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REGIOSELECTIVE OPENING OF 2,3-EPOXY ALCOHOLS WITH ORGANOCUPRATES.
ENHANCED C-2 SELECTIVITY THROUGH SOLVENT EFFECTS.

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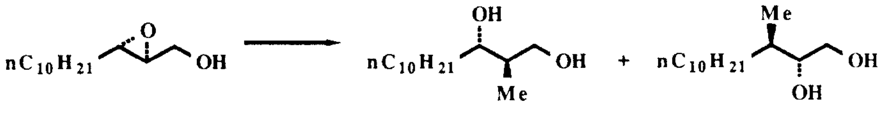
Summary: *In coordinating solvents (THF-DMEU or THF-TMEDA), increased selectivity for opening at C-2 of 2,3-epoxy alcohols is observed with* $Me_2CuCNLi_2$ *prepared from low-halide MeLi.*

Since the discovery of the Sharpless epoxidation in 1980[1] which has allowed for the preparation of homochiral 2,3-epoxy alcohols, considerable attention has been directed at regioselective opening of these compounds with carbon nucleophiles.[2] A number of organometallic reagents, including organocuprates and organoaluminum complexes, have been used with varying degrees of regioselectivity.[3-8] For example, opening of 2,3-epoxy alcohols with Me_3Al generally results in introduction of a methyl group to C-3 with good to excellent regioselectivity.[3-5] With 3-substituted-2,3-epoxy alcohols that are branched at C-4, opening with Me_2CuLi results in exclusive opening at C-2 (to form a 1,3-diol).[6,7] However, with trans 2,3-epoxy alcohols[9] that have a simple alkyl group (not branched at C-4) at C-3, opening with Me_2CuLi is essentially non-regioselective and 1:1 mixtures of 1,2 and 1,3-diols result.[2a,10] Thus when the 1,3-diol (the product of opening at C-2) is the desired product in these cases, one strategy which has been employed recently is to treat the 1:1 mixture with periodate and then to separate the 1,3-diol from the resulting aldehyde.[11,12] This strategy has the obvious disadvantage that the yield of the desired product will not exceed 50%. We now report that the ratio of C-2:C-3 opening in these unbranched cases may be increased from 1:1 to > 5:1 simply by the appropriate choice of reagent and solvent.[13]

Initial studies were carried out using epoxy alcohol **1a** and the higher order cuprate $Me_2CuCNLi_2$ (**4**) which has been shown to be particularly efficient for epoxide openings.[14] Results are summarized in Table I. As expected, reaction of **1a** with **4** under the conditions typically employed (Et_2O, -20°C) gave a mixture of **2a** and **3a** with essentially no selectivity (**2a**:**3a** = 53:47, entry 1). However, with better coordinating solvents, the ratio of **2a**:**3a** increased (entries 2-5). Best results were obtained using THF-TMEDA (N,N,N',N'-tetramethylethylenediamine, **2a**:**3a** =74:26, entry 3) and THF-DMEU (1,3-dimethyl-2-imidazolidinone, **2a**:**3a** =84:16, entry 5) as solvent. Although the reaction using DMEU as cosolvent was quite slow (0°C, 18 h)[15], no side-products were detected and the two regioisomers were isolated in excellent (>90%) yield.

Table I. Reaction of Epoxy Alcohol **1a** with $Me_2CuCNLi_2$ **(4)** and Me_2CuLi **(5)**. [a]

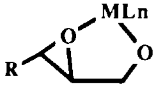


1a **2a** **3a**

Entry	Reagent[b]	Solvent	Conditions[c]	Ratio **2a:3a**[d,e]
1	**4**	Et_2O	A	53:47
2	**4**	THF	A	67:33
3	**4**	THF-TMEDA,4:1	B	74:26
4	**4**	THF-DMEU,9:1	C	70:30
5	**4**	THF-DMEU,4:1	C	84:16
6	**4** •LiBr[f]	THF	B	49:51
7	**4** •LiBr[f]	THF-TMEDA,4:1	B	51:49
8	**4** •BF_3•OEt_2[g]	THF	D	21:79
9	**5**	Et_2O	A	44:56
10	**5**	THF-TMEDA,4:1	B	59:41
11	**5**	THF-DMEU,4:1	C	67:33

[a] Reactions were carried out on 0.5 mmol of substrate using 2.0 mmol of reagent in 10 mL of solvent under the conditions specified. [b] Reagent **4** was prepared by addition of MeLi (low halide) to CuCN at -20°C; for **5**, CuBr•SMe_2 was employed as the copper source. [c] A: -20°C/2 h→0°C/1 h; B: -20°C/2 h→0°C/2 h; C: -20°C/2 h→0°C/18 h; D: -78°C/1 h→0°C/1 h. [d] Ratios were determined by ^1H NMR spectroscopy (250 MHz) on the peracetylated (Ac_2O,pyr, catalytic DMAP) reaction mixture in C_6D_6. [e] The isolated yield of diols was 85-95% in each case. Only **2a** (R_f=0.36) and **3a** (R_f=0.29) were detected by TLC (double elution with CH_2Cl_2-MeOH,20:1). [f] The reagent was prepared using MeLi•LiBr. [g] BF_3•OEt_2 (2.0 mmol) was added to **4** at -78°C.[16]

