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Enantioselective Diels–Alder Reactions with *N*-Hydroxy-*N*-phenylacrylamide

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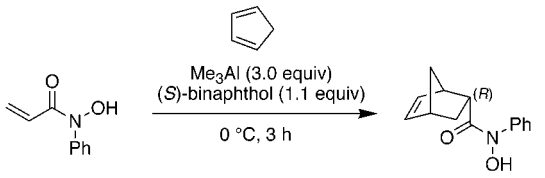
ABSTRACT

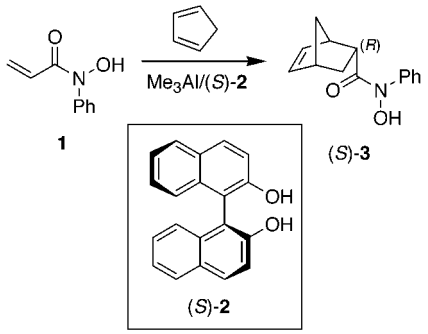


The use of hydroxamic acids as templates for Lewis acid catalyzed enantioselective Diels–Alder reactions has been examined. A very simple chiral Lewis acid, prepared by mixing optically pure binaphthol with 3 equiv of trimethylaluminum, catalyzes the [4 + 2] cycloaddition of *N*-hydroxy-*N*-phenylacrylamide with cyclopentadiene at 0 °C in high yield (>96%) and with a fairly good level of enantioselectivity (91% ee). Facile conversion of the products to the corresponding alcohols or aldehydes makes the hydroxamic acid intermediates particularly useful.

Currently, catalytic enantioselective reactions mediated by chiral Lewis acids are a field of intense development.[1] Diels−Alder reactions of acrylic acid derivatives with cyclopentadiene have often been used as model systems for testing new strategies for enantioselective reactions. Several factors have a determining influence on the stereochemical outcome of the reactions: the Lewis acidic metal center, the ligand, additives, and the achiral template bound to the acroyl residue. While the nature of the metal, chiral ligands, and additives have been the subject of numerous investigations, surprisingly, the nature of the achiral template has not been systematically investigated.[2] The use of 1,3-oxazolidinone has been adopted by the vast majority of researchers, presumably because the bidendate nature of this moiety allows a well-defined conformation of the substrate−Lewis acid complexes. We recently reported our efforts to develop novel achiral auxiliaries that play an active role in a new enantioselective process we have called "chiral relay".[3] During the course of this project, we became interested in exploring hydroxamic acid derivatives as achiral templates.[4] We report herein our preliminary results on Diels−Alder reactions of *N*-hydroxy-*N*-phenyl acrylamides with aluminum-based Lewis acids and binaphthol derivatives as chiral ligands.

The *N*-hydroxy-*N*-phenylacrylamide **1** was readily prepared in 96% yield by treating *N*-phenyl-hydroxylamine[5] with acryloyl chloride. Diels−Alder reaction with cyclopentadiene was investigated (Scheme 1).[6] Readily available methylalu-

Scheme 1



(1) 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.

(2) A paper dedicated to the role of the achiral template in enantioselective reactions has been recently reported: Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984.

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minum-containing Lewis acids,[7] prepared from trimethylaluminum and binaphthol **2**,[8,9] were chosen for this initial study. With this type of Lewis acid, the formation of an aluminum hydroxamate is expected with the consequence of binding the chiral promoter in a covalent manner to the substrate. This offers the advantage of using a well-defined system for our preliminary investigations.

