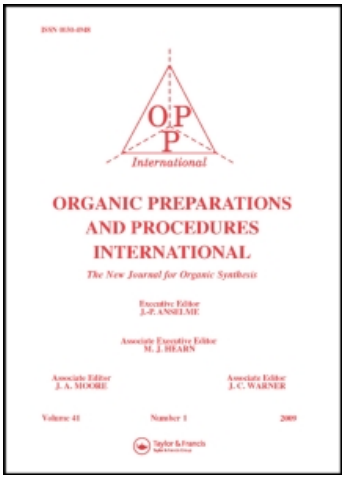

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TANDEM REACTIONS INVOLVING ORGANOLITHIUM REAGENTS. A REVIEW

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INTRODUCTION

Tandem reactions constitute one of the most powerful synthetic strategies developed for building complex molecular structures from rather simple ones in a minimum number of operations. They combine several transformations of the same molecule and often incorporate added components, without the need to isolate the intermediates. Apart from being highly efficient and economical, "such cascade reactions are often viewed as spectacular and aesthetically pleasing events".[1] A very important additional advantage of these synthetic procedures is the minimization of waste, since several bonds could be formed in one sequence without isolation of intermediates or changing the reaction conditions,[2] a spectacular decrease in the amounts of solvents, reagents, adsorbents and energy is obtained, compared with stepwise reactions.[3]

The term "tandem" is the more frequently used to indicate a combination of two or more reactions that proceed in a single synthetic step or in "one pot"; they are also called *cascade* or *domino* reactions. Recently, it has been suggested that, since the word tandem means two at the same time, the name "domino reactions" is more in agreement with the time-resolved succession of reactions that are taking place in these types of transformations.[3] Although this distinction is useful and most of the reactions described in this review should more strictly be called "domino reactions", both terms will be used interchangeably, in agreement with common usage.

These types of synthetic strategies are currently finding increasing use both in total syntheses (as the successful synthesis of the five-membered ring triterpene sophoradiol from an open-chain fluoro polyeneyne[4]) and in the construction of complex intermediates (such as those obtained with lithium 1-(dimethylamino)-naphthalenide (LDMAN) (see *Section* IV.1., p. 475), recently applied to the most efficient reported synthesis of the sesquiterpene racemic cuparene[5]).

These reactions are usually designed on the basis of rational mechanistic considerations and they proceed rapidly upon initiation, leading to the final product through a number of intermediates. Thus, once the reaction sequence is triggered, a reactive intermediate may be formed and it proceeds to the next stage *via* an intramolecular or intermolecular reaction leading to a new compound. The new compound, in turn, may itself be in a favorable situation to undergo for further reactions, thus generating a product of greater complexity.

The usefulness of a domino reaction is correlated firstly to the number of bonds which are formed in one sequence (bond-forming efficiency or bond-forming economy), secondly, to the increase in structural complexity (structure economy), and thirdly, to its suitability for a general application.[2]

Classification of Tandem Reactions

Several reviews have been published in the last few years on tandem reactions.[1-3,6,7] Since this review is not intended to be a general and comprehensive overview, we have chosen to focus on reactions using organolithium reagents, that have not been extensively surveyed previously.

Many tandem strategies for the construction of complex molecules are inspired by biosynthetic schemes through which nature makes them.[1,7] A novel example is the synthesis of endiandric acids, based on a biosynthetic hypothesis postulating acyclic non-chiral precursors and a series of electrocyclizations. It is noteworthy that this process results in the construction of two rather complex polycyclic natural products each containing eight chiral centers from an acyclic, non-chiral precursor and cascade reactions.[1] Since, to the best of our knowledge, there have not been recently published biomimetic tandem reactions involving organolithium reagents, they will be not discussed here.

Although some authors[8] understand that the preliminary formation of a reactive intermediate such as a carbocation or a carbanion is not counted as a reaction step and they restrict the name of domino reaction to the "process involving two or more bond-forming transformations which take place under the same reaction conditions *without* adding additional reagents and catalysts", in the present review we will consider tandem reactions in the usually most widest scope, *i.e.* including those reaction sequences occurring in the same pot *even* if addition of new reagent is needed.

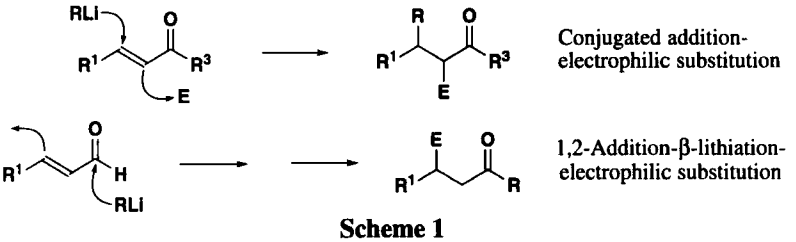
To allow a better understanding of the different types of tandem reactions discussed below, the following classification is based on the mechanism of the first step (carbolithiation, carbanionic addition, nucleophilic substitution, etc.) that can be combined with reactions involving a reaction of similar or different type (cyclization, rearrangement, etc.) in the second reaction step. Although in some cases the classification is not very straightforward, we will illustrate below this road to molecular complexity with a number of typical examples. On the other hand, insertion reactions of CO into C-Li bonds to produce acyl-lithium intermediates for nucle-

ophilic acylations and the use of organometallic catalysts to construct carbon-carbon bonds have brought about a remarkable revolution in organic synthesis in recent years. Particularly effective are tandem palladium-induced reactions that have been applied with great success to the construction of complex molecules.[9] Some recent examples of tandem reactions involving acyllithium intermediates, palladium catalysts, and other types of reactions are discussed under the "miscellaneous" heading.

I. LITHIATION SUBSTITUTION REACTIONS

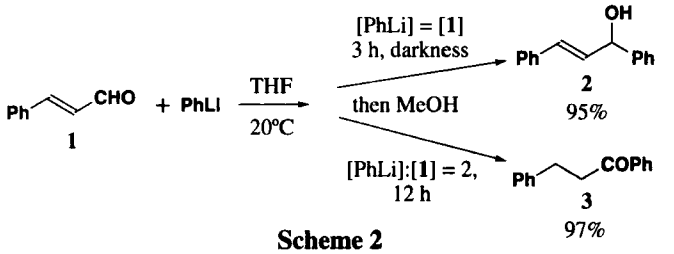
Several studies with organolithiums bridge inorganic, physical, organic, and theoretical chemistry.[10] These reagents are the most widely used organometallics in contemporary organic chemistry,[11] and they can generate enolates, ylides, and dipole-stabilized sp^2 or sp or delocalized carbanions,[12] which are useful intermediates in diverse applications.

Addition of organolithiums to α,β-unsaturated carbonyl compounds is one of the most widely used reactions for the construction of carbon-carbon bonds.[13,14] The versatility of this reaction is such that it can lead to the formation of a broad variety of compounds depending upon the transformation applied. In particular, the conjugate addition followed by electrophilic trapping can give rise to a large number of α,β-disubstituted carbonyl compounds (*Scheme 1*). Nevertheless, we have observed that the addition of aryllithiums to *(E)*-cinamaldehyde is strongly dependent on the reaction conditions; these conditions can be modified leading to a new tandem strategy in which the organolithium adds to the carbonyl group, giving an intermediate which can be trapped by electrophilic attack at the β–position, thus affording carbonyl compounds alkylated at the β–position (*Scheme 1*).



Scheme 1

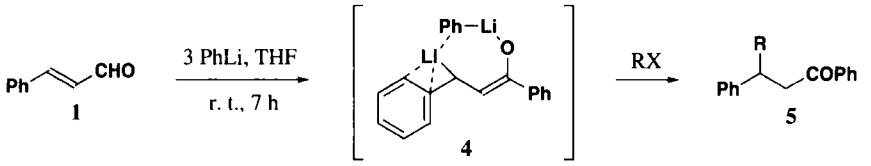
As it is shown in *Scheme 2*, the addition of an equimolar amount of phenyllithium to *(E)*-cinnamaldehyde (**1**) in THF affords the *(E)*-1,3-diphenyl-2-propen-1-ol (**2**) as the main



Scheme 2

product, while the *(E)*-chalcone and *(E)*-1,3-diphenyl-1-propanone (**3**) were found in trace amounts. Nevertheless, by a careful choice of reaction conditions, the product distribution in the reaction mixture can be changed to give a high yield of **3**, the optimum conditions being [PhLi]:[**1**] = 2 and 12 h reaction time. Under these conditions, a brilliant deep violet solution is formed and **3** is obtained in 97% yield, after quenching with MeOH.[15]

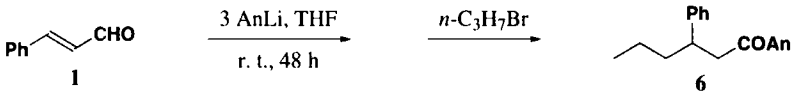
This new tandem addition-β-lithiation-substitution constitutes a "one pot" methodology for the synthesis of β-substituted dihydrochalcones in high yields.[15,16] NMR spectroscopic studies on the reaction mixture, as well as isotopic exchange reactions and trapping of intermediates have shown that the precursor of **3** is a β-lithiated intermediate **4**.[16] Addition of an electrophile to the reaction mixture followed by allowing the reaction to stand at 20°C until decoloration of the solution was observed, (2-8 h depending on RX) gave the β-substituted dihydrochalcone **5** in yields ranging from 77% to 100% (*Scheme 3*). The tandem reaction works



Scheme 3

well with alkyl chlorides as well as with bromides; primary halides gave high yields of the substituted products even for relatively long normal chains (*e. g.* $C_8H_{17}Br$). Hindered alkyl bromides, such as isopropyl (100%) and cyclohexyl (80%), also gave good results and allyl, vinyl and TMS β-substituted dihydrochalcones, could be easily obtained in 77-100% yields (*Table 1*).

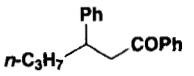
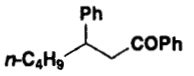
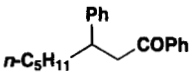
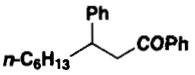
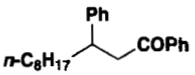
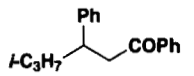
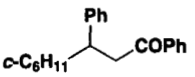
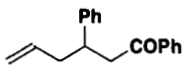
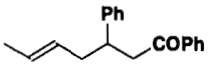
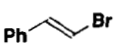
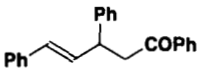
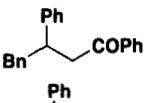
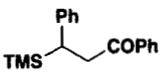
As part of an ongoing effort to extend the scope of this methodology, we investigated the influence of the structure of both the α,β-unsaturated aldehyde and the organolithium reagent on the formation of the tandem product. Aliphatic α,β-unsaturated aldehydes as well as aliphatic lithium reagents failed to afford the tandem reaction, giving mostly the normal adduct, while aromatic lithium reagents, such as anysillithium (AnLi = 2-methoxyphenyllithium), gave good results (*Scheme 4*).



Scheme 4

This one-pot sequence readily creates a wide variety of β-substituted dihydrochalcones besides a new carbon-carbon bond, opening up a new methodology in organic synthesis. As far as we know, this is the only report of this kind of tandem methodology found in the literature. Further work is under way to obtain enantiomerically enriched β-alkyl substituted dihydrochalcones by this approach.

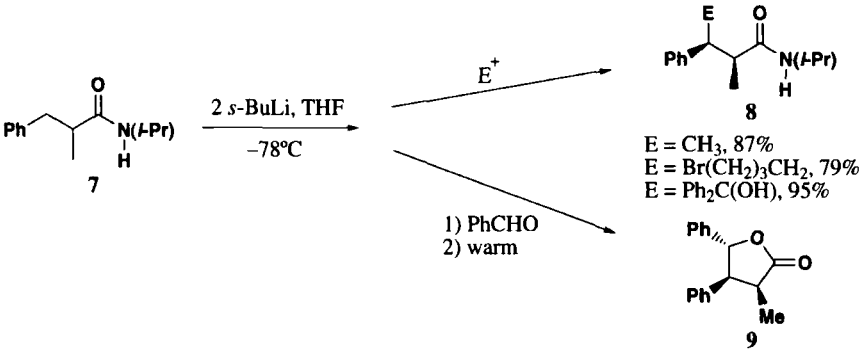
Table 1. Tandem Addition-β-Lithiation-Electrophilic Substitution

RX	β-substituted dihydrochalcone	%Yield[a]
n-C_3H_7Br		91
n-C_4H_9Br (Cl)		83 (100)
n-$C_5H_{11}Br$		92
n-$C_6H_{13}Br$		88
n-$C_8H_{17}Br$		99
i-C_3H_7Br		100
c-$C_6H_{11}Br$		80
CH_2=$CHCH_2Br$ (Cl)		95 (80)
CH_3CH=$CHCH_2Cl$		77
		100
BnBr (Cl)		81 (80)
TMSCl		98

[a] Determined by quantitative GC using Decalin as internal standard

A different approach to tandem sequences of lithiation-substitution are those reactions involving deprotonation-substitutions which are usually governed by the formation of a complex between an organolithium reagent and a functional group prior to a deprotonative directed lithiation. This effect has been termed the complex induced proximity effect (CIPE).[17,18] The CIPE rationalizes the regio- and stereochemistry of reactions of organolithiums with organic precursors involving functionalities such as C=O or P=O and it has been advocated to promote β-substitution.[19,20] Several coordination complexes were structurally characterized using different techniques such as X-ray diffraction,[21] NMR[22] and IR[23] spectroscopies, among others. The proximity between the organolithium reactant and the reactive group in several cases induces a favorable transition structure for the formation of an unexpected product.[24]

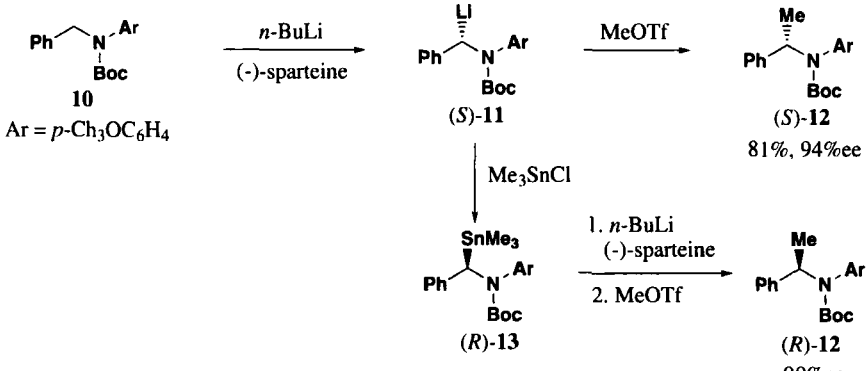
When the lithiation substitution methodology was applied to α-methyl-β-aryl secondary amides, the lithiation occurs regioselectively at the β-position, and the resulting lithiated intermediate reacted with a range of electrophiles to give substituted products with excellent diastereoselectivity (*Scheme 5*).[25] It was reported that the regioselective β-lithiation of *N*-isopropyl-3-phenylpropionamide (**7**), followed by reaction with an electrophile provided **8** as a single



Scheme 5

diastereomer. The reaction of **7** with benzaldehyde to give **9** illustrates the potential of this tandem reaction for the synthesis of three contiguous stereogenic centers in a single transformation.

Chiral ligand-mediated lithiation-substitution sequences to promote stereoselectivity in pro-chiral compounds have been widely exploited over the past decade.[11] An asymmetric deprotonation carried out by the organolithium can be the enantiodetermining step, or an asymmetric substitution as a postdeprotonation step. (-)-Sparteine, a readily available alkaloid, has been extensively used in these types of stereoselective transformations, giving high yields of enantiomeric excess. As an example, it is worth mentioning the excellent enantioselectivity observed in the lithiation-substitution of *N*-Boc-*N*-benzylamine (**10**) (Boc = *tert*-Butoxycarbonyl), that was attributed to an asymmetric deprotonation (*Scheme 6*).[26] It has been reported that the reaction of



Scheme 6

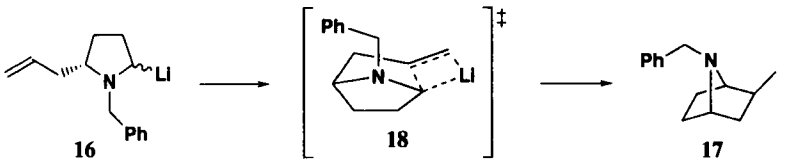
10 with *n*-BuLi in the presence of (-)-sparteine, followed by reaction with methyl triflate gave (*S*)-**12** with high enantiomeric excess. On the contrary, stannylation of **11** gives (*R*)-**13** with inversion of configuration, which by treatment with *n*-BuLi/(-)-sparteine, followed by methyl triflate, produces the opposite enantiomer of **12**.

II. CARBOLITHIATION REACTIONS

1. *Intramolecular Carbolithiations*

Increased use has been made of carbon-carbon bond formation by *intramolecular carbolithiation* (anionic cyclization)[27] which has provided a convenient entry into diversely substituted cyclopentanes,[28] pyrrolidines,[29] tetrahydrofurans,[30] and both fused[31] and bridged[32] bicyclic compounds.

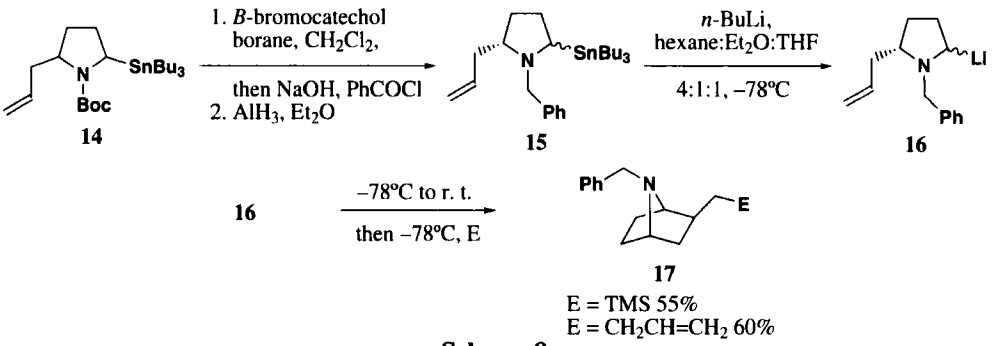
One of the main advantages of the anionic cyclizations is their regioespecificity and stereoselectivity when compared with radical or other types of reactions leading to cyclic systems. This is usually due to the formation of complexes involving the lithiated substrate (alkyl, vinyl or aryl) and an unsaturated, double or triple, C-C bond. As is shown below (*e. g. Scheme 7*), in some cases a heteroatom is involved stabilizing the transition state for the reaction to occur. In other cases, the stereoselectivity of the cyclization is determined by the presence of several functional groups in the substrate.



Scheme 7

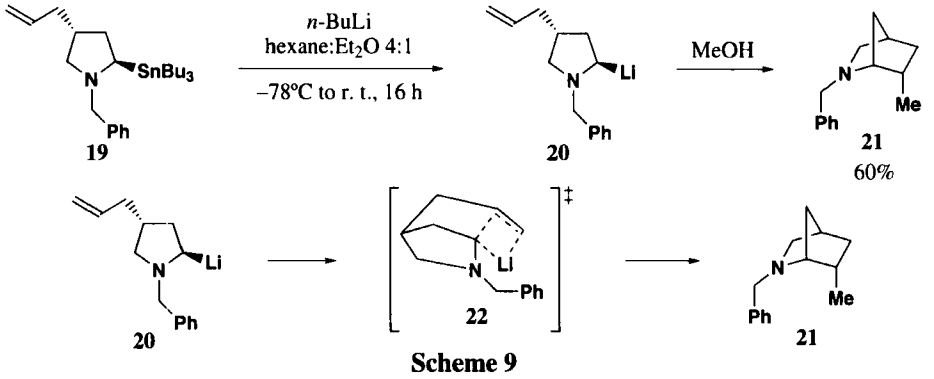
The intramolecular carbolithiation-electrophilic substitution tandem sequence leading to the formation of nitrogen-positional isomers of the azabicyclo[2.2.1]heptane ring system is a very interesting example worthy to be examined.[34] These ring systems are present in several natural products and biologically active compounds.[33] The authors generated the organolithium reagent from a tin-lithium exchange from a conveniently substituted pyrrolidine. The transmetalation occurred with retention of configuration (see below). As it is shown in *Scheme 8*, the 7-azabicyclo[2.2.1]heptane ring system can be formed from either diastereomer of a 2,5-disubstituted pyrrolidine, using a chiral organolithium intermediate. Both isomers gave the *exo* product **17**.[34] Analysis of the transition states that could lead to this product suggests that the *cis* isomer would be the more favored since it forms a chair-like transition state where the lithium atom is coordinated to the π-system (see **18** in *Scheme 7*). Presumably, the *trans* isomer epimerizes to the *cis* isomer to give the product.

A variety of cyclic amine products can be obtained by adding an electrophile to the organolithium intermediate resulting from the anionic cyclization as is shown in *Scheme 8*.[35] The



Scheme 8

authors reported that the yields of the substituted products were modest to good, but the yields could be increased by using a *N*-benzylated 2-tributylstannyl-4-allylpyrrolidine (*Scheme 9*).

