[7] Copies of the NMR spectra recorded in $CDCl_3$ and $[D_6]$DMSO, all binding data from NMR titration and isothermal calorimetry experiments, and Job plots are provided in the Supporting Information.
[8] The binding constants were calculated by fitting the data using NMRTit HG software, kindly provided by Prof. C. A. Hunter, University of Sheffield. See: A. P. Bisson, C. A. Hunter, J. C. Morales, K. Young, *Chem. Eur. J.* **1998**, *4*, 845.
[9] A. Cooper, *Curr. Opin. Chem. Biol.* **1999**, *3*, 557, and references therein.
[10] For the specific application of isothermal calorimetry to dicarboxylate recognition, see a) B. R. Linton, M. S. Goodman, E. Fan, S. A. van Arman, A. D. Hamilton, *J. Org. Chem.* **2001**, *66*, 7313. See also, for example, b) F. P. Schmidtchen, *Org. Lett.* **2002**, *4*, 431; c) B. Linton, A. D. Hamilton, *Tetrahedron* **1999**, *55*, 6027.
[11] The data give binding constants at the upper limit of detectability by NMR titrations (10^4–$10^5\,M^{-1}$) and it can be concluded that $K_a > 10^4\,M^{-1}$, but more precise values cannot be reliably obtained from the NMR titration data: a) L. Fielding, *Tetrahedron* **2000**, *56*, 6151; b) C. S. Wilcox, *Frontiers in Supramolecular Organic Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Dürr), VCH, Weinheim, **1991**, p. 123; c) G. Weber, S. R. Anderson, *Biochemistry* **1965**, *4*, 1942. See also the Supporting Information.
[12] K. A. Connors, *Binding Constants*, Wiley, New York, **1987**.
[13] The ITC data was obtained with a MicroCal VP-ITC isothermal calorimeter. Data was analyzed by nonlinear least-squares fitting using the Origin software supplied by MicroCal: T Wiseman, S. Williston, J. F. Brandts, L.-N. Lin, *Anal. Biochem.* **1989**, *179*, 131. Data was modeled using the 1:1 binding site model, or the model with two independent binding sites in cases where the data could not be fitted with the 1:1 binding site model (see ref. [10c])
[14] T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072.
[15] a) P. Güntert, C. Mumenthaler, K. Wüthrich, *J. Mol. Biol.* **1997**, *273*, 283; L. Brennan, D. L. Turner, A. C. Messias, M. L. Teodoro, J. LeGall, H. Santos, A. V. Xavier, *J. Mol. Biol.* **2000**, *298*, 61. Full details of experimental methods are provided in the Supporting Information.

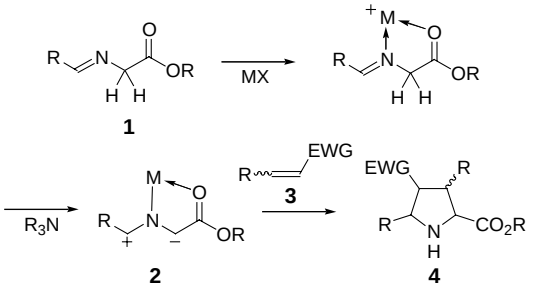
Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides—A Simple Approach to Optically Active Highly Functionalized Proline Derivatives**

Aase Sejr Gothelf, Kurt V. Gothelf, Rita G. Hazell, and Karl Anker Jørgensen*

The 1,3-dipolar cycloaddition reaction constitutes one of the most fundamental reactions for the stereoselective construction of five-membered heterocyclic compounds.[1] In recent years, the development of catalytic asymmetric reactions has been one of the challenging areas within the field of 1,3-dipolar cycloaddition reactions, and especially nitrones have been the focus of attention[2,3] as a result of the importance of the formed isoxazolidines as building blocks for more complex molecules.

Azomethine ylides can react in a 1,3-dipolar cycloaddition reaction with alkenes to form pyrrolidines, and several examples of the formation of optically active pyrrolidines based on diastereoselective reactions are known.[4,5] However, investigations on the metal-catalyzed enantioselective version of the 1,3-dipolar cycloaddition of azomethine ylides with alkenes are very limited. Grigg and co-workers[6] were the first to demonstrate that applying a stoichiometric amount of chiral cobalt or manganese complexes with ephedrine derivatives as the chiral ligand could give the cycloaddition product of azomethine ylides derived from imines of glycine alkyl esters with up to 96% *ee*. It has also been mentioned that silver(I) salts in combination with chiral phosphane ligands can catalyze the 1,3-dipolar cycloaddition reaction of azomethine ylides.[6b,7]

We present herein a new highly diastereo- and enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides with alkenes catalyzed by readily available chiral Lewis acids. Although there are few stable azomethine ylides,[8] most are unstable. Azomethine ylides **2** can be generated from, for example, imines of glycine alkyl esters **1** by reaction with a base in the presence of a Lewis acid complex. The metal-stabilized azomethine ylide **2** reacts with an alkene **3** to give highly functionalized pyrrolidines **4** (Scheme 1).



