Diastereoselection during 1,2-Addition of the Allylindium Reagent to α-Thia and α-Amino Aldehydes in Aqueous and Organic Solvents

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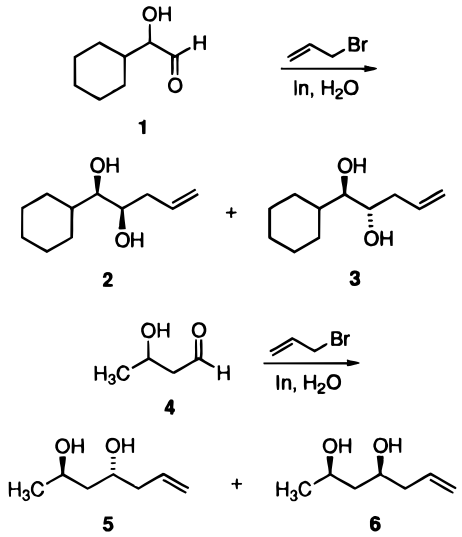
The stereochemistry of the indium-promoted reaction of allyl bromide with α-thia (PhS and MeS), disubstituted α-amino (Bn_2N, Me_2N, isoindolyl), and protected α-amino aldehydes (Ac and Boc) in water has been evaluated. The reactions involving the sulfur derivatives are minimally diastereoselective, indicating that the allylindium reagent is not thiophilic. Chelation is not observed and π-facial discrimination is achieved via Felkin−Ahn transition states under the steric control of the substituents. The Garner aldehyde is also anti-diastereoselective. Interestingly, *N*-acetylmannosamine is appreciably responsive to chelation control and is capable of generating 90% of the syn β-amino alcohol when reacted in a 0.5 M NH_4Cl solution. While the α-dibenzylamino substituent is too bulky to enter into complexation, the α-dimethylamino group is not and can lead to high levels (99%) of syn diastereomer. The size of other neighboring substituents does have an impact on π-facial discrimination in these systems and can erode the stereoselectivity accordingly.

Recent studies have shown that suitably oxygenated acyclic carboxaldehydes experience substantial π-facial discrimination when reacted with an allylindium reagent in water, THF, or mixtures of these solvents.[2−6] For example, the unprotected α-hydroxy aldehyde **1** affords products **2** and **3** with 9.8:1 syn selectivity in H_2O.[6] Under comparable conditions, **4** gives rise to **5** and **6** with 8.5:1 anti selectivity.[6] These product distributions, in combination with the faster reaction rates of the free hydroxyl derivatives, provide convincing evidence that chelation control can indeed operate under aqueous conditions. When methoxy, benzyloxy, and OMOM derivatives are involved, chelation continues to operate although at a reduced level.

In view of the considerable interest in acyclic stereoselective synthesis, a detailed analysis of the stereochemical influence of different classes of α-thia and α-amino substituent on aldehyde diastereofacial selectivity has been undertaken for indium-promoted allylation reactions. α-Alkylthio and α-arylthio carbonyl compounds have already received considerable attention in related contexts. Prominently featured here are the 1,2-additions of Grignard[7] and titanium reagents,[8] Lewis acid-catalyzed allylations with allylstannanes,[9] and bond-forming processes involving silyl enol ethers[10] alongside other carbon nucleophiles.[11] When anti stereoselectivity has prevailed, the results have been rationalized in terms of the Felkin−Ahn model,[12] with the RS group generally serving as the large electronegative substituent.



α-Amino aldehydes have held still greater attraction,[13] principally because of the biological importance of many β-amino alcohols. Dibenzylamino compounds have been the most popular derivatives. They have been brought into reaction with a battery of organometallics (RMgX, RLi, $RTi(O\text{-}i\text{-}Pr)_3$, $RTiCl_3$, $RCeCl_2$, R_2CuLi, R_2Zn, etc.),[14]

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

entry	aldehyde	solvent	product ratio[b] syn	product ratio[b] anti	reaction time, h	yield, %[c]
1	 **7**	H_2O	1	1.4	7.0	89
2		H_2O-THF (1 : 1)	1	1.2	4.5	91
3		THF	1	1.5	10.5	82
4	 **8**	H_2O	1.5	1	6.5	89
5		H_2O-THF (1 : 1)	1.5	1	6.0	84
6		THF	1.3	1	12.0	73
7	 **9**	H_2O	1	4	4.0	82
8		H_2O-THF (1 : 1)	1	3	4.0	87
9		THF	1	3	17.0	70
10	 **10**	H_2O	1	1.5	7.0	82
11	 **11**	H_2O	1	2.3	7.0	86
12	 **12**	H_2O	1	1	7.0	58

[a] All of the reactions were performed at least in duplicate at a concentration of 0.1 M with vigorous stirring. [b] The product distributions for **7** and **8** were determined by ^{1}H NMR integration at 300 MHz and comparison with literature values, for **9** by initial ^{1}H integration followed by coupling constant analysis after conversion to the oxiranes, and for **10-12** by GC analysis of the unpurified mixtures. [c] The yields reported are isolated yields.

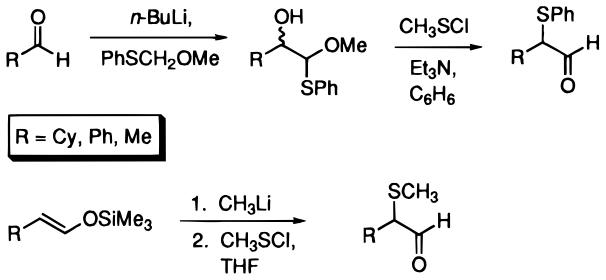
enolates, enol silanes,[15] and allylsilanes.[14a] Boc-[16] and tosyl-protected amino groups[17] have also proven highly serviceable. Most often, anti adducts are formed, contrary to the behavior of α-alkoxy derivatives.

Results and Discussion

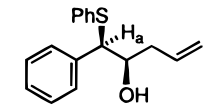
α-Thia Aldehydes. In an effort to vary the basicity of the divalent sulfur and its steric environment to reasonable levels, the six substrates **7**−**12** were examined (Table 1). The preparation of **7**−**9**, adapted from the existing literature,[18] took advantage of the ease of condensation of methoxy(phenylthio)methane with aldehydes to generate carbinols and the susceptibility of these systems to phenylthio migration when treated with methanesulfonyl chloride and triethylamine (Scheme 1).[19] The α-methylthio derivatives **10**−**12** were equally accessible by addition of methanesulfenyl chloride[20] to enolates according to Seebach.[21]

Consistent with our previous effort in this area,[6] the allylation reactions involving **7**−**9** were conducted at room temperature on 0.1 M solutions. Three solvent systems were examined ranging from an entirely organic environment (THF) to pure water and including a 1:1 mixture of the two. The quantities of the reagents were

Scheme 1

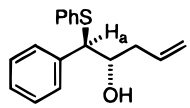


regulated to conform to an aldehyde/indium powder/allyl bromide ratio of 1.0:1.5:1.1. Since entries 1−9 in Table 1 provided indication that chelated transition states were not operational, the three α-methylthio aldehydes were examined only under aqueous conditions (entries 10−12). The two diastereomeric products were distinguished by direct comparison of specific ^{1}H NMR chemical shifts with reported values where available as in the case of **13** and **14**,[7,9] by conversion to epoxides as shown for **15** and **16** for analysis of the oxirane coupling constants as in **17** and **18** (cis > trans), or by determination of vicinal coupling constants[7,22] in the hydroxy sulfides where possible as in **19** and **20**.



