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Organocatalysis of asymmetric aldol reaction. Catalysts and reagents

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Abstract. The review is devoted to the application of organocatalysis for the asymmetric aldol reaction, which is one of the most important methods for carbon – carbon bond formation in organic compounds. The mechanism of enamine catalysis and the main types of organocatalysts for the aldol reaction are considered, data on this type of reactions involving carbonyl compounds with various electronic and spatial structures are classified. The effects of organocatalyst structure on the regio-, stereo- and enantioselectivity of intramolecular and intermolecular aldol reactions are reviewed. The bibliography includes 355 references.

I. Introduction

The goal of this review is to get the reader acquainted with a new rapidly developing area of the modern synthetic organic chemistry that provides solutions to many problems of asymmetric catalysis.

The importance of preparing enantiomerically pure compounds is beyond doubt as well as the fact that the best way for achieving this task is asymmetric catalysis, which provides target products with high enantiomeric purity using catalytic amounts of a chiral compound. Quite recently, the notion 'asymmetric catalysis' has been associated with catalysis by metal complexes where the metal not only activated the reactants, but also transmitted the chiral information through formation of the transition state (TS). The mutual arrangement of the catalyst and the reactants in such a TS ensured the formation of a chiral reaction product. The works on asymmetric hydrogenation and oxidation catalyzed by metal complexes were awarded with the Nobel Prize in chemistry 2001 (B Sharpless, R Noyori and W Knowles).

Small organic molecules have long been used as catalysts in chemical, but not in enzymatic reactions. However, it was not until recently that, despite the known few examples, the idea arose to use the molecules containing chiral centres as catalysts instead of enzymes. Note that these molecules are even more suitable as artificial enzymes than chiral transition metal complexes, as the mechanism of their action (the so-called enamine and iminium catalysis) is similar to that of enzymes aldolase and decarbonylase. It is this type of catalysis that has been called 'organocatalysis'.

In the first review of our series of papers devoted to the use of organocatalysts in organic synthesis, we consider in detail the aldol reaction. This reaction is widely used in nature for the formation of carbon – carbon bonds in living systems (metabolism). Presumably, aldol reactions of formaldehyde and glycolaldehyde catalyzed by enantiomerically enriched amino acids contained in meteorites gave rise to carbohydrates in the Earth.[1] Extensive experimental material has now been accumulated concerning organocatalysis as a whole[2–4] and its application in the asymmetric aldol reactions in particular;[5–7] this was summarized in a number of excellent reviews and books. In view of the considerable amount of information and the dynamics of development of this field, we considered it reasonable to divide all the material into two parts. The first review offered to the readers considers the emerging and development of organocatalysis, the catalysts and reagents used in the asymmetric aldol reaction, their effects on the regio-, stereo-, and enantioselectivity of the processes and reactions induced by immobilized organocatalysts. The second review planned

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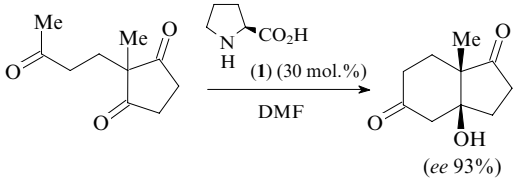
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to be published later in this journal would deal with the effect of the reaction medium on the organocatalytic aldol reactions and their use for preparing chiral natural and synthetic biologically active substances. The present review covers the most important publications, primary attention being given to the works published in 2007–2009 and not included in the earlier papers or monographs.

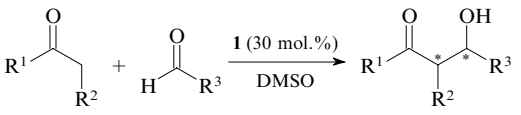
II. Emerging and development of organocatalysis

The term 'organocatalysis' was introduced by Ostwald[8] back in 1900 in relation to catalytically active small organic compounds, thus distinguishing them as a special group from enzymes and inorganic catalysts. A number of papers published in the subsequent 60–70 years described the use of chiral organic compounds, in particular, alkaloids,[9–14] amino acids and short peptides,[15,16] as catalysts of enantioselective organic reactions.

An important milestone in the history of organocatalysis was the discovery of the Robinson asymmetric annulation catalyzed by (*S*)-proline (**1**) made in the early 1970s by two independent groups of researchers. The reaction was called the Hajos–Parrish–Eder–Sauer–Wiechert reaction after the authors.[17–19] This was a facile and convenient route to analogues of the Wieland–Mischer ketone, which is a key intermediate in the synthesis of steroids.[20–22] This reaction was also useful for the synthesis of a broad range of other chiral natural compounds and biologically active compounds containing carbocyclic units.[23,24]



A powerful impetus to the development of studies in the asymmetric organic catalysis as a whole and, in particular, the aldol reaction came from the paper by List, Lerner and Barbas III (Ref. 25) published in 2000 in which the ability of (*S*)-proline to catalyze intermolecular aldol reactions was demonstrated. One of the carbonyl compounds used in the reaction, most often a ketone, functions as the nucleophile (electron donor), and the other one, usually an aldehyde, acts as the electrophile (electron acceptor) in the formation of a new C–C bond.



This paper triggered the sharp growth of the number of publications devoted to the use of organocatalysis in asymmetric synthesis, and this growth is still in progress. According to the CAPlus data (Chemical Abstracts Service, STN International search system), less than 10 papers having 'organocatalysis', 'organocatalyst' and 'organocatalytic' as the keywords appeared in 2000, while the number of such publications in 2008 was about 650 (Fig. 1).

Organic, first of all, enamine catalysis attracts researchers by the fact that this allows preparing diverse organic

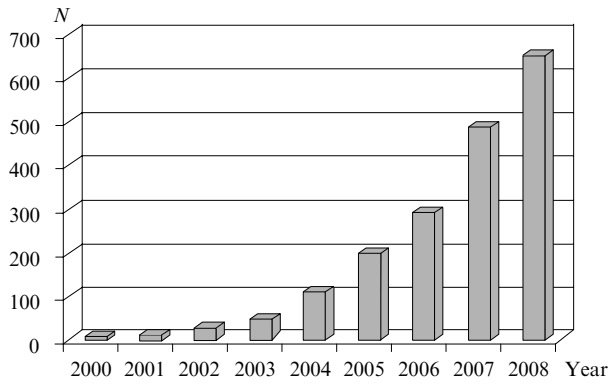


Figure 1. Number (*N*) of papers published in 2000–2008 with 'organocatalysis', 'organocatalyst' and 'organocatalytic' as keywords.

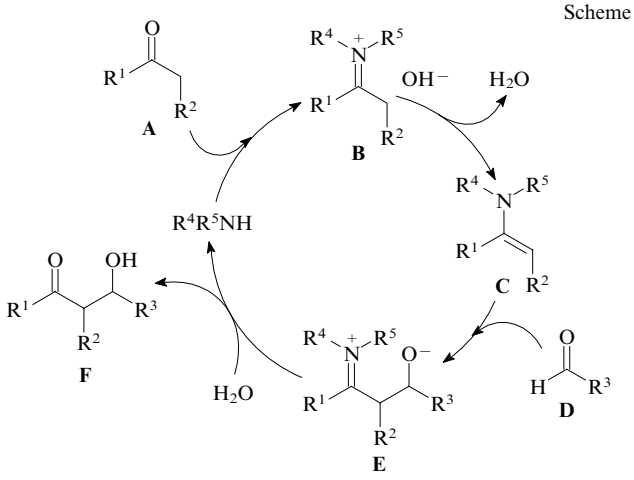
compounds with high enantiomeric purity using rather simple and readily accessible organocatalysts, which are often of natural origin (in particular, derivatives of α-amino acids and chiral amines), and facile experimental procedures. This does not require preliminary introduction of any activating and/or protecting groups into reactant molecules, the syntheses can be carried out in air, without special dehydration of organic solvents and even in water. Owing to high selectivity of organocatalytic reactions and inclusion of all atoms of the reactants into the products (the 'atom efficiency' principle), organocatalysis can be assigned to 'green chemistry' methods.[26]

The concept of enamine asymmetric catalysis and its relationship with the results of biochemical studies of natural enzymes (aldolases) were considered in a recent publication.[27]

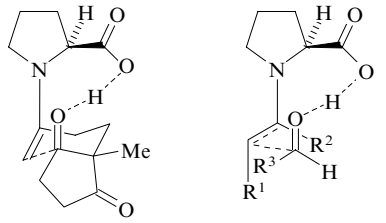
III. The mechanism of enamine catalysis of the aldol reaction

The organocatalysts used in the direct asymmetric aldol reaction are most often chiral compounds containing primary or secondary amino group. The catalytic cycle, which resembles the cycle of carbohydrate synthesis from glyceraldehyde phosphates catalyzed by natural enzymes, *viz*., type I aldolases,[28] is shown in Scheme 1.[25,29] The cycle includes the reaction of the donor ketone $R^1C(O)CH_2R^2$ (**A**) with the catalyst R^4R^5NH resulting in the formation of iminium intermediate **B**, which is then converted into enamine **C**. The addition of the acceptor carbonyl compound R^3CHO (**D**) to the enamine and hydrolytic cleavage of adduct **E** afford aldol **F** and the regenerated catalyst (see Scheme 1). Enamine **C** is the key intermediate in the C–C bond formation in the aldol reaction; therefore, this type of catalysis was termed 'enamine catalysis'.[4] The mechanism of organocatalysis of the asymmetric aldol reaction was studied both experimentally and by computation methods, mainly in relation to proline-catalyzed transformations. In particular, intermediates **C** and **E** were identified by electrospray ionization mass spectrometry (ESI-MS).[29] It was shown that if the aldol reaction catalyzed by compound **1** is carried out in the presence of $H_2^{18}O$, considerable amount of the isotope ^{18}O (~90%) is incorporated into aldol **F** upon hydrolysis of the iminium cation **E**.[30]

Scheme 1



These data, together with the results of quantum chemical calculations confirm the enamine mechanism presented in Scheme 1.[31–33] Moreover, the results of the above-mentioned and some other studies[34–37] provided the conclusion about structural similarity of the transition states of intramolecular (**G**)[38] and intermolecular (**H**)[25,39] aldol reactions containing the donor and acceptor fragments activated by the catalyst.



In both cases, the spatial architecture of activated complexes **G** and **H** favouring the formation of chiral aldol is controlled to a certain extent by hydrogen bonding between the proton of the proline carboxyl group located in the *anti*-arrangement with respect to the enamine double bond and the carbonyl oxygen atom of the acceptor.[40] Thus, proline is able to act simultaneously as a Lewis base and a Brønsted acid and can be considered as a 'bifunctional' catalyst of asymmetric aldol reaction. Apparently, activated complexes of similar structure are also formed in the aldol reactions induced by other chiral organocatalysts, many of which are also bifunctional.[41] The adequacy of the proposed transition state models is indicated by the fact that the computer programme developed recently on the basis of these models allows one, in some cases, to predict the stereochemical outcome of organocatalytic aldol reactions with satisfactory accuracy.[42]

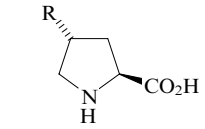
Additional information about the mechanisms of various aldol reactions can be found in numerous publications.[43–54]

IV. Organic catalysts of the aldol reaction

Most of the currently known organocatalysts of asymmetric aldol reactions are derivatives of natural α-amino acids, first of all, proline. In addition, a broad range of catalysts that do not refer to the α-amino acid class and either contain or not contain a pyrrolidine ring have been prepared. We tried to cover most of the known types of organocatalysts in this review. However, since the size of the review is limited, preference was given to the representatives of the considered catalyst types that most often exhibit higher activities and selectivities in the aldol reaction than their analogues. Exhaustive information on the methods of synthesis and properties of organocatalysts can be gained by getting acquainted with the original papers and references cited therein.

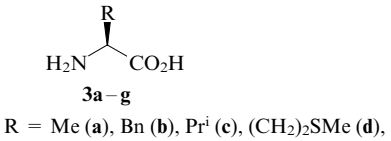
1. α-Amino acids and their derivatives

The most widely used organocatalyst of asymmetric aldol reaction between unmodified aldehydes and ketones is natural α-amino acid **1**; its physicochemical and catalytic properties have been thoroughly studied.[25,34,55] However, 4-hydroxy- (**2a**)[25] and 4-fluoroprolines (**2b**),[56] and α-amino acids with primary amino groups including alanine (**3a**),[57] phenylalanine (**3b**),[58,59] valine (**3c**),[60] methionine (**3d**),[61] tryptophan (**3e**),[62,63] histidine (**3f**),[64] arginine (**3g**),[65] serine (**4a**),[66] threonine (**4b**)[67] and some other[68,69] can also efficiently catalyze this reaction under certain conditions, *e.g.*, in the presence of Brønsted acids.[65] The organocatalytic properties of primary α-amino acids were considered in a recent review.[70]



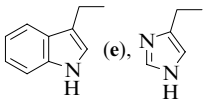
2a,**b**

R = OH (**a**), F (**b**).



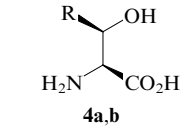
3a–g

R = Me (**a**), Bn (**b**), Pr^i (**c**), $(CH_2)_2SMe$ (**d**),



(**e**), (**f**),

$(CH_2)_3NHCNH_2$ (**g**).



4a,**b**

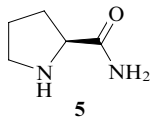
R = H (**a**), Me (**b**).

Despite being readily accessible and inexpensive, chiral α-amino acids suffer, however, from a number of drawbacks. The rates and selectivities of the aldol reactions are usually relatively low, the use of a large amount ($\geqslant$30 mol.%) of the catalyst and considerable excess of the donor are required (the reactions are often carried out in a ketone solution).

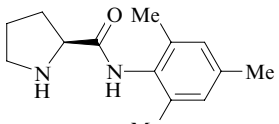
For increasing the activity of the amino-acid catalysts and the selectivity of aldol reactions, a number of α-amino acid derivatives modified at the carboxy group and/or substituents differing in the chemical nature and spatial configurations of the side chain have been synthesized in recent years.

a. Proline derivatives

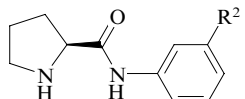
The largest number of studies was devoted to proline derivatives. Prolinamides, some of which have relatively simple structures and contain no additional chirality elements in the structural fragment at the amide nitrogen atom have been prepared and studied in the aldol reaction. These include prolinamide (**5**),[25,71,72] and prolinamides **6**–**9** synthesized from aniline,[73] 2-hydroxyaniline,[74–76] aminonaphthalene[73,77] and 2-aminopyridine[78] derivatives, respectively.



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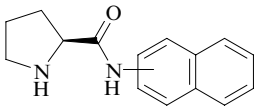


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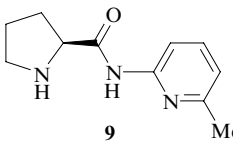


7a–j

R^1 = H: R^2 = H (**a**), Cl (**b**), Bu^t (**c**), NO_2 (**d**), CO_2Et (**e**);
R^1 = Cl: R^2 = H (**f**), Cl (**g**), F (**h**);
R^1 = R^2 = F (**i**), Bu^t (**j**).

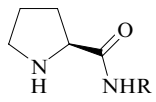


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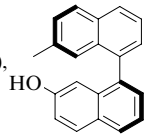
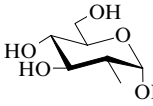
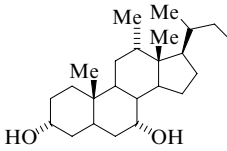
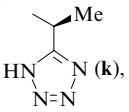
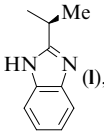
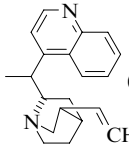
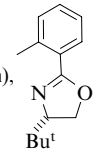
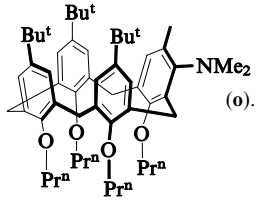


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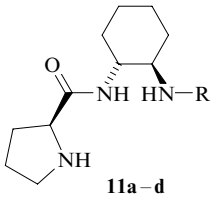
However, more active and selective catalysts for the aldol reaction are, as a rule, prolinamides **10** containing two or more chiral centres in the molecule and based on α-alkylbenzylamines (amide **10a**),[79,80] chiral β-amino alcohols (compounds **10b**,[74] **10c**,**d**,[81] **10e**,[82] **10f**,[83] **10g** [84]), axially chiral amino hydroxy-2,2′-binaphthyl (amide **10h**),[85–87] amino sugar (amide **10i**),[88] steroids (amides **10j**),[89,90] amines with auxiliary nitrogen- and oxygen-containing heterocycles (compounds **10k**,**l**,[91] **10m**,[92] **10n** [93]) and even chiral calix[4]arenes (compound **10o**).[94]



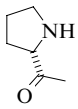
10a–o

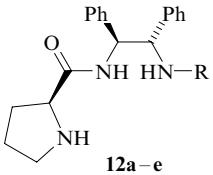
R = Alk/Ph (**a**), Me/HO/Ph (**b**), Bu^i/HO/Ph/Ph (**c**), Ph/HO/Ph/Ph (**d**), Ph/HO/Ph (**e**), CO_2Et/HO/CO_2Et (**f**), SBn/HO/Ph/Ph (**g**),  (**h**),  (**i**),  (**j**),  (**k**),  (**l**),  (**m**),  (**n**),  (**o**).

High catalytic activities and enantioselectivities in the asymmetric aldol reaction were also found for prolinamides **11**–**14** obtained from chiral diamines and their derivatives, in particular, from (1*R*,2*R*)-diaminocyclohexanes (compounds **11a**–**d**),[95–98] (1*R*,2*R*)-diamino-1,2-diphenylethanes (compounds **12a**–**e**),[96,99–102] 2,2′-diaminobinaphthyls (compounds **13a**–**c**)[98,103–106] and a spiro fused diamine containing a C_2-symmetry element (amide **14a**).[107] There is no direct correlation between the number of proline fragments in the catalyst and the catalytic efficiency. Unexpectedly, diamide **14b** in which the prolinamide fragments are connected by a *p*-phenylene linker proved to be a good organocatalyst for aldol reaction between aldehydes.[108]

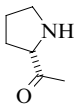


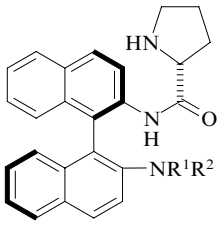
11a–d

R = 4-MeC_6H_4CO (**a**), CF_3CO (**b**),  (**c**), Ts (**d**).

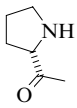


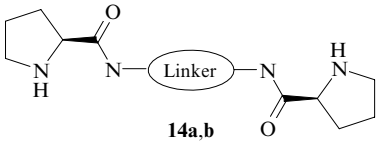
12a–e

R = 4-MeC_6H_4CO (**a**), Ac (**b**),  (**c**), 3,5-$Me_2C_6H_4CO$ (**d**), SO_2Ph (**e**).

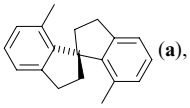
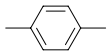


13a–c

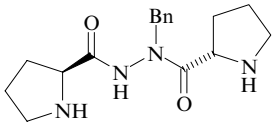
R^1 = R^2 = Me (**a**);
R^1 = H: R^2 = Ac (**b**),  (**c**).



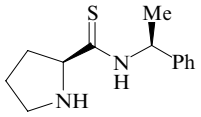
14a,b

Linker =  (**a**),  (**b**).

In addition to prolinamides, the asymmetric aldol reaction can be induced by other (*S*)-proline derivatives funcionalized at the carboxy group such as N-substituted 1,2-bis(prolyl)hydrazine **15**[109] and proline thioamide **16**.[110,111]

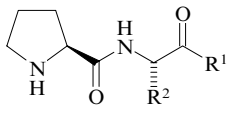


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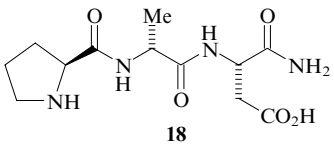


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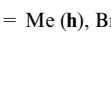
Dipeptides **17** such as prolylglycine (**17a**),[112] prolylphenylalanine (**17b**),[113] prolylserine (**17c**),[114] prolylthreonine (**17d**),[115] prolyltryptophan (**17e**),[116] prolylalanine (**17f**),[114] prolylvaline (**17g**)[114] and some other anilides of prolylalanine and prolylphenylalanine, including compounds (**17h**,**i**)[117] are also quite effective organocatalysts. Good results were obtained also with tri- to pentapeptides **18**, **19**,[118] **20**[115] with N-terminal proline groups and proline-containing dipeptide **21**[119] with a β-amino acid. In some di- and polypeptides, the terminal carboxy groups were esterified.[115,119]

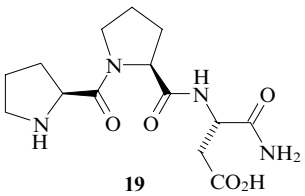


17a–i

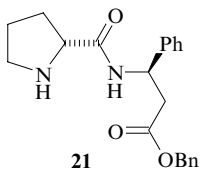


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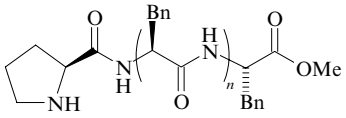
R^1 = OH: R^2 = H (**a**), Bn (**b**), CH_2OH (**c**), CH(Me)OH (**d**),  (**e**), Me (**f**), Pr^i (**g**);
R^1 = NHPh: R^2 = Me (**h**), Bn (**i**).



19



21

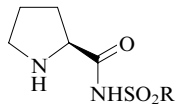


20a,**b**

n = 2 (**a**), 3 (**b**).

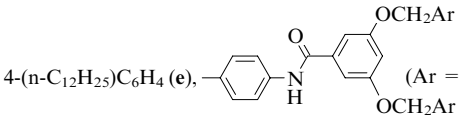
High activities and selectivities of the peptide catalysts are attributable to the resemblance of their spatial architecture to the structure of aldolases.

Sulfonylamides **22** that are obtained from proline or its esters and organic sulfamides in the presence of a base are simple and fairly effective organocatalysts of the aldol reaction. These include compounds **22a**–**d**,[120–124] **22e**[125] and **22f**[126] (*S*-aryl-substituted sulfamides), alkylsulfamides **22g**,[120,121] **22h**,**i**,[127] sulfamide derivatives of camphor **22j**,**k**[120,128] and thiophene **22l**.[129] Of these catalysts, only compounds **22j**,**k** do have chiral centres in the sulfamide group.

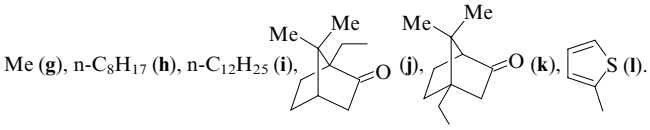


22a–**l**

R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$NO_2C_6H_4$ (**c**), 2,4,6-$Pr^i_3C_6H_2$ (**d**),

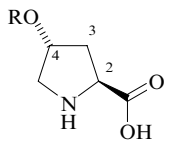


4-(n-$C_{12}H_{25}$)C_6H_4 (**e**), (Ar = 3,5-$(BnO)_2C_6H_3$) (**f**),



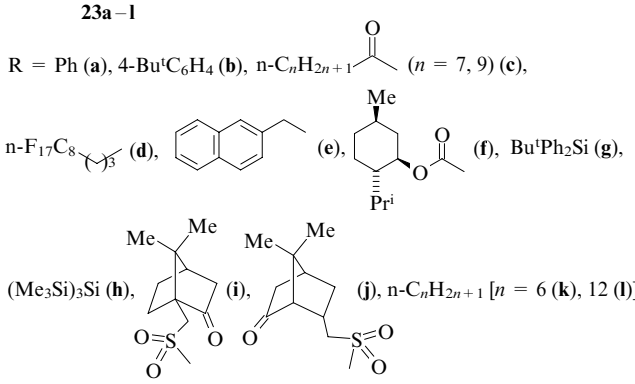
Me (**g**), n-C_8H_{17} (**h**), n-$C_{12}H_{25}$ (**i**), (**j**), (**k**), (**l**).

Derivatives of *trans*-4-hydroxy-(*S*)-proline (**2a**) form a frequently encountered type of organocatalysts of the aldol reaction. For their preparation, amino acid **2a** is usually modified at the hydroxyl or carboxyl group. To date, a representative series of ethers and esters **23** in which the hydroxyl oxygen atom of amino acid **2a** is bonded to aryl (**23a**,[130] **23b**[131]), acyl (**23c**),[132] fluoroalkyl (**23d**),[133] 2-naphthylmethyl (**23e**),[134] alkoxycarbonyl (**23f**),[135] silyl (**23g**,[136,137] **23h**[138]), sulfonyl (**23i**,**j**[135]) and long-chain alkyl groups (**23k**,**l**)[139] have been prepared. The catalytic activity is inherent not only in compounds having free carboxyl groups but in some cases, also their salts, for example, tetrabutylammonium salt of 4-(*tert*-butyldiphenylsilyloxy)-(*S*)-proline **24**.[140]



23a–**l**

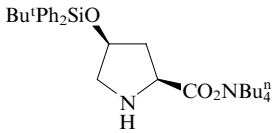
R = Ph (**a**), 4-$Bu^tC_6H_4$ (**b**), n-C_nH_{2n+1} (**c**) (n = 7, 9),



n-$F_{17}C_8$ (**d**), (**e**), (**f**), Bu^tPh_2Si (**g**),

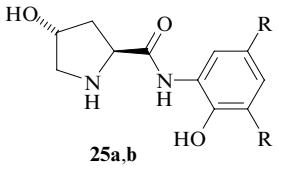
$(Me_3Si)_3Si$ (**h**), (**i**), (**j**), n-C_nH_{2n+1} [n = 6 (**k**), 12 (**l**)].

For some catalysts **23** and compound **24**, diastereomers with *cis*-arrangement of functional groups OR and CO_2H in the pyrrolidine ring (*cis*-**23** and *cis*-**24**) were also obtained.[131,137] 4-Hydroxyproline derivatives immobilized on polymers or containing fragments of ionic liquids are considered in Section IV.3.



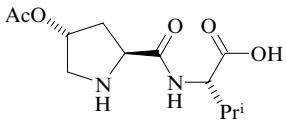
cis-**24**

The asymmetric aldol reaction can also be catalyzed by amides of *trans*-4-hydroxy- (**25a**,**b**),[75] -4-silyloxy- (**26a**,[141,142] **26b**,[143] **26c**[144]) and -4-acetoxy-(*S*)-proline (**27**)[145] and *trans*-4-hydroxy-(*S*)-proline sulfamides (**28a**,**b**).[120]

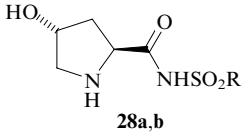


25a,**b**

R = H (**a**), Bu^t (**b**).

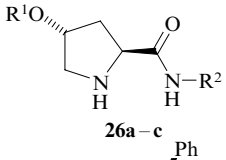


27



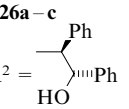
28a,**b**

R = Me (**a**), 4-MeC_6H_4 (**b**).



26a–**c**

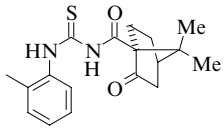
R^1 = Bu^tMe_2Si: R^2 = (**a**),



(**b**);

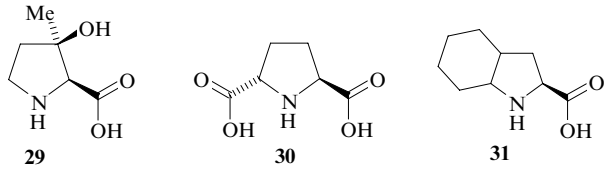
R^1 = Bu^tPh_2Si:

R^2 = (**c**).

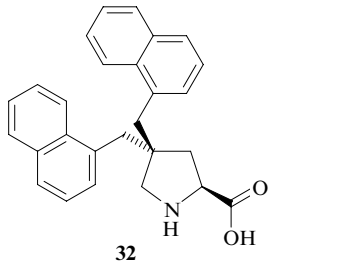


Organocatalytic activities in the aldol reaction were also found for some other (*S*)-proline derivatives containing

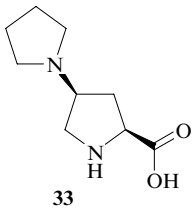
substituents various in positions 2–5 of the pyrrolidine ring. These include (2*S*,3*R*)-3-hydroxy-3-methylproline (**29**),[146] (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**30**)[147] and commercially available (*S*,*S*,*S*)-perhydroindolic acid (**31**).[148] Organocatalysts of this type include the highly effective sterically hindered (*S*)-4,4-bis(1-naphthylmethyl)-proline (**32**)[149] and (*S*)-*cis*-4-pyrrolidinoproline (**33**)[150] containing conformationally proximate pyrrolidine and carboxyl fragments and proline derivative **34**[151] in which the pyrrolidine ring bears four different substituents, in particular, a carbohydrate fragment.



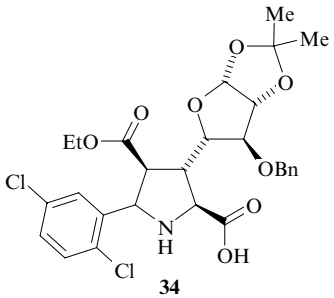
29 **30** **31**



32



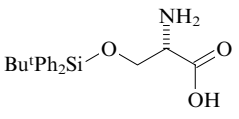
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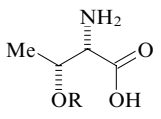
34

b. Derivatives of α-amino acids with primary amino groups

Organocatalysts related to the series of α-amino acids with primary amino groups are usually synthesized, like proline derivatives, by modification of the corresponding amino acids at the hydroxyl group (in the case of α-amino-β-hydroxy acids **4a**,**b**) or the carboxyl group. The former approach was used to prepare silyl ethers of serine (**35**)[152,153] and threonine (**36a**)[154] and threonine *tert*-butyl ether (**36b**),[67,155,156] which quite efficiently catalyze aldol reactions under certain conditions (for example, in the presence of water). Using catalyst **36b**, these reactions occur with unusual *cis*-diastereoselectivity.[155,156]



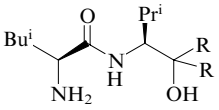
35



36a,**b**

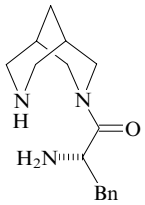
R = Bu^{t}Me$_2$Si (**a**), Bu^t (**b**).

