HETEROCYCLES, Vol. , No. , , pp. -. © The Japan Institute of Heterocyclic Chemistry
Received, , Accepted, , Published online, . COM-06- (Please do not delete.)

ORGANOCATALYTIC ASYMMETRIC SYNTHESIS USING PROLINE AND RELATED MOLECULES. PART 1.

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Abstract – Organocatalytic asymmetric synthesis has been extensively studied and several important procedures for preparing optically active organic compounds have been developed. Research in this area has progressed rapidly in the last ten years. This review addresses the most significant advances in asymmetric synthesis using proline and related chiral organocatalysts mainly focusing on aldol reactions from the viewpoint of synthetic interests. This includes (1) proline-catalyzed aldol reactions, (2) proline-related chiral catalysts, and (3) other types of amino acid catalysts.

INTRODUCTION

Catalytic asymmetric synthesis is one of the most important and rapidly growing areas in modern organic chemistry, and several methods have been developed to date.[1] In this context, chiral metal catalysts hold a central position, and this is why Sharpless, Knowles, and Noyori won the Nobel Prize for Chemistry in 2001.

Although the outstanding ability of asymmetric metal catalysts has been well-established in several fields, including materials science, medicinal chemistry, and natural products chemistry, a great deal of attention has recently been focused on the development of new asymmetric catalyses for organic compounds by organic molecules to give organic products, so-called “asymmetric organocatalysis”. This storm of research started just after the turn of this century, and several papers have been published, as represented by some important monographs and review articles.[2, 3]

Among various types of organocatalysts, L-proline, a naturally occurring cyclic α-amino acid, has been most extensively studied. Historically, before L-proline gained such prominence, Prof. Yamada had noticed the utility of optically active secondary amines in asymmetric Robinson annulation.[4] Soon after

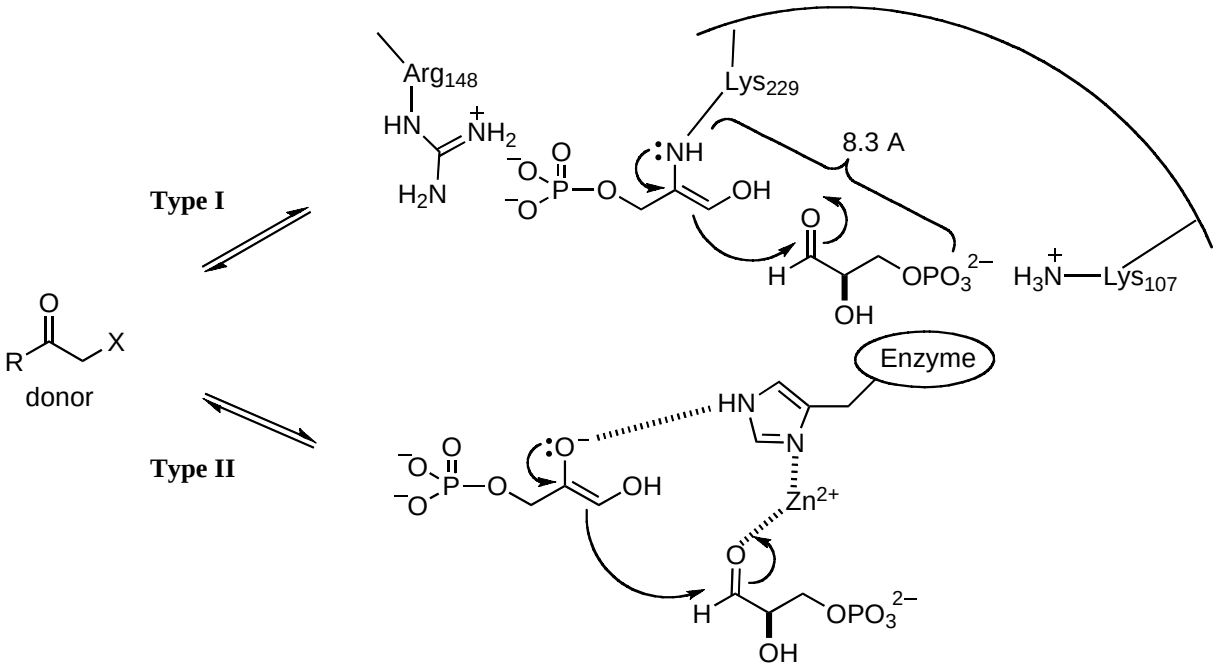
that, Eder, Sauer, and Wiechert,[5] Hajos and Parrish,[6] and Agami[7] reported their monumental works on L-proline-catalyzed asymmetric Robinson annulation with excellent enantioselectivity.

In this and the following reviews, we will be concerned with recent advances in proline-catalyzed asymmetric synthesis as well as the development of proline-related organocatalysts. This covers mostly the significant examples published in the period 2000 to 2006.

1. PROLINE-CATALYZED ALDOL REACTIONS

1.1. INTERMOLECULAR ALDOL REACTIONS

For the design of new catalysts for use in asymmetric synthesis, the most intelligent model is Nature's catalysts, enzymes. In fact, the asymmetric aldol reaction based on aldolase enzymes has inspired many synthetic chemists due to its fundamental importance in carbon-carbon bond-forming reactions. Two types of aldolases are known to exist in biological systems: Type I aldolases, which use enamine-based activation, and Type II aldolases, which use a Zn^{2+} cofactor as a Lewis acid promoter (Scheme 1).[8]

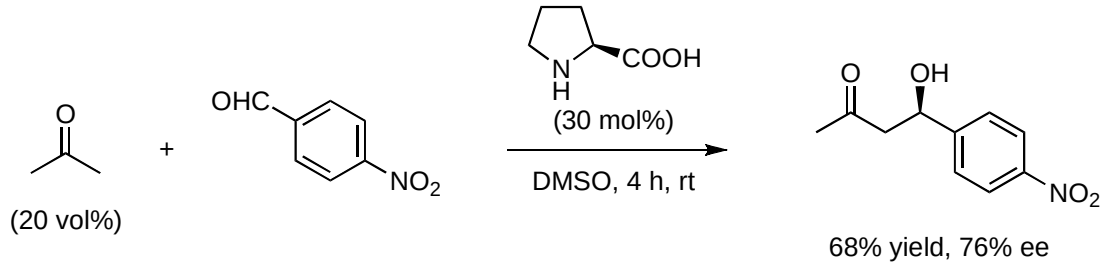


Scheme 1. General mechanism for the Type I and Type II aldolases

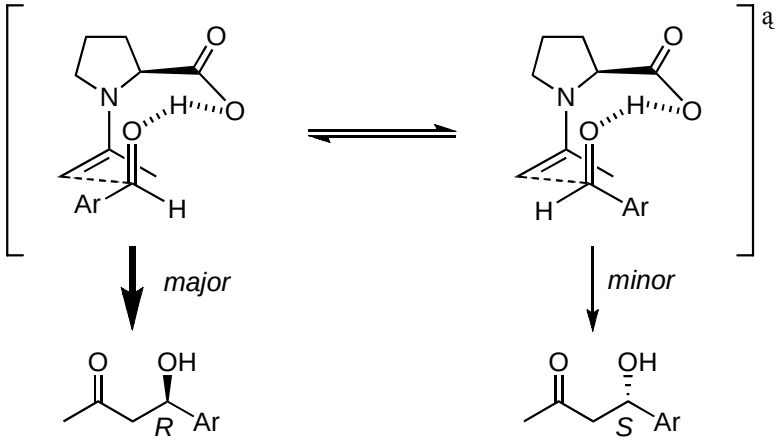
Important contributions in the study of catalytic asymmetric aldol reactions based on a Type II aldolase model were made independently by Watanabe[9] and Shibasaki.[10] On the other hand, much more time was needed for the discovery of new insights into Type I aldolase-based asymmetric aldol reactions, and thereafter the new field of organocatalyst research could flower.[11]

In 2000, List, Lerner, and Barbas III reported the first success in the direct intermolecular asymmetric aldol reaction using L-proline as an organocatalyst.[12, 13] For example, the reaction of acetone (excess) with

p-nitrobenzaldehyde in the presence of L-proline (30 mol%) in DMSO gave the desired aldol adduct in 68% yield with 76% ee (Scheme 2). They screened a variety of different commercially available α-amino acids and found that L-proline or *trans*-4-hydroxy-L-proline was the most promising catalyst in this type of asymmetric aldol reaction. Extensive investigations on the theory and mechanism of this asymmetric aldol reaction have centered on Houk's group,[14, 15] and the generally accepted transition state model for the L-proline-catalyzed aldol reaction is shown in Scheme 3. In this model, the proline catalyst provides dual-mode activation: the pyrrolidine amine condenses with the ketone substrate to form a nucleophilic enamine intermediate, and the carboxylic group increases the electrophilicity of the aldehyde via the formation of an internal hydrogen bond. In the preferred transition state the large Ar group takes the position away from the enamine substituents, leading to *re*-facial selectivity.

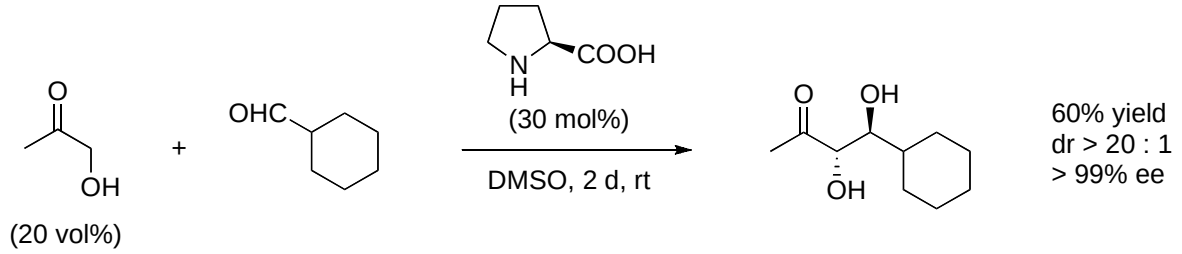


Scheme 2. L-Proline-catalyzed asymmetric aldol reactions

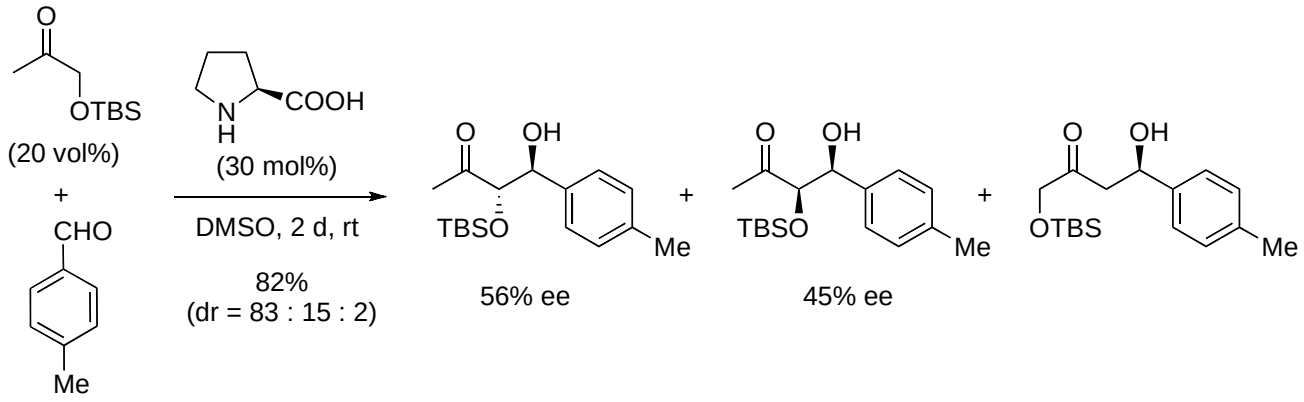


Scheme 3. Proposed transition states for the L-proline-catalyzed asymmetric aldol reactions

These results are useful for combining a variety of ketones with a variety of aldehydes. A typical example is shown in Scheme 4 for the highly diastereoselective and enantioselective synthesis of *anti*-1,2-diol derivatives using hydroxyacetone as a ketone donor component (dr up to >20 : 1, ee up to >99%).[13, 16] In this case, the reaction occurred exclusively at the more substituted carbon atom. On the contrary, when TBS-protected hydroxyacetone was used as the substrate, the corresponding *anti*-adduct was obtained in slightly reduced diastereo- and enantioselectivity (Scheme 5).[17]

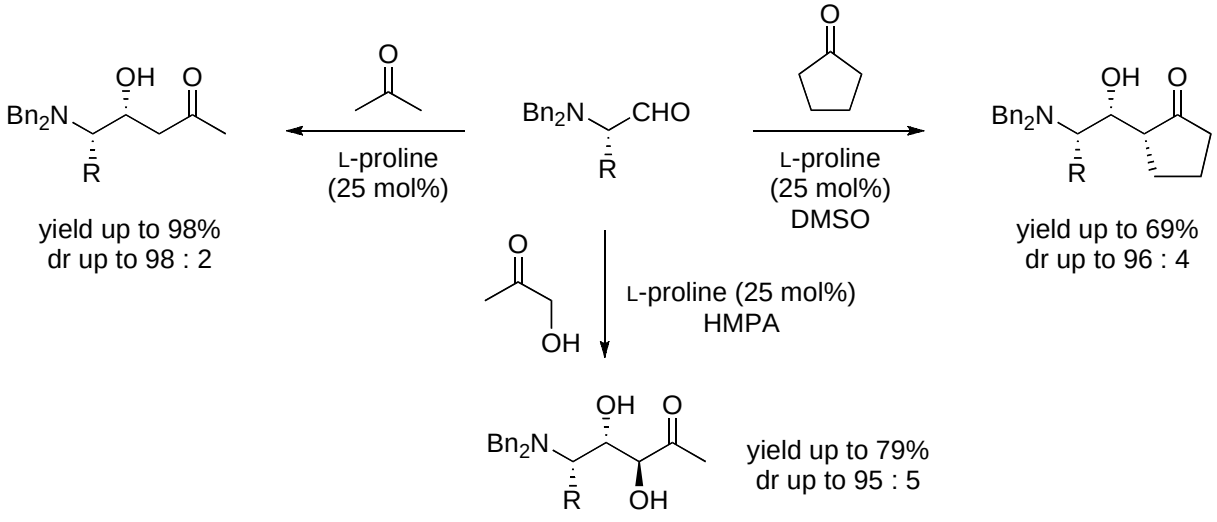


Scheme 4. L-Proline-catalyzed asymmetric synthesis of *anti*-1,2-diol derivatives

