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Bifunctional AgOAc/ThioClickFerrophos complex-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with aryl- and alkylidene malonates

Sayo Watanabe, Atsuo Tada, Yuichiro Tokoro, Shin-ichi Fukuzawa *

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, Tokyo, Japan

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ABSTRACT

AgOAc/ThioClickFerrophos complex-catalyzed 1,3-dipolar cycloaddition of glycine imino ester, the precursor of azomethine ylide, with aryl- and alkylidene malonates afforded the corresponding *exo*-cycloadducts, that is, proline ester derivatives in high yields with high enantiomeric excess (up to 99% ee). The reactions proceeded smoothly under base-free conditions demonstrating the bifunctional catalysis of the silver complex.

The asymmetric 1,3-dipolar cycloaddition of glycine imino ester, the precursor of azomethine ylide, with electron-deficient alkenes may afford diverse optically active proline derivatives that may lead to the discovery of antiviral drugs.[1] For example, a proline derivative acts as the inhibitor of hepatitis C virus (HCV) polymerase.[2] Major interest has been focused on the development of enantioselective catalysts for the asymmetric 1,3-dipolar cycloaddition since Zhang and co-workers succeeded for the first time in developing the catalytic version of this reaction.[3] Among a number of catalysts, the copper[4] and silver[5] phosphine complexes are particularly effective for this reaction. Diverse electron-deficient alkenes such as acrylates, maleates, and maleimides have been extensively investigated as the dipolarophiles for this reaction. On the other hand, aryl- and alkylidene malonates have been rarely studied as the dipolarophiles, even though they have been intensively employed as good Michael acceptors in asymmetric conjugate additions.[6] Aryl- and alkylidene malonates can be replaced for cinnamates and crotonates, which cannot react as the dipolarophiles to afford the corresponding 3-aryl- and alkyl-substituted proline derivatives. Wang and co-workers used arylidene malonates **2** for the first time as the dipolarophiles for the enantioselective 1,3-dipolar cycloaddition with azomethine ylides **1** catalyzed by the silver(I)/TF-BiphamPhos catalyst system.[7] Subsequently, Deng and co-workers reported that a copper(II)/imino alcohol complex can be used as an efficient catalyst for the reaction resulting in high diastereo- and enantioselectivities.[8] Both the catalysts afforded *exo*-cycloadducts **3**, where the 2-ester and 3-aryl groups are *trans* to each other, exclusively with high enantioselectivity (Scheme 1).

We previously reported the highly enantioselective 1,4-conjugate addition of diphenylmethyleneamino ester **4** to arylidene malonates **2** catalyzed by the AgOAc/ThioClickFerrophos (chiral ferrocenyl *P*,*S*-ligand; ThioClickFerrophos is abbreviated as TCF) catalyst system and obtained *syn*-1,4-adducts **5** (2-aryl-3-imino-1,1,3-triesters) diastereoselectively (Scheme 2).[9] Inspired by the success in this conjugate addition, we applied the AgOAc/TCF atalyst system to the reaction of benzylidene amino esters **1**, the precursor of azomethine ylides, with arylidene malonates **2**. The 1,3-dipolar cycloaddition reactions proceeded smoothly in the absence of a base, such as triethylamine, to afford the corresponding *exo*-cycloadducts in good yields with high enantioselectivities. In the previous Letters, the silver and copper catalysts required a base, whereas base is not essential for the function of AgOAc/TCF catalyst system, which works as a bifunctional catalyst (Lewis acid and base).[10] In this study, we report the bifunctional catalysis of AgOAc/*t*-BuTCF catalyst system and the substrate scope with respect to both azomethine ylides **1** and arylidene malonates **2**.

First, AgOAc/*t*-BuTCF (R = *t*-Bu, 5 mol %) catalyst system was tested in the model reaction of methyl 2-phenyleneamino acetate **1** (R^1 = Ph) and diethyl benzylidene malonate **2** (R^2 = Ph) under the similar conditions (room temperature, 15 h in THF) as the

* Corresponding author. Tel.: +81 3 3817 1916; fax: +81 3 3817 1895.
E-mail address: orgsynth@kc.chuo-u.ac.jp (S.-i. Fukuzawa).

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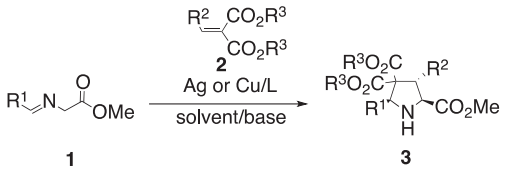
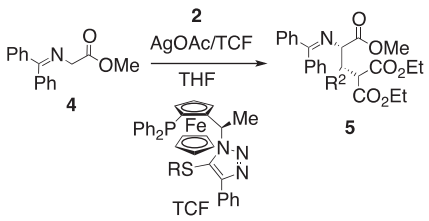


Scheme 1. 1,3-Dipolar cycloaddition of azomethine ylides **1** with alkyl- and arylidene malonates **2**.

