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Chiral Relay Effect: 4-Substituted 1,3-Benzoxazol-2-(3*H*)-ones as Achiral Templates for Enantioselective Diels–Alder Reactions

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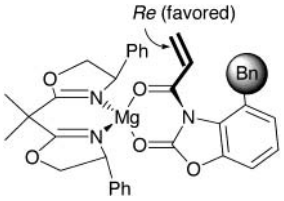
ABSTRACT



A new strategy to control the enantioselectivity of Lewis acid catalyzed reactions has been investigated. The use of *N*-acryloyl-1,3-benzoxazol-2-(3*H*)-ones substituted at position 4 leads to the formation of diastereomeric complexes as a result of the presence of a chiral axis. The stereochemical outcome of the reaction is controlled by the chiral catalyst and by the chiral axis, leading to high enantioselectivity improvements and, in one case, to an inversion of enantioselectivity.

The design of enantioselective Lewis acid catalyzed reactions is currently receiving much attention.[1] Diels−Alder reactions are often used as test systems for the evaluation of the efficiency of novel strategies for enantiocontrol.[2] The vast majority of the research has focused on the development of novel chiral ligands to complex the metal centers used as Lewis acids. For instance, the reaction of *N*-alkenoyl-1,3-oxazolidin-2-ones with dienes has been thoroughly examined, and very high levels of enantioselectivity have been achieved with different types of Lewis acids.[3] The choice of the 1,3-oxazolidinone as template is mainly dictated by the possibility of chelation of the metal catalyst by the two carbonyl groups to ensure a well defined conformation of the intermediate complex.[4] However, the design of an efficient ligand for such reactions is difficult, and excellent results have been obtained with relatively sophisticated chiral ligands able to mask efficiently one face of the alkenoyl group. We are interested in developing alternative achiral templates that actively control the stereochemistry of the reactions and give a high level of enantioselectivity with simple chiral Lewis acids. We report here preliminary results obtained with acrylamides derived from 4-substituted-1,3-benzoxazol-2-(3*H*)-ones.[5] The crucial role of the substituent at C(4) will be rationalized as a chiral relay effect.[6]

The term "chiral relay" was introduced by Davies in chiral auxiliary controlled reactions.[7] Our approach differs because

(1) For an excellent and recent overview, see: *Lewis Acids in Organic Synthesis*; Yamamoto, H. Ed.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.

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

(3) Selected examples of historical importance. Ti(IV): (a) Narasaka, K.; Iwasawa, N.; Inoue, M. Yanmada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345. Iron(III): (b) Corey, E. J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* **1991**, *113*, 728−729. Mg(II): (c) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807−6810. Cu(II): (d) Evans, D. A.; Miller, S. J.; Leckta, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. Zn(II): (e) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484. Al(III): Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938−7939. Yb(III): (f) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535−4538. More example are cited in an excellent full paper: Evans, D. A.; Miller, S. J.; Leckta, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

(4) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

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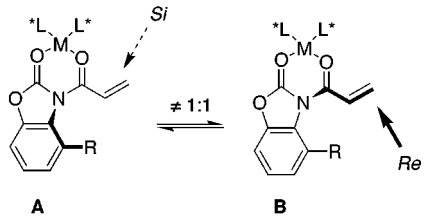
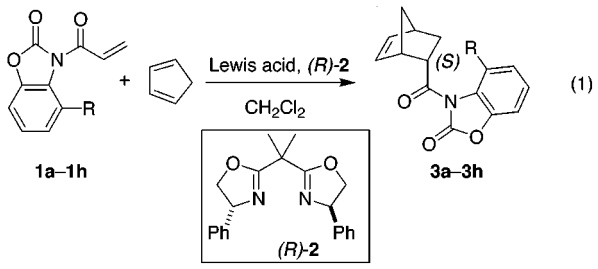
it is based on the development of achiral auxiliaries that can adopt chiral conformations and thus relay the chiral information of the catalyst to the reaction center.[8,9] In this paper we will focus on 4-substituted-1,3-benzoxazol-2-(3*H*)-ones. Upon complexation with a chiral Lewis acid, the acrylamide **1** should lie in the two diastereomeric conformations **A** and **B** as a result of the presence of a chiral axis in the substrate. These two conformers should exist in unequal amounts and react at different rates and with different stereoselectivity. It is expected that by suitable choice of R, the chiral axis will have an important role in controlling the stereoselectivity of the reaction. Indeed, the chiral axis of **A** should favor a *si* face attack of the acrylamide moiety, and the chiral axis of **B** should favor the *Re* attack (Scheme 1).[10] The stereochemical outcome of the reaction will result from a delicate balance between the chiral Lewis acid and the axis of chirality. In an ideal case of chiral relay, the Lewis acid would induce a preferred conformation of the complex (either **A** or **B**) and not influence the stereochemical outcome of the reaction directly. In such a case, the stereochemical outcome would only result from the substrate chiral axis, which is relaying the chiral information present on the metal ligand. The main interest of this approach is the possibility of using simple and easily available chiral Lewis acids.