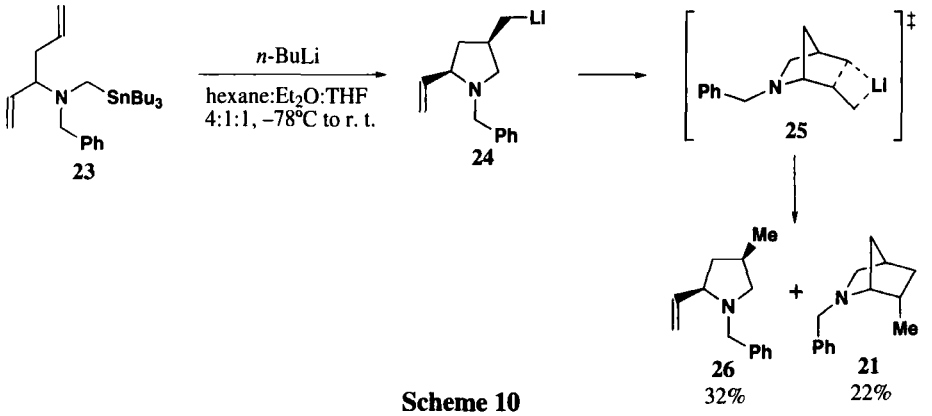


Scheme 9

In this case, the *endo*-**21** product is formed. The authors explain the stereochemistry through a transition state **22** that has a boat conformation. Comparing both transition states it is clear that, besides allowing complexation of the lithium atom with the π–system, the coordination of the lithium atom with the non-bonded electrons of the *N* is also favored. In both states, the *N* is located on the same side as the π–system. It could be presumed that which isomer gives the more favorable transition state, is mainly determined by the position of the *N* in the bicyclic ring.

An alternative route to the same bicyclic compound **21** is a sequence of cascade cyclizations starting from the acyclic precursor **23**. The 2-azabicyclo[2.2.1]heptane ring system is formed stereoselectively from stannane **23**, in low yield by a tandem cyclization, together with the product from monocyclization, the pyrrolidine *cis*-**26** (*Scheme 10*).

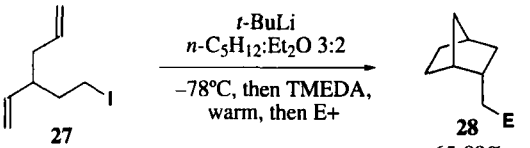
The low yield seems to be due to the protonation of the lithiated product of the monocyclization that competes with the second cyclization. The transition state **25** that gives the *endo*-product **21**, has a chair-like structure but, contrary to **18** and **22**, the *N* is not close to the lithium atom for the coordination to occur. This indicates the influence of the *N* atom on the



Scheme 10

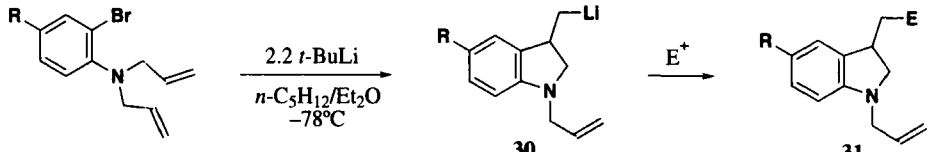
yields and stereochemistry of the cyclization; the conformation of the transition states **18** (*Scheme 7*), **22** (*Scheme 9*) and **25** in *Scheme 10*, are consistent with the results of semiempirical molecular orbital calculations (MOPAC version 6.0, AM1 Hamiltonian).[34]

In contrast, the conversion is greater in the related carbocyclic version. Bailey *et al.*[32] has reported the tandem cyclization of diolefinic alkyllithiums, from acyclic diolefinic alkyl iodides by lithium-iodine exchange at low temperature. The reaction proceeds *via* two highly stereoselective and totally regiospecific 5-*exo*-*trig*[35] ring closures. Functionalized bicyclic molecules could be obtained in good yield by trapping of the organolithium product by addition of an electrophile. By this method, *endo*-2-substituted bicyclo[2.2.1]heptanes (**28**) were prepared in isolated yields of 65-80% from the readily available 3-(2-iodoethyl)-1,5-hexadiene (**27**) (*Scheme 11*).



Scheme 11

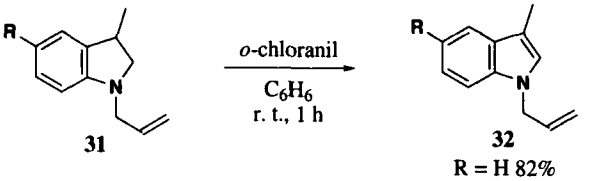
The cascade sequence that affords bicyclic systems fails with the lithium derivatives of the 2-bromo-*N,N*-diallylaniline. The methodology is useful for the synthesis of 3-substituted indolines and indoles, but the substrate undergoes only one anionic cyclization. Alkylidencyclopentanes[36] and indanes[37] have been obtained from alkenyl vinyllithium and alkenyl aryllithium reagents. Additional functionality could also be incorporated in the product *via* the intramolecular addition of vinyllithium reagents to unactivated alkenes.[38] In this context, Bailey[39] and Liebeskind[40] reported a new procedure that should provide a wide variety of substituted indolines and indoles, rapidly and with minimal effort. *o*-Bromo-*N,N*-diallylanilines (**29a-d**) were lithiated at –78°C, and then the reaction mixtures were allowed to warm to room temperature. The intermediate [(1-allyl-3-indolinyl)methyl]lithium (**30**) was trapped by addition of any of a variety of electrophiles to give 3-substituted indolines (**31a-d**) in good to high yields (61-95%) (*Scheme 12*).



29a-d: R = H, OCH_3, CH_3, $(allyl)_2N$ **30** **31**

Scheme 12

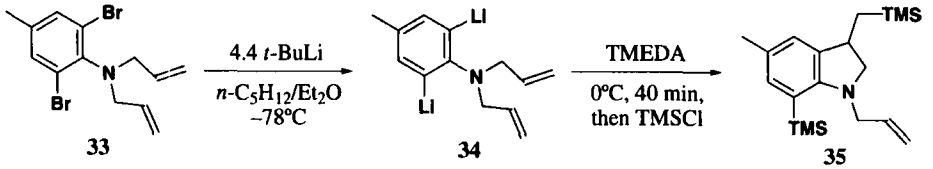
The indolines **31** were oxidized to the respective indoles, by employing several oxidants; two representative examples are presented below by using 1 molar equiv. of *o*-chloranil at room temperature (*Scheme 13*). On the other hand, a variety of protocols are available for *N*-deallylation of the resulting *N*-allylindoles.[41]



31 **32**
R = H 82%
R = CH_3 80%

Scheme 13

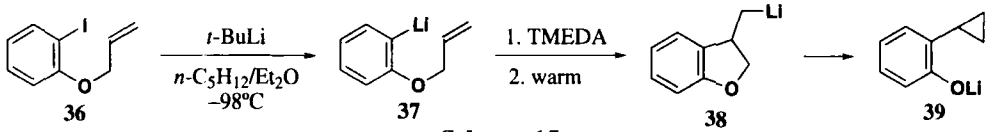
Similarly, treatment of the 2,6-dibromo-4-methyl-*N,N*-diallylaniline at –78°C with *t*-BuLi was used for the synthesis of indolines functionalized at the 3 and 7 positions (*Scheme 14*).[39]



33 **34** **35**
64%

Scheme 14

When the same methodology is applied to an analogous oxygen containing system, with the aim of obtaining substituted 2,3-dihydrobenzofurans, the procedure fails since the course of the reaction is different. Bailey studied the possibility of preparing 3-substituted 2,3-dihydrobenzofurans by cyclization of the 2-(2-propenoxy)phenyllithium (**37**). The 5-*exo* cyclization of the aryllithium **37** on warming in the presence of TMEDA gives (2,3-dihydrobenzofuranyl)methyllithium (**38**), which gives variable amounts of the lithium salt of 2-(cyclopropyl)phenol (**39**) by γ-elimination (*Scheme 15*).[42]

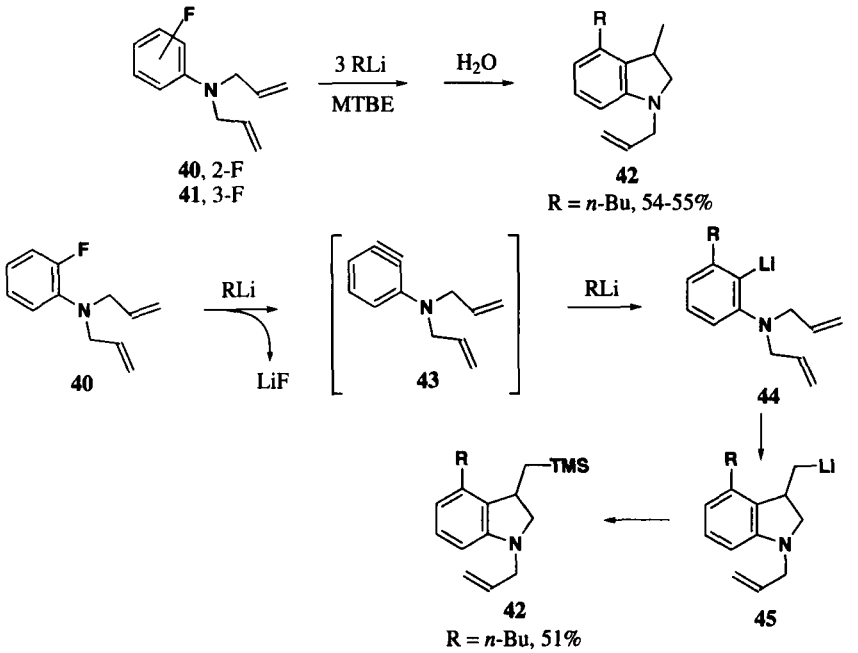


36 **37** **38** **39**

Scheme 15

Another one-pot sequence for the preparation of heterocyclic systems has been recently reported for the regioselective synthesis of 3,4-disubstituted functionalized indoles and other

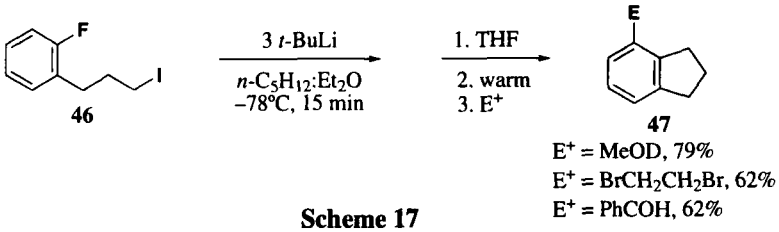
benzo-fused heterocyclic derivatives.[43,44] The key step in this novel methodology is the generation of a benzyne-tethered organolithium compound, which undergoes an intramolecular anionic cyclization. Further reaction with electrophiles provides functionalization of the cyclized product. The *ortho*-lithiation of either 2-fluoro- (**40**) or 3-fluoro- *N,N*-diallylaniline (**41**) initiates an anionic cascade leading to *N*-allyl-3,4-disubstituted indolines **42** (*Scheme 16*).[45] The loss of LiF



Scheme 16

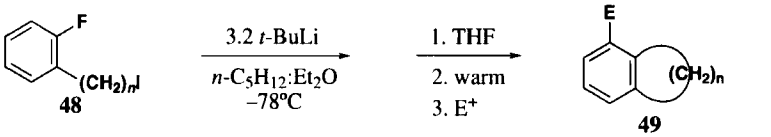
is followed by regioselective intermolecular addition of the organolithium reagent to the benzyne intermediate **43**, and cyclization of the aryllithium **44** giving a [6-substituted-2-(*N,N*-diallylamino)phenyl]lithium **45**, which could be trapped by electrophiles (*Scheme 16*).

The methodology was useful for the preparation of functionalized benzo-fused carbocycles. Isomerically pure 4-substituted indans (**47**) could be synthesized by cyclization of the benzyne-tethered propyllithium generated from 2-fluoro-1-(3-iodopropyl)benzene (**46**) (*Scheme 17*).[46]



Scheme 17

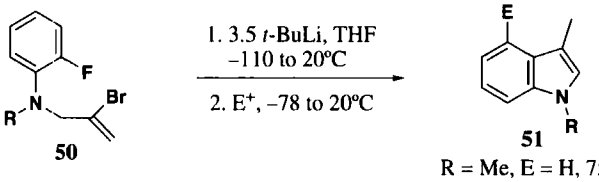
Other benzofused carbocycles could be prepared in moderate yield by a similar strategy. Isomerically pure 3-substituted benzocyclobutenes or 5-substituted tetralins (**49**) were prepared by a five-step sequence from the appropiate α-(2-fluorophenyl)-ω-iododalkane (**48**) (*Scheme 18*).[47]



n = 2, E^+ = MeOH, 45%
n = 4, E^+ = MeOH, 41%

Scheme 18

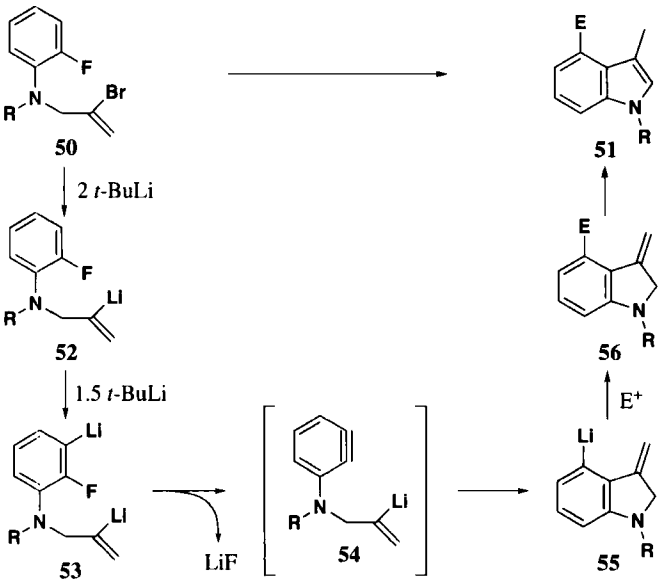
The reaction of *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline (**50**) with 3.5 equiv. *t*-BuLi in THF at –110 to –40°C for 3 h, followed by treatment with different electrophiles at –78 to 20°C, produces 1,3-dimethyl-4-functionalized indoles (**51**) in moderate to good yields (*Scheme 19*).



R = Me, E = H, 75%
R = Me, E = Me_2COH, 73%
R = $CH_2CH{=}CHCH_3$, E^+ = H, 75%

Scheme 19

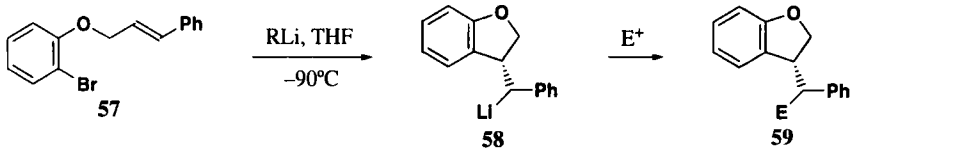
It was shown that the amine **50** reacted with *t*-BuLi to give *N*-(2-lithioallyl)amines (**52**) through halogen-metal exchange; further reaction of **52** with *t*-BuLi results in abstraction of the hydrogen *ortho* to the fluorine to give intermediate **53**. The subsequent elimination of LiF produces the benzyne intermediate **54**, which was efficiently trapped by the 2-lithioallyl unit, affording a C-4-lithiated 3-methyleneindoline derivative **55**. Treatment of **55** with electrophiles allowed the functionalization to the corresponding indole derivatives **51** (*Scheme 20*). The



Scheme 20

authors examined the use of the 2-fluorophenyl ethers and thioethers as potential substrates that could afford oxygen and sulfur heterocycles by the same methodology; however, in those cases the cyclization did not take place because the intermediate had undergone β-elimination.

We recently reported a convenient and efficient synthetic route to new 3-substituted 2,3-dihydrobenzo[b]furans (**59**) based on the tandem cyclization-γ-alkylation of 2-bromophenyl *(E)*-3-phenyl-2-propenyl ether (**57**) whose operational simplicity could find use in many applications.[48] Previous attempts using 2-bromophenyl *(E)*-2-propenyl ether failed because the cyclic intermediate had undergone a γ-elimination. We thought that a likely strategy to overcome the γ-elimination in the cyclic (2,3-dihydrobenzo[b]furanyl)-methyllithium intermediate could be substitution by a phenyl moiety that could provide increased resonance stabilization to the cyclic lithium intermediate **58** (*Scheme 21*). The results shown in *Scheme 21* illustrate that the tandem



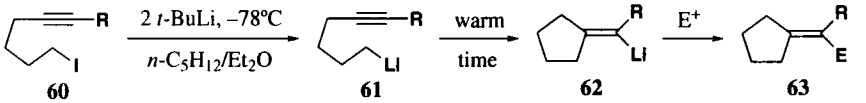
R = *n*-Bu, E = Et 79% (dr 79:21)
R = *n*-Bu, E = *n*-PrBr 77% (dr 99:1)
R = *n*-Bu, E = *n*-Pr 73% (dr 97:3)
R = Ph, E = *n*-Pr 94% (dr 97:3)
R = Ph, E = *n*-PrBr 100% (dr 99:1)

Scheme 21

sequence based on lithiation-cyclization followed by trapping of the lithiated cyclic intermediate by appropriate electrophiles, afforded good to excellent yields of the alkyl substituted 2,3-dihydrobenzo[b]furans (**59**).

The intramolecular addition of an anionic center (alkyllithium) to an unactivated carbon-carbon triple bond is another example of regiospecific and stereoselective cyclizations. So, this methodology constitutes an attractive alternative to other strategies of forming exocyclic alkenes similar to those based on radical cyclizations[49] or the Wittig reaction.

Although the chemistry of anionic cyclizations of organolithium in acetylenic systems has not been thoroughly investigated,[38] studies of some acetylenic alkyllithiums have shown that the ring closure proceeds in a regioespecific and highly stereoselective *syn*-fashion to give exocyclic vinyllithiums **62** (*Scheme 22*).[50]



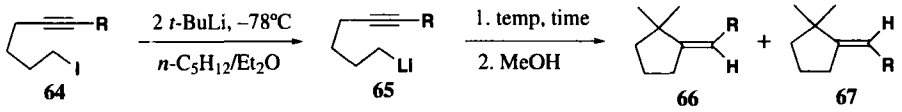
R = *n*-Bu, E^+ = MeOH, 84%
R = Ph, E^+ = CO_2, 76%
R = TMS, E^+ = MeOH, 96%

Scheme 22

The exocyclic vinyllithium produced by cyclization of a 5-hexynyllithium could be trapped by reaction with electrophiles to deliver synthetically useful functionalized derivatives in

good to excellent isolated yields (60-90%).[50] The stereochemical requirements for the preferred *5-exo* ring closures of 5-hexynyllithiums are in agreement with a chair-like transition state complex.

As it is illustrated in *Scheme 23*, cyclization of a 4-substituted 5-hexynyllithium could yield either the *Z*-isomer or the *E*-isomer or even a mixture of the two, depending on the nature of R and the cyclization conditions. At low temperatures, the isomerization of the intermediate **62** does not take place, and **66** is obtained as the only or main product.

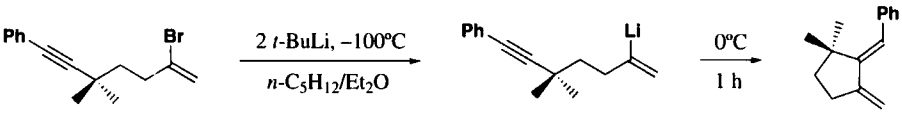


64 65 66 67

	66	67
R = *n*-Pr, 60 min, 20°C	78%	0%
R = Ph, 60 min, -78°C	88%	6%
R = Ph, 60 min, 20°C	29%	67%
R = TMS, 120 min, -78°C	98%	0%

Scheme 23

If the molecule contains a vinyl-lithiated functionality and the triple bond, the reaction product is a *bis* exocyclic 1,3-diene, which can be used as a precursor of polycyclic compounds through a Diels-Alder reaction, providing a diastereoselective route to polycyclic ring systems.[51] Isomerically pure conjugated *bis*-exocyclic 1,3-dienes **70** were obtained in good to excellent yield, from acetylenic vinyl bromides **68**. The corresponding acetylenic vinyllithiums **69** cyclize on warming to give **70**, following quench with water. Both five-membered and six-membered outer-ring dienes may be prepared. In the 5-*exo* cyclization of acetylenic vinyllithium reagents, aryl-, silyl-, or alkyl substituents at the distal acetylenic carbon are not affected; although the 6-*exo* process does occur, it is less facile and appears to be limited to substrates that bear substituents at the terminal acetylenic carbon capable of stabilizing an anion, such as phenyl or trimethylsilyl (*Scheme 24*).



