1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine, (+)-Bicuculline, (+)-Egenine, and (+)-Corytensine, and Preliminary ^{13}C NMR Studies of 1-Lithio- and 1-Magnesiotetrahydroisoquinolyloxazolines†

Robert E. Gawley* and Pingsheng Zhang

Department of Chemistry, University of Miami, Coral Gables, Florida 33124-0431

Received June 20, 1996⊗

Transmetalation of 1-lithiotetrahydroisoquinolyloxazolines with magnesium halides affords Grignard reagents that add to aldehydes with up to 80% selectivity for one of the four possible diastereomeric products. An oxazoline chiral auxiliary derived from camphor provides an optimal blend of diastereoselectivity and isomer separability. Synthetic applications of the optimal auxiliary, patterned after a literature approach in the racemic series, comprise an improved (formal) synthesis of bicuculline, egenine, and corytensine, as well as an efficient synthesis of corlumine. Preliminary NMR studies show that both 1-lithio- and 1-magnesiotetrahydroisoquinolyloxazolines are dynamic mixtures in THF solution at low temperatures. The barrier to pyramidal inversion of the secondary Grignard reagent is in the 9.8−10.1 kcal/mol range, while an upper limit of about 8.2 kcal/mol can be assigned to the barrier to the organolithium inversion.

Introduction

Chiral organometallic compounds in which a metal is bonded to a stereogenic carbon atom are gaining in popularity as tools in asymmetric synthesis. For example, the Meyers group has developed chiral formamidines as auxiliaries for the asymmetric alkylation of lithiated tetrahydroisoquinolines and β-carbolines;[1,2] Hoppe[3−5] and Beak[6,7] have shown that the *sec*-butyllithium−sparteine complex is an excellent reagent for enantioselective deprotonation of carbamates and pyrrolidines. These examples are representative of a growing class of chiral, nonracemic α-amino organolithiums that are finding use in asymmetric synthesis.[8−10]

The utility of α-amino organolithiums is high with electrophiles such as alkyl halides or symmetrical ketones in which there is only one asymmetric center produced in the product, at the former "carbanionic" carbon. When an aldehyde is employed as the electrophile, an additional stereocenter is formed, but the selectivity at the second stereocenter (the former carbonyl carbon) is invariably low or nonexistent.[11−14] On the face of it, this is puzzling, since it implies that the diastereomeric transition states are (nearly) isoenergetic, assuming that the addition occurs by a polar mechanism. For lithiated tetrahydroisoquinolines (pivalamides and oxazoline activating groups), it appears that the lack of stereoselectivity is due to the intervention of a single-electron-transfer mechanism.[15]

In 1984, Seebach reported that transmetalation of lithiated tetrahydroisoquinoline pivalamides from lithium to magnesium affords a reagent that is 100% diastereoselective for the *erythro* (*u*) diastereomer,[12,16,17] and the method was used as the key step in highly stereoselective syntheses of several (hydroxybenzyl)isoquinoline alkaloids (*e.g.*, the phthalide lactone β-hydrastine, the aporphine ushinsunine, and the protoberberine alkaloid ophiocarpine) in racemic form.[18,19] Efforts to extend this method to the synthesis of the phthalide alkaloid corlumine (nonracemic) were not as successful, since the 100% stereoselectivity observed with unsubstituted tetrahydroisoquinolines and 6,7-(methylenedioxy)tetrahydroisoquinolines was lost when a 6,7-dimethoxytetrahydroisoquinoline was employed.[20]

Several years ago, we reported an approach analogous to that of Seebach (but using an oxazoline as a chiral auxiliary) for the asymmetric synthesis of (hydroxybenzyl)isoquinolines.[14] In preliminary work,[13,21] we found

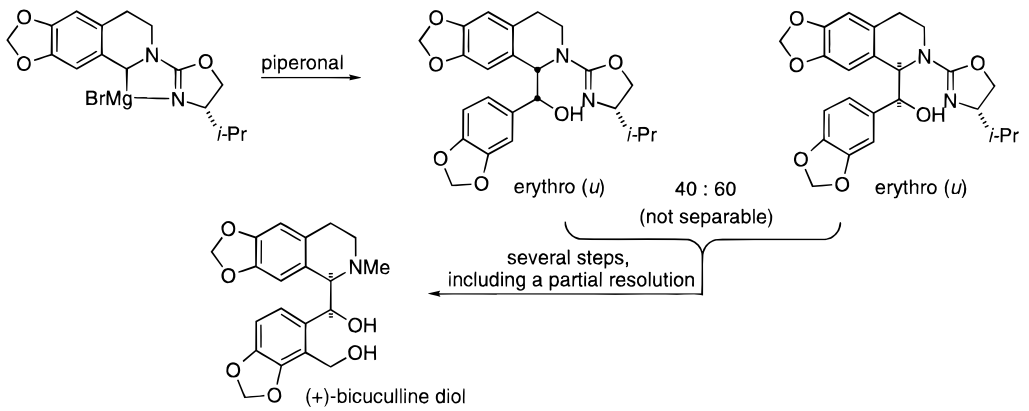
† Dedicated to Professor V. Prelog, on the occasion of his 90th birthday, with respect and admiration for his contributions to our science and to the fellowship of chemists.

⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) Highsmith, T. K.; Meyers, A. I. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI: Greenwich, CT, 1991; Vol. 1, p 95.
(2) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.
(3) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422.
(4) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424.
(5) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479.
(6) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
(7) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(8) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis. Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 65.
(9) Gawley, R. E.; Rein, K. S. In *Comprehensive Organic Synthesis*; Schreiber, S., Ed.; Pergamon: Oxford, 1991; Vol. 1, p 459.
(10) Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077.
(11) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578.
(12) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1.
(13) Rein, K. S.; Gawley, R. E. *Tetrahedron Lett.* **1990**, *31*, 3711.
(14) Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 1564.
(15) Rein, K. S.; Chen, Z.-H.; Perumal, P. T.; Echegoyen, L.; Gawley, R. E. *Tetrahedron Lett.* **1991**, *32*, 1941.
(16) Syfrig, M. A.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 248.
(17) Seebach, D.; Syfrig, M. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *70*, 1944.
(18) Seebach, D.; Huber, I. M. P. *Chimia* **1985**, *39*, 233.
(19) Seebach, D.; Huber, I. M. P.; Syfrig, M. A. *Helv. Chim. Acta* **1987**, *70*, 1375.
(20) Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944.
(21) Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 839.

S0022-3263(96)01164-4 CCC: $12.00

Scheme 1



that tetrahydroisoquinoline Grignard reagents add stereoselectively (60% diastereoselectivity), giving a mixture of the two *erythro* (*u*) diastereomers and none of the *threo* (*l*) isomers. Initially, we used a readily available oxazoline auxiliary, derived from valine,[22,23] to establish the absolute configuration of the major addition product of a 6,7-(methylenedioxy)isoquinoline by correlation of structure with (+)-bicuculinediol (Scheme 1).[13] The asymmetric addition, accompanied by a partial resolution later in the synthesis, was used in syntheses of enantiopure (−)-egenine, (−)-corytensine, and (−)-bicuculline.[13,14] These studies showed that, in contrast to reactions of the lithiated compounds,[23] the electrophile approaches the anionic carbon from the face opposite the isopropyl.[13,14]

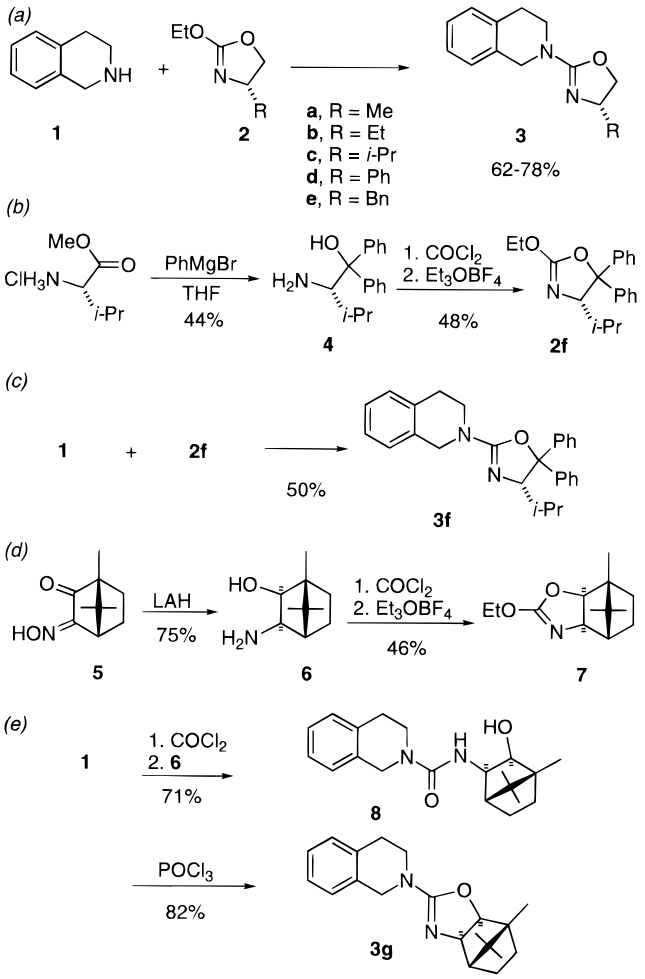
After an extensive search for a better auxiliary, we reported that an oxazoline derived from camphor was superior, affording diastereoselectivities in the 80% range for one of the four possible diastereomers, with the added advantage that separation of the diastereomeric addition products was routine, obviating the need for the partial resolution step.[24]

In this paper, we report the details of these optimization studies, including our rationale for the design of improved auxiliaries, the application of the optimal auxiliary to the asymmetric synthesis of (+)-corlumine, an improved (formal) synthesis of the alkaloids (+)-bicuculline, (+)-egenine, and (+)-corytensine, and preliminary ^{13}C NMR studies of lithiated and magnesiated isoquinolyloxazolines that allow estimation of the barrier to pyramidal inversion in these species.

