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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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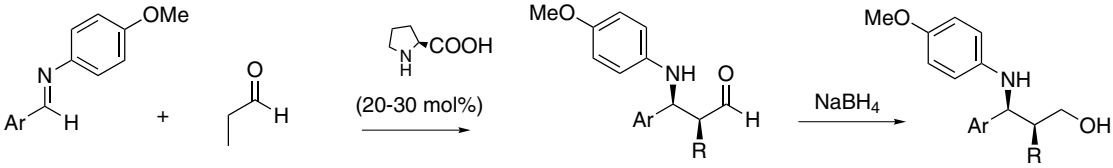
Abstract—Highly enantioselective catalytic routes to Boc protected β-amino aldehydes, β-amino acids and γ-amino alcohols are presented. The organocatalytic asymmetric reactions between unmodified aldehydes and *N*-Boc protected aryl imines proceed with excellent chemo- and enantioselectivities to give 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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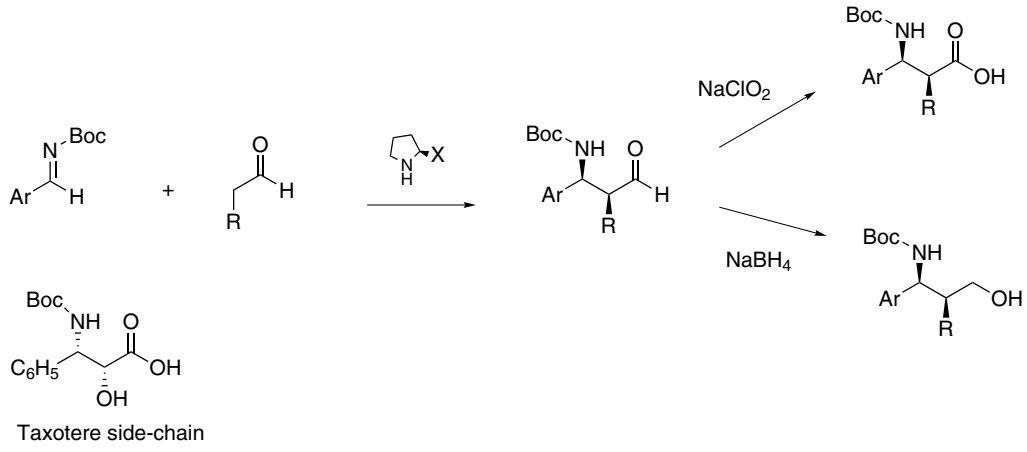


(2)

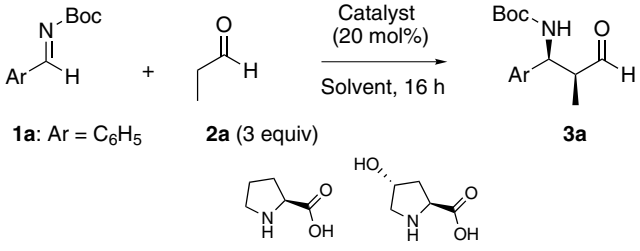
Herein, we present a simple highly enantioselective organocatalytic addition of unmodified aldehydes to *N*-Boc protected imines that gives the corresponding β-amino aldehydes in high yields with >19:1 dr and 93% to >99% ee.

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-

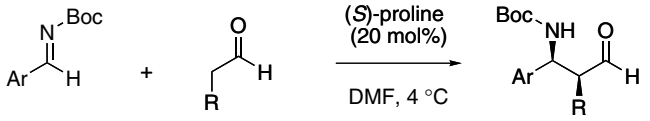
Table 1. Catalyst screen for the enantioselective reactions between **1a** and **2a**[a]



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.

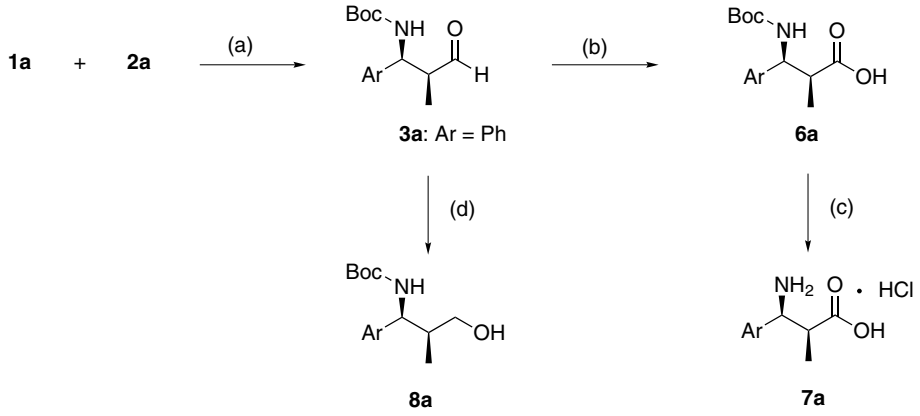
Table 2. Direct organocatalytic asymmetric Mannich reactions between *N*-Boc protected imines **1** and aldehydes **2**[a]



1 **2** **3**

Entry	Ar	R	Product	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	Me	**3a**	16	85	>19:1	>99
2	Ph	*i*-Pr	**3b**	16	77	>19:1	93
3	Ph		**3c**	16	75	>19:1	98
4	4-ClC_6H_4	Me	**3d**	15	73	>19:1	99
5	4-$MeOC_6H_4$	Me	**3e**	16	78	>19:1	99

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), propionaldehyde **2a** (0.50 mmol) and (*S*)-proline (20 mol %) in 1.0 mL DMF was stirred at 4 °C.
[b] Isolated yield of pure compound **3**.
[c] *syn*/*anti* Ratio determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analyses.



