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# Organocatalytic Asymmetric Assembly Reactions: One-Pot Synthesis of Functionalized β-Amino Alcohols from Aldehydes, Ketones, and Azodicarboxylates

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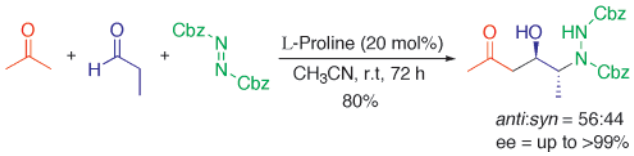
## ABSTRACT




**L-Proline catalyzed the enzyme-like direct asymmetric assembly of aldehydes, ketones, and azodicarboxylic acid esters to provide optically active β-amino alcohols. This assembly reaction uses both aldehydes and ketones as donors in one pot. The aldol-derived stereocenter is formed with a reduced facial selectivity in reactions involving (*R*)-amino aldehydes. The reactions can be performed on a multigram scale under operationally simple and safe conditions without the requirement of an inert atmosphere or dry solvents.**

Directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules has long been the purview of nature's enzymes.[1,2] In organic synthesis, catalysts are traditionally designed and optimized to mediate a single reaction. However, the increasing demand for expedient and efficient synthetic processes requires the development of catalysts that are capable of catalyzing multiple reactions in a single pot. The use of multifunctional catalysts not only generates less waste but ideally obviates the tedious separation and purification of intermediate products.[3] Proline has been found to be effective for enamine-based direct catalytic asymmetric aldol,[4] Mannich,[5] Michael,[6] Diels−Alder,[7] and α-amination reactions.[8] Recently, we described proline-catalyzed asymmetric assembly of polyketides from three aldehyde substrates involving two consecutive aldol reactions in a single pot.[4c,9] In a continuation of our studies of amine-catalyzed aldol reactions,[4,9] we aimed to explore various highly functionalized aldehydes as ac-

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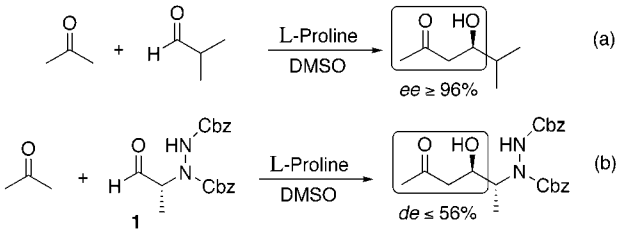
ceptors. Accordingly, we have studied amino aldehydes as acceptors. Herein, we report L-proline-catalyzed direct asymmetric assembly reactions involving three different components, namely, aldehydes, ketones, and azodicarboxylic acid esters, to provide optically active functionalized $\beta$-amino alcohols in an enzyme-like assembly process. To the best of our knowledge, these are the first examples of assembly reactions that use directly both aldehydes and ketones as donors in one pot.

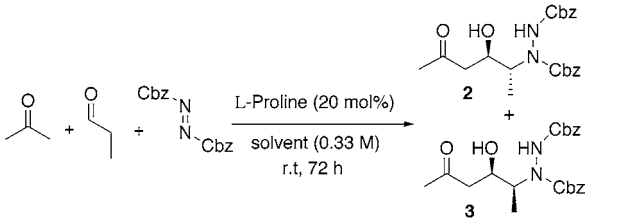
To develop the targeted assembly reaction, we first studied the L-proline-catalyzed aldol reaction of acetone with (*R*)-amino aldehyde (**1**). To our surprise the aldol product was formed with reduced facial selectivity as compared to that observed in other known proline-catalyzed aldol reactions (Scheme 1). Since amino aldehydes such as **1** are accessible

