Regio- and Stereo-selective Ring Opening of Epoxides with Amide Cuprate Reagents

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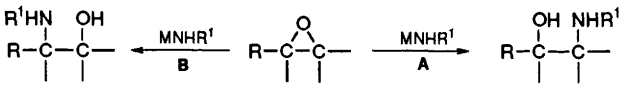
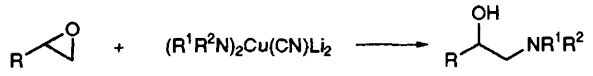
Amide cuprate reagents attack the less hindered carbon atom of epoxides to give 1,2-amino alcohols in good yields; this procedure is applied to the synthesis of an aziridine alcohol bearing a carborane framework which is a potentially useful ^{10}B carrier for boron neutron capture therapy.

There are a number of limitations in the ring opening of epoxides by amines: for example low nucleophilicity of amines requires elevated temperatures, the reactivity of sterically bulky amines is low and the regiocontrol of the ring opening is not so easy.[1] To overcome these problems, several metal amides have been developed (Scheme 1). Basic reagents such as lithium[2] and magnesium[3] amides, and lead amide reagents[4] attack the less hindered carbon atoms with moderate to high regioselectivity (type **A**). A major drawback associated with lithium amides is that the hydrogen α to the epoxide ring is



Scheme 1. Regioselectivity of metal amides. Type **A**: M = Li, Mg, Al, Pb, Me_3Si ($AlCl_3$); R_2NH in the presence of catalysts. Type **B**: M = Al, Me_3Sn.



Scheme 2

abstracted by the amide base and thus the corresponding allylic alcohol is frequently obtained as a major product.[2] Aminostannanes Me_3SnNR_2 provide type **B** ring opening,[5] whereas the Lewis acid-mediated reaction of Me_3SiNEt_2 gives type **A** cleavage.[6] The ring opening promoted by Ph_4SbOTf (Tf = CF_3SO_2),[7] $CoCl_2$,[8] and $LiClO_4$ and related salts[9] proceeds *via* type **A**. Diethylaluminium amides[10] and Al_2O_3 mediated amination[11] generally afford type **A** ring opening. $Ti(OPr^i)_4$-mediated ring opening of 2,3-epoxy alcohols and their derivatives proceeds regioselectively at C-3.[12]

We now report that the regioselective type **A** ring opening may be accomplished with amide cuprates, prepared from 2 equiv. of lithium amide and 1 equiv. of CuCN[13] (Scheme 2); no hydrogen abstraction takes place and normally high chemical yields are obtained. Furthermore, isolation of the product is much easier in the new method in comparison with the lead and tin mediated procedures. The results are summarized in Table 1.

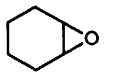
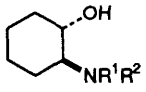
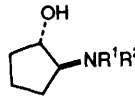
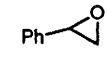
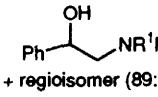
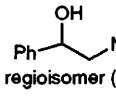
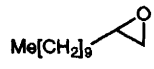
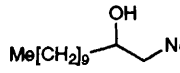
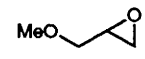
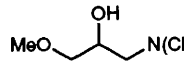
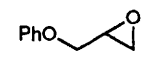
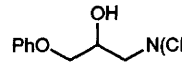
In contrast to lithium diethylamide, which gave the corresponding allylic alcohol in 86% yield along with the desired amino alcohol in 10% yield upon treatment with cyclohexene oxide,[2] diethylamide cuprate afforded the desired amino alcohol in 89% yield without formation of the allylic alcohol (entry 1). Perhaps the lower basicity of the copper amide reagent suppresses the hydrogen abstraction at the α-position. Further examples are shown in entries 2–11. It is clear that amide cuprates are widely applicable for epoxide ring opening; the reagents are easily prepared and handled, and the work-up process is not cumbersome.

