Tetrahedron Letters,Vol.28,No.42,pp 4985-4988,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STEREOSELECTIVE S_N2' ADDITIONS TO CHIRAL ACYCLIC VINYLOXIRANES

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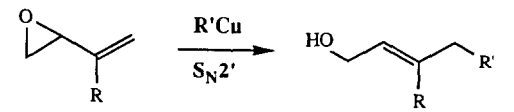
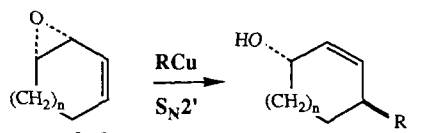
Summary: Additions of $LiMe_2Cu$ to acyclic vinyloxiranes **4**, **5**, **6**, and **7** proceed predominately anti S_N2' to afford the (*E*)-allylic alcohol products.

The S_N2' addition of organocopper reagents to vinyloxiranes is a well established synthetic route to allylic alcohols. However, except for the initial observation of this reaction[1] (eq. 1), all applications

(1) 

R = H[1a] or Me[1b]

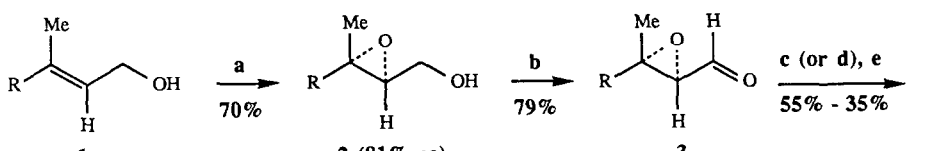
have involved conformationally rigid cyclic systems.[2] In such cases, the displacement generally proceeds anti to the oxirane oxygen (eq. 2).

(2) 

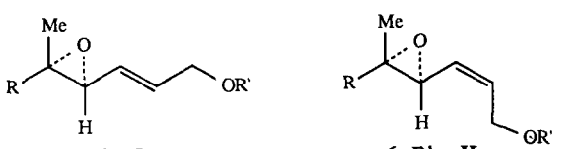
n = 0, 1

Pursuant to synthetic studies on macrocyclic natural products, we developed an interest in the stereochemistry of S_N2' additions to acyclic vinyloxiranes. Initially we sought to identify structural features that might contribute to the regio and stereoselectivity (syn vs. anti and *E* vs. *Z*) of additions involving methylcopper reagents. As a starting point for our investigations we prepared several prototype substrates (**4**-**7**) of high ee via the sequence outlined in Scheme I, employing the Sharpless epoxidation to establish the absolute configuration of the epoxide.[3]

Scheme I [a, b]



1 **2** (81% ee) **3**



4 R' = H
5 R' = TBS

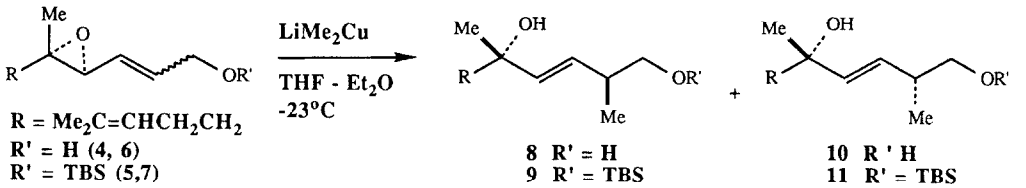
6 R' = H
7 R' = TBS

[a] R=$(CH_3)_2C=CHCH_2CH_2$.

[b] (a) *L*-(+)-DET, TIP, TBHP, CH_2Cl_2, -23°C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (c) $(EtO)_2POCH_2CO_2Et$, NaH, THF, -78°C; DIBAH, CH_2Cl_2, -78°C; (d) $Ph_3P=CHCO_2Me$, MeOH, 0°C; DIBAH, CH_2Cl_2, -78°C; (e) TBSCl, DMAP, Et_3N.

Addition of CH_3MgBr - CuI[4] to the (*E*)-vinyloxirane **4** yielded a complex mixture of products. $LiCuMe_2$, on the other hand, added cleanly to give a 84:16 mixture of the anti and syn allylic alcohols **8** and **10**.[5] Under comparable conditions, the related (*Z*)-vinyloxirane **6** afforded a 97:3 mixture favoring the syn isomer **10**. The selectivity was lower in additions to the TBS[6] ether derivatives **6** and **7**. However, the products of anti S_N2' addition **9** and **11**, respectively, were still favored in these cases.

