Competitive Intramolecular/Intermolecular Chelation Options Operative during Indium-Promoted Additions to Pyridyl Aldehydes and to Glyoxylic Acid under Aqueous Conditions

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The stereochemical course of the 1,2-addition of six allylindium reagents to 2- and 3-pyridinecarboxaldehyde and to glyoxylic acid has been investigated in order to assess the level and direction of diastereoselectivity in these coupling reactions. When 2-PyCHO is involved, the results strongly suggest that the ring nitrogen becomes chelated to the indium atom in the aqueous environment. One striking observation is the crossover in stereoselectivity seen relative to the use of 3-PyCHO. A second revealing fact is the significantly faster rate of reaction of 2-PyCHO, as long as steric effects are not allowed to interfere. The varying product distributions observed in the latter experiments are attributed to other control elements such as intramolecular chelation within the indium reagent and nonbonded steric restrictions resident in either or both reaction partners. In the absence of extramolecular chelating events (e.g., when 3-PyCHO is involved), adherence to Felkin−Anh transition-state alignments is presumably exercised. The previous working assumption that indium(III) is capable of chelation to flanking heteroatomic centers in water is supported by the present investigation.

Indium-promoted nucleophilic carbonyl addition reactions in water continue to be regarded as among the premier methods for C−C bond formation under aqueous conditions.[1,2] Of particular concern to us are the stereochemical aspects of these processes, significant effort having been expended to elucidate the impact of proximal groups on π-facial selectivity. Where α- and β-hydroxy aldehydes are concerned, excellent diastereocontrol is very often realized with resultant delivery of *syn*-1,2-diol and *anti*-1,3-diol products at accelerated rates.[3,4] α-Dimethylamino,[5] α-acylamino,[5,6] and β-carboxy aldehydes[7] behave comparably, and the amide carbonyl in 2,3-azetidinediones can also be conducive to high levels of stereocontrol.[8] Protection of the free hydroxyl by alkyl and silyl groups, as well as substitution of the neighboring nitrogen center with increasingly bulky alkyl residues, results alternatively in predominant conversion to 1,2-anti products. Similar controlling factors have been uncovered for α-hydroxy[9] and α-methoxy ketones.[10]

The preceding observations have been interpreted in terms of the involvement of Cram-like[11] chelated transition states, provided that binding to the indium atom is not sterically inhibited. Otherwise, adherence to the Felkin−Anh model[12] is seemingly operative. Despite the fact that these conclusions are supported by the associated stereochemical outcomes and significant kinetic enhancements,[13] several investigators remain dubious that chelation can continue to operate in water with the required heightened efficiency.[14,15] Their reservations can be summarized as follows:

(a) The Felkin−Anh model would predict the same syn stereochemical outcome if the heteroatomic substituent is viewed to be of medium size.

(b) As a consequence of the aqueous environment, the water molecules should solvate the indium ion, thereby deterring formation of the chelation complex.

(c) Single electron transfer from the metal surface to either the carbonyl reactant or the allylic halide would lead instead to formation of free-radical intermediates.

(d) The rate accelerations can be attributed to inductive effects unique to OH (and related small polar groups) in water, and not necessarily to larger OR, NR_2, and SR substituents.

While the intermolecular chelation model has certainly not been proven, this simple transition-state paradigm

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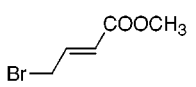
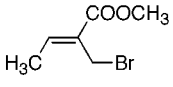
is fully consistent with product stereoselectivity and its erosion when increasingly bulky groups are introduced. The mechanistic proposal is further supported by the impressive enhancement in syn selectivity generally observed in water relative to organic solvents, a phenomenon that is considered indicative of reduced internal mobility about the bonds in close vicinity to the carbonyl group.

Studies featuring placement of the stereocontrolling element on the allylic bromide have additionally been reported.[16,17] This tactic of intramolecular chelation within the organometallic reagent can lead to effective 1,4-asymmetric stereoinduction and to the setting of three contiguous stereogenic centers in water. The conformational restrictions on possible chelation control have been defined and carry important implications relevant to the issues under discussion.

The purpose of the present study was to elucidate the level and direction of the competitive involvement of intermolecular versus intramolecular modes of chelation when these options are allowed to vie for control of π-facial diastereoselectivity. For this purpose, 2-pyridinecarboxaldehyde (2-Py-CHO) and glyoxylic acid were selected as suitable external chelators to the indium reagent.[18] 3-Pyridinecarboxaldehyde (3-Py-CHO) does not share in this property and therefore constitutes a useful reference standard. The six allylic bromides **1**−**6** have served as the reaction partners.



1



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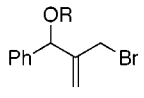
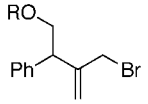


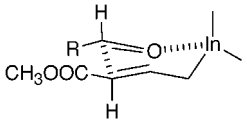
3, R = H
4, R = TBS



5, R = H
6, R = TBS

Results and Discussion

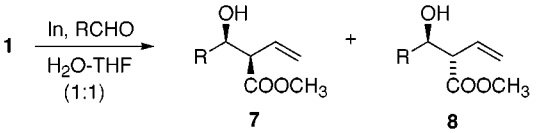
Methyl 4-Bromocrotonate (1). The indium-promoted condensation of **1** with carbonyl compounds is recognized to generate new stereochemical relationships in a reliable and predictable manner.[8,17b] The elevated anti stereoselectivity of these coupling events has been rationalized in terms of the favorable energy of those transition states having structural features defined as in **A**. The reaction



A

proceeds most readily in that direction where the carbomethoxy group in **1** and the R group of the aldehyde are projected equatorially on the developing six-membered ring.

