Supporting Information

Amine-salt-controlled, Catalytic Asymmetric Conjugate Addition of Various Amines and Asymmetric Protonation

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General: NMR spectra were recorded on a JEOL JNM-LA400 spectrometer, operating at 400 MHz for ^1H -NMR, 100.4 MHz for ^{13}C -NMR. Chemical shifts were reported downfield from TMS (= 0) for ^1H -NMR. For ^{13}C -NMR, chemical shifts were reported in the scale relative to CDCl_3 as an internal reference. FAB-LRMS was taken on JEOL JMS GCmate II using *m*-nitrobenzyl alcohol (mNBA) as matrix. FAB-HRMS was also taken on JEOL JMS GCmate II using mNBA as matrix and with PEG 400 as an internal standard. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR was measured on Thermo Nicolet AVATAR 370 FT-IR. Melting points were measured using Yanaco MP-J3. Column chromatography was performed with silica gel 60 (40-100 μm) purchased from KANTO CHEMICAL Co. The enantiomeric excesses (ee's) were determined by chiral HPLC. HPLC analysis was performed on Shimadzu HPLC systems consisting of the followings: pump, LC-10AD; detector, SPD-10A measured at 220 nm or 254 nm. Also, JASCO HPLC systems were used consisting of the followings: pump, PU-2080 Plus; detector, CD-2095 Plus measured at 220 nm or 254 nm; column, DAICEL CHIRALPAK AD-H, AS-H, or DAICEL CHIRALCEL OD-H; mobile phase, hexane / 2-propanol (IPA). Dehydrated stabilizer-free tetrahydrofuran (THF) was purchased from KANTO CHEMICAL Co., and was directly used. Dehydrated MeOH and trifluoromethanesulfonic acid (TfOH), which were purchased from WAKO Pure Chemical Industries, Ltd., were directly used without further purification. Other reagents were purified by usual methods.

Preparation of Palladium Complexes 1 and 2

Palladium complexes **1** and **2** were synthesized according to the reported procedures.¹

Preparation of Alkenoyl Oxazolidinones 3

3a-b: These substrates were synthesized according to Evans' procedure.² These were found to be identical to the reported compounds by comparison with ^1H NMR.^{2, 3}

3c: The corresponding 4-benzyloxybutenoyl chloride was prepared according to the procedure

¹ Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450-5458.

² Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

³ Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339-1350.

reported by Martin.⁴ Coupling reaction with 2-oxazolidone using Evans' method afforded the desired starting material **3c** as a white solid in 73% yield [CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ (1 h), then room temperature (18 h)].

3-(4-Benzyloxy-but-2-enoyl)-oxazolidin-2-one (**3c**):

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 4.08 (t, $J = 8.3$ Hz, 2H), 4.24 (dd, $J = 1.92, 4.36$ Hz, 2H), 4.43 (t, $J = 8.3$ Hz, 2H), 4.58 (s, 2H), 7.16 (ddd, $J = 4.64, 4.64, 15.6$ Hz, 1H), 7.26-7.36 (m, 5H), 7.52 (ddd, $J = 1.96, 1.96, 15.6$ Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 42.7, 62.1, 68.9, 72.8, 120.1, 127.7, 127.8, 128.5, 137.7, 146.3, 153.4, 164.9.

Initial Studies: Unpublished Results from Our Laboratory

Catalytic Asymmetric Conjugate Addition of Various Amines Using Pd Complex **1** in the Absence of TfOH

General Procedure for the Preparation of Salt **6**

Anisidine purified freshly by recrystallization (616 mg, 5 mmol) was dissolved in ether (5 mL). To this solution was added TfOH (0.44 mL, 5 mmol) under ice bath cooling. During the addition, white precipitate appeared. After 5 min, hexane (20 mL) was added, then white solid was collected by filtration. The white solid was washed with hexane several times and was dried under reduced pressure. This salt was directly used in the conjugate addition. $^1\text{H NMR}$ of the representative salt (**6a**) is given below.

