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One-pot highly enantioselective catalytic Mannich-type reactions between aldehydes and stable α-amido sulfones: asymmetric synthesis of β-amino aldehydes and β-amino acids

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ABSTRACT

A highly enantioselective catalytic route to carbamate- and benzoate-protected β-amino aldehydes and β-amino acids is presented. The amino acid-catalyzed one-pot asymmetric reaction between unmodified aldehydes and α-amido sulfones gives the corresponding β-amino compounds with up to 95:5 dr and 97–>99% ee.

The Mannich reaction and similar transformations involving nucleophilic addition to the C=N bond of imine derivatives are of significant importance in organic synthesis.[1] The resulting Mannich bases are valuable amine-containing compounds utilized as building blocks for pharmaceutically valuable compounds and natural products.[2] In the arena of asymmetric catalysis,[3] the first successful examples of catalytic asymmetric additions of enolates to imines led to the beginning of the rapidly growing area of catalytic indirect Mannich-type reactions.[4] Direct catalytic asymmetric Mannich-type reactions have also been developed using heterodimetallic complexes and di-nuclear zinc organometallic complexes, copper(II) bisoxazoline (BOX) complexes and Pd-complexes as catalysts, among others.[5–7] In addition, organocatalytic direct enantioselective Mannich-type reactions have been developed.[3c,3d] These asymmetric transformations are catalyzed by chiral Brønsted acids,[8] cinchona alkaloids,[9] proline and its derivatives,[10] peptide derivatives[11] and acyclic amino acids.[12]

In this context, amino acids and their derivatives have been employed as catalysts for the addition of aldehydes to *N*-*p*-methoxyphenyl (PMP) imines[10,12] and *N*-carbamoyl imines such as *N*-Boc-imines,[13] *N*-Cbz-imines[14] and *N*-(phenylmethylene)benzamides.[15] However, because of their inherent high reactivity, *N*-carbamoyl imines are rather sensitive towards moisture and air, and their preparation is rather troublesome and their storage requires precautions. A possible and economic route to avoid these drawbacks is the in situ generation of the imine through the use of precursors with a good leaving group at the carbon α to the nitrogen atom. For example, α-amido sulfones **1** are useful and highly suitable precursors as they are bench-stable solids and can be obtained readily by condensation of a carbamate and a sodium aryl sulfinate with the desired aldehyde.[16] The α-amido sulfones **1** furnish the corresponding moisture-sensitive imines when treated with a base. In this context, they have been used in reactions employing metal-stabilized enolates,[17] and the in situ formation of the imine has also been used in phase-transfer-catalyzed reactions in combination with an inorganic base.[18] Despite the considerable benefits of this approach, which combines both operational simplicity and high selectivity via small molecule catalysis with the convenience of the employment of α-amido sulfones **1**, it has, to the best of our knowledge, not been applied to Mannich-type reactions employing natural amino acids as catalysts and to *syn*-diastereoselective transformations.[19] Based on this and our previous experience,[13b,15] we decided to investigate this one-pot strategy for the catalytic enantioselective Mannich-type addition of aldehydes to *N*-carbamoyl imines derived in situ from α-amido sulfones **1** using natural amino acids as catalysts. Herein, we present the successful application of this approach to the one-pot, highly enantioselective amino acid-catalyzed synthesis of β-amino aldehydes and β-amino acids with up to 95:5 dr and 97–>99% ee.

In an initial experiment, we found that (*S*)-proline catalyzed the reaction between α-amido sulfone **1a** (0.25 mmol) and propanal **2a** (0.75 mmol) via the intermediacy of imine **4a** with high chemoselectivity to give the corresponding β-amino aldehydes **3a** and **3a′** in high yields in a 50:50 ratio (Eq. 1). To our delight, the enantioselectivity was high (96% ee, *syn*-diastereoisomer; 94% ee, *anti*-isomer).

In order to improve the diastereoisomeric ratio of **3a,** we screened several inorganic bases in combination with proline as the catalyst (Table 1).[20]

