Effective 1,4-Asymmetric C−C/C−O Stereoinduction in Indium-Promoted Coupling Reactions of Aldehydes to Protected and Unprotected [1-(Bromomethyl)vinyl] Alkanols. The Status of Intramolecular Chelation within Functionalized Allylindium Reagents

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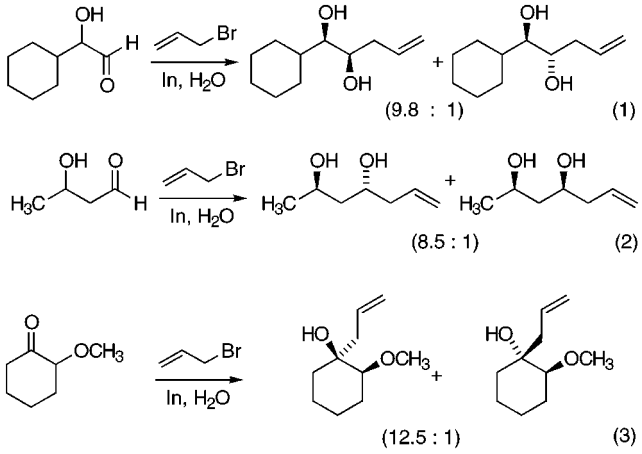
The stereochemistry of the coupling reactions of oxygen-substituted bromides **8**−**10** with isobutyraldehyde, benzaldehyde, and cyclohexanecarboxaldehyde in water is described. The examples involving the O-silylated derivatives **8** exhibit moderate anti stereoselectivity. In contrast, rather high (most often in excess of 80:20) syn diastereofacial bias is observed when hydroxy bromides **10** are involved. Consequently, stereocontrolled 1,4-asymmetric induction under aqueous conditions can be realized in either direction on demand. These results are considered to reflect the fact that the siloxy systems enter into C−C bond formation via conventional Felkin−Anh transition state arrangements. The crossover observed for the unprotected analogues is believed to be a consequence of the preferred adoption of chelated transition states, these interactions likely being fundamental to aqueous organometallic chemistry.

Additions of allylic bromides to aldehydes under the influence of indium metal in water as the reaction solvent are being developed for the purpose of advancing the more widespread utilization of environmentally benign conditions in organic synthesis.[1] These couplings customarily proceed at convenient rates under ambient temperature conditions to afford homoallylic alcohols in high yield.[2] When γ-substituted allyl bromides are involved, 1,3-rearrangement is seen to operate unless steric factors contravene.[3] Furthermore, a wide array of functional groups are well tolerated under these circumstances.[4] The process holds attraction because it is amenable to *intermolecular* chelation control[5] and can exhibit good diastereoselectivity when two or more centers are involved.[6] Extensive studies performed on unprotected α- and β-hydroxy aldehydes have demonstrated that significantly heightened levels of *syn*-1,2- and *anti*-1,3-diols, respectively, are produced at accelerated rates as demanded of chelated transition states (eqs 1 and 2).[5a,b] The extent of chelation control often exceeds that attainable with the corresponding magnesium, cerium, and chromium reagents in anhydrous media by significant margins, and greatly facilitates the stereocontrolled allylation of α-methoxy ketones (eq 3).[5c] When the neighboring oxygen atom is more heavily substituted, or α-thia and α-dialkylamino groups are resident in the electrophilic carbonyl reagent,[5d] good adherence to Felkin−Anh transition state geometry is seen.



Extended application of indium-mediated couplings in synthesis rests on the capability of these processes to be notably diastereoselective when performed in aqueous environments. In fact, highly functionalized acyclic molecules containing three contiguous stereogenic centers can be assembled with high stereoselectivity from simple building blocks such as **1** and **2**.[6j] The success of these

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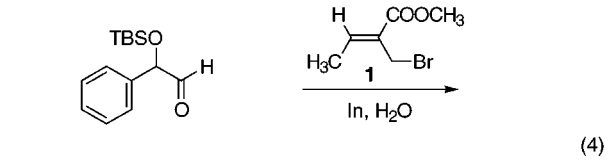
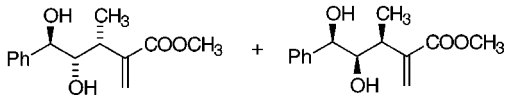
reactions is dependent on preservation within the allylindium species of a strong geometric bias in either an *E* or *Z* sense. When these conditions are met, 3,4-syn; 4,5-anti or 3,4-anti; 4,5-anti diastereomers predominate heavily and in a fully predictable direction (eqs 4 and 5). This stereodifferentiation is not adaptable to crotyl bromide or 1,3-dibromopropene, presumably due to facile geometric equilibration following the oxidative addition of indium,[6d] but improves dramatically with ethyl 4-bromocrotonate,[6c] γ-bromocrotonitrile,[6e] and 1,1,1-trifluoro-4-bromo-2-butene.[6h,l]





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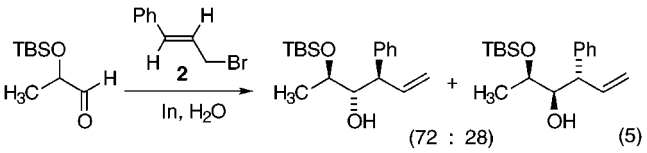
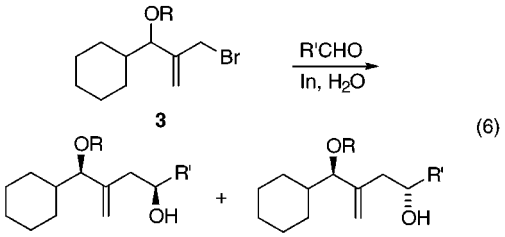


(72 : 28) (5)

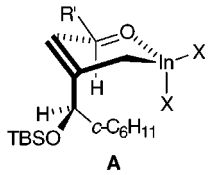
As seen above, the influence on transition state organization of oxygen-containing substituents positioned either α or β to carbonyl groups undergoing nucleophilic attack can be very substantial in water. The consequences of placing comparable groups on the nucleophilic organoindium reagent have only recently been accorded preliminary attention. This issue holds significance because it is the key to realizing practical levels of long-range asymmetric induction under aqueous conditions. Where bromides of type **3** are concerned, the *tert*-butyldimethylsilyl derivative was discovered to react with impressive syn stereoselectivity.[6i] Reduction in the steric bulk of the R substituent as in the methoxy and hydroxy derivatives was met with kinetic acceleration, but significant erosion in the level of diastereoselectivity (eq 6).

When α- and β-oxy aldehydes are involved (eqs 1 and 2), the fastest reactions are the most stereoselective because of chelation involving the two reaction partners. By comparison, the slowest reaction involving **3** delivers the highest level of asymmetric induction. The latter phenomenon is consistent with the intervention of transition state **A** for **3a**, where the overall size of the OTBS substituent is suggested to be the primary stereocontrolling factor. The faster rates witnessed for **3b** and **3c** have been interpreted to reflect the operation of chelation effects during the formation of the respective indium

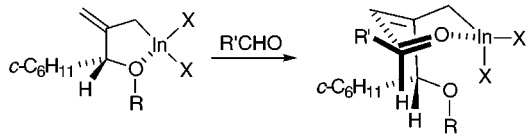


(6)

a, R = TBS; R' = C_6H_5 99 : 1
b, R = CH_3; R' = C_6H_5 69 : 31
c, R = H; R' = C_6H_5 50 : 50



A



B **C**

reagents whose structures can be depicted as in **B**. However, it is not known whether the entrance of an aldehyde into the coordination sphere of the indium disrupts *intramolecular* chelation to the proximal oxygen giving rise to **C**. The present study was undertaken in order to determine if sensitive dependencies of this type might operate in other contexts and to what extent. Specifically addressed in the present work is the effectiveness with which 1,4-asymmetric C−C/C−O stereoinduction can be conveniently made to operate.