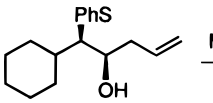
13

H_a: δ 4.16 (d, J = 8.0 Hz)

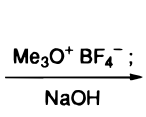


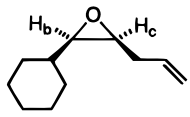
14

H_a: δ 4.27 (d, J = 5.2 Hz)



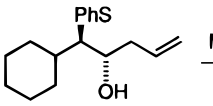
13



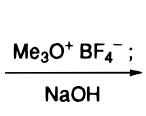


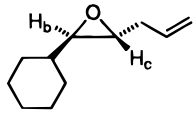
17

H_b: δ 2.66 ($J_{b,c}$ = 4.2 Hz)



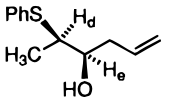
16





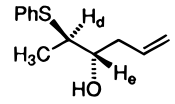
18

H_b: δ 2.50 ($J_{b,c}$ = 2.2 Hz)



19

H_e: δ 3.21 ($J_{d,e}$ = 6.8 Hz)



20

H_e: δ 3.35 ($J_{d,e}$ = 3.3 Hz)

The modest levels of diastereoselectivity observed in all of the sulfur examples, which are seen to be relatively insensitive to solvent environment and biased almost universally in the anti direction, necessarily implicate a kinetic preference for the utilization of a Felkin−Ahn transition state trajectory as in **21**. The maximum level of anti product arises when R is phenyl and R′ is methyl. An increase in the size of R′ should induce a rise in the proportion of syn product, and this is seen (entries 4−6).

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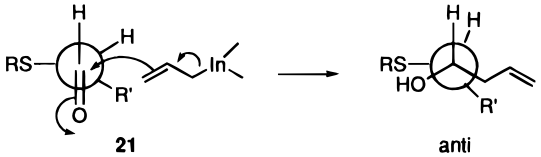
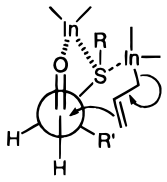
When R = R′ = CH_3, the two groups are probably indistinguishable on steric grounds and consequently provide negligible π-facial discrimination. A 50:50 mixture of carbinols is the result (entry 12).

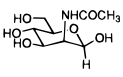
The option exists to involve double chelation,[9] particularly as consumption of In(0) progresses to the point where the buildup of ionic indium bromide becomes significant. Under these circumstances, the model **22** involving In(III) could be considered a plausible transition state representation. Thus, internal chelation of trivalent indium to both the aldehyde carbonyl and the neighboring sulfur atom could set the stage for coordination of the sulfur atom to the allylindium reagent as shown. This type of molecular staging would lead to irreversible formation of the anti allylation product. Despite the attractiveness of this concept, **22** is not viewed by us to be a transition state of any consequence. The substantive change in solvent dielectric constant when progressing from THF to H_2O can be expected to impact significantly on the capability of combining three reaction components in this manner. Recall, however, that product distribution is not demonstrably subject to variability.





Protected α-Amino Aldehydes. In the framework of our analysis, compounds **23**,[23] **24**,[24] and **25**[3,26] were viewed to be relevant for inclusion as a direct consequence of knowledge pertaining to their response under other reaction conditions. As before, concerns about solubility led us to investigate allylations in 1:1 mixtures of water and THF, as well as THF itself (Table 2). In light of the enhanced reactivity observed for allylindations under conditions of acid catalysis,[3,6,26] 0.5 M ammonium chloride was also investigated as the solvent in two of the studies (entries 21 and 26). Also, because there was some question as to whether the sesquihalide intermediate proposed by Butsugan[27] would exist in aqueous solution because of ready protonolysis,[28] a set of reactions involving the preformed intermediate was carried out in anhydrous THF under a nitrogen atmosphere.

Table 2. Indium-Mediated Allylations of Protected α-Amino Aldehydes in Various Solvents (CH_2=$CHCH_2Br$, 25 °C)[a]

entry	aldehyde	solvent	product ratio[b] syn	product ratio[b] anti	reaction time, h	yield, %[c]
13		H_2O	1.3	1	14.0	81
14		H_2O-THF (1 : 1)	1.2	1	16.0	60
15		THF	1.1	1	26.5	34
16	**23**	THF[d]	1	1.2	26.0	75
17		H_2O	1	2.7	2.0	77
18		H_2O-THF (1 : 1)	1	2.5	1.2	90
19		THF	1	2.2	24.0	61
20		THF[d]	1	2.2	0.5	89
21	**24**	0.5 M NH_4Cl	1	3.5	1.7	84
22		H_2O	3.4	1	6.0	41
23		H_2O-THF (1 : 1)	4.3	1	72.0	44
24		THF	5.5	1	72.0	12
25		THF[d]	5.0	1	72.0	21
26	**25**	0.5 M NH_4Cl	8.6	1	8.7	31

[a] See Table 1. [b] The product distributions were determined by ^1H NMR integration at 300 MHz of the unpurified product mixtures. [c] The yields have been adjusted to account for recovered aldehyde [d] The THF solution of allyl bromide was heated to reflux with the indium prior to reaction. The mixture was cooled to rt prior to introduction of the aldehyde and the coupling was performed as in *a*.

The allylations involving **23** were largely unselective, giving diastereomeric ratios on the order of 1:1 (entries 13−16). The very modest increase in syn selectivity noted as the solvent becomes increasingly aqueous suggests that chelation control may be slightly improved when H_2O is present. However, the magnitude of the change is sufficiently small to be attributed simply to an increased hydrophobic effect. In typical fashion, the yields increased in direct proportion to the amount of water present. Reaction times were also shortened. Preformation of the allylindium reagent resulted in an insignificant alteration in product stereoselectivity. The two diastereomers were identified by direct comparison of the 300 MHz ^1H NMR spectra of the pure compounds with those provided by Prof. D. Rich.

For comparison purposes, it is recognized that **23** in THF gives evidence of favoring chelation control with moderate to good selectivity when the chelating atom is lithium, magnesium, or boron. Heightened levels of syn hydride delivery have been noted for $NaBH_4$ in methanol, but not for $LiAlH_4$ in diethyl ether. In CH_2Cl_2, tin favors chelation while aluminum does not. This highly variably pattern has turned up in other contexts as well.[23]

In contrast to the behavior of **23**, the Garner aldehyde **24** gave rise under all circumstances to diastereomeric ratios rich in the anti allylated product (entries 17−21). Additional contrast with the leucinal derivative was manifested by an increase in nonchelate control in H_2O relative to THF. A maximum is reached in 0.5 M NH_4Cl as solvent, in accordance with earlier results from our group[6] which showed that a change in solvent ionic strength can enhance selectivity via an increase in the internal pressure of the system.

These results can be reconciled with a preference by **24** for the Felkin−Ahn transition state **27** rather than the chelation complex **26**. The allylation products **28** and **29** were first isolated by column chromatography in order to determine yields and subsequently cyclized with triflic

