

Enantioselective 1,3-Dipolar Cycloaddition Reaction of Nitrones with α,β-Unsaturated Aldehydes Catalyzed by Cationic 3-Oxobutylideneaminatocobalt(Ⅲ) Complexes

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The enantioselective 1,3-dipolar cycloaddition reaction of nitrones with α,β-unsaturated aldehydes was realized using 3-oxobutylideneaminatocobalt complex catalysts. Varieties of the cobalt(Ⅱ) and cobalt(Ⅲ) complexes were screened and the cationic cobalt(Ⅲ) complex with hexafluoroantimonate was found to be the most effective for the catalytic enantioselective 1,3-dipolar cycloaddition reaction. In the presence of the cobalt(Ⅲ) hexafluoroantimonate complex, the enantioselective 1,3-dipolar cycloaddition reaction of various nitrones with α,β-unsaturated aldehydes afforded the corresponding isoxazolidines in high yields and with high enantioselectivities. The absolute configuration of the optically active products was determined by X-ray analysis. Reasonable explanations for the enantioselection in the present 1,3-dipolar cycloaddition reaction catalyzed by the 3-oxobutylideneaminatocobalt complex were proposed.

The 1,3-dipolar cycloaddition reactions of nitrones with alkenes are some of the most useful and reliable strategies for preparing isoxazolidine derivatives. Because its N–O bond was readily cleaved to form 3-amino alcohol equivalents under the mild reducing conditions, these cyclic compounds have been applied to synthetic intermediates for useful compounds such as alkaloids, β-lactams, amino acids, amino sugars, etc.[1] Since the pioneering contributions to this field of the 1,3-dipolar cycloaddition by Huisgen et al. in the 1960s,[2] various 1,3-dipoles have been developed. Among them, nitrones are some of the most readily available 1,3-dipoles; they are relatively stable and easily isolated. Thus the 1,3-dipolar cycloaddition of nitrones has been widely investigated. The remarkable feature of this cycloaddition reaction is the concerted $[4\pi + 2\pi]$ suprafacial process like the Diels–Alder reaction to simultaneously construct three new chiral centers. The asymmetric approach of the 1,3-dipolar cycloaddition for the isoxazolidine was first tried by employing nitrones and alkenes with chiral auxiliaries.[3] These reactions provided effective methods to prepare several natural products,[3] but stoichiometric chirality was required and the stereoselectivities were not always satisfactory due to the relatively high reaction temperature. The 1,3-dipolar cycloaddition reaction could be explained as a concerted $[4\pi + 2\pi]$ process; therefore, it is expected that a Lewis acid catalyst could accelerate the reaction and also improve the regio- and diastereo-[4] as well as enantioselectivities. Various chiral Lewis acids have been developed for the catalytic and enantioselective versions of electron-rich[5] alkenes or electron-deficient[6] alkenes. In the former combination, the LUMO of the nitrone was lowered by coordinating to a Lewis acid to accelerate the reaction. On the contrary, LUMO-lowering of the electron-deficient alkene, such as alkenoyl derivatives, is expected by coordinating of the carbonyl to a Lewis acid; however, the competitive coordination of the nitrone should be considered over coordination of the monodentate carbonyl compound.[7] Chelation of alkenoyl oxazolidinones was preferred for the cycloaddition reactions[5] (Scheme 1), whereas the study of the 1,3-dipolar cycloaddition of the monodentate α,β-unsaturated aldehyde has been limited. Recently, this type of asymmetric 1,3-dipolar cycloaddition has ultimately been achieved using chiral DBFOX/Ph–Zn or Ni catalysts,[8] CpRu–BIPHOP-F or Fe catalysts,[9] and efficient organocatalysts[10] (Fig. 1).

The optically active 3-oxobutylideneaminatocobalt complexes (Fig. 2) were originally developed as effective catalysts of the enantioselective borohydride reductions;[11] they were recently reported to catalyze the enantioselective cyclopropanation.[12] The enantioselectivities and diastereoselctivities in these reactions could be tuned by the steric and/or electronic factor of the 3-oxobutylideneaminato ligands. During the course of our continuing study of the catalysis using these cobalt complexes, they were found to act as chiral Lewis acid catalysts for the 6π-electrocyclic concerted reaction, an enantioselective hetero Diels–Alder reaction.[13] The corresponding cationic cobalt(Ⅲ) complexes could be employed more effectively than the original cobalt(Ⅱ) complex; their counter anions significantly influenced their Lewis acidities and catalytic abilities.[14] These cationic cobalt(Ⅲ) complexes also catalyzed the enantioselective carbonyl–ene reaction of glyoxal derivatives to afford the corresponding homoallylic alcohols with high enantioselectivities.[15] In this article, we will fully disclose the enantioselective 1,3-dipolar cycloaddition reactions of the α,β-unsat-

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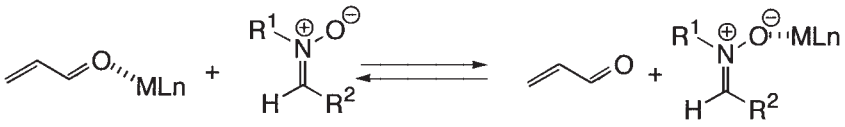


Scheme 1. Equilibrium among aldehyde, nitrone, and Lewis acid catalyst.

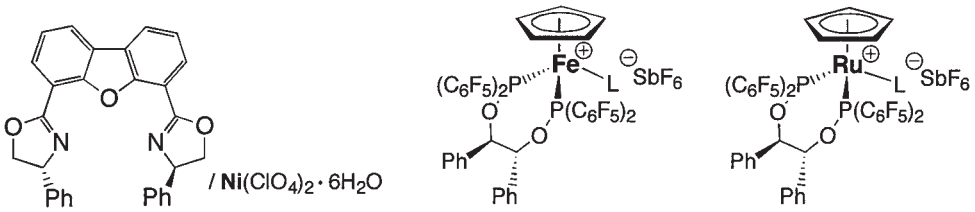


Fig. 1. Effective catalysts for the 1,3-dipolar cycloaddition reaction with α,β-unsaturated aldehydes.

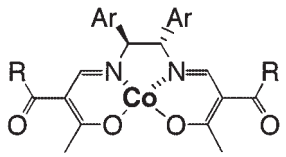


Fig. 2. 3-Oxobutylideneaminato cobalt complex.

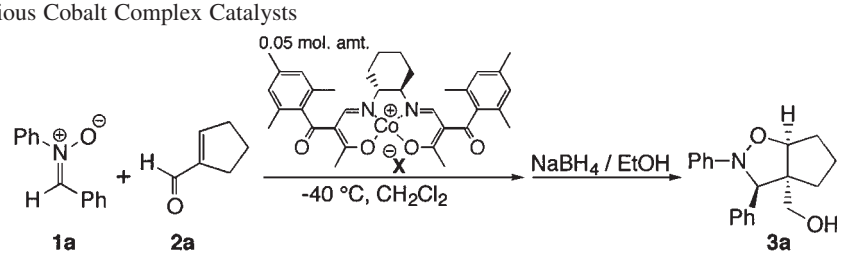
urated aldehyde with nitrones catalyzed by cationic cobalt(Ⅲ) complexes with optically active 3-oxobutylideneaminato ligands.

Results and Discussion

Design of the Cationic Cobalt Complexes and Their Counter Anions. The cationic character of the central cobalt atom has a crucial effect on the reaction rate and on the enantioselectivity, based on the previous examinations of the hetero Diels–Alder reaction and the carbonyl–ene reaction catalyzed by 3-oxobutylideneaminatocobalt complexes.[14,15] When the iodo cobalt(Ⅲ) complex was employed for the hetero Diels–Alder reaction, the reaction time was shortened; the cationic cobalt(Ⅲ) complex was thus proved to be a highly active catalyst. In the carbonyl–ene reactions, the counter anions of the cationic cobalt(Ⅲ) complex significantly influenced the reactivity and selectivity. Various 3-oxobutylideneaminatocobalt(Ⅱ) and cobalt(Ⅲ) complex catalysts were therefore examined for the enantioselective 1,3-dipolar cycloaddition reaction of *N*-benzylideneaniline *N*-oxide (**1a**) with 1-cyclopentene-1-carbaldehyde (**2a**) (Table 1).[16] The cobalt(Ⅱ) complex **4a** catalyzed the reaction at −40 °C to selectively provide the corresponding *endo*-bicyclo adduct in 43% yield in 89 h, but the optical yield was 32% ee. The iodo cobalt(Ⅲ) **4b** and the cationic cobalt(Ⅲ) complexes with various counter anions **4c**–**4e** were used to improve the reactivity and the selectivity. The reaction rate was maintained using the iodo cobalt(Ⅲ) complex, and the enantiomeric excess was up to 46%. The corresponding cobalt(Ⅲ) tetrafluoroborate **4c** and triflate **4d** more smoothly catalyzed the reaction to obtain the corresponding isoxazolidine with good enantioselectivities (Entries 3 and 4). Screening of the counter anions revealed that the cobalt(Ⅲ) hexafluoroantimonate **4e** could be effectively employed as a highly active cationic cobalt(Ⅲ) complex catalyst and that the resulting 4-hydroxymethylisoxazolidine with 51% ee was obtained in 48 h (Entry 5).

