ORGANIC LETTERS

2003
Vol. 5, No. 26
5043−5046

# *exo*- and Enantioselective Cycloaddition of Azomethine Ylides Generated from *N*-Alkylidene Glycine Esters Using Chiral Phosphine–Copper Complexes

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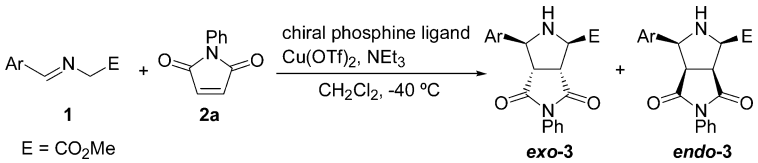
**Received October 24, 2003**

## ABSTRACT




**High diastereo- and enantioselectivities were obtained for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides generated from *N*-alkylideneglycine esters with dipolarophiles using chiral phosphine–copper complexes as catalysts. Whereas the cycloaddition of azomethine ylides catalyzed by metal salts generally afforded *endo*-adducts as the predominant product, the present method is the first example of an *exo*-selective cycloaddition.**

The cycloaddition of azomethine ylides, a representative 1,3-dipole, with alkenes is a useful tool for the construction of the pyrrolidine ring contained in many biologically active compounds,[1a] and the development of methods for the diastereo- and enantioselective cycloaddition of 1,3-dipoles is important in modern synthetic organic chemistry.[1b,c] Thus far, azomethine ylides have been generated by the ring opening of aziridines,[2] the 1,2-proton shift of *N*-arylidenebenzylamines,[3] abstraction of the α-proton from iminium salts[4] or metal complexes of *N*-alkylidene-α-amino acid esters,[5] and related reactions. We are also in the process of studying the cycloaddition of azomethine ylides generated by 1,2-silatropy of *N*-arylidene-α-silylbenzylamines[6] and 1,4-metallatropy of α-metalloamides.[6g,7] Among these, the diastereoselective cycloaddition of azomethine ylides generated from *N*-alkylideneamino acid esters in the presence of metal salts and bases has been a subject of active investigation.

(1) (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.: Pergamon: Oxford, U.K., 1996; Vol. 2, pp 207−257. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98* , 863−909. (c) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, pp 653−732.

(2) Huisgen, R.; Scheer, W.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397−464.

(3) For examples, see: (a) Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109−111. (b) Grigg, R.; Donegan, G.; Gunaratne, H. Q. N. *Tetrahedron* **1989**, *45*, 1723−1746.

(4) Huisgen, R.; Grashey, R. *Tetrahedron Lett.* **1963**, *4*, 1441−1445.

(5) For examples, see: (a) Tsuge, O.; Kanemasa, S.; Yoshioka, M. J. *Org. Chem.* **1988**, *53*, 1384−1391. (b) Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431−10442.

(6) (a) Komatsu, M.; Okada, H.; Yokoi, S.; Minakata, S. *Tetrahedron Lett.* **2003**, *44*, 1603−1606. (b) Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *Tetrahedron* **2003**, *59*, 197−205. (c) Komatsu, M.; Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S. *Org. Lett.* **2002**, *4*, 3505−3508. (d) Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813−5816. (e) Komatsu, M.; Ohno, M.; Tsuno, S.; Ohshiro, Y. *Chem. Lett.* **1990**, 575−576. (f) Iyoda, M.; Sultana, F.; Kato, A.; Yoshida, M.; Kuwatani, Y.; Komatsu, M.; Nagase, S. *Chem. Lett.* **1997**, 63−64. (g) Iyoda, M.; Sultana, F.; Komatsu, M. *Chem. Lett.* **1995**, 1133−1134.

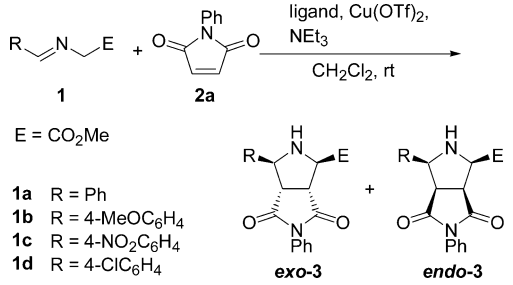
(7) (a) Komatsu, M.; Kasano, Y.; Yamaoka, S.; Minakata, S. *Synthesis* **2003**, 1398−1402. (b) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **2000**, *41*, 691−695. (c) Washizuka, K.-I.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969−12976. (d) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 8849−8853.