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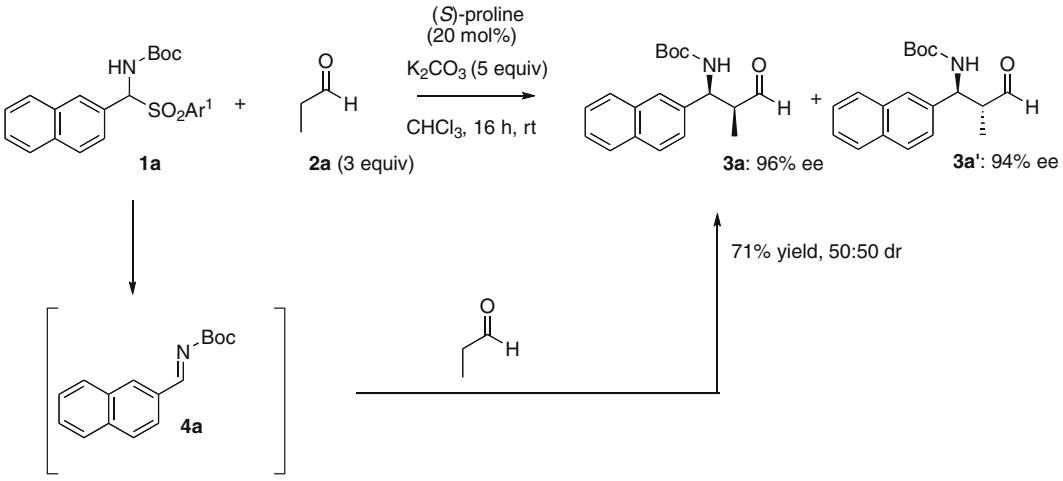
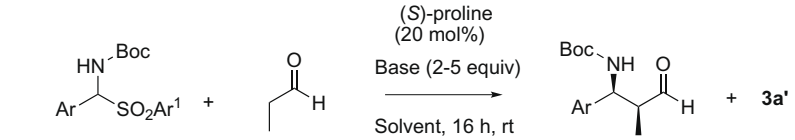


(1)

Several of the inorganic bases investigated in combination with (*S*)-proline enabled the formation of **3a** with high enantioselectivity (entries 1, 2, 4 and 5). The use of NaF and KF enabled the asymmetric assembly of **3a** from **1a** with moderate to high diastereoselectivity (entries 4 and 5).[21] The choice of $CHCl_3$ as a solvent gave the highest stereoselectivity. For example, the combination of KF and proline in $CHCl_3$ gave an 84% combined yield of the two diastereoisomers with 91:9 dr (*syn*/*anti*) and >99% ee (entry 5). Encouraged by these results, we decided to investigate the catalytic one-pot asymmetric reaction between various α-amido sulfones **1** and different aldehydes **2** with KF as the base and (*S*)-proline as the organocatalyst (Table 2).[22]

The one-pot enantioselective reactions proceeded with excellent chemo- and enantioselectivity and the corresponding *N*-Boc-, Cbz- and benzoyl-protected β-aminoaldehydes **3a**–**3j** were obtained in moderate to high yields with 97–99% ee. For example, (*S*)-proline catalyzed the asymmetric reaction between α-amido sulfone **1c** and propanal with high chemoselectivity and Boc-protected β-amino aldehyde **3c** was isolated in 92% yield predominantly as the *syn*-diastereomer with >99% ee (entry 3). The opposite enantiomers *ent*-**3a** and *ent*-**3b** with >99 and 99% ee, respectively, were prepared by using (*R*)-proline as the catalyst. Moreover, the reaction is operationally simple and readily scaled up. For example, to a mixture of **1b** (4 mmol, 1.44 g) in $CHCl_3$ (20 mL) were added KF (7.2 mmol, 1.8 equiv), aldehyde **2a** (12 mmol, 3 equiv) and (*S*)-proline (0.8 mmol, 20 mol %) at room temperature. After stirring for 16 h the reaction was quenched by the addition of water (20 mL). The aqueous layer was extracted with $CHCl_3$ (40 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Silica gel column chromatography (pentane–EtOAc mixtures) furnished the corresponding aldehyde **3b** in 70% yield with 10:1 dr and 99% ee. The β-amino aldehydes **3** were also converted into the corresponding β-amino acid **5b**[23] in high yield or γ-amino alcohol **6** by oxidation and reduction, respectively (Scheme 1). Comparison with the literature established that the absolute stereochemistry of **5b** {$[\alpha]_D^{25}$ −15.2 (*c* 1.0), lit. $[\alpha]_D^{25}$ −15.2 (*c* 1.0)[13b]} was (2*S*,3*R*).

