Addition of Allylindium Reagents to Aldehydes Substituted at C_α or C_β with Heteroatomic Functional Groups. Analysis of the Modulation in Diastereoselectivity Attainable in Aqueous, Organic, and Mixed Solvent Systems

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Abstract: The stereochemical course of indium-promoted allylations to α- and *β*-oxy aldehydes has been investigated in solvents ranging from anhydrous THF to pure H_2O. The free hydroxyl derivatives react with excellent diastereofacial control to give significantly heightened levels of *syn*-1,2-diols and *anti*-1,3-diols. Relative reactivities were determined in the α-series, and the hydroxy aldehyde proved to be the most reactive substrate. This reactivity ordering suggests that the selectivity stems from chelated intermediates. The rate acceleration observed in water can be heightened by initial acidification. Indeed, the indium-promoted allylation reaction mixtures become increasingly acidic on their own. Preliminary attention has been accorded to salt effects, and tetraethylammonium bromide was found to exhibit a positive synergistic effect on product distribution. Finally, mechanistic considerations are presented in order to allow for assessment of the status of these unprecedented developments at this stage of advancement of the field.

The Cram rule,[1] which was put forward more than four decades ago as a predictor of the stereochemical course of nucleophilic additions to acyclic aldehydes and ketones, initiated organic chemists into thinking systematically about diastereomeric transition states. As a consequence of those complications introduced by the dynamic conformational nature of substrates bearing stereogenic centers proximal to the carbonyl group, others have presented paradigms in which the interplay of steric and stereoelectronic effects has been somewhat modified.[2−4] Subtle intramolecular (in the form of torsional strain) and intermolecular interactions (e.g., nonbonded compressions associated with the preferred trajectory for nucleophilic attack[5]) have garnered serious attention. When α- and *β*-alkoxy carbonyl compounds are involved and chelated intermediates intervene, mechanistic analysis is simplified. In such instances, addition often occurs from the sterically less hindered *π*-face of the preorganized complex.[6] Grignard reagents are reputed to be particularly well suited to chelate control,[7−9] while nonchelate behavior has been reported for organolithium,[10] alkyltitanium,[6] and allylchromium reagents,[11] as well as lower-order cuprates.[12]

The sensitivity of the organometallic reagents mentioned above to moisture requires that their addition reactions be performed in *anhydrous* organic solvents. The metal indium has recently been shown to offer intriguing advantages for effecting C−C bond formation in an *aqueous* environment.[12−14] The Cram and Felkin-Anh proposals have not been founded on reactions carried out in water or under "wet conditions" of any type. This change to a significantly more polar hydrogen bonding medium could conceivably damp those factors controlling facial selectivity in the absence of water.[13b,14e] It need not, however, if coordination to the indium ion overrides those solvation forces that would break down the chelate.[15] These and many other related questions were viewed by us to warrant a detailed comparative analysis of the indium-promoted allylation of chiral α- and *β*-oxygenated aldehydes under conditions where the reactive medium would range from anhydrous THF to pure water. The observed stereoselectivities would, without question, lift the limitations imposed by our current knowledge base, which has been confined to observations made in the strict absence of moisture. As others have emphasized,[14−16] organometallic reactions conducted in aqueous media preclude any need to make recourse to protection−deprotection tactics for a number of functional groups. Perhaps still more advantageous is the fact that water is the quintessentially benign solvent from the environmental and flammability perspectives. Furthermore,

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the need to remove water of hydration from compounds and the requirement for a dry atmosphere would cease to exist.

Interest in the synthetic applications of indium, a previously little explored metal, has been on the upswing in recent years.[13−19] At 5.785 eV, the first ionization potential of indium falls well below that of comparable metals such as zinc, magnesium, tin, and aluminum.[14b] Indium metal is roughly comparable to silver in cost. However, regeneration of the indium after completion of the reaction can be readily and efficiently accomplished electrochemically.[16a] As a consequence of the low solubility of certain classes of compounds in water, we have also included experiments in which the medium consists of equivolume amounts of THF and H_2O.[20]

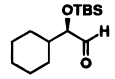
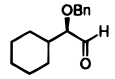
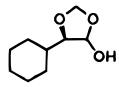
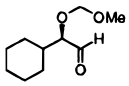
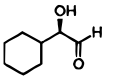
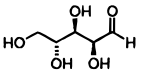
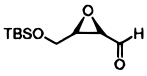
Results and Discussion

α-Oxygenated Aldehydes. A variety of aldehydes containing α-oxy substituents of widely differing basicities, viz. **1**−**8**, were examined for the purpose of elucidating whether Lewis acid−base interactions play a role in indium-promoted reactions and to what extent (Table 1). If chelate control is operational, the expected allylation product is the syn diastereomer; otherwise, conversion to the anti product results (Scheme 1). The known aldehydes **1**,[21] **2**,[21,22] and **5**[21] were complemented by the MOM derivative **4** and cyclic hemiacetal **3**. The preparation of the latter two substrates began with addition of vinylmagnesium bromide to cyclohexanecarboxaldehyde. Whereas hydroxyl protection in **9** followed by oxidative cleavage leads to **4**, direct ozonolysis of **9** gives rise to **3** (Scheme 2). D-Arabinose (**6**) and the highly oxygenated systems **7**[23] and **8**[24] round out this subset.

