exo-Selective asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkylidene malonates catalyzed by AgOAc/TF-BiphamPhos†

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The first *exo*-selective asymmetric 1,3-dipolar cycloaddition of alkylidene malonates with azomethine ylides catalyzed by AgOAc/TF-BiphamPhos has been reported in good yields and good to excellent enantio-/diastereoselectivities.

Five-membered nitrogen heterocycles, especially highly substituted pyrrolidines feature widely in pharmaceuticals, natural alkaloids and organocatalysts and are also useful building blocks in organic synthesis.[1] The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes provides an efficient approach for constructing such structures.[2] Since the pioneering work of Grigg and Allway[3] employing stoichiometric amounts of chiral metal complex and the first catalytic asymmetric version reported by Zhang *et al.*[4] 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 such as Ag^{I},[4,5] Zn^{II},[6] $Cu^{I/II}$,[7] Ni^{II},[8] Ca^{II},[9] and organocatalysts[10] to generate stereochemically complex products with moderate to high enantio-/diastereoselectivities. Although various methods have been developed for this transformation, most of the electron-deficient alkenes applied in the 1,3-dipolar cycloadditions of azomethine ylides are limited to maleates, fumarates, maleimides, acrylates, nitroalkenes and vinyl phenyl sulfones.[3–10] However, alkylidene malonates, which have been employed successfully in many asymmetric Michael addition reactions,[11] have not yet been applied as dipolarophiles in the asymmetric 1,3-dipolar cycloadditions of azomethine ylides. To the best of our knowledge, only limited racemic examples have been reported involving alkylidene malonates as the dipolarophile so far.[12] An enantioselective version of this transformation may not only diversify the existing asymmetric 1,3-dipolar cycloaddition of azomethine ylides but also be valuable in the synthesis of bioactive pyrrolidines. In this communication, we report the first catalytic asymmetric version of the 1,3-dipolar cycloaddition of azomethine ylides to various alkylidene malonates with high diastereoselectivity and good to high enantioselectivity.

Initially, the asymmetric 1,3-dipolar cycloaddition of *N*-benzylidene glycine methyl ester **3a** with diethyl benzylidene malonate **2a** was examined using different metal salts as Lewis acids and TF-BiphamPhos as chiral ligands in the presence of triethylamine at room temperature (Table 1). The reaction was finished in 3 h with $Cu(CH_3CN)_4BF_4$/TF-BiphamPhos **1a** in DCM at room temperature, and *exo*-**4aa** was achieved as the sole product with 82% yield and 19% ee, which was different from the *endo*-preference while using maleates, maleimides and acrylates as dipolarophiles.[13] Encouraged by this result, we screened various copper(I/II) and silver(I) metals, which are known to be suitable precursors for 1,3-dipolar cycloaddition. Both Cu^{I} and Cu^{II} salts combined with TF-BiphamPhos **1a** afforded less than 20% ee although excellent *exo*-selectivities and high reactivities were achieved (Table 1, entries 1–3). Silver(I) salts gave better results than copper salts in terms of the yield and enantioselectivity, and the exclusive *exo*-adduct **4aa** was achieved with 39% ee when AgOAc/**1a** complex was used as the catalyst (Table 1, entries 4–6). Subsequently, AgOAc was selected as the metal catalyst for ligand screening. The catalytic activities of ligands **1a** and **1b** were found to be superior to those of ligands **1c** and **1d** (Table 1, entries 6–9), and further ligand tuning revealed that TF-BiphamPhos **1e** bearing two bromines at the 3,3′-positions of the TF-BIPHAM backbone was the most effective chiral ligand and provided *exo*-**4aa** exclusively in high yield and 67% ee (Table 1, entry 10). These results demonstrated the importance of the steric and electronic effects of the ligands on the enantioselectivities. Other commercially available chiral ligands were also tested in this transformation: 50% ee was observed for the *exo*-product **4aa** when BINAP/AgOAc complex was used as the catalyst; while Monophos produced very low enantioselectivities when AgOAc or $Cu(CH_3CN)_4BF_4$ were chosen as the metal precursor (Table 1, entries 11–14).

