Experimental Test of Setting Three Contiguous Stereogenic Centers in Water. Diastereoselective Coupling of Geometrically Biased Allylic Bromides to α-Oxy Aldehydes with Indium

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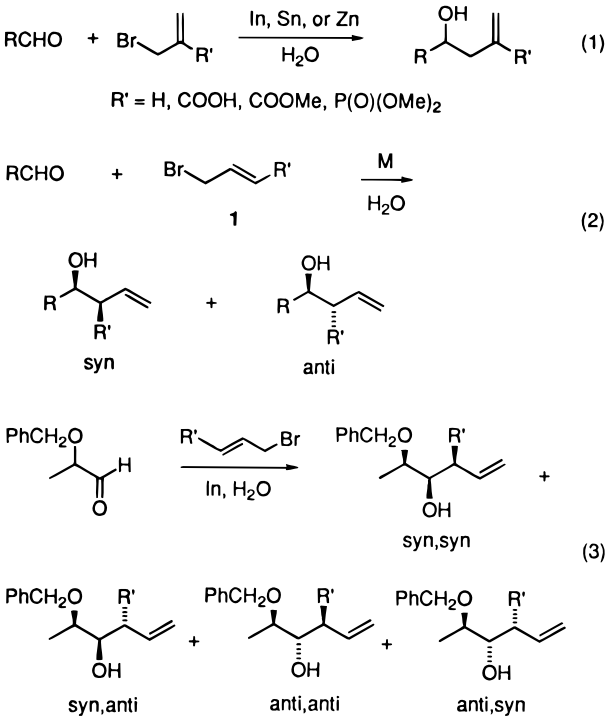
Indium-promoted additions of (*Z*)-2-(bromomethyl)-2-butenoate to several α-(*tert*-butyldimethylsiloxy) and α-(benzyloxy) aldehydes in water have been examined in order to assess the direction and sense of asymmetric induction in these coupling reactions. High levels of the 3,4-syn;4,5-anti diastereomers were produced, reflecting the promising synthetic potential of this chemistry. This stereodifferentiation has been attributed to the strong geometric bias exercised by this allylindium reagent and adherence to a Felkin−Ahn transition-state alignment. Support for this interpretation was gained by comparing the fate of (*E*)-cinnamyl bromide under comparable circumstances. In this case, the 3,4-anti;4,5-anti diastereomer predominated as expected.

The coupling of aldehydes to allylic organometallic compounds generated in water as the reaction medium is currently an active area of research.[1] Allyl bromide,[2] α-(bromomethyl)acrylic acid[3] and its esters,[4] and dimethyl (3-bromopropenyl)-2-phosphonate[5] are recognized to undergo smooth 1,2-addition in the presence of indium to deliver the derived homoallylic alcohols (eq 1). With regard to the stereochemical aspects of this process, significant effort has been expended to gain an appreciation of the underlying cause of the variable syn/anti diastereoselectivity ratios observed as a function of R′ in **1** (eq 2). For the crotyl bromide and R = phenyl examples, no π-facial discrimination is seen.[6,7] In contrast, ethyl 4-bromocrotonate (R′ = COOEt) gives rise to β-hydroxy-α-vinyl carboxylates with high anti selectivity under identical conditions.[7] With $SnI_2/Bu_4N^+Br^-$ as promoter, crotyl bromide enters preferentially into syn addition.[8] The interdependence noted between product stereochemistry and the steric bulk of the substituents on both the allylic bromide and the aldehyde has prompted the consideration of steric constraints within the conventional six-membered transition states.[6,9]



This variability in stereocontrol is exacerbated in those circumstances where the aldehyde is α-substituted (e.g., eq 3).[10] In the illustrated example, the case where R′ is methyl generates no anti,syn product, but affords the syn,syn, syn,anti, and anti,anti diastereomers rather indiscriminately. Further erosion of stereocontrol materializes when R′ is bromine. In this instance, all four possible alcohols result. The lack of stereocontrol in these circumstances has been attributed to facile *E*/*Z* equilibration within the relevant indium reagents,[10] as established previously for the related Grignard, potassium, and lithium derivatives.[11]

These considerations carry important implications for the future use of allylindium reagents in the construction

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(1) Reviews: (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (b) Cintas, P. *Synlett* **1995**, 1087. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (d) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023.

(2) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181 and references cited therein.

