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Highly Enantioselective Ag(I)-Catalyzed [3 + 2] Cycloaddition of Azomethine Ylides

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The reaction of azomethine ylide 1,3-dipoles with olefinic dipolarophiles forms highly substituted five-membered ring nitrogen heterocycles. This extremely versatile and atom economical process has been applied toward the syntheses of substituted prolines, which can be used as new catalysts[1] and served as important motifs in many biologically active molecules.[2,3] Among the different versions of this reaction,[4] the most practical approach has been the interaction between stabilized *N*-metalated azomethine ylides and π-deficient alkenes.[5,6] This method allows the cycloaddition to proceed under mild reaction conditions and with a high degree of diastereocontrol.[7] Silver(I) and lithium(I) metal cations are most commonly used to facilitate the reaction along with an excess of base such as a tertiary amine. The reaction is usually carried out in a stoichiometric fashion, and only few reports mention the use of substoichiometric amounts of metal salts.[8]

We were intrigued by the Ag-catalyzed cycloaddition of azomethine ylides and the corresponding asymmetric reaction. Previous work in this area has focused mainly on the use of chiral auxiliaries on the dipolarophile[9] or dipole[10] substrates. The use of chiral transition metal catalysts is relatively unexplored.[11] Grigg et al. have reported ee's up to 96% using a stoichiometric amount of Co(II) and a chiral ephedrine ligand for the cycloaddition of α-imino esters. In another paper, up to 70% ee has been reported by Grigg using AgOTf and a chiral bisphosphine ligand. However, detailed reaction conditions such as catalyst loading and substrate scope were not reported, and a full account of this work has yet to be disclosed. Herein we wish to report a highly reactive Ag(I)-catalyzed [3 + 2] cycloaddition of azomethine ylides using AgOAc as the catalytic precursor and phosphines as ligands. Using a new chiral ferrocene phosphine as the ligand, we found that high enantioselectivities have been achieved in the [3 + 2] cycloaddition of azomethine ylides.

In our study, we discovered that AgOAc is an excellent catalytic precursor and high activity can be achieved. For example, 1 mol % AgOAc with 2 mol % PPh_3 can effectively catalyze the cycloaddition of **7a** with dimethylmaleate to yield only the endo diastereomer **8a** in high yield (Scheme 1).[12] AgOAc has low solubility in most organic solvents, and addition of PPh_3 forms a highly soluble catalyst. The high reactivity and diastereoselectivity of the AgOAc/PPh_3 system encouraged us to investigate a number of chiral bisphosphine ligands to develop a highly enantioselective process. Some of the phosphine ligands that were screened are listed in Figure 1.

To perform the Ag-catalyzed asymmetric reaction, the cycloaddition was carried out in toluene using 3 mol % AgOAc, 3.3 mol % ligand, and 10 mol % *i*-Pr_2NEt at room temperature. With the exception of BINAP (**1**), all ligands that were screened gave only the endo diastereomer under these reaction conditions. The BINAP (**1**)[13a] and Me-DuPhos[13b] (**3**) ligands gave poor enantioselectivity (13% ee with **1**, 23% ee with **3**), and poor diastereoselectivity was observed in the case of BINAP (endo/exo = 3:1). The PennPhos[13c] (**4**) and BICP[13d] (**5**) ligands, developed in our laboratories, also gave very low enantioselectivities (27% ee with **4** and 13% ee with **5**). Interestingly, the Trost ligand[13e] (**2**) provided a considerably higher enantioselectivity of 59% ee. Recently, we reported the synthesis of a new bis-ferrocenyl amide phosphine (FAP),[13f,g] **6a**, for the Pd-catalyzed allylic alkylation reaction. This ligand is similar to the Trost ligand; however, the ferrocene units add an additional element of chirality and also impart different steric and electronic properties. A significant improvement in reactivity and enantioselectivity was observed with the FAP ligand (**6a**) for the cycloaddition of **7a** providing *endo*-**8a** in 94% isolated yield and 76% ee. Further improvement in enantioselectivity to 86% ee was achieved by replacing the phenyl groups in **6a** to 3,5-dimethylphenyl (xylyl-FAP, **6b**).

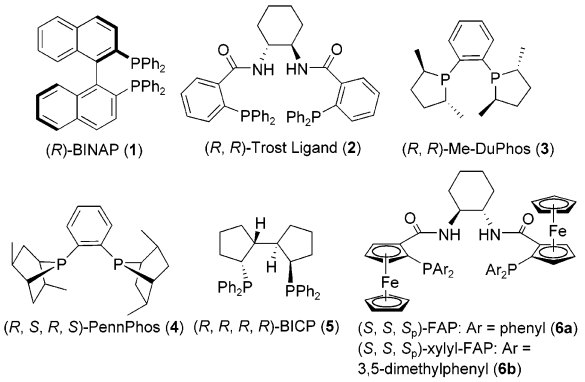
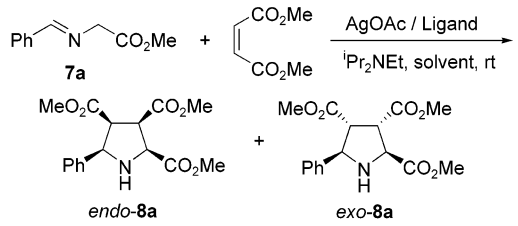


Figure 1. Chiral phosphine ligands screened for the AgOAc catalyzed cycloaddition of **7a** with dimethyl maleate.

