

Functionalised organolithium compounds by sulfur–lithium exchange

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Multifunctional organic molecules can be accessed by reacting functionalised organolithium compounds (they can be prepared following a great number of different methodologies) with electrophilic reagents, this fact makes these intermediates of relevant interest in synthetic organic chemistry. Sulfur containing molecules have been used extensively as precursors of organolithium compounds by applying two different methodologies. One is the well-known α -deprotonation, which is not going to be the subject of this review, and the other methodology consists of sulfur lithium exchange by using lithium metal either alone or in the presence of a stoichiometric or catalytic amount of an arene. In some special cases, for instance in *gem*-dithio- or 1,1,1-trithiosubstituted compounds, sulfur lithium exchange can be performed by means of an alkylolithium reagent. The following *tutorial review* is ordered on the basis of the relative position of the functional group and the carbanionic center, with special mention to the application of these intermediates in organic synthesis.

1. Introduction

Among functionalised organometallic compounds,¹ the corresponding lithium derivatives² are of special interest due to their high reactivity, even under very mild reaction conditions, which is based on the high polarity of the carbon–lithium bond (*ca.* 60% ionic character).³ These intermediates are, in general, unstable species that need to be prepared at low temperatures in order to avoid their decomposition, mainly either by elimination^{2a,b,d} processes or by proton abstraction from the reaction medium.⁴ The arene-promoted lithiation both in the stoichiometric⁵ or catalytic version⁶ is one of the most important methodologies for that purpose. In general, the procedures to generate functionalised organolithium compounds (**1**) are the same as those used for normal organo-

lithiums:⁷ (a) deprotonation from activated materials **2**; (b) halogen–lithium exchange from halogenated precursors **3**; and (c) tin- or mercury–lithium transmetallation from organometallics **4**. In addition, for intermediates **1** a new route consisting in the ring opening of heterocycles **5**⁸ has emerged recently as a versatile technique and very efficient from an atom economy point of view.⁹ A new way to prepare functionalised organolithiums of type **1** has emerged, consisting of sulfur–lithium exchange, mainly from phenyl thioethers **6**, and this topic is the subject of this review (Scheme 1).

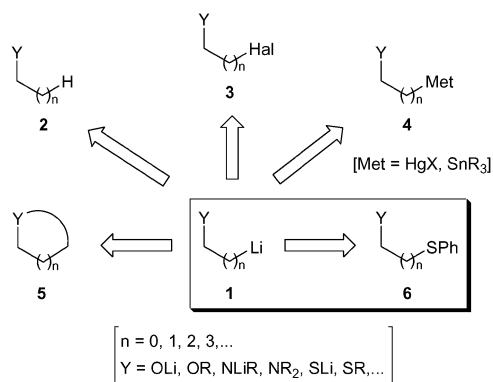
The reductive cleavage of the alkyl carbon–sulfur bond of phenyl thioethers **I** is performed using single electron transfer (SET) reactions. The source of the electrons could be the lithium metal itself (a heterogeneous process that is not efficient at low temperatures) or the THF soluble arene radical anion that results from dissolving the lithium in a stoichiometric amount of the arene [naphthalene (C₁₀H₈), 4,4'-di-*tert*-butylbiphenyl (DTBB) and 1-(dimethylamino)naphthalene (DMAN) are the most frequently used].⁵ However, the use

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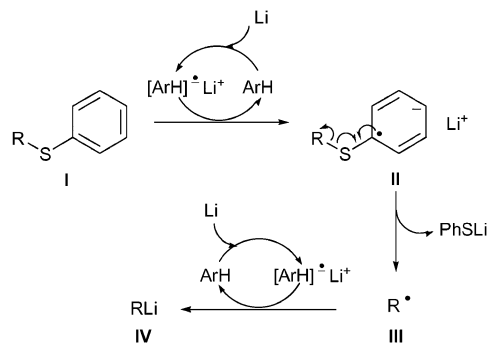
Francisco Foubelo (left) and Miguel Yus (right)

Francisco Foubelo is a professor at the University of Alicante. His research interests are focused on the development of new synthetic methodologies for the preparation of functionalised organolithium compounds. Heterofunctionalisation of alkenes and the development of new synthetic methods for asymmetric synthesis related to chiral sulfinimines are recent interests. Miguel Yus was born in Zaragoza (Spain) in 1947 and became full professor in 1987. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante where he is currently the director of the Organic Synthesis Institute. Professor Yus has been visiting professor at several top universities and is author to more than 400 papers mainly in the field of the development of new methodologies involving organometallic intermediates.



Scheme 1

of a catalytic amount of an arene was also effective in these processes and showed advantages: no by-products, resulting from the reaction of the arene radical anion with the electrophile, were formed in significant amounts, and purification of the reaction products was much easier.⁶ Radical anions of these arenes are highly reactive species that can act as a reductant (transferring one electron) or as a base. The radical anion of DTBB is more stable than the one derived from naphthalene (the cheapest one), which shows a more basic character. The only advantage of using DMAN in these processes is that it can be easily removed from the reaction medium by performing an acidic work-up. Regarding the mechanism, phenyl thioether **I** accepts an electron from the arene radical anion to give a new highly reactive radical anion **II** and the arene, which in the presence of an excess of lithium regenerates the reductive species. Intermediate **II** exclusively undergoes dissociation of the alkyl carbon–sulfur bond to form lithium phenylthiolate and the alkyl radical **III**.¹⁰ Finally, a second electron transfer yields the expected organolithium compound **IV** (Scheme 2). Functional groups which are susceptible to reduction under these reaction conditions (*e.g.* carbonyls, nitro, nitrile, *etc.*)² are not compatible with this methodology.



[ArH = C₁₀H₈, DMAN, DTBB]

Scheme 2

2. α -Functionalised organolithium compounds

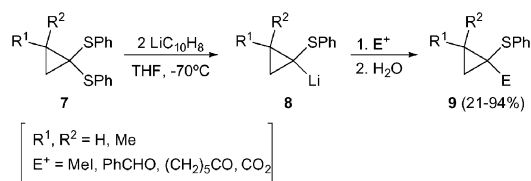
There are several examples of α -oxygen, -nitrogen, -silicon and -sulfur functionalised organolithium compounds with sp³

hybridisation in acyclic and cyclic systems. Except for the sulfur and silicon derivatives, these compounds show a tendency to undergo α -elimination processes to generate carbene intermediates.

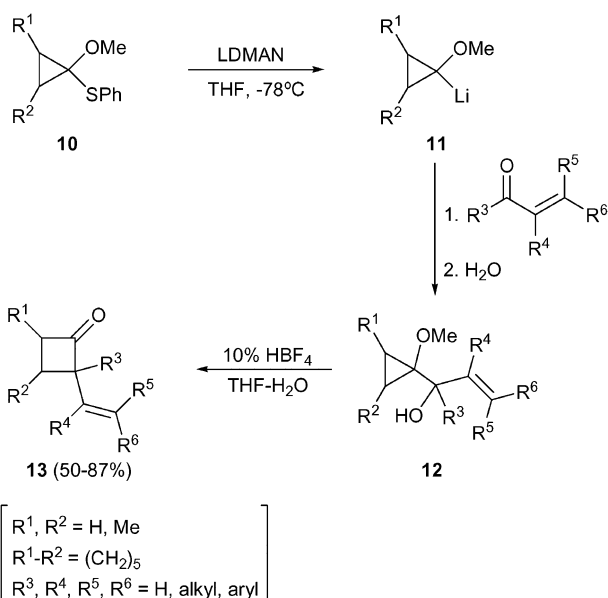
Cohen *et al.* reported for the first time in 1978 the preparation of α -functionalised organolithium compounds through a sulfur–lithium exchange¹¹ by reductive metalation of readily available cyclopropane dithioketals **7**. They found that the reduction, using two equivalents of lithium naphthalenide^{5a} in THF at -70°C , led to sulfur-stabilised cyclopropyl anions **8** in higher yields, shorter reaction times and under milder conditions than using *tert*-butyllithium in THF at 0°C , or lithium metal in a mixture of ether and hexamethylphosphoric triamide. The reaction of intermediates **8** with electrophiles gave substituted cyclopropanes **9** in good yields (Scheme 3). Almost at the same time, Screttas and Micha-Screttas found that the *gem*-disulfide *n*-BuCH(SPh)₂ underwent cleavage with either two equivalents of lithium naphthalenide or with a lithium dispersion in THF and a catalytic amount of naphthalene.¹² The resulting lithio derivative *n*-BuCH(Li)SPh was not accessible through metalation of the corresponding alkyl aryl thioether with *n*-butyllithium.

