Aromatic Amination/Imination Approach to Chiral Benzimidazoles

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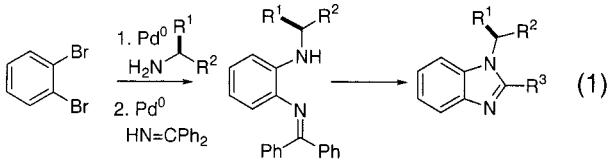
Abstract: The powerful Buchwald−Hartwig amination was utilized for the construction of the benzimidazole nucleus with the substituted nitrogen atom bearing a chiral substituent. A successive amination/imination was followed by an acid-catalyzed ring closure step to give the benzimidazole ring. The products were deprotonated and acylated at the C2 position and could be alkylated on nitrogen to give chiral benzimidazolium salts.

Many of the most utilized methods for benzimidazole synthesis employ the intermediacy of *N*-substituted 1,2-benzenediamines, which can be subsequently cyclized in a number of ways.[1] However, the introduction of chiral centers in the nitrogen side chain of *N*-substituted 1,2-benzenediamines is difficult, although a paper describing the solid-phase preparation of chiral 2-aminobenzimidazoles has recently appeared.[2] Here we describe a novel approach to the synthesis of chirality-bearing *N*-substituted 1,2-benzenediamines using Pd-catalyzed amination and imination (eq 1). The mildness of the procedure allows for the direct introduction of α-chiral primary amines. The second coupling utilizes benzophenone imine as precursor to the unsubstituted nitrogen of the azole ring system. The products can then be cyclized to afford benzimidazoles by using literature methods. The unique chiral benzimidazole products can be acylated or quaternized with alkyl halides.



Interest in benzimidazoles can be attributed to their diverse biological properties.[3] For this reason, substituted benzimidazoles have attracted considerable recent synthetic attention. The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates[1] or resort to direct *N*-alkylation of an unsubstituted benzimidazole.[4] Synthetic strategies that utilize intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid support.[5−11] Benzimidazoles have been used as antifungals,[12,13] antibacterials,[12,14,15] antihelminthics,[16] 5-HT receptor antagonists,[17,18] and thrombin receptor antagonists.[19,20] A weakness in the current preparations of benzimidazoles, identified in our own synthetic studies directed toward chiral benzimidazolium salts, is the incorporation of chiral substitution on the nitrogen atom.

The starting point for the construction of the benzimidazoles are the 2-bromoanilines, which were prepared by amination of 1,2-dibromobenzene, as previously reported.[21] To install the second amine required the use of an ammonia equivalent, and benzophenone imine[22] was chosen for this purpose. Benzophenone imine was coupled to three 2-bromoanilines **1A**−**C**, each with chiral substitution on the position α to nitrogen (Scheme 1). The intermediate iminoanilines **2** were purified and subjected to transimination using the α-effect nucleophile hydroxylamine to provide the respective unprotected anilines **3**. Since Buchwald's original report using benzophenone imine as an ammonia equivalent, other ammonia equivalents for palladium-catalyzed amination have been developed.[23−29] Excellent yields of the 2-aminoanilines **3** are obtained using this two-step procedure.

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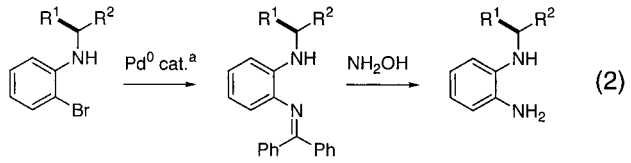
Scheme 1. Imination/Transimination



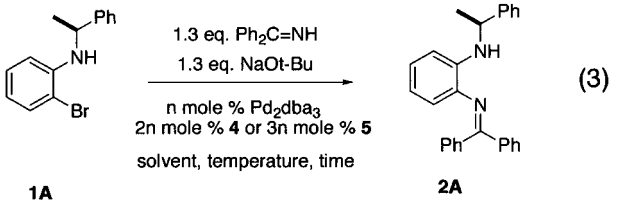
1A R^1 = Me, R^2 = Ph **2A** (99 %, 99 % ee) **3A** (95 %, 99 % ee)
1B R^1 = Me, R^2 = Cy **2B** (96 %, 96 % ee) **3B** (91 %, 97 % ee)
1C R^1 = -CH_2OMe, R^2 = Ph **2C** (96 %) **3C** (92 %)

(a) 2-4 mol % Pd_2dba_3, 4-8 mol % (±) BINAP **4,** 1.3 eq. benzophenone imine, 1.3 eq. NaOt-Bu, toluene, 2.5 h, 110-135 °C.

