Arene-catalysed Lithiation Reactions

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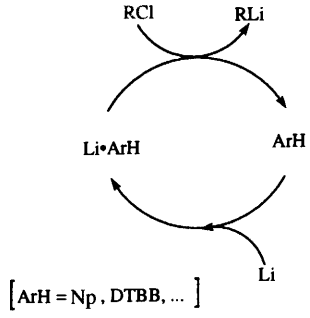
1 Introduction

Organolithium compounds are very useful intermediates in synthetic organic chemistry mainly in carbon–carbon bond forming processes by reaction with carbon electrophiles.[1] Among the different methods to prepare this type of organometallic compound, the most versatile is probably *via* halogen–lithium exchange, bromine and chlorine being the most commonly used halogens. For this purpose commercially available lithium is in general reactive enough to perform this transformation unless the reaction has to be carried out at low temperature; in this case it is necessary to activate the metal.[2] One way to get very active lithium is to dissolve the metal in a stoichiometric amount of an arene,[3] almost always using tetrahydrofuran as solvent. As arenes, naphthalene (Np) and 4,4′-di-*tert*-butylbiphenyl (DTBB) are the most frequently used.

Five years ago[4] we found that the use of a catalytic amount of an arene in the lithiation of functionalised chlorinated precursors is a very powerful method to prepare unstable functionalised organolithium compounds[5] under very mild conditions (Scheme 1). Some advantages of this methodology compared to the use of a stoichiometric amount of arene are: (*a*) yields are similar or better in the catalytic version; (*b*) reaction times are far shorter (1 instead of 8 h); (*c*) reactions are very clean, and form only the desired product (no byproducts resulting from the reaction of the arene radical-anion and the electrophile); (*d*) the method avoids separation of significant amounts of the arene; (*e*) the reaction can be followed by a simple colour change: at the begining (before adding the substrate to be lithiated) the reaction mixture shows the colour of the lithium-arene (dark green for naphthalene and dark blue for DTBB), and after addition of the chlorinated material the colour disappears and the mixture becomes again coloured at the end of the lithiation step, when the substrate has been consumed. Thus no spectroscopic or chromatographic means are necessary to know when the reaction finishes. To the best of our knowledge, before this finding only a few examples had been described in which a catalytic amount of an arene was used as an electron carrier: (*a*) preparation of a strained adamantanol,[6a] (*b*) lithiation of esters,[6b] (*c*) reductive scission of cyclopropylacetylenes[7] and (*d*) reductive opening of oxetane.[8] In addition, in some particular cases, this technique has been applied to the activation of other metals.[9]

In the present review, the synthetic possibilities of the arene-catalysed lithiation will be explored in order to prepare: (*a*) organolithium compounds starting from non-halogenated precursors, (*b*) very unstable functionalised organolithium intermediates and (*c*) polylithium synthons

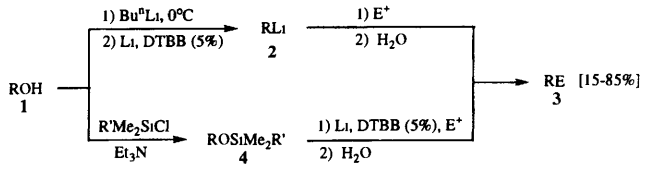


Scheme 1

2 Organolithium Compounds from Non-halogenated Materials

2.1 Reductive Carbon–Oxygen Cleavage

Allylic or benzylic alcohols **1** are transformed into the corresponding organolithium compounds **2** by successive deprotonation with *n*-butyllithium and DTBB-catalysed lithiation; final reaction with different electrophiles gives, after hydrolysis, the expected products **3**. Alternatively, the same reaction products are available starting from the corresponding *O*-silyl derivatives **4**, in this case the catalysed lithiation being performed in the presence of the electrophile (Barbier-type process) (Scheme 2).[10a] Recently, this methodology has been applied to the synthesis of olivetol and related compounds.[10b]



R = CH_2=$CHCH_2$, CH_2=$CMeCH_2$, CH_2=CHCHMe, $PhCH_2$, PhCHMe, geranyl
R′ = Me, Ph
E^+ = Me_3SiCl, Pr^iCHO, PhCHO, Et_2CO, $\overline{CH_2[CH_2]_4CO}$

Scheme 2

Another indirect transformation of alcohols **1** into the corresponding organolithium derivatives consists of their conversion into mesylates **5**. The naphthalene-catalysed lithiation of these materials in the presence of electrophiles yields, after hydrolysis, the expected products **3**. The two-step process can be carried out at

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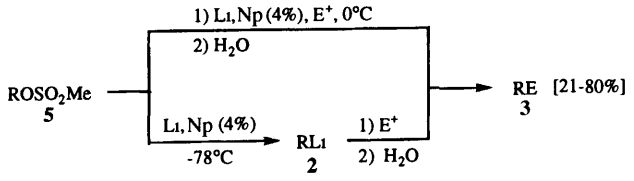
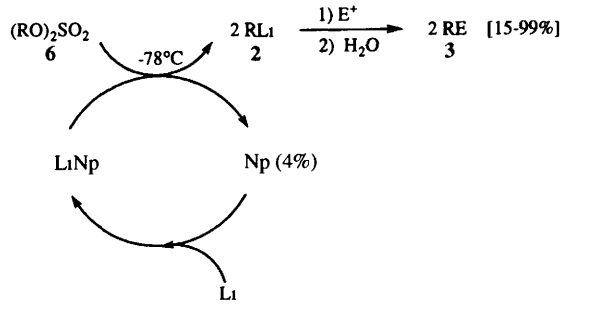
low temperature, so the corresponding solution of the organolithium compound **2** is obtained before the last reaction with the electrophile (Scheme 3) [11]