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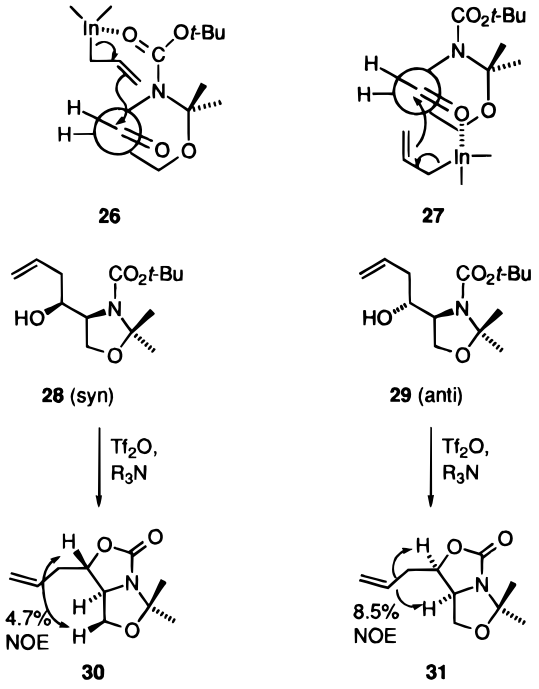
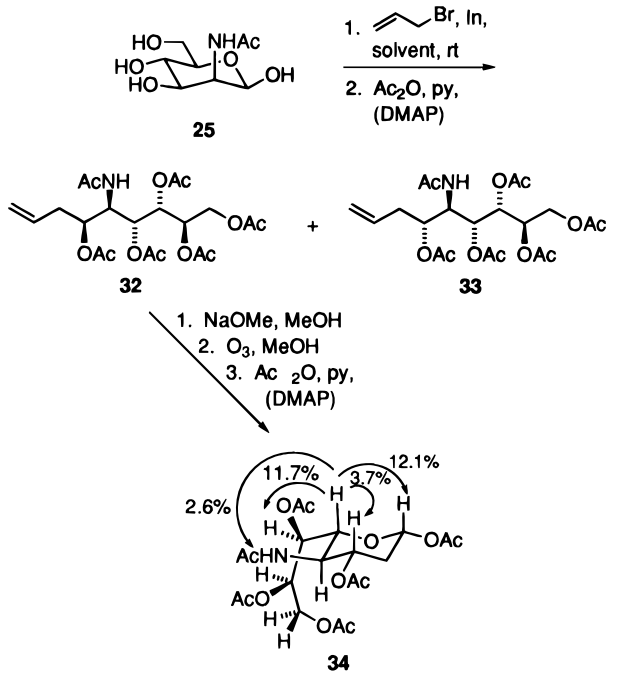
(28) Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S.-J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538.

anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine to give **30** and **31**, respectively. The latter reaction proceeds with inversion of configuration at the secondary carbinol center.[29] The oxazolidinones were distinguished on the strength of COSY and NOE difference experiments. As shown in structures **30** and **31**, the stereochemical relationship of the allyl substituent to the heterobicyclic core was unequivocally apparent. In a global sense, our results involving **24** are similar in direction to the great majority of the findings presented by Coleman and Carpenter for the addition of vinyl organometallics to this aldehyde in various organic media.[24b]



N-Acetylmannosamine (**25**), commercially available as the monohydrate,[30] was allylated in an identical fashion. Following those couplings performed in water, the solvent was removed under high vacuum and the products were acetylated as in **32** and **33** in advance of ^{1}H NMR analysis. As detailed in Table 2, all of the reactions exhibited good syn selectivity, giving diastereomeric ratios ranging from 3.4:1 to 8.6:1. The synthetically useful product distribution realized in 0.5 M NH_4Cl is especially noteworthy and indicates that the role of salt effects in these processes warrants further study, perhaps with the added perspective of increasing yields.[2c,3a] In this instance, the diastereomeric ratios were determined on the **32/33** mixtures prior to their chromatographic separation. Following the lead offered by Whitesides,[3a] we established the stereochemistry of major isomer **32** through sequential saponification, ozonolysis, and reacetylation. COSY and NOE experiments performed on **34** indicated the oxygenated stereocenter α to the protected amine to have its acetoxy group oriented trans and equatorial relative to AcNH.

The high syn selectivity tends to substantiate the operation of an α-chelation mechanism via a 1:1 complex. The observed levels of diastereofacial control may be



realized notwithstanding possible competing indium coordination to the β-hydroxy group, a process known to favor the anti diastereomer.[3] Were this second option to operate, the syn/anti ratio would be lowered accordingly.

Disubstituted α-Amino Aldehydes. Reetz was responsible for first introducing the concept of protective group tuning as a means for realizing high levels of asymmetric control in organometallic additions involving *N*,*N*-disubstituted α-amino aldehydes.[13b,31] Since the importance of this factor on the stereoselectivity of indium-promoted reactions had not yet been explored, we embarked on an extensive study which included α-*N*,*N*-dibenzylamino (**35**−**39**), α-dimethylamino (**40**−**41**), and α-*N*-dihydroisoindoline aldehydes (**42**−**43**, Table 3). The preparative means utilized to produce these configurationally stable reactants are summarized below without comment,[32] except to note that we were unable to obtain a highly purified sample of **35**.

Entries 27−31 provide evidence for substantive rate retardation as the bulk of the neighboring carbon substituent is progressively increased from methyl to *tert*-butyl. While a steric effect is clearly operational, the overall kinetics could reflect as well a diminishing solubility in water. Notwithstanding, the anti diastereomer predominated in all of these experiments (63−86%). For entries 27−30, the NMR data for the isomeric products were directly compared to data previously reported for these β-amino alcohols. The data provided in Table 3 are for reactions conducted in the presence of 1.5 equiv of ammonium chloride. This salt had no effect either on the rate or the stereochemical outcome of the allylation. What then is the role of the NH_4Cl? Present observations indicate that the presence of this salt

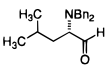
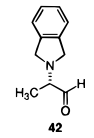
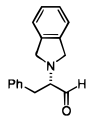
(29) (a) Williams, L.; Zhang, Z.; Ding, X.; Joullié, M. M. *Tetrahedron Lett.* **1995**, *36*, 7031. (b) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331 and relevant references therein.

(30) Purchased from Pfanstiehl Laboratories, Inc., Waukegan, IL.

(31) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A.; Holdgrün, X.; Wünsch, T.; Binder, J. *Phil. Trans. R. Soc. A* **1988**, *326*, 573. (b) Reetz, M. T. *Pure Appl. Chem.* **1988**, *60*, 1607. (c) Reetz, M. T. *Pure Appl. Chem.* **1992**, *64*, 351.

(32) Much of the specific information associated with the first two pathways originally appeared in the Ph.D. Thesis of M. W. Drewes, Universität Marburg, 1988, and the Diplomarbeit of A. Schmitz, Universität Marburg, 1987. We thank Prof. M. Reetz for providing us with excerpts from these documents.

Table 3. Indium-Mediated Allylations of Disubstituted α-Amino Aldehydes in Water (CH_2=$CHCH_2Br$, 25 °C)[a]

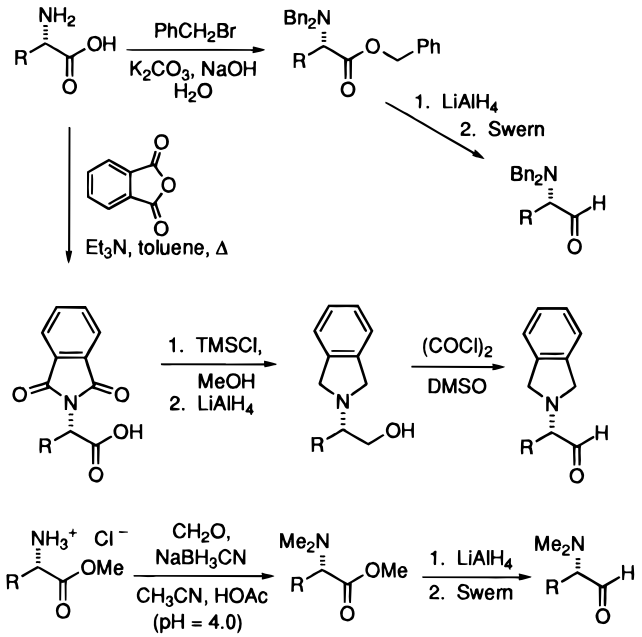
entry	aldehyde	solvent[c]	product ratio[b] syn	product ratio[b] anti	reaction time, h	yield, %[d]
27	 **35**	H_2O	1	3.3	6	50
28	 **36**	H_2O	1	6.1	6	70
29	 **37**	H_2O	1	4.0	24	85
30	 **38**	H_2O	1	3.5	48	93
31	 **39**	H_2O	1	1.9	48	88
32	 **40**	H_2O	>99	1	6	50
33		H_2O (pH 7.0)	>99	1	6	55
34	 **41**	H_2O	1.8	1	6	59
35		H_2O (pH 7.0)	4	1	6	57
36	 **42**	H_2O	1	1	12	20
37		H_2O (pH 7.0)	3	1	12	25
38	 **43**	H_2O	2.4	1	12	36
39		H_2O (pH 7.0)	8.2	1	12	40

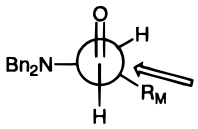
[a] See Table 1. [b] The product distributions were determined by ^1H NMR integration at 300 MHz of the unpurified product mixtures. [c] Ammonium chloride (1.5 equiv) was present in all runs. As usual, the acidity of the reaction medium increases (to a maximum of pH 3-4) as the indium is consumed. Where indicated, pH control was accomplished automatically by means of a pH controller. [d] The yields reported are isolated yields.

