

Preparation and some applications of functionalized organo-lithium compounds in organic synthesis

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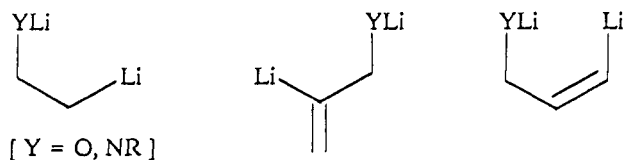
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Abstract. The preparation of β and γ oxygen and nitrogen functionalized organo-lithium compounds through exchange reactions and direct lithiation is presented; special attention is paid to the metallation of allyl and diallyl amines. Some applications of these synthons for the preparation of open-chain and cyclic systems are also included.

The preparation of functionalized organolithium compounds has been an area of active investigation in our laboratories.

In this talk I am going to speak about the preparation and some of the synthetic applications of organolithium compounds bearing oxygen or nitrogen atoms in the β or γ position. In particular, I am going to talk about the following kind of systems (Scheme 1).

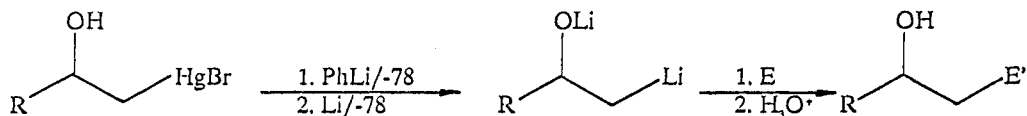
Scheme 1



β -Substituted organolithium compounds in which the metal is linked to an sp^3 hybridized carbon atom, β -substituted organolithium compounds in which the lithium is bonded to an sp^2 hybridized carbon atom, and finally γ -organolithium reagents derived from allylic alcohols and amines. Firstly, I would like to give you a general insight about what we have done in the case of the corresponding oxygenated derivatives.

There are different routes for preparing β -oxygenated organolithium compounds; one of them, designed by us as the mercury route, is outlined in the Scheme 2 and represents the first method for the preparation of this type of compounds (ref. 1).

Scheme 2

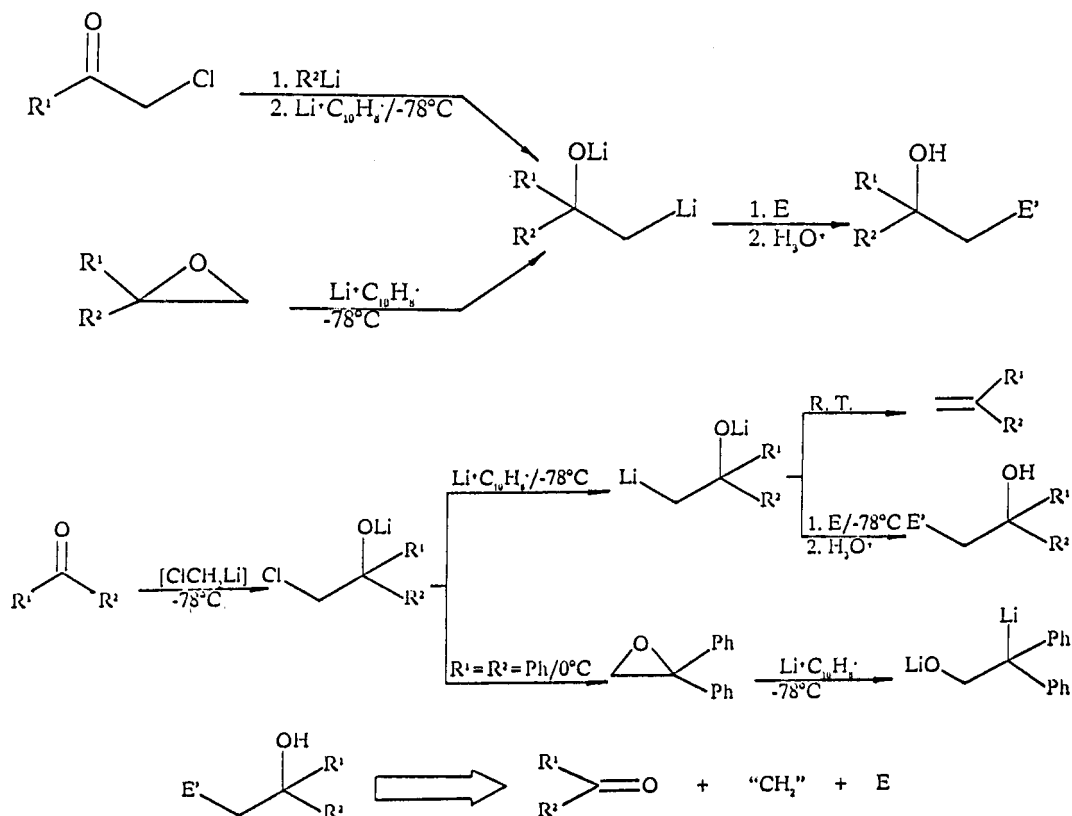


When β -hydroxy mercury (II) compounds, which can be obtained very easily through hydroxymercuration of olefins, were allowed to react with phenyllithium in a 1:1 molar ratio in THF solution at -78°C the corresponding mercuriated lithium alkoxydes were formed. Mercury / lithium exchange gave rise to β -substituted organolithium derivatives, which are versatile synthetic intermediates for the synthesis of a wide range of difunctional compounds.

