# Main group organometallics in synthesis

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## 1 Introduction

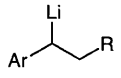
This review concentrates on main group organometallic compounds in synthesis and follows on from the previous coverage[1] (excepting organoboranes and group 15 and 16 compounds, but including all the main elements in groups 1, 2, 13 and 14). As a vast number of publications include such species, this review will focus on synthetic chemistry of novel organometallics that has had, or is expected to have, a significant impact in contemporary organic synthesis.

## 2 Group 1

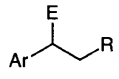
### 2.1 Lithium

#### 2.1.1 Non-stabilised organolithiums

Non-stabilised organolithium reagents continue to provide an effective means for forming carbon–carbon bonds in organic synthesis. Simple, unsubstituted organolithiums (RLi) have been reported to add to imines, to give amines,[2] to carboxylic amides, to give ketones,[3] to aldehydes and epoxides, to give alcohols (for example in the synthesis of a subunit of amphotericin B)[4] and to styrenes, to give branched alkyl-substituted aromatic compounds. By using diethyl ether as solvent, polymerisation of styrene can be avoided and the intermediate benzyllithium **1** can be trapped with electrophiles to give compounds of general structure **2**.[5a] The use of (−)-sparteine has allowed good enantioselection in the addition of alkyllithiums to cinnamyl derivatives.[6]




**1**



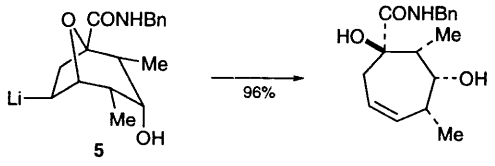

**2**

A synthesis of the polycyclopropane antibiotic FR-900848 uses the coupling of cyclopropyl organolithiums under copper(I) catalysis.[7] The cyclopropyl organolithiums are generated by tin–lithium exchange or bromine–lithium exchange. Dimerisation of the organolithium **3** in the presence of $(ICuPBu_3)_4$ and oxygen gives the tetracyclopropane **4** by a stereospecific coupling.


**3** R = TBDPS

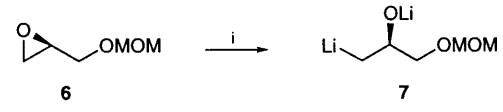

**4** R = TBDPS

Heteroatom-substituted organolithiums have been known for many years, yet these are continuing to grow in popularity for stereocontrolled carbon–carbon bond formation. When a β-oxygen atom is present, elimination normally occurs. This has been used to good effect in the synthesis of cyclohexenes and cycloheptenes by ring-opening of organolithiums such as **5** (**Scheme 1**).[8] Avoidance of




**Scheme 1**

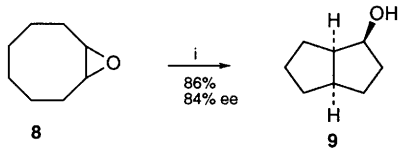
β-elimination can be achieved with a β-metalloxy substituent, generated by reductive ring-opening of epoxides.[9] The chiral epoxide **6**, on treatment with lithium metal and 4,4′-di-*tert*-butylbiphenyl (DBB) as a catalyst gives the dilithiated species **7**, which can be trapped with aldehydes or ketones to give polyoxygenated products (**Scheme 2**).




*Reagents*: i, Li, 5 mol% DBB, THF

**Scheme 2**

Epoxides have been found to remain intact on lithiation at C-2, using a sulfoxide to lithium exchange with *tert*-butyllithium.[10] This allows access to 2-substituted epoxides. Conversely, proton abstraction at C-2 of an epoxide can promote ring-opening to form alcohol products.[11] An enantioselective version of this process, mediated by (−)-sparteine has been investigated by Hodgson and co-workers and allows the conversion of *meso*-epoxides, such as **8**, to chiral cyclic alcohols such as **9** (**Scheme 3**).[11a]

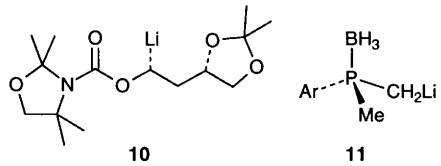



*Reagents*: i, $Pr^iLi$, (–)-sparteine, $Et_2O$, –98 °C

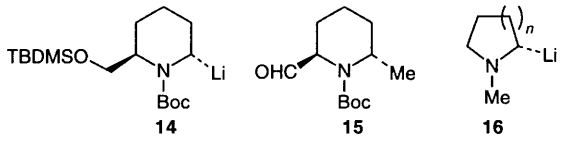
**Scheme 3**

(−)-Sparteine has been used as the chiral ligand of choice for asymmetric deprotonations α to the oxygen atom of carbamates (to give organolithium **10**),[12] α to the phosphorus atom of prochiral phosphines (allowing a synthesis of chiral β-hydroxyphosphines or diphosphines *via* organolithium **11**)[13] and α to the nitrogen atom of *N*-Boc-pyrrolidine (to give **12**).[14] Indeed, of a number of chiral amines tested as ligands for asymmetric deprotonation of *N*-Boc-pyrrolidine, (−)-sparteine remains the most enantioselective.[15]

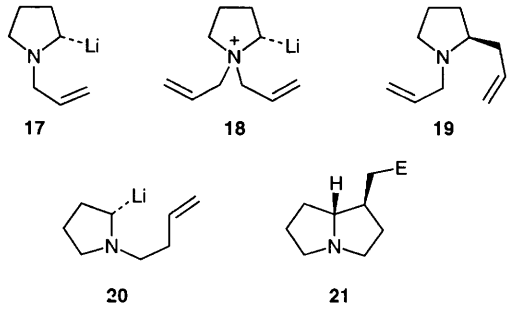
Racemic organolithium **12** and the α-aminoorganolithium **13** have been shown to couple to vinyl trifluoromethanesulfonates using copper(I) cyanide and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)–TMSCl, allowing a useful synthesis of allylic amines.[16] Deprotonation α to the nitrogen atom of a piperidine using *sec*-butyllithium–TMEDA has given rise to organolithium **14**, which, on quenching with methyl iodide, followed by deprotection and oxidation, gives the piperidine **15**, used in the total synthesis of (+)-himbacine and (+)-himbeline.[17] A study by Gawley and Zhang of the electrophilic addition to the chiral organolithiums **16** ($n = 1,2$) concludes that primary alkyl halides have a preference for reacting with inversion of configuration at the carbanion centre. Carbonyl electrophiles give the product of retention. The electrophiles benzophenone, benzyl bromide and *tert*-butyl bromoacetate give rise to racemic products.[18]







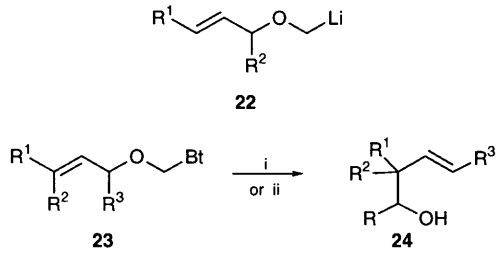

Gawley and co-workers have also investigated the stereochemical outcome at the organolithium centre in [2,3] sigmatropic rearrangements.[19] α-Aminoorganolithiums such as *N*-methyl-2-lithiopyrrolidine are known to racemise at temperatures above −40 °C, so it is notable that the organolithium **17**, on warming above 10 °C in order to effect rearrangement, gives products of significant optical purity (predominant inversion of configuration). The rearrangement occurs partly by a [2,3] mechanism and partly by a [1,2] mechanism. In comparison, essentially complete inversion of configuration, as anticipated, was observed in the more facile rearrangement of the ylide **18** to give pyrrolidine **19**.[19] In contrast to these results, Coldham and co-workers have found that the related organolithium **20** cyclises to (+)-pseudoheliotridane **21** (E = H) with complete retention of configuration at the carbanion centre.[20] In hexane–diethyl ether (10:1), formation of the organolithium **20** (by tin–lithium exchange) and cyclisation occurs only at room temperature, indicating that Li–π coordination plays a part in maintaining the



17 18 19 20 21

stereochemical integrity of such organolithiums. From these results, it appears that intermolecular quenches may take place with retention, inversion or racemisation at the carbanion centre, whereas [2,3] sigmatropic rearrangements occur with inversion of configuration, and anionic cyclisations to five-membered rings occur with retention.

The [2,3] sigmatropic rearrangement of allylic ethers using tin–lithium exchange (Still–Wittig rearrangement) can give rise to high levels of stereoselection of the resulting homoallylic alcohol.[21] Organolithiums **22**, with $R^2 = CH_2CH_2OBz$ give complete or nearly complete *Z* stereoselection. An alternative to tin–lithium exchange using silicon–lithium exchange with excess butyllithium has been reported.[22] Katritzky and co-workers have found that the benzotriazole group acts both as an anion stabilising group for the Wittig rearrangement and, subsequently, as a leaving group.[23] Treatment of the allylic ether **23** with RLi (2.5 equiv.) gives rise to the homoallylic alcohol **24** (**Scheme 4**). This methodology provides an important alternative to the Still–Wittig rearrangement.



22

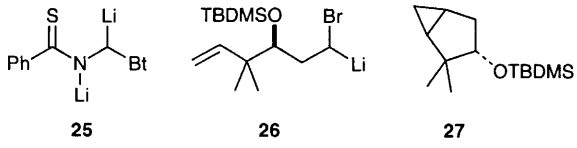
23 24

*Reagents*: i, RLi (81–87%); ii, LDA then $NaBH_4$ (56–60%, $R = R^1 = R^2 = H$)

**Scheme 4**

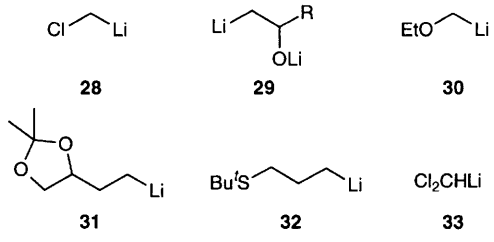
The benzotriazole group has been reported to allow proton abstraction α to the nitrogen atom of a thioamide group.[24] The resulting organolithium **25** can be trapped with a variety of electrophiles, followed by displacement of the benzotriazole group using a Grignard reagent or an alkoxide or thioalkoxide.

The formation of α-halocarbanions by sulfoxide–lithium exchange leads to alkene products (*via* a carbene) or, on deuteriation, to α-deuteriated alkyl halides.[25] When an internal alkene is present, the products of cyclopropanation result.[26a] Interestingly, the two diastereomeric α-bromo organolithiums **26**, each formed by iodine–lithium exchange, give rise to different ratios of the cyclopropanes **27**.[26a] This suggests that a free carbene is not present as an intermediate in this reaction. Similar α-bromo organolithiums can be trapped with carbonyl electrophiles to give epoxide products.[26b]



25 26 27

The simple chloromethyllithium **28** can be generated by reductive lithiation of dichloromethane using lithium powder and DBB.[27] The use of excess lithium and carbonyl electrophiles leads to 1,3-diols, presumably *via* the organolithiums **28** and **29**. Yus and co-workers have used reductive lithiation for the formation of a variety of organolithiums, including ethyl lithiomethyl ether **30**,[28] and even organolithiums with more remote heteroatoms, such as **31**[29] and **32**.[30] The organolithiums react with electrophiles, especially carbonyl compounds, often in good to excellent yields.



28 29 30 31 32 33

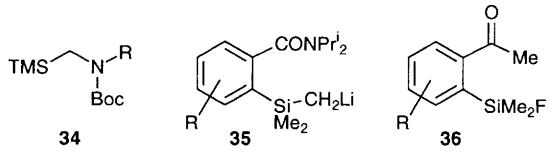
Applications of the use of dichloromethyllithium **33** to insert a chloromethylene unit between an alkyl group and a boron atom have been reported. This is a useful protocol, as the resulting chlorine atom can be displaced by a nucleophile, leaving a new organoborane on which the process can be repeated. Eventual oxidation of the organoborane leads to an alcohol product. Examples of this chemistry are in the synthesis of the C-1 to C-21 fragment of tautomycin[31] and in the synthesis of stegobinone.[32]

### 2.1.2 Organolithiums stabilised by silicon, selenium and sulfur

The previous section discussed the use of non-stabilised organolithiums in synthesis, including substituted derivatives with attached heteroatoms (O, N, Cl, Br, P). Examples of organolithiums stabilised by silicon, selenium and sulfur are given in this section.

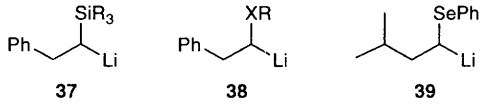
Proton abstraction α to both a nitrogen and a silicon atom takes place on treatment of the silane **34**, R = Bu$^t$ with *sec*-butyllithium.[33] When the

carbamate **34**, R = $CH_2Ph$ is used, however, metallation α to the phenyl group competes with deprotonation α to silicon. Direct, base-induced deprotonation α to silicon is not normally a straightforward process. It is likely that neighbouring groups capable of coordination (complex induced proximity effect), such as the Boc group enhance acidity. In this way, the base LDA is sufficient to allow deprotonation α to silicon,[34] for example of *ortho*-silyl benzamides, to give organolithium **35**.[34a] Cyclisation onto the carbonyl group, followed by treatment with boron trifluoride leads to the ketones **36**. Oxidative removal of both the silyl and acetyl groups gives catechols.




**34** **35** **36**

The substituents R, on the silyl group of secondary α-silyl organolithiums **37** have very little or no effect on the rate of epimerisation at the carbanion centre.[35] These secondary organolithiums are generated by selenium–lithium exchange with *tert*-butyllithium. On the other hand, α-thio, seleno and telluro derivatives **38** (X = S, Se, Te) display notable increases in the rate of epimerisation with bulky R groups. This effect has been ascribed to a rate determining step involving slow rotation about the carbanion–heteroatom bond in sterically hindered systems. The rate limiting step in the phenylthio, seleno and telluro derivatives **38** (X = SPh, SePh, TePh) is thought to be the reorganisation of the contact ion pair.

