Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon−Carbon Bond-Forming Reactions

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Abstract: Direct asymmetric catalytic aldol reactions have been successfully performed using aldehydes and unmodified ketones together with commercially available chiral cyclic secondary amines as catalysts. Structure-based catalyst screening identified L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) as the most powerful amino acid catalysts for the reaction of both acyclic and cyclic ketones as aldol donors with aromatic and aliphatic aldehydes to afford the corresponding aldol products with high regio-, diastereo-, and enantioselectivities. Reactions employing hydroxyacetone as an aldol donor provide *anti*-1,2-diols as the major product with ee values up to >99%. The reactions are assumed to proceed via a metal-free Zimmerman−Traxler-type transition state and involve an enamine intermediate. The observed stereochemistry of the products is in accordance with the proposed transition state. Further supporting evidence is provided by the lack of nonlinear effects. The reactions tolerate a small amount of water (<4 vol %), do not require inert reaction conditions and preformed enolate equivalents, and can be conveniently performed at room temperature in various solvents. In addition, reaction conditions that facilitate catalyst recovery as well as immobilization are described. Finally, mechanistically related addition reactions such as ketone additions to imines (Mannich-type reactions) and to nitro-olefins and α,β-unsaturated diesters (Michael-type reactions) have also been developed.

Introduction

The aldol reaction is widely regarded to be one of the most important carbon−carbon bond-forming reactions utilized in organic synthesis. The development of asymmetric methodologies for this type of reaction has not only broadened its scope and applicability but had also provided insight into fundamental stereochemical aspects important to other carbon−carbon bond forming reactions such as Diels−Alder and Michael reactions. In general, most methodologies available for the asymmetric aldol reaction fall in one of the following categories: (a) the chiral auxiliary-assisted aldol reaction based on the use of stoichiometric quantities of the chiral appendage;[1] (b) chiral Lewis acid-catalyzed Mukaiyama-type[2] and chiral Lewis base-catalyzed[3] aldol reactions; (c) heterobimetallic bifunctional Lewis acid/Brønsted base-catalyzed direct aldol reactions;[4] and (d) Aldol reactions catalyzed by aldolase enzymes[5] and antibodies.[6] A significant characteristic of the latter two methodologies is the employment of unmodified carbonyl compounds as aldol donor substrates, whereas the first two methodologies require some degree of preactivation of the substrates involved.

For the past several years, we spent considerable effort on the development of catalytic asymmetric aldol and related reactions that are facilitated by amine-based mechanisms within antibodies.[6] Catalytic antibodies prepared using diketone haptens and reactive immunization have provided aldolase antibodies with broad scope and excellent enantioselectivities in a wide range of direct asymmetric aldol reactions. Key to the function of these catalysts is an active site lysine residue with a highly perturbed pK_a that is essential to the enamine mechanism of these antibody aldolases and their natural counterparts, the class I aldolase enzymes.[6a,d,j] During the course of mechanistic characterization of aldolase antibodies we have studied the efficacy of small peptides, amines, and amino acids in imine/enamine based decarboxylation and aldol reactions.[6b,d,e,k] While designed[7] and evolved[6k] peptides can function with some efficiency in aqueous buffer by maintenance of a perturbed amino group pK_a through electrostatic effects, amino acids and amines are much more effective catalysts in nonaqueous solvents where the amine functionality can be maintained in its reactive unprotonated state.[6b,e] Indeed, a hydrophobic active site appears to be key to the functioning of aldolase antibodies as well.[6d] Screening of commercially available amino acids and chiral amines in nonaqueous solvents for their ability to catalyze a retro-aldol reaction using a UV sensitive reporter aldol based on 4-dimethylaminocinnamaldehyde generation revealed L-proline as a promising catalyst.[6f] This result immediately suggested the application of this catalyst to intermolecular aldol addition reactions because this reaction is characteristically reversible and varying the concentrations of the reactant with respect to the equilibrium constant allows the reaction to be driven to completion in either direction. L-Proline is also the well-known catalyst of the intramolecular Hajos−Eder−Sauer−Wiechert reaction, an enantiogroup-differentiating aldol cyclodehydration reaction.[8] Evidence suggests that this intramolecular reaction proceeds via an enamine reaction mechanism.[9] Again, mechanistic parallels were observed with antibody aldolases that were demonstrated to catalyze similar aldol cyclodehydration reactions albeit with enhanced ee values.[6c,e,h]

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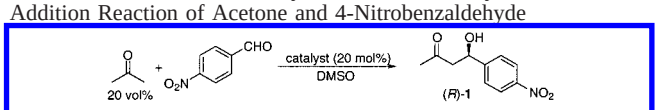
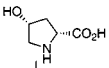
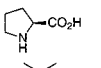
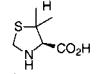
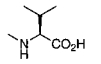
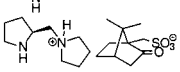
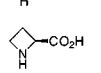
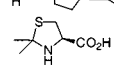
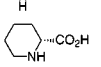
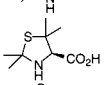
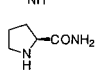
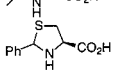
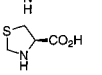
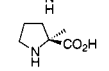
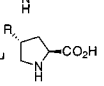
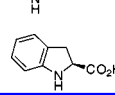
Here we describe (i) structure/activity relationships of proline and proline-like amino acid catalysts of direct asymmetric aldol addition reactions, (ii) the synthetic scope of L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) catalysis in aldol addition reactions, (iii) studies concerning the reaction mechanism, and (iv) catalysis of related enamine-based Mannich and Michael-type addition reactions.

Results and Discussion

Structure/Activity Relationships of Amino Acid Catalysts. In our initial experiments,[10] we studied the model aldol addition reaction of acetone with 4-nitrobenzaldehyde wherein acetone was a component of the solvent system anhydrous DMSO/acetone (4:1). The large excess of acetone was provided to enforce an equilibrium favoring the aldol addition product. Since acetone is also an inexpensive and commonly used solvent, use of a large excess can be justified. Several natural amino acids identified initially by their catalysis of *retro*-aldol reactions were studied (Table 1, entries 1 and 2). We found that, after stirring the homogeneous mixture for 4 h at room temperature,[11] only the reaction catalyzed by L-proline (Table 1, entry 2) resulted in significant quantities of a new product, 68% isolated yield, characterized to be β-hydroxyketone **1** resulting from the cross-aldolization reaction. Moreover, chiral-phase HPLC analysis revealed that **1** was formed in 76% ee. The failure of both *N*-methyl valine (Table 1, entry 3) bearing an acyclic secondary amine functionality and 2-pyrrolidine carboxamide (Table 1, entry 6) to yield significant amounts of the desired aldol product in our model reaction clearly demonstrated that a cyclic secondary amine moiety as well as an acidic proton in appropriate spatial proximity is essential for efficient catalysis to occur. Interestingly, this observation can be correlated to our amine-based antibody catalysis wherein the amino functionality of lysine and the phenolic group of tyrosine are believed to be involved in the enamine-based catalytic cycle.[6d,e] Further, comparison of 2-azetidinecarboxylic acid and pipecolic acid (Table 1, entries 4 and 5) with L-proline showed that the five-membered pyrrolidine ring is best suited as the secondary cyclic amine moiety. This result is in accord with known structure/activity relationships between amines and their enamine reactivity.[12] Provided with this structure/activity relationship we performed a structure-based catalyst screen for the direct asymmetric aldol reaction. We focused our screen on various commercially available or readily prepared chiral amines structurally and chemically related to L-proline (Table 1, entries 7−16) by reacting 4-nitrobenzaldehyde in DMSO/acetone

