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Sulfoxide-Controlled S_N2' Displacements between Cyanocuprates and Epoxy Vinyl Sulfoxides.[1]

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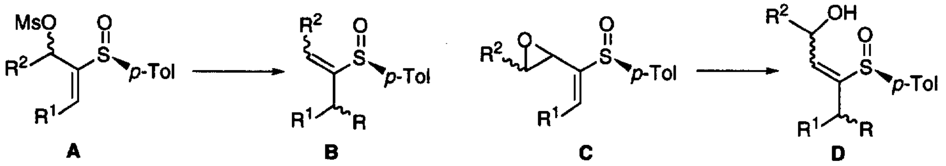
***Abstract*:** Readily available enantiomerically pure epoxy vinyl sulfoxides **10-13** and **15** undergo highly regio-and stereoselective S_N2' displacements with alkyl cyanocuprates. The sulfinyl auxiliary controls the *anti-syn* stereochemistry of the process. Copyright © 1996 Elsevier Science Ltd

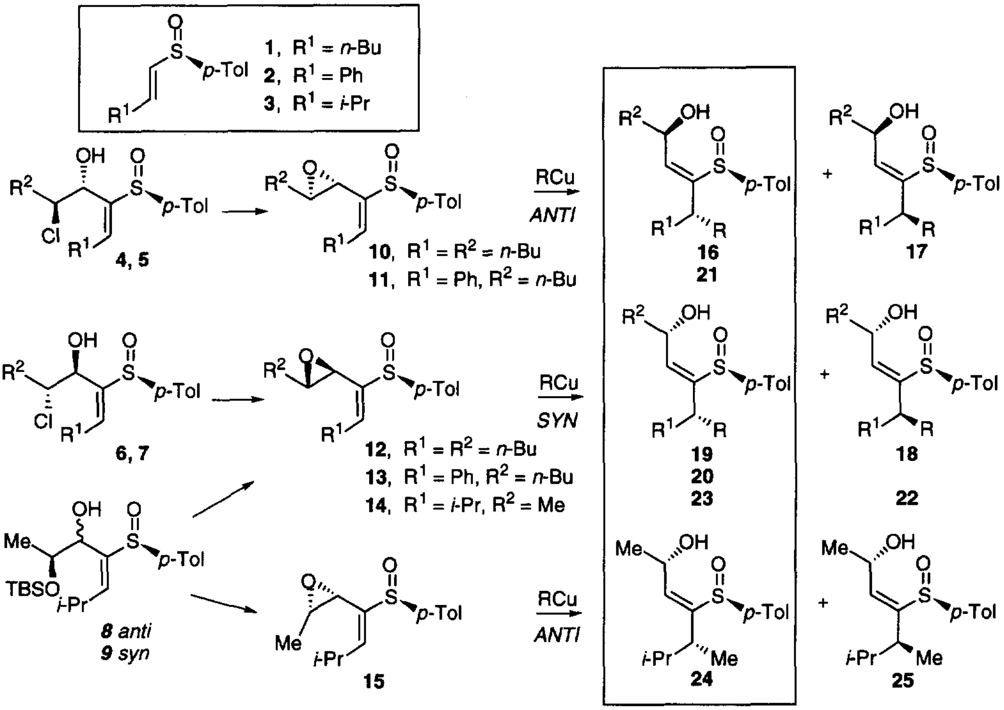
The nucleophilic S_N2' opening of vinyl oxiranes by organocopper reagents is a powerful method for the stereoselective construction of carbon-carbon bonds.[3] The high degree of regio- and stereocontrol (*E-Z* and *anti-syn*) generally associated with this methodology even for acyclic cases has led to a sustained level of interest in these processes.[4] In connection with our previous involvement with studies addressing sulfur-directed S_N2' displacements,[5] particularly those of acyclic mesylates **A** (Scheme 1),[5b] we envisioned that the related enantiomerically pure epoxy vinyl sulfoxides **C** could be useful substrates for effecting allylic displacements with organocopper reagents to produce allylic alcohols **D** which maintain the versatile vinyl sulfoxide functionality. In this paper we report our preliminary results on this subject which have revealed that the facial selectivity of the process is primarily controlled by the chiral sulfur atom.



Scheme 1

After briefly evaluating several routes to oxiranes **C**, we found that the lithiation of enantiomerically pure vinyl sulfoxides **1** and **2** (Scheme 2)[6] and subsequent highly *anti*-selective condensation with racemic 2-chlorohexanal,[7] followed by chromatographic separation and recrystallization led to pure chlorohydrins **4**, **5** and **6**, **7** (33-38% of each *anti*-diastereomer, *ca.* 1:1 ratio) which were transformed into epoxides **10-13** by base induced cyclization (*n*-BuLi, THF, -78 °C to rt, 78-89%). Alternatively, lithiation of **3**, condensation with (2*S*)-2[(*tert*-butyldimethylsilyl)oxy]propanal[8] (*anti*:*syn*, 83:17, 84%) followed by chromatographic separation of **8** and **9** and epoxide formation (1. Ms_2O, pyr, 2. *n*-Bu_4NF, THF, 60-70% overall) produced oxiranes **14** and **15**.[9] From these substrates we selected **10-13** and **15** for our initial studies.

