Synthetic applications of carbolithiation transformations

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Carbolithiation reactions are exceptionally versatile transformations which have been utilised in a remarkably diverse and creative manner. In this review we outline the background and scope of these reactions and then focus on their use in organic synthesis with a particular emphasis on literature examples published since 2000.

Introduction

The addition of alkyl, vinyl and aryllithiums to unactivated alkenes and alkynes is termed carbolithiation and can be viewed as a subset of the broader family of carbometalation reactions.[1] The value of these transformations lies in their ability to regio- and stereoselectively construct carbon–carbon bonds in tandem with generating a new organolithium species. Intermolecular carbolithiation of alkenes and alkynes provides access to acyclic lithiated products whereas the corresponding intramolecular reactions directly give cyclised organolithiums (Scheme 1). In both cases subsequent structural elaboration by electrophile reaction offers an efficient means of expanding their synthetic utility. In this feature article we wish to provide an introduction to the historical background of carbolithiation, including an overview of chemo-, regio- and stereochemical aspects of the reaction. Specific synthetic applications are described, which illustrate a flavour of the recent advances in this field, predominantly related to the preparation of carbocyclic and heterocyclic ring systems.

Background

A potential impediment to the application of carbolithiation reactions for synthetic methods can arise as a consequence of the reactivity of the generated organolithium towards the unsaturated starting substrate. If the generated organolithium reacts with a second molecule of the alkene an anionic polymerisation can propagate. In fact, carbolithiation has its origins in anionic polymerisation.[2] Ziegler *et al.* showed that addition of the alkyllithiums, EtLi, *i*-PrLi and BuLi, to the double bond of styrene **1** allowed the generation of a benzylic lithium species **2** which could in turn add to a second molecule of styrene and thus initiate a polymerisation process.[3] This anionic polymerisation reaction has been extensively investigated with high molecular weight polymers **3** obtained following initiation with BuLi, in conjunction with the tertiary diamine additive *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (Scheme 2). Numerous industrial applications of this living polymerisation process have been developed utilising many olefinic substrates including ethene and butadiene.[2]

The challenge for successfully exploiting intermolecular carbolithiations in non-polymer applications is dependent upon suppressing the anionic polymerisation to produce a solution of the carbolithiated monomer. Thus reaction conditions are required that will facilitate the initial carbolithiation but not favour further addition by the generated organolithium. This was first accomplished by Bartlett *et al.* for the simplest unactivated C–C double bond ethene.[4] The reaction was discovered serendipitously during the preparation of *i*-PrLi and *t*-BuLi in diethyl ether. Side products identified as addition products of *i*-PrLi and *t*-BuLi to ethene, which was formed by decomposition of the diethyl ether solvent, were

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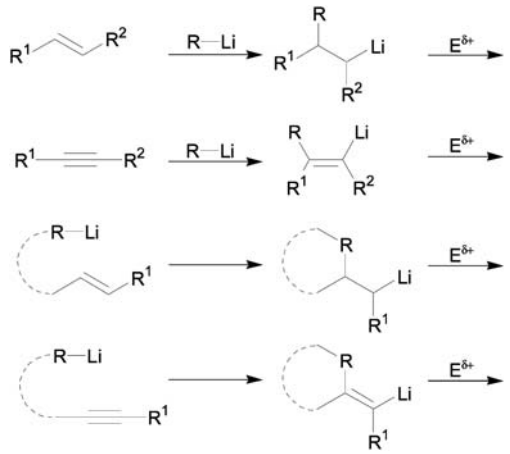
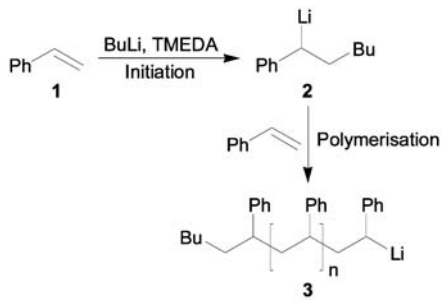


Scheme 1 Inter- and intra-molecular carbolithiations.

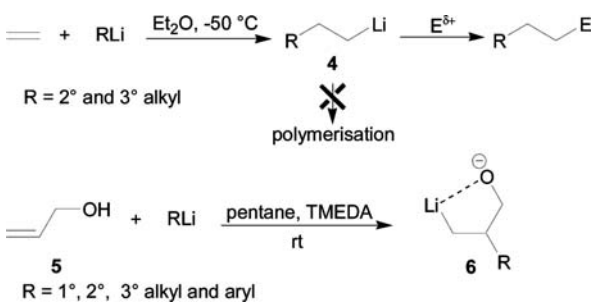


Scheme 2 BuLi initiated living polymerisation of styrene.

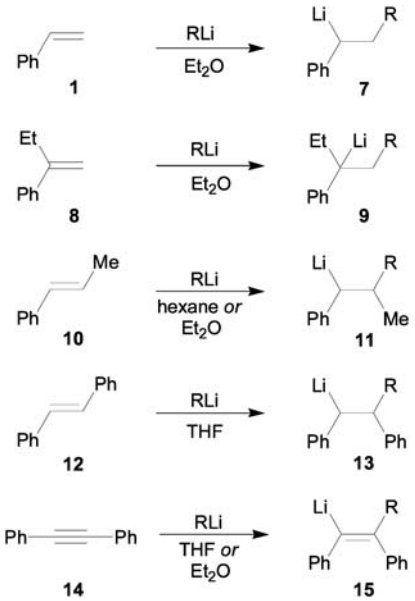
also obtained. This observation prompted further investigation and it was shown that controlled addition of secondary and tertiary alkyllithium reagents (including *s*-BuLi and *c*-HexLi) to ethene could be achieved (Scheme 3). Since the secondary and tertiary alkyllithiums are more reactive than the primary organolithium species **4** generated in the reaction polymerisation is avoided.

A computational study on the transition state structure for intermolecular addition of MeLi to ethene proposed an initial lithium–π-bond interaction as an important component of an overall *syn* addition to the double bond.[5] Carbolithiation of allyl alcohol **5** results in regiospecific alkyllithium addition to generate the primary lithium alkoxides **6**.[6] In this case primary alkyllithium reagents are tolerated as a result of the stabilising intramolecular carbanion/alkoxide coordination.

Further examples of the carbolithition of unsaturated hydrocarbons are numerous. It has been demonstrated that in



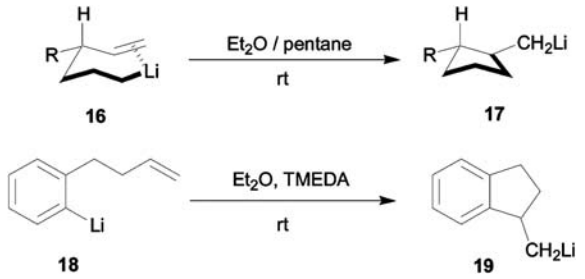
Scheme 3 Carbolithiation of ethene and allyl alcohol.



Scheme 4 Representative examples of intermolecular carbolithiations.

the case of styrene, by employing diethyl ether as the reaction solvent and maintaining a low temperature, polymerisation can be avoided and the generated benzylic lithiated species **7** utilised for further non-polymeric transformations (Scheme 4).[7] As is often the case in organolithium chemistry solvent choice is critical as reactions performed in THF resulted in rapid polymerisation at −78 °C, implying inadequate stabilisation of the benzylic lithiated monomer. Yet in diethyl ether, styrene was shown to undergo efficient carbolithiation from −78 to −25 °C, with organolithium reactivity found to be tertiary > secondary > primary > methyl, phenyl. In this case the scope of the reaction can be extended to include primary alkyllithiums as the benzylic lithium species generated is less reactive than the primary alkyllithium reagent. Similarly, the carbolithiation of various α-alkyl-substituted styrenes, such as 1-ethylvinylbenzene (**8**), have been reported to proceed effectively at −55 °C in diethyl ether to yield carbolithiated products **9** (Scheme 4).[8] The carbolithiation products **11** and **13**, which arise from alkyllithium addition (R = Bu) to (*E*)-β-methylstyrene[9] and (*E*)-stilbene,[10] respectively, have been reported but in moderate yields, which could be attributed to the non-optimised reaction conditions used (Scheme 4). Importantly, additions to styrenes, α- and β-substituted styrenes are regiospecific with the alkyl or aryl group adding exclusively to the double bond such that the more stabilised benzylic lithiated compound is formed. Carbolithiation of the triple bond of diphenylacetylene proceeds *via* a *syn* alkyllithium addition, generating the alkyl substituted lithio-(*Z*)-stilbenes **15** (Scheme 4).[11] Depending upon the nature of the alkyllithium and the reaction solvent a subsequent isomerisation to the more thermodynamically favourable *trans* diphenyl product may be observed.