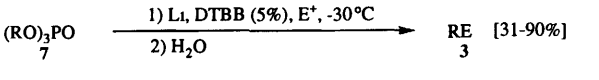
R = CH_3=$CHCH_2$, CH_2=$CMeCH_2$, $PhCH_2$
E^+ = $(PhCH_2S)_2$, Pr^{i}CHO, PhCHO, Et_2CO, $\overline{CH_2|CH_2|_4}CO$, Ph_2CO
Scheme 3

As Schemes 2 and 3 show, the indirect transformation of alcohol derivatives into alkyllithium intermediates is limited to allylic or benzylic systems This limitation has been overcome by working with the corresponding sulfates **6**, in this case the process can be applied to aliphatic derivatives Thus, the two-step process (naphthalene-catalysed lithiation followed by reaction with electrophiles) leads to the expected reaction products **3**, through the corresponding organolithium compounds **2** (Scheme 4) [12a,b] When this methodology is applied to cyclic sulfates derived from 1,3-diols, the corresponding cyclopropanes are easily obtained after the lithiation step [12c]



R = Me, Et, Pr^i, Bu^n, *n* $C_6H_{13}CHMe$
E^+ = $(PhCH_2S)_2$, Pr^{i}CHO, PhCHO, Et_2CO, $\overline{CH_2|CH_2|_4}CO$, Pr^{n}COMe, Ph_2CO
Scheme 4

Another possibility to prepare organolithium compounds indirectly from all type of alcohols is the use of the corresponding phosphates **7** as starting materials and working once again under Barbier-type reaction conditions Thus, using DTBB as the electron transfer catalyst, the expected products **3** are obtained, in which only one group is transferred from the starting phosphate Only in the case of the allyl derivative (it was not possible to prepare the tribenzyl derivative to be tested) are the three allylic moieties converted into allyllithium The facility to form the alkyllithium intermediate, which could be established using mixed phosphates, follows the series allyl ≈ benzyl > phenyl > primary alkyl >> secondary alkyl, that is, in good agreement with the relative stability of the corresponding carbanionic intermediates (Scheme 5) [13]

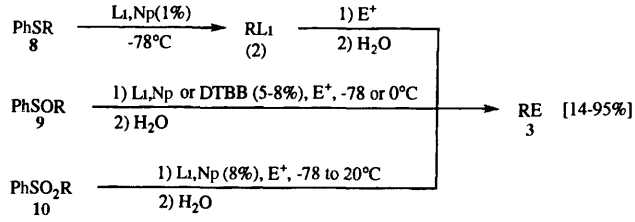


R = Et, CH_2=$CHCH_2$, Pr^i, Bu^n, Ph
E^+ = Me_3SiCl, $PhMe_2SiCl$, PhCHO, Et_2CO, PhCOEt
Scheme 5

Finally, the naphthalene-catalysed lithiation has been used for the preparation of arylmethyllithium reagents from the corresponding methyl ethers [14]

2.2 Reductive Carbon–Sulfur Cleavage

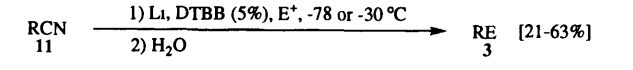
Phenyl sulfides **8** react with lithium powder at low temperature in the presence of a catalytic amount of naphthalene to give the expected alkyllithium compounds **2**, which behave as usual towards electrophiles giving products **3** [4] This reaction has been recently applied to the synthesis of α-silylated organolithium intermediates [15] When the same procedure is used with phenyl sulfoxides **9**[16a] or phenyl sulfones **10**[16a,b] it is necessary to work under Barbier-type reaction conditions in order to avoid decomposition of the *in situ* generated organolithium compound even at low temperatures (Scheme 6)



R = Me, Et, CH_2=$CHCH_2$, Pr^i, $PhCH_2$
E^+ H_2O, Me_3SiCl, Pr^{i}CHO, PhCHO, Et_2CO, $\overline{CH_2|CH_2|_4}CO$, Ph_2CO
Scheme 6

2.3 Reductive Carbon–Carbon Cleavage

Nitriles **11** have been decyanated reductively using a DTBB-catalysed lithiation and working under Barbier-type reaction conditions at low temperature, so the intermediate organolithium compound of type **2** prefers to react with the electrophile present in the reaction medium instead of reacting with the starting nitrile (α-deprotonation or addition to the cyano group) (Scheme 7) [17]