(3) (a) Zhou, J.-Y.; Jia, Y.; Yao, X.-B.; Wu, S.-H. *Synth. Commun.* **1996**, *26*, 2397. (b) Chan, T.-H.; Lee, M.-C. *J. Org. Chem.* **1995**, *60*, 4228.

(4) (a) Gao, J.; Härter, R.; Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 3714. (b) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (c) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937. (d) Chan, T.-H.; Li, C.-J. *J. Chem. Soc., Chem. Commun.* **1992**, 747.

(5) Chan, T.-H.; Xin, Y.-C. *Chem. Commun.* **1996**, 905.

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

(7) Diana, S.-C. H.; Sim, K.-Y.; Loh, T.-P. *Synlett* **1996**, 263.

(8) Masuyama, Y.; Kishida, M.; Kurusu, Y. *Tetrahedron Lett.* **1996**, *37*, 7103.

(9) Araki, S.; Hirashita, T.; Shimizu, H.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1996**, *37*, 8417.

(10) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799.

(11) (a) Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 1769. (b) Nordlander, J. E.; Young, W. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 494. (c) Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1984**, *84*, 2010. (d) Schlosser, M.; Hartmann, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 439. (e) Hartmann, J.; Muthukrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1974**, *57*, 2261. (f) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701. (g) Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674. (h) West, P.; Purmont, J. I.; McKinley, S. V. *J. Am. Chem. Soc.* **1968**, *90*, 797. (i) Bates, R. B.; Beavers, W. A. *J. Am. Chem. Soc.* **1974**, *96*, 5001. (j) Sandel, V. R.; McKinney, S. V.; Freedman, H. H. *J. Am. Chem. Soc.* **1968**, *90*, 495. (k) Schlosser, M. *Chimia* **1974**, *28*, 395. (l) Schlosser, M.; Hartmann, J.; David, V. *Helv. Chim. Acta* **1974**, *57*, 2261. (m) Rauchschwalbe, G.; Schlosser, M. *Helv. Chim. Acta* **1975**, *58*, 1094.

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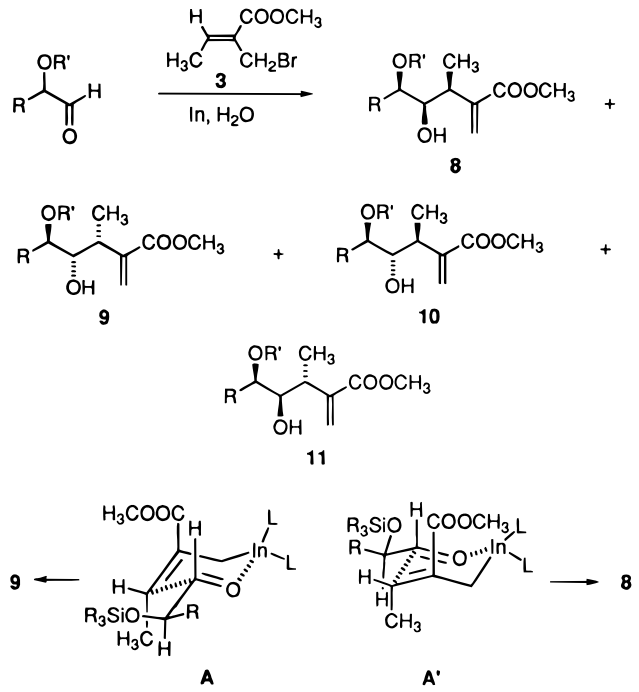
Scheme 1



of stereochemically well-defined homoallylic alcohols. Acyclic control *in water* at this level is important since these couplings would nicely complement aldol reactions. The purpose of this report is to demonstrate the feasibility of setting three contiguous stereogenic centers in highly controlled fashion under aqueous conditions. The experiments to be described illustrate that the useful organizational features of steric control can be combined advantageously with geometric rigidity within the attacking organoindium reagent to reinforce asymmetric induction. Since these stereodifferentiating reactions are dependent upon the local chirality of the individual reaction partners, their stereochemical course can be reliably predicted.

