Highly *Endo*-Selective and Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylide with α-Enones Catalyzed by a Silver(I)/ ThioClickFerrophos Complex

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ABSTRACT



A silver(I)/ThioClickFerrophos complex catalyzed the highly *endo*-selective asymmetric 1,3-dipolar cycloaddition reaction of methyl *N*-benzylideneglycinate (the source of azomethine ylides) with (*E*)-acyclic α -enones having an *endo/exo* ratio of 90/10 to 99/1. The highly functionalized *endo*-4-acyl pyrrolidines were obtained in good yields with high enantioselectivities (up to 98% ee). The complex also effectively catalyzed *endo*-selective reactions with 2-cyclopentenone to give the *endo*-bicyclic pyrrolidine in high enantioselectivity.

We herein report a procedure that achieves the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with (*E*)-acyclic α -enones with *endo*-selectivity using novel silver(I)/ ThioClickFerrophos complexes and also provides *endo*-selective cycloadducts with 2-cyclopentenone.

Proline-derived structures are an important class of heterocyclic compounds with widespread applications in the synthesis of biologically active compounds and natural products,¹ and also have themselves been employed as organocatalysts in many useful transformations.² The catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylide with dipolarophiles such as electron-deficient alkenes should provide a straightforward and atom-economical method for the enantioselective synthesis of proline derivatives.³

A metal-catalyzed reaction seems to be the most efficient and reliable route. The simultaneous formation of the three or four new stereocenters in the resulting pyrrolidine can be achieved by using chiral complexes of silver,⁴ copper,⁵ zinc,⁶ or nickel.⁷ A wide variety of dipolarophiles have been successfully applied in the cycloadditions, including α,β unsaturated esters, vinyl sulfones, and nitroalkenes.^{4–7} On the other hand, the reaction with α -enones has scarcely been studied although they have great synthetic potential.⁸ Recently, Carretero et al. have succeeded in the first catalytic reaction of acyclic α -enones with *exo*-selectivity and 2-cyclopentenone with *endo*-selectivity using their Cu(I)/Fesulphos complex.⁹

We have previously reported ClickFerrophos¹⁰ and Thio-ClickFerrophos¹¹ ligand families (Figure 1), which are



Figure 1. ClickFerrophos and ThioClickFerrophos ligands.

sterically and electronically tunable bidentate chiral ferrocenyl diphosphine and *P*,*S*-ligands, respectively.¹² These have proven to be excellent chiral ligands in a variety of highly enantioselective transition metal-catalyzed reactions,

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such as hydrogenation of alkenes and ketones,^{10a,d} reductive aldol reactions,^{10b} and allylic substitution reactions.¹¹ In particular, Cu(I)/ClickFerrophos (L1) is a highly effective catalyst for the asymmetric 1,3-dipolar cycloaddition of methyl *N*-benzylideneglycinate (the source of azomethine ylide) with vinyl sulfones with *exo*-selectivity.^{10c}

We first examined the reaction of methyl *N*-(4-chlorobenzylidene)glycinate **1a** as an azomethine ylide source with (*E*)-benzalacetone **2** (1.5 equiv to **1a**) as a representative acyclic α -enone employing the AgOAc/L1 complex. The reaction was carried out in toluene at room temperature for 12 h with AgOAc/L1 (5 mol %) and Et₃N (18 mol %). The *endo* to *exo* isomer ratio was determined by ¹H NMR integration of the C-5 protons, and ee (%) of the product was determined by HPLC (Chiralpak AS-H). The reaction proceeded quantitatively to give a mixture of *endolexo* cycloadducts in a 85/15 ratio (Table 1, entry 1). Notably,

Table 1. Optimization of the 1,3-Dipolar Reaction of Methyl N-(4-Chlorobenzylidene)glycinate with (*E*)-Benzalacetone^{*a*}

	4-CIC ₆ [M] toluei rt,	H ₄ N 1a /ligand ne/Et ₃ N 12 h	CO ₂ Me + Me 4-CIC ₆ H ₄ - en	Ph 2 0 0 N H CO ₂ N H H do- 3a (major)	,Me Ле
entry	[M]	ligand	endo/exo ^b	yield, ^c %	ee^d (endo), %
1	AgOAc	L1	85/15	83	43
2	AgOAc	L2	93/7	85	-26
3	AgOAc	L3	80/20	66	90
4	AgOTf	L3	85/15	61	55
5	$AgBF_4$	L3	80/20	71	54
6	$AgSbF_6$	L3	85/15	73	70
7	AgNO ₃	L3	83/17	71	61
8	$CuClO_4$	L3	90/10	66	54
9	CuPF_{6}	L3	72/28	65	96
10	CuOAc	L3	68/32	52	68
11	AgOAc	L4	73/27	60	37
12	AgOAc	L5	81/19	69	85
13	AgOAc	L6	85/15	74	70
14	AgOAc	L7	85/15	74	92
15^e	AgOAc	L7	90/10	83	92
16^{f}	AgOAc	L7	92/8	85	96
17	AgOAc	L8	85/15	73	90