Results and Discussion

Auxiliary Preparation. The synthesis of the isoquinolyloxazolines is detailed in Scheme 2. Condensation of tetrahydroisoquinoline, **1**, with ethoxyoxazolines **2a**−**f** afforded isoquinolyloxazolines **3a**−**f**. Oxazolines **2a**−**e** and **3a**−**e**, summarized in Scheme 2a, have been reported previously.[23] The diphenyloxazoline **2f** was prepared by addition of phenylmagnesium bromide to valine methyl ester hydrochloride to give amino alcohol **4**, which was cyclized with phosgene and *O*-alkylated to give **2f**, as shown in Scheme 2b. Following the same protocol as before, condensation of **1** and **2f** afforded **3f**, as shown in Scheme 2c.

Scheme 2



Thornton reported that reduction of camphor quinone monooxime by a two-step sequence (sodium borohydride followed by hydrogenation over platinum) provided amino alcohol **6**.[25] We find that direct reduction by lithium aluminum hydride works equally well (Scheme 2d). Cyclization and *O*-alkylation afforded the ethoxyoxazoline **7**, but attempted condensation with **1** failed. Instead of condensation to an isoquinolyloxazoline, *N*-ethylation of **1** occurred. Alternatively, the two-pot sequence outlined in Scheme 2e afforded isoquinolyloxazoline **3g**, *via* urea **8**, in good yield.

Selectivity Optimization and Auxiliary Testing. Metalation of the isoquinolyloxazolines was accomplished with butyllithium at −78 °C, and transmetalation with magnesium bromide etherate was complete after 20 min

(22) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076.
(23) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211.
(24) Zhang, P.; Gawley, R. E. *Tetrahedron Lett.* **1992**, *33*, 2945.
(25) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299.

Scheme 3

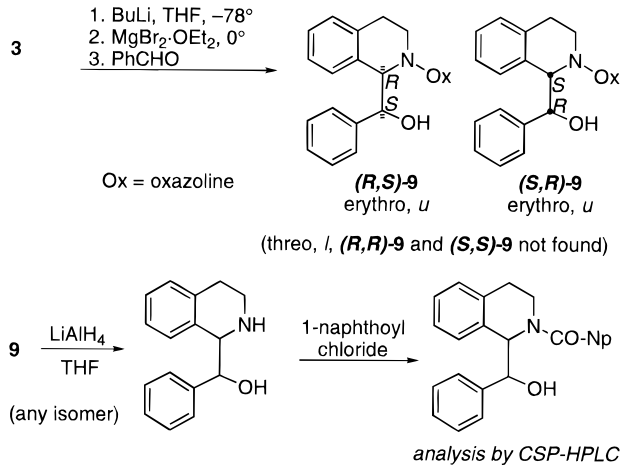


Table 1. Selectivity of Addition of Isoquinolyloxazoline Grignard Reagents to Benzaldehyde (See Scheme 2 for Structure of Oxazolines 3 and Scheme 3 For Structure of 9)

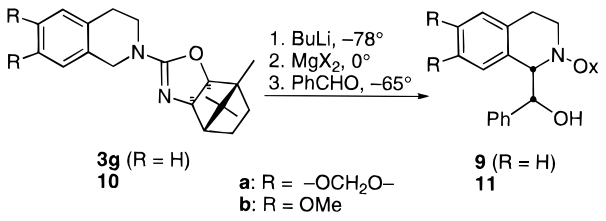
entry	oxazoline	temp, °C	**9** (*R,S*:*S,R*:*R,R*:*S,S*)
1	**3a**	−78	50:50:0:0
2	**3b**	−78	62:38:0:0
3	**3c**	−78	71:29:0:0
4	**3c**	−70	55:45:0:0
5	**3c**	−60	42:58:0:0
6	**3c**	−45	58:42:0:0
7	**3d**	−78	71:29:0:0
8	**3e**	−78	70:30:0:0
9	**3f**	−78	80:20:0:0
10	**3g**	−78	33:67:0:0
11	**3g**	−65	20:80:0:0

at 0 °C. After the solution was cooled to −78 °C, 1.5 equiv of benzaldehyde was added. In all cases (**3a**−**g**) addition afforded a mixture that contained only two of the four possible diastereomeric addition products, as illustrated in Scheme 3. Reduction of the addition product mixture gives amino alcohols that can be acylated with naphthoyl chloride and separated on a Pirkle column.[21] The relative configuration of the two new stereocenters was *u*, as expected.[13−15] The selectivity data are listed in Table 1.

For the monosubstituted oxazolines **3a**−**e**, the maximum diastereoselectivity at −78 °C was about 70% (Table 1, entries 1−3, 7, and 8). For **3c**, experiments at different temperatures show a surprising effect: as the temperature is raised from −78 to −70 °C, the selectivity decreases, reverses at −60 °C, and then reverses again at −45 °C (entries 3−6). NMR studies, discussed below, reveal a complex mixture of species in solution, and rigorous interpretation of this phenomenon is not possible with the data currently in hand. Acting on the hypothesis that substitution at the 5-position of the oxazoline would restrict conformational motion of the isopropyl group, we tested **3f** and found that the selectivity was indeed higher (Table 1, entry 9).

From a preparative viewpoint, 80% diastereoselectivity would be acceptable if the two diastereomers were easily separable. Unfortunately, this is not the case for auxiliaries **3a**−**f**. Thus, we looked for another type of oxazoline, one that had similar steric features and that would give selectivities at least as high as those of **3f** and that may also afford addition products that are easily separable. Regarding isomer separability and crystallinity, camphor-derived auxiliaries are legendary. Thus, after the appearance of Thornton's report of an oxazolidinone derived from camphor,[25] we decided to try adapting it to

Scheme 4



R	X	%ds	Isolated yield (single isomer)
H	Cl or Br	80	50%
-OCH_2O-	Cl or Br	78	53%
MeO	Cl	82	58%

this reaction. In the event, the selectivity at −78 °C was about the same as we had observed with **3c** (Table 1, entry 10), but the product mixture could be purified to diastereomer homogeneity with a single recrystallization. Furthermore, a variable temperature study indicated that addition at −65 °C is optimal (Table 1, entry 11) and that the major diastereomer could be isolated by recrystallization in 50% yield.

In an effort to test the applicability of this auxiliary-based approach to the problem encountered by the Seebach group in the stereoselective addition of isoquinolines to aldehydes,[20] we examined the stereoselectivity of addition of 6,7-(methylenedioxy)- (**10a**) and 6,7-dimethoxytetrahydroisoquinoline (**10b**) derivatized with the camphor−oxazoline auxiliary (**3g**) to benzaldehyde.[24] The results are shown in Scheme 4 and are shown in comparison to the unsubstituted case. Diastereoselectivities were analyzed by removal of the auxiliary and Pirkle analysis, as before.[21] Initially, we used magnesium bromide for the transmetalation, and it worked well for the unsubstituted isoquinoline (**3g**) and for the methylenedioxy derivative (**10a**), providing about 80% diastereoselectivity in both cases. Unfortunately, transmetalation of the lithiated dimethoxy compound (**10b**) and addition to benzaldehyde afforded a mixture of both *erythro* and *threo* products, reminiscent of the results obtained by the Seebach group.[20]

Clearly, there are subtle effects at work here, since the methylenedioxy compound and the dimethoxy compound are electronically similar, yet selectivity is completely lost for the latter. In trying to rationalize this fact, we recalled that the bromine atom and the pivaloyl oxygen were found to be trans to each other in the crystal, as indicated in Figure 1a.[12] Assuming that the oxazoline takes the place of the pivalamide as indicated in Figure 1b, a methylenedioxy substituent would not affect the structure significantly (Figure 1c). However, molecular mechanics calculations (Macromodel[26]) indicated that the most stable conformation of the two methoxy groups has the methyls oriented away from each other,[24] and we reasoned that, in this conformation, the methyl group of the 7-methoxy substituent may encounter the bromine trans to the oxazoline nitrogen (or pivalamide oxygen?, *cf.* ref 20), as shown in Figure 1d. Such an interaction could disrupt the geometry of the reagent in the ground state and cause a change of mechanism or could destabilize the transition state leading to the *erythro* products. We hoped that changing the halide to a (smaller) chlorine

(26) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

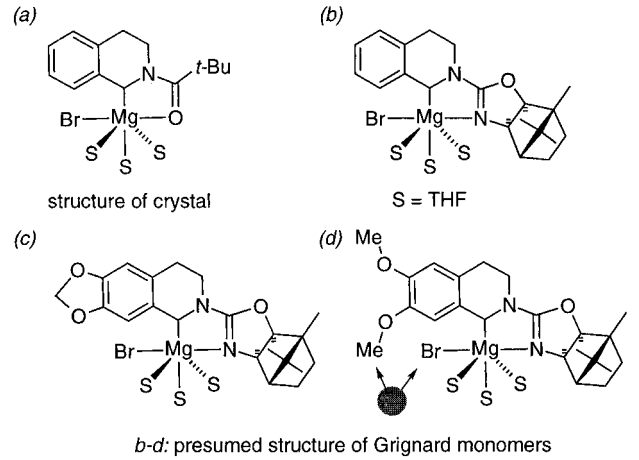


Figure 1.

