Stereoselective Reactions of Acyclic Allylic Phosphates with Organocopper Reagents

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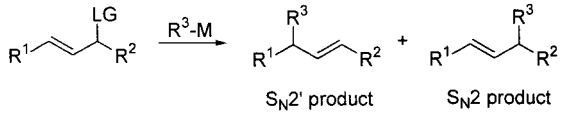
A series of acyclic allylic alcohols of general structure $R^1CH{=}CHCH(OH)R^2$ were resolved by Sharpless kinetic resolution. The hydroxyl groups of these enantiomerically enriched alcohols were derivatized to diethyl phosphates, and the derivatives were reacted with organocopper reagents. Cleanest substitution reactions were observed with reagents $R^3{}_2CuCNLi_2$. With R^1 = Me and R^3 = *n*-Bu, the size of R^2 affected both the regioselectivity and stereoselectivity of the displacement. Larger R^2 groups gave higher regio- and stereoselectivities: with R^2 = 3-pentyl, >98% S_N2' regioselectivity and >98% anti stereoselectivity were observed. $Bn_2CuCNLi_2$ gave stereoselectivities comparable to those observed with *n*-$Bu_2CuCNLi_2$ but *t*-$Bu_2CuCNLi_2$ exhibited much lower diastereofacial preference.

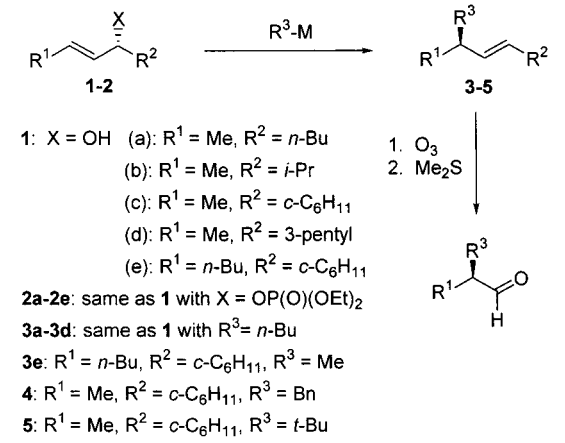
Introduction

Organocopper reagents are widely used in organic synthesis.[1] Among their many applications are substitution reactions on a wide variety of allylic functionalities. Of prime importance in such reactions are regiochemistry and stereochemistry, and many outstanding investigations have been carried out to elucidate factors that influence these outcomes. For example, it is now generally expected that organocuprates will undergo anti, S_N2' reaction with allylic carboxylates, halides, phosphates, and sulfonates, but syn S_N2' reaction with allylic carbamates[2] and allyloxybenzotriazoles.[3] However, most studies in this area have been carried out with cyclic compounds, and relatively little attention has been paid to acyclic systems. Thus, there are scattered examples that demonstrate high anti, S_N2' selectivity with γ-mesyloxy α,β-unsaturated esters,[4] mesyloxy vinyl sulfoxides,[5] allylic mesylates linked to an oxazolidine,[6] and CF_3-containing allylic acetates;[7] also, high syn, S_N2' selectivity has been observed with 3-silylallylic carbamates,[8] but it is still not possible to predict reliably the product distribution of the general reaction shown in Scheme 1.

Scheme 1



Scheme 2



We were particularly interested in examining the reactions of organocopper reagents with substrates derived from allylic alcohols **1** as these are readily available in enantiomerically pure form.[9,10] In particular, we envisaged their use as precursors to α-chiral carbonyl compounds as shown in Scheme 2. Thus, selective γ (S_N2') alkylation of **2** would provide alkenes **3** which could be cleaved by ozonolysis to yield α-chiral aldehydes or carboxylic acids. One major advantage of this approach compared to traditional enolate alkylation strategies is

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(7) Yamazaki, T.; Umetani, H.; Kitamuze, T. *Tetrahedron Lett.* **1997**, *38*, 6705−6708.

(8) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601−1614.

(9) Asymmetric reduction: Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; pp 209−228.

(10) Sharpless kinetic resolution: (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (b) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978−2979.