Results

The conversion of hydroxy esters **4**, readily available by means of the Baylis−Hillman reaction,[7] to the rearranged bromides **5** was effected with *N*-bromosuccinimide and dimethyl sulfide (Scheme 1).[8] Subsequent formation of the homologated γ-hydroxy esters **6** was preferably carried out with aqueous formaldehyde in the presence of indium powder since these conditions obviate the need for thermal cracking of the paraformaldehyde. Once the hydroxy substituent had been protected as the *tert*-butyldimethylsilyl ether,[9] intermediates **7** were reduced with DIBAL-H and transformed into the bromides **8** by reaction with *N*-bromosuccinimide and triphenylphosphine at −40 °C.[10] Treatment of **8** with *p*-toluenesulfonic acid monohydrate in methanol[11] afforded the unprotected hydroxy bromides **10** in good yield. The methoxy bromides **9** were most efficiently prepared from **7** via a

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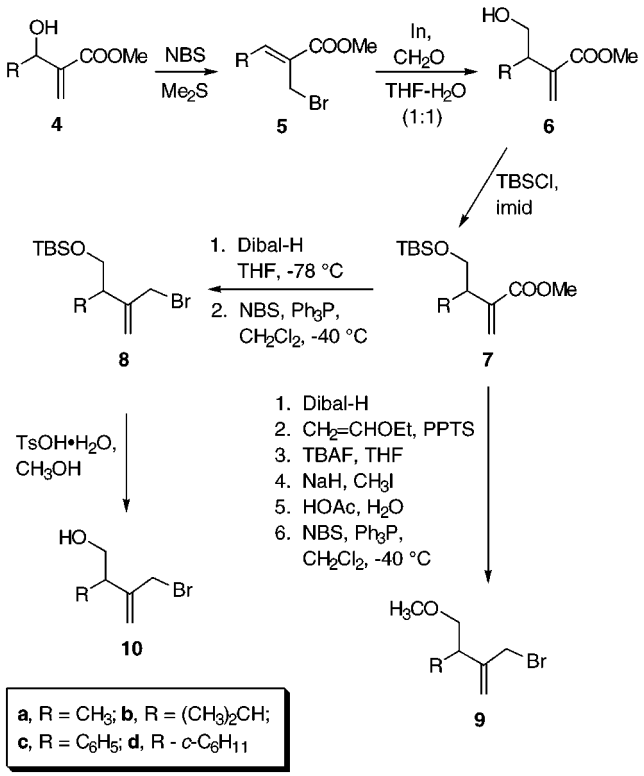
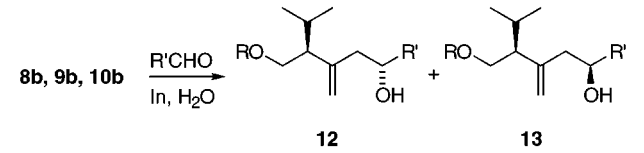
Scheme 1



Scheme 2



	R	R'				
a	TBS	*i*-Pr	(72%)	76	:	24
b	TBS	C_6H_5	(83%)	76	:	24
c	TBS	*c*-C_6H_{11}	(71%)	75	:	25
d	H	*i*-Pr	(95%)	11	:	89
e	H	C_6H_5	(79%)	13	:	87
f	H	*c*-C_6H_{11}	(91%)	14	:	86
g	CH_3	*i*-Pr	(90%)	50	:	50
h	CH_3	C_6H_5	(60%)	42	:	58
i	CH_3	*c*-C_6H_{11}	(64%)	43	:	57

multistep sequence featuring protecting group adjustments within a nonsymmetric 1,4-diol.

With this representative series of [1-(bromomethyl)-vinyl] alkanols in hand, attention was turned to their indium-promoted coupling involving a typical triad of aldehydes. The isopropyl substituted bromides (the *b* series) were examined first because of a perceived substantive steric bias adjacent to the reacting center (Scheme 2). The issue was not only whether the isopropyl group would have a significant influence on the stereochemistry of C−C bond formation. At least one of the bromides, that carrying a free hydroxyl, offered an attractive site for metal ligation. A methoxyl substituent as in **9b**, recognized to play a meaningful role in other contexts (eq 3), was expected to be the less influential. The OTBS functionality is not known for its chelating potential at any level.

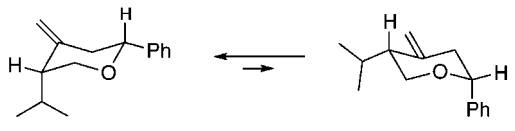
When these three bromides were submitted to typical coupling conditions, it was discovered that the OTBS derivative **8b** consistently gave rise to a predominance of the anti diastereomer **11**, while hydroxy bromide **10b** greatly favored production of the syn diols **12d**−**f** (86−89%), a property also shared by the methoxy congener, but in less impressive fashion (50−58%). In all cases, the product ratios were determined by integration of 300 MHz ^{1}H NMR spectra recorded directly on the unpurified product mixtures in advance of chromatographic purification of the diastereomers. All of the percentage values represent data obtained from at least two individual trials.

Table 1. Distinctive Chemical Shift Data for the Anti and Syn Coupling Products (300 MHz, $CDCl_3$)

compd	anti isomer	syn isomer
	A. Diagnostic Vinylic Protons	
11a,**12a**	4.99 (s, 1 H), 4.87 (s, 1 H)	5.04 (s, 1 H), 4.91 (s, 1 H)
11b,**12b**	5.14 (s, 1 H), 4.98 (s, 1 H)	5.20 (s, 1 H), 5.04 (s, 1 H)
11c,**12c**	4.99 (s, 1 H), 4.88 (s, 1 H)	5.04 (s, 1 H), 4.91 (s, 1 H)
11d,**12d**	4.99 (s, 1 H), 4.87 (s, 1 H)	5.04 (s, 1 H), 4.92 (s, 1 H)
11e,**12e**	5.18 (s, 1 H), 5.05 (s, 1 H)	5.23 (s, 1 H), 5.10 (s, 1 H)
11f,**12f**	4.99 (s, 1 H), 4.87 (s, 1 H)	5.04 (s, 1 H), 4.91 (s, 1 H)
11g,**12g**	5.02 (s, 1 H)[a]	5.04 (s, 1 H)[a]
11h,**12h**	5.08 (s, 1 H), 4.97 (s, 1 H)	5.12 (s, 1 H), 5.00 (s, 1 H)
11i,**12i**	5.01 (s, 1 H)[a]	5.05 (s, 1 H)[a]
15d,**16d**	4.93 (d, J = 4.5, 2 H)	4.95 (d, J = 4.5, 2 H)
15e,**16e**	5.03 (s, 2 H)	5.05 (s, 2 H)
15f,**16f**	4.95 (s, 2 H)	4.97 (s, 2 H)
19a,**20a**	4.99 (s, 1 H), 4.87 (s, 1 H)	5.04 (s, 1 H), 4.91 (s, 1 H)
19b,**20b**	5.13 (s, 1 H), 4.97 (s, 1 H)	5.19 (s, 1 H), 5.02 (s, 1 H)
19c,**20c**	4.96 (s, 1 H), 4.84 (s, 1 H)	5.01 (s, 1 H), 4.88 (s, 1 H)
19d,**20d**	5.02 (s, 1 H), 4.95 (s, 1 H)	5.08 (s, 1 H), 5.00 (s, 1 H)
	B. Diagnostic Methyl Protons	
11f,**12f**	0.92 (d, J = 6.6, 3 H)	0.90 (d, J = 6.2, 3 H)
15a,**16a**	0.99 (d, J = 7.0, 3 H)	1.03 (d, J = 7.0, 3 H)
15b,**16b**	1.01 (d, J = 6.9, 3 H)	1.06 (d, J = 6.9, 3 H)
15c,**16c**	0.99 (d, J = 7.0, 3 H)	1.03 (d, J = 7.0, 3 H)
	C. Diagnostic Allylic Methylene Protons	
11d,**12d**	2.28 (d, J = 14.1, 1 H)	2.14 (d, J = 14.1, 1 H)
19d,**20d**	2.27 (dd, J = 14.0, 2.6, 1 H)	2.13 (d, J = 14.0, 1 H)

[a] Second vinylic proton signal is overlapped.

Distinction between the anti and syn forms was accomplished by the cyclization of **12e** in the presence of *p*-toluenesulfonyl chloride and triethylamine at the reflux temperature of CH_2Cl_2. The resulting 3-methylenetetrahydropyran was readily identified as the cis-disubstituted isomer. Furthermore, it was possible to recognize that adoption of chair conformer **13** was heavily favored relative to **14**. This thermodynamic preference is attributed to destabilizing A1 strain between the exocyclic double bond and the isopropyl substituent in the latter arrangement.

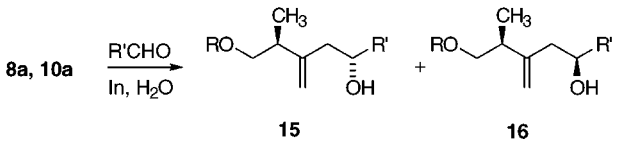


13 **14**

Confirmation that an anti-to-syn crossover had indeed materialized was gained by desilylation of select members of the group **11a**−**c** and comparison of these diols with those generated from the **d**−**f** subset. This protocol was utilized rather extensively in the subsequent segments of the investigation.