6a: $^1\text{H-NMR}$ (400 MHz, $\text{THF-}d_8$) δ 3.80 (s, 3H), 7.10 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H), 9.45 (s, 3H).

⁴ Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003-8010.

General Procedure for the Catalytic Asymmetric Conjugate Addition of Aromatic Amines

The palladium complex **2** (7.2 mg, 2 mol %), starting material **3** (0.2 mmol), and salt **6** (0.3 mmol) were placed in the reaction vessel. To this mixture was added THF (0.2 mL) at room temperature. The resulting solution was allowed to stir at the indicated temperature. The reaction was monitored by TLC (hexane/ether = 1:2) after treating a portion of the reaction mixture with 2% aqueous NH_3/MeOH . After the time given in Table 2, cold saturated aqueous NaHCO_3 (2 mL) was added for quenching under ice bath cooling. Quenching at room temperature sometimes brought about the spontaneous reaction, resulting in the decrease of enantioselectivity. The reaction mixture was diluted with ethyl acetate (5 mL), and the separated aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water and brine. After drying with Na_2SO_4 , solvent was removed under the reduced pressure. Further purification was performed by flash column chromatography on SiO_2 (hexane- Et_2O system) to give the pure product **5**. In the case of **5bc**, preparative TLC was performed for purification.

In the cases of **5bc** and **5cc**, the reactions were slow probably due to the lower nucleophilicity of free amine. Addition of an equimolar amount of *p*-trifluoromethylaniline (**4c**) to palladium ion was found to be effective for acceleration of the reaction. Therefore, a catalytic amount of free trifluoromethylaniline was added as an additive to the above mentioned reaction mixture.

3-[3-(4-Methoxy-phenylamino)-butyryl]-oxazolidin-2-one (**5aa**);

brown crystal; mp 87.5 - 89.5 °C; IR (solid) 3366, 2963, 2924, 2832, 2358, 1769, 1690, 1509, 1477, 1385, 1363, 1309, 1231, 1197, 1144, 1108, 1078, 1033, 968, 821, 756 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.27 (d, J = 6.4 Hz, 3H), 2.96 (dd, J = 5.6, 15.2 Hz, 1H), 3.32 (dd, J = 7.1, 15.2 Hz, 1H), 3.73 (s, 3H), 3.91 (t, J = 8.4 Hz, 2H), 3.98-4.06 (m, 1H), 4.27-4.37 (m, 2H), 6.60 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.2, 41.4, 42.4, 47.5, 55.7, 61.9, 114.8, 115.4, 141.0, 152.3, 153.6, 171.8; FAB-LRMS (mNBA) m/z 279 ($\text{M}+1$)⁺, 278 (M)⁺, 150; $[\alpha]_D^{27}$ - 4.6 (c = 2.59, CHCl_3) (98% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 3 / 1, 1.5 mL / min, 254 nm) t_r (major) = 11.9 min, t_r (minor) = 24.5 min; HRMS (PEG 400/mNBA) Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4$ (M)⁺ 278.1267. Found 278.1270.

3-(3-Phenylamino-butyryl)-oxazolidin-2-one (**5ab**);

colorless crystal; mp 118.5 - 119.0 °C; IR (solid) 3401, 3360, 2978, 2928, 2358, 2342, 1691, 1675, 1600, 1514, 1478, 1390, 1361, 1311, 1210, 1138, 1097, 1031, 1021, 1009, 957, 746 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.30 (d, J = 6.4 Hz, 3H), 2.99 (dd, J = 5.8, 15.4 Hz, 1H), 3.33 (dd, J = 7.1, 15.4 Hz, 1H), 3.83-3.93 (m, 2H), 4.08-4.16 (m, 1H), 4.22-4.34 (m, 2H), 6.62 (d, J = 8.5 Hz, 2H), 6.68 (t, J = 7.3 Hz, 1H), 7.15 (dd, J = 7.3, 8.5 Hz, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.2, 41.4, 42.4, 46.2, 61.9, 113.5, 117.5, 129.2, 146.9, 153.6, 171.9; FAB-LRMS (mNBA) m/z 249 ($\text{M}+1$)⁺, 248 (M)⁺, 120; $[\alpha]_D^{27}$ + 9.3 (c = 1.93, CHCl_3) (96% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 3 / 1,

1.0 mL / min, 254 nm) t_r (major) = 10.0 min, t_r (minor) = 13.8 min; HRMS (PEG400/mNBA) Calcd for $C_{13}H_{16}N_2O_3$ (M)⁺ 248.1161. Found 248.1162.