Examples of the latter approach are provided by the syntheses of leucinamides (compounds **37a**,**b**)[157,158] and *O*-(*tert*-butyl)threonine (**38a**)[159] containing chiral β-amino alcohol fragments, which, like ether **36b**, behave as organocatalysts of asymmetric *syn*-aldol reactions. The recently synthesized compound **38b**, a catalyst of cross-aldol reaction of ketones based on phenylalaninamide in which the amide nitrogen is incorporated into the 3,7-diazabicyclo[3,3,1]nonane fragment, also belongs to this type.[160]

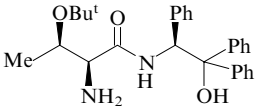


37a,**b**

R = Ph (**a**), 3,5-(CF$_3$)$_2$C$_6$H$_3$ (**b**).

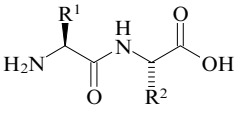


38b

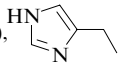


38a

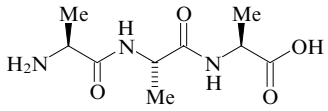
This approach was also used to prepare lower peptides from α-amino acids with primary amino groups. The most effective catalysts of this type contain most often alanine, valine, phenylalanine and/or histidine fragments.[68] These include dipeptides **39a**,[68] **39b**,[161] **39c**,[68] **39d**,[162] **39e**,[68,161] tripeptides **40**[161] and some other compounds.



39a–e

R^1 = Pr^i; R^2 = Me (**a**), Pr^i (**b**), Bn (**c**),  (**d**);

R^1 = R^2 = Me (**e**).



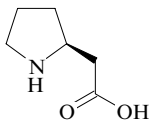
40

2. Catalysts other than α-amino acid derivatives

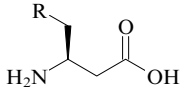
The asymmetric aldol reaction can be induced by not only natural α-amino acids and their derivatives but also by other compounds used as catalysts.

a. β-Amino acids and their derivatives

Examples of enantioselective organocatalysis of intramolecular aldol reactions catalyzed by chiral β-amino acids containing both primary and secondary amino groups are also known. This type of catalysts studied include β^3-homoproline (**41**),[163] β^3-homophenylalanine (**42a**),[164,165] β^3-homoleucine (**42b**)[165] and (1*R*,2*S*)-*cis*-pentacin (**43**).[166] β-Amino-acid carbohydrate derivative **44** catalyzes fairly efficiently intermolecular aldol reactions.[167]

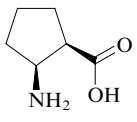


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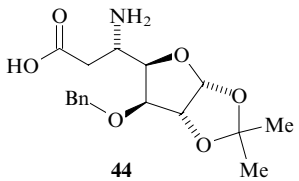


42a,**b**

R = Ph (**a**), Pr^i (**b**).



43



44

b. Catalysts containing a pyrrolidine unit

Some chiral pyrrolidine derivatives devoid of a carboxyl group are also capable of catalyzing asymmetric aldol reactions. This type of catalysts can be divided into four groups:

(1) (*S*)-2-hydroxymethylpyrrolidine (prolinol) and its derivatives;

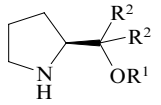
(2) (*S*)-2-aminomethylpyrrolidine derivatives;

(3) pyrrolidine-2-phosphonic acid derivatives;

(4) pyrrolidine derivatives with nitrogen heterocycles in position 2.

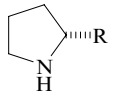
(*S*)-Proline is used most often as the starting compound for the synthesis of the majority of organocatalysts of these groups.

(*S*)-Prolinol (**45a**)[168] prepared by reduction of (*S*)-proline is the simplest and in some cases sufficiently effective catalyst corresponding to the first group. However, compounds **45b**,[169,170] **45c**,[171,172] **45d**[173] and **45e**[174] containing aromatic substituents in the α-position to the hydroxy or trialkylsilyloxy group are more selective organocatalysts of this type. The organocatalytic reactions induced by α,α-diarylprolinol ethers **45b**–**e** have been recently reviewed.[175,176] (*S*)-2-Aaminomethylpyrrolidine derivatives studied in the aldol reaction include *N*,*N*-(dialkylamino)-pyrrolidines **46a**,[177] **46b**,[178] **46c**,[179] **46d**,[180] and perfluoroalkylsulfamides **46e**[181,182] and **46f**.[183,184] Catalysts **46a**–**d** are most efficient in systems containing Brønsted acids,[177,180] which apparently hamper the alternative general basic catalysis of these reactions giving rise to racemic aldols. A fairly high catalytic activity and enantioselectivity were found for D-pyrrolidine-2-phosphonic acid (**47a**) and its dimethyl ester (**47b**).[185,186] Unlike phosphonic acid **47a**, its boron analogue **47c**[187] barely shows catalytic properties in the aldol reaction. Good prospects were found for the pyrrolidine organocatalysts **48** in which the pyrrolidine unit is bonded directly to another nitrogen-containing ring, in particular, tetrazole (**48a**),[188,189] benzimidazole (**48b**),[190,191] pyridine (**48c**)[192] or 1,2,3-triazole (**48d**) ring.[193] Recently, the use of (*S*)-5-(2-methylpyrrolidin-2-yl)-1*H*-tetrazole (**48e**) as the catalyst of aldol reaction has been reported.[194]



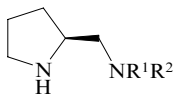
45a–**e**

R^1 = H: R^2 = H (**a**), 3,5-$(CF_3)_2C_6H_3$ (**b**); R^1 = Me_3Si: R^2 = Ph (**c**), 3,5-$(CF_3)_2C_6H_3$ (**d**); R^1 = Et_3Si, R^2 = Ph (**e**).



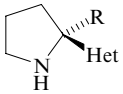
47a–**c**

R = $P(O)(OH)_2$ (**a**), $P(O)(OMe)_2$ (**b**), $B(OH)_2$ (**c**).

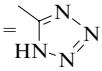


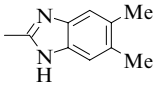
46a–**f**

R^1 = R^2 = Et (**a**), n-$C_{10}H_{21}$ (**b**); R^1–R^2 = $(CH_2)_n$ [*n* = 4 (**c**), 5 (**d**)]; R^1 = H: R^2 = CF_3SO_2 (**e**), n-$C_4F_9SO_2$ (**f**).

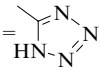


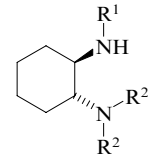
48a–**e**

R = H: Het =  (**a**),

 (**b**),  (**c**),

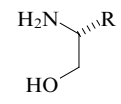
 (**d**);

R = Me, Het =  (**e**).



51a–**g**

R^1 = H: R^2 = Me (**a**), Et (**b**), Pr^i (**c**), Pr^n (**d**), n-$C_{10}H_{21}$ (**e**); R^1 = C(S)NHAr, R^2 = Me (**f**); R^2–R^2 = $(CH_2)_4$ (**g**).

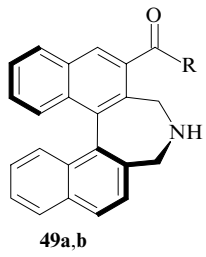


54a,**b**

R = Pr^i (**a**), Bu^i (**b**).

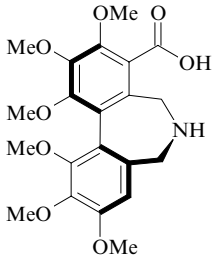
c. Miscellaneous catalysts

Examples of catalysis of the asymmetric aldol reaction by organic compounds that do not belong to the above groups are few but impressive. Exceptionally effective catalysts **49** and **50** are based on axially chiral γ-amino acids and their derivatives containing a binaphthyl (**49a**,[195,196] **49b**[197]) or biphenyl (**50**) fragment.[198]



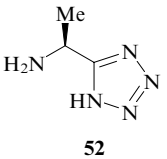
49a,**b**

R = OH (**a**), $NHSO_2CF_3$ (**b**).

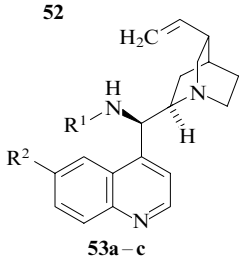


50

Some chiral amines and diamines with relatively simple structures catalyze aldol reactions and exhibit exceptionally high diastereo- and enantioselectivity under certain conditions, for example, in combination with Brønsted acids. These include, in particular, recently obtained N-substituted *trans*-1,2-diaminocyclohexanes containing primary and tertiary amino groups **51a**–**e**[199–201] and *N*-[2-dimethylaminocyclohexyl)- (**51f**)[202] and (2-pyrrolidinocyclohexyl)thiourea derivatives (**51g**).[203] The catalytic properties of chiral thiourea derivatives in enantioselective reactions were considered in a recent review.[204] Reasonable enantioselectivity of the catalysis of aldol reactions was demonstrated by the accessible tetrazole analogue of alanine **52**,[68] quinine amino derivatives **53a**,**b**[205,206] and quinine thiourea derivatives **53c**.[202,207] Valinol (**54a**) and leucinol (**54b**) were found to be simple and efficient catalysts of some types of aldol reactions.[208]



52

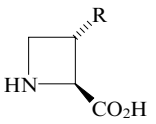


53a–**c**

R^1 = H: R^2 = H (**a**), OMe (**b**); R^1 = C(S)NHAr, R^2 = OMe (**c**).

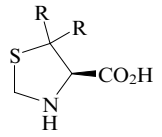
Representatives of at least four types of nitrogen heterocyclic compounds other than pyrrolidine with a secondary amino group incorporated in the heterocycle are known to behave as organocatalysts in the asymmetric aldol reaction. In particular, the activity and enantioselectivity of amino acid azetidine derivatives **55a**,[25] **55b**[209] and thiazole derivatives **56a**,[25] **56b**[71] are comparable with those of proline. Higher enantioselectivities in various aldol reactions were

found for more recently synthesized imidazolidinone **57**[210] and the catalytic system **58** – CF_3CO_2H.[211–214]



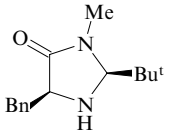
55a,b

R = H (**a**), Bu^n (**b**).

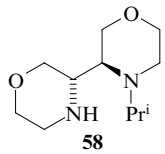


56a,b

R = H (**a**), Me (**b**).

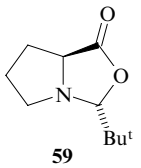


57

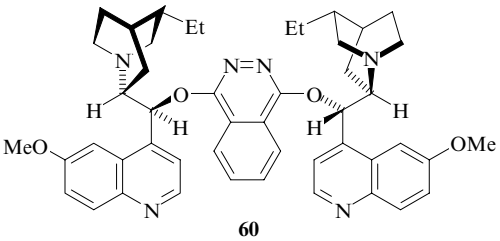


58

Finally, it has recently been found that aldol reaction can be catalyzed by nitrogen heterocycles devoid of primary or secondary amino groups, in particular, oxazolidinone **59**[215] and quinuclidine derivative **60**.[216] The mechanism of catalytic action of these compounds obviously does not include the formation of enamine intermediates.



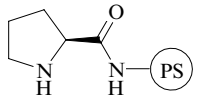
59



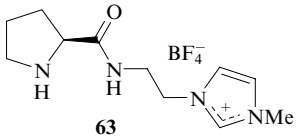
60

3. Immobilized catalysts

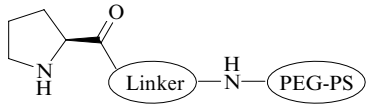
In recent years, proline-containing catalysts of asymmetric aldol reaction immobilized on polymeric supports or anchored to ionic liquids have been prepared (see a review[217]). As a rule, these catalysts are easily separated from the reaction system components due to different solubilities and can be regenerated. Usually, a spacer group is attached to the carboxyl carbon atom of the amino acid or to another functional group introduced in the pyrrolidine ring of proline. The endocyclic amino group functioning as the catalytically active site in the reaction remains free.



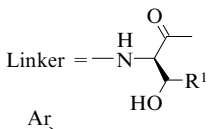
61



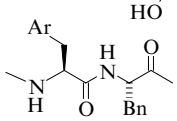
63



62a–d



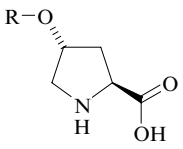
[R^1 = H (**a**), Me (**b**)],



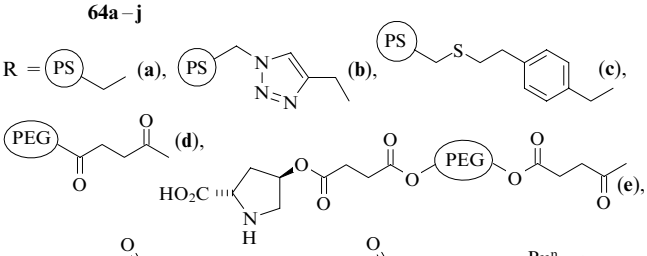
[Ar = Ph (**c**), 4-HOC_6H_4 (**d**)].

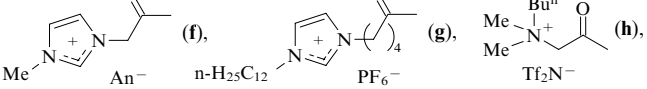
Proline immobilization through the carboxyl group underlies the strategy of synthesis of the heterogeneous catalyst **61**,[218] the proline fragment of which is attached directly to aminopolystyrene (PS). The same immobilization technique was used to prepare compounds **62a,b**[219] and **62c,d**,[220] in which the pyrrolidine ring is linked to a poly(ethylene glycol) (PEG) – PS co-polymer through a linker comprising one or more α-amino acids (in particular, serine, threonine, phenylalanine and tyrosine). The catalyst **63**[221] bearing an imidazolium cation was prepared in the same way.

The possibility of functionalization of the hydroxy group in (*S*)-*trans*-4-hydroxyproline (**2a**) was implemented in the syntheses of a number of immobilized organocatalysts **64** including polystyrene-grafted compounds **64a**,[222] **64b**,[223] **64c**,[224] poly(ethylene glycol)-grafted catalysts **64d**,[225] **64e**,[226] and ionic-liquid-anchored compounds **64f** [An = BF_4,[227] NTf_2 (Ref. 228)], **64g**,[229] **64h**[228] and **64i**,[230] which contain, like catalyst **63**, fragments of ionic liquids extensively studied in recent years.[231,232] Attention is attracted to the structural diversity of spacer groups used: this can be hydrocarbon chains of different length,[230] thioesters,[224] carboxylic[227–229] and dicarboxylic[225,226] acid fragments and heterocycles.[223] Recently,[233] the same strategy was used to synthesize (*S*)-4-hydroxyprolin amide **65** immobilized on a polymer.



64a–j

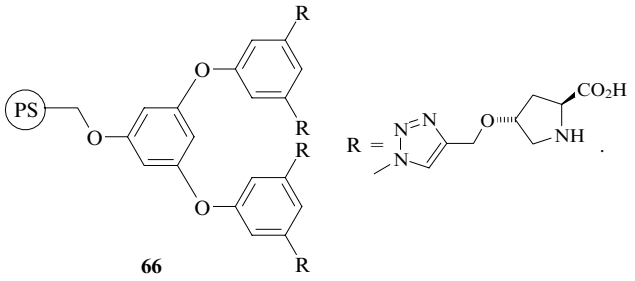
R = 



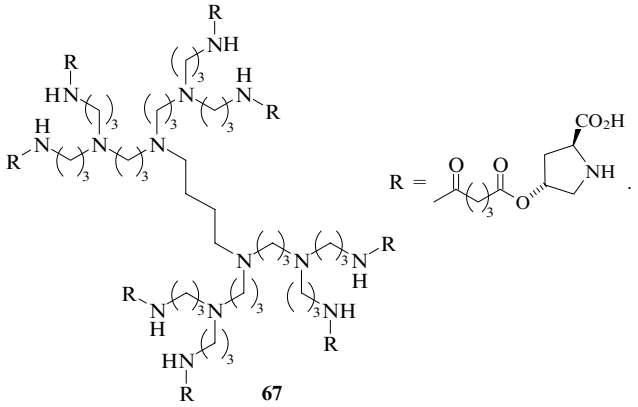
65

In addition to the considered catalysts, derivatives with more complex spatial structures were obtained based on (*S*)-*trans*-4-hydroxyproline, namely, polystyrene-immobilized catalyst **66**[234] with a branched spacer and polyamine **67**[235] in which the proline fragments are connected through glutaric acid-based spacers to each of the eight peripheral

amino groups of a commercially available poly(propyleneimine) dendrimer.

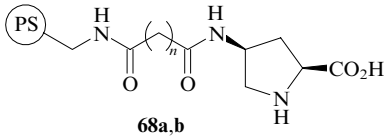


66



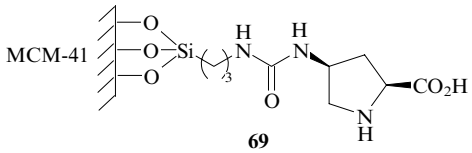
67

The immobilized organocatalysts can be synthesized from 4-aminoproline derivatives. Examples are the catalysts **68a**,**b** [236] grafted to polystyrene through succinic and adipic acid fragments and catalyst **69** immobilized on a mesoporous silicate support MCM-41 by a [1-(trioxysilyl)prop-3-yl]urea fragment.[237, 238] Unlike the (*S*)-*trans*-4-hydroxyproline derivatives **64**–**67** mentioned above, 2- and 4-substituents in the pyrrolidine ring of catalysts **68** and **69**, are *cis*-oriented as a result of configuration inversion at the C(4) atom during the synthesis of *cis*-4-aminoproline from compound **2a**. Proline derivatives can be immobilized using 1,3-dipolar cycloaddition of (*S*)-*trans*-4-azidoproline to the Merrifield resin modified by terminal acetylene groups. This gives catalyst **70** with unusual properties,[239] which is isomeric to compound **64b** obtained from (*S*)-*trans*-4-hydroxyproline (**2a**).

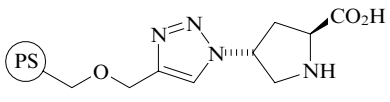


68a,**b**

n = 2 (**a**), 4 (**b**).

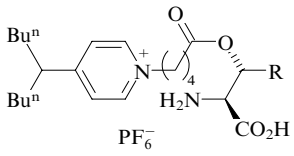


69



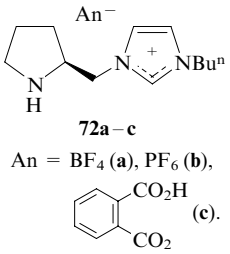
70

Recently, we synthesized serine **71a** and threonine **71b** derivatives anchored to ionic fragments, which are apparently the first representatives of immobilized α-amino acids with primary amino groups.[240] Among the immobilized organocatalysts other than amino acids, mention should be made of pyrrolidine derivatives **72a**–**c** [241, 242] in which the imidazolium cation is connected to the pyrrolidine fragment through the methylene group.



71a,**b**

R = H (**a**), Me (**b**).



72a–**c**

An = BF_4 (**a**), PF_6 (**b**),

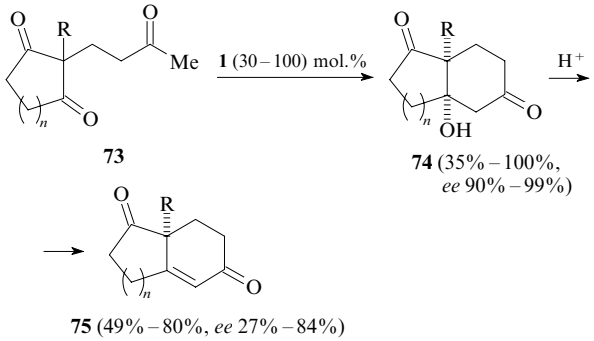
(**c**).

V. Applications of the organocatalytic asymmetric aldol reaction

This Section considers the use of organocatalytic asymmetric aldol reaction. Whenever possible, we compare the outcomes of reactions, *i.e.*, product yields, diastereomeric ratios (*dr*) and enantiomeric excesses (*ee*), involving substrates with different electronic and spatial structures carried out under comparable conditions. The material is divided into two subsections devoted to intra- and intermolecular aldol reactions.

1. Intramolecular aldol reactions

As noted above (see Section II), enantioselective cyclization of triketones **73** to bicyclic carbonyl compounds **74** and **75** induced by (*S*)-proline (**1**) (the Hajos–Parrish–Eder–Sauer–Wiechert reaction) discovered in 1971 is the first example of organic catalysis of asymmetric aldol reaction.[17–19, 243, 244] In this reaction, the methyl ketone group serves as the nucleophile and one of the two endocyclic keto groups of compound **73** is the electrophile. In the 1980–1990s, this reaction was studied in detail by several research groups, and experimental procedures for this reaction were proposed. According to one of them, cyclization is carried out in a neutral medium at room temperature to give aldol **74**.[245, 246] According to another one, the reaction is carried out in the presence of strong acids ($HClO_4$, TsOH), which promotes dehydration of aldols **74** formed *in situ* to enones **75**.[20]



73

74 (35%–100%, *ee* 90%–99%)

75 (49%–80%, *ee* 27%–84%)

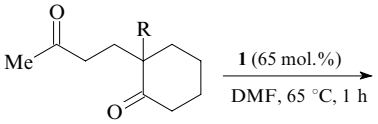
n = 1, 2; R = Me, SPh.

The nature of the substituent R and the ring size in the starting compound **73** have little influence on the reaction selectivity, but determine the product yield.[20] The enantiomeric purity of enones **75** can be increased to more than 99% by recrystallizing the *tert*-butyl ethers obtained by reduction of the non-conjugated carbonyl group in com-

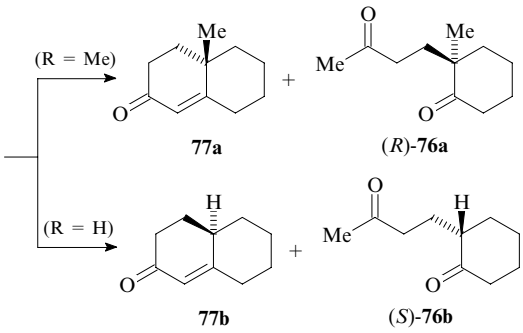
pounds **75** (n = 1, 2; R = SPh) followed by alkylation of the alcohol formed.[247]

The Hajos–Parrish–Eder–Sauer–Wiechert reaction can also be carried out using other organocatalysts. Thus in the presence of the salt of chiral bimorpholine **58** with trifluoromethanesulfonic acid (TfOH), compounds **75** (n = 1, 2; R = Me) were obtained in 60%–84% yields and *ee* 80%–95%. These values are comparable with the yields and *ee* values of enones formed under proline catalysis, but 5 mol.% of catalyst **58**·TfOH is sufficient for effective reaction.[211–214]

A method for kinetic resolution of racemic diketones **76a**,**b** into enantiomers based on intramolecular aldol reaction in the presence of (*S*)-proline (**1**) was proposed.[248] In the case of compound **76a**, chiral cyclization product **77a** (*ee* 43%) is formed leaving enantiomerically enriched diketone (*R*)-**76a** unconsumed (the *ee* value was not determined). Under the same conditions, unsubstituted cyclohexanone **76b** gives cyclization product **77b** (*ee* 46%) in which the chiral centre configuration, like that in unconsumed diketone (*S*)-**76b**, is opposite to that in compounds **77a** and (*R*)-**76a**.[249]

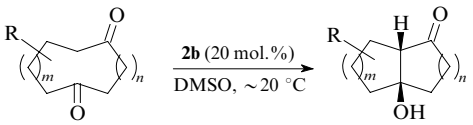


rac-**76a**,**b**

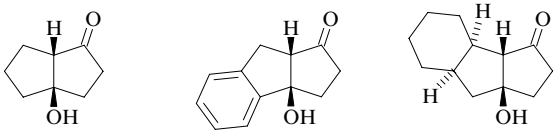


R = Me (**a**), H (**b**).

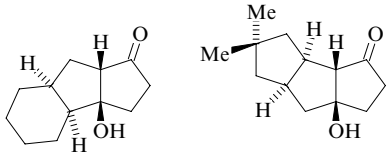
Recently, Chandler and List[56] demonstrated that some cyclic diketones, including cyclooctane-1,4-dione derivatives **78**, can undergo organocatalytic transannular aldol reaction with high stereo- and enantioselectivity. This opens up direct route to the synthesis of chiral polycyclic compounds **79**. *trans*-4-Fluoroproline (**2b**) proved to be the most active and selective catalyst of this reaction: for the tricyclic ketones **79c**–**e** prepared in presence of **26**, the diastereomeric ratio *dr* (*syn* : *anti*) was > 20 : 1.



78 **79a**–**e** (32%–97%)

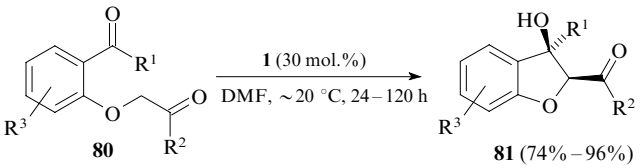


79a (53%, *ee* 95%) **79b** (80%, *ee* 94%) **79c** (68%, *ee* 94%)



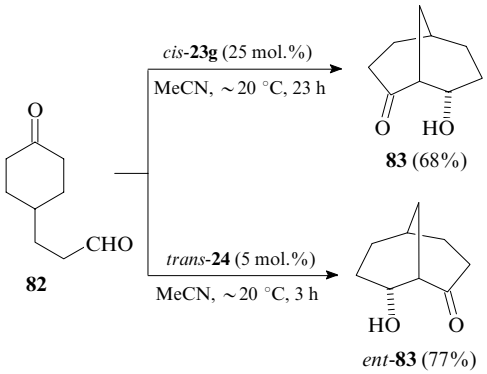
79d (42%, *ee* 90%) **79e** (84%, *ee* 96%)

The compounds containing an aldehyde group along with the keto group can undergo intramolecular aldol reactions. The aldehyde group usually functions as the acceptor component. Thus the (*S*)-proline-catalyzed intramolecular cyclization of *ortho*-substituted aromatic aldehydes (**80**, R^1 = H) and ketones (**80**, R^1 = Me) to chiral 2,3-dihydro-3-hydroxybenzofurans **81** was reported.[250] This reaction manifested high *cis*-diastereoselectivity [*dr* = (93 : 7)–(> 99 : 1)] and enantioselectivity (*ee* 76%–87%). Enantiomerically pure products **81** were isolated by recrystallization of the reaction product from a mixture ethyl–hexane acetate.



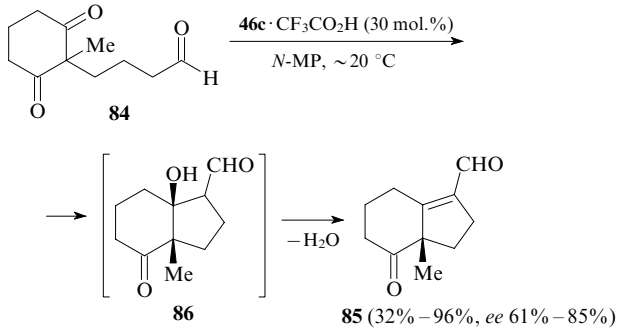
R^1 = H, Me; R^2 = Me, Et; R^3 = H, Me.

Yet another example is intramolecular aldolization of σ-symmetric keto aldehyde **82** to *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one (**83**) induced by 5-hydroxyproline derivatives *trans*-**23g**, *cis*-**23g** and **24**. The reactions proceed with high diastereo- (*dr* > 99 : 1) and enantioselectivity (*ee* 94%). Compound **83** obtained in the presence of amino acid *cis*-**23g** is the optical antipode of *ent*-**83** formed in the reaction catalyzed by tetrabutylammonium salt *trans*-**24**.[140] The latter has higher catalytic activity than amino acid **23g**, which is attributable to higher nucleophilicity of the amino group in **24**. It is noteworthy that, unlike the formation of *ent*-**83** under the action of salt **24**, reaction catalysis by proline tetrabutylammonium salt results in racemate *rac*-**83**.



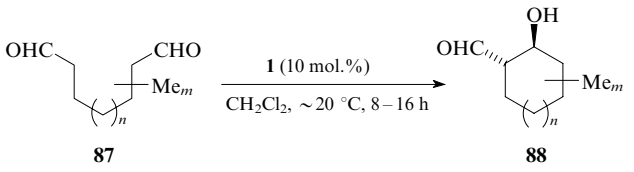
Intramolecular aldol reactions of bifunctional compounds containing aldehyde and keto groups in which the keto group functions as the electrophile are more scarce. Hayashi *et al.*[251] studied intramolecular aldol cyclization of diketoaldehyde **84** catalyzed by pyrrolidine salt **46c**·CF_3CO_2H, which is accompanied by reversal of the electronic functions of the aldehyde and ketone, and developed an original enantioselective synthesis of (*S*)-1-methyl-

2-oxobicyclo[4.3.0]non-6-ene-7-carbaldehyde (**85**). When this reaction is carried out in *N*-methylpyrrolidone (*N*-MP), the yield of product **85** is 96% and the enantioselectivity reaches 85%. In other organic solvents (Et_2O, MeOH, MeCN), the results are somewhat inferior. In addition to the dehydration product, aldol **86** (*ee* 55%–77%) is isolated. Note that the corresponding reaction catalyzed by proline affords mainly the antipode *ent*-**85** (*ee* 43%).

