S_N2' Additions of Organocopper Reagents to Vinyloxiranes

JAMES A. MARSHALL

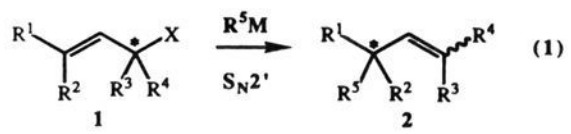
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received January 9, 1989 (Revised Manuscript Received May 25, 1989)

Contents

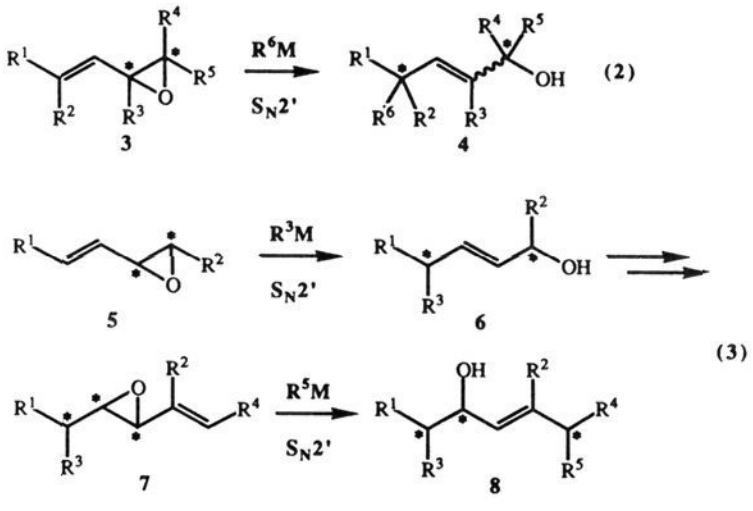
I. Introduction

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



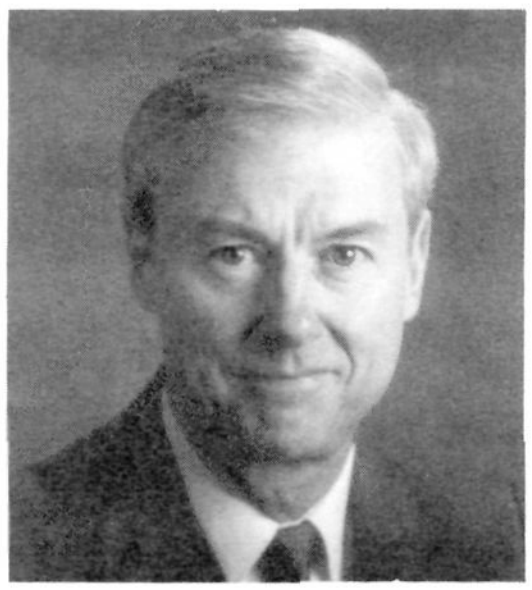
of the S_N2' reaction have been of interest for more than 50 years, but the process is still not well understood.[2] The coupling of organometallic nucleophiles with allylic halides first received attention some 40 years ago.[3] However, because mixtures of regio- and stereoisomeric products were often formed, this reaction found only limited use in synthesis.[2] The discovery that allylic acetates afford S_N2' substitution products with organocuprates[4] 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

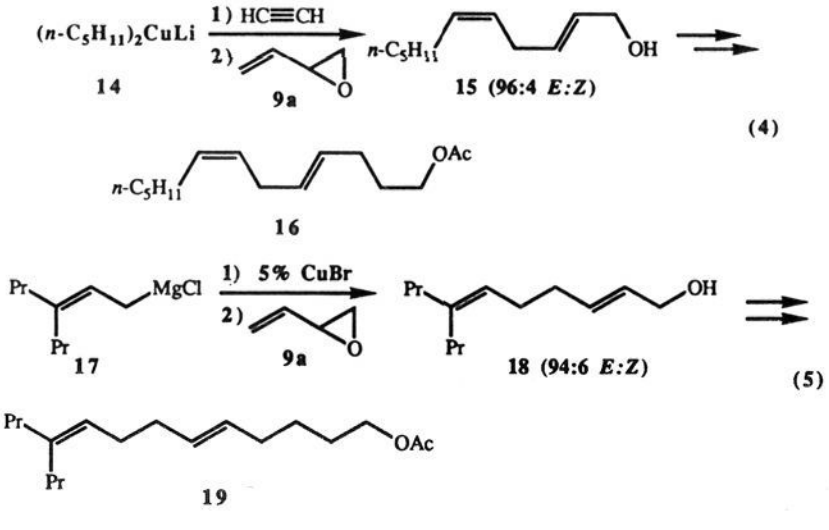
The first S_N2' additions to vinyloxiranes by organocuprates were recorded in 1970.[8] The monoepoxides **9a–c** of 1,3-butadiene and isoprene were shown to give



Professor James A. Marshall received his B.S. degree in 1957 from the University of Wisconsin and his Ph.D. degree in 1960 from the University of Michigan under the direction of Robert E. Ireland. After 2 years of postdoctoral studies at Stanford with William S. Johnson, he joined the faculty of Northwestern University, becoming full professor in 1968. In 1980 he was appointed Professor of Chemistry at the University of South Carolina, and since 1983 he has held the Guy Lipscomb Chair.