3-[3-(4-Trifluoromethyl-phenylamino)-butyryl]-oxazolidin-2-one (5ac);

colorless crystal; mp 91.5 - 92.5 °C; IR (solid) 3381, 2973, 2926, 1770, 1693, 1613, 1532, 1480, 1387, 1315, 1188, 1099, 1063, 827, 760 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.1 Hz, 3H), 3.02 (dd, J = 5.6, 15.6 Hz, 1H), 3.35 (dd, J = 6.8, 15.6 Hz, 1H), 3.88-3.99 (m, 2H), 4.11-4.23 (m, 2H), 4.29-4.40 (m, 2H), 6.62 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 21.0, 41.2, 42.4, 45.9, 62.0, 112.4, 118.9 (q, J = 32 Hz), 124.9 (q, J = 268 Hz), 126.7 (q, J = 3.3 Hz), 149.4, 153.7, 171.4; FAB-LRMS (mNBA) m/z 317 ($M+1$)⁺, 316 (M)⁺, 188; $[\alpha]_D^{27}$ +7.6 (c = 0.82, $CHCl_3$) (93% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 9 / 1, 1.0 mL / min, 254 nm) t_r (major) = 38.0 min, t_r (minor) = 48.6 min; HRMS (PEG 400/mNBA) Calcd for $C_{14}H_{15}N_2O_3F_3$ (M)⁺ 316.1035. Found 316.1035.

3-[3-(4-Methoxy-phenylamino)-pentanoyl]-oxazolidin-2-one (5ba);

pale yellow oil; IR (neat) 3371, 2962, 2928, 1769, 1690, 1509, 1384, 1228, 1194, 1142, 1108, 1032, 958, 821, 757 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 1.64 (dq, J = 6.8, 7.2 Hz, 2H), 3.01 (dd, J = 4.8, 14.8 Hz, 1H), 3.31 (dd, J = 8.0, 14.8 Hz, 1H), 3.73

(s, 3H), 3.81-3.86 (m, 1H), 3.87 (t, J = 8.0 Hz, 2H), 4.24-4.34 (m, 2H), 6.65 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 10.4, 28.0, 39.2, 42.5, 53.8, 55.8, 61.9, 114.9, 115.61, 140.6, 152.6, 153.7, 172.1; FAB-LRMS (mNBA) m/z 292 (M)⁺, 293 ($M+1$)⁺; $[\alpha]_D^{27}$ - 23.1 (c = 0.57, $CHCl_3$) (97% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 1 / 1, 1.0 mL / min, 254 nm) t_r (major) = 9.0 min, t_r (minor) = 11.1 min; HRMS (PEG 400/mNBA) Calcd for $C_{15}H_{20}N_2O_4$ (M)⁺ 292.1423. Found 292.1425.

3-(3-Phenylamino-pentanoyl)-oxazolidin-2-one (5bb);