Results and Discussion

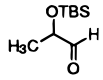
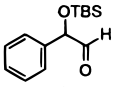
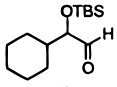
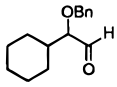
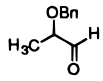
Methyl (*Z*)-2-(bromomethyl)-2-butenoate (**2**) was prepared according to precedence by the reaction of acetaldehyde with methyl acrylate[12] under Baylis−Hillman conditions[13] and subsequent bromination with NBS and dimethyl sulfide[14] (Scheme 1). Relevantly, the latter transformation proceeds in a highly stereoselective manner. Buchholz and Hoffmann have shown the *Z* arrangement in **2** to possess greater thermodynamic stability than the *E* alternative.[15] This feature is central to the mechanistic paradigm that follows.

The addition of **2** to the α-OTBS-substituted aldehydes **3**−**5**, as mediated with indium in water, proved to be entirely γ-regioselective and highly diastereoselective (Table 1 and Scheme 1). The heavy predominance of the 3,4-syn;4,5-anti diastereomers **9** is construed to be telling indication of a high Felkin−Ahn preference in the carbonyl reagent and impressive geometric retention in the allylindium species. The relevant transition state for arrival at **9** is depicted in **A**. When R is methyl, possible steric interaction with the approaching organometallic is minimal and excellent π-facial discrimination is observed. As the relative size of the R substituent is increased to the phenyl and cyclohexyl levels, only very modest erosion of the coupling diastereoselectivities is observed. Thus, although "loosening" of the bonding arrangement implicit in **A** may arise, the steric situation is not improved by a crossover in π-facial selectivity as in **A′**, which leads to **8**. Therefore, the product distributions remain sufficiently biased toward **9** to be synthetically quite useful.

When the α substituent is benzyloxy, the preferred diastereoselectivity remains 3,4-syn;4,5-anti, but to a lesser degree. This is particularly so in entry 5 (Table 1), where the onset of chelation control could be gaining a modicum of importance.[16]

The stereochemical assignments to the allylindation products **9** are based on the chemistry summarized in Scheme 2. Thus, exposure of the silylated hydroxy ester to a catalytic quantity of *p*-toluenesulfonic acid in methanol was met with cyclization to a mixture of **12** and **13** in a 3.3:1 ratio. All three substituents in **12** were easily recognized to be oriented equatorially on the strength of the large 1,2-diaxial coupling constants of the ring protons. Further, the strong NOE interaction shown in the formula was confirmatory of a 1,3-diaxial relationship between this pair of hydrogens.

Table 1. Indium-Mediated Cou;lings of 2 to α-Oxygenated Aldehydes 3-7 in Water at 25 °C[a]

entry	aldehyde	product ratios, % 8	9	10	11	yield, %
1	 **3**	3	97	0	0	75
2	 **4**	5	95	0	0	92
3	 **5**	13	87	0	0	72
4	 **6**	7	88	5	0	79
5	 **7**	29	52	16	4	81

[a] All of the reactions were performed at least in duplicate with vigorous stirring. The product distributions were determined by gas chromatographic analysis on a 2 m × 3.0 mm column packed with 3% OV101 on 100/120 mesh Chromosorb P at 70 °C.

(12) (a) Maurer, B.; Ohloff, G. *J. Chem. Soc., Chem. Commun.* **1977**, 353. (b) Dubs, P.; Schenk, H. P. *Helv. Chim. Acta* **1978**, *61*, 984. (c) Morizur, J. P.; Tortajada, J. *Tetrahedron Lett.* **1982**, *23*, 5275.

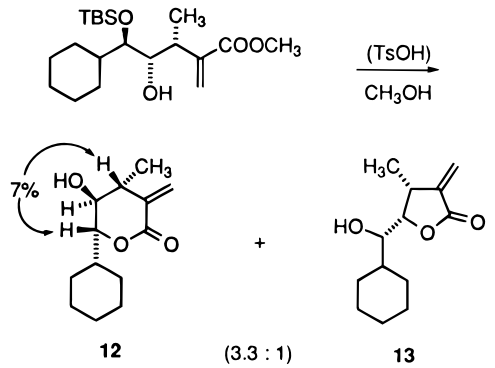
(13) (a) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001. (b) Ciganek, E. *Org. React.* **1997**, *51*, in press.

(14) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795. For the use of other brominating conditions, consult: (a) Drewes, S. E.; Emslie, N. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5095. (c) Rabe, J.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*,796. (d) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849. (e) Ameer, F.; Drewes, S. E.; Houston-McMillan, M. S.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1143.

