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Aza-Morita–Baylis–Hillman-type reactions: highly enantioselective organocatalytic addition of unmodified α,β-unsaturated aldehydes to *N*-Boc protected imines

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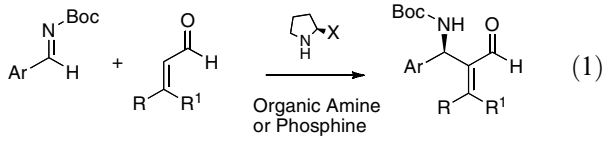
Abstract—Highly enantioselective catalytic routes to Boc protected aza-Morita–Baylis–Hillman-type products are presented. The organocatalytic asymmetric reactions between unmodified α,β-unsaturated aldehydes and *N*-Boc protected aryl imines proceed with excellent chemo- and enantioselectivity to give the corresponding compounds in good yields with 97–99% ee.

β-Amino carbonyl compounds with an α-alkylidene group are an important class of compounds, which are used as functional chiral building blocks for important compounds such as pharmaceuticals and can be prepared by aza-Morita–Baylis–Hillman (aza-MBH) reactions.[1,2] Thus, the development of asymmetric catalytic methods for enantioselective aza-MBH reactions is an active research field.[2] There are several different types of organic compounds that have been used as asymmetric catalysts for the aza-MBH reaction including chiral quinidine derivatives,[2a–c] functionalized 1,1′-bi-2-naphthol (BINOL) derivatives,[2d–i] chiral ionic liquids[2j] and thiourea derivatives.[2k] These reactions are typically limited to the use of cyclic enones (e.g., 2-cyclopentene-1-one) or of β-unsubstituted acyclic α,β-unsaturated compounds such as methyl vinyl ketone and acrylate esters as the donors and arylsulfonyl imines as the acceptors.[2] Moreover, it is known that the aza-MBH and MBH reactions of β-substituted acyclic enones are more problematic than those of β-unsubstituted enones.[3] However, the asymmetric addition of enals to *N*-*p*-methoxyphenyl-(PMP) protected α-imino glyoxylate using a combination of proline as the catalyst and imidazole as the base was recently reported.[4] Based on the use of co-catalyst systems involving proline or peptide derivatives and organic nucleophilic amines for mediating asymmetric MBH[5] and aza-MBH[4] reactions, and our recent findings that amino acids catalyze the asymmetric addition of unmodified aldehydes to *N*-Boc protected imines,[6] we envisioned the possibility of developing an aza-MBH reaction between α,β-unsaturated aldehydes and *N*-Boc protected imines (Scheme 1, Eq. 1).



(1)

Thus, we predicted that a chiral iminium intermediate derived from the reaction between the amino acid catalyst and the enal donor could be activated by a nucleophilic organic amine or phosphine to form two different possible chiral enamine intermediates (Scheme 1). These in situ generated chiral enamines could subsequently react with electrophiles such as *N*-Boc protected imines to give the corresponding aza-MBH products. This type of reaction would be of high synthetic importance since it would be a direct route to Boc protected β-amino aldehydes, which can be used directly in β-amino acid and γ-amino alcohol synthesis. In addition, the Boc protecting group is readily removed in comparison to the removal of arylsulfonyl and PMP protecting groups, which can be cumbersome and low yielding. To the best of our knowledge, no report of an organocatalytic asymmetric aza-MBH reaction involving Boc imines has been reported to date.

Herein, we present a simple, highly enantioselective organocatalytic addition of unmodified enals to *N*-Boc