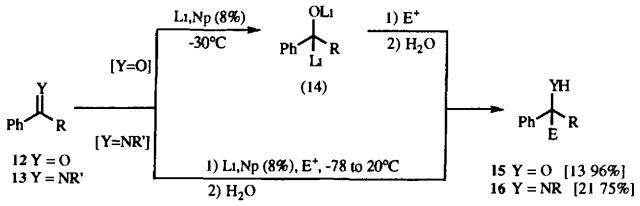


R = Me, Et, c C_3H_5, Ph, $PhCH_2$
E^+ = Me_3SiCl, Pr^{i}CHO, *n* $C_7H_{15}CHO$, Me_2CO, Et_2CO, $\overline{CH_2|CH_2|_4}CO$, Ph_2CO
Scheme 7

3 Preparation of Functionalised Organolithium Compounds

3.1 Lithiation of Phenones and Phenone Imines

Treatment of different phenones **12** with lithium and a catalytic amount of naphthalene yields the dianion **14**, which by reaction with several electrophiles gives, after hydrolysis, the corresponding reaction products **15** (Scheme 8) [18a] When the corresponding imines **13** are used as starting materials the reaction has to be performed at lower temperature and under Barbier-type reaction conditions in order to avoid destruction of the corresponding intermediate of type **14**, after hydrolysis, functionalised amines **16** are prepared (Scheme 8) [18b]

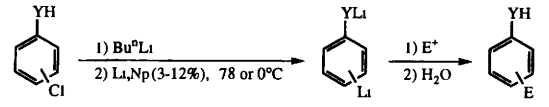


R = H, Me, Ph, 2 MeC_6H_4, 3 MeC_6H_4, 4 MeC_6H_4, 4 $MeOC_6H_4$, 2,4 $Me_2C_6H_3$
R = Me, Ph, c C_6H_{11}
E^+ = MeI, EtBr, Pr^{i}CHO, PhCHO, Me_2CO, Et_2CO, $\overline{CH_2|CH_2|_3}CO$, $\overline{CH_2|CH_2|_4}CO$ MeCN
Scheme 8

3.2 Lithiation of Functionalised Chlorinated Materials

Chlorinated phenols **17** or pivalanilides **20** are transformed into the corresponding dianions **18** and **21**, respectively, by successive

deprotonation with *n*-butyllithium and naphthalene-catalysed lithiation, the subsequent reaction of these intermediates with different electrophiles yields the expected functionalised phenols **19** or anilides **22** (Scheme 9) [19]

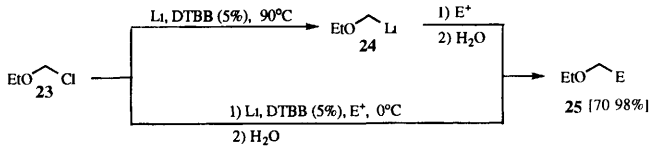


17 Y = O
20 Y = Bu^{t}CON
18 Y = O
21 Y = Bu^{t}CON
19 Y = O [10-78%]
22 Y = Bu^{t}CON [60-90%]

E$^+$ = Pr^{i}CHO, Bu^{t}CHO, Et_2CO, $CH_2[CH_2]_4CO$, PhCN, PhCNO

Scheme 9

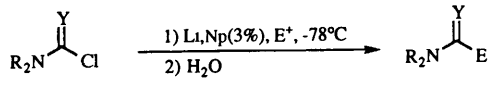
α-Functionalised organolithium compounds, the so-called 'carbenoids,' are very unstable species owing to their tendency to undergo an α-elimination process However, intermediates of the type **24** can be prepared by a DTBB-catalysed lithiation of the corresponding chloroether **23** either in a two-step process at $-90\,^{\circ}C$ or under Barbier-type reaction conditions, working in this case at $0\,^{\circ}C$ Following these two protocols functionalised ethers **25**† are prepared (Scheme 10) [20]



E$^+$ = Bu^{n}CHO, Bu^{t}CHO, PhCHO, Pr$^i_2$CO, Bu$^t_2$CO, $CH_2[CH_2]_4CO$, cyclohex 2 enone, PhCOMe, $PhMe_2SiCl$, CO_2, PhCN, PhCONMe$_2$, cyclo $C_6H_{11}NCO$, PhN=CHPh

Scheme 10

Another type of very unstable α-functionalised organolithium compound are the acyllithium derivatives,[21] namely the corresponding carbamoyl and thiocarbamoyl compounds, which have been prepared *in situ* by naphthalene-catalysed lithiation of the chlorinated precursors **26** and **28**, respectively Working at low temperature and under Barbier-type reaction conditions, the expected functionalised amides **27** or thioamides **29** may be prepared (Scheme 11) [22]

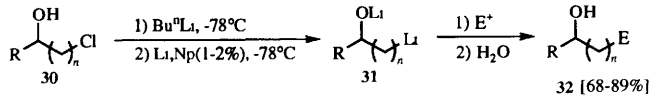


26 Y = O
28 Y = S
27 Y = O [62-79%]
29 Y = S [40-84%]

R = Me, Pr^i
E$^+$ = EtCHO, PhCHO, Me_2CO, PhCOMe

Scheme 11

β-Functionalised organolithium compounds of the type **31** with n = 1 are also very unstable owing to their easy decomposition through a β-elimination process [5] In spite of that, these intermediates and the corresponding γ functionalised derivatives **31** with n = 2 can be prepared at low temperature by successive deprotonation and naphthalene-catalysed lithiation of the corresponding chlorohydrins **30** yielding, after reaction with an electrophile and final hydrolysis, the expected alcohols **32** (Scheme 12) [4]

