ORGANIC LETTERS

2010
Vol. 12, No. 5
1080−1083

Diastereo- and Enantioselective Synthesis of α,γ-Diaminobutyric Acid Derivatives via Cu-Catalyzed Asymmetric Michael Reaction

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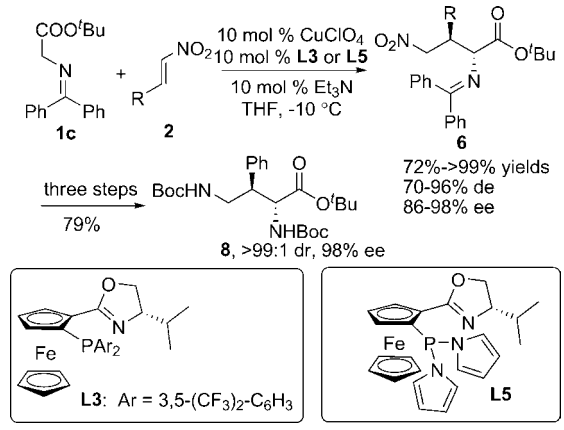
Received January 11, 2010

ABSTRACT



The first highly diastereo- and enantioselective catalytic asymmetric Michael addition of glycine derivatives to nitroalkenes have been developed. The enantioselectivity of *ortho*-substituted products can be significantly improved by using a new 1,2-*P*,*N*-ferrocene ligand L5. The α,γ-diaminoacid derivative was obtained without the loss of optical activity from the adduct.

α,γ-Diaminobutyric acid as a subunit is found in natural products,[1] and it also possesses wide biological activities.[2] In addition, N^{α}-protected derivatives of α,γ-diaminobutyric acid serve as important precursors for the synthesis of structurally diverse analogues of biologically active peptides such as cyclic peptide antibiotics gramicidin S[3a] and the immunosuppressant cyclosporin A.[3b] However, only a limited number of procedures for its synthesis have been reported.[4] Very recently, an enantioselective synthesis of α,γ-diaminobutyric acids appeared, based on the chiral auxiliary strategy.[5] Thus development of a catalytic asymmetric route to α,γ-diaminobutyric acid derivative is highly desirable.

It is conjectured that optically active α,γ-diaminobutyric acids could be obtained via a metal-catalyzed asymmetric Michael addition of glycine derivatives to nitroalkenes.[6] The asymmetric conjugate addition of glycine derivatives to electron-deficient olefins is a highly versatile reaction to afford the relevant α-amino acids.[7] Acrylates,[8] α,β-unsaturated carbonyl compounds,[9] and nitriles[10] have been successfully applied as Michael acceptors in such reaction. The racemic addition of glycine derivatives to nitroalkenes has also been documented;[11,14b,c] however, no catalytic diastereo- and enantioselective version of the reaction appeared. Previ-

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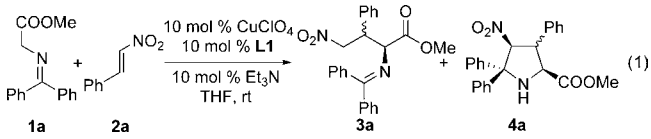
10.1021/ol100060t
Published on Web 02/09/2010

ously, we developed an asymmetric 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes using Cu catalyst.[12,13] The cycloaddition proceeded through stepwise process, specifically, Michael addition followed by cyclization.[12c,14] On that basis we considered the possibility to obtain only the Michael addition product by changing the substrate structure and reaction conditions. Herein, we disclosed the first example of such reaction using Cu/*P*,*N*-ferrocene ligands as catalysts. The transformation of the resulted product to the highly valuable β-substituted-α,γ-diaminobutyric acid derivative is also demonstrated.



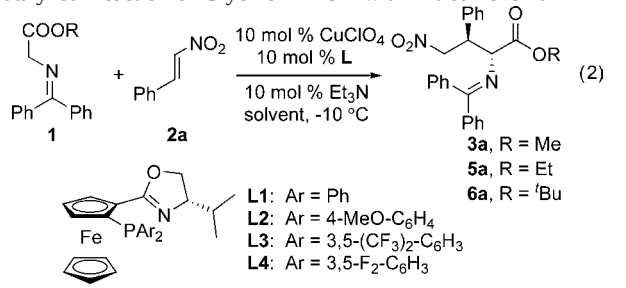
(1)

Initially, the reaction of glycine imine **1a** with nitroalkene **2a** using $CuClO_4$/ligand **L1** as catalyst was tested at room temperature (eq 1), with the expectation that the Michael addition would dominate over the cycloaddition reaction because of the great steric hindrance of the diphenyl methylene group. The source material was consumed completely in 1 h, and a mixture of Michael addition product and cycloaddition product was obtained in the ratio of 2:1. Considering the temperature effect on this reaction, we then ran this reaction at −10 °C and obtained the Michael reaction adduct as only product; the cycloaddition product was not detected.

