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Enantioselective 1,3-Dipolar Cycloaddition of Nitrones Catalyzed by Optically Active Cationic Cobalt(III) Complexes

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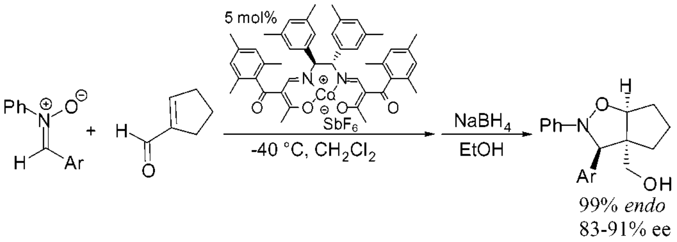
ABSTRACT



The optically active *β*-ketoiminato cationic cobalt(III) complexes were employed as efficient Lewis acid catalysts for the enantioselective 1,3-dipolar cycloaddition reaction of α,*β*-unsaturated aldehydes with nitrones. Excellent *endo* selectivities and high enantioselectivities were achieved in the cycloaddition reaction of 1-cyclopentene-1-carbaldehyde and the nitrones derived from 2-halobenzaldehyde.

The enantioselective 1,3-dipolar cycloaddition reaction of an alkene with a nitrone is one of the most reliable strategies for construction of three contiguous asymmetric centers of five-membered isoxazolidine derivatives.[1] This reaction is supposed to proceed via a concerted mechanism[2] similar to the Diels−Alder reactions.[3] The obtained isoxazolidine can be transformed by reductive cleavage of the N−O bond into the optically active 3-amino alcohol as a useful chiral synthon for synthesis of natural products.[4] Since Kanemasa et al. reported that Lewis acids accelerated the 1,3-dipolar cycloaddition reaction to achieve both high regio- and *endo*/*exo* selectivity,[5a] many varieties of metal-based catalysts, such as zinc, titanium, and magnesium salts, have been proposed for 1,3-dipolar cycloaddition reaction of a nitrone.[5] On the basis of these reports, alkenes[6] and nitrones[7] with many kinds of chiral auxiliaries were subjected to the metal-catalyzed cycloaddition for preparation of optically active isoxazolidine derivatives. The enantioselective versions were also attempted using chiral Lewis acid complex catalysts for the activation of electron-deficient[8] or electron-rich alkenes.[9] For the 1,3-dipolar cycloaddition of the electron-deficient alkenes, LUMO-lowering of the alkene is expected by coordination of the Lewis acid catalyst to enhance the reaction. Because the 1,3-dipoles, such as nitrone, could strongly coordinate with the Lewis acid catalyst, bidentate coordination of a

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(1) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 83. (b) Trossell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (c) Gothelf, K.; Jørgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652. (d) Gothelf, K.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

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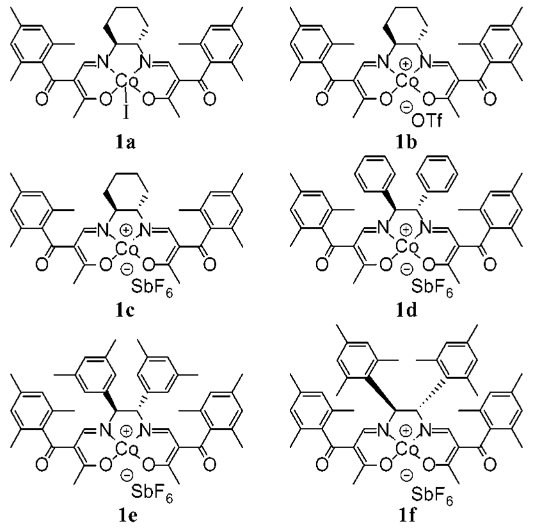


