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ENDO-SELECTIVE ASYMMETRIC INVERSE ELECTRON-DEMAND 1,3-DIPOLAR CYCLOADDITION REACTION OF NITRONES

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Abstract - In the presence of a catalytic amount of the optically active cobalt(III) hexafluoroantimonate, the inverse electron-demand 1,3-dipolar cycloaddition reaction of dihydrofuran with nitrones bearing an electron-withdrawing group effectively proceeded to afford the corresponding adducts with excellent *endo*-selectivity.

The catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones is one of the most practical methods for the construction of enantiomerically pure isoxazolidines, which are then employed as key intermediates in transformation into β-amino alcohols under mild reducing conditions, and as useful synthons for the preparation of various biologically active compounds, such as alkaloids, β-lactams, and β-amino acids.[1] Several groups have recently reported the catalytic enantioselective 1,3-dipolar cycloaddition reactions of nitrones with alkenoyl oxazolidinones, electron-deficient alkenes[2] favorable for the bidentate coordination of a Lewis acid catalyst. However, monodentate alkenals have also been applied[3] to the enantioselective 1,3-dipolar cycloaddition reaction. It was found that cationic 3-oxobutylideneaminatocobalt(III) complexes could be employed as effective Lewis acid catalysts for the enantioselective 1,3-dipolar cycloaddition reaction of alkenals even in the presence of electron-donating nitrones.[4] In these catalytic systems, the HOMO(nitrone)-LUMO(alkene) interaction is assumed to dominate the reactivity and selectivity, but the alternative HOMO(alkene)-LUMO(nitrone) interaction is also expected due to the lowering of the LUMO level through the coordination of the electron-donating nitrone to the Lewis acid catalyst and the raised HOMO level of the electron-rich alkenes

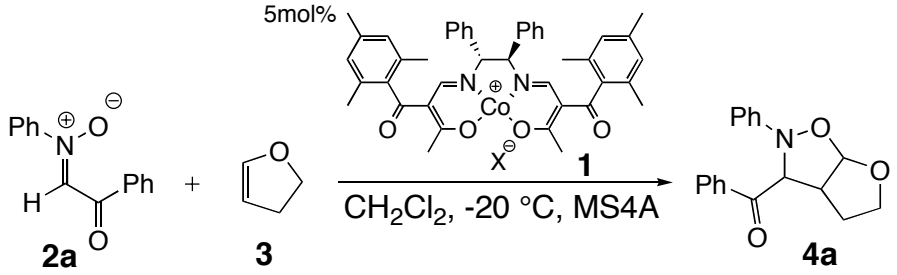
used, such as vinyl ethers.[5] The inverse electron-demand 1,3-dipolar cycloaddition reaction catalyzed by Lewis acids was first reported by Kanemasa. During the reaction of *N*-phenyl-*C*-benzoylnitrone and an allyl alcohol, it was found that the diastereoselectivity was improved along with the reaction rate by the coordination of a Lewis acid, such as $MgBr_2$•Et_2O, $ZnBr_2$, $TiCl_2$(*i*-PrO)$_2$, or BF_3•Et_2O.[6] The first report of the enantioselective version was published by Scheeren[7] using chiral metal complex catalysts. They employed the oxazaborolidines derived from amino acids as the Lewis acid, achieving a moderate enantioselectivity but in low yield. Jørgensen reported that the BINOL derived aluminum complexes[8] and the bisoxazoline-copper(II) complexes[9] could be employed as the efficient catalysts for enantioselective 1,3-dipolar cycloaddition reaction of the glyoxylate derived nitrones with vinyl ethers to achieve a >99% enantioselectivity. In these two pioneering studies on the asymmetric inverse electron-demand 1,3-dipolar cycloaddition reaction, *exo* products only were obtained with high enantioselectivity. The *endo*-selective inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones has been predicted on the basis of a theoretical analysis [10] of the reaction between the nitrones bearing an electron-withdrawing group and vinyl ethers,[11] nevertheless, the catalytic enantioselective version of the *endo*-selective reaction has not yet appeared. We now report the first *endo*- and enantioselective inverse electron-demand 1,3-dipolar cycloaddition of nitrones using cationic 3-oxobutylideneaminatocobalt(III) complexes as efficient Lewis acid catalysts.

