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COMMUNICATION

Asymmetric construction of 3-vinylidene-pyrrolidine derivatives containing allene moiety *via* Ag(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene) malonate†‡

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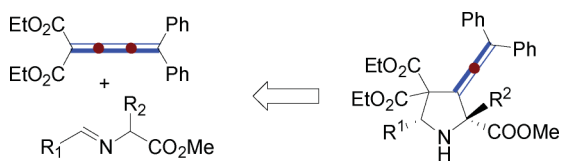
Catalytic asymmetric 1,3-dipolar cycloaddition of various azomethine ylides with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene)malonate has been developed successfully with good to excellent enantioselectivity for the effcient construction of 3-vinylidene-pyrrolidine derivatives containing a unique allene moiety.

Five-membered nitrogen heterocycles, especially the highly substituted pyrrolidines are observed widely in pharmaceuticals, natural alkaloids, organocatalysts and also useful building blocks in synthetic chemistry.[1] The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides generated from readily available imino esters and electron-deficient alkenes provides an efficient approach and powerful diversity-oriented synthesis (DOS)[2] for the construction of the type of structures.[3] Much attention has been paid to develop enantioselective catalytic protocols for 1,3-dipolar cycloaddition since the first report in 2002.[4] During the last decade, asymmetric 1,3-dipolar cycloadditions have been reported using chiral metal-complexes and organocatalysts to generate stereochemically complex pyrrolidine derivatives with moderate to high enantio-/diastereoselectivities.[3] Although various methods have been developed for this transformation, most of the electron-deficient alkenes applied in 1,3-dipolar cycloaddition of azomethine ylides are limited to α-unsaturated compounds such as maleates, fumarates, maleimides, acrylates, nitroalkenes and vinyl phenyl sulfones,[3] proving pyrrolidine derivatives substituted with saturated C–C chemical bond. Cumulene derivatives have attracted much attention in organic chemistry due to their high unique reactivities serving as nucleophiles, electrophiles, and occasionally as dienophiles in many reactions.[5] However, those compounds have seldom been employed as dipolarophiles in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides.[6] To the best of our knowledge, only one recent example reported by Gong[7] has showed that 2,3-allenoates could be employed as dipolarophiles in the organocatalytic asymmetric 1,3-dipolar cycloaddition of *in situ*-formed azomethine ylides, which provided 3-methylenepyrrolidines derivatives containing a C–C double bond in high diastereo-/enantioselectivity. This methodology has also been applied by the same group for the kinetic resolution of racemic 2,3-allenoates with excellent performances.[8]

Recently, we reported that Ag(I)/TF-BiphamPhos complexes exhibited excellent results in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkylidene malonate as dipolarophile.[9,10] Encouraged by those achievements, we envisioned that the 1,2-dienylidene-malonate could be employed as dipolarophiles in the asymmetric 1,3-dipolar cycloaddition for the construction of 3-vinylidene-pyrrolidine derivatives[11] containing a unique allene moiety (Scheme 1). 3-Vinylidene-pyrrolidine derivatives are undoubtedly important building block in synthetic chemistry considering that the allene core structures have resulted in excellent regio- and stereoselectivities for many nucleophilic and electrophilic reactions.[12] Herein, we reported the first catalytic asymmetric version of 1,3-dipolar cycloaddition of various azomethine ylides to easily accessible diethyl 2-(3,3-diphenylpropa-1,2-dienylidene) malonate[13] with high yield and good to excellent enantioselectivity.



Scheme 1 Proposed asymmetric synthesis of 3-vinylidence-pyrrolidines *via* 1,3-dipolar cycloaddition of azomethine yildes using diethyl 2-(3,3-diphenylpropa-1,2-dienylidence)malonate as the dipolarophiles.

Initially, the reaction of *N*-benzylidene glycine methyl ester **3a** with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene) malonate **2** was investigated under the previous reported optimal reaction conditions for asymmetric 1,3-dipolar cycloaddition of

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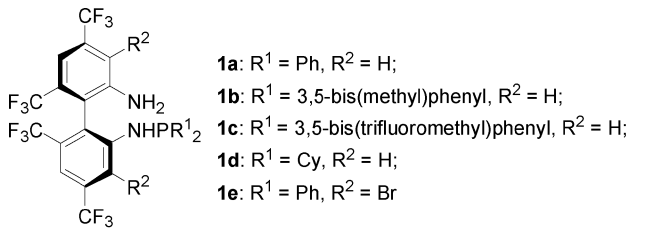
‡ Crystal data for (2*R*,5*R*)-**5**: $C_{40}H_{36}BrNO_7$, M_r = 722.60, T = 293 K, Orthorhombic, space group $P2_12_12_1$, a = 13.323(2), b = 15.987(3), c = 17.448(3) Å, V = 3716.3(11) Å^3, Z = 4, 4470 reflections measured, 3536 unique (R_{int} = 0.0503) which were used in all caclculations. The final wR_2 = 0.1444 (all data). Flack χ = 0.008(18). CCDC 809653 (**5**).

