1,2-Asymmetric Induction in the S_N2'-Allylation of Organocopper and Organozinc Reagents

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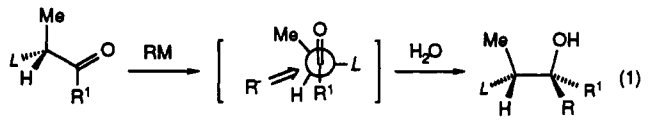
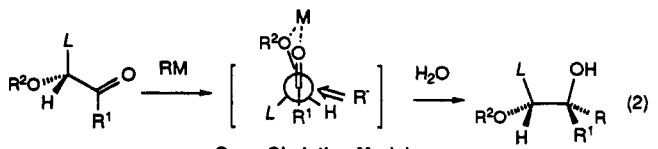
The S_N2'-selective reaction of organocopper or organozinc reagents with allylic chlorides having a chiral center at the δ-position proceeds with up to 100% diastereoselectivity. The observed 1,2-asymmetric induction conforms to pure steric control (Cram–Felkin–Anh model) even in cases where conventional chelation control may seem to operate, and the level of the selectivity was found to be much higher than those found for the additions of organometallics to structurally comparable α-substituted carbonyl compounds.

Studies of diastereoselective conversion of a trigonal carbon center to a tetrahedral one under the stereochemical influence of a nearby chiral center have provided valuable mechanistic and synthetic information for organic chemists. Among such studies, investigations of 1,2-asymmetric induction in the carbonyl additions of an organometallic, generically called Cram's rule, have been most intensive and fruitful.

Through experimental and theoretical analysis of these reactions, the original Cram's rules[1] have been reformulated and are now referred to as the Felkin–Anh[2] and Cram's chelation models.[1,3] In the former (eq 1), the argument is constructed mainly on steric and/or stereoelectronic considerations, and, in the latter (eq 2), primarily



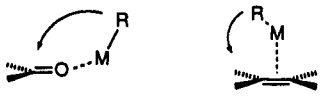
L = Ph, halogen etc. Felkin-Anh Model



Cram Chelation Model

on substrate's bidentate ligation to the metal countercation. The levels of the diastereoselectivities may be 2:1–9:1 for the sterically controlled Felkin–Anh cases, and 9:1–20:1 for the chelation controlled cases (vide infra).

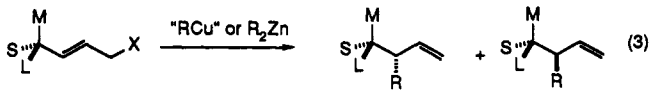
1,2-Asymmetric induction in nucleophilic additions of organometallics (RM) to an olefin have been much less widely studied than carbonyl additions, whereas they are of no less importance. It is useful to note that despite their apparent similarity, these two reactions may differ in the process where stereochemical face-selection is achieved. In the carbonyl addition of an organometallic, the face-selection may be achieved during the course of the *intramolecular* conversion of the initially formed RM/carbonyl complex A to the product (as indicated by an arrow),[3b] while in the olefin reaction, π-face is already selected at the stage of the initial π-metal complex **B**. In addition, the formation of a five-membered chelate such as the one shown in eq 2 seems difficult for the addition of RM to an olefinic substrate (i.e., allylic alcohol derivative), since orbitals of two coordination site—the oxygen lone pair which accepts the metal and the olefinic π-orbital which accepts the R^- group—appear to be misaligned.



A (metal-n complex) **B** (metal-π complex)

Nucleophilic addition of RM to a simple unactivated olefin being difficult, conjugate additions to an electron-deficient olefin have generally served as an operational surrogate and provided a standard criterion for consideration of olefinic Cram's rule. The selectivity of the 1,2-asymmetric induction,[4] however, is not entirely systematic and the level of induction is similar to that observed in Cram carbonyl additions.

Sometime ago, we have focused on the little-explored S_N2'-allylation reaction of an organometallic reagent as a method to accomplish diastereoselective C–C bond formation by nucleophilic attack of an alkyl group to an olefinic carbon center.[5] The general scheme is shown in eq 3. However, in order to make such reactions practically



C (X = Cl etc.)

useful, we first needed to control the S_N2/S_N2' regiochemical problem, and found that organocopper reagents composed of a mixture of R^-, Cu, and a Lewis acidic metal (i.e., Zn[6] and Ti)[7] are particularly S_N2'-selective for the substrates possessing the general structure C.[8] Recently, we also found that dialkylzinc reagents reacting in the

(1) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(2) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(3) (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1992**, *114*, 4536.
(4) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224. (b) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (c) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464. (d) Isobe, M.; Nishikawa, T.; Herunsalee, A.; Tsukiyama, T.; Hirose, Y.; Shimokawa, K.-i.; Goto, T. *Pure Appl. Chem.* **1990**, *62*, 2007 and refs therein. (e) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009.
(5) Preliminary communication: Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091.
(6) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5515.

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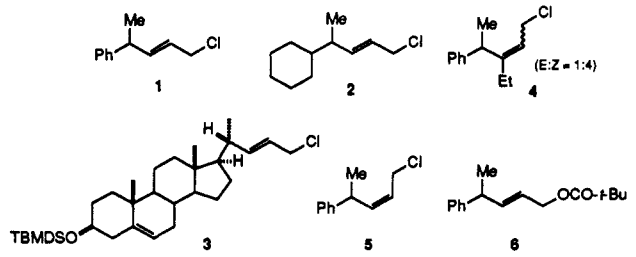
presence of a basic additive are highly regioselective.[9] With these new reagents in hand, we have carried out systematic studies of the 1,2-asymmetric induction to find that the allylation proceed with the same *formal* sense of diastereoselectivity found in the carbonyl additions but with much higher levels of selectivity often approaching 100%. In this article we report the details of the experimental results and propose some mechanistic interpretations.[10]

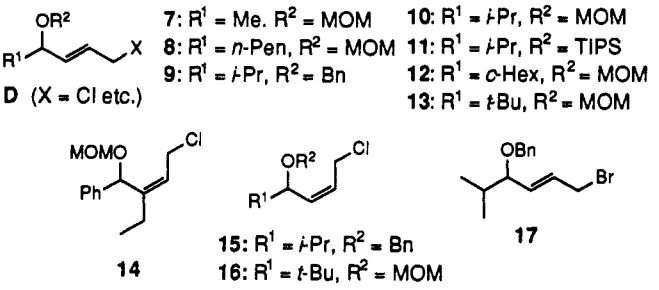
Substrate Selection. The purpose of the present investigations was two-fold to make stereochemical comparison between the carbonyl addition and the alkylation reaction and to establish the latter as a general and reliable synthetic protocol. To these ends, we have examined a variety of allylic halides possessing the general structure C with variation of the substituents, the leaving groups, and the incoming nucleophile to study the S_N2/S_N2'-regiochemistry and the 1,2-asymmetric induction.

2-Phenylpropionaldehyde is an archetypal stereochemical probe in the carbonyl addition chemistry. The Cram selectivity may be typically 3:1 with common organolithium and organomagnesium reagents,[1] and at best 93:7 with other organometallics.[11] We have taken 1-chloro-4-phenyl-2-pentene (**1**) as the corresponding olefinic equivalent in order to determine the basic steric requirements in the S_N2'-allylation reaction.

We have also examined the cyclohexyl substrate **2** and the steroidal allylic chloride **3**. Additions of a magnesium reagent to 2-cyclohexylpropionaldehyde and a steroidal C22-aldehyde corresponding to **3** show the Cram selectivity of only ca. 2:1 (MeMgI)[12] and 7:1 (Et_2Mg),[13] respectively. Addition of a titanium reagent to the same C22 aldehyde shows ca. >6:1 selectivity.[14] In addition to these "aldehyde equivalents", we have also studied a "ketone equivalent" **4**.



To probe the "chelation effects", we examined variation of the structure **D** in two ways: variation of the δ-alkyl substituent and the protective group. We thus studied the basic carbon structures **7**–**13**, which bear methyl (**7**), pentyl (**8**), isopropyl (**9**–**11**), cyclohexyl (**12**), and *tert*-butyl (**13**) groups as R^1. In addition, we have examined benzyl (Bn, **9**), methoxymethyl (MOM, **10**), and triisopropylsilyl (TIPS, **11**) groups as a protective group on the oxygen atom. It is well established in carbonyl chemistry that an α-alkoxy group allows Lewis acidic organometallics to achieve chelation-controlled reactions, and an α-*O*-TIPS group effectively inhibits such chelation.[15] We also investigated **14** as a "ketone equivalent".



