JOC*Note*

Regio- and Stereospecific Syntheses of *syn*- and *anti*-1,2-Imidazolylpropylamines from the Reaction of 1,1′-Carbonyldiimidazole with *syn*- and *anti*-1,2-Amino Alcohols

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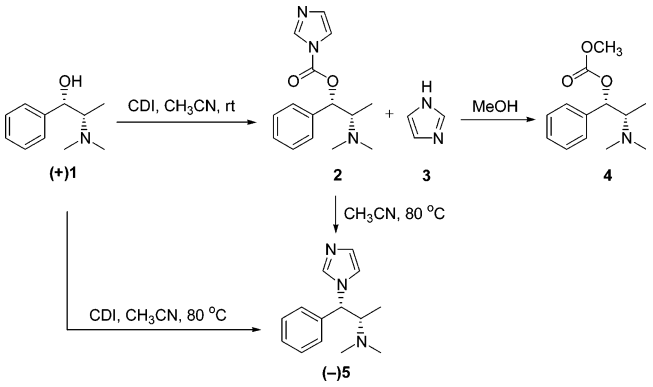
Abstract: The regio- and stereospecific conversion of *syn*- and *anti*-1,2-amino alcohols to their respective *syn*- and *anti*-1,2-imidazolylpropylamines via treatment with 1,1′-carbonyldiimidazole is described. The rationale behind the regio- and stereospecific nature as well as the generality of the reaction is discussed.

The imidazole group is an important heteroaryl residue found in a wide variety of biologically active and medicinally significant molecules, comprising several classes of derivatives that can be found in fungicides,[1] histamine H_2-receptor antagonists,[2] and anticancer agents.[3] Several methods are available for the construction as well as incorporation of an imidazole moiety,[4] with one of the more direct methods involving the reaction of a suitable alcohol with carbonyldiimidazole.[3,5] Literature reports concerning the generality of the CDI/alcohol reaction include the following observations: (1) the reaction proceeds with retention of configuration via an S_Ni mechanism;[5c] (2) the reaction proceeds via an S_N2 mechanism with inversion of configuration;[3d] (3) the reaction proceeds via an S_Ni or double-inversion mechanism with retention of configuration when applied to amino alcohol systems;[3c,5d] and (4) the reaction, in certain instances, does not proceed past the imidazolyl-derived carbamate and does not afford the alkylated imidazolyl product.[5b] With the reported variability in the reaction and our general need, in connection with other studies, to synthesize compounds within this general class, we embarked on, to our knowledge, the first systematic model study designed to test not only the feasibility of preparing both *syn*- and *anti*-1,2-imidazolylpropylamines from their respective *syn*- and *anti*-1,2-aminopropanols but also the regio- and stereochemical implications of the reaction based upon the presence of a neighboring tertiary amino moiety (dialkylamino- and anilino-derived).

SCHEME 1



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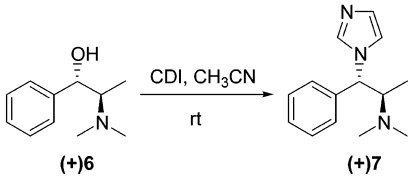

2-Dimethylamino-1-phenylpropan-1-ol, based on the commercial availability of both optically pure *syn*- and *anti*-isomers (+)-**1** and (+)-**6**, was chosen as our model system. With a general respect for the various plausible routes through which the reaction could proceed,[3,5] we embarked on the chemistry by first reacting (1*S*,2*S*)-(+)-*N*-methylpsuedoephedrine **1** with CDI in acetonitrile at room temperature (Scheme 1). After 8 h, imidazolyl-derived carbamate **2** was isolated as the sole product (quenching the reaction with methanol afforded methyl carbonate **4**). Interestingly, under the same conditions, (1*S*,2*R*)-(+)-*N*-methylephedrine **6** afforded exclusively *anti*-imidazolylpropylamine (+)**7** in 85% yield (Scheme 2). With such a promising result, we returned to *syn*-amino alcohol (+)-**1** and discovered that heating the reaction to 80 °C for 8 h afforded exclusively syn-imidazolylpropylamine (−)-**5** in 76% yield. We also discovered that heating imidazolylcarbamate **2** in acetonitrile at 80 °C for 8 h afforded *syn*-imidazolylpropylamine (−)-**5**. The stereochemistry of both compounds (−)-**5** and (+)-**7** was validated by X-ray crystallography analysis, revealing that the *syn*-imidazolylpropylamino product was obtained from the *syn*-precursor and, likewise, the

