Catalytic Enantioselective 5-Hydroxyisoxazolidine Synthesis: An Asymmetric Entry to β-Amino Acids

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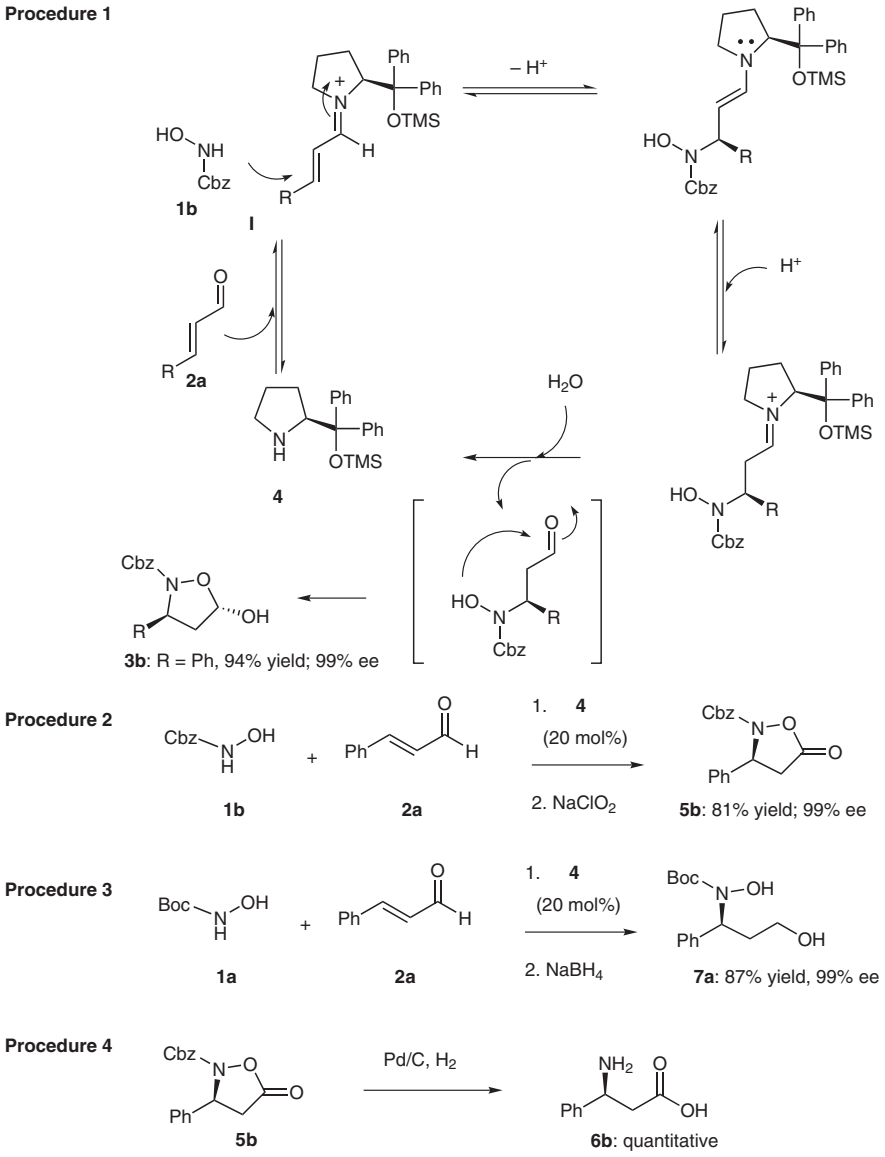
Abstract: The highly chemo- and enantioselective organocatalytic tandem reaction between *N*-carbamate-protected hydroxylamines and α,β-unsaturated aldehydes is presented. The reaction represents a unique entry for the asymmetric synthesis of 5-hydroxyisoxazolidines, oxazolidin-5-ones or γ-hydroxyamino alcohols in high yields and 90–99% ee. A procedure for the conversion of the oxazolidin-5-ones into the corresponding β-amino acids is also described.

