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A Formal Enantioselective Acetate Mannich Reaction: The Nitro Functional Group as a Traceless Agent for Activation and Enantiocontrol in the Synthesis of β-Amino Acids

Bo Shen and Jeffrey N. Johnston*

Department of Chemistry & Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235-1822

jeffrey.n.johnston@vanderbilt.edu

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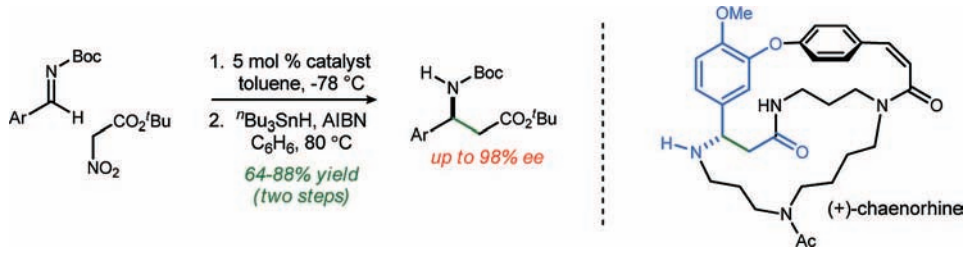
ABSTRACT



A two-step procedure involving the enantioselective addition of α-nitro esters to imines, followed by reductive denitration, provides a convenient new enantioselective synthesis of β-amino acids. Specifically, β-phenyl alanine derivatives with up to 98% ee are formed in good yield (64−88%) over two steps. The utility of the approach is demonstrated through the first enantioselective synthesis of the key β-amino acid of (+)-chaenorhine.

β-Amino acids are constituents of countless natural products,[1] including several contemporary chemotherapeutics such as Taxol.[2] α-Unsubstituted β-amino acids, formally derived from an "acetate" Mannich addition, are also expressed in natural products that include edeines A and B,[3] streptothricin F,[4] C-1027,[5] and (+)-chaenorhine.[6] These occurrences have stimulated the development of addition reactions leading to the β-amino acid motif. Recent preparations of α-unsubstituted β-amino acids include auxiliary-based methods such as the addition of chiral nonracemic amines to unsaturated esters.[7] Enantioselective, catalytic approaches have also been developed, including two-step procedures involving enol silane formation and catalyzed addition,[8] and a three-step sequence involving Mannich addition of a malonate, hydrolysis, and decarboxylation.[9] Beyond β-amino acid synthesis, the general study of Mannich additions for the

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synthesis of chiral amines holds historic and continuing importance in synthesis.[10]

Enantioselective Mannich reactions involving nitroalkanes have been subjected to intensive study over the past decade.[11,12] We and others have also successfully employed α-nitro esters in these additions,[11] but the sole focus has resided in the value of the nitro group as an amine progenitor.[13] We naturally wondered whether the nitro group, which is critical for activation and stereocontrol in the addition reaction, could be readily removed as part of a two-step procedure leading ultimately to the α-unsubstituted *β*-amino acid substructure (Figure 1). The strategy bears

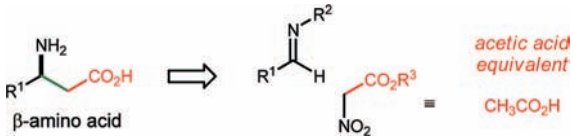
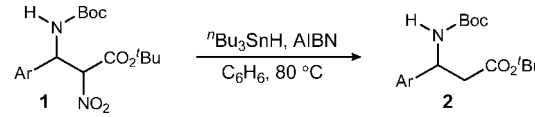


Figure 1. General design of an acetate Mannich equivalent.

analogy to malonate Mannich addition/hydrolysis/decarboxylation, but differs by the potentially mild, pH-neutral conditions typical of stannane-mediated denitration. In this Letter we describe the successful deployment of α-nitro acetates as acetate synthons in the enantioselective construction of *β*-amino acids.[14,15]

The feasibility of the denitration step in this setting was first examined on *β*-amino-α-nitro esters **1** made from triethyl amine-catalyzed aza-Henry reactions of *tert*-butyl nitroacetate with *N*-Boc imines. That these substrates were racemates was of no consequence at this stage. Numerous methods for denitration have been developed,[16] but stannane reductions were particularly attractive for the mild, pH-neutral conditions typical of these free radical-mediated reductive denitrations. Secondary nitroalkanes are suitable substrates, particularly when one substituent further stabilizes the intermediate carbon radical,[17] as are tertiary nitroalkanes.[17−19] As shown in Table 1, the use of standard reagents

