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Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrones to Alkylidene Malonates: Highly Enantioselective Synthesis of Multisubstituted Isoxazolidines

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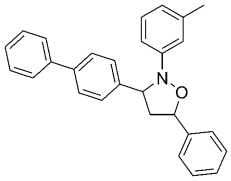
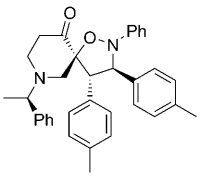
The asymmetric 1,3-dipolar cycloaddition reaction is one of the most powerful methods for the synthesis of enantiomerically enriched five-membered heterocyclic compounds.[1] In particular, the catalytic asymmetric nitrone–alkene cycloaddition reaction has received a great deal of attention because most nitrones are stable compounds that do not require an in situ formation compared with many other 1,3-dipoles. Furthermore, the corresponding isoxazolidines are particularly useful synthetic intermediates for various natural products,[2] in which they are the framework of many biologically active compounds, such as antifungal,[3] anti-tuberculosis,[4] and antiviral agents .[5] Since the pioneering works of Scheeren[6] and Jørgensen in 1994,[7] chiral metal complexes[8–12] as well as organic catalysts[13] have been successfully developed for the catalytic asymmetric 1,3-dipolar cylcloaddition of nitrones to alkenes. Nevertheless, the alkene part was always limited to *N*-alkenoyl amides and generally a high catalyst loading was necessary. On the other hand, alkylidene malonate, which easily undergoes activation by bidentate coordination to various metal ions,[14] was rarely utilized as a dipolarphile in the catalytic asymmetric 1,3-dipolar cycloaddition.[12g] Therefore, the search for more efficient catalyst systems is still desirable and challenging to expand the scope and usage of the reaction. Herein, we report a highly enantioselective [3+2] cycloaddition of nitrones to alkylidene malonates catalyzed by a chiral *N*,*N*′-dioxide–$Ni(ClO_4)_2$·$6H_2O$ complex in good yield with excellent diastereo- and enantioselectivity (Scheme 1).


antifungal drug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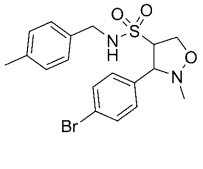
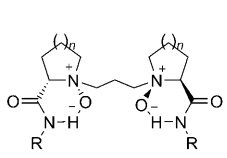

antiviral agent


L1: *n* = 1, R = Ph
L2: *n* = 1, R = 2,6-*i*PrC$_6$H$_3$
L3: *n* = 1, R = *t*Bu
L4: *n* = 2, R = Ph
L5: *n* = 2, R = 2,6-*i*PrC$_6$H$_3$
L6: *n* = 2, R = *t*Bu
L7: *n* = 2, R = diphenylmethyl
L8: *n* = 2, R = 1-adamantyl

Scheme 1. Chiral *N*,*N*′-dioxides used in the cycloaddition reaction.

Initially, the asymmetric 1,3-dipolar cycloaddition of diethyl 2-benzylidenemalonate (**1a**) and *C*,*N*-diphenylnitrone (**2a**) was catalyzed by *N*,*N*′-dioxide–metal complexes, which have shown high levels of enantiocontrol in many reactions.[15] The primary metal-screening was performed with **L1** and the results are listed in Table 1. The **L1**–$Mg(ClO_4)_2$ complex offered high activity and good diastereoselectivity but unsatisfactory enantioselectivity (Table 1, entry 1). Co-$(ClO_4)_2$·$6H_2O$ provided considerable enantioselectivity when it coordinated with **L1**, whereas the yield and diastereoselectivity were very low (Table 1, entry 2). However, the combination of *N*,*N*′-dioxide **L1** with $Ni(ClO_4)_2$·$6H_2O$ provided an efficient catalyst system to afford the desired product in 91% yield with 93:7 diastereomeric ratio (d.r.) and 92% enantiomeric excess (*ee*) (Table 1, entry 3). Encouraged by these results, we modified the complex with different nickel salts and found that the activity of the reaction was heavily dependent on the counterion. For example, $Ni(acac)_2$ or $NiCl_2$ did not promote the reaction at all (Table 1, entries 4 and 5), therefore, $Ni(ClO_4)_2$·$6H_2O$ was chosen as the pre-catalyst. Next, our attention was turned to the structure of the chiral *N*,*N*′-dioxide ligands (Scheme 1). Disappointingly, when bulky ligands **L2** (with a 2,6-diisopropylphenyl group) or **L3** (with a *tert*-butyl group) were utilized instead of the phenyl group on the amide moiety, the diastereoselectivity decreased drastically, whereas **L3** gave a good *ee* value but **L2** gave a low value and reversed enantioselectivity