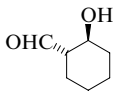
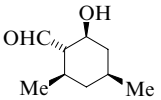
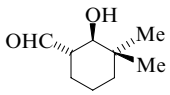
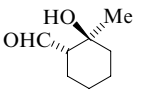
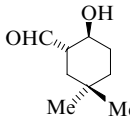
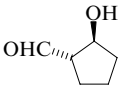


Finally, there are examples of intramolecular aldol reactions involving compounds containing two aldehyde groups. Thus (*S*)-proline (**1**) catalyzes intramolecular cyclizations of hexane- and heptanedials **87** ($n = 0$, 1 respectively) to substituted cyclic aldols **88** (Scheme 2).[252]

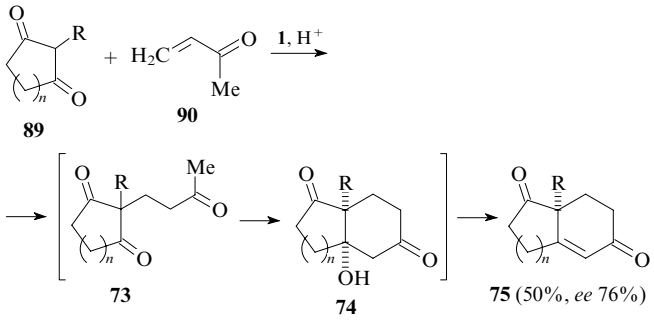
Scheme 2



$m = 0–2$; $n = 0$, 1.

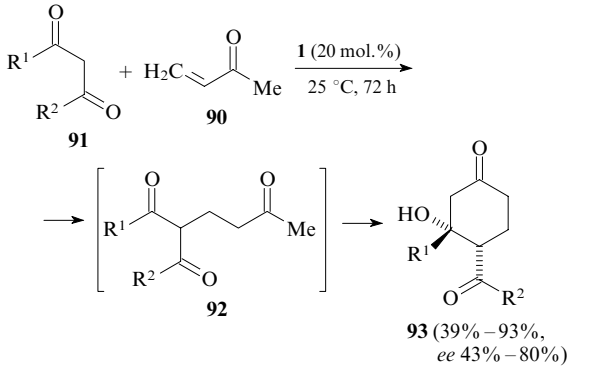
Compound **88**	Yield (%)	*dr* (*anti*:*syn*)	*ee*, %	Compound **88**	Yield (%)	*dr* (*anti*:*syn*)	*ee*, %
	95	10:1	99		88	1:1	99
	74	>20:1	98		92	2:1	99
	75	>20:1	97		85	2:1	79

The reaction proceeds *anti*-diastereoselectively. The *ee* values of products **88** ($n = 1$) obtained from substituted heptanedials are usually high irrespective of the position of the methyl groups in compounds **87** ($n = 1$). The diastereo- and enantioselectivities of aldolization of hexanedials **87** ($n = 0$) are markedly lower.[253] The yields, the *dr* and *ee* values of (*S*)-proline (**1**)-catalyzed intramolecular cyclization products of hexane- and heptanedials **87** are presented in Scheme 2. The intramolecular aldol reaction can serve as one of the stages of a catalytic 'domino' transformation suitable for one-pot synthesis of complex polyfunctional carbo- and heterocyclic compounds from relatively simple starting reactants. Probably, the one-pot version of the Hajos–Parrish–Eder–Sauer–Wiechert reaction was the first example of this type of transformation. Since both the addition of cycloalkane-1,3-diones **89** to but-1-en-3-one (**90**), resulting in triketones **73** and aldol cyclization of the latter are catalyzed by (*S*)-proline (**1**), products **75** can be synthesized in the one-pot reaction from commercially available compounds **89** and **90**.[254]



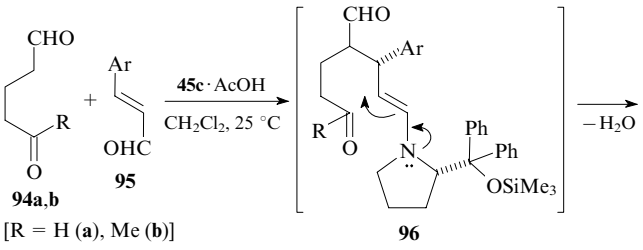
$n = 1$, 2.

Acyclic β-dicarbonyl compounds can also undergo successive Michael reaction and aldol cyclization. Thus in the presence of amino acid **1**, β-diketones **91** react with but-1-en-3-one (**90**) to give adducts **92**, which are converted under reaction conditions into chiral 3-hydroxycyclohexanones **93** in high yields and with moderate enantioselectivity. Under these conditions, non-symmetrically substituted β-diketones **91** ($R^1 \neq R^2$) afford predominantly regioisomer **93** containing a more electron-withdrawing substituent in the α-position to the hydroxy group.[255]

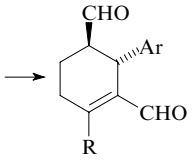


R^1, R^2 = 4-XC_6H_4 (X = H, Cl, Br, OMe), 2-furyl, 2-thienyl, 4-pyridyl.

The reactions of glutaraldehyde (**94a**) or 5-oxohexanal (**94b**) with 3-arylpropenals **95** occurring through the formation of *in situ* adducts **96** give chiral 2-arylcyclohex-3-ene-1,3-dicarbaldehydes **97a–l**. The **45c**–organic acid system is the optimal catalyst for this process. Under proposed conditions, products **97** were obtained in reasonable yields and with high diastereo- (*dr* > 99:1) and enantioselectivity (*ee* 74%–99%).[172] The structure of dialdehyde **97j** was established by X-ray diffraction.



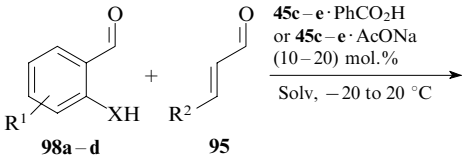
94a,b [R = H (**a**), Me (**b**)] **95** **96**



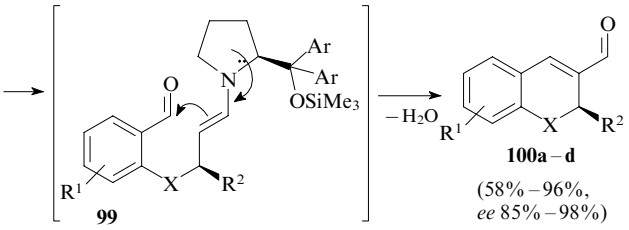
R = H: Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-MeC$_6$H$_4$ (**c**), 2-Bu^{t}Me$_2$SiOC$_6$H$_4$ (**d**), 2-furyl (**e**), 2-O$_2$NC$_6$H$_4$ (**f**), 4-BrC$_6$H$_4$ (**g**); R = Me: Ar = Ph (**h**), 2-furyl (**i**), 2-O$_2$NC$_6$H$_4$ (**j**), 4-BrC$_6$H$_4$ (**k**), 4-MeOC$_6$H$_4$ (**l**).

97a–l (53%–68%)

Chinese and Swedish researchers developed convenient enantioselective methods for the synthesis of diverse chiral heterocyclic compounds by the reaction of anthranilaldehyde (**98a**,**b**) and salicylaldehyde (**98c**) derivatives or 2-mercaptobenzaldehyde (**98d**) with α,β-enals **95** in the presence of silyl ethers of α,α-diarylprolinols **45c–e**. The reactions follow a common route comprising the addition of the heteroatom X of compound **98** to the activated double bond of enal **95** and organocatalytic aldol cyclization of adducts **99** to 1,2-dihydroquinolines **100a**,[171] **100b**,[174] chromenes **100c**[256] or thiochromenes **100d**.[257] Attention is attracted by the high enantioselectivity of the reactions and the possibility of varying the structure of the starting compounds over broad limits.



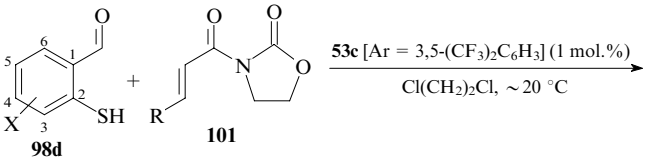
98a–d **95**



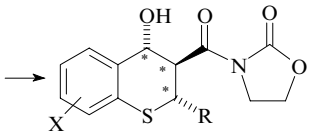
99 **100a–d** (58%–96%, *ee* 85%–98%)

X = NH (**a**), NCbz (**b**), O (**c**), S (**d**); R^1 = H, Cl, F, Me, OMe; R^2 = YC$_6$H$_4$ (Y = H, 4-CN, 4-Cl, 4-F, 4-Br, 4-NO$_2$, 4-OMe, 2-OMe), 2-naphthyl, 2-furyl, CO$_2$Et, n-Alk, CH$_2$OBn; Cbz is benzyloxycarbonyl.

Compounds containing a thiourea fragment are fairly effective catalysts of asymmetric 'domino' reactions comprising the Michael reaction and aldol cyclization. In the presence of only 1 mol.% of catalyst **53c** [Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$], 2-mercaptobenzaldehydes **98d** react with oxazolidinones **101**, which have electron-deficient double bonds, in dichloroethane to give benzothiopyrans **102**



98d **101**

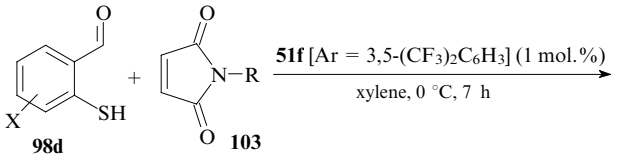


102a–l
(75%–95%, *ee* 91%–99%)

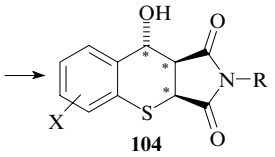
R = Ph: X = H (**a**), 5-Me (**b**), 6-Cl (**c**), 4,6-Me$_2$ (**d**), 5,6-(CH$_2$)$_4$ (**e**); X = H: R = 4-ClC$_6$H$_4$ (**f**), 3-ClC$_6$H$_4$ (**g**), 2-ClC$_6$H$_4$ (**h**), 4-MeOC$_6$H$_4$ (**i**), 3-MeC$_6$H$_4$ (**j**), 1-naphthyl (**k**), 3-thienyl (**l**).

(*dr* > 20 : 1) in high yields and with excellent enantioselectivity.[207]

N-(2-Dimethylaminocyclohexyl)thiourea **51f** [Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$] proved to be a good catalyst for the reaction of *o*-mercaptobenzaldehydes **98d** with maleimides **103** giving rise to substituted thiochromanes **104** [*dr* = (5 : 1)–(20 : 1)].[202] Note that in the reactions catalyzed by thiourea derivatives **51f** and **53c**, unlike the reactions in the presence of prolinol ethers **45c**,**d**, no dehydration of the initially formed aldols takes place. Therefore, heterocyclic products **102** and **104** containing three chiral centres in the molecule can be synthesized from achiral precursors in one experimental step.



98d **103**



104
(83–95%, *ee* 75–94%)

X = H, Me, Cl; R = H, Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 3,5-Me$_2$C$_6$H$_3$, Bn.

As noted above, organocatalyzed intramolecular aldol reactions are of high practical value and are used as key steps of the synthesis of drugs and bioactive natural products.[24]

2. Intermolecular aldol reactions

Over almost 30 years, the scope of application of organic catalysis in the aldol reaction was limited to intramolecular processes. Only in 2000, did List and Barbas III with coworkers[25,71,258,259] establish for the first time that amino acids and some other compounds containing an amino group can catalyze not only intra-, but also intermolecular asymmetric aldol reactions involving unmodified aldehydes and ketones. Under conditions employed (organic solvent, excess ketone), primary (His, Val, Phe, *etc*.) and secondary (*e.g*., *N*-methylleucine) linear α-amino acids showed low activity as catalysts; however, the use of (*S*)-proline (**1**) resulted in aldol reaction products in high yields and with high enantioselectivity. Over the relatively short period of time that passed since this discovery, huge experimental data have been accumulated, which demonstrated the general character of the discovered reaction. Newer data made it possible to reveal the features of behaviour of carbonyl compounds in aldol reactions, specific nature of various types of organocatalysts and the relationships between the

efficiency of organocatalytic reactions and the reaction conditions.

In terms of the chemical nature of the nucleophilic component, the organocatalytic aldol reactions studied to date can be divided into three groups:

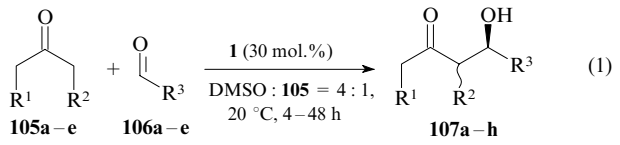
— reactions in which a ketone molecule serves as the nucleophile;

— reactions in which an aldehyde molecule serves as the nucleophile;

— reactions in which a carboxylic acid derivative serves as the nucleophile.

a. Reactions with ketones serving as nucleophiles

The intermolecular aldol reactions of the first group have been studied in most detail. The major part of experimental data has been obtained for donor ketone–acceptor aldehyde systems. Table 1 presents some typical examples of these reactions. In the presence of (*S*)-proline, acetone (**105a**) and cycloalkanones **105b**,**c** react with aromatic aldehydes **106a**,**b** to give aldols **107a**–**c** in up to 94% yields and *ee* up to 60%–89%.[71] These reactions are, as a rule, carried out with a large excess of ketone. Usually, the process rate and the yield of aldols **107** increase upon introduction of electron-withdrawing substituents into the aromatic ring of the aldehyde. Compounds **107b**,**c** obtained from cycloalkanones **105b**,**c** and 4-nitrobenzaldehyde (**106b**) are usually mixtures of *syn*- and *anti*-diastereomers in which the latter predominate. Proline catalyzed reactions of butan-2-one (**105d**) with aromatic aldehydes **106a**,**b** occur regioselectively to give addition products involving the ketone methyl group, namely, aldols **107d**. However, ketones containing bulkier alkyl groups (for example, pentan-3-one, isopropyl methyl ketone, *etc*.), do not react with aldehydes under the studied conditions.



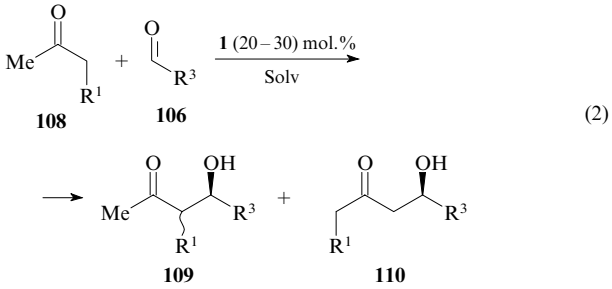
(1)

Aliphatic aldehydes **106c**,**d** also react with ketones **105** in the presence of (*S*)-proline. The reaction product **107e** of acetone (**105a**) with isobutanal (**106c**) is formed in an exceptionally high yield and with good enantioselectivity (*ee* up to 96%).[25, 71] The aldol reaction can be carried out for both individual cycloalkanecarbaldehydes, for example **106d**, and compounds obtained *in situ* by hydroformylation of cycloalkenes in the presence of rhodium complexes.[260] Instead of acetone (**105a**), 4-hydroxy-4-methylpentan-2-one (diacetone alcohol) (**105e**) can be used as the nucleophilic component. In this case, 2 equivalents of the ketone suffice to attain high conversion and enantioselectivity.[261, 262] The unexpectedly high *ee* values of aldols **107h** (up to 99%) were obtained in the reactions of cycloalkanones **105b**,**c** with formaldehyde (**106e**) containing no bulky substituents at the carbonyl carbon atom.[263] In this case, too, 2 equivalents of cycloalkanone suffice for effective reaction to proceed.

Unlike non-symmetrical ketones **105d**,**e**, the addition of acetone derivatives **108a**–**f** containing an α-heteroatom at one of the carbon atoms to aldehydes **106** in the presence of (*S*)-proline involves usually this C atom rather than the methyl group affording predominantly aldols **109**. Apparently, this reaction route is due to the ability of the heteroatom to stabilize the enamine intermediates in which this heteroatom is located at an sp^2-hybridized carbon atom. In compounds **109**, the *anti*-diastereomer usually predominates, the *dr* (*anti* : *syn*) ratio and the *ee* values of diastereomers depend appreciably on the structure of the starting aldehyde and ketone (Table 2).

The highest regio-, diastereo- [*dr* (*anti* : *syn*) > 20 : 1] and enantioselectivities (*ee* > 99%) are attained in the reactions of hydroxyacetone (**108a**) with α-branched aliphatic aldehydes **106c**,**d**, which result in *anti*-2,3-dihydroxyketones **109b**,**c**.[71, 258] This method is a good supplement to the synthesis of chiral *syn*-2,3-dihydroxy ketones by asymmetric dihydroxylation of α,β-enones elaborated by Sharpless and co-workers.[266]

Proline-catalyzed reactions of hydroxyacetone (**108a**) with aromatic (**106a**) and aliphatic aldehydes having no branching in the α-position with respect to the aldehyde group (for example, **106f**) and with (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**106g**) proceed less diastereoselectively [*dr* (*anti* : *syn*) = (1 : 1)–(2 : 1)]; however, the regioselectivity and the *ee* values of the predominant *anti*-isomers of



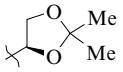
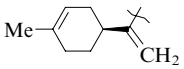
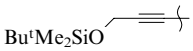
(2)

Table 1. Asymmetric aldol reaction (1) catalyzed by (*S*)-proline.

Ketone			Aldehyde		Aldol			
compound	R^1	R^2	compound	R^3	compound	yield (%)	*dr* (*anti* : *syn*)	*ee* (%)
105a	H	H	**106a**	XC_6H_4 ($X \neq NO_2$)	**107a**	62–94	–	60–77
105b	$(CH_2)_3$		**106b**	$4\text{-}NO_2C_6H_4$	**107b**	65	76 : 24	89 [a]
105c	$(CH_2)_2$		**106b**	$4\text{-}NO_2C_6H_4$	**107c**	73	76 : 24	69 [a]
105d	Me	H	**106a**,**b**	XC_6H_4	**107d**	20–65	–	50–77
105a	H	H	**106c**	Pr^i	**107e**	97	–	96
105a	H	H	**106d**	cyclo-C_6H_{11}	**107f**	60	–	85
105e [b]	$CMe_2(OH)$	H	**106d**	cyclo-C_6H_{11}	**107g**	91	–	86
105b,**c** [b]	$(CH_2)_n$ (n = 2, 3)		**106e**	H	**107h**	25–45	–	95–99

[a] The *ee* values for *anti*-diasteromers. [b] In the reaction 2 equiv. of the ketone were used; in other cases, 20–30 equiv. of the ketone were used.

Table 2. Aldol reaction (2) catalyzed by (*S*)-proline.

Ketone		Aldehyde		Aldol **109**				Aldol **110**			Ref.
compound	R^1	compound	R^3	compound	yield (%)	*dr* (*anti* : *syn*)	*ee* (*anti*), %	compound	yield (%)	*ee* (%)	
108a	OH	**106a**	Ph	**109a**	83	1 : 1	80	–	–	–	71, 258
108a	OH	**106c**	Pr^i	**109b**	60	> 20 : 1	> 99	–	–	–	71, 258
108a	OH	**106d**	cyclo-C_6H_{11}	**109c**	62	> 20 : 1	> 99	–	–	–	71, 258
108a	OH	**106f**	tert-C_5H_{11}	**109d**	38	1.7 : 1.0	> 97	–	–	–	71, 258
108a	OH	**106g**		**109e**	40	2 : 1	> 97	–	–	–	71, 258
108b	Bu^tMe_2SiO	**106a**	Ph	**109f**	85	4 : 1	40	**110a**	5	–	264
108b	Bu^tMe_2SiO	**106h**		**109g**	11	1.5 : 1.0	–	**110b**	43	95	264
108b	Bu^tMe_2SiO	**106i**		**109h**	25	2 : 1	–	**110c**	58	43	264
108c	OPh	**106a**	Ph	**109i**	65	6 : 1	64	**110d**	1	–	123
108c	OPh	**106j**		**109j**	35	24 : 1	93	**110i**	35	96	123
108d	SPh	**106a**	Ph	–	–	–	–	**110f**	27	68	123
108d	SPh	**106j**		**109k**	2	99 : 1	–	**110g**	38	95	123
108e	SMe	**106b**	4-$NO_2C_6H_4$	–	–	–	–	**110h**	10	–	265
108f	Cl	**106b**	4-$NO_2C_6H_4$	**109l**	8	–	–	–	–	–	73

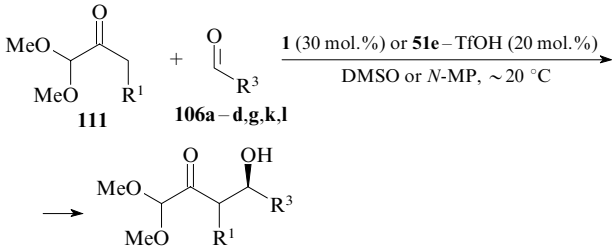
Note. In all reactions except for the last two ones DMSO was used as the solvent (Solv). The reaction **108e** + **106b** was carried out in $CHCl_3$ and the reaction **108f** + **106b** was performed in THF.

compounds **109a**,**d**,**e** remain relatively high (*ee* 80% – 97%).[71, 258] A similar regioselectivity with moderate diastereo- and enantioselectivity is typical of the reactions of (*tert*-butyl-dimethylsilyloxy)acetone (**108b**) with aromatic aldehydes **106a**. Meanwhile, analogous reactions of compounds **108b** with α,β-unsaturated aldehydes **106h**,**i** give mainly regioisomeric aldols, *i.e.*, compounds **110b**,**c**.[264]

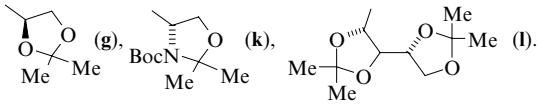
Diastereomeric aldol **109i** is the major proline-catalyzed reaction product of phenoxyacetone (**108c**) with aromatic aldehydes **106a**; however, in the reaction of ketone **108c** with sterically hindered 1-(phenylthio)cyclopropanecarbaldehyde (**106j**), regioisomers **109j** and **110i** are formed in 1 : 1 ratio. The reactions of phenylthioacetone (**108d**) with aldehydes **106a**,**j** proceed with low chemical yields, giving mainly regioisomeric aldols (**110f**,**g**).[123]

(*S*)-Proline-catalyzed reactions of α-methylthioacetone (**108e**)[265] and α-chlorocetone (**108f**)[73] with 4-nitrobenzaldehyde (**106b**) are even less selective, the yields of the corresponding products **110h** and **109l** being not higher than 10%.

Ketones containing two heteroatomic substituents in one α-position relative to the carbonyl group react with aldehydes involving the unsubstituted alkyl group, apparently, due to steric hindrance caused by these substituents. Thus the only products isolated in the reactions of pyruvaldehyde dimethyl acetal (**111**) with aliphatic, including functionally substituted, aldehydes **106c**,**d**,**g**,**k**,**l** catalyzed by amino acid **1** are polyfunctional aldols **112**. Although the yields of products **112** are not always high, attention is attracted by high diastereo- (*dr* = 19 : 1) and enantioselectivities of the process, especially in the case of aldehydes **106g**,**k**,**l**, which contain α- and β-heteroatoms relative to the aldehyde group.[267] The product yields were increased and pyruvaldehyde acetals (**111**) with $R^1 \neq H$ were involved in the reaction using the catalytic system **51e** – TfOH.[201]

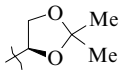
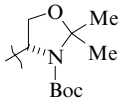
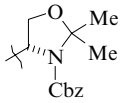


111, **112**: R^1 = H, Me, Et, Pr^n;
106, **112**: R^3 = XC_6H_4 [X = 3-NO_2, 2-NO_2, 4-CF_3, 4-CN, 4-Cl, 3-Br, 4-Ph] (**a**), 4-$NO_2C_6H_4$ (**b**), Pr^i (**c**), cyclo-C_6H_{11} (**d**),

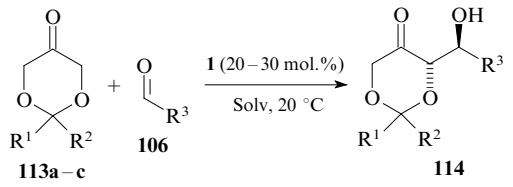

(**g**), (**k**), (**l**).

Ketones containing heteroatoms in both α-positions with respect to the carbonyl group can serve as nucleophiles in organocatalytic aldol reactions. Thus in the presence of (*S*)-proline, 1,3-dioxan-5-one derivatives **113a** – **c**, which represent protected forms of α,α′-dihydroxyacetone, react with aldehydes **106** to yield aldols **114**, precursors for the synthesis of carbohydrate derivatives[268 – 274] (Table 3).

Table 3. Aldol reaction (3) catalyzed by (*S*)-proline.

Ketone			Aldehyde		Aldol				Ref.
compound	R^1	R^2	compound	R^3	compound	yield (%)	*dr* (*anti* : *syn*)	*ee* (*anti*) (%)	
113a	Me	Me	**106b**	4-$NO_2C_6H_4$	**114a**	58	12 : 1	73	268, 269
113b	H	H	**106b**	4-$NO_2C_6H_4$	**114b**	89	2 : 1	92	270
113c	$(CH_2)_5$		**106b**	4-$NO_2C_6H_4$	**114c**	85	5 : 1	59	270
113a	Me	Me	**106c**	Pr^i	**114d**	97	> 49 : 1	94	271, 272
113a	Me	Me	**106d**	cyclo-C_6H_{11}	**114e**	86	> 49 : 1	90	271, 272
113a	Me	Me	**106g**		**114f**	76	> 49 : 1	98	271, 272
113a	Me	Me	**106m**	CH_2OBn	**114g**	40	> 49 : 1	97	271, 272
113a [a]	Me	Me	**106n**	n-$C_{14}H_{29}$	**114h**	60	99 : 1	95	273
113a	Me	Me	**106o**	$CH(OMe)_2$	**114i**	69	> 49 : 1	94	271, 274
113a	Me	Me	**106p**		**114j**	80	> 49 : 1	96	271, 272
113a	Me	Me	**106q**		**114k**	80	> 49 : 1	96	271, 272

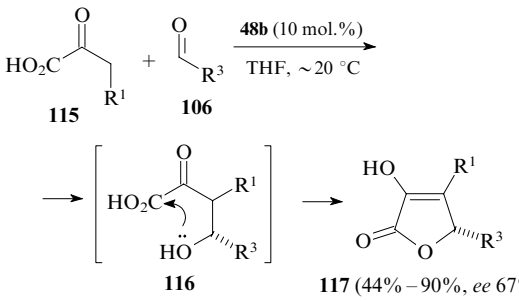
[a] The reaction was carried out in $CHCl_3$, and in other cases, DMF was used.



113a–c **106** **114** (3)

High diastereo- and enantioselectivities are observed in reactions involving both linear (**106m**,**n**)[271–273] and α-branched aliphatic aldehydes (**106c**,**d**,**g**,**o**–**q**),[271,272,274] including compounds **106g**,**o**–**q** containing O or N atoms in the α-position relative to the aldehyde group. In some cases, 1–2 equivalents of compound **113** suffice for effective reaction to occur. Aromatic aldehydes, including 4-nitrobenzaldehyde (**106b**), usually react with 1,3-dioxan-5-one derivatives **113a**–**c** less selectively.[268–270] The dependence of the *dr* and *ee* values of products **114a**–**c** on the structure of cyclic ketals **113a**–**c** follows a complex pattern.[270] Unprotected α,α′-dihydroxyacetone also undergoes organocatalytic reactions with aldehydes under certain conditions.[275,276]

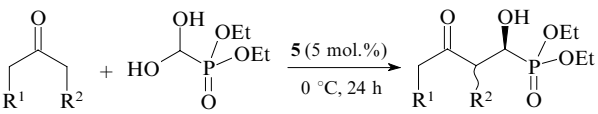
Ketones in which the carbonyl group is deactivated by strong electron-withdrawing substituents cannot act as nucleophiles in the proline-catalyzed aldol reactions. However, in the presence of 2-[(*S*)-pyrrolidin-2-yl]benzimidazole (**48b**), α-oxo acids **115** taken in excess (15 equiv.) react with different aldehydes **106** to afford γ-hydroxy α-oxo acids **116**, which are converted under reaction conditions into chiral isotetronic acids **117**.[191] The process is characterized by relatively high enantioselectivity. Products **117** refer to the class of butenolides many of which are biologically active (see references in Ref. 191).



115 **106** **116** **117** (44%–90%, *ee* 67%–90%)

R^1 = H, Me, Et, Ph; R^3 = Pr^i, Bu^t, CO_2Et, XC_6H_4 (X = H, 4-NO_2, 4-Br, 4-OMe), C_6F_5.

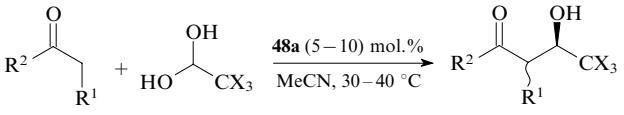
Some aldehydes containing electron-withdrawing substituents at the carbonyl carbon can be introduced in the reactions with ketones as hydrates. Thus proline amide (**5**)-catalyzed reaction of ketones **105** or **108** with diethyl formylphosphonate hydrate (**118**) proved to be a convenient method for the synthesis of chiral α-hydroxyphosphonates **119**.[72] Note that ketones **105b**,**h**,**i** are mainly converted to isomers *anti*-**119** [*dr* (*anti* : *syn*) = 70 : 30], and compounds **105c** give mainly *syn*-**119** [*dr* (*anti* : *syn*) = 5 : 95]. Unlike the reactions with aldehydes presented in Table 2, the reactions of hydroxyacetone (**108a**) and chloroacetone (**108f**) with phosphonate **118** give aldols **119**.



105a–**d**,**f**–**i**; **108a**,**f**,**g** **118** **119** (58%–95%, *ee* 43%– > 99%)

105: R^2 = H: R^1 = H (**a**), Me (**d**), Et (**f**), CH_2Ac (**g**); R^1–R^2 = $(CH_2)_3$ (**b**), $(CH_2)_2$ (**c**), CH_2OCH_2 (**h**), CH_2SCH_2 (**i**);
108: R^2 = H: R^1 = OH (**a**), Cl (**f**), OMe (**g**).

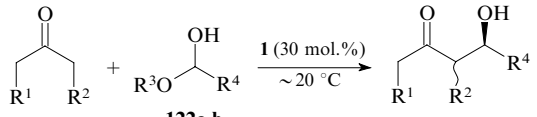
Linear and cyclic ketones **105** react with chloral hydrate **120a** in the presence of [(*S*)-pyrrolidin-2-yl]tetrazole (**48a**) to give the corresponding aldols **121** with high diastereo- and enantioselectivities.[277] Ketone **105b** is mainly converted into diastereomers *anti*-**121** [*dr* (*anti* : *syn*) = 24 : 1], while ketone **105c** predominantly forms *syn*-**121** [*dr* (*anti* : *syn*) = 1 : 9]. Trifluoroacetaldehyde monohydrate (**120b**) reacts similarly to chloral hydrate under these conditions. The reactions involving non-symmetrical methyl ketones occur regioselectively involving the methyl group of the ketones.



