

S_N2' Additions of Organocopper Reagents to Vinyloxiranes

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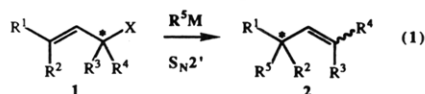
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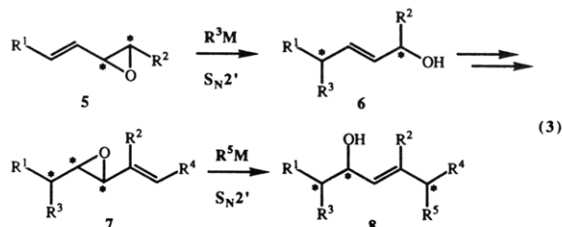
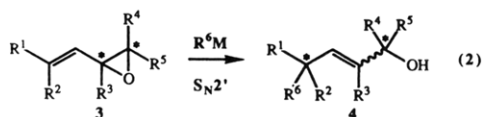
I. Introduction

The coupling of organometallic reagents with alkyl halides and related electrophiles is a fundamental operation of considerable synthetic importance. In the case of allylic electrophiles, the reaction can occur through direct S_N2 displacement or by so-called S_N2' attack on the double bond (eq 1).¹ Mechanistic aspects



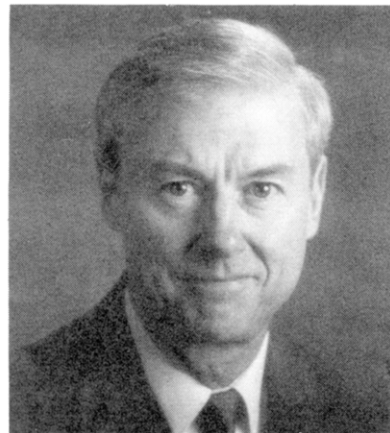
of the S_N2' reaction have been of interest for more than 50 years, but the process is still not well understood.² The coupling of organometallic nucleophiles with allylic halides first received attention some 40 years ago.³ However, because mixtures of regio- and stereoisomeric products were often formed, this reaction found only limited use in synthesis.² The discovery that allylic acetates afford S_N2' substitution products with organocuprates⁴ stimulated additional studies on such couplings, resulting in the subsequent development of useful synthetic methodology.^{5,6}

Vinyloxiranes constitute a special subset of allylic electrophiles. In these cases the product of S_N2' displacement is an allylic alcohol (eq 2). Allylic alcohols, in turn, are readily and stereoselectively transformed into vinyloxiranes,⁷ thus allowing for reiterative stereoselective chain elongation (eq 3).



II. 1,3-Butadiene and Isoprene Epoxides

The first S_N2' additions to vinyloxiranes by organocuprates were recorded in 1970.⁸ The monoepoxides **9a-c** of 1,3-butadiene and isoprene were shown to give



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mainly the E - S_N2' product **10** along with lesser amounts of Z - S_N2' and S_N2 products **11** and **12** (Table I). Later work demonstrated that the use of vinylic cuprates prepared from organolithium (Table I) or Grignard reagents (Table II) provides easy access to various 2,5-dienols.⁹ Allylic Grignard reagents yield analogous 2,6-dienol products (Table II, entries 5 and 6).

In one of the early applications of this methodology, Normant and co-workers employed butadiene epoxide (**9a**) to trap the [(Z)-1-heptenyl]cuprate, prepared in situ from acetylene and the n -pentyl Gilman reagent. The resulting (Z,E)-2,5-dienol **15** was further transformed to acetate **16**, a sex pheromone of *Phthorimaea operculella* (eq 4).¹⁰ In a second pheromone synthesis, the allylic Grignard reagent **17** smoothly coupled with butadiene epoxide (**9a**) in the presence of 5% CuBr to afford the 2,6-dienol **18** in high yield (eq 5). This intermediate was converted to the acetate **19**, a sex attractant of *Pectinophora gossypiella*.

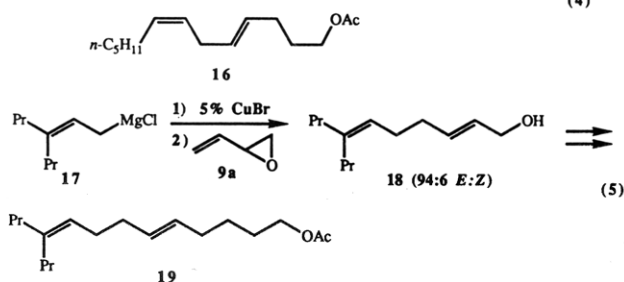
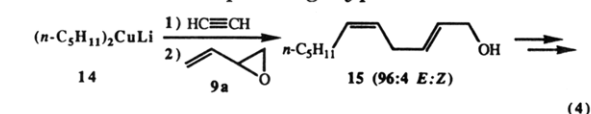
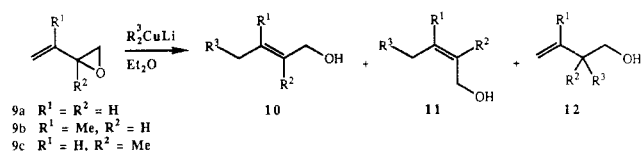
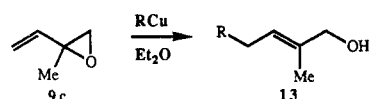


TABLE I. Additions of Gilman Cuprates to Butadiene and Isoprene Epoxides

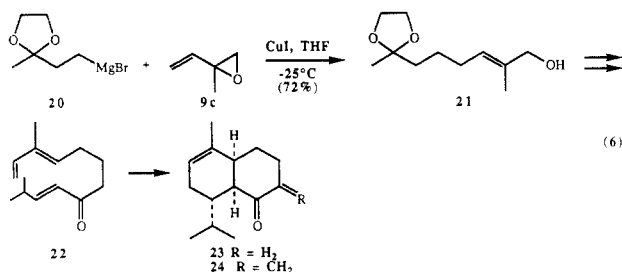
entry	epoxide	R ³	S _N 2'		E:Z	S _N 2	ref
			10	11			
1	9a	Bu	80	13	86:14	4	5
2	9a	Ph	76	8	90:10	15	5
3	9a	Me	74	20	79:21	6	6
4	9b		92	8	92:8	0	5
5	9a	(Z)-EtCH=CH	67	3	96:4	0	7
6	9c		71	11	86:14	0	7
7	9a	Me ₂ C=CH	79	3	96:4	0	7
8	9c		87	7	92:8	0	7
9	9c	BuC=CH ₂	83	8	91:9	0	7

TABLE II. Addition of Cuprates to Isoprene Epoxide

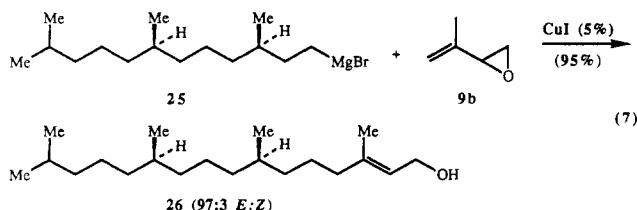
entry	RM	yield, %	E:Z
1	(Me ₂ C=CH) ₂ CuLi	95	92:8
2	Me ₂ C=CHMgBr·CuBr ^d	79 ^b	96:4
3	(Me ₂ C=CH) ₂ Cu·MgBr	34	97:3
4	(E)-Bu(Et)C=CH ₂ Cu·MgBr	78	58:42
5	CH ₂ =CHCH ₂ MgBr·CuBr ^d	90	92:8
6	(Z)-MeCH=CHCH ₂ MgBr·CuBr ^d	95	95:5

^a A catalytic amount of CuBr was used. ^b 19% of the S_N2 product was also formed.