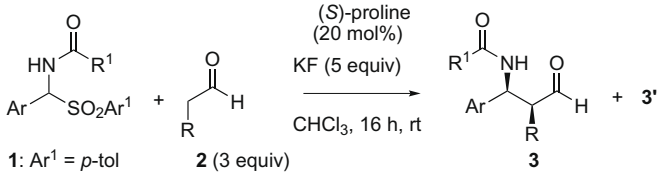
Table 1
Screening of inorganic bases for the enantioselective reactions between **1a** and **2a**[a]



Entry	Base	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	K_2CO_3[e]	$CHCl_3$	71	50:50	96 (94)[g]
2	K_3PO_4[e]	$CHCl_3$	76	50:50	87 (85)[g]
3	Cs_2CO_3[e]	$CHCl_3$	Trace	—	—
4	NaF[e]	$CHCl_3$	14	67:33	99 (99)[g]
5	KF[e]	$CHCl_3$	84	91:9	>99 (n.d.)[g]
6	KF[f]	$CHCl_3$	45	93:7	97 (n.d.)[g]
7	KF[e]	DMF	72	50:50	36 (36)[g]
8	KF[e]	CH_2Cl_2	67	83:17	99 (99)[g]

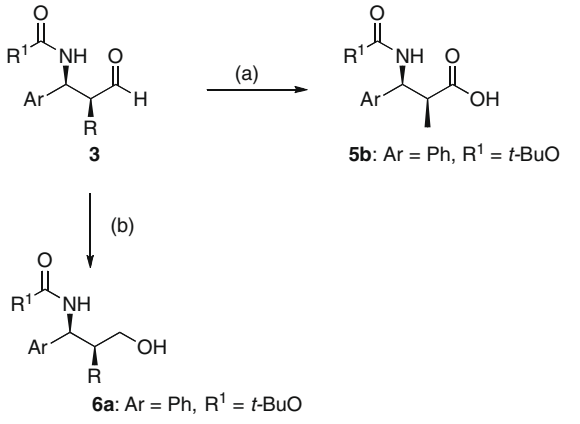
[a] Experimental conditions: a mixture of **1a** (0.25 mmol), propanal **2a** (0.75 mmol), base and catalyst (20 mol %) in solvent (1.25 mL) was stirred under the conditions displayed in the Table.
[b] Combined isolated yield of pure compounds **3a** and **3a**′.
[c] Determined by ^1H NMR analyses of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis of alcohol **6a** obtained by reduction of isolated **3a**.
[e] 5 equiv of base was used.
[f] 2.5 equiv of base was used.
[g] ee of the *anti*-isomer.

Table 2
Direct organocatalytic asymmetric Mannich reactions between α-amido sulfones **1** and aldehydes **2**[a]



Entry	Ar	R	R^1	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	Naphth	Me	*t*-BuO	**3a**	84	91:9	>99[e]
2	Ph	Me	*t*-BuO	**3b**	67	91:9	99
3	4-ClC_6H_4	Me	*t*-BuO	**3c**	92	90:10	>99
4	4-$MeOC_6H_4$	Me	*t*-BuO	**3d**	90	89:11	99
5	4-MeC6H4	Me	*t*-BuO	**3e**	72	95:5	99
6	Ph	Me	BnO	**3f**	83	80:20	99[e]
7	Ph	Me	Ph	**3g**	53	67:33	97
8	Naphth	Me	BnO	**3h**	50	75:25	98
9	Ph	Et	*t*-BuO	**3i**	76	91:9	99
10	Ph	*i*Pr	*t*-BuO	**3j**	47	95:5	99

[a] Experimental conditions: a mixture of **1** (0.25 mmol), aldehyde **2** (0.75 mmol), KF (1.25 mmol) and (*S*)-proline (20 mol %) in $CHCl_3$ (1.25 mL) was stirred at rt for 16 h.
[b] Isolated combined yield of pure compound **3** and **3′**.
[c] *Syn*/*anti* ratio determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analysis of pure aldehyde **3**.
[e] Determined by chiral-phase HPLC analysis of alcohol **6** obtained by reduction of isolated **3**. The ee of the minor diastereoisomer is not shown.



Scheme 1. Reagents: ClO_2, *iso*-butene, KH_2PO_4, *t*-BuOH/H_2O (5:1), 72%. (b) $NaBH_4$, MeOH, 0 °C, 90%.

In summary, we have reported a highly enantioselective catalytic route to carbamate- and benzoate-protected β-amino aldehydes and β-amino acids. The one-pot organocatalytic reactions between α-amido sulfones and unmodified aldehydes proceeded with high chemo- and enantioselectivity to furnish β-amino aldehydes in high yields with 97–>99% ee. Further elaboration of this one-pot transformation and its synthetic application are ongoing in our laboratory. For example, this protocol should also be applicable to other C–C bond-forming reactions such as the Aza–Morita–Baylis–Hillman-type reaction.[13e]

