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Enzymatic Resolution of Bicyclic 1-Heteroarylamines Using *Candida antarctica* Lipase B

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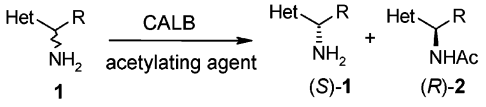
Candida antarctica lipase B has been used to kinetically resolve a structurally diverse series of bicyclic 1-heteroaryl primary amines by enantioselective acetylation. High yields of either enantiomer could be obtained with excellent enantioselectivity (90−99% ee), while the undesired enantiomer could, in some cases, be recycled by thermal racemization. The absolute stereochemistry of the products was confirmed by an X-ray crystal structure.

Given the importance of chiral amines as building blocks in medicinal chemistry and as scaffolds for chiral ligands, efficient and cost-effective methods for the preparation of optically active amines are highly sought after. Traditional synthetic methods to access enantioenriched amines employ either stoichiometric chiral reagents and auxiliaries or chiral catalysts for reduction of amine precursors[1] such as oximes, imines,[2] hydrazones,[3] and enamides.[4] In contrast to these approaches, the preparation of optically active amines via lipase-catalyzed enantioselective acetylation can be accomplished using mild conditions, inexpensive and nontoxic reagents, and facile experimental procedures.[5] As a result, the use of enzymatic methods for resolving racemic amine substrates has rapidly gained prominence, particularly for large-scale industrial applications. An enzyme that has been widely applied in the resolution of alcohols is *Candida antarctica* lipase B[6] (CALB, available immobilized on polyacrylamide as Novozyme 435). As a transesterification catalyst, CALB generally shows high selectivity for the (*R*)-enantiomer of secondary alcohols, leaving the (*S*)-enantiomer unchanged.[7] However, only scattered reports describing the resolution of primary amines with CALB have appeared in the literature;[8−10] of these, only a single example involving 1-heteroarylamines has emerged.[11]

SCHEME 1



In the course of our drug development program, we required both the (*R*)- and (*S*)-enantiomers of a structurally diverse series of bicyclic 1-heteroaryl primary amines. We chose to employ CALB in our investigation (Scheme 1) with an emphasis on determining the general utility of this method for preparing a variety of enantiopure amines.

A number of bicyclic amines containing fused pyridine, pyrazine, furan, and tetrahydropyran heterocycles were prepared as substrates for this study (Scheme 2). Synthesis of the amino-substituted 5,6,7,8-tetrahydroquinoline and 5,6,7,8-tetrahydroisoquinoline compounds **1b**,[12] **1c**, **1d**, and **1g** was accomplished by selective hydrogenation of the corresponding quinoline and isoquinoline substrates **3** and **4**, followed by acetamide hydrolysis.[13] The pyrazine-fused material **1e** was prepared via free-radical benzylic bromination of **5**, followed by displacement of the bromide with sodium azide and subsequent

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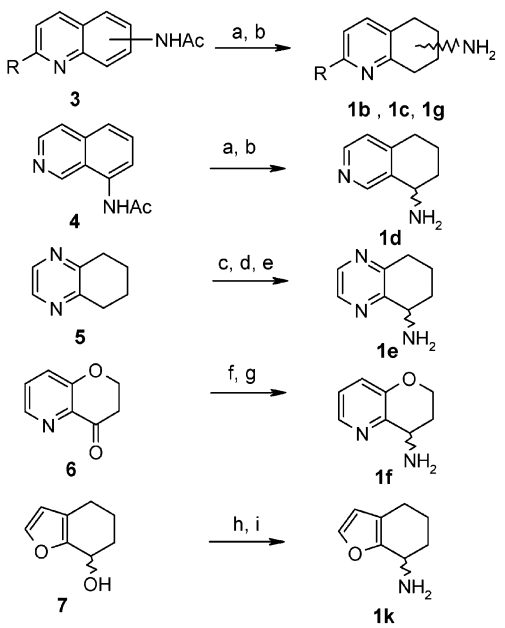
SCHEME 2[a]



[a] Reaction conditions: (a) H_2, PtO_2, CF_3COOH [62% for **1b** (R = H, 8-NH_2), 54% for **1c** (R = H, 5-NH_2), 66% for **1g** (R = Me, 8-NH_2), 45% for **1d**]; (b) 6 N HCl, reflux (98% for **1b**, 94% for **1c**, 99% for **1g**, 97% for **1d**); (c) NBS, benzoyl peroxide, CCl_4, 54%; (d) NaN_3, DMF, 60 °C, 97%; (e) H_2, 10% Pd/C, MeOH, 99%; (f) NH_2OH HCl, MeOH, 99%; (g) Zn, EtOH, NH_4OH, NH_4OAc, 86%; (h) $(PhO)_2PON_3$, DBU, toluene, 63%; (i) H_2, Pd/C, MeOH, 60%.

reduction to the amine. Conversion of the tetrahydropyran-fused ketone **6**[12] to the corresponding oxime followed by reduction to the amine with Zn afforded **1f**. A Mitsunobu reaction[14] converted alcohol **7**[15] to the corresponding azide, and hydrogenation provided the amine **1k**. The remaining substrates **1a**, **1i**,[12] **1j**,[12] and **1l**[16] were prepared using known procedures.