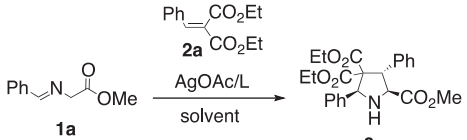


Scheme 2. 1,4-Conjugate addition of glycine imino ester **4** to aryl- and alkylidene malonates **2**.

previous conjugate addition to **4**. The reaction proceeded smoothly and afforded *exo*-cycloadduct **3aa** exclusively in 82% yield with 95% ee; the ^{1}H NMR spectrum of **3aa** was identical to the reported compound. The optimization of solvent showed that diethyl ether was the optimal solvent resulting in the best enantiomeric excess (98% ee) with an excellent yield (99%) at room temperature for 15 h. The reaction proceeded smoothly in the absence of an external base such as triethylamine. Although the addition of triethylamine improved the yield of the product to some extent, it resulted in a lower enantioselectivity. Other TCF variations such as EtTCF (R = Et) and PhTCF (R = Ph) resulted in lower enantioselectivities. From the optimization experiments, as shown in Table 1, the optimized reaction conditions were determined as follows: diethyl ether as the solvent and *t*-BuTCF as the ligand under base-free conditions.

Next, the substrate scope of the reaction was investigated with respect to imino esters **1** and arylidene malonates **2** to determine the effectiveness of AgOAc/*t*-BuTCF catalyst system. Because of the advantage of the bifunctional activity of AgOAc/*t*-BuTCF catalyst, the reactions were usually carried out in the absence of a base. Tables 2 and 3 summarize the substrate scope of imino esters **1** and arylidene malonates **2**, respectively. As shown in Table 1, the reaction of dimethyl benzylidene malonate **1a** with the phenyl derivatives of the imino ester with electron-donating (*p*-Me, *p*-OMe, and *o*-Me) and electron-withdrawing (*p*-Cl, *p*-Br, and *p*-CF_3) substituents afforded the corresponding *exo*-cycloadducts in good to excellent yields with high enantioselectivities; the electronic nature and position of the substituent did not affect the yield and enantioselectivity. The relative and absolute configuration of the cycloadduct were determined by the X-ray crystallography analysis of **3fa** (Flack $\chi = -0.07(6)$); the configuration of **3fa** was determined as *exo*-(2*S*,3*S*,5*S*) (Fig. 1). The 1-naphthyl derivative of the imino ester also reacted with **2** and afforded the corresponding product in a good yield with 85% ee. A heteroaryl imino ester such as a thienyl derivative could be used as the substrate even though it could be coordinated to silver and might affect the enantioselectivity; the cycloadduct was obtained in 75% yield with 99% ee. Thus, the substituent had a limited effect on the reaction. The reaction of the cyclohexyl derivative afforded the corresponding product in a low yield (18% yield) with low catalyst loading (3 mol %), and 20 mol % of the catalyst was required to obtain a reasonable yield.[7] For the AgOAc/TCF-catalyzed reaction, 5 mol % of the catalyst afforded the cyclohexyl derivative in a moderate yield (60% yield).

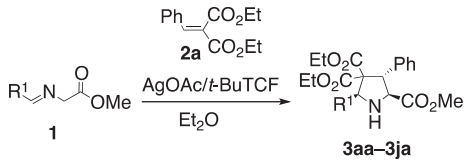
Table 1
Optimization of 1,3-dipolar cycloaddition[a]



Entry	L	Solvent	Yield[b] (%)	Ee[c] (%)
1	*t*-BuTCF	THF	82	95
2	*t*-BuTCF	DME	88	92
3	*t*-BuTCF	1,4-Dioxane	80	97
4	*t*-BuTCF	Et_2O	90	98
5[d]	*t*-BuTCF	Et_2O	99	95
6	EtTCF	Et_2O	84	62
7	PhTCF	Et_2O	93	66

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), AgOAc (0.010 mmol, 5 mol %), TCF (0.011 mmol, 5.5 mol %), solvent (3.0 mL); rt, 15 h.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralpak IA).
[d] Et_3N (18 mol %) was added.

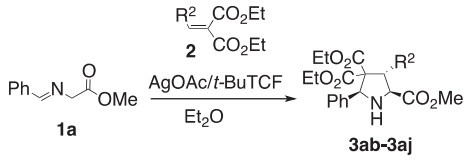
Table 2
Substrate scope of azomethine ylides **1**[a]



Entry	R^1 in **1**	Product	Yield[b] (%)	Ee[c] (%)
1	C_6H_5	**3aa**	90	98
2	*p*-MeC_6H_4	**3ba**	95	99
3	*o*-MeC_6H_4	**3ca**	95	99
4	*p*-$MeOC_6H_4$	**3da**	90	96
5	*p*-$CF_3C_6H_4$	**3ea**	93	98
6	*p*-ClC_6H_4	**3fa**	83	98
7	*p*-BrC_6H_4	**3ga**	91	94
8	1-$C_{10}H_7$	**3ha**	70	85
9	2-Thienyl	**3ia**	75	93
10	*c*-C_6H_{11}	**3ja**	60	99

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), AgOAc (0.010 mmol, 5 mol %), TCF (0.011 mmol, 5.5 mol %), Et_2O (3.0 mL); rt, 15 h.
[b,c] Same as Table 1.

