Enantioselective Henry Reaction Catalyzed by Salen-Cobalt Complexes

Youichi Kogami, Takahiro Nakajima, Taketo Ikeno, Tohru Yamada*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan
Fax +81(45)5661716; E-mail: yamada@chem.keio.ac.jp
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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 enantioregularity.

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

The Henry reaction is one of the most convenient reactions for direct carbon-carbon bond formation without any pretreatment to afford β-hydroxy-nitroalkanes, and the resulting β-hydroxy-nitroalkanes can be further converted to amines by reduction to carbonyl compounds by the Nef reaction and to nitroalkenes by dehydration etc. Since the catalytic enantioselective version of this reaction was first reported by using heterobimetallic lanthanide BINOL catalyst systems various complex catalyst systems have been successfully released; e.g. copper/saloxazoline complexes, dinuclear zinc complexes, etc. While seeking for catalytic activities of ketiminato cobalt complexes, they were found to work as chiral Lewis acid catalysts for hetero Diels–Alder reaction and carbonyl-ene reaction. Although these type of cobalt complexes were prepared in aqueous solution and their axial sites were both occupied by water molecules or oxygen-containing compounds, such as THF, they could be employed as novel Lewis acids compatible with Lewis bases, such as water, nitrones, 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-hydroxy-nitroalkanes in high yields with good-to-high enantioregularity. As the similar salen-cobalt complexes developed for hydrolytic kinetic resolution were also compatible with nucleophilic compounds, such as water and phenols, 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 enantioregularity.

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 disopropylthylamine (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-halobenzaldehyde, o-fluorobenzaldehyde, and o-trifluormethylbenzaldehyde (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, 2,4-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. 1H NMR and 13C NMR spectra were measured using a JEOL Model GX-400 spectrometer with CDCl3 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,
Table 1 Catalytic Enantioselective Henry Reaction of Various Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Cat</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>2a</td>
<td>1b</td>
<td>116</td>
<td>36</td>
<td>62</td>
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<tr>
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<td>1a</td>
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<td>88</td>
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<td>2c</td>
<td>1a</td>
<td>74</td>
<td>quant</td>
<td>92</td>
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<td>95</td>
<td>quant</td>
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<tr>
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<td>1a</td>
<td>64</td>
<td>91</td>
<td>94</td>
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<td>1b</td>
<td>18</td>
<td>quant</td>
<td>98</td>
<td></td>
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<tr>
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<td>2e</td>
<td>1a</td>
<td>63</td>
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<td>90</td>
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<td>94</td>
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<td>2f</td>
<td>1b</td>
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<td>86</td>
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<td>2i</td>
<td>77</td>
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<tr>
<td>13</td>
<td>2j</td>
<td>7a</td>
<td>45</td>
<td>64</td>
<td>93</td>
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</table>

* Isolated yield.
* Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H.
* Reaction temperature is -40 °C.
* Catalyst (5.0 mol%) and amine (2.5 equiv) were used.
* 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 (Chiralpak 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 CH₃Cl 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 CH₃Cl 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 on silica gel (hexane–EtOAc, 4: 1) to obtain the corresponding nitroalcohol, 1-(2-fluorophenyl)-2-nitroethanol (92.8 mg), in quantitative yield. The enantiomeric selectivity was determined by HPLC analysis to be 98% (Daicel Chiralpak AD-H, 5% EtOH in hexane, flow 1.0 mL/min, 254 nm); [α]D₂⁰ = -24.8° (c = 0.46, CH₂Cl₂).

(R)-1-Phenyl-2-nitroethanol (3a)⁵⁸
HPLC: Daicel Chiralpak AD-H (3% EtOH in hexane, flow 1.0 mL/min, 254 nm), tₚ = 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: Lit⁶⁸ [α]D₂⁰ = -41.6° (c = 1.03, CH₂Cl₂), 94% ee (R)-isomer.
IR (NaCl): 3437, 1554, 1495, 1454, 1379, 1066, 895, 766, 700, 609 cm⁻¹.
1H NMR (CDCl₃): 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 (dd, J = 9.6 Hz, 1 H), 7.34–7.41 (m, 5 H).
13C NMR (CDCl₃): δ = 70.9, 81.1, 125.8, 128.8, 128.9, 138.0.

