ORGANIC LETTERS

2005
Vol. 7, No. 19
4241−4244

Cu(I)-Catalyzed Highly Exo-selective and Enantioselective [3 + 2] Cycloaddition of Azomethine Ylides with Acrylates

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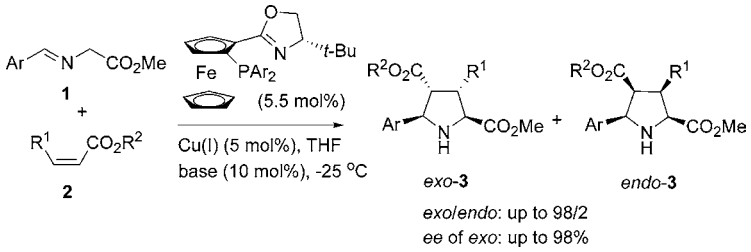
Received July 18, 2005

ABSTRACT



A novel Cu(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with acrylates has been developed. Up to 98/2 exo/endo selectivity and up to 98% enantiomeric excess have been achieved.

1,3-Dipolar cycloaddition is one of the most powerful methods for the construction of highly substituted five-membered heterocycles.[1] More specifically, 1,3-dipolar cycloaddition of azomethine ylides and alkenes afford substituted prolines with high stereoselectivities. It is well-known that substituted prolines are widely used as organic catalysts and also serve as important structural units in many biologically active molecules.[2,3] Among various versions of this reaction,[4] the most practical approach is the combination of *N*-metalated azomethine yildes and electron-deficient alkenes, which has been extensively investigated in both racemic[5,6] and chiral forms.[7,8] To the best of our knowledge, the endo adduct was either the major or the single product in most cases, while highly exo- and enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides has not yet been well developed.[9,10] Our group has explored Ag(I)-catalyzed

(1) (a) Harwood: L. M.; Vickers, R. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley and Sons: New York, 2002. (b) *1,3-Dipolar Cycloaddtion Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2.

(2) (a) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.

(3) (a) Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: New York, 1998; Vol. I, pp 323−358. (b) Obst, U.; Betschmann, P.; Lerner, C.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 855.

(4) For some reviews, see: (a) Kanemasa, S. *Synlett* **2002**, 1371. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927. (d) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.

(5) (a) Kanemasa, S.; Tsuge, O. In *Advances in cycloaddition*; Curran, D. P., Ed.; JAI: London, 1993; Vol. 3, pp 99−159. (b) Grigg, R.; Sridharan, V. In *Advances in cycloaddition*; Curran, D. P., Ed.; JAI: London, 1993; Vol. 3, pp 161−204.

(6) (a) Casas, J.; Grigg, R.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2001**, 1971. (b) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384.

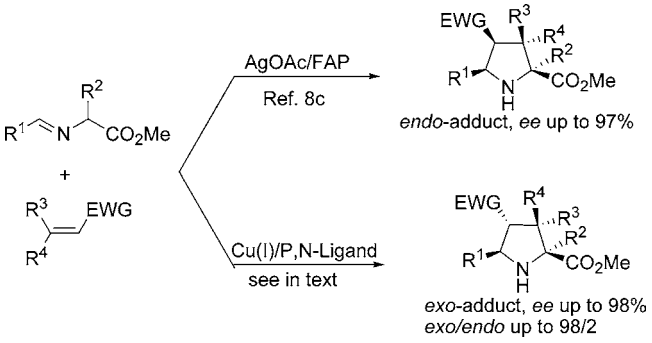
(7) (a) Ruano, J. L. G.; Tito, A.; Peromingo. M. T. *J. Org. Chem.* **2003**, *68*, 10013. (b) Ruano, J. L. G.; Tito, A.; Peromingo. M. T. *J. Org. Chem.* **2002**, *67*, 981. (c) Merino, I.; Laxmi, Y. R. S.; Florez, J.; Barluenga, J.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **2002**, *67*, 648. (d) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791. (e) Gally, G.; Liebscher, J.; Paetzel, M. *J. Org. Chem.* **1995**, *60*, 5005. (f) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475. (g) Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431. (h) Kanemasa, S.; Hayashi, T.; Tanaka, J.; Yamamoto, H.; Sakurai, T. *J. Org. Chem.* **1991**, *56*, 4473.

(8) (a) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (b) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (c) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (d) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (e) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.

10.1021/ol0516925 CCC: $30.25
Published on Web 08/13/2005

highly endo- and enantioselective 1,3-dipolar cyclization reactions.[8c] Herein, we present our investigation on the Cu(I)/P,N-ligand catalyzed [3 + 2] cycloaddition of *N*-metalated azomethine ylides with acrylates (Scheme 1). The exo adduct

Scheme 1. 1,3-Dipolar Cycloaddition of Azomethine Ylides and Alkenes



was obtained as the major product in all cases with high enantioselectivity. In addition, our study is the first to use copper(I) salt as the catalyst in the 1,3-dipolar cycloaddition reaction of azomethine ylides.

