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Enantioselective direct aldol reaction: the blossoming of modern organocatalysis

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Abstract—The use of simple (*S*)-proline as catalyst for the intermolecular direct aldol reaction at the beginning of this century became a true milestone in the growth of organocatalysis as a useful synthetic strategy. Since then, a plethora of new organocatalytic systems have been developed allowing to reach extraordinary levels of efficiencies, widening the scope of substrates used. Several modifications have been introduced to overcome some of the initial drawbacks, such as long reaction times, high catalyst loading, excess of reagents, etc., improving the expectations for their use in large scale synthesis. All these achievements would not be possible without a partial understanding of the involved mechanism. The acquired knowledge in this area has allowed the application of this strategy to be used in the synthesis of natural products. Within this review, a comprehensive look of all these aspects will be discussed.

Contents

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1. Introduction

The aldol reaction[1,2] is one of the most venerable reactions in organic chemistry, firstly discovered by Wurtz in 1872,[1b] although Kane previously described the prevently known aldol condensation.[1a] This useful transformation allows the formation of a C–C bond by reaction of an enolizable carbonyl compound acting as a source of nucleophile with itself or another carbonyl compound acting as an electrophile to give a β-hydroxy carbonyl compound known as aldol. When the aldol product suffers a subsequent dehydration step to give the related α,β-unsaturated carbonyl compound, the process is called aldol condensation. The reaction could be catalyzed by either basic or acidic compounds. Besides the new C–C bond formed, one or more stereogenic centers can also be created. For this reason, this transformation has been chosen historically as a chemical-test to prove the efficiency of new methodology, especially asymmetric ones.[3] Although diastereoselective approaches make the synthesis of all possible stereoisomers possible, the additional steps required to introduce and remove the chiral auxiliaries suppose a great disadvantage for this strategy.[4]

Without any doubt, catalytic enantioselective methods are the most attractive alternative for providing chiral compounds with high selectivity and atom efficiency.[5] Biochemical methods based on the use of aldolase enzymes[6] and antibodies[7] have shown their usefulness to perform this task, with the scope of substrates being very narrow. In search of a wider substrate scope, different enantioselective chemical methods have been extensively developed in recent years, especially after the introduction of the Mukaiyama-aldol version of this reaction.[8] In this case, the generation of a silyl enol ether (or chemical equivalent) is compulsory, requiring the use of stoichiometric amounts of bases and silylating reagents and therefore having low atom efficiencies. In order to enhance the global efficiency of the process, an effort has been made to develop enantioselective direct aldol reactions,[9] where the use of performed enolates (or their equivalents) is avoided.

A remarkable success has been achieved on the substrate scope and reaction selectivities by the use of so-called enantioselective organocatalytic direct aldol processes. The adjective organocatalytic is applied to processes in which reagents and catalysts are all small organic molecules containing only C, H, O, N, S, P, and halogen atoms.[10] Therefore, processes in which a metal (including boron and silicon atom) is involved should be excluded in strict sense. Furthermore, those processes involving high molecular weight organic compounds such as enzymes, antibodies, even polymers, and dendrimers, should be excluded. Although according to the above strict definition, reactions involving silicon atoms, polymers, and inorganic materials should be excluded. We considered that processes where the silyl group has only a steric role (or increase the solubility) should be included as well as cases in which the catalyst is immobilized in a polymer, dendrimer, or inorganic material, since in these cases the matrix does not play any relevant role in the reaction, and is only important in the recovery of catalysts.

The enantioselective organocatalytic aldol reaction has been profusely revised.[11] However, many of these reviews are strongly focused on proline as catalyst as well as on the author's results, but none of them focused on a comprehensive list of catalysts and results, as well as conditions,

while in only a few of them are new data and perspectives on the field given. With this review, we would like to fill this gap, giving a comprehensive overview of the catalyst, providing an easy way for comparison between different catalysts, protocols and results, as well as the possible drawbacks of this methodology. All these facts would allow us to find the best choice for a given problem, as well as to discover new niches and possibilities that are currently unexplored. The final aim of this review will be to reach these goals.

2. Proline as organocatalyst

(*S*)-Proline **1**, known as the simplest enzyme,[11d] is a cornerstone in the field of organocatalysis due to the fact that it has been used as a catalyst in a wide range of asymmetric reactions with excellent results in many cases, its high efficiency being clearly demonstrated in the enantioselective direct aldol reaction.

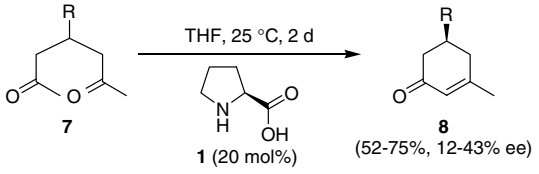
2.1. Intramolecular reactions

The use of proline in the enantioselective intramolecular aldol reaction (Robinson-type annulation) was a crucial event in the history of organocatalytic processes,[12] with it being one of the first examples where the potential of enantioselective reactions for the synthesis of natural products, even at large scale was demonstrated.[13] The 6-(enolendo)-*exo*-trig[14] Robinson annulation (Table 1)[15] was independently discovered by two industrial groups at Schering[12a] and at Hoffmann-La Roche[12b] almost simultaneously. The differences between both procedures relied on the use of perchloric acid as a co-catalyst, which led to the final compound **4**, by an in situ dehydration of product **3**. Under these conditions[15a] (presence of $HClO_4$), the corresponding indanone derivative **4** ($n = 1$, R = Me) could be isolated with a better yield and enantioselectivity than the related naphthalendione **4** ($n = 2$, R = Me; compare entries 1 and 2 in Table 1). The yield could be improved upon by using stoichiometric amounts of catalyst **1** at 20 °C.[15b] However, the absence of an inorganic acid permitted the isolation of alcohol **3** (entry 3 in Table 1). The use of other solvents allowed a decrease the amount of catalyst **1**, isolating the α,β-unsaturated ketone **4** or alcohol **3** depending on nature of solvent, isopropanol or DMF, respectively (entries 4 and 5 in Table 1). The change of the substituent R in **2** did not have any important impact on the enantioselectivity, but did decrease the isolated chemical yield of compound **3**.[15e] The low enantiomeric excess could be enhanced up to >99% by recrystallization of the corresponding *tert*-butyl ether obtained by reduction of non-conjugated carbonyl group in compound **4** and alkylation (entries 6 and 7 in Table 1).[15f]

The long reaction time required for this intramolecular aldol process could be decreased by employing microwave heating (114 W) in conjunction with simultaneous air-cooling at 35 °C,[16] affording the corresponding napthhalenedione **4** ($n = 2$, R = Me) with similar results but in only 15 min (69%, 70% ee).

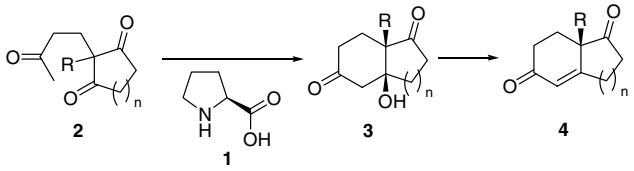
Instead of using the triketone derivative **2** as the starting reagent, methyl vinyl ketone **5** and methylcyclohexane-1,3-dione **6a** could be used. In this case, proline first catalyzes the Michael-type addition and then the aforementioned annulation process obtaining the expected compound **4b** (R = Me, $n = 1$) in 49% yield and 76% ee (compare with entry 2 in Table 1).[17]

This 6-(enolendo)-*exo*-trig process has been expanded to the enantioselective desymmetrization of simple acyclic diketones **7** (Scheme 1).[18] The results were highly dependent upon the bulkiness of the R group, with the best results being obtained for the smallest methyl group.



Scheme 1.

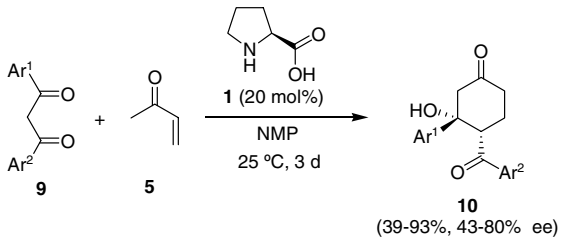
Table 1. Robinson-type annulation



Entry	R	*n*	**1** (mol %)	Reaction conditions	Yield (%)	ee (%)
1	Me	1	50	MeCN, 1 d, 80 °C, $HClO_4$	84	84
2	Me	2	50	MeCN, 1 d, 80 °C, $HClO_4$	71	72
3	Me	1	100	MeCN, 6 d, 20 °C	97[a]	86
4	Me	1	10	Pr^{i}OH, 4 d, 20 °C	75	61
5	Me	1	3	DMF, 1 h, 20 °C	100[a]	93
6	SPh	1	5	DMF, 6 d, 17 °C	64[a]	95
7	SPh	2	5	DMF, 6 d, 17 °C	27[a]	95

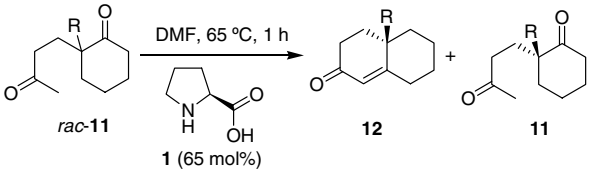
[a] Compound **3** was isolated.

The preparation of highly substituted hydroxycyclohexanones **10** seems to be more successful with regards to the enantioselectivity (Scheme 2).[19] The reaction of different 1,3-diketones **9** with methyl vinyl ketone **5** in *N*-methyl-2-pyrrolidone (NMP) at room temperature gave cylohexanone derivatives **10** with moderate enantioselectivities and as only one diastereoisomer. The tandem process[20] involves an initial Michael-type addition to form the corresponding triketone intermediate, which finally suffers the 6-(enolendo)-*exo*-trig annulation. The chemical yields are affected by the substituents on the aromatic ring of compound **9**, the more the electron-withdrawing character of the substituent the higher the yields obtained. In the case of using unsymmetrical substituted compounds **9** high regioselectivity was found, with the more electrophilic carbonyl group being the electrophilic partner in the cyclization.



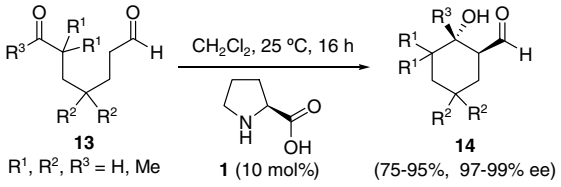
Scheme 2.

As an extension of this annulation process, (*S*)-proline **1** has been used to perform the kinetic resolution of different racemic diketones. So, the reaction of racemic α,α-disubstituted cyclohexanone **11** (R = Me) gave the cyclic product **12** with 43% ee and the chiral starting diketone **11** (ee not determined). However, when the reaction was performed with the related α-monosubstituted cyclohexanone **11** (R = H) under similar reaction conditions and at 50% conversion, product **12** (R = H) was obtained with 46% ee but with the opposite configuration at the stereogenic center. Similar results were obtained in the case of β-monosubstituted cyclohexanone derivatives[21] (Scheme 3).



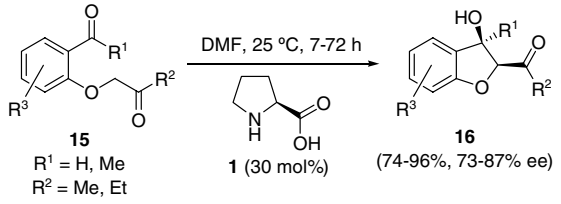
Scheme 3.

According to Baldwin's rules not only 6-(enolendo)-*exo*-trig but also 6-(enolexo)-*exo*-trig processes are permitted. These last cyclization processes have only recently been reported. The intramolecular reaction of compound **13** gave product **14** with moderate to excellent diastereoselectivities (50→98% de) and excellent enantioselectivities, with the absolute configurations being assigned from the specific rotations of known compounds (Scheme 4).[22] The presence of two substitutents on the starting aldehyde **13** was decisive in reaching these results, since the presence of only a single substituent at any position on the chain showed a very important detrimental effect, not only on the diastereoselectivity, but also on the enantioselectivity.



Scheme 4.

The above methodology has also been successfully applied to a 5-(enolexo)-*exo*-trig process (Scheme 5). Thus, the proline-catalyzed reaction of compound **15** gave the cyclic derivative **16** with a diastereomeric excess ranging from 71% to 99%.[23] While the substituent on the aromatic ring had a negligible effect, the R^2-substituent had a very important effect, with the increase of hindrance from methyl to ethyl group providing lower yields and enantioselectivities. It should be pointed out that recrystallization increased the diastereomeric and enantiomeric excesses up to 99%.



Scheme 5.

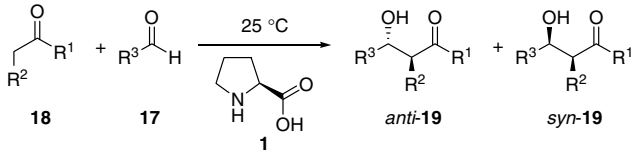
2.2. Intermolecular reactions

Without doubt, the successful use of (*S*)-proline **1** as a catalyst in the intermolecular direct aldol reaction was a high point in the explosion of organocatalysis as a new different research field. This section will be divided according to the combination of the possible nature of the nucleophilic and electrophilic partner used.

2.2.1. Ketones as source of nucleophile

2.2.1.1. Aldehydes as electrophiles. Inspired by the action of class I aldolases, proline was tested in the aldol reaction between ketones **18** and aldehydes **17**, especially α-substituted ones, affording compounds **19** (Table 2), which proved to be excellent catalysts.[24] A large excess of ketone **18** was employed in all of these reactions in order to prevent several side reactions such as self-condensation of the aldehyde, or the formation of the oxazolidinone derived from proline and the aldehyde.

Table 2. Enantioselective aldol reaction catalyzed by proline **1** using ketones as a source of nucleophile



Entry	R^1	R^2	R^3	**18** (equiv)	**1** (mol %)	Reaction conditions	Yield (%)	de (%)	ee[a] (%)
1	Me	H	4-$O_2NC_6H_4$	27.3	30	DMSO/Me_2CO (4:1, v:v), 4 h	68	—	76
2	Me	H	Pr^i	27.3	30	DMSO/Me_2CO (4:1, v:v), 2–8 h	97	—	96
3	Me	H	$CH_3(CH_2)_5$	68.2	10	Me_2CO, 7 d	35[b]	—	73
4	–$(CH_2)_3$–		4-$O_2NC_6H_4$	22.6	20	DMSO/$(CH_2)_4CO$ (4:1, v:v), 1–2 d	73	63	69
5	–$(CH_2)_4$–		4-$O_2NC_6H_4$	19.3	20	DMSO/$(CH_2)_5CO$ (4:1, v:v), 1–2 d	65	63	86
6	Et	H	4-$O_2NC_6H_4$	22.3	20	DMSO/EtCOMe (4:1, v:v), 1–2 d	65	—	77

[a] For the major diastereoisomer.
[b] The corresponding enone was isolated in 40% yield.

Moreover, since the whole process is a series of equilibria, the high amount of one of the reagents drives the process. Notwithstanding this, when the reaction was performed using linear aldehydes, significant amounts of the side-product enone were obtained, arising from the aldol condensation process (entry 3 in Table 2). For the use of simple and volatile ketones, their use in a large amount is not an important problem, neither economical nor practical, but when more sophisticated ketones are employed, this large excess, which is required could be a severe drawback. The use of cyclic ketones such as cyclohexanone **18c** and cyclopentanone, as a source of nucleophile gave modest diastereoselectivities (ca. 60%) and similar enantioselectivities, with *anti*-isomer **19** being the main diastereoisomer (Table 2, entries 4 and 5). For butanone the reaction took place at the less substituted position. Other dialkyl ketones such as 3-pentanone, acetylcyclohexane, isopropylmethyl ketone, 3-methyl-2-butanone, and cyclopropylmethyl ketone were not reactive toward the aldol reaction with *p*-nitrobenzaldehyde under the aforementioned reaction conditions.[24c]

Instead of using acetone **18a** 4-methyl-4-hydroxy-2-pentanone (diacetone alcohol) can be used as a source of the nucleophile.[25] The reaction of 2 equiv of this reagent with different aldehydes gave the expected compounds **19** ($R^2 = H$) with lower enantioselectivities (48–86% ee).

In order to increase the enantioselectivities achieved for the β-hydroxy ketones **19** ($R^2 = H$) a tandem organo- and biocatalytic process has been designed.[26] Thus, after the proline-catalyzed reaction, the resulting mixture was kinetically resolved by acylation catalyzed by *Pseudomonas cepacia* lipase (Amano I).

The scope of aldehydes as electrophiles has been further extended for these simple ketones. Aqueous formaldehyde was reacted with cyclic ketones catalyzed by **1** (10 mol %), to give the expected products with moderate yield (25–45%) and high enantioselectivity (95–99%) in only 1 h and using only 2 equiv of cyclic ketone.[27]

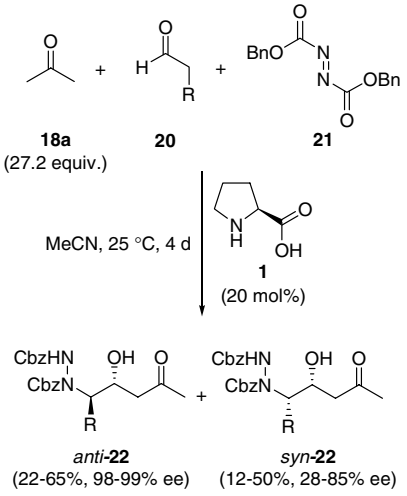
Remarkably, perfluoroalkyl aldehyde ethyl hemiacetals could be used as a source of the electrophile in the aforementioned reaction, allowing the synthesis of β-hydroxy-β-perfluoroalkyl ketones.[28] In this case, the ketone used as a source of the nucleophile was also the reaction solvent, providing the expected products **19** with good diastereoselectivities for cyclic ketones (88–98% de) and moderate to good enantioselectivities (37–93% ee).