Intramolecular carbolithiations are typified by the cyclisation of 1-hex-5-enyllithium **16** to generate cyclopentylmethyllithium **17** (R = H).[12] The 5-*exo-trig* cyclisation is regiospecific, favouring the formation of a five-membered ring and primary



Scheme 5 Intramolecular carbolithaition of 1-hex-5-enyllithiums and 1-but-3-enyl-2-lithiobenzene.

organolithium species (Scheme 5). This transformation offers a facile high yielding approach to cyclopentylmethyl containing products. Extensive studies by Bailey *et al*. on the rate of cyclisation of **16** and the stereochemistry of the cyclised products **17** have established that the cyclisation occurs *via* an anionic rather than radical mechanism.[13] The high stereo and total regioselectivity observed in these isomerisations is attributed to an energetically favourable coordination of the lithium to the double bond. As such the formation of a rigid chair-like transition state, with substituents preferentially occupying a pseudo-equatorial position, provides rationale for the stereoisomers obtained.

Comprehensive studies of the cyclisation of secondary and tertiary alkyllithiums to form 1,2-disubstituted cyclopentanes stereoselectively have also been reported.[14] Additionally, lithio-indane **19** is effectively produced by the isomerisation of *o*-substituted aryllithium **18** in diethyl ether/TMEDA at room temperature.[15]

The natural product (−)-sparteine **20** is strongly associated with enantioselective organolithium chemistry (Fig. 1).[16] The alkaloid is readily available and can be isolated in significant quantities from several species of papilionaceous plants.[17] Solid-state studies have shown BuLi/(−)-sparteine complexes exist as a symmetrical dimeric structure whereas secondary and tertiary alkyllithiums are unsymmetrical dimers and monomers.[18] While (−)-sparteine is not the only chiral ligand to be employed in enantioselective carbolithiation transformations it remains the most widely used.

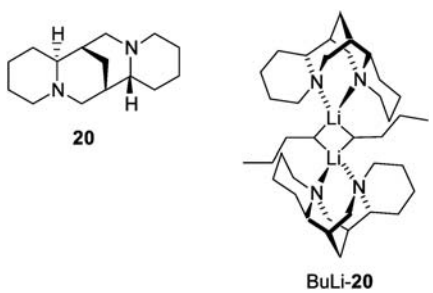
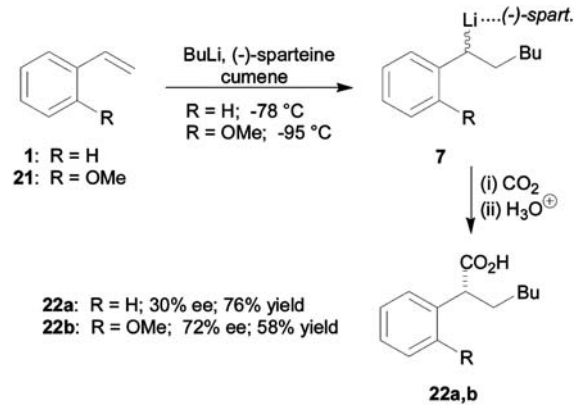


Fig. 1 (−)-Sparteine.

Intermolecular carbolithiations

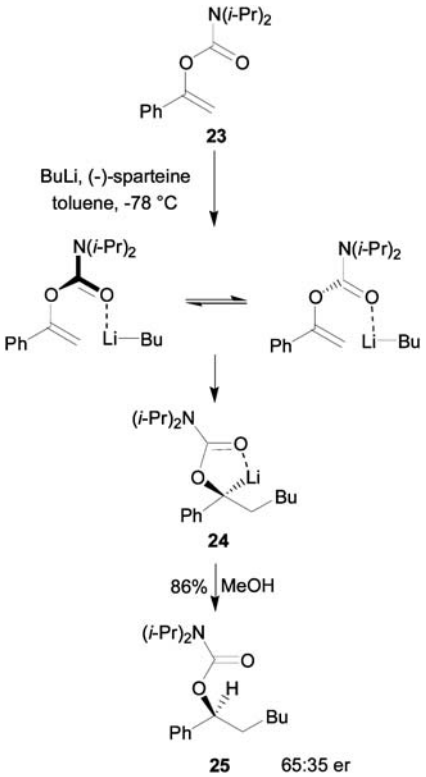
Since carbolithiation enables the generation of both a new C–C bond and C–Li centre in a single transformation the opportunity exists, depending on the substrate employed, for control of stereoselectivity at one or both positions.



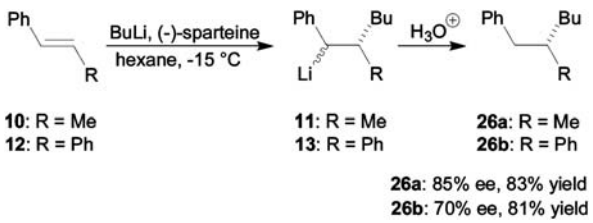
Scheme 6 Styrene carbolithiation/enantioselective electrophile substitution reactions.

The intermolecular addition to alkenes provides examples of the control of each of these stereocentres both independently and simultaneously. Carbolithiation of styrene **1** generates a new configurationally unstable benzyllithium **7**. By exploiting kinetic or thermodynamic resolutions this offers a potential route to enantioenriched products after electrophilic reaction (Scheme 6). These resolution approaches have been extensively studied for benzylic lithium species generated by deprotonation rather than carbolithiation, yet similar principles apply.[19] For example, following carbolithiation of styrene **1** with BuLi in cumene with 2 equivalents of (−)-sparteine at −78 °C and trapping with CO_2, 2-phenylheptanoic acid **22a** was obtained in 30% ee.[20] The screening of several 2-hetero-substituted styrenes, which offer an additional auxiliary binding site, identified *o*-methoxy derivative **21b** as providing the highest selectivity of 72% ee after reaction in cumene at −95 °C and treatment with CO_2 as electrophile (Scheme 6).[20] An alternative approach utilised the configurationally stable lithiated benzylcarbamates **24** generated by the enantioselective carbolithiation of 1-phenylpropenyl-*N*,*N*-diisopropylamine **23** (Scheme 7).[21] The representative example shown employed a (−)-sparteine mediated carbolithiation of **23** with BuLi in toluene at low temperature. After a methanol quench moderate enantiofacial discrimination was revealed in the product **25**.

The carbolithiation of 1,2-disubstituted alkenes generates an organolithium intermediate with two contiguous stereocentres. For example, the enantioselective carbolithiation of (*E*)-β-methylstyrene **10** and (*E*)-stilbene **12** with alkyllithiums has been reported utilising (−)-sparteine to induce asymmetry in the products.[22] In these examples, the chiral centre created as a result of the C–C bond formation is configurationally stable but the benzylic C–Li centre has low configurational stability. Following protonation of the lithiated intermediates **11** and **13**, 2-methylhexylbenzene **26a** and 1,2-biphenylhexane **26b** respectively were isolated in good yield and enantiomeric excess (Scheme 8). The reaction of **10** was successful with a range of primary and secondary alkyllithiums with selectivities ranging from 76–85% ee depending on the alkyllithium employed. Attempts to achieve diastereoselectivity in the reaction sequence gave disappointing results as treatment of **11** with methanol-d_4 yielded the deuterated product with 60 : 40 dr.[22b]

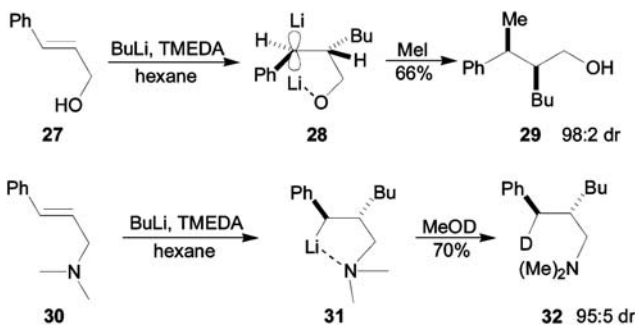


Scheme 7 Enantioselective carbolithiation of 1-phenylpropenyl-*N*,*N*-diisopropylamine.