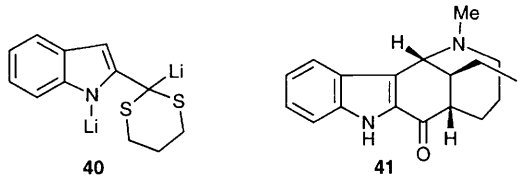



**37** **38** **39**

The α-phenylseleno organolithium **39** reacts with benzaldehyde to give a 55:45 *syn*:*anti* mixture of diastereomeric β-hydroxy selenides.[36] In the presence of chiral 1,2-diamines diastereoselectivities up to 70:30 and enantioselectivities up to 86% have been achieved. The enantiomeric enrichment in the products has been found to reflect the equilibrium ratio of the diamine-complexed organolithiums.

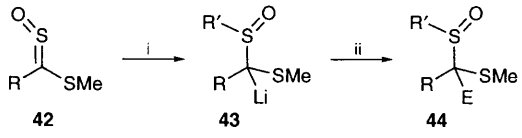
The exchange of both seleno groups for electrophiles in selenoacetals has been achieved *via* two consecutive seleno–lithium exchanges.[37] Addition of butyllithium or LiDBB gives an α-seleno organolithium which, after reaction with an electrophile, can be subjected to a second selenium–lithium exchange with LiDBB (or lithium naphthalenide) followed by addition of a second electrophile.

Dithioacetals and derivatives remain important functional groups in organic synthesis, due to their ability to act as masked acyl anion equivalents. The organolithium **40**, generated by proton abstraction with butyllithium, undergoes conjugate addition with unsaturated lactams to provide, after subsequent interconversions, the indole alkaloid 20-epidasycarpidone **41**.[38]




**40** **41**

An interesting approach to the dithioacetal oxide carbanion **43** has been reported by Metzner and co-workers (**Scheme 5**).[39] Organolithium addition to the *S*-oxide **42** (prepared by oxidation of the dithioester with MCPBA) gives the carbanion **43**, which can be trapped with electrophiles to give mixtures of the diastereomeric dithioacetal oxides **44**.



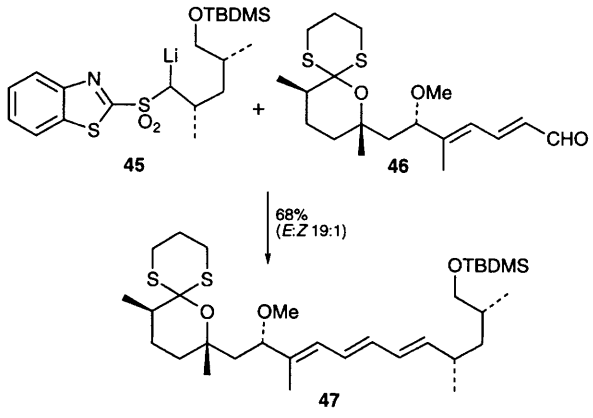

**42** **43** **44**

*Reagents*: i, R'Li, THF, –78 °C; ii, $E^+$

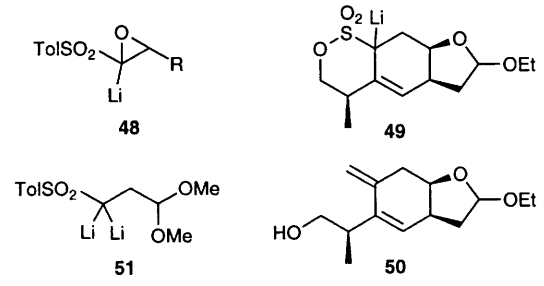
**Scheme 5**

Addition of α-sulfonyl organometallics to electrophiles is a commonly used method for carbon–carbon bond formation. Addition of carbonyl electrophiles leads to β-hydroxy sulfones which act as precursors to alkenes (Julia-type olefination). The effect of various bases on the diastereoselectivity on addition to aldehydes has been investigated.[40] Conversion of the product β-hydroxy sulfone, or preferably *O*-acyl derivative, to the desired alkene, can be effected with $SmI_2$–HMPA.[41] A route to allylic amines has been reported using the more common Na–Hg amalgam reduction (with prior cyclic carbamate formation).[42] Kocienski and co-workers have used the S. Julia modification of this reaction, which involves a useful one-pot tranformation to the alkene without isolation of the β-hydroxy sulfone.[43] The organolithium **45**, formed by proton abstraction with lithium hexamethyldisilazide (LiHMDS), adds to aldehyde **46** to give directly the alkene **47**, the C-10 to C-26 fragment of rapamycin (**Scheme 6**).[43a] The synthesis of herboxidiene A also uses this chemistry.[43b] Intramolecular addition of a β-amino-α-sulfonyl organolithium to a carboxylic ester has provided a route to trihydroxylated indolizidines.[44]

Alkylation of sulfone-stabilised oxiranyl anions **48** with alkyl iodides and trifluoromethanesulfonates provides substituted epoxides with retention of configuration at the carbanion centre.[45] Alkylation of the sulfone-stabilised organolithium **49** with iodomethyl(trimethyl)silane, followed by elimination




**Scheme 6**



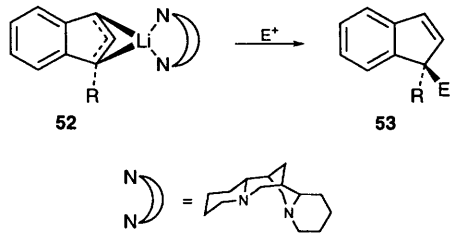

with fluoride, gives the exocyclic alkene **50**, an intermediate in the synthesis of eriolanin and eriolangin.[46]

Dilithiated sulfones, such as **51**, can be prepared by addition of two equivalents of butyllithium to the corresponding alkyl sulfone.[47] The dilithiated sulfone reacts with two equivalents of an electrophile or with one dielectrophile (to give cyclic products). Hydrolysis of the acetal group to the aldehyde gives the product of overall homoenolate dianion addition to electrophiles.

### 2.1.3 Allylic and benzylic organolithiums

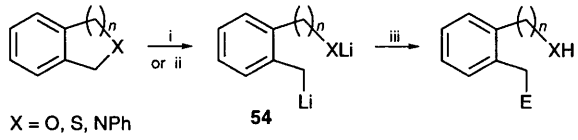
The most common method for forming allylic and benzylic organolithiums is to use direct proton abstraction with a strong base. Both butyllithium–TMEDA and butyllithium–KOBu$^t$ can deprotonate adjacent to an endo- or exo-cyclic alkene.[48] Butyllithium pre-complexed to (−)-sparteine deprotonates 1-alkylindenes to give organolithium **52**.[49] An X-ray crystal structure of the (−)-sparteine-complexed organolithium **52**, R = Bu has been obtained. Reaction with electrophiles gives indenes **53** (>97:3 regioselective, >95% ee, **Scheme 7**). It is crucial that the deprotonation is carried out in diethyl ether and not in THF, as the latter leads to racemic products.

An alternative to direct proton abstraction is the use of reductive lithiation of carbon–heteroatom bonds. The parent allyllithium and benzyllithium can be prepared from allyl alcohol or benzyl alcohol with butyllithium, followed by lithium powder and




**Scheme 7**

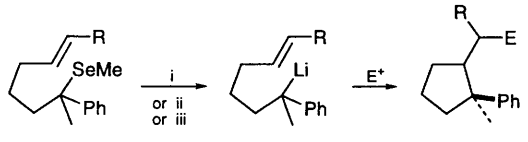
catalytic DBB.[50] This simple procedure provides a new method for preparing allylic and benzylic organolithiums. Reductive lithiation has also been applied to the preparation of benzyllithiums **54** (**Scheme 8**).[51] Cleavage of a C–O, C–S or C–N bond in a five- or six-membered ring is possible and leads to a variety of products resulting from quench with different electrophiles.




*Reagents*: i, LiDBB, THF; ii, Li, naphthalene, THF; iii, $E^+$ then $H_2O/H^+$

**Scheme 8**

The use of lithium arenides, such as LiDBB, has been applied to selenium–lithium exchange, to give benzyllithiums.[52] This provides an alternative to butyllithium[37] and the resulting benzyllithium can be trapped with electrophiles or undergo anionic cyclisation onto an internal alkene.[53] Excellent stereoselectivity for either the *trans* or *cis* ring-substitutents can be achieved in the cyclisation (**Scheme 9**). An alternative method for preparing benzylic organolithiums, discussed in Section 2.1.1, involves alkyllithium addition to styrenes.[5]




R = H, SPh, thiocyclohexyl

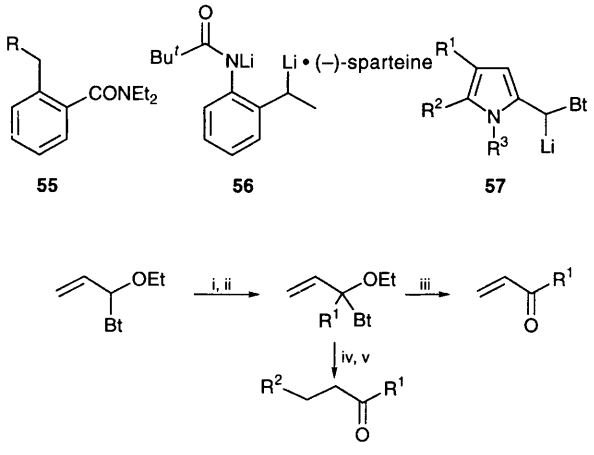
*Reagents*: i, Bu$^t$Li, pentane (*trans*:*cis* ≥90:10); ii, BuLi, THF (*cis*:*trans* ≥95:5); iii, Lithium dimethylamino naphthalenide (LiDMAN), THF, (*cis*:*trans* 98:2, R = E = H)

**Scheme 9**

Benzylic organolithium formation competes with *ortho*-lithiation on treatment of diethylbenzamides **55** with *sec*-butyllithium or LDA.[54] *ortho*-Metallation and aryne formation can be avoided in the deprotonation of diarylmethanes by using LDA–KOBu$^t$ (LIDAKOR).[55] The (−)-sparteine-

complexed diastereomers **56** equilibrate at −25 °C and subsequent reaction with electrophiles (at −78 °C) reflects the equilibrium ratio (≤95:5).[56] Proton abstraction adjacent to heteroaromatics can, likewise, provide an excellent entry to substituted heterocycles, such as indoles,[57] quinazolinones,[58] tetrazoles[59] pyridines[60] and pyrroles.[61] For example, 2-substituted pyrroles can be prepared from the organolithium **57**.[61] After quenching with an electrophile, the benzotriazole group can be displaced with a nucleophile.

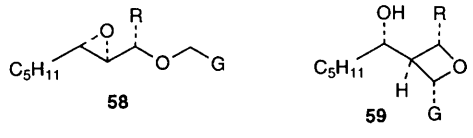
A selection of papers reporting proton abstraction adjacent to the benzotriazole group (Bt) to give allylic,[62] acetylenic[63] and benzylic[64] organolithiums have been published by Katritzky and co-workers. The intermediate organolithiums can be converted to aldehydes, ketones, furans, pyrroles, allylic ethers, cyclopropanes or carboxylic acids. A general representation of the allylic system is given in **Scheme 10**.




*Reagents*: i, BuLi, THF, –78 °C; ii, $R^1X$; iii, $(COOH)_2$, $H_2O$, $SiO_2$, $CH_2Cl_2$; iv, $R^2MgBr$, THF, reflux; v, HCl

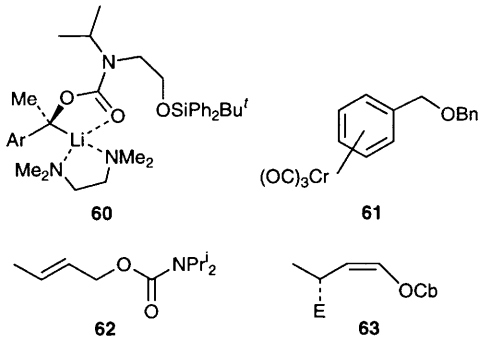
**Scheme 10**

An interesting cyclisation of an allylic or benzylic organolithium onto an epoxide has been reported by Mordini and co-workers.[65] The ether **58** (G = Ph, *p*-F-$C_6H_4$, CH=$CH_2$, SPh; R = H, Me) cyclises to the oxetane **59** on treatment with LIDAKOR.

