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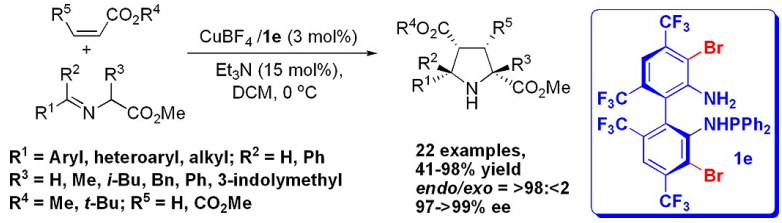

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Highly Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides Catalyzed by Copper(I)/TF-BiphamPhos Complexes

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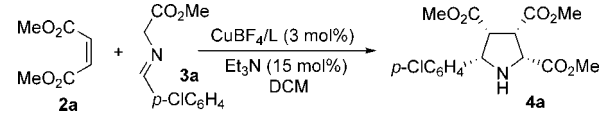
Five-membered nitrogen heterocycles, especially the highly substituted pyrrolidines are very important pharmaceuticals, natural alkaloids, and building blocks in organic synthesis.[1] The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes is one of the most powerful and diversity-oriented synthesis (DOS)[2] for the construction of this type of structures.[3] Since the first catalytic asymmetric 1,3-dipolar cycloaddition reported by Zhang employing the AgOAc/xylyl-FAP system,[4] much attention has been paid to developing enantioselective protocols for the reaction over the past decade. Asymmetric 1,3-dipolar cycloadditions have been reported using chiral metal complexes such as Ag^{I},[4,5] Zn^{II},[6] $Cu^{I/II}$,[7] Ni^{II},[8] Ca^{II},[9] and organocatalysts[10] to afford moderate to high enantio-/diastereoslectivities. Most recently, Carretero and co-workers reported an efficient Cu^{I}/Fesulphos catalyzed 1,3-dipolar cycloadditions of azomethine ylides derived from glycinate, and excellent enantio-/diastereoslectivities were obtained especially when *N*-phenyl or methylmaleimide was used as a dipolarophile.[7e] For azomethine ylides derived from amino esters other than glycinate,[11] however, such high efficiency and excellent enantio-/ diastereoslectivity have not been achieved so far. Therefore, there is substantial room for improvement in terms of efficiency and substrate scopes for 1,3-dipolar cycloadditions.

Recently, we reported the first resolution of the axially chiral TF-BIPHAM, and the effectiveness of the diamine was demonstrated by highly enantioselective hydrogenation.[12] Extending the application of TF-BIPHAM in asymmetric catalysis, herein we report that Cu^{I}/TF-BiphamPhos exhibits high enantio-/diastereoselectivity and broad scope in the asymmetric 1,3-dipolar cycloaddition of various azomethine ylides.

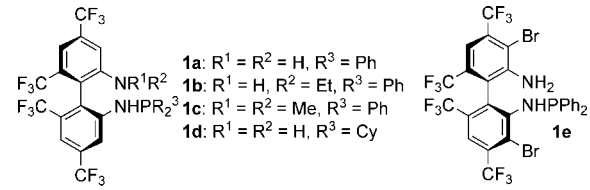
Our initial investigation began with *N*-(4-chlorobenzylidene)-glycine methyl ester **3a** and dimethyl maleate **2a** with 3 mol % Cu^{I}/ligand complex, and the representative results are summarized in Table 1. To our delight, the reaction was finished in less than 10 min at room temperature in DCM with newly designed ligand **1a**, and *endo*-**4a** was achieved as the sole product with 97% yield and 88% ee (Table 1, entry 1),[13] which was different from the exo preference achieved by Cu^{II}/BINAP[7f] or Cu^{I}/ferrocenyl-P,N-ligand[7g] complexes. Encouraged by this result, we synthesized a series of P,N-ligands **1b**−**d** and applied them in the model reaction. The catalytic ability of *N*-ethyl substituted ligand **1b** was inferior to that of *N*-unsubstituted ligand **1a** (Table 1, entry 2). Ligands **1c** or **1d** containing more sterically hindered NMe_2 or cyclohexyl groups on the phosphorus atom, displayed a similar trend on the enantioselectivity and reactivity (Table 1, entries 3 and 4). Considering the significant role that ortho-subsitituted binaphthyl skeleton played in the tremendous asymmetric catalysis,[14] we envisioned that the enantioselectivity could be further improved through the introduction of substituents into the corresponding 3,3′-position of the TF-BIPHAM backbone. Thus, TF-BiphamPhos **1e** was synthesized through highly efficient bromination and then phosphorylation protocol. Both perfect endo selectivity and enantioselectivity (97.3%) were observed with **1e** as the chiral ligand (Table 1, entry 5). Reducing the temperature to 0 °C led to a completed reaction with 99% ee in less than 10 min (Table 1, entry 6). High yield, selectivity, and fast reaction rate remained even when the reaction was performed as low as 0.1−0.5 mol % of catalyst loading (Table 1, entries 7 and 8).

