Supporting Information

A Heterobimetallic Pd-La-Schiff Base Complex for anti-Selective Catalytic Asymmetric Nitroaldol Reactions and Applications to Short Syntheses of β-Adrenoceptor Agonists.**

Shinya Handa, Keita Nagawa, Yoshihiro Sohtome, Shigeki Matsunaga* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan, phone: +81-3-5841-4830, fax: +81-3-5684-5206, E-mail: mshibasa@mol.f.u-tokyo.ac.jp; smatsuna@mol.f.u-tokyo.ac.jp

Experimental Section

General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-LA500 spectrometer, operating at 500 MHz for ¹H NMR and 125.65 MHz for ¹³C NMR. Chemical shifts in CDCl₃, C₆D₆ and d₆-DMSO were reported in the scale relative to CHCl₃ (7.26 ppm), C₆D₅H (7.15 ppm) and d₅-DMSO (2.50 ppm) for ¹H NMR. For ¹³C NMR, chemical shifts were reported in the scale relative to CDCl₃ (77.0 ppm) and d₆-DMSO (39.52 ppm) as an internal reference. Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Optical rotations were measured on a JASCO P-1010 polarimeter. FAB mass spectra were measured on JMS-MS 700V. ESI mass spectra were measured on Waters micromass ZQ. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-2080 plus; detector, UV-2075 plus, measured at 254 nm; column, DAICEL CHIRALPAK AD-H and AS-H, DAICEL CHIRALCEL OJ; mobile phase, hexane-2-propanol and hexane-2-propanol-Et₂NH. Reactions were carried out in dry solvents under argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. La(O-iPr)₃ was purchased from KOJUNDO CHEMICAL LAB CO., LTD (Fax: +81-492-84-1351, sales@kojundo.co.jp), which was dissolved into THF (0.2 M solution) before use. The same quality of La(O-iPr)₃ is also available from Aldrich (Cat. No. 665193). Other reagents were purified by the usual methods.
Preparation of a Pd-Schiff Base 1 Pre-catalyst

\[
\text{OH} \quad \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{OH}
\]

\[
\text{Pd(OAc)}_2 \quad \text{EtOH/H}_2\text{O} \quad \text{reflux, 7 h}
\]

To a solution of (R,R)-Schiff base ligand 1-H₄ (329 mg, 0.93 mmol) in EtOH (8 mL) and H₂O (2 mL), Pd(OAc)₂ (209 mg, 0.93 mmol) was added and stirred for 7 h under reflux. After cooling down to room temperature, a Pd-Schiff base complex was collected by filtration of reaction suspension. Then the solid was washed with EtOH (x 3) and dried under reduced pressure to afford Pd-Schiff base pre-catalyst (426 mg, 78%) as dark green solid.

General Procedure for Catalytic Asymmetric Nitroaldol Reaction Using a Pd/La/Schiff base 1 = 1:1:1 with 4-bromophenol System:

To a suspension of Pd/Schiff base 1 pre-catalyst (9.2 mg, 0.02 mmol) in THF (300 µL) was added La(O-iPr)₃ (100 µL, 0.02 mmol, 0.2 M in THF), and the mixture was stirred at 80 °C for 1 h to give a Pd/La/1 complex. After cooling down the mixture to room temperature, 4-bromophenol (100 µL, 0.02 mmol, 0.2 M in THF) was added, and the mixture was stirred for 15 min at room temperature. The catalyst mixture was cooled down to –40 °C, and nitroethane 4a (140 µL, 2.0 mmol) was added. After stirring for 1 h at –40 °C, aldehyde 3a (0.2 mmol) and xylenes (400 µL) were added slowly. The stirring was continued for 69 h at –40 °C and the reaction mixture was diluted with diethyl ether (4 mL). The resulting mixture suspension was filtered through a pad of Celite to remove the catalyst, and the filtrate solution was evaporated under reduced pressure. The resulting residue was analyzed by ¹H NMR to determine diastereomeric ratio, and was purified by silica gel flash column chromatography (hexane/ethyl acetate = 8/1) to afford anti-5aa.

