New Methodologies Based on Arene-Catalyzed Lithiation Reactions and Their Application to Synthetic Organic Chemistry

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Keywords: Lithium / Arenes / Catalysis / Organolithium / Synthetic methods

The applications of arene-catalyzed lithiation reactions during recent years are reviewed. This methodology has been used to obtain functionalized organolithium compounds from halogenated as well as nonhalogenated materials, such as heterocycles, sulfones, triflates, ethers, thioethers, amides, and esters. This arene-catalyzed lithiation has also been used in the preparation of polylithiated intermediates. Substoichiometric amounts of the arene may be supported on a polymeric material, its catalytic activity being as efficient as in the solution version.

1. Introduction

The importance of lithium derivatives continues to grow due to the versatility of these reagents in the synthesis of novel inorganic, organometallic, organic, and bioorganic compounds. This widespread use, together with the peculiar properties of lithium due to its small size, has led to a considerable interest in the generation, structures, and reactivity of organolithium compounds. The great volume of experimental and theoretical work makes lithium chemistry a branch of chemistry in itself.[1]

The replacement of hydrogen by lithium in an organic compound is a versatile method for preparing organolithium compounds. The general principle involved in this reaction is, on the one hand, the use of a relatively strongly acidic hydrocarbon ($pK_a \leq 33$) or the presence in the α- or β-position of a heteroatom that increases the kinetic and/or thermodynamic acidity of a particular hydrogen atom, and, on the other hand, the use of a strong base such as an organolithium compound or a lithium amide. However, this method is not available for a wide range of organic starting materials. Another important method for preparing organolithium derivatives is by lithium−halogen exchange. How-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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ever, this method has some disadvantages because it is an equilibium process, which makes the reaction useful only for synthesizing organolithium compounds whose structure enables them to accommodate partial carbanionic character better than the starting organolithium compounds (usually commercially available alkyllithiums). Thus, it is particularly useful for preparing aryl- and 1-alkenyllithium derivatives from the corresponding iodo or bromo derivatives of arenes and alkenes; the corresponding chloro derivatives, however, usually give poor results. Moreover, coupling of the starting organolithium compound with the alkyl halide to give the Wurtz-type product cannot be ignored, although this disadvantage can be partly overcome by using two equivalents of the starting alkyllithium. Other methods for the preparation of organolithium derivatives, starting from other organometallic compounds, from sulfonylhydrazones, or by the addition of organolithium compounds to carbon−carbon multiple bonds, are of less general applicability.

Due to the above mentioned reasons, among the many different methods for preparing organolithium compounds,[2] the direct reduction of organic halides by treatment with lithium metal is, in our opinion, the most direct and versatile procedure. However, the use of polylithiated organic compounds or their functionalized derivatives in organic synthesis has emphasized the need for new methods of preparing these intermediates,[3] which often cannot be obtained from lithium metal alone. To this end, several methods have been described involving activation of the metal,[4] the most popular among these perhaps being to dissolve the lithium metal in a stoichiometric amount of certain arenes,[5] usually naphthalene (Np) or 4,4′-di-*tert*-butylbiphenyl (DTBB). An improvement on this method is the use of sub-stoichiometric amounts of the arenes,[6] this method also being used to prepare highly reactive metals.[7] In this way, some of the problems of obtaining by-products, arising from the reaction of arene anions, may be overcome. The reactivity of this mixture (lithium powder and a catalytic amount of an arene) is different and, in general, is much higher than that in other lithiation procedures.

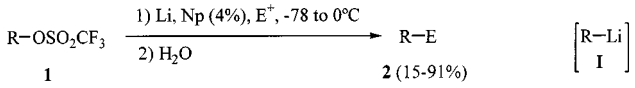
Investigation into the use of arenes as electron shuttles in the preparation of organolithium compounds has been an ongoing concern in these laboratories for some time now.[8] This microreview focuses on efforts made in the last few years to use this lithiation mixture for improving known processes and, perhaps more interestingly, to perform new lithiation processes, which are difficult or impossible to achieve by other methods.

2. Organolithium Compounds from Non-Halogenated Materials

Although the reduction of halogenated compounds with lithium is the most direct way of preparing organolithium derivatives, in some cases the preparation of the appropriate halogenated starting material is difficult or impossible, or the presence of the halogen may even be unsuitable. To overcome this problem, certain functionalities other than halogen may be used as leaving groups in the process of organolithium derivative preparation.[9]

2.1 Reductive Carbon−Oxygen Cleavage

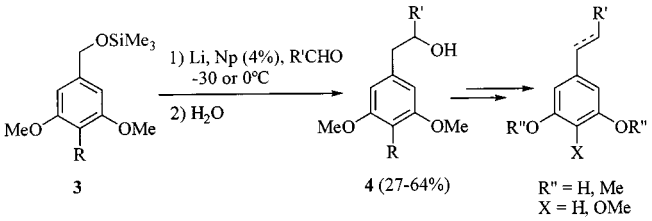
Alkyl triflates **1** are formally transformed into the corresponding alkyllithiums **I** by a lithiation reaction catalyzed by naphthalene and these intermediates react in situ, under Barbier-type conditions,[10] with various electrophiles such as aldehydes, ketones, imines, amides, or disulfides to give, after hydrolysis, the expected products **2**,[11] this method representing a new indirect transformation of alcohols into the corresponding organolithium derivatives (Scheme 1).



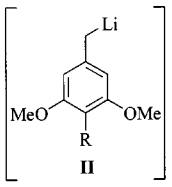
R = Me, Et, MeC≡C(CH$_2$)$_2$, *n*C$_6$H$_{13}$
E$^+$ = *t*BuCHO, PhCHO, 4-MeOC$_6$H$_4$CHO, Me(CH$_2$)$_6$CHO, (CH$_2$)$_5$CO, (*c*C$_3$H$_5$)$_2$CO, PhCOMe, 4-MeC$_6$H$_4$COPh, PhCH=NPh, *n*C$_8$H$_{17}$CON(CH$_2$)$_4$, (PhCH$_2$S)$_2$

Scheme 1

O-Silylated benzylic alcohols **3** can be used as starting materials in the formal preparation of benzyllithiums **II** through a naphthalene-catalyzed lithiation. Their reaction with aldehydes under Barbier-type conditions gives the expected 2-phenylethanol derivatives **4** (Scheme 2), which are easily transformed into several 5-substituted resorcinols such as olivetol, grevillol, dihydropinosilvine, pinosilvine, resveratrol, piceatannol, combretastatin B-4 tetramethyl ether, or chrysotobibenzyl,[12] these compounds possessing a wide variety of biological activities.



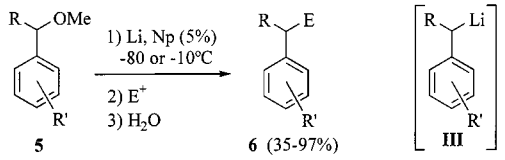
R = H, MeO
R' = Me, *n*Pr, *n*C$_{11}$H$_{23}$, PhCHO, Ph, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$



Scheme 2

Another possible means of preparing these benzyllithium derivatives has recently been reported.[13] In this case, several benzyl methyl ethers **5** can be used as starting materials, which are reduced using an excess of lithium and a catalytic amount of naphthalene, leading to the formation of the cor-

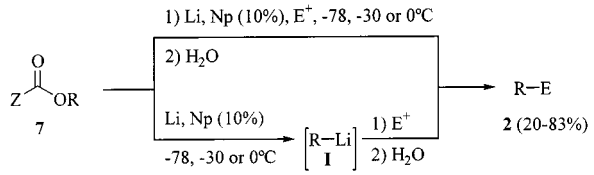
responding benzyllithium derivatives **III**. These then react with various electrophiles giving, after hydrolysis, the expected compounds **6** (Scheme 3).