Scheme 1. Formation of highly functionalized pyrrolidines **4** from azomethine ylides **2** and alkenes **3**. EWG = electron-withdrawing group.

The reactions of *N*-benzylidene- and *N*-(2-naphthylmethylidene) glycinates **1a** and **1b**, respectively, with methyl acrylate (**3a**) and Et_3N as the base in the presence of chiral ligands such as the bisoxazolines (BOX) **5a**,**b**[9] and dibenzofuranyl-2,2′-bisoxazoline (DBFOX) **5c**[10] and Lewis acids were used in the screening process (Scheme 2). Some representative results are listed in Table 1.

The use of copper(II) salts in combination with the chiral bisoxazoline ligands **5a**,**b** as catalysts for the reaction of *N*-benzylidene glycinate **1a** with methyl acrylate (**3a**) gave high conversion only when using the (*S*)-*t*Bu-BOX (**5a**) ligand, but unfortunately product **4a** was formed as a racemate (Table 1, entries 1 and 2). When zinc(II)[9e] was used as the Lewis acid instead, the reaction proceeded smoothly and **4a** was formed with 76% *ee* using **5a** as the chiral ligand and THF as the solvent at room temperature (Table 1, entry 3). Furthermore, the reaction is also highly diastereoselective as only one

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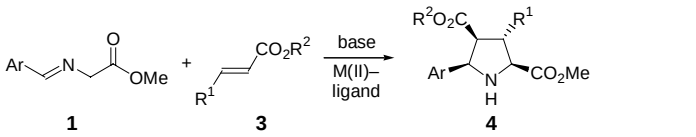
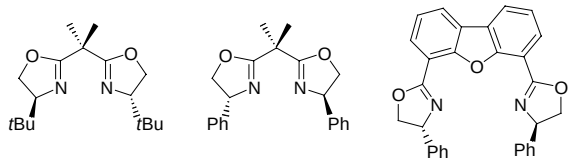


1
a: Ar = Ph
b: Ar = 2-Np
c: Ar = *p*-BrC_6H_4

3
a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Et
c: R^1 = H, R^2 = *t*Bu
d: R^1 = CO_2Me, R^2 = Me

4
a: Ar = Ph, R^1 = H, R^2 = Me
b: Ar = 2-Np, R^1 = H, R^2 = Me
c: Ar = 2-Np, R^1 = H, R^2 = Et
d: Ar = 2-Np, R^1 = H, R^2 = *t*Bu
e: Ar = *p*-BrC_6H_4, R^1 = H, R^2 = Me
f: Ar = Ph, R^1 = CO_2Me, R^2 = Me
g: Ar = 2-Np, R^1 = CO_2Me, R^2 = Me
h: Ar = *p*-BrC_6H_4, R^1 = CO_2Me, R^2 = Me



5a: (*S*)-*t*-Bu-BOX **5b**: (*R*)-Ph-BOX **5c**: (*R,R*)-Ph-DBFOX

Scheme 2. Chiral ligands **5a–c** used in the preparation of optically active pyrrolidines **4**.

Table 1. Representative results for the screening of reaction conditions for the catalytic enantioselective 1,3-dipolar cycloaddition reaction of *N*-benzylidene and *N*-(2-naphthylmethylidene) glycinate **1a**,**b** with methyl acrylate **3a**.[a]

Entry	Lewis acid	Ligand	Solvent	**1**	Conversion[b] (%)	*ee*[c] [%]
1	$Cu(OTf)_2$	**5a**	THF	**a**	**4a** (>95)	rac
2	$Cu(OTf)_2$	**5b**	THF	**a**	**4a** (<10)	n.d.[d]
3	$Zn(OTf)_2$	**5a**	THF	**a**	**4a** (>95)	78
4	$Zn(OTf)_2$	**5a**	neat	**a**	**4a** (>95)	79
5	$Zn(OTf)_2$	**5b**	THF	**a**	**4a** (<50)	n.d.[d]
6	$Zn(OTf)_2$	**5a**	THF	**b**	**4b** (>95)	78
7	$Zn(OTf)_2$	**5a**	neat	**b**	**4b** (>95)	76
8	$Zn(OTf)_2$	**5b**	neat	**b**	**4b** (>95)	17
9	$Zn(OTf)_2$	**5c**	neat	**b**	**4b** (>95)	7