General Procedure with Reduced Catalyst Loading (5 mol %):

To a suspension of Pd/Schiff base 1 pre-catalyst (9.2 mg, 0.02 mmol) in THF (800 µL) was added La(O-iPr)₃ (100 µL, 0.02 mmol, 0.2 M in THF), and the mixture was stirred at 80 °C for 1 h to give a Pd/La/1 complex. After cooling down the mixture to room temperature, 4-bromophenol (100 µL, 0.02 mmol, 0.2 M in THF) was added, and the mixture was stirred for 15 min at room temperature. The catalyst mixture was cooled down to –40 °C, and nitroethane 4a (280 µL, 4.0 mmol) was added. After stirring for 1 h at –40 °C, aldehyde 3a (0.4 mmol) and xylenes (800 µL) were added slowly. The stirring was continued for 120 h at –40 °C and the reaction mixture was diluted with diethyl ether (6 mL). The resulting mixture suspension was filtered through a pad of Celite to remove the catalyst, and the filtrate solution was evaporated under reduced pressure. The resulting residue was analyzed by ¹H NMR to determine diastereomeric ratio, and was purified by silica gel flash column chromatography (hexane/ethyl acetate = 8/1) to afford anti-5aa.
Celite to remove the catalyst, and the filtrate solution was evaporated under reduced pressure. The resulting residue was analyzed by $^1$H NMR to determine diastereomeric ratio, and was purified by silica gel flash column chromatography (hexane/ethyl acetate = 8/1) to afford anti-5aa (59.4 mg, 82%, 85% ee, 16:1 = anti/syn).

**Determination of Relative and Absolute Configurations:**


**Spectra Data of New Compounds:**

*(1S,2R)-2-nitro-1-phenylpropan-1-ol (5aa)*


Colorless oil; IR (neat) ν 3435, 1633, 1548 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 1.50 (d, $J = 7.0$ Hz, 3H), 2.71 (d, $J = 3.7$ Hz, 1H), 4.70 (qd, $J = 3.7$, 7.0 Hz, 1H), 5.40 (dd, $J = 3.7$, 3.7 Hz, 1H), 7.32-7.41 (m, 5H); $^{13}$C NMR (CDCl$_3$) δ 12.1, 73.9, 87.4, 125.9, 128.5, 128.7, 138.4; ESI-MS m/z 204 [M+Na]$^+$; HRMS calcd. for C$_9$H$_{11}$NO$_3$Cs [M+Cs]$^+$: 313.9788, found 313.9791; [α]$_D^{23}$ $-11.9$ (c 1.42, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) t$_R$ 8.0 min (major) and 8.8 min (minor).
(1S,2R)-1-(4-methylphenyl)-2-nitropropan-1-ol (5ba)
Colorless solid; IR (KBr) ν 3465, 1561, 1515 cm⁻¹; ¹H NMR (CDCl₃) δ 1.51 (d, J = 6.7 Hz, 3H), 2.35 (s, 3H), 2.61 (d, J = 3.4 Hz, 1H), 4.68 (qd, J = 3.6, 6.7 Hz, 1H), 5.34 (dd, J = 3.4, 3.6 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H); ¹³C NMR (CDCl₃) δ 12.2, 21.1, 73.9, 87.5, 125.9, 129.4, 135.4, 138.4; ESI-MS m/z 218 [M+Na]⁺; HRMS calcd. for C₁₀H₁₃NO₃Cs [M+Cs]⁺: 327.9944, found 327.9943; [α]_D²³ = -8.4 (c 0.59, CHCl₃); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) tᵣ 8.2 min (major) and 9.3 min (minor).

