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Silver/ThioClickFerrophos Complex as an Effective Catalyst for Asymmetric Conjugate Addition of Glycine Imino Ester to Unsaturated Malonates and α-Enones

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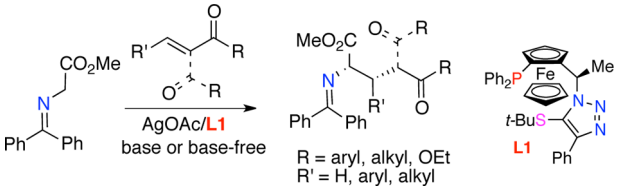
ABSTRACT



The AgOAc/ThioClickFerrophos complex effectively catalyzed the conjugate addition of glycine imino esters to arylidene and alkylidene malonates, furnishing the corresponding adducts in good yields with high enantioselectivities, in the presence or absence of an external base. The complex also catalyzed conjugate addition to α-enones in the presence of 1,4-diazabicyclo[2.2.2]octane with high enantioselectivity, with formation of a small amount of cycloadducts.

Glycine imino esters are often used as building blocks in the synthesis of optically active α-amino acid derivatives.[1] For example, the asymmetric and 1,4-conjugate addition of glycine imino esters to nitroalkenes leads to the formation of α-imino-γ-nitro esters, which can be transformed into α,γ-diaminobutyric acid derivatives after consecutive hydrolysis of the imino group and reduction of the nitro group.[2] On the other hand, 1,4-conjugate addition of glycine imino esters to α,β-unsaturated carbonyl compounds provides an efficient route to obtain optically active glutamic acid derivatives, which exhibit extensive biological activity.[3] Kobayashi et al. successfully executed the conjugate addition of glycine imino esters to acrylate by using a chiral calcium isopropoxide/bisoxazoline (BOX) complex to furnish the conjugate adduct in 98% ee.[3c,d] However, the conjugate adduct could not be obtained in the reaction with crotonate, which instead generated the cycloadduct as a major product. The use of the more sterically hindered *tert*-butyl imino ester enabled exclusive conjugate addition to the crotonate.[3e] Arylidene malonates were demonstrated to be effective alternative Michael acceptors in cases where conjugate addition of glycine imino esters to cinnamate (β-aryl acrylate) was not successful. Chiral *P,S*-(FeSulphos),[4] *P,N*-(FcFOX),[5] and N,O-ligand/copper[6] complexes have been proposed as catalysts for diastereo- and enantioselective conjugate

(1) For examples for the reaction with glycine imino ester in reviews, see: (a) O'Donnel, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. (c) Adrio, J.; Carreteo, J. C. *Chem. Commun.* **2011**, *47*, 6784–6794. (d) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312–4348.

(2) For recent examples, see: (a) Li, Q.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2010**, *12*, 1080. (b) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750. (c) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossio, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.

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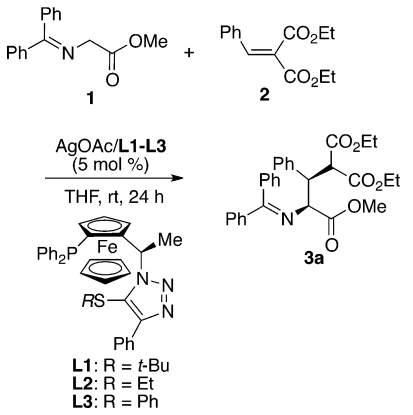
addition, furnishing β-aryl-γ-imino 1,3-esters in good to excellent enantiomeric excess; the β-aryl-γ-imino ester can be used as a precursor for β-substituted glutamic acids such as 3-*p*-chlorophenylglutamic acid (chlorpheg), a selective L-homocysteic acid (HCA) uptake inhibitor. To the best of our knowledge, the only distinctively effective catalysts for the reaction are the FeSulphos/copper complex and other two complexes, which are limited in terms of the diastereo- and enantioselectivity. The development of a new catalyst for the asymmetric conjugate reaction of glycine imino esters to arylidene malonate remains a challenge.

Our previous studies have demonstrated that the silver/ThioClickFerrophos complex is an efficient catalyst for enantioselective [3 + 2] cycloaddition, the Mannich reaction, and conjugate addition reactions of glycine imino esters with activated alkenes, imines, and nitroalkenes, respectively.[7] In the reaction of glycine imino esters with nitroalkenes, the conjugate adducts can be obtained as major products by adding triethyl amine to the reaction, whereas cycloadducts are generated as major products when triethylamine is eliminated from the reaction.[7d] Thus, the product selectivity can be controlled by the presence or absence of an amine. Our ongoing evaluation of the potential catalytic activity of the silver/ThioClickFerrophos complex has revealed that the chiral silver complex works as an efficient bifunctional catalyst for the asymmetric conjugate addition of glycine imino esters to arylidene malonates to give a *syn*-adduct with high enantioselectivity in the absence of an external amine. The scope of this catalyst has been expanded to the asymmetric conjugate addition of imino esters to α-enones, the results of which are disclosed herein.