Key words: organocatalysis, amination reactions, β-amino acid synthesis, isoxazolidines, asymmetric catalysis



Scheme 1

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Introduction

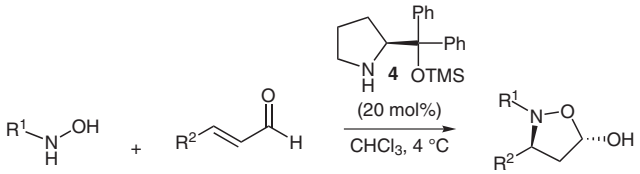
5-Hydroxyisoxazolidines and isoxazolidin-5-ones are important chiral building blocks[1] which are readily converted into the corresponding amino alcohols and β-amino acids.[2] Thus, asymmetric methods have been developed for their preparation.[1] For example, optically active 5-acetoxydihydroisoxazoles can be converted in two steps into the corresponding isoxazolidinones.[1d,e] Moreover, utilization of chiral auxiliaries enables the asymmetric synthesis of isoxazolidin-5-ones.[1e–j] Recently, isoxazolidin-5-ones were prepared by Lewis acid catalyzed enantioselective conjugate addition of hydroxylamines 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 have developed an asymmetric domino amine–conjugate/aldol reaction.[7] Based on these lessons and retrosynthetic analysis, we recently discovered a chiral-amine-catalyzed reaction between N-protected hydroxylamines and enals.[8] The reaction is a simple asymmetric entry to 5-hydroxyisoxazolidines where the subsequent tandem intramolecular hemiacetal formation is an important driving force for product formation (procedure 1, Scheme 1).

Scope and Limitations

The mild reaction conditions for the 2-[diphenyl(trimethylsiloxy)methyl)pyrrolidine (**4**)[9] catalyzed reactions are compatible with several different types of enals. For example, the reaction between cinnamaldehyde (**2a**) and *tert*-butyl *N*-hydroxycarbamate (**1a**) in chloroform afforded the desired product **3a** in 90% yield and 99% ee at room temperature. In fact, the α,β-unsaturated aldehydes **2** reacted with *N*-hydroxycarbamates **1** leading to 5-hydroxyisoxazolidines **3** in excellent yields and enantioselectivities in the presence of chiral amine **4** (Table 1).

Table 1 Scope of the Organocatalytic Tandem Reaction



1 **2** **3**

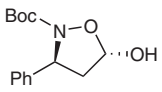
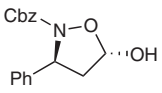
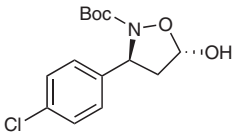
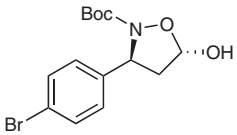
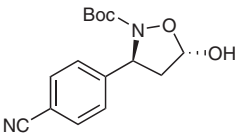
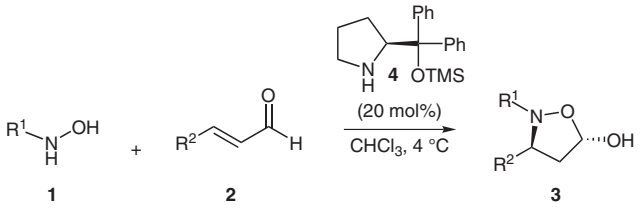
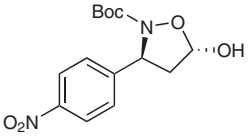
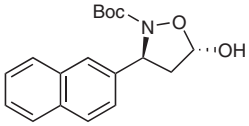
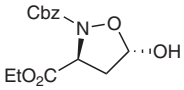
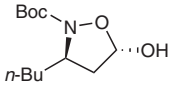
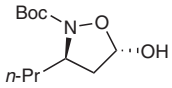
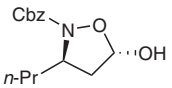
Entry	R^1	R^2	Product	Time (h)	Yield[a] (%)[a]	ee[b] (%)
1	Boc	Ph	 **3a**	3	90[c]	99[c]
2	Cbz	Ph	 **3b**	3	94	99
3	Boc	4-ClC_6H_4	 **3c**	3	89	90
4	Boc	4-BrC_6H_4	 **3d**	3	80	97
5	Boc	4-NCC_6H_4	 **3e**	3	90	97