The results obtained with **1** (entries 1−4) and **2** (entries 5−8) provide important calibration points for non-chelate-controlled behavior. In both instances, the anti product is favored. Presumably because the basicity of the *tert*-butyldimethylsiloxy substituent falls below that of benzyloxy, the anti percentages reach a maximum for **1**. The product distributions were quantified by chemical conversion to the acetonide in advance of high-field ^{1}H NMR analysis[21,25] (entries 1−4, 9−12, and 17), by prior acetylation to gain solubility (entries 18−24),[15a,16a] or most simply by direct spectroscopic integration (entries 5−8). It is noteworthy that in every example allylations performed in either H_2O or H_2O−THF (1:1) proceeded at appreciably more rapid rates than in THF alone. For **1**, the diastereoselectivity realized is constant whether H_2O is present or not. Interestingly, the anti preference in the case of **2** decreases by a factor of about 3 in pure H_2O. Product yields were found to be consistently high.

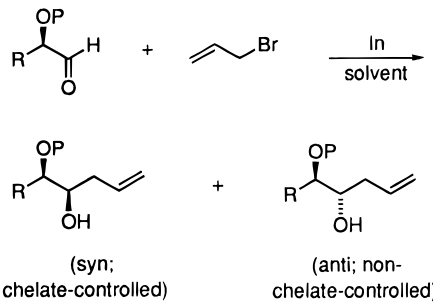
Hemiacetal **3** must, of course, undergo ring opening prior to condensation with the allylindium reagent. Beyond that, it is not clear that C−C bond formation materializes prior to, or only after, the loss of formaldehyde. The two options are approximated in MOM ether **4**, and the α-hydroxy aldehyde **6** and, for this reason, these substrates were also included in the study. Unmasking of the carbonyl group in **3** is without doubt

Table 1. Indium-Mediated Allylations of α-Oxygenated Aldehydes in Various Solvents (CH_2=$CHCH_2Br$, 25 °C)[a]

entry	aldehyde	solvent	reaction time, h	product ratio syn	product ratio anti	yield, %
1		H_2O	3.5	1	3.9	90
2		H_2O-THF (1:1)	2.5	1	4.2	87
3		THF	36-50	1	4.0	92
4	**1**	THF[b]	10	1	4.3	88
5		H_2O	3	1	1.2	92
6		H_2O-THF (1:1)	2.5	1	2.2	93
7		THF	40-47	1	3.9	87
8	**2**	THF[b]	12.5	1	3.1	81
9		H_2O	24-30	2.3	1	90-95
10		H_2O-THF (1:1)	20-26	2.3	1	90-93
11		THF	No reaction			
12	**3**	THF[c]	6-7	2.1	1	80-85
13		H_2O	3.5-4.5	2.1	1	80-85
14		H_2O-THF (1:1)	7	1.7	1	83-86
15		THF	14	1.6	1	78-81
16	**4**	THF[b]	11	1.3	1	82-84
17	 **5**	H_2O	5	9.8	1	85-90[d]
18		H_2O	24-30	10.2	1	90
19		H_2O-THF (1:1)	18-30	8.2	1	87
20		THF	50-76	3.0	1	92
21	**6**	THF[b]	24-30	6.3	1	88
22		THF[e]	22-24	5.7	1	88
23		H_2O-EtOH (1:1)	12	9.1	1	85
24		H_2O-EtOH (1:1)[e]	5	9.3	1	88
25		H_2O	3.5	1	3.2	83
26		H_2O-THF (1:1)	3.5	1	3.9	80
27		THF	21-25	1	5.9	86
28	**7**	THF[b]	12	1	5.5	89
29		H_2O	2.5-3.5	1	2	78
30		H_2O-THF (1:1)	3.5	1	2	82
31		THF	20-25	1	5.2	89
32	**8**	THF[b]	23	1	4.3	77

[a] All of the reactions were performed at least in duplicate at a concentration of 0.1 M with vigorous stirring for the indicated time span. The product distributions for **1**−**5** and **7** were determined by ^{1}H NMR integration at 300 MHz; for **6** and **8**, the relative amounts of products following chromatography are given. [b] The THF solution of allyl bromide was heated to reflux with the indium prior to reaction. The mixture was cooled to rt prior to introduction of the aldehyde, and the coupling was performed as in *a*. [c] Performed at the reflux temperature of the solvent. [d] Based on the chemical purity of the sample of **5** employed. [e] Promoted by sonication.

Scheme 1



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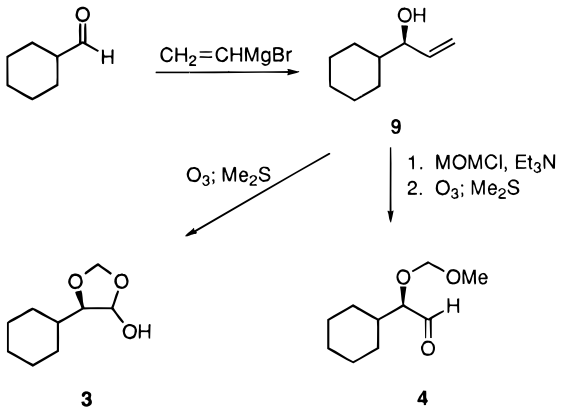
Scheme 2