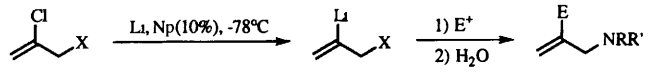


R = Me, Ph
n = 1,2
E$^+$ = H_2O, Pr^{i}CHO

Scheme 12

† With cyclohex 2 enone as electrophile 1 2 addition was the only process observed

The stability of β-functionalised organolithium intermediates can be increased if the metal is attached to an sp^2-hybridised carbon atom An example of this behaviour is the preparation of intermediates **34** by naphthalene-catalysed lithiation of chlorinated allyl amines **33** at low temperature, these species survive under these reaction conditions giving, by treatment with an electrophile followed by final hydrolysis, the expected functionalised allyl amines **35** (Scheme 13) However, the corresponding oxygen- and sulfur-containing derivatives (**34** with X = OR or SR) suffer β-elimination, even at low temperature and/or under Barbier-type reaction conditions, showing as expected, that oxygen- and sulfur-containing groups are better leaving groups than the corresponding nitrogen-containing ones [23]

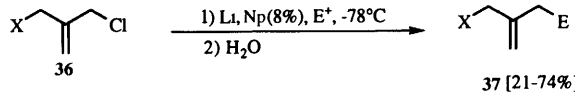


33 X = NRR'
34 X = NRR'
35 [20-77%]

R,R' = Me, Ph, R–R' = $[CH_2]_5O[CH_2]_2$
E$^+$ = Me_3SiCl, Bu^{t}CHO, PhCHO, Me_2CO, (cyclo $C_5H_5)_2CO$, $CH_2[CH_2]_4CO$

Scheme 13

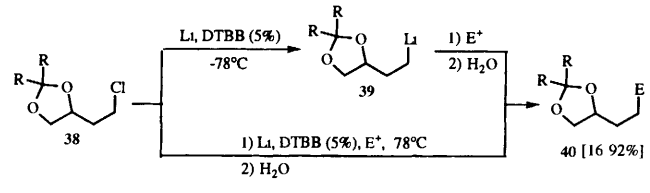
In contrast to the behaviour of systems of the type **33**, the corresponding γ-derivatives resulting from the naphthalene-catalysed lithiation of different oxygen , nitrogen- and sulfur-containing materials **36** can be trapped *in situ* with different electrophiles under Barbier-type reaction conditions giving, after hydrolysis, the corresponding products **37** (Scheme 14) [24] As the starting materials **36** are easily prepared from the corresponding dichlorinated precursor (**36** with X = Cl), the preparation of products **37** represents a successive introduction of a nucleophile X and an electrophile E in the isobutylene skeleton



X = Bu^{n}O, $PhCH_2O$, morpholino, $PhCH_2NMe$, $PhCH_2S$
E$^+$ = Bu^{t}CHO, Et_2CO, $CH_2[CH_2]_4CO$

Scheme 14

γ-Functionalised oxygenated organolithium compounds bearing a protected 1,2-diol moiety of the type **39** have been prepared in a racemic and enantiomerically pure form, depending on the starting material **38** Their low-temperature DTBB-catalysed lithiation can be carried out in a two-step process or in the presence of the electrophile giving, after hydrolysis, products **40**, which are isolated as a 2 1–1 1 diastereoisomeric mixture when the electrophile is prochiral, so the observed asymmetric induction is very low (Scheme 15) [25]

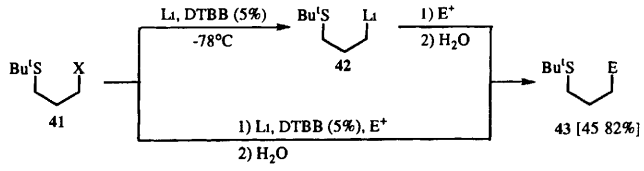


R = R = Me, R–R = $[CH_2]_5$
E$^+$ = Me_3SiCl, Pr^{i}CHO, Bu^{t}CHO, PhCHO, Me_2CO Et_2CO, $CH_2[CH_2]_4CO$, PhCOMe

Scheme 15

Following the same strategy shown in Scheme 15, but combining the effects of both catalysts with the temperature (naphthalene at low temperature and DTBB at room temperature), it is possible to prepare the very unstable sulfur-containing γ-functionalised intermediate **42** from both brominated or chlorinated thioethers **41**, which by reaction with electrophiles leads to products **43** Alternatively, the Barbier-type process performed at ambient temperature affords similar results (Scheme 16) The instability of intermediate **42** arises from the existence of acidic protons at the α

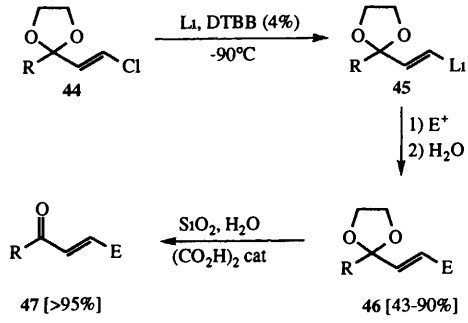
position relative to the sulfur atom Compounds **43** can be easily transformed into the corresponding thiols by reaction with mercury(II) acetate–trifluoroacetic acid followed by treatment with hydrogen sulfide [26]