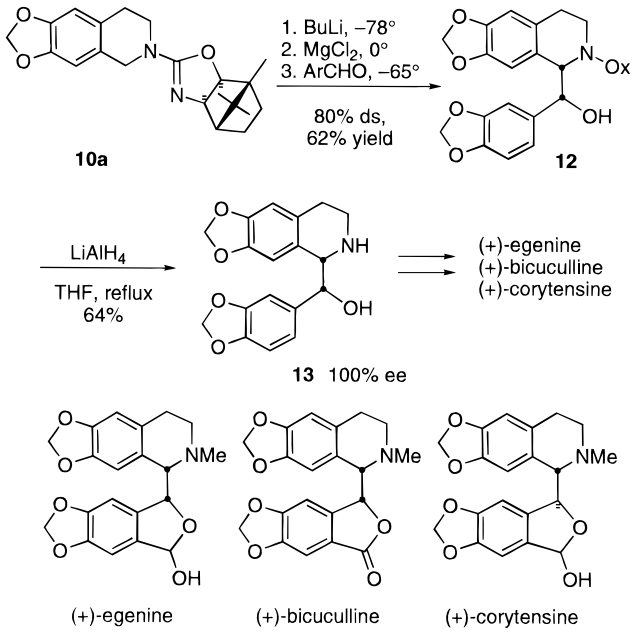
may alleviate such a problem (the van der Waals radii of bromine and chlorine are 195 and 181 pm, respectively[27]). In the event, it did; transmetalation with magnesium chloride restored the *erythro* selectivity to 82% diastereoselectivity, giving **11b** in 58% isolated yield.

In the case of all three products (**9**, **11a**,**b**), recrystallization or column chromatography provided the product as a single diastereomer in the isolated yields indicated. Note that these isolated yields compare favorably with the yield of the more highly stereoselective model reaction reported by the Seebach group.[12,16,17]

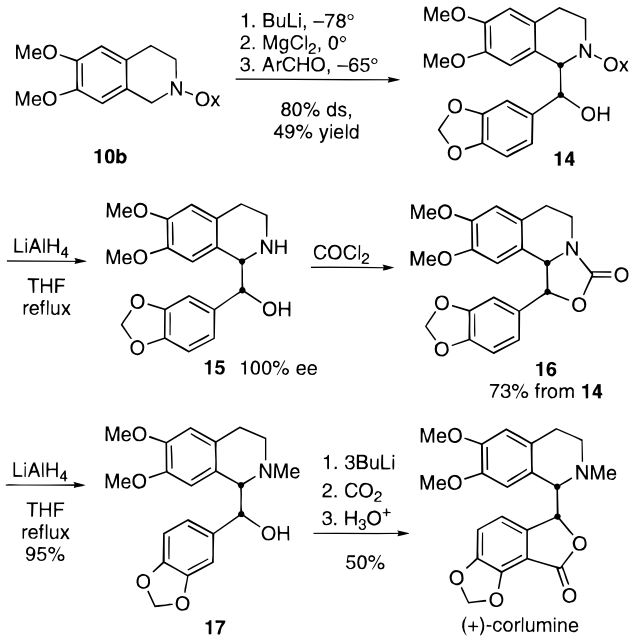
Synthetic Applications. To demonstrate this methodology in natural product synthesis, phthalide isoquinoline alkaloids are an ideal target because of their simplicity and because they may serve as starting materials for synthesis of other (hydroxybenzyl)isoquinoline alkaloid classes by known routes. Thus, we chose phthalide alkaloids in our earlier effort.[13,14] From a synthetic standpoint, a major weakness of that effort was the fact that the two *erythro* isomers could not be separated. In order to obtain enantiopure products, we had to incorporate a partial resolution after auxiliary removal. With **10a** and **10b**, however, that is not necessary, so we used this auxiliary for the asymmetric synthesis of (the enantiomer of) a key intermediate in the previously published synthesis of bicuculline, egenine, and corytensine, as outlined in Scheme 5. Consistent with the model studies outlined above, the (methylenedioxy)isoquinoline **10a**, as its Grignard derivative, added with 80% diastereoselectivity to piperonal, affording (hydroxybenzyl)isoquinoline adduct **12** in 62% yield after purification by flash chromatography. Auxiliary removal afforded the key intermediate **13**, the enantiomer of that prepared previously.[14]

To demonstrate the use of a dimethoxyisoquinoline, we chose as a target corlumine, a phthalide similar to these three, because our results could be compared directly with the Seebach effort.[20] As shown in Scheme 6, lithiation and transmetalation of **10b**, followed by addition to piperonal with 80% diastereoselectivity, afforded adduct **14** in 49% isolated yield. NMR and HPLC data both indicated that this compound was isolated as a single diastereomer. Reductive removal of the oxazoline auxiliary was accomplished as before, and a two-step sequence was employed to methylate the nitrogen. Thus, cyclization of the amino alcohol **15** with phosgene afforded oxazolidinone **16** in 73% yield from **14**. Reduction gave the *N*-methyl compound **17**. Directed metalation and carboxylation were accompanied by lactonization during acidic workup to give (+)-corlumine in 50% yield (17% overall from **10b** in five steps).

Scheme 5



Scheme 6



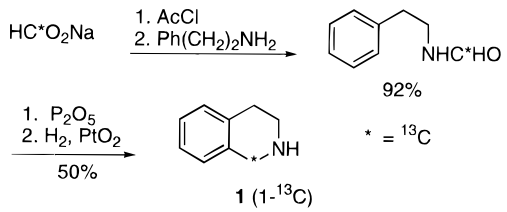
The low yield of the last step is due to large amounts of recovered **17** (the yield based on unrecovered starting material is 93%). We undertook a number of model studies in the hopes of improving the efficiency of this directed metalation, mostly by adding other directing groups in the vicinity of the site of lithiation. None of these efforts was successful, although an interesting rearrangement was discovered in the process.[28]

NMR Studies. In an effort to try to unravel the structure of the metalated isoquinolyloxazoline reagents, we decided to examine the ^{13}C NMR spectrum of these

(27) Emsley, J. *The Elements*; Clarendon: Oxford, 1989.

(28) Zhang, P.; Gawley, R. E. *J. Org. Chem.* **1993**, *58*, 3223.

Scheme 7



species. It is well-known that the NMR spectra of organolithium species are complicated by pyramidal inversion and aggregation phenomena[29−39] and that pyramidal inversion and Schlenk equilibria complicate the NMR spectra of organomagnesium species.[29,40−44] Nevertheless, we thought that such studies might provide direct evidence for the existence of distinct organolithium or organomagnesium diastereomers and that observation of these species may shed some light on the process of asymmetric induction in these reactions.

To that end, we prepared [1-^{13}C]tetrahydroisoquinoline by a Bischler−Napieralski cyclization of the ^{13}C-enriched formamide of phenethylamine, followed by reduction, according to the procedure of Hesse, as shown in Scheme 7.[45] Condensation with **2c** afforded isoquinolyloxazoline **3c** enriched with ^{13}C at C-1.

Metalation with [^{6}Li]butyllithium[31] gave a C−Li doubly labeled lithiated compound whose low-temperature ^{13}C NMR spectrum (C-1 only) is illustrated in Figure 2. The equilibrating diastereomeric organolithiums (and/or equilibrating aggregates) show fast exchange on the NMR time scale, even at −100 °C, where $^{1}J(^{6}\mathrm{Li}-^{13}\mathrm{C})$ coupling is apparent and a shoulder is beginning to appear. Further lowering of the temperature was not possible due to solvent freezing and/or solute crystallization. We cannot say with certainty that the shoulder represents a C-1 epimer or some sort of diastereomeric aggregate. If it is the latter, then the main peak at 61.5 ppm must be a time average of the C-1 epimers and the barrier to inversion must be extremely low. In the former instance, we can estimate $\Delta\nu$ and calculate a limiting value for the inversion barrier. Thus, if one assumes that the shoulder represents the other organolithium diastereomer, the relative ratio is about 70:30 (the approximate ratio of peak heights). This corresponds[46,47] to a process with inversion barriers ($\Delta G^{\ddagger}$) of about 8.0 and 8.2 kcal/mol (see Supporting Information for details on the calculations). Since a lower T_c would correspond to a lower activation barrier, this can be taken as an approximate upper limit for this process. These observations are consistent with interpretations made earlier of a fast equilibrium between such organolithium stereoisomers.[23,48] This tentative conclusion also clarifies the earlier quandary[23,49] between thermodynamic or kinetic control in the stereoselective alkylation of these species. With such a low barrier to inversion for equilibrating organolithium diastereomers, and since the ratio of alkylation products is much higher than 70:30, the alkylation follows Curtin−Hammett kinetics.[50,51]

Transmetalation of the lithiated species with magnesium bromide (3.7 molar equiv) afforded a species (0.14 M) whose partial ^{13}C NMR spectrum is shown in Figure 3 (C-1 only). The spectrum reveals a species that is not a simple monomeric Grignard reagent. Two regions can be discerned: a low-field, temperature-independent region and a higher field region where a dynamic phenomenon is observed. Specifically, the peaks near 47 ppm coalesce at −65 °C.