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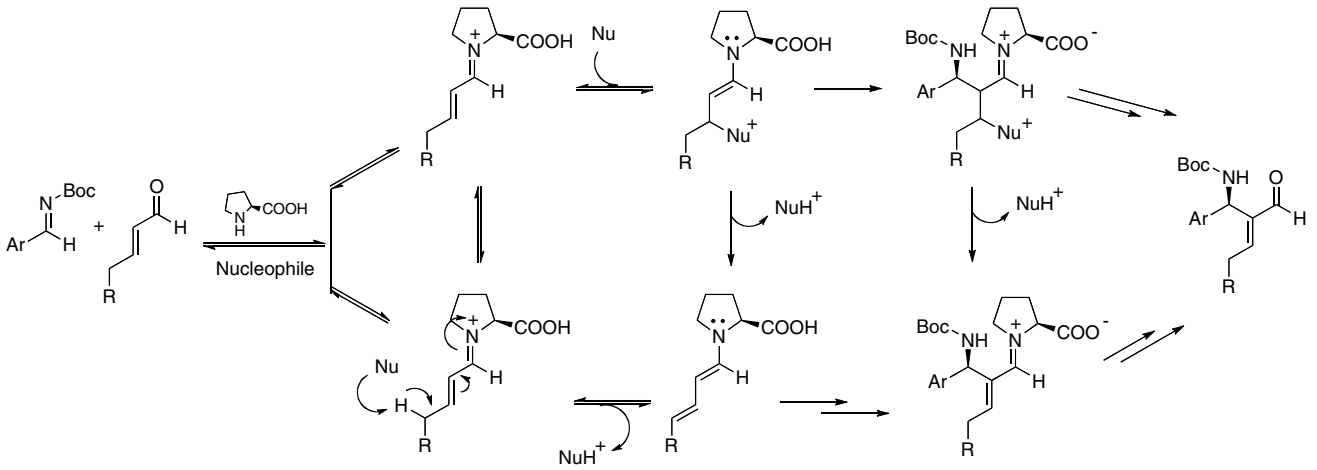


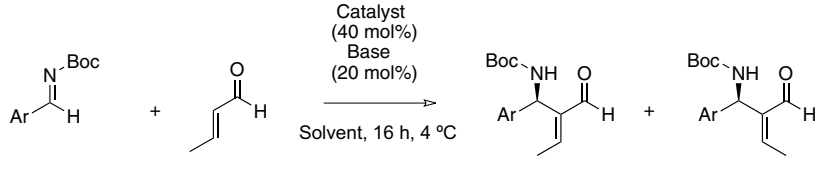
Scheme 1. Suggested activation pathways for the enantioselective aza-MBH type reaction between enals and Boc imines catalyzed by a combination of proline and an organic nucleophile.

protected imines which gives the corresponding β-amino aldehydes in good yields with 97–99% ee.

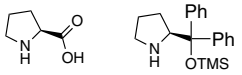
In an initial catalyst, organic base and solvent screen, we found that the combination of (*S*)-proline **4** and 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed the reaction between phenyl *N*-Boc-imine **1a** (0.25 mmol) and buten-2-al **2a** (0.5 mmol) with high chemoselectivity to give the corresponding β-amino aldehydes **3a** in moderate yield with excellent ee (Table 1).

The use of a nucleophilic organic amine base was essential and of the screened bases only DABCO enabled the formation of **3a**. The combination of (*S*)-proline and DABCO was effective in polar aprotic solvents such as DMF, CH_3CN and *N*-methylpyrrolidinone (NMP).

Table 1. Screening of the enantioselective aza-MBH reaction between **1a** and **2a**[a]



1a: Ar = C_6H_5 **2a** (2 equiv) *E*-**3a** *Z*-**3a**



4 **5**

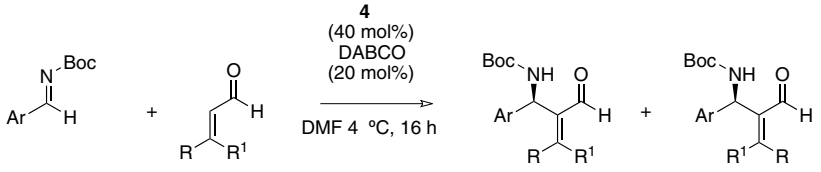
Entry	Catalyst	Base	Solvent	Yield[b] (%)	*E*/*Z*[c]	ee[d] (%)
1	**4**	None	DMF	Traces	n.d.	n.d.
2	**4**	Et_3N[e]	DMF	Traces	n.d.	n.d.
3	**4**	Imidazole[e]	DMF	Traces	n.d.	n.d.
4	**4**	DABCO	DMF	45	4:1	99
5	**4**	DABCO[f]	DMF	22	4:1	97
6	**4**	DABCO[g]	DMF	21	3:1	99
7	**5**	DABCO	DMF	Traces	n.d.	n.d.
8	**4**	DABCO	NMP	20	3:1	95
9	**4**	DABCO	CH_3CN	39	2:3	99
10	**4**	DABCO	CH_2Cl_2	23	5:1	99
11	**4**	DABCO	Toluene	Traces	n.d.	n.d.

