

Organocatalytic Asymmetric Transferhydrogenation of β -Nitroacrylates:
Accessing β^2 -Amino Acids

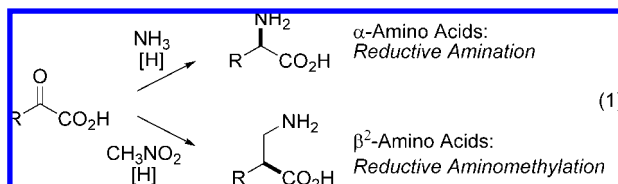
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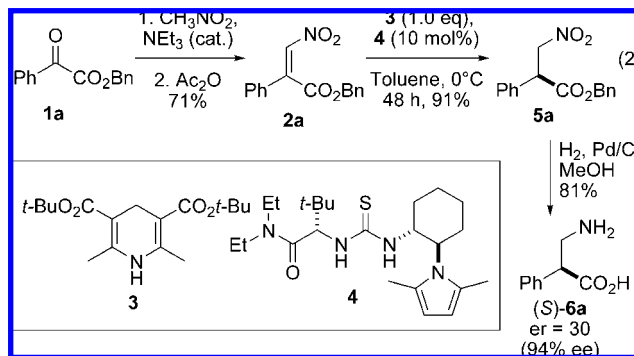
Pioneered by Seebach et al. and Gellmann et al., β -peptides recently emerged as a new class of peptidomimetics with potentially widespread biological and medicinal applications.^{1,2} As a consequence, the synthesis of β -amino acids has attracted considerable attention.³ While β^3 -amino acids, which are branched in the β -position, are now commercially available with most natural substituents, the analogous β^2 -amino acids, branched in the α -position, although particularly promising, are more difficult to obtain.⁴ Very recently, Gellmann et al. reported an elegant organocatalytic Mannich reaction that furnishes β -amino aldehydes in high yields and enantioselectivities.⁵ The products of this reaction can be readily converted into β^2 -amino acids. Here we report an alternative approach that relies on a catalytic asymmetric Hantzsch ester mediated conjugate reduction of readily available β -nitroacrylates to the corresponding β -nitroesters, which themselves are easily converted into β^2 -amino acids via hydrogenation.^{6,7}

Our approach to β^2 -amino acids takes its inspiration from nature. We envisioned that, in analogy to an enzymatic reductive amination of α -keto acids with ammonia,⁸ a hypothetical reductive aminomethylation with nitromethane should lead to the corresponding β^2 -amino acids (eq 1).



Encouragement for this design came from Jacobsen-type thiourea-catalyzed β -nitroolefin reductions previously developed by our group.^{9–11} In addition, a biocatalytic reduction of β -nitroacrylates has been realized during our studies.¹²

Based on our previous results, we identified Jacobsen-type thiourea **4** as a suitable catalyst of the highly enantioselective conjugate reduction of β -nitroacrylates **2**, for which we have developed a simple and practical synthesis. For example, reacting α -ketoester **1a** first with nitromethane in the presence of a catalytic amount of triethylamine (20 mol%), followed by dehydration of the resulting alcohol with acetic anhydride, gave the desired nitroacrylate **2a** in good yield and high (*Z*)-stereoselectivity (eq 2). Treating olefin **2a** (1 M) with commercially available Hantzsch ester **3** (1 equiv) and thiourea catalyst **4** (10 mol%) at 0 °C in toluene gave saturated ester **5a** in good yield and with high enantioselectivity. Hydrogenation in the presence of Pd/C directly gave the free β^2 -amino acid (*R*)-**6a**. The conjugate reduction conditions have been optimized with regard to catalyst structure and loading, solvent, substrate concentration, and Hantzsch ester structure and concentration (see Supporting Information (SI)). The resulting conditions are almost identical to those we have previously used successfully in the analogous reductions of unfunctionalized

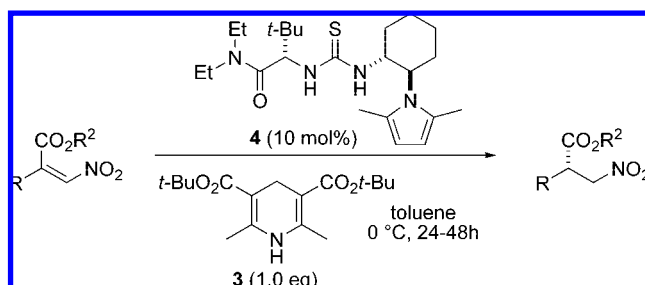


trisubstituted nitroolefins.⁹ The reaction turned out to be rather general and works well with a variety of substrates (Table 1). Subjecting different nitroacrylates **2** to the above reaction conditions for 24–48 h provided saturated β -nitroesters **5** in high yields and enantioselectivities. The ester group can be varied significantly as probed with phenyl-substituted derivatives **2a–e** (entries 1–5). While the yield is high in all cases, the enantioselectivity increases slightly with size and bulkiness of the ester moiety. Other aryl and heteroaryl groups can be utilized as well, furnishing the corresponding products in similar high yields and enantioselectivities (entries 6–10). Gratifyingly, branched as well as unbranched aliphatic nitroacrylates are equally suitable substrates (entries 11–13).

