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Highly Enantioselective and Diastereoselective 1,3-Dipolar Cycloaddition Reactions between Azomethine Imines and 3-Acryloyl-2-oxazolidinone Catalyzed by Binaphthyldiimine–Ni(II) Complexes

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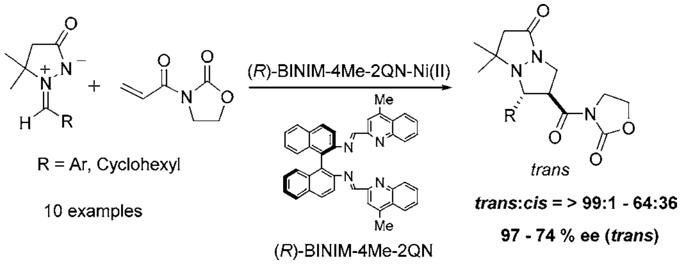
ABSTRACT



We have found the first example of high levels of asymmetric induction (97–74% ee) along with high diastereoselectivity (>99:1–64:36) in dipole-HOMO-/dipolarophile-LUMO-controlled asymmetric 1,3-dipolar cycloaddition reactions between fused azomethine imines and 3-acryloyl-2-oxazolidinone using a chiral BINIM–Ni(II) complex as a chiral Lewis acid catalyst.

Catalytic asymmetric cycloadditions of 1,3-dipoles to olefins have been utilized to prepare optically active five-membered heterocyclic ring systems that can contain up to four asymmetric centers and, therefore, are indispensable for the syntheses of biologically important heterocyclic compounds.[1] During the past decade, highly enantioselective 1,3-dipolar cycloaddition reactions catalyzed by chiral Lewis acids have been developed for several 1,3-dipoles, such as nitrones,[2,3] nitrile oxides,[4] nitrile imines,[5] diazoalkanes,[6] and carbonyl ylids.[7] In contrast, catalytic asymmetric [3+2] cycloadditions of azomethine imines, which can afford medicinally important pyrazolidines[8] and pyrazolines, have not received as much attention; only a few examples of catalytic asymmetric cycloadditions of azomethine imines and related compounds are available. Recently, Fu reported the highly enantioselective [3+2] cycloaddition between azomethine imines

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(1) For recent reviews, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(2) For representative examples: (a) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (d) Simonsen, K. B.; Rita, P. B.; Hazell, G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845. (e) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001. (f) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227. (g) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017. (h) Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327. (i) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (j) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431.

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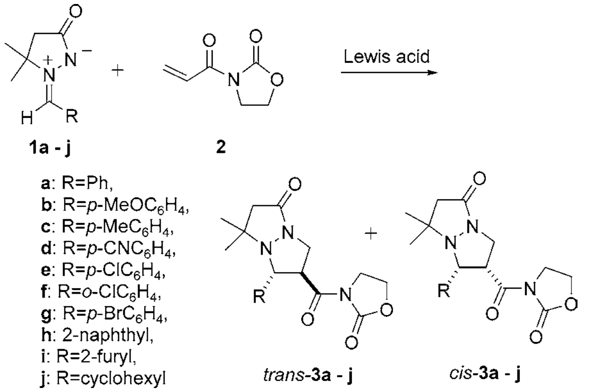
and copper acetylides using a chiral phosphaferrocene−oxazoline ligand.[9] Kobayashi reported the asymmetric [3+2] cycloaddition between hydrazones and electron-rich olefins in the presence of a chiral zirconium catalyst; the reaction presumably involves a Zr-associated azomethine imine species.[10] However, chiral Lewis acid catalyzed asymmetric 1,3-dipolar cycloaddition reactions of azomethine imines with electron-deficient olefins by dipole-HOMO/dipolarophile-LUMO interactions have yet to be reported.[11] In this communication, we describe our success using the binaphthyldiimine−Ni(II) complex to not only obtain high levels of enantioselectivity but also control the diastereoselectivity in the reactions of fused azomethine imines with 3-acryloyl-2-oxazolidinone.

