

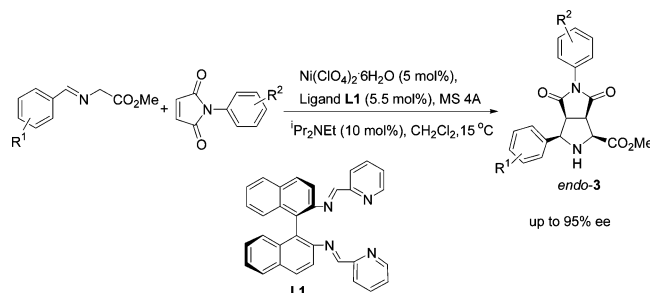
Axially Chiral BINIM and Ni(II)-Catalyzed Highly Enantioselective 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides and *N*-Arylmaleimides

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Axially chiral BINIM–Ni(II) complexes are effective catalysts in the asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides and *N*-arylmaleimides to give the corresponding adducts in good yields and up to 95% enantiomeric excesses.

The catalytic asymmetric 1,3-dipolar cycloaddition reaction is one of the most useful methods for the construction of optically active five-membered heterocycles.¹ More importantly, the reactions between azomethine ylides (from imines) and activated alkenes afforded tetrasubstituted pyrrolidine or proline derivatives in one step along with the four contiguous chiral centers.² Since it is well-known that pyrrolidine or proline

derivatives are the key units or building blocks in many pharmaceuticals, biologically active natural products including alkaloids, and organocatalysts in organic synthesis,³ a catalytic asymmetric version of this 1,3-dipolar cycloaddition reaction has attracted much attention and has developed rapidly during the past decade.⁴ Thus far, many laboratories have reported catalytic asymmetric [3+2] cycloadditions with azomethine ylides (from imines) by means of a variety of ligand–metal combinations.⁵ For example, the asymmetric cycloaddition reactions of imines derived from glycine with electron-deficient alkenes in the presence of chiral Zn(II)/Bu-box (up to 89% yield and 94% ee), Ag(I)/xylyl-FAP (up to 90% yield and 96% ee), Ag(I)-quinap (up to 92% yield and 96% ee), Ag(I)-N,P ligands (up to 98% yield and 98% ee), and Cu(II)-Fesulphos (up to 97% yield and 99% ee) have been reported by Jørgensen,^{5a,b} Zhang,^{5c,d} Schreiber,^{5e} Zhou,^{5f} and Carretero.^{5g} However, compared to other types of catalytic asymmetric 1,3-dipolar cycloadditions, the reaction catalyzed by chiral Ni(II) complexes is still in its infancy especially for those involving azomethine imines as 1,3-dipoles, which remains a great challenge for us to study its scope and limitations. Recently, Suga and his co-workers reported a chiral catalyst consisting of Ni(ClO₄)₂·6H₂O and chiral binaphthyldiimine (BINIM) ligand, indicating high levels of asymmetric induction in Diels–Alder reactions (up to 94% yield and 94% ee as well as >99% yield and 96% ee),^{6a,b} Michael additions between 2-silyloxyfurans and 3-alkenoyl-2-oxazolidinones (up to 95% yield and 97% ee),^{6c} and 1,3-dipolar cycloaddition of nitrones with 3-(2-alkenoyl)-2-thiazolidinethiones (up to 85% yield and 95% ee),^{7a,b} as well as fused azomethine imines and 3-acryloyl-2-oxazolidinone (up to 93% yield and 97% ee).⁸ We envisaged that this catalytic system might be useful in the 1,3-dipolar cycloaddition of *N*-metalated azomethine ylides with *N*-arylmaleimides. Our interests in developing the new chiral catalytic systems with axially chiral binaphthalenediamine (BINAM) and binaphthalenediimine