Scheme 1. Conformations A and B of the Complexed Acrylamide **1**[a]



[a] Direction of attack favored by the atropisomerism is indicated by the arrows.

A series of 4-substituted-1,3-benzoxazol-2-(3*H*)-ones were synthesized and the corresponding *N*-acryloyl derivatives **1a**−**h** were prepared by reaction with acryloyl chloride in the presence of triethylamine (see Supporting Information). Their Diels−Alder reactions with cyclopentadiene were examined in the absence of Lewis acids and in the presence of 30 mol % of Lewis acids using the bisoxazoline (*R*)-**2** as a chiral ligand (eq 1). The simple diphenyl bisoxazoline (*R*)-**2** was chosen as a ligand because it is easily available and known to induce moderate to good enantioselectivity in many reactions.[11] To observe a chiral relay effect, it is important to have a ligand that does not induce a complete face shielding. In the absence of Lewis acids, the reactions were performed at room temperature with 5 equiv of cyclopentadiene. All of the reactions took place within 1−2 h and were moderately *endo* stereoselective (*endo*/*exo* 5:1−15:1) and high yielding (≥95%) (see Supporting Information). No reaction occurred at −40 °C; thus no competitive uncatalyzed reaction would occur when the chiral Lewis acids were used below −40 °C.



Reactions with zinc triflate at −40 °C are reported in Table 1 (entries 1 and 2). The ee's were measured after reduction of the crude product with $LiBH_4$ or $NaBH_4$ and GC analysis on a chiral capillary column. The absolute configuration was established by comparison of the observed $[\alpha]_D$ with literature data (see Supporting Information). As expected, Lewis acid catalysis increased the *endo* selectivity relative to the noncatalyzed reactions. With the nonsubstituted 1,3-benzoxazol-2-(3*H*)-one derivative **1a**, a very low level of enantioselectivity was observed (entry 1, 11% ee). A marked increase of stereoselectivity was observed with the Me-substituted derivative **1b** (42% ee). This first result was very encouraging and supported our chiral relay hypothesis. However, the reaction with zinc Lewis acids were too slow (60 h) and were therefore abandoned. We turned next to copper(II) triflate catalysis. With this system (Table 1, entries 3−5), reactions were over in 90 min and an excellent *endo* selectivity was observed (*endo*/*exo* 100:1). A slight increase

(5) For the use of 1,3-benzoxazol-2-(3*H*)-one in diastereoselective reactions, see: Corey, E. J.; Houpis, I. N *Tetrahedron Lett.* **1993**, *34*, 2421−2424. Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* 2000, 41, 1−5.

(6) Quaranta, L. Ph.D. Thesis, University of Fribourg, Switzerland, 2000. The concept of chiral relay for enantioselective reaction has been presented at the Fall Meeting of the New Swiss Chemical Society, October 12, 1999 (Quaranta, L.; Renaud, P. *Chimia* **1999**, *53*, 364, abstract 154) and at the Second Swiss COST Chemistry Symposium, October 15, 1999 (Corminboeuf, O.; Renaud, P. *Chimia* **1999**, *53*, 398, abstract 25).