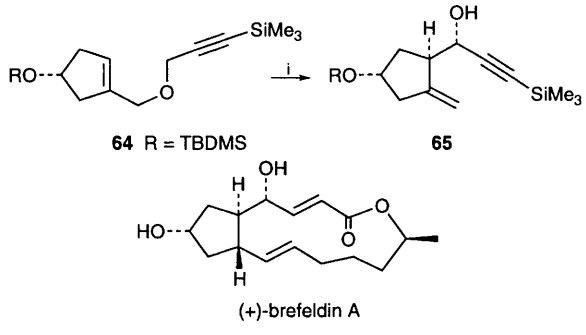



Chiral secondary benzylic organolithiums have been reported to be configurationally stable in diethyl ether or hydrocarbon solvents at −78 °C.[66] The reaction of organolithium **60** with an electrophile proceeds either with retention or inversion of configuration at the carbanion centre, depending on the nature of the electrophile. The carbamate group can be removed under basic conditions to liberate the chiral tertiary alcohol.[66a] The use of a chiral base to abstract a proton from tricarbonylchromium-complexed benzyl ethers (*e.g.* **61**) has led to substituted benzyl ethers with excellent enantioselectivities.[67] Reductive lithiation of acetals has been used to generate racemic chromium-complexed benzylic organolithiums.[68]

Deprotonation of the *O*-allyl carbamate **62** with butyllithium in the presence of (−)-sparteine has now been used by a number of research groups. Transmetallation with $Ti(OPr^i)_4$ and addition of an electrophile gives *Z*-vinyl carbamates **63** (Cb = carbamoyl). These have been used in homoaldol reactions,[69a] the synthesis of herboxidiene A[43b] and the C-10 to C-15 fragment of desepoxyrosaramycin.[69b]




A possible side-reaction on metallation–electrophilic quench of alkyl benzyl ethers is the [1,2] Wittig rearrangement. This can be suppressed at low temperature (−40 °C), to allow substitution of the organolithium with a variety of electrophiles.[70] When the [1,2] Wittig rearrangement is the desired pathway, the organolithium, generated at −78 °C, can be warmed to 0 °C or room temperature. A highly diastereoselective synthesis of *C*-glycosides has been reported by Nakai and co-workers, using the [1,2] Wittig rearrangement of *O*-glycosides.[71] Nakai and co-workers have reported the use of the [2,3] Wittig rearrangement as a key step in the formal synthesis of brefeldin A (**Scheme 11**).[72] The



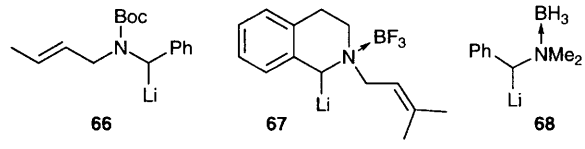

*Reagents*: i, BuLi, THF, –78 °C (77%, 6:1)

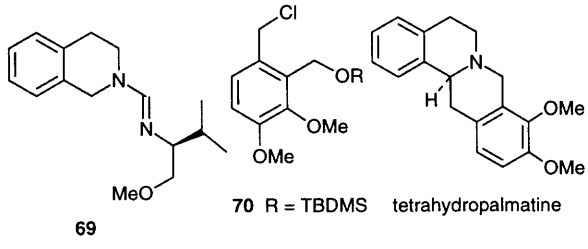
**Scheme 11**

base butyllithium was used to deprotonate the ether **64** and promote rearrangement to the alcohol **65**. The [2,3] Wittig rearrangement of benzylic or propargylic ethers has also been used in the synthesis of a dynemycin A analogue[73] and towards the cytotoxic neolignan (−)-megaphone.[74] Benzotriazole-substituted benzylic organolithiums have been shown to undergo [2,3] Wittig rearrangement.[23]

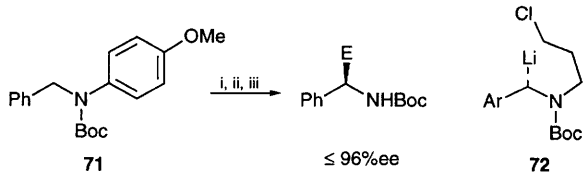
Two examples of the [2,3] Wittig rearrangement of allylic amines, using benzylic organolithiums, have been reported. The *N*-Boc group was found to activate sufficiently the organolithium **66** to promote rearrangement.[75] The organolithium **67**, based on a tertiary amine, requires complexation to $BF_3$ prior to successful rearrangement.[76]

In a similar way, complexation of *N*,*N*-dimethylbenzylamine to $BH_3$ activates the benzylic $CH_2$ towards deprotonation with butyllithium.[77] The benzylic organolithium **68** can be quenched with a variety of electrophiles. Without the complexation of the nitrogen atom to a boron atom, proton abstraction usually requires an aromatic group better able to stabilise an organolithium,[78] or chelation of the lithium atom to an oxygen or nitrogen atom.[79] The chiral formamidine **69** allows deprotonation to the benzylic organolithium with *tert*-butyllithium.[80] Alkylation with the substituted benzyl chloride **70** gives tetrahydropalmatine (88% ee), after cleavage of the formamidine and cyclisation.




Asymmetric deprotonation of the carbamate **71** using butyllithium in the presence of (−)-sparteine leads, on quench with electrophiles and removal of the *p*-methoxyphenyl group with cerium(IV) ammonium nitrate (CAN), to highly enantiomerically enriched substituted benzylamines (**Scheme 12**).[81] The mirror-image products can be prepared using trimethyltin chloride as the electrophile, followed by tin–lithium exchange. Racemic[82] or enantiomerically enriched[81] imidazolidinones result from quenching with imine electrophiles. In contrast to the *N*-methyl analogue,[83] switching to the solvent THF does not reverse the enantioselectivity. Asymmetric deprotonation of benzylamines has been applied to the synthesis of *N*-Boc-phenylsarcosine[84] and to *N*-Boc-2-arylpyrrolidines,[85] the latter by cyclisation of the chiral organolithium **72**. Allylic organolithium formation α to an amino group has been reported using the Brook rearrangement[86a] and α to a silyl group by proton abstraction.[86b,c]

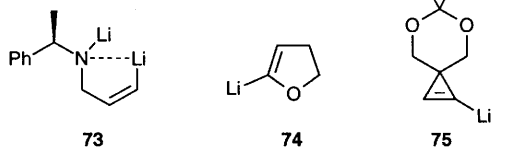


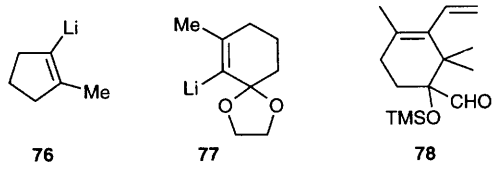

*Reagents*: i, BuLi–(−)-sparteine, PhMe, −78 °C; ii, $E^+$; iii, CAN

**Scheme 12**

### 2.1.4 Alkenyl and alkynyl organolithiums

Electron-withdrawing substituents,[87] or an appropriately positioned chelating group will allow proton abstraction to give an alkenyl (vinyl) organolithium. This is illustrated in the formation (from the allylic amine) of organolithium **73**, *via* successive addition of butyllithium (to generate the amide anion) then *tert*-butyllithium to give **73**.[88] Addition of electrophiles gives *Z*-3-substituted allylic amines. An α-alkoxy group is known to assist deprotonation and the strong base *tert*-butyllithium can convert 2,3-dihydrofuran to the alkenyl organolithium **74**. This species and various cyclopentenyllithiums[89] (generated by halogen–lithium exchange with *tert*-butyllithium) and even the cyclopropenyllithium **75**[90] have been used by Paquette and co-workers in the synthesis of polycyclic products (*e.g.* tetraquinanes), by addition to diisopropyl squarate.

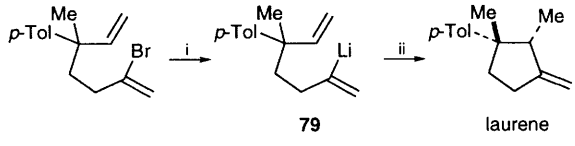



Other cyclopentenyl organolithiums have been prepared by halogen–lithium exchange, a common method for the formation of alkenyl organolithiums. For example, bromine–lithium exchange with *sec*-butyllithium leads to the organolithium **76**, used by Paquette and co-workers in the formation of the core structure of the ceroplastin sesquiterpenes.[91] Alkenyl organolithiums continue to attract interest

for the construction of the taxane ring system.[92] The cyclohexenyl organolithium **77** was formed from its corresponding bromide and adds stereoselectively to the aldehyde **78**.[92a]

The choice of solvent and halogen can affect the extent of halogen–lithium exchange as opposed to direct proton abstraction. *E*-Vinyl bromides are prone to metallation with *tert*-butyllithium in diethyl ether. Vinyl iodides or vinyl bromides in THF tend to yield to halogen–lithium exchange.[93] Pentane–diethyl ether is the solvent of choice for the formation of alkenyl organolithium **79** by bromine–lithium exchange (**Scheme 13**).[94] Anionic cyclisation followed by protonation gives the natural product laurene (60%), together with epilaurene (17%).




**79** laurene

*Reagents*: i, Bu$^t$Li, $C_5H_{12}$–$Et_2O$, –78 °C; ii, TMEDA, 0 °C then MeOH

**Scheme 13**

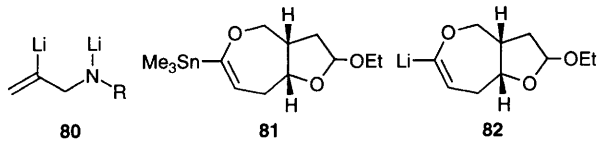
Bromine–lithium exchange with *tert*-butyllithium gives rise to one equivalent of *tert*-butyl bromide. A second equivalent of *tert*-butyllithium may be required (such as for **79**) in order to avoid reaction of the alkenyl organolithium with *tert*-butyl bromide. It has been found that non-polar solvents, such as hexane, allow iodine–lithium exchange with only 1.2 mol. equiv. of butyllithium, without the complication of reaction of the resulting alkenyl organolithium with iodobutane.[95] In the same way, allenyl organolithiums can be prepared.

Halogen–lithium exchange, followed by coupling with α-chloro enamines has led to a synthesis of 2-amino dienes.[96] Although the allylic amine **73** could be prepared by proton abstraction, the formation of the regioisomer **80** requires bromine–lithium or tin–lithium exchange.[97]

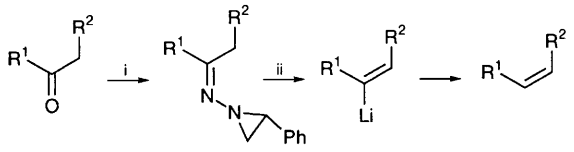
Tin–lithium exchange to alkenyl organolithiums has been employed in the synthesis of polyether toxin frameworks.[98] The synthesis of luffariolide E uses transmetallation of the stannane **81** to the organolithium **82**.[99] Subsequent cuprate addition and 1,2-metallate rearrangement sets up the required carbon skeleton of luffariolide E.

An alternative synthesis of alkenyl organolithiums is the Shapiro reaction. A catalytic version of this process has been reported, which uses hydrazones **83** and LDA (0.1 equiv.) (**Scheme 14**).[100] The organolithium **84** picks up a proton from diisopropylamine, releasing LDA to continue the cycle. The overall transformation is from a ketone to an alkene with a preference for the *Z* alkene (⩾96:4).

The formation of allenyl organolithiums **85** (by tin–lithium exchange) and their regioselectivity on sequential or *in situ* quench with trialkylsilyl chlorides has been studied.[101] Evidence for an initial




**80** **81** **82**

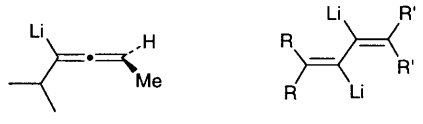



**83** **84**

*Reagents*: i, $H_2N$–N⟨Ph ; ii, LDA, $Et_2O$

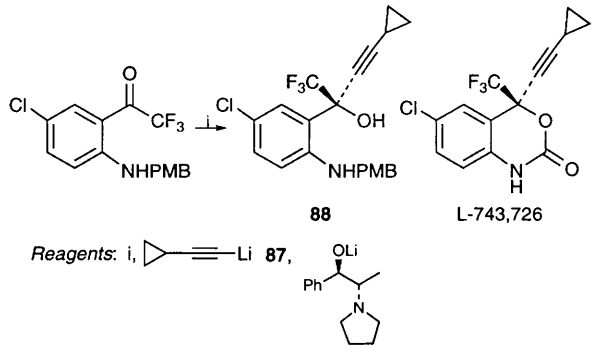
**Scheme 14**

transient solvent-separated ion pair is presented. Dilithiated butadienes **86** can be prepared by addition of lithium metal to alkatrienes or, in one case, by double proton abstraction.[102] The unsaturation pattern in the products depends on the nature of the electrophile.




