Factors Influencing 1,4-Asymmetric Induction during Indium-Promoted Coupling of Oxygen-Substituted Allylic Bromides to Aldehydes in Aqueous Solution

Leo A. Paquette,* George D. Bennett, Adnan Chhatriwalla,† and Methvin B. Isaac

Evans Chemical Laboratories, Columbus, Ohio 43210

Received January 28, 1997[⊗]

The preparation and indium-promoted aldehyde addition reactions of a series of 3-substituted 3-oxy-1-bromo-2-methylidenepropanes under aqueous conditions are described. The (*tert*-butyldimethylsilyl)oxy derivatives **4a**−**d** are the most diastereoselective of this group of reagents, giving rise to levels of syn-1,4-asymmetric induction in the range of 87−99%. Interestingly, syn stereoselectivity is eroded and reactions proceed more rapidly when the steric bulk of the oxygen substituent is reduced as in the hydroxy and methoxy derivatives. This dropoff in π-facial differentiation with kinetic acceleration is attributed to the operation of chelation effects during oxidative addition of the metal into the carbon−bromine bond, but not during the coupling stage. Once the aldehyde enters into the coordination sphere of the indium, internal chelation to the proximal oxygen is disrupted and conformational restrictions are released. These effects, in combination with the absence of a powerful steric control element in the latter examples, permit competitive passage via syn and anti transition states.

The influence on transition-state organization of heteroatom substituents positioned either α or β to carbonyl groups undergoing nucleophilic attack can be very substantial. When chelation operates, reaction diastereoselection is controlled by intramolecular delivery from the sterically less hindered π-face of the preformed complex.[1−3] In substrates lacking the potential for chelate organization, the interplay of steric and electronic forces summed up in the Felkin−Ahn model[4] provides a useful stereoinduction paradigm. Recent studies in these laboratories have addressed the applicability of the above criteria to indium-mediated coupling reactions in water. When *unprotected* hydroxyl groups are involved, reactions are accelerated as a consequence of effective chelation in the aqueous environment, and maximum π-facial diastereoselectivity is realized.[5] A comparable response is elicited by α-(dimethylamino) groups.[6] In other circumstances involving such carbonyl-flanking substituents as *tert*-butyldimethylsiloxy, phenylthio, *N*,*N*-dibenzylamino, *N*-BOC, and methylthio, slower reaction rates are observed with different stereoselectivities. Consequently, the more rapid allylations are the more stereocontrolled processes!

In continuation of our investigation of metal-mediated coupling reactions in aqueous media, we have presently examined the consequences of placing different oxygen substituents on the nucleophilic reaction partner, with particular focus on the issue of 1,4-asymmetric induction. In this study, 11 allylic bromides having different coordination potential and steric demands have been reacted with a triad of aldehydes. The objective of identifying the relative importance of polar, steric, and chelation factors in carbon−carbon bond-forming reactions of this type had not been described at the initiation of our efforts. Since then, Mulzer and his co-workers have described closely related studies involving oxygen-substituted allylic bromides with aldehydes in the presence of chromium(II) (in DMF−THF at −20 °C) and indium metal [in THF−H_2O (1:1) at 20 °C].[7] The work described below significantly extends this complementary effort and underscores the possibilities for attaining reliable 1,4-asymmetric induction in water as the reaction medium.

Results and Discussion

The functionalized allylic bromides were conveniently prepared by initial condensation of methyl acrylate with the aldehyde of choice under Bayliss−Hillman conditions[8] (Scheme 1). After conversion to the individual *tert*-butyldimethylsilyl ethers,[9] the esters **2** were reduced with Dibal-H in THF at −78 °C and transformed into the bromides **4** by exposure to *N*-bromosuccinimide and triphenylphosphine in CH_2Cl_2 at low temperature.[10] The unprotected hydroxy bromides **6** were obtained by mild acidic hydrolysis with *p*-toluenesulfonic acid monohydrate in methanol.[11] The O-methylation of hydroxy esters **1** was effected initially with silver oxide and methyl iodide[12] but proceeded in low yield. Utilization of an alternative more lengthy sequence starting from **2** made available the bromides **5** with greater efficiency.

At a minimum, the additions were carried out in water alone as well as in a 1:1 mixture of water and THF. The

† Undergraduate Research Participant, 1996.