colorless crystal; mp 68.5 - 69.0 °C, IR (solid) 3386, 2964, 2923, 1769, 1691, 1600, 1497, 1385, 1222, 1195, 1143, 1119, 1036, 958, 750, 694 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3H), 1.65 (dq, J = 6.8, 7.2 Hz, 2H), 3.03 (dd, J = 4.8, 14.8 Hz, 1H), 3.31 (dd, J = 8.4, 14.8 Hz, 1H), 3.77-3.88 (m, 2H), 3.91-3.98 (m, 1H), 4.19-4.31 (m, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.66 (t, J = 7.2 Hz, 1H), 7.14 (dd, J = 7.2, 8.8 Hz, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 10.4, 28.5, 39.6, 42.5, 52.2, 61.9, 113.3, 117.4, 129.3, 147.4, 153.7, 172.1; FAB-LRMS (mNBA) m/z 263 ($M+1$)⁺; $[\alpha]_D^{27}$ - 8.1 (c = 0.34, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 9 / 1, 0.5 mL / min, 254 nm) t_r (major) = 36.8 min, t_r (minor) = 39.0 min; HRMS (PEG 400/mNBA) Calcd for $C_{14}H_{19}N_2O_3$ ($M+1$)⁺ 263.1396. Found 263.1400.

3-[3-(4-Trifluoromethyl-phenylamino)-pentanoyl]-oxazolidin-2-one (**5bc**);

pale yellow oil; IR (neat) 3381, 2968, 2972, 2875, 1772, 1693, 1613, 1532, 1480, 1386, 1317, 1187, 1097, 1063, 1036, 825, 758 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.98 (t, $J = 7.2$ Hz, 3H), 1.62-1.70 (m, 2H), 3.03 (dd, $J = 4.8$, 15.2 Hz, 1H), 3.32 (dd, $J = 7.6$, 15.2 Hz, 1H), 3.84-3.91 (m, 2H), 3.93-3.98 (m, 1H), 4.24-4.36 (m, 2H), 6.61 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 10.4, 28.4, 39.4, 42.5, 51.7, 62.0, 112.2, 118.7 (q, $J = 33$ Hz), 124.9 (q, $J = 269$ Hz), 126.6 (q, $J = 4.1$ Hz), 145.0, 153.7, 171.6; FAB-LRMS (mNBA) m/z 331 ($\text{M}+1$) $^+$; $[\alpha]_{\text{D}}^{28} - 7.8$ ($c = 0.81$, CHCl_3) (85% ee); HRMS (PEG 400/mNBA) Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3\text{F}_3$ (M) $^+$ 330.1191. Found 330.1193.

The enantiomeric excess of this product was determined to be 85% after conversion to the corresponding methyl ester: **5bc** was dissolved in MeOH (1 mL), and saturated aqueous NaHCO_3 (1 mL) was added at room temperature. The reaction mixture was stirred for 1 h. For quenching, saturated NH_4Cl was added. Aqueous layer was extracted with CHCl_3 (3 x 5 mL), and the combined layers were washed with water and brine. After drying with Na_2SO_4 , solvent was evaporated under reduced pressure. Further purification was performed by flash column chromatography (hexane : ether = 2 : 1) to afford the corresponding methyl ester as a colorless oil (85%).

3-(4-Trifluoromethyl-phenylamino)-pentanoic acid methyl ester (**5bc-OMe**);

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.98 (t, $J = 7.6$ Hz, 3H), 1.55-1.71 (m, 2H), 2.52 (dd, $J = 6.1$, 15.1 Hz, 1H), 2.58 (dd, $J = 5.9$, 15.1 Hz, 1H), 3.66 (s, 3H), 3.72-3.85 (m, 1H), 4.12 (d, $J = 7.8$ Hz, 1H), 6.62 (d, $J = 8.6$ Hz, 2H), 7.38 (d, $J = 8.6$ Hz, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 10.5, 27.7, 38.5, 51.4, 51.7, 112.3, 118.8 (q, $J = 32.9$ Hz), 124.9 (q, $J = 269.1$ Hz), 126.7 (q, $J = 3.3$ Hz), 149.8, 172.1; HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 9 / 1, 0.5 mL / min, 254 nm) t_r (minor) = 10.3 min, t_r (major) = 12.0 min.