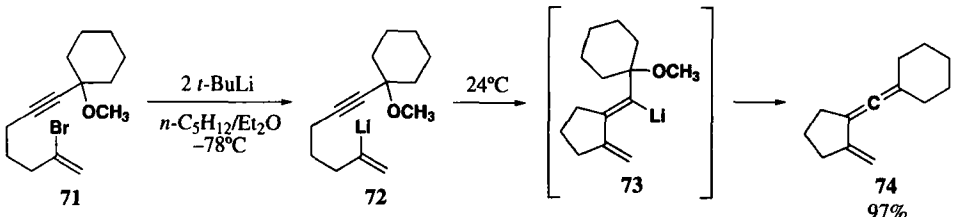
68 69 70

94%

Scheme 24

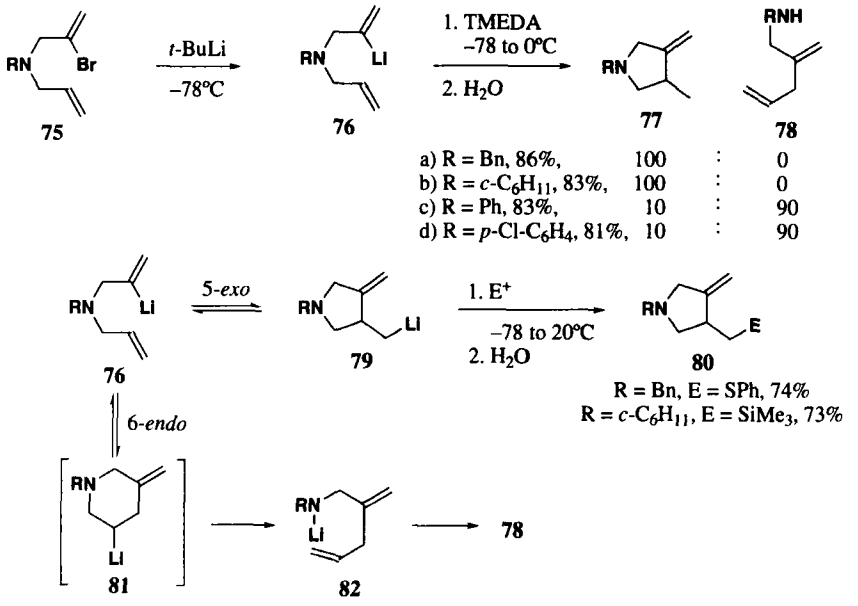
This methodology was modified by incorporation of a leaving group at the distal propargylic position of the acetylenic vinyllithium reagent. This slight modification permitted the acquisition of otherwise relatively inaccessible exocyclic, conjugated allenenes (*s*-annulated 1,2,4-trienes).[52] Thus, the vinyllithium **72** generated from bromide **71**, cyclizes to afford the five-membered exocyclic allenene **74** in 97% isolated yield (*Scheme 25*).

The intramolecular carbolithiation of vinyllithium derivatives of the substituted *N*-allyl-*N*-(2-bromoallyl)amine can lead to the formation of 5- or 6- membered cyclic products, through



Scheme 25

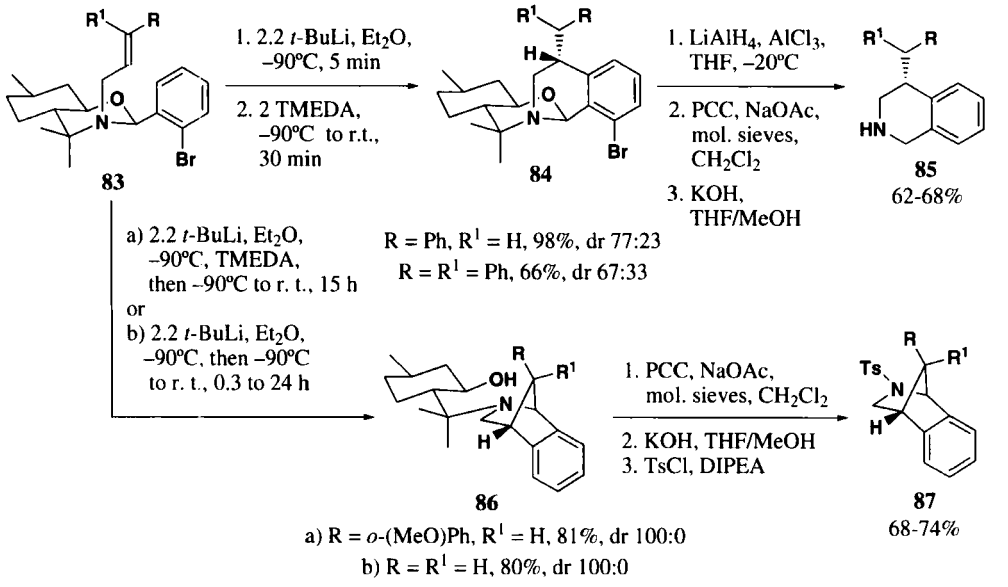
an *5-exo* or *6-endo* process depending on the starting amine. There are few precedents on the preparation of six-membered rings by anionic carbocyclization of unactivated double bonds. The first *6-endo* closure was described by Barluenga *et al.*[53] Treatment of *N*-allyl-*N*-(2-bromoallyl)amines (**75**) with 2 equiv. of *t*-BuLi at –78°C gave the vinyllithium derivatives **76**, that undergo intramolecular addition to the double bond in the presence of TMEDA at low temperatures (*Scheme 26*). When the reaction was carried out with **75a,b**, methylenepyrrolidine



Scheme 26

(**77**) was obtained as the only product. Treatment of **75c,d** under the same reaction conditions led to the 2-methylene-4-pentenylamines (**78**). Products **78** could be obtained by a *6-endo-trig* cyclization that afforded the intermediate **81**, which undergo a β-elimination to give lithium amides, which after hydrolysis produced compounds **78**. The reaction between the intermediate **79** and different electrophiles afforded 3-functionalized 4-methylenepyrrolidines **80** in good yields (*Scheme 26*).[53] This particular behavior can be a consequence of the electronic density on the *N*; the *6-endo* process should be favored over the *5-exo* when the electronic density is low. Once more, it is evidently the influence of the heteroatom which induces cyclization.

On the other hand, alkenyl aryllithiums can undergo diastereoselective cyclizations in very good yields. Pedrosa *et al.*[54] reported that chiral 2-(*o*-bromophenyl)-substituted perhydro-1,3-benzooxazines transformed in aryllithium derivatives, gave the intramolecular 6-*exo* carbolithiation reaction with unactivated double bonds attached to the nitrogen substituent of the heterocycle (*Scheme 27*). By adding 2 equiv. of TMEDA to the lithiated derivative of



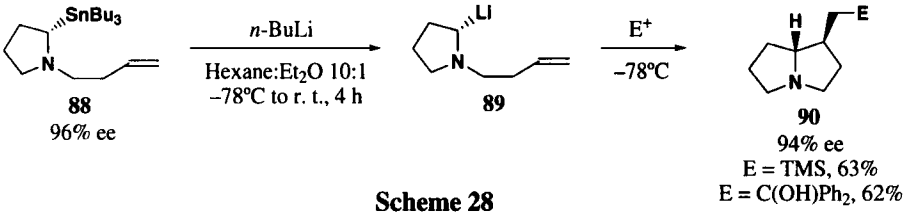
Scheme 27

compounds **83** prepared at –90°C, and allowing the mixture to reach room temperature slowly over 30 min, the *6-exo* cyclization products **84** were obtained. With longer reaction time or if no TMEDA was used, the cyclized lithium intermediates reacted intramolecularly with the *N,O*-acetal system giving to 2-azabenzonorbornane derivatives **86**.

The *6-exo* cyclization is only faster than the *5-exo* if the terminal alkene has a group, that stabilizes the lithiate intermediate generated from the cyclization. Cyclization occurs by coordination of the lithium atom with the π-system, followed by a *syn* insertion through a chair-like transition state. In this case, the heteroatom has no influence. In absence of TMEDA, occurs an intramolecular attack from the alkyllithium to the iminium formed during the opening of the N-O acetal system. The reactions are highly stereoselective and afford a useful methodology for the synthesis of enantiopure 4-substituted tetrahydroisoquinolines (**85**) or 7-substituted 2-azabenzonorbornanes (**87**) through an anionic *6-exo* cyclization of unactivated alkenes.

The usually high configurational stability at the chiral centre in enantiomerically enriched organolithium species made them particularly attractive for their use in asymmetric synthesis.[55] A good example of the retention of the stereoselectivity at the carbanion centre during an anionic cyclization from a chiral α-aminoorganolithium was reported by Coldham *et al.* Thus, the stannane **88**, on treatment with *n*-BuLi gave the pyrrolizidine **90** with complete

diastereoselectivity and enantioespecificity (*Scheme 28*).[56] Racemization usually can compete with cyclization, thereby accounting for the loss in enantiopurity. Unusually, the organolithium

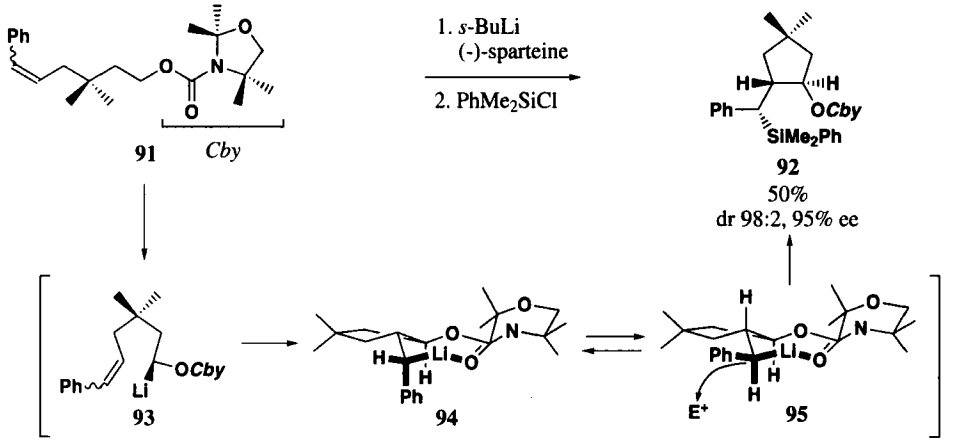


Scheme 28

species **89** is formed at r. t., but no racemization takes place.[57] Trapping of the organolithium, resulting from the anionic cyclization, with a range of electrophiles constitutes a good synthesis of the derivatives **90**. The stereoselectivity of this anionic cyclization contrasts with the radical cyclizations that lead to racemic products.[58]

A way to confer enantiofacial selectivity in cyclizations of achiral olefinic organolithiums is by the use of chiral ligands. The ability to discriminate between the enantiotopic faces of an inactivated carbon-carbon π-bond tethered to a formally carbanionic centre considerably extends the synthetic utility of anionic cyclization.[59]

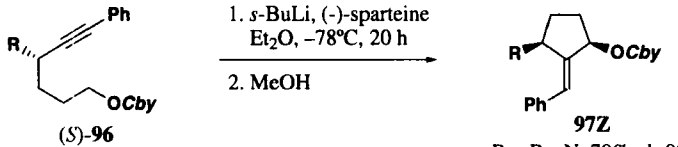
The enantioselective metallation in the α-position of a carbamate in the presence of (-)-sparteine followed by a diastereoselective intramolecular carbolithiation onto a double[60] or triple bond[61] was recently studied. The precursor **91** was deprotonated with *s*-BuLi/(-)-sparteine in Et_2O at –78°C, the reaction mixture was stirred for 20 to 30 h at this temperature, and the electrophilic reagent was subsequently added (*Scheme 29*).[60a] The cyclization showed complete *5-exo* selectivity and led to the *trans*-substituted cyclopentane **92** *via* a chair-like intermediate **95**.



Scheme 29

syn-Addition to the *cis* double bond formed the adduct **94,** which generated the thermodynamically more stable adduct **95** by epimerization. When the *trans* isomer was used, the adduct **95** was formed straightforwardly. The method allowed the stereoselective formation of two C-C bonds and, therefore, the construction of three vicinal stereocenters.

The first stereoselective intramolecular carbolithiation of alkynes was recently achieved by Hoppe *et al.*[62] Several 4-functionalized 5-hexynyl carbamates were efficiently cyclized in the presence of the chiral base (-)sparteine, providing enantiopure substituted alkylidene cyclopentanes (*Scheme 30*).



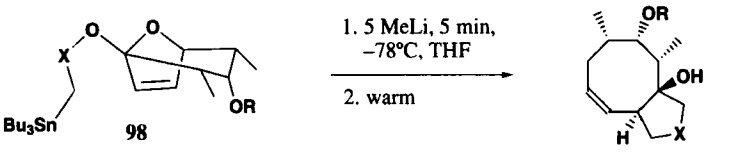
(*S*)-**96** **97Z**

R = Bn_2N, 70%, dr 99:1
R = OTBDMS, 82%. dr 95:5

Scheme 30

In these cyclizations, the presence of a sterically demanding substituent in the propargylic position seems to be essential to inhibit the abstraction of the remaining propargylic proton. High regioselectively (*5-exo* exclusively), diastereoselectively as far as the double bond is concerned (*syn* addition of the lithium carbanion electron pair) and with respect to the newly generated stereocenter (retention of the configuration at the former lithiated carbon) were observed in the cyclization of carbamates **96**.[62]

An elegant tandem processes involving anionic intramolecular cyclization-ring opening of oxabicyclo[3.2.1] systems (**98**) was reported as a route to polycyclic molecules (*Scheme 31*).[63]



98 **99**

R = H, X = O, 85%
R = Me, X = O, 82%
R = H, X = S, 88%
R = Me. X = S, 80%
R = H, X = NMe, 80%

Scheme 31

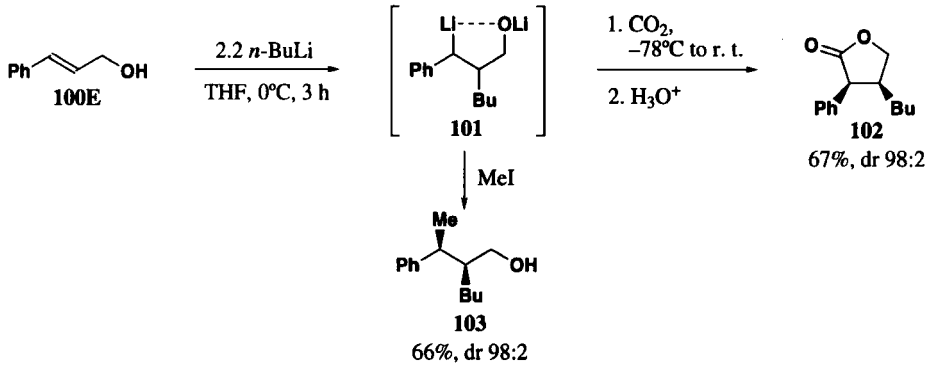
The anionic intramolecular ring opening of oxabicyclic compound is efficient for tethers with a variety of substituents in the tether. Bicyclo[5.3.0] systems (**99**) are generated with complete regio- and stereocontrol.

2. Intermolecular Carbolithiation

The carbolithiation of alkenes and alkynes is a useful transformation for the generation of new carbon-carbon bonds. Similarly to the intramolecular carbolithiation, it is possible to carry out this reaction with high diastereoselectivity.

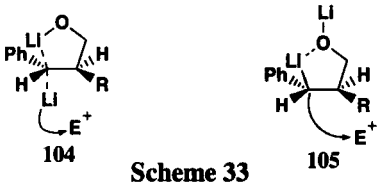
The addition of organolithiums to allylic alcohols followed by trapping of the intermediates by electrophiles, is a good example of the usefulness of this type of carbolithiations. The sequence generally leads to the formation of diastereomeric alcohols, but the use of chiral ligands confer enantioselectivity to the tandem reaction.

The addition of alkyllithiums on allylic alcohols has been of a great deal of interest in recent years.[64] The products **102** or **103** could be obtained in a diastereomeric ratio of 98:2 by treatment of the (*E*)-cinnamyl alcohol (**100E**) with *n*-BuLi and quenching of the resulting solution with CO_2 or MeI, respectively (*Scheme 32*).[65]



Scheme 32

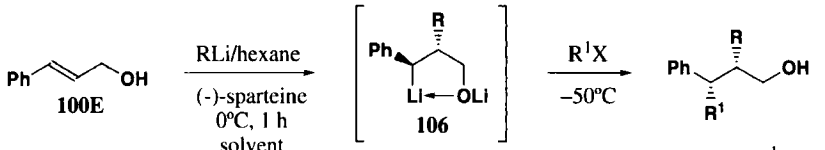
The high *syn*-selectivity seems to be independent of the stereochemistry of the starting material, since the use of **100Z** also resulted in the preferential formation of the *syn*-isomer in a similar ratio. To explain this, the authors proposed 5-membered cyclic benzyllithium species having a sp^2-like carbon to which two lithium atoms coordinate from both upper and lower sites as shown in **104** (*Scheme 33*).[65] Such a dilithiated species would selectively react with electrophiles from the opposite site of the O-Li substituent. Another intermediate, **105**, in which the



Scheme 33

benzylic lithium is coordinated with the heteroatom can be also considered.[66] Both intermediates are likely since in each of them the steric hindrance between the phenyl group and the alkyl group is minimal. If it is assumed that the reaction with an electrophile takes place under retention of the configuration at the benzylic carbon, then the product should be formed through the hetero-chelated diastereomer **105**, from the theoretical point of view that the activation barriers for retentive and inverse attack at the benzylic carbon will not differ very much.[66]

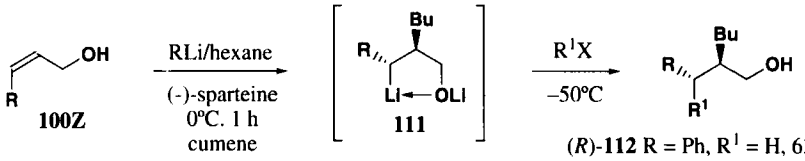
In contrast, when chiral ligands are used, the sterochemistry of the olefin is crucial for the enantioselectivity of the carbolithiation.[67] Thus, asymmetric carbolithiation of **100E** in the presence (-)-sparteine gives the carbometallated product (*S*)-**107** in 80% ee (*Scheme 34*).



hexane: (*S*)-**107** R = *n*-Bu, R^1 = H, 81%, 78% ee
cumene: (*S*)-**107** R = *n*-Bu, R^1 = H, 82%, 80% ee
108 R = *s*-Bu, R^1 = H, 65%, 72% ee
109 R = *n*-Bu, R^1 = PhS, 61%, 83% ee
110 R = *n*-Bu, R^1 = Me, 63%, 82% ee

Scheme 34

Primary as well as secondary alkyllithiums lead to identical enantioselection. Whereas the asymmetric carbolithiation of **100E** gives the (*S*)-alkylated product **107**, the reaction of the **100Z** leads to (*R*)-**112** (*Scheme 35*). When the allylic alcohol is not substituted, a racemic product is formed as is the case with 2-propen-1-ol (**113**).

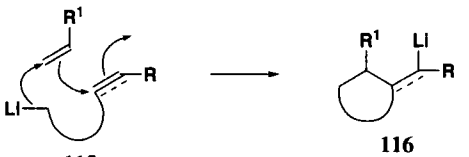


(*R*)-**112** R = Ph, R^1 = H, 63%, 70% ee
113 R = R^1 = H, 64%, 0% ee
114 R = Ph, R^1 = PhS, 60%, 70% ee

Scheme 35

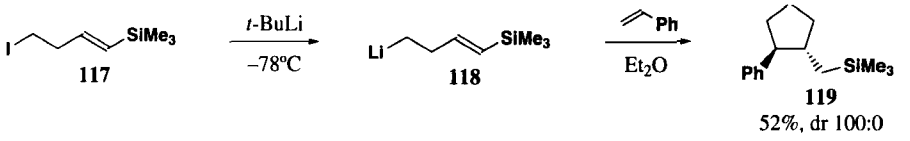
It is presumed that the initial step for the intermolecular as well as intramolecular carbolithiation is an energetically favorable coordination of the lithium atom with the π-system which serves to establish the geometry of the system prior to addition. The chiral benzylic organolithium compound **106**, obtained after the carbolithiation step, reacted diastereoselectively with a number electrophiles, leading to a formal inversion of the configuration.

Major advances have been made in the intermolecular carbolithiation of unactivated alkenes and alkynes in recent years.[68] Taylor designed a tandem intermolecular-intramolecular carbolithiation sequence, (*Scheme 36*) using organolithium reagents as difunctional, conjunctive reagents.[68]



Scheme 36

It was reported that the reaction of the lithiated alkene **118** yielding the cyclopentane **119** proceeded in reasonable yield and excellent stereocontrol (*Scheme 37*). On the other hand, the reaction of the acetylenic reagent **120** gives the cyclopentane **122** in high yield and stereocontrol.[68]



Scheme 37

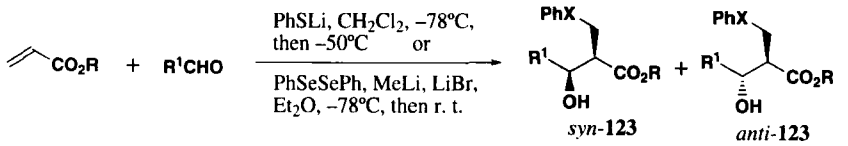
The preponderance of the *E*-alkene is consistent with the accepted *syn*-carbolithiation mechanism. It is proposed that the stereoselectivity of the reaction presumably reflects intramolecular coordination of the intermediate vinyllithium to the phenyl group.[68] This considerably expands the variety of products that can be obtained through this methodology.