The position of the Schlenk equilibrium ($R_2Mg + MgBr_2 \rightleftarrows 2RMgBr$) is affected by the concentrations of magnesium halide and the solvent and the temperature. Relevant to our work are the facts that, in THF at low temperatures, the equilibrium is shifted to the left (relative to its position in ether) and that the Schlenk equilibrium is slow.[52] Control experiments showed that, as the magnesium bromide concentration was varied between 0.2 and 0.5 M (equilibration at 0 °C), the population of the upfield, temperature-dependent region increased at the expense of the downfield region. We interpret this as a shift of the Schlenk equilibrium to the right (toward RMgBr). Thus, the upfield, temperature-dependent region is assigned to the Grignard monomers and the two peaks to the diastereomers epimeric at C-1. Interestingly, integration of these two peaks in the −80 °C spectrum corresponds exactly to the isomer ratio found in the carbonyl addition.

In 1965, Roberts showed that the ^{1}H NMR spectra (in ether) of dialkylmagnesium species change little below +30 °C and that Grignard species do not change below temperatures of −70 °C.[42] Roberts also found that the (Arrhenius) barrier to inversion of primary Grignard reagents was 11 ± 2 kcal/mol (A = exp 9.5 ± 1.5 s^{-1}),[41] and Fraenkel concluded that the mechanism involved a dimeric species and that alkyl bridging is associated with the transition state for inversion.[53] Early attempts at

(29) Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 737.
(30) Fraenkel, G.; Beckenbaugh, W. E.; Yang, P. P. *J. Am. Chem. Soc.* **1976**, *98*, 6878.
(31) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.
(32) Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255.
(33) Heinzer, J.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1848.
(34) Günther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1212.
(35) Bauer, W.; Klusener, P. A. A.; Harder, S.; Kanters, J. A.; Duisenberg, A. J. M.; Brandsma, L.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 552.
(36) Fraenkel, G.; Winchester, W. R. *J. Am. Chem. Soc.* **1989**, *111*, 3794.
(37) Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003.
(38) Bergander, K.; He, R.; Chandrakumar, N.; Eppers, O.; Günther, H. *Tetrahedron* **1994**, *50*, 5861.
(39) Bauer, W.; Schleyer, P. v. R. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI: Greenwich, CT, 1992; Vol. 1, p 89.
(40) Whitesides, G. M.; Kaplan, F.; Roberts, J. D. *J. Am. Chem. Soc.* **1963**, *85*, 2167.
(41) Whitesides, G. M.; Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 2854.
(42) Whitesides, G. M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4878.
(43) Maercker, A.; Geuss, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 270.
(44) Liebfritz, D.; Wagner, B. O.; Roberts, J. D. *Liebigs Ann. Chem.* **1972**, *763*, 173.
(45) Gretler, R.; Askitoglu, E.; Kühne, H.; Hesse, M. *Helv. Chim. Acta* **1978**, *61*, 1730.
(46) Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961.
(47) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982, p 81.
(48) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505.
(49) Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265.
(50) Curtin, D. Y. *Rec. Chem. Progr.* **1954**, *15*, 111.
(51) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(52) Lindsell, W. E. In *Comprehensive Organometallic Chemistry. The Synthesis, Reactions and Structures of Organometallic Compounds*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 1, p 155.
(53) Fraenkel, G.; Cottrell, C. E.; Dix, D. T. *J. Am. Chem. Soc.* **1971**, *93*, 1704.

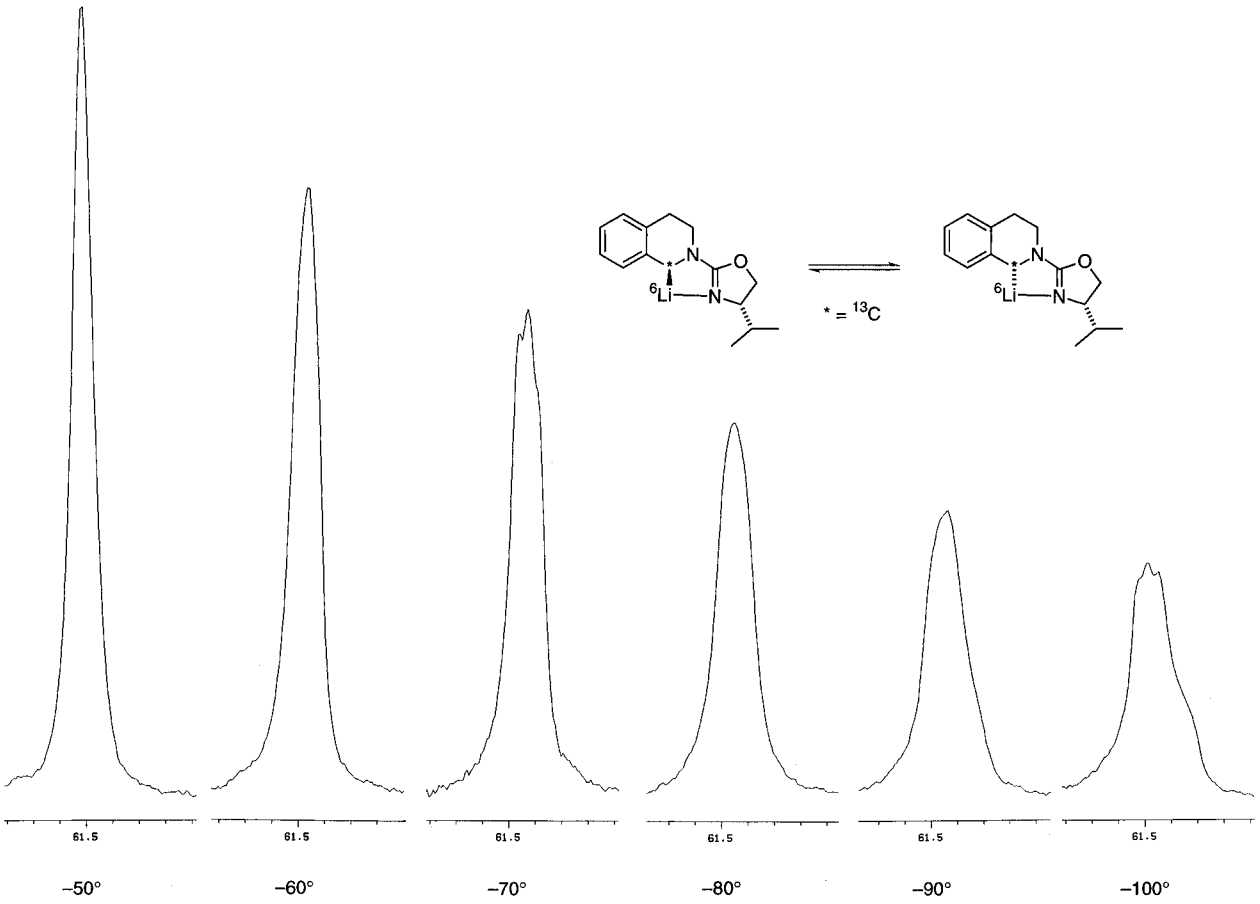


Figure 2. Variable temperature ^{13}C NMR spectrum of C-1 of doubly labeled (^{6}Li and ^{13}C) **3c**−**Li**. Only the signal for C-1 is shown.

