Enantioselective Henry Reaction Catalyzed by Salen-Cobalt Complexes

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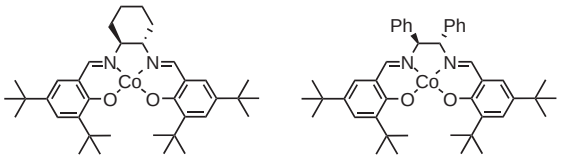
Abstract: The enantioselective Henry reaction catalyzed by the optically active salen-cobalt complexes, proceeded to afford β-hydroxynitroalkanes in good-to-high yields with high enantioselectivity.

Key words: aldehyde, asymmetric catalysis, salen-cobalt complexes, direct nitroaldol reaction, β-hydroxynitroalkanes



1a **1b**

Figure 1

The Henry reaction[1] is one of the most convenient reactions for direct carbon-carbon bond formation[2] without any pretreatment to afford β-hydroxy-nitroalkanes, and the resulting β-hydroxynitroalkanes can be further converted to amines by reduction[3] to carbonyl compounds by the Nef reaction[4] and to nitroalkenes by dehydration[5] etc.[6] Since the catalytic enantioselective version of this reaction was first reported by using heterobimetallic lanthanide BINOL catalyst systems[7] various complex catalyst systems have been successfully released; e.g. copper/bisoxazoline complexes,[8] dinuclear zinc complex catalysts,[9] etc. While seeking for catalytic activities of ketoiminato cobalt complexes, they were found to work as chiral Lewis acid catalysts for hetero Diels–Alder reaction[10] and carbonyl-ene reaction.[11] Although these type of cobalt complexes were prepared in aqueous solution[12] and their axial sites were both occupied by water molecules or oxygen-containing compounds, such as THF,[13] they could be employed as novel Lewis acids compatible with Lewis bases, such as water, nitrones,[14] and amines. In the previous communication, it was reported that enantioselective Henry reaction was catalyzed by these cobalt complexes in the presence of tertiary amine to obtain β-hydroxynitroalkanes in high yields with good-to-high enantioselectivities.[15] As the similar salen-cobalt complexes developed for hydrolytic kinetic resolution[16] were also compatible with nucleophilic compounds, such as water and phenols,[17] it is expected that they could be employed as efficient catalysts for enantioselective Henry reaction in the presence of tertiary amine bases. In this article, we would like to describe that the enantioselective Henry reaction was catalyzed by the optically active salen-cobalt complexes (Figure 1) to afford the β-hydroxynitroalkanes with good-to-high enantioselectivities.

Examination of several salen-cobalt complexes revealed that the commercially available salen-cobalt complex **1a** or its derivative **1b** worked as the efficient catalyst for the enantioselective Henry reaction. Various aldehydes were then applied to the enantioselective Henry reaction with nitromethane in the presence of diisopropylethylamine (Table 1).

Although the nitroaldol reaction of benzaldehyde proceeded to afford the corresponding β-nitroalcohol in poor yield with 62% ee (entry 1), *p*-chlorobenzaldehyde afforded the corresponding β-nitroalcohol with 88% ee (entry 2). It was observed that *ortho*-halo substitution improved the enantioselectivities in the reaction of *o*-chlorobenzaldehyde, *o*-fluorobenzaldehyde, and *o*-trifluoromethylbenzaldehyde (entries 3, 5, 7, 9 and 10). When the catalyst **1b** was used in the reaction of *o*-halobenzaldehyde, the optical yield was improved compared with the reaction by the catalyst **1a** (entries 4, 6 and 8). In the Henry reaction of *ortho*-halo-substituted benzaldehydes, 2,3-dichlorobenzaldehyde (**2g)**, 2,4-dichlorobenzaldehyde (**2h)**, and 2,3,5-trichlorobenzaldehyde (**2i),** the corresponding β-nitroalcohol was obtained in quantitative yield with high enantioselectivity (entries 10–12). The alkanal, such as 3-phenylpropanal, also reacted with nitromethane in the presence of the cobalt-salen complex **1a** to afford the corresponding β-hydroxynitroalkane with high enantioselectivity, 93% ee (entry 13).

In conclusion, it was found that optically active salen-cobalt complexes effectively catalyzed the enantioselective Henry reaction of various aldehydes to afford the corresponding β-hydroxynitroalkane in good-to-high yields with high enantioselectivities.

