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Asymmetric Phase-Transfer-Catalyzed Conjugate Addition of Glycine Imine to Exocyclic α,β-Unsaturated Ketones: Construction of Polycyclic Imines Containing Three Stereocenters

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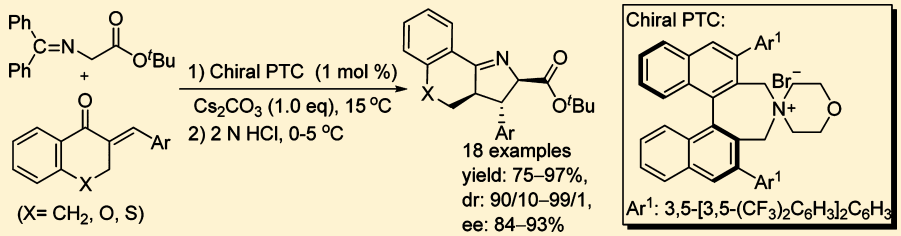
Supporting Information



ABSTRACT: We developed a facile, one-pot, multistep transformation between glycine imine and exocyclic α,β-unsaturated ketones in reactions catalyzed by chiral phase-transfer catalysts (PTC). A series of polycyclic imines containing three adjacent stereocenters were obtained in good to high yields with high diastereo- and enantioselectivities. Further transformation of the imines could afford *N*-fused polycyclic compounds with four adjacent stereocenters.

INTRODUCTION

Asymmetric catalytic conjugate addition (ACCA) of glycine imines to electrophilic acceptor substrates has been recognized as a convenient and powerful methodology for the synthesis of enantiomerically enriched α-amino acids.[1,2] In the past few years, a great effort has been devoted to the development of highly selective and efficient catalytic systems and the utilization of various α,β-unsaturated acceptors including α,β-unsaturated esters, β-aryl nitroalkenes, α,β-unsaturated ketones, arylidene malonates, and alkylidene bisphosphonates in these synthetically useful addition reactions.[3,6b] Furthermore, subsequent transformations of these chiral adducts provide rapid and efficient access to highly functionalized pyrrolidine derivatives, which serve as important synthetic intermediates for the preparation of a vast array of natural products and biologically active compounds.[4] Despite promising progress made in this area, the use of exocyclic olefin acceptors as electrophilic substrates for the construction of three or more stereocenters has not been reported and thus remains an interesting challenge.

Asymmetric phase-transfer catalysis is emerging as an area of intense interest in enantioselective synthesis owing to its operational simplicity, mild reaction conditions, and environmentally benign and safe characters.[5] Efforts from our laboratory have focused on the design and synthesis of new chiral phase-transfer catalysts from readily available chiral 1,1′-binaphthyl-2,2′-diol.[6] These interesting quaternary ammonium and phosphonium salts have been shown to give excellent enantioselectivity for the conjugate additions of sterically hindered nitroalkanes[6a] and glycine imine[6b] to bulky β-aryl-substituted enones as well as asymmetric amination reactions of benzofuranones.[6c] Encouraged by these results and as a part of our continued interest in catalytic asymmetric synthesis, we envisioned that *N*-fused polycyclic compounds with four stereocenters could be constructed by simple multistep transformation between glycine imine **2** and exocyclic olefin acceptors **1** in the presence of chiral phase-transfer catalysts (Figure 1). Herein, we present the first asymmetric catalytic

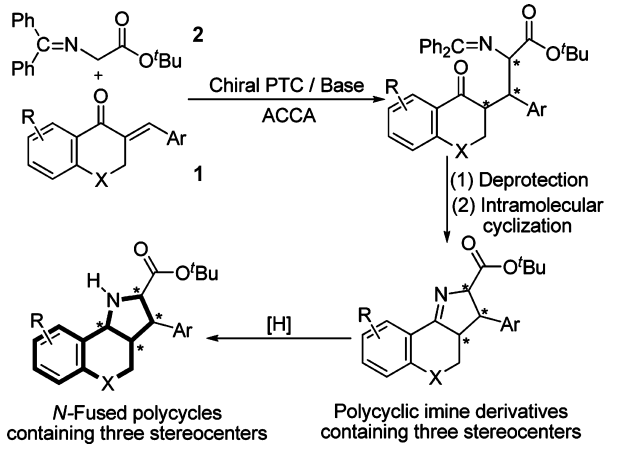


Figure 1. Asymmetric conjugate addition for the construction of polycyclic compounds.

conjugate addition of glycine imines to exocyclic α,β-unsaturated ketones. The reaction proceeded with good stereocontrol to

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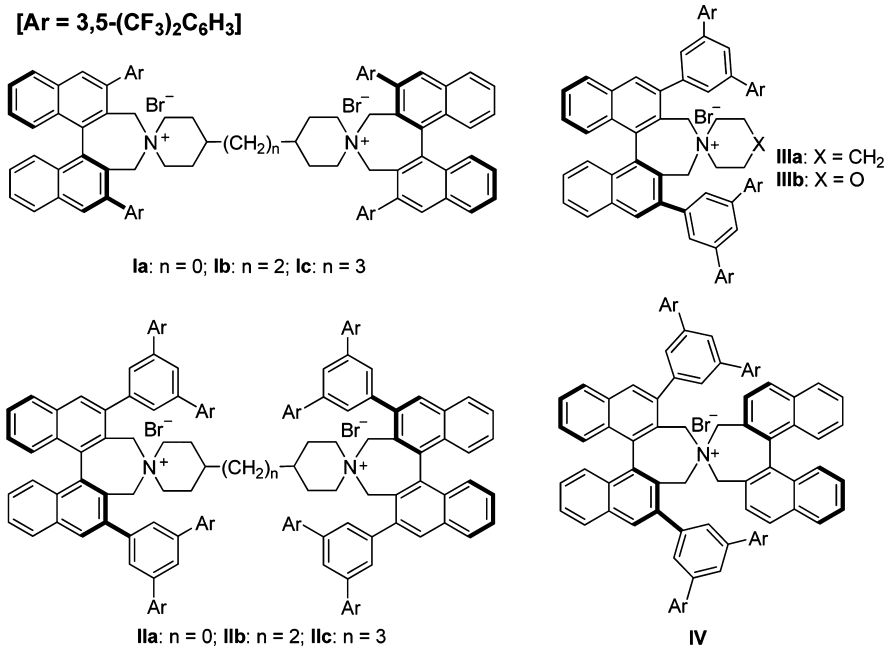

Figure 2. Binol-derived quaternary ammonium salts as chiral phase-transfer catalysts.

give polycyclic imine derivatives with high enantio- and diastereopurity. Such studies would be of immense benefit to expanding the scope of the conjugate reactions of glycine imines in organic synthesis.