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

(1) (a) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.

(2) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(3) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803.

(4) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(5) (a) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863. (b) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (c) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917.

(6) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. Submitted for publication.

(7) (a) Maguire, R. J.; Mulzer, J.; Bats, J. W. *Tetrahedron Lett.* **1996**, *37*, 5487. (b) Maguire, R. J.; Mulzer, J.; Bats, J. W. *J. Org. Chem.* **1996**, *61*, 6936.

(8) (a) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001. (b) Ciganek, E. *Org. React.*, submitted for publication.

(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

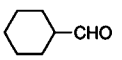
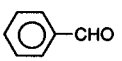
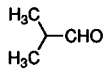
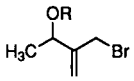
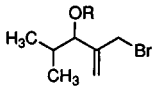
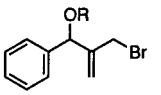
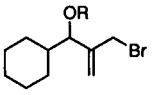
(10) Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. *J. Am. Chem. Soc.* **1985**, *107*, 7515.

(11) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *20*, 3981.

(12) Finch, N.; Fitt, J. J.; Hsu, I. H. S. *J. Org. Chem.* **1975**, *40*, 206.

S0022-3263(97)00158-8 CCC: $14.00

Table 1. 1,4-Syn (7):1,4-Anti (8) Ratios Observed for the Indium-Mediated Coupling of Oxygenated Allylic Bromides to Aldehydes in Water and Other Solvent Systems (25 °C)[a]

allyl bromide		solvent			
			(yields in parentheses)		
	**4a**	H_2O	91 : 9 (54%)	89 : 11 (64%)	91 : 9 (25%)
		H_2O-THF (1 : 1)	91 : 9 (98%)	82 : 18 (82%)	95 : 5 (98%)
	6a	H_2O	59 : 41 (53%)	54 : 46 (70%)	56 : 44 (70%)
		H_2O-THF (1 : 1)	56 : 44 (86%)	60 : 40 (73%)	60 : 40 (77%)
	5a	H_2O		59 : 41 (61%)	
		H_2O-THF (1 : 1)		73 : 27 (96%)	
	**4b**	H_2O	99 : 1 (77%)	97 : 3 (76%)	99 : 1 (62%)
		H_2O-THF (1 : 1)	99 : 1 (91%)	97 : 3 (72%)	91 : 9 (75%)
	6b	H_2O	48 : 52 (55%)	52 : 48 (33%)	50 : 50 (93%)
		H_2O-THF (1 : 1)	63 : 37 (63%)	61 : 39 (88%)	50 : 50 (82%)
		THF			37 : 63 (79%)
	**4c**	H_2O	93 : 7 (84%)	87 : 13 (64%)	89 : 11 (26%)
		H_2O-THF (1 : 1)	87 : 13 (55%)	80 : 20 (59%)	96 : 4 (89%)
		sat NH_4Cl soln			99 : 1 (53%)
	6c	H_2O	60 : 40 (79%)	61 : 39 (83%)	
		H_2O-THF (1 : 1)	65 : 35 (26%)	68 : 32 (58%)	65 : 35 (56%)
	5c	H_2O		66 : 34 (72%)	65 : 35 (38%)
		H_2O-THF (1 : 1)		74 : 26 (72%)	
		THF		68 : 32 (10%)	
	**4d**	H_2O	99 : 1 (50%)	99 : 1 (90%)	99 : 1 (74%)
		H_2O-THF (1 : 1)	88 : 12 (82%)	99 : 1 (81%)	99 : 1 (89%)
	6d	H_2O	35 : 65 (80%)	50 : 50 (87%)	50 : 50 (69%)
		H_2O-THF (1 : 1)	42 : 58 (85%)	47 : 53 (91%)	45 : 55 (86%)
	5d	H_2O		69 : 31 (76%)	
		H_2O-THF (1 : 1)		83 : 17 (92%)	