a relatively slow process in H_2O, since reaction times of 20−30 h were necessary to complete the consumption of starting material (entries 9 and 10). For **5**, allylation was complete in much less time (entry 17). No reaction was observed with **3** in THF unless the reaction mixture was heated. The product distribution in both examples was now in favor of the syn diastereomer, the crossover suggesting that chelate control may now be operating. For **5**, the syn/anti ratio (9.8) is appreciably higher than that observed for **3** (2.3). Evidently, **3** is not undergoing condensation as the free α-hydroxy aldehyde. The results provided by the MOM ether **4** (entries 13−16) hold interest because syn selectivity is operational. When comparison is made with the *O*-benzyl ether **2**, the added oxygen in **4** is seen to exert a respectable directing effect as a consequence of its chelating, or perhaps more accurately co-chelating, ability. However, this capacity falls somewhat short of that exhibited by the ring-opened tautomer of **3** where the side chain features a terminal hydroxyl. The impressive role of OH substituents becomes still more apparent when they reside directly adjacent to the carbonyl as in **5** and **6**.

Extensive studies were not performed on **5** because this substance is difficult to obtain pure and is quite prone to polymerization. On the other hand, D-arabinose (**6**) does not suffer from these drawbacks, although its solubility in THF is low. The responses exhibited by **5** and **6** in H_2O (entries 17 and 18) include the most powerful examples of chelate-controlled diastereoselectivity uncovered to date for reactions promoted by indium.[16b] As concerns **6**, dilution with THF (entry 19) appears to erode syn selectivity to a greater extent than does dilution with ethanol (entries 19 and 23). Sonication accelerates the latter reaction but has little effect on product ratio (entry 24).

pH Considerations. The rate acceleration noted above for allylations promoted in water could, as for example with D-arabinose, be attributed to the improved solubility of the substrate in the aqueous medium. However, the phenomenon persists when the solubilities of the reagents are lower in H_2O than in THF. This behavior could be explained by attributing enhanced stability to the allylindium reagent in THF. Under these circumstances, reactivity toward an incoming aldehyde carbonyl would be reduced and condensation would proceed more slowly. Indeed, an increase in reaction rate has been observed by Araki et al.[26] when progressing from benzene to THF.

In the present study, it was noted that the pH of all allylations performed in water or aqueous THF dropped significantly as the reactions progressed. This aspect of indium-promoted condensations does not seem to have been previously recognized and was therefore explored more fully in order to elucidate the accompanying advantages or disadvantages. As indicated in Table 2, aldehydes **1**−**3** were closely scrutinized.

Table 2. Effect of pH on Rate and Diastereoselectivity of Allylindium Additions in Water at 25 °C[a]

entry	aldehyde	pH	reaction time, h	product ratio syn	product ratio anti	yield, %
1	**1**	*b*	3.5	1	3.9	90
33		7.0	5.5	1	3.0	85
34		4.0	4.0	1	3.0	80
5	**2**	*b*	3.0	1	1.2	92
35		7.0	12.5	1	1.4	84
36		4.0	4.0	1	1.5	86
9	**3**	*b*	24−30	2.3	1	90−95
37		7.0	48	2.0	1	80−87
38		4.0	0.5	10.0	1	85−88

[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments. [b] pH not controlled.

When the pH was maintained at 7 by controlled infusion of sodium hydroxide solution, an increase in reaction times became necessary to achieve complete allylation (entries 33, 35, and 37). This phenomenon could be due in part to increased dilution due to addition of the aqueous base and not constitute a manifestation of the pH itself. Reactions allowed to proceed without pH control were accompanied by a progressive development in acidity to a point below pH 4. When the allylations were initiated at a preset pH of 4 (entries 34, 36, and 38), the transformations took place at notably accelerated rates. As expected on structural grounds, these conditions are notably effective in the case of **3** where the presence of acid serves to facilitate hydrolysis of this acetal to **5**.

Noteworthily, the benzyl- and silyl-protected substrates exhibit the same diastereoselectivities at all ranges of pH tested. These findings dispel any concerns that product distribution might be dependent upon pH to the point where the syn/anti ratios would vary as the reaction progressed. As concerns **1** and **2**, the significant observable associated with the development of acidic character in the reaction mixture is an increase in rate.

This feature of indium catalysis in water requires that care be exercised when acid-sensitive reactants are involved. When working with **7**, for example, the progress of allylation needs to be carefully monitored. If workup is initiated as soon as **7** is completely consumed, good yields of the homoallylic alcohols are obtained (entry 25). Failure to act promptly allows for extensive deprotection of the acetal. Epoxide **8** also exhibits degradation if left unattended, but to a lesser extent. Consequently, these considerations must be taken into account when designing alternative applications of this chemistry.

Salt Effects. Although an increase in acidity per se does not impact on product stereoselectivity, it became of interest to examine if the addition of salts to the reaction mixture would affect product distribution. It is known that, for Diels−Alder cycloadditions performed in water, the presence of salts increases the amount of endo product due to an increase in the internal pressure of the system.[27] Were the reaction volumes for formation of the syn and anti homoallylic alcohols to differ comparably, the possibility exists that product ratios could be conveniently manipulated to synthetic advantage in this manner.