The preparation of β -substituted organolithium derivatives can be carried out avoiding the mercury route by following three different ways, as depicted in Scheme 3. The starting materials are α -chlorocarbonyl compounds, epoxides, and simple ketones, respectively.

Treatment of the α -chlorocarbonyl compounds with *n*-butyllithium at -78°C and then with lithium naphthalenide at the same temperature led to the corresponding β -functionalized organolithium compounds (ref. 2). It is necessary to use lithium naphthalenide instead of lithium powder because the metallation with lithium metal at low temperature failed.

Scheme 3



The direct preparation of the β -functionalized lithium derivatives can be achieved at low temperature by treatment of the corresponding epoxides with lithium naphthalenide (ref. 3).

The lithium derivatives can then react with several electrophiles yielding 1,2-difunctionalized compounds in a regioselective manner.

It can be concluded that the dianionic species described here are highly reactive intermediates which act as synthons for the regioselective introduction of the HO-C-C- group by reaction with electrophiles. Besides the regioselectivity of the process, the high yields for all compounds are worth noting.

The β -oxido alkyl lithium derivatives can be obtained starting from simple ketones and using *in situ* generated chloromethyl lithium (ref. 4).

In this case the simple treatment of different ketones with chloromethyl lithium at -78°C followed by lithiation with lithium naphthalenide at the same temperature afforded the corresponding intermediates (ref. 5). The decomposition of these intermediates by β -elimination took place when the reaction mixture was allowed to warm to room temperature in the metallation step; in this case, the metallation can be performed with lithium powder at temperatures ranging from -60 to 20°C .

This reaction represents a new route for the synthesis of terminal and exocyclic olefins in a regioselective manner.

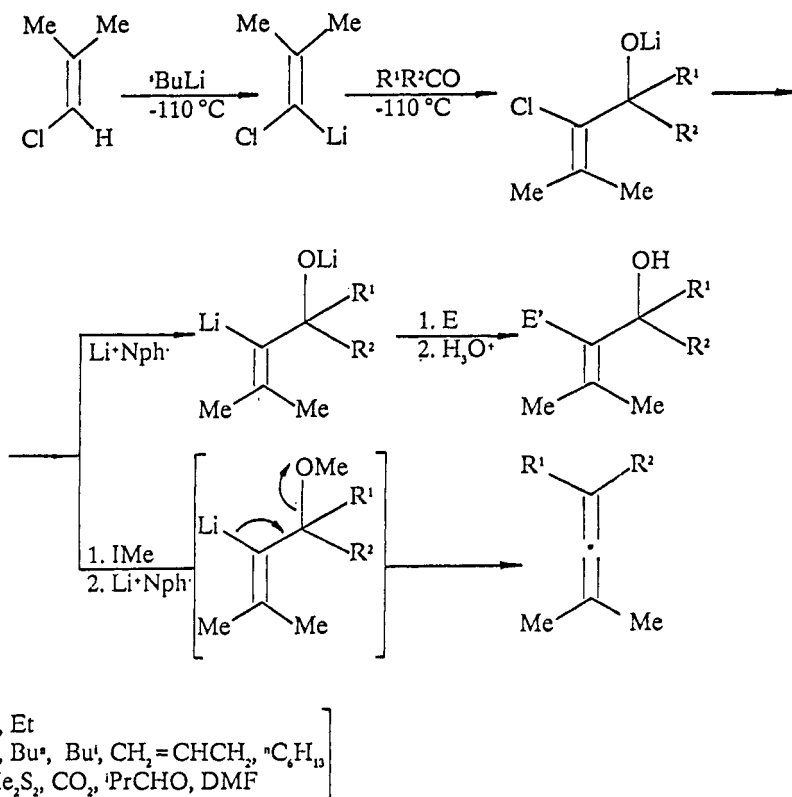
When the dianionic intermediate was treated with different electrophiles the expected products were obtained. It must be pointed out that the use of aldehydes as starting materials instead of ketones led to a complex mixture.

The possibility of obtaining the corresponding regioisomer of the dianion was tested starting from benzophenone ($R^1 = R^2 = \text{Ph}$). Thus, when chloromethyl lithium was added and the reaction mixture allowed to warm to room temperature the expected cyclization took place yielding the epoxide. The *in situ* metallation of this compound with lithium naphthalenide at -70°C yielded the corresponding intermediate, which afforded the corresponding difunctionalized derivatives by reaction with different electrophiles.

The method outlined here can be seen as the reaction of the synthon " CH_2 " with two different electrophiles, one of them being a carbonyl derivative.

The preparation of sp^2 hybridized β -substituted organolithium compounds is depicted in Scheme 4.

Scheme 4



Starting from 1-chloro-2-methylpropene, its treatment with *s*-BuLi at -110°C led to the α -chlorolithium derivative, which reacted with different carbonyl compounds yielding the lithium oxide derivatives; when this intermediate was treated with lithium phenanthrenide, (the exchange reaction using lithium powder failed), the dilithium compounds were obtained (ref. 6). As expected, this dilithium derivative reacted with different electrophiles yielding in a stereoselective manner the functionalized substituted allylic alcohols.

