Saturated oxygen heterocycles

CHRISTOPHER J. BURNS AND DONALD S. MIDDLETON

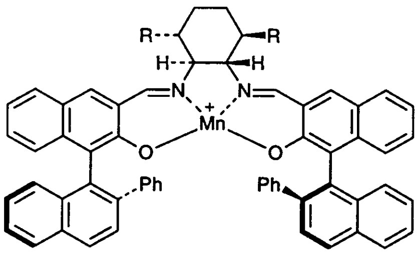
Pfizer Central Research, Sandwich, Kent CT11 7NU, UK

Reviewing the literature published between October 1994 and September 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 189

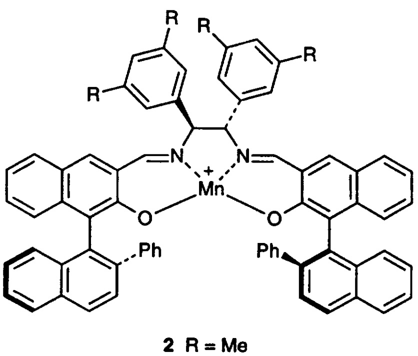
1 Three-membered rings

There have been further illustrations of the use of manganese salen complexes in asymmetric epoxidations of unfunctionalised olefins published over the review period. Katsuki *et al.* have reported on two new manganese salen catalysts, **1** and **2**, which show improved enantioselectivities in the epoxidations of a selected range of disubstituted olefins compared to their desmethyl analogues **3** and **4**, respectively.[1,2]

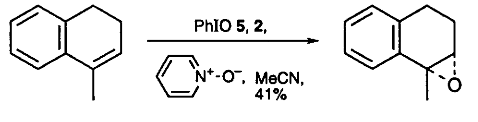
The catalyst **2** has also been employed in the highly enantioselective epoxidation of trisubstituted olefins where either iodosylbenzene **5** or sodium hypochlorite was used as oxidant.[3] Thus, the dihydronaphthalene derivative **6** is transformed into the epoxide **7** in 96% ee. Good to excellent ee's are also obtained with the complex **2** in the epoxidations of *cis*-olefins[4] and *cis*-enynes.[5]



1 R = Me
3 R = H

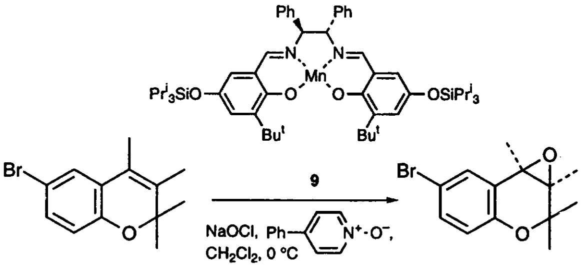


2 R = Me
4 R = H



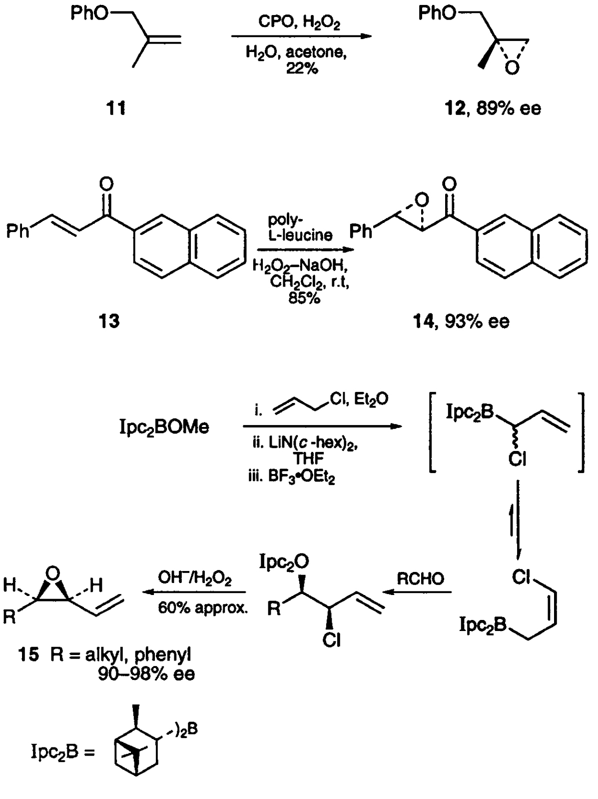
6 **7**, 96% ee

Brandes and Jacobsen have reported that certain tetrasubstituted olefins can be epoxidised with manganese salen catalysts with high enantioselectivity.[6] For example, the chromene derivative **8** is epoxidised with sodium hypochlorite in the presence of the catalyst **9**, to afford the epoxide **10** with 96% ee. Under these conditions, Jacobsen *et al.* have previously shown that styrene is epoxidised with only moderate ee; however this group has recently demonstrated that low temperature (−78°C) epoxidation of styrene using either magnesium monoperoxyphthalate (MMPP) or MCPBA as oxidant with a salen catalyst such as **9** (and NMO as an essential additive) generates styrene oxide with good ee (59–86%).[7] These conditions have recently been shown to be superior to the original aqueous bleach procedure in the epoxidation of a series of monosubstituted and *cis*-olefins.[8] Adam and co-workers have demonstrated that dimethyldioxirane can also be used as the oxidant with manganese salen catalysts.[9]



8 **10**, 94% ee

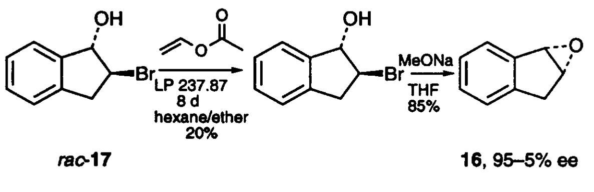
Amongst other routes to chiral epoxides, Hager and colleagues have demonstrated that 1,1-disubstituted olefins can be epoxidised with moderate to excellent enantioselectivity using chloroperoxidase (CPO).[10] For example, the olefin **11** is converted into **12** in low yield but with good enantioselectivity. Lasterra, Sánchez and Roberts have used catalytic poly-L-leucine to affect highly enantioselective epoxidations of a series of α,β-unsaturated ketones with H_2O_2–NaOH.[11] Thus, the olefin **13** was converted into the epoxide **14** in both excellent yield and ee. Jayaraman *et al.* have prepared the chiral *cis*-vinyl epoxides **15** *via* the intermediacy of chiral chlorohydrins, generated by asymmetric chloroallylborations of aldehydes (**Scheme 1**).[12] The product epoxides **15** are formed with excellent ee and in high yield.

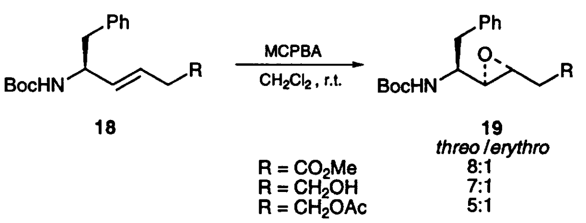


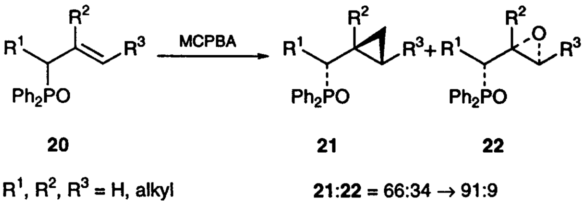
Scheme 1

Mitrochkine *et al.* have employed a lipase catalysed transesterification in the asymmetric synthesis of (1*S*,2*R*)-epoxy indane **16**.[13] Thus, the racemic bromohydrin **17** was treated with vinyl acetate in the presence of the lipase LP 237.87, and after 8 days unreacted bromohydrin was obtained with very high optical purity. The epoxy indane **15** was then formed upon reaction of this chiral bromohydrin with sodium methoxide. The use of epoxide hydrolases in the kinetic resolutions of mono- and 2,2-di-substituted epoxides has also been examined.[14]

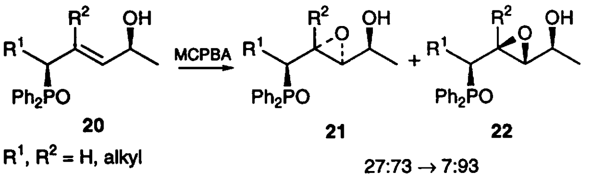
A number of diastereoselective epoxidations have also been reported over the review period. For example, Luthman and co-workers have shown that the allylic carbamates **18** are epoxidised with MCPBA to give predominantly the *threo* epoxides **19**, largely independent of the allylic substituent R.[15] Warren and his group have shown that epoxidations of the allylic phosphine oxides **20** with MCPBA leads preferentially to *anti* epoxides **21**; however the presence of an allylic *syn* hydroxy group reverses this trend giving instead the *syn*-epoxides **22** as the major products.[16]

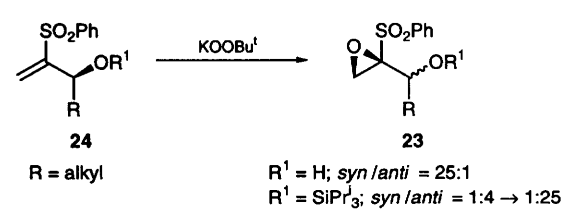


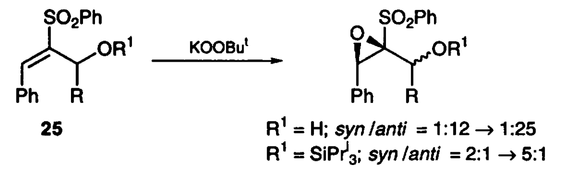




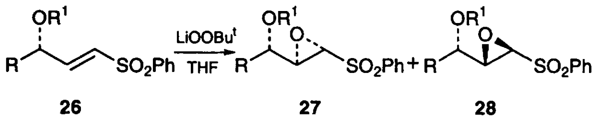
In an extension of previous work, Jackson *et al.* have shown that the stereochemistry of the sulfone epoxides **23** derived from **24** is significantly influenced by the nature of the allylic oxygen substituent; thus the free hydroxy compound (**24**, $R^1 = H$) gives predominantly *syn* epoxides while the silyloxy derivative (**24**, $R^1 = SiPr^i_3$) affords largely the *anti* isomer.[17] Interestingly, the opposite trend is seen for the substituted olefins **25**.







