Comparative Diastereoselectivity Analysis of Crotylindium and 3-Bromoallylindium Additions to α-Oxy Aldehydes in Aqueous and Nonaqueous Solvent Systems

Leo A. Paquette* and Thomas M. Mitzel[†]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received July 16, 1996[⊗]

The couplings of crotyl bromide (**1**) and 1,3-dibromopropene (**2**) to a triad of conformationally unrestricted α-oxy aldehydes in water, aqueous THF (1:1), and anhydrous THF are described. In no example involving **1** was the formation of anti,syn product detected. The proportion of syn isomers reached a maximum (syn/anti = 5.6:1) when the neighboring hydroxyl group was unprotected and water was the reaction medium. Although internal chelation also operates to some degree with **2**, considerable erosion of this mechanistic pathway (maximum now only 2:1) in favor of Felkin and "anti-Felkin" transition states is reflected in the product distributions. This trend can be synthetically advantageous, and a utilitarian example is demonstrated. The indium reagents studied here are notably efficient nucleophilic reaction partners in water.

The desirability of producing functionalized acyclic molecules in a highly diastereoselective manner has prompted extensive examination of the condensation of prochiral allylmetal derivatives with aldehydes.[1] Many types of organometallic reagents, most notably those where M = B, Al, Cr, Si, Sn, Ti, and Zr, are now recognized to be capable of delivering a specific stereochemical outcome. The remarkable and highly utilitarian interdependence of metal, allylic double-bond geometry and syn or anti configuration of the resultant homoallylic alcohol has been conveniently classified into three categories.[2] To rationalize the different carbon−carbon bond-forming stereoselectivities, each type is characterized by a transition state structure featuring a unique arrangement of the reacting double bonds.

All of the above transformations are effected in organic solvent, most often under anhydrous conditions. In light of the ability of indium to be capable of promoting allylations in water[3] and our specific interest in the levels of diastereoselectivity attainable in aqueous media,[4] we have presently undertaken an analysis of the diastereoselectivitity attending the coupling of the two electronically distinctive 3-substituted allylic bromides **1** and **2** to α-oxy aldehydes **3**−**5** in solvents ranging from anhydrous tetrahydrofuran to pure water. Very recently, Isaac and Chan have proposed that the allylindium intermediates formed under these conditions are amenable to regioisomeric equilibration.[5] The pre-equilibrium allows for *E* to *Z* conversion where relevant and makes provision for steric control of the coupling process when the allyl R′ or R″ substituent is sterically bulky. Otherwise, the reaction is γ-regioselective.

1, R = CH_3
2, R = Br

3, R = CH_2Ph
4, R = H
5, R = TBS

In the present investigation, only allyl inversion has been seen. Chelation control again operates to an appreciable level when the aldehyde carries a free hydroxyl substituent as in **4**. A noteworthy feature associated with the use of **2** is the option this dibromide offers for reversing to a significant degree the high syn selectivity associated with the direct condensation of **4** with allyl bromide.[4a,c]

4 (7.5 : 1)

Finally, our findings are rationalized in terms of cyclic transition states in which the aldehyde carbonyl is coordinated via the oxygen atom to the indium of the organometallic. The diastereoselectivity data show that the chiral reagent/chiral substrate pairs are not particularly conducive to high levels of reaction stereoselectivity in most cases.

Results

When 2-(benzyloxy)propanal (**3**)[6] was stirred with crotyl bromide and indium powder in water at rt for 4 h, a mixture of products resulted. Flash chromatography on silica gel resulted in separation of a 1:1 mixture of

[†] Permanent address: Department of Chemistry, Trinity College, Hartford, CT 06106.

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1996.

(1) Reviews: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (e) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (f) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(2) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

(3) (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741.

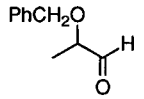
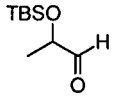
(4) (a) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863. (b) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. (c) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

(5) Isaac, M. B.; Chan, T.-H. *Tetrahedron Lett.* **1995**, *36*, 8957.

(6) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.

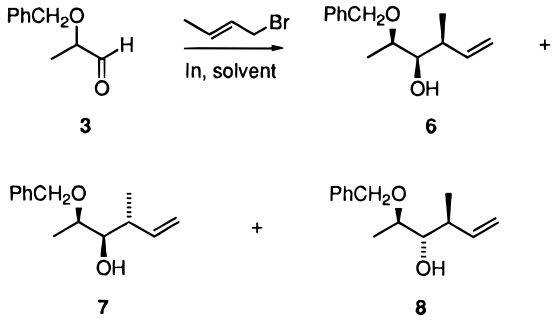
S0022-3263(96)01348-5 CCC: $12.00

Table 1. Indium-Promoted Addition of Crotyl Bromide (1) to α-Oxy Aldehydes at 25 °C[a]

