Effect of Ligand Structure in the Bisoxazoline Mediated Asymmetric Addition of Methyllithium to Imines

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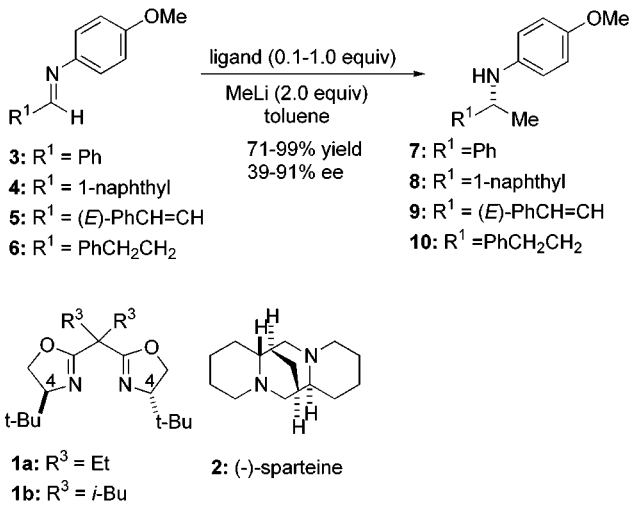
Introduction

The increasing importance of enantiomerically enriched amines in organic chemistry derives from their extensive use as auxiliaries,[1] resolving agents,[2] and intermediates[3] in the synthesis of both natural and unnatural compounds. Moreover, the need for a wider range of structurally diverse and enantiopure amines for solid-phase (combinatorial) synthesis of organic compounds constitutes a continuing challenge. Of the many strategies available for the synthesis of amines, one of the most attractive is the addition of organometallic reagents to C=N functionalities.[4] In comparison to the many successes reported for the enantioselective addition to carbonyl compounds,[5] alkylations of the corresponding azomethine compounds are more limited, but steadily growing.[6]

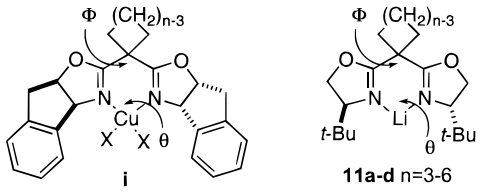
Several years ago, we showed that bisoxazolines[7] **1** and (−)-sparteine **2**, are excellent promoters for the addition of lithium reagents to aromatic, olefinic, and aliphatic aldimines (Scheme 1).[8] Ligands **1a** and **1b** promote the addition of methyl- and vinyllithium to imines **3**−**6**, to provide the desired amines in high yield (79−97%) and enantioselectivity (71−91% ee). For highly reactive species such as *n*-BuLi and PhLi, a more basic ligand, **2**, was necessary. With **2** as the promoter, the addition of *n*-BuLi and PhLi to imine **6** proceeded smoothly to afford the desired amines in 90% and 99% yield and 91% and 82% ee, respectively. Additionally, substoichiometric amounts of the ligands could be used, however with a attendant decrease in selectivity. Clearly, the structure and gross architecture of the ligand play a central role in the activation and stereoselection aspects of this process. In our original report, the primary variation in structure of the bisoxazoline was of the substituents at the C(4) stereogenic center. It was found that the bulkier groups gave enhanced stereoselectivity. In continuation of these studies we have undertaken a systematic examination of the influence of the bridging group by way of bond angle modulation and steric bulk.

Scheme 1



Results and Discussion

Effect of Ligand Bite Angle. A correlation between ligand geometry, specifically chelate bite angle, and enantioselectivity has been reported by several research groups.[9] Davies et al. found that variation of the ring size in spirocyclic bisoxazolines **i** provided different ligand geometries.[9b] As the spiro ring size decreased, the angle, Φ, correspondingly increased. The resulting change in the geometry influenced the stereochemical course of the copper-catalyzed, Diels−Alder reaction. We surmised that a similar structural change in **11** should affect the coordination angle of lithium, θ, which in turn, should have a direct effect on the course of the addition of alkyllithium reagents to aldimines.



Because of the wide application of bisoxazolines as bidentate ligands in numerous reactions, several simple methods for the synthesis of these compounds have been reported.[7,10] Given the basic structural features of the desired spirocyclic bisoxazolines **11a**−**d**, a route involving

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(5) (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Chapter 26.1.

