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Silver/ThioClickFerrophos-Catalyzed Enantioselective Conjugate Addition and Cycloaddition of Glycine Imino Ester with Nitroalkenes

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ABSTRACT

We applied the combination of AgOAc with ThioClickFerrophos, the chiral ferrocenyl triazole-based *P,S*-ligand, to the reaction of glycine imino ester with nitroalkenes. The conjugate addition of the imino methyl ester preferentially produced *anti*-α-imino-γ-nitrobutyrates in good yields with high enantioselectivities (ee) of up to 99% at −25 °C in THF in the presence of triethylamine. Meanwhile, the pyrrolidine cycloadducts were obtained as major products in good yields with high enantioselectivities (up to 96% ee) using *tert*-butyl imino ester in the absence of triethylamine at room temperature.

Glycine imino esters are receiving attention because they are useful building blocks of optically pure α-amino acid derivatives.[1] The asymmetric alkylation,[2] aldol reaction,[3] and Mannich reaction[4] with glycine imino esters provide α-alkyl amino acids, β-hydroxy-β-amino acids, and α,β-diamino acids, respectively.

The asymmetric Michael-type 1,4-addition of glycine esters to α,β-unsaturated carbonyl compounds provides an efficient route to optically active glutamic acid derivatives.[5] Kobayashi et al. developed a chiral calcium catalyst for the asymmetric conjugate addition of glycine imino ester to acrylic acid derivatives, to afford β-alkyl-substituted products in high yields with high enantioselectivities.[6] Carretero et al. recently expanded the scope of the Michael acceptor to β-aryl substituted products (cinnamate derivatives) in the copper-catalyzed conjugate addition to arylidene malonates.[7] Nitroalkenes are also good Michael acceptors for the conjugate addition of glycine imino esters,[8] and the α-imino-γ-nitro ester products can be transformed to α,γ-diamino acids after consecutive hydrolysis and reduction. The α,γ-diaminobutyric acid subunit is found in natural products, and it

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possesses extensive biological activity.[9] To the best of our knowledge, only two examples of metal-catalyzed enantioselective reactions have so far been reported:[10] Hou et al. reported *anti*- and enantioselective conjugate addition of benzophenone imino ester to nitroalkene using the copper/FcFOX complex,[11] and Oh succeeded with the *syn*- and *anti*-stereocontrolled reaction using the copper/brucine derived amino alcohol complex.[12] We previously reported the silver/ThioClickFerrophos-catalyzed asymmetric Mannich reaction of glycine imino esters with tosyl imines where *syn*-adducts were produced preferentially with high enantioselectivities.[13] Our current efforts expand the use of this catalyst to other asymmetric reactions with glycine imino esters. Thus, we applied the silver/ThioClickFerrophos complex to the asymmetric conjugate addition of benzophenone glycine imino ester to β-nitrostyrene and found that the conjugate addition proceeded accompanied by a small amount of [3 + 2] cycloaddition to give an *anti*-adduct in high enantioselectivity. In the course of our research, we found that a [3 + 2] cycloaddition proceeded by modifying the reaction conditions to afford the optically active pyrrolidine derivative as a major product in high enantioselectivity.[14]

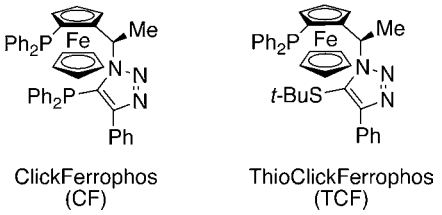

Figure 1. ClickFerrophos and ThioClickFerrophos.