**85** **86**

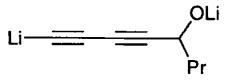
Alkynyl organolithiums, normally generated by proton abstraction, continue to find widespread application in organic synthesis. The reverse transcriptase inhibitor L-743,726 can be prepared using the alkynyl organolithium **87** (**Scheme 15**).[103] An impressive 96–98% ee of the alcohol **88** is obtained when an ephedrine-based chiral ligand is used. Addition of alkynyl organolithiums to carbonyl electrophiles has led to the synthesis of prop-2-ynyl stannanes,[104] trifluorosugars[105] and (+)-isobretonin A.[106] The $C_{12}$-triene side-chain of isobretonin was constructed using the organolithium **89** and the aldehyde **90**. Addition of alkynyl organolithiums **91** to alkenylboranes, followed by addition of a trialkyl-



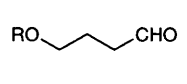

**88** L-743,726

*Reagents*: i,

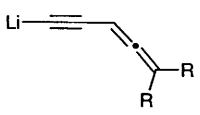
**Scheme 15**



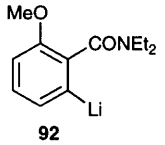
89



90 R = TBDMS



91

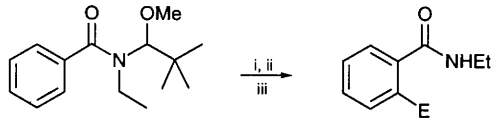


92

tin chloride, has provided an entry to methylene cyclohexadiences.[107]

### 2.1.5 Aryl organolithiums

Alkoxy groups and carboxylic amides are well-known to assist proton abstraction in the *ortho* position of an aromatic ring. The amide has the stronger directing effect, as illustrated in the regio-selective *ortho*-lithiation to give the aryllithium **92** (using *sec*-butyllithium–TMEDA).[108] Organolithium **92** was used in the synthesis of the dihydroiso-coumarin unit of the antiulcerogenic AI-77-B. A solution to the problems which may be encountered on *ortho*-lithiation of secondary carboxylic amides, is the use of the tertiary amide **93**, which can be hydrolysed under mild acid conditions (**Scheme 16**).[109]



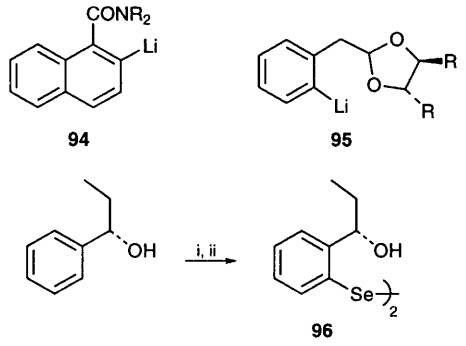
93

*Reagents*: i, Bu$^s$Li, TMEDA, –78 °C; ii, E$^+$; iii, HCl, dioxane

**Scheme 16**

1-Naphthamides can be deprotonated at C-2 of the naphthalene ring with *sec*-butyllithium to give the organolithium **94**. On addition of an aldehyde diastereomeric atropisomeric amides are formed.[110] On alkylation, some enantioselectivity is observed using asymmetric deprotonation mediated by (−)-sparteine.[111] Asymmetric synthesis of 1-aryl tetrahydroisoquinolines *via* addition of the aryl-lithium **95** to imines has been reported.[112] The organolithium **95** is generated by bromine–lithium exchange. The chiral diselenide **96** is prepared by *ortho*-lithiation (**Scheme 17**) and used in the synthesis of (+)-samin.[113] Related diselenides, prepared similarly, are useful asymmetric catalysts for alkylation of aldehydes with diethylzinc (see Section 3.3).[114]

The chiral tricarbonyl(styrene)chromium **97**, which reacts with various organometallics, for example giving access to chiral cyclopropanes, is synthesised by *ortho*-lithiation with *tert*-butyllithium (**Scheme 18**).[115] Quench of the aryllithium with



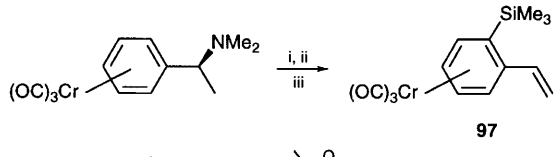
94 95 96

*Reagents*: i, BuLi, TMEDA; ii, Se

**Scheme 17**

trimethylsilyl chloride, followed by Cope elimination gives **97**. A number of reports describing ferrocenyl organolithiums have been published during this review period.[116]

An aromatic aldehyde cannot be used to direct *ortho*-lithiation due to its susceptibility to nucleophilic attack. However, the intermediate formation

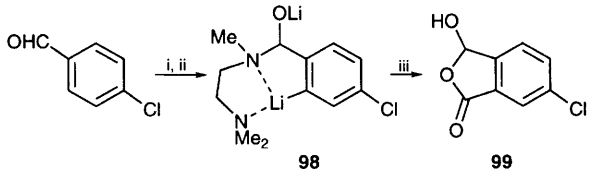


97

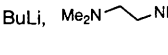
*Reagents*: i, Bu$^t$Li; ii, $Me_3SiCl$; iii, 

**Scheme 18**

of a hemiaminal (as originally described by Comins) has allowed Larsen and co-workers at Merck to effect proton abstraction with butyllithium–TMEDA to give the aryllithium **98** (**Scheme 19**).[117] Quenching with $CO_2$ gives the product **99**, used in the synthesis of $LTD_4$ receptor antagonists.



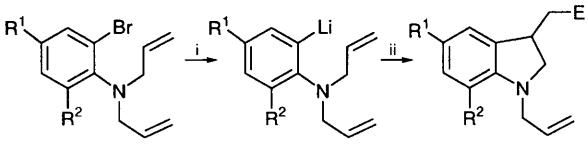
98 99

*Reagents*: i, BuLi,  , ii, BuLi, TMEDA; iii, $CO_2$

**Scheme 19**

A variety of alternative functional groups have been reported to direct *ortho*-lithiation, including alkoxy and thioalkoxy groups,[118] sulfonates[119] and halogens.[120] Halogen–lithium exchange provides a convenient method to access aryl organolithiums. In consecutive papers, Zhang and Liebeskind[121] and

Bailey and Jiang[122] describe the synthesis of indolines by bromine–lithium exchange of *o*-bromo-*N*,*N*-diallylanilines **100** with *tert*-butyllithium (**Scheme 20**). The aryllithiums undergo anionic cyclisation onto one of the *N*-allyl groups and the resulting organolithium can be trapped with a selection of electrophiles. Oxidation to the indole ring is possible using *o*-chloranil and the remaining *N*-allyl group can be cleaved under palladium catalysis.



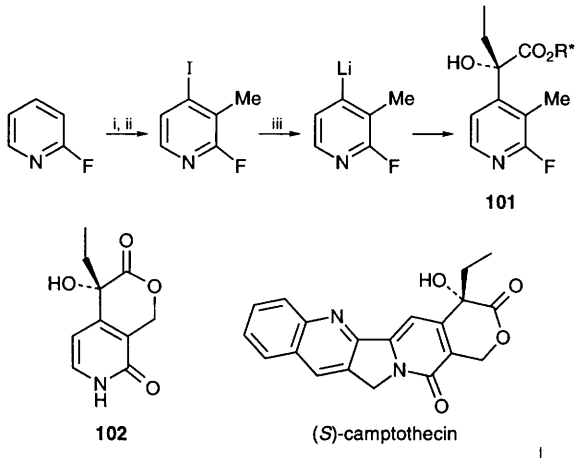
**100**

*Reagents*: i, Bu$^t$Li; ii, $E^+$

**Scheme 20**

The formation and reaction of heteroaromatic organolithiums has been used for the synthesis of substituted heterocycles. Both 2- and 3-lithio pyridines have been prepared by bromine–lithium exchange of dibromopyridines with butyllithium.[123] Comins and Saha have used consecutive *ortho*-lithiations and iodine–lithium exchange to convert 2-fluoropyridine to the pyridine **101** and hence the pyridone **102**.[124] Pyridone **102** was used in the synthesis of camptothecin (**Scheme 21**).

Lithiation of other six-membered heterocycles has been reported, including quinolin-2(1*H*)-one[125] and substituted (3*H*)-quinazolin-4-ones.[126] Five-membered heterocycles, such as isoxazoles can be metallated, for example, to give organolithium **103**.[127] Bromine–lithium exchange has been used to prepare 3-lithiofurans[128] and 2-lithiothiazole **104**.[129] The latter heterocycle provides an acyl anion equivalent and its addition to nitrones leads to α-amino aldehydes and to amino- and aza-sugars. Bromine–lithium exchange with *tert*-butyllithium of thiazole **105** leads to organolithium **106** *via* migration (intermolecular) of the tributyltin group, illustrating the potential pitfalls of attempted halogen–lithium exchange of an arylstannane.[130]

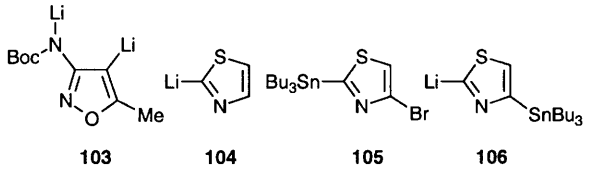


**101**

**102** (*S*)-camptothecin

*Reagents*: i, LDA, $I_2$; ii, LDA, MeI; iii, BuLi, then $EtCOCO_2R^*$ (94% de)

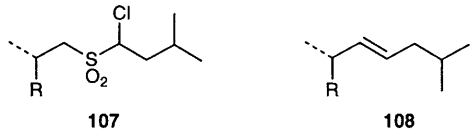
**Scheme 21**



**103** **104** **105** **106**

## 2.2 Sodium and potassium

Examples of organosodium and organopotassium reagents in contemporary organic synthesis are rare (in comparison with organolithiums) and these species were not covered in the previous review on main group organometallic chemistry.[1] There are, however, situations in which the use of a sodium or potassium counter-cation, rather than a lithium cation, can influence favourably the outcome of a desired transformation. The metallation of seleno acetals is best performed using KDA rather than LDA.[131] The simple Wittig methylenation of some bis-heteroaromatic ketones gave none of the desired alkene when using $MePPh_3Br$ and butyllithium; however, using KOBu$^t$, olefination proceeded smoothly.[132] A synthesis of the side-chain of sterols has been accomplished using KOBu$^t$-mediated Ramberg–Bäcklund reaction of sulfone **107** to give alkene **108**.[133] The formation of benzylpotassium and its quench with electrophiles has been reported by Hevesi and Lacave-Goffin.[134]

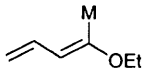


**107** **108**

R = 3α,5α-cyclo-6β-methoxypregnane

Some examples of the use of so-called superbases, such as LICKOR and LIDAKOR, which are thought to result in carbon–lithium and/or carbon–potassium bonds have been described in Section 2.1.3.[48,55,57,65] A further example of the use of LICKOR for metallation has allowed the preparation of the vinyl metal **109** (which was quenched with epoxide electrophiles).[135] Potassium amide-mediated isomerisations of terminal allenes (*e.g.* **110**) with potassium 3-aminopropylamide (KAPA) and potassium *N*-methylbutylamide (KMBA) to give terminal alkynes (*e.g.* **111**) have been described.[136]

A study of the electronic effect of different triarylsilyl groups of the sodium anion **112** in the Peterson olefination has found that electron-withdrawing substituents ($Ar = C_6H_4CF_3$) increase the ratio of *E*:*Z* alkene in the product.[137]



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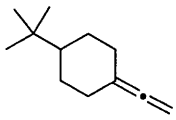

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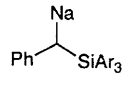

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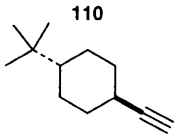
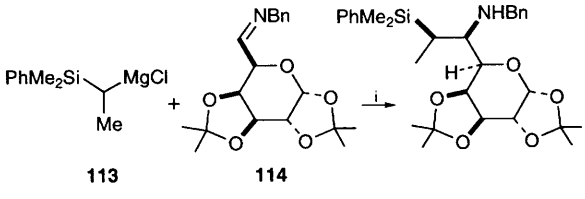


111

## 3 Group 2

### 3.1 Magnesium

The widespread use of organomagnesium reagents, particularly Grignard reagents, in organic synthesis has resulted in a recent text by Wakefield in the *Best Synthetic Methods* series.[138] Grignard reagents continue to be used extensively, for example, in the addition to a carboxylic amide to give a ketone[139] in the synthesis of the C-20 to C-25 unit of calyculin A.[140] Addition to anhydrides[141] or even acid chlorides [with Ni(dppe)$Cl_2$ catalysis][142] also gives ketone products. Addition to carbon disulfide has allowed a one-pot synthesis of thioamides.[143] Ring opening of aziridines by Grignard reagents provides a synthesis of amines[144] or α-amino esters.[145] Various stereoselective carbon–carbon bond forming reactions with Grignard reagents have been reported over the period of this review. Addition to α-thio aldehydes,[146] chiral α-alkoxy aldehydes and ketones[147] and other α-substituted ketones[148] can occur with excellent diastereoselectivity. Stereoselective addition to chiral acetals[149] (giving ethers and a synthesis of eicosanoids), to chiral *N,O*-acetals,[150] hydrazones,[151] oximes[152] and imines (giving amines)[153] have been reported. Addition of the Grignard reagent **113**, under copper catalysis, to the imine **114** was used as part of a synthesis of the lincosamine fragment of the antibiotic lincomycin (**Scheme 22**).[154] An α-silyl Grignard reagent has also been used to effect the selective deprotection of acetals to 1,2-diols.[155]

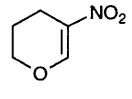


113 114

*Reagents*: i, CuI, $BF_3$•$OEt_2$

**Scheme 22**

The addition of Grignard reagents to chiral *N*-acylpyridinium salts provides a key step in the synthesis of various piperidine-containing alkaloids. The study of a selection of different chiral acyl groups to promote enantioselective carbon–carbon bond formation has been reported.[156] Grignard addition to chiral α,β-unsaturated amides gives, after hydrolysis, β-substituted alkanoic acids with good enantioselectivities.[157] Addition to the unsaturated nitro compound **115** leads to 2-alkyltetrahydropyran-3-ones **116**.[158] Vinyl Grignard addition to the α,β-unsaturated imine **117** provides a route to the di-*O*-methyl ethers of the norlignans of *Coniferae*.[159] A formal synthesis of physostigmine uses conjugate addition of methylmagnesium iodide to the indole derivative **118**.[160] Hutchings and Meyers have described the addition of aryl Grignard **119** to oxazoline **120** as a key step in the synthesis of oxoassoanine and other pyrrolophenanthridine alkaloids (**Scheme 23**).[161]



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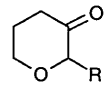

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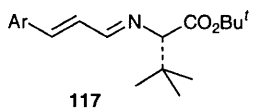

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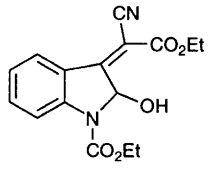

