Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

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*

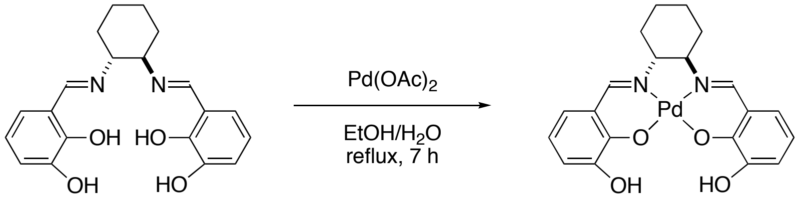
Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan, phone: +81-3-5841-4830, fax: +81-3-5684-5206, E-mail: mshibasa@mol.f.u-tokyo.ac.jp; smatsuna@mol.f.u-tokyo.ac.jp

Experimental Section

Genaral

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 ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$, C_6D_6 and d_6-DMSO were reported in the scale relative to $CHCl_3$ (7.26 ppm), C_6D_5H (7.15 ppm) and d_5-DMSO (2.50 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.0 ppm) and d_6-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-Et_2NH. Reactions were carried out in dry solvents under argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. La(O-*i*Pr)$_3$ 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-*i*Pr)$_3$ 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



To a solution of (*R,R*)-Schiff base ligand **1-H$_4$** (329 mg, 0.93 mmol) in EtOH (8 mL) and H_2O (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-*i*Pr)$_3$ (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 *µ*L) 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 ^{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**.

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-*i*Pr)$_3$ (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 *µ*L) 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** (59.4 mg, 82%, 85% ee, 16:1=*anti*/*syn*).

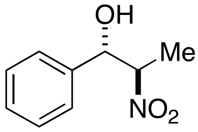
Determination of Relative and Absolute Configurations:

Relative and absolute configurations of β-nitro alcohols **5aa**, **5ba**, **5da**, **5fa**, **5ga**, **5ha**, **5ia**, and **5ab** were determined by comparing ^1H NMR and retention time of HPLC [Lit. (1) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (2) Risgaard, T.; Gothelf, K. V.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153. (3) Gruber-Khadjawi, M.; Purkarthofer, T.; Skrane, W.; Griengle, H. *Adv. Synth. Catal.* **2007**, *349*, 1445. (4) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (5) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272.] For relative and absolute configurations of other β-nitro alcohols **5ca**, **5ea**, **5ja** and **5ka** were determined by analogy of others.

Spectra Data of New Compounds:

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

known compound [Lit. (1) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (2) Gruber-Khadjawi, M.; Purkarthofer, T.; Skrane, W.; Griengle, H. *Adv. Synth. Catal.* **2007**, *349*, 1445. (3) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (4) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272.]

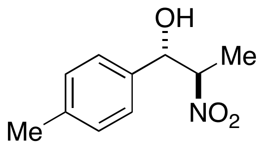


5aa

Colorless oil; IR (neat) ν 3435, 1633, 1548 cm^{-1}; ^1H 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 $C_9H_{11}NO_3Cs$ $[M+Cs]^+$: 313.9788, found 313.9791; $[\alpha]_D^{23}$ –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)

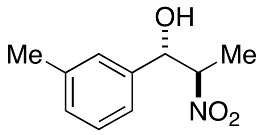
known compound [Lit. (1) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (2) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.]



5ba

Colorless solid; IR (KBr) ν 3465, 1561, 1515 cm^{-1}; ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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 $C_{10}H_{13}NO_3Cs$ [M+Cs]$^+$: 327.9944, found 327.9943; $[\alpha]_D^{23}$ –8.4 (*c* 0.59, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) t$_R$ 8.2 min (major) and 9.3 min (minor).

(*1S,2R*)-1-(3-methylphenyl)-2-nitropropan-1-ol (5ca)

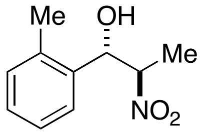


5ca

Colorless oil; IR (neat) ν 3445, 1636, 1543 cm^{-1}; ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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 $C_{10}H_{13}NO_3Cs$ [M+Cs]$^+$: 327.9944, found 327.9940; $[\alpha]_D^{23}$ –4.2 (*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$_R$ 8.5 min (major) and 9.6 min (minor).