It is worth noting the thermal stability of the dianion. It is stable even in a solution of THF at 67°C (reflux).

The treatment of the chloroalkoxy derivative with methyl iodide at temperatures between 0 and 20°C and then with lithium phenanthrenide afforded the unstable β -lithioether which spontaneously underwent β -elimination to give the corresponding cumulene. The transformation of the lithium salt into the chloroether is necessary in order to get a better leaving group which allows the β -elimination.

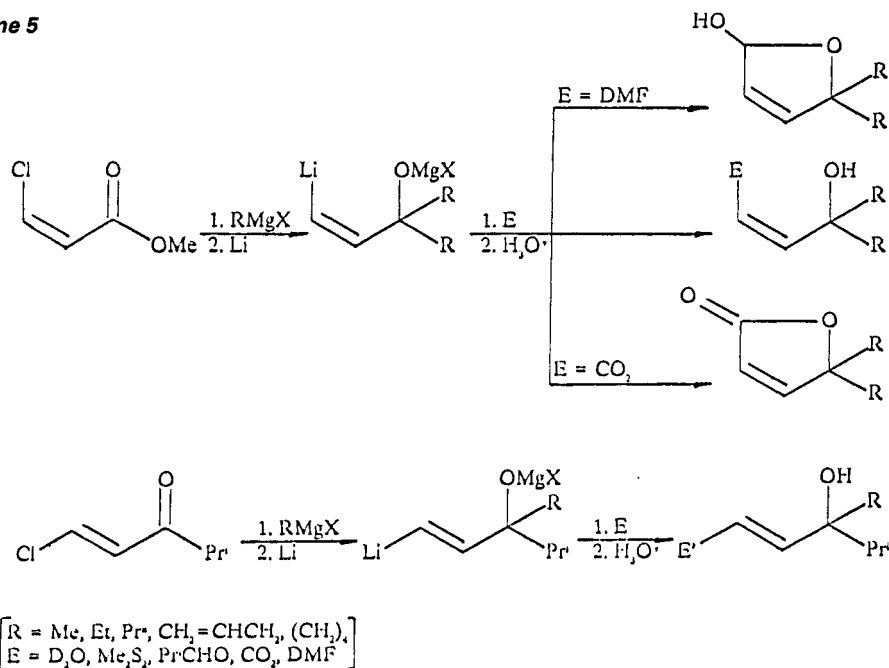
Continuing with the study on oxido functionalized organolithium compounds the next step was the preparation of γ -oxido functionalized sp^2 organolithium intermediates, which is depicted in Scheme 5.

By treatment of methyl(*Z*)-3-chloroacrylate with a Grignard reagent (1:2 molar ratio) followed by lithium powder the corresponding *Z*-dianionic intermediates were obtained. The *in situ* reaction of these intermediates with different electrophiles yielded the expected difunctionalized compounds. When *N,N*-dimethylformamide was used as the electrophilic reagent the cyclic hemiacetal was isolated. The treatment of the dianion with carbon dioxide or ethyl chloroformate afforded directly the corresponding α,β -butenolide. These results confirm that the metallation takes place with retention of the configuration (ref. 7).

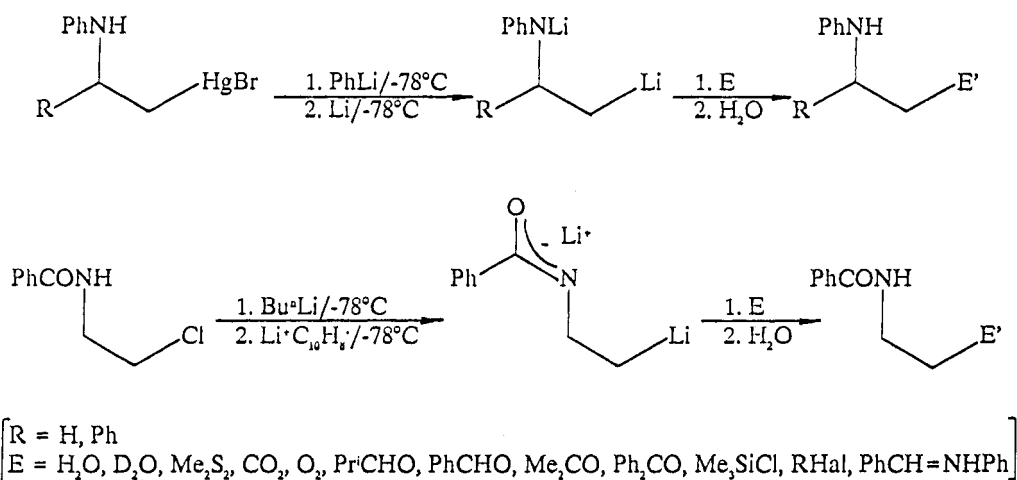
A general method for the preparation of β -nitrogen lithium derivatives is again the mercury route (Scheme 6). The aminomercuriation at room temperature of an olefin led to the corresponding aminomercurial derivative which by successive treatment at -78°C with phenyllithium and lithium powder afforded β -substituted organolithium derivatives. This dianion can react further with different electrophiles giving rise to difunctionalized derivatives in a regioselective manner.