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Table 1. Reactions of Phosphates 2 with Organocopper Reagents

entry	phosphate	reagent	ratio[a] S_N2'/S_N2	ER of phosphate[b]	ER of alkene[c] (no.)	yield[d] (%)
1	**2c**	Bu_2CuLi	97:3	97:3	88:12 (**3c**)	46
2	**2a**	$Bu_2CuCNLi_2$	67:33	97:3	70:30 (**3a**)	74
3	**2b**	$Bu_2CuCNLi_2$	91:9	95:5	88:12 (**3b**)	72
4	**2c**	$Bu_2CuCNLi_2$	95:5	95:5	92:8 (**3c**)	67
5	**2d**	$Bu_2CuCNLi_2$	98:2	92:8	91:9 (**3d**)	53
6	**2e**	$Me_2CuCNLi_2$	85:15	97:3	90:10 (**3e**)	40
7	**2c**	$Bn_2CuCNLi_2$	97:3	97:3	90:10 (**4**)	42
8	**2c**	*t*-$Bu_2CuCNLi_2$	95:5	95:5	66:34 (**5**)	67

[a] Determined by GC−MS analysis of crude reaction mixtures. [b] Enantiomeric ratio assumed to be the same as starting alcohols **1a**−**e** since the C−O bond is not cleaved during derivatization. [c] Determined by GC−MS analysis after ozonolysis/oxidation and conversion to α-methylbenzylamides. [d] Isolated yields of chromatographed products. In most cases, GC yields are >90%; modest isolated yields reflect the volatility of the hydrocarbon products.

that the coupling partner (RM here; RX with enolates) is not limited to primary groups. For example, Spino has recently applied this strategy to introduce *tert*-butyl and phenyl groups to allylic carbonate derivatives of menthone with very high diastereoselectivities.[11] We now disclose our findings in this area.

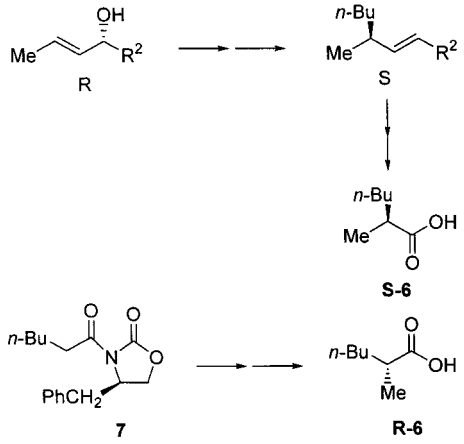
Results and Discussion

Since we were particularly interested in optimizing the regioselectivity for γ-attack, a series of allylic alcohols were prepared with varying sizes of alkyl group (R^2) at the carbinol carbon with the expectation that larger groups would favor S_N2' reactivity. Racemic alcohols were easily made by Grignard addition to α,β-unsaturated aldehydes. Each of the racemic alcohols was then subjected to Sharpless kinetic resolution (SKR) without incident to obtain enantiomerically enriched alcohols in 84−94%ee and reasonable isolated yields. Transformation of the hydroxyl group into a leaving group then furnished substrates for reaction with organocopper reagents.

Phosphate **2c** was used to probe various organocopper reagents and reaction conditions.[12] With both $Bu_2CuCNLi_2$ and Bu_2CuLi,[13] high S_N2' regioselectivity was observed, but there was considerably greater loss of stereochemical integrity with Bu_2CuLi than with the higher order cuprate (Table 1, entry 1 vs 4). Both THF and ether as solvent gave similar results. In contrast to these relatively clean reactions, use of BuMgBr with CuI (cat.) gave a mixture of four isomeric alkenes (by GC−MS analysis) in a ratio of 10:27:46:15, with the major isomer corresponding to the desired S_N2' product **3c**. Interestingly, the results of this reaction are also very different from the previous reports of allylic phosphates reacting with Grignard reagents catalyzed by CuCN·2LiCl, wherein high S_N2' substitution is observed.[14]

Since $Bu_2CuCNLi_2$ gave the highest selectivity with phosphate **2c**, it was also examined with other phosphates (Table 1, entries 2−5). For substrates **2a**−**d**, there was a clear trend wherein both regioselectivity and stereoselectivity increased with increasing size of R^2. Thus, with **2a** (R^2 = *n*-Bu), only 67% S_N2' substitution was observed but this increased to 91% with **2b** (R^2 = *i*-Pr) and to 98% with **2d** (R^2 = 3-pentyl). In a parallel trend, with **2a** (R^2 = *n*-Bu), there was substantial erosion of stereochemical purity but with **2d** (R^2 = 3-pentyl), there was essentially no loss of stereochemistry.

