 (2×CCH$_2$C), 80.9, 83.4, (2×CH), 86.7, 87.0 (4×C), 177.8, 177.9 (2×C=O); *m/z* 282 (M^+, 5%), 225 (19), 210 (12), 209 (77), 135 (10), 109 (11), 97 (10), 84 (11), 83 (80), 82 (10), 81 (15), 79 (13), 70 (10), 69 (39), 67 (21), 57 (87), 56 (15), 55 (100), 54 (16), 53 (17), 44 (18), 43 (90), 42 (22), 41 (94), 40 (23). HRMS calcd for $C_{17}H_{30}O_3$ 282.2195, found 282.2169.

5.4.3. 8,8-Dicyclopropyl-2,2-dimethyl-1,7-dioxaspiro-[4.4]nonan-6-one (6e). Colourless oil; t_r 16.00; R_f 1.29 (hexane/EtOAc 8:2); ν (film) 3048 (cyclopropyl C–H), 1773 cm^{-1} (C=O); δ_H 0.30–0.55 (8H, m, 4×CH_2CH), 0.85–1.15 (2H, 2m, 2×CH), 1.28, 1.35 (6H, 2s, 2×CH$_3$), 1.70–2.00 (4H, m, CH$_2$CH$_2$), 2.03, 2.26 (2H, AB system, J=13.9 Hz, CCH$_2$C); δ_C 0.6, 0.7, 1.3, 1.4 (4×CH$_2$CH), 19.2, 19.3 (2×CH), 28.2, 28.9 (2×CH$_3$), 37.6, 38.5 (CH$_2$CH$_2$), 49.2 (CCH$_2$C), 83.1, 83.8, 83.9 (3×C), 177.7 (C=O); *m/z* 250 (M^+, <1%), 191 (30), 181 (12), 177 (14), 163 (18), 151 (20), 150 (77), 149 (11), 139 (15), 138 (13), 137 (83), 136 (12), 135 (48), 133 (11), 132 (36), 125 (11), 123 (20), 122 (16), 121 (82), 119 (12), 117 (18), 112 (48), 109 (47), 108 (14), 107 (28), 105 (12), 97 (43), 96 (24), 95 (31), 93 (34), 91 (35), 83 (10), 82 (15), 81 (28), 80 (28), 79 (38), 77 (24), 70 (19), 69 (100), 67 (42), 65 (10), 56 (10), 53 (15). HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1572.

5.4.4. 5″,5″-Diethyldispiro[adamantane-2,2′-tetrahydrofuran-5′,3″-tetrahydrofuran-2″-one] (6f). Colourless oil; t_r 18.00; R_f 0.33 (hexane/EtOAc 8:2); ν (film) 1770 (C=O), 1050 cm^{-1} (CO); δ_H 0.80–0.95 (6H, m, 2×CH_3CH$_2$), 1.20–2.40 (24H, m, 2×CH_2CH$_3$, 4×CH, 5×CH_2CH, CH$_2$CH$_2$, CCH$_2$C); δ_C 8.6, 8.8 (2×CH$_3$), 26.5, 26.6, 37.4, 38.0 (4×CH), 29.8, 30.0, 30.6, 32.0, 32.8, 34.5, 36.2, 37.1, 37.5 (5×CH$_2$CH, CCH$_2$$CH_2$C, 2×$CH_2CH_3$), 46.1 (C$CH_2$C), 83.8, 87.4, 89.1 (3×C), 178.0 (C=O); *m/z* 289 (M^+−29, 18%), 274 (13), 246 (15), 245 (82), 177 (17), 175 (13), 149 (24), 107 (10), 105 (11), 98 (11), 97 (12), 95 (11), 93 (24), 92 (14), 91 (32), 84 (15), 81 (15), 80 (12), 79 (40), 77 (16), 69 (32), 67 (31), 57 (100), 56 (12), 55 (90), 54 (13), 53 (26), 44 (10), 43 (54), 42 (11), 41 (90), 40 (17). HRMS calcd for $C_{20}H_{30}O_3$ 318.2195 (M^+−CO_2) 274.2297, found 274.2303.

