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C/Se Bond Cleavage of Functionalized Selenides by Lithium Arenides : Application to the Geminal di-Allylation of the Carbonyl Group of Aldehydes and Ketones.

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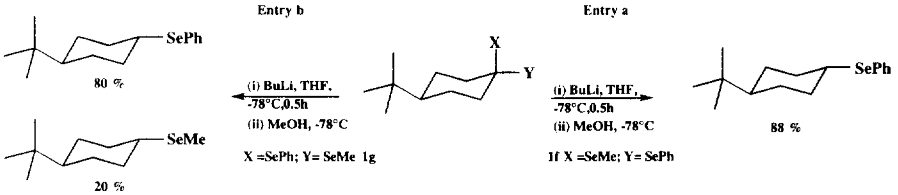
Abstract : Selenoacetals as well as mixed (O,Se) acetals react with lithium arenides and produce, besides lithium selenolates, α-selenoalkyllithiums or α-alkoxyalkyllithiums respectively. We took advantage of these reactions as well as of the ones involving the synthesis of alkyllithiums from selenides to propose an original method for geminal di-allylation of the carbonyl group of aldehydes and ketones.

α-Selenoalkyllithiums are easily available [1,2] from selenoacetals [3] and butyllithiums, and react with a large array of compounds, such as alkyl halides, epoxides, aldehydes and ketones, to produce selenides and functionalized selenides in good yields.[1]

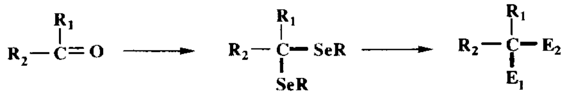
The cleavage of the C-Se bond by butyllithiums occurs with both phenylseleno- and methylseleno acetals. It takes place on the axial seleno group in conformationaly rigid selenoacetals such as those derived from 4-*t*-butylcyclohexanone and provides, besides butylselenides, the axial α-selenoalkyllithiums.[4] Mixed (MeSe, PhSe) acetals also react with butyllithiums providing the more stable α-phenylselenoalkyllithiums by selective cleavage of the C-SeMe bond (Scheme 1, entry a).[4] In the case of conflicting reactivity, as with the acetal shown in Scheme 1, entry b, the formation of the α-phenylselenoalkyllithium prevails, but the resulting equatorial organolithium derivative immediately isomerises to its more stable axial epimer.[4]

Scheme 1



We now report the extension of the work described in the preceding letter,[5] to functionalized selenides, such as selenoacetals,[6] mixed (O,Se) acetals,[6b,c] β-hydroxyalkyl selenides and homoallyl selenides. Some salient observations are reported below. We took advantage of these reactions to design an efficient original synthetic scheme which allows, in a few steps, the geminal difunctionalisation of the carbonyl carbon of aldehydes and ketones (Scheme 2).

Scheme 2

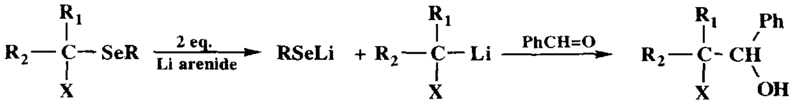


This paper is dedicated to Professor C.W. Jefford at the occasion of his 65 th birthday.

We first found that selenoacetals belonging to both phenyl- and methylseleno series react with lithium arenides, and especially lithium di-*tert*-butylbiphenyl,[7] to produce after quenching with benzaldehyde, the corresponding β-hydroxyalkylselenides in reasonably good yields (Scheme 3, entries a-c). The reaction is less general on the mixed (O,Se) acetal, since it takes place efficiently on the phenylseleno derivatives but does not occur on their methylseleno analogues (Scheme 3, compare entries d and e). It nevertheless allows the synthesis of α-alkoxyalkyllithiums from mixed (O,Se) acetal [6b] which is not possible when butyllithiums are used.[6c]

The difference in reactivity found between the different functionalized selenides reported here follows the trends reported in the preceding letter.[5] Methylseleno derivatives are less prone than their phenylseleno analogues to react with lithium arenides and in order to do so they require the presence of an additional group able to stabilize the carbanionic center.