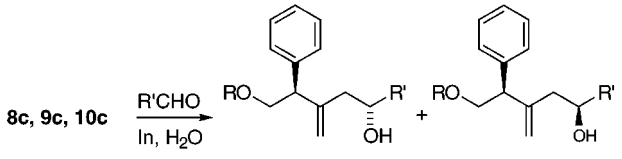
These results eventually led to our realization that the anti/syn distinction could more easily be made with good reliability by comparison of the chemical shifts of the vinylic protons. As seen in Table 1, the diagnostic signals

Scheme 3



	R	R'				
a	TBS	*i*-Pr	(52%)	65	:	35
b	TBS	C_6H_5	(63%)	63	:	37
c	TBS	*c*-C_6H_{11}	(92%)	57	:	43
d	H	*i*-Pr	(62%)	25	:	75
e	H	C_6H_5	(54%)	25	:	75
f	H	*c*-C_6H_{11}	(60%)	25	:	75

Scheme 4



	R	R'				
a	TBS	*i*-Pr	(86%)	56	:	44
b	TBS	C_6H_5	(91%)	67	:	33
c	TBS	*c*-C_6H_{11}	(80%)	51	:	49
d	H	*i*-Pr	(86%)	20	:	80
e	H	C_6H_5	(84%)	13	:	87
f	H	*c*-C_6H_{11}	(94%)	17	:	83
g	CH_3	*i*-Pr	(94%)	57	:	43
h	CH_3	C_6H_5	(85%)	58	:	42
i	CH_3	*c*-C_6H_{11}	(89%)	54	:	46

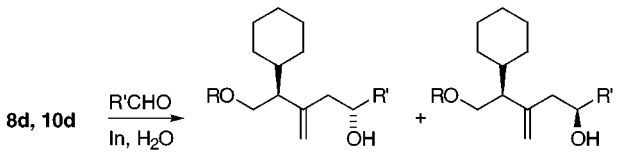
of the syn isomers appear to lower field than their counterparts in the anti series, although phenyl groups as in **17** and **18** exert less predictable shielding effects. In other examples, the location of the allylic or methyl protons was helpful, with downfield displacement now being observed in the anti isomers.

The preceding findings prompted an analysis of the level of stereoinduction that would be observed upon reduction in the substituent size from isopropyl to methyl as in **8a** and **10a**. At the least, this relatively modest structural change could provide indication as to whether the same level of stereoselectivity would be reached. In actuality, **8a** and **10a** exhibit entirely comparable kinetic biases, but with an approximate 10% loss of effective control in both directions (Scheme 3).

This dropoff was expected since the smaller steric demands of a methyl group in the respective transition structures should lessen energetic differences in competing coupling pathways. However, the continued surfacing of a crossover in product distribution suggested that the controlling factor(s) in the free hydroxy and OTBS series involved different structural segments.

Further pursuit of this working hypothesis led us to examine the consequences of phenyl (Scheme 4) and cyclohexyl replacement of the methyl group (Scheme 5). The expectation was that one or more of these bromides would promote a return to the product distributions originally witnessed in Scheme 2. Indeed, the hydroxy bromides **10c** and **10d** both provided syn products in excess of the 80% level. These results are viewed as telltale evidence of the overriding of a normal driving

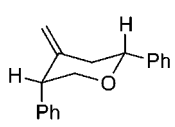
Scheme 5



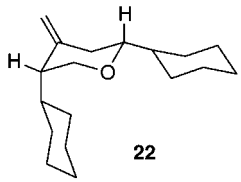
	R	R'				
a	TBS	*i*-Pr	(78%)	78	:	22
b	TBS	C_6H_5	(87%)	67	:	33
c	TBS	*c*-C_6H_{11}	(60%)	70	:	30
d	H	*i*-Pr	(82%)	19	:	81
e	H	C_6H_5	(76%)	14	:	86
f	H	*c*-C_6H_{11}	(91%)	19	:	81

force for anti stereoselectivity by internal chelation between the hydroxyl substituent and indium(III) in the allyl organometallics derived from **10**. When the latter condition takes effect, a distinctively different π-facial preference for attack at the aldehyde carbonyl develops as a direct consequence of conformational rigidification within the chelate that is distinctively different than the nonchelated variant.

As a final confirmation of the stereochemical assignments, **18e** and **10f** were cyclized as before to provide **21** and **22**, respectively. The prevailing conformation in each of these heterocycles is entirely comparable to that resident in **14**.



21

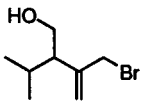
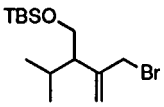
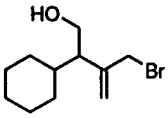
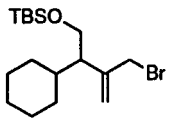
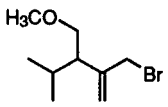
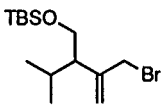
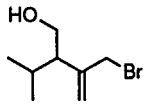
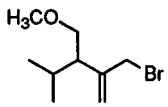


22

Experiments designed to gauge the competitive consumption of **8**−**10** by indium have shown the differences in rate to be great. The experimental tests were conventional, and involved allowing 1 equiv of each bromide to vie with a single molar equivalent of benzaldehyde and indium metal in water (0.1 M in In) at room temperature until the metal was completely consumed (3 h). To minimize complications due to volatility differences in the reactants and significant inequalities in product polarities, the unpurified product mixtures were directly subjected to high field ^{1}H NMR analysis. A potential drawback of this analytical method is the possibility that signals arising from minor constituents might be obscured. To offset this eventuality, ^{1}H NMR analysis was deployed in tandem with thin-layer chromatography because all of the bromides and coupling products stain intensely in the presence of *p*-anisaldehyde and can be readily identified.

The data given in Table 2 show that the siloxy bromides **8** are not competitively reactive with their hydroxy or methoxy analogues within detection limits. Water solubility does not appear to be of major consequence since the product ratios arising from **8b** and **10b** in 1:1 THF−H_2O, a reaction medium in which all components were completely miscible, were unchanged relative to that in pure H_2O. Hydroxy bromide **10b** reacted approximately 2.3 times faster than did methoxy bromide **9b**. Assuming that carbon−carbon bond forma-

Table 2. Competitive Indium-Promoted Allylations in Water at 25 °C (C_6H_5CHO, 3 h)

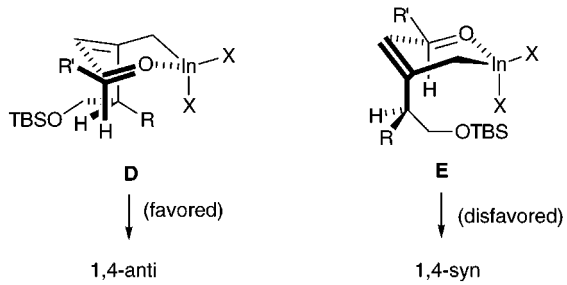
first bromide	second bromide	product ratio: first bromide	product ratio: second bromide
 **10b**	 **8b**	> 99%	< 1%
 **10d**	 **8d**	> 99%	< 1%
 **9b**	 **8b**	> 99%	< 1%
 **10b**	 **9b**	70%	30%

tion proceeds at a similar rate in each case, we interpret these findings to suggest that the overall kinetic enhancement is a function of the rate at which the organoindium reagent is generated.

Discussion

In recent years, many diastereoselective additions of crotylmetal reagents to aldehydes with formation of homoallylic alcohols have been reported.[12] The massive volume of accumulated data attests to the importance held by this C−C bond-forming reaction in synthetic organic chemistry. Although many metal promoters have been examined *in organic solvents*, the reactivity of allylindium reagents was developed by Butsugan in nonaqueous media only in 1988.[13] Adaptation of the latter process to allylation under aqueous conditions followed quickly.[1,2a] The objectives of the present investigation were to establish the scope and limitations associated with the coupling of oxygen-substituted allylindium reagents to aldehydes in water. In addition to realizing useful levels of asymmetric induction, we wanted to compare the relative effectiveness of bromides **8**−**10** with those exhibited by **3** where the oxygen atom resides in closer proximity to the reaction site.[6i] Proper resolution of these issues was expected to provide important insight into the existence and stereochemical significance of intramolecular chelation in suitably functionalized allylindium species during their formation and utilization under aqueous conditions.