RESULTS AND DISCUSSION

To validate our hypothesis, the model reaction of (*E*)-2-benzylidene-1-tetralone **1a** with *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** was performed in the presence of tetrabutylammonium bromide (1.0 equiv) and Cs_2CO_3 (1.0 equiv) in toluene. When the conjugate addition is complete (48 h, detected by TLC), the crude mixture was directly treated with 2 N hydrochloric acid. Gratifyingly, the desired cyclization product **3a** was obtained in 88% isolated yield with moderate diastereoselectivity (75:25 dr). Subsequent attempts to extend this one-pot multistep protocol to the catalytic asymmetric version were carried out by using chiral phase-transfer catalysts **I**–**IV** (Figure 2). The results are listed in Table 1. Our previously reported dinuclear *N*-spiro-ammonium salts **I** and **II** gave uniformly high diastereoselectivities, but low yields and enantioselectivities were observed (entries 1–6). Based on these preliminary results, we felt that dinuclear *N*-spiro-ammonium salts could be unsuitable for this conjugate addition of exocyclic *α*,*β*-unsaturated ketone substrates. Next, several monoquaternary ammonium salts **III and IV** were tested in the same reaction (entries 7–9). We were pleased to find that the morpholine-derived catalyst **IIIb**, bearing bulky aryl groups on 3,3′-positions of the binaphthyl scaffold, afforded the cyclization product **3a** in 59% yield with high diastereo- and enantioselecitivity (95/5 dr, 90% ee). Screening of solvents revealed that toluene was the optimal solvent under the reaction conditions used (entries 10–14 vs 8). Further optimization by changing the concentration of reactants, the catalyst loading, the temperature, and the reaction time (entries 15–19) led to the discovery that the best results were obtained when 1 mol % of **IIIb** was used at 15 °C for 96 h (89% yield, 95/5 dr, 90% ee, entry 19).

With the optimal condition in hand, we subsequently investigated the scope of this asymmetric one-pot multistep synthesis of **3** by employing a series of exocyclic *α*,*β*-unsaturated ketones **1**. As shown in Table 2, various polycyclic imines **3a**–**r** were obtained with uniformly high diastereo- and enantioselectivities. It was found that when aryl aldehyde-derived tetralones with electron-neutral or -withdrawing groups on aromatic rings were used, the multistep reactions proceeded smoothly to give **3a**–**c** in 82–89% yields (entries 1–3). However, the presence of electron-donating substituents on aromatic rings decreased the reaction rate, and relatively lower yields were obtained (entries 4 and 5). *α*,*β*-Unsaturated ketone bearing the naphthyl ring also furnished the corresponding product **3f** in 75% yield with 92/8 dr and 86% ee (entry 6). Notably, 4-chromanone- and 4-thiochromanone-derived exocyclic *α*,*β*-unsaturated ketones[7] are also viable substrates, affording the desired products **3g**–**r** in 81–97% yields (entries 7–18). In addition, we investigated the reactions with exocyclic *α*,*β*-unsaturated ketones derived from alkyl aldehydes. These substrates were found to be unsuitable for this asymmetric transformation and poor yields (<10%) were observed.

To test the feasibility of potential large-scale application of this one-pot multistep transformation, the reaction of (*E*)-2-benzylidene-1-tetralones **1a** was repeated on a 1.48 g (6.3 mmol) scale, and product **3a** was isolated in 90% yield with 95/5 dr and 90% ee (Scheme 1a). Further transformation of the polycyclic imine **3a** furnished the crystalline derivative **4** whose absolute stereochemistry was determined to be (2*R*,3*S*,3a*R*,9b*R*) from single-crystal X-ray structural analysis.[8] Thus, we established that the absolute configuration of the major stereoisomer **3a** is (2*R*,3*S*,3a*R*). In addition, the chiral phase-transfer catalyst **IIIb** can be readily recovered in 97% yield and recycled with one simple regenerating process. Anion exchange of recovered catalyst **IIIb** using Amberlyst-26A (OH^- form) gave (*S*)-**IIIb** (OH^-). The methanol solution of (*S*)-**IIIb** (OH^-) was treated with 40% HBr aqueous solution (excess) at room temperature to give the reactivated catalyst (*S*)-**IIIb** (Br^-) in 92% yield (Scheme 1b). The regenerated catalyst (*S*)-**IIIb** (Br^-) could be

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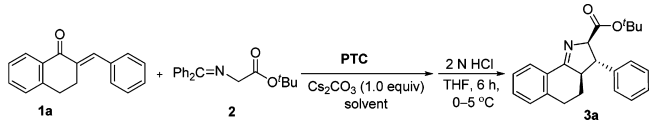
Table 1. Effect of Chiral PTC, Solvent, Temperature, And Other Reaction Conditions for One-Pot Synthesis of Polycyclic Imines[a]



entry	catalyst (mol %)	solvent	temp (°C)	yield[b] (%)	dr[c]	ee[d] (%)
1	**Ia** (1)	toluene	25	20	91:9	6
2	**Ib** (1)	toluene	25	25	90:10	6
3	**Ic** (1)	toluene	25	20	90:10	12
4	**IIa** (1)	toluene	25	22	95:5	11
5	**IIb** (1)	toluene	25	26	94:6	8
6	**IIc** (1)	toluene	25	35	95:5	62
7	**IIIa** (1)	toluene	25	17	94:6	23
8	**IIIb** (1)	toluene	25	59	95:5	90
9	**IV** (1)	toluene	25	38	95:5	<5
10	**IIIb** (1)	THF	25	16	97:3	10
11	**IIIb** (1)	Et_2O	25	52	95:5	86
12	**IIIb** (1)	CH_2Cl_2	25	14	94:6	5
13	**IIIb** (1)	xylene	25	48	97:3	80
14	**IIIb** (1)	benzene	25	33	94:6	82
15[e]	**IIIb** (1)	toluene	25	70	91:9	85
16[f]	**IIIb** (1)	toluene	25	75	91:9	86
17	**IIIb** (3)	toluene	25	62	95:5	90
18[g]	**IIIb** (1)	toluene	25	90	94:6	86
19[g]	**IIIb** (1)	toluene	15	89	95:5	90

[a]Unless otherwise noted, all reactions were carried out with *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** (59.0 mg, 0.2 mmol), (*E*)-2-benzylidene-1-tetralones **1a** (49.2 mg, 0.21 mmol), Cs_2CO_3 (65.2 mg, 0.2 mmol), and 1 mol % of PTC in solvent (1 mL) for the stated time. Then 2 N hydrochloric acid (1.0 mL) and THF (1.0 mL) were added at 0 °C, and stirring was maintained for 6 h. [b]Isolated yield. [c]Determined by HPLC or ^{1}H NMR analysis. [d]Determined by HPLC analysis using a chiral stationary phase. [e]0.5 mol/L of **2** was used. [f]1.0 mol/L of **2** was used. [g]Reaction time was 96 h.

reused without an appreciable loss of reactivity and stereoselectivity.

