JOC The Journal of Organic Chemistry

Article

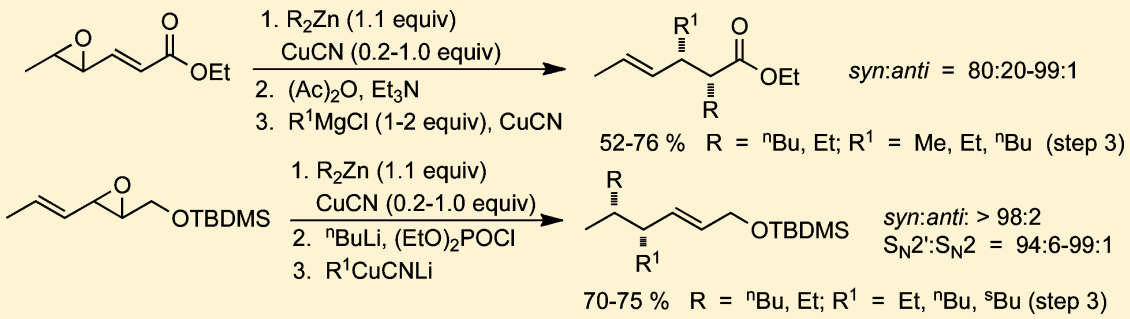
pubs.acs.org/joc

Regio- and Stereoselectivity in the Reactions of Organometallic Reagents with an Electron-Deficient and an Electron-Rich Vinyloxirane: Applications for Sequential Bis-Allylic Substitution Reactions in the Generation of Vicinal Stereogenic Centers

R. Karl Dieter,* Yaxin Huang, and Fenghai Guo

Hunter Laboratory, Department of Chemistry, Clemson University, Clemson, South Carolina 29634-0973, United States

Supporting Information



ABSTRACT: Vinyloxiranes provide opportunities for bis-allylic substitution reactions and the generation of new vicinal stereogenic centers if regio- and stereocontrol can be achieved. Ethyl (*E*)-4,5-epoxy-2-hexenoate affords excellent S_N2':S_N2 regioselectivity and *anti:syn* product diastereoselectivity with dialkyzinc reagents in the presence of CuCN, and conversion of the resultant allylic alcohol to the acetate affords good *syn:anti* product diastereoselectivity in S_N2'-selective allylic substitutions with alkylcyanocuprates in THF. (*E*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-4-hexenonate gives excellent S_N2':S_N2 regioselectivity and *anti:syn* product diastereoselectivity with dialkyzinc reagents in THF or DMF or Grignard reagents in Et_2O/THF (10/1) in the presence of CuCN. Conversion of the product allylic alcohol into the allylic phosphate affords excellent S_N2' regioselectivity and *syn:anti* product diastereoselectivity with lithium alkylcyanocuprates for primary and secondary alkyl transferable ligands, while S_N2 regioselectivity is observed for the *tert*-butyl ligand. Reaction conditions have been developed for regio- and stereocontrolled bis-allylic substitution reactions on both electron-rich and electron-deficient alkenyloxiranes, providing a methodology for the generation of vicinal alkane stereogenic centers.

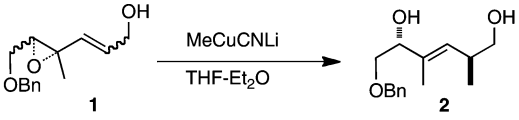
INTRODUCTION

Although cuprate-mediated allylic substitution reactions provide a powerful methodology for the regio-, diastereo-, and enantioselective construction of carbon−carbon bonds, the extent of these selectivities is often dependent upon the cuprate reagent, substrate substitution pattern, leaving group, solvent, and temperature.[1,2] The *anti*-S_N2'-substitution (allylic substitution with rearrangement) reaction pathway predominates,[1−3] and the *syn*-S_N2'-substitution pathway[1b,f] is largely limited to allylic carbamates and *o*-diphenylphosphinobenzoates (*o*-DPPB) involving intramolecular delivery of the transferable ligand. While this reliable reactivity pattern is an attractive feature of these cuprate-mediated allylic substitutions, the method is often limited by modest regio- and/or diastereoselectivities. In early work, Marino[4] showed that lithium alkylcyanocuprates (i.e., RCuCNLi) generally gave superior S_N2' regioselectivity in reactions with cyclic epoxyalkenes in comparison to other cuprate reagents, while Yamamoto (allylic mesylates),[5a] Nakamura (allylic halides),[5b] and Lipshutz (vinyloxiranes)[6] extended the use of CuCN to zinc cuprates for highly regioselective S_N2' pathways. By virtue of chelation effects and intramolecular delivery, allylic *o*-diphenylphosphinobenzoates[1b,f] give exceptional diastereoselectivity. Nevertheless, the reliability of the former protocol is often substrate dependent, and the latter methodology utilizes an expensive auxiliary and is limited to allylic esters. Increased S_N2' regioselectivity has also been reported for cuprate reagents derived from titanium[5b,7] and aluminum[8] organometallics. The recently introduced picolinoxy group gives excellent S_N2' allylic substitution with (*Z*)-alkenes but poor regioselectivity with (*E*)-alkenes.[9] A limited number of studies have explored 1,2-asymmetric induction in copper-mediated allylic substitution[1a,f,5b,7,10] and conjugate addition[1f,11] reactions arising from a pre-existing stereogenic center adjacent to the alkene moiety.

The regioselectivity is more difficult to control in vinyloxiranes (i.e., epoxides), where the S_N2 substitution reaction becomes more competitive with the S_N2' allylic substitution

Received: February 21, 2012
Published: April 23, 2012

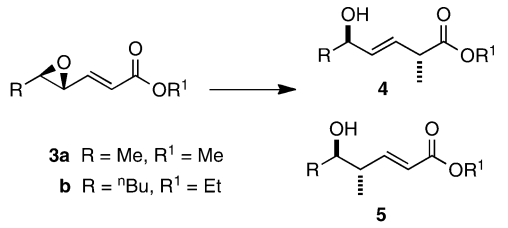
pathway.[2] In a series of studies, Marshall examined a wide range of substituted, nonconjugated, and oxygen-functionalized vinyloxiranes delineating the effects of substrate structure.[2c] Organozinc cuprates[6,12b] and trisubstituted epoxides[2c,d] suppressed S_N2 substitution, but mixtures of (*E*)- and (*Z*)-olefins were often obtained (eq 1[2d]). Studies by Yamamoto[12a] on the



(1)

		% yield	*anti:syn*	*E:Z*
a	*E*-olefin, *trans*-epoxide	76	91:9	75:25
b	*Z*-olefin, *trans*-epoxide	97	98:2	16:84
c	*E*-olefin, *cis*-epoxide	76	97:3	98:2
d	*Z*-olefin, *cis*-epoxide	71	90:10	97:3

epoxy enoate of methyl sorbate achieved the highest S_N2' selectivity with CuCN-derived methylcuprates, while later studies by Miyashita[12b] showed that enhanced regioselectivity and *anti:syn* diastereoselectivity could be achieved with dialkylzinc reagents in the presence of Cu(I) salts in DMF (eq 2). The vast majority of these studies on vinyloxiranes



(2)

	Reagent	% yield	**4**:**5**	**4**-*anti:syn*	**5**-*anti:syn*
3a	Me_2CuLi	58	21:79	71:29	96:4
3a	$Me_2CuLi{\cdot}BF_3$	54	24:76	45:55	63:37
3a	MeCuCNLi	71	68:32	99:1	97:3
3b	Me_2Zn/Cu(0.2 equiv)	81	95:5	>95:5	-

focused on methylcuprate reagents for transfer of the methyl group. S_N2 opening of the vinyloxirane ranges from a minor occurrence to a significant one and is chiefly limited by the choice of substrate structure and utilization of CuCN-derived cuprate reagents.

α,β-Enoates containing a *γ*-mesyloxy or tosyloxy leaving group[13] give significantly better S_N2' regioselectivities than the corresponding *γ,δ*-epoxy[12] or aziridinyl enoates[14] in cuprate-mediated allylic substitutions. Cuprates derived from simple alkyllithium reagents and CuCN required addition of $BF_3{\cdot}Et_2O$ for clean reactions,[13a,b] while the corresponding zinc cuprates did not.[13d] Transferable ligands were limited to simple alkyl ligands, and the reactions gave either recovered starting material[13a] or reductive cleavage[13b] of the leaving group with acetate or benzoate nucleofuges. Variable regio- and diastereoselectivities have also been observed in the reactions of epoxy vinyl sulfoxides with cyanocuprates.[15] Nevertheless, vinyl *γ*-butyrolactones were reported to undergo *anti*-S_N2' substitutions with alkylcyanocuprates.[16] More recently we reported high regioselectivity and *anti:syn* diastereoselectivity for sequential and tandem allylic substitutions on *γ*-chloro *δ*-acyloxy *α,β*-enoates,[17] and the strategy has been extended to the use of $R_3Al/CuCN$[8b] reagent combinations.

In summary, S_N2' substitution is facilitated by phosphate[18] and perfluorobenzoate[19] leaving groups, CuCN-derived cuprates,[4−6,12,15] Mg,[1c,10e,17,18a,b,d,e,20] Zn,[5,6,12b,13d] and Ti[5b,7] cuprates, and steric hindrance[2c,10e] about the leaving group, although exceptions abound (e.g., RMgCl/CuOTf and CuSCN).[18d,e] Temperature variations can effect reversal of S_N2/S_N2' selectivity for sp^2-hybridized transferable ligands,[18e] while chelation can alter *anti:syn* diastereoselectivity.[1b,f,10e,15,21] Monoalkylcuprates (i.e., RCuXM, X = Cl, Br, I, CN)[20a,b] favor S_N2' substitution over S_N2 substitution, while dialkylcuprates (i.e., R_2CuM) give mixed results, depending upon the substrate structure and solvent,[20a,b] and this cuprate stoichiometry effect has been analyzed computationally.[22] What emerges from these portraits is a useful reaction for chirality transfer that is limited by substrate structure, reducing the generality of the strategy. While the *o*-DPPB strategy is general, it precludes the direct use of readily available enantioenriched vinyloxiranes containing two C−O bonds that can be exploited for sequential or tandem allylic substitution reactions. Having achieved excellent regioselectivity and *anti:syn* diastereoselectivity in cuprate-mediated bis-allylic substitution reactions on 4-chloro-5-acetoxy-2,3-hexenoate,[17] we set out to develop procedures for achieving similar selectivities on the complementary vinyloxiranes. We sought to develop general procedures for the regio- and stereocontrolled generation of vicinal stereogenic centers via bis tandem allylic substitution reactions initiated on vinyloxiranes with a range of cuprate reagents. We chose a vinyloxirane conjugated to a carboalkoxy functionality and one containing a protected alcohol functionality. We restricted the study to disubstituted epoxides containing a methyl substituent so as to pose the greatest regio- and stereocontrol challenges to the methodology.

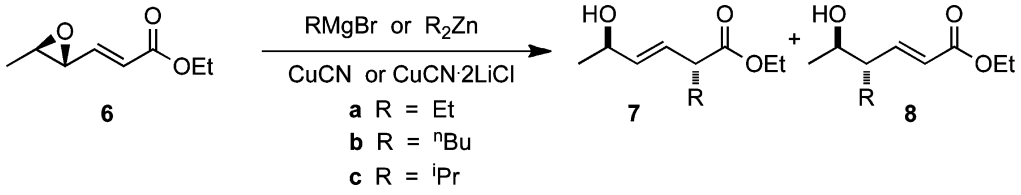
RESULTS

Reaction of epoxyenoate **6** with cuprate reagents gave both regioisomers resulting from S_N2' (**7**) and S_N2 allylic (**8**) substitution (Table 1). The magnesium alkylcyanocuprate reagent (i.e., RCuCNMgBr) gave poor regioselectivity in THF (entry 1), while modest S_N2 regioselectivity could be achieved in Et_2O (entry 2), CH_2Cl_2 (entry 3), 1,2-dichloroethane (entry 4), and toluene (entry 5). Utilization of diethylzinc with catalytic amounts of CuCN gave excellent S_N2' regioselectivity in both THF (entry 6) and DMF (entry 7), although the regioselectivity was slightly higher in DMF. Similar patterns emerged for the *n*-butylcuprates. The magnesium *n*-butylcyanocuprate (entry 8) in CH_2Cl_2 gave modest S_N2 regioselectivity, while the zinc reagents with catalytic amounts of CuCN gave S_N2' substitution with slightly higher selectivity in DMF than in THF (entries 9 and 10). These regioselectivities were lower than those observed for Et_2Zn/CuCN (cat.) where commercial samples of Et_2Zn were free of lithium halide salts. The preparation[23] and use of lithium halide free solutions of di-*n*-butylzinc resulted in a significant increase in S_N2' regioselectivity (entries 11 and 12). Use of ^{n}BuZnBr and stoichiometric amounts of CuCN·2LiCl gave S_N2' selectivities between those observed for the catalytic procedures (entry 13 vs entries 9 and 10), while utilization of ^{n}BuZnBr/CuCN in Et_2O again resulted in S_N2 regioselectivity (entry 14). On utilization of these optimal conditions, employing lithium halide free solutions of $^i Pr_2Zn$, **7c** was obtained in good chemical yields and with excellent S_N2' regioselectivity under conditions stoichiometric or catalytic in copper (entries 15 and 16).

Having found optimal conditions for controlling regioselectivity in the first allylic substitution reaction, we turned our attention to the second copper-mediated allylic substitution.

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

Table 1. Reaction of Organocuprates with Ethyl 4,5-Epoxy-3-hexenoate



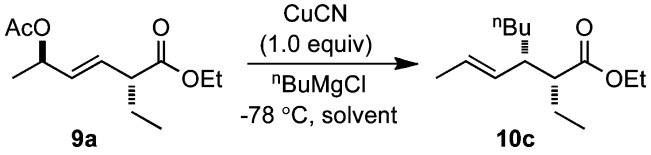
6 7 8

entry	reagent[a]	solvent	T (°C)[b]	product	yield (%)[c]	7:8[d]	7 *anti:syn*[e]
1	EtMgBr (1.0)/CuCN (1.0)	THF	−78	**7a**	71	58:42	94:6
2	EtMgBr (1.0)/CuCN (1.0)	Et_2O	−78	**8a**	65	14:86	
3	EtMgBr (1.0)/CuCN (1.0)	CH_2Cl_2	−78	**8a**	95	18:82	
4	EtMgBr (1.0)/CuCN (1.0)	$(CH_2)_2Cl_2$	−78	**8a**	93	21:79	
5	EtMgBr (1.0)/CuCN (1.0)	PhMe	−78	**8a**	91	15:85	
6	**Et_2Zn (2.1)/CuCN (0.2)**	**THF**	**−23**	**7a**	**90**	**91:9**	**96:4**
7	**Et_2Zn (2.1)/CuCN (0.2)**	**DMF**	**−23**	**7a**	**89**	**94:6**	**97:3**
8	^{n}BuMgBr (1.0)/CuCN (1.0)	CH_2Cl_2	−78	**8b**	100	20:80	
9	$^n Bu_2Zn$ (1.1)/CuCN (0.1)	THF	−78	**7b**	73	76:24	98:2
10	$^n Bu_2Zn$ (2.0)/CuCN (0.2)	DMF	−23	**7b**	80	87:13	97:3
11	**$^n Bu_2Zn$ (2.1)/CuCN (0.5)[f]**	**THF**	**−78**	**7b**	**80**	**94:6**	**97:3**
12	**$^n Bu_2Zn$ (1.1)/CuCN (1.0)[f]**	**THF**	**−78**	**7b**	**82**	**95:5**	**97:3**
13	^{n}BuZnBr (1.0) /CuCN·2LiCl	THF	−78	**7b**	71	82:18	96:4
14	^{n}BuZnBr (1.0)/CuCN (0.5)	Et_2O	−78	**8b**	79	40:60	
15	**$^i Pr_2Zn$ (1.1)/CuCN (1.0)[f]**	**THF**	**−78**	**7c**	**77**	**93:7**	**96:4**
16	**$^i Pr_2Zn$ (1.1)/CuCN (0.2)[f]**	**THF**	**−78**	**7c**	**75**	**90:10**	

[a]Commercially available Et_2Zn was used. *n*-Bu_2Zn was prepared in situ from *n*-BuLi and $ZnBr_2$. [b]The reaction was initiated at the given temperature, and the mixture was warmed to room temperature over 12 h before quenching. [c]Yields are based upon isolated products purified by column chromatography. [d]Determined by ^{1}H NMR integration ratios for the olefinic protons and by ^{13}C NMR peak heights for the olefinic carbon absorptions. [e]Determined by ^{13}C NMR peak heights (e.g., **7b** *anti* (δ 136.6, 128.1), *syn* (δ 136.6, 128.0)) for the olefinic carbon atoms. [f]R_2Zn reagents were prepared free of LiX.

For this purpose, alcohol **7a** was converted into acetate **9a** for reaction with cuprate reagents. To our disappointment, the reaction conditions ($RMgCl/CuCN/CH_2Cl_2$) that worked so well on the tandem bis-allylic substitution reactions of ethyl 4-halo-5-acetoxy-2-hexenoates[17] gave poor diastereoselectivity favoring the S_N2 pathway (Table 2, entry 1). The magnesium

Table 2. Solvent Effect on Diastereoselectivity in the Reaction of Magnesium *n*-Butylcuprates with Ethyl *anti*-2-Ethyl-5-acetoxy-3-hexenoate



9a 10c

entry	solvent	amt of RMgCl (equiv)[a]	yield (%)[b]	dr[c]
1	CH_2Cl_2	2.0	65	45:55
2	THF	2.0	70	68:32
3	THF	1.0	67	90:10
4	THF	2.0[d]	65	80:20[e]

[a]Amount of ^{n}BuMgCl such that 2.0 equiv generates $^n Bu_2CuMgCl$ and 1.0 equiv generates ^{n}BuCuCNMgCl. [b]Yields based upon isolated products purified by column chromatography. [c]Diastereomeric ratios determined by ^{1}H NMR integration ratios on the olefinic absorptions and/or by ^{13}C NMR peak heights for the olefin carbon absorptions. [d]One equivalent of MeMgCl employed to prepare ^{n}BuMeCuMgCl. [e]A trace amount of ethyl *syn*-2-ethyl-3-methyl-4-hexenoate was formed.

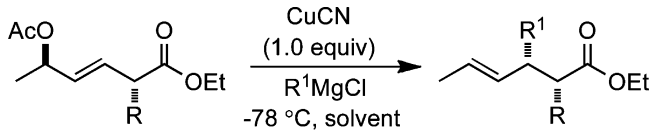
Gilman analogue $^n Bu_2CuMgCl$ in THF gave modest *syn:anti*-diastereoselectivity (entry 2) that could be significantly improved by use of the monoalkyl reagent RCu(CN)MgCl (entry 3). The mixed cuprate ^{n}BuCuMeMgCl gave higher *syn:anti*-diastereoselectivity than $^n Bu_2CuMgCl$ but lower than that obtained with ^{n}BuCu(CN)MgCl (entry 4).

With this solvent study in hand, a series of alkylcuprate reagents were examined in order to explore the scope and limitations of this methodology for preparing *cis*-2,3-dialkyl-substituted 4-hexenoates **10** and **11**. Although MeCuCNMgCl did not react with **9a**, $Me_2CuMgCl$ gave the same diastereoselectivity as that observed for ^{n}BuCu(CN)MgCl (Table 3, entries 1 and 2) and also gave good diastereoselectivity with **9b** (entry 5). However, allylic acetate **9b**, containing a *n*-butyl substituent, gave diastereomeric ratios of *cis*-2,3-dialkyl-4-hexenoates that decreased along the cuprate ligand series in the order Me > Et > ^{n}Bu > ^{i}Pr (entries 5−8), which was also observed for **9a** and ^{i}PrCuCNMgCl (entry 3). Solvent polarity again played a role, with CH_2Cl_2 affording with poor diastereoselectivity (entry 9).