Scheme 2 and Table 1 gather our preliminary results on these displacements. At the initial stage of this project, the reactivity of epoxide **10** with MeCuCNLi was examined and the desired displacement adduct **16** was obtained with remarkable yield and stereoselectivity (96:4, entry 1). In view of this promising result, diastereomeric substrate **12** (entry 2) was subjected to identical reaction conditions to produce a good yield of an inseparable 15:85 mixture of displacement products. It should be pointed out that the NMR spectral features of the major products **16** and **19** were found to be strikingly similar and this suggested that these products were isomeric exclusively at the allylic hydroxyl center and, therefore, that a different *anti-syn* stereochemical pathway was operative for each diastereomer.



Scheme 2

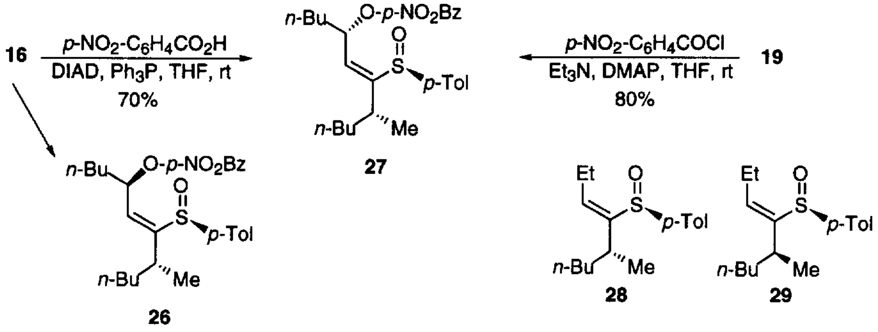
Table 1. Reaction of Cyanocuprate Reagents with Epoxy Vinyl Sulfoxides.

Entry	Substrate	RCu[a]	Products (*anti-syn* ratios)[b]		Yield[c]
1	**10**	MeCuCNLi	**16** (96)	**17** (4)	91%
2	**12**	MeCuCNLi	**18** (15)	**19** (85)	68%
3	**12**	EtCuCNLi	-	**20** (100)	70%
4	**11**	*n*-BuCuCNLi	**21** (100)	-87%	
5	**13**	*n*-BuCuCNLi	**22** (9)	**23** (91)	78%
6[d]	**13**	*n*-BuCuCNLi	**22** (4)	**23** (96)	-
7	**15**	MeCuCNLi	**24** (93)	**25** (7)	70%

[a] Reactions carried out with 6 equiv of organocuprate reagents in Et_2O, from -78 °C to rt. [b] In parentheses ratios of products measured by integration of the 300 MHz ^1H NMR spectra of crude reaction mixtures. [c] Unoptimized combined yields of pure products. [d] Reaction carried out at -100 °C; the yield was not determined.

The scope of the process was then briefly examined both with respect to the use of different alkyl cyanocuprates and with respect to the range of substituents on the vinyl epoxide. The results obtained (entries 3-5) are very similar to those described above. Entry 6 shows that the selectivity of the process may be further improved by lowering the reaction temperature. Finally, the influence of the oxirane geometry on the outcome of the displacement was also studied and comparable results were found (entry 7). It should be mentioned that the displacements of epoxides **12** and **13** (*SRS*$_S$) configuration were generally less selective than those of the corresponding diastereomers. In addition, slightly lower yields were also obtained due to the appearance of other by-products.[9]

To establish conclusively the different *anti-syn* stereochemical pathway suspected for these diastereomeric oxiranes, we prepared the *p*-nitrobenzoates of **16** and **19**, **26** and **27** respectively under standard conditions (Scheme 3). On the other hand, the treatment of **16** with *p*-nitrobenzoic acid, under Mitsunobu conditions,[10] led to a good yield of *p*-nitrobenzoate **27**, of identical physical and spectroscopic data to that obtained from **19** as described above.



Scheme 3

The general structure and geometry of these adducts could be established readily from their ^{1}H and ^{13}C NMR spectral features including differential NOE experiments. The relative stereochemistry of the newly created allylic chiral center was deduced by comparison of the spectra of these adducts with those of related compounds previously characterized by spectroscopic and crystallographic techniques. A particularly distinctive feature found is that the methyl group attached to the allylic position appears substantially more shielded in major diastereomers **16** and **19** (0.63 and 0.65 ppm), as well as in *p*-nitrobenzoates **26** and **27** (0.59 and 0.52 ppm), than in **17** and **18** (1.05 and 1.09 ppm); this is in agreement with the shifts of 0.56 and 1.11 ppm observed for **28** and **29** (Scheme 3), of known relative configuration.[5b]

The stereochemical outcome of these additions may be rationalized in terms of a "matched" situation for **10**, **11** and **15** in which the sulfinyl and vinyl epoxide functionalities display cooperative stereodirecting capabilities. On the other hand, the remarkable reversal of facial selectivity found for **12** and **13**, affording 1,4-*syn* products, suggests a "mismatched" situation in which the sulfinyl group can override the highly *anti*-selective stereochemical pathway associated with S$_N$2' displacements of vinyl oxiranes with organocuprates.[11] It should be pointed out that to the best of our knowledge this reversal of selectivity, under identical reaction conditions, is unprecedented and underlines the extremely powerful chiral controller character of a readily available and synthetically useful sulfinyl funtionality.[12, 13]

In conclusion, we have shown that enantiomerically pure epoxy vinyl sulfoxides, readily available by two short and convergent routes, undergo S$_N$2' displacements with alkyl cyanocuprate reagents with high regio- and stereoselectivity. The *anti-syn* stereochemical course of the process is primarily controlled by the chiral sulfur atom. Further studies to define the scope of this novel finding and apply the resulting hydroxy vinyl sulfoxides in synthesis are underway in our laboratories.

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