(1S,2R)-1-(3-methylphenyl)-2-nitropropan-1-ol (5ca)
Colorless oil; IR (neat) ν 3445, 1636, 1543 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 2.60 (d, J = 3.4 Hz, 1H), 4.66 (qd, J = 3.7, 6.8 Hz, 1H), 5.34 (dd, J = 3.4, 3.7 Hz, 1H), 7.11-7.16 (m, 3H), 7.24 (d, J = 6.7 Hz, 1H); ¹³C NMR (CDCl₃) δ 12.1, 21.4, 73.9, 87.5, 123.0, 126.6, 128.6, 129.3, 138.4, 138.5; ESI-MS m/z 218 [M+Na]⁺; HRMS calcd. for C₁₀H₁₃NO₃Cs [M+Cs]⁺: 327.9944, found 327.9940; [α]_D²³ = -4.2 (c 0.74, CHCl₃); HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) tᵣ 8.5 min (major) and 9.6 min (minor).

(1S,2R)-1-(2-methylphenyl)-2-nitropropan-1-ol (5da)
Colorless solid; IR (neat) ν 3446, 1636, 1548 cm⁻¹; ¹H NMR (CDCl₃) δ 1.50 (d, J = 6.7 Hz, 3H), 2.35 (s, 3H), 2.50 (d, J = 3.2 Hz, 1H), 4.62 (qd, J = 3.2, 6.7 Hz, 1H), 5.61 (dd, J = 3.2, 3.2 Hz, 1H), 7.15 (d, J = 7.0 Hz, 1H), 7.20-7.26 (m, 2H), 7.52 (d, J = 7.3 Hz, 1H); ¹³C NMR (CDCl₃) δ 11.6, 18.8, 70.9, 85.3, 126.0, 126.5, 128.4, 130.8, 134.3, 136.6; ESI-MS m/z 218 [M+Na]⁺; HRMS calcd. for C₁₀H₁₃NO₃Cs [M+Cs]⁺: 327.9944, found 327.9940; [α]_D²² = -6.6 (c 1.11, CHCl₃); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) tᵣ 7.0 min (major) and 7.7 min (minor).
(1S,2R)-1-(4-methoxyphenyl)-2-nitropropan-1-ol (5ea)
Colorless solid; IR (KBr) ν 3486, 1613, 1546, 1514 cm⁻¹; ¹H NMR (CDCl₃) δ 1.52 (d, J = 6.7 Hz, 3H), 2.59 (d, J = 3.4 Hz, 1H), 3.81 (s, 3H), 4.67 (qd, J = 4.0, 6.7 Hz, 1H), 5.31 (dd, J = 3.4, 4.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 9.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 12.5, 55.3, 73.8, 87.6, 114.1, 127.2, 130.5, 159.7; ESI-MS m/z 234 [M+Na]⁺; HRMS calcd. for C₁₀H₁₃NO₄Cs [M+Cs]⁺: 343.9894, found 343.9897; [α]D₂₀ -13.4 (c 0.65, CHCl₃); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) tₚ 11.4 min (major) and 12.9 min (minor).

(1S,2R)-1-(4-chlorophenyl)-2-nitropropan-1-ol (5fa)
Colorless solid; IR (KBr) ν 3518, 1547, 1492, 1389 cm⁻¹; ¹H NMR (CDCl₃) δ 1.49 (d, J = 7.0 Hz, 3H), 2.73 (d, J = 3.7 Hz, 1H), 4.66 (qd, J = 3.7, 7.0 Hz, 1H), 5.39 (dd, J = 3.7, 3.7 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 12.0, 73.2, 87.2, 127.3, 129.0, 134.4, 136.8; ESI-MS m/z 238 [M+Na]⁺; HRMS calcd. for C₉H₁₀ClNO₃Cs [M+Cs]⁺: 347.9398, found 347.9397; [α]D₂₂ +1.5 (c 1.07, CHCl₃); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) tₚ 7.9 min (major) and 8.4 min (minor).