(*1S,2R*)-1-(2-methylphenyl)-2-nitropropan-1-ol (5da)

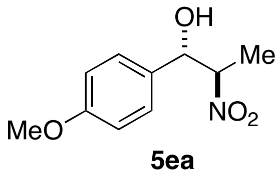
known compound [Lit. Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272.]



5da

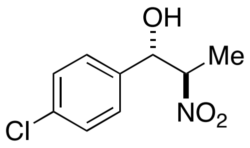
Colorless solid; IR (neat) ν 3446, 1636, 1548 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.50 (d, *J* = 6.7 Hz, 3H), 2.35 (s, 3H), 2.50 (d, *J* = 3.2 Hz, 1H), 4.62 (qd, *J* = 3.2, 6.7 Hz, 1H), 5.61 (dd, *J* = 3.2, 3.2 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 1H), 7.20-7.26 (m, 2H), 7.52 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (CDCl$_3$) 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 $C_{10}H_{13}NO_3Cs$ [M+Cs]$^+$: 327.9944, found 327.9940; $[\alpha]_D^{22}$ –6.6 (*c* 1.11, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) t$_R$ 7.0 min (major) and 7.7 min (minor).

(*1S,2R*)-1-(4-methoxyphenyl)-2-nitropropan-1-ol (5ea)


5ea

Colorless solid; IR (KBr) ν 3486, 1613, 1546, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{10}H_{13}NO_4Cs$ [M+Cs]$^+$: 343.9894, found 343.9897; $[\alpha]_D^{20}$ −13.4 (*c* 0.65, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) t_R 11.4 min (major) and 12.9 min (minor).

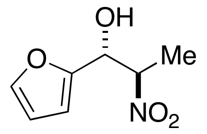
(*1S,2R*)-1-(4-chlorophenyl)-2-nitropropan-1-ol (5fa)


5fa

known compound [Lit. Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.]

Colorless solid; IR (KBr) ν 3518, 1547, 1492, 1389 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_9H_{10}ClNO_3Cs$ [M+Cs]$^+$: 347.9398, found 347.9397; $[\alpha]_D^{22}$ +1.5 (*c* 1.07, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) t_R 7.9 min (major) and 8.4 min (minor).

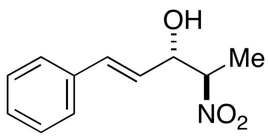
(*1R,2R*)-1-(2-furyl)-2-nitropropan-1-ol (5ga)


5ga

known compound [Lit. Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.]

pale yellow oil; IR (neat) ν 3433, 1635, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_7H_9NO_4Cs$ [M+Cs]$^+$: 303.9581, found 303.9589; $[\alpha]_D^{20}$ +3.7 (*c* 0.48, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 0.5 mL/min, detection at 254 nm) t_R 17.6 min (major) and 18.5 min (minor).

(*3S,4R,E*)-4-nitro-1-phenylpent-1-en-3-ol (5ha)

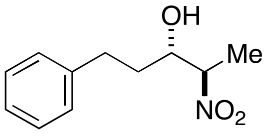

5ha

known compound [Lit. Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.]

colorless solid; IR (KBr) ν 3484, 1553, 1390, 1368, 1137 cm^{-1}; ^{1}H NMR

(CDCl$_3$) δ 1.59 (d, *J* = 7.0 Hz, 3H), 2.52 (d, *J* = 4.3 Hz, 1H), 4.66 (qd, *J* = 3.7, 7.0 Hz, 1H), 4.86-4.89 (m, 1H), 6.12 (dd, *J* = 6.4, 15.9 Hz, 1H), 6.76 (d, *J* = 15.9 Hz, 1H), 7.27-7.40 (m, 5H); ^{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 $C_{11}H_{13}NO_3Cs$ [M+Cs]$^+$: 339.9944, found 339.9944; $[\alpha]_D^{22}$ -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).