Scheme 1



7 **8**

entry	R	designation	syn/anti	yield, %
1	3-Py	**a**	22 : 78	62
2	2-Py	**b**	94 : 6	81
3	$COOCH_3$	**c**	88 :12	52

In the present context, all allylations were carried out in a 1:1 mixture of water and THF in order to guarantee solubility on the part of all the reactants. The results for **1** are depicted in Scheme 1. All product ratios were determined by 300 MHz ^{1}H NMR integration of the diastereomeric mixtures prior to MPLC separation (where possible). Bromide **1** proved to be appreciably more reactive than **2**−**6** as revealed by the liberation of heat following introduction of the aldehydes and more rapid onset of the milky appearance that denotes completion of the coupling. In general, however, the pyridinecarboxaldehydes were found to react sluggishly. This observation was not unexpected as the basic nature of the nitrogen center should offset the autocatalysis brought on by the development of acidity under normal circumstances.[3] No attempt was made to offset this reduced rate with additives such as NH_4Cl and Et_4NI, since any alteration of the basic properties of the pyridine derivative could be accompanied by a reduction in chelation capacity. A related rate acceleration was observed for the allylations of glyoxylic acid, a likely consequence of lowered pH. To facilitate handling, the products formed from glyoxylic acid were esterified with diazomethane. The lower yields realized upon subsequent workup can be attributed to the inherent volatility of the resulting methyl esters. To permit proper comparative analysis, all allylations were allowed to proceed for 48 h.

Distinction between the 1,2-syn and 1,2-anti diastereomers **7** and **8** in entries 1 and 2 was achieved by high-field ^{1}H NMR analysis and chemical derivatization. For example, the chemical shifts of the methine vinylic proton in **7a** (δ 5.69−5.57) and in **7b** (δ 5.88−5.76) appear characteristically to higher field than their counterparts in the anti diastereomers **8a** (δ 5.98−5.85) and **8b** (δ 5.90−5.78). Beyond this, these hydroxy esters were reduced to the diol level with lithium aluminum hydride and cyclized with 2-methoxypropene under conditions of *p*-toluenesulfonic acid catalysis (Scheme 2).

The acetonides **9** and **10** so formed were amenable to chromatographic separation. The trans diaxial nature of the ring methine protons in **9** was easily recognized on the basis of the large vicinal J values observed for the minor 3-Py isomer **9a** (J = 10.5 Hz) and the major 2-Py isomer **9b** (J = 9.3 Hz). At this point, the evidence that a crossover in stereoselectivity had occurred was incontrovertible.

The stereochemical assignments to **7c** and **8c** (see entry 3) are based on detailed chemical shift correlations (see **11** and **12**) with a diverse array of analogues including **13** and **14** for which X-ray data are available.[8]

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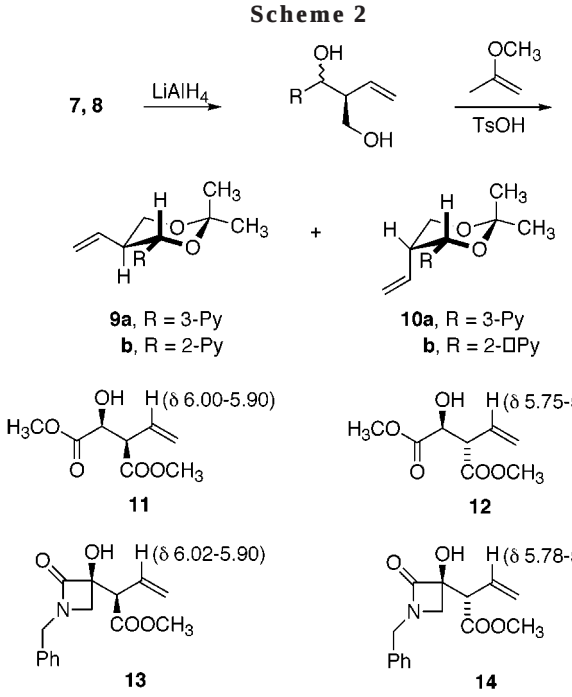
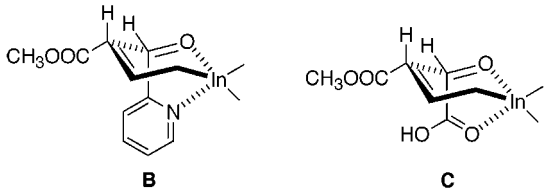
Scheme 2

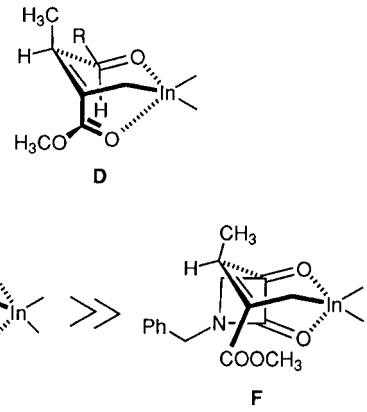


Interestingly, one consequence of an added flanking carbonyl substituent is to reverse the relative positioning of the methine vinylic proton relative to **7**, **8**, and their congeners.

The diastereoselectivities observed in Scheme 1 can be explained in terms of the adherence by 3-pyridinecarboxaldehyde to transition state **A** where coordination of the indium atom to the carbonyl provides a suitable means for activation, S_N' delivery of the allyl residue, and favored formation of the anti diastereomer **8a**. Where 2-pyridinecarboxaldehyde and glyoxylic acid are concerned, the heavy predominance of syn adduct formation requires that a different reaction trajectory be favored. The influence of proximal binding sites to indium conforms to expectations based on chelated transition states **B** and **C**.[19]



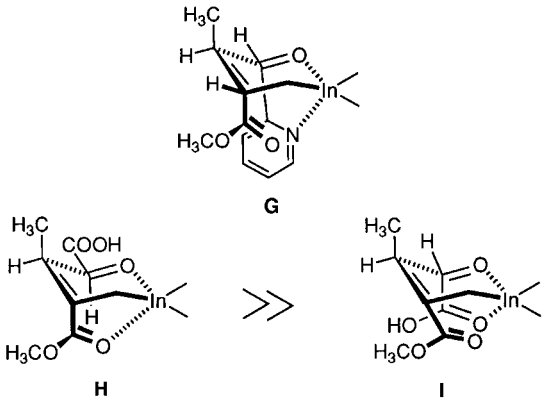
Methyl (*Z*)-2-(Bromomethyl)-2-butenoate (2). The *Z* double bond arrangement in **2**, earlier demonstrated in convincing fashion to be thermodynamically advantaged relative to the *E* alternative,[20] has lent itself well to the stereoselective formation of syn adducts.[8,17b,21] The possibility has been advanced that this contrasting outcome may reflect secondary binding to the ester carbonyl as in **D**. Although this feature has not been established with certainty, the choice by indium of this mode of internal chelation would be expected to preclude intermolecular coordination. The diastereofacial selectivity observed for the indium-promoted coupling of **2** to