III. MICHAEL REACTIONS

1. Michael-Aldol

As we have seen, one of the most outstanding features of organolithium compounds in modern organic synthesis is that the reactions take place with remarkable regioselectivity and stereoselectivity. In particular, the use of organolithium compounds improved the stereochemical course of several Michael addition reactions, one of the most powerful synthetic methodologies.[69]

The reaction involves the addition of a nucleophilic carbon species to an electrophilic multiple bond. The electrophilic partners are typically α,β-unsaturated ketones, esters, or nitriles, but other electron-withdrawing substituents can be used to activate the carbon-carbon double bond to nucleophilic attack.[14] Thiolate and its analogues are known as good nucleophiles that give Michael adducts quantitatively. The reaction begins with the nucleophilic attack of thiolate on the β-carbon of a Michael acceptor,[70] generating an enolate intermediate. A tandem Michael/aldol process is achieved when the active enolate intermediate is trapped by an aldehyde.[71] The thio-functional group serves as a precursor of other functional groups and/or acts as a good activator for a further carbon-carbon bond-forming reaction.[72] A three-component condensation of lithium thiophenolate, an α,β-unsaturated ester and an aldehyde afforded Michael/aldol tandem adducts, β-hydroxy-α-(1-phenylthioalkyl) esters, in moderate to good yields with a high *syn*-aldol selectivity (*Scheme 38*).[73] The stereoselectivity was significantly

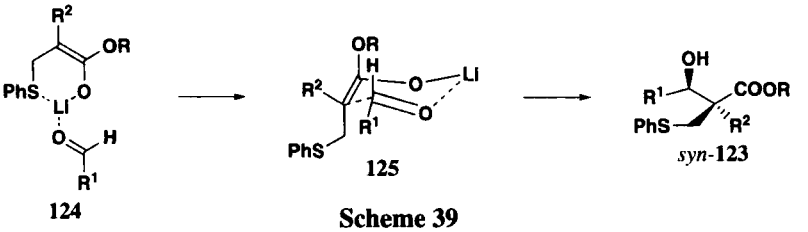


R = Me, R^1 = Ph, X = S, 62%, *syn:anti* 71:29
R = *t*-Bu, R^1 = Ph, X = S, 80%, *syn:anti* 92:8
R = *t*-Bu, R^1 = 1-naphthyl, X = S, 92%, *syn:anti* 88:12
R = *t*-Bu, R^1 = Ph, X = Se, 97%, *syn:anti* 87:13

Scheme 38

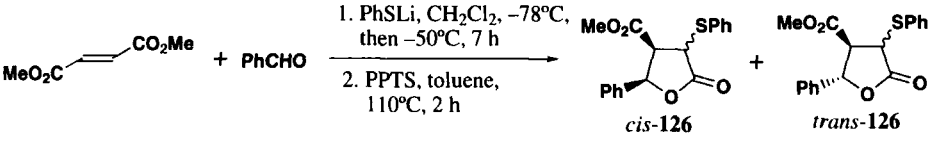
improved using *tert*-butyl acrylate, and starting from other aromatic aldehydes, the tandem adduct **123** was prepared in similar yields with high *syn*-selectivity. Analogues of thiolate, such as lithium phenylselenolates, were found to be effective for the reaction.[74]

The reaction with methacrylate proceeds through a stereochemical course similar to that of the reaction of acrylates.[74] The authors explain the stereochemical course of the reaction as follows. The addition of the acrylate and the aldehyde to the suspension of the lithium thiophenolate in CH_2Cl_2 or ether, dissolves the precipitate giving a homogeneous mixture. The formation of an acrylate-thiolate-aldehyde complex (**124**) is proposed, which undergoes several structural changes to give the complex **125** that is selectively transformed into the *syn* aldol adduct (*Scheme 39*).[74]



Scheme 39

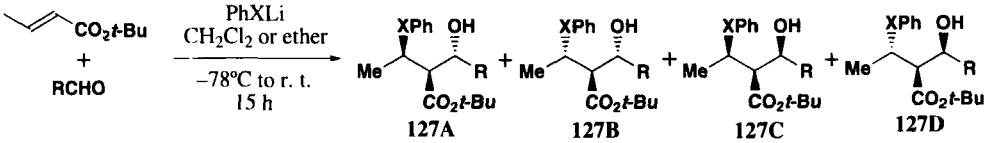
When the reaction was carried out in THF, the yield and selectivity of the sequence decreased, it was proposed that the lithium coordination with the THF molecules hinders the formation of the complex **126**. The authors concluded that the Lewis acidity of naked lithium cation is the key driving force to allow the reaction to proceed successfully.[74] The tandem reaction with lithium thiophenolate, fumarate ester and benzaldehyde constitutes a useful methodology for the preparation of γ-butyrolactone (*Scheme 40*).[73]



64%, *cis*:*trans* 80:20

Scheme 40

With crotonate esters, it was observed that the presence of the β-methyl group spoiled the electrophilic reactivity: the *anti*-Michael selectivity prevailed over the *syn*-aldol selectivity (*Scheme 41*). The presence of three contiguous stereogenic centers in adduct **127** affords to a mixture of four diastereomers (A-D), two of which were obtained as major isomers (A and C).[74]

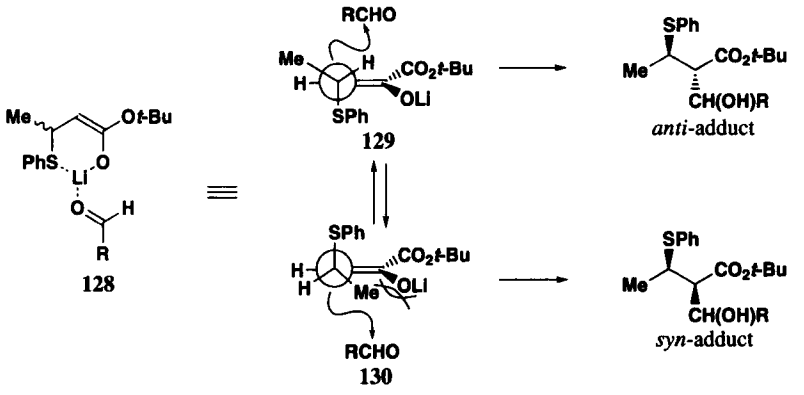


R = Ph, X = S, 55%, A/B/C/D 53/1/45/1
R = 1-naphthyl, X = S, 60%, A/B/C/D 75/1/15/9
R = Ph, X = Se, 62%, A/B/C/D 56/1/42/1

Scheme 41

In this case, the stereochemical course of the reaction can be explained by the formation of the three-component complex **128**, which transforms into two conformational isomers **129** and

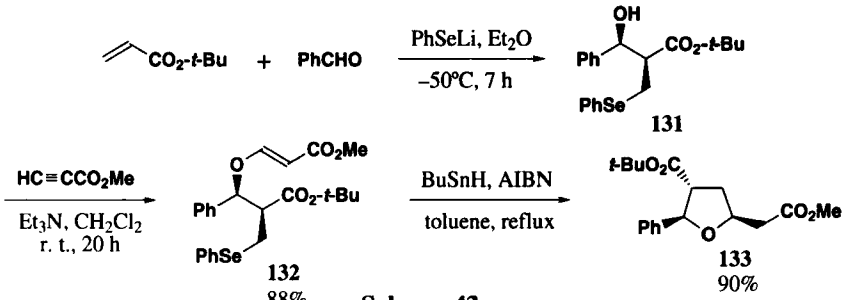
130 (*Scheme 42*). Due to the steric demands of the phenylthio group in conformer **129**, the aldehyde preferentially attacks the top face of the enolate giving an *anti*-Michael adduct, while with



Scheme 42

conformer **130**, the aldehyde comes from the bottom face to give a *syn*-Michael adduct. Conformer **129** should be the more favorable conformation, due to the steric repulsion between the methyl group and the oxygen atom in the enolate unit.

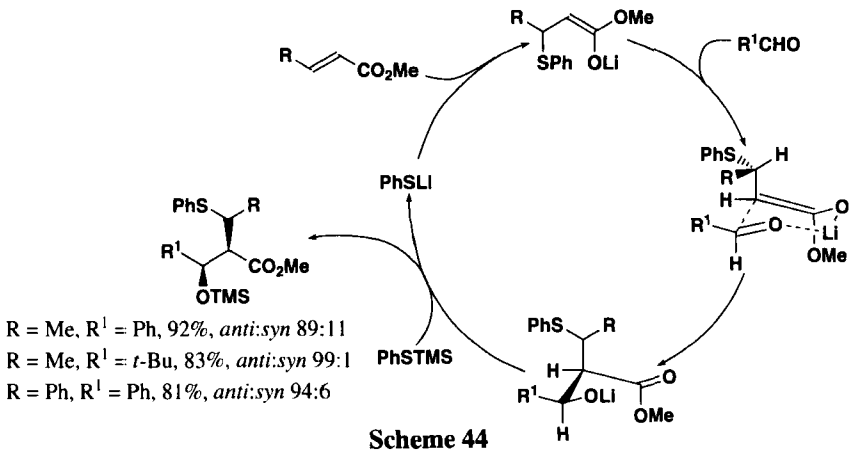
The authors examined the applicability of the present method, for the stereoselective preparation of trisubstituted tetrahydrofuran (*Scheme 43*).[73] The seleno tandem adduct **131** was O-alkenylated with methyl propiolate. Under the standard radical cyclization conditions, ester **132** afforded **133** as the sole isomer.



Scheme 43

Recently, a similar Michael-aldol tandem sequence has been reported, using *catalytic* amounts of the organolithium reagent. Reactions of α,β-unsaturated esters with aldehydes were catalyzed by 0.2 equiv. of lithium phenylthiolate in the presence of phenyl trimethylsilyl sulfide to afford *anti*-stereoselectively and in good to high yields, the conjugate addition-aldol tandem reaction products, after protodesilylation (*Scheme 44*).[75]

As in the case of crotonate esters, the tandem reaction afforded a mixture of four isomers. The reaction proceeds with *anti* stereoselectivity and high yield: the best results were obtained with pivalaldehyde which gave only one isomer. With esters having *E* or *Z* configuration the addition-aldol tandem product has the same configuration. The stereoselectivity is then

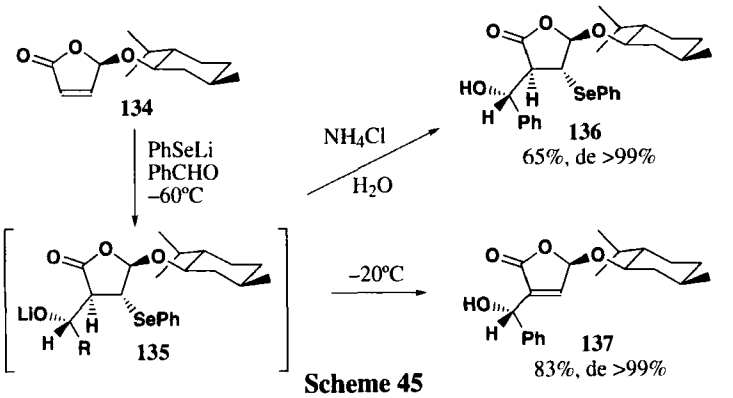


R = Me, R^1 = Ph, 92%, *anti*:*syn* 89:11
R = Me, R^1 = *t*-Bu, 83%, *anti*:*syn* 99:1
R = Ph, R^1 = Ph, 81%, *anti*:*syn* 94:6

Scheme 44

the same observed by Kamimura *et al.* with crotonate esters, with the advantage of using catalytic amounts of the organolithium reagent.

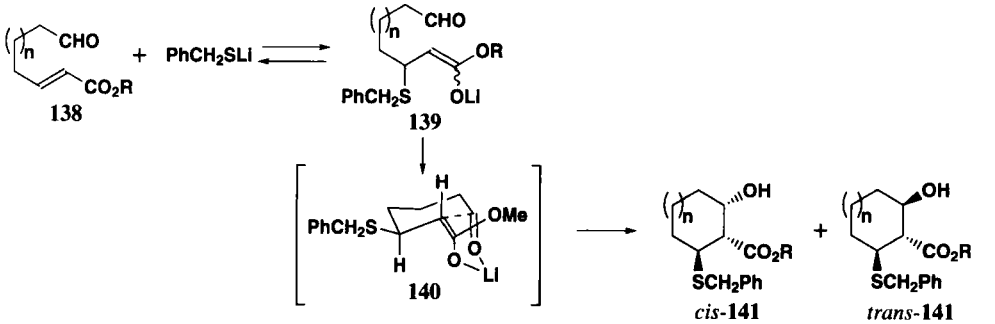
Another tandem sequence that has drawn considerable attention over the past few years is the diasteroselective and enantioselective Baylis-Hillman reactions.[76] Chiral activated olefins, chiral aldehydes, chiral catalysts, or chiral solvents had been used but only with moderate success at atmospheric pressure. A simple protocol for a highly diastereoselective and enantiomeric variant of the Baylis-Hillman reaction was recently reported.[77] The reaction of 4-menthyloxy-butenolide **134** with benzaldehyde in THF at –60°C, in the presence of lithium phenylselenide gives, after quenching with saturated NH_4Cl solution, the Michael-aldol adduct **136**, in high yield and excellent diastereoselectivity (*Scheme 45*). On the other hand, simply warming the reaction mixture to –20 °C led to the Baylis-Hillman product **137**, again in excellent yield and diastereoselectivity.[77]



Scheme 45

An intramolecular tandem Michael aldol reaction was described for esters that have an enolizable aldehyde in the molecule. The lithium ester enolate generated through the Michael reaction undergoes an intramolecular aldol reaction. Thus, the reaction of ω-oxo-α,β-unsatured

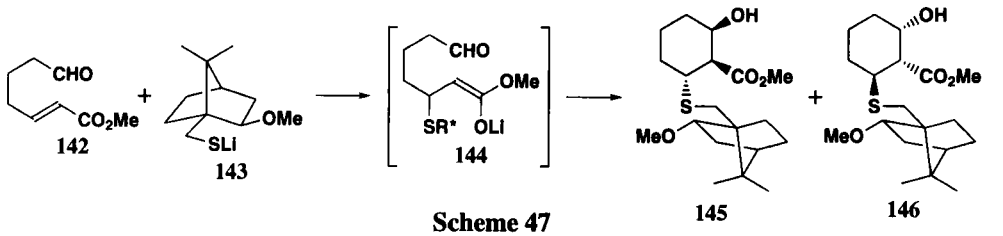
esters **138** with benzylthiolate provided the expected cyclization product **141** *via* ω–formylenolate **139** in an excellent *cis* stereoselectivity (*Scheme 46*).[78]



Scheme 46

The authors rationalized the formation of *cis*-**141** as a major diastereomer through the intermediate **140**. The Michael addition of lithium benzylthiolate with enolate **138** generates the *cis*-enolate **139,** coordination of the lithium by the formyl oxygen, gives **140** where the benzylsulfanyl group is *anti* to the coming formyl group. The more nucleophilic reagent, lithium benzylthiolate was used, since the stereoselectivity was good with benzenethiolate but poor yields were obtained.

The process was recently extended into the asymmetric cyclization of ω-oxo-α,β-unsaturated esters **142** with the use of a lithium thiolate of 10-mercaptoisoborneol (**143**) as an initiating chiral thiolate, thus providing a new methodology for the asymmetric building of chiral carbocycles (*Scheme 47*).[79]

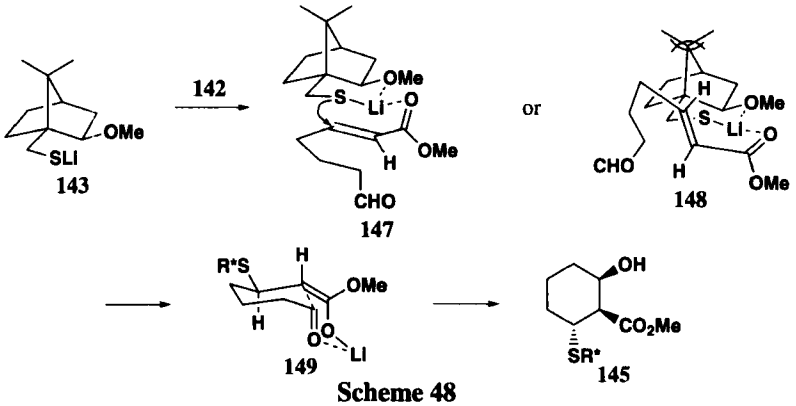


Scheme 47

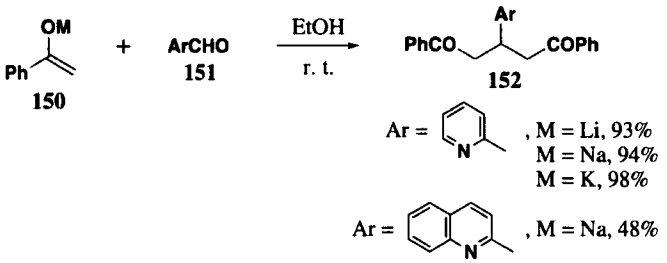
The cyclization gave the Michael-aldol tandem cyclization products (**145** and **146**) in a perfect *syn*-aldol stereoselectivity. The stereochemistry of the tandem reaction is rationalized by the model **147**, which is sterically more favorable than **148** (*Scheme 48*). The oxo-ester **142** reacts in *s-cis* form to generate *cis*-enolate, which then reacts intramolecularly with the lithium-coordinated carbonyl group shown in **149** resulting in the observed major *syn*-only aldol product **145**.[79]

Other tandem aldol-Michael reactions have been examined. Wachter-Jurcsak *et al.*[80] reported that the reactions involving 2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde with the enolates of acetophenone afforded the unexpected symmetric 1,5-diphenyl-3-(2-

heteroaryl)-1,5-pentanediones (*Scheme 49*). The unusual reactivity of these aldehydes had been previously noted.[81]



Scheme 48



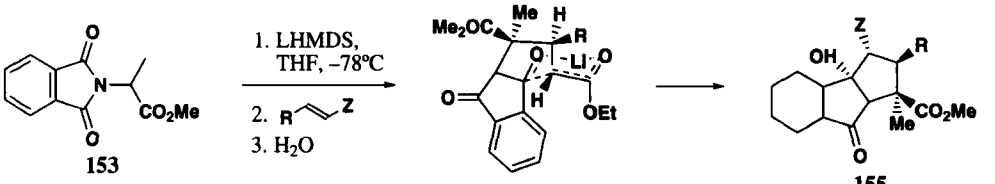
Scheme 49

The authors explained these results on the basis of an intramolecular complexation of the metal ion by the aldolate, giving a conformation where the pyridinyl ring is *gauche*, rather than *anti*, to the benzoyl group. Thus, β-elimination from the chelated aldolate would generate the thermodynamically less stable *cis*-alkene which rapidly undergoes Michael addition with a second equivalent of the enolate. The addition of pyridine improved the yields of the aldol condensation product since pyridine competes with the aldolate nitrogen for chelation of the metal ion.

2. Michael-Cyclization

The Michael adduct can be the precursor of several cyclizations giving rise to new tandem sequences. This has been mainly due to the mechanistic aspects of the process itself, and to the synthetic potential of the resultant products.

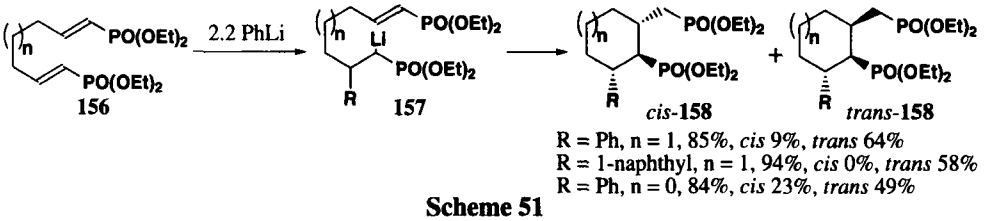
A new stereoselective synthesis of pyrrolo[2,1-a]isoindol-5-ones has been described.[82] It consisted of a sequential Michael addition to the *in situ* generated anion of methyl *N*-phthaloylalaninate (**153**), onto a series of conjugate acceptors. Cyclization of the resultant anion intermediate by condensation with one of the carbonyl imido groups gave the desired products in good yields as single isomers in only one step (*Scheme 50*).



Scheme 50

The authors rationalized the high stereoselectivity observed in terms of the six-centered chair-like transition state mode, the *Z*-enolate **154,** which involves the coordination of the two oxygen atoms to the lithium ion.[82]

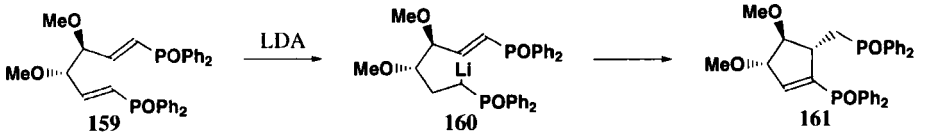
Another addition-cyclization tandem protocol has been described using alkylphosphonates. They are versatile analogues of natural phosphates, nucleotides, amino acids, and so on,[83] and also useful synthetic precursors of olefins[84] as well as chiral phosphine ligands.[85] Efficient synthetic applications of α,β-unsaturated phosphonates were described.[86] Recently, Tomioka *et al.*[87] have reported an organolithium-initiated conjugate addition-Michael tandem cyclization of α,β,ψ,ω-unsaturated bisphosphonates (**156**), giving the corresponding carbocycles **158**, bearing two phosphonate moieties (*Scheme 51*).