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

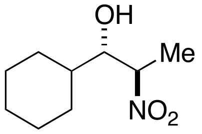


5ia

known compound [Lit. Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.]

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 $C_{11}H_{15}NO_3Cs$ [M+Cs]$^+$: 342.0101, found 342.0099; $[\alpha]_D^{26}$ -21.6 (*c* 1.75, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 1.0 mL/min, detection at 254 nm) t_R 8.5 min (major) and 9.0 min (minor).

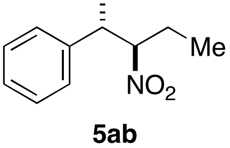
(*1S,2R*)-1-cyclohexyl-2-nitropropan-1-ol (5ja)



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 $C_9H_{17}NO_3Cs$ [M+Cs]$^+$: 320.0257, found 320.0258; $[\alpha]_D^{26}$ -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).

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

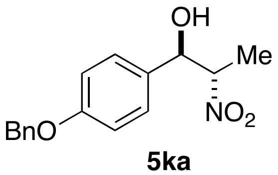


5ab

known compound [Lit. (1) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (2) Risgaard, T.; Gothelf, K. V.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153. (3) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.]

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), 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 ($CDCl_3$) δ 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 $C_{10}H_{13}NO_3Cs$ $[M+Cs]^+$: 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 (*1R,2S*)-1-(4-Benzyloxyphenyl)-2-nitropropan-1-ol (5ka) with Catalytic Asymmetric Nitroaldol Reaction Using a Pd/La/Schiff base 1 = 1:1:1 with 4-Bromophenol System:



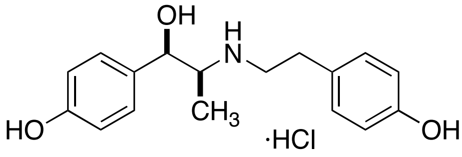
5ka

To a suspension of Pd-Schiff base pre-catalyst (45.9 mg, 0.1 mmol) in THF (1.5 mL), La(O-*i*Pr)$_3$ solution (500 μL, 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 μL, 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 °C and nitroethane (700 μL, 10 mmol) was added at the same temperature. After stirring for 1 h at –30 °C, aldehyde **3k** (2.0 mL, 1.0 mmol, 0.5 M in xylenes) was added. The stirring continued for 85 h at –30 °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) ν 3511, 1611, 1551, 1512, 1388 cm^{-1}; ^{1}H NMR (C_6D_6) δ 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 ($CDCl_3$) δ 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 $C_{15}H_{17}NO_4Cs$ $[M+Cs]^+$: 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:

(*1R,2S*)-2-(4-hydroxyphenetylamino)-1-(4-hydroxyphenyl)propan-1-ol hydrochloride Ritodrine hydrochloride (2a·HCl):



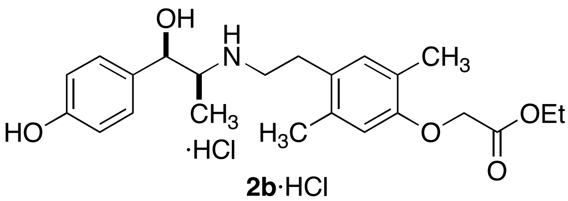
2a·HCl

known compound [Lit. Yamazaki, N.; Fukuda, Y.; Shibazaki, Y.; Niizato, T.; Kosugi, I.; Yoshioka, S. US Patent 5,449,694, **1995**.]

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 H_2 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 H_2 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, H_2O/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, 1515, 1443, 1218 cm^{-1}; ^{1}H NMR (d$_6$-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 (brs, 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 (brs, 2H), 9.42 (s, 1H), 9.47 (s, 1H); ^{13}C NMR (d$_6$-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 calcd. for $C_{17}H_{22}NO_3$ [M-Cl]$^+$: 288.1594, found 288.1592; $[\alpha]_D^{29}$ –10.8 (*c* 0.19, EtOH for 84% ee); lit. $[\alpha]_D^{20}$ –13.2 (*c* 0.24, EtOH); HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol/Et$_2$NH = 75/25/0.1, flow 1.0 mL/min, detection at 278 nm) t$_R$ 10.5 min (major) and 16.4 min (minor).