N-benzyl-2,3-azetidinedione is most simply interpreted in terms of preferred intramolecular ligation as in **E** relative to the intermolecular alternative **F**.[8]

The product distribution determined for the reaction of **2** with 3-pyridinecarboxaldehyde (entry 4, Scheme 3) conforms to the π-facial stereoselectivity anticipated from utilization of transition state **D**. When comparison is made with the 2-pyridyl isomer (entry 5), the simple change in the locus of the nitrogen is seen to be adequate to favor almost total production of anti product **16b**. These findings again dispel the notion that steric effects alone control the stereochemical course of reactions performed in aqueous environments. Rather, it appears that chelation of indium to the pyridine nitrogen is sufficiently favorable to override intramolecular ligation to the ester carbonyl. Passage through **G** would give rise to hydroxy ester **16b**.

The selectivity associated with entry 6 reveals that coordination to the free carboxyl as in **I** is less important than that involving the ester functionality (see **H**). The enhanced electron density at the carbonyl oxyen in **H** resulting from the presence of the *O*-methyl substituent could be a responsible factor. However, the diaxial projection of the COOH and $COOCH_3$ groups in **I** is unquestionably a detractive feature.



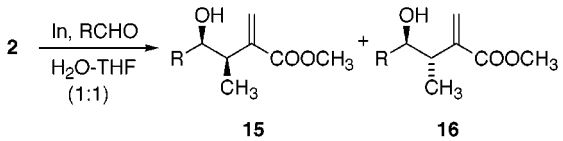
Diastereomers **15** and **16** were differentiated by the chemical shifts and multiplicities of the vinylic protons as previously established in related studies.[8] The diagnostic signals of the anti isomers are generally deshielded relative to their counterparts in the syn series. However, since the presence of phenyl groups has been found to exert less predictable shielding effects,[17c] additional confirmation was sought by means of the cyclization of **15a** to the α-methylene lactone **17** with sodium hydride. NOE experiments performed on **17** showed an enhance-

(19) Entirely comparable deductions have been made by others in different contexts.[18]

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

(21) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457.

Scheme 3



entry	R	designation	syn/anti	yield, %
4	3-Py	**a**	64 : 36	82
5	2-Py	**b**	6 : 94	74
6	$COOCH_3$	**c**	81 : 19	61

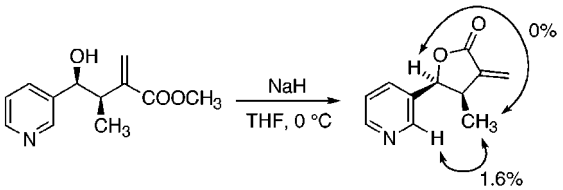
Table 1. Diagnostic Vinyl Proton Chemical Shift Data for 15a−c and 16a−c (300 MHz, $CDCl_3$)

compd	δ values
15a	6.25 (s, 1 H), 5.54 (s, 1 H)
15b	6.26 (d, J = 3.0 Hz), 5.58 (d, J = 3.0 Hz)
15c	6.21 (s, 1 H), 5.82 (s, 1 H)
16a	6.15 (m, 1 H), 5.51 (m, 1 H)
16b	6.22 (s, 1 H), 5.85 (s, 1 H)
16c	6.30 (s, 1 H), 5.72 (s, 1 H)

Table 2. Diagnostic Benzylic and Vinylic Chemical Shift Data for 18a,b, 19a,b, 20a,b, and 21a,b (300 MHz, $CDCl_3$)

compd	δ values
18a	4.82 (dd, J = 7.2, 4.0 Hz, 1 H); 5.21, 5.10, 4.75 (s, 1 H each)
19a	4.70 (dd, J = 9.0, 4.1 Hz, 1 H); 5.30, 5.27, 5.06 (s, 1 H each)
18b	4.95 (dd, J = 7.0, 4.3 Hz, 1 H); 5.24, 5.08, 4.79 (s, 1 H each)
19b	4.90 (dd, J = 8.3, 5.3 Hz, 1 H); 5.32, 5.30, 5.08 (s, 1 H each)
20a	4.82 (dd, J = 7.2, 4.0 Hz, 1 H); 5.26, 5.23 (s, 1 H each)
21a	4.76 (dd, overlapping, 1 H); 5.31, 5.11 (s, 1 H each)
20b	4.92 (dd, J = 9.4, 3.8 Hz, 1 H); 5.23, 5.18 (s, 1 H each)
21b	4.90 (dd, J = 8.0, 5.2 Hz, 1 H); 5.13, 5.11 (s, 1 H each)

ment of the signal due to the proximal α-pyridyl hydrogen upon double irradiation of the methyl protons but no effect at the α-oxygenated center. The heterocyclic ring and methyl substituent in **17** need therefore be cis-oriented. The major and minor isomers **15c** and **16c** could be clearly distinguished by direct spectroscopic comparison with **15b** and **16b** (Table 1).

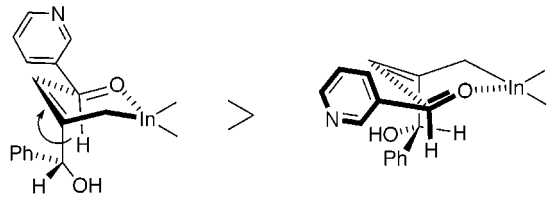


15a **17**

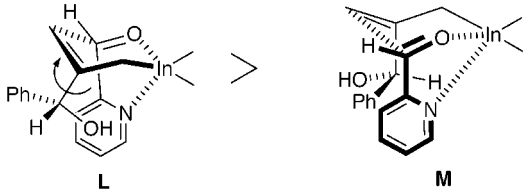
The 3-Oxygenated 1-Bromo-3-phenyl-2-methylidenepropanes 3 and 4. When hydroxy bromide **3** was subjected to typical coupling conditions (entries 7 and 8), it was discovered that neither the 3- nor the 2-pyridinecarboxaldehyde discriminated well between the two stereochemical options. A bias in opposite directions persisted but did not extend beyond the 60−65% level. The OTBS functionality in **4** had no effect on the marginal predominance of syn isomer **18** (entry 9). No reaction was observed with 2-pyridinecarboxaldehyde during the standard 48 h time period (entry 10).