**Scheme 1.** L-Proline-Catalyzed Aldol Reactions: (a) Previous Work and (b) Present Work




through proline catalysis,[8] we studied the reaction of acetone, propionaldehyde, and dibenzyl azodicarboxylate in one pot with L-proline (20 mol %) in DMSO at room temperature for 3 days. The functionalized amino alcohol diastereomers (anti/syn = 13:87) **2** and **3** were obtained in good yield (72%) and with an enantioselectivity of >99% for the anti product (Table 1, entry 1). Given the solvent dependence we have noted in organocatalytic reactions, we investigated a variety of solvents for this one-pot reaction. Interestingly the reaction works well in a range of solvents such as DMSO, DMF, $CH_2Cl_2$, dioxane, acetone, and $CH_3CN$. The use of acetone as a reactant−solvent also afforded the expected $\beta$-amino alcohols in 68% yield along with aminated acetone in 9% yield. With the exception of the use of acetone as a solvent, other solvents suppressed the formation of aminated acetone. Scaling of the reaction to 20 mmol of reactants afforded identical results (Table 1, entry 1). Significantly, the use of DMSO or DMF as solvents enhances the syn selectivity of the reaction.

**Table 1.** Proline-Catalyzed Asymmetric Assembly Reaction of Acetone, Propionaldehyde, and Dibenzyl Azodicarboxylate in Various Solvents




| entry | solvent | yield (%) | dr (anti:syn) | ee[a] (%) (anti/syn) |
|---|---|---|---|---|
| 1 | DMSO | 72 | 13:87 | >99/74 (>99/98)[b] |
| 2 | DMF | 79 | 28:72 | >99/65 |
| 3 | $CH_2Cl_2$ | 75 | 62:38 | >99/49 |
| 4 | dioxane | 77 | 44:56 | >99/49 |
| 6 | acetone | 68 | 55:45 | >99/28 |
| 5 | $CH_3CN$ | 80 | 56:44 | >99/54 |
| **7**[c] | **$CH_3CN$** | **82** | **28:72** | **98/78** |
| 8[d] | $CH_3CN$ | 80 | 43:57 | 99/55 |

[a] Ee determined by HPLC analysis on a Chiralcel OD-R column using 35% $CH_3CN$ in water (0.1% TFA) as an eluent; flow rate = 1 mL/min. [b] Ee of the enantioenriched mother liquor obtained after crystallization of racemate from $CH_2Cl_2$−hexane. [c] This experiment was carried out in tandem using D,L-proline for amination and L-proline for aldol reaction. [d] D-Proline is used as a catalyst, and ees are provided for the opposite enantiomers.

The success of this assembly reaction can be attributed to the higher reactivity of propionaldehyde over acetone in the proline-catalyzed α-amination reaction. When we compared the reactivity of these two donors in the proline-catalyzed α-amination reaction, propionaldehyde exhibited a 100-fold higher reactivity than acetone when the reactions were performed under identical conditions in $CH_3CN$. The reaction conditions for the assembly reaction are very simple: the reactants are mixed in the presence of catalyst and stirred. The products are readily purified, and the syn diastereomer can be enantioenriched by recrystallization from $CH_2Cl_2$−hexane. The two diastereomers can also be separated by recrystallization from $CH_2Cl_2$−hexane. Under D-proline catalysis, amino alcohols with the opposite stereoconfigurations were obtained.

To further understand the diastereoselectivity and reaction mechanism, additional experiments were performed. When we treated racemic aminated propionaldehyde (**1**) with acetone in the presence of L-proline, products **2** and **3** were obtained with yield, diastereoselectivity, and enantioselectivity identical to those found in the reaction involving (*R*)-amino aldehyde (**1**) (Table 1, entry 7, and Scheme 2). Next we performed a reaction with propionaldehyde and azodicarboxylate for 3 days and determined that the resulting amino aldehyde was racemic. Thus, proline can act to racemize the amino aldehyde over time. These two findings suggest that the reaction proceeds as outlined in Scheme 2. Amination of propionaldehyde using D,L-proline or L-proline with extended reaction times (3 days) provides racemic amino aldehyde (**1**). The reaction of rac-amino aldehyde (**1**) with acetone in the presence of L-proline in $CH_3CN$ afforded

