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Highly *Exo*-Selective and Enantioselective Cycloaddition Reactions of Nitrones Catalyzed by a Chiral Binaphthyldiimine–Ni(II) Complex

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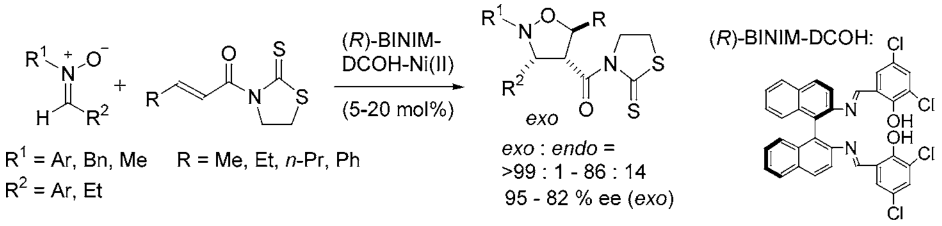
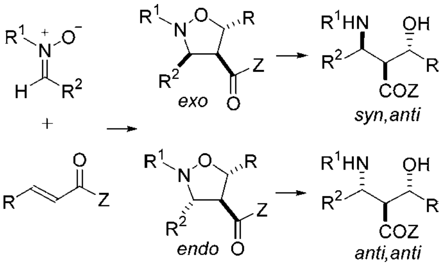
ABSTRACT



Significant levels of *exo*-selectivity (*exo*:*endo* = >99:1 to 86:14) and enantioselectivity (95–82% ee) were obtained in the 1,3-dipolar cycloadditions of a number of nitrones with 3-(2-alkenoyl)-2-thiazolidinethiones, using the chiral binaphthyldiimine–Ni(II) complex (5–20 mol %), which was easily prepared form *N*,*N*′-bis(3,5-dichrolo-2-hydroxybenzylidene)-1,1′-binaphthyl-2,2′-diamine and Ni(ClO_4)$_2$·6H_2O in $CHCl_3$ in the presence of 4 Å molecular sieves, as a chiral Lewis acid catalyst.

Asymmetric 1,3-dipolar cycloaddition reactions between nitrones and alkenes are among the most efficient methods for the construction of optically active isoxazolidines, which are readily converted to synthetically useful chiral γ-amino alcohols (Scheme 1).[1] Recently, a number of chiral Lewis acids have been shown to possess high enantioselectivity in the reactions of nitrones with electron-rich and -deficient olefins.[1a−d] For the reactions of electron-deficient alkenes, 3-(2-alkenoyl)-2-oxazolidinones often have been employed as the dipolarophiles to yield, in most cases, the *endo*-cycloadducts with high enantioselectivity.[2,3] On the other hand, the efficient synthesis of enantiomerically pure γ-amino alcohols having a *syn,anti* diastereomeric structure via nitrone cycloaddition reactions would require a chiral Lewis acid that favors the *exo*-selective and enantioselective cycloadditions (Scheme 1). For example, a formal synthesis of thienamycin and a key intermediate synthesis of carbapenems with the enantiomerically pure *syn*,*anti*-γ-amino alcohols, which were obtained from the cycloaddition reactions of

Scheme 1. Stereoselective Synthesis of Chiral γ-Amino Alcohols



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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 Commun.* **2000**, 1449. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (d) Frederickson, M. *Tetrahedron* **1997**, 53, 403. (e) *1,3-Dipolar Cycloaddition Chemistry*; General heterocyclic chemistry series; Padwa, A., Ed.; John Wiley and Sons: New York, 1984; Vol. 2, pp 83−168.

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nitrones attached to a chiral auxiliary with crotonate ester, were reported.[4] To date, however, only a few examples of the *exo*-selective cycloadditions of nitrones with 2-alkenoic acid derivatives in the presence of a chiral Lewis acid have been reported.[5] More recently, Sibi has reported on highly *exo*-selective cycloadditions that also possess high enantioselectivity using the chiral relay in reactions with 2-(2-alkenoyl)-3-pyrazolidinones as the dipolarophiles.[5f] This procedure, however, remains problematic in terms of the catalyst loading (30−50 mol %) and the generality of nitrones. In this Letter, we report on a facile methodology for the highly *exo*-selective and enantioselective cycloaddition reactions between various nitrones and 3-(2-alkenoyl)-2-thiazolidinethiones in the presence of a chiral binaphthyldiimine (BINIM)−Ni(II) complex[5e,6] (5−20 mol %) as the Lewis acid catalyst.