The pair of representative aldehydes selected for study were the MOM-protected derivative **4** and D-arabinose (**6**). The first example exhibits only modest stereoselectivity in water (entry

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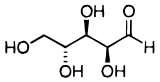
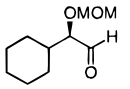
Table 3. Salt Effects on Indium-Promoted Allylations in Water at 25 °C[a]

entry	aldehyde	added salt (no. of equiv.)	reaction time, h	product ratio syn	product ratio anti
39		LiBr (1)	18	8.5	1
40		$MgCl_2$ (1)	20	8.5	1
41		Et_4NBr (1)	12.5	13.5	1
42		Et_4NBr (5)	0.5	13.5	1
43	**6**	$(n\text{-Bu})_4NI$ (1)	9.5	7	1
44		$(n\text{-Bu})_4NI$ (5)	10	7.1	1
45		LiBr (1)	10	2.1	1
46		$MgCl_2$ (1)	3	2.2	1
47		Et_4NBr (1)	3	8.3	1
48	**4**	Et_4NBr (5)	3	8.2	1

[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments.

13), while **6** represents the most discriminating example under standard aqueous conditions (entry 18). When arabinose was admixed with 1 mol equiv of LiBr or $MgCl_2$ and subjected to conventional allylation in H_2O, the syn/anti ratios fell somewhat to 8.5:1 in both cases (Table 3, entries 39 and 40). On the other hand, the use of tetraethylammonium bromide resulted in a substantial increase to a record level of 13.5:1 (entry 41). Increasing the relative amounts of this salt to 5 equiv did not lead to a further increase in the level of syn product but did promote a faster reaction presumably because of the accompanying increase in the ionic strength of the medium (entry 42). For reasons not yet understood, tetra-*n*-butylammonium iodide was not comparably effective (entries 43 and 44). In fact, the quaternary salt performed less well than the lithium and magnesium halides.

Aldehyde **4** was unresponsive to the presence of LiBr and $MgCl_2$, giving rise to the same product distribution (syn/anti 2.1−2.2:1) as observed in H_2O alone (entries 45 and 46). However, tetraethylammonium bromide caused an almost 4-fold increase in formation of the chelation-controlled product (entry 47)! As before, an increase in the relative proportion of this salt above the 1 equiv level had no additional effect (entry 48).

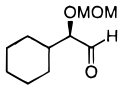
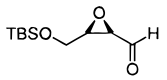
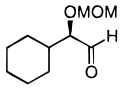
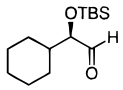
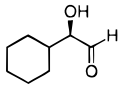
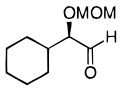
Accordingly, a synergistic effect is observed when tetraethylammonium bromide is added at a modest level to the allylindium reagent. Although the conditions of the selectivity enhancement appear to be somewhat restrictive at this point in time, additional studies need to be implemented before proper rationalization of these observations can be offered.

Competition Studies. Internal chelation, if operative, can be expected to lend itself to more rapid conversion to product if the chelated intermediate resides on the direct reaction pathway.[28] The increase in reaction rate is linked in turn to a lowering in transition state energy associated with preformation of the complex. The corollary to this analysis is that the more selective substrates are also the more reactive.

In order to gauge the relative reactivity of selected α-oxy aldehydes, the OMOM derivative **4** was allowed to vie competitively with **1**, **5**, and **8** for a limited amount of the allylindium reagent. The results are compiled in Table 4. It is immediately obvious that **4** is somewhat more reactive than **1** and **8** (entries 49 and 50) but appreciably less reactive than **5** (entry 51). This ordering conforms very well with the stereoselectivity exhibited by these aldehydes. We have already recognized that the presence of a free hydroxyl group as in **5** is particularly conducive to high-level syn selectivity. The

(28) (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.

Table 4. Competitive Indium-Promoted Allylations in Water at 25 °C[a]

entry	first aldehyde	second aldehyde	reaction time, h	product ratio first ald	product ratio : second ald
49			4.0	2.6	1
	4	**8**			
50			5.0	3.2	1
	4	**1**			
51			3.5	11.1	1
	5	**4**			

[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments.

significant differences in allylation rate between **5** and **8** (35-fold) as well as **5** and **1** (29-fold) are very telling and indicate that the adjacent epoxide and *tert*-butylsilyl groups are not at all conducive to chelation. The somewhat more comparable kinetic behavior of **4** agrees with the concept that a chelated transition state competes favorably with a non-chelated alternative when a methoxymethyl protecting group is positioned α.

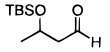
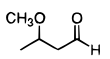
As pointed out by others,[28,29] steric and electronic factors also impact on relative rate. The extent to which these influences are contributory under the present circumstances remains to be evaluated. Notwithstanding, the results reported here show conclusively that chelates are true intermediates in the allylation in water of acyclic aldehydes carrying proper α-substituents.

***β*-Oxy-Substituted Aldehydes.** As a class, *β*-alkoxy aldehydes respond with high diastereofacial selectivity to Lewis acid-promoted condensations. These reactions include the $TiCl_4$-mediated addition of enolsilanes[30] and allylsilanes,[30,31] the use of acidic titanium reagents,[32] and recourse to other promoters such as stannic chloride[33] and boron trifluoride etherate.[34] In contrast, organometallic reagents of the RMgX, RLi, and R_2CuLi type do not generally perform well despite the potential for chelation control.[35−39] In our view, a free hydroxyl substituent *β* to a carbonyl group was considered to be exploitable for 1,3-asymmetric induction during condensation with allylindium reagents in water.