Optimization of Temperature and Solvents for the Enantioselective 1,3-Dipolar Cycloaddition Reaction. The temperature and reaction solvents generally influence the selectivities and catalytic activities of the Lewis acid catalysis. The regio-, diastereo-selectivity as well as enantioselectivity should be regulated by the reaction solvent and temperature during the enantioselective 1,3-dipolar cycloaddition reaction. The re-

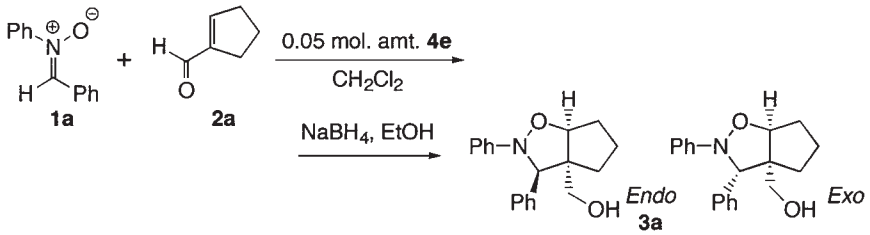
Table 1. Various Cobalt Complex Catalysts



Entry	Catalyst		Time/h	Yield/%[a]	*Endo*/*Exo*[b]	Ee (*Endo*)/%[c]
1[d]	Co	**4a**	89	43	>99/1	32
2[d]	Co–**I**	**4b**	97	59	>99/1	46
3	Co–**BF_4**	**4c**	53	46	>99/1	40
4	Co–**OTf**	**4d**	53	63	>99/1	47
5	Co–**SbF_6**	**4e**	48	89	>99/1	51

a) Isolated yield after the reduction with $NaBH_4$. b) Determined by ^1H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H. d) 0.1 mol. amt. catalyst was employed.

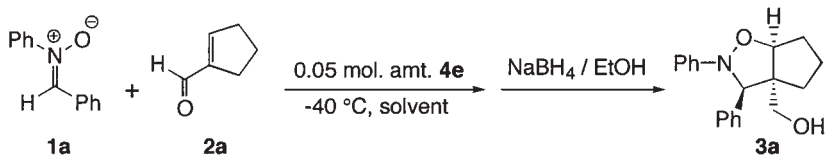
Table 2. Temperature Effect



Entry	Temp/°C	Time/h	Yield/%[a]	*Endo*/*Exo*[b]	Ee (*Endo*)/%[c]
1	r.t.	6	91	87/13	3
2	0	24	92	94/6	15
3	−20	24	94	97/3	27
4	−40	48	89	>99/1	51

Reaction conditions: Cobalt(Ⅲ)–SbF_6 catalyst **4e** 0.015 mmol (0.05 mol. amt.), aldehyde 0.45 mmol, and nitrone 0.3 mmol in CH_2Cl_2. a) Isolated yield after the reduction with $NaBH_4$. b) Determined by ^{1}H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H.

Table 3. Various Solvents



Entry	Solvent	Time/h	Yield/%[a]	*Endo*/*Exo*[b]	Ee (*Endo*)/%[c]
1	$CHCl_3$	66	29	98/2	33
2	$PhCH_3$	65	38	98/2	37
3	PhCl	66	70	98/2	31
4	C_2H_5CN	53	23	>99/1	45
5	THF	53	22	>99/1	46
6	CH_2Cl_2	48	89	>99/1	51

a) Isolated yield after the reduction with $NaBH_4$. b) Determined by ^{1}H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H.

action temperature was therefore examined and the results are shown in Table 2. The *endo*-selective products were obtained in 91% yield, but with no enantioselectivity at room temperature (Entry 1). The diastereo- and enantio-selectivities were slightly improved at 0 °C and −20 °C (Entries 2 and 3). At −40 °C, the corresponding isoxazolidine was obtained in 89% yield in 48 h with excellent *endo*-selectivity and with 51% ee (Entry 4). At lower temperatures, the selectivities increased but the yield of the isoxazolidine decreased; therefore, the reaction temperature was fixed based on the reactivity and selectivity.

Various solvents were next examined for the enantioselective 1,3-dipolar cycloaddition reaction of nitrones. The yields and enantiomeric excesses of the resulting product are shown in Table 3. In chloroform, the most suitable solvent for the enantioselective carbonyl–ene reaction, the isoxazolidine was obtained only in 29% yield in 66 h and with 33% ee. The product was obtained in moderate yields but with similar selectivities in toluene and chlorobenzene (Entries 2 and 3). The coordinating solvents, such as propiononitrile and tetrahydrofuran (THF), decreased the catalytic activity but the selectivity was improved up to 45% ee (Entries 4 and 5). In dichloromethane, the reaction was completed in 48 h to afford the corresponding *endo*-selective-isoxazolidine with 51% ee (Entry 6). These examinations indicated that dichloromethane was the most suitable solvent for the present enantioselective 1,3-dipolar cycloaddition reaction with nitrone.

Enantioselective 1,3-Dipolar Cycloaddition Reaction of Various Nitrones and α,β-Unsaturated Aldehydes. The highly active catalysts, cobalt(Ⅲ) hexafluoroantimonate complexes (Fig. 3), were successfully applied to the enantioselec-

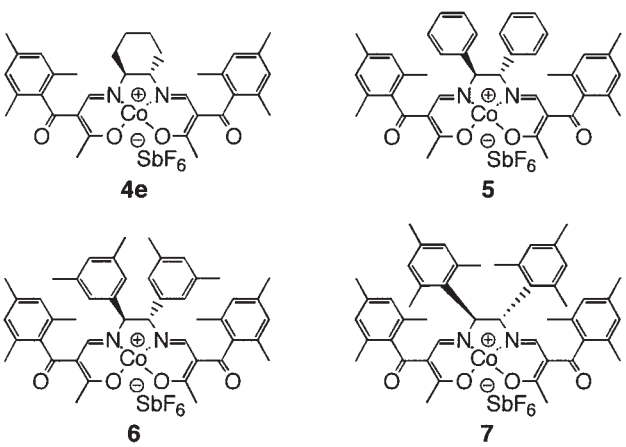
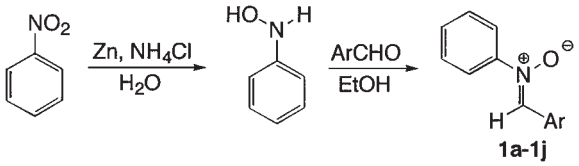


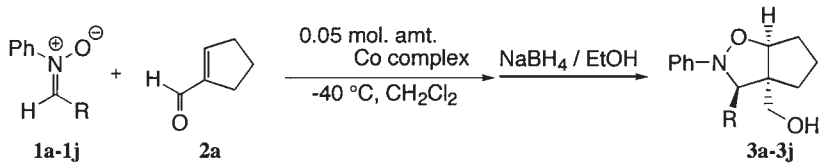
Fig. 3. Various cobalt(Ⅲ) hexafluoroantimonate complexes.

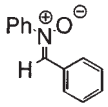
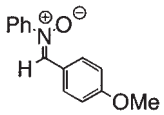
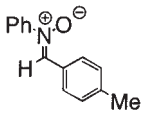
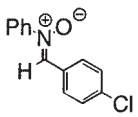
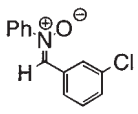
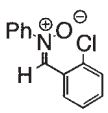
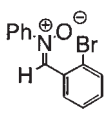
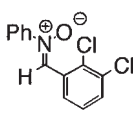
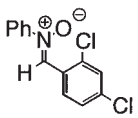
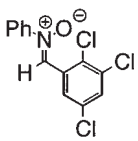


Scheme 2. Preparation of nitrones.

tive 1,3-dipolar cycloaddition reaction of various nitrones (Scheme 2) with 1-cyclopentene-1-carbaldehyde (**2a**) (Table 4). The chiral diaryl diamine parts of the complexes were examined for the reaction with *N*-benzylideneaniline *N*-oxide (**1a**) and the corresponding isoxazolidine was obtained with 51% ee using the complex **4e** derived from the optically active cyclohexanediamine (Entries 1–4). Moreover, the absolute configuration was reversed when the complexes **6** and **7**, derived from 1,2-bis(3,5-dimethylphenyl)ethylenediamine