Scheme 3



Analysis of the stereochemical purity of alkenes **3a**−**d** was carried out by ozonolysis/oxidation to the carboxylic acid followed by derivatization with α-methylbenzylamine[15] to give diastereomeric amides that were easily separable by GC. This derivatization procedure also allowed for the assignment of absolute configuration for alkenes **3a**−**d** (Scheme 3). An authentic sample of *R*-**6** was prepared using Evans oxazolidinone alkylation chemistry,[16] and the derived amides were compared by GC. For each alkene, *S*-**6** was the major acid formed. (Alkenes **3a**−**d** all give acid **6** since the fragment containing R^2 is cleaved by ozonolysis.) Since alcohols **1a**−**d** have *R* stereochemistry, reactions to form **3a**−**d** must have taken place in an anti fashion.

With phosphate **2e**, reaction with $Me_2CuCNLi_2$ furnished the enantiomer of **3c** as the major product as expected for an anti S_N2' substitution (Table 1, entry 6). Results with phosphate **2c** and $Bn_2CuCNLi_2$ were comparable to those with $Bu_2CuCNLi_2$. However, reaction of **2c** with *t*-$Bu_2CuCNLi_2$ gave alkene **5** with considerable loss of stereochemical purity (Table 1, entry 8). It is not clear why *t*-$Bu_2CuCNLi_2$ is atypical in reacting with substantial racemization. Attempts to probe the possibility of a SET pathway (which could explain partial racemization) by adding HMPA, a reagent known to affect SET reactions[17] and cuprate structure,[18] were thwarted by the poor reactivity observed when HMPA

(11) Spino, C.; Beaulieu, C.; Lafrenière, J. *J. Org. Chem.* **2000**, *65*, 7091−7097.

(12) Carboxylate esters (e.g., trifluoroacetate, pivalate) of **1c** returned mostly alcohol **1c** when treated with $Bu_2CuCNLi_2$ or Bu_2CuLi while the benzenesulfonate of **1c** gave complex mixtures.

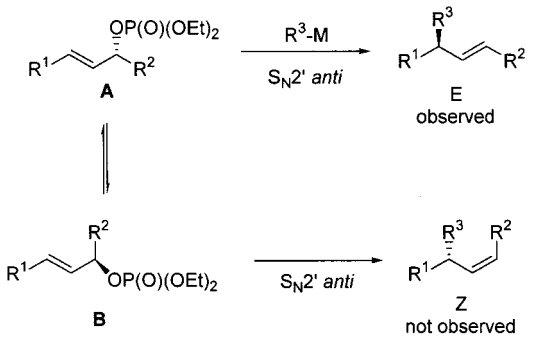
(13) Formulas for these copper reagents are intended to show stoichiometry only. For discussions of structure, see: (a) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4031−4043. (b) Bertz, S. H.; Nilsson, K.; Davidson, Ô.; Snyder, J. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 314−317.

(14) Highly regioselective anti S_N2' reactions of allylic phosphates have been demonstrated: (a) Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489−5491. (b) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 271−253. (c) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130−1136. (d) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689−690. (e) Torneiro, M.; Fall, Y.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1997**, *62*, 6344−6352.

(15) α-Methylbenzylamine of 97%ee was obtained from Aldrich and purified to 99.7%ee by recrystallization of its D-tartaric acid salt: Ault, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 932−936.

(16) (a) Evans, D. A.; Bartoli, J.; Shih, T L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

Scheme 4



was added. Nonetheless, it seems unlikely that SET chemistry plays a role in these reactions since $Bn_2CuCNLi_2$ shows a similar stereochemical outcome to $Bu_2CuCNLi_2$.

Overall, the regiochemistry of the reactions of phosphates **2** with $R_2CuCNLi_2$ can be readily explained on steric grounds: as the size of R^2 increases, S_N2 reaction is more disfavored and thus the ratio of S_N2'/S_N2 reaction increases. To explain the dependence of stereochemical outcome on the size of R^2, it is tempting to suggest that larger R^2 groups serve to bias the conformation of **2** such that anti attack will take place on only one face of the alkene (Scheme 4). However, since the product alkenes isolated all have *E* stereochemistry, anti substitution on conformer **B** (which would provide alkenes of *Z* stereochemistry) seems unreasonable. Rather, it is more likely that the partial racemization observed arises from syn substitution on conformer **A**; larger R^2 groups may decrease the amount of syn substitution observed by inhibiting coordination of the phosphate group with the cuprate reagent.