5.4.5. Trispiro[cyclohexane-1,2′-tetrahydrofuran-5′,3″-tetrahydrofuran-2′-one-5″,1‴-cyclohexane] (6h). Colourless oil; t_r 15.95; R_f 0.33 (hexane/EtOAc 8:2); ν (film) 1770 (C=O); δ_H 1.20–2.40 (24H, m, 12×CH_2CH$_2$), 2.02, 2.25 (2H, AB system, J=13.7 Hz, CH$_2$C); δ_C 22.5, 22.6, 23.7, 23.9, 24.9, 25.5, 35.8, 36.1, 37.5, 37.6, 37.8, 38.0 (12×CH$_2$), 47.6 (CCH$_2$C), 83.3, 83.9, 85.8, (3×C), 177.8 (C=O); *m/z* 234 (M^+−44, 20%), 191 (14), 152 (17), 137 (10), 125 (39), 97 (27), 96 (12), 95 (32), 94 (36), 93 (16), 82 (14), 81 (41), 79 (22), 69 (14), 68 (13), 67 (38), 55 (88), 54 (22), 53 (22), 44 (15), 43 (57), 42 (29), 41 (100), 40 (24). HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1879.

5.4.6. (2*R,3a*S**,7a*R**) and (2*R**,3a*R**,7a*S**)-4′,4′-Dicyclopropyldispiro[perhydrobenzo[*b*]furan-2,3′-tetrahydrofuran-2′-one] (6o).** Colourless oil; t_r 15.70; R_f 0.34 (hexane/EtOAc 8:2); ν (film) 3045 (cyclopropyl C–H), 1772 (C=O), 1030 cm^{-1} (CO); δ_H 0.20–0.50 (16H, m, 8× cyclopropyl CH_2CH), 0.75–1.00 (4H, m, 4×cyclopropyl CH), 1.05–2.25 [26H, m, 2×(CH$_2$)$_4$, 2×CCH_2CH, 2×CHCHO, 2×CCH$_2$C], 3.00–3.15 (2H, m, CHO); δ_C 0.0, 0.2, 0.3, 0.5, 0.9, 1.1, 1.2, 1.3 (8×cyclopropyl CH$_2$CH), 18.8, 18.9, 19.0, 19.1 (4×cyclopropyl CH), 24.2, 24.7, 25.3, 28.0, 29.1, 29.9, 31.3, 32.1, 40.0, 40.1 [2×(CH$_2$)$_4$, 2×CCH$_2$CH], 44.9 (2×CHCHO), 50.1, 51.3 (2×CCH$_2$C), 83.5, 85.8 (2×CHO), 83.7, 88.9, 89.0, 89.1 (4×C), 177.1 (2×C=O); *m/z* 276 (M^+, <1%), 121 (10), 95 (18), 82 (15), 81 (16), 79 (13), 67 (60), 57 (20), 55 (35), 54 (29), 44 (100). HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1731.

5.4.7. (2″*R,3a″*S**,7a″*R**)-Dispiro[cyclohexane-1,5′-tetrahydrofuran-2′-one-3′,2″-perhydrobenzo[*b*]furan] (6p).** Colourless oil; t_r 14.99; R_f 0.30 (hexane/EtOAc 8:2); ν (film) 1773 (C=O), 1025 cm^{-1} (CO); δ_H 1.20–2.10 (21H, m, 9×CH_2CH$_2$, CCH_2CH, CHCHO), 2.05, 2.21 (2H, AB system, J=14.0 Hz, CCH$_2$C), 3.00 (1H, td, J=10.1, 3.4 Hz, CHO); δ_C 23.6, 23.7, 24.9, 25.8, 25.9, 28.5, 30.2, 35.5, 37.1, 40.0 (9×CH$_2$CH$_2$, CCH$_2$CH), 46.0 (*C*HCHO), 51.6 (CCH$_2$C), 84.0, 87.9 (2×C), 86.2 (CHO), 177.5 (C=O); *m/z* 264 (M^+, 7%), 217 (16), 166 (12), 151 (12), 150 (35), 149 (12), 147 (11), 138 (48), 137 (70), 136 (24), 135 (22), 134 (17), 132 (36), 123 (28), 122 (19), 121 (100), 119 (15), 118 (10), 117 (25), 109 (25), 108 (46), 107 (31), 105 (17), 98 (12), 96 (17), 95 (74), 94 (29), 93 (84), 91 (51), 83 (10), 82 (19), 81 (67), 80 (41), 79 (81), 77 (35), 69 (46), 68 (14), 67 (61), 66 (12), 65 (15), 55 (35), 54 (17), 53 (20). HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, (M^+−CO_2) 220.1827, found 220.1822.

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