Study of the enantioselective reactions using the optically active ketoiminatocobalt(II) complexes as the Lewis acid catalyst, including the hetero Diels-Alder reaction,[12] the carbonyl-ene reaction,[13] and the 1,3-dipolar cycloaddition of nitrones has indicated that the enantioselectivity as well as the reactivity are affected by the counter anions of the cationic cobalt complexes. Various counter anions of the cationic cobalt(III) complexes were examined as catalysts for the inverse electron-demand 1,3-dipolar cycloaddition reaction of *N*-phenyl-*C*-benzoylnitrone with 2,3-dihydrofuran (Table 1). When the cobalt(II) complex was employed, the reaction did not proceed (Entry 1). The iodo cobalt(III) complex catalyzed the reaction at -20 °C to provide the corresponding isoxazolidine in moderate yield and *endo*-selectivity, but with a low enantioselectivity (Entry 2), whereas use of cationic cobalt(III) complexes with appropriate anions led to an improved reaction rate and the *endo*-selectivity (Entries 3-6). In particular, the triflimide and hexafluoroantimonate anions of the cationic cobalt(III) complex afforded the corresponding cycloadducts with high *endo*-selectivity and moderate enantioselectivity (Entries 7-9).[14]

To improve the enantioselectivity of the *endo* product, the ligand structures of the cationic cobalt(III) hexafluoroantimonate complexes were examined in the catalytic inverse

electron-demand 1,3-dipolar cycloaddition reaction of *N*-phenyl-*C*-benzoylnitrone with 2,3-dihydrofuran (Table 2). When the complexes (**1i**) and (**1j**), bearing 1,2-diaminocyclohexane and 1,2-dimethylethylenediamine as the chiral diamine were employed as catalysts, the corresponding isoxazolidine was obtained in 87% and 73% yield with 36% ee and 38% ee, respectively (Entries 1 and 2). The cationic cobalt(III) complexes with the optically active 1,2-diphenylethylenediamine (**1h**) afforded the cycloadduct in good yield with a 90% *endo*-selectivity and 47% ee (Entry 3), while the sterically demanding complexes (**1k**) derived from 1,2-bis(3,5-dimethylphenyl)ethylenediamine afforded the cycloadduct with a high *endo*-selectivity, but only 31% ee (Entry 4). For the reaction catalyzed by the most sterically demanding cobalt(III) complex (**1l**), derived from 1,2-bis(2,4,6-trimethylphenyl)ethylenediamine, the *endo*-selectivity decreased (Entry 5). The side chains of the ketoiminato ligand were also examined. Employing the complexes (**1m**) and (**1n**) bearing the acetyl and *tert*-butyl ester side chains, gave maintained *endo*-selectivities, but decreased enantioselectivities for the cycloadducts, 6% and 19%, respectively (Entries 6 and 7).

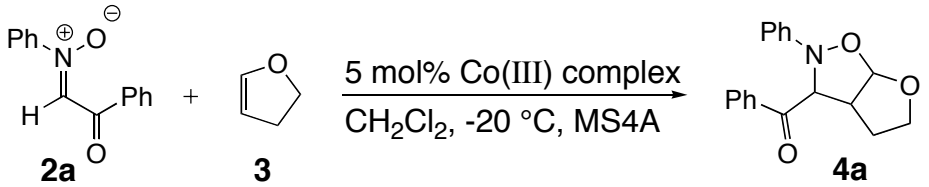
Table 1. Various counter anions of the cationic cobalt complex catalysts