The monosubstituted 1,2 benzenediamines **3** bear a chiral substituent. Due to the possibility of racemization during and after the Pd-catalyzed coupling reaction, the enantiomeric excesses of **2** were analyzed by HPLC. The imination of Scheme 1 requires rather high catalyst loadings which is probably necessary due to the steric bulk of the substituted ortho nitrogen substituent and the electron rich nature of the aromatic ring. Buchwald has reported the use of low catalyst loadings for the coupling to less-hindered aromatic halides,[22] and further improvement in the imination of Scheme 1 might be possible using other phosphine donors. The phenylglycinol-derived aniline required higher reaction temperatures for the coupling using BINAP as the diphosphine ligand. The latter conditions had previously been found to be suitable for the synthesis of hindered 1,2-phenylene diamines;[21] however, the extreme temperatures were not necessary for iminations to form **2A** and **2B**.

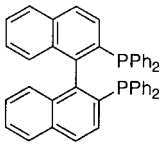
In general, higher catalyst loadings (4 mol % Pd atom) were needed to drive the imination to completion; however, we examined the effect of catalyst loading on the coupling of **1A** with benzophenone imine to see if the reaction could function at lower catalyst loadings (Table 1).

Table 1. Effect of Catalyst Loading

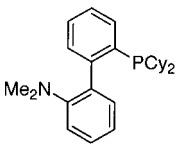


1A **2A**

entry	*n*	ligand	solvent	temp, C°	time, h	% conversion
1	0.5	**4**	toluene	110	28	58
2	2.0	**4**	toluene	110	2.5	100
3	0.07	**5**	DME	80	19.5	<1
4	1.0	**5**	DME	80	28	31
5	3.4	**5**	DME	80	0.5	100



(±) **4**



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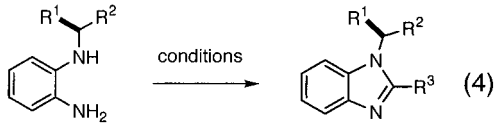
In each of the iminations of Table 1, the palladium precatalyst and the donor ligand **4** or **5** were heated together for 0.5 h before the reactants were introduced, which were then heated in a sealed reaction vessel. With 1 mol % Pd-atom (n = 0.5), a 58% conversion was achieved with ligand **4**, but only after 28 h reaction time (entry 1). The reaction is about 10 times faster using 4 mol % Pd-atom (n = 2, entry 2). The mixed donor ligand **5** was also effective in catalyzing the coupling in eq 3, but like BINAP, it proved most effective at higher palladium loadings. Short reaction time (0.5 h, entry 5) was realized at 80 °C when 6.8 mol % Pd atom was used.

The synthesis of benzimidazoles bearing a chiral substituent on nitrogen is summarized in Table 2. The sequence constitutes a ring synthesis of the benzimidazole nucleus from the substituted 1,2-benzenediamine. The cyclization reactions were carried out using excess of the required ortho ester.[30,31] In some cases, the reaction could be catalyzed by *p*-TsOH; however, in the more demanding cyclizations using $(EtO)_3CCH_3$ and $(EtO)_3$-CPh, the use of 1 equiv of hydrochloric acid proved necessary. Basicification and extractive workup then provided the benzimidazole free bases. Purification of the benzimidazoles was possible through chromatography or recrystallization.