The results of the enzymatic resolution study are shown in Table 1. Ethyl acetate was used as the acylating agent, either in isopropyl ether (condition A) or neat in instances when the amine was insoluble in $^iPr_2O$ (condition B). The enantioselectivity (E) for each example was calculated from the percent conversion and the enantiomeric excess (ee) of the amine.[17] In cases where the selectivity was moderate, the reactions were allowed to exceed 50% conversion until the ee of the unreacted (*S*)-amine was satisfactory (>90%). We initially investigated the resolution of 1-pyridin-2-ylethylamine (**1a**)[11] by CALB at 60 °C in neat ethyl acetate, which provided a 41% yield of (*S*)-**1a** in 99% ee after 56% conversion ($E = 40$, reaction time = 7 h, entry 1).[18] For this substrate, we observed that reactions performed at lower temperatures were sluggish, requiring over 24 h to produce (*S*)-**1a** with >90% ee, and often stalled due to (apparent) deactivation of the enzyme. We therefore carried out all subsequent reactions at a temperature of 60 °C.

Applying these conditions to the amino-substituted 5,6,7,8-tetrahydroquinoline substrates **1b** and **1c** produced highly satisfactory results: in each case, the (*R*)-amine was acetylated with excellent selectivity ($E > 500$). Both unreacted (*S*)-**1b**[19] and (*S*)-**1c** were isolated in 48% yield and >99% ee (entries 2 and 3). The corresponding acetamides **2b** and **2c** were obtained in 48% yield and 98% ee. A comparison of entries 1 and 2 indicates that the introduction of a fused cyclohexane ring results in a greater than 10-fold increase in enantiodifferentiation. This explanation for this effect is unclear, but factors such as increased molecular rigidity and favorable hydrophobic interactions within the active site of the enzyme are most likely involved. The 5,6,7,8-tetrahydroisoquinoline substrate **1d** was also resolved with high selectivity ($E = 210$, entry 4), as were the pyrazine-fused bicyclic amine **1e** (entry 5) and the pyridine-fused tetrahydropyran substrate **1f** (entry 6). A marked decrease in enzyme specificity ($E = 47$) was observed for **1g**, which bears a methyl group at the 2-position (entry 7); this result suggests that the enantiodiscrimination of CALB is compromised by the presence of a sterically demanding substituent at this position.

Interestingly, the tetrahydronaphthalene amine **1h** displayed much lower selectivity ($E = 17$)[20] under the same conditions, and it was necessary to drive the reaction to 64% completion in order to obtain (*S*)-**1h** with 99% ee (entry 8). In this case, a blank reaction was carried out in which **1h** was heated at 60 °C in isopropyl ether with 5 equiv of EtOAc for 24 h. No conversion of **1h** to **2h** was observed under these conditions, demonstrating that the rate of the (uncatalyzed) background reaction is negligible and is not the explanation for the low selectivity of **1h**. The excellent enantiodiscrimination observed for substrates **1c**,**d** (entries 3 and 4) also rules out anchimeric assistance from a vicinal heteroatom as a requirement for high selectivity. A plausible explanation is that the higher pK_a of the primary amine function in **1h** ($pK_a = 9.7$, compared to 8.9 for **1b**) may result in enhanced reactivity of both enantiomers in the CALB-catalyzed aminolysis reaction, thereby diminishing selectivity. The results obtained for **1l** ($E = 120$, entry 12, $pK_a = 8.3$) and **1m** ($E = 5$, entry 13, $pK_a = 9.5$)[21] also support the notion that pK_a may be a factor influencing selectivity in resolutions by CALB.

Finally, decreasing the size of the cycloalkyl ring in **1b** to a five-membered ring (**1i**, entry 9) reduced selectivity ($E = 49$), while increasing the ring size to seven-membered (**1j**, entry 10) resulted in much lower enantioselectivity ($E = 5$). Similarly, replacing the pyridine ring in **1b** with a furan ring (**1k**, entry 11) also lowered selectivity ($E = 27$). These observations suggest that a 6,6-fused bicyclic ring system may result in optimal chiral recognition for CALB.