Scheme 8 Enantioselective carbolithiation of (*E*)-β-methylstyrene and (*E*)-stilbene.

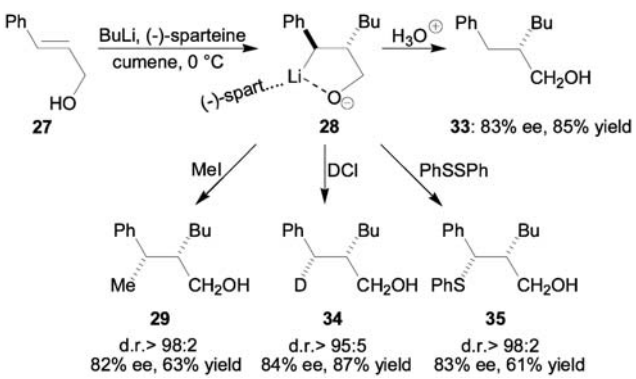
The carbolithiation of (*E*)-cinnamyl alcohol **27** and amine **30** illustrates how stereocontrol over both centres can be accomplished (Scheme 9). The reaction was initially investigated for the addition of BuLi in diethyl ether in the presence of the achiral additive TMEDA. Remarkably, it has been shown that subsequent electrophilic substitution gave the products with excellent levels of diastereoselectivity.[23]



Scheme 9 Diastereoselective electrophile substitution.

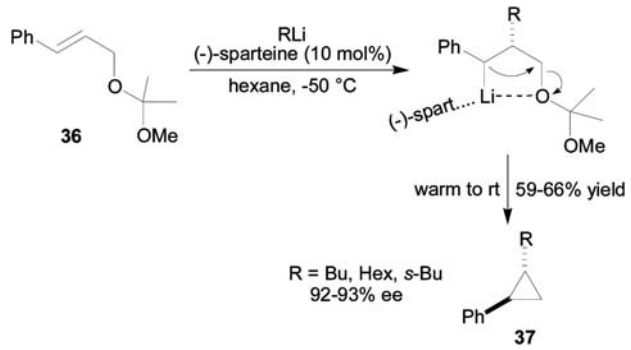
To rationalise the *syn*-selectivity of **29**, obtained by treatment of **28** with MeI, the formation of a five-membered cyclic benzyllithium species **28** having a sp^2-like carbon to which two lithium atoms coordinate from both upper and lower sites was proposed. Thus, reaction with the electrophile proceeds selectively from the upper site to afford **29**. The related example of (*E*)-cinnamyl amine **30** provided similar diastereoselectivity for numerous electrophiles with the selectivity attributed to a heteroatom lock of intermediate **31** by nitrogen–lithium coordination.[22b,24] In all cases the selectivity is attained without the addition of any chiral additive and is independent of both the reaction solvent (THF and hexane give the same selectivity) and the stereochemistry of the alkene substrate as both (*E*) and (*Z*) alkenes yield the same product.

The seminal work of Normant, Marek *et al.* led to the development of enantioselective carbolithiations of β-substituted styrenes by replacing TMEDA with the chiral diamine (−)-sparteine.[22b,25] As a representative example, the enantioselective carbolithiation of cinnamyl alcohol **27** with BuLi and subsequent hydrolysis of the lithiated intermediate **28** allowed the preparation of 2-benzylhexan-1-ol **33** in good yield and 83% ee. This reaction sequence was tolerant of several alkyllithiums with selectivities ranging from 72–87% ee depending upon alkyllithium employed. (−)-Sparteine, which was initially employed in stoichiometric quantities, had the most pronounced effect in non-donor hydrocarbon solvents such as hexane and cumene whereas use of diethyl ether or THF resulted in lower selectivities or racemic products. Expansion to electrophiles such as MeI, DCl and PhSSPh facilitated the formation of two chiral centres in a one-pot diastereospecific and enantioselective manner to provide the acyclic systems **29**, **34** and **35**, respectively (Scheme 10).[22b] A further attraction of this methodology is that employing the alkene of opposing stereochemistry (*e.g.* (*Z*)-cinnamyl alcohol) allows access to the opposite enantiomer of **33** from the same (−)-sparteine chiral source.[22b]



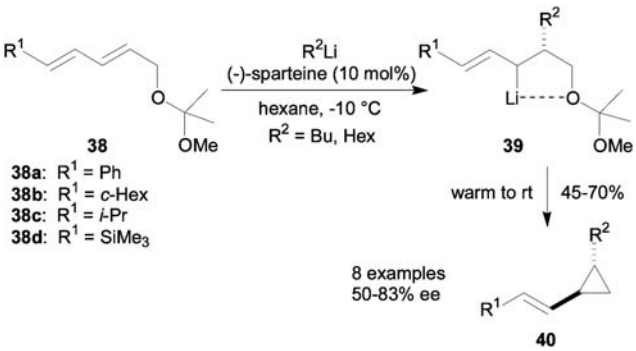
Scheme 10 Enantioselective carbolithiation with diastereoselective electrophile substitution.

Conversion of the allyl alcohol **27** to its corresponding acetal **36** allowed for an elegant approach to chiral cyclopropanes (Scheme 11).[26] Carbolithiation of **36** in the presence of catalytic (−)-sparteine at −50 °C followed by warming to room temperature resulted in cyclopropanation to **37** by a 1,3-elimination of the acetal group from the lithiated intermediate.



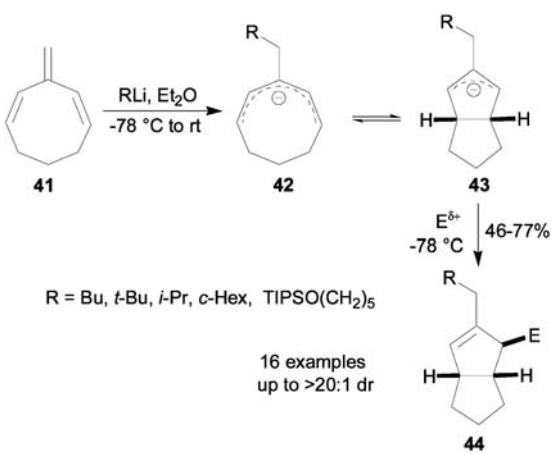
Scheme 11 Stereoselective synthesis of cyclopropanes.

This method has also been applied to carbolithiation of acetal protected dienols **38**.[27] Addition of BuLi or HexLi to **38a–d** in the presence of catalytic (−)-sparteine generated the allylic organolithium derivatives **39** which upon raising the temperature led to intramolecular nucleophilic substitution and formation of vinylcyclopropanes **40** in isolated yields of 45–70% and 50–83% ee (Scheme 12).[27a]



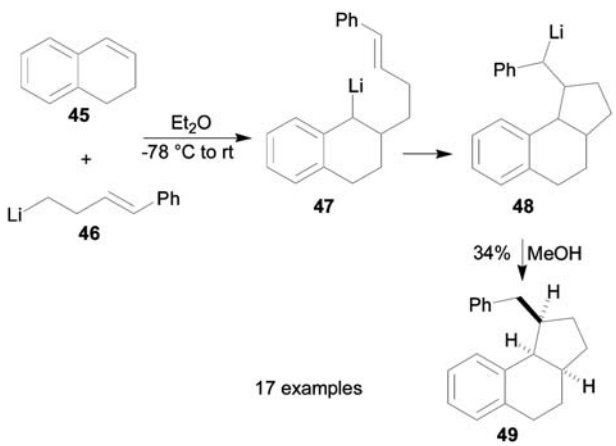
Scheme 12 Stereoselective synthesis of vinylcyclopropanes.

The carbolithiation transformation has also been employed in the synthesis of *cis*-bicyclo[3.3.0]octenes from the readily available 3-methylene-1,4-cyclooctadiene **41** (Scheme 13).[28] The reaction sequence, which facilitates the formation of three new C–C bonds and three stereogenic centres in a single synthetic operation, was initiated by intermolecular carbolithiation of the exocyclic double bond of the triene **41** to generate the cyclooctadienyl anion **42**. Subsequent six-electron disrotatory ring closure to the *cis*-bicyclo[3.3.0]octenyl anion **43** and electrophilic capture provided the functionalised *cis*-bicyclo[3.3.0]octenes **44**.