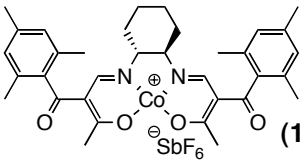
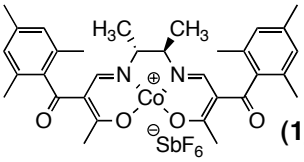
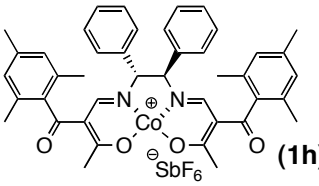
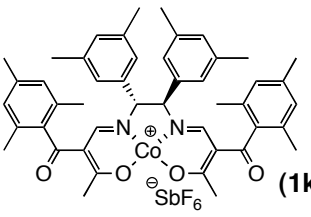
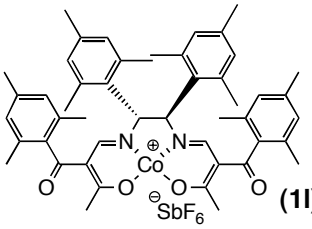
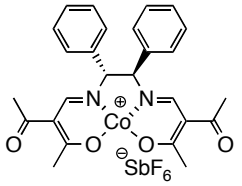
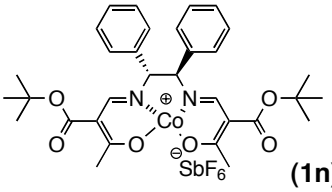


Entry[a]	X		Time / h	Yield / %[b]	*Endo* / *Exo*[c]	Ee (*Endo*) / %ee[d]
1	Co(II)	(**1a**)		Trace		
2	Iodide	(**1b**)	87	65	79 / 21	10
3	OTs	(**1c**)	11	70	83 / 17	16
4	BF_4	(**1d**)	5	55	87 / 13	21
5	OTf	(**1e**)	5	55	91 / 9	25
6	PF_6	(**1f**)	11	63	91 / 9	24
7	NTf_2	(**1g**)	2	66	>99 / 1	46
8	SbF_6	(**1h**)	8	76	90 / 10	47
9[e]			27	56	89 / 11	54

a) Two equiv. of 2,3-dihydrofuran was empoloyed. b) Isolated yield. c) Determined by ^{1}H NMR analysis. d) Determined by HPLC analysis using Daicel Chiralcel OD-H. e) 1.2 equiv. of 2,3-dihydrofuran was used.

Table 2. Examination of various ligands of the cobalt(III) complexes

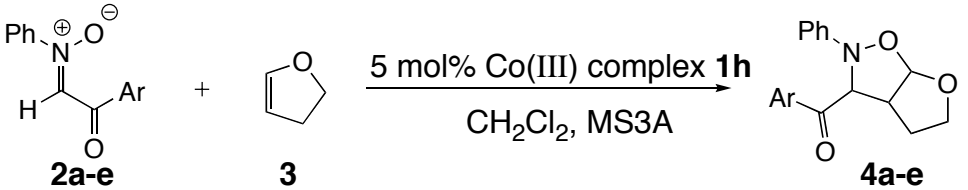


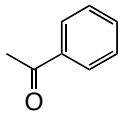
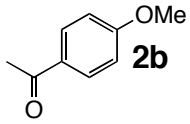
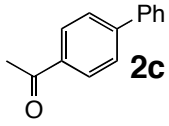
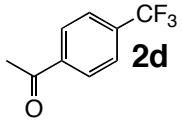
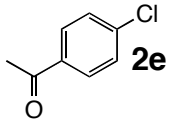
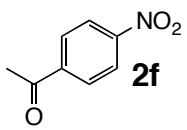
Entry	Co(III)complex	Time / h	Yield / %[a]	*Endo* / *Exo*[b]	Ee (*Endo*) / %[c]
1	 **(1i)**	7	87	92 / 8	36
2	 **(1j)**	14	73	92 / 8	38
3	 **(1h)**	8	76	90 / 10	47
4	 **(1k)**	3	71	90 / 10	31
5	 **(1l)**	3	58	64 / 36	14
6	 **(1m)**	5	69	90 / 10	6
7	 **(1n)**	70	58	81 / 19	19

a) Isolated yield. b) Determined by ^{1}H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralcel OD-H.