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(7) (a) Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 542. (b) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (c) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.

(8) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797.

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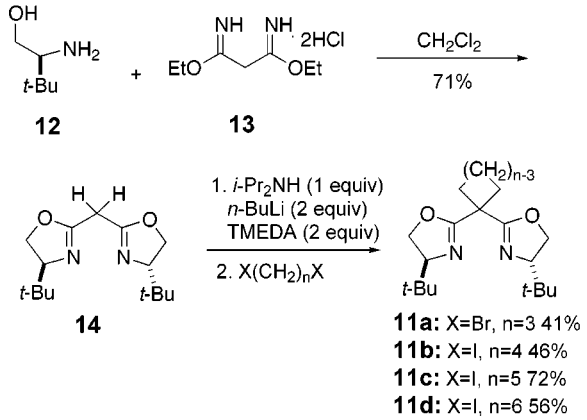
a common intermediate was envisioned (Scheme 2). All of the spirocyclic bisoxazolines in this study were derived from the unsubstituted parent compound **14**[11] which is easily accessible from the condensation of L-*tert*-leucinol, **12**, and diethyl malonimidate **13**.[12] Treatment of **14** with lithium diisopropylamide (LDA) at −78 °C followed by addition of an α,ω-diiodo- or dibromoalkane and warming to room temperature afforded the desired spirocyclic bisoxazolines in usable yields (41−72%).

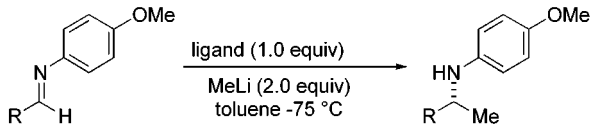
Scheme 2



With the desired spiro-bisoxazolines in hand, the addition of MeLi to imines **3**, **5**, and **6** promoted by **11a**−**d** could be surveyed, and the results are collected in Table 1. In our previous studies, we found that optimal yields and enantioselectivities were obtained when 2 equiv of MeLi was combined with 1 equiv of the bisoxazoline in toluene for 30 min at low temperature prior to addition of the imine. For this study, the imine was allowed to react with the preformed complex at −75 °C and the reaction was then quenched with methanol at that temperature.

Benzaldehyde imine **3** was the first substrate to be examined (Table 1, entries 1−4). The addition product **7** was isolated in high yield (82−97%) from each reaction;[13] however, only modest enantioselectivities were seen (51−73%). Interestingly three of the four ligands provided the amine with approximately the same ee; only the cyclopropyl ligand **11a** gave a significantly different result. A similar trend in enantioselectivity was seen in the reactions with cinnamyl and hydrocinnamyl imines, **5** and **6**. Again the desired amines were isolated in high yield (75−94%) and varying levels of enantioenrichment (4−94%) (Table 1, entries 5−12). As was seen in the reaction with **3**, cyclopropyl bisoxazoline **11a** afforded **9** and **10** in low ee, 2 and 44% respectively. The other bisoxazolines all promoted the reaction with a high degree of selectivity. If the geometric constraints of the spirocyclic bisoxazolines do produce geometrically unique complexes, the range of enantioselectivities seen suggests that the bite angle can have a dramatic effect on the course of the reaction.

Table 1. Asymmetric Addition of MeLi to Imines[a]

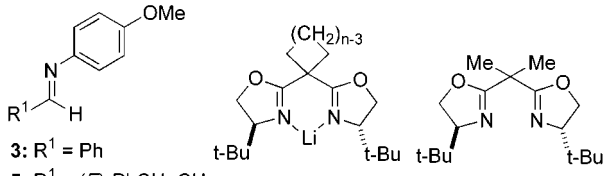


entry	imine	R	ligand	yield,[b] %	ee,[c] %
1	**3**	Ph	**11a**	82	51
2	**3**	Ph	**11b**	97	73
3	**3**	Ph	**11c**	94	71
4	**3**	Ph	**11d**	87	70
5	**5**	PhCH=CH	**11a**	93	2
6	**5**	PhCH=CH	**11b**	87	84
7	**5**	PhCH=CH	**11c**	92	90
8	**5**	PhCH=CH	**11d**	81	91
9	**6**	$PhCH_2CH_2$	**11a**	81	44
10	**6**	$PhCH_2CH_2$	**11b**	82	90
11	**6**	$PhCH_2CH_2$	**11c**	75	91
12	**6**	$PhCH_2CH_2$	**11d**	92	75

[a] MeLi (low halide, ether). All reactions performed on a 1.0 mmol scale. [b] Yield of chromatographically homogeneous material. [c] Determined by CSP HPLC analysis.

