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The Proline-Catalyzed Double Mannich Reaction of Acetaldehyde with *N*-Boc Imines**

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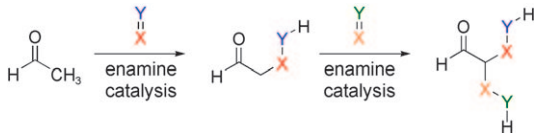
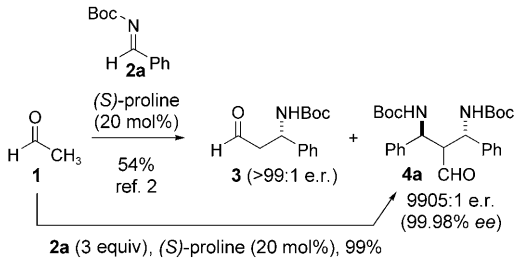
Within the last decade, enamine catalysis has become a powerful strategy, delivering several enantioselective transformations of ketones and aldehydes.[1] Very recently, the scope of this concept was further advanced with the utilization of acetaldehyde, the simplest of all enolizable carbonyl compounds, as a nucleophile. We have developed a proline-catalyzed Mannich reaction of acetaldehyde with *N*-Boc-imines, which gives α-unbranched β-aminoaldehydes with near perfect enantioselectivities.[2–4] Independently, Hayashi and co-workers reported the application of acetaldehyde in cross-aldol reactions.[5] Acetaldehyde was also found to be a suitable nucleophile in related Michael reactions with nitroalkenes.[6]

Interestingly, the products derived from all these transformations are α-unbranched aldehydes themselves and should be suitable substrates for a separate enamine catalytic activation. Moreover, enamine catalytic in situ sequences of acetaldehyde with two electrophiles can be envisioned (Scheme 1). Herein, we report the first successful realization of this concept with a proline-catalyzed double Mannich reaction of acetaldehyde with either a single or two different *N*-Boc-imines.



Scheme 1. Concept: in situ sequences of enamine-catalyzed reactions of acetaldehyde with two electrophiles.

During our initial studies of the Mannich reaction of acetaldehyde with *N*-Boc-imines, we detected traces of bis-addition product **4a**, resulting from the reaction of product **3**, with an additional imine equivalent (Scheme 2).[7] Having undergone two cycles of enamine activation during the course of the reaction, this pseudo-C_2-symmetric compound contains a chirotopic nonstereogenic center embedded between two new stereogenic centers.



Scheme 2. Double Mannich reaction of acetaldehyde with imine **2a**.

Being the result of two concomitant highly enantioselective catalyst-controlled transformations,[8] we were not surprised to find the enantiomeric ratio of bis-addition product **4a** to be extremely high (≥99:1 e.r.), challenging the detection limits of our HPLC instruments. Realizing that such aldehydes may be interesting precursors for various chiral molecules including β,β′-diamino acids, we became interested in optimizing the reaction towards the formation of the double addition product. Indeed, if one equivalent of acetaldehyde was treated with three equivalents of imine **2a**, compound **4a** was obtained in essentially quantitative yield. Careful HPLC analysis, including the determination of the detection limit of the enantiomers, revealed an enantiomeric ratio (e.r.) of 9905:1, corresponding to an *ee* value of 99.98%. Remarkably, other diastereomers could not be detected by NMR spectroscopy of the crude reaction mixture.

Encouraged by this exciting result, we performed the reaction under optimized conditions with a variety of *N*-Boc imines to evaluate the scope of the double Mannich reaction (Table 1). Aromatic ring substitution is well tolerated and imines with differing electronic properties (Table 1, entries 1–5) provided products in high yields (76–99%) and with exceptionally high diastereo- and enantioselectivities (>99:1 d.r., >300:1 e.r.). A heteroaromatic thiophene-substituted imine also participated in the reaction, furnishing product **4f** in 93% yield with similar stereoselectivity (Table 1, entry 6). Even the aliphatic isovaleraldehyde-derived *N*-Boc imine, which is much more difficult to handle, gave the double Mannich adduct highly enantioselectively (>300:1 e.r.) albeit in moderate yield (30%) owing to the instability of the imine (Table 1, entry 7).

