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Enantioselective Organocatalytic Michael Addition of Aldehydes to Nitroethylene: Efficient Access to γ^2 -Amino Acids

Yonggui Chi, Li Guo, Nathan A. Kopf, and Samuel H. Gellman*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

The development of asymmetric conjugate addition reactions for C–C bond formation remains an important challenge in organic synthesis.^{1,2} Much recent work has focused on organocatalytic Michael addition of carbonyl compounds to nitroalkenes.^{3–5} Among these reactions, Michael addition of aldehydes to nitroalkenes is of particular interest because of the valuable synthetic intermediates that are generated.⁴ β -Aryl nitroalkenes have been the most common Michael acceptors for reactions developed by other research groups.^{3–5} These Michael reactions provide α,β -disubstituted- γ -nitrobutanals. Our attention was drawn to nitroethylene as a Michael acceptor because the adducts would bear a single substituent adjacent to the carbonyl and could be readily converted to γ^2 -amino acids. γ^2 -Amino acids represent potential building blocks for γ -peptide⁶ and heterogeneous backbone foldamers.⁷ In addition, derivatives of the neurotransmitter γ -amino butyric acid (GABA)⁸ are of potential biomedical utility, as illustrated by the use of Pregabalin and Baclofen to treat neurological disorders.⁹

The preparation of enantiomerically pure γ -amino acids is challenging, and this synthetic burden has limited the study of γ -peptide foldamers to date. A variety of routes to enantioenriched γ^2 -amino acids have been described,¹⁰ but these approaches often involve specialized chiral auxiliaries and may not be ideal for preparing multigram quantities of protected γ^2 -amino acids bearing diverse side chain functionality, which is necessary for foldamer research.^{6,7} Here we report an asymmetric organocatalytic method for aminoethylation of aldehydes, which leads to a new and efficient synthesis of γ^2 -amino acids (Scheme 1). Our approach pairs a chiral pyrrolidine catalyst with a carefully chosen acidic co-catalyst to promote Michael addition of aldehydes to nitroethylene with high enantioselectivity.

We initially evaluated two widely used chiral pyrrolidines, L-proline and (*S*)-diphenylprolinol silyl ether (**A**),¹¹ for the ability to promote the Michael reaction between *n*-pentanal and nitroethylene (2:1 molar ratio). We assumed that such reactions would proceed via enamine intermediates. L-Proline (20 mol %) provided very little of the Michael adduct; instead the major product in a variety of solvents resulted from aldol condensation of *n*-pentanal, a process that is known to be catalyzed by proline.¹² In contrast, when 20 mol % of **A** was employed in toluene, the desired Michael adduct was generated in 95% yield with >95% ee, and little or no aldol product was formed.

Previous work has shown that carefully chosen acidic co-catalysts can enhance pyrrolidine- or imidazolidinone-catalyzed Michael addition of aldehydes to enones,¹³ and we therefore examined co-catalyst effects¹⁴ on the Michael addition of *n*-pentanal to nitroethylene. When 5 mol % of **A** was employed as catalyst, without any co-catalyst, <10% Michael adduct was generated after 1 h, and little further adduct was generated after 24 h (Table 1). However, use of 5 mol % of **A** along with 200 mol % of acetic acid gave a 95% yield of the Michael adduct after 24 h with excellent stereoselectivity (>95% ee).¹⁵ These observations suggest that the role of the acidic component may be to facilitate catalyst turnover and/or to prevent catalyst deactivation pathways.

Many pyrrolidine-catalyzed processes require relatively high levels of catalyst (10–20 mol %). Use of 2 mol % of **A** with 20 mol % of acetic acid led to a substantial decline in efficiency (30% Michael adduct; Table 1). Switching to a more acidic co-catalyst, trifluoroacetic acid (20 mol %), caused a decrease in yield (8% Michael adduct). Increasing the amount of acetic acid to 200 mol % led to only a modest improvement (55% Michael adduct). Evaluation of a number of other potential acidic co-catalysts identified 3-nitrobenzoic acid (**B**) as particularly effective: combining 2 mol % of pyrrolidine **A** with 5 mol % of **B** provided the Michael adduct in 96% yield with >95% ee.

Having established **A** + **B** as an effective catalyst/co-catalyst pair for enantioselective Michael reaction of *n*-pentanal, we next investigated the scope for the aldehyde substrate (Table 2). These reactions were carried out with 2 mol % of **A** and 20 mol % of **B** at 3 °C. Enantioselectivity was determined in most cases after reduction of the initial aldehyde product to the corresponding β -substituted- δ -nitrobutanol derivative. This approach enabled ee determination via HPLC because aldehyde reduction eliminates the possibility of epimerization. As initially observed for *n*-pentanal, a variety of aldehydes with hydrocarbon appendages give excellent yields and enantioselectivities. Even a β -branched substrate, 3-methylbutanal, can be employed, although elevated temperature (23 °C) is required to achieve full conversion (Table 2, entry 3). Our long-term interest in using γ -amino acids to construct biologically active foldamers¹⁷ will require access to examples that bear appropriately protected functional groups in the side chain. Entries 9–11 of Table 2 show that our catalytic Michael addition method enables incorporation of side chains corresponding to those of glutamic acid, tyrosine, and lysine into γ^2 -amino acid precursors, with excellent yields and enantioselectivities.