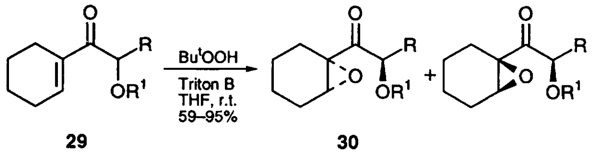
In related work, epoxidation of the olefin **26** is shown to generate predominantly the *syn* epoxide **27** unless the hydroxy protecting group is methoxyethoxymethyl or the alkyl substituent is bulky (*e.g.* Pr^i), when the *anti* epoxide **28** is favoured.[18] Linderman *et al.*[19] have demonstrated that the epoxidation of cyclohexenyl ketones **29** with *tert*-butyl hydroperoxide/Triton B gives preferentially the *anti* epoxides **30**, the ratio being largely independent of alkyl group R, or oxygen protecting group R^1.



26 **27** **28**

R = alkyl
R^1 = silyl, MEM

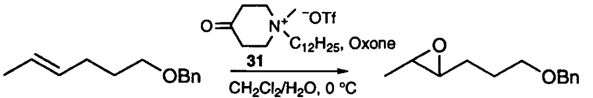
25:1 → 1:25



29 **30**

R = alkyl
R^1 = MOM, BOM,
COBu^t, Bn

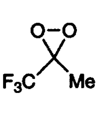
A number of significant reports on the use of dioxiranes in the synthesis of epoxides have been reported recently. Denmark and co-workers have reported the first catalytic epoxidation of alkenes with dioxiranes using the rationally designed phase transfer catalyst **31**.[20] The optimised conditions for the reaction include careful control of pH (7.5–8.0), slow addition of Oxone® and the use of the triflate salt of **31**, conditions which allow for high yielding epoxidations as shown in the conversion of **32** into **33**.



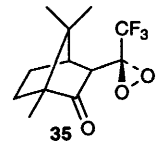
32 **33**

The *in situ* generation of methyl(trifluoromethyl)-dioxirane **34** for use in epoxidations has been disclosed by Yang *et al.*[21] The reactions are conducted in a homogeneous mixture of water and acetonitrile at neutral pH generating epoxides in excellent yield. Similarly, the *in situ* generation and reactions of the chiral dioxiranes **35** and **36** has been reported by Curci and colleagues.[22] While epoxides can be formed efficiently with these reagents, asymmetric induction is poor (<20% ee). Similar results have been reported for chiral tetralone-derived dioxiranes such as **37**.[23]

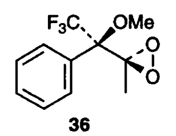
Murray *et al.* have shown that the diastereoselectivity observed in the epoxidation of cyclohex-2-en-1-ol **38** using dimethyldioxirane (DMDO) is dramatically affected by reaction solvent; a 1 : 1 mixture of *cis* and *trans* epoxides **39** and **40** is formed in acetone, and a 6 : 94 ratio is obtained in carbon tetrachloride/acetone (95 : 5).[24] Interestingly, when the hydroxy group in **38** is protected, altering the reaction solvent has little effect on the diastereoisomeric ratio.



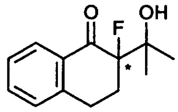
34



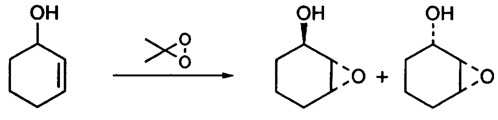
35



36



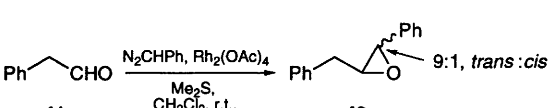
37



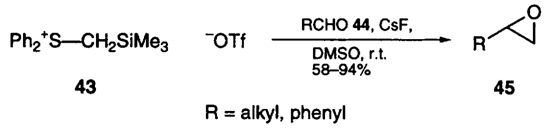
38

Solvent	39	:	40
acetone	54	:	46
CCl$_4$/acetone	6	:	94

While the formation of epoxides from the reaction of sulfur ylides and aldehydes has been known for some time, Aggarwal *et al.* have now shown that their recently disclosed catalytic process for sulfur ylide generation is sufficiently mild to be used with base sensitive aldehydes; the conversion of phenyl acetaldehyde **41** into the epoxide isomers **42** is representative.[25] Hioki *et al.* have also reported a non-basic procedure for sulfur ylide generation.[26] Exposure of the sulfonium triflate salt **43** to caesium fluoride in the presence of aldehydes **44**, furnishes the epoxides **45** in good to excellent yield. Matano has demonstrated that 2-oxobismuthonium ylides, prepared from the corresponding salts by treatment with base, also react with a range of aldehydes to give predominantly *trans*-substituted epoxides, as depicted for the conversion of salt **46** into the epoxide **47**.[27]

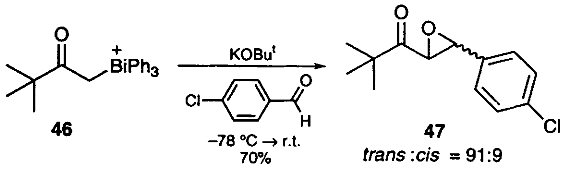


41 **42**



43 **45**

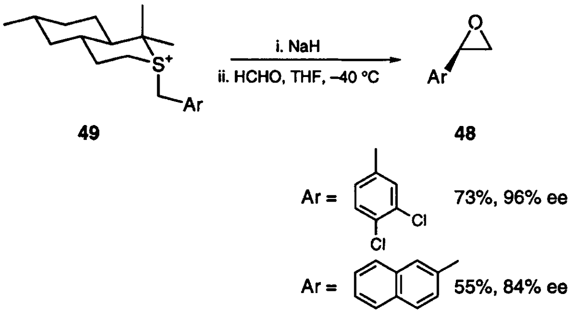
R = alkyl, phenyl

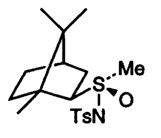


46 **47**

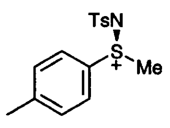
trans : *cis* = 91:9

Chiral sulfur ylides have been employed in the asymmetric synthesis of the aryl epoxides **48**.[28] Thus, the ylide is generated from the salt **49** by treatment with a suitable base, and subsequent reaction with paraformaldehyde gives the desired products. Chiral sulfoximines, such as **50**, have been used in asymmetric epoxidations of aryl aldehydes, with product ee's of 19–86%.[29] Variable ee's (21–70%) have also been obtained for epoxides generated from the reactions of a series of aldehydes and ketones with the ylide derived from the sulfimide **51**.[30]



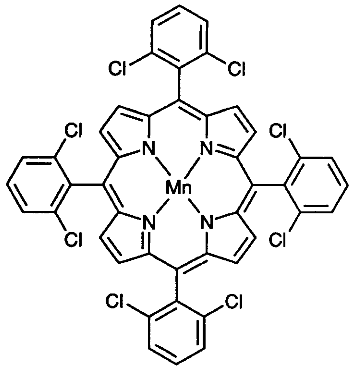


50



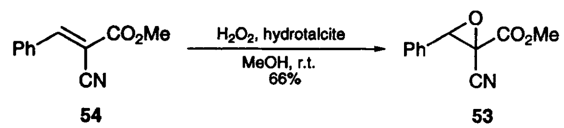
51

A review on the use of porphyrin and related transition metal complexes in the aerobic epoxidation of olefins has been published recently.[31] Manganese porphinoid complexes such as **52** have also been examined as epoxidation catalysts using peracetic acid as the oxidant.[32]

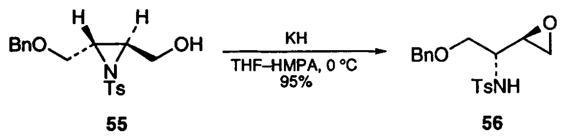


52

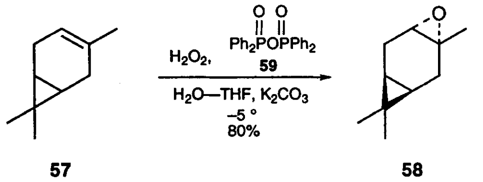
There have been a number of reports on the use of zeolites as catalysts for alkene epoxidation, and a review has also been published.[33] Kumar *et al.* report that the titanium silicate TS-1 catalyses the epoxidation of allylic alcohols with hydrogen peroxide efficiently, leading predominantly to *trans* products in good yield.[34] Catalysts related to TS-1 that can catalyse the epoxidation of large bulky alkenes have been reported by Fraile *et al.*[35] and by Jorda *et al.*[36] The catalysts used by each research group are readily prepared from silica and either titanium tetra-isopropoxide[35] or titanium tetrafluoride.[36] The synthetic anionic clay hydrotalcite has been shown to catalyse the epoxidation of a variety of electron deficient alkenes with hydrogen peroxide and the synthesis of the epoxide **53** from the olefin **54** is representative.[37]

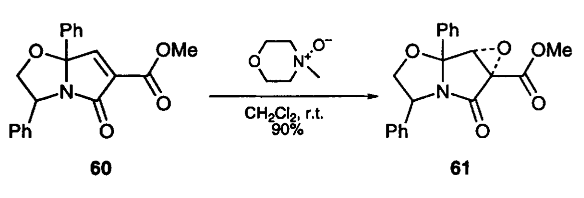


Three routes to epoxyalkylamines have been reported recently. Asensio and co-workers have demonstrated that protonation of the amino function in aminoalkenes with an arenesulfonic acid prior to epoxidation of the alkene moiety [with either DMDO, methyl(trifluoromethyl)dioxirane or MCPBA] leads to the corresponding aminoepoxides without the formation of any *N*-oxide.[38] The amino function can be similarly protected with boron trifluoride in diethyl ether prior to alkene epoxidation.[39] Ibuka *et al.* have used the aza-Payne rearrangement of a variety of chiral hydroxy aziridines in the synthesis of chiral *β*-amino epoxides.[40] For example, treatment of the hydroxy aziridine **55** with potassium hydride under the conditions shown gives the epoxide **56** in excellent yield.



