

REGIOSELECTIVE OPENINGS OF 2,3-EPOXY ACIDS WITH ORGANOCUPRATES

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Abstract: Lithium organocuprates react with 3-alkyl-2,3-epoxy acids (glycidic acids) to afford the products of ring-opening in good yield. The regiochemistry of ring-opening is dependent on the stereochemistry of the epoxy acid.

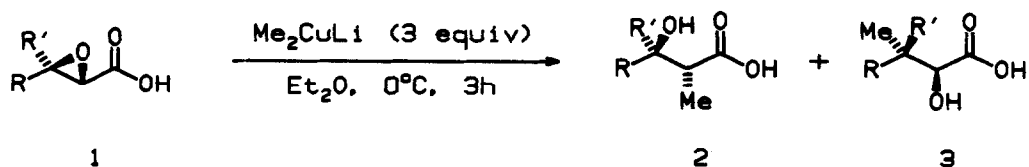
Organocuprates are useful reagents for nucleophilic opening of epoxides.¹ As part of investigations into regioselective transformations of 2,3-epoxy alcohols² and related derivatives, we have examined the reaction of 2,3-epoxy acids³ with some organocuprate reagents. While the reactions of 2,3-epoxy esters with lithium dimethylcuprate are documented,⁴ reactions of 2,3-epoxy acids with organocuprates have to our knowledge not been described. This report discloses our findings in this area.

The results of the reaction of a number of 2,3-epoxy acids with lithium dimethylcuprate are shown in the Table. When the trans-glycidic acid **1a** was allowed to react with LiMe_2Cu (entry 1), the regioisomers **2a** and **3a** were formed in a ratio of 8:1, respectively. This is in accord with previous observations on the reaction of LiMe_2Cu with glycidic esters: ethyl trans-2,3-epoxybutanoate gave only the product of attack at C-2.⁴ As expected, additional substitution at C-4 of the 2,3-epoxy acid as in **1b** (entry 2) gave increased selectivity for attack at C-2 (**2b**:**3b** = 12:1). Similarly, the presence of an electron-withdrawing t-butyldiphenylsiloxy group at C-4 (entry 4) further enhanced the C-2 effect (**2d**:**3d** = 30:1).

Somewhat surprisingly,⁵ while reaction of the cis-glycidic acid **1c** with LiMe_2Cu (entry 3) afforded predominantly one regioisomer, the major product was the result of attack at C-3 (**2c**:**3c** = 1:17). In the case of epoxy acid **1e** which is cis-substituted but also contains an electron-withdrawing (deactivating) t-butyldiphenylsiloxy group at C-4,

opening by LiMe_2Cu proceeded with poor selectivity (2e:3e = 1.6:1).

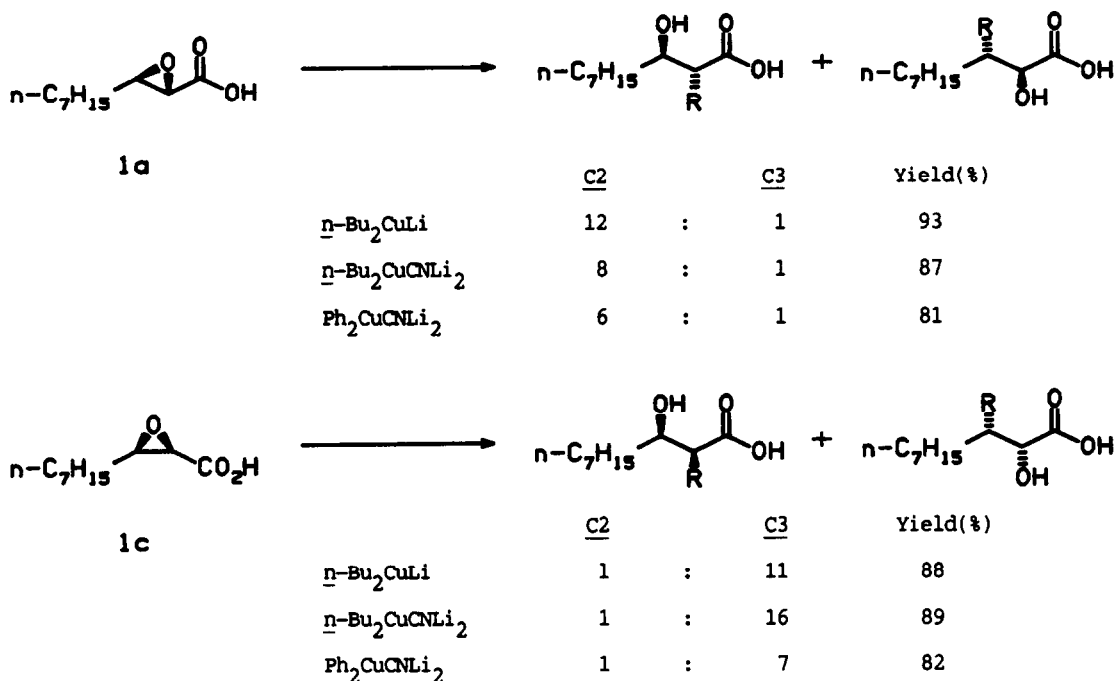
Table: Reaction of Epoxy Acids with LiMe_2Cu .^a