The mercury route can be avoided by using halogenated compounds, for example *N*-(2-chloroethyl)benzamide. The use of the corresponding halogenated amine gives rise to the aziridine

Scheme 5



Scheme 6

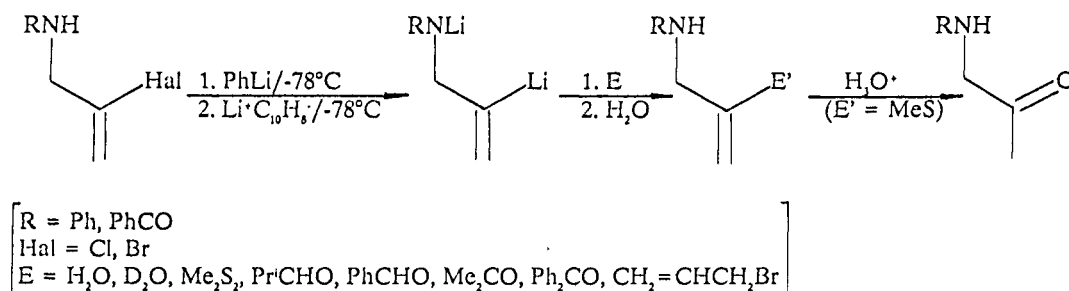


derivatives. The successive treatment of the benzamide derivative with butyllithium and lithium naphthalene afforded the β -substituted organolithium derivative (ref. 8). The *in situ* reaction of this dianion with different electrophilic reagents yielded the expected β -substituted *N*-ethylbenzamides.

This methodology represents a useful way of introducing the $\text{H}_2\text{N-C-C-}$ unit in an electrophilic reagent.

The *N*-phenyl or *N*-benzoyl-2-halogeno allylamines are adequate starting materials for the preparation of the corresponding β -nitrogenated lithium derivatives in which the lithium atom is bonded to an sp^2 hybridized carbon atom. The successive treatment of 2-chloro or 2-bromoallylaniline with phenyllithium and lithium naphthalene at -78°C led to the corresponding organolithium derivative (ref. 9), which on treatment with different electrophiles, yielded the expected products. The *N*-benzoyl derivatives were found to behave as above. In spite of the fact that these organolithium derivatives are stable at -40°C the reaction has to be carried out at -80°C in order to avoid the formation of the propargylamine derivative through hydrogen halide elimination from the corresponding lithium amide formed in the first step. This is always the main reaction observed when aliphatic amines (for example, $\text{R} = \text{Cy, Pr}$) were used. The dehydrohalogenation reaction is easier for aliphatic systems than for aromatic ones due to their higher basicity.

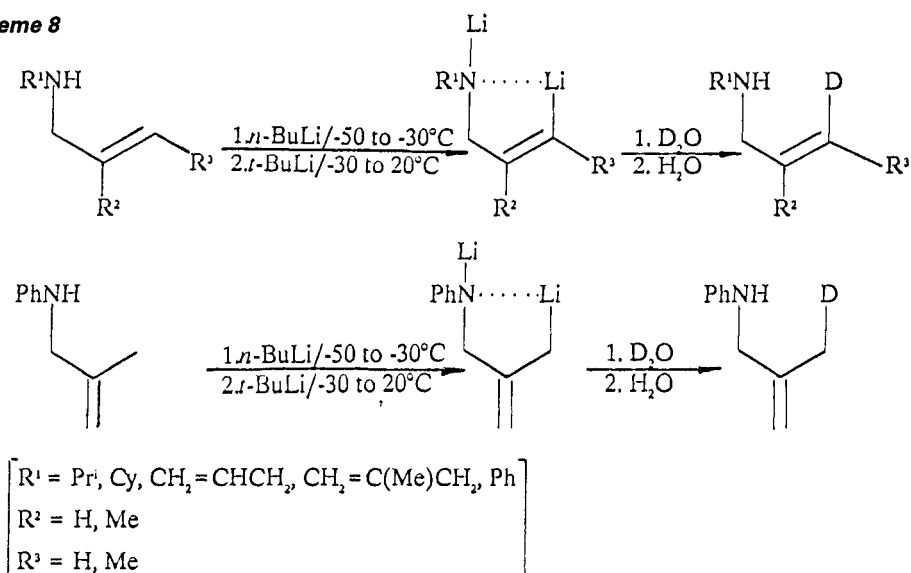
Scheme 7



Regarding the different types of compounds which can be prepared *via* this route, it is worth pointing out that α -aminoketones can be obtained by hydrolysis of sulphides (Scheme 7).