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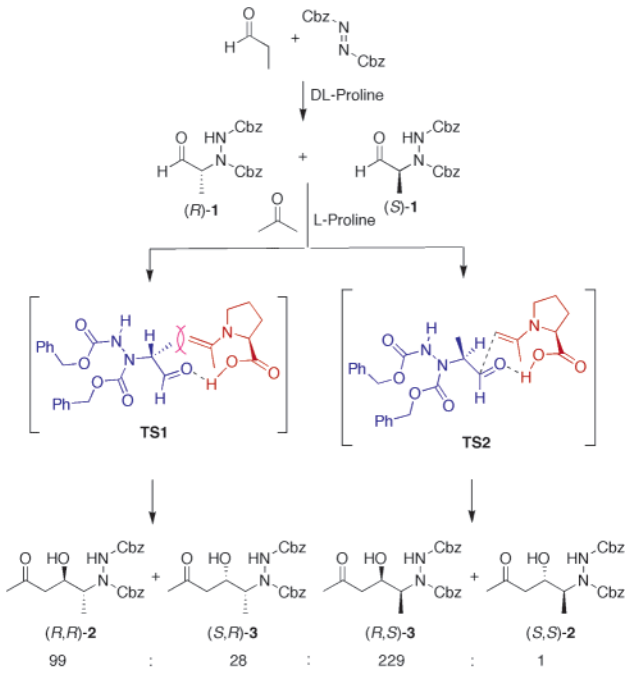
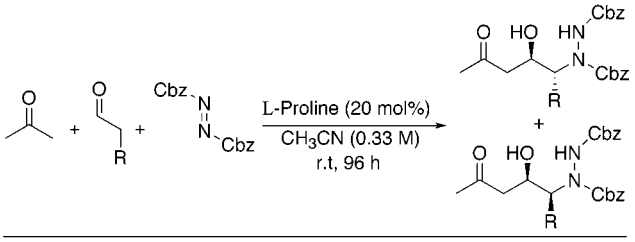
**Scheme 2.** Proposed Reaction Pathway for the Proline-Catalyzed Assembly Reaction

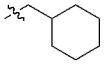



the four possible enantiomers in a ratio of 99:28:229:1 (HPLC data). The amino aldehyde reacts on the exo face of 1-isopropenyl pyrrolidine-2-carboxylic acid, the typical face selectivity observed in the proline-catalyzed aldol reactions since this approach facilitates hydrogen bonding between the carboxylate and the aldehyde acceptor.[4] Intermolecular hydrogen bonding and steric hindrance between enamine and amino aldehydes as shown in TS 1 and TS 2 then likely control the facial reactivity of the amino aldehyde. In the case of (*R*)-amino aldehyde, intermolecular hydrogen bonding between the carboxylate group and the aldehyde oxygen is less effective due to steric hindrance between N-substituted groups or the α-methyl group and the enamine, affording diastereomers (*R*,*R*)-**2** and (*S*,*R*)-**3** with a modest de of 56%. The (*S*)-amino aldehyde afforded diastereomers (*R*,*S*)-**3** and (*S*,*S*)-**2** with a very high de of 99%. Here, potential intermolecular hydrogen bonding between the aldehyde oxygen and carboxylate group effectively directs the facial selectivity of the attack of the enamine on the aldehyde. The enantiofacial selectivity involving (*R*)-amino aldehydes is decreased as compared to other known proline-catalyzed aldol reactions involving simple aldehydes. This is the first observation that substituent modifications on the acceptor aldehyde can alter the stereochemistry of proline-catalyzed aldol reactions. Since racemization of the amination product is faster than the subsequent aldol reaction, the aldol reaction occurs between the ketone donor and racemic aminated propionaldehyde. These reactions can be performed either in one pot or sequentially since identical results are obtained in both approaches.