Distinction between the syn and anti products **18a,b** and **19a,b** rests on direct NMR correlations with the prior results of Mulzer[16] and Bennett,[17c] which in turn are correlated to crystallographic data (Table 2). The silylated products **18c** and **19c** were desilylated for proper correlation with **18a** and **19a**, respectively. These structural interconversions established that a modest crossover in stereoselectivity had indeed materialized.

The low-level stereochemical bias exhibited by **3** toward 3-pyridinecarboxaldehyde can be concisely accounted for in terms of the Felkin-Anh transition states **J** and **K**. In the absence of internal chelation to the hydroxyl group, a phenomenon earlier encountered,[7c] there exists no apparent hold on the rotational conformation of the PhCH(OH)- substituent other than the usual steric constraints. For reasons that are not clearly apparent, advancement to product along trajectory **J** is somewhat more kinetically favorable than the pathway defined by **K**. In neither case do we necessarily imply the orientation of the carbinol center to be fixed in the rotamer illustrated.

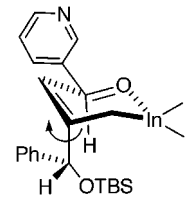


J **K**



L **M**

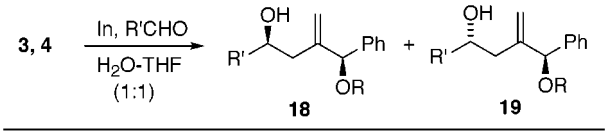
When 2-pyridinecarboxaldehyde is involved, the intramolecular chelation option **L** is favored over **M** despite the obvious steric congestion associated with the onset of intermolecular chelation in both transition states. This outcome is assumed to be due to the appreciable stabilization that arises from the ligation of indium to pyridyl nitrogen. The unreactivity of **4** toward 2-pyridinecarboxaldehyde indicates that the steric compression resident within the silylated variants of **L** and **M** impedes their transient formation. At the moment, we can only assume that the reason Felkin−Anh trajectories such as that given by **N** are not adopted as serviceable alternatives for coupling is the overriding binding capacity of In(III) for pyridyl nitrogen.



N

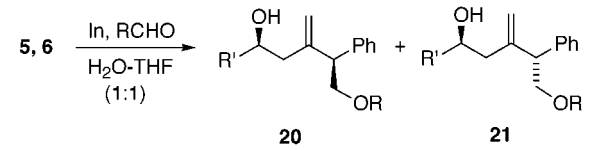
The 4-Oxygenated 1-Bromo-3-phenyl-2-methylidenebutanes 5 and 6. The preceding findings prompted an analysis of the level of stereoinduction that would be observed upon chain extension of the functionalized allylic bromide. Where **5** is concerned, this relatively modest structural change was sufficient to disclose the first example where 3-pyridinecarboxaldehyde exhibited higher syn selectivity than the 2-isomer (Scheme 5, entries 11 and 12). Furthermore, **6** also provided predominantly syn product in its coupling to 3-PyCHO

Scheme 4



entry	R	R'	designation	syn/anti	yield, %
7	H	3-Py	**a**	64 : 36	65
8	H	2-Py	**b**	40 : 60	63
9	TBS	3-Py	**c**	66 : 34	64
10	TBS	2-Py	**d**	no reaction	

Scheme 5

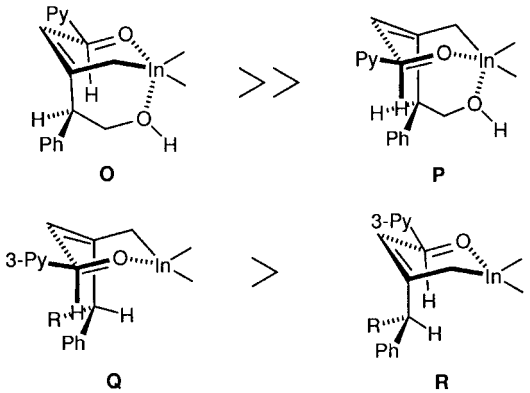


entry	R	R'	designation	syn/anti	yield, %
11	H	3-Py	**a**	80 : 20	71
12	H	2-Py	**b**	65 : 35	62
13	TBS	3-Py	**c**	66 : 34	69
14	TBS	2-Py	**d**	no reaction	

(entry 13). As before, this silylated bromide did not react under the conditions defined in entry 14.

The ^{1}H NMR data given in Table 2 show that diols **20a,b** and **21a,b** adhere to the telltale trend defined earlier.[17c] Once again, products **18c** and **19c** were desilylated for the purposes of direct correlation.

Of the allylic bromides examined herein, **5** holds the unique position of not exhibiting a crossover in stereoselectivity based upon differential chelation demands in the associated transition states. The appreciable syn stereoinduction apparent in entries 11 and 12 can be explained in terms of models **O** and **P** where the CH_2OH group is locked below the developing chair because of strong intramolecular chelation. Nonchelating aldehydes adhere to the same pattern of stereoselectivity.[17c]



Since the hydroxy-substituted indium reagent is preformed, the internally chelated organometallic presumably persists sufficiently long to control the stereochemical outcome. The erosion of syn selectivity evident in entry 12 may originate from some level of competitive chelation to nitrogen.

The essentially identical product distributions observed for entries 9 and 13 can be accounted for by operation of the accepted nonchelated transition state models **Q** and **R**.

Table 3. Competitive Indium-Promoted Couplings of 1−5 to 2- and 3-Pyridinecarboxaldehydes in 1:1 THF/H_2O at 25 °C[a]

entry	bromide	reactivity (2-Py/3-Py)
15	**1**	4:1
16	**2**	>97:3
17	**3**	95:5
18	**4**	<3:97
19	**5**	95:5
20	**6**	<3:97

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

Competition Experiments. Eliel and Frye have pointed out that intermolecular chelation should lend itself to more rapid conversion to product with increased selectivity if the chelated intermediates reside directly on the reaction pathway.[13] A lowering of the transition-state energy associated with preformation of the complex is responsible. To gain added insight into the relative reactivity of bromides **1**−**5** toward the pair of pyridinecarboxaldehydes, each indium reagent was allowed to vie competitively for an excess of equimolar mixture of these carbonyl compounds. The results are compiled in Table 3.