Scheme 1. Reagents and conditions: (a) (*S*)-proline (20 mol %), DMF, 4 °C, 18 h, 85%; (b) $NaClO_2$, *iso*-butene, KH_2PO_4, *t*-BuOH/H_2O 2:1, 68%; (c) HCl (8 M), dioxane, rt, 99%; (d) $NaBH_4$, MeOH, 0 °C, 79%.

verted to the corresponding β-amino acids **6** or γ-amino alcohols **8** by oxidation and reduction, respectively (Scheme 1).

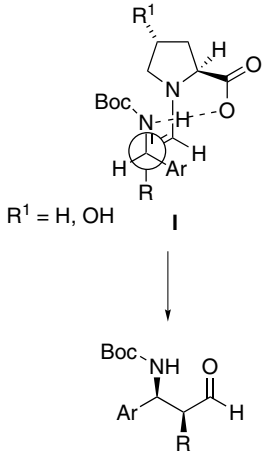


Figure 1. Transition-state models evoked to account for the enantioselectivity of the (*S*)-proline and hydroxyproline catalyzed reactions.

For example, aldehyde **3a** was oxidized to β-amino acid **6a** in high yield.[23] Subsequent deprotection gave the corresponding β-amino acid **7a** as the hydrochloride salt. Comparison with the literature established that the absolute stereochemistry of **7a** ($[\alpha]_D^{25}$ +1.8 (*c* 1.0)), lit. ($[\alpha]_D^{25}$ +1.7 (*c* 1.06)[24]) was (2*S*,3*S*). On the basis of the absolute configuration, we propose transition-state model **I** to account for the diastereo- and enantioselectivity of the amino acid catalyzed formation of β-amino aldehydes **3** (Fig. 1). Hence, the (*S*)-proline derivative forms an enamine with the aldehyde which is attacked by the *N*-Boc protected imine from its Si-face providing (3*S*)-*syn*-β-amino acid derivatives. This is in accordance with the transition states of previously reported proline-catalyzed Mannich reactions, in which Si-facial attack occurs.[12,15,16]

In summary, we have reported a simple, highly enantioselective, organocatalytic asymmetric Mannich reaction. The chiral pyrrolidine catalyzed reactions between aryl Boc imines and unmodified aldehydes proceeded with high chemo- and enantioselectivities to furnish β-amino aldehydes in high yields with 93% to >99% ee. Further elaboration of this novel transformation, its synthetic

application and mechanistic studies are ongoing in our laboratory.[25]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.076.

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22. *Typical experimental procedure*: To a stirred solution of (*S*)-proline (20 mol %) and imine **1a** (1.0 equiv, 0.25 mmol) in DMF (1.0 mL) at 4 °C was added aldehyde **2** (2 equiv, 0.5 mmol). The reaction was vigorously stirred for the reported time. Next, the reaction was directly loaded on a silica gel column and immediate chromatography (pentane/EtOAc-mixtures or toluene/EtOAc-mixtures) furnished the corresponding aldehyde. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.71$ (br s, 1H), 7.39–7.23 (m, 5H), 5.22–5.08 (m, 2H), 2.86 (br s, 1H), 1.41 (s, 9H), 1.06 (d, $J = 6.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.2$, 155.5, 134.6, 128.9, 127.8, 126.8, 79.5, 54.8, 51.7, 28.4, 9.4; $[\alpha]_D^{25}$ +2.4 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD with hexane/*i*-PrOH (90:10) as the eluent. Flow: 0.5 mL/min; minor isomer: $t_R = 18.1$ min; major isomer: $t_R = 23.5$ min; HRMS (ESI): calcd for $[M+Na]^+$ ($C_{15}H_{21}NO_3$) requires *m*/*z* 286.1414, found 286.1400.
23. *Preparation of acid* **6a**: To a solution of **3a** (26 mg, 0.1 mmol) in chloroform (1 mL), isobutene (0.1 mL), *tert*-butanol (0.4 mL), H_2O (0.2 mL), KH_2PO_4 (54.4 mg, 4.0 mmol) and $NaClO_2$ (36 mg, 4.0 mmol) were added sequentially at room temperature. After 16 h, the crude product was purified by column chromatography (pentane/EtOAc mixtures) to afford 19 mg (68%) of the desired acid **6a**; $[\alpha]_D^{25}$ −15.2 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.24 (m, 5H), 5.43 (br s, 1H), 4.99 (br s, 1H), 2.94 (br s, 1H), 1.41 (s, 9H), 1.16 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.6$, 155.3, 133.8, 128.6, 127.7, 126.9, 79.9, 56.4, 45.0, 28.4, 13.2. HRMS (ESI): calcd for $[M+Na]^+$ ($C_{15}H_{21}NO_4$) requires *m*/*z* 302.1363, found 302.1349.
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25. The reaction also works for Cbz protected alimines. For instance, the reaction between benzaldehyde derived Cbz protected imine (0.25 mmol) and propionaldehyde (0.5 mmol) in DMF at 4 °C gave the corresponding Cbz protected β-aminoaldehyde after 17 h in 80% yield with 4:1 dr and 72% ee.