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Stereochemical Outcome of Benzyllithiums Synthesis from Selenides

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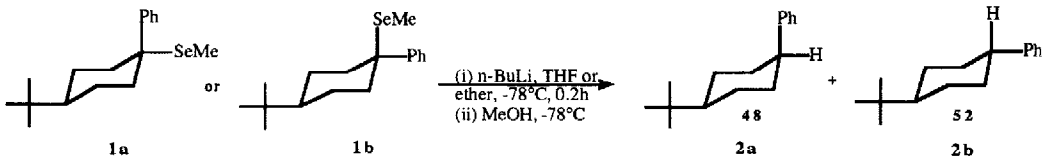
Abstract: Epimerisation usually occurs during the synthesis of arylalcanes from the corresponding benzylselenides which involves benzyllithiums as intermediates. This has been used to produce stereoselectively arylcyclopentanes and arylcyclopropanes. γ-Benzenesulfonyloxyalkyl selenides substituted on the carbon bearing the benzenesulfonyl group behave differently and lead stereospecifically to arylcyclopropane derivatives.

In the course of a work directed towards the synthesis of benzyllithiums [1] from the corresponding selenides and butyllithiums, we became interested to look at the stereochemical outcome of he C-Se bond cleavage as well as on the stereochemical stability of the resulting benzyllithiums.

This reaction, when performed on each stereoisomer of 1-methylseleno-1-phenyl-4-tert-butyl-cyclohexanes **1** occurs in a non stereoselective manner since it led to a 1:1 diastereoisomeric mixture of cis- and trans-1-phenyl-4-tert-butyl-cyclohexanes **2** [(i) n-BuLi, THF, -78°C, 0.2h (ii) MeOH, -78°C (Scheme 1)].[2]

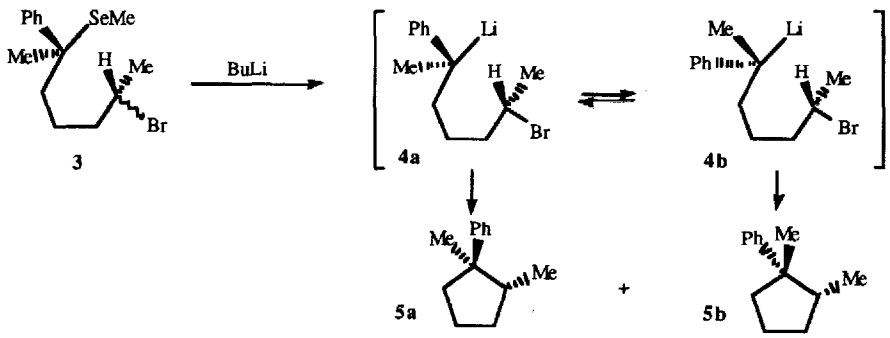
Scheme 1



In order to avoid the epimerisation of the organolithium intermediate, we decided to try to intercept it once produced and choose to perform , for that purpose, an intramolecular alkylation which was expected to lead to a five or a three membered cycle in a particularly favored exo-tet process.[3]

Our first trial involved the formation of the arylcyclopentane derivatives **5** from a stereoisomeric (1/1) mixture of 2-methylseleno-2-phenyl-6-bromoheptane **3** and butyllithiums. We observed under the above mentioned conditions [n-BuLi, THF, -78°C, 0.2h] the high yield formation of 1,2-dimethyl-1-phenyl cyclopentane as a mixture of stereoisomers (**5a/5b**: 80/20).[4] A similar stereoisomeric ratio (cis/trans: 80/20) was obtained when ether or THF-HMPA were used (Scheme 2, entry a). We however completely inverted this ratio ((**5a/5b**: 20/80) if the reaction was instead performed in pentane (Scheme 2, entry b). Thus the control of the stereochemistry on the cyclopentane derivative **5** is not related to the stereochemistry of the starting material and can be achieved by the appropriate choice of the solvent.

Scheme 2

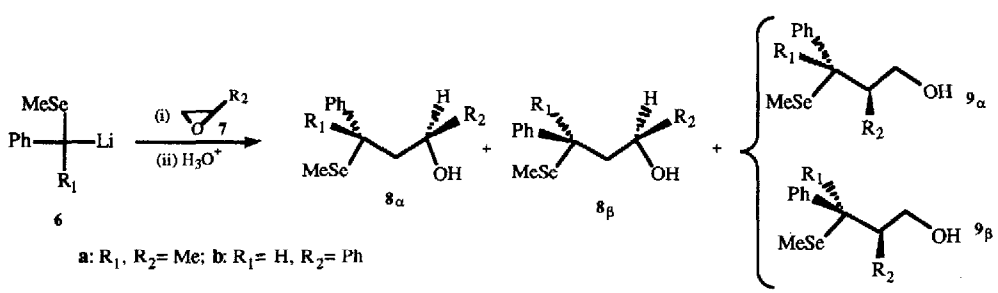


(a) n-BuLi, THF or s-BuLi, ether or s-BuLi, ether - HMPT	80%	80	20
(b) s-BuLi, pentane	73%	19	81

Stereochemical control has been observed when the reaction was carried out on benzenesulfonates derived from the γ-hydroxyalkyl selenides **8** and **9** but whereas a stereoselective reaction took place from **9** which bear a substituent β to the reactive site, a stereospecific one occurred when their regioisomers **8** are involved.