CONCLUSION

In summary, we have successfully developed a convenient and efficient one-pot multistep transformation of glycine imine and exocyclic α,β-unsaturated ketones by using chiral phase-transfer catalysts. A series of polycyclic imines with three adjacent stereocenters were obtained under mild reaction conditions in good to excellent yields with high diastereo- and enantioselectivities. Subsequent synthetic transformation of polycyclic imines could secure the formation of *N*-fused polycyclic compounds featuring four adjacent stereocenters. Moreover, the chiral phase-transfer catalyst could be easily recovered and reused after one simple regenerating process. Further extension of this protocol to the synthesis of natural products and compounds of pharmaceutical significance is underway in our laboratory.

EXPERIMENTAL SECTION

Materials. Tetrahydrofuran (THF), diethyl ether, benzene, and toluene were distilled from sodium/benzophenone prior to use; CH_2Cl_2 was distilled from CaH_2. All purchased reagents were used without further purification. 3,3-Disubstituted (*S*)-Binol-derived phase-transfer catalysts **Ia**−**c**,[6a] **IIa**−**c**,[6b] **IIIa,b**,[3b,c,6b] and and **IV**,[9] as well as exocyclic α,β-unsaturated ketones,[10] were synthesized according to the literature.

General Procedure for One-Pot Multistep Synthesis of Polycyclic Imines 3. *N*-(Diphenylmethylene)glycine *tert*-butyl ester (59.0 mg, 0.2 mmol) was added to a mixture of substituted enones (0.21 mmol), (*S*)-**IIIb** (2.9 mg, 0.002 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (0.2 mL) under argon atmosphere, the resulting solution was stirred at 15 °C for 96 h, 2 N hydrochloric acid (1.0 mL) and THF (1.0 mL) were added at 0 °C, and stirring was maintained for 6 h at 0 °C. The resulting mixture was neutralized by addition of solid $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/petroleum ether = 1/10 as eluant) to furnish the conjugate adducts.

*(2R,3S,3aR)-tert-Butyl 3-phenyl-3,3a,4,5-tetrahydro-2H-benzo[g]-indole-2-carboxylate (**3a**):* 61.8 mg, 89% yield; yellow oil; $[\alpha]^{20}_D$ −55.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.75−1.86 (m, 1H), 2.18−2.24 (m, 1H), 2.94−2.98 (m, 2H), 3.11−3.19 (m, 1H), 3.35 (t, *J* = 6.0 Hz, 1H), 4.67 (dd, *J* = 7.6 and 2.4 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 6.4 Hz, 2H), 7.33−7.40 (m, 5H), 8.28 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 171.9, 141.0, 140.1, 131.3, 129.6. 128.7, 128.6, 127.8, 127.0, 126.5, 126.4, 81.2, 80.2, 55.9, 55.6, 29.8, 28.2, 28.0; MS (ESI) *m*/*z* 348.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 348.1958 $[M + H]^+$, calcd for $C_{23}H_{25}NO_2$ + H 348.1960; IR (KBr) ν 3059, 2975, 2930, 2868, 1734, 1618, 1578, 1458, 1366, 1255, 1152, 1071, 1031, 959, 845, 700 cm^{-1}; dr = 95/5, er = 95/5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 10.3 min (minor) and t_R = 14.0 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2H-benzo[g]indole- 2-carboxylate (**3b**):* 59.8 mg, 82% yield; white solid; mp 120−121 °C; $[\alpha]^{20}_D$ −67.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.72−1.83 (m, 1H), 2.16−2.20 (m, 1H), 2.93−2.96 (m, 2H), 3.05−3.12 (m, 1H), 3.32 (t, *J* = 10.0 Hz, 1H), 4.60 (dd, *J* = 7.6 and 2.4 Hz, 1H), 7.06 (t, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.27−7.32 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 171.7, 163.1, 160.6, 141.0, 135.7, 131.3, 129.5. 129.3 (d, J_{C-F} = 7.8 Hz), 128.7, 126.5, 126.4, 115.6, 115.4, 81.3, 80.1, 55.6, 55.2, 29.8, 28.1, 28.0;

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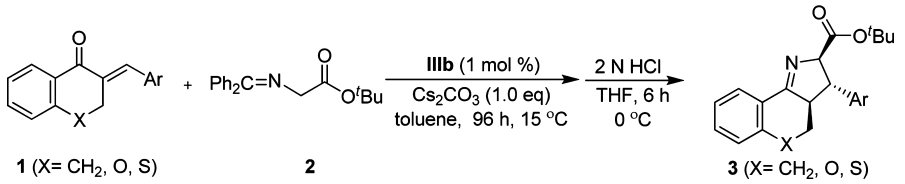
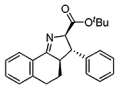
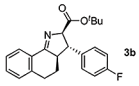
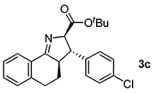
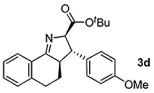
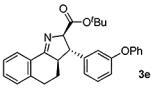
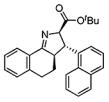
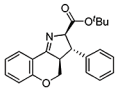
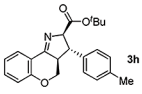
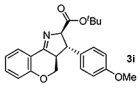
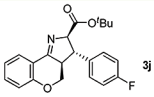
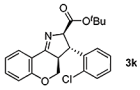
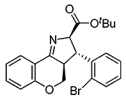
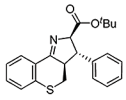
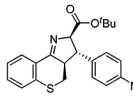
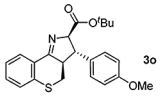
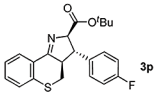
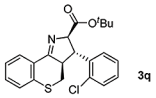
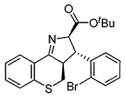
Table 2. Scope of Chiral PTC-Catalyzed One-Pot Multistep Synthesis of Polycyclic Imines 3[a]



entry	product	yield (%)[b]	dr[c]	ee (%)[d]
1	 3a	89	95:5	90
2	 3b	82	96:4	90
3	 3c	88	92:8	91
4	 3d	75	94:6	91
5	 3e	77	96:4	87
6	 3f	75	92:8	86
7	 3g	93	90:10	91
8	 3h	96	93:7	90
9	 3i	90	96:4	93
10	 3j	97	95:5	88
11	 3k	96	>99:1	87
12	 3l	97	97:3	90
13	 3m	95	90:10	93
14	 3n	94	92:8	93
15	 3o	94	97:3	93
16	 3p	96	93:7	84
17	 3q	86	99:1	91
18	 3r	81	99:1	85

[a]Unless otherwise noted, all reactions were carried out with *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** (59.0 mg, 0.2 mmol), exocyclic α,β-unsaturated ketones **1** (0.21 mmol), Cs_2CO_3 (65.2 mg, 0.2 mmol), and 1 mol % of PTC **IIIb** (2.9 mg, 0.002 mmol) in 0.2 mL of toluene at 15 °C for 96 h. Then 2 N hydrochloric acid (1.0 mL) and THF (1.0 mL) were added at 0 °C, and stirring was maintained for 6 h. [b]Isolated yield. [c]Determined by ^{1}H NMR or HPLC analysis. [d]Determined by HPLC analysis using a chiral stationary phase.