Epoxy enoate **6** contains an electron-deficient alkene that might be more reactive toward cuprate reagents and thus bias the inherent regio- and diastereoselectivities. For comparison, the cuprate-mediated sequential bis-allylic substitution reactions of *trans*-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-4-hexene (**12**) were also examined (Table 4). Treatment of epoxide **12** with cuprate reagents gave a mixture of products arising via allylic S_N2' substitution (i.e., **13**−**15**) and S_N2 substitution (i.e., **16**). The ^{13}C NMR spectrum for reaction of **12** with *n*-butylcuprates displayed four sets of olefinic carbon absorptions, which proved difficult to assign unambiguously to possible structures. Consequently, several possible stereo- and regioisomers of **13a** were prepared for structural assignments

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

Table 3. Reaction of *anti*-5-Acyloxy-2-alkyl-3,4-enoates with Magnesium Cuprates



9a R = Et
b R = ^{n}Bu

a R^1 = Me
b R^1 = Et
c R^1 = ^{n}Bu
d R^1 = ^{i}Pr

10 R = Et
11 R = ^{n}Bu

entry	R	R^1	ROAc	solvent	amt of R^1MgCl (equiv)[a]	product	yield (%)[b]	*syn:anti* dr[c]
1	Et	Me	**9a**	THF	2.0	**10a**	52	90:10
2	Et	^{n}Bu	**9a**	THF	1.0	**10c**	67	90:10
3	Et	^{i}Pr	**9a**	THF	1.0	**10d**	62	72:28
4	^{n}Bu	Me	**9b**	THF	1.0	**11a**	0	
5	^{n}Bu	Me	**9b**	THF	2.0	**11a**	56	91:9
6	^{n}Bu	Et	**9b**	THF	2.0	**11b**	76	80:20
7	^{n}Bu	^{n}Bu	**9b**	THF	2.0	**11c**	73	77:23
8	^{n}Bu	^{i}Pr	**9b**	THF	1.0	**11d**	63	72:28
9	^{n}Bu	^{i}Pr	**9b**	CH_2Cl_2	2.0	**11d**	72	41:59

[a]Amount of R^1 MgCl such that 2.0 equiv generates $(R^1)_2$CuMgCl and 1.0 equiv generates R^1CuCNMgCl. [b]Yields are based upon isolated products purified by column chromatography. [c]Diastereomeric ratios determined by ^{1}H NMR integration ratios on the olefinic absorptions and/or by ^{13}C NMR peak heights for the olefin carbon absorptions.

(Scheme 1). The *syn* diastereomer of **13a** (i.e., **14a**) was readily prepared from dienol **17** via epoxidation, alcohol silylation, and *anti*-S_N2' substitution with lithium dimethylcuprate (Scheme 1A) and displayed ^{1}H and ^{13}C NMR and GC-MS data identical with those obtained for **13a**. Careful ^{13}C measurements at 125 MHz resolved the diastereomeric carbinol (δ 72.9 (*anti*), 73.0 (*syn*)) and the diastereomeric olefinic (δ 139.7 and 126.2 (*anti*), 139.8 and 126.3 (*syn*)) absorptions, and control experiments revolving around mixing samples of **13a** and **14a** in various proportions confirmed both the assignments and the calculated amounts via ^{13}C peak heights. *cis*-Alkene **15a** was prepared from the known 1,1-dibromoalkene **19** via in situ acetylide formation and trapping with ethyl glyoxalate to afford **20**. Reduction of the alkyne and ester functional groups in **20** followed by protection of the primary alcohol as the *tert*-butyldimethylsilyl ether (Scheme 1B) afforded **15a**. The non-allylic S_N2 substitution product **25** was prepared by alkylation of ethyl hexanoate with crotonaldehyde to afford **23**, followed by ester reduction (**24**) and silylation of the primary alcohol (Scheme 1C) and shown not to be a product of these reactions. The allylic S_N2 substitition product **16** was not synthesized and its structure established by COSY NMR experiments, which showed a correlation with an upfield methine proton but no correlation with the downfield proton absorption assigned to the proton nucleus attached to the carbinol carbon. Since **13a** and **14a** initially displayed overlapping ^{13}C absorptions at 75 MHz, there remained a fifth set of olefinic absorptions unaccounted for. Considering the possibility of silyl migration, silyl regioisomer **13′** was prepared via silylation of **13a** (*t*-BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2) followed by chemoselective desilylation of the primary alcohol (pyridinium *p*-toluene sulfonate (0.3 equiv), MeOH), confirming the presence of this product in the reaction mixtures.

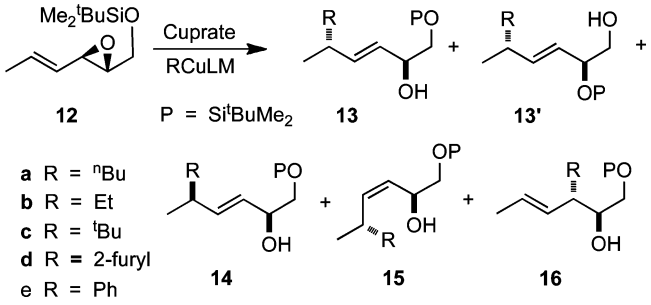
Reaction of lithium dialkylcuprates with epoxide **12** gave allylic alcohols in modest yields with good *E*:*Z* selectivity, good to excellent *anti:syn* product diastereoselectivity, and excellent regioselectivity (Table 4, entries 1−3), although the reaction could be capricious. Utilization of lithium *n*-butylcyanocuprate gave low yields of **13a** with excellent regioselectivity, good to excellent *anti:syn* diastereoselectivities (entries 4−6), and good *E*:*Z* selectivity. Use of HMPA as an additive diminished the *E*:*Z* stereoselectivity and increased the amount of silyl migration while maintaining excellent *anti:syn* product diastereoselectivity and regioselectivity (entry 7). The low yields were reflected in recovered starting material (i.e., **12**).

Although ^{n}Bu$_2$Zn with catalytic amounts of CuCN in DMF or THF gave excellent S_N2':S_N2 regioselectivity and *anti:syn* diastereoselectivity, the protocol gave modest *E*:*Z* selectivity when conducted at elevated temperatures (entries 8−14). Utilization of lower temperatures gave excellent selectivities across all levels irrespective of whether the reaction mixture was slowly warmed to room temperature (entry 10) or quenched at low temperature (entries 11 and 12). The reaction was complete in 1 h at −35 °C (9 h at −78 °C) with a significant decrease in the *E*:*Z* selectivity (entries 13 and 14) while still retaining excellent regioselectivity and *anti:syn* diastereoselectivity. The stoichiometric use of CuCN also gave diminished *E*:*Z* selectivity while retaining excellent diastereo- and regioselectivity (entry 15). The use of Et$_2$Zn and catalytic quantities of CuCN gave uniformly excellent selectivities across the board in both DMF and THF (entries 16 and 17, respectively). Addition of 5 equiv of LiBr had little effect (entry 18). The ^{t}Bu$_2$Zn reagent in the presence of CuCN gave modest *E*:*Z* selectivity and excellent regioselectivity and *anti:syn* diastereoselectivity (entry 19), while the heteroaryl (entries 20 and 21) and aryl (entries 22 and 23) zinc reagents gave modest chemical yields, modest regioselectivity (i.e., ∼75:25), excellent *anti:syn* diastereoselectivity, and variable *E*:*Z* selectivity. Ph$_2$Zn gave excellent *E*:*Z* selectivity with substoichiometric amounts of CuCN (entry 22) and reduced selectivity with stoichiometric amounts of CuCN (entry 23).

The use of Grignard reagents in the presence of CuCN generally gave modest to excellent selectivities across the board (entries 24−33), which were sensitive to solvent composition and transferable ligand. The *n*-BuMgCl-derived reagent gave excellent *E*:*Z* selectivity and *anti:syn* diastereoselectivity in

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

Table 4. Copper-Mediated Reactions of *trans*-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-4-hexene

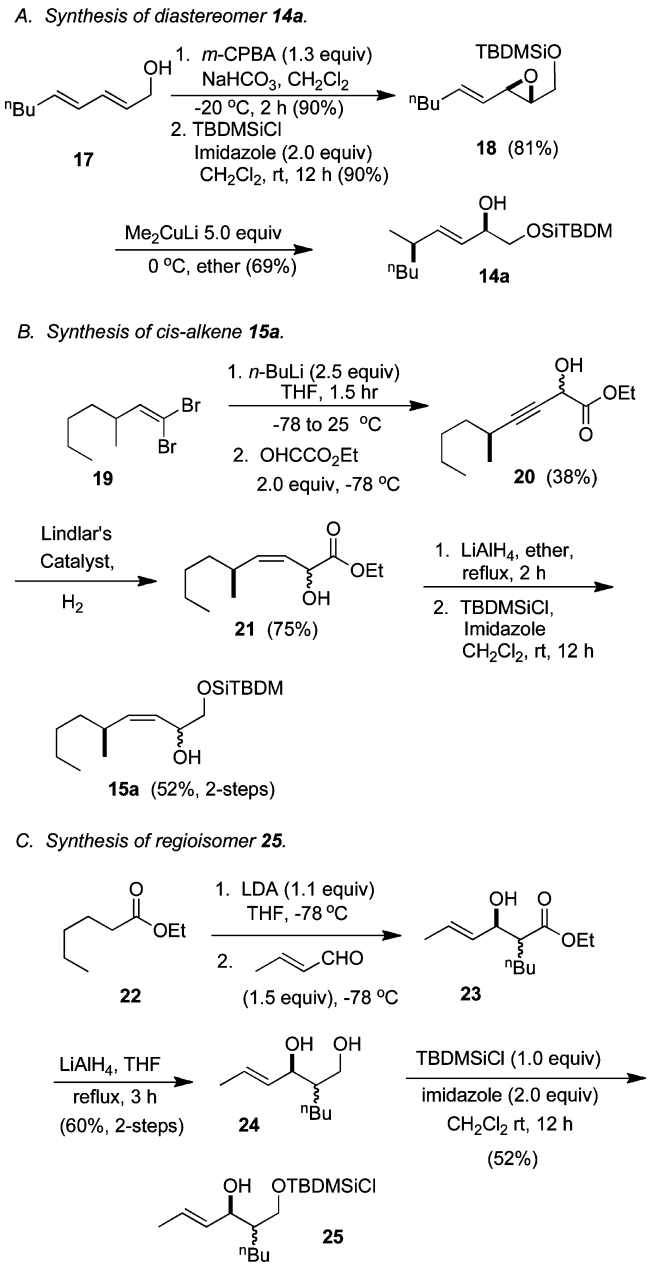


entry	cuprate	solvent	T (°C) (t (h))[a]	yield (%)[b]	(**13** + **13′** + **14**):**15** (*E*:*Z*)[c]	dr (*anti*:*syn*) (**13** + **13′**):**14** yield of **13′** (%))[d]	S_N2':S_N2[e] (**13**−**15**):**16**
1	$^nBu_2CuLi$ (1.0)	THF	−78 (12)	52	90:10	83:17 (2)	98:2
2	$^nBu_2CuLi$ (1.0)	THF	−78 (12)	70	88:12	93:7 (2)	94:6
3	$^nBu_2CuLi$ (1.0)	THF	−78 (12)	55[f]	88:12	93:7 (8)	97:3
4	^{n}BuCuCNLi (1.0)	THF	−78 (12)	24[g]	90:10	87:13 (14)	99:1
5	^{n}BuCuCNLi (1.0)	THF	−78 (12)	N/A	89:11	93:7 (8)	99:1
6	^{n}BuCuCNLi (1.0)	THF	−78 (12)	14[h]	90:10	88:12 (12)	99:1
7	^{n}BuCuCNLi (1.0)	THF/HMPA	−78 (12)	44[g]	76:24	98:2 (23)	100:0
8	$^nBu_2Zn$/CuCN (0.2)	DMF	−23 (12)	40[g]	82:18	100:0 (18)	96:4
9	$^nBu_2Zn$/CuCN (0.2)	THF	−23 (12)	77	88:12	100:0 (17)	99:1
10	**$^nBu_2Zn$/CuCN (0.2)**	**THF**	**−78 (12)**	**89**	**91:9**	**96:4**	**99:1**
11	**$^nBu_2Zn$/CuCN (0.2)**	**THF**	**−78 (9)[i]**	**N/A**	**91:9**	**99:1**	**99:1**
12	$^nBu_2Zn$/CuCN (0.2)	**THF**	**−78 (8)[i]**	**54[j]**	**94:6**	**100:0**	**100:0**
13	$^nBu_2Zn$/CuCN (0.2)	THF	−35 (1)[i]	N/A	84:16	100:0	96:4
14	$^nBu_2Zn$/CuCN (0.2)	THF	−35 (1)[i]	87	85:15	100:0	97:3
15	$^nBu_2Zn$/CuCN (1.0)	THF	−78 (12)	81	88:12	100:0	99:1
16	**Et_2Zn/CuCN (0.2)[k]**	**DMF**	**−23 (12)**	**53**	**92:8**	**100:0**	**99:1**
17	**Et_2Zn/CuCN (0.2)[k]**	**THF**	**−78 (12)**	**54**	**94:6**	**100:0**	**94:6**
18	**Et_2Zn/CuCN(0.2)/ LiBr(5.0)**	**THF**	**−78 (12)**	**47**	**91:9**	**94:6**	**99:1**
19	$^tBu_2Zn$/CuCN (0.2)	THF	−78 (12)	56	86:14	96:4	100:0
20	$(furyl)_2Zn$/CuCN (0.2)	THF	−78 (12)	41	50:50	97:3	75:25
21	$(furyl)_2Zn$/CuCN (1.0)	THF	−40 (12)	47	67:33	98:2	74:26
22	Ph_2Zn/CuCN (0.2)	THF	0 (12)	40	94:6	91:9	74:26
23	Ph_2Zn/CuCN (1.0)	THF	0 (12)	58	85:15	97:3	72:28
24	^{n}BuMgCl(1.2)/ CuCN(0.2)	THF/Et_2O 10/1	−78 (12)	70	91:9	100:0	88:12
25	^{n}BuMgCl(1.2)/ CuCN(0.2)	Et_2O	−78 (12)	75	100:0	79:21	71:29
26	^{n}BuMgCl(1.2)/ CuCN(0.2)	Et_2O	−78 (12)	79	97:3	72:28	69:31
27	**^{n}BuMgCl (1.2)/CuCN (0.2)**	**Et_2O/THF 10/1**	**−78 (12)**	**87**	**96:4**	**98:2**	**93:7**
28	**^{n}BuMgCl (1.2)/CuCN (0.2)**	**Et_2O/THF 10/1**	**−78 (12)**	**64**	**96:4**	**99:1**	**88:12**
29	^{n}BuMgCl (1.2)/CuCN (0.2)	Et_2O/Et_3N[l]	−78 (12)	78	92:8	50:50	61:39
30	EtCuCNMgCl (1.0)	THF	−78 (12)	72	85:15	91:9	93:7
31	EtMgCl (1.2)/ CuCN (0.2)	THF	−78 (12)	78	88:12	97:3	88:12
32	**EtCuCNMgCl (1.0)**	**Et_2O/THF 10/1**	**−40 (12)**	**67**	**94:6**	**98:2**	**93:7**
33	**EtMgCl (1.2)/CuCN (0.2)**	**Et_2O/THF 10/1**	**−78 (12)**	**76**	**93:7**	**98:2**	**91:9**

[a]The reactions were run at −78 °C, and the mixtures were then slowly warmed to room temperature and stirred for the indicated time unless otherwise noted. [b]Yields based upon isolated products purified by column chromatography. [c]The *E*:*Z* ratios were determined from ^{13}C NMR peak heights for the olefinic carbon atoms. [d]Diastereomeric ratios for **13** (i.e., **13**:**14**) were determined from ^{13}C NMR ratios (125 MHz) for the olefinic carbon absorptions. [e]Regioisomeric ratios were determined from ^{13}C NMR ratios for the olefinic carbon absorptions and compared against the ^1H NMR ratios for the methyl absorptions. [f]The diol (21%) arising from desilylation of **13** was also obtained. [g]Vinyl oxirane **12** was recovered: entry 4 (34%); entry 7 (15%); entry 8 (30%). [h]Vinyl oxirane **12** (29%) and the diol (13%) from **13** were obtained. [i]The reaction was quenched at the indicated temperature after the indicated time in parentheses. [j]Vinyl oxirane **12** (22%) was recovered. [k]Lithium halide free zinc reagents were employed. [l]Et_2O/Et_3N (20/1).

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

Scheme 1. Stereochemical and Regiochemical Assignments for Reaction of ^{n}BuCuLM with Vinyl Epoxide 12



THF but modest regioselectivity (entry 24), while the use of diethyl ether showed enhanced *E*:*Z* selectivity and reduced the last two selectivities (entries 25 and 26). In contrast, the *E*:*Z* selectivity was reduced in THF (entries 30 and 31) and enhanced in Et_2O (entries 32 and 33) for EtMgCl. In the latter solvent (i.e., Et_2O/THF, 10/1, v/v) all selectivities were uniformly excellent (entries 32 and 33). The use of an Et_2O/THF (10/1) solvent mixture also improved both the *anti:syn* diastereoselectivity and the regioselectivity in the reactions of *n*-BuMgCl/CuCN (entries 27 and 28), although the use of Et_2O/Et_3N (20/1) significantly degraded both the *anti:syn* diastereoselectivity and the $S_N2':S_N2$ regioselectivity (entry 29).

Lithium tri-*n*-butylzincate gave poor regioselectivity at elevated temperatures (Table 5, entry 1) and modest selectivity with reversal of regiochemistry in nonpolar solvents (entries 3 and 4), although excellent regioselectivity was obtained in THF at room temperature (entry 2). Excellent *E*:*Z* selectivity and poor *anti:syn* diastereoselectivity was obtained in all cases for the allylic S_N2' substitution pathway with reversal to *syn* selectivity at higher temperatures. Silyl migation occurred at higher temperatures and in polar solvents (entries 1 and 2). Trimethylzincate was unreactive at room temperature and when heated to reflux in THF gave poor $S_N2':S_N2$ regioselectivity (entry 5).

Protection of the alcohol in **13a** as the acetate or phosphate gave **26a**,**b**, respectively, which were subjected to a second copper-mediated allylic substitution (Table 6). Although EtCuCNMgCl gave excellent regio- and diastereoselectivity, it displayed low reactivity with acetate **26a**, giving substantial amounts of recovered starting material and/or cleavage of the acetate moiety in **26a** (entries 1 and 2). The $Et_2CuMgCl$ reagent gave S_N2 selectivity in THF as well as ester cleavage products in THF or CH_2Cl_2/THF, showing the important role of THF in these reaction pathways (entries 3 and 4), while excellent S_N2' selectivity and modest *syn:anti* diastereoselectivity was obtained in CH_2Cl_2 (entry 5). THF facilitates acetate cleavage and S_N2 selectivity (entries 3−5) with $Et_2CuMgCl$. Similar patterns were observed for the *n*-butylcuprates, with magnesium *n*-butylcyanocuprate giving modest yields, excellent S_N2' regioselectivity, and modest *syn:anti* diastereoselectivity in Et_2O (entry 6), while *n*-$Bu_2CuMgCl$ gave reduced yields and S_N2 selectivity in THF (entry 7) and significantly improved yields, excellent S_N2' selectivity, and modest *syn:anti* selectivity in less polar solvents (entries 8−10). Zinc cuprates were unreactive (entry 11) with **26a**. In CH_2Cl_2 and Et_2O, *i*-$Pr_2CuMgCl$ gave selectivities identical with those of *n*-$Bu_2CuMgCl$, showing no effect of the increased ligand size (entries 12 and 13), although a slight improvement in the *syn:anti* ratio was observed in Et_2O.