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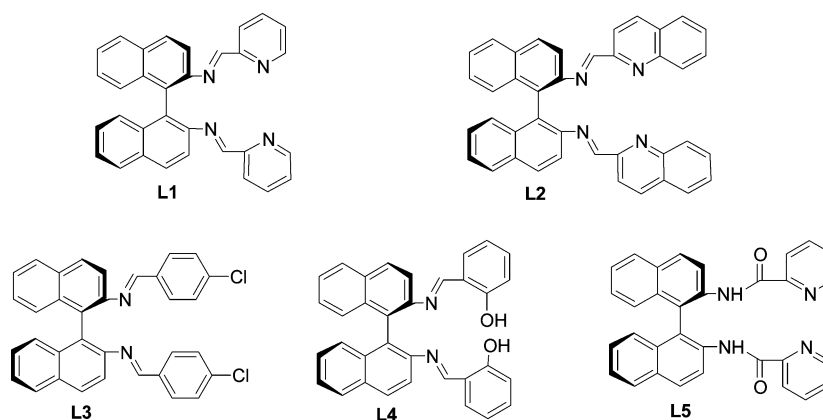
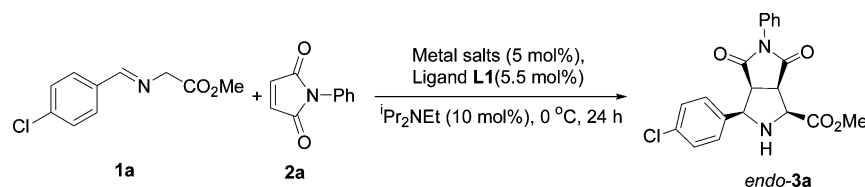


FIGURE 1. Structures of chiral ligands.

TABLE 1. Optimization of the Reaction Conditions in the 1,3-Dipolar Cycloaddition of Azomethine Ylides (from Imines) and *N*-Phenylmaleimide

entry	Lewis acid	solvent	yield (%) ^a	ee (%) ^b
1	CH ₃ CO ₂ Ag	CH ₂ Cl ₂	53	4
2	Cu(CH ₃ CN) ₄ ClO ₄	CH ₂ Cl ₂	41	2
3	Mg(ClO ₄) ₂	CH ₂ Cl ₂	22	9
4	Zn(OTf) ₂	CH ₂ Cl ₂		
5	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	78	79
6	Ni(ClO ₄) ₂ ·6H ₂ O	THF	66	78
7	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₃ CN	30	8
8	Ni(ClO ₄) ₂ ·6H ₂ O	toluene	trace	

^a Isolated yields. ^b Determined by chiral HPLC.

(BINIM),^{9,4f} which can be easily prepared and handled in very simple experimental procedures, for 1,3-dipolar cycloadditions led us to undertake the current study. Herein we wish to report our investigations on this subject.

The chiral binaphthalenediimine (BINIM) ligands **L1**–**L3** were synthesized from the reaction of commercially available (*R*)-1,1'-binaphthyl-2,2'-diamine (binaphthalenediamine, BINAM) with a variety of aldehydes in the presence of 4 Å MS in toluene, respectively.^{8,10} The ligands **L4**¹¹ and **L5**¹² were also prepared from BINAM according to the previous literature (Figure 1).

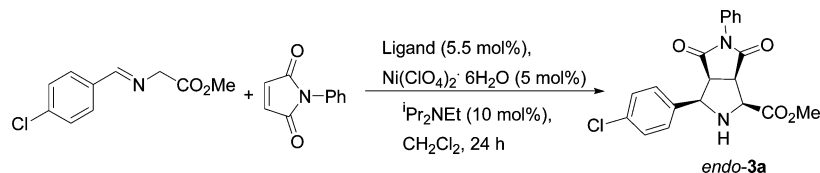
Initial examinations with imine **1a** and *N*-phenylmaleimide **2a** as the substrates in the presence of chiral BINIM ligand **L1** (5.5 mol %), *i*Pr₂NEt (10 mol %), and various metal salts (5 mol %) at 0 °C were aimed at determining the optimal conditions and the results of these experiments are summarized in Table 1. As expected, Ni(ClO₄)₂·6H₂O was found to be a fairly effective catalyst to promote 1,3-dipolar cycloaddition of imine **1a** and *N*-phenylmaleimide **2a**, affording the correspond-

ing adduct *endo*-**3a** in 78% yield and 79% ee in CH₂Cl₂ (Table 1, entry 5). Other metal salts, such as CH₃CO₂Ag or Cu(CH₃CN)₄ClO₄ and Mg(ClO₄)₂ (5 mol %), produced *endo*-**3a** in moderate yields and lower enantioselectivities under the standard conditions (Table 1, entries 1–3). No reaction occurred if using Zn(OTf)₂ as a Lewis acid under otherwise identical conditions (Table 1, entry 4). Among the solvents examined, in CH₃CN, a more polar solvent, *endo*-**3a**, was formed in 30% yield along with 8% ee, and when using toluene as the solvent, a trace of *endo*-**3a** was observed (Table 1, entries 7 and 8). Although *endo*-**3a** could be produced in comparable enantioselectivity (78% ee) in THF, the isolated yield slightly decreased (Table 1, entry 6). Therefore, Ni(ClO₄)₂·6H₂O is the most effective Lewis acid and dichloromethane is the solvent of choice in this reaction.

