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Ag_2CO_3/CA-AA-AmidPhos Multifunctional Catalysis in the Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides

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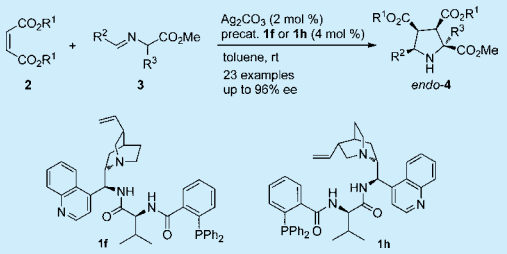
Supporting Information

ABSTRACT: The new Ag_2CO_3/CA-AA-amidphos complexes have been demonstrated as highly efficient multifunctional catalysts in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides. Under optimal conditions, highly functionalized *endo*-**4** pyrrolidines were obtained with excellent yields (up to 99% yield) and enantioselectivities (up to 96% ee).



Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes has inspired much research interest, as the reaction is one of the most powerful methods and diversity-oriented synthesis is desired for the construction of highly substituted pyrrolidine rings, which are structural motifs widely present in many natural alkaloids and pharmaceutically useful agents.[1] Since the pioneering work of Grigg employing stiochiometric amounts of chiral metal complexes,[2] effective chiral catalytic systems based on a combination of chiral metal Lewis acids and tertiary amine bases have thus far been reported to catalyze the process with high *endo*/*exo*-diastereo- and enantioselectivities.[3−5] In particular, the catalytic systems, including Zhang's Ag(I)/xylyl-FAP/*i*-Pr_2NEt,[6] Schreiber's Ag(I)/QUINAP/*i*-Pr_2NEt,[7] Carretereo's Cu(I)/Fe-sulphos/Et_3N,[8] Wang's Cu(I)/TF-Biphamphos/Et_3N,[9] and Jørgensen's Zn(II)/*t*-BuBox/Et_3N,[5a] afford high *endo*-selectivities and asymmetric inductions in the intermolecular 1,3-dipolar cycloaddition of glycine derivatives with electron-deficient alkenes, while Komatsu's Cu(II)/BINAP/Et_3N,[10] Zhang's Cu(I)/P,N-ligands/Et_3N,[11] and Deng's Cu(II)/N,O-ligands/K_2CO_3[5d] have been reported as efficient catalytic systems with some *exo*-selective cycloadditions. Despite these impressive advances, there are still some problems that have yet to be solved for the reaction: (1) an excess of base such as tertiary amine or inorganic base is involved in most cases; (2) these bidentate ligands are mainly focused on bisphosphanes, nitrogenated phosphanes, sulfur-containing phosphanes, and bisimines, which easily form relatively rigid and stable complexes with metal cations; and (3) applicable substrates of various azomethine ylides, especially derived from aminoesters other than glycinate, are still limited. Furthermore, successful examples of obtaining the opposite absolute configuration with such high enantioselectivities are very rare.[12] It is thus highly desirable to develop an innovative, multifunctional catalytic system which is easily prepared with a tertiary amine and a different phosphane, while it can also tolerate variation of the dipole components.

Recently, amidophosphane ligands have aroused great attention in the asymmetric reaction,[13] such as Pd-catalyzed asymmetric allylations,[13a,c] hydrogenations,[13f] Michael-type conjugate additions,[13d] and imine additions.[13b,e] However, to the best of our knowledge, coordination between a multifunctional amidophosphane and a metal ion has not been reported in the 1,3-dipolar cycladdition of azomethine ylides. Here, we report that cinchona alkaloid-amino acid derived amidophosphanes (CA-AA-amidphos) serve as the desired multifunctional precatalysts in combination with transition-metal ions to cooperatively catalyze 1,3-dipolar cycloaddition of azomethine ylides with high diastereo- and enantioselectivities (Figure 1).