Although recovered starting material and acetate cleavage products were obtained with acetate **26a** (entry 14), the best

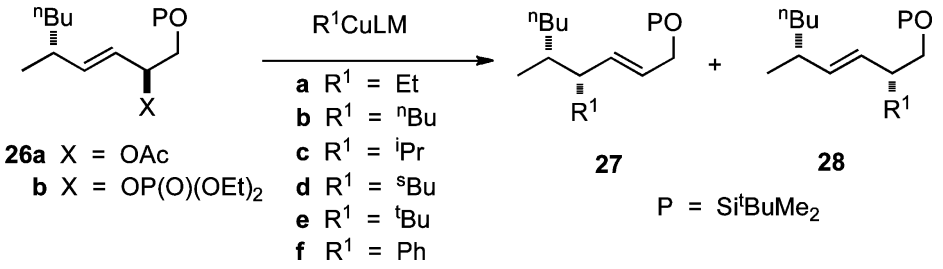
Table 5. Zincate-Mediated Reactions of *trans*-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-4-hexene

entry	zincate	solvent	*T* (°C)[a]	yield (%)[b]	*E*:*Z*[c] (**13** + **13′** + **14**):**15**	dr (*anti:syn*) (**13** + **13′**):**14** (yield of **13′** (%))[c]	$S_N2':S_N2$[d]
1	$^{n}Bu_3ZnLi$	THF	66	49[e]	95:5	34:66 (14)	70:30
2	$^{n}Bu_3ZnLi$	THF	25	69	92:8	63:37 (11)	99:1
3	$^{n}Bu_3ZnLi$	Et_2O	25	92	97:3	74:26	19:81
4	$^{n}Bu_3ZnLi$	hexane	25	82	98:2	70:30	15:85
5	Me_3ZnLi	THF	66	53	97:3		58:42

[a]The reaction was quenched after 12 h. [b]Yields based upon isolated products purified by column chromatography employing 1.5 equiv of zincate reagent. [c]*E*:*Z* diastereomeric ratios for **13** (i.e., (**13** + **13′**):**14**) were determined from ^{13}C NMR ratios (125 MHz) for the olefinic carbon absorptions. [d]Regioisomeric ratios were determined from ^{13}C NMR ratios for the olefinic carbon absorptions and compared against the ^{1}H NMR ratios for the methyl absorptions. [e]Homoallylic alcohol **16** was also obtained (8%). Vinyloxirane (24%) was also recovered.

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

Table 6. Copper-Mediated Reactions of *trans*-1-(*tert*-Butyldimethylsilyloxy)-5-(1-butyl)-3-hexen-2-ol Derivatives



entry	substrate	reagent (amt (equiv))[a]	solvent[b]	yield (%)[c]	27:28[d]	dr 27 (dr 28)[d]
1	**26a**	EtCuCNMgCl (2.0)	THF	30[e]	95:5	97:3
2	**26a**	EtCuCNMgCl (2.0)	CH_2Cl_2[f]	36[e]	99:1	94:6
3	**26a**	$Et_2CuMgCl$ (2.0)	THF	25[g]	20:80	
4	**26a**	$Et_2CuMgCl$ (2.0)	CH_2Cl_2[f]	49[g]	57:43	
5	**26a**	$Et_2CuMgCl$ (1.0)	CH_2Cl_2[h]	86	99:1	84:16
6	**26a**	$^nBuCuCNMgCl$ (1.1)	Et_2O	60[i]	94:6	85:15
7	**26a**	$^nBu_2CuMgCl$ (1.1)	THF	52[e]	17:83	(100:0)
8	**26a**	$^nBu_2CuMgCl$ (1.1)	Et_2O	73	95:5	89:11
9	**26a**	$^nBu_2CuMgCl$ (1.1)	^tBuOMe	72	98:2	89:11
10	**26a**	$^nBu_2CuMgCl$ (1.1)	CH_2Cl_2	90	96:4	83:17
11	**26a**	$^nBu_2Zn$ (2.0)/CuCN (1.0)	THF	0[j]		
12	**26a**[k]	$^iPr_2CuMgCl$ (1.0)	CH_2Cl_2	64	98:2	87:13
13	**26a**	**$^iPr_2CuMgCl$ (1.0)**	**Et_2O**	**75**	**97:3**	**93:7**
14	**26a**	$^nBuCuCNLi$ (1.3)	THF	0[l]		
15	**26b**	**EtCuCNLi (1.3)**[m]	**THF**	**70**	**99:1**	**99:1**
16	**26b**	**EtCuCNLi (1.3)**[m]	**THF/Et_2O**[n]	**75**	**99:1**	**98:2**
17	**26b**	**$^nBuCuCNLi$ (1.3)**	**THF**	**71**	**99:1**	**98:2**
18	**26b**	$^nBuCuCNLi$ (1.3)	Et_2O	46[o]	97:3	92:8
19	**26b**	$^nBu_2CuLi$ (1.3)	THF	27[o]	94:6	92:8
20	**26b**	**$^sBuCuCNLi$ (1.3**	**THF**	**70**	**94:6**	**98:2**
21	**26b**	$^tBuCuCNLi$ (1.3)	THF	73	14:86	(98:2)
22	**26b**	$^tBuCuCNLi$ (1.3)	Et_2O	55[p]	7:93	(99:1)
23	**26b**	PhCuCNLi (1.3)	THF	85	72:25	97:3
24	**26b**	PhLi (1.3)/CuCN (0.3)	THF	45	9:91	(97:3)

[a]Reactions were conducted at −78 °C, and then the mixtures were warmed to room temperature and stirred for 12 h. [b]The solvent composition consists of the reaction solvent/organometallic solvent (approximately 10/1) unless otherwise noted. RM (solvent): EtMgCl (THF), EtMgCl (^tBuOMe), ^nBuMgCl and ^iPrMgCl (Et_2O), EtLi and PhLi ($^nBu_2O$), ^nBuLi and ^sBuLi (hexane), ^tBuLi (pentane). [c]On the basis of isolated products purified by column chromatography. [d]Determined from ^{13}C NMR absorption peak heights for the olefinic carbon atoms. [e]Starting acetate (entry (%): 1 and 2 (50−59%); 7 (15%)) and the alcohol from acetate cleavage were recovered (entry (% yield): 1 and 2 (4−9%); 7 (19%)). [f]Solvent composition: CH_2Cl_2/THF (10/1). [g]Alcohol from acetate cleavage was obtained (entry (% yield): 3 (65%); 5 (51%)). [h]Solvent composition: CH_2Cl_2/^tBuOMe (10/1). [i]Starting material recovered (30%). [j]Only starting material was recovered. [k]Similar results were obtained with the Et analogue (i.e., the acetate of **13b**) of **26a** (53% yield, S_N2':S_N2 98:2, dr S_N2' product 85:15). [l]Starting material (50%) and acetate cleavage product (25%) were obtained. [m]Commercial EtLi was employed. [n]A 1/1 solvent mixture was used. [o]Recovered alcohol **13a** arising from cleavage of phosphate **26b** (entry (% yield): 18 (15%), 19 (60%)). [p]Starting phosphate recovered (15%).

results were obtained with lithium alkylcyanocuprates (e.g., RCuCNLi, R = Et, *n*-Bu, *s*-Bu), where good chemical yields and excellent S_N2' regioselectivity and *syn:anti* diastereoselectivity could be achieved in THF with phosphate **26b** (entries 15−18). Utilization of the bulky *t*-Bu ligand afforded S_N2 selectivity in THF (entry 21) and in Et_2O (entry 22), while the phenyl reagent gave diminished S_N2' selectivity and excellent *syn:anti* diastereoselelctivity (entry 23). Reaction of PhLi and substoichiometric amounts of CuCN gave excellent S_N2 selectivity but low chemical yields (entry 24).

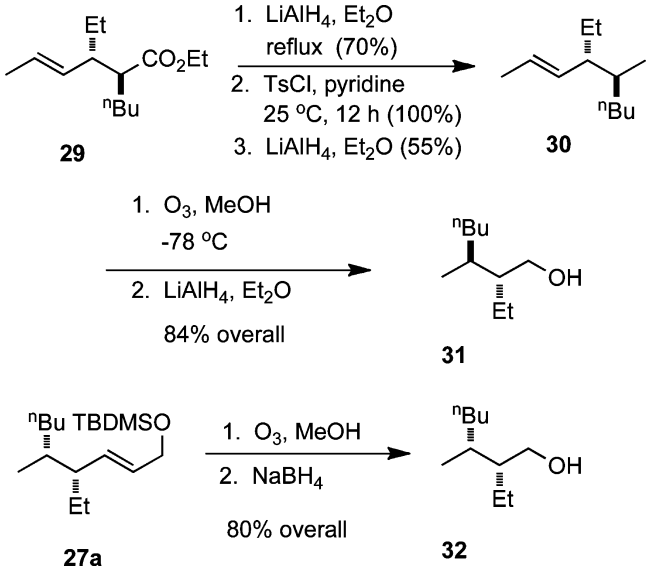
The stereochemistry of *syn* stereoisomers **27** was confirmed by conversion of **27a** into alcohol **32** and comparison of its NMR spectrum with that of the *anti* isomer **31**, which could be prepared from readily available **29** (Scheme 2). To this end, reduction of ester **29**, followed by tosylation and dexoygenation of the resultant primary alcohol, afforded **30**, which gave the *R**/*S** diastereomer **31**, upon ozonolysis of **30** followed by reductive workup. Ozonolysis of **27a** with reductive workup gave the *R**/*R** diastereomer **32**, which displayed ^{13}C NMR absorptions different from those of **31**.

DISCUSSION

The mechanistic framework for understanding regio- and stereocontrol in copper-mediated allylic substitution reactions involves the preference for *anti* S_N2' attack of the cuprate reagent on the allylic substrate rationalized by interactions of the copper d_{xy} orbital with the mixed alkene π^* and $\sigma^*_{C\text{-}LG}$ orbitals[3,22a−c] followed by either partitioning between two σ-allyl copper(III) complexes[24] via the intermediacy of a π-allyl complex[20,24a] or regioselective reductive elimination from the π-allyl complex itself or from resultant enyl[σ + π] complexes arising from substituent perturbation of the π-allyl complex.[22,24]

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

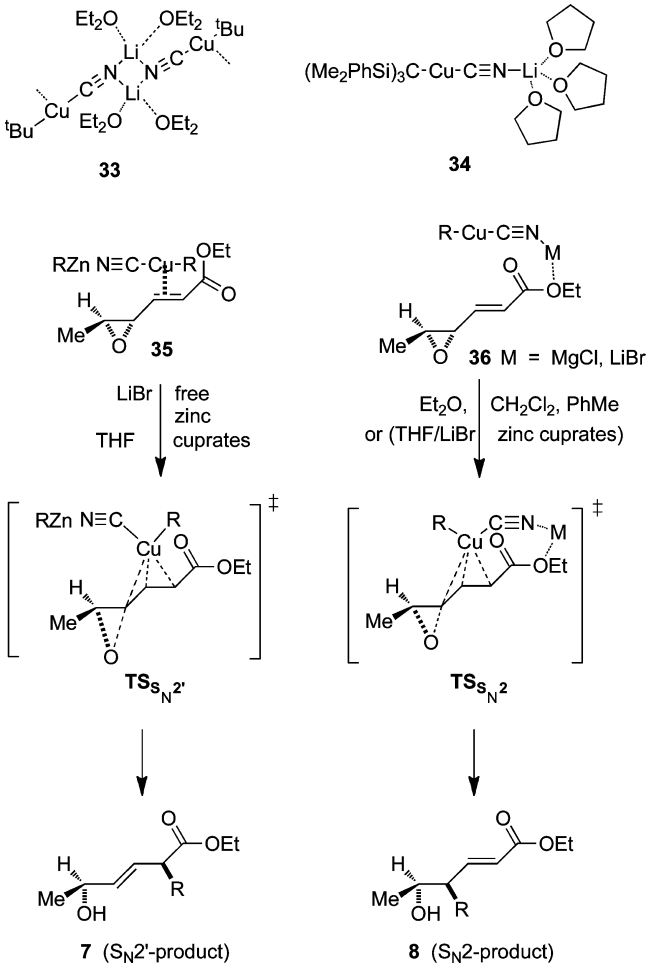
Scheme 2. Stereochemical Assignments



The work of Bertz and Ogle has also shown that ligand exchanges can occur in Cu(III) intermediates and that the stability of the tetracoordinate square-planar complexes observed by rapid-injection NMR techniques is a function of the ligands (e.g., R, CN, Ph_2P, Cl, SPh, SCN, etc.) attached to copper.[24a−c] For the copper-catalyzed reactions of Grignard reagents and allylic substrates, conditions favoring rapid reductive elimination (e.g., cuprate ligand effects, substrate structure, solvent) favor S_N2' allylic substitution, while slower reductive elimination allows partitioning between the initial σ-allyl or enyl[$\sigma + \pi$] complex, leading to S_N2' substitution, and the σ-allyl or enyl[$\sigma + \pi$] copper complex, leading to S_N2 substitution, which may be favored on steric[10e,20] or electronic[22a,d] grounds. Computationally, Nakamura and co-workers have shown that alkylcyanocuprates pass through a lower energy transition state when the electron-rich alkyl group is *trans* (i.e., *trans* effect) to the leaving group, resulting in a *cis* orientation of the copper transferable ligand and the allyl group in the σ complex leading to S_N2' substitution and an unfavorable *trans* orientation in the σ complex leading to S_N2 substitution, accounting for the significantly higher S_N2' regioselectivity observed for these reagents.[22a−c]

For epoxy enoate **6**, the magnesium alkylcyanocuprates give very poor S_N2' regioselectivity in THF (58:42 for Et) and modest S_N2 regioselectivity in less polar solvents (e.g., S_N2':S_N2 (EtCuCNMgBr): Et_2O (14:86), CH_2Cl_2 (18:82), PhMe (15:85)), while the zinc cuprates give excellent S_N2' regioselectivity in DMF or THF with commercial samples of Et_2Zn or with samples of $^nBu_2Zn$ from which lithium bromide had been removed. The presence of LiBr in the zinc cuprate solutions increased the amount of S_N2 substitution byproduct. This pattern is consistent with chelation phenomena involving magnesium and lithium cuprate counterions that are not significant with zinc cations.[25] X-ray structural studies[26a,b] of lithium alkylcyanocuprates depict oligomers joined through the nitrile ligand by coordination of lithium cations[26c] (e.g., **33**, Scheme 3), and magnesium diorganocuprates[27] display structural characteristics similar to those of the lithium reagents. Evidence of the propensity for lithium coordination to the N atom of cyanocuprates is provided by X-ray[28] (e.g., **34**[28b]) and solution-phase NMR studies.[29] From this vantage point,

Scheme 3. Mechanistic Rationale for Regioselectivity in the Reactions of Epoxy Enoate 6 with Cuprates

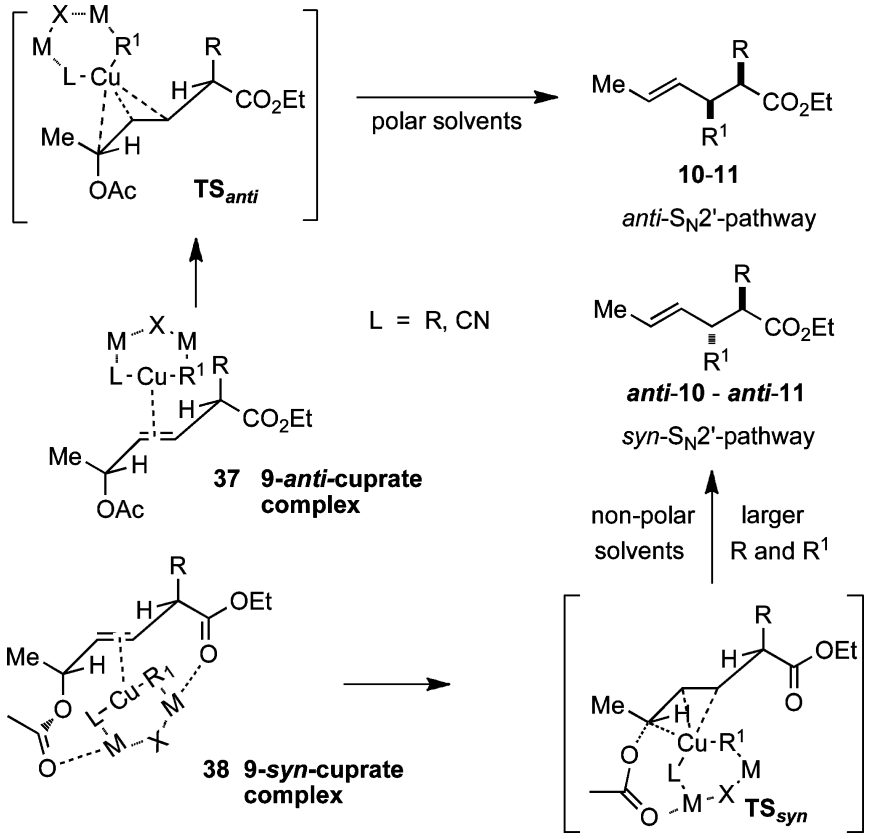


coordination of the cuprate nitrile ligand and the ester carbonyl or ether oxygen atom to a metal cation (e.g., Li, Mg in **36**) would orient the alkylcyanocuprate in such a way as to favor[22c] the S_N2 pathway through transition state $\mathbf{TS_{SN2}}$. Given that four-coordinate Li^+ (0.73 Å), Mg^{2+} (0.71 Å), and Zn^{2+} (0.74 Å) all have comparable ionic radii[30] and that Zn^{2+} and Mg^{2+} have comparable charge densities roughly twice that of lithium (Li^+, 1.8; Mg^{2+}, 3.9; Zn^{2+}, 3.6) it seems unlikely that the divergent behavior of the zinc cuprates lies in the inherent properties of the metal counterions, although Li^+ and Mg^{2+} are designated as hard acids and Zn^{2+} as borderline.[31] It is also noteworthy that while soft-metal (e.g., Hg, Au, Tl) enolates prefer C−M bonding to O−M bonding, zinc ketone enolates exist as O−Zn-bound structures, although C,O-bridging structures have been observed for zinc amide enolates.[32]

The fact that excellent regioselectivities are achieved with dialkylzinc reagents in the presence of stoichiometric or catalytic quantities of CuCN raises questions as to the nature of these zinc cuprate reagents. The excellent S_N2' regioselectivity obtained with these reagents, coupled with Nakamura's computational study,[22c] suggests the formation of a zinc alkylcyanocuprate reagent (i.e., RCu(CN)ZnR) rather than formation of a zinc dialkylcuprate (i.e., $R_2CuZn(CN)_2$) under conditions catalytic in copper.[33] These experimental results are also consistent with the supposition that chelation effects are minimal in the reactions involving zinc cuprate reagents.