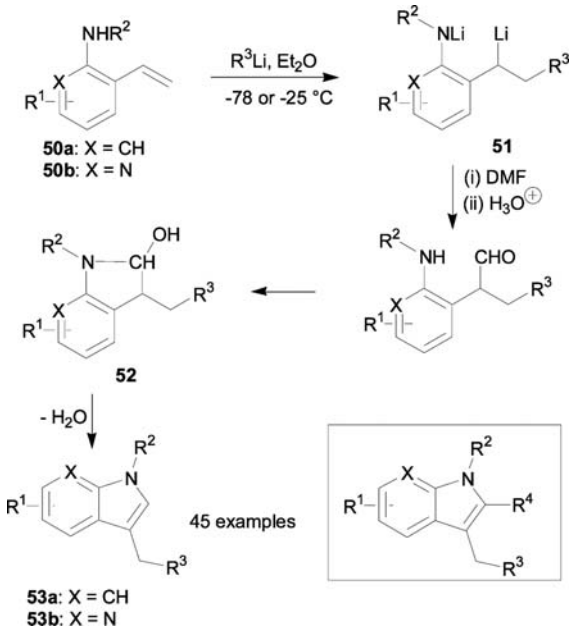
Scheme 13 Synthesis of *cis*-bicyclo[3.3.0]octenes.

A tandem intermolecular-intramolecular carbolithiation sequence was exploited for the preparation of tetralins, cyclopentanes and related carbocycles (Scheme 14).[29] This approach centres on a dual function organolithium containing an alkene or alkyne functional group. Following intermolecular carbolithiation the newly formed lithiated intermediate *in situ* performs an intramolecular carbolithiation at the unsaturated C–C bond. A representative example applied to the synthesis of tricyclic hydrocarbon **49** is outlined in Scheme 14. Carbolithiation of 1,2-dihydronaphthalene **45** with the lithiated β-alkylstyrene **46** generated the lithiated tetralin **47** which underwent an *in situ* intramolecular carbolithiation to form the benzyllithiated tricycle **48**. Protonation resulted in isolation of 1-benzylhexahydro-1*H*-cyclopenta[*a*]naphthalene **49** in 34% yield.[29b] A related method has been developed for the synthesis of silacyclopentanes.[30]



Scheme 14 Synthesis of substituted cyclopenta[*a*]naphthalenes.

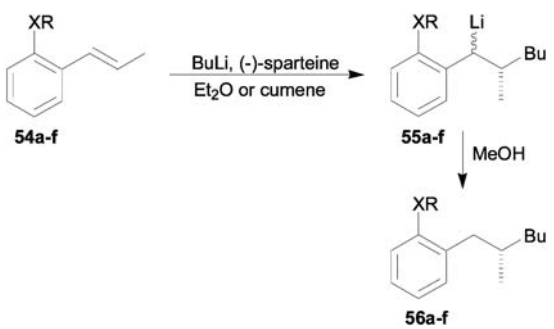
Contributions from our laboratory have shown the advantage of using intermolecular carbolithiations of *o*-substituted styrenes and stilbenes for the synthesis of achiral and chiral heterocycles. This methodology was first developed for carbolithiation of *o*-amino substituted styrenes **50a**, as a one-pot indole synthesis and later expanded to the preparation of 7-azaindoles from 3-vinylpyridin-2-ylamines **50b** (Scheme 15).[31] The reaction sequence involved initial NH deprotonation of **50**, followed by addition of alkyllithium to the vinyl double bond providing the key intermediate dianions **51**. Reaction of DMF with the carbanion generated an aldehyde precursor, which upon acidification underwent ring closure by intramolecular nucleophilic addition of the *o*-nitrogen to the aldehyde forming 2-hydroxy(aza)indoles **52**. *In situ* dehydration of **52** completed the reaction sequence and provided the indoles **53a**[31c,d] and azaindoles **53b**.[31a,b] This method allows for incorporation of substituents at all positions of the (aza)indole ring with functionality at C-2 introduced by using alternative electrophiles such as nitriles (R^4CN) (Scheme 15, inset).



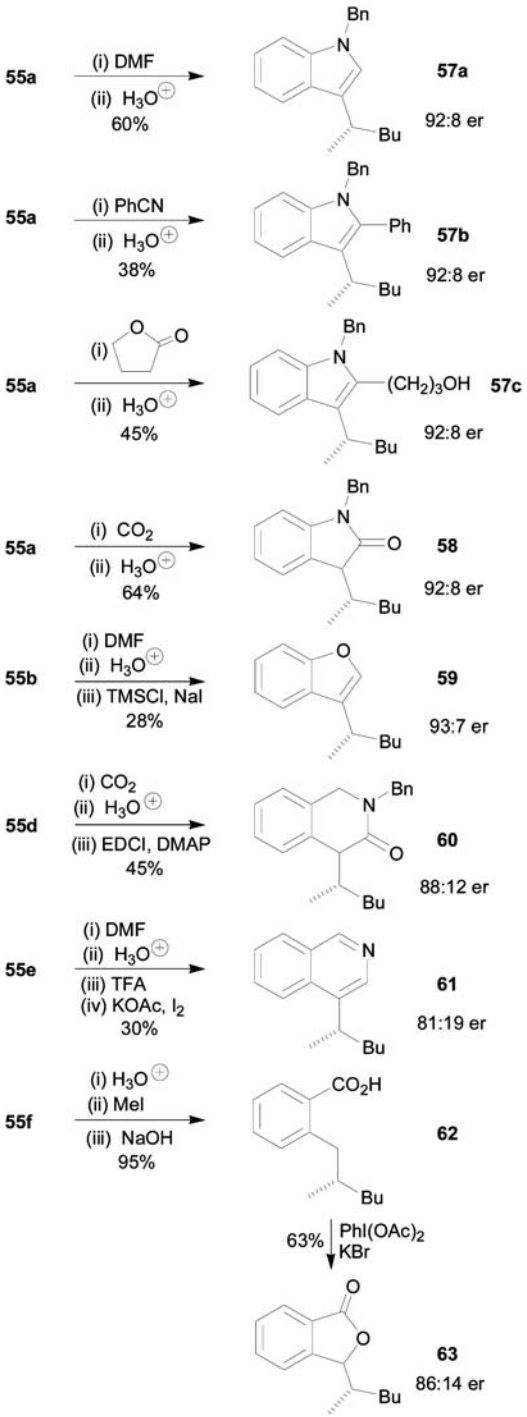
Scheme 15 Synthesis of indoles and 7-azaindoles.

Extending this approach to chiral heterocycles we have shown that the (−)-sparteine mediated enantioselective carbolithiation of a series of *o*-substituted β-methylstyrenes **54a–f** can be achieved with good enantiomeric ratios (ers) (Table 1).[32] The best selectivities were obtained for the *o*-aniline **54a** and anisole **54b** derivatives which gave ers of 92 : 8 and 93 : 7 respectively, as judged by analysis of the products **56a,b** obtained following the treatment of **55a,b** with MeOH (Table 1, entries 1, 2). The synthetic potential of the lithiated intermediates **55a–f** was demonstrated by their conversion to a diverse set of chiral heterocycles (Scheme 16). Derivatives

Table 1 Enantioselective carbolithiation of *o*-substituted β-methylstyrenes



Entry	54	XR	*T*/°C	56	Yield (%)	er
1	**a**	NHBn	−15	**a**	89	92 : 8
2	**b**	OMe	−40	**b**	60	93 : 7
3	**c**	OCH_2OMe	−40	**c**	42	89 : 11
4	**d**	CH_2NHBn	−15	**d**	75	88 : 12
5	**e**	CH_2NHBoc	−15	**e**	46	81 : 19
6	**f**		−78	**f**	79	86 : 14



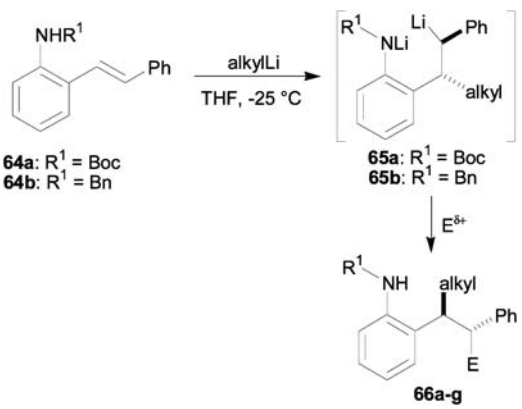
Scheme 16 Synthesis of chiral heterocycles.