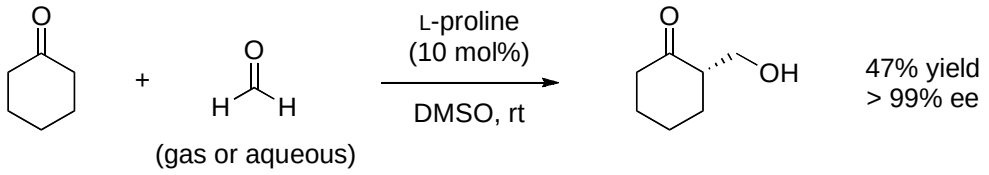


Scheme 5. L-Proline-catalyzed asymmetric aldol reactions of TBS-protected hydroxyacetone

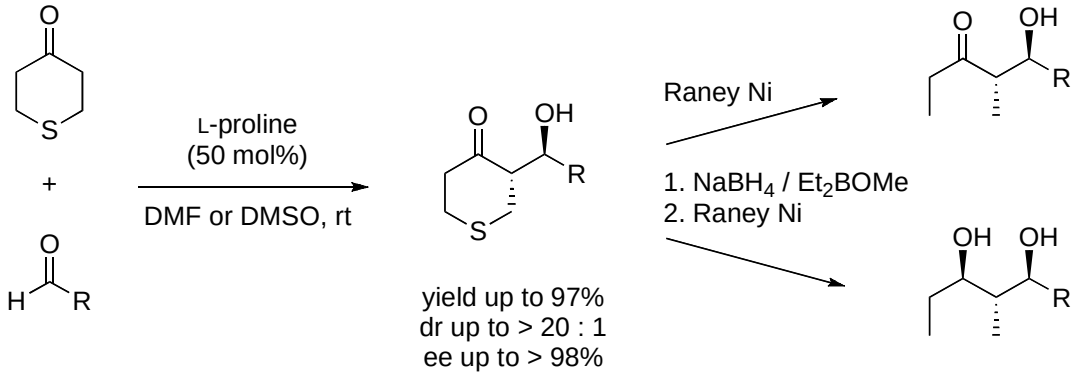
Other examples employing a variety of ketone-aldehyde combinations clearly demonstrate the general utility of proline-catalyzed asymmetric aldol reactions for preparing several substituted hydroxyketone derivatives: the diastereoselective synthesis of γ-amino-β-hydroxyketone derivatives with α-amino aldehydes in moderate to excellent yields (Schemes 6),[18] asymmetric α-hydroxymethylation with formaldehyde with >99% ee (Scheme 7),[19] and convenient route to a 3-pentanone equivalent with tetrahydro-4*H*-thiopyran-4-one with excellent enantioselectivities (Scheme 8).[20]



Scheme 6. L-Proline-catalyzed asymmetric aldol reactions of chiral α-amino aldehydes[18a]

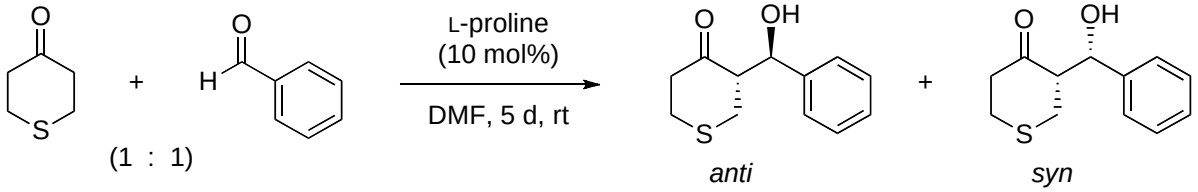


Scheme 7. L-Proline-catalyzed asymmetric aldol reactions of formaldehyde



Scheme 8. L-Proline-catalyzed asymmetric aldol reactions of thiopyranone

It has been reported that the addition of water could accelerate the aldol reaction (Scheme 9)[21] and the enantioselectivity could be considerably improved in the presence of chiral diols as an additive.[22]



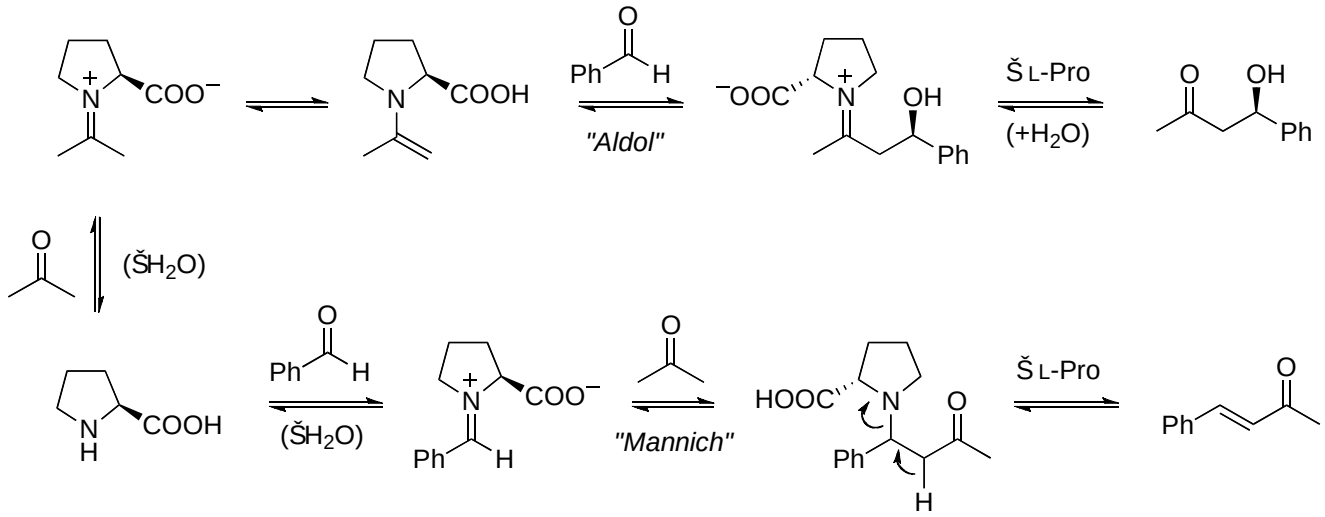
water (mol%)	conversion (%)	*anti / syn*	ee *(anti)* (%)
0	3	> 20 :1	65
100	22	> 20 :1	86
200	37	> 20 :1	93
500	60	> 20 :1	98
1000	41	> 20 :1	92

Scheme 9. Effect of water on the L-proline-catalyzed asymmetric aldol reaction[21a]

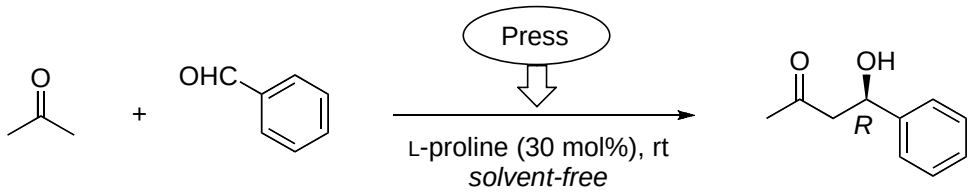
The synthetic utility of proline-catalyzed asymmetric aldol reactions has also been recognized for other substrates such as thiomethoxyacetone and 2-hydroxyacetophenones.[23-26]

The major limitations in these aldol reactions are the need for high-boiling-point polar solvents such as DMF and DMSO, a relatively long reaction period, and the formation of significant amounts of dehydrated by-products. The formation of enone by-products indicates that the normal aldol and Mannich-type processes compete with each other in the proline-catalyzed asymmetric aldol reactions as

depicted in Scheme 10. We found that this problem could be solved by conducting the reaction under high-pressure (Scheme 11).[27] It can be conceivable that the rate of aldol process might be much greater than that of Mannich one, probably due to the low nucleophilicity of the donor acetone molecule (pK_a 26.5 in DMSO) compared with its enamine congener under these virtually neutral conditions. It does not limit to this example, and the use of physical force, such as microwave, could generally serve as a powerful technique for accelerating proline-catalyzed asymmetric aldol reactions.[28, 29]



Scheme 10. Plausible mechanism for the L-proline-catalyzed asymmetric aldol reactions



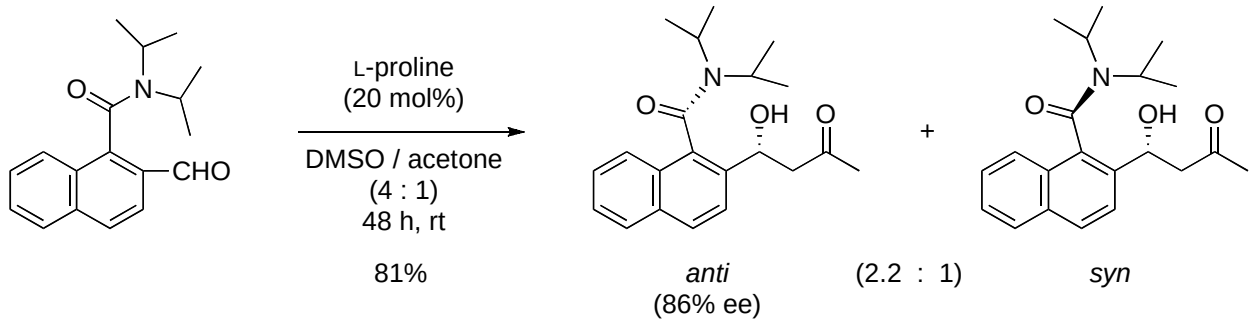
conditions	yield (%)	ee (%)
0.1 MPa, 24-48 h	62	60
0.2 GPa, 24 h	90	72
0.5 GPa, 24 h	90	64
0.8 GPa, 24 h	88	63

Scheme 11. Pressure effect for the L-proline-catalyzed asymmetric aldol reaction

In many cases, the direct condensation of ketones with α-unsubstituted aldehydes under the catalysis of L-proline does not give rise to the corresponding aldol adducts in good yields.[30] This might be ascribed to the tendency of those aldehydes to undergo self-aldol condensation. We found that this problem could be solved by devising new synthons of straight chain aliphatic aldehydes, and this will be discussed later.

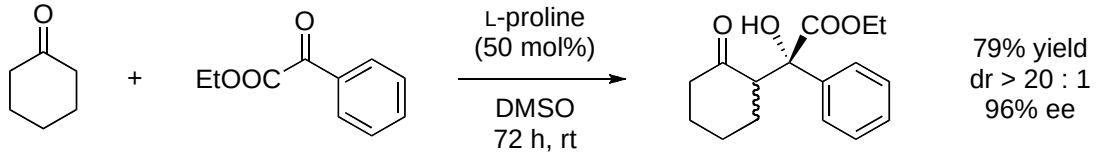
Some attractive approaches to the dynamic kinetic resolution of atropisomeric amides based on proline-catalyzed asymmetric aldol reactions have appeared in the literature (Scheme 12)[31] and

asymmetric transfer aldol reactions (40-91% yields, 48-86% ee).[32] The former method might be of great value in simultaneously producing two or more stereogenic carbon centers in a single-step operation with high enantioselectivities (major compound, ee up to 95%).

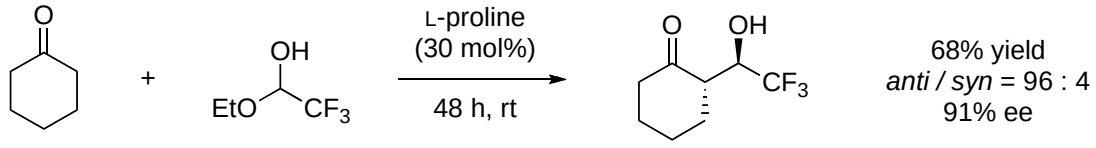


Scheme 12. Dynamic kinetic resolution of atropisomeric amides based on the L-proline-catalyzed asymmetric aldol reaction

Proline-catalyzed asymmetric aldol reactions have also been shown to be effective for a variety of other activated carbonyl compounds as aldol acceptors: ketomalonates,[33] acyl cyanides,[34] phenylglycolates (Scheme 13),[35] 1,2-diketones,[36] α-keto phosphonates,[37] trifluoroacetaldehyde ethyl hemiacetal (Scheme 14),[38] and isatins.[39]



Scheme 13. L-Proline-catalyzed asymmetric aldol reactions of phenylglycolate

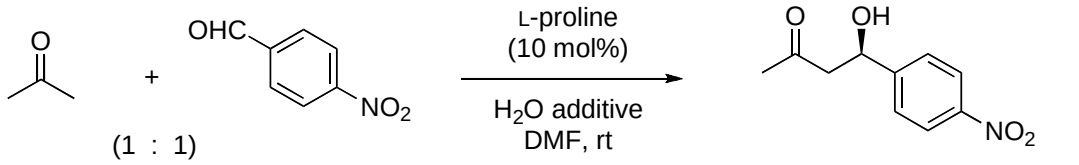


Scheme 14. L-Proline-catalyzed asymmetric aldol reactions of the CF_3CHO derivative

1.2. ALDOL REACTIONS IN UNUSUAL MEDIA

The solvent plays an important role in asymmetric catalysis. In this sense, a great deal of attention has recently been focused on the use of water as a solvent. Although there is some controversy on organocatalysis in aqueous media,[40] asymmetric reactions in aqueous media are probably very useful in view of the increasing importance of environment-friendly systems.