Scheme 1



Using ligand **6b**, we investigated a variety of α-iminoester substrates (Table 1). A number of α-(arylimino)esters were cyclized in good yields and high enantioselectivities (up to 97% ee) (entries 1−11). On the other hand, α-(alkylimino)esters are less reactive, requiring prolonged reaction times at room temperature and yielding cycloaddition products of slightly lower enantioselectivity (entries 12 and 13). Again, only the endo products were observed.

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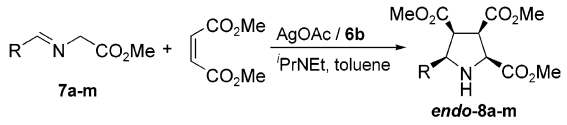
Table 1. Variation of the R-Substituent on **7** for the Cycloaddition with Dimethylmaleate

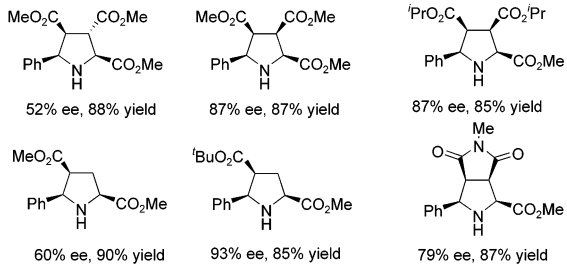


7a-m *endo*-**8a-m**

			endo-8	
entry[a]	**7**, R=	time (h)	% yield[c]	% ee[d]
1	Ph (**7a**)	7	87	87
2	*p*-toluyl (**7b**)	7	93	88
3	*p*-anisole (**7c**)	7	98	92
4	4-chlorophenyl (**7d**)	7	96	92
5	4-fluorophenyl (**7e**)	7	96	90
6	4-cyanophenyl (**7f**)	7	90	96
7	2-chlorophenyl (**7g**)	7	96	86
8	*o*-toluyl (**7h**)	7	97	90
9	1-naphthyl (**7i**)	7	73	85
10	2-naphthyl (**7j**)	14	98	97
11	3-pyridyl (**7k**)	7	98	84
12[b]	*i*-Pr (**7l**)	48	82	70
13[b]	cyclohexyl (**7m**)	48	82	81

[a] Conditions: imine (1.0 equiv), dimethyl maleate (1.2 equiv), AgOAc (3 mol %), ligand **6b** (3.3 mol %), $^{i}Pr_2NEt$ (10.0 mol %), toluene (3 mL) at 0 °C, unless indicated otherwise. [b] Reactions were run at room temperature. [c] Isolated yield by silica gel chromatography. [d] Enantiomeric excess determined by HPLC.

Table 2. Cycloaddition of **7a** with Various Dipolarophile Substrates Catalyzed by Ag(I)-**6b**



A variety of dipolarophiles were explored in the cycloaddition with **7a** as outlined in Table 2. Only the endo products were isolated in all cases. With dimethyl fumarate, the enantioselectivity is considerably reduced as compared with dimethyl maleate (52% ee versus 86% ee). Much lower enantioselectivity was also observed with methyl acrylate (60% ee). The most interesting result is the markedly improved enantioselectivity on going from methyl acrylate to a bulky *tert*-butyl acrylate, 60 and 93% ee, respectively. A fused bicyclic pyrrolidine was also synthesized in good yield and enantioselectivity using *N*-methyl maleimides as the dipolarophile.

Following is our working model: Coordination of the α-iminoester to the chiral Ag(I) catalyst, followed by deprotonation with i-Pr_2NEt, forms the reactive metal-bound azomethine ylide dipole. Chiral ligand **6b** effectively blocks one enantiotopic face of the azomethine ylide, providing pyrrolidine products with high enantioselectivity. The higher ee observed with dimethyl maleate versus dimethyl fumarate and *tert*-butyl acrylate versus methyl acrylate can be explained by the endo-transition state model. More steric interaction between these substrates and the chiral ligand results in better enantiodescrimination. This can explain the improved enantioselectivity observed with xylyl-FAP (**6b**) as compared to FAP (**6a**). The 3,5-dimethyl substitution extends the steric environment of the ligand and effectively blocks one of the enantiotopic faces of the azomethine ylide.

In conclusion, we have developed a highly enantioselective Ag(I)-catalyzed azomethine ylide [3 + 2] cycloaddition reaction. These results demonstrate that FAP ligands are unique for this transformation. Up to four stereogenic centers can be established in this multicomponent coupling reaction from readily available materials such as aldehydes, aminoesters, and dienophiles. Further work toward exploring the asymmetric intramolecular azomethine ylide [3 + 2] cycloaddition reaction and rapid synthesis of biologically active compounds will be forthcoming.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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