Having established the optimal ligand and metal precursor, the effect of the ester functional group of the alkylidene malonates **2** was investigated to further improve the enantioselectivity for this novel asymmetric 1,3-dipolar cycloaddition (Table 2). The ester functional group of **2** has a significant influence on the reactivity and enantioselectivity. By changing the ester moiety of the alkylidene malonates from an ethyl (**2a**) to a phenyl group (**2c**), the enantioselectivity of the corresponding adducts improved from 67% ee to 78% ee, respectively (Table 2, entries 1 and 3). When the ethyl group was replaced by the sterically hindered *tert*-butyl group (**2d**), the enantioselectivity of the *exo*-adduct **4da** was improved to 82% ee at the expense of reaction rate (Table 2, entry 4). Fortunately, the yield of **4da** could be improved remarkably through switching the organic base Et_3N for K_2CO_3, and the enantioselectivity was unchanged (Table 2, entry 5). Reducing the temperature from room temperature to 0 °C or −20 °C did not improve the enantioselectivity (Table 2, entries 6 and 7), and carrying out

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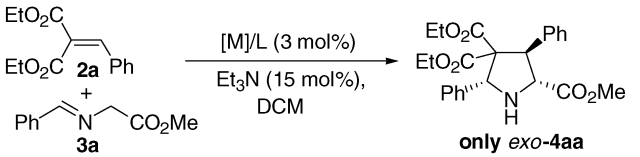
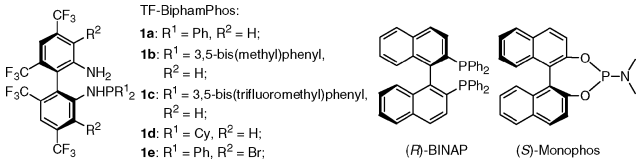
Table 1 Asymmetric 1,3-dipolar cycloaddition of diethyl benzylidene malonate **2a** with azomethine ylide **3a**[a]



Entry	Ligand	[M]	Time/h	Yield (%)[b]	Ee (%)[c]
1	(*S*)-**1a**	$CuBF_4$[d]	3	82	19
2	(*S*)-**1a**	$Cu(OTf)_2$	3	89	15
3	(*S*)-**1a**	CuBr	3	65	13
4	(*S*)-**1a**	$AgSbF_6$	3	85	33
5	(*S*)-**1a**	$AgClO_4$	3	79	31
6	(*S*)-**1a**	AgOAc	3	87	39
7	(*S*)-**1b**	AgOAc	3	83	32
8	(*S*)-**1c**	AgOAc	5	85	25
9	(*S*)-**1d**	AgOAc	5	74	11
10	(*S*)-**1e**	AgOAc	5	88	67
11	(*R*)-BINAP	$CuBF_4$	8	65	19
12	(*R*)-BINAP	AgOAc	8	85	50
13	(*S*)-Monophos	$CuBF_4$	5	52	11
14	(*S*)-Monophos	AgOAc	5	62	7

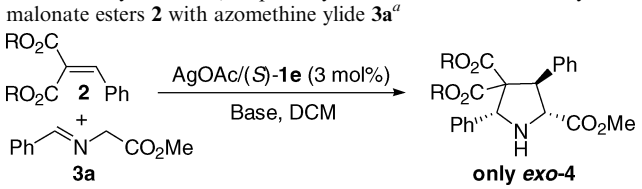
[a] The reactions were carried out with 0.23 mmol of **2a** and 0.45 mmol of **3a** in 2 mL DCM at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] $CuBF_4 = Cu(CH_3CN)_4BF_4$.



the reaction at room temperature provided the best results (Table 2, entry 5).

The scope and generality of this catalytic system with regard to iminoester and alkylidene malonate were investigated under the optimized experimental conditions. As shown in Table 3, a wide array of iminoesters derived from aromatic aldehydes, which bear electron-rich, electron-neutral, or electron-deficient groups on the phenyl ring, reacted smoothly with di-*tert*-butyl 2-benzylidene malonate **2d** to afford the corresponding

Table 2 Asymmetric 1,3-dipolar cycloaddition of various benzylidene malonate esters **2** with azomethine ylide **3a**[a]



Entry	R	**2**	Base	*T*/°C	Time/h	**4**	Yield (%)[b]	Ee (%)[c]
1[d]	Et	**2a**	Et_3N	rt	5	**4aa**	88	67
2[d]	Bn	**2b**	Et_3N	rt	5	**4ba**	90	65
3[d]	Ph	**2c**	Et_3N	rt	5	**4ca**	90	78
4[d]	*t*-Bu	**2d**	Et_3N	rt	48	**4da**	14	82
5[e]	*t*-Bu	**2d**	K_2CO_3	rt	3	**4da**	85	82
6[e]	*t*-Bu	**2d**	K_2CO_3	0	6	**4da**	89	78
7[e]	*t*-Bu	**2d**	K_2CO_3	−20	12	**4da**	80	74