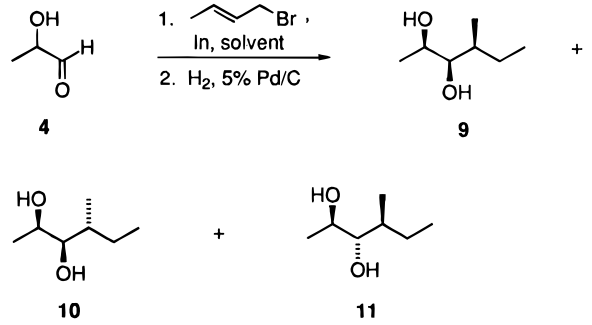
entry	aldehyde	solvent	reaction time, h	yield, %	product ratios *syn, syn*	*syn,anti*	*anti,anti*	*anti,syn*
1	 **3**	H_2O	4	89	0.5	0.5	1	0
2		H_2O-THF (1:1)	4	87	0.5	0.5	1	0
3		THF	12	74	0.5	0.5	1	0
4	 **4**	H_2O	3.5	79[b]	2.8	2.8	1	0
5		H_2O-THF (1:1)	3.5	78[b]	1.5	1.5	1	0
6		THF	7.5	64[b]	2.3	2.3	1	0
7	 **5**	H_2O	4.5	91	0.5	0.5	3	0
8		H_2O-THF (1:1)	4	88	0.5	0.5	3	0
9		THF	11	71	0.5	0.5	3	0

[a] All of the reactions were conducted minimally in duplicate at a concentration of 0.1 M with vigorous stirring for the indicated time span. The product distributions in all cases were determined by ^{1}H NMR integration at 300 MHz. [b] Yields determined after hydrogenation; all other yields refer to post-chromatographic purification.

the syn,syn (**6**) and syn,anti (**7**) alcohols from the anti,anti diastereomer **8**. None of the anti,syn product could be detected by either high-field ^{1}H or ^{13}C NMR (Table 1, entry 1). The stereochemical assignments are based on direct comparison of the ^{13}C NMR signals with those assigned earlier by Martin and Li[7] (see Experimental Section). The 0.5:0.5:1 diastereoselectivity of this reaction was observed as well in 1:1 H_2O−THF and in THF, although the reaction rate in pure organic solvent was notably slower (entry 3).



The next series of experiments was performed with the unprotected 2-hydroxypropanal (**4**).[8] Admixing of this aldehyde with crotyl bromide and indium in the same three solvent systems led again to only three diastereomeric products (entries 4−6). The polarity differences of these diols on silica gel allowed for their partial chromatographic separation. Once these fractions had been individually subjected to catalytic hydrogenation, it proved conveniently possible to isolate pure **11** and a 1:1 mixture of **9** and **10**. The product ratios given in Table 1 were derived from ^{1}H NMR integrations and from sample weights determined at this stage. Structural assignments were made possible by direct ^{13}C NMR comparisons with authentic samples.[7]



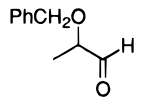
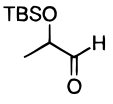
For convenience, the product mixtures derived from adding the crotylindium reagent to **5**[6] were directly hydrolyzed with *p*-toluenesulfonic acid in methanol and hydrogenated to **9**−**11** for characterization purposes (entries 7−9). We have previously reported that indium-promoted allylations performed in water become increasingly acidic (to a pH level of approximately 2.9) as they proceed to completion. The same phenomenon was, of course, observed here. Where entries 7 and 8 are concerned, deprotection of the silyl ether can materialize, particularly if stirring is allowed to proceed for an extended period of time. The predescribed workup protocol obviates any complications in determining product ratios stemming potentially from this source.

In addition to the persistent absence of the anti,syn diastereomer in entries 1−9, attention is called to the trend reflected in the product compositions. In the absence of a hydroxyl protecting group α to the aldehyde carbonyl as in **4**, the syn diols are favored by as much as 5.6:1 (in H_2O) over the anti isomer. The loss of this acidic proton as in **3** and **5** results in a decrease in the relative proportion of the syn diols. In the most extreme case, the presence of a *tert*-butyldimethylsilyl residue favors anti diol formation by a factor of 3:1.

(7) Martin, S. F; Li, W. *J. Org. Chem.* **1989**, *54*, 6129. The compilations of ^{13}C NMR shifts provided for **6** and **8** in this paper are incomplete. As shown herein, the syn,syn isomer exhibits a necessary 12th carbon peak at 126.5 ppm. For the anti,anti isomer, the unlisted carbon signal is seen at 127.0 ppm.

