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Proline-Catalyzed Mannich Reaction of Aldehydes with *N*-Boc-Imines**

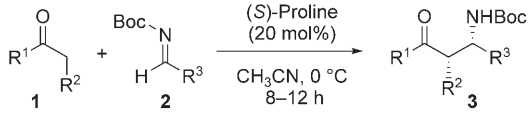
*Jung Woon Yang, Michael Stadler, and Benjamin List**

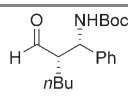
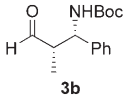
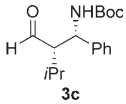
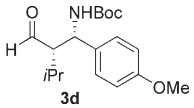
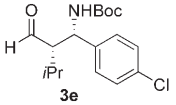
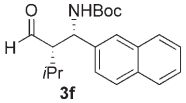
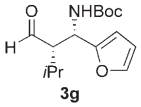
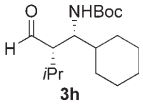
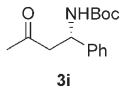
The catalytic asymmetric Mannich reaction is arguably the most useful approach to synthesize chiral β-amino carbonyl compounds.[1] Six years ago, we discovered a proline-catalyzed version of this powerful reaction.[2] Originally, ketones, aldehydes, and an aniline as the amine component were used in a catalytic asymmetric three-component reaction. Since then, the reaction has found utility in the synthesis of chiral nonracemic nitrogenous compounds, such as amino acids and amino alcohols. Recently, several new catalysts and substrate classes have been developed to expand the scope of the reaction and to modify its remarkably high *syn* diastereo- and enantioselectivity.[3] Despite its frequent use, both in an academic as well as an industrial context, the main limitation of the proline-catalyzed Mannich reaction has been the requirement to use anilines as the amine component. Although optically enriched *p*-anisidylamines are of potential utility in asymmetric synthesis, facile and efficient removal of the *N*-protecting group to yield the unfunctionalized amine is required. Generally, the removal of the most commonly used *p*-methoxyphenyl (PMP) group from nitrogen requires rather drastic oxidative conditions involving harmful reagents, such as ceric ammonium nitrate, which are not compatible with all substrates. We have now identified reaction conditions that allow for the use of simple preformed aromatic *N*-Boc-imines (Boc = *tert*-butoxycarbonyl) in proline-catalyzed Mannich reactions. Remarkably, the reaction provides chiral β-amino aldehydes and ketones as stable, crystalline compounds in generally high diastereo- and enantioselectivities without the requirement for chromatographic purification.

After a short screening of reaction conditions, an optimal procedure was found. If the benzaldehyde-derived *N*-Boc-imine **2a** (R^3 = Ph) was treated with hexanal in the presence of (*S*)-proline (20 mol%) in acetonitrile at 0°C for 8 h, the desired product **3a** precipitated during the reaction and could be isolated by filtration. The product had an e.r. value greater than 99:1, a d.r. value greater than 99:1, and the yield of the isolated product was 84% (Table 1, entry 1). Similarly, the reaction of **2a** with propionaldehyde resulted in the formation of crystalline product **3b** with the same diastereoselectivity and enantioselectivity (Table 1, entry 2). In this case, product **3b** did not precipitate but its isolation proved similarly simple: After an aqueous workup, the crude product was triturated with cool hexanes to afford the pure, crystalline product.

The remarkably high enantioselectivity is at least not entirely based on an enantioenrichment during the precip-

Table 1: Proline-catalyzed asymmetric Mannich reaction of aldehydes with *N*-Boc-imines.[a]



Entry	Product	Yield [%]	d.r.	e.r.[a]
1	 **3a**	84	>99:1	>99:1[b]
2	 **3b**	91	>99:1	>99:1
3	 **3c**	88	>99:1	>99:1
4	 **3d**	80	>99:1	>99:1
5	 **3e**	59	99:1	98.5:1.5
6	 **3f**	82	>99:1	>99:1[c]
7[d]	 **3g**	74	97:3	99:1
8	 **3h**	<5	n.d.[f]	n.d.[f]
9[e]	 **3i**	73		>99:1

[a] Yields, diastereoselectivities, and enantioselectivities of precipitated products. [b] Crude e.r. 99:1. [c] Crude e.r. 96:4. [d] Product isolated by chromatography. [e] Reaction run at room temperature in acetone. [f] Not determined.