Table 3
Substrate scope of arylidene malonates **2**[a]



Entry	R^2 in **2**	Product	Yield[b] (%)	Ee[c] (%)
1	*p*-MeC_6H_4	**3ab**	95	97
2	*o*-MeC_6H_4	**3ac**	95	95
3	*p*-$MeOC_6H_4$	**3ad**	85	95
4	*p*-$CF_3C_6H_4$	**3ae**	98	94
5	*p*-ClC_6H_4	**3af**	95	97
6	*p*-BrC_6H_4	**3ag**	85	96
7	1-$C_{10}H_7$	**3ah**	99	88
8	2-Thienyl	**3ai**	99	97
9	*c*-C_6H_{11}	**3aj**	90	87

[a–c] Same as Table 2.

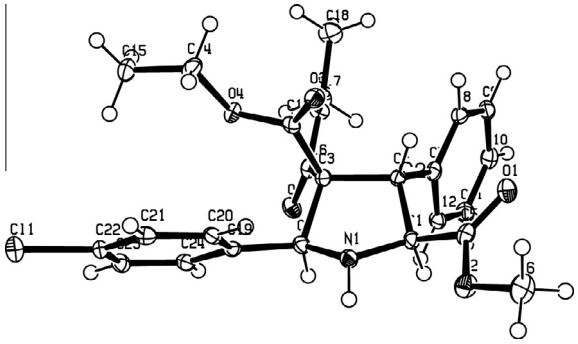


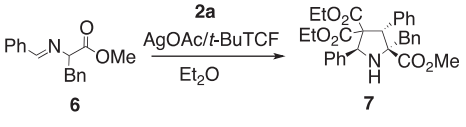
Figure 1. X-ray structure of **3fa**.

In the case of arylidene malonates **2**, the substituent effect was hardly observed on the reaction. Regardless of the electronic nature and position of the substituent, the corresponding *exo*-cycloadducts were obtained in excellent yields (>95%) with excellent enantioselectivities (>95% ee). The reaction of 2-thienylidene and 1-naphthylidene malonates also afforded the corresponding adducts in excellent yields and enantioselectivities. Interestingly, the reaction of cyclohexylidene malonate proceeded smoothly in the absence of a base and afforded the corresponding product in an excellent yield (90% yield, 87% ee), whereas the addition of a base (Cs_2CO_3) was essential in the conjugate addition of glycine imino ester **4** to **2**.

In the reaction of **2a** with α-benzyl substituted azomethine ylide **6**, the *exo*-pyrrolidine ester **7** bearing a chiral quaternary carbon was obtained as a single diastereomer in 55% yield with 89% ee (Scheme 3).

Based on the absolute configuration of the *exo*-cycloadduct, a plausible *tetra*-coordinated transition state was proposed, as shown in Figure 2.[7,8] The azomethine ylide coordinates with silver in the preferred orientation in which the imino nitrogen is *trans* to the phosphine group (the carbonyl oxygen atom is *trans* to the sulfur atom). An inverse orientation in which the nitrogen atom is *trans* to the sulfur atom would not be favored because of the steric repulsion between the phenyl group on the phosphine moiety and the aryl group of the azomethine ylide. The arylidene malonate would attack the *si* face of the azomethine ylide to avoid the sterically hindered *t*-butylthio group, thus affording the *exo*-(2*S*,3*S*,5*S*)-configured adduct.

In conclusion, AgOAc/TCF catalyst system was found to be an efficient bifunctional catalyst for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides to arylidene and alkylidene malonates. The catalyst system did not require extra base and afforded the corresponding *exo*-cycloadducts exclusively in high yields with high enantioselectivities (up to 99% ee). The substrate scopes with respect to both azomethine ylides and arylidene malonates were diverse, and the reaction was hardly affected by the electronic nature of the substituent on the substrates. Further, diverse proline esters could be prepared by this method.



Scheme 3. The reaction of α-benzyl substituted azomethine ylide.

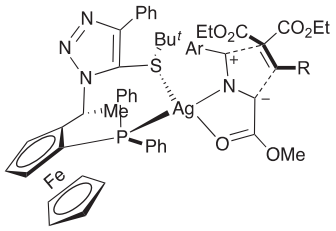


Figure 2. Plausible transition state of 1,3-dipolar cycloaddition.

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Supplementary data

Supplementary data (full experimental procedures, the characterization data for novel compounds, and the crystallographic data for **3fa** are provided in a CIF file (CCDC 959135)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.101.

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