Having the partially optimized reaction conditions in hand, we next carefully examined the temperature effect on this reaction. No significant improvement could be realized at –20 °C or under reflux in CH₂Cl₂ at 40 °C (Table 2, entries 1 and 4). However, to our delight, raising the temperature to 15 °C improved the yield of **3a** to 84% along with 82% ee (Table 2, entry 2).

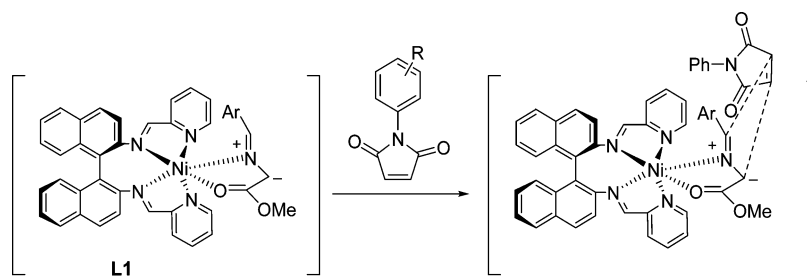
To better understand the nature of the catalytic system and to propose a possible transition state for the reaction, a few experiments for comparison with the performance of the ligands **L2**–**L5** were carried out under the standard conditions. The

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TABLE 2. Optimization of the Reaction Conditions in the 1,3-Dipolar Cycloaddition of Azomethine Ylides (from Imines) and *N*-Phenylmaleimide

entry	ligand	temp (°C)	yield (%) ^a	ee (%) ^b
1 ^c	L1	40	72	75
2	L1	15	84	82
3	L1	0	78	79
4	L1	−20	67	56
5	L2	0	20	8
6	L3	0	45	2
7	L4	0	trace	
8	L5	0	trace	

^a Isolated yields. ^b Determined by chiral HPLC. ^c Reaction time is 2 h.

**FIGURE 2.** Proposed mechanism for the enantioselectivity.

results are summarized in Table 2 (entries 5–8). As can be seen from Table 2, the strong interaction of the nitrogen atoms in imine moiety and pyridine seems to be very important in the assembly of chiral ligand with nickel cation. For those ligands without imine or pyridine structure, **3a** could not be obtained in satisfactory yields and enantioselectivities (Table 2, entries 6–8). However, to our surprise, BINIM ligand **L2** bearing two quinoline moieties also did not effectively catalyze the 1,3-dipolar cycloaddition to give **3a** in only 20% yield along with 8% ee presumably due to the steric hindrance, which blocks out the approach of *N*-phenylmaleimide (Table 2, entry 5). Therefore, the best reaction conditions is to carry out the reaction with $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ as a metal salt and **L1** as a chiral ligand in CH_2Cl_2 at 15 °C. The possible transition state of this highly enantioselective 1,3-dipolar addition can be explained as the approach of *N*-phenylmaleimide toward the hexacoordinated Ni(II) complex as illustrated in Figure 2.¹⁰

The generality of this $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}/\text{L1}$ -catalyzed enantioselective 1,3-dipolar cycloaddition reaction was examined by using a variety of imines and several *N*-arylmaleimides. The results are summarized in Table 3. All reactions proceeded smoothly to give the corresponding products **3** in moderate to good yields and good to high enantioselectivities under the optimal conditions (Table 3). As for imine **1** bearing an electron-donating methoxy group on the benzene ring, the corresponding 1,3-dipolar cycloaddition adduct **3c** was obtained in 52% yield and 72% ee (Table 3, entry 3). Higher enantioselectivity was obtained in the reaction of imine **1j**, derived from 1-naphthaldehyde, with **2a** to afford the adduct **3j** in 90% yield and up to 95% ee (Table 3, entry 10). In other cases, 1,3-dipolar cycloaddition adducts **3** were formed in good yields and 82–

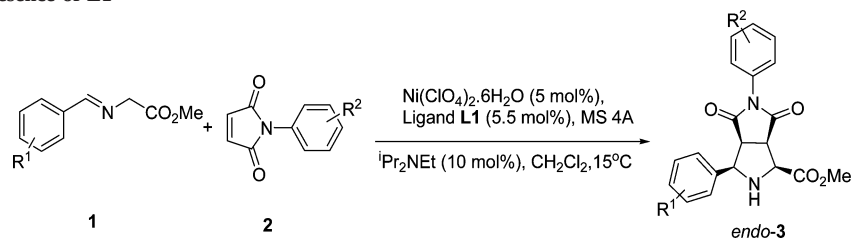
91% ee values (Table 3, entries 1, 2, and 4–9). By using other *N*-arylmaleimides as the substrates, the corresponding 1,3-dipolar cycloaddition adducts **3k–n** were obtained in 73–83% yields and 84–90% ee values (Table 3, entries 11–14).