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

Scheme 4. Mechanistic Rationale for *Syn* Diastereoselectivity in Reactions of 9 with Cuprates



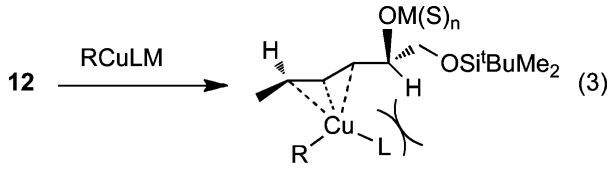
Although dialkylzinc reagents are generally monomers, reflecting the reluctance of zinc to participate in alkyl or aryl bridging, the reagents readily coordinate to donor atoms (e.g., ethers)[34] and, as noted above, Zn ketone enolates[32a] favor O−Zn bonding. It should be noted that Nakamura performed gas-phase calculations[22c] and that both lithium and magnesium cuprates appear to be monomeric SSIPs in THF and dimeric or even supramolecular aggregate CIPs in Et_2O,[27a,29a,b] while the structural elements of zinc cuprates[27b,33,35] appear to be unstudied. Although neither solution or solid-state structures have been elucidated for the zinc cuprates, our results point to structural differences in either the reactive zinc cuprate species or in the transition state structures relative to the lithium and magnesium cuprates. The work of Bertz and Ogle showing ligand exchange in Cu(III) intermediates and their stability as a function of the ligands on copper allows for structural differences to arise from the Cu(III) intermediates before reductive elimination occurs.[24a−c]

Epoxy enone **6** provides opportunities for sequential allylic substitutions, and the second allylic substitution carried out on allylic acetate **9a** shows excellent S_N2' regioselectivity but modest *syn:anti* product diastereoselectivity with magnesium dialkylcuprates in THF and poor diastereoselectivity in CH_2Cl_2. Very good *syn* diastereoselectivity can be achieved with the magnesium alkylcyanocuprate reagent and good *syn* diastereoselectivity with the mixed magnesium dialkylcuprate (i.e., ^{n}BuCuMeMgCl) via *anti*-S_N2' allylic substitution, implicating the importance of ligand size in stereocontrol. These results implicate both chelation and steric effects in determining diastereoselectivity. In polar solvents, approach of the cuprate follows the normal *anti* attack, leading to ***9-anti*-cuprate** complex and $\mathbf{TS}_{anti}$ (Scheme 4) and formation of the *syn* diastereomers **10** and **11**. Minimization of $A^{1,3}$ strain in the reacting conformers and subsequent transition states brings the cuprate ligand R^1 and the substrate substituent R into proximity in $\mathbf{TS}_{anti}$, thus decreasing the *syn* diastereoselectivity as either R or R^1 increases in steric size. Moderately good *syn*- diastereoselectivity can be achieved with the magnesium dialkylcuprates with the Me/Et and Me/^{n}Bu R^1/R combinations, but it decreases as the R^1/R groups increase in steric size. The ^{i}Pr/^{n}Bu combination leads to moderate *syn:anti* product diastereoselectivity even with ^{i}PrCuCNMgCl. In nonpolar solvents, coordination between the cuprate counterion and the acetate leaving group or the ethyl ester increases the amount of *anti*-**10**-**11** via $\mathbf{TS}_{syn}$. Chelation effects directing *syn*-S_N2' allylic substitution have been exploited with carbamate and *o*-OPDPP leaving groups,[1b,f] and chelation-controlled regio- and stereoselectivities have also been observed in Et_2O for propargyl substrates[36] and with allylic alcohols,[10e,21,] vinyl sulfoxides,[15] and magnesium cuprate reagents.[20] In view of Nakamura's calculations,[22c] it is surprising that the magnesium dialkylcuprates give excellent S_N2' regioselectivity. Here, the unfavorable Me−L (L = R^1) steric interaction in $\mathbf{TS}_{anti}$ may be more severe than the R^1−R interaction (Scheme 4), which can be minimized by rotations about the C2−C3 bond, thereby favoring reductive elimination leading to the S_N2' product. It is also interesting that these results are consistent with Streitwieser's observations and calculations[37] suggesting that solvent-separated ion pair (SSIP) nucleophiles favor S_N2 and *anti*-S_N2' substitution pathways while contact ion pair (CIP) nucleophiles favor *syn*-S_N2' substitution pathways, since lithium and magnesium cuprates exist as SSIP in THF and CIP in Et_2O and less polar solvents.[27a,29] Nonetheless, the Streitwieser

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

model for S_N2'/S_N2 reactivity is inconsistent with the patterns observed for epoxy enoate **6**.

Alkyl (i.e., Et, ^{n}Bu, ^{t}Bu) cuprate mediated allylic substitution on epoxide **12** follows the normal patterns. Lithium dialkylcuprates give very good to excellent S_N2' regioselectivity (88−96% regioisomeric excess (re)) in THF governed by either steric (i.e., more stable Cu(III) σ complex)[1e] or electronic[22d] effects in the copper(III) intermediate **39** (eq 3).



39 L = R, CN

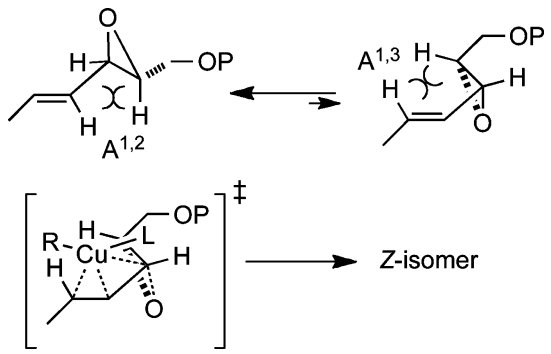
Nakamura's calculations predict that electron-donating substituents on the allyl system lower the transition state energy for reductive elimination, favoring ligand transfer to the remote C atom, and are more important than steric factors.[22d] Since the alkoxyalkyl substituent (i.e., $-CH(OM)CH_2OSi^tBuMe_2$) is expected to be more electron rich by inductive effects than the methyl substituent, the observation is in accord with the prediction. As predicted by the *trans* effect, use of lithium alkylcyanocuprates gives increased S_N2' regioselectivity (≥98% re), which is also observed by the use of dialkylzinc reagents and substoichiometric amounts of CuCN (92 to ≥98% re). Similarly high S_N2' regioselectivities are also achieved with magnesium alkylcyanocuprates (86% re), while alkyl Grignard reagents and 20 mol % of CuCN display poor S_N2' regioselectivities in Et_2O (38−42% re) and very good S_N2' selectivities in THF (76%) or in a 10/1 Et_2O/THF solvent mixture (76−86% re). Here the solvent effect is opposite to that reported by Backvall for primary allylic acetates.[20a,b] The change in regioselectivities upon addition of small amounts of THF to Et_2O is reminiscent of reactivity changes observed in the 1,4-addition of $Me_2CuLi{\cdot}LiX$ (X = I, CN) to a cyclohexenone, which was attributed to THF-promoted disaggregation or structural change of a supramolecular cuprate cluster.[27b,38] The results are also consistent with the electronic effect,[22d] since in THF the metal alkoxide should exist as SSIPs, while addition of small amounts of THF to Et_2O could facilitate formation[39] of the Cu(III) intermediate **39** by THF coordination to Cu but not stabilize **39** to the point where the reductive elimination step is significantly slowed. This phenomenon is observed in the chemoselectivity change from lithium diorganocuprate 1,2-additions to α,β-enones in toluene to 1,4-additions upon addition of small amounts of Et_2O[40a,b] or Me_2S[40c] and in the acceleration of cuprate conjugate additions upon addition of small amounts of pyridine,[41] Et_3N,[41] or chlorotrimethylsilane.[42] The diminished S_N2' selectivity upon addition of Et_3N can arise if Et_3N stabilizes **39** to the point of increasing the transition state barrier for reductive elimination, thus allowing equilibration between two σ-allyl or enyl[$\sigma + \pi$] complexes, affording the mixture of regioisomers. The S_N2' regioselectivity decreases along the series RCuCNLi (≥98% re) > R_2Zn/CuCN (0.2−1.0 equiv; 88 to ≥98% re) > R_2CuLi (88−96% re) > RCuCNMgX (82−86% re) > $R_2CuMgCl$ (76−86% re) for the alkylcuprates in THF or 10/1 Et_2O/THF.

The π-face selectivity for the reaction of **12** and subsequent *anti:syn* product diastereomeric ratios for the S_N2' substitution products are modest for the lithium dialkylcuprates (66−86% de) and good for the zinc cuprates at low temperatures (82−88% de) and the magnesium cuprates in THF or Et_2O/THF (10/1) (86 to ≥98% de). Poor diastereomeric ratios (44−58% de) are obtained for *n*-BuMgCl/CuCN (0.2 equiv) in Et_2O, suggesting the importance of chelation effects and perhaps cuprate aggregation.[29b] Thus, product *anti:syn* diatereoselectivity decreases along the series R_2Zn/CuCN (0.2−1.0 equiv; 92 → 98% de), RMgX/CuCN (0.2−1.0 equiv; 82 → 98% de in THF or Et_2O/THF (10/1)), RCuCNLi (74 → 96 de) > R_2CuLi (66 → 86 de). With the magnesium cuprates, *anti:syn* distereoselectivity is greater in THF than in Et_2O and provides evidence against isomerization of intermediate Cu(III) complexes via SSIPs and for chelation effects between the cuprate reagent and substrate.

Thus, product *anti:syn* diastereoselectivity in the reactions of **12** is modest to good for lithium dialkylcuprates in THF, excellent for zinc and magnesium cuprates in THF, and poor for magnesium cuprates in Et_2O, although for the last compound excellent *anti:syn* selectivity can be restored by use of small amounts of THF (i.e., Et_2O/THF, 10/1) but not with Et_3N (i.e., Et_2O/Et_3N, 10/1; 1:1 dr). These observations suggest that *anti:syn* product diastereoselectivity in these allylic substitutions of epoxide **12** are governed by a combination of electronic and steric interactions, chelation effects, cuprate aggregation, and perhaps cuprate reactivity. In considering cuprate and/or the intermediate Cu(III) reactivity,[24] the rate for oxidative addition and reductive elimination generally move in opposite directions with respect to electronic effects of the copper ligands.[22a,b] Rapid oxidative addition to allylic substrates favored by cuprate composition[20a] (e.g., R_2CuM > RCuCNM[20b] and R_2CuLi > $R_2CuMgCl$) and nonpolar solvents favoring chelation is expected to favor diminished diastereoselectivity (i.e., *anti* vs *syn* oxidative addition of the cuprate). Regioselectivity, on the other hand, is govern by steric (i.e., more stable Cu(III) σ complex)[1e] and electronic effects in the allyl ligand[22a,d] of **39**, the *trans* effect for the alkylcyanocuprates[22a,c] (i.e., **39**, L = CN), and the rate of reductive elimination.[20]

The *E*/*Z* geometry of the product allylic alcohols derived from epoxide **12** appears to be largely determined by allylic strain in the transition states.[1a] In the ground state, the conformer leading to the *trans*-alkene displays $A^{1,2}$ strain while the conformer leading to the *cis*-alkene displays $A^{1,3}$ strain (Scheme 5), which usually exhibits the higher strain energy.[43]

Scheme 5. Allylic Strain in Epoxide 12 and Resultant TS



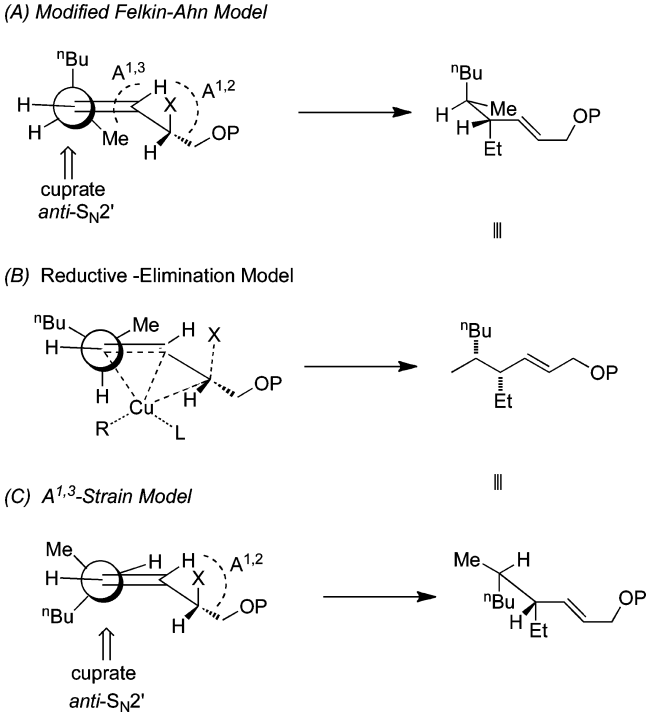
The transition state geometries will undoubtedly alter the energy differences between the two types of allylic strain. Although not universally observed, the amount of *Z* isomer

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

(Table 4) generally increases at higher temperatures, in more polar solvents (e.g., THF/HMPA > THF > Et_2O), and with increasing size of the transferable ligand (e.g., ^{t}Bu, Ph > ^{n}Bu > Et). Additionally, there appears to be some dependence upon the cuprate counterion (i.e., Li ≈ Mg > Zn). These observations suggest that nonpolar solvents (CIPs vs SSIPs), smaller transferable ligands, and zinc cuprates (coordination effects or cuprate structures) favor a tighter transition state geometry, magnifying the energy differences between the $A^{1,3}$ and $A^{1,2}$ steric interactions.

The stereoselective substitution reactions of **26a,b** have several potential control elements that may govern the stereochemical outcome of the reaction. These include the newly introduced stereogenic center, the stereoelectronic preference for *anti*-S_N2' pathways, and $A^{1,3}$ strain at both stereogenic allylic centers. Observed diastereoselectivities in S_N2' products obtained from allylic substrates containing a δ stereogenic center have been rationalized by both modified Felkin–Ahn[1a,5] and $A^{1,3}$ strain[1a] models. More recently a reductive elimination model[11d] has been proposed for conjugate addition reactions to γ-oxy α,β-enoates (Scheme 6). In all instances, *syn*-**27** is observed as the major

Scheme 6. Models for Diastereocontrol in Allylic Substitutions of Allylic Substrates 16a,b



product, indicating that the dominant stereocontrolling element is the strong stereoelectronic preference for *anti*-S_N2' substitution, which is diminished slightly in the reactions of dialkylmagnesium cuprates with **26a**. The product *syn:anti* diastereoselectivity for the magnesium cuprates is solvent and cuprate reagent dependent and could reflect the cuprate structure and/or chelation of the cuprate reagent with the leaving group.[1a] In THF, these cuprates are expected to be SSIPs in equilibrium with RM (M = Li, Mg) and in less polar solvents homodimers,[29] and this is consistent with the observed reaction at the ester carbonyl (i.e., **26a**) in THF. In the modified Felkin–Ahn and reductive elimination models drawn to reflect the dominant *anti*-S_N2' stereoelectronic control, steric hindrance for approach of the cuprate reagent is minimized at the expense of $A^{1,3}$ strain in the transition state conformation, while in the $A^{1,3}$ strain model the $A^{1,3}$ strain is minimized at the expense of an increased steric interaction for the approaching cuprate reagent (Scheme 6). Since all three models under the *anti*-S_N2' constraint predict the same diastereomer, it is tempting to favor the $A^{1,3}$ model as the more predictive one, arguing that the preference for S_N2 substitution with ^{t}BuCuCNLi arises from steric interactions (i.e., ^{t}Bu–^{n}Bu crowding) overriding the *trans* effect for RCuCNLi reagents[22c] favoring S_N2' pathways.

The regioselectivity in the reactions of **26a,b** is sensitive to cuprate reagent, solvent, and size of the transferable ligand. The magnesium and lithium phenyl- and alkylcyanocuprates give S_N2' selectivity that diminishes significantly for phenyl (75:25, "*A* value" = 2.8) and reverses for ^{t}Bu (14:86, "*A* value" = 4.7–4.9 kcal/mol), appearing to reflect "*A*-values"[44] ("*A* value" = 1.79, 2.21 for Et, ^{i}Pr, respectively) consistent with the $A^{1,3}$ strain model (Scheme 6). The magnesium dialkylcuprates and Ph_2CuLi give S_N2 selectivity in THF and S_N2' selectivity in less polar solvents (i.e., Et_2O, CH_2Cl_2, ^{t}BuOMe), and for the magnesium cuprates reacting with **26a** S_N2 selectivity is proportional to the amount of THF present in the solvent mixture, consistent with the dissociation of supramolecular aggregates.[29b] This regioselectivity seems contrary to the allylic-substituent electronic effects of calculations[22d] and is reminiscent of the ion-pair model for S_N2:S_N2' selectivity proposed by Streitwieser,[37] where anionic nucleophiles (e.g., SSIP) favor S_N2 pathways and ion-pair nucleophiles favor S_N2' pathways, albeit with *syn* selectivity between the leaving group and attacking nucleophile. Thus, it is noteworthy that in THF ^{t}BuCuCNLi has a molar conductivity (Λ = 4.0 ± 0.5 S cm^2 mol^{-1}) comparable to that observed for $R_2CuLi{\cdot}LiCN$ (R = ^{n}Bu, Ph: 13 ± 1, 8.2 ± 0.3 S cm^2 mol^{-1}, respectively) and 10 times greater than that of RCuCNLi (R = ^{n}Bu, Ph: 0.3 ± 0.1, 0.42 ± 0.04 S cm^2 mol^{-1}, respectively).[29c] However, the same S_N2 selectivity is also observed with ^{t}BuCuCNLi in Et_2O, suggesting that steric factors are the overriding influence, as argued above.

SUMMARY

In summary, sequential copper mediated bis-allylic substitution reactions on vinyloxiranes generating two new vicinal sterogenic centers can be carried out with high degrees of regio- and stereocontrol by judicious manipulation of reaction conditions. For the vinyloxirane containing an electron-deficient alkene (i.e., **6**) optimal S_N2' regioselectivity and *anti* diasteroselectivity requires use of lithium halide free dialkylzinc reagents and CuCN in THF or DMF, while vinyloxirane **12** with an electron-rich alkene requires either lithium halide free dialkylzinc reagents with CuCN in THF or low reaction temperatures (e.g., −78 °C). Mixed Et_2O/THF (10/1) solvent mixtures are generally required to achieve excellent S_N2' regioselectivity and *anti* diasteroselectivity with vinyloxirane **12** and Grignard reagents in the presence of CuCN (catalytic or stoichiometric amounts) and for this system formation of the (*Z*)-alkene is also minimized with the mixed solvent system. Copper-mediated allylic substitution of **6** affords an allylic alcohol whose acetate (i.e., **9**) reacts with Grignard reagents and CuCN to afford products with excellent S_N2' regioselectivity in THF but variable *syn* diastereoselectivity depending upon the relative steric size of the sequentially introduced alkyl

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949–4967

ligands. In less poor solvents, allylic acetate **9** affords poor *syn* diastereoselectivity with magnesium dialkylcuprates attributable to chelation effects. Allylic phosphate **26b** gives excellent S_N2' regioselectivity and *syn* distereoselectivity with lithium alkylcyanocuprates (i.e., RCuCNLi·LiCN, R = primary alkyl).

Several general trends emerge from the data. Although reagent-controlled *anti*-S_N2' allylic substitution is the dominant reaction pathway in all four systems studied, regioselectivity, *E*:*Z* diastereoselectivity, and *anti*:*syn* reaction pathways are sensitive to substrate and cuprate structure, cuprate composition, and solvent effects. Nonpolar solvents increase and sometimes favor S_N2 over S_N2' pathways and *syn* (*anti* product diastereoselectivity in the second allylic substitution) over *anti* pathways, as does the presence of lithium halide salts. Similarly, S_N2 and *syn* pathways increase along the series Mg > Li > Zn for the cuprate counterions. These general trends are consistent with cuprate−substrate chelation effects where cuprate counterions (e.g., Li, Mg, Zn) bridge copper ligands and heteroatoms in the substrate. Although the increased yields of S_N2 products in nonpolar solvents appears to be opposite to the Streitwieser model, where ion-pair nucleophiles favor *syn*-S_N2' pathways and anionic nucleophiles S_N2 pathways, the Streitwieser model invokes chelation of the reagent to the leaving group for ion-pair nucleophiles. In our systems, the cuprate reagent can coordinate to functional groups other than the leaving group, with the resultant geometry leading to competitive S_N2 pathways.

In most instances, *E*:*Z* diastereoselectivity is governed by $A^{1,3}$ strain in the allylic framework while S_N2' regioselectivity is enhanced by use of alkylcyanocuprates (i.e., RCuCNM), consistent with the *trans*-effect and Nakamura's model and calculations, but can be reversed by use of ^{t}BuCuCNLi in THF or Et_2O, refecting steric effects. However, the level of solvent-dependent cuprate aggregation (e.g., CIPs, SSIPs, supramolecular structures) also plays a role in determining regio- and diastereoselectivities (i.e., both *E*:*Z* and *syn*:*anti* pathways).

In conclusion, very good to excellent regio- and stereocontrol has been achieved in these systems only by using different combinations of CuCN-derived cuprate reagents, solvents, and reaction conditions for each of these allylic substrates. The choice of cuprate reagent is often dictated by the cuprate−substrate reactivity profile, while reaction conditions must be empirically determined to optimize the regio- and diastereoselectivities. We focused exclusively on CuCN-derived cuprate reagents,[45] given prior literature precedents,[4−6,12,15] for their effective utility in S_N2' allylic substitutions supported by recent theoretical[22c] and experimental considerations.[24a,c,d] A synthetically useful[46] approach to generating vicinal stereogenic centers[47] via sequential bis-allylic substitutions has been demonstrated.

EXPERIMENTAL SECTION

General Experimental Considerations. NMR spectra were recorded as $CDCl_3$ solutions on a 500 MHz instrument. The ^{1}H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) or $CHCl_3$ (δ = 7.26) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to $CDCl_3$ signal (triplet, centerline δ 77.00 ppm). Infrared (IR) spectra were recorded as neat samples. Gas chromatography−mass spectrometry measurements were performed on a mass spectrometer with quadrapole detection. Analytical thin-layer chromatography (TLC) was performed on silica gel plates, 200 μm mesh with F_{254} indicator. Visualization was accomplished by UV light (254 nm) and/or a 10% ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 200−400 μm mesh silica gel. Elemental analyses were determined on flash column chromatography purified samples. The chemical yields are of materials isolated by flash column chromatography.