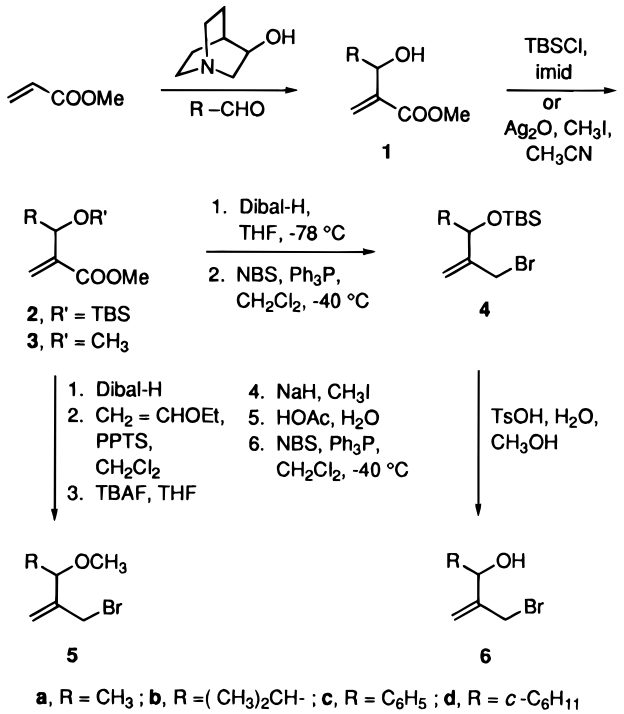
[a] All of the reactions were performed at least in duplicate at a concentration of 0.1 M with vigorous stirring. The product distributions in all cases were determined by ^{1}H NMR integration at 300 MHz of the unpurified reaction mixtures. The error limits are ≤ 3%.

dropoff in yields observed in water is considered to stem from the quite limited solubility of many of the reactants in this medium. This was not an issue when an organic cosolvent was present. Several experiments were also performed in dry THF in order to observe the consequences of a purely organic environment and to permit direct comparison. The results are compiled in Table 1.

All product ratios were determined by 300 MHz ^{1}H NMR analysis of the unpurified product mixtures in advance of chromatographic separation of the diastereomers. Distinction between the 1,4-syn and 1,4-anti diastereomers (**7** and **8**, Scheme 2) was readily accomplished on several fronts. As the Mulzer group has convincingly established,[7] the chemical shift of the newly generated carbinol proton invariably appears to lower field in **7** than in **8**. This pattern was observed irrespective of whether this hydrogen is benzylic or not. The phenomenon may arise as a direct consequence of intramolecular hydrogen bonding between the two heteroatoms, this alignment thrusting the carbinol proton more deeply into the deshielding π-cloud of the double bond within the syn isomers. In certain cases, particularly those products from the *a* series, other protons were also found to be highly diagnostic of stereochemistry. In addition, all of the syn isomers were less polar than their anti counterparts.

Where the TBSO-substituted bromides **4a**−**d** are concerned, attractively high syn stereoselectivity was invariably observed. The coupling reactions involving **4**, when performed in water, were typically somewhat more diastereoselective than those conducted in the mixed solvent system. Higher yields were generally noted in the latter context, especially when improved solubility was gained by having THF present. The availability of a free hydroxyl group as in **6** led to increased production of the anti diastereomer. This trend was little modified when the methyl ethers **5** were brought into reaction.

Scheme 1



a, R = CH_3 ; **b**, R =(CH_3)$_2$CH- ; **c**, R = C_6H_5 ; **d**, R = *c*-C_6H_{11}