(7) (a) Bull, S. D.; Davies, S. G.; Garner, A. C.; Seller, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501−1506. (b) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Chem. Commun.* **1998**, 659−660. (c) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321−2330.

(8) Recently, Sibi has presented a nice example of chiral relay using alkylated pyralozidinones alkylated at N(1) and taking advantage of a labile chiral nitrogen center: Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444−8445.

(9) Several examples of chiral relay in enantioselective reactions have been identified in the literature. However, the concept of "chiral relay" has only been explicitely used by us (ref 6) and Sibi (ref 8). (a) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981−2984. (b) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435−2448. (c) Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, 41, 7071−7074. (d) Ramón, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996**, *79*, 875−894. (e) Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939−2945. (f) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C.; Campos, K. R.; Connel, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (g) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089−12090.

(10) Recently, an example of chiral relay in a chiral auxiliary controlled reaction involving atropisomerism has been reported: Clayden, J.; Wah, L.; Helliwell, M. *Tetrahedron: Asymmetry* **2001**, *12*, 695−698. Clayden, J.; Pink, J. H.; Yasin, S. H. *Tetrahedron Lett.* **1998**, *39*, 105−108. See also 9g for a related enantioselective reaction.

(11) Review: Gosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

Table 1. Diels−Alder Reaction According to Equation 1 in the Presence of 30 mol % $Zn(OTf)_2$ and $Cu(OTf)_2$ and (*R*)-**2**

entry	substrate	R	Lewis acid	time (h)	yield (*endo*/*exo*)	ee (*endo*)
1	**1a**	H	$Zn(OTf)_2$	60	96% (34:1)	(*S*) 11%
2	**1b**	Me	$Zn(OTf)_2$	60	97% (18:1)	(*S*) 42%
3	**1a**	H	$Cu(OTf)_2$	1.5	96% (100:1)	(*S*) 44%
4	**1b**	Me	$Cu(OTf)_2$	1.5	95% (100:1)	(*S*) 55%
5	**1d**	Bn	$Cu(OTf)_2$	1.5	93% (100:1)	(*S*) 64%

of enantioselectivity was observed on going from **1a** (R = H) to **1b** (R = Me) and **1d** (R = Bn), supporting a chiral relay effect. These results were obtained by running the reactions in parallel with the same solution of copper triflate. However, this reaction was extremely sensitive to moisture, and results varied for each new set of reactions. So, even if this system was very promising from a synthetic point of view, it was not pursued because a high reproducibility was necessary to identify clearly the chiral relay effect.

We investigated next magnesium-based Lewis acids (Table 2). In the presence of the $MgBr_2 \cdot Et_2O$/bisoxazoline **2** (30

Table 2. Diels−Alder Reaction of **1a**−**h** in the Presence of 30 mol % $MgBr_2$ and (*R*)-**2** According to Equation 1

entry	substrate	R	time (h)	yield (*endo*/*exo*)	ee (*endo*)
1	**1a**	H	3	98% (22:1)	(*S*) 14%
2	**1b**	Me	7	97% (32:1)	(*S*) 74%
3	**1c**	Et	7	97% (33:1)	(*S*) 76%
4	**1d**	Bn	5	97% (11:1)	(*S*) 86%
5	**1e**	PMB	5	98% (16:1)	(*S*) 88%
6	**1f**	CH_2t-Bu	10	98% (20:1)	(*S*) 10%
7	**1g**	$CH(Ph)_2$	9	97% (17:1)	(*S*) 72%
8	**1h**	$SiMe_3$	9	95% (40:1)	(*S*) 40%