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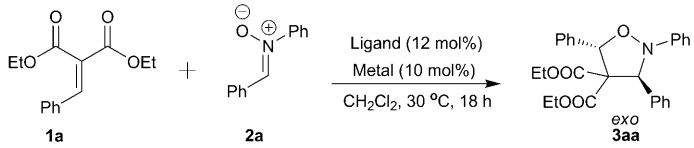
Table 1. Screening of metals and ligands for the catalytic asymmetric 1,3-dipolar cycloaddition of **2a** to **1a**.[a]



1a 2a 3aa

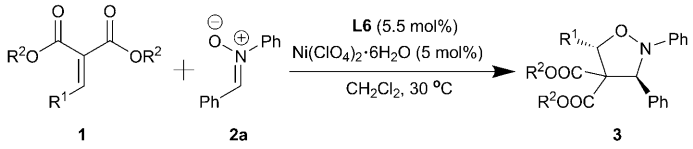
Entry	Ligand	Metal	Yield [%][b]	d.r.[c] (*exo*/*endo*)	*ee* [%][c,d] (*exo*)
1	**L1**	$Mg(ClO_4)_2$	98	94:6	58
2	**L1**	$Co(ClO_4)_2{\cdot}6H_2O$	22	58:42	81
3	**L1**	$Ni(ClO_4)_2{\cdot}6H_2O$	91	93:7	92
4	**L1**	$[Ni(acac)_2]$	n.r.[e]	–	–
5	**L1**	$NiCl_2$	n.r.[e]	–	–
6	**L2**	$Ni(ClO_4)_2{\cdot}6H_2O$	59	44:56	−29
7	**L3**	$Ni(ClO_4)_2{\cdot}6H_2O$	80	58:42	93
8	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	99	96:4	60
9	**L5**	$Ni(ClO_4)_2{\cdot}6H_2O$	53	48:52	−37
10	**L6**	$Ni(ClO_4)_2{\cdot}6H_2O$	98	94:6	99
11	**L7**	$Ni(ClO_4)_2{\cdot}6H_2O$	97	91:9	99
12	**L8**	$Ni(ClO_4)_2{\cdot}6H_2O$	90	77:23	98
13[f]	**L6**	$Ni(ClO_4)_2{\cdot}6H_2O$	94	93:7	99 (3*S*,5*S*)

[a] Reaction conditions: nitrone **2a** (29.6 mg, 0.15 mmol), *N*,*N*′-dioxide **L** (0.012 mmol), and metal (0.01 mmol) in CH_2Cl_2 (0.5 mL) were placed in a dry tube and stirred at 30 °C for 1.0 h, then dialkyl benzylidenemalonate **1a** (24.8 mg, 0.1 mmol) was added. [b] Yield of isolated product. [c] Determined by HPLC analysis; the absolute configuration was determined to be (3*S*, 5*S*) by comparison with the optical rotation values in the literature.[12g] [d] The *ee* value of *exo*-**3aa**. [e] No reaction. [f] $Ni(ClO_4)_2{\cdot}6H_2O$ (5 mol%) and **L6** (5.5 mol%) were used and the reaction was stirred for 45 h.