containing *o*-amino, ether, methylamino and oxazoline substituents provided stereoselective routes to indoles, indolones, benzofurans, isoquinolines, isoquinolinones and isobenzofuranones. For example, *o*-amino carbolithiated intermediate **55a** was converted to substituted indoles **57a–c** and indolone **58** by reaction with the electrophiles DMF, PhCN, γ-butyrolactone and CO_2 respectively. As the chiral centre, generated during the C–C bond formation in the first carbolithiation step, is carried through the electrophile reaction sequence to the final products, selectivity at this stereocentre is solely dependent

upon achieving an enantioselective alkyllithium addition. In addition, this approach was shown to be tolerant of various alkyllithiums and both electron donating and withdrawing substituents in the aryl ring.[32a,b] The concept was generalised to numerous heterocyclic systems as follows.[32c] Formylation of the *o*-methoxy analogue **55b** with DMF, followed by methoxy demethylation (with chlorotrimethylsilane and sodium iodide), cyclisation and dehydration generated benzofuran **59**. Treatment of *N*-benzyl lithiated intermediate **55d** with CO_2 introduced a carboxylic acid functional group, which following intramolecular amide coupling with 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI) generated the C-3 substituted isoquinolinone **60**. Reaction of **55e** with DMF resulted, following acidification, in the formation of a dihydroisoquinoline which after Boc deprotection with trifluoroacetic acid (TFA) and oxidation with KOAc/iodine gave the aromatic isoquinoline **61** in a 30% overall yield. Protonation and deprotection of the *o*-oxazoline derivative **55f** provided the chiral benzoic acid **62** which underwent direct γ-lactone formation by treatment with $PhI(OAc)_2$/KBr to yield the isobenzofuranone **63**. In each case the reaction sequences were shown to be tolerant of alternative alkyllithiums.[32c] The value of this approach to the synthesis of chiral heterocycles lies in the wide-ranging possibilities for the use of the carbolithiated intermediates **55a–f** by reaction with different electrophiles.

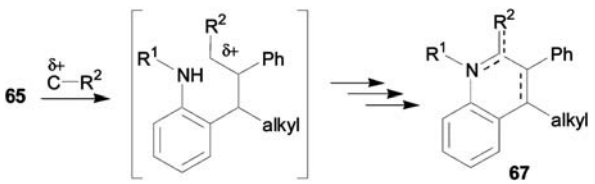
As demonstrated above, carbolithiation of styrenes and β-alkylstyrenes is regiospecific with the more stabilised benzylic lithiated regioisomer generated exclusively in each case. In contrast, the addition to unsymmetrical stilbenes such as **64** poses a considerable regioselectivity challenge with the possibility of forming two benzylic lithiated regioisomers (Table 2). An investigation of the specific case of *o*-amino substituted stilbenes **64a,b** revealed that a single regioisomer was generated if the reaction was performed in THF. The selectivity was shown to be solvent dependent as when the less coordinating diethyl ether or cumene were employed mixtures of regioisomers were obtained.[33] Moreover, high levels of diastereoselectivity were achieved following reaction of the lithiated intermediates **65** with electrophiles such as MeOD, CO_2 and Bu_3SnCl (Table 2).

Table 2 Regioselective carbolithiation with diastereoselective electrophile substitution



Entry	R	Alkyl	E	**66**	Yield (%)	dr
1	Boc	Et	D	**a**	75	95 : 5
2	Boc	Bu	D	**b**	61	95 : 5
3	Boc	*t*-Bu	D	**c**	85	95 : 5
4	Boc	*t*-Bu	CO_2H	**d**	78	95 : 5
5	Boc	*t*-Bu	$SnBu_3$	**e**	34	95 : 5
6	Bn	*t*-Bu	D	**f**	70	95 : 5
7	Bn	*t*-Bu	CO_2H	**g**	64	60 : 40

The diastereoselectivity was influenced by both the *o*-amino substituent and the alkyllithium utilised for carbolithiation with *N*-Boc substituent and *t*-BuLi proving optimal. In the case of intermediate **65a** (R^1 = Boc, alkyl = *t*-Bu), obtained from the reaction of **64a** with *t*-BuLi, ^1H and ^{13}C NMR analysis revealed predominantly one diastereoisomer at room temperature. The proposed explanation for the diastereoselectivity was the formation of a six-membered ring by coordination of the benzylic lithium with the *N*-Boc group (similar to that observed *via* five-membered ring formation for cinnamyl alcohol as shown in Scheme 9).[33a] The atypical lithiation pattern obtained in these reactions, which placed the benzylic lithium centre at the position β to the *o*-substituted aryl ring, provided a new access to the fused six-membered quinoline ring system **67** following electrophile reaction (Scheme 17).



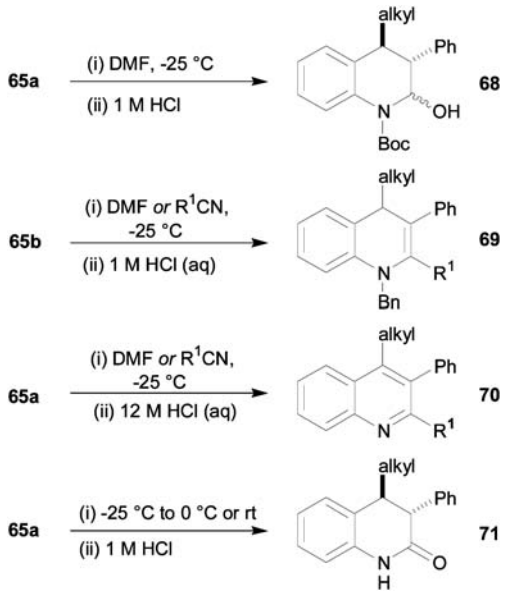
Scheme 17 Carbolithiation/electrophile reaction sequence.

Representative examples of this route involved reaction of the lithiated intermediates **65a** or **65b** with DMF, following which an intramolecular cyclisation yielded the substituted 1,2,3,4-tetrahydroquinolines **68** and 1,4-dihydroquinolines **69** (with *in situ* dehydration), respectively (Scheme 18).[33] More forcing acidic conditions lead directly to aromatised quinolines **70** in a one-pot reaction. Notably, the quinolin-2-ones **71** could be generated from **65a** without the need of an electrophile as intramolecular nucleophilic substitution of the benzylic lithium centre of **65a** at the Boc group was readily achieved by raising the reaction temperature to 0 °C.

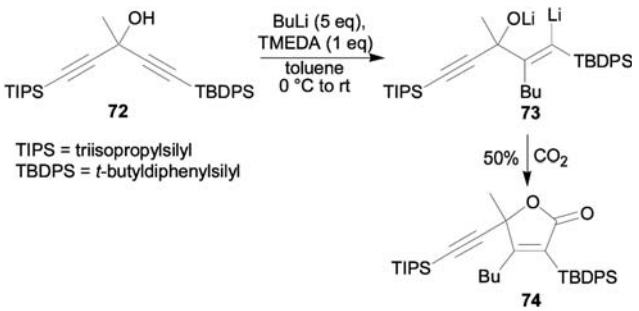
The carbolithiation regioselectivity of other unsymmetrical stilbenes with alkyllithiums and lithiated dithianes has been investigated though their application to ring synthesis has yet to be reported.[34]

Regioselectivity is also a key issue in the carbolithiation of the unsymmetrical dialkyne **72** (Scheme 19).[35] Addition of BuLi to **72** occured with excellent regioselectively at the TBDPS alkyne which acted as an activating group for the alkynyl moiety. The activating ability of the TBDPS group is attributed to a stereoelectronic effect of the phenyl group on silicon which increases the electrophilicity of the β-carbon atom of the alkyne due to hyperconjugation of the phenyl and alkyne π orbitals through the Si–C σ* bond. Treatment of vinyllithium species **73** with CO_2 and intramolecular cyclisation afforded furan-2-one **74** in 50% yield (Scheme 19).[35]

The inclusion of $Fe(acac)_3$ catalyst has been shown to promote the regio- and stereoselective intermolecular



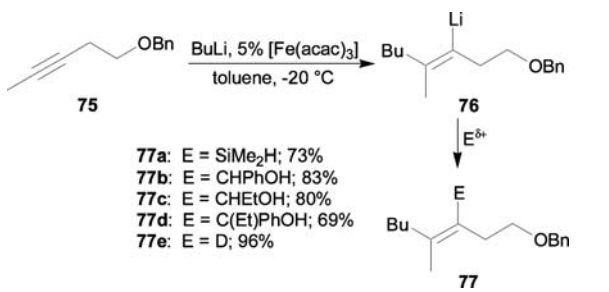
Scheme 18 Synthesis of the quinoline ring system (19 examples).