New methods for alkene epoxidation include the use of hydrogen peroxide in conjunction with organophosphorus electrophiles.[41] For example, the epoxide **58** is prepared from the olefin **57** using hydrogen peroxide with the phosphorus anhydride **59** as promoter, though phosphoryl chlorides may also be used. Formamide has also been reported as a promoter of hydrogen peroxide epoxidations of a series of trisubstituted olefins.[42] Lastly, Meyers and co-workers have reported that tertiary amine *N*-oxides alone may act as epoxidising reagents for a

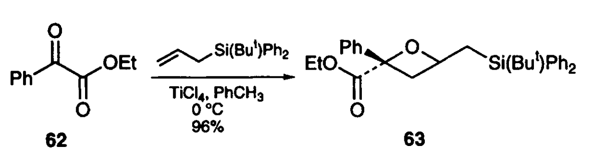


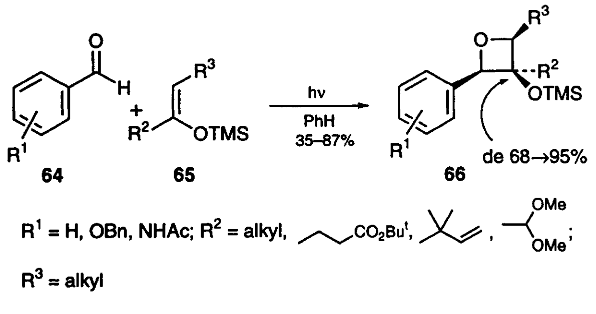


selected range of lactams, as shown for the conversion of **60** into **61**.[43]

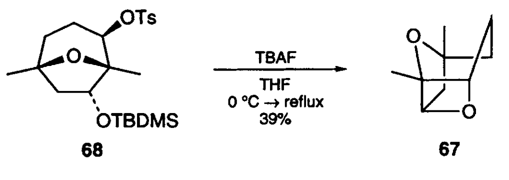
2 Four-membered rings

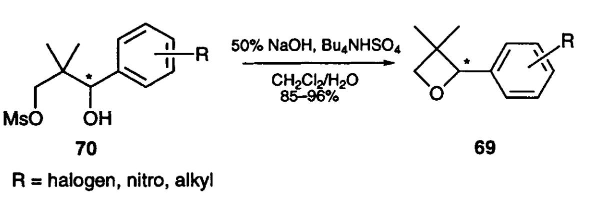
Akiyama and Kirino have disclosed a novel synthesis of oxetanes involving a titanium(IV) chloride promoted [2+2] cycloaddition process between a keto ester and an allyl silane.[44] The procedure, shown for the conversion of keto ester **62** into the oxetane **63**, has been carefully optimised to avoid formation of the simple allyl addition product and isomeric tetrahydrofurans. Bach has extended his work on the Paterno–Büchi reaction between benzaldehydes **64** and silyl enol ethers **65** leading to substituted 3-oxetanols **66**.[45] The reactions proceed with high diastereoselectivity largely independent of enol ether substitution, and they tolerate a variety of functionality on both the enol ether and the benzaldehyde.





Reinecke and Hoffmann have published a synthesis of the oxetane-containing core **67** of the natural product dictyoxetane. The oxetane ring is formed in a one-pot fluoride induced desilylation/cyclisation reaction generating **67** from the silyl ether **68** in moderate yield.[46] Phase-transfer catalysis has been shown to be the best method for the synthesis of the oxetanes **69** by base-induced cyclisation of the hydroxy mesylates **70**, the chiral centre being unaffected by these conditions.[47]

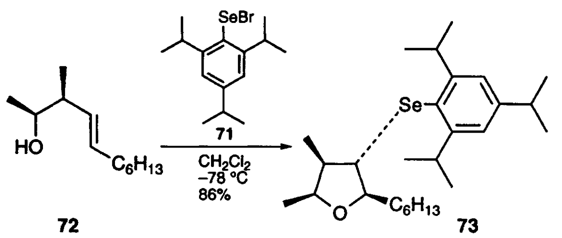


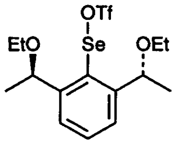


3 Five-membered rings

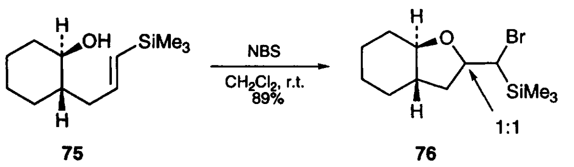
New and improved routes to tetrahydrofurans and tetrahydrofuran-containing natural products continue to be an active area of research, and there have been several important contributions over the review period.

The synthesis of tetrahydrofurans *via* formation of a C–O bond from an acyclic precursor is a particularly common approach to this ring system. Lipshutz and Gross have reported that the *in situ* generated selenium compound **71** converts homoallylic alcohols to tetrahydrofurans with remarkably high diastereoselectivity, particularly if the olefin is *trans*; the conversion of **72** into **73** is representative.[48] Similarly, Déziel and Malenfant have disclosed that the chiral C$_2$ symmetric selenium compound **74** also effects cyclisation of homoallylic alcohols with high diastereoslectivity.[49] The ability of silicon to stabilise a positive charge *β* to it has been exploited by a number of research groups in electrophile-induced cyclisations of alkenols. Thus, Schaumann and co-workers have reported that the vinyl silane **75** cyclises smoothly with either NBS or phenyl sulfenyl chloride as electrophile source, to generate tetrahydrofurans in good yield as shown for the synthesis of **76**.[50] Hosomi *et al.* have shown that tosic acid and titanium tetrachloride will also promote the cyclisation of *ω*-hydroxy vinyl silanes.[51]

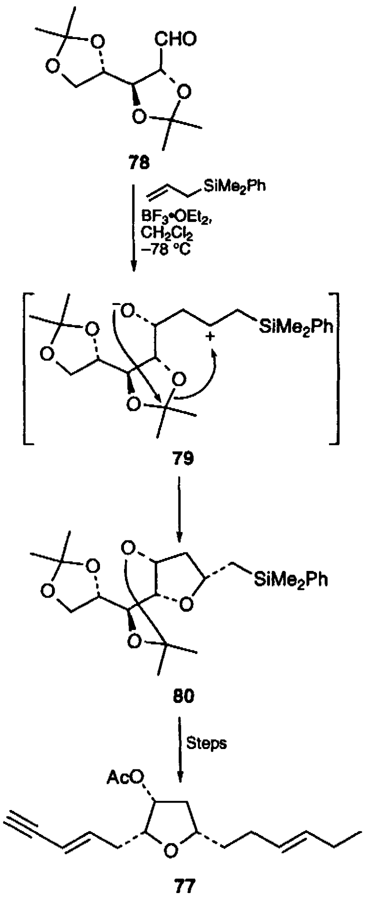


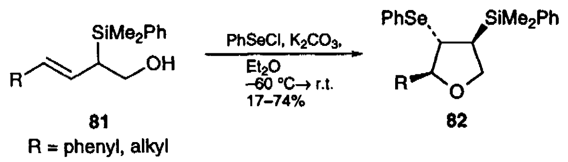


74

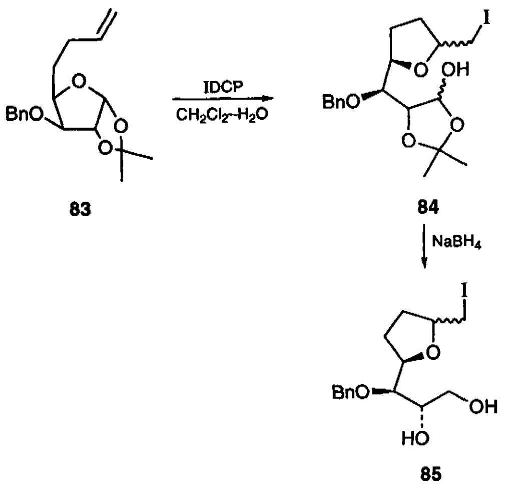


The natural product (−)-*trans*-kumausyne **77** has been synthesised utilising the cyclisation of an incipient *β*-silyl carbocation as the key step.[52] Thus, allyl silane addition to the chiral aldehyde **78** gives the intermediate **79** which then cyclises to the tetrahydrofuran **80**. An allylic silicon substituent can also significantly effect the diastereoselectivity of ring formation, *e.g.* the tetrahydrofurans **82** are generated as the sole diastereomer from cyclisation of the silenols **81**.[53]



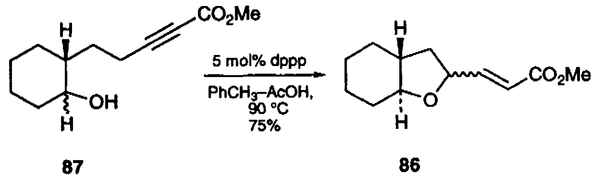


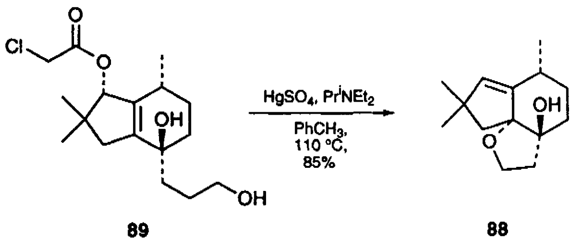
The preparation of chiral 2,5-disubstituted tetrahydrofurans from monosaccharide alkenes has been reported by Mootoo *et al.*[54] For example, exposure of the sugar derivative **83** to iodonium dicollidine perchlorate (IDCP) in wet dichloromethane generates the unstable tetrahydrofuran **84** which is further reduced to the stable product **85**.