Scheme 3

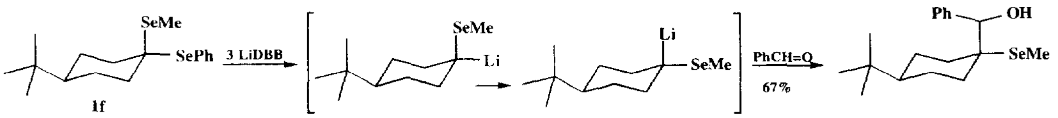


	R	X	R_1	R_2	1	Conditions *	Yield in 5 % [reagent]
a	Ph	SePh	$C_{10}H_{21}$	H	1a	*Method A*	60 (LiDBB)
b	Me	SeMe	$C_{10}H_{21}$	H	1b	*Method A*	53 (LiDBB)
c	Me	SeMe	Ph	H	1c	*Method A*	72 (LiDBB)
d	Ph	OMe	$C_{10}H_{21}$	H	1d	*Method A*	62 (LiDBB)
						Method B	59 (LiN)
e	Me	OMe	$C_{10}H_{21}$	H	1e	*Method B*	0 (LiN)

* *Method A* : selenide added to the Li arenide (THF, -78°C); *Method B* : Li arenide added to the selenide (THF, -78°C).

We also found that LiDBB selectively cleaves the C-SePh bond of the mixed (PhSe, MeSe) acetal derived from 4-*tert*-butylcyclohexanone **1f**. This provides, at first, the less stable α-methylselenoalkyllithium in which the lithium occupies the equatorial position. We have not been able to trap it since it immediately epimerises to its axial stereoisomer prior to reaction with benzaldehyde [(i) 3 LiDBB, THF, -78°C, 0.5 h (ii) 1.2 PhCH=0, -78°C, 67%; compare the results in Scheme 4 with those reported in Scheme 1, entry a for the same selenoacetal]. The same alcohol is obtained in 62 % yield if the same series of reactions are performed on **1g**, the stereoisomer of **1f**.

Scheme 4

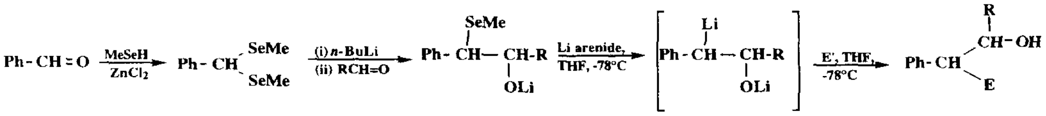


We have recently described that selenoacetals derived from aromatic aldehydes and ketones produce benzylselenides on sequential reaction with butyllithium and alkyl iodide.[8] We also described the same set of reactions, applied to benzylselenides, allows the synthesis of aryl alkanes and therefore the whole process permits the geminal di-alkylation of the carbonyl group of aromatic aldehydes and ketones.[8]

Unfortunately however, the same reaction cannot be extended to β-hydroxyalkylselenides, available from the same selenoacetals butyllithium and carbonyl compounds which are not cleaved to a reasonable extent with butyllithiums (2 equiv., *n*-, *s*- or *t*-BuLi, THF, -78°C).

We now report that the desired β-alkoxybenzyllithiums can be formed by using a lithium arenide (at least 2 eq., -78°C, 0.5 h, Scheme 5) and can be trapped with methanol or with benzaldehyde. The corresponding alcohols or diols (as a mixture of stereoisomers) have been obtained in fair yields (50-60 %), directly from bis(methylseleno)toluene (Scheme 5, entries a,b). Stilbene (in reactions described in Scheme 5, entries a,b) and 1-phenyl-heptene (in reactions described in Scheme 5, entries a,b) resulting from competing β-elimination reactions, have been also isolated. It should be pointed out that this reaction should allow the regioselective synthesis of β-alkoxyalkyllithiums otherwise available only as a mixture of regioisomers by cleavage of the C-O bond of epoxides by lithium arenide.[7a,9] The whole process described in Scheme 5 allows the geminal di-functionalisation of the carbonyl carbon of carbonyl compounds and its generalisation is under progress.