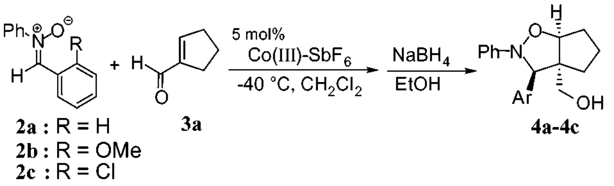
1a **1b** **1c** **1d** **1e** **1f**

Figure 1. Various cobalt(III) complex catalysts.

dipolarophile should be required for the effective activation of alkenes; e.g., *N*-alkenoyl-2-oxazolidinones[8] or *N*-alkenoylsuccinimides[10] have been generally employed for this type of 1,3-dipolar cycloaddition. Because of the undesired coordination of the nitrone, the catalytic reaction of monodentate enones, such as α,*β*-unsaturated aldehydes, was realized using pinhole aluminum catalysts,[11] chiral DBFOX/Ph-Zn or Ni catalysts,[12] (CpRu-BIPHOP-F) or Fe catalysts,[13] and chiral organic catalysts.[14]

The *β*-ketoiminato cobalt(II) complex catalysts were originally developed for the enantioselective borohydride reduction of ketones.[15] In the course of studying the catalytic activities of these complexes, it was found that they could also be employed as characteristic Lewis acid catalysts for the enantioselective hetero-Diels−Alder reaction.[16] The corresponding cationic cobalt(III) complexes (Figure 1) were synthesized for the efficient Lewis acid catalyst of the enantioselective hetero-Diels−Alder reaction[17] and the enantioselective carbonyl−ene reaction.[18] On the basis of the X-ray analysis of the cationic cobalt(III) complex,[17b] the centered cobalt(III) cation was coordinated by a square-planar *β*-ketoiminato ligand, and two apical sites were occupied by water molecules. A similar cobalt(II) complex could catalyze the cyclopropanation reaction of diazoacetates and styrene derivatives even in alcoholic solvents.[19] These observations would suggest that the Lewis acidity of the *β*-ketoiminato cobalt(III) complexes would remain in the presence of nitrones and that they are expected to activate monodentate aldehydes effectively and to catalyze the 1,3-dipolar cycloaddition reaction of nitrones. In this communication, we would like to report the catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones and α,*β*-unsaturated aldehydes using the optically active *β*-ketoiminato cationic cobalt(III) complexes.

Table 1. Various Cobalt Complex Catalysts for Asymmetric 1,3-Dipolar Cycloaddition[a]



2a : R = H
2b : R = OMe
2c : R = Cl
3a
4a-4c

entry	nitrone	catalyst	time/h	yield[b]/%	endo/exo[c]	ee (endo)[d]/%
1	**2a**	**1a**	97	59	>99/1	−46
2	**2a**	**1b**	53	63	>99/1	−47
3	**2a**	**1c**	51	81[e]	99/1	−51
4	**2a**	**1c**	48	89	>99/1	−51
5	**2a**	**1d**	65	87	>99/1	−8
6	**2a**	**1e**	41	68	>99/1	7
7	**2a**	**1f**	55	86	>99/1	37
8	**2b**	**1c**	179	21	93/7	16
9	**2c**	**1c**	73	84	>99/1	65
10	**2c**	**1d**	96	89	99/1	78
11	**2c**	**1e**	96	96	99/1	80
12	**2c**	**1f**	48	98	99/1	67

[a] Reaction conditions: cobalt(III)−SbF$_6$ catalyst 0.015 mmol (5.0 mol%), aldehyde 0.45 mmol, and nitrone 0.3 mmol in CH$_2$Cl$_2$. [b] Isolated yield after the reduction with NaBH$_4$. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H. [e] Resulting aldehyde was isolated without NaBH$_4$ treatment.

A variety of *β*-ketoiminato cationic cobalt(III) complexes were examined as Lewis acid catalysts of the 1,3-dipolar cycloadditon reaction of nitrones **2a**, **2b**, and **2c** with 1-cyclopentene-1-carbaldehyde (**3a**) (Table 1). The corre-

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(8) (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (c) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001. (d) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (e) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017. (f) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (g) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227.