The use of the more complex 1-(phenylsulfanyl)cycloalkane-carboxaldehydes as electrophiles in proline **1** (20 mol %) catalyzed aldol reaction with a large excess of aliphatic ketones in DMSO led to the corresponding aldol products **19** with yields ranging from 21% to 80% and excellent enantiomeric excesses (up to 99%). The chiral aldols obtained were further transformed into the corresponding *cis*-fused spirocyclic tetrahydrofurans and cyclopentanones, after carbonyl reduction and an acid-catalyzed cyclization process.[29]

The diastereoselective aldol reaction catalyzed by (*S*)-proline and different chiral aldehydes, such as protected sugars,[30a] protected α-aminoaldehydes,[30b] 4-formyl-2,2-dimethyloxazolidine (Garner's aldehyde),[30c] and 4-oxo-azetidine-2-carboxaldehydes[30d] have been used in order to prepare possible biologically active compounds.

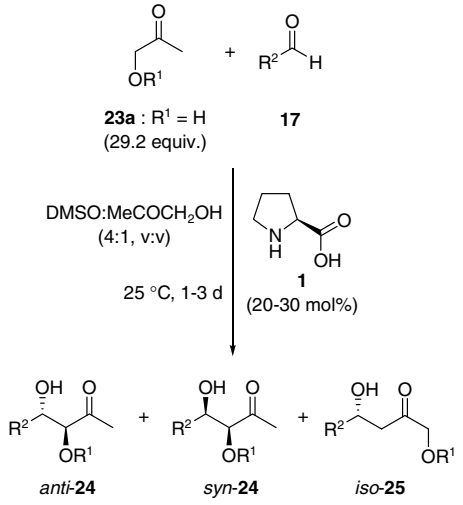
A multicomponent reaction[10u,31] between acetone **18a**, benzyl azodicarboxylate **21** and enolizable aldehydes **20** catalyzed by substoichiometric amounts of (*S*)-proline **1** yielded ca. 1:1 mixture of the corresponding diastereoisomers **22** (Scheme 6).[32] The success of the reaction can be attributed to the higher reactivity as a source of the nucleophile of aldehydes over acetone (about 100-fold) toward the azodicarboxylate under proline-catalyzed conditions. In this manner, an α-amino aldehyde derivative is created in situ, which is, in turn, the electrophilic partner for the further aldol reaction. The disappointing diastereomeric ratio was attributed to the easy and fast racemization of the initially formed α-amino aldehyde, compared to its reaction with acetone. This strategy has been used in the synthesis of a rennin inhibitor, despite the disappointing diastereoselectivity.

The use of α-functionalized ketones as a nucleophilic source has permitted access to chiral compounds of high



Scheme 6.

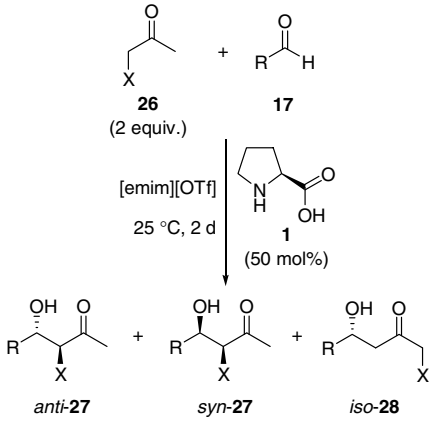
interest. Thus, the use of an excess of α-hydroxyacetone **23a** ($R^1 = H$) allows the synthesis of chiral diols (Scheme 7). Excellent regio-, diastereo-, and enantioselectivities (up to 99%) were obtained when α-substituted aliphatic aldehydes were used as electrophiles, with the *anti*-**24** isomer being the main/only isolated product. When aromatic, linear aliphatic aldehydes, and chiral (*R*)-glyceraldehyde derivatives were used the results were significantly lower, with diastereoselectivities ranging from 0% to 75% and enantiomeric excesses from 67% to 97%. The *iso*-isomer **25** was only detected when aromatic carboxaldehydes were used, although in low yields (ca. 4%). The use of (*R*)-2,3-*O*-(isopropylidene)glyceraldehyde gave *anti*-**24** compound as the main diastereoisomer (40%, 66% de, >97% ee), which is a known D-tagatose derivative.[24c,33]



Scheme 7.

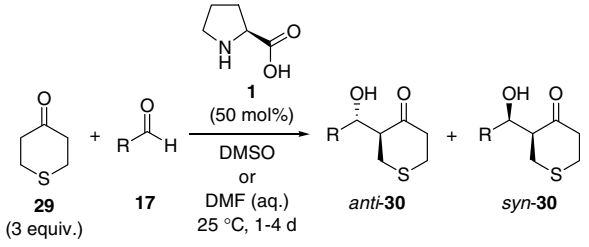
Following the same procedure and under the same reaction conditions, *tert*-butyl(dimethyl)silyloxy]acetone **23b** (R^1 = TBS) reacted with aromatic carboxaldehydes affording a product of type *anti*-**24** with enantioselectivities from 28% to 95%.[34] Surprisingly, when α-substituted-α,β-unsaturated aldehydes were used as electrophiles, the major product obtained was a compound of type *iso*-**25** with variable enantioselectivities (10–95% ee).

The use of an ionic liquid allows a reduction in the amount of ketones used. The reaction of α-hydroxyacetone **23a** ($R^1 = H$), as well as α-methoxyacetone **23c** ($R^1 = Me$) with *p*–(trifluoromethyl)benzaldehyde derivatives gave a mixture of three possible isomers of type **24** and **25** with mediocre diastereoselectivities (no enantioselectivities were reported) when 1-ethyl-3-methyl-1*H*-imidozolium trifluoromethane-sulfonate ([emim][OTf]) was used.[35] α-Fluoro and α-chloroacetone **26** were also used as a source of nucleophile (Scheme 8), giving a mixture of two isomers **27** (60% de). The mixture of isomers **27b** (X = Cl) could be easily transformed in the corresponding (3*R*,4*S*)-*trans*-epoxides by treatment with triethylamine with yields from 69% to 83% and enantioselectivities around 70%, with the related *cis*-epoxides not being detected.



Scheme 8.

Since the corresponding products **19** arising from the direct aldol reaction of 3-pentanone with aldehydes are not suitable for the proline-catalyzed reaction, an indirect alternative has been introduced. The reaction of tetrahydro-4*H*-thiopyran-4-one **29** with aldehydes gave the expected products **30** (Scheme 9). The reductive desulfurization using Raney nickel (W-2) gave the corresponding 5-hydroxy-4-methylpentanone derivatives, impossible to prepare by a direct pathway. As in the previous cases, the main diastereoisomer was the corresponding *anti*-**30** (up to 95% de) and the enantiomeric excess ranged from 76% to 98%.

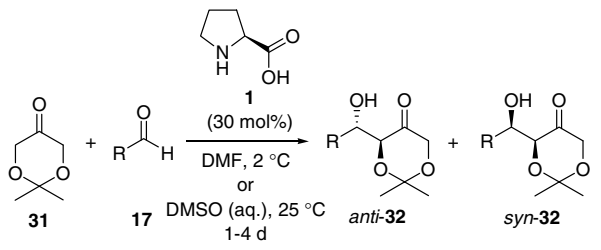


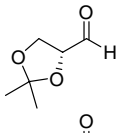
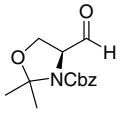
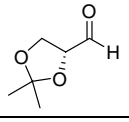
Scheme 9.

The best results for aromatic aldehydes were obtained in aqueous DMF, whereas dry DMSO was generally superior with aliphatic aldehydes.[36]

The proline-catalyzed aldol reaction between 2,2-dimethyl-1,3-dioxan-5-one **31** and aldehydes is an excellent approach to the enantioselective synthesis of carbohydrates, since compound **31** is a synthetic equivalent of dihydroxyacetone (Table 3). When the reaction was performed in DMF at 2 °C using only 1 equiv of compound **31** (Table 3, entries 1–5),[37] good yields, diastereo- and enantioselectivities were obtained with aliphatic α-branched aldehydes. However, the chemical yield was lower for α-unsubstituted aldehydes (see for instance entry 2 in Table 3), as well as the diastereo- and enantioselectivity for benzaldehyde (entry 3 in Table 3). Surprisingly, the related diastereoselective reaction using (*S*)-proline **1** and either (*R*)-2,3-*O*-(isopropylidene)glyceraldehyde (entry 4) or (*S*)-Garner's aldehyde (entry 5 in Table 3) gave in both cases excellent results, with catalyst **1** and chiral aldehydes being the match pair for both cases. The reaction using sterically demanding or α,β-unsaturated aldehydes, as well as aqueous formaldehyde, failed. The reaction of ketone **31** with α,α-dimethoxyacetaldehyde allowed the synthesis of partly orthogonally protected aldopentoses and derivatives.[37c]

Table 3. Enantioselective aldol reaction using dioxane **31**



Entry	17	Solvent	Yield (%)	de (%)	ee[a] (%)
1	Pr^{i}CHO	DMF	97	96	97
2	BnOCH$_2$CHO	DMF	40	96	90
3	PhCHO	DMF	57	60	76[b]
4		DMF	76	>96	>98
5		DMF	80	>96	>96
6	BnOCH$_2$CHO	DMSO	85	95	98
7	PhCHO	DMSO	80	0	97
8		DMSO	74	95	>98

[a] ee of the *anti*-**32**.
[b] 49% ee for the *syn*-**32**.

Similar results were obtained under aqueous DMSO conditions at 25 °C and using 2 equiv of the expensive ketone **31** (see for examples entries 6–8 in Table 3).[38] However, other synthetic equivalents of dihydroxyacetone, such as 1,3-dioxan-5-one or 1,5-dioxaspiro[5.5]undecan-3-one gave lower results, compared with those of using dioxanone **31**.[39]

Following the aforementioned strategy, different azasugars (iminocyclitols) have been successfully prepared. The diastereoselective aldol reaction between ketone **31** and chiral protected 3-amino-2,4-dihydroxypentanal catalyzed by proline **1** gave the expected compounds, which after simple manipulation, such as deprotection and reduction could be transformed into iminocyclitols.[40]

As was been previously mentioned, some of the general drawbacks of the enantioselective aldol reaction catalyzed by proline are: (a) the high catalyst loading usually required, (b) the huge excess of starting ketone needed, and (c) the long reaction times required for completion. In order to avoid some of these inconveniences several modifications of the standard protocols have been introduced.

The influence of additives in the reaction media was first explored. Early studies revealed that the proline-catalyzed aldol reaction between an excess of ketone and aldehydes was possible in aqueous media[41] (for a complete discussion on the problem of water in organic solvents see Section 3.2.1.1). As a result, when (*S*)-proline (20 mol %) was used as a catalyst in the standard aldol reaction (see Table 2), using as reaction media a 0.01 M phosphate buffer (pH = 7.4) in the presence of sodium dodecyl sulfate (0.1 equiv) at 25 °C, the expected aldol product **19** was obtained as a nearly racemic mixture in a shorter reaction time (16–24 h) compared with that registered in only an organic medium (1–2 days). However, the aldol product could be obtained enantioselectively by performing the reaction in aqueous organic solvents. For instance, the reaction of acetone with *p*-nitrobenzaldehyde gave product **19a** with 40% ee when the reaction was performed in DMSO/H_2O (9:1, v:v), with 35% ee in DMF/H_2O (10:1, v:v), and with 63% ee in 1,4-dioxane/H_2O (10:1, v:v).

This acceleration of the reaction rate by the addition of water allowed a reduction in the excess of ketone to a stoichiometric amount. The addition of 100–500 mol % of water to dry DMF provided the aldol products **19** using only stoichiometric amount of all reagents **17** and **18**, affecting neither the diastereoselectively nor the enantioselectivity.[42]

The use of Brønsted/Lewis acids in the aforementioned reaction has also been evaluated. Thus, the reaction using chiral camphorsulfonic acid (10 mol %) and proline (20 mol %) in a mixture of acetone/water (4:1, v:v; 54.4 equiv of **18a**) with *p*-nitrobenzaldehyde as electrophile gave the expected aldol product **19a** (R^2 = H) with 74% yield and 61% ee in only 1 day (compare with entry 1 in Table 2). The same protocol was also employed with cyclic ketones obtaining the corresponding products with good enantioselectivities (44–99% ee).[43] The use of other acids, such as pyridinium *p*-toluenesulfonate (100 mol %) or lithium chloride (150 mol %) had also an important effect in the reaction of ketone **31** and aldehydes increasing some ee values from 66% to 92%.[44] On the contrary, the presence of either acids, such as acetic and trifluoroacetic acid, or

bases, such as DBU or triethylamine, did not have any significant beneficial effect when the reaction was performed using acetone **18a** (27.3 equiv) in DMF.[45] However, under these conditions, the addition of water (100–500 mol %) speeded up the reaction, increasing slightly the enantioselectivities, especially for cyclic ketones.[45]

The presence of chiral diols seems to have a beneficial effect on the aldol reaction.[46] Thus, the reaction of acetone **18a** (8.18 equiv) with benzaldehyde in DMSO at 0 °C catalyzed by (*S*)-proline (30 mol %) gave the expected product **19** ($R^2 = H$) with 72% ee, which was increased up to 96% when the same reaction was performed in the presence of (*R*)-BINOL (0.5 mol %). Although the reason for this enhancement is not clear, the authors suggested a possible template effect of the chiral diol, activating and ordering the aldehyde and enamine nucleophile.

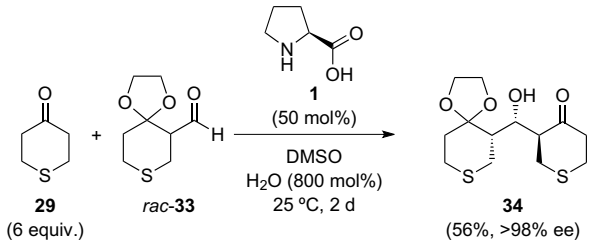
The negative activation volume of the proline-catalyzed aldol reaction anticipated the possible beneficial use of high pressure conditions. Thus, when the reaction was performed using acetone **18a** as a source of the nucleophile and solvent and *p*-nitrobenzaldehyde in the presence of proline **1** (30 mol %) at 25 °C and pressures of 0.2 GPa, the only effect was suppression of the condensation by-product. However, for other aldehydes, a slight increase of the enantioselectivity was produced.[47a] Similar results were found when the high pressure (0.2 GPa) was induced by water freezing conditions at −20 °C.[47b]

An important acceleration effect was observed when the aldol reaction was performed under microwave conditions (15 W) with external cooling, providing the aldol products **18** with similar results (see Table 2) but in very short reaction times (15–60 min).[48]

Although the previous protocol modifications had some beneficial effect, perhaps the best modifications was the introduction of solvent-free conditions (do not be confused with the use of a large excess of ketone as a source of nucleophile and solvent at the same time). The use of a ball-milling technique facilitated the aldol reaction using only 1 equiv of ketone **18**, 10 mol % of (*S*)-proline, reducing the reaction time from days to hours and increasing in some cases the enantioselectivity.[49] The reaction can be performed under conventional magnetic stirring using an excess of ketone **18** (5 equiv) and 30 mol % of catalyst **1**, affording the expected aldol products **19** in longer reaction times but with similar enantioselectivities. The addition of a small amount of water (up to 5 equiv) had a beneficial effect on the diastereo- and enantioselectivities (for example from 75% de and 84% ee without water to 93% de and 97% ee with 500 mol % of water).[50]

Finally, (*S*)-proline has shown its efficiency as a catalyst in dynamic kinetic resolution processes.[51] The aldol reaction of racemic atropisomeric *N*,*N*-diisopropyl-2-formylbenzamide derivatives with an excess of acetone (**18a**, 27.3 equiv) in DMSO at room temperature gave mixtures of diastereoisomers depending on the nature of the benzamide substituents from 36% to 78% de, and the major diastereoisomer reaching up to 95% ee.[52]

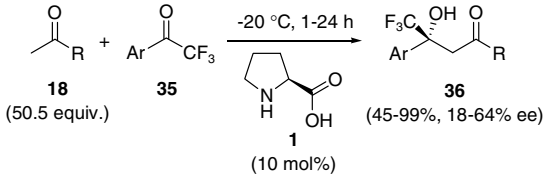
This strategy has also been used to perform the dynamic kinetic resolution of racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde **33** using ketone **29** as the source of the nucleophile with an excellent enantioselectivity (Scheme 10).[53] The protocol has been successfully extended to the related 6,10-dicarboxaldehyde, as a mixture of racemic and *meso*-compounds.



Scheme 10.