(R)-1-(4-Chlorophenyl)-2-nitroethanol (3b)⁵⁸
[α]D₂⁰ = -40.4° (c = 0.27, CH₂Cl₂). HPLC: Daicel Chiralcel OD-H (3% EtOH in hexane, flow 1.0 mL/min, 254 nm), tₚ = 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: Lit⁶⁸ [α]D₂⁰ = -37.6° (c = 2.03, CH₂Cl₂), 90% ee, (R)-isomer.
IR (NaCl): 3450, 1554, 1493, 1414, 1379, 1090, 1014, 897, 829, 741, 661, 528 cm⁻¹.
1H NMR (CDCl₃): 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).
13C NMR (CDCl₃): δ = 70.2, 80.9, 127.1, 129.1, 134.6, 136.4.

(R)-1-(2-Chlorophenyl)-2-nitroethanol (3c)⁵⁸
[α]D₂⁰ = -54.6° (c = 0.21, CH₂Cl₂). HPLC: Daicel Chiralpak AD-H (3% EtOH in hexane, flow 1.0 mL/min, 254 nm), tₚ = 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: Lit⁶⁸ [α]D₂⁰ = -52.7° (c = 1.21, CH₂Cl₂), 91% ee, (R)-isomer.
IR (NaCl): 3514, 1556, 1473, 1440, 1417, 1379, 1213, 1130, 1088, 1034, 899, 760, 739, 661 cm⁻¹.
1H NMR (CDCl₃): 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).
13C NMR (CDCl₃): δ = 67.8, 79.3, 127.4, 127.5, 130.0, 131.3, 135.4.

(R)-1-(2-Fluorophenyl)-2-nitroethanol (3d)
[α]D₂⁰ = -48.9° (c = 0.24, CH₂Cl₂). HPLC: Daicel Chiralpak AD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), tₚ = 21.6 min (minor), 24.6 min (major).
IR (NaCl): 3529, 1556, 1489, 1458, 1379, 1228, 1074, 810, 762 cm⁻¹.
1H NMR (CDCl₃): 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).
13C NMR (CDCl₃): 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).

(R)-1-(2-Bromophenyl)-2-nitroethanol (3e)
[α]D₂⁰ = -44.6° (c = 0.21, CH₂Cl₂). HPLC: Daicel Chiralpak AD-H (5% EtOH in hexane, flow 1.0 mL/min, 254 nm), tₚ = 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$_3$): $\delta$ = 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).

(1) C NMR (CDCl$_3$): $\delta$ = 69.9, 79.3, 121.3, 127.7, 128.0, 130.1, 132.8, 137.0.

Anal. Calcd for C$_8$H$_8$BrNO$_3$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.07; H, 3.35; N, 5.68.

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

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

(4) -1-(2-Trifluoromethylphenyl)-2-nitroethanol (3f)

(5) -1-(3,5-Dichlorophenyl)-2-nitroethanol (3g)

(6) -1-(4-Chloro-2-nitrophenyl)-2-nitroethanol (3e)

(7) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

IR (NaCl): 3390, 2949, 2363, 1556, 1584, 1577, 1413, 1385, 1337, 1323, 1304, 1301, 1270, 1259, 1237, 1207, 1179, 1108, 1044, 972, 916, 886, 826, 793, 758, 756, 735, 715, 652, 472 cm$^{-1}$.

(1) H NMR (CDCl$_3$): $\delta$ = 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).

(1) C NMR (CDCl$_3$): $\delta$ = 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).

Anal. Calcd for C$_8$H$_8$Cl$_2$NO$_3$: C, 140.5; H, 3.05; N, 5.68. Found: C, 140.5; H, 3.07; N, 5.58.


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(2) -1-Nitro-4-phenyl-2-nitrobutanol (3j)

(3) -1-(2,4-Dinitrophenyl)-2-nitroethanol (3d)

(4) -1-(2,3,5-Trichlorophenyl)-2-nitroethanol (3i)


(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$_2$Cl$_2$ 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.