Of the bromides examined, the OTBS derivatives were found to give rise to modest anti diastereoselectivity (Schemes 2−4). The product ratios were largely independent of the aldehydes involved and, in fact, fluctuated only modestly as the R group in **8** was varied from methyl to cyclohexyl. The latter insensitivity to substitution does not conform to the recognized impact of comparable changes at C-3 in aldehydes during reaction with crotylmetals,[14,15] but has been observed in our earlier investigation involving bromides of type **3a**.[6i] The aldehyde phenomenon has been attributed to "a significant and previously unappreciated variable in determining diastereofacial selectivity."[14] In contrast, the stereochemical bias exhibited by the oxygenated bromides **3a** and **8** can be concisely accounted for in terms of Felkin−Anh transition states,[16] viz. **D**, and **E**. The methylene spacer in **D** and **E** displaces the OTBS substituent to a different



locale relative to the reaction site, thus modulating to some extent its role in controlling the direction of approach of the aldehyde. Since 1,4-anti isomers dominate the product population, the R- - - -X nonbonded interaction shown in **D** gives indication of being somewhat less destabilizing than the alternative **E** generated by 120° rotation about the bond to the methylene carbon. Under these circumstances, the π-facial selectivity for attack at the aldehydes is ultimately governed by approach to the less hindered surface of the allylindium reagent in **D** and **E**. However, these transition states are not mutually exclusive. It is possible that a different rotamer about the stereogenic center is populated along the least energetically demanding pathway and that interactions between R or CH_2OTBS and the nearby vinylic proton are controlling instead.

The preceding analysis focuses exclusively on nonbonded interactions as a means of rationalizing the behavior of the O-silylated bromides. Since the structurally related hydroxy bromides **10** show very appreciable syn selectivity, an entirely different diastereocontrol element must be operational when the oxygen atom is not protected. The appreciable stereoinduction exhibited by **10** and the strongly enhanced relative rates associated

(12) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

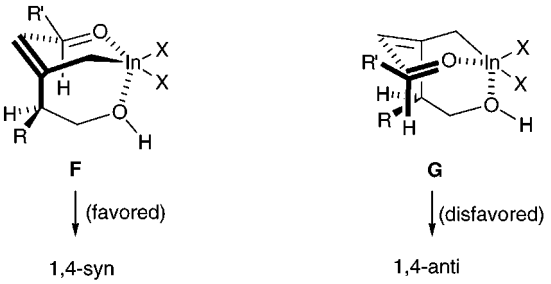
(13) For selected references, see: (a) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (b) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (c) Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* **1989**, *30*, 1581. (d) Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2395. (e) Araki, S.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1991**, *415*, 7. (f) Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S.-J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538. (g) Araki, S.; Imai, A.; Shimizu, K.; Butsugan, Y. *Tetrahedron Lett.* **1992**, *33*, 2581. (h) Jin, S.-J.; Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1528.

(14) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

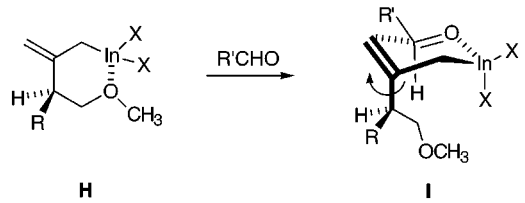
(15) (a) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881. (b) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966.

(16) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

with their reactions with indium prompt us to describe their coupling reactions tentatively in terms of the chelated transition state models **F** and **G**.[17] With the CH_2OH now locked below the developing chair, the R substituent could become the key factor in dictating π-facial diastereoselection. The obvious ease of accessibility of the reactants to each other that operates in **F** leads to the highly preferred formation of 1,4-syn products.

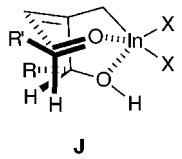


This working assumption accepts the fact that the chelated structure in which the hydroxy-substituted indium reagent is presumably generated persists sufficiently long in the coupling transition state to control diastereoselectivity. Because allylic rearrangement does operate routinely in these reactions, the aldehyde is thought to require activation by coordination of the carbonyl oxygen to indium as shown. The rate of oxidative addition of indium into the methoxy bromides **9** compares closely to that observed for **10**. The rates at which the methoxy-substituted indium reagents couple to aldehydes are similar to their hydroxy counterparts (Table 2). However, the methoxy substituted reagents exhibit essentially no diastereofacial selectivity. The enhanced rates at which **9a**−**d** react with indium are once again fully consistent with the concept of chelation



during the generation of **H**.[18] The destabilizing effect of the *O*-methyl group in **H** relative to **F** (attributable to its inductive and steric contributions) is suggested to surface as the aldehyde approaches. Should the indium not now find it possible to coordinate simultaneously to both oxygenated centers, the OCH_3 will be released and the entire side chain now finds it possible to rotate as shown by the arrow in **I**. The consequence will be a serious erosion of diastereoselectivity during coupling, as is observed.

Although the preceding mechanistic picture holds internal consistency, there remains at least one troublesome issue. The chelated transition state **J**, which embodies a five-membered indium-containing ring and is actually a lower homologue of **F**, is presumably not generated during reaction of **B** (R = H) with aldehydes. Despite the very obvious structural similarity, the approach of an aldehyde in the latter instance appears to disrupt coordination between indium and the hydroxy group as in **C**. In effect, the data suggest that the



stereogenic hydroxyl-substituted carbon is no longer rigidified in its conformation. Future work must focus on unraveling the root cause of such differences in diastereoselectivity.

In summary, the ability of indium-promoted couplings involving hydroxy bromides **10** and aldehydes to proceed with high levels of 1,4-asymmetric induction has been shown to be quite good and broadly based. A chelate transition state model, which takes into account the dual coordination of indium intramolecularly to the nearby hydroxyl and intermolecularly to activate the aldehyde carbonyl, is proposed to be fundamental in nature to these reactions. In contrast, the silyl-protected bromides react via more conventional transition states. The prospects for extension of these considerations into the realm of longer-range (1,5-, 1,6-, 1,7-, etc.) stereoinduction *in water* are currently under active investigation.

Experimental Section

The generic experimental details given in ref 5c apply as well to this study.

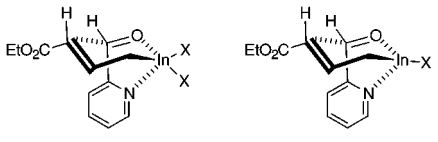
General Procedure for the Bromination of 4. A solution of *N*-bromosuccinimide (5.33 g, 30 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and sequentially treated dropwise with dimethyl sulfide (1.86 g, 30 mmol) and a solution of **4a** (2.60 g, 20 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred overnight at room temperature, diluted with pentane (50 mL), and poured into cold brine (75 mL). The separated aqueous phase was extracted with pentane (3 × 75 mL), and the combined organic solutions were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel (elution with 10:1 hexanes/ethyl acetate) to give **5a** as a volatile colorless oil (2.1 g, 56%).[19]

5b: colorless oil (70%); IR (CH_2Cl_2, cm^{-1}) 1740, 1648; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J = 10.5 Hz, 1 H), 4.23 (s, 2 H), 3.80 (s, 3 H), 2.83−2.71 (m, 1 H), 1.09 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.3, 154.4, 127.0, 52.1, 28.5, 24.2, 21.6 (2 C); MS m/z ($M^+ - OCH_3$) calcd 141.0915, obsd 141.0916 (100%).

5c: colorless oil (82%).[18]

5d: colorless oil (50%); IR (CH_2Cl_2, cm^{-1}) 1705, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 10.4 Hz, 1 H), 4.24 (s,

(17) The two modes of depicting intramolecular/intermolecular chelation to allylindium reagents have evolved. In the first, the indium is shown to be covalently linked to the allylic carbon atom and to a pair of X substituents irrespective of the level of added coordination. An example is given in **a**.[6c] Alternatively, an increase in the level of chelation has been depicted to be accompanied by a loss of X. Structure **b** is exemplary.[2b] Many will certainly construe **a** to reflect an In(III) species and **b** to be in the In(II) state. To avoid misunderstanding at this level, we have adopted the notation shown in **a** in this paper.



(18) (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.

(19) Isaac, M. B. Ph.D. Thesis, McGill University, 1996.

2 H), 3.79 (s, 3 H), 2.50−2.40 (m, 1 H), 1.88−1.68 (m, 5 H), 1.42−1.13 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.4, 152.9, 127.3, 52.1, 38.2, 31.5 (2 C), 25.7, 25.2 (2 C), 24.4; MS *m*/*z* (M^+ − Br) calcd 181.1228, obsd 181.1230.

General Hydroxymethylation Procedure. A mixture of **5a** (0.93 g, 4.8 mmol), indium powder (0.65 g, 5.4 mmol), THF (20 mL), and aqueous formaldehyde (20 mL of 37%, excess) was stirred vigorously for 20 h. The milky-white mixture was diluted with ethyl acetate, and the separated aqueous phase was extracted with this solvent (3 × 10 mL). The combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% hexanes/ethyl acetate) gave **6a** as a colorless oil (0.43 g, 62%); IR (CH_2Cl_2, cm^{-1}) 3340, 1700, 1627; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (s, 1 H), 5.60 (s, 1 H), 3.75 (s, 3 H), 3.74−3.58 (m, 3 H), 3.12−2.87 (m 1 H), 1.12 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.8, 142.8, 124.6, 63.3, 51.9, 35.2, 15.2; MS *m*/*z* (M^+) calcd 144.0786, obsd 144.0791. Anal. Calcd for $C_7H_{12}O_3$: C, 58.30; H, 8.39. Found: C, 58.07; H, 8.34.