Our initial study began with *N*-(4-chlorobenzylidene)-glycine methyl ester (**1a)** as the 1,3-dipole and *tert*-butyl acrylate (**2a)** as the dipolarophile, and the experimental results are summarized in Table 1 and Figure 1. The first

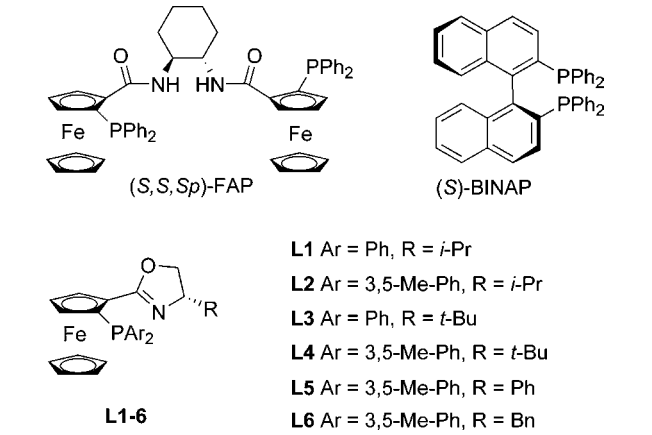


Figure 1. Structure of ligands for 1,3-dipolar cycloaddition.

attempt, using CuOAc (3 mol %) and (*S*,*S*,*Sp*)-FAP (3.3 mol %), afforded the desired product *exo*-**3a** in 62% yield and 22% ee along with 15% of *endo*-**3a** (entry 1, Table 1). The stereochemistry was confirmed by the NOESY spectrum (see the Supporting Information). Higher enantioselectivities could be achieved when methanol was applied as the solvent; however, the yields were still only moderate (entries 2 and 3, Table 1). Various chiral ligands other than FAP were next employed in this reaction (Figure 1). We found that several phosphino-oxazoline ligands **L1**−**6**,[11] in combination with CuOAc, could catalyze this [3 + 2] cycloaddition reaction, providing good exo selectivity and high enantiomeric excesses of exo adduct (entries 5−10, Table 1). Notably, the highest exo selectivity (exo adduct 76%; endo adduct 5% based on isolated yield) and enantiomeric excess (89% ee for exo adduct) were obtained when **L4**, which is derived from (*S*)-*tert*-leucinol, was employed (entry 8, Table 1). The yield and enantiomeric excess of the exo adduct could be further improved by applying $CuClO_4$ as the copper precursor and conducting the reaction at a lower temperature (compare entries 8 and 12, Table 1). Thus, the optimized reaction conditions were established as 5 mol % of $CuClO_4$, 5.5 mol % of **L4**, and 10 mol % of Et_3N in THF at −25 °C.[12] In contrast to the excellent enantiomeric excess of the exo adduct, very low enantiomeric excesses (about 5%) of the corresponding endo adduct were observed under the optimized conditions.

To explore the scope of Cu(I)/**L4** catalytic system, the [3 + 2] cycloadditions of various imines **1a**−**i** with several dipolarophiles **2a**−**d** were carried out under the optimized

Table 1. Screening Reaction Conditions for the Enantioselective Cu(I)-Catalyzed [3 + 2] Cycloaddition Reaction of *N*-(4-Chlorobenzylidene)glycine Methyl Ester **1a** and *tert*-Butyl Acrylate **2a**[a]

entry	Cu(I) (5 mol %)	ligand (5.5 mol %)	solvent	*T* (°C)	yield[b] (%) exo	yield[b] (%) endo	ee of exo[c] (%)
1[d]	CuOAc	(*S*,*S*,*Sp*)-FAP	THF	rt	62	15	−22
2[d]	CuOAc	(*S*,*S*,*Sp*)-FAP	MeOH	rt	58	10	−75
3[d]	CuOAc	(*S*,*S*,*Sp*)-FAP	MeOH	−20	46	9	−83
4[d]	CuOAc	(*S*)-BINAP	MeOH	rt	54	<5	<2
5	CuOAc	**L1**	THF	0	62	20	70
6	CuOAc	**L2**	THF	0	72	11	76
7	CuOAc	**L3**	THF	0	67	16	86
8	CuOAc	**L4**	THF	0	76	5	89
9	CuOAc	**L5**	THF	0	64	12	77
10	CuOAc	**L6**	THF	0	69	16	72
11	$CuClO_4$	**L4**	THF	0	92	6	89
12[e]	$CuClO_4$	**L4**	THF	−25	85	4	91