Aldehydes **10**−**13** were selected because of their structural simplicity, similarity to **1**, **2**, **4**, and **5**, and varied basicity at the *β*-oxygen. If chelation were to gain importance and nucleophilic attack were to occur from the less hindered diastereotopic *π*-face of the aldehyde carbonyl, then anti adduct

(29) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302.
(30) (a) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (b) Reetz, M. T.; Kesseler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079. (c) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.
(31) Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem.* **1993**, *58*, 3787.
(32) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.
(33) (a) Kiyooka, S.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4765. (b) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.
(34) (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (b) Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889.
(35) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989.
(36) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019.
(37) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.
(38) Davis, A. P.; Jaspars, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2111.
(39) Braun, M.; Mahler, H. *Liebigs Ann.* **1995**, 29.

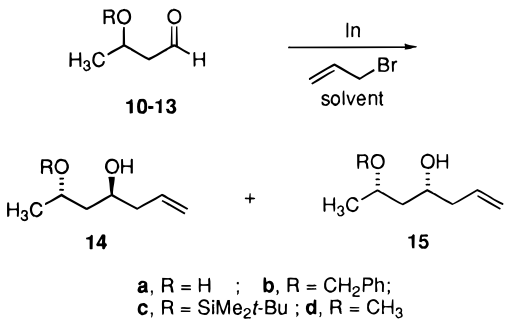
Table 5. Indium-Promoted C-Allylations of β-Oxygenated Aldehydes in Various Solvents (CH_2=$CHCH_2Br$, 25 °C)[a]

entry	aldehyde	solvent	reaction time, h	product ratio syn	product ratio anti	yield, %
52		H_2O	2	1	8.5	77
53		H_2O-THF (1:1)	2	1	8.2	74
54	**10**	THF		No reaction		
55		H_2O	2.5	1	1	80
56		H_2O-THF (1:1)	2.7	1	1	84
57	**11**	THF	10	1	1	72
58		THF[b]	8	1	1	82
59		H_2O	3.5	1	1	84
60		H_2O-THF (1:1)	3.5	1.2	1	83
61	**12**	THF	8.5	1.7	1	77
62		H_2O	2.7	1	4	78
63		H_2O-THF (1:1)	3	1	4	78
64		THF	8.5	1	3.3	69
65	**13**	THF[b]	7.7	1	3.5	75

[a] All of the reactions were performed at least 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] The THF solution of allyl bromide was heated to reflux with the indium prior to reaction. The mixture was cooled prior to introduction of the aldehyde and the coupling was performed as in *a*.

14 would result. Homoallylic alcohols **15** are the Felkin-Anh (non-chelation-controlled) products.

The diastereomeric ratios of **14** and **15** resulting from exposure of **10**−**13** to allyl bromide and indium in solvents ranging from anhydrous THF to water are compiled in Table 5. The product distributions are seen to correlate closely with

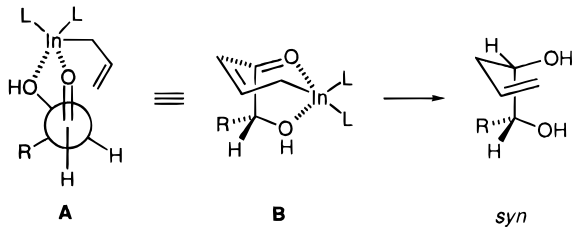


the α-alkoxy series. Thus, a β-methoxyl substituent is capable of modest levels of chelation control, irrespective of whether the allylation is performed in an anhydrous or aqueous medium (entries 62−65). Since a benzyloxy or a *tert*-butyldimethylsiloxy group results in production of totally stereorandom mixtures of **14** and **15** (entries 55−60), there is no evidence for transient structural rigidification prior to nucleophilic attack in these examples. Aldehyde **12** actually produces syn isomer **15c** preferentially to **14c** when THF is the reaction medium (entry 61). This crossover could reflect the operation of a steric effect.

The unprotected hydroxyl derivative **10** exhibits the most pronounced face selectivity as anticipated (entries 52 and 53). In fact, the 8.5:1 ratio of **14a** to **15a** compares quite favorably with the product distributions exhibited by the α-hydroxy aldehydes **5** and **6**. Clearly the free β-OH group is capable of chelation control in water, finding it possible to coordinate to the indium ion despite its preexisting solvation by water molecules.

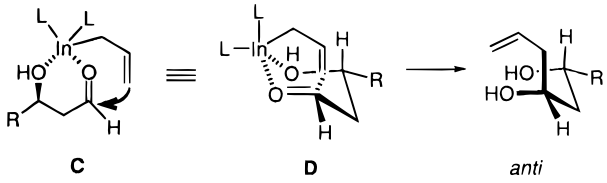
Mechanistic Considerations. Additions of the allylindium reagent to α- and β-hydroxy aldehydes in water have been demonstrated to be highly stereoselective and synthetically useful operations. The corresponding methoxy and MOM derivatives exhibit comparable properties, although to a demonstrably lessened degree. The free hydroxyl derivatives represent the more reactive substrates in either series, this reactivity ordering conforming expectedly to chelation-controlled addition. This ability of the indium cation to lock the carbonyl substrate conformationally prior to nucleophilic attack is indicative that coordination to the substrate can indeed overcome the H_2O solvation forces, especially when the neighboring functionality is an unprotected hydroxyl substituent.

