Proline Catalyzed Intermolecular Direct Asymmetric Aldol Reaction

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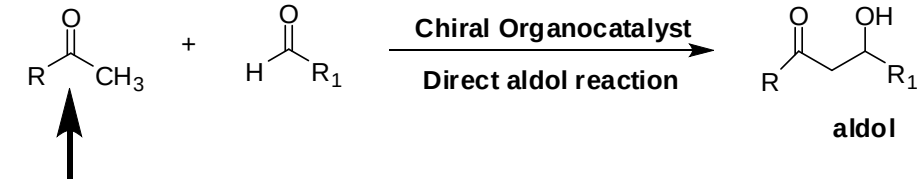
Abstract: The classic and contemporary asymmetric direct aldol reaction involving organocatalyst, mainly proline as catalyst, is reviewed. This short review describes how organocatalysts cause rate acceleration and induce high stereoselectivity.

Keywords: organocatalyst, proline, direct aldol reaction, streoselectivity**.**

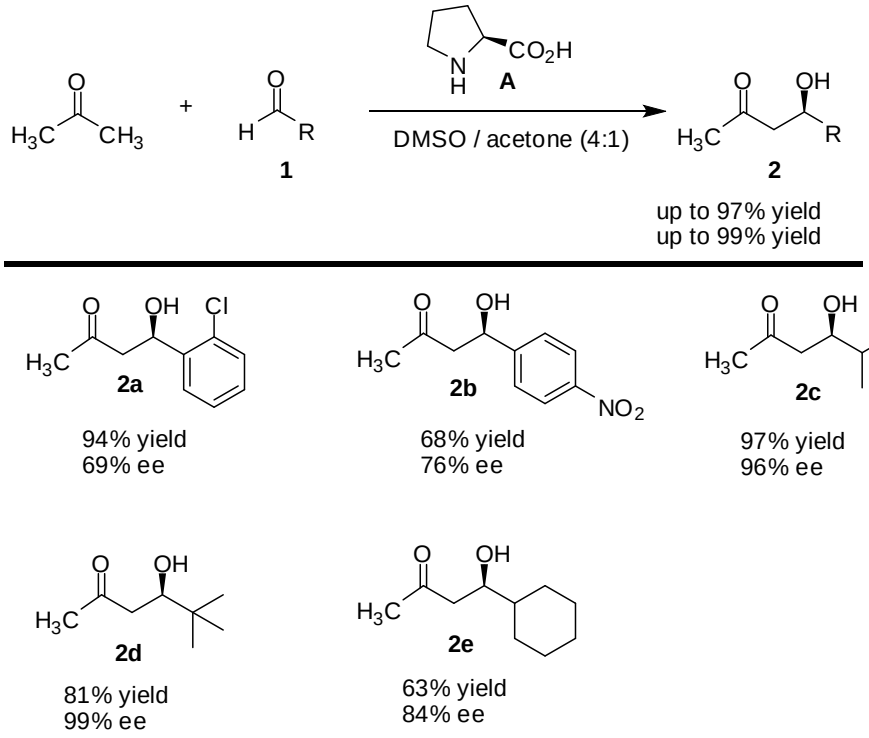
Introduction: The catalytic asymmetric aldol reaction is a fundamental C-C bond forming reaction in organic chemistry and the products, namely β-hydroxy carbonyl compounds, have a broad range of applications and play a key role in the production of pharmaceuticals [1]. The reaction also constitutes an important transformation in several biosynthetic pathways, particularly those involving carbohydrates and polyketides [2]. The seminal research from the laboratories around the globe, it has been established that the aldol reaction as the principal chemical reaction for the stereoselective construction of complex polyol architecture [3]. The organocatalytic direct aldol reactions are important transformations that do not require the pregeneration of enolates or enolate equivalents. Resultant metal-free small organic molecules as organocatalysts may have extraordinary advantages under the condition that they can be efficiently recovered and recycled. Naturally, the efficient recovery and recycling of organocatalysts are of considerable significance in terms of cost-effectiveness and environmental acceptance of synthetic processes. During the last few years, several new concepts have been developed which are based on the use of organocatalysts. In this article we wish to highlight the recent advances of the proline catalyzed direct intermolecular aldol reaction only.