R = H, Me
R' = Me, MeO, Me_2N, F
E^+ = D_2O, MeI, *n*BuBr, *t*BuCHO, PhCHO

Scheme 3

Benzyl- or allyllithium derivatives can also be prepared from the corresponding pivalates, carbonates, or *O*-benzyl carbamates **7**.[14] Thus, their naphthalene-catalyzed reduction gives the expected organolithium compounds (**I**), which, either in a two-step reaction or under Barbier-type conditions, are trapped with electrophiles to yield after hydrolysis the expected products **2** (Scheme 4). Two aspects of these reactions must be pointed out: firstly, the reaction generally gives better yields under Barbier-type conditions, and secondly, when the reaction is performed using symmetrical carbonates only one of the two possible equivalents of the corresponding organolithium **I** is generated, probably due to decomposition of the allyl- or benzyllithium carbonate intermediate, yielding carbon dioxide and the corresponding lithium alcoholate.



R = CH_2=$CHCH_2$, geranyl, Bzl, PhCHMe
Z = *t*Bu, CH_2=$CHCH_2O$, *t*BuCO, BzlO
E^+ = Me_3SiCl, *i*PrCHO, *t*BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, Ph_2CO

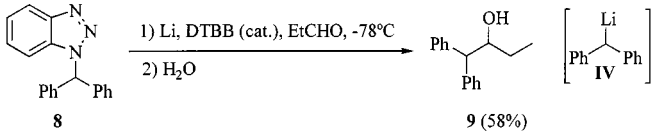
Scheme 4

Very recently, 1-(benzyldimethylsilyl)naphthalene[15] has been introduced in order to prepare ethyl- and phenyllithiums from the corresponding triethyl- or triphenyl phosphates. Here, an excess of lithium is used, with the aforementioned arene in a 5% molar ratio. However, the yields are similar to those obtained from naphthalene-catalyzed lithiations. Alkyllithium derivatives may also be prepared from the corresponding alkyl phenyl ethers through a DTBB-catalyzed lithiation process at temperatures ranging from −40 to 0°C.[16]

2.2 Reductive Carbon−Nitrogen Cleavage

N-Allyl and *N*-benzyl triflamide derivatives may be used as starting materials for preparing the corresponding allyl- or benzyllithium derivatives. Their reactions with lithium powder and a catalytic amount of naphthalene in the presence of electrophiles such as aldehydes and ketones give, after hydrolysis, the expected products in 25−94% yield.[11] It is worthy of note that in this case, when the reaction is performed using *N,N*-diallyl triflamide, two equivalents of the expected allyllithium are generated.

Another nitrogen-containing functionality, playing the role of a leaving group in a reduction catalyzed by DTBB, is benzotriazole.[17] Reaction of the benzotriazole derivative **8** with an excess of lithium and a catalytic amount of DTBB in the presence of propionaldehyde gives, after hydrolysis, the expected 1,1-diphenyl-2-butyl alcohol (**9**), as well as some diphenylmethane, probably due to the abstraction of a proton from the medium by the corresponding organolithium **IV** (Scheme 5).

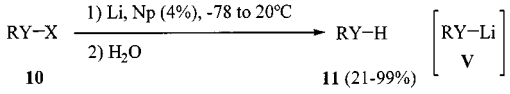


Scheme 5

Finally, *N*-benzyl pivalamide, urea, or carbamate derivatives may be lithiated in naphthalene-catalyzed processes to give the corresponding benzyllithium intermediates of type **I**, which can be trapped in Barbier-type reactions with electrophiles such as aldehydes or ketones affording, after hydrolysis, the expected benzylic derivatives in 30−85% yield.[14]

2.3 Reductive Deprotections

A naphthalene-catalyzed lithiation process has been employed for the reductive deprotection of allyl-, benzyl-, and sulfonyl-substituted alcohols, amines and amides **10** at temperatures ranging from −78 to 25°C (Scheme 6).[18] The chemoselective reductive deprotection of one group in the presence of other protecting groups has also been studied. For example, allyl benzyl ether derivatives can be reduced to the corresponding allyl alcohols without obtaining any benzyl alcohol. *N*-Substituted tosylamides can also be reduced, but the reaction does not proceed with the corresponding mesylamides. However, *N,N*-disubstituted mesylamides are reduced to give, after hydrolysis, the expected secondary amines. In the case of benzyl, allyl, or acyl sulfonamides, the reductive cleavage invariably leads to the corresponding benzyl or allyl amines or carboxamide derivatives, except in the case of *N*-substituted *N*-allyl mesylamides, where the corresponding *N*-substituted mesylamides are isolated in excellent yields. This methodology has recently been extended to sulfonyl aziridines, using DTBB as an electron shuttle, giving, after hydrolysis, the expected aziridine derivatives in 40−85% yield.[19]



Y = O, NH, NR, NBzl, NCOR, NCO_2tBu, $NCONiPr_2$
R = Alkyl, CH_2=$CHCH_2$
X = CH_2=$CHCH_2$, Bzl, Ms, Ts

Scheme 6

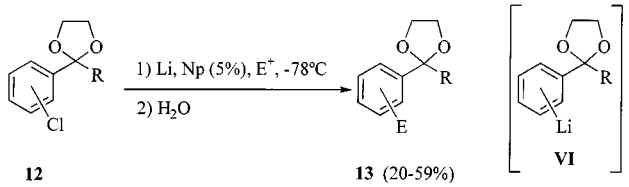
3. Preparation of Functionalized Organolithium Compounds

Functionalized nonstabilized organolithium derivatives[20] are interesting intermediates for the construction of organic structures due to the fact that their reactions with electrophiles usually lead directly to polyfunctionalized molecules. Their stability depends strongly on three factors: (a) the type of functionality, (b) the relative position between the functional group and the lithium atom, and (c) the hybridization of the carbanionic atom.

3.1 Lithiation of Functionalized Halogenated Materials

1-(Benzyldimethylsilyl)naphthalene has been used as an electron shuttle in the lithiation of chlorobenzene and 9-chloroanthracene yielding the expected aryllithium derivatives.[15] A similar process has been used to prepare ketones from alkyl chlorides and carboxylic acids with yields ranging from 18 to 97%, using in this case naphthalene as the catalyst for the lithiation step.[21]

Functionalized halogenated arenes have been submitted to naphthalene-catalyzed lithiations. Thus, lithiation of 2-(chlorophenyl)-1,3-dioxolanes **12** in the presence of carbonyl compounds gives, after hydrolysis, the expected benzylic derivatives **13** with masked carbonyl functionalities,[22] formally *via* the intermediate **VI** (Scheme 7). When the reaction is performed with DTBB as electron shuttle, besides the chlorine/lithium exchange, a reductive opening of the heterocycle takes place, again highlighting the importance of choosing an appropriate arene as the catalyst.

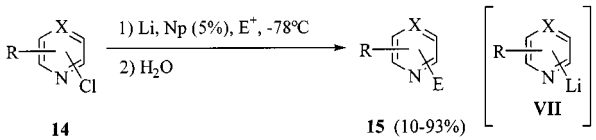


R = H, Me
E^+ = *t*BuCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe

Scheme 7

Naphthalene-catalyzed lithiation of 2-(4-bromophenyl)butan-2-ol has been used to reduce the carbon−bromine bond to afford the corresponding 2-phenylbutan-2-ol, and in this way, to assign the absolute configuration of the starting bromo derivative.[23] In this process, the lithiation and subsequent reaction with water proceed without any racemization.