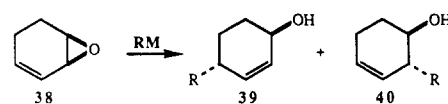
The Grignard reagent of 4-bromobutanone ethylene ketal (20) was shown to react with isoprene epoxide 9c to yield the allylic alcohol 21 (eq 6).¹¹ This alcohol was



converted to the trienone 22, which underwent facile intramolecular Diels-Alder cycloaddition and α -metylenation to ketone 24, the alleged structure of chiloscyphone, an essential oil constituent. The isomeric isoprene epoxide 9b was used by Fujisawa et al.¹² in a synthesis of (R,R)-phytol (eq 7). CuI-catalyzed S_N2' addition of the Grignard reagent 25 afforded a 97:3 mixture favoring the E isomer 26 in 95% yield.



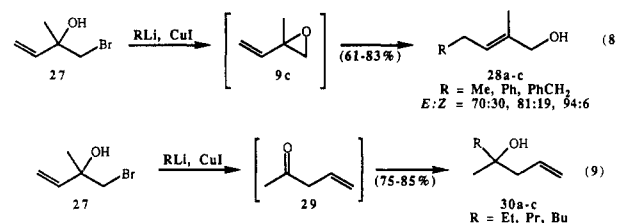
One problem inherent in the foregoing applications is the difficulty associated with the preparation and handling of the volatile and highly refractory vinyl-

TABLE III. Addition of Gilman Cuprates to 1,3-Cyclohexadiene Epoxide (38)

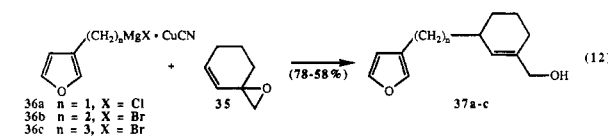
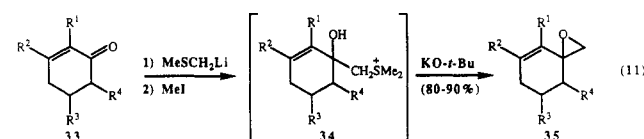
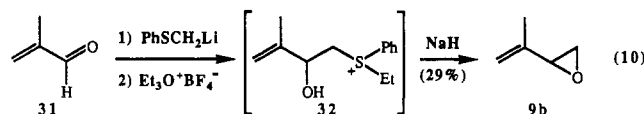
RM	yield, %	39:40	ref
Me ₂ CuLi		42:35 ^a	13a
Me ₂ CuLi	91	54:46 ^b	13b
Ph ₂ CuLi	87	69:31	13b
(t-Bu) ₂ CuLi	72	65 ^c :35 ^d	13b

^a Plus 23% of 3-cyclohexenone. ^b Plus variable amounts (0–6%) of 3-cyclohexenone. ^c 7:1 trans:cis. ^d 2:1 cis:trans.

oxiranes 9a–c. A possible solution to this problem was explored by Araki and Butsugan,¹³ who introduced the bromohydrin 27 as an in situ source of vinyloxirane 9c. With methyl-, phenyl-, and benzylcuprates, addition proceeded as planned, affording the allylic alcohols 28a–c in 61–83% yield (eq 8). However, with the less stable ethyl-, propyl-, and butylcuprates, semipinacolic rearrangement preceded addition, leading to the homoallylic alcohols 30a–c (eq 9).



Fujisawa prepared the isoprene epoxide 9b by addition of [(phenylthio)methyl]lithium to methacrolein (31) followed by base treatment of the derived sulfonium salt 32 (eq 10).¹² This approach was later adapted to spirocyclic vinyloxiranes by Tanis with good results (eq 11).¹⁴ Additions of the CuCN complexes of various ω -(3-furfuryl)alkyl Grignard reagents 36a–c to the cyclohexylidene epoxide 35 (R¹ = R² = R³ = R⁴ = H) proceeded readily to give the allylic alcohols 37 in satisfactory yield (eq 12).¹⁴

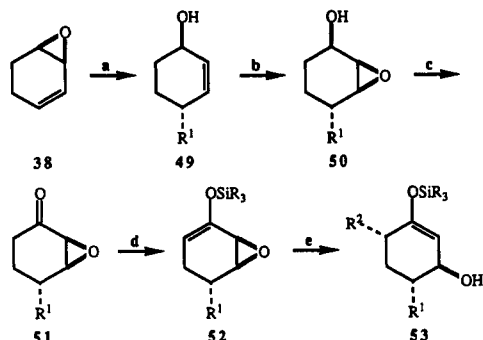


III. Cyclic 1,3-Diene Monoepoxides

Initial stereochemical studies on the S_N2' addition of cuprates to cyclic vinyloxiranes employed the monoepoxide of 1,3-cyclohexadiene (38) as the substrate (Table III).¹⁵ In general, a strong preference for anti addition was observed, contrary to the then current dogma on S_N2' reactions.^{1,16} Anti addition was also observed with the monoepoxide of 1,3-cycloheptadiene

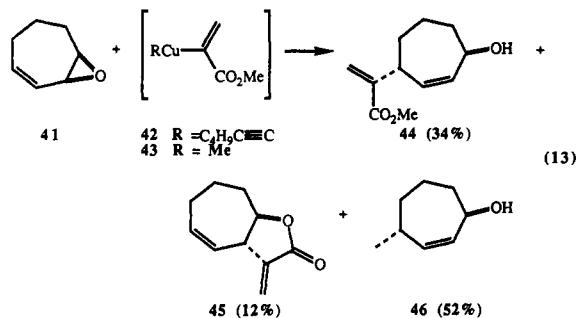
TABLE IV. Addition of Mixed Cuprates to 1,3-Cycloheptadiene Epoxide (41)

R	R'	yield, %	47:48
Me	Me	91	70:30
Me	BuC≡C	95	85:15
Me	CN	95	90:10
Me	CH ₂ =CCO ₂ Me	98	97:3
Bu	CN	"high"	100:0

SCHEME I^a

^a (a) R¹Cu(CN)Li; (b) ArCO₃H; (c) CrO₃·py₂; (d) LDA; R₃SiCl; (e) R²Cu(CN)Li.

