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L-Proline catalyzed asymmetric transfer aldol reaction between diacetone alcohol and aldehydes†

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We demonstrate for the first time, L-proline as a chiral catalyst for transfer aldol reaction between aldehydes and diacetone alcohol.

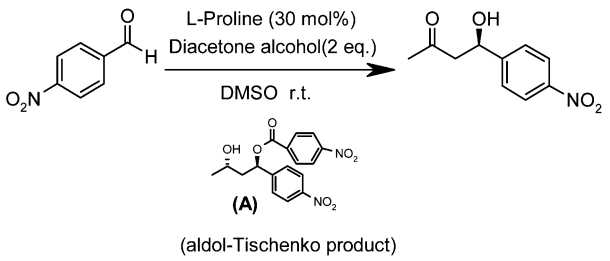
Aldol reactions for new C–C bond formation has been well established.[1] The asymmetric version of this reaction is a relatively new challenge and several modifications are presently pursued. Most well studied reactions involved addition of enol silyl ethers to carbonyl compounds in the presence of Lewis acids[2] or Lewis bases[3] as catalysts. A few direct aldol reactions are also reported in the recent literature catalysed by Brønsted base as well as Lewis acid activity, to form the metal enolate *in situ* and activate the aldehyde, respectively. List *et al.*[4] have for the first time discovered L-proline as a small molecule chiral catalyst for asymmetric aldol reaction. Several attempts by various groups by changing solvent, amount of catalyst or substrates[5] were only moderately successful in ee enhancement though good yields were observed.

In an alternate concept, transfer aldol reaction involving diacetone alcohol as source of ketone (acetone) has been studied with several alkoxides[6] and researchers observed the aldol–Tischenko reaction as a competitive reaction leading to mono-protected 1,3-diols and, in a few cases, normal aldol products, namely β-hydroxyketones,[7] were observed. This concept of transfer aldol reaction has its origin from cyanide transfer reaction as reported by Inoue and co-workers,[8] allyl transfer reaction as observed by Nokami *et al.*[9] and alkynyl transfer reactions as reported by Maruoka and co-workers.[10]

We anticipated the modification of diacetone alcohol as one of the partners in the aldol reaction catalyzed by L-proline and anticipated the following objectives: (1) the pyrrolidine nitrogen should assist in retro-aldol reaction of the diacetone alcohol. (2) it should participate in asymmetric induction as reported. (3) the sometimes unwanted consumption of aldehyde by the Tishchenko reaction should be inhibited.

The observed results were found to be in agreement with our assumptions and details are presented herein (Scheme 1)

A typical protocol involved simple stirring of 4-nitrobenzaldehyde (2 mmol), diacetone alcohol (4 mmol) and L-proline (30 mol%) in DMSO (3 mL) for 4 h to obtain the adduct in over 86% yield and 71% ee (by chiral HPLC using a Chiralcel-OB-H column, hexane–isopropyl alcohol eluent). However, while there is no direct evidence for the mechanism by which the reaction proceeds, we suggest a cyclic transition state as shown in Scheme 2, wherein retro-aldol and aldol reactions are initiated by the same catalyst. The 'double action' of L-proline as reagent for enamine formation of acetone as well as reagent for retro-aldol initiator for diacetone alcohol is novel.



Scheme 1

We then studied various aromatic aldehydes (Table 1, entries 2–7) and aliphatic aldehydes (entries 9 and 10) for the above transformation, and observed the aldol adducts in good yields (40–91%) and reasonable enantiomeric excess (48–86%).

To check the time dependency of the enantioselectivity, a series of four experiments using 4-nitrobenzaldehyde and diacetone alcohol as substrates was carried out. Each reaction was quenched at different intervals (4, 8, 12 and 24 h) and found that an increase in time beyond 4 h did not influence the optical purity, however, the formation of dehydrated aldol condensation product was observed after 8 h.

To check the advantages and limitations of this protocol, 3-phenylpropanal (having an α-hydrogen) was subjected to the current procedure, however, self-aldolization of aldehyde was competitive. Electron-rich 4-methoxybenzaldehyde (entry 8) resulted in aldol product only after 5 days of stirring at room temperature with an optical purity of 48% ee along with the dehydrated aldol condensation product (25%).

In conclusion, we have demonstrated that L-proline as a natural small amino acid metal-free catalyst for the synthesis of asymmetric transfer aldol reaction products. This asymmetric transfer aldol reaction incidentally did not yield any aldol–Tischenko product **A** unlike other reported methods.[11] Further studies are aimed at the understanding of the exact mechanism and tailoring the amino acid[12] for enhanced enantioselectivities.[13]

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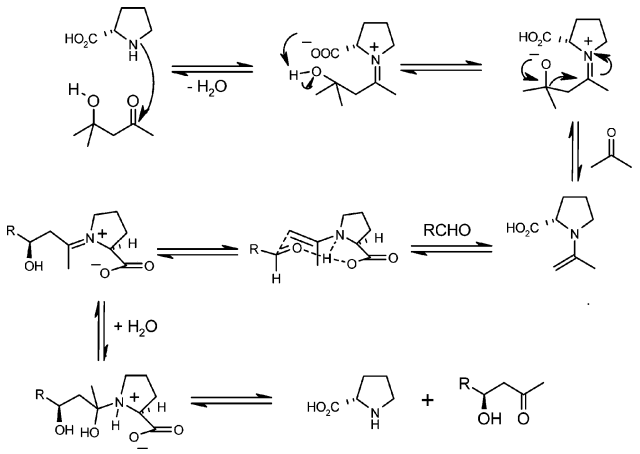

Scheme 2

† Electronic supplementary information (ESI) available: General procedures and characterization data. See http://www.rsc.org/suppdata/cc/b4/b409053p/

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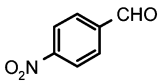
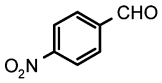
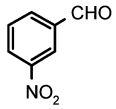
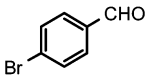
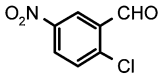
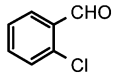
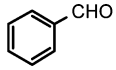
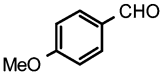
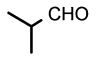
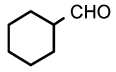
Table 1 L-Proline catalyzed asymmetric transfer aldol reaction

Entry	Substrate	Time/h	Yield[a] (%)	ee (%)
1		4	86	71[c]
2		4	85	72[bc]
3		6	88	70[c]
4		12	65	71[d]
5		6	82	60[c]
6		8	70	60[d]
7		12	50	57[c]
8		120	40	48[c]
9		12	80	84[d]
10		12	91	86[d]

[a] Isolated yields after chromatography; the products were characterized by spectral data. [b] Amount of L-proline used 100 mol% [c] ee% by chiral HPLC. [d] ee% by optical rotation.

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13 Based on one of the referee's suggestion, 5-ethyl-5-hydroxy-4-methyl-3-heptanone was used in place of diacetone alcohol as ketone equivalent, however only traces of the aldol product were obtained.