In the first series of experiments, we examined the effect of varying the binaphthol (*S*)-**2**/Me_3Al ratio. The results are reported in Table 1. In the absence of Lewis acid, the reaction

Table 1. Diels−Alder Reaction According to Scheme 1 Promoted by Me_3Al/(*S*)-**2** at Room Temperature

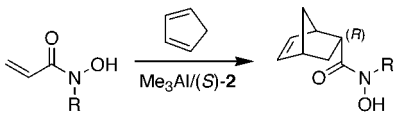
	equiv of Lewis acid	reaction time (yield)	endo:exo	ee endo
1	no	16 h (86%)	67:33	
2	1.1 Me_3Al	45 min (98%)	83:17	
3	0.55 Me_3Al 1.1 (*S*)-**2**	12 h (96%)	59:51	36% (*R*)
4	1.1 Me_3Al 1.1 (*S*)-**2**	12 h (97%)	74:26	40% (*R*)
5	1.7 Me_3Al 1.1 (*S*)-**2**	12 h (95%)	77:23	31% (*R*)
6	2.2 Me_3Al 1.1 (*S*)-**2**	6 h (98%)	82:18	55% (*R*)
7	3.3 Me_3Al 1.1 (*S*)-**2**	30 min (97%)	88:12	72% (*R*)
8[a]	3.3 Me_3Al 1.1 (*S*)-**2**	72 h (98%)	91:9	86% (*R*)
9	4.4 Me_3Al 1.1 (*S*)-**2**	15 min (97%)	87:13	32% (*R*)
10[b]	3.0 Me_3Al 1.1 (*S*)-**2**	3 h (98%)	97:3	91% (*R*)

[a] $T = -40$ °C. [b] $T = 0$ °C.

afforded the cyclodaddition product in 86% yield with a modest endo selectivity (Table 1, entry 1). When the reaction was performed in the presence of 1.1 equiv of Me_3Al, it was considerably faster (45 min at room temperature) and the endo selectivity was enhanced (Table 1, entry 2). Although this reaction was very clean, the isolated yield was poor (10−20%). This is presumably due to difficulties in the hydrolysis of the aluminum hydroxamate. Treating the crude reaction residue with a 1 M aqueous solution of citric acid made it possible to obtain the bicyclic hydroxamic acid **3** in 98% yield. The reaction was then performed in the presence of 1.1 equiv of the binaphthol (*S*)-**2** and various amounts of Me_3Al. This had a striking effect on the enantioselectivity. With 0.55−2.2 equiv of Me_3Al, the reactions were complete in 12 h at room temperature and the enantiomeric excesses were between 36 and 55% (entries 3−6). An increase in selectivity (72% ee) was observed with 3.3 equiv of Me_3Al (entry 7). Running the reaction at low temperatures (−40 °C) increased the selectivity to 86% ee; however, the reaction was very slow at this temperature (entry 8). With larger excesses of Me_3Al, the enantioselectivity of the reaction decreased dramatically (entry 9). After careful optimization of the reaction conditions, we found that the use of 3.0 equiv of Me_3Al at 0 °C gave the highest selectivity (entry 10, 91% ee) and reasonable reaction time (3 h). Enantiomerically pure binaphthol (*S*)-**2** could be recovered in 95% yield by filtration of the crude reaction residue on a short pad of silica gel with dichloromethane as the eluent. The Diels−Alder adduct **3** was then isolated by elution with ethyl acetate.[10]

The role of the substitution at nitrogen was then investigated. For this purpose, the hydroxamic acids **4** and **5** were allowed to react under the optimized reaction conditions (Scheme 2). Going from a phenyl substituent (91% ee) to a methyl substituent leads to a strong decrease in selectivity (47% ee). The *tert*-butyl substituent is only marginally better (67% ee).

Scheme 2



1 R = Ph
4 R = Me
5 R = *t*-Bu

(*R*)-**3** R = Ph (91% ee, 98% yield)
(*R*)-**6** R = Me (47% ee, >95% yield)
(*R*)-**7** R = *t*-Bu (67% ee, >95% yield)

(3) Quaranta, L. Ph.D. Thesis (No. 1297), Faculté des Sciences, Université de Fribourg, Switzerland, 2000. Quaranta, L.; Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 39.

(4) Diels−Alder reaction of acrylate-derived hydroxamic acids has been reported to take place under high pressure and has been applied as a key step in a short synthesis of peduncularine: Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333. Weinreb type acrylamides have been used in enantioselective radical cyclizations: Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *Chem. Commun*. **1996**, 479.