Table 2. Ring Synthesis of *N*-Chiral Benzimidazoles



3A-B **6-12**

series A: R^1 = Me, R^2 = Ph
series B: R^1 = Me, R^2 = Cy
series C: R^1 = -CH_2OMe, R^2 = Ph

entry	diamine	reagents	product	R^3	yield
1	**3A**	$(MeO)_3CH$, TsOH (cat.)	**6A**	H	91% (99% ee)
2	**3A**	$(MeO)_3CCH_3$, HCl	**7A**	CH_3	98% (99% ee)
3	**3A**	$(MeO)_3CPh$, HCl	**8A**	Ph	97% (99% ee)
4	**3A**	CNBr, EtOH	**9A**	NH_2	89% (99% ee)
5	**3B**	$(MeO)_3CH$, TsOH (cat.)	**10B**	H	88% (98% ee)
6	**3C**	$(MeO)_3CH$, TsOH (cat.)	**11C**	H	90%
7	**3C**	$(MeO)_3CCH_3$, HCl	**12C**	CH_3	86%

From Table 2 it is evident that a variety of substitution patterns can be introduced on the *N*-chiral benzimidazole. Using commercially available orthoformate or ortho esters, proton, methyl, or phenyl could be introduced in the C2 position. Cyclization using cyanogen bromide was used to form the 2-amino-substituted benzimidazole **9A**.[32] The cyclizations proceed without racemization, a process that could have occurred through azolium species. In the first five entries, the enantiomeric excess was checked against authentically prepared racemates, synthesized starting from commercially available racemic α-methylbenzylamine. The optical activities of compounds **11C** and **12C** were established by optical rotation. Although

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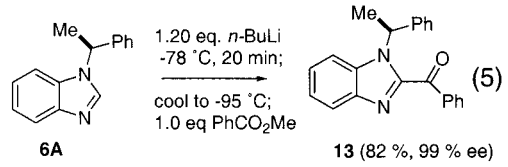
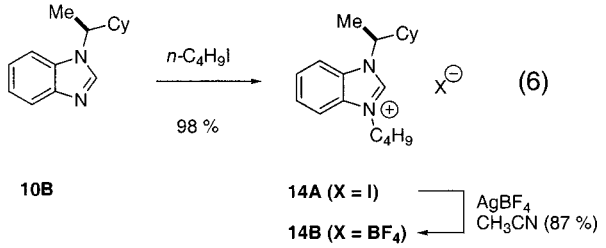
11C was not prepared as its racemate for authentication of enantiomeric purity, its HPLC trace showed a single peak.

The chiral benzimidazoles could be further functionalized by acylation. For instance, benzimidazole **6A** was deprotonated with BuLi and benzoylated with methyl benzoate (eq 5).[33,34] Addition of the metalated benzimidazole to the electrophile at −78 °C gave variable yields. Similar results were observed by Davies et al. in the low-temperature acylation of 2-lithioimidazoles.[33] To improve the yields, the C2 metalated benzimidazole was precooled to −95 °C before the dropwise introduction of the electrophile. In this way, consistent results were obtained. As expected, the enantiomeric excess of the chiral center present in the side chain was not diminished under strongly basic conditions.



Due in part to the current interest in room-temperature ionic liquids[35] and our long standing interest in chiral benzimidazolium salts, we elaborated the chiral benzimidazoles into *N*-alkyl benzimidazolium salts (eq 6). The approach in eq 6 offers a complementary strategy



to the direct synthesis of benzimidazolium salts reported from these laboratories[36] and is an efficient way to introduce simple alkyl groups. Butyl iodide alkylation provided the quaternary salt **14A** in 98% yield. Counterion exchange on **14A** using excess NH_4BF_4 proved inefficient, giving mixtures of the iodide and tetrafluoroborate salts which are distinguishable by TLC. However, treatment of iodide **14A** with $AgBF_4$ in CH_3CN gave a high yield of the desired tetrafluoroborate **14B**, which was obtained as a solid, mp 126−127 °C. Similar alkylations of long chain normal alkyl iodides is expected to give similar results and may result in salts with lower melting points. Further studies are in progress.

In conclusion, an efficient synthesis of benzimidazoles that bear chiral substituents on the nitrogen atom has been achieved using an amination/imination/ring synthesis approach. The methods used for the synthesis of the benzimidazoles do not result in racemization of the chirality in the side chain at nitrogen. The incorporation of substitution at the C2 position may be accomplished in the cyclization step or in subsequent functionalization at the C2 position.