In S_N2'-alkylation chemistry, there are unique issues that are not present in carbonyl chemistry: geometrical isomerism and the leaving group. To address the former issue, we have examined three substrates, **5**, **15**, and **16**. The latter was investigated for pivaloxy (**6**) and bromide groups (**17**).

S_N2'-Selective Organometallics. The standard Gilman reagents (R_2CuLi) and RCu reagents showed rather poor S_N2'-regioselectivity for the substrates that we examined. We thus developed a new regioselective reagent, a reagent mixture consisting of an alkyl anionic group, copper(I), and zinc(II) or titanium(IV). Two types of reagents were examined with equal success: stoichiometric copper reagents prepared by mixing 1 equiv each of a Gilman reagent and $ZnCl_2$ or $TiCl(O\text{-}i\text{-}Pt)_3$ in THF,[5] and a catalytic copper reagent generated from R_2Zn[3b] or $RTi(O\text{-}i\text{-}Pr)_3$[7] and a catalytic amount of Cu(I) halide (e.g., 5-7.5 mol% of CuI:2LiCl) in THF.[16]

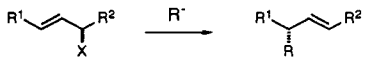
Besides organocopper reagents, we were intrigued by the chemistry of organozinc reagents[9] because of the following reasons. While RCu(I) reagents have been widely employed for the allylation reactions, they are by no means a good prototype for rational interpretation of the observed stereoselectivities, because of mechanistic ambiguity of the allylation of organocopper reagents.[17] Since this problem arises from the possibility of intervention of a Cu(III) intermediate,[18,19] the behavior of organozinc reagents (R_2Zn), for which such a hypervalent species is improbable, should be amenable to more straightforward interpretations.

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

(8) Yamamoto's "$RCu\cdot BF_3$" reagent is also highly regioselective for the substrate **D**: Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.

(9) Arai, M.; Kawasuji, T.; Nakamura, E. *Chem. Lett.* **1993**, 357.

(10) Another stereochemical problem, which is not directly related to the subject of the present research, is the stereochemical relationship between the leaving and the incoming groups. We have shown for the titanium/copper reagents that the stereochemistry is anti as shown below (ref 7).



(11) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem. Int., Ed. Engl.* **1982**, *21*, 135.

(12) Cram, D. J.; Greene, F. D. *J. Am. Chem. Soc.* **1953**, *75*, 6005.

(13) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1985**, *107*, 6411.

(14) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 2138.

(15) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.

(16) Recent spectroscopic studies indicated that complete transfer of the alkyl group from copper to zinc or titanium takes place (unpublished results by Arai, M.; Nakamura, E.; Lipshutz, B. H.); however, it is clear that a certain type of mixed copper/zinc or copper/titanium reagent is responsible for the observed high S_N2'-regioselectivity, since neither alkylzinc or alkyltitanium reagents themselves are reactive alkyl donors under the low-temperature conditions examined.

(17) Alexakis, A.; Marek, I.; Mageney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

(18) Crabbé, P.; Barreiro, E.; Dollat, J.-M.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1976**, 183. Dollat, J.-M.; Luche, J.-L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1977**, 761.

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

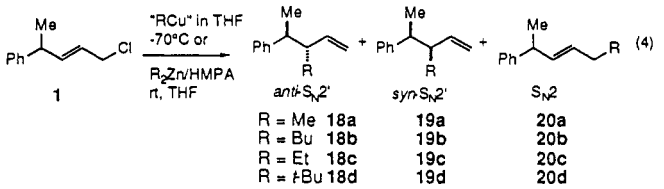
Table I. S_N2'-Allylation of Various Organocopper Reagents with 1, 5, and 6 (eq 4)[a]

entry	substrate	"RCu"	% yield (18 + 19 + 20)	% S_N2'[b] (18 + 19 vs 20)	% ds[b] (18/19)	major product
1	1	Bu_2CuLi	87	37	96	**18b**
2	1	$Bu_2CuLi/ZnCl_2$	83	95	95	**18b**
3	1	(at −95 °C)	85	99.5	97	**18b**
4	1	$Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$/cat. Cu[c]	91	99.2	95	**18b**
5	1	$BuCu\cdot BF_3$	92	98	96	**18b**
6	1	$Me_2CuLi/ZnCl_2$	72	98	95	**18a**
7	6	$Bu_2CuLi/ZnCl_2$	NR[f]	NR	NR	–
8	6	BuMgBr/cat. Cu[d]	97	44	92	**18b**
9	6	$BuCu\cdot BF_3$[e]	15	4	84	**18b**
10	5	$Bu_2CuLi/ZnCl_2$	77	99	78	**18b**
11	5	$Me_2CuLi/ZnCl_2$	48	99	88	**18a**

[a] Reactions were carried out in THF at −70 °C except as noted otherwise. Yields were not optimized. [b] Determined by GC. [c] At −70 °C; 6 h. Six mole percent CuI·2LiCl. [d] At 0 °C, 1 h; 5 mol% CuCN. [e] At −70 °C to room temperature, 6 h. [f] No reaction.

Results

Investigation of Steric Effects. The chloride **1** was studied as a prototypical probe of the steric effects (eq 4, Table I). The reaction was various S_N2'-selective reagents



based on copper/Lewis acid combinations proceeded highly stereoselectively (entries 2–6) giving a mixture of three products **18**, **19**, and **20**. The regioselectivity [(**18** + **19**)/**20**] was 95–99%, and the diastereomeric selectivity (**18**/**19**) was 95–96% at −70 °C. The observed sense of the diastereoselectivity conforms to the standard Cram's rule, but the level is much higher than in the Cram additions to a carbonyl group (vide supra). At lower temperature (−95 °C, entry 3), the regio- and diastereofacial selectivities were improved to the level of 99.5 and 97%, respectively. The $R_2CuLi/ZnCl_2$ reagent was unreactive to pivalate **6** (entry 7).

It is notable that, regardless of the level of the S_N2'-regioselectivity, high *anti*-diastereoselectivity was consistently observed for a variety of reagents. Thus, the reaction of the chloride **1** with zinc/copper, titanium/copper, and BF_3/copper reagents (entry 5) as well as the standard Gilman reagents (entry 1) and the reactions of the allylic pivalate **6** (entries 7 and 8) exhibited the same level of diastereoselectivity. The stereochemical assignments was made for **18a** through chemical correlation to (2*R**,3*S**)-2,3-dimethylsuccinic acid (see supplementary material).

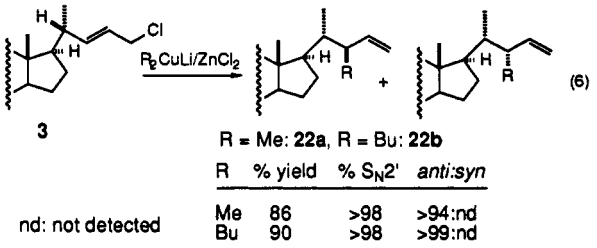
The reaction of the *cis*-allylic chloride **5** was also selective (entries 10 and 11), yet the selectivity was shifted slightly toward the *syn* product **19** as was also observed for other cases (vide infra).

Replacement of the phenyl group with a cyclohexyl or a steroidal group improved the diastereoselectivity to 100% without affecting either the sense of the diastereoselectivity or the S_N2'-regioselectivity (eqs 5 and 6). Thus, the reaction of allylic chlorides **2** and **3** with $Bu_2CuLi/ZnCl_2$ and $Me_2CuLi/ZnCl_2$ gave a single, stereochemically pure S_N2'-product in high yield. Stereochemical assignment of **21b** was made by correlation to the phenyl compound **18b** through hydrogenation and that of **22a** by single crystal X-ray crystallography.[20]

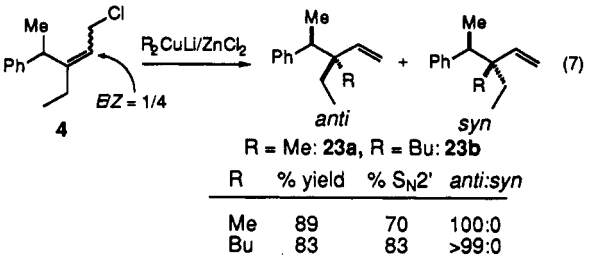
Table II. Diastereoselective S_N2' Reaction of Dialkylzinc with 1 (eq 4)[a]

entry	R_2Zn	additive	% yield	% S_N2'	% ds (18/19)[b]	major product
1	$Bu_2Zn\cdot 2LiCl$	HMPA	87	97	89	**18b**
2	$Bu_2Zn\cdot 2LiCl$	TMEDA	83	97	87	**18b**
3	$Bu_2Zn\cdot 2LiCl$	DMF	48	96	87	**18b**
4	$Me_2Zn\cdot 2LiCl$	HMPA	68	83	84	**18a**
5	Et_2Zn	TMEDA	87	97	87	**18c**
6	$t\text{-}Bu_2Zn\cdot 2LiCl$	HMPA	52	49	87	**18d**

[a] The reaction period is 12–24 h in entries 1–3, 5, and 6, and 72 h in entry 4. The reactions were carried out in THF, and yields are not optimized. [b] Determined by capillary GC analysis.