General Procedure A: Preparation of Salt-Free Dialkylzinc Reagents from Grignard Reagents and Zinc Bromide ($ZnBr_2$). Using an established procedure,[23] to a flame-dried $ZnBr_2$ sample (20 mmol, 4.5 g) in dry diethyl ether (30 mL) under argon was added slowly dropwise a Grignard reagent as a diethyl ether solution at 0 °C. The reaction mixture was stirred for an additional 6 h while it was slowly warmed to room temperature. Then dry dioxane (10 mL, dried by sodium metal) was added and the mixture was stirred for an additional 2 h. A white solid precipitated out of the solution, and this precipitate was removed by vacuum filtration under an argon atmosphere.

General Procedure B: Reaction of Salt-Free Dialkylzinc Reagents with Allylic Epoxides. To a suspension of CuCN (0.5 mmol, 45 mg) in dry THF (3 mL) at −78 °C was added dropwise a dialkylzinc solution (1.10 mmol in diethyl ether), and the reaction mixture was stirred for 30 min. Then the allylic epoxide (1.0 mmol, 156 mg) was added neat in a dropwise fashion. The reaction mixture was warmed to room temperature and stirred for an additional 6 h. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether (3 × 10.0 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 10% ethyl acetate/90% petroleum ether, v/v) to give the allylic alcohols.

General Procedure C: Reaction of Dialkylmagnesium Cuprates with 2-Alkyl-5-acetoxy-3-hexenoates. To CuCN (0.5 mmol, 45 mg) in dry THF (3 mL) under argon at −78 °C was added Grignard reagent (1.0 mmol), and the reaction mixture was stirred for 30 min. Then the enoate (0.5 mmol) was added dropwise as a neat sample. The reaction mixture was stirred for an additional 6 h and warmed to room temperature. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether (3 × 10.0 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 5% ethyl acetate/petroleum ether, v/v) to give 2,3-dialkyl-substituted 4-enoates.

General Procedure D: Reaction of Alkylcyanomagnesium Cuprates with 2-Alkyl-5-acetoxy 3-hexenoates. To CuCN (0.5 mmol, 45 mg) in dry THF (3 mL) under argon at −78 °C was added a solution of Grignard reagent (0.5 mmol), and the mixture was stirred for 30 min. Then starting enoate (0.5 mmol) was added dropwise as a neat sample. The reaction mixture was stirred for an additional 6 h and warmed to room temperature. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether (3 × 10.0 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v) to give 2,3-dialkyl-substituted 4-enoates.

Ethyl (*E*)-5-Hydroxy-2-ethyl-3-hexenoate (7a). Employing general procedure B, diethylzinc (1.1 mmol in hexane) and 4,5-epoxy-2,3-hexenoate gave, after purification by flash column chromatography (silica gel, 10% ethyl acetate/90% petroleum ether, v/v), **7a** (165 mg, 89%, dr = 98:2, regio 96:4) as an oil: IR (neat) 3443, 2966, 2929, 2872, 1728, 1650, 1458, 1368, 1299, 1258, 1176, 1095, 1058, 1029, 972, 940, 862; ^{1}H NMR δ [regioisomer] 0.91 (t, J = 7.50 Hz, 3H), 1.22−1.32 (m, 6H), 1.50−1.65 (m, 2H), 1.71−1.88 (m, 1H), 2.90 (q, J = 7.50 Hz, 1H), 4.16 (q, J = 7.20 Hz, 2H), 4.32 (br s, 1H), 5.63−5.67 (m, 2H), [5.90 (d, J = 15.60 Hz, 0.05H), 6.84 (dd, J = 9.60, 15.60 Hz, 0.05H)]; ^{13}C NMR δ 11.6, 14.2, 23.3, 25.8, 50.4, 60.5, 68.5, 127.9, 136.8, 174.3; mass spectrum m/z (relative intensity) EI 186 (M^+, 0.04), 169 (2), 157 (9), 140 (26), 129 (24), 125 (55), 116 (79), 112 (71), 101 (100), 97 (74), 83 (33), 71 (71), 69 (57), 57 (32), 55 (78).

Ethyl (*E*)-5-Hydroxy-2-(1-butyl)-3-hexenoate (7b). Salt-free diisopropylzinc was prepared according to general procedure A. Employing general procedure B, di-*n*-butylzinc (1.1 mmol in diethyl

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

ether) and 4,5-epoxy-2,3-hexenoate gave, after purification by flash column chromatography (silica gel, 10% ethyl acetate/90% petroleum ether, v/v), **7b** (175 mg, 82%, dr = 97:3, regio 95:5) as an oil: IR (neat) 3440, 2958, 2929, 2860, 1732, 1650, 1458, 1368, 1250, 1221, 1176, 1033, 968, 935, 862; ^{1}H NMR δ [regioisomer] 0.87 (t, J = 7.30 Hz, 3H), 1.20−1.33 (m, 10H), 1.45−1.53 (m, 1H), 1.68−1.77 (m, 1H), 2.94 (q, J = 7.35 Hz, 1H), 4.12 (q, J = 7.35 Hz, 2H), 4.29 (quintet, J = 5.95 Hz, 1H), 5.56−5.68 (m, 2H) [5.84 (d, J = 15.60 Hz, 0.032H), 6.80 (dd, J = 9.65, 15.60 Hz, 0.032H)]; ^{13}C NMR δ 14.0, 14.3, 22.5, 23.4, 29.3, 32.3, 48.9, 60.6, 68.6, 128.2, 136.7, 174.4; mass spectrum m/z (relative intensity) EI 214 (M^+, 6), 197 (4), 171 (10), 157 (28), 153 (28), 129 (20), 112 (48), 111 (67), 101 (100), 97 (57), 83 (49), 73 (52), 69 (28), 55 (92).

Ethyl (*E*)-5-Hydroxy-2-(1-methylethyl)-3-hexenoate (7c). Salt-free diisopropylzinc was prepared according to general procedure A. Employing general procedure B, diisopropylzinc (1.1 mmol in diethyl ether) and 4,5-epoxy-2,3-hexenoate gave, after purification by flash column chromatography (silica gel, 10% ethyl acetate/90% petroleum ether, v/v), **7c** (154 mg, 77%, dr = 96:4, regio 93:7) as an oil: IR (neat) 3443, 2962, 2928, 2876, 1727, 1648, 1467, 1370, 1260, 1238, 1174, 1151, 1034, 974; ^{1}H NMR δ [regioisomer] 0.77 (t, J = 6.85 Hz, 3H), 0.82 (d, J = 6.90 Hz, 3H), 1.16 (t, J = 6.85 Hz, 3H), 1.18 (d, J = 6.45 Hz, 3H), 1.67 (s, 1H), 1.83−1.93 (m, 1H), 2.57 (t, J = 8.25 Hz, 1H), 4.00−4.08 (m, 2H), 4.22 (quintet, J = 6.40 Hz, 1H), 5.48−5.59 (m, 2H), [5.76 (d, J = 15.55 Hz, 0.035H), 6.80 (dd, J = 10.55, 16.05 Hz, 0.035H)]; ^{13}C NMR δ 14.3, 19.8, 20.7, 23.5, 31.0, 56.6, 60.5, 68.7, 127.1, 137.8, 174.1; mass spectrum m/z (relative intensity) EI 200 (M^+, 0.04), 183 (2), 157 (76), 143 (23), 125 (60), 112 (48), 111 (100), 97 (100), 83(60), 69 (99), 55 (52).

Ethyl (*E*)-2-Ethyl-3-methyl-4-hexenoate (10a). Employing general procedure D, MeMgCl (0.05 mmol, 0.25 mL of 2.00 M) and 2-ethyl-5-acetoxy-3-hexenoate (113 mg, 0.50 mmol) gave, after purification by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v), ethyl (*E*)-2-ethyl-3-methyl-4-hexenoate (48 mg, 52%) as a colorless oil: IR (neat) 2960, 2929, 2855, 1731, 1458, 1374, 1262, 1151, 1023; ^{1}H NMR δ 0.88 (t, J = 7.35 Hz, 3H), 0.92−1.08 (m, 3H), 1.16−1.40 (m, 3H), 1.65 (t, J = 6.90 Hz, 3H), 1.89 (d, J = 6.00 Hz, 1H), 2.00−2.20 (m, 1H), 2.25−2.45 (m, 2H), 4.05−4.27 (m, 2H), 5.30−5.50 (m, 2H); ^{13}C NMR δ 12.2, 14.4, 18.2, 20.2, 22.6, 39.3, 53.6, 59.8, 124.7, 134.3, 175.5; mass spectrum m/z (relative intensity) EI 184 (M^+, 3), 169 (1), 155 (95), 139 (18), 127 (35), 116 (53), 101 (48), 95 (31), 69 (100), 55 (50).

Ethyl (*E*)-2-Ethyl-3-(1-butyl)-4-hexenoate (10c). Employing general procedure D, *n*-BuMgCl (0.06 mmol, 0.25 mL of 2.00 M) and 2-ethyl-5-acetoxy-3-hexenoate (136 mg, 0.60 mmol) gave, after purification by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v), ethyl (*E*)-2-ethyl-3-(1-butyl)-4-hexenoate (91 mg, 67%) as a colorless oil: IR (neat) 2958, 2929, 2856, 1732, 1458, 1377, 1343, 1262, 1225, 1176, 1152, 1095, 1025; ^{1}H NMR δ [diastereomer] 0.80 (t, J = 7.35 Hz, 6H), 1.03−1.12 (m, 2H), 1.12−1.25 (m, 7H), 1.35−1.55 (m, 2H), 1.57 (dd, J = 1.40, 6.40 Hz, 3H), 1.98−2.07 (m, 1H), 2.10−2.16 (m, 1H), 4.00−4.12 (m, 2H), 5.15 (dd, J = 9.65, 15.10 Hz, 1H), [4.95 (dd, J = 10.55, 11.00 Hz, 0.11H)], 5.25−5.34 (m, 1H), [5.47−5.55 (m, 0.11H)]; ^{13}C NMR δ 12.3, 14.2, 14.5, 18.0, 22.7, 23.2, 29.5, 32.2, 45.5, 52.5, 59.8, 126.4, 132.6, 175.3; mass spectrum m/z (relative intensity) EI 226 (M^+, 4), 197 (52), 169 (33), 141 (6), 116 (56), 101 (26), 95 (16), 81 (18), 69 (100), 55 (96).

Ethyl (*E*)-2-Ethyl-3-(1-methylethyl)-4-hexenoate (10d). Employing general procedure D, *i*-PrMgCl (0.05 mmol, 0.25 mL of 2.00 M) and 2-ethyl-5-acetoxy-3-hexenoate (113 mg, 0.50 mmol) gave, after purification by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v), ethyl (*E*)-2-ethyl-3-(1-methylethyl)-4-hexenoate (75 mg, 71%) as a colorless oil: IR (neat) 2953, 2929, 2862, 1732, 1464, 1370, 1259, 1173, 1031, 967; ^{1}H NMR δ 0.74 (t, J = 6.40 Hz, 3H), 0.78 (dd, J = 2.30, 6.90 Hz, 6H), 1.13 (t, J = 7.30 Hz, 3H), 1.40−1.49 (m, 2H), 1.54 (dd, J = 1.35, 5.95 Hz, 3H), 1.64 (sextet, J = 6.45 Hz, 1H), 1.83 (td, J = 9.15, 5.50 Hz, 1H), 2.23−2.30 (m, 1H), 3.95−4.03 (m, 2H), 5.16 (ddd, J = 1.35, 9.60, 15.10 Hz, 1H), 5.21−5.30 (m, 1H); ^{13}C NMR δ 12.1, 14.5, 17.9, 18.0, 21.7, 23.6, 28.1, 49.9, 51.7, 59.8, 127.6, 129.2, 175.6; mass spectrum m/z (relative intensity) EI 212 (M^+, 3, 197 (1), 184 (17), 183 (96), 169 (35), 167 (23), 141 (51), 139 (5), 138 (6), 116 (98), 97 (100), 81 (47), 69 (83), 55 (100);

Anti Diastereomers: ^{1}H NMR δ 0.68 (d, J = 6.85 Hz, 6H), 0.74 (t, J = 6.40 Hz, 3H), 1.17 (t, J = 6.85 Hz, 3H), 1.40−1.49 (m, 2H), 1.51 (dd, J = 1.85, 6.85 Hz, 3H), 1.56−1.60 (m, 1H), 2.19 (dt, J = 3.20, 10.55 Hz, 1H), 2.19 (dt, J = 3.65, 10.10 Hz, 1H), 4.06 (q, J = 7.30 Hz, 2H), 5.00 (ddd, J = 1.40, 11.00, 22.00 Hz, 1H), 5.52−5.59 (m, 1H); ^{13}C NMR δ 12.1, 14.5, 16.7, 18.0, 21.7, 23.6, 30.4, 44.8, 50.5, 60.0, 127.1, 128.6, 176.2.

Ethyl (*E*)-2-(1-Butyl)-3-methyl-4-hexenoate (11a). Employing general procedure D, MeMgCl (0.05 mmol, 0.25 mL of 2.00 M), and 2-*n*-butyl-5-acetoxy-3-hexenoate (128 mg, 0.50 mmol) gave, after purification by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v), ethyl (*E*)-2-(1-butyl)-3-methyl-4-hexenoate (59 mg, 56%) as a colorless oil: IR (neat) 2959, 2929, 2858, 1731, 1463, 1377, 1341, 1262, 1221, 1175, 1152, 1096, 967; ^{1}H NMR δ 0.89 (t, J = 9.00 Hz, 3H), 1.01 (d, J = 6.00 Hz, 3H), 1.13−1.35 (m, 7H), 1.40−1.59 (m, 2H), 1.64 (t, J = 6.00 Hz, 3H), 2.25−2.39 (m, 1H), 2.15−2.25 (m, 1H), 4.05−4.21 (m, 2H), 5.30−5.45 (m, 2H); ^{13}C NMR δ 14.0, 14.4, 17.9, 18.2, 22.7, 29.2, 30.0, 39.6, 51.8, 59.8, 124.7, 134.3, 175.4; mass spectrum m/z (relative intensity) EI 212 (M^+, 10), 197 (3), 183 (2), 169 (13), 167 (24), 155 (99), 144 (41), 127 (44), 115 (40), 101 (98), 95 (30), 83 (62), 69 (100), 55 (79).

Ethyl (*E*)-2-(1-Butyl)-3-ethyl-4-hexenoate (11b). To CuCN (0.5 mmol, 45 mg) in dry THF (3 mL) under argon at −78 °C was added EtMgBr (1.0 mmol, 1.0 mL of 1.0 M in *t*-BuOMe), and the mixture was stirred for 30 min. Then 2-*n*-butyl-5-acetoxy-3-hexenoate (0.5 mmol, 128 mg) was added dropwise as a neat sample. The reaction mixture was stirred for an additional 6 h and warmed to room temperature. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether (3 × 10.0 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 10% ethyl acetate/90% petroleum ether, v/v) to give ethyl (*E*)-2-(1-butyl)-3-ethyl-4-hexenoate (85 mg, 75%, dr = 76:24) as a colorless oil: IR (neat) 2953, 1929, 2856, 1733, 1464, 1377, 1252, 1173, 1033, 966; ^{1}H NMR δ 0.80 (t, J = 7.35 Hz, 3H), 0.85 (t, J = 7.35 Hz, 3H), 1.21 (t, J = 7.30 Hz, 3H), 1.10−1.30 (m, 4H), 1.35−1.57 (m, 2H), 1.62 (dd, J = 1.80, 6.40 Hz, 3H), 1.98 (ddd, J = 3.65, 7.35, 16.50 Hz, 1H), 2.25 (ddd, J = 4.60, 5.95, 11.45 Hz, 1H), 4.02−4.09 (m, 2H), 5.19 (ddd, J = 1.80, 9.15, 15.10 Hz, 1H), 5.36 (qd, J = 6.40, 8.70 Hz, 1H); ^{13}C NMR δ 11.8, 14.1, 14.5, 17.8, 22.7, 25.3, 29.9, 30.0, 47.4, 50.4, 59.8, 126.7, 132.2, 175.5; mass spectrum m/z (relative intensity) EI 226 (M^+, 3), 225 (0.42), 211 (0.15), 197 (91), 181 (16), 170 (21), 169 (72), 144 (38), 115 (31), 101 (90), 97 (22), 83 (100), 69 (31), 55 (100);

Diastereomer: ^{1}H NMR δ 0.80 (t, J = 7.35 Hz, 3H), 0.85 (t, J = 7.35 Hz, 3H), 1.21 (t, J = 7.30 Hz, 3H), 1.10−1.30 (m, 4H), 1.35−1.57 (m, 2H), 1.59 (dd, J = 2.15, 6.90 Hz, 3H), 2.13 (dd, J = 9.15, 14.65 Hz, 1H), 2.50 (ddd, J = 3.20, 10.05, 15.10 Hz, 1H), 4.13 (t, J = 6.90 Hz, 3H), 4.98 (dt, J = 1.85, 10.85 Hz, 1H), 5.58 (qd, J = 6.85, 11.00 Hz, 1H); ^{13}C NMR δ 11.6, 13.5, 14.1, 18.0, 22.7, 26.5, 29.9, 30.3, 41.3, 51.1, 60.0, 126.1, 132.3, 176.3.

Ethyl (*E*)-2-(1-Butyl)-3-(1-butyl)-4-hexenoate (11c). Employing general procedure C, *n*-BuMgCl (2.0 mmol, 1.0 mL of 2.00 M) and 2-*n*-butyl-5-acetoxy-3-hexenoate (254 mg, 1.00 mmol) gave, after purification by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v), ethyl (*E*)-2-(1-butyl)-3-(1-butyl)-4-hexenoate (185 mg, 73%) as a colorless oil: IR (neat) 2955, 2928, 2857, 1735, 1464, 1377, 1343, 1298, 1223, 1174, 1034, 967, 733; ^{1}H NMR δ 0.83−0.91 (m, 6H), 1.24 (t, J = 6.90 Hz, 3H), 1.10−1.35 (m, 10H), 1.40−1.51 (m, 2H), 1.64 (dd, J = 1.40, 6.40 Hz, 3H), 2.02−2.11 (m, 1H), 2.21−2.29 (m, 1H), 4.05−4.13 (m, 2H), 5.20 (ddd, J = 1.40, 9.65, 15.15 Hz, 1H), 5.38 (qd, J = 6.40, 15.15 Hz, 1H); ^{13}C NMR δ 14.1, 14.2, 14.5, 18.0, 22.6, 22.7, 29.5, 29.8, 30.1, 32.2, 45.7, 50.7, 59.8, 126.4, 132.6, 175.5; mass spectrum m/z (relative intensity) EI 254 (M^+, 2), 225 (1), 211 (2), 197 (46), 169 (8), 144 (22), 115 (12), 101 (36), 69 (100), 55 (62).

dx.doi.org/10.1021/jo300304n | *J. Org. Chem.* 2012, 77, 4949−4967

Diastereomer: ^{1}H NMR δ 0.83−0.91 (m, 6H), 1.10−1.26 (m, 12H), 1.28 (t, J = 7.35 Hz, 3H), 1.51−1.59 (m, 2H), 1.62 (dd, J = 1.80, 6.85 Hz, 3H), 2.11−2.18 (m, 1H), 2.54−2.63 (m, 1H), 4.16 (q, J = 7.35 Hz, 2H), 5.02 (td, J = 10.55, 1.85 Hz, 1H), 5.58 (qd, J = 6.85, 10.55 Hz, 1H); ^{13}C NMR δ 13.5, 14.1, 14.5, 22.4, 22.6, 22.8, 29.3, 30.0, 33.3, 34.2, 39.6, 51.3, 60.0, 125.7, 132.8, 176.1;

Ethyl (*E*)-2-(1-Butyl)-3-(1-methylethyl)-4-hexenoate (11d). Employing general procedure D, *i*-PrMgCl (0.05 mmol, 0.25 mL of 2.00 M) and 2-*n*-butyl-5-acetate enoate (128 mg, 0.50 mmol) gave, after purification by flash column chromatography (silica gel, 5% ethyl acetate/95% petroleum ether, v/v), ethyl (*E*)-2-(1-butyl)-3-(1-methylethyl)-4-hexenoate (76 mg, 63%) as a colorless oil: IR (neat) 2959, 2925, 2864, 1731, 1464, 1369, 1257, 1170, 1098, 1027, 967, 801; ^{1}H NMR δ 0.77 (t, J = 7.35 Hz, 3H), 0.81 (dd, J = 1.40, 7.35 Hz, 6H), 1.16 (t, J = 7.35 Hz, 3H), 1.35−1.45 (m, 2H), 1.57 (dd, J = 1.40, 6.45 Hz, 3H), 1.68 (sextet, J = 5.50 Hz, 1H), 1.85 (td, J = 9.15, 5.50 Hz, 1H), 2.32−2.39 (m, 1H), 3.97−4.05 (m, 2H), 5.18 (ddd, J = 1.35, 10.10, 15.10 Hz, 1H), 5.23−5.32 (m, 1H); ^{13}C NMR δ 14.1, 14.5, 17.8, 18.0, 21.7, 22.8, 28.0, 29.9, 30.2, 48.2, 51.9, 59.7, 127.7, 129.2, 175.7, diastereomer 0.70 (d, J = 6.85 Hz, 6H), 0.77 (t, J = 7.35 Hz, 3H), 1.20 (t, J = 7.30 Hz, 3H), 1.42−1.49 (m, 2H), 1.54 (dd, J = 1.40, 6.85 Hz, 3H), 2.25−2.31 (m, 1H), 2.49 (td, J = 4.10, 10.10 Hz, 1H), 4.05−4.12 (m, 2H), 5.03 (td, J = 11.00, 1.40 Hz, 1H), 5.59 (qd, J = 6.85, 11.00 Hz, 1H); ^{13}C NMR δ 14.0, 14.1, 16.9, 17.8, 18.0, 21.7, 28.0, 29.9, 30.3, 45.0, 48.8, 60.0, 127.1, 128.7, 176.4; mass spectrum m/z (relative intensity) EI 240 (M+, 1), 225 (0.42), 211 (1), 197 (16), 183 (77), 169 (7), 155 (14), 144 (47), 123 (37), 101 (63), 97 (74), 81 (33), 69 (57), 55 (100).