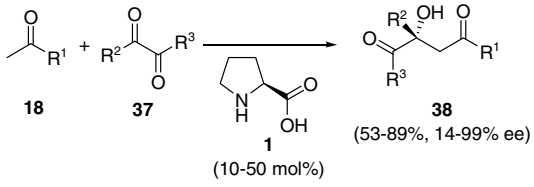
2.2.1.2. Ketones as electrophiles. Although ketones are poor electrophiles and therefore are considered a non-suitable partner for the aldol reaction, this transformation has been achieved in certain cases using very high active non-enolizable ketones, leading to chiral compounds bearing tertiary alcohols.[54]

The reaction of 1-aryl-2,2,2-trifluoroethanones **35** with a large excess of alkyl methyl ketones **18**, acting at the same time as the source of the nucleophile and as solvent, in the presence of substoichiometric amounts of (*S*)-proline **1** gave the expected trifluoromethyl aldol products **36** with modest enantioselectivities (Scheme 11). The nature of substitution on the aromatic ring of **35** determined the success of the reactions. Thus, the presence of an electron-donating group at the *para*-position causes the reaction to fail, whereas electron-withdrawing groups facilitate it.[55]



Scheme 11.

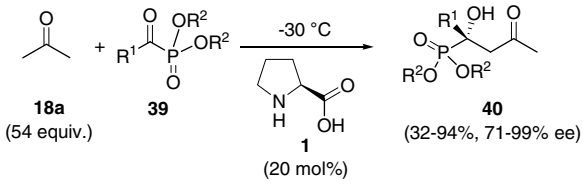
α-Keto carbonyl compounds are also reactive enough to be used as an electrophilic partner in this transformation (Scheme 12). Although the reaction of acyclic α-keto ester



Scheme 12.

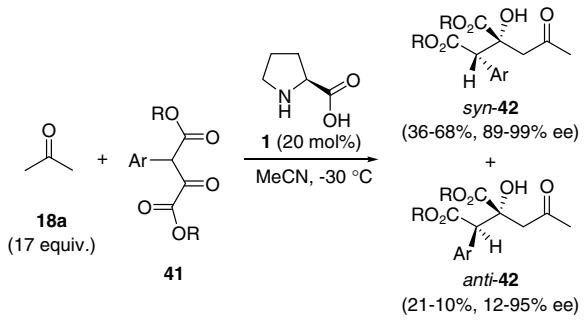
derivatives gave very low enantioselectivities, the results were increased up to 81% ee when the reaction was performed using alkyl methyl ketones **18** (67 equiv) as the source of the nucleophile (and as solvent) and α-oxolactones of type **37**.[56a] Better results were obtained when 1,2-diketone derivatives **37** were used as electrophiles using DMSO as solvent, giving enantioselectivities up to 99%.[56b]

Acetone **18a** was reacted with α-keto phosphonates **39** to give the corresponding α-hydroxy phosphonates **40** with excellent enantioselectivities (Scheme 13). The results seemed to be practically independent of the nature of ketone substituent R^1, and only the size of the ester moiety R^2 had a marginal effect, with the best results being obtained for isopropyl derivatives.[57]



Scheme 13.

The dynamic kinetic resolution of 2-oxo-3-arylsuccinate derivatives **41** by reaction with acetone **18a** (17 equiv) in acetonitrile has been described (Scheme 14). The reaction gave a mixture of products with diastereomeric excess



Scheme 14.

never higher than 60%. In all the cases tested, the *syn*-**42** was the mayor diastereoisomer in high ee, with the absolute configuration being determined by X-ray. These results were independent of the nature of the substitution on the aryl group, as well as on the ester group.[58]

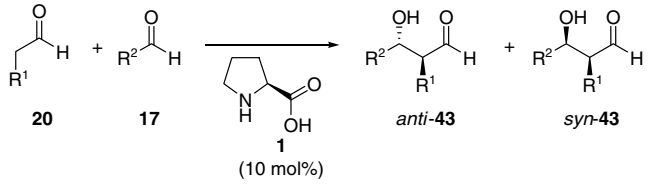
2.2.2. Aldehydes as source of nucleophile. Although the organocatalytic intermolecular aldol reaction was initially developed using only ketones as the source of the nucleophile, two years later the use of aldehydes as a source of nucleophiles was introduced.

2.2.2.1. Aldehydes as electrophiles. Two possible general transformations can arise from the intermolecular aldol reaction using aldehydes. The first one is the auto-aldol dimerization process of a single aldehyde. The second general transformation is the cross-aldol process between two different aldehydes. The latter case is a really more challenging problem, since there are two possible auto-aldol dimerization processes to be avoided, and two possible cross-aldol processes to be discriminated.

However, both the auto-aldol and the cross-aldol reactions have been successfully achieved using (*S*)-proline **1** as catalyst (Table 4). Thus, the auto-aldol process using propionaldehyde ($R^1 = Me$ in **20** and $R^2 = Et$ in **17**) gave the expected β-hydroxyaldehyde **43** as a mixture of *anti*- and *syn*-diastereoisomers with an excellent enantioselectivity for the major *anti*-**43** isomer (entry 1 in Table 4).

Moreover, the cross-aldol reaction has been performed under similar reaction conditions, and for example using propionaldehyde **20** as the source of the nucleophile ($R^1 = Me$) other different aliphatic and aromatic aldehydes could be used as electrophilic partners yielding in all cases tested the *anti*-**43** isomer as the main diastereoisomer (entries 2–4 in Table 4).[59] This behavior was attributed to the steric hindrance in the case of β,β-disubstituted aldehydes ($R^2 = Bu^i$ in **17**) as well as the kinetic inaccessibility of the hydrogen in α,α-disubstituted aldehydes [$R^2 = (CH_2)_5CH$ or Pr^i in **17**], making in both cases the corresponding nucleophilic enamine intermediate thermodynamically unstable (see Section 7.2).

Table 4. Enantioselective aldol reaction catalyzed by proline **1** using aldehydes as a source of nucleophile



Entry	R^1	R^2	Reagent (equiv)	Reaction conditions	Yield[a] (%)	de (%)	ee (%)
1	Me	Et	—	DMF, 4 °C, 10 h	80	80	99
2	Me	Bu^i	**20** (2)	DMF, 4 °C, 16 h	88	75	97
3	Me	$(CH_2)_5CH$	**17** (2)	DMF, 4 °C, 20 h	87	94	99
4	Me	Ph	**17** (10)	DMF, 4 °C, 16 h	81	75	99
5	Bu^n	Pr^i	**17** (3)	DMF, 25 °C, 24 h	80	96	98
6	$PhCH_2$	$S(CH_2)_3SCH$	**17** (2)	DMF, 25 °C, 46 h	73	97	97
7	Pr^i	H	**20** (2)	DMF, 25 °C, 16 h	52	—	99

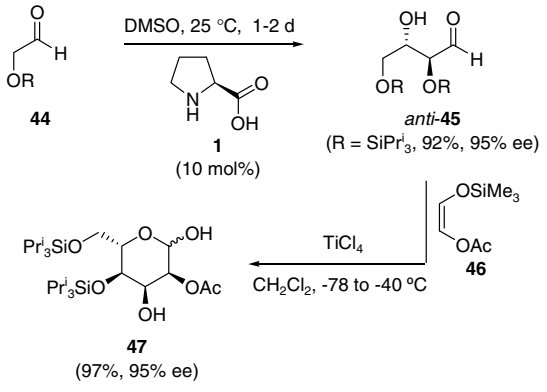
[a] Results for the *anti*-diastereoisomer.

The great success obtained in the cross-aldol reaction has been further expanded to other electrophilic aldehydes such as 1,3-dithianyl-2-carboxaldehyde[60] and aqueous formaldehyde[27] (entries 6 and 7 in Table 4, respectively).

Aldehydes *anti*-**43** can be easily transformed into 1,2-diols by an allylation reaction mediated by indium. The reaction gave modest diastereoselectivities, except for the prenylation process.[61] It is possible to obtain different δ-lactone derivatives by Horner–Wittig–Emmons reaction of aldehydes *anti*-**43** with methyl 2-(diethoxyphosphoryl)acetate followed by dihydroxylation using osmium tetraoxide and final cyclization.[62]

A careful study of the reaction conditions showed that the cross-aldol reaction can be performed using an excess of aldehyde **20** (500 mol %), which is the source of nucleophile and solvent at the same time, with the presence of water (300 mol %) increasing the obtained enantiomeric excess.[50]

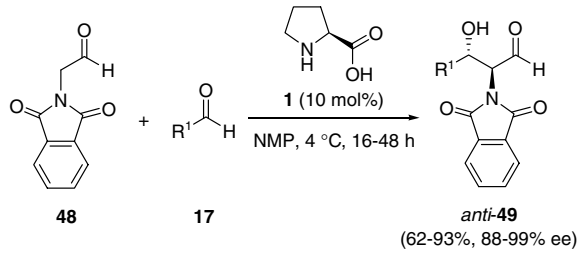
The use of α-alkoxyacetaldehydes **44** allowed access to polyol architectures. The nature of the protecting group is crucial in order to forecast the possible role of this aldehyde. Thus, when the protecting group is either an alkyl or silyl, the corresponding aldehyde **44** could play either the role of the source of the nucleophile, in reactions with α,α-disubstituted aldehydes, or the role of an electrophile, in reactions with simple aliphatic aldehydes. In both cases, products were obtained with good yields (33–84%), high diastereoselectivities (60–78%) and excellent enantioselectivities (94–99%).[63] The auto-aldol reaction of α-(triisopropylsilyloxy)acetaldehyde **44** (R = $SiPr^i$) gave the corresponding aldehyde *anti*-**45** with 75% diastereoselectivity, which after reaction with silyl enol ether **46** in the presence of titanium tetrachloride[64] yielded the corresponding allose **47** (Scheme 15).[65]



Scheme 15.

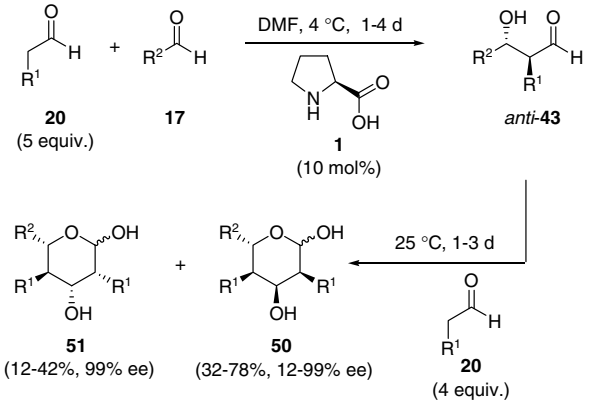
The use of $MgBr_2$ as a Lewis acid for the last Mukaiyama-aldol reaction gave the diastereomeric mannose derivative with similar results. A positive non-linear effect was detected in the above auto-aldol reaction,[66] which was attributed to the different reaction rates of both enantiomers of proline with *anti*-**45** (R = Bn) to form the inactive imidazolidinone derivative, resulting in a kinetic resolution of proline by the final product.

Other α-functionalized aldehydes have been used as sources of nucleophile. Thus, the reaction of glycine aldehyde derivative **48** with an excess of different aldehydes **17** gave, as the main product, the corresponding *anti*-β-hydroxy-α-amino aldehyde *anti*-**49**, with excellent results (Scheme 16). The subsequent oxidation of aldehydes **49** provided a new entry to the synthesis of the corresponding amino acids.[67]



Scheme 16.

(*S*)-Proline **1** was able to catalyze the auto-aldol reaction to obtain dimers as well as trimers, affording directly polyketide derivatives. Thus, the trimerization of acetaldehyde can be achieved in a THF/acetaldehyde mixture (4:1) at 0 °C, giving (5*S*)-hydroxy-2-hexenal in low yield (12%) but with high ee (84%).[68] This result could be improved by the slow addition of acetaldehyde to the in situ formed dimer of type *anti*-**43**. For instance, the trimerization of propionaldehyde (R^1 = Me, R^2 = Et in Scheme 17) catalyzed by (*S*)-proline **1** (10 mol %) in DMF afforded after 3 days, a mixture of diastereoisomers **50** and **51** (78% de) in 53% yield (Scheme 17).[69]



Scheme 17.

The use of a different electrophilic aldehyde, such as isobutyraldehyde ($R^2 = Pr^i$ in **17**) led to the formation of a single diastereoisomer **50** (R^1 = Me) but with low yields and enantioselectivity, the last fact being attributed to the mismatched pair of intermediate *anti*-**43** and (*S*)-proline. The enantioselectivity of the process could be improved up to 99% by carrying out the reaction in a stepwise manner, using (*S*)-proline for the first aldol process, and (*R*)-proline

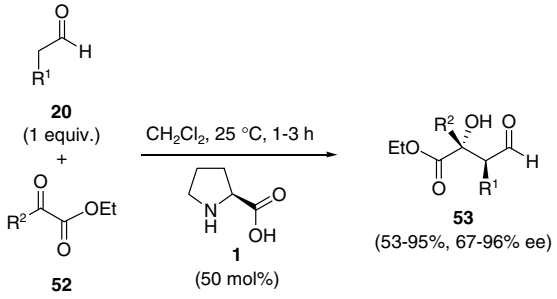
for the final aldol reaction between isolated *anti*-**43** and aldehyde **20**.[70,71]

When α-(benzyloxy)acetaldehyde was used in the above trimerization process, the corresponding allose derivative **50** ($R^1 = OBn$, $R^2 = CH_2OBn$) was obtained in 48% yield and 99% ee. An important non-linear effect was detected,[72] as in the previous example of an auto-aldol reaction. This fact has been employed in dynamic kinetic resolution processes of compounds of type *anti*-**43** by reaction with aldehydes.[73]

When the trimerization process was performed using water as a solvent a dramatic decrease with regard to the enantioselectivity was found, demonstrating the high importance of the hydrophobic environment in the transition state.[71]

The use of an ionic liquid as a reaction media for the above di- and trimerization processes led to a clear acceleration of the reaction time, simplifying the product isolation and catalyst recycling. Thus, the dimerization of propionaldehye using a 1.5:1 mixture of 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmin]PF_6) and DMF and only 5 mol % of (*S*)-proline **1** gave the product *anti*-**43** ($R^1 = Me$ and $R^2 = Et$) in 74% yield with a 60% de and 99% ee. The reaction can be performed fivefold without affecting the yields or enantioselectivities. When this media was applied to the one-pot sequential polyketide synthesis of **50** ($R^1 = Me$ and $R^2 = Et$ in Scheme 17), the yield was 38% in only 22 h (49% ee).[74]

2.2.2.2. Ketones as electrophiles. The strategy discussed in this review is so wide spread that the most complicated combination for the aldol reaction (aldehyde as source of nucleophile and ketone as electrophile) has been successfully introduced. The reaction of different aldehydes with high electrophilic ketones **52**, such as diethyl ketomalonate or ethyl trifluoropyruvate, in the presence of (*S*)-proline gave the expected products **53** with good chemical yields, enantioselectivities, and poor diastereoselectivities (Scheme 18).



Scheme 18.

The instability of compound **53** during the work-up and purification process requires these aldehydes to be transformed into either the corresponding ketals by reaction with ethylene glycol[75] or nitrones by reaction with substituted *N*-hydroxylamine.[76] The last class of products can be obtained alternatively through the reaction of nitrones with ketones **52** catalyzed by (*S*)-proline.[77]

3. Proline derivatives as organocatalysts

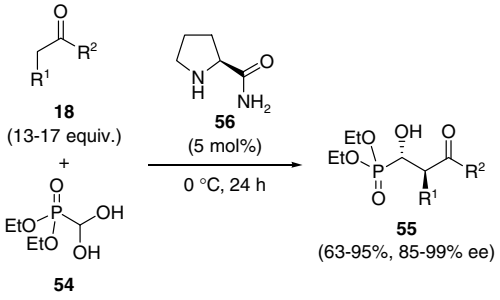
Although (*S*)-proline **1** has shown its efficiency in the aldol reaction affording the corresponding products with high regio-, diastereo-, and enantioselectivities, there are some aspects of such transformations that could be improved. Those aspects, such as the typical high catalyst loading, excess of source of nucleophile, and long reaction times, are sometimes attributed to the low solubility of catalyst **1** in organic media. In order to overcome these drawbacks and modulate its reactivity some modifications in the nature of structure of (*S*)-proline have been reported, thus allowing the fine-tuning of catalytic properties and improving the activities and conditions.

3.1. Prolinamide derivatives

The most commonly used group of proline derivatives are prolinamides. Some general facts have made these derivatives useful. First, the easy preparation of these starting from (*S*)-proline **1**. Second, the robust amide linkage provides very stable compounds, which in some cases can be recovered and reused without detrimental effects. Finally, the hydrogen of NH moiety is acidic enough to activate electrophiles by hydrogen bonding (see Section 7.2).

3.1.1. Ketones as source of nucleophile

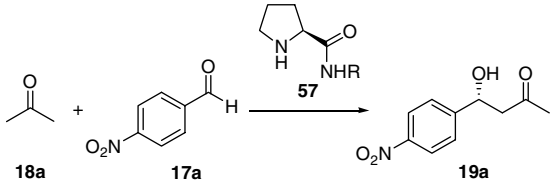
3.1.1.1. Aldehydes as electrophiles. Although the simple prolinamide-catalyzed intermolecular aldol reaction failed,[24a] this compound has shown its efficiency in the intermolecular aldol reaction between ketones **18** and diethyl formylphosphonate **54**, affording the expected secondary α-hydroxyphosphonates **55** (Scheme 19).[78] The best results were found when using the ketone as both the source of the nucleophile and solvent, with moderate to good diastereoselectivities (30–90%).



