

Proline-Catalyzed Asymmetric Aldol Reactions between Ketones and α -Unsubstituted Aldehydes

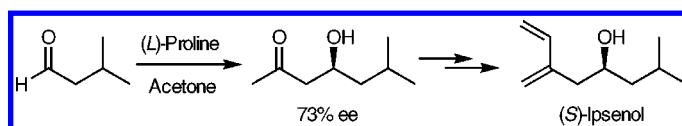
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Received December 7, 2000

ABSTRACT



With this communication we extend the methodology of proline-catalyzed direct asymmetric aldol reactions to include α -unsubstituted aldehydes as acceptors. This important aldehyde class gives the corresponding aldols in 22–77% yield and up to 95% ee when the reactions are performed in pure acetone or in ketone/chloroform mixtures. On the basis of these results we have developed a concise new synthesis of (*S*)-iposenol.

We recently described effective proline-catalyzed direct asymmetric intermolecular aldol reactions between ketones and aldehydes.^{1,2} In these studies, aromatic aldehydes gave aldol products with ee's around 70%, while α -mono- and α -disubstituted³ aliphatic aldehydes provided aldols in excess of 95% ee (Table 1). However, until now our method was

of the desired cross aldols. Herein we disclose the development of reaction conditions that allow the use of α -unsubstituted aldehydes in proline-catalyzed enantioselective aldol reactions. These studies culminate in a short asymmetric total synthesis of the bark beetle pheromone (*S*)-iposenol.

Although α -unsubstituted aldehydes have been used successfully in catalytic enantioselective Mukayama aldol reactions,⁴ the direct catalytic asymmetric aldol reaction involving this important substrate-class has proven to be an extremely challenging task. The fundamental problem is for the catalyst to differentiate between the α -protons of the acceptor aldehyde and the donor ketone, as deprotonation of the aldehyde may lead to undesirable self-aldolization products. Enzymatic methods have been employed to address this problem and have produced aldols in excellent enantioselectivity.⁵ However, these methods are limited both with respect to substrate scope and reaction scale. The com-

Table 1

product	R	yield	ee
1	<i>p</i> -O ₂ NPh	68%	76%
2	<i>i</i> Pr	97%	96%
3	<i>t</i> Bu	81%	>99%
4	CH ₂ R ¹	< 2%	-

not widely applicable to aldol reactions with α -unsubstituted aldehydes. Previous reactions performed with these compounds under our standard conditions furnished mainly aldol condensation and aldehyde self-aldolization products instead

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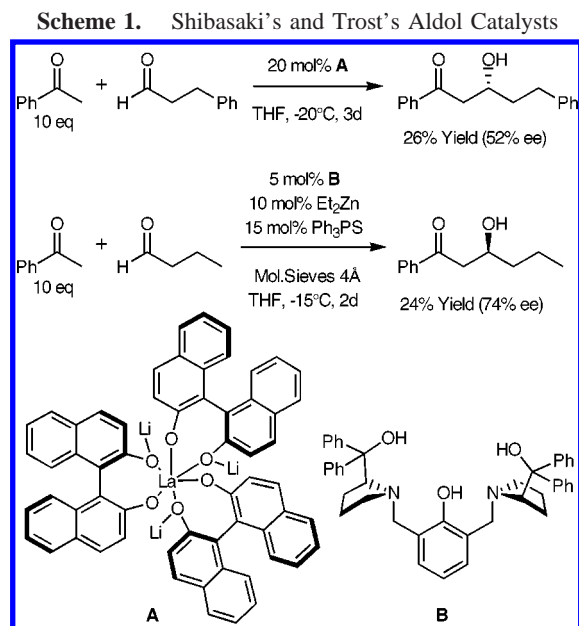
(2) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

(3) Unpublished result.

(4) For an excellent review, see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.