Table 1. Exploration of Various Amino Acids and Commercially Available Derivatives as Catalysts of the Direct Asymmetric Aldol Addition Reaction of Acetone and 4-Nitrobenzaldehyde



Entry	Catalyst	Yield[a]	ee[b]	Entry	Catalyst	Yield[a]	ee[b]
1	(L)-His, (L)-Val, (L)-Tyr, (L)-Phe	< 10%	n.d.[c]	9		> 50%[d]	62%[e]
2		68%	76%	10		66%	86%
3		< 10%	n.d.	11		41%	81%
4		55%	40%	12		<10%	n.d.
5		< 10%	n.d.	13		< 5%	n.d.
6		< 10%	n.d.	14		<10%	n.d.
7		67%	73%	15		26%	61%
8a R=OH 8b R=OtBu 8c R=OAc		85% > 50%[d] 70%	78% 62% 74%	16		<10%	n.d.

[a] Isolated yields after column chromatography. [b] The ee was determined by chiral-phase HPLC analysis. [c] Not determined. [d] Yield was estimated from HPLC analysis. [e] Opposite enantiomer.

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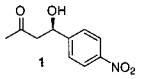
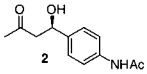
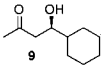
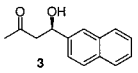
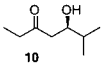
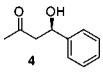
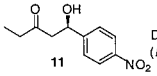
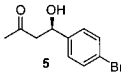
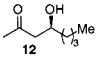
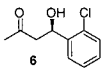
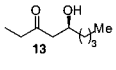
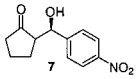
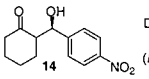
(4:1) with 20 mol % catalyst at room temperature for 4−24 h. In each case, the aldol product was purified by column chromatography and analyzed by chiral-phase HPLC techniques. The results of this screening are summarized in Table 1. We observed that most of the amino acids studied catalyzed the aldol reaction albeit with varying yields. In these studies catalyst loading was reduced from 30 to 40 mol % used in the preliminary screen to 20 mol %. Whereas the commercially available L-proline derivatives (Table 1, entries 8 and 9) as well as L-thiaproline (Table 1, entry 7) showed approximately the same enantioselectivities as L-proline itself, catalysis by 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC, Table 1, entry 10) provided aldol product **1** with 86% ee and 66% yield, which represents a 10% increase in enantiomeric excess compared to the L-proline-catalyzed reaction. In contrast to this, catalysts bearing substituents at the 2-position of the thiazolidinium-4-carboxylate scaffold (Table 1, entries 12−14) provided aldol product **1** in dramatically reduced yield (<10%). In these cases, even higher temperatures (37 and 50 °C) did not increase the yield of the aldol product. Instead, the formation of the aldol condensation product was observed. Similar effects were observed with α-methylproline (Table 1, entry 15) and a diamine salt[13] (Table 1, entry 11) as catalysts where the major product of the reaction was the condensation product. This result can be rationalized by the fact that the assumed enamine formation is disturbed by steric factors together with a change in the pK_a value of the amine functionality due to additional substitution at the centers adjacent to the amino group. We questioned if an amino acid-catalyzed enantioselective dehydration reaction might influence the ee values of aldol products where the condensation product is also found. We found that the ee of the addition products is not affected by enantioselective dehydration, since no resolution of racemic **1** was observed upon treatment with L-proline or DMTC under the same reaction conditions for 3 days. On the basis of this screening, we conclude that substitution at the 4-position of L-proline and of the 5-position of L-thiaproline does not abolish the catalytic activity, but increases the enantioselectivity of the reaction.

Table 2. Direct Asymmetric Aldol Reactions Catalyzed by L-Proline and DMTC[e]

Product	Catalyst	Yield[a]	ee[b]	Product	Catalyst	Yield[a]	ee[b]
 **1**	DMTC	60%	86%	 **8**	DMTC	61%	94%
	(*L*)-Pro	68%	76%		(*L*)-Pro	97%	96%
 **2**	DMTC	60%	80%	 **9**	DMTC	45%	83%
	(*L*)-Pro	62%	69%		(*L*)-Pro	60%	85%
 **3**	DMTC	60%	88%	 **10**	DMTC	<5%	n.d.
	(*L*)-Pro	54%	77%		(*L*)-Pro	60%	80%
 **4**	DMTC	60%	89%	 **11**	DMTC	57%	74%
	(*L*)-Pro	62%	60%		(*L*)-Pro	65%	77%
 **5**	DMTC	65%	67%	 **12**	(*L*)-Pro	75%	73%[c]
	(*L*)-Pro	74%	65%		(*L*)-Pro	56%	68%[d]
 **6**	DMTC	71%	74%	 **13**	DMTC	<5%	n.d.
	(*L*)-Pro	94%	69%		(*L*)-Pro	65%	58%
 **7**	DMTC	*syn* 24%	60%	 **14**	DMTC	*syn* 21%	69%
		anti 39%	63%			*anti* 35%	90%
	(*L*)-Pro	*syn* 27%	63%		(*L*)-Pro	*syn* 24%	67%
		anti 46%	69%			*anti* 41%	89%

[a] Isolated yields after column chromatography. [b] The ee was determined by chiral-phase HPLC analysis. [c] The reaction was performed in neat acetone. [d] Chloroform was used as solvent. [e] Typically, the reactions were performed in DMSO with the corresponding ketone donor substrate (20 vol %), aldehyde acceptor substrate (0.1 M), and catalyst (20 mol %) for 24−48 h at room temperature. Following aqueous workup with saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered, and concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate) to afford the corresponding aldol product.