(1R,2R)-1-(2-furyl)-2-nitropropan-1-ol (5ga)
pale yellow oil; IR (neat) ν 3433, 1635, 1550 cm⁻¹; ¹H NMR (CDCl₃) δ 1.60 (d, J = 7.0 Hz, 3H), 2.74 (d, J = 4.6 Hz, 1H), 4.86 (qd, J = 4.6, 7.0 Hz, 1H), 5.35 (dd, J = 4.6, 4.6 Hz, 1H), 6.36-6.39 (m, 2H), 7.40 (m, 1H); ¹³C NMR (CDCl₃) δ 13.2, 68.9, 84.9, 108.2, 110.6, 142.8, 151.1; ESI-MS m/z 194 [M+Na]⁺; HRMS calcd. for C₇H₉NO₄Cs [M+Cs]⁺: 303.9581, found 303.9589; [α]D₂₀ +3.7 (c 0.48, CHCl₃); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 0.5 mL/min, detection at 254 nm) tₚ 17.6 min (major) and 18.5 min (minor).

(3S,4R,E)-4-nitro-1-phenylpent-1-en-3-ol (5ha)
colorless solid; IR (KBr) ν 3484, 1553, 1390, 1368, 1137 cm⁻¹; ¹H NMR
$^{13}$C NMR (CDCl$_3$) δ 12.9, 73.2, 86.0, 125.0, 126.7, 128.4, 128.7, 133.8, 135.6; ESI-MS m/z 230 [M+Na]$^+$; HRMS calcd. for C$_{11}$H$_{13}$NO$_3$Cs [M+Cs]$^+$: 339.9944, found 339.9944; $\text{[D]}$$^2$ -2.1 (c 1.06, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 0.5 mL/min, detection at 254 nm) $t_R$ 24.3 min (major) and 28.8 min (minor).

(3$S$,4$R$)-4-nitro-1-phenylpentan-3-ol (5ia)


colorless oil; IR (neat) ν 3446, 1548, 1454, 1392 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 1.56 (d, $J = 6.9$ Hz, 3H), 1.69-1.84 (m, 2H), 2.46 (brd, $J = 4.6$ Hz, 1H), 2.68-2.74 (m, 1H), 2.87-2.93 (m, 1H), 4.18-4.21 (m, 1H), 4.51 (qd, $J = 3.1$, 6.9 Hz, 1H), 7.20-7.24 (m, 3H), 7.29-7.32 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 12.5, 31.9, 34.6, 71.1, 86.3, 126.2, 128.4, 128.6, 140.7; ESI-MS m/z 232 [M+Na]$^+$; HRMS calcd. for C$_{11}$H$_{15}$NO$_3$Cs [M+Cs]$^+$: 342.0101, found 342.0099; [α]$_D$$^2$ -21.6 (c 1.75, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 220 nm) $t_R$ 8.5 min (major) and 9.0 min (minor).

(1$S$,2$R$)-1-cyclohexyl-2-nitropropan-1-ol (5ja)

colorless oil; IR (neat) ν 3437, 1549, 1450, 1392 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.90-1.40 (m, 7H), 1.54 (d, $J = 7.0$ Hz, 3H), 1.66-1.81 (m, 3H), 2.05-2.07 (m, 1H), 2.16 (d, $J = 4.6$ Hz, 1H), 3.93-3.96 (m, 1H), 4.64 (qd, $J = 3.4$, 7.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 11.9, 25.6, 25.8, 26.1, 28.9, 29.0, 40.1, 76.2, 84.3; ESI-MS m/z 210 [M+Na]$^+$; HRMS calcd. for C$_9$H$_{17}$NO$_3$Cs [M+Cs]$^+$: 320.0257, found 320.0258; [α]$_D$$^2$ -6.4 (c 1.33, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 20/1, flow 1.0 mL/min, detection at 220 nm) $t_R$ 11.1 min (minor) and 12.7 min (major).

