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Highly enantioselective organocatalytic addition of unmodified aldehydes to *N*-Boc protected imines: one-pot asymmetric synthesis of β-amino acids

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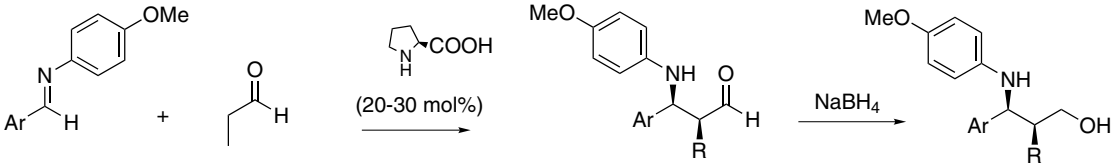
Abstract—Highly enantioselective catalytic routes to Boc protected β-amino aldehydes, β-amino acids and γ-amino alcohols are presented. The organocatalytic asymmetric reactions between unmodified aldehydes and *N*-Boc protected aryl imines proceed with excellent chemo- and enantioselectivities to give the corresponding compounds in high yields with up to >19:1 dr and 93% to >99% ee.

The Mannich reaction has found a multitude of applications in organic chemistry. The resulting Mannich bases are of particular interest due to their utilization as synthetic building blocks and precursors of pharmaceutically valuable compounds.[1,2] Chemists have developed several stoichiometric indirect stereoselective Mannich transformations that utilize preformed enol equivalents or imines.[3,4] The first successful examples of catalytic asymmetric additions of enolates to imines led to an intense study of catalytic indirect Mannich reactions.[5] Recently, heterodimetallic complexes and di-nuclear zinc organo-metallic complexes were reported as catalysts for highly enantioselective direct Mannich-type reactions.[6,7] Moreover, chiral copper(II) bisoxazoline (BOX) complexes are also catalysts for direct asymmetric Mannich-type reactions.[8] Recently, organocatalysis has been added to the synthetic repertoire for this important transformation.[9] These direct asymmetric Mannich reactions are catalyzed by chiral Brønsted acids,[10] cinchona alkaloids,[11] proline and its derivatives,[12] peptide derivatives[13] and amino acids.[14] In this context, we and Hayashi have reported the amino acid catalyzed addition of unmodified aldehydes to aryl *N*-*p*-methoxyphenyl (PMP) imines Eq. 1.[15,16]



(1)

The corresponding PMP-protected β-amino aldehydes are not very stable and are therefore reduced in situ to the corresponding γ-alcohols. In addition, removal of the PMP group requires oxidative conditions and can be low yielding. Enders recently reported two elegant examples of addition of ketones to Boc imines.[17] Based on this and our previous experience in organocatalysis,[18] we envisioned an organocatalytic reaction between Boc protected imines and unmodified aldehydes.[19] This possible reaction would be of high synthetic importance since it would be a direct route to Boc protected β-amino acids,[2f,20] which can be used directly in peptide and γ-amino alcohols synthesis (Eq. 2). Moreover, the side chain of Docetaxel (Taxotere), one of the most important cancer chemotherapeutic substances, is a Boc protected α-hydroxy-β-amino acid.[21]

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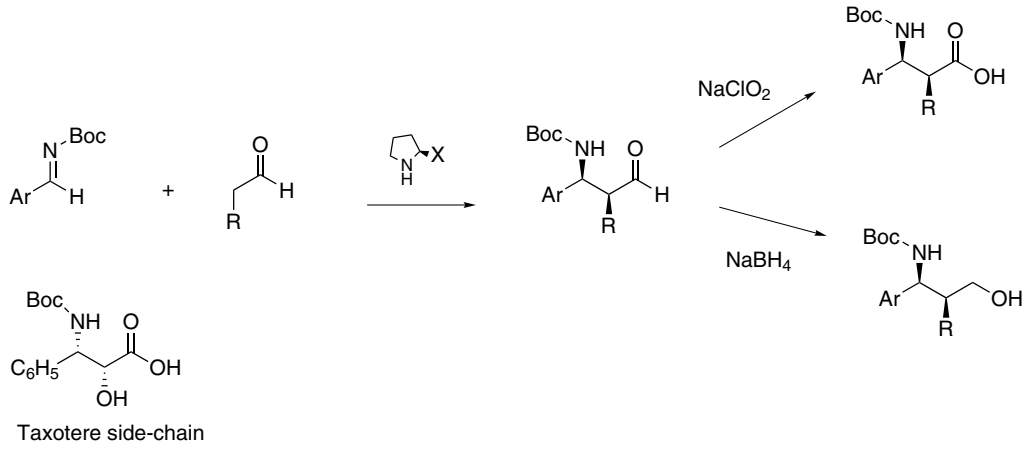