In 2002, Barbas III and coworkers reported that the L-proline-catalyzed asymmetric aldol reaction proceeded quite smoothly in aqueous media.[41] Thereafter, other groups also found that the selectivities and reaction rates were both considerably improved in aqueous media compared with reactions in standard organic solvents.[42-45] For example, in the asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde, the addition of water dramatically increased the product yield without the use of excess ketone (Scheme 15).[43] The best result was obtained with 500 mol% of water, which gave the product in 66% ee. In spite of these important observations, the role of water in asymmetric aldol reactions of this type is still unclear and remains a challenging subject.

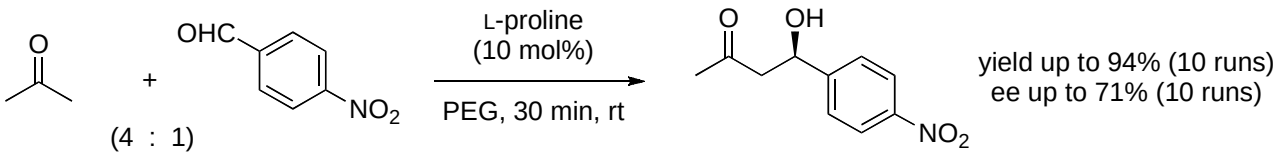


H_2O (mol%)	reaction time (d)	yield (%)	ee (%)
0	6	10	58
50	3	20	65
100	3	24	69
200	3	27	68
300	3	32	69
500	3	41	66
1000	3	78	49

Scheme 15. Effect of water on the L-proline-catalyzed asymmetric aldol reaction

Similarly, asymmetric aldol reactions in aqueous media using a Zn-proline catalyst have also been reported, albeit with mostly moderate enantioselectivity.[46]

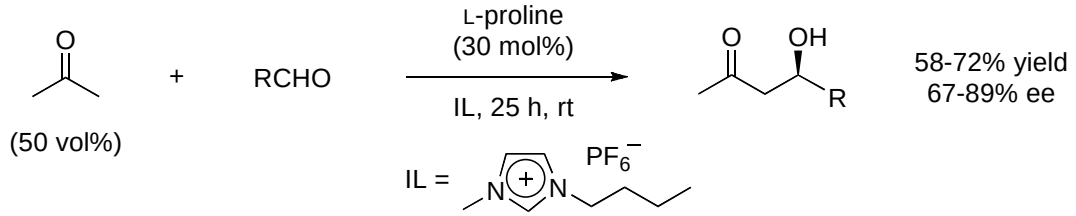
The use of poly(ethylene glycol) (PEG) as the solvent in proline-catalyzed asymmetric aldol reactions suggests that it may be possible to reuse the solvent as well as the catalyst (Scheme 16).[47] Even after the catalyst and solvent were used 10 times, no significant loss of catalytic activity was observed.



Scheme 16. L-Proline-catalyzed asymmetric aldol reactions in PEG

Based on a similar notion to explore the scope of organocatalytic transformations in green media, asymmetric reactions in ionic liquids have been developed (Scheme 17).[48-53] Thus, in many cases it might

be possible to decrease Mannich-type by-product formation and to reuse the proline catalyst with comparable yields and ee values, leading the overall economy of the reactions.

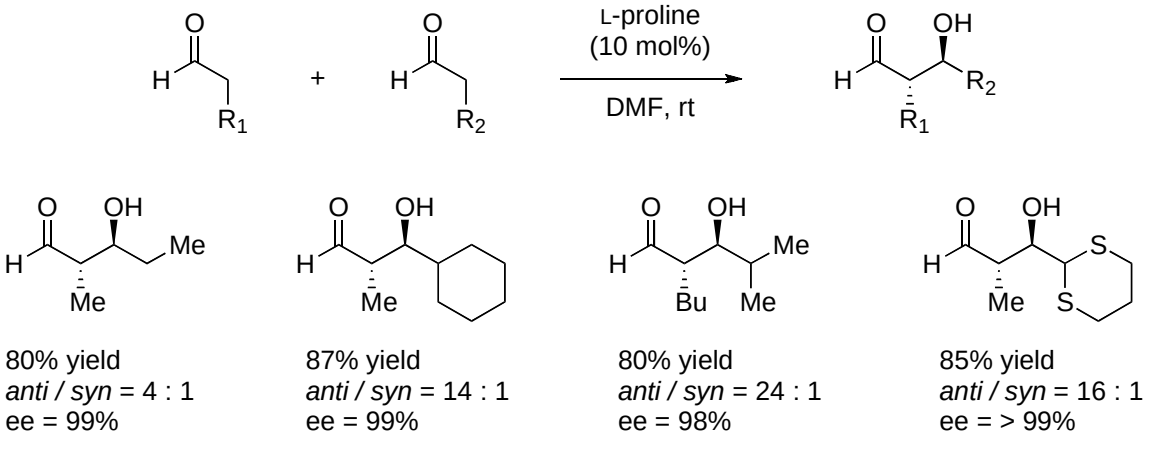


Scheme 17. L-Proline-catalyzed asymmetric aldol reactions in ionic liquid[48]

Although the synthetic value is still unclear at the present, there have been reports of high-grade asymmetric induction in heterogeneous media.[54-56] Along with this approach, thermodynamic investigation to better understand asymmetric amplification in amino acid-catalysis is now becoming a hot area.[57]

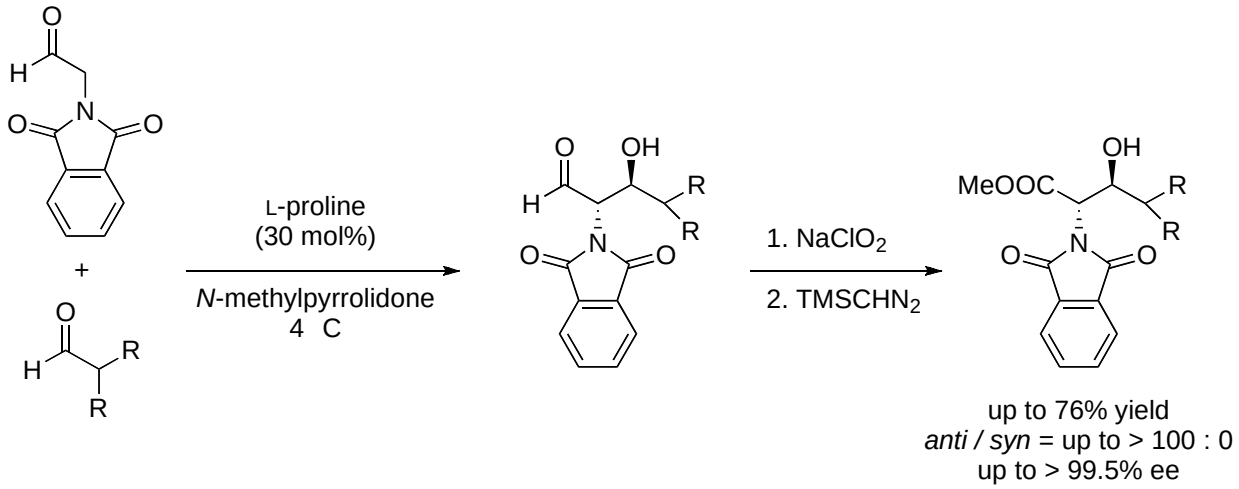
1.3. CROSS-ALDOL REACTIONS

As described above, in proline-catalyzed asymmetric aldol reactions, considerable effort has been paid to the condensation of ketone (donor) with aldehyde (acceptor). In contrast, advances have recently been made in proline-catalyzed asymmetric aldehyde-aldehyde coupling, i.e., cross-aldol reaction. This can serve as a straightforward method for obtaining a variety of optically active β-hydroxy aldehydes in a single-step operation. For example, MacMillan and coworkers reported a highly diastereoselective and enantioselective procedure for the cross-aldol reaction using equivalent or nonequivalent aldehydes by taking advantage of a syringe pump addition technique (dr up to 24 : 1, ee up to 99%) (Scheme 18).[58] Córdova found that reactions in ionic liquid were also successful.[59]



Scheme 18. L-Proline-catalyzed asymmetric cross-aldol reactions

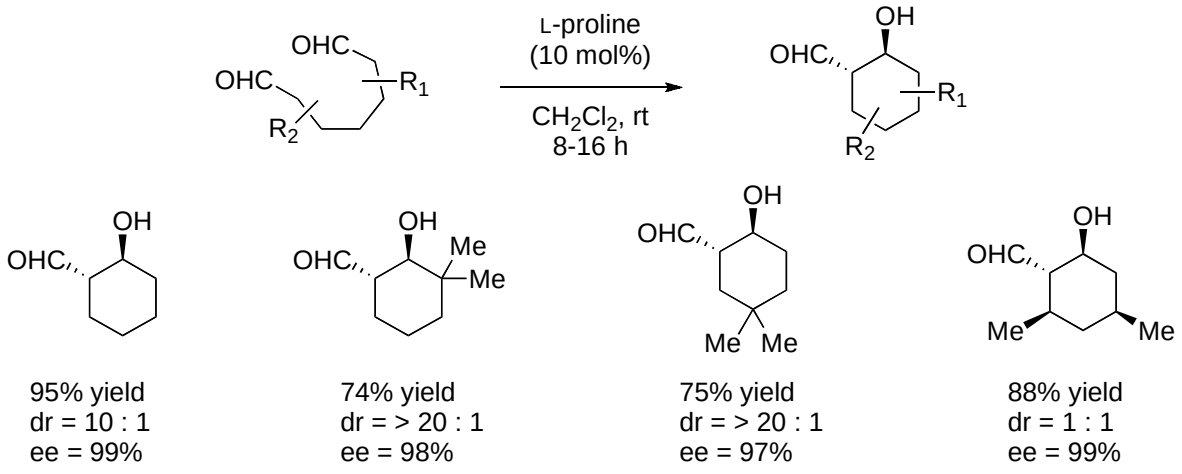
The proline-catalyzed asymmetric cross-aldol reaction is also effective with *N*-protected aminoacetaldehydes as an aldehyde donor, and provides an expedient way to *anti*-β-hydroxy-α-amino acid derivatives (Scheme 19).[60] The application of an asymmetric cross-aldol reaction of this type in conjunction with other methods of forming carbon-carbon bonds, such as metal-mediated allylations, gives a new attractive strategy for constructing polyketide building blocks in a one-pot operation sequence.[61]



Scheme 19. L-Proline-catalyzed asymmetric cross-aldol reactions of *N*-protected aminoacetaldehyde

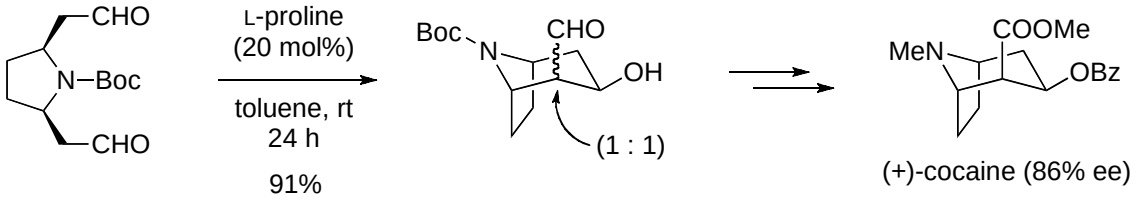
1.4. INTRAMOLECULAR ALDOL REACTIONS

Extension of the above strategy to intramolecular transformations provides a rapid route to cyclic aldol products. In fact, List and coworkers established a highly diastereo- and enantioselective method for performing proline-catalyzed intramolecular aldol reactions using dialdehyde substrates, while the reactions might be limited to the construction of six-membered ring compounds (Scheme 20).[62]



Scheme 20. L-Proline-catalyzed intramolecular asymmetric aldol reactions

On the other hand, Pearson and coworkers developed a much more ingenious strategy based on intramolecular asymmetric aldol reactions of *meso*-dialdehydes for preparing tropane alkaloid skeletons (Scheme 21).[63] Thus, a 5-step conversion of the aldol adduct gave the total synthesis of (+)-cocaine with 86% ee.