Intermolecular direct aldol reaction: The synthesis which allow the direct use of ketone, (does not require the use of the enolate or modified ketone as a starting material) in a non-activated form as a nucleophile is known as the direct aldol reaction (**Scheme 1**).



Scheme 1

The possibility of using a simple organic molecule to act like an enzyme for the catalytic intermolecular aldol reaction has recently been reported by the List and Barbas groups. L-proline, **A**, was chosen as the simple unmodified catalytic molecule from the chiral pool [4]. The proline-catalyzed reaction of acetone with an aldehyde, **1**, at room temperature resulted in the formation of the desired aldol products **2** in a very good yields and with enantioselectivity up to >99% ee. The List and Barbas groups also studied the reaction with varieties of substrates. The reaction proceeds well when aromatic aldehydes (product **2a** & **2b**), isobutyraldehyde (product **2c**) and pivaldehyde are used as substrates (product **2d**). Cyclohexyl carbaldehyde is also a good substrate furnishing the aldol product, **2e,** in good yield with good enantioselectivity, i.e., 84% ee (**Scheme 2)**.

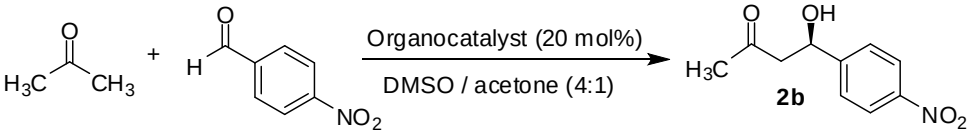


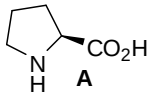
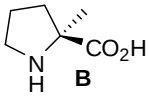
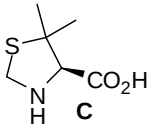
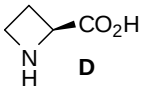
Scheme 2

Vey recently Martinez and his group developed useful and optimal conditions for the (S)-proline-catalyzed asymmetric direct aldol reaction of aliphatic aldehydes with acetone. They also demonstrated the possibility to suppress the undesired reaction pathways such as aldol condensation and self-aldolization by optimizing the reaction conditions [4d].

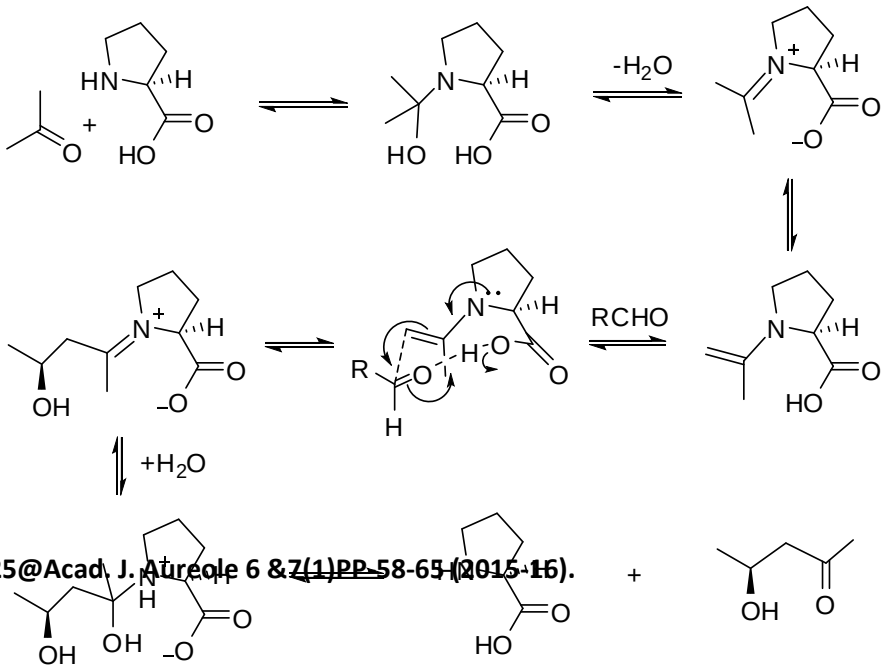
Barbas groups tested the aldol reaction of aromatic aldehyde and acetone with varieties of commercially available amino acid derivatives. They have observed that the primary amino acids and acyclic secondary amino acid derivatives failed to give the significant amount of desired aldol products. It was then suggested that both the pyrrolidine ring and the carboxylate are essential for efficient catalytic aldol reaction to occur. After screening the aldol reaction with various catalysts they characterized L-proline and 5,5-Dimethylthiazolidinium-4-carboxylate (DMTC) as good catalysts for this reaction [4e]. Selected organocatalysts and their performances are summarized in **table 1**.