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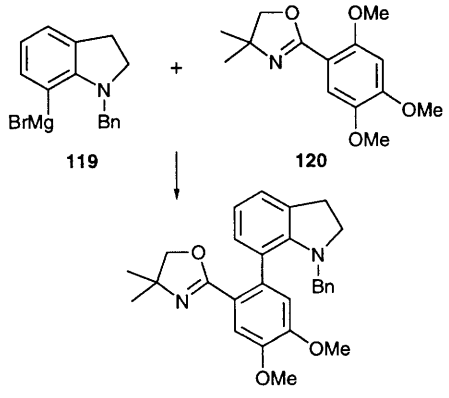
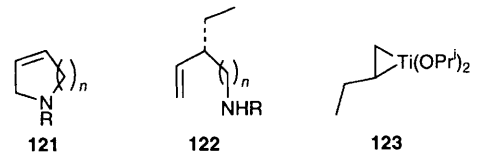


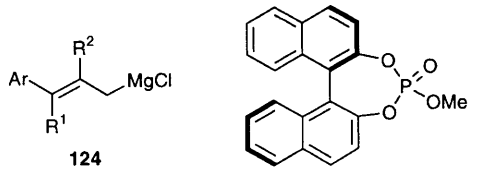
119 120

**Scheme 23**

The use of transition metal catalysts in conjunction with Grignard reagents has led to some interesting transformations in organic chemistry. Ring-opening of unsaturated cyclic amines **121** ($n = 1$–4) with ethylmagnesium chloride under chiral zirconium catalysis gives acyclic amines **122** with >98% ee.[162] The method has also been applied to unsaturated cyclic ethers[163] and their kinetic resolution.[162] Addition to acyclic allylic ethers has proved efficient with $(Ph_3P)_2NiCl_2$ catalysis.[164] Allylmagnesium halide addition to alkynes, mediated by a manganese catalyst gives 1,4-dienes.[165] No metal catalyst is needed for vinyl Grignard addition to the triple bond of a prop-2-ynyl alcohol.[92b] Loss of a β-hydrogen atom from BuMgCl using $Ti(OPr^i)_3Cl$



121 122 123

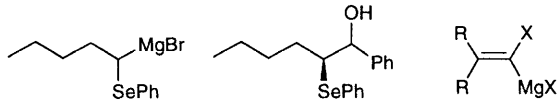


124 125

leads to reagent **123**, used for intramolecular hydroxycyclopropanation.[166]

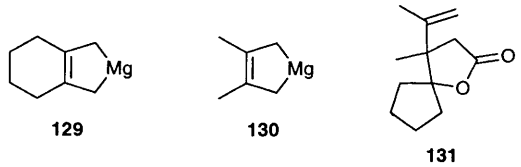
The coupling of Grignard reagents to alkyl halides is possible with catalysis by $Li_2CuCl_4$, or better, $Li_2CuCl_3$.[167] Diarylmethanes related to 5-lipoxygenase inhibitors can be prepared using this methodology.[168] Poor to modest enantioselectivities have been obtained in the $\gamma$-methylation of allylic Grignard reagents **124** with the phosphate **125**.[169]

An interesting account of $\alpha$-seleno organomagnesium compounds has shown that they possess considerably greater configurational stability than the corresponding organolithium compounds.[170] This has allowed the kinetic resolution of the Grignard reagent **126** on reaction with 0.59 equiv. of a chiral aldehyde. The unreacted Grignard reagent can be trapped with benzaldehyde to give the alcohols **127** (38%, *anti*:*syn* 68:32, 80–86%ee).



126 127 128

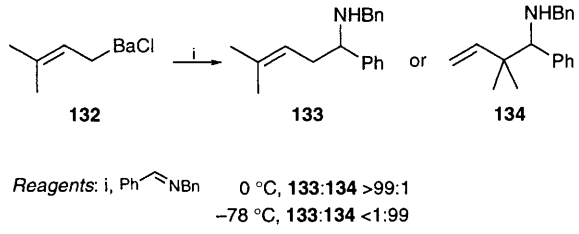
The formation and reaction with electrophiles of $\alpha$-halovinyl organomagnesium compounds **128** has been reported using exchange of sulfoxides for magnesium (using EtMgX).[171] Direct proton abstraction to aryl organomagnesium compounds has been used for the regioselective *ortho*-magnesiation of substituted pyridines.[172] A synthesis of spirocyclic lactones by quench of the organomagnesium complexes **129** or **130** with an epoxide or ketone, followed by $CO_2$, has been reported by Rieke and co-workers.[173] For example, quench of **130** with cyclopentanone, followed by $CO_2$ gives the $\gamma$-lactone **131**. Acidic hydrolysis, rather than $CO_2$ quench, leads to alcohol products.



129 130 131

### 3.2 Barium

Over the last few years allylic barium reagents have shown promise as highly regioselective allylating agents. In contrast to other allylic organometallics, reaction with aldehydes and ketones and conjugate addition with enones occurs at the least hindered, normally $\alpha$-, position of the allyl group. A recent paper by Yamamoto and co-workers describes the regioselective allylation of imines with allylic barium reagents, especially prenylbarium chloride **132**.[174] Quite remarkably, reaction occurs at either the $\alpha$- or $\gamma$-position of the allyl group, with very high or complete regioselectivity for either isomer, depending only on the reaction temperature. At 0 °C the homoallylic amine **133** (the $\alpha$-adduct) is the exclusive product, whereas at −78 °C, the $\gamma$-adduct **134** is formed (**Scheme 24**).



132 133 134

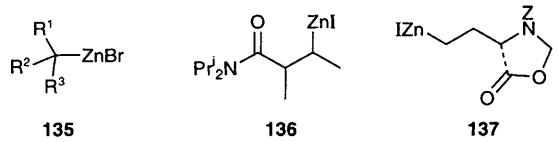
*Reagents*: i, Ph⁄⁄NBn 0 °C, **133**:**134** >99:1
−78 °C, **133**:**134** <1:99

**Scheme 24**

### 3.3 Zinc

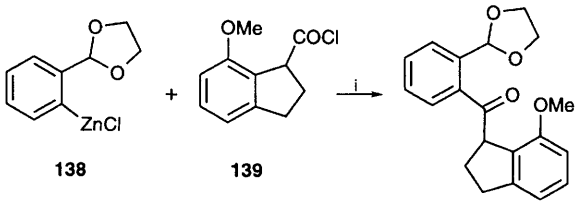
Organozinc compounds are less reactive than their corresponding Group 1 or Group 2 organometallics. Despite this, their popularity in organic synthesis continues to grow, mostly due to their selective, controlled carbon–carbon bond forming reactions. A number of methods are available for the preparation of organozinc reagents. An attractive approach is the direct insertion of zinc into a carbon–halogen bond. This is most effective for a primary alkyl iodide. Insertion into a carbon–bromine bond is more sluggish, especially for secondary or tertiary alkyl bromides. Rieke and co-workers have reported a solution to this problem using activated zinc.[175] Hindered (and unhindered) alkylzinc bromides **135** can be prepared and coupled (using copper catalysis) with acid chlorides or enones. The use of alkylzinc reagents is attractive as functional groups such as amides, esters and nitriles can be tolerated.

Insertion of zinc into a $\beta$-iodo amide gives the organozinc homoenolate **136**, which reacts with aromatic aldehydes in the presence of TMSI.[176] Coupling to acid chlorides is possible with palladium catalysis.



135 136 137

Transition metal-catalysed couplings of organozinc reagents are a very valuable method for carbon–carbon bond formation. The organozinc iodide **137** couples to acid chlorides in the presence of palladium catalysts.[177] The choice of solvent is important in order to optimise the yields. A synthesis of the BCDE rings of fredericamycin A has been accomplished using a palladium-catalysed coupling of arylzinc chloride **138** with acid chloride **139** (**Scheme 25**).[178] The arylzinc chloride is prepared from the corresponding aryllithium and $ZnCl_2$.



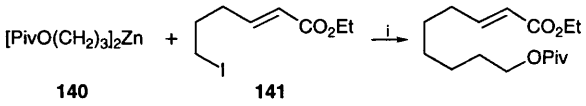

**138** **139**

*Reagents*: i, $Pd(PPh_3)_4$, 0 °C

**Scheme 25**

An alternative approach to the use of an acid chloride is to couple an organozinc reagent with an aryl iodide in the presence of carbon monoxide.[179] This procedure has been used for the synthesis of kynurenine. The direct coupling of an organozinc halide with an aryl or vinyl halide (or trifluoromethanesulfonate) under palladium catalysis has been employed by a number of research groups.[180] Of note are the extensive number of examples from the Knochel group, illustrating the scope of the reaction. For example, coupling of an arylzinc bromide with an aryl iodide occurs at room temperature, whereas coupling with an aryl trifluoromethanesulfonate requires warming to 60 °C.[180c] The use of iodoaryl trifluoromethanesulfonates therefore allows the selective synthesis of various terphenyls. The coupling of an organozinc reagent to an $sp^3$ carbon centre would expand even further the potential of these reagents. This has now been achieved by Knochel and co-workers using catalysis with $Ni(acac)_2$.[181] A representative example is shown in **Scheme 26**, in which the functionalised dialkylzinc reagent **140** couples efficiently with the unsaturated alkyl iodide **141**. The presence of the alkene in **141** (which is thought to complex to the nickel) is essential to promote coupling.

The formation of symmetrical ketones has been reported by carbonylation (with carbon monoxide)

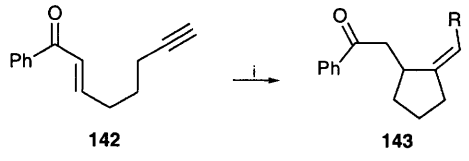



**140** **141**

*Reagents*: i, $Ni(acac)_2$, THF:NMP (2:1), –35 °C, 79%

**Scheme 26**

of functionalised organozinc halides in the presence of cobalt dibromide.[182] The use of organozinc reagents with copper catalysis has been employed for conjugate addition reactions.[175,180f,183] Nickel catalysis allows an intramolecular conjugate addition to give a cyclopentane.[184] In related chemistry, addition to an alkyne can take place to give a $\beta$-alkenyl ketone.[185] For example, cyclization of the alkynyl enone **142** in the presence of organozinc reagents and $Ni(cod)_2$ gives the geometrically pure alkene **143** (**Scheme 27**).[185a]

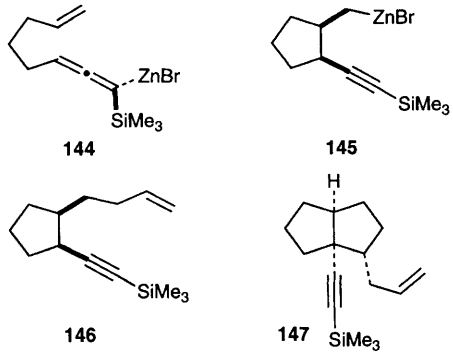



**142** **143**

*Reagents*: i, $R_2Zn$, RZnCl, $Ni(COD)_2$, THF, 0 °C

**Scheme 27**

A useful route to cyclopentanes is the cyclisation of allenylzinc bromide **144**, prepared by proton abstraction of an alkyne (*sec*-butyllithium, $ZnBr_2$).[186] The intermediate organozinc bromide **145** can be coupled with electrophiles, such as allyl bromide (using copper catalysis) to give cyclopentane **146**. This product can be subjected to a second zinca-ene–allene cyclisation to give the bicyclo enyne **147**, after coupling with vinyl iodide (using palladium catalysis). Further manipulations lead to the angular triquinane skeleton.

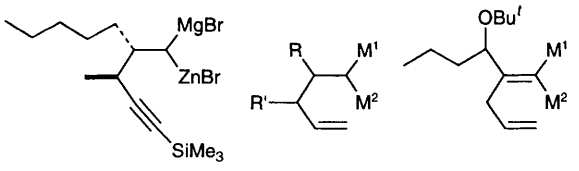



**144** **145**

**146** **147**

Intramolecular addition of an allenylzinc bromide to the vinyl Grignard reagent *Z*-1-magnesiohept-1-ene, leads to the intermediate 1,1-bismetallic species **148**.[187] Only the *anti* isomer **148** is formed and the bismetallic species can be hydrolysed to generate a $CH_3$ group. Related 1,1-bismetallic reagents **149** and **150** can be formed by addition of an allylzinc bromide to a vinyl or alkynyl metal.[187,188] Sequential quenching of the bismetallic species with two different electrophiles is possible.

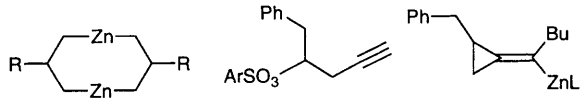
An efficient synthesis of the 1,3-dizinc compounds **151** (R = H, Bu) has been achieved using boron–zinc exchange.[189] These dimetallic reagents couple,



148 149 150

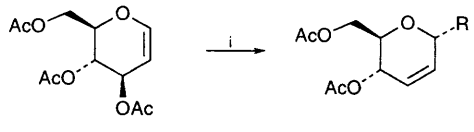
in the presence of CuCN·2LiCl, with various electrophiles.

The vinylzinc reagent **153** is formed on treatment of the alkyne **152** with $Bu_3ZnLi$.[190] Migration of a butyl group from zinc to the alkyne is thought to occur simultaneously with the loss of the sulfonate group and formation of the cyclopropane ring. The organozinc reagent **153** can be trapped with a range of electrophiles.



151 152 153

Stereoselective cyclopropanation reactions with organozinc reagents such as $Et_2Zn$–$CH_2I_2$, $Zn(CH_2I)_2$ and $IZnCH_2I$,[191] have received further study during the period of this review. Allylic alcohols are good substrates for enantioselective cyclopropanation.[192] Double Simmons–Smith cyclopropanation has been used by Barrett and co-workers for the structural assignment of the antifungal agent FR-900848.[193] The use of diethylzinc for the formation of oxyallyl cations and their [3+4] cycloaddition with furans has been reported.[194] Diethylzinc or functionalised alkylzinc halides react with glycals, such as **154** to provide a useful entry to *C*-glycosides **155** (**Scheme 28**).[195] Moderate to excellent selectivity for the α- isomer is obtained.