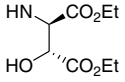
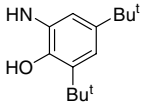
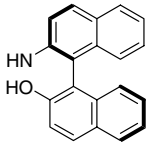
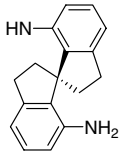
Scheme 19.

The use of amides derived from proline and chiral amines has allowed us to perform the intermolecular aldol reaction. In order to compare different systems, different results have been collected in Table 5 (compare with entry 1 in Table 2). The reaction between *p*-nitrobenzaldehyde **17a**

Table 5. Enantioselective aldol reaction using amides **57**



18a **17a** **19a**

Entry	HNR	Reaction conditions	Yield (%)	ee (%)
1		H_2O/Me_2CO (1:1, v:v), **57a** (20 mol %)[a], **18a** (10 equiv), 25 °C, 8 h	83	46
2		Me_2CO, **57b** (5 mol %), **18a** (13.1 equiv), −40 °C, 1 d	70	99
3		Me_2CO, **57c** (10 mol %), **18a** (13.1 equiv), −40 °C, 2 d	78	85
4		Me_2CO, **57d** (20 mol %), **18a** (27.2 equiv), −25 °C, 2 d	66	93
5		[bmim]BF_4, **57d** (20 mol %), **18a** (27.2 equiv), 0 °C, 1 d	82	94
6		Me_2CO, **57e** (2 mol %), **18a** (27.2 equiv), −25 °C, 1 d	62	99
7		Me_2CO, **57f** (20 mol %), **18a** (27.2 equiv), 25 °C, 3 d	16	68
8		hexane, **57g** (5 mol %), **18a** (3 equiv), 25 °C, 10 h	99	70
9		Me_2CO, **57h** (1 mol %), **18a** (27.2 equiv), −25 °C, 5 h	82	55

[a] Catalyst used as hydrobromide derivative.

and acetone **18a** to give the corresponding aldol product **19a** could be performed in the presence of simple *N*-alkyl prolinamide derivatives. However, the best results could be obtained using the corresponding hydrobromide **57a** in the presence of water (Table 5, entry 1). However, the use of a diastereomeric amide derived from (*R*)-1-phenyl-1-propylamine showed higher reactivity but lower enantioselectivity. When the reaction was carried out using different aromatic aldehydes, the best results were found for those possessing electron-withdrawing groups, with the *ortho*-substituted aromatic aldehydes giving higher enantioselectivities than the related *para*-substituted ones.[79]

The use of prolinamide derived from 1,2-aminoalcohols has been more successful for this proposal. Thus, prolinamides **57b** and **57c** (entries 2 and 3 in Table 5, respectively) were shown to be very efficient in this reaction (even better than proline, compare with entry 1 in Table 2), although the reaction must be performed at −40 °C. The replacement of diphenyl or di-isobutyl moieties by other less hindered alkyl groups or by hydrogen led to a dramatic decrease in the enantioselectivities, this effect can be attributed to a more restricted conformation, to a higher hydrogen bonding ability and to a higher solubility of compounds **57b** and **57c**. Also, the use of the corresponding diastereomeric amides gave worse results.[80a] Both catalysts **57b** and **57c** have shown their efficiency in the reaction between ketones and aromatic aldehydes performing the reaction in brine at −5 °C, and affording the corresponding aldol products **19** with even better results.[80b]

Other 1,2-aminoalcohols bearing two stereogenic centers have been used in the preparation of the corresponding amides **57**. The use of the hindered amide derived from (*S*,*S*)-1,2-diphenyl-2-aminoethanol **57d** gave excellent enantioselectivities (entry 4 in Table 5).[81] The use of other electrophilic aldehydes other than from **17a** afforded different results depending on the nature of the aldehyde, with good yields and enantioselectivities for compounds **19** (48–93% and 81–93% ee) derived from aromatic aldehydes and modest yields and excellent enantioselectivities for aliphatic compounds **19** (12–77% and 86–99% ee).[81a] In the case of using other alkyl methyl ketones **18**, such as butanone, the reaction mainly took place through the methyl group giving the corresponding *iso*-regioisomer derivative with moderate yields and high enantiomeric excesses.[81b] Better results were obtained when an ionic liquid ([bmin]BF_4) was used as the reaction media (Table 5, entry 5), permitting the catalyst recycling twice without losing its initial yield and enantioselectivity.[81c]

The replacement of the phenyl groups in the above organocatalyst for more electron-withdrawing groups such as ethoxycarbonyl led to a new organocatalyst **57e** with stronger acidity, and therefore forming stronger hydrogen bonds.[82] This catalyst gave slightly better results than the previous one (compare entries 4 and 6 in Table 5), with homogenous yields and enantioselectivities for the cases of using acetone and aromatic aldehydes, increasing the enantiomeric excess to only one enantiomer in the case of using α-branched aldehydes.

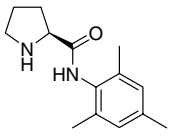
For methyl alkyl ketones, such as butanone, the reaction using **57e** mainly gave the *iso*-regioisomer derivative (43–62% yield) with excellent enantiomeric excess (98–99%), together with a minor amount of *anti*-**19** isomer (21–42%, 98% de, and 98–99% ee). The results were also excellent for cyclic ketones, although the diastereomeric excess depended on the ring size (90% de for the *anti*-**19e** of cyclohexanone and 0% de for cyclopentanone).[82a] The high activity of this catalyst has permitted the use of other less reactive ketones as a source of the nucleophile. In the reaction using α-hydroxyacetone **23a** (15 equiv) in THF/H_2O (2:1 v:v) at −15 °C, only regioisomers *iso*-**25** were isolated with good results, with similar results being found for the related α-fluoroacetone (X = F in **26**). In contrast, when the reaction was performed only in THF, the main product for the reaction using α-fluoroacetone was the isomer *anti*-**27** (X = F) giving good results (89–96% yield, 33–60% de, 94–98% ee).[82b] The use of α-(methylsulfanyl)acetone (X = MeS in **26**) drives the reaction to only give regioisomer *iso*-**28** with up to 99% ee.[82c]

Although the change of the hydroxy group of the alcohol with a more acidic phenol derivative seems to be inefficient (entry 7 in Table 5), the results obtained in water, when a large excess of cyclohexanone (11.7 equiv) was used as the source of the nucleophile, were very good, affording aldol products with high yields and selectivities.[83]

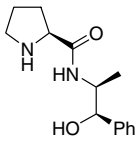
The NOBIN-prolinamide derivative **57g** has been shown to be an active catalyst for the aldol reaction under unusual conditions, such as the use of hexane as reaction media or the use of only 3 equiv of source of nucleophile (entry 8 in Table 5).[84] The important role of phenolic OH was demonstrated by the very low results obtained when the related methyl ether derivative was used as catalyst. Catalyst **57g** has been used in combination with trifluoroacetic acid in pure water in the aldol reaction (for a complete discussion on the implication of using water see following Section 3.2.1.1) between cyclic ketones (only 2 equiv used) and aromatic aldehydes affording good results (53–99% yield, 40–98% de, 62–97% ee).[85]

The use of prolinamide derivatives bearing a stereogenic axis has been further explored with the spiro compound **57h**. Although its high activity permitted a reduction in the amount of catalyst to only 1 mol % (entry 9 in Table 5), the results were in general modest.[86]

Other prolinamides have been used as catalyst in the direct intermolecular aldol reaction. Thus, the simple amide **57i** has been used in the reaction between α-chloroacetone (X = Cl in **26**) and aromatic aldehydes, affording mainly compound *anti*-**27** (18–57% yield, 66–94% de, 91–98% ee) with a minor amount of *iso*-**28** (X = Cl).[87]



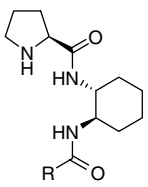
57i



57j

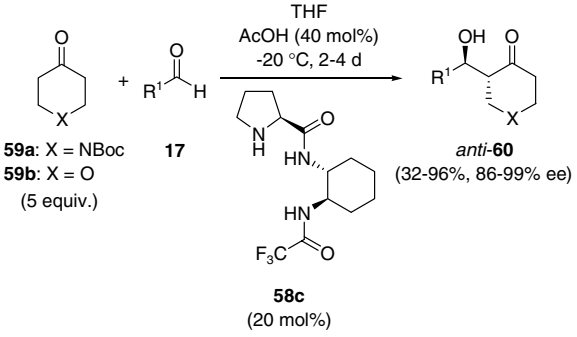
The norephedrine derivative **57j** has also been used as a catalyst. The reaction of different aldehydes **17** in neat acetone at −40 °C gave modest results (22–67% yield and 60–80% ee).[88]

Prolinamides derived from chiral diamines have been synthesized and employed as catalysts in the intermolecular aldol reaction. The results achieved with bisprolinamides are generally superior to those obtained with other diamides. The first example of these types of compounds was diamide **58a**, which bears only one unit of proline and is used in substoichiometric amounts (20 mol %) in the aldol reaction between cyclohexanone (19.2 equiv) and different aromatic aldehydes. For this catalyst, the use of 20 mol % of acetic acid was beneficial in order to enhance its catalytic activity.[89] Better results were obtained with bisprolinamide catalyst **58b**, affording aldol products *anti*-**19** with high diastereo- (60–98%) and enantioselectivities (77–97%).[90]



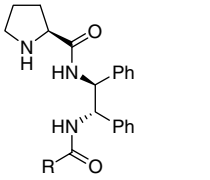
58a: RCO = 4-MeC_6H_4CO
58b: RCO = (*S*)-$(CH_2)_3NHCHCO$

It has been hypothesized that the NH group of diamide play an important role in the stabilization of the transition state, activating the electrophile. Therefore, the change of the R group in **58** could have an important effect on the selectivity of the reaction, since the acidity is altered. For instance, catalyst **58c**, which has a lower pK_a, has been used in the reaction of *N*-Boc-4-piperidone **59a** with different aromatic and heteroaromatic aldehydes giving mainly the isomer *anti*-**60** with diastereoselectivity higher than 90% (Scheme 20). However, catalyst **58a** gave better results in the related reaction using tetrahydro-4*H*-pyran-4-one **59b**.[90]



Scheme 20.

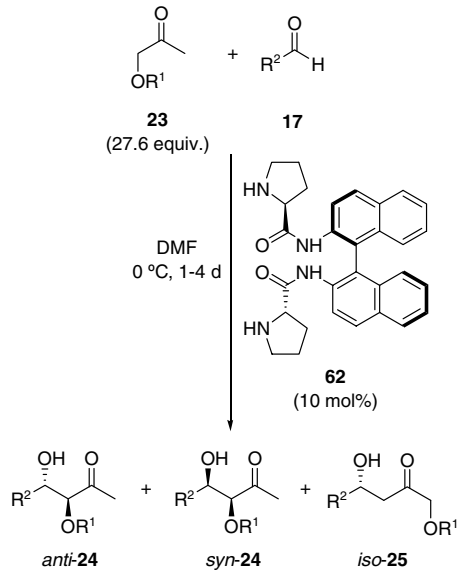
Catalyst **61a** has shown its superiority in the aldol reaction between tetrahydro-4*H*-thiopyran-4-one **29**, affording the product *anti*-**30** in 37–99% yield, 78–99% de and 90–99% ee.[90] The presence of two units of proline in these derivatives increases the catalytic activity, and although for catalysts **58** the above affirmation is not very clear, for catalyst **61** it is true. In fact, the reaction between acetone **18a** (27.2 equiv) and *p*-nitrobenzaldehyde **17a** at −35 °C catalyzed by amide **61b** (10 mol %) gave the expected compound **19a** with an excellent result (75% yield, 98% ee, compare with those presented in Table 5 and entry 1 in Table 2) in only 5 h, with this result not being quite dependent upon the nature of the electrophilic aldehyde (aromatic or aliphatic) used. Conversely, the same reaction catalyzed by amide **61c** gave a worse result.[91]



61a: RCO = 4-MeC_6H_4CO
61b: RCO = (*S*)-$(CH_2)_3$NHCHCO
61c: RCO = MeCO

The bisprolinamide derived from 1,1′-binaphthyl-2,2′-dimine(BINAM) **62** has attracted a great deal of attention as a possible catalyst for the intermolecular aldol reaction. This compound was almost simultaneously reported by two different research groups as an efficient catalyst in the aldol reaction between ketones **18** and aldehydes **17**. In both articles, the matched combination was the use of (*S*)-proline and (S_a)-BINAM units. However, the best reaction conditions were quite different. One group found that the mixture of 1,4-dioxane/ketone **18** (4:1, v:v) at 4 °C was the ideal reaction conditions, obtaining the corresponding aldols **19** with yields ranging from 9% to 79% and enantiomeric excess from 50% to 88%.[92] However, another group found that either DMF/water (1:1, v:v) at 0 °C or DMF at 25 °C was the ideal conditions, affording the corresponding products **19** with slightly better results (52–99% yield, 78–95% ee).[93] Under the latter conditions, the reaction took place nearly exclusively at the methyl position, when 2-butanone was used as the source of the nucleophile and gave the corresponding isomer *anti*-**19e** when cyclohexanone **18c** was used as the starting reagent. The above conditions (either DMF or DMF/water) permitted the easy recovery of catalyst **62** just by an aqueous acidic basic extraction, as well reuse without any detrimental effect on the obtained yields and enantioselectivities, at least during threefold cycles.[93] Further alternative reaction conditions, such as $CHCl_3$:ketone **18** (1:1, v:v) at −27 °C, have been reported.[94] However, the results were, in general, worse than previously reported ones.

Catalyst **62** has been used in the reaction between α-(alkoxy)acetones **23** and aldehydes **17** (Scheme 21) to mainly give regioisomer **24**, with small amounts of corresponding *iso*-**25**. The diastereoselectivity depended upon the nature of the R^1 group, giving always compound *anti*-**24** as the main product, with the enantioselectivity reaching values of up to 99%.[95] It should be pointed out that simple α-hydroxyacetone **23a** can be also used as a source of nucleophile, but in this case the best reaction conditions were DMSO at 25 °C, affording *anti*-**24** with a 85% ee. The results were compared with those obtained using (*S*)-proline (**1**) under similar reaction conditions, showing that catalyst **62** gave comparable or, in many cases, better results.

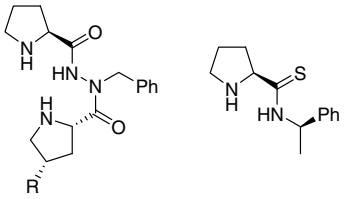


Scheme 21.

The addition of substoichiometric amounts of carboxylic acids permitted the enhancement of the reaction rate.

Among all the tested acids, benzoic acid emerged as the best one, for instance its addition (20 mol %) to the reaction media reduced the reaction time from the original 3 days to only 1.5 h, while maintaining the enantioselectivity of **19a**. This fact permitted a decrease in the reaction temperature from 25 °C to −20 °C, increasing the corresponding enantioselectivity (86–99%). Moreover, the use of benzoic acid allowed the reaction to be performed using only water as a solvent with similar results.[96]

Other carboxylic acids have been further proposed as an alternative. In the first case, aldol products **19** (45–91% yield, 40–96% de, 67–95% ee) were obtained using acetic acid as a co-catalyst in toluene at −40 °C but in longer reaction times (2–3 days).[97] The amount of ketone **18** could be reduced to 3 equiv, just by using water and a micellar agent stearic acid (20 mol %) as a co-catalyst at 2 °C.[98] Under these conditions, compounds **19** (61–99% yield, 58–93% ee) were obtained in 12 h (for a complete discussion on the implication of water in this type of reaction, see Section 3.2.1.1).



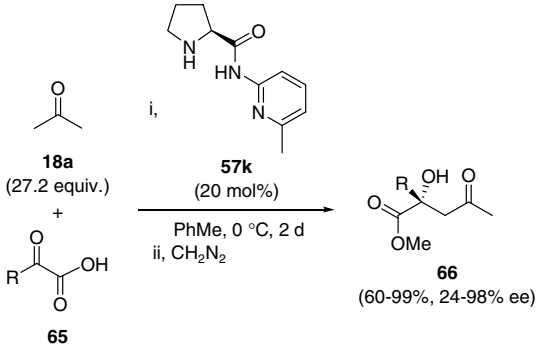
The combination of catalyst **62** (10 mol %) and benzoic acid (20 mol %) in either DMF or pure water permitted the use of less reactive ketones as the initial source of nucleophile. The reaction of α-(methylsulfanyl)acetone (X = MeS in **26**) with *p*-nitrobenzaldehyde **17a** could be performed, giving *iso*-**28** as the main product in either DMF/water or pure water with an excellent 93% yield.[99] The reaction using related α-alkoxy acetones **23** gave similar results, but in shorter reaction times (3–24 h).