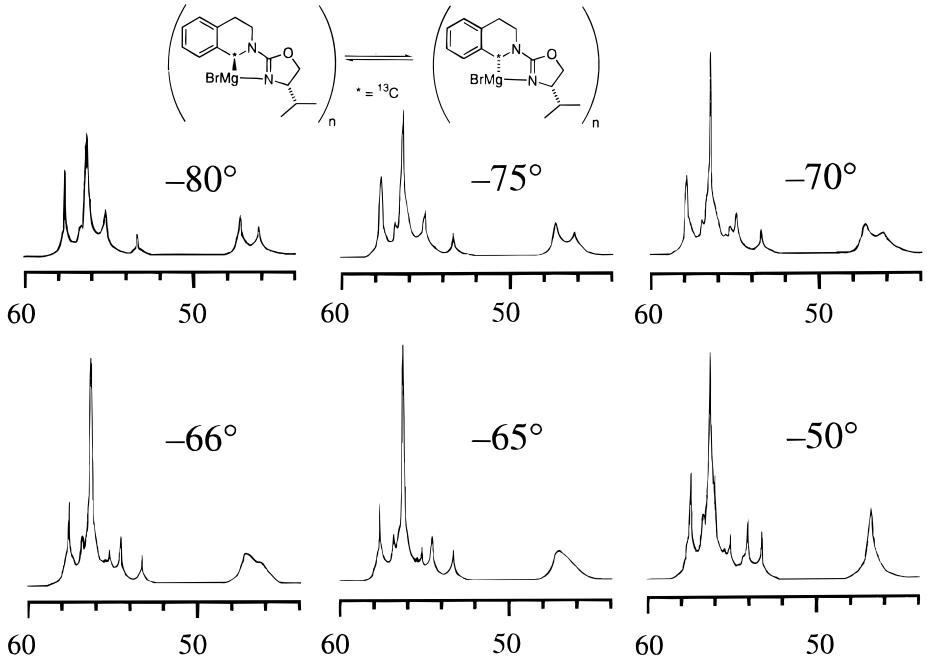


Figure 3. Variable temperature ^{13}C NMR spectrum of C-1 of **3c**−**MgBr**. Only the signals for C-1 are shown. See text for explanation.

observation of inversion of secondary organomagnesium reagents (4−6-membered saturated rings) showed that the barrier to inversion was quite high,[42,54,55] although Maercker showed that a 3-cyclohexenyl Grignard reagent undergoes somewhat more rapid inversion, with a lower barrier in THF than in ether.[43] The high barrier is generally attributed to difficulty in bridging of the

(54) Davies, A. G.; Roberts, B. P. *J. Chem. Soc. (B)* **1969**, 317.

(55) Pechhold, E.; Adams, D. G.; Fraenkel, G. *J. Org. Chem.* **1971**, *36*, 1368.

saturated secondary Grignard reagents, while the lower barrier in the cyclohexenyl system is ascribed to assistance by the double bond.[52]

The coalescence data from Figure 3 correspond to free energies of activation ($\Delta G^{\ddagger}$) in the 9.8−10.1 kcal/mol range at −65 °C, with $\Delta G° = 0.3$ kcal/mol for the two C-1 epimers (see Supporting Information for details).[46,47] This low barrier suggests that chelation, dipole stabilization, and benzylic activation combine to lower the barrier to inversion in these species, although further experiments on simpler systems will be necessary to establish this conclusively.

Summary. NMR studies indicate that both the organolithium and the organomagnesium species undergo pyramidal inversion with barriers to inversion ($\Delta G^{\ddagger}$) of less than 10 kcal/mol. The mechanism of the stereoselective addition of these Grignard reagents is complex, in that it involves equilibrating organomagnesium diastereomers that, as chiral nucleophiles, add stereoselectively to the enantiotopic faces of aldehydes. We cannot say much about the mechanism because we do not know the configuration (at C-1) of the nucleophile. We therefore cannot say whether the reaction proceeds with retention or inversion of configuration at the benzylic carbon, and without that we cannot offer an explanation for the observed *erythro* selectivity.

Mechanistic ignorance notwithstanding, we have developed a general, auxiliary-based method for the stereoselective addition of tetrahydroisoquinoline Grignard reagents to aldehydes and have demonstrated its usefulness in efficient asymmetric synthesis of four phthalide isoquinoline alkaloids.

Experimental Section

Combustion analyses were performed by Atlantic Microlab. NMR spectra were recorded (ppm) at an operating frequency of 400 MHz for protons and 100 MHz for carbon. All reactions were run under a balloon of nitrogen. THF was freshly distilled from benzophenone sodium ketyl. Benzaldehyde and piperonal were distilled and stored under nitrogen. Toluene solutions of phosgene were purchased from Fluka. Magnesium bromide solutions were prepared by the reaction of magnesium with ethylene bromide in ether.[56] The product of this reaction is a two-phase mixture, the bottom of which is 2.56 M in $MgBr_2$. Magnesium chloride solutions in THF are prepared in the same way or by reaction of $HgCl_2$ with Mg (magnesium does not react with ethylene chloride in ether).[57] In this case, the product is a homogeneous solution, and it can be standardized by evaporation of an aliquot and weighing. The use of inexpensive magnesium is satisfactory for these reactions, but the use of high-purity magnesium (≥99.98%) produces an etherate solution with a longer shelf life. CSP−HPLC refers to a Bakerbond DNBPG (covalent) Pirkle column, available from J. T. Baker, Co. The stationary phase is (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine. Rotations were measured at rt. IR spectral data are reported in cm^{-1}.

(*S*)-2-Amino-3-methyl-1,1-diphenyl-1-butanol (4) and (*S*)-3,3-Diphenyl-4-isopropyl-2-oxazolidinone. In a 1 L round-bottom flask fitted with a reflux condenser and a dropping funnel was placed 4.8 g (198 mmol) of magnesium. The dropping funnel was charged with a solution of 28.2 g (180 mmol) of freshly distilled bromobenzene in 150 mL of THF, and 10 mL of the solution was added to the flask. The flask was heated gently to start the reaction. The rest of the solution was added at such a speed that gentle reflux was maintained. After the addition, the mixture was refluxed for 1 h. The solution was then cooled to 0 °C, and to it was added, portionwise, 6 g (36 mmol) of L-valine methyl ester hydrochloride. After the addition, the mixture was warmed to rt and stirred overnight. The mixture was diluted with ether, and the reaction was quenched with saturated NH_4Cl solution. The organic phase was separated, washed with brine, and dried with Na_2CO_3. The drying agent was filtered, the solvent removed, and the residue purified with flash chromatography (ethyl acetate:hexane, 1:2) to afford 4.0 g (44% yield) of **4**: mp 94−95 °C; ^{1}H NMR 0.80−0.95 (6H, dd), 1.75 (1H, m), 2.20 (3H, br), 3.80 (1H, s), 7.10−7.70 (10 H, m). The amino alcohol obtained in this fashion was used in the next step without further purification.

To a solution of 2.0 g (7.8 mmol) of **4** and 2 mL of triethylamine in 12 mL of THF at rt was added 4.4 mL (8.5 mmol) of phosgene solution (1.93 M in toluene, Fluka). A white precipitate formed immediately. After the mixture was stirred for 2 h, saturated Na_2CO_3 solution was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 twice. The organic phase was washed with brine, dried with $MgSO_4$, and evaporated. The residue was washed with ether to afford 2.1 g of oxazolidinone as a white solid (95% yield): mp 250−251 °C; ^{1}H NMR 0.7 (3H, d, $J = 8.2$ Hz), 0.9 (3H, d, $J = 8.2$ Hz), 1.80−1.95 (1H, m), 4.2 (1H, d, $J = 5.1$ Hz), 6.3 (1H, s), 7.2−7.6 (10H, m); ^{13}C NMR 158.5, 143.9, 139.1, 128.5, 128.2, 128.1, 127.9, 126.3, 125.7, 89.4, 65.8, 29.6, 20.9, 15.6; IR 1740; MS (DCI/NH_3) 282 (MH^+), 183 (100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76. Found: C, 77.05; H, 6.82.

(*S*)-2-Ethoxy-4,5-dihydro-5,5-diphenyl-4-isopropyloxazole (2f). To a solution of 3.6 g of oxazolidinone (9.25 mmol) in 30 mL of CH_2Cl_2 at 0 °C was added slowly a solution of 2.1 g (11.1 mmol) of Meerwein's reagent[58] in 10 mL of CH_2Cl_2. The mixture was warmed slowly to rt and stirred overnight. The solution was poured into a cooled aqueous Na_2CO_3 solution. The organic phase was dried over anhydrous Na_2CO_3. The solvent was evaporated, and the residue was purified by flash chromatography (ethyl acetate:hexane, 1:2) to afford **2f** (1.4 g, 50% yield) as a white solid: ^{1}H NMR 0.58 (3H, d, $J = 6.7$ Hz), 0.96 (3H, d, $J = 6.7$ Hz), 1.37 (3H, d, $J = 7.8$ Hz), 1.77 (1H, m), 4.2−4.4 (2H, m), 4.55 (1H, d, $J = 4.4$ Hz), 7.1−7.6 (10H, m); ^{13}C NMR 160.4, 145.1, 140.4, 128.2, 127.8, 127.7, 127.1, 126.6, 93.4, 76.4, 66.4, 30.1, 21.7, 16.3, 14.3; IR 1640; MS (DCI/NH_3) 309 (M^+), 182 (PhCOPh). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.67; H, 7.44. Found: C, 77.68; H, 7.51.

(*S*)-2-(4,5-Dihydro-5,5-diphenyl-2-oxalyl)-1,2,3,4-tetrahydroisoquinoline (3f). A solution of 1.13 g of oxazoline **2f** (3.66 mmol), 1.08 g (8.1 mmol) of 1,2,3,4-tetrahydroisoquinoline, and a catalytic amount of *p*-toluenesulfonic acid in 20 mL of benzene was refluxed for 3 d. The solution was cooled to rt, washed with a saturated Na_2CO_3 solution and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2:ethanol, 10:1) to afford 1.45 g (50% yield) of **3f** as an oil: ^{1}H NMR 0.58 (3H, d, $J = 6.5$ Hz), 0.95 (3H, d, $J = 6.5$ Hz), 1.65−1.77 (1H, m), 4.55 (1H, d, $J = 2$ Hz), 4.70 (2H, s), 7.0−7.6 (14H, m); ^{13}C NMR 158.7, 145.5, 140.9, 134.2, 133.2, 128.6, 128.0, 127.7, 127.4, 126.7, 126.4, 126.0, 76.9, 47.2, 42.7, 30.4, 28.6, 21.6, 16.3; IR 1620; MS (DCI/NH_4^+) 397 (MH^+). Anal. Calcd for $C_{27}H_{28}N_2O$: C, 81.82; H, 7.07. Found: C, 81.63; H, 7.07.