Initially, we examined the silver-catalyzed asymmetric conjugate addition of glycine imino methyl ester **1a** to β-nitrostyrene under the following reaction conditions: 5 mol % of AgOAc and 5.5 mol % of the ThioClickFerrophos ligand (TCF, Figure 1) in THF at room temperature for 3 h. ^{1}H NMR of the crude product revealed the presence of a mixture of α-imino-γ-nitrobutyrate **3** (the conjugate adduct) and 3-nitropyrolidine **4** (the cycloadduct) in a ratio of 25:75. The reaction proceeded diastereoselectively to produce *anti*-**3** and *endo*-**4** as the sole diastereomers. Although the conjugate adduct was a minor product, ee of this adduct reached 98%. Encouraged by high ee%, we attempted to optimize the reaction conditions to obtain the conjugate adduct **3** as a major product. The results from the optimization experiment for the conjugate adduct are shown in Table 1. When the reaction temperature was lowered to −25 °C, the selectivity for the conjugate adduct was slightly improved, and the ratio of **3** to **4** was 31:69 (entry 2). The addition of triethylamine (18 mol % to glycine imino ester) to the reaction mixture dramatically increased the selectivity for the conjugate adduct, and the ratio of **3** to **4** was 97:3 (entry 3). The conjugate adduct was obtained selectively with high enantioselectivity (98% ee) in the presence of triethylamine. The use of a more sterically hindered amine such as diisopropylethylamine (DIPEA) had the opposite effect on selectivity, and the ratio of **3** to **4** changed to 62:38 (entry 4). We used the glycine imino *tert*-butyl ester **1b** instead of the methyl ester in order to improve the selectivity for the conjugate adduct; however, the selectivity decreased in the opposite direction (entry 5). THF was chosen as the best choice for solvent since other solvents such as toluene, diethyl ether, and dichloromethane afforded reduced selectivity for the conjugate adduct, even though they also favored the conjugate adduct (entries 6−8). Other silver salts such as AgOTf, $AgPF_6$, and $AgBF_4$ were examined; however, AgOAc produced the best result with respect to selectivity for the conjugate addition and enantioselectivity of the product (entries 9−11). The combination of CuOAc/ClickFerrophos (CF) also produced the conjugate adduct selectively but with lower ee% (70% ee) than the combination of AgOAc/TCF (entry 12).

Thus, we determined that optimum reaction conditions were obtained when using THF as the solvent, AgOAc as the metal salt, Et_3N as the base, and the methyl ester **1a** as the glycine imino ester at −25 °C. Here, the relative and absolute configuration of a conjugate adduct was confirmed by X-ray analysis of methyl 3-ferrocenyl butanoate **3j**; the configuration was revealed to be *anti*-(2*S*,3*S*) (see Supporting Information (SI)). The substrate scope of nitroalkenes was examined with respect to the electronic property and the position of the substituents under the optimized conditions. The results of the reaction with (*E*)-2-aryl-1-nitroalkenes are summarized in Table 2. The selectivity for the conjugate adduct was almost independent of the substituents, with the ratio of the conjugate adduct to the cycloadduct being in the range of 93:7 to 97:3. The *anti*-conjugate adducts were produced exclusively with excellent enantioselectivities (97−99% ee) regardless of the electronic properties and position of the substituents. The reaction with (*E*)-2-(2-nitrovinyl)naphthalene **2i** and 2-nitrovinylferrocene **2j** also gave the *anti*-adducts (**3i** and **3j**) in good yields with excellent ee's (entries 9 and 10).

In the initial experiment, the pyrrolidine cycloadduct was obtained as a major product with high ee% when the reaction was carried out at rt in the absence of triethylamine (Table 1, entry 1). Since the optically active pyrrolidine is a biologically and pharmaceutically

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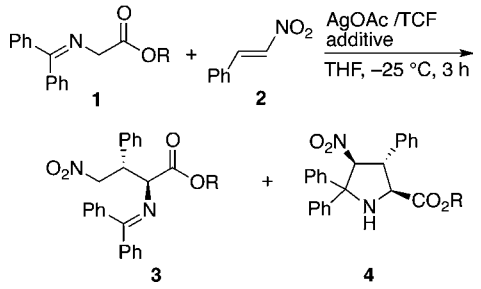
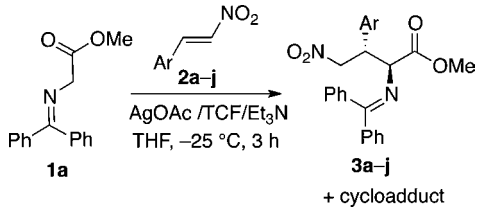
Table 1. Optimization of the Conjugate Addition of Glycine Imino Ester to Nitrostyrene[a]