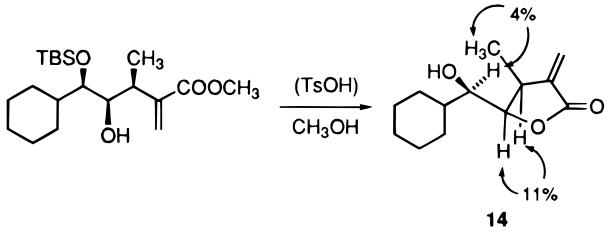
(15) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213.

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

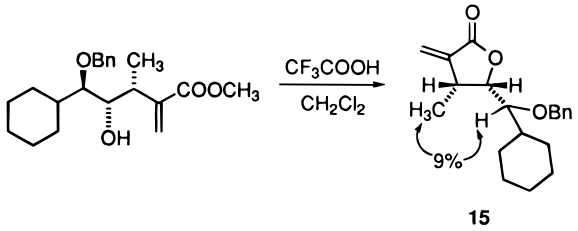
Scheme 2



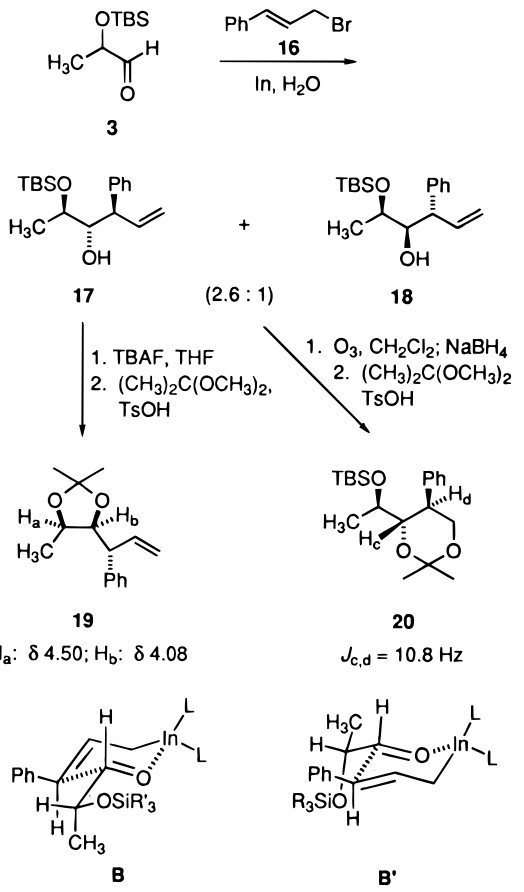
Scheme 3



Scheme 4



Scheme 5



In contrast, the coupling products of type **8** underwent acid-catalyzed cyclization to produce only γ-butyrolactones of type **14**, as evidenced by strong infrared absorption in the vicinity of 1760 cm^{-1}. Relevantly, the relatively intense NOE interactions exhibited by this lactone class (shown in Scheme 3) simultaneously confirm the stereochemical relationship of the vicinal hydroxyl and methyl groups, as well as the syn,syn arrangement of the three contiguous stereogenic methine carbons in **8**.

Comparable cyclization of the *O*-benzyl derivative gave rise to **15**, whose NOE response established the cis relationship of the two ring substituents (Scheme 4).

The sense of asymmetric induction in **8** is consistent with the stereochemical analysis presented previously for the condensation of *cis*- and *trans*-crotylboranes[17] and boronates[18] and related allylindium reagents to α-alkoxy aldehydes.[16] The latter study demonstrated a reluctance on the part of these reagent combinations to form 3,4-anti;4,5-syn products. This outcome is assumed to be applicable as well to the couplings described in this paper.

In order to generalize on our central theme that a thermodynamic organizational feature in the allylic indium reagent is a highly important determinant of stereocontrolled 1,2-addition to chiral aldehydes, (*E*)-cinnamyl bromide (**16**) has also been studied. In prior work, the (*Z*)- and (*E*)-cinnamyl bromides were shown to converge to the same coupled alcohols without regard for the starting bromide geometry.[6] Attainment of the identical sense of diastereoinduction was properly construed to be an indicator that the cinnamyl unit has a kinetic propensity for reaction from its transoid arrangement.