(1$S$,2$R$)-2-nitro-1-phenylbutan-1-ol (5ab)


Colorless oil; IR (neat) ν 3453, 1549, 1456 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.94 (dd, $J = 7.4$, 7.4 Hz, 3H), 1.87-1.95 (m, 1H), 2.12-2.21 (m, 1H), 2.71 (d, $J = 2.9$ Hz, 1H), S-6
4.56-4.60 (m, 1H), 5.18 (dd, \(J = 2.9, 5.2\) Hz, 1H), 7.31-7.40 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 10.4, 21.3, 74.2, 94.7, 126.2, 128.7, 128.7, 138.5; ESI-MS \(m/z\) 218 [M+Na]\(^{+}\); HRMS calcd. for C\(_{10}\)H\(_{13}\)NO\(_3\)Cs [M+Cs]\(^{+}\): 327.9944, found 327.9940; \([\alpha]_D^{23}\) \(-13.8\) (c 0.87, CHCl\(_3\)); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) \(t_R\) 7.3 min (major) and 7.7 min (minor).

**Procedure for \((IR,2S)\)-1-(4-Benzylxyphenyl)-2-nitropropan-1-ol (5ka) with Catalytic Asymmetric Nitroaldol Reaction Using a Pd/La/Schiff base 1 = 1:1:1 with 4-Bromophenol System:**

To a suspension of Pd-Schiff base pre-catalyst (45.9 mg, 0.1 mmol) in THF (1.5 mL), La(O-iPr)\(_3\) solution (500 \(\mu\)L, 0.1 mmol, 0.2 M in THF) was added and stirred for 1 h under reflux. After cooling down to the ambient temperature, 4-bromophenol (500 \(\mu\)L, 0.1 mmol, 0.2 M in THF) was added to the resulting suspension and stirred for 15 min. Next, resulting reaction suspension was cooled down to \(-30^\circ\)C and nitroethane (700 \(\mu\)L, 10 mmol) was added at the same temperature. After stirring for 1 h at \(-30^\circ\)C, aldehyde 3k (2.0 mL, 1.0 mmol, 0.5 M in xylenes) was added. The stirring continued for 85 h at \(-30^\circ\)C and the reaction mixture was quenched with 0.5 M citric acid in THF (1.0 mL). The resulting reaction suspension was poured into diethyl ether (20 mL) then filtered through a pad of Celite to remove catalyst. The filtrate solution was evaporated under reduced pressure. The resulting residue was analyzed by \(^1\)H NMR to determine diastereomeric ratio, and was purified by silica gel flash column chromatography (hexane/ethyl acetate = 5/1) to afford anti-5ka (244 mg, 85%, 83% ee, 14:1=anti/syn):

Colorless solid; IR (KBr) \(\nu\) 3511, 1611, 1551, 1512, 1388 cm\(^{-1}\); \(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 1.11 (d, \(J = 6.7\) Hz, 3H), 1.66 (d, \(J = 4.0\) Hz, 1H), 4.11 (qd, \(J = 4.0, 6.7\) Hz, 1H), 4.64 (s, 2H), 4.84 (dd, \(J = 4.0, 4.0\) Hz, 1H), 6.75 (d, \(J = 8.9\) Hz, 2H), 6.92 (d, \(J = 8.9\) Hz, 2H), 7.05-7.23 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 12.4, 70.0, 73.7, 87.5, 115.0, 127.3, 127.5, 128.1, 128.6, 130.7, 136.6, 158.9; ESI-MS \(m/z\) 310 [M+Na]\(^{+}\); HRMS calcd. for C\(_{15}\)H\(_{17}\)NO\(_4\)Cs [M+Cs]\(^{+}\): 420.0207, found 420.0201; \([\alpha]_D^{25}\) \(+9.0\) (c 0.74, CHCl\(_3\)); HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) \(t_R\) 27.0 min (minor) and 33.3 min (major).
Syntheses of β-Adrenoceptor Agonists 2a·HCl (Ritodrine hydrochloride) and 2b·HCl:

**Ritodrine hydrochloride (2a·HCl):**


To a solution of 5ka (90.8 mg, 0.316 mmol) in EtOAc (1.58 mL) was added Pd/C (10%, 33.6 mg) at room temperature. The resulting mixture was stirred vigorously at same temperature under H₂ atmosphere (1 atm) for 12 h. After checking the completion of the reaction by TLC, aldehyde 7a (64.9 mg, 0.287 mmol) [Lit. Aberle, N.; Catimel, J.; Nice, E. C.; Watson, K. G. Bioorg. Med. Chem. Lett. 2007, 17, 3714.] was added at room temperature. The resulting mixture was stirred vigorously at 60 °C under H₂ atmosphere (1 atm). After stirring for 24 h, Pd/C was filtered off and the mixture was concentrated in vacuo. To a solution of the residue in MeOH (2 mL) was added 10% HCl/MeOH at 0 °C. The mixture was concentrated in vacuo, and the residue was purified by reversed phase column chromatography (Cosmosil 140C18-PREP, Nacalai tesque, H₂O/MeOH = 80/20) to give ritodrine 2a·HCl (86.6 mg, 0.268 mmol, 93%) as colorless solid. All spectral data were well consistent with those reported.

Colorless solid; IR (KBr) ν 3389, 3013, 2854, 1613, 1594, 1443, 1218 cm⁻¹; ¹H NMR (d₆-DMSO) δ 0.96 (d, J = 6.8 Hz, 3H), 2.92-2.95 (m, 2H), 3.16-3.18 (m, 2H), 3.30 (brd, J = 5.5 Hz, 1H), 5.11 (bri, 1H), 5.95 (brd, J = 4.0 Hz, 1H), 6.74 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 8.97 (bri, 2H), 9.42 (s, 1H), 9.47 (s, 1H); ¹³C NMR (d₆-DMSO) δ 9.4, 31.0, 46.2, 58.6, 69.3, 114.9, 115.4, 126.9, 127.4, 129.6, 131.3, 156.2, 156.6; HRMS calcld. for C₁₇H₂₂NO₃ [M-Cl]+: 288.1594, found 288.1592; [α]D²⁰ –10.8 (c 0.19, EtOH for 84% ee); lit. [α]D²⁰ –13.2 (c 0.24, EtOH); HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol/Et₂NH = 75/25/0.1, flow 1.0 mL/min, detection at 278 nm) tᵣ 10.5 min (major) and 16.4 min (minor).

**ethyl 2-(4-((1R,2S)-1-(4-hydroxyphenyl)-1-hydroxypropan-2-ylamino)ethyl-2,5-dimethylphenylox y)acetate hydrochloride (2b·HCl):**


To a solution of 5ka (99.7 mg, 0.347 mmol) in
EtOAc (1.74 mL) was added Pd/C (10%, 36.9 mg) at room temperature. The resulting mixture was stirred vigorously at same temperature under H₂ atmosphere (1 atm) for 12 h. After checking the completion of the reaction by TLC aldehyde 7b (73.6 mg, 0.294 mmol) [Lit. Tanaka, N.; Tamai, T. JP Patent JP2002-64840.] was added at room temperature. The resulting mixture was stirred vigorously at 60 °C under H₂ atmosphere (1 atm). After stirring for 24 h, Pd/C was filtered off and the mixture was concentrated in vacuo. To a solution of the residue in MeOH (2 mL) was added 10% HCl/MeOH at 0 °C. The mixture was concentrated in vacuo, and the residue was purified by reversed phase column chromatography (Cosmosil 140C18-PREP, Nacalai tesque, H₂O/MeOH = 80/20, 70/30) to give 2b·HCl (93.8 mg, 0.215 mmol, 73%) as colorless solid. All spectral data were well consistent with those reported.