Deprotonation of an α -carbon atom of an ether that has a special anion-stabilising feature is a way of preparing α -lithioethers. In addition, a variety of unstabilised and stabilised α -lithioethers were prepared in tetrahydrofuran at -63 or -78°C from the corresponding α -(phenylthio)ether by reductive lithiation with lithium 1-(dimethylamino)naphthalenide (LDMAN) or lithium naphthalenide.¹³ Thus, the reductive lithiation of 1-phenylthio-1-methoxycyclopropanes **10** with LDMAN led to anionic intermediates **11**, which upon reaction with α,β -unsaturated aldehydes or ketones gave 1-cyclopropylallyl alcohols **12**. Acid catalysed rearrangement of alcohols **12** produced 2-vinylcyclobutanones **13**, interesting intermediates in the synthesis of cyclohex-3-enones (Scheme 4).¹⁴ Conversion of carbinols **12** to cyclobutanones **13** can be carried out in the absence of protonic acids by treatment with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine.¹⁵

2-Phenylthiosubstituted tetrahydrofurans and tetrahydropyrans **14** are easily accessible from the corresponding lactones. These compounds are suitable substrates for the preparation of the corresponding α -lithio derivatives **15** upon treatment with two equivalents of LDMAN at low temperature. The reaction of intermediates **15** with carbonyl compounds yielded the expected alcohols **16**, after hydrolysis with water. This methodology was applied to the synthesis of (\pm)-*trans*-rosoxide (**17**) (Scheme 5).¹⁶ Tetrahydropyran derivatives of type **15** with a vinylic substituent at C-6 undergo totally stereoselective competing [1,2]- and [2,3]-Wittig



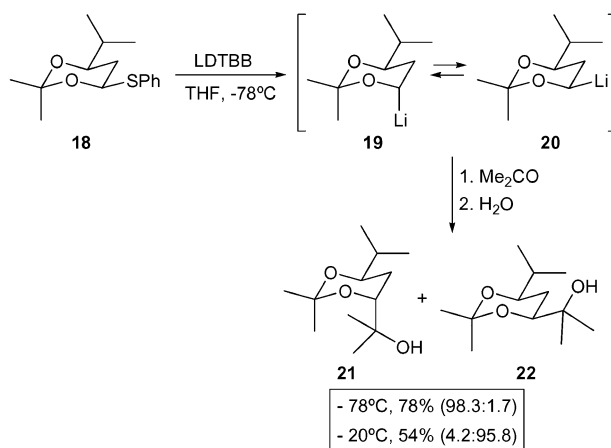
Scheme 3



Scheme 4

rearrangements with inversion of the configuration at the lithium-bearing carbon atom.¹⁷

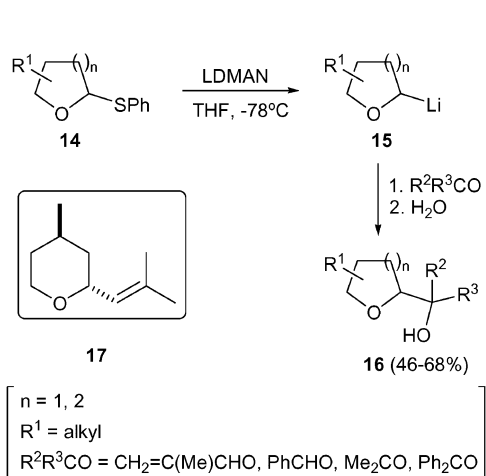
Concerning the stereochemistry of the lithiation in tetrahydropyran derivatives, axial 2-lithiotetrahydropyrans are the products of reductive lithiation of 2-(phenylthio)tetrahydropyrans, but they equilibrate to the more stable equatorial organolithiums. For instance, Rychnovsky and Mickus proved that the reduction of *cis*-4-phenylthio-1,3-dioxane **18** with two equivalents of lithium 4,4'-di-*tert*-butylbiphenylide (LDTBB) at -78°C followed by addition of acetone at the same temperature led, after hydrolysis, to a 98.3 : 1.7 mixture of axial and equatorial products **21** and **22**, respectively. The same results were obtained starting from the *trans*-4-phenylthio-1,3-dioxane, the stereochemistry of the alkyl lithium **19/20** in these systems being independent of the stereochemistry of the starting material. However, if after lithiation of **18** at -78°C , the resulting reaction mixture is maintained at -20°C for 30 min, the addition of acetone followed by hydrolysis yielded a 4.2 : 95.8 mixture of axial and equatorial



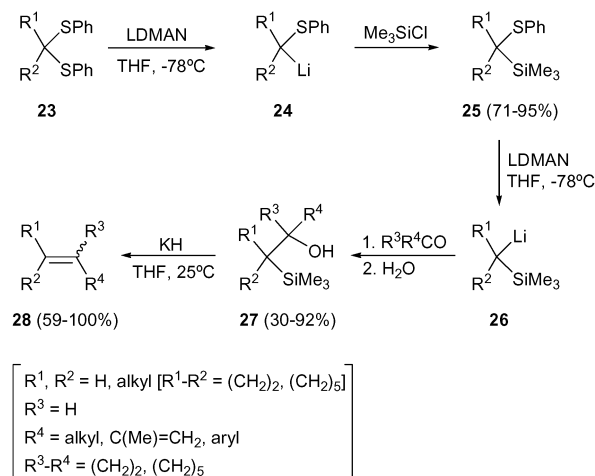
Scheme 6

products (Scheme 6). So, the epimerisation results were strongly dependent upon the temperature.¹⁸

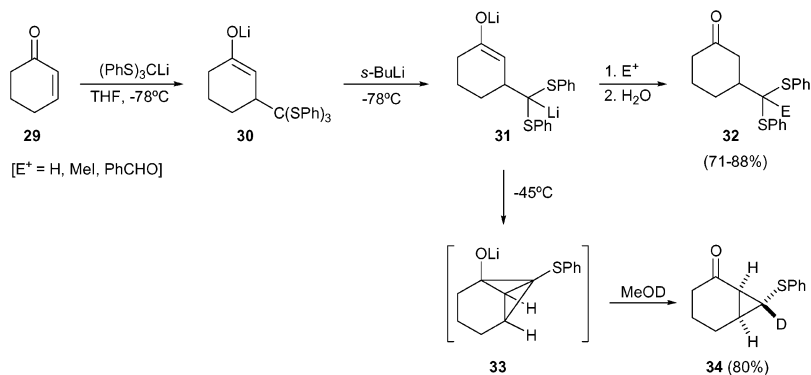
Cohen *et al.* developed also a convenient method for the preparation of stabilised α -lithiosilanes **26** starting from diphenyl thioacetals **23**. It consisted of the reductive lithiation of diphenyl thioacetals with LDMAN, followed by treatment of the resulting intermediate **24** with trimethylsilyl chloride, and a subsequent reductive lithiation of the resulting α -(phenylthio)silane **25** with the same reducing agent.¹⁹ The generality of the procedure was demonstrated by the preparation of α -lithiosilanes **26**, in which the negatively charged carbon atom was secondary, tertiary, vinylic, or part of a cyclopropyl ring. These species reacted with aldehydes and ketones to produce, after hydrolysis, alcohols **27**, which in all cases (except the allylic alcohol produced from the vinylic α -lithiosilane) could be induced to form an olefin **28** by loss of the elements of trimethylsilanol upon treatment with potassium hydride or acid (Peterson olefination; Scheme 7).²⁰ Allylidene cyclopropanes, which were prepared following the previously reported methodology (using α,β -unsaturated aldehydes as electrophiles), showed synthetic interest because they underwent thermal rearrangement either in a sealed tube or in a flash vacuum pyrolysis apparatus to give among other products cyclopenteno-cyclohexenes or -cycloheptenes (hydroazulenes).^{21,22}