(1*R*,2*S*,3*R*,4*S*)-3-*exo*-Amino-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (6). To a suspension of $LiAlH_4$ (7 g, 180 mmol) in 400 mL of ether was added a solution of camphorquinone oxime **5**[25] (10 g, 55 mmol) in 200 mL of ether over a period of 1 h, and the suspension was then stirred at rt for 2 d. The reaction was quenched slowly at 0 °C with 15 mL of water followed by 17 mL of 10% NaOH and 24 mL of water.[59] The solid was removed by filtration, and the filtrate was concentrated. The residue was purified by sublimation. The amino alcohol (**6**) was obtained in 75% yield (6.9 g): mp 190−194 °C (lit.[25] mp 190−194 °C); ^{1}H NMR 0.8 (3H, s), 0.95

(56) House, H. O.; Traficante, D. D.; Evans, R. A. *J. Org. Chem.* **1963**, *28*, 348.
(57) Ashby, E. C.; Arnott, R. C. *J. Organomet. Chem.* **1968**, *14*, 1.
(58) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 581.
(59) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. 1, p 581.

(3H, s), 1.08 (3H, s), 1.10−2.00 (5H, m), 3.05 (1H, d, J = 7.2 Hz), 3.45 (1H, d, J = 7.2 Hz).

Urea 8 (Prepared from 1,2,3,4-Tetrahydroisoquinoline, Phosgene, and 6). General Procedure. To a solution of 4.0 equiv of phosgene (1.93 M in toluene, Fluka) and excess triethylamine in THF (or CH_2Cl_2) at −78 °C was added slowly a solution of 1.0 equiv of 1,2,3,4-tetrahydroisoquinoline in THF (or CH_2Cl_2). The mixture was stirred at −78 °C for 1 h. The mixture was slowly warmed to rt, and the unreacted phosgene was removed by evaporation with an aspirator. More solvent was added, and the mixture was cooled to −78 °C. To this solution was added a solution of 0.95 equiv of **6** and excess triethylamine in THF (or CH_2Cl_2). The solution was warmed to rt and stirred overnight. Water was added to the mixture. The aqueous phase was extracted twice with CH_2Cl_2. The organic phases were washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (ethyl acetate:hexane, 1:1 to 2:1), giving **8** as a white solid, 71% yield: $[\alpha]_D$ +31.7 (c = 6.7, CH_2Cl_2); ^{1}H NMR 0.80 (3H, s), 0.95 (3H, s), 1.15 (3H, s), 1.0−1.3 (2H, m), 1.40−1.55 (1H, m), 1.6−1.9 (2H, m), 2.8−2.9 (2H, m), 3.5−3.7 (2H, m), 3.7−3.9 (2H, m), 4.5 (2H, m), 5.35 (1H, s), 7.00−7.15 (4H, m); ^{13}C NMR 156.6, 139.0, 131.6, 129.2, 126.2, 123.9, 79.8, 58.6, 50.5, 48.9, 46.5, 43.3, 33.1, 26.9, 26.0, 23.6, 21.1, 20.6, 11.1; IR 1640; MS (DCI/NH_3) 329 (MH^+), 311, 196, 134 (100). Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.17; H, 8.54. Found: C, 73.04; H, 8.61.

Isoquinolyloxazoline 3g (by Cyclization of 8 with $POCl_3$). General Procedure. A 0.2 M solution of **8** and 8.0 equiv of $POCl_3$ in toluene was refluxed overnight. The solution was concentrated to near dryness, washed with saturated Na_2CO_3, and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with $MgSO_4$. After the solvent was removed, the residue was purified with flash chromatography (ethanol:CH_2Cl_2, 1:20). Isoquinolyloxazoline **3g** was obtained as a colorless oil in 82% yield: $[\alpha]_D$ −30.0 (c = 2.55, CH_2Cl_2); ^{1}H NMR 0.81 (3H, s), 0.90 (3H, s), 1.05 (3H, s), 0.9−1.20 (2H, m), 1.40−1.50 (1H, s), 1.60−1.70 (1H, m), 1.90−2.00 (1H, m), 2.85 (2H, t, J = 5.3 Hz), 3.65 (2H, t, J = 5.3 Hz), 3.95 (1H, d, J = 9.5 Hz), 4.30 (1H, d, J = 9.5 Hz), 4.55 (2H, s), 7.05−7.30 (4H, m); ^{13}C NMR 161.3, 133.9, 133.0, 128.4, 125.9, 125.8, 91.5, 73.7, 48.9, 47.9, 46.8, 46.6, 42.4, 31.7, 28.5, 25.3, 23.2, 18.5, 11.1; IR 1635; MS 311(MH^+). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.42; H, 8.39. Found: C, 77.12; H, 8.43.

General Procedure for the Selectivity Studies. To a 0.1−0.2 M solution of isoquinolyloxazoline **3** in THF at −78 °C was added 1.2 equiv of a BuLi solution in hexane. After the solution was stirred at this temperature for 20 min, 1.5 equiv of a 2.56 M solution of $MgBr_2{\cdot}OEt_2$ was added. The reaction mixture was stirred at 0 °C for 20 min and then cooled back to the temperature indicated in Table 1. To this solution was added 1.5 equiv of benzaldehyde, and the mixture was stirred at this temperature overnight. A saturated NH_4Cl solution was added, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were collected, washed with brine, and dried with $MgSO_4$. After the solvents were removed, the residue was dissolved in THF. To this solution was added 4.0 equiv of $LiAlH_4$ at rt. The mixture was stirred for 10 min and then refluxed overnight. The solution was cooled with ice−water, and to it was added water dropwise. When no more gas was formed, 10% NaOH solution was added. The mixture was stirred for 10 min. The solid was filtered off, and the solution was concentrated. The residue was purified by flash chromatography (CH_2Cl_2:EtOH, 10:1) to afford a mixture of amino alcohols. To a solution of the above mixture and excess triethylamine in CH_2Cl_2 was added 1.5 equiv of 1-naphthoyl chloride. The mixture was stirred at rt overnight. Saturated Na_2CO_3 was added and the organic phase separated. The organic phase was dried over $MgSO_4$ and analyzed by CSP−HPLC with a Pirkle column.[21] The amino alcohols and naphthamides obtained by this procedure from **3a**−**g** were identical to those reported previously.[14,21]

6,7-(Methylenedioxy)isoquinolyloxazoline 10a. Following the general procedures given for compounds **8** and **3g**, compound **10a** was obtained in two steps. The 6,7-methylenedioxy analog of urea **8** was obtained in 71% yield: $[\alpha]_D$ +31.7 (c = 2.5, CH_2Cl_2); ^{1}H NMR 0.80 (3H, s), 0.95 (3H, s), 1.15 (3H, s), 1.00−1.20 (2H, m), 1.40−1.60 (1H, m), 1.65−1.80 (2H, m), 2.72 (2H, t, J = 6.5 Hz), 5.30 (1H, s), 5.90 (2H, s), 6.55 (1H, s), 6.60 (1H, s); ^{13}C NMR 157.5, 146.2, 146.1, 128.1, 126.3, 108.2, 106.3, 100.8, 58.8, 50.7, 49.0, 46.7, 45.3, 41.2, 33.5, 28.9, 26.1, 21.7, 11.3; IR 1630; MS 373 (MH^+), 306 (100). Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.74; H, 7.53. Found: C, 67.83; H, 7.65.

Cyclization to **10a** was accomplished according to the procedure given for **3g**, 75% yield: $[\alpha]^{24}_D$ −24.8 (c = 8.15, CH_2Cl_2); ^{1}H NMR 0.8 (3H, s), 0.90 (3H, s), 1.00 (3H, s), 0.85−1.05 (2H, m), 1.40−1.50 (1H, m), 1.60−1.75 (1H, m), 1.90−2.00 (1H, m), 2.60−2.80 (2H, m), 3.50−3.65 (2H, m), 3.95 (1H, d, J = 8.4 Hz), 4.28 (1H, d, J = 8.4 Hz), 4.40−4.50 (2H, m), 5.90 (2H, s), 6.50 (1H, s), 6.55 (1H, s); ^{13}C NMR 161.5, 145.9, 127.1, 126.0, 108.3, 106.0, 100.5, 91.8, 74.0, 49.0, 48.0, 47.1, 46.2, 42.6, 31.9, 28.6, 25.6, 23.5, 19.0, 11.3; IR 1640; MS 355 (MH^+, 100). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.19; H, 7.34. Found: C, 70.93; H, 7.38.