MS (ESI) m/z 366.2 $[M + H]^+$; HRMS (ESI) found: m/z 366.1864 $[M + H]^+$, calcd for $C_{23}H_{24}FNO_2$ + H 366.1864; IR (KBr) ν 3069, 2977, 2934, 2886, 1727, 1620, 1602, 1510, 1459, 1367, 1214, 1158, 1076, 1033, 848, 768 cm^{-1}; dr = 96/4, er = 95/5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 13.8 min (minor) and t_R = 17.1 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(4-chlorophenyl)-3,3a,4,5-tetrahydro-2H-benzo[g]indole-2-carboxylate (**3c**).* 67.4 mg, 88% yield; white solid; mp 127−128 °C; $[\alpha]^{20}_D$ −52.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.73−1.84 (m, 1H), 2.15−2.21 (m, 1H), 2.94−2.96 (m, 2H), 3.06−3.13 (m, 1H), 3.32 (t, *J* = 10.0 Hz, 1H), 4.61 (dd, *J* = 7.6 and 2.4 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 3H), 7.34−7.41 (m, 3H), 8.25 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.6, 140.9, 138.6, 132.7, 131.4, 129.5. 129.1, 128.8, 128.7, 126.6, 126.5, 81.4, 80.1, 55.6, 55.2, 29.8, 28.1, 28.0; MS (ESI) m/z 382.2 $[M + H]^+$; HRMS (ESI) found: m/z 382.1568 $[M + H]^+$, calcd for $C_{23}H_{24}ClNO_2$ + H 382.1572; IR (KBr) ν 3064, 2976, 2947, 2888, 1726, 1620, 1604, 1493, 1458, 1367, 1212, 1150, 1076, 1012, 844, 759 cm^{-1}; dr = 92/8, er = 95.5/4.5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 13.1 min (minor) and t_R = 15.9 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(4-methoxyphenyl)-3,3a,4,5-tetrahydro-2H-benzo[g]indole-2 -carboxylate (**3d**):* 56.8 mg, 75% yield; white solid; mp 108−110 °C; $[\alpha]^{20}_D$ −59.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.72−1.83 (m, 1H), 2.17−2.22 (m, 1H), 2.93−2.97 (m, 2H), 3.05−3.12 (m, 1H), 3.30 (t, *J* = 10.4 Hz, 1H), 3.83 (s, 3H), 4.60 (dd, *J* = 7.6 and 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.20−7.30 (m, 4H), 7.38 (t, *J* = 6.8 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 172.0, 158.6, 141.0, 131.9, 131.2, 129.6. 128.7, 126.5, 126.4, 114.1, 81.1, 80.2, 55.5, 55.3, 55.2, 29.8, 28.2, 28.0; MS (ESI) m/z 378.2 $[M + H]^+$; HRMS (ESI) found: m/z 378.2064 $[M + H]^+$, calcd for $C_{24}H_{27}NO_3$+H 378.2054; IR (KBr) ν 2996, 2975, 2936, 2841, 1733, 1614, 1601, 1518, 1455, 1362, 1253, 1150, 1076, 1032, 836 cm^{-1}; dr = 94/6, er = 95.5/4.5,

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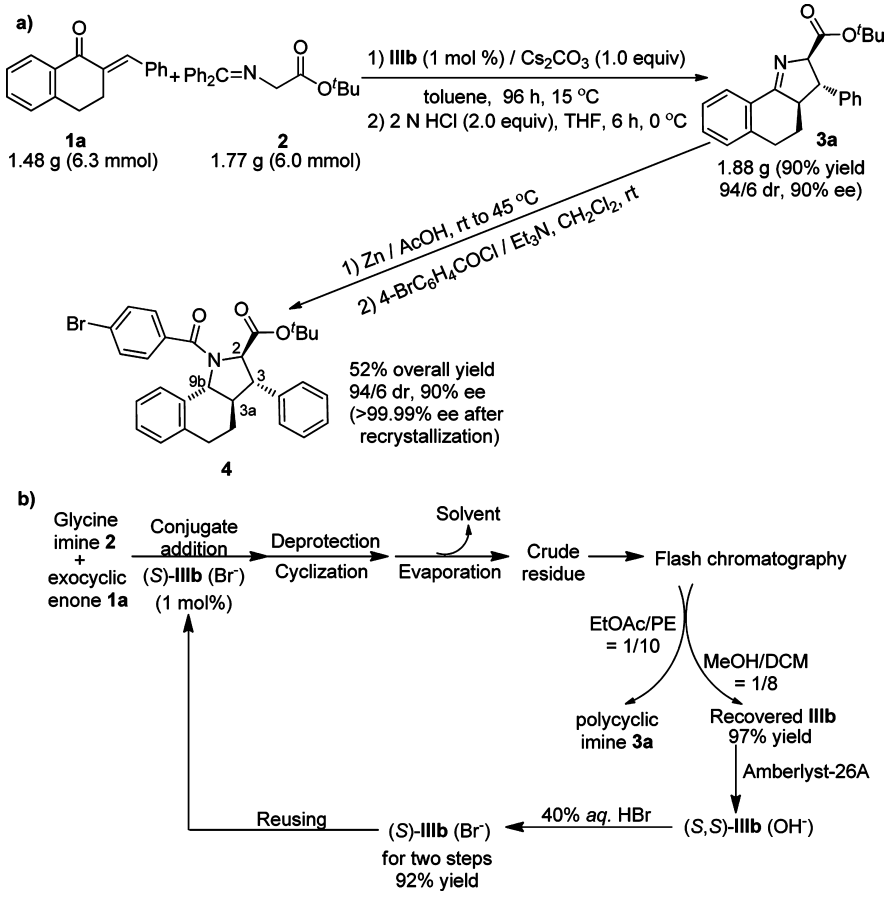
Scheme 1. Large-Scale Synthesis, Recovery of Catalyst IIIb, and Further Transformation of Polycyclic Imine 3a



determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 17.9 min (minor) and t_R = 27.2 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(3-phenoxyphenyl)-3,3a,4,5-tetrahydro-2H-benzo[g]indole-2-carboxylate (**3e**):* 67.7 mg, 77% yield; yellow oil; $[\alpha]^{20}_D$ −40.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.74−1.85 (m, 1H), 2.20−2.26 (m, 1H), 2.95−2.99 (m, 2H), 3.09−3.16 (m, 1H), 3.34 (t, *J* = 10.0 Hz, 1H), 4.65 (dd, *J* = 7.6 and 2.4 Hz, 1H), 6.92−6.95 (m, 1H), 7.04−7.15 (m, 5H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.27−7.41 (m, 5H), 8.27 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 171.7, 157.5, 157.1, 142.3, 141.0, 131.3, 129.9. 129.8, 129.5, 128.7, 126.5, 126.4, 123.4, 122.7, 118.9, 118.3, 117.3, 81.3, 80.1, 55.7, 55.5, 29.8, 28.3, 28.1; MS (ESI) *m*/*z* 440.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 440.2220 $[M + H]^+$, calcd for $C_{29}H_{29}NO_3$ +H 440.2235; IR (KBr) ν 3033, 2976, 2929, 2866, 1732, 1601, 1580, 1487, 1456, 1367, 1250, 1215, 1151, 1071, 1012, 959, 849, 753 cm^{-1}; dr = 96/4, er = 93.5/6.5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 12.6 min (minor) and t_R = 21.8 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(naphthalen-1-yl)-3,3a,4,5-tetrahydro-2H-benzo[g]indole-2-carboxylate (**3f**):* 59.6 mg, 75% yield; yellow oil; $[\alpha]^{20}_D$ −78.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.89−1.99 (m, 1H), 2.15−2.21 (m, 1H), 2.92−2.95 (m, 2H), 3.40−3.47 (m, 1H), 4.21 (t, *J* = 9.6 Hz, 1H), 5.00 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.38−7.43 (m, 1H), 7.49−7.53 (m, 3H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.91−7.93 (m, 1H), 8.10−8.12 (m, 1H), 8.34 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 172.0, 141.1, 137.0, 134.2, 132.3, 131.3, 129.8. 129.1, 128.8, 127.5, 126.6, 126.5, 126.1, 125.6, 125.5, 124.9, 123.3, 81.2, 81.0, 57.0, 50.8, 29.9, 29.1, 27.8; MS (ESI) *m*/*z* 398.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 398.2115 $[M + H]^+$, calcd for $C_{27}H_{27}NO_2$ + H 398.2124; IR (KBr) ν 3021, 2960, 2926, 2868, 1733, 1618, 1601, 1515, 1459, 1366, 1253, 1151, 1071, 1032, 845, 764 cm^{-1}; dr = 92/8, er = 93/7, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 15.0 min (minor) and t_R = 33.9 min (major).

*(2R,3S,3aR)-tert-Butyl 3-phenyl-2,3,3a,4-tetrahydrochromeno-[4,3-b]pyrrole-2-carboxylate (**3g**):* 65.3 mg, 93% yield; white solid; mp 90−92 °C; $[\alpha]^{20}_D$ −90.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.40 (t, *J* = 10.0 Hz, 1H), 3.49−3.56 (m, 1H), 4.02−4.09 (m, 1H), 4.57−4.61 (m, 1H), 4.65 (dd, *J* = 7.2 and 2.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.28−7.32 (m, 3H), 7.36−7.41 (m, 3H), 8.09 (dd, *J* = 6.4 and 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 169.1, 158.0, 138.9, 133.5, 128.9, 127.6. 127.4, 126.4, 121.4, 117.6, 117.4, 81.6, 80.7, 70.5, 52.1, 52.0, 28.0; MS (ESI) *m*/*z* 350.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 350.1751 $[M + H]^+$ calcd for $C_{22}H_{23}NO_3$ + H 350.1762; IR (KBr) ν 3030, 2975, 2925, 2871, 1733, 1623, 1620, 1574, 1472, 1456, 1367, 1315, 1219, 1151, 1031, 1004, 957, 835, 760 cm^{-1}; dr = 90/10, er = 95.5/4.5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 13.5 min (minor) and t_R = 15.5 min (major).

*(2R,3S,3aR)-tert-Butyl 3-p-tolyl-2,3,3a,4-tetrahydrochromeno-[4,3-b]pyrrole-2-carboxylate (**3h**):* 70.2 mg, 96% yield; white solid; mp 127−128 °C; $[\alpha]^{20}_D$ −58.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.37 (s, 3H), 3.38 (t, *J* = 10.0 Hz, 1H), 3.47−3.53 (m, 1H), 4.05 (t, *J* = 11.6 Hz, 1H), 4.56−4.63 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.17−7.22 (m, 4H), 7.39 (t, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.1, 158.0, 137.0, 135.7, 133.4, 129.5. 127.5, 126.4, 121.4, 117.6, 117.4, 81.6, 80.7, 70.6, 52.1, 51.7, 28.0, 21.1; MS (ESI) *m*/*z* 364.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 364.1907 $[M + H]^+$, calcd for $C_{23}H_{25}NO_3$ + H 364.1916; IR (KBr) ν 3056, 2972, 2913, 2882, 1743, 1625, 1609, 1571, 1517, 1460, 1366, 1313, 1213, 1152, 1037, 1000, 956, 811, 764 cm^{-1}; dr = 93/7, er = 95/5, determined by