Scheme 5



Scheme 7

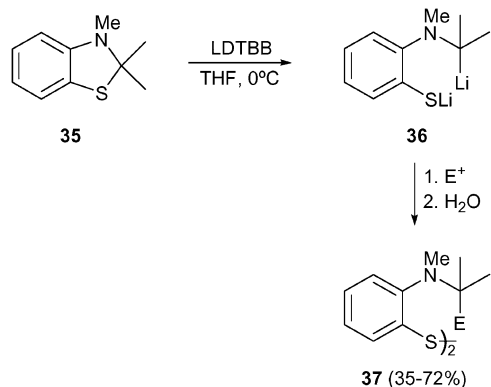


Scheme 8

The lithium enolate **30**, formed by the addition of tris(phenylthio)methyl lithium to 2-cyclohexen-1-one (**29**), reacted with *sec*-butyllithium at $-78\text{ }^{\circ}\text{C}$ to form a highly stabilised enolate thioacetal dianion **31**, which can be considered an α -sulfurfunctionalised organolithium compound. In this case, *sec*-butyllithium was used as the lithiating reagents instead of lithium metal in the presence of an arene. Dianion **31** reacted with different electrophiles at the thioacetal carbanionic site to give ketones **32**, but alkylating agents bulkier than methyl iodide are unreactive toward this site (Scheme 8).²³ A similar dianion was produced when (–)-carvone was the substrate; in this case, the conjugate addition took place from the side opposite the isopropenyl

substituent and upon low-temperature decomposition of carbenoid **31** a cyclopropanation took place. There are evidences that this process proceeded through the lithium bicyclo[1.1.0]butan-2-olate intermediate **33**, which can be trapped by *O*-deuterated methanol to give cyclopropyl ketone **34** (Scheme 8).²⁴

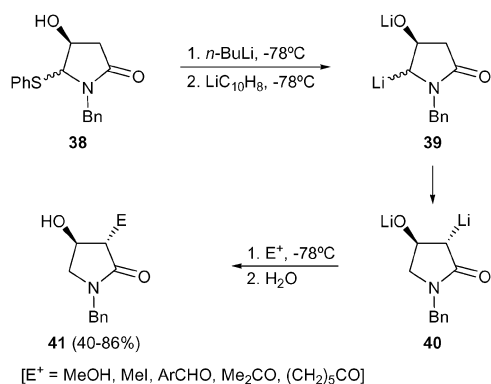
Florio *et al.* found that trimethylbenzo-1,3-thiazolidine (**35**), in which the sulfur atom is attached to a fused aromatic ring, was reductively opened by LDTBB at $0\text{ }^{\circ}\text{C}$ to give the dianion **36**, a non-stabilised tertiary α -amino organolithium compound. The reaction of this intermediate with electrophiles, followed by hydrolysis and subsequent oxidation, gave polyfunctionalised disulfides **37** (Scheme 9).²⁵



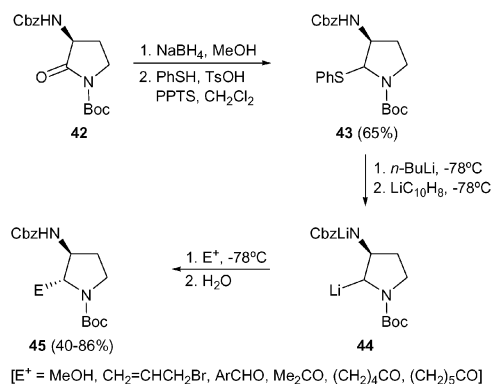
Scheme 9

Other examples of α -nitrogen functionalised organolithium compounds obtained from a sulfur–lithium exchange were reported by Huang's group. Thus, successive treatment of the phenyl thioether **38** [derived from (*S*)-malic acid] with *n*-butyllithium, lithium naphthalenide, and electrophiles at low temperature led to 4-hydroxy-3-substituted 2-pyrrolidinones **41** in a one-pot process and with high regio- and diastereoselectivity at C-3. The initially formed organolithium compound **39** isomerised to the more stable enolate derivative **40**, which reacted with electrophiles to yield compounds **41** (Scheme 10).²⁶

The phenyl sulfide derivative **43** was obtained from 3-amino-2-pyrrolidinone **42** as a single diastereomer in good yield. Applying the same strategy as shown in Scheme 10 to compound **43** (deprotonation with *n*-butyllithium, followed by sulfur–lithium exchange with lithium naphthalenide) led to an α,β -diamino functionalised organolithium compound **44**, which after reaction with electrophiles and final hydrolysis gave pyrrolidine derivatives **45** in good yields and high



Scheme 10



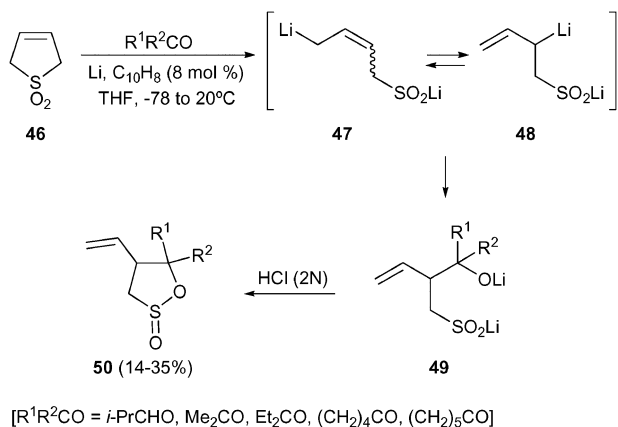
Scheme 11

stereoselectivities (Scheme 11). This strategy was applied to the synthesis of the alkaloid (+)-absoulone.²⁷

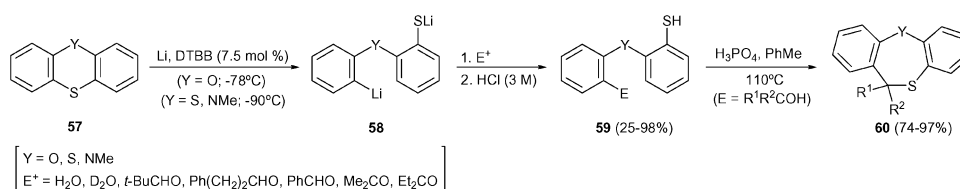
3. β -Functionalised organolithium compounds

Organolithium compounds bearing a functional group at the β -position are unstable species. They show a great tendency to undergo a β -elimination process to give olefins; the better the leaving group the higher instability. The hybridisation of the carbon atom attached to the lithium also plays an important role in the stability of these systems, sp^2 derivatives being considerably more stable than sp^3 ones. Electropositive metals in the presence of a proton source have shown to be very effective for the reductive cleavage of carbon–sulfur bonds in sulfones and sulfoxides. It was possible to generate an organolithium compound from these functional groups under anhydrous reaction conditions. Thus, the reaction of commercially available cyclic sulfone sulfolene (**46**) with an excess of lithium and a catalytic amount of naphthalene in the presence of a carbonyl compound (Barbier type reaction conditions) in THF at temperatures ranging between -78 and 20 °C gave, after acidic hydrolysis, cyclic sulfinates **50** in modest yields. The isolation of compounds **50** can be explained considering the equilibrium between intermediates **47** and **48**. The low yields obtained could be due to a possible δ - or β -elimination from **47** and/or **48** to give 1,3-butadiene. The reaction of β -sulfur functionalised allylic organolithium compound **48** with aldehydes and ketones led to alcoholates **49**, which under the work-up acidic conditions cyclised to yield the obtained reaction products **50** (Scheme 12).²⁸

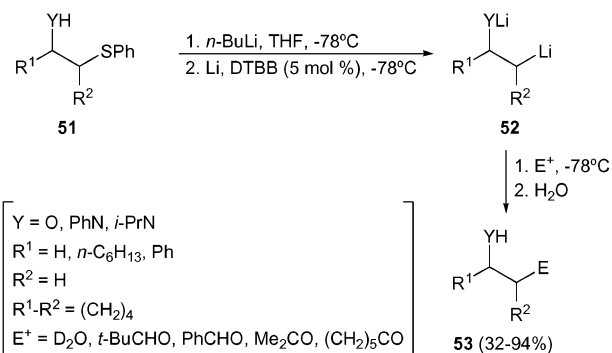
Highly reactive β -oxygen and β -amino functionalised organolithium intermediates **52** were also accessible from different



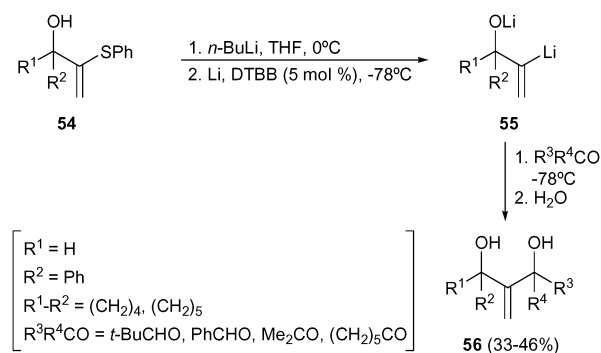
Scheme 12



Scheme 15



Scheme 13



Scheme 14

β -hydroxyl and β -phenylamino and β -isopropylamino phenyl thioethers **51** by first deprotonation with *n*-butyllithium followed by a sulfur–lithium exchange by means of an excess of lithium in the presence of a catalytic amount of DTBB at -78 °C. One way to prevent the decomposition of β -functionalised organolithium compounds is by making the development of a negative charge on the heteroatom. The reaction of intermediates **52** with electrophiles, and final hydrolysis, led to the formation of functionalised alcohols and amines **53** in a completely regioselective manner (Scheme 13).²⁹