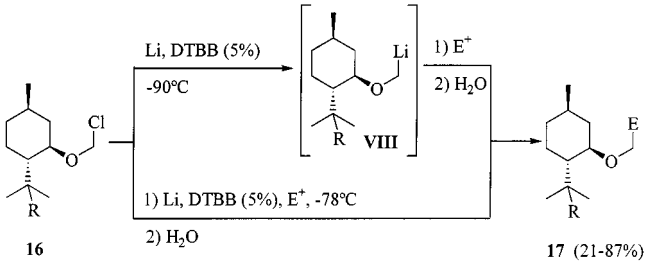
Chlorinated azines **14** have been successfully lithiated by means of a naphthalene-catalyzed process.[24] The reaction proceeds under Barbier-type conditions *via* the intermediate **VII** and is compatible with all types of azines, such as pyridines, quinolines, pyrimidines, pyrazines, and 1,2,3-triazines, even those bearing methyl or methoxy substituents (Scheme 8). When the reaction is carried out in the absence of an arene, a mixture of di-, tri-, and oligoazines is formed initially, which can play the role of the catalyst for the lithiation reaction, therefore giving a lower yield than with the naphthalene-catalyzed process.



X = CH, N
E^+ = *t*BuCHO, PhCHO, Et_2CO, PhCOMe, PhCH=NPh, PhCN

Scheme 8

α-Functionalized organolithium compounds, the so-called "carbenoids", have been prepared from several chlorinated materials. Thus, the DTBB-catalyzed lithiation of chiral chloromethyl menthyl ethers **16** at −90°C gives the expected chiral carbenoids **VIII**, which can be trapped by reaction with various electrophiles (Scheme 9). The same reaction can be performed at −78°C, although the electrophile must be present in order to avoid the corresponding α-elimination.[25] In the case of prostereogenic carbonyl compounds, the diastereomeric ratio never exceeds 65:35.

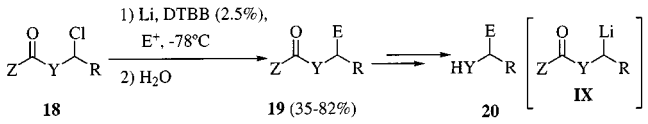


R = H, Ph
E^+ = H_2O, D_2O, Me_3SiCl, *t*BuCHO, PhCHO, Et_2CO, $(CH_2)_4CO$, PhCOMe, Ph_2CO, PhCH=NPh, DMF

Scheme 9

Functionalities other than ether can be used in the generation of α-functionalized organolithiums. Thus, *O*-(α-chloroalkyl) carbamate derivatives **18** (Y = O) can be lithiated in a DTBB-catalyzed reaction under Barbier-type conditions, to afford, after hydrolysis, the functionalized carbamates **19**, formally *via* the intermediate **IX**, which can be deprotected with either DIBALH or lithium hydroxide to give compounds **20**[26] (Scheme 10). This process gives a clear indication that the chlorinated compound **18** can play the role of an α-hydroxy carbanionic reagent of a synthon of the type HOC^-. The aforementioned strategy has been

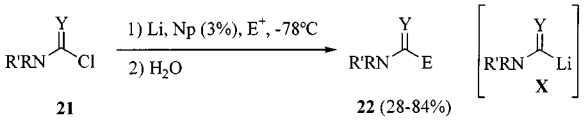
expanded to *N*-(chloromethyl) carbamates **18** (Y = NMe),[27] which were submitted to DTBB-catalyzed lithiation in the presence of various electrophiles to give the expected functionalized carbamates **19**. Their deprotection under acidic conditions yielded the corresponding *N*-methylamino derivatives **20** (Scheme 10).



Y = O, NMe
Z = $(CH_2)_4N$, *t*BuO
R = H, Me, *c*C_6H_{11}
E^+ = Me_3SiCl, *i*BuCHO, *t*BuCHO, PhCHO, 4-MeOC_6H_4CHO, Et_2CO, $(CH_2)_5CO$, *n*PrCOMe, PhCOMe, *n*BuCOPh, Ph_2CO

Scheme 10

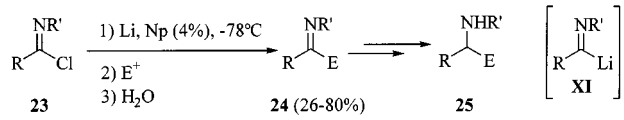
Another class of α-functionalized organolithium compounds comprises the acyllithium intermediates.[28] Reaction of various carbamoyl and thiocarbamoyl chlorides **21** with electrophiles in the presence of excess lithium powder and a catalytic amount of naphthalene leads, after hydrolysis, to the expected amides and thioamides **22**, respectively, through the intermediate **X** (Scheme 11).[29] In the case of allylic or benzylic derivatives, when longer reaction times are used, the corresponding *N*-monosubstituted amides, resulting from a deallylation or debenzylation process, are obtained. When a chiral carbamoyl chloride is reacted with prostereogenic carbonyl derivatives the diastereomeric ratio is never higher than 75:25.



Y = O, S
R, R' = Me, *i*Pr, CH_2=$CHCH_2$, (*R*)-PhCH(Me)
E^+ = EtCHO, *i*PrCHO, *n*BuCHO, *t*BuCHO, PhCHO,4-MeOC_6H_4CHO, Me_2CO, $(CH_2)_5CO$, *i*BuCOMe, PhCOMe, PhNCO

Scheme 11

Imidoyllithium intermediates can also be obtained from the corresponding imidoyl chlorides **23** through a naphthalene-catalyzed lithiation. The lithium intermediate **XI** reacts with electrophiles in a two-step reaction or under Barbier-type conditions to yield, after hydrolysis, the functionalized imines **24**.[30] It must be pointed out that, depending on the reaction conditions, it is also possible to obtain amino derivatives. Thus, longer reaction times and higher temperatures favour reduction of the iminic functionality to the corresponding secondary amine **25** (Scheme 12). In this way, it is possible to obtain α-amino esters in a one-pot process from the corresponding imidoyl chloride and alkyl chloroformate. When the reaction is carried out using menthyl chloroformate as the electrophile, a 1:1 mixture of both diastereomeric α-amino esters is isolated. However, only one diastereoisomeric 1,2-amino alcohol is isolated from this one-pot reaction when it is carried out using a ketone or an aldehyde as the electrophile. The same 1,2-amino alcohol with the same relative *u*-configuration can be obtained by reduction of the previously isolated hydroxy imine with lithium aluminium hydride. In both cases (in situ reduction of the iminic functionality with lithium and naphthalene as catalyst or further reduction with lithium aluminium hydride), the observed relative *u*-configuration can be accounted for in terms of a chelated Cram model.

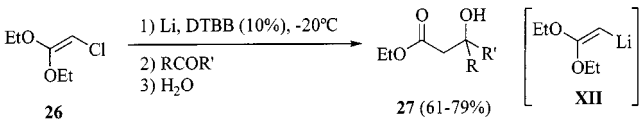


R = *t*Bu, *n*C_6H_{13}, *c*C_6H_{13}
R' = 2,6-$Me_2C_6H_3$, *n*C_8H_{17}
E^+ = *i*PrCHO, *t*BuCHO, PhCHO, Et_2CO, MeOCSCl, menthylOCOCl, *n*C_7H_{15}CON(Me)OMe

Scheme 12

The stability of a β-functionalized organolithium compound is strongly dependent on the hybridization of the carbanionic center. For example, in the case of sp^3-hybridized carbanions, the corresponding β-functionalized organolithium compounds are very unstable and, by a β-elimination process, yield olefins even at very low temperatures.[20] However, this problem may be overcome by transforming the neutral functionality into an anionic one. This strategy has been used, for instance, to reduce a bromohydrin to the corresponding alcohol. Thus, reaction of one equivalent of *n*-butyllithium with 1-bromo-2-phenylpropan-2-ol, followed by reductive naphthalene-catalyzed lithiation of the corresponding alkoxide at −78°C gives the expected organolithium compound, which is trapped by reaction with water to afford 2-phenylpropan-2-ol in practically quantitative yield.[23]

Very recently, Duhamel *et al.*[31] have used a DTBB-catalyzed lithiation of 2-chloro-1,1-diethoxyethene (**26**) to obtain the corresponding organolithium derivative **XII**, which could be trapped by reaction with carbonyl compounds to give, after hydrolysis, the corresponding 3-hydroxy esters **27** (Scheme 13).