(41) and the mixed cuprate 42 of methyl α-bromoacrylate and 1-hexyne (eq 13).¹⁷ Surprisingly, the major



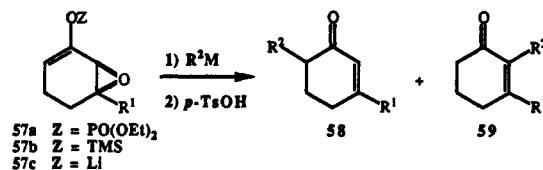
product was the methyl adduct 46. This product was surmised to have arisen from cuprate 43 as a consequence of incomplete alkynylcuprate formation during preparation of cuprate 42. When the methylcuprate 43 was deliberately used, the S_N2' product 46 was highly favored (97:3). That only 3% of the S_N2 product was formed in this latter reaction suggested that the acrylic ligand modifies the characteristics of the cuprate to enhance S_N2' displacement. In support of this rationale, the reaction of epoxide 41 with Me₂CuLi afforded a 70:30 mixture of S_N2' and S_N2 methyl adducts. Of the several mixed methylcuprates examined, the acrylic reagent was most effective at directing S_N2' methylation followed closely by cyano (Table IV). Attempts to prepare higher homologues of cuprate 43 failed, so attention was focused on the cyanocuprate reagents. BuCu(CN)Li afforded only the S_N2' product 47 of undetermined stereochemistry with epoxide 41. Addition of MeCu(CN)Li to 1,3-cyclohexadiene epoxide (38) gave the anti S_N2' product 39 in high yield.

A significant extension of this methodology followed the discovery that enol derivatives of cyclic α,β-epoxy ketones undergo highly stereoselective anti S_N2' addition by mixed cyanocuprate reagents.¹⁸ Sequential S_N2'

TABLE V. S_N2' Additions of Cyanocuprates to the TMS Enol Ether of α,β-Epoxy cyclohexanones

entry	R ¹	R ²	R ³	R ⁴	R ⁵	yield of 55, %
1	H	H	H	H	Me	75
2	H	H	H	H	<i>t</i> -Bu	100
3	H	Me	H	H	Me	95
4	H	Me	H	H	<i>n</i> -Bu	80
5	α-Me	Me	H	H	Me	80
6	α-Me	Me	H	H	<i>n</i> -Bu	94
7	β-Me	Me	H	H	<i>n</i> -Bu	70
8	H	H	Me	H	Me	93
9	H	H	Me	H	<i>n</i> -Bu	100
10	H	H	Me	H	<i>t</i> -Bu	100
11	H	Me	H	Me	Me	87
12	H	Me	H	Me	<i>n</i> -Bu	74
13	H	Me	H	Me	<i>t</i> -Bu	5 ^a
14	H	H	H	H	Ph	72
15	H	H	H	H	CH ₂ =CH	0 ^b
16	H	Me	H	H	CH ₂ =CH	80
17	α-Me	H	H	H	CH ₂ =CH	50 ^c

^a 70% S_N2. ^b 80% S_N2. ^c 20% S_N2.

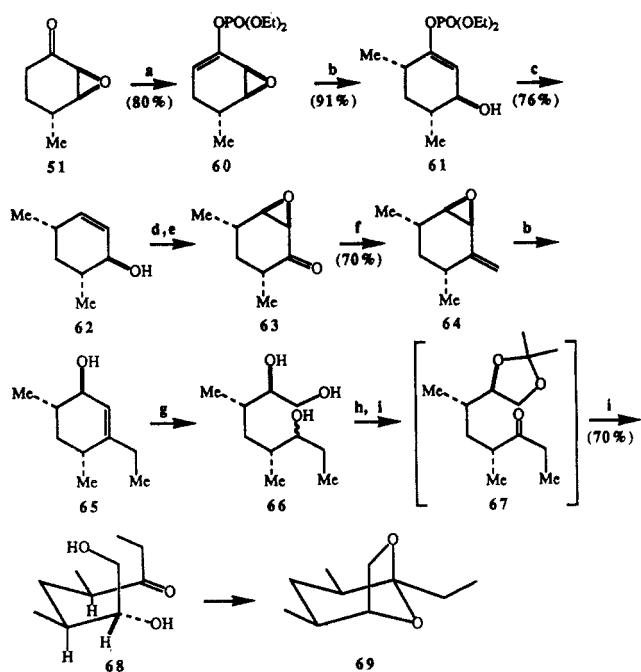
TABLE VI. S_N2' Additions of Cuprates to α,β-Epoxy cyclohexanone Derivatives

entry	Z	R ¹	R ² M	yield, %	
				58	59
1	PO(OEt) ₂	H	Me ₂ CuLi	83 ^a	
2	TMS	H	Me ₂ CuLi	55	
3	Li	H	Me ₂ CuLi	65	
4	TMS	Me	Me ₂ CuLi	97	
5	Li	Me	Me ₂ CuLi	80	
6	TMS	Me	Ph ₂ CuLi		95
7	Li	Me	Ph ₂ CuLi		72
8	TMS	Me	CH ₂ =CHMgBr·CuI		93

^a Yield of anti S_N2' product before dehydration.

additions can thus be employed to introduce multiple stereocenters in cyclic systems, as illustrated in Scheme I. The reaction was found to be applicable to a variety of substituted epoxy cyclohexenyl silyl ethers (Table V).¹⁹ Substituents on or next to the epoxide grouping effectively block S_N2 attack (compare entries 15–17), whereas substituents at the terminal double-bond position retard the S_N2' process, at least with bulky cuprates (entry 13). The approach is applicable to a variety of 3-hydroxycyclohexenyl ethers 55 and their dehydration products 56.

Enol phosphate derivatives of cyclic α,β-epoxy ketones also undergo anti S_N2' additions with cuprates^{20,21} as do the enolates themselves.²⁰ Yields are comparable for all three derivatives 57a–c, but the overall process is most direct with enolates (Table VI, entries 1–3). The phenyl Gilman reagent and the cuprate derived from vinylmagnesium bromide give only the S_N2 adduct with the TMS enol ether 57b, whereas the related cyanocuprates favor S_N2' substitution (compare Table VI,

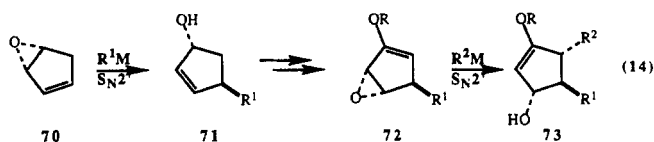
SCHEME II^a

^a (a) LDA, $\text{ClPO}(\text{OEt})_2$; (b) $\text{MeCu}(\text{CN})\text{Li}$; (c) Li, NH_3 , MeOH; (d) $m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}$; (e) $\text{CrO}_3\cdot\text{py}_2$; (f) $\text{Ph}_3\text{P}=\text{CH}_2$; (g) AcCl, py; O_3 ; LiAlH_4 ; (h) CH_3COCH_3 , TsOH; (i) H_2CrO_4 .