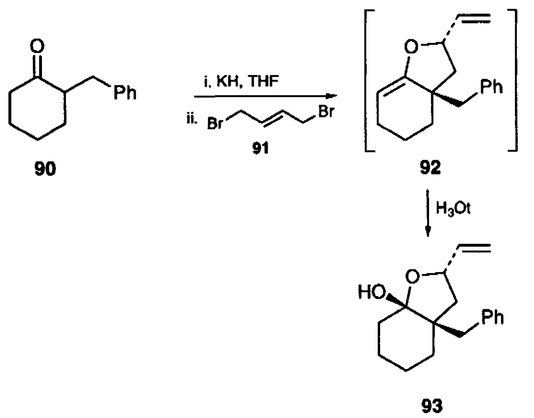


Other work has shown that increasing the size of the anomeric substituent improves the *cis* to *trans* ratio.[55]

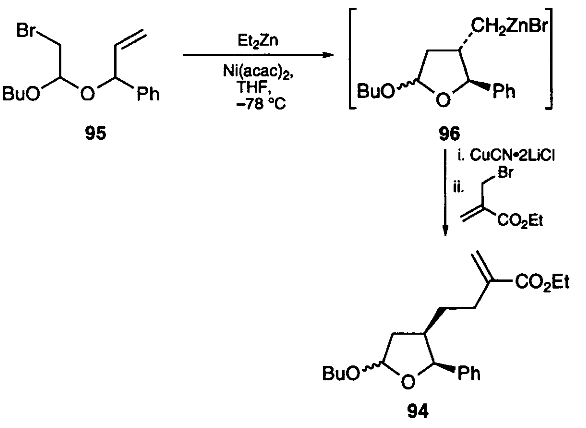
Trost and Li have disclosed a new route to tetrahydrofurans involving a phosphine catalysed intramolecular oxygen addition to 2-alkynoates as shown for the preparation of **86** from **87**.[56] La Clair *et al.* have used an $S_{N'}$ process to generate the fused tetrahydrofuran **88** from the bicycle **89** in a synthesis of the fungal metabolite alliacol-A.[57] Sequential *C* and *O* alkylation of cyclic enolates forms the basis of a very efficient and diastereoselective formation of bicyclic lactols. Thus, treatment of the cyclohexanone **90** with excess potassium hydride followed by the dibromide **91** gives the enol ether **92**, and after acidic work-up, the product **93**.[58]

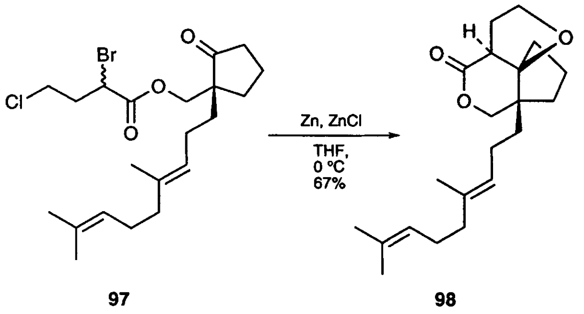






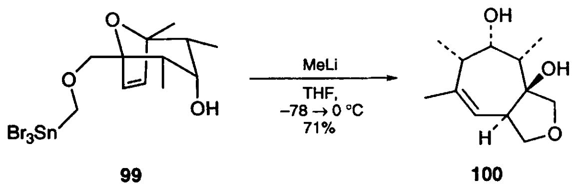
New routes to tetrahydrofurans that involve C–C bond closure of acyclic systems have also been reported over the last twelve months by a number of workers using organozinc reagents. For example, Vaupel and Knochel have disclosed a novel nickel catalysed carbozincation reaction which generates 2-alkoxytetrahydrofurans such as **94**, from bromoacetals such as **95**.[59,60] The reaction proceeds through the organometallic reagent **96** which is readily functionalised as shown. Heathcock and co-workers have used an intramolecular Reformatsky reaction in the total synthesis of (+)-codaphniphylline.[61] Thus, treatment of the α-bromoester **97** with zinc generates the tricycle **98**



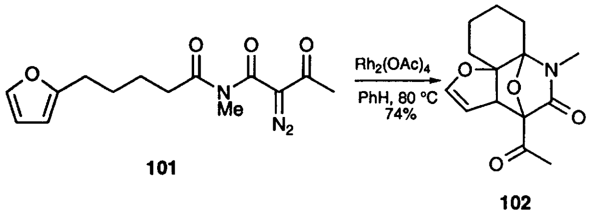


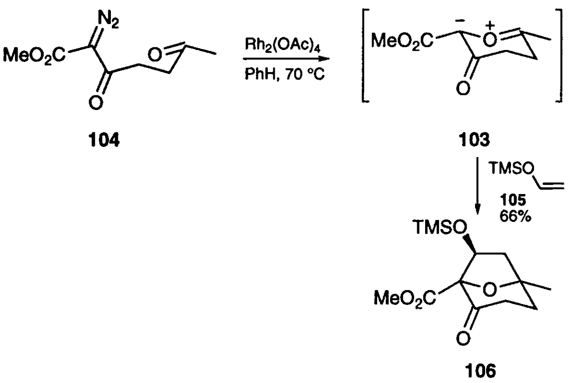
in good yield. The use of allyl zinc reagents in the palladium mediated synthesis of 3-methylenetetrahydrofurans has been recently reviewed.[62]

In an alternative anionic approach to substituted tetrahydrofurans, Lautens and Kumanovic have utilised α-stannyl ethers as starting materials in an intramolecular $S_{N'}$ reaction of oxabicyclo[3.2.1] systems; the conversion of **99** into **100** is representative.[63]

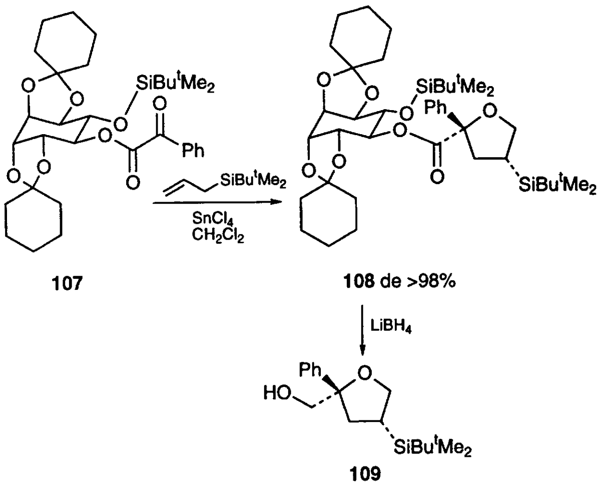


There have been a number of recent reports on the use of carbenoids in the synthesis of tetrahydrofurans. Padwa and his group have extended their work on the cycloaddition of isomünchnone dipoles, derived from reaction of α-diazo imides and catalytic rhodium(II), to include reactions with heteroaromatic π-systems.[64] Thus, treatment of the imide **101** with rhodium acetate generates the complex polyheterocycle **102** in good yield and with complete diastereospecificity. An approach to lysergic acid, using an intramolecular isomünchnone cycloaddition reaction has also been published,[65] as have related dipolar cycloaddition routes to tigliane diterpenes[66] and analogues of zaragozic acid A.[67] In this latter work, the dipole **103**, generated from the diazo compound **104**, reacts intermolecularly with a variety of dipolarophiles, such as **105**, as shown for the synthesis of **106**.

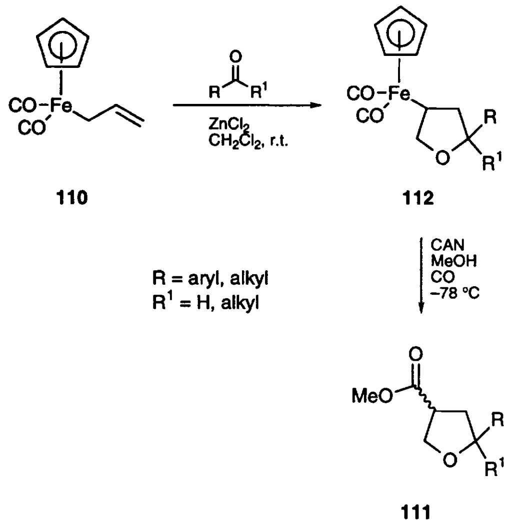




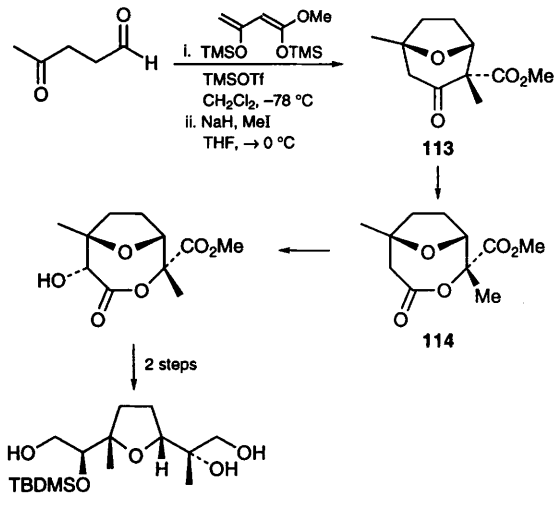
Other cycloaddition routes to tetrahydrofurans have also been published. For example, Akiyama *et al.* have extended their work on the stannic chloride catalysed additions of allyl silanes to α-keto esters, and have shown that use of the chiral auxiliary L-quebrachitol leads to tetrahydrofurans of high optical purity, as shown for the conversion of ester **107** into **108** and after reductive removal of the auxiliary, **109**.[68]



Jiang and Turos have reported an alternative [3 + 2] cycloaddition route to tetrahydrofurans employing the allyl iron(II) dicarbonyl complex **110**. Reaction of **110**[69] with aldehydes or ketones, in the presence of zinc chloride or titanium tetrachloride, leads to the tetrahydrofuran esters **111**, after oxidative destruction of the iron species **112**. Bicyclic tetrahydrofurans, prepared by Molander's previously reported [3 + 4] cycloaddition protocol, have been shown to be useful precursors to *cis*-2,5-disubstituted tetrahydrofurans.[70] The procedure,

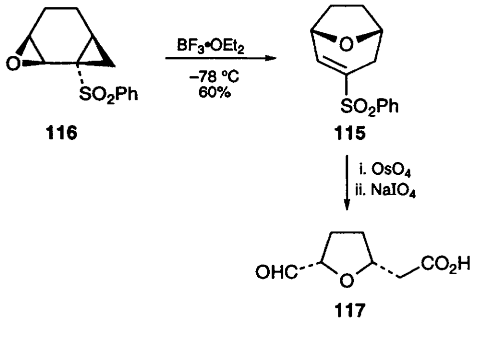


which involves a Baeyer–Villager reaction of the bicycle **113**, followed by oxygenation α to the newly formed lactone **114** and subsequent reductive ring opening, is shown in **Scheme 2**.

