

Proline-Catalyzed Direct Asymmetric Aldol Reactions

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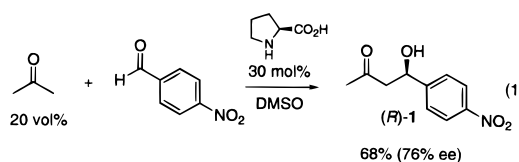
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Most enzymatic transformations have a synthetic counterpart. Often though, the mechanisms by which natural and synthetic catalysts operate differ markedly. The catalytic asymmetric aldol reaction as a fundamental C–C bond forming reaction in chemistry and biology is an interesting case in this respect. Chemically, this reaction is dominated by approaches that utilize preformed enolate equivalents in combination with a chiral catalyst.¹ Typically, a metal is involved in the reaction mechanism.^{1d} Most enzymes, however, use a fundamentally different strategy and catalyze the direct aldolization of two unmodified carbonyl compounds. Class I aldolases utilize an enamine based mechanism,² while Class II aldolases mediate this process by using a zinc cofactor.³ The development of aldolase antibodies that use an enamine mechanism and accept hydrophobic organic substrates has demonstrated the potential inherent in amine-catalyzed asymmetric aldol reactions.⁴ Recently, the first small-molecule asymmetric class II aldolase mimics have been described in the form of zinc, lanthanum, and barium complexes.^{5,6} However, amine-based asymmetric class I aldolase mimics have not been described in the literature.⁷ Here we report our finding that the amino acid proline is an effective asymmetric catalyst for the direct aldol reaction between unmodified acetone and a variety of aldehydes.

Recently we developed broad scope aldolase antibodies that show very high enantioselectivities, have enzymatic rate accelerations, and use the enamine mechanism of class I aldolases.⁴ During

the course of these studies, we found that one of our aldolase catalytic antibodies (Aldolase Antibody 38C2, Aldrich) is an efficient catalyst for enantiogroup-differentiating aldol cyclodehydrations of 2,6-heptanediones to give cyclohexenones, including the Wieland–Miescher ketone.^{8,9} These intramolecular reactions are also catalyzed by proline (Hajos–Eder–Sauer–Wiechert reaction)¹⁰ and it has been postulated that they proceed via an enamine mechanism.¹¹ However, the proline-catalyzed direct intermolecular asymmetric aldol reaction has not been described. Further, there are no asymmetric small-molecule aldol catalysts that use an enamine mechanism.⁷ Based on our own results and Shibasaki's work on lanthanum-based small-molecule aldol catalysts,^{4,6} we realized the great potential of catalysts for the direct asymmetric aldol reaction.

We initially studied the reaction of acetone with 4-nitrobenzaldehyde. Reacting proline (30 mol %) in DMSO/acetone (4:1) with 4-nitrobenzaldehyde at room temperature for 4 h furnished aldol product (*R*)-**1** in 68% yield and 76% ee (eq 1). This result



is quite remarkable since it is known that proline can undergo a variety of reactions with aldehydes. For example, aliphatic aldehydes react with proline to give either the oxazolidinone and/or various other compounds, including products of self-aldolization.¹² Aromatic aldehydes (including 4-nitrobenzaldehyde) can condense with proline to form azomethine ylides that undergo further 1,3-dipolar cycloaddition reaction.¹³ The high concentration of acetone we use in the reaction mixture suppresses these side reactions. The only significant side product is the α,β -unsaturated ketone, formed by aldol (or Mannich-type) condensation. After screening several solvents,¹⁴ we found anhydrous DMSO at room temperature to be the most suitable condition regarding reaction times and enantioselectivity. We also compared a variety of different commercially available amino acid derivatives under standard conditions with 30–40 mol % of catalyst (Table 1). Interestingly, primary amino acids and acyclic secondary amino acids failed to give significant amounts of the desired product (entries 1 and 2). While 2-azetidinedicarboxylic acid showed some catalysis (entry 3), both pipercolic acid (entry 5) and 2-pyrrolidine carboxamide (entry 6) were ineffective. Clearly both the pyrrolidine ring and the carboxylate are essential for efficient catalysis to occur. On the other hand, none of the commercially available proline derivatives (entries 7–9) showed significantly improved enantioselectivity compared to proline itself. Synthesis of other

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(14) Solvent (ee): CH₃CN (56%), acetone (67%), THF (60%), DMF (76%), DMF/H₂O [10:1] (35%), DMSO (76%).