(2)

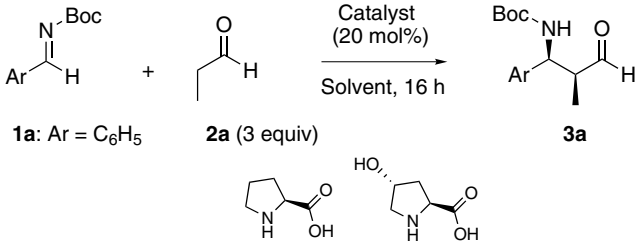
Herein, we present a simple highly enantioselective organocatalytic addition of unmodified aldehydes to *N*-Boc protected imines that gives the corresponding β-amino aldehydes in high yields with >19:1 dr and 93% to >99% ee.

In an initial catalyst and solvent screen, we found that (*S*)-proline **4** and 4-hydroxyproline **5** catalyzed the reaction between phenyl *N*-Boc imine **1a** (0.25 mmol) and propionaldehyde **2a** (0.75 mmol) with high chemoselectivity to give the corresponding β-amino aldehyde **3a** in high yields with excellent diastereomeric ratios and ee's (Table 1).[22]

(*S*)-Proline catalyzed the formation of β-amino aldehyde **3a** in good to high yields with >19:1 dr (*syn*:*anti*) and 96% to >99% ee in all the solvents tested. Moreover, hydroxyproline **5** catalyzed the formation of **3a** in 62% yield with >19:1 dr and >99% ee (entry 7). In addition, the optically active aldehyde **3a** was quite stable and precipitated in CH_3CN and $CHCl_3$ at 4 °C as a white solid. The highest yield and enantioselectivity were obtained when DMF was used as the solvent. Encouraged by these excellent results, we decided to investigate the catalytic asymmetric Mannich reaction between various *N*-Boc protected imines **1** and different aldehydes **2** with (*S*)-proline as the organocatalyst (Table 2).[22]

The catalytic Mannich reactions proceeded with excellent chemo- and enantioselectivities and the corresponding β-amino aldehydes **3a**–**e** were obtained in high yields with 93% to >99% ee. For instance, (*S*)-proline catalyzed the asymmetric reaction between imine **1d** and propanal with high chemoselectivity, and Boc protected β-amino aldehyde **3d** was isolated in 73% yield as the predominant diastereomer and >99% ee (entry 4). Moreover, the reactions were operationally simple and readily scaled-up. The β-amino aldehydes were also con-

Table 1. Catalyst screen for the enantioselective reactions between **1a** and **2a**[a]



Entry	Catalyst	Solvent	Temp (°C)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4**	CH_3CN	rt	62	>19:1	99
2	**4**	CH_3CN	4	70	>19:1	>99
3	**4**	$CHCl_3$	4	82	>19:1	96
4	**4**	DMSO	4	67	>19:1	97
5	**4**	DMF	4	85	>19:1	>99
6	**4**	NMP	4	80	>19:1	99
7	**5**	DMF	4	62[e]	>19:1	>99

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), propionaldehyde **2a** (0.75 mmol) and catalyst (20 mol %) in 1.0 mL solvent was stirred under the conditions displayed in the Table.
[b] Isolated yield of pure compound **3a**.
[c] Determined by ^1H NMR.
[d] Determined by chiral-phase HPLC analysis.
[e] Reaction stopped after 6 h, 30 mol % catalyst.