Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with α , β -Unsaturated Ketones

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 α , β -Unsaturated ketones are no longer the missing dipolarophiles in catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. In the presence of Cu^I-Fesulphos complexes as catalysts (5 mol %), these substrates combine high reactivity, wide substitution tolerance, moderate to good *endo/exo* selectivities, and high enantiocontrol. The *endo/exo*-diastereoselectivity of the reaction is strongly dependent on the *cis* or *trans* nature of the enone moiety.

Owing to the wide-range significance of the pyrrolidine ring structural unit in pharmacy, organocatalysis, and as a synthetic building block, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to alkenes has been a subject of intense research¹⁻⁷ since the first report in 2002.^{2,3} As a result, a number of efficient protocols relying on the combination of Lewis acidic metal salts, especially copper⁴ and silver salts,^{5,6} with appropriate chiral ligands has been developed. Since 2007, several organocatalytic asymmetric versions of this reaction have also appeared.⁷ With regard

to dipolarophile scope, unsaturated acid derivatives such as acrylates, maleates, fumarates, maleimides, and fumaronitrile, as well as nitroalkenes and alkenyl sulfones, have been successfully employed in this reaction. However, despite this impressive progress, a review of the literature reveals that α , β -unsaturated ketones, which hold great interest because of their synthetic potential,⁸ have not yet been incorporated to the arsenal of suitable dipolarophiles for the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. To the best of our knowledge, the moderately enantioselective (70% ee) and noncatalytic reaction of 2-naphtylidenealanine methyl ester with methyl vinyl ketone in the presence of a stoichiometric amount of a diphosphine–Ag^I complex constitutes the only isolated example on the use of a chiral Lewis acid complex.³

Herein, we wish to fill this literature gap by reporting a highly enantioselective catalytic azomethine ylide dipolar cycloaddition procedure with α , β -unsaturated ketones.

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⁽¹⁾ Reviews on catalytic asymmetric 1,3-dipolar cycloaddition: (a) Pellissier, H *Tetrahedron* **2007**, *63*, 3235. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. Reviews on cycloaddition with azomethine ylides: (c) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *16*, 2047. (2) (a) Longmire L M.; Wang B.; Zhang X. L Am. *Chem. Sci.* **2007**.

^{(2) (}a) Longmire, J. M.; Wang, B.; Zhang, X. J. Am. Chem. Soc. 2002, 124, 13400. (b) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. Angew. Chem., Int. Ed. 2002, 41, 4236.

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Table 1. Optimization Experiments in the Cycloaddition of 2 with Cyclopentenone Catalyzed by Fesulphos Complexes

		Ph $^{N}E + $ 2 (E = CO ₂ Me)	[M] (x mo 1a (x mo base (18 mol CH ₂ Cl ₂ , rt,	M %) M %) M H H H H H H H H H H H H H H	E 1a, R = Ph 1b, R = 1-Naph		
entry	[M]	ligand	x	base	$endo/exo^a$	yield ^{b} (%)	ee^{c} (%)
1	AgOAc	1a	10	$\mathrm{Et}_3\mathrm{N}$	80:20	72	63
2^d	AgOAc	1a	10	$\mathrm{Et}_{3}\mathrm{N}$	87:13	69	78
3	$Cu(MeCN)_4ClO_4$	1a	10	$\mathrm{Et}_{3}\mathrm{N}$	90:10	71	93
4	$Cu(MeCN)_4ClO_4$	1a	5	$\mathrm{Et}_{3}\mathrm{N}$	90:10	70	94
5	$Cu(MeCN)_4ClO_4$	1a	3	$\mathrm{Et}_{3}\mathrm{N}$	88:12	52^e	94
6	$Cu(MeCN)_4ClO_4$	1a	5	DIPEA	88:12	66	89
7	$Cu(MeCN)_4ClO_4$	1a	5	$\mathrm{Et}_{3}\mathrm{N}$	85:15	62	91
8^d	$Cu(MeCN)_4ClO_4$	1a	5	${ m Et}_3{ m N}$	90:10	58^e	95
9	$Cu(MeCN)_4ClO_4$	1b	5	$\mathrm{Et}_{3}\mathrm{N}$	70:30	60	90

^{*a*} Determined by NMR from the crude reaction mixture. ^{*b*} Of pure *endo-***3** after chromatographic purification. ^{*c*} ee of *endo-***3** determined by chiral HPLC (Chiralcel IB). ^{*d*} Reaction performed at 0 °C. ^{*e*} The reaction did not reach complete conversion.