The reaction of chloroacetone (X = Cl in **26**) with aromatic aldehydes catalyzed by amide **62** (10 mol %) and benzoic acid (20 mol %) gave the isomer *anti*-**27** (see Scheme 8) as the main product (27–96% yield, 50–98% de, and 40–97% ee), which could be easily converted into the corresponding chiral (3*R*,4*S*)-*trans*-epoxides by treatment with triethylamine with excellent enantioselectivities.[100]

Other catalytic systems which can be included into this group are hydrazide derivatives and thioamides. The additional nitrogen atom at the hydrazide derivatives **63** provides a new hydrogen-bonding site, improving the activity of these catalysts compared with simple prolinamides **57**. The reaction between cyclohexanone (27.2 equiv) with different aldehydes in toluene at 0 °C using catalyst **63a** (20 mol %) and trifluoroacetic acid (20 mol %) gave the expected aldol product with good enantioselectivities (for comparison with Table 5, compound **19a** was obtained in 7 h, 95% yield and 96% ee). However, these results were lower when aromatic aldehydes bearing electron-donating groups were used, even slowing down the reaction rate.[101] The use of hydroxy derivative **63b** did not provoke any important change in the aforementioned results.[102]

The conversion of the amide compound into the corresponding thioamide derivative increases the acidity of the NH hydrogen and therefore would form a stronger hydrogen bond, favoring its catalytic activity. With this idea in mind, catalyst **64** was prepared and tested in the intermolecular aldol reaction.[103] Thus, the standard reaction between acetone **18a** (27.2 equiv) and *p*-nitrobenzaldehyde **17a** at 4 °C catalyzed by thioamide **64** (20 mol %) in the presence of trifluoroacetic acid (20 mol %) gave the expected compound **19a** in 81% yield and 94% ee (compare with entry 1 in Table 5). Although this result seems to confirm that thioamides could perform the reaction more selectively than the related amides and other results using aromatic aldehydes bearing strong electron-withdrawing groups are in consonance with the previous one, the reaction with less reactive aldehydes gave lower enantioselectivities. Other thioamides assayed gave lower or similar results, as well as other acidic catalysts. For instance, the use of stronger acids than trifluoroacetic acid led to the deactivation of catalyst **64**, whereas the use of acids with similar pK_a such as trifluoro-, difluoro-, or dichloroacetic acid gave similar results.[104] Thus, the aldol reaction between cyclic ketones and aromatic aldehydes catalyzed by thioamide **64** (10 mol %) and dichloroacetic acid (10 mol %) could be performed in brine as the reaction media and using only 1.2–3 equiv of ketone as the source of the nucleophile. The corresponding products *anti*-**19**, *anti*-**30**, and *anti*-**60** were obtained with moderate to good results (32–97% yield, 20–90% de, and 68–98% ee).[105]

3.1.1.2. Ketones as electrophiles. As was presented above, the use of ketones as a electrophilic partner of the aldol reaction is a more challenging task. However, it has also been accomplished by using the amide catalyst **57k** (Scheme 22). In order to obtain good results, the ketone partner should have a carboxylic acid moiety and the catalyst, a pyridine ring. The use of either ester derivative **52** or non-heteroaromatic ring catalyst had a strongly detrimental effect on the yields and enantioselectivities. This fact has been attributed to the presence of a strong interaction between the hydrogen from the carboxylic moiety and the basic nitrogen atom of pyridine ring, which facilities the



Scheme 22.

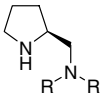
recognition and approach of reagents.[106] The reaction is not only restricted to acetone and other ketones, such as cyclopentanone, could be used with a slightly lower enantioselectivity. Finally, it should be pointed out that catalyst **57k** can be recovered and reused threefold just by aqueous acidic–basic extraction.

3.1.2. Aldehydes as source of nucleophile. The auto-aldol dimerization reaction between aldehydes has only been reported very recently. The reaction of neat propionaldehyde ($R^1 = Me$ in **20** and $R^2 = Et$ in **17**, Table 4) catalyzed by (*S*)-prolinamide (**56**, 20 mol %) in the presence of 20 equiv of water gave the expected product *syn*-/*anti*-**43** as a 1.3:1 diastereoisomeric mixture. The enantiomeric excess of both diols obtained after reduction with $NaBH_4$ was practically identical (78% and 74% ee for *anti*- and *syn*-**43**, respectively).[107]

3.2. Prolinamine derivatives

3.2.1. Ketones as source of nucleophile

3.2.1.1. Aldehydes as electrophiles. Shortly after (*S*)-proline **1** was reported as a suitable catalyst for the intermolecular aldol reaction, prolinamide derivatives **67** were tested in the same type of transformation. Several diamines derived from proline in combination with protic acids were screened in the aldol reaction between acetone **18a** and aldehydes **17**.[108] Among the catalysts tested, prolinamines bearing a tertiary amine group gave better results, with the reaction rate decreasing as the above moiety become bulkier. The catalyst **67a** (3 mol %) showed an excellent catalytic efficiency in the reaction of acetone (source of nucleophile and solvent) with aldehydes in the presence of carboxylic acids and, for instance, using trifluoroacetic acid (3 mol %), the aldol compound **19a** could be obtained after 2 h at 30 °C in a reasonable result (51% yield and 82% ee), but together with the corresponding α,β-unsaturated compound. In order to minimize the amount of this by-product, the amount of carboxylic acid was reduced although the decrease of by-reaction was marginal. The reaction has been also expanded to other ketones, such as cyclic ketones and, surprisingly, 3-pentanone, giving the main diastereoisomer *anti*-**19** with lower enantioselectivities (81–97% yield, 84–96% de, and 8–48% ee).

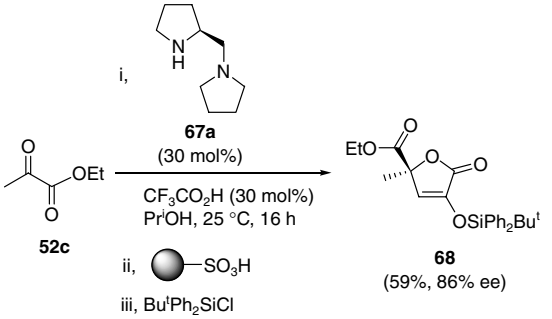


67a: R-R = $(CH_2)_4$
67b: R = $(CH_2)_9CH_3$

The hydrophobic catalyst **67b** (10 mol %) in combination with trifluoroacetic acid (10 mol %) has been designed and used in the intermolecular aldol reaction between ketones (2 equiv) and aromatic aldehydes in pure water as solvent. The expected products **19** were obtained with good yields (46–99%), when highly electrophilic aldehydes were used, very low to good diastereoselectivities (8–82%) and enantioselectivities (22–99%). The presence of the carboxylic acid was of vital importance, since the reaction in the absence of trifluoroacetic acid gave the product as a racemic mixture. The reaction media was in fact an emulsion mixture under carboxylic acid catalysis, which allowed the easy isolation of products by centrifugal separation of water.[109]

After the publication of the last article, as well as others, on the use of water as a reaction media, a deep discussion about the water-media concept began.[110] The beneficial effect of the addition of water in the intermolecular aldol reaction was recognized early, since at least one water molecule participates in the catalytic cycle.[42] However, water is a co-solvent of an organic media in many of these reaction protocols (aqueous reactions). In other protocols, water is the only solvent used but the large amount used as the source of the nucleophile means that the reaction has to be recognized as the aforementioned protocol (aqueous reaction), since the excess of reagent plays the role of the organic solvent media for the reaction. The use of pure water as solvent is considered, in general, to be of high interest because water is an inexpensive, safe, and environmentally benign solvent. However, to honestly claim the environmental beneficial effects of using water as solvent, several requirements should be addressed.[111] The green perspective of such processes is clearly in doubt if either a large excess of one reagent is used or a surfactant/micellar agent is added. Pure water should be considered as a green solvent only if it can be directly discharged to a biological effluent plant. Moreover, the work-up of the reaction should count when looking at the whole process as a green approach, with the extraction having to be performed by using minimal amounts of environmental friendly organic solvent, such as ethyl acetate.

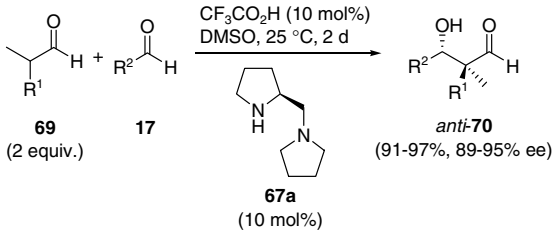
3.2.1.2. Ketones as electrophiles. Ethyl pyruvate **52c** has been used as both the source of the nucleophile and electrophile in the aldol reaction catalyzed by catalyst **67a** (Scheme 23). Initially, the results gave a complicated mixture of different products derived from the aldol process. However, the use of polymer-supported sulfonic acid Amberlist 15, in order to eliminate the catalyst, and final treatment of reaction mixture with a silylating agent, permitted the isolation of isotetronic acid derivative **68**.[112]



Scheme 23.

3.2.2. Aldehydes as source of nucleophile. Catalyst **67a** in combination with trifluoroacetic acid has permitted the intermolecular aldol reaction between α-methylaldehydes

69 (source of the nucleophile) and aromatic aldehydes in DMSO at 25 °C (Scheme 24), affording *anti*-**70** as the main diastereoisomer, although with moderate diastereoselectivity (24–70% de).[113] Whereas, the enantioselectivity was homogeneous, and independent of the size of the R^1 group and on the electronic nature of the substituent on the aromatic ring of the electrophilic aldehyde, the chemical yields depended strongly on the last factor. Thus, compound **70** was obtained with low chemical yields for aldehydes bearing electron-donating groups.



Scheme 24.

3.3. Proline sulfonimide derivatives

3.3.1. Aldehydes as electrophiles. The conversion of the carboxylic moiety of (*S*)-proline into the corresponding sulfonimide derivative would provide a catalytic system with, in general, similar acidity, but in which the acidic, steric, and electronic properties could be fine tuned, just by a simple change of the sulfonyl moiety. The synthesis of these catalysts **71** was easily accomplished by coupling the corresponding aryl- or alkylsulfonamide with proline (Table 6).

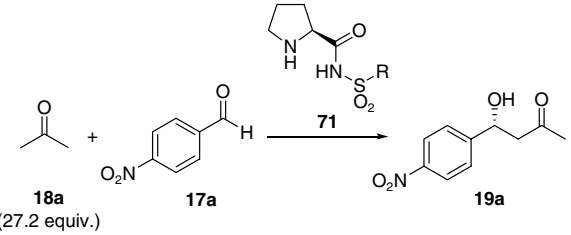
The first example was imide **71a**, which gave excellent results in the intermolecular aldol reaction performed in polar aprotic solvents such as DMSO, THF, and ketones **18**.[114] The use of protic solvents, such as methanol, led to a diminution of the yields and enantioselectivities. Catalyst **71a** gave better results in the preparation of compound **19a** (Table 6, entry 1), than simple (*S*)-proline (entry 1 in Table 2), with these results being attributed to a better shielding of one of the two possible enantiotopic faces of the aldehyde by the aryl ring. Similar yields but slightly decreased enantioselectivities were obtained when the reaction was carried out using an ionic liquid as solvent (entry 2 in Table 6).[115] Attempts to recycle and reuse catalyst **71a** under the aforementioned conditions failed, as a decrease in the yield and enantioselectivity was observed with the reaction cycles. These results were explained by a possible leaching of the catalyst during product extraction.

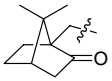
Worse results were obtained when catalysts **71b** and **71c** were used (entries 3 and 4 in Table 6), the best results being achieved by using methylenechloride as a solvent. Under these conditions different acyclic, as well as cyclic, ketones could be used as the source of the nucleophile giving the expected products **19** with, in general, modest results (42–88% yield, 28–38% de, and 23–94% ee).[116]

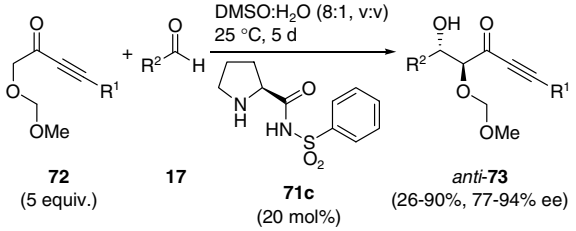
Attempts to improve the aforementioned results by using diastereomeric camphorsulfonimide derivatives **71d** and **71e** also failed (entries 5 and 6 in Table 6), both catalysts giving similar enantioselectivities independent of the diastereoisomer used.[117]

Catalyst **71c** has been surprisingly and successfully used in the aldol reaction using ynones **72** as the source of the nucleophile giving as the main product *anti*-**73** with good diastereoselectivities (50–90%) and enantioselectivities (Scheme 25), with the best results being obtained for the less bulky ynone (R^1 in **72**).[118] Compounds **73** are very unstable and could be transformed into the corresponding 3-oxotetrahydrofuranone derivative by the addition of an alkoxy moiety at the α-position of the triple carbon–carbon bond, catalyzed by phosphine compounds.

Table 6. Enantioselective aldol reaction using imides **71**

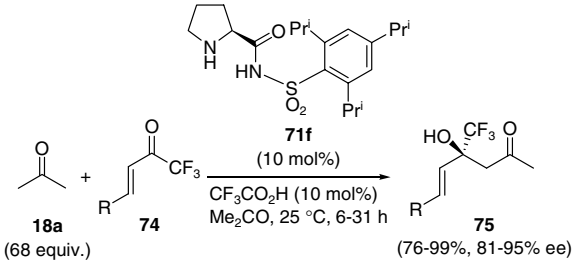


Entry	R	Reaction conditions	Yield (%)	ee (%)
1	4-MeC_6H_4	DMSO/Me_2CO (4:1, v:v), **71a** (30 mol %), 25 °C, 24 h	92	98
2	4-MeC_6H_4	[bmim]BF_4, **71a** (30 mol %), 25 °C, 22 h	96	84
3	Me	CH_2Cl_2/Me_2CO (4:1, v:v), **71b** (20 mol %), 25 °C, 2 d	78	79
4	Ph	CH_2Cl_2/Me_2CO (4:1, v:v), **71c** (20 mol %), 25 °C, 24 h	49	84
5		DMF/Me_2CO (4:1, v:v), **71d** (20 mol %), 25 °C, 24 h	47	63
6		DMF/Me_2CO (4:1, v:v), **71e** (20 mol %), 25 °C, 24 h	78	60



Scheme 25.

3.3.2. Ketones as electrophiles. The very bulky sulfinimide **71f** has allowed the intermolecular aldol reaction using highly electrophilic ketones, such as compounds **74** (Scheme 26). The addition of trifluoroacetic acid (10 mol %) was critical in order to obtain products **75** with good results. The absolute configuration of the final aldol was determined on basis of crystallographic determinations. Finally, it should be pointed out that other different methyl alkyl ketones could be used with similar results, the reaction always taking place at the methyl group.[119]

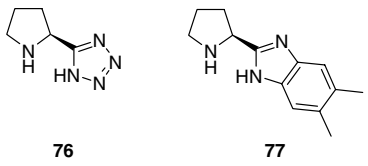


Scheme 26.

3.4. Heteroaromatic pyrrolidine derivatives

Tetrazoles and carboxylic acids have similar aqueous pK_a values. However, tetrazole has a higher pK_a value in DMSO (8.2) than in acetic acid (12.3).[120] Moreover, tetrazoles showed higher solubility, lipophilicity, and metabolic stability than the analogous carboxylic acids, being frequently used as their bioisosteres. The reaction between different ketones **18** (2 equiv) and chloral monohydrate ($R^3 = CCl_3$ in **17**, Table 2) has been catalyzed by tetrazole **76** (5 mol %) in acetonitrile affording the expected products **19** with high yields (35–88%) and enantioselectivities (36–97%).[121] As usual, when the reaction was performed using cyclopentanone as the source of the nucleophile, isomer *syn*-**19** was the main product (80% de), whereas using cyclohexanone, the main product was *anti*-**19** (92% de). Other alkyl methyl ketones, as well as aldehydes (trifluoroacetaldehyde monohydrate or aqueous formaldehyde) could be used successfully, with the reaction always taking place at the methylene position of the ketone. Finally, it should be pointed out that the reaction can be also performed with aryl methyl ketones, this being the only example presented in the literature where aryl ketones have been used.

Catalyst **76** (20 mol %) has shown its activity in the reaction between acetone **18a** (34 equiv) and several aromatic



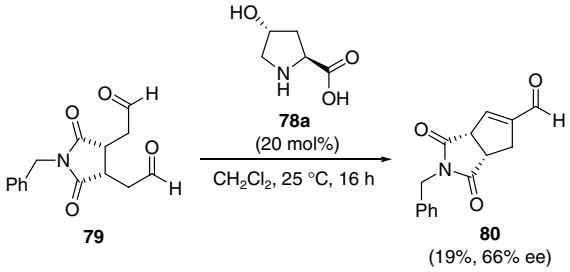
or aliphatic aldehydes in DMSO/Me_2CO mixture (4:1, v:v), achieving products **19** with good yields (65–82%) and enantioselectivities (63–99%) in very short reaction times (10 min–13 h). The high solubility of catalyst **76** permitted its use in other solvents, as well as in the presence of 10 mol % of water without affecting the aforementioned results.[122]

The related heterocyclic compound **77** (20 mol %), in conjunction with trifluoroacetic acid (20 mol %), has been used as a catalyst in the now classical intermolecular aldol reaction giving good results.[123] For example, and only for comparison with other catalysts, the reaction between equimolecular amounts of acetone **18a** and *p*-nitrobenzaldehyde **17a** in THF at −5 °C gave the expected product **19a** with 67% yield and 82% ee (for instance compare with entry 1 in Table 2 and Tables 5 and 6).

3.5. 4-Hydroxyproline derivatives

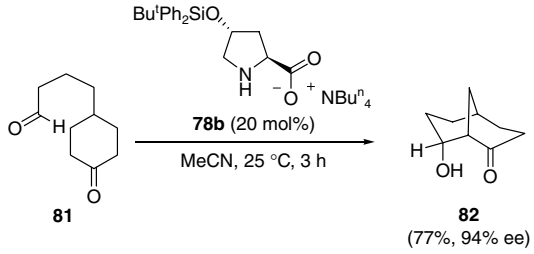
Although 4-hydroxyproline **78a** is a less common amino acid, it has been extensively used in asymmetric synthesis due to it being inexpensive and the possibilities of structural modification, which offers the additional hydroxy group.