The sense of asymmetric induction in the α-series, viz. a strong kinetic preference for formation of the syn diol, is consistent with operation of the classic Cram model as in **A**. Once complexation occurs, the allyl group is transferred to the carbonyl carbon from the less hindered π-surface opposite to that occupied from the R group. In **B**, the chelation pathway



is seen to be capable of adoption of a chair confomation which concisely accommodates favored formation of the syn diol. The reversal in stereoselectivity in going from **1** to **5** in the same aqueous environment is the classical test for chelation.

For the β-chelate reactions, the factors which influence product formation appear to be the same. When **C** forms, intramolecular attack is guided to occur syn to the preexisting hydroxyl. This reaction trajectory leads preferentially to the anti diol, provided that a chairlike transition state approximating **D** is followed.[40] Importantly, it is one single allylindium that



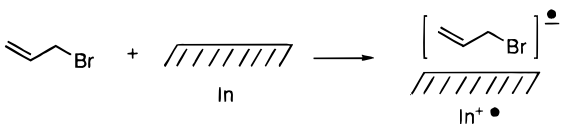
chelates and reacts. Although similar working models have been advanced in explanation of the mode of addition of titanium[32] or borane reagents,[41] this behavior is distinct from other chelation-controlled reactions where the reacting reagent is different from the chelating agent. This may well be an argument that the indium-mediated reaction takes place on the metal surface.

The present studies have demonstrated a direct kinetic link between stereoselectivity and the presence of a neighboring hydroxyl group. While this relationship has been extensively discussed,[28,42] the support of this concept is not universal. Several experimental and theoretical reports have appeared supporting the notion that π-complexation is not a kinetically

(40) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morukuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055.
(41) (a) Narasaka, K.; Pai, H. C. *Chem. Lett.* **1980**, 1415. (b) Narasaka, K.; Pai, H. C. *Tetrahedron* **1984**, *12*, 2233. (c) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(42) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1992**, *114*, 4536.

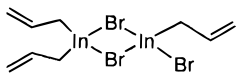
important event.[40,43] Clearly, additional studies of this entire question would be welcomed.

Despite the considerable success of the present investigation, the precise mechanism of indium-promoted reactions remains unclear. In the mid-1980s, the involvement of radical pairs was advanced in explanation of tin-promoted allylations.[44] Subsequent recourse to radical clock experiments demonstrated unambiguously that radicals could not be involved.[45] We have come to favor a single electron transfer process similar to that advanced by Chan.[13b] According to this reaction profile, the allyl bromide approaches the surface of the indium metal where the SET process generates the reactive radical anion/indium radical cation pair **E**. These conditions operate, of course, only



E

when indium metal is present as a reactant. Acyclic diastereofacial control is presently recognized to occur in a wide range of reactions.[46,47] Suffice it to indicate at this point that the preformation of allylindium reagents may well bypass the involvement of **E**, suggesting an alternative pathway involving the more conventional species **F** can also operate.[17a,48] Proper selection of reaction conditions could alter the precise pathway at work.



F

Experimental Section[49]

5-Cyclohexyl-1,3-dioxolan-4-ol (3). A solution of vinylmagnesium bromide in THF [from 11.36 g (107.2 mmol) of vinyl bromide] was treated dropwise with cyclohexanecarboxaldehyde (3.00 g, 26.8 mmol). The reaction mixture was refluxed for 5 h, cooled to 20 °C, treated with 1 N HCl, and extracted with ether (4 × 50 mL). The combined organic layers were washed sequentially with 1 N HCl, water, and brine, then dried and evaporated. The residue was purified by chromatography on silica gel (elution with 4:1 hexanes−ethyl acetate) to give **9** as a colorless oil (3.60 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1 H), 5.13 (m, 1 H), 3.83 (t, J = 6.4 Hz, 1 H), 1.86−0.95 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 115.4, 76.6, 43.5, 29.0, 28.3, 26.5, 26.1, 26.0.

A solution of **9** (1.00 g, 7.14 mmol) in CH_2Cl_2 (65 mL) was cooled to −78 °C, ozonolyzed for 15 min, purged with oxygen, and treated with dimethyl sulfide (12 mL). After 30 min, the cooling bath was removed and the reaction mixture was stirred at 20 °C for 15 h prior to solvent evaporation. Flash chromatographic purification (silica gel, elution with 5:1 hexanes−ethyl acetate) gave **3** as a colorless oily diasteromeric mixture (858 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (d, J = 2.9 Hz, 1 H), 5.08 (d, J = 9.8 Hz, 2 H), 3.50 (d, J = 2.9 Hz, 1 H), 3.34 (br s, 1 H), 1.83−1.01 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.2, 93.7, 87.4, 39.3, 28.9, 28.7, 26.3, 25.7. 25.6; MS m/z (M^+) calcd 172.1099, obsd 172.1093.

α-(Methoxymethoxy)cyclohexaneacetaldehyde (4). A magnetically stirred solution of **9** (900 mg, 6.42 mmol) in a 1:1 mixture of THF and DMF (30 mL) was treated with sodium hydride (277 mg, 11.56 mmol) and chloromethyl methyl ether (616 mg, 7.70 mmol), and the reaction was allowed to proceed at 20 °C for 48 h. Water (25 mL) and CH_2Cl_2 (25 mL) were introduced, and the separated aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried and concentrated, and the residue was purified by chromatography on silica gel (elution with 10:1 hexanes−ethyl acetate) to give the protected alcohol as a colorless oil (945 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70−5.58 (m, 1 H), 5.25−5.11 (m, 2 H), 4.69 (d, J = 6.7 Hz, 1 H), 4.50 (d, J = 6.7 Hz, 1 H), 3.70 (t, J = 7.4 Hz, 1 H), 3.36 (s, 3 H), 1.94−1.00 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 118.0, 93.7, 82.5, 55.4, 42.2, 29.0, 26.6, 26.1, 26.0.

