

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/7464039>

Highly Enantioselective Copper(I)–Fesulphos–Catalyzed 1,3–Dipolar Cycloaddition of Azomethine Ylides

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · NOVEMBER 2005

Impact Factor: 12.11 · DOI: 10.1021/ja0552186 · Source: PubMed

CITATIONS

177

READS

80

3 AUTHORS, INCLUDING:



Silvia Cabrera

Universidad Autónoma de Madrid

52 PUBLICATIONS 1,438 CITATIONS

SEE PROFILE



Ramón Gómez Arrayás

Universidad Autónoma de Madrid

110 PUBLICATIONS 3,103 CITATIONS

SEE PROFILE

Highly Enantioselective Copper(I)–Fesulphos-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides

Silvia Cabrera, Ramón Gómez Arrayás, and Juan C. Carretero*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Received August 1, 2005; E-mail: juancarlos.carretero@uam.es

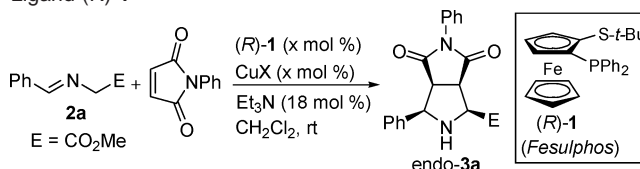
The catalytic asymmetric 1,3-dipolar cycloaddition reaction is conceptually an extremely powerful and efficient strategy for the enantioselective construction of five-membered heterocycles.¹ Of particular interest is the reaction between azomethine ylides and activated alkenes to form functionalized pyrrolidines,² which are key units in medicinal chemistry and highly valuable synthetic building blocks.^{2b} In addition, proline derivatives have found outstanding applications as organic catalysts in many asymmetric transformations.³ Despite its great synthetic potential, only a few protocols for the catalytic enantioselective 1,3-dipolar reaction of azomethine ylides have been developed to date.⁴ In particular, the catalytic systems Zn(II)/*t*-BuBOX,^{4h} Ag(I)/xylyl-FAP,^{4g} and Ag(I)/P,N-ligands^{4a,f} afford high endo-selectivities and asymmetric inductions in the intermolecular 1,3-dipolar cycloaddition of arylidene imines of α -aminoesters with some typical electron-deficient alkenes. On the other hand, Cu(II)/BINAP^{4e} and, quite recently, Cu(I)/P,N-ligands^{4b} have been reported as efficient catalytic systems for some exo-selective cycloadditions. However, compared to other catalytic enantioselective 1,3-dipolar cycloadditions, especially those involving nitrones,⁵ the reaction of azomethine ylides is in its infancy and the development of novel catalysts showing high reactivity and enantioselectivity with regard to a broad variety of dipolarophiles and azomethine ylides remains a great challenge.⁶

We recently described a novel family of readily available planar chiral P,S-ligands, Fesulphos ligands⁷ (**1**), whose copper(I) complexes showed excellent performance in catalytic enantioselective formal aza-Diels–Alder reactions of *N*-sulfonyl imines.⁸ Extending the interest of these ligands in asymmetric catalysis, herein we report that the combination of copper(I) salts and ligand **1**⁹ results in a highly reactive catalyst system displaying exceptional enantioselectivity and broad scope in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides.

The cycloaddition of *N*-benzylideneglycine methyl ester (**2a**) with *N*-phenylmaleimide in the presence of catalytic amounts of Et₃N (18 mol %) and ligand (*R*)-**1** (10 mol %) was selected as a model reaction for the screening of several copper(I) salts¹⁰ (10 mol %). For this transformation it was reported that the use of Cu(II)/chiral diphosphine complexes resulted in the formation of adduct **3a** with high exo-selectivity and enantioselectivity, while *endo*-**3a** was isolated as a minor product with very low enantiomeric excess.^{4e}

In our case, adduct *endo*-**3a** was obtained in all cases with very high endo-selectivity (Table 1). However, while CuCl displayed low reactivity and very poor enantioselectivity (entry 1), more electrophilic copper sources such as Cu(MeCN)₄PF₆ (entry 2) or Cu(MeCN)₄ClO₄ (entry 3) led to *endo*-**3a** in good yields and with complete enantiocontrol (>99% ee) within 15 min at room temperature. The outstanding reactivity of the combination of CuClO₄–Fesulphos allowed a sharp reduction of the catalyst loading. For instance, using 0.5 mol % of the catalyst system, the reaction was complete in 1 h, preserving the high yield (86%) and

