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N-Alkoxyacrylamides as Substrates for Enantioselective Diels–Alder Reactions

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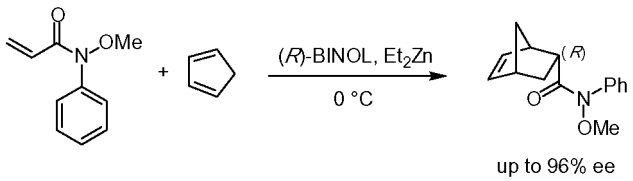
ABSTRACT



The use of *N*-alkoxyacrylamides as substrates for Lewis acid catalyzed Diels–Alder reactions has been examined. Enantioselectivities up to 92% ee have been achieved using very simple chiral Lewis acids prepared from triisobutylaluminum and 2,2-dimethyl-α,α,α′,α′-tetra-1-naphthalenyl-TADDOL (1-NaphtTADDOL). The use of Yamamoto's Zn–BINOL, easily prepared from Et_2Zn and 1,1′-bi-2-naphthol (BINOL), proved to be even more efficient, and enantioselectivities up to 96% ee were achieved.

Recently, we reported the use of hydroxamic acids in enantioselective Diels−Alder reactions using polynuclear aluminum Lewis acids.[1] Enantioselectivities up to 91% ee were obtained for the reaction between an acrylate derivative and cyclopentadiene. Due to the covalent nature of the complex involved in these reactions, it was not possible to perform them with a substoichiometric amount of the chiral Lewis acid. Therefore, we decided to investigate the use of hydroxamate esters derived from acrylic acids in Diels−Alder reactions.[2,3] Our preliminary results with chiral Lewis acids prepared from simple chiral diols such as TADDOLs or binaphthols and trimethylaluminum or diethylzinc are presented here.[4]

The *N*-alkoxyacrylamides **1a**−**g** are easily available from acryloyl chloride by reaction with the corresponding *N*-alkoxyamine or *N*-hydroxyamine followed by *O*-alkylation (see Supporting Information). As model systems, Diels−Alder reactions between acrylamide derivatives and cyclopentadiene were investigated (Scheme 1).

Aluminum Lewis Acids. In the first series of experiments, different chiral aluminum Lewis acids obtained from Me_3-Al, 1,1′-binaphthalene-2,2′-diol (BINOL), or 3,3′-ditriphenylsilyl-1,1′-binaphthalene-2,2′-diol ($diPh_3SiBINOL$) were tested for the reaction of **1c** with cyclopentadiene (Scheme

(1) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731.

(2) Nishida has recently used an α,β-unsaturated Weinreb amide for an enantioselective radical cyclization with moderate success (26% ee by using 4 equiv of a chiral aluminum Lewis acid): Nishida, M.; Hayashi, H.; Nishida, A.; Kamahara, N. *Chem. Commun*. **1996**, 579.

(3) It was shown by an NMR study that Weinreb amides form mono- and bicoordinated complexes with magnesium bromide: Martin, R.; Pascual, O.; Romea, P.; Rovira, R.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett*. **1997**, *38*, 1633.

(4) For an excellent and comprehensive treatment of the use of Lewis acids in organic synthesis, see: *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2001; Vols. 1 and 2.

(5) For a review on chiral aluminum Lewis acids, see: Wulff, W. D. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany; Vol. 1, pp 283−354.

(6) The use of Me_3Al−binaphthol complexes in cycloaddition reactions has been reported. For Diels−Alder reactions, see: Ketter, A.; Glahsi, G.; Herrmann, T. *J. Chem. Res. Synop.* **1990**, 278−279. Ketter, A.; Glahsi, G.; Herrmann, T. *J. Chem. Res. Miniprint* **1990**, 2118−2156. Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501. Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, 115, 3814. For hetero-Diels−Alder reactions, see: Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310−312. Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749−1760. Graven, A.; Johannsen, M.; Jørgensen, K. A. *Chem. Commun*. **1996**, 2373. Roberson, M.; Jepsen, A. S.; Jørgensen, K. A. *Tetrahedron* **2001**, *57*, 907−913. For [3 + 2] cycloaddition (aldol), see: Suga, H.; Shi, X.; Fujieda, H.; Ibata, T. *Tetrahedron Lett.* **1991**, *32*, 6911−6914. Suga, H.; Ikai, K.; Ibata, T.