To better correlate the ligand geometries with the reaction selectivities, we carried out computational modeling of the ground state of the free ligand and the corresponding ligand/MeLi complexes. As noted before, it was predicted that as ring size increased the bridge angle would decrease. However from the results of both molecular mechanics (MM2) and semiempirical (PM3) calculations this trend did not manifest in the results of the geometry optimizations (Table 2). In particular, the spiro cyclopentyl compound **11c** gave an unexpectedly large bite angle of 111.8°. For comparison, the calculated angle and stereoselectivities for acyclic bisoxazoline **1c** are also provided (vide infra).

Table 2. Correlation of Enantioselectivity and Ligand Geometry (Bridge Angle)



ligand	**11a**	**11b**	**11c**	**11d**	**1c**
bridge angle (deg)	112.7	110.0	111.8	106.8	109.7
3	51	73	71	70	67
5	2	84	90	91	94
6	44	90	91	75	93

In all cases examined, the cyclopropyl-based ligand **11a** gave the lowest enantioselectivity (Table 2). This low selectivity may be due to a steric resistance to the complexation of MeLi. None of the many low energy conformations produced in the geometry minimization with molecular mechanics had the nitrogens in a coplanar or nearly coplanar relationship. Coplanarity of the nitrogens is believed to facilitate the complexation of Li by both sp^2 lone pairs, thereby increasing the rigidity of the system and, presumably, the selectivity of the ligand. From the remaining data it would appear that the optimal angle around the bridging carbon is between 109° and 111°. It seems that if the bridge angle is too large or small the enantioselectivity decreases, although the effect is

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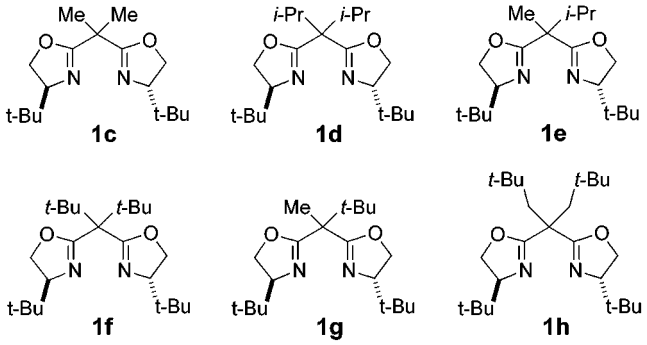
(13) In all cases the ligand was recovered after chromatography in 81−99% yield.

more pronounced at larger angles. There does not appear to be a dramatic correlation between enantioselectivity and any ligand geometry predicted by these calculations. Indeed it seems that the enantioselectivity of the reaction is rather more substrate dependent. Moreover, the nature of the complexation of MeLi is still unclear.

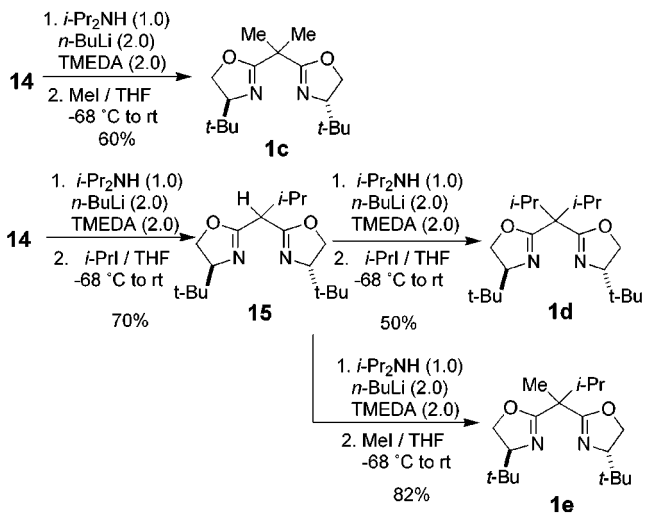
Chart 1



Effect of Bridge Group Size. In the initial survey of bisoxazolines, we investigated the effect of the size of the substituents in a cursory fashion by examining both ethyl (**1a**) and isobutyl groups (**1b**). This change had a small influence on the enantioselectivity which was also substrate dependent; i.e., **1b** was better with aromatic imines while **1a** was better with olefinic and aliphatic imines. To further explore this variable, we prepared the simplest member of the group, dimethyl substituted bisoxazoline **1c**, the bulkier representative **1d** and the hybrid of these two, the unsymmetrical bisoxazoline **1e** (Chart 1). The most congested member in this series, **1f**, was considered to be impracticably difficult to prepare; thus again, the hybrid analogue **1g** was targeted. Finally, in view of the success with **1b**, we also sought the more flexible neopentyl analogue **1h**.