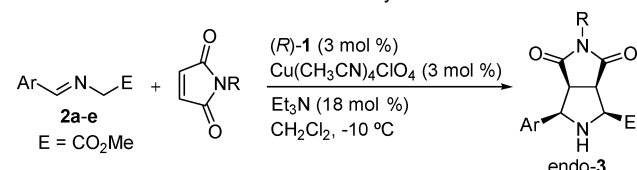
Table 1. Cu(I)-Catalyzed Reaction of *N*-Benzylideneglycine Methyl Ester **2a** with *N*-Phenylmaleimide in the Presence of Ligand (*R*)-**1**



entry	CuX	x (mol %)	time (min)	endo: exo ^a	yield (%) ^b	ee (%) ^c
1	CuCl	10	1440	94:6	51	30
2	Cu(MeCN) ₄ PF ₆	10	15	96:4	74	>99
3	Cu(MeCN) ₄ ClO ₄	10	15	98:2	78	>99
4	Cu(MeCN) ₄ ClO ₄	0.5	60	97:3	86	>99
5 ^d	Cu(MeCN) ₄ ClO ₄	3	30	>98:<2	81	>99

^a Determined from the crude ¹H NMR spectra. ^b Isolated yield of *endo*-**3a** after column chromatography. ^c Determined by HPLC (Chiralpak AS column). ^d Reaction performed at –10 °C.

Table 2. Structural Variations at the Aryl Imine and Maleimide



entry	Ar	R	time (min)	endo: exo ^a	product	yield (%) ^b	ee (%) ^c
1	2-Naph	Ph	60	97:3	3b	81	>99
2	(<i>p</i> -F)C ₆ H ₄	Ph	60	>98:<2	3c	82	>99
3	(<i>p</i> -OMe)C ₆ H ₄	Ph	60	>98:<2	3d	81	>99
4	<i>o</i> -Tol	Ph	30	>98:<2	3e	85	>99
5 ^d	Ph	Me	15	>98:<2	4a	97	>99

^a Determined from crude ¹H NMR spectra. ^b Isolated yield. ^c Determined by HPLC (Chiralpak AS and Chiralcel OD columns). ^d Reaction performed at room temperature.

the virtually complete enantioselectivity (entry 4). To the best of our knowledge, these levels of reactivity and enantiocontrol are the highest reported so far for catalytic asymmetric [3+2] cycloaddition of azomethine ylides. Interestingly, upon lowering the reaction temperature to –10 °C, both perfect endo-selectivity (>98% endo) and enantioselectivity (>99% ee) were observed within 30 min of reaction (3 mol % of catalyst; entry 5).

To evaluate the scope of this cycloaddition protocol, a representative set of aryl imines of glycine methyl ester was surveyed under the optimal experimental conditions (3 mol % of catalyst at –10 °C in CH₂Cl₂). As shown in Table 2, the reactions occurred with high yield (81–97%) and exceptional levels of endo-selectivity and enantioselectivity (ee > 99%), regardless of the aryl substitution at the imine and at the maleimide (R² = Ph or Me).

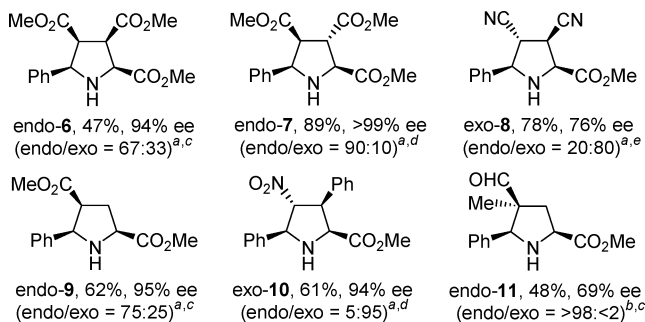
Table 3. Enantioselective Synthesis of Pyrrolidines Having a Quaternary Center at C-2 or C-5

R^1
 R^2
 R^3
4a-e
 $\text{E} = \text{CO}_2\text{Me}$

$(R)\text{-1}$ (3 mol %)
 $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$ (3 mol %)
 Et_3N (18 mol %)
 CH_2Cl_2 , -10°C

Ph
 O
 O
 R^1
 R^2
 R^3
 H
endo-5a-e

entry	R ¹	R ²	R ³	time (h)	endo:exo ^a	product	yield (%) ^b	ee (%) ^c
1	Ph	H	Me	48	>98:<2	5a	50	80
2	2-Naph	H	Me	1	>98:<2	5b	78	92
3 ^d	Ph	Ph	H	1	>98:<2	5c	92	93
4	Ph	Me	H	1	>98:<2	5d	78	94
5	(<i>p</i> -Cl)C ₆ H ₄	Me	H	1	>98:<2	5e	80	>99

^a Determined by ¹H NMR from the crude reaction mixture. ^b Isolated yield.^c Determined by HPLC (Chiralpak AS and Chiralcel OD columns).^d E = CO₂Et**Figure 1.** 1,3-Dipolar cycloaddition with other dipolarophiles. ^aIn THF. ^bIn CH₂Cl₂. ^cReaction at room temperature. ^dReaction at −10 °C. ^eReaction at −30 °C.