Table 1. Screening Studies of the Asymmetric Cu^{I}−Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylied **3a** with Dimethyl Maleate **2a**[a]



entry	ligand	Cu/L (mol%)	time (min)	*T* (°C)	yield (%)[b]	ee (%)[c]
1	**1a**	3	10	room temp	97	88
2	**1b**	3	720	room temp	76	57
3	**1c**	3	720	room temp	77	8
4	**1d**	3	1440	room temp	64	28
5	**1e**	3	10	room temp	98	97
6	**1e**	3	10	0	97	>99
7	**1e**	0.5	10	0	96	>99
8	**1e**	0.1	60	0	85	97

[a] All of the reaction was carried out with 0.33 mmol of **2a** and 0.40 mmol of **3a** in 2 mL of solvent. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Determined by HPLC analysis.



The 1,3-cycloaddition of various imino ester **3** and dimethyl maleate **2a** in the presence of ligand **1e** was investigated under the optimized experimental condition. As shown in Table 2, a variety of azomethine ylides from aromatic aldehydes, which bear electron-rich, electron-neutral, or electron-deficient groups on the phenyl ring, reacted with dimethyl maleate to afford the corresponding *endo*-**4** exclusively in high yields (85−99%) and excellent ee's (>99%) within 10 min (Table 2, entries 1−11);[13] 98% ee was still obtained for the heteroaromatic 3-pyridyl imino ester **3k** (Table 2, entry 12). Noticeably, the challenging and less reactive azomethine ylide **3l** from aliphatic aldehyde also works well in this transformation producing the *endo*-**4l** with remarkably high ee (97%), albeit moderate yield (41%), in 24 h (Table 2, entry 13). The best literature report for **3l** is only 81% ee using Ag^{I}/P,N-ligand complex.[4]

The scope and generality of this catalytic system with regard to iminoesters and dipolarophiles were also investigated. The present catalytic system is remarkably tolerant and remains high in reactivity for azomethine ylides derived from amino esters other than glycinate (Table 3). Although the generated pyrrolidines containing a

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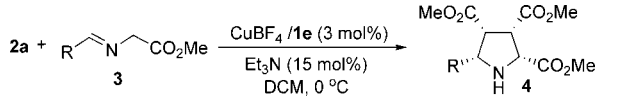
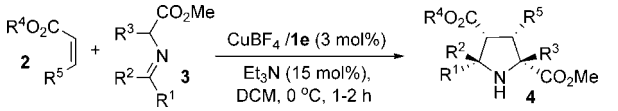
Table 2. Enantioselective Cu^{I}/**1e** Catalyzed 1,3-Dipolar Cycloaddition of Various Azomethine Ylied **3** with Dimethyl Maleate **2a**[a]



entry	R	4	time (min)	yield (%)[b]	ee (%)[c]
1	*p*-Cl-Ph (**3a**)	**4a**	10	97	>99
2	*p*-Me-Ph (**3b**)	**4b**	10	97	>99
3	*o*-Me-Ph (**3c**)	**4c**	10	98	>99
4	*p*-MeO-Ph (**3d**)	**4d**	10	98	>99
5	Ph (**3e**)	**4e**	10	93	>99
6[e]	Ph (**3e**)	**4e**	10	90	99
7	*o*-Cl-Ph (**3f**)	**4f**	10	98	>99
8	*p*-F-Ph (**3g**)	**4g**	10	97	>99
9	*p*-CN-Ph (**3h**)	**4h**	10	96	>99
10	1-naphthyl (**3i**)	**4i**	10	98	>99
11	2-naphthyl (**3j**)	**4j**	10	98	>99
12	3-pyridyl(**3k**)	**4k**	60	85	98
13	cyclohexyl (**3l**)	**4l**	1440	41	97

[a] All of the reaction was carried out with 0.33 mmol of **2a** and 0.40 mmol of **3a** in 2 mL of solvent. $CuBF_4 = Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Determined by HPLC analysis. [e] Run using 0.5 mol% catalyst.