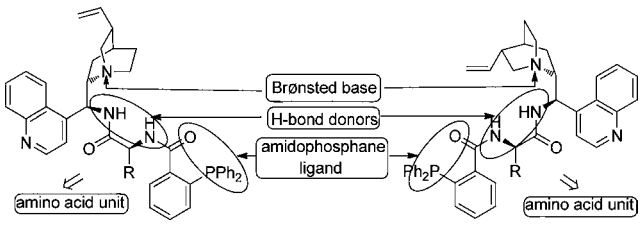


Figure 1. Pseudoenantiomeric cinchona alkaloid-amino acid derived potential amidophosphine precatalysts.

We first investigated the 1,3-dipolar cycloaddition of the iminoester **3a** and diethyl maleate **2a** using a combination of different silver(I) salts and cinchonidine-derived amidophosphane **1a**, which was used in the isocyanoacetate aldol reaction by Dixon's group (Table 1, entries 1−5).[14] From a screen of silver(I) salts, we found that the Ag_2CO_3/**1a** system gave relatively high reactivity and enantioseletivity (Table 1, entry 5). For obtaining higher enantioselectivity in the cycloaddition, we envisioned it may be effective by incorporating primary amino acid moieties into the amidophosphane **1a**, and thus, a

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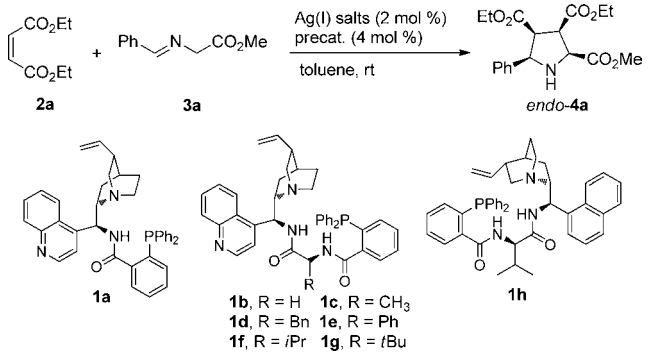
Table 1. Screening Studies of Asymmetric 1,3-Dipolar Cycloaddition of the Iminoester 3a with Diethyl Maleate 2a[a]



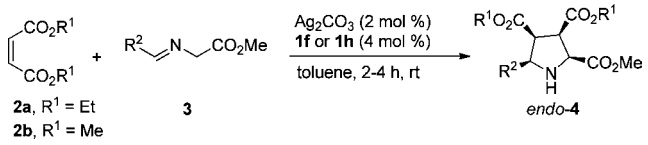
entry	precat	Ag(I) salts	time (h)	yield[c] (%)	ee[d] (%)
1[b]	**1a**	AgOAc	18	41	−17
2[b]	**1a**	AgOTf	18	34	−4
3[b]	**1a**	$AgClO_4$	24	<10	
4	**1a**	Ag_2O	2	82	−12
5	**1a**	Ag_2CO_3	2	91	−24
6	**1b**	Ag_2CO_3	2	89	26
7	**1c**	Ag_2CO_3	2	90	74
8	**1d**	Ag_2CO_3	2	96	81
9	**1e**	Ag_2CO_3	2	95	90
10	**1f**	Ag_2CO_3	2	96	96
11	**1g**	Ag_2CO_3	2	92	86
12	**1h**	Ag_2CO_3	2	94	−92
13[e]	**1f**	Ag_2CO_3	16	79	88

[a]All reactions run using **2a** (0.2 mmol), **3a** (0.3 mmol), and toluene (1.4 mL). [b]4 mol % of Ag(I) salt was used. [c]Isolated yield. [d]Determined by HPLC. [e]temp = 0 °C.