Scheme 51

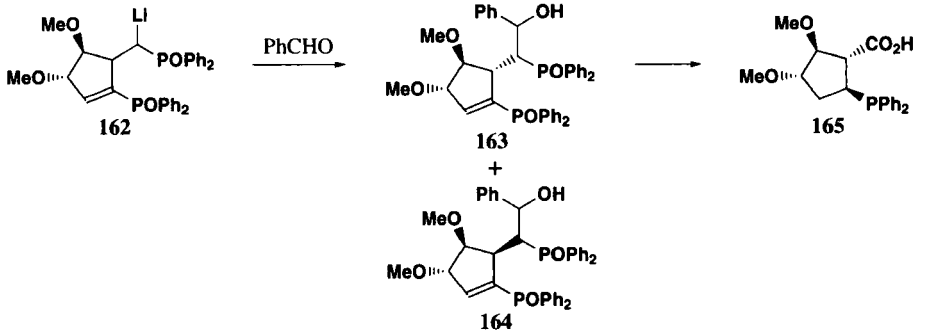
The reaction afforded the tandem cyclization product **158** as a mixture of two separable isomers together with an α,β-unsaturated cyclic bisphosphonate, which is formed by a direct deprotonation of the vinylic α-proton of **156** and subsequent intramolecular Michael cyclization. The authors described formation of **158** by the conjugate addition of **156** to 2.2 equiv. of PhLi and subsequent intramolecular Michael reaction in the intermediate **157**. It is likely that coordination of the lithium atom to the oxygens of the phosphonates favors formation of the *trans*-isomer. As shown in *Scheme 51*, the reactions with bulky naphthyllithiums gave only *trans*-**158** isomer. This novel methodology can provide a rapid entry into a variety of cyclic bisphosphonates in good stereoselectivity.

It was recently reported that upon treatment with lithium diisopropylamide achiral and chiral α,β,ψ,ω-unsaturated bisphosphine oxides underwent lithiation-conjugate addition tandem cyclization to afford the corresponding *endo*-α,β-unsaturated cyclic bisphosphine oxides (*Scheme 52*).[88]



Scheme 52

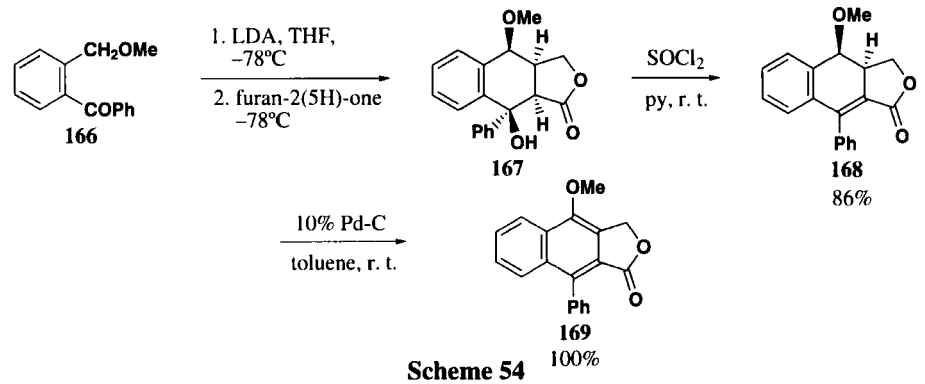
The chiral bisphosphine oxides were stereoselectivily reduced to chiral *trans*- and *cis*-bisphosphines that can be useful ligands in catalytic asymmetric hydrogenation.[88] When lithiated **161** was treated with benzaldehyde gave a cyclized alcohol **163** and its diastereoisomer **164** in 54% and 8% isolated yields, respectively (*Scheme 53*).[89]



Scheme 53

Chiral monophosphine bearing an additional functional group such as a carboxyl could be a more useful chiral ligand for a metal catalyst. Stereoselective reduction of **163** with super hydride ($LiBEt_3H$) in THF and subsequent Horner-Wadsworth-Emmons olefination with KH gave the corresponding monophosphine oxide (*Scheme 53*). Oxidative conversion of the olefin moiety into a carboxyl group and subsequent esterification, deoxygenation of the oxide and hydrolysis gave the corresponding chiral phosphinocarboxylic acid **165** (*Scheme 53*). This new monophosphine was successfully applied as a chiral and functionalized monophosphine ligand in a palladium-catalysed asymmetric allylic alkylation.[89]

A tandem Michael addition/cyclization was also the key step in the synthesis of furanone lignan derivatives recently described (*Scheme 54*).[90] The tandem sequence occurs between *o*-aroylbenzyllithiums and furan-2-(5H)-one.[91]



Scheme 54

The *o*-benzoyl-α-methoxybenzyllithium intermediate was generated by deprotonation of 2-methoxymethylphenyl phenyl ketone (**166**), with LDA. Treatment of the α-lithiated product with furan-2-(5H)-one afforded the Michael addition/cyclization product **167**. The 9-aryl-9-hydroxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1-(3H)-one (**167**) thus obtained was converted into the corresponding 9-aryl-4-methoxy-3a,4-dihydronaphtho[2,3-c]furan-1-(3H)-one (**168**) in good yield; the subsequent dehydrogenation gave the desired product 4-methoxy-9-phenyl-naphtho[2,3-c]furan-1(3H)-one (**169**).[91]

IV. ADDITION REACTIONS

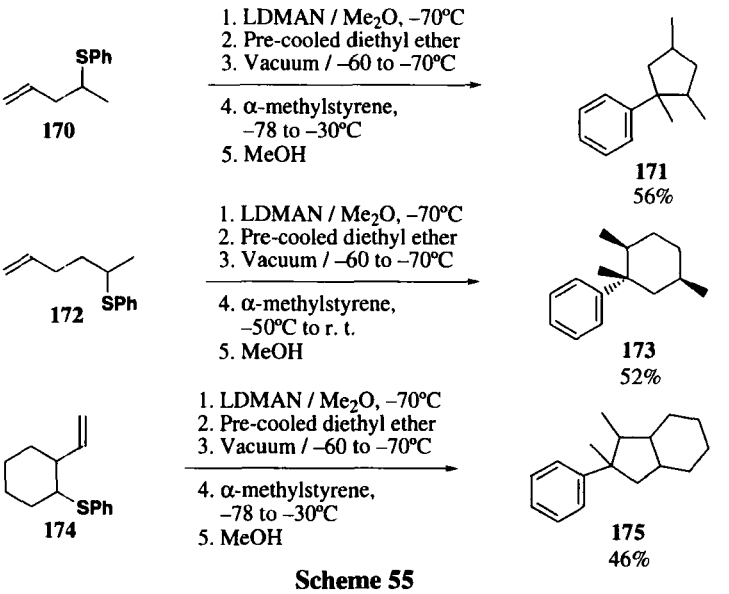
1. Addition – Cyclization

The preceding sections have illustrated the versatility of tandem reactions involving organolithium compounds and how, usually, the nature of the reagent and the experimental conditions lead the reactions to occur with high regiochemistry and stereoselectivity.[92,93] It is then of paramount relevance to search for new organolithiums or reaction conditions to provide alternative synthetic methodologies. In this sense, the reductive lithiation of phenylthioethers with aromatic radical-anions is becoming one of the most general methods for organolithium production;[64c,94] its great versatility has been demonstrated repeatedly.[12,95] Nevertheless, one disadvantage of this method is the necessity of using THF as the solvent, because of the ability of organolithiums to remove a proton from the 2-position of THF. As an example, in the tandem addition-cyclization on α-methylstyrene, the yields are compromised by the presence of THF which promotes an unwanted side-reaction.[96]

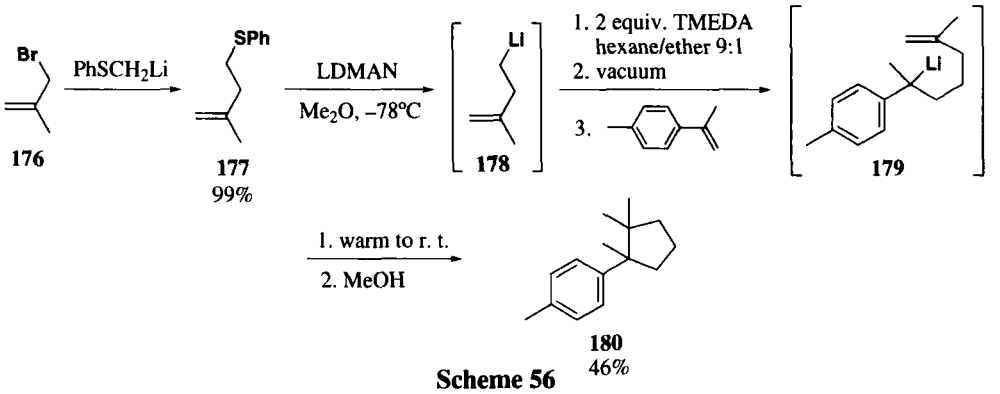
When subsequent tandem reactions are desired, the *in situ* formation of the 2-tetrahydrofuryllithium, may be a competitive major problem. To avoid the use of THF, Cohen *et al.*[97] have developed a new radical anion, the lithium 1-(dimethylamino)-naphthalenide (LDMAN), in diethyl ether: this finding should considerably enhance the utility of the widely used reductive lithiation for the preparation of organolithium compounds. The authors reported preparation of homo- and bishomoallyllithium by reductive lithiation of the corresponding phenyl thioethers by the LDMAN.[5] Upon addition of these organolithium reagents to α-methylstyrene, a tandem addition/cyclization to a phenyl-substituted five- or six-membered ring occurs, giving the product in high yields, and avoiding the α-methylstyrene polymerization (*Scheme 55*).[86] The method provided a strategy for the formation of annulated hydrocarbon systems. As it can be observed in *Scheme 55*, considerably improved yields were achieved in tandem addition/cyclization reactions conducted in diethyl ether.

This novel methodology was also efficiently used to the two-pot synthesis of the sesquiterpene (±)-cuparene (**180**).[98] The tandem addition/cyclization reaction afforded the synthetic intermediate **180** in 46% yield, the most efficient reported (*Scheme 56*).[5]

Among organolithium reagents, lithium dialkylamides are frequently used as highly reactive and selective bases for the formation of a wide range of stabilized carbanions,[10b] and

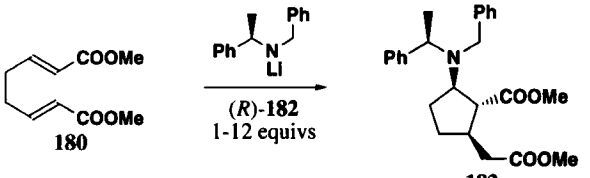


Scheme 55



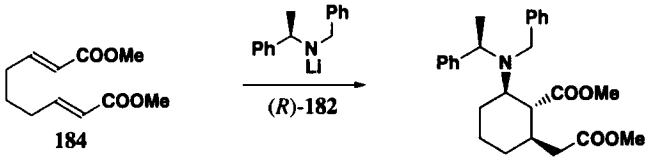
Scheme 56

they have also played a prominent role in the development of carbon-carbon bond forming reactions. Thus, we have demonstrated that carbonylation of lithium dialkylamides is a synthetically useful reaction.[99] Also, in the search of novel methods to achieve stereoselective C-C bond formation, chiral lithium amides appear to be very useful tools. For example they have been used in asymmetric alkylation reactions[100] and in tandem addition-cyclization protocol for asymmetric synthesis.[101] Reactions of this type involving (α,β)(α',β')-diendioate esters as potential substrates have been studied in the racemic series.[102] On the other hand, Garrido *et al.*[103] have demonstrated the use of homochiral lithium (α-methylbenzyl)benzylamide (**182**) to initiate the highly stereoselective conjugate addition-cyclization of dimethyl (*E,E*)-octa-2,5-dienoate (**181**) to generate the homochiral cyclopentane derivative (-)-(1R,2R,5R,αR)-**183** with complete control over the configuration of C-1 and C-2 and excellent control over C-5 (*Scheme 57*).



Scheme 57

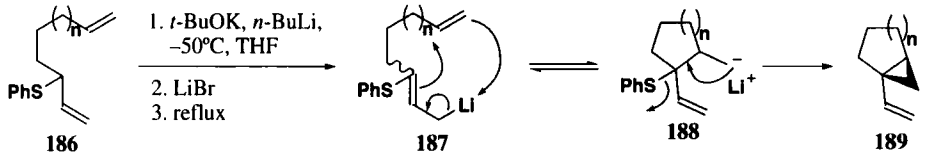
The same authors have demonstrated that addition of a slight excess of the lithium amide (*R*)-**182** to dimethyl (*E*,*E*)-nona-2,7-diendioate (**184**) gave stereoselectively (+)-(1*R*,2*R*,6*R*,α*R*)-**185** as the sole product in 72% yield (*Scheme 58*).[104]



Scheme 58

The addition-cyclization protocol can be also carried out using allylic lithium compounds for the synthesis of cyclopropanes.[81] The allylic substitution of a leaving group by a carbon nucleophile is one of the most important reactions in organic synthesis; in intramolecular variants, the rapid formation of five-memebered rings is strongly favored.[105] Recently, Cohen *et al.*[106] reported the first synthetic method based on the surprisingly facile lithium-ene cyclization followed by thiophenoxide expulsion to yield vinylcyclopropanes. These are a particularly useful class of compounds that includes the large group of pyrethroid insecticides, as well as other natural products which can be transformed further into other compounds.

The protocol for this tandem cyclization (*Scheme 59*) involves deprotonation of allylic phenyl thioethers such as **186**;[107] the authors observed that transmetallation with LiBr was

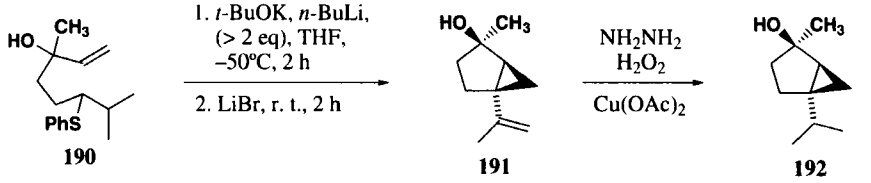


Scheme 59

required to obtain high yields of the cyclization product. Conversion of the resulting allyllithium **187** to the monocyclic intermediate **188** followed by intramolecular displacement of the thiophenoxide ion efficiently afforded the fused vinylcyclopropane **189**. Formation of the five-membered ring was quantitative from the substrate in which both alkene functions were mono-substituted (*Scheme 59*).[106]

The use of an allylic lithium oxyanionic group is of great significance to enhance reactivity and control stereochemistry in an anionic cyclization. Thus, it was reported that the

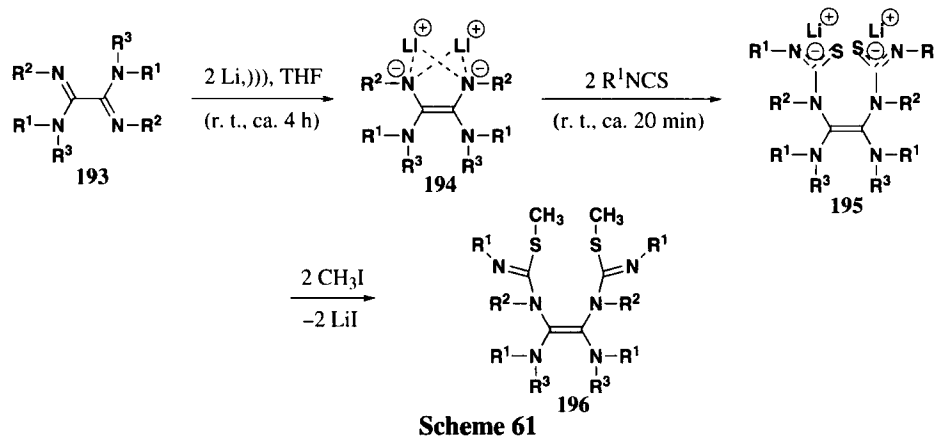
cyclization of the suitable substrate **190** to **191** occurs at room temperature rather than the reflux temperature required in the absence of allylic hydroxy groups, and proceeds stereoselectively in high yield (*Scheme 60*). The reduction product **192** was shown to have the hydroxy *cis* to the cyclopropyl ring. This methodology was applied to achieve the most efficient synthesis of *cis*-sabinene hydrate **192**, a terpene of the thujane class.[106]



Scheme 60

A novel synthetic strategy for the preparation of 3-alkyl-5-hydroxycyclohex-2-ones was recently reported. The methodology implies an intramolecular cyclization achieved through an aldolic addition/sulfinate elimination tandem reaction.[108] The addition-cyclization protocol is also useful for the one-pot synthesis of new macrocyclic compounds. Hoffman *et al.*[109] have described a general synthetic method for the incorporation of the dithiomaleonitrile unit into macrocycles containing various donor atoms; the dithiomaleonitrile substructure bears an electron-deficient C=C double bond and therefore reduces the σ-donating ability of the sulfur atoms.

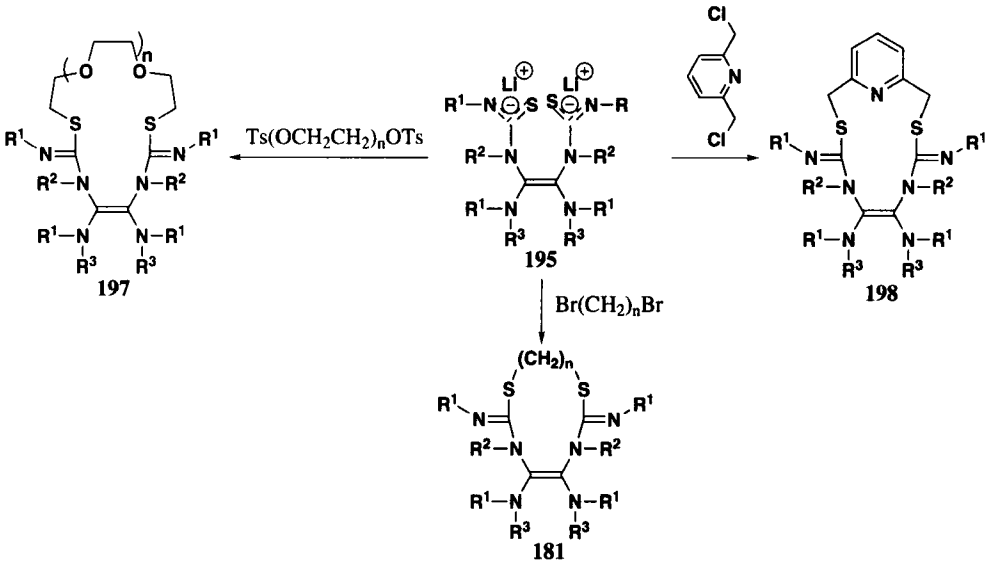
In contrast, macrocycles with an electron-rich C=C double bond seem to be of interest because of their interaction with metal cations likely involves electron-transfer processes. In this sense, the new synthetic route to tetraaminoethene derivatives developed by Görls *et al.*[110] involves a reduction/substitution sequence: the oxalic amidines **193**, were reduced with lithium under sonication and the subsequent addition of phenyl isothiocyanate afforded the anionic *bis*(thiocarbamoyl) derivatives **195** (*Scheme 61*).[111] Treatment of **195** with methyl iodide gave, in a nearly quantitative yield, the isothiourea derivative **196**.



Scheme 61

It is worth mentioning that, in this sequence, the organolithium reagent is formed *in situ* from lithium metal; there is a renewed concern about reactions that occur on metal surfaces.[112] In organic synthesis, special attention is being paid to organometallic reagents that can be obtained from the direct interaction between the metal and the organic substrate.[113]

The open-chain intermediate **195**, was used for the synthesis of several macrocyclic compounds; thus, a ring-closure reaction using a large number of α,ω-dielectrophilic building blocks yielded new macrocyclic compounds such as **197-199** (*Scheme 62*).[93] This approach constitutes a novel general methodology for the synthesis of a wide variety of macrocycles.

