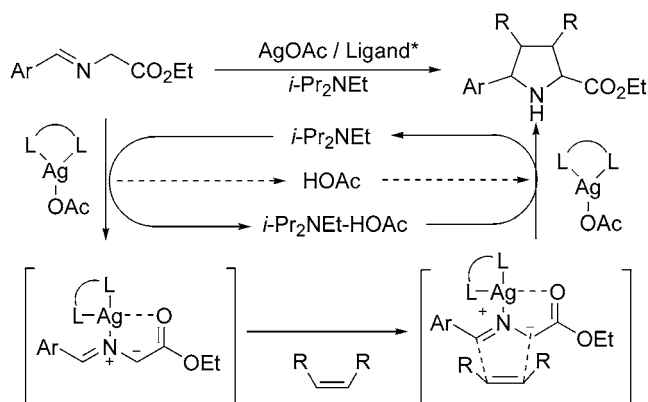


The most accepted mechanism^{5,8} for the cycloaddition of azomethine ylides is shown in Scheme 1. Coordination of

Scheme 1. Mechanism of AgOAc-Catalyzed 1,3-Dipolar Cycloaddition



the iminoester to chiral Ag(I) or Cu(II) catalyst, followed by deprotonation with base to form the reactive metal-bound azomethine ylide dipole, which reacts with dipolarophiles, was followed by elimination of cycloadduct to regenerate the chiral catalyst. Thus, for the above catalytic systems, an excess of base such as tertiary amine was involved. By analyzing the above mechanism carefully, we think that extra base is not necessary for AgOAc-catalyzed cycloaddition of azomethine ylide because the AgOAc bearing a moderately basic charged ligand acetate would facilitate deprotonation of iminoesters to generate the azomethine ylide.¹⁰ Intrigued by the effectiveness of ferrocene-derived chiral N,P ligands in asymmetric reactions,¹¹ we developed highly enantioselective AgOAc-catalyzed asymmetric [3 + 2] cycloaddition of azomethine ylides using ferrocenyloxazoline-derived chiral N,P ligands without extra base.

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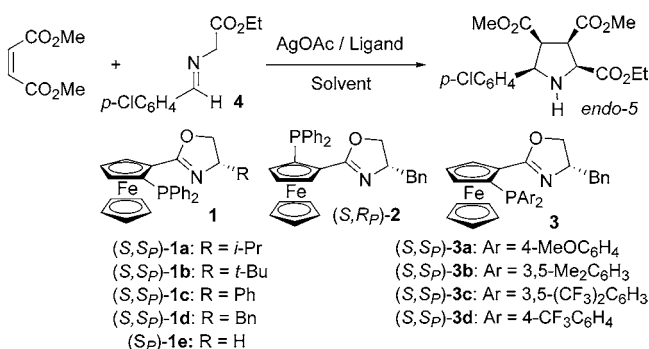
(9) During preparation of this manuscript, Zhang reported a Cu(I)/P, N-ligand-catalyzed asymmetric 1,3-polar cycloaddition of azomethine ylides with high *exo* selectivity; see: (a) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241–4244. (b) Pfaltz reported a base-free AgOAc/PHOX-catalyzed intramolecular [3 + 2] cycloaddition of azomethine ylides; see: Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431–1436.

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In our initial investigation, we found AgOAc/**1a** system can efficiently catalyze the cycloaddition of **4** with dimethyl maleate in toluene with high activity and moderate enantioselectivity in the absence of base (entry 1, Table 1); only

Table 1. AgOAc-Catalyzed Asymmetric Cycloaddition of **4**^a



entry	ligand	solvent	<i>T</i> (°C)	yield ^b (%)	ee ^c (%)
1	1a	toluene	0	89	68
2	1b	toluene	0	86	53
3	1c	toluene	0	88	69
4	1d	toluene	0	98	81
5	1d	THF	0	86	86
6	1d	DME	0	96	78
7	1d	Et ₂ O	0	93	88
8	1e	Et ₂ O	0	98	81
9	2	Et ₂ O	0	96	–78
10	3a	Et ₂ O	0	91	84
11	3b	Et ₂ O	0	88	89
12	3c	Et ₂ O	0	89	83
13	3d	Et ₂ O	0	94	94
14	3d	Et ₂ O	–25	88	98
15	3d	Et ₂ O	–40	98	98

^a Conditions: iminoester **4** (1.0 equiv), dimethyl maleate (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration (0.15 M). ^b Isolated yields based on **4**. ^c Determined by HPLC.

the *endo* isomer **5** was detected by ¹H NMR analysis of reaction mixtures.