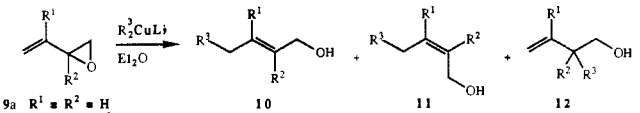
mainly the *E*-S_N2' product **10** along with lesser amounts of *Z*-S_N2' and S_N2 products **11** and **12** (Table I). Later work demonstrated that the use of vinylic cuprates prepared from organolithium (Table I) or Grignard reagents (Table II) provides easy access to various 2,5-dienols.[9] Allylic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



0009-2665/89/0789-1503$06.50/0

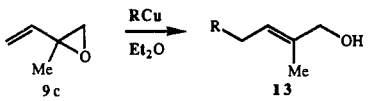
TABLE I. Additions of Gilman Cuprates to Butadiene and Isoprene Epoxides



9a $R^1 = R^2 = H$
9b $R^1 = Me$, $R^2 = H$
9c $R^1 = H$, $R^2 = Me$

entry	epoxide	R^3	S_N2' 10	S_N2' 11	E:Z	S_N2 12	ref
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_2C=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

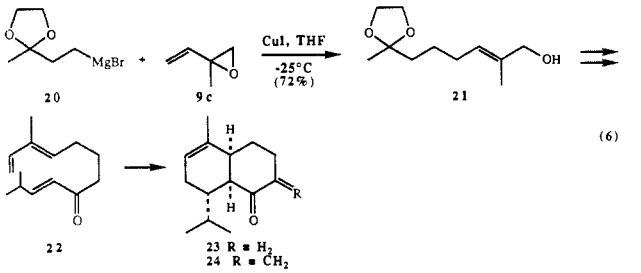
TABLE II. Addition of Cuprates to Isoprene Epoxide



entry	RM	yield, %	E:Z
1	$(Me_2C$=$CH)_2CuLi$	95	92:8
2	Me_2C=CHMgBr·CuBr[a]	79[b]	96:4
3	$(Me_2C$=$CH)_2Cu$·MgBr	34	97:3
4	((E)-Bu(Et)C=$CH)_2Cu$·MgBr	78	58:42
5	CH_2=$CHCH_2MgBr$·CuBr[a]	90	92:8
6	(Z)-MeCH=$CHCH_2MgBr$·CuBr[a]	95	95:5

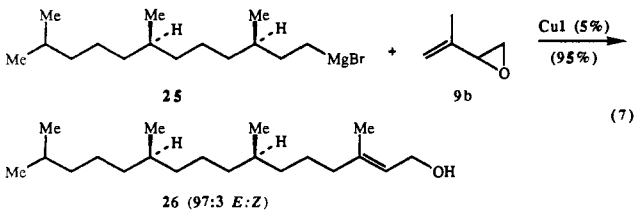
[a] A catalytic amount of CuBr was used. [b] 19% of the S_N2 product was also formed.

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



(6)

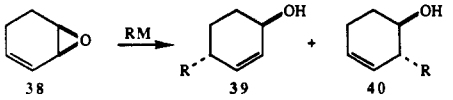
converted to the trienone **22**, which underwent facile intramolecular Diels–Alder cycloaddition and α-methylenation to ketone **24**, the alleged structure of chiloscyphone, an essential oil constituent. The isomeric isoprene epoxide **9b** was used by Fujisawa et al.[12] in a synthesis of (*R*,*R*)-phytol (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.



(7)

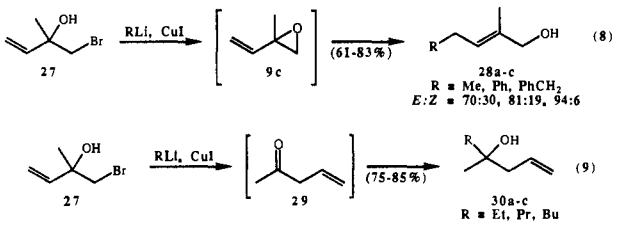
One problem inherent in the foregoing applications is the difficulty associated with the preparation and handling of the volatile and highly refractory vinyloxiranes **9a–c**. A possible solution to this problem was explored by Araki and Butsugan,[13] who introduced the bromohydrin **27** as an in situ 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).

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



RM	yield, %	39:40	ref
Me_2CuLi		42:35[a]	13a
Me_2CuLi	91	54:46[b]	13b
Ph_2CuLi	87	69:31	13b
$(t\text{-Bu})_2CuLi$	72	65[c]:35[d]	13b

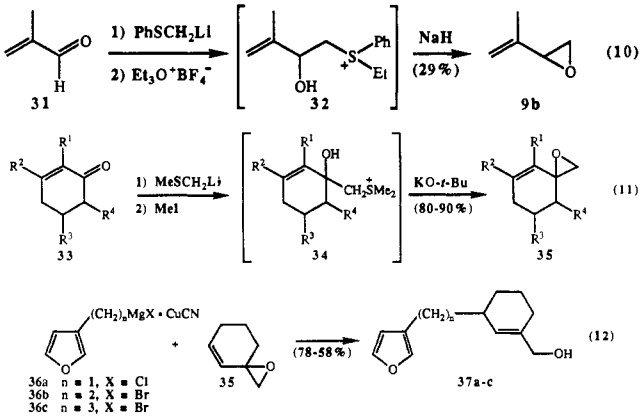
[a] Plus 23% of 3-cyclohexenone. [b] Plus variable amounts (0–6%) of 3-cyclohexenone. [c] 7:1 trans:cis. [d] 2:1 cis:trans.