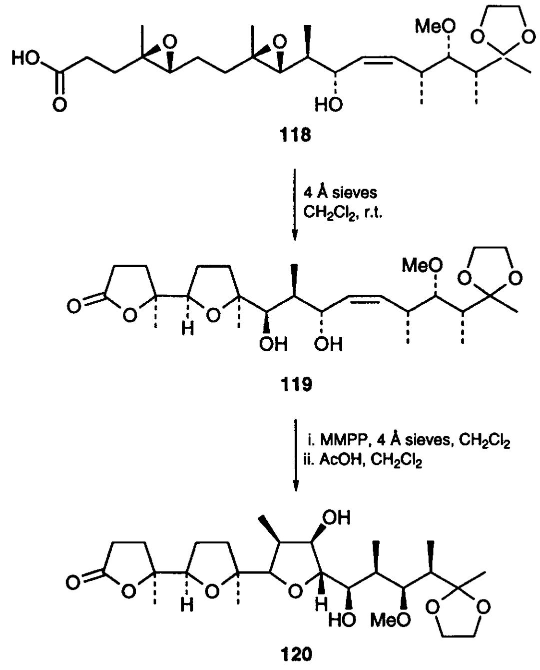


Scheme 2

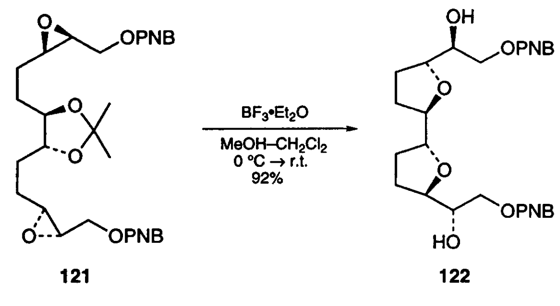
The related bicycle **115** can be prepared by the Lewis acid catalysed rearrangement of the epoxy cyclopropane **116**, and can in turn be manipulated to give the tetrahydrofuran **117**, as shown.[71]

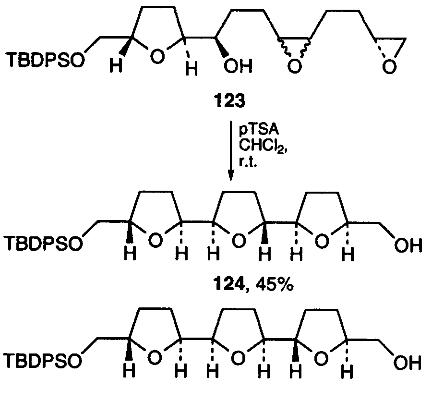


There have been a number of papers published in the last twelve months devoted to the synthesis of oligotetrahydrofurans, and a review has also been published in the area.[72] Evans and co-workers have reported the first synthesis of lonomycin A, a naturally occurring antibiotic possessing three contiguous tetrahydrofuran rings.[73] The key ring forming process was achieved in three steps from the chiral diepoxy acid **118**, firstly generating the bis-tetrahydrofuran **119** *via* a self-catalysed epoxide cascade, and then, after hydroxy directed epoxidation, acid catalysed ring closure to generate the tricycle **120** as shown.



An epoxide ring opening process was also used in a synthesis of the bis-tetrahydrofuran portion of the natural product (+)-bullatacin, with Lewis acid catalysed removal of the acetonide in **121** and simultaneous epoxide ring opening giving **122**.[74] Koert and co-workers have also employed an acid-catalysed epoxide cascade reaction in the synthesis of tetrahydrofurans.[75] Thus, the 1:1 mixture of the diepoxy alcohols **123** generated the two tetrahydrofuran oligomers **124** and **125** in excellent overall yield. This research group has also published alternative procedures for the synthesis of related tetrahydrofuran oligomers.[76]



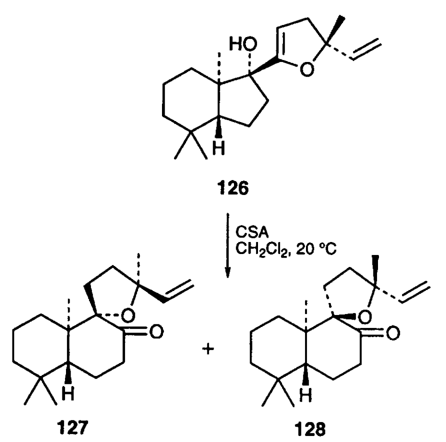


123

124, 45%

125, 45%

Paquette and his group have reported further examples of the use of oxonium ions in the synthesis of spirocyclic tetrahydrofurans, as in the syntheses of the natural products dactyloxene-B and -C,[77] and grindelic acid.[78] In this latter work, exposure of the dihydrofuran **126** to acid led to the tetrahydrofurans **127** and **128** in the ratio shown, the major isomer being further converted into the natural product grindellic acid.

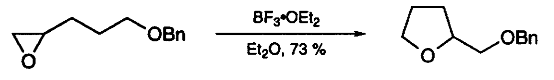


126

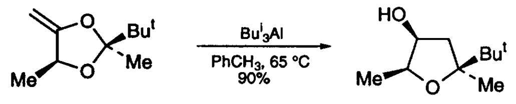
127 **128**

1 : 10.4

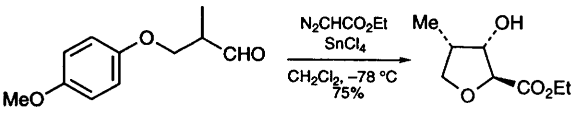
The rearrangement of epoxides to tetrahydrofurans has been reported by Itoh *et al.*; the conversion of **129** into **130** being representative.[79] Petasis and Lu have disclosed a novel rearrangement of 4-methylene-1,3-dioxolanes to generate 3-hydroxy tetrahydrofurans in good yield and with good diastereoselectivity.[80] For example, the dioxolane **131** rearranges to the tetrahydrofuran **132** predominantly as the *syn* diastereoisomer. Angle and his group have reported a novel reaction of β-benzyloxy aldehydes and ethyl diazoacetate generating substituted 3-hydroxy tetrahydrofurans.[81] The reaction, illustrated for the conversion of aldehyde **133** into **134**, generates only the *anti* diastereoisomer shown.



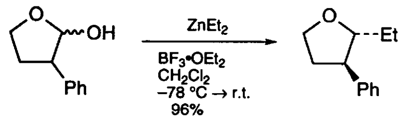
129 **130**



131 **132** (71% *syn*)



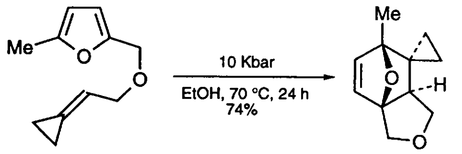
133 **134**



135 **136** 80% de

Lastly, Schmitt and Reissig have shown that a range of organometallic reagents add to γ-lactols in the presence of boron trifluoride etherate, to generate 2-substituted tetrahydrofurans.[82] The diastereoselectivity of these additions is high for 3- and 4-substituted lactols (*e.g.* **135** to **136**), but poor for 5-substituted substrates.

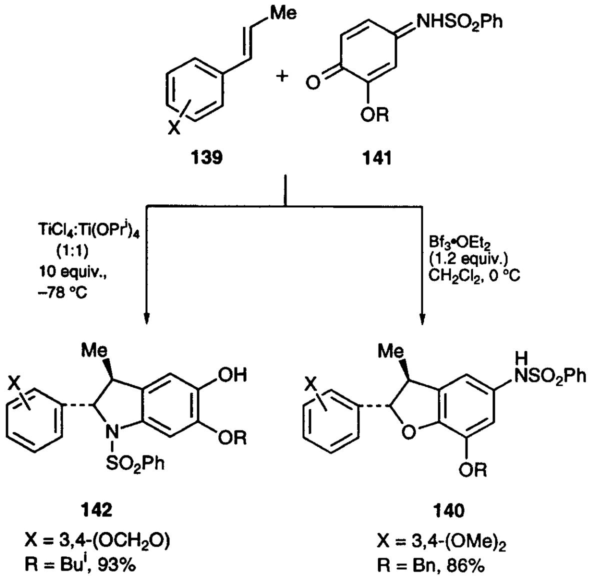
High pressure mediated intramolecular Diels–Alder reactions of furans tethered to a methylenecyclopropane moiety have recently been reported by de Meijere.[83] Thus, heating a solution of the furan **137** in ethanol at 70 °C at 10 Kbar pressure for 24 h gave the spirocyclopropane **138** as a single diastereomer. The exocyclic double bond attached to the cyclopropane ring in **137** facilitates cycloaddition due to release of ring strain. The *exo* configuration of **138** was established by X-ray crystallographic analysis.

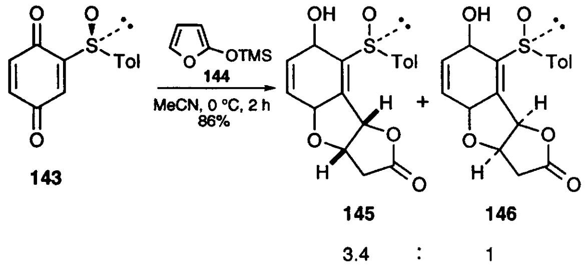


137 **138**

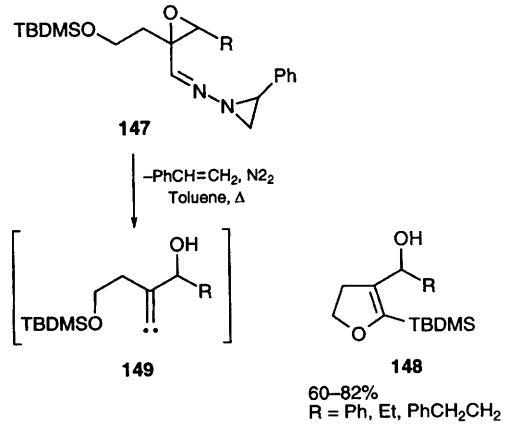
Engler has reported further examples of Lewis acid-promoted additions of styrenyl systems **139** to benzoquinones to yield dihydrobenzofurans[84] **140**, and has extended the scope of the reaction to include 2-alkoxy-4-(*N*-phenylsulfonyl)-1,4-benzoquinone monoimides **141**.[85] The regiochemistry of the cycloaddition in these cases may be controlled by the choice of Lewis acid. Use of $BF_3 \cdot OEt_2$ favours formation of the dihydrobenzofuran **140**, whereas use of excess Ti^{IV} as the Lewis acid yields the dihydroindole **142**.