Colorless solid; IR (KBr) ν 3348, 2813, 1736, 1613, 1513, 1298, 1265, 1199 cm⁻¹; ¹H NMR (d₆-DMSO) δ 0.96 (d, J = 6.7 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 2.14 (s, 3H), 2.25 (s, 3H), 2.90-2.94 (m, 2H), 3.10-3.18 (m, 2H), 3.69 (s, 1H), 4.16 (q, J = 7.0 Hz, 2H), 4.75 (s, 2H), 5.08 (m, 1H), 5.96 (d, J = 4.0 Hz, 1H), 6.68 (s, 1H), 6.76 (d, J = 8.5 Hz, 2H), 6.96 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 8.90 (m, 2H), 9.42 (s, 1H); ¹³C NMR (d₆-DMSO) δ 9.4, 14.1, 15.5, 18.9, 28.5, 45.1, 58.5, 60.5, 65.0, 69.3, 113.5, 114.9, 123.4, 126.9, 127.8, 131.2, 131.5, 134.4, 154.4, 156.6, 168.9; ESI-MS m/z 424 [M-HCl+Na⁺]; HRMS calcd. for C₂₃H₃₂NO₅ [M-Cl⁺]: 402.2275, found 402.2279; [α]D²⁹ -12.5 (c 0.40, EtOH); HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol/Et₂NH = 75/25/0.1, flow 1.0 mL/min, detection at 278 nm) tᵣ 14.0 min (major) and 28.7 min (minor).
Mechanistic Insight:

For anti-selective nitroaldol reaction, both Pd and La were essential as suggested by the results shown in Table S1. A Pd-Schiff base 1 complex did not catalyze the reaction (entry 2), and even in the presence of 20 mol % \( \text{iPr}_2\text{NEt} \), much lower reactivity and stereoselectivities were observed (entry 3). In the case of a La-Schiff base 1 complex, product 5aa was obtained in 33\% yield, and stereoselectivities were poor (entry 4). 4-Bromophenol additive was also indispensable for good diastereo- and enantioselectivities (entry 1 vs 5).

Table S1. Control Experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>M (^a)</th>
<th>RE (^b)</th>
<th>additive (x mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Dr (anti:syn)</th>
<th>% ee of anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd</td>
<td>La</td>
<td>4-Br-phenol (10)</td>
<td>69</td>
<td>92</td>
<td>19:1</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Pd</td>
<td>none</td>
<td>4-Br-phenol (10)</td>
<td>72</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Pd</td>
<td>none</td>
<td>4-Br-phenol (10)  + iPr(_2)NEt (20)</td>
<td>72</td>
<td>6</td>
<td>2.8:1</td>
<td>36(^c)</td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>La</td>
<td>4-Br-phenol (10)</td>
<td>72</td>
<td>33</td>
<td>1.8:1</td>
<td>4(^c)</td>
</tr>
<tr>
<td>5</td>
<td>Pd</td>
<td>La</td>
<td>none</td>
<td>72</td>
<td>86</td>
<td>6:1</td>
<td>71</td>
</tr>
</tbody>
</table>

\(^a\) Pd(OAc)\(_2\) was used. \(^b\) La(O-iPr)\(_3\) was used. \(^c\) ent-5aa was major.
ESI-MS Analysis of Pd/La/Schiff base 1 = 1:1:1 Mixture:

To gain insight for positive effects of 4-bromophenol, we conducted ESI-MS (Waters-ZQ4000) analysis of Pd/La/Schiff base 1 complex in the absence and in the presence of 4-bromophenol additive. ESI-MS charts are summarized in Figure S1 and S2.

A: Pd/La/Schiff base 1 = 1:1:1 mixture without 4-bromophenol additive:

**sample preparation:** To a suspension of Pd/Schiff base 1 pre-catalyst (9.2 mg, 0.02 mmol) in THF (300 µL) was added La(O-iPr)₃ (100 µL, 0.02 mmol, 0.2 M in THF), and the mixture was stirred at 80 °C for 1 h to give a Pd/La/1 complex. After cooling down the mixture to room temperature, the mixture was diluted with iPrOH (600 µL) and CH₃CN (2.5 mL). The resulting solution was injected for analysis. ESI-MS chart is shown in Figure S1.