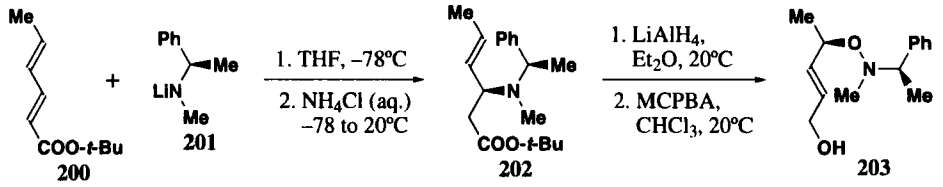


Scheme 62

2. Addition-Rearrangement

The addition-rearrangement constitutes a normal tandem protocol to carry out enantioselective synthesis; organolithium compounds and lithium amides are frequently used in the addition step. Special attention is being paid to the preparation of chiral allylic amines suitable for undergoing a stereospecific Meisenheimer rearrangement. A way to prepare such amines in high enantiomeric purity is to employ the highly diastereoselective conjugate addition to α,β-unsaturated esters of secondary lithium amides derived from α-methylbenzylamine.[114] Thus, the lithium derivative of the *N*-methyl-α-methylbenzylamine was added to the unsaturated ester **200**, which then undergoes a Meisenheimer rearrangement. The rearrangement consists of migration of one of the substituents of the tertiary amine *N*-oxide from nitrogen to oxygen, resulting in an *O*-substituted hydroxylamine.[115] If the migration involves an allyl group, the rearrangement is usually a [2,3]-sigmatropic shift.[116] There are not many examples of asymmetric Meisenheimer rearrangements of chiral allylic amine *N*-oxides reported in the literature.[117]

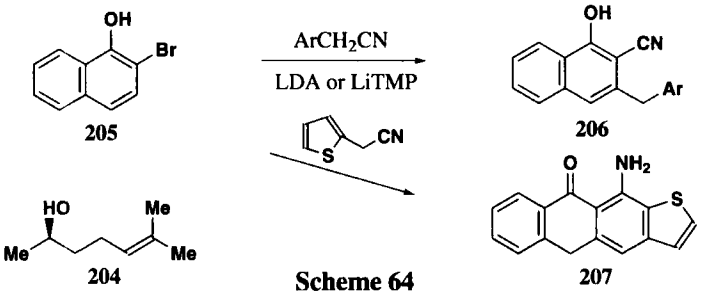
Davies *et al.*[118] have reported a sequence consisting of a highly stereoselective conjugate addition followed by a stereospecific Meisenheimer rearrangement, which affords alcohols in high enantiomeric excess. Accordingly, the conjugate addition of (*R*)-lithium *N*-methyl-(α-methylbenzyl)amine (**201**) to *tert*-butyl (*E,E*)-hexa-2,4-dienoate (**200**), gives the ester **202**. Reduction of **202** to the corresponding alcohol, afforded a substrate which, upon oxidation, undergoes a stereospecific Meisenheimer rearrangement to give a single diastereomer of the corresponding trialkylhydroxylamine **203** (*Scheme 63*).[119]



Scheme 63

As usual, if the steric bulk of the substituents on nitrogen is reduced, the yield of the sequence increases although the diastereoselectivity of addition does decrease somewhat as the size of the substituent decreases. This protocol of a tandem asymmetric conjugate addition reaction and stereoselective Meisenheimer rearrangement has also been applied to the synthesis of the insect pheromone sulcatol **204** [(*R*)-6-methylhept-5-en-2-ol] from *tert*-butyl (*E,E*)-hexa-2,4-dienoate.[98]

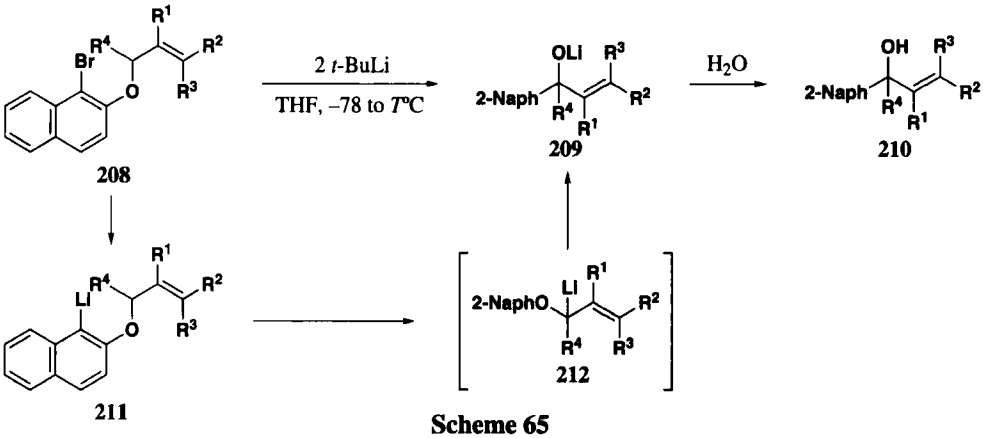
Other lithium amides, such as LDA or LiTMP, have also been used to carry out this type of tandem protocol. Biehl *et al.*[120] have described a facile one-step preparation of 3-benzyl-1-hydroxynaphthalene-2-carbonitriles (**206**), and 11-amino-5H-anthra[2,3-b]thiophen-10-one (**207**) *via* 2,3-didehydronaphthalene 1-oxide, starting from 2-bromo-1-naphthol (**205**) and arylacetonitriles and 3-thienylacetonitrile, respectively, in the presence of LDA or LiTMP (*Scheme 64*). The reactions proceed *via* a tandem addition-rearrangement pathway involving a non-synchronous [2 + 2] cycloaddition of *N*-lithiated ketenimine and 2,3-didehydronaphthalene 1-oxide.



Scheme 64

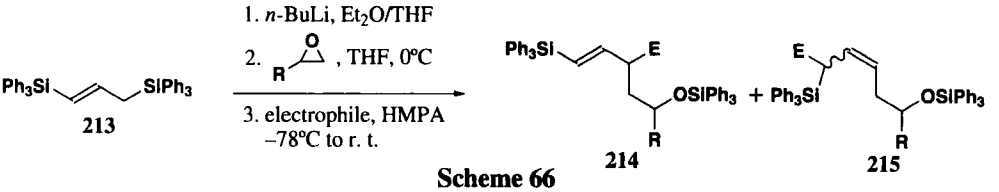
Barluenga *et al.*[121] have recently reported the transformation of 2-lithioaryl allyl and benzyl ethers into allyl and benzyl alcohol derivatives through a tandem anion translocation-[1,2]-Wittig rearrangement. The initial organolithium compounds, generated by treatment of the

allyl and benzyl 1-bromo-2-naphthyl ethers **208** with *t*-BuLi, underwent an anion translocation process generating new anions (*Scheme 65*). The Wittig rearrangement of these anions afforded the alkoxides, which upon hydrolysis produced the alcohols. This type of reaction constitutes an alternative to new organolithium compounds that are difficult to obtain by traditional methods.



Scheme 65

The tandem carbolithiation-rearrangement of silyl derivatives also constitutes a useful synthetic methodology. The carbon-carbon bond formation is triggered by anionic rearrangement of a silyl group from carbon to oxygen and constitutes a new methodology for the construction of complex organic molecules.[122,123] Accordingly, Oshima *et al.*[124] have recently reported that in the reaction of 1-triphenylsilyl-2-propenyllithium **213** with ethylene oxide, an HMPA-induced anionic 1,4-rearrangement of a silyl group from carbon to oxygen occurred, giving rise to an allylic lithium intermediate. The intermediate could be trapped in one-pot by various electrophiles to provide the corresponding adducts **214** and **215** as regioisomeric mixtures (*Scheme 66*).

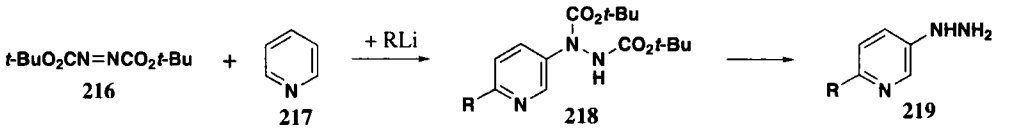


Scheme 66

3. Nucleophilic Addition

The alkyllithium reagents to be used in tandem reactions can be prepared by direct alkylation or by an aldol reaction involving nucleophilic addition of the alkyllithium as the first step. Several complex heteroaromatic compounds, which can serve as pivotal intermediates in synthetic strategy of biologically active species, could be synthesized by this procedure. The preparation of polysubstituted pyridines, has been an active research area for many years.[125] The

synthesis of 2-alkyl- or 2-aryl-5-hydrazinopyridines (**219**) has never been performed directly from pyridine. The reported methods involve several steps and expensive intermediates.[126] Zhang and Tan[127] described a new one-pot method for the synthesis of 2-alkyl- and 2-phenyl-5-hydrazinopyridine using C-Li compounds. The complex alkyl substituted pyridine **218**, was generated from pyridine by reaction with an organolithium compound followed by reaction with di-*t*-butyl azodicarboxylate (DBAD, **216**). The feature of this synthesis is to carry out three chemical reactions, double nucleophilic addition and aromatization in one-pot (*Scheme 67*).

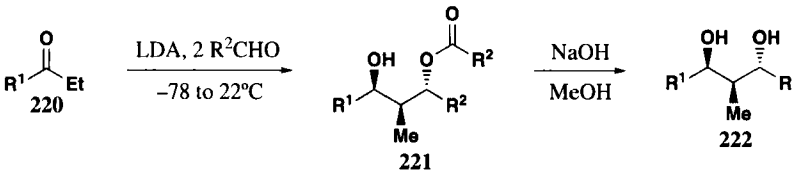


Scheme 67

The first nucleophilic addition of the organolithium compound to pyridine **217**, occurred between –10°C and 20°C; the second nucleophilic addition, dihydropyridine to DBAD, was carried out initially at –70°C followed by warming to room temperature. Finally, stirring of the 2,5-substituted dihydropyridines at room temperature in air afforded the aromatic products **218**, which after removing of the *t-Boc* produced **219** (*Scheme 67*).

The tandem reactions involving metal enolates constitute important methods for the construction of carbon-carbon bonds.[128] LDA has attained a prominence in organic chemistry enjoyed by very few reagents, playing a central role in the generation of enolates and related carbanions;[129] there are several reports that describe stereoselective reactions of lithium ketone enolates.[130,131] Woerpel *et al.*[132] have reported the tandem aldol-Tischenko reaction of lithium enolates, which is a simple method for the synthesis of polyoxygenated organic compounds. Three or five stereocenters were created in a single operation with high stereoselectivity.

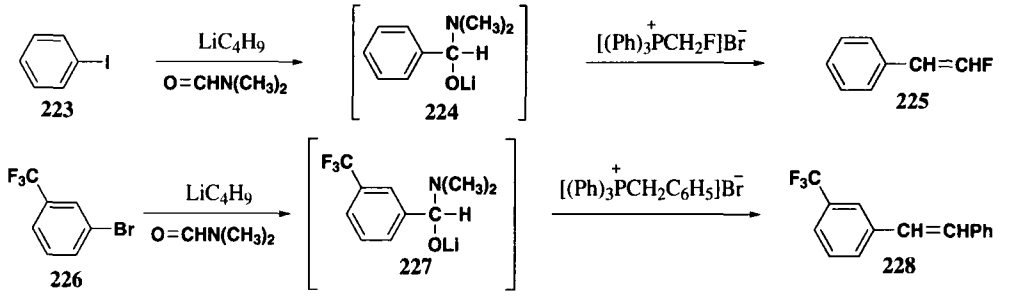
When the lithium enolate of ketones **220**, generated with LDA, was treated with 2.2 equiv. of various aldehydes at –78°C followed by warming to 22°C, a mixture of acetates **221** was obtained; hydrolysis provided the diol **222** with high diastereomeric excess (de >98%) (*Scheme 68*). The authors conducted several experiments to provide insight into the reaction



Scheme 68

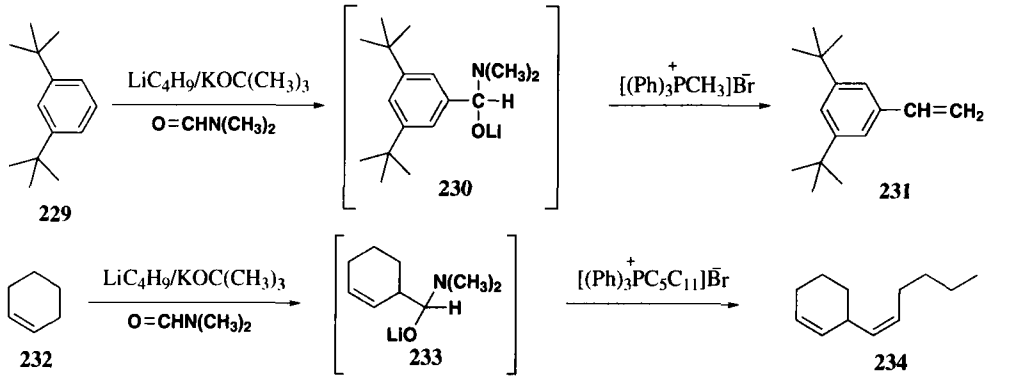
mechanism, and demonstrated that neither the stereochemical relationship of the products nor the nature of the alkyl group is dependent upon the structure of the aldolate. In addition, the reduction step is slower than aldol addition. The authors concluded that the high stereoselectivity of this reaction can be rationalized by a mechanism involving reversible aldol addition and hemiacetal formation, followed by rate- and stereochemistry-determining hydride transfer from a lithium hemiacetal.

The nucleophilic addition of an organolithium reagent to a *N,N*-disubstituted amide gives an aminoalkoxide intermediate which is generally unstable giving rise to aldehydes or ketones by decomposition. Schlosser *et al.*[133] used this reaction in a tandem sequence for the synthesis of substituted olefins, by *in situ* addition of phosphorous ylides. The adduct of phenyllithium with *N,N*-dimethylformamide afforded ω-fluorostyrene **225** (*Z/E* 50:50) in excellent yield (87%). The same methodology was applied for the preparation of 3-(trifluoromethyl)stilbene **228** (85%, *Z/E* 41:59) starting with 3-bromobenzotrifluoride and benzyltriphenylphosphonium bromide (*Scheme 69*).[134]



Scheme 69

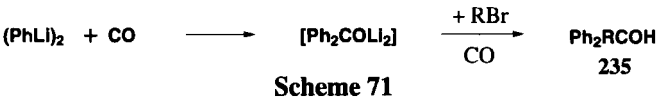
Highly reactive lithium alkoxides are the so-called *superbases*, SBs. Heavy alkali metal alkoxides undergo a metal interchange with organolithium species, giving rise to heavy alkali metal organic compounds and lithium alkoxides; these types of systems are denominated superbases due to increased reactivity of the organolithium compound.[107,135,136] The use of SBs have been demonstrated *e. g.* in the metallation[137] of 1,3-di-*tert*-butylbenzene; subsequent addition of *N,N*-dimethylformamide and methyltriphenylphosphonium bromide gave 3,5-di-*tert*-butylstyrene (**231**) in 85% yield. The (*Z*)-3-(1-hexenyl)cyclohexene (**234**) (51%, *Z/E* 97:3) was obtained in a similar reaction sequence employing cyclohexene and hexyltriphenylphosphonium bromide as main components (*Scheme 70*).[137]



Scheme 70

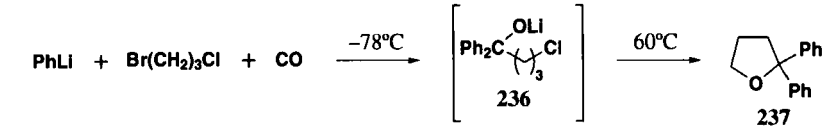
V. MISCELLANEOUS REACTIONS

The reaction of organolithium compounds with carbon monoxide has found a wide application in organic synthesis.[138,139] The carbonylation provides a useful tool for the preparation of a wide diversity of molecules containing one or more carbonyl functionalities; the synthetic usefulness of the carbonylation of numerous organolithiums has been demonstrated.[140] Acyl anions of the main row elements are of prime interest since they are expected to be potent nucleophilic reagents. The high reactivity of these reagents can be constructively used to perform one-pot sequences of reactions that lead to useful intermediates. We have earlier reported a procedure which combines nucleophilic acylation of an alkyl halide with organolithium addition to produce diarylalkylcarbinols, some of which are of industrial interest.[141] Diphenylalkylcarbinols (**235**) were easily prepared by carbonylation of phenyllithium in THF in the presence of the appropriate alkyl bromide (*Scheme 71*).



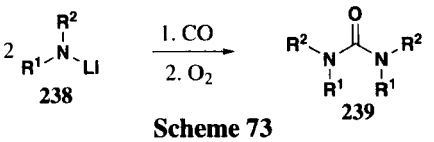
Scheme 71

This reaction was easily extended to produce substituted cyclic ethers in a one-pot synthesis (*Scheme 72*). By carrying out the carbonylation of phenyllithium in the presence of a suitably substituted chloroalkylbromide at –78°C, the oxo-lithiated intermediates **236** are obtained which cyclize by warming up the reaction mixture.



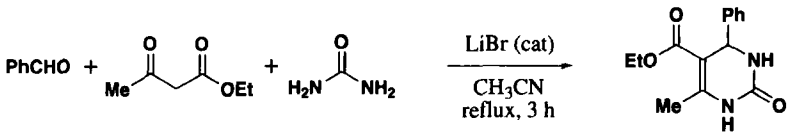
Scheme 72

The utility of carbonylation of lithium amides for the synthesis of complex molecules have also been demonstrated. *N,N,N',N'*-tetrasubstituted ureas **239** were obtained in good yields by reaction of lithium alkyl amides in THF solution with carbon monoxide under mild conditions (0°C, 1013 mbar), followed by treatment with oxygen prior to work up (*Scheme 73*).[99a]



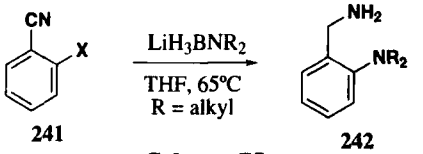
Scheme 73

Very recently, the use of LiBr as mild Lewis acid catalyst in the reaction of Biginelli was reported. Maiti *et al.*[142] have developed a new methodology for the synthesis of dihydropyrimidones by a one pot three-component condensation using a catalytic amount of LiBr, under very mild reaction conditions (*Scheme 74*).



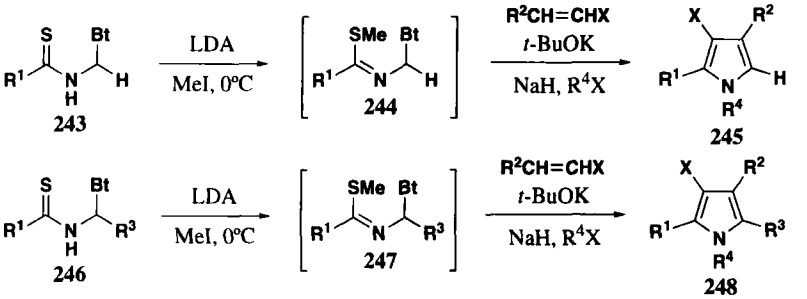
Scheme 74

One of the most useful synthetic characteristics of lithium aminoborohydrides (LABs) is their ability to react as powerful and chemoselective reducing agents.[143] It has been recently reported that LABs reduce aromatic nitriles containing electron-donating substituents to give benzylamines in very good yields.[144] On the other hand, aryl halides containing a cyano group behaved differently with LAB reagents and gave a uniquely novel tandem amination-reduction reaction in which 2-(*N,N*-dialkylamino)-benzylamines **242** are generated from 2-halobenzonitriles **241**. The authors proposed that these reactions occur through a tandem S_NAr amination-reduction mechanism wherein the LAB reagent promotes halide displacement by the *N,N*-dialkylamino group, and the nitrile is subsequently reduced (*Scheme 75*).[145]



Scheme 75

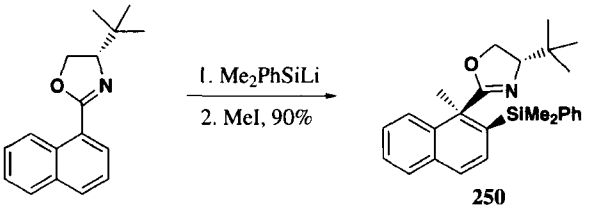
LDA has also been used to generate enolates in the one-pot synthesis of substituted pyrroles, which are common pharmacophores for numerous natural compounds including antibiotics, alkaloids, and other therapeutic agents with a wide spectrum of biological activity.[146] Katritzky *et al.*[147] have developed a one-pot sequence for the synthesis of polysubstituted pyrroles, starting from thioamides (*Scheme 76*).



Scheme 76

By treatment of the thioamides **243** and **246** with LDA at –30°C (or *t*-BuOK in THF at 0°C), followed by the addition of MeI, the corresponding S-methylthioamidates **244** and **247** were formed. Conversion into the desired pyrroles, **245** and **248**, was achieved by subsequent addition of 3 equiv. of *t*-BuOK and an activated olefin to the reaction mixture at 25°C. This method allowed the introduction of various substituents.

The 2-aminotetralins are another group of biologically active compounds, structurally simplified analogues of apomorphine, a potent anti-Parkinsonian.[148] Meyers *et al.*[149] has recently developed an interesting tandem methodology for the synthesis of 2-aminotetralins, in which the first step is the highly diastereoselective conjugate addition of dimethylphenylsilyllithium to chiral naphthyloxazoline **249**. Electrophilic trapping of the resulting aza-enolate afforded the tandem addition product **250** in high yields as a single diastereomer (*Scheme 77*). The authors

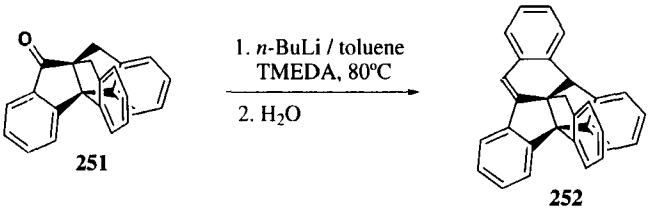


249 **250**

Scheme 77

proposed that the silicon served as a surrogate first for oxygen and later for nitrogen. As oxygen anions are not sufficiently nucleophilic to undergo the tandem addition reaction to naphthyl oxazolines, this represents a convenient entry into this important class of compounds.[150]

Novel carbon frameworks have been developed from polycyclic hydrocarbons. Thus, Kuck *et al.*[151] have recently reported an unexpected tandem reaction, which formally consists of a condensation/cyclodehydrogenation sequence starting from triptidan-9-one (**251**) leading to the *trifuso*-tetracyclic propellane **252** (*Scheme 78*). The reaction of the tribenzo[3.3.3]propellane

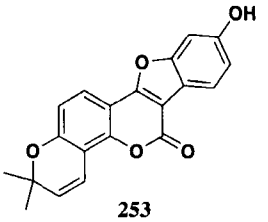


251 **252**
75%

Scheme 78

ketone **251** with benzyllithium/TMEDA afforded an efficient one-pot *peri* annulation of a dihydronaphthalene (Scheme *78*). The key step of this unexpected tandem reaction was determined to be a nucleophilic cyclization followed by hydride elimination.