3-[4-Benzyloxy-3-(4-methoxy-phenylamino)-butyryl]-oxazolidin-2-one (**5ca**);

colorless crystal; mp 85.0-86.5 $^{\circ}\text{C}$; IR (solid) 3364, 3025, 2993, 2921, 2857, 2344, 1770, 1691, 1509, 1384, 1363, 1309, 1230, 1192, 1103, 1071, 1034, 821, 752, 735, 699 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 3.17 (dd, $J = 6.4$, 15.6 Hz, 1H), 3.37 (dd, $J = 6.6$, 15.6 Hz, 1H), 3.59 (dd, $J = 5.6$, 9.2 Hz, 1H), 3.64 (dd, $J = 3.6$, 9.2 Hz, 1H), 3.74 (s, 3H), 3.79 (t, $J = 8.0$ Hz, 2H), 4.08-4.13 (m, 1H), 4.20-4.25 (m, 2H), 4.50 (s, 2H), 6.63 (d, $J = 8.8$ Hz, 2H), 6.76 (d, $J = 8.8$ Hz, 2H),

7.28-7.36 (m, 5 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 36.9, 42.4, 51.6, 55.7, 61.8, 71.5, 73.2, 114.9, 115.6, 127.6, 127.7, 128.3, 138.1, 140.7, 152.5, 153.6, 171.9; FAB-LRMS (mNBA) m/z 385 ($\text{M}+1$) $^+$; $[\alpha]_{\text{D}}^{28} + 6.6$ ($c = 1.32$, CHCl_3) (86% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 1 / 3, 0.5 mL / min, 254 nm) t_{r} (major) = 26.1 min, t_{r} (minor) = 40.8 min; HRMS (PEG 400/mNBA) Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_5$ ($\text{M}+1$) $^+$ 384.1685. Found 384.1685.

3-(4-Benzoyloxy-3-phenylamino-butyryl)-oxazolidin-2-one (5cb);

colorless crystal; mp 96.5 - 98.0 °C; IR (solid) 3379, 3026, 2921, 2855, 2357, 2340, 1770, 1692, 1601, 1497, 1385, 1311, 1222, 1196, 1105, 1067, 1039, 1026, 750, 695 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 3.21 (dd, $J = 6.0, 15.6$ Hz, 1H), 3.39 (dd, $J = 6.8, 15.6$ Hz, 1H), 3.60 (dd, $J = 5.6, 9.2$ Hz, 1H), 3.67 (dd, $J = 3.6, 9.2$ Hz, 1H), 3.78 (t, $J = 8.0$ Hz, 2H), 4.17-4.27 (m, 1H), 4.19-4.23 (m, 2H), 4.51 (s, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 6.70 (t, $J = 7.6$ Hz, 1H), 7.16 (dd, $J = 7.6, 8.4$ Hz, 2H), 7.28-7.36 (m, 5 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 36.9, 42.4, 50.3, 61.9, 71.5, 73.2, 113.7, 117.9, 127.7, 127.7, 128.4, 139.3, 138.0, 146.7, 153.6, 171.8; FAB-LRMS (mNBA) m/z 355 ($\text{M}+1$) $^+$; $[\alpha]_{\text{D}}^{28} + 14.0$ ($c = 0.34$, CHCl_3) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 1 / 1, 0.5 mL / min, 254 nm) t_{r} (major) = 19.3 min, t_{r} (minor) = 22.5 min; HRMS (PEG 400/mNBA) Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$ ($\text{M}+1$) $^+$ 355.1653. Found 355.1658.

3-[4-Benzoyloxy-3-(4-trifluoromethyl-phenylamino)-butyryl]-oxazolidin-2-one (5cc);

