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Catalytic highly enantioselective 1,3-dipolar cycloaddition reaction of nitrones with 3-alkenoyl-2-oxazolidinones by use of a bidentate chiral bis(imine) ligand–Cu(II) triflate complex

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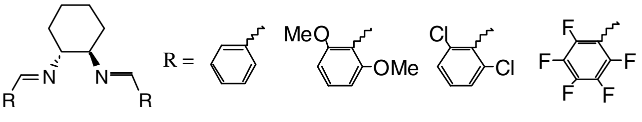
Abstract—A copper(II) triflate complex with bidentate, chiral C_2-symmetric cyclohexane-1,2-bis[(2,6-dichlorophenylmethylene)amine] catalyzed the 1,3-dipolar cycloaddition reactions of nitrones with electron-deficient dipolarophiles, 3-(2-alkenoyl)-1,3-oxazolidin-2-ones to give isoxazolidine cycloadducts with extremely high *endo*- and enantioselectivities.

In recent years much attention has been paid to the design and preparation of chiral ligands for their use in catalytic asymmetric organic synthesis.[1] For example, oxazoline-derived C_2-symmetric chiral ligands have extensively been developed[2] and also applied in enantioselective nitrone 1,3-dipolar cycloaddition (1,3-DC) reactions.[3–9] However, there is still only a very limited number of reports of enantioselective nitrone 1,3-DC reactions in which bis(imine) functionalities are used as chiral ligands in metal complexes, in spite of their promising potential for chelation by virtue of tuning electronic and steric properties with variable substituent(s).[10,11]

We recently reported the catalytic enantioselective nitrone 1,3-DC reaction using an amino-indanol-derived bis(oxazoline) [IndaBOX]–Cu(II) complex as a bidentate chiral catalyst.[12] The enantioselectivities were exceptionally high (95 to >99% ee) compared to those hitherto reported among bidentate ligand–metal complex catalysts such as TADDOL-Ti(IV),[13] 4-*R*-BOX-Mg(II),[3,4] BINOL-Yb(III)(OTf),[14] BINAP-Pd(II),[15] binaphthyldiamine-derived chiral bis(imine) [BINIMs]-Ni(II)[10] used in the nitrone cycloaddition. However, the *endo*/*exo* selectivities in the reaction by the use of [IndaBOX]–Cu(II) complex remained moderate to good (50:50–91:9).[12] To resolve this problem, we applied cyclohexane-1,2-bis(arylmethyleneamine) (**1**)–metal complex catalyst to the nitrone 1,3-DC reaction, a catalyst that was successfully used in enantioselective thiabutadiene Diels–Alder reaction for the first time.[16]

In this letter, we wish to report examples of both highly *endo*- and enantioselective nitrone 1,3-DC reactions using the simple and readily available bidentate ligand, bis(imine) **1**, with optimization of various factors and reaction conditions.

Based on the previous results obtained in the thiabutadiene Diels–Alder reaction,[16] we selected copper triflate [Cu(II)(OTf)$_2$] as Lewis acid for the complex with **1**.



Bis(imine)1 **1a** **1b** **1c** **1d**

Initially, effects of substituent(s) of the bis(benzaldimine) ligand **1** were examined using 20 mol% of the catalyst in a model reaction of nitrone **2a** with *N*-crotonoyloxazolidinone **3a** under the conditions at room temperature in dichloromethane in the presence of

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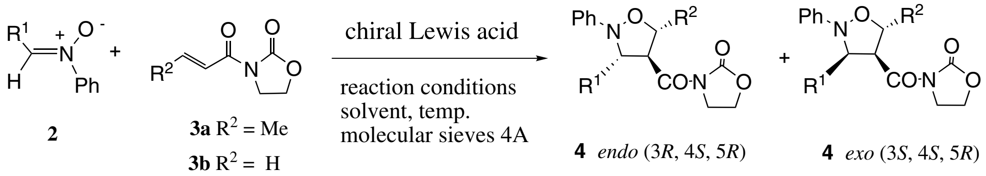
Table 1. Effects of substituent R in the bis(imine) ligand **1** of the $Cu(OTf)_2$ complex for catalytic enantioselective 1,3-DC reaction of nitrone **2a** with dipolarophile **3a**[a]



Entry	Bis(imine)	R	Time (h)	Yield (%)[b]	*endo*/*exo*[c]	*endo* ee (%)[c]
1	**1a**	Ph	72	37[d]	88/12	7
2	**1b**	2,6-$(MeO)_2C_6H_3$	120	32[d]	90/10	78
3	**1c**	2,6-$Cl_2C_6H_3$	15	94	91/9	90
4	**1d**	C_6F_5	72	84	95/5	−13

[a] Reaction of **2a** (0.22 mmol) with **3a** (0.20 mmol) was carried out in CH_2Cl_2 (2 mL) at room temperature in the presence of 20 mol% catalyst ($Cu(OTf)_2$–**1** = 1.0:1.1) and MS 4A (200 mg), unless otherwise noted.

[b] Isolated yield.

[c] Determined by ^1H NMR spectroscopy and/or chiral HPLC analysis.

[d] Incomplete.