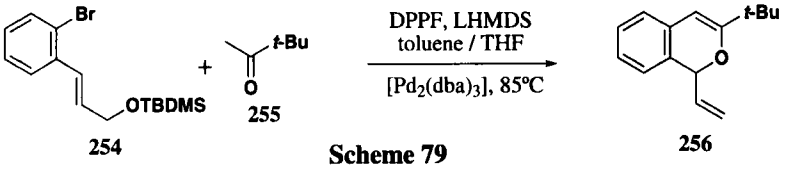
The use of organolithium compounds together with transition metals is of great utility to carry out very important transformations in synthetic organic chemistry and they have been recently used in tandem sequences. Transition metal-catalyzed reactions provide unique stereoselective routes, especially when chiral ligands are present and among the transition metals; palladium is one of the most frequently used metals.[152,153] As an example, Snieckus *et al.*[154] reported a sequential process, for the synthesis of plicadin (**253**), a natural product isolated from *Psoralea plicata*. In the first step of the tandem sequence different organolithiums (*n*-BuLi, *t*-BuLi) are used in a strategy of



253

ortho-directed metallation with high regiochemistry. In subsequent steps, LDA and Pd catalysts ($[PdCl_2(PPh_3)_2]$, $[Pd(OAc)_2(PPh_3)_2]$) were used in the Sonogashira/Castro-Stephens process, thus showing the usefulness of this synthetic methodology.

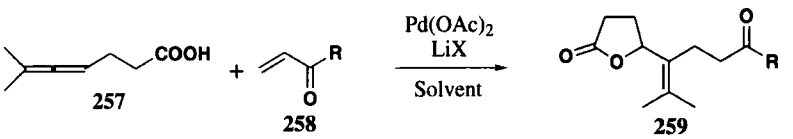
Another example that shows the versatility of the Pd catalysts is the synthesis of 1-vinyl-1-*H*-isochromene derivatives.[155] The reaction of pinacolone **255** with *tert*-butyldimethyl(3-(2-bromophenyl)allyloxy)-silane (**254**) resulted in direct formation of 1-vinyl-3-*tert*-butyl-1-*H*-isochromene (**256**) (*Scheme 79*). For this process, it was essential to use lithium diamide base and a coordinating solvent.[156]



254 255 256

Scheme 79

A novel tandem intramolecular oxypalladation and conjugate addition reactions was recently reported. The palladium(II)-catalyzed nucleophile-allene-α,β-unsaturated carbonyl coupling using lithium halides allowed the one-step synthesis of functionalized lactones, tetrahydropyranones and dihydropyranones in very good yields and with high regioselectivity (*Scheme 80*).[157]



257 258 259

Scheme 80

VI. CONCLUSIONS

Tandem reactions involving organolithium reagents combine the very well known versatility of the organolithiums and their highly stereoselective chemistry with the ecological and economic advantages of the "one-pot" strategy when compared with the conventional step-wise synthetic pathways. Tandem intra- and/or intermolecular carbolithiations followed by substitution reactions or trapping with electrophiles, addition-cyclizations sequences that occur with high stereocontrol, powerful synthetic methodologies such as the Michael and aldol reactions combined in a tandem sequence, and the use of chiral ligands that confer enantiofacial selectivity in cyclizations of achiral olefinic organolithiums or lithiated alkynes, are recently proposed new strategies for the synthesis of complex targets or for attaining difficult key synthetic pathways. The high reactivity of the anionic intermediates combined with the high stereochemical control than can be achieved, allows the triggering of a reaction sequence producing complex molecules in a very efficient mode and minimizing waste. Since the amount of solvents, reagents, adsorbents, and energy are dramatically decreased, it is to be expected that the development of tandem synthetic strategies for the economical and environmentally friendly production of complex molecules will be increasing.

VII. EXPERIMENTAL DETAILS

This section describes briefly the preparation and handling of the most frequently used organolithium reagents. All reactions involving organolithium reagents should be carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.[158] All glassware, syringes and needles are recommended to be dried in a vacuum oven and cooled in a desiccator.

Solvents: All the solvents were made anhydrous.[159] Hexane was purified by refluxing with sulfuric acid (c) for 2 h, then distilled and stored over sodium hydroxide pellets; it was distilled over sodium benzophenone ketyl immediately prior to use. Ethyl ether and THF were passed through a column with alumina, then refluxed over sodium benzophenone ketyl and distilled; they were stored over sodium/benzophenone and distilled immediately prior to use.

Organolithium reagents: n-BuLi was prepared by cutting lithium wire (4.6 g, 0.66 mol) in small pieces into a flask containing boiling hexane (250 mL), the flask was capped with a non-air stopper, and kept at 54-58°C. Butyl chloride (31.3 mL, 0.33 mol) was syringed in small aliquots into the flask during 3 h and the mixture left to react for 1 h at 56°C.[160] The *n*-BuLi solution was manipulated under dry oxygen-free nitrogen and titrated by the method of Watson prior to use.[161] PhLi and AnLi were prepared as previously described.[162] Cooled (0°C) *n*-BuLi (2.5 mL, 0.8 M in hexane) was syringed into a tube under nitrogen atmosphere, and the corresponding halobenzene (2 mmol) was added dropwise. The white aryllithium precipitate was centrifuged, the solution was removed, and the crystals were washed thrice with 2 mL of anhydrous hexane followed by centrifugation each time. The resulting solid was dried under vacuum at room temperature. Atmospheric pressure was restored by flushing with dry, oxygen-free nitrogen. The concentrations of the aryllithium compounds were determined by double titration technique using ethylene 1,2-dibromide.

SELECTED EXPERIMENTAL PROCEDURES

Typical Procedure for Tandem addition-β-lithiation Substitution Reaction. Synthesis of alkylsubstituted dihydrochalcones (5).[15,16] In a typical procedure, 3 mL of 1M PhLi in anhydrous THF were placed in a septum-capped round-bottomed reaction flask provided with a stirring bar, under nitrogen atmosphere; then 12 mL of THF and 132 mg (1 mmol) of **1** freshly distilled, were added all at once to the stirred solution. The temperature was kept at 20°C. After 7 h, 1 mmol of the electrophile was added. The resulting solution was allowed to stir until decoloration at 20°C before 0.2 mL of methanol was added. The product was purified by preparative TLC. The alkyl substituted dihydrochalcone obtained was fully characterized by melting point, ^{1}H and ^{13}C NMR spectroscopy and HRMS.

Typical Procedure for Tandem Intramolecular Carbolithiation.[34] *n*-BuLi (2.5 M in hexane, 0.25 mL, 0.6 mmol) was added to the stannane **23** (100 mg, 0.2 mmol) in dry hexane-Et_2O-THF (2.5 mL, 4:1:1) under argon at –78°C. The mixture was stirred for 30 min and was allowed to warm slowly to 25°C for 9 h. The mixture was quenched with MeOH (0.2 mL) at –78°C and was

allowed to warm to room temp. for 30 min. The solvent was evaporated, and the mixture was purified by chromatography on alumina, to give the amine **21** (9 mg, 22%) and the pyrrolidine **26** (13 mg, 32%).

Typical Procedure for Tandem Intramolecular Carbolithiation of Alkenes.[48] A solution of 0.5 mmol of **57** in 10 mL of THF (0.05 M) was cooled to –85°C under a blanket of dry nitrogen and 1.5 equiv of *n*-BuLi as a solution in hexane (1M) was added dropwise *via* syringe over a 1-2 min. period. The temperature was maintained at –80°C during a given time and the reaction mixture was quenched with a molar equiv. of the corresponding electrophile. The reaction mixture was washed with aqueous NH_4Cl solution, extracted with Et_2O, and dried ($MgSO_4$). The product **59** was purified by recrystallization.

Typical Procedure for Tandem Intramolecular Carbolithiation.[50,51] An approximately 0.1 M solution of the appropriate acetylenic vinyl bromide (**60** or **64**) in *n*-pentane-diethyl ether (different proportions) was cooled under argon atmosphere to –78°C (bath temperature; acetone-solid CO_2); then, 2.0-2.2 molar equiv of *t*-BuLi in pentane was added with stirring *via* syringe over a 5 min period. The reaction mixture was stirred for an additional 5 min at low temperature, and quenched with either deoxygenated water of MeOH. The products **63**, **66** and **67** were extracted and purified by recrystallization.

Typical Procedure for the Stereoselective Cyclocarbolithiation of Alkynes.[62] To a solution of (*S*)-**96** (0.21 mmol) and (-)-sparteine (0.31 mmol, 1.5 equiv) in Et_2O (3 mL) was added *s*-BuLi (0.31 mmol, 1.5 equiv, 1.25 M) at –78°C. This solution was stirred for 20 h at –78°C, and after methanolysis (2.5 mL) at –78°C the reaction mixture was brought to ambient temperature. The crude product was purified by flash chromatography to yield *cis*-**97** (70%).

Typical Procedure for Intermolecular Carbolithiation of Unactivated Alkenes and Alkynes.[68] *t*-BuLi (1.24 mL, 1.7 M solution in hexane, 2.1 mmol) was added dropwise to a stirred solution of the corresponding iodoalkene **117** or -alkyne **120** (1.0 mmol) in Et_2O (9 mL) at –78°C and under an inert atmosphere. The cooling bath was removed after 15 min and the solution of organolithium reagent (**118** or **119**) was allowed to warm up to room temperature. A solution of $PhCH{=}CH_2$ (0.50 mmol) in Et_2O (3 mL) was added slowly with a syringe pump over 1 h at room temperature. Upon completion, the reaction mixture was stirred for another 5 min and quenched with the specified electrophilic reagent. After extraction with diethyl ether, the cyclized product **119** or **122** was obtained (52 and 61% respectively).

Typical Procedure for Michael/Aldol Tandem Reaction to α,β-Unsaturated Esters with Thiolate Anion.[74] To a solution of thiophenol (0.20 mmol) in CH_2Cl_2 (2 mL) was added *n*-BuLi (2.2 mmol, 1.1 M in hexane) at –78°C, and lithium thiophenolate precipitated as white solid. To the heterogeneous mixture were added *t*-butyl acrylate (2.0 mmol) and benzaldehyde (2.0 mmol) at –78°C; the reaction mixture turned to a pale yellow solution, which was maintained at –50°C for 7 h. Aqueous HCl (5 mL, 1M) was added, and the mixture was extracted with ethyl acetate. After purification the desired tandem product **123** was obtained in 80% yield.

Typical Procedure for Tandem Michael-Intramolecular Cyclization.[89] A solution of bisphosphine oxide 159 (2.71 g, 5 mmol) in THF (75 mL) was added dropwise over a period of 5 min to a solution of LDA (10 mmol) in THF (175 mL) at –78°C. Benzaldehyde (1.55 mL, 15 mmol) was added, and then the mixture was stirred for 20 min at –78°C. Then MeOH (5 mL) and saturated solution NH_4Cl (100 mL) were added, and the mixture was extracted with ethyl acetate. Recrystallization gave **163** (1.75 g, 54%) and **164** (259 mg, 8%).

Typical Procedure for Tandem Addition-Cyclization. Synthesis of Cuparene.[5] To a solution of 2.4 mL (20.4 mmol) of thioanisole and 7.7 mL (51.1 mmol) of TMEDA in 40 mL of THF was added 17.5 mL (22.75 mmol) of 1.3 M *s*-BuLi dropwise under argon atmosphere at –20°C. The reaction mixture was stirred for 2 h and then 2.1 mL (20.2 mmol) of **176** was added slowly. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with NH_4Cl, the product was extracted with ether. To a solution of LDMAN prepared from lithium ribbon (18.0 mg, 2.60 mmol) and 1-(dimethylamino)naphthalene (0.45 mL, 2.7 mmol) in dimethyl ether (15 mL) at –70°C for 5-6 h, was added a solution of 1.0 mmol of **23** in 1 mL of ether *via* a syringe. The dark red solution was stirred at –70°C for 15 min. Then, 0.30 mL (2.0 mmol) of TMEDA and 8 mL of precooled hexane were added. The punctured rubber stopper was replaced by a new one. Ether was removed by connecting the reaction system to a mechanical pump. The reaction system was refilled with argon and a solution of 1.2 mL of α,4-dimethylstyrene in 1 mL of hexane was added dropwise *via* a syringe pump at –30°C over 30 min. The reaction mixture was stirred for an additional 30 min at –30°C before it was slowly warmed to 0°C, stirred at 0°C for 30 min, and at room temp. for 30 min. The reaction was quenched with 1 mL of methanol at –78°C. Flash chromatography on SiO_2 provided 60 mg (46%) of the product **180**.

Typical Procedure for Tandem Reduction-substitution Sequence.[111] Five hundred mg (1.1 mmol) of **193** was dissolved under argon in ca. 30 mL of THF in a 250-mL Schlenk vessel and 0.3 g (4.3 mmol) of lithium was added. The mixture was brought to reaction in an ultrasonic bath. After 3 h, a clear red solution was obtained from which excess lithium was removed by filtration. Then 0.3 g (2.2 mmol) of phenyl isothiocyanate was added to a solution of **194** under stirring at room temp. After completion of the addition, the mixture was stirred until the solution was pale yellow (20 min). To the solution of dilithium salt **195**, 1.1 mmol of the corresponding electrophile was added under stirring at room temp. After completion of the addition, the mixture was stirred for 24-48 h. The solvent was evaporated in vacuum, the residue taken up in toluene and the lithium salt filtered off. The products were purified by column chromatography or by recrystallization.

Typical Procedure for Tandem Carbolithiation-Rearrangement Reaction.[124] To a solution of **213** (279 mg, 0.5 mmol) in a mixed solvent of ether (5.6 mL) and THF (2.8 mL) was added *n*-BuLi in hexane (1.57 M, 0.32 mL, 0.5 mmol) at 0°C. After stirring for 2 h at that temp., to the resulting solution ethylene oxide (0.5 mmol) in THF was added and stirred for 1 h. Then, after the mixture was cooled to –78°C, benzaldehyde (2.0 mmol) and HMPA (2 mmol) was added and

the whole reaction mixture was allowed to warm to ambient temp. with stirring for another 6 h. The mixture was poured into a saturated aqueous ammonium chloride and extracted with ethyl acetate. The residual oil was diluted with THF (5 mL) and a solution of tetrabutylammonium fluoride (1.0 M, 1.0 mL, 1.0 mmol) was added at 0°C and the mixture was stirred for 1 h. Extractive work-up followed by silica gel column purification gave a mixture of **214** and **215** in 50% yield.

Typical Procedure for Tandem Nucleophilic Addition Reaction.[133] *n*-BuLi (25 mmol), from which the solvent (hexane) had been stripped off, was dissolved in precooled (-75°C) THF (50 mL). Still at –75°C, iodobenzene **223** (2.8 mL, 25 mmol) and, in 10-min intervals, N,N-dimethylformamide (2.0 mL, 25 mmol) and (fluoromethyl)triphenylphosphonium tetrafluoroborate (9.6 g, 25 mmol) were added. The mixture was vigorously stirred for 2 h at 25°C and, after addition of potassium *tert*-butoxide (2.8 g, 25 mmol), for another 2 h. A sample was withdrawn to determine the yield and isomeric composition by gas chromatography. The reaction mixture was poured into water (50 mL) and extracted with hexane. Upon distillation the product **225** was collected as a colorless liquid.

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REFERENCES

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1. K. C. Nicolau, E. W. Yue and T. Oshima, "*New Roads to Molecular Complexity*" in "*The New Chemistry*", p. 178. N. Hall, Cambridge University Press: Cambridge, U.K., 2000.

2. H. Waldmann, "*Domino Reaction*" in "*Organic Synthesis Highlight II*", p. 193. H. Waldmann, VCH: Weinheim, 1995.

3. L. F. Tietze, *Chem. Rev.*, **96**, 115 (1996).

4. P. V. Fish and W. S. Johnson, *J. Org. Chem.*, **59**, 2324 (1994).

5. T. Cohen, T. Kreethadumrongdat, X. Liu and V. Kulkarni, *J. Am. Chem. Soc.*, **123**, 3478 (2001).

6. T.-L. Ho, "*Tandem Organic Reactions*", Wiley, New York, 1992.

7. R. Grigg, "*Cascade Reactions*", Pergamon Press, Oxford, 1996.

8. See *e. g.* ref. 3.

9. J. Tsuji, "*Palladium Reagents and Catalysis*", Wiley, New York, 1995.

10. (a) M. Schlosser, *Tetrahedron*, **50**, 5845 (1994); (b) D. B. Collum, *Acc. Chem. Res.*, **26**, 227 (1993); (c) G. Boche, *Angew. Chem., Int. Ed. Engl.*, **28**, 277 (1989).

11. P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, **29**, 552 (1996).

12. M. Gray, M. Tinkl and V. Snieckus, "*Comprehensive Organometallic Chemistry*", Vol. 11, chapter 1. E. W. Abel, F. G. A. Stone, G. Wilkinson, Elsevier Science Ltd.: New York, 1995.

13. B. J. Wakefield, "*Organolithium Methods*", Academic Press: London ,1988.

14. V. J. Lee, "*Comprehensive Organic Synthesis*", Vol. 4, chapter 1.2. B. M. Trost, I. Fleming, Pergamon Press: Oxford, 1991.

15. N. S. Nudelman, G. V. García and H. G. Schulz, *J. Org. Chem.*, **63**, 5730 (1998).

16. N. S. Nudelman and G. V. García, *J. Org. Chem.*, **66**, 1387 (2001).

17. P. Beak and A. I. Meyers, *Acc. Chem. Res.*, **19**, 356 (1986).

18. K. M. Bertini Gross and P. Beak, *J. Am. Chem. Soc.*, **123**, 315 (2001) and references cited therein.

19. P. G. Williard, Q. Y. Liu and L. Lochmann, *J. Am. Chem. Soc.*, **114**, 348 (1992).

20. D. R. Armstrong, M. G. Davidson, R. P. Davies, H. J. Mitchell, R. M. Oakley, P. R. Raithby, R. Snaith and S. Warren, *Angew. Chem., Int. Ed. Engl.*, **35**, 1942 (1996).

21. R. P. Davies, P. R. Raithby and R. Snaith, *Angew. Chem., Int. Ed. Engl.*, **36**, 1215 (1997).

22. A. Sekiguchi, Y. Sugai, K. Ebata, C. Kabuto and H. Sakurai, *J. Am. Chem. Soc.*, **115**,1144 (1993).

23. M. A. Al-Aseer, B. D. Allison and S. G. Smith, *J. Org. Chem.*, **50**, 2715 (1985).

24. D. R. Anderson, N. C. Faibish and P. Beak, *J. Am. Chem. Soc.*, **121**, 7553 (1999).

25. G. P. Lutz, H. Du, D. J. Gallagher and P. Beak, *J. Org. Chem.*, **61**, 4542 (1996).

26. Y. S. Park, M. L. Boys and P. Beak, *J. Am. Chem. Soc.*, **118**, 3757 (1996).

27. T. F. Jamison, S. Shambayati, W. E. Crowe and S. L. Schreiber, *J. Am. Chem. Soc.*, **119**, 4353 (1997).

28. (a) W. F. Bailey and K. V. Gavaskar, *Tetrahedron*, **50**, 5957 (1994); (b) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel and K. B. Wiberg, *J. Am. Chem. Soc.*, **113**, 5720 (1991); (c) W. F. Bailey, T. T. Nurmi, J. J. Patricia and W. Wang, *J. Am. Chem. Soc.*, **109**, 2442 (1987).

29. I. Coldham and R. Hufton, *Tetrahedron Lett.*, **36**, 2157 (1995).

30. C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, **111**, 2981 (1989).

31. W. F. Bailey and K. Rossi, *J. Am. Chem. Soc.*, **111**, 765 (1989).

32. W. F. Bailey, A. D. Khanolkar and K. V. Gavaskar, *J. Am. Chem. Soc.*, **114**, 8053 (1992).

33. Z. Chen and M. L. Trudell, *Chem Rev.*, **96**, 1179 (1996).

34. I. Coldham, J-C. Fernández, K. N. Price and D. J. Snowden, *J. Org. Chem.*, **65**, 3788 (2000).

35. *Exo* and *Endo* are defined according to Baldwin's system; J. E. Baldwin, *J. Chem. Soc., Chem. Comm.*, 734 (**1976**).

36. A. R. Chamberlin, S. H. Bloom, L. A. Cervini and C. H. Fotsch, *J. Am. Chem. Soc.*, **110**, 4788 (1988).

37. G. A. Ross, M. D. Koppang, D. E. Bartak and N. F. Woolsey, *J. Am. Chem. Soc.*, **107**, 6742 (1985).

38. W. F. Bailey and T. V. Ovaska, "*Advances in Detailes Reaction Mechanism*", Vol 3, p. 251. J. M. Coxon., JAI Press: Greenwich, CT, 1994.