The reaction of the "ketone equivalent" **4** also showed 100% diastereoselectivity (eq 7), but the regioselectivity



was lowered probably due to steric reasons. The stereochemistry of **23** was assigned by analogy to the above cases.

Dialkylzinc reagents undergo S_N2'-regioselective reaction with allylic chlorides at room temperature in the presence of a coordinating ligand such as HMPA and TMEDA (eq 4, Table II).[9] The sense and level of the diastereoselectivity were found to be very similar to those of the organocopper reagents. Thus, the reaction of Bu_2Zn/HMPA with **1** at 25 °C showed 89% *anti*-selectivity with 97% regioselectivity (entries 1–3). This level of selectivity roughly corresponds to 95% found for the $Bu_2CuLi/ZnCl_2$ reagent at −70 °C (Table I, entry 2). Parallel

(20) Results to be published by Professor Y. Ohashi and A. Uchida.

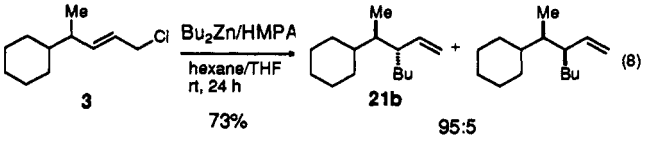
Table III. Diastereoselective S_N2'-Allylation of γ-Alkoxy Allylic Chlorides (eq 9)[a]

run	RCl	"RCu"	%-yield	%-S_N2'[b]	%ds[b] (*antisyn*)	S_N2' product
1	7	$Bu_2CuLi/ZnCl_2$	79	98	65	**24b**
2	8	$Me_2CuLi/ZnCl_2$	90	90	70	**26a**
3	8	$Bu_2CuLi/ZnCl_2$	73	99	75	**26b**
4	9	$Me_2CuLi/ZnCl_2$	98	90	100	**29a**
5	9	$Bu_2CuLi/ZnCl_2$	100	98	100	**29b**
6	9	Bu_2Zn/cat. Cu[c]	80	98	100	**29b**
7	9	$Bu_2Ti(O\text{-}iPr)_3$/cat Cu[c]	92	99	100	**29b**
8	9	$BuCu\cdot BF_3$	87	99	100	**29b**
9	9	Bu_2CuLi	61	12	100	**29b**
10	10	$Bu_2CuLi/ZnCl_2$	67	99	100	**30b**
11	11	$Bu_2CuLi/ZnCl_2$	93	98	100	**32b**
12	12	$Bu_2CuLi/ZnCl_2$	86	99	100	**34b**
13	13	$Bu_2CuLi/ZnCl_2$	79	99	100	**36b**

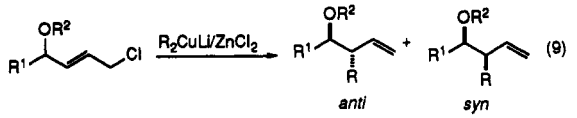
[a] Reactions were carried out in THF at −70 °C except in entries 2 and 4 at −70 °C to room temperature. Yields were not optimized. [b] Determined by capillary GC analysis. [c] Six mole percent $CuBr\cdot Me_2S$. [d] Six mole percent CuI·2LiCl.

results were found for $Me_2Zn\cdot LiCl$, *tert*-$Bu_2Zn\cdot LiCl$, and salt-free Et_2Zn (entries 4–6, Table II). The stereochemistry of **18a** and **18c** was assigned by chemical correlation of (2*R**,3*S**)-2,3-dimethylsuccinic acid and (2*R**,3*S**)-2-ethyl-3-methylsuccinic acid, respectively, and that of **18b** and **18d** by analogy.

As in the organocopper reactions, higher diastereoselectivity was observed with δ-cyclohexyl-substituted allylic chloride **12** (eq 8).



Investigation of "Chelation Effects". The diastereoselectivity of the δ-alkoxy allylic chloride was next examined to probe the "chelation effects" in the allylation reaction (eq 9, Table III). As in the previous cases, the



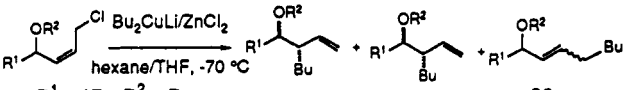
	anti	*syn*
7: R^1 = Me, R^2 = MOM	24	25
8: R^1 = *n*-Pen, R^2 = MOM	26	27
9: R^1 = *i*-Pr, R^2 = Bn	28	29
10: R^1 = *i*-Pr, R^2 = MOM	30	31
11: R^1 = *i*-Pr, R^2 = TIPS	32	33
12: R^1 = *c*-Hex, R^2 = MOM	34	35
13: R^1 = *t*-Bu, R^2 = MOM	36	37

a: R = Me, b: R = Bu

reactions of the S_N2'-selective reagents with *trans*-allylic chlorides proceeded smoothly at −70 °C in THF to give the desired regioisomer in high yield. Most surprisingly, the stereoselectivity was always ~100% (generally >99.7% ds by capillary GC) except for the straight-chain substrates **7** and **8** (entries 1–3). The sharp contrast between the primary alkyl R^1 group (**7** and **8**) and the secondary or tertiary R^1 group (others) is remarkable. Stereochemistry was assigned for **26**, **28**, **30**, **32**, and **36** by chemical derivatization (see supplementary material).

The observed selectivity conforms, at least formally, to the "chelation control". However, if chelation is indeed important, much lower selectivity would result for the TIPS-protected substrate **11**, since this group strongly inhibits chelation.[15] In actuality, the TIPS-protected substrate **11** reacted with equally high *anti*-diastereoselectivity of 100% (entry 11), demonstrating that simple steric effects are effective enough to induce 100% diastereoselectivity. It may also be noted that, as in the cases listed in Table I, the diastereoselectivity is insensitive to the exact nature of the copper reagent.

To investigate the effects of *E*/*Z* isomerism, we examined the substrates **15** and **16** (eq 10). The reaction of the

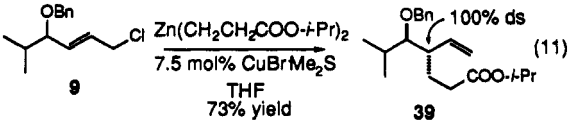


15: R^1 = *i*-Pr, R^2 = Bn — **28** — **29** — **38**
16: R^1 = *t*-Bu, R^2 = MOM — **36** — **37** (10)

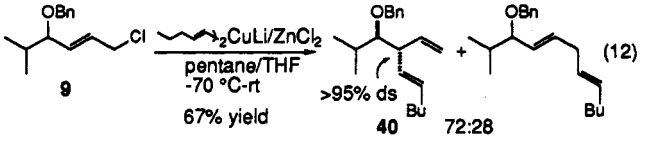
chloride	%yield	% S_N2'	*anti*:*syn*
15	100 %	98	90:10
16	37%	99	40:60

Z-allylic chloride **15** exhibited the same *anti*-selectivity but with lower ds of 90%. Most interestingly, the *tert*-butyl-substituted Z-allylic chloride **16** reacted very slowly at −70 °C (62% recovery of **16** after 15 h) and exhibited 60:40 diastereoselectivity. This sluggishness of the reaction suggests that the electrophilic trigonal center is severely hindered. Interestingly, in the reaction of **15** with Bu_2CuLi, the S_N2-product **38** produced was a 1:1 mixture of *cis* and *trans* isomer, indicating that the product was not formed via a simple S_N2-mechanism.

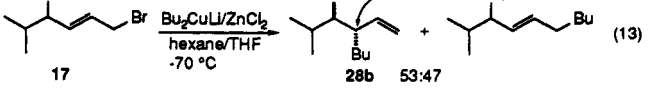
The excellent *anti*-selectivity was found to be general for more complex copper reagents. Thus, copper-catalyzed reaction of zinc homoenolate[21] with **9** proceeded regio- and stereoselectively to afford the S_N2'-allylation product **39** in quantitative yield (eq 11), but the selectivity dropped



for the primary alkyl-substituted substrate **8** was also moderate (76% ds, 96% S_N2'). The reaction of **9** with a vinyl copper reagent was only 72% regioselective, but hghly diastereoselective (>95% *anti*, stereochemistry assigned by analogy) to give 1,4-diene **40** in a stereocontrolled manner (eq 12).