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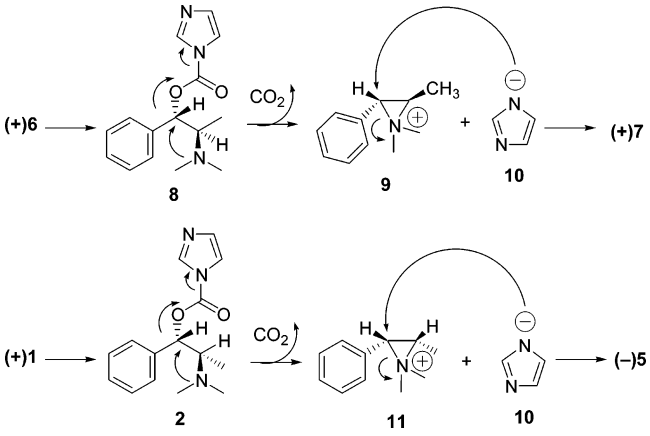
SCHEME 3

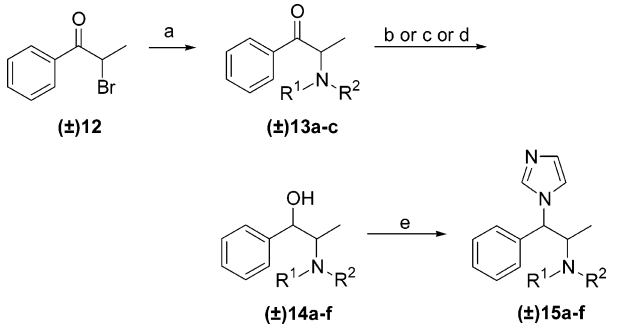


anti-imidazolylpropylamino product was obtained from the *anti*-precursor.

Based on the net retention of stereochemistry in each respective reaction, we postulate a mechanism involving double-inversion of configuration. The reaction proceeds by the initial formation of the imidazolyl-derived carbamate (**2** and **8**) followed by displacement of the carbamoyl group via neighboring group participation by the dimethylamino moiety to afford an aziridinium intermediate (**9** and **11**), which undergoes subsequent regiospecific ring opening at the benzylic position by attack of imidazolide **10** to afford the respective imidazolylpropylamino product ((+)-**7** and (−)-**5**) (Scheme 3).[6,7] Upon examining the two aziridinium species **9** and **11**, *trans*-aziridinium species **9** is derived from the *anti*-amino alcohol (+)-**6** and the more hindered *cis*-aziridinium species **11** is derived from the *syn*-amino alcohol (+)-**1**. As a consequence, the anti reaction proceeds at room temperature while the syn reaction requires higher temperatures to drive the reaction beyond the isolated imidazolylcarbamate intermediate **2**, therefore overcoming a greater steric constraint in the *cis*-aziridinium species.