Table 1. Reductive Denitration of α-Nitro Esters[a]



entry	Ar		yield (%)[b]
1	$^{p}MeC_6H_4$	**a**	91
2	$^{p}MeOC_6H_4$	**b**	90
3	$^{p}FC_6H_4$	**c**	97
4	$^{m}MeC_6H_4$	**d**	90
5	$^{p}PhC_6H_4$	**e**	89
6	^{2}Np	**f**	83
7	$^{m}PhOC_6H_4$	**g**	83
8	$^{p}ClC_6H_4$	**h**	73
9	$^{p}AcOC_6H_4$	**i**	82
10	$^{2}C_4H_3O$	**j**	93
11	$^{3}C_4H_3S$	**k**	0

[a] All reactions were 0.10 M in substrate and proceeded to complete conversion. [b] Isolated yields.

and stannyl radical-generating conditions provided the desired *β*-amino ester products **2** in high isolated yield. Not

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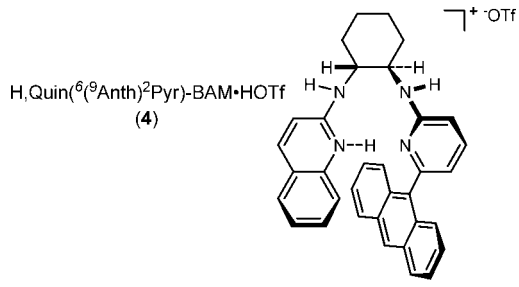
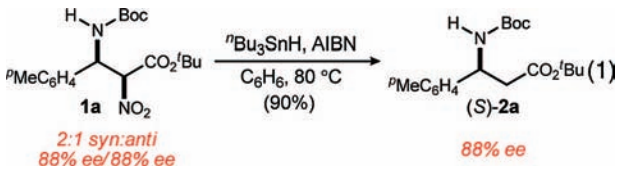
unexpectedly, a variety of functionalized aryl groups furnished the denitrated products (**2a**−**j**) in good to excellent yield (Table 1, entries 1−10). Fluorinated (**1c**) and chlorinated (**1h**) (Table 1, entries 3 and 8) substrates are tolerated, as well as the electronically rich furyl-derived β-amino ester **1j**. Unfortunately, thiophenyl substrates are unsuitable at the present time (Table 1, entry 11).



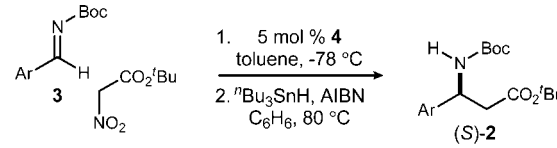
The experiments in Table 1 merely confirmed the expectation that denitration is possible, but did not prognosticate the feasibility of the overall strategy with regard to enantioenriched product formation. α-Nitro esters **1** are obtained as a thermodynamic ratio of diastereomers at room temperature. The enantiomeric ratio for each diastereomer, however, is at the 94:6 level (88% ee each, eq 1). We were gratified to find that reductive denitration of this mixture resulted in convergence to the desired amine with identical enantiomer enrichment (88% ee). This finding indicated that stereocontrol to establish the benzylic carbon proceeds with the same azomethine facial selectivity regardless of the diastereomer produced. Furthermore, the selectivity is at the same level in each case. Had the minor diastereomer formed with *R* configurational selectivity and 88% ee, the product of eq 1 would have been isolated in 29% ee.



We investigated the scope of this overall approach as a two-step protocol as outlined in Table 2. Optimized conditions for the aza-Henry step provided (*S*)-**2a** with slightly improved selectivity after reductive denitration (94% ee and 80% overall yield, Table 2, entry 1). The β-amino tyrosine derivative (*S*)-**2b** was produced in 85% ee and 88% yield overall with use of an identical protocol. Substitutions of the aromatic ring, varing both electronically and by position, provided the derived β-amino acids with good enantioselectivity and overall yield (87−98% ee, 68−87% overall yield, Table 2, entries 3−9). Furthermore, an electron rich heterocycle such as the furyl β-amino acid (*S*)-**2j** was obtained in 85% ee and 64% yield overall (Table 2, entry 10).