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HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 13.7 min (minor) and t_R = 16.5 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(4-methoxyphenyl)-2,3,3a,4-tetrahydrochromeno[4,3-b]pyrrole-2-carboxylate (**3i**):* 68.4 mg, 90% yield; white solid; mp 112−113 °C; $[\alpha]^{20}_D$ −61.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.35 (t, *J* = 10.0 Hz, 1H), 3.43−3.50 (m, 1H), 3.83 (s, 3H), 4.04 (t, *J* = 11.6 Hz, 1H), 4.55−4.60 (m, 2H), 6.90−6.96 (m, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.1, 158.9, 158.0, 133.4, 130.7, 128.6. 126.3, 121.4, 117.6, 117.4, 114.2, 81.6, 80.7, 70.6, 55.3, 52.0, 51.4, 28.0; MS (ESI) *m*/*z* 380.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 380.1856 $[M + H]^+$, calcd for $C_{23}H_{25}NO_4$ + H 380.1872; IR (KBr) ν 3033, 2974, 2905, 2833, 1726, 1634, 1611, 1515, 1469, 1417, 1370, 1312, 1250, 1160, 1031, 1007, 825, 755 cm^{-1}; dr = 96/4, er = 96.5/3.5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol =90/10, 1.0 mL/min, 254 nm UV detector), t_R = 13.2 min (minor) and t_R = 17.6 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(4-fluorophenyl)-2,3,3a,4-tetrahydrochromeno[4,3-b]pyrrole-2 -carboxylate (**3j**):* 71.3 mg, 97% yield; white solid; mp 107−109 °C; $[\alpha]^{20}_D$ −82.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 3.37 (t, *J* = 10.0 Hz, 1H), 3.42−3.50 (m, 1H), 4.03 (t, *J* = 11.6 Hz, 1H), 4.54−4.60 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.00−7.08 (m, 3H), 7.26−7.30 (m, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 168.9, 163.2, 160.8, 158.0, 134.5, 133.5, 129.1 (d, J_{C-F} = 7.9 Hz), 126.4. 121.5, 117.5, 117.4, 115.9, 115.6, 81.7, 80.7, 70.4, 52.1, 51.3, 28.0; MS (ESI) *m*/*z* 368.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 368.1657 $[M + H]^+$, calcd for $C_{22}H_{22}FNO_3$+H 368.1667; IR (KBr) ν 2976, 2926, 2871, 1732, 1651, 1609, 1557, 1512, 1471, 1456, 1367, 1315, 1227, 1150, 1002, 956, 833, 759 cm^{-1}; dr = 95/5, er = 94/6, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 19.3 min (minor) and t_R = 21.0 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(2-chlorophenyl)-2,3,3a,4-tetrahydrochromeno[4,3-b]pyrrole-2-carboxylate (**3k**):* 74.0 mg, 96% yield; white solid; mp 115−116 °C; $[\alpha]^{20}_D$ −152.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 3.47−3.54 (m, 1H), 3.93 (t, *J* = 10.0 Hz, 1H), 4.07−4.13 (m, 1H), 4.55−4.59 (m, 1H), 4.87 (dd, *J* = 7.6 and 2.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.22−7.26 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.36−7.43 (m, 3H), 8.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.7, 158.0, 137.0, 134.2, 133.5, 130.0, 128.7, 128.4. 127.4, 126.5, 121.4, 117.6, 117.4, 81.5, 79.5, 70.5, 53.2, 48.2, 27.9; MS (ESI) *m*/*z* 384.1 $[M + H]^+$; HRMS (ESI) found *m*/*z* 384.1361 $[M + H]^+$, calcd for $C_{22}H_{22}ClNO_3$ + H 384.1374; IR (KBr) ν 3064, 2976, 2930, 2885, 1721, 1631, 1611, 1574, 1472, 1456, 1364, 1314, 1224, 1156, 1061, 1034, 1003, 841, 762 cm^{-1}; dr > 99/1, er = 93.5/6.5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 19.9 min (minor) and t_R = 25.5 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(2-bromophenyl)-2,3,3a,4-tetrahydrochromeno[4,3-b]pyrrole-2-carboxylate (**3l**):* 83.5 mg, 97% yield; white solid; mp 110−111 °C; $[\alpha]^{20}_D$ −158.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 3.40−3.47 (m, 1H), 3.97 (t, *J* = 10.0 Hz, 1H), 4.08−4.14 (m, 1H), 4.56−4.60 (m, 1H), 4.85 (dd, *J* = 7.6 and 1.6 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.33−7.43 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.7, 158.0, 138.9, 133.5, 133.3, 128.7, 128.6, 128.0, 126.5, 124.9, 121.4, 117.5, 117.3, 81.6, 79.8, 70.4, 53.9, 50.5, 27.9; MS (ESI) *m*/*z* 428.1 $[M + H]^+$; HRMS (ESI) found *m*/*z* 428.0856 $[M + H]^+$, calcd for $C_{22}H_{22}BrNO_3$ + H 428.0856; IR (KBr) ν 3063, 2977, 2930, 2872, 1737, 1626, 1609, 1573, 1471, 1456, 1367, 1314, 1220, 1151, 1022, 1002, 957, 835, 759 cm^{-1}; dr = 97/3, er = 95/5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 21.7 min (minor) and t_R = 28.2 min (major).

*(2R,3S,3aR)-tert-Butyl 3-phenyl-2,3,3a,4-tetrahydrothiochromeno[4,3-b]pyrrole-2-carboxylate (**3m**):* 69.3 mg, 95% yield; yellow oil; $[\alpha]^{20}_D$ −160.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.98 (dd, *J* = 8.0 and 4.4 Hz, 1H), 3.20 (t, *J* = 12.4 Hz, 1H), 3.38 (t, *J* = 9.6 Hz, 1H), 3.46−3.54 (m, 1H), 4.63 (dd, *J* = 6.8 and 2.4 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.29−7.33 (m, 4H), 7.31−7.41 (m, 2H), 8.37 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.7, 139.2, 137.8, 131.3, 128.9, 128.3. 127.8, 127.7, 127.4, 126.9, 124.9, 81.5, 79.7, 56.0, 55.1, 30.9, 28.0; MS (ESI) *m*/*z* 366.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 366.1522 $[M + H]^+$, calcd for $C_{22}H_{23}NO_2S$ + H 366.1521; IR (KBr) ν 3062, 2976, 2928, 1733, 1647, 1558, 1541, 1457, 1363, 1213, 1152, 1079, 1029, 955, 844, 759 cm^{-1}; dr = 90/10, er = 96.5/3.5, determined by HPLC analysis (Chiralpak IA, *n*-hexane/2-propanol =97/3, 1.0 mL/min, 254 nm UV detector), t_R = 12.8 min (major) and t_R = 14.9 min (minor).

*(2R,3S,3aR)-tert-Butyl 3-p-tolyl-2,3,3a,4-tetrahydrothiochromeno[4,3-b]pyrrole-2-carboxylate (**3n**).* 71.4 mg, 94% yield; yellow oil; $[\alpha]^{20}_D$ −140.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.38 (s, 3H), 2.98 (dd, *J* = 7.6 and 4.8 Hz, 1H), 3.19 (t, *J* = 12.4 Hz, 1H), 3.62 (t, *J* = 9.6 Hz, 1H), 3.43−3.51 (m, 1H), 4.60 (dd, *J* = 6.8 and 2.4 Hz, 1H), 7.15−7.25 (m, 6H), 7.31 (t, *J* = 7.2 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.7, 137.9, 137.0, 136.2, 121.3, 129.5. 128.7, 127.8, 127.6, 126.9, 124.9, 81.5, 79.7, 55.5, 55.1, 30.9, 28.0, 21.1; MS (ESI) *m*/*z* 380.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 380.1679 $[M + H]^+$, calcd for $C_{23}H_{25}NO_2S$ + H 380.1678; IR (KBr) ν 3053, 2978, 2920, 1732, 1607, 1591, 1516, 1442, 1367, 1216, 1153, 1088, 1030, 956, 845, 760 cm^{-1}; dr = 92/8, er = 96.5/3.5, determined by HPLC analysis (Chiralpak IA, *n*-hexane/2-propanol =97/3, 1.0 mL/min, 254 nm UV detector), t_R = 12.7 min (major) and t_R = 14.3 min (minor).