With a better understanding of the regio- and stereospecific nature of the reaction, a focused series of *syn*- and *anti*-amino alcohols were synthesized in which the dimethylamino group was replaced with diethylamino, morpholino, and *N*-methylanilino groups to probe increased sterics as well as the inherent nucleophilicities of the amino moieties (Table 1). Commercially available bromopropiophenone (±)-**12** was treated with the above amines to afford α-aminoketones (±)-**13a**−**c**.[8−11] Attempts to reduce α-aminoketones (±)-**13a**−**c** with $NaBH_4$ to afford both *syn*- and *anti*-amino alcohols (±)-**14a**−**f** gave varying results.[12] Reduction of α-diethylaminoketone (±)-**13a** with $NaBH_4$ smoothly afforded both *syn*- and *anti*-amino alcohols (±)-**14a** and (±)-**14b** in a 1:1 ratio.[13] However, when α-morphilinoketone (±)-**13b** was treated with $NaBH_4$, the *syn*-amino alcohol (±)-**14c**[14] was the major product (10:1 syn/anti ratio), and in the case of anilinoketone (±)-**13c**, only the syn product (±)-**14e** was isolated. With our desire to explore the CDI reaction with both *syn*- and *anti*-amino alcohols, α-aminoketones (±)-**13b** and (±)-**13c** were subjected to hydrogenation

TABLE 1. Synthesis of *syn*- and *anti*-Amino Alcohols (14) and Their Respective Imidazole Products (15)



compd	NR^1R^2	conditions[a]	stereochemistry	yield (%)
(±)-**13a**	$N(Et)_2$	a		85
(±)-**13b**	morphilino	a		82
(±)-**13c**	N(Me)Ph	a		69
(±)-**14a**	$N(Et)_2$	b	syn	45
(±)-**14b**	$N(Et)_2$	b	anti	38
(±)-**14c**	morphilino	b	syn	78
(±)-**14d**	morphilino	c	anti	76
(±)-**14e**	N(Me)Ph	b/f	syn	84
(±)-**14f**	N(Me)Ph	d	anti	15
(±)-**15a**	$N(Et)_2$	e/f	syn	62
(±)-**15b**	$N(Et)_2$	e/f	anti	67
(±)-**15c**	morphilino	e/f	syn	80
(±)-**15d**	morphilino	e	anti	81
(±)-**15e**	N(Me)Ph	e	syn	no reaction
(±)-**15f**	N(Me)Ph	e/f	anti	66

[a] Conditions: (a) HNR^1R^2, DIEA, NaI, CH_3CN, 40 °C, 16 h; (b) $NaBH_4$, MeOH, 0 °C, 20 min, separation of isomers via column chromatography; (c) H_2, Pd/C, MeOH, rt, 1 h; (d) $Al(i\text{-}OPr)_3$, *i*-PrOH, 60 °C, 2 d; (e) CDI, CH_3CN, reflux, 8 h; (f) compounds **(±)-14e**, **(±)-15a**−**c**, and **(±)-15f** were converted to their respective bis-hydrochloride salts via treatment with 2 M HCl in ether.

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with Pd/C catalyst. Under these conditions, the *anti*-morpholino alcohol (±)-**14d**[14] was successfully produced; however, the reduction of α-anilinoketone (±)-**13c** was unsuccessful. To our satisfaction, we discovered that treatment of anilinoketone (±)-**13c** under Meerwein−Pondorff−Verley conditions afforded a 3:1 ratio of the *syn*- to *anti*-anilino alcohols (±)-**14e** and (±)-**14f**.[11,15a]

Treatment of the *anti*-amino alcohols (±)-**14b** and (±)-**14d** with CDI afforded the respective *anti*-imidazolyl products (±)-**15b** and (±)-**15d**, while the *syn*-amino alcohols (±)-**14a** and (±)-**14c** afforded the respective *syn*-imidazolyl products (±)-**15a** and (±)-**15c** as demonstrated previously in the *N*-methylephedrine cases. Interestingly, treatment of *syn*-anilino alcohol (±)-**14e** with CDI in refluxing acetonitrile did not afford the desired imidazolyl product(±)-**15e**; we observed the imidazolyl-derived carbamate which was hydrolyzed to starting material during aqueous workup. However, *anti*-anilino alcohol (±)-**14f** afforded *anti*-imidazolyl product (±)-**15f** when refluxed with CDI in acetonitrile. We postulate that the weakened nucleophilicity of the anilino nitrogen in concert with the inability of the *syn*-isomer to progress through the more sterically hindered *cis*-aziridinium intermediate results in the failed conversion. It is interesting to note that without neighboring group participation by the amino moiety to displace the imidazolylcarbamate, the reaction fails to afford any of the imidazolylpropylanilino product, whether via an S_N1, S_N2, or S_Ni mechanism. Conversely, the *trans*-anilino-derived aziridinium intermediate is generated readily under refluxing conditions in acetonitrile, as is predicted for a less hindered species, and the reaction proceeds to give the *anti*-imidazolylpropylamino product (±)-**15f**.[15b]