Encouraged by these results, the effect of substituent of oxazoline ring on the conversion and enantioselectivity was investigated in toluene (Table 1). The results showed that Bn-substituted ligand **1d** (entry 4) is superior to **1a** (R = *i*-Pr), **1b** (R = *t*-Bu) and **1c** (R = Ph). The solvent effect was also studied (entries 4–7), the reaction proceeded well in Et₂O, THF and DME, and low activity was observed in CH₂Cl₂. The highest enantioselectivity was obtained in ether.

To investigate the effect of planar chirality on the enantioselectivity and absolute configuration of the products,¹¹ (S_P)-**1e** with only planar chirality was used, and lower ee was observed (81% ee, entry 8). (S,*R*_P)-**2** with the same central chirality and opposite planar chirality to (S,*S*_P)-**1d** was also used in the cycloaddition of **4** with dimethyl maleate. Under the same conditions, lower enantioselectivity and the opposite absolute configuration were observed (–78% ee, entry 9). The lower ee with (S,*R*_P)-**2** suggests the mismatched nature of the (*R*) planar chirality with the

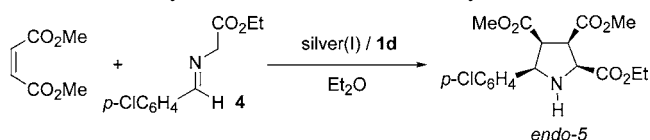
(*S*) central chirality on the oxazolinyl ring. It is noteworthy that, compared to the enantioselectivity of the reaction catalyzed by **1a** with the counterpart of the phenyloxazoline *i*-Pr-Phox, low ee (14%) was obtained.⁶

The influence of the electronic property¹² of the phosphorus substituent in ligand **1d** was also studied (entries 10–13, Table 1). Four ligands were synthesized¹³ by replacing the phenyl groups in **1d** to 4-methoxyphenyl (**3a**), 3,5-dimethoxyphenyl (**3b**), 3,5-ditrifluoromethylphenyl (**3c**), and 4-trifluoromethylphenyl (**3d**), respectively. Interestingly, the change of electronic property of aromatic ring has a clear effect on enantioselectivity,¹⁰ although ligands **3a–d** all can catalyze this reaction smoothly. Ligand **3a** (entry 10) and ligand **3c** (entry 12) slightly decreased the enantioselectivity. Gratifyingly, an improvement in enantioselectivity (94% ee, entry 13) was observed with ligand **3d** bearing a strong electronic-withdrawing trifluoromethyl at the para position of the phenyl ring under the same conditions. The ee could be enhanced to 98% (entry 14) at –25 °C, but no further improvement in enantioselectivity was obtained at –40 °C. Thus, the optimal conditions for asymmetric cycloaddition of azomethine ylides are AgOAc/**3d**/Et₂O/–25 °C. AgOAc-catalyzed cycloaddition of **4** and dimethyl maleate can proceed for 2 h at –25 °C with equally high enantioselectivity when catalyst loading is reduced to only 1%.

To further understand the role of silver salts, AgOCOPh, silver 4-cyclohexylbutyrate, AgOTf, and AgOCOCF₂CF₃ were investigated in the cycloaddition of **4** with dimethyl maleate using the Ag(I)/**1d**/Et₂O system at 0 °C (Table 2). The reaction can proceed smoothly with AgOCOPh or silver 4-cyclohexylbutyrate, anions having similar basicity with acetate, giving the same enantioselectivities. The activity decreased dramatically using AgOCOCF₂CF₃ as a catalyst, probably due to its anion's weak basicity. The reaction could not occur under the same conditions when AgOTf was used as a catalytic precursor without extra base. Only 62% conversion was obtained even if 10 mol % of (*i*-Pr)₂NEt was added. Therefore, AgOAc proved to be an efficient Lewis acid catalyst as well as a base, playing a bifunctional role in this reaction.