The reaction of allylic bromide **17** proceeded smoothly, with poor S_N2'-selectivity (53%),[22] but notably, with 100% *anti*-selectivity for the S_N2'-reaction pathway (eq 13).



(21) Nakamura, E.; Kuwajima, I. *Org. Synth.* **1987**, *66*, 43. Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056.

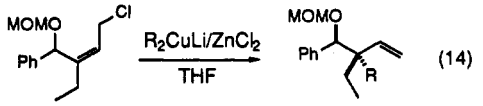
(22) S_N2'-selective reactions of allylic bromides have been noted in some cases: Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395.

Table IV. Reaction of R_2Zn·2LiCl/2HMPA with δ-Alkoxy Allylic Chloride (eq 15)[a]

entry	chloride	R_2Zn (R)	reaction time (h)	%-yield	%-S_N2'	%ds (*antisyn*)	major product
1	8	Me	48	62	88	74:26	**26a**
2	9	Bu	18	70	94	100:0[b]	**28b**
3	11	Bu	24	55[c]	92	100:0[b]	**32b**
4	12	Bu	20	85	75	100:0[b]	**34b**
5	13	Bu	12	89	96	100:0[b]	**36b**

[a] The reactions were carried out in THF at room temperature. [b] Single isomer by GC and ^1H NMR. [c] The starting halide (36%) was recovered.

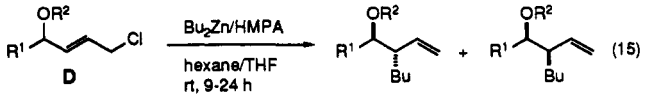
The ketone equivalent" **14** was also completely *anti*-diastereoselective but with slightly reduced regioselectivity. Stereochemistry was assigned by correlation to an aldol of known stereochemistry (see supplementary material).



14 **41a**: R = Me; **41b**: R = Bu

R	temp	% yield	% S_N2'	*anti*:*syn*
Me	-40 °C	89	70	100:0
Bu	-70 °C	83	83	>99:0

The diastereoselectivity of organozinc reagents was also examined for some representative δ-alkoxy allylic chlorides (Table IV). As in the sterically controlled cases (vide supra), the results were surprisingly similar to those obtained for organocopper reactions. First, δ-primary alkyl-substituted δ-alkoxy allylic chloride **8** reacted with much lower diastereoselectivity than secondary and tertiary alkyl-substituted chlorides (**9** and **11-13**, entries 2–5). Second, TIPS protection did not change the diastereoselectivity, but the reaction was distinctly slower than the corresponding benzyl compound **9**, leaving much of the starting material unreacted.



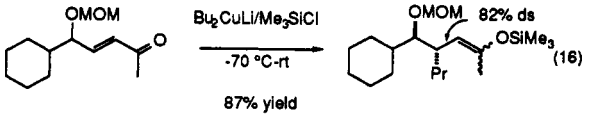
Discussion

There have been found several notable features of the allylation reaction. The observations are summarized below.

(1) The S_N2'/S_N2-regioselectivity is sensitive to the nature of the organocopper and organozinc reagents, but the diastereoselectivity of the S_N2'-allylation pathway is dependent only on the substrate. More importantly, the selectivity profiles of organocopper and organozinc reagents over a wide range of substrates are essentially the same as summarized in Table V.

(2) For the cases where pure steric effects operate (i.e., substrate type **C**), the selectivity conforms to the standard Cram's rule established for carbonyl additions. However, the level of the selectivity is much higher, reaching 100% for the selection between cyclohexyl, methyl, and hydrogen substituents (eq 5). Some literature examples of Cram additions are shown in Figure 1 for comparison.

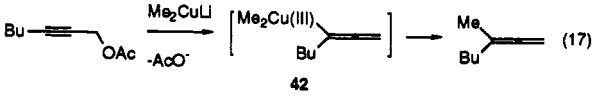
(3) For the reaction of δ-alkoxy allylic chlorides, the diastereoselectivity was virtually complete in many cases (eq 9) and conforms, at least formally, to chelation control. The level of the selectivity is higher than the comparable cases of the conjugate addition reaction of organocopper reagents[4] as illustrated by the example in Figure 1[23] and in eq 16 (stereochemistry assigned by analogy to the present



and the related cases). However, the insensitivity of the selectivity to the oxygen protective group (i.e., **9** vs **11**) indicates that chelation is *not required* to obtain the observed sense and level of diastereoselectivity, and that the selectivity can be rationalized by simple steric effects (vide infra). On the other hand, a significantly reduced rate of the reaction with Bu_2Zn/HMPA upon going from the benzyloxy compound **9** to the TIPS-ether **11** may suggest that chelation may also play some role in the reaction of benzyl- and MOM-protected substrates.

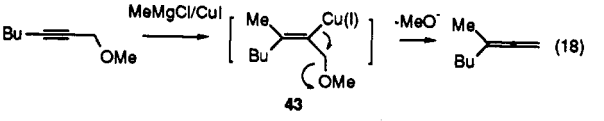
(4) *cis*-Olefins consistently exhibit lower selectivity than the corresponding *trans*-olefins. Favoring the *syn*-diastereomer, the *tert*-butyl-substituted *cis*-olefin **16** may represent the extreme end of this trend (eq 10).

There have been proposed two mechanisms for S_N2'-allylation of organocopper reagents, both of which have received experimental support for the reactions of propargylic substrates. One assumes that the *nucleophilic attack of the copper atom* to the olefinic carbon forms a Cu(III) intermediate such as **42**,[18] which then undergoes reductive elimination to give the allylation product (eq 17).[19] Another involves a straightforward nucleophilic



42

mechanism proceeding through *nucleophilic attack of the alkyl group* on the copper atom leading directly to the allylation product (eq 18). In the case of the propargyl



43

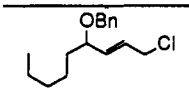
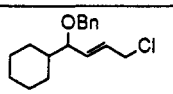
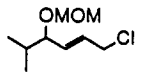
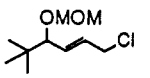
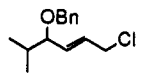
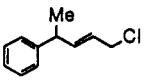
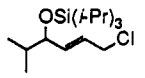
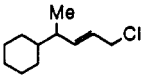
alkoxide, the carbometalation intermediate **43** has been chemically characterized.[17]

Of these two possibilities, only the latter is available for the allylation of organozinc reagents described above, since a hypervalent Zn(IV) species corresponding to **42** is improbable. Carbometalation reactions of organozinc compounds are well known,[24] and a mechanism related to the one shown in eq 18 appears entirely feasible. In the light of the observed stereochemical parallelism between organocopper and organozinc reagents, it is probable that the second mechanism operates also for the organocopper reactions.

Taken together, the experimental observation for **C** favors a transition state model **E** for the 1,2-asymmetric induction in the allylation of organocopper and organozinc compounds (eq 19). This model assumes the standard, sterically controlled Felkin–Anh substituent conformation

(23) Heathcock, C. H.; Kiyooka, S.-i.; Blumenkopf, J. A. *J. Org. Chem.* **1984**, *49*, 4214.
(24) Cf. Lehmkuhl, H. *Organometallics in Organic Synthesis*; de Meijere, A.; tom Dieck, H., Eds.; Springer: Berlin, 1988; p 185.

Table V. Comparison of the Diastereoselectivity (%ds favoring *anti* products) between Organocopper and Zinc Reagents

	"BuCu" (−70 °C)	Bu_2Zn (rt)		"BuCu" (−70 °C)	Bu_2Zn (rt)
	70% ds (MeCu)	74 (Me_2Zn)		100	100
	100	100		100	100
	100	100		95	89
	100	100		100	95

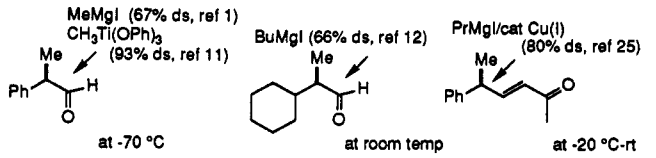
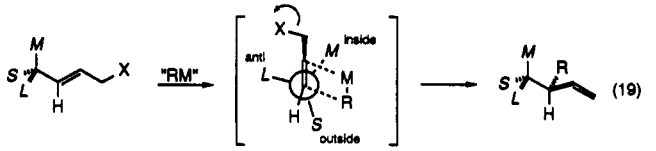


Figure 1. Literature examples of Cram-type additions.