6,7-Dimethoxyisoquinolyloxazoline 10b. Following the general procedures given for compounds **8** and **3g**, compound **10b** was obtained in two steps. The 6,7-dimethoxy analog of urea **8** was obtained in 66% yield: $[\alpha]_D$ +20.7 (c = 0.4, CH_2Cl_2); ^{1}H NMR 0.80 (3H, s), 0.95 (3H, s), 1.15 (3H, s), 1.00−1.25 (2H, m), 1.40−1.60 (1H, m), 1.60−1.85 (2H, m), 2.60−2.80 (2H, m), 3.40−3.70 (2H, m), 3.70−4.00 (8H, m), 4.40 (2H, s), 5.40 (1H, s), 6.50−6.70 (2H, m); ^{13}C NMR 157.6, 147.7, 126.9, 125.1, 111.3, 109.3, 80.1, 58.8, 50.9, 49.2, 58.8, 46.9, 45.2, 41.2, 33.4, 28.5, 26.2, 21.6, 21.2, 11.4; IR 1630; MS 389 (MH^+). Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.04; H, 8.25. Found: C, 67.86; H, 8.27.

Cyclization to **10b** was accomplished according to the procedure given for **3g**, 70% yield: $[\alpha]_D$ −36.4 (c = 3.55, CH_2Cl_2); ^{1}H NMR 0.85 (3H, s), 0.95 (3H, s), 1.05 (3H, s), 0.90−1.10 (1H, m), 1.40−1.50 (1H, m), 1.60−1.80 (1H, m), 1.90−2.00 (1H, m), 2.80 (2H, m), 3.60 (2H, m), 3.85 (6H, d), 3.97 (1H, d, J = 8.2 Hz), 4.30 (1H, d, J = 8.2 Hz), 4.50 (2H, s), 6.58 (1H, s), 6.62 (1H, s); ^{13}C NMR 160.1, 148.1, 147.9, 124.4, 121.5, 111.1, 108.9, 94.8, 64.4, 55.8, 55.7, 48.7, 47.7, 47.5, 45.3, 46.3, 30.8, 27.5, 24.1, 22.8, 18.5, 10.5; IR 1640; MS 371 (MH^+). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.35; H, 8.11. Found: C, 71.55; H, 8.18.

General Procedure for Preparative Additions to Aldehydes. To a 0.1 M solution of isoquinolyloxazoline **3g** or **10** in THF at −78 °C was added 1.2 equiv of BuLi (1.6 M solution in hexane). After the solution was stirred at that temperature for 20 min, 1.5 equiv of magnesium halide solution was added. The mixture was stirred at 0 °C for 20 min and then cooled to −65 °C. To this solution was added 1.5 equiv of aldehyde. The mixture was stirred at that temperature for 2 d. A saturated NH_4Cl solution was added, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was purified by either recrystallization from chloroform and hexane or flash chromatography (ethyl acetate:hexane, 2:1 to 4:1).

1-Hydroxybenzylisoquinolyloxazoline 9g was prepared by the general procedure, 50% yield: mp 210−211 °C; $[\alpha]_D$ −80.7 (c = 1.9, CH_2Cl_2); ^{1}H NMR 0.85 (3H, s), 0.90 (3H, s), 1.00 (3H, s), 0.90−1.10 (2H, m), 1.40−1.60 (2H, m), 1.60−1.80 (1H, m), 1.90−2.00 (1H, m), 2.20−2.40 (1H, m), 2.80−3.00 (1H, m), 3.10−3.30 (1H, m), 4.12 (1H, d, J = 8.5 Hz), 4.48 (1H, d, J = 8.5 Hz), 5.15 (1H, s), 5.50 (1H, s), 6.80−7.50 (9H, m); ^{13}C NMR 165.0, 141.0, 135.6, 133.7, 127.8, 127.4, 126.9, 126.4, 92.8, 82.1, 72.9, 63.7, 49.5, 48.3, 46.4, 41.8, 31.9, 27.8, 25.5, 18.9, 11.2; IR 1635; MS 417 (MH^+), 311, 107. Anal. Calcd for $C_{27}H_{32}N_2O_2P$: C, 77.88; H, 7.69. Found C, 77.66; H, 7.74.

1-[2-(Hydroxybenzyl)-6,7-(methylenedioxy)isoquinolyl]oxazoline 11a was prepared by the general procedure, 58% yield: mp 193−195 °C; $[\alpha]_D$ −36.2 (c = 2.85, CH_2Cl_2); ^{1}H NMR 0.85 (3H, s), 0.88 (3H, s), 0.98 (3H, s), 0.95−1.10 (2H, m), 1.40−1.80 (3H, m), 2.10−2.30 (1H, m), 2.89−2.90 (1H, m), 3.10−3.25 (1H, m), 4.10 (1H, d, J = 8.4 Hz), 4.42 (1H, d, J = 8.4 Hz), 5.05 (1H, s), 5.40 (1H, s), 5.92 (1H, s), 5.98 (1H, s), 6.40

(1H, s), 6.80−7.00 (3H, m), 7.10−7.20 (3H, m); ^{13}C NMR 164.8, 146.4, 146.1, 141.0, 129.2, 127.4, 127.1, 126.9, 126.6, 107.8, 100.9, 92.7, 82.1, 72.9, 63.8, 49.6, 48.3, 46.4, 42.0, 32.3, 28.9, 25.7, 23.7, 19.1, 11.5; IR 1640; MS 461 (MH^+, 100), 353. Anal. Calcd for $C_{28}H_{32}N_2O_4$: C, 73.04; H, 6.96. Found: C, 72.85; H, 7.11.

1-[2-(Hydroxybenzyl)-6,7-dimethoxyisoquinolyl]oxazoline (11b) was prepared by the general procedure, 53% yield: $[\alpha]_D$ −47.9 (c = 2.75, CH_2Cl_2); ^{1}H NMR 0.83 (3H, s), 0.87 (3H, s), 0.98 (3H, s), 0.95−1.10 (2H, m), 1.40−1.70 (3H, s), 1.92 (1H, d, J = 0.50 Hz), 2.20−2.35 (1H, m), 2.70−2.90 (1H, m), 3.20−3.30 (1H, m), 3.83 (3H, s), 3.86 (3H, s), 4.12 (1H, d, J = 7.4 Hz), 4.42 (1H, d, J = 7.4 Hz), 5.15 (1H, s), 5.40 (1H, s), 6.43 (1H, s), 6.80 (1H, s), 6.90−7.00 (2H, m), 7.10−7.25 (3H, m); ^{13}C NMR 164.8, 147.8, 147.4, 141.1, 127.8, 127.4, 127.0, 126.8, 125.2, 110.6, 92.8, 81.6, 72.8, 63.3, 56.2, 49.2, 48.2, 46.4, 41.7, 31.8, 27.5, 25.8, 23.7, 18.9, 11.6; IR 1634; MS 477 (MH^+). Anal. Calcd for $C_{29}H_{36}N_2O_4$: C, 73.11; H, 7.56. Found: C, 73.22; H, 7.60.

Addition Product (12) was prepared by the general procedure, 62% yield: $[\alpha]_D$ −40.2 (c = 9.5, CH_2Cl_2); ^{1}H NMR 0.83 (3H, s), 0.86 (3H, s), 0.98 (3H, s), 0.95−1.10 (2H, m), 1.40−1.60 (3H, m), 1.92 (1H, d, J = 5.1 Hz), 2.10−2.30 (1H, m), 2.90−3.00 (1H, m), 3.10−3.30 (1H, m), 4.10 (1H, d, J = 9.2 Hz), 4.45 (1H, d, J = 9.2), 4.97 (1H, s), 5.35 (1H, s), 5.88 (2H, s), 5.93 (1H, s), 5.97 (1H, s), 6.25 (1H, d, J = 10.2 Hz), 6.41 (1H, s), 6.50−6.62 (2H, m), 6.82 (1H, s); ^{13}C NMR 165.0, 147.0, 146.5, 146.2, 135.2, 129.2, 126.7, 120.2, 107.9, 107.7, 107.4, 101.0, 100.7, 93.0, 81.6, 72.8, 63.8, 49.3, 48.3, 46.5, 42.0, 31.9, 28.0, 25.6, 23.5, 18.9, 11.4; IR 1635; MS 505 (MH^+), 353. Anal. Calcd for $C_{29}H_{32}N_2O_6$: C, 69.05; H, 6.35. Found: C, 68.99; H, 6.41.

Amino Alcohol 13. To a suspension of $LiAlH_4$ (117 mg, 3.1 mmol) in 10 mL of THF at 0 °C was added dropwise a solution of **12** (310 mg, 0.62 mmol) in 10 mL of THF. The reaction mixture was warmed to rt and then refluxed for 1 d. After being cooled to 0 °C, the mixture was diluted with an equal volume of ether. The unreacted $LiAlH_4$ was decomposed by the dropwise addition of water and 10% NaOH.[59] The solid was filtered, and the filtrate was washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2:ethanol, 10:1) to afford amino alcohol **13** (130 mg, 64%), identical spectroscopically to that obtained previously:[14] ^{1}H NMR 2.45−2.63 (2H, m), 2.73−2.91 (2H, m), 4.13 (1H, d, J = 4 Hz), 4.84 (1H, d, J = 4 Hz), 5.92 (4H, s), 6.51 (1H, s), 6.68−6.80 (4H, m).