We used compound **2b**, prepared on a 10 mmol scale reaction, to show that the β -substituted- δ -nitrobutanol derivatives generated via the Michael addition/reduction sequence could be converted in a straightforward manner to appropriately protected, enantioenriched γ^2 -amino acids (Scheme 2). Jones oxidation of **2b** provided the γ -nitro- α -alkylbutyric acid **3**, which was then transformed to protected γ^2 -amino acid **4** in an efficient one-pot operation involving nitro group reduction followed by Boc protection. The absolute configuration of **2b** was determined as (*R*) by the X-ray structure analysis of the L-phenylalanine derivative **5** (Scheme 3), and other β -substituted- δ -nitrobutanol configurations were assigned by analogy. The enantiomeric excess of **3** and **4** was measured by ¹H NMR after coupling of these acids to L- and D-phenylalanine methyl ester. The short synthetic route in Scheme 2 provides a high overall yield (62% from nitroethylene) and is operationally simple.

Incorporation of γ -amino acid residues into a growing peptide chain can be difficult because of cyclization side reactions. For example, carbodiimide-mediated coupling of Boc-protected γ^2 -amino acid **4** (30 mM) to L-phenylalanine methyl ester provides only 13% yield of the desired amide; the major product under these conditions is the *N*-Boc γ -lactam derived from **4** (69%; Scheme 3). However, the analogous reaction with γ -nitro acid **3**,

under identical conditions, gives the desired amide in 88% yield. The nitro group can be subsequently reduced via hydrogenation and protected. Thus, γ -nitro acids such as **3**, intermediates in our synthetic route, are valuable building blocks for γ -peptide synthesis, with the nitro group serving as a protected amino group.

The highly enantioselective Michael additions reported here constitute a method for formal *aminoethylation* of aldehydes. The reaction is catalyzed by a chiral pyrrolidine, and relatively low catalyst loading is possible if a carboxylic acid co-catalyst is used. When coupled with subsequent aldehyde reduction, this process provides β -substituted- δ -nitrobutanol derivatives, which are potentially valuable chiral intermediates. We have shown that such intermediates can be converted expeditiously to protected γ^2 -amino acids, which are interesting as foldamer building blocks. Relatively few methods have been previously described for γ^2 -amino acid synthesis,¹⁰ and these approaches might be challenging to apply to examples featuring diverse side chain functionality. Mechanistic studies regarding the role of acid co-catalyst and the catalytic pathway are in progress.¹⁸

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Organocatalyzed Michael Reaction

entry	catalyst	co-catalyst	yield ^b (%)	ee ^c
1	20 mol %	none	95	>95%
2	5 mol %	none	<10	n.d. ^d
3 ^a	5 mol %	HOAc (200 mol %)	95	>95%
4	2 mol %	HOAc (20 mol %)	30	n.d. ^d
5	2 mol %	TFA (20 mol %)	8	n.d. ^d
6 ^a	2 mol %	HOAc (200 mol %)	55	n.d. ^d
7	2 mol %	B (5 mol %)	96	>95%

^a HOAc used as solvent.^b From ¹H NMR of the crude reaction mixture.^c Determined by a ¹H NMR ee assay.¹⁶^d Not determined.

Table 2

Highly Efficient and Enantioselective Michael Reaction of Aldehydes with Nitroethylene

entry	product	R	t (h)	yield ^a (%)	ee ^b (%)
1	2a	Me	48	95	98
2	2b	Et	48	96	98
3	2c ^{c,d}	<i>i</i> -Pr	32	94	97
4	2d	<i>n</i> -Bu	48	95	99
5	2e	<i>i</i> -Bu	54	94	>99
6	2f	Bn	32	93	99
7	2g ^c	CH ₂ - <i>c</i> -Hex	48	93	>99
8	2h ^c	CH ₂ COOMe	54	92	96
9	2i	(CH ₂) ₂ COO ^t Bu	54	94	97
10	2j	4-O ^t BuC ₆ H ₄ CH ₂	32	94	98
11	2k	(CH ₂) ₄ N(Boc) ₂	48	92	98

^a Isoated yield.

^b Determined by chiral HPLC analysis.

^c Determined by chiral HPLC analysis on the corresponding aldehyde.

^d At 23 °C.