colorless oil; IR (neat) 3380, 2923, 2860, 2360, 1772, 1693, 1614, 1532, 1478, 1386, 1317, 1187, 1099, 1062, 1039, 826, 698 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 3.20 (dd, $J = 6.4, 16.0$ Hz, 1H), 3.39 (dd, $J = 6.0, 16.0$ Hz, 1H), 3.61 (dd, $J = 4.8, 9.2$ Hz, 1H), 3.66 (dd, $J = 4.0, 9.2$ Hz, 1H), 3.81 (t, $J = 8.4$ Hz, 2H), 4.21-4.25 (m, 1H), 4.27 (t, $J = 8.4$ Hz, 2H), 4.51 (s, 2H), 4.51 (br, 1H), 6.64 (d, $J = 8.4$ Hz, 2H), 7.29-7.39 (m, 7 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 36.6, 42.4, 49.7, 61.9, 71.1, 73.3, 112.6, 119.2 (q, $J = 32.9$ Hz), 124.8 (q, $J = 269.1$ Hz), 126.7 (q, $J = 3.3$ Hz), 127.8, 137.8, 149.3, 153.6, 171.5; FAB-LRMS (mNBA) m/z 422 M^+ , 423 ($\text{M}+1$) $^+$; $[\alpha]_{\text{D}}^{28} + 12.1$ ($c = 2.07$, CHCl_3) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 9 / 1, 0.5 mL / min, 254 nm) t_{r} (major) = 90.0 min, t_{r} (minor) = 95.1 min; HRMS (PEG 400/mNBA) Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{F}_3$ ($\text{M}+1$) $^+$ 423.1532. Found 423.1531.

Procedure for the Catalytic Asymmetric Conjugate Addition with Benzylamine Salt 7

The palladium complex **2** (7.2 mg, 2 mol %), the starting material **3** (0.2 mmol), and salt **7** (77 mg, 0.3 mmol) were placed in the reaction vessel. To this mixture was added THF (0.2 mL) at room temperature. The resulting solution was allowed to stir at 40 °C for 60 h. The reaction was monitored by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20:1$) after quenching a portion of the reaction mixture. After the completion of the reaction, cold saturated NaHCO_3 (2 mL) was added for quenching on an ice bath. The reaction mixture was diluted with ethyl acetate (5 mL), and the separated aqueous layer was

extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water and brine. After drying with Na₂SO₄, solvent was evaporated under reduced pressure. Removal of the less polar compounds, the Pd complex, and excess benzylamine was carried out by silica gel column chromatography (CH₂Cl₂ : ethyl acetate = 3 : 1 ~ CH₂Cl₂ : MeOH = 20 : 1) to give the roughly purified product (~90%). This crude product was treated with MeOH (2 mL) in the presence of a catalytic amount of NaOMe. In the case of the reaction with **3a**, additional NaOMe was not necessary. After the completion of the reaction (TLC: hexane / ethyl acetate = 1 / 1), saturated aqueous NH₄Cl (2~3 drops) was added. Excess MeOH was evaporated, and then usual workup, followed by column chromatography (hexane / ethyl acetate = 1 / 1, or CH₂Cl₂ / MeOH = 20 / 1) afforded the desired benzylamino methyl ester **8** as a colorless oil.

3-Benzylamino-butyric acid methyl ester (**8a**):

This product was found to be identical to the reported compound by comparison with ¹H-NMR.⁵

¹H-NMR (400 MHz, CDCl₃) δ 1.16 (d, *J* = 6.1 Hz, 3H), 1.95 (brs, 1H), 2.32 (dd, *J* = 6.1, 15.4 Hz, 1H), 2.50 (dd, *J* = 7.1, 15.4 Hz, 1H), 3.16 (ddq, *J* = 6.1, 6.1, 7.1 Hz, 1H), 3.67 (s, 3H), 3.76 (d, *J* = 12.9 Hz, 1H), 3.83 (d, *J* = 12.9 Hz, 1H), 7.22-7.36 (m, 5H); ¹³C-NMR (100 MHz, CDCl₃) δ 20.4, 41.4, 49.6, 51.2, 51.5, 126.9, 128.0, 128.4, 140.3, 172.8; [α]_D²³ + 15.7 (c = 0.56, CHCl₃) (86% ee); HPLC (DAICEL CHIRALCEL OD-H, hexane / IPA = 99 / 1, 1.0 mL / min, 254 nm) t_r (minor) = 11.2 min, t_r (major) = 14.5 min.