In summary, we have shown that acyclic allylic alcohols of general structure **1** can undergo S_N2' reactions with organocopper reagents with >98% regioselectivity and >98% anti selectivity via their phosphate esters. The nature of the leaving group, the size of R^2, and the organocopper reagent used all influence the outcome of these reactions. Nonetheless, we are beginning to understand how to manipulate these factors to achieve high selectivities.

Experimental Section

General Methods. All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether and THF were freshly distilled from Na/benzophenone. Pyridine was distilled from CaH_2. The known allylic alcohols **1a**,[19] **1b**,[20] and **1c**[10a] were prepared by reacting freshly distilled crotonaldehyde with the corresponding Grignard reagent in diethyl ether under typical reaction conditions; analogously, **1e**[21] was prepared by reacting *E*-2-heptenal with cyclohexylmagnesium chloride in ether. Benzyltributylstannane was prepared by a method similar to one developed by Seitz and co-workers.[22] Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

(*2E*)-5-Ethyl-2-hepten-4-ol, 1d. Freshly distilled crotonaldehyde (6.8 mL, 82.1 mmol) in Et_2O (15 mL) was added to the Grignard derivative of 3-bromopentane (12.4 mL, 0.10 mol; 2.6 g, 0.11 mol Mg) in Et_2O (65 mL, 0 °C to room temperature). The reaction mixture was quenched with aqueous NH_4Cl (25 mL), and the resulting solid was washed twice with Et_2O. The combined washings were dried with $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography (30% hexane in ethyl acetate) to give 7.4 g (63%) of a clear, yellow oil: IR (neat) 3381 (br), 1672 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.68 (1H, dq, J = 15.3, 6.2 Hz), 5.50 (1H, J = 15.3, 7.2 Hz), 4.04 (1H, m), 1.70 (3H, d, J = 6.2 Hz), 1.49−1.15 (6H, m), 0.97−0.81 (6H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.9, 126.8, 74.4, 46.8, 21.6, 21.3, 17.5, 11.5, 11.2; MS (EI) *m*/z 142 (M^+, 0.1), 71 (100). Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 75.88; H, 12.66.

General Procedure for the Kinetic Resolution of Allylic Alcohols 1a−e. Each of the allylic alcohols was kinetically resolved using the Sharpless protocol[10a] with L-(+)-dicyclohexyl tartrate (DCHT). The reaction progress was monitored by GC and was stopped when >50% complete. The formed allylic epoxide and the desired allylic alcohol were separated by flash chromatography. Enantiomeric purities were determined by conversion to the corresponding (*R*)-MTPA ester and analysis by ^1H and/or ^{19}F NMR spectroscopy.

(2*E*,4*R*)-2-Octen-4-ol, (*R*)-1a. The reaction was run using 10.30 g (80.4 mmol) of substrate for 5 h. The crude reaction mixture was purified by column chromatography (30% Et_2O in hexane) to give 2.42 g (47%) of a clear, colorless oil: $[\alpha]_D$ = −6.10 (c = 3.31, EtOH); enantiomeric excess = 94%.

(4*E*,3*R*)-2-Methyl-4-hexen-3-ol, (*R*)-1b. The reaction was run using 10.04 g (87.9 mmol) of substrate for 13 h using decane as an internal standard. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to give 3.51 g (70%) of a clear, slightly yellow oil: $[\alpha]_D$ = −13.9 (c = 1.17, EtOH); enantiomeric excess = 90%.

(2*E*,1*R*)-1-Cyclohexyl-2-buten-1-ol, (*R*)-1c. The reaction was run using 10.08 g (65.3 mmol) of substrate for 15 h. The crude reaction mixture was purified by column chromatography (30% Et_2O in hexane) to give 3.02 g (60%) of a clear, slightly yellow oil: $[\alpha]_D$ = −13.4 (c = 3.14, EtOH); enantiomeric excess = 94% [lit.[10a] $[\alpha]_D$ = −13.24 (c = 2.62, EtOH), ee = 95%]. In another run, material of 90% ee was obtained.

