Highly enantioselective 1,3-dipolar cycloaddition of azomethine ylides catalyzed by AgOAc/TF-BiphamPhos†

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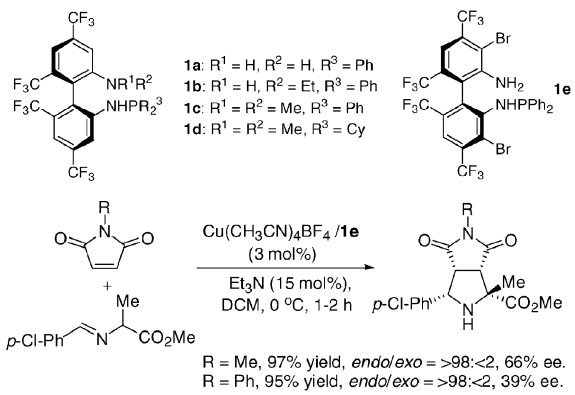
A novel and highly efficient AgOAc/TF-BiphamPhos catalytic system shows excellent reactivity, diastereo-/enantioselectivity and structural scope in asymmetric 1,3-dipolar cycloaddition of azomethine ylides, especially derived from various α-substituted α-amino acids, with *N*-substituted maleimides and other electron-deficient alkenes.

The catalytic asymmetric 1,3-dipolar cycloaddition[1] of azomethine ylides to electron-deficient alkenes has become one of the most powerful and diversity-oriented synthesis (DOS)[2] for the construction of highly substituted pyrrolidines with up to four stereogenic centers. It is well known that substituted pyrrolidines are prevalent in many natural alkaloids, compounds of pharmaceutical significance, organocatalysts, and building blocks in organic synthesis.[3] Since the pioneering work of Grigg[4] employing stoichiometric amounts of chiral metal complex, and the first catalytic asymmetric version reported by Zhang[5] using the Ag^{I}/xylyl-FAP system, much attention has been paid to developing enantioselective catalytic protocols for the reaction over the past decade. Asymmetric 1,3-dipolar cycloadditions have been reported using chiral metal complexes of Ag^{I},[5,6] Zn^{II},[7] $Cu^{I/II}$,[8] Ni^{II},[9] Ca^{II},[10] and organocatalysts,[11] to afford moderate to high enantio/diastereoselectivities. Although various methods are developed for this transformation, most of them rely on the use of less sterically hindered azomethine ylides derived from glycinate. In contrast, successful examples of the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides derived from amino esters other than glycinate are very limited.[6j,12] Recently, we reported a novel and highly efficient Cu^{I}/TF-BiphamPhos catalytic system that exhibited excellent results (97–99% ee and >98/<2 dr) in asymmetric 1,3-dipolar cycloaddition of various azomethine ylides, especially derived from α-substituted α-amino acids, with several dipolarophiles such as dimethyl maleate, methyl and *tert*-butyl acrylate.[13] However, when *N*-methyl and phenyl maleimide were used as the dipolarophiles, only 66 and 39% ee were achieved for the 1,3-dipolar cycloaddition of alanine derived azomethine ylides, although the corresponding diastereoselectivities still remained high (Scheme 1).[14] To further broaden the substrate scope and improve the enantioselectivity for the cycloaddition of *N*-substituted maleimide, the screening of various metal precursors would be desirable and practicable considering the good to excellent results achieved by the above-mentioned chiral metal complexes for the cycloaddition of less sterically hindered azomethine ylides.[5–10,13] In this communication, we describe the development of a AgOAc/TF-BiphamPhos system for the highly enantio/diastereoselective 1,3-dipolar cycloaddition of various azomethine ylides, especially derived from α-substituted α-amino acids, with *N*-substituted maleimides and other dipolarophiles.