3-Benzylamino-4-benzyloxy-butyric acid methyl ester (**8c**):

colorless oil; IR (neat) 3328, 3084, 3061, 3026, 2948, 2856, 1732, 1453, 1435, 1090, 733, 696 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.89 (s, 1H), 2.53 (d, *J* = 6.4 Hz, 2H), 3.23-3.29 (m, 1H), 3.48 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.52 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.63 (s, 3H), 3.79 (s, 2H), 4.49 (s, 2H), 7.21-7.37 (m, 10H); ¹³C-NMR (100 MHz, CDCl₃) δ 36.9, 51.2, 51.5, 71.5, 73.1, 126.9, 127.6, 128.3, 138.1, 140.3, 172.6; FAB-LRMS (mNBA) m/z 313 M⁺, 314 (M+1)⁺; [α]_D²⁸ + 5.3 (c = 1.92, CHCl₃) (80% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 99 / 1, 1.0 mL / min, 220 nm) t_r (minor) = 32.0 min, t_r (major) = 43.5 min; HRMS (PEG 400/mNBA) Calcd for C₁₉H₂₃NO₃ (M)⁺ 313.1678. Found 313.1678.

Determination of the Absolute Configuration of **5ab**

The absolute configuration of **5ab** was determined to be *S* by comparing with optical rotation of the known compound **B**.⁶ The conversion of **5ab** into **B** was carried out as follows.

The product **5ab** (52.6 mg, 0.212 mmol, 94% ee) was treated with the catalytic amount of NaOMe (3 mg) in anhydrous MeOH (2 mL). The reaction was completed after 10 min at room temperature.

⁵ Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886-2887.

⁶ Paradisi, M. P.; Romeo, A. *J. Chem. Soc. Perkin Trans. 1* **1977**, 596-600.

The reaction was quenched by adding saturated aqueous NH_4Cl , and the organic compounds were extracted with ethyl acetate (3 x 10 mL). Further purification was performed by column chromatography (hexane : ethyl acetate = 3 : 1) to afford the desired methyl ester **A** in 71% yield. This product was found to be identical to the reported compound by comparison with $^1\text{H-NMR}$,⁶ and the ee of this methyl ester was determined to be 94% by chiral HPLC.

(S)-Phenylamino-butyric acid methyl ester (A):

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.27 (d, J = 6.4 Hz, 1H), 2.43 (dd, J = 7.1, 15.0 Hz, 1H), 2.64 (dd, J = 5.4, 15.0 Hz, 1H), 3.68 (s, 3H), 3.74 (brs, 1H), 3.94 (ddq, J = 5.4, 7.1, 7.1 Hz 1H), 6.58-6.63 (m, 2H), 6.70 (tt, J = 1.0, 7.4 Hz, 1H), 7.15-7.20 (m, 2H): HPLC (DAICEL CHIRALCEL OD-H, hexane / IPA = 99 / 1, 1.0 mL / min, 254 nm) t_r (minor) = 17.8 min, t_r (major) = 19.5 min.

Subsequent hydrolysis of **A** (29 mg, 0.15 mmol) was carried out in MeOH/1N LiOH (3/1)(1.2 mL). The reaction mixture was stirred for 18 h at room temperature, and 1N HCl (0.3 mL) was added for quenching. After adjusting pH at ~7, aqueous layer was extracted with CHCl_3 (10 mL x 4) and the combined organic layers were dried with Na_2SO_4 . Column chromatography (CH_2Cl_2 : MeOH = 30 : 1) gave the corresponding carboxylic acid **B** (14 mg) as a yellowish oil in 52% yield. This product was found to be identical to the reported compound by comparison with $^1\text{H-NMR}$.