The most revealing piece of information to emerge from this aspect of the study is the significantly increased reactivity of 2-pyridinecarboxaldehyde relative to the 3-isomer toward bromides **1**, **2**, **3**, and **5**. This favored status is not seen in those coupling reactions involving the TBS-protected reagents **4** and **6**. This ordering is not satisfactorily accommodated by the theory that an increase in possible electron withdrawal within 2-PyCHO is kinetically controlling. In this event, direct competition would invariably be biased in the same direction throughout the series. On the other hand, the proclivity of the 2-isomer for acclerated participation in the allylindation process correlates reasonably well with the intervention of intermolecularly chelated intermediates when this is possible.

Conclusions

Indium-promoted couplings involving variously substituted allylic bromides have been shown generally to proceed more rapidly and stereoselectively with 2-pyridinecarboxaldehyde than the 3-isomer. These features are characteristic of processes that are mediated by chelation control when the ring nitrogen can position itself in close proximity to the metal center. The crossover in diastereoselectivity often encountered with use of this pair of heterocyclic aldehydes is in full agreement with this mechanistic proposal. Intramolecular ligation within the allylindium species and steric effects generated during C−C bonding also hold importance when operative.

By every indication, the present work strongly suggests that chelation by indium(III) does operate in water with resultant control of reaction diastereoselectivity. Binding of indium to a pyridine nitrogen is more effective than to a free carboxyl group as in glyoxylic acid, although the latter interaction is not without merit. The added clarification of these issues provided herein enhances our ability to apply this chemistry in a range of synthetic objectives.

Experimental Section[22]

General Procedure for the Allylation of 2- and 3-Pyridinecarboxaldehyde. A mixture of the bromide (1.5 mmol), indium powder (2 mmol), and aldehyde (1 mmol) in THF/H_2O (1:1; 5 mL to 1 mmol of aldehyde) was stirred vigorously for 48 h. After dilution with CH_2Cl_2, the separated aqueous phase was basified with aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3×). The combined organic solutions were dried and concentrated. The residue was subjected to high-field ^{1}H NMR analysis and subsequently purified by flash chromatography or MPLC on silica gel.

Entry 1: elution with 5% methanol in CH_2Cl_2 afforded 128 mg (62%) of a 22:78 mixture of **7a** and **8a**. For the syn/anti diastereomeric mixture: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3416, 1732, 1636, 1456; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51−8.41 (m, 2H), 7.72−7.65 (m, 2H), 7.26−7.21 (m, 4H), 5.27−4.94 (m, 6H), 3.43−3.28 (m, 2H); MS *m*/*z* (M^+) calcd 207.0895, obsd 207.0891.

For **7a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69−5.57 (m, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.9, 149.0, 148.3, 137.0, 134.5, 131.5, 123.4, 120.4, 72.7, 58.0, 52.2.

For **8a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.85 (m, 1H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.6, 148.8, 147.9, 136.7, 134.4, 130.9, 123.2, 121.1, 71.6, 57.8, 52.1.

Entry 2: elution with 5% methanol in CH_2Cl_2 afforded 168 mg (81%) of a 94:6 mixture of **7b** and **8b**.

For **7b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3440, 1716, 1644; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54−8.53 (m, 1H), 7.70−7.62 (m, 1H), 7.34−7.14 (m, 2H), 5.88−5.76 (m, 1H), 5.14−4.92 (m, 3H), 4.40 (br s, 1H), 3.69 (s, 3H), 3.53 (t, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.7, 159.1, 148.6, 136.3, 132.1, 122.8, 121.8, 119.7, 74.4, 57.6, 52.0; MS *m*/*z* (M^+) calcd 207.0895, obsd 207.0875.

For **8b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3435, 1732, 1639; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56−8.54 (m, 1H), 7.69−7.63 (m, 1H), 7.27−7.19 (m, 2H), 5.90−5.78 (m, 1H), 5.16−4.95 (m, 3H), 4.26 (br s, 1H), 3.71 (s, 3H), 3.54 (t, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.5, 159.0, 148.4, 136.6, 131.2, 122.6, 121.0, 119.9, 73.5, 56.7, 52.0; MS *m*/*z* (M^+) calcd 207.0895, obsd 207.0897.

Entry 4: elution with 10% methanol in CH_2Cl_2 afforded 181 mg (82%) of a 64:36 mixture of **15a** and **16a**.

For **15a**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3388, 1713, 1648; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51−8.42 (m, 2H), 7.70−7.67 (m, 1H), 7.27−7.21 (m, 1H), 6.25 (d, J = 3.0 Hz, 1H), 5.54 (s, 1H), 4.89 (d, J = 4.2 Hz, 1H), 3.74 (s, 3H), 3.50 (br s, 1H), 3.13−3.10 (m, 1H), 1.05 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.0, 148.4, 148.0, 141.9, 138.1, 134.1, 126.7, 123.0, 73.6, 52.1, 42.6, 12.8; MS *m*/*z* (M^+) calcd 221.1052, obsd 221.1026.

For **16a**: characteristic ^{1}H NMR peaks appear at δ 6.15 (s, 1H), 5.51 (s, 1H), 4.46 (m, 1H), 3.78 (s, 3H), 1.94 (d, J = 7.3 Hz, 3H); MS *m*/*z* (M^+) calcd 221.1052, obsd 221.1051.

Entry 5: elution with 10% methanol in CH_2Cl_2 afforded 164 mg (74%) of a 6:94 mixture of **15b** and **16b**.

For **15b**: yellow oil; IR (CH_2Cl_2, cm^{-1}) 3418, 1714; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 4.7 Hz, 1H), 7.73−7.67 (m, 1H), 7.40−7.37 (m, 1H), 7.25−7.21 (m, 1H), 6.26 (d, J = 3.0 Hz, 1H), 5.58 (d, J = 3.0 Hz, 1H), 3.74 (d, J = 6.8 Hz, 1H), 4.31 (br s, 1H), 3.72 (s, 3H), 3.20−3.15 (m, 1H), 1.39 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 178.9, 157.8, 149.4, 140.1, 136.9, 123.3, 120.4, 85.2, 56.7, 41.2, 17.4; MS *m*/*z* (M^+) calcd 221.1052, obsd 221.1022.