At this point, the following reasonable step would be perhaps the preparation of γ -nitrogenated lithium derivatives in which the lithium atom is linked to an sp^2 carbon atom, that is, γ -functionalized allylamines. In this case, we did not follow the strategy shown so far in this lecture, but we used this time the exchange reaction between hydrogen and lithium, as depicted in Scheme 8. The successive treatment of various allylic and methylallylic secondary amines with *n*-butyllithium and *t*-butyllithium at temperatures

Scheme 8

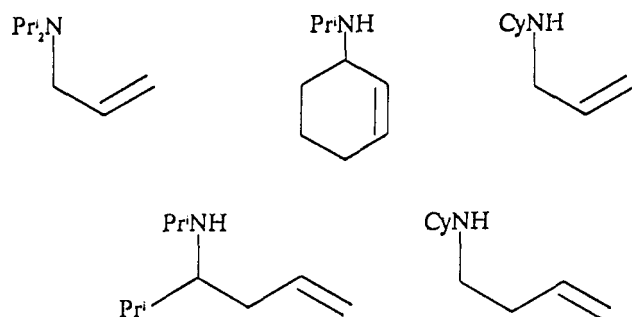


ranging from -50 to 20°C led to the vinylic lithiated dianions in a regio and stereoselective manner (ref. 10). Further reaction of these d^2 -reagents with deuterium oxide occurred with retention of the configuration yielding, after hydrolysis, the corresponding deuterated allylic or methylallylic amines. Although this reaction seems to be of wide applicability, there are some particular cases in which the reaction does not work fine; for instance, allylic rather than vinylic lithiation took place exclusively in the case of *N*-(methylallyl)aniline under the same reaction conditions, leading to the corresponding dianionic intermediate, which on treatment with deuterium oxide and hydrolysis gave the expected deuterated product.

In this context we have checked other allylamines, such as those indicated in Scheme 9, under the reaction conditions given above, that is, treatment with *n*-butyllithium and *t*-butyllithium at -30 to 25°C . In all cases no reaction was observed, but the starting allylamines were recovered unchanged. Perhaps, we can learn from these results that the basicity of tertiary allylamines is not strong enough to promote the reaction. The geometry of secondary allylamines depicted here, whose basicity should be enough, must be responsible for the reaction failing; finally, homoallylamines do not react, so the relative position between the nitrogen and the double bond is essential.

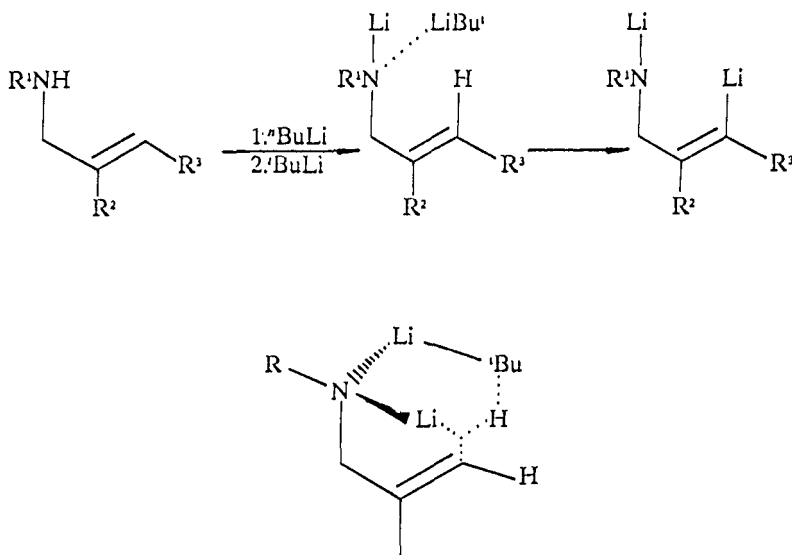
In agreement with the results indicated above, a two-step mechanism for the lithiation of allylamines is proposed (Scheme 10); firstly, the formation of the amide takes place and secondly the metallation itself. The nitrogen atom of the lithium amide formed in the first step, can coordinate to the lithium

Scheme 9



atom of the *t*-butyllithium increasing the reactivity of the organolithium reagent and inducing a proximity effect; the other lithium atom interacts with the double bond fixing the *s-c/s* geometry since only the vinyl hydrogen placed in a *cis* position relative to the nitrogen substituent is removed. When there is no *cis* hydrogen the reaction does not take place.

Scheme 10



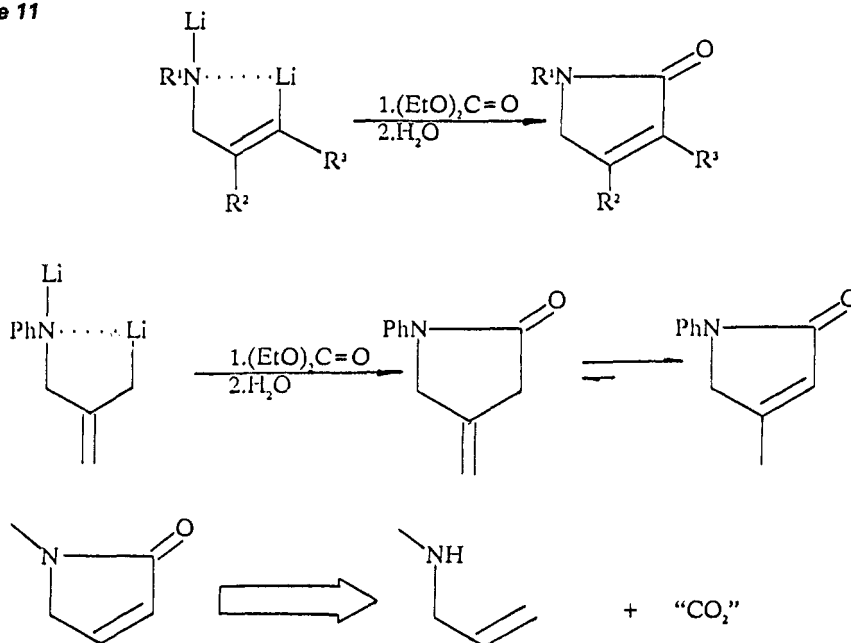
From a synthetic point of view the metallated allylamines can react with several electrophilic reagents yielding, after hydrolysis, the corresponding open-chain functionalized allylamines.