In conclusion, chiral binaphthalenediimine (BINIM) ligand **L1**, which can be readily prepared from commercially available (*R*)-1,1'-binaphthyl-2,2'-diamine (BINAM) and 2-pyridinecarboxaldehyde, has been found to be an effective chiral ligand for Ni(II)-promoted 1,3-dipolar cycloaddition of azomethine ylides and *N*-arylmaleimides to give the corresponding adducts in good to high yields and enantioselectivities. These results will allow us to design and synthesize a new effective chiral catalytic system for this interesting asymmetric 1,3-dipolar cycloaddition reaction. Further investigations to explore other diploes as well as azomethine ylides and dipolarophiles are currently underway.

Experimental Section

Typical Reaction Procedure. The catalyst was prepared by stirring $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (5.5 mg, 0.015 mmol, 5 mol %), powdered 4 Å MS (100 mg), and ligand **L1** (7.6 mg, 0.0165 mmol, 5.5 mol %) in CH_2Cl_2 (2.0 mL) for 1 h at room temperature. After imine substrate **1** (0.30 mmol), *N*-phenylmaleimide **2** (0.45 mmol, 1.5 equiv),¹³ and *i*Pr₂NEt (0.03 mmol, 5.0 μL, 10 mol %) were added subsequently to the catalyst suspension, the resulting mixture was stirred at 15 °C for 24 h. When the reaction was complete as monitored by TLC plates, and the corresponding crude adduct was purified by column chromatography on silica gel [petroleum ether/

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TABLE 3. Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides (from Imines) and *N*-Arylmaleimides Catalyzed by $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in the Presence of **L1**

entry	R ¹	R ²	product	yield (%) ^a	ee (%) ^b
1	<i>p</i> -Cl (1a)	H (2a)	3a	84	82
2	<i>p</i> -Br (1b)	H (2a)	3b	86	89
3	<i>p</i> -MeO (1c)	H (2a)	3c	52	72
4	<i>p</i> -Me (1d)	H (2a)	3d	84	84
5	<i>o</i> -Cl (1e)	H (2a)	3e	92	91
6	H (1f)	H (2a)	3f	81	87
7	<i>m</i> -Br (1g)	H (2a)	3g	80	82
8	<i>p</i> -F (1h)	H (2a)	3h	78	84
9	<i>o</i> -Br (1i)	H (2a)	3i	82	85
10	1-naphthyl (1j)	H (2a)	3j	90	95
11	1-naphthyl (1j)	<i>p</i> -Me (2b)	3k	75	88
12	1-naphthyl (1j)	<i>m</i> -Cl (2c)	3l	73	84
13	1-naphthyl (1j)	<i>p</i> -MeO (2d)	3m	82	90
14	1-naphthyl (1j)	<i>p</i> -F (2e)	3n	83	86

^a Isolated yields. ^b Determined by chiral HPLC.

ethyl acetate (1% of triethylamine) = 2:1] to give the pure product. Since a trace of *exo*-adducts might be included in the products, in some cases the ¹³C NMR spectra are not very clean.

General Procedure for the Synthesis of α -Imino Esters.^{4f} To a suspension of the corresponding amino acid ester hydrochloride (23.9 mmol) and anhydrous MgSO_4 (25.0 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (3.4 mL, 23.9 mmol). The mixture was stirred at room temperature for 1 h, then the corresponding aldehyde (20.0 mmol) was added. The reaction was stirred at room temperature overnight, and then the resulting precipitate was removed by filtration. The filtrate was washed with water (15 mL), the aqueous phase was extracted with CH_2Cl_2 (10 mL), and the combined organic phases were washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The resulting

pure imino esters were directly used in 1,3-dipolar cycloadditions without further purification.

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Supporting Information Available: The 1,3-dipolar cycloaddition procedures, spectroscopic data of adducts **3**, and chiral HPLC traces of the enantiomeric excesses of adducts **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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