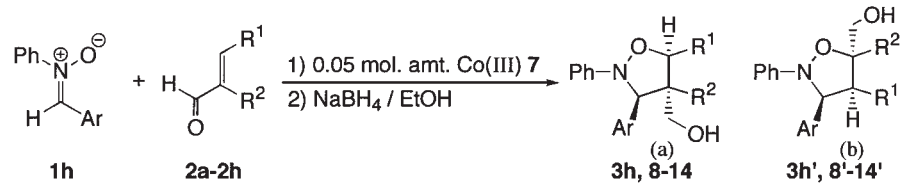
Table 4. Nitrone Cycloadditions of Various Nitrones



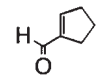
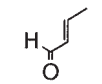
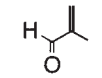
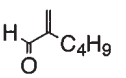
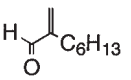
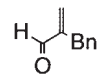
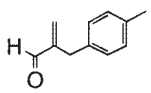
Entry	Nitrone		Product	Catalyst	Time/h	Yield/%[a]	*Endo*/*Exo*[b]	Ee (*Endo*)/%[c]
1		**1a**	**3a**	**4e**	48	89	>99/1	−51
2				**5**	65	87	>99/1	−8
3				**6**	41	68	>99/1	7
4				**7**	55	86	>99/1	37
5		**1b**	**3b**	**4e**	134	82	99/1	−53
6		**1c**	**3c**	**4e**	48	91	>99/1	−43
7		**1d**	**3d**	**4e**	73	83	99/1	−52
8		**1e**	**3e**	**4e**	108	94	>99/1	5
9				**6**	96	76	98/2	22
10		**1f**	**3f**	**4e**	73	84	>99/1	65
11				**5**	96	89	99/1	78
12				**6**	96	96	99/1	80
13				**7**	48	98	99/1	67
14		**1g**	**3g**	**6**	96	85	99/1	85
15[d]				**6**	96	18	>99/1	91
16		**1h**	**3h**	**6**	60	quant	>99/1	87
17		**1i**	**3i**	**6**	96	quant	>99/1	83
18		**1j**	**3j**	**6**	83	93	>99/1	85

a) Isolated yield after the reduction with $NaBH_4$. b) Determined by ^1H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H. d) Reaction temp: −78 °C.

Table 5. Various α,β-Unsaturated Aldehydes



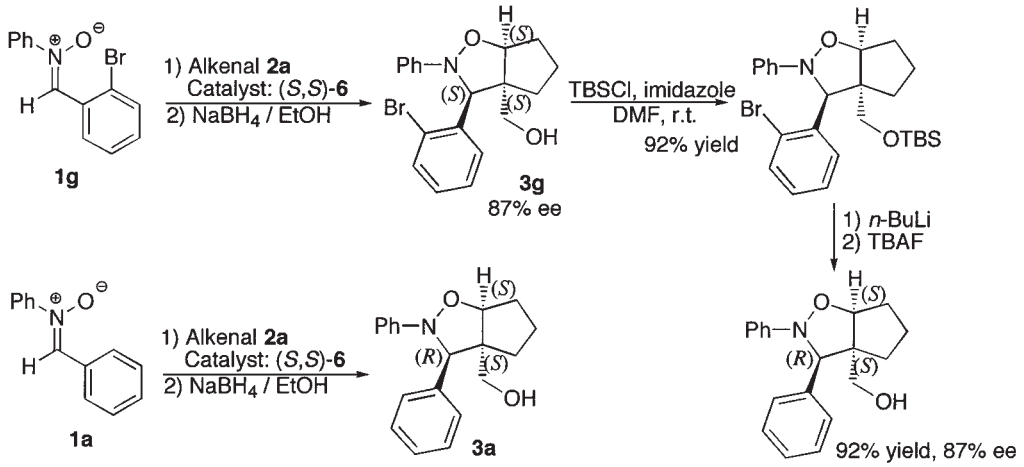
1h **2a-2h** **3h, 8-14** **3h', 8'-14'**

Entry	Aldehyde		R^1	R^2	Product	Yield/%[a]	rs(a/b)[b]	*Endo*/*Exo*[b]	Ee(*Endo*)/%[c]
1[d]		**2a**	–$(CH_2)_3$–		**3h**	quant	>99/1	>99/1	87
2[e]		**2b**	H	H	**8**	90	89/11	>99/1	79
3		**2c**	CH_3	H	**9**	94	>99/1	98/2	63
4[f]		**2d**	H	CH_3	**10′**	91	5/95	>99/1	82
5[d]		**2e**	H	C_4H_9	**11′**	60	1/>99	>99/1	79
6[d]		**2f**	H	C_6H_{13}	**12′**	80	3/97	84/16	77
7[d]		**2g**	H	$C_6H_5CH_2$	**13′**	93	1/99	>99/1	92
8[d,g]		**2h**	H	H_3C–  –CH_2	**14′**	quant	1/>99	>99/1	90

Reaction time: 24–144 h. Reaction temp: −40 °C. a) Isolated yield after the reduction with $NaBH_4$. b) Determined by ^1H NMR analysis. c) Determined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H. d) Complex **6** was employed. e) Reaction temp: −78 °C. f) 0.08 mol. amt. complex **6** was employed at −60 °C and five portions of nitrone was added at 24 h intervals. g) Reaction temp: −30 °C.

and 1,2-bis(2,4,6-trimethylphenyl)ethylenediamine, were employed. The reactions with the nitrone derived from the *p*-substituted benzaldehyde, *N*-(4-methoxybenzylidene)aniline *N*-oxide, *N*-(4-methylbenzylidene)aniline *N*-oxide and *N*-(4-chlorobenzylidene)aniline *N*-oxide, were examined. The products were obtained with moderate enantioselectivities (Entries 5–7). In contrast, the optical yield of the cyclo adduct derived from nitrone **1e** decreased to 5% (Entry 8, vs Entry 7) but, in the case of the *o*-chloro derivative **1f**, it increased to 65% (Entry 10, vs Entry 7). The optically active ligands were screened again and the complex **6** was found to be the most suitable (Entries 10–13). The cobalt-complex-catalyzed cycloaddition reaction using nitrone **1g** also occurred and the corresponding *endo*-adduct was selectively obtained with 85% ee (Entry 14). At −78 °C, the resulting isoxazolidine was obtained in low yield, but the optical yield was improved to 91% ee (Entry 15). The nitrones **1h**, **1i**, and **1j** derived from 2,3-dichlorobenzaldehyde, 2,4-dichlorobenzaldehyde, and 2,3,5-trichlorobenzaldehyde were reacted to afford the corresponding isoxazolidines with perfect *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 a high enantioselectivity was achieved with nitrones derived from the *ortho*-substituted benzaldehyde.

The cycloaddition reaction with various α,β-unsaturated aldehydes was then attempted in the presence of cobalt(III) hexafluoroantimonate (Table 5). The reaction with acrylaldehyde smoothly proceeded to afford the corresponding isoxazolidine with 89% regioselectivity, 99% diastereoselectivity, and 79% enantioselectivity (Entry 2). Crotonaldehyde, a β-substituted α,β-unsaturated aldehyde, was also allowed to react with the nitrone **1h** and the resulting alcohol was 63% ee (Entry 3). The regioselectivity was reversed in the case of employing the α-substituted aldehydes; this reversal could be attributed to their steric factor rather than their electronic density.[17] The regio- and diastereo-selectivities of the corresponding isoxazolidines were high-to-excellent in all cases for the α-substituted α,β-unsaturated aldehydes. The reaction with methacrylaldehyde was induced by the cationic cobalt complex and the corresponding *endo*-adduct was selectively obtained with 82% ee (Entry 4). The α-alkyl derivatives, **2e** and **2f**, were next attempted and the corresponding *endo* products were regioselectively obtained with moderate enantioselectivities (Entries 5 and 6). For the reaction of 2-benzyl-2-propenal (**2g**) and its derivatives **2h**, only the corresponding *endo* cycloadducts were obtained and their enantioselectivities were up to 92% and



Scheme 3. Determination of the absolute configuration of cycloadducts **3a** and **3g**.

90%, respectively (Entries 7 and 8).

Absolute Configuration of the Optically Active Isoxazolidine Derivatives. The absolute configuration of the cycloadduct **3j** was determined by X-ray analysis. The cycloadduct **3j** of 85% ee was recrystallized from ethanol to afford the optically pure **3j**, which was again crystallized from ethanol for preparation of the single crystals. The X-ray analysis of the optically pure **3j** 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 Fig. 4. The absolute configurations of **3a** and **3g** were then determined. As shown in Scheme 3, the hydroxy group of the cycloadduct **3g** was protected with the *tert*-butyldimethylsilyl group and then it was treated with *n*-butyllithium and TBAF to obtain the isoxazolindine **3a** in high yield without any loss of optical purity. The HPLC retention time and peak area of the obtained **3a** were compared with those of compound **3a** from the nitrone **1a**. It was confirmed that they had the same absolute configuration (1*S*,4*R*,5*S*) and that the enantioselective sense was not affected by the halogen on the *ortho* position of the nitrones.