Table 1. Amino Acid Derivatives Tested as Catalysts for the Asymmetric Aldol Reaction of Acetone with 4-Nitrobenzaldehyde^c

Compound	Entry	Yield	ee ^a
(L)-His, (L)-Val (L)-Tyr, (L)-Phe	1	< 10%	n. d. ^b
	2	< 10%	n. d.
	3	55%	40%
	4	68%	76%
	5	< 10%	n. d.
	6	< 10%	n. d.
	7	67%	73%
	8a R = OH 8b R = O ^t Bu 8c R = OAc	85% ^c > 50% ^c 70%	78% 62% 74%
	9	> 50% ^c	62% ^d

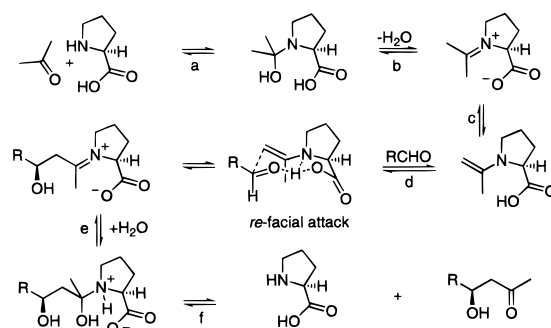
^a The ee was determined by chiral HPLC analysis (Chiralpak AD, Daicel Chemical Industries, Ltd.). ^b Not determined. ^c Yield is estimated from HPLC analysis. ^d Opposite enantiomer. ^e Conditions: The amino acid derivative (0.03–0.04 mmol) was stirred in 1 mL of DMSO/acetone (4:1) for 15 min. 4-Nitrobenzaldehyde (0.1 mmol) was added and the mixture was stirred for 4–24 h. The mixture was treated with 1 mL of saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried (MgSO₄), filtered, and concentrated to give after column chromatography (hexanes/ethyl acetate (3:1)) pure aldol **1**.

Table 2. Yields and ee's of Aldol Products^f

Product	Yield	ee ^a	[α] _D ^b
	68%	76%	
	62%	60%	+ 41.8° (c = 1.1) ^c
	74%	65%	
	94%	69%	
	54%	77%	
	97%	96%	+ 61.7° (c = 0.6) ^d

^a Determined by chiral HPLC analysis (Chiralpak AD, Daicel Chemical Industries, Ltd.). ^b All optical rotations were measured in CHCl₃. ^c Lit.^{15a} +32.4°, c = 1.0, ee = 77%; Lit.^{1d} (S)-isomer: -51.4°, c = 1, ee = 87%. ^d Lit.¹⁶: +43.4°, c = 1.4, ee = 61%. ^e Reaction time was 48 h. ^f Conditions as in Table 1, reaction times were 2–8 h.

aromatic aldols using proline catalysis provided products **2–5** with similar enantiomeric excess (Table 2). Unbranched aldehydes (e.g. pentanal) did not yield any significant amounts of the desired cross aldol product. However, the reaction of acetone with isobutyraldehyde gave aldol **6** in 97% yield and 96% ee. The

Scheme 1. Proposed Enamine Mechanism of the Proline-Catalyzed Asymmetric Aldol Reaction

absolute configuration of aldols **2** and **6** has been assigned based on their known optical rotation.^{1d,15,16}

Currently, we assume this novel asymmetric aldol reaction occurs via an enamine mechanism (Scheme 1). Proline, perhaps, functions as a “micro-aldolase” that provides both the nucleophilic amino group and an acid/base cocatalyst in the form of the carboxylate. This cocatalyst may facilitate each individual step of the mechanism, including the nucleophilic attack of the amino group (a), the dehydration of the carbinol amine intermediate (b), the deprotonation of the iminium species (c), the carbon-carbon bond forming step (d), and both steps of the hydrolysis of the iminium-aldol intermediate (e and f). The enantioselectivity can be explained with a metal free version of a Zimmerman–Traxler type transition state.¹⁷ The tricyclic hydrogen bonded framework provides for enantiofacial selectivity. We cannot rule out other possible mechanisms at this point. However, heterogeneous catalysis may be excluded at least in the reaction of isobutyraldehyde with acetone because this reaction mixture is completely homogeneous.¹⁸

In summary, we have demonstrated the use of proline as a catalyst for the direct asymmetric aldol reaction between acetone and a variety of aldehydes. Yields and enantioselectivities are moderate to good. Important features of this reaction are the following: (1) Proline is nontoxic, inexpensive, and readily available in both enantiomeric forms. (2) The reactions do not require inert conditions and are run at room temperature. (3) No prior modification of the carbonyl substrates such as deprotonation or silylation is required. (4) The catalyst is water soluble and can be readily removed by aqueous extraction. (5) Potentially, the reactions may be run on an industrial scale. (6) This is the first example of a nonmetallic small-molecule catalyst for direct intermolecular asymmetric aldol reactions. (7) Proline most likely functions as a micro-aldolase with enamine formation as in the aldolase catalytic antibodies and natural class I aldolases.

While nature's aldolase enzymes and our aldolase antibodies exhibit rate accelerations exceeding 10⁸ (*k*_{cat}/*k*_{uncat}) and can be used in multigram syntheses with as little as 0.0004 mol % catalyst,^{4f–h} proline catalysis is comparable to the best organometallic catalysts of the direct aldol reaction.⁶ The amine catalyzed asymmetric intermolecular aldol reaction is conceptually novel and may ultimately lead to new catalysts with higher enantioselectivities. The design and screening of these catalysts is one of our future aims. Further studies concerning the mechanism and scope of proline catalysis, particularly as it relates to reactions that may be facilitated by imine and enamine type mechanisms, are ongoing.

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