Encouraged by the results above, we set out to optimize the reaction conditions (Table 1). Investigation of the glycine imine **1** led to the bulky *tert*-butyl esters **1c** as the optimal substrate, and the adduct **6a** was provided in quantitative yield with 94/6 dr and 90% ee (entry 3 vs entries 1 and 2). The evaluation of ferrocene ligands **L1**−**4** with different electronic properties revealed that the electronic factor of ligands did not influence the diastereoselectivity but rather the enantioselectivity of the reaction (entries 5 and 6 vs entries 3 and 4). This differs from our previous observation,[12b,c] presumably due to the steric factor of the glycine esters **1c**. The solvents have a strong effect on the stereochemistry of the reaction, and THF was the best among the solvents screened, including toluene, CH_3CN, Et_2O, and CH_2Cl_2 (entry 6 vs entries 7−10). The screening of Lewis acid showed that $CuPF_6$ and AgOAc were also able to smoothly catalyze the Michael reaction albeit with poor selectivity, whereas CuI and $Cu(OTf)_2$ retarded the reaction (not shown in Table 1).

The substrate scope of nitroalkenes **2** was examined under optimized conditions (Table 2). Reactions of glycine imine **1c** with various (*E*)-2-aryl-1-nitroalkenes with substituents at the *para*- and *meta*-positions of the phenyl ring proceeded with quantitative yields, the diastereoselectivity being 92:8−98:2 and the enantioselectivity being 95−98% (entries 1−8). The electronic properties of the substituents exerted limited impact on the diastereo- and enantioselectivity. Notably, the (*E*)-2-(furan-2-yl)-1-nitroalkene **2i** underwent Michael addition in

Table 1. Optimization of Reaction Conditions for the $CuClO_4$-Catalyzed Reaction of Glycine Imine **1** with Nitroalkene **2a**[a]

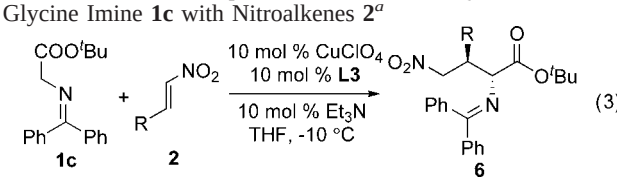


(2)

entry	**1**, R	**L**	solvent	yield (%)[b]	*anti*:*syn*[c]	ee (%) (*anti*/*syn*)[d]
1	**1a**, Me	**L1**	THF	>99	78:22	79/88
2	**1b**, Et	**L1**	THF	>99	78:22	85/–
3	**1c**, ^{t}Bu	**L1**	THF	>99	94:6	90/–
4	**1c**, ^{t}Bu	**L2**	THF	>99	92:8	84/–
5	**1c**, ^{t}Bu	**L3**	THF	>99	94:6	97/–
6	**1c**, ^{t}Bu	**L4**	THF	>99	94:6	95/–
7	**1c**, ^{t}Bu	**L3**	toluene	>99	86:14	93/80
8	**1c**, ^{t}Bu	**L3**	CH_3CN	>99	85:15	91/95
9	**1c**, ^{t}Bu	**L3**	Et_2O	65	76:14	96/84
10	**1c**, ^{t}Bu	**L3**	CH_2Cl_2	82	65:35	92/89

[a] Molar ratio of **1/2a**/$CuClO_4$/**L**/Et_3N = 1/1/0.1/0.1/0.1. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

Table 2. Substrate Scope for the $CuClO_4$-Catalyzed Reaction of Glycine Imine **1c** with Nitroalkenes **2**[a]



(3)

entry	**2**, R	yield (%)[b]	*anti*:*syn*[c]	ee (%) *anti*[d]
1	**2a**, Ph	>99	94:6	97
2	**2b**, *p*-Br-C_6H_4	>99	95:5	97
3	**2c**, *p*-Cl-C_6H_4	>99	98:2	98
4	**2d**, *p*-F-C_6H_4	>99	98:2	97
5	**2e**, *p*-OMe-C_6H_4	>99	98:2	98
6	**2f**, *p*-Me-C_6H_4	>99	95:5	97
7	**2g**, *m*-Br-C_6H_4	>99	92:8	98
8	**2h**, *m*-OMe-C_6H_4	>99	96:4	97
9	**2i**, 2-fural	>99	94:6	95
10	**2j**, *o*-Br-C_6H_4	>99	90:10	76
11	**2k**, *o*-CF_3-C_6H_4	>99	82:18	64
12	**2l**, *o*-Cl-C_6H_4	>99	90:10	89

[a] Molar ratio of **1c/2**/$CuClO_4$/**L3**/Et_3N = 1/1/0.1/0.1/0.1. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

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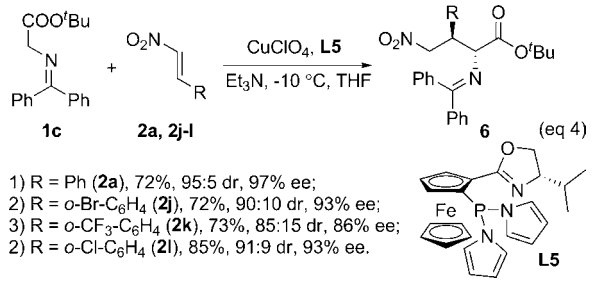
quantitative yield with 96:4 dr and 95% ee (entry 9). The versatility of furan in several types of reactions such as the Diels−Alder reaction will provide the resulted Michael product as a useful intermediate in organic synthesis. Disappointingly, much lower enantioselectivities were obtained when (*E*)-2-(*o*-substituted aryl)-1-nitroalkenes **2j**−**l** were the substrates (entries 10−12).[15] Aliphatic nitroalkene **2** (R = ^{i}Pr) was investigated in the same conditions above, and unexpectedly, we obtained the sole cycloaddition product (dr > 99:1, ee = 97%).