On the basis of these observations and the related discussions on the hetero Diels–Alder and the carbonyl–ene reaction catalyzed by the cationic cobalt(Ⅲ) complexes, the sense of chiral induction of the present cycloaddition reaction could be explained as follows. The coordination of the α,β-unsaturated aldehyde with the cobalt atom would be similar to that of aldehydes in the hetero Diels–Alder reaction. The axial coordination site of cobalt(Ⅲ) was occupied by the oxygen atom of the aldehyde carbonyl *anti* to the alkyl group, which was expected to orient between two coordinating oxygen atoms on the planar 3-oxobutylideneaminato ligand. It is also reasonable to assume that the conformation of the α,β-unsaturated aldehyde during the reaction could be *s*-trans. The nitrone could favorably approach the formed complex of the α,β-unsaturated aldehyde with the cobalt catalyst, as illustrated as Fig. 5, avoiding the steric hindrance of the chiral diamine and the bulky aryl group of the side chain of the 3-oxobutylideneaminato ligand, to afford the corresponding cycloadduct with high regio-, diastereo- and enantioselectivities. In the reactions catalyzed by the cobalt(Ⅲ) complex **4e** derived from cyclohexanediamine, the contribution of the coordination depicted in Fig. 6 should be considered because of the less hindered blocking of the disfavored coordination. Thus the corresponding cycloadduct with the opposite chirality was obtained. It should be pointed out here that the *ortho*-halo substituted nitrones such as **1f**–**1j** could increase the enantioselectivity. It can be explained as follows: The disfavored coordination should be suppressed by the steric repulsion between the *ortho*-halo substitution and the bulky side chain of the ligand (Fig. 7), whereas the halogen atom on the *ortho*-position of the donor molecule could coordinate with the metal-complex to improve the enantioselectivity in the present 1,3-dipolar cycloaddition (Fig. 5).

In Table 5, that shows the cycloaddition reaction with a variety of aldehydes, the 4-formyl cycloadducts were selectively obtained from the alkenals **2a**, **2b** and **2c** and the 5-formyl cycloadducts from the alkenals **2d**–**2h**. The regioselectivity for the 4-formyl cycloadducts can be attributed to the frontier orbital interaction. The secondary orbital interaction could enhance the regioselectivity (Fig. 8). On the contrary, the steric effect should be considered for the regioselectivity of the 5-formyl cycloadducts from the alkenals **2d**–**2h**. The absolute configuration of the cycloadduct **13′** derived from **2g** was determined to be (*S*,*S*) by X-ray analysis of the 2,4-dinitrophenylhydrazone derivative **15** (Fig. 9). The α-substituted 2-alkenal could coordinate the cobalt(Ⅲ) complex in an *s*-cis conformer. Avoiding the steric repulsion between the α-substitutent of the aldehyde and the *N*-phenyl group of the nitrone, the cycloaddition reaction produced the 5-formyl adduct with excellent regioselectivity. The enantioselection of the 5-formyl adduct was also regulated by the steric-demanding aryl groups of the optically active diamine part and the side chain of the 3-oxobutylideneaminato ligand (Fig. 10).

Conclusions

In summary, the cationic cobalt(Ⅲ) hexafluoroantimonate complex with an optically active 3-oxobutylideneaminato ligand effectively catalyzed the asymmetric 1,3-dipolar cycloaddition reaction of various nitrones with aldehydes to afford the corresponding isoxazolidines in high yield and with high enantioselectivities.

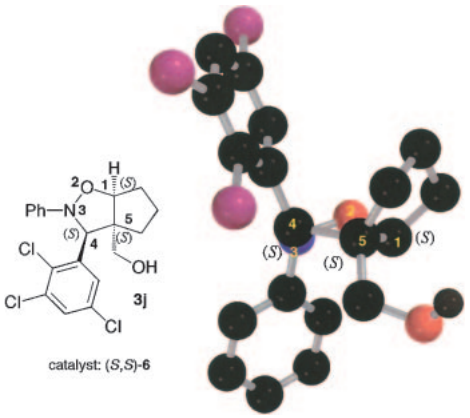


Fig. 4. Absolute configuration of the cycloadduct **3j**.

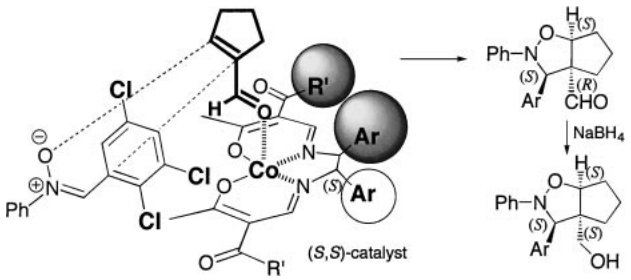


Fig. 5. Reasonable explanation for the enantioselection.

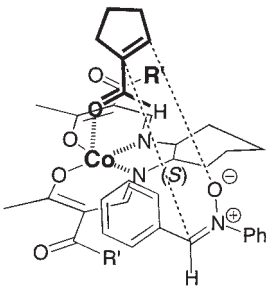


Fig. 6. Favored coordination of complex **4e** catalyzed reaction.

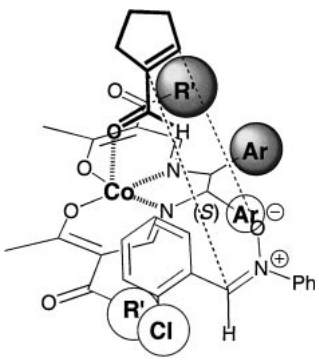


Fig. 7. Effect of *o*-substituted halogen.

Experimental

General. The infrared (IR) spectra were recorded using a JASCO Model FT/IR-410 infrared spectrometer on KBr pellets or liquid film on NaCl. The ^{1}H NMR spectra and ^{13}C NMR spectra were measured using a JEOL Model GX-400 spectrometer with $CDCl_3$ or C_6D_6 as the solvent and tetramethylsilane as the internal standard. High-resolution mass spectra were obtained with a Hitachi M-80B. For the thin-layer chromatography (TLC) analysis throughout this study, Merck precoated TLC plates (silica gel 60 F254, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N). High-performance liquid chromatography (HPLC) analyses were performed using a Shimadzu LC-6A chromatograph with an optically active column (Chiralcel OB-H, Chiralcel OD-H, and Chiralpak AD-H columns, Daicel Ltd., Co.); the peak areas were obtained with a Shimadzu chromatopack C-R4A or a Varian Dynamax MacIntegrator. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. *N*-Benzylideneaniline *N*-oxide (**1a**), *N*-(4-methoxybenzylidene)aniline *N*-oxide (**1b**), *N*-(4-methylben-

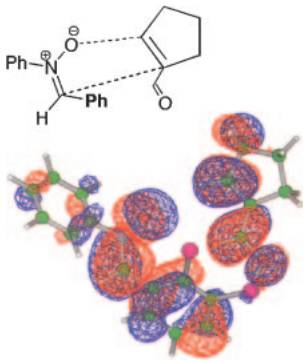


Fig. 8. Regioselectivity for 4-formyl cycloadducts.

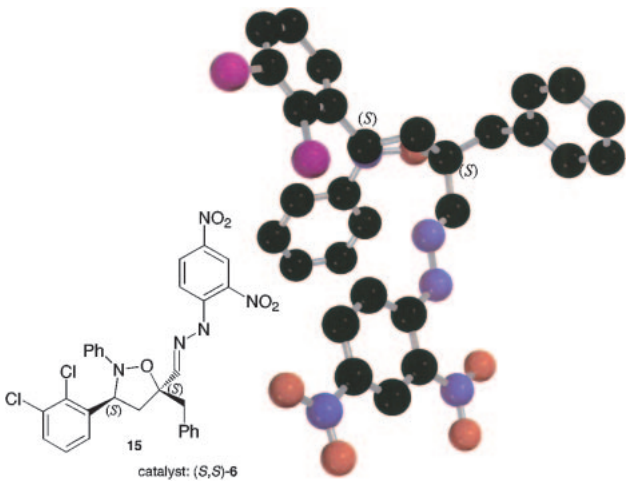


Fig. 9. Absolute configuration of a hydrazone of cycloadduct **13′**.

