Connective (C–C) Route to Hindered Epoxides and Olefins from Hindered Ketones

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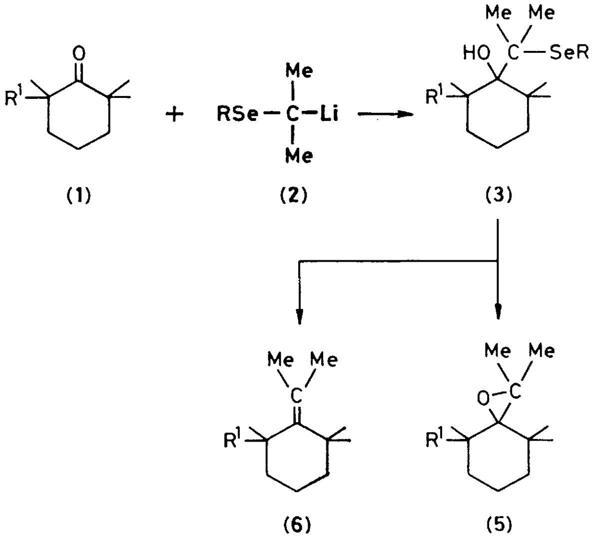
Hindered ketones have been transformed into hindered epoxides (**5**) and olefins (**6**) with the concomitant formation of new carbon–carbon bonds using β-hydroxyselenides as key intermediates; the unusual reactivity of such crowded molecules is reported.

The regioselective synthesis of olefins and epoxides from hindered carbonyl compounds is a problem often encountered during the synthesis of natural products for which a general solution has not yet been found.[1] *E.g.*, sulphur[2] and phosphorus ylides,[1b,3] even those derived from methylene groups, do not produce the corresponding epoxides and olefins from hindered carbonyl compounds such as 2,2,6,6-tetramethyl- and 2,2,6-trimethyl-cyclohexanones under normal conditions.[4]†

The discovery that epoxides and olefins can be formed in high yield from β-hydroxyselenides[6] (readily prepared from α-selenoalkyl-lithium and carbonyl compounds) led us to investigate these reactions with the hindered carbonyl compound (**1**) as a model (Scheme 1).

We found that 2-lithio-2-selenopropanes[7] (**2**) (R = Me or Ph), readily available from 2,2-bis-selenopropanes and



Scheme 1

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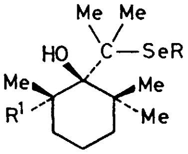
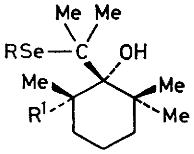
† Other α-heterosubstituted organometallic compounds bearing a non-charged heteroatom such as α-thioalkyl-lithiums and α-trimethylsilylalkyl-lithiums[6] have been successfully used for epoxide [2b,5a] and olefin[1b,5b–c] synthesis from hindered carbonyl compounds.



(3′)



(3″)

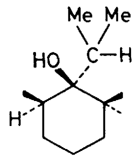
Table 1

	R	R^1	Conditions	Yield as (3), % (3′:3″)
(3a)	Me	Me	THF, −45 °C, 3h	77
			Ether, −78 °C, 4h	83
(3b)	Ph	Me	THF, −78 °C, 3h	00
			Ether, −78 °C, 4h	60
(3c)	Me	H	THF, −45 °C, 4h	48 (33:67)
			Ether, −78 °C, 1h	85 (95:5)
(3d)	Ph	H	THF, −78 °C, 1h	00
			Ether, −78 °C, 0.5h	84 (95:5)

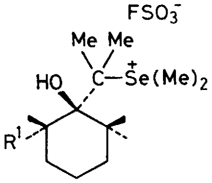
butyl-lithium,‡ exhibit an unusual nucleophilicity towards the hindered carbonyl compound **(1)**. The methyl-seleno derivative was found to be the best reagent § producing the corresponding β-hydroxymethylselenide **(3)** (R = Me) in good yield (*ca.* 80%) if the reaction is conducted in ether–pentane (1:1) instead of tetrahydrofuran (THF)–hexane as reported previously[5] (Table 1). The right choice of solvent was found to be even more important‡ for phenyl-selenoalkyl-lithiums for which no reaction was detected in THF–hexane whereas modest to good yields were obtained in ether–pentane.

Equatorial attack leading to **(3′)** predominates in the case of trimethylcyclohexanone. However the ratio of the two stereoisomers differs with the solvent used (Table 1). We have purified the two stereoisomers **(3′)** and **(3″)** by preparative layer chromatography (SiO$_2$, Merck, pentane–ether, 95:5, R_F 0.6 and 0.55 respectively) and we have correlated the stereoisomers **(3′)** of different origins (R = Me, Ph) by reducing their selenyl moieties with tributyltin hydride in the presence of 10% azobisisobutyronitrile[8] [80 °C, 0.2 h, quantitative yield as **(7′)**]. The stereochemistry of the isomer **(3c′)** has been unambiguously ascertained by an *X*-ray crystallographic study on a related derivative.¶