For **16b**: characteristic ^{1}H NMR peaks appear at δ 6.22 (s, 1H) and 5.85 (s, 1H).

Entry 7: elution with 5% methanol in CH_2Cl_2 afforded 166 mg (65%) of a 64:36 mixture of **18a** and **19a**. For the syn/anti diastereomeric mixture: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3267, 1644; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.27 (m, 4H), 7.65−7.61 (m, 2H), 7.35−7.17 (m, 12H), 5.27−4.94 (m, 3H), 3.33−2.75 (m, 2H); MS *m*/*z* (M^+) calcd 255.1259, obsd 255.1236.

(22) For generic experimental details, consult ref 10b.

For **18a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.10 (s, 1H), 4.82 (dd, J = 7.2, 4.0 Hz, 1H), 4.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.7, 147.2, 146.5, 142.2, 140.0, 134.2, 128.3 (2C), 127.4, 126.3 (2C), 126.1, 123.3, 116.9, 70.6, 42.0.

For **19a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H), 5.27 (s, 1H), 5.06 (s, 1H), 4.70 (dd, J = 9.0, 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.0, 140.0, 133.9, 127.3 (2C), 123.5, 116.2, 72.0, 41.7, remaining signals overlap.

Entry 8: elution with 5% methanol in CH_2Cl_2 afforded 161 mg (63%) of a 40:60 mixture of **18b** and **19b**. For the syn/anti diastereomeric mixture: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3330, 1666; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50−8.46 (m, 4H), 7.71−7.64 (m, 2H), 7.42−7.16 (m, 10H), 4.26 (br s, 4H), 2.67−2.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 161.3, 161.26, 147.8, 147.75, 147.7, 147.0, 143.0, 142.3, 137.1, 137.0, 128.2 (2C), 128.15 (2C), 127.2, 127.1, 126.4 (2C), 126.1 (2C), 122.5, 122.4, 120.8, 120.3, 116.2, 116.15, 116.13, 73.5, 72.2, 40.9, 40.7, one signal overlaps; MS *m*/*z* (M^+) calcd 255.1259, obsd 255.1258.

For **18b:** characteristic ^{1}H NMR peaks appear at δ 5.24 (s, 1H), 5.09 (s, 1H), 4.95 (dd, J = 7.0, 4.3 Hz, 1H), 4.79 (s, 1H).

For **19b**: characteristic ^{1}H NMR peaks appear at δ 5.32 (s, 1H), 5.30 (s, 1H), 5.08 (s, 1H), 4.90 (dd, J = 9.4, 3.9 Hz, 1H).

Entry 9: elution with 5% methanol in CH_2Cl_2 afforded 236 mg (64%) of a 66:34 mixture of **18c** and **19c**.

For **18c**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3384, 1646; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49−8.41 (m, 2H), 7.67−7.57 (m, 1H), 7.36−7.18 (m, 6H), 5.28 (s, 1H), 5.23 (s, 1H), 4.91 (s, 1H), 4.74 (dd, J = 8.5, 4.1 Hz, 1H), 2.43−2.22 (m, 2H), 0.93 (s, 9H), −0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.4, 147.8, 147.0, 142.2, 139.6, 133.4, 128.2 (2C), 127.4, 126.2 (2C), 123.2, 115.7, 79.0, 70.1, 41.6, 25.9 (3C), −4.9 (2C); MS *m*/*z* (M^+) calcd 369.2124, obsd 369.2134.

Anal. Calcd for $C_{22}H_{31}NO_2Si$: C, 71.49; H, 8.45. Found: C, 71.36; H, 8.38.

For **19c**: characteristic ^{1}H NMR peaks appear at δ 5.17 (s, 1H), 5.15 (s, 1H), 0.85 (s, 9H), −0.01 (s, 6H).

Entry 11: elution with 5% methanol in CH_2Cl_2 afforded 191 mg (71%) of an 80:20 mixture of **20a** and **21a**.

For **20a**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3369, 1645; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43−8.39 (m, 2H), 7.65−7.61 (m, 1H), 7.34−7.20 (m, 6H), 5.26 (s, 1H), 5.23 (s, 1H), 4.82 (dd, J = 8.3, 5.3 Hz, 1H), 4.08−4.01 (m, 1H), 3.93−3.87 (m, 1H), 3.63−3.58 (m, 1H), 3.02 (s, br, 2H), 2.33−2.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.4, 147.4, 144.9, 139.7, 139.6, 133.6, 128.7 (2C), 128.1 (2C), 127.2, 123.4, 115.1, 69.7, 64.6, 53.1, 45.5; MS *m*/*z* (M^+) calcd 269.1416, obsd 269.1437.

For **21a**: characteristic ^{1}H NMR peaks appear at δ 5.13 (s, 1H), 5.11 (s, 1H), 4.75 (m, 1H).

Entry 12: elution with methanol in CH_2Cl_2 afforded 167 mg (62%) of a 65:35 mixture of **20b** and **21b**.

For **20b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3362, 1645; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49−8.47 (m, 1H), 7.70−7.61 (m, 1H), 7.32−7.14 (m, 7H), 5.23 (s, 1H), 5.18 (s, 1H), 4.92 (dd, J = 9.4, 3.8 Hz, 1H), 4.10−4.03 (m, 1H), 3.91−3.85 (m, 1H), 3.72−3.67 (m, 1H), 2.47−2.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 161.5, 148.1, 145.2, 140.1, 136.8, 128.5 (2C), 128.1 (2C), 126.8, 122.4, 120.3, 114.9, 71.9, 64.3, 53.6, 43.8; MS *m*/*z* (M^+) calcd 269.1416, obsd 269.1403.