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mercially available aldolase antibody 38C2 is useful for large scale kinetic resolutions of aromatic aldols⁶ but has been used on a semipreparative scale with only two α -unsubstituted aldehydes.⁷ In addition to these biochemical methods, elegant chemical methods have been developed by Shibasaki's group and recently by Trost's group which provide aldols from α -unsubstituted aldehydes in modest yields and enantioselectivities (Scheme 1).⁸



For the development of a proline-catalyzed direct asymmetric aldol reaction with α -unsubstituted aldehydes as acceptors we initially studied the effect of solvent polarity and reaction temperature. We hoped that varying these parameters could improve selectivity toward cross aldol formation thus reducing the formation of self-aldolization products. As a model reaction we studied the proline-catalyzed aldol reaction of acetone with *n*-valeraldehyde. While cooling the reaction mixture in DMSO to 0 °C did not improve yields, screening diverse solvents of varying polarity revealed that aldol **4a** was obtained in acceptable yields when the reactions were performed in pure acetone or in 20 vol % acetone in chloroform.¹⁰ As expected, aldehyde self-aldolization was completely suppressed. Yields

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(10) DMSO, pyridine, NEt₃, EtOH, <5% yield. DMF, MeCN, THF, 10–20% yield. Acetone, CHCl₃, >25% yield. Acetone and chloroform are also useful solvents in proline-catalyzed Mannich reactions: List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

(31% vs 29%) and enantioselectivities (67% vs 70%) of aldol **4a** were similar in both solvents (Table 2). Unfortunately, the formation of significant amounts of the aldol *condensation* product (**5a**) could not be circumvented.

Table 2. Aldol Reactions of α -Unsubstituted Aldehydes

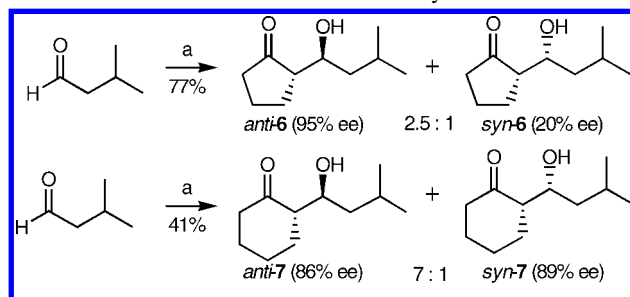
R =	yield of 4(5)	ee ^a	solvent
	31% (38%) 29%	67% 70%	Acetone CHCl ₃
	35% (40%)	73%	Acetone
	34% (35%)	72%	CHCl ₃
	34% (42%) 23% (46%)	73% 61%	Acetone CHCl ₃
	22% (50%)	36%	CHCl ₃

^a The ee's were determined by chiral-phase HPLC analysis using Chiralpak AS, AD, and AD-RH columns (Daicel Chemical Industries, Ltd.) with hexane/2-propanol and H₂O (0.1% TFA)/CH₃CN mixtures as eluents. ^b [α]_D = +33° (*c* = 1.1, CCl₄). Lit.⁹ [α]_D = +41° (*c* = 1.8, CCl₄) for >99% ee.

We have studied aldol reactions of acetone with five different α -unsubstituted aldehydes using our newly developed conditions (Table 2). Yields of aldol products **4a–e** range from 22% to 35%. The ee's are typically around 70%. Yields and enantioselectivities (in CHCl₃) erode with increasing steric demand of the aldehyde substituent (**4d,e**). In all cases the only other products found were enones **5** and small quantities of diacetone alcohol.

Cyclic ketones can be used as well (Scheme 2). For example, cyclopentanone reacts with isovaleraldehyde in chloroform to furnish two readily separable diastereomeric

Scheme 2. Aldol Reactions of Cyclic Ketones

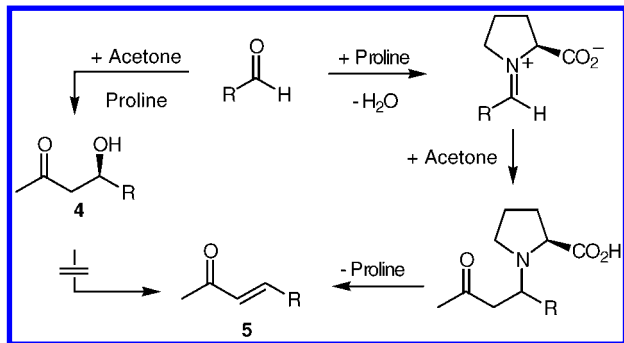


^a L-Proline (20 mol %), cyclopentanone (cyclohexanone)/CHCl₃ (1:4), 72 h.