Initially, we selected the asymmetric 1,3-dipolar cycloaddition of *N*-phenyl maleimide with imino ester **3c** as the model reaction in the presence of chiral TF-BiphamPhos and various metal salts to establish the optimal reaction conditions and results are given in Table 1. Except for the low activity of $Ni(ClO_4)_2{\cdot}6H_2O$ and $Zn(OTf)_2$ as metal precursors (Table 1, entries 3 and 4), $Cu^{I/II}$ salts combined with the chiral ligand **1a** showed high reactivities albeit unsatisfactory diastereo/enantioselectivities (Table 1, entries 1 and 2). To our delight, combinations of silver(I) salts with **1a** gave the *endo*-product exclusively in good yields with much higher enantioselectivities (Table 1, entries 5, 6 and 8). Among the examined silver precursors, AgOAc gave the best results in terms of the yield and diastereo/enantioselectivity (Table 1, entry 9). Another attractive advantage of AgOAc over other silver(I) salts is that no extra base was required in the reaction, which is similar to the cases reported by Zhou[6f] and Fukuzawa.[8a] Subsequently, other TF-BiphamPhos were also examined (Table 1, entries 9–13). The asymmetric induction of ligand **1a** was superior to that of **1b** or **1c** with substituent groups on the N atom and **1d** with a bulky cyclohexyl group on the P atom. Ligand **1e** bearing two bromines at the 3,3′-position of TF-BIPHAM backbone emerged as the most effective chiral ligand in this reaction and provided *endo*-**4c** as the sole product in high yield and excellent enantioselectivity of 96% ee. The solvent effect



Scheme 1 The results for Cu^{I}/TF-BiphamPhos catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides derived from alanine with *N*-substituted maleimide.

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Table 1 Screening studies of the asymmetric 1,3-dipolar cycloaddition of azomethine ylide **3c** with *N*-phenyl maleimide **2a**[a]

Entry	L	[M]	Solvent	*t*/h	Yield[b] (%)	*Endo*/*Exo*[c]	Ee[de] (%)
1[f]	**1a**	$CuClO_4$[g]	DCM	0.2	78	>98/<2	54
2[f]	**1a**	$Cu(OTf)_2$	DCM	0.2	88	80/20	37
3[f]	**1a**	$Ni(ClO_4)_2$	DCM	3	75	60/40	0
4[f]	**1a**	$Zn(OTf)_2$	DCM	3	73	73/27	0
5[f]	**1a**	$AgClO_4$	DCM	0.2	87	>98/<2	82
6[f]	**1a**	$AgSbF_6$	DCM	0.2	90	>98/<2	87
7	**1a**	$AgSbF_6$	DCM	3	36	>98/<2	81
8[f]	**1a**	AgOAc	DCM	0.2	97	>98/<2	84
9	**1a**	AgOAc	DCM	3	85	>98/<2	90
10	**1b**	AgOAc	DCM	8	90	>98/<2	35
11	**1c**	AgOAc	DCM	8	88	>98/<2	19
12	**1d**	AgOAc	DCM	8	95	>98/<2	19
13	**1e**	AgOAc	DCM	3	94	>98/<2	96
14	**1e**	AgOAc	PhMe	3	90	>98/<2	83
15	**1e**	AgOAc	MeOH	15	97	>98/<2	88
16[h]	**1e**	AgOAc	DCM	6	89	>98/<2	80
17[i]	**1e**	AgOAc	DCM	15	76	>98/<2	77

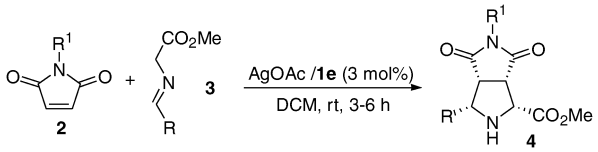
[a] All reactions were carried out with 0.23 mmol of **2a** and 0.45 mmol of **3c** in 2 mL of solvent at r.t. unless specified. [b] Isolated yield. [c] Determined from crude ^{1}H NMR spectra. [d] Enantiomeric excesses were determined by chiral HPLC analysis. [e] The absolute configuration of **4c** was determined by comparing the optical rotation with the reported data. [f] 15 mol% Et_3N was added as the base. [g] $CuClO_4$ = $Cu(CH_3CN)_4ClO_4$. [h] T = 0 °C. [i] T = −20 °C.

was then studied, and DCM was revealed to be the best solvent of choice (Table 1, entries 13–15). Reducing the temperature from room temperature to 0 °C or −20 °C had detrimental effect on the reactivity and enantioselectivity (Table 1, entries 16 and 17).