(Table 1, entries 6 and 7). However, the following ligand screening indicated that (*S*)-pipecolic acid was a superior skeleton than L-proline and **L6** was found to be the best chiral ligand for the cycloaddition reaction, which gave the product in 98% yield, with 94:6 d.r. and 99% *ee* (Table 1, entries 8–12). Notably, the amount of the **L6**–nickel(II) complex could be reduced to 5 mol% without any significant change in results (Table 1, entry 13). Therefore, the best results were achieved by using the **L6**–$Ni(ClO_4)_2{\cdot}6H_2O$ complex (5 mol%; molar ratio **L6**/$Ni(ClO_4)_2{\cdot}6H_2O$ (1.1:1.0)), nitrone (0.15 mmol), and alkylidiene malonate (0.1 mmol) in CH_2Cl_2 (0.5 mL) at 30 °C.

Under the optimal reaction conditions, the scope of the dipolarophiles was first examined for the catalytic asymmetric 1,3-dipolar cycloaddition reaction (Table 2). The ester group of the alkylidene malonates had a slight effect on the diastereo- and enantioselectivities (Table 2, entries 1–5). Even when R^2 was a bulky *t*Bu group, up to 99:1 d.r. and 99% *ee* could still be obtained, despite the decreased catalytic activity (Table 2, entry 4). Additionally, alkylidene malonates with either an electron-withdrawing or electron-donating substituent on the aromatic ring in the R^1 group could be converted to the corresponding isoxazolidine derivatives in good yields with up to 99:1 d.r. and up to 99% *ee* (Table 2, entries 6–11). It was notable that the system demonstrated good tolerance to fused-ring and heteroaromatic substrates (Table 2, entries 12 and 13). Additionally, cyclohexylmethylene malonate is also a suitable substrate for the cycloaddition reaction with high yield and enantioselectivity (Table 2, entry 14).

Table 2. Scope of alkylidene malonates in the catalytic asymmetric 1,3-dipolar cycloaddition with **2a**.[a]



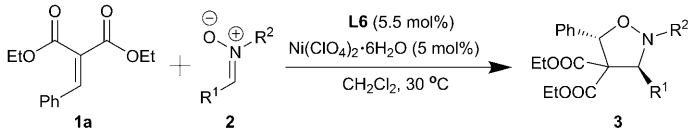
1 2a 3

Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	Ph	Et	**3aa**	45	94	93:7	99
2	Ph	Me	**3ba**	64	89	96:4	97
3	Ph	*i*Pr	**3ca**	70	86	97:3	99
4	Ph	*t*Bu	**3da**	94	72	99:1	99
5	Ph	Bn	**3ea**	20	83	99:1	95
6	$pNO_2C_6H_4$	Et	**3fa**	24	99	99:1	96
7	$pBrC_6H_4$	Et	**3ga**	24	91	98:2	97
8	$mClC_6H_4$	Et	**3ha**	45	86	95:5	99
9	$pClC_6H_4$	Et	**3ia**	48	94	97:3	98
10	$pMeOC_6H_4$	Et	**3ja**	80	86	96:4	97
11	$pMeC_6H_4$	Et	**3ka**	45	80	90:10	99
12	2-naphthyl	Et	**3la**	102	86	94:6	97
13	2-thienyl	Et	**3ma**	96	46	92:8	97
14	cyclohexyl	Et	**3na**	40	84	87:13	83

[a] Reaction conditions: nitrone **2a** (0.15 mmol), *N*,*N*′-dioxide **L6** (2.4 mg, 0.0055 mmol), and $Ni(ClO_4)_2{\cdot}6H_2O$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) were placed in a dry tube and stirred at 30 °C for 1.0 h, then alkyl benzylidenemalonate **1** (0.1 mmol) was added. [b] Yield of isolated product. [c] Determined by HPLC analysis.