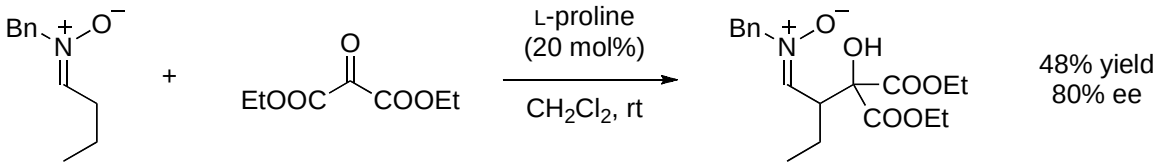


Scheme 21. Enantioselective synthesis of (+)-cocaine via intramolecular asymmetric aldol reaction

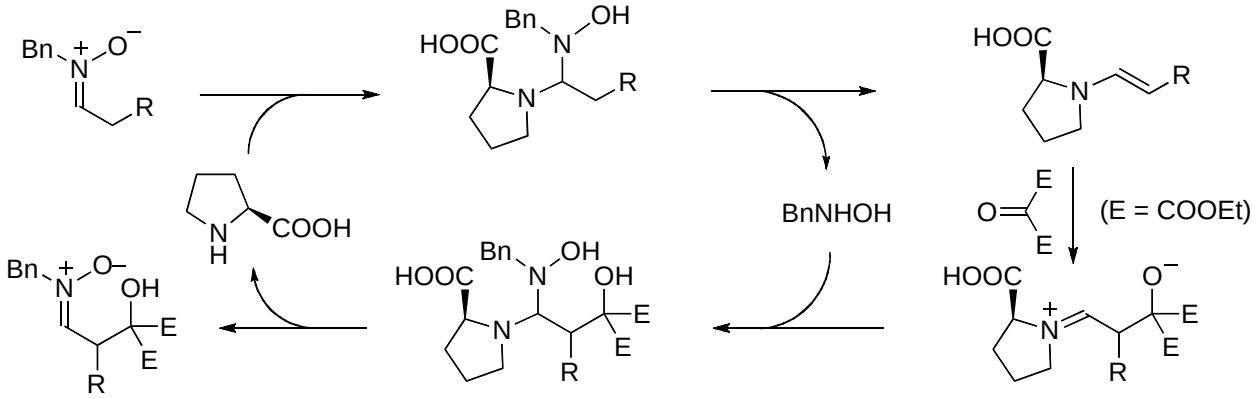
As these examples demonstrate, it is easy to imagine that the intramolecular version of proline-catalyzed asymmetric aldol reaction provides an elegant and convenient method for producing cyclic chiral molecules from acyclic nonchiral compounds.[64, 65]

1.5. ALDOL-RELATED REACTIONS

Nitrones can also serve as useful nucleophiles towards reactive carbonyl compounds under proline-catalysis, i.e., nitrone-aldol reaction.[66, 67] A typical example is shown in Scheme 22. A plausible mechanism to account for this reaction is outlined in Scheme 23. It can be considered that proline-induced enantioselection took place at the stage of the addition of an enamine species with diethyl oxomalonate.



Scheme 22. L-Proline-catalyzed asymmetric nitrone-aldol reactions



Scheme 23. Plausible mechanism for the L-proline-catalyzed asymmetric nitrone-aldol reaction

As described above, the utility of a proline-catalyzed asymmetric reaction in Robinson annulation has been well established by Eder, Sauer, and Wiechert,[5] Hajos and Parrish.[6] Recently, extensions of this chemistry have been published and much more selective organocatalysts have been developed.[68-71]

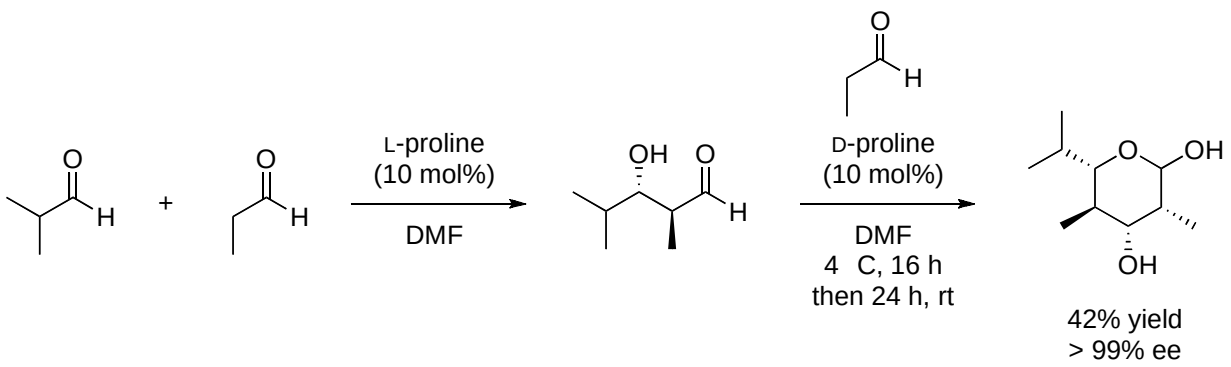
The combination of proline-catalyzed aldol reactions with other methods of forming carbon-carbon bonds leads to a versatile strategy for multi-component condensation: with Knoevenagel,[72] with self-aldol,[73] with aldehyde α-amination,[74] and with Knoevenagel-reduction.[75]

1.6. APPLICATION TO NATURAL PRODUCT SYNTHESIS

The enzyme-catalyzed aldol process is well known to play an important role in carbohydrate synthesis, and several approaches to incorporate this biochemical system to organocatalytic aldol mimics have been reported.[76] For this chemistry to succeed in the laboratory, suitable starting materials must be chosen carefully.

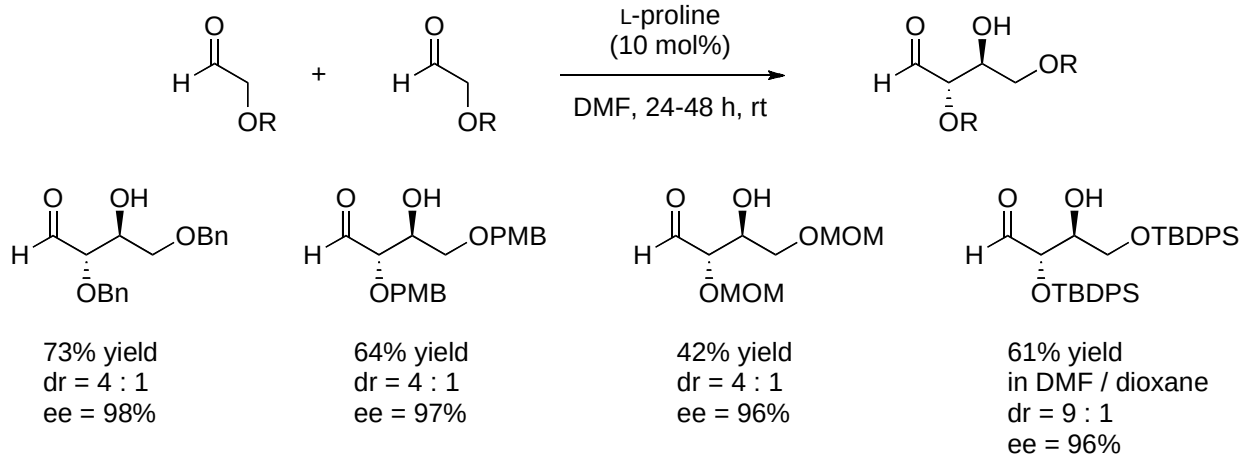
In 2002, Barbas III and coworkers reported a prebiotic system for assembling three aldehyde substrates in a one-pot operation in the presence of L-proline as a catalyst, to give hexose derivatives with high diastereoseletivity, albeit with low ee values (Scheme 24).[77] Later, Córdova and coworkers found that the enantioselectivity could be considerably improved to >99% ee by carefully conducting a two-step cross-aldol process via addition of L- and D-proline catalysts, respectively, in a step-wise manner (Scheme 25).[78] This method is of great value in constructing four contiguous stereogenic carbon centers with excellent stereocontrol.

Scheme 24. L-Proline-catalyzed self-aldol reaction of propionaldehyde



Scheme 25. Enantioselective synthesis of hexoses via tandem proline-catalyzed cross-aldol reacion[78a]

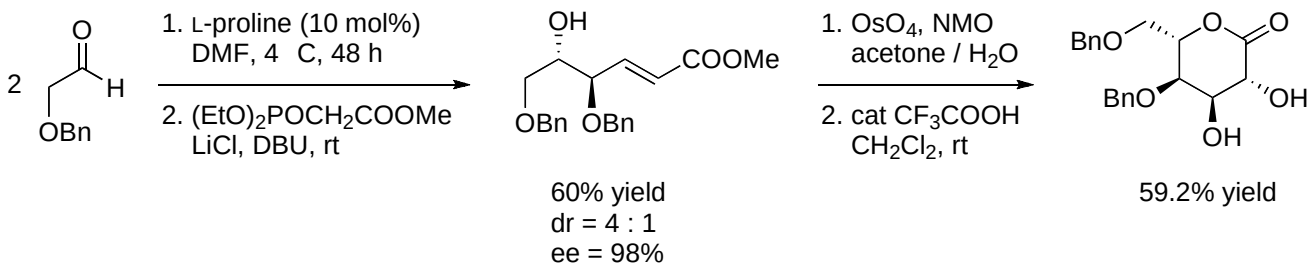
The use of α-oxygenated aldehydes as both aldol donors and aldol acceptors provides a new expedient method for constructing the polyol framework of carbohydrates. Accordingly, MacMillan and coworkers established a highly successful strategy for deriving differentially protected polyol compounds with high regio-, diastereo- and enantio-control (Scheme 26).[79]



Scheme 26. L-Proline-catalyzed asymmetric cross-aldol reactions of α-oxyaldehydes

As already discussed in Section 1.2,[46] the use of Zn-proline catalyst is also effective for promoting the cross-aldol reaction of this type in aqueous media.[80] On the other hand, Enders and coworkers discovered that pyruvic aldehyde acetals could act as an efficient phosphoenolpyruvate equivalent.[81]

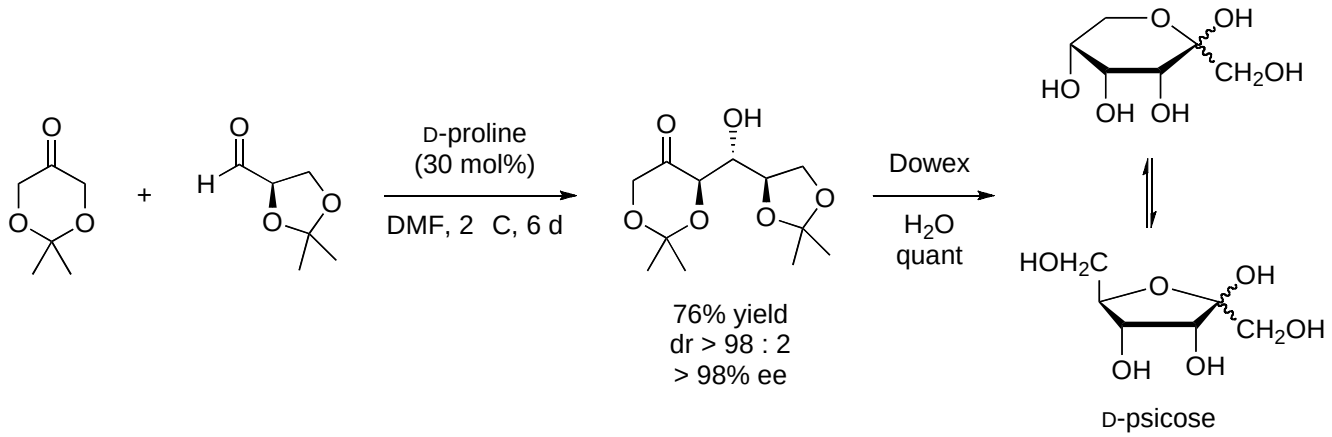
One of the interesting approaches in this field is the tandem use of the cross-aldol reaction and Horner-Wadsworth-Emmons olefination.[82] A typical example of the asymmetric synthesis of altronic acid lactone is shown in Scheme 27, where the diastereoselective dihydroxylation of olefins is essential for the manipulation of whole hydroxy functionalities.



Scheme 27. Enantioselective synthesis of altronic acid derivative via tandem cross-aldol-Horner-Wadsworth-Emmons reaction

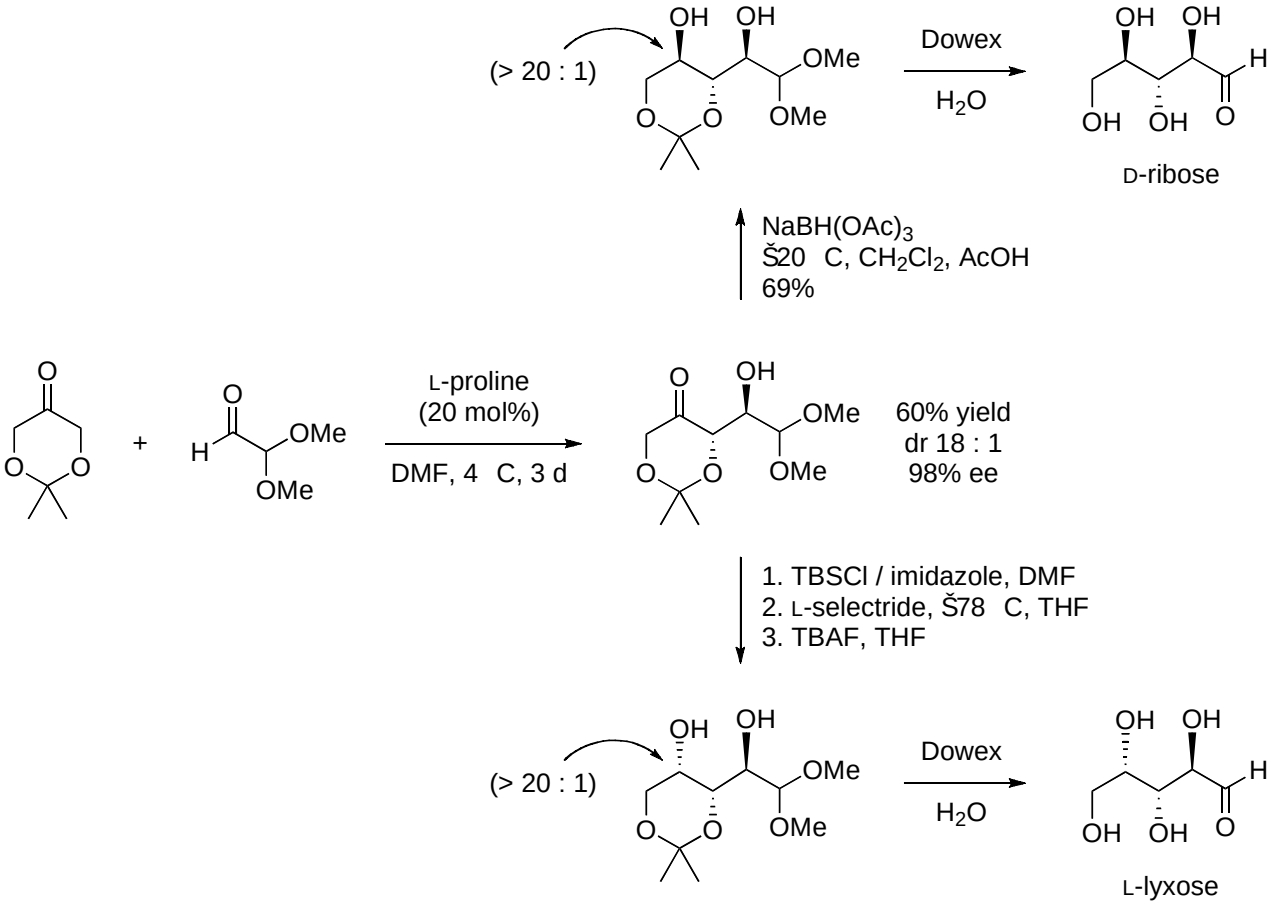
The inherent utility of dihydroxyacetone or its equivalent in asymmetric aldol reactions has been extensively studied,[83] and their use in asymmetric organocatalysis provides a rapid entry to carbohydrate

synthesis. For example, Enders and coworkers are engaged in this field and reported a new biomimetic protocol for preparing carbohydrates and related compounds (Scheme 28).[84]