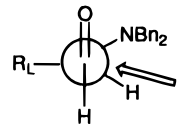
reduces the induction period associated with the reaction. Concentration ranges from 0.15 to 0.5 M and beyond do not appear to impact on product ratios.[6] In our view, these "salt effects" exert little effect on those processes that proceed via open, Felkin−Ahn transition states. This insensitivity is in contrast to allylations involving α-hydroxy aldehydes and *N*-acetylmannosamine where Cram chelation operates and dramatic increases in diastereofacial selectivity can be realized on appropriate choice of salt.

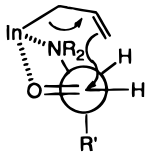
In the case of entry 32, the stereochemical assignments are founded on the lower polarity of the syn isomers as compared to their anti counterparts.[33] This sequencing of R_f values was found to apply to all of the many isomer pairs prepared in this phase of the investigation. Although such trends should not be regarded as ultrarigorous proof of relative configuration, this property in tandem with ^1H and ^{13}C NMR correlations (Table 4) was taken as reliable stereochemical indicators for this class of compounds.[32,33] The ^1H and ^{13}C NMR data for the isoindoline adducts closely mirror those of the methyl analogs prepared by Reetz.

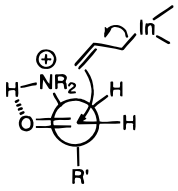
The uniformly preferred formation of anti products in entries 27−31 reflects the fact that internal chelation and its associated reduction in the degrees of freedom available for allyl delivery are not operative. In view of precedence for *N*,*N*-dibenzyl derivatives, these findings occasioned no surprise. Comparable nonchelation control is likewise exhibited by most organometallic reagents.[34] Not previously appreciated is the significant impact on the course of allylindation as α-branching of the side chain increases. The drop in the levels of anti amino alcohol that accompany this enhancement of steric bulk can be concisely rationalized in terms of increased adoption of conformer **45** at the expense of the Felkin−Ahn arrangement **44**, thus establishing a closer balance in the rate of allyl transfer.




44


45


46

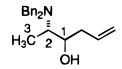
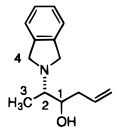
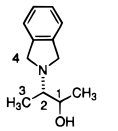
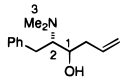
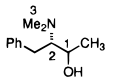

47

We concur with the analysis that chelation as in **46** is rendered nonoperational when R is benzyl for steric reasons. As the spatial demands of R are reduced (see **40**−**43**), prior coordination of indium to the basic nitrogen center as in **46** is made possible and syn selectivity materializes. However, the situation with basic α-amino aldehydes is not so simple. Indium-promoted allylations are recognized to proceed with the generation of acid. To the extent that carbon−carbon bond formation advances, increasing levels of protonation of the amino group will transpire. These events can be expected to foster arrival at **47**. The generation of syn product could then occur via intramolecular (**46**) or intermolecular options (**47**).

(33) This phenomenon was previously noted by A. Wehrsig, Ph.D. Dissertation, Universität Hamburg, 1991.

(34) CH_3TiCl_3[14a] and $(C_2H_5)_2Zn$[14c] are exceptions. For reactions with chiral boron enolates, consult ref 15c.

Table 4. Representative ^1H and ^{13}C NMR Chemical Shift Data for Selected β-Amino Alcohols (300 and 75 MHz, $CDCl_3$)

		syn isomer		anti isomer	
compound	position	^1H (ppm)	^{13}C	^1H (ppm)	^{13}C
	1	3.57	70.4	3.68	72.3
	2	2.61	57.9	2.69	57.0
	3	1.04	8.0	1.18	8.5
	1	3.54	71.9	3.93	70.5
	2	2.86	59.6	2.64	62.4
	3	1.06	8.8	1.14	11.4
	4	4.04	53.1	3.91, 4.10	56.9
	1	3.55	68.7	4.08	66.5
	2	2.72	61.9	2.57	63.9
	3	1.02	8.6	1.13	11.2
	4	4.02	52.9	3.95, 4.11	57.0
	1	3.47	70.3	3.60	71.1
	2	2.65	69.6	2.75	69.5
	3	1.92	40.6	2.10	41.8
	1	3.41	72.4	3.71	70.4
	2	2.65	66.8	2.82	67.3
	3	2.21	40.7	2.32	43.0

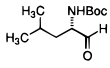
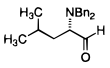
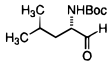
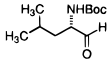
In an effort to gain insight into the operability of **46**, several allylations were carried out under conditions where a pH of 7.0 was maintained throughout the entire course of reaction (entries 33, 35, 37, and 39). In every instance, the relative proportion of syn product was elevated when neutrality was preserved. These findings suggest that the utilization of chelated transition state **46** can indeed be very effective when the size of R is sufficiently small.

Competition Experiments. As Frye, Eliel, and their co-workers have clearly delineated,[35] the involvement of a chelated intermediate on a reaction pathway must necessarily lend itself to more rapid conversion to product. This increase in rate materializes because of the lowering in transition state energy associated with prefomation of the complex. Consequently, the more chelation-selective substrates must also be the more reactive.

Since three distinctively different types of α-substitution were examined in this study, some gauge of relative reactivity between these classes was deemed desirable. Accordingly, the α-thia derivative **7** and the *N*-Boc-protected aldehyde **23** were allowed to vie with related compounds for a limited amount of the allylindium reagent. The results, which are compiled in Table 5, reveal that **7** is approximately as reactive as **48** and only slightly more reactive than **36**. None of the three α-substituents involved in this comparison enter into effective chelation with the allylindium reagent. In contrast, the free hydroxyl group in **49** has been shown to be especially conducive to high-level syn selectivity. Consequently, the 25-fold higher reactivity of **49** relative to that of **7** is commensurate with the high coordinating ability of a neighboring OH under these circumstances.

The rather comparable kinetic behavior of **23** and the *N*,*N*-dibenzylamino aldehydes **35**, **36**, and **38** agrees with the concept that the NHBoc group may be engaged in chelation to the indium reagent to some degree. However, this reaction pathway cannot be adopted in a wholesale manner, a conclusion in agreement with the position of **23** in the relative rate profile and its very modest proclivity for conversion to a syn β-amino alcohol.

Table 5. Competitive Indium-Promoted Allylations in Water at 25 °C[a]

entry	first aldehyde	second aldehyde	reaction time, h	product ratio: first ald	: second ald
40	 **7**	 **48**	10	1	1
41	 **7**	 **36**	10	1.5	1
42	 **7**	 **49**	10	1	25
43	 **23**	 **38**	12	1.9	1
44	 **23**	 **35**	5	1.3	1
45	 **23**	 **36**	5	1.2	1
46	 **40**	 **35**	6	2.4	1

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

The above generalizations hold true as well for **35** and **40**. While the 6 h reaction time reported in Table 3 for this pair of aldehydes was adopted because of a desire to utilize a common procedure where applicable, **40** is the more reactive substrate (Table 5, entry 46). However, neither of these two α-amino derivatives compare closely to the significantly more reactive α-hydroxy derivative.