(S)-3-Phenylamino-butyric acid (B):

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.31 (d, J = 6.4 Hz, 3H), 2.50 (dd, J = 6.4, 15.4 Hz, 1H), 2.67 (dd, J = 5.8, 15.4 Hz, 1H), 3.94 (ddq, J = 5.8, 6.4, 6.4 Hz, 1H), 6.60-6.70 (m, 4H), 7.18-7.23 (m, 2H); $[\alpha]_D^{23} + 18.0$ (c = 0.70, MeOH) [Lit: $[\alpha]_D - 24$ (c = 3, MeOH) (*R* enantiomer)]⁶

By comparing the optical rotation with the reported one, the absolute configuration of **14** from **5ab** was determined to be *S*. Therefore, it is concluded that the sense of enantioselection of the conjugate addition catalyzed by Pd catalyst **2** consisting of (*R*)-BINAP is *S*-selective.

Catalytic Asymmetric Protonation in the Conjugate Addition of Anisidine

1) Preparation of the Substrate **9**

Methacryl amide (1.5 g, 17.7 mmol) was dissolved in THF. To this solution was added EtMgBr (19.5 mmol, 0.86 M in THF solution) slowly at -20°C . After stirring for 1 h, Cbz-Cl (3.45 mL, 26.6 mmol) was added. The resulting mixture was stirred for 2 h at the same temperature, and warmed up to room temperature. After 1 h, saturated NH_4Cl (10 mL) was added for quenching. Water layer was extracted with ethyl acetate, and the combined organic layers were washed with water and brine. After drying over Na_2SO_4 , solvent was evaporated under reduced pressure. Recrystallization from CHCl_3 -hexane gave **9** in 54% (2.08 g) as a white solid.

9: ^1H -NMR (400 MHz, CDCl_3) δ 1.99 (dd, $J = 1.5, 1.0$ Hz, 3H), 5.24 (s, 2H), 5.55-5.56 (m, 1H), 5.72-5.73 (m, 1H), 7.26-7.42 (m, 5H), 7.79 (bs, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 18.3, 67.8, 121.9, 128.5, 128.6, 128.7, 134.9, 139.7, 150.6, 165.4.

2) Procedure for Asymmetric Protonation

Pd complex **2** (9 mg, 0.005 mmol, 5 mol %), salt **6a** (41 mg, 0.15 mmol), and substrate **9** (22 mg, 0.1 mmol) were placed in a reaction vessel. THF (0.2 mL) was added, and the reaction mixture was stirred at 20°C . The reaction was monitored by TLC (hexane / ethyl acetate = 1 / 1). After 8 h, the reaction mixture was diluted with ethyl acetate under ice bath cooling. Then, saturated NaHCO_3 (2 mL) was added for neutralization. Aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na_2SO_4 . After evaporation of solvent, Pd complex was removed by short column chromatography (Et_2O). Further purification was carried out by medium pressure column chromatography (hexane / ethyl acetate = 2 / 1) to afford **10** (80%) as a pale yellow solid. The ee of the product was determined by chiral HPLC.

10: IR (solid) 3276, 1762, 1702, 1510, 1232, 1177; ^1H -NMR (400 MHz, CDCl_3) δ 1.23 (d, $J = 3.4$ Hz, 3H), 3.18 (dd, $J = 1.8, 6.0$ Hz, 1H), 3.37-3.42 (m, 2H), 3.74 (s, 3H), 5.16 (s, 2H), 6.57-6.61 (m, 2H), 6.75-6.79 (m, 2H), 7.23-7.41 (m, 5H), 8.06 (bs, 1H); ^{13}C -NMR (100 MHz, Acetone- d_6) δ 15.5, 40.8, 48.6, 55.8, 67.4, 115.1, 115.4, 128.9, 129.0, 129.2, 137.0, 143.0, 152.1, 153.1, 175.7; FAB-LRMS (mNBA) m/z 342 (M^+), 343 ($\text{M}+1$) $^+$; $[\alpha]_{\text{D}}^{28} - 26.0$ ($c = 1.43$, CHCl_3) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane / IPA = 1 / 1, 1.0 mL / min, 254 nm) t_{r} (minor) = 6.1 min, t_{r} (major) = 7.1 min.; HRMS (PEG 400/mNBA) Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$ (M) $^+$ 324.1580. Found 342.1588.