(*E*)-2,3-Epoxy-1-(1,1-dimethylethyldimethylsiloxy)-4-hexene (12). To a solution of epoxy alcohol **1** (1.12 g, 9.64 mmol) in dichloromethane (60 mL) was sequentially added triethylamine (1.947 g, 19.28 mmol, 2.0 equiv), imidazole (1.311 g, 19.28 mmol, 2.0 equiv), and dimethylaminopyridine (20 mg). The mixture was cooled to 0 °C, and a solution of *t*-BuMe$_2$SiCl (1.43 g, 9.64 mmol, 1.0 equiv) in dichloromethane (20 mL) was added dropwise over a period of 30 min. The mixture was gradually warmed to room temperature over 12 h, and H_2O (20 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo to afford an oil. Flash column chromatography on silica gel (petroleum ether/diethyl ether/NEt$_3$, 97/2/1) afforded 2.01 g (91%) of **12** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dq, J = 15.6, 6.4 Hz, 1H), 5.22 (ddq, J = 15.6, 8.25, 1.85 Hz, 1H), 3.84 (dd, J = 11.9, 3.2 Hz, 1H), 3.69 (dd, J = 12.35, 4.55 Hz, 1H), 3.24 (dd, J = 8.25, 2.3 Hz, 1H), 3.00−2.98 (m,1H), 1.74 (dd, J = 5.05, 1.8 Hz, 3H), 0.90(s, 9H), 0.07 (d, J = 4.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.9, 128.1, 63.2, 60.2, 56.1, 25.9, 18.4, 17.9, −5.3.

General Procedure E: Reaction of CuCN-Mediated Dialkylzinc (R_2Zn) Allylic Substitution of Vinyl Epoxide 12. Copper(I) cyanide (90 mg, 1.0 mmol, 0.2 equiv) was dispersed in 40 mL of anhydrous THF, the flask was cooled to −78 °C, and a solution of R_2Zn (10.0 mmol, 2.0 equiv) in THF was added dropwise. The mixture was stirred at −78 °C for 15 min before treatment with a solution of **12** (1.14 g, 5.0 mmol, 1.0 equiv) in THF (2.0 mL). After 12 h, H_2O (10 mL) was added, and the reaction mixture was filtered through Celite, extracted with ether (3 × 30 mL), dried over $MgSO_4$, and then concentrated in vacuo to afford a crude oil. Flash column chromatography (silica gel, ether/petroleum ether, 5/95, v/v) afforded the allylic alcohol.

(*E*)-(2*R,5*S**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-methylnon-3-en-2-ol (13a).** Employing general procedure E, **13a** was prepared (1.19 g, 83%) after flash column chromatography (silica gel, ether/petroleum ether, 5/95, v/v) as a colorless oil: IR (neat) 3436 (br, s), 2958 (s), 2930 (s), 2859 (s), 2244 (w), 1463 (m), 1382 (m), 1255 (m), 1111 (m), 1007 (w), 909 (w), 837 (m), 778 (m), 734 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (dd, J = 15.55, 7.8 Hz, 1H), 5.35 (dd, J = 15.6, 6.85 Hz, 1H), 4.11 (dt, J = 10.3, 3.2 Hz, 1H), 3.61 (dd, J = 10.1, 3.65 Hz, 1H), 3.42 (dd, J = 10.1, 7.75 Hz, 1H), 2.12−2.09 (m, 1H), 1.31−1.20 (m, 7H), 0.98 (d, J = 6.85 Hz, 3H), 0.91 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 126.2, 72.9, 67.4, 36.5, 36.4, 29.5, 25.9, 22.8, 19.3, 18.3, 14.1, −5.3, −5.4; mass spectrum, EI, m/z (relative intensity), 287 (0.01), 175 (17), 137 (16), 117 (20), 105 (75), 95 (43), 81 (52), 75 (100), 73 (61), 69 (68), 55 (53). Anal. Calcd for $C_{16}H_{34}O_2Si$: C, 67.07; H, 11.96. Found: C, 66.92; H, 11.89.

General Procedure F: Reaction of CuCN-Catalyzed Dialkylzinc (R_2Zn) Allylic Substitution of Vinyl Epoxide 12. Copper(I) cyanide (90 mg, 1.0 mmol, 0.2 equiv) was dispersed in 40 mL of anhydrous THF and , cooled to −78 °C, and a solution of Et_2Zn (10.0 mmol, 2.0 equiv) in hexanes was added dropwise. The mixture was stirred at −78 °C for 15 min before treatment with a solution of **12** (1.14 g, 5.0 mmol, 1.0 equiv) in THF (2.0 mL). After 12 h, 10 mL of H_2O was added, and the reaction mixture was filtered through Celite, extracted with ether (3 × 30 mL), dried over $MgSO_4$, and then concentrated in vacuo to afford a crude oil. Flash column chromatography (silica gel, ether/petroleum ether, 10/90, v/v) afforded the allylic alcohol.

(*E*)-(2*R,5*S**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-methylhept-3-en-2-ol (13b).** Employing general procedure F, **13b** was prepared (1.00 g, 78%) after flash column chromatography (silica gel, ether/petroleum ether, 10/90, v/v) as a colorless oil: IR (neat) 3436 (br, s), 2091 (br), 1646 (s), 1462 (w), 1383 (w), 1256 (w), 1110 (w), 734 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (dd, J = 15.55, 7.8 Hz, 1H), 5.34 (dd, J = 15.6, 6.85 Hz, 1H), 4.11 (dt, J = 3.7, 2.75 Hz, 1H), 3.61 (dd, J = 10.1, 3.65 Hz, 1H), 3.43 (dd, J = 10.05, 8.25 Hz, 1H), 2.56 (s, 1H), 2.06−1.98 (m, 1H), 1.33−1.24 (m, 2H), 0.97 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.84 (t, J = 7.35 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 126.5, 73.0, 67.4, 38.1, 29.4, 25.9, 19.8, 18.3, 11.7, −5.3, −5.4; mass spectrum, EI, m/z (relative intensity), 241 (0.05), 201 (2), 131 (27), 109 (89), 89 (57), 75 (100), 73 (73), 67 (51), 57 (33). Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 64.85; H, 11.84.

(*E*)-(2*R,5*R**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5,6,6-trimethylhept-3-en-2-ol (13c).** Employing general procedure E, **13c** was prepared (160 mg, 56%) as a colorless oil after flash column chromatography (silica gel, ether/petroleum ether, 5/95, v/v): IR (neat) 3436 (br, s), 2959 (m), 2860 (w), 1647 (s), 1112 (m), 837 (m), 778 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (dd, J = 15.15, 8.7 Hz, 1H), 5.27 (dd, J = 15.1, 6.4 Hz, 1H), 4.05−4.03 (m, 1H), 3.53 (dd, J = 10.05, 3.65 Hz, 1H), 3.35 (dd, J = 9.65, 7.8 Hz, 1H), 2.44 (d, J = 2.3 Hz, 1H), 1.85−1.79 (m, 1H), 0.87 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H), 0.76 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 128.0, 73.0, 67.4, 47.0, 32.7, 27.4, 25.9, 18.3, 15.3, −5.3, −5.4; mass spectrum, EI, m/z (relative intensity), 269 (0.04), 229 (0.7), 155 (17), 137 (23), 105 (31), 89 (58), 81 (95), 73 (67), 57 (100); HR mass spectrum m/z 229.162 78 (M$^+$ − ^{t}Bu) (calcd for $C_{12}H_{25}O_2Si$, 229.162 39).

(*E*)-(2*R,5*R**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-furylhex-3-en-2-ol (13d).** Difurylzinc ((2-furyl)$_2$Zn) was prepared in the following fashion: at −78 °C, *n*-BuLi (0.86 mL, 2.1 mmol, 2.0 equiv) was added dropwise to a solution of furan (144 mg, 2.1 mmol, 2.0 equiv) in 5.0 mL of THF, and the solution was warmed to 0 °C and maintained at that temperature for 1.5 h. The mixture was then added to a −78 °C solution of $ZnBr_2$ (238 mg, 1.05 mmol, 1.0 equiv) in 3.0 mL of THF, and the mixture was stirred for 20 min at −78 °C, Employing general procedure E, **13d** was obtained (139 mg, 47%, light yellow oil) as a mixture of diastereomers (50:50) after flash column chromatography (silica gel, ether/petroleum ether, 10/90, v/v): IR (neat) 3501 (br, s), 2983 (s), 2874 (m), 1445 (m), 1383 (m), 1298 (w), 1130 (m), 934 (w), 845 (w), 794 (w), 738 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 1.0 Hz, 1H, diastereomer), 6.31−6.30 (m, 1H), 6.02 (d, J = 3.0 Hz, 1H), 6.00 (d, J = 3.5 Hz, 1H, diastereomer), 5.88 (ddd, J = 16.0, 7.5, 1.5 Hz, 1H), 5.51 (ddd, J = 15.5, 6.5, 1.0 Hz, 1H), 5.58 (dt, J = 10.0, 1.0 Hz, 1H, diastereomer), 5.44 (dd, J = 12.0, 8.5 Hz, 1H, diastereomer), 4.60 (dt, J = 3.5, 1.0 Hz, 1H, diastereomer), 4.18 (dt, J = 9.0, 4.0 Hz, 1H), 3.89−3.87 (m, 1H, diastereomer), 3.65 (dd, J = 10.0, 3.5 Hz, 1H), 3.70 (dd, J = 10.0, 3.5 Hz, 1H, diastereomer), 3.57−3.55 (m, 1H), 3.47 (dd, J = 17.5, 7.5 Hz, 1H), 2.63 (d, J = 2.8 Hz, 1H), 2.51 (d, J = 2.8 Hz, 1H, diastereomer), 1.38 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 141.1, 134.9, 128.4, 110.1, 104.1,

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

72.5, 67.2, 36.1, 25.9, 19.4,18.8, −5.2, −5.3 and (158.4, 141.1, 135.5, 128.0, 110.0, 103.8, 68.6, 66.8, 32.3, 25.9, 18.3, 18.2, −0.5.2, −5.2. diastereomer); mass spectrum, EI, *m*/*z* (relative intensity), 282 (20), 281 (73), 221 (15), 147 (19), 105 (17), 75 (69), 73 (100).

(*E*)-(2*R,5*R**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-phenylhex-3-en-2-ol (13e).** Employing general procedure E, **13e** was prepared (129 mg, 42%) as a yellow oil after flash column chromatography (silica gel, ether/petroleum ether, 5/95, v/v): IR (neat) 3351 (br, s), 2957 (s), 2929 (s), 2858 (s), 2361 (w), 1596 (w), 1472 (m), 1254 (m), 1072 (m), 837 (s), 699 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.11 (m, 5H), 5.88 (ddd, J = 15.55, 6.85, 0.95 Hz, 1H), 5.37 (ddd, J = 15.55, 6.4, 1.35 Hz, 1H), 4.12−4.06 (m, 1H), 3.55 (dd, J = 10.1, 3.7 Hz, 1H), 3.42−3.35 (m, 1H), 3.36 (dd, J = 10.1, 7.8 Hz, 1H), 2.63 (s, 1H), 1.29 (d, J = 6.85 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 138.2, 128.5, 127.3, 127.2, 126.2, 72.9, 67.2, 42.2, 25.9, 21.2, 18.4, −5.2, −5.3; mass spectrum, EI, *m*/*z* (relative intensity), 291 (0.01), 275 (0.2), 231 (2), 157 (96), 143 (42), 131 (89), 129 (91), 105 (82), 91 (49), 89 (66), 75 (100), 73 (97).

(*E*)-2,3-Epoxy-1-(1,1-dimethylethyldimethylsiloxy)non-4-ene (18). Using the same experimental procedure as was used in the preparation of **12**, **18** was prepared (1.22 g, 90%) as a colorless liquid from the corresponding epoxy alcohol, which was prepared from (*E*,*E*)-2,4-nonadien-1-ol using a published procedure:[48] IR (neat) 3356 (br, s), 2957 (s), 2929 (s), 2858 (s), 1643 (w), 1463 (w), 1254 (m), 1098 (s), 837 (s), 778 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dt, J = 15.1, 6.9 Hz, 1H), 5.11 (dd, J = 15.1, 8.2 Hz, 1H), 3.77 (dd, J = 11.9, 3.2 Hz, 1H), 3.62 (dd, J = 12, 4.6 Hz, 1H), 3.16 (dd, J = 8.2, 2.3 Hz, 1H), 2.92−2.89 (m, 1H), 1.98 (dt, J = 6.9, 6.9 Hz, 2H), 1.31−1.21 (m, 4H), 0.82 (s, 9H), 0.82−0.80 (m, 3H), 0.00 (d, J = 4.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 126.8, 63.2, 60.3, 56.3, 32.0, 31.0, 25.9, 22.2, 18.3, 13.9, −5.3; mass spectrum, EI, *m*/*z* (relative intensity), 256 (0.3), 255 (1.1), 214 (11), 213 (62), 143 (30), 117 (15), 97 (15), 89 (24), 75 (57), 73 (57), 55 (100).

(*E*)-(2*R,5*R**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-methylnon-3-en-2-ol (14a).** To a slurry of CuI (475 mg, 2.5 mmol, 5.0 equiv) in anhydrous ether (2 mL) was added MeLi (5.0 mmol, 10.0 equiv) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 5 min before slowly adding a solution of starting epoxide **18** (135 mg, 0.5 mmol, 1.0 equiv) in ether (2 mL). The mixture was warmed to room temperature over 12 h and quenched with a saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with ether, and the organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford a colorless oil. Flash column chromatography (silica gel, ether/petroleum ether, 5/95, v/v) afforded pure **14a** as a colorless oil (99 mg, 69%): IR (neat) 3434 (br, s), 2957 (s), 2930 (s), 2859 (s), 1646 (br, w), 1463 (m), 1254 (m), 1113 (m), 970 (w), 837 (s), 778 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (dd, J = 15.5, 7.3 Hz, 1H), 5.27 (dd, J = 15.6, 6.9 Hz, 1H), 4.05−4.00 (m, 1H), 3.53 (dd, J = 10.1, 3.7 Hz, 1H), 3.34 (dd, J = 10, 7.8 Hz, 1H), 2.44 (d, J = 2.8 Hz, 1H), 2.06−1.99 (m, 1H), 1.24−1.15 (m, 6H), 0.89 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H), 0.83−0.77 (m, 3H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 126.3, 73.0, 67.5, 36.6, 36.5, 29.5, 25.9, 22.9, 20.4, 18.4, 14.1, −5.2, −5.3; mass spectrum, EI, *m*/*z* (relative intensity), 268 (0.6), 137 (27), 131 (26), 105 (15), 95 (45), 89 (53), 81 (89), 75 (100), 73 (75), 57 (32).

1,1-Dibromo-3-methyl-1-heptene (19). This compound was prepared according to a published experimental procedure[48−51] (192 mg, 71%) as a colorless liquid.

(2*R,5*S**)- and (2*S**,5*S**)-Ethyl 2-Hydroxy-5-methyl-3-nonoynoate (20).** 1,1-Dibromoalkene **19** (774 mg, 2.87 mmol, 1.0 equiv) was dissolved in dry THF (4 mL), and the mixture was cooled to −78 °C before adding a *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 equiv, 2.5 M in hexane) solution dropwise. The resulting solution was stirred at −78 °C for 1 h and then gradually warmed to room temperature and stirred for another 30 min. Then the mixture was cooled to −78 °C again and treated with a solution of ethyl glyoxalate (freshly distilled, 33 mol % in toluene) in THF (10 mL), and the reaction mixture was kept at −78 °C for 2 h more before quenching with a saturated aqueous NH_4Cl solution (10 mL). After extraction of the aqueous phase with ether (3 × 25 mL), the combined organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford a colorless oil. Flash column chromatography (silica gel, hexane/EtOAc, 85/15, v/v) afforded pure **20** (243 mg, 38%) as a 50:50 mixture of diastereomers: ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (d, J = 1.4 Hz, 1H), 4.36−4.24 (m, 2H), 3.02 (s, 1H), 2.49- 2.42 (m, 1H), 1.46−1.27 (m, 6H), 1.33 (t, J = 6.9 Hz, 3H), 1.15 (d, J = 7.3 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 90.9, 75.7, 62.5, 61.6, 36.2, 29.4, 25.8, 22.4, 20.6, 14.0, 14.0.

(*Z*)-(2*S,5*S**)- and (*Z*)-(2*R**, 5*S**)-5-Methyl-3-nonene-1,2-diol (21a).** Alcohol **20** (210 mg, 1.36 mmol) was dissolved in dry MeOH (7 mL), and to the mixture was added quinoline (0.1 mL) and Lindlar's catalyst (20 mg). The resulting mixture was stirred vigorously under an atmosphere of H_2 for 3 h before diluting with ether (20 mL) and was then filtered through a pad of Celite; solvent was removed in vacuo to afford crude **21** (212 mg) as a yellow oil. The crude material (80 mg, 1.0 equiv) was dissolved in dry ether (8 mL), and lithium aluminum hydride (43 mg, 2.0 equiv) was cautiously added at 0 °C. The mixture was refluxed for 2 h before cautiously quenching with 10 drops of water at 0 °C, and EtOAc (30 mL) was added to dilute the solution, whereupon the resulting mixture was stirred for 5 min until it became clear. The aqueous phase was extracted with EtOAc (3 × 25 mL), and the organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford **21a** (48 mg, 75%) as a yellow oil. Crude **21a** was used in the next step without further purification.