The dimethyl, diisopropyl, and mixed bisoxazolines **1c**, **1d**, and **1e** were synthesized as described previously for compounds **11** (Scheme 3). Alkylation of **14** with methyl iodide in the presence of LDA afforded **1c** uneventfully in good yield. Analogous alkylation of **14** with LDA followed by isopropyl iodide afforded intermediate **15**, which was subsequently alkylated under the same conditions with either isopropyl iodide or methyl iodide to provide **1d** and **1e** in 35% and 57% overall yields, respectively.

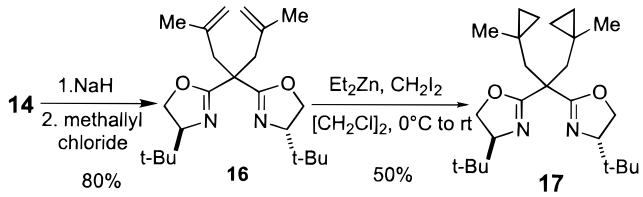
Scheme 3



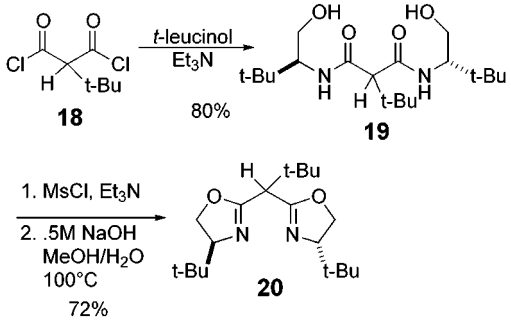
The synthesis of ligand **1h** began with the alkylation of **14** with methallyl chloride (Scheme 4). Simmons–Smith cyclopropanation[14] using either the traditional zinc–copper couple or Furakawa conditions afforded **17** in 50% yield. Although catalytic hydrogenation of cyclopropane rings is well documented,[15] the rings in **17** proved unreactive even under extreme pressures of H_2 (5000 psi) and with a variety of metal catalysts. Consequently, we decided to employ **17** instead of **1g** in the reaction with imines **3**, **5**, and **6** and methyllithium.

The preparation of unsymmetrical bisoxazoline **1g** began by combination of *tert*-butyl malonyl dichloride **18** with *tert*-leucinol **12** to afford bishydroxyamide **19** in 80% yield. Activation of the terminal hydroxyl groups with methanesulfonyl chloride, followed by treatment with base provided *tert*-butyl bisoxazoline **20**. Not surprisingly, **20** proved impossible to alkylate with methyl iodide (or methallyl halides as well).

Scheme 4



Scheme 5



The results from methyllithium addition to the three different imines in the presence of these variously substituted bisoxazolines are collected in Table 3 along with the results from our previous studies. The trends identified with **1a** and **1b** were followed at both ends of the spectrum. For benzaldehyde imine **3** (wherein bulkier group seemed to be beneficial), the smaller ligand **1c** gave the poorest selectivity, whereas the largest ligand **1d** gave the highest. The hybrid **1e** gave an intermediate selectivity, though somewhat closer to the lower end. Interestingly, the neopentyl and isobutyl ligands, **1h** and **1b**, gave the same selectivity. For the cinnamaldehyde (**5**) and hydrocinnamaldehyde (**6**) imines, the opposite trend was observed. In these cases, the smaller ligand **1c** gave the best selectivities whereas the larger ones (**1d** and **17**) gave the lowest. It is striking that the simple change from ethyl to methyl groups has such a beneficial effect.