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



2b·HCl

known compound [Lit. Tanaka, N.; Tamai, T. JP Patent JP2002-64840.]

To a solution of **5ka** (99.7 mg, 0.347 mmol) in

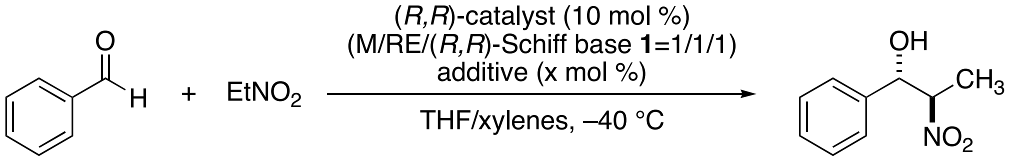
EtOAc (1.74 mL) was added Pd/C (10%, 36.9 mg) at room temperature. The resulting mixture was stirred vigorously at same temperature under H_2 atmosphere (1 atm) for 12 h. After checking the completion of the reaction by TLC aldehyde **7b** (73.6 mg, 0.294 mmol) **[**Lit. Tanaka, N.; Tamai, T. JP Patent JP2002-64840.**]** was added at room temperature. The resulting mixture was stirred vigorously at 60 °C under H_2 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, H_2O/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 (d_6-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); ^{13}C NMR (d_6-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 $[M\text{-}HCl+Na]^+$; HRMS calcd. for $C_{23}H_{32}NO_5$ $[M\text{-}Cl]^+$: 402.2275, found 402.2279; $[\alpha]_D^{29}$ −12.5 (*c* 0.40, EtOH); HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol/Et_2NH = 75/25/0.1, flow 1.0 mL/min, detection at 278 nm) t_R 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 % $i\text{Pr}_2\text{NEt}$, 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.



3a **4a** **5aa**

Entry	M[a]	RE[b]	additive (x mol %)	Time (h)	Yield (%)	Dr (*anti*:*syn*)	% ee of *anti*
1	Pd	La	4-Br-phenol (10)	69	92	19:1	84
2	Pd	none	4-Br-phenol (10)	72	0	—	—
3	Pd	none	4-Br-phenol (10) + $i\text{Pr}_2\text{NEt}$ (20)	72	6	2.8:1	36[c]
4	none	La	4-Br-phenol (10)	72	33	1.8:1	4[c]
5	Pd	La	none	72	86	6:1	71

[a] Pd(OAc)_2 was used. [b] $\text{La(O-}i\text{Pr)}_3$ 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-*i*Pr)$_3$ (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 *i*PrOH (600 μL) and CH$_3$CN (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