10.1021/ol036076s CCC: $25.00 
**Published on Web 12/03/2003**

Moreover, several examples of the asymmetric cycloaddition of azomethine ylides catalyzed by chiral metal complexes have been reported.[8] However, most 1,3-dipolar cycloadditions of azomethine ylides catalyzed by chiral metal complexes have shown only *endo*-selectivity. Because it is important that any of the desired diastereomers of cycloadducts can be synthesized selectively, a study of methods of *exo*-selective cycloaddition controlled by metal complexes is also needed. Herein, we report on the asymmetric cycloaddition of azomethine ylides with dipolarophiles catalyzed by copper(II)−chiral phosphine complexes. Surprisingly, this new method afforded the corresponding *exo*-cycloadducts exclusively in high enantioselectivity.

Our initial study showed that the Cu(II)−triphenylphosphine complex successfully catalyzes the *exo*-selective cycloaddition of *N*-benzylideneglycine methyl ester (**1a**) with *N*-phenylmaleimide (**2a**) in the presence of triethylamine at room temperature (*endo*/*exo* = 36/64, Scheme 1). To extend

**Scheme 1.** Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides Catalyzed by Chiral Phosphine Ligands




the result to higher *exo*- and enantioselectivities, several chiral phosphine ligands (Figure 1, ligands 4−7) were examined.

In the reactions using 20 mol % of $Cu(OTf)_2$ and 10 mol % of chiral phosphine ligands at room temperature, the use of BINAP (**7**) showed the best *exo*- and enantioselectivity (*exo*/*endo* = 87/13; ee of *exo*-adduct = 34%). To improve the *exo*- and enantioselectivities, reactions using BINAP and BINAP derivatives **8**−**10** under low-temperature conditions

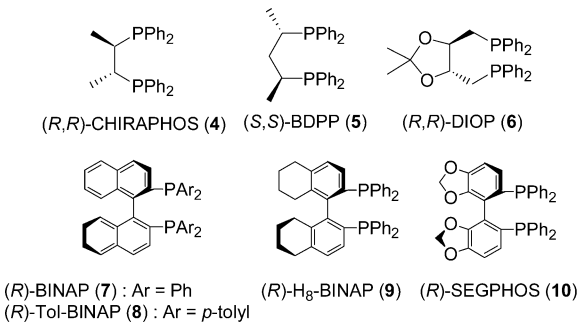
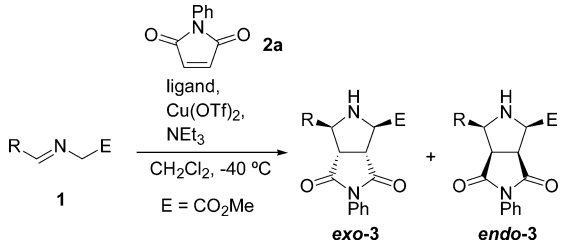



**Figure 1.** Chiral phosphine ligands[9] used in the asymmetric cycloaddition with imines **1** and dipolarophiles.

**Table 1.** Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with *N*-Phenylmaleimide (**2a**)[a]




| | | | | | cycloadducts | |
|---|---|---|---|---|---|---|
| entry | R | ligand | time (h) | yield (%) | *exo*/*endo*[b] | ee (*exo*, %) |
| 1 | Ph (**1a**) | **7** | 24 | 71 (**3a**) | >95/<5 | 64[c] |
| 2 | Ph (**1a**) | **8** | 24 | 40 (**3a**) | >95/<5 | 47[c] |
| 3 | Ph (**1a**) | **9** | 48 | 25 (**3a**) | 93/7 | 60[c] |
| 4 | Ph (**1a**) | **10** | 48 | 78 (**3a**) | 85/15 | 72[c] |
| 5 | 4-$MeOC_6H_4$ (**1b**) | **7** | 48 | 83 (**3b**) | >95/<5 | 87[d] |
| 6 | 4-$MeOC_6H_4$ (**1b**) | **10** | 48 | 0 (**3b**) | −/− | |
| 7 | 4-$NO_2C_6H_4$ (**1c**) | **7** | 24 | 77 (**3c**) | >95/<5 | 62[d] |
| 8 | 4-$NO_2C_6H_4$ (**1c**) | **10** | 24 | 32 (**3c**) | >95/<5 | 19[d] |
| 9 | 4-$ClC_6H_4$ (**1d**) | **7** | 48 | 83 (**3d**) | >95/<5 | 65[d] |
| 10 | 4-$ClC_6H_4$ (**1d**) | **10** | 48 | 94 (**3d**) | >95/<5 | 75[d] |

[a] Reaction conditions: imine **1** (1.0 equiv), **2a** (1.1 equiv), $Cu(OTf)_2$ (2.0 mol %), ligand (2.2 mol %), $NEt_3$ (4 mol %), $CH_2Cl_2$ (2.5 mL) at −40 °C. [b] Determined by $^1H$ NMR analysis. [c] Determined by HPLC analysis using DAICEL CHIRALPAK AS. [d] Determined by $^1H$ NMR analysis of the cycloadduct (*exo*) in the presence of $Eu(hfc)_3$.