[a] Lewis acid, ligand, and Et_3N (10 mol% each) were used. For experimental details, see Supporting Information. [b] Conversion determined by crude ^1H NMR spectroscopy. [c] Enantiomeric excesses were measured by chiral HPLC. [d] Not detected.

diastereomer of **4a** was observed by ^1H NMR spectroscopy. The same trends are found for *N*-(2-naphthylmethylidene) glycinate **1b** in the presence of Zn^{II}-*t*Bu-BOX (Table 1, entries 6 and 7), whereas the use of the Zn^{II}-Ph-BOX and Zn^{II}-Ph-DBFOX catalysts in the absence of solvent gave **4b** with low enantiomeric excess (Table 1, entries 8 and 9).

The reaction of *N*-(2-naphthylmethylidene) glycinate **1b** with methyl acrylate (**3a**) and Et_3N as the base catalyzed by Zn^{II}-*t*Bu-BOX was studied in different solvents. In less polar solvents such as Et_2O and toluene in which **1b** has a low solubility, the enantiomeric excess of **4b** was decreased to 23 and 25% *ee*, respectively, although complete conversion and diastereoselectivity was observed. In solvents such as CH_2Cl_2 and MeCN, the enantiomeric excess of **4b** was only slightly lower (65 and 62% *ee*) than in reactions performed in THF.

The influence of the amount of base on the enantiomeric excess of the reaction of **1b** with **3a** catalyzed by Zn^{II}-*t*Bu-BOX (10 mol%) in THF at room temperature was investigated. The addition of Et_3N (5–20 mol% relative to the azomethine ylide) showed that the enantioselectivity of **4b** was independent of the amount of base used, as *ee* values of 78–80% were found for all the reactions studied.

The potential of this new catalytic enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides with alkenes is demonstrated in the reactions of a series of imines of glycine methyl ester **1a-d** with different electron-deficient alkenes **3a–d** catalyzed by Zn^{II}-*t*Bu-BOX (Scheme 2). The results are presented in Table 2.

Table 2. Catalytic enantioselective 1,3-dipolar cycloaddition reaction of **1a–d** with various alkenes **3a–d** in the presence of Zn^{II}-*t*Bu-BOX (10 mol%) as catalyst in THF.[a]

Entry	Azomethine ylide	Dienophile	Yield[b] (%)	*ee*[c] [%]
1	**1a**	**3a**	**4a** (>95[d])	78
2[e]	**1a**	**3a**	**4a** (80)	88
3	**1b**	**3a**	**4b** (93)	78
4[e]	**1b**	**3a**	**4b** (84)	91
5[e,f]	**1b**	**3a**	**4b** (86)	87
6	**1b**	**3b**	**4c** (76)	68
7	**1b**	**3c**	**4d** (12)	<5
8	**1c**	**3a**	**4e** (89)	61
9[e]	**1c**	**3a**	**4e** (89)	94
10[e]	**1a**	**3d**	**4f** (78)	76
11	**1b**	**3d**	**4g** (84)	90
12	**1c**	**3d**	**4h** (87)	68

[a] $Zn(OTf)_2$-*t*Bu-BOX and Et_3N (10 mol% each) were used. For experimental details, see Supporting Information. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Conversion based on ^1H NMR spectroscopy. [e] Reaction temperature −20°C. [f] Reaction in the absence of solvent.