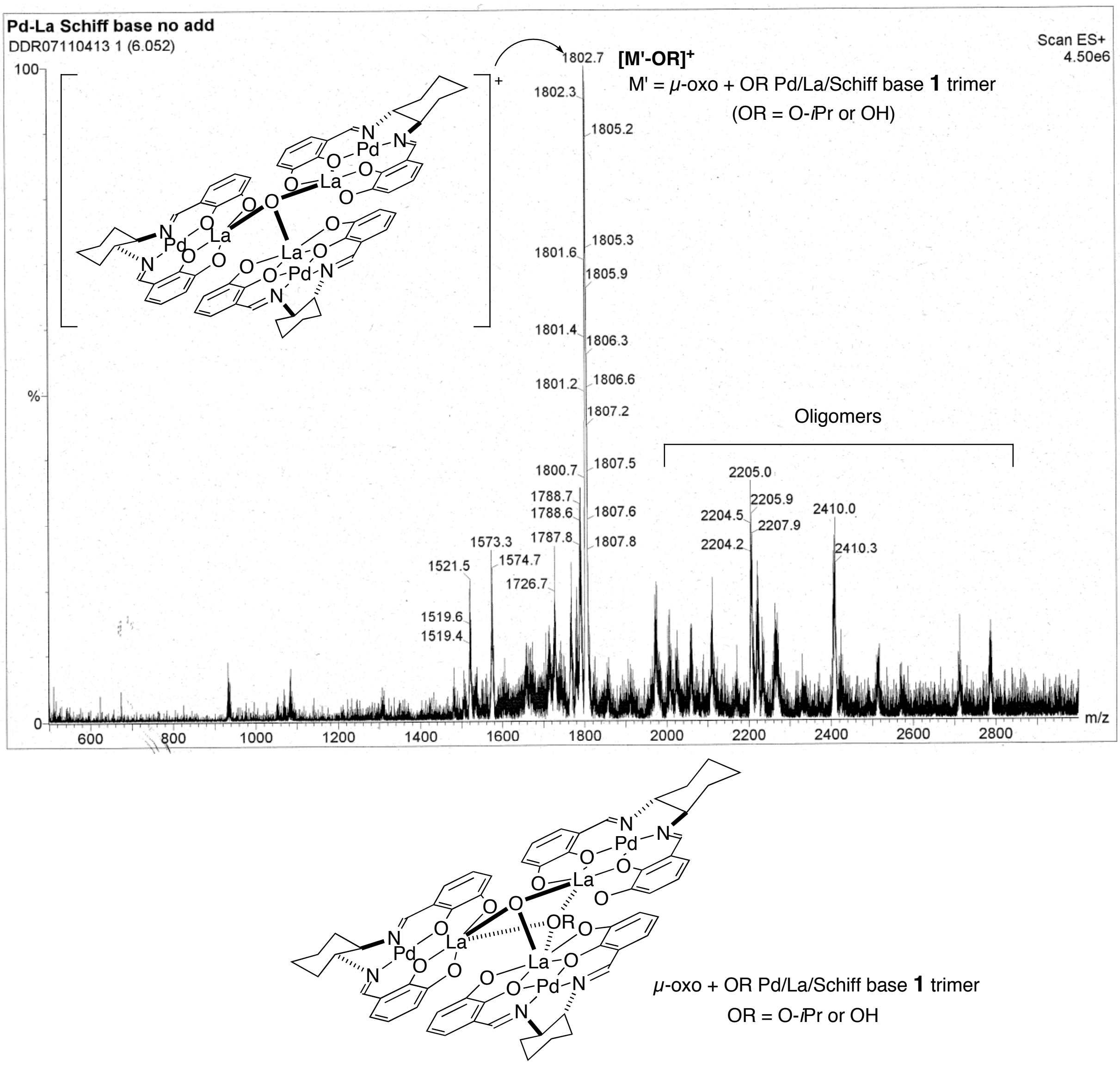


Figure S1. ESI-MS of Pd/La/Schiff base **1** = 1:1:1 mixture without 4-bromophenol additive.

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-*i*Pr)$_3$ (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 *i*PrOH (600 μL) and CH$_3$CN (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