(9) (a) Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419. (b) Seerden, J.-P. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843. (c) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353. (d) Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845.

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(12) (a) Shirahase, M.; Oderaotoshi, Y.; Kanemasa, S. 78th Annual Meeting of the Chemical Society of Japan, March 2000, 4G1 08, Funabashi, Japan. (b) Shirahase, M.; Kanemasa, S. 80th Annual Meeting of the Chemical Society of Japan, March 2001, 2H6 08 and 2H6 09, Kobe, Japan. (c) Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Ed.; Wiley-VCH: Weinheim, 2002; p 274.

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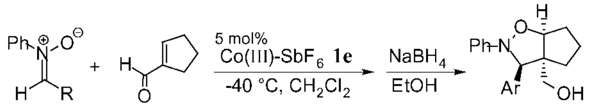
(19) (a) Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* **2001**, 406. (b) Ikeno, T.; Sato, M.; Sekino, H.; Nishizuka, A.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2139.

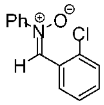
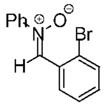
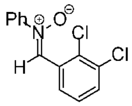
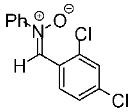
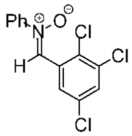
sponding cobalt(II) complex could scarcely catalyze the 1,3-dipolar cycloadditon reaction. When the iodide complex **1a** and the trifluoromethanesulfonate complex **1b** were employed (entries 1 and 2), isoxazolidine was obtained in moderate yield. On the contrary, in the presence of hexafluoroantimonate catalyst **1c**, the reaction of nitrone **2a** with alkene **3a** at −40 °C smoothly proceeded to afford the corresponding isoxazolidine-4-carbaldehyde in high yield with excellent *endo* selectivity and moderate enantioselectivity (entry 3). The reaction was quenched with an ethanolic solution of NaBH$_4$ for the transformation of the aldehyde in the resulting cycloadduct into the stable primary alcohol **4a**. It was confirmed that the *endo*/*exo* ratio and the enantioselectivity were completely retained after this treatment (entry 4). The chemical yield, diastereoselectivity, and enantioselectivity listed in Tables 1 and 2 were determined as the corresponding alcohol obtained after reductive quenching. The cobalt complexes having optically active 1,2-diarylethylenediamines **1d**−**f** were then subjected to the reaction. The cobalt complex **1d** was employed as a Lewis acid catalyst to afford the cycloadduct **4a** with 8% ee (entry 5), whereas the enantioselective sense was reversed in the reaction catalyzed by the complex **1e** (entry 6). When the cobalt complex **1f** having bulky 1,2-bis(2,4,6-trimethylphenyl)-ethylenediamine was used, the enantioselectivity of the cycloaddition was improved to 37% (entry 7). In the cycloaddition of nitrone **2c** derived from 2-chlorobenzaldehyde and *N*-phenylhydroxylamine, a similar tendency was observed for the enantioselectivities for the cobalt complex catalysts. Compared with the reaction catalyzed by complex **1c**, the complex catalysts **1d** and **1e** improved the enantioselectivity (entries 9−11). When the cationic cobalt(III) complex **1e** having 1,2-bis(3,5-dimethylphenyl)ethylenediamine was used as catalyst in the cycloaddition of nitrone **2c**, excellent *endo* selectivity was achieved, and the corresponding isoxazolidine was obtained in high yield with up to 80% ee (entry 11).