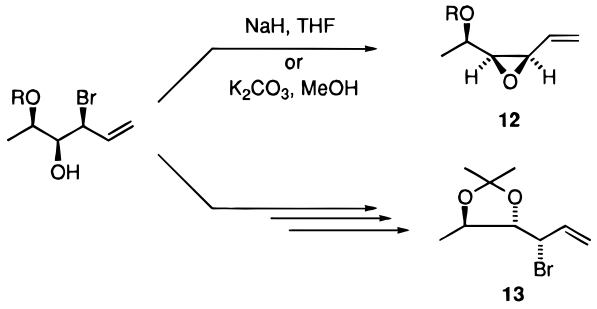
(8) Schlosser, M.; Brich, Z. *Helv. Chim. Acta* **1978**, *61*, 1903.

Table 2. Indium-Promoted Addition of 1,3-Dibromopropene (2) to α-Oxy Aldehydes at 25 °C[a]

entry	aldehyde	solvent	reaction time, h	yield, %	product ratios: *syn, syn*	*syn,anti*	*anti,anti*	*anti,syn*
10	 **3**	H_2O	2.5	88	0.5	0.5	1	1
11		H_2O-THF (1:1)	2.5	88	0.5	0.5	1	1
12		THF	7.0	75	0.5	0.5	1	1
13	 **4**	H_2O	4.0	80[b]	1	1	0.5	0.5
14		H_2O-THF (1:1)	4.5	80[b]	1	1	0.5	0.5
15		THF	9.0	68[b]	0.8	0.8	0.5	0.5
16	 **5**	H_2O	2.5	88	0.5	0.5	4.5	4.5
17		H_2O-THF (1:1)	2.0	90	0.5	0.5	5	5
18		THF	10	79	0.5	0.5	5	5

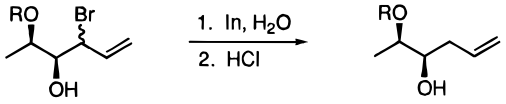
[a] Consult footnote *a* of Table I. [b] Yields based on unpurified products; all other yields refer to post-chromatographic purification.

A quick scan of Table 2 will reveal that the reactions of dibromide **2** with **3** and **5** are more anti selective than those involving crotyl bromide. In each of the alkylations represented by entries 10−18, it was necessary to monitor reaction progress carefully, especially when complete consumption of the aldehyde was being approached, in order to minimize unwanted reductive debromination of the halohydrin products.[9] With this precaution in place, each of the processes was found to deliver all four possible diastereomers. In order to secure proper stereochemical assignments, attention was initially directed to chemical correlation with epoxides on the one hand and acetonides on the other. Through analysis of the oxirane proton coupling constants in **12**, the syn/anti relationship of the

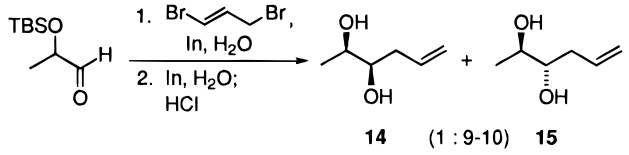


neighboring bromine- and hydroxyl-substituted carbons would be made apparent. With subsequent scrutiny of the spectral details of **13**, full analysis of the interrelationship of all three stereogenic centers would be realized. Unfortunately, overlapping absorptions in the ^{1}H NMR spectra of **13** and its diastereomers precluded the use of these derivatives for characterization purposes.

An alternative workable solution consisted of removal of the allylic bromine via reduction with indium in water. This protocol operates without migration of the double bond to deliver known diols,[10] thereby permitting direct comparison of ^{1}H and ^{13}C NMR features.

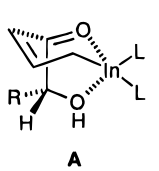


From the results compiled in Table 2, the apparent role played by the vinylic bromine in **2** would appear to be significant erosion of the chelation capability of the neighboring α-hydroxyl substituent in **4**. Not surprisingly, the presence of an *O*-benzyl group as in **3** does not give rise to any improved stereochemical bias. In contrast, the bulky *tert*-butyldimethylsilyl residue in **5** increases the anti selectivity rather steeply to a level approaching 1:10. This finding is significant in that a route complementary to the syn-selective direct allylation of the α-hydroxy aldehyde is now opened.

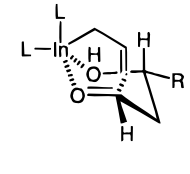


Discussion

We have previously demonstrated that the stereochemical course of allylindium reactions to α- and β-oxy aldehydes in water as the reaction medium is strongly influenced by the protecting group resident on the neighboring oxygen.[4a,c] Significantly, free hydroxyl derivatives react with excellent diastereofacial control at accelerated rates to provide heightened percentages of syn-1,2-diol and anti-1,3-diol products. These observations have given rise to the conclusion that the chelated transition states **A** and **B** are adopted in these reactions.