A 630 mg (3.38 mmol) sample of this ether was ozonolyzed in the predescribed manner and purified by flash chromatography on silica gel to give **4** as an unstable colorless oil (472 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 2.5 Hz, 1 H), 4.71 (d, J = 6.8 Hz, 1 H), 4.66 (d, J = 6.8 Hz, 1 H), 3.65 (dd, J = 5.5, 3.1 Hz, 1 H), 3.39 (s, 3 H), 1.81−1.64 (m, 6 H), 1.28−1.17 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 97.0, 86.5, 55.9, 39.5, 28.9, 27.8, 26.1, 26.0, 25.9.

Prototypical Allylation Reactions. A. In H_2O. A magnetically stirred solution of **4** (150 mg, 0.806 mmol) in water (8.9 mL) was treated with indium powder (101 mg, 0.887 mmol) and allyl bromide (145 mg, 1.21 mmol). The reaction was allowed to proceed until no **4** remained (TLC analysis). Ethyl acetate was added, stirring was maintained for 60 min, and the separated aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried and evaporated. The residue was taken up in anhydrous methanol (15 mL) containing a few milligrams of *p*-toluenesulfonic acid and refluxed for 12 h to provide the diol. The methanol was removed in vacuo and replaced by acetone (15 mL). The resulting solution was stirred for 6 h and concentrated to leave an oil, purification of which was accomplished by flash chromatography on silica gel (elution with 50:1 hexanes−ethyl acetate) to give the acetonide in 80−95% yield (Table 1).

The determination of diastereomer composition was performed as described by Keck.[25] The key identifying NMR signals are as follows: syn, dd at δ 3.46 and ^{13}C absorptions at 107.9, 84.5, and 78.0 ppm. For the anti isomer: dd at δ 3.73 and ^{13}C peaks at 107.2, 82.3, and 76.9 ppm.

Comparable processing of **7** (200 mg, 1.54 mmol) afforded 207 mg (83%) of a 1:3.2 mixture of syn and anti alcohols.[50] Syn isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.93−5.76 (m, 1 H), 5.12 (d, J = 17 Hz, 1 H), 5.11 (d, J = 10.5 Hz, 1 H), 4.07−3.95 (m, 2 H), 3.78−3.67 (m, 1 H), 3.58 (quintet, J = 6.3 Hz, 1 H), 3.27−2.19 (series of m, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 117.8, 109.4, 78.5, 71.5, 66.0, 38.2, 27.0, 25.3. Anti isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.92−5.75 (m, 1 H), 5.25 (d, J = 16 Hz, 1 H), 5.13 (d, J = 10.5 Hz, 1 H), 4.05−3.87 (m, 3 H) 3.77 (dq, J = 8.8, 4.4 Hz, 1 H), 2.43−2.10 (m, 2 H), 2.00 (d, J = 3.4 Hz, 1 H), 1.43 (s, 3 H), 1.37 (s, 3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9, 118.2, 109.0, 78.1, 70.4, 65.2, 37.6, 26.5, 25.2.

Analogous treatment of **8** (100 mg, 0.463 mmol) gave rise to 94 mg (78%) of a 1:2 mixture of syn and anti alcohols.[24] Syn isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 5.15 (m, 2 H), 3.78 (m, 2 H), 3.59 (m, 1 H), 3.19 (m, 1 H), 2.98 (dd, J = 4.4, 7.5 Hz, 1 H), 2.37 (t, J = 6.7 Hz, 2 H), 2.21 (br s, 1 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.2, 118.3, 68.9, 61.6, 59.8, 57.6, 38.7, 25.8 (3 C), 18.2, −5.3, −5.4. Anti isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1 H), 5.25 (m, 2 H), 4.01 (dd, J = 5.6, 11.6 Hz, 1 H), 3.71 (dd, J = 6.5, 11.6 Hz, 1 H), 3.57 (m, 1 H), 3.14 (m, 1 H), 2.94 (dd, J = 4.3, 7.9 Hz, 1 H), 2.69 (d, J = 1.7 Hz, 1 H), 2.42 (m, 2 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 118.1, 69.2, 62.0, 58.3, 55.4, 39.4, 25.8 (3 C), 18.2, −5.3, −5.5.

(43) (a) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112. (b) Buhro, W. E.; Georgiou, S.; Fernández, J. M.; Patton, A. T.; Strouse, C. E.; Gladysz, J. A. *Organometallics* **1986**, *5*, 956. (c) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121.

(44) (a) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (b) Einhorn, C.; Luche, J. L. *J. Organomet. Chem.* **1987**, *322*, 177.

(45) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.

(46) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.

(47) Smadja, W. *Synlett* **1994**, 1.

(48) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920.

(49) For generic experimental details, see: Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917.