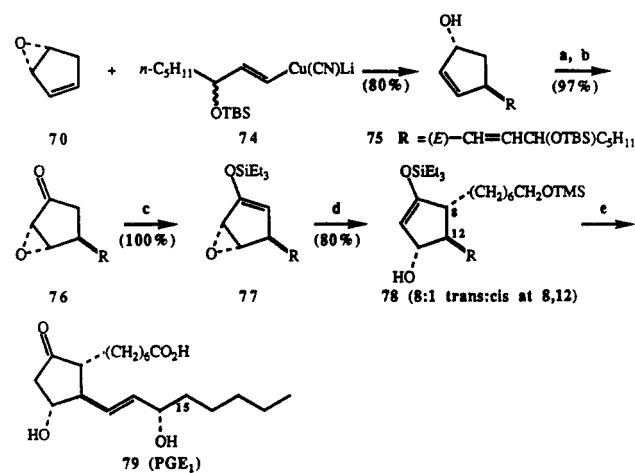
entries 6 and 8, with Table V, entries 14 and 16).

Marino applied the enol phosphate methodology to a synthesis of α -multistriatin, an aggregation pheromone of the European elm bark beetle (Scheme II).²¹ This synthesis is noteworthy for its use of sequential regio- and stereoselective $\text{S}_{\text{N}}2'$ additions for elaboration of the carbon framework. The epoxy ketone 51, available from 1,3-cyclohexadiene monoepoxide (38) as outlined in Scheme I, was converted to the enol phosphate 60. Addition of $\text{MeCu}(\text{CN})\text{Li}$ gave the anti $\text{S}_{\text{N}}2'$ product 61 in 91% yield. Hydrogenolysis of the phosphonate with Li in NH_3 yielded the allylic alcohol 62, which underwent sequential hydroxy-directed epoxidation and oxidation to the epoxy ketone 63. This was converted to the alkylidene epoxide 64 through Wittig methylenation. Methylation of 64 with $\text{MeCu}(\text{CN})\text{Li}$ gave the $\text{S}_{\text{N}}2'$ product 65 exclusively. Acetylation, followed by ozonolysis and reduction, afforded triol 66. Oxidation of the acetonide derivative of this triol with Jones reagent at 0 °C led to the unisolated keto ketal 67, which underwent hydrolysis to diol 68 and cyclization to (\pm) - α -multistriatin (69) in situ.

The sequential $\text{S}_{\text{N}}2'$ addition strategy depicted in Scheme I leads to 2,4-dialkylated cyclohexanone derivatives. The use of 1,3-cyclopentadiene monoepoxide in an analogous sequence would afford 2,3-dialkylated cyclopentanones of possible value in prostanoid synthesis. A potential application is depicted in eq 14.



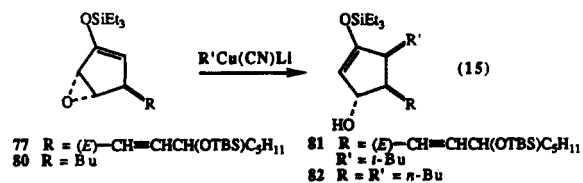
However, it should be noted that the stereochemistry of the second $\text{S}_{\text{N}}2'$ addition must be syn, in contrast to the first and to all known examples in cyclohexene systems. Nonetheless, a fortuitous occurrence allowed

SCHEME III^a

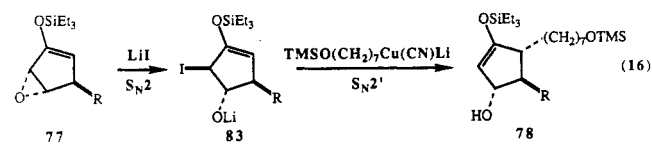
^a (a) $\text{VO}(\text{acac})_2$, $t\text{-BuOOH}$; (b) $\text{CrO}_3\cdot\text{py}_2$; (c) LDA; Et_3SiCl ; (d) $\text{TMSOCH}_2(\text{CH}_2)_6\text{Cu}(\text{CN})\text{Li}$; (e) KF, pH 7; O_2 , PtO_2 ; HF, CH_3CN .

Marino to reduce this strategy to practice (Scheme III).²² Accordingly, the epoxy enol silyl ether 77 afforded an 8:1 mixture of $\text{S}_{\text{N}}2'$ adducts in 80% yield upon treatment with the cyanocuprate derived from 7-iodo-1-heptanol TMS ether. Separation of C-15 diastereoisomers, followed by sequential deprotection and oxidation, led to racemic PGE_1 (79), thus establishing the relative stereochemistry of the side chains as trans and the predominant $\text{S}_{\text{N}}2'$ pathway for step d as syn.

It was initially presumed that the substituent R in epoxy cyclopentene 77 directed the relatively bulky cyanocuprate to the less hindered α -face, leading to the observed syn $\text{S}_{\text{N}}2'$ product 78. However, subsequent studies of this reaction suggested an alternative explanation.²³ Thus, it was found that addition of $n\text{-BuCu}(\text{CN})\text{Li}$ to the n -butyl analogue 80 of epoxide 77 and, more impressively, $t\text{-BuCu}(\text{CN})\text{Li}$ to epoxide 77 gave only the anti $\text{S}_{\text{N}}2'$ products 82 and 81 (eq 15). Evi-

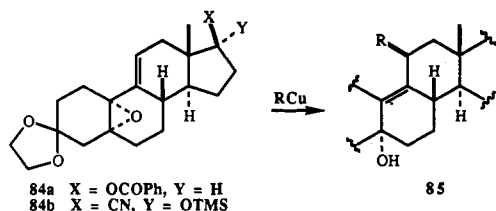


dently steric repulsion does not deter the anti pathway in these seemingly more demanding cases. The apparent discrepancy was resolved in the realization that both the $n\text{-BuCu}(\text{CN})\text{Li}$ and $t\text{-BuCu}(\text{CN})\text{Li}$ came from commercial samples of organolithium reagents, whereas the cyanocuprate employed for the PGE_1 synthesis was prepared from the alkyl iodide through lithiation with $t\text{-BuLi}$. It is proposed that the LiI produced in this lithiation adds to vinyloxirane 77. Subsequent anti $\text{S}_{\text{N}}2'$ displacement on the resulting allylic iodide 83 then leads to the observed product 78 (eq 16).



