Influence of the Aromatic Substituent on the Reactivity of (*R*)-*N*-Methyl-1-phenyl-2-(1-piperidinyl)ethanamine Cuprates in Enantioselective Conjugate Addition[1]

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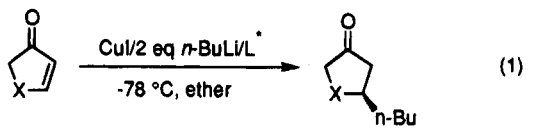
Introduction

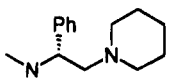
Enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates is a potentially useful synthetic transformation that has attracted a great deal of attention.[2] Even though many efforts have been made to find a method by which this transformation can be accomplished efficiently and catalytically in high enantiomeric excess for a broad variety of α,β-unsaturated substrates, little is known about the relationship between the structure of organometallic reagents used and the origins of enantioselectivity. Several years ago, we reported that scalemic lithium organo(amido)cuprates derived from copper(I) iodide and (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine, (*S*)-MAPP, promoted high enantioselection during the conjugate addition of alkyl and aryl moieties to some cycloalkenones (eq 1).[3]



(1)

X = $(CH_2)_m$ where m = 1-3 45 -97 % ee

L* = (S)-MAPP [(*S*)-*N*-Methyl-1-phenyl-2-(1-piperdinyl)ethanamine]



On the basis of our observations and evidence in the literature, we proposed that these scalemic lithium organo(amido)cuprates have a dimeric structure in solvents such as diethyl ether and dimethyl sulfide and that the enantioselectivity exhibited by these reagents originates in the structure of the dimer.[3d] In previous studies, we have modified various parts of the ligand in order to discern the influence of the ligand on the enantioselectivity of these reagents.[3] Recently, we further proposed

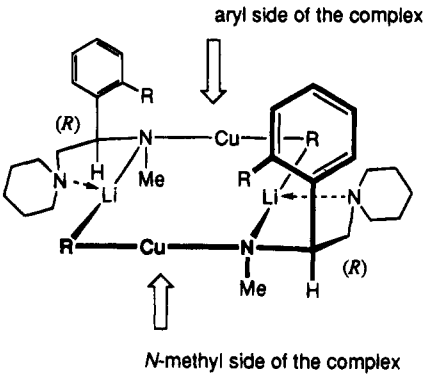
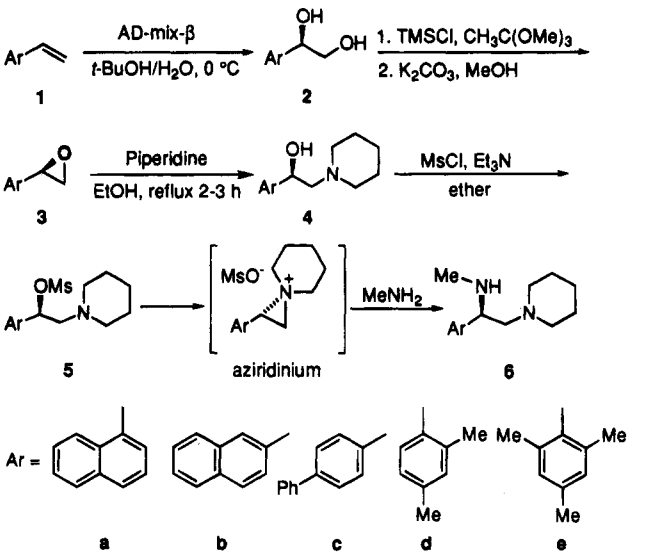


Figure 1. Proposed scalemic lithium organo(amido)cuprate structure for conjugate addition to enones.

Scheme 1



that the cycloalkenone approaches and interacts with the cuprate dimer from the aryl side of the cuprate dimer (Figure 1).[4]

We desired to know how changing the aryl group in chiral auxiliary would affect the enantioselectivity of the conjugate addition to cycloalkenones by scalemic lithium organo(amido)cuprates. In order to learn more about the aryl group, we have synthesized five enantiomerically pure ligands and have evaluated their ability to affect enantioselective conjugate addition of an *n*-butyl group to 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone. This paper reports these new results.