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TABLE 1. Enzymatic Resolution of Primary Amines 1a−m (Scheme 1)

Entry		Substrate	conditions[a]	conversion[b] (%)	ee[c] (%) (*S*)-**1**	ee[c] (%) (*R*)-**2**	E	isolated yield (%) (*S*)-**1**	isolated yield (%) (*R*)-**2**
1	**1a**		B	56	99	75	41	41	52
2	**1b**		A	50	>99	98	>500	48	48
3	**1c**		A	50	>99	98	>500	48	48
4	**1d**		A	51	99	94	210	43	51
5	**1e**		B	50	99	98	>500	45	47
6	**1f**		B	50	99	98	>500	43	47
7	**1g**		A	51	91	88	47	38	48
8	**1h**		A	64	99	48	17	32	56
9	**1i**		B	55	99	79	49	42	55
10	**1j**		A	58	61	45	5	41	55
11	**1k**		A	55	94	79	27	39	53
12	**1l**		A	51	97	94	120	48	51
13	**1m**		B	70	82	40	5	29	70

[a] All reactions were performed at 60 °C. Reaction times varied from 2 to 24 h. Condition A: reaction carried out in isopropyl ether with 4−5 equiv of EtOAc. Condition B: reaction carried out in neat EtOAc. [b] Percent conversion determined by ^{1}H NMR. [c] Enantiomeric excess determined by chiral GC.

The absolute configuration of the resolved amine **1b** was confirmed by X-ray crystallography. Treatment of enantiopure (*S*)-**1b** with chloro-(3-thiapentane-1,5-dithiolato)oxorhenium **8**[22] provided the crystalline rhenium complex **9**, which clearly shows the (*S*)-stereochemistry for the 8-amino-5,6,7,8-tetrahydroquinoline ligand (Figure 1).

The enantioenriched (*R*)-isomer of each amine could be readily obtained by hydrolysis of the corresponding acetamide under acidic conditions (6 N HCl, reflux); notably, this procedure did not promote racemization. However, in the case of **1b** both the enantiopure amine and the acetamide **2b** could easily be thermally racemized and recycled (Scheme 3). For example, heating (*R*)-**2b** for 30 min to 150 °C afforded racemic **2b**, which was subsequently hydrolyzed to **1b**. Alternatively, hydrolysis of (*R*)-**2b** provided (*R*)-**1b** with no loss of enantiomeric purity. Heating (*R*)-**1b** to 150 °C for 30 min provided racemic **1b** in 87% yield. The racemization of **2a** and **2d** was effected under analogous conditions.

In conclusion, we have demonstrated the utility of *C. antarctica* lipase B as a versatile biocatalyst for the kinetic resolution of a variety of bicyclic 1-heteroarylamines. Both enantiomers are available in high (90−99%) ee via this protocol, and in several cases either enantiomer may be thermally racemized and recycled. This procedure represents a valuable method for preparing enantioenriched amines in a cost-effective manner, and studies on a number of extensions to this work are currently underway.

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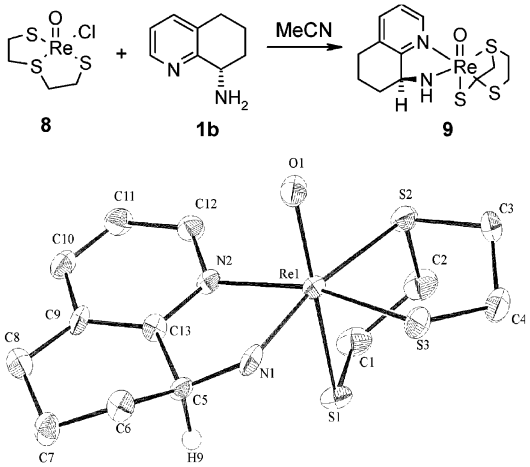
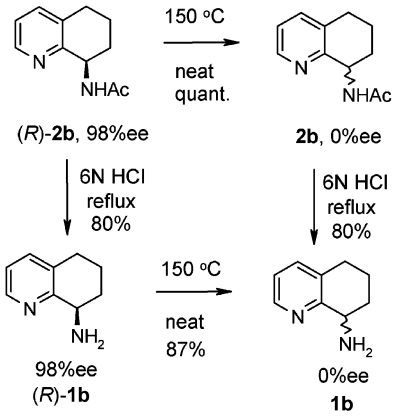


FIGURE 1. X-ray crystal structure of **9**.

SCHEME 3. Racemization of (*R*)-2b and (*R*)-1b



Experimental Section

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ with TMS as an internal standard. Mass spectra were obtained by EI methods. Column chromatography was performed using 230−400 mesh silica gel, and thin-layer chromatography (TLC) was performed on precoated silica plates. Commercial anhydrous solvents (99.9%), 1-tetrahydronaphthylamine (**1h**), and 1-naphthylen-1-ylethylamine (**1m**) were used without further purification. Compounds **1b**,[11] **1c**,[12] **1d**,[12] **1g**,[12] **1h**,[11] **1i**,[11] and **1j**[15] were obtained via previously reported methods. Compound **1a** has previously been resolved using CALB and EtOAc.[10]

General Procedure for Resolution Reaction. A mixture of the amine (1 equiv; ~0.2 M), *C. antarctica* lipase B (Novozyme 435) (30 wt %), and ethyl acetate (4−5 equiv) in isopropyl ether (condition A) or neat ethyl acetate (condition B) was heated to 60 °C and stirred vigorously. The progress of the reaction was monitored by GC using a chiral J&W CycloSil B column. Upon completion of the reaction (typically 2−24 h), the mixture was filtered through a glass sintered funnel, washed with EtOAc or methanol, and concentrated in vacuo. The unreacted amine and the acetamide were separated by chromatography on silica gel. The enantiomeric excess of the amine and the acetamide were determined by chiral GC by comparison of the retention times with independently prepared racemic samples.