On the basis of our previous investigations of the stereoselectivity of cycloaddition reactions between nitrones and 3-crotonoyl-2-oxazolidinone catalyzed by BINIM−Ni(II) complexes,[5e] cycloaddition reactions between *N*-benzylideneaniline *N*-oxide (**1a**) and 3-crotonoyl-2-thiazolidinethione (**2a**) in the presence of BINIM−Ni(II) complexes (10 mol %) were initially examined (Scheme 2 and Table 1). These complexes were prepared from several BINIM ligands (see Figure 1) and Ni(ClO$_4$)$_2$·6H$_2$O in the presence of 4 Å molecular sieves (MS 4A). Surprisingly, for almost all BINIM ligands that were tested, the *exo*-cycloadduct was preferably obtained when thiazolidinethione **2a** was used as a dipolarophile. Although the *exo*-selectivities were unsatisfactory, quinoline-based BINIM−Ni(II) catalysts showed high enantioselectivities toward the *exo*-cycloadducts (entries 2−4). Interestingly, when 2-hydroxybenzylideneamine-type ligands were used in combination with **2a** as a dipolarophile, high *exo*-selectivities were observed (entries 5−8). Furthermore, the use of BINIM-DCOH or BINIM-DBOH indicated promising levels of asymmetric induction with extremely high *exo*-selectivities (entries 7 and 8). For the BINIM-DCOH−Ni(II)-catalyzed reactions, a survey of the reaction solvents (entries 9−11) revealed that CHCl$_3$ provided the most favorable results in terms of *exo*-selectivity (>99:1) and enantioselectivity (93% ee) (entry 11).

Scheme 2. Asymmetric Cycloadditions between Nitrones and 3-Alkenoyl-2-thiazolidinethiones Catalyzed by Chiral BINIM−Ni(II) Complexes

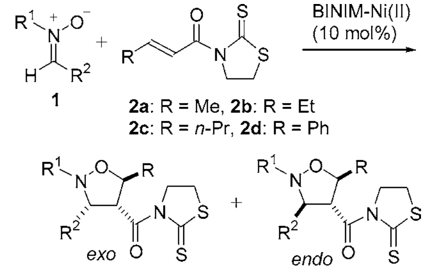

Table 1. BINIM−Ni(II)-Catalyzed Enantioselective Cycloadditions of Nitrone **1a** with 3-Crotonoyl-2-thiazolinethione (**2a**)[a]

entry	BINIM	solvent	time (h)	yield (%)	*exo*:*endo*[b]	ee[c] (%)
1	(*R*)-BINIM-DC	CH$_2$Cl$_2$	24	59	62:38	−31
2	(*R*)-BINIM-2QN	CH$_2$Cl$_2$	80	83	58:42	89
3	(*R*)-BINIM-4Me-2QN	CH$_2$Cl$_2$	64	66	72:28	91
4	(*R*)-BINIM-4Ph-2QN	CH$_2$Cl$_2$	72	86	59:41	90
5	(*S*)-BINIM-OH	CH$_2$Cl$_2$	115	26	97:3	−25
6	(*R*)-BINIM-5ClOH	CH$_2$Cl$_2$	20	40	98:2	−29
7	(*R*)-BINIM-DBOH	CH$_2$Cl$_2$	30	77	97:3	88
8	(*R*)-BINIM-DCOH	CH$_2$Cl$_2$	15	93	98:2	90
9	(*R*)-BINIM-DCOH	THF	48	77	91:9	74
10	(*R*)-BINIM-DCOH	Toluene	40	90	98:2	83
11	(*R*)-BINIM-DCOH	CHCl$_3$	15	87	>99:1	93

[a] The reaction was carried out in the presence of BINIM−Ni(II) catalyst (10 mol %), which was prepared by mixing BINIM, Ni(ClO$_4$)$_2$·6H$_2$O, and MS 4A in the corresponding solvent, at room temperature. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess (ee) of the *exo*-adduct was determined by HPLC.

The optimized conditions with (*R*)-BINIM-DCOH were subsequently applied to reactions between various nitrones and 3-crotonoyl-2-thiazolidinethione (**2a**) (Scheme 2 and Table 2). Regardless of the electron-donating or -attracting character of the *p*-substituents on the *N*-benzene ring, high *exo*-selectivities (93:7 − >99:1) and high enantioselectivities (88−95% ee) were observed in the reactions of several *C*-phenyl-*N*-*p*-substituted phenyl nitrones (**1b**−**e**, entries 2−4 and 6). It should be noted that the reactions of nitrones **1a** and **1d** with **2a** in the presence of 5 mol % of the (*R*)-BINIM-DCOH−Ni(II) complex afforded the products in good yields with extremely high *exo*-selectivities and enantioselectivities (entries 1 and 5).[7] The cycloaddition reactions of *C*-*p*-substituted phenyl-*N*-phenyl nitrones **1f**−**h** and *C*,*N*-bis(*p*-chlorophenyl)nitrone **1i** with **2a** in the presence of (*R*)-BINIM-DCOH−Ni(II) complex (10 mol %) also showed