On the basis of the good performance of copper(I) and silver(I) complexes of Fesulphos ligands⁹ (1) as catalysts in the azomethine imine cycloaddition with several acid derivatives^{4b,f} (maleimides and α,β -unsaturated esters) and bis-sulfonylethylenes,⁴ⁱ an extension of this catalyst system to α,β -unsaturated ketones was particularly attractive. Therefore, the reaction of N-benzylideneglycine methyl ester (2) 2-cyclopentenone catalyzed by Ag^Iwith and Cu^I-Fesulphos complexes was initially investigated. Optimization experiments listed in Table 1 led us to identify the superiority of cationic copper(I) complexes¹⁰ of **1a** (entries 3-8) over the corresponding silver catalyst (entries 1 and 2), as well as Et₃N and CH₂Cl₂¹¹ as the optimal base and solvent, respectively. The reaction was found to require 5

mol % of metal/ligand catalyst to reach complete conversion at room temperature (compare entries 4 and 5). Under such conditions, the bicyclic pyrrolidine **3** was obtained with high *endo*-selectivity (*endo/exo* = 90:10), enantioselectivity (94% ee *endo*-**3**), and chemical yield (70% in *endo*-**3** after standard silica gel chromatographic purification). Lowering the reaction temperature (0 °C) had a detrimental effect on the reactivity (58% isolated yield) without a significant impact on the stereocontrol (*endo/exo* = 90:10, 95% ee, entry 8). The bulkier Fesulphos ligand **1b** (R = 1-Naph) also proved to be suitable, yet slightly less effective, providing *endo*-**3** in 60% yield and 90% ee (entry 9).

To evaluate the scope of this cycloaddition protocol, a representative set of aryl imines of glycine methyl ester was surveyed under the optimized conditions (5 mol % of chiral catalyst, 18 mol % of Et₃N, CH₂Cl₂ at rt, Table 2). The corresponding *endo*-adduct was isolated in good yields (61-70%) and high levels of *endo*-selectivity (90:10–98: 2) and enantiocontrol (91–95% ee), except for the electron-

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⁽¹⁰⁾ Other cationic Cu¹ complexes provided similar results. For instance, the model reaction of **2** with 2-cyclopentenone in the presence of Cu(CH₃CN)₄PF₆ (5 mol %), **1a** (5 mol %), and Et₃N (18 mol %) afforded *endo-3* in 52% isolated yield (*endo/exo* = 87:13) and 93% ee.

⁽¹¹⁾ The model reaction catalyzed by $Cu(CH_3CN)_4PF_6/1a$ (5 mol %) in THF led to a much lower conversion (30% isolated yield of *endo-3*). Very low conversion was observed in acetonitrile.



R∕ [^] N′	∕CO₂Me ⁺		CuClO ₄ / 1a (5 mol %) 3N (18 mol ¹ H ₂ Cl ₂ , rt, 10		CO ₂ M	+ exo e
	.				yield ^b	ee ^c
entry	R (imine)	imine	product	endo/exo ^a	(%)	(%)
1	Ph	2	3	$90:10^d$	70	94
2	2-Naph	4	8	$98:2^{d}$	61	91
3	$4\text{-}\mathrm{ClC}_6\mathrm{H}_4$	5	9	$98:2^{d}$	67	94
4	$4\text{-}\mathrm{BrC}_6\mathrm{H}_4$	6	10	$98:2^{d}$	68	95
5	$4-MeOC_6H_4$	7	11	75:25	52	85
6	Су	8	NR^{e}			
7	PhCH=CH	9	NR^{e}			

^{*a*} Determined by NMR from the crude reaction mixture. ^{*b*} Of pure adduct *endo* after chromatographic purification. ^{*c*} ee of *endo*-adduct; determined by chiral HPLC (Chiralcel IB and IA). ^{*d*} A minor amount (5–10%) of the ring-opened Michael addition product was also detected in the crude reaction mixture. ^{*e*} No reaction.

rich imine **7**, derived from *p*-methoxybenzaldehyde, which showed a lower reactivity and stereochemical control (52% yield, 85% ee, entry 5). The relative and absolute stereochemistry of the major cycloadduct was established by single X-ray diffraction analysis of the bromine-containing adduct *endo*-**10** (Figure 1, left).^{12,13}



Figure 1. Crystal X-ray structures of *endo*-10 (left) and *exo*-20 (right).