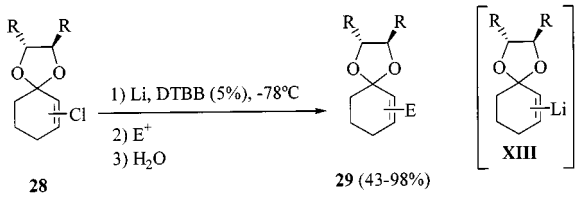


R, R' = H, Me, *i*Bu, Ph; R-R' = $(CH_2)_4$, $(CH_2)_5$

Scheme 13

A similar strategy has been used to prepare α- and β-acylvinyl anion equivalents. DTBB-catalyzed lithiation of α- or β-chloro ketals **28** gives the expected α- or β-functionalized organolithium intermediates **XIII**, which react with various electrophiles to give the expected ketals **29**

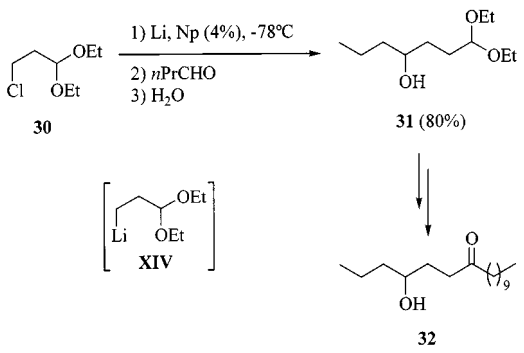
(Scheme 14). Careful deprotection of these ketals affords the expected ketones.[32] It is noteworthy that when the reaction is performed using a chiral α-chloro ketal and pivalaldehyde a ca. 1:1 diastereomeric mixture is obtained.



R = H, Me
E^+ = H_2O, D_2O, Me_3SiCl, *t*BuCHO, PhCHO, Me_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe

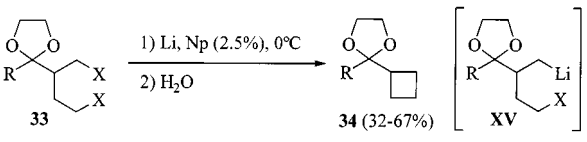
Scheme 14

An sp^3-hybridized masked lithium homoenolate **XIV** has been generated through naphthalene-catalyzed lithiation of compound **30** and trapped with butanal, the product being an intermediate in the synthesis of some biologically active hydroxy ketones, such as compound **32**[33] (Scheme 15).



Scheme 15

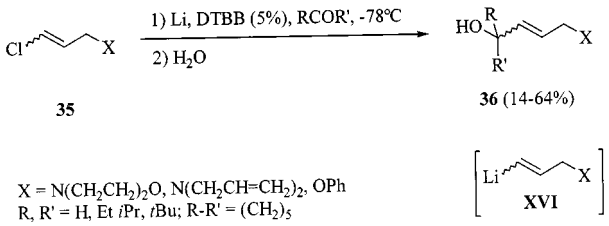
Naphthalene-catalyzed lithiation has also been used to prepare alkyl cyclobutyl ketones. Reaction of the dibromo or diiodo ketal **33** with an excess of lithium ribbon and a catalytic amount of naphthalene gives the expected cyclobutyl derivatives **34** (Scheme 16), probably through the intermediate **XV**, which can easily be deprotected to give the corresponding ketones.[34]



X = I, Br
R = Me, Et, *n*Pr

Scheme 16

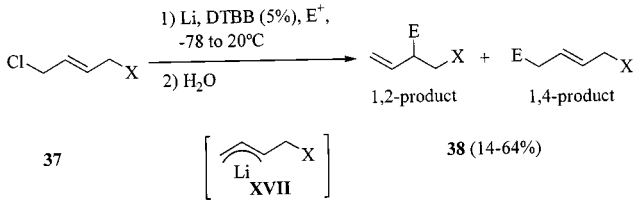
The last example of γ-functionalized organolithium compounds arises from DTBB-catalyzed lithiation of chlorinated allyl *N,N*-disubstituted amines or phenyl ether **35** with formal generation of the intermediate **XVI**, which, after in situ reaction with carbonyl compounds and final hydrolysis, furnishes the expected functionalized allylic systems **36** (Scheme 17).[35] The diastereomeric ratio of the starting materials **35** is not preserved, the *E*/*Z* ratio in the products ranging from a total preference for the *E* diastereomer to a total preference for the *Z* form. This ratio depends only on the electrophile used and on the heteroatom present in the functionality: reaction of a *Z*/*E* mixture of the starting material gives the same *Z*/*E* mixture of products as obtained using purely the *E* starting compound. An explanation for this behaviour might be found in the possible sp^2-carbanion equilibration through the corresponding inversion.[36]



X = $N(CH_2CH_2)_2O$, $N(CH_2CH{=}CH_2)_2$, OPh
R, R' = H, Et *i*Pr, *t*Bu; R-R' = $(CH_2)_5$

Scheme 17

Although δ-functionalized organolithium compounds are usually more stable than those with a shorter carbon chain, the presence of multiple bonds may introduce more difficulties in their preparation and lead to unwanted reactivity.[20] DTBB-catalyzed lithiation of *N,N*-disubstituted chlorobutenamines **37** gives, after in situ reaction with electrophiles and final hydrolysis, a mixture of 1,4 and 1,2 reaction products **38** (Scheme 18), formally *via* the delocalized intermediate **XVII**.[37] The 1,4:1,2 isomeric ratio obtained depends mainly on the electrophile, and is found to range from 11:1 to 1:19.



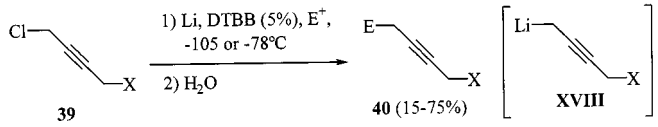
X = $N(CH_2CH_2)_2O$, $N(CH_2CH{=}CH_2)_2$, $NBzl_2$
E^+ = Me_3SiCl, *t*BuCHO, PhCHO, Me_2CO, $(CH_2)_5CO$, $(cC_3H_5)_2CO$

Scheme 18

A δ-functionalized dienic organolithium compound has been prepared through a DTBB-catalyzed lithiation of 4-ethyloxy-2-methyl-1,3-butadienyl chloride, the corresponding organolithium compound being the key intermediate in a synthesis of retinal.[31]

δ-Functionalized propargyllithium reagents **XVIII** can formally be prepared by DTBB-catalyzed lithiation of the corresponding chlorides **39**, their reaction under Barbier-type conditions yielding, after hydrolysis, the expected products **40** (Scheme 19).[38] When the reaction is performed using *N*-substituted propargylamine or propargyl alcohol derivatives, it is not necessary to use one equivalent of a base (e.g. *n*-butyllithium) to deprotonate the starting

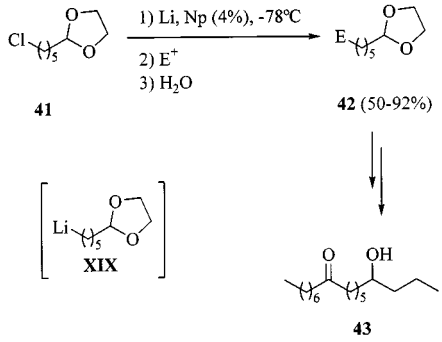
material since the lithium/DTBB mixture is able to reduce the active proton.



X = $N(CH_2CH_2)_2O$, $N(CH_2CH{=}CH_2)_2$, NHPh, OH, OTHP
E^+ = Me_3SiCl, *i*PrCHO, *t*BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$

Scheme 19

Naphthalene-catalyzed lithiation has been used to generate the lithium ε-acetal **XIX** from the corresponding 2-(5-chloropentyl)-1,3-dioxolane **41**, which reacts with various electrophiles to give, after hydrolysis, the expected products **42**.[33] This lithium ε-acetal is the key intermediate in the synthesis of the biologically active hydroxy ketone **43** (Scheme 20).