Conclusions

The present study has provided insight into the capabilities of α-thia and α-amino substituents in aldehydes to guide the course of 1,2-asymmetric induction during allylindation in water as solvent. The behavior of the SPh and SCH_3 derivatives shows convincingly that the allylindium reagent exhibits essentially no thiophilic properties. No rate acceleration is observed relative to the nonchelation standard (OTBS), and the product distributions are skewed toward the anti isomers. These features are consistent with adherence by these systems to a Felkin−Ahn transition state model.

The Garner aldehyde (**24**) exhibits an entirely similar profile and is considered to adopt a similar reaction trajectory. For the leucinal and acetylmannosamine congeners, the sense of asymmetric induction shifts into the syn direction and a modest enhancement in reaction rate was noted. These experimental findings indicate that precomplexation to the organometallic is operational, but to quite different levels.

This phenomenon, in tandem with steric effects, allows for convenient tuning of the stereoselectivity of aqueous allylation. Entries 27/28 and 33/35 provide the most dramatic contrast. Thus, recourse to *N*,*N*-dibenzyl sub-

(35) (a) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862. (b) Chen, X.; Hortelano, E. R.; Elile, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130.

stitution can give rise to proportions of anti amino alcohol as high as 96% while *N*,*N*-dimethyl analogs lend themselves to chelation control levels (syn product) as high as 99%. However, considerable variability in the degree of stereoselectivity is seen in water as it is in anhydrous organic solvents.[36,37] Additional work involving modification of the substituents at nitrogen is clearly needed before control of all the factors involved in aqueous environments is at hand.

Experimental Section[38]

Allylation of 7. A. In Water. A mixture of **7** (370 mg, 1.59 mmol), allyl bromide (287 mg, 2.39 mmol), and indium powder (201 mg, 1.75 mmol) in water (17.5 mL) was stirred vigorously for 7 h. Ethyl acetate (20 mL) was introduced, and 30 min later the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic solutions were dried and concentrated to leave an oil, which was subjected to flash chromatography on silica gel (elution with 50:1 hexanes/ethyl acetate). There was obtained 383 mg (89%) of a colorless oil consisting of a 1:1.4 mixture of syn and anti isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 2 H), 7.18 (m, 3 H), 5.75 (m, 1 H), 5.00 (m, 2 H), 3.80 (m, 1 H), 2.97 (m, 1 H), 2.25 (m, 2 H), 2.11 (m, 5 H), 1.69 (m, 1 H), 1.20 (m, 5 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (137.4, 137.1), (135.0, 134.6), 131.0 (2 C), 130.9 (2 C), 128.9, (117.8, 117.6), (71.2, 70.9), (64.1, 63.7), (41.0, 39.3), (39.8, 38.4), (31.7, 31.6), (29.8, 29.6), (26.3, 26.2).

Anal. Calcd for $C_{17}H_{24}OS$: C, 73.87; H 8.76. Found: C, 73.61; H, 8.61.

Identification of the two diastereomers was accomplished as follows. A solution of the alcohol mixture (60 mg, 0.217 mmol) in CH_2Cl_2 (4 mL) was treated with trimethyloxonium tetrafluoroborate (36 mg, 0.240 mmol), stirred at rt for 4 h, and diluted with a 7% NaOH solution (2 mL). After 10 min of stirring, the separated organic layer was dried and concentrated. Flash chromatography of the residue on silica gel (elution with 100:1 hexanes/ethyl acetate) gave the oxirane diastereomers **17** and **18** as a colorless oil in a 1:1.4 ratio (100 mg, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1 H), 5.13 (m, 2 H), 3.00 (m, 0.6 H), 2.79 (m, 0.4 H), 2.66 (dd, J = 4.2, 8.2 Hz, 0.4 H), 2.49 (dd, J = 2.2, 6.5 Hz, 0.6 H), 2.30 (m, 2 H), 1.72 (m, 6 H), 1.22 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (133.9, 133.3), (117.2, 117.0), (64.9, 62.7), (56.3, 56.1), (39.9, 36.5), (36.4, 34.5), 28.9, 25.5, 25.4; MS m/z (M^+) calcd 166.1358, obsd 166.1362.

B. In 1:1 Water/THF. A mixture of **7** (110 mg, 0.472 mmol), allyl bromide (86 mg, 0.798 mmol), and indium powder (60 mg, 0.519 mmol) in 1:1 THF/H_2O) (5.2 mL) was vigorously stirred for 4.5 h and worked up as described above. There was isolated 130 mg (91%) of a 1:1.2 mixture of syn/anti diastereomers.

C. In THF. After a mixture of **7**, allyl bromide, and indium powder (amounts identical to part B) in THF (5.2 mL) for 10.5 h was stirred, the aldehyde was fully consumed and 107 mg (82%) of a 1:1.5 mixture of diastereomers was obtained.

Representative Allylations of 8. Samples of **8** (120−150 mg) were processed as above to give the results reported in Table 1. The spectral features of **13** and **14** has been previously reported.[7]

Representative Allylations of 9. Processing of 120 mg lots of **9** in the manner outlined above gave rise to mixtures of **18** and **19** as detailed in Table 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2 H), 7.27 (m, 3), 5.78 (m, 1 H), 5.11 (m, 2 H), 3.68 (m, 0.75 H), 3.57 (m, 0.25 H), 3.35 (dt, J = 6.8, 3.3 Hz, 0.75 H), 3.21 (dt, J = 6.8, 3.3 Hz, 0.25 H), 2.31 (m, 2 H), 1.30 (d, J = 6.9 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (134.5, 133.6), 134.1, 132.9 (2 C), 128.94 (2 C), 128.89, (117.9, 117.8), (73.1, 71.3), (50.1, 49.1), (38.2, 38.0), (17.8, 14.2); MS m/z (M^+) calcd 208.0922, obsd 208.0921.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 69.19; H, 7.73. Found: C, 69.09; H, 7.73.

General Allylation Procedure for 10−12. To a vigorously stirred mixture of **10**, **11**, or **12** (1.0 mmol) and allyl bromide (1.5 mmol) in water (2 mL) was added indium powder (1.5 mmol). The reaction mixture was stirred for 7 h, extracted with ether (3 × 10 mL), and processed in the predescribed fashion. The results have been compiled in Table 1. The relevant spectral data are as follows.

For 10:[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95−5.80 (m, 1 H), 5.18−5.08 (m, 2 H), 3.90−3.78 (m, 1 H), 3.76−3.70 (m, 1 H), 2.60−2.19 (series of m, 2 H), 2.16 (s, 3 H, syn isomer), 2.13 (s, 3 H, anti isomer), 1.98−1.00 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (135.4, 134.8), (117.6, 117.4), (70.8, 70.6), (63.0, 62.6), (40.7, 39.6), (39.7, 38.0), (31.6, 31.5), (30.1, 29.0), (26.5−26.0 overlapping peaks), (18.1, 17.6).

For 11:[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.20 (m, 2 H), 5.90−5.70 (m, 1 H), 5.20−5.00 (m, 2 H), 4.00−3.90 (m, 1H), 3.78 (d, J = 6.0 Hz, 1 H, syn isomer), 3.69 (d, J = 6.0 Hz, 1 H, anti isomer), 2.80−2.00 (m, 2 H), 1.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (139.5, 138.4), 134.6, (134.4, 134.2), 129.4−126.3 (overlapping peaks), (117.9, 117.8), (72.5, 71.6), (58.7, 57.3), (43.2, 41.1), (38.7, 38.6), 14.7, 14.1.

For 12 (syn/anti isomer mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.75 (m, 1 H), 5.20−5.10 (m, 2H), 3.77−3.70 (m, 1 H), 3.60−3.50 (m, 1 H), 2.50−2.20 (m, 2 H), 2.11 (s, 3 H), 1.25−1.20 (overlapping d's, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (134.8, 134.6), (117.7, 117.6), (72.5, 71.0), (47.4−47.2), 38.0, (31.9, 31.6), (14.1, 14.0); MS m/z (M^+) calcd 146.0765, obsd 146.0736.

