Improved Conditions for the Proline-Catalyzed Aldol Reaction of Acetone with Aliphatic Aldehydes

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Dedicated to Max Malacria on the occasion of his 65th birthday

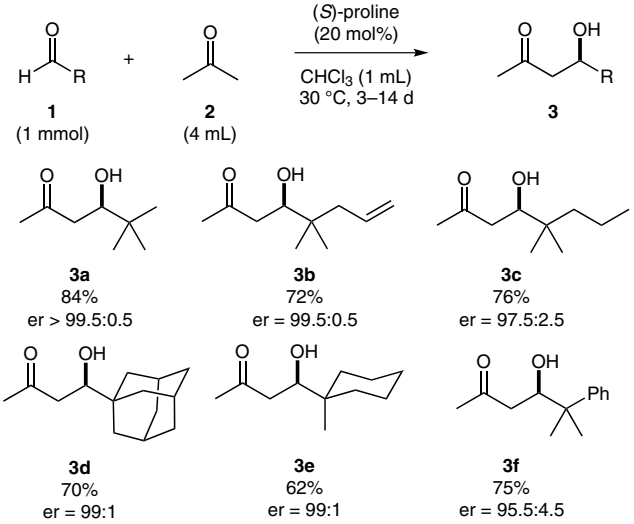
Abstract: The proline-catalyzed asymmetric aldol reaction between aliphatic aldehydes and acetone has, to date, remained underdeveloped. Challenges in controlling this reaction include avoiding undesired side reactions such as aldol condensation and self-aldolization. In recent years we have developed optimized conditions, which enable high yields and good to excellent enantioselectivities, and which are presented in this communication.

Key words: aldehydes, aldol reaction, asymmetric catalysis, organocatalysis, proline

Since the advent of modern organocatalysis, the asymmetric aldol reaction of simple ketones such as acetone with aldehydes catalyzed by proline and its derivatives has occupied a prominent position in this field.[1,2] However, the reaction of aliphatic aldehydes has remained underdeveloped, presumably due to the many possible side reactions such as self aldolizations and aldol condensation reactions. Most studies have focused on aromatic aldehydes or branched aldehydes such as isobutyraldehyde, where these undesired reactions are impossible or minimal. Proline-catalyzed aldol reactions of acetone with α-unbranched aldehydes have proven to be extremely challenging and even those utilizing α-trisubstituted aldehydes have rarely been reported. Herein we present our studies on improving the proline-catalyzed aldol reaction of acetone with all types of aliphatic aldehydes, which have led to, what has proven to be in our laboratories, optimal conditions.

As the reactivity of aliphatic aldehydes in this reaction varies significantly with the degree of substitution in the α-position, we chose to study α-trisubstituted, α-branched, and α-unbranched aldehydes separately, and to develop optimal conditions for each substrate class.

We began our studies with the nonenolizable α-quaternary derivatives. After optimizing the reaction conditions using pivaldehyde as the model substrate,[3] we found a solvent mixture of acetone and chloroform to be optimal, and explored a series of α-trisubstituted aldehydes, which all reacted smoothly under our newly developed conditions and gave aldol products in excellent enantioselectivity (Scheme 1).



Scheme 1 Enantioselective aldol reaction of α-quaternary aldehydes **1** with acetone

While the analogous reaction with α-branched aldehydes such as isobutyraldehyde has already been highly developed and generally gives good yield and enantioselectivity, we also attempted at further optimizing the conditions for these substrates.[3] An in-depth study of possible cosolvents in this reaction revealed that the presence of both $CHCl_3$ and DMSO is beneficial for the reaction. We found that when both cosolvents are applied simultaneously, high chemoselectivity and stereoselectivity can be obtained. We examined the generality of our new reaction conditions for the proline-catalyzed enantioselective aldol reaction of α-branched aldehydes (Scheme 2).

Our protocol proved to be suitable for a number of α-branched aldehydes with both open chain (**5a** and **5b**) as well as cyclic (**5c**–**f**) substituents. While the cyclopentyl-substituted product **5c** was obtained with modest enantioselectivity, presumably due to the low steric demand of the cyclopentyl substituent, aldehydes bearing larger rings led to highly enantioselective product formation.