Next, the scope of the nitrones was investigated (Table 3). When the substituent R^2 on the nitrogen atom was changed from a phenyl group to a methyl or a benzyl group, high enantio- and diastereocontrol were observed, but the yields decreased dramatically, even when the reaction time was prolonged to more than four days (Table 3, entries 1 and 2). However, the electronic character and the position of the

Table 3. Scope of nitrones in the catalytic asymmetric 1,3-dipolar cycloaddition with **1a**.[a]



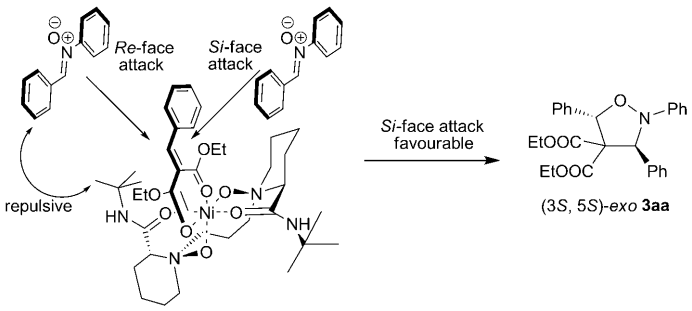
1a 2 3

Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	Ph	Me	**3ab**	104	54	>99:1	94
2	Ph	Bn	**3ac**	104	71	>99:1	97
3	$oNO_2C_6H_4$	Ph	**3ad**	48	80	99:1	99
4	$pBrC_6H_4$	Ph	**3ae**	48	83	95:5	98
5	pFC_6H_4	Ph	**3af**	48	96	97:3	98
6	$pMeOC_6H_4$	Ph	**3ag**	40	80	99:1	97
7	$pMeC_6H_4$	Ph	**3ah**	48	86	97:3	97
8	2-naphthyl	Ph	**3ai**	40	85	97:3	99

[a] Reaction conditions: nitrone **2** (0.15 mmol), *N*,*N*′-dioxide **L6** (2.4 mg, 0.0055 mmol), and $Ni(ClO_4)_2{\cdot}6H_2O$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) were placed in a dry tube and stirred at 30 °C for 1.0 h, then diethyl benzylidenemalonate **1a** (0.1 mmol) was added. [b] Yield of isolated product. [c] Determined by HPLC analysis.

substituent on the phenyl group in R^1 had no obvious effects on the activity, diastereo- and enantioselectivity, and various optically pure isoxazolidines could be achieved in good yields (Table 3, entries 3–7). Moreover, a fused-aromatic-ring-containing nitrone also exhibited excellent diastereo- and enantioselectivity in good yield (Table 3, entry 8).[16]

Based on the experiments and previous reports,[14c,15i] a possible transition state was proposed to elucidate the origin of the asymmetric stereoselectivity. As shown in Scheme 2,



Scheme 2. The possible transition state.

the tetradentate *N,N′*-dioxide **L6** and the bidentate alkylidene malonate **1a** coordinated with nickel(II) and formed an octahedral geometry. Then the 1,3-dipole could only attack at the *Si* face because the *Re*-face attack is unfavorable due to the steric hindrance between the *tert*-butyl group and the C-phenyl group of the nitrone (Scheme 2).

In brief, we have developed a catalytic asymmetric 1,3-dipolar cylcloaddition reaction of nitrones to alkylidene malonates, catalyzed by a chiral nickel(II)/*N,N′*-dioxide complex, which gives good yields, excellent diastero- and enantioselectivities (up to 98% yield, with 94:6 d.r., and 99% *ee*). A variety of nitrones and alkylidene malonates could be converted into the desired enantiomerically pure isoxazolidine derivatives using a 5 mol% catalyst loading. Moreover, the reaction was not sensitive to air or moisture and featured a simple procedure. A possible transition state has been proposed to explain the observed high enantioselectivities. Application of the catalyst system to other 1,3-dipoles and further investigation of the reaction mechanism are still in progress.

Experimental Section

Typical experimental procedure: Nitrone **2a** (29.6 mg, 0.15 mmol), *N,N′*-dioxide **L6** (2.4 mg, 0.0055 mmol), and $Ni(ClO_4)_2{\cdot}6H_2O$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) were placed in a dry tube and stirred at 30°C for 1 h. Next, diethyl benzylidenemalonate **1a** (24.8 mg, 0.1 mmol) was added and the process was monitored by TLC. After **1a** had disappeared, the reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 25:1) on silica gel to afford the desired product as a white solid in 94% yield, 93:7 d.r., and 99% *ee*.

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Keywords: asymmetric catalysis · cycloaddition · diastereoselectivity · enantioselectivity · nickel

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