Experimental Section

General. Reactions were conducted under an argon atmosphere in oven-dried, sealable Schlenk or pressure tubes equipped with a threaded Teflon plug and magnetic stirbar. Column chromatography was carried out on Merck silica gel 60 (230−400 mesh). ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz in $CDCl_3$. Optical rotations were measured using the sodium D line in a thermostated cell held at 25 °C. Enantiomeric and diastereomeric excesses were determined by HPLC using a Chiralcel OD-H column, 2-propanol/hexane, at the indicated ratio and rate, and UV-254 unless stated otherwise. Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Toluene was distilled from CaH_2 immediately prior to use. Tetrahydrofuran (THF) and ethylene glycol dimethyl ether (DME) was distilled from sodium benzophenone ketyl prior to use. Pd_2dba_3 and (±)-BINAP were purchased from Strem Chemical Company. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co. and transferred inside a drybox to small vials that were then stored in a desiccator filled with anhydrous calcium sulfate and weighed in the air. Methyl benzoate was dried with Na_2SO_4 and fractionally distilled prior to use. (*R*)-(−)-1-Amino-1-phenyl-2-methoxyethane was prepared as reported.[37] 1-(*N*,*N*-Dimethylamino)-1′-(dicyclohexylphosphino)-biphenyl **5** was prepared as reported.[38] (2-Bromophenyl)-(*S*)-1-phenylethylamine, (2-bromophenyl)-(*S*)-1-cyclohexylethylamine, and (2-bromophenyl)-(*R*)-2-methoxy-1-phenylethylamine were prepared according to the literature.[36] All other reagents were purchased from Aldrich Chemical company and used without additional purification.

General Procedure for the Imination of (2-Bromophenyl)amines: *N*-[(*S*)-1-Phenylethyl]-*N*′-(diphenylmethylene)-1,2-benzenediamine 2A. An oven-dried pressure tube equipped with magnetic stirbar and rubber septum was cooled under argon. The pressure tube was charged with 70.9 mg of Pd_2dba_3 (0.0774 mmol, 2.0 mol %), 96.4 mg of *rac*-BINAP (0.155 mmol, 4.0 mol %), and toluene (15.0 mL). The rubber septum was replaced with a Teflon screwcap, and the mixture was heated at 110 °C in an oil bath for 30 min. The solution was then allowed to cool to room temperature, and 844 μL of benzophenone imine (5.03 mmol, 1.30 equiv), 1.07 g of **1A** (3.87 mmol, 1.00 equiv), and 483.4 mg of sodium *tert*-butoxide (5.03 mmol, 1.30 equiv) were added. The pressure tube was sealed and heated in an oil bath at 110 °C with stirring for 2.5 h. The solution was then allowed to cool to room temperature, diluted with diethyl ether, filtered through a pad of Celite, and concentrated in vacuo (rotatory evaporator) to give a crude dark brown-black oil which was purified by flash chromatography (gradient elution with 10% CH_2Cl_2/hexane to 50% CH_2Cl_2/hexane) to provide 1.44 g of **2A** (99%) as a yellow oil. Analytical TLC (50% CH_2Cl_2/hexane) R_f 0.14. ^{1}H NMR (500 MHz, $CDCl_3$) 7.84 (d, J = 7.5 Hz, 2 H), 7.50−7.32 (m, 5 H), 7.31−7.28 (m, 5 H), 7.23−7.15 (m, 3 H), 6.70 (t, J = 7.5 Hz, 1 H), 6.36 (d, J = 7.5 Hz, 1 H), 6.26 (t, J = 7.5 Hz, 1 H), 6.13 (d, J = 7.5 Hz, 1 H), 4.86 (s, 1 H), 4.55 (m, 1 H), 1.54 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 145.7, 141.3, 139.9, 136.7, 136.4, 130.5, 129.4, 129.1, 128.8, 128.5, 128.1, 128.1, 126.7, 125.8, 125.0, 119.2, 116.1, 111.3, 53.7, 25.4; FT-IR (film, NaCl) 3402, 1593 cm^{-1}; High-resolution MS (EI$^+$, m/z) molecular ion calcd for $C_{27}H_{24}N_2$ 376.1939, found 376.1935; error 1.1 ppm. Enantiomeric excess determination by HPLC (0.50 mL/min, 10% 2-propanol/hexane, t_R = 8.0 (*S*) and 9.6 (*R*) min) indicated 99% ee.