(8)

(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** ($R^1 = R^2 = R^3 = R^4 = H$) proceeded readily to give the allylic alcohols **37** in satisfactory yield (eq 12).[14]



(10)

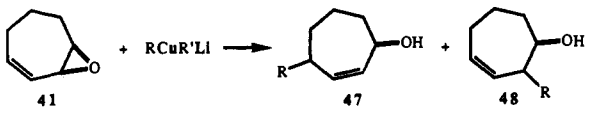
(11)

(12)

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

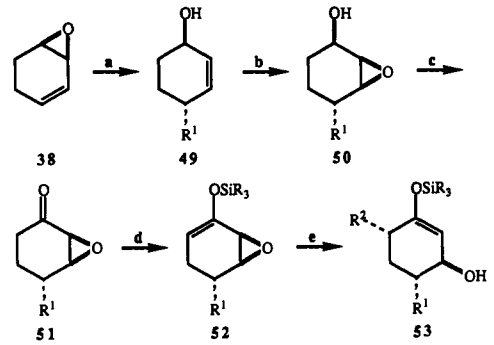
TABLE IV. Addition of Mixed Cuprates to 1,3-Cycloheptadiene Epoxide (41)



41 47 48

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_2Me	98	97:3
Bu	CN	"high"	100:0

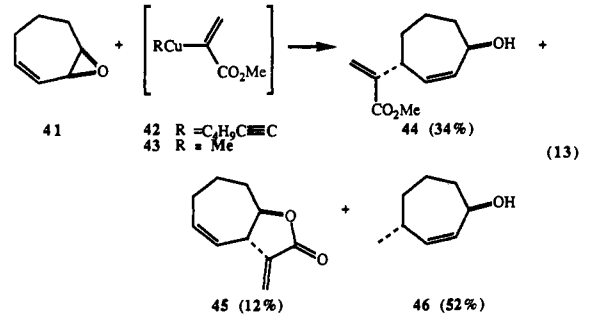
SCHEME I[a]



38 49 50 51 52 53

[a] (a) $R^1Cu(CN)Li$; (b) $ArCO_3H$; (c) $CrO_3 \cdot py_2$; (d) LDA; R_3SiCl; (e) $R^2Cu(CN)Li$.

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



41 42 R = C_4H_9C≡C; 43 R = Me 44 (34%) (13)

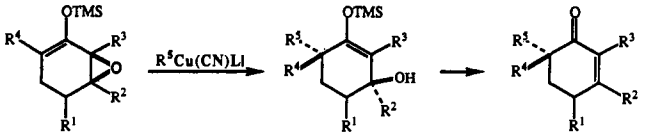
45 (12%) 46 (52%)

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 Me_2CuLi 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' 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,

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

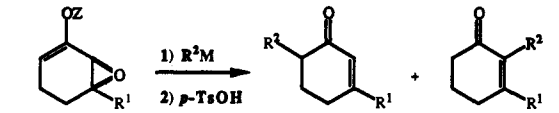


54 55 56

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	*t*-Bu	100
3	H	Me	H	H	Me	95
4	H	Me	H	H	*n*-Bu	80
5	α-Me	Me	H	H	Me	80
6	α-Me	Me	H	H	*n*-Bu	94
7	β-Me	Me	H	H	*n*-Bu	70
8	H	H	Me	H	Me	93
9	H	H	Me	H	*n*-Bu	100
10	H	H	Me	H	*t*-Bu	100
11	H	Me	H	Me	Me	87
12	H	Me	H	Me	*n*-Bu	74
13	H	Me	H	Me	*t*-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-Epoxycyclohexanone Derivatives



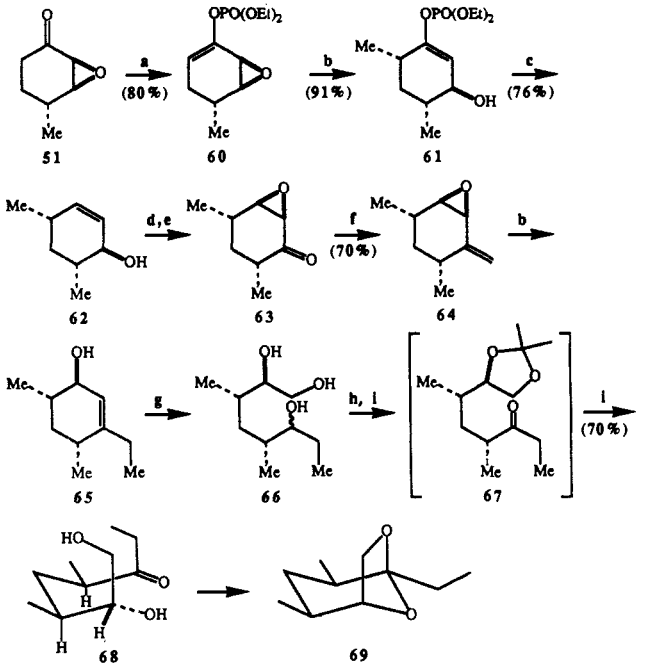
57a Z = $PO(OEt)_2$
57b Z = TMS
57c Z = Li

58 59

entry	Z	R^1	R^2M	yield, % 58	59
1	$PO(OEt)_2$	H	Me_2CuLi	83[a]	
2	TMS	H	Me_2CuLi	55	
3	Li	H	Me_2CuLi	65	
4	TMS	Me	Me_2CuLi	97	
5	Li	Me	Me_2CuLi	80	
6	TMS	Me	Ph_2CuLi		95
7	Li	Me	Ph_2CuLi		72
8	TMS	Me	CH_2=CHMgBr·CuI		93

[a] Yield of anti S_N2' product before dehydration.