Table 1 Scope of the Organocatalytic Tandem Reaction (continued)



1 2 3

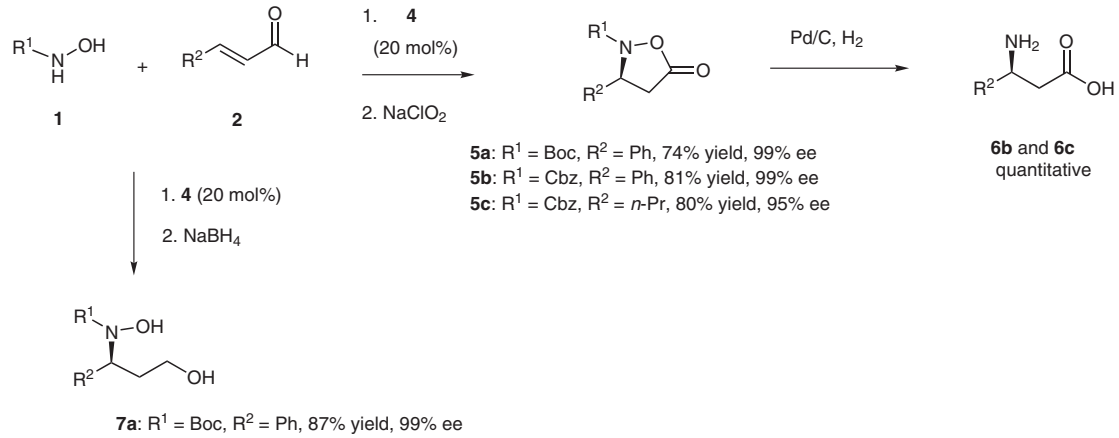
Entry	R^1	R^2	Product	Time (h)	Yield[a] (%)[a]	ee[b] (%)
6	Boc	4-$O_2NC_6H_4$	 **3f**	3	75	98
7	Boc	2-naphthyl	 **3g**	3	77	95
8	Cbz	CO_2Et	 **3h**	16	85	97
9	Boc	*n*-Bu	 **3i**	16	94	91
10	Boc	*n*-Pr	 **3j**	16	93	91
11	Cbz	*n*-Pr	 **3k**	16	92	95

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

Thus, the reactions work well with aliphatic and aromatic α,β-unsaturated aldehydes. Moreover the reaction with *N*-Cbz-protected hydroxylamine **1b** gave the corresponding products **3** in 85–94% yield and 95–99% ee (entries 2, 8 and 11). Moreover, products **3** were formed as single anomers. The tandem reactions with a,b-unsaturated aliphatic acceptor aldehydes **2** (entries 9–11) were slower as compared to the aryl-substituted enals **2** (entries 1–7). In addition, the organocatalytic reaction is readily scaled up and gives access to a variety of 5-hydroxyisoxazolidines. Notably, the pK_a of the hydroxylamine is important since changing the carbamate group of the *N*-hydroxycarbamate **1** to an aryl group led to a complete change of chemoselectivity and 1,3-dipolar addition with the enal.[10]

The chiral-amine-catalyzed reaction between *N*-hydroxycarbamates **1** and enals **2** is also suitable for the one-pot asymmetric synthesis of oxazolidin-5-ones **5** and γ-hydroxyamino alcohols **7** (Scheme 2).