Unfortunately, iminoesters derived from an aliphatic aldehyde (8, R = Cy) or an α,β -unsaturated aldehyde (9, R = cinnamyl) proved to be unreactive under identical conditions, resulting in the recovery of the starting material (entries 6 and 7). Similarly, a very low conversion was observed in the reaction with a six-membered cyclic enone such as 2-cyclohexenone.¹⁴

Acyclic enones proved to be excellent dipolarophiles under the optimized reaction conditions, leading to complete conversions at room or lower temperatures (Table 3). Unlike the reaction with cyclopentenone, the cycloadditions of the trans-substituted enones¹⁵ took place with moderate to high exo-selectivity (endo/exo from 30:70 to 2:98, entries 1-26), while maintaining an excellent enantiocontrol (81-96% ee for the major exo isomer). The exo+endo adduct mixtures were readily separated by silica gel chromatography (45-85%)isolated yield for the exo adduct). In contrast, the simplest enone, methyl vinyl ketone (entry 27), provided an opposite endoselectivity (endo/exo = 80:20) and low asymmetric induction (35% ee for the major endo-38),¹⁶ showing that the presence of a substitutent at β -position is critical for achieving both high exo-selectivity and enantioselectivity. The absolute and relative configuration of the exo adducts was unequivocally assigned by single X-ray diffraction analysis of the 4-chlorophenyl-substituted adduct exo-20 (Figure 1).^{12,17}

This procedure displays wide structural scope and high enantiocontrol, especially in the case of acyclic enones, tolerating the presence of aryl, alkenyl, and alkyl substituents at both the carbonylic carbon (\mathbb{R}^2) and the β -position (\mathbb{R}^3). This reaction is also compatible with the presence of an additional functional group at the β -position, such as silyl ether (entry 24), thioether (entry 22), or carbonyl group (entries 25 and 26). The dicarbonyl dipolarophiles are so reactive that the reactions were completed in 15 min at -78°C. In some reactions, the sterically more demanding Fesulphos^{Naph} ligand **1b** provided appreciably higher diastereoselectivity and asymmetric induction than that obtained from the parent ligand **1a** (entries 5, 13, 15, 23, and 25; values in parentheses), while in other cases the performance of **1a** and **1b** proved to be very similar (entries 10 and 17).

The high enantioselectivity observed in the reaction with both cyclic (cyclopentenones) and acyclic enones in favor of the pyrrolidine with (2S,5R) configuration can be explained assuming the participation of the presumed Fesulphos-Cu-azomethine complex intermediate I (Figure 2). According to our previous computational studies,^{4f} the tetracoordinated complex I, showing a highly distorted tetrahedral structure around the copper atom, was found to be the most stable geometry in the coordination of the metal atom with the P,S-ligand Fesulphos and the azomethine species. In this complex, the high steric congestion imposed by the *tert*-butyl group at the sulfur atom in close proximity to the copper center hinders the approach of the dipolarophile from the Si C=N face of the azomethine. The reaction from the more accessible Re C=N face of the dipole accounts for the high selectivity attained in the formation of the pyrrolidines with (2S,5R) configuration. Although we do not yet have a conclusive explanation for the opposite endo/exo selectivity showed by cyclopentenone and acyclic trans-configured

⁽¹²⁾ See the Supporting Information for details.

⁽¹³⁾ CCDC 704924 [unit cell parameters: a 8.8746(2) Å, b 8.9732(2) Å, c 17.6982(5) Å, space group P212121] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccd-c.cam.ac.uk/data_request/cif.

⁽¹⁴⁾ \leq 10% conversion was observed in the reaction of **2** with 2-cyclohexenone under the optimized conditions after 48 h at rt.

⁽¹⁵⁾ The reaction of *cis*-configured chalcone with **2** under optimized conditions led to much lower reactivity (50% conversion after 24 h at rt) and poor diastereocontrol (*exolendo* = 60:40).

⁽¹⁶⁾ Racemic *endo-38* and *exo-38* were already reported: Tsuge, O.; Kanemasa, S.; Yoshioka, M. J. Org. Chem. **1988**, 53, 1384

⁽¹⁷⁾ CCDC 704925 [unit cell parameters: *a* 22.8459(15) Å, *b* 5.6625(3) Å, *c* 16.0875(8) Å, β 98.411(3)°, space group *C*2] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif.