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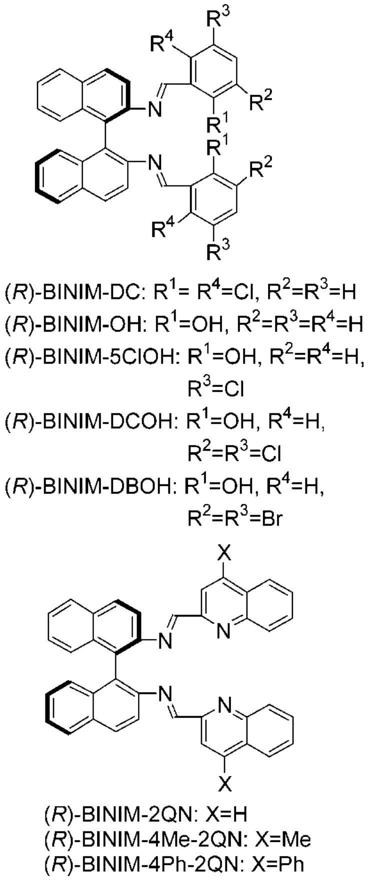


Figure 1. Structures of chiral binaphthyldiimine ligands.

satisfactory results in terms of *exo*-selectivities (98:2 − >99:1) and enantioselectivities (92−95% ee) (entries 7−10), and were independent of the electronic character of the *p*-substituents of the *C*-benzene ring.

It is noteworthy that the catalytic activities of (*R*)-BINIM-DCOH−Ni(II) catalyst can be extended to *N*-alkyl nitrones **1j** and **1k** and *C*,*N*-dialkyl nitrone **1*l*** with good *exo*-selectivities and enantioselectivities (entries 11, 12, and 13). This chiral Ni(II) catalytic system was also applicable to 1,3-dipolar cycloaddition reactions of several nitrones with 3-(2-pentenoyl)- (**2b**), 3-(2-hexenoyl)- (**2c**), and 3-cinnamoyl-2-thiazolidinethione (**2d**) with satisfactory *exo*-selectivities and enantioselectivities (entries 14−22). Although 20 mol % catalyst was needed in the cases of the reactions of nitrone **1l** with olefin **2a** and nitrone **1a** with olefin **2d** for moderate yield (entries 13 and 22), catalytic activity of the BINIM−Ni(II) complex is noteworthy because these reactions under reflux in toluene or with Sc(OTf)$_3$ as a Lewis acid gave almost no cycloadducts.[8]

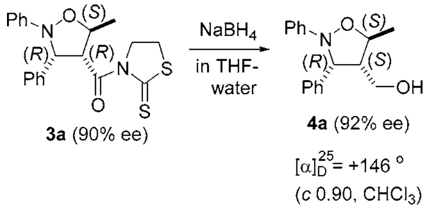
Table 2. BINIM-DCOH−Ni(II)-Catalyzed Enantioselective Cycloadditions of Nitrones **1a**−***l*** with 3-(2-Alkenoyl)-2-thiazolinethiones **2a**−**d**[a]

	nitrone			**2**	time	yield	*exo*:	ee[c]
entry	R^1	R^2	**1**	R	(h)	(%)	*endo*[b]	(%)
1[d]	Ph	Ph	**1a**	Me	69	70	99:1	90
2	*p*-MeC$_6$H$_4$	Ph	**1b**	Me	19	78	93:7	88
3	*p*-MeOC$_6$H$_4$	Ph	**1c**	Me	22	36	>99:1	>90
4	*p*-ClC$_6$H$_4$	Ph	**1d**	Me	15	98	>99:1	95
5[d]	*p*-ClC$_6$H$_4$	Ph	**1d**	Me	64	80	>99:1	95
6	*p*-BrC$_6$H$_4$	Ph	**1e**	Me	20	90	98:2	92
7	Ph	*p*-MeC$_6$H$_4$	**1f**	Me	41	78	>99:1	93
8	Ph	*p*-MeOC$_6$H$_4$	**1g**	Me	48	92	99:1	92
9	Ph	*p*-ClC$_6$H$_4$	**1h**	Me	60	85	>99:1	95
10	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	**1i**	Me	60	85	98:2	93
11	Bn	Ph	**1j**	Me	78	60	93:7	90
12	Me	Ph	**1k**	Me	117	68	86:14	85
13[f]	Bn	Et	**1*l***	Me	96	42	90:10	82
14	Ph	Ph	**1a**	Et	52	74	97:3	91
15	*p*-ClC$_6$H$_4$	Ph	**1d**	Et	15	73	93:7	91
16	Ph	*p*-MeOC$_6$H$_4$	**1g**	Et	98	49	>99:1	83
17	Ph	*p*-ClC$_6$H$_4$	**1h**	Et	64	64	94:6	92
18	Ph	Ph	**1a**	*n*-Pr	45	73	99:1	91
19	*p*-ClC$_6$H$_4$	Ph	**1d**	*n*-Pr	45	75	>99:1	93
20	Ph	*p*-ClC$_6$H$_4$	**1g**	*n*-Pr	70	95	>99:1	90
21	Ph	Ph	**1a**	Ph	150	35	>99:1	87[e]
22[f]	Ph	Ph	**1a**	Ph	69	59	>99:1	87[e]