number of cinchonidine-amino acid derived amidophosphines **1b−g** were prepared. Interestingly, by investigating the effect of Ag_2CO_3/**1b−g** systems on the cycloaddition, good to excellent reversals of enantioselectivity were observed (Table 1, entries 6−11). Glycine-containing precatalyst **1b** was not very effective (Table 1, entry 6); however, high enantioselectivity (74% ee) was achieved with the L-alanine-containing precatalyst **1c** (Table 1, entry 7). L-Phenylalanine-containing precatalyst **1d** and L-phenylglycine-containing precatalyst **1e** were better than the precatalyst **1c** with an L-alanine moiety (Table 1, entries 8 and 9).We were pleased to find that precatalyst **1f**, with a L-valine moiety incorporated, afforded the desired adduct in 96% yield and 96% ee (Table 1, entry 10). Further tuning of the steric hindrance at the amino acid side chain did not result in better precatalyst **1g** (Table 1, entry 11). When the pseudoenantiomeric **1h** derived from cinchonine and D-valine was used, the opposite configuration was also observed with excellent enantioselectivity of −92% ee (Table 1, entry 12). However, lowering the reaction temperature from room temperature to 0 °C had detrimental effects on the yield (77% yield) and the enantioselectivity (88% ee) (Table 1, entry 13). Thus, the optimal conditions for the asymmetric cycloaddition of azomethine ylides is Ag_2CO_3/**1f** or **1h**/toluene at room temperature.

1,3-Cycloaddition of various iminoesters **3** and the maleates **2** in the presence of precatalyst **1f** or **1h** was investigated under the optimized experimental conditions. As shown in Table 2, α-iminoesters **3b−j** from aromatic aldehydes with different steric hindrance and electronic properties reacted with diethyl maleate **2a** to afford the corresponding *endo*-**4b−j** exclusively

Table 2. Enantioselective Ag_2CO_3-Catalyzed 1,3-Dipolar Cycloaddition of Various Iminoesters 3 with the Maleates 2[a]



entry	2	3, R^2	cat.	4, yield[b] (%)	ee[c] (%)
1	**2a**	**3b**, 4-MePh	**1f**	**4b**, 95	94
2	**2a**	**3c**, 4-MeOPh	**1f**	**4c**, 92	96
3	**2a**	**3d**, 4-FPh	**1f**	**4d**, 93	94
4	**2a**	**3e**, 4-ClPh	**1f**	**4e**, 99	92
5	**2a**	**3f**, 4-BrPh	**1f**	**4f**, 92	91
6[d]	**2a**	**3g**, 4-CNPh	**1f**	**4g**, 99	91
7	**2a**	**3h**, 4-^{t}BuPh	**1f**	**4h**, 90	90
8	**2a**	**3i**, 1-naphthyl	**1f**	**4i**, 99	91
9	**2a**	**3j**, 2-naphthyl	**1f**	**4j**, 95	91
10[d]	**2a**	**3k**, 2-thienyl	**1f**	**4k**, 92	88
11	**2a**	**3l**, 2-furyl	**1f**	**4l**, 81	89
12[e]	**2a**	**3m**, Cyclohexyl	**1f**	**4m**, 47	86
13	**2b**	**3a**, Ph	**1f**	**4n**, 94	93
14	**2a**	**3b**, 4-MePh	**1h**	**4b**, 91	−91
15	**2a**	**3c**, 4-MeOPh	**1h**	**4c**, 97	−95
16	**2a**	**3d**, 4-FPh	**1h**	**4d**, 99	−94
17	**2a**	**3e**, 4-ClPh	**1h**	**4e**, 96	−93

[a]All reactions run using **2a** (0.2 mmol), **3a** (0.3 mmol), and toluene (1.4 mL). [b]Isolated yield. [c]Determined by HPLC. [d]2.8 mL of toluene was used. [e]Run in 24 h.

