Enantioselective 1,3-Dipolar Cycloaddition Reactions between Nitrones and α-Substituted α,β-Unsaturated Aldehydes Catalyzed by Chiral Cationic Cobalt(III) Complexes

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Abstract: The optically active β-ketoiminato cationic cobalt(III) complexes catalyzed the 1,3-dipolar cycloaddition reaction of nitrones with α,β-ununsaturated aldehydes. In the reaction of nitrones derived from 2-halobenzaldehyde, excellent endo-enantioselectivities were observed. The α-substituted α,β-unsaturated aldehyde, such as 2-benzylpropenal, afforded the corresponding isoxazolidine in high stereoselectivity.

Key words: aldehyde, asymmetric catalysis, complexes, cycloadditions, nitrones

Optically active isoxazolidine derivatives have been extensively utilized as 3-aminoalcohol equivalents and applied to the synthesis of a wide variety of natural products, such as alkaloids, β-lactams, amino acids, and amino sugars, etc.1 Many efforts have been made for the stereoselective preparation of isoxazolidine derivatives, while the 1,3-dipolar cycloaddition reactions of nitrones with alkenes1,2 could provide a reliable method of obtaining the optically pure isoxazolidines. The asymmetric approach towards the 1,3-dipolar cycloaddition reaction for isoxazolidines was first tried by employing nitrones and alkenes with chiral auxiliaries,26 and they were successfully applied to the total synthesis of (+)-thienamycin.3 Where- as, a catalytic enantioselective version of the cycloaddition reaction has been developed, using a LUMO lowering effect with a chiral Lewis acid has also been developed. Two combinations of HOMO/LUMO can be expected for the Lewis acid-mediated 1,3-dipolar cycloaddition reaction of nitrones with alkenes from the standpoint of the Frontier Orbital Method.4 One of them is the reverse-electron-demand cycloaddition, based on the combination of the LUMO of the activated nitrones and the HOMO of electron-rich alkenes; the other is the normal-electron-demand cycloaddition reactions, with the LUMO of α,β-carbonyl compounds activated by Lewis acid interacting with the HOMO of nitrones. It was considered that control by the latter strategy would be a disadvantage for enantioselective synthesis because of the competitive coordination of nitrones to the Lewis acid. In order to overcome these drawbacks, alkenyloxyazolidino- nes have been adopted. Their bidentate coordination to a Lewis acid catalyst could preferentially activate the alkene, and the reaction rate and stereoselectivity both were remarkably improved. Since the catalytic enantioselective reactions were originated in 1994 by Jørgensen, employing TiCl2-TADDOLates in the reaction of the nitrones with alkenyloxyazolidinones,5 various chiral transition-metal complexes have been subjected to this useful synthesis as Lewis acid catalysts.6 Simple α,β-unsaturated aldehydes could be employed as dipolarophiles for the reaction; however, a couple of catalysts have been reported to catalyze the enantioselective 1,3-dipolar cycloaddition reaction of nitrones with 1-cyclopentene-1-carbaldehyde.9 In the previous communication,9 various counter anions of the cationic cobalt(III) complex catalysts were examined in the enantioselective 1,3-dipolar cycloaddition reaction, and the cobalt(III) hexafluoroantimonate complex was found to catalyze the reaction effectively. Excellent endo selectivities and high enantioselectivities were observed in the cycloaddition of nitrones derived from 2-halobenzaldehyde. In this article, we would like to report that the 1,3-dipolar cycloaddition reactions of various α-substituted α,β-unsaturated aldehydes were catalyzed by optically active ketoiminato cobalt(III) complexes to afford the corresponding isoxazolidines in excellent regio- and endo selectivities and good-to-high enantioselectivity. The cobalt(III) hexafluoroantimonate complexes were applied to the enantioselective 1,3-dipolar cycloaddition reaction of various nitrones with 1-cyclopentene-1-carbaldehyde (Table 1). First of all, the chiral diamine parts of the complexes (Figure 1) were examined in the reaction with benzylidenephenylamine-N-oxide (5). The corresponding isoxazolidine was obtained in 51% ee using the complex I derived from optically active cyclohexanediamine (Entry 1). The absolute configuration of the product was reversed when the complexes 3 and 4, derived from 1,2-bis(3,5-dimethylphenyl)ethylenediamine and 1,2-bis(2,4,6-trimethylphenyl)ethylenediamine, respectively, were employed (Entries 3 and 4). The reactions with nitrones derived from p-substituted
benzaldehydes, \(N\)-(4-methoxybenzylidene)phenylamine-\(N\)-oxide \(6\), \(N\)-(4-methylbenzylidene)phenylamine-\(N\)-oxide \(7\), and \(N\)-(4-chlorobenzylidene)phenylamine-\(N\)-oxide \(8\), were examined and the cycloaddition products were obtained with moderate enantioselectivities (Entries 5–7). In contrast, the optical yield of the cycloadduct derived from nitrone \(9\) was decreased to 5% (Entry 8, vs. Entry 7), but in the case of \(o\)-chloro derivative \(10\), it increased to 65% (Entry 10, vs. Entry 7). The optically active ligands were screened again, and the complex \(3\) was found to be the most suitable for the reaction of \(o\)-chloronitrone (Entries 10–13). The cobalt-complex-catalyzed cycloaddition reaction with \(o\)-bromonitrone \(11\) also proceeded, and the corresponding \(endo\)-adduct was selectively obtained in 85% ee (Entry 14). Though at \(-78^\circ \text{C}\), the resulting isoxazolidine was obtained in low yield, the optical yield was improved to 91% ee (Entry 15). The nitrones \(12, 13\), and \(14\) derived from 2,3-dichlorobenzaldehyde, 2,4-dichlorobenzaldehyde, and 2,3,5-trichlorobenzaldehyde were utilized to afford the corresponding isoxazolines with complete \(endo\) selectivities in high yields with high enantioselectivities (Entries 16–18). Examination of the various types of nitrones revealed that the 1,3-dipolar cycloaddition reaction catalyzed by the cationic cobalt complexes proceeded with excellent \(endo\) selectivity and that high enantioselectivity was achieved in the reaction of nitrones derived from \(o\)-halo-substituted benzaldehyde.