For **21b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3397, 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 4.6 Hz, 1H), 7.70−7.62 (m, 1H), 7.33−7.17 (m, 7H), 5.13 (s, 1H), 5.11 (s, 1H), 4.90 (dd, J = 8.0, 5.2 Hz, 1H), 4.07−4.00 (m, 1H), 3.90−3.84 (m, 1H), 3.61−3.57 (m, 1H), 2.57−2.50 (m, 1H), 2.38−2.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 161.7, 148.1, 145.4, 140.2, 136.8, 128.6 (2C), 128.3 (2C), 126.9, 122.4, 120.4, 114.2, 72.3, 65.2, 54.2, 45.2; MS *m*/*z* (M^+) calcd 269.1416, obsd 269.1436.

Entry 13: elution with 5% methanol in CH_2Cl_2 afforded 246 mg (69%) of a 66:34 mixture of **20c** and **21c**.

For **20c**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3380, 1645; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47−8.40 (m, 2H), 7.65−7.63 (m, 1H), 7.36−7.18 (m, 6H), 5.25 (s, 1H), 5.22 (s, 1H), 4.80 (dd, J = 8.9, 4.6 Hz, 1H), 4.07−3.90 (m, 1H), 3.89−3.83 (m, 1H), 3.56−3.53 (m, 1H), 2.80 (br s 1H), 2.42−2.22 (m, 2H), 0.85 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.6, 147.7,

144.9, 140.0, 137.8, 133.5, 128.5 (2C), 128.2 (2C), 127.0, 123.3, 115.4, 69.2, 65.7, 52.8, 46.5, 25.9 (3C), 18.3, −5.5 (2C); MS *m/z* (M^+) calcd 383.2281, obsd 383.2310.

Anal. Calcd for $C_{22}H_{31}NO_2Si$: C, 71.49; H, 8.45. Found: C, 71.36; H, 8.38.

For **21c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53−8.46 (m, 2H), 7.68−7.65 (m, 1H), 7.35−7.20 (m, 6H), 5.18 (s, 1H), 5.17 (s, 1H), 4.76 (dd, J = 13.5, 4.2 Hz, 1H), 4.06−4.02 (m, 1H), 3.99−3.85 (m, 1H), 3.61−3.56 (m, 1H), 2.75 (br s 1H), 2.51−2.30 (m, 2H), 0.86 (s, 9H), −0.01 (s, 6H); MS *m/z* (M^+) calcd 383.2281, obsd 383.2319.

General Procedure for the Allylation of Glyoxylic Acid. A mixture of the allyl bromide (1.5 mmol), indium powder (2 mmol), and glyoxylic acid (1 mmol as a 1:1 mixture in water) in THF/H_2O (1:1; 5 mL per mmol of acid) was stirred vigorously overnight. After reaction was complete, the solution was evaporated to one-half of the original volume, and diazomethane (1.5 equiv) in diethyl ether was added. The solution was evaporated via rotary evaporation to one-third the original volume, taken up in CH_2Cl_2, and washed with brine. The brine solution was back-extracted with CH_2Cl_2 (3×) and the combined organic layers were dried and evaporated. The residue was subjected to high-field ^{1}H NMR analysis and then purified by flash chromatography or MPLC on silica gel.

Entry 3: elution with 1:1 ethyl acetate in hexanes afforded 98 mg (52%) of an 88:12 diastereomeric mixture of **7c** and **8c**.

For **7c**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3562, 1666; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00−5.90 (m, 1H), 5.31−5.25 (m, 2H), 4.40−4.36 (m, 1H), 3.79 (m, 6H), 3.57−3.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.0, 171.3, 131.3, 120.0, 72.0, 53.6, 52.6, 52.3; MS *m/z* (M^+) calcd 188.0685, obsd 188.0671.

For **8c**: characteristic ^{1}H NMR peaks appear at δ 5.75−5.48 (m, 1H).

Entry 6: elution with 30% ethyl acetate in hexanes afforded 123 mg (61%) of an 81:19 mixture of **15c** and **16c**.

For **15c**: yellowish oil; IR (CH_2Cl_2, cm^{-1}) 3418, 1715, 1630; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (s, 1H), 5.82 (s, 1H), 4.64−4.60 (m, 1H), 3.79 (s, 6H), 2.67 (br s 1H), 1.38 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.2, 167.1, 143.5, 124.2, 83.1, 67.1, 52.1, 22.0, 14.5; MS *m/z* (M^+) calcd 202.0841, obsd 202.0829.

For **16c**: characteristic ^{1}H NMR peaks appear at δ 6.30 (s, 1H), 5.72 (s, 1H), 3.80 (s, 6H), 1.46 (d, J = 6.44 Hz, 3H).

Formation of Acetonides 9a and 10a. A solution of 330 mg (1.59 mmol) of the **7a/8a** mixture in 25 mL of ether was added at 0 °C to 200 mg (5.27 mmol) of lithium aluminum hydride. The suspension was stirred at 0 °C for 30 min, warmed to room temperature, quenched with Rochelle's salt solution (10 mL), and stirred overnight. The phases were separated, and the aqueous layer was back-extracted with CH_2Cl_2 (3 × 20 mL). The combined organic solutions were dried and concentrated. Silica gel chromatography (elution with 10% methanol in CH_2Cl_2) afforded 200 mg (61%) of the diol mixture as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 3443, 1643; MS *m/z* (M^+) calcd 179.0946, obsd 179.0966.

For the anti isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50−8.38 (m, 2H), 7.68 (d, J = 7.9 Hz, 1H), 7.27−7.23 (m, 2H), 5.84−5.72 (m, 1H), 5.15 (dd, J = 10.5, 1.3 Hz, 1H), 5.04−4.99 (m, 1H), 3.86−3.80 (m, 2H), 2.63−2.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.1, 138.9, 138.8, 137.8, 123.4, 118.7, 64.9, 62.3, 52.1.

For the syn isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57−5.48 (m, 1H), 4.98−4.70 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.4, 147.7, 138.4, 134.7, 134.1, 123.3, 119.5, 72.6, 63.7, 52.7, one signal overlaps with anti isomer.

A solution of 100 mg (0.6 mmol) of the diol mixture, 2-methoxypropene (121 mg, 1.7 mmol), and *p*-toluenesulfonic acid (10 mg) in 5 mL of CH_2Cl_2 was stirred at room temperature for 30 min and concentrated. The residue was chromatographed on silica gel (elution with 5% methanol in CH_2Cl_2) to afford 101 mg (78%) of **9a** and **10a** as a clear oil. The diastereomers were separated by MPLC (1% methanol in CH_2Cl_2) for characterization purposes.