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B. In THF. A magnetically stirred slurry of D-arabinose (150 mg, 1.0 mmol) in THF (11 mL) was treated with indium powder (126 mg, 1.1 mmol) and allyl bromide (180 mg, 1.5 mmol). Reaction was allowed to proceed until TLC analysis showed no residual starting material to be present. After the evaporation of solvent, the residue was taken up in pyridine (4 mL) and acetic anhydride (4 mL), and the mixture was allowed to stir for 12 h prior to concentration in vacuo. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL), and the separated aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic solutions were dried and concentrated. Chromatography of the residue on silica gel (elution with 5:1 ethyl acetate−hexanes) afforded the two diastereomeric pentaacetates.

Syn (threo) isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (m, 1 H), 5.41 (dd, J = 11.1, 4.2 Hz, 1 H), 5.29 (dd, J = 10.8, 4.2 Hz, 1 H), 5.09 (m, 2 H), 5.05 (m, 1 H), 5.03 (m, 1 H), 4.23 (dd, J = 12.4, 3.4 Hz, 1 H), 4.10 (dd, J = 12.4, 5.4 Hz, 1 H), 2.39−2.26 (m, 2 H), 2.11 (s, 3 H), 2.06 (s, 3 H), 2.052 (s, 3 H), 2.048 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 169.8 (2 C), 169.7, 132.0, 118.9, 70.7, 70.4, 68.9, 68.7, 61.5, 35.1, 20.8, 20.7, 20.6, 20.5 (2 C).

Anti (erythro) isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1 H), 5.43 (dd, J = 11.3, 2.4 Hz, 1 H), 5.29 (dd, J = 10.7, 2.4 Hz, 1 H), 5.07 (m, 2 H), 5.03 (m, 1 H), 5.02 (m, 1 H), 4.21 (dd, J = 12.5, 2.8 Hz, 1 H), 4.06 (dd, J = 12.5, 5.4 Hz, 1 H), 2.39−2.28 (m, 2 H), 2.082 (s, 3 H), 2.078 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.0, 169.7, 169.62, 169.59, 131.9, 118.8, 70.6, 70.2, 68.8, 68.6, 61.3, 35.0, 20.7, 20.6, 20.50 (2 C), 20.4.

Reactions performed in 1:1 H_2O−THF were carried out in analogous fashion.

C. With Preformation of the Allylindium Reagent in THF. To a magnetically stirred solution of allyl bromide (82 mg, 0.68 mmol) in dry THF (5 mL) was added powdered indium metal (58 mg, 0.50 mmol), and the mixture was treated at reflux for 1 h and allowed to cool to rt. An 80 mg (0.45 mmol) sample of **11** was introduced, and the progress of reaction was monitored by TLC, which indicated the reaction to be complete after 8 h. After water had been added, stirring was prolonged for 5 min prior to extraction of the product into ethyl acetate (3 × 15 mL). The combined organic layers were dried and evaporated, and the resulting residue was purified by flash chromatography on silica gel (elution with 5:1 hexanes−ethyl acetate) to give the mixture of homoallylic alcohols as a colorless oil (82 mg, 82%). Diastereomers **14b** and **15b** were distinguished by ^{1}H NMR spectroscopy, and the isomer distribution was quantified by integration of the methyl doublets at δ 1.25 and 1.27 (in $CDCl_3$). The ^{13}C NMR spectra also agreed fully with the literature data.[25]

From allyl bromide (260 mg, 1.66 mmol), indium metal (140 mg, 1.22 mmol), and aldehyde **13** (116 mg, 1.11 mmol), there was isolated 143 mg (91%) of unpurified homoallylic alcohols. This mixture was dissolved in $CHCl_3$ (50 mL), treated with iodotrimethylsilane (640 mg, 3.1 mmol) at room temperature (rt), and stirred for 12 h before water (50 mL) was introduced. After 2 h, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with water and brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with 1:3 hexanes−ethyl acetate) to give **14a** and **14b** in a combined yield of 120 mg (93%). Anti isomer **14a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.14 (m, 2 H), 4.14 (m, 1 H), 3.99 (m, 1 H), 2.67 (br s, 2 H), 2.27 (m, 2 H), 1.61 (t, J = 5.7 Hz, 2 H), 1.23 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 118.0, 68.1, 65.3, 43.6, 41.9, 23.4. The key ^{1}H NMR signal for syn isomer **15a** is the methyl doublet (J = 6.3 Hz) at δ 1.20.

In those examples where the silylated aldehyde **12** was studied, the homoallylic alcohol mixture was deprotected by stirring with a catalytic quantity of *p*-toluenesulfonic acid in methanol[51] at rt for 90 min. The solvent was removed in vacuo, and the resulting diols were separated by flash chromatography on silica gel (elution with 1:2 hexanes−ethyl acetate). The syn and anti isomers were identified by comparison of their ^{1}H NMR spectra with literature data.[34b]

Competition Experiments. To a mixture of 1 mmol of each of two aldehydes in water (11 mL) was added 1.1 mmol of powdered indium metal and 1.5 mmol of allyl bromide. The reaction mixture was stirred at rt for approximately 5 h. Ethyl acetate (50 mL) was introduced, and after a period of vigorous mixing, the aqueous layer was separated and extracted with additional ethyl acetate (3 × 15 mL). The combined organic layers were dried and concentrated, and the products were separated by flash chromatography on silica gel as described above. The product ratios given in Table 4 are based upon the weights of isolated homoallylic alcohols.

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