^{*a*} **1a** (0.2 mmol), **2** (0.3 mmol), metal salt (0.01 mmol), Et₃N (0.036 mmol), ligand (0.01 mmol), toluene (2.0 mL); rt, 12 h. ^{*b*} Determined by ¹H NMR. ^{*c*} Isolated yield (*endo*). ^{*d*} Determined by HPLC. ^{*e*} In CH₂Cl₂, rt, 5 h. ^{*f*} In CH₂Cl₂, 0 °C, 5 h.

the *endo* product was produced preferentially in contrast to Carretero's Cu(I)/Fesulphos complex.⁹ However, the enantiomeric excess of the *endo* adduct **3a** was low (43% ee). Since Carretero's Fesulphos is a *P*,*S*-ligand, we thought that ThioClickFerrophos as a *P*,*S*-ligand could work effectively on the reaction.¹³ For the representative ThioClickFerrophos ligands, ligands bearing an ethylthio (EtS) group on the

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ferrocene (L2) or the 1,2,3-triazole group (L3) were chosen. The reactions with the AgOAc/L2 and L3 complexes were carried out under the same conditions as with AgOAc/L1. The AgOAc/L3 complex gave the *endo* adduct **3a** preferentially with 90% ee (Table 1, entry 3), while AgOAc/L2 gave the enantiomer of **3a** with low ee (Table 1, entry 2). The stereochemistry and absolute configuration of **3a** were confirmed by X-ray crystallographic analysis (Supporting Infomation) and revealed to be (2S,3R,4S,5R). ThioClick-Ferrophos L3 was found to be the most suitable ligand.

Next, combinations with several metal salts were screened. Several kinds of Ag(I) and Cu(I) salts were examined (Table 1, entries 3–10). The reaction proceeded smoothly to give the *endo* adduct preferentially, using all combinations with Ag(I) or Cu(I) salts. The combination with Cu(MeCN)₄PF₆ gave the *endo* adduct in the highest ee (96% ee) but with low *endo*-selectivity (*endolexo* = 72/28) (entry 9). We concluded that AgOAc was the most suitable salt to obtain the *endo* adduct in good diastereo- and enantioselectivities. Thus, AgOAc/ThioClickFerrophos is the first catalyst that can achieve the *endo*-selective 1,3-dipolar cycloaddition of azomethine ylide with acyclic α -enones in high enantioselectivity.

We prepared variations of L3 by replacing the EtS group with other alkyl- and arylthio groups differing in steric and electronic properties, and screened these ligands (L4–L8) for improved stereoselectivity (Table 1, entries 11-17).¹⁴ The 4-phenyl group in the 1,2,3-triazole ring was found to be essential for high stereoselectivity. The ee value was drastically decreased when using L4 (without the phenyl group of L3) (entry 11). The *tert*-butylthio (*t*-BuS) derivative L7 was the most effective for the reaction giving the *endo*

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product in 92% ee with *endolexo* = 90/10 (entry 15). The ee was further improved (96% ee) by carrying out the reaction in dichloromethane at 0 °C, and the reaction was complete in 5 h (entry 16).

From the optimization experiments shown in Table 1, we concluded that AgOAc/L7, dichloromethane, and Et₃N were the optimal catalyst, solvent, and base, respectively. The reaction should be carried out at 0 °C to obtain a higher ee value of the product, but the ratio of *endolexo* is only slightly improved. The reaction with **2** was then expanded to other azomethine ylide precursors (dipoles) including 4-substituted phenyl derivatives, 2-naphthyl, and cyclohexyl derivatives (**1a**-**f**) under the optimized conditions. The results are summarized in Table 2. The

Table 2. Scope of the Reaction of (E)-Benzalacetone with Respect to Azomethine Ylide^{*a*}

	R∕ [™] N∕ [∽] 1a-f	`CO₂Me	2 Ma AgOAc/L7 H₂Cl₂/Et₃N 0 °C, 5 h	O P R − N − C H endo- 3a-f (ma	O ₂ Me ajor)
entry	R	product	yield, b $\%$	endo/exo ^c	ee^{d} (endo), %
1	4-ClPh	3a	85	92/8	94
2	4-BrPh	3b	82	90/10	96
3^e	4-MeOPh	3c	85	95/5	96
4	Ph	3d	74	95/5	94
5	2-Naph	3e	78	90/10	86
6^e	2-Naph	3e	78	91/9	94
7^e	Су	3f	70	92/8	92

^{*a*} **1a**–**f** (0.2 mmol), benzalacetone (0.3 mmol), AgOAc (0.01 mmol), Et₃N (0.036 mmol), **L7** (0.01 mmol), CH₂Cl₂ (2.0 mL); 0 °C, 5 h. ^{*b*} Isolated yield (*endo*). ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by HPLC. ^{*e*} The reaction was carried out at -20 °C for 12 h.