Conclusions

Investigations into the effect that ligand architecture has on the bisoxazoline promoted addition of MeLi to

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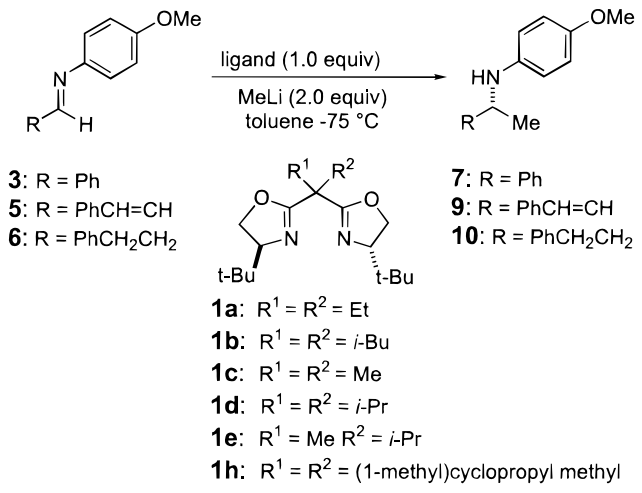
(15) Newham, J. *Chem. Rev.* **1963**, *63*, 123.

Table 3. Correlation of Enantioselectivity to Ligand Substituent



	ligand, enantioselectivity, % (yield, %)					
imine	**1a**	**1b**	**1c**	**1d**	**1e**	**17**
3	75 (95)	85 (95)	67 (90)	89 (87)	74 (97)	85 (85)
5	85 (79)	73 (90)	94 (73)	81 (77)	n/a	77 (87)
6	91 (96)	87 (97)	93 (81)	87 (77)	n/a	77 (92)

[a] MeLi (low halide, ether). All reactions performed on a 1.0 mmol scale. [b] Yield of chromatographically homogeneous material. [c] Determined by CSP HPLC analysis.

imines revealed that while ligand bite angle plays only a small role in the course of the reaction, the size of the bridging substituents has a dramatic effect on the reaction selectivity. From the data presented two generalizations can be made: (1) for reactions with aromatic imines, bisoxazolines with large groups provide amines in high enantiomeric excess, and conversely (2) high enantioselectivity is seen in reactions with olefinic and aliphatic imines when the promoters have small substituents. Further studies on the contribution of electronic effects on the stereochemical course of the addition as well as mechanistic investigation of the origin of catalysis and enantioselection are in progress.

Experimental Section

General Experimental Data (See the Supporting Information). General Procedure for the Synthesis of Spirocyclic Bisoxazolines. 1,1′-Bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)]cyclopropane (11a) To a solution of **14** (750 mg 2.8 mmol) in THF (50 mL) in a flame-dried, 100 mL, three-necked, round-bottom flask equipped with a stir bar, septum, thermometer, and nitrogen inlet were added TMEDA (850 μL, 5.6 mmol, 2.0 equiv) and *i*-Pr_2NH (400 μL, 2.8 mmol, 1.0 equiv). The solution was cooled in a dry ice/2-propanol bath (−75 °C internal). *n*-BuLi (3.8 mL of a 1.5 M solution in hexane, 5.6 mmol, 2.0 equiv) was added to the cold solution via syringe. The reaction mixture was warmed to −20 °C and stirred at that temperature for 30 min. The solution was cooled back below −70 °C, and 1,2-dibromoethane (243 μL, 2.8 mmol, 1.0 equiv) was added via syringe. After the addition, the cold bath was removed and the mixture was allowed to stir at room temperature for an additional 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (25 mL) and diluted with water (10 mL) to dissolve the resulting salts. The mixture was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with brine (1 × 75 mL), dried over $MgSO_4$, and concentrated to a thick oil. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 1/1) to give 338 mg (41%) of **11a** as white solid after Kugelrohr distillation. For **11a**: bp 125−130 °C (0.4 mmHg); mp 79.0−80.0 °C; $[\alpha]_D$ −83.8° ($CHCl_3$, c = 1.115); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (dd, J = 10.0, 8.6, 2H), 4.10 (dd, J = 8.6, 7.4, 2H), 3.82 (dd, J = 10.0, 7.2, 2H), 1.50 (m, 2H), 1.27 (m, 2H), 0.86 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.38, 75.22, 69.13, 33.82, 25.66, 18.19, 15.11; IR ($CHCl_3$) ν 2959, 2904, 2869, 1667, 1552, 1478, 1393, 1363. Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65; N, 9.58. Found: C, 69.92; H, 9.56; N, 9.81.