Following the same methodology as above, sp^2 β -oxygen functionalised organolithium compounds **55** were prepared starting from allylic alcohols **54**. The reaction of intermediates **55** with carbonyl compounds led, after hydrolysis, to the corresponding methylenic 1,3-diols **56** in moderate yields (Scheme 14).³⁰

Reductive opening of 4-hetero-substituted dibenzothiins **57** [phenoxathiin (Y = O), phenothiazine (Y = NMe), and thianthrene (Y = S)] with an excess of lithium and a catalytic amount of DTBB at low temperature gave the corresponding β -functionalised organolithium intermediates **58**, which by reaction with different electrophiles and final hydrolysis

afforded the expected functionalised thiols **59**. The cyclisation of some carbonyl compound derivatives **59** gave the corresponding homologous seven-membered dibenzo heterocycles **60** (Scheme 15).³¹

4. γ -Functionalised organolithium compounds

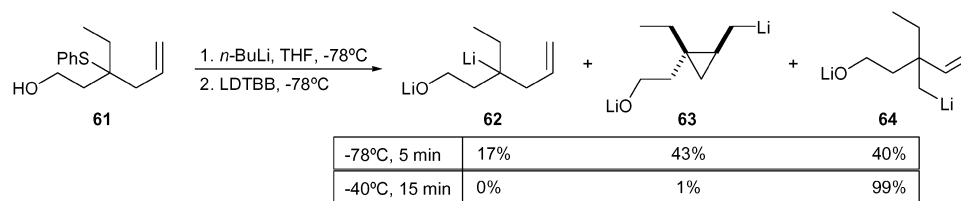
Organolithium compounds with a functional group at the γ position can be represented by a great number of general structures depending on the hybridisation of the carbon atoms bearing both the lithium and the functional group. These intermediates are considerably more stable than the previously mentioned β -functionalised ones.

Mudryk and Cohen found that secondary and tertiary homoallyllithiums, which can be prepared readily by reductive lithiation of the corresponding phenyl thioethers, can often be induced to rearrange to less substituted and more stable homoallyllithiums *via* intermediate (cyclopropylcarbinyl)-lithiums. They discovered also that this process is considerably accelerated when lithium alkoxides are present in the substrate. For instance, deprotonation of the alcohol derivative **61** followed by reductive cleavage of the carbon–sulfur bond with LDTBB at -78°C initially produced the γ -oxydo functionalised organolithium compound **62**. However, after 5 min at that temperature, addition of isobutyraldehyde gave a mixture of reaction products derived from intermediates **62**, **63** and **64**. Only 17% of **62** remained unrearranged, cyclopropyl derivative **63** and rearranged homoallyllithium **64** being the major

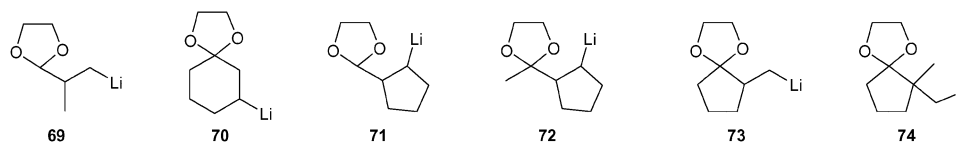
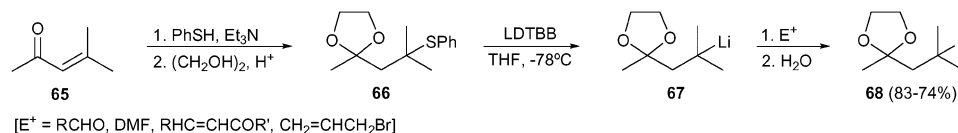
intermediates. When the reaction mixture was allowed to warm to -40°C , the open chain primary homoallyllithium **64** was the most stable form of the anion, so was therefore the only anion trapped (Scheme 16).³²

Several homoenolate synthetic equivalents were also prepared by reductive lithiation with lithium 4,4'-di-*tert*-butylbiphenylide (LDTBB) from the acetals of β -(phenylthio)carbonyl compounds. These substrates are easily accessible, for instance in the case of **66**, by thiophenol addition to the enone followed by acetal formation. Reductive cleavage of the carbon–sulfur bond in compound **66** led to the γ -functionalised organolithium compound **67**, which reacted with electrophiles to yield, after hydrolysis, polyfunctionalised compounds **68**. Homo enolate synthetic equivalents **69–74** were prepared through this methodology (Scheme 17).³³

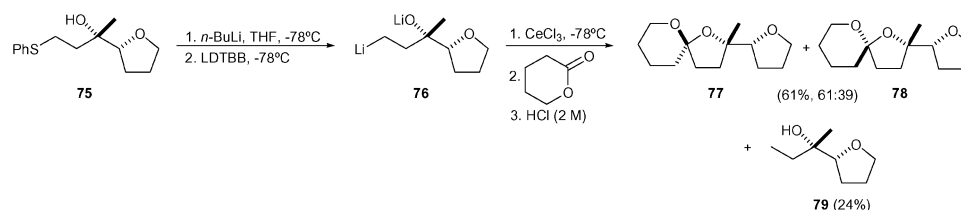
Spiroacetals are present in a large number of natural ionophores. Ahn and Cohen reported a stereoselective synthesis of spiroacetals in which a γ -oxygen functionalised organolithium compound acted as a reaction intermediate. The *erythro* alcohol **75** (prepared from intermediates of type **15**, Scheme 5) was deprotonated first with *n*-butyllithium, followed by reductive lithiation with LDTBB to give the dilithium intermediate **76**. Further addition of CeCl_3 and δ -valerolactone led, after acidic hydrolysis, to a mixture of spiroacetals **77** and **78** in 61% yield. The alcohol **79** (24%) was also formed, presumably by proton abstraction by the intermediate carbanion from the reactant lactone (Scheme 18).³⁴ Each pure diastereomer **77** or **78** equilibrated



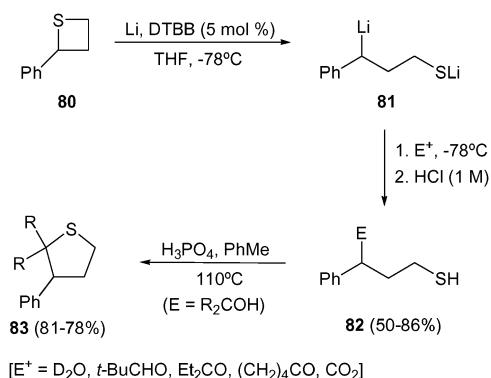
Scheme 16



Scheme 17



Scheme 18



Scheme 19

to form a mixture of both diastereomers (**77** : **78** = 60 : 40) by epimerisation in a weakly acidic medium such as deuteriochloroform.

The reaction of 2-phenylthietane (**80**) with an excess of lithium powder and a catalytic amount of DTBB (5 mol%) in THF at $-78\text{ }^{\circ}\text{C}$ led to dilithio intermediate **81**. Under these reaction conditions the highly reactive benzylic carbon–sulfur bond was reductively cleaved leading to benzylic γ -sulfur functionalised organolithium compound **81**. Treatment of dianion **81** with different electrophiles at the same temperature gave, after acidic hydrolysis, the expected functionalised mercaptans **82** in a completely regioselective manner. Some reaction products, resulting from the use of ketones as electrophiles, were cyclised under acidic conditions to yield the corresponding homologous substituted tetrahydrothiophenes **83** (Scheme 19).³⁵

5. Remote functionalised organolithium compounds

The influence of the functional group on the reactivity and the stability of functionalised organolithium compounds decreases as it gets further from the carbanionic center. Thus, these compounds behave in many cases as normal organolithium compounds and can be prepared through classical methodologies. In this section we will pay attention to δ -, ϵ -,... ω -functionalised organolithium compounds.