*(2R,3S,3aR)-tert-Butyl 3-(4-methoxyphenyl)-2,3,3a,4-tetrahydrothiochromeno[4,3-b]pyrrole-2-carboxylate (**3o**):* 74.8 mg, 94% yield; yellow oil; $[\alpha]^{20}_D$ −106.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.98 (dd, *J* = 8.0 and 4.4 Hz, 1H), 3.18 (t, *J* = 12.4 Hz, 1H), 3.33 (t, *J* = 9.6 Hz, 1H), 3.40−3.47 (m, 1H), 3.83 (s, 3H), 4.55 (dd, *J* = 7.2 and 2.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 3H), 7.31 (t, *J* = 7.6 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.8, 158.9, 137.8, 131.3, 131.0, 128.7. 128.2, 127.8, 126.9, 124.9, 114.3, 81.5, 79.7, 55.3, 55.2, 55.0, 30.8, 28.0; MS (ESI) *m*/*z* 396.2 $[M + H]^+$; HRMS (ESI) found *m*/*z* 396.1628 $[M + H]^+$, calcd for $C_{23}H_{25}NO_3S$ + H 396.1626; IR (KBr) ν 3062, 2976, 2929, 2835, 1731, 1613, 1589, 1514, 1441, 1366, 1248, 1150, 1068, 1030, 954, 828, 759 cm^{-1}; dr = 97/3, er = 96.5/3.5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 16.9 min (minor) and t_R = 20.8 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(4-fluorophenyl)-2,3,3a,4-tetrahydrothiochromeno[4,3-b]pyrrole-2-carboxylate (**3p**):* 74.1 mg, 96% yield; white solid; mp 88−90 °C; $[\alpha]^{20}_D$ −130.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.95 (dd, *J* = 8.0 and 4.4 Hz, 1H), 3.18 (t, *J* = 12.4 Hz, 1H), 3.36 (t, *J* = 9.6 Hz, 1H), 3.39−3.47 (m, 1H), 4.56 (dd, *J* = 6.8 and 2.8 Hz, 1H), 7.07 (t, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.22−7.32 (m, 4H), 8.35 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.6, 163.3, 160.8, 137.7, 134.8, 131.4, 129.3 (d, J_{C-F} = 7.8 Hz), 128.3. 127.6, 126.9, 125.0, 115.8, 115.6, 81.7, 79.6, 55.2, 55.1, 30.8, 28.0; MS (ESI) *m*/*z* 384.1 $[M + H]^+$; HRMS (ESI) found *m*/*z* 384.1428 $[M + H]^+$, calcd for $C_{22}H_{22}FNO_2S$ + H 384.1435; IR (KBr) ν 3063, 2978, 2918, 1732, 1606, 1590, 1511, 1441, 1367, 1224, 1151, 1088, 1030, 956, 833, 760 cm^{-1}; dr = 93/7, er = 92/8, determined by HPLC analysis (Chiralpak OD-H, *n*-hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm UV detector), t_R = 15.0 min (minor) and t_R = 17.3 min (major).

*(2R,3S,3aR)-tert-Butyl 3-(2-chlorophenyl)-2,3,3a,4-tetrahydrothiochromeno[4,3-b]pyrrole-2-carboxylate (**3q**):* 68.6 mg, 86% yield; white solid, mp 90−92 °C; $[\alpha]^{20}_D$ −160.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.01 (dd, *J* = 8.0 and 4.4 Hz, 1H), 3.27 (t, *J* = 12.8 Hz, 1H), 3.49−3.56 (m, 1H), 3.98 (t, *J* = 9.6 Hz, 1H), 4.80 (dd, *J* = 6.8 and 2.4 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.21−7.25 (m, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.38−7.44 (m, 2H), 8.36

(d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 137.8, 137.5, 134.3, 131.4, 130.0, 128.9, 128.4, 127.7, 127.4, 126.8, 124.9, 81.5, 78.8, 55.8, 51.7, 31.1, 27.9; MS (ESI) m/z 400.1 $[M + H]^+$; HRMS (ESI) found m/z 400.1133 $[M + H]^+$, calcd for $C_{22}H_{22}ClNO_2S$ + H 400.1142; IR (KBr) ν 3061, 2977, 2930, 2872, 1738, 1613, 1591, 1477, 1441, 1367, 1218, 1152, 1087, 1033, 956, 843, 758 cm^{-1}; dr > 99/1, er = 95.5/4.5, determined by HPLC analysis (Chiralpak IA, *n*-hexane/2-propanol =97/3, 1.0 mL/min, 254 nm UV detector), t_R = 17.9 min (major) and t_R = 21.6 min (minor).

*(2R,3S,3aR)-tert-Butyl 3-(2-bromophenyl)-2,3,3a,4-tetrahydrothiochromeno[4,3-b]pyrrole-2-carboxylate (**3r**):* 72.3 mg, 81% yield; white solid; mp 65−67 °C; $[\alpha]^{20}_D$ −161.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.04 (dd, J = 8.4 and 4.4 Hz, 1H), 3.29 (t, J = 12.8 Hz, 1H), 3.43−3.50 (m, 1H), 4.03 (t, J = 9.6 Hz, 1H), 4.77 (dd, J = 6.8 and 2.4 Hz, 1H), 7.13−7.18 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.28−7.39 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.4, 139.4, 137.8, 133.2, 131.4, 128.7, 128.6. 128.4, 128.1, 127.6, 126.8, 125.0, 124.9, 81.5, 79.3, 56.5, 53.9, 31.0, 27.9; MS (ESI) m/z 444.1 $[M + H]^+$; HRMS (ESI) found m/z 444.0627 $[M + H]^+$, calcd for $C_{22}H_{22}BrNO_2S$ + H 444.0624; IR (KBr) ν 3058, 2977, 2929, 1736, 1610, 1591, 1578, 1474, 1440, 1367, 1253, 1152, 1087, 1022, 956, 843, 759 cm^{-1}; dr > 99/1, er = 92.5/7.5, determined by HPLC analysis (Chiralpak IA, *n*-hexane/2-propanol =97/3, 1.0 mL/min, 254 nm UV detector), t_R = 20.3 min (major) and t_R = 22.9 min (minor).