Scheme 1. Improvement of Enantioselectivity for the Reaction of Glycine Imine **1c** with Nitroalkenes **2a**, **2j**−**2l** Using **L5**[a]

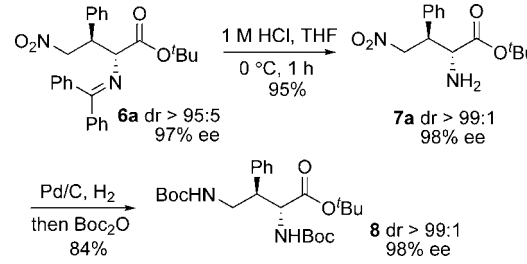


To circumvent the aforementioned problem that stemmed from *ortho*-substituents on the phenyl ring of nitroalkenes **2**, we designed and synthesized a novel type of 1,2-*P*,*N*-ferrocene ligands **L5** with a P-bound pyrrole group because pyrrole features strong π-acceptor and weak σ-donor properties and *N*-pyrrolylphosphine ligands have shown greatly improved selectivity in some reactions.[16] We then utilized **L5** in the Michael addition of glycine ester **1c** to nitroalkenes **2j-l**, which showed amazing positive effect for the stereocontrol in the Michael reaction of (*E*)-2-(*ortho*-substituted aryl)-1-nitroalkenes. The ee values of the Michael products **6j**, **6k**, and **6l** increased from 76%, 64%, and 89% to 93%, 86%, and 93%, respectively, by employing **L5** as ligand (Scheme 1), while the excellent diastereo- and enantioselectivity was still maintained at the expense of chemical yield when **2a** was the substrate.

The reaction proceeded smoothly even on a 10 mmol scale under the same condition. Treatment of 2.95 g of **1c** with 1.49 g of **2a** using **L3** as ligand still afforded product **6a** in >99% yield with 94:6 dr and 97% ee, which established the practical utility of the reaction.

Hydrolysis of the adduct **6a** afforded a free amino ester **7a**, which was subjected to hydrogenation of the nitro group followed by protection of the free amino groups. The α,γ-diaminobutanoate **8** was provided without the loss of optical activity in 79% overall yield (Scheme 2).

Scheme 2. Transformation of Adduct **6a** to α,γ-Diaminobutyric Acid Derivative **8**



The absolute configuration of Michael addition product **6b** was assigned as (2*R*,3*R*) by conversion of the adduct **6b** to free amino ester **7b** followed by the X-ray diffraction analysis (Figure 1).

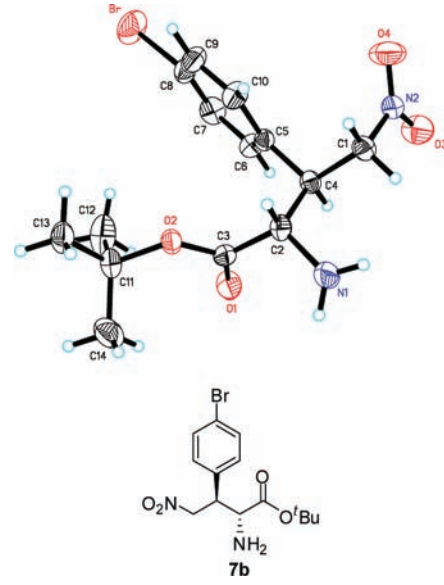


Figure 1. ORTEP drawing of the amino ester **7b**.

In summary, we report the first catalytic asymmetric Michael addition of glycine derivatives to nitroalkenes by using Cu/1,2-*P*,*N*-ferrocene ligand as catalyst, providing β-substituted-α,γ-diaminobutyric acid derivatives in high diastereo- and enantioselectivities. A novel type of 1-dipyrrolylphosphanes Fc-Phox **L5** was designed and synthesized

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for the first time. The Fc-Phox **L5** dramatically improved the enantioselectivity for the Michael reaction of (*E*)-2-(*ortho*-substituted aryl)-1-nitroalkenes. Further studies on the applications of this new ligand in asymmetric catalysis are in progress.

Acknowledgment. Financially supported by the Major Basic Research Development Program (2010CB833300), National Natural Science Foundation of China (20872161, 20821002, 20932008), Chinese Academy of Sciences, and Science and Technology Commission of Shanghai Municipality.

Supporting Information Available: General experimental procedure, spectral data for **6a**−**6l** and **7a**, **7b**, and **8**, and X-ray analysis data of **7b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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