Synthetic Scope of L-Proline and 5,5-Dimethylthiazolidinium-4-carboxylate (DMTC) Catalyzed Aldol Addition Reactions. On the basis of the results of these screenings, we characterized L-proline and DMTC as catalysts of aldol addition reactions involving a variety of ketone donors and a number of aromatic and aliphatic aldehyde acceptor substrates (Table 2). In all other reactions of acetone with aromatic aldehydes, the corresponding products **2**−**6** (Table 2) were formed in yields and ee values similar to the model reaction with 4-nitrobenzaldehyde. Interestingly, catalysis by DMTC generally provided increased ee values for the products derived from aromatic aldehydes compared to catalysis with L-proline whereas both L-proline and DMTC afforded all other products **7**−**14** with comparable ee values. Remarkably, in the case of benzaldehyde as aldol acceptor, an increase of 29% in the ee of **4** was obtained by catalysis with DMTC, whereas both catalysts afforded the corresponding aldol products **8** and **9** from the reaction of acetone with isobutyraldehyde and cyclohexanecarboxaldehyde, respectively, in excellent ee's. These results suggest that DMTC is the preferred catalyst of aldol addition reactions involving aromatic aldehyde acceptor substrates.

However, although DMTC demonstrates improved enantioselectivities in reactions with aromatic aldehydes and comparable enantioselectivities in all the other examples studied, the chemical yields of the reactions employing DMTC as catalyst

(6) (a) Wagner, J.; Lerner, R. A.; Barbas, C. F., III *Science* **1995**, *270*, 1797. (b) Björnestedt, R.; Zhong, G.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1996**, *118*, 11720. (c) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas, C. F., III *J. Am. Chem. Soc.* **1997**, *119*, 8131. (d) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. A. *Science* **1997**, *278*, 2085. (e) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1998**, *120*, 2768. (f) Zhong, G.; Shabat, D.; List, B.; Anderson, J.; Sinha, S. C.; Lerner, R. A.; Barbas, C. F., III *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2481. (g) Sinha, S. C.; Barbas, C. F., III; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14603. (h) List, B.; Lerner, R. A.; Barbas, C. F., III *Org. Lett.* **1999**, *1*, 59. (i) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1999**, *121*, 7283. (j) Zhong, G.; Lerner, R. A.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **1999**, *38*, 3738. (k) Tanaka, F.; Barbas, C. F., III *Chem. Commun.* **2001**, *8*, 769.

(7) For examples regarding peptide catalysis in other organic transformations, see: Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (c) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635.

(8) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358−360.

(9) (a) Agami, C.; Puchot, C.; Sevestre, H. *Tetrahedron Lett.* **1986**, *27*, 1501. (b) Agami, C. *Bull. Soc. Chim. Fr.* **1988**, *3*, 499. (c) For an excellent review on nonlinear effects in asymmetric synthesis see: Girard, C.; Kagan, H. B. Angew. *Chem., Int. Ed.* **1998**, *37*, 2922.

(10) Preliminary results of this screen have been reported. See: List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(11) In this context, room temperature refers to a temperature range of 24−26 °C.

(12) For an excellent review concerning enamine chemistry see: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

(13) The diastereomeric salt from the less expensive enantiomeric (1S)-camphorsulfonic acid has also been employed in this study and (*R*)-**1** was formed in 45% yield and 79% ee.

are somewhat lower than in the case of catalysis by L-proline. This is mainly due to a decreased rate of formation of the desired aldol product, as determined in HPLC studies.

To extend the scope of donors used in our amino acid-catalyzed direct catalytic asymmetric aldol reactions, we investigated cyclopentanone and cyclohexanone as potential cyclic ketones, and found that both of these substrates undergo the desired cross-aldolization to afford *syn*/*anti*-mixtures of the corresponding aldol products **7** and **14**. In these two cases, DMTC and L-proline were comparable with respect to enantioselectivity, whereas L-proline gave a slightly better *syn*/*anti*-ratio as well as chemical yields. The diastereoselectivity of the reactions in favor of the corresponding *anti*-products was modest for both catalysts. Nonetheless, *anti*-**14** could be isolated in 90% ee from the reaction with DMTC as catalyst.

Next, we turned our attention to 2-butanone as an aldol donor substrate. This is of particular interest, since this substrate could form two regioisomeric products, one of which gives rise to possible *syn*/*anti* isomers. However, upon stirring a solution of the catalyst in 2-butanone/DMSO (1:4) together with isobutyraldehyde or 4-nitrobenzaldehyde, only products **10** and **11**, respectively (Table 2), were formed, resulting from the nucleophilic attack of the methyl group of the ketone. Since the inherent allylic strain in the more substituted enamine is also present in the regioisomeric enamine involved in the transition state of this reaction mechanism (*vide infra*), it is most likely that, in this case, sterics are responsible for the observed selectivity. Therefore, we propose that regioselective formation of the enamine intermediate is merely a kinetic phenomenum. Again, catalysis by DMTC afforded higher enantioselectivities (74% ee vs 59% ee) for the aromatic aldehyde as compared to the aliphatic isobutyraldehyde where only L-proline was an efficient catalyst, providing the corresponding aldol product **10** in 60% yield and 80% ee.

In our preliminary communication,[10] with the exception of isobutyraldehyde, only aromatic aldehydes were used as acceptors. For these studies, anhydrous DMSO was found to be the best solvent for the model reaction providing **1** (*vide infra*). However, aliphatic α-unsubstituted aldehydes, e.g. pentanal, did not yield any cross-aldol products under these conditions, but reacted to provide mainly self-aldolization products. We have found, however, that use of chloroform as solvent affords the desired crossed-aldol product **12** in 56% yield and 68% ee. In this solvent, L-proline was insoluble and the heterogeneous mixture was simply stirred at room temperature for 24 h. Both the chemical and the optical yield could be further improved by performing the reaction in neat acetone which afforded **12** in 75% yield and 73% ee. Moreover, 2-butanone served as an aldol donor in the reaction with pentanal as well, when chloroform was used as solvent and L-proline as catalyst thereby affording the crossed-aldol product **13** in 58% ee and 65% yield. In addition to the donors described, various other donors, e.g. 3-pentanone, acetylcyclohexane, isopropylmethyl ketone, 3-methyl-2-butanone, and cyclopropylmethyl ketone, were studied with 4-nitrobenzaldehyde as acceptor but did not yield significant amounts of the corresponding aldol products with either of the catalysts. The absolute configurations of aldols **1**−**14** were assigned based on chiral-phase HPLC analysis and comparison of optical rotations with previously reported compounds.

Tertiary Aldols. Tertiary aldols present significant challenges for the design of enantioselective small molecule catalysts. This challenge becomes apparent upon examination of Zimmerman−Traxler transition state models that we have proposed previously for this reaction.[6i] Given our success in applying aldolase antibodies to kinetic resolution of tertiary aldols,[6i] we attempted several L-proline and DMTC catalyzed resolutions of tertiary aldols in DMSO. We noted significant catalysis of the corresponding retro-aldol reaction; however, we were unable to detect enantiomeric enrichment in the unreacted tertiary aldols.

