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Highly Enantioselective Cu-Catalyzed Conjugate Addition−Elimination of Activated Allylic Acetates with Glycine Derivatives

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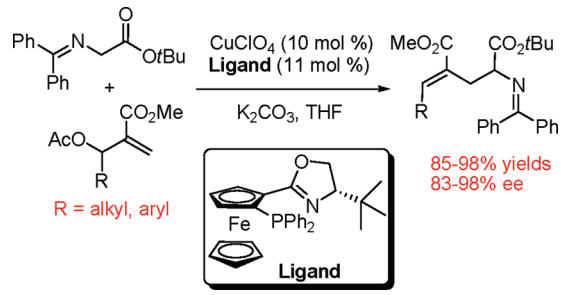
ABSTRACT



The reaction of a glycinate Schiff base with the activated alkyl- and aryl-substituted allylic acetates afforded 4-alkylidenylglutamic acid derivatives in high yields and high enantioselectivities by using Cu/P,N-FcPhox as the catalyst.

Glycinate benzophenone Schiff bases have been widely used as glycine anion equivalents in the alkylations, the Michael reactions, the Mannich reactions, and the aldol reactions to afford many different types of α-amino acid derivatives.[1,2] In many cases, phase-transfer catalysts and some other organic small molecules have been used as the catalysts.[2a−k] Although chiral transition-metal complexes have been recognized as efficient catalysts in asymmetric catalysis,[3] only a limited number of examples were reported to use such complexes in the asymmetric transformation of the glycine derivatives.[2l−p,4] The utility of transition-metal catalysts in these reactions remains to be explored further. On the other hand, 4-substituted glutamate analogues such as 4-substituted alkylidene glutamic acids are a class of amino acids having high biological activities.[5] Many efforts have been focused on their synthesis by using the optically active glycine Schiff bases and pyroglutamate.[6] Recently, Ramachandran realized the enantioselective synthesis of 4-substituted alkylidene glutamic acid derivatives under PTC catalytic conditions.[7] However, there are some limitations regarding the scope of the substrates as well as the enantioselectivities in some cases. The asymmetric catalytic version of effective syntheses of 4-alkylidenyl glutamic acids still remains to be explored. As a program aimed at the synthesis and applications of chiral ligands in asymmetric catalysis, we studied the use of glycine derivatives in asymmetric reactions.[8] Further studies revealed that Cu^{I}/P,N-ferrocene ligands are effective catalysts in the tandem conjugate addition−elimination reaction of a glycine Schiff base with allylic acetates, providing the 4-alkylidenyl glutamic acid

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(1) For reviews of the synthesis of α-amino acid derivatives, see: (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (b) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. (c) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682.

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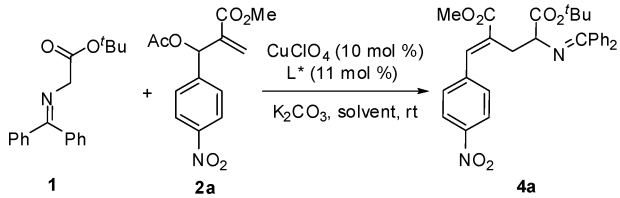
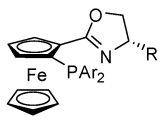
derivatives in high yield and enantioselectivity. In this paper, we disclose our preliminary results.

Initially, the reaction of the benzophenone imine of the glycine *tert*-butyl ester **1** with the allylic acetate **2a** was examined in the presence of ligand **3a**/$CuClO_4$ and K_2CO_3 (eq 1). The desired 4-alkylidenyl glutamic acid derivative **4a** was obtained in 95% yield and with 86% ee. Encouraged by this result, a series of the P,N-ferrocenyl ligands bearing various aryl groups on the P atom and substituents R on the oxazoline ring were examined under the conditions of eq 1 (Table 1).



(1)



3a: R = *i*-Pr, Ar = Ph
3b: R = *i*-Pr, Ar = 3,5-$(CF_3)_2C_6H_3$
3c: R = *i*-Pr, Ar = 4-$MeOC_6H_4$
3d: R = *t*-Bu, Ar = Ph
3e: R = Ph, Ar = Ph
3f : R = Bn, Ar = Ph
3g: R = *t*-Bu, Ar = 3,5-$Me_2C_6H_3$

Table 1. Optimization of the Cu-Catalyzed Asymmetric Alkylation of the Glycine Derivative **1**[a]

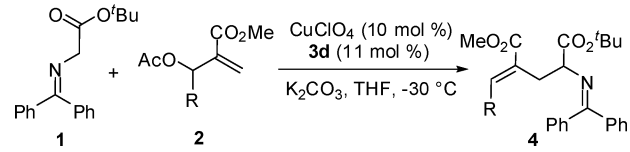
entry	ligand	solvent	yield[b] (%)	ee[c] (%)
1	**3a**	THF	95	86
2	**3b**	THF	97	77
3	**3c**	THF	90	86
4	**3d**	THF	95	91
5	**3e**	THF	97	8
6	**3f**	THF	82	72
7	**3g**	THF	94	90
8	**3d**	CH_2Cl_2	95	85
9	**3d**	Et_2O	89	90
10	**3d**	toluene	91	85
11[d]	**3d**	THF	91	92

[a] Molar ratio of glycine ester **1**/allylic acetate **2**/$CuClO_4$/ligand/K_2CO_3 = 1:1:0.1:0.11:4, concentration (0.1 M). [b] Isolated yields. [c] Determined by HPLC. [d] The reaction was carried at −30 °C.