SCHEME II[a]

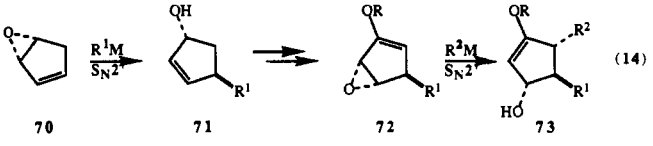


[a] (a) LDA, $ClPO(OEt)_2$; (b) MeCu(CN)Li; (c) Li, NH_3, MeOH; (d) m-$ClC_6H_4CO_3H$; (e) $CrO_3 \cdot py_2$; (f) $Ph_3P{=}CH_2$; (g) AcCl, py; O_3; $LiAlH_4$; (h) CH_3COCH_3, TsOH; (i) H_2CrO_4.

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 S_N2' 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 MeCu(CN)Li gave the anti S_N2' product **61** in 91% yield. Hydrogenolysis of the phosphonate with Li in NH_3 yielded the allylic alcohol **62**, which underwent sequential hydroxyl-directed epoxidation and oxidation to the epoxy ketone **63**. This was converted to the alkylidene epoxide **64** through Wittig methylenation. Methylation of **64** with MeCu(CN)Li gave the S_N2' 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 (±)-α-multistriatin (**69**) in situ.

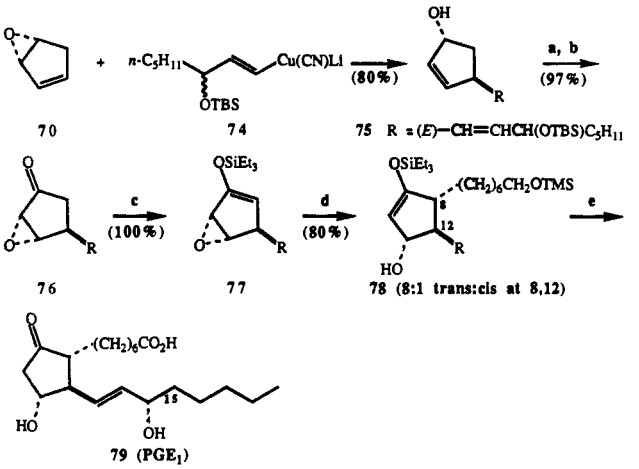
The sequential S_N2' addition strategy depicted in Scheme I leads to 2,4-dialkylated cyclohexanone derivatives. The use of 1,3-cyclopentadiene monoepoxide in an analogous sequence would afford 2,3-dialkylated cyclopentanones of possible value in prostanoid synthesis. A potential application is depicted in eq 14.



(14)

However, it should be noted that the stereochemistry of the second S_N2' addition must be syn, in contrast to the first and to all known examples in cyclohexene systems. Nonetheless, a fortuitous occurrence allowed

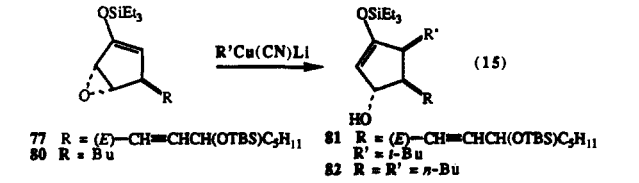
SCHEME III[a]



[a] (a) $VO(acac)_2$, t-BuOOH; (b) $CrO_3 \cdot py_2$, (c) LDA; Et_3SiCl; (d) $TMSOCH_2(CH_2)_6Cu(CN)Li$; (e) KF, pH 7; O_2, PtO_2; HF, CH_3CN.

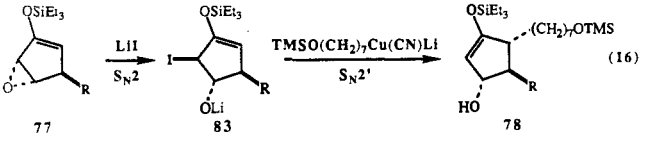
Marino to reduce this strategy to practice (Scheme III).[22] Accordingly, the epoxy enol silyl ether **77** afforded an 8:1 mixture of S_N2' adducts in 80% yield upon treatment with the cyanocuprate derived from 7-iodo-1-heptanol TMS ether. Separation of C-15 diastereoisomers, followed by sequential deprotection and oxidation, led to racemic PGE_1 (**79**), thus establishing the relative stereochemistry of the side chains as trans and the predominant S_N2' pathway for step d as syn.

It was initially presumed that the substituent R in epoxycyclopentene **77** directed the relatively bulky cyanocuprate to the less hindered α-face, leading to the observed syn S_N2' product **78**. However, subsequent studies of this reaction suggested an alternative explanation.[23] Thus, it was found that addition of n-BuCu(CN)Li to the n-butyl analogue **80** of epoxide **77** and, more impressively, t-BuCu(CN)Li to epoxide **77** gave only the anti S_N2' products **82** and **81** (eq 15). Evi-



(15)

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-BuCu(CN)Li and t-BuCu(CN)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-BuLi. It is proposed that the LiI produced in this lithiation adds to vinyloxirane **77**. Subsequent anti S_N2' displacement on the resulting allylic iodide **83** then leads to the observed product **78** (eq 16).