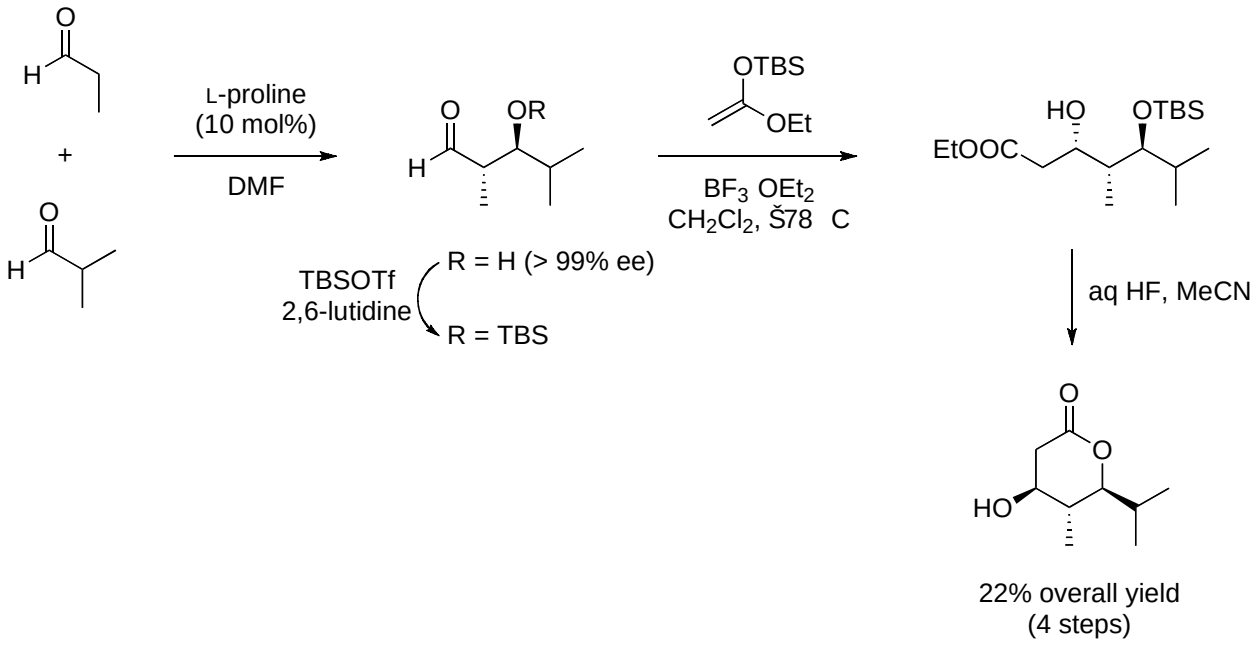
Scheme 28. D-Proline-catalyzed asymmetric approach to D-psicose

In a very similar manner Barbas III (Scheme 29),[85] Córdova,[86] and others[87] have also established the concise enantioselective synthesis of a variety of carbohydrates, including aza-sugars.



Scheme 29. L-Proline-catalyzed asymmetric approach to D-ribose and L-lyxose[85b]

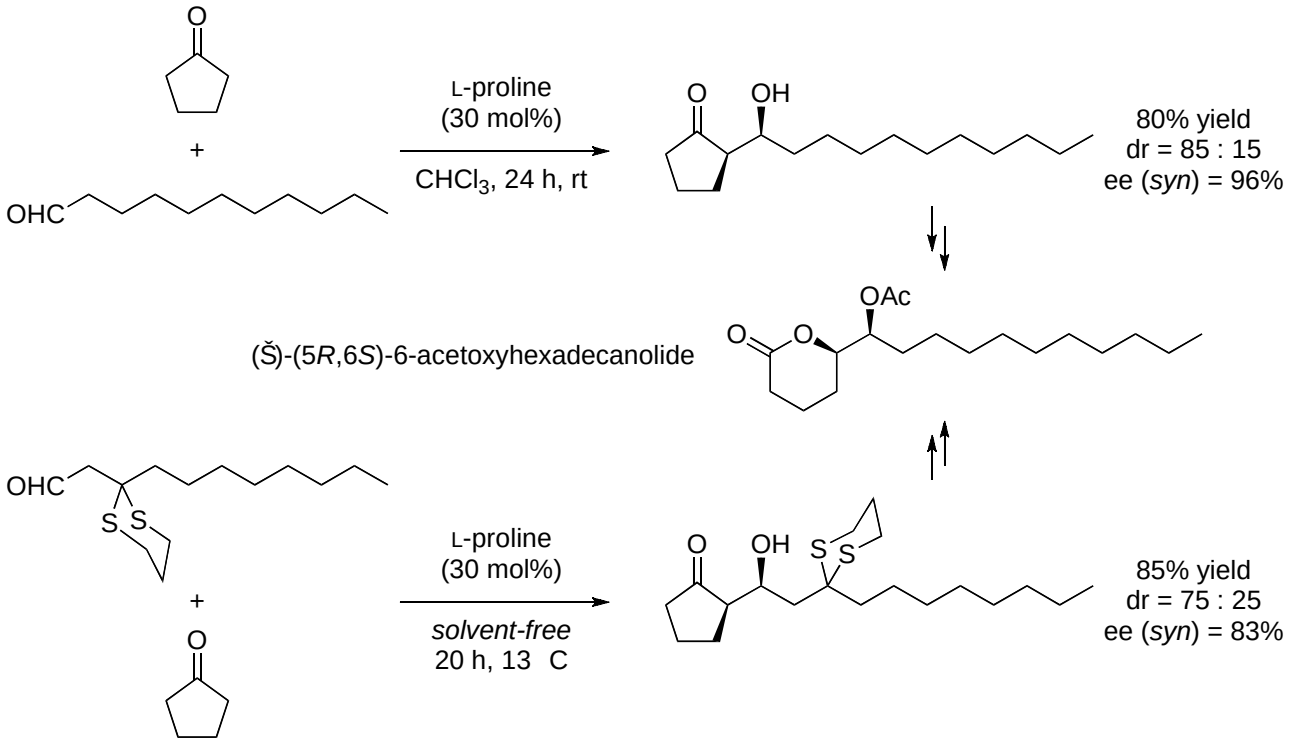
The proline-catalyzed asymmetric aldol reaction can serve as a powerful tool for synthesizing complex natural products other than carbohydrates, and some interesting works on its use in natural product synthesis have been reported.[88-90] For example, Pihko and coworkers described the successful use of proline-catalyzed cross-aldol reaction as a key step in the enantioselective synthesis of prelactone B (Scheme 30).[91] Thus, starting from the asymmetric aldol reaction between isobutyraldehyde and propionaldehyde, highly diastereoselective synthesis of (–)-prelactone B was completed in only four steps and 22% overall yield.



Scheme 30. Short-step synthesis of (Š)-prelactone B based on the L-proline-catalyzed asymmetric aldol reaction

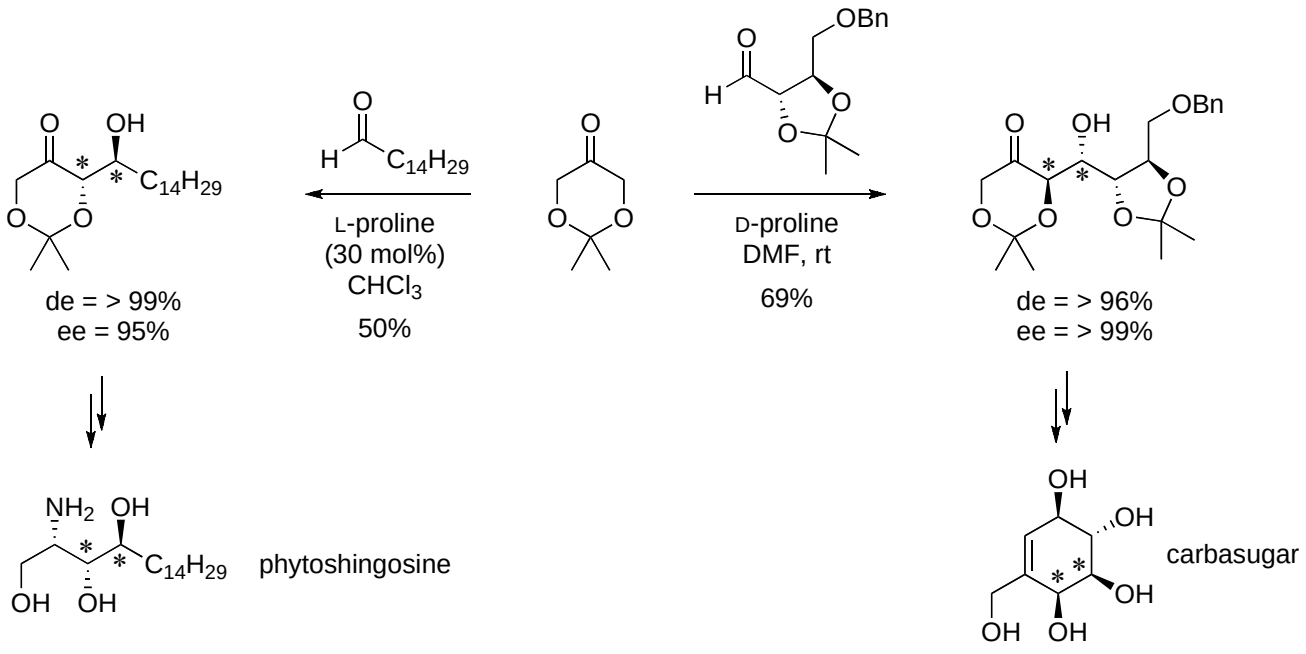
Li and we independently succeeded in applying the proline-catalyzed aldol strategy to the enantioselective synthesis of (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide, an oviposition attractant pheromone of mosquito (Scheme 31).[92, 93] As mentioned in Section 2.1, it was generally accepted that α-unsubstituted aldehydes could not act as an efficient electrophile in the aldol reaction of this type.[30] In this sense, Li's work seems to be an exceptional success.

In contrast, we found that aldehydes bearing a dithiane moiety at the β-position of aldehydes could act as much more convenient synthons for straight-chain aliphatic aldehydes. Since the dithiane appendage can be easily removed by exposure to Raney Ni and might be possible to regenerate ketone functionality by deprotection, the whole process opens the substantial utility in applying to natural product synthesis. We are now actively working to explore the generality of this method in the application to some other natural product syntheses.[94]



Scheme 31. Short-step synthesis of (Š)-(5*R*,6*S*)-6-acetoxyhexadecanolide based on the L-proline-catalyzed asymmetric aldol reaction

Finally, recent results from the Enders' group demonstrate the exceeding utility of dihydroxyacetone strategy in the enantioselective synthesis of oxygenated natural products (Scheme 32):[95, 96] the asterisks indicate the stereogenic carbon centers formed via a proline-catalyzed aldol sequence.



