The Direct Catalytic Asymmetric Aldol Reaction

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In the synthesis of complex molecular targets, the ability to control the stereoselectivity of the aldol reaction has raised this process to a level of prominence shared by few reactions. In most cases, however, the stoichiometric transformation of the active methylene partner into its enolate or an enol derivative is a drawback. Only recently have several reports addressed simple aldol addition involving both chemo- and enantioselectivity through use of catalysts. This paper presents recent advances in the direct catalytic asymmetric aldol reaction with chemical catalysis.

Introduction

The aldol reaction is one of the most powerful methods of forming carbon−carbon bonds, and few chemical reactions have matched the promise of the aldol reaction in its importance in the synthesis of complex molecules.[1] The classical aldol reaction is highly atom-economic, but suffers from problems in selectivity, notably chemo- and regioselectivity. A further challenge is to perform these reactions asymmetrically.[2] The potential to control the absolute configurations of newly formed stereogenic centers is of paramount importance for the synthesis of natural products. In general, control of stereochemistry has been accomplished diastereomerically through the use either of chiral aldehyde starting materials or of stoichiometric chiral auxiliaries attached to the donor enolate. However, the more elegant and economically most attractive way to introduce chirality into a molecule is undoubtedly through the use of a catalytic amount of chiral controller to induce the chiral transformation. Enantiocatalytic reactions have had the most significant impact on the development of synthetic organic chemistry over the last few years. The emergence of homogeneous enantioselective organometallic catalysis has had a decisive effect on the development of enantioselective organocatalytic reactions. There is a dichotomy between organic and organometallic/bioorganic catalysis, particularly with respect to their reactivity and applications. In metal-mediated enantioselective catalytic reactions, the metal atom plays an organizational role, by translating chiral in-

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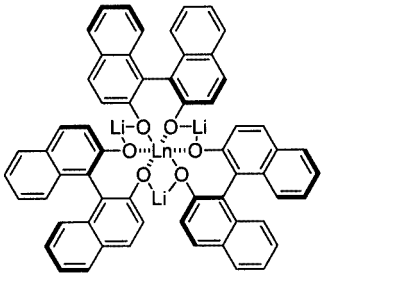
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

formation and activating the reagents. In the absence of a metal atom, the well-organized transition state required for enantioselective transformation can be formed either by passive or by dynamic interactions, as is the case in biological systems. Small organic molecules can be more closely related to enzyme- or antibody-catalyzed reactions than to organometallic processes. Indeed, these small organic molecules are often also known as artificial enzymes or enzyme mimics, because they show some characteristic features of bioorganic reactions. There has been some success in the use of asymmetric catalysts, although they normally rely on a Mukaiyama-type process, involving enol silyl ethers.[3] In these cases, stoichiometric amounts of base and/or adjunct reagents (such as silylating agents to form the enol silyl ethers) are required, decreasing the atom efficiency of the process. An exciting challenge in enhancement of the efficiency of the aldol reaction is to find a compound that will catalyze direct aldol addition without prior stoichiometric formation of the nucleophile and to do so asymmetrically. Biological-type catalysts (enzyme and antibodies) have had some selected successes.[4] In addition, direct catalytic asymmetric aldol addition involving α-unsubstituted aldehydes is an extremely challenging task. The fundamental problem is for the catalyst to differentiate between the α-protons of the acceptor aldehyde and of the donor ketone, as deprotonation of the aldehyde may result in undesirable self-aldolization products. Here we focus on recent advances in the direct catalytic asymmetric aldol reaction with chemical catalysis.