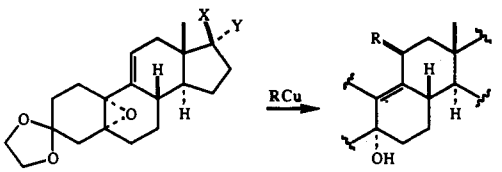


(16)

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 $\Delta^{9,11}$-5α,10α-Epoxy Steroids



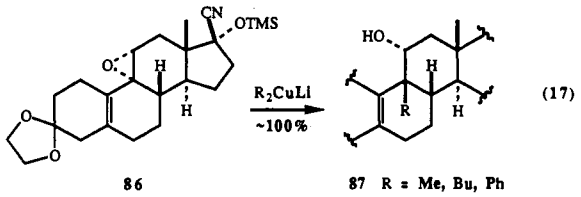
84a X = OCOPh, Y = H
84b X = CN, Y = OTMS

85

epoxide	RCu	yield, %
84a	Me_2CuLi	100
84a	Et_2CuLi	85
84a	Ph_2CuLi	82
84b	t-Bu_2CuLi	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 11β-alkyl products **85** upon treatment of the $\Delta^{9(11)}$-5α,10α-epoxy-19-norandrostane systems **84a** and **84b** with Gilman cuprates and CuCl–Grignard reagents (Table VII).[24] These additions are noteworthy for their excellent regio- and stereoselectivity despite the potentially adverse steric influence of the 13β-methyl substituent. Interestingly, the isomeric $\Delta^{5(10)}$-9α,11α-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

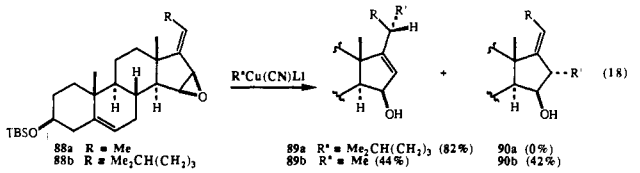


(17)

86 **87** R = Me, Bu, Ph

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-15β,16β-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



(18)

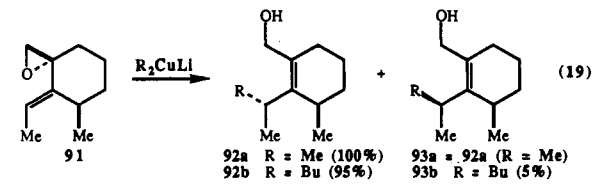
88a R = Me
88b R = $Me_2CH(CH_2)_3$

89a R' = $Me_2CH(CH_2)_3$ (82%) **90a** (0%)
89b R' = Me (44%) **90b** (42%)

the 16 double bond led to 15β-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 15β-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 13β-methyl and the isohexyl 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

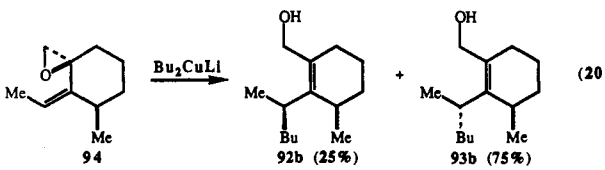
Ziegler and Cady were the first to employ exocyclic epoxides for the introduction of stereocenters in side chains by S_N2' alkylation.[27] Addition of the Gilman methyl- or butylcuprate to the (*E*)-*cis*-ethylidene epoxide **91** gave only S_N2' products. Surprisingly, with the butylcuprate a 95:5 mixture 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



(19)

91

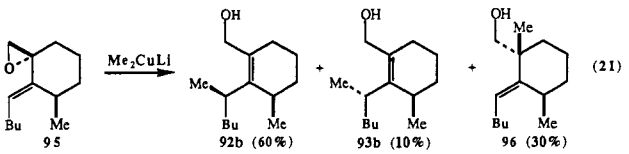
92a R = Me (100%) **93a** = **92a** (R = Me)
92b R = Bu (95%) **93b** R = Bu (5%)



(20)

94 **92b** (25%) **93b** (75%)

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 Me_2CuLi (eq 21). In this case the cuprate reagent attacks anti to

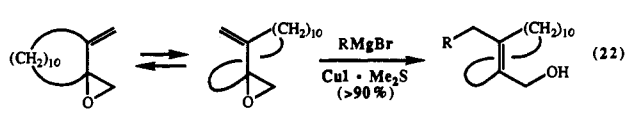


(21)

95 **92b** (60%) **93b** (10%) **96** (30%)

the epoxide oxygen and syn to the presumed axial methyl substituent of **95**. The lower steric requirements of Me_2CuLi vs Bu_2CuLi are thought to account for the contrasting behavior of **91** and **95**.

Cuprate additions to the methylene cyclododecylidene 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]

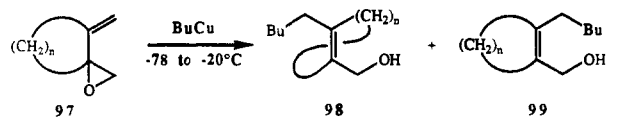


(22)

97b (*s-cis*) **97b** (*s-trans*) **98b**

R = *n*-Bu, $(CH_2)_2CH{=}CH_2$, $(CH_2)_9CH{=}CH_2$

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



entry	n	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·Me_2S, THF; B = Bu_2CuLi, THF; C = BuCu(CN)Li, THF.