4-substituent on the phenyl group had little effect on the reaction. Similar high *endo*-selectivity and high ee (94–96% ee) of *endo* adducts (**3a**–**d**) were obtained (entries 1–4) with the electron-withdrawing (Cl and Br) and -donating (OMe) groups. The reaction with 2-naphthyl derivative **1e** resulted in a lower enantioselectivity than the phenyl derivatives, and ee could be improved by decreasing the reaction temperature (-20 °C) (entry 6). The reaction could be applied to cyclohexyl derivative **1f**, yielding the *endo* adduct with 92% ee (entry 7).

To evaluate the scope of the 1,3-dipolar cycloaddition, we applied the AgOAc/L7 catalyst to the reaction with (*E*)-acyclic α -enones including (*E*)-chalcone derivatives 4, (*E*)-3-pentene-2-one (Table 3), using 1a as a dipole. In the reaction with chalcone (4: $\mathbb{R}^1 = \mathbb{R}^2 = \mathbb{P}h$), the reaction completed in 10 min to give almost a single isomer of the adduct 5 in good yield. In this case, the stereochemistry of the adduct 5 was determined by ¹H NMR spectroscopy. The methyl ester group appears at around 3.7 ppm as in the benzalacetone adduct, while the methyl ester group of the *exo* isomer shifted upfield to 3.3 ppm due to the shielding

Table 3. Reaction of Various Acyclic α -Enones with Azomethine Ylides^{*a*}

	4-CIC ₆ H₄					
		1a	4	er	ndo (major)	
entry	\mathbb{R}^1	\mathbb{R}^2	product	yield, ^b %	$endo/exo^{c}$	ee^{d} (endo), %
1	Ph	Ph	5	91	95/5	98
2	Ph	$4-ClC_6H_4$	6	86	94/6	97
3	Ph	$4-MeOC_6H_4$	7	91	95/5	97
4	Ph	2-Naph	8	74	95/5	95
5	$4-ClC_6H_4$	Ph	9	90	97/3	95
6	$4-MeOC_6H_4$	Ph	10	89	90/10	87
7^e	4-MeO C ₆ H ₄	Ph	10	92	93/7	96
8	$4-CF_3 C_6H_4$	Ph	11	92	93/7	96
9	2-Naph	Ph	12	91	98/2	90
10	Me	Me	13	83	98/2	98
11	Ph	CH=CHPh	14	75	98/9	95

^{*a*} Imine (0.2 mmol), α -enone (0.3 mmol), AgOAc (0.01 mmol), Et₃N (0.036 mmol), Iigand (0.01 mmol), CH₂Cl₂ (2.0 mL); 0 °C, 10 min. ^{*b*} Isolated yield (*endo*). ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by HPLC. ^{*e*} The reaction was carried out at -20 °C for 0.5 h.

effect of the adjacent *cis*-phenyl group.⁹ A similar effect and upfield shift (4.17 ppm) was observed in the C-2 proton of **5** compared to that of the *exo* adduct (4.4–4.5 ppm). The downfield shift of the methyl ester and the upfield shift of the C-2 proton suggest that the ester and phenyl groups are *trans* (the protons are *cis*) to each other, identifying **5** as an *endo* adduct. The stereochemistry was confirmed by the NOESY spectrum (Supporting Information).

Reactions with 4-aryl-substituted chalcones were carried out, and the results are also summarized in Table 3. These results demonstrate that the reaction displays a wide scope and high *endo*-selectivity (*endolexo* = 90/10 to 98/2) with high enantioselectivity (up to 98% ee), tolerating the presence of electron-withdrawing and -donating groups in both aryl groups of **4**. The *endo* cycloadducts were also obtained selectively from the reaction with (*E*)-3-penten-2-one and dibenzylidene acetone in good yields with high ee (entries 10 and 11).¹⁵



The reaction of **1a** with a cyclic α -enone such as 2-cyclopentenone **15** proceeded but required a long reaction time (24 h) and more catalyst loading (10 mol %) to give the *endo* bicyclic pyrrolidine **16** as the sole isomer (73%, Scheme 1). This is in contrast to Carretero's Cu/Fesulphos catalyst which gave the *endo* bicyclic product from **16**,⁹ while it gave *exo* products from acyclic α -enones. Thus, the Ag(I)/ ThioClickFerrophos complex catalyzed *endo*-selective 1,3-dipolar cycloaddition with both acyclic and cyclic α -enones.

In conclusion, Ag(I)/ThioClickFerrophos is an efficient catalyst for the *endo*-selective asymmetric 1,3-dipolar cycloaddition of azomethine ylide with (*E*)-acyclic and cyclic α -enones. The *endo*-4-acyl-substituted pyrrolidines can be obtained in good yields with high *endo/exo* selectivities and enantioselectivities (up to 98% ee).

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Supporting Information Available: Full experimental procedures, characterization data, HPLC, and NMR spectra (PDF) for L3–L8, pyrrolidine derivatives 3a–f, 5–14, and 16, and crystallographic data in CIF files for L7, 3a, and the AgOAc/L5 complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁵⁾ The reaction with a vinyl kenone such as 1-phenyl-2-propen-1one was also examined (Supporting Information).