The reaction of *N*-benzylidene glycinate **1a** with methyl acrylate (**3a**) proceeds in high yield and only one diastereomer of **4a** is formed at room temperature with 78% *ee* (Table 2, entry 1). Performing the reaction at −20°C leads to an improvement in the enantioselectivity of **4a** to 88% *ee* (Table 2, entry 2). *N*-(2-Naphthylmethylidene) glycinate **1b** was treated with the different acrylates **3a-c** under various reaction conditions. At room temperature, the 1,3-dipolar cycloaddition adduct **4b** was obtained in high yield and as a diastereomerically pure product with 78% *ee* and an improvement in the enantioselectivity to 91% ee was observed at −20°C (Table 2, entries 3,4). The enantiomeric excess of the 1,3-dipolar cycloadducts formed is dependent on the ester substituent of the acrylate used. Ethyl acrylate (**3b**) reacted with **1b** to give the pyrrolidine **4c** in the same high yield and diastereoselectivity as did the methyl acrylate; however, the enantiomeric excess of **4c** dropped to 68% *ee* (Table 2, entry 6). For *tert*-butyl acrylate (**3c**), pyrrolidine **4d** was obtained in only 12% yield with <5% *ee* (Table 2, entry 7). The *p*-bromo-*N*-benzylidene glycinate **1c** reacted smoothly with **3a** in a highly diastereo- and enantioselective reaction with up to 94% *ee* (Table 2, entries 8 and 9). Dimethyl fumarate (**3d**) reacted in a highly diastereo- and enantioselective 1,3-dipolar cycloaddition reaction with the different azomethine ylides **1a–c**. The reaction of **1a** with **3d** gives four new stereogenic centers in the addition step, and in this reaction pyrrolidine **4f** was obtained in high yield and as one diastereomer with 76% *ee* (Table 2, entry 10). The 1,3-dipolar cycloaddition reaction of **1b** with **3d** at −20°C provided **4g**

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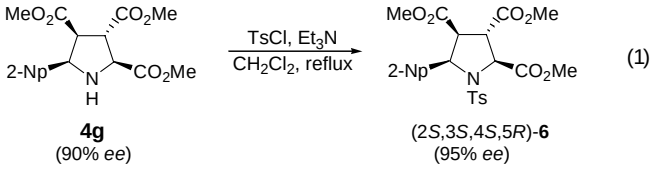
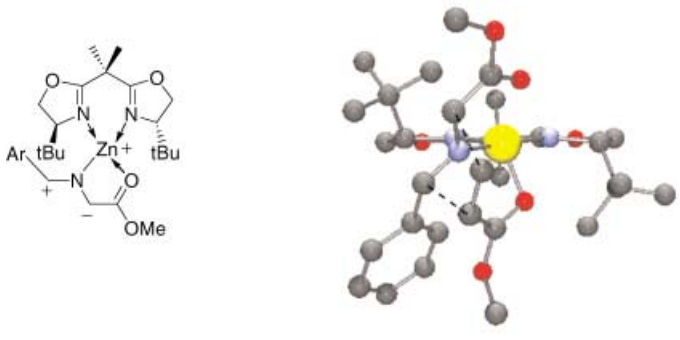
(Table 2, entry 11) in high yield and with excellent enantioselectivity (90% *ee*), whereas the reaction of **1c** gives a slightly lower enantiomeric excess, but the same high yield and diastereoselectivity (Table 2, entry 12).

To determine the absolute configuration of the product of the asymmetric Zn^{II}-*t*Bu-BOX-catalyzed 1,3-dipolar cycloaddition, compound **4g** was converted into **6** by tosylation [Eq. (1)]. An X-ray analysis of crystals of **6** revealed a 2*S*,3*S*,4*S*,5*R* configuration for **6** and therefore also for **4g** (see Supporting Information. CCDC 188992 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).).



4g (90% *ee*) (2*S*,3*S*,4*S*,5*R*)-**6** (95% *ee*) (1)

Based on the absolute configuration of **6**, we propose a model for the intermediate in the Zn^{II}-*t*Bu-BOX-catalyzed 1,3-dipolar cycloaddition reactions. This intermediate **7** (Figure 1), which consists of the azomethine ylide coordinating to the Zn^{II}-*t*Bu-BOX catalyst is an 18-electron complex and should, from an electronic point of view, give a tetrahedral arrangement of the ligands around the zinc center.[9d] The tetrahedral conformation would, however, lead to the opposite enantiomer as observed in the reaction. To account for the stereochemical outcome of the reaction, we propose a bipyramidal intermediate **8**, which also involves coordination of the α,β-unsaturated ester carbonyl group to the metal center (Figure 1). This additional coordination activates the α,β-unsaturated ester for reaction with the azomethine ylide, thus leading to the experimentally observed diastereomer and enantiomer of the product. Experimentally, the additional coordination is supported by the fact that acrylonitrile does not undergo reaction with metal-stabilized azomethine ylides, whereas the acrylates **3a–c** do.