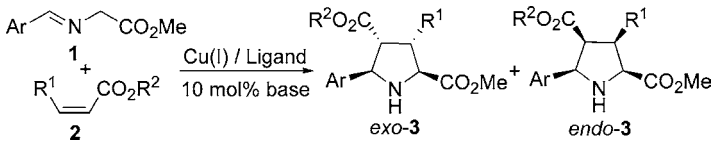
[a] 10 mol % of Et_3N was applied as the base. For experimental details, see the Supporting Information. [b] Isolated yields after column chromatography. [c] Enantiomeric excesses were measured by chiral HPLC. [d] 3 mol % of CuOAc, 3.3 mol % of ligand, and 10 mol % of $(i\text{-Pr})_2NEt$ were applied. [e] NMR spectroscopic analysis of the crude product indicated the ratio of exo/endo was 96/4; also see entry 1, Table 2.

(9) (a) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*, 12776. (b) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043. (c) Ayerbe, M.; Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **1998**, *63*, 1795. (d) Nyerges, M.; Rudas, M.; Toth, G.; Herenyi, B.; Kadas, I.; Bitter, I.; Toke, L. *Tetrahedron* **1995**, *51*, 13321. (e) Harwood: L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D. J.; Walliams, C. E. *Synlett* **1993**, 777.

(10) For asymmetric exo-selective [3 + 2] cycloaddition of nitrones, see: Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (b) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349.

(11) For Cu(I)-P,N-ligand catalyzed asymmetric mannich reactions of glycine derivatives with immines, see: Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583 and references therein.

Table 2. Cu(I)-Catalyzed Enantioselective Cycloaddition of **1a**−**i** with Various Dipolarophile Substrates **2a**−**d**[a]

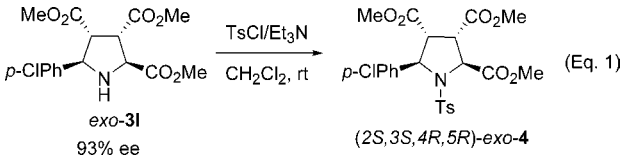


entry	Ar in **1**	R^1,R^2 in **2**	base	adduct	exo/endo[b]	yield of exo[c] (%)	ee of exo[d] (%)
1	*p*-ClPh (**1a**)	H,*t*-Bu (**2a**)	Et_3N	**3a**	96/4	85	91
2[e]	*o*-ClPh (**1b**)	**2a**	Et_3N	**3b**	76/24	71	98
3	*m*-ClPh (**1c**)	**2a**	Et_3N	**3c**	96/4	80	91
4	*p*-FPh (**1d**)	**2a**	Et_3N	**3d**	94/6	70	91
5	*p*-CNPh (**1e**)	**2a**	DBU	**3e**	95/5	84	91
6	Ph (**1f**)	**2a**	DBU	**3f**	95/5	65	84
7	*p*-MePh (**1g**)	**2a**	DBU	**3g**	97/3	61	89
8	*p*-OMePh (**1h**)	**2a**	DBU	**3h**	97/3	82	91
9	*β*-Naph (**1i**)	**2a**	DBU	**3i**	98/2	84	90
10[f]	**1a**	H,Me (**2b**)	Et_3N	**3j**	83/17	77	91
11[g]	**1a**	H,Et (**2c**)	Et_3N	**3k**	84/16	79	91
12[h]	**1a**	CO_2Me,Me (**2d**)	Et_3N	**3l**	98/2	87	93

[a] All of the reactions were carried out under the optimized reaction conditions: 5 mol % of $CuClO_4$, 5.5 mol % of **L4**, and 10 mol % of base in THF at −25 °C for 20 h. [b] The ratio of exo/endo was determined by NMR spectroscopic analysis of the crude product; exo and endo diastereoisomers were readily separated by flash column chromatography. [c] Isolated yields after column chromatography. [d] Enantiomeric excesses were measured by chiral HPLC. [e] 20% of *endo*-**3b** (42% ee) was isolated. [f] 13% of *endo*-**3j** (67% ee) was isolated. [g] 16% of *endo*-**3k** (58% ee) was isolated. [h] Reaction was carried at 0 °C, and 1 mol % of CuOAc and 1.1 mol % of **L4** were employed.