X = Br, Cl
E^+ = H_2O, D_2O, Me_2S_2, CO_2, Me_3SiCl, Bu'CHO, PhCHO, Me_2CO, $CH_2[CH_2]_4CO$, cyclo-C_3H_5COPh

Scheme 16

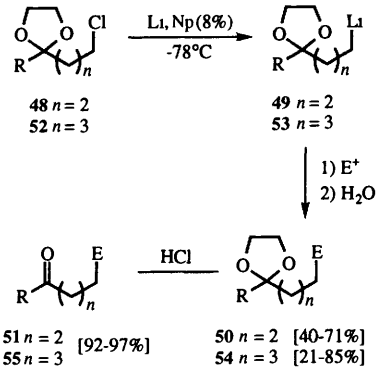
As mentioned above for intermediate **34** (Scheme 13), the presence of a lithium atom attached to an sp^2-hybridised carbon atom stabilises the species This is also the case for the γ-functionalised intermediates **45**, which can be prepared by low temperature DTBB-catalysed lithiation of the starting materials **44** and react with electrophilic reagents to give, after hydrolysis, products **46** The very low temperature used in the lithiation step is necessary to avoid partial decomposition of the chlorinated precursor **44** by dehydrochlorination The final deprotection of compound **46** has to be performed carefully to yield functionalised unsaturated ketones **47** and avoid decomposition of the final products (Scheme 17) [27]



R = Pr^n, Pr^i
E^+ = H_2O, D_2O, Bu'CHO, PhCHO, $CH_2[CH_2]_3CO$, PhCOMe

Scheme 17

Masked high-order lithium enolates† of the type **49** and **53** are interesting intermediates to transfer a remote carbonyl functionality to electrophilic reagents The naphthalene-catalysed lithiation of the corresponding chlorinated precursors **48** or **52** followed by reaction with different electrophiles yields, after under neutral hydrolysis conditions, compounds **50** and **54**, respectively, which could be easily transformed into functionalised ketones **51** and **55** under acidic conditions (Scheme 18) [28] Some of the products prepared are interesting for further synthetic manipulations, thus, when the electrophile is a carbonyl compound, the corresponding hydroxy carbonyl compounds are transformed into alcohols and cyclic ethers using a boron trifluoride-catalysed reaction with silyl derivatives [28a,b] On the other hand, for **48** (n = 2) and using an *O*-protected α-hydroxy carbonyl compound as electrophile, 6,8-dioxabicyclo[3 2 1]octanes are prepared as final products, after acid hydrolysis, some of them (frontalin, brevicomins) being important biologically active molecules [28c] Alternatively, intermediate **49** can also be prepared using lithium–naphthalene (stoichiometric amount of the arene) as lithiating agent [28d–f]

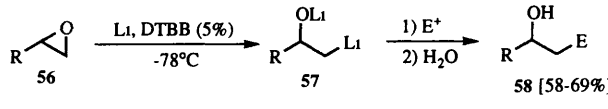


R = H, Me, Et, Ph
E^+ = H_2O, D_2O, $(PhCH_2S)_2$, Pr'CHO, Bu'CHO, PhCHO, Et_2CO, $CH_2[CH_2]_4CO$, $Pr^nCON[CH_2]_3CH_2$, $PhCON[CH_2]_3CH_2$, PhCN, EtOCOCl, PhCH=NPh

Scheme 18

3.3 Reductive Opening of Saturated Heterocycles

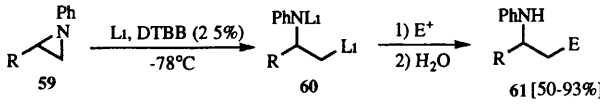
The reductive opening of epoxides, which may be carried out with a stoichiometric amount of an arene,[29a,b] can also be performed in a catalytic fashion starting from chiral epoxides **56** and using DTBB as the electron-carrier agent Thus, *via* chiral intermediates **57**, β-functionalised organolithium compounds, enantiomerically pure products **58** may be prepared (Scheme 19) As described above for intermediates **39** and owing to the high reactivity of this type of functionalised species, asymmetric induction was almost non-existent with prochiral electrophiles Nevertheless, when products **58** are mixtures of diastereoisomers, they can be easily separated by flash chromatography, so giving both diastereoisomers enantiomerically pure This is a typical example of enantiomerically pure compounds (EPC) synthesis [29c] This methodology has been applied to the synthesis of chiral polyols using a protected hydroxy epoxide (**56** with R = $MOMOCH_2$) as starting material



R = Me, $MOMOCH_2$
E^+ = CO_2, Bu'CHO, PhCHO $CH_2[CH_2]_4CO$, PhCOMe

Scheme 19

In contrast to the behaviour illustrated in Scheme 19 for epoxides, aziridines **59** cannot be opened by a lithium–arene reagent However, they suffer reductive opening using a catalytic amount of naphthalene, so β-nitrogenated organolithium intermediates **60** may be prepared, which by reaction with different electrophiles give the expected functionalised amines **61**, after the final hydrolysis‡ A limitation of this reaction is that it works only if a phenyl group is attached somewhere on the aziridine ring Scheme 20 shows the reaction with substituted *N*-phenylaziridines **59** The process has been applied to chiral aziridines [easily prepared from enantiomerically pure (−)-ephedrine], so chiral products of the type **61** are accessible by this methodology [30]