(2*E*,4*R*)-5-Ethyl-2-hepten-4-ol, (*R*)-1d. The reaction was run using 6.04 g (42.5 mmol) of (±)-**1d** for 13 h with decane as an internal standard. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to give 2.51 g (83%) of a clear, colorless oil: $[\alpha]_D$ = −11.25 (c = 1.28, EtOH); enantiomeric excess = 84%.

(2*E*,1*R*)-1-Cyclohexyl-2-hepten-1-ol, (*R*)-1e. The reaction was run using 2.48 g (12.7 mmol) of substrate for 8 h with decane as an internal standard. The crude reaction mixture was purified by column chromatography (20% Et_2O in hexane) to give 0.66 g (53%) of a clear, colorless oil: $[\alpha]_D$ = −7.88 (c = 1.14, EtOH); enantiomeric excess = 94%.

General Procedure for the Conversion of Allylic Alcohols 1a−e to Phosphate Esters 2a−e. Diethyl chlorophosphate (1.1 equiv) was added dropwise to a solution of the allylic alcohol (1.0 equiv) in pyridine (2.5 mL/g substrate) at 0 °C. After 1 h, the reaction mixture was quenched with water (2 mL/mL pyridine) and extracted twice with the same volume of Et_2O. The combined extracts were washed with 1 M H_2SO_4, 1 M $NaHCO_3$, and water. After the organic layer was dried over $MgSO_4$, the solvent was removed in vacuo. The crude phosphate esters were unstable to silica gel chromatography and distillation and so were used without further purification.

General Procedure for Reaction of Cuprates with Phosphate Esters To Form Alkenes 3−5. CuCN (2.0 equiv) was added to a three-necked flask equipped with a stir bar, low-temperature thermometer, argon inlet, and stopcock. The flask was flushed with argon and evacuated three times. Either Et_2O or THF (25 mL/g substrate) was added via syringe, and the system was cooled to −78 °C. The alkyllithium (4.0 equiv) of choice was added dropwise, and the reaction mixture

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(18) Cabezas, J. J.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1997**, *119*, 3878−3886.
(19) Corey, L. D.; Singh, S. M.; Oehlschlager, A. C. *Can. J. Chem.* **1987**, *65*, 1821−1827.
(20) McKee, B. H.; Kalantar, T. H. Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 6966−6968.
(21) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454−6455.
(22) Seitz, D. D.; Carroll, J. J.; Cartaya, C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129−134.

was allowed to stir until a clear solution was formed. At this time, the phosphate ester (1.0 equiv) was added in solvent (2.5 mL/g substrate). The reaction mixture was allowed to stir for 1 h at −78 °C. Completion of the reaction was checked by TLC (hexane as solvent). When complete, the reaction was quenched with 10% NH_4OH in saturated NH_4Cl solution (5 mL/mmol cuprate). The precipitate was removed by filtration, and the filter cake was washed thoroughly with Et_2O. The organic layer was separated and dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was purified using column chromatography (hexane as solvent). All enantiomeric excesses were determined by ozonolysis followed by derivatization.

(6*E*,5*S*)-5-Methyl-6-undecene, 3a, (2*E*)-4-Butyl-2-octene, and (2*Z*)-4-butyl-2-octene.[23] The reaction was performed using 923.3 mg (3.39 mmol) of **2a** in Et_2O and yielded 401.9 mg (74%) of a clear, colorless oil. GC−MS analysis (30 m × 0.25 mm DB-5, 70 °C for 2 min then 10 °C/min to 250 °C) showed a mixture of three isomers in a ratio of 67:25:8; the components were not separable by flash chromatography: IR (neat) 2959, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39−5.09 (2H, m), 2.03−1.94 (2.01H, m), 1.83 (0.33H, m), 1.67 (0.75H, d, J = 6.3 Hz), 1.60 (0.24H, d, J = 7.0 Hz), 1.34−1.24 (10.66H, m), 0.95 (2.01H, d, J = 6.8 Hz), 0.93−0.86 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ136.5, 136.4, 128.4, 128.3, 124.1, 42.9, 37.0, 36.8, 35.3, 32.3, 32.2, 32.0, 31.7, 29.8, 29.7, 29.6, 29.4, 27.2, 22.9, 22.7, 22.2, 21.0, 17.9, 14.1, 14.0; GC−MS retention times, (EI) m/z 7.31 min (25), 168 (M^+, 0.6); 7.40 min (8), 168 (M^+, 7), 69 (100); 7.54 min (67), 168 (M^+, 5), 69 (100). Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.76, 14.21.