The cycloaddition reaction with various \(\sigma,\beta\)-unsaturated aldehydes was then attempted in the presence of cobalt(III) hexafluoroantimonate (Table 2). The reaction with acrolein proceeded smoothly to afford the corresponding isoxazolidine with 88% regioselectivity, 99% diastereoselectivity, and 71% enantioselectivity (Entry 2). Crotonaldehyde, \(\beta\)-substituted \(\sigma,\beta\)-unsaturated aldehyde, was also allowed to react with nitrile derived from 2,3-dichlorobenzaldehyde, and the resulting alcohol was obtained in 63% ee (Entry 3). The regioselectivity was reversed in the case of employing the \(\sigma\)-substituted \(\alpha,\beta\)-unsaturated aldehyde, and this could be attributable to their steric factor, rather than electronic density. The regio- and diastereoselectivities of the corresponding isoxazolines were high-to-excellent in all cases for \(\sigma\)-substituted \(\alpha,\beta\)-unsaturated aldehydes. The reaction with methacrolein proceeded with the cationic cobalt(III) complex, and the corresponding \(endo\)-adduct was selectively obtained in 78% ee (Entry 4). The \(\sigma\)-alkyl derivatives, \(15\) and \(16\), were next attempted and the corresponding \(endo\)-products were regioselectively obtained with moderate enantioselectivities (Entries 5 and 6). In the reaction of 2-
benzylpropenal (17) and its derivatives 18, the corresponding endo-cycloadducts were solely obtained and their enantioselectivities were up to 92% and 90%, respectively (Entries 7 and 8).