Scheme 2

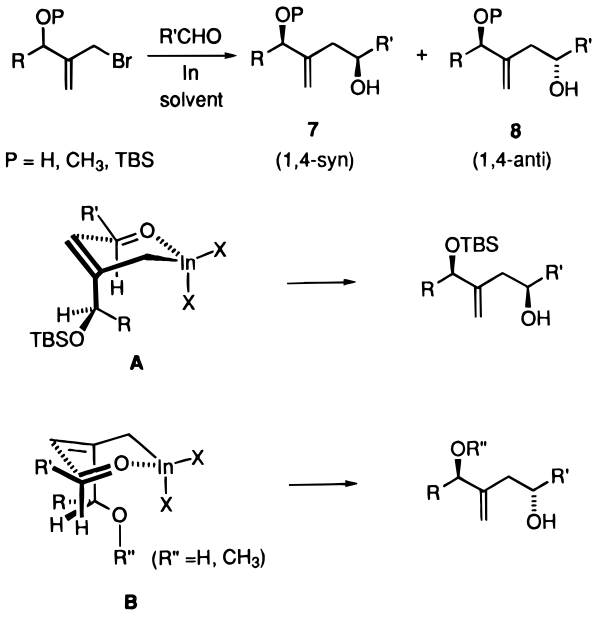


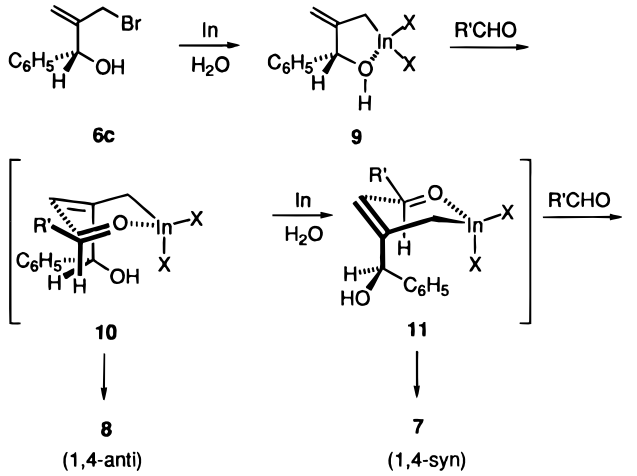
Figure 1. Transition state models.

However, the hydroxy bromides **6** did react at significantly accelerated rates, and the methoxy systems **5** were of intermediate reactivity. The coaddition of inorganic salts such as ammonium chloride and indium tribromide had little effect on product ratios. No advantage was gained by performing the couplings in anhydrous THF where appreciably lower yields were often observed.

These data indicate that the formation of 1,4-syn products becomes significant only when the steric bulk of the oxygenated substituent in the allylic bromide is appreciably increased by formation of the *tert*-butyldimethylsilyl ether. This stereochemical bias is consistent with intervention of the nonchelated transition state **A** depicted in Figure 1 where the overall size of the OTBS group is controlling. For the hydroxy and methoxy bromides, it is possible that the erosion of syn-selectivity occurs because the O-inside conformer **B** is now reasonably populated due to the more closely balanced steric demands of the R and OR″ substituents. This interpretation assumes that little if any inherent difference exists in the reactivity of **A** and **B**. However, evidence in support of the assumption that the product composition mirrors the approximate population of these conformers has been difficult to come by.

Notwithstanding, the substantive kinetic acceleration observed with the hydroxy bromides **6** warrants detailed consideration. Customarily, increases in reaction rate have been linked to lowerings in transition-state energies brought on by preformation of kinetically relevant chelated complexes.[13] The present context differs from the norm in that two distinctively different steps comprise the overall coupling process. The first involves formation of the allylindium reagent, and the second culminates in actual carbon−carbon bond formation. It is entirely likely that the *overall* rate enhancement is a function of the rate at which the organoindium reagent is generated. Formation of a chelate such as **9** during oxidative addition of the metal into the C−Br bond would very likely reduce energy demands and increase production of this organometallic intermediate (Scheme 3). Experiments designed to gauge the competitive consumption of **4c** and **6c** by indium in water have shown the difference in rate to be considerable (i.e., >3:1). We interpret this phenomenon to be general and to be the root cause of the overall kinetics.

Scheme 3



Approach of an aldehyde to a chelate such as **9** appears to induce coordination of indium to the carbonyl oxygen at the expense of the hydroxy (or methoxy) group.

While this process lends itself to activation of the aldehyde, the stereogenic hydroxyl-substituted carbon is no longer rigidified in its conformation. Access to **10** and **11** becomes possible, these activated complexes leading competitively to anti and syn products, respectively.

The contrast between the present study and earlier investigations involving the allylindation of α-hydroxy carbonyl compounds is striking. When the hydroxy substituent resides α or β to the carbonyl, chelation operates, bond rotation becomes restricted, and high stereoselectivity accompanies the more rapid reactions. When the hydroxyl group resides in the allylic bromide, all of the above factors operate during the metalation process, but the chelate so formed is disrupted when the aldehyde is brought into the indium coordination sphere. As a result, stereoselectivity is decreased and the coupled product composition comes entirely under steric control. Since −OTBS is the largest group, it does not engage in preliminary chelation, but does control the subsequent coupling diastereoselectivity at a notably high level. Under these circumstances, the slowest reactions deliver the highest levels of 1,4-asymmetric induction! Whether the same sensitive dependencies operate in other contexts remains to be elucidated. To this end, further studies in this area are presently being pursued.

