Organocatalytic asymmetric 5-hydroxyisoxazolidine synthesis: A highly enantioselective route to β-amino acids†

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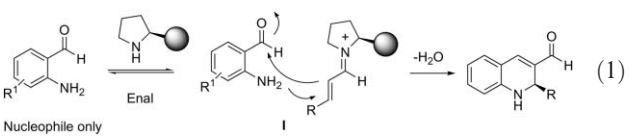
The highly chemo- and enantioselective organocatalytic tandem reaction between *N*-protected hydroxyl amines and α,β-unsaturated aldehydes is presented; the reaction provides access to 5-hydroxyisoxazolidines and β-amino acids in high yields and with 90–99% ee.

5-Hydroxyisoxazolidines and 5-isoxazolidinones are important chiral building blocks[1] that are readily converted into the corresponding amino alcohols and β-amino acids.[2] Thus, asymmetric methods have been developed for their preparation.[1] For instance, optically active 5-acetoxyisoxazolines can be converted in two steps to the corresponding isoxazolidinones.[1d–e] Moreover, utilization of chiral auxiliaries enables the asymmetric synthesis of 5-isoxazolidinones.[1e–f] Recently, 5-isoxazolidinones were prepared by the Lewis acid-catalyzed enantioselective conjugate addition of hydroxyl amines to α,β-unsaturated amide derivatives.[1b–c,3]

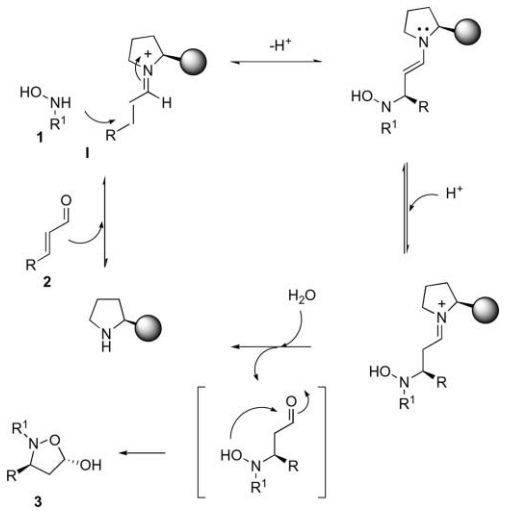
In the field of organocatalysis, amine-catalyzed reactions that involve catalytic domino, tandem or cascade reaction pathways have recently been developed.[4–6] In this context, we most recently found that chiral pyrrolidines catalyze the formation of 1,2-dihydroquinoline derivatives *via* an asymmetric domino amine-conjugate/aldol reaction pathway between 2-aminobenzaldehyde and enals (eqn. (1)).[7]



(1)

Despite all the chemoselectivity issues that could arise in the amine conjugate addition step, such as non-productive imine formation and racemic background reactions, the subsequent intramolecular aldol addition kinetically controls the desired reaction pathway and pushes the equilibrium towards product formation. Based on these lessons and retrosynthetic analysis, we envisioned that the chiral amine-catalyzed reaction between *N*-protected hydroxylamines and enals would be a simple asymmetric entry route to 5-hydroxyisoxazolidines, where subsequent tandem intramolecular hemiacetal formation is an important driving force for product formation (Scheme 1).[8]

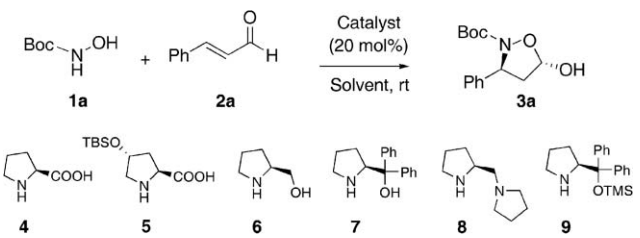
Herein, we present a highly enantioselective catalytic route to the synthesis of 5-hydroxyisoxazolidines (75–94% yield, 90–99% ee), which are converted in one-pot to 5-isoxazolidinones (up to 99% ee) or in two steps to β-amino acids (up to 99% ee).



Scheme 1 A plausible reaction pathway for a chiral amine-catalyzed enantioselective formation of 5-hydroxyisoxazolidines.

In an initial catalyst screen for the reaction between *N*-Boc-protected hydroxylamine **1a** (0.30 mmol) and cinnamic aldehyde

Table 1 Catalyst screen for the reaction between **1a** and **2a**



Entry	Catalyst	Solvent	Time/h	Yield (%)[a]	ee (%)[b]
1	**4**	DMF	13	0	—
2	**5**	DMF	14	0	—
3	**6**	$CHCl_3$	13	39	−40
4	**7**	$CHCl_3$	13	26	9
5	**8**	$CHCl_3$	13	70	10
6	**9**	$CHCl_3$	3	90	99
7	**9**	CH_2Cl_2	3	88	99
8	**9**	CH_3CN	3	85	84
9	**9**	DMF	3	60	89
10	**9**	EtOH	3	70	77
11	**9**	Toluene	3	71	97

[a] Isolated yield of the pure product compound **3a**. [b] Determined by chiral-phase HPLC analyses.