The addition of **16** to **3**, performed in water as before, furnished **17** and **18** in a 2.6:1 ratio (Scheme 5). The formation of **17** is consistent with preferred adherence to the original trans geometry and adoption of the Felkin−Ahn paradigm as in **B**. Since it is highly improbable that **18** materializes because of internal chelation, which is strongly disfavored toward OTBS, an alternate probable explanation lies in the breakdown of electrostatic effects and adoption of the sterically uncongested arrangement **B′**. This analysis is in agreement with the generalization that polar influences alone do not provide a strong diastereofacial bias for related aldol reactions.[19]

The relative stereochemistry resident in **17** was established by desilylation and acetonide formation on the one hand and ozonolytic cleavage followed by elaboration of a 1,3-dioxane ring on the other. In **19**, the relative orientations of the two oxygenated centers were clearly revealed by ^1H NMR coupling constants and NOE analyses. Similar processing of **20** provided complementary evidence for the third stereogenic center.

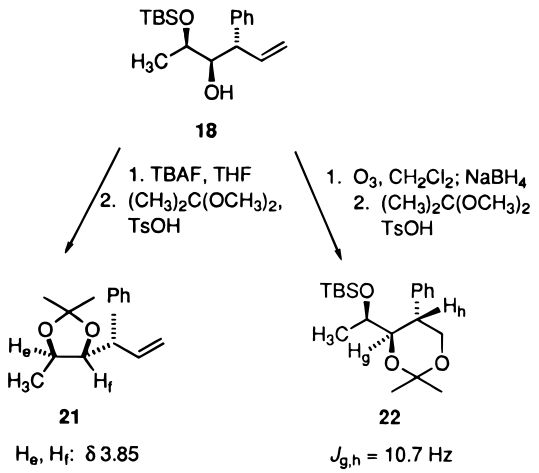
The minor diastereomer **18** was subjected to the identical pair of reactions (Scheme 6). Unexpectedly, H_e

(17) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

(18) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Roush, W. R. ; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (c) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.

(19) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537.

Scheme 6



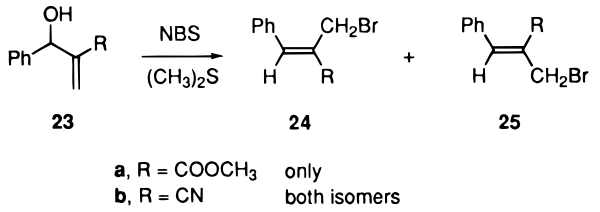
and H_f in **21** were found to exhibit near-identical chemical shifts in various solvents (compare the situation in **19**), rendering NOE analysis ineffective as a tool for stereochemical determination. However, $J_{g,h}$ in **22** proved to be large (10.7 Hz) and confirmatory of a trans-diaxial relationship between these protons (see also **20**). The fact that the newly generated stereocenters in **18** bear an anti relationship requires further that the resident OTBS substituent be syn to the hydroxyl. This is because an anti arrangement would constitute an enantiomeric relationship to **17**, which is not possible.

Conclusions

We have established that highly functionalized acyclic molecules containing three contiguous stereogenic centers can be assembled with high stereoselectivity from simple building blocks in water as the reaction medium. As long as the geometry inherent in the allylindium reagent is biased strongly in either a *Z* or *E* sense, control of product stereochemistry as in **9** or **17** can be expected to operate at synthetically practical levels.

Two independent control features, which appear to be fully operational despite the aqueous nature of the environment, determine the success of these condensation reactions. In addition to the persistence of a single geometry in the organometallic species, adherence to Felkin−Ahn transition states allows access to only one face of the α-oxygenated aldehyde. However, when small substituents are involved, solvation by water may alter the balance of steric forces sufficiently to effect exclusive operation of this model and cause other transition states to be operational. Additional work is required to allow improved understanding of these conformational alternatives.

The benefits associated with the strategy outlined herein are intimately linked to the structural integrity of the allylindium species employed. The analysis becomes more complex for bromides that find it possible to undergo *E*/*Z* equilibration readily. Cases in point are the cyano bromides **24a**/**25a**. Unlike the syntheses of **2** and **16**, which proceed to deliver a single bromide, **23b** is transformed into both possible isomers under identical conditions.[20] The reduced steric demands of the nitrile group are likely responsible for this loss of control (Scheme 1). This feature extends into the present investigation since attempts to couple **24** with **3**−**7** in the presence of indium gave complex isomeric mixtures.[21]



To the best of our knowledge, the stereocontrolled condensations involving **2** and **16** represent the first fully documented examples in which the persistent geometry of the derived allylindiums is shown to play a decisive role in determining the overall stereoselectivity of carbon−carbon bond formation.