Among the products in Table 2, protected β-tyrosines are of particular note as they can be structural elements of natural products. We targeted one additional β-tyrosine derivative particularly for its relevance to natural product synthesis. (+)-

Table 2. A Catalytic Asymmetric Acetate Mannich Reaction in Two Steps[a]

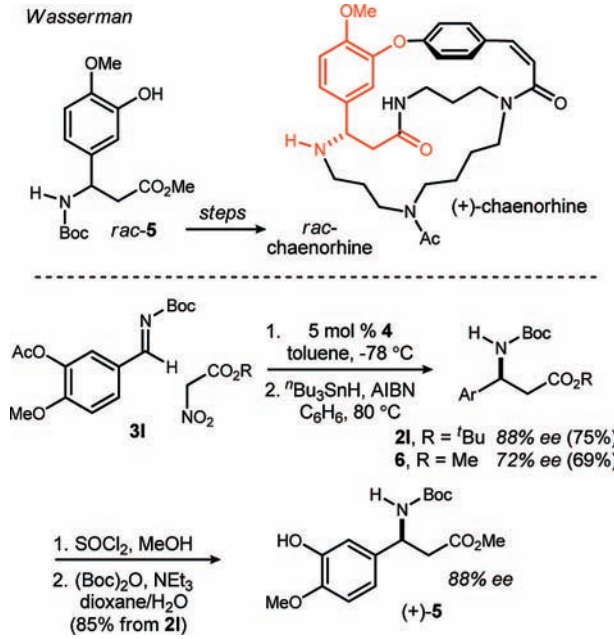


entry	Ar		ee (%)[b]	yield (%)[c]
1	$^{p}MeC_6H_4$	**a**	94	80
2	$^{p}MeOC_6H_4$	**b**	85	88
3	$^{p}FC_6H_4$	**c**	93	85
4	$^{m}MeC_6H_4$	**d**	87	87
5	$^{p}PhC_6H_4$	**e**	92	81
6	^{2}Np	**f**	95	77
7	$^{m}PhOC_6H_4$	**g**	89	67
8	$^{p}ClC_6H_4$	**h**	98	73
9	$^{p}AcOC_6H_4$	**i**	91	68
10	$^{2}C_4H_3O$	**j**	85	64

[a] All reactions were 0.30 (step 1) and 0.10 M (step 2) in substrate and proceeded to complete conversion. [b] Enantiomer ratios were measured using chiral stationary phase HPLC. [c] Isolated yields (two steps).

Chaenorhine is a macrocyclic spermine alkaloid isolated from *C. origanifolium* in which a β-amino acid is present as a key constituent of the macrobicyclic core structure (Scheme 1).[6]

Scheme 1. Enantioselective Synthesis of Wasserman's Chaenorhine Protected β-Amino Acid Intermediate

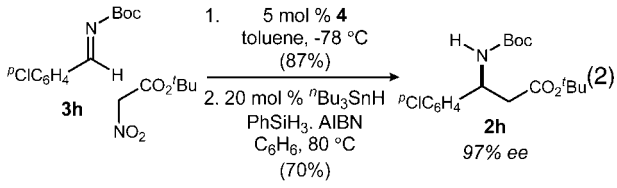


Wasserman has reported the only total synthesis of record, and this provided access to racemic chaenorhine.[20]

Addition of *tert*-butyl nitroacetate to imine **3l**, followed by denitration, produced β-amino ester **2l** in 88% ee and 75% yield overall (Scheme 1). Methanolysis and selective

reprotection of the free amine then furnished the Wasserman β-amino ester intermediate **5** in 85% yield (two steps), but in enantioenriched form as the *S* enantiomer. Incidentally, this methyl ester could be formed directly from commercially available methyl nitroacetate, albeit with slightly diminished enantiomeric excess (72% ee).

As a representative example, we examined the protocol developed by Fu,[19] which employs a substoichiometric amount of stannane, in conjunction with a stoichiometric amount of silane (eq 2). In our hands, this method worked well to provide **2h** in 70% isolated yield, requiring only a longer reaction time when compared to the use of stannane alone. Again, no loss in enantiomeric enrichment was observed, as **2h** was delivered in 97% ee (cf. Table 2, entry 8).



In summary, the enantioselective synthesis of β-phenyl alanine derivatives with use of a two-step procedure has been developed. The successful application of this strategy is in large part due to the ability of chiral proton catalyst **4** to provide each intermediate α-nitro ester diastereomer with high enantioselectivity and consistent configuration at the benzylic amine carbon. Convergence of these diastereomers to enantioenriched β-amino ester products is therefore possible by stannyl radical-mediated denitration. The Mannich addition/denitration protocol can be considered an equivalent to the analogous addition/decarboxylation sequence involving β-diesters. Whereas the latter requires ester to carboxylic acid conversion under either acidic or basic conditions,[9] the free radical conditions used here for denitration are considered pH-neutral—in the present work, for example, the acetate in **2i**/**l** was retained. The practitioner can now choose from among this range of possibilities. Moreover, the lower molecular weight of the nitro group compared to an ester might render it more attractive when employed as a disposable functional group. The utility of the strategy and method was successfully applied to the β-amino acid component of (+)-chaenorhine, which should now be accessible in enantioenriched form following the synthesis of Wasserman.

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Supporting Information Available: Preparation and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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