It is noted that the 1,3-dipolar cycloaddition of nitrones derived from 2-halobenzaldehyde with α-substituted α,β-unsaturated aldehydes was effectively catalyzed by the optically active cationic ketoiminato cobalt(III) complexes possessing hexafluoroorantimonate. The corresponding cycloadducts were obtained completely regioselectively,

Table 2  Enantioselective 1,3-Dipolar Cycloaddition of Various α,β-Unsaturated Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield/%b</th>
<th>A/Bc</th>
<th>Endo/Exod</th>
<th>ee (endo)/%d</th>
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</thead>
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<tr>
<td>1</td>
<td></td>
<td>quant.</td>
<td>&gt;99:1</td>
<td>&gt;99:1</td>
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</tr>
<tr>
<td>2c</td>
<td></td>
<td>97</td>
<td>88:12</td>
<td>99:1</td>
<td>71</td>
</tr>
<tr>
<td>3c</td>
<td></td>
<td>94</td>
<td>&gt;99:1</td>
<td>98:2</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>quant.</td>
<td>6:94</td>
<td>&gt;99:1</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>80</td>
<td>1:99</td>
<td>99:1</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>80</td>
<td>3:97</td>
<td>84:16</td>
<td>77</td>
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<tr>
<td>7f</td>
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<td>93</td>
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<td>&gt;99:1</td>
<td>92</td>
</tr>
<tr>
<td>8g</td>
<td></td>
<td>quant.</td>
<td>1:99</td>
<td>&gt;99:1</td>
<td>90</td>
</tr>
</tbody>
</table>

a Reaction time: 24–144 h. Reaction temperature: −40 °C.
b Isolated yield after reduction with NaBH₄.
c Determined by ¹H NMR analysis.
d Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H.
e Complex 4 was employed.
f Reaction temperature: −60 °C.
g Reaction temperature: −30 °C.
endoselectively, and in good-to-high enantioselectivities. The present catalytic system was further examined for application in the reverse-electron-demand 1,3-cycloaddition.

IR spectra were recorded on a JASCO Model FT/IR-410 infrared spectrometer on KBr pellets or liquid film on NaCl. ¹H NMR spectra and ¹³C NMR spectra were measured on a JEOL Model GX-400 spectrometer using CDCI₃ as a standard solvent and with tetramethylsilane as an internal standard. HRMS were obtained with an HITACHI M-80B. HPLC analyses were performed with a Shimadzu LC-6A chromatograph using an optically active column (Chiralcel OB-H, Chiralcel OD-H, and Chiralpak AD-H columns, Daicel Co. Ltd.); the peak areas were obtained with a Shimadzu chromatograph CR-4A or a Varian Dynamax MacIntegrator. Optical rotations were measured with a JASCO DIP-370 digital polarimeter.

13-Dipolar Cycloadditions of Various α,β-Unsaturated Aldehydes; General Procedure

To a stirred solution of Co(III)-SbF₅ (3, 14.8 mg, 0.015 mmol) in CH₂Cl₂ (0.5 mL) at −60 °C were added α-benzylidene-2-propanol (17, 222 mg, 1.5 mmol) and nitrone (12, 79.8 mg, 0.3 mmol) in CH₂Cl₂ (1.0 mL). After stirring the reaction mixture at −60 °C for 84 h, the reaction was quenched by the addition of NaBH₄ (85.1 mg, 2.25 mmol) in EtOH. The product was extracted with EtOAc. The organic extract was washed with brine and dried over anhyd Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (hexane–EtOAc, 20:1) to afford the product (116.0 mg, 93% yield, dr 99:1, endoxo >99:1, 92% ee (endo) (Table 2, entry 7). The present catalytic system was further examined for application in the reverse-electron-demand 1,3-cycloaddition.

13C NMR (100 MHz): δ = 132.9, 130.1, 132.9, 142.1, 150.4.

HRMS: m/z calcd for C₁₇H₁₃Cl₂NO₂ (M⁺), 337.0636; found, 337.0620.

(3R,4R,5R)-3-(2,3-Dichlorophenyl)-2-phenyl-isoxazolidine-4-methanol (Table 2, Entry 4)

Complex (S,S)-3 was used as the catalyst; [α]₂⁰D −54.1 (c 0.821, CHCl₃); HPLC (Chiralcel OD-H, 2-propanol–hexane, 3:97, flow 1.0 mL/min) tR 23.9 min (major), tR 30.6 min (minor), 64% ee. HRMS: m/z calcd for C₁₇H₁₅Cl₂NO₂ (M⁺), 337.0636; found, 337.0662.