General Procedure[22] for the Transimination: *N*-[(*S*)-1-Phenylethyl]-1,2-benzenediamine 3A. To a 50 mL round-bottom flask equipped with a magnetic stirbar were added 504.0 mg of **2A** (1.339 mmol, 1.0 equiv), methanol (30.0 mL), 263.3 mg of sodium acetate (3.210 mmol, 2.4 equiv), and 167.5 mg of

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hydroxylamine hydrochloride (2.410 mmol, 1.8 equiv). The resulting solution was then stirred at room temperature for 1 h. The solution was partitioned between 0.1 M NaOH and CH_2Cl_2, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo (rotatory evaporator). The resulting oil was purified by flash chromatography (elution with 6:1 hexane/ethyl acetate, then 4:1 hexane/ethyl acetate) to yield 268.8 mg of **3A** (95%) as a colorless oil that turned light red upon standing in solution or neat. Analytical TLC (30% hexane/ethyl acetate) R_f 0.21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.22 (t, J = 7.5 Hz, 1 H), 6.72 (dd, J = 7.5, 1.3 Hz, 1 H), 6.66 (td, J = 7.5, 1.3 Hz, 1 H), 6.61 (td, J = 7.5, 1.0 Hz, 1 H), 6.42 (d, J = 7.5 Hz, 1 H), 4.49 (q, J = 6.5 Hz, 1 H), 3.75 (br s, 1 H), 3.37 (br s, 2 H), 1.55 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 136.9, 133.8, 128.6, 126.8, 125.9, 120.7, 118.4, 116.6, 113.1, 53.5, 25.2; FT-IR (film, NaCl) 3392, 3328, 741, 701 cm^{-1}; High-resolution MS (EI$^+$, m/z) molecular ion calcd for $C_{14}H_{16}N_2$ 212.1313, found 212.1312; error 0.5 ppm. Enantiomeric excess determination by HPLC (0.50 mL/min, 25% 2-propanol/hexane, t_R = 21.2 (*S*) and 27.2 (*R*) min) indicated 99% ee.

General Procedure for the Synthesis of Benzimidazole Method A: 1-[(*S*)-1-Phenylethyl]-1*H*-benzimidazole 6A. To a 15 mL round-bottom flask equipped with magnetic stirbar was added 194.8 mg of **3A** (0.918 mmol, 1.0 equiv), 10.0 mL of triethyl orthoformate, and 17.5 mg of *p*-toluenesulfonic acid monohydrate (0.0918 mmol, 0.10 equiv), and the resulting solution was stirred for 8 h. The solution was then diluted with ethyl acetate and washed with $NaHCO_3$. The aqueous layer was back-extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo (rotatory evaporator) to give a brown oil. Purification by flash chromatography (elution with 1% MeOH/CH_2Cl_2) provided 185 mg of **6A** (91%) as a white solid, mp 151−152 °C (lit.[38] 114−115 °C for racemic **6A**). Analytical TLC (5% methanol/CH_2Cl_2) R_f 0.26. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 7.35−7.22 (m, 4 H), 7.19 (m, 4 H), 5.62 (q, J = 7.0 Hz, 1 H), 2.00 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 144.1, 140.9, 140.6, 133.6, 128.9, 128.0, 125.9, 122.8, 122.2, 120.4, 110.6, 55.2, 21.6; FT-IR (KBr) 1615, 1479 cm^{-1}; High-resolution MS (EI$^+$, m/z) molecular ion calcd for $C_{15}H_{14}N_2$ 222.1157, found 222.1156; error 0.5 ppm. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05%; H, 6.35%; N, 12.60%, found C, 80.90%; H, 6.44%; N 12.62%. Enantiomeric excess determination by HPLC (0.50 mL/min, 10% 2-propanol/hexane, t_R = 24.0 (*S*) and 32.4 (*R*) min) indicated 99% ee.