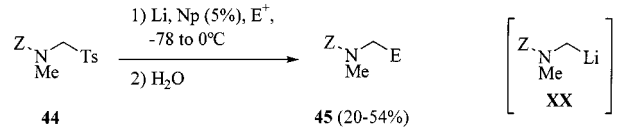
E^+= H_2O, *t*BuCHO, PhCHO, Et_2CO, $(CH_2)_5CO$,
$Me(CH_2)_nCON(Me)OMe$ (n = 5 , 6)

Scheme 20

3.2 Lithiation of Functionalized Sulfur Derivatives

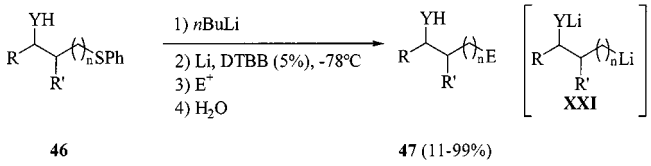
As mentioned above, leaving groups other than halogens can be reduced to allow the preparation of organolithium compounds. One of these is the tosyl group, which can be used to generate α-functionalized organolithium intermediates through naphthalene-catalyzed reductive cleavage.[39] Thus, α-amidomethyl and α-aminomethyl sulfones **44** are reductively cleaved in a naphthalene-catalyzed reaction and the in situ formed α-functionalized organolithium intermediates **XX** are trapped by reaction with various electrophiles affording, after hydrolysis, the expected functionalized amides and amines **45**, respectively (Scheme 21).

An elegant process for obtaining organolithium compounds was introduced by Screttas *et al.*[6e] and involves the reductive cleavage of phenyl thioethers. This approach has recently been used under catalytic conditions to prepare β-[40] and γ-functionalized[40b] organolithium intermediates. Thus, reaction of the corresponding β- or γ-functionalized phenyl thioethers **46** with *n*-butyllithium, followed by treatment with an excess of lithium powder and a catalytic amount of DTBB, affords the expected dilithium intermediates **XXI**, which are trapped by reaction with various electrophiles giving, after hydrolysis, the expected functionalized amines or alcohols **47** (Scheme 22). It must be pointed out that in the case of *trans*-(2-phenylsulfanyl)cyclohexanol, a mixture of *cis* and *trans* products is isolated after the reaction. The observed *cis:trans* ratio depends on the electrophile, from which it is concluded that the corresponding dilithiated intermediates of type **XXI** are not configurationally stable. When (*S*)-1-phenyl-(2-phenylsulfanyl)-propan-1-ol is lithiated and reacted with benzaldehyde, a ca. 1:1 mixture of both epimers is isolated. One important point merits comment: aliphatic and nonsubstituted amines can be used as starting materials, which are not compatible with the other methodologies.



Z = Ph, *t*BuOCO
E^+ = Me_3SiCl, *t*BuCHO, PhCHO, Et_2CO, iPr_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe

Scheme 21

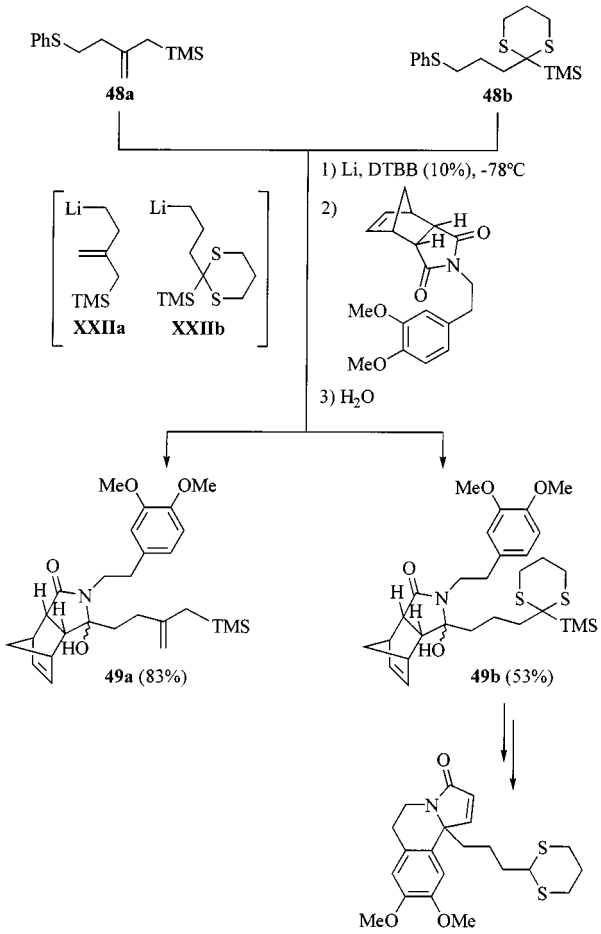


n = 0, 1
Y = NH, N*i*Pr, NPh, O
R, R' = H, Me, nC_6H_{13}, Ph; R-R' = $(CH_2)_4$
E^+ = D_2O, *t*BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$

Scheme 22

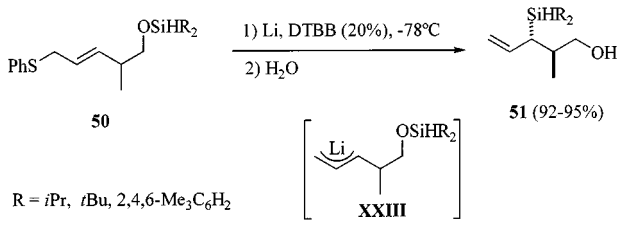
Very recently, two examples of δ-functionalized organolithium intermediates have been reported that permit access to functionalized dihydropyrrolo[2,1-*a*]isoquinolinones.[41] Reductive cleavage of phenyl thioethers **48a** and **48b** using an excess of lithium powder and a catalytic amount of DTBB gives the expected δ-functionalized organolithium intermediates **XXII**, which are trapped by reaction with *N*-[2-(2,3-dimethoxyphenyl)ethyl]-*cis*-norborn-5-ene-2,3-dicarboximide, yielding in both cases, after hydrolysis, the expected products **49**. Product **49b** undergoes further transformation to give the corresponding pyrroloisoquinolinone derivative (Scheme 23).

Substituted allyl phenyl thioethers **50** have been used as starting materials in the diastereoselective synthesis of various polyols. Reductive lithiation of thioethers **50** using DTBB as catalyst gives the corresponding delocalized dialkylsilyloxy organolithium intermediates **XXIII**, which undergo a regio- and stereoselective intramolecular silyl group



Scheme 23

migration to afford the corresponding hydroxyallylsilanes **51** (Scheme 24).[42] This intramolecular migration is the key step for further diastereoselective epoxidation and transformation into various polyols. In the cases tested, the corresponding *u*:*l* relative configuration ratio of diastereoisomers **51** has been found to be higher than 93:7.