105 **120a,b** **121a,b** (55%–93%, *ee* 82%–99%)

105: R^1–R^2 = $(CH_2)_3$, $(CH_2)_4$; R^1 = H: R^2 = Pr^i, $CH_2CH{=}CMe_2$, Bu^n, CO_2Et, Ph, 2-naphthyl;
120, **121**: X = Cl (**a**), F (**b**).

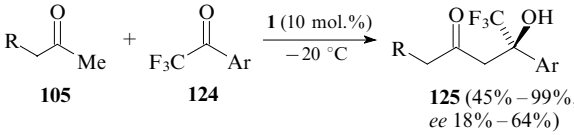
Hemiacetals of electron-deficient aldehydes can also react with ketones. The (*S*)-proline-catalyzed reactions of trifluoroacetaldehyde hemiacetal (**122a**) with acetone (**105a**) or cycloalkanones **105b**,**c** give higher yields of fluorinated aldols **123** than similar transformations with hydrate **122b**.[278] Note that reactions of aldehyde hemiacetal hydrates with cyclohexanone (**105b**) and cyclopentanone (**105c**) afford different regioisomers: *anti*-isomer in the case of ketone **105b** [*dr* (*anti* : *syn*) = 96 : 4] and *syn*-isomer in the case of ketone **105c** [*dr* (*anti* : *syn*) = 2 : 98].



105a–c **122a,b** **123** (68%–96%, *ee* 41%–93%)

105: R^1–R^2 = 2 H (**a**), $(CH_2)_3$ (**b**), $(CH_2)_2$ (**c**);
122: R^4 = CF_3, R^3 = Et (**a**); R^4 = C_2F_5, R^3 = H (**b**).

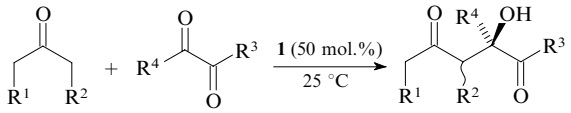
Apart from transformations in the nucleophilic ketone–electrophilic aldehyde systems, asymmetric cross-aldol reactions between two ketones are also known. This type of reactions occur only if the acceptor ketone molecule contains strong electron-withdrawing substituents, which increase the electrophilicity of the carbonyl carbon atom. In addition, for reactions to be selective, it is desirable that no hydrogen atoms be present at the α-position relative to the carbonyl group of the acceptor component. These requirements are satisfied, for example, for α,α,α-trifluoroacetophenone derivatives **124**. The reaction of compounds **124** with excess (50 equiv.) ketone **105** in the presence of (*S*)-proline affords fluorinated aldols **125** in rather high yields and with moderate enantioselectivities.[279] In the presence of electron-withdrawing groups in the aromatic ring of the acceptor ketone **124**, the reaction rate increases.



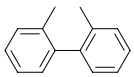
105 **124** **125** (45%–99%, *ee* 18%–64%)

R = H, Me, Pr^i, Bu^n; Ar = 4-XC_6H_4 (X = H, Cl, F), 1-naphthyl.

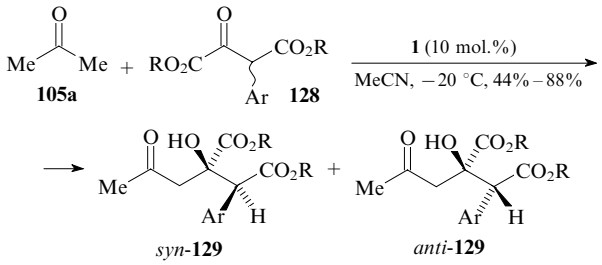
Various 1,2-dicarbonyl compounds can be used as acceptors in the cross-aldol reactions catalyzed by (*S*)-proline derivatives. Thus donor ketones **105a–d** react with 1,2-diketones **126a–c**,**e**,**f** (see Ref. 280) and α-keto esters **126d**,**g** (see Refs 281 and 282) to give 2-hydroxy-1,4-diketones or 2-hydroxy-4-ketoesters **127**. The reaction route depends on the reactant structures. 1-Aryl-1,2-dioxopropanes **126a–c** react with involvement of the keto group attached to the aromatic ring. Butan-2-one (**105d**) forms addition products involving the ketone methyl group. The highest diastereo- ($dr \geqslant 20:1$) and enantioselectivity (*ee* 80%–99%) were achieved in the reactions with cyclic ketones **105b**,**c** and **126f**,**g**. In all cases, considerable excess (64 equiv.) of nucleophile **105** is required for suppression of side processes.



105a–d **126a–g** **127** (53%–89%, *dr* > 95 : 5, *ee* 14%–99%)

105: R^2 = H: R^1 = H (**a**), Me (**d**); R^1–R^2 = $(CH_2)_3$ (**b**), $(CH_2)_2$ (**c**);
126: R^3 = Me: R^4 = 4-XC_6H_4 [X = H (**a**), NO_2 (**b**), CF_3 (**c**)]; R^3 = OEt, R^4 = Ph (**d**); R^3–R^4 = $(CH_2)_4$ (**e**),  (**f**),  (**g**).

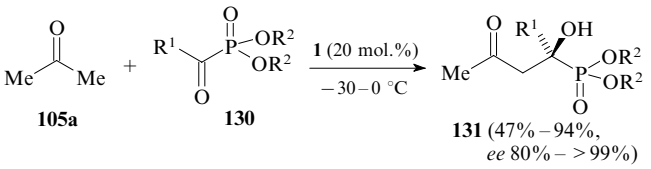
The aldol reaction in the donor ketone–acceptor ketone system was used for dynamic kinetic resolution of oxosuccinic acid esters. The reaction of racemic 2-oxo-3-arylsuccinates **128** with an excess of acetone (**105a**) in MeCN in the presence of 10 mol.% of proline (**1**) furnishes diastereomeric aldols *syn*-**129** and *anti*-**129** [*dr* (*syn* : *anti*) = (72 : 28)–(87 : 13)], which contain two interrelated stereogenic centres, with high enantiomeric purity.[283] The absolute configuration of isolated diastereomers was confirmed by X-ray diffraction studies.



105a **128** *syn*-**129** *anti*-**129**

R = Me, Et, Bn;
Ar = XC_6H_4 (X = 2-F, 4-F, 2-Cl, 4-Cl, 2-CF_3, 4-Br, 4-OMe).

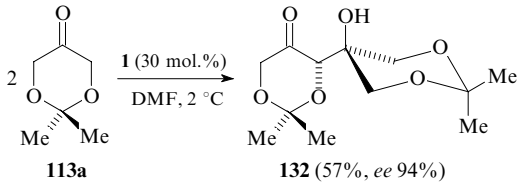
In addition to 1,2-dicarbonyl compounds, alkyl α-oxo phosphonates also undergo (*S*)-proline-catalyzed asymmetric aldol reaction with donor ketones. The reaction of α-oxo phosphonates **130** with an excess (54 equiv.) of donor **105a** in the presence of 20 mol.% of amino acid **1** at –30–0 °C affords chiral α-hydroxy phosphonates **131**, which possess valuable biological properties, in reasonable yields and with fairly high enantioselectivity.[284] The outcome of reactions is almost unaffected by the nature of substituent R^1 in the starting phosphonates **130**; however, the introduction of bulky substituents (R^2 = Pr^i) into the phosphonate group of compounds **130** leads to an increase in enantiomeric excess of products **131.**



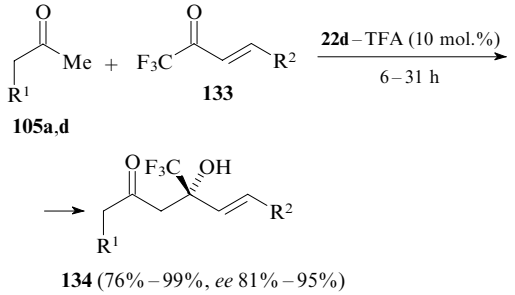
R^1 = 4-XC_6H_4 (X = H, Cl, F, Br, I, Me, OMe), Me, Bn, CH_2CH_2Ph, *trans*-CH=CHMe; R^2 = Me, Et, Pr^i.

A rare example of successful asymmetric aldol reaction in a ketone–ketone system with the acceptor ketone containing α-hydrogen atoms relative to the keto group is (*S*)-proline-catalyzed dimerization of 2,2-dimethyl-1,3-dioxan-5-one (**113a**). The reaction affords chiral aldol **132** with rather high optical purity; this compound is a protected form of (*S*)-dendroketose (Scheme 3).[271]

Scheme 3

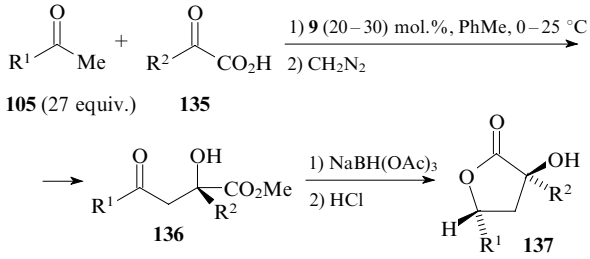


In some cases, an asymmetric aldol reaction between a donor ketone and an acceptor ketone requires the use of more active catalysts instead of proline. Thus fluorine-containing α,β-unsaturated ketones **133** react with an excess (70 equiv.) of donor ketones **105a**,**d** in the presence of the **22d**–trifluoroacetic acid (TFA) (each 10 mol.%) catalytic system yielding fluorine-containing chiral allylic hydroxy ketones **134**, that are difficult to obtain, with optical purity reaching 95%.[285] When butan-2-one (**105d**) is used as the donor ketone, the addition product to the methyl group is solely formed. This reaction can also be induced by (*S*)-proline; however, the yields (50%–93%) and the enantiomeric excess (52%–74%) of products **134** are much lower in this case.[138]



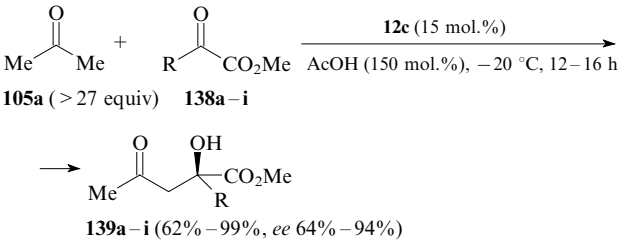
R^1 = H, Me; R^2 = 4-XC_6H_4 (X = H, Cl, Br, Me, OMe), 1-naphthyl, 2-furyl, C≡CPh, CH=CHPh, $(CH_2)_3Ph$.

Using *N*-(6-methyl-2-pyridyl)-(*S*)-prolinamide (**9**) as the catalyst, asymmetric aldol reactions of ketones **105** with different α-keto acids **135** were performed.[78,286] The resulting aldols were isolated as methyl esters **136** with high enantiomeric purity by treating the reaction mixture with diazomethane. Catalyst **9**, which is a base, can be isolated from the reaction mixture by acid extraction and used repeatedly. In the case of ketones **105** with $R^1 \neq Me$, the reaction proceeded regioselectively involving the methyl group. Products **136** were converted to chiral 2-hydroxy-γ-butyrolactones **137** [*dr* (*anti*:*syn*) = (95:5)–(99:1)], which are valuable 'building blocks' for the synthesis of natural products and biologically active compounds,[287] using the reaction sequence comprising diastereoselective reduction with $NaBH(OAc)_3$ and lactonization.



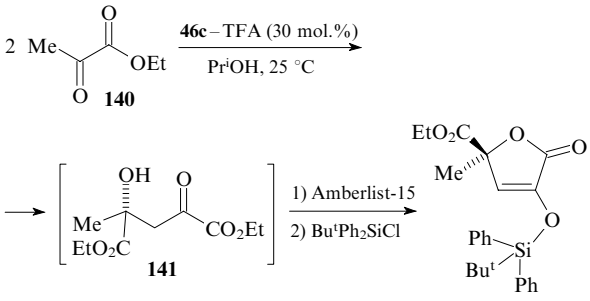
R^1 = n-C_nH_{2n+1} (n = 1–8), $(CH_2)_2Ph$, CH_2SMe, cyclo-C_3H_5; R^2 = Me, Et, Bu^i, Ph, Bn, 3-$NO_2C_6H_4CH_2$, 2-furyl, 2-thienyl.

Aliphatic, heteroaromatic and aromatic α-oxo esters **138** containing either electron-donating or electron-withdrawing substituents in the aromatic unit react with acetone (**105a**), which serves also as the solvent, in the presence of 1,2-diphenyl-1,2-bis(prolinamido)ethane (**12c**) and AcOH to give the corresponding aldols **139** in high yields and with high enantioselectivity.[100] The reaction proceeds efficiently even at −20 °C. By analogy with published data,[78,282] (*S*)-configuration was assigned to the major enantiomers of products **139**.



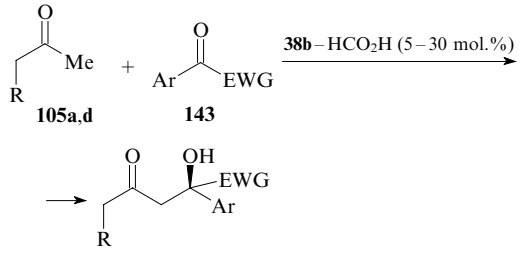
138, **139**: R = XC_6H_4 [X = H (**a**), 2-Me (**b**), 3-Me (**c**), 4-Me (**d**), 3-F (**e**)], 1-naphthyl (**f**), 2-naphthyl (**g**), 2-thienyl (**h**), cyclo-C_6H_{11} (**i**).

In the aldol dimerization of ethyl pyruvate **140** catalyzed by a salt of chiral pyrrolidine **46c** with trifluoroacetic acid, as in the dimerization of 2,2-dimethyl-1,3-dioxan-5-one (**113a**) (see Scheme 3), the MeCO group in one molecule of the starting compound functions as a donor, and the keto group in the other molecule is an acceptor. In this reaction, which is not induced by proline, aldol **141** formed initially is converted with relatively high enantioselectivity to isotetronic acid **142** derivative upon successive treatment of the reaction mixture with ion-exchange resin Amberlist-15 and *tert*-butyldiphenylsilyl chloride.[179]



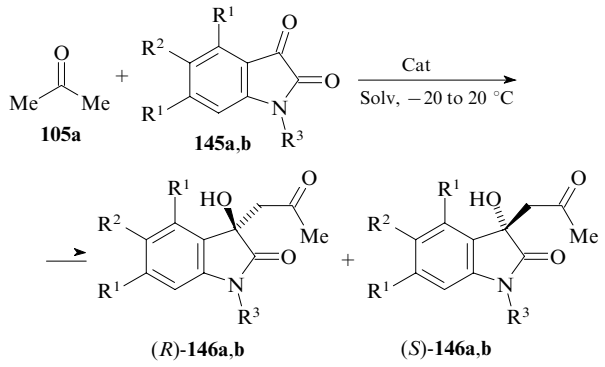
The recently synthesized phenylalanine derivative **38b** containing a 3,7-diazabicyclo[3.3.1]nonane fragment is a

good catalyst for the asymmetric aldol reaction of donor ketones **105a**,**d** and acceptor ketones **143** containing various electron-withdrawing groups (EWG). This catalyst, in combination with an equimolar amount of formic acid, can be used to perform this reaction with a broad range of electrophiles **143**, including α-oxo phosphonates, α-oxo esters, α-oxo aldehyde acetals, and to synthesize there from functionally substituted aldols **144** in high yields and with high enantioselectivities.[160]



R = H, Me; Ar = XC_6H_4 (X = H, 4-NO_2, 4-Me, 4-OMe, 4-Cl, 4-F, 3-NO_2, 3-Me, 3-Br, 3-F), 2-naphthyl; EWG = P(O)(OAlk)$_2$, CO_2Me, (4-$O_2NC_6H_4CH_2O)_2CH$, (4-$O_2NC_6H_4O)_2CH$.

Acetone (**105a**) reacts with isatin derivatives **145** in the presence of some organocatalysts, in particular (*S*)-proline,[288] **12d** – AcOH system,[101] dipeptide **21** comprising (*S*)-proline and β-phenylglycine,[119,288] thiophene-containing proline sulfamide **22l**,[129] and valinol **54a** and leucinol **54b** antipodes[208] to give chiral 3-(2-oxopropyl)-3-hydroxyindolin-2-one derivatives **146** in high yields. This method was used, in particular, to synthesize the (*R*)-enantiomer of 4,6-dibromoisatin **146b** identical to the alkaloid convolutamidine isolated from marine bryozoan *Amathia convoluta* in 1995, which proved to be a powerful inhibitor of differentiation of the leukemia HL-60 cells.[289] Note that compound (*R*)-**146b** was obtained with high enantioselectivity in reactions catalyzed by dipeptide **21**, sulfamide **22l** and

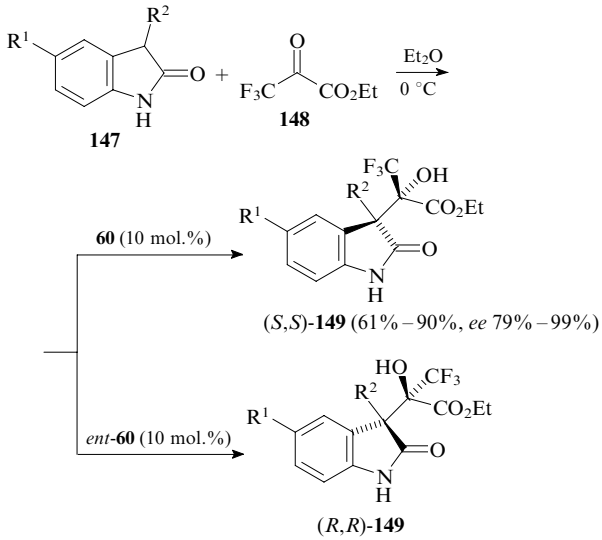


R^1 = H (**a**); R^2 = H, Br; R^3 = H, Me, Et, Bn;
R^1 = Br (**b**), R^2 = R^3 = H.

Cat	C_{cat} /mol.%	Solv	Yield of **146b** (%)	*ee* **146b** (%) (configuration)
1	10	Me_2CO	86	55 (*S*)
12d + 2 AcOH	10	Me_2CO	45	87 (*S*)
21	10	Me_2CO	50	97 (*R*)
22l	5	$Me_2CO – H_2O$	99	95 (*R*)
(*S*)-**54b**	20	CH_2Cl_2	98	95 (*S*)
(*R*)-**54b**	20	CH_2Cl_2	98	94 (*R*)

(*R*)-leucinol (*R*)-**54b**, whereas in the presence of catalysts **1**, **12d** and (*S*)-**54b**, aldol (*S*)-**146b**, the optical antipode of natural convolutamidine, was formed predominantly.

The asymmetric aldol reaction of oxindoles **147** with trifluoropyruvate **148** catalyzed by quinuclidine derivative **60** affords spirooxindoles **149**, which possess valuable biological properties.[216]



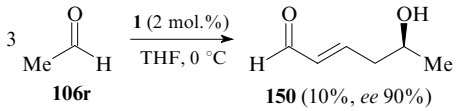
R^1 = H, Me; R^2 = Me, Et, Bn, 4-$XC_6H_4CH_2$ (X = Me, Cl, Br), $YNHCH_2CH_2$ (Y = Boc, Cbz, Bn).

The reaction has excellent enantioselectivity and high diastereoselectivity [*dr* = (88 : 12) – (97 : 3)]. Using together with catalyst **60** its optical isomer *ent*-**60**, Ogawa *et al.*[216] managed to prepare (*S*,*S*)- and (*R*,*R*)-enantiomers of compounds **149** and to establish their absolute configurations. Unlike isatin derivatives **145** (*cf.* their reactions with acetone) indole derivative **147** serves as the nucleophilic component. The proposed reaction mechanism includes deprotonation of compound **147** under the action of the quinuclidine fragment of the catalyst and spatial fixation of the resulting enolate and trifluoropyruvate **148** in the chelate cavity of the catalyst by hydrogen bonds.

b. Reactions with aldehydes as nucleophiles

The donor component in (*S*)-proline-catalyzed aldol reactions may be represented by aliphatic aldehydes containing α-hydrogen atoms relative to the aldehyde group. Thus Barbas III and co-workers[290] isolated (5*S*)-hydroxyhex-(2*E*)-enal (**150**) resulting upon aldol trimerization of acetaldehyde (**106r**) induced by amino acid **1**. Although the yield of compound **150** did not exceed 10%, the enantioselectivity of the process was relatively high (Scheme 4).

Scheme 4

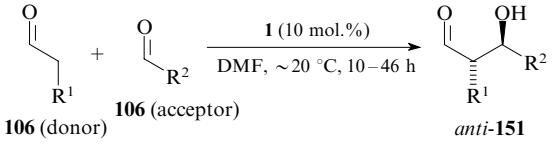


The studies of intermolecular aldol reactions in the aldehyde – aldehyde systems by several groups of researchers, first of all, MacMillan's group,[291] resulted in the development of preparative procedures for such syntheses. Under thoroughly controlled conditions in the absence of atmospheric oxygen, (*S*)-proline-catalyzed cross-aldol reaction (4) between two aldehydes results in aldols *anti*-**151** in

Table 4. Cross-aldol reaction (4) catalyzed by (*S*)-proline.

Donor aldehyde	R^1	Acceptor aldehyde	R^2	Aldol				Ref.
				compound	yield (%)	*dr* (*anti*:*syn*)	*ee* (*anti*) (%)	
106s	Me	**106s**	Et	**151a**	80	4:1	99	291
106s	Me	**106v**	Bu^i	**151b**	88	3:1	97	291
106s	Me	**106d**	cyclo-C_6H_{11}	**151c**	87	14:1	99	291
106s	Me	**106a**	Ph	**151d**	81	3:1	99	291
106t	Bu^n	**106c**	Pr^i	**151e**	80	24:1	98	291
106u	Bn	**106c**	Pr^i	**151f**	75	19:1	91	291
106v	Pr^i	**106e**	H	**151g**	52	—	99	263
106s	Me	**106y**	$CH(SEt)_2$	**151h**	70	10:1	97	293
106u	Bn	**106z**		**151i**	73	20:1	97	293
106w	OBn	**106w**	CH_2OBn	**151j**	73	4:1	98	292
106x	$OSiPr^i_3$	**106x**	$CH_2OSiPr^i_3$	**151k**	92	4:1	95	292

good yields and with high diastereo- and enantioselectivities (Table 4).



(4)

Aldehydes **106** having no branching in the α-position are used most often as nucleophiles, while α-branched aldehydes serve as electrophiles. However, an aldol reaction with formaldehyde (**106e**) as the electrophile has been reported.[263] The substituent R^1 in the nucleophilic component may consist of carbon and hydrogen atoms or contain an α-heteroatom, as, for example, in glycolaldehyde derivatives **106w**,**x**.[292] Apart from aromatic and aliphatic aldehydes, electrophiles can be represented by glycolaldehyde derivatives, including compounds **106w**,**x**[292] and glyoxal **106y**,**z** in which one aldehyde group is protected by a linear or cyclic dithioacetal group.[293]

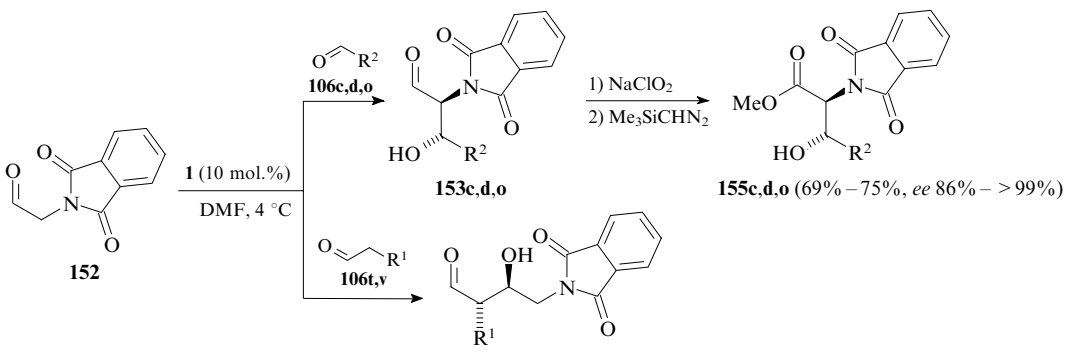
Proline-catalyzed cross-aldol reaction of compound **152** containing an α-nitrogen atom and representing a protected form of glycinaldehyde, with aliphatic aldehydes has been described.[294] Note that in the reaction with α-branched aldehydes **106c**,**d**,**o**, compound **152** functions as the donor, while with α-unbranched aldehydes **106t**,**v**, this is the acceptor. The reactions give the corresponding α-amino (**153c**,**d**,**o**) and γ-amino aldehyde derivatives **154t**,**v** (Scheme 5).

The discovery of asymmetric cross-aldol reaction between aldehydes has become an important milestone in the development of organocatalysis, because its products are valuable building blocks for asymmetric organic synthesis. α-Amino aldehydes **153** obtained from glycinaldehyde **152** can be used as the starting compounds for the synthesis of α-amino-β-hydroxy acid derivatives **155c**,**d**,**o**; the ratio of diastereomers **155** can vary in the range *dr* = (1:1)–(>99:1).[294]

Aldols **151h**,**i** (see Table 4) and their dithioacetal derivatives are used to prepare a broad range of natural products and their analogues.[295] Aldols **151** can be reduced to chiral 1,3-diols[296] or converted to chiral δ-lactones by Wittig–Horner–Emmons reaction.[297]

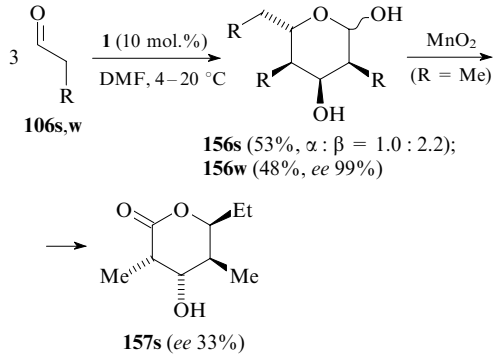
However, the main synthetic value of the cross-aldol reaction between aldehydes is in the fact that it opens up a direct way to stereocontrolled synthesis of polyhydroxy compounds including representatives of an important class of natural products, carbohydrates.[298,299] For example, polyketide **156s** as a mixture of α- and β-epimers is the product of (*S*)-proline-catalyzed aldol trimerization of propanal (**106s**). Oxidation of polyketide **156s** gives δ-lactone **157s**; however, its enantiomeric purity is relatively low.[300] Trimerization of α-(benzyloxy)acetaldehyde (**106w**)

Scheme 5



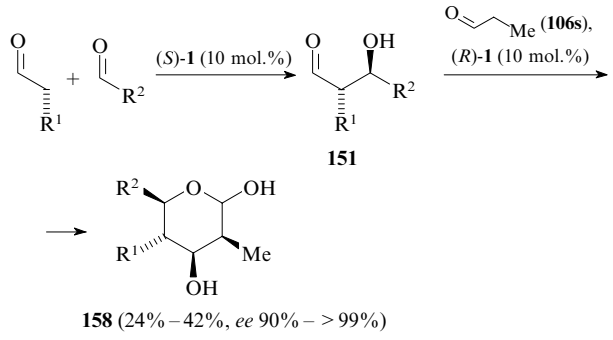
R^1 = Bu^n (**t**), Pr^i (**v**); R^2 = Pr^i (**c**), cyclo-C_6H_{11} (**d**), $CH(OMe)_2$ (**o**).

affords allose derivative **156w** with very good enantioselectivity;[301] the enantiomeric excess of compound **156w** obeys a non-linear dependence on the proline *ee*. This fact was interpreted [301] as indicating that the amino acid-catalyzed reaction of formation of carbohydrates from carbonyl compounds could have played an important role in the evolution of homochirality in living nature.



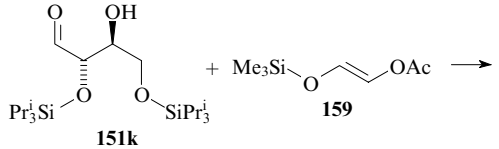
R = Me (**s**), OBn (**w**).

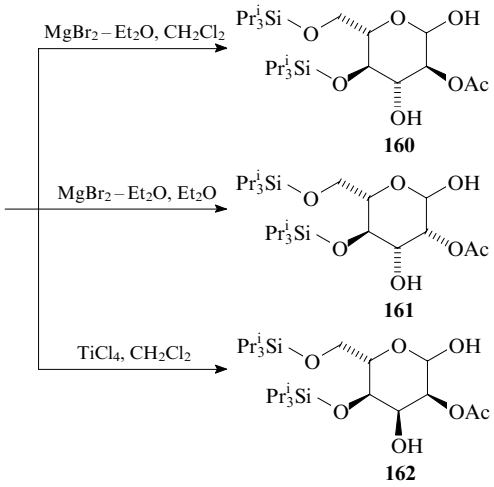
In the presence of proline, propanal (**106s**) reacts with products **151** of the aldol dimerization of aldehydes to give polyketide carbohydrate derivatives **158** containing different substituents R^1 and R^2. The enantiomeric purity of products **158** reaches 99% when two steps of the process are carried out with proline enantiomers: for example, the aldol reaction is catalyzed by (*S*)-proline and the addition of aldehyde **106s** to aldol **151** is catalyzed by (*R*)-proline.[302, 303] The aldol cyclization reaction was used also for kinetic resolution of racemic aldols *rac*-**151** and for the synthesis of chiral polyketides **158** characterized by high diastereoselectivity (*dr* > 19 : 1) and enantiomeric purity.[304]



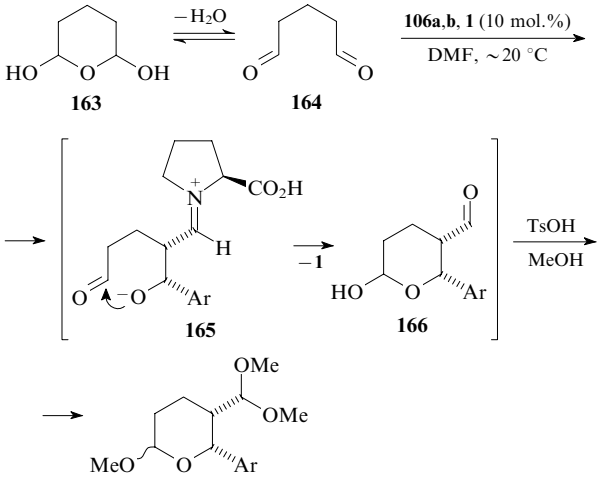
R^1 = Me, OBn; R^2 = Et, Pr^i, Bu^i, cyclo-C_6H_{11}, OBn.