Results and Discussion

Scheme 1 shows the procedure we used to synthesize the enantiomerically pure ligands **6a–e** in this study. They differ from the MAPP ligand in that the phenyl group in MAPP is replaced by either a naphthyl or a substituted phenyl group. The vinylaryl compounds **1** were obtained commercially (see Experimental Section) or by synthesis.[5] The olefins were oxidized using the Sharpless asymmetric dihydroxylation reaction[6] to provide the enantiomerically pure diols **2**. These diols were

† Deceased Feb 5, 1995. Inquiries concerning this paper should be directed to Professor Jerald S. Bradshaw at the BYU address.

(1) Part 6. For parts 1–5 see refs 3 and 4.

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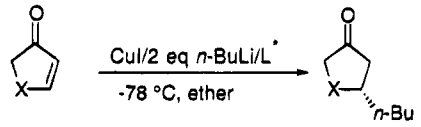
Table 1. Enantioselective Conjugate Addition of Lithium Organo(amido)cuprate to Cyclic Enones



L* = Chiral diamine ligands; **6a-e** X = $(CH_2)_m$ where m = 1-3

	2-cyclopentenone			2-cyclohexenone			2-cycloheptenone		
ligand	ee[a]	% yield[c]	*R/S*	ee[a]	% yield[c]	*R/S*	ee[b]	% yield[c]	*R/S*
6a	10	58	*R*	60	50	*R*	73	44	*R*
6b	44	65	*R*	85	70	*R*	95	60	*R*
6c	40	59	*R*	74	55	*R*	90	61	*R*
6d	37	47	*R*	65	47	*R*	65	84	*R*
6e	18	50	*R*	45	35	*R*	30	59	*R*
6f[d]	45	50	*S*	92	83	*S*	97	63	*S*

[a] The diastereomeric purities of (+)-diethyl tartrate ketal were determined by GC. [b] The enantiomeric purities were determined by GC. [c] GC yields using *n*-dodecane as an internal standard. [d] **6f** is (*S*)-MAPP.

transformed to the epoxides **3**[7] and then treated with 2 equiv of piperidine in refluxing ethanol to generate the 1-aryl-2-amino alcohols **4** which were then reacted with methanesulfonyl chloride and triethylamine to form mesylates **5**.[8] Treatment of the crude mesylates with aqueous methylamine in ether affords the enantiomerically pure ligands **6a–e**. This final step proceeds with retention of configuration, presumably through an intermediate aziridinium species.[8] The enantiomeric purities of these ligands were determined by ^{19}F NMR analysis of the corresponding Mosher amides.[9] The enantiomeric excesses of these ligands were found to be >95%.

Table 1 summarizes the results of conjugate addition reactions using cuprates prepared from enantiomerically pure ligands **6a–e** and BuLi. These results are compared with previous results obtained by using the (*S*)-MAPP ligand **6f** with the same substrates: 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone. Of the ligands tested, the 2-naphthyl-substituted ligand **6b** is the best; the ee's and yields of the conjugate additions to 2-cyclopentenone and 2-cycloheptenone are almost identical to the results obtained with (*S*)-MAPP. However, ligand **6b** is a crystalline solid that can be easily purified by recrystallization. (MAPP is an oil.) We have analyzed **6b** by X-ray diffraction and shown it to have the correct configuration. Interestingly, the cuprate derived from the 1-naphthyl-substituted ligand **6a** exhibited lower enantiomeric excesses and yields of (*R*)-3-butylcyclohexanone and 3-butylcycloheptanone relative to the (*S*)-MAPP-derived cuprates. In the series **6f**, **6d**, and **6e** where the aryl substituent is changed from phenyl to 2,4-dimethylphenyl to 2,4,6-trimethylphenyl, the decrease in ee of 3-butylcyclopentanone, 3-butylcyclohexanone, and 3-butylcycloheptanone can be attributed to the steric hinderance of the Me substituents on the aryl group. In their observations, Hammond and Hawthorne found that in the nitration of alkylbenzenes, the steric effect of an *o*-methyl substituent on the aryl group caused the ratio of 2 to 4 position products to be dramatically reduced.[10] The fact that there is a reduction in sterioselectivity as methyl groups are added in *ortho* positions (**6f** to **6d** to **6e**) indicates that greater steric bulk greatly interferes with the enantioselectivity of these reactions. This greater bulk may either prevent the dimer from forming efficiently or prevent the substrate from approaching the cuprate close enough to result in conjugate addition. A similar steric argument can be used to explain why 2-naphthyl-substituted ligand **6b** provides better enantioselectivity than 1-naphthyl-substituted ligand **6a**. Here, the second ring of naphthalene would provide a greater steric bulk in the 1-naphthyl derivative **6a**. The results obtained using the cuprate derived from the *para*-substituted 4-biphenyl ligand **6c** gave results comparable to the (*S*)-MAPP derived cuprate.