Prototypical Allylation of 23. A. Direct Reaction with Indium Metal. A mixture of **23** (97 mg, 0.45 mmol), allyl bromide (104 mg, 0.86 mmol), and solvent (15 mL) was treated with indium powder (104 mg, 0.86 mmol), stirred vigorously at rt until TLC showed complete reaction, and quenched with water (10 mL) and CH_2Cl_2 (35 mL). The separated aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), the combined organic solutions were dried and concentrated, and the residue was subjected to MPLC on silica gel (elution with 5:1 hexanes/ethyl acetate) after recording of its ^{1}H NMR spectrum. The results are compiled in Table 2.

For the syn isomer: mp 105 °C; IR ($CHCl_3$, cm^{-1}) 3620, 3420, 1710, 1510; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.82 (m, 1 H), 5.16 (dd, J = 2.9, 1.6 Hz, 1 H), 5.11 (s, 1 H), 4.54 (br s, 1 H), 3.66 (br s, 2 H), 2.25−2.14 (m, 2 H), 1.85 (br s, 1 H), 1.73−1.62 (m, 1 H), 1.45 (s, 9 H), 1.34−1.23 (m, 1 H), 0.93 (dd, J = 7.9, 1.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.3, 134.9, 117.8, 79.5, 73.9, 53.2, 38.5, 38.0, 28.4, 24.8, 23.7, 21.6; MS m/z (M^+) calcd 184.1337, obsd 184.1329.

For the anti isomer: colorless oil; IR ($CHCl_3$, cm^{-1}) 3620, 3420, 1710, 1510, 1370, 1170; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87−5.77 (m, 1 H), 5.11 (d, J = 7.0 Hz, 1 H), 5.07 (s, 1 H), 4.75 (d, J = 9 Hz, 1 H), 3.65 (br s, 1 H), 3.55 (br s, 1 H), 2.45 (br s, 1 H), 2.31−2.13 (m, 2 H), 1.67−1.58 (m, 1 H), 1.41 (s, 9 H), 1.36−1.17 (m, 2 H), 0.89 (dd, J = 7, 2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.2, 134.6, 118.4, 79.2, 72.7, 52.0, 41.9, 39.1, 28.4, 24.8, 23.2, 22.2; MS (M^+) calcd 258.2069, obsd 258.2097.

B. Preformation of the Allylindium Reagent. A mixture of allyl bromide (104 mg, 0.86 mmol) and indium powder (104 mg, 0.86 mmol) in dry THF (12 mL) was refluxed for 1 h, cooled to rt, and treated with **23** (97 mg, 0.45 mmol) dissolved in THF (3.5 mL). The reaction mixture was stirred at rt until **23** was completely consumed and processed in the predescribed fashion. Consult Table 2 for results.

Studies Involving 24. Samples of **24** (100 mg, 0.44 mmol) were reacted in an entirely parallel manner to **23**. Chromatography of the product mixture in this case did not result in separation of the diastereomers. Spectroscopic analysis allowed determination of the product distributions reported in Table 2. In each instance, the **28/29** mixture (22 mg, 0.082

(36) In the *N*,*N*-dimethyl series, Reetz observed stereoselectivity to vary widely depending on the choice of organometallic.[13b,14,15,33] Whereas methyl Grignard additions gave a 1.9:1 ratio of syn and anti products, methyl cuprate additions occurred with high syn selectivity (99%).

(37) For the isoindoline compounds **42** and **43**, Reetz has reported cuprate additions to occur with good syn selectivity (>90%).

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

mmol) was dissolved with 2,6-di-*tert*-butyl-4-methylpyridine (37 mg, 0.18 mmol) in dry CH_2Cl_2 (0.5 mL), cooled to 0 °C, and treated with triflic anhydride (27 mg, 0.094 mmol) in 0.75 mL of CH_2Cl_2. The reaction mixture was allowed to warm to 20 °C, stirred for 2 h, and quenched by the addtion of a saturated $NaHCO_3$ solution (1 mL). The products were extracted into ethyl acetate, dried, and concentrated. Chromatography of the residue on silica gel (gradient elution from 6:1 ethyl acetate/hexanes to pure ethyl acetate) gave pure samples of **30** and **31**.

For 30: ^{1}H NMR (300 MHz, C_6D_6) δ 5.54−5.36 (m, 1 H), 4.97−4.82 (m, 2 H), 4.01 (dd, J = 7.7, 14.7 Hz, 1 H), 3.60−2.41 (m, 1 H), 3.39−3.27 (m, 2 H), 2.16−2.04 (m, 1 H), 1.82 (s, 3 H), 1.77−1.67 (m, 1 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.6, 132.4, 118.3, 94.7, 73.2, 63.4, 60.9, 34.8, 28.3, 23.7; MS m/z (M^+) calcd 197.1052, obsd 197.1059.

For 31: ^{1}H NMR (300 MHz, C_6D_6) δ 5.54−5.36 (m, 1 H), 5.00−4.87 (m, 2 H), 3.71 (dd, J = 6.3, 11.4 Hz, 1 H), 3.60−3.41 (m, 2 H), 3.11 (t, J = 6.8 Hz, 1 H), 2.16−2.04 (m, 1 H), 2.01−1.90 (m, 1 H), 1.80 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.6, 131.6, 119.1, 94.7, 76.7, 68.1, 63.1, 38.8, 27.7, 23.6; MS m/z (M^+) calcd 197.1052, obsd 197.1059.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67. Found: C, 60.80; H, 7.71.

Studies Involving 25. A mixture of **25** (53 mg, 0.22 mmol), allyl bromide (48 mg, 0.40 mmol), and indium powder (28 mg, 0.24 mmol) in the solvent of choice (3.9 mL) was stirred vigorously at rt until reaction was complete and freed of solvent. The product mixture was dissolved in pyridine (3 mL), treated with acetic anhydride (3 mL) together with DMAP (10 mg), stirred at rt for 24 h, and evaporated in vacuo. Chromatography of the residue on silica gel (elution with 2:1 hexanes/ethyl acetate) and the diastereomeric ratios were determined by ^{1}H NMR prior to this process.

For 32: colorless solid, mp 146 °C; IR ($CHCl_3$, cm^{-1}) 1750, 1690, 1510, 1375, 1220, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.64 (m, 1 H), 5.53 (d, J = 10.6 Hz, 1 H), 5.34 (dd, J = 2.2, 8.2 Hz, 1 H), 5.23 (dd, J = 2.2, 5.2 Hz, 1 H), 5.06−4.99 (dm, J = 2.9 Hz, 1 H), 4.85−4.80 (m, 2 H), 4.83 (dt, J = 1.6, 6.8 Hz, 1 H), 4.47 (dt, J = 1.6, 10.5 Hz, 1 H), 4.25 (dd, J = 3.1, 12.5 Hz, 1 H), 2.23 (t, J = 6.0 Hz, 2 H), 2.09 (d, J = 14.4 Hz, 6 H), 2.06−1.85 (br s, 12 H), 1.78 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.6, 170.04, 170.00, 169.91, 169.88, 169.83, 132.5, 118.7, 70.4, 68.8, 68.3, 68.0, 62.1, 58.8, 35.9, 23.2, 21.0, 20.9, 20.8, 20.7, 20.6; MS m/z (M^+) calcd 473.1897, obsd 473.1871.

Anal. Calcd for $C_{21}H_{31}NO_{11}$: C, 53.27; H, 6.60. Found: C, 53.40; H, 6.65.