(5) Prepared according to: Kamm, O. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 445.

(6) For a review, see: Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332.

(7) 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, 2001; Vol. 1, pp 283−354.

(8) Optically pure (*S*)- and (*R*)-**2** are prepared according to: Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1995**, *36*, 7991−7994.

(9) 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. Nishiuchi, M.; Honda, K.; Nakai, T. *Chem. Lett.* **1996**, 321. 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. *Tetrahedron Lett.* **1998**, *39*, 869−872. For dipolar cycloaddition, see: Simonsen, K. B.; Bayon, P.; Hazel, R. G.; Gothelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845−3853. Jensen, K. B.; Roberson, M.; Jorgensen, K. A. *J. Org. Chem.* **2000**, *65*, 9080−9084. For [2 + 2] cycloaddition, see: Tamai, Y.; Someya, M.; Fukumoto, J.; Niyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1549.

(10) **Optimized Procedure.** A solution of Me_3Al in toluene (2.2 M 1.4 mL, 3.0 mmol) was added dropwise at room temperature to a solution of (*S*)-**2** (320 mg, 1.1 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred for 30 min at room temperature. A solution of **1** (160 mg, 1.0 mmol) in toluene (1.0 mL) was then added dropwise. The reaction mixture was stirred for 1 h at room temperature and 30 min at 0 °C. Freshly distilled cyclopentadiene (660 mg, 10 mmol) was added dropwise under N_2 to the solution, and the mixture was stirred until completion of the reaction. Volatiles were removed in vacuo, and the resulting residue was dissolved in Et_2O and stirred overnight 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 filtration through a short pad of silica gel (elution with CH_2Cl_2 to remove the (*S*)-**2** and hexane/EtOAc 8:1 to elute **3**).

Finally, several binaphthol[11] ligands were screened with *N*-phenyl-*N*-hydroxy-acrylamide **1** using the optimized conditions (Figure 1). However, none proved to be better than

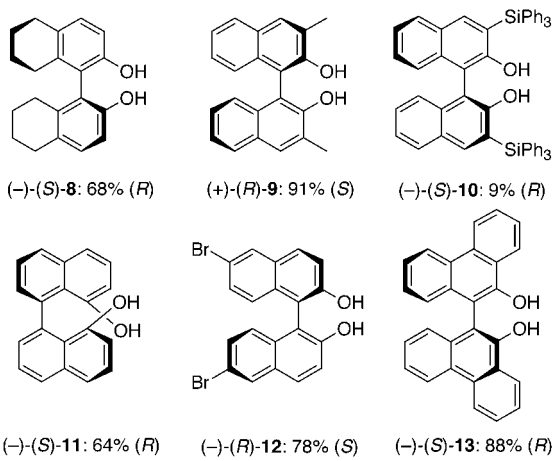


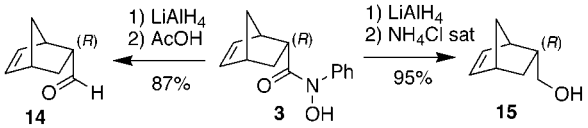
Figure 1. Screening of binaphthol-type ligands.

the nonsubstituted binaphthol **2**. Substituted binaphthols **9** and **13** gave enantioselectivities close to those observed with binaphthol **2**. TADDOL derivatives[12] and bis-sulfonamides[13] were also investigated, but the enantioselectivity remained very low (<20% ee).

In the course of the complex preparation, gas evolution was observed during the addition of the first 2 equiv of the Me_3Al solution to the chiral ligand but not during the addition of the third one. Gas evolution was again observed during the addition of the hydroxamic acid solution to the chiral catalyst. Changing the order of addition of the reagents had no influence on the enantioselectivity of the reaction. We believe that a trimetallic complex is formed with one of the metal centers covalently linked to the hydroxamic acid moiety. This is in close analogy to a recent work of Yamamoto where dialuminum complexes of binaphthol **10** were used to catalyze Diels−Alder reactions.[14,15] The geometry of the acrylamide is unkown,[16] and the positive role of the *N*-phenyl substituent is not clear at the moment. Further experiments and modeling will be performed to gain more information about the factors involved in the stereochemical outcome of these reactions.