(3*E*,5*S*)-2,5-Dimethyl-2-nonene, 3b. The reaction was performed using 405.4 mg (1.62 mmol) of **2b** in THF and yielded 179.8 mg (72%) of a clear, colorless oil: $[\alpha]_D$ = +14.9 (c = 1.93, CH_2Cl_2), 76% ee; IR (neat) 1718, 969 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ5.30 (1H, dd, J = 15.4, 6.3 Hz), 5.20 (1H, dd, J = 15.4, 7.1 Hz), 2.15 (1H, m), 2.00 (1H, m), 1.43−1.04 (9H, m), 1.03−0.79 (9H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ135.7, 133.4, 37.0, 36.6, 31.0, 29.6, 22.8 (3C), 20.9, 14.1; MS (EI) m/z 154 (M^+, 8), 55 (100). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.56; H, 14.40.

(1*E*,3*S*)-1-Cyclohexyl-3-methyl-1-heptene, 3c. The reaction was performed using 305.8 mg (1.05 mmol) of **2c** in THF and yielded 136.0 mg (67%) of a clear, colorless oil: $[\alpha]_D$ = +13.2 (c = 1.32, EtOH), 84% ee; IR (neat) 1666 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ5.31 (1H, A of ABXY-type pattern, dd, J_{obs} = 15.7, 5.9 Hz), 5.20 (1H, B of ABXY-type pattern, dd, J_{obs} = 15.7, 7.0 Hz), 2.02−1.81 (2H, XY of ABXY-type pattern, m), 1.71−1.67 (2H, m), 1.34−0.97 (13H, m), 0.95−0.67 (7H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ135.0, 134.4, 41.3, 37.6, 37.3, 34.0, 32.2, 30.2, 26.9, 26.7, 23.4, 23.2, 21.5, 14.6; MS (EI) m/z 194 (M^+, 17), 81 (100). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.60; H, 13.26.

(4*E*,6*S*)-3-Ethyl-6-methyl-4-decene, 3d. The reaction was performed using 205.3 mg (0.74 mmol) of **2d** in Et_2O and yielded 70.7 mg (53%) of a clear, colorless oil: $[\alpha]_D$ = +16.0 (c = 0.67, EtOH), 82% ee; IR (neat) 1664, 969 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ5.17 (1H, dd, J = 15.3, 7.8 Hz), 5.02 (1H, dd, J = 15.3, 8.4 Hz), 2.05 (1H, m), 1.62 (1H, m), 1.43−1.01 (13H, m), 0.97−0.79 (9H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 136.8, 132.5, 46.4, 37.0, 36.9, 29.7, 27.9 (2C), 22.8, 21.3, 14.1, 11.7 (2C); MS (EI) m/z 182 (M^+, 5), 69 (100), 55 (99). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.56; H, 14.46.

(1*E*,3*R*)-1-Cyclohexyl-3-methyl-1-heptene, 3e (= *ent*-3c). The reaction was performed using 154.4 mg (0.53 mmol) of **1e** with $Me_2CuCNLi_2$ (preformed at 0 °C for 30 min) in Et_2O and yielded 41.2 mg (40%) of a clear, colorless oil: $[\alpha]_D$ = −13.4 (c = 1.06, EtOH), 80% ee. Spectral data were identical to that reported for **3c** with the exception of optical rotation.

(23) The major isomer (67%) of this complex mixture is the desired, S_N2' product as shown by the large doublet in the ^1H NMR spectrum at 0.95 ppm, representing the methyl group β to the double bond. Evidence for the other two isomers (25 and 8%) is seen by the appearance of doublets at 1.67 and 1.60 ppm, which presumably represent vinyl methyl groups.