IV. Alkylidene Cycloalkene Epoxides

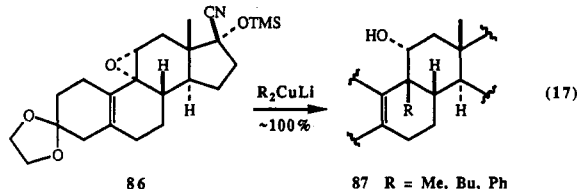
Anti addition was also found to be highly preferred with heteroannular 1,3-diene epoxides. Teutsch and

TABLE VII. Additions of Cuprates to $\Delta^{9,11-5\alpha,10\alpha}$ -Epoxy Steroids

epoxide	RCu	yield, %
84a	Me ₂ CuLi	100
84a	Et ₂ CuLi	85
84a	Ph ₂ CuLi	82
84b	<i>t</i> -Bu ₂ CuLi	100
84b	EtMgBr·CuCl ^a	100
84b	BuMgBr·CuCl ^a	100
84b	PhMgBr·CuCl ^a	100
84b	CH ₂ =CHMgBr·CuCl ^a	100

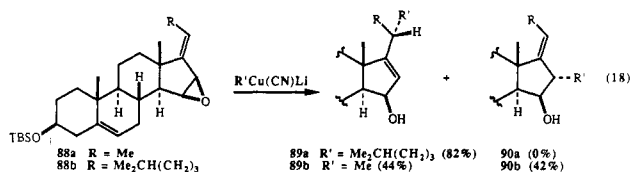
^a 5 mol %.

Belanger obtained only the 11 β -alkyl products 85 upon treatment of the $\Delta^{9(11)-5\alpha,10\alpha}$ -epoxy-19-norandrostane systems 84a and 84b with Gilman cuprates and CuCl-Gignard reagents (Table VII).²⁴ These additions are noteworthy for their excellent regio- and stereoselectivity despite the potentially adverse steric influence of the 13 β -methyl substituent. Interestingly, the isomeric $\Delta^{5(10)-9\alpha,11\alpha}$ -epoxy-19-norandrostane derivative 86 showed a strong preference for S_N2 addition of cuprate reagents (eq 17).²⁵ The contrasting behavior of 84 and



86 was explained by a two-step mechanism involving initial attack of the cuprate on the allylic epoxide position. In the case of 84 subsequent 1,3-rearrangement and reductive elimination lead to 85. Analogous 1,3-rearrangement in the intermediate derived from 86 was postulated as unfavorable owing to conformational constraints.

Marino and Abe found that cyanocuprate additions to 17-alkylidene-15 β ,16 β -epoxyandrostanes 88a and 88b constitute a rational and selective method for introducing the C-20 stereocenter in cholesterol derivatives.²⁶ Isohexylcyanocuprate adds to the ethylidene compound 88a, affording the isomerically pure anti S_N2' product 89a in 82% yield (eq 18). Selective hydrogenation of

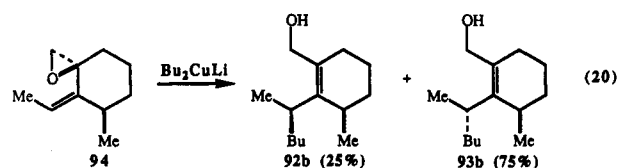
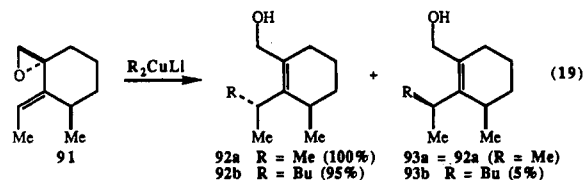


the 16 double bond led to 15 β -hydroxycholesterol. The isoheptylidene steroid 88b afforded a nearly 1:1 mixture of S_N2' and S_N2 products 89b and 90b upon treatment with MeCu(CN)Li. The S_N2' product 89b was transformed to 15 β -hydroxyisocholesterol and thence isocholesterol as proof of the C-20 stereochemistry. Thus, both cuprates exhibit a high preference for anti S_N2'

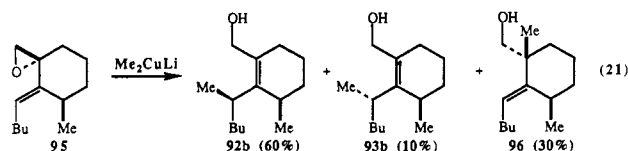
addition. Presumably, the formation of S_N2 product from 88b results from unfavorable steric interactions between the 13 β -methyl and the isoheptyl substituents which cause conformational distortions unfavorable to the transition state of S_N2' displacement. Such distortions could likewise disfavor 1,3-isomerization of an initial S_N2 Cu(III) species, as suggested by Teutsch.²⁴

V. Alkylidene Exocyclic Epoxides

Ziegler and Cady were the first to employ exocyclic epoxides for the introduction of stereocenters in side chains by S_N2' alkylation.²⁷ Addition of the Gilman methyl- or butylcuprate to the (*E*)-*cis*-ethylidene epoxide 91 gave only S_N2' products. Surprisingly, with the butylcuprate a 95:5 mixture of syn and anti adducts 92b and 93b was formed (eq 19). The isomeric (*Z*)-*trans*-ethylidene epoxide 94 afforded a 25:75 mixture of syn and anti S_N2' products 92b and 93b (eq 20). The



differing steric preferences of these two additions was attributed to hindrance by the cyclohexyl methyl substituent of 91, which adopts an axial orientation in the transition state to avoid an unfavorable A^{1,3} interaction with the ethylidene methyl group. The (*E*)-pentylidene epoxide 95, however, yielded the anti product 92b as the major adduct upon treatment with Me₂CuLi (eq 21). In this case the cuprate reagent attacks anti to



the epoxide oxygen and syn to the presumed axial methyl substituent of 95. The lower steric requirements of Me₂CuLi vs Bu₂CuLi are thought to account for the contrasting behavior of 91 and 95.

Cuprate additions to the methylene cyclodecylidene epoxide 97b were studied by Marshall and Flynn in connection with their synthesis of [a,b]betweenanenes.²⁸ These reactions are highly selective, affording the *E*-S_N2' products 98b of over 95% isomeric purity in >90% yield (eq 22). Evidently the *s*-*trans* conformer of vinyloxirane 97b is highly preferred in the transition state. A series of methylene cycloalkylidene epoxides 97a-f gave analogous results with various butylcuprates (Table VIII).²⁹

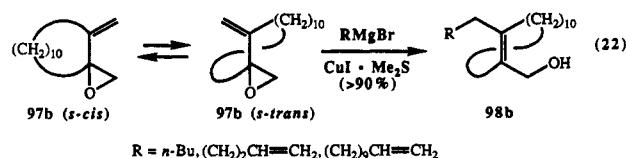
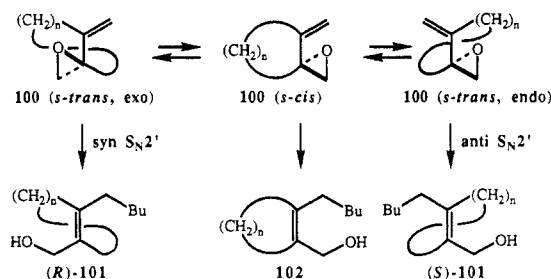