A

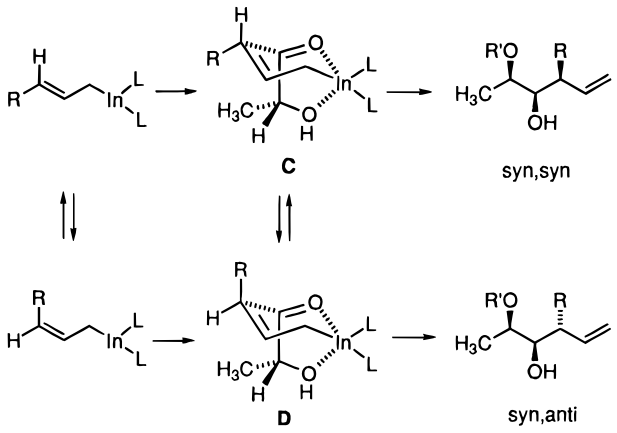


B

(9) Chen, D.-L.; Li, C.-J. *Tetrahedron Lett.* **1996**, *37*, 295.
(10) (a) Li, C.-J.; Chan, T.-H. *Can. J. Chem.* **1992**, *70*, 2726. (b) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann Chem.* **1987**, 881.

Substitution of the hydroxyl proton by CH_3, $C_6H_5CH_2$, or CH_3OCH_2[11] is predictably ameliorative of the chelation control pathway as reflected in a modest erosion of the allylation diastereoselectivity. Larger groups such as *tert*-butyldimethylsilyl effectively deter transient binding of the attached oxygen to the indium, at least in water, and promote alternative conversion to product via Felkin−Ahn transition states.[12] Thus, steric effects appear to exert a significant influence on the outcome of these single asymmetric induction processes.

The focus of the present investigation was to determine to what extent and in which direction the stereochemistry inherent in the olefin geometry of **1** and **2** would be transmitted to the newly formed C−C bond in the product. Although crotyl bromide added to **4** with a preference for adoption of the cyclic chelated transition states **C** and **D** (syn selectivity as high as 5.6:1), the

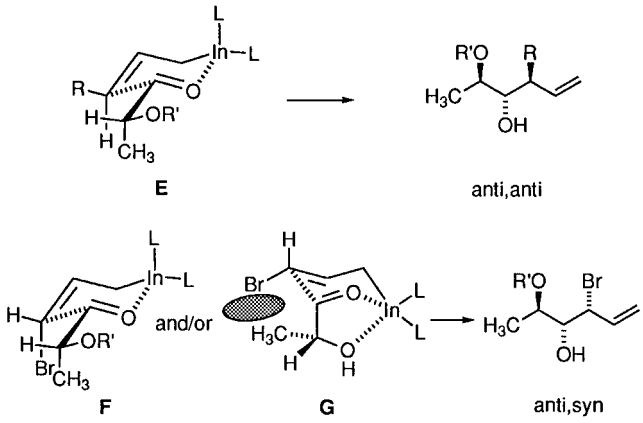


replacement of methyl by a γ-bromine is accompanied by an unexpected dropoff in the level of syn product (now only 2:1). Bromine substitution also has the effect of eroding the diastereofacial selectivity of the reactions.[13] Whereas the crotyl bromide experiments provided no detectable evidence for the formation of anti,syn products, those involving **2** are fully nonselective with generation of approximate 1:1 mixtures in each example.

Recognition must necessarily be given to the fact that crotyl organometallics such as the Grignard,[14] potassium,[15] and lithium derivatives[16] undergo *E*/*Z* equilibration with considerable ease. Higher homologs behave analogously.[17] In TMEDA under equilibrating conditions, the *Z* form of crotyllithium predominates over the *E* form to the extent of 85:15.[16b] The prevailing hypothesis is that this *Z* stereoselectivity probably does not have its origin in the particular binding features of any specific metal but can be attributed to the intrinsic properties of the allyl anion itself.[15d] If so, then ready access to transition states **C** and **D** could be made possible by an entirely comparable geometric isomerization of the crotylindium reagent. Under these circumstances, the distribution of syn,syn, and syn,anti diastereomers would come under the control of the relative rates at which **C** and **D** advance to product. In light of the product distributions, these rates are closely comparable.

These considerations carry important implications for allylindium reagents where *E*/*Z* equilibration does not operate due to structural circumstances. Under conditions where double-bond configuration is not compromised as in the predescribed scenario, high stereoselectivitiy should be observed during coupling to aldehydes. The stereochemical outcome of these considerations will depend as usual on whether chelation control is operative or not. These aspects of the problem are currently under active investigation.

At the present time, it is unclear whether the γ-bromine outcome is due to an electronic effect, to the large steric size of this atom, to the longer C−Br bond, or to a combination of these influences. The indication exists that *E*/*Z* equilibration is also facile in this instance. The



notable preference exhibited by **2** for reaction via the transition states **E** and **F** or **G** is sufficiently elevated when R′ is TBS to favor formation of the anti isomer to the extent of 10:1! This appreciable kinetic selectivity holds synthetic utility. Following reductive debromination and desilylation, anti diol **15** is obtained predominantly. This diastereoselection is opposite to that realized upon direct condensation of **4** with allylindium in water, a process which is highly syn-selective.