Experimental Section[14]

Bromides **4a**−**c** have been previously reported,[7b] and their spectral properties are not documented here.

General Procedure for the Desilylation of 4. A solution of **4c** (1.70 g, 5.00 mmol) in methanol was treated with *p*-toluenesulfonic acid monohydrate (950 mg, 5.00 mmol), stirred overnight at rt, and concentrated. The residue was chromatographed on silica gel (elution with 15% ethyl acetate in hexanes) to give 840 mg (74%) of **6c** as a colorless oil, which crystallized on standing: mp 40−41 °C; IR (CH_2Cl_2, cm^{-1})

(13) (a) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130; **1992**, *114*, 1778. (b) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862.

(14) For generic experimental details, consult ref 5c.

3605, 1490, 1450, 1215, 1047; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.32 (m, 5 H), 5.46 (s, 1 H), 5.40 (d, J = 6.4 Hz, 2 H), 4.02 (d, J = 10.5 Hz, 1 H), 3.73 (d, J = 10.5 Hz, 1 H), 2.46 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.8, 141.0, 128.6, 128.1, 126.8, 115.8, 74.1, 33.1; MS m/z (M^+) calcd 225.9993, obsd 225.9981.

Anal. Calcd for $C_{10}H_{11}BrO$: C, 53.10; H, 4.90. Found: C, 53.13; H, 4.89.

For **6a**: 74% yield; colorless oil; IR ($CHCl_3$, cm^{-1}) 3604, 1219, 1093; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30−5.28 (m, 2 H), 4.54 (q, J = 6.5 Hz, 1 H), 4.53 (d, J = 10.5 Hz, 1 H), 4.49 (d, J = 10.5 Hz, 1 H), 1.93 (s, 1 H), 1.38 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.9, 115.1, 68.1, 32.8, 22.2; MS m/z (M^+) calcd 163.9864, obsd 163.9887.

Anal. Calcd for C_5H_9BrO: C, 36.59; H, 5.53. Found: C, 36.46; H, 5.53.

For **6b**: 60% yield; colorless oil; IR (CH_2Cl_2, cm^{-1}) 3620, 1465, 1390, 1370, 1213, 1022; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1 H), 5.30 (s, 1 H), 4.07 (d, J = 5.5 Hz, 1 H), 4.01 (q, J = 10.3 Hz, 2 H), 1.90 (heptet, J = 6.6 Hz, 1 H), 1.64 (br s, 1 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.8, 117.1, 78.0, 32.8, 31.5, 19.6, 16.8; MS m/z (M^+ − Br) calcd 113.0966, obsd 113.0923.

For **6d**: 60% yield; colorless oil; IR ($CHCl_3$, cm^{-1}) 3605, 1450, 1210, 1020; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (s, 1 H), 5.25 (s, 1 H), 4.03 (d, J = 0.6 Hz, 1 H), 4.02 (d, J = 15 Hz, 1 H), 4.00 (d, J = 15 Hz, 1 H), 1.95−1.00 (series of m, 11 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.4, 117.3, 77.6, 41.3, 32.6, 29.8, 27.6, 26.3, 26.1, 25.9; MS m/z (M^+) calcd 232.0462, obsd 232.0470.

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.35. Found: C, 51.41; H, 7.32.

General Procedure for the O-Methylation of 1. A mixture of **1c** (3.84 g, 20.0 mmol), methyl iodide (15.0 g, 100 mmol), and silver(I) oxide (23.2 g, 100 mmol) in acetonitrile (50 mL) was stirred rapidly in the absence of light for 48 h, filtered through a Celite pad, and concentrated. The residue was chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to give **3c** (1.99 g, 48%) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 1724; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.24 (m, 5 H), 6.34 (s, 1 H), 5.94 (s, 1 H), 5.14 (s, 1 H), 3.70 (s, 3 H), 3.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.3, 141.1, 139.5, 132.6, 129.6, 128.3, 127.9, 127.5, 124.9, 81.0, 57.0, 51.8; MS m/z (M^+) calcd 206.0943, obsd 206.0942.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.85. Found: C, 69.78; H, 6.83.