For **9a**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 1641, 1380; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74−8.73 (m, 1H), 8.53−8.51 (m, 1H), 7.52−7.48 (m, 1H), 6.82−6.78 (m, 1H), 5.10 (dd, J = 2.1, 10.5 Hz, 1H), 4.76 (d, J = 10.1 Hz, 1H), 4.63−4.56 (m, 1H), 3.90 (d, J = 10.4 Hz, 1H), 3.79−3.61 (m, 2H), 2.47−2.35 (m, 1H), 1.58 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.8, 149.7, 136.0, 134.4, 133.7, 123.2, 118.9, 98.7, 74.1, 64.0, 46.8, 30.0, 18.9; MS *m/z* (M^+) calcd 219.1259, obsd 219.1247.

For **10a**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 1636; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54−8.52 (m, 1H), 7.48−7.44 (m, 1H), 6.87−6.82 (m, 1H), 6.15 (dd, J = 1.2, 9.2 Hz, 1H), 4.90 (d, J = 10.4 Hz, 1H), 4.85 (s, 1H), 4.73 (d, J = 10.4 Hz, 1H), 3.88 (dd, J = 14.2, 2.8 Hz, 1H), 3.67 (dd, J = 14.2, 2.8 Hz, 1H), 1.82−1.60 (m, 1H), 1.57 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.8, 148.3, 136.4, 135.3, 133.4, 122.8, 117.6, 99.3, 71.4, 65.2, 44.8, 29.8, 18.9; MS *m/z* (M^+) calcd 219.1259, obsd 219.1231.

Formation of Acetonides 9b and 10b. A solution of 66 mg (0.32 mmol) of the **7b/8b** mixture in 5 mL of ether was added at 0 °C to 30 mg (0.50 mmol) of lithium aluminum hydride. The suspension was stirred at 0 °C for 30 min, warmed to room temperature, quenched with Rochelle's salt solution (10 mL), and stirred overnight. The phases were separated, and the aqueous layer was back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solutions were dried and concentrated. Silica gel chromatography (elution with 10% methanol in CH_2Cl_2) afforded 50 mg (88%) of the diol mixture as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 3408, 1641; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 4.6 Hz, 2H), 7.70−7.65 (m, 2H), 7.31−7.20 (m, 4H), 5.78−5.66 (m, 1H), 5.15−4.75 (m, 4H), 3.72 (d, J = 5.9 Hz, 2H); MS *m/z* (M^+) calcd 179.0946, obsd 179.0962.

For the anti diastereomer, characteristic ^{1}H NMR peaks appear at δ 6.17−5.88 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.2, 147.8, 136.8, 134.2, 122.4, 120.8, 118.7, 73.2, 64.2, 52.6.

For the syn isomer: ^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.3, 148.2, 136.6, 135.5, 122.6, 121.5, 118.6, 75.4, 63.9, 54.5.

A solution of 200 mg (1.2 mmol) of the diol mixture, 2-methoxypropene (242 mg, 3.4 mmol), and *p*-toluenesulfonic acid (15 mg) in 5 mL of CH_2Cl_2 was stirred at room temperature for 30 min and concentrated. The residue was chromatographed on silica gel (elution with 65% ethyl acetate in hexanes) to afford 187 mg (72%) of **9b** and **10b** as a clear oil. The diastereomers were separated by MPLC (1:1 ethyl acetate/hexanes) for characterization purposes.

For **9b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 660, 1238; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54−8.52 (m, 1H), 7.78−7.67 (m, 1H), 7.49−7.47 (m, 1H), 7.22−7.16 (m, 1H), 5.55 (dd, J = 2.5, 9.3 Hz, 1H), 4.98−4.73 (m, 3H), 3.98−3.84 (m, 2H), 2.72−2.62 (m, 1H), 1.60 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.5, 148.5, 136.8, 133.6, 122.9, 121.9, 118.3, 98.8, 64.1, 45.5, 29.7, 24.4, 19.1; MS *m/z* (M^+) calcd 219.1259, obsd 219.1254.

For **10b**: characteristic ^{1}H NMR peaks appear at δ 5.96 (dd, J = 1.4, 8.4 Hz, 1H), 1.98−1.75 (m, 1H).

Lactone 17. A solution of enriched **15a** (92 mg, 0.45 mmol) in 5 mL of THF was added at 0 °C to sodium hydride (24 mg, 0.68 mmol, 80% dispersion in mineral oil) that had been washed with hexanes (3 × 10 mL). This suspension was stirred at 0 °C for 30 min and quenched with saturated NH_4Cl solution (15 mL). The layers were separated, and the aqueous phase was back-extracted with CH_2Cl_2 (3 × 15 mL). The combined organic solutions were dried and evaporated, and the residue was chromatographed on silica gel (elution with 1% methanol in CH_2Cl_2) to afford 61 mg (78%) of **17** as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 3386, 1767, 1648; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60−8.58 (m, 1H), 8.47 (d, J = 2.1 Hz,1H), 7.53−7.49 (m, 1H), 7.33−7.29 (m, 1H), 6.35 (d, J = 2.8 Hz, 1H), 5.66−5.62 (m, 2H), 3.52−3.47 (m, 1H), 0.83 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.8, 147.7, 139.3, 133.5, 132.1, 123.4, 122.5, 79.8, 38.7, 15.6; MS *m/z* (M^+) calcd 188.0771, obsd 188.0713.

Competition Experiments. Indium powder (2 mmol) was stirred for 20 min with 1.1 mmol of the allyl bromide in 2 mL of THF/H_2O (1:1). A solution containing 1.0 mmol of each pyridinecarboxaldehyde in the same medium (2 mL) was added, and the reaction mixture was stirred vigorously overnight and extracted with CH_2Cl_2. After drying and concentra-

tion of the combined organic phases, the residue was examined by ^{1}H NMR at 300 MHz. The ratios of the residual aldehydes were determined by integration of the distinctive C*H*O signals arising from the 2-Py (δ 10.03) and 3-Py isomers (δ 10.08).

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Supporting Information Available: Copies of the high-resolution ^{1}H NMR spectra of all new compounds not accompanied by elemental analyses (21 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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