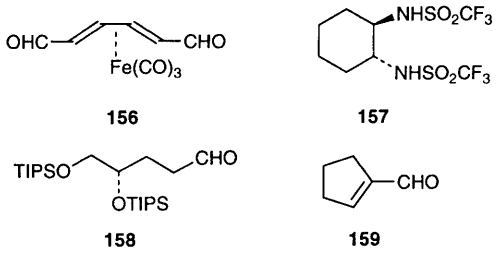
154 155

*Reagents*: i, $Et_2Zn$ or RZnX, $CH_2Cl_2$, $BF_3$•$OEt_2$ (or TMSOTf)

**Scheme 28**

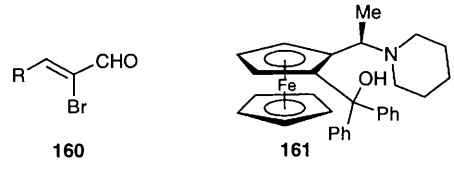
Carbon–carbon bond formation with allylzinc reagents to give bismetallic compounds has been mentioned above.[187,188] Allylzinc reagents also react with carbonyl[196] and imine[153b,197] electrophiles. Their regioselectivity[198] and stereoselectivity on addition to aldehydes[199] has been investigated.

Addition of organozinc reagents to chiral aldehydes[4,200] or chiral activated ketones[201] can give rise to alcohols with high levels of diastereoselectivity. The use of a chiral ligand to promote enantioselective addition to aldehydes continues to attract much research effort. Very good diastereoselectivities and excellent enantioselectivities have been achieved in the addition of dialkylzinc reagents to the *meso* dialdehyde **156**, using a chiral prolinol-based auxiliary.[202] The chiral ligand **157** is the dominant controlling factor in the diastereoselective addition of dialkylzinc reagents to aldehyde **158**.[203] Selectivities greater than 98:2 for either *syn* or *anti* diastereomer can be achieved by selection of the desired enantiomer of ligand **157**. Ring closure to stereodefined 2,5-disubstituted tetrahydrofurans was then straightforward.



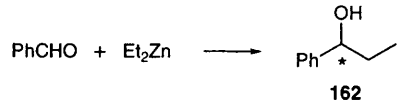
156 157 158 159

The chiral ligand **157** is an effective catalyst (normally 5–8 mol%), in conjunction with $Ti(OPr^i)_4$ and $Ti(OBu^t)_4$, for the addition of a variety of dialkylzinc reagents to different aldehydes. For example, addition to the aldehyde **159** occurs in up to 98% ee.[204] The product alcohols were then transformed to chiral cyclopentadienylmetal complexes. Addition to acetylenic aldehydes gives enantioselectivities up to 96%, on the condition that an increased amount (15 mol%) of the catalyst **157** is used.[205] The α-bromo-α,β-unsaturated aldehydes **160** (which can then be converted to the same prop-2-ynlic alcohols with NaH) are better substrates and give selectivities greater than 96% ee (R = Pr, 8 mol% **157**).[205] Aldehydes **160** with other R groups also give impressive results (84–96% ee). Addition of dimethylzinc to acetylenic aldehydes using titanium TADDOLate catalysts (20 mol%) gives selectivities up to 96% ee.[206] The addition of dimethylzinc to benzaldehyde or metallocenyl aldehydes using the chiral ferrocenyl amino alcohol **161** has been reported to give excellent selectivities (98 to >99% ee) of the alcohol products.[207]



160 161

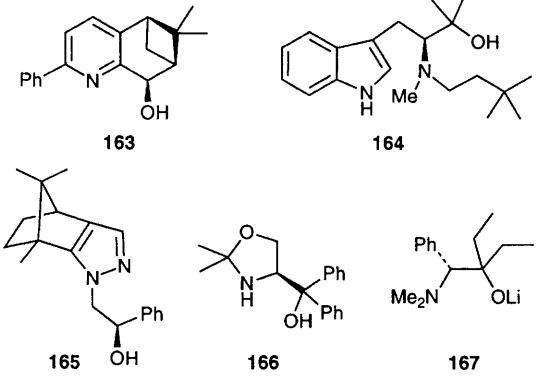
The addition of diethylzinc to benzaldehyde (Scheme 29) is a standard test of a new ligand's ability to induce high levels of enantioselectivity. The ligands **163**–**170** (normally 5–10 mol%) have all been reported to give excellent selectivities (over 90% ee) for this transformation. Chiral β-amino alcohols remain popular ligands, for example **163**[208]

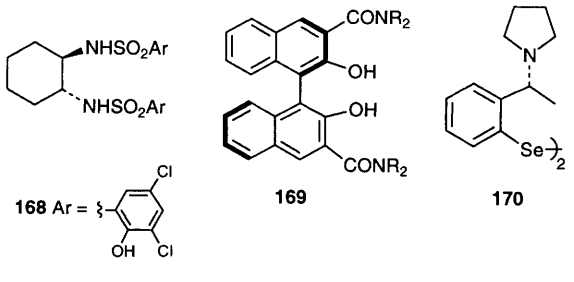



**162**

**Scheme 29**

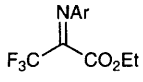
and **164**[209] give the product 1-phenylpropan-1-ol **162** in 91% ee and 94% ee respectively. The ligand **165** gives *R*-**162** (93% ee), whereas the diastereomer of **165** gives the enantiomer *S*-**162** (87% ee).[210] The oxazoline **166** is reported to give the alcohol **162** with complete enantioselectivity (100% ee).[211] The use of the lithium alkoxide of oxazoline **166** was stated as giving lower selectivity. In contrast, the ligand **167** is reported to be best used in the form of its lithium alkoxide (96% ee).[212] Replacement of the alcohol group for a different heteroatom has provided some useful chiral ligands. For example, the titanate complex of the $C_2$-symmetric ligand **168** gives the alcohol **162** in 99% ee.[213] The same high level of selectivity (99% ee) is achieved using the binaphthol dicarboxamide **169** (R = Bu or Pr$^i$).[214] Most dialkylzinc additions are carried out in non-polar solvents such as toluene and/or hexane, because polar solvents (THF, MeCN) tend to slow the addition and reduce the enantioselectivity. The high levels of selectivity with binaphthol **169** are, however, reported using THF as solvent. Only 1 mol% of the diselenide **170** is required for high enantioselectivity (98% ee).[114] Chiral disulfides have also been reported to give excellent enantioselectivities in addition of dialkylzinc reagents to benzaldehyde or other aldehydes.[215] A number of other research groups have published good to excellent selectivities for this transformation.[216]




Asymmetric autocatalysis of the addition of diisopropylzinc to pyrimidine-5-carbaldehyde and quinoline-3-carbaldehyde has been reported.[217] The product alcohols act as the chiral ligand, thereby simplifying the separation and allowing chiral amplification.[218]

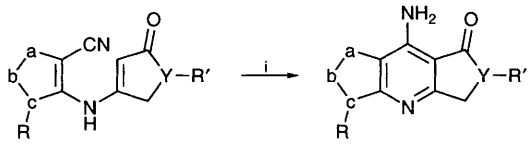
Organozinc reagents can add to imines,[219] as already mentioned in this section,[153b,197] as well as to nitrones.[220] An interesting switch from the normal *C*-addition (to the imine **171**) using EtZnBr, to *N*-addition occurs using $Et_2Zn$.[221] Addition of alkylzinc bromides to oxygen to give hydroperoxides has been reported using perfluorohexane solvents.[222]




**171** Ar = *p*-$MeOC_6H_4$

### 3.4 Cadmium and mercury

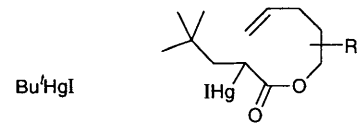
Of a range of Lewis acids tested for the cyclisation of an enamine onto a nitrile group (to give a tricyclic 4-aminopyridine), cadmium(II) chloride proved the most efficient (**Scheme 30**).[223] Prior deprotonation of the enamine with sodium hydride allows milder reaction conditions. Alternatively, the organocadmium reagent dibutylcadmium effects both the proton abstraction and the cyclisation at room temperature.




*Reagents*: i, NaH, $CdCl_2$, 60 °C or $Bu_2Cd$, room temp.

**Scheme 30**

Organomercury compounds are popular for promoting cyclisation reactions. A mercury(II) salt is normally used in order to generate a mercuronium ion, which can be attacked by a heteroatom or soft carbon nucleophile. This protocol has been used by Shrader and Imperiali (cyclisation by the nitrogen atom of an imidate) to give allosamidin pseudodisaccharides,[224] by Huang and Forsyth (cyclisation by a silyl enol ether) to give trifarienol sesquiterpenes[225] and by Nishizawa and Yamada (cyclisation by an alkene) to give baiyunoside aglycone, a diterpene glycoside.[226] Russell and Li have used the alkylmercury iodide **172** to effect conjugate addition of the *tert*-butyl group to give new organomercurials, for example **173**.[227] Photolysis of the organomercurial, in the presence of PhSSPh, gives the free radical and allows cyclisation to eight-membered ring lactones.

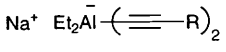



172 173

## 4 Group 13

### 4.1 Aluminium

Stereoselective additions of organoaluminium reagents to aldehydes[228] and ketones[229] have been reported during the period of this review. The addition of trimethylaluminium to acid chlorides occurs under aluminium chloride catalysis to give methyl ketones.[230] Yoon and co-workers have reported the alkynylation of carbonyl compounds by addition of sodium diethyldialkynylaluminate **174** or sodium trimethylethynylaluminate **175** with aldehydes and ketones.[231] Only the product of 1,2-addition is formed on alkynylation of an unsaturated carbonyl compound and the reagents show excellent chemoselectivity.

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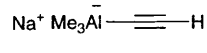


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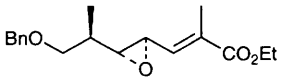


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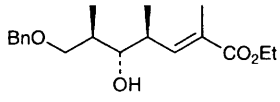
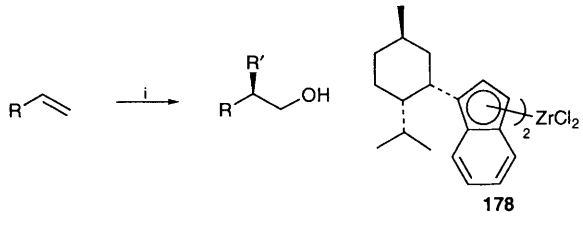



177

Ring-opening of epoxide **176** with trimethylaluminium occurs with complete regio- and stereoselectivity to give alcohol **177**, as part of a synthesis of tirandamycin B.[232] An unusual *N*-ethylation of aromatic amines by diethylaluminium chloride occurs in the presence of copper(II) pivalate.[233]

Carboalumination of terminal alkenes using a chiral zirconocene catalyst provides, after oxidation with $O_2$, 2-alkylalkan-1-ols in high yields and high enantioselectivities (**Scheme 31**).[234] Significant solvent effects are observed and the best results have been achieved using $CH_3CHCl_2$ (or $CH_2Cl_2$)



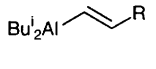

178

*Reagents*: i, $R'_3Al$, $CH_3CHCl_2$, 8 mol% **178** then $O_2$ (≤96% ee)

**Scheme 31**

and 8 mol% of the catalyst **178**. The carboalumination of a terminal alkene of a diene or triene with diethylaluminium chloride and $Ti(OPr^i)_4$, provides five- and six-membered carbocycles (by inter- then intra-molecular carboalumination).[235]

Hydroalumination of an alkyne (with $Bu^i_2AlH$) gives vinylalanes **179**, which have been found to undergo efficient coupling with benzyl chlorides under nickel(0) catalysis.[236] The vinylalanes **180** (formed by carboalumination with trimethylaluminium) were coupled with the benzyl chloride **181** to give precursors of coenzyme $Q_n$.[237] The method is general for the preparation of a variety of allylated aromatic compounds. Coupling of $\pi$-deficient heteroaromatic halides with trialkylaluminium reagents and palladium(0) catalysis provides a route to substituted quinazolines.[238]

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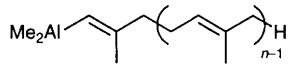


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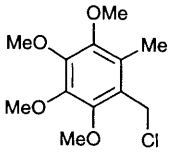


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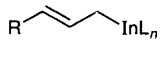


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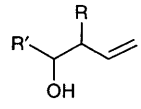
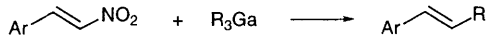



183

### 4.2 Gallium, indium and thallium

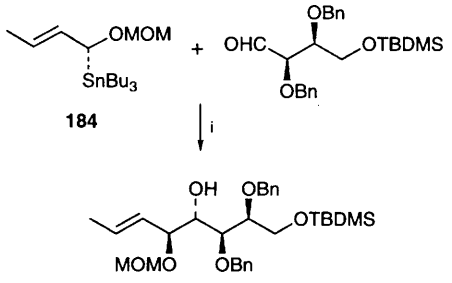
Rather than conjugate addition, the unexpected exchange of a nitro group for an alkyl group occurs on reaction of trialkylgallium reagents with 2-aryl-1-nitroalk-1-enes (**Scheme 32**).[239] The mechanism is thought to involve alkyl radical addition to the alkene.