Experimental Section[22]

General Indium-Promoted Allylation Procedure. To a vigorously stirred mixture of the aldehyde (1.0 mmol) and **2** (1.5 mmol) in water (2 mL) was added indium powder (1.5 mmol). The reaction mixture was stirred at 20 °C for 8 h and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated. After GC analysis, the residue was purified by flash chromatography on silica gel.

In entries 4 and 5 (Table 1) where the rate of hydrolysis of **2** proved to be significant, the bromide was used as the limiting reagent instead of the aldehyde.

Entry 1, (Table 1), ester **9**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3500−3300, 1714; ^1H NMR (300 MHz, C_6D_6) δ 6.12 (d, J = 1.3 Hz, 1 H), 5.37 (s, 1 H), 3.79 (m, 1 H), 3.72 (m, 1 H), 3.36 (s, 3 H), 3.08 (m, 1 H), 2.45 (d, J = 2.8 Hz, 1 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.23 (d, J = 6.0 Hz, 3 H), 0.93 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 167.5, 144.4, 125.4, 77.7, 70.0, 51.4, 38.1, 26.0, 18.5, 18.1, 15.1, −4.2, −4.9; MS m/z ($M^+ - 1$) calcd 285.1886, obsd 285.1884.

Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.01. Found: C, 59.67; H, 9.99.

Acid-Catalyzed Cyclization of Entry 5-9. A solution of this ester (80 mg, 0.20 mmol) in methanol (3 mL) was treated with 5 mg of *p*-toluenesulfonic acid monohydrate, stirred at room temperature for 24 h, and concentrated. The residue was purified by flash chromatography on silica gel to give 45 mg (88%) of **12** and **13**: IR ($CHCl_3$, cm^{-1}) 3625 (br), 1722; MS m/z (M^+) calcd 224.1412, obsd 224.1398.

For **12**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J = 2.5 Hz, 1 H), 5.68 (d, J = 2.5 Hz, 1 H), 3.94 (dd, J = 9.6, 2.0 Hz, 2 H), 3.45 (t, J = 9.6 Hz, 1 H), 2.52 (m, 1 H), 1.90−1.30 (series of m, 11 H), 1.29 (d J = 6.4 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.5, 138.1, 127.9, 85.7, 69.6, 40.1, 38.0, 29.5, 26.5 (2 C), 26.0 (2 C), 15.9.

For **13**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 2.0 Hz, 1 H), 5.58 (d, J = 2.0 Hz, 1 H), 4.38 (dd, J = 8.8, 6.7 Hz, 1 H), 3.59 (dd, J =6.7, 3.0 Hz, 1 H), 3.30 (m, 1 H), 1.90−1.30 (series of m, 11 H), 1.22 (d, J = 6.6 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.3, 141.2, 121.1, 79.3, 73.5, 39.5, 36.9, 29.7, 26.1 (2 C), 25.8 (2 C), 15.1.

(20) Drewes, S. E.; Hoole, R. F. A. *Synth. Commun.* **1985**, *15*, 1067.

(21) Isaac, M. B. Unpublished observations from this laboratory.

(22) For generic experimental details, see ref 16b.

Acid-Catalyzed Cyclization of Entry 3-8. To a methanolic solution (1 mL) of this ester (30 mg, 0.08 mmol) was added *p*-toluenesulfonic acid (2 mg), and the mixture was stirred at 20 °C for 24 h, concentrated in vacuo, and rapidly purified by flash chromatography on silica gel to give 12.9 mg (71%) of **14**: IR ($CHCl_3$, cm^{-1}) 1761, 1450, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (d, J = 3.4 Hz, 1 H), 5.44 (d, J = 3.4 Hz, 1 H), 4.66 (dd, J = 1.3, 7.8 Hz, 1 H), 3.42 (t, J = 7.8 Hz, 1 H), 3.20 (m, 1 H), 2.0−0.9 (series of m, 11 H), 1.33 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.9, 140.6, 118.3, 79.3, 74.8, 40.5, 36.7, 29.3, 28.9, 26.1, 25.8, 25.7, 13.2; MS m/z (M^+) calcd 224.1412, obsd 224.1404.