Table 1. S_N2' Additions of $LiMe_2Cu$ to Acyclic Vinyloxiranes



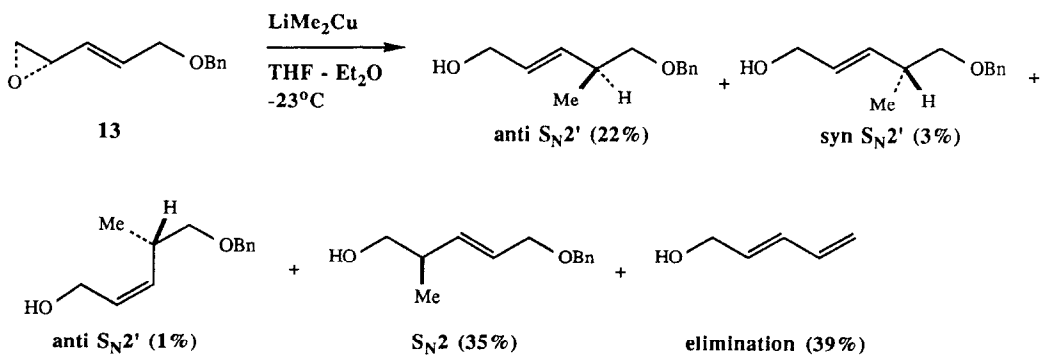
R = $Me_2C{=}CHCH_2CH_2$
R' = H (4, 6)
R' = TBS (5,7)

8 R' = H
9 R' = TBS

10 R ' H
11 R' = TBS

	Yield (%)	S_N2' Products (%)	
(*E*)-isomer			
4 R'=H	81	**8** (84)	**10** (16)
5 R'=TBS	77	**9** (70)	11 (30)
(*Z*)-isomer			
6 R'=H	75	**8** (3)	**10** (97)
7 R'=TBS	78	**9** (18)	11 (82)

These results contrast sharply with our earlier observations on additions of $LiMe_2Cu$ to the unbranched vinyloxirane **13** which gave predominantly S_N2 substitution and appreciable elimination product under identical reaction conditions.[7]



13

anti S_N2' (22%)

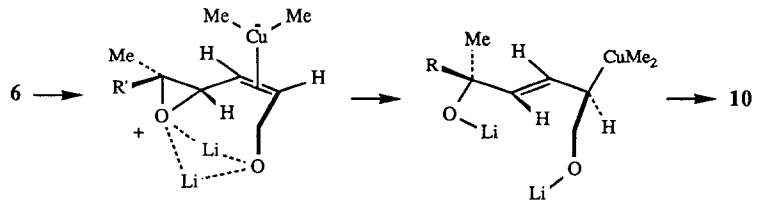
syn S_N2' (3%)

anti S_N2' (1%)

S_N2 (35%)

elimination (39%)

Our findings suggest that the S_N2 process is effectively blocked by substitution on or adjacent to the epoxide allylic center. In addition, an allylic hydroxyl grouping exerts a significant directing influence, particularly on the (*Z*)-isomer **6**. The strong preference for (*E*) double bond geometry in the products of S_N2' addition is also noteworthy. Evidently these additions proceed via a highly ordered transition state involving the *s*-trans conformation of the vinyloxirane. Facial selectivity may be enhanced by chelation in the case of the (*Z*) allylic alcohol **6**.



Typical Experimental Procedure: To a slurry of 331 mg of CuI in 20 mL of dry THF at -23°C was added 2.40 mL of 1.45 *M* ethereal CH_3Li. The mixture was stirred for 10 min at -23°C and then a solution of 75.2 mg (0.383 mmol) of alcohol **4** (derived from epoxy alcohol **2** of 81% ee)[3,9] in 5 mL of dry THF was added over 5 min. The resulting mixture was stirred at -15°C for 16 h, 10 mL of 3% aqueous NH_4OH was added and the product was extracted with ether. The extracts were washed with 3% NH_4OH to remove copper salts, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording a yellow oil. Flash chromatography on silica gel eluting with 80% ether-hexanes gradient afforded 66 mg (81%) of diols **8** and **10**. IR (film) v 3350, 2970, 2920, 2875, 1450, 1375, 1110, 1080, 1035, 975 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.56 (d, J = 15.7 Hz, 1H, vinyl H), 5.44 (dd, J = 7.4, 15.7 Hz, 1H, vinyl H), 5.08 (m, 1H, vinyl H), 3.40 (m, 2H, carbinyl CH_2), 2.31 (m, 1H), 1.97 (m, 2H), 1.80 (bs, 2H, -OH), 1.64 (s, 3H, vinyl CH_3), 1.56 (s, 3H, vinyl CH_3), 1.52 (m, 2H), 1.24 (s, 3H, carbinyl CH_3), 0.95 (d, J = 6.8 Hz, 3H, $-CH_3$). $[\alpha]_D^{21}$ -13.79 (c 3.30, $CHCl_3$).