Recovery and Reuse of the Catalyst. We have studied two routes to catalyst recycling. The first route involves direct recovery of the catalyst from the reaction mixture. We noted that while reactions performed in DMSO provide a homogeneous reaction, L-proline and DMTC dissolve, reactions in chloroform are facile; however, the catalysts do not dissolve to any significant extent. When the reaction was performed in chloroform,[14] **1** was obtained in 61% ee. While this marks a reduction in ee as compared to the reaction performed in DMSO, we could quantitatively recover L-proline by simple filtration from the reaction mixture. Further, reuse of the catalyst in a second reaction indicated that there was no loss in activity suggesting that many rounds of catalyst use and recovery should be possible. As a second route to catalyst recovery and reuse, we studied catalyst immobilization. In this study, L-proline (20 mol %) was immobilized on a silica gel column, cyclohexanecarboxaldehyde in DMSO/acetone (4:1) was introduced into the column and incubated for 48 h at room temperature, and then the column was thoroughly washed with ethyl acetate. After purification aldol product **9** was subjected to chiral-phase HPLC analysis and shown to be formed in 53% ee and 63% yield. The recovered silica gel column was then reused for a second aldol reaction where isobutyraldehyde in DMSO/acetone (4:1) was allowed to react within the column. In this case, aldol product **8** was isolated in 56% yield and 63% ee. While silica gel immobilization and recovery of L-proline is facile, the reduced optical yields that are obtained may not justify this approach.

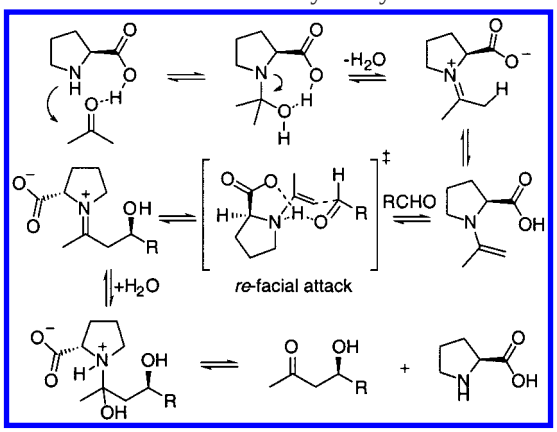
Reaction Mechanism. As proposed for the Hajos−Eder−Sauer−Wiechert reaction, we assume that the key intermediate of the direct intermolecular asymmetric aldol reactions described is an enamine formed between L-proline and the corresponding ketone donor substrate.[8,9] In analogy to the mechanism of aldolase antibody 38C2, this enamine attacks the carbonyl group of the aldehyde acceptor with high enantiofacial selectivity which is imposed by a highly organized tricyclic hydrogen bonded framework resembling a metal-free Zimmerman−Traxler type transition state (Scheme 1).

This mechanism reflects our observation that both a base and an acidic proton are required for effective catalysis to occur. Further support for hydrogen bonding as an essential feature of the transition state comes from our findings that the addition of water severely compromises the enantioselectivity and furthermore decreases the rate of formation of the aldol product. Yet, it is interesting that the reaction tolerates a small amount of water (<4 vol %) without affecting the enantiomeric excess of aldol product **1** (Figure 1).

Since, in principle, aldol reactions are reversible, another question to be addressed in this context is whether the ee varies as a function of time. This is an important feature to be determined and we found that the ee of aldol product (*R*)-**1** in our model reaction does not vary significantly (ee = 75 ± 2%) when monitored over a period of 24 h.

(14) There is, however, a marked dependence of the ee on the solvent used. Study of the solvent dependence of the model aldol addition reaction of acetone to 4-nitrobenzaldehyde to provide aldol **1** resulted in ee values of 76% (DMSO), 76% (DMF), 67% (acetone), 61% ($CHCl_3$), 60% (THF),and 56% (CH_3CN). While chloroform was not the optimal solvent for this aldol reaction, it has provided improvements over DMSO in cases involving aliphatic acceptor substrates (see Table 2, entries 12 and 13).

Scheme 1. Enamine Mechanism of the Direct Catalytic Asymmetric Aldol Reaction Catalyzed by L-Proline



To gain further insight into the mechanism of this reaction we were motivated to use potential nonlinear effects as a mechanistic probe.[9c] Previous studies of the intramolecular Hajos−Eder−Sauer−Wiechert reaction had reported a nonlinear relationship between the ee of L-proline and the ee of the cyclodehydration product.[9a,b] This effect had been interpreted to suggest that two molecules of L-proline were involved in the transition state of this ketone−ketone intramolecular addition. In contrast to this report, however, we observed a linear effect for the reaction of acetone and 4-nitrobenzaldehyde in DMSO with L-proline as a catalyst (Figure 2). This result is consistent with the transition state proposed above, involving a single molecule of catalyst at the carbon−carbon bond-forming step. Two potential explanations for the differences between these two studies are (1) that the ketone−aldehyde addition reactions studied here are more facile and do not require a second molecule of L-proline or (2) that the intramolecular Hajos−Eder−Sauer−Wiechert reaction is sterically constrained such that the transition state we propose for our reactions is not accessible.

According to our reaction mechanism, formation of the enamine occurs following the formation of an iminium ion intermediate which can, in principle, partition between two different enamines. One pathway is depicted in Scheme 1 and leads to the acetone enamine that serves as *C*-nucleophile in the carbon−carbon bond-forming step. Another possible enamine is the one that results from abstraction of the α-hydrogen of L-proline thereby eliminating the chiral content of the molecule which upon hydrolysis leads to racemization of the catalyst. This potential side reaction might ultimately be responsible for decreased enantioselectivities. To rule out this possibility, we recovered L-proline from the reaction of acetone and 4-nitrobenzaldehyde in chloroform, determined its optical rotation, and compared it with the optical rotation of the catalyst prior to the reaction. We found that the value of the optical rotation determined in water for the recovered catalyst ($[\alpha]_D = -68.6$) was essentially the same as unreacted L-proline ($[\alpha]_D = -68.9$). We interpret this as strong evidence that racemization of the catalyst during the course of the reaction does not occur.

Aldol Reactions with Hydroxyacetone as an Aldol Donor Substrate. In addition to simple aliphatic ketones, we have investigated whether L-proline[15] and DMTC are capable of catalyzing aldol addition reactions using unprotected hydroxyacetone as a particularly intriguing member of the α-heteroatom-substituted family of ketone donors. In our studies with aldolase antibodies, we demonstrated for the first time that the hydroxyacetone aldol reaction is particularly valuable since a 1,2-diol unit is formed concurrently with carbon−carbon bond formation.[6d] A number of natural aldolase enzymes use dihydroxyacetone phosphate as substrates wherein the phosphate group is an essential component of the substrate.[5] Like 2-butanone, a hydroxyacetone donor may provide three different regio- and diastereomeric products and their corresponding enantiomers, and to date, only hydroxyl protected glyoxalate esters have been employed in the Mukaiyama-type catalytic asymmetric aldol reaction with aldehydes.[16]

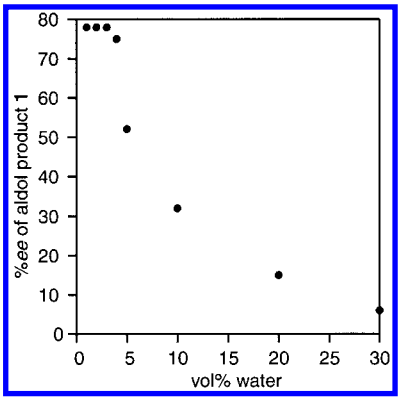


Figure 1. Effect of water on the enantiomeric excess of aldol product **1**.