Entry	Epoxy Acid	Ratio 2:3 ^b	Yield (%) ^c
1	1a	8:1 ^d	91
2	1b	12:1	92
3	1c	1:17	84
4	1d	30:1	89
5	1e	1.6:1	98

- ^a Reactions were performed at a substrate concentration of 0.05 M.
^b As determined by 250 MHz ^1H NMR spectroscopy on the derived methyl ester (CH_2N_2)-acetates (Ac_2O , pyr, cat. DMAP).
^c Isolated yield of methyl esters.
^d Reaction in THF afforded the same ratio of products along with $\approx 50\%$ recovered starting material.

The tendency of trans-epoxy acids to be opened at C-2 by LiMe_2Cu while cis-epoxy acids show a tendency to be opened at C-3 was found to be general for the three other organocuprates examined (Scheme).



Scheme. Reaction of 1a and 1c with organocuprate reagents. Reactions were performed at 0.05 M in Et₂O at -20°C ($n\text{-Bu}_2\text{CuLi}$ and $n\text{-Bu}_2\text{CuCNLi}_2$) for 3h or at 0°C, ($\text{Ph}_2\text{CuCNLi}_2$) for 3h. Ratios are based on GC (SE-30^o capillary column, FID detector) and/or ¹H NMR analysis (250 MHz) of the derived (CH₂N₂) methyl esters. Yields are for the isolated methyl esters.

From a synthetic viewpoint, the results of this study should allow one to reliably predict the regiochemical outcome of the reaction of organocuprate reagents with 3-alkyl-2,3-epoxy acids. Especially useful should be the ability to transfer an alkyl group to C-3 of cis-epoxy acids with good regioselectivity.⁶ It is interesting to note that while Me₃Al opens both cis and trans-2,3-epoxy acids regioselectively at C-3,⁷ competing hydride transfer⁸ makes the higher alkylaluminum species, such as Et₃Al, inefficient reagents for the transfer of alkyl groups to C-3 of 2,3-epoxy acids. Thus the problem of transferring an alkyl group bearing β-hydrogens to C-3 of trans-epoxy acids remains to be solved.⁹

Acknowledgements

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 - Caron, M.; Sharpless, K.B. *J. Org. Chem.* **50**, 1557 (1985)
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- These compounds may be readily prepared in homochiral form by oxidation of homochiral 2,3-epoxy alcohols with RuO_4 . See Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **46**, 3936 (1981) and especially footnote 4 of reference 2d. It should also be noted that, contrary to the impression of most chemists, the disubstituted glycidic acids described in this work are quite stable. They are easily recrystallized and can be stored in the freezer for months with no detectable decomposition. The literature on glycidic acids is exceedingly sparse. Certainly, some glycidic acids are very unstable, but we are finding that many members of this class of compounds are easy to work with.
- Herr, R.W.; Wieland, D.M.; Johnson, C.R. *J. Am. Chem. Soc.* **92**, 3813 (1970)
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- While it has been observed (see reference 2d) that nucleophiles react with trans-2,3-epoxy acids with better regioselectivity (C-2:C-3 \approx 5:1) than with cis-epoxy acids (C-2:C-3 \approx 1:1), such a dramatic shift in regioselectivity under the same reaction conditions has not been previously observed.
- This C-3 regioselectivity complements the C-2 regioselectivity observed in the reaction of trans-2,3-epoxy esters with organocuprates. Cis-substituted epoxy esters also show C-2 selectivity: we found that reaction of the methyl ester of 1c with LiMe_2Cu (Et_2O , 0°C) gave only the product of substitution at C-2.
- Still, W.C.; Ohmizu, H. *J. Org. Chem.* **46**, 5242 (1981) and reference 11 cited therein
 - With cis-epoxy acid 1c, we observed 3c as essentially the only product (91%) upon reaction with AlMe_3 , while the trans-epoxy acid 1a afforded 2a and 3a (88%) in a ratio of 1:7, respectively.
- This problem was encountered during studies on the reactions of trialkylaluminum reagents with 2,3-epoxy alcohols: Roush, W.R.; Adam, M.A.; Peseckis, S.M. *Tetrahedron Lett.* **24**, 1377 (1983). See also Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **23**, 3597 (1982)
 - We found that reaction of epoxy acid 1c with Et_2Al (hexane, 25°C , 24h) gave alkyl and hydride transfer products (C-3 opening) in a ratio of 85:15, respectively.
- Note however that alkynyl groups may be transferred to C-3 of trans-epoxy esters using alkynylaluminum reagents: (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **100**, 3950 (1978), (b) Trost, B. M.; McDougal, P. G. *Tetrahedron Lett.* **23**, 5497 (1982).

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