Acknowledgements. We are grateful to the National Science Foundation for support of this work through a research grant (CHE-8615569) and through funding of an AM-300 NMR spectrometer (CHE-8411172).

References and Notes

1. (a) Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 4978. (b) Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4919.

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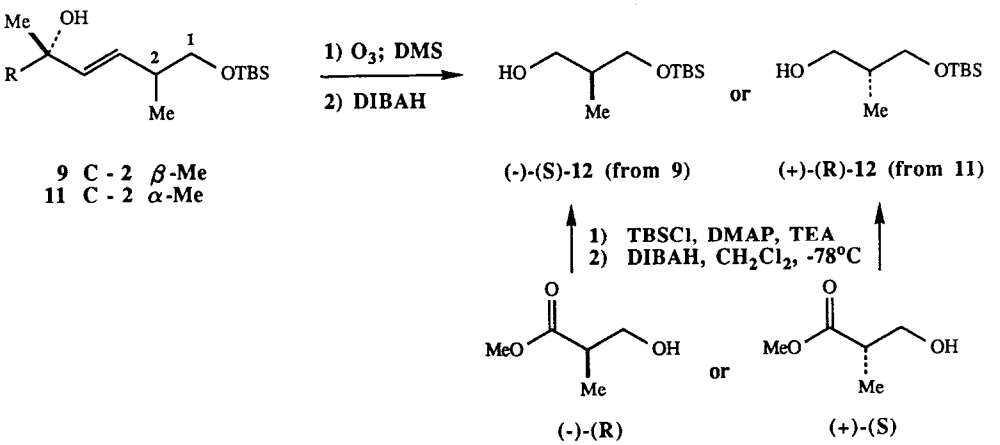
3. Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Epoxy alcohol **2** of 80-90% ee, as determined through ^1H NMR analysis of O-methyl mandelates, was employed for these studies.

4. *Cf.* Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106.

5. Product ratios were obtained from capillary gc analysis of the TBS ethers **9** and **11**. The stereochemistry at C2 was ascertained via ozonolysis-reduction of these ethers to alcohols (*S*) or (*R*)-**12**. Authentic samples of **12** were obtained from the known (*R*)-(-) and (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (Aldrich Chemical Co.).



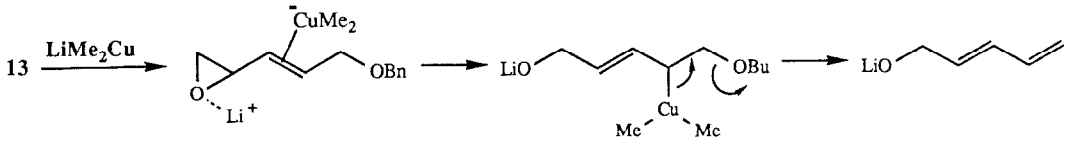
9 C - 2 β-Me
11 C - 2 α-Me

(-)-(S)-**12** (from **9**) (+)-(R)-**12** (from **11**)

(-)-(R) (+)-(S)

6. **Abbreviations:** Bn = benzyl, DET = diethyl tartrate, DIBAH = diisobutylaluminum hydride, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMSO = dimethylsulfoxide, TBHP = *tert*-butyl hydroperoxide, TBS = *tert*-butyldimethylsilyl, TEA = triethylamine, THF = tetrahydrofuran, TIP = titanium tetraisopropoxide.

7. D. G. Cleary and J. D. Trometer, unpublished results. The elimination product is thought to arise from the presumed η^1 complex.[8]



8. For a mechanistic discussion of the analogous S_N2' displacement of allylic esters, see Goering, H. L.; Kantner, S. D.; Sietz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495. Goering, H. L.; Kantner, S. D. *J. Org. Chem.* **1984**, *49*, 422. For recent work on allylic mesylates see Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420.

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(Received in USA 8 July 1987)