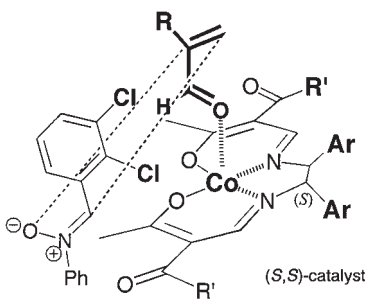


Fig. 10. Enantio- and regioselectivity for 5-formyl adduct.

zylidene)aniline *N*-oxide (**1c**), *N*-(4-chlorobenzylidene)aniline *N*-oxide (**1d**), *N*-(3-chlorobenzylidene)aniline *N*-oxide (**1e**), *N*-(2-chlorobenzylidene)aniline *N*-oxide (**1f**), *N*-(2-bromobenzylidene)aniline *N*-oxide (**1g**), *N*-(2,3-dichlorobenzylidene)aniline *N*-oxide (**1h**), *N*-(2,4-dichlorobenzylidene)aniline *N*-oxide (**1i**), and *N*-(2,3,5-trichlorobenzylidene)aniline *N*-oxide (**1j**) were prepared using previously reported methods.[18] Acrylaldehyde (**2b**), crotonaldehyde (**2c**), and methacrylaldehyde (**2d**) were purchased from Tokyo Kasei Kogyo (TCI) Co., Ltd. 1-Cyclopentene-1-carbaldehyde (**2a**),[19] 2-butyl-2-propenal (**2e**),[20] 2-hexyl-2-propenal (**2f**),[20] 2-benzyl-2-propenal (**2g**),[20] and 2-(4-methylbenzyl)-2-propenal (**2h**)[20] were prepared by previously published methods.

Preparation of Optically Active 3-Oxobutylideneaminatocobalt Complexes. Complexes **4a**–**4e**, **5**, **6**, and **7** were prepared by a reported method.[14b]

General Procedure for Enantioselective 1,3-Dipolar Cycloaddition Reaction of α,β-Unsaturated Aldehyde. Under nitrogen, to the *N*,*N*′-bis[3-oxo-2-(2,4,6-trimethylbenzoyl)butylidene]-(1*R*,2*R*)-cyclohexane-1,2-diaminatocobalt(Ⅲ) hexafluoroantimonate (12.9 mg, 0.015 mmol, 0.05 molar amount) was added 1-cyclopentene-1-carbaldehyde (43.8 mg, 0.46 mmol) in dichloromethane (1.0 mL). A solution of the *N*-benzylideneaniline *N*-oxide (59.3 mg, 0.30 mmol) in dichloromethane (1.0 mL) was then added at −40 °C. The mixture was stirred for 48 h at −40 °C, followed by treatment with a solution of sodium borohydride (21.0 mg, 0.56 mmol) in ethanol at −40 °C for 1 h; it was finally left to room temperature. After standard work-up and chromatography on silica gel (Hexane:AcOEt = 4:1) afforded (1*R**,4*S**,5*R**)-5-hydroxymethyl-3,4-diphenyl-2-oxa-3-azabicyclo[3.3.0]octane (79.5 mg, diastereomer ratio >99/1) in 89% yield.

(1*R,4*S**,5*R**)-5-Hydroxymethyl-3,4-diphenyl-2-oxa-3-azabicyclo[3.3.0]octane (3a, Chart 1):** ^{1}H NMR ($CDCl_3$) δ 1.08–1.14 (1H, m), 1.39–1.90 (5H, m), 2.03–2.06 (1H, m), 3.55 (2H, s), 4.56–4.57 (1H, m), 4.89 (1H, s), 6.87–6.90 (1H, m), 6.99 (2H, dd, J = 1.0, 8.8 Hz), 7.18–7.28 (3H, m), 7.34 (2H, t, J = 7.6 Hz), 7.45 (2H, d, J = 7.3 Hz); NOE: H^4–H^a 5.0%, H^a–H^4 4.1%, H^1–H^4 0.9%, H^4–H^1 0.4%, H^1–H^a 4.9%, H^a–H^1 3.3%; ^{13}C NMR ($CDCl_3$) δ 24.8, 31.1, 31.6, 66.9, 67.5, 75.5, 86.8, 114.4, 121.1, 127.0, 127.3, 128.1, 128.7, 139.8, 151.1; IR (NaCl) 3427, 3087, 3061, 3027, 2957, 2873, 1710, 1598, 1488, 1250, 1075, 1042, 923, 752, 700 cm^{-1}. HRMS: Calcd for $C_{19}H_{21}NO_2$: M^+ = 295.1572. Found: m/z 295.1566. $[\alpha]_D^{25}$ −76.3° (c 0.832, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol 2.0% in hexane, Flow 1.0 mL/min, 29.5 min (major), 40.5 min (minor), 51% ee, (*R*,*R*)-**4e**).

(1*R,4*R**,5*R**)-5-Hydroxymethyl-4-(4-methoxyphenyl)-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3b):** ^{1}H NMR ($CDCl_3$) δ 1.03–1.08 (1H, m), 1.35–1.64 (5H, m), 1.96–2.01 (1H, m), 3.49 (2H, s), 3.74 (3H, s), 4.48–4.49 (1H, m), 4.77 (1H, s), 6.80–6.84 (3H, m), 6.91–6.93 (2H, m), 7.14–7.16 (2H, m), 7.30 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 24.8, 31.3, 31.6, 55.2, 66.7, 67.6, 75.1, 86.8, 113.5, 114.6, 121.1, 128.4, 128.7, 131.8, 151.1, 158.4; IR (KBr) 3414, 2956, 1598, 1512, 1488, 1249, 1174, 1032, 753, 695 cm^{-1}. HRMS: Calcd for $C_{20}H_{23}NO_3$: M^+ = 325.1678. Found: m/z 325.1687. $[\alpha]_D^{27}$ −87.6° (c 0.189, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 5.0% in hexane, Flow 1.0 mL/min, 11.9 min (major), 29.2 min (minor), 53% ee, (*R*,*R*)-**4e**).

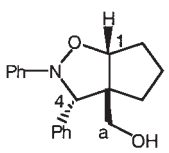


Chart 1.

(1*R,4*R**,5*R**)-5-Hydroxymethyl-4-(4-methylphenyl)-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3c):** ^{1}H NMR ($CDCl_3$) δ 1.05–1.12 (1H, m), 1.41–1.70 (4H, m), 1.79 (1H, s), 2.00–2.06 (1H, m), 2.34 (3H, s), 3.49–3.55 (2H, m), 4.54–4.55 (1H, m), 4.83 (1H, s), 6.88 (1H, t, J = 7.3 Hz), 6.98 (2H, d, J = 7.8 Hz), 7.13–7.21 (4H, m), 7.32 (2H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2, 24.8, 31.2, 31.5, 66.7, 67.4, 75.3, 86.7, 114.5, 121.1, 127.1, 128.7, 128.8, 136.5, 136.6, 151.1; IR (KBr) 3414, 3024, 2953, 1596, 1514, 1488, 1249, 1041, 758, 694 cm^{-1}. HRMS: Calcd for $C_{20}H_{23}NO_3$: M^+ = 309.1729. Found: m/z 309.1720. $[\alpha]_D^{27}$ −76.0° (c 0.467, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol 2.0% in hexane, Flow 1.0 mL/min, 33.8 min (major), 44.7 min (minor), 43% ee (*R*,*R*)-**4e**).

(1*R,4*R**,5*R**)-4-(4-Chlorophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3d):** ^{1}H NMR ($CDCl_3$) δ 1.09–1.17 (1H, m), 1.36–1.42 (1H, m), 1.50–1.70 (4H, m), 2.02–2.07 (1H, m), 3.54 (2H, s), 4.55–4.56 (1H, m), 4.91 (1H, s), 6.91 (1H, t, J = 7.3 Hz), 6.97 (2H, d, J = 7.8 Hz), 7.21–7.28 (2H, m), 7.32 (2H, d, J = 8.3 Hz), 7.41 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 24.8, 31.0, 31.8, 66.9, 67.6, 75.0, 86.9, 114.3, 121.3, 128.2, 128.7, 128.8, 132.6, 138.4, 150.8; IR (KBr) 3427, 2958, 2873, 1597, 1489, 1091, 1041, 1014, 756, 695 cm^{-1}. HRMS: Calcd for $C_{19}H_{20}ClNO_2$: M^+ = 329.1183. Found: m/z 329.1199. $[\alpha]_D^{28}$ −82.3° (c 0.300, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol 1.5% in hexane, Flow 1.0 mL/min, 38.6 min (major), 58.1 min (minor), 52% ee, (*R*,*R*)-**4e**).

(1*R,4*R**,5*R**)-4-(3-Chlorophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3e):** ^{1}H NMR ($CDCl_3$) δ 1.10–1.18 (1H, m), 1.39–1.43 (1H, m), 1.44–1.73 (5H, m), 2.03–2.08 (1H, m), 3.53 (2H, s), 4.55–4.56 (1H, m), 4.91 (1H, s), 6.91 (1H, t, J = 7.3 Hz), 6.98 (2H, d, J = 7.8 Hz), 7.21–7.28 (4H, m), 7.35 (1H, d, J = 7.3 Hz), 7.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.8, 30.8, 31.8, 67.1, 67.5, 75.2, 87.0, 114.1, 121.3, 125.5, 127.2, 127.3, 128.8, 129.4, 134.1, 142.1, 150.8; IR (NaCl) 3389, 3065, 2962, 1596, 1487, 1202, 1043, 757, 694, 517 cm^{-1}. HRMS: Calcd for $C_{19}H_{20}ClNO_2$: M^+ = 329.1183. Found: m/z 329.1185. $[\alpha]_D^{26}$ −34.8° (c 0.756, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 2.0% in hexane, Flow 1.0 mL/min, 12.8 min (major), 32.1 min (minor), 22% ee, (*S*,*S*)-**6**).