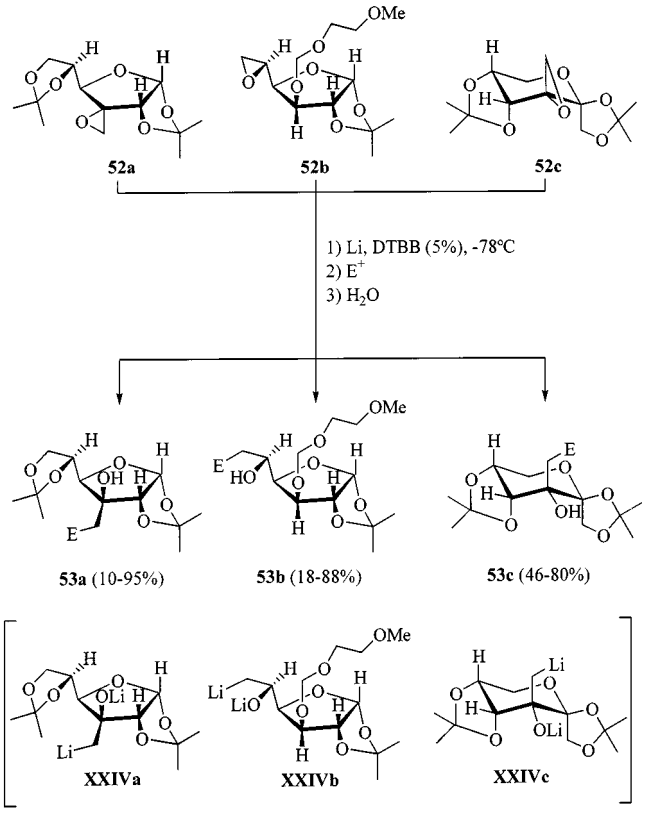


Scheme 24

3.3 Reductive Opening of Heterocycles

An important route leading to functionalized organolithium compounds is the reductive opening of heterocycles.[43] In recent years, we and others have employed this strategy either to prepare new organolithium derivatives or to use them in novel syntheses.

Chiral epoxides have been used as a source of chiral β-oxido-functionalized organolithium compounds.[44] Their generation at low temperature and reaction with electrophiles gives, after hydrolysis, the expected chiral alcohols. Using prostereogenic electrophiles, a ca. 1:1 mixture of both epimers is obtained, this mixture being readily separable by chromatography. This strategy has been used to functionalize carbohydrates such as D-glucose[44c,d] and D-fructose.[44d] The reductive ring-opening of epoxides **52a**,**b** derived from D-glucose and of **52c** derived from D-fructose using lithium powder and a catalytic amount of DTBB gives the expected β-functionalized organolithium derivatives **XXIV**, which can be trapped by reaction with electrophiles yielding, after hydrolysis, the expected functionalized carbohydrates **53** (Scheme 25).

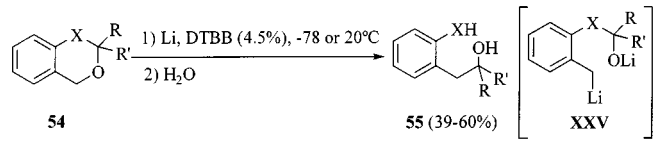


Scheme 25

The reductive ring-opening of oxetanes using 1 equivalent of DTBB and 10 equivalents of lithium in the presence of triethylaluminium has recently been reported. In this way, the reductive cleavage occurs between the oxygen and the more substituted carbon. Presumably, after coordination of the oxetane oxygen atom to the Lewis acid, a one-electron reduction promotes a heterolytic fragmentation of the carbon−oxygen bond to produce the more stable radical.[45]

Other γ-oxygen- or γ-sulfur-containing organolithium intermediates **XXV** can be prepared through the reductive cleavage of benzo-1,3-dioxane and benzo-1,3-oxathiane de-

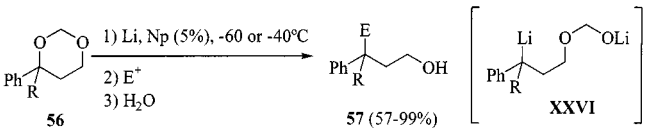
rivatives **54**, using an excess of lithium and a catalytic amount of DTBB. In this way, reduction at the benzylic position liberates the formerly masked carbonyl compound, which is the electrophile in the reaction.[46] After hydrolysis, the expected 2-hydroxyethyl phenols or thiophenols **55** are isolated (Scheme 26).



X = O, S
R, R' = H, Me, *i*Pr, *i*Bu, *t*Bu, $Ph(CH_2)_2$; R-R' = $(CH_2)_5$

Scheme 26

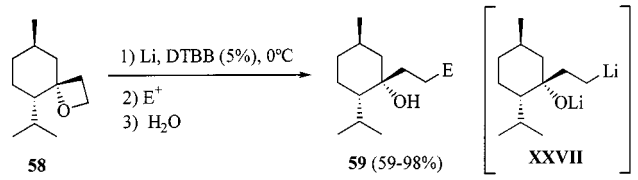
Very recently, reductive cleavage of 4-phenyl-1,3-dioxane derivatives has been used in the preparation of γ-oxido-functionalized organolithium compounds.[47] Thus, naphthalene-catalyzed lithiation of 1,3-dioxane **56** gives the expected γ-functionalized benzyllithium derivatives **XXVI**, which may be trapped by reaction with various electrophiles to afford, after hydrolysis, the expected primary alcohols **57** (Scheme 27).



R = H, Me, Ph
E^+ = H_2O, MeOD, Me_3SiCl, *n*BuBr, *i*PrBr, $C_6H_{13}Br$, *t*BuCHO, Me_2CO, CO_2

Scheme 27

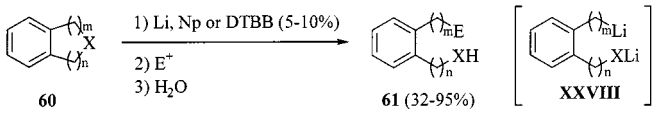
It has been possible to prepare chiral γ-oxido-functionalized organolithium compounds from chiral oxetanes through a DTBB-catalyzed lithiation process.[48] The organolithium intermediate **XXVII** was reacted with various electrophiles giving, after hydrolysis, the expected chiral functionalized alcohols **59** (Scheme 28). Using prostereogenic carbonyl compounds, a ca. 1:1 mixture of epimers is isolated, which can be separated by chromatography.



E^+ = H_2O, D_2O, *t*BuCHO, PhCHO, Me_2CO, $(CH_2)_5CO$, CO_2

Scheme 28

δ-Oxido-functionalized organolithium compounds can be prepared from the corresponding 2,3-dihydrobenzofuran[16] (**60**, $m = 2$, $n = 0$, X = O) by means of a DTBB-catalyzed lithiation, giving the corresponding intermediate **XXVIII**, which is trapped by reaction with various electrophiles to yield the expected functionalized phenols **61** (Scheme 29). Using carbonyl compounds as electrophiles, the hydroxyphenol can undergo cyclization to the corresponding benzopyran under Mitsunobu conditions. The above DTBB-catalyzed lithiation and cleavage has also been applied to benzofuran affording, after reaction with electrophiles and final hydrolysis, the expected alkenyl-functionalized phenols in poor yields.[49]



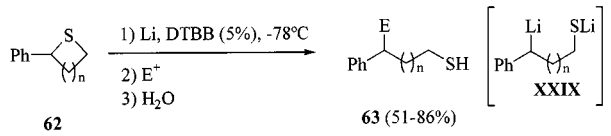
m = 1, 2
n = 0, 1, 2
X = O, S, NPh
E^+ = H_2O, D_2O, Me_3SiCl, MeI, EtBr, *i*PrBr, EtCHO, *i*PrCHO, *i*BuCHO, *t*BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, 2-cyclohexenone, PhCOMe, Ph_2CO, CO_2

Scheme 29

Various δ- and ε-functionalized organolithium compounds have been prepared by reductive cleavage of phthalan[50] (**60**, $m = n = 1$, X = O), isochroman[51] (**60**, $m = 1$, $n = 2$, X = O), thiophthalan (**60**, $m = n = 1$, X = S), thioisochroman[52] (**60**, $m = 1$, $n = 2$, X = S), *N*-phenyl dihydroisoindole (**60**, $m = n = 1$, X = NPh), and *N*-phenyl tetrahydroisoquinoline[53] (**60**, $m = 1$, $n = 2$, X = NPh) by arene-catalyzed lithiation processes, using naphthalene or DTBB as the catalyst and at a cleavage temperature of 20°C for oxygen or nitrogen derivatives or −78°C for the sulfur ones. The reaction with the electrophile must be carried out at −78°C in order to maximize the yield of the desired functionalized alcohol, thiol, or amine **61** (Scheme 29). Using an enone as the Michael acceptor, after reductive cleavage of phthalan, the corresponding functionalized cuprate can be formed by adding copper(I) salts leading to a predominant 1,4-addition.[50d] Several alcohols and thiols, which are obtained from reaction of the corresponding organolithium intermediate **XXVIII** with aldehydes or ketones, may be dehydrated to give the corresponding homologous heterocycles, thereby affording substituted isochromans,[50a−c] isothiochromans, and 3-benzothiepine[52] derivatives.