In conclusion, we report the regio- and stereospecific conversion of *syn*- and *anti*-amino alcohols to their respective *syn*- and *anti*-imidazolylpropylamines via treatment with CDI. The reactions proceed with net retention of stereochemistry leading us to speculate that the reaction is proceeding through a required aziridinium intermediate. The *anti*- and *syn*-amino alcohols would likely proceed through their respective *trans*- and more hindered *cis*-aziridinium intermediates, explaining why the CDI reaction with the *syn*-amino alcohols required higher temperatures in the subsequent conversion to the imidazolyl products. The anilino-derived systems were generally less reactive than their dialkylamino counterparts, as demonstrated with *syn*-anilino alcohol (±)-**14e**, which was unable to form its respective imidazolyl product; however, the *anti*-anilino alcohol (±)-**14f** was able to afford the imidazole product (±)-**15f**. With this result, the reaction appears to be dependent upon the participation of the neighboring amino group through formation of an aziridinium intermediate in order to drive the reaction past the imidazolyl-derived carbamate intermediate and to the 1,2-imidazolylpropylamino product.

(15) (a) The diastereomeric ratios of *syn*-amino alcohols (±)-**14a**,**c**,**e** and *anti*-amino alcohols (±)-**14b**,**d**,**f** were determined by reported differences in the carbinolic proton in the ^{1}H NMR spectra. Also, direct comparison to the chemical shifts and coupling constants observed for *N*-methylpseudoephedrine and *N*-methylephedrine reveals that the carbinolic proton of the *anti*-amino alcohols is downfield with respect to the carbinolic proton of the *syn*-amino alcohols, a trend that was observed in the *anti*-amino alcohols (±)-**14b**,**d**,**f** and *syn*-amino alcohols (±)-**14a**,**c**,**e**, respectively. (b) In the case of *syn*-imidazolylpropylamine (−)-**5** and *anti*-imidazolylpropylamine (+)-**7**, the benzylic proton of the *anti*-imidazolylpropylamine (+)-**7** is downfield with respect to the benzylic proton of the *syn*-imidazolylpropylamine (−)-**5**; the chemical shifts of *syn*-imidazolylpropylamines (±)-**15a**,**c** and *anti*-imidazolylpropylamines (±)-**15b**,**d**,**f** were assigned with respect to the chemical shifts observed in the *syn*-imidazolylpropylamine (−)-**5** and *anti*-imidazolylpropylamine (+)-**7**, respectively.

Experimental Section

(1*S*,2*S*)-2-(Dimethylamino)-1-phenylpropyl-1*H*-imidazole-1-carboxylate (2). An acetonitrile solution (28 mL) of (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine **1** (1.0 g, 5.7 mmol) was charged with 1,1′-carbonyldiimidazole (CDI) (1.1 g, 6.8 mmol) and stirred at rt for 8 h. The reaction mixture was concentrated in vacuo and partitioned between water (15 mL) and diethyl ether (15 mL), and the organic layer was washed with water (3 × 15 mL) and brine (1 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was recrystallized from CH_2Cl_2/hexanes to afford carbamate **2** as white crystals (956 mg, 61%): mp = 81−82 °C; IR (film) cm^{-1} 2973, 1756, 1474, 1287, 1239, 1001, 753; ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 3H, J = 6.8 Hz), 2.37 (s, 6H), 3.10−3.17 (m, 1H), 5.80 (d, 1H, J = 9.2 Hz), 7.06 (s, 1H), 7.36−7.42 (m, 5H), 7.44−7.46 (m, 1H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0, 40.7, 62.9, 81.4, 117.2, 127.5, 128.8, 128.9, 130.4, 137.1, 137.2, 148.1. Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.77; H, 7.01; N, 15.34.