1-[(1*E*,3*S*)-3-Methyl-4-phenyl-1-butenyl]cyclohexane, 4. To a mixture of CuCN (125.4 mg, 1.40 mmol) and THF (5 mL) at 0 °C was added dropwise MeLi (1.34 M, 2.10 mL, 2.81 mmol). After 0.5 h, benzyltributyltin (823.7 mg, 2.16 mmol) in THF (1 mL) was added, and the reaction mixture was allowed to stir for 0 °C for 0.5 h. After the mixture was cooled to −78 °C, phosphate **1c** (209.2 mg, 0.72 mmol) in THF (0.5 mL) was added dropwise, and the mixture was stirred for 1 h. Usual workup and purification as stated in the general procedure yielded 69.5 mg (42%) of a clear, colorless oil: $[\alpha]_D$ = +26.4 (c = 1.05, EtOH), 80% ee; IR (neat) 1699, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ7.32−7.14 (5H, m), 5.38 (1H, A of ABXY-type pattern, dd, J_{obs} = 15.4, 5.9 Hz), 5.27 (1H, B of ABXY-type pattern, dd, J_{obs} = 15.4, 5.4 Hz), 2.64 (1H, dd, J = 13.1, 7.0 Hz), 2.52 (1H, dd, J = 13.1, 7.3 Hz), 2.34 (1H, X of ABXY-type pattern, m), 1.86 (1H, Y of ABXY-type pattern, m), 1.73−1.44 (4H, m), 1.34−0.80 (6H, m), 0.99 (3H, d, J = 6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ141.1, 134.9, 132.9, 129.3 (2C), 128.0 (2C), 125.6, 44.0, 40.6, 38.4, 33.3 (2C), 26.3, 26.1 (2C), 20.1; MS (EI) m/z 228 (M^+, 2), 81 (100). Anal. Calcd for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.19; H, 10.30.

1-[(1*E*,3*R*)-3,4,4-Trimethyl-1-pentenyl]cyclohexane, 5. After addition of *t*-BuLi, the reaction mixture was allowed to warm to 0 °C for 5 min, after which time it was recooled to −78 °C before addition of phosphate **1c**. The reaction was performed using 102.8 mg (0.35 mmol) of **1c** in Et_2O and yielded 46.0 mg (67%) of a clear, colorless oil: $[\alpha]_D$ = +10.53 (c = 7.61, CH_2Cl_2), ee = 32%; IR (neat) 1664, 969 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ5.38−5.13 (2H, AB of ABXY-type pattern, m), 1.71−1.56 (2H, XY of ABXY-type pattern, m), 1.25−0.96 (8H, m), 0.91 (3H, d, J = 6.9 Hz), 0.90−0.85 (2H, m), 0.82 (9H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ136.0, 131.0, 47.1, 40.8, 33.4 (2C), 29.8, 27.5 (3C), 26.3, 26.2 (2C), 15.7; MS (EI) m/z 194 (M^+, 3), 81 (100). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.56; H, 13.27.

General Procedure To Determine Facial Selectivity of Copper Coupling Reactions. Derivatizations were typically run with ∼10 mg of the alkene. The alkene (1.0 equiv) was dissolved in acetone (1 mL/mg substrate), cooled to −78 °C, and treated with an excess of ozone. The reaction mixture was purged with argon, treated with Jones reagent (2.7 equiv), and allowed to warm to room temperature. The excess Jones reagent was quenched with 2-propanol (excess), and the solvent was removed in vacuo. The resulting residue was partitioned in Et_2O and water (∼4:1 ratio) and the layers were separated. The organic layer was washed three times with 1 M HCl. The carboxylic acids were extracted with 1 M NaOH. The aqueous layer was cooled to 0 °C and reacidified with 6 M HCl. The carboxylic acids were extracted into Et_2O. The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo. The resulting mixture of carboxylic acids (1.0 equiv each) in CH_2Cl_2 (0.4 mL/mg substrates) was treated with diisopropyl carbodiimide (2.2 equiv), *S*-α-methylbenzylamine (2.2 equiv), HOBT (0.2 equiv), and DMAP (0.2 equiv). Completion of the reaction was monitored by TLC. Et_2O was added, and the reaction mixture was washed with cold 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$, and the solvent was removed by rotary evaporation. The crude reaction mixture was analyzed by GC−MS to determine the diastereomeric ratio of the formed amides.

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Supporting Information Available: Details of the preparation of racemic allylic alcohols and acid *R*-**6**, assignment of absolute configuration for acid *S*-**6**, and product characterization data for phosphates **2a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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