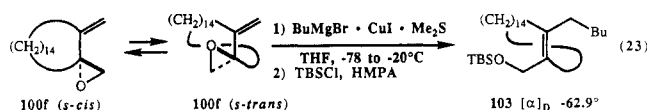
TABLE VIII. S_N2' Additions of Butylcopper Reagents to Methylene Cycloalkylidene Epoxides

entry	<i>n</i>	series	BuCu ^a	yield, %	98:99
1	8	a	A	87	85:15
2	10	b	A	76	98:2
3	10	b	B	77	98:2
4	10	b	C	61	95:5
5	11	c	A	52	95:5
6	12	d	A	82	90:10
7	13	e	A	71	93:7
8	14	f	A	87	94:6

^a A = BuMgBr·CuI·Me₂S, THF; B = Bu₂CuLi, THF; C = BuCu(CN)Li, THF.

**Figure 1.** Possible modes of S_N2' addition to methylene cycloalkylidene epoxides.

Syn-anti preferences of these additions were determined through studies on the (*R*)-cycloalkylidene epoxides **100** (Figure 1).³⁰ If it is assumed that attack of the cuprate is blocked by the bridging methylene chain in the *s-trans* conformer of the cycloalkylidene epoxide **100**, then the *exo* conformer must undergo syn S_N2' addition and the *endo* conformer can only give the anti S_N2' adduct. These two reaction pathways yield enantiomeric *trans*-cycloalkenylcarbinols (*R*)-**101** and (*S*)-**101**, respectively. In fact, the cyclododecylidene and the cyclotetradecylidene epoxides **100b** and **100d** afforded the *R* alcohols **101** of 92 and 82% ee upon treatment with BuMgBr·CuI·Me₂S (Table IX). The cyclohexadecylidene homologue **100f**, on the other hand, gave rise to the racemic alcohol **101f** under these conditions owing to facile interconversion of the *R* and *S* enantiomers through jump rope rotation during product isolation.³¹ This rotation could be blocked by conversion of the alcohol **101f** to the TBS derivative **103**. Thus, when cuprate addition to **100f** was effected at -20 °C and the resulting alkoxide product was treated with (TBS)Cl at that temperature, an optically active TBS ether **103** could be isolated whose rotation was comparable to that of the 14-membered homologue (eq 23). Cleavage of the TBS ether at room temperature afforded racemic **101f**, as expected.



The preferred syn S_N2' addition to epoxides **100** is thought to reflect differences in the ability of the epoxide oxygen to coordinate with metal cations (XMg^+ , Li^+) in the *exo* and *endo s-trans* conformers (Figure 1). Such coordination would be hampered by the bridging

TABLE IX. Addition of BuMgBr·CuI·Me₂S to (*R*)-Cycloalkylidene Epoxides **100**

epoxide	<i>n</i>	yield of 101 , %	ee, %	<i>Z</i> : <i>E</i>
100b	10	68	92	99:1
100d	12	59	82	94:6
100f	14	66	0	89:11

TABLE X. S_N2' Additions to Nonracemic Acyclic Vinyloxiranes Derived from Geraniol and Nerol

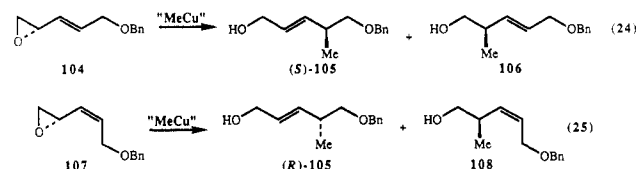
entry	vinyloxirane	method ^a	yield, %	anti:syn
1	109	A	81	85:15
2	113	A	75	97:3
3	109	B	84	88:12
4	113	B	88	99:1
5	110	A	77	70:30
6	114	A	78	82:18
7	110	B	81	75:25
8	114	B	79	84:16
9	117	A	95	86:14
10	118	A	93	95:5
11	117	B	90	90:10
12	118	B	95	97:3

^a A = Me₂CuLi, THF-Et₂O, 0 °C; B = MeCu(CN)Li, Et₂O, 0 °C.

methylene chain in the *endo* conformer, thereby decreasing its reactivity toward S_N2' attack. The *exo* oxygen, on the other hand, is readily accessible to metal ions.

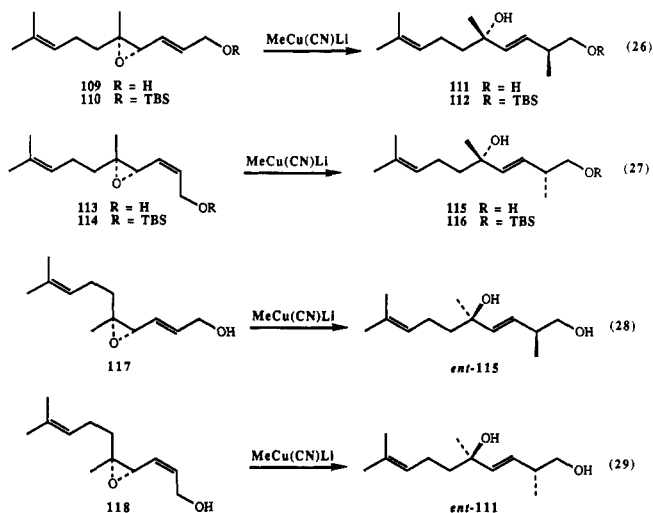
VI. Acyclic Vinyloxiranes

In work aimed at exploring the use of nonracemic acyclic vinyloxiranes for the enantioselective synthesis of acyclic allylic alcohols, Marshall, Trometer, and Cleary examined the addition of various methylcuprates to the (*S*)-vinyloxiranes **104** and **107** (eq 24 and 25).³²



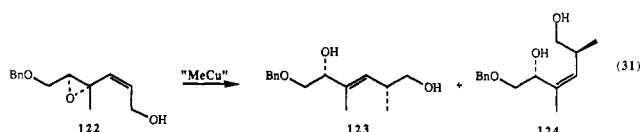
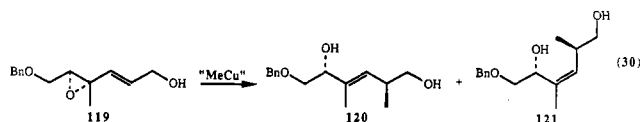
The highest ratio of S_N2' : S_N2 products was obtained through MeCu(CN)Li addition to the (*Z*)-vinyloxirane **107** in ether (**105**:**108** = 9). The Gilman cuprate showed poor S_N2' : S_N2 ratios in THF-ether with both **104** and **107** (0.2 for **104** and 1.2 for **107**). However, in ether alone, the (*Z*)-vinyloxirane **107** gave rise to a 7.4:1 mixture of S_N2' and S_N2 products **105** and **108**. A similar enhancement was not observed with the *E* isomer **104** in ether (**105**:**106** = 0.7). The anti S_N2' addition products, (*S*)- and (*R*)-**105**, respectively, predominated over the corresponding syn adducts in these additions.