reaction conditions, and the results are summarized in Table 2. Very high exo selectivities and excellent enantiomeric excesses were observed in all of the reactions. The cycloaddition of **1b** with *tert*-butyl acrylate **2a** gave the best enantiomeric excess (98%) of the exo adduct **3b** in 71% isolated yield, though a relatively higher percentage of the endo adduct was observed (exo/endo = 76/24, entry 2, Table 2). For imines bearing an electron-withdrawing substituent on the phenyl, the reactions proceeded smoothly in the presence of 10 mol % of triethylamine as the base (entries 1−4, Table 2), while for substrates having no substituent or an electron-donating substituent, such as a methyl or methoxy group, on the phenyl unit, the reactions were sluggish and could not reach complete conversion under the same reaction conditions (even with a prolonged reaction time). However, we were pleased to find that the reactions of these substrates could take place more efficiently when a stronger base, such as 8-diazabicyclo[5.4.0]undec-7-ene (DBU), was used instead of triethylamine, leading to the desired exo adducts in high yields and excellent enantioselectivities (entries 5−9, Table 2). The reactions of **1a** with other acrylates, such as methyl acryate (**2b)** and ethyl acrylate (**2c)**, also proceeded smoothly at −25 °C with the same catalytic system. The corresponding exo adducts **3j** and **3k** were obtained with high ee's (91% for both) and good yields (entries 10 and 11, Table 2).

Cu(I)/**L4**-catalyzed 1,3-dipolar cycloaddition between imine **1a** and dimethyl maleate **2d** afforded exo adduct **3l** in excellent diastereo- and enantioselectivities (87% yield, exo/endo = 98/2, 93% ee), furnishing four new stereogenic centers in one cycloaddition process (entry 12, Table 2). Notably, this transformation reached completion within a few hours even with catalyst loading as low as 1 mol %. The absolute configuration of the exo adduct **3l** was determined by X-ray analysis of its corresponding tosylate derivative **4** (eq 1), and it was assigned as 2*S*,3*S*,4*R*,5*R* (see the Supporting Information).[13]



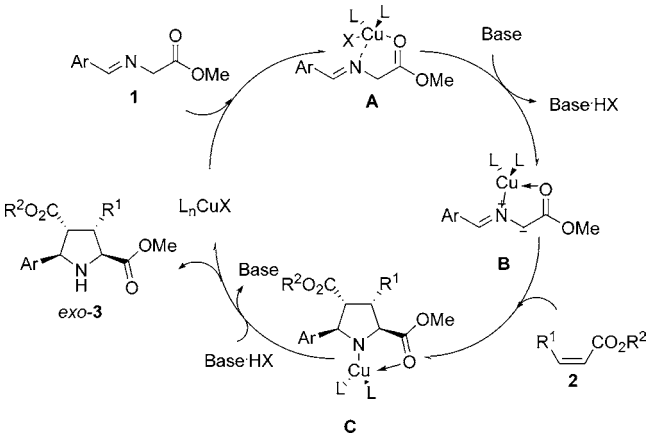
(Eq. 1)

On the basis of our results, we propose the following reaction pathway (Scheme 2). The first step is the formation of complex **A** by coordination of imine **1** to the copper(I) catalyst. The reactive azomethine ylide−copper(I) complex **B** is generated through the abstraction of a proton by the amine base. Complex **B** reacts with different dipolarphiles to give intermediate **C**, which releases the desired cycloaddition product and regenerates both the active catalyst and the base. The intermediate **B** is an 18-electron complex and has a tetrahedral arrangement of the ligands around the copper metal atom. The steric repulsion between the electron-

(12) **General Procedure.** The catalyst was prepared by stirring $Cu(CH_3CN)_4ClO_4$ (8.2 mg, 0.025 mmol, 5 mol %) and ligand **L4** (15.1 mg, 0.0275 mmol, 5.5 mol %) in THF (2 mL) for 1 h at room temperature. The mixture was then cooled to −25 °C, imine substrate **1** (0.50 mmol), dipolarophile **2** (0.75 mmol, 1.5 equiv), and base (0.05 mmol, 10 mol %) were added subsequently, and the resulting mixture was stirred at −25 °C for 20 h. When the reaction was complete as monitored by TLC, the mixture was passed through a short column of silica gel and the diastereometric ratio (exo/endo) was determined by the NMR spectroscopic analysis of the crude product. The pure adducts were then purified by column chromatography on silica gel (hexanes/ethyl acetate/1% triethylamine).

(13) CCDC-268934 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 depost@ccdc.cam.ac.uk).

Scheme 2. Mechanism of Cu(I)-Catalyzed 1,3-Dipolar Cycloaddition



withdrawing group of dipolarophiles and the substituent of the ligand inhibits the endo approach. This may contribute to the good exo selectivity that is observed for this Cu(I)-catalyzed transformation.

In conclusion, we have developed a novel Cu(I)/P,N-ligand catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with acrylates, providing exo products of polysubstituted proline derivatives in up to 98% enantiomeric excess. To our knowledge, these results are the best to date for metal-catalyzed 1,3-dipolar cycloaddition of *N*-metalated azomethine ylides in terms of both exo selectivities and enantioselectivities. Further investigation of the reaction scope and detailed mechanism study are underway.

Acknowledgment. This work was supported by National Institutes of Health grants, and we thank Dr. H. Yennawar for solving the crystal structure.

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

OL0516925