Melting points were measured on an Electrothermal IA9100 apparatus and are uncorrected. IR spectra were recorded on a JASCO Model FT-IR-410 spectrometer as KBr pellets or as liquid film on NaCl. ^{1}H NMR and ^{13}C NMR spectra were measured using a JEOL Model GX-400 spectrometer with $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectra were obtained with a Hitachi M-80B. For the thin-layer chromatography (TLC) analyses,

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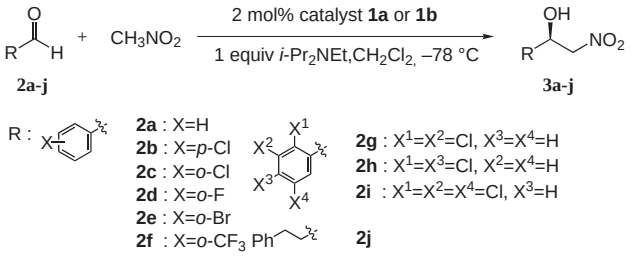
Table 1 Catalytic Enantioselective Henry Reaction of Various Aldehydes



Entry	Aldehyde	Cat	Time (h)	Yield (%)[a]	ee (%)[b]
1[c]	**2a**	**1b**	116	36	62
2	**2b**	**1a**	98	45	88
3[d]	**2c**	**1a**	74	quant	92
4		**1b**	95	quant	95
5	**2d**	**1a**	64	91	94
6		**1b**	18	quant	98
7	**2e**	**1a**	63	94	90
8		**1b**	94	quant	94
9[d]	**2f**	**1b**	116	86	79
10	**2g**	**1b**	43	quant	81
11[d]	**2h**	**1a**	78	quant	87
12[e]	**2i**	**1a**	77	quant	77
13	**2j**	**1a**	45	64	93

[a] Isolated yield.
[b] Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H.
[c] Reaction temperature is –40 °C.
[d] Catalyst (5.0 mol%) and amine (2.5 equiv) were used.
[e] Catalyst (10 mol%) and amine (5.0 equiv) were used.

Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel 60N. HPLC analyses were performed using a Shimadzu LC-6A chromatograph with an optically active column (Chiracel OB-H, OD-H, and Chiralpak AD-H columns, Daicel Ltd., Co.); the peak areas were obtained with a Shimadzu Chromatopack CR-4A or a Varian Dynamax MacIntegrator. Optical rotations were measured with a JASCO DIP-370 digital polarimeter.

Preparation of β-Nitroalcohol; Typical Procedure

Under an anhyd nitrogen atmosphere, a CH_2Cl_2 solution (1.0 mL) of 2-fluorobenzaldehyde (62.1 mg, 0.5 mmol) and nitromethane (1.0 mL, 18.5 mmol) was added to a CH_2Cl_2 solution (2.0 mL) of cobalt complex **1b** (7.02 mg, 2.0 mol% against aldehyde) at –78 °C and the mixture was stirred for 18 h. After removal of the solvent, the residue was purified by column chromatography[18] on silica gel (hexane–EtOAc, 4: 1) to obtain the corresponding nitroalcohol, 1-(2-fluorophenyl)-2-nitroethanol (92.8 mg), in quantitative yield. The enantioselectivity was determined by HPLC analysis to be 98% (Daicel Chiralpak AD-H, 5% EtOH in hexane, flow 1.0 mL/min, 254 nm); $[\alpha]^{21}_D$ –24.8° (*c* = 0.46, CH_2Cl_2).

(*R*)-1-Phenyl-2-nitroethanol (3a)[8b]

HPLC: Daicel Chiralpak AD-H (3% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 41.3 min (minor), 43.2 min (major). Configuration assignment: The absolute stereochemistry was assigned as (*R*) by comparison of the optical rotation with the following literature values: Lit[8b] $[\alpha]^{21}_D$ –41.6° (*c* = 1.03, CH_2Cl_2), 94% ee, (*R*)-isomer.

IR (NaCl): 3437, 1554, 1495, 1454, 1379, 1066, 895, 766, 700, 609 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.18 (br s, 1 H), 4.47 (dd, *J* = 13.1, 2.9 Hz, 1 H), 4.57 (dd, *J* = 13.1, 9.6 Hz, 1 H), 5.41 (d, *J* = 9.6 Hz, 1 H), 7.34–7.41 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 70.9, 81.1, 125.8, 128.8, 128.9, 138.0.

(*R*)-1-(4-Chlorophenyl)-2-nitroethanol (3b)[8b]

$[\alpha]^{23}_D$ –40.4° (*c* = 0.27, CH_2Cl_2). HPLC: Daicel Chiralcel OD-H (3% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 25.8 min (major), 31.4 min (minor). Configuration assignment: The absolute stereochemistry was assigned as (*R*) by comparison of the optical rotation with the following literature values: Lit[8b] $[\alpha]^{23}_D$ –37.6° (*c* = 2.03, CH_2Cl_2), 90% ee, (*R*)-isomer.