The first example of an addition reaction to a quinone bearing a chiral auxiliary has recently been reported, although the diastereoselectivity is poor.[86] Reaction of the chiral sulfoxide **142**, with 1 equiv. of silyloxyfuran **144** in acetonitrile at 0 °C for 2 h gave the cycloaddition products **145** and **146** as a separable 3.4 : 1 mixture of diastereoisomers in 86% yield.

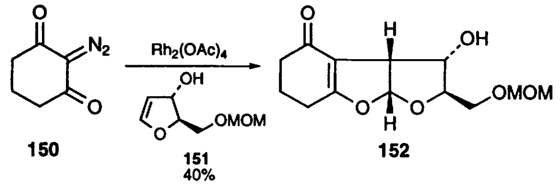




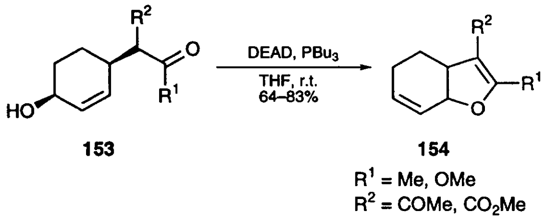
Kim[87] has shown that the thermolysis of α,β-epoxy-*N*-aziridinyl imines **147** yields the dihydrofuran derivatives **148** *via* the alkylidenecarbene **149**. Whether the reaction proceeds *via* 1,5-O–Si insertion or initial oxonium ylide formation, remains to be elucidated. Attempts to extend the scope of the reaction to include 1,6- and 1,7-O–Si insertion yielded predominantly the product of C–H insertion.



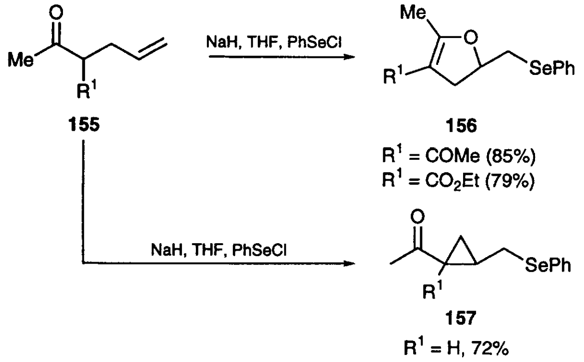
Pirrung has reported an extension of the Rh-mediated cycloaddition to diazocarbonyl compounds **150**[88] using vinyl ethers containing an allylic hydroxy function.[89] The allylic hydroxy group present in the vinyl ether **151** directs *syn* cycloaddition, forming **152** as a single diastereomer.



Hydroxy β-diketones, β-keto esters and β-diesters of general structure **153** have been shown to undergo stereoselective dehydrative alkylation/annulation to yield *cis*-fused bicyclic dihydrofurans **154** under Mitsunobu-type conditions.[90] The reaction presumably proceeds *via* 5-enol *endo–exo-trig* cyclisation.



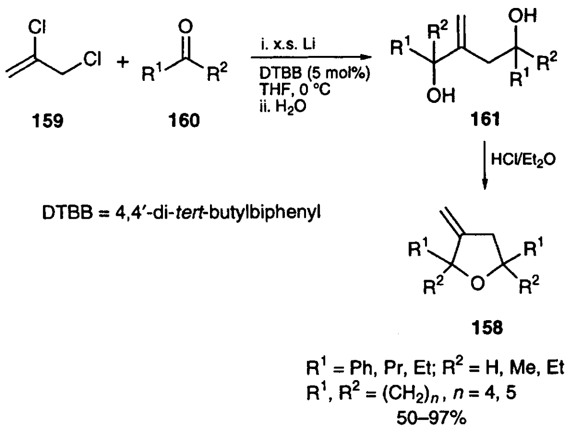
γ,δ-Unsaturated ketones **155** bearing an electron-withdrawing group at the α-carbonyl position yield the dihydrofuran products **156** upon treatment with PhSeCl under basic conditions. In the absence of this functionality, regioselective cyclopropane formation to give **157** is the predominant pathway.[91]



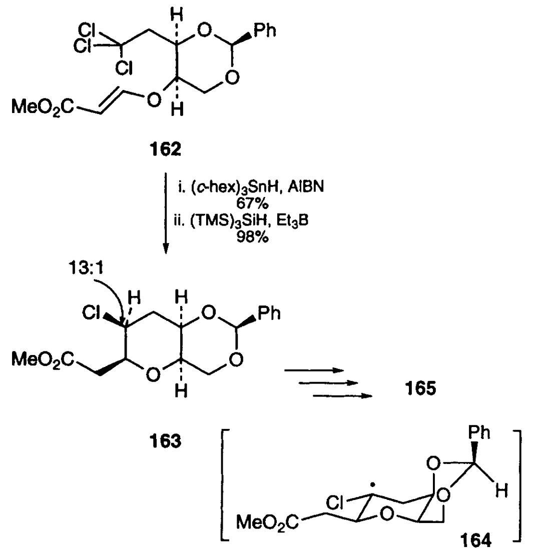
Yus[92] and co-workers have reported further examples of DTBB-catalysed lithiation, to encompass the synthesis of the substituted furan derivatives **158**. Thus, lithiation of 2,3-dichloropropene **159** followed by reaction with ketones **160** gives intermediate diols **161** in modest to good yield. Acid-catalysed cyclisation then readily gives the furan product **158**. The formation of **161** probably proceeds *via* two sequential lithiation *in situ* electrophilic quench cycles. Conducting the reaction at 0 °C suppresses allene formation.

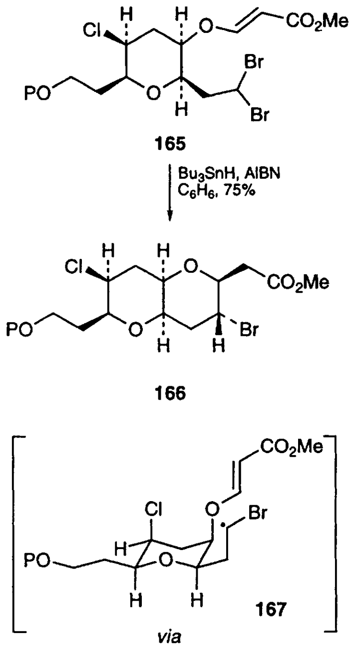
4 Six-membered rings

An interesting stereocontrolled radical cyclisation approach to the *cis*-fused pyranopyranyl skeleton of the dactomelynes has recently appeared.[93] Starting

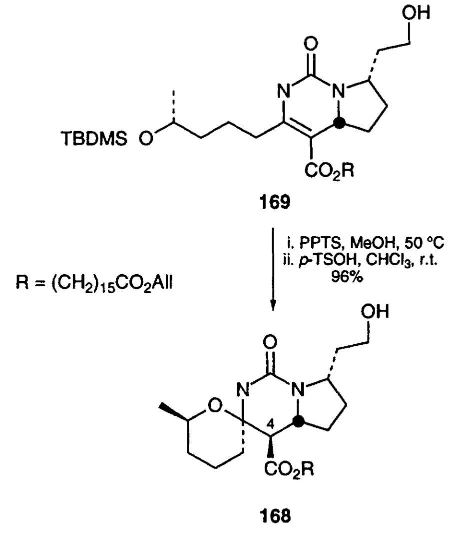


from (−)-diethyl tartrate, the radical cyclisation precursor **162** was prepared in 45% yield in seven steps. Initial radical cyclisation using tricyclohexylstannane under high dilution conditions gave the dichloro product in 67% yield. This intermediate was then dechlorinated stereoselectively using tris(trimethylsilyl)silane in the presence of triethylborane to give a 13:1 mixture of diastereoisomers, with **163** as the major product; the stereoselective formation of **163** occurs *via* trapping of the intermediate radical **164**. Conversion of **162** into the dibromo radical precursor **165** was then readily accomplished. Reaction of **165** with n-tributylstannane and AIBN in benzene, again under high dilution conditions, gave the product **166** as a single stereoisomer. The formation of **166** as a single isomer presumably reflects a high steric preference for the radical intermediate **167** in which the bromine substituent is orientated away from the existing tetrahydropyranyl ring.

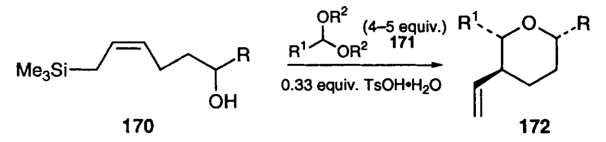




Michael additions of alcohols to α,β-unsaturated esters or ketones continue to be a popular approach to the tetrahydropyran ring system, and their application in total synthesis has been reported by several research groups.[94,95] Overman's elegant synthesis of the unusual guanidinium alkaloid (−)-ptilomycalin A is illustrative of this approach.[96] The key step of establishing the spirocyclic central template **168** was optimally accomplished in two steps *via* TBDMS ether cleavage of **169** and subsequent cyclisation using tosic acid, to give a single product. Although epimeric with the natural material at C-4, the centre was readily epimerised later in the synthesis to give the natural configuration.