Substituents on the oxirane ring were found to strongly disfavor the S_N2 pathway. Thus, vinyloxiranes derived from geraniol and nerol gave only S_N2' products upon treatment with both MeCu(CN)Li and Me₂CuLi (eq 26–29). The anti:syn selectivity was highest for the (*Z*)-allylic alcohol derivative **113** and lowest for the TBS ether derivatives **110** and **114** (Table X), suggestive of a hydroxyl directing effect. The (*E*)- and (*Z*)-vinyloxiranes **117** and **118** derived from nerol showed uniformly high anti:syn preferences with both of the methylcuprates examined (Table X, entries 9–12). The two epoxide systems are complementary in that the (*E*)-*trans*-vinyloxirane **109** and the (*Z*)-*cis*-vinyloxirane **118** give rise to enantiomeric products, **111** and *ent*-**111**,

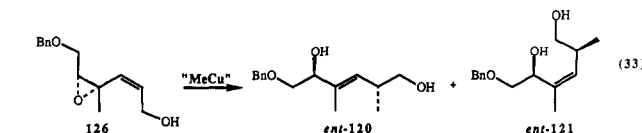
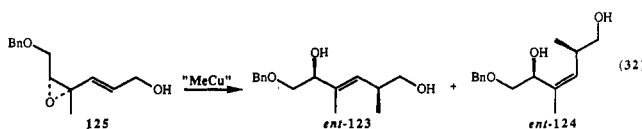


as do the related *Z*-*trans* and *E*-*cis* pair 113 and 117. The enantiomers of these vinyl oxiranes are also readily available. Thus, by the proper choice of epoxide configuration, epoxide geometry, and double-bond geometry isomerically pure diols 111, 115, *ent*-111, and *ent*-115 can be readily prepared.

The effect of substituents and geometry on stereoselectivity was further explored with the nonracemic vinyl oxiranes 119, 122, 125, and 126.³³ The *E*-*trans* isomer 119 yielded mixtures of the *E* and *Z* products 120 and 121 with Me₂CuLi and MeCu(CN)Li (eq 30). Addition of these cuprates to the (*Z*)-*trans*-vinyl oxirane 122 gave the (*Z*)-allylic alcohol 124 preferentially (eq 31). All four products 120, 121, 123, and 124 derive



from anti S_N2' addition. The (*E*)- and (*Z*)-*cis*-vinyl oxiranes 125 and 126 show the highest selectivity, giving rise to the (*E*)-allylic alcohols *ent*-123 and *ent*-120, respectively (eq 32 and 33). These results are summarized in Table XI. Once again, through proper choice of starting vinyl oxirane any of the four diols 120, 123, *ent*-120, or *ent*-123 can be prepared efficiently.



The differing *E*:*Z* ratios exhibited by the foregoing sets of vinyl oxiranes can be qualitatively understood by analysis of steric interactions in reactant-like transition-state conformers (Figure 2). Stereoelectronic considerations require the epoxide and vinylic carbon

TABLE XI. S_N2' Additions to Nonracemic Acyclic Vinyl oxiranes 119, 122, 125, and 126

entry	vinyl oxirane	method ^a	yield, %	anti:syn ^b	<i>E</i> : <i>Z</i>
1	119	A	89	99:1	55:45
2	119	B	76	91:9	75:25
3	122	A	88	>99:1	13:87
4	122	B	97	98:2	16:84
5	125	A	57	96:4	84:16
6	125	B	76	97:3	98:2
7	126	A	63	99:1	94:6
8	126	B	71	90:10	97:3

^a A = Me₂CuLi, THF-Et₂O, -20 to 0 °C; B = MeCu(CN)Li, THF-Et₂O, -20 to 0 °C. ^b Major product.

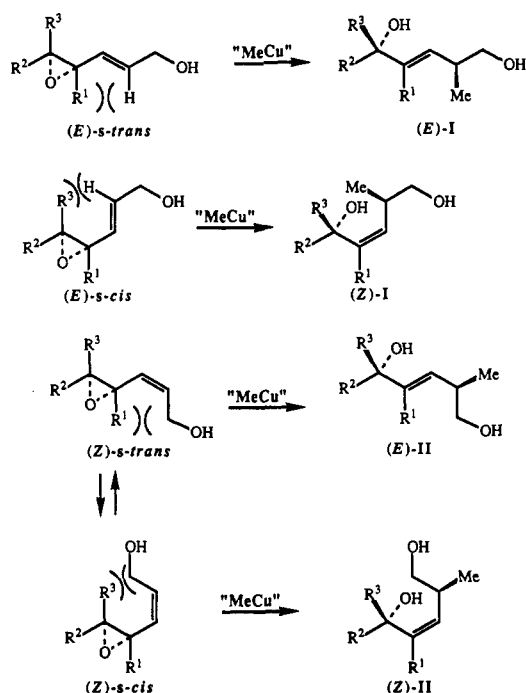
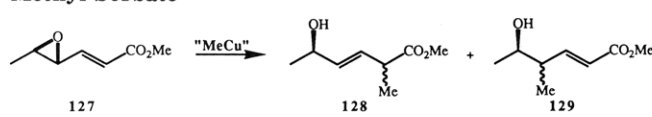


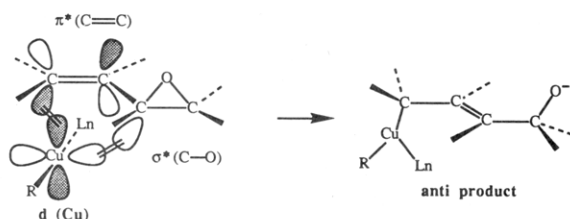
Figure 2. Transition-state analysis for *E*- and *Z*-selective anti S_N2' additions to acyclic vinyl oxiranes.

centers to assume a nearly coplanar arrangement for effective interaction between the π-orbitals and the breaking C–O bond. This requirement is met in two conformers, the *s*-*cis* and the *s*-*trans*. When R² and R³ are both alkyl substituents and R¹ is H, as in 109, 110, 113, 114, 117, and 118, steric interactions between R³ and the (*Z*)-vinylic substituent (H or CH₂OH) strongly disfavor the *s*-*cis* conformers. As a result, only the *E* products (*E*)-I and (*E*)-II are obtained. When R¹ is alkyl and R³ is H, as in vinyl oxirane 119, the steric interactions present in conformers *E*-*s*-*trans* and *E*-*s*-*cis* are closely balanced and a mixture of (*E*)- and (*Z*)-allylic alcohols is formed. In the *Z* isomer, the R¹/CH₂OH interaction of the *s*-*trans* conformer outweighs the H/CH₂OH interaction of the *s*-*cis* conformer and the *Z* product (e.g., 124) is actually favored. The presence of an alkyl substituent R³ causes the *s*-*cis* conformer to be disfavored in both the (*E*)- and (*Z*)-vinyl oxiranes, leading to a strong preference for the (*E*)-allylic alcohols (e.g., *ent*-123 and *ent*-120). The enhanced anti:syn ratios observed for the free alcohols vs the TBS ether derivatives of the vinyl oxirane substrates is suggestive of a directing effect through coordination of the OH grouping with the cuprate.³⁴ The *Z* systems 113, 118, 122, and 126 are also capable of chelation or hydrogen bonding between the OH and epoxide oxygens.