mol %), the reactions were performed at −78 °C in 2−10 h. The nonsubstituted substrate **1a** (R = H) gave the *endo* product with a good diastereoselectivity (*endo*/*exo* 22:1) but low enantioselectivity (14% ee). The methyl-substituted derivative **1b** showed a dramatic increase of enantioselectivity (entry 2, 74% ee). The ethyl-substituted derivative **1c** gave a slightly higher selectivity (entry 3, 78% ee). The best results were obtained with the benzyl and *p*-methoxybenzyl derivatives **1d** and **1e** (entries 4 and 5) with 86% and 88% ee, respectively. Replacing the aryl group by the bulkier *tert*-butyl group (compound **1f**) led to a drop of ee (entry 6, 10% ee). The diphenylmethyl-substituted substrate **1g** afforded a selectivity lower than that of the benzyl derivatives **1d** and **1e** (entry 7, 72% ee). Finally, the trimethylsilylsubstituted compound **1h** showed only a small increase of stereoselectivity relative to the nonsubstituted system **1a** (entry 8, 40% ee).

A final series of experiments were run with magnesium perchlorate (Table 3). In this case also, the system was sensitive to water content (compare entries 1, 3 and 2, 4). When magnesium perchlorate was used without extra drying, substrate **1a** gave a moderate 46% ee (entry 1), and the

Table 3. Diels−Alder Reactions of **1a**−**h** in the Presence of 30 mol % $Mg(ClO_4)_2$ and (*R*)-**2** According to Equation 1

entry	substrate	R	time (h)	yield (*endo*/*exo*)	ee (*endo*)
1	**1a**	H	1.5	97% (10:1)	(*R*) 46%
2[a]	**1a**	H	15	96% (12:1)	(*R*) 70%
3	**1b**	Me	1.5	96% (40:1)	(*S*) 82%
4[a]	**1b**	Me	17	98% (34:1)	(*S*) 86%
5	**1d**	Bn	2	92% (32:1)	(*S*) 88%

[a] Freshly dried $Mg(ClO_4)_2$ was used.

reaction was finished within 90 min. With dried magnesium perchlorate, the enantioselectivity went up to 70% ee, but the reaction was slower and took 15 h (entry 2). In contrast to all the previous examples, the major isomer had (*R*)-configuration. By running the reaction with **1b**, the absolute configuration of the product was reversed to the "normal" (*S*)-isomer; an enantiomeric excess of 82% was obtained with magnesium perchlorate out of the bottle (entry 3) and 86% ee with dried Lewis acid (entry 4). Again, the benzyl derivative **1d** was more selective, and an enantiomeric excess of 88% was obtained without drying the magnesium perchlorate within 2 h.[12,13]

The structure of the magnesium complexes is highly dependent on the counterion, reaction conditions (water content), and steric bulk of the ligand. This renders the discussion of the mechanism quite difficult, but it seems reasonable to assume that the reactions with $MgBr_2$ are going through an octahedral complex and that reactions with dried magnesium perchlorate are going through a tetrahedral transition state.[14] From Tables 2 and 3, it is clear that the presence of a simple methyl group at C(4) has a dramatic influence on the stereochemical outcome of the magnesium-catalyzed processes. This correlates well with an increase of the twisting angle (see Figure 1) around the C(O)−N bond and to an increase of the steric bulk near the reactive olefinic moiety.

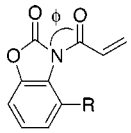
In the case of the tetrahedral magnesium perchlorate complexes, the nonsubstituted benzoxazolone reacts from the

(12) The reaction of 3-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene catalyzed by $Mg(ClO_4)_2$/**2** affords the Diels−Alder adduct in 72−73% ee: Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099−6110. Takacs, J. M.; Lawson, E. C.; Reno, M. J.; Youngman, M. A.; Quincy, D. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3073−3078.

(13) For magnesium(II)-catalyzed enantioselective Diels−Alder reactions, see refs 3c and 12 and (a) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671−7688. (b) Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron Lett.* **1996**, *37*, 3027−3030. (c) Takacs, J. M.; Quincy, D.; Shay, W.; Jones, B. E.; Ross, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3079−3087. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815−3818. (e) Ordonez, M.; Guerrero-de la Rosa, V.; Labastitda, V.; Llera, J. M. *Tetrahedron: Asymmetry* **1996**, 7, 2675−2686.