The tandem sequence including the Mukaiyama addition of aldol **151k** to α-acetoxyenolate **159** and cyclization yielded a series of functionally substituted hexose derivatives **160** – **162** [*dr* = (10 : 1) – (> 19 : 1)].[305] Note that compounds **160** – **162** (yields 79% – 97%, *ee* 95%) have different configurations of the stereogenic centres depending on the Lewis acid used and the solvent.





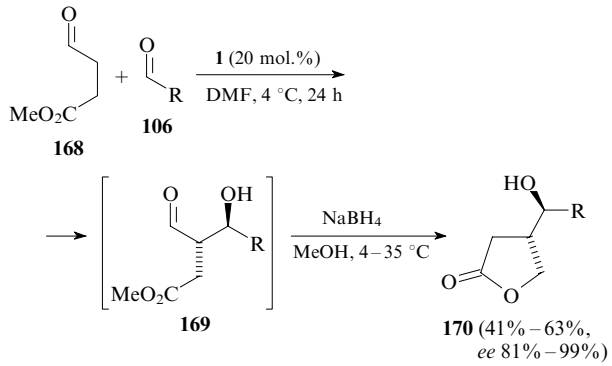
Broad possibilities for the synthesis of chiral pyran derivatives are opened up by involvement of functionally substituted aldehydes in the aldol reaction. Thus the products formed in the (*S*)-proline-catalyzed reactions of tetrahydro-2*H*-pyran-2,6-diol (**163**) in an aqueous solution, in which this compound occurs in equilibrium with glutaraldehyde (**164**), with aromatic aldehydes **106a**,**b** are tetrahydropyran derivatives containing three chiral centres.[306] This cascade reaction comprises the steps of formation of aldol **165,** its cyclization to 2-hydroxytetrahydropyran-4-carbaldehyde **166** and the subsequent acetalization resulting in product **167**.



Ar = XC_6H_4 (X = H, 2-NO_2, 3-NO_2, 4-NO_2, 4-CF_3, 4-CN, 4-OTf, 2-Cl, 4-Br).

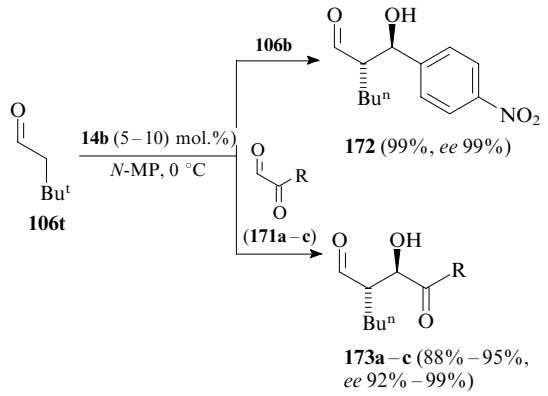
The aldol reaction has high diastereo- [*dr* (*cis* : *trans*) = (4 : 1) – (7 : 1)] and enantioselectivities (*ee* up to 99%); however, the ratio of α- and β-anomers of compounds **167** [α : β = (1.5 : 1.0) – (2 : 1)] determined by the cyclization step is close to the statistical value.

The cross-aldol reaction of methyl 4-oxobutyrate (**168**) with aldehydes **106** catalyzed by amino acid **1** and the subsequent reduction of the aldol **169** formed *in situ* with $NaBH_4$ result in 3-(α-hydroxyalkyl)-γ-butyrolactones **170**, which are valuable intermediates for the synthesis of natural and pharmacologically active furan derivatives.[307] Lactones **170** were isolated in moderate yields but had high *dr* [(4.5 : 1.0) – (24 : 1)] and *ee* values.



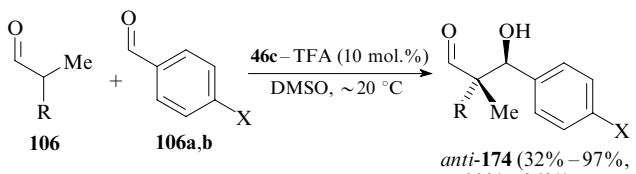
R = XC_6H_4 (X = H, 3-NO_2, 4-NO_2, 3-Br, 4-F, 4-OBz), 2-naphthyl, Pr^i, cyclo-C_6H_{11}.

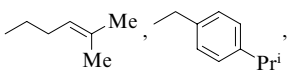
Asymmetric aldol reactions involving aldehydes as nucleophiles can be induced by not only proline but also other catalysts. Thus bis(prolinamide) **14b** containing a *p*-phenylenediamine fragment catalyzes efficiently the reaction of hexanal **106t** with 4-nitrobenzaldehyde (**106b**) and α-oxo aldehydes **171a–c**. The reactions occur in *N*-methylpyrrolidone furnishing the *anti*-isomers of aldols **172** and **173a–c** with relatively high diastereoselectivity [*dr* = 11.5 : 1.0 and (3.5 : 1.0)–(4 : 1), respectively] and high enantioselectivity.[108]



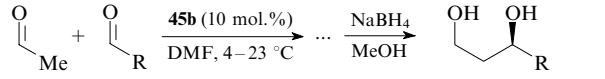
171, **173**: R = Ph (**a**), 2-naphthyl (**b**), CH=CHPh (**c**).

Under the action of the **46c**–TFA system, it was possible to conduct aldol reactions with α-branched aliphatic and aliphatic-aromatic donor aldehydes **106**, which cannot be carried out using proline catalysis. These reactions afford mixtures of diastereomeric aldols **174** [*dr* = (2 : 1)–(5 : 1)]; the major *anti*-diastereomers have rather high *ee* values.[308]



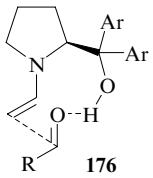
R = Me, Et, Pr^n, Bu^n, ; X = H, NO_2, CN, Cl, Br, OMe.

Recently, the first examples of enantioselective cross-aldol reactions with acetaldehyde (**106r**) as the nucleophile have been reported.[169, 170] Due to the high reactivity of acetaldehyde, these transformations cannot usually be arrested after the formation of aldol (see Scheme 4); however, the use of diarylprolinol **45b** as the catalyst markedly increased the process selectivity. The reduction of aldols formed *in situ* afforded diols **175** in good yields and with exceptionally high enantioselectivity.

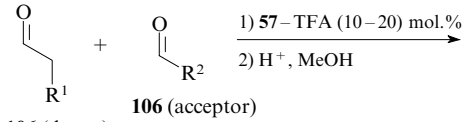


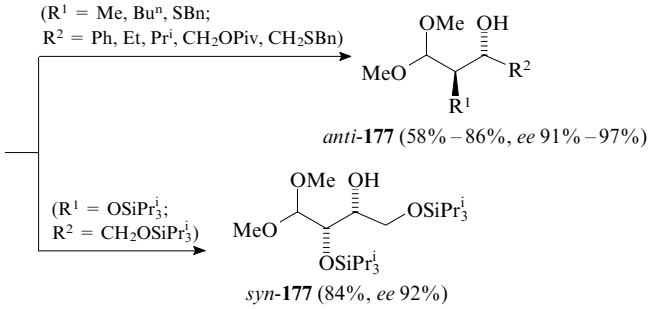
R = XC_6H_4 (X = H, 2-Cl, 2-NO_2, 3-NO_2, 4-NO_2, 4-CF_3, 4-Br, 4-OTf), 2,6-$Cl_2C_6H_3$, 3,5-$(CF_3)_2C_6H_3$, C_6F_5, 4-Py, 2-naphthyl, $CH(OMe)_2$.

This route was used, for example, to prepare compound **175** (R = Ph), which is the key intermediate for the production of fluoxetine employed as a selective inhibitor of serotonin receptors.[309] High activity and enantioselectivity of catalyst **45b** in this reaction was attributed[169] to hydrogen bonding between the catalyst OH group and the oxygen atom of the acceptor aldehyde in transition state **176**.



Compounds devoid of a pyrrolidine ring can also serve as effective organocatalysts of asymmetric aldol reactions between two aldehydes. MacMillan[210] proposed using the **57**–TFA system as the catalyst in this type of reaction. The aldols formed were isolated as dimethyl acetals *anti*-**177** [*dr* = (4 : 1)–(11 : 1)], the enantiomeric excess reaching 97%. It is noteworthy that β-silyloxy alcohols *syn*-**177** [*dr* = 4 : 1] with *syn*-arrangement of the hydroxy and silyloxy groups are formed as the major products in reactions involving α-silyloxy aldehydes unlike other transformations studied.

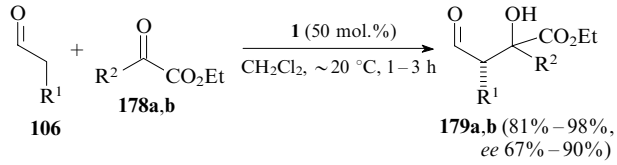




Aldol reactions between donor aldehydes and acceptor ketones have been studied to much lesser extent. These reactions occur only for highly electrophilic ketones. In 2002, Jørgensen and co-workers[310] described the first and

perhaps the only examples of this type of transformation, which include the reaction of aldehydes **106** having no α-branching with oxo malonate (**178a**) or ethyl trifluoropyruvate (**178b**) in the presence of (*S*)-proline. Under the conditions used, the reactions were over in 1–3 h giving rise to aldols **179** in high yields. Products **179** obtained from aldehydes **106** indicated in Scheme 6 were characterized by high *ee* values; however, the reactions involving acetaldehyde **106r** (R^1 = H) or phenylacetaldehyde (**106**, R^1 = Ph) resulted in racemic aldols. Upon the reaction of ethyl trifluoropyruvate (**178b**), a mixture of diastereomeric aldols in a 3 : 2 ratio was isolated.

Scheme 6



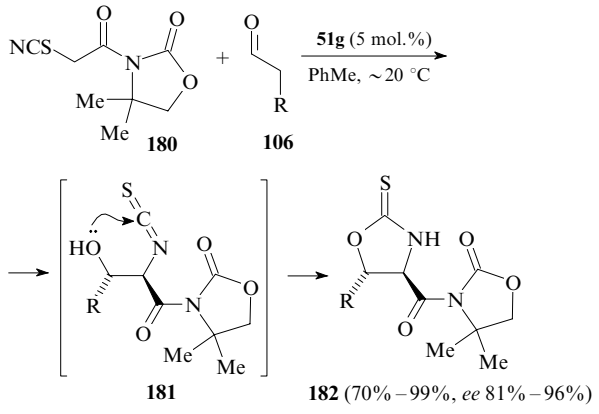
R^1 = Me, Et, Pr^i, n-C_6H_{13}, $CH_2CH{=}CH_2$; R^2 = CO_2Et (**a**), CF_3 (**b**).

c. Reactions with carboxylic acid derivatives as nucleophiles

In rare cases, carboxylic acid derivatives in which the carbonyl group is activated by strong electron-withdrawing substituents can act as nucleophiles in enantioselective aldol reactions. Thus recently it has been found that imides **180** containing α-isothiocyanate group undergo asymmetric aldol reaction with aromatic, heteroaromatic and aliphatic aldehydes **106** in the presence of thiourea derivative **51g**. The aldols **181** thus formed cyclize under the reaction conditions to chiral oxazolidine-2-thione derivatives **182** with good diastereoselectivity [*dr* = (88 : 12)–(98 : 2)].[203] This is one of the most effective stereo- and enantioselective methods for the synthesis of protected chiral α-amino-β-hydroxy acids present in many natural compounds.

VI. Effect of the catalyst structure on the course of aldol reactions

As can be seen from the examples given in Section V, the course of organocatalytic aldol reactions is considerably affected by the electronic and spatial structure of the catalyst. In this Section a more systematic account is given of various aspects of the effect of organocatalysts on the regio-, diastereo- and enantioselectivities of intramolecular

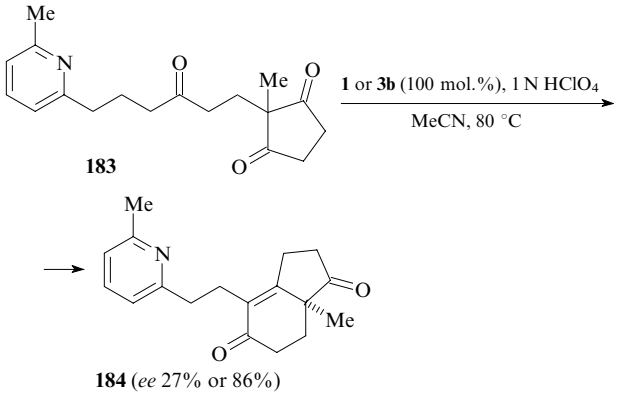


R = XC_6H_4 (X = H, 4-NO_2, 4-Br, 3-Br, 2-F, 4-F, 2-Cl, 2-Me, 4-Me, 4-OMe), C_6F_5, 1-naphthyl, 2-naphthyl, 2-thienyl, CH=CHPh, CH_2CH_2Ph, Bu^n.

and intermolecular aldol reactions, and the catalysts that are to be preferred for one or another type of asymmetric aldol reactions are elucidated.

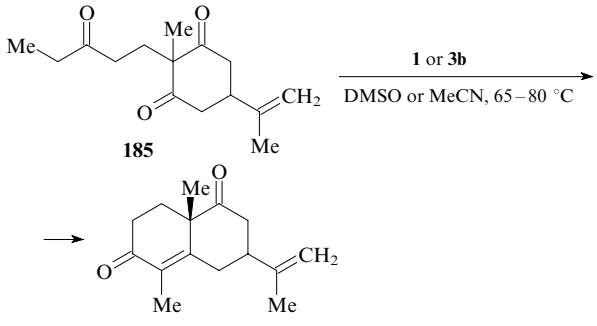
1. Intramolecular aldol reactions

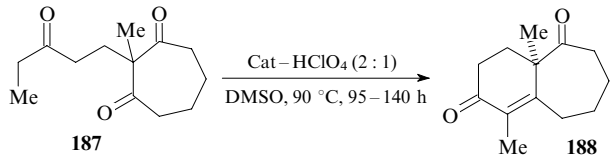
Back in 1976 it was found that the intramolecular Robinson annulation of ketones containing substituents other than methyl at the carbon atom of the exocyclic carbonyl group proceed at higher rates and with higher enantioselectivities under the action of α-amino acids with primary amino groups than under the action of proline. Thus aldol cyclizations of cyclopentane-1,3-dione derivatives **183** catalyzed by (*S*)-proline (**1**) and (*S*)-phenylalanine (**3b**) result in product **184** in 67% and 82% yield and with enantiomeric excess of 27% and 86%, respectively.[58] Note that the reaction is much faster when catalyzed by amino acid **3b** than by (*S*)-proline (40 and 240 h, respectively).



(*S*)-Phenylalanine also induces highly selective (*ee* 95%) aldol cyclization of cyclohexane-1,3-dione derivative **185** to bicyclic diketone **186**.[59] In a similar reaction of dione **185** with (*S*)-proline, the *ee* value of product **186** was only 32%.

Recently, it has been found that aldol cyclization of oxoalkylcycloheptanedione **187** catalyzed by some α-amino acids containing primary amino groups in the presence of $HClO_4$ yields bicyclic enedione **188** with abnormal *R*-configuration.[61] The unusual configuration of product **188** compared to reactions of the corresponding oxoalkylcyclohexane- and cyclopentanediones was attributed [61] to specific conformational features of the cycloheptane ring, which has the *Z-trans-anti* configuration in the transition state rather than the *Z-cis-anti* configuration typical of cyclohexane and cyclopentane derivatives. In this case, too, (*S*)-proline was found be inefficient as a catalyst.

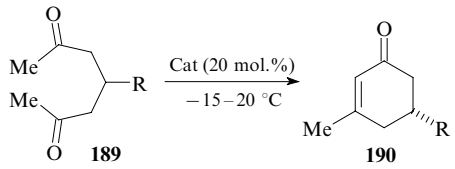




187 **188**

Cat	Yield of **188** (%)	*ee* (%)
3b	68	48
3c	44	41
3d	99	53
1	7	6

The difference between the catalytic properties of primary and secondary amines was clearly manifested in the aldol cyclodehydration of 4-substituted heptane-2,6-diones **189** to chiral cyclohexenones **190**, which are components [311] and intermediates for the preparation of natural products [312] and 'building blocks' for the synthesis of biologically active compounds.[313] Whereas in the presence of amino acid **1**, the yields and *ee* values of **190** are moderate,[314, 315] in the case of **53b** – AcOH system as the catalyst, they increase to 98% and 94%, respectively.[206]



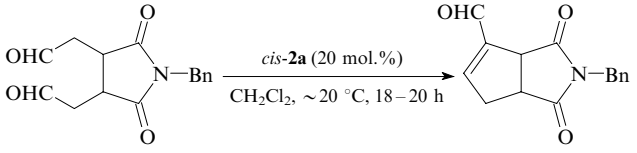
189 **190**

R = Alk, Ar, Het.

Cat	Yield of **190** (%)	*ee* (%)
1	< 30	< 47
53b – AcOH (1 : 3)	80 – 98	86 – 94

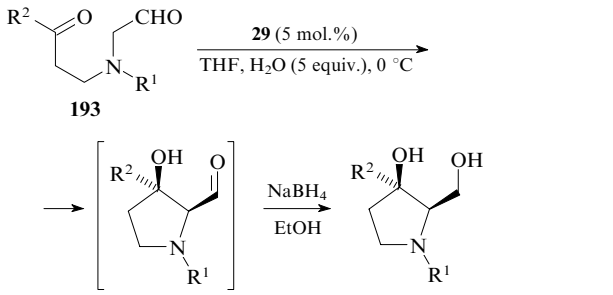
The more pronounced catalytic impact of compound **53b** containing a primary amino group compared to proline was attributed [206] to the decrease in steric hindrance upon the formation of enamine intermediates and to higher efficiency of hydrogen bonding involving the second hydrogen atom of the amino group in the reaction transition state.

The use of *cis*-4-hydroxy-(*S*)-proline (*cis*-**2a**) as the organocatalyst made it possible to convert *meso*-1,6-dialdehyde **191** to enantiomerically enriched bicyclic product **192**, which is formed only as the racemate (yield 73%, *ee* 0%) under catalysis by (*S*)-proline. However, the yield of compound **192** was relatively low under the proposed conditions.[316]



191 **192** (19%, *ee* 66%)

The replacement of proline **1** by *cis*-3-hydroxy-(*S*)-proline (**29**) considerably increased the diastereo- and enantioselectivities of the intramolecular organocatalytic cyclization of oxo aldehydes **193**, which is the key stage of the synthesis of chiral *syn*-diols **194** of the pyrrolidine series. Whereas in the presence of proline, the diastereomer ratio *syn*-**194** : *anti*-**194** (R^1 = Ts, R^2 = Me) was 78 : 22 and the enantiomeric excess for the major *syn*-diastereomer did not exceed 49%, in a similar reaction involving catalyst **29** under the same conditions (THF, 0 °C); the *syn*-**194** : *anti*-**194** ratio was 95 : 5 and *ee* 62% (see Ref. 146). Higher *ee* values (73% – 88%) were attained and the scope of the reactions was extended by the addition of 5 equivalents of water.



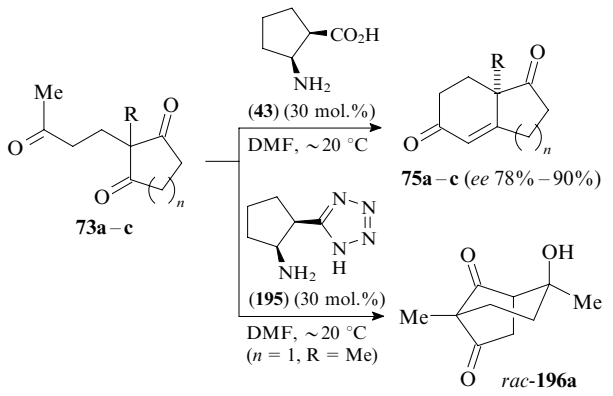
193

194 [49% – 90%, *dr* = (89 : 11) – (99 : 1), *ee* 49% – 88%]

R^1 = Ts, Cbz, SO_2Bn; R^2 = Me, Et, *iso*-C_5H_{11}.

The effect of water on the asymmetric aldol reaction will be considered in more detail in our next review.

The catalyst nature affects not only the yield and the enantiomeric excess of products but also, in some cases, the reaction regioselectivity. Indeed, whereas the cyclization of triketones **73a** – **c** catalyzed by β-amino acid **43**, as in the case of proline catalysis, affords the Wieland – Mischer ketone analogues (**75a** – **c**), in the presence of amine **195**, an analogue of compound **43** containing a tetrazole ring instead of the carboxyl group, the reaction follows a different pathway, namely, compound **73a** is converted to the isomeric racemic diketone **196a** with a different pattern of fusion of alicyclic fragments.[166]



73a – **c** **75a** – **c** (*ee* 78% – 90%) *rac*-**196a**

n = 1: R = Me (**a**), Et (**b**); *n* = 2, R = Me (**c**).

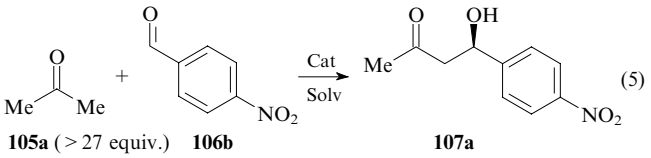
2. Intermolecular aldol reactions

Since 2000 up to now, about 300 papers have been published describing organocatalyzed intermolecular aldol reactions of aldehydes and ketones. The available data allow one to compare the catalytic activities of various types of organocatalysts and their effects on the enantio-, diastereo-, and regioselectivities of aldol reactions.

a. Effect of the catalyst on the rate and enantioselectivity of aldol reactions

The dependence of the activity and enantioselectivity of organocatalysts on their structure can be traced using the

reaction of acetone (**105a**) with 4-nitrobenzaldehyde (**106b**) carried out in excess acetone or in dipolar aprotic solvents (DMSO, DMF) and resulting in aldol **107a** (Table 5).



105a (> 27 equiv.) **106b** **107a**

It can be seen from Table 5 that α-amino acids with primary amino groups, in particular, phenylalanine (**3b**), valine (**3c**) or histidine (**3f**), which are fairly effective catalysts of intramolecular aldol reactions, can hardly catalyze the reactions between compound **105a** and **106b** (see Table 5, entry *1*). Meanwhile, the reaction of these compounds is induced by (*S*)-proline or α-amino acid **55a**, which contain a secondary amino group incorporated in the heterocycle (entries *2*, *3*).[25,71] The activity and enantioselectivity of chiral 1,3-thiazolidine derivatives **56a**,**b** isoelectronic to proline **1** in the reaction of **105a** with **106b** is comparable to that of **1**; however, their preparation in the optically pure state is faced with certain difficulties (see Table 5, entries *4*, *5*).

The introduction of substituents of different chemical nature into the pyrrolidine ring does not exert unambiguous effect but, in some cases, this noticeably increases the activity and/or selectivity of the catalyst. A relatively high yield of aldol **107a** was noted in the presence of (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**30**); however, the enantioselectivity of the reaction was lower than in reactions catalyzed by (*S*)-proline (see Table 5, entry *6*).[147] In this case, for maintaining the optimal pH of the medium, the reaction should better be carried out in the presence of an organic base, NEt_3 (30 mol.%). (*S*,*S*,*S*)-Perhydroindolic acid (**31**) structurally related to acid **30** catalyzes the aldol

Table 5. Asymmetric aldol reaction (5) in the presence of different organocatalysts.

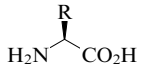
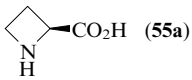
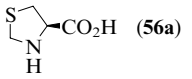
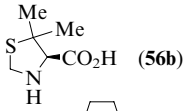
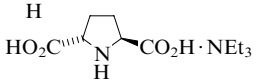
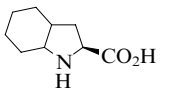
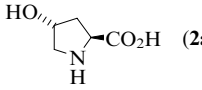
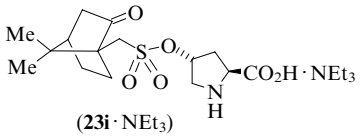
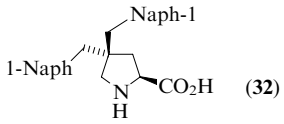
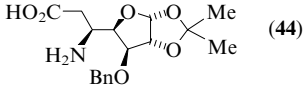
Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time/h	Aldol **107a**		Ref.
						yield (%)	*ee* (%)	
1	 (**3b**,**c**,**f**)	30	DMSO	25	24	< 10	see [a]	25, 71
2	(*S*)-Proline (**1**)	30	DMSO	25	24	68	76	25, 71, 317
3	 (**55a**)	30	DMSO	25	24	55	40	25, 71
4	 (**56a**)	30	DMSO	25	24	67	73	25, 71
5	 (**56b**)	30	DMSO	25	24	66	86	71
6	 (**30** · NEt_3)	30	**105a**	25	30	91	65	147
7	 (**31**)	10	**105a**	25	68	45	81	148
8	 (**2a**)	30	DMSO	25	24	85	78	25, 71
9	 (**23i** · NEt_3)	10	DMF	25	18	71	90	135
10	 (**32**)	10	DMF	−10	48	87	95	149
11	 (**44**)	20	**105a**	23	15	60	86	167

Table 5 (continued).

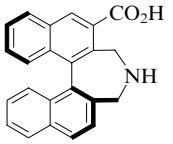
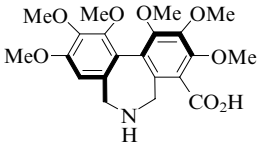
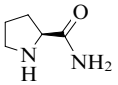
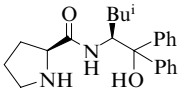
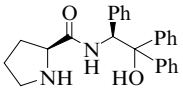
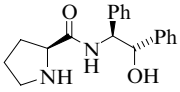
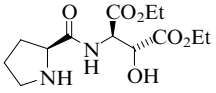
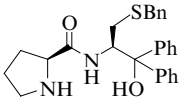
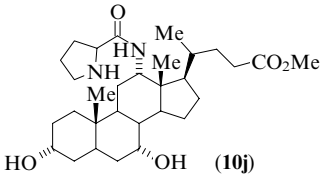
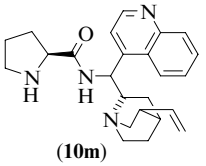
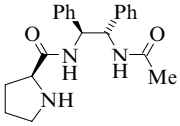
Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time /h	Aldol **107a**		Ref.
						yield (%)	*ee* (%)	
12	 (**49a**)	5	DMF	25	24	82	95	195, 196
13	 (**50**)	0.5	**105a**	25	48	90	96	198
14	 (**5**)	20	DMSO	25	24	< 10	ü.[a]	71
15	 (**10c**)	10	**105a**	25	3	68	92	81
16	**10c**	10	**105a**	0	14	72	98	81
17	 (**10d**)	5	**105a**	25	6	71	84	81
18	**10d**	5	**105a**	−40	22	77	99	81
19	 (**10e**)	20	**105a**	25	12	89	69	82
20	**10e**	20	**105a**	−25	24	66	93	82
21	 (**10f**)	2	**105a**	−25	24	62	99	83
22	 (**10g**)	10	**105a**	−15	24	40	64	84
23	 (**10j**)	10	**105a**	0	48	99	64	89
24	 + AcOH (**10m**)	10 + 20	**105a**	−30	23	85	90	92
25	 (**12b**)	10	**105a**	−35	5	35	98	99

Table 5 (continued).

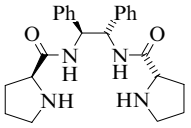
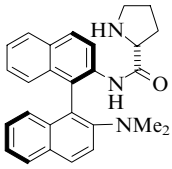
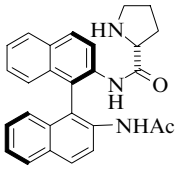
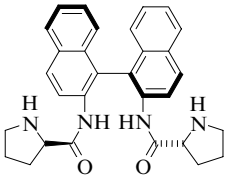
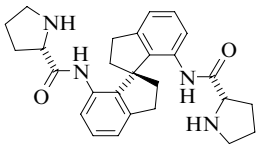
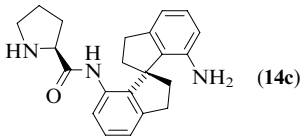
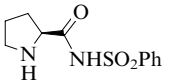
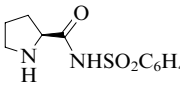
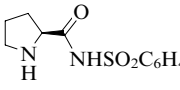
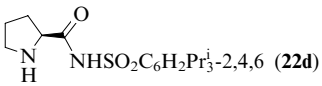
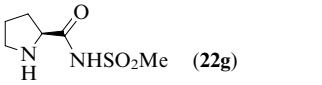
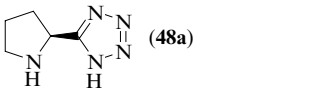
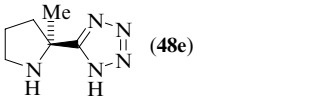
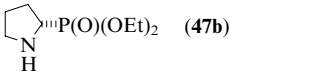
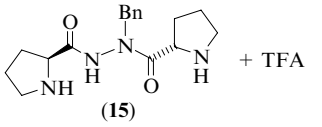
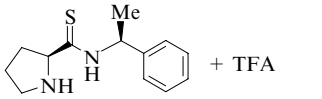
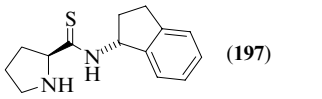
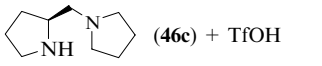
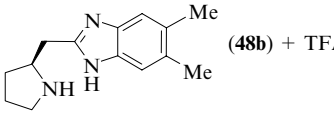
Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time /h	Aldol **107a**		Ref.
						yield (%)	*ee* (%)	
26	 (**12c**)	10	**105a**	−35	5	75	98	99
27	 (**13a**)	10	**105a**	25	12	90	85	105
28	**13a**	10	**105a**	−27	88	92	90	105
29	 (**13b**)	10	**105a**	25	12	65	85	105
30	 (**13c**)	10	**105a**	25	12	98	44	105
31	**13c**	10	**105a**	−27	88	74	67	107
32	 (**14a**)	1	**105a**	−25	4.5	75	52	107
33	 (**14c**)	1	**105a**	−25	4.5	80	51	107
34	Pro-Ser (**17c**)	30	DMSO	25	18	87	77	114
35	Pro-Ala (**17f**)	30	DMSO	25	18	90	70	114
36	Pro-Val (**17g**)	30	DMSO	25	18	89	70	114
37	H-L-Pro-D-Ala-D-Asp-NH_2 [(*R*)-**18**]	10	**105a**	25	4	73	70	118
38	(*R*)-**18**	10	**105a**	−20	24	53	81	118
39	H-L-Pro-L-Pro-L-Asp-NH_2 [(*S*)-**19**]	1	**105a**	25	4	99	80	118, 318
40	(*S*)-**19**	1	**105a**	−20	24	98	90	118, 318
41	H-Leu-His-OH (**39d**)	30	DMSO	25	240	87	71	162
42	 (**22a**)	20	**105a**	20	24	100	92	121
43	 (**22b**)	30	**105a**	20	24	98	93	124
44	 (**22c**)	30	**105a**	20	24	98	90	124

Table 5 (continued).

Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time /h	Aldol **107a**		Ref.
						yield (%)	*ee* (%)	
45		30	**105a**	20	24	98	71	124
46		10	DMF	20	24	63	89	120
47	 (**48a**)	20	DMSO	25	4	93	76	188
48	 (**48e**)	20	DMSO	25	68	60	88	194
49	 (**47b**)	5	DMSO	25	24	69	82	185
50	 (**15**) + TFA	20	**105a**	20	3	54	92	109
51	 (**16**) + TFA	20	**105a**	4	68	81	94	110, 111
52	 (**197**)	5	**105a**	0	48	80	80	319
53	 (**46c**) + TfOH	3	**105a**	30	2	60 [b]	88	320
54	 (**48b**) + TFA	2	**105a**	−5	24	87	82	190

[a] No data are given. [b] Together with aldol **107a**, 4-nitrobenzylideneacetone is formed.

reaction with rather high enantioselectivity but is inferior to compound **30** as regards the catalytic activity (see Table 5, entry *7*).[148]

4-Hydroxy-(*S*)-proline (**2a**)[25, 71] and some its hydroxyl-modified derivatives, for example, sulfate **23i** containing camphor as a chiral auxiliary,[135] exhibit higher activities and enantioselectivities in the asymmetric aldol reaction of compound **105a** with **106b** than (*S*)-proline (see Table 5, entries *8*, *9*). Under certain conditions, in particular, in an aqueous medium, some esters of 4-hydroxy-*trans*-(*S*)-proline (**2a**) also demonstrate exceptionally high diastereo- and enantioselectivities in aldol reactions.[136, 139]

In the series of proline derivatives substituted in the heterocyclic ring, compound **32** containing two bulky 1-naphthylmethyl substituents in position 4 of the pyrrolidine ring possesses, perhaps, the best catalytic properties in this model reaction. In the presence of 10 mol.% of this catalyst, the reaction occurs at −10 °C resulting in aldol **107a** with enantiomeric purity *ee* 95% (see Table 5, entry *10*).[149]

Among the effective amino acid organocatalysts other than (*S*)-proline derivatives, noteworthy are β-amino acid of the carbohydrate series **44** (see Table 5, entry *11*)[167] and axially chiral γ-amino acids **49a** and **50** containing binaphthyl[195, 196] and biphenyl[198] structural fragments, respectively (see Table 5, entries *12*, *13*). The effective reaction in the presence of amino acid **50** occurred with only 0.5 mol.% of the catalyst, although the required excess of the donor was more than 130 equivalents.

Amides of α-amino acids, first of all, (*S*)-prolinamides have found extensive use as organocatalysts of the asymmetric aldol reaction. With a few exceptions, amides possess

higher activities than the corresponding α-amino acids, which is probably due to lack of the possibility of deactivation of the Lewis centre at the amino group upon hydrogen bonding with the carboxyl proton. Under the action of these organocatalysts, aldol reactions can often be carried out at low temperatures in the presence of a lesser amount of the catalyst than that required in the case of amino acid catalysis.

Although unsubstituted prolinamide **5** barely catalyzes the reaction of ketone **105a** with aldehyde **106b** (see Table 5, entry *14*)[71] and simple prolinanilides do not exhibit high enantioselectivies in this reaction, many compounds of this series containing chiral fragments in the amide moiety can induce the synthesis of enantiomeric aldols with comparable or higher *ee* values than (*S*)-proline. High enantioselectivity of these catalysts is attributable to the fact that chiral fragments dictate the spatial architecture of the reaction transition state, which is fixed through hydrogen bonding between the amide proton and carbonyl oxygen of the acceptor.

Most often, high enantioselectivity is achieved in aldol reactions catalyzed by (*S*)-prolinamides **10c**–**f** developed by Indian and Chinese researchers.[81–83] These catalysts contain fragments of chiral β-amino alcohols with bulky substituents (see Table 5, entries *15*–*21*). The *ee* are maximum (up to 99%) in reactions carried out at reduced temperatures (−40–0 °C); in some cases, these values can be attained in the presence of only 2 mol.%–5 mol.% of the catalyst. The enantioselectivity of reactions catalyzed by prolinamide **10g** obtained on the basis of cysteine is somewhat lower (see Table 5, entry *22*).[84] The influence of the structure of the amide group on the stereochemical outcome of the process is indicated by the fact that prolinamide **10j** (see Ref. 89) gives aldol **107b** with moderate enantioselectivity despite the presence of the bulky chiral steroidal fragment in the molecule (entry *23*).

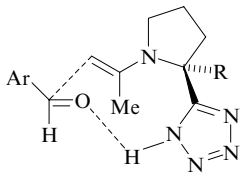
The activities prolinamides **10m**, **12**–**14** obtained from chiral diamines and selectivities of reactions depend also on the structure of substituents attached to the amide nitrogen. Thus high enantioselectivity in this model reaction was demonstrated amide with **10m** in which one amino group is incorporated in the alkaloid fragment (see Table 5, entry *24*).[92] For other catalysts of this type, no direct correlation was observed between these characteristics and the number of pyrrolidine groups in the molecule. Thus in the series of (1*S*,2*S*)-diphenyl-1,2-diaminoethane derivatives, amide **12c** with two proline fragments ensures higher conversion of the starting compounds than the catalyst **12b** containing one amino acid fragment with retention of the process enantioselectivity (see Table 5, entries *25*, *26*).[99] Monoprolinamides **13a**,**b** based on axially chiral 2,2′-diaminobinaphthyl (see Table 5, entries *27*–*29*) surpassed in the selectivity the bisproline analogue **13c** (entries *30*, *31*).[105] Aldol reactions induced by spirobis- (**14a**) and mono- (**14c**) prolinamides were characterized by similar yields and *ee* of product **107a** (see Table 5, entries *32*, *33*).[107]

Dipeptides and tripeptides, especially those containing a proline fragment, proved to be rather promising organocatalysts of asymmetric aldol reaction. The advantages of this type of catalyst include their ready accessibility and the possibility of varying the structures of the constituent amino acid fragments over a broad range. In 2003, Martin and List[114] found that proline-containing dipeptides, in particular Pro-Ser (**17c**), Pro-Ala (**17f**) and Pro-Val (**17g**), catalyze the reaction under consideration in DMSO resulting in aldol **107a** in high yield and with moderate enantioselectivity (up to *ee* 77%) (see Table 5, entries *34*–*36*).

Using combinatorial 'co-immobilization' method, Wennemers and co-workers[321] identified two most active and selective catalysts (**18** and **19**) of the asymmetric aldol reaction among 3375 tripeptides.[118,318] Tripeptide **19** having two proline residues was much more active than tripeptide **18** containing only one proline residue (see Table 5, entries *37*–*40*). It is of interest that the reactions catalyzed by compounds **18** and **19** afford optical antipodes of aldol **107a**. Probably, this is a result of different conformations of the peptide units in these catalysts. In some cases, the aldol reaction can proceed, although at a lower rate, under the action of di- and tripeptides devoid of proline residues, in particular, in the presence of catalyst **39d** composed of leucine and histidine (see Table 5, entry *41*).[162] The slight catalytic activity of proline-free di- and tripeptides can be considerably increased by conducting the aldol reaction in the presence of water.

Unexpectedly, fair catalytic properties in the asymmetric aldol reaction were found for mixed imides of proline and aryl(alkyl)sulfonic acids **22a**–**d** having no complex spatial architecture. In the presence of these catalysts (30 mol.%), acetone **105a** and aldehyde **106b** form aldol **107a** in good yield and with good enantioselectivity (see Table 5, entries *42*–*45*).[120–124] The high *ee* values of the products were attributed[120] to effective shielding of one of the enantiotopic sides of aldehyde **106b** by the aromatic ring bound to the sulfimide group. This assumption, however, does not account for the relatively high activity and selectivity of sulfimide **22g** containing an *S*-methyl group even at lower catalyst load (see Table 5, entry *46*).[120]

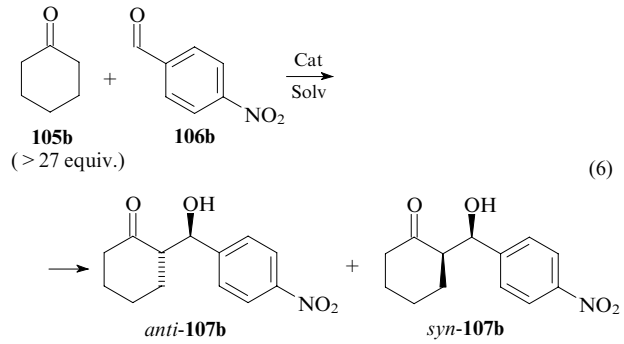
Some other chiral compounds containing a pyrrolidine ring are also rather efficient organocatalysts of this reaction. Indeed, the model reaction with (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**48a**) (see Table 5, entry *47*)[188] and (*S*)-5-(2-methylpyrrolidin-2-yl)-1*H*-tetrazole (**48e**) (entry *48*)[194] exhibited relatively high enantioselectivity comparable with, or higher than, that of (*S*)-proline. The yield of aldol **107a** in the presence of compound **48a** was higher than that with amino acid **1** as the catalyst (entry *2*). The high activity and selectivity of catalysts **48a**,**e** is apparently caused by the formation of a stronger intermolecular hydrogen bond between the active proton of the tetrazole ring (in DMSO, the pK_a values of tetrazole and AcOH are 8.2 and 12.3, respectively)[322] and the carbonyl oxygen atom in compound **106b** and by better solvation of the transition state shown below.[41,323]



R = H, Me.

However, the presence of active proton in the substituent bound to the pyrrolidine ring is not obligatory for high chiral induction. For example, diethyl 2-(*S*)-(*O*,*O*-diethylphosphoryl)pyrrolidine (**47b**) was found to be an active and selective catalyst of model reaction (5).[185] In the presence of 5 mol.% of this catalyst, aldol **107a** was obtained in 69% yield with *ee* 82% (see Table 5, entry *49*).

A number of chiral pyrrolidine derivatives having basic substituents efficiently catalyze the asymmetric aldol reaction between aldehydes and ketones in the presence of strong (usually fluorinated) organic acids. These include, in particular, 1,2-bis[(*S*)-prolyl]hydrazine (**15**) (see Table 5, entry *50*),[109] (*S*)-prolylthioamides **16** (entry *51*)[110,111] and **197** (entry *52*),[319] (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**46c**) (entry *53*)[320] and 2-[(*S*)-pyrrolidin-2-yl]benzimidazole (**48b**) (entry *54*).[190] To attain high yields and *ee* values for aldol **107a**, it is sufficient to use only 2 mol.% – 3 mol.% of catalyst **46c** or **48b** in the reaction.



(6)

b. Effect of organocatalyst on the diastereoselectivity of the aldol reaction

The asymmetric aldol reactions involving electrophiles containing substituents at the α-carbon atom(s) can result in *anti*- and *syn*-diastereomeric aldols, *anti*-diastereomers being normally the major products. The diastereomeric composition of aldols **107b** depends on the reactant and catalyst structure and reaction conditions. We will consider the effect of the structure of some types of organocatalysts on the diastereoselectivity of the asymmetric aldol reaction in relation to the reaction of cyclohexanone (**105b**) with 4-nitrobenzaldehyde (**106b**) carried out in excess ketone or in organic solvents under identical or comparable conditions (Table 6).

It can be seen from Table 6 that relatively low diastereoselectivities in the considered reaction characterize catalysts like (*S*)-proline (**1**) (entry *1*),[71] (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**30**) (entry *2*)[147] and 2-(*S*)-(*O*,*O*-diethylphosphoryl)pyrrolidine (**47b**) (entry *3*)[185] *dr*(*anti* : *syn*) ⩽ 2 : 1. The catalytic properties of (*S*)-proline *N*-sulfonylamides depend on the structure of the substituent at the sulfur atom. In the presence of benzene- (**22a**) or methanesulfonamide (**22g**), the process has low diastereoselectivity (entries *4*, *5*).[121] However, in the reactions catalyzed by arenesulfonamide **22e**, which contains a long-chain alkyl group in the *para*-position of the aromatic ring, the *trans* to *cis* diastereomeric ratio reaches 15 : 1 under similar condi-

Table 6. Asymmetric aldol reaction (6) in the presence of different organocatalysts.

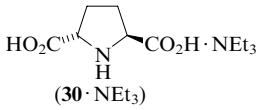
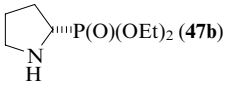
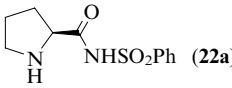
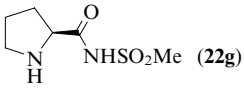
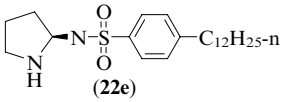
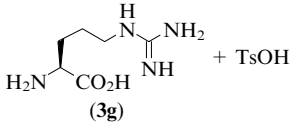
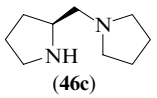
Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time/h	Aldol **107b**			Ref.
						yield (%)	*dr* (*anti* : *syn*)	*ee* (*anti*) (%)/ *ee* (*syn*) (%)	
1	(*S*)-Proline (**1**)	20	DMSO	25	24	65	1.7 : 1	89 / 67	71
2	 (**30** · NEt_3)	30	DMSO	25	see [a]	55	1 : 1.5	87 / 88	147
3	 (**47b**)	5	DMSO	25	96	73	2 : 1	96 / 96	185
4	 (**22a**)	20	CH_2Cl_2	20	24	88	1.5 : 1	90 / 63	121
5	 (**22g**)	20	CH_2Cl_2	20	24	80	1.8 : 1	78 / 74	121
6	 (**22e**)	20	CH_2Cl_2	20	36	51	15 : 1	97 / see [a]	125
7	 (**3g**)	10	DMSO	25	24	74	3 : 1	94 / see [a]	65
8	 (**46c**)	5	**105b**	30	29	97	2.8 : 1	96 / 61	320

Table 6 (continued).

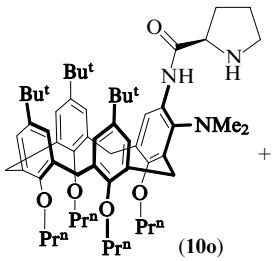
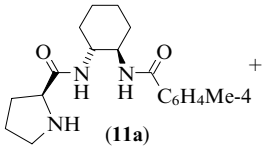
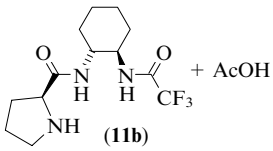
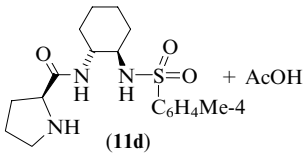
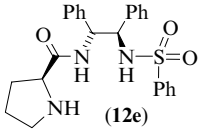
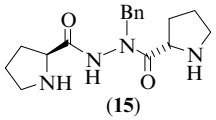
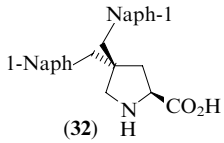
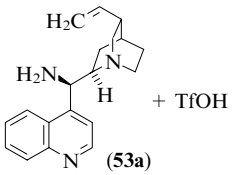
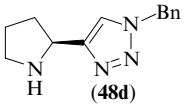
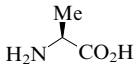
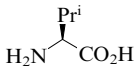
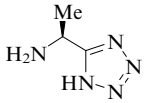
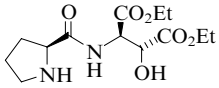
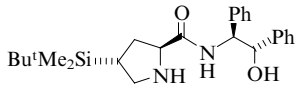
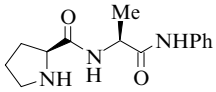
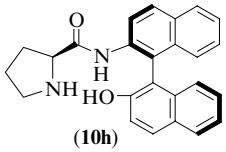
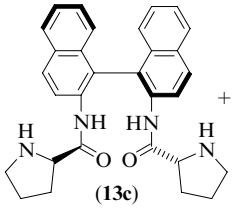
Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time/h	Aldol **107b**			Ref.
						yield (%)	*dr* (*anti* : *syn*)	*ee* (*anti*) (%)/ *ee* (*syn*) (%)	
9	 (**10o**) + AcOH	10 + 20	DMSO	−20	36	75	6 : 1	75 / see [a]	94
10	 (**11a**) + AcOH	20	$CHCl_3$	25	5	81	3 : 1	86 / see [a]	95, 96
11	**11a** + AcOH	20	$CHCl_3$	−25	24	89	24 : 1	92 / see [a]	95, 96
12	**11a** + AcOH	20	$CHCl_3$	−40	72	81	49 : 1	97 / see [a]	95, 96
13	 (**11b**) + AcOH	20	$CHCl_3$	25	12	63	3 : 1	73 / see [a]	95, 96
14	 (**11d**) + AcOH	20	$CHCl_3$	25	2	73	5.2 : 1	54 / see [a]	95, 96
15	 (**12e**)	2	H_2O	−5	24	90	9 : 1	81 / see [a]	102
16	 (**15**) + TFA	20	PhMe	0	7	98	12 : 1	92 / see [a]	109
17	 (**32**)	10	DMF	−10	48	90	9 : 1	94 / 92	149
18	 (**53a**) + TfOH	10 + 15	**105b**	25	9	99	9.2 : 1	99 / see [a]	205
19 [b]	 (**48d**)	10	**105b**	0	12	93	11 : 1	23 / see [a]	193

Table 6 (continued).

Entry	Cat	C_{Cat} (mol.%)	Solv	T/°C	Time/h	Aldol **107b**			Ref.
						yield (%)	*dr* (*anti* : *syn*)	*ee* (*anti*) (%)/ *ee* (*syn*) (%)	
20	 (**3a**)	30	DMSO + H_2O (10 equiv.)	25	72	95	15 : 1	99 / see [a]	57, 68
21	 (**3c**)	30	DMSO + H_2O (10 equiv.)	25	72	98	37 : 1	> 99 / see [a]	57, 68
22	 (**52**)	30	DMSO + H_2O (10 equiv.)	25	8	84	14 : 1	> 99 / see [a]	57, 68
23	 (**10f**)	2	CH_2Cl_2	−25	[a]	83	19 : 1	79 / see [a]	83
24	 (**26a**)	5	CH_2Cl_2	−40	72	95	> 99 : 1	99 / see [a]	142
25	 (**17h**) + AcOH	20 + 20	$CHCl_3$	−20	24	98	49 : 1	93 / see [a]	117
26	 (**10h**)	10	dioxane + H_2O (1 equiv.)	4	65	86	49 : 1	92 / see [a]	87
27	 (**13c**) + $PhCO_2H$	5 + 10	**105b**	0	4	85	24 : 1	90 / see [a]	106

[a] No data are given in the publications. [b] 3-Nitrobenzaldehyde was used in the reaction.

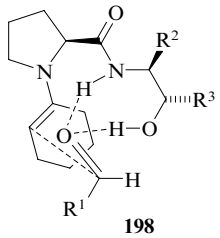
tions (entry *6*) with high enantioselectivity.[125] The observed effect was rationalized[125] as being due to much better solubility of catalyst **22e** (300 mg ml^{-1}) in the reaction medium (CH_2Cl_2) compared to catalysts **22a**,**g** (< 5 mg ml^{-1}).

p-Toluenesulfonic acid salt of arginine (**3g**) (entry *7*),[65] trifluoromethanesulfonic acid salt of (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**46c**) (entry *8*),[320] prolinamides containing chiral calix[4]arene fragments (**10o**) (entry *9*),[94] *trans*-1,2-diaminocyclohexane (**11a**,**b**,**d**) (entries *10*–*14*),[95,96] 1,2-diamino-1,2-diphenylethane[102] (**12e**) (entry *15*), trifluoroacetatic acid salt of 1,2-bis[(*S*)-prolyl]-hydrazine (**15**) (entry *16*),[109] (*S*)-4,4-bis(1-naphthylmethyl)-proline (**32**) (entry *17*),[149] quinine amino-derivative **53a** (entry *18*)[205] and (*S*)-2-(triazolyl)pyrrolidine (**48d**) (entry *19*)[193] afford aldols **107b** with relatively high *trans*-diastereoselectivity [3 : 1 ⩽ *dr*(*anti* : *syn*) ⩽ 12 : 1] and, except for compounds **11d** and **48d**, enantioselectivity. The *dr*(*anti* : *syn*) value for the model reaction induced by diamide **11a** was increased to 49 : 1 by conducting the reaction at −40 °C (entries *10*–*12*).[95,96]

Fairly high diastereoselectivities [14 : 1 ⩽ *dr*(*anti* : *syn*) ⩽ 37 : 1] are characteristic of the reactions catalyzed by some α-amino acids with primary amino groups, in particular, alanine (**3a**) and valine (**3c**) (see Table 6, entries *20*, *21*)[57,68] and by a heterocyclic alanine analogue, 5-(1-aminoethyl)tetrazole (**52**) (entry *22*).[57,68] The addition of small amount

($\leqslant$10 equiv.) of water have a favourable effect on the diastereoselectivity of these reactions.

As regards diastereoselectivity, prolinamides based on chiral β-amino alcohols (the Gong amides), for example compounds **10f** (see Table 6, entry *23*)[83] and **26a** (entry *24*),[142] some proline-containing dipeptides, in particular, compound **17h** (entry *25*),[117] as well as prolinamides **10h** (entry *26*)[87] and **13c** (entry *27*)[106] comprising a 2,2′-diaminobinaphthyl fragment are not inferior (in some cases, even superior) to the above-mentioned catalysts. Thus by using highly active catalyst **26a** (5 mol.%), almost individual *anti*-isomer of aldol **107b** was synthesized at −40 °C in an enantiomerically pure state in 95% yield. The high stereocontrol level observed in reactions catalyzed by prolinamides containing β-amino alcohol structural fragments was rationalized[83] by stabilization of transition state **198** through hydrogen bonding with amino and hydroxy groups of these catalysts.

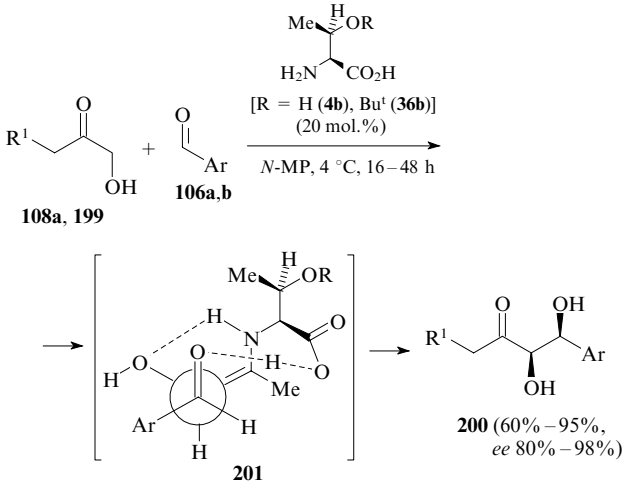


198

The predominant formation of *anti*-diastereomers of aldols is observed not only in the examples considered here but also in most other organocatalytic aldol reactions in which nucleophiles are represented by six-membered cyclic (heterocyclic) ketones including 1,3-dioxan-5-one,[268–270] pyran-4-one and thiopyran-4-one derivatives (Refs 96, 142, 189, 319, 324) and linear ketones containing substituents other than methyl at the carbonyl carbon.[123,264] One of the few exceptions to this rule is the reaction between compounds **105b** and **106b** catalyzed by triethylammonium hydrogen (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylate (**30**), which yields a mixture of diastereomeric aldols *anti*-**107b** and *syn*-**107b**, the latter somewhat predominating (see Table 6, entry *2*).[147]

In aldol reactions involving five- and seven-membered cyclic ketones, the situation is ambiguous. These reactions are usually non-selective[83,196] or have either relatively low[109,320] and in some cases, reasonable *syn*-diastereoselectivity,[325] which is probably due to conformational features of these ketones. The problem of selective synthesis of *syn*-diastereomers of aldols from cyclic and unsymmetrically substituted ketones or α-branched donor aldehydes have remained unsolved until recently.

Only quite recently, did several groups of researchers have developed effective catalysts providing predominant formation of *syn*-diastereomers in the asymmetric aldol reactions of different carbonyl compounds. Thus Barbas III and co-workers[67] found that in the presence of amino acids with primary amino group, in particular, (*S*)-threonine (**4b**) and its *tert*-butyl ether **36b**, aldol reactions of α-hydroxy ketones **108a**, **199** with aromatic aldehydes **106a**,**b** are *syn*-diastereoselective [*dr*(*syn* : *anti*) = (5 : 1) – (18 : 1)], unlike the reactions of these substrates catalyzed by (*S*)-proline derivatives (see Table 2). When these reactions are carried out in *N*-methylpyrrolidone at 4 °C, the *dr* value for aldols **200** (*syn* : *anti*) is 18 : 1, the enantiomeric excess of the major *syn*-diastereomer reaching 98%. Presumably, the formation of two hydrogen bonds in the reaction transition state **201** is the key stereochemical factor determining the reaction *syn*-diastereoselectivity, namely, an H-bond between the catalyst amino group and the hydroxyl group of the donor ketone and an H-bond between the catalyst carboxyl group and the C=O group of the acceptor aldehyde **106a**,**b**.[67]



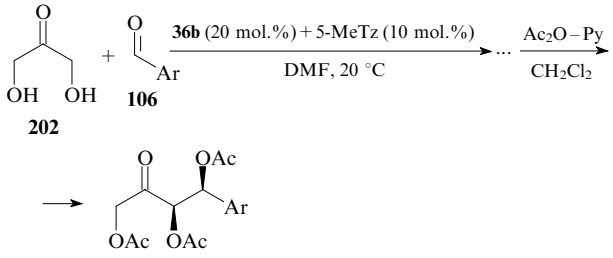
108a, **199** **106a**,**b** [R = H (**4b**), Bu^t (**36b**)] (20 mol.%) *N*-MP, 4 °C, 16–48 h

201

200 (60%–95%, *ee* 80%–98%)

R^1 = H (**108a**), Me (**199**); Ar = 4-XC_6H_4 (X = Cl, Br, CN, NO_2), 1-naphthyl.

The *syn*-addition pathway is also observed for the reaction of 1,3-dihydroxyacetone (**202**) with aldehydes **106a**,**b** in the presence of the **36b**–organic acid catalytic system.[155] The resulting aldols are converted without isolation to stable triacetates **203** [*dr*(*syn* : *anti*) = (7 : 1) – (99 : 1)]. The best diastereo- and enantioselectivity values were obtained when 5-methyltetrazole (5-MeTz) served as the organic acid and the reactions were carried out in DMF. *syn*-Diastereoselectivity was also noted in aldol reactions of the silyl or benzyl ethers of hydroxy- and dihydroxyacetone.[156]

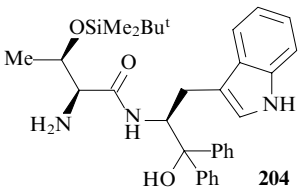


202 **106** **36b** (20 mol.%) + 5-MeTz (10 mol.%) DMF, 20 °C Ac_2O–Py CH_2Cl_2

203 (62%–92%, *ee* 92%–99%)

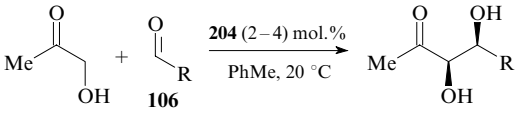
Ar = XC_6H_4 (X = 4-NO_2, 4-Br, 4-CN, 4-CF_3, 3-F), 1-naphthyl, 3-furyl.

Amides of α-amino acids with primary amino groups and chiral β-amino alcohols proved to be effective catalysts of *syn*-aldol reactions of hydroxy- and dihydroxyacetone with aromatic and aliphatic aldehydes. Thus hydroxyacetone (**108a**) reacts with alkanals and benzaldehyde derivatives **106** in the presence of amide **204**



204

giving rise to *syn*-α,β-dihydroxyketones **205** [*dr*(*syn* : *anti*) = (3 : 1) – (30 : 1)] containing structural fragments of natural macrolides.[326] The highest diastereo- and enantioselectivities were observed in reactions with alkanals.

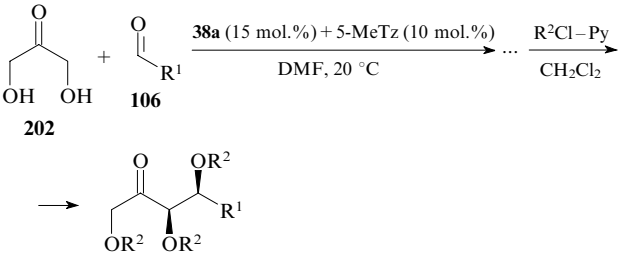


108a **106** **205** (68% – 99%, *ee* 76% – 98%)

R = n-C_mH_{2m+1} (*m* = 3 – 5), Bu^i, CH(Me)CH_2CH(Me)$OSiMe_2Bu^t$, XC_6H_4 (X = 4-NO_2, 4-Cl, 4-Br, 2-Cl, 2-Br).