3.5.1. Intramolecular reactions. Among more than forty organocatalysts tested in the enantioselective desymmetrization of *meso*-3,4-disubstituted-1,6-dialdehydes **79**, 4-hydroxyproline **78a** emerged as the best catalyst with regard to enantioselectivity concerns (Scheme 27). The intramolecular aldol reaction gave the corresponding chiral bicyclic compound **80** albeit in low yield and in 66% ee.[124]



Scheme 27.

The tetrabutylammonium salt **78b** derived from 4-*tert*-butyldiphenylsilyloxyproline was a very active catalyst in the 6-(enolexo)-*exo*-trig process to give chiral 8-hydroxybicyclo[3.3.1]nona-2-one **82** with an excellent result (Scheme 28), including diastereoselectivity (98% de). The best reaction conditions involved the use of acetonitrile as the solvent and ammonium salt as the catalyst. The latter fact is still unclear but it should be related with the



Scheme 28.

increment in the effective concentration of the catalyst avoiding the zwitterionic form of the simple amino acid.[125]

The diastereoselective annulation of compounds of type **2** (R = chiral moiety, $n = 2$) has recently been performed using 4-*tert*-butyldiphenylsilyloxyproline **78c**.[126]

3.5.2. Intermolecular reactions

3.5.2.1. Ketones as source of nucleophile. Different substitutents have been attached to the hydroxylic group of catalyst **78a** in order to improve their efficiencies and to facilitate their recovery and recyclable properties (Table 7).

The first example was catalyst **78d**, which has a polyfluorous tail anchored to the hydroxyl group (entry 1 in Table 7). As a result, the reaction could be performed in a biphasic trifluoromethylbenzene/acetone system affording the expected product **19a** with similar results to those obtained using proline **1** in DMSO (compare with entry 1 in Table 2). Decreasing the amount of catalyst **78d** to 7 mol % led to an important detrimental effect in not only the yield, but also the enantioselectivity.[127]

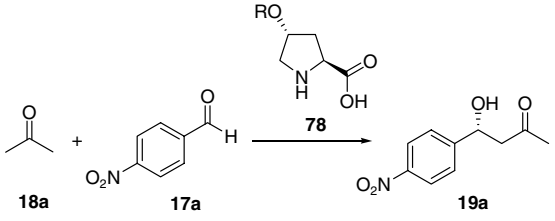
Catalyst **78e** allowed the reaction in either classical organic solvents or ionic liquid to be carried out.[128] The reaction using acetone as both source of nucleophile and organic solvent gave the expected product **19a** with similar results to those using an ionic liquid (entries 2 and 3 in Table 7). However, the catalyst could be reused at least four-times with erosion on the initial results, under the latter reaction conditions. Similar yields and enantioselectivities were found when other highly electrophilic aromatic aldehydes were used, while results were accountably lower when benzaldedyde or *p*-methylbenzaldehyde were used as the electrophilic partner of the aldol reaction.

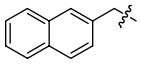
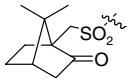
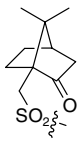
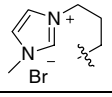
In order to increase the solubility of the catalyst in common solvents, compound **78f** was prepared. However, the reaction had to be carried out at low temperature in order to improve the previous enantioselectivities, with the normal cost of decreasing the chemical yield (Table 7, entry 4).[129]

The preparation of very hindered catalysts **78g** and **78h** allowed us to reach very good levels of enantioselectivity (entries 5 and 6 in Table 7), with the camphorsulfonyl derivative **78h** giving better results even when using half the amount of catalyst.[130]

The introduction of an ionic liquid motif at the hydroxy group in catalyst **78i** allowed to perform the reaction under

Table 7. Enantioselective aldol reaction using 4-hydroxy-proline derivatives **78**



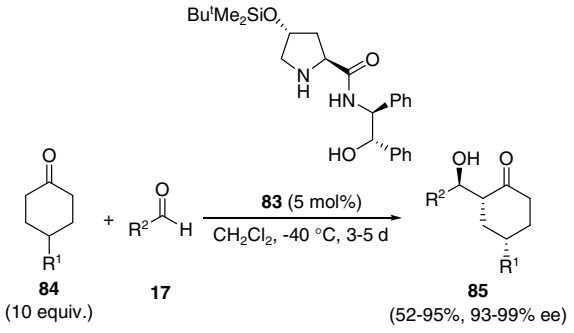
Entry	R	Reaction conditions	Yield (%)	ee (%)
1	$C_8F_{17}(CH_2)_2$	$PhCF_3/Me_2CO$ (4:1, v:v), **78d** (25 mol %), **18a** (27.2 equiv), 25 °C, 24 h	72	73
2	Ph	Me_2CO, **78e** (5 mol %), **18a** (27.2 equiv), 25 °C, 8 h	75	76
3	Ph	[bmim]PF_6, **78e** (5 mol %), **18a** (27.2 equiv), 25 °C, 2 d	81	75
4		Me_2CO, **78f** (5 mol %), **18a** (n.d. equiv), −25 °C, n.d. h	41	86
5		DMF/Me_2CO (4:1, v:v), **78g** (20 mol %), **18a** (11 equiv), 25 °C, 18 h	60	81
6		DMF/Me_2CO (4:1, v:v), **78h** (10 mol %), **18a** (11 equiv), 25 °C, 18 h	71	90
7		[bmim]PF_6/Me_2CO (1:1, v:v), **78i** (10 mol %), **18a** (27.2 equiv), 25 °C, 24 h	94	82

n.d. stands for not determined.

ionic liquid phase conditions with very good results (entry 7 in Table 7). Although the enantioselectivity was constant after a sixfold recycling process, the chemical yield suffered a minor decrease.[131]

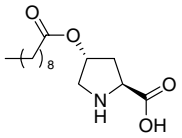
In addition to acetone **18a**, other aliphatic ketones have been used as a source of nucleophile in the intermolecular aldol reaction. Thus, catalyst **78c** (10 mol %) has shown to be very efficient in the reaction between cyclopentanone and cyclohexanone (**18c**, 5 equiv) and different aromatic aldehydes bearing electron-withdrawing groups in the presence of water (3 equiv) at room temperature affording mainly the corresponding *anti*-**19** isomer with good yields (78–92%), diastereoselectivities (64–90%) and excellent enantioselectivities (95–99%). However, moderate yields (21–76%), albeit good diastereo- and enantioselectivities, were obtained using either aromatic aldehydes bearing electron-donating moieties or aliphatic aldehydes, including aqueous formaldehyde. Other different ketones such as α-hydroxyacetone **23a** gave worse results. Finally, it should be noted that the amount of catalyst **78c** could be reduced to 1 mol % without affecting the yields or enantioselectivities, but increasing the corresponding reaction times.[132]

Amide derivative **83**[133] has been used as a catalyst in the aldol reaction using different ketones and aldehydes. Although the results using acyclic ketones were good (for comparison compound **19a** was obtained in 57% yield and 91% ee in CH_2Cl_2 at −40 °C),[133b] better results were obtained using cyclic ketones, such as cyclohexanone, tetrahydro-4*H*-thiopyran-4-one, and tetrahydro-4*H*-pyran-4-one, affording in all cases the corresponding isomer *anti*-**19**, **30**, and **60**, respectively. More interesting has been its use in the enantioselective desymmetrization of cyclic ketones **84** by aldol reaction with substituted benzaldehyde derivatives (Scheme 29), which gave as the main compound isomer **85**. In this process, molecules **85** with three different stereogenic centers could be obtained in only one synthetic operation.[133a]



Scheme 29.

3.5.2.2. Aldehydes as source of nucleophile. Catalyst **78j** (10 mol %) emerged as the best catalyst from another related ester derivative set for the intermolecular aldol reaction using enolizable aldehydes **20** (5 equiv) as the source of the nucleophile (for comparison see Table 4) and water (18 equiv) as the additive (for a discussion on the problem of water in organic solvents see previous Section 3.2.1.1). The main product was the isomer *anti*-**43**, which in fact was isolated after in situ reduction to the corresponding 1,3-diol (29–97% yield, 60–90% de, 77–99% ee). The length of the alkyl chain of the catalyst seemed to play an important role, with longer or shorter chains giving lower results; this fact might be connected with the emulsion character of the reaction.[134]



78j

3.6. Proline peptide derivatives

Peptide-based catalyst containing (*S*)-proline would provide an asymmetric environment similar to that existing in most enzymes and therefore would allow the enantioselective synthesis of aldol products.

3.6.1. Aldehydes as electrophiles. Several structurally different peptides have been prepared and used in the aldol reaction. Among them, better conversions were obtained with N-terminal proline-based peptide of type **86**. When simple dipeptide **86a** was used as the catalyst in the presence of trifluoroacetic acid and *N*-methylmorpholine (NMM), product **19a** was obtained almost quantitatively in a discrete enantioselectivity (Table 8, entry 1).[135] This result could be slightly improved upon by increasing the peptide sequence to a tetrapeptide.

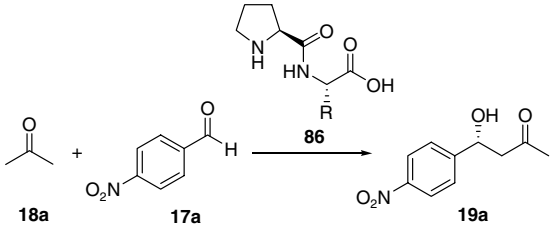
Dipeptide **86b** (entry 2 in Table 8) emerged from a seven N-terminal proline-based dipeptide set as the best catalyst with regards to the enantioselectivity.[136]

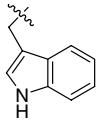
Similar results were obtained with catalyst **86c** (Table 8, entry 3), with the use of *N*-methylmorpholine (NMM) and propylene glycol methyl ether (PGME-5000) being compulsory in order to obtain good yields and enantioselectivities.[137] Under these conditions several aldehydes, including aromatic ones bearing either electron-withdrawing or electron-donating groups and aliphatic derivatives, afforded aldol products **19** with high yields (62–96%) and good enantioselectivities (53–99%).

Water can be used as the solvent in reactions promoted by dipeptide **86d** (entry 4 in Table 8). However, the use of *N*-methylmorpholine (NMM) and sodium dodecyl sulfate (SDS) was necessary in order to obtain good results. The enantioselectivities found could be improved upon by the use cyclic ketones instead of simple acetone **18a** giving the expected products **19** with good yields (67–94%) and enantioselectivities (72–95%). Surprisingly in these cases, the major diastereoisomer was *anti*-**19** for the case of cyclohexanone (50–99% de), whereas diastereoisomer *syn*-**19** was mainly obtained (18–30% de) for the case of cyclopentanone.[138]

The C-terminal carboxylic acid group of different N-terminal proline based dipeptide has been converted into

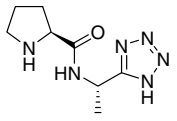
Table 8. Enantioselective aldol reaction using proline peptide derivatives **86**



Entry	R	Reaction conditions	Yield (%)	ee (%)
1	H	DMSO/Me_2CO (4:1, v:v), **86a** (40 mol %), CF_3CO_2H (40 mol %), NMM (100 mol %) **18a** (27.2 equiv), 25 °C, 18 h	99	46
2	CH_2OH	DMSO, **86b** (30 mol %), **18a** (n.d.), 25 °C, 18 h	87	77
3	CH_2Ph	DMSO/Me_2CO (4:1, v:v), **86c** (20 mol %), NMM (100 mol %), PGME-5000 (5 mol %) **18a** (13.6 equiv), 0 °C, 24 h	96	73
4		H_2O, **86d** (20 mol %), NMM (20 mol %), SDS (5 mol %) **18a** (6 equiv), 0 °C, 3 h	94	58

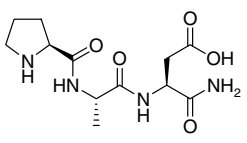
n.d. stands for not determined.

benzoimidazole or tetrazole in order to increase their solubility in typical organic solvents. Thus, the tetrazolic catalyst **87** (10 mol %), in combination with triethylamine (10 mol %), was active in the intermolecular aldol reaction between acetone **18a** (10.9 equiv) and several highly electrophilic aldehydes in DMF, giving the corresponding aldols **19** with good yields (48–69%) and enantioselectivities (74–96%). However, the use of other less electrophilic aldehydes, such as benzaldehyde or aromatic aldehydes bearing electron-donating groups did not afford the expected aldol products.[139]

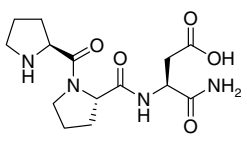


87

A library of 3375 different tripeptides linked to a Tentagel resin by means of a bifunctional lysine linker, which was functionalized at the other end with a ketone derived from levulinic acid was allowed to react with a dye-marked benzaldehyde derivative at 25 °C.[140] Only 1% of the aforementioned beads were bright red colored, indicating that tripeptides of these beads might catalyze the aldol reaction, since they were able to form iminium salts. The isolation of these tripeptides showed the presence of two main consensus sequences **88** and **89**, all structures having a proline residue at the N-terminal position, and a carboxylic acid moiety. Peptides without any of these two groups gave poorer results. Even peptides having these moieties but at different positions resulted in catalysts with lower activities than **88** and **89**.



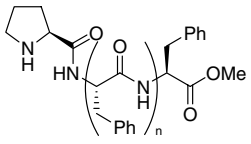
88



89

The conformational analysis of these two sequences showed a preferred turn-like structure, in which the secondary amine of proline was very close to the carboxylic acid moiety of the aspartic acid residue. However, catalyst **89** (1 mol %) was 30-fold more active than compound **88**, for instance, giving product **19a** in 99% yield and 80% enantiomeric excess, in only 4 h at room temperature, and using only a slight excess of acetone **18a** (5.1 equiv). Remarkably, the absolute configuration of product **19a** was opposite to that obtained using (*S*)-proline **1** and also to that obtained using catalyst **88**. The possible reason for this behavior resides in that catalyst **88** is a left-handed turn peptide structure, whereas catalyst **89** is a right-handed one, and therefore behaves almost as a mirror image as far as the aspartate acid residue, and stereochemistry outcome of the reaction, is concerned.[140]

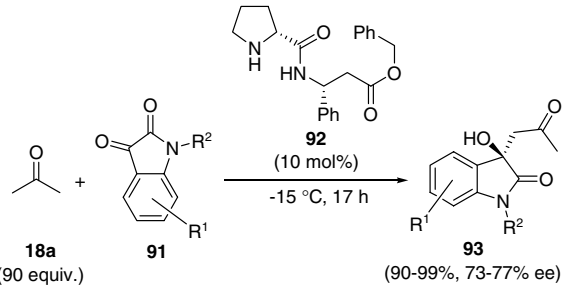
Functionalized ketones, such as α-hydroxyacetone **23a** (29.2 equiv) have been used as a source of nucleophile in the intermolecular aldol reaction with highly electrophilic aldehydes, using different N-terminal proline peptide derivatives (10–20 mol %) in mixtures of THF/water at 0 °C. Among ten different di-, tri-, tetra-, penta-, and hexapeptides catalysts tested **90a** and **90b** emerged as the best sequences giving mainly product *iso*-**25** ($R^1 = H$) in 82% and 76% yield, and 82% and 87% ee, respectively,[141] the presence of lipophilic phenylalanine residues being necessary to obtain good results.



90a: n = 2
90b: n = 3

3.6.2. Ketones as electrophiles. Only one example of using ketone derivatives as electrophiles has been reported, using N-terminal (*S*)- or (*R*)-proline dipeptide derivatives. From

a set of 15 different dipeptides bearing α- or β-amino acid residues tested in the reaction between acetone **18a** (source of the nucleophile and solvent) and isatins **91**, catalyst **92** afforded the best enantioselectivities (Scheme 30).[142]

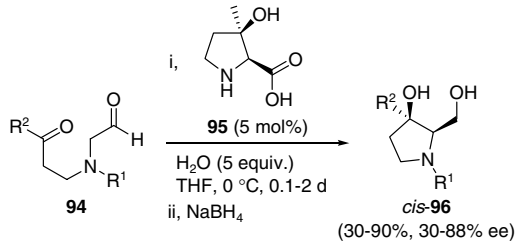


Scheme 30.

3.7. Other pyrrolidine derivatives

As has shown in previous sections, proline and its direct derivatives are very efficient catalysts for the aldol reaction. In this section, other systems, which contain the successful pyrrolidine motif with other functionalities, will be introduced.

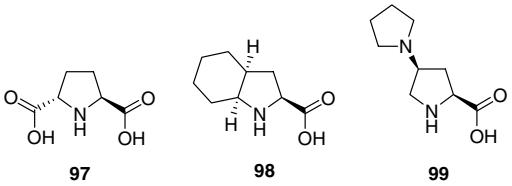
3.7.1. Intramolecular reactions. (2*S*,3*R*)-3-Hydroxy-3-methylproline **95** has been used as a catalyst in the 5-(enol-exo)-*exo*-trig process, is outlined in Scheme 31. While simple proline **1** afforded product **96**, after in situ reduction, as a racemic mixture, catalyst **95** gave moderate to good results, with the *cis*-**96** being the main, even the only, isolated product. The nature of R^1 and R^2 has an important effect not only on the enantiomeric excess but also on the reaction rate, with aliphatic ketones and tosylamides reaching the best results.[143] Further oxidation of primary alcohol of compound *cis*-**96** and amine deprotection process afforded different prolines of type **95** bearing a quaternary stereocenter,[54] some of which are components of polyoxypeptins.