39. W. F. Bailey and X-L. Jiang, *J. Org. Chem.*, **61**, 2596 (1996).

40. D. Zhang and L. S. Liebeskind, *J. Org. Chem.*, **61**, 2594 (1996).

41. (a) S. Lemaire-Audoire, M. Savignac, J. P. Genêt and J. M. Bernard, *Tetrahedron Lett.*, **36**, 1267 (1995); (b) J. H. Tidwell and S. L. Buchwald, *J. Am. Chem. Soc.*, **116**, 11797 (1994).

42. W. F. Bailey and E. R. Punzalan, *Tetrahedron Lett.*, **37**, 5435 (1996).

43. J. Barluenga, F. J. Fañanás, R. Sanz and Y. Fernández, *Tetrahedron Lett.*, **40**, 4865 (1999).

44. J. Barluenga, F. J. Fañanás, R. Sanz and Y. Fernández, *Chem. Eur. J.*, **8**, 2034 (2002).

45. W. F. Bailey and M. W. Carson, *Tetrahedron Lett.*, **38**, 1329 (1997).

46. W. F. Bailey and S. C. Longstaff, *J. Org. Chem.*, **63**, 432 (1998).

47. W. F. Bailey and S. C. Longstaff, *Tetrahedron Lett.*, **40**, 6899 (1999).

48. N. Bodineau, N. S. Nudelman, G. V. García, J.-M. Mattalia, R. Martins, M. Arbelot and M. Chanon, *ARKIVOC*, **5**, 139 (2002)

49. (a) D. P. Curran, *Synthesis*, 417 and 489 (**1988**); (b) B. Giese, *Angew. Chem., Int. Ed. Engl.*, **28**, 969 (1989).

50. W. F. Bailey and T. V. Ovaska, *J. Am. Chem. Soc.*, **115**, 3080 (1993).

51. W. F. Bailey, N. M. Wachter-Jurcsark, M. R. Pineau, T. V. Ovaska, R. R. Warren and C. E. Lewis, *J. Org. Chem.*, **61**, 8216 (1996).

52. W. F. Bailey and P. H. Aspris, *J. Org. Chem.*, **60**, 754 (1995).

53. J. Barluenga, R. Sanz and F. J. Fañanás, *Tetrahedron Lett.*, **38**, 2763 (1997).

54. R. Pedrosa, C. Andrés, J. M. Iglesias and A. Pérez-Encabo, *J. Am. Chem. Soc.*, **123**, 1817 (2001).

55. For chiral organolithium species with configurational stability see: (a) R. E. Gawley, Q. Zhang and S. Campagna, *J. Am. Chem. Soc.*, **117**, 11817 (1995); (b) D. Hoppe, B. Kaiser, O. Stratmann and R. Fröhlich, *Angew. Chem., Int. Ed. Engl.*, **36**, 2784 (1997); (c) F. Marr, R. Fröhlich and D. Hoppe, *Org. Lett.*, **1**, 2081 (1999).

56. I. Coldham, R. Hufton and D. J. Snowden, *J. Am. Chem. Soc.*, **118**, 5322 (1996).

57. I. Coldham and G. P. Vennall, *J. Chem. Soc., Chem. Comm.*, 1569 (**2000**).

58. (a) G. Pandey, G. D. Reddy and D. Chakrabarti, *J. Chem. Soc., Perkin Trans. 1*, 219 (**1996**); (b) S. F. Martin, C.-P. Yang, W. L. Laswell and H. Rüeger, *Tetrahedron Lett.*, **29**, 6685 (1988); (c) D. A. Burnett, J.-K. Choi, D. J. Hart and Y.-M. Tsai, *J. Am. Chem. Soc.*, **106**, 8201 (1984).

59. W. F. Bailey and M. J. Mealy, *J. Am. Chem. Soc.*, **122**, 6787 (2000).

60. (a) M. J. Woltering, R. Fröhlich and D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, **36**, 1764 (1997); (b) D. Hoppe and T. Hense, *Angew. Chem., Int. Ed. Engl.*, **36**, 2282 (1997).

61. M. Oestreich, R. Fröhlich and D. Hoppe, *Tetrahedron Lett.*, **39**, 1745 (1998).

62. M. Oestreich, R. Fröhlich and D. Hoppe, *J. Org. Chem.*, **64**, 8616 (1999).

63. M. Lautens and S. Kumanovic, *J. Am. Chem. Soc.*, **117**, 1954 (1995).

64. (a) S. Klein, I. Marek and J-F. Normant, *J. Org. Chem.*, **59**, 2925 (1994); (b) S. Marumoto and I. Kuwajima, *J. Am. Chem. Soc.*, **115**, 9021 (1993); (c) T. Cohen and M. Bhupathy, *Acc. Chem. Res.*, **22**, 152 (1989).

65. T. Kato, S. Marumoto, T. Sato and I. Kuwajima, *Synlett*, 671 (**1990**).

66. C. M. Lichtenfeld and H. Ahlbrecht, *Tetrahedron*, **52**, 10025 (1996).

67. I. Marek, *J. Chem. Soc., Perkin Trans. 1*, 535 (**1999**).

68. X. Wei and R. J. K. Taylor, *Angew. Chem., Int. Ed. Engl.*, **39**, 409 (2000).

69. (a) M. E. Jung, "*Comprehensive Organic Synthesis*", Vol. 4, chapter 1, p. 1. B. M. Trost, I. Fleming, Pergamon Press: Oxford, 1991; (b) P. Perlmutter, "*Conjugated Addition Reactions in Organic Synthesis*", Pergamon Press: Oxford, 1992.

70. (a) R. Clauss, W. Hinz and R. Hunter, *Synlett*, 57, (**1997**); (b) O. Miyata, T. Shinada, I. Ninomiya, T. Naito, T. Date, K. Okamura and S. Inagaki, *J. Org. Chem.*, **56**, 6556 (1991).

71. (a) S. G. Davies and D. R. Fenwick, *J. Chem. Soc., Chem. Commun.*, 565 (**1997**); (b) N. Tsukada, T. Shimada, Y. S. Gyoung, N. Asao and Y. Yamamoto, *J. Org. Chem.*, **60**, 143 (1995); (c) Y. Yamamoto, N. Asao and T. Yuehara, *J. Am .Chem. Soc.*, **114**, 5427 (1992); (d) J. F. G. A. Jansen and B. L. Feringa, *Tetrahedron Lett.*, **32**, 3239 (1991).

72. N. S. Simpkins, "*Sulphones in Organic Synthesis*", Pergamon Press: Oxford, 1993.

73. A. Kamimura, H. Mitsudera, S. Asano, A. Kakehi and M. Noguchi, *J. Chem. Soc., Chem. Commun.*, 1095 (**1998**).

74. A. Kamimura, H. Mitsudera, S. Asano, S. Kidera and A. Kakehi, *J. Org. Chem.*, **64**, 6353 (1999).

75. M. Ono, K. Nishimura, Y. Nagaoka and K. Tomioka, *Tetrahedron Lett.*, **40**, 1509 (1999).

76. (a) P. Langer, *Angew. Chem., Int. Ed. Engl.*, **39**, 3049 (2000); (b) E. Ciganek, *Org. React.*, **51**, 201 (1997); (c) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, **52**, 4653 (1996).

77. J. Jauch, *J. Org. Chem.*, **66**, 609 (2001).

78. M. Ono, K. Nishimura, Y. Nagaoka and K. Tomioka, *Tetrahedron Lett.*, **40**, 6979 (1999).

79. K. Nishimura, H. Tsubouchi, M. Ono, T. Hayama, Y. Nagaoka and K. Tomioka *Tetrahedron Lett.*, **44**, 2323 (2003).

80. N. Wachter-Jurcsak, C. Radu and K. Redin, *Tetrahedron Lett.*, **39**, 3903 (1998).

81. (a) S. V. Tsukerman, K-S. Chang and V. F. Lavrushin, *Zh. Obshch. Khim.*, **34**, 832 (1964); (b) C. S. Marvel, L. E. Coleman and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).

82. A. Reyes, I. Regla, M. C. Fragoso, L. A. Vallejo, P. Demare, H. A. Jiménez-Vázquez, Y. Ramírez, E. Juaristi and J. Tamariz, *Tetrahedron*, **55**, 11187 (1999).

83. (a) R. Engel, "*Handbook of Organophosphorus Chemistry*", chapter 11. R. Engel, Marcel Dekker: New York, 1992; (b) G. A. Rodan, *Annu. Rev. Pharmacol. Toxicol.*, **38**, 375 (1998).

84. S. E. Kelly, "*Comprehensive Organic Synthesis*", Vol. 1, chapter 3, p. 729. B. M. Trost, I. Fleming, Pergamon Press: Oxford, 1991.

85. K. Inoguchi and K. Achiwa, *Synlett*, 49 (**1991**).

86. (a) Y. Nagaoka and K. Tomioka, *J. Org. Chem.*, **63**, 6428 (1998); (b) M. Mizuno, K. Fujii and K. Tomioka, *Angew. Chem., Int. Ed. Engl.*, **37**, 515 (1998).

87. Y. Nagaoka and K. Tomioka, *Org. Lett.*, **1**, 1467 (1999).

88. Y. Nagaoka, H. Inoue, N. El-Koussi and K. Tomioka, *J. Chem. Soc., Chem. Commun.*, 122 (**2002**).

89. H. Inoue, Y. Nagaoka and K. Tomioka, *J. Org. Chem.*, **67**, 5864 (2002).

90. (a) S. Ghosal, P. S. Ramaballav and R. S. Srivastava, *Phytochemistry*, **13**, 1933 (1974); (b) M. Okigawa, T. Maeda and N. Kawanoe, *Tetrahedron*, **26**, 4301 (1970).

91. K. Kobayashi, Y. Kajimura, K. Maeda, T. Uneda, O. Morikawa and H. Konishi, *Heterocycles*, **45**, 1593 (1997).

92. (a) E. Weiss, *Angew. Chem. Int. Ed. Engl.*, **32**, 1501 (1993); (b) S. S-W. Leung and A. Streitwieser, *J. Am. Chem. Soc.*, **120**, 10557 (1998).

93. M. B. Smith, *Organic Synthesis*, McGraw-Hill: New York, 1994.

94. (a) F. Foubelo and M. Yus, *Tetrahedron Lett.*, **41**, 5047 (2000); (b) C. Strohmann, S. Lüdtke and O. Ulbrich, *Organometallics*, **19**, 4223 (2000); (c) T. Ireland, J. J. A. Perea and P. Knochel, *Angew. Chem., Int. Ed. Engl.*, **38**, 1457 (1999).

95. (a) F. Chen, B. Mudryk and T. Cohen, *Tetrahedron*, **55**, 3291 (1999); (b) T. Cohen, B. Zhang and J. P. Cherkauskas, *Tetrahedron*, **50**, 11569 (1994).

96. D. Cheng, S. Zhu, X. Liu, S. H. Norton and T. Cohen, *J. Am. Chem. Soc.*, **121**, 10241 (1999).

97. B. Mudrik and T. Cohen, *J. Am. Chem. Soc.*, **115**, 3855 (1993).

98. A. Krief and P. Barbeaux, *Synlett*, 511 (**1990**).

99. (a) N. S. Nudelman, E. S. Lewkowicz and D. G. Perez, *Synthesis*, 917 (**1990**); (b) D. G. Perez and N. S. Nudelman, *J. Org. Chem.*, **53**, 408 (1988); (c) N. S. Nudelman, E. S. Lewkowicz and J. P. J. Furlong, *J. Org. Chem.*, **58**, 1847 (1993).

100. P. I. Arvidsson, G. Hilmersson and Ö. Davidsson, *Chem. Eur. J.*, **5**, 2348 (1999).

101. N. Shida, T. Uyehara and Y. Yamamoto, *J. Org. Chem.*, **57**, 5049 (1992).

102. (a) T. Uyehara, N. Shida and Y. Yamamoto, *J. Org. Chem.*, **57**, 3139 (1992); (b) T. Uyehara, N. Shida and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 113 (**1989**).

103. J. G. Urones, N. M. Garrido, D. Díez, S. H. Dominguez and S. G. Davies, *Tetrahedron: Asymmetry*, **8**, 2683 (1997).

104. J. G. Urones, N. M. Garrido, D. Díez, S. H. Dominguez and S. G. Davies, *Tetrahedron: Asymmetry*, **10**, 1637 (1999).

105. (a) R. C. Hartley and S. T. Caldwell, *J. Chem. Soc. Perkin Trans. 1*, 477 (**2000**); (b) A. Deiters and D. Hoppe, *J. Org. Chem.*, **66**, 2842 (2001).

106. D. Cheng, K. R. Knox and T. Cohen, *J. Am. Chem. Soc.*, **122**, 412 (2000).

107. M. Schlosser, "*Modern Synthetic Methods 1992*", p. 227. R. Scheffold, Wiley VCH: New York, 1992.

108. E. Pandolfi and H. Comas, *Tetrahedron Lett.*, **44**, 4631 (2003).

109. S. J. Lange, J. W. Sibert, C. L. Stern, A. G. M. Barret and B. M. Hoffmann, *Tetrahedron*, **51**, 8175 (1995).

110. M. Wenzel, D. Lindauer, R. Beckert, R. Boese and E. Anders, *Chem. Ber.*, **129**, 39 (1996).

111. M. Wenzel, R. Beckert, W. Günther and H. Görls, *Eur. J. Org. Chem.*, 1803 (**1998**).

112. A. Fürstner, "*Active Metals: Preparation, Characterisation, Applications*" Wiley VCH: Weinheim, 1996.

113. W.-C. Zhang and C.-J. Li, *J. Org. Chem.*, **64**, 3230 (1999).

114. S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, **2**, 183 (1991).

115. J. Meisenheimer, *Ber. Dtsch. Chem. Ges.*, **52**, 1667 (1919).

116. A. Albini, *Synthesis*, 263 (**1993**).

117. (a) D. Enders and H. Kempen, *Synlett*, 969 (**1994**); (b) M. T. Reetz and E. H. Lauterbach, *Tetrahedron Lett.*, **32**, 4481 (1991). (c) Y. Yamamoto, J. Oda and Y. Inouye, *J. Org. Chem.*, **41**, 303 (1976).

118. S. G. Davies and G. D. Smyth, *Tetrahedron: Asymmetry*, **7**, 1001 (1996).

119. S. G. Davies and G. D. Smyth, *J. Chem. Soc., Perkin Trans. 1*, 2467 (**1996**).

120. S. Tandel, A. Wang, H. Zhang, P. Yousuf and E. R. Biehl, *J. Chem. Soc., Perkin Trans. 1*, 3149 (**2000**).

121. J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos and M. Trabada, *Org. Lett.*, **4**, 1587 (2002).

122. (a) A. B. Smith III and A. M. Boldi, *J. Am. Chem. Soc.*, **119**, 6925 (1997); (b) H. Shinokubo, K. Miura, K. Oshima and K. Utimoto, *Tetrahedron*, **52**, 503 (1996); (c) K. Takeda, M. Takeda, A. Nakajima and E. Yoshii, *J. Am. Chem. Soc.*, **117**, 6400 (1995).

123. P. Jankowski, P. Raubo and J. Wicha, *Synlett*, 985 (**1994**).

124. K. Takaku, H. Shinokubo and K. Oshima, *Tetrahedron Lett.*, **39**, 2575 (1998).

125. D. L. Comins and S. O'Connor, *Adv. Heterocycl. Chem.*, **44**, 199 (1998).

126. J. W. Cooke, M. J. Coleman, D. M. Caine and K. P. Jenkins, *Tetrahedron Lett.*, **39**, 7965 (1998).

127. L-H. Zhang and Z. Tan, *Tetrahedron Lett.*, **41**, 3025 (2000).

128. (a) A. S. Franklin and I. Paterson, *Contemp. Org. Synth.*, **1**, 317 (1994); (b) C. H. Heathcock, "*Comprehensive Organic Synthesis*", Vol. 2, chapter 1, p. 181. B. M. Trost, I. Fleming, Pergamon Press: Oxford, 1991.

129. X. Sun and D. B. Collum, *J. Am. Chem. Soc.*, **122**, 2452 (2000).

130. (a) Y. Horiuchi, M. Taniguchi, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, **36**, 5353 (1995); (b) A. Baramee, N. Chaichit, P. Intawee, C. Thebtaranonth and Y. Thebtaranonth, *J. Chem. Soc., Chem. Commun.*, 1016 (**1991**).

131. (a) S. Caron, D. Stoermer, A. K. Mapp and C. H. Heathcock, *J. Org. Chem.*, **61**, 9126 (1996); (b) R. Mahrwald and B. Costisella, *Synthesis*, 1087 (**1996**).

132. P. M. Bodnar, J. T. Shaw and K. A. Woerpel, *J. Org. Chem.*, **62**, 5674 (1997).

133. Q. Wang, H-X. Wei and M. Schlosser, *Eur. J. Org. Chem.*, 3263 (**1999**).

134. M. Schlosser, F. Faigl, L. Franzini, H. Geneste, G. Katsoulos and G.-F. Zhong, *Pure Appl. Chem.*, **66**, 1439 (1994).

135. L. Lochman, *Eur. J. Inorg. Chem.*, 1115 (**2000**) and references cited therein.

136. Reviews on use of SBs in organic synthesis: M. Schlosser, *Pure Appl. Chem.*, **60**, 1627 (1988).

137. M. Schlosser, J. H. Choi and S. Takagishi, *Tetrahedron*, **46**, 5633 (1990).

138. N. S. Nudelman, *"The Chemistry of Double-Bonded Functional Group"*, chapter 13. S. Patai, Z. Rappoport, Wiley: Chichester, 1989.

139. D. Seyferth, R. C. Hui and W. L. Wang, *J. Org. Chem.*, **58**, 5843 (1993) and references cited therein.

140. (a) N. S. Nudelman and G. E. García Liñares, *J. Org. Chem.*, **65**, 1629 (2000); (b) N. S. Nudelman, H. G. Schulz, G. E. García Liñares, A. Bonatti and G. Boche, *Organometallics*, **17**, 146 (1998); (c) N. S. Nudelman and H. G. Schulz, *J. Chem. Res., (S)*, 422 (**1999**).

141. (a) A. A. Vitale, F. Doctorovich and N. S. Nudelman, *J. Organometal. Chem.*, **332**, 9 (1987); (b) N. S. Nudelman and A. A. Vitale, *J. Org. Chem.*, **46**, 4625 (1981).

142. G. Maiti, P. Kundu and C. Guin, *Tetrahedron Lett.*, **44**, 2757 (2003).

143. C. J. Collins, G. B. Fisher, A. Reem, C. T. Goralski and B. Singaram, *Tetrahedron Lett.*, **38**, 529 (1997).

144. C. J. Collins, M. Lanz, C. T. Goralski and B. Singaram, *J. Org. Chem.*, **64**, 2574 (1999).

145. S. Thomas, C. J. Collins, J. R. Cuzens, D. Spiciarich, C. T. Goralski and B. Singaram, *J. Org. Chem.*, **66**, 1999 (2001).

146. A. F. Barrero, J. F. Sánchez, J. E. Oltra, D. Teva, R. R. Ferrol, J. Elmerabet, R. G. Del Moral, M. A. Lucena and F. O'Valle, *Eur. J. Med. Chem.*, **29**, 773 (1994).

147. A. R. Katritzky, T.-B Huang, M. V. Voronkov, M. Wang and H. Kolb, *J. Org. Chem.*, **65**, 8819 (2000).

148. G. C. Cotzias, P. S. Papavasiliou, C. Fehling, B. Kaufman and I. Mena, *New Engl. J. Med.*, **282**, 31 (1970).

149. (a) A. N. Hulme, S. S. Henry and A. I. Meyers, *J. Org. Chem.*, **60**, 1265 (1995); (b) A. I. Meyers and *J. Heterocycl. Chem.*, **35**, 991 (1998).

150. A. P. Degnan and A. I. Meyers, *J. Org. Chem.*, **65**, 3503 (2000).

151. T. Hackfort, B. Neumann, H-G. Stammler and D. Kuck., *Eur. J. Org. Chem.*, 2879 (**1999**).

152. B. M. Trost and A. J. Frontier, *J. Am. Chem. Soc.*, **122**, 11727 (2000).

153. M. Murata, T. Oyama, S. Watanabe and Y. Masuda, *J. Org. Chem.*, **65**, 164 (2000).

154. B. A. Chauder, A. V. Kalinin, N. J. Taylor and V. Snieckus, *Angew. Chem., Int. Ed. Engl.*, **38**, 1435 (1999).

155. R. Mutter, I. B. Campbell, E. M. Martin de la Nava, A. T. Merritt and M. Wills, *J. Org. Chem.*, **66**, 3284 (2001).

156. B. M. Trost and G. M. Schroeder, *J. Am. Chem. Soc.*, **121**, 6759 (1999).

157. G. Liu and X. Lu, *Tetrahedron Lett.*, **44**, 127 (2003).

158. D. F. Shriver, *"The Manipulation of Air Sensitive Compounds"*, Wiley, New York, 1989.

159. N. S. Nudelman and F. Doctorovich, *Tetrahedron*, **50**, 4651 (1994).

160. N. S. Nudelman, A. A. Vitale, *Org. Prep. Proc. Int.* **13**, 144 (1981).

161. G. M. Whitesides, C. P. Casey and J. K. Krieger, *J. Am. Chem. Soc.* **93**, 1379 (1971).

162. A. A. Vitale, F. Doctorovich and N. S. Nudelman, *J. Organomet. Chem.*.**332**, 9 (1987).

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