To explore the scope of the AgOAc/**3d**/Et₂O catalyzed [3 + 2] azomethine ylide cycloaddition, we investigated a variety of α -iminoester substrates derived from aldehydes with a variety of steric and electronic properties (Table 3). The reaction of α -iminoester **6a–j** with dimethyl maleate proceeds in excellent levels of yield and enantioselectivity. The reaction is also highly diastereoselective, and only *endo* isomers were obtained. Excellent enantioselectivity (entries 1–9) and high isolated yield were obtained regardless of the electronic properties and steric hindrance of the phenyl ring of iminoester **6**. A slightly lower ee was obtained when R was heteroaromatic 3-pyridyl (entry 10). α -(Alkylimino)

Table 2. Effect of Silver Precursors on Enantioselectivity and Conversion of Cycloaddition of **4** with Dimethyl Maleate^a



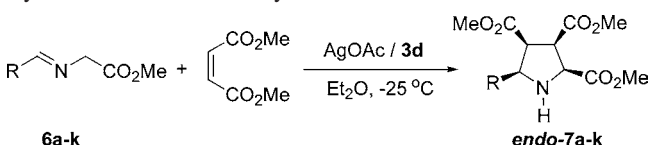
entry	silver(I)	time (h)	yield ^b (%)	ee ^c (%)
1	AgOAc	3	93	88
2	AgOCOPh	2	95	89
3	<i>c</i> -C ₆ H ₁₁ (CH ₂) ₃ CO ₂ Ag	2	94	87
4	AgOCOCF ₂ CF ₃	24	35 ^e	94
5	AgOTf	20	<5	
6 ^d	AgOTf	20	48 ^f	91

^a Conditions: **4** (1.0 equiv), dimethyl maleate (1.5 equiv), silver(I) (3 mol %), ligand **1d** (3.3 mol %), concentration (0.15 M) at 0 °C. ^b Isolated yields based on **4**. ^c Determined by HPLC. ^d 10 mol % of (*i*-Pr)₂NEt was added. ^e 46% conversion of **4** detected by ¹H NMR of the crude reaction mixture. ^f 62% conversion of **4** detected by ¹H NMR of the crude reaction mixture.

ester was less reactive (entry 11), requiring prolonged reaction time and yielding cycloaddition product with slightly low enantioselectivity. *It is noteworthy that the enantioselectivity is the best for asymmetric cycloaddition of azomethine ylides with dimethyl maleate.*

We also probed other three dipolarophiles as outlined in Figure 1. The iminoester **6a** reacted smoothly with *N*-phenylmaleimide in 93% ee (*endo*/*exo* > 20:1). For *tert*-butyl acrylate, relatively low reactivity was observed when reacted at –25 °C, and 88% ee and 97% isolated yield were achieved when the reaction occurred at 0 °C for 20 h. Dimethyl fumarate gave the major *endo* cycloadduct **10** (*endo*/*exo* = 93/7) in 89% ee with 96% combined yield.

Table 3. Variation of the R-Substituent on **6** for the Cycloaddition with Dimethyl Maleate^a



entry	R in 6	time (h)	yield ^b (%)	ee ^c (%)
1	Ph (6a)	3	85	97
2	<i>p</i> -anisole(6b)	3	94	98
3	4-chlorophenyl (6c)	3	99	97
4	4-fluorophenyl (6d)	3	96	97
5	4-cyanophenyl (6e)	3	91	97
6	2-chlorophenyl (6f)	3	98	97
7	<i>o</i> -toluyl (6g)	3	99	98
8	1-naphthyl (6h)	3.5	85	98
9	2-naphthyl (6i)	3	95	98
10	3-pyridyl (6j)	3.5	76	93
11	<i>i</i> -Pr (6k)	20	56	88

^a Conditions: iminoester (1.0 equiv), dimethyl maleate (1.5 equiv), AgOAc (3 mol %), ligand (**3d**) (3.3 mol %), concentration (0.15 M) at –25 °C. ^b Isolated yields by silica gel chromatography. ^c Determined by HPLC.

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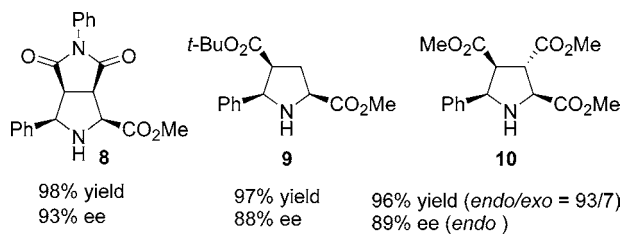


Figure 1. Cycloaddition of **6a** with other dipolarophiles catalyzed by AgOAc/**3d**.

In summary, we have developed a system for bifunctional AgOAc-catalyzed asymmetric cycloaddition of azomethine ylides with electronic-deficient alkenes in high yield and excellent levels of enantioselectivity. The reactive metal-

bound azomethine ylide dipole is formed by the deprotonation with acetate that plays a role of base, and extra base is not necessary. This method provides an efficient and convenient route to synthesize optically active highly substituted pyrrolidine derivatives.

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Supporting Information Available: Spectroscopic data, GC and HPLC spectra, and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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