Scheme 31.

3.7.2. Intermolecular reactions

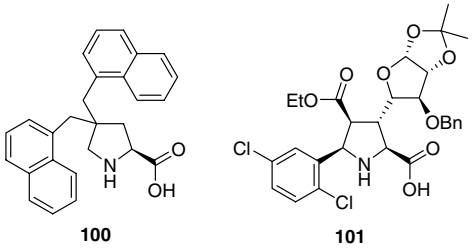
3.7.2.1. Ketones as source of nucleophile. The C_2-symmetry (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid **97** (30 mol %) has been used in a combination of triethylamine (30 mol %) as a catalyst in the intermolecular aldol reaction between acetone (**18a**, 36 equiv) used as source of nucleophile and solvent, and different aromatic aldehydes to achieve the expected products **19** with good yields (40–99%) and moderate enantioselectivities (47–73% ee).[144] Other sources of the nucleophile used, such as α-hydroxyacetone (**23a**), did not improve the previous results. Surprisingly, the use of cyclohexanone as the source of nucleophile gave *syn*-**19** in all cases tested as the main product, albeit with low diastereoselectivities.



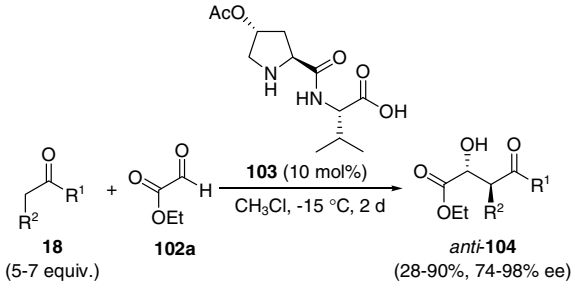
Moderate yields (5–73%) were obtained in the aldol reaction catalyzed by (*S,S,S*)-perhydroindolic acid **98** (10 mol %) between acetone **18a** (28 equiv) and aromatic aldehydes, with the best enantioselectivities being obtained for aromatic aldehydes possessing electron-withdrawing groups (38–87% ee). In this case, the addition of water to the reaction media had a detrimental effect not only on the enantioselectivities, but also on the reaction rates.[145]

(*S*)-*cis*-4-(Pyrrolidin-1-yl)proline **99** seems to be a more efficient catalyst. The reaction of cyclohexanone **18c** (19.2 equiv) with aromatic and heteroaromatic aldehydes in DMF at 0 °C using the aforementioned catalyst (20 mol %) and trifluoroacetic acid (20 mol %) afforded the expected products *anti*-**19e** with good to excellent results (28–99% yield, 88–99% de, and 97–99% ee). These excellent results were attributed to the special proximity of the *cis*-substituent to the carboxylic moiety in the transition state, which would have a beneficial steric and electronic effect. The careful examination of reaction parameters showed that the stronger Brønsted acid in combination with very high concentration reaction conditions provided the best results, although the limitation for the use of aliphatic aldehydes could not be overcome. As in the precedent case, the presence of water was unfavorable with regards to yields and enantioselectivities.[146]

Highly sterically hindered (*S*)-4,4-di(naphtha-1-ylmethyl)proline **100** has been employed as catalyst. The reaction between acetone **18a** (27.2 equiv) and *p*-nitrobenzaldehyde **17a** in DMF at −10 °C catalyzed by **100** (10 mol %) gave the expected products **19a** with good results (87% yield and 95% ee), with these figures being consistent independent of either the aromatic or aliphatic aldehyde used.[147] A slightly lower result was obtained when the more complicated amino acid **101** was used.[148]



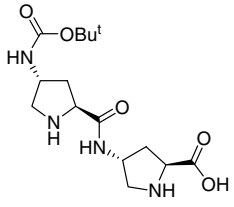
Different peptides having a pyrrolidine motif have been used as a catalyst for the intermolecular aldol reaction between ketones and aldehydes. Ethyl glyoxylate **102a** has been used as an electrophile in the aldol reaction with different aliphatic ketones **18** promoted by the N-terminal acetoxyproline dipeptide **103**, affording the expected hydroxy ester derivative **104** in general, with moderate diastereoselectivities (20–90% de) and enantioselectivities (Scheme 32), the *anti*-isomer being the major product.[149]



Scheme 32.

The main product obtained when either 2-pentanone or 4-methyl-2-pentanone was used as the source of nucleophile was the corresponding *anti*-**104**, the reaction not taking place at the methyl group. As it was previously presented for other proline amide derivatives, the reaction with cyclopentanone gave *syn*-**104** as the main product, whereas other cyclic ketones afforded the expected *anti*-**104** as the main aldol product.

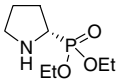
γ-Amino acids have been tested as building blocks in the preparation of peptidic catalyst, such as **97p**. The reaction of acetone **18a** (54.4 equiv) and *p*-nitrobenzaldehyde **17a** in DMSO/acetone mixture (4:1, v:v) at 25 °C catalyzed by **105** (15 mol %) gave the expected aldol **19a** in only 62% yield and 75% ee.[150]



105

Not only is the carboxylic acid moiety, and its related amide, the structural motif joined to the pyrrolidine ring, but also other moieties have been tested. Thus, simple prolinol **106** has been used as a catalyst (35 mol %) in the reaction between fluoroacetone (X = F in **26**, 27.7 equiv) and different aromatic and aliphatic aldehydes in DMSO at 25 °C affording, after 1–4 days, a mixture of all possible isomers (see Scheme 8), with the diastereoisomers *anti*-: *syn*-**27** being the major regioisomer except for glyoxalate derivatives **102**, in which compound *iso*-**28** was the main isolated compound. The overall yields were good (29–82%), *anti*-**27** compound being the main product (50–82% de) isolated in good enantioselectivities (79–87%).[151]

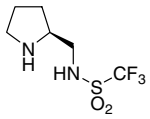
106



107

The high reactivity of aminophosphonate **107** in the aldol reaction permitted the decrease in the amount of catalyst to only 5 mol %, as well as the source of nucleophile **18**, **29**, and **59b** to 2 equiv, affording the corresponding *anti*-aldol products **19**, **30**, and **60** with moderated yields (36–79%), diastereoselectivities (0–80% de), and excellent enantioselectivities (89–98%).[152] It should be pointed out that the reaction between 4-*tert*-butylcyclohexanone ($R^1 = Bu^t$ in **84**) and *p*-nitrobenzaldehye **17a** only gave a 1:1 mixture of corresponding isomers *anti-trans* and *syn-trans*-**85** (compare with results outlined in Scheme 29).

3.7.2.2. Aldehydes as source of nucleophile. The reaction between α-methyl substituted aldehydes **69** (10 equiv) and aromatic aldehydes **17** could be efficiently promoted by the sulfonamide catalyst **108** (20 mol %) in DMSO at 25 °C to afford products *anti*-**70** with high yields (81–97%), and enantioselectivities (91–97%), with the diastereomeric excesses being about 85%.[153]



108

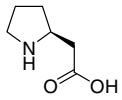
4. Other organocatalysts

Despite the great success obtained when using a chiral catalyst with a pyrrolidine motif, mainly proline amino acid derivatives, other catalysts have been tested in the reaction review here, achieving in some cases better results than the previously reported compounds.

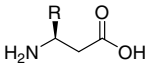
4.1. Intramolecular reactions

Shortly after the enantioselective synthesis of bicyclic dione **4** was reported by industrial research groups,[12] another two groups reported in 1977 their independent work on the synthesis of the opposite enantiomer of compound **4** (*ent*-**4a**: $n = 1$ and R = Me, see Table 1). Compound *ent*-**4a** was obtained in 58% and 83% enantiomeric excess, using β-amino acids, such as β^3-homoproline **109**, (in a strict sense these results would be included in the previous Section 3.7.1, but because it was the first use of a β-amino acid we will include here)[154] and β^3-homophenylalanine **110a**,[155] respectively. After these findings, other β-amino acids were tested as a catalyst for this annulation process. Thus, when (1*R*,2*S*)-*cis*-pentacin **111** (30 mol %) was used as a catalyst for the cyclization of **2a** ($n = 1$, R = Me), the corresponding aldol intermediate *ent*-**3** was obtained in an excellent 90% ee, which was further converted into the corresponding compound *ent*-**4a** by treatment with *p*-toluenesulfonic acid with 94% overall yield.[156] Better results (93% yield

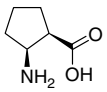
and 86% ee) than proline were obtained when the reaction was performed with starting ketone **2b** ($n = 2$, R = Me; compare with entries 1 and 2 in Table 1).



109



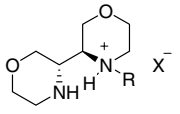
110a: R = CH_2Ph
110b: R = CH_2Pr^i



111

A series of eight different β-amino acids (20 mol %) were tested as catalysts in the 6-(enolendo)-*exo*-trig Robinson annulation of compound **2a** ($n = 1$, R = Me), in DMF at 25 °C.[157] Those bearing aliphatic side chains, such as β-homoleucine **110b**, gave compound *ent*-**4a** with modest yields (29%) but good enantioselectivities (83%), whereas β-amino acids with an aromatic side chain, such as β-phenylalanine **110a** gave the same compound with better yield (64%) but lower enantiomeric excess (75%).

Bimorpholine derivatives of type **112** have shown their efficiency in the intramolecular cyclization of compound **2**.[158] The high solubility of these types of salts allowed the use of different solvents for the annulation process. The best results were obtained with **112a** (5 mol %) in MeCN at reflux after several days, giving compounds **4** in 60–84% yield and 80–95% ee. While trifluoroacetic salt led to the highest conversions, the triflic salt gave the highest enantioselectivities, the addition of water having an important detrimental effect.



112a: R = Pr^i, X = CF_3CO_2
112b: R = Pr^i, X = CF_3SO_3

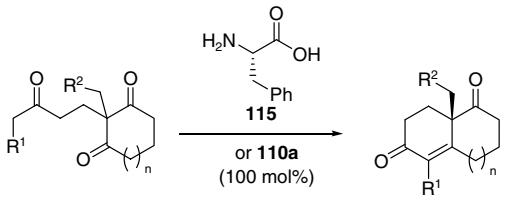
Wieland–Miescher ketone analogues **114** were synthesized by using stoichiometric amounts of either α- or β-amino acids under different reaction conditions (Table 9).

Thus, from a set of 15 different α-amino acids, (*S*)-phenylalanine **115** emerged as the best device to promote the cyclization of triketone **113a** ($R^1 = Me$, $R^2 = H$) in DMSO at 90 °C in the presence of $HClO_4$ (50 mol %), affording bicyclic compound *ent*-**114a** with moderate yield and good enantiomeric excess. The same protocol for the seven-membered ring *ent*-**114b** ($n = 2$) gave good chemical yield and modest enantioselectivity (entries 1 and 2 in Table 9), with the presence of a proton source being beneficial for both examples.[159] Ketone *ent*-**114a** has been also prepared with good chemical yield and enantioselectivity by using amino acid *ent*-**115** and camphorsulfonic acid (CSA, 50 mol %) in an ionic liquid (hexylmethylimidazolinium hexafluorophospate, [hmim]PF_6) with good results (entry 3 in Table 9).[160] The presence of *N*,*N*′-dimethyl-2-imidazolidinone (DMI) as a co-solvent increased the solubility of the catalyst (*R*)-phenylalanine, permitting its reuse for five times with only a slight decrease in the yields obtained and enantioselectivities. Comparable results were obtained for the synthesis of ketone **114a** using β^3-homophenylalanine **110a** as a catalyst and DMF as solvent in the presence of camphorsulfonic acid (CSA, 50 mol %, entry 4 in Table 9).[161]

Other Wieland–Miescher ketone analogues bearing an angular protected hydroxymethyl group have been successfully synthesized by using either catalyst *ent*-**115** or **110a**.[162] Although the concrete reaction conditions depended strongly on the catalyst used, the results were quite similar for both protocols (entries 5 and 6 in Table 9).

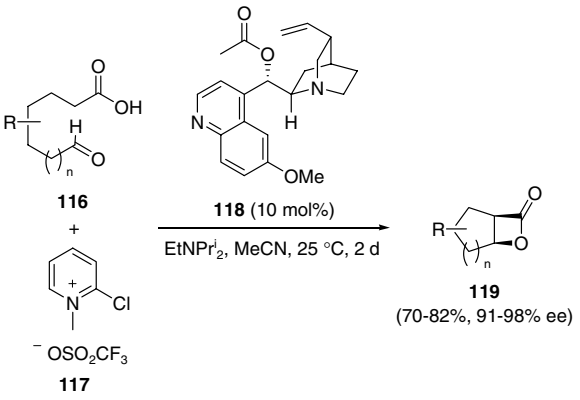
The intramolecular aldol-lactonization process of compound **116** has been catalyzed by *O*-acetyl quinidine (**118**, 10 mol %). The reaction using Mukaiyama's reagent (**117**, 3 equiv) and Hünig's base (4 equiv) in acetonitrile gave the β-lactone system **119** with excellent results (Scheme 33). The use of other esters similar to **118** did not improve the results obtained. Moreover, the change of reagent **117** possessing a more nucleophilic counter ion increases the ring opening process and decreased the chemical yield, with the best results being obtained with compound **117** and the corresponding tetrafluoroborate derivative.[163]

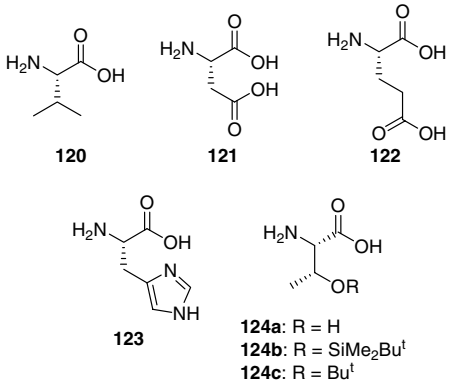
Table 9. Robinson-type annulation



113 **114**

Entry	R^1	R^2	*n*	Reaction conditions	Yield (%)	ee (%)
1	Me	H	1	DMSO, **115**, 1 d, 90 °C, $HClO_4$	56	91
2	Me	H	2	DMSO, **115**, 4 d, 90 °C, $HClO_4$	86	48
3	Me	H	1	[hmim]PF_6, DMI, *ent*-**115**, 15 h, 70 °C, CSA[b]	87	86
4	Me	H	1	DMF, **110a**, 5 d, 70 °C, CSA	83	80
5	Me	AcO	1	MeCN, *ent*-**115**, 4 d, 80 °C, $HClO_4$	80	85
6	Me	AcO	1	DMF, **110a**, 9 d, 60 °C, CSA	77	90





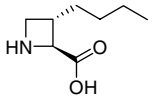
Scheme 33.

4.2. Intermolecular reactions

4.2.1. Ketones as source of nucleophile

4.2.1.1. Aldehydes as electrophiles. Although it was initially reported that acyclic aliphatic α-amino acids were inefficient catalysts for promoting the intermolecular aldol reaction,[24a,c] choosing the reaction conditions carefully the process can be carried out. Thus, six different α-amino acids such as (*S*)-phenylalanine **115**, (*S*)-valine **120**, (*S*)-aspartic acid **121**, (*S*)-glutamic acid **122**, (*S*)-histidine **123**, and (*S*)-threonine **124a** (R = H) were tested in the aldol reaction between acetone **18a** (13.6 equiv) and *p*-nitrobenzaldehyde **17a** in DMSO/Me_2CO (3:1, v:v) at 35 °C containing 1 equiv of water, affording the expected product **19a** with modest results (25–58% yield and 12–53% ee),[164] with compound **120** giving the best results. Several different aromatic aldehydes were used under other solvents (DMF), improving the initial results up to 50–87% yield and 42–72% ee.

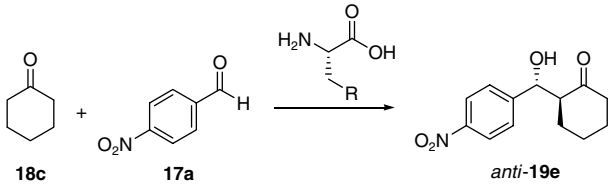
The cyclic azetidine derivative **125** (10 mol %) was also able to promote the reaction between acetone **18a** (27.2 equiv) and aldehyde **17a** giving the expected aldol compound **19a** with a 62% yield and 59% ee.[165]

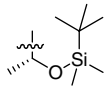
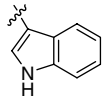
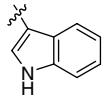
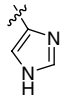


125

Besides the aforementioned modest success found in the standard aldol reaction using simple α-amino acids, several α-amino acids have been tested in the same reaction but using cyclic ketones as source of nucleophile, reaching higher levels of enantioselectivity. For the sake of comparison, results of the reaction of cyclohexanone **18c** with *p*-nitrobenzaldehyde **17a** are presented in Table 10. When the reaction was carried out in DMSO as solvent and in the presence of a small amount of water, (*S*)-alanine **126** was an excellent catalyst, affording a mixture of com-

Table 10. Enantioselective aldol reaction using cyclohexanone **18c**



Entry	R	Reaction conditions	Yield (%)	de (%)	ee (%)
1	H	DMSO, **126** (30 mol %), H_2O (10 equiv), **18c** (3 equiv), 25 °C, 3 d	95	88	99
2	$OSiPh_2Bu^t$	$(CH_2)_5CO$:H_2O (4:1, v:v), **127** (130 mol %), **18c** (5 equiv), 25 °C, 16 h	95	74	98
3		$(CH_2)_5CO/H_2O$ (11:1, v:v), **124b** (2 mol %), **18c** (2 equiv), 25 °C, 20 h	99	82	96
4		$(CH_2)_5CO/H_2O$ (1.4:1, v:v), **128** (10 mol %), **18c** (5 equiv), 25 °C, 19 h	91	66	96
5		H_2O, **128** (20 mol %), **18c** (2 equiv), 25 °C, 1 d	62	82	88
6		DMSO, **123** (30 mol %), SDS (20 mol %), **18c** (5 equiv), 38 °C, 3 d	95	10	42

pounds *anti*-:*syn*-**19c** with good results (entry 1 in Table 10). Using these reaction conditions, another cyclic ketone **31** and different aldehydes yielded the expected products **19** and **32** in generally good yields (42–95%), diastereoselectivities (66–90%) and enantioselectivities (97–99%).[166]

Other α-amino acids containing hydroxy groups have been efficiently used as catalysts in this process (entries 2 and 3 in Table 10). Thus, serine derivative **127**[167] and threonine derivative **124b** (R = $SiMe_2Bu^t$),[168] both protected as silyl ethers, mainly gave compound *anti*-**19e** with excellent results. However, lower chemical yields were found when the reaction was performed using aromatic aldehydes without electron-withdrawing groups.