From the result it was determined that the cationic cobalt(III) hexafluoroantimonate complex (**1h**) was a suitable catalyst for the *endo*- and enantioselective inverse electron-demand 1,3-dipolar cycloaddition reaction. In the presence of MS 3A, various nitrones with electron-withdrawing groups were subjected to the present reaction system (Table 3). For the reactions of the nitrones bearing 4-methoxybenzoyl (**2b**) and 4-phenylbenzoyl (**2c**) groups, excellent *endo*-selectivities were observed; the enantioselectivities of the *endo* products were 64% ee and 63% ee, respectively, at -40 °C (Entries 2-4). The nitrone bearing the 4-(trifluoromethyl)benzoyl (**2d**) group afforded the *endo* product with 90% selectivity, though the enantioselectivity was ca. 30% (Entry 5). The reaction of the nitrones derived from the *p*-chloro (**2e**) and *p*-nitro (**2f**) substituted phenacyl-pyridinium-bromides [15] smoothly proceeded to afford the corresponding cycloadducts with excellent *endo*-selectivities and good-to-high enantioselectivities (Entries 6-9).[16]

Table 3. *Endo*-selective inverse electron demand 1,3-dipolar cycloaddition of nitrones



Entry	ArC=O	Temp / °C	Time / h	Yield / %[a]	*Endo* / *Exo*[b]	Ee (*Endo*) / %[c]
1	 **2a**	-20	4	72	>99 / 1	64
2	 **2b**	-40	66	56	>99 / 1	64
3	 **2c**	-20	12	65	>99 / 1	43
4		-40	48	72	>99 / 1	63
5	 **2d**	-20	10	71	90 / 10	31
6	 **2e**	-20	41	72	>99 / 1	62
7		-40	43	67	>99 / 1	72
8	 **2f**	-20	0.5	40	>99 / 1	72
9		-40	15	53	>99 / 1	73

a) Isolated yield. b) Determined by ^{1}H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralcel IA.

Single crystals of the optically pure cycloadduct (**4e**) were obtained from a tetrahydrofuran and hexane solution.[17] X-Ray analysis revealed that the cycloadduct (**4e**) was the *endo*-adduct with the (*R*,*S*,*R*)-absolute configuration corresponding to the (*S*,*S*)-cobalt complex catalyst as depicted in Figure 1. On the basis of this observation, transition states of the present 1,3-dipolar cycloaddition are proposed as plausible candidates (Figure 2). It is fair to assume that the lone pair of the oxygen atom in the nitrone might contribute to coordination of the cobalt atom, and that the nitrone residue could be oriented between two coordination oxygen atoms on the planar 3-oxobutylidenaminato ligand. The TS model in Figure 2 was constructed as a superimposed display of the MM-optimized nitrone molecule based on the coordinate data obtained from X-Ray analysis of the cationic β-ketoiminatocobalt(III) triflate.[12] Viniyl ethers, such as 2,3-dihydrofuran, should approach the activated nitrone from the direction that avoids the aryl groups attached to the chiral diamine and the side chain of the 3-oxobutylideneaminato ligand, thus affording the (*R*)-*endo* cycloadduct in good-to-high enantioselectivity and excellent *endo*-selectivity. This proposed transition state can clearly explain the observed stereochemistry of the present *endo*- and enantio-selective inverse electron-demand 1,3-dipolar cycloaddition of nitrones, and is also consistent with the results[4,12,13] of the corresponding Lewis acid catalyses using the optically active β-ketoiminatocobalt complexes.