Acknowledgements

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19. During our investigations, an elegant one-pot *anti*-selective synthesis of **3b′** and **3f′** which requires 4 day reactions was reported, see Ref. 13f.
20. *Typical experimental procedure*: To a mixture of **1a** (0.25 mmol) in solvent (1.25 mL) were added base, aldehyde **2a** (0.75 mmol) and (*S*)-proline (20 mol %) at room temperature. After stirring for 16 h, the reaction was quenched by the addition of brine (5 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed under reduced pressure. Silica gel column chromatography of the residue (pentane–EtOAc mixtures or toluene–EtOAc mixtures) furnished the corresponding aldehyde **3a**. $[\alpha]_D^{25}$ −17.8 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 9.75 (s, 1H), 7.85–7.81 (m, 3H), 7.70 (s, 1H), 7.52–7.46 (m, 2H), 7.38–7.36 (m, 1H), 5.35 (br s, 1H), 5.24 (br s, 1H), 2.97 (s, 1H), 1.43 (s, 9H), 1.10 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.1, 155.3, 132.9, 129.2, 128.8, 128.0, 127.7, 126.5, 126.2, 125.6, 124.7, 122.9, 79.7, 51.6, 28.4, 28.3, 9.4; HRMS (ESI) ($C_{19}H_{23}NO_3Na$) $[M+Na]^+$ requires *m*/*z* 336.1570, found *m*/*z* 336.1558. For the ee determination, the aldehyde **3a** was reduced in situ by diluting the reaction mixture with MeOH (1 mL) and adding excess $NaBH_4$ at 0 °C. After stirring for 10 min, the reaction mixture was transferred to a stirred mixture of EtOAc (20 mL) and 2 M HCl (3 mL) at 0 °C. Next, Na_2SO_4 was added, the solution was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (pentane–EtOAc, 2:1) to give pure alcohol **6a**. $[\alpha]_D^{25}$ −48.3 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84–7.81 (m, 3H), 7.68 (s, 1H), 7.51–7.39 (m, 3H), 5.41 (d, *J* = 9.6 Hz, 1H), 5.24 (d, *J* = 7.2 Hz, 1H), 3.54 (br s, 1H), 3.42 (t, *J* = 10.4 Hz, 1H), 3.33 (br s, 1H), 2.32–2.25 (m, 1H), 1.48 (s, 9H), 0.72 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 138.1, 133.4, 132.6, 128.3, 127.9, 127.7, 126.4, 126.0, 125.1, 123.7, 80.3, 65.2, 54.4, 41.2, 28.5, 10.8; The ee of the product was determined by chiral HPLC analysis (Chiralpak ODH column, *n*-hexane-2-propanol = 95/5, 1.0 mL/min, 210 nm, t_R (minor) = 13.9 min, t_R (major) = 17.1 min; HRMS (ESI) ($C_{19}H_{25}NO_3Na$) $[M+Na]^+$ requires *m*/*z* 338.1727, found *m*/*z* 338.1713.
21. It is important to fine-tune the number of equivalents of KF in order to achieve the optimum diastereoselectivity.
22. *Typical experimental procedure*: To a mixture of **1** (0.25 mmol) in $CHCl_3$ (1.25 mL) were added KF (5 equiv), aldehyde **2** (0.75 mmol) and (*S*)-proline (20 mol %) at room temperature. After stirring for 16 h, the reaction was quenched by the addition of brine (5 mL) and extracted with EtOAc (3 × 25 mL). Next, the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography (pentane–EtOAc mixtures or toluene–EtOAc mixtures) furnished the corresponding aldehydes **3**. Data for **3c**: ^1H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 5.22–5.04 (m, 2H), 2.86–2.78 (m, 1H), 1.40 (s, 9H), 1.06 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 155.3, 129.1, 128.3, 79.8, 51.5, 36.7, 28.5, 9.6; $[\alpha]_D^{25}$ −3.6 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD column with hexane-*i*-PrOH (98:2) as the eluent. Flow: 0.5 mL/min; minor isomer: t_R = 18.8 min; major isomer: t_R = 28.8 min; HRMS (ESI): calcd for ($C_{15}H_{20}NO_3Cl$) $[M+Na]^+$ requires *m*/*z* 320.1024, found 320.1035.
23. The β-amino aldehyde **3b** (2.1 mmol) was added to *t*-BuOH/water (5:1, 24 mL), followed by addition of *iso*-butene (9 mmol), KH_2PO_4 (3.2 mmol) and $NaClO_2$ (7.2 mmol). After stirring for 24 h, the reaction mixture was quenched with brine (25 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane–EtOAc mixtures) to afford pure acid **5b** (72%). The spectral data were in accordance with the literature, see Ref. 13b.