

# Highly Enantioselective Synthesis of 1,2-Amino Alcohol Derivatives via Proline-Catalyzed Mannich Reaction

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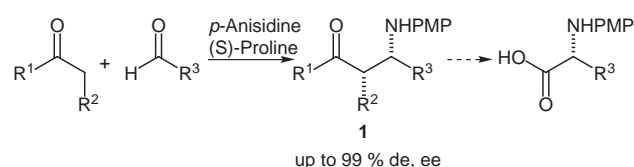
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**Abstract:** Here we report a new catalytic asymmetric synthesis of oxazolidin-2-ones **4** and Cbz-protected 1,2-amino alcohols **5**. Our sequence is based on the chemistry of previously unknown 5-acyloxy-oxazolidin-2-ones, which are obtained via proline-catalyzed direct asymmetric three-component Mannich reaction and Baeyer–Villiger oxidation.

**Key words:** multicomponent reactions, organocatalysis, oxazolidinones, aminoalcohols

The proline-catalyzed direct asymmetric three-component Mannich reaction between ketones, aldehydes, and *p*-anisidine produces  $\beta$ -amino ketones **1** in enantio- and diastereoselectivities of up to >99% (Scheme 1).<sup>2,3</sup> A useful application of our reaction would be a general synthesis of  $\alpha$ -amino acid derivatives. We pursue a route that centers on the oxidative glycol- or Baeyer–Villiger-type  $\alpha$ -cleavage of products **1** with  $R^2 = \text{OH}$ .<sup>4</sup> Combined with an oxidative removal of the *N*-protecting group such a sequence could result in a short and practical catalytic asymmetric synthesis of  $\alpha$ -amino acids. Here we present significant progress towards this goal with an efficient conversion of Mannich products **1** ( $R^1 = \text{Me}$ ,  $R^2 = \text{OH}$ ) into 1,2-amino alcohol derivatives via previously unknown 5-acyloxy-oxazolidin-2-ones.



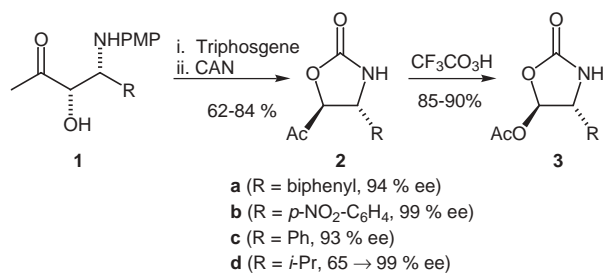
**Scheme 1** The proline-catalyzed direct asymmetric three-component Mannich reaction (PMP = *p*-methoxyphenyl)

Chiral 1,2-amino alcohol derivatives are useful precursors of important non-racemic compounds such as drugs, amino acids, and chiral auxiliaries and ligands. The development of new efficient methods for their asymmetric synthesis is of high current interest.<sup>5</sup> In this regard, the Sharpless catalytic asymmetric amino-hydroxylation is one of the most powerful procedures previously described.<sup>6,7</sup> In addition, several other interesting methods have been reported.<sup>8</sup>

Our strategy for a new organocatalytic synthesis of chiral 1,2-amino alcohols is based on our proline-catalyzed asymmetric Mannich reaction with hydroxyacetone as the donor component. We expected the produced  $\alpha$ -hydroxy- $\beta$ -amino ketones (**1**,  $R^2 = \text{OH}$ , Scheme 1) to be useful precursors of 1,2-amino alcohols via straightforward redox processes. These could involve an oxidative PMP-removal and  $\alpha$ -hydroxy ketone cleavage,<sup>9</sup> followed by a reduction. Our first generation approach was developed to determine the absolute configuration of the Mannich products and was based on a lead tertacetate mediated glycol cleavage.<sup>2a</sup> The sequence, starting from the Mannich product to give *N*-BOC-protected valinol, required seven chemical operations. Later we developed an improved synthesis by using a Baeyer–Villiger-oxidation-based approach that gave *N*-BOC-protected 1,2-amino alcohols in high yields and in five chemical operations.<sup>2b</sup> This second-generation approach worked well with aliphatic and aromatic substituents. However, we found that the use of aromatic aldehydes with electron-withdrawing groups, which gave excellent ee's in the Mannich reaction, led to extensive racemization in the final reduction step. We now report a significantly improved, high-yielding, and racemization-free third-generation approach that gives oxazolidin-2-ones **4** and Cbz-protected 1,2-amino alcohols **5** in only three steps from Mannich products **1**. Further, we use previously undescribed 5-acetoxy substituted oxazolidin-2-ones **3** as new chiral  $\alpha$ -amino aldehyde equivalents.