We have thus synthesized, as reported (scheme 3),[5] the γ-hydroxyalkyl selenides **8a**, **8b** and **9b** (R_1, R_2= Me, **8a**: 96% yield, (**8a**$_\alpha$/ **8a**$_\beta$: ~50/50) ; R_1= H, R_2= Ph, **8b**: 56% yield, (**8b**$_\alpha$/ **8b**$_\beta$: 34/66), **9b**: 15% yield, (**9b**$_\alpha$/**9b**$_\beta$: ~50/50)] and have been able to separate quite easily, when produced, the two regioisomeric γ-hydroxyalkyl selenides [**8b** and **9b** (PLC, SiO_2, ether/pentane (8/2), **8b** rf: 0.29; **9b** rf: 0.15]. The separation of each diastereoisomer proved to be more laborious. It was achieved on **8a** by preparative column chromatography (Lobar Merck, medium pressure, SiO_2, hexane/ethyl acetate 95/5, **8a**$_\alpha$ rf: 0.09, **8a**$_\beta$ rf: 0.12) whereas the one of **8b** required the use of HPLC (SiO_2 reverse phase C-18, Sorbax, methanol/water: 60/40). Unfortunately, we have been unable to separate the stereoisomeric mixture of **9b**.

Scheme 3

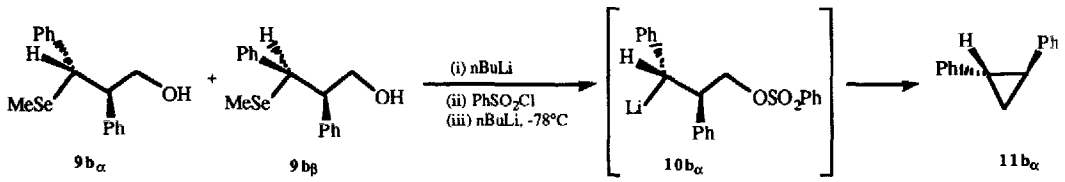


a: R_1, R_2= Me; **b**: R_1= H, R_2= Ph

We have then transformed the stereoisomeric mixture of **9b**$_\alpha$+**9b**$_\beta$ and each of the two stereoisomers **8**$_\alpha$ and **8**$_\beta$ of γ-hydroxyalkylselenides to their corresponding benzenesulfonates which were reacted without further purification with n-butyllithium in THF. We obtained the corresponding cyclopropane derivatives in good yield [(i) 1 equiv. n-BuLi, THF, -78°C (ii) 1.1 equiv. $PhSO_2Cl$, -78°C to 20°C, 1h (iii) 1.1 equiv. n-BuLi, -78°C, 0.7h, schemes 4 and 5].

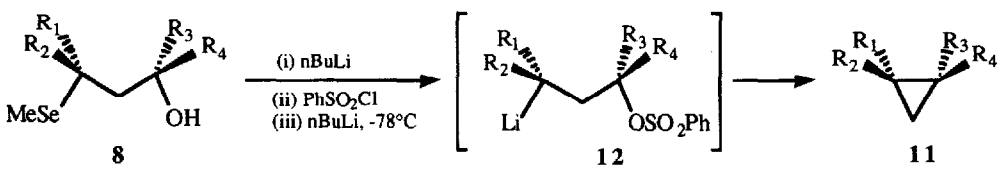
The reaction, when performed in THF-pentane on the stereoisomeric mixture of $\mathbf{9b_\alpha}$+$\mathbf{9b_\beta}$, led exclusively to the trans-1,2-diphenylcyclopropane, [6] attesting that a complete epimerisation of one of the two stereoisomeric benzyllithiums has taken place (Scheme 4).[8]

Scheme 4



At the contrary, we found that the reaction proceeds with very high stereospecificity [6] when performed on each of the two stereoisomers $\mathbf{8_\alpha}$ and $\mathbf{8_\beta}$ of γ-hydroxyalkyl selenides (scheme 5).