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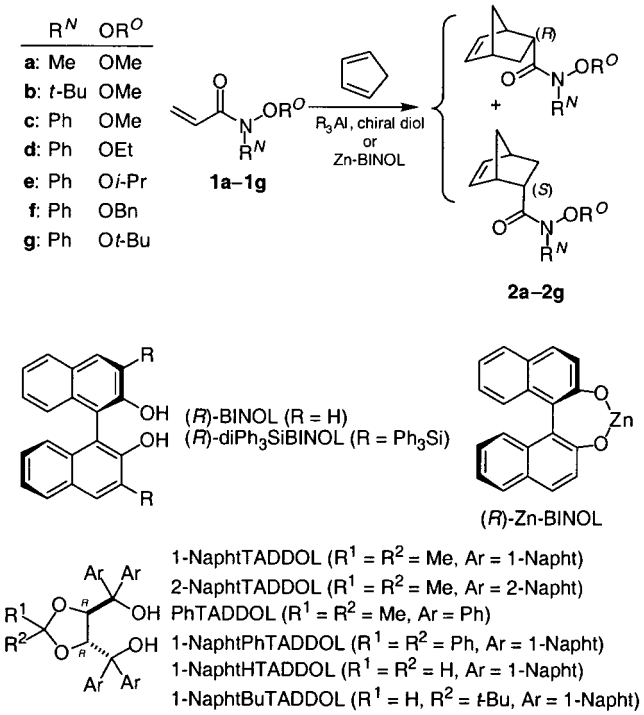
Scheme 1



1).[5,6] All reactions were run using 1.1 equiv of the binaphthol ligand and varying the amount of Me_3Al between 0.25 and 3.3 equiv (Table 1, entries 1−5).[7] A moderate endo selectivity and low enantioselectivities were obtained. Additives such as Et_2O were found to have no effect on the enantioselectivities. Using $diPh_3SiBINOL$ as the ligand (Table 1, entries 6−8) afforded an enantioselectivity up to 58% for the endo isomer. The endo:exo selectivity was very low (from 1.1:1 to 1.7:1) with this ligand. Interestingly, the enantiomeric excess was higher for the exo isomer (up to 91% ee, entry 7).

Table 1. Reaction of **1c** with Cyclopentadiene at 0 °C in the Presence of Me_3Al and 1.1 equiv of (*R*)-BINOL or (*R*)-$DiPh_3SiBINOL$ According to Scheme 1

	chiral diol	equiv of Me_3Al	endo:exo	ee endo (ee exo)
1	BINOL	0.25	4.7:1	8% *S* (6% *S*)
2	BINOL	0.55	4.2:1	26% *S* (19% *S*)
3	BINOL	1.1	4.2:1	8% *R* (38% *R*)
4	BINOL	2.20	10.3:1	16% *R* (14% *R*)
5	BINOL	3.30	4.8:1	0% (2% *R*)
6	$diPh_3SiBINOL$	0.55	1.1:1	45% *R* (72% *R*)
7	$diPh_3SiBINOL$	1.10	1.4:1	58% *R* (91% *R*)
8	$diPh_3SiBINOL$	2.20	1.7:1	34% *R* (72% *R*)

In the second series of experiments, Lewis acids derived from TADDOLs and Me_3Al were tested for catalysis of the same Diels−Alder reactions of **1c** (Scheme 1).[8,9] The reaction conditions were optimized with 1-NaphtTADDOL (Table 2, entries 1−5). With 1.1 equiv of the diol, the best enantioselectivity was obtained using 0.55 equiv of Me_3Al (Table 2, entry 3), indicating that a seminuclear complex was the most effective catalyst. Running the reaction from −78 °C to room temperature over 12 h afforded an enantioselectivity of 67%. Interestingly, using a substoichiometric amount of the Lewis acid (0.25 equiv of the diol and 0.14 equiv of Me_3Al) does not greatly alter the stereochemical outcome (Table 2, entry 6, 62% ee). Finally, it was observed that using *i*-Bu_3Al provides a slightly better selectivity (72% ee under the substoichiometric conditions). Other TADDOLs were also tested (entries 8−12), but none of them proved to be as good as the 1-NaphtTADDOL. Small modifications at the acetal center of the chiral ligand had a highly negative effect on the enantioselectivity (compare entries 7 and 11).