Resolution of 1b. Following the general procedure, 5,6,7,8-tetrahydroquinolin-8-ylamine (**1b**) (412.7 mg, 2.78 mmol), CALB (128 mg), EtOAc (1.09 mL), and ^{i}Pr$_2$O (7 mL) were stirred for 4 h. The conversion determined from ^{1}H NMR by integration of the peaks at 4.88 ppm (C*H*NHAc) and 4.00 ppm (C*H*NH$_2$) was 50%. Flash chromatography of the material on silica gel using 1:10 MeOH−CH_2Cl_2 then 10:1:1 CH_2Cl_2−MeOH−NH_4OH furnished (*R*)-*N*-(5,6,7,8-tetrahydroquinolin-8-yl)acetamide[12] ((*R*)-**2b**) (254 mg, 48%) in 98% ee (chiral GC method: 160 °C for 10 min, ramp rate 1 °C/min to 150 °C, hold at 150 °C for 50 min, $t_R(S) = 57.5$ min, $t_R(R) = 58.6$ min); $[\alpha]_D = -90$ (*c* 0.52, $CHCl_3$). The unreacted (*S*)-5,6,7,8-tetrahydroquinolin-8-ylamine ((*S*)-**1b**)[11,18] was isolated in 48% yield (198 mg) and 99% ee (chiral GC: $t_R(S) = 7.9$ min, $t_R(R) = 8.2$ min); $[\alpha]_D = +49$ (*c* 1.31, $CHCl_3$);^{1}H NMR δ 1.65−1.75 (m, 2H), 1.91−1.98 (m, 1H), 2.04 (br s, 2H), 2.15−2.21 (m, 1H), 2.70−2.83 (m, 2H), 3.99−4.01 (m, 1H), 7.04 (dd, 1H, $J = 8$, 5 Hz), 7.34 (dd, 1H, $J = 8$, 1 Hz), 8.39 (d, 1H, $J = 5$ Hz); ^{13}C NMR δ 19.6, 28.7, 31.7, 51.0, 121.3, 131.2, 136.4, 146.7, 159.2; MS *m*/*z* 149 (M + H$^+$).

Resolution of 1c. Following the general procedure, 5,6,7,8-tetrahydroquinolin-5-ylamine (**1c**) (213.2 mg, 1.44 mmol), CALB (64 mg), EtOAc (0.56 mL), and ^{i}Pr$_2$O (4.8 mL) were stirred for 6 h. The conversion determined from ^{1}H NMR by integration of the peaks at 5.07 ppm (C*H*NHAc) and 3.91 ppm (C*H*NH$_2$) was 50%. Flash chromatography of the material on silica gel using 1:10 MeOH−CH_2Cl_2 then 20:2:1 CH_2Cl_2−MeOH−NH_4OH furnished (*R*)-*N*-(5,6,7,8-tetrahydroquinolin-5-yl)acetamide[2] ((*R*)-**2c**) (132 mg, 48%) in 98% ee (chiral GC method: isothermal at 85 °C for 220 min ramp 5 °C/min to 210 °C, hold 5 min, $t_R(S) = 248.2$ min, $t_R(R) = 248.5$ min); $[\alpha]_D = +110$ (*c* 1.32, $CHCl_3$). The unreacted (*S*)-5,6,7,8-tetrahydroquinolin-5-ylamine ((*S*)-**1c**) was isolated in 48% yield (103 mg) and 99% ee (chiral GC: $t_R(S) = 236.0$ min, $t_R(R) = 236.6$ min); $[\alpha]_D = +39$ (*c* 1.03, $CHCl_3$);^{1}H NMR δ 1.50−1.70 (m, 3H), 1.74−1.85 (m 1H), 1.86−2.09 (m, 2H), 2.76−2.99 (m, 2H), 3.94 (m, 1H), 7.07 (dd, 1H, $J = 7.8$, 4.5 Hz), 7.70 (d, 1H, $J = 7.8$ Hz), 8.35 (dd, 1H, $J = 4.5$, 1.5 Hz); ^{13}C NMR δ 19.8, 32.9, 34.0, 49.6, 121.7, 136.2, 136.6, 148.1, 157.3; MS *m*/*z* 149 (M + H$^+$).