The **38a** – 5-methyltetrazole system catalyzes the formation of *syn*-diastereomers of aldols from dihydroxyacetone (**202**) and various aldehydes **106**, including functionally substituted ones.[159] The reaction products were isolated as acetates or benzoates **206**.

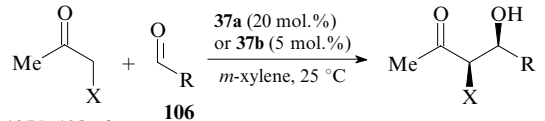
Leucinamides **37a**,**b** containing chiral amino alcohol fragments are *syn*-diastereoselective catalysts of the aldol reactions of α-substituted acetone derivatives **105d**, **108a**,**f**,**g** with aldehydes **106**.



202 **106** **206** (62% – 74%, *dr*(*syn* : *anti*) = (2 : 1) – (8 : 1), *ee* 94% – 99%)

R^1 = $(CH_2)_2$Ph, n-C_5H_{11}, cyclo-C_6H_{11}, $CH(OMe)_2$, 4-XC_6H_4 (X = NO_2, CF_3); R^2 = Ac, Bz.

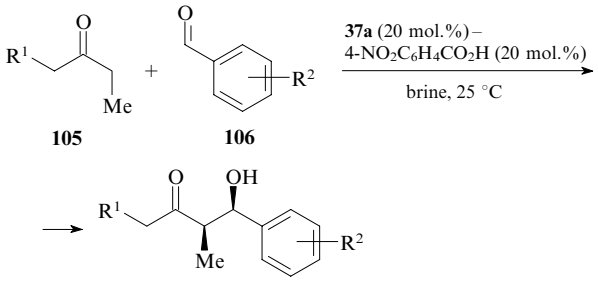
The aldols *syn*-**207** are formed with fairly high diastereoselectivity [*dr*(*syn* : *anti*) = (2 : 1) – (20 : 1)] and enantiomeric purity, which can be as high as *dr*(*syn* : *anti*) > 20 : 1 and *ee* 99% for the reactions of hydroxyacetone (**108a**).[157]



105d, **108a**,**f**,**g** **106** *syn*-**207** (61% – 97%, *ee* 80% – 99%)

X = Me (**105d**), OH (**108a**), Cl (**108f**), F (**108g**);
R = Ar, 1-bromonaphthyl, cyclo-C_6H_{11}, Pr^i.

The use of the **37a** – 4-nitrobenzoic acid system as the catalyst and brine as the reaction medium made it possible to involve linear alkan-3-ones **105** containing 5 to 9 carbon atoms in highly *syn*-diastereoselective reactions with aromatic aldehydes. According to the authors' statement,[158] the reaction was 2-regioselective to yield predominantly *syn*-diastereomers of aldols **208** [*dr* (*syn* : *anti*) = (4 : 1) – (7 : 1)].[158]

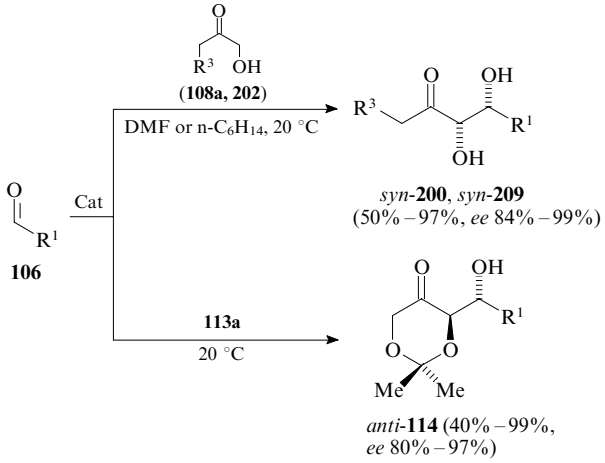


105 **106** *syn*-**208** (78% – 98%, *ee* 73% – 95%)

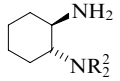
R^1 = n-C_nH_{2n+1} (*n* = 1 – 5); R^2 = 4-NO_2, 3-NO_2, 4-CO_2Me, 4-CF_3, 2-Cl, 2-Br, 2-F, 3-Br, 3-Cl, 2,3-Cl_2, 2,3,4-F_3, 3,4,5-F_3.

High *syn*-diastereoselectivity [*dr*(*syn* : *anti*) = (7 : 1) – (99 : 1)] was noted for the aldol reactions of ketones **108a** and **202** with aromatic aldehydes **106** in the presence of mixed salts of *trans*-1-amino-2-(dialkylamino)cyclohexane **51b**,**d**,**e** with trifluoromethanesulfonic and *p*-nitrobenzoic acids.[200] The *dr*(*syn* : *anti*) ratio for products **200** and **209** was in some cases as high as 99 : 1. The protected cyclic form of 1,3-dihydroxyacetone, 2,2-dimethyl-1,3-dioxan-5-one (**113a**), also reacts under proposed conditions, but in this case, *anti*-diastereomers of aldols **114** were formed as the major products [*dr*(*anti* : *syn*) = (4 : 1) – (> 10 : 1)] (Scheme 7).

Scheme 7



R^1 = XC_6H_4 (X = H, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 4-Cl, 2-Br, 3-Br, 4-CF_3, 4-CN, 4-Ph, 4-OMe), CH_2OBn;

Cat =  + 4-$O_2NC_6H_4CO_2H$ + TfOH;

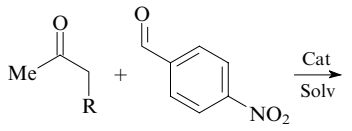
51b,**d**,**e** (10 mol.%)
[R^2 = Et (**b**), Pr^n (**d**), n-$C_{10}H_{21}$ (**e**)]

R^3 = H (**108a**, **200**), OH (**202**, **209**).

Generally, the *syn*-diastereoselective strategies of the asymmetric aldol reaction developed in recent years open up direct route to natural products, including carbohydrates and their derivatives, which could formerly be synthesized only by biochemical route under the action of enzymes (aldolases).[27] The described methods make a good supplement to the *anti*-selective aldol reactions catalyzed by proline and its derivatives, which allows targeted diastereo- and enantioselective synthesis of a variety of polyfunctional compounds with different structures.

c. Effect of the organocatalyst on the regioselectivity of the aldol reaction

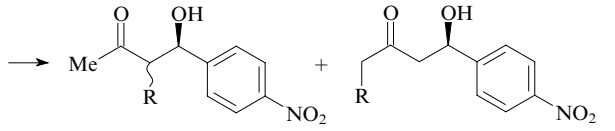
In Section V (see Tables 1, 2) it was noted that both *anti*- or *syn*-diastereomeric aldols **109** and regioisomeric aldols **107d** and **110** may be formed as products of asymmetric aldol reactions in which unsymmetrically substituted ketones acted as the donors. It was found that the nature of the organocatalyst can considerably influence the regioselectivity of these transformations. Some examples of asymmetric aldol reactions (7) of 4-nitrobenzaldehyde (**106b**) with acetone derivatives **105d** and **108a**,**e**–**g** induced by various organocatalysts in which regioisomers may be formed are given in Table 7.



105d, **108a**,**e**–**g** **106b**

R = Me (**105d**), OH (**108a**), SMe (**108e**), Cl (**108f**), F (**108g**).

(7)



109l–**p** **107d**, **110h**–**k**

R = Cl (**l**), Me (**m**), OH (**n**), SMe (**o**), F (**p**).

R = Me (**107d**), SMe (**110h**), OH (**110i**), Cl (**110j**), F (**110k**).

Under conditions proposed by Barbas III and co-workers [71, 327] in 2001, which imply the use of (*S*)-proline (**1**) or (*S*)-5,5-dimethylthiazolidine-4-carboxylic acid (**56b**) as the catalyst and DMSO as the solvent, the aldol reaction of butan-2-one (**105d**) with aldehyde **106b** affords aldol **107d** (see Table 7, entries *1*–*3*). Enantiomeric excess of the product did not exceed 74%. The selectivite formation of regioisomers was also noted in aldol reactions catalyzed by proline derivatives **64f** [227] and **32**,[149] which contain different substituents in the pyrrolidine ring (entries *4*, *5*). However, in the case of sterically hindered catalyst **32**, the formation of aldol **107d** (33%) was accompanied by the formation of minor (10%) regioisomer **109m** having high diastereo- [*dr*(*anti*:*syn*) = 19:1] and enantiomeric (*ee* 99%) purities.

The regioselectivity of the aldol reaction in the presence of prolinamides depends on the structure of the amide group and reaction conditions. Aldol **107d** is formed as the major product in reaction (7) of compounds **105d** and **106b** in DMF catalyzed by diamide **13c** (10 mol.%) containing a 2,2′-diaminobinaphthyl fragment (see Table 7, entries *6*–*8*).[104, 328] The fraction of regioisomer **109m** formed on long-term (264 h) keeping of the reactants in the dry solvent is very low (~1%) (thermodynamic control), but increases with the decrease in the reaction time to 31 h (kinetic control) and/or when a DMF–H_2O mixture (1:1) is used as the solvent. However, modification of catalyst **13c** by addition of benzoic acid (10 mol.%) and performing the reaction under solvent-free conditions (entry *9*) afford comparable amounts of regioisomers **109m** and **107d** with high diastereo- [*dr*(*anti*:*syn*) >99:1] and enantioselectivities (*ee* 90% and 99%, respectively).[106, 329] Similar results were obtained in reactions catalyzed by amide **10m** containing proline and alkaloid quinconidine fragments [92] in combination with AcOH (entry *10*) or polyfunctional amide **10f** (entry *11*). Futhermore, owing to the high activity of the catalyst **10f**, the process can occur at −25 °C in the presence of only 2 mol.% of the catalyst.[83]

When (*S*)-alanine (**3a**) (see Table 7, entry *12*),[57] axially chiral amino acid **49a** (entry *13*),[196] *trans*-1,2-diaminocyclohexane derivatives **11a** [95] and **51d** (entries *14*, *15*),[199] and (*S*)-proline sulfamide containing a dendrimer group (**22f**) (entry *16*) are used as the catalysts,[126] aldol **109m** is formed as the major reaction product (7). Attention is attracted by the above-noted (see Scheme 7) [200] abnormal *syn*-diastereoselectivity of the reaction induced by diamine **51d**.[199]

The nature of the organocatalyst can change, to a certain extent, the chemo- and regioselectivity of aldol reactions involving acetone derivatives that contain heteroatomic substituents. Thus aldol reactions of hydroxyacetone (**108a**) with aldehyde **106b** catalyzed by α-amino acids, in particular, proline **1**,[330] L-threonine (**4b**) [67] or its *tert*-butyl ether **36b** (see Table 7, entries *17*–*19*),[67] α-amino acid amides **13c** [330, 331] and **37a** (entries *20*, *21*) [157] or *trans*-1,2-diaminocyclohexane derivative **51d** (entry *22*) [200] give *syn*- and *anti*-diastereomeric aldols **109n** almost regioselectively. However, when this reaction is catalyzed by the methyl ester of dipeptide **17d** (MeO-**17d**) (entries *23*, *24*),[115] amide **10f** (entries *25*, *26*) [332] or diamide **12c** (entries *27*),[99] the isomeric aldol **110i** is formed together with aldols **109n**. When compounds **10f** and MeO-**17d** are used as the catalysts, the addition of water to the reaction mixture results in 1,4-diol **110i** as the major product.

In the reactions involving α-(methylthio)acetone (**108e**) and α-haloketones **108f**,**g**, the variation of the catalyst usually has little influence on the reaction regioselectivity but markedly increases the chemoselectivity compared to the (*S*)-proline-catalyzed transformations. Whereas in the presence of proline **1**, the reaction between compounds **108e** and **106b** is non-selective resulting in aldol **110h** in a yield not exceeding 10% (see Table 7, entry *28*),[265] under the action of prolinamides **10e**,**f** and **13c**, the yields of compounds **110h** reach 43%, 72% and 70%, respectively, under comparable conditions (entries *29*–*31*).[106, 265, 329] The formation of regioisomeric *syn*/*anti*-aldols **109o** was detected, although in insignificant amounts (3%–13%).

Unlike aldol reactions involving α-(methylthio)acetone (**108e**), in organocatalytic reactions of 4-nitrobenzaldehyde (**106b**) with α-chloroacetone (**108f**) or α-fluoroacetone (**108g**), β-halohydrins **109l** or **109p** are most often formed as the major products. In this case, too, the influence of the catalyst structure on the process chemoselectivity can be followed quite clearly. In the presence of proline **1** and 5,5-dimethylthiazolidine-4-carboxylic acid (**56b**), the reactions are highly non-selective, resulting in the formation of complex product mixtures from which chlorohydrin **109l** was isolated in only 8% yield (see Table 7, entry *32*) [73] and individual fluorine-containing aldols **109p** or **110k** were not obtained at all.[168] Meanwhile, performing these reactions under the action of organocatalysts based on α-amino acid amides **6**,[73] **10f**,[265, 332] **13c**,[106] **37a**,**b** [157] or (*S*)-prolinol (**45a**) [168] (entries *33*–*39*) allows one to synthesize compounds **109l** and **109p** in 50%–94% yields and with relatively high enantioselectivity (up to 95%). On catalysis by compounds **6**, **10f** and **45a**, the *anti*-diastereomeric aldols **109l**, **109p** predominate and on catalysis by amides **37a**,**b**, *syn*-diastereomers are the major products. The important role of the reaction medium (this will be considered in more detail in our next review) attests to reversal of the regioselectivity for the amide **10f**-catalyzed reaction between compounds **106b** and **108g** upon addition of water (entry *40*).[332]

Table 7. Asymmetric aldol reactions (7) of acetone derivatives **105d**, **108a**,**e** – **g** with 4-nitrobenzaldehyde (**106b**) in the presence of different organocatalysts.

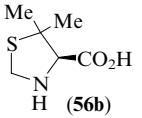
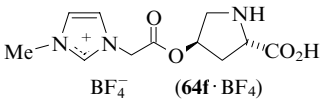
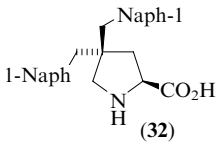
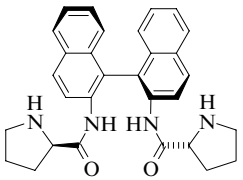
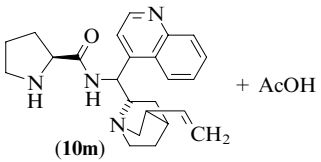
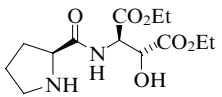
Entry	Cat	C_{Cat} (mol.%)	R	Solv	T /°C	Time /h	Aldol **109l** – **p**			Aldol **107d**, **110h** – **k**		Ref.
							product [yield (%)]	*dr* (*anti* : *syn*)	*ee* (*anti*) (%) / *ee* (*syn*) (%)	product [yield (%)]	*ee* (%)	
1	(*S*)-Proline (**1**)	30	Me	DMSO	25	see [a]	**109m** (see [a])	see [a]	see [a]	**107d** (61)	59	71, 327
2	**1**	30	Me	DMSO	25	25	**109m** (see [a])	see [a]	see [a]	**107d** (53)	70	227
3	 (**56b**)	30	Me	DMSO	25	see [a]	**109m** (see [a])	see [a]	see [a]	**107d** (57)	74	71, 327
4	 (**64f** · BF_4)	30	Me	DMSO	25	25	**109m** (see [a])	see [a]	see [a]	**107d** (56)	75	227
5	 (**32**)	10	Me	DMF	−10	48	**109m** (10)	19 : 1	99 / see [a]	**107d** (33)	88	149
6	 (**13c**)	5 – 10	Me	DMF	25	264	**109m** (1)	> 99 : 1	31 / see [a]	**107d** (95)	96	104, 328
7	**13c**	5 – 10	Me	DMF	25	31	**109m** (12)	> 99 : 1	4 / see [a]	**107d** (58)	75	104, 328
8	**13c**	5 – 10	Me	DMF + H_2O (1:1)	25	20	**109m** (30)	> 99 : 1	78 / see [a]	**107d** (69)	88	104, 328
9	**13c** + $PhCO_2H$	(5 – 10) + 10	Me	**105d**	0	24 – 40	**109m** (53)	> 99 : 1	90 / see [a]	**107d** (44)	99	106, 329
10	 + AcOH (**10m**)	20 + 40	Me	**105d**	−30	48	**109m** (53)	13 : 1	98 / see [a]	**107d** (32)	75	92
11	 (**10f**)	2	Me	**105d**	−25	24	**109m** (42)	> 99 : 1	99 / see [a]	**107d** (56)	98	83

Table 7 (continued).

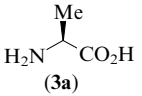
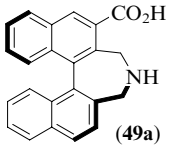
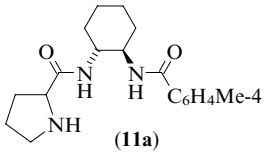
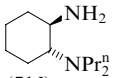
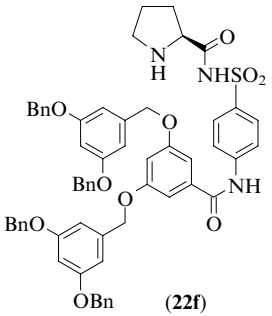
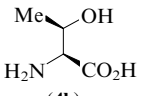
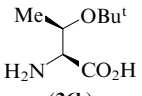
Entry	Cat	C_{Cat} (mol.%)	R	Solv	T /°C	Time /h	Aldol **109l – p**			Aldol **107d**, **110h – k**		Ref.
							product [yield (%)]	*dr* (*anti* : *syn*)	*ee* (*anti*) (%) / *ee* (*syn*) (%)	product [yield (%)]	*ee* (%)	
12	 (**3a**)	10	Me	DMSO + H_2O (10 equiv.)	25	96	**109m** (56)	3 : 1	75 / see [a]	**107d** (see [a])	see [a]	57
13	 (**49a**)	10	Me	DMSO	25	48	**109m** (52)	> 15 : 1	99 / see [a]	**107d** (20)	91	196
14	 (**11a**)	2	Me	$CHCl_3$	−40	72	**109m** (63)	19 : 1	99 / see [a]	**107d** (9)	see [a]	95
15	 (**51d**) + TfOH + 3-$NO_2C_6H_4CO_2H$	10	Me	**105d**	4	see [a]	**109m** (85)	1 : 10	see [a] / 96	**107d** (10)	see [a]	199
16	 (**22f**)	10	Me	H_2O	25	72	**109m** (70)	7 : 1	89 / see [a]	**107d** (see [a])	see [a]	126
17	**1**	40	OH	DMSO	25	36	**109n** (79)	3 : 1	85 / 42	**110i** (see [a])	see [a]	330
18	 (**4b**)	20	OH	*N*-MP	4	16	**109n** (75)	1 : 15	see [a] / 90	**110i** (see [a])	see [a]	67
19	 (**36b**)	20	OH	*N*-MP	4	16	**109n** (> 95}	1 : 18	see [a] / 98	**110i** (see [a])	see [a]	67

Table 7 (continued).

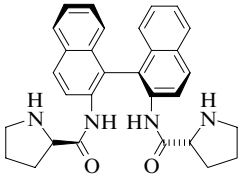
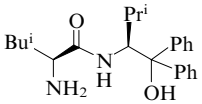
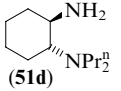
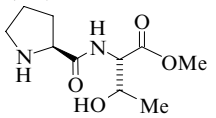
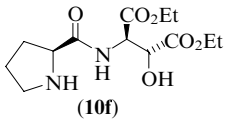
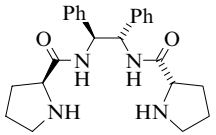
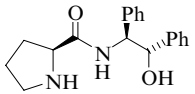
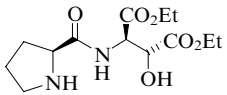
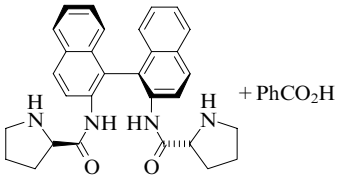
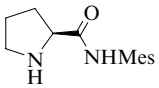
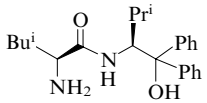
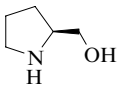
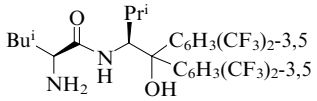
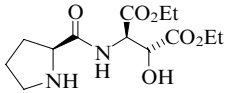
Entry	Cat	C_{Cat} (mol.%)	R	Solv	T /°C	Time /h	Aldol **109l – p**			Aldol **107d**, **110h – k**		Ref.
							product [yield (%)]	*dr* (*anti* : *syn*)	*ee* (*anti*) (%) / *ee* (*syn*) (%)	product [yield (%)]	*ee* (%)	
20	 (**13c**)	20	OH	DMSO	25	24	**109n** (86)	3 : 1	82 / 35	**110i** (see [a])	see [a]	330, 331
21	 (**37a**)	20	OH	THF	25	36	**109n** (95)	1 : 19	see [a] / 96	**110i** (see [a])	see [a]	157
22	 (**51d**) + TfOH + 3-$NO_2C_6H_4CO_2H$	10	OH	n-C_6H_{14}	25	15	**109n** (> 99)	1 : 16	see [a] / 96	**110i** (see [a])	see [a]	200
23	 (MeO-**17d**)	30	OH	THF	25	96	**109n** (71)	2 : 1	61 / see [a]	**110i** (16)	60	115
24	MeO-**17d**	30	OH	THF + H_2O (1 : 1)	25	96	**109n** (13)	0.8 : 1.0	28 / see [a]	**110i** (50)	62	115
25	 (**10f**)	20	OH	THF	0	60	**109n** (58)	see [a]	see [a]	**110i** (36)	97	332
26	**10f**	20	OH	THF + H_2O (2 : 1)	−15	60	**109n** (< 5)	see [a]	see [a]	**110i** (95)	95	332
27	 (**12c**)	10	OH	CH_2Cl_2	−35	see [a]	**109n** (38)	see [a]	see [a] / 66	**110i** (50)	97	99
28	**1**	20	SMe	$CHCl_3$	25	see [a]	**109o** (see [a])	see [a]	see [a]	**110h** (10)	see [a]	265
29	 (**10e**)	5	SMe	CH_2Cl_2	−25	3	**109o** (3)	see [a]	see [a]	**110h** (43)	91	265

Table 7 (continued).

Entry	Cat	C_{Cat} (mol.%)	R	Solv	T /°C	Time /h	Aldol **109l–p**			Aldol **107d**, **110h–k**		Ref.
							product [yield (%)]	*dr* (*anti* : *syn*)	*ee* (*anti*) (%) / *ee* (*syn*) (%)	product [yield (%)]	*ee* (%)	
30	 (**10f**)	5	SMe	CH_2Cl_2	−25	124	**109o** (5)	see [a]	see [a]	**110h** (72)	95	265
31	 + $PhCO_2H$ (**13c**)	5 + 10	SMe	**108e**	0	48	**109o** (13)	1 : 1	see [a]	**110h** (70)	86	106, 329
32	**1**	20	Cl	THF	25	96	**109l** (8)	see [a]	74 / see [a]	**110j** (see [a])	see [a]	73
33	 (**6**)	30	Cl	THF	25	96	**109l** (50)	7 : 1	91 / see [a]	**110j** (7)	see [a]	73
34	**13c** + $PhCO_2H$	5 + 10	Cl	**108f**	0	45	**109l** (71)	4.2 : 1.0	66 / see [a]	**110j** (5)	see [a]	106
35	 (**37a**)	20	Cl	Et_2O	25	40	**109l** (81)	1.0 : 2.5	see [a] / 89	**110j** (see [a])	see [a]	157
36	**13c** + $PhCO_2H$	5 + 10	F	**108g**	0	17	**109p** (65)	2.2 : 1.0	80 / see [a]	**110k** (21)	see [a]	106
37	 (**45**)	35	F	DMSO	25	48	**109p** (77)	2.3 : 1.0	84 / see [a]	**110k** (5)	see [a]	168
38	 (**37b**)	5	F	CH_2Cl_2	25	48	**109p** (76)	1 : 5	see [a] / 94	**110k** (see [a])	see [a]	157
39	 (**10f**)	20	F	THF	0	72	**109p** (94)	2 : 1	95 / see [a]	**110k** (2)	see [a]	265, 332
40	**10f**	20	F	THF + H_2O (1 : 1)	0	72	**109p** (10)	see [a]	see [a]	**110k** (62)	80	332

[a] No data are given in the publications.

It should be emphasized that chiral organofluorine compounds are valuable intermediates for drug production [333, 334] and play important role in the biochemistry of carbohydrates.[335, 336] Prior to the development of organocatalytic methods, fluorine-containing β-hydroxycarbonyl compounds could be obtained only by enzymatic route, their yields being not higher than 40%.[337]

VII. Aldol reactions in the presence of immobilized organocatalysts

Since asymmetric aldol reactions usually occur at high rates and with high selectivities only in the presence of a relatively large amount of amino acid (20 mol.% – 30 mol.%) and more effective modern synthetic organocatalysts have complicated structures, in recent years much emphasis has been given to the development of recoverable catalysts, which can be isolated from the reaction mixtures and used repeatedly. In addition, development of the methods for catalyst regeneration is one of 'green chemistry' problems and is important as regards environmental protection.[26]

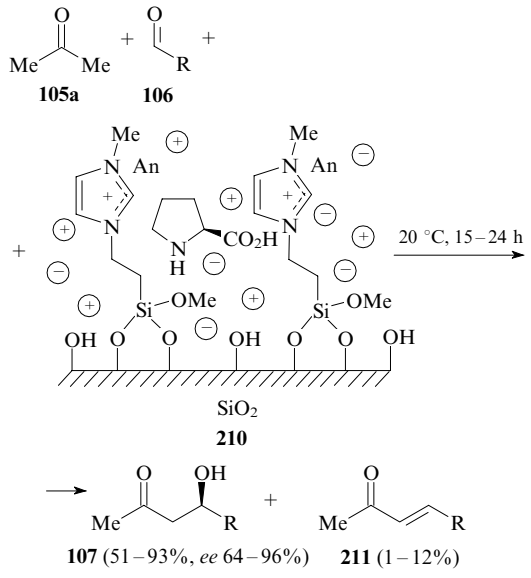
The recoverable forms of organocatalysts obtained to date can be divided into two groups, *viz*., non-covalently immobilized catalysts and catalysts covalently bound to polymers or anchored to ionic liquids.

1. Reactions in the presence of non-covalently immobilized catalysts

The non-covalent way of immobilization of organocatalysts is based on the ability of these, most often polar compounds to be held, by electrostatic forces, on the surface of inorganic or organic polymers containing polar groups or polarized chemical bonds.

For example, (*S*)-proline (**1**) can be adsorbed on silica gel. The activity of the supported catalyst is rather high; however, the enantioselectivity of the aldol reaction is lower than that in homogeneous catalysis.[71]

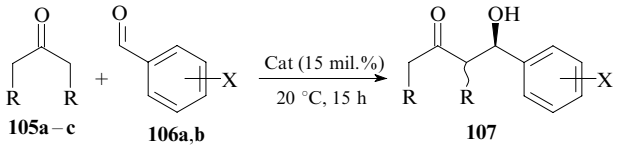
The selectivity of the reaction of acetone (**105a**) (27 equiv.) with aldehyde **106a** can be increased to *ee* 64% – 96% by performing the reaction under the action of heterogeneous catalyst **210** consisting of (*S*)-proline (**1**) (30 mol.%) and an ionic liquid, for example, 1-butyl-3-methylimidazolium tetrafluoroborate (bmim[BF_4]) adsorbed simultaneously on silica gel. The ionic liquid is held on the silica gel surface by means of alkylimidazolium cations bound to silyloxy groups. The activity of the catalyst and enantioselectivity do not change after four reaction cycles.[338, 339] The reaction gives α,β-enones **211** as by-products.



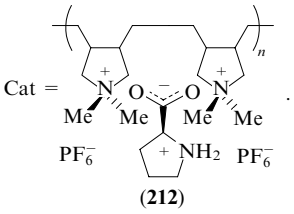
⊕⊖ = bmim[BF_4]; R = Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, Pr^i.

Multilayer inorganic substrates containing metal hydroxides capable of adsorbing (*S*)-proline on their surface can act as heterogeneous supports. However, the enantiomeric purity of the aldol formed from acetone **105a** (27 equiv.) and benzaldehyde **106** in the presence of the Mg/Al/NO_3/**1** system (1 mol.%) does not exceed 6%.[340] Much higher enantioselectivity (up to 94%) is observed with the Mg/Al/CO_3/**1** system (35 mol.%) used as the catalyst.[341]

For 'heterogenization' of (*S*)-proline (**1**), we used for the first time an organic cationic polymer, poly(diallyldialkylammonium) hexafluorophosphate with the molecular weight of 400 000 – 500 000 Da obtained from commercially available 20% aqueous solution of the corresponding chloride.[342] The efficient adsorption of proline is apparently provided by the ion – dipole interactions of the polar catalyst and the ionic polymer. Catalyst **212** has high activity and moderate enantioselectivity (62% – 91%) in the aldol reaction of ketones **105a – c** with aldehydes **106a**,**b**. Moreover, proline is not 'washed away' from the polymer under the studied conditions, which allows using this catalytic system at least six times without decrease in the yields and *ee* values of the products.

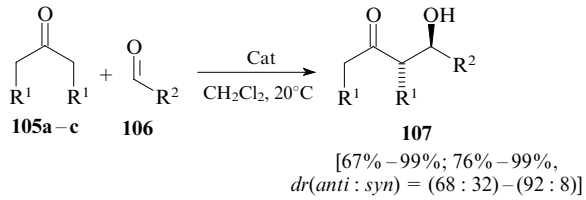


R = H; R – R = $(CH_2)_2$, $(CH_2)_3$;
X = 3-NO_2, 4-NO_2, 2-Cl, 4-Cl, 4-CO_2Me, 4-CHO;



The immobilization of proline **1** on a polyelectrolyte can change the diastereomeric composition of the resulting aldols **107**. Thus the major product formed in the reaction of cyclopentanone (**105c**) with 4-nitrobenzaldehyde (**106b**) in DMSO catalyzed by compound **1** is aldol *anti*-**107c**;[71] however, in the presence of system **212**, diastereomer *syn*-**107c** predominates.