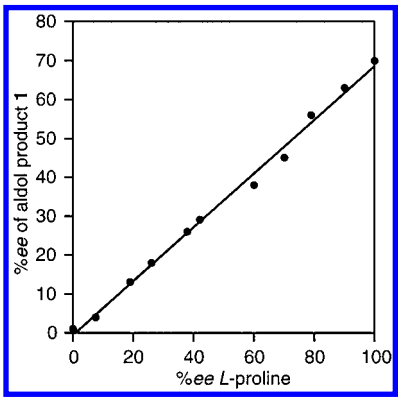


Figure 2. Linear effect in the L-proline catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde in DMSO. The line fits the equation $y = 0.69x - 0.47$, $R^2 = 0.995$.

We found that the aldol reaction between hydroxyacetone and cyclohexanecarboxaldehyde is catalyzed by both L-proline[15] and DMTC providing the corresponding *anti*-diols in 60% and 45% yield, respectively. In contrast, aldolase catalytic antibodies selectively provide the *syn*-diastereomer.[6d,e] We noted that DMTC-catalyzed hydroxyacetone reactions are significantly slower than the corresponding L-proline-catalyzed reactions at room temperature, therefore we performed these reactions at 37 °C. Most significantly, aldol product **15** (Table 3) was formed with excellent diastereoselectivity (dr >20:1) and enantioselectivity (ee >99%), and furthermore, no regioisomeric aldol products were detected by HPLC analysis.

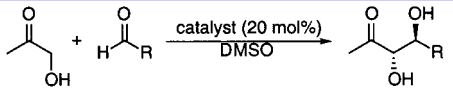
For these cases, the diastereoselectivities and enantioselectivities were determined by comparison with the *syn*-enantiomers obtained from aldehydes via the Horner−Wadsworth−Emmons reaction followed by Sharpless asymmetric dihydroxylations using either AD-mix-α or AD-mix-*β*.[17] The proline-catalyzed reactions were performed with both D- and L-proline rendering all four stereoisomers available and the establishment of

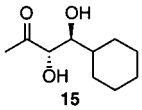
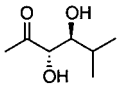
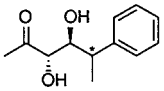
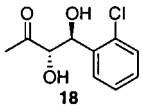
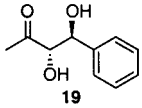
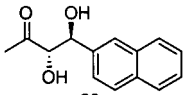
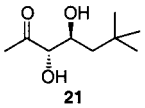
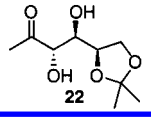
(15) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

(16) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708.

(17) Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605.

Table 3. Direct Asymmetric Aldol Reaction of Hydroxyacetone Catalyzed by L-Proline and DMTC as a Route to Anti-Diols



Product	Catalyst	dr[a]	Yield[b]	ee[c]
 **15**	(*L*)-Pro	>20:1	60%	>99%
	DMTC	>20:1	45%	95%
 **16**	(*L*)-Pro	>20:1	62%	>99%
	DMTC	n.d.	<5%	n.d.
 **17a + 17b** (2:1)	(*L*)-Pro	>20:1	51%	>95%[d]
	DMTC	n.d.	<5%	n.d.
 **18**	(*L*)-Pro	3:2[e]	95%[f]	67% (32%)
	DMTC	3:2	60%[f]	92% (76%)
 **19**	(*L*)-Pro	1:1	83%[f]	80% (n.d.)
	DMTC	1:1	52%[f]	95% (50%)
 **20**	(*L*)-Pro	3:1	62%[f]	79% (33%)
	DMTC	1:1	57%[f]	91% (36%)
 **21**	(*L*)-Pro	1.7:1	38%[f]	>97% (84%)[g]
	DMTC	n.d.	<5%	n.d.
 **22**	(*L*)-Pro	2:1	40%[f]	>97% (97%)[h]
	DMTC	n.d.	<5%	n.d.

[a] dr = anti:syn. The ratio was determined by ^{1}H NMR spectroscopy or weighing of the separated diastereomers. [b] Isolated yields after column chromatography. [c] ee of the anti isomer (ee of the syn isomer). Ee values were determined by chiral-phase HPLC analysis. [d] Identical ee and dr values for **17a** and **17b**. [e] Diastereomers could not be separated. [f] Combined yield of separated diastereomers. [g] Opposite absolute configuration of the β-position (Sharpless AD-β-product). [h] From optical rotation.

conditions for the separation of all four stereoisomers by chiral-phase HPLC techniques permitted an unambiguous assignment of the *anti*-configuration shown in Table 3 to aldol product diol **15**, which is further supported by its crystal structure.[15]

Similarly, high enantioselectivities were obtained for the *anti*-diols obtained from the reaction of hydroxyacetone with isobutyraldehyde, *rac*-2-phenylpropionaldehyde, 3,3-dimethyl butyraldehyde, and protected D-glyceraldehyde to afford aldol products **16**, **17a** and **17b**, **21**, and **22**, respectively (Table 3). In these cases, however, DMTC did not yield substantial amounts of any of the possible aldol products. The *anti*- and *syn*-1-deoxyhexose aldol products **22** provide an indication of the utility of these types of asymmetric aldol reactions as applied to carbohydrate chemistry.

In the case of α-substituted aliphatic aldehydes, excellent

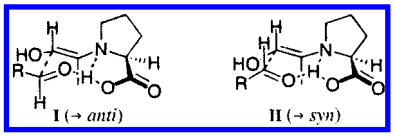


Figure 3. Potential transition states for the aldol reaction of hydroxyacetone with aldehydes.

diastereoselectivities can be obtained whereas aromatic as well as α-unsubstituted aldehydes and protected D-glyceraldehyde show only low diastereoselectivities. Again, catalysis by DMTC afforded significantly higher enantiomeric excesses for aromatic aldols **18**, **19**, and **20** with comparable diastereoselectivities albeit with reduced chemical yield as compared to L-proline. At this point, it can only be assumed that the additional heteroatom substitution within the ring system and the dimethyl substitution pattern of DMTC affects the conformation of the five-membered ring, thereby providing a different steric environment that ultimately leads to enhanced enantiomeric excesses. However, we have no evidence suggesting a mechanism by which the 5,5-dimethyl substitution improves the enantioselectivity for aromatic aldols.