(1*S*,2*S*)-2-(Dimethylamino)-1-phenylpropyl Methyl Carbonate (4). An acetonitrile solution (28 mL) of (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine **1** (1.0 g, 5.7 mmol) was charged with CDI (1.1 g, 6.8 mmol) and stirred at rt for 8 h. The reaction mixture was charged with methanol (20 mL) and stirred at rt for 2 h. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by silica gel chromatography eluting with EtOAc to afford methyl carbonate **4** as a white solid (935 mg, 69%): mp = 66−67 °C; IR (film) cm^{-1} 1746, 1441, 1265, 945; ^{1}H NMR ($CDCl_3$) δ 0.68 (d, 3H, J = 6.0 Hz), 2.35 (s, 6H), 3.03−3.10 (m, 1H), 3.72 (s, 3H), 5.48 (d, 1H, J = 8.0 Hz), 7.30−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.5, 40.8, 54.6, 62.5, 81.1, 127.4, 128.3, 128.5, 138.5, 155.2. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.81; H, 8.18; N, 5.74.

(1*S*,2*S*)-*N*-[2-(1*H*-Imidazol-1-yl)-1-methyl-2-phenylethyl]-*N*,*N*-dimethylamine [(−)-5]. An acetonitrile solution (28 mL) of (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine **1** (1.0 g, 5.7 mmol) was charged with CDI (1.1 g, 6.8 mmol) and stirred at reflux for 8 h. The reaction mixture was concentrated in vacuo and partitioned between satd $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography eluting with 97:2:1 CH_2Cl_2/MeOH/7 N NH_3 in MeOH to afford *syn*-imidazolylpropylamine (−)-**5** as a white solid (986 mg, 76% yield). An analytical sample was recrystallized from hot EtOAc/hexanes to afford white crystals. Crystals were grown by slow diffusion from methylene chloride to hexanes from which X-ray crystallography data was obtained: mp = 81−82 °C; IR (film) cm^{-1} 2969, 2938, 2789, 1498, 1221, 1082, 907; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, 3H, J = 6.8 Hz), 2.22 (s, 6H), 3.39−3.47 (m, 1H), 4.97 (d, 1H, J = 10.4 Hz), 6.97−6.98 (m, 1H), 7.02−7.03 (m, 1H), 7.24−7.36 (m, 5H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.1, 40.1, 61.5, 65.5, 118.8, 127.4, 127.8, 128.8, 129.3, 136.9, 139.0; $[\alpha]^{27}_D$ −23.0 (*c* 0.25, $CHCl_3$); λ_{max} 208 (ϵ 11 000). Anal. Calcd for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.41; H, 8.25; N, 18.50.

(1*S*,2*R*)-*N*-[2-(1*H*-Imidazol-1-yl)-1-methyl-2-phenylethyl]-*N*,*N*-dimethylamine [(+)-7]. The title compound was prepared as a white solid (1.1 g, 85% yield) according to the procedures described for the synthesis of [(−)-**5**] above except for the replacement of (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine **1** with (1*S*,2*R*)-(+)-*N*-methylephedrine **6** (1.0 g, 5.7 mmol), CDI (1.1 g, 6.8 mmol), and performing the reaction at rt: mp = 113−114 °C; IR (film) cm^{-1} 2969, 2938, 2789, 1498, 1221, 1082, 907; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, J = 6.8 Hz), 2.22 (s, 6H), 3.29−3.52 (m, 1H), 5.14 (d, 1H, J = 9.2 Hz), 7.00 (s, 1H), 7.05 (s, 1H), 7.26−

7.36 (m, 5H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.7, 40.7, 61.2, 65.1, 118.2, 127.7, 128.4, 129.0, 129.2, 137.0, 138.5; $[\alpha]^{27}_D$ +67.7 (*c* 0.23, $CHCl_3$); λ_{max} 206 (ϵ 13 200). Anal. Calcd for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.34; H, 8.29; N, 18.47.