(1*R,4*R**,5*R**)-4-(2-Chlorophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3f):** ^{1}H NMR ($CDCl_3$) δ 1.14–1.19 (1H, m), 1.25–1.61 (5H, m), 1.99–2.04 (1H, m), 3.64 (1H, d, J = 10.7 Hz), 3.71 (1H, d, J = 10.7 Hz), 4.72–4.73 (1H, m), 5.23 (1H, s), 6.90 (1H, t, J = 7.3 Hz), 7.00 (2H, d, J = 7.8 Hz), 7.21–7.30 (4H, m), 7.38 (1H, dd, J = 1.5, 7.8 Hz), 7.81 (1H, dd, J = 1.5, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 30.8, 30.9, 67.0, 67.2, 73.0, 88.0, 113.5, 121.0, 126.8, 128.4, 128.7, 129.0, 129.6, 132.8, 137.7, 150.6; IR (KBr) 3400, 2958, 2874, 1596, 1487, 1470, 1056, 1035, 751, 706 cm^{-1}. HRMS: Calcd for $C_{19}H_{20}ClNO_2$: M^+ = 329.1183. Found: m/z 329.1170. $[\alpha]_D^{25}$ −62.7° (c 0.733, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 1.0% in hexane, Flow 1.0 mL/min, 18.1 min (major), 26.2 min (minor), 80% ee, (*S*,*S*)-**6**).

(1*R,4*R**,5*R**)-4-(2-Bromophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3g):** ^{1}H NMR ($CDCl_3$) δ 1.15–1.62 (6H, m), 2.00–2.05 (1H, m), 3.68 (1H, d, J = 10.8 Hz), 3.76 (1H, d, J = 10.8 Hz), 4.72–4.74 (1H, m), 5.21 (1H, s), 6.90 (1H, t, J = 7.3 Hz), 6.99 (2H, d, J = 7.8 Hz), 7.13–7.17 (1H, m), 7.23–7.34 (3H, m), 7.56 (1H, dd, J = 1.2, 8.1 Hz), 7.81

(1H, dd, $J = 1.7$, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 30.8, 30.9, 67.1, 67.3, 75.0, 88.1, 113.5, 121.0, 123.4, 127.4, 128.7, 129.0, 130.0, 131.9, 139.3, 150.5; IR (KBr) 3418, 2956, 2874, 1595, 1487, 1236, 1040, 1024, 750, 695 cm^{-1}. HRMS: Calcd for $C_{19}H_{20}BrNO_2$: $M^+ = 373.0677$. Found: m/z 373.0674. $[\alpha]_D^{27}$ -36.8° (c 0.937, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 3.0% in hexane, Flow 1.0 mL/min, 8.9 min (major), 11.0 min (minor), 85% ee, (*S*,*S*)-**6**).

(1*R,4*R**,5*R**)-4-(2,3-Dichlorophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3h):** ^{1}H NMR ($CDCl_3$) δ 1.08–1.10 (1H, m), 1.26–1.42 (2H, m), 1.47–1.59 (2H, m), 1.86 (1H, s), 1.98–2.02 (1H, m), 3.60 (1H, d, $J = 10.7$ Hz), 3.67 (1H, d, $J = 10.7$ Hz), 4.71–4.72 (1H, m), 5.24 (1H, s), 6.90 (1H, t, $J = 7.3$ Hz), 6.97 (2H, d, $J = 8.3$ Hz), 7.19–7.27 (3H, m), 7.40 (1H, d, $J = 6.8$ Hz), 7.74 (1H, d, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 30.6, 30.9, 66.7, 67.2, 73.5, 88.1, 113.4, 121.0, 127.2, 127.8, 128.9, 129.0, 230.9, 132.1, 140.3, 150.3; IR (NaCl) 3425, 2959, 2875, 1596, 1488, 1420, 1238, 1039, 755, 696 cm^{-1}. HRMS: Calcd for $C_{19}H_{19}Cl_2NO_2$: $M^+ = 363.0793$. Found: m/z 363.0799. $[\alpha]_D^{26}$ -37.5° (c 1.029, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 1.0% in hexane, Flow 1.0 mL/min, 22.7 min (major), 35.5 min (minor), 87% ee, (*S*,*S*)-**6**).

(1*R,4*R**,5*R**)-4-(2,4-Dichlorophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3i):** ^{1}H NMR ($CDCl_3$) δ 1.11–1.16 (1H, m), 1.26–1.36 (2H, m), 1.45–1.59 (2H, m), 1.67 (1H, s), 1.98–2.02 (1H, m), 3.59 (1H, d, $J = 10.7$ Hz), 3.65 (1H, d, $J = 10.7$ Hz), 4.69–4.70 (1H, m), 5.17 (1H, s), 6.90 (1H, t, $J = 7.3$ Hz), 6.97 (2H, d, $J = 7.8$ Hz), 7.23–7.26 (3H, m), 7.39 (1H, d, $J = 1.5$ Hz), 7.75 (1H, d, $J = 8.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 30.7, 30.9, 66.8, 67.2, 72.6, 88.1, 113.4, 121.1, 127.1, 128.4, 129.0, 130.6, 133.29, 133.33, 136.5, 150.3; IR (NaCl) 3434, 2959, 2875, 1596, 1488, 1469, 1039, 868, 752, 695 cm^{-1}. HRMS: Calcd for $C_{19}H_{19}Cl_2NO_2$: $M^+ = 363.0793$. Found: m/z 363.0796. $[\alpha]_D^{25}$ -76.6° (c 1.020, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 1.0% in hexane, Flow 1.0 mL/min, 21.0 min (major), 33.0 min (minor), 83% ee, (*S*,*S*)-**6**).

(1*S*,4*S*,5*S*)-5-Hydroxymethyl-3-phenyl-4-(2,3,5-trichlorophenyl)-2-oxa-3-azabicyclo[3.3.0]octane (3j): ^{1}H NMR ($CDCl_3$) δ 1.08–1.26 (1H, m), 1.31–1.42 (2H, m), 1.53–1.58 (3H, m), 2.02–2.06 (1H, m), 3.62 (1H, d, $J = 10.7$ Hz), 3.66 (1H, d, $J = 10.7$ Hz), 4.71–4.72 (1H, m), 5.23 (1H, s), 6.93 (1H, t, $J = 7.3$ Hz), 6.97 (2H, d, $J = 8.4$ Hz), 7.25–7.29 (2H, m), 7.43 (1H, d, $J = 2.0$ Hz), 7.77 (1H, d, $J = 2.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 25.2, 30.5, 31.0, 66.7, 67.3, 73.6, 88.2, 113.3, 121.3, 128.0, 128.9, 129.1, 129.4, 132.9, 133.1, 141.8, 150.1; IR (KBr) 3588, 3081, 2941, 2868, 1490, 1219, 1056, 863, 764, 702 cm^{-1}. Found: C, 57.08; H, 4.70; N, 3.47%. Calcd for $C_{19}H_{18}Cl_3NO_2$: C, 57.24; H, 4.55; N, 3.51%. Mp 185.8–187.1 °C $[\alpha]_D^{25}$ -61.2° (c 1.043, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 1.0% in hexane, Flow 1.0 mL/min, 23.9 min (major), 35.8 min (minor), 85% ee, (*S*,*S*)-**6**). The optically pure **3j** was obtained with recrystallization from ethanol. $[\alpha]_D^{26}$ -71.962° (c 0.650, $CHCl_3$). The absolute configuration of cycloadduct **3j** was determined by X-ray analysis.

X-ray Analysis of 3j: The crystals were grown from an ethanol solution over the course of one day. A crystal specimen of approximate dimension $0.68 \times 0.50 \times 0.40$ mm^3 was chosen. The X-ray intensities were measured on a Rigaku AFC-7R diffractometer with Mo Kα radiation. The structure was solved by direct methods using SIR92 and refined by full-matrix least-squares calculations on F^2 using SHELXL-97. The refinement of the absolute configurations was performed and the structure presented yielded a value of $-0.10(7)$ for the Flack parameter, indicating that the structure had the correct absolute configurations.

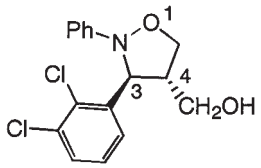


Chart 2.