[a] See Table 1. [b] See Table 1. [c] See Table 1. [d] 15 mol% Et_3N. [e] 2 eq. K_2CO_3.

exo-adducts (**4da–4dg**) exclusively in high yields (69–98%) and good enantioselectivities (78–86%) (Table 3, entries 1–8). It appears that the position and the electronic properties of the substituents on the aromatic rings have very limited effect on the enantioselectivities. Iminoesters from α- or β-naphthylaldehyde also work well in this transformation producing the *exo*-**4dh** and **4di** with 82% and 80% ee, respectively (Table 3, entries 9 and 10). Notably, the iminoester **3j** from aliphatic cyclohexanecarbaldehyde was tolerated in this reaction, and the corresponding adduct could be obtained in 80% yield and remarkably 99% ee, although the catalyst loading should be improved to 20 mol% probably due to the lower reactivity of **3j** (Table 3, entries 11 and 12). For the dipolarophile partner, both electron-rich (**2e**) and electron-deficient (**2f**) benzylidene malonates gave the *exo*-adducts in high yields and good enantioselectivities (Table 3, entries 13 and 14). Alkylidene malonates with alkyl substitution (**2g–2j**) proved to be excellent dipolarophiles in this transformation affording the *exo*-adducts with good yields and 82–83% ee (Table 3, entries 15–18). Iminoesters **3k** and **3l** derived from (±)- or (*S*)-alanine were also tolerated in this reaction producing *exo*-**4fk** bearing a nitrogen-substituted quaternary stereogenic center with almost the same enantioselectivity due to the *in situ*-formed same azomethine ylide (Table 3, entries 19 and 20). To our delight, most of the adducts are solid, and enantiopure compounds can be easily obtained by direct crystallization of the crude products from petroleum ether (Table 3, entries 9 and 14).

The relative configuration of **4dh** was assigned as *exo* and the absolute configuration of **4fd** and **4fk** achieved by AgOAc/(*R*)-TF-BiphamPhos **1e** was unequivocally determined as (2*S*,3*S*,5*S*) by X-ray diffraction analysis (see ESI†).‡ Those of other adducts were deduced on the basis of these results. Based on the relative and absolute configuration of **4dh**, **4fd** and **4fk**, the high *exo*-selectivity observed in the AgOAc/TF-BiphamPhos catalyzed asymmetric 1,3-dipolar cycloaddition reaction can be rationalized from the proposed tetracoordinated complex[5b] shown in Fig. 1. The *in situ*-formed azomethine ylide is coordinated to the metallic center and oriented in such a transition state because of the steric repulsion between the phenyl group in the ylide and the phenyl ring on the phosphorus atom of the chiral ligand, and the high steric congestion imposed by the latter effectively blocks the dipolarophile approach from the *Re* (C=N) face of the azomethine ylide and forms the *exo*-(2*R*,3*R*,5*R*) product through *Si* face attack (See ESI for more information†).

In conclusion, we have successfully developed the first catalytic enantioselective 1,3-dipolar cycloaddition of various alkylidene malonates with azomethine ylides. The highly efficient AgOAc/TF-BiphamPhos catalytic system exhibited the best performance, providing *exo*-adducts of poly-substituted pyrrolidine derivatives in good yields, excellent diastereoselectivities, and good enantioselectivities (78–99% ee). Further investigation of the mechanism and the reaction scope are ongoing in our laboratory and will be reported in due course.

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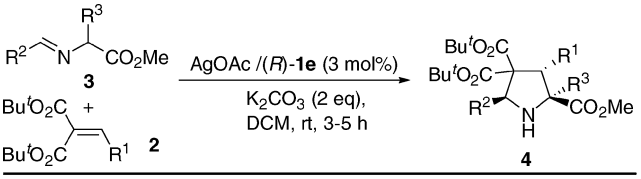
Table 3 Asymmetric 1,3-dipolar cycloaddition of alkylidene malonates **2** with azomethine ylides **3** catalyzed by AgOAc/**1e**[a]