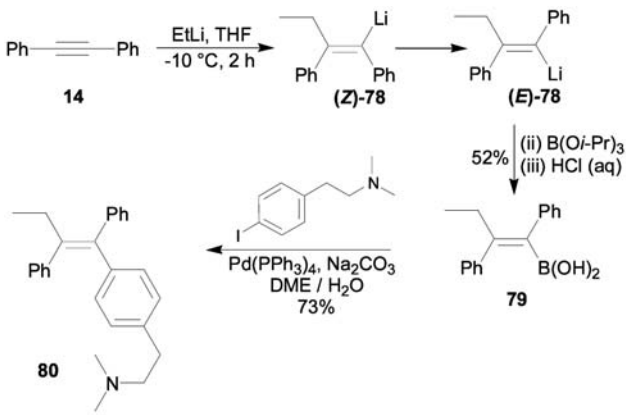
Scheme 19 Carbolithiation route to furan-2-ones.

carbolithiation of unsymmetrical alkynes bearing alkoxy and amino groups.[36] Tetrasubstituted alkenes have been prepared as single stereoisomers by addition of BuLi to **75** in the presence of 5 mol% $Fe(acac)_3$ (Scheme 20). The presence of the catalyst does not effect the ability of the vinyllithium intermediate **76** to undergo reaction with various electrophiles ($ClSiMe_2H$, PhCHO, EtCHO, PhCOEt), stereoselectively providing **77a–d**. In particular, treatment of **76** with DCl–D_2O led to isolation of **77e** in 96% yield with 94% incorporation of D.[36]

A report from our group employed an intermolecular carbolithiation as the key synthetic step in a concise and highly stereoselective synthesis of (*Z*)-tamoxifen **80**, the most commonly utilised therapeutic agent for the treatment of estrogen-dependent breast cancer.[37] Starting from diphenylacetylene **14**, *syn* addition of EtLi yields the vinylic lithium species **(*Z*)-78** which rapidly isomerises to the more thermodynamically favoured **(*E*)-78** under the strongly coordinating solvent conditions. Subsequent reaction of this intermediate with triisopropylborate yields the (*E*)-vinyl boronic acid **79**. (*Z*)-Tamoxifen was generated by Suzuki–Miyaura cross-coupling of **79** with the aryl iodide in 38% overall yield (Scheme 21).



Scheme 20 Stereoselective synthesis of tetrasubstituted alkenes.



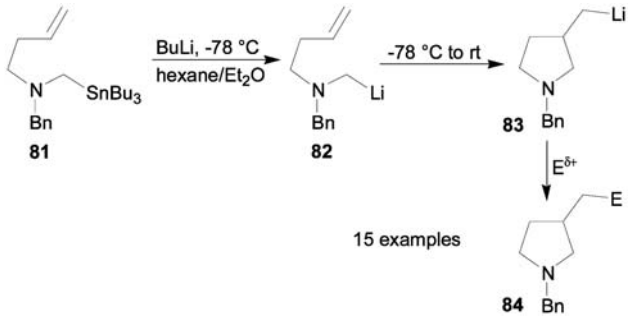
Scheme 21 Stereoselective synthesis of (*Z*)-tamoxifen.

Intramolecular carbolithiations

A primary consideration for intramolecular carbolithiations is the requirement to generate the organolithium in the presence of the electrophilic alkene or alkyne. Numerous approaches exist to achieve this including deprotonation, halogen–lithium exchange, tin–lithium exchange, selenium–lithium exchange[14g] and reductive lithiation of alkyl chlorides[14c] or phenyl thioethers.[14b] Advantages of this intramolecular anionic methodology over analogous radical cyclisations include the ease of introduction of further functionality by electrophilic reaction on the cyclised organolithium and often better stereoselectivity (attributable to the rigid structure of the transition state for anionic cyclisation).

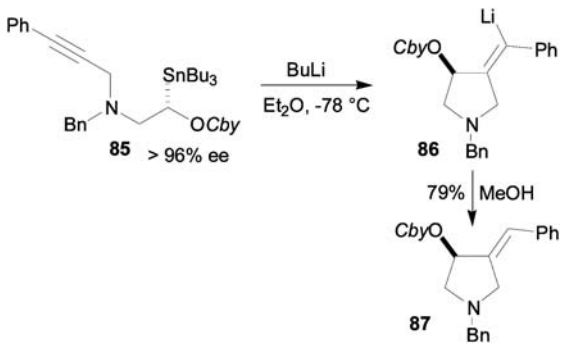
Related to the intramolecular carbolithiation of 1-hex-5-enyllithium (Scheme 5) is the development of intramolecular cyclisation for pyrrolidine synthesis which has been successfully achieved from aminoalkylstannane **81** (Scheme 22).[38] Tin–lithium exchange with BuLi was used to generate the lithiated species **82** which rapidly cyclised to organolithium **83** which was in turn trapped with a range of electrophiles. Enantioselective cyclisation of **82** in the presence of 2 molar equivalents of (−)-sparteine gave, after protonation of the intermediate lithiated species, benzyl-3-methylpyrrolidine in 84% yield and 28% ee.[38a] A related reaction sequence has been utilised for the preparation of 3-alkenylpyrrolidines[39] and furans.[40]

The use of carbolithiation methodology for enantioselective synthesis of 3-benzylidenepyrrolidine **87** was achieved by tin–lithium exchange of enantiomerically enriched stannane **85** followed by 5-*exo*-*dig* intramolecular carbolithiation to



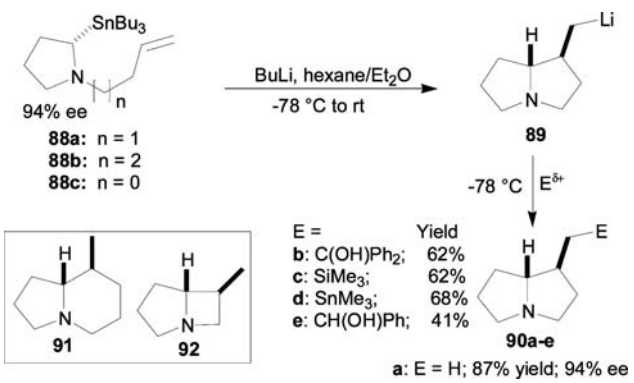
Scheme 22 Pyrrolidine synthesis.

generate chiral lithiated species **86** (Scheme 23).[41] Protonation with methanol yielded **87** as a single diastereoisomer with the (*S*) absolute configuration of the chiral centre carried through the cyclisation from the stannane precursor. The asymmetric synthesis of 2-alkenyl-1-cyclopentanols from 5-alkenyl carbamates by this route has also been reported.[42]



Scheme 23 Enantioselective pyrrolidine synthesis.