Procedure for Enantioselective 1,3-Dipolar Cycloaddition Reaction of *N*-2,3-Dichlorobenzylideneaniline *N*-oxide and Methacrylaldehyde. Under nitrogen, to the *N*,*N*′-bis[3-oxo-2-(2,4,6-trimethylbenzoyl)butylidene]-(1*S*,2*S*)-1,2-bis(3,5-dimethylphenyl)ethylenediaminatocobalt(Ⅲ) hexafluoroantimonate (14.8 mg, 0.015 mmol, 0.08 molar amount) was added methacrylaldehyde (115.6 mg, 1.5 mmol) in dichloromethane (1.0 mL). Three portions of *N*-2,3-dichlorobenzylideneaniline *N*-oxide (16.0 mg, 0.06 mmol) in dichloromethane (0.5 mL) was added at 24 h intervals to the reaction mixture at -60 °C. The mixture was stirred for 90 h at -60 °C, followed by treatment with a solution of sodium borohydride (85.2 mg, 2.25 mmol) in ethanol at -60 °C for 1 h, and then left to room temperature. Standard work-up and chromatography on silica gel (Hexane:AcOEt = 5:1) afforded (3*R**,5*R**)-3-(2,3-dichlorophenyl)-5-hydroxymethyl-5-methyl-2-phenylisoxazolidine (55.3 mg, regioisomer ratio 95/5, diastereomer ratio >99/1) in 91% yield.

(3*R,4*R**)-3-(2,3-Dichlorophenyl)-4-hydroxymethyl-2-phenylisoxazolidine (8, Chart 2):** ^{1}H NMR ($CDCl_3$) δ 1.58 (1H, brs), 2.26–2.86 (1H, m), 3.59–3.73 (1H, m), 3.95 (1H, dd, $J = 4.7$, 10.7 Hz), 4.09 (1H, dd, $J = 5.6$, 8.8 Hz), 4.25 (1H, dd, $J = 6.8$, 8.8 Hz), 6.85–7.00 (3H, m), 7.18–7.33 (3H, m), 7.42 (1H, dd, $J = 1.5$, 7.8 Hz), 7.74 (1H, dd, $J = 1.5$, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 55.9, 62.9, 68.8, 69.3, 114.0, 121.6, 126.9, 127.9, 128.9, 129.3, 130.1, 132.9, 142.1, 150.4; IR (NaCl) 3410, 2931, 2877, 1599, 1489, 1450, 1421, 1043, 756, 696 cm^{-1}. HRMS: Calcd for $C_{16}H_{15}Cl_2NO_2$: $M^+ = 323.0480$. Found: m/z 323.0472. $[\alpha]_D^{29}$ -35.3° (c 0.307, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol 3.0% in hexane, Flow 1.0 mL/min, 17.1 min (major), 22.9 min (minor), 79% ee, (*S*,*S*)-**7**).

(3*R,4*R**,5*R**)-3-(2,3-Dichlorophenyl)-4-hydroxymethyl-5-methyl-2-phenylisoxazolidine (9):** ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, d, $J = 6.4$ Hz), 1.33–1.60 (1H, brs), 2.28–2.40 (1H, m), 3.66 (1H, dd, $J = 7.3$, 10.7 Hz), 3.91 (1H, dd, $J = 3.9$, 10.7 Hz), 4.20–4.33 (1H, m), 6.84–7.01 (3H, m), 7.16–7.31 (3H, m), 7.39 (1H, dd, $J = 1.5$, 8.1 Hz), 7.77 (1H, dd, $J = 1.5$, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.1, 61.6, 63.2, 69.9, 78.0, 113.5, 121.3, 127.2, 128.0, 129.0, 129.2, 129.9, 132.6, 142.8, 151.2; IR (KBr) 3288, 2885, 1595, 1489, 1419, 1072, 1030, 785, 760, 698 cm^{-1}. HRMS: Calcd for $C_{17}H_{17}Cl_2NO_2$: $M^+ = 337.0636$. Found: m/z 337.0620. $[\alpha]_D^{27}$ $+2.6^\circ$ (c 0.749, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol 2.0% in hexane, Flow 1.0 mL/min, 23.3 min (major), 38.9 min (minor), 63% ee, (*S*,*S*)-**7**).

(3*R,5*R**)-3-(2,3-Dichlorophenyl)-5-hydroxymethyl-5-methyl-2-phenylisoxazolidine (10′):** ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, s), 2.03 (1H, dd, $J = 7.3$, 12.5 Hz), 3.12 (1H, dd, $J = 8.8$, 12.5 Hz), 3.47 (1H, d, $J = 11.7$ Hz), 3.54 (1H, d, $J = 11.7$ Hz), 5.10–5.14 (1H, m), 6.85 (2H, d, $J = 7.8$ Hz), 6.91 (1H, t, $J = 7.3$ Hz), 7.18–7.26 (3H, m), 7.39 (1H, dd, $J = 1.5$, 7.8 Hz), 7.67 (1H, dd, $J = 1.5$, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.1, 45.7, 66.2, 66.7, 84.2, 113.8, 121.3, 125.9, 127.9, 129.0, 129.2, 130.1, 133.1, 142.0, 150.4; IR (NaCl) 3429, 2933, 1598, 1490, 1420, 1181, 1043, 872, 753, 694 cm^{-1}. HRMS: Calcd for $C_{17}H_{17}$-

Cl_2NO_2: $M^+ = 337.0636$. Found: m/z 337.0620. $[\alpha]_D^{29}$ −55.1° (c 0.487, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 3.0% in hexane, Flow 1.0 mL/min, 11.4 min (major), 18.0 min (minor), 82% ee, (*S*,*S*)-**6**).

(3*R,5*R**)-5-Butyl-3-(2,3-dichlorophenyl)-5-hydroxymethyl-2-phenylisoxazolidine (11′):** ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, $J = 7.1$ Hz), 1.20–1.47 (4H, m), 1.59–1.70 (1H, m), 1.78 (1H, t, $J = 6.7$ Hz), 1.82–1.93 (1H, m), 2.06 (1H, dd, $J = 8.1$, 12.7 Hz), 3.03 (1H, dd, $J = 8.1$, 12.7 Hz), 3.47 (1H, dd, $J = 6.7$, 12.0 Hz), 3.58 (1H, dd, $J = 6.7$, 12.0 Hz), 5.11 (1H, t, $J = 8.1$ Hz), 6.81–6.86 (2H, m), 6.90 (1H, t, $J = 7.8$ Hz), 7.17–7.26 (3H, m), 7.39 (1H, dd, $J = 1.5$, 7.8 Hz), 7.64 (1H, dd, $J = 1.5$, 7.8 Hz); ^{13}C NMR ($CDCl_3$) 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; IR (NaCl) 3431, 2956, 2870, 1599, 1490, 1450, 1419, 1041, 785, 752, 694 cm^{-1}. HRMS: Calcd for $C_{20}H_{22}Cl_2NO_2$: $(M - 1)^+ = 378.1027$. Found: m/z 378.0999. $[\alpha]_D^{28}$ −64.5° (c 0.684, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 5.0% in hexane, Flow 1.0 mL/min, 6.0 min (major), 7.6 min (minor), 79% ee, (*S*,*S*)-**6**).

(3*R,5*R**)-3-(2,3-Dichlorophenyl)-5-hexyl-5-hydroxymethyl-2-phenylisoxazolidine (12′):** ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, $J = 6.8$ Hz), 1.15–1.48 (8H, m), 1.55–1.71 (1H, m), 1.74–1.94 (1H, m), 2.05 (1H, dd, $J = 7.6$, 12.4 Hz), 3.03 (1H, dd, $J = 8.5$, 12.4 Hz), 3.46 (1H, dd, $J = 5.1$, 12.1 Hz), 3.57 (1H, dd, $J = 5.9$, 12.1 Hz), 5.11 (1H, t, $J = 8.0$ Hz), 6.83 (2H, d, $J = 7.8$ Hz), 6.90 (1H, t, $J = 7.6$ Hz), 7.15–7.30 (3H, m), 7.39 (1H, dd, $J = 1.5$, 8.3 Hz), 7.63 (1H, dd, $J = 1.5$, 8.1 Hz); ^{13}C NMR ($CDCl_3$) 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; IR (NaCl) 3444, 2929, 2858, 1599, 1491, 1419, 1271, 1041, 752, 694 cm^{-1}. HRMS: Calcd for $C_{22}H_{27}Cl_2NO_2$: $M^+ = 407.1419$. Found: m/z 407.1406. $[\alpha]_D^{27}$ −63.0° (c 0.552, $CHCl_3$). HPLC (Chiralcel OD-H, 2-propanol 3.0% in hexane, Flow 1.0 mL/min, 7.0 min (major), 12.7 min (minor), 77% ee, (*S*,*S*)-**6**).