6b: colorless oil (75%); IR (CH_2Cl_2, cm^{-1}) 3620, 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, J = 1.2 Hz, 1 H), 5.60 (dd, J = 0.75, 1.1 Hz, 1 H), 3.77 (dd, J = 7, 3 Hz, 1 H), 3.75 (s, 3 H), 3.74 (dd, J = 7, 3 Hz, 1 H), 2.45 (m, 1 H), 1.90 (m, 1 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.3, 140.8, 126.2, 62.7, 51.6, 50.5, 27.6, 20.5, 20.1; MS *m*/*z* (M^+) calcd 172.1099, obsd 172.1093. Anal. Calcd for $C_9H_{16}O_3$: C, 62.75; H, 9.37. Found: C, 62.47; H, 9.31.

6c: colorless oil (70%); IR ($CHCl_3$, cm^{-1}) 3435, 1717, 1628; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5 H), 6.39 (s, 1 H), 5.70 (s, 1 H), 4.10 (t, J = 6.9 Hz, 1 H), 3.93 (m, 2 H), 3.66 (s, 3 H), 2.24 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.2, 140.4, 139.5, 128.4 (2 C), 128.1 (2 C), 126.9, 125.6, 64.8, 51.8, 48.7; MS *m*/*z* (M^+) calcd 206.0943, obsd 206.0954.

6d: colorless oil (90%); IR (CH_2Cl_2, cm^{-1}) 3478, 1708, 1624; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1 H), 5.59 (s, 1 H), 3.76 (s, 3 H), 3.84−3.68 (m, 2 H), 2.51 (td, J = 8.1, 4.2 Hz, 1 H), 1.92−1.82 (m, 1 H), 1.81−1.50 (m, 6 H), 1.37−1.06 (m, 3 H), 0.99−0.84 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.4, 141.1, 126.5, 101.6, 63.1, 52.0, 50.5, 37.3, 31.3, 30.8, 26.2 (2 C); MS *m*/*z* (M^+) calcd 212.1412, obsd 212.1446. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.50. Found: C, 67.83; H, 9.48.

General Procedure for the Silylation of 6. A mixture of **6a** (5.7 g, 43.8 mmol), *tert*-butyldimethylchlorosilane (8.0 g, 52.9 mmol), imidazole (9.53 g, 131 mmol), and CH_2Cl_2 (170 mL) was stirred magnetically for 17 h and diluted with water. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic solutions were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 20:1 hexanes/ethyl acetate) furnished **7a** as a colorless oil (5.4 g, 64%); IR ($CHCl_3$, cm^{-1}) 1704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.57 (s, 1 H), 3.74 (s, 3 H), 3.65 (dd, J = 9.7, 5.5 Hz, 1 H), 3.45 (dd, J = 9.7, 6.6 Hz, 1 H), 2.87 (q, J = 6.7 Hz, 1 H), 1.10 (d, J = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.7, 142.8, 124.5, 66.9, 51.7, 37.4, 25.8 (3 C), 18.2, 16.1, −5.5 (2 C); MS *m*/*z* (M^+) calcd 258.1651, obsd 258.1676.

7b: colorless oil (75%); IR (CH_2Cl_2, cm^{-1}) 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1 H), 5.58 (s, 1 H), 3.75−3.64 (m, 2 H), 3.74 (s, 3 H), 2.53−2.46 (m, 1 H), 1.95−1.88 (m, 1 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.85 (s, 9 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.00 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.1, 141.2, 125.8, 63.5, 51.7, 49.6, 28.3, 25.8 (3 C), 20.8, 20.6, 18.2, −5.5, −5.6; MS *m*/*z* (M^+) calcd 286.1964, obsd 286.1929.

7c: colorless oil (85%); IR ($CHCl_3$, cm^{-1}) 1716; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5 H), 6.39 (s, 1 H), 5.72 (s, 1 H), 4.07 (t, J = 6.5 Hz, 1 H), 3.92 (m, 2 H), 3.68 (s, 3 H), 0.84 (s, 9 H), −0.04 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.4, 140.7, 140.5, 128.4 (2 C), 128.2 (2 C), 126.6, 125.6, 65.4, 51.8, 48.9, 25.8 (3 C), 18.2, −5.5, −5.6; MS *m*/*z* (M^+ − OCH_3) calcd 320.1808, obsd 320.1777. Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.54; H, 8.82.

7d: colorless oil (100%); IR (CH_2Cl_2, cm^{-1}) 1715; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1 H), 5.58 (s, 1 H), 3.74 (s, 3 H), 3.77−3.68 (m, 2 H), 2.62−2.52 (m, 1 H), 1.90−1.57 (m, 7 H), 1.32−1.05 (m, 2 H), 1.03−0.80 (m, 2 H), 0.86 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.2, 141.2, 125.8, 63.2, 51.7, 48.7, 38.1, 31.0 (2 C), 26.5, 26.4 (2 C), 25.8 (3 C), 18.4, −5.5, −5.6; MS *m*/*z* (M^+) calcd 326.2277, obsd 326.2249.

General Procedure for DIBAL-H Reduction and Bromination of 7. A cold (−78 °C), magnetically stirred solution of **7a** (18.2 g, 75 mmol) in dry THF (32 mL) was treated dropwise with DIBAL-H (153 mL of 1 M in hexanes, 153 mmol). After 3 h at this temperature and 1 h at 0 °C, saturated Rochelle salt solution (200 mL) was introduced and the heterogeneous reaction mixture was allowed to warm to room temperature overnight. The separated aqueous phase was extracted with ethyl acetate, and the combined organic solutions were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 1:1 hexanes/ethyl acetate) gave the alcohol as a colorless oil (3.3 g, 73%); IR (CH_2Cl_2, cm^{-1}) 3450, 1635; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 1 H), 4.92 (s, 1 H), 4.07 (dd, J = 23.7, 12.7 Hz, 2 H), 3.60 (dd, J = 9.6, 5.4 Hz, 1 H), 3.53 (dd, J = 9.6, 7.0 Hz, 1 H), 2.87 (br s, 1 H), 2.44 (dd, J = 12.8, 6.7 Hz, 1 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.9, 111.2, 68.7, 65.6, 39.8, 25.8 (3 C), 18.3, 16.3, −5.5; MS *m*/*z* (M^+) calcd 230.1702, obsd 230.1691.

Alcohol from 7b: colorless oil (84%); IR (CH_2Cl_2, cm^{-1}) 3455, 1648; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (s, 1 H), 4.90 (s, 1 H), 4.09 (dd, J = 12.5, 2.6 Hz, 1 H), 3.96 (dd, J = 12.4, 5.8 Hz, 1 H), 3.77 (dd, J = 9.7, 4.0 Hz, 1 H), 3.66 (dd, J = 9.7, 7.5 Hz, 1 H), 3.00 (s, 1 H), 2.00−1.93 (m, 1 H), 1.84−1.77 (m, 1 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.89 (s, 9 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.4, 113.0, 66.3, 65.8, 53.1, 28.0, 25.8 (3 C), 21.3, 20.8, 18.2, −5.5 (2 C), −5.6; MS *m*/*z* (M^+) calcd 258.2015, obsd 258.1981. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.07; H, 11.71. Found: C, 64.98; H, 11.72.

Alcohol from 7c: colorless oil (90%); IR ($CHCl_3$, cm^{-1}) 3406; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5 H), 5.25 (d, J = 1.2 Hz, 1 H), 5.04 (s, 1 H), 4.04 (dd, J = 9.9, 7.2 Hz, 1 H), 4.01 (s, 2 H), 3.91 (dd, J = 9.9, 6.3 Hz, 1 H), 3.56 (t, J = 7.0 Hz, 1 H), 2.30 (br, 1 H), 0.86 (s, 9 H), −0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.1, 140.9, 128.3 (2 C), 128.2 (2 C), 126.6, 111.5, 66.2, 65.8, 50.7, 25.8 (3 C), 18.2, −5.6, −5.7; MS *m*/*z* (M^+ + H) calcd 293.1867, obsd 293.1974. Anal. Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.67; H, 9.60.