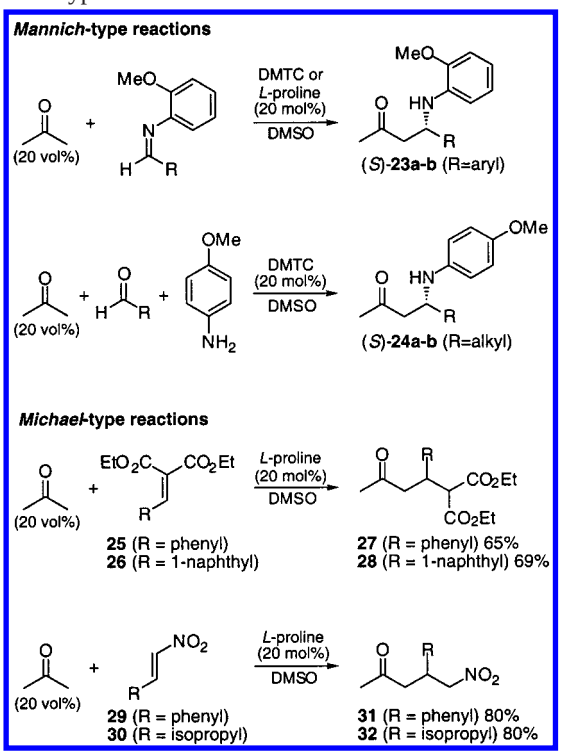
The following factors contribute to the excellent stereoselectivities observed for the aldol reaction of unmodified hydroxyacetone with aldehydes. In contrast to 2-butanone, the regiochemistry of enamine formation is controlled by the π-donating OH group, which interacts with the π^*-orbital of the C=C bond thereby stabilizing the hydroxyl enamine,[6e,18] and furthermore, the enamine double bond is presumed to possess a (*E*)-configuration due to minimization of 1,3-allylic strain.[19] However, it should be noted that the geometry of enamine formation may not necessarily be reflected in the diastereoselectivity of the products obtained. Thus, upon *re*-facial attack of the aldehyde by the *si*-face of the hydroxyacetone enamine, the anti-product is formed via a six-membered chairlike transition state **I** whereas the formation of the *syn*-products can be rationalized by boatlike transition state **II**, where the facial selectivity of the hydroxyacetone enamine is reversed (Figure 3).

We assume that due to decreased eclipsing interactions with sterically less hindered aldehydes or hydrogen bonding with α-oxygenated aldehydes, other transition states such as the boatlike transition state **II** may become increasingly important. Similar transition states have been proposed for other stereoselective reactions.[20]

Amino Acid-Catalyzed Mannich- and Michael-Type Reactions. To further expand the scope of amino acid based catalysis, we have examined other important carbon−carbon bond-forming reactions (Scheme 2). We recently reported the utility of this approach in catalysis of Mannich-type reactions.[21] In this study, L-proline and DMTC were also determined to be the most promising catalysts. In a typical reaction, the catalyst (20 to 30 mol %) was allowed to react with a variety of either preformed or in situ generated imines (using anisidine and various aldehydes) in DMSO/acetone (4:1) at room temperature for 24−48 h and the β-aminoketones of structural types **23a**−**b** and **24a**−**b** were isolated in up to 89% ee as products. Provided this success, here we have extended our amino acid based catalysis approach to Michael-type addition reactions of acetone

(18) Lin, J.-F.; Wu, C.-C.; Lien, M.-H. *J. Phys. Chem.* **1995**, *99*, 16903.
(19) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(20) For example, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.
(21) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 199.

Scheme 2. Amino Acid Catalyzed Mannich- and Michael-Type Reactions



to various Michael acceptors.[22] When L-proline (20 mol %) in DMSO/acetone (4:1) was reacted with alkylidene malonates **25** and **26** at room temperature for 12 h the Michael adducts **27** and **28** were isolated in 65% and 69% yield, respectively. These reactions, however, were not enantioselective. Further, as seen in our aldol and Mannich studies, a variety of ketones could be used as donor substrates. Similar results were obtained when β-nitro-olefins **29** and **30** were reacted with acetone in DMSO with L-proline catalysis. The acetone addition products **31** and **32** were isolated as the sole products in 80% yield each, but again the products were racemic. Nonetheless, these are the first catalytic acetone addition reactions to Michael acceptors and these mild reaction conditions may be of use in the construction of nonchiral compounds, and further studies concerning catalyst structure and reaction conditions might provide useful asymmetric variants of these reactions.[23]

Conclusions

In summary, we have demonstrated the scope and utility of the first amine catalysts of the direct asymmetric aldol reaction. Structure-based catalyst screening of available chiral amines revealed L-proline and DMTC as powerful catalysts of aldol addition reactions of unmodified ketones such as acetone, 2-butanone, and cyclic ketones with a variety of aldehydes. Both aromatic and aliphatic aldehydes react with acetone to provide the corresponding aldols in moderate to excellent ee values. 2-Butanone reacts with high regioselectivity, and in the case of hydroxyacetone, the aldol reaction proceeds with excellent regio-, diastereo-, and enantioselectivity to form *anti*-1,2-diols. Notably, even linear α-unsubstituted aliphatic aldehydes, e.g. pentanal, can be successfully employed in these direct aldol reactions. In comparison to L-proline, DMTC is the preferred catalyst of aldol reactions involving aromatic acceptor aldehydes. We assume that these novel reactions proceed via an enamine mechanism and a highly organized metal-free Zimmerman−Traxler-type transition state, which is supported by the observation of a linear effect for our model reaction and the loss of enantioselectivity upon addition of water to the reaction medium. The catalysts remain configurationally stable during the course of the reaction and are readily recovered for reuse under certain reaction conditions. Further, these catalysts are functional in related ketone addition reactions such as Mannich and Michael-type reactions.[23] The catalysts L-proline and DMTC are environmentally safe and available in both enantiomeric forms. The reactions do not require an inert atmosphere or heavy metals and can be performed at room temperature without preactivation of the donor substrates. Given the capacity of amines to act as catalysts via both nucleophilic (enamine-based) and electrophilic (iminium-based)[24] activation, their potential in catalytic asymmetric synthesis remains to be fully tapped.

Experimental Section

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concentrated H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), concentrated H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed by using silica gel Merck 60 (particle size 0.040−0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AMX 300 or a Bruker AMX 250. Chemical shifts are given in δ relative to tetramethylsilane (TMS); the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature; TMS served as internal standard ($\delta = 0$ ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR. HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-Detector, and a L-6200A Intelligent Pump. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\lambda = 589$ nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB matrix. Gas chromatography mass spectrometry (GCMS) experiments were performed on a Hewlett-Packard 5890 gas chromatograph and a 5971A mass selective detector. Electrospray ionization (ESI) mass spectrometry experiments were performed on an API 100 Perkin-Elmer SCIEX single quadrupole mass spectrometer.