In order to obtain cyclic compounds (Scheme 11), diethyl carbonate was used. The *in situ* treatment of the dianionic intermediates with diethyl carbonate afforded, after hydrolysis, the corresponding α,β -unsaturated butyrolactams in very high yields (ref. 11). When dianion derived from methylallylaniline was employed α,β -unsaturated butyrolactams were directly obtained under the same reaction conditions; these compounds probably come from the methylene isomers formed in the first step of the reaction, through an isomerization process in the basic media. The formation of the α,β -unsaturated butyrolactams can be seen as the reaction of a "CO₂" equivalent with an allylamine.

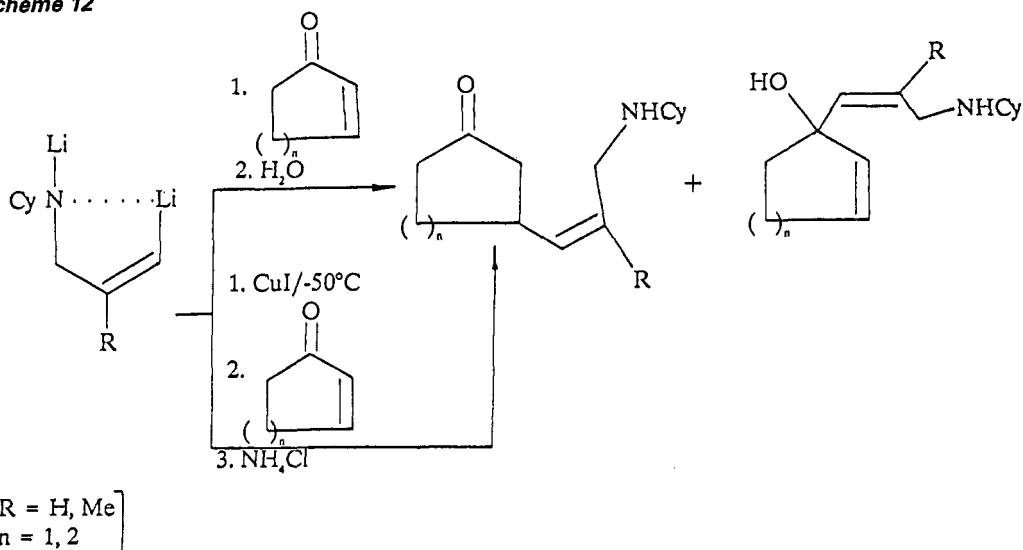
Before finishing with the reactivity of these dilithium derivatives, one more example of their synthetic applications is shown in Scheme 12. This dianionic synthon reacts with α,β -unsaturated carbonyl compounds, e. g. cyclopentenone or cyclohexenone, to give rise to a mixture of the expected 1,2 and 1,4 addition products. However, the treatment of the dianion with an equimolecular amount of copper iodide at -50°C for 30 minutes and then with the corresponding carbonyl compound at -80°C afforded, after aqueous work-up, the 1,4 addition product, exclusively. This methodology represents a simple way of introducing remote functionalization in carbonyl compounds.

In the last few minutes of this talk I am going to show the results reached by using diallylamines and related compounds.