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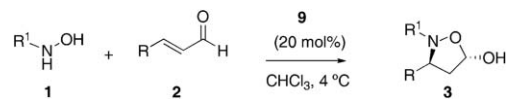
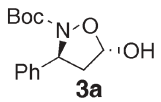
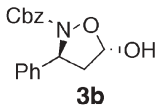
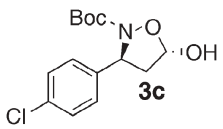
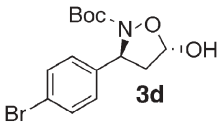
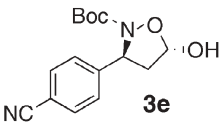
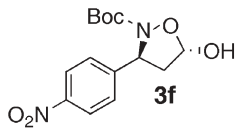
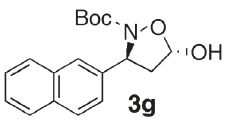
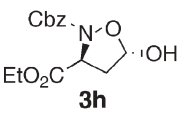
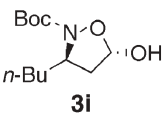
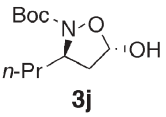
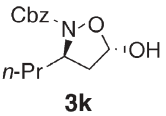
Table 2 Scope of the organocatalytic tandem reaction



1 2 3

Entry	R	R^1	Product	Time/h	Yield (%)[a]	ee (%)[b]
1	Ph	Boc	 **3a**	3	80	99
2	Ph	Cbz	 **3b**	3	94	99
3	4-ClC_6H_4	Boc	 **3c**	3	89	90
4	4-BrC_6H_4	Boc	 **3d**	3	80	97
5	4-CNC_6H_4	Boc	 **3e**	3	90	97
6	4-$NO_2C_6H_4$	Boc	 **3f**	3	75	98
7	Naphthyl	Boc	 **3g**	3	77	95
8	CO_2Et	Cbz	 **3h**	16	85	97
9	*n*-Bu	Boc	 **3i**	16	94	91
10	*n*-Pr	Boc	 **3j**	16	93	91
11	*n*-Pr	Cbz	 **3k**	16	92	95

[a] Isolated yield of the pure product **3** after silica-gel chromatography. [b] Determined by chiral-phase HPLC or GC analyses.

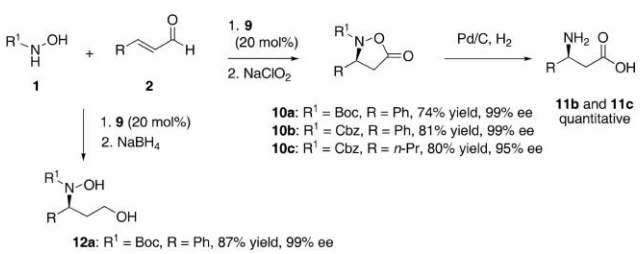
2a (0.25 mmol), we found that simple chiral pyrrolidines such as **6–9** catalyzed the chemoselective formation of 5-hydroxyisoxazolidine **3a** (Table 1). However, (*S*)-proline was not a catalyst for this transformation. To our delight, protected diarylprolinol **9**[9] catalyzed the formation of **3a** with high efficiency and selectivity under various reaction conditions (Table 1, entries 6–11). The highest enantioselectivity was achieved when $CHCl_3$ and toluene were used as the solvent.

Thus, we decided to investigate the scope of the catalytic asymmetric tandem reaction using $CHCl_3$ as the solvent (Table 2).

The organocatalytic enantioselective tandem reactions were highly chemo- and enantioselective at 4 °C, and the corresponding 5-hydroxyisoxazolidines **3** were isolated in 75–94% yield with a 90–99% ee. Moreover, the reactions with *N*-Cbz-protected hydroxylamine **1b** gave the corresponding products **3** in 85–94% yield and in 95–99% ee (Table 2, entries 2, 8 and 11). The tandem reactions with α,β-unsaturated aliphatic acceptor aldehydes **2** (Table 2, entries 9–11) were slower compared to the aryl substituted enals **2** (Table 2, entries 1–7). In addition, the organocatalytic reaction was readily scaled up, giving access to a variety of 5-hydroxyisoxazolidines. Next, a one-pot protocol for the asymmetric synthesis of 5-oxazolidinones **10** was developed (Scheme 2).

Thus, *in situ* oxidation of 5-hydroxyisoxazilidones **3** with $NaClO_2$ gave the corresponding *N*-protected 5-oxazilidinones **10** in high overall yield with 95–99% ee. Moreover, *in situ* reduction with $NaBH_4$ gave direct access to γ-amino alcohols **12**. Notably, hydrogenolysis of the isolated oxazolidinones **10b** and **10c** with 10% Pd/C led to efficient N–O bond cleavage and removal of the Cbz group to quantitatively give the corresponding β-amino acids **11**. Comparison with the literature revealed that the absolute configuration of **11b** at C3 was *S* ($[\alpha]_D^{25} = -6.9$ (*c* 1 in H_2O); lit. $[\alpha]_D^{25} = -6.9$ (*c* 0.8 in H_2O)[10]). Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of **9** leads to stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the amino group of **1**. Next, the released *N*-hydroxy-β-aminoaldehyde intermediate undergoes a favored hemiacetal formation to give 5-hydroxyisoxazolidine **3**. The importance of hemiacetal formation in pushing the equilibrium towards product formation in the presence of catalyst **9** was established by the fact that O-protected hydroxylamines **1** did not form any conjugate addition products with the cinnamic aldehydes **2** under our reaction conditions.

In summary, we report a highly chemo- and enantioselective organocatalytic synthesis of 5-hydroxyisoxazolidines and 5-oxazolidinones, which are formed in high yield with 90–99% ee. Moreover, the organocatalytic tandem reaction represents a



Scheme 2 One-pot organocatalytic enantioselective syntheses of 5-oxazolidinones **10**, amino alcohol **12a** and β-amino acids **11**.

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versatile asymmetric entry point to different β-amino acid and γ-amino alcohol derivatives. Mechanistic studies and synthetic applications of this transformation, as well as the development of other enantioselective tandem reactions, are ongoing in our laboratory.

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