Table 3. Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylids **3** Derived from α-Amino Acids Catalyzed by Cu^{I}/ **1e**[a]



entry	R^1	R^2	R^3	R^4	R^5	4	yield (%)[b]	ee (%)[c]
1	Ph	H	Me	Me	CO_2Me	**4m**	95	>99
2	*p*-MeO-Ph	H	Me	Me	CO_2Me	**4n**	72	>99
3	*p*-Cl-Ph	H	Me	Me	CO_2Me	**4o**	92	>99
4[d]	*p*-Cl-Ph	H	Me	Me	CO_2Me	**4o**	83	98
5	*p*-Br-Ph	H	Ph	Me	CO_2Me	**4p**	87	>99[e]
6	Ph	H	Bn	Me	CO_2Me	**4q**	90	99
7	Ph	H	*i*-Bu	Me	CO_2Me	**4r**	89	98
8	Ph	H	E[f]	Me	CO_2Me	**4s**	80	97
9	Ph	Ph	H	Me	CO_2Me	**4t**	75	97[g]
10	Ph	H	H	Me	H	**4u**	90	97[h]
11	Ph	H	H	*t*-Bu	H	**4v**	94	97[i]

[a] All of the reaction was carried out with 0.33 mmol of **2a** and 0.40 mmol of **3a** in 2 mL of solvent. $CuBF_4 = Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Run using 1 mol% catalyst. [e] Run in 12 h. [f] E = 3-indolymethyl, 24 h. [g] Glycine ethyl ester benzophenone Schiff base was used. [h] Run at −40 °C, 1 h. [i] Run at −25 °C, 1 h.

quaternary stereocenter[15] at the 2-position are of great importance and synthetic potential, only limited successful protocols have been reported in achieving moderate to high levels of enantioselectivity.[11] Under the optimized reaction conditions, the azomethine ylides derived from alanine, leucine, phenylalanine, and tryptophan, successfully reacted with dimethyl maleate leading to perfect *endo*-selectivities (>98 to <2) and excellent enantioselectivities (97 to >99% ee) (Table 3, entries 1−8). Furthermore, glycine ethyl ester benzophenone Schiff base works well affording the corresponding *endo*-product **4t** in good yield and excellent ee (Table 3, entry 9). Methyl and *tert*-butyl acrylate (**2b** and **2c**) also proved to be excellent dipolarophiles in this transformation (Table 3, entries 10 and 11).[16] This methodology presented herein is the best result for asymmetric 1,3-dipolar cycloaddition of azomethine ylides, especially derived from amino esters other than glycinate in terms of reactivity and enantioselectivity.

In conclusion, Cu^{I}/TF-BiphamPhos complex served as a novel and highly efficient catalyst for the asymmetric 1,3-dipolar cycloaddition reaction. Excellent reactivity, selectivity, and structural scope were uniformly observed for various azomethine ylides, especially derived from amino esters other than glycinate. In addition, the azomethine ylide from aliphatic cyclohexanecarbaldehyde has been successfully employed in the cycloaddition leading to the corresponding adduct in remarkably high enantioselectivity. The mechanistic origin of the high enantiocontrol and efficiency and future application of TF-BiphamPhos in asymmetric catalysis are ongoing.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Exceptionally, 97% ee was achieved for the cycloaddition of the in situ azomethine ylide derived from leucine and dimethyl maleate with 20 mol % organocatalyst at 50 °C in 60 h, see ref 10c. The ee was 98% for the cycloaddition of azomethine ylide derived from phenylalanine and *tert*-butyl acrylate catalyzed by 5 mol % Ag(I)/phosphoramidite in 48 h, see ref 5j.
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(13) The absolute configurations of the known products **4a**−**l** and **4p** were assigned by HPLC and optical rotation comparisons with the reported data (see ref 4, 5f, 10c and Supporting Information), and those of other adducts were deduced on the basis of these results.
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(16) Yields of 90%, 88%, and 86% ee were achieved when dimethyl fumarate, *N*-phenyl maleimide and *N*-methyl maleimide were used as dipolarophiles, and the corresponding endo/exo ratios were 86 to 14, >98 to <2, and >98 to <2, respectively (also see Supporting Information).

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