Lastly, we point out the greater efficiency of indium-promoted crotylation and bromoallylation in water and aqueous THF. A 10−20% enhancement in combined product yield was universally observed. Although these C−C bond-forming reactions happen not to be particularly diastereoselective when conducted in aqueous environments, each transformation occurs with remarkably few, if any, side reactions. The higher reaction rate in water than in aqueous THF may be a result of the

(11) (a) Still, W. C; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1984**, *25*, 729.

(12) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(13) Selected examples include the following: (a) Williams, D. R.; Klingler, F. D. *Tetrahedron Lett.* **1987**, *28*, 869. (b) Roush, W. R.; Peseckis, S. M.; Walts, A. C. *J. Org. Chem.* **1984**, *49*, 3429. (c) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227. (d) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489. (e) Hoffmann, R. W.; Zeiss, H.-J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982**, *115*, 2357. (f) Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (g) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229. (h) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1072.

(14) (a) Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 1769. (b) Nordlander, J. E.; Young, W. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 494. (c) Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1984**, *84*, 2010.

(15) (a) Schlosser, M.; Hartmann, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 439. (b) Hartmann, J.; Muthukrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1974**, *57*, 2261. (c) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701. (d) Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674.

(16) (a) West, P.; Purmont, J. I.; McKinley, S. V. *J. Am. Chem. Soc.* **1968**, *90*, 797. (b) Bates, R. B.; Beavers, W. A. *J. Am. Chem. Soc.* **1974**, *96*, 5001.

(17) (a) Sandel, V. R.; McKinney, S. V.; Freedman, H. H. *J. Am. Chem. Soc.* **1968**, *90*, 495. (b) Schlosser, M. *Chimia* **1974**, *28*, 395. (c) Schlosser, M.; Hartmann, J.; David, V. *Helv. Chim. Acta* **1974**, *57*, 2261. (d) Rauchschwalbe, G.; Schlosser, M. *Helv. Chim. Acta* **1975**, *58*, 1094.

hydrostatic pressure that materializes around the small globules that make their appearance in purely aqueous environments. This phase separation is not seen in 1:1 aqueous THF.

Experimental Section[18]

Additions Involving Crotyl Bromide and Aldehyde 3. A. In H_2O. To a magnetically stirred mixture of **3** (100 mg, 0.617 mmol) and water (6.7 mL) were added crotyl bromide (123 mg, 0.914 mmol) and indium powder (77 mg, 0.670 mmol). After 4 h, ethyl acetate (10 mL) was introduced and the layers were separated 45 min later. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic solutions were dried and concentrated. Chromatography of the residue on silica gel (elution with 20:1 hexanes/ethyl acetate) gave a fraction containing a 1:1 mixture of two syn diastereomers (61 mg) and a second pure anti fraction (60 mg, 89% combined yield). The components were identified on the basis of their ^{13}C NMR chemical shifts in $CDCl_3$[7] (at 75 MHz): syn,syn, 141.6, 138.4, 128.4 (2 C), 127.8 (2 C), 127.6, 126.5, 114.5, 78.3, 70.9, 40.8, 16.1, 15.0 ppm; syn,anti, 139.8, 138.4, 128.4 (2 C), 127.8 (2 C), 127.7, 115.2, 78.2, 76.5, 70.9, 40.2, 17.6, 15.3 ppm; anti,anti, 140.5, 138.4, 128.4 (2 C), 127.6 (2 C), 127.0, 115.4, 76.4, 75.7, 70.6, 39.5, 16.3, 13.7 ppm.

B. In H_2O−THF (1:1). A mixture of **3** (100 mg, 0.617 mmol), crotyl bromide (123 mg, 0.914 mmol), and indium powder (77 mg, 0.670 mmol) in 1:1 H_2O−THF (6.6 mL) was stirred for 4 h. Following product isolation in the predescribed manner, there was isolated 60 mg of a 1:1 mixture of the syn diastereomers together with 58 mg of the anti,anti diol (87% combined). The products were identified on the basis of their ^{13}C NMR chemical shifts.

C. In THF. A mixture of **3** (100 mg, 0.617 mmol), crotyl bromide (127 mg, 0.914 mmol), and indium powder (77 mg, 0.670 mmol) in THF (6.7 mL) was stirred at rt for 12 h before being processed in the usual way. The first chromatographic fraction (50 mg) consisted of equal amounts of the syn,syn and syn,anti diols. To elute subsequently was a pure fraction of the anti,anti product (51 mg, 74% combined).

