Ring Opening Alkylation of Cyclic Ethers with α-Halogenoalkyllithiums in the Presence of Boron Trifluoride–Diethyl Ether

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It is demonstrated for the first time that α-halogenoalkyllithium reagents can be utilized for ring opening alkylation of various oxiranes, oxetane and oxolane (THF) in the presence of boron trifluoride–diethyl ether at low temperatures.

Although α-halogenoalkyllithium reagents[1] have a strong tendency to split into the corresponding carbene and lithium halide, they can be generated and handled as relatively stable species at lower temperatures and can be utilized for such reactions as addition to carbonyl compounds,[2] substitution of alkyl halides,[3] *etc.* Ring opening of oxiranes by these reagents, however, has not been reported to our knowledge. It seems likely that, at the low temperatures required for handling these carbenoid species, they may not be sufficiently reactive to open the oxirane ring, while, at higher temperatures, they may decompose before undergoing the desired reaction.

Indeed, $LiCCl_3$ for example did not react with hex-1-ene oxide at between −95 and −60 °C in THF. We anticipated that the activation protocol with BF_3[4] might be suitably applied for promoting the present transformation of oxiranes at the low temperatures, and indeed found it to be successful (Scheme 1).

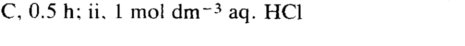
Thus, the carbenoid was generated at −95 °C by metallating chloroform (6.0 mmol) with *n*-butyllithium (1.64 mol dm^{-3} hexane solution, 6.0 mmol) in THF (20 ml). To it was added hex-1-ene oxide (5.0 mmol) and $BF_3{\cdot}OEt_2$ (6.0 mmol) successively, and the temperature was allowed to come to −65 °C over a period of *ca.* 0.5 h. After usual work-up, flash chromatography and bulb-to-bulb distillation, there was obtained 1,1,1-trichloroheptan-3-ol (0.934 g, 85%, bath temperature 115–120 °C at 3 Torr).

Reversal of the order of addition of the oxirane and the Lewis acid in the above reaction gave practically the same result (86% isolated yield of the trichloroheptanol). Here, the last addition of the Lewis acid was taken as the standard procedure, and reactions of some representative oxiranes with $LiCCl_3$ $LiCHCl_2$, and a few other carbenoid reagents were studied (Table 1). Mono- and 1,1-di-substituted oxiranes were ring opened at the unsubstituted site regioselectively. Cyclohexene oxide was converted to *trans*-2-trichloromethylcyclohexanol† (solid, mp 82.5–84.5 °C) with inversion as normally observed in reactions with ordinary organolithium reagents.

Generally, $LiCHCl_2$ gave lower yields of ring opened products than $LiCCl_3$ in spite of the reported higher thermal stability of the former reagent.[5] Use of a larger excess (2.5 equiv.) of $LiCHCl_2$ improved the yield in some cases (entries 3 and 5).

It should be noted that, in the reaction with an olefinic oxirane (entries 4, 5 and 6), neither reagent gave any cyclopropanation product even though an excess of the reagent was used, particularly in the case of $LiCHCl_2$ (2.5 equiv.).

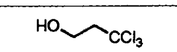
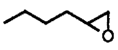
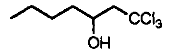
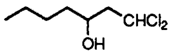
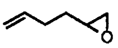
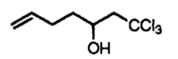
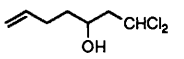
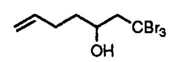
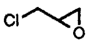
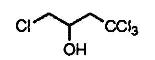
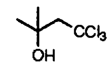
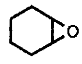
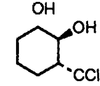
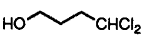
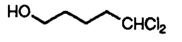
From the reactions of epichlorohydrin and ethylene oxide with $LiCCl_3$ (entries 1 and 7), 5,5,5-trichloropentan-1-ol was isolated as a common byproduct in 28 and 4% yield, respectively, based on the amount of chloroform used. This might have been produced by cleavage of the solvent THF. It was a rather surprising finding since THF has often been used as the solvent in the closely related[4] and other organometallic reactions and is considered tacitly to be practically unreactive towards this type of ring opening. The reactivity of THF could be confirmed by the independent runs with $LiCCl_3$ and $LiCHCl_2$ (entries 13 and 14), although the yields of the ring opened products were only moderate.



Scheme 1 *Reagents and conditions*: i, $LiCCl_3$, $BF_3{\cdot}OEt_2$, THF, −95 to −65 °C, 0.5 h; ii, 1 mol dm^{-3} aq. HCl

Naturally, oxetane also reacts smoothly with these reagents. In the reaction with dichlorobenzyllithium (entry 12), however, the expected product 4,4-dichloro-4-phenylbutan-1-ol was again accompanied by a fair amount of the THF-

Table 1 Ring opening alkylation of cyclic ethers with α-halogenoalkyllithiums in the presence of boron trifluoride–diethyl ether[a]

Entry	Substrate	Reagent	Product	Yield (%)[b]
1		$LiCCl_3$		79[c]
2		$LiCCl_3$		85
3		$LiCHCl_2$[d]		77
4		$LiCCl_3$		84
5		$LiCHCl_2$[d]		74
6		$LiCHBr_3$[e]		57
7		$LiCCl_3$		49
8		$LiCCl_3$		88
9		$LiCCl_3$		88
10		$LiCCl_3$		96
11		$LiCHCl_2$		79
12		$LiCCl_2Ph$[g]		78[h]
13		$LiCCl_3$		47
14		$LiCHCl_2$		21

[a] The reaction conditions given in the text were followed, unless otherwise indicated. [b] Isolated yield based on the amount of the cyclic ether used is given, unless otherwise indicated. [c] The major product was accompanied by 5,5,5-trichloropentan-1-ol, and their yields based on the amount of chloroform used were 64 and 4%, respectively. [d] A larger exess (2.5 equiv.) of both $LiCHCl_2$ and $BF_3{\cdot}OEt_2$ were used. [e] The first stage of the reaction was conducted at −110 °C. [f] The major product was accompanied by 5,5,5-trichloropentan-1-ol, and their yields based on the amount of chloroform used were 41 and 28%, respectively. [g] The first stage of the reaction was conducted at −100 °C. [h] The major product was accompanied by 5,5-dichloro-5-phenylpentan-1-ol, and their yields based on the amount of benzal chloride were 65 and 14%, respectively.

cleavage product 5,5-dichloro-5-phenylpentan-1-ol (65 and 14% yield, respectively, based on the amount of benzylidene chloride used).

We are studying these transformations with some other type of carbenoid reagents, and the results will be reported in due course.

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Footnote

† The *trans* geometry was assigned based on the vicinal coupling constant (10 Hz) of the two methine protons by 400 MHz ^{1}H NMR.

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