Scheme 11



Scheme 12

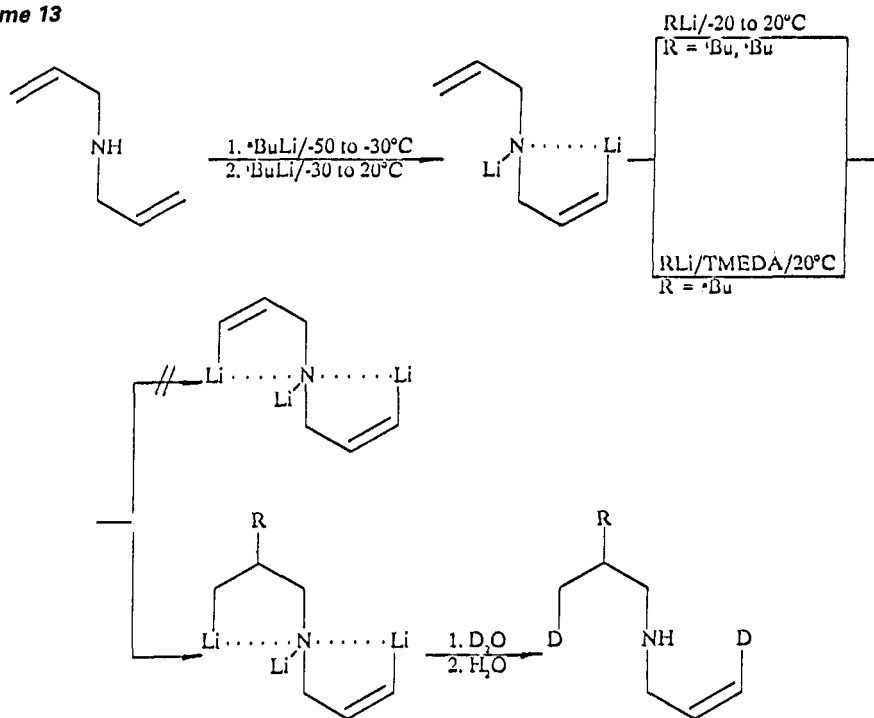


Starting from the diallylamine itself (Scheme 13), its successive treatment with *n*-butyllithium and *t*-butyllithium at -50 °C afforded the expected dianion by removing the vinylic hydrogen. Treatment of this intermediate with an equimolar amount of *t*-butyllithium at temperatures between -20 and 20 °C, did not result in abstraction of the vinylic hydrogen of the second allyl group; instead of that, quantitative addition of the alkyl lithium to that double bond yielding the corresponding trianion, was observed; further hydrolysis with deuterium oxide afforded the corresponding dideuterated derivatives (ref. 13).

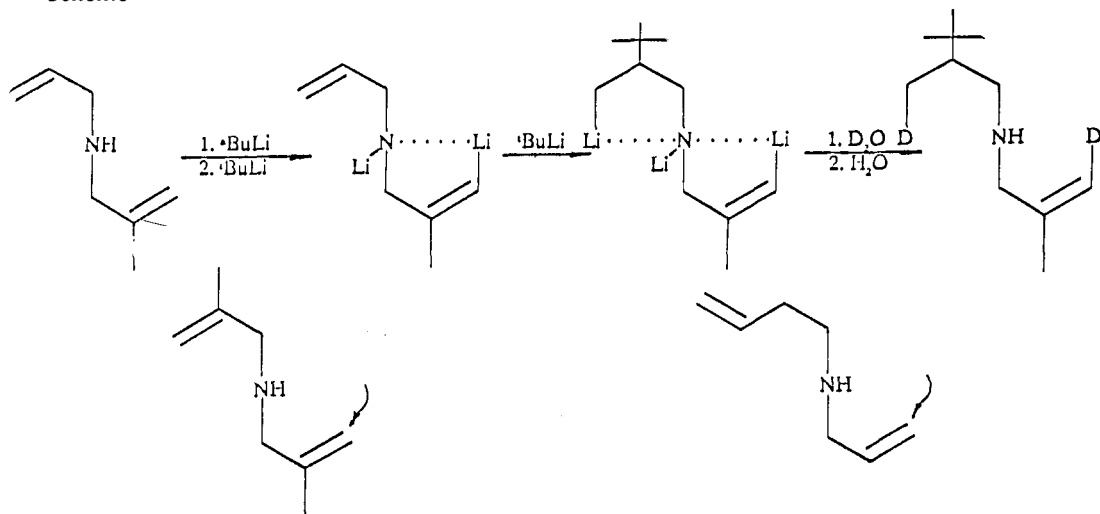
When *s*-butyllithium instead of *t*-butyllithium was used the corresponding addition product was again formed. The addition of *n*-butyllithium occurs in a similar manner, though the presence of TMEDA is necessary in order to increase the reactivity of the organolithium reagent.

The methallylamine behaves in the same way as the diallylamine (Scheme 14); moreover, the lithiation of the vinylic carbon takes place with total regioselectivity (the vinylic hydrogen of the methallyl moiety was exclusively removed) affording the corresponding dianion.

Scheme 13



Scheme 14



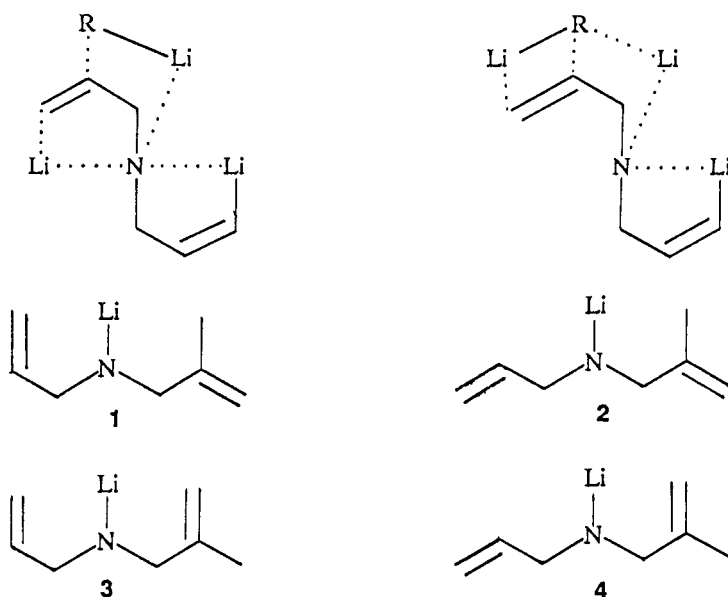
The reaction of this dianion with one equivalent of *t*-butyllithium yielded the addition product, which on treatment with deuterium oxide furnished the corresponding deuterated compounds.

The diallylamine derivatives depicted below, dimethylallyl-, crotylallyl-, and allylbromoallylamines, show a common behaviour. Thus, these amines react with *n*-butyllithium and *t*-butyllithium producing the abstraction of a vinyl hydrogen; however, the addition reaction of another equivalent of *t*-butyllithium to these intermediates failed and the corresponding addition compounds were not obtained.