Scheme 32. L-Proline-catalyzed asymmetric aldol reactions in natural product synthesis

2. PROLINE-RELATED CHIRAL CATALYSTS

2.1. OXYPROLINE CATALYSTS

Ever since the sensational comeback of proline-based asymmetric catalysis by List, Lerner, and Barbas III,[12, 13] it has become an important challenge worldwide to discover new and more effective catalysts than proline itself. Among them, the development of new catalysts based on 4-hydroxyproline seems to be quite reasonable: the attachment of a lipophilic functionality on the side chain by taking advantage of the 4-hydroxy group can increase the solubility in most organic solvents, and hence catalyst activity can be considerably improved. Typical examples are listed in Chart 1.[97-103]

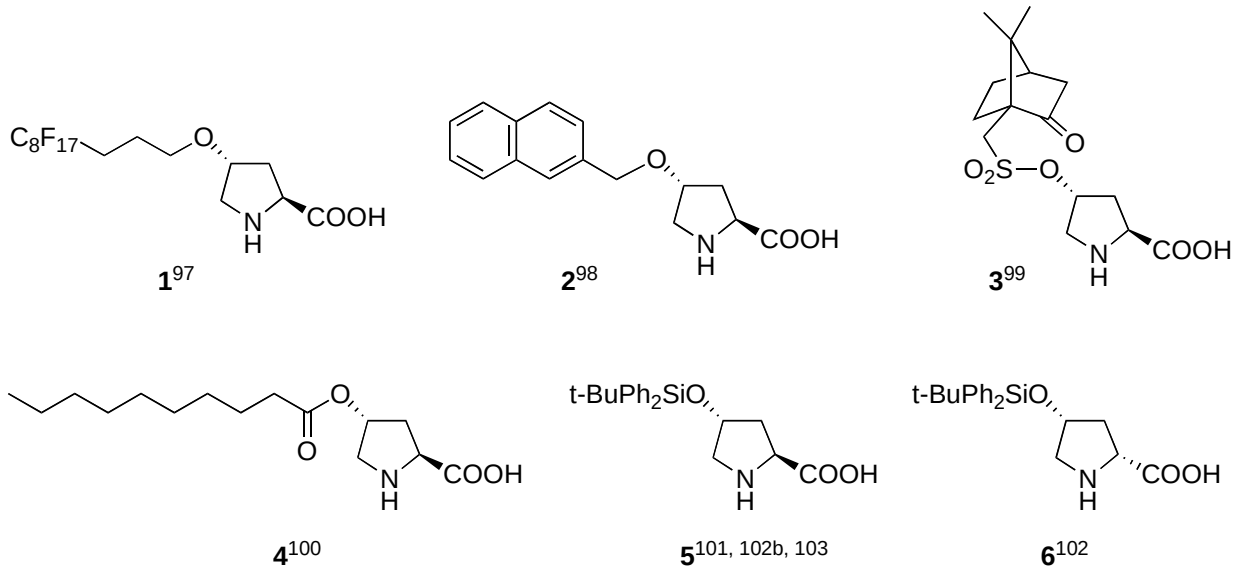
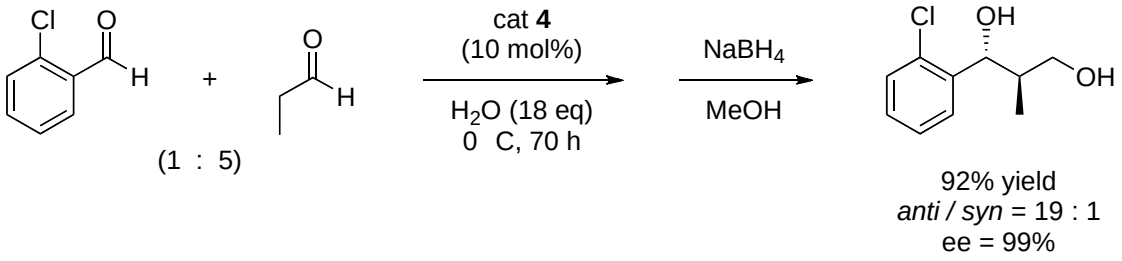


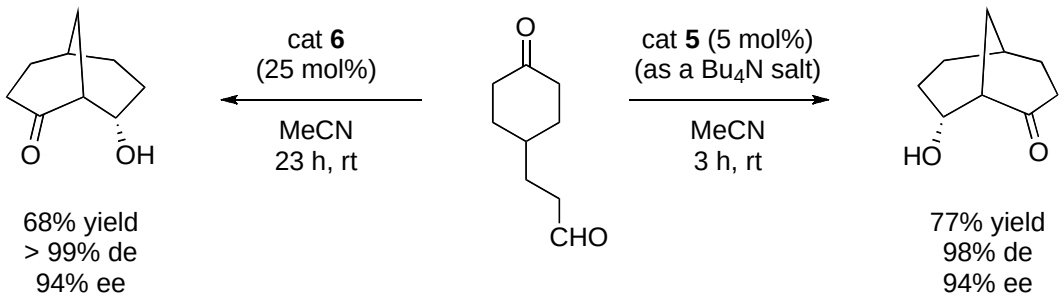
Chart 1. Various types of 4-oxy-proline catalysts

Interestingly, Hayashi and coworkers discovered that 4-decanoyloxyproline **4** efficiently catalyzed the cross-aldol reaction of aldehydes in aqueous media (yield up to 92%, dr up to >20 : 1, ee up to 99%) (Scheme 33).[100, 103] Although the precise mechanism is unclear, it is possible that the surfactant-like nature of catalyst **4** brought the acceptor and donor molecules together on the water surface.



Scheme 33. Enantioselective aqueous cross-aldol reactions catalyzed by **4**[100]

Paquette and Iwabuchi independently developed a highly effective desymmetrization methodology for achiral compounds using siloxy-protected catalysts such as **5** and **6**.[101, 102] A typical example is shown in Scheme 34.[102b] Thus, the use of catalyst **5** as its tetra-*n*-butylammonium salt gave the expected (1*S*,5*R*,8*R*)-*endo*-adduct in 77% yield with 98% de and 94% ee. On the other hand, when catalyst **6** was used the corresponding antipode was obtained in 68% yield with >99% de and 94% ee. The advantage of this method is clear: construction of three stereogenic carbon centers in a single-step operation, high enantioselectivity, and facile accessibility to both enantiomers starting from the σ-symmetric substrate.



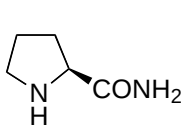
Scheme 34. Enantiodifferentiation methodology using siloxy-protected catalysts **5** and **6**[102b]

A synthetic study of an immobilized catalyst based on (4*S*)-phenoxy-L-proline has also been reported in the literature.[104]

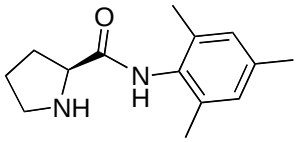
2.2. PROLINAMIDE CATALYSTS

Since amide functionality possesses an enough acidity to form a hydrogen-bond with carbonyl electrophiles (e.g., pK_a of CH_3CONH_2, 15.1 in H_2O and 25.5 in DMSO; $CH_3SO_2NH_2$, 17.5 in DMSO)[105] it can be expected that organocatalysts derived from L-proline can sufficiently promote aldol reactions with great reactivity and high selectivity. Accordingly, the development of new catalysts based on the inherent nature of L-proline has been intensively studied in recent years. Generally, there are two major directions for proline modification, i.e., carboxamides and sulfonamides. Typical examples are listed in Chart 2.

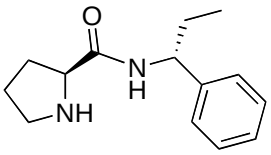
Although there have been only a few studies, the utility of prolinamide catalyst **7** in some cross-aldol reactions has been confirmed.[106, 107] Important contributions in this area have been made by the development of a variety of *N*-substituted prolinamide catalysts.[108-113] The unique behavior of catalyst **9** in water reflects the important role of an aromatic core on the side arm to provide a favorable hydrophobic interaction between the catalyst and the aldehydes, thereby giving good enantioselectivity (Scheme 35).[111] Instead, the install of a heteroaromatic system as in catalyst **11** allows the creation of a dual hydrogen-bonding recognition site within the catalyst molecule (Scheme 36).[114, 115]



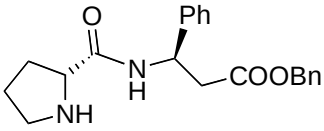
7[106]



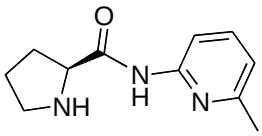
8[110]



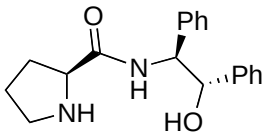
9[111]



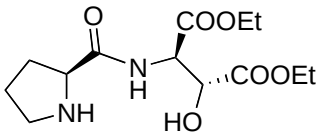
10[112]



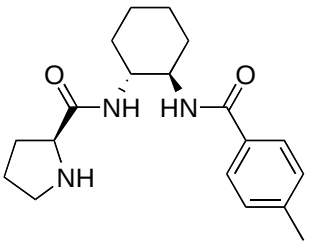
11[114]



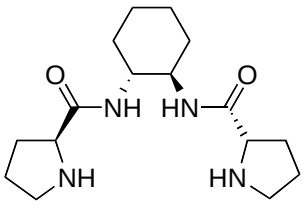
12[116]



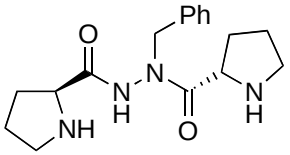
13[117]



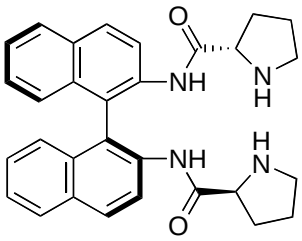
14[119]



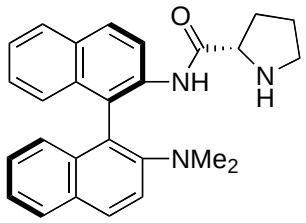
15[120]



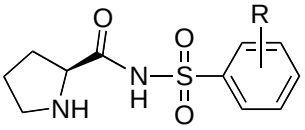
16[121]



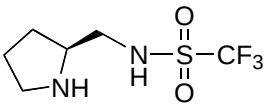
17[122, 123, 125]



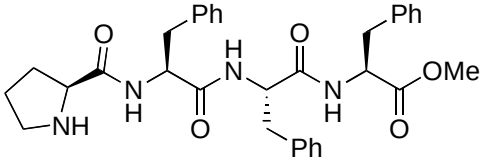
18[124]



19 (R = p-Me or H)[126-128]

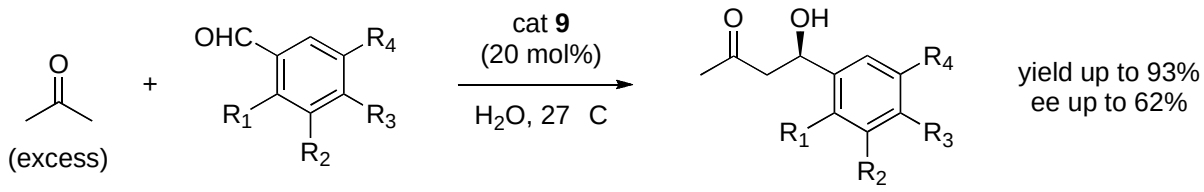


20[131]

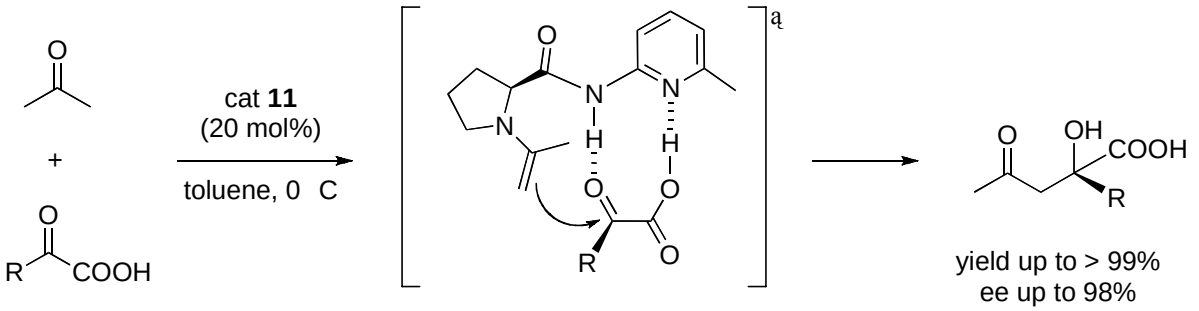


21[134]

Chart 2. Various types of prolinamide-related organocatalysts

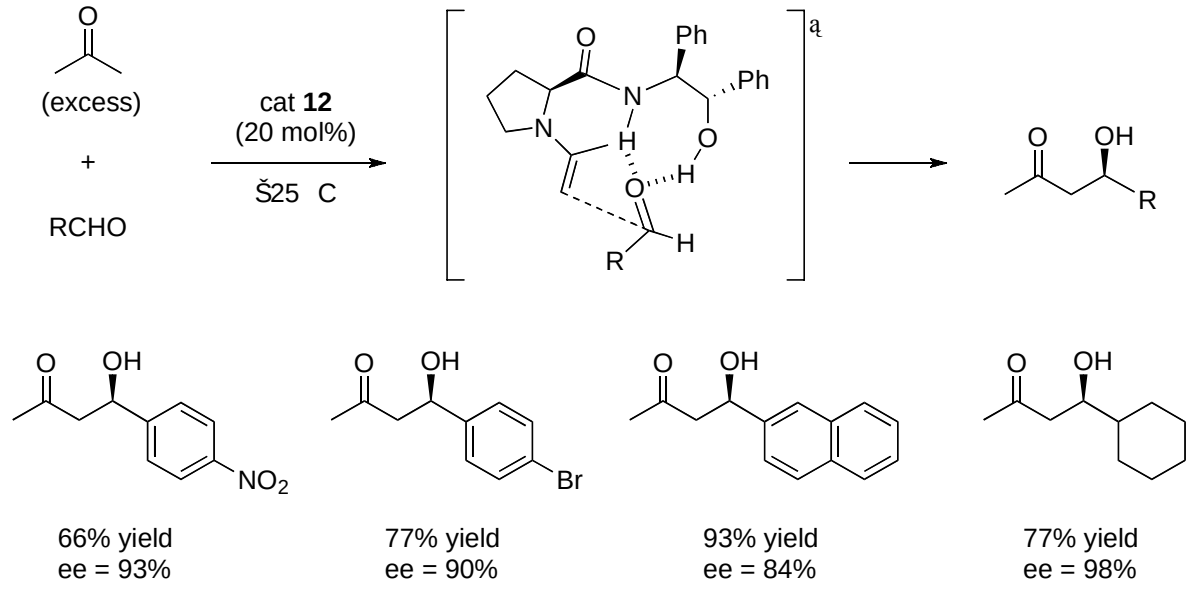


Scheme 35. Enantioselective aldol reacions in water catalyzed by **9**



Scheme 36. Enantioselective aldol reacions based on the molecular recognition of **11**[114]