Overall, the results are consistent with our recent proposal that conjugate addition takes place with a dimeric reagent on the aryl side of the complex and that the aromatic substituents assume the primary role of defining the chiral topology responsible for the enantioselectivity manifest with these reagents (Figure 1).

Experimental Section

General. All cuprate conjugate additions were carried out under a positive atmosphere of dry N_2 or Ar using standard Schlenk techniques. Anhydrous ether for cuprate conjugate additions was dried by distillation from Na/benzophenone immediately before use. Compound **1a** was prepared according to the literature.[6] Compounds **1b**, **1c**, $K_2OsO_2(H_2O)_4$, and $(DHQD)_2$-PHAL were purchased from Aldrich Chemical Co. Compounds **1d** and **1e** were purchased from Lancaster Synthesis, Inc. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 200 MHz. ^{19}F NMR spectra for Mosher's amides were obtained at 500 MHz. The enantiomeric purity of 3-*n*-butylcycloheptanone was determined by GC using a 30 m, 0.25 mm i.d. β-cyclodextrin 120 column (Supelco). The diastereomeric purities of the ketals formed from 3-*n*-butylcyclopentanone and (+)-diethyl tartrate or from 3-*n*-butylcyclohexanone and (+)-diethyl tartrate were determined by GC using a 30 m, 0.32 mm i.d. DB1 column (J&W Scientific). The ketal formed from 3-*n*-butylcyclohexanone or 3-*n*-butylcyclopentanone with (+)-diethyl tartrate was prepared according to the procedure of Rossiter et al.[3d]

Typical Experimental Conditions for the Conjugate Addition to Enones. CuI (127 mg, 0.67 mmol) and chiral diamine (1 equiv) were added to an oven-dried Schlenk flask which was then equipped with a stir bar and a rubber septum and purged with several vacuum/N_2 cycles. Dry ether (distilled from Na/benzophenone) was added via syringe. The solution was cooled to −78 °C in a dry ice/isopropyl alcohol bath, and

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n-BuLi (2 equiv) was added via syringe. The reaction mixture was warmed slowly to −40 °C, stirred for 10 min, and then cooled to −78 °C. The enone (1 equiv) was then added neat dropwise via syringe to the reaction mixture. After ca. 1 h, the reaction mixture was quenched with a saturated 9:1 NH_4Cl:NH_4OH solution (15 mL). Dodecane (50 μL) was added as an internal standard, and the product was extracted into ether. The ether extract was washed with 1 N HCl, dried (Na_2SO_4), and analyzed by GC to obtain the yield and enantiomeric purity.[3]