Additions Involving Crotyl Bromide and Aldehyde 4. A. In H_2O. A mixture of **4** (80 mg, 1.08 mmol), crotyl bromide (218 mg, 1.62 mmol), and indium powder (136 mg, 1.18 mmol) in water (11.8 mL) was stirred at rt for 3.5 h and worked up in the predescribed manner. The mixture was subjected to flash chromatography (silica gel, elution with 2:1 hexanes/ethyl acetate) to give two fractions in a 5.5:1 ratio. Each fraction was separately hydrogenated at 600 psi in ethanol over 5% palladium on carbon. Following removal of the catalyst by filtration and concentration in vacuo, there was isolated 95 mg of a mixture of **9** and **10** as well as 17 mg of **11** (79% combined yield). The saturated diols were identified on the basis of their ^{13}C NMR chemical shifts in $CDCl_3$[7] (at 75 MHz): **9**, 79.9, 67.9, 36.8, 23.5, 19.9, 15.9, 11.5 ppm; **10**, 78.6, 68.8, 36.3, 26.9, 19.2, 12.7, 11.7 ppm; **11**, 78.2, 68.2, 36.7, 25.3, 15.3, 14.4, 10.6 ppm.

B. In H_2O−THF (1:1). A mixture of **4** (80 mg, 1.08 mmol), crotyl bromide (218 mg, 1.62 mmol), and indium powder (136 mg, 1.18 mmol) in 1:1 H_2O−THF (11.8 mL) was stirred for 3.5 h before being processed in the manner just described. After catalytic hydrogenation, there was obtained 84 mg of a mixture of **9** and **10** together with 28 mg of **11** (78% combined).

C. In THF. A mixture of **4** (200 mg, 2.70 mmol), crotyl bromide (546 mg, 4.05 mmol), and indium powder (341 mg, 2.97 mmol) in THF (29.7 mL) was stirred at rt for 7.5 h before being processed in the usual way and hydrogenated. The two chromatography fractions (5.5:1 ratio) were hydrogenated to give 193 mg of a mixture of **9** and **10** together with 35 mg of **11** (64% combined yield).

Additions Involving Crotyl Bromide and Aldehyde 5. A. In H_2O. A mixture of **5** (100 mg, 0.532 mmol), crotyl bromide (107 mg, 0.798 mmol), and indium powder (67 mg, 0.585 mmol) in water (5.9 mL) was stirred for 4.5 h. After the customary workup and flash chromatography, a colorless oil (118 mg, 91%) was obtained. This material was dissolved in anhydrous methanol (20 mL) containing 5 mg of *p*-toluenesulfonic acid and stirred for 6 h, at which time ethyl acetate (20 mL) and water (20 mL) were introduced. The separated aqueous phase was extracted with ethyl acetate (4 × 10 mL), and the combined organic layers were dried and evaporated. Purification via flash chromatography (silica gel, elution with 1:1 hexanes/ethyl acetate) gave two fractions in a 1:3 ratio (61 mg, 97%). Independent hydrogenation of each fraction gave a 1:1 mixture of **9** and **10** (15 mg) and pure **11** (46 mg). These diols were identified by means of their ^{13}C NMR spectra as described above.

B. In H_2O−THF (1:1). From 300 mg (1.59 mmol) of **5**, 321 mg (2.39 mmol) of crotyl bromide, and 201 mg (1.75 mmol) of indium powder in 17.6 mL of 1:1 H_2O−THF that had been stirred for 4 h, chromatographed (340 mg, 88%), and hydrogenated, there was isolated via chromatography 45 mg of a 1:1 mixture of **9** and **11** in addition to 133 mg of **11**.

C. In THF. A mixture of **5** (300 mg, 1.59 mmol), crotyl bromide (321 mg, 2.39 mmol), and indium powder (201 mg, 1.75 mmol) was stirred in THF (17.5 mL) for 11 h before being processed in the usual way to give two fractions in a 1:3 ratio (combined weight of 272 mg or 71%). Independent hydrogenation of each fraction gave 35 mg of the **9/10** mixture and pure **11** (106 mg). These diols were identified by the ^{13}C NMR spectra.

Additions Involving Dibromide 2 and Aldehyde 3. A. In H_2O. A mixture of **3** (135 mg, 0.834 mmol) and water (8.7 mL) was treated with 1,3-dibromopropene (334 mg, 1.668 mmol) and indium powder (101 mg, 0.876 mmol) and stirred at rt for 2.5 h. Following the addition of ethyl acetate (15 mL) and additional stirring (30 min), the separated aqueous layer was extracted with ethyl acetate and the combined organic phases were dried and evaporated. The residue was subjected to flash chromatography on silica gel (elution with 30:1 hexanes/ethyl acetate) to give a colorless oil (209 mg, 88%).

An 80 mg (0.280 mmol) sample of this bromohydrin was dissolved in dry THF (20 mL), treated with sodium hydride (13 mg, 0.54 mmol), and stirred at rt for 7.5 h. After the addition of CH_2Cl_2 (15 mL) and water (10 mL), the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (2 × 20 mL), dried, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 20:1 hexanes/ethyl acetate) to yield the stereoisomeric epoxides as a colorless oil (76 mg, 95%).