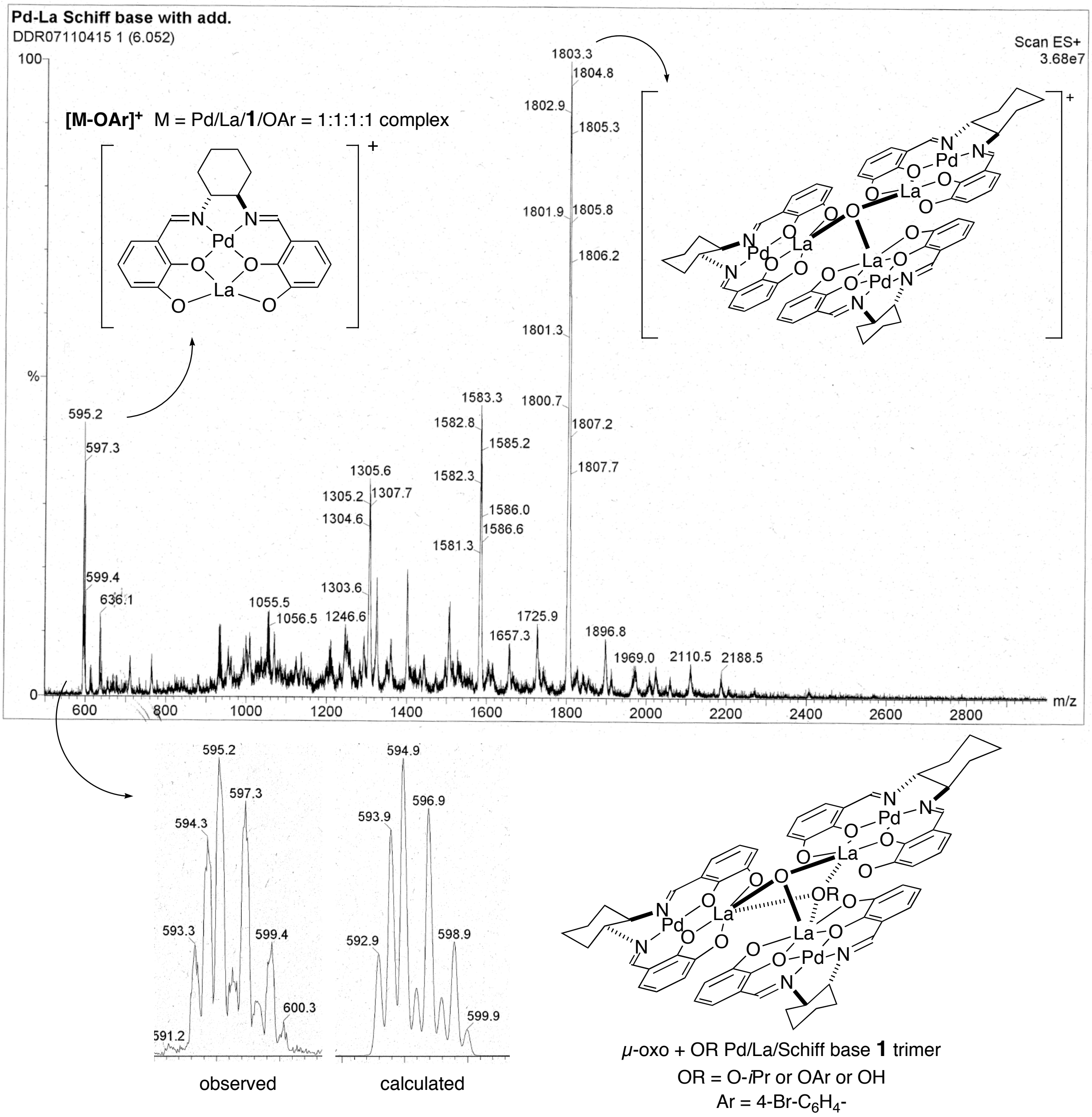


Figure S2. ESI-MS of Pd/La/Schiff base **1** = 1:1:1 mixture with 4-bromophenol additive.

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-*i*Pr or OH) (*m*/*z* = 1803, $[\text{M-OR}]^+$) 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 $[\text{M-OAr}]^+$ (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-*i*Pr or OH). For each complex, several peaks were observed depending on Pd natural isotopes distribution pattern (^{102}Pd: 1.0%, ^{104}Pd: 11.0%, ^{105}Pd: 22.2%, ^{106}Pd: 27.3%, ^{108}Pd: 26.7%, ^{110}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.