Table 1



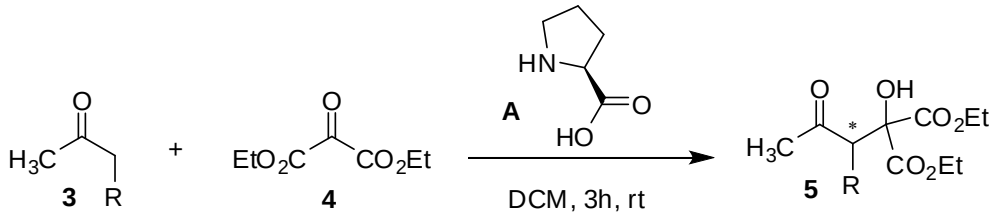
Organocatalyst	Yield (%)	ee (%)
 **A**	68	76
 **B**	26	61
 **C**	66	86
 **D**	55	40

It was proposed that the proline catalyzed asymmetric aldol reaction proceeds via an enamine mechanism. The steps involved the nucleophilic attack of the amino group to the carbonyl group followed by the enamine formation and subsequent carbon-carbon bond forming step produces the iminium-aldol intermediate which on hydrolysis regenerated the catalyst and give the desired aldol (**Scheme 3**). The enantioselectivity of the reaction can be best explained by the Zimmerman-Traxler type transition state [5].



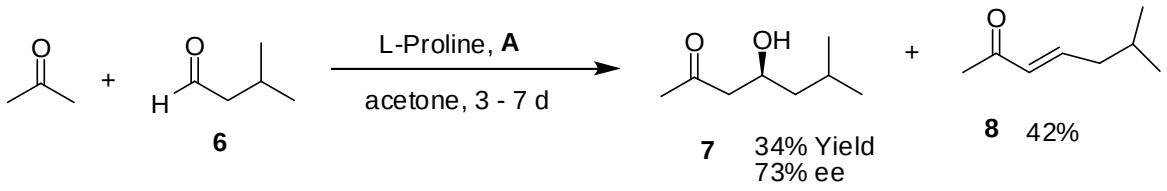
Scheme 3

An interesting proline-catalyzed aldol reaction was recently reported by the Jørgensen group, who used keto malonates as acceptors and a-substituted acetone derivatives as donors [6]. In contrast with the proline-catalyzed reaction discussed above, in this reaction the stereogenic center is formed at the nucleophilic carbon atom of the donor. The resulting products of type **5** are formed in good yields with high enantioselectivity (**Scheme 4**).



Scheme 4

Another extension of proline catalyzed direct asymmetric aldol reaction of α-unsubstituted aldehyde **6** as acceptor and acetone as a donor was described by List and coworkers [7]. The overall yield of the reaction was not good and it was a time taking reaction to complete but the operational simplicity is recognizable (**Scheme 5**).

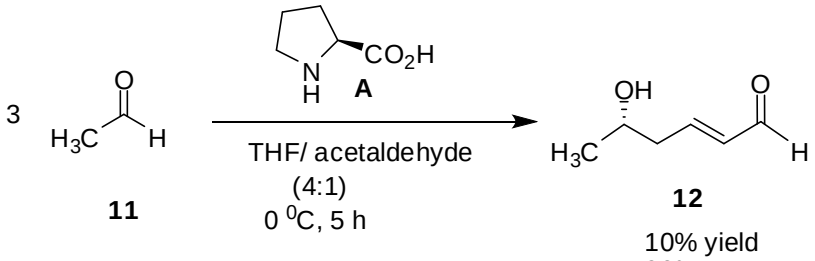


Scheme 5

D. W. C. MacMillan and his group recently reported the proline catalyzed direct enantioselective cross aldol reaction using aldehydes as both aldol donor and aldo acceptor [8]. The reaction was carried out in the presence of catalytic amount of proline and 2 equivalents of aldehyde **9** in DMF. The product β-hydroxy aldehyde **10** was obtained in high yield with excellent enantioselectivity (**Scheme 6**).