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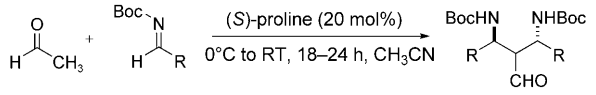
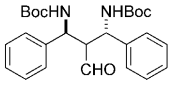
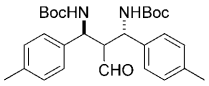
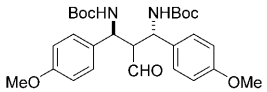
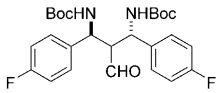
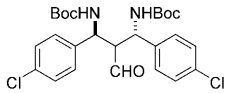
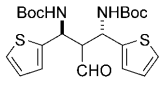
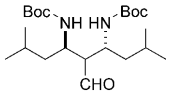
Table 1: Double Mannich reactions of acetaldehyde.[a]

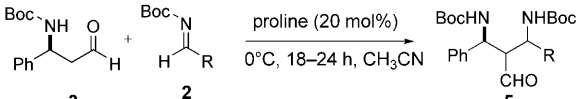


1 **2** (3 equiv) **4**

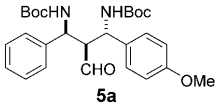
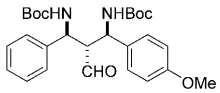
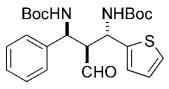
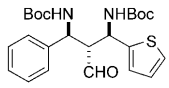
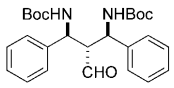
Entry	Product	Yield [%][b]	d.r.[c]	e.r. (*ee* %)[d]
1[e]	 **4a**	99	>99:1	9905 (99.98)
2	 **4b**	86	>99:1	>300 (>99)
3	 **4c**	90	>99:1	>300 (>99)
4	 **4d**	85	>99:1	>300 (>99)
5	 **4e**	76	>99:1	>300 (>99)
6[e]	 **4f**	93	>99:1	>300 (>99)
7[f]	 **4g**	30	>99:1	>300 (>99)

[a] Unless otherwise noted, reactions were run with imine **2** (0.75 mmol) and acetaldehyde (0.25 mmol) in CH_3CN at 0 °C for 2 h and then allowed to warm to room temperature for 18–22 h. [b] Yield of isolated product. [c] Determined by NMR spectroscopy of the crude mixture. [d] Determined by HPLC analysis of the corresponding alcohol. [e] Reaction run at 0 °C for 24 h. [f] A solution of the *N*-Boc imine (0.31 mmol, 1 equiv) and acetaldehyde (1.5 equiv) in CH_3CN was added to a solution of (*S*)-proline (0.2 equiv) in CH_3CN at 0 °C. The solution was allowed to stir for 2 h at 0 °C before a second portion of freshly prepared *N*-Boc imine (1.5 equiv) was added.

Table 2: Mannich reactions of compound **3** with different imines **2**.



3 **2** (1.5 equiv) **5** e.r. > 300 (> 99% *ee*)

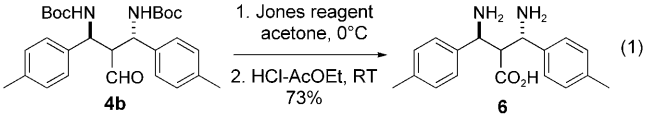
Entry	Product	Yield [%][a]	d.r.[b]
1[c]	 **5a**	61	45:2:1:0
2[d]	 **5b**	59	70:2:1:0
3[c,e]	 **5c**	58	>20:1:1:1
4[d,e]	 **5d**	60	>20:1:1:1
5[d]	 **5e**	53	>20:1:1:1

[a] Yield of the isolated corresponding alcohol after in situ reduction. [b] The d.r. refers to the ratio of the four possible diastereomers and was determined by HPLC analysis of the corresponding crude alcohol mixture after in situ reduction (entries 1 and 2) or following column chromatography (entries 3–5). [c] Using (*S*)-proline. [d] Using (*R*)-proline. [e] Reaction carried out with 1.3 equivalents of imine **2**.