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itation. When product **3a** was isolated through an aqueous/organic extraction, its crude e.r. value was determined to be 99:1. The reaction conditions turned out to be of use for several substrate combinations (Table 1, entries 3–7). In general, the derivatives of **3** either directly precipitated from the reaction mixtures in the given stereoselectivities and yields or were isolated through trituration with hexanes. Only furan derivative **3g** was isolated through chromatography. Although several different aromatic imines could be used, aliphatic imines proved less reactive and did not provide the desired product under the reaction conditions (Table 1, entry 8). However, ketones undergo the reaction with similar enantioselectivities. Treating benzaldehyde-derived *N*-Boc-imine **2a** with (*S*)-proline (20 mol%) in acetone gave Mannich product **3i** in good yields and close to perfect enantioselectivity.[4]

A typical experimental procedure is illustrated in Figure 1. Mixing the 2-naphthaldehyde-derived *N*-Boc-imine (**2f**; R^3 = 2-naphthyl) with isovaleraldehyde in the

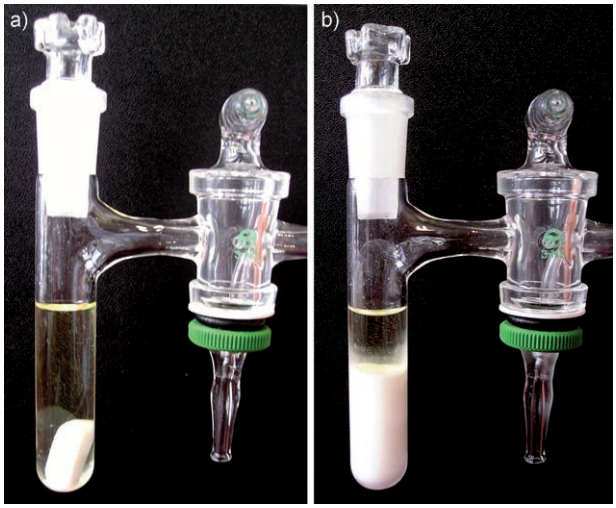
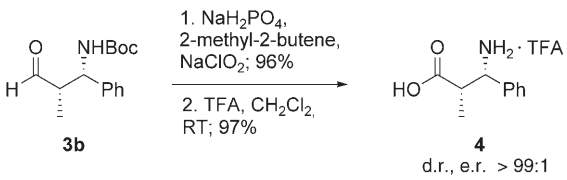


Figure 1. The reaction of isovaleraldehyde with 2-naphthyl *N*-Boc-imine in the presence of (*S*)-proline (20 mol%; Table 1, entry 6) in CH_3CN.
a) Homogenous reaction mixture after mixing all components.
b) Reaction mixture after completion of the reaction (10 h).

presence of (*S*)-proline (20 mol%) in acetonitrile at 0°C resulted in an initially homogenous reaction mixture (Figure 1a). After complete consumption of the starting material (10 h), a large amount of the desired product **3f** had precipitated and could easily be collected by filtration (Figure 1b).

The *N*-Boc-imine-derived Mannich products **3a**–**g** can readily be converted into the corresponding α,β-branched-β-amino acids ($\beta^{2,3}$-amino acids). For example, oxidation of product **3b** to the carboxylic acid followed by acid-mediated deprotection provided amino acid salt **4** without loss of stereochemical integrity [Eq. (1); TFA = trifluoroacetic acid]. Measuring NMR spectra and optical rotation of the corresponding HCl salt allowed us to confirm the expected absolute and relative configuration of the product.[5]

In summary, we have developed a remarkably efficient and enantioselective variant of the proline-catalyzed Mannich



3b → **4**, d.r., e.r. > 99:1 (1)

reaction. In our new procedure, aldehydes react with preformed *N*-Boc-imines in the presence of proline to give the corresponding β-amino aldehydes in excellent diastereoselectivities and enantioselectivites. Our reaction is useful for the synthesis of α,β-branched-β-amino acids, which are of great potential value in the synthesis of peptide derivatives and related biologically active compounds.[6] In addition to aldehydes, ketones can also be used. The reaction is highly practical in that it does not require chromatographic purification and in all cases provides crystalline products in almost perfect enantioselectivities. The product either directly precipitates from the reaction mixture or is isolated after aqueous workup and trituration with hexanes. A current limitation is the incompatibility of aliphatic imines with our process and the requirement to preform the *N*-Boc-imines. Although the synthesis of the required imines is well established,[1g,u,7] a direct three-component reaction, which potentially would be compatible with the use of aliphatic aldehydes similar to our original protocol, would further improve the proline-catalyzed Mannich reaction. Nonetheless, our new process is expected to find application, particularly in the synthesis of β-amino acids.

Experimental Section

General procedure for the (*S*)-Proline-catalyzed asymmetric Mannich reaction between *N*-Boc-protected imines and aldehyde donors: The *N*-Boc-protected imine (0.5 mmol) was dissolved in anhydrous acetonitrile (5 mL) and the corresponding aldehyde (2 equiv) was added. The mixture was cooled to 0°C and (*S*)-proline (0.1 mmol) was added. After 8–12 h at 0°C, the reaction was worked up either by filtering off the precipitate and washing it with hexanes (−78°C) or by pouring the reaction mixture into distilled water and extracting with diethyl ether (three times). In the latter case, the organic layers were then combined, dried over $MgSO_4$, filtered, concentrated, and purified by trituration with cool hexanes (−78°C) to afford the corresponding pure *syn*-Mannich products. The enantiomeric ratios of all products were determined by chiral-phase HPLC analysis.

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