The presence of all four possible diastereomers was readily discerned by ^1H NMR spectroscopy at 300 MHz (in $CDCl_3$). The two trans epoxides exhibited key signals at δ 3.16−3.12 (m, 0.11 H) and δ 3.04 (dd, J = 4.0, 8.2 Hz, 0.2 H), while the corresponding absorptions of the cis epoxides appeared at δ 2.97 (dd, J = 2.2, 6.7 Hz, 0.1 H) and 2.86 (dd, J = 2.1, 5.3 Hz, 0.2 H). On the basis of the ensuing experiment, these epoxides are recognized to be **a**−**d**, respectively. The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of this mixture exhibited nonoverlapping sets of signals at (138.4, 138.3, 138.2, 138.0), (137.6, 135.1, 134.9, 132.2), (120.6, 120.4, 119.7, 119.5), (75.5, 73.9, 71.5, 71.2), (71.1, 71.0, 70.7, 69.8), (63.3, 62.2, 61.9, 60.7), (58.0, 57.4, 54.9, 54.7), and (21.1, 18.7, 17.7, 17.4) ppm.

In a separate experiment, a sample of the bromohydrin mixture (256 mg, 0.900 mmol) and indium powder (103 mg, 0.900 mmol) was stirred in H_2O (9 mL) at rt for 8 h, at which time 1 N HCl (10 mL) was added with stirring. Ethyl acetate (15 mL) was next introduced, and the separated aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried and evaporated, and the residual oil was purified via flash chromatography (silica gel, elution with 20:1 hexanes/ethyl acetate) to give a mixture of two diastereomeric alcohols (174 mg, 95%). The syn and anti configurations were elucidated by comparison of ^1H NMR spectra with those of known compounds.[10b] Integration of the distinctive methyl doublets (δ 15.3 for syn, δ 13.7 for anti) showed the syn/anti ratios to be 1:2.

(18) For general experimental details, consult ref 4b.

(19) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.

B. In H_2O−THF (1:1). Reaction of **3** (200 mg, 1.21 mmol) with 1,3-dibromopropene (484 mg, 2.42 mmol) and indium powder (153 mg, 1.33 mmol) in 1:1 H_2O−THF (13.2 mL) for 2.5 h gave 291 mg (88%) of the bromohydrin diastereomers. Following cyclization to epoxides **a**−**d** and independent indium-promoted reduction, the product ratio was determined to be closely comparable to that observed in part A.

C. In THF. Reaction of **3** (200 mg, 1.21 mmol) with 1,3-dibromopropene (484 mg, 2.42 mmol) and indium powder (153 mg, 1.33 mmol) in THF (13.2 mL) for 7 h afforded 268 mg (75%) of bromohydrin isomers. Subsequent to chemical correlation in the predescribed manner, the product distribution was found to be identical to that established in experiments A and B.

Additions Involving Dibromide 2 and Aldehyde 4. A. In H_2O. A mixture of **4** (80 mg, 1.08 mmol), 1,3-dibromopropene (432 mg, 2.16 mmol), and indium powder (130 mg, 1.13 mmol) in water (11.3 mL) was stirred at rt for 4 h and processed as described above to give 168 mg (80%) of the bromohydrin as a colorless oil.

To a solution of this material (249 mg, 1.28 mmol) in anhydrous methanol (25 mL) was added potassium carbonate (270 mg, 1.92 mmol), and stirring was maintained for 12 h prior to solvent evaporation. The solid was separated by filtration, and the filtrate was concentrated to give the epoxy alcohol (127 mg, 87%). This oil was dissolved in CH_2Cl_2 (25 mL), admixed with *tert*-butyldimethylsilyl chloride (300 mg, 2.00 mmol) and imidazole (330 mg, 4.85 mmol), and stirred for 12 h. The solvent was removed in vacuo at 20 °C, and the product was purified by flash chromatography on silica gel (elution with 50:1 hexanes/ethyl acetate) to give a colorless oil (353 mg, 78% overall).

The presence of all four epoxides was readily discerned by ^{1}H NMR spectroscopy at 300 MHz (in $CDCl_3$). The two trans epoxides exhibited key signals at δ 3.10 (dd, J = 4.1, 7.8 Hz, 0.35 H) and δ 2.96 (dd, J = 4.1, 7.9 Hz, 0.18 H), while the corresponding absorptions of the cis epoxides appeared at δ 2.85 (dd, J = 2.2, 4.5 Hz, 0.28 H) and δ 2.77 (dd, J = 2.2, 4.5 Hz, 0.18 H). On the basis of the ensuing experiment, these epoxides are recognized to be **e**−**h**, respectively.