(*R*)-1-(2-Naphthyl)-1,2-ethanediol, 2b. The procedure of Sharpless et al. was used for the asymmetric dihydroxylation reactions.[7] The following procedure is representative of the procedures used. A 1 L three-necked flask was charged with $K_3Fe(CN)_6$ (64.0 g, 194 mmol), K_2CO_3 (26.8 g, 194 mmol), potassium osmate(VI) dihydrate (47.7 mg, 0.13 mmol), and $(DHQD)_2$-PHAL (504 mg, 0.65 mmol). The flask was fitted with a mechanical stirrer and charged with a 1:1 mixture of *tert*-butyl alcohol and water (600 mL). The mixture was stirred until a homogenous solution was attained and then cooled in a cold bath to 0 °C. Upon cooling, some precipitation of the reaction ingredients occurred. 2-Vinylnaphthalene (10.0 g, 65 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at 0 °C for ca. 12 h. Following this, sodium sulfite (97 g) was added to the reaction mixture with stirring and gradual warming to room temperature. Ethyl acetate (ca. 100 mL) was added to the mixture. After resolution of the organic and aqueous phases, the aqueous phase was removed and extracted two times with 100-mL portions of ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated by rotary evaporation to give a crude solid product. The product was purified by flash chromatography (silica gel, 1:1 EtOAc/hexanes) to give a white crystalline product (6.5 g, 54%): mp 135−136 °C (lit.[11] mp 134−135 °C); $[\alpha]_D$ −43.9° (*c* 1.00, MeOH) (lit.[12] $[\alpha]^{21}_D$ −33.7° (*c* 1.20, EtOH); IR (KBr) 3298, 3010, 2873, 1362, 1085, 828, 740 cm^{-1}; ^1H NMR δ 3.7−3.9 (m, 2H), 4.90−5.10 (dd, 1H), 7.40−7.60 (m, 3H), 7.80−7.90 (m, 4H); ^{13}C NMR δ 68.0, 74.4, 124.4, 124.7, 125.5, 125.8, 127.4, 127.6, 127.7, 132.7, 133.0, 139.3.

(*R*)-1-(1-Naphthyl)-1,2-ethanediol, 2a. This material was prepared from **1a** (6.0 g, 38.0 mmol) using the method described for **2b** to give a white crystalline product (5.3 g, 88%): mp 85−86 °C (lit.[12] mp 90−139 °C); $[\alpha]_D$ −76.8° (*c* 1.00, MeOH) (lit.[11] $[\alpha]^{10}_D$ −81° (*c* 1.36, EtOH); IR (KBr) 3384, 3015, 2924, 1459, 1074, 1021, 796, 778 cm^{-1}; ^1H NMR δ 2.20 (s, 1H), 2.65 (s, 1H), 3.90−4.10 (m, 2H), 5.65 (d, 1H), 7.55 (m, 3H), 7.60−7.80 (m, 3H), 8.10−8.20 (m, 1H); ^{13}C NMR δ 68.0, 72.1, 123.2, 124.0, 126.0, 126.1, 126.7, 128.7, 129.4, 130.9, 134.1, 136.6.

(*R*)-1-(4-Phenylphenyl)-1,2-ethanediol, 2c. This material was prepared from **1c** (6.0 g, 33.0 mmol) using the method described for **2b** to give a white crystalline product (4.7 g, 57%): mp 150−152 °C; $[\alpha]_D$ −38.9° (*c* 1.03, $CHCl_3$); IR (KBr) 3320, 3040, 1487, 1396, 1076, 831, 760, 689 cm^{-1}; ^1H NMR δ 2.10 (dd, 1H), 2.50 (d, 1H), 3.85, (m, 2H), 4.85 (dd, 1H), 7.30−7.50 (m, 5H), 7.55−7.65 (m, 4H); ^{13}C NMR δ 68.5, 74.9, 127.0, 127.6, 127.8, 127.9, 129.3, 141.5.

(*R*)-1-(2,4-Dimethylphenyl)-1,2-ethanediol, 2d. This material was prepared from **1d** (5.0 g, 37.8 mmol) using the method described for **2b** to give a white crystalline product (5.3 g, 85%): mp 64−65 °C; $[\alpha]_D$ −75.8° (*c* 1.24, $CHCl_3$); IR (KBr) 3263, 3020, 2931, 1261, 1087, 1026, 796 cm^{-1}; ^1H NMR δ 2.30 (s, 6H), 2.71 (s, 1H), 2.90 (s, 1H), 3.55−3.75 (m, 2H), 5.00−5.05 (dd, 1H), 6.90−7.10 (m, 2H), 7.35 (d, 1H); ^{13}C NMR δ 18.9, 20.9, 66.9, 71.3, 125.6, 126.9, 131.2, 134.7, 135.5, 137.4.