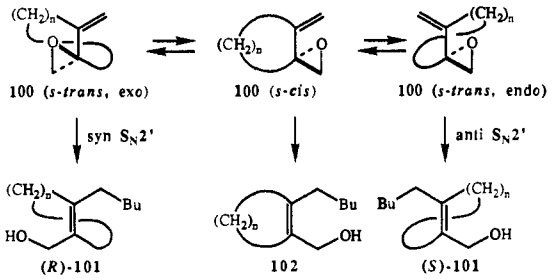
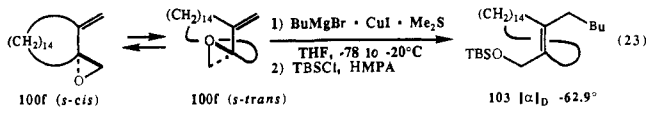


Figure 1. Possible modes of S_N2' addition to methylene cycloalkylidene epoxides.

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·Me_2S (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 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.

TABLE IX. Addition of BuMgBr • CuI • Me_2S to (*R*)-Cycloalkylidene Epoxides 100

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

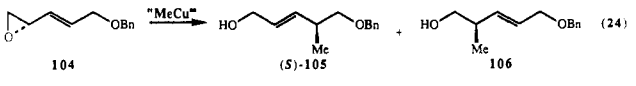
TABLE X. S_N2' Additions to Nonracemic Acyclic Vinyloxiranes Derived from Geraniol and Nerol

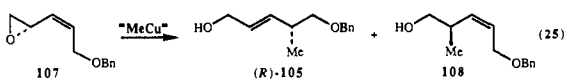
entry	vinyloxirane	method[a]	yield, %	anti:syn
1	109	A	81	85:15
2	113	A	75	97:3
3	109	B	84	88:12
4	113	B	88	99:1
5	110	A	77	70:30
6	114	A	78	82:18
7	110	B	81	75:25
8	114	B	79	84:16
9	117	A	95	86:14
10	118	A	93	95:5
11	117	B	90	90:10
12	118	B	95	97:3

[a] A = Me_2CuLi, THF–Et_2O, 0 °C; B = MeCu(CN)Li, Et_2O, 0 °C.

VI. Acyclic Vinyloxiranes

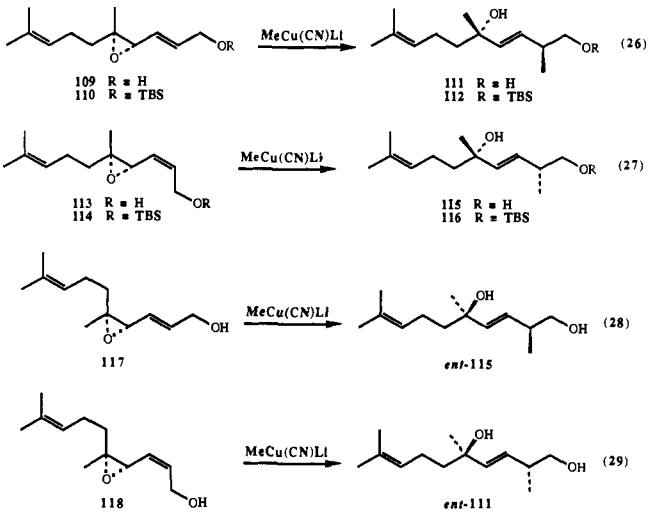
In work aimed at exploring the use of nonracemic acyclic vinyloxiranes for the enantioselective synthesis of acyclic allylic alcohols, Marshall, Trometer, and Cleary examined the addition of various methylcuprates to the (*S*)-vinyloxiranes **104** and **107** (eq 24 and 25).[32]





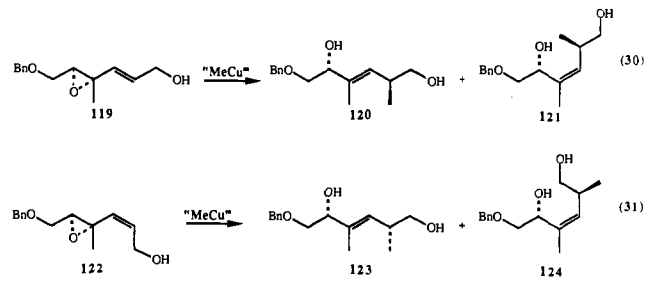
The highest ratio of S_N2':S_N2 products was obtained through MeCu(CN)Li addition to the (*Z*)-vinyloxirane **107** in ether (**105**:**108** = 9). The Gilman cuprate showed poor S_N2':S_N2 ratios in THF–ether with both **104** and **107** (0.2 for **104** and 1.2 for **107**). However, in ether alone, 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 Me_2CuLi (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**,

