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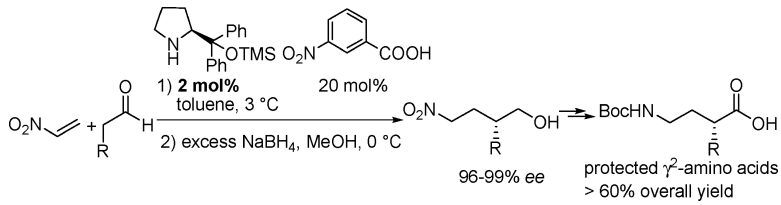

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Enantioselective Organocatalytic Michael Addition of Aldehydes to Nitroethylene: Efficient Access to γ^2-Amino Acids

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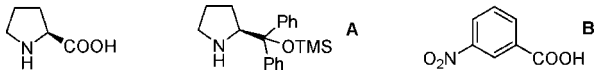
The development of asymmetric conjugate addition reactions for C−C bond formation remains an important challenge in organic synthesis.[1,2] Much recent work has focused on organocatalytic Michael addition of carbonyl compounds to nitroalkenes.[3–5] Among these reactions, Michael addition of aldehydes 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-peptide[6] 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 effects[14] 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

Scheme 1

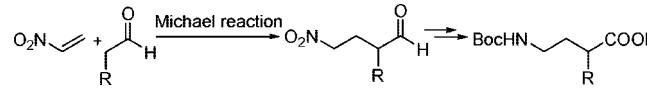
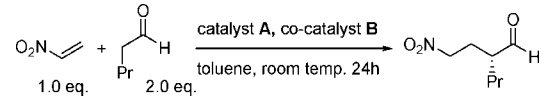


Table 1. Organocatalyzed Michael Reaction



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 ^{1}H NMR of the crude reaction mixture. [c] Determined by a ^{1}H NMR ee assay.[16] [d] Not determined.

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 foldamers[17] 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

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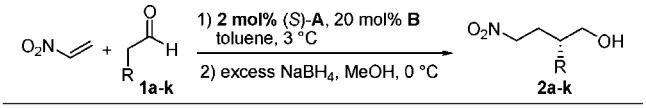
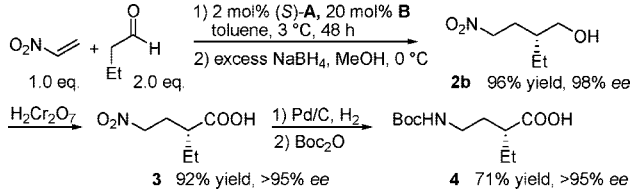
Table 2. Highly Efficient and Enantioselective Michael Reaction of Aldehydes with Nitroethylene



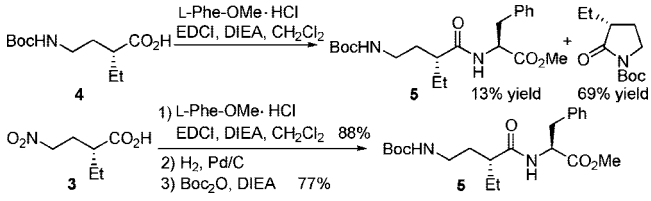
entry	product	R	*t* (h)	yield[a] (%)	ee[b] (%)
1	**2a**	Me	48	95	98
2	**2b**	Et	48	96	98
3	**2c**[c,d]	*i*-Pr	32	94	97
4	**2d**	*n*-Bu	48	95	99
5	**2e**	*i*-Bu	54	94	>99
6	**2f**	Bn	32	93	99
7	**2g**[c]	CH_2-*c*-Hex	48	93	>99
8	**2h**[c]	CH_2COOMe	54	92	96
9	**2i**	$(CH_2)_2COO^tBu$	54	94	97
10	**2j**	4-$O^tBuC_6H_4CH_2$	32	94	98
11	**2k**	$(CH_2)_4N(Boc)_2$	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.

Scheme 2



Scheme 3



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 ^{1}H 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]

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Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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