in high yields (90−99%) and excellent enantiselectivties (90−96% ee) in the presence of precatalyst **1f** (Table 2, entries 1−9). α-Iminoesters **3k,l** containing heteroatoms in their aromatic rings also worked well without significant loss in selectivity (Table 2, entries 10 and 11). Noticeably, when R^2 was aliphatic cyclohexyl, the *endo*-**4m** was successfully obtained with slightly low enantioselectivity (86% ee) and moderate yield (47%) in 24 h (Table 2, entry 12). Dimethyl maleate as a popular dipolarophile in the reported literature was also used to react with α-iminoester **3a** in 94% yield and 93% enantioselectivity (Table 2, entry13).[15] Gratifyingly, when precatalyst **1h** was used, reversal of the absolute configuration was successfully realized with excellent levels of yield and enantioselectivity in the reactions of iminoester **3b−e** and diethyl maleate regardless of electron-rich, electron-neutral, or electron-deficient groups on the phenyl ring of iminoester **3** (Table 2, entries 14−17).

Encouraged by the results for less sterically hindered azomethine ylides from glycinate, 1,3-dipolar cycloaddition of the iminoesters **3** derived from α-substituted amino esters and the maleates **2** was also investigated, as shown in Table 3.[15] The tested substrates generate pyrrolidines with a quaternary center at the 2-position; several limited successful protocols have been reported in achieving moderate to high levels of enantioselectivity.[16] As depicted in Table 3, the reaction of iminoesters **3** derived from alanine with the maleates **2** using Ag_2CO_3/**1f** catalytic system led to pyrrolidines **4o−u** with perfect *endo*-selectivity and excellent enantioselectivity ranging from 88% to 96% regardless of the steric hindrance and electronic properties of the phenyl ring of iminoesters **3** (Table 3, entries 1−7). We also examined the iminoesters derived from phenylglycine (Table 3, entry 8) and tryptophan (Table 3, entry 9). Good enantioselectivity (83−91% ee) was observed in both cases, although the process was sluggish. These results strongly

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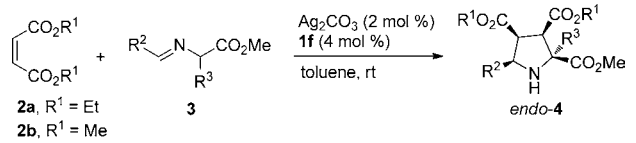
Table 3. Asymmetric 1,3-Dipolar Cycloaddition of α-Substituent Iminoesters 3 Catalyzed by Ag_2CO_3/1f[a]



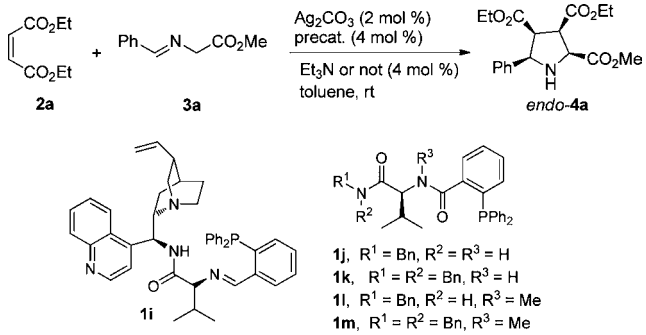
entry	2	3, R^2, R^3	time (h)	4, yield[b] (%)	ee[c] (%)
1	2a	3o, Ph/Me	48	4o, 83	93
2	2b	3o, Ph/Me	48	4p, 95	95
3	2a	3q, 4-MePh/Me	48	4q, 90	92
4	2a	3r, 4-MeOPh/Me	48	4r, 87	96
5	2a	3s, 4-FPh/Me	48	4s, 99	95
6	2a	3t, 4-ClPh/Me	48	4t, 96	94
7	2a	3u, 2-naphthyl/Me	48	4u, 99	88
8	2a	3v, Ph/Bn	72	4v, 67	91
9[d]	2a	3w, Ph/E	72	4w, 61	86

[a]All reactions run using **2a** (0.2 mmol), **3a** (0.3 mmol), and toluene (1.4 mL). [b]Isolated yield. [c]Determined by HPLC. [d]E = 3-indolylmethyl.

suggest that use of a suitable catalytic system can lead to a high diastereo- and enantioselectivity in reactions with a variety of substrates.[17]