Both aromatic and aliphatic enals are suitable as substrates for these organocatalytic one-pot reactions. Thus, in situ oxidation with sodium chlorite of the 5-hydroxyisoxazilidones **3** gave the corresponding N-protected 5-oxazolidinones **5** in high overall yield with 95–99% ee. Moreover, in situ reduction with sodium borohydride gave a direct access to γ-amino alcohol **7a**. Notably, hydrogenolysis of the isolated oxazolidinones **5b** and **5c** with 10% palladium-on-carbon led to efficient N–O bond cleavage and removal of the Cbz group to quantitatively give the corresponding β-amino acids **6**. Comparison with the literature revealed that the absolute configuration of **6b** at C3 was *S* {$[\alpha]_D^{25}$ –6.9 (*c* 1, H_2O), Lit.[11] $[\alpha]_D^{25}$ –6.9 (*c* 0.8, H_2O)}.



Scheme 2 One-pot organocatalytic enantioselective synthesis of oxazolidin-5-ones **5** and amino alcohol **7a** and β-amino acid **6** synthesis

In summary, we report highly chemo- and enantioselective catalytic procedures for the synthesis of 5-hydroxyisoxazolidines, oxazolidin-5-ones, and γ-amino alcohols, which are formed in high yields with 90–99% ee. Moreover, the organocatalytic tandem reaction represents a versatile asymmetric entry to different β-amino acid and γ-amino alcohol derivatives.

Procedures

Herein, we describe four typical experimental procedures demonstrating the synthetic scope of the chiral amine-catalyzed tandem reaction between hydroxylamines and enals. In Procedure 1, we report the preparation of 5-hydroxyisoxazolidine **3b** (94% yield; 99% ee) starting from commercially available hydroxylamine **1b** and enal **2a** in the presence of chiral amine **4**. The second procedure (Procedure 2) describes the in situ conversion of **3b**, which is generated by **4** catalyzed reaction between **1b** and **2a** in one-pot, into the corresponding oxazolidin-5-one **5b** in 81% yield and 99% ee. In Procedure 3, we report the one-pot synthesis of γ-hydroxyamino alcohol **7a** (87% yield; 99% ee) starting from hydroxylamine **1a** and enal **2a** in the presence of a catalytic amount of **4** followed by in situ reduction with $NaBH_4$. In the last procedure (Procedure 4), the Pd/C promoted N–O bond cleavage of oxazolidin-5-one **5b**, which quantitatively gives the corresponding known β-amino acid **6b**, is described.

(–)-(3*S*,5*R*)-2-(Benzyloxycarbonyl)-3-phenylisoxazolidin-5-ol (3b); Typical Procedure

To a stirred soln of catalyst **4** (20 mol%) in $CHCl_3$ (0.5 mL) at 4 °C was added α,β-unsaturated aldehyde **2a** (33 mg, 0.25 mmol) and hydroxycarbamate **1b** (55 mg, 0.3 mmol). The reaction was vigorously stirred for 3 h. Next, the mixture was directly loaded upon a column and immediate subjected to chromatography (silica gel, pentane–EtOAc mixtures or toluene–EtOAc mixtures) to furnish the pure 5-hydroxyisoxazolidine **3b** (70 mg, 94%) as a clear oil.

The enantiomeric excess value was determined by HPLC with an Daicel Chiralpack ODH column (*n*-hexene–*i*-PrOH, 98.0:2.0), 1.0 mL/min): t_R = 35.9 (major isomer), 30.8 min (minor isomer).

$[\alpha]_D^{25}$ –22.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28–2.32 (m, 1 H), 2.78 (dd, *J* = 8.4 Hz, *J′* = 12.8 Hz, 1 H), 5.18 (s, 2 H), 5.39 (t, *J* = 8.4 Hz, 1 H), 5.84 (d, *J* = 4.4 Hz, 1 H), 7.20–7.40 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.2, 61.3, 68.1, 98.7, 126.0, 127.4, 127.7, 128.1, 128.4, 128.6, 135.6, 141.4, 159.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}NO_4$: 300.1230; found: 300.1233.