TABLE XII. Addition of Methylcuprates to the Epoxide of Methyl Sorbate


entry	"MeCu" ^a	yield, %	S _N 2':S _N 2	anti:syn	
				128	129
1	A	58	21:79	71:29	96:4
2	A·BF ₃	54	42:76	45:55	63:37
3	B	71	68:32	99:1	97:3
4	B·BF ₃	53	61:39	80:20	89:11
5	C	71	64:36	97:3	95:5
6	C·BF ₃	65	68:32	79:21	94:6

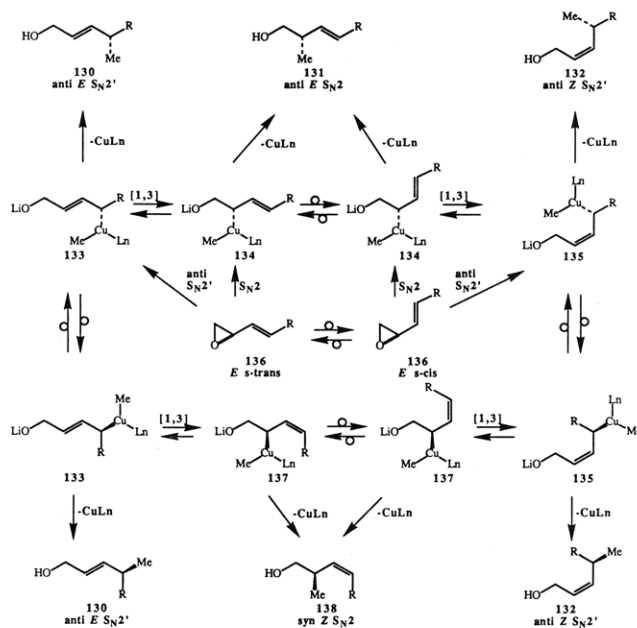
^a A = Me₂CuLi; B = MeCu(CN)Li; C = Me₂Cu(CN)Li₂.

**Figure 3.** Orbital overlap for S_N2' addition of organocuprates to vinyloxiranes.

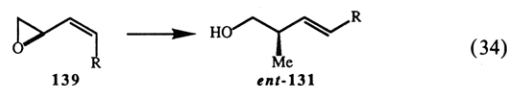
A recent study on additions of various cuprates to the monoepoxide of methyl sorbate (127) showed that both S_N2':S_N2 and anti:syn ratios can be significantly affected by the presence of BF₃ (Table XII).³⁵ Substantially more S_N2 displacement was observed with the "harder" Me₂CuLi reagent than with the "softer" cyanocuprates. It is assumed that BF₃ coordinates with the cyano ligands of these latter reagents. Partial dissociation of the epoxide ring was postulated to account for the decreased anti:syn ratios when BF₃ was present. The absence of 1,4-addition products and Z-S_N2' products is noteworthy. The trends in regioselectivity were explained on the basis of electron density calculations.

VII. Mechanistic Considerations

The vast majority of S_N2' displacements involving organocopper reagents proceed with anti stereoselectivity. Corey and Boaz have suggested that this preference derives from orbital symmetry.³⁶ Accordingly, a filled d¹⁰ orbital of the cuprate can interact with both the π* and σ* antibonding orbitals of the vinyloxirane as pictured in Figure 3. It is the d-σ* (S_N2) component of this interaction that actually directs the stereochemistry of the reaction. Once formed, the postulated σ organocopper(III) intermediate can undergo reductive elimination to product or it can rearrange by a (presumed) suprafacial [1,3] shift to an isomeric organocopper(III) species as illustrated in Figure 4.³⁷ Thus, direct S_N2' displacement on the (*E*)-vinyloxirane 136 could yield either the (*E*)-allylcopper 133 or the (*Z*)-allylcopper 135 via the *s*-trans or the *s*-cis conformer. Collapse of these allylcopper intermediates would afford the (*E*)- and (*Z*)-allylic alcohols 130 and 132. Alternatively, alcohols 130 and 132 could arise from the S_N2 intermediate 134 following [1,3] isomerization and reductive elimination. The syn *Z*-S_N2 product 138 could likewise be formed from the S_N2' adduct 133 via the rearranged organocopper species 137. An analogous sequence can be devised for (*Z*)-vinyloxiranes. It should

**Figure 4.** Possible reaction pathways for the addition of MeCu(Ln)Li to an (*E*)-vinyloxirane.

be noted that the otherwise surprising formation of the syn *Z*-S_N2 product 138 from the (*E*)-vinyloxirane 136 and the formation of the syn *E*-S_N2 product *ent*-131 from the (*Z*)-vinyloxirane 139 (eq 34) are readily accommodated by these proposed pathways.³²



Steric factors play a major role in the regiochemical outcome of cuprate additions to vinyloxiranes. In general, substituents on the oxirane moiety hinder S_N2 addition.^{32,33} Double-bond substituents, on the other hand, do not adversely affect the S_N2' process except with bulky (*t*-Bu) cuprates.¹⁹ Solvent also exerts a strong influence on regioselectivity, especially with cyclic vinyloxiranes, where the use of THF can lead to virtually exclusive S_N2 displacement.³⁸ Ether, on the other hand, tends to strongly favor the S_N2' pathway.^{38,39} Displacements in cyclic vinyloxiranes are also highly sensitive to the type of cuprate reagent. Lower order cyanocuprates are generally superior to Gilman or higher order cuprates. Marino has suggested that a cyano ligand increases the Lewis acidity of the cuprate, thereby favoring its complexation with the epoxide oxygen, enhancing the polarization of the allylic double bond.¹⁹ Alternatively, this Cu-epoxide complex could undergo direct S_N2 displacement followed by 1,3-isomerization (Figure 4, 136 → 134 → 133).^{19,24} In systems where such 1,3-isomerization is sterically or electronically disfavored, S_N2 products predominate.^{19,24} In acyclic systems regioselectivity is more sensitive to steric effects than to solvent or nature of the cuprate.

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References and Notes

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