(*R*)-1-(2,4,6-Trimethylphenyl)-1,2-ethanediol, 2e. This material was prepared from **1e** (5.0 g, 34.2 mmol) using the method described for **2b** to give a white crystalline product (5.0 g, 80%): mp 106−107 °C; $[\alpha]_D$ −53.0° (*c* 1.01, $CHCl_3$); IR (KBr) 3288, 3030, 2974, 1449, 1405, 1090, 1010, 882, 857, 799 cm^{-1}; ^1H NMR δ 2.20 (s, 3H), 2.31 (s, 3H), 2.45 (s, 2H), 3.60−4.10 (m, 2H), 5.28 (dd, 1H), 6.80 (s, 2H); ^{13}C NMR δ 21.2, 31.7, 65.1, 73.1, 130.7, 133.0, 137.1, 137.7.

(*R*)-2-(2-Naphthyl)oxirane, 3b. The oxiranes, **3a−e**, were prepared from the corresponding diols using the procedure of Kolb and Sharpless.[7] The following is representative of the procedures used. Trimethylsilyl chloride (0.85 mL, 6.7 mmol) was added slowly to a solution of **2b** (5.1 g, 27 mmol) and $CH_3C(OMe)_3$ (0.91 mL, 6.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. The residue was dissolved in dry MeOH (150 mL) and treated with K_2CO_3 (9.0 g, 65 mmol). The resulting solution was stirred vigorously at rt for 2 h and then filtered. The residue was dissolved in CH_2Cl_2 (200 mL), filtered, and concentrated under reduced pressure at rt. The residue was further purified by flash chromatography (silica gel, 1:3 EtOAc/hexanes) to give the product as a white crystalline solid (2.7 g, 60%): mp 65−66 °C (lit.[13] mp 57−58 °C (racemic)); ^1H NMR δ 2.90 (dd, 1H), 3.23 (dd, 1H), 4.05 (dd, 1H), 7.30−7.50 (m, 3H), 7.85 (m, 4H); ^{13}C NMR δ 51.8, 53.1, 123.1, 125.7, 126.6, 126.8, 128.3, 133.7, 133.8, 124.5.

(*R*)-2-(1-Naphthyl)oxirane, 3a. This material was prepared from **2a** (3.2 g, 17.0 mmol) using the method described for **3b** to give a white solid (2.4 g, 86%): mp 85−86 °C; ^1H NMR 2.85 (dd, 1H), 3.20 (dd, 1H), 4.10 (dd, 1H), 7.35−7.60 (m, 4H), 7.80−7.90 (m, 2H), 8.10 (m, 1H).

(*R*)-2-(4-Phenylphenyl)oxirane, 3c. This material was prepared from **2c** (4.3 g, 20.0 mmol) using the method described for **3b** to give a white solid (3.3 g, 85%): mp 115−117 °C (lit.[14] mp 96−97 °C (racemic)); ^1H NMR δ 2.80 (dd, 1H), 3.20 (dd, 1H), 3.90 (dd, 1H), 7.30−7.40 (m, 5H), 7.60 (m, 4H); ^{13}C NMR δ 66.8, 68.7, 124.0, 124.5, 125.5, 125.9, 127.7, 127.9, 128.0, 133.0, 133.3, 139.9.

(*R*)-2-(2,4-Dimethylphenyl)oxirane, 3d. This material was prepared from **2d** (6.2 g, 38.0 mmol) using the method described for **3b** to give a white solid (3.9 g, 70%): ^1H NMR δ 2.30 (s, 3H), 2.34 (s, 3H), 2.65 (dd, 1H), 3.10 (dd, 1H), 3.90 (dd, 1H), 6.95−7.10 (m, 3H); ^{13}C NMR δ 19.1, 25.5, 50.5, 50.6, 51.0, 124.6, 127.2, 131.1, 133.3, 136.6, 137.7.

(*R*)-2-(2,4,6-Trimethylphenyl)oxirane, 3e. This material was prepared from **2e** (6.2 g, 34.0 mmol) using the method described for **3b** to give a white solid (4.2 g, 76%): mp 40−42 °C (lit.[15] mp 29 °C (racemic)); ^1H NMR δ 2.25 (s, 3H), 2.40 (s, 3H), 2.74 (dd, 1H), 3.15 (dd, 1H), 3.90 (t, 1H), 6.85 (s, 2H); ^{13}C NMR δ 20.1, 21.4, 49.1, 51.4, 129.2, 131.5, 137.7, 137.9.