Initially, the ThioClickFerrophos (TCF) ligands were optimized in the reaction of diphenylene glycine imino methyl ester with diethyl benzylidene malonate (Scheme 1). The reaction was carried out in tetrahydrofuran (THF), at room temperature, for 24 h, using 5 mol % AgOAc and 5 mol % TCF. *tert*-Butyl-TCF (**L1**) was the most effective ligand, affording the *syn* adduct (3-phenyl-4-imino glutarate) as a major diastereomer (*syn*/*anti* = 97/3) in 76% yield with 99% ee; 93% ee (42% yield, *syn*/*anti* = 91/9) and 90% ee (69% yield, *syn*/*anti* = 93/7) were respectively obtained with ethyl-TCF (**L2**) and phenyl-TCF (**L3**). Here, the stereochemistry of the conjugate adduct was assigned as *syn* according to Carretero's definition.[4] The reaction proceeded without addition of an external base such as triethyl amine, whereas addition of Cs_2CO_3 (20 mol %) accelerated the reaction to reach completion within 2 h with improved yield (with 98% ee). The conjugate adduct was the sole product, with no cycloadduct being produced in spite of the absence of an external base; this is markedly different from the previous reaction with nitroalkenes.[7d] Thus, the AgOAc/TCF complex proved to be a bifunctional (Lewis acid and base) catalyst for the reaction; this is the first bifunctional catalysis in conjugate addition.[8]

Scheme 1. Reaction of Glycine Imino Ester **1** with Benzylidene Malonate



The scopes of arylidene and alkylidene malonates were examined under generally base-free conditions, but occasionally, Cs_2CO_3 was used as an external base when the yield of the product was not satisfactory. Table 1 summarizes the results obtained with substituted benzylidene malonates bearing electron withdrawing and donating substituents. Regardless of the electronic nature of the substituent, the corresponding *syn* adducts were obtained as the major diastereomer in good yields with high enantioselectivities (entries 3–9). Interestingly, heteroaryl substituents such as 2-pyridylidene and 2-thienylidene malonates were tolerated in the reaction to give the corresponding *syn* adducts in good yields with high enantioselectivities (entries 10–11). Carretero et al. highlighted that coordinating groups, such as the pyridyl group, tend to bind to the catalyst.[4] The relative and absolute configuration of the conjugate adduct was confirmed via X-ray analysis of the 2-thienyl glutarate (**3j**); the configuration was revealed to be *syn*-(2*S*,3*S*) (see Supporting Information (SI)). With the use of ferrocenyl substituents, the addition of Cs_2CO_3 improved the reaction performance to give *syn* adducts in 82% yield with 97% ee, whereas, in the absence of external base, the reaction yield was low (entries 12–13). The addition of Cs_2CO_3 was critical to obtain a product from alkylidene malonates such as cyclohexylidene malonate; nevertheless, the yield of the product was moderate (entries 14–15).

Inspired by the success of the conjugate addition of the glycine imino esters to a variety of arylidene malonates, we then explored the potential of the silver catalyst in conjugate addition to α-enones. To the best of our knowledge, only one report of a successful chiral metal complex

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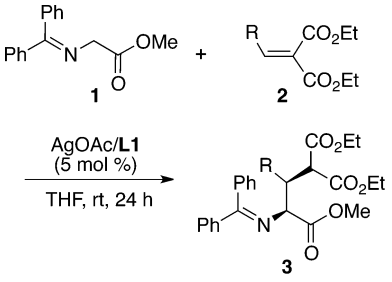
(8) For a review of AgOAc bifunctional catalysis (base-free conditions), see: Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G. *Chem. Commun.* **2010**, *46*, 4043–3051.

catalyzed asymmetric conjugate addition to an α-enone has been published,[9] although some successful organocatalysts (phase transfer catalysts) have been reported.[10] According to the literature, the conjugate adduct **5** becomes a good precursor for substituted proline esters after sequential hydrolysis and intramolecular cyclization followed by hydrogenation.

Table 1. Substrate Scope of Arylidene and Alkylidene Malonates[a]

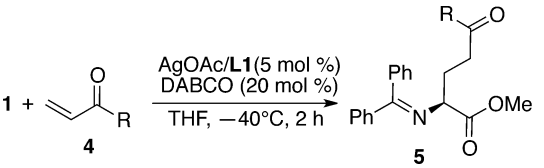


entry	R	product	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d] *syn*
1	C_6H_5	**3a**	76	97/3	99
2[e]	C_6H_5	**3a**	97	97/3	98
3	*o*-MeC_6H_4	**3b**	86	97/3	95
4	*p*-MeC_6H_4	**3c**	87	96/4	93
5	*p*-$MeOC_6H_4$	**3d**	83	97/3	98
6	*p*-FC_6H_4	**3e**	95	97/3	98
7	*p*-ClC_6H_4	**3f**	83	97/3	98
8	*p*-BrC_6H_4	**3g**	99	97/3	99
9	2-$C_{10}H_7$	**3h**	74	96/4	97
10	2-pyridyl	**3i**	70	93/7	97
11	2-thienyl	**3j**	92	94/6	98
12	$(C_5H_5)_2Fe$	**3k**	36	94/6	90
13[e]	$(C_5H_5)_2Fe$	**3k**	82	89/11	94
14	*c*-C_6H_{11}	–	NR	–	–
15[e]	*c*-C_6H_{11}	**3l**	60	80/20	97