(*Z*)-(2*R,5*S**)- and (*Z*)-(2*S**,5*S**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-methylnon-3-en-2-ol (15a).** This compound was prepared (149 mg, 52%, colorless oil) as a pair of diastereomers (58:42) using the same experimental procedure used to prepare **12**: IR (neat) 3393 (br, m), 2957 (s), 2928 (s), 2859 (s), 1463 (m), 1377 (w), 1253 (m), 1105 (s), 838 (s), 779 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) as a pair of diastereomers (58:42) δ 5.38−5.26 (m, 2H), 4.49−4.45 (m, 1H), 3.63−3.56 (m, 1H), 3.43 (dd, J = 10, 8.5 Hz, 1H), 2.59 (d, J = 1.5 Hz, 1H), 2.53 (d, J = 1.5 Hz, 1H, diastereomer) 2.49−2.40 (m, 1H), 1.35−1.18 (m, 6H), 1.00 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H, diastereomer) 0.93 (s, 9H), 0.93−0.88 (m, 3H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) (diastereomer) δ 140.8, (140.4), (126.4), 126.1, (68.8), 68.5, (67.3), 67.1, (37.1), 37.0, 32.7, (32.6), 29.9 (29.6), 25.9, 22.8, (21.6), 21.3, 18.3, 14.0, (14.0), −5.3, −5.4; mass spectrum, EI, *m*/*z* (relative intensity), 268 (0.12), 171 (1), 137 (22), 131 (22), 105 (39), 95 (45), 89 (63), 8 1(74), 75 (100), 73 (73), 57 (26).

(*E*)-(2*R,3*S**)- and (*E*)-(2*S**,3*S**)-2-*n*-Butyl-4-hexene-1,3-diol (24).** Diisopropylamine (528 mg, 5.22 mmol, 1.2 equiv) was dissolved in THF (20 mL) at 0 °C, whereupon it was treated with *n*-BuLi (1.91 mL, 4.78 mmol, 2.5 M in hexane, 1.1 equiv) dropwise. After 15 min, the resultant solution was cooled to −78 °C and ethyl hexanoate (626 mg, 4.35 mmol, 1.0 equiv) was added slowly. The mixture was stirred at −78 °C for 1 h before a solution of crotonaldehyde (457 mg, 6.53 mmol, 1.5 equiv) in THF (5 mL) was added dropwise, and this mixture was warmed to room temperature over 2 h before quenching with a saturated aqueous NH_4Cl solution (10 mL). After ether extraction (3 × 30 mL), drying over $MgSO_4$, and removal of solvent in vacuo, **23** was obtained as a colorless oil. Without further purification, this oil was dissolved in THF (28 mL), and lithium aluminum hydride (320 mg, 8.42 mmol, 2.0 equiv) was added with caution at 0 °C. The resulting suspension was then heated at reflux for 3 h and then quenched with water (1.0 mL). The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic phase was dried over $MgSO_4$ and then concentrated in vacuo to afford **24**, consisting of a 1:1 mixture of diastereomers (450 mg, 60% over two steps, colorless oil): ^1H NMR (300 MHz, $CDCl_3$) δ 5.79−5.50 (m, 2H), 4.31 (dd, J = 6, 3 Hz, 1H, diastereomer) 4.09 (t, J = 9 Hz, 1H), 3.88 (dd, J = 9, 3 Hz, 1H), 3.75−3.61 (m, 2H), 2.57 (s, 2H), 1.76−1.73 (m, 3H), 1.40−1.18 (m, 6H), 0.95−0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (diastereomer) 133.2, (130.7), 128.1, (128.0), 77.7, (76.3), 64.8, (64.5), 45.1, (44.8), 29.7, (29.4), 27.7, (26.2), 22.9, (22.9), 17.8, (17.7), 14.0, (14.0).

(*E*)-(2*R,3*S**)- and (*E*)-(2*S**,3*S**)-1-[(1,1-Dimethylethyldimethylsilyl)oxy]-2-*n*-butyl-4-hexen-3-ol (25).** Diol **24** (450 mg,

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

2.6 mmol, 1.0 equiv) was dissolved in dichloromethane (20 mL), and imidazole (265 mg, 2.6 mmol, 1.5 equiv) and *t*-BuMe$_2$SiCl (392 mg, 3.9 mmol, 1.0 equiv) were added sequentially at 0 °C. The reaction mixture was stirred for 12 h before quenching with water (10 mL). After extraction of the aqueous layer with ether and drying the organic layer over MgSO$_4$, **25** was obtained as a colorless oil consisting of a 1:1 mixture of diastereomers (390 mg, 52%): IR (neat) 3413 (br, s), 2956 (s), 2931 (s), 1471 (m), 1379 (w), 1255 (s), 1091 (s), 967 (m), 837 (s), 776 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.67−5.55 (m, 1H), 5.49−5.40 (m, 1H), 4.02−3.96 (t, J = 5.5 Hz, 1H), 3.86−3.82 (d, J = 9.6 Hz, 1H), 3.56- 3.51 (dd, J = 10.1, 6.0 Hz, 1H), 1.65 (s, 3H), 1.25−1.11 (m, 6H), 0.88−0.74 (m, 5H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (diastereomer) 133.3, (131.1), (126.9), 126.8, 76.6, (75.8), (65.4), 65.2, (44.8), 44.7, (29.8), 29.6, 27.9, 25.9, 23.0, 18.2, (17.9), 14.1, −5.5, −5.6; mass spectrum, EI, m/z (relative intensity), 285 (0.01), 269 (0.05), 229 (4), 211 (3), 145 (13), 137 (6), 105 (77), 95 (12), 81 (17), 75 (100), 73 (29).

(*E*)-(2*S,5*R**)-2-[(1,1-Dimethylethyldimethylsilyl)oxy]-5-methylnon-3-en-1-ol (13a′).** Starting allylic alcohol **13a** (110 mg, 0.38 mmol, 1.00 equiv) was dissolved in dichloromethane (3.5 mL), whereupon 2,6-lutidine (61 mg, 0.57 mmol, 1.50 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 132 mg, 0.50 mmol, 1.31 equiv) was sequentially added to the reaction flask at 0 °C. The reaction mixture was gradually warmed to room temperature over 1 h and then quenched with 2 drops of MeOH, followed by addition of water (10 mL). Extraction of the aqueous phase with ether, drying with MgSO$_4$, and concentration in vacuo afforded the bis-silylated diol (146 mg) as a colorless oil, which was used in the next step without further purification. The crude material (44 mg, 0.11 mmol, 1.0 equiv) was dissolved in dry MeOH (2 mL), and pyridium *p*-toluenesulfonate (10 mg, 0.03 mmol, 0.3 equiv) was added at room temperature. The resulting mixture was stirred at room temperature for 12 h before water (5 mL) was added. The aqueous phase was extracted with ether, and the combined organic phase was dried over MgSO$_4$ and concentrated in vacuo. Purification by column chromatography (SiO$_2$, diethyl ether/hexane, 5/95, v/v) afforded **13a′** (16 mg, 49% over two steps) as a colorless liquid: IR (neat) 3414 (br, s), 2958 (s), 2929 (s), 2858 (s), 2360 (w), 1463 (m), 1377 (w), 1254 (m), 1102 (m), 1056 (m), 972 (m), 837 (s), 778 (s), 670 (w) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.56 (ddd, J = 16, 8, 1 Hz, 1H), 5.34 (ddd, J = 15, 7, 1 Hz, 1H), 4.18 (dt, J = 7, 4 Hz, 1H), 3.52 − 3.39 (m, 2H), 2.15 − 2.08 (m, 1H), 2.00 (dd, J = 8.5, 5 Hz, 1H), 1.32−1.18 (m, 6H), 0.99 (d, J = 6.5 Hz, 3H), 0.93 (s, 9H), 0.93−0.88 (t, J = 7.5 Hz, 3H), 0.09 (d, J = 11.5 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.4, 127.7, 74.6, 67.2, 36.4, 36.3, 29.5, 25.8, 22.7, 20.3, 18.1, 14.0, −4.0, −4.7; mass spectrum, EI, m/z (relative intensity), 267 (0.02), 255 (13), 229 (4), 175 (24), 159 (11), 119 (13), 117 (76), 115 (15), 103 (49), 81 (22), 75 (84), 73 (100), 55 (54).

General Procedure G: Reaction of Allylic Phosphate 26b with Lithium Alkylcyanocuprate (RCuCNLi). In a 25 mL round-bottom flask flushed with argon, starting alcohol **13a** (287 mg, 1.0 mmol) was dissolved in 3 mL of anhydrous THF and the mixture was cooled to −78 °C in a dry ice bath. The mixture was slowly treated with *n*-BuLi (0.41 mL, 2.45 M in hexane, 1.0 mmol), stirred for 10 min, warmed to −40 °C, stirred for 30 min, and then cooled to −78 °C, whereupon a solution of diethyl chlorophosphate (183 mg, 1.05 mmol) in 3.0 mL of THF was added dropwise. The resulting solution was then stirred at −78 °C for 1 h and then at −40 °C for 30 min. Meanwhile, in a separate round-bottom flask, LiCl (111 mg, 2.6 mmol, flame-dried) and CuCN (117 mg, 1.3 mmol) were dissolved in anhydrous THF (5.0 mL), the mixture was then cooled to −78 °C, and *n*-BuLi (1.3 mmol, 2.45 M in hexane) was added dropwise. This mixture was stirred at −78 °C for 45 min before adding it to the previously prepared reaction mixture dropwise at −78 °C. The reaction mixture was kept at −78 °C for 2 h before gradually warming to room temperature over 12 h. Saturated aqueous ammonium chloride solution (10 mL) was used to quench the reaction mixture, followed by extraction with diethyl ether (3 × 25 mL). The organic phase was dried over MgSO$_4$ and concentrated in vacuo to afford an oil as the crude product. Flash column chromatography on silica gel (ether/petroleum ether, 1/99, v/v) afforded 221 mg of pure **27b** (68%):

(*E*)-(4*S,5*S**)-(1,1-Dimethylethyl)dimethyl[(4-*n*-butyl-5-methyl-2-nonenyl)oxy]silane (27b).** Employing general procedure G, **27b** was prepared (221 mg, 68%) after flash column chromatography on silica gel (ether/petroleum ether, 1/99, v/v) as a colorless oil: IR (neat) 2956 (s), 2927 (s), 2857 (s), 1462 (m), 1379 (m), 1253 (m), 1103 (m), 1060 (w), 973 (w), 836 (w), 776 (w) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.42−5.30 (m, 2H), 4.08 (d, J = 3.65 Hz, 2H), 1.88−1.82 (m, 1H), 1.48−1.00 (m, 13H), 0.84 (s, 9H), 0.84−0.78 (m, 6H), 0.71 (d, J = 6.85 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 132.7, 130.2, 64.2, 46.7, 36.8, 34.9, 32.5, 30.1, 29.7, 26.0, 23.1, 22.9, 18.5, 15.5, 14.3, 14.2, −4.9, −5.0; mass spectrum, EI, m/z (relative intensity), 325 (0.01), 269 (81), 185 (19), 171 (41), 115 (31), 101 (29), 75 (100), 73 (70), 55 (20); HR mass spectrum m/z 326.300 32 (M$^+$) (calcd for $C_{20}H_{42}OSi$, 326.300 50).

General Procedure H: Reaction of Allylic Acetate 26a with Magnesium Cuprates (R$_2$CuMgCl). In a 25 mL round-bottom flask flushed with argon, CuCN (45 mg, 0.5 mmol) was dispersed in 10 mL of dichloromethane, and the starting material **26a** (300 mg, 1.0 mmol) was added at room temperature. The mixture was stirred for 5 min before cooling to −78 °C, whereupon ^{i}PrMgCl (1.65 M in THF, 1.0 mmol, 0.61 mL) was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h before it was gradually warmed to room temperature over 12 h. Saturated aqueous NH$_4$Cl solution (10 mL) was used to quench the reaction mixture, followed by extracting with dichloromethane (3 × 25 mL) and drying the organic phase over MgSO$_4$. After concentration in vacuo and flash column chromatography of the resulting oil on silica gel (100% petroleum ether), the pure product **27** was obtained as a colorless oil.

(*E*)-(4*S,5*S**)-(1,1-Dimethylethyl)dimethyl[4-(1-methylethyl)-5-methyl-2-heptenyl)oxy]silane (27c).** Employing general procedure H, **27c** (151 mg, 53%) was prepared as a colorless oil after flash column chromatography on silica gel (100% petroleum ether): IR (neat) 2958 (s), 2857 (s), 1462 (m), 1381 (m), 1254 (m), 1100 (m), 1057 (w), 976 (w), 836 (m), 776 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.41−5.26 (m, 2H), 4.08 (d, J = 6 Hz, 2H), 1.61−1.47 (m, 2H), 1.23−1.12 (m, 5H), 0.83 (s, 9H), 0.82−0.77 (m, 8H), 0.73 (d, J = 3 Hz, 3H), 0.70 (d, J = 3 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 131.3, 130.8, 64.1, 53.7, 35.4, 33.2, 29.4, 28.6, 26.0, 23.1, 21.2, 20.6, 18.5, 15.4, 14.3, −5.0, −5.1; mass spectrum, EI, m/z (relative intensity), 283 (0.02), 227 (71), 171 (23), 157 (35), 143 (68), 115 (36), 95 (36), 75 (100), 73 (85), 57 (24); HR mass spectrum m/z 312.285 20 (M$^+$) (calcd for $C_{19}H_{40}OSi$, 312.284 85).

(*E*)-(4*S,5*S**)-(1,1-Dimethylethyl)dimethyl[(4-ethyl-5-methyl-2-nonenyl)oxy]silane (27a).** Employing general procedure H, **27a** was prepared (241 mg, 81%) as a colorless oil after flash column chromatography (silica gel, ether/petroleum ether, 1/99, v/v): IR (neat) 3434 (br, s), 2958 (s), 2929 (s), 2858 (m), 1638 (br), 1462 (m), 1253 (m), 1103 (m), 836 (s), 775 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.50 (dt, J = 15, 5 Hz, 1H), 5.42 (dd, J = 14.5, 9 Hz, 1H), 4.17 (dd, J = 5, 1.5 Hz, 2H), 1.89−1.82 (m,1H), 1.50−1.22 (m, 9H), 0.93 (s, 9H), 0.91 (t, J = 3 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H), 0.81 (d, J = 7 Hz, 3H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 132.2, 130.4, 64.1, 48.6, 36.4, 34.8, 29.6, 26.0, 25.4, 23.0, 18.4, 15.4, 14.1, 12.3, −5.0, −5.1; mass spectrum, EI, m/z (relative intensity), 283 (0.3), 241 (24), 143 (12), 115 (11), 75 (100), 73 (27). Anal. Calcd for $C_{18}H_{38}OSi$: C, 72.41; H, 12.83. Found: C, 72.68; H, 12.85.

(*E*)-(4*S,5*S**)-(1,1-Dimethylethyl)dimethyl[(4-(1-methylpropyl)-5-methyl-2-nonenyl)oxy]silane (27d).** Employing general procedure G, **27d** was prepared (261 mg, 70%, colorless oil) as a pair of diastereomers (53:47) after flash column chromatography (silica gel, 100% petroleum ether): IR (neat) 2958 (s), 2928 (s), 2857 (m), 1462 (m), 1378 (m), 1254 (m), 1101 (m), 853 (w), 774 (w) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.50−5.42 (m, 1H), 5.41−5.34 (m, 1H), 4.18 (d, J = 5.05 Hz, 2H), 1.77−1.05 (m, 11H), 0.93 (s, 9H), 0.91−0.77 (m, 12H), 0.1 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) (minor diastereomer) δ (131.2), 131.1, (131.1), 130.9, 64.1, (64.0), 52.2, (51.1), (35.5), 35.2, (34.8), 34.7, (33.1), 32.9, 29.7, 29.5, (29.2),

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

27.5, (26.7), 26.0, (25.9), 23.2, (23.1), 18.5, (17.0), (16.4), 16.2, (15.2), 14.3, 11.4, (11.3), −5.0; mass spectrum, EI, *m*/*z* (relative intensity), 311 (0.2), 269 (19), 143 (15), 75 (100), 73 (32).

(*E*)-(2*R,5*S**)-(1,1-Dimethylethyl)dimethyl[(2-(1,1-dimethylethyl)-5-methyl-3-nonenyl)oxy]silane (28e).** Employing general procedure G, **28e** was prepared (218 mg, 67%) as a colorless oil after flash column chromatography (silica gel, ether/petroleum ether, 1/99, v/v) along with the S_N2' product (36 mg, 11%, colorless oil): IR (neat) 2957 (s), 2928 (s), 2858 (m), 1464 (m), 1363 (m), 1253 (m), 1101 (s), 1022 (w), 1003 (w), 853 (m), 774 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.24−5.18 (m, 2H), 3.73 (dd, J = 10, 4.1 Hz, 1H), 3.50 (dd, J = 10.1, 7.8 Hz, 1H), 2.15−2.03 (m, 1H), 1.82−1.76 (m, 1H), 1.30−1.17 (m, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.92−0.82 (m, 3H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 127.9, 64.0, 55.6, 37.0, 37.0, 32.3, 29.8, 28.4, 26.1, 23.0, 21.1, 18.4, 14.2, −5.1, −5.2; mass spectrum, EI, *m*/*z* (relative intensity), 325 (0.03), 269 (83), 213 (100), 199 (36), 115 (29), 89 (79), 75 (99), 73 (95), 57 (90). S_N2' product: ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (dd, J = 15.0, 10.5 Hz, 1H), 5.34 (dt, J = 15.1, 5 Hz, 1H), 4.09 (dd, J = 5.5, 1.4 Hz, 2H), 1.70−1.62 (m, 1H), 1.59 (d, J = 10.6 Hz, 1H), 1.22−1.10 (m, 6H), 0.83 (s, 9H), 0.81 (s, 9H), 0.82−0.76 (m, 3H), 0.73 (d, J = 6.9 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.6, 129.3, 64.1, 56.3, 37.8, 33.6, 32.4, 29.8, 28.8, 26.0, 23.0, 18.5, 17.1, 14.3, −4.9; HR mass spectrum *m*/*z* 325.292 13 ($M^+ - 1$) (calcd for $C_{20}H_{41}OSi$, 325.292 68).

(*E*)-(4*S,5*S**)-(1,1-Dimethylethyl)dimethyl[(4-phenyl-5-methyl-2-nonenyl)oxy]silane (27f).** Employing general procedure G, **27f** was prepared (294 mg, 85%) as a colorless oil after flash column chromatography (silica gel, ether/petroleum ether, 1/99, v/v): IR (neat) 2957 (s), 2928 (s), 2856 (m), 1461 (w), 1377 (w), 1258 (m), 1099 (m), 835 (w), 775 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2H), 7.18−7.10 (m, 3H), 5.80 (dd, J = 15.1, 9.6 Hz, 1H), 5.51 (dt, J = 15.1, 5.5 Hz, 1H), 4.10 (d, J = 5.05 Hz, 2H), 3.03 (t, J = 8.25 Hz, 1H), 1.78−1.70 (m, 1H), 1.30−1.15 (m, 6H), 0.85 (s, 9H), 0.88−0.76 (m, 6H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 132.5, 130.4, 128.3, 128.1, 125.9, 63.9, 54.8, 37.9, 34.4, 29.3, 26.0, 22.9, 18.5, 17.0, 14.2, −5.0; mass spectrum, EI, *m*/*z* (relative intensity), 346 (0.02), 289 (25), 205 (14), 191 (14), 130 (24), 129 (63), 114 (22), 91 (24), 75 (100), 73 (66); HR mass spectrum *m*/*z* 346.268 50 (M^+) (calcd for $C_{22}H_{38}OSi$, 346.269 20).