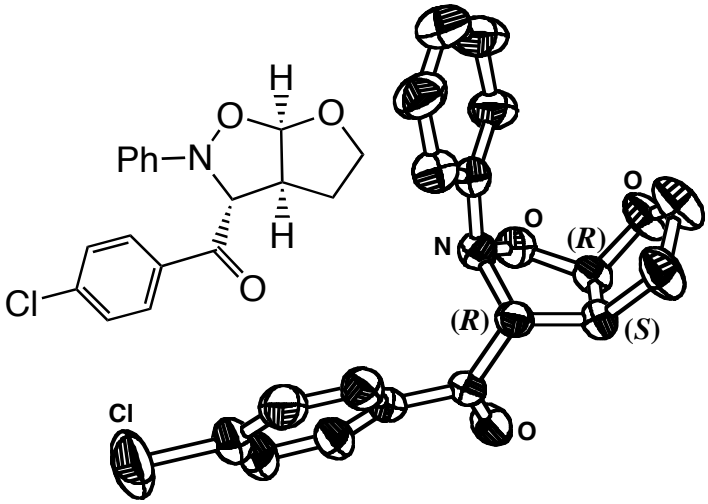


Figure 1. Absolute configuration of *endo*-cycloadduct corresponding to (*S*,*S*)-catalyst.

The cationic cobalt(III) complexes thus successfully catalyzed the *endo*- and enantioselective inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones bearing electron-withdrawing groups. The addition of MS 3A was effective in improving the reaction rate and *endo*-selectivity, giving the corresponding cycloadducts with high enantioselectivity.

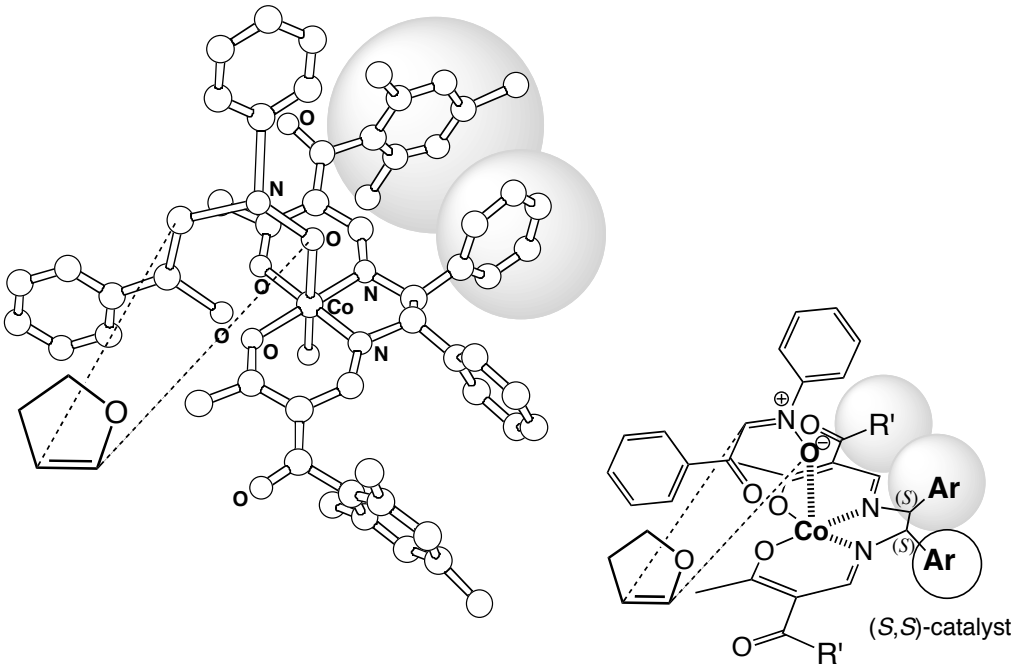


Figure 2. TS model of *endo* and enantio-selective inverse electron-demand 1,3-dipolar cycloaddition.

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14. It should be pointed out that molecular sieves effectively improved the enantioselectivity of the *endo* adduct. Among the various molecular sieves, MS 3A and 4A were the most effective additives for the present catalytic reaction. K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, 1989, **111**, 5340.