Alcohol from 7d: colorless oil (65%); IR (CH_2Cl_2, cm^{-1}) 3428, 1641; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (s, 1 H), 4.89 (s, 1 H), 4.07 (d, J = 12.4 Hz, 1 H), 3.94 (d, J = 12.5 Hz, 1 H), 3.76 (dd, J = 9.7, 4.0 Hz, 1 H), 3.67 (dd, J = 9.6, 7.6 Hz, 1 H), 3.04 (br s, 1 H), 2.08−2.01 (m, 1 H), 1.82−1.57 (m, 5 H), 1.57−1.43 (m, 1 H), 1.26−1.10 (m, 2 H), 1.02−0.78 (m, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.3, 113.1, 66.2, 65.2, 51.8, 37.5, 31.4, 31.1, 26.5, 26.34, 26.27, 25.8 (3 C), 18.4, −5.5 (2 C); MS *m*/*z* (M^+ − OH) calcd 281.2301, obsd 281.2322. Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.40; H, 11.49. Found: C, 68.18; H, 11.38.

A solution of the alcohol derived from **7a** (19.14 g, 88.6 mmol) in dry CH_2Cl_2 (175 mL) was cooled to −40 °C and treated under N_2 with triphenylphosphine (27.9 g, 106 mmol) and *N*-bromosuccinimide (17.35 g, 97.5 mmol). The mixture was stirred for 1 h, diluted with ether (200 mL), washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated. The residue was triturated with pentane (250 mL), and the solids were removed by filtration. Chromatography of the evaporated filtrate on silica gel (elution with 20:1 hexanes/ethyl acetate) gave **8a** as a colorless oil (3.4 g, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 1 H), 5.01 (s, 1 H), 4.04 (dd, J = 17.1, 10.0 Hz, 2 H), 3.60 (dd, J = 9.7, 6.1 Hz, 1 H), 3.53 (dd, J = 9.7, 6.5 Hz, 1 H), 2.55 (q, J = 6.7 Hz, 1 H), 1.11 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.5, 114.8, 67.9, 39.2, 37.3, 25.9 (3 C), 18.3, 16.7, −5.4 (2 C); MS *m*/*z* (M^+) calcd 292.0858, obsd 292.0897.

8b: colorless oil (77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1 H), 5.02 (s, 1 H), 4.00 (dd, J = 3.3, 0.8 Hz, 2 H), 3.68 (dd,

J = 7.1, 5.5 Hz, 2 H), 2.07−2.01 (m, 1 H), 1.90 (d of heptet, J = 8.8, 6.6 Hz, 1 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.5, 116.1, 64.7, 52.0, 38.7, 28.1, 25.9 (3 C), 20.9, 20.6, 18.2, −5.5, −5.6; MS m/z (M^+ − Br) calcd 241.1988, obsd 241.1997.

8c: colorless oil (75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5 H), 5.39 (s, 1 H), 5.18 (s, 1 H), 4.00 (dd, J = 9.9, 3.4 Hz, 1 H), 3.93 (m, 3 H), 3.80 (t, J = 6.0 Hz, 1 H), 0.83 (s, 9 H), −0.06 (s, 3 H), −0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.7. 140.3, 128.6 (2 C), 128.3 (2 C), 126.8, 115.8, 65.8, 50.3, 37.2, 25.8 (3 C), 18.2, −5.6 (2 C); MS m/z (M^+ − Br) calcd 275.1831, obsd 275.1802. Anal. Calcd for $C_{17}H_{27}BrOSi$: C, 57.45; H, 7.66. Found: C, 57.55; H, 7.69.

8d: colorless oil (19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1 H), 5.01 (s, 1 H), 4.00 (dd, J = 13.8, 10.3 Hz, 2 H), 3.71 (dd, J = 9.9, 4.9 Hz, 1 H), 3.65 (dd, J = 9.9, 6.3 Hz, 1 H), 2.13−2.07 (m, 2 H), 1.84−1.53 (m, 5 H), 1.26−1.14 (m, 4 H), 1.01−0.82 (m, 1 H), 0.88 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.3, 116.0, 64.2, 51.0, 38.7, 37.9, 31.0 (3 C), 26.5 (2 C), 25.9 (3 C), 18.2, −5.5, −5.6; MS m/z (M^+ − Br) calcd 281.2301, obsd 281.2317.

General Desilylation Procedure for 8. A solution of **8a** (8.0 g, 28.8 mmol) in methanol (300 mL) containing *p*-toluenesulfonic acid monohydrate (5.5 g, 28.8 mmol) was stirred overnight at room temperature and concentrated. Purification of the hydroxy bromide by chromatography on silica gel (elution with 5:1 hexanes/ethyl acetate) gave **10a** as a pale yellow oil (0.90 g, 90%) that was used immediately because of its inherent instability.

10b: unstable pale yellow oil (61%); IR (CH_2Cl_2, cm^{-1}) 3630, 1637; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 5.11 (s, 1 H), 3.99 (d, J = 2.1, 2 H), 3.73 (dd, J = 6.3, 3.6 Hz, 2 H), 2.17 (td, J = 8.0, 5.2 Hz, 1 H), 1.80 (d of heptet, J = 8.7, 6.7 Hz, 1 H), 1.48 (s, 1 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.4, 117.9, 62.9, 53.1, 36.8, 28.4, 21.1, 20.4; MS m/z (M^+ − Br) calcd 127.1123, obsd 127.1126.

10c: pale yellow oil (88%); IR ($CHCl_3$, cm^{-1}) 3597; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 5.43 (s, 1 H), 5.20 (s, 1 H), 4.03 (dd, J = 10.5, 6.6 Hz, 1 H), 3.91 (d, J = 10.3 Hz, 1 H), 3.87 (m, 2 H), 3.75 (d, J = 10.3 Hz, 1 H), 1.71 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.1, 139.1, 128.8 (2 C), 128.3 (2 C), 127.3, 115.9, 64.9, 50.6, 36.4; MS m/z (M^+) calcd 240.0150, obsd 240.0124. Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.52; H, 5.51.

10d: pale yellow oil (70%); IR (CH_2Cl_2, cm^{-1}) 3422; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 5.10 (s, 1 H), 3.98 (d, J = 2.2 Hz, 2 H), 3.73 (dd, J = 7.1, 5.1 Hz, 1 H), 3.72 (dd, J = 7.4, 5.7 Hz, 1 H), 2.22 (dd, J = 7.5, 5.5 Hz, 1 H), 1.84−1.66 (m, 4 H), 1.48−1.40 (m, 2 H), 1.26−1.10 (m, 4 H), 1.01−0.88 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.2, 117.9, 62.6, 52.1, 38.1, 36.8, 31.3 (2 C), 30.8, 26.42, 26.37; MS m/z (M^+ − Br) calcd 167.1436, obsd 167.1446.

***β*-[1-(Bromomethyl)vinyl]-*γ*-methyl-*n*-butyl Methyl Ether (9b).** In 25 mL of CH_2Cl_2 were dissolved 3.90 g (15 mmol) of the alcohol derived from reduction of **7b**, 10.8 g (150 mmol) of ethyl vinyl ether, and 50 mg (0.20 mmol) of pyridinium *p*-toluenesulfonate. The mixture was stirred at room temperature for 5 h, concentrated, and redissolved in 10 mL of THF. To this solution was added 15 mL of a 1.0 M (15 mmol) solution of tetra-*n*-butylammonium fluoride in THF. The resultant mixture was stirred overnight, diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and concentrated. The residue was dissolved in 20 mL of THF, and to this solution was added 412 mg (17 mmol) of sodium hydride followed by 2.8 g (20 mmol) of methyl iodide. The mixture was stirred for 3 h, quenched with methanol, and diluted with ether and water. The separated aqueous phase was extracted (3×) with ether. The combined organic solutions were concentrated, stirred with 20 mL of a 1:1 acetic acid−water solution for 2 h, and diluted with ethyl acetate. The separated organic phase was dried, concentrated, redissolved in 36 mL of CH_2Cl_2, cooled to −40 °C, and treated with 4.72 g (18 mmol) of triphenylphosphine followed by 2.85 g (16.5 mmol) of *N*-bromosuccinimide. The mixture was stirred for 1 h, diluted with 110 mL of ether, and washed with saturated $NaHCO_3$ solution and brine. The separated organic phase was dried, concentrated, and diluted with 70 mL of pentane. This solution was filtered and concentrated to leave a residue that was purified by chromatography on silica gel (elution with hexanes). There was isolated 1.77 g (54%) of **9b** as a volatile colorless oil; IR (neat, cm^{-1}) 1640; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1 H), 5.04 (s, 1 H), 4.00 (s, 2 H), 3.49 (dd, J = 9.4, 5.1 Hz, 1 H), 3.43 (dd, J = 9.4, 7.1 Hz, 1 H), 3.31 (s, 3 H), 2.26−2.19 (m, 1 H), 1.85 (heptet, J = 6.7 Hz, 1 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.0, 116.6, 74.2, 58.9, 49.9, 37.5, 28.6, 21.0, 20.4; MS m/z (M^+) calcd 220.0462, obsd 220.0425.