**Scheme 32**

There has been a significant expansion of organoindium chemistry in the last few years.[240] This has concentrated on allylic indium reagents and, in particular, their reaction with carbonyl electrophiles.[241] A number of studies of the regio- and stereo-selectivity of the addition of allylic indium reagents **182** to aldehydes have been reported.[242] Except for very bulky R groups, the products **183** of $\gamma$-addition to R'CHO are obtained. Although this type of reaction can be carried out in organic solvents (for example, to give allylsilanes[243]), the ability to effect carbon–carbon bond formation in aqueous solution has attracted considerable interest. Addition of allylindium **182**, R = H, generated from allyl bromide and indium in water, to $\alpha$- or $\beta$-alkoxy carbonyl compounds occurs with high diastereoselectivity.[244] The intramolecular addition of an

allylic indium reagent to a ketone can lead to a two-carbon ring expansion reaction.[245] An alternative method for the generation of allylic indium reagents is to transmetallate allylstannanes with indium trichloride.[246] Marshall and Hinkle have reported the stereoselective synthesis of precursors to the hexoses, using transmetallation of the enantio-enriched stannane **184** with indium trichloride and reaction with threose and erythrose aldehydes (**Scheme 33**).[247] Alkynyl indium reagents can also be prepared from alkynylstannanes and indium trichloride.[248]

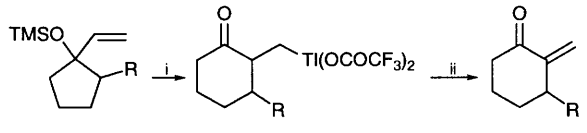



*Reagents*: i, $InCl_3$, EtOAc (89%)

**Scheme 33**

Examples of the reactions of *gem*-dihalo compounds with indium metal have been reported.[249] Allylic indium reagents have recently been found to add to allenols to give *E*-hepta-2,6-dien-1-ol and derivatives.[250]

The use of organothallium compounds in organic synthesis is rare, although thallium(III) salts are well-known to promote oxidative coupling reactions. An example of the formation of an organothallium species, using thallium(III) trifluoroacetate addition to an alkene and subsequent ring expansion, is shown in **Scheme 34**.[251] The intermediate organothallium **185** eliminates to give the α-exo-methylenecycloalkanone product after treatment with aqueous sodium hydrogen carbonate.




$R = C_9H_{19}$

*Reagents*: i, $Tl(OCOCF_3)_3$, MeCN, room temp.; ii, $NaHCO_3$ (aq) (84%)

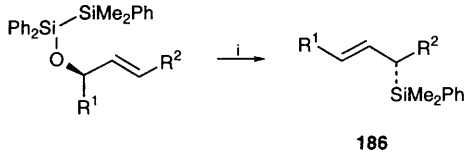
**Scheme 34**

## 5 Group 14

### 5.1 Silicon

#### 5.1.1 Allylsilanes

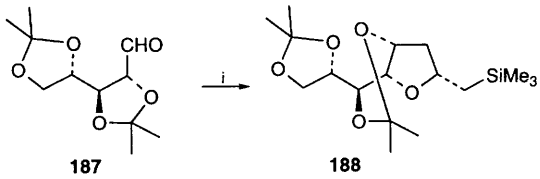
Allylsilanes are popular organosilicon reagents which allow regio- and stereo-selective allylations. As a result, various methods for the preparation of allylsilanes have been reported.[243,252] Highly enantiomerically enriched *E*-allylsilanes **186** can be prepared by a diastereoselective intramolecular bissilylation of chiral allylic alcohols (**Scheme 35**).[253] Excellent reviews have been published on the stereoselective reactions of chiral allylsilanes with C=X π-bonds[254] and on the use of allylsilanes (and other organosilanes) for natural product synthesis.[255]




*Reagents*: i, 2 mol% $Pd(acac)_2$, 8 mol% $Bu^tCH_2C(Me)_2NC$, PhMe; ii, BuLi or PhLi

**Scheme 35**

In the presence of a Lewis acid, an allylsilane reacts with an aldehyde or ketone in a γ-regioselective manner.[256] A theoretical study suggests that a pentacoordinated silicon species is involved in the transition state.[257] As little as 2 mol% scandium trifluoromethanesulfonate can catalyse the allylation.[258] Highly diastereoselective additions to aldehydes with but-2-enylsilanes[259] or pentadienylsilanes[260] have been reported. A synthesis of (−)-*trans*-kumausyne has been accomplished by Osumi and Sugimura using allyltrimethylsilane addition to aldehyde **187** (**Scheme 36**).[261] The major product from this reaction is tetrahydrofuran **188** (73%), rather than the homoallylic alcohol (12%).

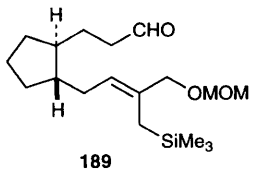



*Reagents*: i, 

, $CH_2Cl_2$, $BF_3{\bullet}OEt_2$

**Scheme 36**

Titanium tetrachloride catalysed addition of allylsilanes to α-chloroacylsilanes generates intermediate silyl enol ethers, which can be trapped with carbonyl electrophiles.[262] No Lewis acid is required for the addition of allyltrihalosilanes to carbonyl electrophiles.[263] Kuroda and Ito report examples of the intramolecular allylation of aldehydes, such as **189**.[264] The product cycloheptanols **190** are intermediates for the synthesis of the guaianolide sesquiterpenes. The danger of the presence of a reactive alkene within the molecule is illustrated in the attempted intramolecular addition to the aldehyde **191**.[265] Rather than direct allylsilane addition to the



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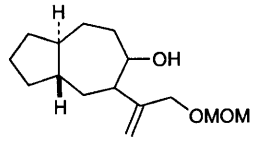

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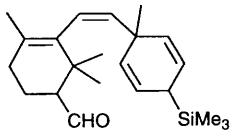

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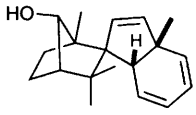
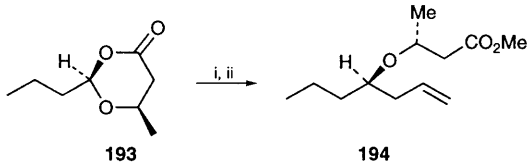


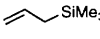
192

aldehyde, the tetrasubstituted alkene attacks the carbonyl group to generate a carbocation, which is trapped by the allylsilane to give the spirocycle **192**.

As an alternative to an aldehyde, an oxonium ion, generated from an acetal with a Lewis acid, can be used as the electrophile in an intra-[266] or intermolecular[267] allylation with an allylsilane. *C*-Glycosides have been prepared by addition of allyltrimethylsilane to glycals using montmorillonite K-10 catalysis.[268] Mixed *O,Se*-acetals can also act as electrophiles (with predominant C–Se cleavage).[269] High levels of asymmetric induction in the allylation of chiral acetals have been reported.[270] For example, the acetal **193** gives ether **194**, on addition of allyltrimethylsilane in the presence of $Pr^iOTiCl_3$ (followed by $CH_2N_2$), which was used in the synthesis of 18-hydroxyeicosatetraenoic acid (**Scheme 37**).[149b] The asymmetric allylation of butan-2-one using allyltrimethylsilane and the protected amino alcohol **195** has been reported to give selectivities up to 18:1.[271]

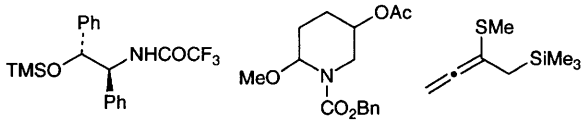


193 194

*Reagents*: i,  , $CH_2Cl_2$, $Pr^iOTiCl_3$; ii, $CH_2N_2$

**Scheme 37**

The addition of allyltrimethylsilane to an iminium ion has been used to prepare 3-substituted tetrahydroisoquinolines[272] and 2-allyl cyclic amines.[273] High *trans* selectivity was observed in the allylation of piperidine **196**, used for the synthesis of the alkaloid (+)-pseudoconhydrine.[273b] Cyclisation to give piperidines or pyrrolidines by intramolecular attack of an allylsilane onto an iminium ion is also possible.[274] It is worth noting in this section that the related allenylsilanes undergo an intramolecular imino ene reaction.[275] Heating the aldehyde allenylsilane **197** with 0.5 equiv. of 1,3-diaminopropane gives the tetracycle **198** (70%) as a single stereoisomer.[276] Further manipulations, including macrocyclisation gave the alkaloid (−)-papuamine. The



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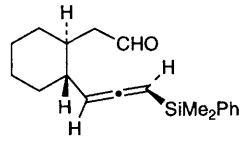

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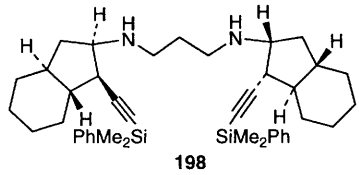

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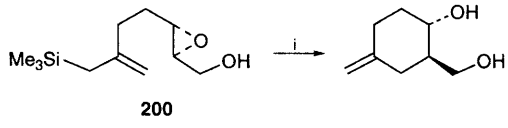


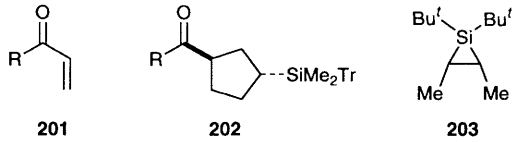
200

*Reagents*: i, $Et_2AlF$, $CH_2Cl_2$ (75%)

**Scheme 38**

allenylmethylsilane **199** also shows a preference for ene-type reaction.[277]

Cyclisation of an allylsilane onto an epoxide is a useful method for preparing hydroxylated carbocycles. The epoxy allylsilane **200** cyclises on treatment with diethylaluminium fluoride (**Scheme 38**).[278] Intramolecular conjugate addition of an allylsilane gives access to substituted carbocycles.[279] This strategy, using a prop-2-ynylsilane, has been used by Schinzer and Ringe for the synthesis of *β*-pinguisene and pinguisenol.[280] The addition of allyldimethyltritylsilane to electron-deficient alkenes **201** gives the products **202** of overall [3+2] cycloaddition.[281] Conversion of the silyl group to a hydroxy group can be accomplished by attack of a fluoride ion, followed by hydrogen peroxide. Tamao and co-workers have reported that an allylsilane (prepared by ring-opening of a vinyl epoxide) can be converted to an allylic alcohol using hydrogen peroxide.[282] The regioisomeric allylic alcohols can be prepared by epoxidation of an allylsilane, followed by ring-opening with acetic acid.[283] Ring-opening of a cyclopropylmethylsilane with protic or Lewis acids gives the product of overall methyl group addition to the allylsilane.[284] Dihydroxylation



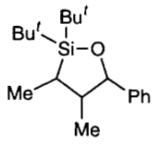
201 202 203

of allylsilanes has also been used in organic synthesis.[285]

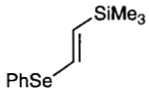
Finally in this section, the coupling of allylsilanes with allyl trimethylsilyl ethers using Lewis acids such as zinc chloride has been found to give 1,5-dienes.[286] A route to 1,4-dienes by addition of allylsilanes across phenylalkynes is possible in the presence of aluminium chloride.[287]

### 5.1.2 Other organosilanes

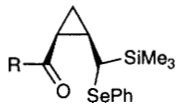
Reviews covering organosilicon-directed reactions illustrate the prominence of organosilanes in organic synthesis.[255,288] The ability to convert a silicon group stereospecifically to a hydroxy group is a very useful feature of this class of organometallic compounds.[289] Cleavage of the carbon–silicon bond of the oxasilacyclopentane **204** with *tert*-butyl hydroperoxide gives 1,3-diols.[290] The organosilane **204** can be prepared by reaction of benzaldehyde with silirane **203**, itself prepared from but-2-ene. Other cyclic alkylsilanes have been prepared from dihalides,[291] cycloaddition using a silene[292] or intramolecular ene reaction of a vinylsilane.[293] The intramolecular closure of a vinylsilane onto an oxonium[294] or iminium[274a] ion leads to six-membered heterocycles. The reaction of vinylsilane **205** with $\alpha,\beta$-unsaturated ketones **201** in the presence of a Lewis acid gives the overall [2 + 1]-cycloaddition products **206**.[295]




**204**




**205**




**206**

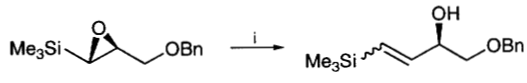
Vinylsilanes can be prepared by hydrosilylation of alkynes[296] and are useful intermediates in synthesis. Platinum-catalysed hydrosilylation of alkyne **207** occurs with high regioselectivity to give *E*-vinylsilane **208** (**Scheme 39**).[297] Coupling of vinylsilane **208** with an aryl iodide under palladium catalysis leads to the HMG-CoA reductase inhibitor NK-104. An isoquinolone intermediate for the synthesis of nitidine was prepared by palladium-catalysed coupling of an aryl iodide with a vinylsilane.[298] The conversion of vinylsilanes to vinylboronates, followed by cross-coupling reactions has been described.[299]


**207** **208**

*Reagents*: i, $ClMe_2SiH$, 0.5 mol% $Bu^t_3P{\bullet}Pt(CH_2{=}CHSiMe_2)_2O$

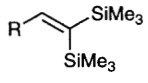
**Scheme 39**

Iterative one-carbon homologations of vinylsilanes can be achieved by epoxidation of the vinylsilane, followed by opening of the epoxide with the anion of phenylthio(trimethylsilyl)methane to give the new vinylsilane (**Scheme 40**).[300] Intramolecular attack by a hydroxy group onto an epoxysilane[301] or vinylsilane[302] leads to cyclic ethers. Epoxidation of the vinyldisilanes **209** followed by treatment with acid gives a novel route to acylsilanes **210**.[303] Conversely, acylsilanes have been used for the preparation of vinylsilanes[304] and 2-silylfurans.[305] An enantioselective synthesis of $\alpha$-silyl carbonyl compounds using (*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrolidine (SAMP/RAMP) hydrazones has been reported by Enders and co-workers.[306] The preparation of $\beta$-silyl aldehydes has been accomplished using a highly stereoselective intramolecular hydrosilylation of an alkene.[307] For example, in the presence of 0.1 mol% of a platinum catalyst, the alkene **211** is converted to the organosilane **212** (93%, >25 : 1). Hydrogenolysis of the benzyl group and Swern oxidation gives the $\beta$-silyl aldehyde.