Resolution of 1d. Following the general procedure, 5,6,7,8-tetrahydroisoquinolin-5-ylamine (**1d**) (268.3 mg, 1.81 mmol), CALB (80 mg), EtOAc (0.71 mL), and ^{i}Pr$_2$O (6.0 mL) were stirred for 23 h. The conversion determined from ^{1}H NMR by integration of the peaks at 5.16 ppm (C*H*NHAc) and 3.90 ppm (C*H*NH$_2$) was 51%. Flash chromatography of the material on silica gel using 1:4 MeOH−CH_2Cl_2 then 4:1:1 CH_2Cl_2−MeOH−NH_4OH furnished (*R*)-*N*-(5,6,7,8-tetrahydroquinolin-5-yl)acetamide[12] ((*R*)-**2d**) (181 mg, 51%) in 94% ee (chiral GC method: 160 °C for 20 min, ramp rate 5 °C/min to 200 °C, hold at 200 °C for 20 min, $t_R(S) = 38.3$ min, $t_R(R) = 39.1$ min); $[\alpha]_D = +95$ (*c* 1.81, $CHCl_3$). The unreacted (*S*)-5,6,7,8-tetrahydroisoquinolin-5-ylamine ((*S*)-**1d**) was isolated in 43% yield (114 mg) and 99% ee (chiral GC: $t_R(S) = 15.9$ min, $t_R(R) = 16.2$ min); $[\alpha]_D = +63$ (c 1.14, $CHCl_3$).^{1}H NMR δ 1.26−1.69 (m, 3H), 1.70−1.85 (m, 1H), 1.86−2.11 (m, 2H), 2.67−2.79 (m, 2H), 3.91 (t, 1H, $J = 5.4$ Hz), 7.32 (d, 1H, $J = 4.3$ Hz), 8.32 (s, 1H), 8.37 (d, 1H, $J = 4.3$ Hz); ^{13}C NMR δ 20.1, 26.7, 33.7, 49.3, 122.5, 132.6, 147.6, 149.9, 150.8; MS *m*/*z* 149 (M + H$^+$).

Resolution of 1e. Following the general procedure, 5,6,7,8-tetrahydroquinoxalin-5-ylamine (**1e**) (263 mg, 1.76 mmol), CALB (45 mg), and EtOAc (7.0 mL) were stirred for 2 h. The conversion determined from ^{1}H NMR by integration of the peaks at 4.94 ppm (C*H*NHAc) and 4.01 ppm (C*H*NH$_2$) was 50%. Flash chromatography of the material on silica gel using 1:4 MeOH−EtOAc followed by 1:1:4 NH_4OH−MeOH−EtOAc furnished (*R*)-*N*-(5,6,7,8-tetrahydroquinoxalin-5-yl)acetamide ((*R*)-**2e**) (157 mg, 47%) in 98% ee (chiral GC method: 130 °C for 180 min, $t_R(S) = 183.5$ min, $t_R(R) = 183.7$ min); $[\alpha]_D = -78$ (*c* 1.40, $CHCl_3$); ^{1}H NMR δ 1.62−1.75 (m, 1H), 1.85−2.04 (m, 2H), 2.06 (s, 3H), 2.48−2.57 (m, 1H), 2.90−3.13 (m, 2H), 4.96−5.03 (m, 1H), 6.34 (br s, 1H), 8.35 (d, 1H, $J = 2.4$ Hz), 8.39 (d, 1H, $J = 2.4$ Hz); ^{13}C NMR δ 19.9, 23.6, 29.7, 31.8, 50.6, 142.1, 143.3, 152.0, 154.0, 170.7; MS *m*/*z* 214 (M + Na$^+$). The unreacted (*S*)-5,6,7,8-tetrahydroquinoxalin-5-ylamine ((*S*)-**1e**) was isolated in 45% yield (118 mg) and 99% ee ($t_R(S) = 25.9$ min, $t_R(R) = 29.0$ min); $[\alpha]_D = +61$ (*c* 0.71, $CHCl_3$) and displayed spectra identical with those of the starting material.

Resolution of 1f. Following the general procedure, 3,4-dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamine (**1f**) (243 mg, 1.62 mmol), CALB (73 mg), and EtOAc (6.0 mL) were stirred for 2 h. The conversion determined from ^{1}H NMR by integration of the peaks at 7.93 and 8.16 ppm was 50% (C*H*NH$_2$ and C*H*NHAc signals were not distinct). Flash chromatography of the material on silica gel using 1:10 MeOH−CH_2Cl_2 followed by 1:1:10 NH_4OH−MeOH−CH_2Cl_2 furnished (*R*)-*N*-(3,4-dihydro-2*H*-pyrano[3,2-*b*]pyridin-4-yl)acetamide ((*R*)-**2f**) (145 mg, 47%) in 98% ee (chiral GC method: 140 °C for 16 min, ramp rate 5 °C/min to 160 °C, hold at 160 °C for 50 min, $t_R(S)$ = 41.5 min, $t_R(R)$ = 40.9 min); $[\alpha]_D$ = −69 (c 1.45, $CHCl_3$); ^{1}H NMR δ 1.91−2.00 (m, 1H), 1.97 (s, 3H), 2.47−2.57 (m, 1H), 4.18−4.22 (m, 2H), 4.85−4.92 (m, 1H), 6.97 (m, 2H), 7.24 (br s, 1H), 7.93−7.95 (dd, 1H, *J* = 1.8, 3.9 Hz); ^{13}C NMR δ 23.3, 28.9, 47.2, 64.4, 124.3, 124.7, 141.3, 141.7, 152.0, 170.9; MS *m*/*z* 215 (M + Na^+). The unreacted (*S*)-3,4-dihydro-2*H*-pyrano-[3,2-*b*]pyridin-4-ylamine ((*S*)-**1f**) was isolated in 43% yield (104 mg) and 99% ee ($t_R(S)$ = 14.7 min, $t_R(R)$ = 15.6 min); $[\alpha]_D$ = −13 (*c* 0.72, $CHCl_3$) and displayed spectra identical with those of the starting material.