For **3a**: IR ($CHCl_3$, cm^{-1}) 1715, 1450, 1293, 1089; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 1 H), 5.81 (s, 1 H), 4.17 (q, J = 6.4 Hz, 1 H), 3.74 (s, 3 H), 3.26 (s, 3 H), 1.26 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.7, 141.9, 124.1, 75.2, 56.6, 51.7, 21.4; MS m/z (M^+) calcd 144.0786, obsd 144.0781.

General Procedure for Dibal-H Reduction and Bromination of 3. A cold (−78 °C), magnetically stirred solution of **3c** (4.21 g, 20.4 mmol) in dry THF (20 mL) was treated dropwise with Dibal-H (40 mL of 1.0 M in hexanes, 40.0 mmol). After 1 h at this temperature, saturated Rochelle salt solution (55 mL) was introduced, and the heterogeneous reaction mixture was allowed to warm to rt overnight. The separated aqueous phase was extracted with ethyl acetate (3×), and the combined organic solutions were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) furnished 2.30 g (63%) of alcohol as a faint yellow oil: IR (CH_2Cl_2, cm^{-1}) 3620, 1494, 1452, 1385, 1190, 1096, 1078; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.22 (m, 5 H), 5.25 (s, 1 H), 5.15 (s, 1 H), 4.80 (s, 1 H), 4.11 (d, J = 13.5 Hz, 1 H), 3.99 (d, J = 13.5 Hz, 1 H), 3.35 (s, 3 H), 1.86 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.0, 139.6, 128.5, 128.4, 127.6, 127.0, 126.8, 113.7, 85.5, 63.6, 56.9; MS m/z (M^+) calcd 178.0994, obsd 178.0995.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 73.84; H, 7.79.

A cold (−40 °C) solution of the alcohol (1.58 g, 8.87 mmol) in CH_2Cl_2 (22 mL) was treated sequentially with triphenylphosphine (3.49 g, 13.3 mmol) and *N*-bromosuccinimide (2.11 g, 12.2 mmol). The reaction mixture was stirred for 2 h, diluted with ether (65 mL), and allowed to warm to rt prior to washing with saturated $NaHCO_3$ solution and brine, drying, and solvent evaporation. Following the addition of pentane (45 mL), the insoluble solid was removed by filtration, and the filtrate was concentrated and purified chromatographically (silica gel, elution with 2% ethyl acetate in hexanes) to give 986 mg (46%) of **5c** as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 1450, 1210, 1097; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5 H), 5.40 (s, 1 H), 5.32 (s, 1 H), 4.94 (s, 1 H), 4.08 (d, J = 10.6 Hz, 1 H), 3.76 (d, J = 10.6 Hz, 1 H), 3.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.3, 139.1, 128.9, 128.7, 128.4, 128.0, 127.3, 116.3, 83.0, 57.0, 33.3; MS m/z (M^+) calcd 240.0149, obsd 240.0133.

5a. The alcohol was obtained in 29% yield as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3512, 1456, 1376, 1090; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1 H), 5.17 (s, 1 H), 4.21 (d, J = 13.8 Hz, 1 H), 4.16 (d, J = 13.8 Hz, 1 H), 3.87 (q, J = 6.5 Hz, 1 H), 3.26 (s, 3 H), 1.29 (d, J = 6.5 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.4, 112.4, 79.6, 62.8, 56.1, 19.8; MS m/z (M^+) calcd 116.0837, obsd 116.0812.

Conversion to bromide **5a** in the predescribed manner proceeded in 62% yield: colorless oil; IR ($CHCl_3$, cm^{-1}) 1210, 1114, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (s, 1 H), 5.26 (s, 1 H), 4.04 (d, J = 11.3 Hz, 1 H), 3.95 (q, J = 6.6 Hz, 1 H), 3.94 (d, J = 11.3 Hz, 1 H), 3.28 (s, 3 H), 1.32 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.2, 116.5, 77.6, 56.2, 32.1, 20.1; MS m/z (M^+) calcd 177.9993, obsd 178.0012.