The enantioselective 1,3-dipolar cycloaddition reaction of 1-cyclopentene-1-carbaldehyde (**3a**) catalyzed by the cationic cobalt(III) complex **1e** was successfully applied to various nitrones derived from *o*-halo-substituted benzylidenephenylamine *N*-oxide **2c**−**g** (Table 2). The reaction of nitrone **2c** at −40 °C was completed in 96 h to afford the corresponding cycloadduct with excellent *endo* selectivity with 80% ee (entry 1). In the reaction of the nitrone **2d**, the corresponding *endo* adduct was selectively obtained with 85% ee (entry 2). At −78 °C, the resulting isoxazolidine was obtained in low yield, but the optical yield was improved to 91% ee (entry 3). The nitrones **2e**, **2f**, and **2g** derived from 2,3-dichlorobenzaldehyde, 2,4-dichlorobenzaldehyde, and 2,3,5-trichlorobenzaldehyde, respectively, were subjected to the cobalt-complex-catalyzed cycloaddition to afford the corresponding isoxazolidines with perfect *endo* selectivities in high yields with high enantioselectivities (entries 4−6). 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, with nitrones derived from *o*-halo-substituted benzaldehyde, high enantioselectivity was achieved.[20,21]

Table 2. Asymmetric 1,3-Dipolar Cycloaddition Reaction of Various Nitrones[a]



2c-g **3a** **4c-g**

entry	nitrone		time / h	yield / %[b]	*endo* / *exo*[c]	ee (*endo*) / %[d]
1		**2c**	96	96	99 / 1	80
2		**2d**	96	85	99 / 1	85
3[e]			96	18	>99 / 1	91
4		**2e**	60	quant	>99 / 1	87
5		**2f**	96	quant	>99 / 1	83
6		**2g**	83	93	>99 / 1	85 (100[f])

[a] Reaction conditions: cobalt(III)−SbF$_6$ catalyst 0.015 mmol (5.0 mol%), aldehyde 0.45 mmol, and nitrone 0.3 mmol in CH$_2$Cl$_2$. [b] Isolated yield after the reduction with NaBH$_4$. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H. [e] Reaction temperature: −78 °C. [f] After a recrystallization from ethanol.

The absolute configuration of cycloadduct **4g** was determined by X-ray analysis. The cycloadduct of 85% ee was recrystallized from ethanol to afford the optically pure **4g**, which was again crystallized from ethanol for preparation of single crystals. The X-ray analysis of optically pure **4g** confirmed that it was an *endo* adduct and revealed that its absolute configuration for the reaction catalyzed by the (*S*,*S*)-cobalt complex catalyst was the *S*,*S*,*S* form as depicted in Figure 2.[22]

On the basis of the experimental results mentioned above and the X-ray structure of cycloadduct **4g**, a transition-state model for the present reaction could be proposed as follows. The coordination of an α,β-unsaturated aldehyde with the cobalt catalyst in this 1,3-dipolar cycloaddition reaction could be explained similarly to the hetero Diels−Alder reaction.[23] The axial coordination site of cobalt(III) was then occupied by a lone pair of aldehyde carbonyls anti to the alkyl group,

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(20) 1,3-Dipolar cycloaddition of 3-chlorobenzylidenphenylamine *N*-oxide proceeded in 76% yield with 98% *endo* selectivity and 22% ee (*endo*) using the cationic cobalt(III) catalyst **1c**.

(21) Reaction of 2,3-dichlorobenzylidenphenylamine-*N*-oxide (**2e**) and methacrolein in the presence of cobalt catalysts **1e** at −40 °C afforded the corresponding cycloadduct quantitatively in 94/6 regio selectivity and with complete *endo* selectivity with 78% ee. See the Supporting Information.

(22) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 186919.

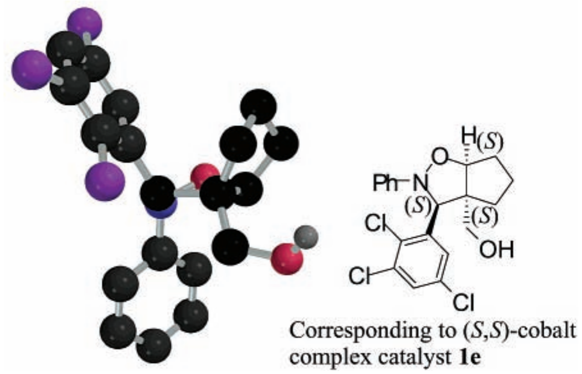

Figure 2. Absolute configuration of **4g** determined by the X-ray analysis.