***syn*-*N*,*N*-Diethyl-*N*-[2-(1*H*-imidazol-1-yl)-1-methyl-2-phenylethyl]amine [(±)-15a]·Bis-hydrochloride Salt.** *syn*-Imidazolylpropylamine (±)-**15a** was prepared according to the procedure for (−)-**5**; tan oil (62%). An EtOAc solution of *syn*-imidazolylpropylamine (±)-**15a** (300 mg, 1.2 mmol) was added to 2 M HCl in diethyl ether. The resulting precipitate was filtered and washed with diethyl ether to afford (±)-**15a**·bis-HCl salt as a tan solid (315 mg, 96%), from which all analytical data was obtained: mp = 194−196 °C; IR (film) cm^{-1} 2968, 1492, 1454, 1382, 1223, 1074; ^{1}H NMR (D_2O) δ 1.23 (d, 3H, *J* = 6.8 Hz), 1.34 (t, 6H, *J* = 7.2 Hz), 3.15−3.27 (m, 2H), 3.53−3.61 (m, 2H), 4.72−4.77 (m, 1H), 5.92 (d, 1H, *J* = 11.2 Hz), 7.48−7.50 (m, 3H), 7.54−7.55 (m, 1H), 7.57−7.60 (m, 2H), 7.97−7.98 (m, 1H), 9.16 (bs, 1H); ^{13}C NMR (D_2O) δ 10.1, 10.3, 10.7, 46.3, 48.8, 59.5, 63.9, 120.7, 122.6, 128.4, 130.4, 131.0, 134.2, 135.4. Anal. Calcd for $C_{16}H_{25}N_3Cl_2$·0.5H_2O: C, 56.64; H, 7.72; N, 12.38. Found: C, 57.04; H, 7.78; N, 12.28.

***anti*-*N*,*N*-Diethyl-*N*-[2-(1*H*-imidazol-1-yl)-1-methyl-2-phenylethyl]amine [(±)-15b]·Bis-hydrochloride Salt.** *anti*-Imidazolylpropylamine (±)-**15b** (tan oil, 67%) was prepared according to the procedure for (−)-**5**; the salt, (±)-**15b**·bis-HCl (tan solid, 309 mg, 94%), was prepared as described for (±)-**15a** from which all analytical data was obtained: mp = 187−189 °C; IR (film) cm^{-1} 2968, 2809, 1492, 1454, 1382, 1223, 1074, 905; ^{1}H NMR (D_2O) δ 1.11−1.21 (m, 6H), 1.26 (d, 3H, *J* = 12.4 Hz), 3.12−3.16 (m, 2H), 3.39−3.42 (m, 2H), 4.63−4.66 (m, 1H), 6.00 (d, 1H, *J* = 6.4 Hz), 7.45−7.50 (m, 4H), 7.63−7.67 (m, 2H), 7.78 (bs, 1H), 8.97 (bs, 1H); ^{13}C NMR (D_2O) δ 9.7, 10.0, 47.0, 48.7, 58.3, 64.5, 120.7, 122.1, 128.9, 131.3, 132.0, 132.2, 135.6. Anal. Calcd for $C_{16}H_{25}N_3Cl_2$·0.5H_2O: C, 56.64; H, 7.72; N, 12.38. Found: C, 56.84; H, 7.69; N, 12.20.