At this point, it is necessary to rationalize the behaviour of diallylamines towards alkylolithium reagents. The first metallation can be understood by assuming a proximity effect induced by the nitrogen atom, as explained above. Two models can account well for the addition steps (Scheme 15); a) the lithium

atom linked to nitrogen coordinates to the carbon-carbon double bond increasing its electrophilic character and so allowing the addition of the organometallic reagent, b) interaction of the lithium atom of the amide with the alkyl group of the organometallic reagent would result in an increasing of its reactivity, which, along with the simultaneous proximity effect, would allow the carbon-carbon double bond-to-lithium coordination.

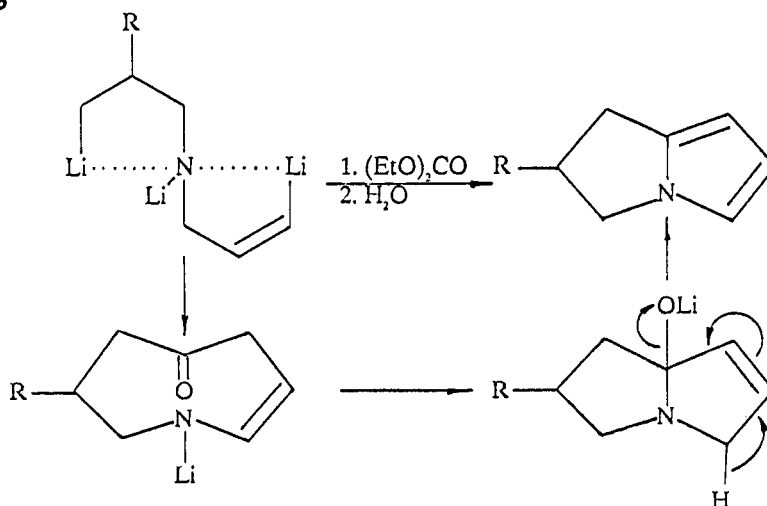
Scheme 15



The high selectivity found in the case of metallation of methallylamine can be probably understood by taking into account the four possible conformations depicted in Scheme 15. Conformations 1 and 2 are expected to be destabilized relative to 3 and 4 due to steric interaction of the alkyl lithium with the methyl substituent of the methallyl group. Among structures 3 and 4, the *cisoid* conformation 3 is probably higher in energy than 4, which represents the *transoid* version.

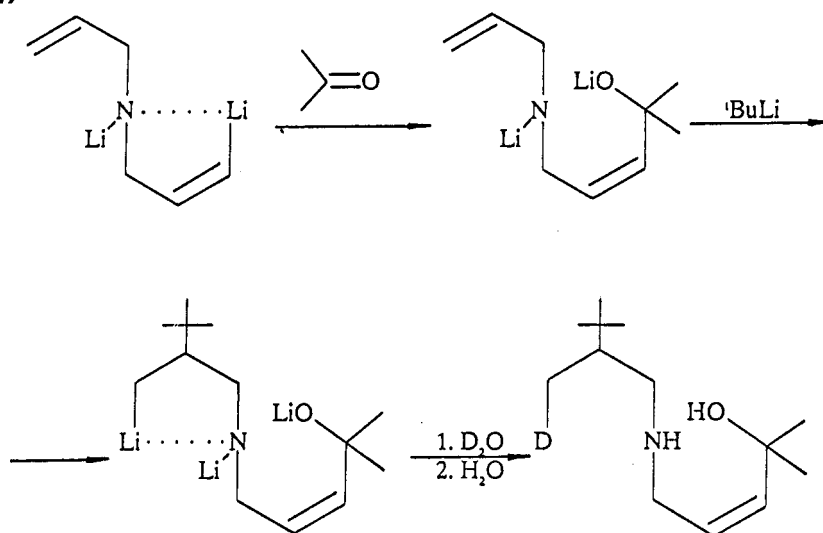
The synthetic utility of the metallated diallylamines was studied and two examples are given here. The reaction of the trianion derived from diallylamine with diethyl carbonate afforded directly the pyrrolizidine derivative shown in Scheme 16. This process presumably involves the formation of an eight membered ring, which spontaneously cyclizes to yield the corresponding hemiaminal derivative; this intermediate loses a proton under the basic reaction conditions to give the pyrrolizidine derivative.

Scheme 16



On the other hand, the dianion derived from diallylamine is able to react with carbonyl compounds in the expected way, affording the corresponding addition compounds, as shown in Scheme 17. The treatment of these intermediates with *t*-butyllithium gave rise quantitatively to the trianionic

Scheme 17



derivative; these species led to the deuterated derivatives by treatment with deuterium oxide followed by hydrolysis. These results allow an entry to either cyclic systems or highly functionalized open-chain compounds by regioselective reactions of diallylamines with several electrophiles. Finally it should be emphasized that more work is necessary in order to determine the synthetic usefulness of this type of compounds in organic chemistry.

Acknowledgement I wish to express my sincere appreciation to my collaborators, whose names appear in the references, specially to Prof. Dr. M. Yus, for their efforts and valuable contribution. I wish to express my gratitude to Dr. F.J. Fañanás and to Dr. J.M. Concellón for fruitful discussions.

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