Addition Product 14 was prepared by the general procedure, 49% yield: $[\alpha]_D$ −37.42 (c = 1.4, CH_2Cl_2); ^{1}H NMR 0.83 (3H, s), 0.86 (3H, s), 1.00 (3H, s), 0.90−1.10 (2H, m), 1.40−1.80 (3H, m), 1.95 (1H, m), 1.25−1.40 (1H, m), 2.80−2.90 (1H, m), 3.25−3.35 (1H, m), 3.85 (3H, s), 3.90 (3H, s), 4.12 (1H, d, J = 9.7 Hz), 4.45 (1H, d, J = 9.7 Hz), 5.09 (1H, s), 5.40 (1H, s), 5.90 (2H, s), 6.20−6.30 (1H, m), 6.45 (1H, s), 6.50−6.62 (2H, m), 6.80−6.90 (1H, m); ^{13}C NMR 164.5, 147.9, 147.6, 147.0, 146.6, 135.2, 127.8, 125.5, 120.1, 110.7, 110.5, 107.6, 107.3, 100.6, 92.9, 81.6, 72.9, 63.3, 56.0, 55.8, 49.3, 48.3, 46.4, 41.8, 31.9, 27.8, 25.5, 23.5, 18.9, 11.4; IR 1630; MS 521 (MH^+), 369, 192 (100%). Anal. Calcd for $C_{30}H_{36}N_2O_6$: C, 69.23; H, 6.92. Found: C, 68.98; H, 6.95.

Oxazolidinone 16. To a suspension of $LiAlH_4$ (146 mg, 3.85 mmol) in 10 mL of THF was added dropwise a solution of **14** (400 mg, 0.77 mmol) in 10 mL of THF at 0 °C. The reaction mixture was warmed to rt and then refluxed for 1 d. After being cooled 0 °C, the mixture was diluted with an equal volume of ether. The unreacted $LiAlH_4$ was decomposed by the dropwise addition of water and 10% NaOH.[59] The solid was filtered, and the filtrate was washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2:ethanol, 10:1) to afford amino alcohol **15**. To a solution of **15** (200 mg, 0.58 mmol) and 0.5 mL of triethylamine in 10 mL of THF was added 0.36 mL of phosgene (0.69 mmol, 1.93 M solution in toluene). The mixture was stirred at rt for 2 h. Saturated Na_2CO_3 solution was added, and the solution was stirred for 30 min. The organic phase was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified with flash chromatography (CH_2Cl_2:ethanol, 20:1) to afford 200 mg of **16** (73% yield from **14**): $[\alpha]_D$ +57.2 (c = 2.0, CH_2Cl_2); ^{1}H NMR 2.50−2.62 (1H, m), 2.90−3.04 (1H, m), 3.07−3.20 (1H, m), 3.52 (3H, s), 3.80 (3H, s), 4.4.12−4.22 (1H, m), 5.24 (1H, d, J = 10.5 Hz), 5.77 (1H, d, J = 10.5 Hz), 5.86 (2H, s), 5.90 (1H, s), 6.42−6.50 (2H, m), 6.64 (2H, s); ^{13}C NMR 157.4, 148.0, 147.9, 147.8, 147.0, 129.2, 126.9, 122.5, 121.3, 111.6, 110.1, 107.7, 107.6, 101.2, 80.5, 59.3, 55.6, 39.5, 27.6; IR 1730; MS 369 (M^+), 191 (100). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.04; H, 5.15. Found: C, 64.75; H, 5.25.

***N*-Methylamino Alcohol 17.** To a suspension of $LiAlH_4$ (103 mg, 2.71 mmol) in 10 mL of THF was added a solution of compound **6** (200 mg, 0.54 mmol) in 5 mL of THF at 0 °C. The solution was warmed to rt and refluxed overnight. The solution was cooled to 0 °C and was diluted with an equal volume of ether. The unreacted $LiAlH_4$ was decomposed by the dropwise addition of water and 10% NaOH.[59] The solid was filtered, and the filtrate was washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2:ethanol, 10:1) to afford compound **17** (183 mg, 95%): $[\alpha]_D$ −7.92 (c = 3.7, CH_2Cl_2); ^{1}H NMR 2.50−2.70 (2H, m), 2.60 (3H, s), 2.70−2.80 (1H, m), 2.95−3.05 (1H, m), 3.47 (3H, s), 3.70 (1H, d, J = 3.1 Hz), 3.83 (3H, s), 5.02 (1H, d, J = 3.1 Hz), 5.80 (1H, s), 5.90 (2H, s), 6.55 (1H, s), 6.60−6.80 (3H, m); ^{13}C NMR 147.3, 146.3, 145.9, 135.5, 129.1, 123.9, 119.5, 111.8, 110.8, 107.7, 107.3, 100.7, 73.9, 70.1, 58.2, 55.6, 55.2, 50.5, 44.0, 28.1, 18.3; IR 3400 (OH); MS 358 (MH^+), 206 (100). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.23; H, 6.44. Found: C, 67.50; H, 6.48.

(+)-Corlumine. To a solution of well-dried alcohol **17** (43 mg, 0.12 mmol) in 3 mL of THF was added 0.28 mL of a BuLi solution (1.3 M in hexane) at −40 °C. The mixture was stirred at this temperature for 2 h. The solution turned deep red. The solution was then cooled to −78 °C, and through it a CO_2 stream was bubbled in for 10 min. The mixture was warmed to rt, and 5 mL of water was added. The aqueous phase was extracted twice with ether. The combined organic phases were washed with brine and dried with $MgSO_4$. Evaporation of the solvent afforded 20 mg (47%) of starting material. The aqueous phase was made acidic by the addition of concd HCl and was then stirred at 50 °C for 30 min. The solution was then made basic by the addition of saturated Na_2CO_3 solution and extracted three times with CH_2Cl_2. The combined organic phases were washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2:ethanol, 95:5) to afford 23 mg of (+)-corlumine (50%): $[\alpha]_D$ +70 (c = 0.75, CH_2Cl_2); ^{1}H NMR 2.30−2.40 (1H, m), 2.50−2.68 (2H, m), 2.60 (3H, s), 2.90−3.00 (1H, m), 3.70 (3H, s), 3.90 (3H, s), 4.10 (1H, d, J = 3.6 Hz), 5.64 (1H, d, J = 3.6 Hz), 6.15 (2H, s), 6.21 (1H, d, J = 8.0 Hz), 6.40 (1H, s), 6.60 (1H, s), 6.92 (1H, d, J = 8.0 Hz).

***N*-(2-Phenylethyl)formamide-*1*-^{13}*C*.** On the basis of the procedure in Fieser and Fieser,[60] sodium formate is converted to acetic formic anhydride, which is then used to acylate phenethylamine. To 200 mg (2.9 mmol) of finely grounded sodium ^{13}C-formate in 1 mL of ether was added 226 mg (2.9 mmol) of acetyl chloride at rt. The mixture was then stirred at rt overnight. To this solution were added 2 mL of THF and 701 mg (5.8 mmol) of phenethylamine at rt. The mixture was again stirred overnight at rt. The solid was then filtered and the filtrate concentrated. The residue was purified by flash chromatography (CH_2Cl_2:ethanol, 100:8). The product was obtained in 92% yield from sodium formate (400 mg). This compound was used immediately to prepare [1-^{13}C]tetrahydroisoquinoline by the procedure of Hesse.[45] Then, condensation with **2c** using the procedure described above afforded **3c** (1-^{13}C), which showed a molecular ion at m/z 245 and an enriched ^{13}C resonance at 47.1 ppm.

^{13}C NMR Spectra of *(S)*-[1-^{6}Li,1-^{13}C]-2-(4,5-Dihydro-4-isopropyl-2-oxazolyl)-1,2,3,4-tetrahydroisoquinoline. Compound **3c** (1-^{13}C) was distilled from calcium hydride under

(60) Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*; Wiley-Interscience: New York, 1969; Vol. 2, p 10.

reduced pressure (Kugelrohr oven) and dissolved in THF. The solution was transferred into a 10 mm NMR tube and cooled to −78 °C. To this solution was added BuLi [^{6}Li^{31}]. The whole operation was done under the protection of argon. The NMR tube was put into an NMR probe, and the temperature was lowered to −100 °C. After 10 min for thermal equilibration, the ^{13}C NMR spectra were recorded. After the temperature was changed incrementally, the system was equilibrated for 10 min and the magnet was reshimmed.

^{13}C NMR Spectra of [(*S*)-[1-^{13}C]-2-(4,5-Dihydro-4-isopropyl-2-oxazolyl)-1,2,3,4-tetrahydroisoquinolyl]magnesium Halide. To the lithium compound solution used above was added magnesium bromide etherate (or magnesium chloride in THF). The mixture was shaken at 0 °C for 20 min. The NMR tube was then put into the probe, and the NMR spectra were recorded as described above.

Acknowledgment. We are grateful for the support of this work by the National Institutes of Health (NIH) (Grant GM-37985) and by a Maytag fellowship to P.Z. NMR spectroscopy and MS instrumentation were purchased with the help of grants from NIH (Grants RR-03351 and RR-04680).

Supporting Information Available: Details for the DNMR calculations and 400 MHz ^{1}H NMR spectra of compounds **3g**, **9**, **10a,b**, **11a,b**, **12**−**14**, **16**−**17**, and corlumine (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be downloaded from the internet, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961164U