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), buten-2-al **2a** (0.50 mmol), chiral pyrrolidine (40 mol %) and DABCO (20 mol %) in 1.0 mL of solvent was stirred at 4 °C under the conditions displayed in the Table.
[b] Isolated yield *E*-**3a** and *Z*-**3a**.
[c] *E*/*Z* ratio determined by ^1H NMR.
[d] Determined by chiral-phase HPLC analysis.
[e] Reaction performed with 1 equiv of base.
[f] Reaction performed with 20 mol % of proline **4**.
[g] Reaction performed with 30 mol % of DABCO. n.d. = not determined. NMP = *N*-methylpyrrolidinone.

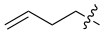
For example, the combination of (*S*)-proline and DABCO catalyzed the formation of β-amino aldehyde **3a** in 45% yield with 99% ee in DMF (entry 4). The *E*/*Z* ratio was 4:1 as determined by NMR analysis of the crude reaction mixture. The highest yield and enantioselectivity were obtained when DMF was used as the solvent and 20 mol % of DABCO was used as the amine nucleophile or base. Encouraged by these promising results, we decided to investigate the catalytic asymmetric aza-MBH-type reaction between various *N*-Boc protected imines **1** and different α,β-unsaturated aldehydes **2** with (*S*)-proline as the organocatalyst and DABCO as the organic amine nucleophile (Table 2).[7]

The catalytic aza-MBH type reactions proceeded with excellent chemo- and enantioselectivity and the corresponding β-amino aldehydes **3a**–**f** were obtained in good yields with 97–99% ee. For example, the combination of (*S*)-proline and DABCO catalyzed the asymmetric reaction between imine **1a** and isovaleraldehyde with high chemoselectivity and Boc-protected β-amino aldehyde **3d** was isolated in 61% yield and 97% ee (entry 4). Moreover, the reaction tolerated α,β-unsaturated aldehyde donors with a terminal olefin functionality (entry 3). The *E*/*Z* ratio increased with the length of the enal donor and the corresponding β-amino aldehydes **3b** and **3c** were formed in *E*/*Z* ratios of 9:1 and 8:1, respectively. In addition, the catalytic aza-MBH reactions between 4-substituted *N*-Boc protected imines and buten-2-al **2a** gave the corresponding β-amino aldehydes **3e** and **3f** in 9:1 *E*/*Z* ratio and 99% ees, respectively (entries 5 and 6). The β-amino aldehydes **3** were converted to the corresponding γ-amino alcohols **6** by reduction with $NaBH_4$ (Scheme 2).