Table 2. Reaction of **1c** with Cyclopentadiene at Room Temperature in the Presence of R_3Al and TADDOLs According to Scheme 1

	TADDOL (equiv)	R_3Al (equiv)	endo:exo	ee endo
1	1-Napht (1.2)	Me_3Al (2.20)	10:1	36% *S*
2	1-Napht (1.2)	Me_3Al (1.10)	9:1	34% *S*
3	1-Napht (1.2)	Me_3Al (0.55)	11:1	51% *S*
4[a]	1-Napht (1.2)	Me_3Al (0.55)	31:1	67% *S*
5[a]	1-Napht (1.2)	Me_3Al (0.25)	18:1	62% *S*
6[a]	1-Napht (0.25)	Me_3Al (0.14)	18:1	62% *S*
7[a]	1-Napht (0.25)	*i*-Bu_3Al (0.14)	24:1	72% *S*
8	Ph (1.2)	Me_3Al (0.55)	6:1	31% *S*
9[a]	2-Napht (1.2)	Me_3Al (0.55)	13:1	45% *S*
10[a]	1-NaphtPh (0.25)	*i*-Bu_3Al (0.14)	17:1	58% *S*
11[a]	1-NaphtH (0.25)	*i*-Bu_3Al (0.14)	4:1	14% *S*
12[a]	1-NaphtBu (0.25)	*i*-Bu_3Al (0.14)	9:1	29% *S*

[a] Reaction performed from −78 °C to room temperature.

In the third series of experiments, the role of the N-substitution of the acrylamide was investigated. The reactions were run under the optimized conditions found in Table 2 (Table 2, entry 7), i.e., with a substoichiometric amount of *i*-Bu_3Al and 1-NaphtTADDOL in a 1:2 ratio. The results are summarized in Table 3. Entries 1−3 show that the *N*-phenyl derivative gives a better enantioselectivity than the corresponding *N*-methyl and *N*-*tert*-butyl derivatives. A

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(7) The use of Me_2AlCl and $EtAlCl_2$ was also investigated but led to either no reaction or decomposition of the starting material.

(8) For a review on the use of TADDOLs, see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, 40, 92.

(9) TADDOLates have been used in enantioselective $LiAlH_4$ reduction of ketones: Beck, A. K.; Dahinden, R.; Kühnle, F. N. M. ACS Symposium Series 641; American Chemical Society: Washington DC, 1996; p 52. Seebach, D.; Beck, A. K.; Dahinden, R.; Hoffmann, M.; Kühnle, F. N. M. *Croat. Chem. Acta* **1996**, *69*, 459. Vinogradov, M. G.; Gorshkova, L. S.; Pavlov, V. A.; Mikhalev, O. V.; Chel'tsova, G. V.; Razmanov, I. V.; Ferapontov, V. A.; Malyshev, O. R.; Heise, G. L. *Russ. Chem. Bull.* **2000**, *49*, 460. Only few applications of aluminum TADDOLates as Lewis acids for enantioselective reactions have been reported: Manickam, G.; Sundararajan, G. *Tetrahedron* **1999**, *55*, 2721. Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1998**, 1291. Fhal, A. R.; Renaud, P. *Tetrahedron Lett.* **1997**, *38*, 2661.

Table 3. Reaction of **1a**−**g** with Cyclopentadiene Catalyzed by *i*-Bu_3Al (0.14 equiv) and 1-NaphtTADDOL (0.25 equiv) According to Scheme 1[10]

	substrate	R^N	OR^O	endo:exo	ee (endo)
1	**1a**	Me	OMe	11:1	23% *S*
2	**1b**	*t*-Bu	OMe	*a*	21% *R*
3	**1c**	Ph	OMe	24:1	72% *S*
4	**1d**	Ph	OEt	18:1	75% *S*
5	**1e**	Ph	O*i*-Pr	33:1	89% *S*
6	**1f**	Ph	OBn	21:1	69% *S*
7	**1g**	Ph	O*t*-Bu	>50:1	92% *S*

[a] Not precisely determined, about 7:1.

similar result was already observed when hydroxamic acids were employed with aluminum Lewis acids.[1] It is worth mentioning that an inversion of the sense of induction was observed with the *t*-Bu substituent (entry 2). The role of the alkyl group at the *N*-alkoxy substituent was investigated next. Increasing the size of the alkyl group led to an enhancement of the enantioselectivity (entries 4−7). The best substrate for the aluminum-catalyzed reactions was found to be the *N*-*tert*-butoxy-*N*-phenylacrylamide (entry 7, 92% ee).

The rationalization of these results is not clear at the moment due to the lack of structural information about the Lewis acid.