It is interesting to note that this enhanced selectivity was seen only when the cuprate was prepared from low-halide MeLi; use of MeLi-LiBr consistently resulted in essentially no selectivity regardless of the solvent (entries 6,7). Also, the addition of BF_3-OEt_2[16] resulted in enhanced selectivity for opening at C-3 (**2a:3a** = 21:79, entry 8). These results may be rationalized by suggesting that opening of the epoxide at C-3 may be taking place through intermolecular attack on a complex such as I;[17] this complex would be favoured with Lewis acids and disfavoured in strongly coordinating solvents. "Intramolecular" opening of the epoxide through a complex such as II would be expected to favour attack at C-2.



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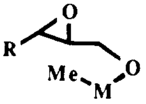
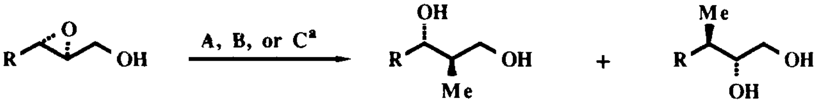


II

With the reagent Me$_2$CuLi **(5)**, there was a similar but less pronounced solvent effect (entries 9-11); the ratios of **2a:3a** varied from 44:56 (Et$_2$O) to 67:33 (THF-DMEU).

We have compared the opening of a number of other trans-2,3-epoxy alcohols using Me$_2$CuLi in Et$_2$O (classical conditions[18,19]) with opening using Me$_2$CuCNLi$_2$ in THF-TMEDA and THF-DMEU and have found the enhanced C-2 selectivity to be consistent (Table II). Thus epoxides **1a-1c**, each possessing a methylene unit at C-4, are opened with **5** in Et$_2$O with essentially no regioselectivity. Much better yields of the 1,3-diol were obtained using **4** in THF-TMEDA or THF-DMEU. In THF-TMEDA opening at C-2 was favoured to the extent of ≈74:26; in THF-DMEU the ratio of **2:3** was consistently 84:16. The cyclohexyl substituted epoxide **1d** showed a similar trend but with more bias towards C-2 as would be expected on the basis of steric arguments. The oxygen-substituted epoxide **1e** gave somewhat anomalous results in that very little differences in selectivity were observed for the three different conditions tried; nevertheless, all three conditions afforded reasonable selectivities for opening at C-2.

Table II. Reaction of Epoxy Alcohols **1** with Me$_2$CuCNLi$_2$ **(4)** and Me$_2$CuLi **(5)**.



1 **2** **3**

Entry	Epoxy Alcohol[d]	R	Ratio 2:3[b,c] A	B	C
1	**1a**	n-C$_{10}$H$_{21}$	44:56	74:26	84:16
2	**1b**	Ph(CH$_2$)$_3$	44:56	73:27	84:16
3	**1c**	n-C$_6$H$_{13}$	42:58	69:31	84:16
4	**1d**	c-C$_6$H$_{11}$	71:29[e]	91:9[e]	95:5[f]
5	**1e**	4-BrC$_6$H$_4$CH$_2$OCH$_2$	89:11	83:17	91:9

[a] Conditions: A: **5** (4 equiv), Et$_2$O, -20°C/2 h→0°C/1 h; B: **4** (4 equiv), THF-TMEDA (4:1), -20°C/2 h→0°C/2 h; C: **4** (4 equiv), THF-DMEU (4:1), -20°C/2 h→0°C/18 h. [b] Ratios were determined by ^{1}H NMR spectroscopy (250 MHz) on the peracetylated reaction mixture in C$_6$D$_6$ (entries 1-3) or CDCl$_3$ (entries 4,5). [c] The isolated yield of diols was 85-95% in each case. [d] Epoxy alcohols were prepared using catalytic [5-10 mol% Ti(OiPr)$_4$, 6-12 mol%(+)-DIPT] asymmetric epoxidation of the corresponding allylic alcohols.[20] [e] Reaction was run at 0°C for 6 h. [f] After 18 h, reaction was only 70% complete.

While the results described herein are not a perfect solution to the problem of regioselectively introducing a methyl group into C-2 of simple 2,3-epoxy alcohols, they are a considerable improvement on the conditions which are currently available (which give at best a 1:1 mixture of isomers). Further work may provide better solutions.

Acknowledgments

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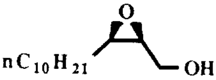

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