Some γ-, δ-, and ε-sulfur-containing benzylic organolithium derivatives have been prepared by reductive ring-opening of the corresponding substituted thiacycloalkane **62** through a DTBB-catalyzed lithiation.[54] The organolithium intermediates **XXIX** involved are reacted with electrophiles to afford, after hydrolysis, the expected functionalized thiols **63** (Scheme 30).

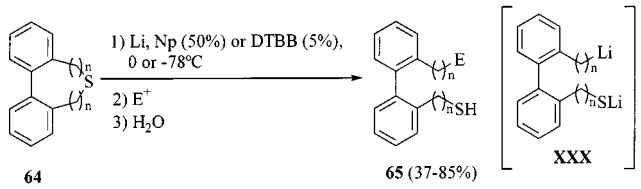
δ-[55a] and ζ-sulfur-containing[55b] organolithium compounds can be prepared through an arene-catalyzed reductive ring-opening lithiation of the corresponding dibenzothiacycles **64**. The corresponding lithium intermediates **XXX** are trapped by reaction with carbonyl compounds to afford, after hydrolysis, the expected sulfanyl alcohols **65** (Scheme 31). Using bis(cyclopentadienyl)titan-



n = 1, 2, 3,
E^+ = D_2O, *t*BuCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, CO_2

Scheme 30

ium dichloride as a di-electrophile, the corresponding thiatitanacycle derivative is obtained. NMR studies on this titanacycle derivative reveal a nonplanar structure for the organosulfur ligand, the free activation energy for its conformational inversion being estimated as 78 kJ/mol.[55a]



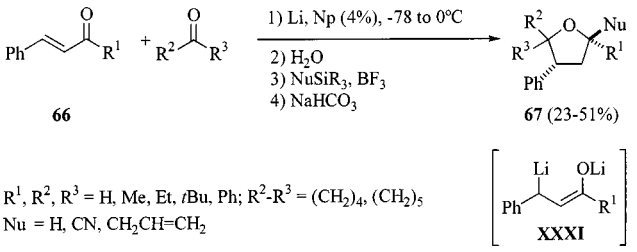
n = 0, 1
E^+ = Me_2CO, Et_2CO, $(CH_2)_5CO$, Cp_2TiCl_2

Scheme 31

3.4 Carbon−Carbon Bond Cleavage

The naphthalene-catalyzed lithiation process has been used for breaking carbon−carbon σ- and π-bonds. Thus, reaction of *meso-N,N′*-dimethyl-1,2-diphenylethane-1,2-diamine with two equivalents of *n*-butyllithium generates the corresponding dilithium amide, which is then reacted with an excess of lithium and 10% naphthalene at room temperature giving, after hydrolysis, the isomerized *l*-diastereoisomer. This isomerization from the *u*- to the *l*-diastereoisomer can be explained in terms of a homolytic cleavage of a carbon−carbon σ-bond, as catalyzed by naphthalene-activated lithium, to give the corresponding lithium amide benzylic radical. Recombination of two radicals gives the most stable dilithium *l*-diamide.[56]

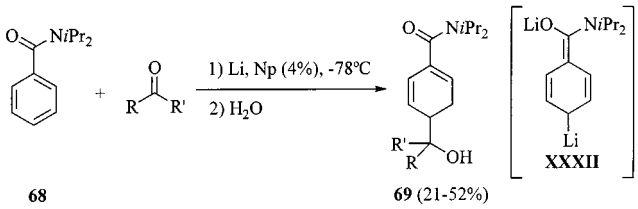
The addition of lithium to carbon−carbon double bonds catalyzed by naphthalene has also been used to prepare functionalized organolithium intermediates. Thus, reaction of 3-phenyl α,β-unsaturated ketones **66** with an excess of lithium powder and a catalytic amount of naphthalene formally affords the corresponding nonmasked lithium homoenolate **XXXI**, which can be trapped by in situ reaction with carbonyl compounds yielding, after hydrolysis, the expected 4-phenyl-5-hydroxypentan-2-one derivatives (Scheme 32). The yields of these ketone derivatives are improved significantly by carrying out the reactions in the presence of BF_3. However, the existence of an equilibrium between the aforementioned hydroxy ketone and the corresponding hemiketal makes difficult the isolation and characterization of these products. To overcome this problem, the above crude mixture is submitted to a BF_3-assisted nucleophilic substitution with silylated nucleophiles in dichloromethane at temperatures ranging from −78 to 20°C, affording the expected tetrahydrofuran derivatives **67**.[57] The observed stereochemistry may be explained in terms of a pseudoaxial nucleophilic attack of the silyl derivative on the more stable conformer of the cyclic oxonium intermediate. When the same naphthalene-catalyzed lithiation reaction is undertaken starting from the corresponding β-arylacrylic esters, the expected lactones can be isolated directly in yields ranging from 36 to 86%.



R^1, R^2, R^3 = H, Me, Et, *t*Bu, Ph; R^2-R^3 = $(CH_2)_4$, $(CH_2)_5$
Nu = H, CN, $CH_2CH{=}CH_2$

Scheme 32

Reaction of *N,N*-disubstituted benzamide derivatives **68** with lithium powder and a catalytic amount of naphthalene in the presence of carbonyl compounds leads to the formation of the corresponding 3,4-dihydro-4-substituted benzamides **69**, formally *via* the intermediate **XXXII** (Scheme 33). The presence of a 4-*tert*-butyl group in the starting benzamide changes the position of the electrophilic fragment so as to give the 3,4-dihydro-4-*tert*-butyl-3-substituted benzamide, the relative configuration being *trans*. When the same reaction is performed with the corresponding methoxybenzamides, only reductive demethoxylation takes place, giving the corresponding substituted aromatic benzamides.[58]



R, R' = H, Et, *i*Pr, *t*Bu

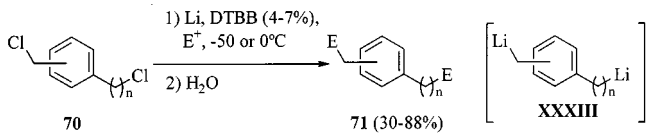
Scheme 33

4. Preparation of Polylithiated Reagents

Polylithium organic intermediates[59] can be prepared following the same methodologies as used for single organolithium compounds, one of them being to use the arene-catalyzed process.