It was found that varying the substituent on the P atom to 3,5-ditrifluoromethylphenyl (**3b**) or 4-methoxylphenyl (**3c**) led to the product with either a decreased enantioselectivity or a similar result (Table 1, entries 2 and 3). A better result was obtained with ligand **3d**, which had a *tert*-butyl group on the oxazoline ring and phenyl groups on the P atom: the corresponding product was formed in 95% yield and with 91% ee (Table 1, entry 4). Varying the substituent on the oxazoline ring to a phenyl group led to the product with much decreased enantioselectivity (Table 1, entry 5). When ligand **3f** was employed, the product was obtained in 82% yield and with 72% ee (Table 1, entry 6). The more bulky ligand **3g** slightly decreased the enantioselectivity to 90% ee (Table 1, entry 7). The solvent effect was also studied. THF proved to be a better solvent than CH_2Cl_2, Et_2O and toluene in terms of enantioselectivities (Table 1, entries 8−10). The ee could be enhanced to 92% at −30 °C (Table 1, entry 11).

The tandem conjugate addition−elimination reactions of various substituted active allylic acetates[9] with the benzophenone imine of the glycine *tert*-butyl ester **1** were studied under the optimized conditions, and the results are summarized in Table 2. The reaction was general regardless of

Table 2. Asymmetric Alkylation of **1** Using the Cu/Ligand **3d**[a]



entry	R	yield[b] (%)	ee[c] (%)
1	*p*-$NO_2C_6H_4$ (**2a**)	91	92
2	Ph (**2b**)	85	94
3	*p*-FC_6H_4 (**2c**)	96	90
4	*p*-ClC_6H_4 (**2d**)	92	83
5	*p*-BrC_6H_4 (**2e**)	92	90
6	*m*-ClC_6H_4 (**2f**)	99	91
7	*p*-MeC_6H_4 (**2g**)	98	92
8	2-thienyl (**2h**)	88	98
9	2-furanyl (**2i**)	96	92
10[d]	Et (**2j**)	94	92
11[d]	*i*-Pr (**2k**)	97	98
12[d]	phenylethyl (**2l**)	85	93

[a] Molar ratio of glycine ester **1**/allylic acetate **2**/$CuClO_4$/ligand **3d**/K_2CO_3 = 1:1:0.1:0.11:4, concentration (0.1 M). [b] Isolated yields. [c] Determined by HPLC. [d] Run at room temperature.

the substitutions of the allylic acetates. The yields were high, and the ee values ranged from 83% to 98%. Phenyl and para- and meta-substituted aromatic allylic acetates gave the corresponding products in high yields and with good to excellent enantioselectiveties (Table 2, entries 1−7). High ee values were also obtained when the heterocyclic allylic acetates were used (Table 2, entries 8 and 9). For aliphatic

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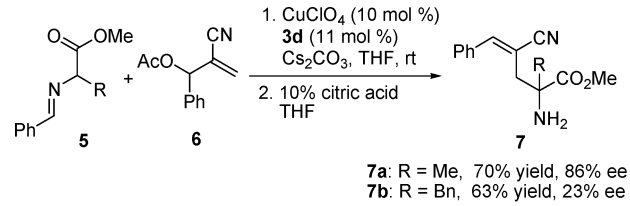
allylic acetates, the reaction was sluggish and could not reach complete conversion at −30 °C. However, we were pleased to find that the reactions proceeded smoothly at room temperature with good yields and excellent enantioselectivities (Table 2, entries 10−12).

Furthermore, the Cu^{I}/P,N-ferrocene ligand **3d** was applied to the asymmetric reaction of α-substituted iminoester **5**,[10] with the allylic acetate **6**[11] to construct a quaternary carbon center. For the aldimine Schiff base **5a**, derived from alanine methyl ester, good yield and enantioselectivity (70% yield and 86% ee) were achieved. For the benzyl-substituted iminoester **5b**, the product was obtained in 63% yield and 23% ee (eq 2).[12]



(2)

It seems that the reaction proceeds in the addition−elimination way[7] as no product was given when the glycine *tert*-butyl ester **1** reacted with $CH_2{=}CHCH_2OAc$ under the above reaction conditions.

In summary, we have reported a general and practical method for the preparation of 4-alkylidenyl glutamic acid derivatives with high yield and enantioselectivity by using a Cu/P,N-ferrocene catalyst. Further studies of the catalyst and its application are in progress.

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Supporting Information Available: Detailed experimental procedures, ^{1}H and ^{13}C NMR data, and HPLC spectra for **4** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Allylic acetate **2a** was also tried, but a complicated mixture of products was afforded after hydrolysis perhaps caused by the reactivity of the methyl ester and the PhCH=N− groups.

(12) The ee value was obtained by HPLC analysis of **7**.