Acid-Catalyzed Cyclization of Entry 4-9. A vigorously stirred solution of the ester (70 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic acid (68 mg, 0.60 mmol), stirred overnight, quenched with saturated $NaHCO_3$ solution, diluted with water, and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated to leave a residue that was subjected to chromatography on silica gel. There was isolated 62 mg (96%) of **15** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1762; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 6.14 (d, J = 2.4 Hz, 1 H), 5.50 (d, J = 2.2 Hz, 1 H), 4.63 (d, J = 11.0 Hz, 1 H), 4.58 (t, J = 6.8 Hz, 1 H), 4.53 (d, J = 11.0 Hz, 1 H), 3.47 (t, J = 6.8 Hz, 1 H), 3.22 (m, 1 H), 2.00−1.10 (series of m, 11 H), 1.26 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.2, 141.5, 138.3, 128.3, 127.5, 127.4, 119.8, 83.1, 79.6, 74.1, 40.2, 37.3, 30.0, 28.6, 26.5, 26.4, 26.3, 15.2; MS m/z (M^+) calcd 315.1960, obsd 315.1945.

Coupling of (*E*)-Cinnamyl Bromide to 3. Reaction of **16** (300 mg, 1.50 mmol) with **3** (400 mg, 2.13 mmol) according to the general procedure afforded 298 mg (65%) of a 72:28 mixture of **17** and **18**. Chromatography on silica gel (elution with 5% ethyl acetate in hexanes) resulted in diastereomer separation.

For **17**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3565 (br), 1638; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5 H), 6.20 (ddd, J = 17.3, 10.0, 8.5 Hz, 1 H), 5.14 (d, J = 10.0 Hz, 1 H), 5.07 (d, J = 17.3 Hz, 1 H), 3.89 (dd, J = 8.5, 3.3 Hz, 1 H), 3.55 (m, 1 H), 3.32 (t, J = 8.5 Hz, 1 H), 2.45 (br s, 1 H), 1.06 (d, J = 6.2 Hz, 3 H), 0.86 (s, 9 H), −0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.8, 139.3, 128.7, 128.1, 126.7, 116.3, 77.5, 69.0, 52.3, 25.8, 18.0, 16.0, −4.6, −4.9; MS m/z (M^+ − OH) calcd 289.1988, obsd 298.2015.

Anal. Calcd for $C_{18}H_{30}O_2Si$: C,70.54; H, 9.87. Found: C, 70.43; H, 9.84.

For **18**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3565 (br), 1638; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5 H), 6.25 (ddd, J = 18.4, 10.2, 8.1 Hz, 1 H), 5.14 (d, J = 10.2 Hz, 1 H), 5.04 (d, J = 18.4 Hz, 1 H), 3.66 (m, 1 H), 3.58 (m, 1 H), 3.38 (t, J = 8.1 Hz, 1 H), 2.54 (d, J = 7.0 Hz, 1 H), 1.15 (d, J = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.0, 138.9, 128.6, 128.2, 126.5, 116.3, 78.1, 68.7, 53.3, 25.9, 20.8, 18.0, −3.8, −4.8; MS m/z (M^+ − OH) calcd 289.1988, obsd 289.2015.

A solution of **17** (58 mg, 0.19 mmol) in THF (1 mL) was treated with tetra-*n*-butylammonium fluoride (0.3 mL of 1.0 M in THF, 0.3 mmol), stirred at 20 °C for 1 h, diluted with ether (5 mL), and quenched with saturated NH_4Cl solution (5 mL). The separated organic phase was washed with brine, dried, and concentrated. Rapid flash chromatography of the residue on silica gel afforded 32 mg (87%) of the diol, which was used immediately.

Acetalization of 17. A solution of the above diol (32 mg, 0.16 mmol) in 2,2-dimethoxypropane (2 mL) was treated with 5 mg of *p*-toluenesulfonic acid monohydrate, stirred overnight at room temperature, quenched with 1 drop of saturated $NaHCO_3$ solution, diluted with water (2 mL), and extracted with ether. The combined organic layers were concentrated, and the residue was purified by flash chromatography on silica gel to give 34 mg (88%) of **19**: colorless oil; IR ($CHCl_3$, cm^{-1}) 1623, 1453, 1389, 1235; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.15 (m, 5 H), 6.14 (ddd, J = 17.2, 10.2, 7.0 H, 1 H), 5.08 (d, J = 10.2 Hz, 1 H), 4.96 (d, J = 17.2 Hz, 1 H), 4.50 (dd, J = 10.0, 5.3 Hz, 1 H), 4.08 (m, 1 H), 3.47 (dd, J = 10.0, 7.0 Hz, 1 H), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.10 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.0, 140.0, 128.7, 128.2, 126.8, 115.5, 107.8, 79.8, 73.0, 49.7, 28.5, 26.0, 16.3; MS m/z (M^+) calcd 232.1463, obsd 232.1454.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.65; H, 8.70.