Importantly, the reactions of both α-quaternary and α-tertiary aldehydes could be carried out on a multigram scale. Products **3a** (250 mmol scale, 74%, er >99.5:0.5) and **5a** (256 mmol scale, 75%, er = 98.5:1.5) were obtained in similar yields and enantioselectivities as those obtained

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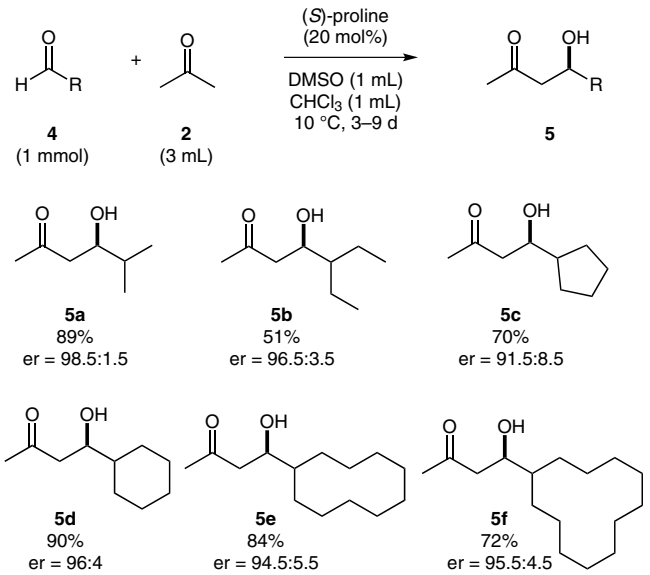
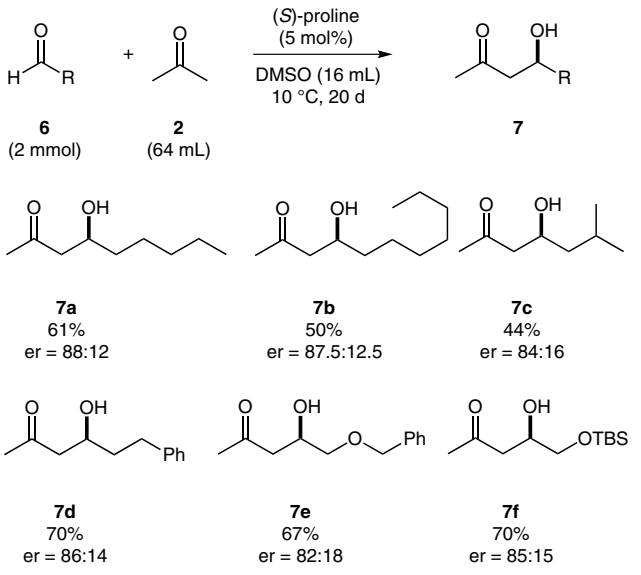


Scheme 2 Enantioselective aldol reaction of α-branched aldehydes **4** with acetone



Scheme 3 Enantioselective aldol reaction of α-unbranched aldehydes **6** with acetone

on a small scale. At the same time most of the proline used could be reisolated.[4]

We were also interested in developing robust reaction conditions for the reaction between acetone and the notorious α-unbranched aliphatic aldehydes. Despite numerous attempts,[2b,5] this reaction has remained challenging due to the difficulties in controlling undesired side reactions such as aldol condensation[6] and/or self aldolization of the aldehyde.[7]

The ratio, in which these diverse possible products are formed, is strongly dependent on factors such as solvent, temperature, catalyst loading, and concentration, which rendered an extensive screening of reaction conditions necessary for this process.[3] We found that conducting the reaction with a lowered catalyst loading and under diluted conditions and allowing for prolonged reaction times led to the best possible reaction outcome.

Having developed these very mild reaction conditions, we explored the scope of this reaction with different α-unbranched aliphatic aldehydes (Scheme 3).

While the reactions are rather slow, and full conversion was not even achieved after 20 days, the desired products **7** could be obtained with reasonable yields and enantioselectivities. The model substrate *n*-hexanal (**6a**) reacted smoothly yielding 61% of aldol product **7a** with 88:12 enantiomeric ratio. *n*-Octanal (**6b**) and isopentanal (**6c**) were less reactive but gave similar enantioselectivity.

Furthermore products **7d–f**, in some cases bearing oxygenated side chains, were obtained with similar yields and enantioselectivities. While these reaction conditions are obviously not perfect, especially in terms of reaction times, it should be noted that an almost complete suppression of the undesired reaction pathways was achieved.

In summary, we have found useful and optimal conditions for the (*S*)-proline-catalyzed asymmetric direct aldol reaction of aliphatic aldehydes with acetone. To the best of our knowledge the enantioselectivities and yields obtained in this study equal or exceed many previously reported methods, including those involving more elaborate and expensive aminocatalysts. While the results obtained with α-unbranched aliphatic aldehydes are not yet satisfactory, the possibility to suppress the undesired reaction pathways by optimizing the reaction conditions was demonstrated. This challenge will hopefully be addressed in the near future by combining the results presented herein with the application new proline-derived catalysts.

(*S*)-Proline (0.2 mmol) was added to a solution of aldehyde **1** (1 mmol) in acetone (4 mL) and $CHCl_3$ (1 mL) and was stirred at 30 °C. After this time the reaction mixture was extracted with Et_2O and brine (3×). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Hydroxy ketone **3** was isolated by column chromatography (silica, pentane–Et_2O).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(3) For the optimization of reaction conditions, see the Supporting Information.
(4) Between 84–87% of the total (*S*)-proline was reisolated and reused in different experiments, without loss catalytic activity.
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