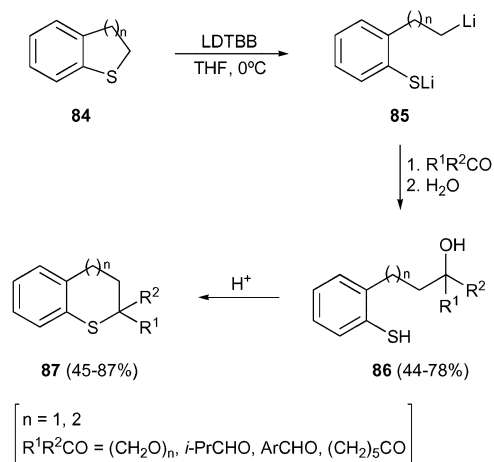
Sulfur-containing heterocycles, such as dihydrobenzothio-phenene (**84**, $n = 1$) and 3,4-dihydro-2*H*-benzothiane (**84**, $n = 2$) in which the sulfur atom is attached to a fused aromatic ring, have been reductively opened by the mixture lithium–DTBB at $0\text{ }^{\circ}\text{C}$ to give dianions **85**. The reaction of these dianionic intermediates with carbonyl compounds as electrophiles led, after hydrolysis, to hydroxythiophenols **86**. Dehydration of these substituted thiophenols under acidic conditions gave new heterocycles **87**, which are homologous to the starting materials (Scheme 20).^{25,36}

The sequential deprotonation and reductive lithiation of (*S*)-5-(phenylthio)-2-pentanol (**88**) (prepared efficiently in high enantiomeric excess by enzymatic reduction of the corresponding readily available ketone) led to a chiral δ -oxygen functionalised organolithium compound **89**. The reaction of dianion **89** with lactones in the presence of cerium trichloride gave spiro acetals **90** with high enantiomeric excess. These

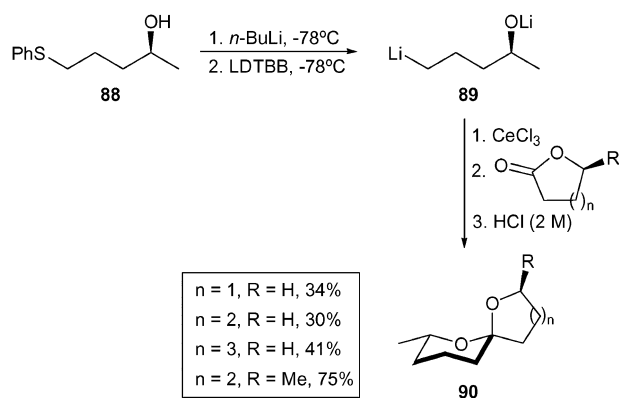
spiro compounds are insect pheromonal components (Scheme 21).³⁷

Zhu and Cohen prepared primary and tertiary organolithiums by reductive cleavage of the carbon–sulfur bond in acetals or thioacetals of δ -, ϵ -,... ω -(phenylthio)ketones. These intermediates are δ -, ϵ -,... ω -lithioketone equivalents and provided great applicability in organic synthesis. For instance, starting from the phenylthioacetal **91** and after treatment with LDTBB, ϵ -functionalised organolithium compound **92** was obtained. Its conversion to a mixed cuprate and subsequent reaction with acetyl chloride yielded the 1,6-monoprotected diketone **93**, which after acidic hydrolysis led to diketone **94**. The mixed cuprate also underwent conjugate addition with cyclohex-2-enone to give the compound **95**. Meanwhile, the reaction of **92** with benzaldehyde provided, after hydrolysis, the alcohol **96**.³⁸ Other functionalised organolithium compounds **97–103**^{38,39} were prepared through this methodology (Scheme 22).

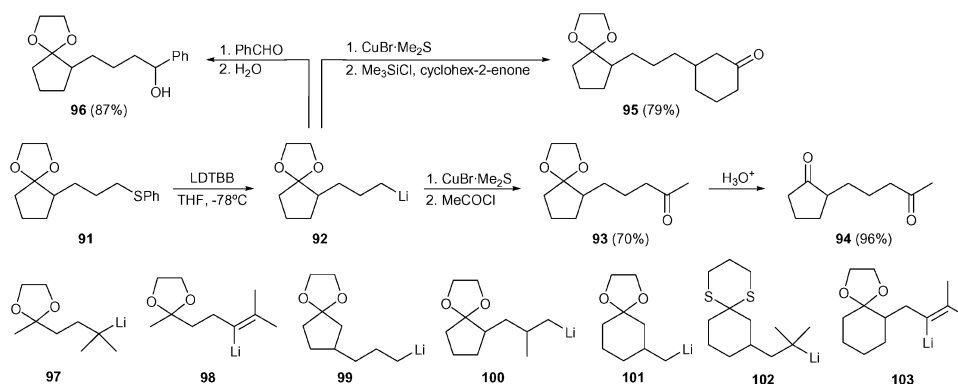
Reductive lithiation of 1,4- or 1,5-bis(phenylthio)-1-alkenes **104** with LDTBB at $-78\text{ }^{\circ}\text{C}$ occurred with total chemoselectivity: replacement of the phenylthio group attached to the sp^3 carbon atom took place exclusively to give first δ - ($n = 1$) and ϵ -functionalised ($n = 2$) organolithium compounds **105**. After an intramolecular nucleophilic addition to the vinyl sulfide moiety (even at $-78\text{ }^{\circ}\text{C}$) a phenylthio-stabilised cyclopropyl- or cyclobutylcarbyllithium **106** was



Scheme 20



Scheme 21

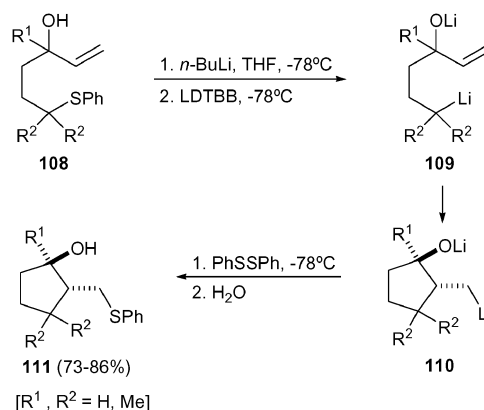


Scheme 22

generated. The addition of different electrophiles, followed by final hydrolysis, allowed the preparation of substituted cyclopropane and cyclobutane derivatives **107** (Scheme 23).⁴⁰ Analogous systems, but lacking the vinyl phenylthio substituent at the carbon-carbon double bond also underwent cyclisation, but at elevated temperatures.

The presence of the lithium oxyanionic group facilitated cyclisation of primary as well as tertiary alkylolithiums of type **109** to give cyclic dianions **110**, even at -78° in THF. However, the most surprising result in Scheme 24 is that a single diastereomer was isolated in all cases with the oxygen functionality and the resulting carbanionic center on the opposite side of the cyclopentane ring. Intermediates **109** (δ -oxygen functionalised organolithium compounds) are easily accessible from allylic alcohols **108** by a tandem deprotonation reductive lithiation with *n*-butyllithium and LDTBB, respectively.⁴¹

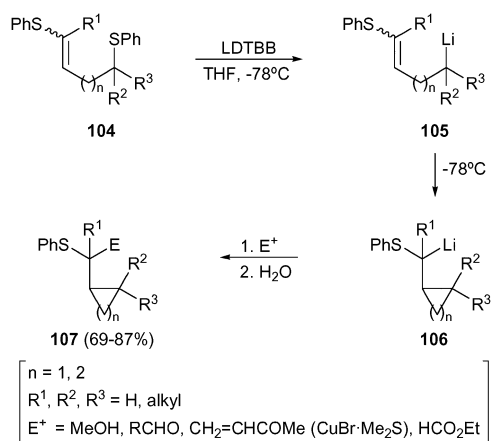
Following the same strategy shown in Scheme 24, the dianionic intermediate **113** was prepared from the allylic alcohol **112**, however, it behaved differently from **109**. In the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), **113** cyclised to the cyclopentylmethylolithium derivative **114**, which was finally trapped with diphenyl disulfide to give compound **115**. The stereochemistry of **114** showed that the oxyanion and the carbanionic center were *cis* instead of *trans* as in **110** (Scheme 25). The hybridisation of the



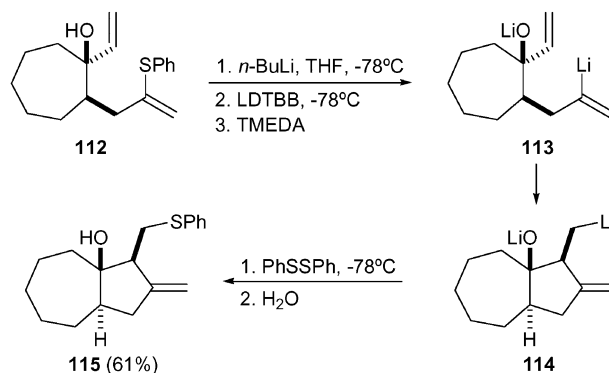
Scheme 24

carbanionic centers in **109** and **113** were different, and it could be a reason for this discrepancy.⁴²