Alternative Synthesis of 5d. To a solution of the alcohol produced by reduction of **2d** (3.60 g, 12.7 mmol) in CH_2Cl_2 (20 mL) were added ethyl vinyl ether (4.0 g, 56 mmol) and pyridinium *p*-toluenesulfonate (5 mg). The mixture was stirred at rt for 1 h and concentrated in vacuo to leave a residue that was dissolved in THF (10 mL) and treated with tetra-*n*-butylammonium fluoride (25 mL of 1 M in THF, 25 mmol). This solution was diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and concentrated. The resulting oil was dissolved in THF (5 mL) and added to a suspension of sodium hydride (206 mg, 8.6 mmol) in THF (5 mL). Following the addition of methyl iodide (1.4 g, 10 mmol), the mixture was stirred for 5 h, quenched with methanol (2 mL), diluted with ether, washed with water, and concentrated. The residue was treated with a 1:1 mixture of acetic acid and water (10 mL), stirred for 3 h, and diluted with ethyl acetate (20 mL). The separated organic phase was washed with brine, dried, and concentrated. The alcohol was purified by flash chromatography on silica gel to give 300 mg (13% overall) of colorless oil: IR ($CHCl_3$, cm^{-1}) 3469, 1450, 1219; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (dd, J = 3.1, 1.5 Hz, 1 H), 5.00 (d, J = 1.0 Hz, 1 H), 4.22 (dt, J = 14, 1.5 Hz, 1 H), 4.05 (dt, J = 14, 1.0 Hz, 1 H), 3.25 (s, 3 H), 3.22 (d, J = 14 Hz, 1 H), 1.90−0.70 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.4, 114.8, 90.5, 63.1 56.8, 40.1, 29.8, 29.4, 26.5, 25.9, 25.8; MS m/z (M^+) calcd 184.1463, obsd 184.1462.

The conversion of this alcohol to bromide **5d** by the procedure described above was accomplished in 74% yield: colorless oil; IR ($CHCl_3$, cm^{-1}) 1450, 1220, 746; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (d, J = 1.0 Hz, 1 H), 5.20 (s, 1 H), 3.95 (d, J = 11 Hz, 1 H), 3.88 (d, J = 11 Hz, 1 H), 3.39 (d, J = 7.4 Hz, 1 H), 3.23 (s, 3 H), 2.00−0.80 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.1, 119.0, 88.2, 56.8, 40.9, 31.8, 29.8, 29.4, 26.5, 25.9, 25.8; MS m/z (M^+) calcd 246.0619, obsd 246.0593.

Anal. Calcd for $C_{11}H_{19}BrO$: C, 53.45; H, 7.75. Found: C, 53.20; H, 7.72.

General Allylation Procedure. A mixture of the bromide (1 equiv), indium powder (1 equiv), and aldehyde (1 equiv) in the solvent of choice (10 mL/mmol of bromide) was stirred vigorously overnight or until reaction was complete. After dilution with ethyl acetate, the separated aqueous phase was extracted with ethyl acetate (3×), and the combined organic solutions were dried and concentrated. The residue was subjected to high-field ^{1}H NMR analysis and then purified by flash chromatography on silica gel.

Competitive Consumption of 4c and 6c. A mixture of bromides **4c** (170 mg, 0.50 mmol) and **6c** (113 mg, 0.50 mmol in water (5 mL) was treated with indium powder (57 mg, 0.50 mmol) and stirred vigorously at rt. Aliquots were removed after 2 and 6 h and diluted with ethyl acetate. The organic phase was dried and concentrated, and the residue was subjected to ^{1}H NMR analysis at 300 MHz. The **4c**/**6c** ratios were determined to be 64:36 and 75:25, respectively. Beyond 6 h, the onset of hydrolytic decomposition was noted.

Acknowledgment. Funds in support of this research were generously provided by the U.S. Environmental Protection Agency (Grant No. R82-4725-010). G.D.B. is a GAANN Fellow (1993−1997), and M.B.I. is an Ohio State University Postdoctoral Fellow (1996−1997).

Supporting Information Available: Characterization data for all coupling products along with copies of the high-resolution ^{1}H and ^{13}C NMR spectra of those new compounds for which elemental analyses are not reported (30 pages). This material is contained in libraries on microfiche, immediately folllows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970158A