General Procedure for the Synthesis of Benzimidazole Method B: 2-Methyl-1-[(*S*)-1-phenylethyl]-1*H*-benzimidazole 7A. To a 10 mL round-bottom flask equipped with magnetic stirbar were added 197.9 mg of **3A** (0.932 mmol, 1.0 equiv), 5.0 mL of triethyl orthoacetate, and 80 μL of 12.1 N HCl (0.968 mmol, 1.0 equiv), and the resulting solution was stirred for 45 min. The solution was then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The aqueous layer was back-extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo (rotatory evaporator). Purification by flash chromatography (gradient elution with 1:2 ethyl acetate/hexane to ethyl acetate) provided 215.1 mg of **7A** (98%) as a white solid, mp 78−79 °C. Analytical TLC (5% methanol/CH_2Cl_2) R_f 0.31. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.5 Hz, 1 H), 7.35−7.27 (m, 3 H), 7.21−7.16 (m, 3 H), 7.09−7.02 (m, 2 H), 5.76 (q, J = 7.0 Hz, 1 H), 2.58 (s, 3 H), 1.97 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 151.5, 142.9, 139.5, 134.1, 128.8, 127.7, 126.2, 121.8, 121.6, 119.2, 111.0, 53.4, 18.7, 15.0; FT-IR (film, NaCl) 1613, 1516 cm^{-1}; High-resolution MS (EI$^+$, m/z) molecular ion calcd for $C_{16}H_{16}N_2$ 236.1313, found 236.1314; error 0.4 ppm. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32%; H, 6.82%; N, 11.85%, found C, 81.10%; H, 6.73%; N 11.88%. Enantiomeric excess determination by HPLC (0.50 mL/min, 20% 2-propanol/hexane, t_R = 14.4 (*S*) and 25.7 (*R*) min) indicated 99% ee.

2-Amino-1-[(*S*)-1-phenylethyl]-1*H*-benzimidazole 9A. To a 15 mL round-bottom flask were added 202.4 mg of **3A** (0.953 mmol, 1.0 equiv), ethanol (11.0 mL), and 158.9 mg of BrCN (1.50 mmol, 1.5 equiv). The reaction mixture was stirred overnight, diluted with 30 mL of CH_2Cl_2, and treated with saturated Na_2CO_3. The aqueous layer was back-extracted with fresh CH_2Cl_2, and the combined organic layers were dried with Na_2SO_4, filtrated, and concentrated in vacuo (rotatory evaporator). Purification by flash chromatography (gradient elution with CH_2Cl_2 to 5% MeOH/CH_2Cl_2) provided 200.3 mg of **9A** (89%) as a white solid, mp 97 °C (lit.[4] 120−122 °C for racemic **9A**). Analytical TLC (10% methanol/CH_2Cl_2) R_f 0.32. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 1 H), 7.39−7.30 (m, 5 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.07 (d, J = 7.5 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 5.61 (q, J = 7.0 Hz, 1H), 4.69 (br s, 2 H), 1.90 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 153.4, 141.9, 139.0, 133.8, 129.1, 128.2, 126.5, 121.4, 119.6, 116.5, 108.6, 52.2, 17.5; FT-IR (film, NaCl) 3451, 3314, 1644, 1537 cm^{-1}; High-resolution MS (EI$^+$,m/z) molecular ion calcd for $C_{15}H_{15}N_3$ 237.1266 found, 237.1269; error = 1.3 ppm. Enantiomeric excess determination by HPLC (1.00 mL/min, 5.0% 2-propanol/hexane, t_R = 30.6 (*R*) and 40.5 (*S*) min) indicated 99% ee.