Having established the optimal reaction conditions, we then investigated a series of representative imino esters **3** derived from glycinate. As shown in Table 2, a wide array of imino esters derived from aromatic aldehyde reacted smoothly with *N*-phenyl or methyl maleimide to afford the corresponding *endo*-adducts exclusively in high yields and excellent enantioselectivities (Table 2, entries 1–10). It appears that the position and the electronic property of the substituents on the aromatic rings have a very limited effect on the enantioselectivities. Azomethine ylides from aliphatic aldehydes has been seldom studied in the asymmetric 1,3-dipolar cycloaddition reaction probably due to their lower reactivity. Remarkably, the relatively challenging azomethine ylide **3i** from *tert*-butyl aldehyde also works well in this transformation producing the *endo*-**4k** with high enantioselectivity (92% ee) albeit with moderate yield (45%) (Table 2, entry 11).

Encouraged by the results for less sterically hindered azomethine ylides from glycinate, we then investigated 1,3-dipolar cycloaddition of azomethine ylides derived from α-substituted amino acids in which a quaternary stereogenic center[15] was generated among the four contiguous stereocenters in the corresponding highly substituted pyrrolidines. The results are summarized in Table 3. Gratifyingly, alanine

Table 2 Asymmetric 1,3-dipolar cycloaddition of azomethine ylides **3** derived from glycinate with maleimide **2** catalyzed by AgOAc/**1e**[a]

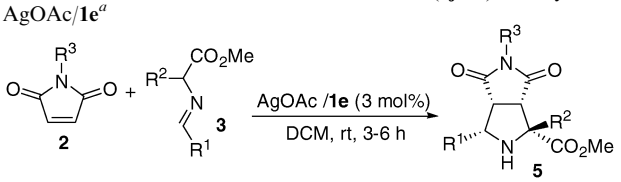


Entry	R	**3**	R^1	**4**	Yield[b] (%)	Ee[cd] (%)
1	Ph	**3a**	Ph	**4a**	88	95 (99)[e]
2	4-MeC_6H_4	**3b**	Ph	**4b**	85	93
3	4-ClC_6H_4	**3c**	Ph	**4c**	95	96 (99)[e]
4	2-ClC_6H_4	**3d**	Ph	**4d**	94	94
5	4-FC_6H_4	**3e**	Ph	**4e**	98	95
6	4-CNC_6H_4	**3f**	Ph	**4f**	81	96
7	Ph	**3a**	Me	**4g**	99	95
8	2-MeC_6H_4	**3g**	Me	**4h**	90	96
9	4-$MeOC_6H_4$	**3h**	Me	**4i**	93	94
10	4-ClC_6H_4	**3c**	Me	**4j**	99	97
11	*t*-Bu	**3i**	Ph	**4k**	45	92

[a] All reactions were carried out with 0.23 mmol of **2** and 0.45 mmol of **3** in 2 mL DCM. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] The absolute configurations were determined by comparing the optical rotation with reported data. [e] Data in parentheses refer to enantiomeric excesses after recrystallization.

derived imino ester and various aromatic aldehydes have proved to be excellent substrates affording the corresponding *endo*-adducts with high yields and excellent enantioselectivities, regardless of the position and electronic property of the substituents on the aromatic ring (Table 3, entries 1–9). Noticeably, up to 96% ee and almost quantitative yield was

Table 3 Asymmetric 1,3-dipolar cycloaddition of azomethine ylides derived from α-substituted-α-amino acids (**3j–3v**) catalyzed by AgOAc/**1e**[a]



Entry	R^1	R^2	**3**	R^3	**5**	Yield[b] (%)	Ee[cd] (%)
1	Ph	Me	**3j**	Me	**5a**	95	98
2	4-$MeOC_6H_4$	Me	**3k**	Me	**5b**	92	95
3	4-MeC_6H_4	Me	**3l**	Me	**5c**	83	97
4	2-MeC_6H_4	Me	**3m**	Me	**5d**	99	97
5	4-ClC_6H_4	Me	**3n**	Me	**5e**	87	97
6	2-ClC_6H_4	Me	**3o**	Me	**5f**	99	96
7	3-ClC_6H_4	Me	**3p**	Me	**5g**	99	95
8	4-BrC_6H_4	Me	**3q**	Me	**5h**	97	97
9	4-FC_6H_4	Me	**3r**	Me	**5i**	90	98
10	2-Furyl	Me	**3s**	Me	**5j**	99	96
11	3-ClC_6H_4	Me	**3p**	Ph	**5k**	92	96
12	Ph	E[e]	**3t**	Me	**5l**	90	94
13	Ph	Bn	**3u**	Me	**5m**	96	91
14	4-BrC_6H_4	Ph	**3v**	Me	**5n**	93	96[f]