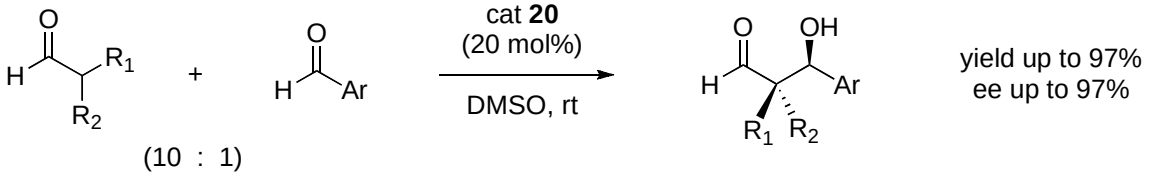
In an attempt to incorporate the synergistic effect into the catalysts, prolinamide **12** bearing an additional hydroxyl group on the side chain was developed, where it is important to match the configuration of the proline core with that of the side arm (Scheme 37).[116] Thus, catalyst **12**, prepared from L-proline and (1*S*,2*S*)-diphenyl-2-aminoethanol, showed the highest levels of enantioselectivity (up to 99% ee). As a closely related system, catalyst **13**, prepared from L-proline and diethyl (2*R*,3*R*)-2-amino-3-hydroxysuccinate, has also been reported.[117, 118]



Scheme 37. Enantioselective aldol reacions catalyzed by **12** and the proposed transition state

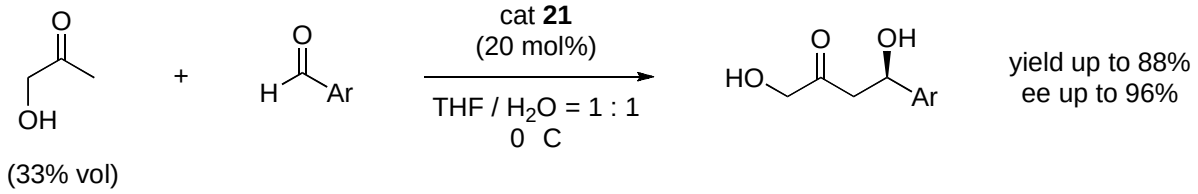
Bis-amide catalysts **14-16** have also been used in asymmetric aldol reactions, and similar results were obtained with respect to enantioselectivity.[119-121] Furthermore, the combination of a bis-amide function with an axially chiral binaphthyl backbone provides a new class of prolinamide-based catalysts such as **17** and **18**.[122-125] Despite these extensive efforts, it is not easy to identify if the axial chirality effect is crucial or not (< 98% ee). It seems probable that the hydrophobic effect of the relatively large-sized aromatic rings more or less influences their catalyst activity.

In some cases it has been reported that proline-derived sulfonamide catalysts like **19** possess excellent catalyst activity.[126-130] This can be ascribed simply to the effect of the increase in the acidity of N–H bonds, which enhances their hydrogen bond donating ability. Based on a very similar strategy, a slightly different type of trifluoromethanesulfonamide catalyst **20** was developed (*cf*. pK_a of $CF_3SO_2NH_2$, 9.7 in DMSO).[105] This catalyst gives exceptionally high levels of enantioselectivity in cross-aldol condensation between α,α-dialkyl aldehydes and aromatic aldehydes (yield up to 97%, ee up to 97%) (Scheme 38).[131]



Scheme 38. Enantioselective cross-aldol reacions catalyzed by **20**

Finally, proline-derived small peptides can frequently serve as efficient chiral organocatalysts.[132-137] Although the peptide-series catalysts usually have molecular weights about five times as large as proline itself, they work well even in THF/water mixed solvent system to give excellent enantioselectivities of up to 96% ee (Scheme 39).[134]



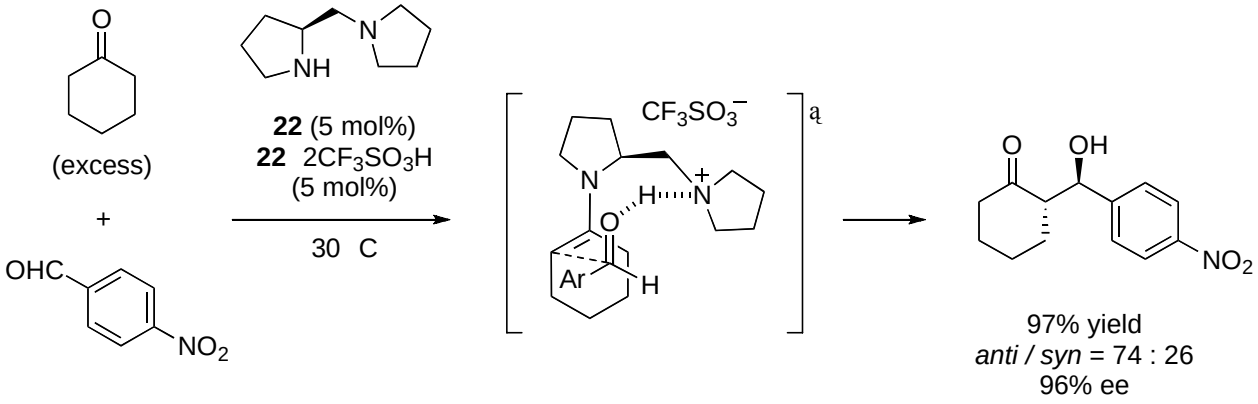
Scheme 39. Enantioselective aldol reacions catalyzed by peptide **21**

A surprising result in this system is their reversed regioselectivity with regard to the methyl group: the reaction took place preferentially at the methyl group of hydroxyacetone to give the 1,4-diol products. This is remarkably different than the L-proline catalysis: the exclusive formation of the 1,2-diol products is observed in Scheme 4. The fact that the same reaction in pure THF gave a mixture of the 1,2- and

1,4-diols in 58% and 36% yields, respectively, reveals the important role of water in determining the regioselectivity through the multiple hydrogen-bond network between water and the amide oxygen of the catalyst and the hydroxy group of the substrate.

2.3. PYRROLIDINE CONJUGATE CATALYSTS

To design a new proline-like organocatalyst, protonated nitrogen heterocycles can also act as a favorable substitute for the carboxylic acid. Yamamoto and coworkers first confirmed the efficiency of this approach by carefully screening a variety of combinations of prolinamines and protonic acids, and found that, when catalyst **22** was used with its TfOH-salt (each 5 mol%), the sufficient catalytic activity was attained (Scheme 40).[138] The observed high enantioselectivity (84-96% ee) can be explained by invoking a transition state very similar to that in proline catalysis (see Scheme 3). Barbas III and Dondoni also reported the general utility of the same type of catalyst in other asymmetric aldol reactions.[139, 140]

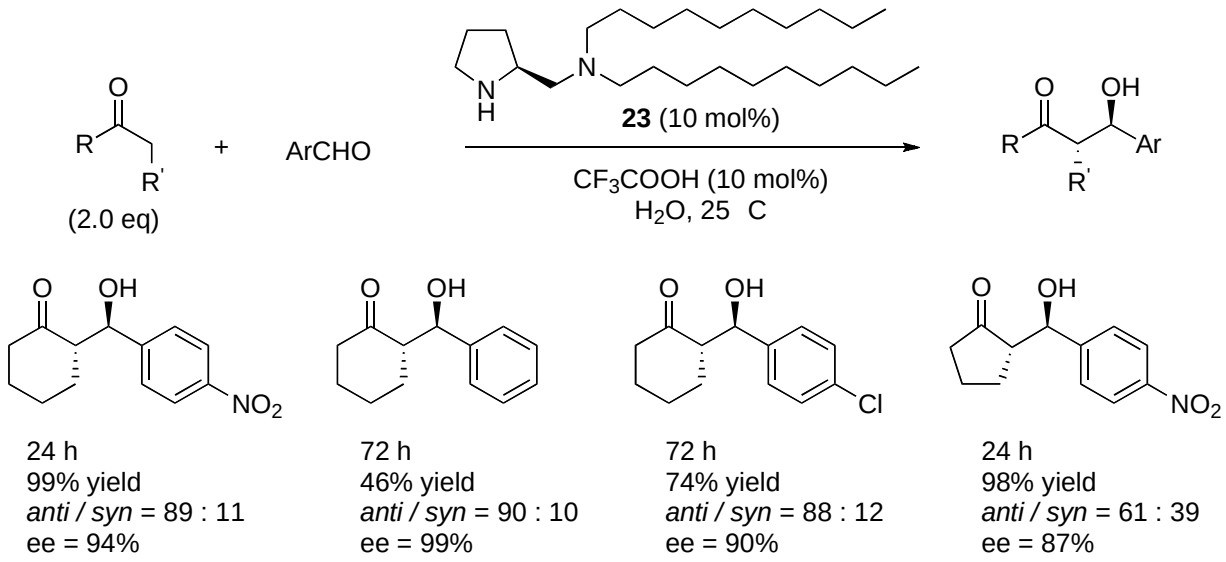


Scheme 40. Enantioselective aldol reacions catalyzed by **22** and the proposed transition state

As a closely related example, the novel catalyst having a bis-morpholine structure is also known.[141]

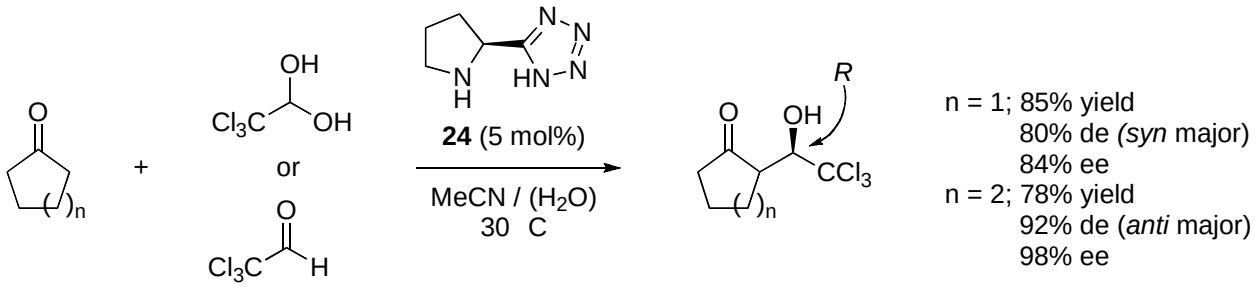
In their extensive research efforts in this area, Barbas III and coworkers recently developed a new type of diamine catalyst **23** bearing hydrophobic aliphatic side chains.[142] Thus, the diamine **23**/CF_3COOH bifunctional catalyst system showed excellent reactivity, diastereoselectivity, and enantioselectivity in asymmetric aldol reaction in water (yield up to 99%, *anti/ syn* up to 91 : 9, ee up to 99%) (Scheme 41). In this case, there is again some possibility that the straight chain alkyl groups acted as an effective surfactant to cause favorable interactions of the catalyst with the substrates.

The notice that the proton-donating ability of tetrazole (pK_a value, 8.2 in DMSO)[105] is very close to that of carboxylic acid (pK_a of acetic acid, 12.3 in DMSO)[105] opens a vast research area in scrutinizing the catalytic property of pyrrolidine-tetrazole conjugate catalyst **24**.[143-147] Additionally, the incorporation of a tetrazole unit into the catalyst core should show promise as a new class of catalysts, e.g., high solubility in



Scheme 41. Diamine **23**·TFA-catalyzed asymmetric aldol reactions in water

organic solvent and a resonance stabilization effect of the deprotonated anion charge over the tetrazole ring. In fact, Yamamoto and coworkers reported that the reaction of cyclohexanone or cyclopentanone with chloral proceeded quite smoothly in the presence of 5 mol% of **24** to afford the desired aldol adduct in high diastereo- and enantioselectivity (Scheme 42).[144] Interestingly, in this case the addition of a small amount of water led the reaction to completion.



Scheme 42. Enantioselective aldol reacions of cyclic ketones with chloral catalyzed by **24**

Based on a very analogous concept, benzimidazole, a structural relative of tetrazole, has also been introduced in the catalyst framework.[148]

2.4. POLYMER-SUPPORTED CATALYSTS AND OTHERS

Generally, the important aspects in the immobilization of the reagent as a polymeric form are the simplification of separation procedures and in many cases the ease of handling and reusability of the reagents. Accordingly, there have been some interesting investigations to apply this concept to proline-catalyzed asymmetric aldol reactions.[149-152]

In designing a catalyst of this type, the essential point is how to expose the active site of the proline catalyst on the polymeric supports. For this purpose, commercially available *trans*-4-hydroxy-L-proline is frequently used, and some typical examples are shown in Chart 3. Interestingly, catalyst **27** was quite effective to carry out the aldol reaction in water, and the best result was obtained in the presence of water-soluble DiMePEG (MW ca 2000) (yield up to 97%, *anti/syn* up to 98 : 2, ee up to 97%) (Scheme 43).[152] In this case, again it seems probable that the reaction took place at the interface between the hydrophobic polymer and the aqueous phase.