R = H, Me
E = H_2O, D_2O, Me_2S_2, MeI, CH_2=$CHCH_2Br$, Bu'CHO, PhCHO, Me_2CO, $CH_2[CH_2]_4CO$, $(EtO)_2CO$, CH_2=$CHCO_2Me$, $PhCON[CH_2]_3CH_2$, PhCH=NPh

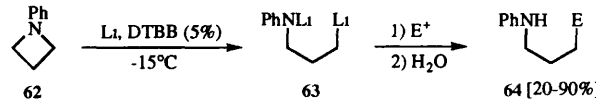
Scheme 20

Azetidines suffer ring opening by means of a DTBB-catalysed lithiation but the process has to be performed at higher temperature in order to obtain a γ-nitrogenated organolithium intermediate,

† These types of intermediates are masked lithium ω enolates in which the lithium atom is attached to a carbon atom different from the corresponding one at the α position with respect to the carbonyl group

‡ Only conjugate additon was observed in the reaction of intermediate **60** with methyl acrylate as electrophile

which by reaction with electrophiles followed by hydrolysis gives the final functionalised amines The process, which also needs the presence of a phenyl group on the azetidine ring, is exemplified in Scheme 21 for the case of the phenyl-azetidine **62**, which *via* the intermediate **63** affords the final products **64** [31]

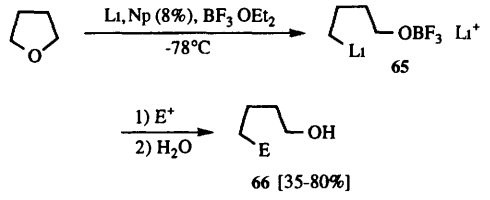


62 63 64 [20-90%]

E^+ = H_2O D_2O CO_2, Bu^tCHO PhCHO Me_2CO $\overbrace{CH_2[CH_2]_4CO}$ PhCH=NPh

Scheme 21

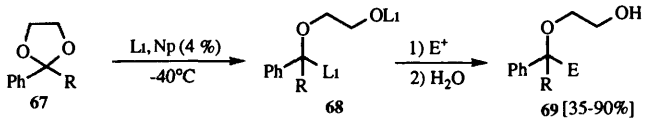
As was mentioned in the Introduction, oxetanes can be reductively opened using a DTBB-catalysed process [8] Tetrahydrofuran itself has been reductively opened using lithium and a stoichiometric amount of DTBB in the presence of boron trifluoride [32a] The catalytic version of this process allows the transformation of tetrahydrofuran into the corresponding intermediate **65**, which reacts with different carbonyl compounds to give, after hydrolysis, the expected 1,5-diols **66** Considering that these reaction products can be easily cyclised to the corresponding tetrahydropyrans under acidic conditions, this methodology represents a homologation of the starting heterocycles (Scheme 22) [32b]



E^+ = Pr^iCHO, Bu^nCHO Bu^tCHO PhCHO, Et_2CO, Bu^tCOMe, PhCOMe

Scheme 22

Substituted 2-phenyl-1,3-dioxolanes **67** are prone to be reductively opened using naphthalene as the catalyst giving dianions **68** and products **69** after successive reaction with electrophiles and hydrolysis (Scheme 23) [33a,b] The same process has been applied to 2-vinyl-1,3-dioxolanes, such as the 2-cyclopentenone derivative **70**, affording products **72** in moderate yields *via* the dianion **71** (Scheme 24) [33c] It is noteworthy that compounds **72** are the corresponding umpoled† variants when compared to the Michael-type addition of a nucleophile to cyclopent-2-enone

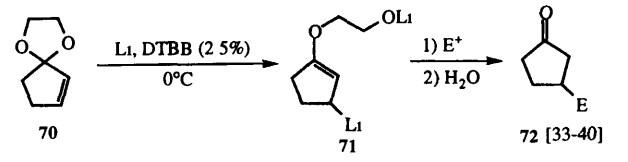


67 68 69 [35-90%]

R = H, Me, Ph

E^+ = H_2O, D_2O, Me_2CO, Et_2CO, $\overbrace{CH_2[CH_2]_nCO}$ (n = 3, 4, 6)

Scheme 23

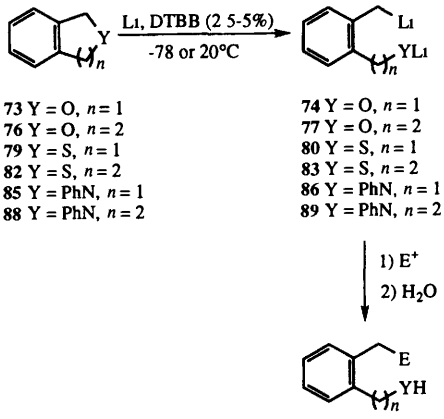


70 71 72 [33-40]