Discussion

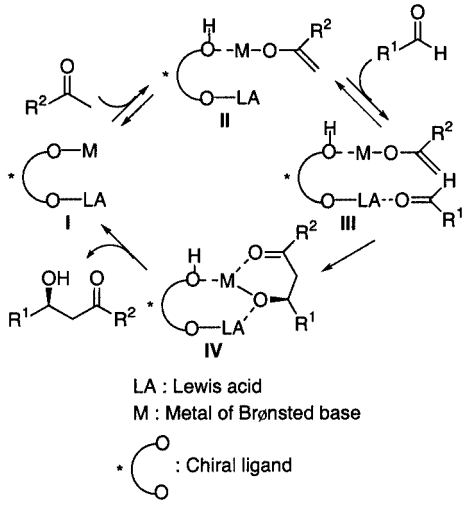
Organometallic Catalysts

The search for catalysts that mimic the selectivity of biochemical methods has been the subject of intense efforts in recent years. In particular, heterodimetallic complexes have been found to be suitable catalysts for the direct asymmetric aldol reaction. These catalysts can be regarded as enzyme mimics of the metal-containing type II aldolases (with a zinc cofactor) and they gave excellent yields and enantioselectivities. The first report of chemical catalysis in the direct catalytic asymmetric aldol reaction appeared in 1997, by Shibasaki et al.,[5] who developed a direct catalytic asymmetric aldol reaction between aldehydes **1** and unmodified ketones **2** by employing 20 mol% of the multifunctional catalyst (*R*)-LLB, which has an $LnLi_3$tris[(*R*)-binaphthoxide] structure. The reaction affords aldol adducts **3** in good to excellent yields (53−90%) and with moderate to high levels of enantiomeric excess, ranging from 44 to 94% *ee* (Scheme 1). Anhydrous LLB was more efficient than hydrated LLB, and higher yields were obtained when an excess of ketone was used.



Scheme 1. Direct asymmetric aldol reactions between aldehydes and unmodified ketones catalyzed by (*R*)-LLB

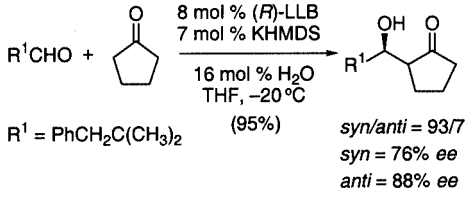
The catalyst incorporates a central lanthanum atom, which acts as a Lewis acid, and a lithium binaphthoxide moiety, which acts as a Brønsted base. This cooperative mode of action of the heterodimetallic catalyst makes efficient asymmetric aldol reactions possible without the need for any other activation of the starting materials. A proposed mechanism for this transformation is outlined in Scheme 2. The Brønsted base unit (OM) of catalyst **I** could deprotonate an α-proton of a ketone to generate the metal enolate **II**, while at the same time a Lewis acid unit (LA) could activate an aldehyde to give **III**. These reaction partners might react in the chelation-controlled, asymmetric environment to afford a metal β-oxoalkoxide **IV**. Proton exchange between the metal alkoxide moiety and a hydroxy proton of the aryl unit or an α-proton of a ketone could then generate an optically active aldol adduct with regeneration of the catalyst **I**.



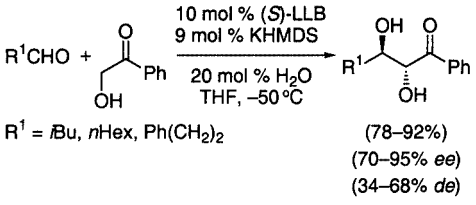
Scheme 2. Catalytic cycle for direct asymmetric aldol reactions with (*R*)-LLB

This direct asymmetric aldol reaction was further greatly improved by the development of a new heteropolymetallic asymmetric catalyst [(*R*)-LLB, KOH, and H_2O]. KOH was generated in situ by treatment of potassium hexamethyldisilazane with water. With 3−8 mol% of this catalyst, a variety of direct catalytic asymmetric aldol reactions were again found to proceed smoothly, affording aldol products in

good to excellent yields and in moderate to good enantiomeric excess (30−93% *ee*).[6] Interestingly, the use of this new heteropolymetallic asymmetric catalyst has for the first time resulted in a diastereoselective and enantioselective aldol reaction with cyclopentanone (Scheme 3). The LLB·KOH complex was able to catalyze an enantio- and diastereoselective direct aldol reaction with 2-hydroxyacetophenone, which provided the *anti*-α,β-dihydroxy ketones (Scheme 4).[7] It is also noteworthy that chiral aldehydes containing an acidic α-hydrogen atom can produce the corresponding aldol products with negligible racemization (0−4%). This reaction was found to be catalyst-controlled. Mechanistic studies of the reaction suggest that deprotonation of the ketone is rate-determining, and the water molecule may coordinate to La and K during the catalytic process. The aldol products have been successfully converted into synthetic key intermediates of epothilone A and bryostatin **7** (Scheme 5).[6]