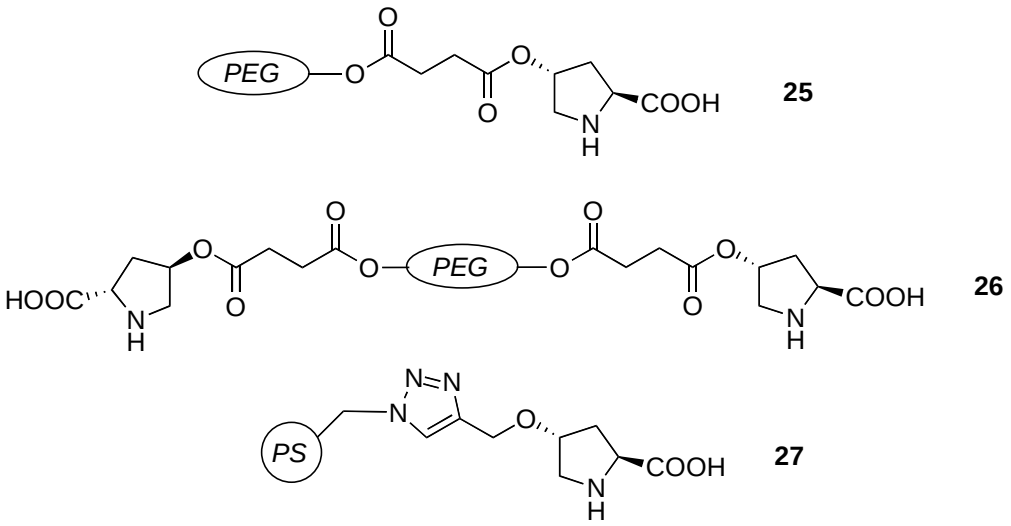
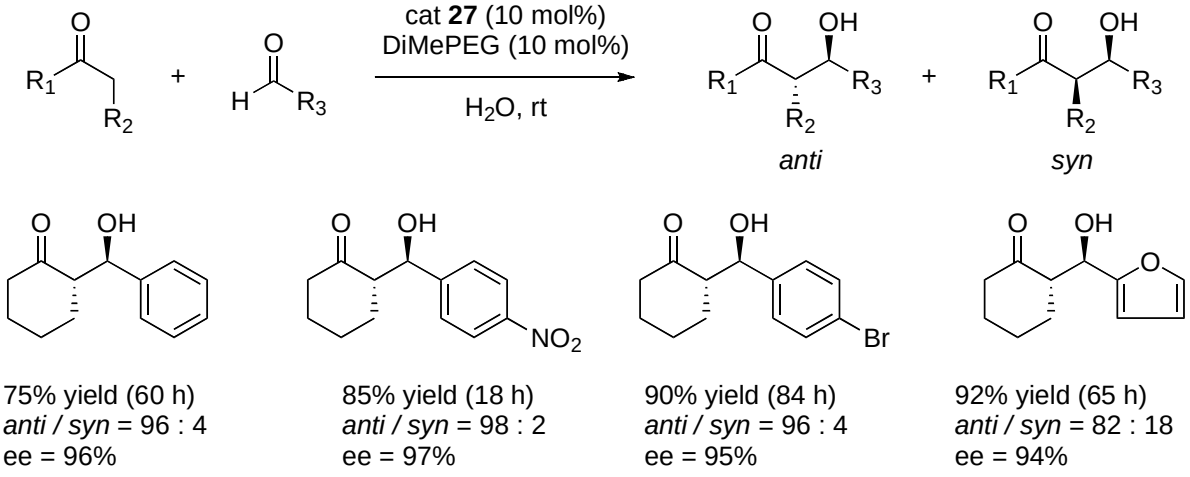


Chart 3. Representative examples of polymer-supported proline catalysts (*PEG* = polyethylene glycol; *PS* = polystyrene)[149, 152]



Scheme 43. Polymer-supported hydroxyroline-catalyzed asymmetric aldol reactions

Beside these examples, a variety of solid materials can be used to support the proline catalyst: dendrimers,[153] mesoporous materials,[154] polyelectrolytes,[155] and layered double hydroxides.[156]

Although their utility is somewhat limited, other miscellaneous catalysts have been reported (Chart 4): prolinol,[157] imidazolidinone **28**,[158] pyrrolidine-2,5-dicarboxylic acid **29**,[159] indoline-2-carboxylic acid **30**,[160, 161] spiroborate ester,[162] pyrrolidinylphosphonic acid **31**,[163] and 4-pyrrolidinylproline **32**.[164, 165]

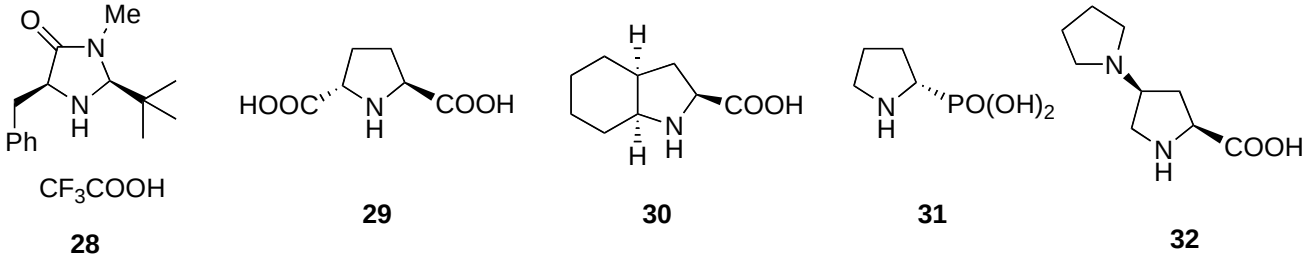
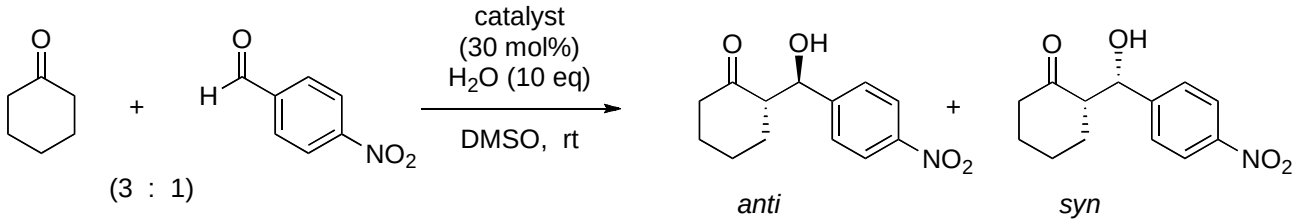


Chart 4. Miscellaneous types of proline-related organocatalysts

3. OTHER TYPES OF AMINO ACID CATALYSTS

Amino acid-catalyzed asymmetric aldol reactions are not restricted only to proline, but are also applicable to other α-amino acids or their equivalents. However, it would be difficult to provide an overview here. Therefore, only some representative examples are briefly explained.

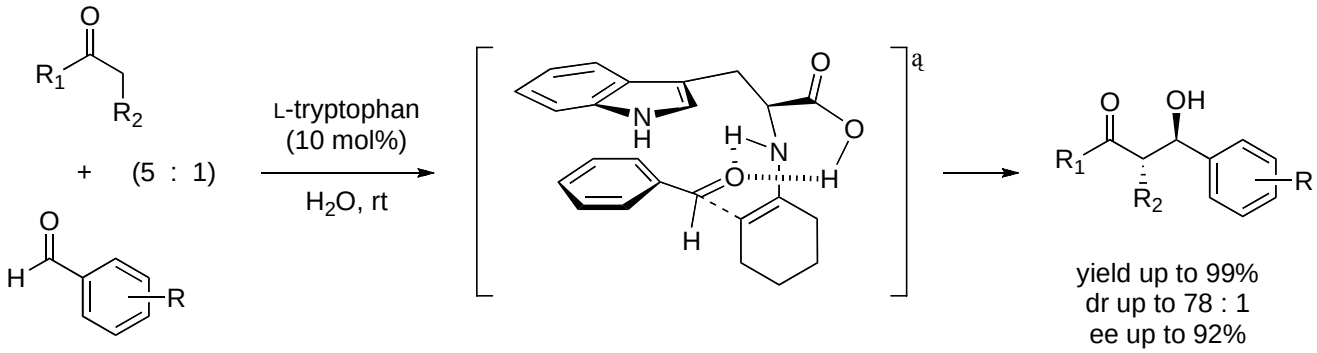
Córdova and coworkers developed that simple acyclic α-amino acids and related small dipeptides such as (*S*)-alanine, (*S*)-valine, and (*S*)-ala-(*S*)-ala could efficiently catalyze the direct intermolecular asymmetric aldol reaction.[166] They found that the reaction was remarkably effective by the addition of a small amount of water, giving the aldol adduct in good yield and in high enantioselectivity (Scheme 44). Inomata and coworkers reached the similar conclusions using L-methionine, an acyclic amino acid, as a catalyst for the intramolecular asymmetric aldol reaction.[167]



catalyst	time (h)	yield (%)	dr	ee (%)
(*S*)-alanine	72	95	15 : 1	92
(*S*)-valine	72	98	37 : 1	> 99
(*S*)-leucine	51	60	10 : 1	92
(*S*)-phenylalanine	48	70	3 : 1	73
(*S*)-ala-(*S*)-ala	24	73	8 : 1	91
(*S*)-ala-(*S*)-phe	24	70	2 : 1	93
(*S*)-ala-(*S*)-val	41	87	1 : 1	87
(*S*)-val-(*S*)-ala	48	92	1 : 1	98

Scheme 44. Asymmetric aldol reactions catalyzed by acyclic amino acids and small peptides[166g]

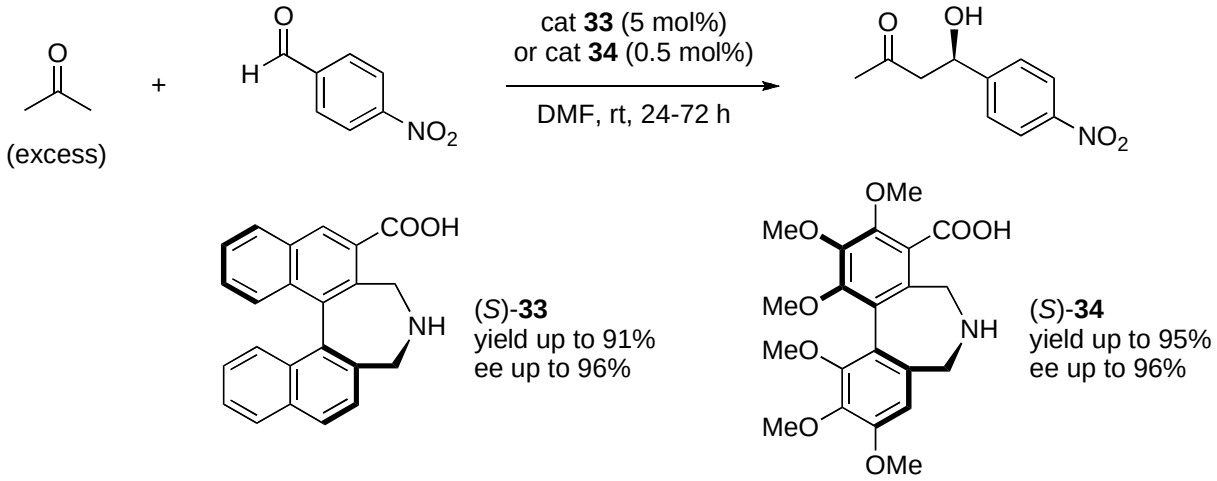
Recently, Lu and Barbas III independently found that L-tryptophan could act as an efficient catalyst, especially in water (yield up to 99%, dr up to 78 : 1, ee up to 92%) (Scheme 45).[168, 169] The proposed transition state suggests that L-tryptophan acts as a versatile catalyst not only to facilitate the formation of a hydrophobic interface between the catalyst and the aqueous phase, but also to arrange the aromatic aldehyde electrophiles in a most favorable position through π–π stacking stabilization.



Scheme 45. L-Tryptophan-catalyzed asymmetric aldol reactions in water and the proposed transition state[168]

Other examples of the use of amino acid homologs[170, 171] and amino acid-carbohydrate conjugates in asymmetric aldol reactions have also been reported.[172]

Recently, Maruoka and coworkers successfully extended the concept of amino acid catalysis to novel robust types of catalysts with a binaphthyl or biphenyl axial chirality, as represented by **33** and **34** (Scheme 46).[173] Notably, catalyst **34** is remarkably effective, and hence the catalyst loading can be reduced to only 0.1 mol% in acetone without a loss of yield or enantioselectivity (yield up to 95%, ee up to 96%).



Scheme 46. Asymmetric aldol reactions catalyzed by chiral amino acid **33** or **34**

Some related works arising from the interest in prebiotic systems have also been reported.[174, 175] Finally, for non-chiral transformations using proline or related catalysts, only a few reports have been published.[176-182]

CONCLUSIONS

The research area of asymmetric catalysis using commercially available L-proline is growing rapidly after the pioneering work by List, Lerner, and Barbas III in 2000. As described in this and the following review articles, proline catalysis has several advantageous characteristics, for example, availability of both enantiomers of proline catalyst, simplicity in handling and catalyst recovering, ease of catalyst design, and in some cases environment-friendly processes. This might be the main reason for the large number of papers on this subject. In asymmetric aldol reactions, while Nature's catalysts, enzymes, show great generality, the development of proline catalysis may have now almost reached a practical level of synthetic quality. We can expect that much more efficient catalysts will be discovered and expanded to commercial grades of transformations in the near future.

NOTE ADDED IN PROOF

Recently, an important publication that describes the mechanistic investigation of proline-catalyzed asymmetric Michael and aldol reactions has appeared. (D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, and B. Linder, *Helv. Chim. Acta*, 2007, **90**, 425).

ACKNOWLEDGEMENTS

The authors would like to acknowledge the past and present members of our research group for their enthusiastic contributions in the field of organocatalysis. The authors also thank Prof. Y. Ichikawa and Dr. K. Nakano for their fruitful discussions and encouragement. Our research project in this field was supported by a Scientific Research on Priority Areas (18037053 & 18032055) of MEXT, as well as by a Special Research Grant for Green Science from Kochi University. We also thank the Asahi Glass Foundation for financial support.

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