Encouraged by these promising results, we next explored the scope of the assembly reaction using various aldehyde donors. Aldehydes bearing olefin, aromatic and alicyclic substituents reacted smoothly in the one-pot assembly reaction to provide various functionalized amino alcohols with excellent yields and ees. A β-branched aldehyde afforded the product with high anti selectivity (Table 2, entry 8). The use of ethyl azodicarboxylate as an acceptor afforded products with yields (80%) and diastereoselectivity (1:1) analogous to those seen with dibenzyl azodicarboxylate. The absolute configuration of the amino alcohols prepared here are assigned on the basis of analogy with our X-ray structure of the *O*-acetyl derivative of (*R*,*S*)-**3** (Figure 1).

**Table 2.** Proline-Catalyzed Asymmetric Assembly Reactions of Acetone and Dibenzyl Azodicarboxylate with a Variety of Aldehydes




| entry | R | yield (%) | dr (*anti* : *syn*) | ee (%) (*anti*/*syn*) |
|---|---|---|---|---|
| 1 | Me | 85 | 54:46 | >99/34 |
| 2 | Bn | 83 | 45:55 | >99/91 |
| 3 |  | 80 | 45:55 | 99/13 |
| 4 | *n*-Pent | 82 | 44:56 | >99/61 |
| 5 |  | 76 | 29:71 | >99/70 |
| 6 | Et | 83 | 40:60 | nd/43 |
| 7 | allyl | 82 | 39:61 | nd/60 |
| 8 | *i*-Pr | 75 | 85:15 | nd/85 |

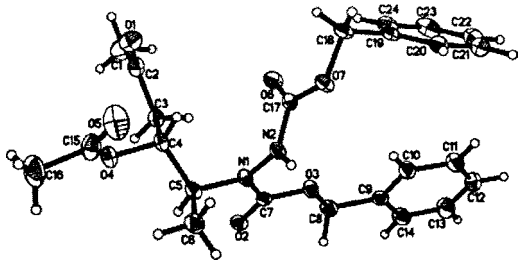
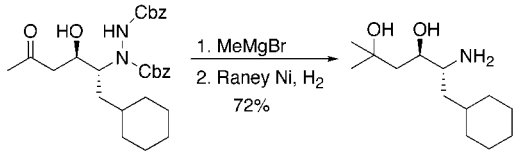


**Figure 1.** X-ray crystal structure of the *O*-acetyl derivative of (*R*,*S*)-**3**.

Optically active β-amino alcohol units containing two stereocenters are often found in natural products and drugs.[10,11] The products of the assembly reactions described here should be directly applicable as chiral synthons for

natural product and pharmaceutical synthesis. To demonstrate this, we have synthesized a known potent renin inhibitor.[11] Reaction of the product in entry 3, Table 2, with methylmagnesium bromide afforded the corresponding *tert*-alcohol. Subsequent deprotection of the hydrazine group using Raney Ni under hydrogen provided the amino diol renin inhibitor (Scheme 3).[1] Thus, the asymmetric assembly reaction enables an expedient three-step synthesis of this enzyme inhibitor.

**Scheme 3.** Synthesis of a Renin Inhibitor




In conclusion, we have demonstrated for the first time L-proline-catalyzed enzyme-like assembly of amino alcohols from three readily available precursors. This simple one-pot procedure provides direct access to chiral functionalized amino alcohols. Furthermore, the reactions can be performed on a multigram scale under operationally simple and safe conditions. These results provide further evidence that the assembly of complex products from simple starting materials is within the realm of organocatalysis involving the simple naturally occurring amino acid proline. Further studies aimed at exploring novel amine-catalyzed assembly reactions are ongoing.

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**Supporting Information Available:** Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **General Experimental Procedure.** To a mixture of solvent (3 mL), dibenzyl azodicarboxylate (90%, 330 mg, 1 mmol), L-proline (23 mg, 0.2 mmol), and propionaldehyde (79 $\mu$L, 1.1 mmol) was added acetone (2 mL), and the reaction was stirred at room temperature for 72 h. Then, half-saturated $NH_4Cl$ solution and ethyl acetate were added with vigorous stirring; the layers were separated, and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($Na_2SO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired amino alcohol as a white solid as a mixture of diastereomers.