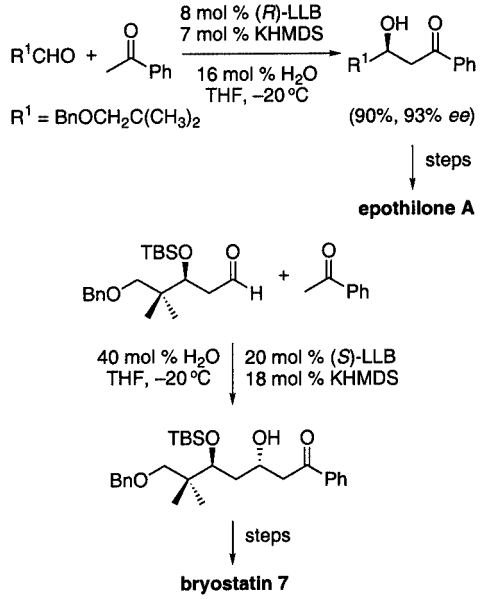


Scheme 3. Direct catalytic aldol reactions between cyclopentanone and aldehydes, mediated by LLB



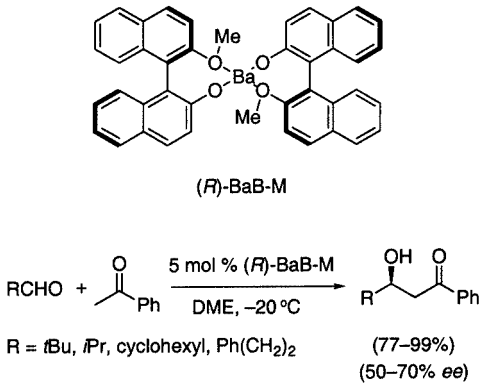
Scheme 4. LLB−promoted direct catalytic asymmetric aldol reactions between 2-hydroxyacetophenone and aldehydes

The similar catalyst BaB-M, derived from barium phenoxide, was developed by Shibasaki's group in order to eliminate the shortcomings of the LLB catalyst (requirements of excess amounts of ketone, 20 mol% of LLB, and a reaction time of more than 3 d).[8] After screening of a variety of ligands, solvents, and metal sources, it was found that the most effective barium catalyst, BaB-M, could be prepared from $Ba(OiPr)_2$ and 2.5 mol-equiv. of (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl (BINOL-Me) in DME. The asymmetric barium complex is possibly a monometallic bifunctional catalyst that possesses the functions of a Lewis acid and a Brønsted base. Shibasaki et al. were pleased to find that, in the presence of 5 mol% of BaB-M, the reaction between any aldehyde and 2 mol-equiv. of unmodified acetophenone proceeded much more rapidly than the same reactions in the presence of 20 mol% of LLB and 5 mol-equiv. of the ketone. Interestingly, as well as tertiary aldehydes, secondary aldehydes with acidic α-hydrogen atoms are also



Scheme 5. Synthesis of key intermediates en route to natural products

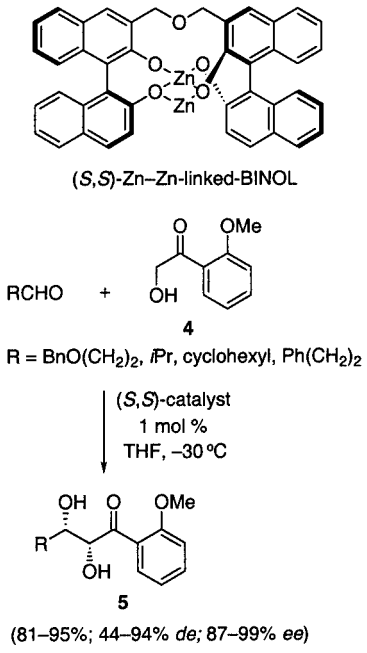
suitable substrates and result in cross-aldol condensation without the formation of self-aldol adducts. The aldol adducts were obtained in excellent yields, but unfortunately the enantioselectivities were rather modest (Scheme 6).



Scheme 6. Direct asymmetric aldol reactions between aldehydes and unmodified acetophenone, catalyzed by (*R*)-BaB-M

α-Hydroxy ketone donors are particularly interesting because of the utility of the polyoxygenated products, but they represent one of the most troublesome donors because of chemoselectivity issues. An advantage of asymmetric aldol condensation over asymmetric dihydroxylation is the formation of both stereocenters simultaneously with carbon−carbon bond formation. Shibasaki et al. recently reported that direct catalytic enantio- and diastereoselective aldol reactions with 2-hydroxy-2′-methoxyacetophenone (**4**) proceeded smoothly with as little as 1 mol% of a dinuclear zinc catalyst, Zn−Zn-linked BINOL, to afford α,β-dihydroxy ketones **5** in a highly *syn*-selective manner (*syn*/*anti* up to 97:3) and in excellent yields (up to 95%) and enanti-