Resolution of 1g. Following the general procedure, 2-methyl-5,6,7,8-tetrahydroquinolin-8-ylamine (**1g**) (412.7 mg, 2.78 mmol), CALB (128 mg), EtOAc (0.63 mL), and ^{i}Pr$_2$O (7 mL) were stirred for 9 h. The conversion determined from ^{1}H NMR by integration of the peaks at 4.73 ppm (C*H*NHAc) and 4.00 ppm (C*H*NH$_2$) was 51%. Flash chromatography of the material on silica gel using 1:10 MeOH−CH_2Cl_2 then 10:1:1 CH_2Cl_2−MeOH−NH_4OH furnished (*R*)-*N*-(2-methyl-5,6,7,8-tetrahydroquinolin-8-yl)acetamide[2] ((*R*)-**2g**) (167 mg, 47%) in 88% ee (chiral GC method: initial temperature 140 °C, initial time 22 min, ramp rate 1 °C/min, final temperature 150 °C, final time 70 min, $t_R(S)$ = 89.4 min, $t_R(R)$ = 91.6 min); $[\alpha]_D$ = −102 (*c* 1.67, $CHCl_3$). The unreacted (*S*)-2-methyl-5,6,7,8-tetrahydroquinolin-8-ylamine ((*S*)-**1g**) was isolated in 38% yield (107 mg) and 91% ee (chiral GC: $t_R(S)$ = 19.9 min, $t_R(R)$ = 20.6 min); $[\alpha]_D$ = +65 (*c* 1.07, $CHCl_3$);^{1}H NMR δ 1.62−1.82 (m, 2H), 1.84−2.00 (m, 3H), 2.11−2.20 (m, 1H), 2.49 (s, 3H), 2.61−2.82 (m, 2H), 3.93−4.00 (m, 1H), 6.91 (d, 1H, *J* = 7.8 Hz), 7.25 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR δ 20.4, 24.6, 29.1, 32.6, 51.8, 121.7, 128.6, 137.6, 155.9, 159.0; MS *m*/*z* 163 (M + H^+), 146 (M − NH_2).

Resolution of 1i. Following the general procedure, 6,7-dihydro-5*H*-[1]pyrindin-7-ylamine (**1i**) (271 mg, 2.02 mmol), CALB (81 mg), and EtOAc (6.5 mL) were stirred for 7 h. The conversion determined from ^{1}H NMR by integration of the peaks at 5.17 ppm (C*H*NHAc) and 4.21 ppm (C*H*NH$_2$) was 55%. Flash chromatography of the material on silica gel using 1:10 MeOH−CH_2Cl_2 followed by 1:1:4 NH_4OH−MeOH−CH_2Cl_2 furnished (*R*)-*N*-(6,7-dihydro-5*H*-[1]pyrindin-7-yl)acetamide ((*R*)-**2i**) (194 mg, 41%). The two enantiomers of the acetamide could not be resolved by GC nor HPLC, and hence the % ee had to be determined indirectly. A small sample of the acetamide was treated with 1N HCl to convert it to the amine, and the resulting amine was resolved by chiral GC (chiral GC method: 85 °C for 120 min, ramp rate 5 °C/min to 210 °C, final time 5 min; $t_R(S)$ = 124.3 min, $t_R(R)$ = 126.1 min) to give % ee of 79%; $[\alpha]_D$ = −41 (*c* 1.49, $CHCl_3$); ^{1}H NMR δ 1.75−1.89 (m, 1H), 2.07 (s, 3H), 2.80−2.98 (m, 3H), 5.19−5.27 (m, 1H), 6.32 (br s, 1H), 7.14 (dd, 1H, *J* = 7.5, 5.0 Hz), 7.55 (d, 1H, *J* = 7.5 Hz), 8.39 (d, 1H, *J* = 4.5 Hz); ^{13}C NMR δ 23.6, 28.3, 33.9, 55.7, 123.0, 133.3, 137.2, 148.2, 148.4, 162.7, 171.0. The unreacted (*S*)-6,7-dihydro-5*H*-[1]pyrindin-7-ylamine ((*S*)-**1i**) was isolated in 42% yield (113 mg) and 99% ee (chiral GC, $t_R(S)$ = 124.3 min, $t_R(R)$ = 126.1 min) and displayed spectra identical to the starting material: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68−1.88 (m, 1H), 2.50−2.61 (m, 3H), 2.75−2.86 (m, 1H), 2.92 (ddd, 1H, *J* = 13.2, 9.0, 3.0 Hz), 4.32 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.08 (dd, 1H, *J* = 7.8, 4.8 Hz), 7.51 (d, 1H, *J* = 7.8 Hz), 8.40 (d, 1H, *J* = 4.8 Hz). The dark color of the amine after purification by column chromatography prevented determination of its optical rotation.