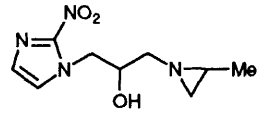
The ring opening of cyclohexene oxide with aniline, which is a weak nucleophile, is representative. To a solution of aniline (0.55 ml, 6.0 mmol) in tetrahydrofuran (THF; 5 ml) was added a solution of Bu^nLi (6 mmol, 3.64 ml × 1.65 mol l^{-1}) in hexane at 0 °C. The reaction mixture was stirred for 30 min at this temperature then cooled to −78 °C. CuCN (268.7 mg, 3.0 mmol) was added at −78 °C. The resulting suspension was allowed to warm to −30 °C and a homogeneous solution was obtained. The solution was cooled to −78 °C and cyclohexene oxide (0.101 ml; 1.0 mmol) was added at this temperature. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with a mixture of saturated aqueous NH_4Cl and 28% aqueous NH_3 (1 : 1; 10 ml). The usual work-up gave the crude material, which was purified by flash chromatography on silica gel using benzene–EtOAc (4 : 1) as eluent, affording *trans*-2-anilinocyclohexanol (154 mg, 81% yield).

We next applied this new procedure to the synthesis of the carboranyl aziridine **1** which was expected to be an efficient boron carrier for neutron capture therapy.[14] RSU1131 **2** has strong affinity to B-16 melanoma cells; its biological activity is considered to be due to the very reactive aziridine ring which irreversibly forms a tight covalent bond with DNA.[15] Therefore we expected that **1** may also be accumulated in certain cancer cells.

The reactions of the metallated methylaziridine **4** with the carboranyl epoxide **3a**[16] are shown in Scheme 3. Unsatisfactory results were obtained with the lithium and aluminium

Table 1 Ring opening of epoxides with amide cuprates

Entry	Epoxide	$(R^1R^2N)_2Cu(CN)Li_2$ R^1	R^2	Product	Yield (%)
1		Et	Et		89
2		$PhCH_2$	$PhCH_2$		66
3		$PhCH_2$	H		67
4					78
5		Ph	H		81
6		$PhCH_2$	$PhCH_2$		79
7		$PhCH_2$	$PhCH_2$	 + regioisomer (89:11)	91
8		$PhCH_2$	H	 + regioisomer (88:12)	93
9		$PhCH_2$	$PhCH_2$		84
10		$PhCH_2$	$PhCH_2$		88
11		$PhCH_2$	$PhCH_2$		94



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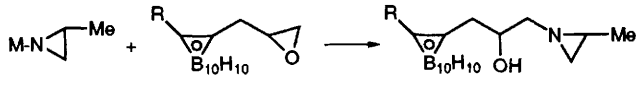

3a; R = H
b; R = $CH_2OCH(OCH_2Ph)_2$

1a; R = H
b; R = $CH_2OCH(OCH_2Ph)_2$

M (equiv.)	*T*/°C, *t*/h	**1a**, yield (%) (recovery of **3a**)
Li (1.3)	−10 → rt,[a] 0.75	<5
$AlEt_2$ (1.2)	−10 → rt, 12	0 (100)
MgBr (1.2)	−10 → rt, 42	43
$PbBu_3$ (3)	−10 → rt, 15	53 (28)
Cu(CN)Li (3)	−78 → rt, 3	39 (38)
$[Cu(CN)Li_2]_{1/2}$ (2)	−78 → rt, 3	50 (28)

[a] rt = room temp.

Scheme 3

reagents. The magnesium reagent gave **1a** in 43% yield along with unidentified by-products, but a rather longer reaction time was needed. The lead reagent produced **1a** in 53% yield without by-products, but separation of **1a** from the tributyllead residue was cumbersome. Among the metal amides examined, the higher order cuprate derivative gave the best result in respect of the product yield and ease of handling.[17] The reaction of **3b** with 5 equiv. of the higher order cyanocuprate reagent gave **1b** in 78% yield. The aziridine cuprate (5 equiv.), prepared from 2-methylaziridinyllithium (10 equiv.) and CuI (5 equiv.), also gave **1b** in 77% yield. Accordingly, it is clearly demonstrated that ring opening with copper amide reagents is applicable to epoxides containing a carborane framework which is labile under basic conditions.

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