E

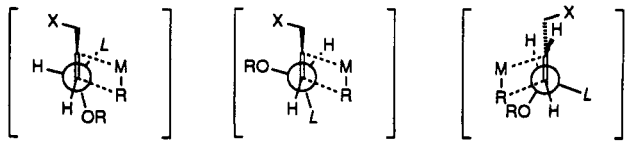
L, M, S = *tert*-butyl>steroid>cyclohexyl, *iso*-propyl>phenyl>1°alkyl>methyl>RO>H

and thus places the smallest group (*S*) at the most-hindered inside position and the largest at the least-hindered anti position.[25] The *anti*-relationship between the incoming organometallic and the leaving group is based on the experimental finding made with the copper/titanium complex reagent.[10]

The unimportance of chelation suggests that the reaction of the δ-alkoxy substrates **D** also conforms to this model under the assumption that the alkoxy group is bigger than hydrogen and smaller than the alkyl and phenyl groups. This assignment of steric bulk is consistent with the substituent A values.[26] The low selectivity for the substrates 7 and 8 (Table II) may be due to poor differentiation between a primary alkyl and an alkoxy group. The relative steric bulk of substituents shown under eq 19 offers reasonable accounts of the observed diastereoselectivity.

The model **E** with *M* equal to an alkoxy group is operationally equivalent to the conventional chelation model. The TIPS protection clearly indicated that chelation is *not required* in order for the reaction to exhibit the observed sense and level of diastereoselectively.

Besides the model **E**, there remains two other transition state models **F** and **G** to be considered for the δ-alkoxy substrates. The model **F**, which places the larger groups at the hindered positions, however, is highly unlikely. Although model **G** appears to be of some significance in view of possible effects of σ^*_{C-O} antibonding, the *L* group located at the outside location (i.e., the most-hindered position) seems to suffer considerable torsional strain. The conformation of the stereogenic center in **G** is the one generally favored for *cis*-olefins since the sterically least-demanding allylic hydrogen comes closest to the *cis*-olefinic substituent.[27] Thus, if model **G** were to represent the lowest energy pathway to the observed product, then the selectivity would have been the highest for *cis*-substrates. This prediction, however, is contrary to the experimental findings (vide supra).



F G H

This analysis about **G** suggests, in turn, that model **H** may account for the reversal of the selectivity observed for the *cis-tert*-butyl compound **16**. Thus, for the *cis*-allylic substrates (eq 10), the conformation **H** would become energetically accessible and contribute to reduce (e.g., L = *i*-Pr) or to even change the diastereofacial selectivity (e.g., L = *t*-Bu).

Finally, considerations on the extremely high levels of diastereoselectivities may be due. The mechanism of the allylation reaction being ambiguous, precise analysis is obviously difficult. However, on the basis of the assumption that the reaction involves direct nucleophilic attack of the alkyl nucleophile to the olefinic carbon, the following argument may be constructed. It may be deduced from the Hammond postulate as supported by the ab initio theoretical calculations that the forming C–C bond in a carbometalation-like reaction would be shorter than that in the extremely exothermic carbonyl additions. The shorter C–C bond length would obviously make the steric requirements in the transition state more demanding than in the carbonyl additions. There is an additional possibility that the difference of the attack angle (i.e., the angle Nu···C=X) affects the selectivity.[28] The generally lower level of selectivity for organozinc reagents than for organocopper reagents may be ascribed largely to the higher reaction temperature employed for the former.

(25) Note that we have retracted our previous suggestion (ref 5 and Nakamura, E. *Synlett* **1991**, 539; see ref 4 for similar suggestions for conjugate additions) based on the assumption that *the nucleophilic attack of the copper* atom is crucial in the allylation reaction (ref 20). This latter assumption stands in contrast to the carbometalation mechanism, in which the R group acts as a nucleophile and the copper atom as an electrophile. For theoretical discussion on the electronics of carbometalation of olefins, see: Nakamura, E.; Nakamura, M.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 99.

(26) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(27) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167. Wiberg, K. B. Adv. Mol. Model. **1988**, *1*, 101.

(28) It has been observed in the ab initio calculations at HF/3-21G level that the attack angle in the Me^- addition to ethylene and acetylene is bigger than that in the Me^- addition to formaldehyde. Ethylene: Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821. Acetylene: Nakamura, E.; Miyachi, Y.; Koga,

In summary, we have demonstrated that S_N2'-allylation of an acyclic allylic chloride bearing a δ-stereogenic center shows moderate to extremely high levels of 1,2-asymmetric induction under the control of steric bulk of the substituents on the stereogenic center. The sense and level of the diastereoselectivity are surprisingly similar for organocopper and zinc reagents and can be rationalized by invoking a carbometalation-like transition state model. With the generality of the S_N2'-regioselectivity of the allylation of organocopper and zinc reagents combined with the diastereoselectivity approaching 100%, the S_N2'-allylation reaction provides a new avenue for the diastereoselective construction of stereogenic centers in acyclic systems.

Experimental Section

General. All reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under nitrogen. Routine chromatography was carried out as described by Still.[29] ^1H NMR (200, 270, and 500 MHz) and ^{13}C NMR (50, 67.5, and 125 MHz) spectra were measured for a $CDCl_3$ or CD_3CN solution of a sample on JEOL FX-200, GSX-270, and GSX-500 instruments, respectively. ^1H NMR spectra are reported in parts per million from internal tetramethylsilane and ^{13}C NMR spectra from $CDCl_3$ (77.0 ppm). IR spectra were recorded on a Hitachi 260-10 instrument or a JASCO IR-800; absorptions are reported in cm^{-1}. Gas chromatographic (GC) analysis was performed on a Shimadzu 8A or 14A machine equipped with glass capillary columns (0.25-mm i.d. × 25 m). Samples for elemental analysis were obtained by purification with a recycling preparative HPLC (Japan Analytical Industry, LC908; GPC with styrene–divinylbenzene resin).

Typical Procedure for the S_N2' Allylation of $Bu_2CuLi/ZnCl_2$ Reagents. (3*R,4*S**)-3-(Benzyloxy)-4-ethenyl-2-methyloctane (28b).** To a suspension of $CuBr/SMe_2$ (0.5 mmol, 102.8 mg) in THF (0.5 mL) was added BuLi (1.74 M hexane solution, 1.0 mmol, 0.57 mL) at −70 °C. The resulting mixture was warmed to −40 °C, stirred for 40 min, and then cooled to −70 °C again. A 1 M THF solution of $ZnCl_2$ (0.5 mmol, 0.5 mL) was added, and after 10 min, *trans*-4-(benzyloxy)-1-chloro-5-methyl-2-hexene (0.5 mmol, 119 mg) was added at the same temperature. After stirring for 15 h, the reaction mixture was diluted with hexane, washed with saturated $NaHCO_3$ (0.5 mL × 2) and then with saturated NaCl (0.5 × 2), and dried over $MgSO_4$. After removal of the solvent, GC analysis (HR-1, 145 °C) of the crude product indicated an S_N2'/S_N2 ratio of 98:2 (retention times; 18.2 and 23.7 min, respectively). Purification on silica gel column chromatography (2% ethyl acetate/hexane) afforded 23.5 mg (95%) of the titled product: IR (neat), 1470, 1455, 1110, 1070, 975, 920, 720, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.25–1.38 (m, 4H), 1.86 (sep, *J* = 6.8 Hz, 1H), 1.98–2.05 (m, 2H), 3.00 (br q, *J* = 5.7 Hz, 1H), 3.08 (t, *J* = 5.7 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 5.03–5.09 (m, 2H), 5.41 (m, 2H), 5.94–6.03 (m, 1H), 7.23–7.40 (m, 5H). Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.94; H, 10.94.

The stereochemistry was assigned by analogy to the corresponding methylated product **28a** (vide infra).