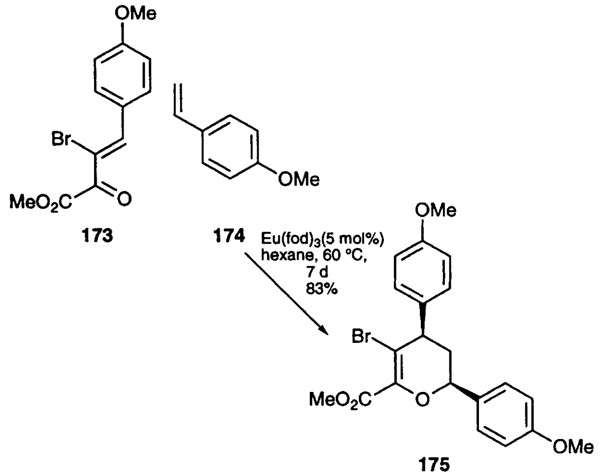


Mohr has reported an extension to the acid-catalysed intramolecular addition of an allyl silane to an oxocarbenium ion, in a synthesis of tetrahydropyrans with high regiocontrol.[97] Treatment of the allyl silane **170** with 4–5 equiv. of the acetal **171** at room temperature gives the tetrahydropyran product **172** in moderate to good yields *via in situ* transacetalisation and subsequent ring closure. In each case the all-equatorial product predominated with >95% diastereocontrol.



During this review period, the report of Nicolaou's impressive total synthesis of the marine neurotoxin brevitoxin B is particularly noteworthy.[98]

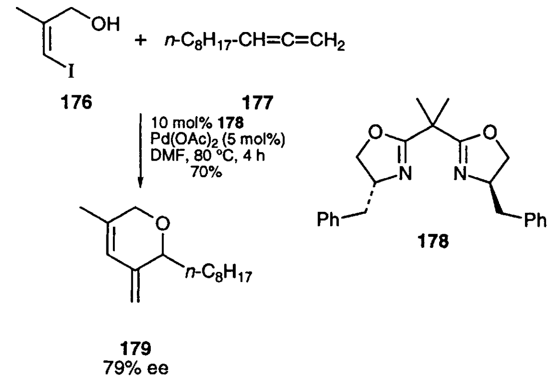
The hetero Diels–Alder reaction continues to be a popular approach to the synthesis of dihydropyrans with numerous reports being described during the review period. Further developments of the asymmetric variant of this process have been reported using BINOL-based[99,100] and chiral lanthanide bis-trifylamide complexes.[101] High-pressure approaches *via* reactions of vinyl ethers with α,β-unsaturated aldehydes[102] and enamino ketones[103] continue to be reported. The first efficient examples of heterocycloaddition involving styrene derivatives without the use of high pressure techniques have been disclosed.[104] Treatment of activated heterodiene **173** with the styrene **174** in the presence of Eu(fod)$_3$ (5 mol%) in hexane under reflux gave the cycloadduct **175** in good yield and with high *endo* selectivity.

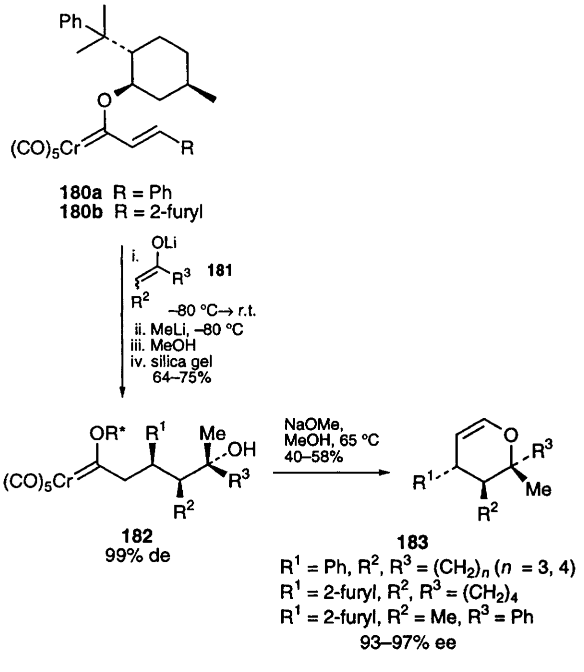


>97:3 *endo*:*exo*

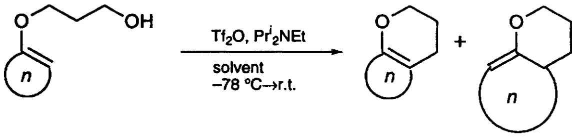
High enantioselectivities have been reported recently for the Pd-catalysed hetero- and carbo-annulations of allenes with aryl and vinylic iodides.[105] For example, treatment of the vinyl iodide **176** with the allene **177** in the presence of 10 mol% of the bis-oxazoline **178** and 5 mol% Pd(OAc)$_2$ in DMF gives the dihydropyran **179** in 79% ee.

A recent report has described the highly *syn*-selective Michael addition of lithium enolates to optically active Fischer vinyl carbene complexes.[106] Treatment of the Fischer carbene **180** [derived from (−)-8-phenylmenthol] with the ketone lithium enolate **181**, followed by treatment with 2 equiv. of methyllithium, led to the *syn*-Michael adducts **182** as a single diastereoisomer in all but one case. Dropwise addition of these carbenes to sodium methoxide in methanol under reflux then afforded the corresponding optically active enol ethers **183** in high enantiomeric excess.



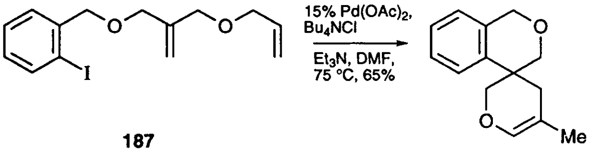


Yamamoto *et al.* have reported a highly regio- and stereo-selective annulation of cycloalkenyl-3-hydroxypropyl ethers to yield dihydropyrans.[107] The regioselectivity of the elimination step is highly base and solvent dependent. For example, treatment of the acyclic enol ether **184** with triflic anhydride in the presence of *N*,*N*-diisopropylethylamine using toluene as solvent gave predominantly the endocyclic enol ether product **185**. However, treatment of **184** under the same conditions using dichloromethane as the solvent yields predominantly **186**. This methodology offers the first practical access to enol ethers of the type **186**.



	184	185		186
	toluene	97	:	3
	CH$_2$Cl$_2$	13	:	87

Overman *et al.* have reported extensions to the intramolecular Heck reaction to encompass the first examples of the synthesis of spirocyclic polyethers.[108] Thus treatment of the aryl iodide **187** with 15% $Pd(OAc)_2$ and tetrabutylammoniun chloride in DMF at 75°C yielded the spiroether **188** in 60% yield. Unfortunately, the utility of the reaction appears limited by unwanted palladium-catalysed isomerisations of the starting allylic polyether substrates to the more stable enol ethers.



187

188

5 References

1 T. Kuroki, T. Hamada and T. Katsuki, *Chem. Lett.*, 1995, 39.
2 H. Sasaki, R. Irie, T. Hamada, K. Suzuki and T. Katsuki, *Tetrahedron*, 1994, **50**, 11827.
3 T. Fukuda, R. Irie and T. Katsuki, *Synlett*, 1995, 197.
4 D. Mikame, T. Hamada, R. Irie and T. Katsuki, *Synlett*, 1995, 827.
5 T. Hamada, K. Daikai, R. Irie and T. Katsuki, *Synlett*, 1995, 407.
6 B. D. Brandes and E. N. Jacobsen, *Tetrahedron Lett.*, 1995, **36**, 5123.
7 M. Palucki, P. J. Pospisisl, W. Zhang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1994, **116**, 9333.
8 M. Palucki, G. J. McCormick and E. N. Jacobsen, *Tetrahedron Lett.*, 1995, **36**, 5457.
9 W. Adam, J. Jekö, A. Lévai, C. Nemes, T. Patonay and P. Sebök, *Tetrahedron Lett.*, 1995, **36**, 3669.
10 A. F. Dexter, F. J. Lakner, R. A. Campbell and L. P. Hager, *J. Am. Chem. Soc.*, 1995, **117**, 6412.
11 M. E. Lasterra Sánchez and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1467.
12 S. Jayaraman, S. Hu and A. C. Oehlschlager, *Tetrahedron Lett.*, 1995, **36**, 4765.
13 A. Mitrochkine, F. Eydoux, M. Martres, G. Gil, A. Heumann and M. Réglier, *Tetrahedron: Asymmetry*, 1995, **6**, 59.
14 M. Mischitz, W. Kroutil, U. Wandel and K. Faber, *Tetrahedron: Asymmetry*, 1995, **6**, 1261.
15 A. Jenmalm, W. Berts, K. Luthman, I. Csöregh and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 1026.
16 J. Clayden, E. W. Collington, E. Egert, A. B. McElroy and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2801.
17 R. F. W. Jackson, S. P. Standen, W. Clegg and A. McCamley, *J. Chem. Soc., Perkin Trans. 1*, 1995, 141.
18 R. F. W. Jackson, S. P. Standen and W. Clegg, *J. Chem. Soc., Perkin Trans. 1*, 1995, 149.
19 R. J. Linderman, R. J. Claassen and F. Viviani, *Tetrahedron Lett.*, 1995, **36**, 6611.
20 S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue and R. G. Wilde, *J. Org. Chem.*, 1995, **60**, 1391.
21 D. Yang, M.-K. Wong and Y.-C. Yip, *J. Org. Chem.*, 1995, **60**, 3887.
22 R. Curci, L. D'Accolti, M. Fiorentino and A. Rosa, *Tetrahedron Lett.*, 1995, **36**, 5831.
23 D. S. Brown, B. A. Marples, P. Smith and L. Walton, *Tetrahedron*, 1995, **51**, 3587.
24 R. W. Murray, M. Singh, B. L. Williams and H. M. Moncrieff, *Tetrahedron Lett.*, 1995, **36**, 2437.
25 V. K. Aggarwal, H. Abdel-Rahman, R. V. H. Jones and M. C. H. Standen, *Tetrahedron Lett.*, 1995, **36**, 1731.
26 K. Hioki, S. Tani and Y. Sato, *Synthesis*, 1995, 649.
27 Y. Matano, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2703.
28 A. Solladié-Cavallo and A. Diep-Vohuule, *J. Org. Chem.*, 1995, **60**, 3494.
29 S. S. Taj, A. C. Shah, D. Lee, G. Newto and R. Soman, *Tetrahedron: Asymmetry*, 1995, **6**, 1731.
30 C. P. Baird and P. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 893.
31 T. Mukaiyama and T. Yamada, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 17.
32 S. Banfi, F. Montanari, S. Quici, S. V. Barkanova, O. L. Kaliya, V. N. Kopranenkov and E. A. Luk'yanets, *Tetrahedron Lett.*, 1995, **36**, 2317.
33 P. Kumar, R. Kumar and B. Pandey, *Synlett*, 1995, 289.
34 P. Kumar, G. C. G. Pais, B. Pandey and R. Kumar, *J. Chem. Soc., Chem. Commun.*, 1995, 1315.
35 J. M. Faile, J. I. García, J. I. Mayoral, L. C. de Mènorval and F. Rachdi, *J. Chem. Soc., Chem. Commun.*, 1995, 539.
36 E. Jorda, A. Tuel, R. Teissier and J. Kervennal, *J. Chem. Soc., Chem. Commun.*, 1995, 1775.
37 C. Cativiela, F. Figueras, J. M. Fraile, J. I. García and J. A. Mayoral, *Tetrahedron Lett.*, 1995, **36**, 4125.
38 G. Asensio, R. Mello, C. Boix-Bernardini, M. E. González-Núñez and G. Castellano, *J. Org. Chem.*, 1995, **60**, 3692.
39 M. Ferrer, F. Sánchez-Baeza, A. Messeguer, A. Diez and M. Rubiralta, *J. Chem. Soc., Chem. Commun.*, 1995, 293.
40 T. Ibuka, K. Nakai, H. Habashita, Y. Hotta, A. Otaka, H. Tamamura, N. Fujii, N. Mimura, Y. Miwa, T. Taga, Y. Chounan and Y. Yamamoto, *J. Org. Chem.*, 1995, **60**, 2044.
41 A. S. Kende, P. Delair and B. E. Blass, *Tetrahedron Lett.*, 1994, **35**, 8123.
42 Y. Chen and J.-L. Reymond, *Tetrahedron Lett.*, 1995, **36**, 4015.
43 C. J. Andres, N. Spetseris, J. R. Norton and A. I. Meyers, *Tetrahedron Lett.*, 1995, **36**, 1613.
44 T. Akiyama and M. Kirino, *Chem. Lett.*, 1995, 723.
45 T. Bach, *Liebigs Ann. Chem.*, 1995, 855.
46 J. Reinecke and H. M. R. Hoffmann, *Chem. Eur. J.*, 1995, **1**, 368.
47 H. Xianming and R. M. Kellogg, *Synthesis*, 1995, 533.
48 B. Lipshutz and T. Gross, *J. Org. Chem.*, 1995, **60**, 3572.
49 R. Déziel and E. Malenfant, *J. Org. Chem.*, 1995, **60**, 4660.
50 G. Adiwidjaja, H. Flörke, A. Kirschning and E. Schaumann, *Liebigs Ann. Chem.*, 1995, 5601.
51 K. Miura, S. Okajima, T. Hondo and A. Hosomi, *Tetrahedron Lett.*, 1995, **36**, 1483.
52 K. Osumi and H. Sugimura, *Tetrahedron Lett.*, 1995, **36**, 5789.
53 Y. Landais, D. Planchenault and V. Weber, *Tetrahedron Lett.*, 1995, **36**, 2987.
54 W. Shan, P. Wilson, W. Liang and D. R. Mootoo, *J. Org. Chem.*, 1994, **59**, 7986.
55 H. Zhang, P. Wilson, W. Shan, Z. Ruan and D. R. Mootoo, *Tetrahedron Lett.*, 1995, **36**, 649.
56 B. M. Trost and C.-J. Li, *J. Am. Chem. Soc.*, 1994, **116**, 10819.