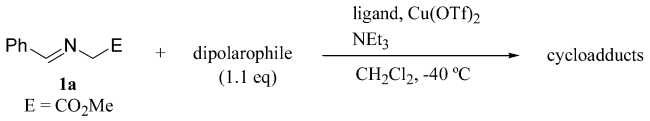
were examined (Table 1, entries 1−4). When the BINAP−Cu(II) complex was used, cycloadducts were obtained with the highest *exo*-selectivity (*exo*/*endo* = 99/1). In the case of SEGPHOS (**10**), the reaction afforded the highest ee of the *exo*-adduct (72% ee).

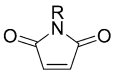
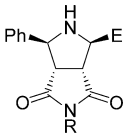
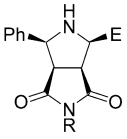
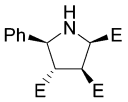
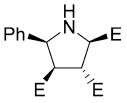
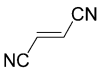
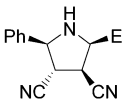
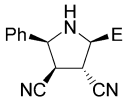
To extend the scope of this reaction, some other imines **1b**−**d** were employed in reactions catalyzed by BINAP− or SEGPHOS−$Cu(OTf)_2$ complexes (entries 5−10). Complete *exo*-selectivity was observed in the reactions of imines **1b**−**d**. When imines **1b** and **1c** were used, reactions using BINAP as the ligand showed reactivity and enantioselectivity higher than those for SEGPHOS. However, in the case of imine **1d**, having a chloro group on the phenyl ring, the reaction in the presence of SEGPHOS−$Cu(OTf)_2$ catalyst

(8) (a) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817−5820. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475−2486. (c) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236−4238. (d) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400−13401. (e) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174−10175.

(9) A part of references of chiral phosphine ligands are as follows. CHIRAPHOS: Fryzuk, M. D.; Bosnish, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262−6267. BDPP: MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273−2280. DIOP: Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481. BINAP: Miyashita, A.; Takeya, H.; Souchi, T.; Noyori R. *Tetrahedron* **1984**, *40*, 1245−1253. Tol-BINAP: Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 9, 3064. H8-BINAP: Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H.; *J. Org. Chem.* **1996**, *61*, 5510. SEGPHOS: Saito, T.; Sayo, N.; Xiaoyaong, Z.; Yokozawa, T. Patent EP 0850945, 1998.

**Table 2.** Asymmetric 1,3-Dipolar Cycloaddition of an Azomethine Ylide with Dipolarophiles[a]




| entry | dipolarophile | ligand | time (h) | total yield (%) | cycloadducts (diastereomer ratio)[b] | ee (%) |
|---|---|---|---|---|---|---|
| |  | | | |  *exo*-**3** :  *endo*-**3** | |
| 1 | R = Ph (**2a**) | **7** | 24 | 71 | **3a** (>95 : <5) | 64 (***exo***)[c] |
| 2 | | **10** | 48 | 78 | **3a** ( 89 : 11) | 72 (***exo***)[c] |
| 3 | R = Me (**2b**) | **7** | 24 | 64 | **3e** ( 72 : 28) | 55 (***exo***)[c] |
| 4 | | **10** | 24 | 64 | **3e** ( 86 : 14) | 62 (***exo***)[c] |
| |  **2c** | | | |  **11** :  **12** | |
| 5 | | **7** | 48 | 80 | (36 : 64) | 81 (**11**), 77 (**12**)[d] |
| 6 | | **10** | 60 | 0 | - | - |
| |  **2d** | | | |  **13** :  **14** | |
| 7 | | **7** | 24 | 57 | (14 : 86) | 75 (**13**), 82 (**14**)[e] |
| 8 | | **10** | 24 | 54 | (63 : 37) | 92 (**13**), 83 (**14**)[e,f] |

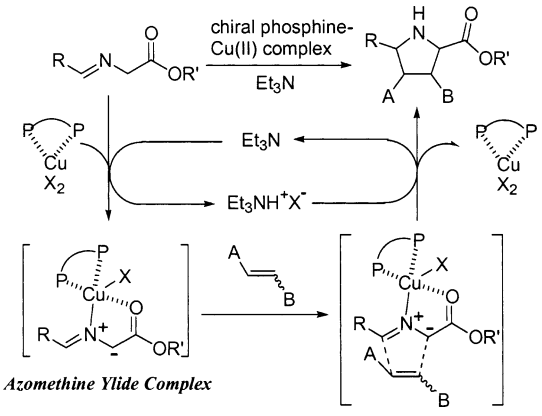
[a] Reaction conditions: imine **1a** (1.0 equiv), dipolarophile (1.1 equiv), $Cu(OTf)_2$ (2.0 mol %), ligand (2.2 mol %), $NEt_3$ (4 mol %), $CH_2Cl_2$ (2.5 mL) at −40 °C. [b] Determined by $^1H$ NMR analysis. [c] Determined by HPLC analysis using DAICEL CHIRALPAK AS. [d] Determined by HPLC analysis using DAICEL CHIRALCEL OD. [e] Determined by $^1H$ NMR analysis of the cycloadduct (*exo*) in the presence of $Eu(hfc)_3$. [f] In comparison with the result of entry 6, the enantioselectivities were reversed in the reaction giving cycloadducts **13** and **14** in entry 7.