Zinc Lewis Acids. Dialkylzinc represents an attractive alternative to trialkylaluminum for preparation of mild Lewis acids.[11] The Lewis acid obtained from dimethylzinc and BINOL has been reported in the pioneering work of Yamamoto to catalyze enantioselective cyclizations of unsaturated aldehydes.[12] We decided to investigate this Lewis acid for the Diels−Alder reactions of *N*-alkoxyacrylamides. The results of the study are described in Table 4. Using a stoichiometric amount of the Lewis acid, the reaction with the Weinreb amide **1a** at 0 °C gave a very encouraging 89% ee and a moderate endo selectivity (Table 4, entry 1). The *N*-methoxy-*N*-phenylacrylamide **1c** furnished under the same reaction conditions the Diels−Alder adduct **2c** in 96% ee and excellent endo selectivity. The use of a substoichiometric amount of Lewis acid (0.25 equiv) allows an enantioselectivity of 90% (entry 3). In this case, the reaction took 5 h to go to completion instead of 1 h when a stoichiometric amount of catalyst was used. When bulkier alkoxy groups were used, the level of enantioselectivity decreases slightly as demonstrated by the results of entries 4 and 5. However, the nature of the substrate is less important with this Lewis acid than with the aluminum derivatives. The simplicity of the Zn−BINOL experimental procedure makes it very attractive from a synthetic point of view.

Table 4. Reaction of **1** with Cyclopentadiene Catalyzed by (*R*)-Zn−BINOL According to Scheme 1[13]

	substrate	R^N	OR^O	equiv of catalyst	endo:exo	ee (endo)
1	**1a**	Me	OMe	1.1	7:1	89% *R*
2	**1b**	*t*-Bu	OMe	1.1	nd	60% *R*
3	**1c**	Ph	OMe	1.1	54:1	96% *R*
4	**1c**	Ph	OMe	0.25	41:1	90% *R*
5	**1d**	Ph	OEt	1.1	29:1	86% *R*
6	**1e**	Ph	O*i*-Pr	1.1	14:1	76% *R*

The stereochemical outcome of these reactions can be rationalized by the formation of a bidentate complex with an s-cis geometry (Figure 1).

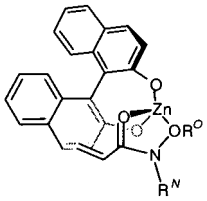

Figure 1. Proposed model for the stereochemical outcome of the reaction catalyzed by (*R*)-Zn−BINOL.

In conclusion, we have demonstrated that *N*-alkoxyacrylates are suitable substrates for enantioselective Diels−Alder reactions. Interestingly, very mild and simple Lewis acids prepared from binaphthols or TADDOLs and trialkylaluminum or dialkylzinc provide a good level of enantioselectivity. The conversion of the *N*-alkoxyamide Diels−Alder adducts into useful building blocks should be facilitated by the well-

(10) General procedure (Al-1-NaphtTADDOL): A solution of Me_3Al in toluene (1.11 M, 0.13 mL, 0.14 mmol) was added dropwise at room temperature to a solution of 1-NaphtTADDOL (187 mg, 0.28 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred for 30 min at room temperature. A solution of **1g** (219 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was then added dropwise. The reaction mixture was stirred for 1 h at room temperature and 30 min at −78 °C. Freshly distilled cyclopentadiene (660 mg, 10 mmol) was added dropwise under N_2 to the solution at −78 °C, and the mixture was allowed to warm to room temperature overnight (12 h). Volatiles were removed in vacuo, and the resulting residue was dissolved in Et_2O and stirred for 1 h at room temperature with a 1 N aqueous solution of citric acid. After extraction with Et_2O, the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc 12:1).

(11) For a review on chiral zinc Lewis acids, see: Motoyama, Y.; Nishiyama, H. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 59−88.

(12) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *43*, 2203.

(13) Identical results where observed when Me_2Zn was employed to prepare the complex with BINOL rather than Et_2Zn. As described by Yamamoto, the catalyst solution was clear when prepared at low temperatures (−78 °C) and turned to a white suspension while warming to room temperature. In our case, this had no marked influence on the reaction selectivity. The general procedure used for the Zn−BINOL catalyst preparation is the following: A solution of Et_2Zn (15 wt % in hexane, 1.1 mmol) was added dropwise at room temperature to a solution of (*R*)-BINOL (320 mg, 1.1 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was heated at reflux for 1 h, cooled to 0 °C, and stirred for 30 min before the addition of a solution of **1c** (177 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL). The resulting suspension was stirred for 1 h at 0 °C before the addition of freshly distilled cyclopentadiene (660 mg, 10 mmol). After completion of the reaction, volatiles were removed in vacuo and the resulting residue was dissolved in Et_2O and stirred for 1 h at room temperature with a 1 N aqueous solution of citric acid. After extraction with Et_2O, the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc 8:1).

known synthetic versatility of this type of compound (Weinreb amides). Further application of these substrates in enantioselective reactions is under investigation.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1a**−**2g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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