To ascertain the possible contributions of the functional groups in the precatalyst **1f** to the observed reactivity, imidophosphane **1i** and L-valine-derived amidophosphanes **1j−m** without the scaffolds of cinchona alkaloids were synthesized to catalyze the cycloaddition with or without Et_3N. As shown in Table 4, the amidophosphane group on phenyl ring was also irreplaceable; once the group was changed into iminophosphane, poor results were obtained, and especially the enantioselectivity was decreased to 2% ee (Table 4, entries 1 and 2). When the ligand **1j** was used with or without Et_3N, the former had the same reaction rate as precatalyst **1f** with a slightly decreased enantioselectivity to 84% ee, whereas the latter required prolonged reaction time to 4 h for obtaining 100% conversion without a loss of enantioselectivity (Table 4, entries 3 and 4). In terms of the above experiments, we postulate the tertiary amine in precatalyst **1f** should have the same significant rate acceleration effect as Et_3N. To further understand the role of N−H bonds on the two amides, ligands **1k−m** which were synthesized by replacing the different hydrogen atoms of the amides in **1j** to benzyl, methyl, and benzyl and methyl, respectively, were investigated. Interestingly, when any one of the ligands **1k−m** was used to catalyze the process with Et_3N, lower reactivity and enantioselectivity were observed (Table 4, entries 5−7). Furthermore, ligand **1l** led to the reversal of the absolute configuration, while ligand **1m** afforded only 75% conversion even if the reaction time was prolonged to 12 h (Table 4, entries 6 and 7). These results indicate the importance of the amide N−H bonds in the rate-determining step and stereocontrol.

Table 4. Studies of the Reactivity of Precatalyst 1f, 1i, and L-Valine-Derived Amidophosphines 1j−m in the Cycloaddition[a]



entry	precat	base	time (h)	conv[b] (%)	ee[c] (%)
1	1f		2	100	95
2	1i		5	100	2
3	1j	Et_3N	2	100	84
4	1j		4	100	84
5	1k	Et_3N	5	100	16
6	1l	Et_3N	6	100	−11
7	1m	Et_3N	12	75	12

[a]All reactions run using **2a** (0.2 mmol), **3a** (0.3 mmol), and toluene (1.4 mL). [b]Determined by ^1H NMR. [c]Determined by HPLC.

These data suggest a cooperative mechanism where the silver(I) ion, the tertiary amine, the two N−H bonds on the amide group, and amidophosphane in **1f** are all essential for the observed reactivity. Although further mechanistic studies are required, we postulate that the precatalyst **1f** has three distinct roles: (1) the tertiary amine as a Brønsted base can accelerate the reaction by the deprotonation of the azomethine ylide; (2) the two amide groups as H-bond donors should have the potential interaction with the substrates; and (3) the amidophosphane group serves as an effective ligand in combination with silver ions to afford high levels of enantiocontrol.

In conclusion, we have developed the Ag_2CO_3/CA-AA-amidphos complexes serving as a class of novel and highly efficient multifunctional catalysts for the asymmetric 1,3-dipolar cycloaddition reaction without the addition of an extra excess of base. High to very high levels of reactivity, selectivity, and structural scope were uniformly observed for various azomethine ylides. In addition, reversal of the absolute configuration of the *endo*-adducts is also realized with excellent levels of yield and enantioselectivity, which benefits from both pseudoenantiomers of the new catalyst systems easily prepared from commercially available reagents. Furthermore, the possible contributions of the functional groups in the CA-AA-amidphos precatalysts to the 1,3-dipolar cycloaddition have also been investigated. Further investigations in this field of catalysis are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03430.

Experimental procedures and detailed characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) For 1,3-dipolar cycloaddition with a quaternary center at the 2-position, see ref 9.

(17) For other 1,3-dipolar cycloadditions of *N*-methylmaleimide, methyl acrylate, and dimethyl fumarate, see the Supporting Information.

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