7 **8**

Figure 1. Coordination complex **7** (unspecified geometry) consisting of the Zn^{II}-*t*Bu-BOX catalyst and the azomethine ylide, and the proposed bipyramidal intermediate **8**, involving coordination of the α,β-unsaturated ester carbonyl group to the metal center.

In conclusion, we have developed a new catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with alkenes. The reactions are catalyzed by zinc(II) bisoxazolines and proceed in high yield, thus giving diastereomerically pure products with up to 94% *ee*. This reaction provides an easy entry to optically active highly substituted pyrrolidines.

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[1] a) *Synthetic Applications of Dipolar Cycloaddition Chemistry towards Heterocyclic and Natural Products* (Eds.: A. Padwa, W. Pearson), Wiley-VCH, Weinheim, **2002**; b) P. A. Wade in *Comprehensive Organic Synthesis, Vol 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon Press, Oxford, **1991**, p. 1111; c) K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, Weinheim, **1988**.

[2] For reviews, see: a) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, 1449; c) M. Frederickson, *Tetrahedron* **1997**, *53*, 403; d) S. Karlsson, H.-E. Högsberg, *Org. Prep. Proced. Int.* **2001**, *33*, 103.

[3] Other types of dipoles: nitrile oxides: Y. Yoshida, Y. Ukaji, S. Fujinami, K. Inomata, *Chem. Lett.* **1998**, 1023; carbonyl ylides: D. M. Hodgson, P. A. Stubble, C. Johnstone, *Chem. Commun.* **1999**, 2185; A. Padwa, D. J. Austin, S. F. Hornbuckle, *J. Org. Chem.* **1996**, *61*, 63; S. Kitagaki, A. Anada, K. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417; diazoalkanes: S. Kanemasa, T. Kanai, *J. Am. Chem. Soc.* **2000**, *122*, 10710.

[4] M. Pichon, B. Figadère, *Tetrahedron: Asymmetry* **1996**, *7*, 927.

[5] a) J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, F. Fernández-Mari, A. Salinas, B. Olano, *Chem. Eur. J.* **2001**, *7*, 3533; b) R. Chinchilla, L. R. Falvello, N. Galindo, N. Carmen, *Eur. J. Org. Chem.* **2001**, 3133; c) S. Karlsson, H.-E. Högberg, *Tetrahedron: Asymmetry* **2001**, *12*, 1977; d) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666; e) A. Viso, R. Pradilla, A. Garcia, M. Alonso, C. Guerrero-Strachan, I. Fonseca, *J. Org. Chem.* **1997**, *62*, 2316; f) M. E. Kopach, A. H. Fray, A. I. Meuers, *J. Am. Chem. Soc.* **1996**, *118*, 9876; g) H. Waldmann, E. Blaeser, M. Jansen, H.-P. Letschert, *Chem. Eur. J.* **1995**, *1*, 150; h) A. D. Reed, L. S. Hegedus, *J. Org. Chem.* **1995**, *60*, 3787; i) M. T. Rispens, E. Keller, B. de Lange, R. W. J. Zijlstra, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 607; j) J. E. Baldwin, S. C. M. Turner, M. G. Moloney, *Synlett* **1994**, *925*; k) P. Garner, W. B. Ho, H. Shin, *J. Am. Chem. Soc.* **1993**, *115*, 10742; l) P. Deprez, J. Royer, H. P. Husson, *Tetrahedron: Asymmetry* **1991**, *2*, 1189; m) S. Kanemasa, T. Hayashi, J. Tanaka, H. Yamamoto, T. Sakurai, *J. Org. Chem.* **1991**, *56*, 4473.

[6] a) P. Allway, R. Grigg, *Tetrahedron Lett.* **1991**, *32*, 5817; b) R. Grigg, *Tetrahedron: Asymmetry* **1995**, *6*, 2475.

[7] Patent application: X. Zhang, **2002**, WO 01/58588 A1.

[8] G. Kill, J.-P. Fleury, *Bull. Soc. Chim. Fr.* **1968**, 4636.

[9] For reviews on *C*2-bisoxazoline–Lewis acid complexes as catalysts, see: a) A. K. Ghosh, P. Matahvivan, J. Capiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; b) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrian, J. Thorhauge, *J. Acc. Chem. Res.* **1999**, *32*, 605; c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *32*, 325; see also: d) J. Thorhauge, M. Roberson, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888, and references therein; e) S. Yao, M. Johansen, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans.* **1997**, 2345.

[10] S. Kanemasa, S. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074.

  0044-8249/02/11422-4412 $ 20.00+.50/0