Initially, the catalyzed reactions of azomethine imine **1a** with 3-acryloyl-2-oxazolidinone (**2**) were carried out using several achiral Lewis acids (10 mol %) in the presence of 4 Å molecular sieves (MS 4 Å) at 25 °C in CH_2Cl_2 (Scheme 1).[12] Results show that the trans selectivities and rate accelerations were influenced by the type of the Lewis acids. Surprisingly, the use of $Ni(ClO_4)_2\cdot 6H_2O$ as the Lewis acid exhibited high trans selectivity (98:2), along with good rate acceleration.[12] On the basis of these encouraging results, we proposed to use a chiral catalyst consisting of $Ni(ClO_4)_2\cdot 6H_2O$ and chiral binaphthyldiimine (BINIM) ligands, which has shown high levels of asymmetric induction in Diels−Alder reactions,[13a,b] cycloadditions of nitrones,[2h,j] and Michael additions of silyloxyfurans.[13c] The (*R*)-BINIM ligands (Figure 1) and $Ni(ClO_4)_2\cdot 6H_2O$ were combined in the presence of MS 4 Å in CH_2Cl_2 for 6 h to afford the catalysts (10 mol %), which were utilized for the reactions between **1a** and **2** at room temperature (Table 1, entries 1−5). Among the catalysts, the quinoline-based BINIMs exhibited favorable enantioselectivity; additionally, those also exhibited good diastereoselectivity (entries 4 and 5).[14] The use of BINIM-4Me-2QN as the ligand, in conjuction with $CHCl_3$ as the solvent, provided the highest enantioselectivity (97% ee, Table 2, entry 7). As a note, the use of $Ni(BF_4)_2\cdot 6H_2O$ instead of $Ni(ClO_4)_2\cdot 6H_2O$ for the preparation of the catalyst also resulted in extremely high enantio- and diastereoselectivity (entry 8).

Scheme 1. Cycloaddition Reactions of Azomethine Imines **1** with 3-Acryloyl-2-oxazolidinone (**2**)



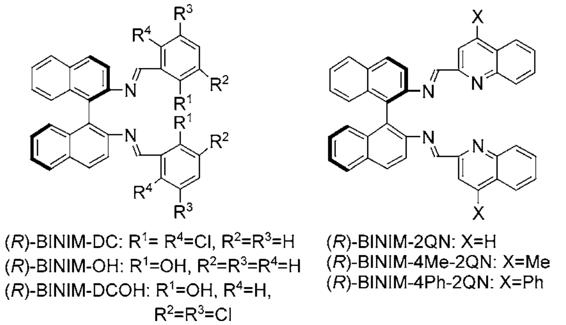


Figure 1. Structures of (*R*)-BINIM ligands.

Table 1. Asymmetric Cycloaddition Reaction of Azomethine Imine **1a** with 3-Acryloyl-2-oxazolidinone (**2**) Catalyzed by (*R*)-BINIM−Ni(II) Complexes[a]

entry	ligand	solvent	time (h)	yield (%)	dr[b]	ee[c] (%)
1	BINIM-DC	CH_2Cl_2	60	92	98:2	23
2	BINIM-OH[d]	CH_2Cl_2	285	57	72:28	−9
3	BINIM-DCOH	CH_2Cl_2	159	78	89:11	−8
4	BINIM-4Me-2QN	CH_2Cl_2	74	90	85:15	88
5	BINIM-4Ph-2QN	CH_2Cl_2	79	93	84:16	85
6	BINIM-2QN	$CHCl_3$	50	94	91:9	93
7	BINIM-4Me-2QN	$CHCl_3$	39	93	89:11	97
8[e]	BINIM-4Me-2QN	$CHCl_3$	62	93	93:7	97

[a] The reaction was carried out with a 0.5 mmol scale (**1a**/**2** = 1:1) in the presence of the Ni(II) complex (10 mol %), which was prepared from (*R*)-BINIM, $Ni(ClO_4)_2\cdot 6H_2O$, and MS 4 Å, at room temperature. [b] Trans/cis ratio determined by ^1H NMR (400 MHz). [c] Enantiomeric excess of the trans-adduct determined by chiral HPLC (CHIRALPAK IA). [d] (*S*)-BINIM-OH was used. [e] $Ni(BF_4)_2\cdot 6H_2O$ was used instead of $Ni(ClO_4)_2\cdot 6H_2O$.

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(3) For reactions with α,β-unsaturated aldehydes, see: (a) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968. (b) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457. (c) Shirahase, M.; Kamenasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675. (d) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716. (e) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926.

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(8) For synthetic utilities of chiral pyrazolidines as building blocks, see: Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974. Also see ref 10a.

(9) (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (b) Suárez, A.; Downey, W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244.