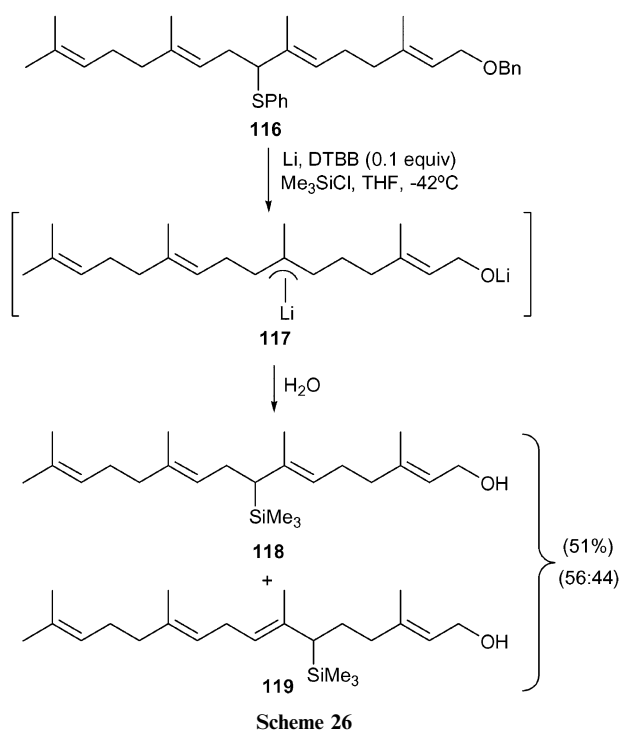
Désaubry *et al.* studied the reductive lithiation of allylthioethers bearing various substituents to prepare allyl-silanes, and they found that the regioselectivity of these processes were strongly dependent on the reaction conditions. The best yields and selectivities were obtained using an excess of lithium and 0.1 equivalents of DTBB in the presence of trimethylchlorosilane at -42°C (Barbier-type reaction conditions), this introduced the silicon at the terminal position. In the case of compound **116**, an almost 1 : 1 mixture of regioisomers **118** and **119** was obtained through the allylic dianion **117**. During the course of the reaction the benzyl group was removed, the low selectivity being due to the



Scheme 23



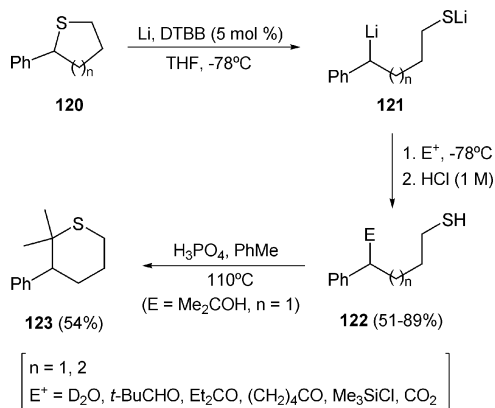
Scheme 25



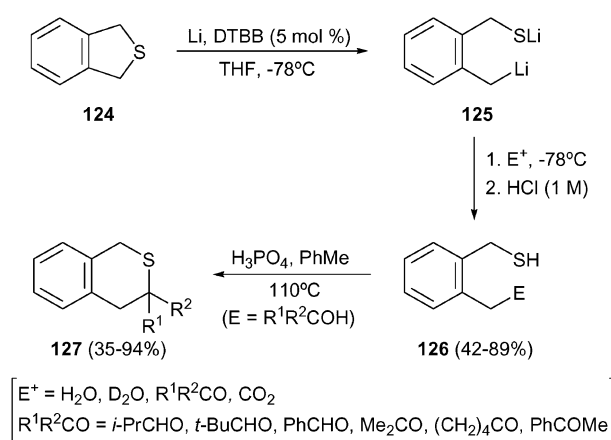
similar level of substitution in the allylic dianion **117** (Scheme 26).⁴³

One direct way to access functionalised organolithium compounds is by the reductive opening of appropriate heterocycles (*vide supra*)⁸ such as, for instance, those with activated benzylic carbon–sulfur bonds. Examples of reductive opening lithiation of sulfur-containing heterocycles of this type follows. In a similar way as for 2-phenylthietane (**80**, Scheme 19), the reductive lithiation of 2-phenyltetrahydrothiophene (**120**, $n = 1$) and 2-phenylthian (**120**, $n = 2$) led to dilithio intermediates **121**, which upon reaction with electrophiles, followed by acidic hydrolysis gave functionalised thiols **122**. Treatment of hydroxythiol **122**, resulting from the reaction of **121** ($n = 1$) with acetone as electrophile, with 85% phosphoric acid at 110 °C gave tetrahydrothiopyran **123** (Scheme 27).³⁵

As it could be expected by considering the reactivity of heterocycles **80** (Scheme 19) and **120** (Scheme 27), thiophthalan **124** was reductively opened with lithium and a catalytic



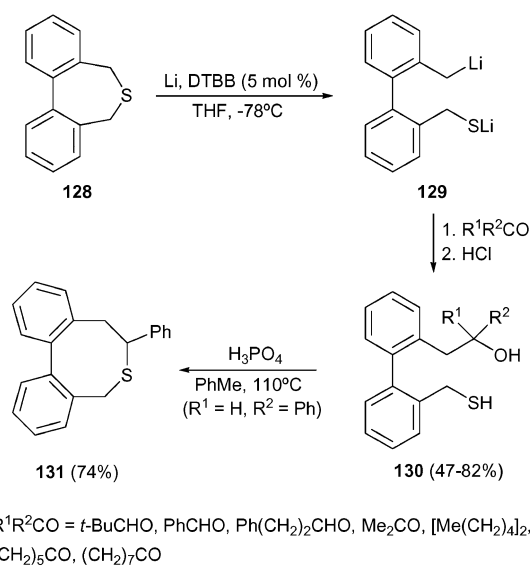
Scheme 27



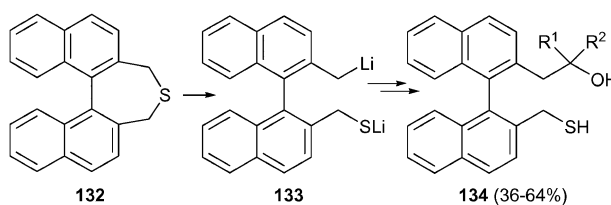
Scheme 28

amount of DTBB at -78 °C. The dianionic intermediate **125** reacted with different electrophiles leading to compounds **126**, after acidic hydrolysis. Thiols **126**, derived from the reaction of intermediate **125** with carbonyl compounds ($E = R^1R^2CO$), cyclised at 110 °C under acidic conditions to give thioisochromans **127** (Scheme 28).⁴⁴

As expected, the treatment of 2,7-dihydrodibenzothiepin **128** with an excess of lithium and a catalytic amount of DTBB at -78 °C produced the remote sulfur functionalised organolithium compound **129**. Sulfanyl alcohols **130** were obtained when carbonyl compounds reacted with the intermediate **129**. The one derived from benzaldehyde was cyclised upon treatment with 85% phosphoric acid under toluene reflux to yield



Scheme 29



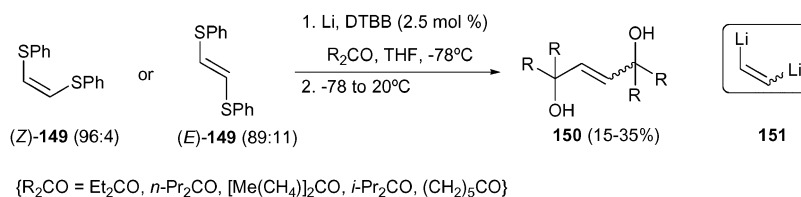
dihydrodibenzothiocine **131** (Scheme 29).⁴⁵ Under the same reaction conditions, 2,7-dihydrodinaphthothiepin **132** underwent double lithiation (*vide infra*, section 6). However, when the lithiation was performed with two equivalents of lithium naphthalenide followed by addition of an electrophile, 2,2'-disubstituted 1,1'-binaphthyls **134** were obtained after hydrolysis, the functionalised organolithium compound **133** acting as a reaction intermediate (Scheme 29).^{45b,46}

6. Organodilithium compounds

The importance of dilithium (polylithium, in general) organic compounds is due to the fact that by reaction with either two different or equal electrophiles, polyfunctionalised molecules can be prepared in one single synthetic operation. The reductive cleavage of molecules having more than one phenylthio unit in the structure allows the synthesis of these polyanionic intermediates **135–142** by using: lithium naphthalenide as the lithiating reagent for compounds **135**, **136**^{5a,12} and **137**;⁴⁷ LDTBB for tris(lithiomethyl)silanes **138** and tetrakis(lithiomethyl)silane **139**;⁴⁸ the mixture lithium–lithium bromide for compound **140**;⁴⁹ and an excess of lithium in the presence of a catalytic amount of naphthalene (12 mol%) for lithio-methyl functionalised dendrimer **141**⁵⁰ and DTBB (2.5 mol%) for non-branched derivatives **142**⁵¹ (Chart 1).