Scheme 5



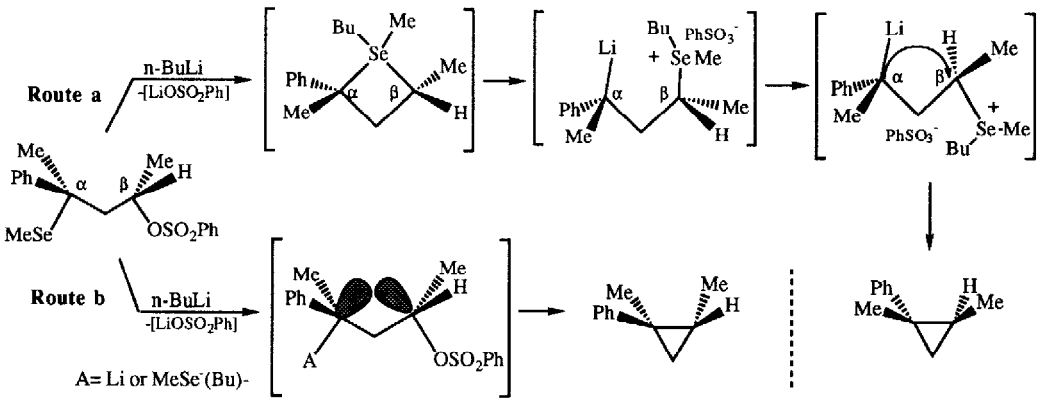
Entry	Starting material	R_1	R_2	R_3	R_4	Product	Yield %	Stereoisom. ratio	d.e.%
1	$\mathbf{8a_\alpha}$	Ph	Me	H	Me	$\mathbf{11a_\alpha}$	79	94/06 ($\mathbf{11a_\alpha}$/$\mathbf{11a_\beta}$)	88
2	$\mathbf{8a_\beta}$	Me	Ph	H	Me	$\mathbf{11a_\beta}$	73	96/04 ($\mathbf{11a_\beta}$/$\mathbf{11a_\alpha}$)	92
3	$\mathbf{8b_\alpha}$	Ph	H	H	Ph	$\mathbf{11b_\alpha}$	74	97/03 ($\mathbf{11b_\alpha}$/$\mathbf{11b_\beta}$)	94
4	$\mathbf{8b_\beta}$	H	Ph	H	Ph	$\mathbf{11b_\beta}$	64	81/18 ($\mathbf{11b_\beta}$/$\mathbf{11b_\alpha}$)	63

The results described in scheme 5 are consistent with a mechanism which proceeds either with (i) retention or (ii) inversion at each of the two reactive sites. Two different processes can be proposed, among others, to explain these observations.

The former one, described in scheme 6 (route a), implies a retention at the benzylic site and a sequence of two consecutive inversions at the other reactive site. It involves the intermediary formation of a four membered selenurane bearing a tetracoordinated selenium atom which is expected to produce the aryl cyclopropane by one of the mechanism already proposed to explain the stereoselective synthesis of cyclopropane derivatives from thietanonium salts and butyllithium.[9] The second one is reminiscent to the one proposed [9] to rationalize the formation of *trans* -1,2-dimethyl cyclopropane from (d,l)-2,4-dibromopentane. It can occur through a sequence of reactions taking place on the starting material adopting a W conformation (scheme 6, route b).[10] The (scheme 6, route b).

Intermediary formation of biradicals which collapse through a conrotatory mode to the cyclopropane derivative or intervention in the cyclisation step of a "seleno ate" complex instead of the organolithium compound derived from its decomposition cannot be confirmed or ruled out, at this stage of the work.[9] Work is in progress in order to discriminate between the two processes detailled in scheme 6.

Scheme 6



In conclusion almost all of the possible stereochemical outcome have been found in the reaction of benzylselenides and butyllithiums: (**a**) *epimerisation in the case of* (**i**) 1-methylseleno-1-phenyl-4-tert-butyl-cyclohexanes which leads to a 1/1 stereoisomeric mixture of the corresponding selenides (scheme 1) (**ii**) ε-hydroxyalkylselenides which finally lead, depending upon the nature of the solvent, to the stereoselective formation of each stereoisomeric aryl cyclopentane derivative (scheme 2) (**iii**) γ-hydroxyalkyl selenides bearing two substituents on the adjacent carbon which lead to the exclusive formation of the trans cyclopropane derivatives irrespective of the nature of the solvent (scheme 4) (**b**) *complete control of the stereochemistry* at the benzylic site from γ-hydroxyalkyl selenides bearing a substituent at the two carbons (scheme 5).

The synthesis of cyclopropane derivatives from α,γ-diheterosubstituted alkanes is quite well documented in the literature and also often produces diastereoisomers.[11]

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6 The stereochemistry of the starting materials has been unambiguously assessed by X ray crystallography of the γ-hydroxyalkyl selenide **8a**$_\beta$ and of the camphanic ester derived from **8b**$_\alpha$ (manuscript in preparation). The structures of the resulting cyclopropane derivatives has been determined by comparison of their ^{1}H NMR with those described in the literature [7] and ascertained by ^{13}C and 2D NMR.

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