15. The nitrones subjected to the present reaction were prepared as follows. Typical preparation of *N*-phenyl-*C*-benzoylnitrone (**2a**): Under a nitrogen atmosphere, to a stirred solution of nitrosobenzene (1.1 g, 10.2 mmol) in acetone (6 mL), a solution of phenacylpyridinium bromide (3.0 g, 10.8 mmol) in water (5 mL) was added at -20 °C, and stirring was continued for 1 h at -20 °C. An aqueous solution of NaOH (1 M, 3 mL) was dropwise added to the solution and a yellow solid precipitated. The precipitate was collected by filtration, washed with water, and dried in vacuo. The yellow solid was used without any further purification. R. Huisgen, H. Hauck, H. Seidl, and M. Burger, *Chem. Ber.*, 1969, **102**, 1117.
16. Typical procedure is as follows: Under a nitrogen atmosphere, to a stirred solution of the cationic cobalt complex Co(III)SbF_6 (**1h**) (14.0 mg, 0.015 mmol, 5.0 mol%) and MS3A (25 mg) in CH_2Cl_2 (0.5 mL) at -20 °C were added *N*-phenyl-*C*-benzoylnitrone (**2a**) (67.6 mg, 0.3 mmol) in CH_2Cl_2 (1.0 mL) and 2,3-dihydrofuran (25.2 mg, 0.36 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 4 h at -20°C, the reaction was quenched by the addition of buffer (pH 7) and then stood at rt. The product was extracted twice with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The residue was purified by SiO_2 column chromatography (hexane: AcOEt =10:1) to afford the product. **(3*R**,3a*S**,6a*R**)2,3,3a,4,5,6a-Hexahydro-3-benzoyl-2-phenylfuro[3,2-d-]isoxazolidine (*endo*-4a)**: Following the general procedure, the cycloadduct (**4a**) was obtained in 72% yield (63.7 mg) from the nitrone (**2a**) (67.6 mg, 0.3 mmol); Yellow solid; mp. 122-133 °C; R_f=0.30 (Hexane:AcOEt, 3:1); Daicel Chiralcel OD-H, 1.0 ml min^{-1}, hexane/2-propanol 97/3: minor isomer 17.01 min, major isomer 19.79 min, 64% ee; IR (KBr): 3062 (w), 2975 (w), 1693 (s), 1596 (s), 1490 (m), 1284 (m), 1093 (s), 931 (m), 752 (s), 696 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.85-1.98 (m, 1H), 2.03-2.18 (m, 1H), 3.37-3.50 (m, 1H), 3.61-3.70 (m, 1H), 3.78 (dt, *J* = 8.5 Hz, *J* = 2.1 Hz, 1H), 4.97 (d, *J* = 2.0 Hz, 1H), 5.94 (d, *J* = 5.4 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 7.03 (dd, *J* = 8.3 Hz, *J* = 1.0 Hz, 2H), 7.11-7.26 (m, 2H), 7.32-7.55 (m, 3H), 7.94 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 31.1, 50.2, 68.2, 73.9, 108.8, 114.2, 121.6, 128. 6, 128.7, 128.7, 133. 4, 134.8, 149.4, 195.7.
17. The *endo* cycloadduct (**4e**) obtained from the reaction (Entry 7 in Table 3) was purified by preparative HPLC using Daicel Chiralcel IA to afford the optically pure sample of the cycloadduct (**4e**) for X-Ray analysis. The crystals were grown from a THF-hexane

solution over the course of three days. A crystal specimen of suitable dimensions is shown. Crystal data: $C_{18}H_{16}NO_3Cl$, Mr=329.77, Monoclinic, P2yb, a=11.873(3) Å, b=5.8199(14) Å, c=11.4619(17) Å, α=90°, β=93.266(15)°, γ=90°, V=790.7(3) $Å^3$, Z=2. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number : CCDC 607825.