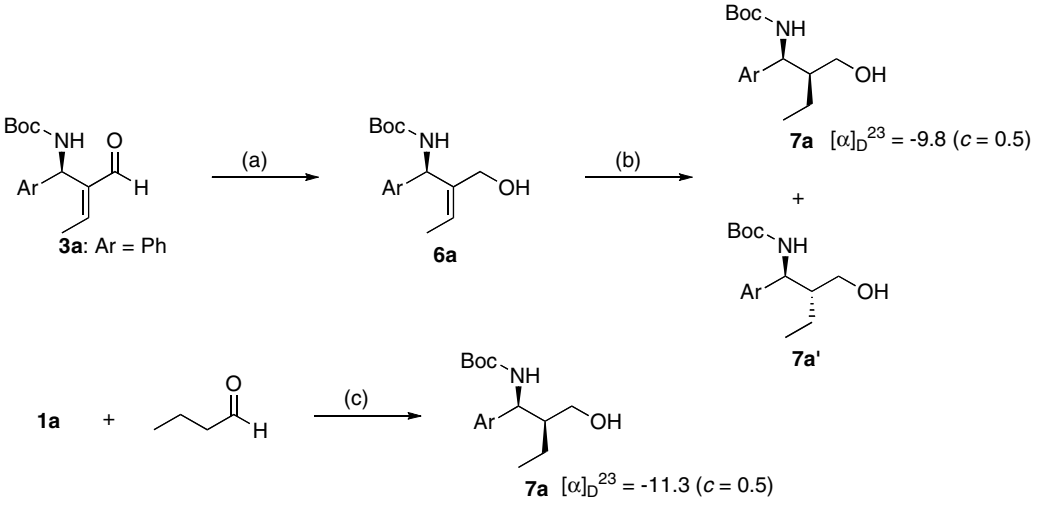
Table 2. Direct organocatalytic asymmetric aza-MBH type reactions between *N*-Boc protected imines **1** and, -unsaturated aldehydes **2**[a]



1 **2** (2 equiv) *E*-**3** *Z*-**3**

Entry	Ar	R	R^1	Product	Yield[b] (%)	*E*/*Z*[c]	ee[d] (%)
1	Ph	Me	H	**3a**	45	4:1	99
2	Ph	Et	H	**3b**	51	9:1	99
3	Ph		H	**3c**	47	8:1	>99
4	Ph	Me	Me	**3d**	61	—	97
5	4-ClC_6H_4	Et	H	**3e**	53	9:1	99
6	4-$MeOC_6H_4$	Et	H	**3f**	56	9:1	99

[a] Experimental conditions: A mixture of **1** (0.25 mmol), enal **2** (0.50 mmol), (*S*)-proline (40 mol %) and DABCO (20 mol %) in 1.0 mL of DMF was stirred at 4 °C.
[b] Isolated yield of *E*/*Z*-**3**.
[c] *E*/*Z* ratio determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analyses.



Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, −20 °C, 83%; (b) Pd/C (10% w/w), H_2, MeOH, rt, 85%; (c) (i) (*S*)-proline (20 mol %), DMF, 4 °C, 18 h; (ii) $NaBH_4$, MeOH, 0 °C, 5 min, 85%.

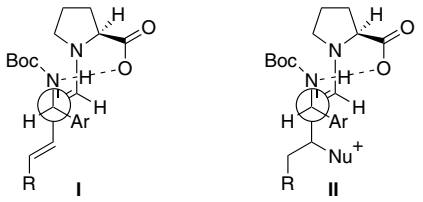


Figure 1. Suggested transition state models evoked to account for the enantioselectivity of the (*S*)-proline catalyzed aza-MBH type reactions.

For example, aldehyde **3a** was reduced to unsaturated γ-amino alcohol **6a** in high yield. Subsequent palladium-catalyzed hydrogenation of the olefin gave the corresponding γ-amino alcohols **7a** and **7a′** in 57% and 28% yields, respectively.[8] Comparison with the γ-amino alcohol **7a** ($[\alpha]_D^{23}$ −11.3 (*c* 0.5)) derived by a one-pot (*S*)-proline catalyzed Mannich/reduction reaction sequence[6a] between imine **2a** and butanol established that the absolute stereochemistry of **7a** derived by the catalytic aza-MBH reaction ($[\alpha]_D^{23}$ −9.8 (*c* 0.5)) was (2*S*,3*S*). On the basis of the absolute configuration, we propose transition-state models **I** and/or **II** to account for the enantioselectivity of the amino acid catalyzed formation of β-amino aldehydes **3** (Fig. 1). Hence, the (*S*)-proline derivative forms a chiral enamine with the enal which is attacked by the *N*-Boc protected imine from its *Si*-face providing (3*S*)-β-amino aldehyde derivatives. In comparison, *Si*-facial attack also occurs in similar transition states of previously reported proline-catalyzed Mannich-type reactions with Boc imines.[6]

The role of DABCO is still under investigation. It could either work as a base enabling the formation of a conjugated chiral enamine and/or act as a nucleophile to generate a chiral enamine intermediate according to Scheme 1.