Table 2. Dependence of stoichiometry of $Cu(OTf)_2$–bis(imine) ligand **1c** catalyst for the 1,3-DC reaction of nitrone **2a** with dipolarophile **3a**[a]

Entry	Mol% of **1c**	Solvent	Time (h)	Yield (%)[b]	*endo*/*exo*[c]	*endo* ee (%)[c]
1	50	CH_2Cl_2	15	37	84/16	95
2	20	CH_2Cl_2	15	94	91/9	90
3	20[d]	CH_2Cl_2	6	90	87/13	88
4	20	THF	36	92	91/9	90
5	10	CH_2Cl_2	15	94	85/15	88

[a] Reaction of **2a** (0.22 mmol) with **3a** (0.20 mmol) was carried out in 2 mL of solvent at room temperature in the presence of 10–50 mol% catalyst $Cu(OTf)_2$–**1c** and MS 4A (200 mg), unless otherwise noted.

[b] Isolated yield.

[c] Determined by ^1H NMR spectroscopy and/or chiral HPLC analysis.

[d] At 40 °C under reflux.

molecular sieves 4 A.[†] The results are summarized in Table 1. All the reactions using **1a–d** proceeded regiospecifically to afford cycloadduct **4a**. Among the bis(imines) examined, **1c** bearing the electron-withdrawing and relatively bulky Cl substituents at the 2- and 6-positions of the benzene ring was found to give the best enantioselectivity of 90% ee and chemical yield of 94% in high *endo*/*exo* ratio of 91/9.

Based on the results, we next examined the dependence of stoichiometry of the $Cu(OTf)_2$–**1c** catalyst (Table 2). The reaction using 50 mol% of the catalyst offered the best asymmetric induction of 95% ee, whereas the chemical yield (37%) and *endo*/*exo* ratio (84/16) turned out to be lower than those in the other cases (entry 1). The reaction using 20 mol% of the catalyst in dichloromethane at room temperature provided the best results overall (entry 2). In the reaction in refluxing dichloromethane at 40 °C, the stereoselectivities and yield were somewhat reduced (entry 3), while the reaction in tetrahydrofuran at room temperature proceeded slowly and retained both high levels of the stereoselectivities (entry 4). The reaction using 10 mol% of the catalyst still afforded satisfactory results (entry 5).

The 1,3-DC reactions of nitrones **2b–j** bearing a variety of *C*-substituents (R^1) with dipolarophile **3a** were performed in the presence of 20 mol% of $Cu(OTf)_2$–**1c** catalyst in dichloromethane at room temperature (Table 3). Although the reaction with nitrone **2b** bearing an electron-donating substituent $R^1 = 4\text{-}CH_3C_6H_4$ (entry 2) gave moderate *endo*/*exo* (80/20) and enantioselectivities (76% ee), extremely high enantioselectivity (90 to >99% ee) and *endo*/*exo* selectivity (91/9 to >99/1) were attained for various nitrones **2** as a whole. The reaction of nitrone **2a** with acryloyl dienophile **3b** also afforded cycloadduct **4k** in good yield (90%) with high enantioselectivity (90% *endo* ee, 96% *exo* ee) albeit in a 56/44 *endo*/*exo* ratio.

Compared to the various bidentate ligands reported so far in catalytic enantioselective nitrone cycloadditions, bis(imine) **1c** complexed with $Cu(OTf)_2$ was found to show the highest level of *endo*- and enantioselectivities.[17] It should be noted that the presence of molecular sieves in the catalytic system is crucial.

In summary, we have developed an asymmetric 1,3-DC reaction of nitrones to give isoxazolidine cycloadducts

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[†] In the absence of molecular sieves, almost no cycloadduct was obtained.

Table 3. Catalytic enantioselective 1,3-DC reaction of nitrones **2a–j** with dipolarophiles **3a**,**b** in the presence of Cu(OTf)$_2$–ligand **1c** catalyst[a]

Entry	R^1	R^2	Time (h)	Cycloadduct	Yield (%)[b]	*endo*/*exo*[c]	*endo* ee (%)[c]
1	Ph	Me	15	**4a**	94	91/9	90
2	4-$CH_3C_6H_4$	Me	48	**4b**	26[d]	80/20	76
3	4-FC_6H_4	Me	12	**4c**	96	92/8	95
4	4-ClC_6H_4	Me	12	**4d**	99	95/5	97
5	4-BrC_6H_4	Me	12	**4e**	92	95/5	93
6	4-$CF_3C_6H_4$	Me	12	**4f**	99	>99/1	92
7	4-NCC_6H_4	Me	48	**4g**	87	97/3	>99
8	4-$NO_2C_6H_4$	Me	12	**4h**	99	97/3	98
9	2-Naphthyl	Me	24	**4i**	90	92/8	97
10	2-Furyl	Me	12	**4j**	99	99/1	98
11	Ph	H	12	**4k**	90	56/44	90 (96)[e]

[a] Reaction of **2a–j** (0.22 mmol) with **3a**,**b** (0.20 mmol) was carried out in CH_2Cl_2 (2 mL) at room temperature in the presence of 20 mol% catalyst Cu(OTf)$_2$–**1c** and MS 4A (200 mg), unless otherwise noted.

[b] Isolated yield.

[c] Determined by ^{1}H NMR spectroscopy and/or chiral HPLC analysis.

[d] Incomplete.

[e] In parentheses, *exo* ee.

in good yields with extremely high *endo*- and enantioselectivities, which is catalyzed by a readily available bidentate C_2-symmetric chiral bis(imine)–Cu(OTf)$_2$ complex.

Acknowledgements

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