(*R*)-1-(2-Naphthyl)-2-(1-piperidinyl)ethanol, 4b. The ethanols, **4a−e**, were prepared by the following method. To a solution of **3b** (2.7 g, 16 mmol) in EtOH (50 mL) was added piperidine (2.6 mL, 26 mmol) in one portion. The reaction mixture was refluxed for 2−3 h and then concentrated under reduced pressure to give the crude product. This was further purified by chromatography (silica gel, 1:3 EtOAc/hexanes) to afford a white crystalline solid (2.3 g, 62%): mp 110−112 °C; $[\alpha]_D$ −66.4° (*c* 1.00, $CHCl_3$); IR (KBr) 3378, 3015, 2928, 1443, 1061, 1032, 861, 820, 749 cm^{-1}; ^1H NMR δ 1.45−1.75 (m, 6H), 2.35−2.77 (m, 1H), 4.30 (s, 1H), 4.90 (dd, 1H), 7.30−7.50 (m, 3H), 7.80 (d, 4H); ^{13}C NMR δ 24.8, 26.7, 54.9, 67.3, 124.5, 125.0, 126.1, 126.4, 128.2, 128.5, 133.5, 134.0, 140.5.

(*R*)-1-(1-Naphthyl)-2-(1-piperidinyl)ethanol, 4a. This material was prepared from **3a** (2.4 g, 14.0 mmol) using the method described for **4b** to give a white solid (1.4 g, 40%): mp 100−101 °C, ^1H NMR δ 1.35−1.55 (m, 6H), 2.40−2.65 (m, 7H), 4.85 (dd, 1H), 7.45 (m, 3H), 7.80 (m, 4H); ^{13}C NMR δ 24.8 26.6, 27.0 55.0, 67.3, 69.2, 124.5, 125.0, 126.5, 128.0, 128.2, 128.4, 128.5, 133.5, 133.7, 140.4.

(*R*)-1-(4-Phenylphenyl)-2-(1-piperidinyl)ethanol, 4c. This material was prepared from **3c** (4.0 g, 20.0 mmol) using the method described for **4b** to give white needles (2.6 g, 46%): mp 107−108 °C (lit.[16] 120 °C (racemic)); $[\alpha]_D$ −57.8° (*c* 0.53, $CHCl_3$); IR (KBr) 3130, 3050, 2933, 2801, 1483, 1119, 1093, 1043, 832, 763 cm^{-1}; ^1H NMR δ 1.55−1.75 (m, 6H), 2.30−2.83 (m, 6H), 4.35 (s, 1H), 4.64 (dd, 1H), 7.30−7.40 (m, 5H), 7.50−7.60 (m, 4H); ^{13}C NMR δ 24.7, 26.6, 55.0, 67.4, 69.0, 126.8, 127.6, 127.7, 129.9, 140.8, 141.5, 142.0.

(*R*)-1-(2,4-Dimethylphenyl)-2-(1-piperidinyl)ethanol, 4d. This material was prepared from **3d** (3.9 g, 26.0 mmol) using

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(16) Work, T. S. *J. Chem. Soc.* **1940**, 1315.

the method described for **4b**. Purification by Kugelrohr distillation (158–160 °C, 1 mmHg) afforded a light yellow oil (4.5 g, 73%): IR (neat) 3416, 3050, 2932, 1614, 1499, 1451, 1155, 1116, 1032, 817, 755 cm^{-1}; ^1H NMR δ 1.30–1.65 (m, 6H), 2.30 (s, 3H), 2.42 (s, 3H), 2.50–2.70 (m, 4H), 2.75 (m, 1H), 3.50–3.90 (m, 2H), 4.90 (dd, 1H), 6.90–7.10 (m, 2H), 7.40 (d, 1H).