E^+ = Bu^tCHO, Et_2CO, Pr^i_2CO, MeCOEt, $\overbrace{CH_2[CH_2]_4CO}$

Scheme 24

The DTBB-catalysed lithiation of phthalan **73** [34a] and isochroman **76** [34b] affords the corresponding dianions **74** and **77**, respectively, which by treatment with different electrophiles followed by final hydrolysis leads to the formation of products **75** and **78**, respectively (Scheme 25) Diols derived from the reaction of intermediates **74** and **77** with carbonyl compounds are easily cyclised under acidic conditions to give 6- or 7-membered cyclic ethers, so the whole process represents a homologation of the starting materials **73** and **76** Similar results are obtained starting from thio derivatives, namely thiophthalan **79** and thioisochroman **82**, which are easily opened with DTBB as the arene catalyst yielding finally products **81** and **84**, respectively, through the corresponding dianionic intermediates **80** and **83**, respectively (Scheme 25) [34c] Also in this case, the corresponding carbonyl derivatives are easily cyclised to yield 6- or 7-membered cyclic thioethers under acidic conditions Finally, and showing a parallel behaviour, 5- or 6-membered nitrogen-containing heterocycles **85** and **88** suffer reductive opening giving dianions **86** and **89**, respectively, the expected functionalised amines **87** and **90**, respectively, being isolated after reaction with electrophiles followed by hydrolysis (Scheme 25) [34d]



73 Y = O, n = 1
76 Y = O, n = 2
79 Y = S, n = 1
82 Y = S, n = 2
85 Y = PhN, n = 1
88 Y = PhN, n = 2

74 Y = O, n = 1
77 Y = O, n = 2
80 Y = S, n = 1
83 Y = S, n = 2
86 Y = PhN, n = 1
89 Y = PhN, n = 2

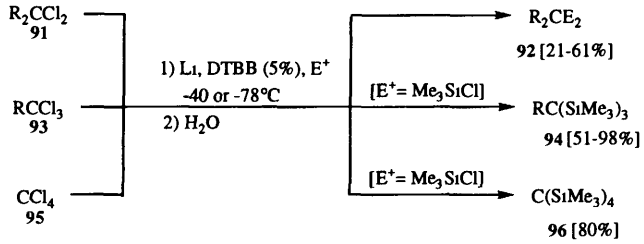
75 Y = O, n = 1 [51-82%]
78 Y = O, n = 2 [44-89%]
81 Y = S, n = 1 [42-89%]
84 Y = S, n = 2 [52-71%]
87 Y = PhN, n = 1 [32-70%]
90 Y = PhN, n = 2 [34 89%]

E^+ = H_2O, D_2O, CO_2, EtCHO, Pr^iCHO, Bu^nCHO, Bu^tCHO, PhCHO, Me_2CO, Et_2CO, Pr^nCOMe, $\overbrace{CH_2[CH_2]_3CO}$, $\overbrace{CH_2[CH_2]_4CO}$, PhCOMe

Scheme 25

4 Preparation of Polylithiated Synthons

Dichloromethane or dideuteriodichloromethane (**91** with R = H,D) are lithiated under Barbier-type reaction conditions using DTBB as the arene catalyst and a carbonyl compound as electrophile to afford, after hydrolysis, the expected 1,3-diols **92** The same process may be applied to substituted trichloromethane **93** or even to tetrachloromethane **95**, in these cases chlorotrimethylsilane being the electrophile used, so persilylated compounds **94** and **96**, respectively, are obtained (Scheme 26) [35]



R = H, D, Me, Ph

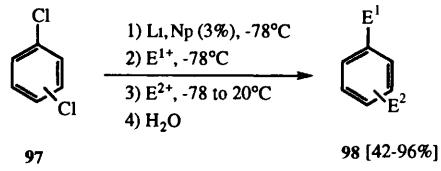
E^+ = Me_3SiCl, Pr^iCHO, Bu^tCHO, Bu^tCHO, $\overbrace{CH_2[CH_2]_3CO}$, $\overbrace{CH_2[CH_2]_4CO}$

Scheme 26

Dichlorobenzene **97** can be sequentially lithiated, with naphthalene as the catalyst, so two different electrophiles can be introduced in the molecule However, only the *meta*- and *para*-derivatives give the expected products **98**, the corresponding monosubstituted compound being the only product isolated starting from *o*-dichlorobenzene (Scheme 27) [19] In this last case the first intermediate,

† The term Umpolung which was introduced by D Seebach (*Angew Chem Int Ed Engl* 1979 **18** 239) means in a general context inversion of the reactivity

o-chlorophenyllithium decomposes under the reaction conditions used, probably taking a proton from the reaction medium, so after the second lithiation the final reaction product arises from phenyllithium as the organometallic component

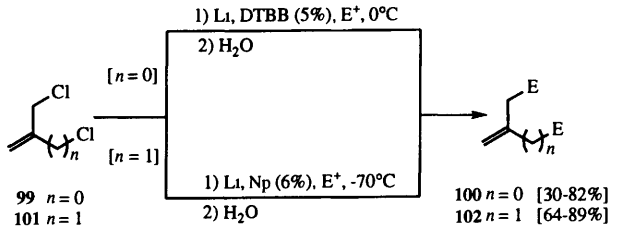


97 **98** [42-96%]