Shimizu *et al.* reported the preparation of 2,2,3,3,5,5,6,6,7,7,8,8,-dodecamethyl-2,3,5,6,7,8-hexasilbicyclo[2.2.2]octane (**148**) in a three step process, with 56% overall yield, taking advantage of this strategy. The reaction of dichlorodimethyldisilane (**143**) with the anion resulting from the deprotonation of bis(phenylthio)methane afforded compound **144**, which by reductive lithiation with LDTBB led to the dilithium intermediate **145**. Subsequent silylation of compound **145** with dichlorodimethyldisilane (**143**) gave the cyclic tetrasiladerivative **146**. Finally, reduction of this material with LDTBB led to a new dilithium compound **147** which by silylation successfully produced the cage polycarbosilane **148** (Scheme 30).⁵² The molecular structure of **148** (determined by X-ray analysis) was shown to be slightly distorted from an ideal bicyclo[2.2.2]octane skeleton. Functionalisation of compound **148** at bridgehead positions was achieved by treatment with *n*-BuLi/*t*-BuOK followed by reaction with electrophiles.

The reaction of (*Z*)- or (*E*)-1,2-bis(phenylsulfanyl)ethene (**149**) with an excess of lithium and a catalytic amount of DTBB (2.5 mol%) in the presence of a carbonyl compound as electrophile (Barbier conditions) in THF at $-78\text{ }^{\circ}\text{C}$ led, after hydrolysis with water at temperatures ranging between $-78\text{ }^{\circ}\text{C}$ and room temperature, to a mixture of the corresponding (*Z/E*)-unsaturated 1,4-diols **150**, the diastereomers ratio being independent of the stereochemistry of the starting materials.



Scheme 31

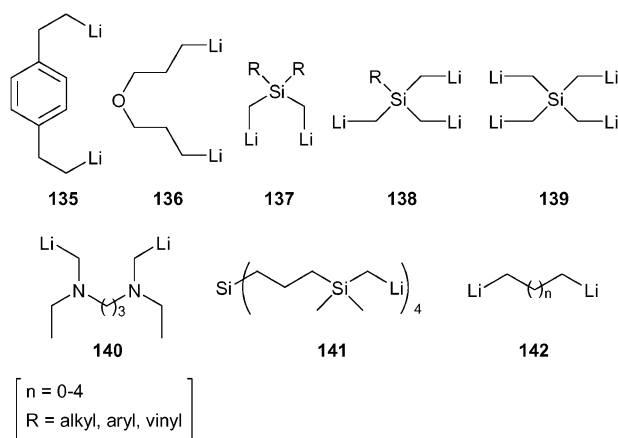
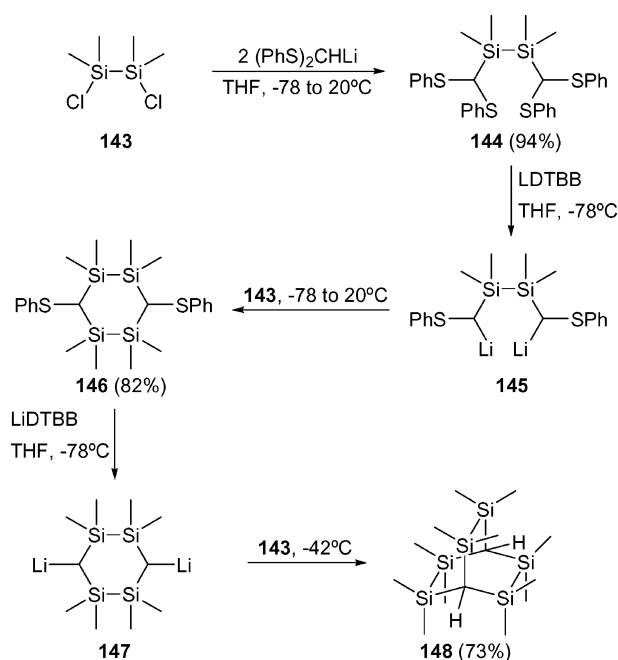


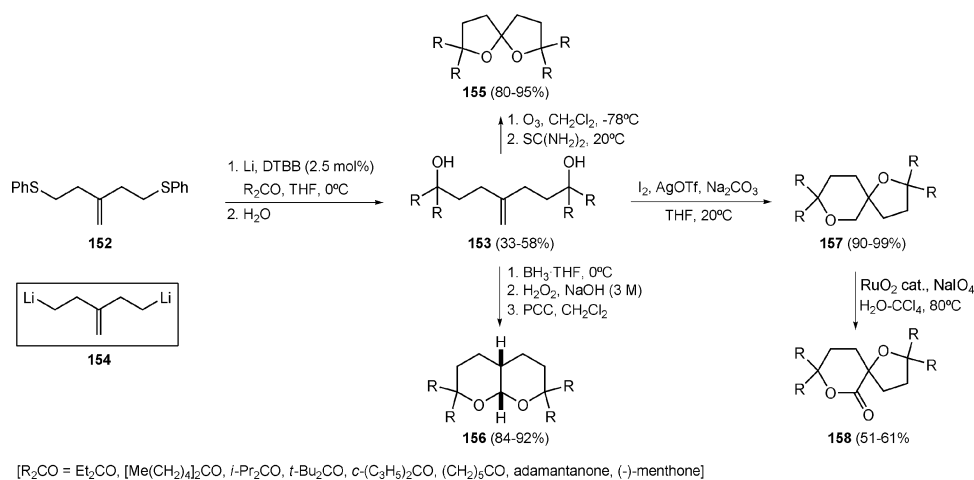
Chart 1



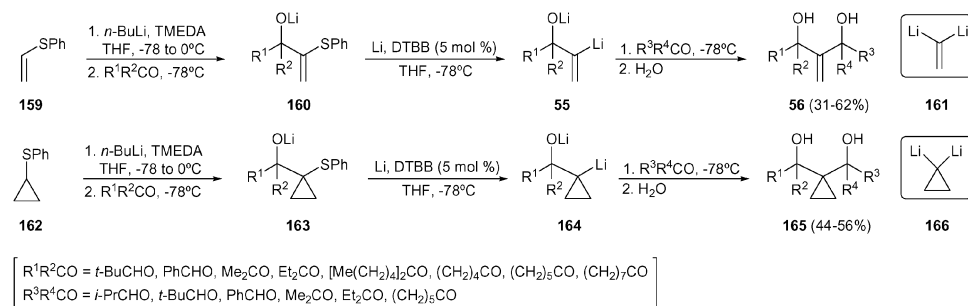
Scheme 30

Even working with poor yields the reaction allowed the introduction of two electrophilic fragments at both carbon atoms of ethylene so, in this way, compounds **149** act as synthetic equivalents of the unknown ethene 1,2-dianion **151** (Scheme 31).⁵³

4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**152**) has proved to be an appropriate and new 3-methylidene-pentane-1,5-dianion synthon **154**. The reaction of **152** with an excess of lithium powder and a catalytic amount of DTBB