Table 2. Asymmetric Cycloaddition Reactions of Azomethine Imines **1b**−**j** with 3-Acryloyl-2-oxazolidinone (**2**) Catalyzed by the (*R*)-BINIM-4Me-2QN−Ni(II) Complex[a]

entry	R (**1**)	time (h)	yield (%)	dr[b]	ee[c] (%)
1	*p*-MeOC$_6$H$_4$ (**1b**)	336	47 (27)[d]	70:30	75 (44)[i]
2	*p*-MeOC$_6$H$_4$ (**1b**)	35[f]	98	80:20	90 (89)[i]
3	*p*-MeC$_6$H$_4$ (**1c**)	136	99	91:9	93
4	*p*-MeC$_6$H$_4$ (**1c**)	14[f]	96	95:5	88
5	*p*-CNC$_6$H$_4$ (**1d**)	57	96	97:3[e]	92
6	*p*-ClC$_6$H$_4$ (**1e**)	59	quant	91:9	95
7	*o*-ClC$_6$H$_4$ (**1f**)	254	63	>99:1	93
8	*o*-ClC$_6$H$_4$ (**1f**)	48[f]	74	>99:1	72
9	*p*-BrC$_6$H$_4$ (**1g**)	140	81	93:7[e]	92
10	*p*-BrC$_6$H$_4$ (**1g**)	24[g]	95	93:7[e]	94
11	2-naphthyl (**1h**)	48	quant	93:7[e]	96
12	2-furyl (**1i**)	72[g,h]	83	64:36[e]	95 (79)[i]
13	cyclohexyl (**1j**)	96[f,h]	41	82:18[e]	74 (8)[i]

[a] The reaction was carried out with a 0.5 mmol scale (**1**/**2** = 1:1) in the presence of the (*R*)-BINIM-4Me-2QN−Ni(II) complex (10 mol %) at room temperature. [b] Trans/cis ratio determined by ^{1}H NMR (400 MHz). [c] Enantiomeric excess of the trans-adduct determined by chiral HPLC (CHIRALPAK IA). [d] Recovery of **2**. [e] Determined by HPLC. [f] The reaction was carried out at 50 °C. [g] The reaction was carried out at 40 °C. [h] Ni(BF$_4$)$_2$•6H$_2$O was used. [i] Enantiomeric excess of the cis-adduct.

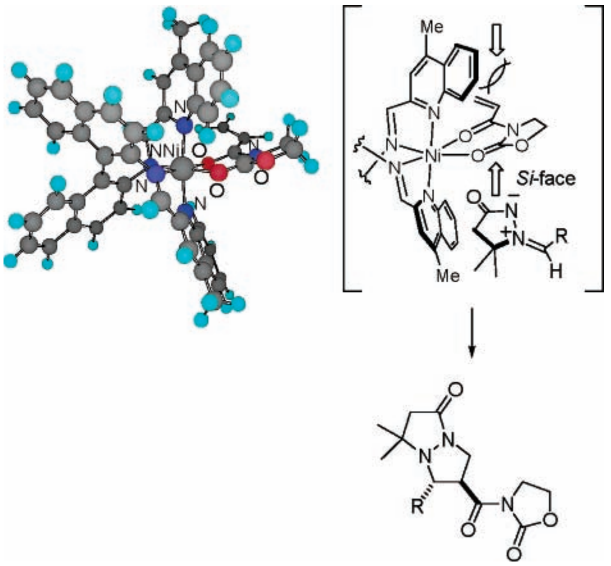
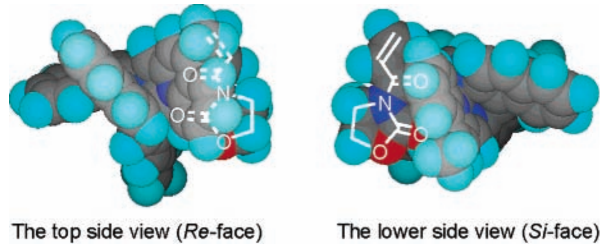


Figure 2. Proposed mechanism for enantioselectivity.