(*R*)-1-(2,4,6-Trimethylphenyl)-2-(1-piperidinyl)ethanol, 4e. This material was prepared from **3e** (5.2 g, 32.0 mmol) using the method described for **4b**. Purification by Kugelrohr distillation (138–140 °C, 0.5 mmHg) afforded a light yellow oil (5.8 g, 73%): $[\alpha]_D$ +27.8° (*c* 1.01, $CHCl_3$); IR (KBr) 3385, 3040, 2929, 1610, 1441, 1116, 1039, 850, 756 cm^{-1}; ^1H NMR δ 1.30–1.65 (m, 6H), 2.30 (s, 3H), 2.35–2.62 (m, 13H), 3.70–3.96 (m, 3H), 5.23 (dd, 1H), 6.80 (s, 2H); ^{13}C NMR δ 21.3, 25.4, 26.7, 27.0, 53.5, 64.3, 66.4, 130.6, 134.1, 136.6, 137.5.

(*R*)-*N*-Methyl-1-(2-naphthyl)-2-(1-piperidinyl)ethanamine, 6b. The ethanamines, **6a–e**, were prepared from the corresponding 1-aryl-2-amino alcohols, **4a–e**, using the procedure of Dieter et al.[8] The following experimental procedure is representative of those used. To a stirred solution of **4b** (0.84 g, 3.2 mmol) in anhyd ether (15 mL) were added, dropwise at 0 °C, Et_3N (0.97 g, 9.6 mmol) and MsCl (0.73 g, 6.4 mmol). Stirring was continued for 0.5 h. To this solution was added, with stirring overnight at rt, Et_3N (0.65 g, 6.4 mmol) and $MeNH_2$ in water (4 mL of a 40% solution). The organic and aqueous layers were separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed successively with 5% $NaHCO_3$ and water. The ether extracts were dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 1:3 EtOAc/hexanes) and then recrystallized from hexane to afford white needles (0.76 g, 89%): mp 119–120 °C; $[\alpha]_D$ −66.4° (*c* 1.31, $CHCl_3$); IR (KBr) 3319, 3060, 2942, 2778, 1466, 1120, 862, 824, 744 cm^{-1}; ^1H NMR δ 1.55–1.75 (m, 6H), 2.32 (m, 4H), 2.50–2.60 (m, 3H), 3.80 (dd, 1H), 7.40–7.50 (m, 3H), 7.75–7.90 (m, 4H); ^{13}C NMR δ 25.0, 26.7, 35.3, 55.4, 63.0, 67.1, 126.0, 126.2, 126.3, 126.7, 128.1, 128.2, 128.5, 133.5, 134.0, 140.8; CIMS *m/z* 269 ($M^+ + 1$, 3), 170 (30), 98 (100). Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.60; H, 8.89; N, 10.51. Found: C, 80.57; H, 8.86; N, 10.57.

(*R*)-*N*-Methyl-1-(1-naphthyl)-2-(1-piperidinyl)ethanamine, 6a. This material was prepared from **4a** (1.4 g, 5.6 mmol) using the method described for **6b**. Purification by chromatography (silica gel, 1:1 EtOAc/hexanes) and then recrystallization from hexanes afforded a white crystalline solid (1.0 g, 67%): mp 82–83 °C; $[\alpha]_D$ −169° (*c* 0.98, $CHCl_3$); IR (KBr) 3331, 3048, 2932, 2803, 1427, 1139, 1101, 992, 794, 776 cm^{-1}; ^1H NMR δ 1.40–1.65 (m, 6H), 2.42 (s, 3H), 2.45–2.70 (m, 7H), 4.55 (dd, 1H), 7.40–7.50 (m, 3H), 8.18 (d, 1H); ^{13}C NMR δ 25.0, 26.7, 35.4, 55.3, 58.3, 66.2, 123.1, 124.5, 125.6, 126.1, 126.4, 127.7, 127.9, 129.5, 132.3, 134.5; CIMS *m/z* 269 ($M^+ + 1$, 35), 179 (64), 98 (100). Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.59; H, 8.95; N, 10.46. Found: C, 80.58; H, 8.85; N, 10.55.