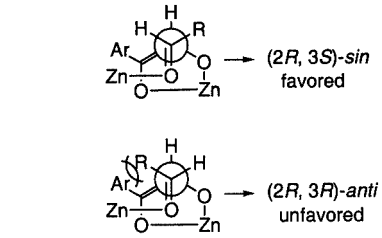
omeric excess (up to 99% *ee*) (Scheme 7).[9] In terms of catalyst loading, this is the most effective known small molecular catalyst for direct asymmetric aldol reactions. Efficient transformations of the α,β-dihydroxy ketones into α,β-dihydroxy esters and α,β-dihydroxy amides by regioselective rearrangements were also described.



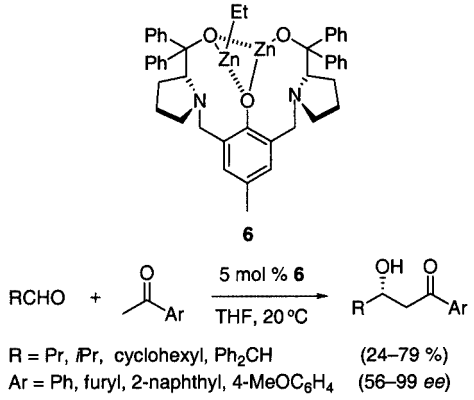
Scheme 7. Direct catalytic aldol reactions of 2-hydroxy-2′-methoxyacetophenone mediated by a Zn−Zn-linked BINOL catalyst

The formation of a chelate complex between the (*S*,*S*) catalyst and the enolate generated from **4** results in an efficient shielding of the (*Si*) face of the enolate, so that both *syn* and *anti* aldol adducts were obtained with an identical configuration at the α-position (2*R*) after the attack toward the aldehyde. Moreover, the electron-donating substituent (methoxy group) on the aromatic ring should increase the preference for one chelate complex [shielding (*Si*) face] over the other [shielding (*Re*) face] through participation of the 2′-methoxy group in chelate formation. Thus, the (*Si*) face shielding would become more effective, resulting in higher *ee* values in both *syn* and *anti* products. On the other hand, enhanced *syn* selectivity can be explained by the steric hindrance to aldehydes by the aromatic ring in the enolate. In view of the positions of the two Zn atoms in the proposed structure of Zn−Zn-linked BINOL, it seems reasonable to assume that the enolate would coordinate to one Zn metal atom and the aldehyde would coordinate to the other in a manner such as shown in Scheme 8. The transition state producing *syn*-diols is sterically more favorable.

Trost and co-workers used a novel design of catalyst to prepare **6**, which was used in a direct asymmetric aldol reaction between aryl ketones and aldehydes (Scheme 9).[10] The required crown ligand was prepared from methyl prolinate and *p*-cresol. Thus, the known 2,6-bis(bromomethyl)-*p*-cresol, prepared in two steps from *p*-cresol with formaldehyde followed by HBr, reacts smoothly with the hydrochloride of methyl prolinate in the presence of triethylamine in dichloromethane at room temperature (85% yield). Addition of phenylmagnesium chloride in THF at room temperature completes the synthesis of the crown compound (> 99.5% *ee* by chiral HPLC), in 74% yield. The solution formed by treating the above ligand in THF with a solution of diethylzinc in hexane in the presence of triphenylphosphane sulfide and molecular sieves provided the catalyst **6**.