[a] The reaction was carried out in the presence of BINIM-DCOH−Ni(II) (10 mol %), which was prepared by mixing (*R*)-BINIM-DCOH, Ni(ClO$_4$)$_2$·6H$_2$O, and MS 4A in CHCl$_3$ at room temperature. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess (ee) of the *exo*-adduct was determined by HPLC. [d] 5 mol % of catalyst was used. [e] Determined by ^{1}H NMR after conversion to diastereomeric amides of (*R*)-(+)-α-methylbenzylamine. [f] 20 mol % of catalyst was used.

The absolute configuration of the cycloadduct **3a** obtained from nitrone **1a** and olefin **2a** was determined after conversion to the corresponding 4-hydroxymethylisoxazolidine by NaBH$_4$ reduction. Thus isoxazolidine **3a** (90% ee by HPLC) obtained from the above reaction was treated with NaBH$_4$ in THF−water to give alcohol **4a** (92% ee by HPLC) possessing 3*R*,4*S*,5*S* configuration, which was determined by comparison with the sign of specific rotation in the literature ($[\alpha]^{25}_D$ +176.0 (*c* 1.0, CHCl$_3$), (3*R*,4*S*,5*S*), 99% ee),[5f] in 53% yield (Scheme 3). Therefore, the absolute configuration of the cycloadduct **3a** was assigned as 3*R*,4*R*,5*S*. The other cycloadducts were also presumed to have the same absolute configuration.

Scheme 3. Determination of Absolute Configuration



Although the detailed structure of the catalyst remains unclear,[9] it is apparent that 2-hydroxybenzylideneamine moiety of the BINIM ligands in the Ni(II) complexes in conjunction with 3-(2-alkenoyl)-2-thiazolidinethiones as di-

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(7) For the reaction of **1d**, decreasing the catalyst loading to 1 or 2 mol % (rt for 112 h) resulted in lower yields (36% and 50%, respectively) and enantioselectivity (62%ee and 83% ee, respectively), but with high *exo*-selectivity (95:5 and 97:3, respectively).

(8) Reaction of **1*l*** with **2a**: reflux in toluene for 23 h, trace; Sc(OTf)$_3$ (10 mol %) in CH$_2$Cl$_2$ for 160 h, 0% yield. Reaction of **1a** with **2d**: reflux in toluene for 20 h, 0% yield.

polarophiles is extremely important for unusual *exo*-selectivity in the Lewis acid-catalyzed cycloaddition reactions of nitrones. We also revealed that halogen atoms substituted at the 3-position on benzene rings in the 2-hydroxyphenyl-based BINIM ligands played an important role for high enantioselectivity. The sufficient improvement of enantioselectivity and somewhat different ligand dependence on *exo*-selectivity utilizing 3-(2-alkenoyl)-2-thiazolidinethiones as dipolarophiles compared with using 3-crotonyl-2-oxazolidinone are probably due to longer and more suitable bond lengths of Ni−S and S═C than those of Ni−O and O═C in the BINIM−Ni(II)-catalyzed cycloaddition reactions of nitrones.

In conclusion, highly *exo*-selective and enantioselective 1,3-dipolar cycloaddition reactions between nitrones and 3-(2-alkenoyl)-2-thiazolidinethiones were carried out by using (*R*)-BINIM-DCOH−Ni(II) as a chiral Lewis acid catalyst. In contrast to other chiral Lewis acids that have been reported for nitrone cycloadditions, it is noteworthy that our methodology offers extremely high *exo*-selectivity along with high enantioselectivity for a number of nitrones. Furthermore, only the catalyst loading as small as 5−10 mol % was active enough in most cases.

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Supporting Information Available: Representative experimental procedures and spectroscopic data of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The structures of the BINIM−Ni(II) complexes were discussed in the previous paper[5e,6] on the basis of the X-ray structure analysis of DBFOX/Ph•Ni$(ClO_4)_2$•$3H_2O$ complex, which was shown as an octahedral structure.[10]

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