which was expected to orient between two coordinating oxygen atoms on the planar *β*-ketoiminato ligand, and it is assumed that the conformation of the α,*β*-unsaturated aldehyde in the transition state was *s-trans*.[24] The favorable approach of the nitrone to the α,*β*-unsaturated aldehyde coordinated to the cobalt complex catalyst is outlined in Figure 3. Avoiding the steric hindrance of the chiral diamine and the bulky aryl group of the side chain of the *β*-ketoiminato ligand, the nitrone should approach from the least hindered direction leading to the highly regio-, diastereo-, and enantioselective reactions (Figure 3). It should be pointed out here that *o*-halo-substituted nitrones such as **2c**−**g** could increase the enantioselectivity in the present reaction.[25] Thus, the *o*-halo substitution would promote the enantio sense. A similar effect of *o*-halo substitution was observed in the hetero-Diels−Alder reaction reported previously,[17] and the acceptor was activated by LUMO-lowering of coordination between the metal complex and the *o*-halo benzaldehyde.[26] On the contrary, in the present 1,3-dipolar cycloaddition, it is postulated that the halogen atom on the *ortho* position of the donor molecule could coordinate with the metal complex to improve the enantioselectivity. The detailed investigation of these observations is currently underway.

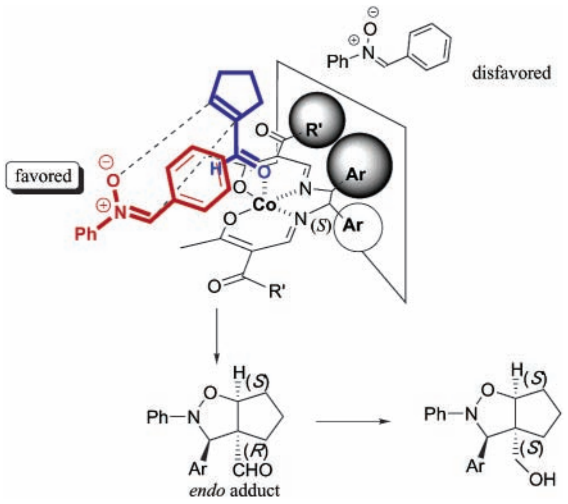

Figure 3. Reasonable explanation for the diastereo- and enantioselection in the 1,3-dipolar cycloaddition reaction catalyzed by the (*S*,*S*)-cobalt catalyst.

In summary, the cationic cobalt(III) complex with an optically active *β*-ketoiminato ligand effectively catalyzed the enantioselective 1,3-dipolar cycloaddition reaction of α,*β*-unsaturated aldehydes and nitrones derived from 2-halo benzaldehyde to afford the corresponding isoxazolidines in high yields with excellent *endo* selectivities and high enantioselectivities.

Supporting Information Available: Experimental procedures and spectral data for new compounds. X-ray analysis data in CIF format. This information is available free of charge via the Internet at http://pubs.acs.org.

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[23] We proposed the transition state in the hetero Diels−Alder reaction between Danishefsky's diene and aldehydes previously, which showed the optimized structure of the cobalt catalyst/benzaldehyde complex. See ref 17b.

[24] Loncharich, R. J.; Schwartz. T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

[25] The cycloadduct **4d** was debrominated by treatment with *n*-BuLi at −78 °C to afford **4a** without loss of optically purity. HPLC analysis of these compounds revealed that the absolute configuration of the debrominated product was the same as that of **4a** afforded by complex **1e**. Therefore, it is reasonable to consider that a halide on the *ortho* position could have little influence on enantioselectivity.

[26] Recently, it was reported that *ortho*-substituted benzaldehyde derivatives displayed particularly good reactivity and enantioselectivity relative to other substituted derivatives in the hetero−ene reactions with tridentate Schiff base chromium(III) complexes. Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882.