(3R,4R,5R)-3-(2,3-Dichlorophenyl)-2-phenyl-isoxazolidine-5-methanol (Table 2, Entry 2)

Complex (S,S)-4 was used as the catalyst; [α]₂⁰D −26.7 (c 0.181, CHCl₃); HPLC (Chiralcel OD-H, 2-propanol–hexane, 3:97, flow 1.0 mL/min) tR 17.1 min (major), tR 22.9 min (minor), 71% ee. HRMS: m/z calcd for C₁₇H₁₃Cl₂NO₂ (M⁺), 337.0620; found, 337.0636.

(3R,4R,5R)-3-(2,3-Dichlorophenyl)-2-phenyl-isoxazolidine-5-methanol (Table 2, Entry 5)

Complex (S,S)-5 was used as the catalyst; [α]₂⁰D −53.1 (c 0.806, CHCl₃); HPLC (Chiralcel OD-H, 2-propanol–hexane, 1:9, flow 1.0 mL/min) tR 6.0 min (major), tR 7.6 min (minor), 68% ee.
IR (NaCl): 3431, 2956, 2870, 1599, 1490, 1450, 1419, 1041, 785, 752, 694 cm⁻¹.

¹H NMR (400 MHz): δ = 0.90 (3 H, t, J = 7.1 Hz), 1.20–1.47 (4 H, m), 1.59–1.70 (1 H, m), 1.78 (1 H, t, J = 6.7 Hz), 1.82–1.93 (1 H, m), 2.06 (1 H, dd, J = 8.1, 12.7 Hz), 3.03 (1 H, dd, J = 8.1, 12.7 Hz), 3.47 (1 H, dd, J = 6.7, 12.0 Hz), 3.58 (1 H, dd, J = 6.7, 12.0 Hz), 5.11 (1 H, t, J = 8.1 Hz), 6.81–6.86 (2 H, m), 6.90 (1 H, t, J = 7.8 Hz), 7.17–7.26 (3 H, m), 7.39 (1 H, dd, J = 1.5, 7.8 Hz), 7.64 (1 H, dd, J = 1.5, 7.8 Hz).

¹³C NMR (100 MHz): δ = 14.0, 23.2, 26.5, 34.7, 44.3, 64.7, 66.0, 86.6 113.6, 121.2, 125.8, 127.9, 129.0, 129.2, 130.0, 133.1, 142.1, 150.5.

HRMS: m/z calcd for C₂₉H₂₉Cl₂NO₂ (M+) 407.1419; found, 407.1406.

(3R*·5R*)-3-(2,3-Dichlorophenyl)-5-hexyl-2-phenyl-isoxazoline-5-methanol (Table 2, Entry 8)
Complex (S,S)-3 was used as the catalyst; [α]D ⁰ ²⁰ ₂⁰ –75.4 (c 0.991, CHCl₃); HPLC (Chiralcel OD-H, 2-propanol–hexane, 3:97, flow 1.0 mL/min) tₘ  7.0 min (major), tₘ  12.7 min (minor), 77% ee.

IR (NaCl): 3444, 2929, 2858, 1599, 1491, 1419, 1271, 1041, 752, 694 cm⁻¹.

¹H NMR (400 MHz): δ = 0.87 (3 H, t, J = 6.8 Hz), 1.15–1.48 (8 H, m), 1.55–1.71 (1 H, m), 1.74–1.94 (2 H, m), 2.05 (1 H, dd, J = 8.0, 12.5 Hz), 2.03 (1 H, dd, J = 8.0, 12.5 Hz), 3.46 (1 H, dd, J = 5.1, 12.1 Hz), 3.57 (1 H, dd, J = 5.9, 12.1 Hz), 5.11 (1 H, t, J = 8.0 Hz), 6.83 (2 H, d, J = 7.8 Hz), 6.90 (1 H, t, J = 7.6 Hz), 7.15–7.30 (3 H, m), 7.39 (1 H, dd, J = 1.3, 8.3 Hz), 7.63 (1 H, dd, J = 1.3, 8.1 Hz).

¹³C NMR (100 MHz): δ = 14.1, 22.6, 24.3, 29.8, 31.7, 34.9, 44.3, 64.7, 66.0, 86.6, 113.6, 121.2, 125.8, 127.9, 129.0, 129.1, 130.0, 133.1, 142.0, 150.5.

HRMS: m/z calcd for C₂₉H₂₉Cl₂NO₂ (M⁺) 407.1419; found, 407.1406.

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