Consequently, reactions between *C*-aryl azomethine imines **1b**−**g** and oxazolidinone **2** were carried out under the optimized conditions featuring (*R*)-BINIM-4Me-2QN (Table 2). In all cases, high levels of enantio- and trans selectivities were obtained; apparently, the reactions are independent of the electronic character of the benzene ring substituents (entries 2−7, 9, and 10). Increasing the reaction temperature to 40 or 50 °C resulted in mostly favorable selectivities but with significantly shorter reaction times (entries 2, 4, 8, and 10). It is interesting to note that the enantio- and diastereoselectivity dramatically improved upon increasing the reaction temperature in the case of **1b** (entry 2), whereas the enantioselectivity decreased in the case of **1f** (entry 8). Reactions of **1c** or **1g** at higher temperature showed almost parallel or slightly lower enantio- and diastereoselectivities (entries 4 and 10). A reason for this difference between azomethine imines is not clear at this point, but enhancing the ligand exchange rate of the Ni(II) complex between **1** and **2** by increasing the reaction temperature may be important in the cases exhibiting higher selectivity (see also Supporting Information for an ^{1}H NMR study).[15] Although the reaction of *C*-cyclohexyl-azomethine imine **1j** resulted in a moderate yield with a slight decrease in enantioselectivity, the cycloadditions of naphthyl- (**1h**) and heteroaryl azomethine imines (**1i**) afforded extremely high enantioselectivities (entries 11−13). Unfortunately, the other 3-(2-alkenoyl)-2-oxazolidinones such as 3-crotonoyl-2-oxazolidinone did not react under similar conditions at 50 °C.

The high enantioselectivity of the cycloaddition reactions can be explained as the approach of the azomethine imines toward the hexacoordinated Ni(II) complex, as illustrated in Figure 2 (see also Supporting Information).[13b,16] In the proposed mechanism, during the transition state, the 4-methylquinoline moiety of the Ni(II) complex efficiently shields the *re* face of oxazolidinone **2** (Figure 3). The trans selectivity is presumably attributable to the increased secondary orbital interactions between the empty N orbital of the azomethine imines and oxazolidinone **2**, when a Lewis acid coordinates to the dipolarophile.



The top side view (*Re*-face) The lower side view (*Si*-face)

Figure 3. Space-filling model of the (*R*)-BINIM-4Me-2QN−Ni(II)-3-acryloyl-2-oxazolidinone complex.

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(10) (a) Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, J. *J. Am. Chem. Soc.* **2002**, *124*, 13678. (b) Kobayashi, S.; Yamashita, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11279.

(11) During the preparation of this manuscript, a related paper using chiral organocatalysts has been reported. See: Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818.

(12) Lewis acid, reaction time, trans/cis ratio, and yield were shown in order: TiCl$_4$, 240 h, 62:38, 14%; Et$_2$AlCl, 240 h, 58:42, 8%; Zn(OTf)$_2$, 240 h, 71:29, 26%; Yb(OTf)$_3$, 192 h, 89:11, 88%; Mg(OTf)$_2$, 264 h, 96:4, 90%; Co(ClO$_4$)$_2$•6H$_2$O, 90 h, 91:1, 98%; Ni(ClO$_4$)$_2$•6H$_2$O, 21 h, 98:2, 95%. Without Lewis acid, reflux in CHCl$_3$ for 24 h, 49:51, 52%.

(13) (a) Suga, H.; Kakehi, A.; Mitsuda, M. *Chem. Lett.* **2002**, 900. (b) Suga, H.; Kakehi, A.; Mitsuda, M. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 561. (c) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414.

(14) It is noteworthy that a 5,5-dimethyl moiety played an important role for high enantioselectivity. The reaction of 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide under conditions similar to entry 4 gave a trans-adduct selectively (trans/cis = 93:7) with only 35% ee (yield of 86%).

In conclusion, high enantioselectivity was obtained in the dipole-HOMO/dipolarophile-LUMO-controlled asymmetric 1,3-dipolar cycloaddition reactions of azomethine imines using a BINIM−Ni(II) complex as a chiral Lewis acid catalyst. To the best of our knowledge, this is the first example of such cycloaddition reactions. Studies to expand this methodology to other dipoles as well as other azomethine imines and dipolarophiles are currently underway.

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Supporting Information Available: Representative experimental procedures, spectroscopic data of the products, and mechanistic consideration for enantioselectivity are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Although the reaction proceeded smoothly, the ^{1}H NMR study indicated that the Ni(II) complex mainly coordinated to **1a** rather than to **2**.

(16) The structure of the complex was optimized by PM3 calculations (Spartan 04).