alkylidene malonates, and the representative results are summarized in Table 1. To our delight, this reaction was finished in 30 min with 3 mol% AgOAc/TF-BiphamPhos **1a** and 15 mol% K_2CO_3 powder in CH_2Cl_2 at room temperature, and the 1,3-dipolar cycloaddition reaction selectively occurs on the C2-3 double bond to afford the cycloadduct **4a** containing an allene moiety with 89% yield and 86% ee (Table 1, entry 1). Only moderate enantioselectivity was obtained when switching the metal precursor from AgOAc into $Cu(CH_3CN)_4BF_4$ (Table 1, entry 2). The experimental results disclosed that the corresponding active intermediate generated from silver(I) cation, chiral ligand and the *in situ*-formed azomethine ylide has more appropriate interaction with the dipolarophile cumulene diester, which affords higher asymmetric inducing capability (Table 1, entries 1 and 2). Encouraged by these results, the reaction conditions described in entry 1 were chosen for subsequent screening of other TF-BiphamPhos ligands with different substituents either on the phenyl ring of diaryl phosphine group or on the chiral backbone. It was found that the enantioselectivity in this 1,3-dipolar cycloaddition was greatly affected by the properties of the substitutes. Although no difference was observed when the phenyl group on the phosphorous atom of ligand **1a** was replaced by xylyl group (**1b**), much lower asymmetric induction and catalytic ability were obtained by ligand **1c** and **1d** containing strongly electron-withdrawing 3,5-bis(trifluoromethyl)-phenyl group and the bulky cyclohexyl group on the phosphorus atom, respectively (Table 1, entries 3–5). Gratifyingly, ligand **1e** bearing two bromines at the 3,3′-positions of the TF-BIPHAM backbone was the most effective chiral ligand affording the cycloadduct **4a** in high yield and 90% ee (Table 1, entry 6). To examine the effect of solvent, the reaction of **2** with **3a** in the presence of AgOAc/(*S*)-TF-BiphamPhos (**1e**) was performed in DCM, THF, ether, ethyl acetate, toluene and CH_3CN, and dichloromethane was found to be the best solvent in terms of the yield and enantioselectivity (Table 1, entries 6–11). Reducing the temperature to 0 °C in DCM led to full conversion in 60 min with 93% ee (Table 1, entry 12), but further lowering the temperature could not improve the enantioselectivity (Table 1, entry 13).

Next, the scope and generality of this novel 1,3-dipolar cycloaddition of diethyl 2-(3,3-diphenylpropa-1,2-dienylidene) malonate **2** with a series of representative imino esters **3** derived from glycinate were investigated under the optimized experimental conditions. As shown in Table 2, a variety of aromatic aldehydes derived imino esters, which bear electron-rich (Table 2, entries 2 and 3), electron-neutral (Table 2, entries 1 and 9), and electron deficient groups (Table 2, entries 4–8) on the aryl rings, reacted smoothly with 2-(3,3-diphenylpropa-1,2-dienylidene) malonate **2** to afford the corresponding cycloadducts (**4a–4j**) in high yields (82–92%) and good enantioselectivities (90–93%) at 0 °C within 1–2 h. It is noteworthy that comparable excellent performance was still achieved for the sterically hindered *ortho*-chloro-substituted imino ester **3e** in terms of enantioselectivity and reactivity (Table 2, entry 5), which demonstrated that the substitution pattern of the arene

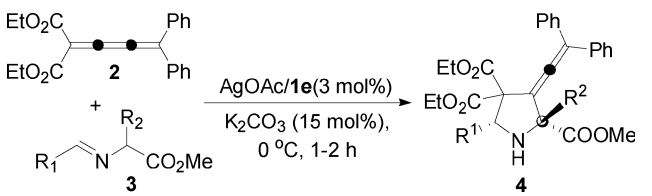
Table 1 Screening studies of the asymmetric 1,3-dipolar cycloaddition of azomethine ylide **3a** with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene)malonate **2**[a]



Entry	L	[M]	Solvent	T/°C	Time (min)	Yield[b] (%)	Ee[c] (%)
1	**1a**	AgOAc	DCM	rt	30	89	86
2	**1a**	$CuBF_4$	DCM	rt	60	75	59
3	**1b**	AgOAc	DCM	rt	30	85	86
4	**1c**	AgOAc	DCM	rt	30	73	23
5	**1d**	AgOAc	DCM	rt	30	68	65
6	**1e**	AgOAc	DCM	rt	30	91	90
7	**1e**	AgOAc	THF	rt	30	90	33
8	**1e**	AgOAc	Et_2O	rt	30	63	68
9	**1e**	AgOAc	EtOAc	rt	30	68	29
10	**1e**	AgOAc	PhMe	rt	30	81	21
11	**1e**	AgOAc	MeCN	rt	30	52	30
12	**1e**	AgOAc	DCM	0	60	90	93
13	**1e**	AgOAc	DCM	–20	60	87	90

[a] All reactions were carried out with 0.23 mmol of **2** and 0.40 mmol of **3a** in 2 mL solvent. $CuBF_4 = Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Ee was determined by chiral HPLC analysis.