Typical Procedure for the S_N2' Allylation of $Me_2CuLi/ZnCl_2$ Reagents. (3*R,4*S**)-4-(Methoxymethoxy)-3-methyl-1-nonene (26a).** To a suspension of $CuBr\cdot SMe_2$ (0.2 mmol, 41.1 mg) in THF (0.3 mL) was added MeLi (1.48 M ether solution, 0.4 mmol, 0.27 mL) at −70 °C. The resulting mixture was warmed to 0 °C, stirred for 10 min, and then cooled to −70 °C again. A 1 M THF solution of $ZnCl_2$ (0.2 mmol, 0.2 mL) was added and after 10 min of stirring, *trans*-1-chloro-4-(methoxymethoxy)-2-nonene (0.2 mmol, 44.1 mg) was added at the same temperature. After stirring for 15 h, the reaction mixture was warmed to −40 °C over 2 h an diluted with hexane, washed with saturated $NaHCO_3$ aqueous (0.5 mL × 2), and then with satuated NaCl aqueous (0.5 × 2), and dried over $MgSO_4$. After removal of the solvent, capillary GC analysis (HR-1, 110 °C) of the crude product indicated an S_N2'/S_N2 ratio of 70:30 (retention times; 9.4 and 10.6 min, respectively). Purification on silica gel column chromatography (3% ethyl acetate/hexane) afforded 34.9 mg (95%) of the titled product: IR (neat, cm^{-1}) 1720, 1645, 1470, 1465, 1380, 1100, 1060, 1015, 915; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (br t, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.14–1.71 (m, 9H), 2.37, 2.50 (m, 1H), 3.41 (s, 3H), 4.68 (s, 2H), 4.99–5.13 (m, 2H), 5.80 (ddd, *J* = 7.6, 10.2, 17.5 Hz, 1H). The compound was identical with an authentic sample prepared by MOM protection of the adduct obtained by stereoselective coupling of a crotylchromium reagent with hexanal.[30]

(4*R,5*S**)-Isopropyl 5-(Benzyloxy)-4-ethenyl-6-methylheptanoate (39).** To freshly fused $ZnCl_2$ (0.3 mmol, 40.9 mg) was added 1-isopropoxy-1-(trimethylsiloxy)cyclopropane (0.6 mmol, 118.9 mg) in ether (3 mL).[23] After 3 h at room temperature, $CuBr\cdot SMe_2$ (0.005 mmol, 1 mg) and 4-(benzyloxy)-5-methyl-2-hexenyl chloride (0.20 mmol, 47.7 mg) in DMF (2 mL) was added. The reaction mixture was stirred for 15 h at room temperature, and KF (100 mg) in water (20 μL) was added. After stirring for 1 h, the mixture was filtered through a short column of silica gel with ether to obtain 48.2 mg (73%) of the ester as an oil, which was homogeneous by TLC, 200 MHz ^1H NMR, and capillary GC: (neat) 1735, 1470, 1460, 1380, 1260, 1185, 1115, 1080, 920, 740, 700; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 6H), 1.66–1.94 (m, 3H), 2.06–2.41 (m, 3H), 3.01 (dd, *J* = 2.5, 6.3 Hz, 1H), 4.60 (s, 2H), 4.91–5.17 (m, 3H), 5.76 (ddd, *J* = 10.1, 10.1, 17.1 Hz, 1H), 7.20–7.49 (m, 5H). Anal. Calcd for $C_{20}H_{30}O_3$: 75.43; H, 9.50. Found: C, 75.51; H, 9.56.

The *anti*-S_N2'- and S_N2-allylation products exhibited GC retention times (OV-17, 200 °C) of 21.0 and 26.9 min, respectively.

(3*R,4*R**)-3-(Benzyloxy)-4-ethenyl-2-methyl-5-decene (40).** To a solution of hexenyl iodide (0.2 mmol, 42 mg, 28.4 μL) in ether (0.2 mL) was added *t*-BuLi (1.51 M in pentane, 0.4 mmol, 0.26 mL) at −70 °C and the reaction mixture was stirred for 2 h. After addition of $CuBr\cdot SMe_2$ the mixture was warmed to −45 °C and stirred for 40 min and then cooled to −70 °C again. After addition of a solution of $ZnCl_2$ (1 M in THF, 0.1 mmol, 0.1 mL) *trans*-4-(benzyloxy)-1-chloro-5-methyl-2-hexene (0.1 mmol, 23.4 mg) was added and the reaction mixture was stirred for 16 h at −70 °C and warmed to room temperature over 10 h. Purification of the crude product on silica gel yielded 38.2 mg (67%) of the pure product, which was determined to be at least 95% pure by capillary GC analysis: IR (neat; cm^{-1}) 1470, 1455, 1110, 1100, 1070, 975, 720, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.25–1.38 (m, 4H), 1.86 (sep, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.98–2.05 (m, 2H), 3.00 (br q, *J* = 5.7 Hz, 1H), 3.08 (t, *J* = 5.7 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 5.03–5.09 (m, 2H), 5.41–5.62 (m, 2H), 5.94–6.03 (m, 1H), 7.23–7.04 (m, 5H). Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.95; H, 10.44.

The stereochemistry was assigned by analogy to the methylation product **28a**.

Typical Procedure for the Copper-Catalyzed S_N2'-Allylation of Organotitanium Reagents. (3*R,4*R**)-3-(Benzyloxy)-4-ethenyl-2-methyl-5-decene (28b).** To a solution of $TiCl(O\text{-}i\text{-}Pr)_3$ (1.64 M in hexane, 0.146 mL) in THF (0.6 mL) was added BuLi (1.64 M in hexane, 0.4 mmol, 0.24 mL) at −70 °C. A THF solution of $CuI\cdot 2LiCl$ (1 M, 0.012 mmol) was added to the orange solution which then turned brown. 4-(Benzyloxy)-1-chloro-5-methylhex-1-ene (0.2 mmol, 23 mg) was added and the reaction mixture was stirred for 6 h at −70 °C. After addition of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 140 °C) of the filtrate indicated an *anti*-S_N2'/S_N2 ratio of 98.7:1.3 (retention time; 14.4 min and 18.7 min, respectively). Capillary GC and ^1H

N.; Morokuma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6686. Formaldehyde: Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. Bachrach, S. M.; Streitwieser A. Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946.

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(30) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685.

NMR indicated that no trace of the *syn*-isomer could be detected by these criteria. Purification of the crude product by silica gel column chromatography afforded 38.4 mg (92.3%) of the allylation product, which was identical with the one described above.

Typical Procedure for the S_N2'-Allylation of Organozinc Reagents. (2*R,3*R**)-3-ethenyl-2-phenylheptane (18b).** To a solution of $ZnCl_2$ (1.0 M in THF, 0.3 mmol, 0.3 mL) in THF (1.0 mL) was added BuLi (1.64 M in hexane, 0.6 mmol, 0.36 mL) and HMPA (0.6 mmol, 107.5 mg) at −70 °C. After 10 min stirring, (*E*)-1-chloro-4-phenyl-2-pentene (0.2 mmol, 36.1 mg) was added at the same temperature. The reaction mixture was warmed to room temperature and was stirred for 24 h at the same temperature. After addition of ca. 2 mL of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 100 °C) of the filtrate indicated an *syn*-S_N2'/*anti*-S_N2'/S_N2 ratio of 81.8:10.9:7.3 (retention times; 7.8, 8.5, and 12.0 min, respectively). Purification of the crude product by silica gel column chromatography afforded 35.1 mg (87%) of the allylation product: IR (neat, cm^{-1}) 1730, 1500, 1455, 1380, 1070, 1030, 910, 763, 705; ^1H NMR (270 MHz, $CDCl_3$) δ 0.71–1.41 (m, involve d at 1.01, *J* = 7.4 Hz, 12 H), 2.02–2.17 (m, 1H), 2.55 (dq, *J* = 7.4, 7.4 Hz, 1H), 4.95 (d, *J* = 16.6 Hz, 1H), 5.06 (d, *J* = 9.8 Hz, 1H), 5.53 (ddd, *J* = 7.0, 9.8, 16.6 Hz, 1H), 7.10–7.34 (m, 5H). Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96, Found C, 89.02; H, 11.02.

The stereochemistry was assigned by analogy to the methylated product **18a** (vide infra).

(3*R,4*R**)-3-Ethyl-4-phenylheptene (18c).** To a solution of Et_2Zn (0.98 M in hexane, 0.3 mmol, 0.31 mL) in THF (1.0 mL) was added TMEDA (0.6 mmol, 69.7 mg) at −70 °C, and (*E*)-1-chloro-4-phenyl-2-pentene (0.2 mmol, 36.1 mg) was subsequently added at the same temperature. The reaction mixture was warmed to room temperature and was stirred for 24 h at the same temperature. After addition of ca. 2 mL of hexane saturated with water, the reaction mixture was passed through a pad of silica gel: GC analysis (HR-1, 100 °C) of the filtrate indicated an *syn*-S_N2'/*anti*-S_N2'/S_N2 ratio of 80.8:16.6:2.6 (retention times; 7.0, 7.3, and 9.6 min, respectively). Purification of the crude product by silica gel column chromatography afforded 30.2 mg (87%) of the allylation product: IR (neat, cm^{-1}) 1645, 1610, 1560, 1500, 1380, 1080, 763, 705, 555; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10, (d, *J* = 10.3, 1H), 2.65 (m, 1H), 4.90 (dd, *J* = 2.3, 10.5 Hz, 1H), 5.10 (dd, *J* = 2.3, 17.1 Hz, 1H), 5.60 (ddd, *J* = 9.5, 10.5, 17.1 Hz, 1H), 7.10–7.50 (m, 5H). Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.52; H, 10.38.