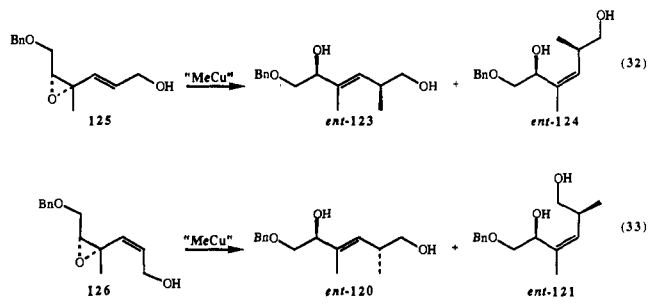


as do the related *Z*-trans and *E*-cis pair **113** and **117**. The enantiomers of these vinyloxiranes are also readily available. Thus, by the proper choice of epoxide configuration, epoxide geometry, and double-bond geometry isomerically pure diols **111**, **115**, *ent*-**111**, and *ent*-**115**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

The effect of substituents and geometry on stereoselectivity was further explored with the nonracemic vinyloxiranes **119**, **122**, **125**, and **126**.[33] The *E*-trans isomer **119** yielded mixtures of the *E* and *Z* products **120** and **121** with Me_2CuLi and MeCu(CN)Li (eq 30). Addition of these cuprates to the (*Z*)-*trans*-vinyloxirane **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*-vinyloxiranes **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 vinyloxirane 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 vinyloxiranes 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 Vinyloxiranes 119, 122, 125, and 126

entry	vinyloxirane	method[a]	yield, %	anti:syn[b]	*E*:*Z*
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 = Me_2CuLi, THF–Et_2O, −20 to 0 °C; B = MeCu(CN)Li, THF–Et_2O, −20 to 0 °C. [b] Major product.

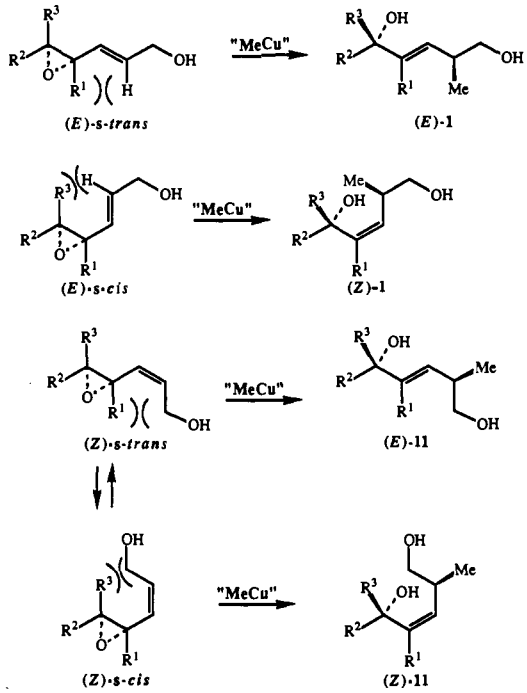
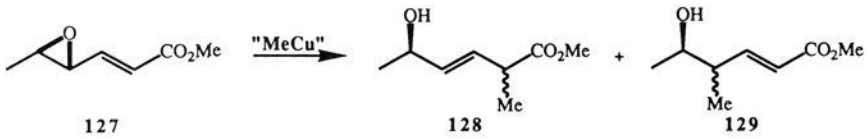


Figure 2. Transition-state analysis for *E*- and *Z*-selective anti S_N2' additions to acyclic vinyloxiranes.

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 R^2 and R^3 are both alkyl substituents and R^1 is H, as in **109**, **110**, **113**, **114**, **117**, and **118**, steric interactions between R^3 and the (*Z*)-vinylic substituent (H or CH_2OH) strongly disfavor the s-cis conformers. As a result, only the *E* products (*E*)-I and (*E*)-II are obtained. When R^1 is alkyl and R^3 is H, as in vinyloxirane **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 R^1/CH_2OH interaction of the s-trans conformer outweighs the H/CH_2OH interaction of the s-cis conformer and the *Z* product (e.g., **124**) is actually favored. The presence of an alkyl substituent R^3 causes the s-cis conformer to be disfavored in both the (*E*)- and (*Z*)-vinyloxiranes, 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 vinyloxirane 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, %	$S_N2':S_N2$	anti:syn 128	anti:syn 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 = Me_2CuLi; B = MeCu(CN)Li; C = $Me_2Cu(CN)Li_2$.

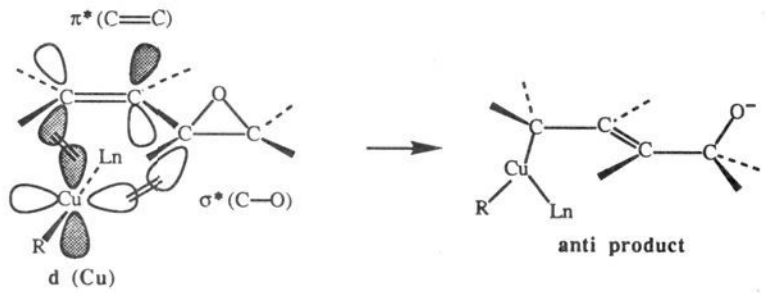


Figure 3. Orbital overlap for S_N2' addition of organocuprates to vinyloxiranes.