We also made attempts at developing analogous cross-Mannich reactions with two different imines by sequencing their addition. Initial attempts lead to formation of both homocoupling products, as well as the corresponding cross-Mannich products under a variety of conditions.[9] However, the desired products **5** were obtained when the initial mono-addition products were first isolated and then subjected to a second reaction, similar to our previously described conditions.[10] Indeed, treating isolated Mannich product **3** (>99:1 e.r.) with two different second aromatic *N*-Boc imines in the presence of either (*S*)- or (*R*)-proline gave the corresponding cross-Mannich products in reasonably good yields and with high diastereoselectivities and, as anticipated, with enantiomeric ratios greater than 99:1 (Table 2). Judging from the high diastereoselectivity using either (*R*)- or (*S*)-proline, these reactions are essentially catalyst controlled. Using (*S*)-proline, the reaction leads to products **5a** and **5c** (Table 2, entries 1 and 3), resulting from the inherent *syn* diastereoselectivity and imine *si*-facial enantioselectivity of the (*S*)-proline-catalyzed Mannich reaction. In contrast, when we used (*R*)-proline as the catalyst, diastereomers **5b** and **5d** were obtained. In these cases, the two new stereogenic centers were formed with the opposite configuration (Table 2, entries 2 and 4).

The strategy of utilizing first (*S*)-proline and then (*R*)-proline in subsequent acetaldehyde Mannich reactions with the same imine (**2a**) was used to afford the corresponding *meso* product **5e** highly diastereoselectively (Table 2, entry 5). In this rather sophisticated symmetrization process, two highly enantioselective catalytic reactions were sequenced to create an achiral molecule.

Finally, aldehyde **4b** was readily converted into the corresponding diamino acid **6** by a straightforward two-step oxidation–deprotection sequence in 73% overall yield [Eq. (1)].[11]



4b **6** (1)

In summary, a double enamine catalysis sequence using acetaldehyde as the nucleophile has been realized. We developed an efficient method for the one-pot catalytic asymmetric synthesis of pseudo-C_2-symmetric β,β′-diaminoaldehydes with extremely high stereoselectivities, starting from acetaldehyde and either aromatic or aliphatic *N*-Boc imines. The method was extended to cross-Mannich reactions, furnishing β,β′-diamino aldehydes **5** containing stereotriads (three adjacent stereogenic centers). The general strategy should be of use for alternative double enamine catalysis sequences using different reactions and even triple enamine catalysis sequences of acetaldehyde.

Experimental Section

General procedure for the (*S*)-proline-catalyzed asymmetric homo double Mannich reaction of acetaldehyde and aromatic *N*-Boc imines: The *N*-Boc imine (0.75 mmol, 3 equivalents) was dissolved in anhydrous CH_3CN (3.75 mL) and stirred under an atmosphere of argon. The solution was cooled to 0 °C and freshly distilled acetaldehyde (0.25 mmol, 1 equivalent) and (*S*)-proline (0.05 mmol, 0.2 equivalents) were added. The reaction mixture was stirred for 2 h at 0 °C and then allowed to warm to room temperature. After stirring for 18–22 h, the reaction mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic fractions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/ethyl acetate, 90:10) afforded **4a**–**f** as white solids.

Typical procedure for the (*S*)-proline-catalyzed asymmetric double Mannich reaction of acetaldehyde and isovaleraldehyde-derived *N*-Boc imine: A solution of the *N*-Boc imine (0.31 mmol, 1 equivalent) in CH_3CN (1.3 mL) was added to a solution of (*S*)-proline (0.062 mmol, 0.2 equivalents) in CH_3CN (250 μL) at 0 °C. Freshly distilled acetaldehyde (0.465 mmol, 1.5 equivalents) was immediately added and the resulting solution was allowed to stir for 2 h at 0 °C. A second solution of *N*-Boc imine (0.465 mmol, 1.5 equivalents) in CH_3CN (1 mL) was added and the mixture was allowed to stir an additional 3 h at 0 °C. The reaction mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic fractions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/ethyl acetate, 95:5) afforded **4g** as a white solid.

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[9] A representative in situ attempt for the synthesis of cross double Mannich products is as follows: A standard Mannich reaction mixture of (*S*)-proline (20 mol%), imine **2a** (1 equivalent), and acetaldehyde (1.5 equivalents) was stirred for 3 h. *N*-Boc imine **2b** (1.5 equivalents) was added, resulting in a complex mixture of the two first Mannich adducts (**3**), the two homo double Mannich products **4a** and **4b**, and the desired cross-Mannich product (**5**). The ratio **4b**/**5** was close to 1:1 and could be slightly improved to 0.6:1 by slowly adding imine **4b** under dilute conditions.

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