Scheme 5



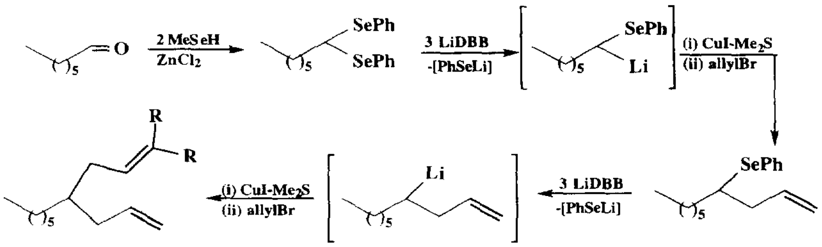
	R	Li arenide	E'	E	Yield % [a]
a	Ph	2.5 eq. LiN, -78°C, 0.5h	MeOH	H	50
b	Ph	2.5 eq. LiN, -78°C, 0.5h	PhCH=O	PhCHOH	57 [b,c]
c	Pentyl	2.5 eq. LiN, -78°C, 0.5h	MeOH	H	58
d	Pentyl	3 eq. LiDBB, -78°C, 0.5h	i-PrCH=O	i-PrCHOH	47 [b,c]

(a) Overall yield from the selenoacetal (b) the alcohol resulting from the protonation of the β-alkoxyalkyllithium has been obtained in up to 27% (c) obtained as a mixture of stereoisomers

As mentioned above, the geminal dialkylation of the carbonyl carbon of aromatic aldehydes and ketones has been successfully achieved taking advantage of the easy access to α-selenobenzyllithiums and to benzyllithiums on reaction of the corresponding selenoacetals and selenides with butyllithiums. The same transformation, which cannot be accomplished using aliphatic aldehydes and ketones due to the lack of methods to generate alkyllithiums from selenides, is now feasible using lithium arenides.

It has been used for the synthesis, in more than 50 % overall yield, of 1,6-dienes by geminal di-allylation of the carbonyl group of heptanal as described in the Scheme 6.[5,7a] It involves the preparation of the phenylselenoacetal derived from heptanal [2 eq. PhSeH, $ZnCl_2$, CH_2Cl_2, 20°C, 3h, 85%] [2] and allylation [10] [1 eq. CH_2=CH-CH_2-Br, -78°C, 1h] of the cuprate obtained on reaction of this selenoacetal with LiDBB [3 eq., THF, -78°C, 0.5h] and CuI-SMe_2 [(a) 2 eq. , -78°C, 0.5h]. The same sequence of reactions performed on the resulting γ,δ-alkenylselenide [(i) LiDBB,[5] 3 eq., THF, -78°C, 0.5h, (ii) CuI-SMe_2, 1 eq., -78°C, 0.5h, (iii) 2 eq. R_2C=CH-CH_2-Br, -78°C, 1h] affords the of 1,6-dienes [R= H : 54% yield, R= Me : 51% yield].[10]

Scheme 6

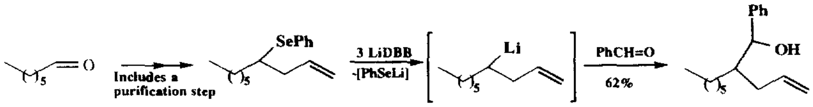


The choice of the phenylseleno series was dictated by the knowledge that it is the only one able to produce the alkenyllithium from a selenide. [5] The use of LiDBB instead of n-BuLi to cleave the C-Se bond of the selenoacetal was intended to avoid the presence of butyl phenyl selenide which is difficult to separate from 4-phenylseleno-1-decene and which would have reacted competitively to produce butyllithium instead of 4-lithio-1-decene.

Copper salts are known to favor the allylation of α-selenoalkyllithiums [10] and of alkyllithiums as well.[11] They are also expected to decrease the aptitude of the lithium phenylselenolate formed, concomitantly in the organolithium derivatives of reacting competitively with the allyl halide and, although CuI was unable to suppress this side reaction totally in our transformation , it could lower it substantially.

The presence of copper salts in the medium is not always beneficial for this transformation. For example benzaldehyde does not react with the cuprate derived from 4-lithio-1-decene, but successful reaction takes place if a purification step is included (Scheme 7).

Scheme 7



Although we have unambiguously proved the feasibility of the synthetic transformations reported here much more work is required to promote it to a useful level. We are working towards this end.

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