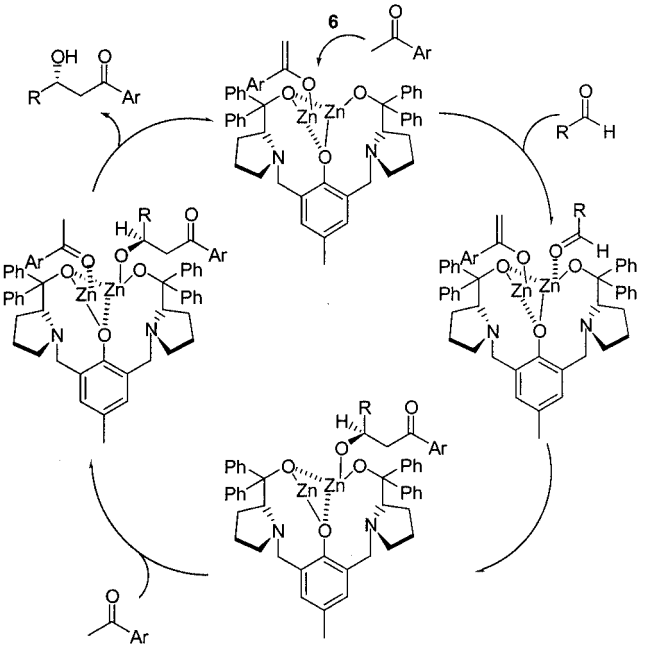


Scheme 8. Transition states resulting in *anti* or *syn* diols through use of a Zn−Zn-linked BINOL catalyst



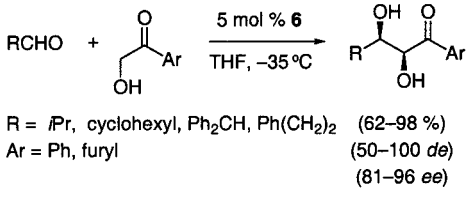
Scheme 9. Direct asymmetric aldol reactions between aldehydes and unmodified ketones promoted by the dimetallic catalyst **6**

To establish the nature of the catalysis, the stoichiometry of the metal catalyst to the ligand was examined through the evolution of ethane gas. The presence of three active hydrogen atoms suggested the possible involvement of more than one zinc atom; indeed, addition of 2 equiv. of diethylzinc per ligand liberated 3 equiv. of ethane to form **6**. That one additional alkyl−metal bond remained was revealed by addition of water, which liberated the fourth equivalent. These observations support the proposed structure for **6**, invoking a dimetallic catalyst as the initial species, which reacts with a ketone to liberate the fourth equivalent of ethane and initiate the catalytic cycle as depicted in Scheme 10. The role of two proximal zinc species is to provide both an initial zinc atom to form the requisite enolate and a second zinc atom to function as a Lewis acid to coordinate the aldehyde.



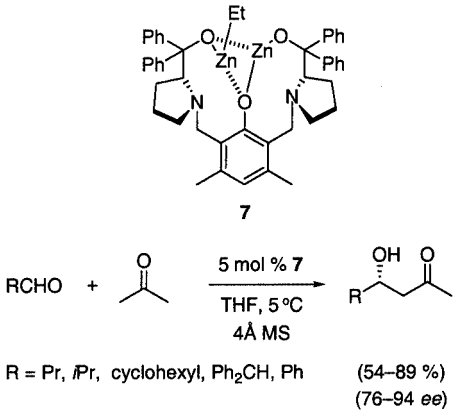
Scheme 10. Catalytic cycle of the direct asymmetric aldol reaction mediated by compound **6**

The catalyst **6** has been recently used by Trost et al. in direct asymmetric aldol reactions with α-hydroxy ketones as donors (Scheme 11).[11] The effectiveness of this catalyst permits the use of nearly stoichiometric amounts of both partners. This catalytic system comes closest to reaching the ideal atom-economical version of the asymmetric aldol condensation (the ideal being stoichiometric amounts of the two reactants, with anything else being needed only catalytically). In addition, a surprising effect of the donor on facial selectivity with respect to the aldehyde was found.



Scheme 11. Direct catalytic aldol reaction of α-hydroxy ketones mediated by compound **6**

Trost et al. have more recently explored the use of acetone as the active methylene partner, α-unbranched aldehydes as the carbonyl partner, and a second generation of dinuclear zinc catalyst **7** in the direct asymmetric aldol reaction (Scheme 12).[12] Somewhat improved results were obtained when using catalyst **7** over **6** under otherwise identical conditions. The absolute configuration with the same catalyst is the same for both acetone and acetophenone. For α-unbranched aldehyde partners, the catalyst **7** gives the best results yet recorded. The active catalyst **7** was prepared in situ by treatment of the appropriate ligand with 2 equiv. of diethylzinc, involving the liberation of 3 equiv. of ethane, followed by a fourth equivalent by reaction with the active methylene partner (acetone). The chiral space arises from the conformational preferences of the diphenylcarbinol moieties. Thus, the two zinc atoms act in concert to activate each of the two partners. The better results obtained with catalyst **7** than with **6** may result, in the former case, from minimization of the distortion of the chiral pocket in the case of acetone because of the buttressing effects with the 3,5-dimethyl groups of the phenol ring.