E^{1+} = Bu^{t}CHO, $\overbrace{CH_2[CH_2]_4}$CO
E^{2+} = H_2O, D_2O, Et_2CO

Scheme 27

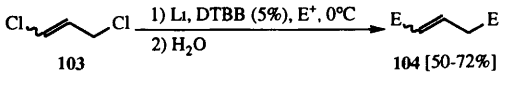
In the case of the dichlorinated propene **99**[23,36a] or isobutene **101**[24,36b] it is neccessary to work under Barbier-type reaction conditions in order to avoid decomposition of the intermediate dilithiated species Working with DTBB (for **99**) or naphthalene (for **101**) the expected products **100** and **102** are, respectively, obtained, using in all cases a carbonyl compound as electrophile (Scheme 28)[23,34,36] Diol derivatives **100** and **102** are easily cyclised to the corresponding cyclic ethers under acidic reaction conditions



E^+ = Pr^{i}CHO, Bu^{t}CHO, PhCHO, Me_2CO, Et_2CO, Pr^{n}COMe, Pr^i_2CO, $\overbrace{CH_2[CH_2]_n}$CO (n = 3, 4, 6), PhCOEt

Scheme 28

A *ca* 1 1 mixture of diastereoisomers of 1,3-dichloropropenes **103** is easily lithiated in the presence of a catalytic amount of DTBB and an electrophile to give, after hydrolysis, the corresponding *ca* 1 1 diastereoisomeric mixture of products **104**, which in the case of the *Z*-diastereoisomer can be cyclised to the corresponding dihydropyrans (Scheme 29)[37]



103 **104** [50-72%]

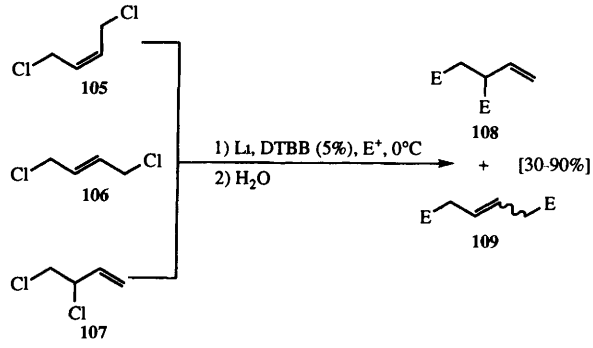
E^+ = Me_3SiCl, Bu^{t}CHO, Me_2CO, Et_2CO, $\overbrace{CH_2[CH_2]_3}$CO, $\overbrace{CH_2[CH_2]_4}$CO

Scheme 29

The DTBB-catalysed lithiation under Barbier-type reaction conditions of the three isomers of dichlorobutene **105**, **106** and **107**, gives, after reaction with an electrophile and final hydrolysis, the same mixture of 1,2- and 1,4-reaction products (**108** and **109**, respectively) and the same *Z*/*E* molar ratio for **109**, independently of the starting material used This fact would suggest that the intermediates derived from **105**—**107** are the same (Scheme 30)[38]

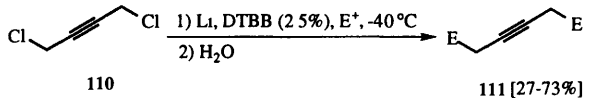
Finally, 1,4-dichlorobut-2-yne **110** is lithiated under DTBB catalysis and in the presence of an electrophile giving the corresponding diaddition products **111** (Scheme 31)[39]

Concerning probable mechanistic pathways involved in the lithiation of polychlorinated materials under Barbier-type reaction conditions described in this section, two possible routes may be involved (*a*) a sequence of lithiation reactions with the electrophile and (*b*) the formation of polylithiated intermediates In general, and owing to the high instability of polylithiated species, we think that the most probable pathway involves the route (*a*) In all cases the lithiated intermediate resulting from the first lithiation would decompose (by elimination processes or proton abstraction from the reaction media) if the electrophile were not present in the reaction



E^+ = Me_3SiCl, Bu^{t}CHO, $\overbrace{CH_2[CH_2]_3}$CO

Scheme 30



E^+ = Me_3SiCl, Bu^{t}CHO, Me_2CO, Et_2CO, $\overbrace{CH_2[CH_2]_n}$CO (n = 3, 4, 6)

Scheme 31

mixture, so the Barbier-type reaction conditions are essential in order to get successful results

5 Conclusions

From the results shown in this review it can be concluded that the arene-catalysed lithiation of different substrates (non-halogenated precursors, functionalised chlorinated materials, saturated heterocycles and polychlorinated compounds) is a powerful methodology for preparation of a wide range of very reactive or unstable organolithium intermediates, which are versatile species in synthetic organic chemistry A question remains to be answered why is the catalytic version more effective than the stoichiometric one? A possible explanation could be that in the presence of a deficiency of the arene, the excess of lithium provokes the formation, at least to some extent, of the corresponding arene-dianion (from the initially formed arene-radical anion) This dianionic species is very powerful as a reduction (lithiation) agent For this reason, most of the reactions described in this review do not work with a lithium–arene mixture (stoichiometric ratio) under the reaction conditions described here, on the other hand, when the process was successful in the stoichiometric version, yields were lower and reaction times were significantly longer In addition, combining an arene-catalysed lithiation with Barbier-type reaction conditions (performing the reaction in the presence of the electrophile) the method is very effective in some cases, mainly when polychlorinated compounds are used as synthons for polylithium intermediates

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