The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of this mixture exhibited nonoverlapping sets of signals at (135.4, 135.2, 132.4, 132.3), (120.4, 120.2, 119.3, 119.1), (67.4, 67.0, 65.5, 65.1), (63.5, 63.1, 62.7, 62.3), and (57.7, 57.3, 56.6, 56.5) ppm.

In a separate experiment, a sample of the original bromohydrin mixture (168 mg, 0.864 mmol) was stirred with indium powder (100 mg, 0.864 mmol) in water (8.6 mL) at rt for 7 h, at which time the reaction mixture was worked up in the usual manner to afford a mixture of two diols as a viscous, colorless oil (90 mg, 90%). Distinction between the syn and anti isomers was accomplished by ^{1}H NMR spectroscopy. Their methyl shifts appear at δ 1.16 (d, J = 6.3 Hz) and δ 1.13 (d, J = 6.4 Hz), respectively.[13] Integration of these peaks showed the syn/anti ratio to be 2:1.

B. In H_2O−THF (1:1). A mixture of **4** (148 mg, 2.0 mmol), 1,3-dibromopropene (800 mg, 4.0 mmol), and indium powder (252 mg, 2.2 mmol) in 1:1 H_2O−THF (22 mL) was stirred at rt for 4.5 h. Comparable processing gave 311 mg (80%) of the bromohydrin mixture as a colorless oil. This unpurified material was taken to **e**−**h** as described above and analyzed in this manner.

C. In THF. A mixture of **4** (148 mg, 2.0 mmol), 1,3-dibromopropene (800 mg, 4.0 mmol), and indium powder (252 mg, 2.2 mmol) in THF (22 mL) was stirred at rt for 9 h and processed as described above to give 265 mg (68%) of the bromohydrin mixture as a colorless oil. This sample was transformed into **e**−**h** as before for product analysis.

Additions Involving Dibromo 2 from Aldehyde 5. In H_2O. A mixture of **5** (190 mg, 1.0 mmol), 1,3-dibromopropene (400 mg, 2.0 mmol), and indium powder (126 mg, 1.1 mmol) in water (11 mL) was stirred at rt for 2.5 h and worked up in the predescribed manner to give 272 mg (88%) of bromohydrin mixture as a colorless oil. To a solution of this material (270 mg, 0.870 mmol) in THF (10 mL) was added sodium hydride (24 mg, 0.979 mmol). After 10 h of stirring, water was added, and the separated aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water, dried, and evaporated. The residue was purified via flash chromatography on silica gel (elution with 20:1 hexanes/ethyl acetate) to give epoxides **e**−**h** as a colorless oil (182 mg, 92%). The relative percentages of the four epoxides were ascertained by integration of the characteristic peaks denoted earlier.

In a separate experiment, 300 mg (0.971 mmol) of the bromohydrin mixture in water (10 mL) was treated with indium powder (115 mg, 0.971 mmol) and stirred for 8 h. A white precipitate was formed during this time. Hydrochloric acid (10 mL of 1 N) was added, and after 10 min of stirring the reaction mixture was extracted with ethyl acetate (3 × 15 mL), the combined organic phases were dried and concentrated, and the residue was purified by flash column chromatography (silica gel, eluton with 50:1 hexanes/ethyl acetate). The colorless oil so obtained (198 mg, 89%) was dissolved in anhydrous methanol (10 mL), treated with a crystal of *p*-toluenesulfonic acid, and stirred at rt for 5 h prior to solvent evaporation. Purification of the residue by flash chromatography on silica gel (elution with 2:1 hexanes/ethyl acetate) gave a 1:9 mixture of the syn and anti diols (85 mg, 85%), as determined by ^{1}H NMR analysis (see above).

B. In H_2O−THF (1:1). From a mixture of **5** (190 mg, 1.0 mmol), 1,3-dibromopropene (400 mg, 2.0 mmol), and indium powder (126 mg, 1.1 mmol) in 1:1 H_2O−THF (11.0 mL), there was isolated after 2 h 278 mg (90%) of the bromohydrin mixture as a colorless oil. This unpurified material was transformed into the epoxides as described above and comparably analyzed.

C. In THF. Stirring **5** (190, 1.0 mmol) and 1,3-dibromopropene (400 mg, 2.0 mmol) with indium powder (126 mg, 1.1 mmol) in THF (11 mL) for 10 h gave 244 mg (79%) of the bromohydrin mixture. Conversion to the epoxides in the predescribed manner allowed for analysis of the product ratios reported in Table 2.

Acknowledgment. Financial support from the Environmental Protection Agency and the Emissions Reduction Research Center at the New Jersey Institute of Technology is greatfuly acknowledged. The authors thank Prof. S. F. Martin for an authentic sample of the anti,syn diol analogue of **9**−**11** which permitted verification of its absence from the crotyl bromide additions to **3**−**5**, and Dr. Methvin Isaac for relevant discussions.

JO9613489