Finally, we have shown that the hydroxamic acid **3** is a useful building block (Scheme 3). It is easily converted by

Scheme 3. Conversion of **3** into Aldehyde **14** or Alcohol **15**



treatment with an excess of $LiAlH_4$ at 0 °C into aldehyde **14** or alcohol **15** depending on the reaction conditions.

In conclusion, we have demonstrated that enantioselective Diels−Alder reactions of *N*-hydroxy-*N*-phenyl acrylamide can be efficiently promoted by using 3 equiv of Me_3Al and 1.1 equiv of binaphthol. The reaction presumably proceeds via a complex containing three aluminum atoms. This system requires the use of a stoichiometric amount of the chiral ligand, but binaphthol is easily recovered at the end of the reaction by filtration. The development of a catalytic version of this reaction is currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1**, **3**, **4**−**7**, **14**, and **15** as well as a detailed procedure for the determination of the enantioselectivities. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Ligands are available according to literature procedures. **8** and **9**: Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Dotsevi, G.; Sogah, Y. *J. Org. Chem.* **1978**, *43*, 1930. **10**: Gong, L.-Z.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 2327. Racemic-**11**: Artz, S. P.; deGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* **1985**, *50*, 1486. Resolution of **11**: Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1995**, *60*, 6599. **12**: Dotsevi, G.; Sogah, Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035. Racemic-**13**: Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett*. **1994**, *35*, 7983. Resolution of **13**: Toda, F.; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607.

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

(13) Corey, E. J.; Imwinkelried, T.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(14) Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett* **2001**, *3*, 394.

(15) The use of chiral heterobimetallic catalysts has been pioneered by Shibasaki; for a review, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1237. The use of polynuclear chiral Lewis acids has recently attracted much attention. Aluminum: Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, *118*, 11307. Ooi, T.; Tayama, E.; Takahashi, M.; Maruoka, K. *Tetrahedron Lett*. **1997**, *38*, 7403. Ooi, T.; Miura, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **1998**, *110*, 2347. Simpura, I.; Nevalainen, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3422. Boron: Reilly, M.; Oh, T. *Tetrahedron Lett*. **1995**, *36*, 221. Reilly, M.; Oh, T. *Tetrahedron Lett.* **1994**, *35*, 7209. Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545. Mercury: Lee, H.; Diaz, M.; Hawthorne, M. F. *Tetrahedron Lett.* **1999**, *40*, 7651. Oh, T.; Lopez, P.; Teilly, M. *Eur. J. Org. Chem.* **2000**, 2901. Lopez, P.; Oh, T. *Tetrahdron Lett.* **2000**, *41*, 2313. Titanium: Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusakawa, F. *Organometallics* **1994**, *13*, 2218. Hanawa, H.; Kii, S.; Maruoka, K. *Adv. Synth. Catal*. **2001**, *343*, 57. Asao, N.; Kii, S.; Hanawa, H.; Maruoka, K. *Tetrahedron Lett*. **1998**, *39*, 3729. Kii, S.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 1935. Zirconium and hafnium: Kobayashi, S. *Chirality* **2000**, *12*, 540. Hanawa, H.; Kii, S.; Asao, N.; Maruoka, K. *Tetrahedron Lett*. **2000**, *41*, 5543. Zinc: Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibazaki, M. *Org. Lett.* **2001**, *3*, 1539. Iron: Bach, T.; Fox, N. A.; Reetz, M. T. *J. Chem. Soc., Chem. Commun.* **1992**, 1634.

(16) Ishihara, K.; Inanaga, K.; Kondo, S.; Funahashi, M.; Yamamoto, H. *Synlett* **1998**, 1053.