General Procedure for the Preparation of Aldol Products. To a mixture of anhydrous DMSO (4 mL) and ketone donor (1 mL) was added the corresponding aldehyde (0.5 mmol) followed by L-proline or DMTC (20−30 mol %) and the resulting mixture was stirred at room temperature for 4−72 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated, and the aqueous layer was extracted several times with ethyl acetate, dried with anhydrous $MgSO_4$, and evaporated. The pure aldol products were obtained by flash column chromatography (silica gel, mixture of hexanes/ethyl acetate).

(4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone (1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.83 (m, 2H), 3.56 (d, $J = 3.2$ Hz, 1H), 5.25 (m, 1H), 7.52 (d, $J = 7$ Hz, 2H), 8.20 (d, $J = 7.0$ Hz, 2H); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O = 30:70, flow rate 0.5 mL/min, $\lambda = 254$ nm) t_R(major) = 18.76 min, t_R(minor) = 22.56 min;

(22) We have recently reported amine catalyzed sequential Michael−Aldol reactions to effect an asymmetric Robinson annulation reaction, see: Bui, T.; Barbas, C. F., III *Tetrahedron Lett.* **2000**, *41*, 6951.

(23) We have recently described enantioselective direct Michael additions of ketones to alkylidene malonates and β-nitro-olefins using (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine as a catalyst. Further, asymmetric three-component one-pot Knovenagel-Michael reactions are also catalyzed. Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett.* **2001** ASAP.

(24) (a) Jen, W.; Wiener, J. M. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *121*, 9874. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

$[\alpha]_D$ +46.2 (*c* 1, $CHCl_3$); HR-MS $C_{10}H_{11}NO_4Na^+$ 232.1411 (calcd. 232.0586), $C_{10}H_{11}NO_4$ 209.20.

(4*R*)-(4-Acetamidophenyl)-4-hydroxy-2-butanone (2): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.01 (s, 3H), 2.65 (m, 2H), 4.91 (m, 1H), 5.25 (m, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 9.88 (s, 1H); HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 85:15, flow rate 0.8 mL/min, λ = 254 nm) t_R(major) = 23.25 min, t_R(minor) = 20.12 min; $[\alpha]_D$ +12.5 (*c* 1, $CHCl_3$); HR-MS $C_{12}H_{15}NO_3Na^+$ 244.0955 (calcd. 244.0949), $C_{12}H_{15}NO_3$ 244.26.

(4*R*)-4-(1-Naphthyl)-4-hydroxy-2-butanone (3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.95 (m, 2H), 3.44 (bs, 1H), 5.34 (m, 1H), 7.45 (m, 3H), 7.82 (m, 4H); HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92.5:7.5, flow rate 1 mL/min, λ = 254 nm) t_R(major) = 17.86 min, t_R(minor) = 14.64 min; $[\alpha]_D$ +36.6 (*c* 0.5, $CHCl_3$); HR-MS $C_{14}H_{14}O_2Na^+$ 237.2604 (calcd. 237.2549), $C_{14}H_{14}O_2$ 214.26.

(4*R*)-4-(Cyclohexyl)-4-hydroxy-2-butanone (9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97−1.25 (m, 6H), 1.62−1.77 (m, 5H), 2.18 (s, 3H), 2.55 (m, 2H), 2.89 (bs, 1H), 3.80 (m 1H); HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 97:3, flow rate 1 mL/min, λ = 280 nm) t_R(major) = 11.54 min, t_R(minor) = 8.46 min; $[\alpha]_D$ +41.5 (*c* 1, $CHCl_3$); HR-MS $C_{10}H_{18}O_2Na^+$ 193.2561 (calcd. 193.2524), $C_{10}H_{18}O_2$ 170.254.

(5*R*)-6-Methyl-5-hydroxy-3-heptanone (10): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 6H), 1.14 (t, 3H), 1.75 (m, 1H), 2.52 (m, 4H), 3.02 (bd, 1H), 3.81 (m, 1H); HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99.4:0.6, flow rate 1 mL/min, λ = 280 nm) t_R(major) = 25.80 min, t_R(minor) = 19.98 min; $[\alpha]_D$ +49.8 (*c* 1, $CHCl_3$); ESI-MS $C_8H_{16}O_2$-144.1152 (calcd. 144.1152), $C_8H_{16}O_2$ (144.121).

(5*R*)-5-(4-Nitrophenyl)-5-hydroxy-3-pentanone (11): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, 3H), 2.5 (q, 2H), 2.82 (m, 2H), 3.7 (bd, 1H), 4.08 (m, 1H), 5.28 (m, 1H), 7.53 (d, J = 7 Hz, 2H), 8.20 (d, J = 7 Hz, 2H); ^{13}C NMR δ 7.4, 13.6, 19.1, 30.5, 36.8, 50.2, 68.9, 123.7, 126.3, 150.1, 211.3; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 90:10, flow rate 1 mL/min, λ = 280 nm) t_R(major) = 17.96 min, t_R(minor) = 14.72 min; $[\alpha]_D$ +43.7 (*c* 1, $CHCl_3$); ESI-MS $C_{11}H_{13}NO_4Na^+$ 246 (calcd. 246.0737).

(4*R*)-4-Hydroxy-2-octanone (12): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.4 (m, 6H), 2.18 (s, 3H), 2.57 (m, 2H), 3.01 (bs, 1H), 4.04 (bs, 1H); ^{13}C NMR δ 13.9, 22.5, 27.5, 30.7, 36.0, 49.8, 67.4, 210.1; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99.4:0.6; flow rate 1 mL/min, λ = 280 nm) t_R(major) = 24.04 min, t_R(minor) = 21.18 min; $[\alpha]_D$ +37.4 (*c* 1, $CHCl_3$); GC-MS $C_8H_{16}O_2^+$ 144 (calcd. 144.11).

(5*R*)-5-Hydroxynonane-3-one (13): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.16 (t, 3H), 1.39 (m, 6H), 2.54 (m, 4H), 3.07 (bs, 1H), 4.11 (bs, 1H); HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 99.4:0.6; flow rate 1 mL/min, λ = 280 nm) t_R(major) = 42.96 min, t_R(minor) = 28.50; $[\alpha]_D$ +31.6 (*c* 1, $CHCl_3$); GC-MS $C_9H_{18}O_2^+$ 158 (calcd.158.13).

General Procedure for the Catalytic Asymmetric Mannich-Type Reaction of Acetone and Preformed Aldimines. To a mixture of anhydrous DMSO (4 mL) and acetone (1 mL) was added the corresponding aldimine (0.5 mmol) followed by L-proline or DMTC (20 mol %) and the resulting homogeneous reaction mixture was stirred at room temperature for 24−48 h. Then, half-saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated, and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino ketones. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases.