α-[1-(Bromomethyl)vinyl]phenyl Methyl Ether (9c). Entirely comparable processing of the alcohol derived from reduction of **7c** (750 mg, 2.6 mmol) furnished the methoxy alcohol and subsequently **9c** in 55% overall yield.

For the methoxy alcohol: colorless oil: IR (neat, cm^{-1}) 3450; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5 H), 5.27 (s, 1 H), 5.05 (s, 1 H), 3.99 (s, 2 H), 3.82 (dd, J = 11.0, 10.5 Hz, 1 H), 3.70 (m, 2 H), 3.36 (s, 3 H), 2.08 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.9, 140.5, 128.5 (2 C), 128.0 (2 C), 126.8, 111.6, 75.2, 65.5, 58.8, 48.3; MS m/z (M^+) calcd 192.1150, obsd 192.1156.

For **9c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 5.40 (s, 1 H), 5.15 (s, 1 H), 3.95 (dd, J = 8.0, 7.0 Hz, 1 H), 3.92−3.65 (m, 4 H), 3.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.5, 139.9, 128.6 (2 C), 128.3 (2 C), 127.0, 115.9, 74.9, 58.8, 47.8, 36.6; MS m/z (M^+) calcd 254.0306, obsd 254.0294. Anal. Calcd for $C_{12}H_{15}BrO$: C, 56.49; H, 5.93. Found: C, 56.60; H, 5.93.

General Allylation Procedure. A mixture of the bromide (1 equiv), indium powder (1 equiv), and aldehyde (1 equiv) in water (10 mL/mmol 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.

Couplings Involving 8b. A. To Isobutyraldehyde. Anti/syn ratio of 76:24 (72%). For **11a**: colorless oil; IR (neat, cm^{-1}) 3454, 1640; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (s, 1 H), 4.87 (s, 1 H), 3.80−3.74 (m, 1 H), 3.64−3.56 (m, 1 H), 3.47−3.40 (m, 1 H), 3.03 (br s, 1 H), 2.28 (ddd, J = 13.5, 2.4, 1.0 Hz, 1 H), 2.08−2.00 (m, 1 H), 1.92 (dd, J = 13.4, 10.3 Hz, 1 H), 1.64 (heptet, J = 6.6 Hz, 2 H), 0.93 (d, J = 7.7 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 7.4 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, J = 7.0 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.0, 112.9, 76.2, 65.6, 54.9, 42.7, 33.6, 29.7, 25.9 (3 C), 21.1, 20.8, 18.7, 18.3, 18.1, −5.4, −5.5; MS m/z (M^+) calcd 314.2641, obsd 314.2631. Anal. Calcd for $C_{18}H_{38}O_2Si$: C, 68.73; H, 12.19. Found: C, 68.45; H, 12.09.

For **12a**: characteristic ^{1}H NMR peaks appear at δ 5.04 (s, 1 H), 4.91 (s, 1 H), 2.92 (br s, 1 H), 2.11 (d, J = 10.6 Hz, 1 H); characteristic ^{13}C NMR peaks appear at ppm 147.7, 113.6, 73.1, 65.1, 53.6, 42.3, 33.4, 30.0, 26.0, 20.9, 18.5, −5.6.

B. To Benzaldehyde. Anti/syn ratio of 76:24 (83%). For **11b**: colorless oil; IR (neat, cm^{-1}) 3406, 1639; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.22 (m, 5 H), 5.14 (s, 1 H), 4.98 (s, 1 H), 4.83 (dd, J = 10.3, 2.9 Hz, 1 H), 4.67 (d, J = 2.2 Hz, 1 H), 3.74−3.56 (m, 2 H), 2.53 (dd, J = 13.7, 2.1 Hz, 1 H), 2.39−2.17 (m, 1 H), 1.88−1.59 (m, 2 H), 0.96−0.84 (m, 6 H), 0.90 (d, J = 6.9 Hz, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.2, 144.5, 128.3 (2 C), 127.1, 125.7 (2 C), 113.7, 74.5, 65.8, 55.0, 48.7, 30.1, 26.0 (3 C), 20.9 (2 C), 18.4, −5.4, −5.5; MS m/z (M^+) calcd 348.2484, obsd 348.2511. Anal. Calcd for $C_{21}H_{36}O_2Si$: C, 72.36; H, 10.42. Found: C, 72.36; H, 10.35.

For **12b**: characteristic ^{1}H NMR peaks appear at δ 5.20 (s, 1 H), 5.04 (s, 1 H), 4.89 (dd, J = 9.9, 3.6 Hz, 1 H), 4.79 (d, J = 2.3 Hz, 1 H), 3.84 (d, J = 4.6 Hz, 1 H), 0.91 (d, J = 7.9 Hz, 9 H), 0.11 (s, 3 H); characteristic ^{13}C NMR peaks appear at ppm 146.8, 114.7, 71.5, 64.8, 54.3, 47.3.

C. To Cyclohexanecarboxaldehyde. Anti/syn ratio of 75:25 (71%). For **11c**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3440, 1638; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (s, 1 H), 4.88 (s, 1 H), 3.80−3.68 (m, 1 H), 3.65−3.51 (m, 1 H), 3.49−3.41 (m, 1 H), 3.03 (br s, 1 H), 2.30 (dd, J = 13.5, 2.4 Hz, 1 H), 2.19−1.85 (m, 3 H), 1.76−1.57 (m, 5 H), 1.43−0.97 (m, 6 H), 0.89 (d, J = 7.4 Hz, 3 H), 0.88 (s, 9 H), 0.86 (d, J = 7.4 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.0, 113.0, 75.6, 65.6, 55.0, 43.7, 42.8, 29.7, 29.1 (2 C), 28.6, 26.3 (2 C), 25.9 (3 C), 20.8 (2 C), 18.3, −5.6 (2 C); MS m/z (M^+ − t-Bu) calcd 297.2250, obsd 297.2220. Anal. Calcd for $C_{21}H_{42}O_2Si$: C, 71.13; H, 11.95. Found: C, 71.25; H, 11.88.

For **12c**: characteristic ^1H NMR peaks appear at δ 5.04 (s, 1 H), 4.92 (s, 1 H); characteristic ^{13}C NMR peaks appear at ppm 147.8, 113.6, 72.3, 65.1, 53.6, 43.4, 42.6, 30.1.

Couplings Involving 10b. A. To Isobutyraldehyde. Anti/syn ratio of 11:89 (95%). For **11d**: characteristic ^1H NMR peaks appear at δ 2.28 (d, J = 14.1 Hz, 1 H).

For **12d**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3424; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (s, 1 H), 5.01 (s, 1 H), 3.77 (dd, J = 10.7, 4.6 Hz, 1 H), 3.72−3.54 (m, 2 H), 2.67 (br s, 2 H), 2.14 (d, J = 14.1 Hz, 1 H), 2.06−1.97 (m, 2 H), 1.68 (heptet, J = 6.7 Hz, 1 H), 1.59 (heptet, J = 6.7 Hz, 1 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.3, 114.4, 74.7, 63.3, 54.9, 39.3, 33.9, 29.5, 21.2, 20.7, 18.6, 17.9; MS m/z (M^+) calcd 200.1776, obsd 200.1740. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.94; H, 12.08. Found: C, 71.86; H, 11.97.

B. To Benzaldehyde. Anti/syn ratio of 13:87 (79%). For **11e**: characteristic ^1H NMR peaks appear at δ 5.18 (s, 1 H), 5.05 (s, 1 H); characteristic ^{13}C NMR peaks appear at ppm 117.6, 62.8, 52.7, 28.2, 20.9, 20.3.

For **12e**: colorless oil; IR (neat, cm^{-1}) 3404, 1643; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.25 (m, 5 H), 5.23 (s, 1 H), 5.10 (s, 1 H), 4.94 (dd, J = 8.7, 5.1 Hz, 1 H), 3.82 (dd, J = 10.7, 4.6 Hz, 1 H), 3.65 (t, J = 10.6 Hz, 1 H), 3.08 (br s, 1 H), 2.43−2.32 (m, 2 H), 2.10 (td, J = 9.7, 4.7 Hz, 1 H), 1.65−1.53 (m, 1 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 3 H) (one OH not apparent); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.5, 144.3, 128.5 (2 C), 127.5, 125.7 (2 C), 115.2, 72.6, 63.3, 55.3, 45.0, 29.4, 21.2, 20.8; MS m/z (M^+ − H_2O) calcd 216.1514, obsd 216.1551.

C. To Cyclohexanecarboxaldehyde. Anti/syn ratio of 14:86 (91%). For **11f**: characteristic ^1H NMR peaks appear at δ 0.92 (d, J = 6.1 Hz, 3 H), 0.86 (d, J = 6.3 Hz, 3 H); characteristic ^{13}C NMR peaks appear at ppm 75.5, 63.6, 55.9, 41.4, 28.3, 20.5.