proceeded in higher yield and enantioselectivity than with the BINAP catalyst.

Reactions using several other dipolarophiles were also investigated in a similar manner (Table 2). In the reaction with *N*-methylmaleimide (**2b**), *exo*-selectivity decreased in comparison with the reaction with *N*-phenylmaleimide (entries 1 and 2). Use of SEGPHOS (**10**) led to enantioselectivity higher than that with BINAP (**7**). In the cases where acyclic dipolarophiles such as dimethyl fumarate (**2c**) and fumaronitrile (**2d**) were used, both diastereomers were obtained in high enantioselectivity, except for the reaction with dipolarophile **2c** catalyzed by the SEGPHOS−Cu(II) complex (entries 5, 7, and 8). Interestingly, the reversal of enantioselectivity of the *exo*-adduct between the reactions catalyzed by BINAP− and SEGPHOS−Cu(II) complex was observed for the reactions with fumaronitrile (**2d**). These results strongly suggest that use of a suitable chiral ligand can lead to a high diastereo- and enantioselectivity in reactions with a variety of substrates.

A plausible mechanism for the cycloaddition reaction and explanation for diastereoselectivity are shown in Scheme 2 and Figure 2, respectively. Imines **1** coordinate to the chiral phosphine−Cu(II) complexes, and azomethine ylide−Cu(II) complexes are then generated by abstraction of α-protons

**Scheme 2.** Plausible Mechanism of the 1,3-Dipolar Cycloaddition of Azomethine Ylides Catalyzed by Chiral Phosphine−Cu(II) Complexes



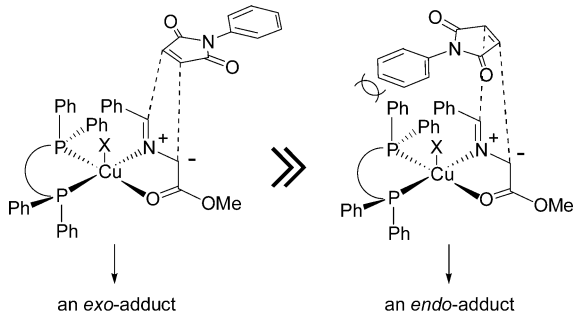



**Figure 2.** Proposed transition states leading to *exo*- and *endo*-cycloadducts.

of imine **1**−Cu(II) complexes by $NEt_3$. The azomethine ylide−Cu(II) complexes react with dipolarophiles, followed by elimination of the cycloadducts from the chiral Cu(II) complexes.

Transition state models of *exo*- and *endo*-selective reactions are shown in Figure 2. Stable isomers of azomethine ylide−Cu(II)−BINAP complexes were calculated by the ZINDO method.[10] It is thought that an *exo* approach of *N*-substituted maleimides to the Cu(II) complexes occurs predominantly because of steric repulsion between the substituents on the nitrogen atom of the N-substituted maleimides and the phenyl group on the phosphorus atom of the chiral phosphine ligands in the transition state corresponding to the *endo* approach. Reactions with *N*-phenylmaleimide gave higher *exo*-selectivity than those with *N*-methylmaleimide (Table 2, entries 1−4), since the phenyl group is bulkier than a methyl group.

In summary, we report here on the high *exo*- and enantioselective 1,3-dipolar cycloaddition of azomethine ylides catalyzed by chiral phosphine ligand−Cu(II) complexes. As a result, *exo*- and *endo*-selectivity can be controlled by the nature of the chiral metal complexes used in the reaction. An appropriate combination of chiral phosphine complexes and substrates led to the production of cycloadducts with high diastereo- and enantioselectivities. A detailed mechanistic study on enantioselectivity is currently, underway.

**Acknowledgment.** This work was supported, in part, by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science and a Grant-in-Aid from Handai Frontier Research Center. We also wish to acknowledge Dr. T. Saito, Takasago International Co., for providing some of the chiral phosphine ligands and the Instrumental Analysis Center, Faculty of Engineering, Osaka University.

**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The method is in Cache ver. 4.0 program (Fujitsu Corporation).