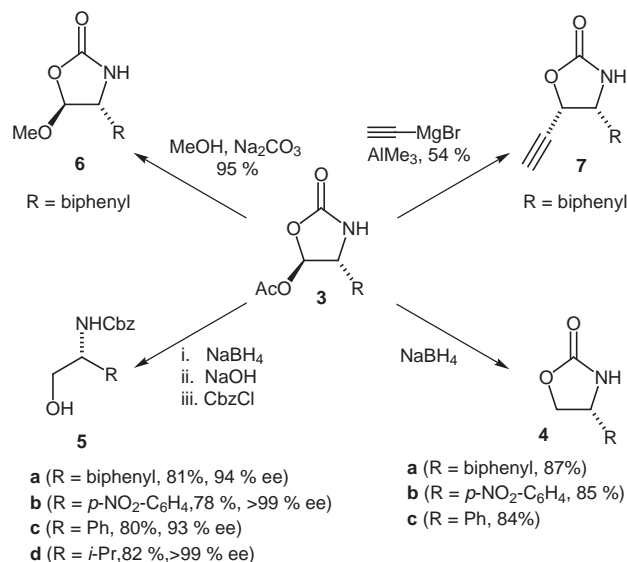
The required diastereomerically pure *syn*- $\alpha$ -hydroxy- $\beta$ -aminoketones **1a–d** were synthesized in good yields and in high diastereoselectivities and enantioselectivities via proline-catalyzed three-component Mannich reaction of hydroxyacetone with *p*-anisidine, and aldehydes as described earlier.<sup>2b</sup> Reacting Mannich products **1a–d** with triphosgene followed by cerium ammonium nitrate (CAN) gave oxazolidinones **2** in good yields (Scheme 2). Baeyer–Villiger oxidation of 5-acyl-oxazolidinones **2** with in situ generated trifluoroacetic acid<sup>10</sup> then gave 5-acetoxy oxazolidin-2-ones **3** (*trans*-stereochemistry assigned from <sup>1</sup>H NMR). Although Baeyer–Villiger oxidations of such  $\alpha$ -carbamoyl-oxyketones are unprecedented, the observed complete regioselectivity was expected and is based on the high migratory aptitude of oxyalkyl groups.<sup>11</sup>

To explore the utility of 5-acetoxy substituted oxazolidin-2-ones (**3**) as chiral  $\alpha$ -amino aldehyde equivalents we



**Scheme 2** Synthesis of 5-acetoxy oxazolidin-2-ones **3**

studied their reactivity towards nucleophiles. Remarkably, NaBH<sub>4</sub>-reduction of acetals **3a–c** did not provide the expected 1,2-amino alcohols but oxazolidin-2-ones **4a–c** in high yields (Scheme 3). Evidently, instead of reducing the ester functionality, the hydride source directly substitutes OAc with hydrogen. The corresponding Cbz-protected amino alcohols (**5a–d**) can also be obtained after a work-up that consists of base-treatment followed by in situ protection. That no racemization occurred during the reduction was confirmed in all cases by measuring the ee of the produced amino alcohols **5**.<sup>12</sup> The preference of 5-acetoxy oxazolidin-2-ones **3** to react with nucleophiles via substitution instead of nucleophilic addition was further confirmed by treating ester **3a** with Na<sub>2</sub>CO<sub>3</sub>/MeOH, which gave methoxy derivative **6** as a single stereoisomer (*trans*-stereochemistry assigned from <sup>1</sup>H NMR). Moreover, if ester **3a** was treated with a 1:1 mixture of ethynylmagnesium bromide and AlMe<sub>3</sub>, alkyne **7** was obtained in 54% yield as a single stereoisomer (*cis*-stereochemistry assigned from <sup>1</sup>H NMR).



**Scheme 3** Reactions of 5-acetoxy oxazolidin-2-ones **3**

While the complete *cis*-stereoselectivity in this novel carbon-carbon bond-forming reaction is consistent with an S<sub>N</sub>2-type mechanism, the complete *trans*-selectivity in

the synthesis of acetal **6** may be thermodynamic in nature and is likely the result of a double S<sub>N</sub>2 reaction at the labile acetal center. The intrinsic propensity of 5-acyloxy-oxazolidin-2-ones **3** to undergo nucleophilic substitutions at their acetal center is remarkable and contrasts the known behavior of *N*-BOC-substituted oxazolidinones, which invariably react with nucleophiles at their ring carbonyl carbon.<sup>2,8b</sup> Presumably, the C–OAc-bond is weakened by an anomeric effect of the ring oxygen atom.

In conclusion, we have developed an efficient and highly enantioselective synthesis of  $\alpha$ -amino acid derivatives **3–7**. Our sequence is based on the proline-catalyzed asymmetric three-component Mannich reaction, combined with a Baeyer–Villiger oxidation to furnish previously undescribed 5-acyloxy-oxazolidin-2-ones **3**. All steps of the developed sequence are operationally simple, rapid, give good chemical yields, and provide the products in high optical purity. Our methodology is best suited for the synthesis of aryl glycine derivatives because the initial Mannich reaction provides the highest stereoselectivities with aromatic aldehydes. As such, the presented scheme nicely complements our recently developed catalytic asymmetric aldehyde  $\alpha$ -amination reaction, which furnishes aliphatic  $\alpha$ -amino acid derivatives in excellent enantioselectivities.<sup>13</sup> Future work will focus on the intriguing yet underexplored chemistry of 5-acyloxy-oxazolidin-2-ones **3** and on the application of our methodology to the synthesis of biologically active compounds.

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