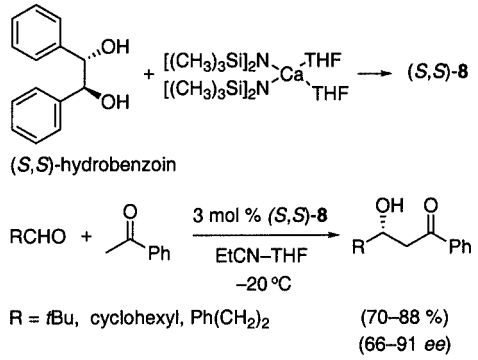


Scheme 12. Direct aldol reactions between acetone and α-unbranched aldehydes, catalyzed by dinuclear zinc compound **7**

Noyori et al. devised a chiral (hydrobenzoin)Ca complex (*S*,*S*)-**8**, which catalyzes the asymmetric aldol reaction between acetophenone and aliphatic aldehydes directly without structural modification (Scheme 13).[13] The corresponding aldol products were obtained in enantiomeric excesses of up to 91% *ee*. The reactivity of this Ca catalyst is several times higher than those of the other known catalyst systems. There is a notable nonlinear relationship between the enantiomeric excess of the chiral hydrobenzoin and an aldol product. Although the detailed structure of the (*S*,*S*)-**8** catalysts remains unclear, coldspray ionization mass spectrometry demonstrated that the major species is oligomeric. The properties of the Ca catalysts are capable of further modification, with the possibility of providing more efficient catalysts, as various chiral hydrobenzoin derivatives are available.

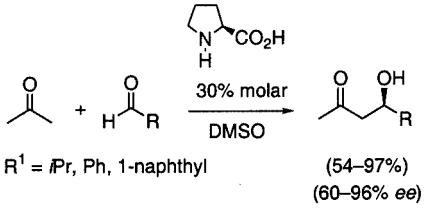
Metal-Free Organocatalysis

Since its discovery, amino acid catalyzed asymmetric Robinson annulation has received a considerable amount of synthetic and mechanistic interest.[14] Of the amino acids, L-proline was found to be the most general catalyst, and L-phenylalanine the most efficient. List et al. initially asked a seemly question: If proline, like natural and antibody aldolases, catalyzes intramolecular aldol reactions through an enamine mechanism, could it also catalyze the intermolecular aldol reaction? Indeed, this group has recently established that a simple organic molecule, L-proline, can act like an enzyme in promoting reactions between acetone and

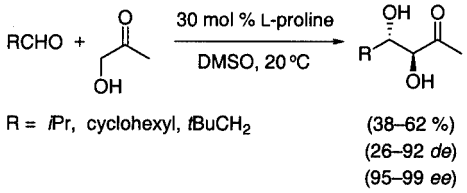


Scheme 13. Aldol reactions between acetophenone and aliphatic aldehydes, directly catalyzed by the chiral (hydrobenzoin)Ca complex (*S*,*S*)-**8**

various aldehydes (Scheme 14).[15] In these studies, aromatic aldehydes gave aldol products with *ee* values of around 70%, while α-mono- and α-disubstituted aliphatic aldehydes provided aldols in excess of 95% *ee*. This result constitutes the first low-molecular-weight amine-catalyzed direct asymmetric aldol reaction. It represents a promising alternative catalytic concept to the commonly used metal-containing catalysts. List and Notz demonstrated that proline can also catalyze a highly regio- and diastereoselective aldol reaction between hydroxyacetone and aldehydes to provide *anti*-1,2-diols with excellent enantioselectivities (Scheme 15).[16] While the *syn*-1,2-diol unit may be viewed as an accessible stereochemical element, thanks to Sharpless asymmetric dihydroxylation (AD) of (*E*)-olefins, the diastereomeric *anti*-1,2-diols are more difficult to obtain, mainly because the corresponding (*Z*)-olefins show reduced enantioselectivity in AD.