***syn*-4-[2-(1*H*-Imidazol-1-yl)-1-methyl-2-phenylethyl]morpholine [(±)-15c]·Bis-hydrochloride Salt.** *syn*-Imidazolylpropylamine (±)-**15c** (white solid, 80%) was prepared according to the procedure for (−)-**5**; the salt, (±)-**15c**·bis-HCl (white solid, 352 mg, 93%), was prepared as described for (±)-**15a** from which all analytical data was obtained: mp = 148−150 °C dec; IR (film) cm^{-1} 1586, 1569, 1496, 735, 701; ^{1}H NMR (D_2O) δ 1.20 (d, 3H, *J* = 6.4 Hz), 3.08−3.11 (m, 2H), 3.28−3.34 (m, 2H), 3.80−3.91 (m, 4H), 4.39−4.41 (m, 1H), 5.90 (d, 1H, *J* = 10.8 Hz), 7.48−7.53 (m, 6H), 7.58 (bs, 1H), 9.07 (bs, 1H); ^{13}C NMR (D_2O) δ 11.7, 49.4, 63.5, 64.1, 64.2, 121.1, 121.9, 128.5, 130.5, 131.0, 134.4, 135.5. Anal. Calcd for $C_{16}H_{23}N_3OCl_2$: C, 55.82; H, 6.73; N, 12.20. Found: C, 55.62; H, 6.76; N, 12.06.

***anti*-4-[2-(1*H*-Imidazol-1-yl)-1-methyl-2-phenylethyl]morpholine [(±)-15d].** *anti*-Imidazolylpropylamine (±)-**15d** (white solid, 81%) was prepared according to the procedure for (−)-**5**. An analytical sample was recrystallized from EtOAc/hexanes: mp = 114−115 °C; IR (film) cm^{-1} 1586, 1569, 1496, 735, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3H, *J* = 6.8 Hz), 2.43−2.52 (m, 4H), 3.42−3.47 (m, 1H), 3.50−3.58 (m, 4H), 5.03 (d, 1H, *J* = 8.8 Hz), 7.04−7.07 (m, 2H), 7.29−7.37 (m, 5H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 49.8, 62.7, 65.7, 67.8, 118.5, 128.2, 128.6, 129.1, 130.1, 137.4, 139.1. Anal. Calcd for $C_{16}H_{21}N_3O$·0.3H_2O: C, 69.29; H, 7.87; N, 15.15. Found: C, 68.99; H, 7.67; N, 15.21.

***anti*-*N*-[2-(1*H*-Imidazol-1-yl)-1-methyl-2-phenylethyl]-*N*-methyl-*N*-phenylamine [(±)-15f]·Bis-hydrochloride Salt.** *anti*-Imidazolylpropylamine (±)-**15f** (white solid, 66%) was prepared according to the procedure for (−)-**5**; the salt, (−)-**15f**·bis-HCl (tan solid, 210 mg, 85%), was prepared as described for (±)-**15a** from which all analytical data was obtained: mp = 115−116 °C dec; IR (film) 2927, 1596, 1503, 1289, 1116, 749, 721; ^{1}H NMR (400 MHz, D_2O) δ 1.15 (d, 3H, *J* = 6.8 Hz), 2.71 (s, 3H), 4.97−5.01 (m, 1H), 5.84 (d, 1H, *J* = 2.8 Hz), 6.80−6.84 (m, 1H), 6.89 (d, 2H, *J* = 8.4 Hz), 7.24−7.26 (m, 2H), 7.36−7.38 (m, 3H), 7.50−7.51 (m, 1H), 7.57−7.59 (m, 2H), 7.83−7.84 (m, 1H), 9.03−9.04 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 13.1, 31.1, 57.5, 67.5, 115.6, 119.5, 121.0, 128.4, 129.8, 130.0, 130.1, 134.7, 136.1, 149.9; HRMS *m*/*z* calcd for $C_{19}H_{21}N_3$ 292.1814, found 292.1824.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and IR spectra of **2**, **4**, (−)-**5**, (+)-**7**, (±)-**14a**−**f**, (±)-**15a**−**d**, and (±)-**15f**, elemental analysis of **2**, **4**, (−)-**5**, (+)-**7**, (±)-**14c**, (±)-**14e**, and (±)-**15a**−**d**, HRMS of (±)-**14f** and (±)-**15f**, and X-ray crystallography data of (−)-**5** and (+)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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