Entry	2	R^1	3	R^2	R^3	4	Yield (%)[b]	Ee (%)[c]
1	**2d**	Ph	**3a**	Ph	H	**4da**	83	81
2[d]	**2d**	Ph	**3a**	Ph	H	**4da**	85	82
3	**2d**	Ph	**3b**	*p*-Me-Ph	H	**4db**	88	84
4	**2d**	Ph	**3c**	*m*-Me-Ph	H	**4dc**	81	83
5	**2d**	Ph	**3d**	*p*-MeO-Ph	H	**4dd**	81	86
6	**2d**	Ph	**3e**	*p*-F-Ph	H	**4de**	88	85
7	**2d**	Ph	**3f**	*o*-Cl-Ph	H	**4df**	69	78
8	**2d**	Ph	**3g**	*m*-Cl-Ph	H	**4dg**	98	80
9	**2d**	Ph	**3h**	1-Naphthyl	H	**4dh**	80	82 (99)[f]
10	**2d**	Ph	**3i**	2-Naphthyl	H	**4di**	74	80
11	**2d**	Ph	**3j**	Cy	H	**4dj**	18	99
12[e]	**2d**	Ph	**3j**	Cy	H	**4dj**	80	99
13	**2e**	*p*-MeO-Ph	**3d**	*p*-MeO-Ph	H	**4ed**	94	78
14	**2f**	*p*-Br-Ph	**3d**	*p*-MeO-Ph	H	**4fd**	84	82 (99)[f]
15[g]	**2g**	Et	**3a**	Ph	H	**4ga**	85	82
16	**2h**	Et	**3a**	Ph	H	**4ha**	85	83
17	**2i**	Bu	**3a**	Ph	H	**4ia**	87	82
18	**2j**	*i*-Bu	**3a**	Ph	H	**4ja**	80	82
19[h,i]	**2f**	*p*-Br-Ph	**3k**	Ph	Me	**4fk**	72	76 (99)[f]
20[h,j]	**2f**	*p*-Br-Ph	**3l**	Ph	Me	**4fk**	70	72

[a] See Table 1. [b] See Table 1. [c] See Table 1. [d] (*S*)-TF-BiphamPhos was used. [e] 20 mol% catalyst was used. [f] Data in parentheses were obtained after simple recrystallization. [g] Diethyl 2-propylidene malonate was used as the dipolarophile. [h] 10 mol% catalyst was used. [i] (±)-Alanine derived **3k** was used as the iminoester. [j] (*S*)-Alanine derived **3l** was used as the iminoester.

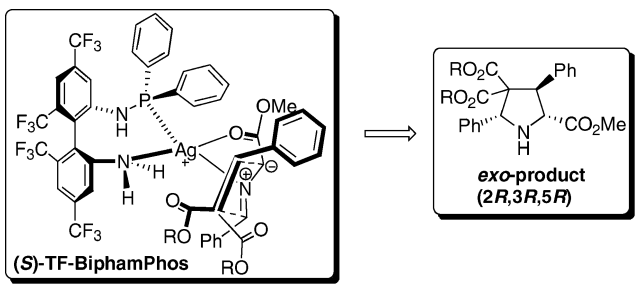


Fig. 1 Proposed transition state leading to *exo*-adducts.

Notes and references

‡ Crystal data for racemic *exo*-**4dh**: $C_{32}H_{37}NO_6$, M_r = 531.63, T = 293 K, triclinic, space group $P\bar{1}$, a = 10.0784(12), b = 12.2383(14), c = 12.8767(15) Å, V = 1463.4(3) Å^3, Z = 2, 8636 reflections measured, 5649 unique (R_{int} = 0.0136) which were used in all calculations. The final wR_2 = 0.1176 (all data). For (2*S*,3*S*,5*S*)-**4fd**: $C_{29}H_{36}BrNO_7$, M_r = 590.50, T = 293 K, orthorhombic, space group $P2_12_12_1$, a = 9.7742(8), b = 15.7902(13), c = 18.9829(16) Å, V = 2929.8(4) Å^3, Z = 4, 16 920 reflections measured, 5717 unique (R_{int} = 0.0328) which were used in all calculations. The final wR_2 = 0.1127 (all data), Flack χ = 0.013(9). For (2*S*,3*S*,5*S*)-**4fk**: $C_{29}H_{36}BrNO_6$, M_r = 574.50, T = 293 K, orthorhombic, space group $P2_12_12_1$, a = 11.202(2), b = 11.863(2), c = 22.167(5) Å, V = 2945.5(10) Å^3, Z = 4, 17 768 reflections measured, 6077 unique (R_{int} = 0.0285) which were used in all calculations. The final wR_2 = 0.1460 (all data), Flack χ = 0.008(12). CCDC 747638 (**4dh**), CCDC 739450 (**4fd**), CCDC 761891 (**4fk**).

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