(*S*)-4-(2-Methoxyphenylamino)-4-(4-nitrophenyl)butan-2-one (23a): ^{1}H NMR δ 2.15 (s, 3H), 2.99 (m, 2H), 3.87 (s, 3H), 4.97 (m, 2H), 6.29 (m, 1H), 6.64−6.79 (m, 3H), 7.55 (d, J = 10.5 Hz, 2H), 8.15 (d, 2H, J = 10.5 Hz); ^{13}C NMR δ 30.5, 50.9, 53.3, 55.4, 109.5, 111.1, 117.6, 120.9, 123.9, 127.3, 135.8, 146.9, 150.6, 205.4; HPLC (Daicel Chiralpak AD-RH, H_2O/MeCN = 90:10, 0.1% TFA, flow rate 0.5 mL/min, λ = 254 nm) t_R(minor) = 49.63 min, t_R(major) = 45.14 min; $[\alpha]_D$ +11.7 (*c* 1, $CHCl_3$); HR-MS $C_{17}H_{17}N_2O_3^+$ 297.1242 ($MH^+ - H_2O$: calcd. 297.1231), $C_{17}H_{18}N_2O_4$ (314.34).

(*S*)-4-(2-Methoxyphenylamino)-4-(1-naphthyl)butan-2-one (23b): ^{1}H NMR δ 2.16 (s, 3H), 2.98 (dd, J = 8.3, 16.2 Hz), 3.09 (dd, J = 4.0, 16.6 Hz), 3.88 (s, 3H), 4.96 (b, 1H), 5.70 (dd, J = 4.0, 8.3 Hz, 1H), 6.29 (m, 1H), 6.59−6.62 (m, 2H), 6.76 (m, 1H), 7.37 (m, 1H), 7.49−7.61 (m, 3H), 7.74 (m, 1H), 7.90 (m, 1H), 8.17 (m, 1H); ^{13}C NMR δ 30.6, 49.9, 50.5, 55.4, 109.3, 111.1, 116.9, 121.0, 122.1, 123.0, 125.5, 125.7, 126.4, 127.8, 129.2, 130.4, 134.0, 136.4, 137.3, 206.8; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 11.78 min, t_R(minor) = 8.61 min; $[\alpha]_D$ +115.6 (*c* 1, $CHCl_3$); HR-MS $C_{21}H_{20}NO^+$ 302.1526 ($MH^+ - H_2O$: calcd. 302.1539), $C_{21}H_{21}NO_2$ 319.40.

Typical Experimental Procedure for the Catalytic Asymmetric Three-Component One-Pot Mannich-Type Reaction of Acetone, *p*-Anisidine, and Aldehydes. To a mixture of anhydrous DMSO (4 mL) and acetone (1 mL) was added *p*-anisidine (0.5 mmol) and the corresponding aldehyde (0.5 mmol) followed by L-proline or DMTC (20 mol %) and the resulting homogeneous reaction mixture was stirred at room temperature for 24−48 h. The reaction mixture was further processed as described above.

(*R*)-4-Cyclohexyl-4-(4-methoxyphenylamino)butan-2-one (24a): ^{1}H NMR δ 0.96−1.25 (m, 5H), 1.45−1.87 (m, 6H), 2.13 (s, 3H), 2.58 (m, 2H), 3.62 (m, 1H), 3.74 (s, 3H, OMe), 6.56 (d, 2H, J = 8.8 Hz), 6.75 (d, 2H, J = 8.8 Hz); ^{13}C NMR δ 26.3, 26.4, 29.3, 29.5, 30.6, 41.7, 45.5, 55.7, 114.7, 114.9, 141.7, 151.9, 208.6; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 8.23 min, t_R(minor) = 14.88 min; $[\alpha]_D$ +3.1 (*c* 1, $CHCl_3$); HR-MS $C_{17}H_{26}NO_2^+$ 275.1885 (MH^+: calcd. 276.1970), $C_{17}H_{25}NO_2$ 275.39.

(*R*)-4-(4-Methoxyphenylamino)-5-methylhexan-2-one (24b): ^{1}H NMR δ 0.89 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 1.91 (m, 1H), 2.14 (s, 3H), 2.55 (m, 2H), 3.64 (m, 1H), 3.73 (s, 3H), 6.57 (d,J = 9.2 Hz, 2H), 6.75 (d, J = 9.2 Hz, 2H); ^{13}C NMR δ 18.4, 18.8, 30.6, 31.3, 45.2, 55.7, 56.2, 115.0, 141.6, 152.1, 208.4; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 97:3, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 15.35 min, t_R(minor) = 11.90 min; $[\alpha]_D$ +1.5 (*c* 1, $CHCl_3$); GC-MS $C_{14}H_{21}NO_2$ 235.32.

General Procedure for the Preparation of Michael Adducts 27, 28, 31, and 32. L-Proline (20 mol %) is added to a solution of β-nitroolefine or alkylidene malonate (1 mmol) in DMSO/acetone (4:1, 10 mL) and the mixture is stirred for 24 h at room temperature. The reaction mixture was treated with saturated ammonium chloride solution and the product was extracted with diethyl ether, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (silica gel, mixture of hexanes/ethyl acetate) afforded the corresponding Michael adducts. See also ref 23.

Ethyl 2-carboethoxy-5-oxo-3-phenylhexanoate (27): ^{1}H NMR δ 1.01 (t, 3H), 1.26 (d, 3H), 2.03 (s, 3H), 2.94 (m, 2H), 3.69 (d, 1H), 3.94 (m, 3H), 4.19 (q, 2H), 7.24 (m, 5H); HR-MS $C_{17}H_{22}O_5^+$ 306.3521 (MH^+: calcd. 306.3576), $C_{17}H_{22}O_5$ 306.25.

Ethyl 2-carboethoxy-3-(1-naphthyl)-5-oxohexanoate (28): ^{1}H NMR δ 0.87 (t, 3H), 1.21 (t, 3H), 2.02 (s, 3H), 3.14 (m, 2H), 3.86 (m, 3H), 4.17 (q, 2H), 7.36−7.84 (m, 6H), 7.84 (bd, 1H); HR-MS $C_{21}H_{24}O_5^+$ 356.4123 (MH^+: calcd. 356.4192), $C_{21}H_{24}O_5$ 356.41.

1-Nitro-2-phenylpentan-4-one (31): ^{1}H NMR δ 2.12 (t, 3H), 2.91 (d, J = 8 Hz, 2H), 4.00 (q, 1H), 4.66 (m, 2H), 7.20−7.30 (m, 5H); HR-MS $C_{11}H_{13}NO_3^+$ 207.2312 (MH^+: calcd. 207.2325), $C_{11}H_{13}NO_3$ 207.23.

5-Methyl-4-nitromethyl-2-hexan-2-one (32): ^{1}H NMR δ 0.92 (t, 6H), 1.82 (m, 1H), 2.16 (s, 3H), 2.43−2.63 (m, 3H), 4.41 (d, J = 5.8 Hz, 2H); GC-MS $C_8H_{15}NO_3$ 173 (calcd. 173.21).

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