For **12f**: colorless oil; IR (neat, cm^{-1}) 3405, 1644; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 1 H), 4.99 (s, 1 H), 3.75 (dd, J = 10.6, 4.9 Hz, 1 H), 3.61−3.53 (m, 2 H), 2.87 (br s, 2 H), 2.16 (d, J = 14.1 Hz, 1 H), 2.06−1.96 (m, 2 H), 1.88−1.53 (m, 6 H), 1.37−0.93 (m, 6 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.3, 114.3, 73.9, 63.1, 54.7, 43.9, 39.3, 29.4, 28.5 (2 C), 26.4, 26.2, 26.1, 21.1, 20.7; MS m/z (M^+ − H_2O) calcd 222.1984, obsd 222.1972.

Couplings Involving 9b. A. To Isobutyraldehyde. Anti/syn ratio of 50:50 (90%). For **11g**: characteristic ^1H NMR peaks appear at δ 5.02 (s, 1 H), 2.29 (d, J = 1.8 Hz, 1 H); characteristic ^{13}C NMR peaks appear at ppm 113.3, 75.3, 74.0, 32.4, 16.6.

For **12g**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3400, 1636 ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (s, 1 H), 4.94 (s, 1 H), 3.53 (dd, J = 9.0, 4.7 Hz, 1 H), 3.50−3.37 (m, 2 H), 3.30 (s, 3 H), 2.63 (br s, 1 H), 2.19−2.00 (m, 3 H), 1.96−1.78 (m, 2 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.4, 113.6, 74.7, 73.2, 58.8, 50.6, 41.8, 39.0, 32.5, 18.6, 17.2 (2 C), 16.7; MS m/z (M^+) calcd 214.1933, obsd 214.1886.

B. To Benzaldehyde. Anti/syn ratio of 42:58 (60%). For **11h**: characteristic ^1H NMR peaks appear at δ 5.08 (s, 1 H), 4.97 (s, 1 H), 4.76 (dd, J = 10.3, 3.0 Hz, 1 H), 3.30 (s, 3 H), 2.48 (dd, J = 13.9, 2.3 Hz, 1 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H); characteristic ^{13}C NMR peaks appear at ppm 148.1, 113.9, 75.5, 74.5, 58.9, 53.4, 47.9, 30.2.

For **12h**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3395, 1636; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5 H), 5.12 (s, 1 H), 5.00 (s, 1 H), 4.83 (dd, J = 9.5, 4.2 Hz, 1 H), 3.55 (dd, J = 8.9, 4.7 Hz, 1 H), 3.43−3.35 (m, 1 H), 3.31 (s, 3 H), 2.36−2.10 (m, 3 H), 1.65−1.52 (m, 1 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H) (OH not apparent); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.9, 144.2, 128.2 (2 C), 127.0, 125.7 (2 C), 114.3, 75.0, 70.9, 58.8, 51.0, 48.3, 30.6, 20.94, 20.89; MS m/z (M^+) calcd 248.1776, obsd 248.1777.

C. To Cyclohexanecarboxaldehyde. Anti/syn ratio of 43:57 (64%). For **11i**: characteristic ^1H NMR peaks appear at δ 5.01 (s, 1 H), 2.31 (dd, J = 13.6, 1.6 Hz, 1 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H); characteristic ^{13}C NMR peaks appear at ppm 148.6, 113.3, 75.3, 53.5, 50.7, 43.8, 41.9, 29.9.

For **12i**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3416, 1630; ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 1 H), 4.95 (s, 1 H), 3.53 (dd, J = 8.9, 4.5 Hz, 1 H), 3.50−3.33 (m, 2 H), 3.30 (s, 3 H), 2.19−2.05 (m, 3 H), 2.05−1.87 (m, 1 H), 1.77−1.54 (m, 6 H), 1.43−0.95 (m, 5 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H) (OH not apparent); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.5, 113.6, 74.7, 72.6, 58.8, 51.0, 43.4, 42.0, 30.4, 29.1 (2 C), 28.8, 26.7 (2 C), 21.1, 20.9; MS m/z (M^+) calcd 254.2246, obsd 254.2264.

***cis*-5-Isopropyl-2-phenyltetrahydro-4-methylene-2*H*-pyran (13 ⇄ 14).** A solution of 54 mg (0.23 mmol) of **12e**, 57 mg (0.30 mmol) of *p*-toluenesulfonyl chloride, 232 mg (2.3 mmol) of triethylamine, and a catalytic amount of DMAP in 3 mL of CH_2Cl_2 was refluxed overnight, cooled, and diluted with water. The separated aqueous phase was extracted three times with CH_2Cl_2. The combined organic solutions were washed with saturated NH_4Cl and $NaHCO_3$ solutions and brine, dried, and concentrated. Silica gel chromatography (elution with hexanes) afforded 17 mg (34%) of the cyclic ether as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5 H), 4.83 (s, 1 H), 4.79 (s, 1 H), 4.31 (d, J = 13.0 Hz, 1 H), 4.31 (d, J = 6.0 Hz, 1 H), 3.60 (dd, J = 11.4, 2.8 Hz, 1 H), 2.35 (d, J = 10.3 Hz, 1 H), 2.31 (dd, J = 13.0, 3.7 Hz, 1 H), 2.25−2.05 (m, 1 H), 1.71 (dd, J = 10.2, 2.3 Hz, 1 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.9, 142.6, 128.4 (2 C), 127.5, 125.8 (2 C), 109.9, 81.4, 70.7, 51.8, 40.8, 25.7, 21.3, 21.0; MS m/z (M^+ − CH_2O) calcd 186.1409, obsd 186.1390. Anal. Calcd for $C_{15}H_{20}O$: C, 83.27; H, 9.33. Found: C, 83.20; H, 9.50.

***cis*-2,5-Diphenyl-4-methylene-2*H*-pyran (21).** A solution of **20f** (180 mg, 0.67 mmol) in dry CH_2Cl_2 (5 mL) was treated with *p*-toluenesulfonyl chloride (152 mg, 0.80 mmol), triethylamine (1 mL), and DMAP (3 mg) and heated at reflux overnight. Removal of the solvent in vacuo followed by chromatography on silica gel (elution with hexanes) furnished 89 mg (53%) of **21** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1642; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 2 H), 7.45−7.20 (m, 8 H), 5.10 (s, 1 H), 4.92 (s, 1 H), 4.69 (dd, J = 11.6, 1.3 Hz, 1 H), 4.47 (dd, J = 10.6, 3.3 Hz, 1 H), 4.00 (dd, J = 11.6, 3.3 Hz, 1 H), 3.55 (m, 1 H), 2.41 (dd, J = 11.0, 12.0 Hz, 1 H), 2.33 (dd, J = 12.0, 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.9, 142.2, 141.9, 130−125.0 (10 C), 110.3, 81.2, 71.2, 47.9, 39.7; MS m/z (M^+) calcd 250.1358, obsd 250.1363. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.06; H, 7.11.

***cis*-2,5-Dicyclohexyltetrahydro-4-methylene-2*H*-pyran (22).** A solution of 28 mg (0.10 mmol) of diol **18e**, 23 mg (0.12 mmol) of *p*-toluenesulfonyl chloride, 102 mg (1.0 mmol) of triethylamine, and a catalytic amount of DMAP in 2 mL of CH_2Cl_2 was stirred at room temperature for 4 days and diluted with water. The separated aqueous phase was extracted three times with CH_2Cl_2. The combined organic solutions were washed with saturated NH_4Cl and $NaHCO_3$ solutions and brine, dried, and concentrated. Silica gel chromatography (elution with hexanes) afforded 12 mg (44%) of **22** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (s, 1 H), 4.65 (s, 1 H), 4.16 (d, J = 11.3 Hz, 1 H), 3.32 (dd, J = 11.3, 2.5 Hz, 1 H), 2.97 (ddd, J = 10.2, 6.5, 3.1 Hz, 1 H), 2.13−1.89 (m, 3 H), 1.77−1.41 (m, 10 H), 1.40−0.77 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.5, 109.3, 83.8, 69.8, 50.8, 43.1, 39.7, 35.5, 34.5, 31.5, 31.3, 29.7 (2 C), 29.3, 26.6, 26.52, 26.46,

26.2; MS *m*/*z* (M^+) calcd 262.2297, obsd 262.2296. Anal. Calcd for $C_{18}H_{30}O$: C, 82.37; H, 11.53. Found: C, 82.44; H, 11.40.

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Supporting Information Available: Characterization data for all coupling products where not reported in the text along with copies of the high-resolution ^1H and ^{13}C NMR spectra of those new compounds for which elemental analyses are not reported (87 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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