(3*S*,5*S*)-3-(2,3-Dichlorophenyl)-5-hydroxymethyl-5-benzyl-2-phenylisoxazolidine (13′): ^{1}H NMR ($CDCl_3$) δ 1.84 (1H, s), 2.12 (1H, dd, $J = 7.6$, 12.5 Hz), 2.94 (1H, d, $J = 13.7$ Hz), 2.98 (1H, dd, $J = 8.8$, 12.5 Hz), 3.24 (1H, d, $J = 13.7$ Hz), 3.44 (1H, dd, $J = 5.6$, 12.0 Hz), 3.51 (1H, dd, $J = 5.6$, 12.0 Hz), 5.05 (1H, t, $J = 8.3$ Hz), 6.84 (2H, d, $J = 7.8$ Hz), 6.92 (1H, t, $J = 7.8$ Hz), 7.14 (1H, t, $J = 7.8$ Hz), 7.18–7.33 (7H, m), 7.38 (1H, dd, $J = 1.5$, 7.8 Hz), 7.48 (1H, dd, $J = 1.5$, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 41.0, 44.0, 64.2, 65.9, 86.1, 114.2, 121.5, 125.8, 126.6, 128.0, 128.2, 128.9, 129.2, 130.0, 130.3, 133.0, 136.3, 141.8, 150.1; IR (NaCl) 3444, 3028, 2927, 1712, 1597, 1489, 1261, 1041, 752, 528 cm^{-1}. HRMS: Calcd for $C_{23}H_{21}Cl_2NO_2$: $M^+ = 413.0962$. Found: m/z 413.0997. $[\alpha]_D^{29}$ −84.1° (c 0.895, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol 10.0% in hexane, Flow 1.0 mL/min, 10.2 min (major), 11.6 min (minor), 92% ee, (*S*,*S*)-**6**).

(3*R,5*R**)-3-(2,3-Dichlorophenyl)-5-hydroxymethyl-5-(4-methylbenzyl)-2-phenylisoxazolidine (14′):** ^{1}H NMR ($CDCl_3$) δ 1.89 (1H, s), 2.15 (1H, dd, $J = 8.3$, 12.7 Hz), 2.31 (3H, s), 2.88 (1H, d, $J = 13.7$ Hz), 2.96 (1H, dd, $J = 8.3$, 12.7 Hz), 3.20 (1H, d, $J = 13.7$ Hz), 3.42 (1H, d, $J = 11.7$ Hz), 3.50 (1H, d, $J = 11.7$ Hz), 5.04 (1H, t, $J = 8.3$ Hz), 6.81–6.87 (2H, m), 6.91 (1H, t, $J = 7.3$ Hz), 7.05–7.17 (5H, m), 7.18–7.25 (2H, m), 7.37 (1H, dd, $J = 1.6$, 8.2 Hz), 7.50 (1H, dd, $J = 1.6$, 8.2 Hz); ^{13}C NMR (CD_3OD) δ 21.2, 41.2, 44.8, 65.0, 67.1, 87.4, 115.6, 122.3, 127.4, 129.1, 129.5, 129.6, 130.1, 130.9, 131.6, 133.9, 134.9, 137.0, 143.5, 151.9; IR (NaCl) 3442, 3022, 2922, 1597, 1489, 1448, 1421, 1041, 754, 694 cm^{-1}. HRMS: Calcd for $C_{24}H_{24}Cl_2NO_2$: $(M + 1)^+ = 428.1184$. Found: m/z 428.1205. $[\alpha]_D^{28}$ −75.4° (c 0.991, $CHCl_3$). HPLC (Chiralpak AD-H, EtOH 2.0% in hexane, Flow 1.0 mL/min, 13.2 min (major), 26.0 min (minor), 90% ee, (*S*,*S*)-**6**).

Transformation of 3g into 3a. Silylation of (1*R,4*R**,5*R**)-4-(2-Bromophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3g):** To a solution of (1*R**,4*R**,5*R**)-4-(2-bromophenyl)-5-hydroxymethyl-3-phenyl-2-oxa-3-azabicyclo-[3.3.0]octane (**3g**, 70.6 mg, 0.189 mmol) in DMF (2.5 mL) was added imidazole (38.4 mg, 0.56 mmol) and *tert*-butyldimethylsilyl chloride (87.2 mg, 0.58 mmol) at 0 °C. The reaction mixture was then warmed to r.t. and stirred for 12 h. Standard work-up and chromatography on silica gel (Hexane:AcOEt = 40:1) afforded the corresponding silyl ether **3g′** (85.1 mg) in 92% yield.

(1*R,4*R**,5*R**)-4-(2-Bromophenyl)-5-(*tert*-butyldimethylsiloxymethyl)-3-phenyl-2-oxa-3-azabicyclo[3.3.0]octane (3g′):** ^{1}H NMR ($CDCl_3$) δ −0.143 (3H, s), −0.136 (3H, s), 0.75 (9H, s), 1.07–1.14 (1H, m), 1.25–1.56 (4H, m), 1.97–2.02 (1H, m), 3.63 (1H, d, $J = 9.3$ Hz), 3.70 (1H, d, $J = 9.3$ Hz), 4.71–4.72 (1H, m), 5.21 (1H, s) 6.87 (1H, t, $J = 7.3$ Hz), 6.96 (1H, d, $J = 7.3$ Hz), 7.13 (1H, dt, $J = 1.5$, 7.8, 13.7 Hz), 7.21–7.20 (2H, m), 7.31 (1H, t, $J = 7.3$ Hz), 7.55 (1H, dd, $J = 1.5$, 8.1 Hz), 7.81 (1H, dd, $J = 1.5$, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.3, 25.2, 25.75, 25.85, 30.67, 30.70, 67.0, 67.6, 75.0, 88.5, 113.3, 120.6, 123.3, 127.3, 128.5, 128.9, 130.1, 131.9, 140.1, 151.1; IR (NaCl) 3066, 2954, 2928, 2856, 1596, 1487, 1469, 1440, 1361, 1254, 1105, 839, 779, 749, 695 cm^{-1}.

Debromination of 3g′: Under nitrogen atmosphere, to a solution of the silyl ether **3g′** (45 mg, 0.092 mmol) in THF (1.5 mL) was added *n*-butyllithium (1.58 M (1 M = 1 mol dm^{-3}) solution in hexane, 0.1 mL) at −78 °C. The mixture was stirred for 5 min, followed by treatment with water and warmed to room temperature. The organic extracts were concentrated to afford the crude debrominated product. The debrominated silyl ether was treated with tetrabutylammonium fluoride (1 mol/L in THF, 2 mL) and stirred for 30 min at room temperature. Standard work-up and chromatography on silica gel (Hexane:AcOEt = 4:1) afforded (1*R**,4*S**,5*R**)-5-hydroxymethyl-3,4-diphenyl-2-oxa-3-azabicyclo[3.3.0]octane (**3a**, 25.0 mg) in 92% yield. HPLC (Chiralpak AD-H, 2-propanol 2.0% in hexane, Flow 1.0 mL/min, 21.3 min (major), 32.1 min (minor), 87% ee, corresponding to (*S*,*S*)-**6**).

Preparation of 15: To a solution of 2,4-dinitrophenylhydrazine (55.2 mg, 0.28 mmol) and sulfuric acid (370 mg) in H_2O (0.3 mL)–EtOH (1 mL), was added a solution of aldehyde (95.7 mg, 0.23 mmol), precursor of cycloadduct **13′**, in MeOH (15 mL) under nitrogen atmosphere. After 10 min at room temperature, the precipitate was filtered to afford the product, (3*S*,5*S*)-5-benzyl-3-(2,3-dichlorophenyl)-5-(2,4-dinitrophenylhydrazono)-2-phenylisoxazolidine (**15**), in 95% yield (130.0 mg).

X-ray Analysis of 15: The crystals were grown from THF–hexane solution over the course of one day. A crystal specimen of suitable approximate dimensions was chosen. The X-ray intensities were measured on a Rigaku AFC-7R diffractometer with Mo Kα radiation. The structure was solved by direct methods using SIR92 and refined by full-matrix least-squares calculations on F^2 using SHELXL-97. The refinement of the absolute configurations was performed and the structure presented yielded a value of −0.1(2) for the Flack parameter, indicating that the structure had the correct absolute configurations.

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16 The reaction was quenched with an ethanolic solution of $NaBH_4$ for the transformation of the produced aldehyde into the stable primary alcohol. It was confirmed that the *endo*/*exo* ratio and the enantioselectivity were completely retained after this treatment. Without $NaBH_4$ treatment in the reaction of **1a** and **2a** catalyzed by the complex **4e** (Entry 5, Table 1), the resulting aldehyde was isolated by the rapid work-up in 81% yield with 99% *endo*-selectivity and 51% ee. In this article, the chemical yield, diastereoselectivity, and enantioselectivity listed in Tables 1–5 were determined as the corresponding alcohol obtained after reductive quenching.

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