Resolution of 1j. Following the general procedure, 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylamine (**1j**) (195 mg, 1.20 mmol), CALB (59 mg), EtOAc (0.48 mL), and ^{i}Pr$_2$O (4.6 mL) were stirred for 24 h. The conversion determined from ^{1}H NMR by integration of the peaks at 5.05 ppm (C*H*NHAc) and 4.34 ppm (C*H*NH$_2$) was 58%. Flash chromatography of the material on silica gel using 1:10 MeOH−CH_2Cl_2 followed by 1:1:4 NH_4OH−MeOH−CH_2Cl_2 furnished the (*R*)-*N*-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)acetamide ((*R*)-**2j**) (134 mg, 55%) in 45% ee (chiral GC method: 180 °C for 15 min, ramp rate of 10 °C/min to 210 °C, hold 10 min, $t_R(S)$ = 17.4 min, $t_R(R)$ = 17.1 min); $[\alpha]_D$ = −10 (*c* 1.34, $CHCl_3$); ^{1}H NMR δ1.09−1.31 (m, 2H), 1.80−2.03 (m, 3H), 2.06 (s, 3H), 2.24 (d, 1H, *J* = 13.5 Hz), 2.65−2.71 (m, 1H), 2.75−2.85 (m, 1H), 4.96−5.01 (m, 1H), 7.06 (dd, 1H, *J* = 7.0, 4.8 Hz), 7.38 (d, 1H, *J* = 7.0 Hz), 8.11 (br s, 1H), 8.28 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR δ 24.0, 27.3, 30.1, 34.5, 34.8, 53.8, 122.8, 137.0, 137.5, 145.5, 159.2, 169.6; MS *m*/*z* 205 (M + H^+). The unreacted (*S*)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ylamine ((*S*)-**1j**) was isolated in 41% yield (81 mg) and 61% ee (chiral GC, $t_R(S)$ = 5.81 min, $t_R(R)$ = 6.00 min); $[\alpha]_D$ = +2 (*c* 1.13, $CHCl_3$); and displayed spectra identical to the starting material: ^{1}H NMR δ 1.20−1.35 (m, 1H), 1.36−1.53 (m, 1H), 1.75−2.01 (m, 4H), 2.15 (br s, 2H), 2.69−2.77 (m, 2H), 4.16 (d, 1H, *J* = 8.7 Hz), 6.95−7.06 (m, 1H), 7.32 (d, 1H, *J* = 6.0 Hz), 8.34 (br s, 1H).

Resolution of 1k. Following the general procedure, 4,5,6,7-tetrahydrobenzofuran-7-ylamine (**1k**) (150 mg, 1.09 mmol), CALB (45 mg), EtOAc (0.43 mL), and ^{i}Pr$_2$O (4.0 mL) were stirred for 17 h. The conversion determined from ^{1}H NMR by integration of the peaks at 5.09 ppm (C*H*NHAc) and 3.95 ppm (C*H*NH$_2$) was 55%. Flash chromatography of the material on silica gel using 1:20 MeOH−CH_2Cl_2 followed by 1:1:4 NH_4OH−MeOH−CH_2Cl_2 furnished (*R*)-*N*-(4,5,6,7-tetrahydrobenzofuran-7-yl)acetamide ((*R*)-**2k**) (104 mg, 53%) in 79% ee (chiral GC method: 120 °C for 15 min, ramp rate of 2 °C/min to 160 °C, hold 20 min at 160 °C, $t_R(S)$ = 43.6 min, $t_R(R)$ = 45.8 min); $[\alpha]_D$ = +58 (*c* 1.04, $CHCl_3$); ^{1}H NMR δ 1.65−1.86 (m, 3H), 1.90−1.2.04 (m, 1H), 1.94 (s, 3H), 2.30−2.50 (m, 2H), 5.01−5.05 (m, 1H), 6.07 (br s, 1H), 6.16 (s, 1H), 7.24 (s, 1H); ^{13}C NMR δ 20.6, 22.4, 23.6, 31.0, 43.6, 110.7, 120.9, 142.2, 148.8, 170.1; MS *m*/*z* 180 (M + H^+). The unreacted (*S*)-4,5,6,7-tetrahydrobenzofuran-7-ylamine ((*S*)-**1k**) was isolated in 39% yield (59 mg) and 94% ee (chiral GC, $t_R(S)$ = 12.6 min, $t_R(R)$ = 13.5 min); $[\alpha]_D$ = −18 (*c* 0.59, $CHCl_3$).