entry	metal salts	additive[b]	%, yield[c]	**3**/**4**[d]	%, ee of **3**[e]
1[f]	AgOAc	–	99	25/75	98[g]
2	AgOAc	–	99	31/69	98
3	AgOAc	Et_3N	99	97/3	98
3[h]	AgOAc	Et_3N	99	95/5	98
4	AgOAc	DIPEA	99	62/38	97
5[i]	AgOAc	Et_3N	99	86/14	96
6[j]	AgOAc	Et_3N	99	94/6	99
7[k]	AgOAc	Et_3N	99	88/12	99
8[l]	AgOAc	Et_3N	99	91/9	99
9	AgOTf	Et_3N	99	87/13	40
10	$AgPF_6$	Et_3N	99	80/20	99
11	$AgBF_4$	Et_3N	99	88/12	55
12[m]	CuOAc	Et_3N	99	93/7	70

[a] Glycine imino methyl ester **1** (0.1 mmol), **2** (0.11 mmol), AgOAc (0.005 mmol), TCF (0.0055 mmol); THF (2.0 mL), −25 °C, 3 h. [b] 18 mol % to **1**. [c] Combined yield of **3** and **4**. [d] Determined by ^1H NMR. [e] Determined by chiral HPLC. [f] The reaction was carried out at rt. [g] **4** was produced in 98% ee. [h] 10 mol % of Et_3N. [i] *tert*-Butyl imino ester **1b** was used as **1**. [j] Toluene was used as a solvent. [k] Diethyl ether was used as a solvent. [l] Dichloromethane was used as a solvent. [m] CF was used as a ligand.

Table 2. Substrate Scope of the Conjugate Addition of Glycine Imino Ester to Nitroalkenes[a]

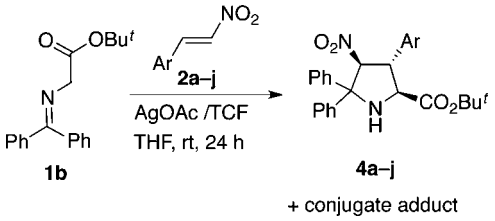


entry	nitroalkene, Ar	%, yield[b]	%, ee of **3**[c]
1	Ph, **2a**	97, **3a**	99
2	*p*-MeC_6H_4, **2b**	96, **3b**	97
3	*o*-MeC_6H_4, **2c**	93, **3c**	97
4	*p*-$MeOC_6H_4$, **2d**	96, **3d**	98
5	*p*-FC_6H_4, **2e**	93, **3e**	95
6	*p*-ClC_6H_4, **2f**	93, **3f**	98
7	*p*-BrC_6H_4, **2g**	95, **3g**	97
8	*p*-$CF_3C_6H_4$, **2h**	95, **3h**	99
9	2-Naph, **2i**	93, **3i**	99
10	Fc, **2j**	80, **3j**	99

[a] **1a** (0.1 mmol), **2** (0.11 mmol), AgOAc (0.005 mmol), TCF (0.0055 mmol), Et_3N (0.018 mmol); THF (2.0 mL), −25 °C, 3 h. [b] Isolated yield of conjugate adduct **3**. [c] Determined by chiral HPLC.

important compound, it is also essential to prepare the cycloadduct as a major product.[15] We therefore optimized the reaction conditions to improve the selectivity for the cycloadduct. When *tert*-butyl glycine imino ester was used in the reaction with *β*-nitrostyrene, selectivity toward the cycloadduct improved dramatically, and the ratio of **3:4** switched to 4:96. Here, the absolute configuration of the cycloadduct was confirmed by X-ray crystal analysis of **4d** (see SI): The (2*S*,3*R*,4*S*) configuration of cycloadduct **4** was consistent with the stereochemistry of the conjugate adduct **3**, which can be cyclized to pyrrolidine.[12] Thus, we determined that the optimized reaction conditions for the formation of **4** include using the AgOAc/TCF complex as the catalyst, *tert*-butyl ester as the glycine imino ester, no additives, and THF at rt. Following this, we examined the substrate scope of nitroalkenes using these optimized conditions, and the results from the reactions with various (*E*)-2-aryl-1-nitroalkenes are summarized in Table 3. High enantioselectivity was obtained regardless of the properties and position of the substituents, while cycloadduct selectivity was somewhat affected by the substituents. Electron neutral and/or donating substituents such as *p*-methyl, *o*-methyl, and *p*-methoxy substituents favor cycloadducts in high selectivities (entries 1−4). Electron withdrawing substituents such as *p*-halogeno (entries 5−7) and *p*-trifluoromethyl (entry 8) also favor cycloadducts but with lower selectivities. The cycloadducts **4i** and **4j** were obtained in high selectivities and enantioselectivities from (*E*)-2-(2-nitrovinyl)naphthalene **2i** and 2-nitrovinylferrocene **2j**, respectively (entries 9 and 10).