(–)-(3*S*)-2-(Benzyloxycarbonyl)-3-phenylisoxazolidin-5-one (5b); Typical Procedure

To a stirred soln of catalyst **4** (20 mol%) in $CHCl_3$ (0.5 mL) at 4 °C was added α,β-unsaturated aldehyde **2a** (33 mg, 0.25 mmol) and hydroxycarbamate **1b** (55 mg, 0.3 mmol). The reaction was vigorously stirred for 3 h. Upon completion (a small aliquot was removed for ee determination) The reaction temperature was increased to r.t., isobutene (0.1 mL), *t*-BuOH (0.4 mL), H_2O (0.2mL), KH_2PO_4 (54.4 mg, 4 mmol), and $NaClO_2$ (36 mg, 4mmol) were added sequentially. After 16 h, the crude product **5b** was purified by column chromatography (pentane–EtOAc mixtures) to afford isoxazolidin-5-one **5b** (60 mg, 81%) as a clear oil.

$[\alpha]_D^{25}$ – 33.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85 (dd, *J* = 5.1 Hz, *J′* = 15.9 Hz, 1 H), 3.26 (dd, *J* = 10.5 Hz, *J′* = 15.9 Hz, 1 H), 5.20–5.10 (m, 2 H), 5.60 (dd, *J* = 5.1 Hz, *J′* = 10.5 Hz, 1 H), 7.20–7.42 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.6, 59.1, 68.3, 127.2, 127.9, 128.1, 128.2, 128.5, 128.6, 135.5, 138.1, 157.4, 175.3.

HRMS (ESI): *m/z* $[M + H_2O + Na]^+$ calcd for $C_{17}H_{17}NNaO_5$: 338.0999: found: 338.1002.

(–)-(3*S*)-3-[(*tert*-Butoxycarbonyl)(hydroxy)amino]-3-phenylpropan-1-ol (7a)

To a stirred soln of the catalyst **4** (16 mg, 20 mol%) in $CHCl_3$ (1 mL) was added α,β-unsaturated aldehyde **2a** (33 mg, 0.25 mmol) and **1a** (40 mg, 0.3 mmol). The reaction was vigorously stirred at r.t. for 4 h. Next, the mixture was diluted with MeOH (1 mL) and cooled to 0 °C followed by addition of $NaBH_4$ (19 mg, 0.5 mmol). The mixture was then stirred for 10 min, quenched with 1 M HCl, and extracted with EtOAc. The organic layer was separated and dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, pentane–EtOAc, 4:1) to give **7a** (58 mg, 87%).

$[\alpha]_D^{25}$ –52.0 (*c* 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.02–2.11 (m, 1 H), 2.36–2.47 (m, 1 H), 3.76–3.81 (m, 2 H), 5.21 (dd, *J* = 10.8, 2.1 Hz, 1 H), 6.91 (br s, 1 H), 7.27–7.42 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 34.2, 60.1, 60.3, 82.0, 127.4, 127.6, 128.5, 140.3, 157.2.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{21}NNaO_4$: 290.1363; found: 290.1355.

(–)-(3*S*)-3-Phenyl-2-aminopropanoic Acid (6b)[11]

To a stirred soln of Cbz-protected isoxazolidinone **5b** (149 mg, 0.5 mmol) in MeOH (5 mL, 0.1 M), was added 10% (in weight) of Pd/C (10%). The reaction was stirred under H_2 (91 bar) overnight. Next, the crude reaction was filtered through a plug of Celite. The solvent was removed under reduced pressure to afford the pure β-amino acid **6b** (83 mg, 100%).

$[\alpha]_D^{25}$ –6.9 (*c* 1, H_2O) {Lit.[11] $[\alpha]_D^{25}$ –6.9 (*c* 0.8, H_2O)}.

^{1}H NMR (400 MHz, D_2O/K_2CO_3): δ = 2.45–2.60 (m, 2 H), 4.27 (t, *J* = 7.2 Hz, 1 H), 7.30–7.40 (m, 5 H).

^{13}C NMR (100 MHz, D_2O/K_2CO_3): δ = 46.7, 53.1, 127.6, 128.7, 128.8, 128.9, 179.4.

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