[a] All reactions were carried out with 0.23 mmol of **2** and 0.45 mmol of **3** in 2 mL DCM. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] The absolute configuration of the known compounds **5a** and **5m** were determined by optical rotation comparisons with reported data. [e] E = 3-indolymethyl, 24 h. [f] $AgSbF_6$/**1e** (3 mol%) and Et_3N (15 mol%) was used as the catalyst and the base, 0.5 h; 90% ee was achieved when AgOAc/**1e** (3 mol%) was used.

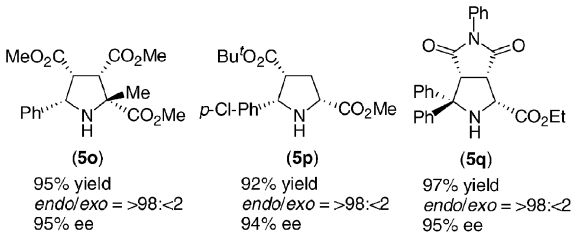


Fig. 1 The results of 1,3-dipolar cycloaddition of other dipolarons/dipolarophiles catalyzed by AgOAc/**1e**.

still obtained even for heteroaromatic 2-furyl imino ester (Table 3, entry 10). High yield and excellent diastereo/enantioselectivity was also observed when *N*-phenyl maleimide was used as the dipolarophile (Table 3, entry 11). Furthermore, under the optimized reaction conditions, the azomethine ylides derived from tryptophan, phenylalanine and 2-phenylglycine, successfully reacted with *N*-methyl maleimide leading to high *endo*-selectivities (>98/<2) and excellent enantioselectivities (91–96% ee) (Table 3, entries 12–14). Fortunately, all the products are solid, and enantiopure compounds can be easily obtained by direct crystallization of the crude products.

Finally, in order to probe more deeply the scope and generality of this AgOAc/TF-BiphamPhos catalytic system, other dipolarophiles were also examined under the optimized reaction conditions. As shown in Fig. 1, *tert*-butyl acrylate and dimethyl maleate proved to be excellent dipolarophiles affording high yields and excellent diastereo/enantioselectivities for this transformation. Moreover, the commercially available glycine ethyl ester benzophenone Schiff base was an equally acceptable dipolar partner.

In conclusion, we have developed a novel and highly efficient AgOAc/TF-BiphamPhos catalytic system, which exhibited excellent reactivity, diastereo/enantioselectivity, and structural scope in asymmetric 1,3-dipolar cycloaddition of azomethine ylides derived from various α-substituted α-amino acids with *N*-substituted maleimides and other electron-deficient alkenes. This methodology presented herein nicely complements the highly efficient Cu(I)/TF-BiphamPhos catalytic system.[13] Future applications of TF-BiphamPhos in asymmetric catalysis are ongoing in our laboratory and will be reported in due course.

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12 64–92% ee were achieved for transition-metal-catalyzed cycloadditions of azomethine ylides derived from imino esters other than glycinate with *tert*-butyl acrylate or *N*-phenyl/methyl maleimide, see ref. 6*a*, 6*i*, 8*e* and 10. Exceptionally, 97% ee was achieved for the cycloaddition of the *in situ* azomethine ylide derived from α-phenylglycine methyl ester and dimethyl maleate with 20 mol% organocatalyst at 50 °C in 60 h, see ref. 11*c*; 98% ee for the cycloaddition of the azomethine ylide derived from phenylalanine and *tert*-butyl acrylate catalyzed by 5 mol% Ag(I)/phosphoramidite in 48 h, see ref. 6*j*.

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