[a] **1** (0.20 mmol), **2** (0.24 mmol), AgOAc (0.01 mmol, 5 mol %), **L1** (0.011 mmol, 5.5 mol %), THF (2.0 mL); rt, 24 h. [b] Combined isolated yield of *syn* and *anti* isomers. [c] Determined by ^1H NMR. [d] Determined by HPLC. [e] Cs_2CO_3 (0.05 mmol) was added; reaction time was 2 h.

The reaction of the glycine imino ester with 1-phenylprop-3-enone proceeded (**4a**) at −40 °C in THF for 2 h under external-base-free conditions to give a mixture of the conjugate adduct (**5a**) and cycloadduct (**5a′**) in 77% and 21% yields, respectively; the enantiomeric excess of the conjugate adduct was 97%. The reaction conditions were optimized in order to suppress the production of the unwanted cycloadduct, and it was found that 1,4-diazabicyclo[2.2.2]octane (DABCO) was the most effective additive for promoting conjugate adduct selectivity; the conjugate adduct was obtained in up to 88% yield, contaminated with a slight amount (4%) of the cycloadduct (see SI). Thus, the substrate scope of α-enones was evaluated under the optimized conditions. The results of the reaction with 1-aryl-2-propene-1-one are summarized in Table 2. Electron donating substituents such as *p*-methylphenyl and *p*-methoxyphenyl produced similarly good yields and high enantioselectivities as in the case of electron neutral substrates (entries 2 and 4). The presence of a sterically crowded substituent, i.e., a mesityl (2,6-dimethylphenyl) group, hardly affected the reaction (entry 3). The halogen substituted phenyl groups afforded good yields of the corresponding conjugate adduct with excellent enantioselection (entries 5−7). In the reaction with ferrocenyl substituents, the yield of the conjugate adducts was good (entry 8). The reaction with aliphatic α-enones, such as methyl vinyl ketone, also gave the corresponding conjugate adduct in a good yield with high enantioselectivity (entry 9).

Table 2. Substrate Scope of α-Enones[a]



entry	R	product	yield (%)[b]	ee (%)[c]	config.
1	C_6H_5	**5a**	89	99	(−)
2	*p*-MeC_6H_4	**5b**	82	99	(−)
3	2,6-$Me_2C_6H_3$	**5c**	90	98	(−)
4	*p*-$MeOC_6H_4$	**5d**	83	98	(−)
5	*p*-FC_6H_4	**5e**	87	99	(−)
6	*p*-ClC_6H_4	**5f**	93	99	(−)
7	*p*-BrC_6H_4	**5g**	92	97	(−)
8	$(C_5H_5)_2Fe$	**5h**	84	90	(−)
9	Me	**5i**	92	96	(−)

[a] **1** (0.20 mmol), **4** (0.24 mmol), AgOAc (0.01 mmol, 5 mol %), **L1** (0.011 mmol, 5.5 mol %), THF (2.0 mL); −40 °C, 2 h. [b] Isolated yield of **5**. [c] Determined by HPLC.

The absolute configuration of **5a** was determined by converting it into the corresponding dihydropyrrole **6a** via treatment with acid and comparing the optical rotation of **6a** with that of the reported compound; the stereochemistry was determined to be the *S* configuration (Scheme 2); the stereochemistry was consistent with that of the reaction with 2-thienylidene malonate.[11]

In conclusion, the AgOAc/TCF complex is an effective bifunctional catalyst for the conjugate addition of glycine imino esters to arylidene and alkylidene malonates to give the corresponding adducts in good yields with high enantioselectivities without requiring the addition of an

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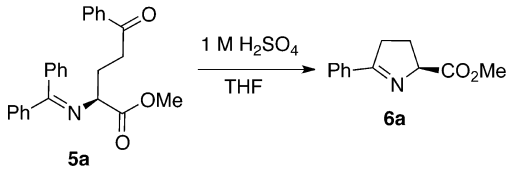
Scheme 2. Conversion of **5a** to **6a**



external amine. AgOAc/TCF also catalyzed the conjugate addition to α-enones with high enantioselectivity. This reaction was accompanied by the formation of the cycloadduct as a byproduct; nevertheless, the yield of the conjugate adducts could be improved by the addition of an external amine such as DABCO.

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Supporting Information Available. Full experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra (PDF) for new compounds, and crystallographic data for **3j** as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.