IR (NaCl): 3450, 1554, 1493, 1414, 1379, 1090, 1014, 897, 829, 741, 661, 528 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.26 (br s, 1 H), 4.48 (dd, *J* = 13.2, 2.9 Hz, 1 H), 4.55 (dd, *J* = 13.2, 9.3 Hz, 1 H), 5.42 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.32–7.38 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 70.2, 80.9, 127.1, 129.1, 134.6, 136.4.

(*R*)-1-(2-Chlorophenyl)-2-nitroethanol (3c)[8b]

$[\alpha]^{21}_D$ –54.6° (*c* = 0.21, CH_2Cl_2). HPLC: Daicel Chiralpak AD-H (3% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 28.3 min (minor), 31.7 min (major). Configuration assignment: The absolute stereochemistry was assigned as (*R*) by comparison of the optical rotation with the following literature values: Lit[8b] $[\alpha]^{21}_D$ –52.7° (*c* = 1.21, CH_2Cl_2), 91% ee, (*R*)-isomer.

IR (NaCl): 3514, 1556, 1473, 1440, 1417, 1379, 1213, 1130, 1088, 1034, 899, 760, 739, 661 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.21 (br s, 1 H), 4.44 (dd, *J* = 13.4, 9.4 Hz, 1 H), 4.66 (dd, *J* = 13.4, 2.2 Hz, 1 H), 5.83 (d, *J* =9 .4 Hz, 1 H), 7.26–7.39 (m, 3 H), 7.66 (dd, *J* = 7.6, 2.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 67.8, 79.3, 127.4, 127.5, 130.0, 131.3, 135.4.

(*R*)-1-(2-Fluorophenyl)-2-nitroethanol (3d)

$[\alpha]^{21}_D$ –48.9° (*c* = 0.24, CH_2Cl_2). HPLC: Daicel Chiralpak AD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 21.6 min (minor), 24.6 min (major).

IR (NaCl): 3529, 1556, 1489, 1458, 1379, 1228, 1074, 810, 762 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.18 (br s, 1 H), 4.55–4.64 (m, 2 H), 5.72–5.74 (m, 1 H), 7.05–7.10 (m, 1 H), 7.20–7.26 (m, 1 H), 7.32–7.38 (m, 1 H), 7.53–7.57 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 65.4 (d, *J* = 2.5 Hz), 79.6 (d, *J* = 1.7 Hz), 115.5 (d, *J* = 21.6 Hz), 124.7 (d, *J* = 3.3 Hz), 125.0 (d, *J* = 13.3 Hz), 127.5 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 8.3 Hz), 159.2 (d, *J* = 245.5 Hz).

MALDI–TOF–MS (Matrix; Dithranol): *m*/*z* $[M + H]^+$ calcd for $C_8H_8FNO_3$: 186.0566; found: 186.0559.

(*R*)-1-(2-Bromophenyl)-2-nitroethanol (3e)

$[\alpha]^{21}_D$ –44.6° (*c* = 0.21, CH_2Cl_2). HPLC: Daicel Chiralpak AD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 20.3 min (minor), 24.1 min (major).

IR (NaCl): 3529, 2924, 1556, 1468, 1415, 1377, 1211, 1126, 1083, 1024, 899, 760, 733, 611 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.19 (br s, 1 H), 4.42 (dd, *J* = 13.4, 9.8 Hz, 1 H), 4.68 (dd, *J* = 13.4, 2.0 Hz, 1 H), 5.79 (d, *J* = 9.8 Hz, 1 H), 7.20–7.30 (m, 1 H), 7.38–7.42 (m, 1 H), 7.56 (d, *J* = 8.3 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 69.9, 79.3, 121.3, 127.7, 128.0, 130.1, 132.8, 137.0.

Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.07; H, 3.35; N, 5.68.

(*R*)-1-(2-Trifluoromethylphenyl)-2-nitroethanol (3f)

$[\alpha]^{23}_D$ –34.8° (*c* = 0.26, CH_2Cl_2). HPLC: Daicel Chiralpak AD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 11.7 min (minor), 15.2 min (major).

IR (NaCl): 3523, 1558, 1456, 1419, 1381, 1315, 1167, 1117, 1080, 1059, 1036, 901, 771, 715, 656, 621 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.23 (br s, 1 H), 4.50–4.52 (m, 2 H), 5.87–5.90 (m, 1 H), 7.47–7.50 (m, 1 H), 7.63–7.70 (m, 2 H), 7.84 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 66.6 (q, *J* = 2.5 Hz), 80.6, 123.9 (q, *J* = 273.1 Hz), 125.9 (q, *J* = 5.5 Hz), 126.8 (q, *J* = 30.4 Hz), 127.9, 128.9, 132.7 (m), 136.7 (m).