(14) For a discussion of the structure of magnesium(II)-bisoxazolines complexes with 3-acryloyl-1,3-oxazolidin-2-one, see ref 13a.

	R	ϕ
1a	H	14°
1b	Me	43°
1c	Et	47°
1d	CH_2Ph	46°



	R	ϕ
1e	CH_2(*p*-MeOPh)	46°
1f	CH_2*t*-Bu	64°
1g	$CHPh_2$	59°
1h	$SiMe_3$	59°

Figure 1. Dihedral angle ϕ as function of R calculated at the AM1 semiempirical level for the *Z*-s-*cis* conformer. (A more stable *E*-s-*cis* conformer also exists but is not relevant for chelation-controlled reactions).

si face to give the (*R*)-Diels−Alder adduct. This face is more shielded by the ligand, but because of twisting of the system it becomes less hindered than the *Re* face (Figure 2, **C**). Introducing a methyl group at C(4) of the benzoxazolone enhances the twisting and efficiently shields the *Si* face and the reaction occurs again from the *Re* face (Figure 2, **D**).

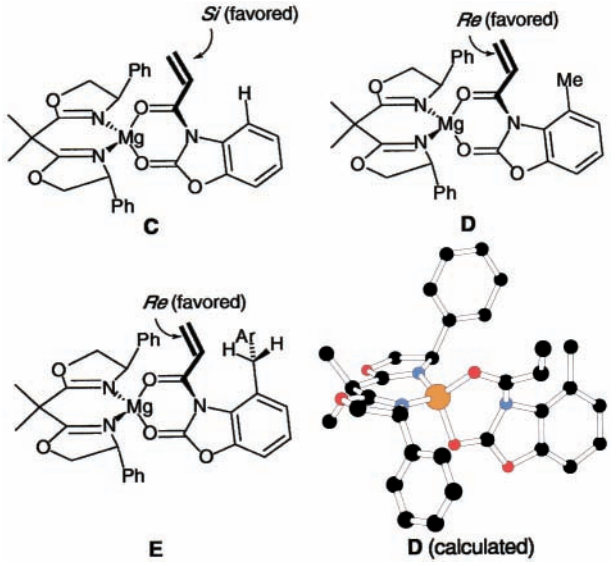


Figure 2. Proposed models for the magnesium-catalyzed reaction (based on PM3 calculations).

This complex has been examined by semiempirical PM3 calculations and a tentative model for the reactive conformation is presented in Figure 2. The model shows well the important shielding role of the methyl group at C(4) of the 1,3-benzoxazol-2-(3*H*)-one moiety. The size and nature of the R groups have a secondary influence on the stereohemical outcome of the reaction since it can participate more or less efficiently to the face shielding. For instance, we think that the good result obtained with the benzyl group can be attributed to a preferred conformation controlled by allylic 1,3-strain (Figure 2, **E**). The lower enantioselectivites observed for larger substituents such as CH_2*t*-Bu (**1f**), $CH(Ph)_2$ (**1g**), and $SiMe_3$ (**1h**) may possibly be attributed to a large twisting (ϕ = 59−64°) that does not allow for an efficient chelation of the metal ion.

Conclusions

By using a nonoptimized diphenyl bisoxazoline ligand **2**, we have demonstrated that proper choice of an achiral template on the acrylamide facilitates a good level of stereocontrol in Diels−Alder reactions with cyclopentadiene. These results fit well with a chiral relay effect in which the achiral template transmits the chiral information from the Lewis acid to the reacting center via a preferred conformation where a novel element of chirality (a chiral axis) is created. This strategy combines the advantage of the double induction (chiral catalyst plus chiral auxiliary) without the necessity of using an enantiopure chiral auxiliary, since the element of chirality is temporarily introduced during the chelation step.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1a**−**h** and **3a**−**h**, as well as analytical procedure for the determination of ee's. This material is available free of charge via the Internet at http://pubs.acs.org.

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