(*E*)-(2*R,5*S**)-(1,1-Dimethylethyl)dimethyl[(2-phenyl-5-methyl-3-nonenyl)oxy]silane (28f).** In a round-bottom flask flushed with argon, starting alcohol **13a** (197 mg, 0.69 mmol, 1.0 equiv) was dissolved in 3.0 mL of anhydrous THF, the mixture was cooled to −78 °C in a dry ice bath, and *n*-BuLi (0.29 mL, 2.40 M, 0.69 mmol, 1.0 equiv) was added dropwise. The mixture was stirred for 10 min and then warmed to −40 °C for 30 min, whereupon diethyl chlorophosphate (126 mg, 0.72 mmol, 1.05 equiv) in 3.0 mL of THF was added at −78 °C dropwise. The resulting solution was stirred at −78 °C for 50 min and then at −40 °C for 50 min. Meanwhile, in a separate round-bottom flask, CuCN (25 mg, 0.27 mmol, 0.39 equiv) dispersed in 3.0 mL of THF was cooled to −78 °C and then treated with PhLi (0.52 mL, 1.7 M in di-*n*-butyl ether, 0.89 mmol, 1.3 equiv) dropwise and stirred for 30 min at −78 °C before adding to the previous reaction flask at −78 °C. The combined reaction mixture was kept at −78 °C for 2 h before it was gradually warmed to room temperature over 12 h. Saturated aqueous ammonium chloride solution (10 mL) was used to quench the reaction mixture, followed by extraction with diethyl ether (3 × 25 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford an oil as the crude product. Flash column chromatography on silica gel (ether/petroleum ether, 2/98, v/v) afforded 107 mg of pure **28f** (107 mg, 45%) as a light yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5H), 5.65−5.60 (dd, J = 15.6, 7.35 Hz, 1H), 5.44−5.43 (dd, J = 15.1, 7.35 Hz, 1H), 3.80 (dd, J = 7.3, 3.65 Hz, 2H), 3.46 (q, J = 7.35 Hz, 1H), 2.18−2.11 (m, 1H), 1.34−1.22 (m, 6H), 1.01 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.92−0.86 (m, 3H), 0.00 (d, J = 9.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 138.3, 128.5, 128.3, 128.2, 126.3, 67.7, 51.3, 36.9, 36.8, 29.7, 26.0, 22.9, 20.8, 18.4, 14.2, −5.3, −5.4.

(*E*)-(2*S,3*S**)-2-*n*-Butyl-3-ethyl-4-hexen-1-ol (40).** Ethyl-2-*n*-butyl-3-ethyl-4-hexenoate (**29**; 1.0 g, 4.4 mmol) was dissolved in 20 mL of anhydrous ether and cooled to 0 °C in an ice bath, whereupon lithium aluminum hydride (168 mg, 4.4 mmol) was added slowly to the reaction flask. The mixture was heated at reflux for 12 h and then cooled in an ice bath, whereupon 1 mL of H_2O was added cautiously; the reaction mixture was diluted with 20 mL of ether, filtered through Celite, dried over $MgSO_4$, and concentrated in vacuo to afford a crude oil. Flash column chromatography on silica gel (ether/petroleum ether, 5/95, v/v) afforded 570 mg (70%) of pure **40** as a colorless oil: IR (neat) 3400 (br, s), 2958 (s), 2929 (s), 2872 (m), 1456 (m), 1377 (m), 1041 (m), 970 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49−5.44 (m, 1H), 5.28- 5.22 (m, 1H), 3.63 (dd, J = 11, 4.5 Hz, 1H), 3.57 (dd, J = 10.5, 6.5 Hz, 1H), 2.11−2.04 (m, 1H), 1.70 (dd, J = 6.5, 1.5 Hz, 3H), 1.52−1.13 (m, 9H), 0.91 (t, J = 7 Hz, 3H), 0.86 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 126.5, 64.6, 46.1, 44.9, 30.3, 26.4, 25.3, 23.1, 18.0, 14.1, 12.4; mass spectrum, EI, *m*/*z* (relative intensity), 184 (0.3), 137 (9), 97 (10), 82 (18), 69 (17), 67 (18), 83 (63), 55 (100).

(*E*)-(2*S,3*S**)-1-Tosyloxy-2-*n*-butyl-3-ethyl-4-hexene (41).** (*E*)-2-*n*-Butyl-3-ethyl-4-hexen-1-ol (**40**; 560 mg, 3.0 mmol) was dissolved in 10 mL of dry pyridine, and *p*-toluenesulfonyl chloride (1145 mg, 6.0 mmol) was added in one portion at room temperature. After it was stirred at room temperature for 12 h, the reaction mixture was quenched with 10 mL of H_2O and extracted with ether (3 × 25 mL), and the organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford **41** as an oil (924 mg, 100%). The crude material was used for the next step without any purification: IR (neat) 2959 (s), 2931 (s), 2873 (m), 1458 (m), 1364 (s), 1178 (s), 1098 (m), 962 (s), 834 (s), 667 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 6.5 Hz, 2H), 7.37 (d, J = 8 Hz, 2H), 5.18−5.13 (m, 1H), 5.01−4.96 (m, 1H), 4.00 (dd, J = 9.5, 4.5 Hz, 1H), 3.84 (dd, J = 10, 7.5 Hz, 1H), 2.47 (s, 3H), 2.00−1.92 (m, 1H), 1.57 (dd, J = 6.5, 1.5 Hz, 3H), 1.39−1.06 (m, 9H), 0.86 (t, J = 7 Hz, 3H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 139.3, 131.1, 129.7, 128.0, 127.5, 71.7, 44.8, 41.8, 29.9, 26.3, 25.0, 22.9, 21.6, 17.9, 13.9, 12.2; mass spectrum, EI, *m*/*z* (relative intensity), 281 (0.3), 225 (0.6), 207 (0.8), 166 (14), 137 (75), 109 (43), 96 (31), 95 (31), 91 (51), 83 (84), 82 (71), 81 (51), 67 (42), 55 (100).

(*E*)-(4*R,5*S**)-4-Ethyl-5-methyl-2-nonene (30).** To a suspension of lithium aluminum hydride (570 mg, 15.0 mmol, 5.0 equiv) in 15 mL of diethyl ether at 0 °C was added a solution of **62** (924 mg, 3.0 mmol, 1.0 equiv) in 5 mL of ether. The mixture was stirred at room temperature for 2 h before quenching with H_2O (5 mL). After extraction with ether (3 × 25 mL), the organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford a colorless oil. Flash column chromatography (silica gel, 100% petroleum ether) afforded pure **30** (260 mg, 55%) as a colorless oil: IR (neat) 2960 (s), 2929 (s), 2873 (m), 2361 (w), 1457 (m), 1378 (m), 969 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37−5.29 (m, 1H), 5.21−5.14 (m, 1H), 1.67 (dd, J = 6.4, 1.4 Hz, 3H), 1.44- 1.12 (m, 9H), 0.90−0.78 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 125.3, 50.4, 37.0, 33.1, 30.0, 24.2, 23.1, 18.1, 17.2, 14.2, 12.4; mass spectrum, EI, *m*/*z* (relative intensity), 168 (0.4), 126 (17), 84 (41), 83 (86), 69 (29), 55 (100).

(2*R,3*S**)-2-Ethyl-3-methyl-1-heptanol (31).** Starting material **30** (100 mg, 0.6 mmol, 1.0 equiv) was dissolved in a mixed solvent of dry methanol (10 mL) and dichloromethane (1 mL), the mixture was cooled to −78 °C, and a stream of O_3 was bubbled through the solution until a faint blue color appeared. Then the O_3 stream was maintained for 10 min more before the solution was purged with nitrogen gas for 5 min. The dry ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 2 h more. The solvent was then removed by rotary evaporator, the residue was dissolved in dry ether (5 mL), lithium aluminum hydride (240 mg, 6.0 mmol, 10.0 equiv) was added in one portion, and the mixture was then stirred at room temperature for 12 h. Water (2 mL) was slowly added to quench the excess lithium aluminum hydride, followed by extraction with ether (3 × 25 mL) and concentration in vacuo to afford a colorless liquid. Flash column chromatography on silica gel (ether/petroleum ether, 5/95, v/v) afforded pure **31** (80 mg, 84%) as a

dx.doi.org/10.1021/jo300304n | J. Org. Chem. 2012, 77, 4949−4967

colorless liquid: IR (neat) 3339 (br, s), 2959 (s), 2927 (s), 2874 (s), 1463 (m), 1380 (m), 1040 (m), 962 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.56−3.48 (m, 2H), 1.63−1.56 (m, 1H), 1.34−1.03 (m, 9H), 0.88−0.81 (m, 6H), 0.76 (d, J = 6.85 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.9, 47.2, 34.0, 32.7, 30.1, 23.1, 19.7, 15.7, 14.2, 12.7; mass spectrum, EI, m/z (relative intensity), 140 (1), 111 (13), 98 (19), 85 (68), 84 (69), 71 (87), 70 (58), 69 (65), 57 (100), 55 (96).

(2S*,3S*)-2-Ethyl-3-methyl-1-heptanol (32).[52] Following the protocols for the preparation of **31**, pure **32** (126 mg, 80%) was synthesized as a colorless oil from starting material **27f** after flash column chromatography (silica gel, ether/petroleum ether, 5/95, v/v): IR (neat) 3338 (br, s), 2960 (s), 2928 (s), 2874 (m), 2366 (w), 1460 (w), 1379 (w), 1036 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.58 (dd, J = 11, 5 Hz, 1H), 3.47 (dd, J = 11, 6 Hz, 1H), 1.55−1.50 (m, 1H), 1.33−1.02 (m, 9H), 0.88−0.81 (m, 6H), 0.78 (d, J = 6.85 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.4, 47.3, 33.9, 33.0, 30.1, 23.1, 21.4, 16.2, 14.2, 12.4; mass spectrum, EI, m/z (relative intensity), 140 (1), 111 (12), 98 (17), 85 (69), 84 (76), 71 (86), 69 (62), 59 (31), 57 (100), 55 (95).

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for **7a−c**, **10a,c,d**, **11a−d**, **12**, **13a−e**, **13a′**, **14a**, **15a**, **18−20**, **21a**, **24**, **25**, **27a−d,f**, **28e,f**, **30−32**, and **40−41**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dieterr@clemson.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was generously supported by the ACS Petroleum Research Fund (ACS-PRF 42853-AC). Support of the NSF Chemical Instrumentation Program for purchase of a JEOL 500 MHz NMR instrument is gratefully acknowledged (CHE-9700278).

■ REFERENCES

(1) For general reviews see: (a) Spino, C. In *The Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, U.K., 2009; Chapter 13, Part 2, pp 603−691. (b) Breit, B.; Schmidt, Y. *Chem. Rev.* **2008**, *108*, 2928−2951. (c) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995−3022. (d) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439. (e) Karlstrom, A. S. E.; Backvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; Chapter 8, pp 259−288. (f) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; Chapter 6, pp 188−223.

(2) For reviews focused on vinyl oxiranes see: (a) Pineschi, M.; Bertolini, F.; Di Bussolo, V.; Crotti, P. *Curr. Org. Syn.* **2009**, *6*, 290−324. (b) Hertweck, C.; Boland, W. *Recent Res. Dev. Org. Chem.* **1999**, *3*, 219−235. (c) Marshall, J. A. *Chem. Rev.* **1989**, 1503−1511. (d) Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *J. Org. Chem.* **1988**, *53*, 4274−4282.

(3) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063−3067.

(4) (a) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675−678. (b) Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898−4913 and references cited therein..

(5) (a) Yamamoto, Y.; Chounan, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 1024−1026. (b) Arai, M; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121−5129.

(6) Lipshutz, B. H.; Woo, K.; Gross, T.; Buzard, D. J.; Tirado, R. *Synlett* **1997**, 477−478.

(7) (a) Arai, M.; Lipshutz, B. H.; Nakamura, E. *Tetrahedron* **1992**, *48*, 5709−5129. (b) Aria, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489−5491.

(8) (a) Flemming, S.; Kabbara, J.; Nickisch, K.; Westermann, J.; Mohr, J. *Synlett* **1995**, 183−185. (b) Yoshimura, F.; Matsui, A.; Hirai, A.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2009**, *50*, 5126−5129.

(9) (a) Kiyotsuka, Y.; Katayama, Y.; Acharya, H. P.; Hyodo, T.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 1939−1951. (b) Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 7256−7259. (c) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719−1722.

(10) (a) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091−3093. (b) Aria, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1999**, *58*, 5121−5129. (c) Wu, Y.; De clercq, P.; vandewalle, M.; Bouillon, R.; Verstuyf, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1633−1636. (d) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676−10681. (e) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000−3006.

(11) (a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572−1573; *Tetrahedron: Asymmetry* **1997**, *8*, 3821−3828. (b) Yamamoto, K.; Ogura, H.; Jukuta, J.-i.; Inoue, H.; Hamada, K.; Sugiyama, Y.; Yamada, S. *J. Org. Chem.* **1998**, *63*, 4449−4458. (c) Chounan, Y.; Ono, Y.; Nishii, S.; Kitahara, H.; Ito, S.; Yamamoto, Y. *Tetrahedron* **2000**, *56*, 2821−2831. (d) Kireev, A.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630−2640.

(12) (a) Ibuka, T.; Tanaka, M.; Nemoto, H.; Yamamoto, Y. *Tetrahedron* **1989**, *45*, 435−442. (b) Hirai, A.; Matsui, A.; Komatsu, K.; Tanino, K.; Miyashita, M. *Chem. Commun.* **2002**, 1970−1971.

(13) (a) Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055−4061. (b) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864−72. (c) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem.* **1990**, *102*, 816−18. (d) Yamamoto, Y.; Chounan, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 1024−1026.

(14) (a) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875−4886. (b) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652−654.

(15) Marino, J. P.; Anna, L. J.; Fernandez de la Pradilla, R.; Martinez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462−6473.

(16) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4257−4259.

(17) Dieter, R. K.; Guo, F. *Org. Lett.* **2008**, *10*, 2087−2090.

(18) (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251−253. (b) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689−690. (c) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552−5555. (d) Dieter, R. K.; Gore, V. K.; Chen, N. *Org. Lett.* **2004**, *6*, 763−766. (e) Niida, A.; Tanigaki, H.; Inokuchi, E.; Sasaki, Y.; Oishi, S.; Ohno, H.; Tamamura, H.; Wang, Z.; Peiper, S. C.; Kitaura, K.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2006**, *71*, 3942−3951. (f) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017−6028.

(19) (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111−2114. (b) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059−1061.

(20) (a) Backvall, J.-E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615−6621. (b) Persson, E. S. M.; Backvall, J.-E. *Acta Chem. Scand.* **1995**, *49*, 899−906. (c) Yamazaki, T.; Umetani, H.; Kitazume, T. *Tetrahedron Lett.* **1997**, *38*, 6705−6708.

(21) Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985−4988.

(22) For reviews see: (a) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339−2372. (b) Nakamura, E, Yoshikai, N. In *The Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, U.K., 2009; Chapter 1, Part 1, pp 1−21. (c) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862−12863. (d) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287−6293.

(23) Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771−2773.
(24) For experimental confirmation of Cu(III) complexes in allylic systems see: (a) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244−11245. (b) Bartholomew, E. R.; Bertz, S. H.; Cope, S. K.; Murphy, M. D.; Ogle, C. A.; Thomas, A. A. *Chem. Commun.* **2010**, *46*, 1253−1254. For Cu(III) complexes prepared from various Cu(I) precursors see: (c) Bertz, S. H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7082−7085. For Cu(III) complexes prepared from Me_4CuLi see: (d) Bertz, S. H.; Murphy, M. D.; Ogle, C. A.; Thoms, A. A. *Chem. Commun.* **2010**, *46*, 1255−1256. For Cu(III) complexes in 1,4-additions see: (e) Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208−7209.
(25) The addition of Lewis acids (e.g., BF_3, $ZnCl_2$, Ti^{IV}, $AlCl_3$) to organocopper compounds increases the S_N2' selectivity: see ref 22b, p 329, and references cited therein. Thus, while a Lewis acid additive favors S_N2' selectivity, intramolecular chelation by the cuprate counterion in an olefin−cuprate complex provides alternative possiblities.
(26) (a) Boche, G.; Bosold, F.; Marsch, M.; Harms, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1684−1686. (b) Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 79−81. For an extensive NMR study of Li cation cuprate ligand coordination effects see: (c) Bertz, S. H.; Hardin, R. A.; Murphy, M. D.; Ogle, C. A.; Richter, J. D.; Thomas, A. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 2681−2685.
(27) (a) Bomparola, R.; Davies, R. P.; Hornauer, S.; White, A. J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5812−5815. (b) Davies, R. P. *Coord. Chem. Rev.* **2011**, *255*, 1226−1251.
(28) (a) Eaborn, C.; El-Hamruni, S. M.; Hill., M. S.; Hitchcock, P. B.; Smith, J. D. *Dalton Trans.* **2002**, 3975−3979. (b) Eaborn, C.; Hill, M. S.; Hitchcock, P. B.; Smith, J. D. *Organometallics* **2000**, *19*, 5780−5783.
(29) (a) Gschwind, R. M. *Chem. Rev.* **2008**, *108*, 3029−3053. (b) Gartner, T.; Gschwind, R. M. In *The Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, U.K., 2009; Chapter 4, Part 1, pp 163−215. (c) Putau, A.; Koszinowski, K. *Organometallics* **2011**, *30*, 4771−4778.
(30) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley-Interscience: New York, 1988; Appendix 4, pp 1386−1387.
(31) Huheey, J. E. *Inorganic Chemistry: Principles of Structure and Reactivity*, 3rd ed.; Harper Collins: New York, 1983; Chapter 7, p 314.
(32) (a) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2006**, *25*, 3501−3507. (b) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2005**, *24*, 4116−4118.
(33) Neither solution nor X-ray crystal structures have been determined for zinc cuprate reagents, and transmetalation of a methyl ligand from lithium dimethylcuprate to $TiCl(OiPr)_3$ and to $ZnCl_2$ has been reported (see ref 7a, footnote 24, and ref 5b, footnote 16).
(34) Jastrzebski, J. T. B. H.; Boersma, J.; Van Koten, G. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, U.K., 2006; Chapter 2, Part 1, pp 31−135.
(35) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 348−350.
(36) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042−8047.
(37) Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. S.-H. *J. Org. Chem.* **2008**, *73*, 9426−9434.
(38) Henze, W.; Vyater, A.; Krause, N.; Gschwind, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 17335−17342.
(39) Simple cuprate S_N2 substitution reactions are faster in THF than in Et_2O; see: Whitesides, G. M.; Fischer, W. F., Jr.; Filippo, J. S., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871−4882.
(40) (a) Kingsbury, C. L.; Smith, R. A. J. *J. Org. Chem.* **1997**, *62*, 4629−4634. (b) Kingsbury, C. L.; Smith, R. A. J. *J. Org. Chem.* **1997**, *62*, 7637−7643. (c) Kingsbury, C. L.; Sharp, K. S.; Smith, R. A. J. *Tetrahedron* **1999**, *55*, 14693−14700.
(41) Bertz, S. H.; Miao, G.; Eriksson, M. *J. Chem. Soc., Chem. Commun.* **1996**, 815−816.
(42) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023−11024.
(43) This general trend is illustrated by the preferential formation of the least substituted pyrrolidine enamine of 2-methylcyclohexanone. For a review see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413.
(44) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; Chapter 11, pp 696−697.
(45) For studies on the effect of Cu(I) precursor (i.e., CuX, X = Cl, Br, I, CN) in allylic substitution reactions see refs 9a, 10e, 18f, and 20b, with ref 20b providing a detailed study.
(46) The overall yields for the three-step sequence **7a** to **10** (**a** (45%), **c** (53%), **d** (52%)), **7b** to **11** (**a** (45%), **b** (60%), **c** (57%), **d** (57%)), and **12a** to **27** (**a** (65%), **b** (52−77%), **c** (55−65%), **d** (60%), **e** (63%), **f** (39−73%)) are all generally in the 50% range or better. Acetates **9a**,**b** were prepared in 90% yield.
(47) For alternative approaches to α,β-disubstituted γ,δ-enoates and synthetic applications see citations 12−14 in ref 17.
(48) Kobayashi, Y.; Yoshida, S.; Asano, M.; Takeuchi, A.; Acharya, H. P. *J. Org. Chem.* **2007**, *72*, 1707−1716.
(49) Zhu, G.; Negishi, E.-i. *Chem. Eur. J.* **2008**, *14*, 311−318.
(50) Crandall, J. K.; Rojas, A. C. *Org. Synth.* **1976**, *55*, 1−3.
(51) Martin, R.; Schmidt, A. W.; Theumer, G.; Krause, T.; Entchev, E. V.; Kurzchalia, T. V.; Knolker, H.-J. *Org. Biomol. Chem.* **2009**, *7*, 909−920.
(52) Note that the ^1H and ^{13}C NMR data of **32** are inconsistent with a previous literature report: Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535−2538.