1,1′-Bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)]cyclobutane (11b): white solid; bp 125−130 °C (0.4 mmHg); mp 60.0−61.0 °C; $[\alpha]_D$ −69.8° ($CHCl_3$, c = 1.02); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (dd, J = 10.1, 8.7, 2H), 4.11 (dd, J = 8.6, 7.2, 2H), 3.89 (dd, J = 10.1, 7.1, 2H), 2.71 (m, 2H), 2.50 (m, 2H), 2.02 (pentet, J = 7.9, 2H), 0.89 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.19, 75.37, 69.27, 42.14, 33.92, 30.29, 25.67, 16.76; IR ($CHCl_3$) ν 2957, 2903, 2869, 1664. Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.74; H, 10.06; N, 9.22.

1,1′-Bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)]cyclopentane (11c): bp 125−130 °C (0.4 mmHg); mp 51.0−52.0 °C; $[\alpha]_D$ −63.4° ($CHCl_3$, c = 1.195); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.15 (dd, J = 10.1, 8.6, 2H), 4.08 (dd, J = 8.5, 7.1, 2H), 3.85 (dd, J = 10.0, 7.1, 2H), 2.38 (m, 2H), 2.12 (m, 2H), 1.71 (m, 4H), 0.87 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.96, 75.25, 69.04, 49.07, 35.38, 33.90, 25.66, 24.98; IR ($CHCl_3$) ν 2958, 2904, 2870, 1661. Anal. Calcd for $C_{19}H_{32}N_2O_2$: C, 71.21; H, 10.06; N, 8.74. Found: C, 71.28; H, 10.17; N, 8.83.

1,1′-Bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)]cyclohexane (11d): bp 140−150 °C (0.4 mmHg); mp 79.0−80.0 °C; $[\alpha]_D$ −55.9° ($CHCl_3$, c = 1.045); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (dd, J = 10.1, 8.8, 2H), 4.05 (dd, J = 8.6, 7.2, 2H), 3.87 (dd, J = 10.2, 7.1, 2H), 2.10 (m, 2H), 1.94 (m, 2H), 1.67 (m, 2H), 1.47 (m, 4H), 0.87 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.40, 75.51, 68.50, 43.13, 33.86, 32.50, 25.82, 25.41, 22.48; IR ($CHCl_3$) ν 2957, 2904, 2868, 1659. Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.24; N, 8.37. Found: C, 71.94; H, 10.36; N, 8.33.

General Procedure for the Addition of MeLi to Imines: (*R*)-*N*-(4-Methoxyphenyl)-α-methylbenzenemethanamine (7). A solution of **1c** (294 mg, 1.0 mmol) in toluene (10 mL) in a flame-dried, 50 mL, three-neck, round-bottom flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was cooled in a CO_2/2-propanol bath (−75 °C internal). MeLi (1.6 mL of a 1.27 M solution in low halide Et_2O, 2.0 mmol) was added to the solution via syringe and the resulting mixture was stirred at −75 °C for 30 min. A solution of imine **3** (211 mg, 1.0 mmol) in toluene (10 mL) was slowly added to the reaction mixture, maintaining an internal temperature below −70 °C. The resulting yellow solution was stirred at −75 °C for 2 h. The reaction was quenched at low temperature with MeOH (2.5 mL). The reaction was warmed to room temperature and diluted with water (10 mL). The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated to a yellow oil. Purification by chromatography (SiO_2, hexane/EtOAc, 4/1) afforded the amine 204 mg (90%) after Kugelrohr distillation. Further elution gave recovered **1c** (270 mg, 92%). Data for **7**: bp 150−160 °C (0.5 mmHg); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17−7.38 (m, 5H), 6.65−6.71 (m, 2H), 6.42−6.49 (m, 2H), 4.41 (q, J = 6.7, 1H), 3.79 (br s, 1H), 3.69 (s, 3H), 1.50 (d, J = 6.7, 3H); HPLC t_R(*R*)-**7**, 23.60 (83.5%); t_R(*S*)-**7**, 27.87 (16.5%) 67% ee (hexane/EtOH, 99.2/0.8, 0.5 mL/min).

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Supporting Information Available: Preparation and characterization of compounds **1c**−**e**,**h**, **11a**−**d**, **14**−**17**, **19**, and **20** is provided along with experimental details of all data presented in Tables 1 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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