The DTBB-catalyzed lithiation of bis(chloromethyl)benzenes[60a] and chlorobenzyl chlorides[60b,c] **70** under Barbier-type conditions formally gives the expected benzyllithium

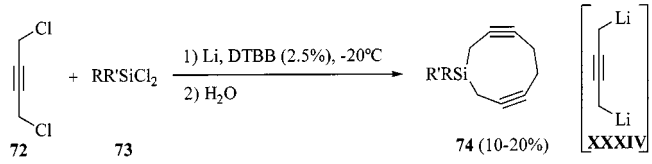
derivatives **XXXIII**, which can then be reacted with various electrophiles yielding, after hydrolysis, the corresponding functionalized compounds **71** (Scheme 34). Using prostereogenic carbonyl compounds, a ca. 1:1 mixture of both diastereoisomers is obtained.



n = 0, 1
E^+ = *i*PrCHO, *t*BuCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe

Scheme 34

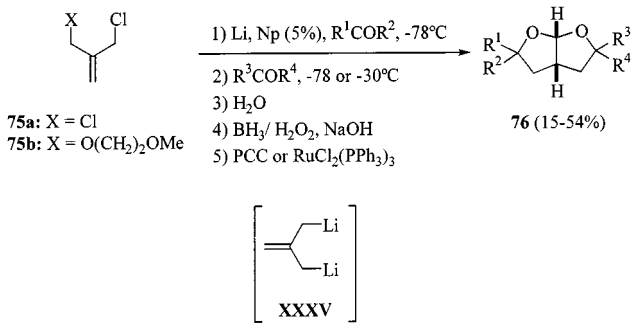
DTBB-catalyzed lithiation has also been used to prepare ethano-bridged cyclic diynes from the corresponding dichloro system (Scheme 35). Lithiation of 1,4-dichlorobut-2-yne (**72**) with an excess of lithium and a catalytic amount of DTBB in the presence of dichlorosilane derivatives **73** gives, after hydrolysis, the cyclic diynes **74**, formally through the intermediate **XXXIV**.[61]



R, R' = Me, $SiMe_3$

Scheme 35

A trimethylenemethane dianion has been used as the key nucleophilic intermediate in the preparation of substituted 1,7-dioxabicyclo[3.3.0]octanes.[62] Reaction of 3-chloro-2-(chloromethyl)-1-propene[62a] (**75a**) with lithium and a catalytic amount of naphthalene in the presence of various carbonyl compounds at −78 °C affords, after hydrolysis, the expected symmetrical methylenic diols, formally *via* the intermediate **XXXV** (Scheme 36). These are then transformed into the corresponding perhydrofurofurans **76** through a tandem hydroboration−oxidation with hydrogen peroxide, followed by treatment with PCC (for ketone derivatives) or $RuCl_2(PPh_3)_3$ (for aldehyde derivatives). These perhydrofurofurans constitute the heterocyclic core of important natural products such as aflatoxins, asteltoxin, and other potent biologically active products. However, it is not possible to introduce two different electrophilic fragments using the dichlorinated starting material **75a**. In order to overcome this inconvenience, 2-chloromethyl-3-(2-methoxyethyloxy)-propene (**75b**) has been used as starting material.[62b] In this case, a sequential naphthalene-catalyzed reductive lithiation is possible, firstly on the carbon−chlorine bond at −78 °C, reacting under Barbier-type conditions with a carbonyl compound, and then the carbon−oxygen bond is cleaved by warming the mixture up to −30 °C, yielding the expected allylic organolithium intermediate. This, in turn, can react with a second carbonyl compound affording, after final hydrolysis, the corresponding unsymmetrical methylenic diols. Following the above described procedure, these can be transformed into the corresponding substituted 1,7-dioxabicyclo[3.3.0]octanes **76**.

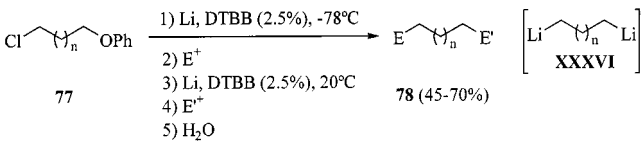


R^1COR^2, R^3COR^4 = *i*PrCHO, *t*BuCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, *t*BuCOMe, PhCOMe, $(cC_6H_{11})_2CO$

Scheme 36

The aforementioned dichlorinated materials **70** and **75a** have been lithiated using a catalytic amount of polymer-supported arene.[63] In this way, at the end of the reaction the catalyst can be removed by simple filtration and may be re-used many times. These polymers are prepared by copolymerization of vinylbenzene, divinylbenzene, and 2-vinylnaphthalene or 4-vinylbiphenyl, and are remarkable in that, generally speaking, the yields they produce are similar to those obtained in solution.

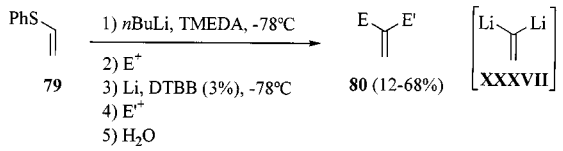
The different reactivities of chlorine−carbon and oxygen−carbon bonds observed in the DTBB-catalyzed reductive lithiation has been used advantageously to prepare 1,3- and 1,4-dilithium intermediates.[55b,64] Thus, low-temperature DTBB-catalyzed lithiation of 3-chloropropyl or 4-chlorobutyl phenyl ether (**77**) leads exclusively to chlorine/lithium exchange, by formation of a functionalized organolithium which can react with an electrophile. Subsequent DTBB-catalyzed cleavage of the phenyloxyalkyl moiety at room temperature generates a new organolithium derivative, which may be trapped by reaction with a second electrophile affording, after hydrolysis, the corresponding 1,5- or 1,6-diols **78** (Scheme 37). Thus, the overall process can be likened to a sequential reaction of an intermediate of type **XXXVI**.



n = 1, 2
E^+, E'^+ = *t*BuCHO, PhCHO, Me_2CO, *n*PrCOMe, $(CH_2)_5CO$

Scheme 37

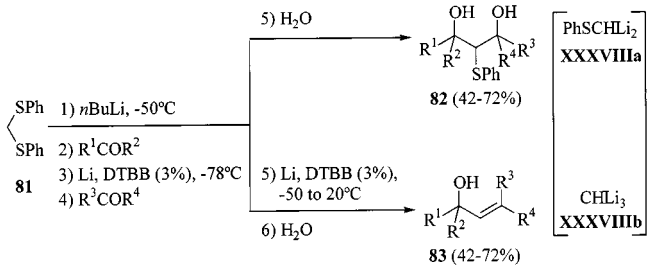
Another possibility is to exploit the capacity of phenyl thioethers to α-stabilize carbanions. In this way, it is possible to prepare 1,1-dilithio intermediates of type **XXXVII** through a sequence of α-deprotonation and reductive cleavage of phenyl thioethers. Thus, abstraction of a proton from the α-position of phenyl vinyl thioether (**79**) with *n*-butyllithium followed by reaction with one equivalent of an electrophile gives the expected product. Then, a one-pot reductive cleavage of the phenyl thioether intermediate using an excess of lithium and a catalytic amount of DTBB, followed by reaction with a different electrophile leads, after hydrolysis, to the methylenic diols **80** (Scheme 38).[65]



E^+, E'^+ = *t*BuCHO, PhCHO, Me_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$

Scheme 38

The aforementioned strategy has also been used with the thio ketal derivative **81**. Thus, a tandem deprotonation reaction with a carbonyl compound followed by reductive cleavage and reaction with a second electrophile leads to the expected phenylthio diol **82**. Depending on the reaction conditions, it is possible to prepare the corresponding allylic alcohols **83** through a reductive cleavage of the phenyl thioether intermediate followed by a spontaneous β-elimination process (Scheme 39).[65] In this case, polylithiated intermediates of types **XXXVIIIa** and **XXXVIIIb** can formally be considered to be involved in the process.



R^1COR^2, R^3COR^4 = *t*BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$

Scheme 39

Phthalan has been used as starting material in the preparation of 1,2-bis(lithiomethyl)benzene. Sequential reduction of each carbon−oxygen bond using an excess of lithium and a catalytic amount of DTBB followed by reaction with various electrophiles permits the multiple functionalization of 1,2-substituted benzene derivatives.[50a]

Conclusion

In summary, this microreview has shown that the arene-catalyzed lithiation process is a powerful method for preparing functionalized organolithium and polylithium intermediates from classical halogenated materials, usually chlorinated materials, as well as from nonhalogenated precursors. This methodology is being increasingly used in preference to lithium or lithium arenide since (a) only a small amount of by-products results from the arene, (b) this mixture shows higher reactivity, and (c) there is no need to remove a large amount of arene at the end of the process. A possible explanation for this higher reactivity may be found in the fact that the excess lithium leads to formation, at least to some extent, of arene dianion species, which are soluble and more powerful lithiating agents compared to the corresponding arene radical anions or lithium metal. The frequency of application of this methodology, as well as the range of amenable starting materials, will undoubtedly increase further in the near future.

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