(*R*)-*N*-Methyl-1-(4-phenylphenyl)-2-(1-piperidinyl)ethanamine, 6c. This material was prepared from **4c** (2.6 g, 9.2 mmol) using the method described for **6b**. Purification by chromatography (silica gel, 1:1 EtOAc/hexanes) and then recrystallization from hexanes to afford a light-yellow crystalline solid (1.8 g, 65%): mp 92–93 °C; $[\alpha]_D$ −88.3° (*c* 1.20, $CHCl_3$); IR (KBr) 3312, 3060, 2914, 1778, 1484, 1434, 1159, 1110, 837, 732, 693 cm^{-1}; ^1H NMR δ 1.40–1.70 (m, 6H), 2.32 (m, 6H), 2.40–2.50 (m, 4H), 3.70 (dd, 1H), 7.30–7.50 (m, 5H), 7.60 (m, 4H); ^{13}C NMR δ 25.1, 26.7, 35.4, 35.8, 62.7, 67.3, 127.6, 128.4, 129.2, 140.5, 141.6, 142.4; CIMS *m/z* 295 ($M^+ + 2$, 5), 196 (58), 98 (100). Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.60; H, 8.80; N, 9.60. Found: C, 81.60; H, 8.70; N, 9.70.

(*R*)-*N*-Methyl-1-(2,4-dimethylphenyl)-2-(1-piperidinyl)-ethanamine, 6d. This material was prepared from **4d** (2.6 g, 9.2 mmol) using the method described for **6b**. Purification by Kugelrohr distillation (203–205 °C, 1 mmHg) afforded a light yellow oil: $[\alpha]_D$ −128° (*c* 1.20, $CHCl_3$); IR (neat) 3320, 3030, 2935, 1496, 1440, 1348, 1153, 1108, 826, 755 cm^{-1}; ^1H NMR δ 1.35–1.55 (m, 6H), 2.20–2.35 (m, 14H), 2.50–2.60 (m, 2H), 3.90 (dd, 1H), 6.90–7.10 (m, 2H), 7.40 (d, 1H); ^{13}C NMR δ 19.6, 21.5, 25.1, 26.7, 35.3, 55.4, 58.0, 66.2, 126.8, 127.5, 131.6, 136.1, 136.3, 137.7; CIMS *m/z* 247 (M + 1, 100), 216 (40), 148 (18). Anal. Calcd for $C_{16}H_{26}N_2$: C, 78.05; H, 10.58; N, 11.37. Found: C, 77.89; H, 10.45; N, 11.66.

(*R*)-*N*-Methyl-1-(2,4,6-trimethylphenyl)-2-(1-piperidinyl)-ethanamine, 6e. This material was prepared from **4e** (5.9 g, 23.0 mmol) using the method described for **6b**. Purification by Kugelrohr distillation (195–197 °C, 0.5 mmHg) afforded a light-yellow crystalline product (2.3 g, 39%): mp 46–47 °C; $[\alpha]_D$ −69° (*c* 1.10, $CHCl_3$); IR (KBr) 3307, 3055, 2933, 2778, 1607, 1439, 1302, 1110, 851, 786 cm^{-1}; ^1H NMR δ 1.35–1.60 (m, 6H), 2.20–2.30 (d, 12H), 2.50–2.80 (m, 8H), 4.20 (dd, 1H), 6.85 (s, 2H); ^{13}C NMR δ 21.2, 21.4, 21.8, 25.1, 26.8, 35.5, 55.2, 58.8, 63.1, 129.5, 131.8, 134.6, 136.2, 137.5, 138.3; CIMS *m/z* 261 ($M^+ + 1$, 2), 162 (88), 98 (100). Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.40; H, 10.80; N, 10.80. Found: C, 78.54; H, 10.63; N, 10.82.

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Registry numbers provided by the author: **2a**, 16651-65-3, 13603-64-3; *rac*-**2b**, 13603-65-1; **2e**, 139016-19-6; **3b**, 20861-99-8; **3c**, 36099-26-0; **3d**, 141303-36-8; **3e**, 50447-68-2; **4c**, 100462-61-1, 63992-40-5.

Supporting Information Available: Spectra for **2a–e**, **3a–e**, **4a–e**, and **6a–e** (57 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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