aldols, *anti*-**6** and *syn*-**6** in 55% and 22% yield and in 95% and 20% ee, respectively. Cyclohexanone gave aldol **7** as an inseparable 7:1 mixture of *anti* and *syn* diastereomers in 41% yield. The major isomer, *anti*-**7**, was formed in 86% ee and the minor isomer, *syn*-**7**, in 89% ee. The assignment of the absolute configurations of aldols **6** and **7** is based on the results obtained in the reaction of cyclohexanone with benzaldehyde.¹¹

As in the aldol reactions with acetone, we found that the only significant side products with cyclic ketones were the corresponding aldol condensation products, albeit in lower yields. Independent experiments allowed us to establish that the elimination products do not arise from the proline-catalyzed dehydration of aldols **4**.¹² On the basis of these results, we propose that the aldol condensation products are formed in a Mannich-reaction-elimination sequence as outlined in Scheme 3.

Scheme 3. Enones **5** Are Formed via Mannich Condensation

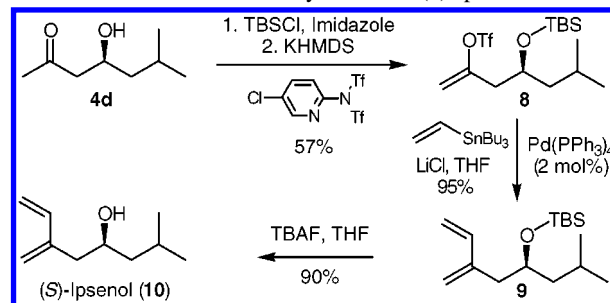


Despite the rather modest yields typically obtained under the new conditions, the reactions can easily be scaled up to generate useful quantities for natural product synthesis. To illustrate this point, we have developed a new asymmetric synthesis of the bark beetle pheromone (*S*)-ipsenol (**10**), which is used in insect traps and needed in kilogram quantities.¹³ Aldol **4d** was protected and converted to enoltriflate **8**.¹⁴ A highly efficient Stille coupling¹⁵ with tributyl(vinyl)tin furnished known diene **9**,¹³ which after

(11) Unpublished results. The four stereoisomeric products of the proline-catalyzed aldol reaction between cyclohexanone and benzaldehyde are known and have been characterized by: Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.

deprotection gave (*S*)-ipsenol (**10**) in good overall yield (Scheme 4).¹⁶

Scheme 4. Total Synthesis of (*S*)-Ipsenol.



The procedure we describe extends the methodology of proline-catalyzed direct asymmetric aldol reactions to include reactions using α -unsubstituted aldehydes as acceptors. Although the method is limited by modest yields and long reaction times, we feel the accessibility of both enantiomeric forms of proline, as well as the operational simplicity¹⁷ of this process, make it compare favorably to other methods for the direct catalytic asymmetric aldol reaction between ketones and α -unsubstituted aldehydes.

Acknowledgment. We are most grateful to Richard A. Lerner, The Scripps Research Institute, for his generous support and encouragement.

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(12) Treating aldol **4e** in acetone/ CHCl_3 with L-proline for 3 days did not yield any significant amounts of enone **5e**.

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(17) Hexanal (2.40 mL, 20 mmol) and L-proline (230 mg, 2 mmol, 10 mol %) were stirred in 100 mL of dry acetone for 168 h. Silica gel (ca. 5 g) was added, and the mixture was evaporated. The residue was pored on a preloaded silica gel column and chromatographed with hexanes/ethyl acetate (4:1) to give enone **5b** (1.12 g, 40%) and aldol **4b** (1.11 g, 35%) in 73% ee (AS, 2% 2-propanol/hexanes, 1 mL/min, t_R = 13.3 min, t_S = 15.7 min). Almost identical results were obtained using an aqueous workup (phosphate-buffered saline/ethyl acetate). All new compounds described herein gave satisfactory spectroscopic data.