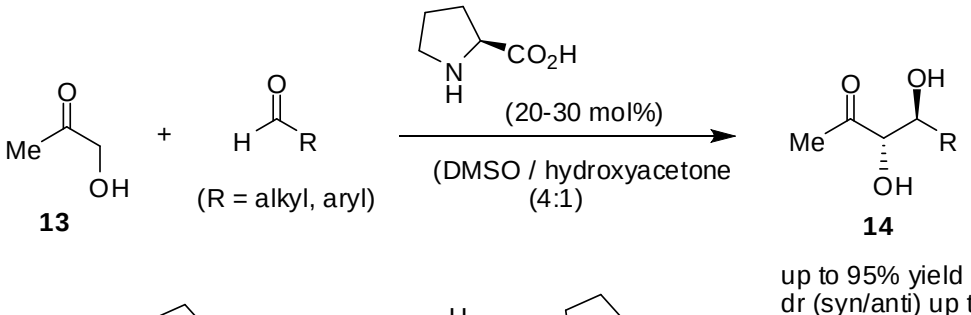
Scheme 6

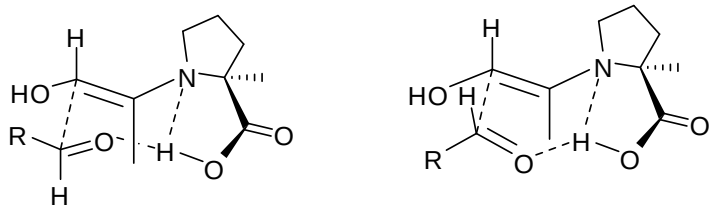
Recently, an enantioselective proline-catalyzed self-aldolization of acetaldehyde, **11**, was reported by Barbas and co-workers [9]. Starting from acetaldehyde, the valuable building block 5-hydroxy-(2E)-hexenal, **12**, was obtained as a product in 10 % yield with up to 90% ee (**Scheme 7**). The reaction was carried out at low temperature to avoid the formation of side product. They also performed the reaction on a multigram scale yielding the triketide **12** with 84% ee. The triketide 1**2** is a versatile synthon for other synthetically valuable building blocks. For example, the aldehyde functionality of 1**2** can be readily oxidized or reduced to afford the corresponding carboxylic acid or allylic alcohol respectively.



Scheme 7

In an elegant example, α-hydroxyacetone **13** was tested as aldol donor together with the aldehydes as aldol acceptors to form the corresponding optically active anti diols **14** as aldol products [10]. The organocatalyst L-proline was found to be a very efficient catalyst in this reaction. The overall yield of the reaction was moderate but with this catalyst high diastereoselectivity and an excellent enantioselectivity were observed (**Scheme 8**). The preferred diastereo- and enantioselectivity were explained in terms of the potential transition states for the aldol reaction using hydroxyacetone shown in Scheme 8. The *Re*-facial attack of the aldehyde at the *Si*-face of hydroxyacetone leads to the formation of a six-membered transition state **I** which gives the *anti*-aldol products. In contrast, reversed facial selectivity of the enamine derived from hydroxyacetone in a boat-like transition state **II** would lead to preferred formation of *syn* products.





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Scheme 8

Conclusion: The asymmetric synthesis of aldol products with one or more stereogenic center is one of the most advanced types of synthesis in the field of organocatalysis. In contrast with diastereoselective syntheses using chiral auxiliaries – these reactions require achiral starting materials only. The desired aldol products can be obtained in high yields and with good to excellent enantioselectivity. The proline was found to be very simple but efficient catalyst for the asymmetric aldol reactions that allow the organic chemist for efficient preparation of optically active aldol derivatives. The methodology is useful for the synthesis of *syn*-aldol as well as *anti*-aldol aaducts. In summary, organocatalytic aldol reactions provide the organic chemist with a valuable and versatile tool for efficient preparation of optically active aldol adducts.

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