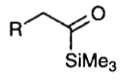



*Reagents*: i, $Me_3SiCH_2SPh$, BuLi

**Scheme 40**




**209**

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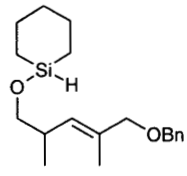
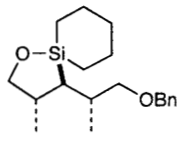
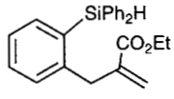


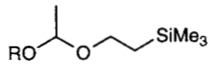

**211**




**212**




**213**

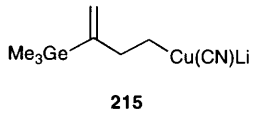



**214**

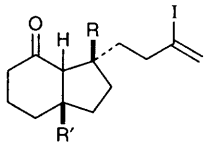
The hydrogen atom of the silyl hydride **213** acts as the internal carbon radical trap on intermolecular radical addition to the alkene unit of **213**.[308] Carbon radicals may be formed by homolytic carbon–silicon bond cleavage of $\alpha$-silyl carbamates using photoinduced electron transfer.[309] Intermolecular addition to electron-poor alkenes gives $\gamma$-amino carbonyl compounds. Heterolytic carbon–silicon bond cleavage has provided a route to azomethine ylides (and hence pyrrolidines on cycloaddition)[310] and to 2,2-difluoroalcohols.[311] A new protecting group for alcohols, the 1-[(2′-trimethylsilyl)ethoxy]ethyl (SEE) group gives the acetals **214** under mild acid conditions and can be cleaved by the neutral fluoride ion.[312]

## 5.2 Germanium

A vinylgermane can act as a masked vinyl iodide, its conversion to the iodide being possible using iodine. Piers and co-workers have used conjugate addition of cuprates, *e.g.* **215** (prepared from the corresponding iodide with *tert*-butyllithium, CuCN), followed by germanium–iodine exchange to prepare the substrates **216**, ready for palladium-catalysed cyclisation to tricyclic compounds.[313] More reactive in palladium-catalysed Stille-type couplings than organotributylgermanes is the organogermane **217**.[314] Successful couplings with *p*-tolyl bromide are reported using **217**, R = allyl, phenyl, vinyl or ethynyl. Reaction of bis[bis-(trimethylsilyl)aminato]-germanium(II) with 2-vinylpyridine gives the enamine **218** (95%).[315] Enamine **218** reacts with aldehydes to give the organogermanium compound **219**. Synthesis of an organogermanium compound by cycloaddition of a germene with butadiene has been reported.[316]




**215**

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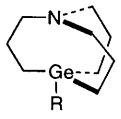
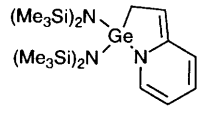
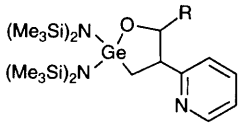



**217**




**218**

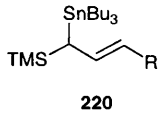



**219**

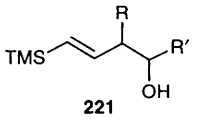
## 5.3 Tin

### 5.3.1 Allylstannanes

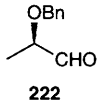
A direct, one-pot synthesis of allylstannanes from allylic alcohols[317] and an efficient synthesis of γ-alkoxyallylstannanes[318] have been published. The allylation of aldehydes is the most common use of allylstannanes[319] and Marshall and co-workers, in competitive experiments, have found that methyl- and unsubstituted allyl-stannanes are more reactive than their α- or γ-oxygenated derivatives.[320] The bimetallic α-silylated derivative **220** reacts with aldehydes (R′CHO) by cleavage of the carbon–tin bond, to give the vinylsilanes **221**.[321] The formation of allylstannanes from allyl halides and tin or tin(II) halides in the presence of an aldehyde (or imine) (Barbier type reaction) can avoid the isolation of the allylstannane.[241,322]




**220**

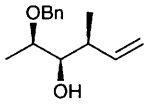



**221**

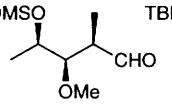



**222**

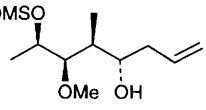
The addition of allylstannanes to chiral aldehydes[323] or oxonium ions[324] can occur with high diastereoselectivity. Keck and co-workers have used iterative allylstannylations of aldehydes **222**, **224** and **226** to give homoallylic alcohols **223**, **225** and **227** respectively, as part of a synthesis of the C-10 to C-26 fragment of rhizoxin.[325] Homoallylic alcohols can be prepared with high enantioselectivities using chiral ligand–Lewis acid complexes, such as BINOL–Zr(OPr$^i$)$_2$[326] and BINAP–AgOTf.[327] Chiral diamines promote asymmetric allylation of aldehydes with diallyltin dibromide in the absence of a Lewis acid.[328]




**223**




**224**

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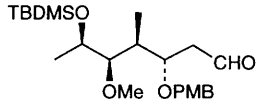
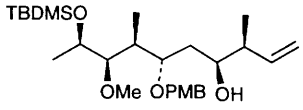


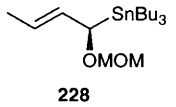

**226**




**227**

Chiral allylstannanes are popular reagents in organic synthesis. Methoxymethyl-protected α- and γ-hydroxy allylstannanes have been popularised by Marshall and co-workers.[246,247,329] Double addition of α-alkoxy allylstannane **228** to dialdehyde **229**, in the presence of indium trichloride, followed by functional group interconversions and cyclisations, gives the bistetrahydrofuran **230**, a core unit of the acetogenins.[246b] Boron trifluoride-catalysed allylation with γ-siloxy allylsilanes has provided a route to aminosugars destomic acid and lincosamine.[330] Reactions of the related chiral γ-*O*-carbamato allylsilanes with $TiCl_4$ and aldehydes have been reported by Hoppe and co-workers.[331] Maguire and Thomas have found high levels of 1,5-asymmetric induction in the reactions of allylstannanes **231** with tin(IV) chloride and aldehydes.[332] The product homoallylic alcohols can be converted to substituted dihydro- and tetrahydro-pyrans. Chiral dihydrofurans can be prepared by cyclisation of allenylmethanols, which are made by allenylstannane addition to $BuSnCl_3$ and aldehydes.[333] Addition of allenylstannanes to aldehydes with other Lewis acids tend to favour the but-3-ynyl alcohol products.[334]

Cyclisation of an allyl-, allenyl- or prop-2-ynyl-stannane onto an aldehyde has been investigated by

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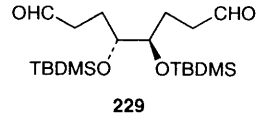


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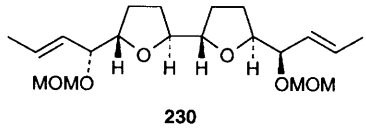
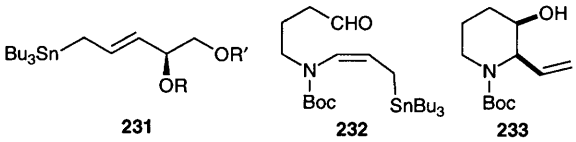



**230**

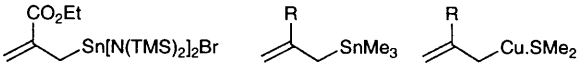
Yamamoto and co-workers, for the synthesis of cyclic amines[335] and cyclic ethers.[336] For example, thermal cyclisation of the γ-aminoallylstannane **232** gave the piperidine *cis*-**233** with very high stereoselectivity, whereas Lewis acid promoted cyclisation normally gave *trans*-**233** as the major product.[335] The synthesis of cyclic ethers by cyclisation of γ-alkoxyallylstannanes onto hydrazones has been reported.[337]




**231** **232** **233**

The addition of allylstannanes to imines can be promoted with $TiCl_4$,[338] TMSCl,[339] lanthanide trifluoromethanesulfonates[340] or palladium(II) (even in the presence of aldehydes).[341] Addition of tin(IV) chloride to the allylstannane, followed by the imine, gives complementary regioselectivity of the allyl group and can promote excellent asymmetric induction.[342] Addition of allylstannanes to cyclic iminium ions is an efficient method for preparing 2-allyl cyclic amines.[343]

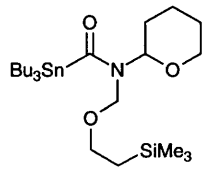
Allylstannanes have been found to add to α-diazo carbonyl compounds by a radical process to give γ,δ-unsaturated carbonyls after hydrolytic work-up.[344] Allyl radical transfer to an alkyl halide using the monoallylstannane **234** avoids triorganotin-containing by-products.[345] Selective transmetallation of the allylstannanes **235**, R = $GeMe_3$ or $SnMe_3$ with methyllithium, followed by copper(I) bromide gives the allylcuprates **236**, used for conjugate addition.[313b]




**234** **235** **236**

### 5.3.2 Other organostannanes

α-Alkoxy organostannanes are useful intermediates in organic synthesis and can be prepared stereoselectively from α-stannyl substituted acetals.[346] Recent applications of α-alkoxy organostannanes have been found in the synthesis of *C*-glycosides[347] and *O*-alkylated sugars.[348] Ring-opening of stannyl-substituted sugars (β-elimination upon treatment with $ZnCl_2$) to unsaturated aldehydes has been reported.[349] Transmetallation of the acylstannane **237** with butyllithium and addition of ester **238** gave the 1,2-dicarbonyl **239**, a model for the mycalamides and pederins.[350] Transmetallation of the 2-azaallyl-stannane **240** and intramolecular cycloaddition of the resulting 2-azaallyl anion provides a route to the amaryllidaceae alkaloids (−)-amabiline and (−)-augustamine.[351] A single tin–lithium exchange of the bis-stannane **241** with butyllithium, followed by reaction with a carbonyl electrophile then methanesulfonyl chloride, gives alkene products.[352]

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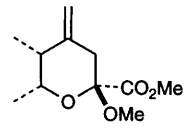
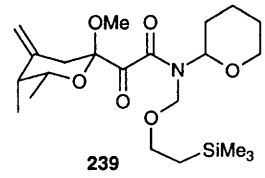
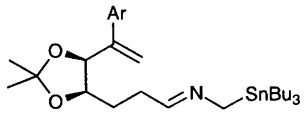


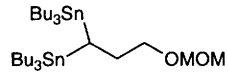

**238**




**239**

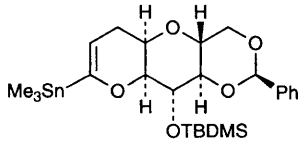



**240**

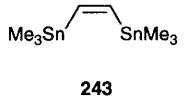



**241**

Aryl- and vinyl-stannanes are important substrates for cross-coupling reactions. Arylstannanes can be prepared from aryl bromides[353] and vinylstannanes are normally made by addition of a tin compound across an alkyne.[354] Novel vinylstannanes can be prepared by Claisen rearrangement of stannyl-substituted allyl vinyl ethers.[355] Although palladium-catalysed couplings of aryl- and vinyl-stannanes with organohalides are particularly prevalent,[356] copper-mediated couplings are also possible.[357] Copper(I) chloride promotes the inter- and intra-molecular coupling of two vinylstannanes.[358] Coupling reactions with iodanes[359] and vinyl trifluoromethanesulfonates[360] have been reported. Intermolecular couplings pertinent to this review include the reaction of vinylstannanes such as **242** with vinyl trifluoromethanesulfonates to construct polyether




**242**

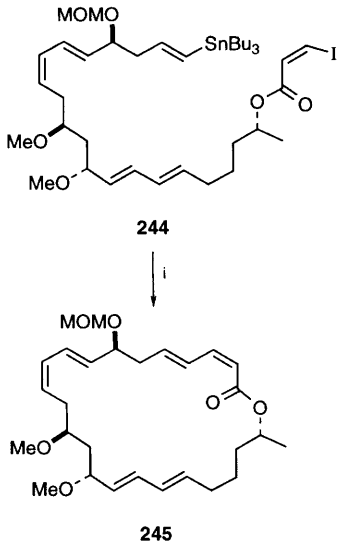



**243**

frameworks.[361] Both inter- and intra-molecular couplings of alkynyl iodides with the bis-stannane **243** have been used for the synthesis of calicheamicinone.[362] Intramolecular coupling with a vinylstannane is an efficient method for macrocyclisation[363] and has been exploited for the synthesis of papuamine[276,364] and the virginiamycin 14,15-anhydropristinamycin $II_B$.[365] Intramolecular coupling of the vinylstannane **244** using palladium catalysis gives **245**, the *O*-protected aglycone of macrolactin A (**Scheme 41**).[366]

## 5.4 Lead

Aryllead compounds, $ArPb(OAc)_3$, have been found to be useful in coupling reactions with β-keto




*Reagents*: i, $Pd^0$, $Ph_3As$, DMF, 50 °C

**Scheme 41**

esters[367] to give 2′-hydroxyisoflavones[368] and in the arylation of benzopyran-2-ones to give the 3-arylpyranocoumarins robustin and robustic acid.[369] The *N*-arylation of azoles with *p*-tolyllead triacetate in the presence of copper(II) acetate has been reported.[370]

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