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 BF_3 (Table XII).[35] Substantially more S_N2 displacement was observed with the "harder" Me_2CuLi reagent than with the "softer" cyanocuprates. It is assumed that BF_3 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 BF_3 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 d^{10} 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

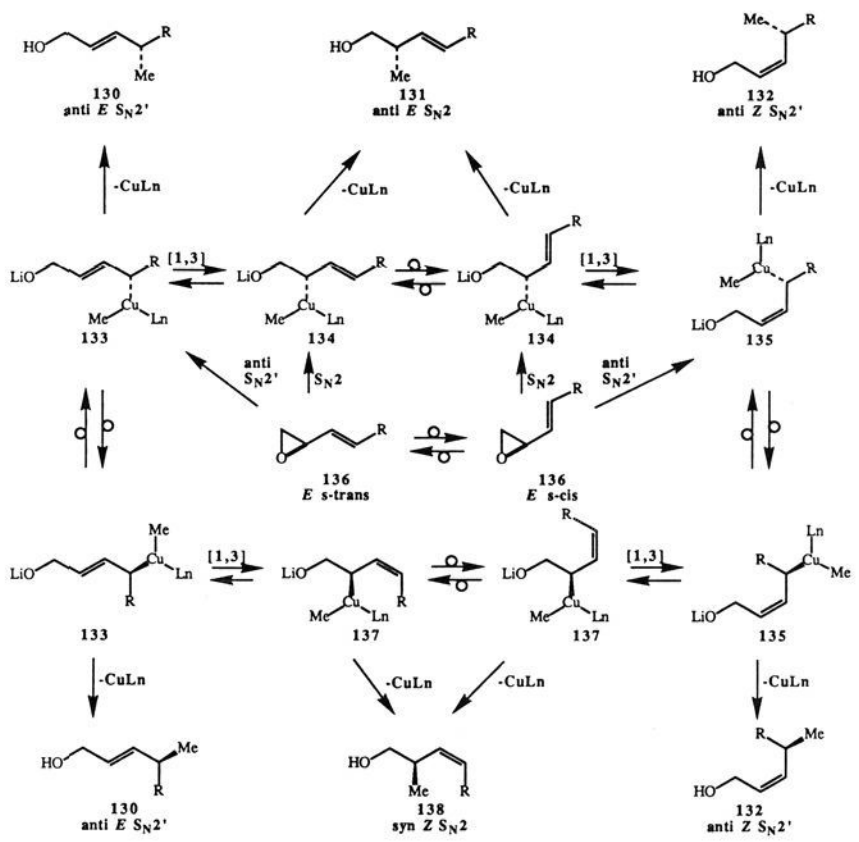
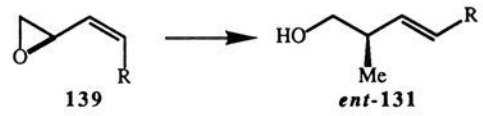


Figure 4. Possible reaction pathways for the addition of MeCu(Ln)Li to an (*E*)-vinyloxirane.

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]



(34)

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.

Acknowledgments. We are indebted to the National Science Foundation for their continuing support of our work on vinyloxirane and cuprate chemistry, most recently through Grant CHE-8615569.

References and Notes

(1) The terms "S_N2" and "S_N2'" will be used as operational definitions in this review to designate the regiochemistry of the

substitution without mechanistic implications.
(2) For an excellent comprehensive review, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.
(3) Wilson, K. W.; Roberts, J. D.; Young, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 2019.
(4) Cf.: Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945. Lipschutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197. The formulas used for organocuprates indicate the stoichiometry of the reagents only. No structural significance is implied.
(5) Rona, P.; Tökes, L.; Tremble, J.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1969**, 43.
(6) For leading references, see: Goering, H. L.; Kantner, S. S.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495. Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420.
(7) Cf.: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Soo, Y. K.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(8) Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 4978. Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4979.
(9) Cahiez, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1978**, 528.
(10) Alexakis, A.; Cahiez, C.; Normant, J. F. *Tetrahedron Lett.* **1978**, 2027.
(11) Gras, J.-L. *J. Org. Chem.* **1981**, *46*, 3738.
(12) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823.
(13) Araki, S.; Butsugan, Y. *Chem. Lett.* **1980**, 185.
(14) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988.
(15) (a) Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* **1971**, *93*, 3046. (b) Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 3047.
(16) Cf.: Bordwell, F. G. *Acc. Chem. Res.* **1970**, *3*, 281.
(17) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675.
(18) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467.
(19) Marino, J. P.; Jaën, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.
(20) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.
(21) Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379.
(22) Marino, J. P.; Fernandez de la Pradillo, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.
(23) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389.
(24) Teutsch, G.; Belanger, A. *Tetrahedron Lett.* **1979**, 2051.
(25) Teutsch, G. *Tetrahedron Lett.* **1982**, *23*, 4697.
(26) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907.
(27) Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122.
(28) Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1984**, *106*, 723.
(29) Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1985**, *50*, 1607.
(30) Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106.
(31) Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986**, *42*, 1703.
(32) Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985. Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.
(33) Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *J. Org. Chem.* **1988**, *53*, 4274.
(34) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702.
(35) Ibuka, T.; Tanaka, M.; Nemoto, H.; Yamamoto, Y. *Tetrahedron* **1989**, *45*, 435.
(36) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. For a recent molecular orbital description of cuprate additions, see: Hamon, L.; Levisalles, J. *Tetrahedron* **1989**, *45*, 489.
(37) A π-allyl complex has been suggested as an intermediate in such isomerizations. Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422.
(38) Schlecht, M. F. *J. Chem. Soc., Chem. Commun.* **1982**, 1331.
(39) S_N2 displacements on epoxides by higher order cuprates have been found to be faster in diethyl ether than in THF. Lipshutz, B. H.; Wilhilm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.