Large-Scale Synthesis of 3a. *N*-(Diphenylmethylene)glycine *tert*-butyl ester **2** (1.77 g, 6.0 mmol) was added to a mixture of enone **1a** (1.48 g, 6.3 mmol), (*S*)-**IIIb** (87.0 mg, 0.3 mmol), and Cs_2CO_3 (1.96 g, 6.0 mmol) in toluene (6.0 mL) under argon atmosphere, the resulting solution was stirred at 15 °C for 96 h, 2 N hydrochloric acid (30 mL) and THF (30 mL) were added at 0 °C, and stirring was maintained for 6 h at 0 °C. The resulting mixture was neutralized by addition of solid $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/petroleum ether =1/10 as eluant) to furnish the conjugate adducts **3a** (1.88 g, 90% yield, 95/5 dr, 90% ee, determined by ^{1}H NMR and HPLC analysis).

Recovery and Reuse of Catalyst of IIIb. The catalyst **IIIb** was recovered ($MeOH/CH_2Cl_2$ = 1/8 as eluent) in 97% yield. Anion exchange of recovered catalyst **IIIb** using Amberlyst-26A (OH^- form) gave (*S*)-**IIIb** (OH^-). The methanol solution of (*S*)-**IIIb** (OH^-) was treated with 40% HBr aqueous solution (excess) at room temperature. The resulting mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with 5% K_2CO_3 aqueous solution and dried over $MgSO_4$. Evaporation of solvents gave reactivated catalyst (*S*)-**IIIb** of 77.6 mg in 92% yield.

N-(Diphenylmethylene)glycine *tert*-butyl ester (59.0 mg, 0.2 mmol) was added to a mixture of substituted enones (49.2 mg, 0.21 mmol), recovered (*S*)-**IIIb** (2.9 mg, 0.002 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (0.2 mL) under argon atmosphere, the resulting solution was stirred at 15 °C for 96 h, 2 N hydrochloric acid (1.0 mL) and THF (1.0 mL) were added at 0 °C, and stirring was maintained for 6 h at 0 °C. The resulting mixture was neutralized by addition of solid $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatographyon silica gel (AcOEt/petroleum ether =1/10 as eluant) to furnish the conjugate adducts **3a** (61.8 mg, 90% yield, 94/6 dr, 90% ee, determined by ^{1}H NMR and HPLC analysis).

Synthetic Transformations of 3a. *Step 1: (2R,3S,3aR,9bR)-tert-Butyl 3-Phenyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[g]indole- 2-carboxylate.* To a solution of (2*R*,3*S*,3a*R*)-*tert*-butyl 3-phenyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indole-2-carboxylate (139.0 mg, 0.4 mmol) in 4 mL of AcOH was added zinc powder (30 equiv in portions at room temperature. The resultant mixture was stirred for 1.5 h at 45 °C (monitored by TLC). After zinc powder was filtered off, the filtrate was cooled to 0 °C. The filtrate was diluted with ethyl acetate and neutralized by the addition of sodium hydrogen carbonate (70% saturated aq). The mixture was extracted with dichloromethane (10 mL × 4), washed with brine, and dried with $MgSO_4$. Concentration and flash chromatography (AcOEt/petroleum ether = 1/10−1/4 as eluant) afforded (2*R*,3*S*,3a*R*,9b*R*)-*tert*-butyl 3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*g*]indole-2-carboxylate (76.9 mg, 0.22 mmol, 55% yield) as a white solid: mp 69−70 °C; $[\alpha]^{20}_D$ −22.9 (*c* 1.0, CH_2Cl_2); H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.63−1.73 (m, 1H), 1.92 (s, 1H), 2.15−2.24 (m, 1H), 2.85−3.03 (m, 4H), 4.06 (dd, J = 28.0 and 8.8 Hz, 2H), 7.12−7.27 (m, 4H), 7.31 − 7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 140.9, 139.9, 135.6, 128.5, 128.4, 127.9, 126.8, 126.4, 125.8, 124.3, 81.3, 68.8, 63.4, 56.4, 50.9, 28.9, 28.0, 24.1; MS (ESI) m/z 350.2 $[M + H]^+$; HRMS (ESI) found m/z 350.2115 $[M + H]^+$, calcd for $C_{23}H_{27}NO_2$ + H 350.2110; IR (KBr) ν 3334, 3063, 3029, 2977, 2926, 2865, 1723, 1603, 1492, 1455, 1367, 1316, 1229, 1158, 1106, 1031, 951, 910, 847, 742 cm^{-1}; er = 95/5, determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol = 90/10, 0.8 mL/min, 254 nm UV detector), t_R = 10.8 min (minor) and t_R = 11.7 min (major).

*Step 2: (2R,3S,3aR,9bR)-tert-Butyl 1-(4-bromobenzoyl)-3-phenyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[g]indole-2-carboxylate (**4**).* (2*R*,3*S*,3a*R*,9b*R*)-*tert*-Butyl 3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*g*]indole-2-carboxylate (52.4 mg, 0.15 mmol) in 0.5 mL of CH_2Cl_2 was added to a mixture of 4-bromobenzoyl chloride (66.0 mg, 0.3 mmol) and Et_3N (63 μL, 0.45 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under argon atmosphere, and then stirring was maintained for 24 h at room temperature. The resulting mixture was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatographyon silica gel (AcOEt/petroleum ether = 1/5 as eluant) to afford the product (75.1 mg, 0.14 mmol, 94% yield) as a white solid. Recrystallization of this product from CH_2Cl_2/hexane furnished suitable crystals for X-ray structure analysis: mp 207−208 °C; $[\alpha]^{20}_D$ −161.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.73−1.86 (m, 2H), 2.29−2.33 (m, 1H), 2.86−2.92 (m, 1H), 3.05−3.18 (m, 2H), 4.61 (d, J = 8.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 7.13−7.23 (m, 6H), 7.29−7.36 (m, 3H), 7.56 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ170.2, 139.9, 136.9, 136.0, 135.5, 131.6, 130.2, 128.8, 128.7, 128.0, 127.8, 126.4, 125.6, 125.5, 123.1, 82.1, 73.3, 64.3, 57.1, 49.0, 30.6, 27.3, 22.2; MS (ESI) m/z 554.1 $[M + H]^+$; HRMS (ESI) found m/z 554.1301 $[M + Na]^+$, calcd for $C_{30}H_{30}BrNO_3$ + Na 554.1301; IR (KBr) ν 3059, 3034, 2977, 2934, 2869, 1729, 1642, 1587, 1483, 1456, 1401, 1368, 1347, 1253, 1200, 1152, 1066, 1009, 995, 848, 745 cm^{-1}; er = 95/5 (>99.99/0.01 after recrystallization), determined by HPLC analysis (Chiralpak AD-H, *n*-hexane/2-propanol =80/20, 1.0 mL/min, 254 nm UV detector), t_R = 20.9 min (major) and t_R = 24.8 min (minor).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC analytic results for products **3a−r** and **4**, as well as crystallographic data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The absolute configuration of compound **4** was confirmed by X-ray crystal structure analysis. CCDC 824515 (**4**) contains the supplementary crystallographic data for this paper (see the Supporting Information). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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