1-[(*S*)-1-Phenylethyl]-3-butyl-1*H*-benzimidazolium iodide 14A. Into an oven-dried 10 mL round-bottom flask equipped with magnetic stirbar, reflux condenser, and rubber septum was added 195.1 mg of **10B** (0.854 mmol 1.0 equiv) and 3.0 mL of 1-iodobutane, and the resulting solution was heated to 100 °C for 1.5 h. After cooling to room temperature, 9 mL of hexane was added, and the resulting solution was separated from the precipitate by decantation. The resulting yellow solid was filtered through a plug of silica gel (elution 5% MeOH in CH_2Cl_2) to provide a pale yellow solid that was recrystallized from toluene/CH_3CN and dried under vacumm (1 mmHg) at 30 °C over P_2O_5 to provide 345.8 mg of **14A** (98%) as white crystals, mp 185−186 °C. Analytical TLC (5% MeOH in CH_2Cl_2) R_f 0.29. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.18 (s, 1H), 7.82 (m, 2H), 7.69 (m, 2 H), 4.78 (app t, J_{app} = 7.5 Hz, 2 H), 4.70 (quin, 1 H), 2.13−2.02 (m, 3 H), 1.90−1.79 (m, 5 H), 1.66 (m, 2 H), 1.47 (app sex, J_{app} = 7.5 Hz, 2 H), 1.34−1.02 (m, 6 H), 1.00 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 131.2, 130.9, 127.2, 127.1, 113.9, 113.2, 61.0, 47.3, 42.6, 31.4, 29.7, 29.1, 25.5, 25.4, 25.3, 19.6, 18.2, 13.5; FT-IR (KBr) 1556 cm^{-1}; Low resolution FAB-MS molecular ion calcd for $C_{19}H_{29}N_2$(−I) 285.2, found 285.2. Anal. Calcd. for $C_{19}H_{29}IN_2$: C, 55.34%; H, 7.09%; N, 6.79%, found C, 55.20%; H, 7.11%; N 6.65%. $[\alpha]^{25}_D$= + 3.6 (c = 0.50, CH_2Cl_2).

1-[(*S*)-1-Phenylethyl]-3-butyl-1*H*-benzimidazolium Tetrafluoroborate 14B. Into a plastic vial capped with a septum were added 249.8 mg of **14A** (0.606 mmol, 1.0 equiv) and 2.5 mL of dry acetonitrile. To the resulting solution was added 119.1 mg of $AgBF_4$ (0.606 mmol, 1.0 equiv) in one portion. The resulting yellow precipitate was filtered, and the resulting clear solution was concentrated in vacuo (rotatory evaporator). Purification by flash chromatography using a 1.5 in. plug of silica gel (elution 1% MeOH in CH_2Cl_2) followed by drying under vacuum (1 mmHg) at 30 °C over P_2O_5 provided 195.6 mg of **14B** (87%) as a white solid, mp 126−127 °C. Analytical TLC (5% MeOH in CH_2Cl_2) R_f 0.39. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1 H), 7.78 (m, 2 H), 7.67 (m, 2 H), 4.60−4.51 (m, 3 H), 1.99 (app quin, 3 H), 1.89−1.74 (m, 5 H), 1.66 (m, 2 H), 1.42 (app sex, J_{app} = 7.5 Hz, 2 H), 1.32−1.07 (m, 5 H), 1.04−0.96 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 131.4, 131.2, 127.2, 127.1, 113.9, 113.3, 61.3, 47.6, 42.5, 31.3, 29.7, 29.2, 25.6, 25.5, 25.4, 19.6, 17.5, 13.4; FT-IR (KBr) 1556, 1082 cm^{-1}; Low resolution FAB-MS molecular ion calcd. for $C_{19}H_{29}N_2$(−I) 285.2, found 285.2. Anal. Calcd for $C_{19}H_{29}BF_4N_2$: C, 61.30%; H, 7.85%; N, 7.53%, found C, 61.37%; H, 7.83%; N 7.51%. $[\alpha]^{25}_D$ = −8.3 (c = 3.50, CH_2Cl_2).

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Supporting Information Available: Detailed experimental procedures and characterization data for compounds **2B**, **2C**, **3B**, **3C**, **8A**, **10B**, **11C**, **12C**, and **13** are available as Supporting Information. This information is available free of charge via the Internet at http://pubs.acs.org.

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