57 J. J. La Clair, P. T. Lansbury, B. Zhi and K. Hoogsteen, *J. Org. Chem.*, 1995, **60**, 4822.
58 T. Wang, J. Chen and K. Zhao, *J. Org. Chem.*, 1995, **60**, 2668.
59 A. Vaupel and P. Knochel, *Tetrahedron Lett.*, 1994, **35**, 8349.
60 A. Vaupel and P. Knochel, *Tetrahedron Lett.*, 1995, **36**, 231.
61 C. H. Heathcock, J. C. Kath and R. B. Ruggeri, *J. Org. Chem.*, 1995, **60**, 1120.
62 J. L. van der Baan, T. A. J. van der Heide, J. van der Louw and G. W. Klumpp, *Synlett*, 1995, 1.
63 M. Lautens and S. Kumanovic, *J. Am. Chem. Soc.*, 1995, **117**, 1954.
64 A. Padwa, D. L. Hertzog and W. R. Nadler, *J. Org. Chem.*, 1994, **59**, 7072.
65 J. P. Marino, M. H. Osterhout and A. Padwa, *J. Org. Chem.*, 1995, **60**, 2704.
66 M. C. Mills, L. Zhuang, D. L. Wright and W. Watt, *Tetrahedron Lett.*, 1994, **35**, 8311.
67 H. Koyama, R. G. Ball and G. D. Berger, *Tetrahedron Lett.*, 1994, **35**, 9185.
68 T. Akiyama, T. Yasusa, K. Ishikawa and S. Ozaki, *Tetrahedron Lett.*, 1994, **35**, 8401.
69 S. Jiang and E. Turos, *Tetrahedron Lett.*, 1994, **35**, 7889.
70 G. A. Molander and S. Swallow, *J. Org. Chem.*, 1994, **59**, 7148.
71 C. M. G. Löfström, A. M. Ericsson, L. Bourrinet, S. K. Juntunen and J.-E. Bäckvall, *J. Org. Chem.*, 1995, **60**, 3586.
72 U. Koert, *Synthesis*, 1995, 115.
73 D. A. Evans, A. M. Ratz, B. E. Huff and G. S. Sheppard, *J. Am. Chem. Soc.*, 1995, **117**, 3448.
74 H. Naito, E. Kawahara, K. Maruta, M. Maeda and S. Sasaki, *J. Org. Chem.*, 1995, **60**, 4419.
75 U. Koert, H. Wagner and M. Stein, *Tetrahedron Lett.*, 1994, **35**, 7629.
76 U. Koert, M. Stein and H. Wagner, *Liebigs Ann. Chem.*, 1995, 1415.
77 M. D. Lord, J. T. Negri and L. A. Paquette, *J. Org. Chem.*, 1995, **60**, 191.
78 L. A. Paquette and H.-L. Wang, *Tetrahedron Lett.*, 1995, **36**, 6005.
79 A. Itoh, Y. Hirose, H. Kashiwagi and Y. Masaki, *Heterocycles*, 1994, **38**, 2165.
80 N. A. Petasis and S.-P. Lu, *J. Am. Chem. Soc.*, 1995, **117**, 6394.
81 S. R. Angle, G. P. Wei, Y. K. Ko and K. Kubo, *J. Am. Chem. Soc.*, 1995, **117**, 8041.
82 A. Schmitt and H.-U. Reissig, *Chem. Ber.*, 1995, **128**, 871.
83 T. Heiner, S. Michalski, K. Gerke, G. Kuchta, M. Buback and A. de Meijere, *Synlett*, 1995, 355.
84 T. A. Engler, G. A. Gfesser and W. W. Draney, *J. Org. Chem.*, 1995, **60**, 3700.
85 T. A. Engler, W. Chai and K. O. Lynch, Jr., *Tetrahedron Lett.*, 1995, **36**, 7003.
86 M. A. Brimble, L. J. Duncalf and D. C. W. Reid, *Tetrahedron: Asymmetry*, 1995, **6**, 263.
87 S. Kim and C. M. Cho, *Tetrahedron Lett.*, 1995, **36**, 4845.
88 M. C. Pirrung, J. Zhang, K. Lackey, D. D. Sternbach and F. Brown, *J. Org. Chem.*, 1995, **60**, 2112.
89 M. C. Pirrung and Y. R. Lee, *J. Chem. Soc., Chem. Commun.*, 1995, 673.
90 A. Tenaglia, J.-Y. Le Brazidec and F. Souchon, *Tetrahedron Lett.*, 1995, **36**, 4241.
91 L. Dechoux, L. Jung and J. F. Stambach, *Synlett*, 1994, 965.
92 F. F. Huerta, C. Gómez, A. Guijarro and M. Yus, *Tetrahedron*, 1995, **51**, 3375.
93 E. Lee, C. M. Park and J. S. Yun, *J. Am. Chem. Soc.*, 1995, **117**, 8017.
94 J. Nokami, T. Taniguchi and Y. Ogawa, *Chem. Lett.*, 1995, 43.
95 K. Fujiwara, S. Amano, T. Oka and A. Murai, *Chem. Lett.*, 1994, 2147.
96 L. E. Overman, M. H. Rabinowitz and P. A. Renhowe, *J. Am. Chem. Soc.*, 1995, **117**, 2657.
97 P. Mohr, *Tetrahedron Lett.*, 1995, **36**, 2453.
98 K. C. Nicolaou, F. P. J. T. Rutjes, E. A. Theodorakis, J. Tiebes, M. Sato and E. Untersteller, *J. Am. Chem. Soc.*, 1995, **117**, 1173 and references cited therein.
99 G. E. Keck, X-Y. Li and D. Krishnamurthy, *J. Org. Chem.*, 1995, **60**, 5998.
100 Y. Motoyama, M. Terada and K. Mikami, *Synlett*, 1995, 967.
101 K. Mikami, O. Kotera, Y. Motoyama and H. Sakaguchi, *Synlett*, 1995, 975.
102 D. A. L. Vandenput and H. W. Scheeren, *Tetrahedron*, 1995, **51**, 8383.
103 L. F. Tietze, T. Hübsch, C. Ott, G. Kuchta and M. Buback, *Liebigs Ann. Chem.*, 1995, 1; 1995, 9 and references cited therein.
104 G. Dujardin, M. Maudet and E. Brown, *Tetrahedron Lett.*, 1994, **35**, 8619.
105 R. C. Larock and J. M. Zenner, *J. Org. Chem.*, 1995, **60**, 482.
106 J. Barluenga, J. M. Montserrat, J. Flórez, S. Garcia-Granda and E. Martín, *Chem. Eur. J.*, 1995, **1**, 236.
107 K. Ishihara, N. Hanaki and H. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1995, 1117.
108 S. D. Knight and L. E. Overman, *Heterocycles*, 1994, **39**, 497.