Table 3. Acyclic α,β -Unsaturated Ketones as Dipolarophiles in the 1,3-Dipolar Cycloaddition of Azomethine Ylides

R ¹	[≪] N [∕] CO₂Me +	R^2 R^3 R^3	(CH ₃ CN) ₄ ClO ₄ /1a (or 1b) (5 mol %) Et ₃ N (18 mol %) CH ₂ Cl ₂	$R^{2} \xrightarrow{O} R^{3}$ $R^{1} \xrightarrow{N} CO_{2}$ endo	R Me ⁺ I	R ¹ R ³ CO ₂ Me	Fe Fe 1a, R = F 1b, R = 7	·S- <i>t</i> Bu PR ₂ Ph 1-Naph
entry	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	conditions	product	endo/exo ^{a, b}	yield ^{c, b} (%)	$ee^{d,b}$ (%)
1	Ph	Me	Me	−10 °C, 12 h	12	20:80	45	85
2	Ph	Me	Ph	rt, 5 h	13	18:82	60	87
3	Ph	Ph	Ph	rt, 5 h	14	2:98	69	96
4	$4\text{-BrC}_6\text{H}_4$	Ph	Ph	rt, 5 h	15	12:88	65	95
5	$4-OMeC_6H_4$	Ph	Ph	rt, 5 h	16	30:70 (15:85)	52(67)	82 (86)
6	2-Naph	Ph	Ph	rt, 5 h	17	2:98	68	96
7	Ph	Ph	Ph	rt, 5 h	18	20:80	55	94
8	(E)-PhCH=CH	Ph	Ph	−10 °C, 6 h	19	10:90	52	91
9	Ph	$4-ClC_6H_4$	Ph	rt, 5 h	20	4:96	75	95
10	Ph	$4-OMeC_6H_4$	Ph	rt, 5 h	21	32:68 (30:70)	49 (55)	89 (89)
11	Ph	2-Naph	Ph	rt, 5 h	22	3:97	76	98
12	Ph	CF_3	Ph	rt, 5 h	23	25:75	57	87
13	Ph	(E)-PhCH=CH	Ph	−40 °C, 3 h	24	40:60 (30:70)	55(64)	93 (96)
14	Ph	Ph	$4-FC_6H_4$	rt, 5 h	25	18:82	70	94
15	Ph	Ph	$4-OMeC_6H_4$	rt, 5 h	26	30:70 (3:97)	58 (65)	85 (94)
16	Ph	Ph	2-Naph	rt, 5 h	27	15:85	62	93
17	Ph	Ph	2-Furyl	rt, 5 h	28	12:88 (10:90)	75(73)	81 (82)
18	Ph	Ph	2-Thienyl	rt, 5 h	29	12:88	70	93
19	Ph	Ph	(E)-PhCH=CH	−10 °C, 6 h	30	15:85	74	89
20	Ph	$4-NO_2C_6H_4$	$2 - MeC_6H_4$	rt, 5 h	31	15:85	69	95
21	Ph	$2\text{-BrC}_6\text{H}_4$	$4\text{-BrC}_6\text{H}_4$	rt, 5 h	32	5:95	75	92
22	Ph	$3-ClC_6H_4$	$MeS-(CH_2)_2-$	−20 °C, 12 h	33	25:75	60	87
23	Ph	$3-ClC_6H_4$	<i>n</i> -Bu	−20 °C, 12 h	34	23:77 (20:80)	63 (62)	69 (81)
24	Ph	$3-ClC_6H_4$	TBDMSO-(CH ₂) ₃ -	−20 °C, 12 h	35	12:88	69	84
25	Ph	Me	MeCO	−78 °C, 15 min	36	25:75 (10:90)	79 (85)	74(82)
26	Ph	Ph	PhCO	−78 °C, 15 min	37	20:80	75^e	98
27	Ph	Me	Н	−10 °C, 12 h	38	80:20	51^f	35^{f}

^{*a*} Determined by NMR from the crude reaction mixture. ^{*b*} In parenthesis, values obtained using ligand **1b**. ^{*c*} Of pure isolated *exo* adduct. ^{*d*} For the *exo*-cycloadduct; determined by chiral HPLC (Chiralcel IB and IA). ^{*e*} Yield of the *endo/exo* mixture. ^{*f*} For the major isomer *endo-38*.



enones with this Cu–Fesulphos catalyst system, their stereochemical behavior parallels nicely to that previously found with other cyclic and *trans*-acyclic dipolarophiles such as maleimides^{4a,e} (*endo*-selectivity), fumaronitrile^{4b,f} (*exo*selectivity), *trans*- α , β -unsaturated nitro compounds^{4b,f} (*exo*selectivity), or *trans*-bissulfonyl ethylenes⁴ⁱ (*exo*-selectivity). In summary, α , β -unsaturated ketones were demonstrated to be efficient dipolarophiles in catalytic asymmetric 1,3dipolar cycloaddition of azomethine ylides. The efficiency of this protocol strongly relies on the use of Cu¹–Fesulphos catalysts, leading to highly functionalized acyl-substituted pyrrolidine derivatives in good yields, moderate to high *endol exo*-selectivities and high enantiocontrol (81–96% ee).

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

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