Resolution of 1l. Following the general procedure, 1-quinolin-4-ylethylamine (**1l**) (279 mg, 1.62 mmol), CALB (84 mg), EtOAc (0.63 mL), and ^{i}Pr$_2$O (6.0 mL) were stirred for 24 h. The conversion determined from ^{1}H NMR by integration of the peaks at 5.77 ppm (C*H*NHAc) and 4.90 ppm (C*H*NH$_2$) was 51%. Flash chromatography of the material on silica gel using 1:4 MeOH−CH_2Cl_2 followed by 1:1:4 NH_4OH−MeOH−CH_2Cl_2 furnished (*R*)-*N*-(1-quinolin-4-ylethyl)acetamide ((*R*)-**2l**) (177 mg, 51%) in 94% ee (determined by chiral HPLC, Chiralcel OD column, solvent A (90%) hexanes−reagent alcohol + 0.1% DEA, solvent B (10%) hexanes, column temperature 10 °C: $t_R(S)$ = 7.8 min, $t_R(R)$ = 22.0 min); $[\alpha]_D$ = +70 (*c* 1.58, $CHCl_3$); ^{1}H NMR δ 1.60 (d, 3H, *J* = 6.9 Hz), 2.01 (s, 3H), 5.81−5.90 (m, 1H), 6.13 (br s, 1H), 7.33 (d, 1H, *J* = 4.5 Hz), 7.58 (ddd, 1H, *J* = 8.1, 6.9, 1.2 Hz), 7.72 (ddd, 1H, *J* = 7.5, 6.9, 0.9 Hz), 8.07 (d, 1H, *J* = 8.1 Hz), 8.10 (d, 1H, *J* = 7.5 Hz), 8.82 (d, 1H, *J* = 4.5 Hz); ^{13}C NMR δ 21.2, 23.6, 44.7, 117.3, 123.6, 126.5, 127.4, 129.8, 130.5, 148.7, 149.0, 150.4, 169.7; MS *m*/*z* 237 (M + Na^+). The unreacted (*S*)-1-amino-1-(4-quinolyl)ethane ((*S*)-**1l**) was isolated in 48% yield (134 mg) and 97% ee (chiral GC method: isothermal at 180 °C for 20 min: $t_R(S)$ = 12.6 min, $t_R(R)$ = 13.2 min); $[\alpha]_D$ = −53 (*c* 1.33, $CHCl_3$). ^{1}H NMR δ 1.53 (d, 3H, *J* = 6.6 Hz), 1.88 (s, 3H), 4.95 (q, 1H, *J* = 6.6 Hz), 7.52−7.60 (m, 2H), 7.70 (ddd, 1H, *J* = 8.4, 6.9, 1.5 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 8.13 (dd, 1H, *J* = 8.4, 0.9 Hz), 8.89 (d, 1H, *J* = 4.5 Hz).

Procedure for Acetamide Hydrolysis. A stirred solution of (*R*)-(−)-*N*-(5,6,7,8-tetrahydroquinolin-8-yl)acetamide (230

mg, 1.21 mmol, 98% ee) in 6 N aqueous HCl (4.0 mL) was heated to 130 °C for 2 h. At this time, the reaction mixture was cooled to room temperature, cautiously rendered basic with a minimum amount of saturated aqueous NaOH, and then diluted with CH_2Cl_2 (10 mL). The phases were separated, the aqueous phase was washed with CH_2Cl_2 (5 × 20 mL), and then the combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography through a plug of silica gel (elution with 20:2:1 CH_2Cl_2−MeOH−NH_4OH) afforded 143 mg (80%) of (*R*)-(−)-8-amino-5,6,7,8-tetrahydroquinoline in 98% ee.

Representative Procedure for Thermal Racemization. (*R*)-5,6,7,8-*N*-(Tetrahydroisoquinolin-8-yl)acetamide ((*R*)-**2b**) (200 mg; 98% ee determined by chiral GC) was placed in a sealed pressure tube flushed with argon. The reaction tube was placed in a hot (150 °C) oil bath until the starting material melted and heating was continued for 30 min. The material at this point (200 mg recovery, quant. yield) had an enantiomeric excess of 0% and its ^{1}H NMR was unchanged in comparison with the starting material.

(*R*)-(5,6,7,8-Tetrahydroquinolin-8-yl)-amine ((*R*)-**1b**) (38 g; 98% ee determined by chiral GC) was heated to 150 °C in a round-bottom flask using a heating mantle. Complete racemization was observed (chiral GC) after 30 min, and the material turned dark in color. The reaction vessel was cooled to room temperature. Kugelrohr distillation of the material provided the amine in 87% yield (33 g).

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Supporting Information Available: Preparation of **1e**,**f**,**k** and **9** and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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