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
Introduction

5-Hydroxyisoxazolidines and isoxazolidin-5-ones are important chiral building blocks which are readily converted into the corresponding amino alcohols and β-amino acids. Thus, asymmetric methods have been developed for their preparation. For example, optically active 5-acetoxydihydroisoxazoles can be converted in two steps into the corresponding isoxazolidinones. Moreover, utilization of chiral auxiliaries enables the asymmetric synthesis of isoxazolidin-5-ones. Recently, isoxazolidin-5-ones were prepared by Lewis acid catalyzed enantioselective conjugate addition of hydroxylamines to α,β-unsaturated amide derivatives.

In the field of organocatalysis, amine-catalyzed reactions that involve catalytic domino, tandem, or cascade reaction pathways have recently been developed. In this context, we have developed an asymmetric domino amine–conjugate/aldol reaction. Based on these lessons and retrosynthetic analysis, we recently discovered a chiral-amine-catalyzed reaction between N-protected hydroxylamines and enals. 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(trimethylsilyl)methyl)pyrrolidine] catalyzed reactions are compatible with several different types of enals. For example, the reaction between cinnamaldehyde and tert-butyl N-hydroxycarbamate in chloroform afforded the desired product in 90% yield and 99% ee at room temperature. In fact, the α,β-unsaturated aldehydes reacted with N-hydroxycarbamates leading to 5-hydroxyisoxazolidines in excellent yields and enantioselectivities in the presence of chiral amine 4 (Table 1).

![Table 1](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt; (%)</th>
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<tr>
<td>1</td>
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<td>Ph</td>
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<td>3</td>
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<td>99</td>
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<tr>
<td>2</td>
<td>Cbz</td>
<td>Ph</td>
<td>3b</td>
<td>3</td>
<td>94</td>
<td>99</td>
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<tr>
<td>3</td>
<td>Boc</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3c</td>
<td>3</td>
<td>89</td>
<td>90</td>
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<tr>
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<td>Boc</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3d</td>
<td>3</td>
<td>80</td>
<td>97</td>
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<td>Boc</td>
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<td>3e</td>
<td>3</td>
<td>90</td>
<td>97</td>
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Thus, the reactions work well with aliphatic and aromatic $\alpha,\beta$-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 $\alpha,\beta$-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 $N$-hydroxy- carbamates $1$ and enals $2$ is also suitable for the one-pot asymmetric synthesis of oxazolidin-5-ones $5$ and $\gamma$-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-hydroxyisoxazolidones $3$ 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 $\gamma$-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 $\beta$-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, H2O), Lit.$^{11}$ [\alpha]_D^{25} –6.9 (c 0.8, H2O)}].

Table 1  Scope of the Organocatalytic Tandem Reaction (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield$^a$ (%)</th>
<th>ee$^b$ (%)</th>
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<td>6</td>
<td>Boc</td>
<td>4-O$_2$NC$_6$H$_4$</td>
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<tr>
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<td>CO$_2$Et</td>
<td>$3h$</td>
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<td>97</td>
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<tr>
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<td>Boc</td>
<td>n-Bu</td>
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<td>16</td>
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<td>10</td>
<td>Boc</td>
<td>n-Pr</td>
<td>$3j$</td>
<td>16</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>Cbz</td>
<td>n-Pr</td>
<td>$3k$</td>
<td>16</td>
<td>92</td>
<td>95</td>
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</table>

$^a$ 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.
One-pot organocatalytic enantioselective synthesis of oxazolidin-5-ones and amino alcohol

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 aldehydes. In Procedure 1, we report the preparation of 5-hydroxyisoxazolidine (94% yield; 99% ee) starting from hydroxylamine and an unsaturated aldehyde. In the last procedure (Procedure 4), the Pd-promoted N–O bond cleavage of oxazolidin-5-one was added, which quantitatively gives the corresponding known amino acid.

(−)-(3S,5R)-2-(Benzyloxycarbonyl)-3-phenylisoxazolidin-5-one (5b); Typical Procedure

To a stirred soln of the catalyst (20 mol%) in CHCl3 (0.5 mL) at 4 °C was added a β-unsaturated aldehyde (33 mm, 0.25 mmol) and hydroxycarbamate (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 (70 mg, 94%) as a clear oil.


−(−)−(3S)-3-(tert-Butyloxycarbonyl)(hydroxy)amino]-3-phenylpropan-1-ol (7a); Typical Procedure

To a stirred soln of the catalyst (16 mg, 20 mol%) in CHCl3 (1 mL) was added a β-unsaturated aldehyde (33 mm, 0.25 mmol) and hydroxycarbamate (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 NaBH4 (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 (Na2SO4) and the solvent was removed. The residue was purified by column chromatography (silica gel, pentane–EtOAc, 4:1) to give 7a (58 mg, 87%).


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 H₂ (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%).

References

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References