The stereochemistry was assigned by chemical correlation of (2*R**,3*S**)-2-ethyl-3-methylsuccinic acid (see supplementary material).

(3*R,4*S**)-4-Ethenyl-3-(triisopropylsiloxy)-2-methyloctane (32b).** To a solution of $ZnCl_2$ (1.0 M in THF, 0.75 mmol, 0.75 mL) in THF (1.5 mL) was added BuLi (1.47 M in hexane, 1.5 mmol, 1.0 mL) at −70 °C. After addition of HMPA (1.5 mmol, 268.8 mg), (*E*)-1-chloro-4-(triisopropylsiloxy)-5-methyl-2-pentene (0.5 mmol, 152.5 mg) was added at the same temperature. The reaction mixture was warmed to room temperature and was stirred for 24 h at the same temperature. After addition of ca. 5 mL of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 140 °C) of the filtrate indicated the absence of the *syn* isomer (>99.8% *anti*) and an S_N2'/S_N2 ratio of 91.6:8.4 (retention times; 9.0 and 10.1 min, respectively). Purification of the crude product by silica gel column chromatography afforded 89.8 mg (55%) of the allylation product, and 54.9 mg (36%) of starting material was recovered. The product was correlated to the corresponding benzyloxy composed through fluoride removal of the TIPS group followed by benzylation: IR (neat, cm^{-1}) 1645, 1470, 1390, 1370, 1095, 1065, 1020, 1005, 920, 890, 680; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77–1.56 (m involving s at 1.09, 36H), 1.81 (dtt, *J* = 4.8, 4.8, 4.8 Hz, 1H), 2.14–2.21 (m, 1H), 3.61 (dd, *J* = 3.6, 4.8 Hz, 1H), 4.95 (dd, *J* = 1.8, 17.4 Hz, 1H), 5.00 (dd, *J* = 2.1, 10.4 Hz, 1H), 5.83 (ddd, *J* = 8.2, 10.4, 17.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 14.1, 18.4, 19.2, 19.6, 22.9, 30.1, 31.7, 33.1, 48.5, 81.0, 115.1, 140.7. Anal. Calcd for $C_{20}H_{42}OSi$: C, 73.54; H, 12.96. Found: C, 73.64; H, 13.00.

The stereochemistry was assigned by correlation to the benzyloxy compound **28b** (desilylation and benzylation).

(3*R,4*R**)-3-*tert*-Butyl-4-phenyl-1-heptene (18d).** To a solution of $ZnCl_2$ (1.0 M in THF, 0.3 mL) in THF (0.6 mL) was added *t*-BuLi (1.64 M in hexane, 0.4 mmol, 0.24 mL) at −70 °C. After an addition of HMPA (0.6 mmol, 107.5 mg), 1-chloro-4-phenyl-2-pentene (0.2 mmol, 0.035 mL) was added at same temperature. Then, the ice bath was removed and allow to warm to room temperature. The reaction mixture was stirred for 12 h at room temperature. After addition of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 120 °C) of the filtrate indicated an *anti*/*syn* ratio of 87:13 (retention times; 7.0 and 6.9 min, respectively). Purification of the crude product by silica gel column chromatography afforded 21.0 mg (52%) of the products: IR (neat, cm^{-1}) 2880, 2850, 2830, 1605, 1500, 1480, 1455, 1365, 915, 760, 700; (S_N2' product) ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.98 (d, *J* = 10.6 Hz, 1H), 3.05 (q, *J* = 7.2 Hz, 1H), 4.77 (d, *J* = 10.3 Hz, 1H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.82 (ddd, *J* = 10.3, 10.6, 17.1 Hz, 1H), 7.11–7.35 (m, 5H). Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.14; H, 11.09.

The stereochemistry was assigned by analogy to the methylated product **28a** (vide infra).

Physical Properties of S_N2'-Allylation Products. (3*R,4*R**)-3-Methyl-4-phenyl-1-pentene (18a):** IR (neat, cm^{-1}) 1730, 1500, 1455, 1380, 1070, 1030, 910, 765, 705; ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, *J* = 7.4 Hz, 3H), 1.20 (d, *J* = 7.4 Hz, 3H), 2.29 (ddt, *J* = 6.7, 7.4, 7.4 Hz, 1H), 2.47 (dq, *J* = 7.4, 7.4 Hz, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 8.6 Hz, 1H), 5.66 (ddd, *J* = 6.7, 8.6, 10.8 Hz, 1H), 7.04–7.39 (m, 5H). Anal. Calcd for $C_{13}H_{18}$: C, 89.93; H, 10.07. Found: C, 89.96; H, 10.05.

The *anti*-S_N2'-, *syn*-S_N2-, and S_N2-allylation products have GC retention times (HF-1, 100 °C) of 8.5, 7.8, and 12.0 min, respectively. The stereochemistry was assigned by chemical correlation to (2*R**,3*S**)-2,3-dimethylsuccinic acid (see supplementary material).

(3*R,4*R**)-2-Cyclohexyl-3-ethenylheptane (21b):** IR (neat, cm^{-1}) 1640, 1450, 1380, 1000, 910; ^1H NMR (270 MHz, $CDCl_3$) δ 0.65–1.82 (m, inolving d and t at 0.75, 0.89, *J* = 7.4 Hz, 24 H), 2.01–2.15 (m, 1H), 4.91 (dd, *J* = 2.4, 17.3 Hz, 1H), 4.98 (dd, *J* = 2.4, 10.5 Hz, 1H), 5.55 (ddd, *J* = 9.56, 10.5, 17.3 Hz, H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 12.2, 14.1, 22.8, 26.7, 26.8, 29.2, 30.4, 31.7, 32.7, 40.1, 41.6, 45.7, 114.9, 141.1. Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 84.16; H, 13.29.

The *anti*-S_N2'- and S_N2-allylation products exhibited GC retention times (HR-1, 120 °C) of 10.6 and 12.0 min, respectively. The stereochemistry was correlated to the phenyl-containing product **18b** through a hydrogenation reaction over Rh/Al_2O_3.

(22*R*)-3β-(*tert*-Butyldimethylsiloxy)-22-methylchola-5,23-diene (22a): mp 151–152 °C (needles); ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.65–2.38 (m involving s at 0.68, d at 0.83, *J* = 6.8 Hz, s at 0.89, d at 0.97, *J* = 7.4 Hz, s at 0.99, 43H), 3.42–3.60 (m, 1H), 4.95 (d, *J* = 16.4 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 5.31 (br d, *J* = 5.0 Hz, 1H), 5.73 (ddd, *J* = 7.4, 11.2, 16.4 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.58, 11.86, 12.96, 18.25, 19.06, 19.43, 21.08, 24.38, 25.94, 27.89, 31.92, 32.08, 36.57, 37.38, 39.76, 39.79, 41.35, 42.24, 42.82, 50.18, 54.19, 56.63, 72.62, 113.98, 121.14, 140.53, 141.54. Anal. Calcd for $C_{31}H_{54}OSi$: C, 79.08; H, 11.56. Found: C, 79.29; H, 11.50.

The S_N2'-allylation product gave a single peak on capillary GC analysis (HR-1, 290 °C; retention time 8.0 min) and was pure by ^{13}C NMR (>94%). The stereochemistry was determined by single crystal X-ray analysis.[22]

(22*R*)-22-Butyl-3β-(*tert*-Butyldimethylsiloxy)chola-5,23-diene (22b): mp 104–109 °C (powder); ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.65–2.36 (m involving s at 0.68, d at 0.86, *J* = 6.8 Hz, s at 0.89, s at 1.00, 50H), 3.40–3.59 (m, 1H), 4.94 (d, *J* = 17.0 Hz, 1H), 4.99 (d, *J* = 10.2 Hz, 1H), 5.31 (br d, *J* = 5.0 Hz, 1H), 5.60 (ddd, *J* = 7.4, 10.2, 17.0 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.58, 11.88, 13.30, 14.12, 18.25, 19.43, 21.06, 22.83, 24.28, 25.94, 27.88, 29.95, 31.91, 32.09, 33.03, 36.57, 37.38, 39.79, 39.93, 42.21, 42.82, 46.41, 50.20, 53.94, 56.62, 72.62, 115.06, 121.16, 139.66, 141.53.