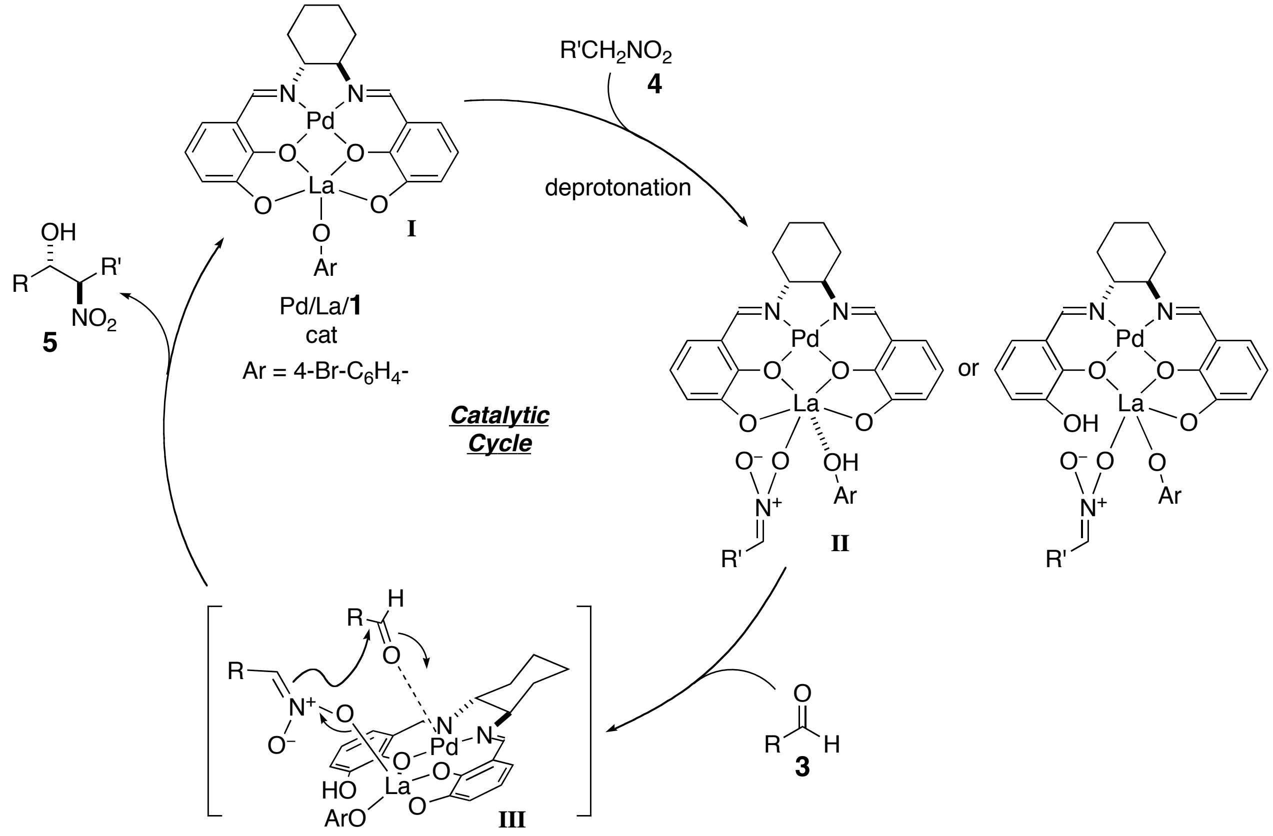


Figure S3. Postulated catalytic cycle.

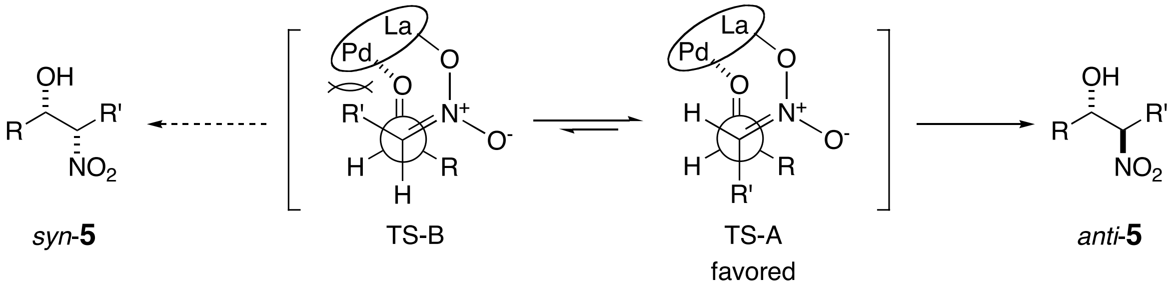


Figure S4. Postulated transition state model for *anti*-selectivity.