(*R*)-1-(2,3-Dichlorophenyl)-2-nitroethanol (3g)

$[\alpha]^{23}_D$ –48.5° (*c* = 0.32, CH_2Cl_2). HPLC: Daicel Chiralpak AD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 15.7 min (minor), 17.1 min (major).

IR (NaCl): 3519, 2922, 1556, 1452, 1421, 1377, 1340, 1288, 1207, 1180, 1159, 1095, 1043, 901, 874, 789, 756, 735, 715, 652, 472 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.34 (d, *J* = 4.4 Hz, 1 H), 4.42 (dd, *J* =1 3.6, 9.3 Hz, 1 H), 4.67 (dd, *J* = 13.6, 2.1 Hz, 1 H), 5.85 (dt, *J* = 7.8, 2.1 Hz, 1 H), 7.26–7.34 (m, 1 H), 7.44–7.51 (m, 1 H), 7.56–7.62 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 68.2, 79.0, 125.6, 127.9, 129.5, 130.5, 133.3, 137.7.

MALDI–TOF–MS (Matrix; Dithranol–HCCA mixture): *m*/*z* [M + H]$^+$ calcd for $C_8H_7Cl_2NO_3$: 235.9881; found: 235.9881.

(*R*)-1-(2,4-Dichlorophenyl)-2-nitroethanol (3h)

$[\alpha]^{23}_D$ –47.6° (*c* = 0.95, CH_2Cl_2). HPLC: Daicel Chiralpak AD-H (10% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 8.50 min (major), 11.6 min (minor).

IR (NaCl): 3519, 3095, 2924, 1591, 1556, 1471, 1415, 1381, 1286, 1213, 1144, 1088, 1049, 897, 864, 825, 785, 690, 658, 565 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.28 (br s, 1 H), 4.42 (dd, *J* = 13.7, 9.3 Hz, 1 H), 4.64 (dd, *J* = 13.7, 2.0 Hz, 1 H), 5.79 (d, *J* = 9.3 Hz, 1 H), 7.30–7.43 (m, 2 H), 7.56–7.65 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 67.4, 79.0, 127.8, 128.4, 129.3, 131.9, 134.0, 135.1.

MALDI–TOF–MS (Matrix; Dithranol/HCCA mixture): *m*/*z* [M + H]$^+$ calcd for $C_8H_7Cl_2NO_3$: 235.9881, found: 235.9855.

(*R*)-1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)

$[\alpha]^{23}_D$ –37.7° (*c* = 0.53, CH_2Cl_2). HPLC: Daicel Chiralcel OD-H (1% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 29.5 min (minor), 31.4 min (major).

IR (NaCl): 3521, 3080, 2924, 1556, 1415, 1342, 1286, 1225, 1115, 1286, 1225, 1115, 1047, 937, 897, 868, 822, 754, 710, 660, 559 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.44 (br s, 1 H), 4.41 (dd, *J* = 13.7, 9.5 Hz, 1 H), 4.67 (dd, *J* = 13.7, 2.0 Hz, 1 H), 5.82 (d, *J* = 9.5 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.60–7.65 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 67.9, 78.7, 126.1, 127.9, 130.2, 133.7, 134.0, 138.9.

MALDI–TOF–MS (Matrix; Dithranol–HCCA mixture): *m*/*z* [M + H]$^+$ calcd for $C_8H_6Cl_3NO_3$: 269.9491; found: 269.9491.

(*R*)-1-Nitro-4-phenyl-2-nitrobutanol (3j)[9]

Mp 101.5–102.8 °C; $[\alpha]^{23}_D$ 11.4° (*c* = 0.22, CH_2Cl_2). HPLC: Daicel Chiralcel OD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), t_R = 19.6 min (minor), 20.9 min (major). Configuration assignment: The absolute stereochemistry was assigned as (*R*) by comparison of the optical rotation with the following literature values: Lit[9]: $[\alpha]^{25}_D$ –13.6° (*c* = 1.32, CH_2Cl_2), 85% ee, (*S*)-isomer.

IR (KBr): 3390, 2949, 1556, 1385, 1205, 1101, 1041, 935, 910, 881, 758, 729, 704, 646, 586, 513 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.73–1.90 (m, 2 H), 2.69–2.88 (m, 3 H), 4.29–4.41 (m, 3 H), 7.18–7.32 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 31.3, 35.1, 67.7, 80.5, 126.2, 128.3, 128.5, 140.5.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.71; H, 6.84; N, 6.98.

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(18) In case of contamination with the cobalt-salen complex after the purification by the column chromatography, the pure product could be obtained as follows: To the CH_2Cl_2 solution of the contaminated product (ca. 0.5 mmol), silver hexafluoroantimonate (34.3 mg, 0.1 mmol) was added at –78 °C. After stirring for 30 min, the mixture was purified by a short column chromatography to afford the pure product.