The S_N2'-allylation product gave a single peak on capillary GC analysis (HR-1, 300 °C: retention time 9.8 min). The stereochemistry was assigned by analogy by **22a**.

(3*R,4*S**)-3-Ethyl-3-methyl-4-phenyl-1-pentene (23a)**: IR (neat, cm^{-1}) 2880, 2870, 2835, 1640, 1605, 1500, 1455, 1420, 1380, 1075, 1060, 1030, 1010, 915, 770, 705; ^1H NMR (270 MHz, $CDCl_3$) δ 0.75 (t, J = 7.4 Hz, 3H), 0.98 (s, 3H), 1.23 (d, J = 7.4 Hz, 3H), 1.24 (q, J = 7.4 Hz, 2H), 1.67 (q, J = 7.4 Hz, 1H), 4.84 (d, J = 17.4 Hz, 1H), 5.05 (d, J = 10.8 Hz, 1H), 5.68 (dd, J = 10.8, 17.4 Hz, 1H), 7.10–7.32 (m, 5H). Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.50; H, 10.97.

The major-*anti*-S_N2'-, minor-*anti*-S_N2'-, and S_N2-allylation products exhibited GC retention times (HR-1, 120 °C) of 5.9, 6.3, and 6.6 min, respectively.

(2*R,3*R**)-3-Ethenyl-3-ethyl-2-phenylheptane (23b)**: IR (neat, cm^{-1}) 2880, 2860, 2840, 1500, 1455, 1380, 915, 705; ^1H NMR (270 MHz, $CDCl_3$) δ 0.68 (t, J = 7.1 Hz, 3H), 0.80–1.53 (m, 11H), 1.16 d, J = 7.1 Hz, 3H), 2.78 (q, J = 7.1 Hz, 1H), 4.88 d, J = 17.9 Hz, 1H), 5.16 (d, J = 11.0 Hz, 1H), 5.59 (dd, J = 11.0, 17.9 Hz, 1H), 7.10–7.35 (m, 5H). Anal. Calcd for $C_{17}H_{26}$: C, 88.26; H, 11.38. Found: C, 88.52; H, 11.47.

The major-*anti*-S_N2'-, minor-*anti*-S_N2'-, and S_N2-allylation products exhibited GC retention times (HR-1, 140 °C) of 10.5, 10.7, and 11.6 min, respectively. The stereochemistry was assigned by analogy to the reaction of the corresponding allylic chloride **1** lacking the olefinic ethyl group.

(5*R,6*S**)-5-Ethenyl-6-(methoxymethoxy)undecane (26b)**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (br t, J = 7.1 Hz, 6H), 1.00–1.70 (m, 14H), 2.2 (br s, 1H), 3.37–3.53 (m involving s at 3.45, 4H), 4.52 (s, 2H), 5.01 (dd, J = 1.9, 17.5 Hz, 1H), 5.07 (dd, J = 1.9 8.6 Hz, 1H), 5.67 (ddd, 8.6, 10.5 17.5 Hz, 1H). Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48. Found: C, 74.21; H, 12.58.

The major-*anti*-S_N2'-, minor-*anti*-S_N2'-, and S_N2-allylation products exhibited GC retention times (HR-1, 140 °C) of 17.1, 17.5, and 23.3 min, respectively. The stereochemistry was assigned by analogy to the methylated compound **26a** (vide supra).

(3*R,4*S**)-3-(Benzyloxy)-3,5-dimethyl-1-hexene (28a)**: IR (neat, cm^{-1}) 3050, 3020, 2950, 2925, 2860, 1625, 1490, 1450, 1380, 1360, 1095, 1060, 1020, 1000, 905, 725, 690; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 3H), 0.98 (d, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.83 (dqq, J = 7, 7, 7 Hz, 1H), 2.48 (q, J = 7 Hz, 1H), 2.95 (dd, J = 5, 7 Hz, 1H), 4.55 (d, J = 11 Hz, 1H), 4.61 (d, J = 11 Hz, 1H), 5.03 (m, 2H), 5.95 (ddd, J = 8, 10, 17 Hz, 1H), 7.35 (m, 5H). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.38; H, 10.06.

The *anti*-S_N2'- and S_N2-allylation products exhibited GC retention times (HR-1, 140 °C) of 10.1 and 10.6 min, respectively. The stereochemistry was assigned by chemical derivatization to a cyclic 1,3-dioxane whose stereochemistry was determined by the ^1H NMR analysis of coupling constants (see supplementary material).

(1′*R,3*S**)-3-[1′-cyclohexyl-1′-(methoxymethoxy)methyl]-1-heptene (34b)**: IR (neat, cm^{-1}) 1645, 1470, 1455, 1215, 1150, 1105, 1050, 1010, 925, 915. ^1H NMR (270 MHz, $CDCl_3$) δ 0.83–1.98 (m, involving t at 0.88 J = 7.8 Hz, 20H), 2.17–2.29 (m, 1H), 3.14 (dd, J = 3.4, 7.2 Hz, 1H), 3.40 (s, 3H), 4.62, (d, J = 13.4 Hz, 1H), 4.66, (d, J = 13.4 Hz, 1H), 4.98 (dd, J = 2.2, 17.7 Hz, 1H), 5.06 (dd, J = 2.4, 10.4 Hz, 1H), 5.72 (ddd, J = 10.4, 10.4, 17.6 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 22.7, 26.2, 26.3, 25.5, 29.1, 29.7, 30.0, 31.8, 41.0, 46.4, 56.1, 87.0, 98.5, 115.8, 139.6. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89, Found: C, 75.30; H, 11.94.

The *anti*-S_N2'- and S_N2-allylation products exhibited GC retention times (HR-1, 130 °C) of 17.9 and 25.2 min, respectively. The stereochemistry was assigned by analogy to the isopropyl-substituted compound **28b**.

(3*R,4*S**)-4-Ethenyl-3-(methoxymethoxy)-2-methyloctene (36b)**: IR (neat, cm^{-1}) 3080, 2350, 1640, 1460, 1380, 1150, 1100, 1040, 910; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83–0.99 (m, 9H), 1.15–1.50 (m, 6H), 1.81 (dqq, J = 7, 7, 7 Hz, 1H), 2.12–2.28 (m, 1H), 3.11 (dd, J = 4, 7 Hz, 1H), 3.41 (s, 3H), 4.64 (d, J = 7 Hz, 1H), 4.65 (d, J = 7 Hz, 1H), 5.00 (dd, J = 2, 17 Hz, 1H), 5.05 (dd, J = 2, 11 Hz, 1H), 5.70 (ddd, J = 9, 11, 17 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 18.9, 19.9, 23.0, 29.8, 31.2, 31.9, 47.2, 56.2, 87.8, 98.5, 115.9, 139.6. Anal. Calcd for $C_{14}H_{28}O_2$: C, 76.63; H, 12.35. Found: C, 73.44; H, 12.36.

The *anti*-S_N2'- and S_N2-allylation products exhibited GC retention times (HR-1, 140 °C) of 12.8 and 16.8 min, respectively. The stereochemistry was assigned by chemical derivatization to a cyclic 1,3-dioxane whose stereochemistry was determined by the ^1H NMR analysis of coupling constants (see supplementary material).

(1*R,2*R**)-2-Ethyl-1-(methoxymethoxy)-2-methyl-1-phenyl-3-butene (41a)**: GC analysis (HR-1, 140 °C) S_N2'/S_N2 = 70:30 (12.6 and 12.8 min, respectively); IR (neat, cm^{-1}) 1460, 1155, 1105, 1080, 1040, 980, 920, 740, 710; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3H), 1.03 (s, 3H), 1.44 (q, J = 7.3 Hz, 2H), 3.35 (s, 3H), 4.49 (d, J = 6.7 Hz, 1H), 4.54 (d, J = 6.7 Hz, 1H), 4.89 (dd, J = 1.5, 17.5 Hz, 1H), 5.09 (dd, J = 1.5, 10.5 Hz, 1H), 5.83 (dd, J = 10.5, 17.5 Hz, 1H), 7.23–7.43 (m, 5H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.00; H, 9.51.

The *anti*-S_N2'- and S_N2-allylation products exhibited GC retention times (HR-1, 140 °C) of 12.6 and 12.8 min, respectively. The stereochemistry was assigned by chemical degradation to an aldol of known stereochemistry (see supplementary material).

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Supplementary Material Available: Representative procedures for the preparation of starting materials (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.