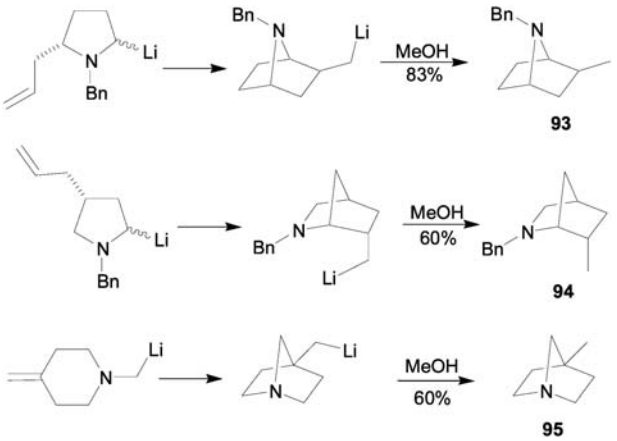
The expansion of this synthetic theme to bicyclic hetero and carbocyclic systems has also been accomplished. The enantiomerically enriched α-aminoorganolithium species, generated by tin–lithium exchange of stannane **88a**, has been shown to undergo cyclisation to form the bicyclic hexahydropyrrolizine with complete retention of configuration at the carbanion centre. Thus a short synthesis of (+)-pseudoheliotridane **90a** (94% ee) was achieved (Scheme 24). Furthermore, functionalisation by treatment of the lithiated bicycle **89** with electrophiles allowed access to derivatives of the alkaloid **90b–e**. 1-Methylindolizidine **91** and azabicyclo[3.2.0]heptane **92** were



Scheme 24 Enantioselective synthesis of azabicycles.

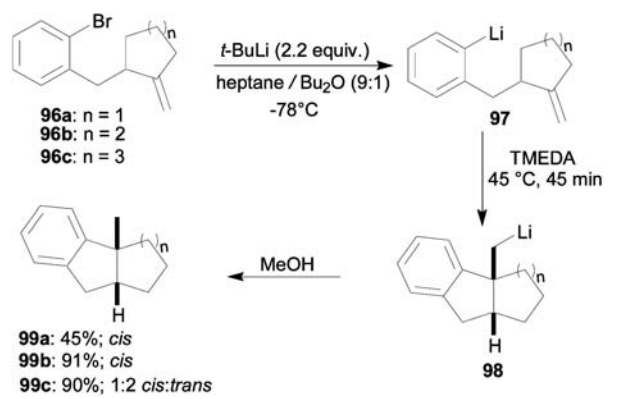
both accessible by this route (albeit with lower selectivity) utilising substrates **88b,c** where $n = 2$ and 0, respectively (Scheme 24, inset).[43]

Complementary routes to three nitrogen-positional isomers of the azabicycloheptanes **93–95** have been reported with anionic cyclisation generating the bicyclic ring. In each case an α-aminoorganolithium species, formed by tin-lithium exchange, was employed as the carbolithiation substrate. (Scheme 25).[44] Additional functionality could be incorporated into the final products by treatment with electrophiles.



Scheme 25 Synthesis of azabicycloheptanes.

The intramolecular carbolithiaton approach to the synthesis of indanes (Scheme 5) offers the framework for expansion of these methods to more complex carbocycles and heterocycles. The enantioselective synthesis of 1-methylindan by this route has been achieved in 42% ee using (−)-sparteine as the chiral ligand.[45] Cyclisation of aryllithium tethered methylenecycloalkanes **97a–c** (formed by bromine–lithium exchange of **96a–c**) facilitated the synthesis of carbotricyclic structures **99a–c** (Scheme 26).[46] The rigid transition state geometry for ring closure with resulting conformational constraints of the substituents enabled formation of stereoisomerically pure *cis*-fused products when the methylenecycloalkane is five- or six-membered (**99a,b**). However, due to the greater flexibility, cyclisation of the larger seven-membered substrate **99c** is less stereoselective and a 1 : 2 mixture of *cis* : *trans* isomers was isolated after protonation with methanol. The stereoselective



Scheme 26 Stereoselective preparation of *cis*-hexahydrofluorenes.

preparation of a range of 4a-substituted *cis*-hexahydrofluorenes has been demonstrated by treatment of **98b** with alternative electrophiles.[46]

The regiospecific intramolecular carbolithiation of 2-lithio-*N*,*N*-diallylanilines was reported simultaneously by Liebeskind and Bailey as a route to 3-substituted indolines.[47] Following these reports several enantioselective variants of this methodology were developed (Table 3). Bromine–lithium exchange with *t*-BuLi (−78 °C, pentane/diethyl ether) generated the aryllithium **100a** which, at elevated temperatures, underwent a facile intramolecular cyclisation to the lithiated indoline ring **101a**. Affecting the cyclisation at −40 °C with 2.1 equivalents of (−)-sparteine gave the indoline **102a**, following protonation with methanol, in 69% yield and 93 : 7 er (Table 3, entry 1).[45] Interestingly, replacement of one of the *N*-allyl groups with a methyl group results in isolation of (−)-1,3-dimethylindoline **102b** with a poorer er of 85 : 15 (entry 2).[45] An investigation of the 2-(*N*-allyl-*N*-benzyl)aryllithium derivative **100c** as the starting substrate showed optimal er of 94 : 6 in toluene (entry 3).[48a] Carbolithiation of the diallyl substrate **100a** was used as the model reaction for screening a range of chiral diamine, aminoether and ether ligands. Although (−)-sparteine was shown to be the best ligand for the reaction, (1*S*,2*S*)-*N*,*O*-(+)-dimethylpseudoephedrine **103**, which is also readily available as the (1*R*,2*R*) enantiomer, showed efficiency for the reaction approaching that of (−)-sparteine (entry 4) (see inset).[48b] Employing the mono-alkylated, *N*-allyl-*N*-lithio-2-lithioaniline **100d** as the starting substrate the reaction proceeds effectively in diethyl ether with achiral TMEDA as additive. Surprisingly no cyclisation was observed when (−)-sparteine was employed as additive but use of the more conformationally flexible ligand **103** successfully affected the ring closure to the dilithiated indoline ring **101d**. Sequential addition of ethanol which protonated the carbanion and allyl bromide which alkylated at nitrogen allowed isolation of the 1,3-disubstituted indoline **102a** with an er of 84 : 16 (Table 3, entry 5).[48c] In each case the synthetic scope of these methods was extended by reaction of lithiated intermediates **101** with numerous different electrophiles.

Related methods (without the use of chiral additives) have been applied to a series of (*N*,*N*-diallylamino)bromopyridines and 1-allyloxy-2-bromobenzenes providing general routes to racemic 4-, 5-, 6- and 7-azaindolines **104a–d**[49] and dihydrobenzofurans **105**,[14c,50] respectively (Fig. 2). A (−)-sparteine controlled enantioselective route to the dihydrobenzofurans **106** has been reported with selectivities up to 87% ee (9 examples) (Fig. 2).[51] It was shown that a competitive *in situ* rearrangement to *o*-cyclopropyl phenols could be suppressed by the inclusion of the R^1 substituent in the starting substrates.[52]

The intramolecular aryllithium addition to lithiated double

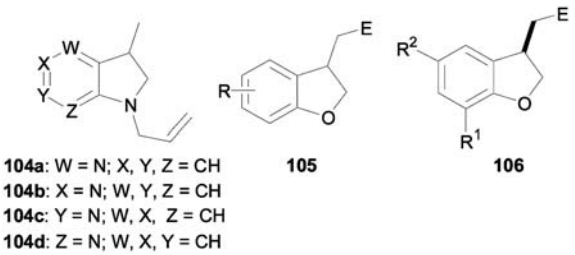
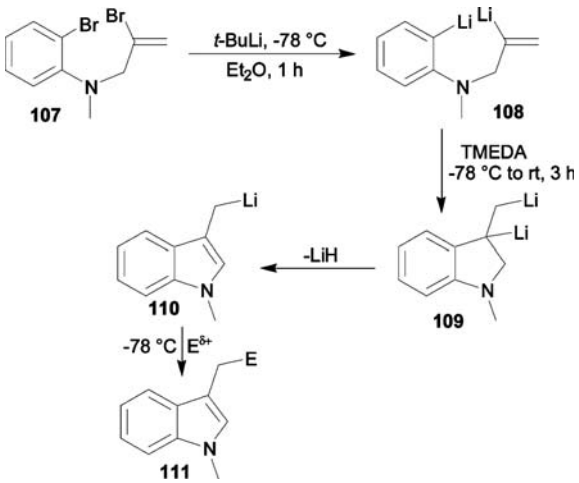


Fig. 2 Azaindolines and dihydrobenzofurans.