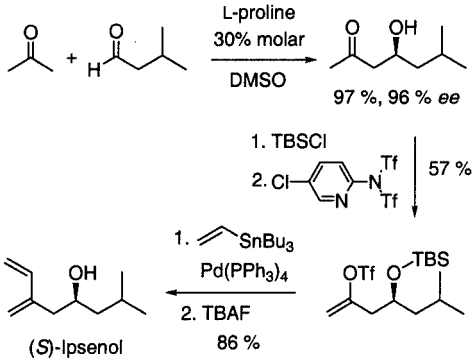


Scheme 14. L-Proline-catalyzed direct aldol reactions between acetone and aldehydes



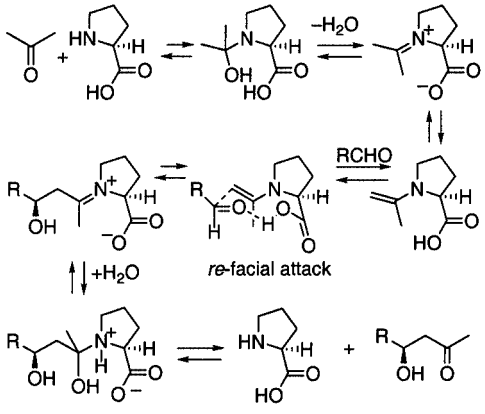
Scheme 15. L-Proline-catalyzed direct aldol reactions between hydroxyacetone and aldehydes, affording *anti*-1,2-diols

The proline-catalyzed direct asymmetric aldol reaction was extended to α-unsubstituted aldehydes to give the corresponding aldols in 22−77% yields and up to 95% *ee*. Yields and *ee* values are modest in some cases, but similar to those obtained with Shibasaki's, Trost's, and Noyori's catalysts. The reaction can easily be performed on a multigram scale, required for complex molecule syntheses. This was demonstrated with a short asymmetric total synthesis of (*S*)-ipsenol, a major component of the sex pheromone of the bark beetle, needed in kilogram quantities for insect traps. This synthesis is one of the shortest reported, and highlights the potential of the proline-catalyzed aldol reaction for the asymmetric synthesis of biologically active compounds (Scheme 16).[17] Advantages of the proline-catalyzed reactions include operational simplicity and availability of both enantiomeric catalysts. For an efficient catalytic process, however, a decrease in the required amount of catalyst (typically around 30 mol%) would be desirable. In addition, the large excess of the ketone component is another disadvantage.



Scheme 16. Asymmetric total synthesis of (*S*)-ipsenol through a proline-catalyzed aldol reaction

The postulated mechanism for the L-proline-catalyzed direct aldol reaction closely resembles the aldolase type I reaction mechanism. These enzymes work through an enamine-based mechanism and do not require a metal cofactor. This catalyst can hence be regarded as an enzyme mimic of the metal-free aldolase of type I. According to this proposal, proline functions as a microaldolase, with the secondary amine acting as a nucleophilic enamine catalyst and the carboxylic acid moiety as a general Brønsted co-catalyst (Scheme 17).[18]



Scheme 17. Mechanistic explanation of the L-proline-catalyzed direct aldol reaction

C. F. Barbas III et al. have studied model aldol addition reactions between acetone and 4-nitrobenzaldehyde with several amino acids as catalysts.[19] These workers focused their screening on various commercially available or readily prepared chiral compounds structurally and chemically related to L-proline. Comparison of 2-azetidinecarboxylic acid and pipecolic acid with L-proline showed that the five-membered pyrrolidine ring is best suited as the secondary cyclic amine moiety. Structure-based catalyst screening identified L-proline and 5,5-dimethylthiazolidinium-4-carboxylate (DMTC) as the most powerful amino acid catalysis for the reaction of both acyclic and cyclic ketones as aldol donors with aromatic and aliphatic aldehydes to afford the corresponding aldol products with modest to good diastereo- and enantioselectivities. These reactions are assumed to proceed through a metal-free Zimmerman−Traxler-type transition state and involve an enamine intermediate, which is supported by the observation of a linear effect for the model reaction and the loss of enantioselectivity upon addition of water to the reaction medium.

Conclusions

This article focuses on recent advances in the chemically catalyzed direct catalytic asymmetric aldol reaction. Among the newly developed catalysts are dimetallic complexes that incorporate a metal center acting as a Lewis acid, together with a metal moiety that acts as a Brønsted base. This cooperative mode of action of the heterodimetallic catalysts makes efficient asymmetric aldol reactions possible without the need for any other activation of the starting materials. Some amino acids, particularly L-proline, are able to catalyze the intramolecular aldol reaction by an enamine mechanism, as in natural and antibody aldolases. This represents an alternative catalytic concept to the commonly used metal-containing catalysts.

Acknowledgments

Support for this work by the DGI-MCYT (Project BQU2000−0645) is gratefully acknowledged.

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