We have also investigated the effect of the nitroacrylate olefin geometry on the outcome of the reaction (Scheme 1). In contrast to our stereoconvergent iminium catalytic enal reductions,¹³ the enantioselectivity of the nitroolefin reductions strongly depends on substrate olefin geometry. Accordingly, nitroolefins (*E*)- or (*Z*)-**2k** gave opposite enantiomers of product **5k**, each with high enantioselectivity while a 1:1 (*E*)/(*Z*)-mixture gave essentially racemic **5k**. Remarkably though, stereoconvergence can be established upon adding a catalytic quantity of triphenylphosphine. We propose this additive to create a rapid equilibrium between (*E*)-**2k** and (*Z*)-**2k** via a conjugate addition/elimination pathway. That (*R*)-**5k** is the major product under these conditions indicates a faster reaction of the corresponding (*E*)-starting material, which should also dominate the equilibrium of the two **2k** olefin isomers.

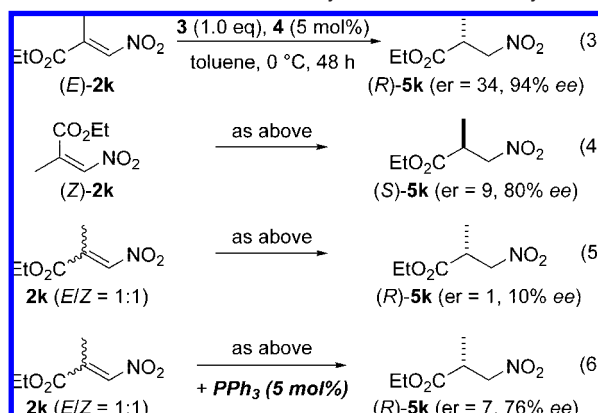
The absolute configuration of compounds **5a**, **5b**, and **5k** was determined by measuring their known optical rotation or that of their corresponding known β^2 -amino acids (see SI).

In summary we have developed a short new approach to enantiopure β^2 -amino acids. A key step in our sequence is a highly enantioselective thiourea **4**-catalyzed conjugate reduction of β -nitroacrylates **2** to their saturated analogues **5**. In addition we have developed a convenient synthesis of the required nitroacrylates **2** via Henry reaction followed by an acetic anhydride mediated dehydration. The conversion of our reduction products into β^2 -amino acids is facile and direct if benzyl esters are utilized. In the

Table 1. Preliminary Scope of the Transfer Hydrogenation

| | Nitroacrylate ^a | Product | Yield [%] | er (ee%) |
|-----------------|--|-----------|-----------|----------|
| | | | | |
| 1 | 2a R ¹ H R ² Bn | 5a | 91 | 30 (94) |
| 2 | 2b R ¹ H R ² Me | 5b | 86 | 17 (89) |
| 3 | 2c R ¹ H R ² Et | 5c | 95 | 23 (92) |
| 4 | 2d R ¹ H R ² ⁱ Pr | 5d | 91 | 37 (95) |
| 5 | 2e R ¹ H R ² ^t Bu | 5e | 92 | 35 (94) |
| 6 | 2f R ¹ ^p Me R ² Et | 5f | 92 | 28 (93) |
| 7 | 2g R ¹ ^p MeO R ² Et | 5g | 87 | 19 (90) |
| 8 | 2h R ¹ ^p MeO R ² ^t Bu | 5h | 61 | 30 (94) |
| 9 | 2i R ¹ ^p F R ² ^t Bu | 5i | 85 | 23 (92) |
| 10 | 2j | 5j | 81 | 26 (93) |
| 11 ^b | 2k | 5k | 97 | 34 (94) |
| 12 ^b | 2l | 5l | 91 | 42 (95) |
| 13 | 2m | 5m | 92 | 26 (93) |

^a Isomeric purity is >98:2. ^b Yields determined by GC (volatile products).

Scheme 1. Effect of Olefin Geometry on Enantioselectivity^a

^a Yields and er's from GC. All yields are >89%.

case of β -nitroesters with ester groups other than benzyl, conversion into the corresponding β^2 -amino acids is equally facile and involves a hydrogenation–hydrolysis sequence as outlined in the SI. Our organocatalytic asymmetric nitroolefin reduction complements a recently developed biocatalytic version¹² but has a significantly broader scope. The modest atom economy of our procedure may be counterbalanced by the practical and convenient use of bench stable, crystalline Hantzsch esters and a readily available catalyst. For practical considerations, it is important to note that both the Hantzsch ester oxidation product and the catalyst are easily separable from the less polar reaction products by flash chromatography and our reaction tolerates air, moisture, and up-scaling.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC and GC traces. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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