Scheme 32

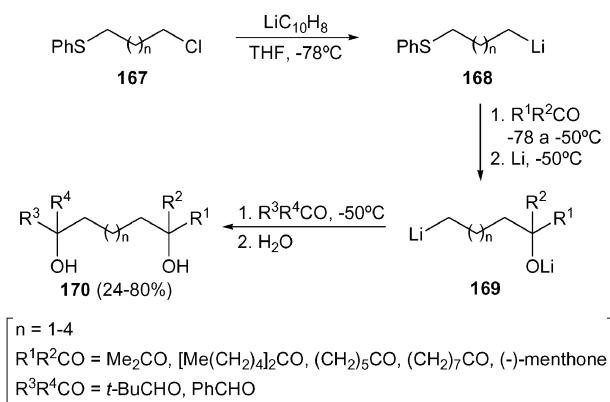


Scheme 33

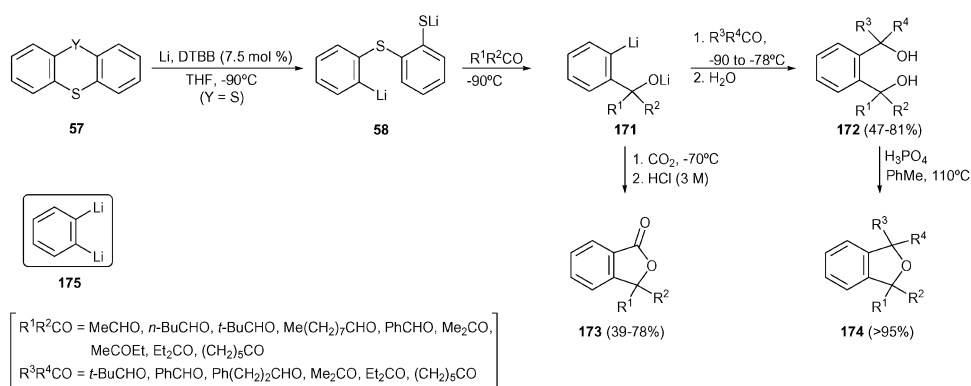
(2.5%) in the presence of a carbonyl compound in THF at 0 °C, led, after hydrolysis, to the expected methylenic diols **153**. These diols have found a great applicability in synthesis. Thus, they were converted into 1,6-dioxaspiro[4.4]nonanes **155** after ozonolysis (Scheme 32)⁵⁴ and to the target perhydro-pyrano[2,3-*b*]pyrans **156** by tandem hydroboration–oxidation with alkaline hydrogen peroxide followed by treatment with PCC (Scheme 31).⁵⁵ On the other hand, the methylenic bis-homoallylic diols **153** led to the corresponding 1,7-dioxaspiro[4.5]-decanes **157** upon treatment with iodine and silver(I) triflate in a mixture of dioxane–water as solvent. Selective oxidation of **157** gave spiro lactones **158** in moderate yields (Scheme 32).^{55,56}

Taking advantage of two well established reactions (α -deprotonation of a thioether and sulfur–lithium exchange) it was possible to generate synthetic equivalents of 1,1-dilithioethylene (**161**)^{30,57} and 1,1-dilithiocyclopropane (**166**)⁵⁷ starting from phenylthioethers **159** and **162**, respectively. Thus, deprotonation of thioethers **159** and **162** by means of *n*-butyllithium, followed by addition of a first carbonyl compound yielded alcoholates **160** and **163**, which reacted with an excess of lithium metal in the presence of a substoichiometric amount of DTBB: carbon–sulfur bond cleavage took place under these reaction conditions yielding highly reactive β -functionalised organolithium compounds **55** and **164**, respectively. Diols **56** and **165** were obtained as reaction products after addition of a second carbonyl compound as electrophile and final hydrolysis (Scheme 33).

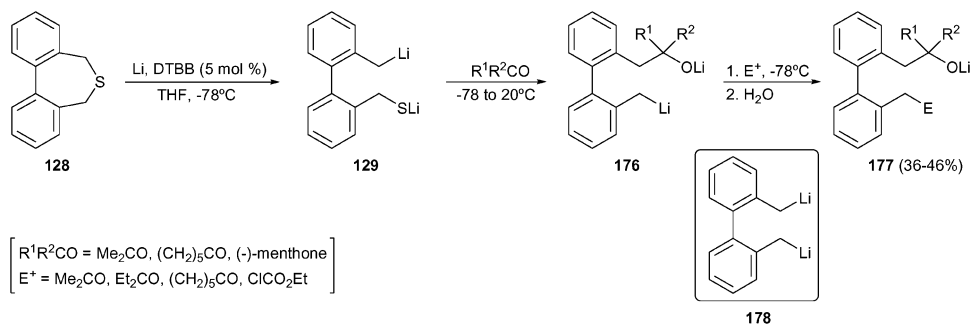
It was also possible to perform a sequential double lithiation in the case of using chloroalkyl phenyl thioethers **167** as starting material. The first selective lithiation was achieved by treatment of compound **167** with a stoichiometric amount of lithium naphthalenide as the lithiating mixture. Under these reaction conditions a selective chlorine–lithium exchange took place to give the intermediate **168**, which by reaction with a carbonyl compound followed by addition of lithium metal and subsequent sulfur–carbon bond cleavage led to dianionic intermediates **169**. Diols **170** were obtained by reaction of dianions **169** with a second carbonyl compound and



Scheme 34



Scheme 35

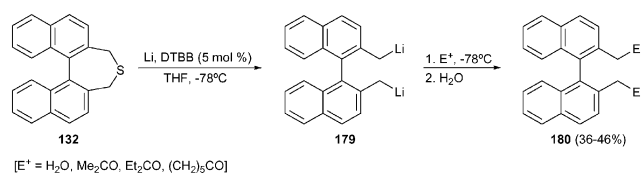


Scheme 36

final hydrolysis (Scheme 34).⁵⁸ From these results, the carbon–chlorine bond seemed to be more reactive towards the reducing reagent than the carbon–sulfur bond.

Thianthrene (**57**, $Y = \text{S}$, Scheme 15) is a special case of a phenyl thioether. The DTBB catalysed monolithiation of thianthrene can be performed at -90°C to give the intermediate **58** ($Y = \text{S}$, Scheme 15), which by reaction with a first carbonyl compound as electrophile and further selective reductive cleavage of one of the remaining carbon–sulfur bonds, in the highly reductive reaction medium, led to a new dianionic intermediate **171**. The reaction of this intermediate with a second carbonyl compound, followed by hydrolysis, yielded diols **172**, which under acidic conditions afforded substituted phthalans **174** in almost quantitative yields. On the other hand, phthalides **173** are directly obtained as reaction products when carbon dioxide is used as the second electrophile (Scheme 35).⁵⁹ By applying this methodology, thianthrene (**57**, $Y = \text{S}$) could be considered as a 1,2-dilithiobenzene (**175**) synthetic equivalent.

Allyl and benzyl thioethers suffer also reductive cleavage of carbon–sulfur bonds by means of lithium metal to give allylic and benzylic organolithium compounds, respectively. The lithiation of 2,7-dihydrodibenzothiepin (**128**) can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. Thus, once the first lithiation with an excess of lithium in the presence of a catalytic amount of DTBB took place, giving the intermediate **129** (see above, Scheme 29), the addition of a carbonyl compound at low temperature, followed by reaction at room temperature in this highly reductive medium, led to the dianionic intermediate **176** (formed after reductive cleavage



Scheme 37

of the remaining benzylic carbon–sulfur bond). The reaction of compound **176** with a second electrophile, and final hydrolysis, yielded difunctionalised biphenyls **177** (Scheme 36).⁴⁵ In this case, 2,7-dihydrodibenzothiepin (**128**) acts as a precursor of 2,2'-bis(lithiomethyl)biphenyl (**178**) synthetic equivalent.

It was not possible to control the monoreductive cleavage of 2,7-dihydrodinaphthothiepin **132** by applying the same methodology as above. In order to perform the monoreductive cleavage, two equivalents of the lithiating reagent have to be employed (*vide supra*, section 5, Scheme 29). When the lithiation of compounds **142** was performed at -78°C with an excess of lithium and a catalytic amount of DTBB, a double reductive cleavage took place to give the dilithium derivative **179**, which reacted with electrophiles to give symmetrically 2,2'-disubstituted binaphthyls **180** (Scheme 37).^{45,46}

Conclusions

The sulfur–lithium exchange has been shown to be a versatile method to prepare functionalised organolithium compounds starting from adequate functionalised phenylthioethers as well as benzylic thioethers, and using different lithiation

conditions. The critical lithiation step, depending on the reaction temperature, has to include promotion by an arene, in order to generate efficient metalation reactions. The reaction is in general high-yielding and regioselective, the sulfur-carbon cleavage always taking place at the sulfur-alkyl bond. The problem of the low atom-efficiency for open chain systems is overcome in the case of using cyclic derivatives, for which the starting material is a source of both the lithium intermediate and the functionality. In addition, poly(phenylthioethers) are appropriate starting materials for the preparation of polythioethers through this methodology.

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