In summary, we have reported a simple, highly enantioselective, organocatalytic asymmetric aza MBH-type reaction. The combined proline and DABCO catalyzed reactions between aryl Boc imines and unmodified α,β-unsaturated aldehydes proceeded with high chemo- and enantioselectivity to furnish β-amino aldehydes with an α-alkylidene group in good yields with 93–99% ee. Further elaboration of this novel transformation, its synthetic application and mechanistic studies are ongoing in our laboratory.

Acknowledgement

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7. *Typical experimental procedure for the organocatalytic aza-MBH reactions:* To a stirred solution of *S*-proline (0.1 mmol, 40 mol %), DABCO (0.05 mmol, 20%) and Boc imine **1** (0.25 mmol) in DMF (1.0 mL) at 4 °C, was added α,β-unsaturated aldehyde **2** (0.5 mmol). The reaction was vigorously stirred for 16 h at the same temperature. Next, the crude product was purified by silica gel column chromatography (pentane–EtOAc-mixtures) to give the corresponding aldehyde **3**. Compound **3a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.37$ (s, 1H), 7.30–7.23 (m, 5H), 6.79 (q, $J = 7.2$ Hz, 1H), 6.19 (d, $J = 9.2$ Hz, 1H), 5.91 (d, $J = 9.6$ Hz, 1H), 2.19 (d, $J = 7.2$ Hz, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 195.2, 152.3, 143.2, 140.3, 128.7, 127.3, 126.1, 79.8, 50.4, 28.6, 15.4. $[\alpha]_D^{23}$ +68.0 (*c* 1.0, $CHCl_3$). HRMS (ESI): Calcd for $[M+Na]^+$ ($C_{16}H_{21}O_3NNa$) requires *m*/*z* 298.1414. Found: 298.1420. The enantiomeric excess was determined by HPLC with an OD–H column. (*n*-hexane–*i*-PrOH = 99:1, $\lambda = 230$ nm), 0.5 mL/min; t_R = major enantiomer 23.0 min, minor enantiomer 25.8 min.
8. *Asymmetric synthesis of alcohol* **7a**: To a stirred solution of **3a** (0.25 mmol) in MeOH (2.0 mL) at −20 °C was added an excess of $NaBH_4$ in small portions. The reaction was vigorously stirred at the same temperature for 5 min and then poured into a mixture of EtOAc (20 mL) and aqueous NH_4Cl (1 M, 2 mL), which was stirred for 5 min followed by addition of Na_2SO_4 to dry the organic solvent. Next, the Na_2SO_4 was removed by filtration and the crude product was purified by silica gel column chromatography (pentane–EtOAc-mixtures) to give the α,®-unsaturated alcohol

6a in 83% yield. Next, to a solution of alcohol **6a** (0.2 mmol) in MeOH (2 mL), Pd/C (10% w/w) was added and the mixture was stirred under a H_2 atmosphere (70 psi) overnight. The reaction mixture was filtered through Celite and the crude product was purified by silica gel column chromatography (pentane–EtOAc-mixtures) to give the corresponding alcohols **7a** and **7a′** in 57% and 28% yields, respectively. Compound **7a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.11 (m, 5H), 5.37 (br s, 1H), 5.07 (br s, 1H), 3.68 (br d, $J = 10.4$ Hz, 1H), 3.38 (t, $J = 10.0$ Hz, 1H) 1.96 (br s, 1H), 1.44 (s, 9H), 1.30–0.92 (m, 2H), 0.86 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 156.6, 140.7, 128.5, 127.0, 126.7, 80.1, 62.9, 54.4, 47.8, 28.5, 19.0, 12.2. $[\alpha]_D^{23}$ −9.8 (*c* 0.5, $CHCl_3$). HRMS (ESI): Calcd for $[M+Na]^+$ ($C_{16}H_{25}O_3NNa$) requires *m*/*z* 302.1727. Found: 302.1726.