Next, we studied the effect of incorporating an α -substituent at the azomethine on the reactivity and enantioselectivity of the process. Although such dipoles are of great interest because they generate pyrrolidines with a quaternary stereocenter at C-2, only the AgOAc-QUINAP catalyst system had been studied with this type of dipoles.^{4f} As depicted in Table 3, the reaction of iminoesters **4a** and **4b** with *N*-phenylmaleimide at −10 °C using 3 mol % of catalyst led to **5a** and **5b** with complete endo-selectivity and good enantiocontrol (80–92% ee, entries 1 and 2).¹¹ We also tested the commercially available glycine ethyl ester benzophenone Schiff base **4c**.¹² Pleasingly, its reaction with *N*-phenylmaleimide was complete in 1 h under identical reaction conditions, affording **endo-5c** in 92% yield and 93% ee (entry 3). Encouraged by this result, we extended this study to azomethine ylide precursors having two different groups at the ketimine moiety, a kind of azomethine ylides not yet explored even in non-enantioselective 1,3-dipolar cycloadditions. Remarkably, the 1,3-dipoles derived from the ketimines of acetophenone and *p*-chloroacetophenone (entries 4 and 5, respectively) reacted mildly under the standard reaction conditions, providing with virtually complete diastereoselectivity the pyrrolidines **5d** and **5e**, with a stereogenic quaternary center at C-5, in 94% ee and >99% ee, respectively.

Finally, to explore more deeply the scope and generality of this novel [2+3] cycloaddition protocol, other dipolarophiles of varied nature were also examined with a 3 mol % of catalyst loading. As shown in Figure 1, both *cis* and *trans* diactivated acyclic alkenes (dimethyl maleate, dimethyl fumarate, and fumarodinitrile¹³) proved to be excellent substrates for this reaction, providing high asymmetric inductions (76 → 99% ee), although the endo/exo selectivity¹¹ was poorer than in the case of the maleimide dipolarophiles.

Interestingly, complete regioselectivity and high reactivity were also observed with a variety of monoactivated alkenes, such as methyl acrylate, β -nitrostyrene,¹³ and methacrolein, providing the corresponding pyrrolidines in 95%, 94%, and 69% ee, respectively. The reaction with methacrolein, which allows the creation of a quaternary stereocenter at C-4 (product **endo-11**), deserves particular attention.

In conclusion, the Cu(I)–Fesulphos catalyst system shows excellent performance in enantioselective 1,3-dipolar cycloadditions of azomethine ylides. High to very high levels of reactivity, endo/exo selectivity, and enantioselectivity are achieved with a wide variety of azomethine ylides and dipolarophiles with 0.5–3 mol % of catalyst loading. Mechanistic studies, as well as the extension of this protocol to other dipoles and dipolarophiles, are under current investigation in our laboratory.

Acknowledgment. Financial support by the MEC (project BQU2003-0508) and Consejería de Educación de la CAM (MAT/0016/2004) is gratefully acknowledged. S.C. thanks the UAM for a Predoctoral Fellowship. R.G.A. thanks the MEC for a Ramón y Cajal Contract. We thank the reviewers for helpful suggestions.

Supporting Information Available: Experimental procedures, characterization data of new compounds, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For recent reviews, see: (a) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; p 211. (b) Gothelf, K. V.; Jørgensen, K. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W., Eds.; Wiley & Sons: New York, 2002; Chapter 12, p 817. (c) Kanemasa, S. *Synlett* **2002**, 1371.
- (2) Recent reviews: (a) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, 16, 2047. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W., Eds.; Wiley & Sons: New York, 2002; Chapter 3.
- (3) For a recent review, see: Bolm, C.; Rantanen, T.; Schiffrers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, 44, 1758.
- (4) (a) Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, 7, 5055. (b) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, 7, 4241. (c) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431. (d) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, 43, 5971. (e) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, 5, 5043. (f) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, 125, 10174. (g) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, 124, 13400. (h) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, 41, 4236.
- (5) For some very recent reports, see: (a) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, 44, 6187. (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, 127, 5764. (c) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, 7, 1431. (d) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabakaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, 7, 2349.
- (6) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, 44, 6272.
- (7) (a) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, 43, 3944. (b) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, 68, 3679. (c) Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512.
- (8) Mancheño, O. G.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, 126, 456.
- (9) Gram quantities of ligand (*R*)-**1** are readily obtained in three steps from ferrocene (see ref 7b).
- (10) Copper(II) salts led to oxidation of the Fesulphos ligand to the corresponding phosphine oxide.
- (11) The stereochemical assignment of the endo/exo adducts has been established by comparison with bibliographic data for known compounds, as well as NMR studies (for details see Supporting Information). In the case of the *trans* disubstituted dipolarophiles, endo refers to the pyrrolidine with *cis* stereochemistry at C4–C5.
- (12) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, 122, 6078.
- (13) For exo-selective 1,3-dipolar cycloadditions of fumarodinitrile and *trans*- β -nitrostyrene, see ref 4e and Ayerle, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, 63, 1795.

JA0552186