Table 2 Substrate scope of AgOAc/(*S*)-**1e**-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides **3** with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene)malonate **2**[a]



Entry	R_1	R_2	4	Yield (%)[b]	Ee (%)[c]
1	Ph (**3a**)	H	**4a**	90	93
2	*p*-Me-Ph (**3b**)	H	**4b**	92	90
3	*m*-Me-Ph (**3c**)	H	**4c**	90	92
4	*p*-Cl-Ph (**3d**)	H	**4d**	85	93
5	*o*-Cl-Ph (**3e**)	H	**4e**	90	92
6	*m*-Cl-Ph (**3f**)	H	**4f**	88	90
7	*p*-Br-Ph (**3g**)	H	**4g**	89	91
8	*p*-CF_3-Ph (**3h**)	H	**4h**	88	93
9	2-Naphthyl (**3i**)	H	**4i**	85	91
10	2-Furyl (**3j**)	H	**4j**	82	90
11	PhCH═CH (**3k**)	H	**4k**	85	91
12	Cyclohexyl (**3l**)	H	**4l**	82	88
13[d]	Ph (**3m**)	Me	**4m**	88	93
14[d]	*p*-Cl-Ph (**3n**)	Me	**4n**	85	95
15[d]	*p*-Br-Ph (**3o**)	Me	**4o**	85	96
16[d]	*p*-Br-Ph (**3p**)	Ph	**4p**	82	96

[a] All reactions were carried out with 0.23 mmol of **2** and 0.40 mmol of **3a** in 2 mL DCM. [b] Isolated yield. [c] Ee was determined by chiral HPLC analysis. [d] The reactions were carried out in 24h.

had little effect on the selectivity of the reaction. Additionally, heteroaromatic 2-furyl imino ester **3j** was also a viable substrate as condensed-ring imino ester **3i** and α-unsaturated imino ester **3k** (Table 2, entries 9-11). Remarkably, the less reactive imino ester **3l** derived from aliphatic cyclohexanecarbaldehyde also work in this transformation to give 88% ee (Table 2, entry 12). Notably, imino esters (**3m–3p**) derived from α-substituted amino acids, such as alanine and 2-phenylglycine, have also proven to be excellent substrates for this reaction, producing the desired 3-vinylidene-pyrrolidines bearing a nitrogen-substituted quaternary stereogenic centre[14] with high reactivity and excellent enantioselectivity (Table 2, entries 13–16).

To determine the relative and absolute configuration of cycloadduct **4o**, the derived amide **5** was synthesized *via* highly efficient and simple benzoylation protocol (Fig. 1). A X-ray analysis of the crystal of **5** revealed (2*R*,5*R*) configuration for the two stereogenic centers around the N atom therefore also for the corresponding moiety in **4o** (Fig. 1). The absolute configuration of all other cycloadducts was assigned by analogy.

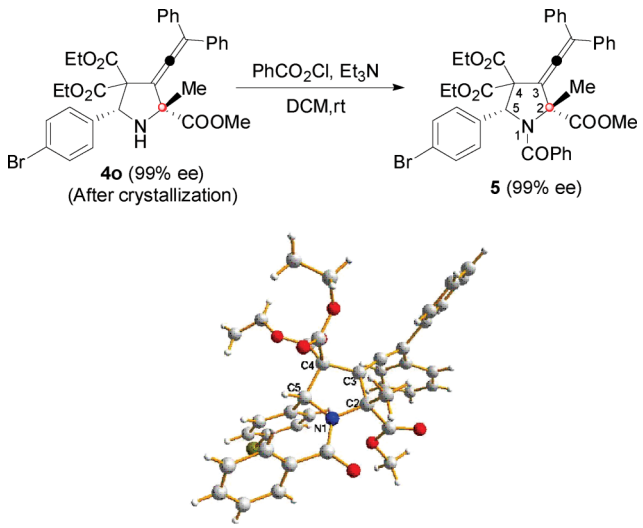


Fig. 1 X-Ray Structure of (2*R*, 5*R*)-**5**.

In summary, we have found that AgOAc/TF-BiphamPhos complex is an efficient catalyst for the highly enantioselective 1,3-dipolar cycloaddition of azomethine ylides with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene) malonate as the novel dipolarophile for the construction of 3-vinylidene-pyrrolidine derivatives containing a unique allene moiety. Excellent reactivity, enantioselectivity, and structural scope were uniformly observed for various azomethine ylides, especially derived from amino esters other than glycinate. The ready availability of the starting materials and the great importance of the enantiopure products make the current methodology particularly interesting in synthetic chemistry. Further investigations of the scope and synthetic application of this methodology are ongoing, and the results will be reported in due course.

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