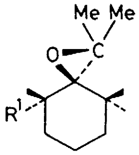
The methods we have reported for the synthesis of epoxides and olefins from β-hydroxyselenides were found unsuitable for the synthesis of compounds **(5)** and **(6)** from the hindered methylseleno-derivatives **(3a)** and **(3c′)**. Thus the β-hydroxyselenonium salts **(4a)** and **(4c′)** needed for the synthesis of epoxides are not produced on reaction with MeI[7b] but require the more electrophilic methyl fluorosulphonate (1 equiv., ether, −78 °C, 0.5 h, then −78 °C to 0 °C, 1 h). These salts are particularly unstable when liberated from ether and rearrange immediately in Me$_2$SO or CH$_2$Cl$_2$ (the solvents used for further transformation to epoxide).[7b] Thus **(4a)** leads to an 80:20 mixture of the allyl alcohol **(8a)** and the ring-enlarged ketone **(9a)** in Me$_2$SO (20 °C, 0.9 h) and a 66:34 mixture of the same ketone **(9a)** and the diene **(10a)** in CH$_2$Cl$_2$ (20 °C, 0.3 h). Under the latter conditions, the β-hydroxyselenonium salt



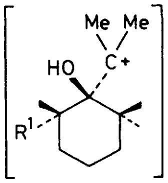
(7c′)



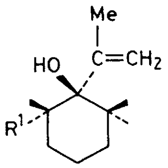
(4a) R^1 : Me
(4c′) R^1 : H



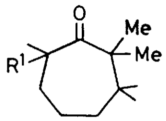
(5a) R^1 : Me
(5c′) R^1 : H



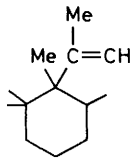
(11a) R^1: Me
(11b) R^1: H



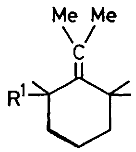
(8a) R^1: Me
(8c′) R^1: H



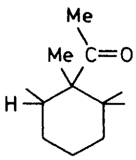
(9a) R^1: Me
(9c) R^1: H



(10a)



(6a) R^1: Me
(6c) R^1 : H



(12c)

(4c′) only produces the ketone **(9c)**, by exclusive migration of the dimethyl-substituted carbon atom.

Compounds **(8)**, **(9)**, and **(10)** can be formed by the loss of dimethyl selenide from **(4)** which reduces the strain present and leads to a particularly well stabilized carbenium ion **(11)**; this should produce **(8)** by loss of a proton and **(9)** by migration of one side of the six-membered ring (related to the Demjanov or pinacol rearrangements).[9] These reactions produce fluorosulphonic acid which can account for the formation of the diene ****(10a)** by protonation of the hydroxy-moiety of either **(4a)** or **(8a)**.

In agreement with these proposals we found that the allyl alcohol **(8a)**, prepared[11] from the β-hydroxyselenide **(3a)** [Bu^t O$_2$H (4 equiv.), basic alumina (8 equiv.), THF, 55 °C, 3 h, 95% yield] rearranges to the diene **(10a)** on reaction with catalytic amounts of fluorosulphonic acid (CH$_2$Cl$_2$, −40 °C, 0.2 h, 85% yield). The less hindered allyl alcohol **(8c)** [from **(3c)**, Bu^{t}O$_2$H, basic alumina, tetrahydrofuran, 55 °C, 3 h, 86% yield] is recovered unchanged after the same treatment.

The synthesis of the desired epoxides **(5a)** and **(5c′)** was finally achieved in high yield (95%) by the reaction of the corresponding selenonium salts **(4a)** and **(4c′)** suspended in ether with a 10% aqueous solution of KOH (0 °C, 1 h). We found that they behave differently in acid media. The epoxide **(5a)** derived from tetramethylcyclohexanone exclusively produces the ring-enlarged ketone **(9a)** on reaction with BF$_3$·OEt$_2$ [CH$_2$Cl$_2$ (0.5 equiv.), −78 °C, 0.1 h; 0 °C, 0.3 h, 95%]; the epoxide **(5c′)** under similar conditions leads to the rearranged **(12c)** and the ring-enlarged **(9c)** ketones [**(12c)**:**(9c)**, 90:10] in 62% overall yield.

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‡ These reactions have been performed at −78 °C for 0.5 h with Bu^{n}Li in THF–hexane or with Bu^{s}Li in ether–pentane.

§ These findings seems to be general. For example, 1-selenoethyl-lithium and selenomethyl-lithium behave similarly with these two ketones.

¶ Details will be reported in the full paper.

** A closely related rearrangement has been described by Trost[10] for a β-hydroxycyclopropyl sulphide derived from tetramethylcyclohexanone.

The synthesis of the olefins (**6a**) and (**6c**) was the last objective and from the results just described a rearrangement of the type (**3a**) → (**10a**) should occur when the hydroxy-group of (**3**) is transformed into a better leaving group, and the hindered carbon–carbon double bond in the expected olefins (**6c**) could migrate readily.

Our previously described method[12] ($SOCl_2$, NEt_3, CH_2Cl_2, 20 °C, 4 h) applied to (**3**) leads to a moderate yield (63%) of the required olefin (**6**). This is not formed if $POCl_3$[13] is used instead of $SOCl_2$. We discovered however that PI_3 (1 equiv., CH_2Cl_2, NEt_3, 20 °C, 0.5 h) reacts instantaneously and allows the synthesis of (**6a**) (95%) and (**6c**) (84%) in very high yield.

The reactions described here show how versatile the β-hydroxyselenides are for the selective syntheses of various selenium-free molecules.

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