Table 3. Substrate Scope of the Cycloaddition of Glycine Imino Ester with Nitroalkenes[a]



entry	nitroalkene, Ar	%, yield[b]	**3**/**4**	%, ee of **4**[c]
1	Ph, **2a**	99, **4a**	4/96	96
2	*p*-MeC_6H_4, **2b**	99, **4b**	8/92	92
3	*o*-MeC_6H_4, **2c**	99, **4c**	16/84	93
4	*p*-$MeOC_6H_4$, **2d**	99, **4d**	8/92	92
5	*p*-FC_6H_4, **2e**	94, **4e**	33/67	97
6	*p*-ClC_6H_4, **2f**	99, **4f**	17/83	98
7	*p*-BrC_6H_4, **2g**	95, **4g**	12/88	97
8	*p*-$CF_3C_6H_4$, **2h**	91, **4h**	8/92	97
9	2-Naph, **2i**	99, **4i**	6/94	98
10	Fc, **2j**	99, **4j**	1/99	98

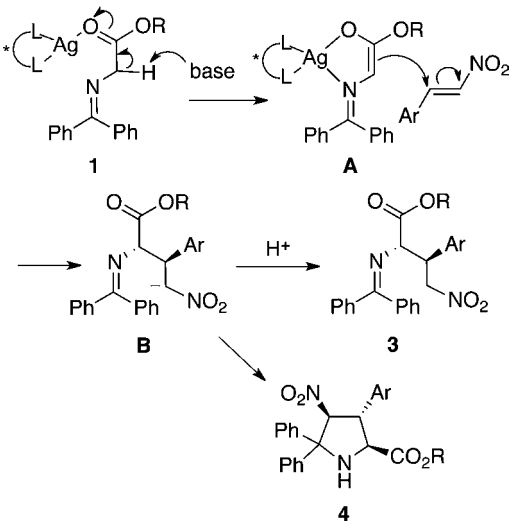
[a] **1b** (0.1 mmol), **2** (0.11 mmol), AgOAc (0.005 mmol), TCF (0.0055 mmol), Et_3N (0.018 mmol); THF (2.0 mL), rt, 24 h. [b] Combined yield of conjugate adduct and cycloadduct. [c] Determined by chiral HPLC.

It has been reported that bases such as triethylamine and DBU added to the copper-catalyzed reactions of glycine imino ester with nitroalkenes do not affect the product selectivity for the conjugate adduct or cycloadduct. However, copper salts do control the product selectivity: CuOTf and CuCl favor the conjugate adduct and cycloadduct, respectively.[12] In our silver-catalyzed reaction, addition of triethylamine is critical for favoring the conjugate adduct while the absence of triethylamine favors the cycloadduct (in this situation *tert*-butyl ester and the reaction temperature might control product selectivity).

The proposed reaction pathway is as follows. Bases such as triethylamine can generate the enolate **A** from the imino ester by abstracting the α-proton followed by conjugate addition of the enolate to nitroalkene. The resulting enolate intermediate **B** can undergo either protonation to produce the conjugate adduct or cyclization to produce the proline ester. In the absence of triethylamine, the acetate ion from AgOAc may act as a base and the reaction would proceed at a slower rate than the amine-catalyzed reaction (Scheme 1).[16]

In conclusion, the AgOAc/ThioClickFerrophos complex catalyzed the conjugate addition of imino methyl esters to nitroalkenes and preferentially produced *anti*-α-imino-γ-nitrobutyrates in good yields with high enantioselectivities in the presence of triethylamine. In addition, the pyrrolidine cycloadducts were obtained as the major product in good yields with high enantioselectivities using *tert*-butyl imino ester in the absence of triethylamine.

Scheme 1. Proposed Reaction Pathway



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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** and **4d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(16) The cycloadduct **4** may be produced by [3 + 2] cycloaddition, not consecutive cyclization of the conjugate adduct **3**.