For 33: colorless solid, mp 117 °C (from ether−hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10.4 Hz, 1 H), 5.76−5.63 (m, 1 H), 5.35 (dd, J = 2.8, 7.9 Hz, 1 H), 5.17 (dd, J = 2.8, 8.8 Hz, 1 H), 5.09 (dd, J = 1.4, 11.2 Hz, 1 H), 5.06−4.97 (m, 2 H), 4.76 (m, 1 H), 4.56 (dt, J = 3.8, 9.6 Hz, 1 H), 4.30 (dd, J = 3.0, 12.5 Hz, 1 H), 4.00 (dd, J = 5.7, 12.5, Hz, 1 H), 2.46−2.12 (m, 2 H), 2.08−1.90 (six s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.9, 170.6, 170.23, 170.17, 170.0, 169.8, 133.1, 118.2, 73.1, 69.3, 68.7, 68.4, 61.8, 49.8, 34.8, 23.3, 20.9 (2 C), 20.8, 20.7, 20.6; MS m/z (M^+) calcd 473.1897, obsd 473.1872.

Anal. Calcd for $C_{21}H_{31}NO_{11}$: C, 53.27; H, 6.60. Found: C, 53.27; H, 6.53.

Ozonolysis of 32. To a solution of **32** (77 mg, 0.16 mmol) in dry methanol (11 mL) was added sodium metal (260 mg, 11.3 mmol) under N_2 at 0 °C. The reaction mixture was stirred at rt for 3 h, quenched by the addition of dry ice until near-neutral, filtered, and freed of solvent. The residue (36 mg, 79%) was taken up in methanol (15 mL) and CH_2Cl_2 (4 mL), cooled to −78 °C, ozonolyzed for 10 min, flushed with oxygen, and quenched with 50 mg of Na_2SO_3. This mixture was stirred at rt for 21 h, filtered, and evaporated to leave a gum that was dissolved in pyridine (5 mL) and treated with acetic anhydride (3 mL) and DMAP (10 mg). This solution was refluxed for 1 h and stirred at rt before the excess reagents were removed in vacuo. The residue was purified by chromatography on silica gel (elution with 5:1 hexanes/ethyl acetate) to give 19 mg (41%) of **34**, a colorless solid of mp 162 °C (from ether/hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (dd, J = 2.1, 10.3 Hz, 1 H), 5.43 (d, J = 10.0 Hz, 1 H), 5.37 (dd, J = 2.3, 7.0 Hz, 1 H), 5.20−5.09 (m, 1 H), 5.03 (ddd, J = 2.7, 6.3, 12.4 Hz, 1 H), 4.39 (dd, J = 2.6, 12.5 Hz, 1 H), 4.14−3.98 (m, 1 H), 4.03 (dd, J = 6.7, 12.4 Hz, 1 H), 3.76 (dd, J = 2.4, 10.4 Hz, 1 H), 2.20 (ddd, J = 2.1, 5.1, 12.3 Hz, 1 H), 2.12 (s, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.94−1.83 (m, 1 H), 1.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.9, 170.6, 170.3, 170.1, 169.8, 168.7, 73.7, 70.2 (2 C), 70.1, 67.1, 62.0, 49.3, 35.1, 23.2, 20.9, 20.8 (2 C), 20.74, 20.72; MS m/z (M^++1) calcd 476.1767, obsd 476.1790.

Anal. Calcd for $C_{20}H_{29}NO_{12}$: C, 50.52; H, 6.15. Found: C, 50.40; H, 6.10.

General Procedure for the Allylation of 35−43. A mixture consisting of the aldehyde (3.24 mmol), indium powder (409 mg, 3.56 mmol), and ammonium chloride (260 mg, 4.86 mmol) in water (21 mL) was stirred vigorously for 5−10 min prior to the addition of allyl bromide (841 μL, 9.72 mmol). Reaction was allowed to proceed until no starting material was evident by TLC analysis. Ethyl acetate (20 mL) and saturated $NaHCO_3$ solution were introduced, the mixture was stirred for 30 min, and the solids were removed by filtration through a pad of Celite. The aqueous phase was separated and extracted with ethyl acetate (2 × 10 mL). The combined organic solutions were washed with brine, dried, and concentrated to leave a residue which was chromatographed on silica gel (elution with 0−10% ethyl acetate in hexanes). The results are compiled in Table 3, and the pertinent spectral data are provided below.

Entry 27. Syn diastereomer: IR (neat, cm^{-1}) 3404, 1494, 1453; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.22 (m, 10 H), 5.84 (m, 1 H), 5.03 (m, 2 H), 3.84 (d, J = 13.3 Hz, 2 H), 3.57 (m, 1 H), 3.33 (d, J = 13.3 Hz, 2 H), 2.62 (m, 1 H), 2.30 (m, 1 H), 1.98 (m, 1 H), 1.80 (br s, 1 H), 1.04 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.8−127.2 (12 C), 135.1, 116.4, 70.4, 57.9, 53.2 (2 C), 38.0, 8.0; MS m/z (M^+) calcd 295.1935, obsd 295.1930.

Anti diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.26 (m, 10 H), 5.68 (m, 1 H), 5.10 (d, J = 12.6 Hz, 2 H), 3.80 (d, J = 13.7 Hz, 2 H), 3.68 (m, 1 H), 3.48 (d, J = 13.7 Hz, 2 H), 2.70 (m, 2 H), 2.09 (m, 1 H), 1.84 (br m, 1 H), 1.18 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.0−126.9 (12 C), 135.4, 118.1, 72.3, 57.0, 55.5 (2 C), 39.3, 8.5; MS m/z (M^+) calcd 295.1935, obsd 295.1926.

Entry 28. Syn diastereomer: IR (neat, cm^{-1}) 3506, 1494, 1454, 1265; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 15 H), 5.74 (m, 1 H), 5.16 (m, 2 H), 3.92 (m, 1 H), 3.83 (d, J = 13.9 Hz, 2 H), 3.75 (d, J = 13.9 Hz, 2 H), 3.12 (m, 2 H), 2.97 (dd, J = 5.2, 12.8 Hz, 1 H), 2.51 (m, 1 H), 2.19 (m, 1 H), 1.97 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.9−125.8 (18 C), 135.2, 117.9, 70.7, 62.9, 54.8 (2 C), 39.8, 32.0; MS m/z (M^+) calcd 371.2248, obsd 371.2244.

Anti diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.11 (m, 15 H), 5.74 (m, 1 H), 5.09 (m, 2 H), 3.89 (m, 1 H), 3.78 (d, J = 13.8 Hz, 2 H), 3.70 (d, J = 13.8 Hz, 2 H), 3.12 (dd, J = 7.0, 12.9 Hz, 1 H), 3.04 (m, 1 H), 2.93 (dd, J = 5.4, 12.9 Hz, 1 H), 2.47 (m, 1 H), 2.15 (m, 1 H), 1.80 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.0−125.9 (18 C), 135.5, 116.5, 70.8, 63.0, 54.9 (2 C), 39.9, 32.2; MS m/z (M^+) calcd 371.2248, obsd 371.2214.

Entry 29. Syn diastereomer: IR (neat, cm^{-1}) 3490, 1494, 1453; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.18 (m, 10 H), 5.87 (m, 1 H), 5.05 (m, 2 H), 3.96 (d, J = 13.0 Hz, 2 H), 3.50 (d, J = 13.0 Hz, 2 H), 2.33 (m, 3 H), 1.97 (m, 2 H), 1.06 (d, J = 3.3 Hz, 3 H), 1.04 (d, J = 3.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.9−127.1 (12 C), 135.5, 116.5, 66.4, 65.3, 54.0 (2 C), 39.7, 25.1, 23.8, 19.5.