**conditions:** capillary 3.60 kV, cone 115 V, source temp 80 °C, desolvation temp 150 °C

![ESI-MS chart](image)

**Figure S1.** ESI-MS of Pd/La/Schiff base 1 = 1:1:1 mixture without 4-bromophenol additive.
B: Pd/La/Schiff base 1 = 1:1:1 mixture with 4-bromophenol additive:

**Sample preparation:** To a suspension of Pd/Schiff base 1 pre-catalyst (9.2 mg, 0.02 mmol) in THF (300 µL) was added La(O-iPr)₃ (100 µL, 0.02 mmol, 0.2 M in THF), and the mixture was stirred at 80 °C for 1 h to give a Pd/La/1 complex. After cooling down the mixture to room temperature, 4-bromophenol (500 µL, 0.1 mmol, 0.2 M in THF) was added, and the mixture was stirred for 15 min at room temperature. The mixture was diluted with iPrOH (600 µL) and CH₃CN (2.5 mL). The resulting solution was injected for analysis. ESI-MS chart is shown in Figure S2.

**Conditions:** capillary 3.60 kV, cone 115 V, source temp 80 °C, desolvation temp 150 °C

---

**Figure S2.** ESI-MS of Pd/La/Schiff base 1 = 1:1:1 mixture with 4-bromophenol additive.
Discussion:

In ESI-MS chart of Pd-La-Schiff base 1 mixture without 4-bromophenol additive, peaks corresponding to a μ-oxo + OR Pd-La-Schiff base 1 trimer complex (OR = O-iPr or OH) \((m/z = 1803, [M-OR]^+)\) and other oligomers were observed. In Figure S1, a peak corresponding to a monomeric Pd-La-Schiff base 1 = 1:1:1 complex was not detected. On the other hand, in Figure S2, with 4-bromophenol additive, a new peak corresponding to a monomeric Pd-La-Schiff base 1 = 1:1:1 complex \((m/z = 595)\) appeared. The peaks of \(m/z = 595\) can be assigned to \([M-OAr]^+\) (\(M = \) Pd-La-Schiff base 1-OAr = 1:1:1:1, Ar = 4-Br-C_6H_4-). The peak of \(m/z = 1803\) in Figure S1 can be assigned to an μ-oxo + OR Pd-La-Schiff base 1 trimer complex (OR = OAr or O-iPr or OH). For each complex, several peaks were observed depending on Pd natural isotopes distribution pattern (\(^{102}\text{Pd}: 1.0\%, \text{ }^{104}\text{Pd}: 11.0\%, \text{ }^{105}\text{Pd}: 22.2\%, \text{ }^{106}\text{Pd}: 27.3\%, \text{ }^{108}\text{Pd}: 26.7\%, \text{ }^{110}\text{Pd}: 11.8\%). Especially, distribution pattern of a peak corresponding to a monomeric Pd-La-Schiff base 1 = 1:1:1 complex \((m/z = 595)\) matched nicely with its calculated distribution pattern.

These observations and the positive effects of 4-bromophenol additive suggested that a monomeric Pd-La-Schiff base 1/OAr = 1:1:1:1 complex might be an active species. Although all the mechanisms are speculative in this stage, the postulated catalytic cycle is depicted in Figure S3. La-OAr moiety would function as a Brønsted base to deprotonate α-proton of nitroalkane, affording La-nitronate (II). Taking necessity of both Pd and La into consideration, we assumed that La-nitronate would react with aldehyde coordinated to Pd metal center (III and Figure S4). TS-A is speculated to be more favorable than TS-B due to the steric repulsion between R and Pd-La-catalyst complex, affording anti-5. In this stage, other mechanisms such as coordination of aldehyde with La and participation of oligomeric Pd-La Schiff base 1 complex as active species cannot be ruled out. Further mechanistic studies are ongoing.
**Figure S3.** Postulated catalytic cycle.

**Figure S4.** Postulated transition state model for anti-selectivity.