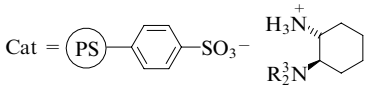
A similar approach has been used by Chinese researchers to immobilize *trans*-(1*R*,2*R*)-diaminocyclohexane derivatives on sulfopolystyrene. The catalytic systems **213a – c** can be regenerated and used six times; the enantioselectivity remains the same and the yield of products **107** decreases only slightly.[180]



105a–c **106** **107**

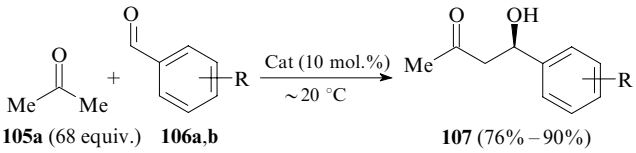
[67%–99%; 76%–99%, *dr*(*anti* : *syn*) = (68 : 32)–(92 : 8)]

R^1 = H, R^1–R^1 = $(CH_2)_2$, $(CH_2)_3$; R^2 = XC_6H_4 (X = H, 3-NO_2, 4-NO_2, 2-NO_2, 2-Cl, 4-CN, 4-Cl, 4-Br, 4-CF_3), 1-naphthyl;

Cat =  [R^3 = Me (**a**), Et (**b**), Pr^i (**c**)].

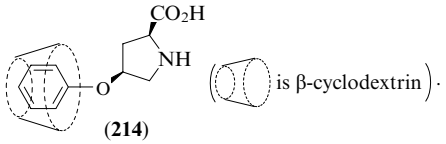
(**213a–c**)

An interesting example of non-covalent immobilization of organocatalysts is their incorporation into the β-cyclodextrin cavity. According to ^{13}C NMR spectroscopy, *cis*-4-phenoxy-(*S*)-proline (*cis*-**23a**) forms inclusion compound **214** with β-cyclodextrin, which behaves as a heterogeneous catalyst of the aldol reaction of acetone **105a** (68 equiv.) with aromatic aldehydes **106a**,**b**. The corresponding aldols **107** were obtained in high yields and highly enantioselectively (*ee* 71%–83%), which was not lost upon four reaction cycles with this catalyst.[343]



105a (68 equiv.) **106a**,**b** **107** (76%–90%)

R = 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl;



(**214**)

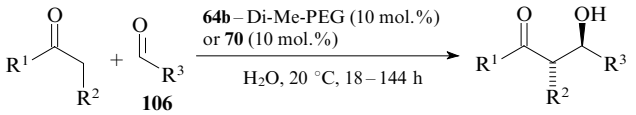
The known methods for non-covalent immobilization of organocatalysts on polymeric supports are experimentally facile and, as a rule, do not require expensive reagents. A drawback of the heterogeneous associates thus formed is, however, the tendency for washing away of the catalytically active molecules by highly polar solvents, which decreases the scope of application and the operation period of the catalysts.

2. Reactions in the presence of catalysts covalently bound to polymers or anchored to ionic liquids

A more frequently used method for the preparation of recoverable organocatalysts is based on their covalent binding to a polymer or an ionic liquid. This modification results in chemically stable catalysts, which are readily separated from the reactants and products without losing their catalytic properties. Attachment to an amino acid through a bifunctional spacer involves usually an additional chemically reactive (for example, hydroxyl) group to be bound to this group or a carboxyl group. The amino group of the catalyst remains free and forms chiral enamine intermediates of the aldol reaction. Most of this type of the modified organocatalysts obtained by now are proline derivatives.

a. Organocatalysts immobilized on polystyrene

Polystyrene derivatives, in particular, the Merrifield resins containing chemically reactive substituents, for example, halogen atoms or aminomethyl groups, in monomer units are used most often for immobilization of organocatalysts. Pericás and co-workers synthesized polystyrene-immobilized isomeric derivatives of proline **64b**[223] and **70**[239] in which the role of a spacer group is played by disubstituted 1,2,3-triazole formed in a 'click' reaction. These compounds showed good catalytic properties in the reactions of aldehydes with ketones in aqueous medium. With compound **64b** as the catalyst, the reaction was carried out in a two-phase system in the presence of dimethyl polyethylene glycol (DiMePEG), which served as the phase transfer catalyst. When compound **70** swellable in water served as the catalyst, the reaction occurred in the resulting gel. The highest yields of aldols **107** and diastereo- [*dr*(*anti* : *syn*) = (90 : 10)–(98 : 2)] and enantioselectivities (*ee* 93%–97%) were attained in the reactions of cycloalkanones **105b**,**c** with aromatic aldehydes **106a**,**b**. Compound **70** catalyzed also the aldol dimerization of propanal (**106s**) with *ee* 96%–97%, which markedly exceeded the enantioselectivity attained in the presence of prolinamide **5** (78%).[344] Acetone (**105a**) and hydroxyacetone (**108a**) also reacted with aldehydes under these conditions; however, the selectivity was lower (*ee* 45%–59%). Catalysts **64b** and **70** are easily regenerated and can be recycled more than five times.

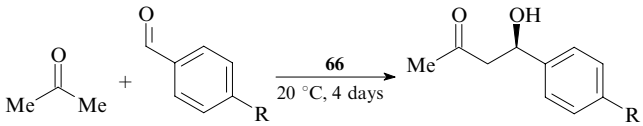


105a–c, **106s**, **108a** **106**

107 [24%–97%, *ee* 45%–97%, *dr*(*anti* : *syn*) = (1 : 1)–(98 : 2)]

R^1–R^2 = $(CH_2)_3$, $(CH_2)_4$; R^1 = Me, R^2 = H, OH;
R^1 = H, R^2 = Me; R^3 = XC_6H_4 (X = H, 4-NO_2, 4-Br, 4-CF_3, 4-OMe, 2-Cl), 2-naphthyl, 2-furyl, Et.

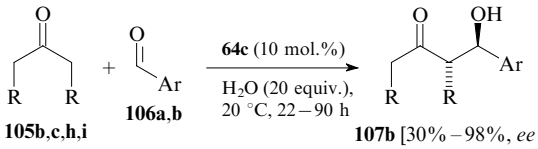
The activity and selectivity of the organocatalysts immobilized on polystyrene resins can be increased by introducing branching. Thus in the presence of catalyst **66** in which the amino acid is linked to the polymer through the triazole linker and a branched polyphenol fragment, the enantiomeric purity of products **107** formed in the reactions of acetone (**105a**) with aromatic aldehydes **106a**,**b** reaches 85%. However, the catalyst **66** loses activity after regeneration.[234, 345]



105a **106a**,**b** **107** (52%–95%, *ee* 68%–85%)

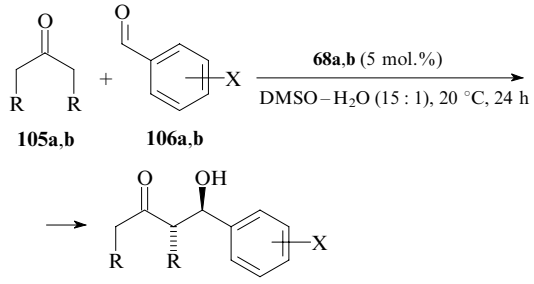
R = H, NO_2.

The synthesis of 4-hydroxyproline derivative **64c** grafted to the hydrophobic polystyrene Merrifield resin has been described.[224, 346] This is able to catalyze the aldol reaction of cyclic ketones **105b**,**c**,**h**,**i** with aromatic aldehydes **106a**,**b** in aqueous medium. The aldol addition products **107b** are formed under these conditions with high *anti*-diastereo- and enantioselectivities. Catalyst **64c** retains the selectivity for five reaction cycles. In the absence of water, the reaction does not take place.



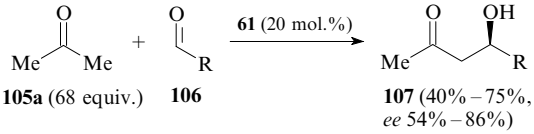
R–R = $(CH_2)_2$, $(CH_2)_3$, CH_2OCH_2, CH_2SCH_2;
Ar = XC_6H_4 (X = H, 2-Cl, 3-Cl, 4-Cl, 4-Br, 3-NO_2, 4-NO_2, 4-CN, 4-CF_3), C_6F_5, 2-naphthyl, 2-furyl.

cis-4-Amino-(*S*)-proline derivatives **68a**,**b** grafted to polystyrene through succinic and adipic acid linkers also proved to be effective recoverable organocatalysts of aldol reaction carried out in wet DMF. The use of 5 mol.% of the catalysts gave aldols in high yields and with excellent *anti*-diastereo- [up to *dr*(*anti* : *syn*) = 96 : 4] and enantioselectivities (up to *ee* 96%).[236] Catalysts **68a**,**b** regenerated by precipitation with Et_2O from the reaction mixture were recycled five more times without loss of the catalytic activity.



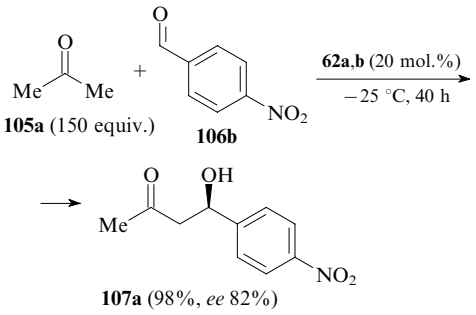
R–R = $(CH_2)_2$, $(CH_2)_3$; R = H;
X = 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl, 4-Cl, 3-Br.

Proline derivatives can be immobilized on polystyrene not only through position 4 of the pyrrolidine ring, but also through the carboxyl group of the amino acid. Thus the reaction of 4-methylbenzhydrylamine–polystyrene resin with proline yielded amide **61**, which was used as the catalyst of the aldol reaction of acetone (**105a**) with aliphatic aldehydes **106**. Aldols **107** are formed in high yields and with high enantiomeric purity; however, regeneration deteriorates the catalyst.[218]

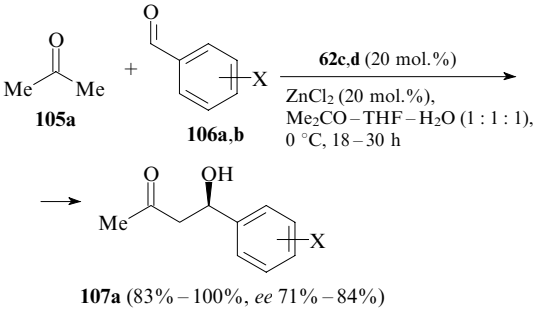


R = Pr^n, Pr^i, Bu^n, Bu^i, Bu^t, n-C_7H_{15}.

British researchers synthesized proline-containing di- and tripeptides immobilized on styrene–ethylene glycol copolymer with terminal amino groups (NovaSyn TG) and studied them as heterogeneous catalysts of the aldol reaction of acetone with 4-nitrobenzaldehyde.[219] In the presence of dipeptides **62a**,**b** containing serine or threonine, aldol **107a** is formed in nearly quantitative yield with high enantiomeric purity. Unfortunately, the possibility of regeneration of the heterogeneous catalysts was not mentioned.[219]

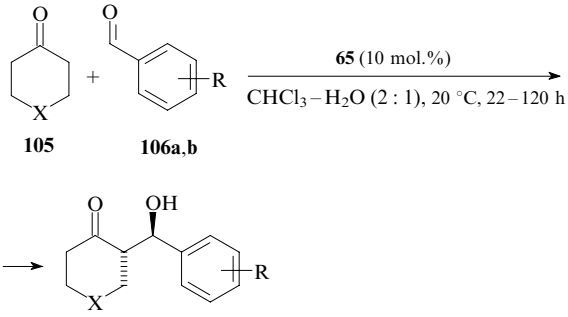


Tripeptide **62d** containing an N-terminal proline residue immobilized on polystyrene–poly(ethylene glycol) copolymer also efficiently catalyzes the aldol reaction of acetone (**105a**) with electron-deficient aromatic aldehydes **106a**,**b**.[220] The highest yields and *ee* values of products **107** are attained when the reaction is carried out in the acetone–water–THF system (1 : 1 : 1) in the presence of $ZnCl_2$. The catalysts obtained withstand at least five regeneration cycles.



X = 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 4-Cl.

Polystyrene-immobilized (*S*)-prolinamide **65** was obtained from chiral β-amino alcohol, [(2*S*)-2-amino-1,1,2-triphenylethanol]. Heterogeneous catalyst **65** ensures high activity and selectivity of the aldol reaction of cyclic ketones **105** with aromatic aldehydes **106a**,**b** in a chloroform–water heterogeneous system. When anhydrous media are used, as in the case of catalyst **64c**, the efficiency of the process is lower. Catalyst **65** retains its activity and selectivity at least for 12 reaction cycles.[233]

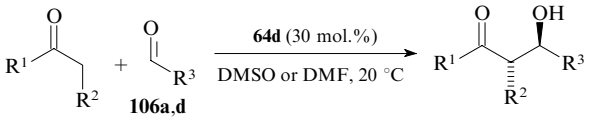


R = H, 3-NO_2, 4-OMe, 4-Me, 4-CN, 4-CF_3, 3-Cl, 4-NO_2;
X = CH_2, O, S, NBoc, CHMe.

b. Organocatalysts immobilized on other organic and inorganic polymers

Italian researchers synthesized immobilized forms of 4-hydroxyproline **64d**[225] and **64e**[226] on poly(ethylene gly-

col) by means of succinate spacer. The resulting organocatalysts were employ in intermolecular aldol reactions of ketones (acetone or hydroxyacetone) with aldehydes **106a**,**d** and in the intramolecular Robinson annulation. The yields and *ee* values of products **107a**,**f** and **109c** are comparable with those obtained in the reactions catalyzed by (*S*)-proline (**1**). Catalyst **64d** regenerated by precipitation with diethyl ether, the recovery was 70%–80%. It was repeatedly used in the reactions with equal enantioselectivity and only small loss of the catalytic activity.

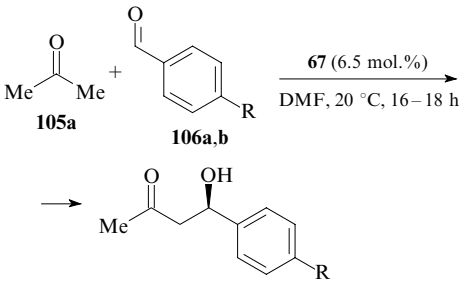


105a, **108a** **106a**,**d** **107a**,**f**, **109c**

[45%–77%, *ee* 59%–98%, *dr*(*anti* : *syn*) > (20 : 1)]

R^1 = Me, R^2 = H, OH; R^3 = 4-XC_6H_4 (X = H, Br, NO_2), cyclo-C_6H_{11}.

trans-4-Hydroxyproline was attached to commercially available 1,4-diaminobutane poly(propyleneimine) dendrimers with a glutaric acid linker.[235] Compound **67** based on second-generation that dendrimer contained eight free amino groups at the periphery of the molecule has moderate activity and enantioselectivity in the aldol reaction of acetone **105a** with aromatic aldehydes **106a**,**b** in DMF comparable to the activity and selectivity of proline. However, the load of catalyst **67**, which corresponds to 50 mol.% with respect to the proline constituent, exceeds that of (*S*)-proline (**1**) under comparable conditions (20 mol.%). In addition, the possibility of regeneration of catalyst **67**, which is readily soluble in the reaction medium, is not obvious.

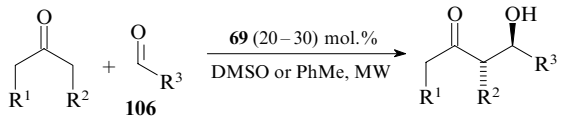


105a **106a**,**b**

107a (61%–78%, *ee* 64%–67%)

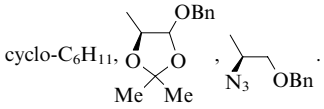
R = NO_2, Br, Cl.

cis-4-Aminoproline was immobilized on a mesoporous silicate support MSM-41 using 3-(triethoxysilyl)propyl isocyanate. In the presence of heterogeneous catalyst **69**, α-hydroxyacetone (**108a**)[237] and protected form of dihydroxyacetone **113a**[238] react with aromatic and aliphatic (including functionally substituted) aldehydes **106** in DMSO or toluene, in particular, under microwave (MW) irradiation to give aldols **109** and **114** in moderate yields and with high diastereo- and enantioselectivities (up to *ee* 99%). In some cases, the diastereoselectivity was inverted compared to analogous reactions catalyzed by (*S*)-proline (**1**) under homogeneous conditions, which is caused by the effect of the solid support. Catalyst **69** was used three times without loss of the activity or selectivity.



108a, **113a** (27 equiv.) **106** **109**, **114** (30%–72%, *ee* 70%–99%)

R^1 = H, R^2 = OH, R^1–R^2 = $OCMe_2O$; R^3 = 4-$NO_2C_6H_4$, Pr^i,

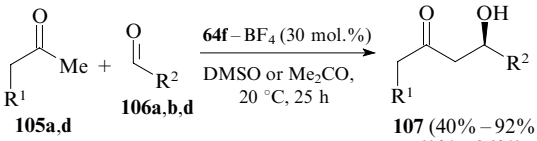


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c. Organocatalysts modified by ionic groups

Recently it was reported that organocatalysts incorporating fragments of salts of nitrogen bases with fluorine-containing anions, including those that belong to the class of ionic liquids, have been synthesized and used in aldol reactions. The ionic catalysts can be readily separated from the reactants and products due to the different solubility in organic solvents. By varying the structures of the cation and the anion, one can change deliberately the catalyst solubility in different types of solvents and thus to select the optimal phase composition of the catalytic system. Furthermore, the use of ionic modifying groups usually results in higher capacity (the content of catalytically active fragments per unit weight) of the catalyst compared to the analogues immobilized on polymeric supports.

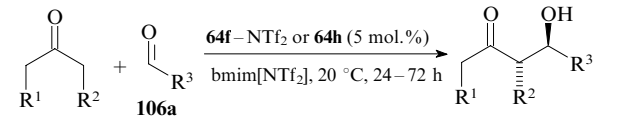
Researchers of the Montreal University[227] obtained (*S*)-*trans*-4-hydroxyproline derivative **64f** ($An^- = BF_4^-$) containing a side-chain methylimidazolium group. Compound **64f**–BF_4 was used as an organocatalyst in the aldol reactions of alkanones **105a**,**d** with aldehydes **106a**,**b**,**d** carried out in excess ketone or DMSO. The yields and the *ee* values of aldols **107** were somewhat higher than those in the reactions induced by (*S*)-proline or PEG-immobilized catalyst **64e**.[226] It was assumed[227] that the 1,3-dialkylimidazolium cation promotes the aldol reaction being a weak Lewis acid. Catalyst **64f**–BF_4 easily be separated from the reaction mixture and recycled four times without considerable decrease in the aldol yield and *ee*.



105a,**d** **106a**,**b**,**d** **107** (40%–92%, *ee* 60%–86%)

R^1 = H, Me; R^2 = XC_6H_4 (X = H, 4-CN, 4-NHAc, 4-Br, 4-NO_2, 2-Cl), 2-naphthyl, cyclo-C_6H_{11}.

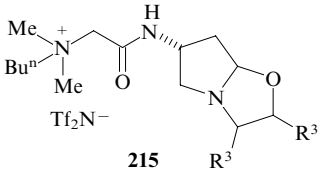
4-Hydroxyproline derivatives modified by ionic groups **64f**–NTf_2 and **64h** were used as catalysts of the aldol reaction of aldehydes with ketones in an ionic liquid, 1-butyl-3-methylimidazolium bis(triflyl)imide (bmim[NTf_2]).[228] This combination made it possible to decrease the catalyst load to 5 mol.% and increase the reaction rates and selectivities compared to the same reactions carried out in organic solvents.



105a,**b**, **108a**, **113a** (10 equiv.) + **106a** → **107**, **109**, **114** [35% – 78%, *ee* 75% – 94%, *dr*(*anti* : *syn*) = (67 : 33) – (85 : 15)]

$R^1 = R^2 = H$; $R^1 – R^2 = (CH_2)_3$, $OCMe_2O$; $R^1 = H$, $R^2 = OH$; $R^3 = XC_6H_4$ (X = H, 4-NO_2, 4-Cl), 2-naphthyl.

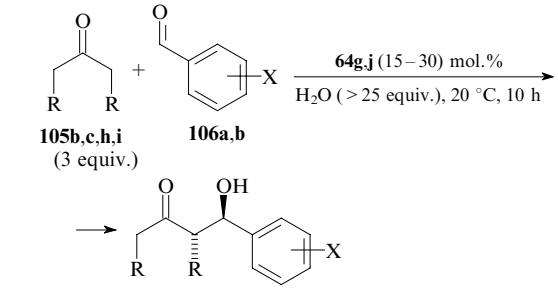
However, after regeneration, the **64h** – bmim[NTf_2] system lost the activity, which may be attributed to washing away of catalyst **64h** by the solvent during extraction of the aldol and/or to its transformation to oxazolidine **215** upon side reaction with aldehyde **106** in the ionic medium.



215

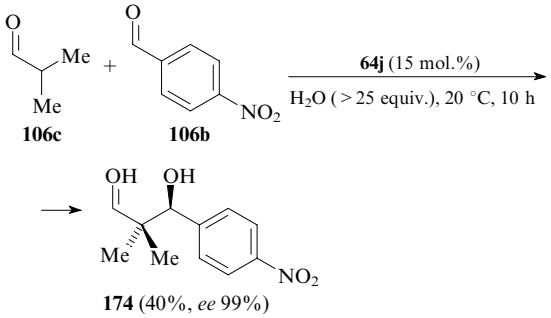
The latter suggestion is supported by the fact that the turnover number value characterizing the productivity of catalyst **64f** – NTf_2 (Ref. 347) and its isomer *cis*-**64f** – NTf_2 (Ref. 348) in the reaction of cyclohexane (**105b**) with 4-nitrobenzaldehyde (**106b**) increases from 17 to 930 when the reaction is carried out in excess ketone in the presence of a minor (1 – 2 equiv.) amount of water, which suppresses the side process.[349] For effective reaction to occur, it is sufficient to use 0.1 mol.% of catalyst *cis*-**64f** – NTf_2, which can be reused three times without decrease in the yield and *ee* of aldol **107b**.

We found that the operation period of amino acid catalysts anchored to ionic liquids in reactions in an aqueous medium can be extended with retention of, or even some increase in, the diastereo- and enantioselectivities of the aldol reactions by introducing long-chain alkyl groups. Indeed, amphiphilic proline-containing imidazolium **64g**[229] and pyridinium **64j**[240] salts are quite effective and selective catalysts of aldol reactions of cyclic ketones **105b**,**c**,**h**,**i** (3 equiv.) with aromatic aldehydes **106a**,**b** in water (≥25 equiv. H_2O). Branched aliphatic aldehydes, for example, compound **106c** can also be used as donors under these conditions.



105b,**c**,**h**,**i** (3 equiv.) + **106a**,**b** → **107** [40% – 97%, *ee* 92% – > 99%, *dr*(*anti* : *syn*) = (80 : 20) – (98 : 2)]

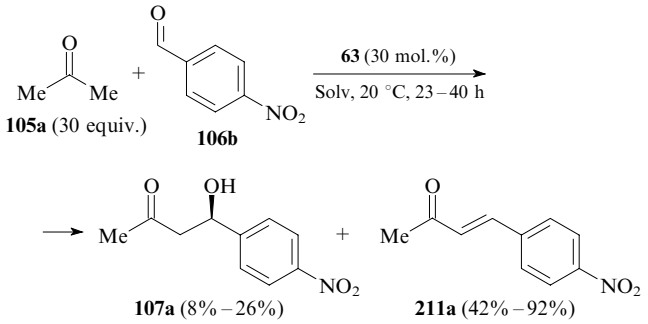
R – R = $(CH_2)_2$, $(CH_2)_3$, CH_2OCH_2, CH_2SCH_2; X = H, 4-NO_2, 4-CN, 4-CO_2Me, 4-OMe, 3-OPh.



106c + **106b** → **174** (40%, *ee* 99%)

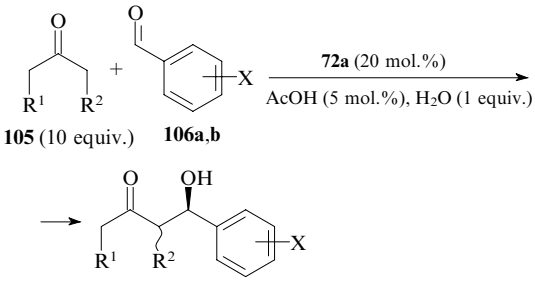
Apparently, catalysts **64g**,**j** containing a lipophilic alkyl group apart from the hydrophilic ionic fragments occupy the water – organic solvent interface during the reaction, and the catalytic transformation takes place at the interface. Compound **64g** retained the catalytic properties over at least five reaction cycles and compound **64j** was active for at least eight cycles. These cyclic ketones react with aromatic aldehydes **106a**,**b** also in the presence of immobilized serine and threonine derivatives **71a**,**b** (see Section IV.3); however, characteristics of the conversion (84% – 89%) and the diastereo- [*dr*(*anti* : *syn*) = (87 : 13) – (90 : 10)] and enantioselectivities (*ee* 91% – 97%) are somewhat lower.[240]

The use of proline and pyrrolidine derivatives modified by ionic fragments at position 2 of the heterocycle to catalyze the aldol reaction usually provides less impressive results. Thus in the presence of prolinamide **63** containing a cationic fragment in the amide group, the reaction of acetone (**105a**) with 4-nitrobenzaldehyde (**106b**) results mainly in enone **211a**. The regenerated catalyst **63** was recycled seven times.[221]



105a (30 equiv.) + **106b** → **107a** (8% – 26%) + **211a** (42% – 92%)

Chinese researchers synthesized a series of chiral pyrrolidine derivatives containing fragments of imidazolium salts and tested them in the aldol reaction between ketones **105** and aldehydes **106**, which was carried out in excess ketone. Among these catalysts, compound **72a** (20 mol.%) combined with AcOH (5 mol.%) was found to be most effective; the reaction was carried out in the presence of a small amount of water (1 equiv.).[241]



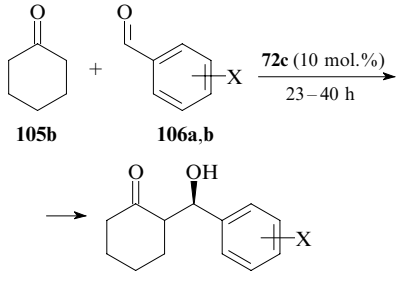
105 (10 equiv.) + **106a**,**b** → **107** [0% – 99%, *dr*(*anti* : *syn*) = (1 : 5) – (1.3 : 1.0)]

R^1 = H: R^2 = H, Me, Bu^n, OBn; $R^1 = R^2$ = H, Me; $R^1 – R^2 = (CH_2)_n$ (*n* = 2 – 5); X = 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 2-Br, 4-OH, 4-Ph.

The diastereo- [*dr*(*anti* : *syn*) = (1 : 5) – (1.3 : 1.0)] and enantioselectivity values (*ee* 5% – 63%) for these transformations were relatively low, which was attributed[241] to the

influence of the imidazolium cation. As with amide **63**, a considerable amount of α,β-enones **211** is formed in addition to aldols **107**. However, catalyst **72a** demonstrated high stability under reaction conditions and was reused six times with insignificant decrease in the activity.

The diastereo- and enantioselectivities of the reactions of cyclohexanone (**105b**) with aromatic aldehydes **106a**,**b** can be increased by using catalyst **72c** containing the phthalate anion as the counter-ion.[242]



107b [66% – 94%, *ee* (*anti*) 50% – 65%, *dr*(*anti* : *syn*) = (60 : 40) – (70 : 30)]

X = 2-NO_2, 3-NO_2, 4-NO_2, 4-CN.

VIII. Conclusion

This review demonstrates that asymmetric organic catalysis, in particular the catalysis of aldol reaction frequently encountered in nature and widely used in the syntheses, is a new promising and vigorously developing area of research in modern organic chemistry. Under the action of organocatalysts, it is possible to synthesize complex chiral organic compounds with high enantiomeric purity from readily accessible achiral precursors under simple experimental conditions. The organocatalytic aldol reaction can be performed for diverse carbonyl compounds, including functionally substituted ones, and activated carboxylic acid derivatives able to form enamine intermediates with the catalysts containing amino groups. The carbonyl groups involved in the reaction can belong to either one molecule (intramolecular reactions) and molecules of different compounds (intermolecular reactions). In some cases, organocatalytic aldol reactions are integrated in a series of tandem transformations taking place in the presence of the same catalyst. The variation of the nature of the organocatalyst allows one to control the reaction rates and regioselectivities, thus providing the formation of aldols of the desired structure. Immobilized organocatalysts can find use in new environmentally safe industrial chemical processes that meet the requirements of 'green chemistry'.

The material covered in this review mainly deals with reactants and organocatalysts used in the asymmetric aldol reactions. Highly important aspects concerning the role of the medium and reaction conditions and its application for the synthesis of natural and synthetic biologically active compounds are almost not addressed. We plan to consider these aspects in a separate review. In addition, the papers published during the preparation of the manuscript for publication have remained beyond the scope of Sections I – VII; these include an excellent review[350] devoted to the achievements of organocatalysis, papers that describe the mechanistic features of proline-catalyzed intramolecular aldol reactions,[351] the use of novel types of natural[352] and synthetic,[353] in particular, immobilized[354] organocatalysts, the organocatalytic synthesis of chiral 4-hydroxybenzothiopyrans[355] and some other.

Nevertheless, we hope that the performed analysis of organocatalytic asymmetric aldol reactions will be of interest for specialists in the field of organic synthesis and catalysis, the chemistry of natural products and 'green chemistry' and will stimulate the development of this fascinating and challenging trend of research.

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