Anti diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.18 (m, 10 H), 5.87 (m, 1 H), 5.10 (m, 2 H), 3.83 (d, J = 13.5 Hz, 2 H), 3.75 (d, J = 13.5 Hz, 2 H), 3.77 (m, 1 H), 2.40 (m, 2 H), 2.19 (m, 2 H), 1.22 (d, J = 6.7 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 139.8−127.1 (12 C), 136.2, 117.1, 69.5, 66.4, 55.9 (2 C), 38.8, 27.5, 23.3, 20.6; MS m/z (M^+) calcd 323.2248, obsd 323.2222.

Entry 30. Syn diastereomer: IR (neat, cm^{-1}) 3429, 1494, 1454; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.18 (m, 10 H), 5.87 (m, 1 H), 5.05 (m, 2 H), 3.98 (d, J = 13.2 Hz, 2 H), 3.45 (d, J = 13.2 Hz, 2 H), 3.51 (m, 1 H), 2.56 (m, 2 H), 2.19 (m, 1 H),

1.95 (m, 1 H), 1.79 (m, 1 H), 1.40 (m, 2 H), 1.04 (d, $J = 6.7$ Hz, 2 H), 0.98 (d, $J = 7.4$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.9−127.0 (12 C), 136.1, 117.4, 69.4 (2 C), 55.5 (2 C), 39.2, 33.4, 28.9, 16.2, 11.7; MS m/z ($M^+ + 1$) calcd 338.2485, obsd 338.2493.

Anti diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.20 (m, 10 H), 5.85 (m, 1 H), 5.13 (m, 2 H), 3.89 (m, 1 H), 3.84 (d, $J = 13.5$ Hz, 2 H), 3.69 (d, $J = 13.5$ Hz, 2 H), 2.56 (m, 2 H), 2.19 (m, 1 H), 1.98 (m, 1 H), 1.79 (m, 1 H), 1.40 (m, 2 H), 1.04 (d, $J = 6.7$ Hz, 3 H), 0.98 (d, $J = 7.4$ Hz, 3 H).

Entry 31. Syn diastereomer: IR (neat, cm^{-1}) 3445, 2495, 1453, 1070, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.19 (m, 10 H), 5.44 (m, 1 H), 4.80 (m, 2 H), 4.19 (m, 3 H), 4.16 (m, 3 H), 3.05 (m, 1 H), 2.12 (m, 1 H), 1.98 (m, 1 H), 1.09 (s, 9 H); ^{13}C NMR 75 MHz, $CDCl_3$) ppm 140.0−127.0 (12 C), 135.5, 118.0, 70.5, 68.2, 57.0 (2 C), 41.5, 38.8, 29.9 (3 C); MS m/z (M^+) calcd 337.2406, obsd 337.2367.

Anti diastereomer: IR (neat, cm^{-1}) 3445, 1495, 1453, 1358, 1070, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.14 (m, 10 H), 5.77 (m, 1 H), 5.18 (m, 2 H), 4.06 (m, 3 H), 3.65 (m, 2 H), 2.49 (d, $J = 2.7$ Hz, 1 H), 2.42 (m, 2 H), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.5−126.8 (12 C), 135.9, 118.3, 70.6, 67.8, 57.0 (2 C), 43.1, 37.4, 29.9 (3 C); MS m/z (M^+) calcd 337.2406, obsd 337.2367.

Entry 32. Syn diastereomer: IR (neat, cm^{-1}) 3432, 1473, 1391, 1178, 1130, 995; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85−5.71 (m, 1 H), 5.19−5.13 (m, 2 H), 4.47 (m, 1 H), 3.04 (m, 2 H), 2.68 (s, 3 H), 2.67 (s, 3 H), 2.21 (t, $J = 7.0$ Hz, 2 H), 1.28 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.5, 119.4, 67.7, 67.6, 51.7, 48.9, 46.8, 7.3; MS m/z (M^+) calcd 143.1310, obsd 143.1303.

Entry 34. Syn diastereomer: IR (neat, cm^{-1}) 3412, 1455, 1030; ^{1}H NMR (300 MHz, C_6D_6) δ 7.11−6.99 (m, 5 H), 6.21 (m, 1 H), 5.06 (m, 2 H), 3.41 (m, 1 H), 2.65 (m, 1 H), 2.63 (dd, $J = 2.4$, 6.0 Hz, 1 H), 2.44 (s, 1 H), 2.24 (dd, $J = 5.6$, 14.2 Hz, 1 H), 2.03 (m, 1 H), 1.92 (m, 7 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 141.1−126.2 (6 C), 135.9, 116.5, 70.3, 69.6, 40.6 (2 C), 38.8, 31.4; MS m/z (M^+) calcd 219.1623, obsd 219.1628.

Anti diastereomer: IR (neat, cm^{-1}) 3412, 1456, 1034; ^{1}H NMR (300 MHz, C_6D_6) δ 7.12−7.01 (m, 5 H), 5.80 (m, 1 H), 5.00 (m, 2 H), 3.60 (m, 1 H), 2.74 (m, 3 H), 2.28 (m, 1 H), 2.10 (m, 7 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 141.8−125.7 (6 C), 135.9, 117.0, 71.1, 69.5, 41.8 (2 C), 39.7, 31.6; MS m/z (M^+) calcd 219.1623, obsd 219.1624.

Entry 36. Syn diastereomer: IR (neat, cm^{-1}) 3391, 1666, 1469, 1409, 1377, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 4 H), 6.06−5.92 (m, 1 H), 5.19−5.09 (m, 2 H), 4.21 (br s, 1 H), 4.05 (s, 4 H), 3.51 (m, 1 H), 2.86 (m, 1 H), 2.45 (m, 1 H), 2.20−2.10 (m, 1 H), 1.04 (d, $J = 3.2$ Hz, 3 H), ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.2−122.4 (6 C), 134.8, 116.9, 71.8, 59.6, 53.0 (2 C), 37.6, 8.8; MS m/z (M^+) calcd 217.1467, obsd 217.1461.

Anti diastereomer: IR (neat, cm^{-1}) 3433, 1641, 1423, 1385, 1290, 1224, 1082; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 4 H), 5.87 (m, 1 H), 5.14 (m, 2 H), 4.10−3.91 (m, 5 H), 3.39 (m, 1 H), 2.64 (m, 1 H), 2.33 (m, 1 H), 2.20 (m, 1 H), 1.14 (d, $J = 3.2$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.5−122.2 (6 C), 135.3, 117.0, 70.5, 62.4, 56.9 (2 C), 37.9, 11.4; MS m/z (M^+) calcd 217.1467, obsd 217.1466.

Entry 38. Syn diastereomer: IR (neat, cm^{-1}) 3352, 1670, 1449, 1062; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.00 (m, 9 H), 6.17 (m, 1 H), 5.15 (m, 2 H), 3.97 (dd, $J = 2.2$, 11.1 Hz, 4 H), 3.65 (m, 1 H), 3.30 (br, 1 H), 3.15 (m, 1 H), 2.70 (m, 2 H), 2.53 (m, 1 H) 2.32 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.2−122.5 (12 C), 132.5, 116.8, 71.0, 65.4, 54.3 (2 C), 38.6, 32.2; MS m/z (M^+) calcd 293.1780, obsd 293.1783.

Anti diastereomer: IR (neat, cm^{-1}) 3332, 1675, 1467, 1411, 1054; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17−6.88 (m, 9 H), 5.89 (m, 1 H), 5.06 (dd, $J = 2.3$, 1.5 Hz, 2 H), 3.92 (d, $J = 10.7$ Hz, 2 H), 3.79 (m, 3 H), 2.96 (m, 2 H), 2.78 (dd, $J = 8.0$, 15.9 Hz, 1 H), 2.27 (t, $J = 6.8$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.4−122.4 (12 C), 136.1, 117.1, 72.0, 67.5, 56.5 (2 C), 39.1, 33.6; MS m/z (M^+) calcd 293.1780, obsd 293.1786.

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Supporting Information Available: High-field ^{1}H and ^{13}C NMR spectra of those pure compounds for which elemental analyses are not reported (40 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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