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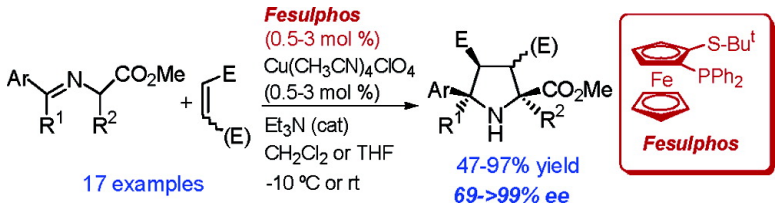

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Highly Enantioselective Copper(I)−Fesulphos-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides

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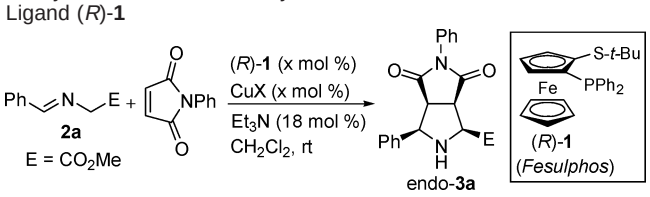
The catalytic asymmetric 1,3-dipolar cycloaddition reaction is conceptually an extremely powerful and efficient strategy for the enantioselective construction of five-membered heterocycles.[1] Of particular interest is the reaction between azomethine ylides and activated alkenes to form functionalized 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 catatytic 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 ligands[7] (**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 Et_3N (18 mol %) and ligand (*R*)-**1** (10 mol %) was selected as a model reaction for the screening of several copper(I) salts[10] (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 $Cu(MeCN)_4PF_6$ (entry 2) or $Cu(MeCN)_4ClO_4$ (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 $CuClO_4$−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

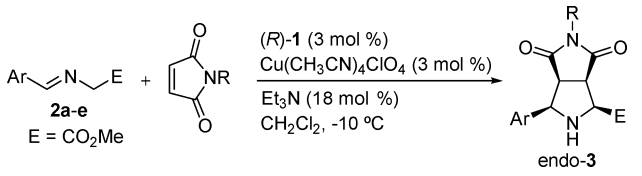
Table 1. Cu(I)-Catalyzed Reaction of *N*-Benzylideneglycine Methyl Ester **2a** with *N*-Phenylmaleimide in the Presence of Ligand (*R*)-**1**



entry	CuX	*x* (mol %)	time (min)	endo:exo[a]	yield (%)[b]	ee (%)[c]
1	CuCl	10	1440	94:6	51	30
2	$Cu(MeCN)_4PF_6$	10	15	96:4	74	>99
3	$Cu(MeCN)_4ClO_4$	10	15	98:2	78	>99
4	$Cu(MeCN)_4ClO_4$	0.5	60	97:3	86	>99
5[d]	$Cu(MeCN)_4ClO_4$	3	30	>98:<2	81	>99

[a] Determined from the crude ^{1}H 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	(*p*-F)C_6H_4	Ph	60	>98:<2	**3c**	82	>99
3	(*p*-OMe)C_6H_4	Ph	60	>98:<2	**3d**	81	>99
4	*o*-Tol	Ph	30	>98:<2	**3e**	85	>99
5[d]	Ph	Me	15	>98:<2	**4a**	97	>99

[a] Determined from crude ^{1}H 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 CH_2Cl_2). 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 (R^2 = Ph or Me).

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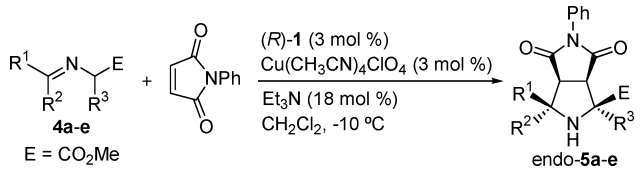
Table 3. Enantioselective Synthesis of Pyrrolidines Having a Quaternary Center at C-2 or C-5



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	(*p*-Cl)C_6H_4	Me	H	1	>98:<2	**5e**	80	>99

[a] Determined by ^{1}H NMR from the crude reaction mixture. [b] Isolated yield. [c] Determined by HPLC (Chiralpak AS and Chiralcel OD columns). [d] E = CO_2Et

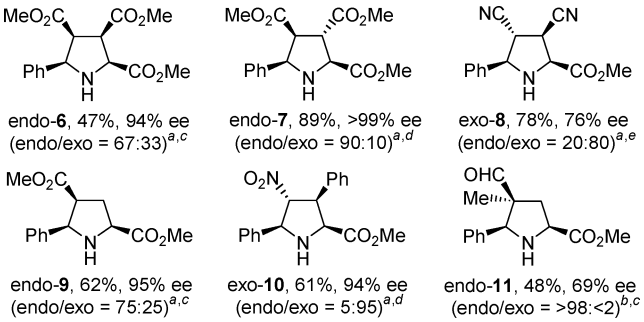


Figure 1. 1,3-Dipolar cycloaddition with other dipolarophiles. [a]In THF. [b]In CH_2Cl_2. [c]Reaction at room temperature. [d]Reaction at −10 °C. [e]Reaction at −30 °C.

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 fumarodinitrile[13]) proved to be excellent substrates for this reaction, providing high asymmetric inductions (76 → 99% ee), although the endo/exo selectivity[11] 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.

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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.

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(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.

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