Ozonolytic Degradation of 17. Ozone was bubbled through a cold (−78 °C), magnetically stirred solution of **17** (50 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) until a blue color persisted. After replacement with oxygen for 10 min, methanol (3 mL) and sodium borohydride (30 mg, 0.8 mmol) were introduced and the mixture was stirred overnight at 20 °C. After slow quenching with water, the product was extracted into ether (3 × 15 mL), and the combined organic phases were dried and concentrated. Rapid flash chromatography of the residue on silica gel afforded 40 mg (81%) of diol, which was dissolved in 2,2-dimethoxypropane (3 mL), treated with *p*-toluenesulfonic acid (5 mg), and allowed to react as described above. The same workup afforded **20** (27 mg, 60%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1454, 1386, 1256; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5 H), 4.05 (dd, J = 10.8, 1.4 Hz, 1 H), 3.93 (d, J = 11.2 Hz, 1 H), 3.82 (dd, J = 11.2, 5.4 Hz, 1 H), 3.67 (dq, J = 6.6, 1.4 Hz, 1 H), 2.97 (dt, J = 10.8, 5.4 Hz, 1 H) 1.58 (s, 3 H), 1.47 (s, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.85 (s, 9 H), −0.03 (s, 3H), −0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.3, 128.6, 128.4, 127.0, 98.3,77.4, 67.6, 65.5, 42.8, 29.4, 25.9, 19.4, 18.4, 18.2, −4.6, −4.8; MS m/z (M^+ − CH_3) calcd 335.2042, obsd 335.2040.

Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.36; H, 9.74.

Acetalization of 18. A solution of **18** (43 mg, 0.14 mmol) was dissolved in THF (1 mL), treated with tetra-*n*-butylammonium fluoride (0.3 mL of 1.0 M in THF, 0.3 mmol), stirred at 20 °C for 1 h, diluted with ether (5 mL), and quenched with saturated NH_4Cl solution (5 mL). The separated organic layer was washed with brine, dried, and concentrated to leave an oil that was dissolved in 2,2-dimethoxypropane (2 mL), treated with *p*-toluenesulfonic acid (5 mg), and stirred overnight. The predescribed workup delivered 20 mg (64%) of **21** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1623, 1453, 1389, 1235, 1169, 1071; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 6.20 (ddd, J = 7.6, 10.3, 17.9 Hz, 1 H), 5.16 (m, 2 H), 3.85 (m, 2 H), 3.35 (dd, J = 6.5, 7.6 Hz, 1 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 0.84 (d, J = 5.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.5, 138.2, 128.6 (2 C), 128.4 (2 C), 126.9, 116.5, 107.9, 84.5, 75.8, 53.1, 27.4, 27.0, 18.2; MS m/z (M^+) calcd 232.1463, obsd 232.1476.

Ozonolytic Degradation of 18. Ozonolysis of a 30 mg sample of **18** with subsequent borohydride reduction and acetalization in the manner described earlier af-

forded 10 mg (30% overall) of **22** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1454, 1386, 1256, 1108, 1062; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5 H), 3.94 (dd, J = 2.4, 10.7 Hz, 1 H), 3.86 (d, J = 11.8 Hz, 1 H), 3.83 (dd, J = 5.9, 11.8 Hz, 1 H), 3.70 (m, 1 H), 3.07 (dt, J = 5.9, 10.7 Hz, 1 H), 1.56 (s, 3 H), 1.46 (s, 3 H), 1.02 (d, J = 6.4 Hz, 3 H), 0.82 (s, 9 H), −0.02 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.4, 128.5, 128.4, 126.7, 98.3, 76.6, 69.3, 65.8, 42.6, 29.2, 19.7, 19.5, 19.4, −3.9, −4.6; MS m/z (M^+) calcd 335.2042, obsd 335.2043.

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Supporting Information Available: Physical data for Table 1, entries 2−5, together with copies of the high-field ^1H and ^{13}C NMR spectra of those pure compounds for which elemental analyses are not reported (9 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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