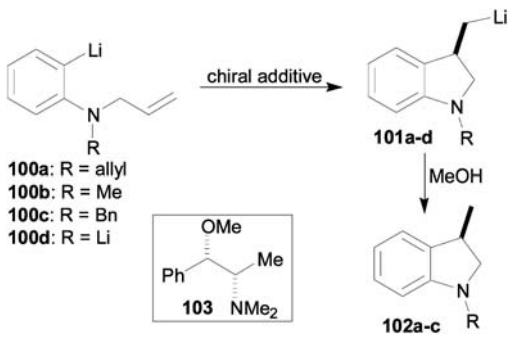
bonds has been applied to indole synthesis (Scheme 27). Double halogen–lithium exchange of **107** with *t*-BuLi generated the dilithio species **108** which following treatment with TMEDA and warming to room temperature cyclised to **109**. Subsequent elimination of lithium hydride afforded 3-lithioindole **110**, which was readily derivatised by treatment with electrophiles.[53]



Scheme 27 Carbolithiation of lithiated double bonds.

2,6-Dilithio-1,6-heptadiene **112a** and bis-(2-lithioallyl)-amines **112b–d** were formed by a double bromine–lithium exchange from their halogenated precursors. Upon the addition of TMEDA, cycloisomerisation to **113** occurred by

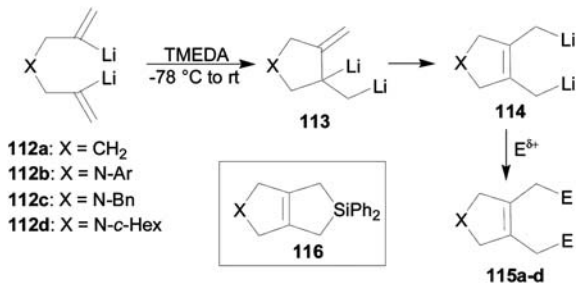
Table 3 Enantioselective indoline synthesis



Entry	100	Additive	102	R	Yield (%)	er
1	**a**	(−)-Sparteine	**a**	Allyl	69	93 : 7
2	**b**	(−)-Sparteine	**b**	Me	88	85 : 15
3	**c**	(−)-Sparteine	**c**	Bn	85	94 : 6
4	**a**	**103**	**a**	Allyl	87	90 : 10
5	**d**	**103**	**a**	Allyl	62	84 : 16[a]

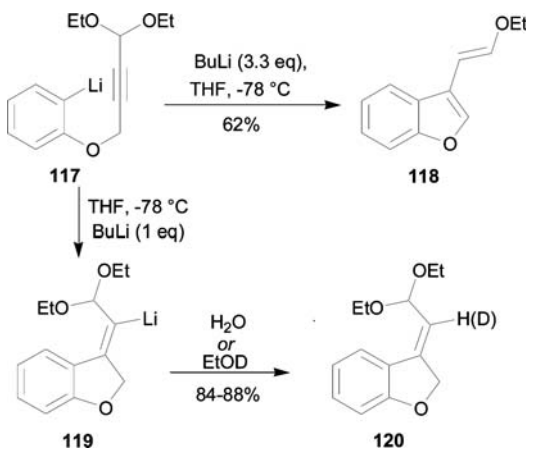
[a] Converted to *N*-allyl derivative by *in situ* reaction of **101d** with (i) EtOH and (ii) $BrCH_2CH{=}CH_2$.

carbolithiation of one vinyllithium moiety with the other (Scheme 28).[54] Subsequent allylic rearrangement gave the dianions **114** which could be trapped with electrophiles to yield 1,2-disubstituted cyclopentenes and dihydropyrroles **115a–d**. A further versatile use of the dilithiated compounds **114** was shown by their reaction with bis-electrophiles such as dichlorodiphenylsilane (Ph_2SiCl_2) which gave the bicyclic silicon containing heterocycles **116** in high yields (Scheme 28, inset).[55]



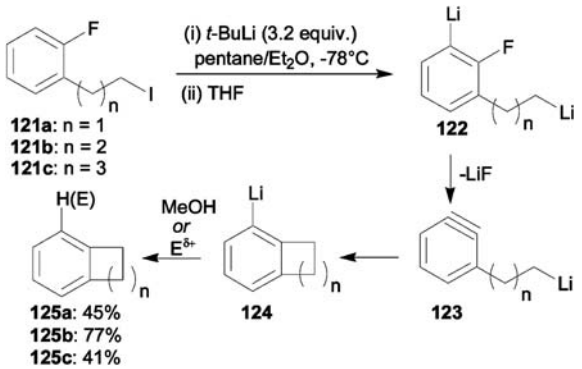
Scheme 28 Vinyllithium addition to vinyllithiums.

The intramolecular aryllithium addition to the alkyne in **117** initiated a cascade route to vinyl substituted benzofurans (Scheme 29).[56] The reaction sequence involved the generation of vinyllithium intermediate **119** which eliminates lithium ethoxide forming an allene which following rearrangement gave the 3-vinylbenzofuran product, **118**. This reaction sequence has also been applied to the synthesis of vinylindoles and furo[3,2-*b*]pyridines. An investigation of the mechanism of the addition–elimination reaction of **117** revealed that while greater than stoichiometric quantities of BuLi were required for formation of benzofuran **118**, a single equivalent of BuLi resulted in the isolation of 3-(2,2-diethoxyethylidene)-2,3-dihydrobenzofuran **120** in good yield, exclusively as the (*E*)-isomer (Scheme 29).[57] A DFT computational study indicated that intramolecular coordination between the lithium cation and one of the oxygens of the acetal moiety of **117** during the carbolithiation step, resulted in an overall *anti* addition to the alkyne and formation of the alkene as the (*E*)-isomer.[57]



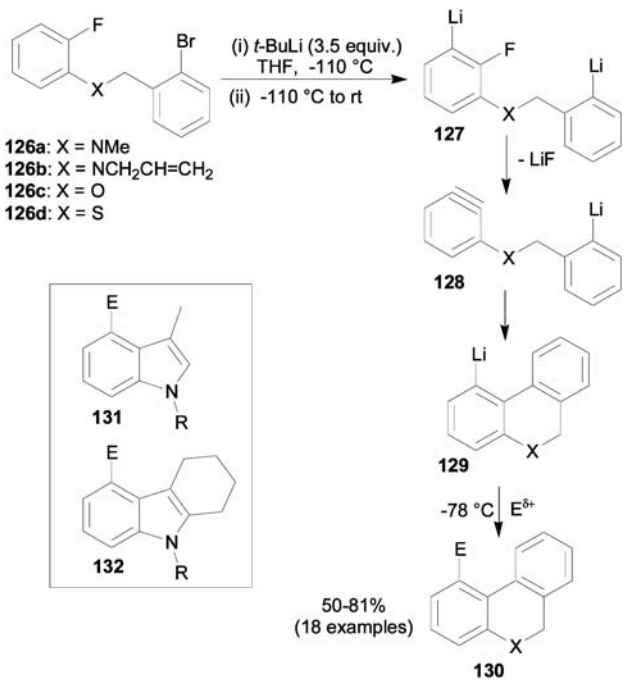
Scheme 29 Dihydrobenzofuran synthesis.

Carbolithiation methodology has even been extended to addition across benzynes with procedures developed for the synthesis of substituted benzocyclobutenes, indanes and tetralins (Scheme 30).[58] The steps involved in the reaction sequence are iodine–lithium exchange of **121**, *o*-lithiation of the resulting 2-(fluorophenyl)alkyllithiums generating **122** with subsequent loss of LiF from **122** producing the benzyne intermediate **123**. Cyclisation by addition of the alkyllithium to the benzyne gave the aryllithiated intermediates **124** which could be protonated to form hydrocarbons **125a–c** or further substituted by reaction with electrophiles (14 examples).



Scheme 30 Benzyne carbolithiation.

In applications of this synthetic approach to heterocycles, the cyclisation of benzyne-tethered aryllithiums **128** have been successfully exploited for the generation of the lithiated six-membered benzo-fused *N*-, *O*- and *S*-heterocycles **129** which could be further reacted with electrophiles forming **130** (Scheme 31)[59] Related cyclisations have been utilised for the synthesis of C-4 substituted indoles **131** and tetrahydrocarbazoles **132**.[59]



Scheme 31 Benzyne carbolithiation.

Conclusions

The imaginative uses of carbolithiation chemistry continue to provide fascinating new approaches to challenging synthetic issues. The subtle control of chemo-, regio- and stereoselectivity achievable within this class of transformation points the way towards more exciting future applications in carbocyclic, heterocyclic, alkene and alkane synthesis. Direct methods to diverse structural architectures, often in one-pot procedures from simple precursors, is the hallmark of this transformation.

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