Other α-amino acids containing aromatic side chain have also been used successfully in this transformation. Hence, (*S*)-tryptophan **128** has been tested under different reaction conditions. The use of a mixture of ketone **18c**/water mainly gave *anti*-**19e** with good yield, moderate diastereoselectivity, and high enantioselectivity (Table 10, entry 4).[169] The use of pure water led to a lower yield and enantioselectivity (entry 5 in Table 10).[170] Under the former wet organic media conditions, several aromatic and heteroaromatic aldehydes were used as electrophiles, providing in all cases tested isomer *anti*-**19** as the main compound of the reaction, with similar results. The protocol was also applied to other cyclic ketones such as thia-derivative **29** and pyranone **59b**, giving similar results for compounds **30** and **60**, respectively. However, the reaction failed when using either acyclic ketones or non-aromatic aldehydes. Moreover, the presence of a carboxylic acid moiety is crucial since the reaction with the methyl ester derived from **128** gave the product as a racemic mixture, the amount of cyclic ketone and water also being very important.[169]

(*S*)-Histidine **123** can be also used as a catalyst on water (no wet organic media, for a complete discussion on the problem of water in organic solvents see previous Section 3.2.1.1), although the presence of a micellar agent such as sodium dodecyl sulfate (SDS) provided the best results, while the use of other different non-ionic or cationic surfactants gave worse results in longer reaction times.[171] In general, the chemical yields were high and independent of the nature of the ketone used (cyclic or acyclic). However, the diastereoselectivity and enantioselectivity were moderate (see for instance entry 6 in Table 10). The change of the reaction media from water-surfactant to poly(ethylene glycol) (PEG-500) had an important and beneficial effect on the results (12-96% yield, 0–98% de, and 26–88% ee).

Different threonine derivatives **124** have been used in the reaction between α-hydroxyacetone derivatives **23** and aldehydes **17**. The use of *O*-*tert*-butyldiphenylsilyl derivative **124b** (R = $SiMe_2Bu^t$, 2 mol %) in a mixture of water/**23a** (2:1, v:v) at 25 °C afforded, contrary to all previous examples, isomer *syn*-**24** (R^1 = H in Schemes 7 and 21) with good results (76–92% yield, 50–78% de, and 91–98% ee),[168] as well as the *O*-*tert*-butyl ester derivative **124c** (R = Bu^t, 20 mol %) using in this case only 2 equiv of **23a** in a mixture of *N*-methylpyrrolidone/water (9:1, v:v) at 4 °C.[172] In both cases the unusual diastereoselectivity was explained as a function of the preferential formation of the *Z*-enamine in the catalytic cycle (see Fig. 1 and Section 7.2) due to the formation of stabilizing hydrogen bonds.

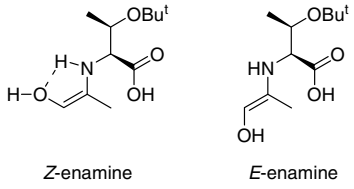
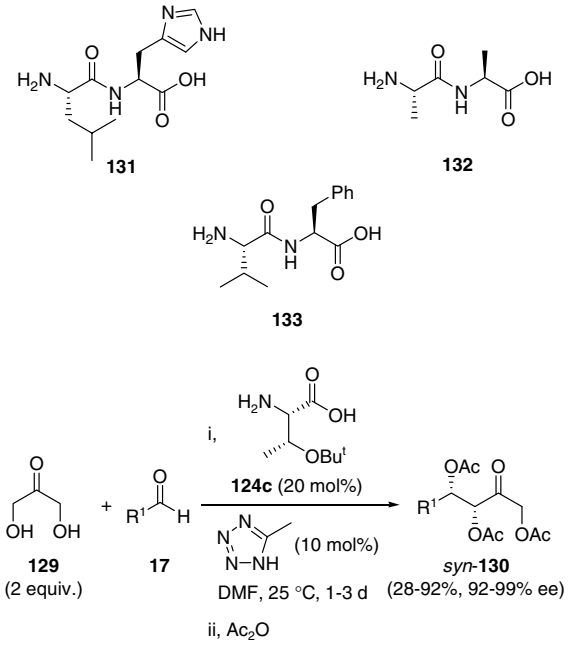


Figure 1.

More interesting is, however, the use of unprotected α,α′-dihydroxyacetone **129** as the source of the nucleophile (Scheme 34). Its reaction with different aromatic, heteroaromatic, and aliphatic aldehydes in DMF catalyzed by threonine derivatives **124c** and 5-methyl-1*H*-tetrazole again gave mainly isomer *syn*-**130** (66–94% de) with excellent results, after the acetylation process.[173] Although, the enantioselectivity was very homogenous, independent of the nature of aldehyde **17**, the chemical yield showed a clear tendency, with the lowest values being achieved for aliphatic aldehydes.

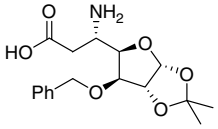


Scheme 34.

Different peptides not containing N-terminal proline residues have also been used as catalysts in the intermolecular aldol reaction. For instance, the dipeptide **131** (30 mol %), containing leucine and histidine residues, was used in the reaction between acetone **18a** (27.2 equiv) and different aldehydes **17** in DMSO/acetone (4:1, v:v) at 25 °C, giving after 10 days the expected compounds **19** with yields ranging from 55% to 86% and with moderate enantiomeric excesses (50–76%). The addition of a co-catalyst, such as *trans*-2,5-dimethylpiperazine (10 mol %), increased the reaction rate, and decreased the reaction time to only 1 day, but decreasing also the enantioselectivity (in the case of compound **19a** from 71% to 55% ee).[174]

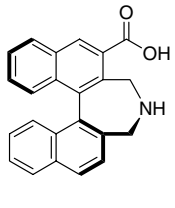
The reaction between cyclic ketones (3 equiv) and aromatic or aliphatic aldehydes using the dipeptide derived from alanine **132** (30 mol %) in wet DMSO (10 equiv of water) afforded the expected isomers *anti*-**19** with good results (50–88% yields, 32–84% de, and 92–99% ee).[166b,175] The use of dipeptide **133** did not produce any important improvement in the previous results.[176]

The glycosyl-β-amino acid **134** (20 mol %) has been successfully been used in the aldol reaction between acetone **18a** (40.8 equiv), used as the solvent and source of the nucleophile, with different aldehydes, reaching up to 90% ee.[177]

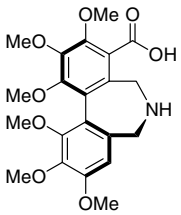


134

The design and use of γ-amino acids **135** as the catalyst and **136** in the aldol reaction has been very successful.[178] Catalyst **135** (5 mol %) was able to promote the reaction between acetone **18a** (27.2 equiv) with aromatic and heteroaromatic aldehydes in DMF/acetone (4:1, v:v), giving the corresponding products **19** with moderate-good yields (22–91%) and excellent enantioselectivities (90–95%) in 24 h. When cyclic ketones, such as cyclohexanone **18c**, tetrahydro-4*H*-thiopyran-4-one **29**, and tetrahydro-4*H*-pyran-*4*-one **59b** were used the best solvent proved to be DMSO, obtaining in all cases the corresponding *anti*-isomer as the main product (38–98% yield, 76–90% de, and 95–99% ee). However, the reaction with cyclopentanone gave a poor result for compound *anti*-**19d** (30% yield, 0% de, 75% ee, compare with entry 4 in Table 2). Surprisingly, the reaction using alkyl methyl ketones took place mainly at the methylene position. In order to increase the nucleophilicity of the amine, and therefore the activity of catalyst, the permethoxylated derivative **136** was prepared.[178c] The amount of catalyst **136** could be reduced to only 0.5 mol % and under these conditions, the reaction of acetone (**18a**, 136 equiv), used as source of nucleophile and solvent, with different aliphatic and aromatic aldehydes **17** gave the expected products **19** with good yields (50–95%), excellent enantioselectivities (91–96%) and reaction rates similar to those found for catalyst **135**.



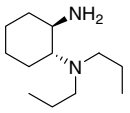
135



136

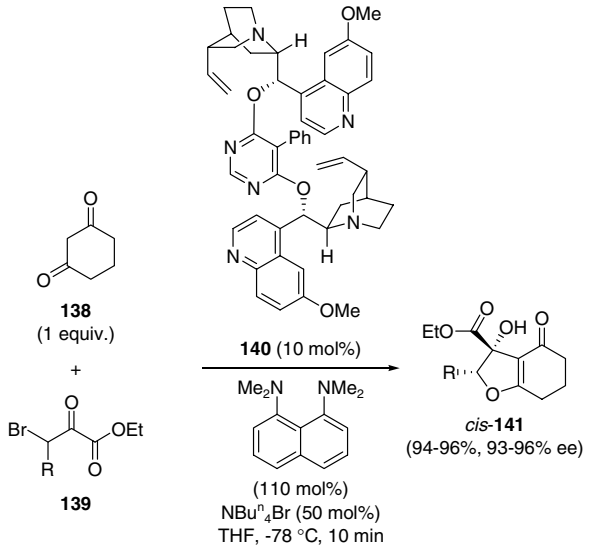
Catalyst **112b** (30 mol %), which has shown its efficiency in the intramolecular aldol reaction (see Section 4.1), was able to promote the intermolecular version, using acetone **18a** (27.2 equiv) as solvent and source of nucleophile and different aromatic aldehydes. The results depended strongly on the nature of the aldehydes, with the best chemical yields of compounds *ent*-**19** being obtained for aldehydes bearing electron-withdrawing groups (48–91%), with other aromatic aldehydes giving very poor yields (10–18%). The enantioselectivities were good (76–94%) in all cases tested and independent of the nature of the aldehyde.[158c]

The reaction of different ketones **18** (20 equiv), acting as a source of nucleophile and solvent, and aromatic aldehydes catalyzed by diamine **137** (10 mol %) in the presence of triflic acid (10 mol %) and *m*-nitrobenzoic acid (10 mol %) gave, surprisingly, compound *syn*-**19** as the main isomer. The results were in general very good (21–99% yield, 60–84% de, and 85–98% ee), although the lowest chemical yields were obtained for reactions using aromatic aldehydes without electron-withdrawing groups.[179]



137

4.2.1.2. Ketones as electrophiles. As in other previous sections, the number of examples of reactions using ketone derivatives is very limited. In fact, only the reaction depicted in Scheme 35 fits into this class. The enantioselective aldol reaction between 1,3-cyclohexanoedione **138** and different α-bromoketoesters **139** followed by final cyclization gave as the main isomer compound *cis*-**141** (92–96% de). Among the different *Cinchona* alkaloid derivatives used, the dimeric system **140** showed the best results, with the presence of a proton sponge and an ammonium salt being of vital importance in order to obtain these good results.[180]

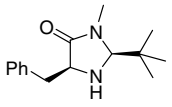


Scheme 35.

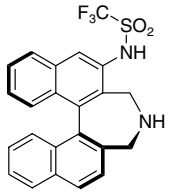
4.2.2. Aldehydes as source of nucleophile. The imididazolidinone **142** (10–20 mol %) catalyzed not only the autoaldol dimerization process of a single aldehyde but also the cross-aldol reaction between aliphatic aldehydes **20**

(source of nucleophile, 10 equiv) and aromatic aldehydes **17** (electrophile). In both cases the yields were high (58–90%), the diastereoselectivity was moderate (60–86% de) and the enantioselectivity was excellent (91–97% ee, compare with Table 4). As the initial aldol product **43** suffered a hemiacetal reaction process with another equivalent of aldehyde, the quench of the reaction was a methanolysis process to form the corresponding dimethyl acetal.[181]

The chiral binaphthylsulfonamide derivative **143** (5 mol %) has been successfully used as the catalyst in the cross-aldol reaction using only 2 equiv of the source of nucleophile in *N*-methylpyrrolidone (NMP). Surprisingly and contrary to other catalyst (see for instance Table 4 and Scheme 17), the main diastereoisomer obtained was *syn*-**19** (40–90% de). These compounds *syn*-**19** were isolated with good chemical yields (22–99%) and excellent enantioselectivities (92–99%).[182]

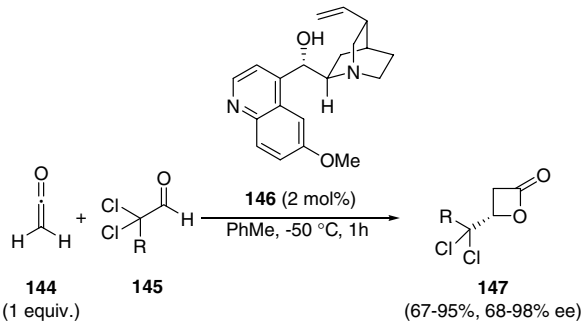


142



143

4.2.3. Ketenes as source of nucleophile. Quinidine **146** was used several years ago as a catalyst in the reaction of ketene **144** (acting as acetic acid equivalent) and different α,α-dichloroaldehydes **145** to give after the cyclization process the corresponding β-lactones **147** in good results (Scheme 36).[183] Similar results were obtained when the ketene was prepared in situ by dehydrochlorination of the corresponding acyl chloride by reaction with the Hünig's base.[183c] A step further was the dimerization of ketenes of type **144** in situ formed from different alkanoyl chlorides, in which 1 equiv of ketene was the source of the nucleophile (by reaction with quinidine) and an equivalent played the role of the electrophile to afford 3,4-dialkyl-*cis*-β-lactone derivatives.[184]



144 (1 equiv.) **145** **147** (67-95%, 68-98% ee)

Scheme 36.

5. Supported organocatalysts

In this section, we will compile different examples of supported catalysts found in the literature and will be presented following the criteria outlined in the content section. Many of the examples presented in this section could be placed in previous ones, as well as some of the previous examples could be included here, however, we prefer to place similar compounds in different sections to draw the reader's attention to the similarities and differences. In all cases, the representative previous results will be referenced when necessary. In these examples proline, as well as its derivatives, has been incorporated into inorganic or organic supports affording new catalytic systems, which can be used under either homogeneous or heterogeneous conditions, with the principal aim of recovering the catalytic species and reusing them. In a strict sense, some of the following examples do not fit the requirements (small organic molecules) to be included in this review. However, we have considered and covered them, since in all cases, the attached polymer or support only plays a marginal role in the catalytic process, although it can modulate the activity, rendering different results to those using the so-called free catalyst.

Attempts to reuse (*S*)-proline **1** have been done by carrying out the aldol reaction in recyclable media such as poly(ethylene glycol)[185] which is a non-toxic solvent (we have already introduced the use of solvents of this type; see entry 3 in Table 8 and entry 6 in Table 10). As a result, the reaction between acetone **18a** (4 equiv) with different aromatic or aliphatic aldehydes at 25 °C has been performed using PEG-400 as a support of proline **1** (10 mol %). Compounds **19** were obtained with good results (58–94% yield and 58–84% ee). These compounds **19** were isolated by diethyl ether extraction from the poly(ethylene glycol) medium, which contained organocatalyst **1**. The reaction media (including catalyst) could be reused tenfold with a slight decrease in the yield, while maintaining the enantioselectivity.

Proline can also be recycled by using ionic liquid medium as a support[186] (we have already introduced the use of ionic liquid solvents; see for instance Sections 2.2.1.1 and 2.2.2.1). Thus, the reaction between acetone **18a** (27.2 equiv) with aromatic or aliphatic aldehydes using proline **1** (30 mol %) was carried out in 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmin]PF_6) affording compounds **19** with moderate results (58–83% yield and 67–71% ee, for previous results using ionic liquids see Refs. 81c, 115, 128, and 160). Together with aldol compound **19**,[186a] a considerable amount of aldol condensation byproduct was detected (10–23% yield of the corresponding α,β-unsaturated ketone). Under the aforementioned conditions, the reaction media could be reused fourfold with a slight decrease in the results. Surprisingly, the chemical yields of reaction could be increased just by decreasing the ketone amount to 7 equiv, with the reaction media being recycled without serious variations in the previous results.[186b]

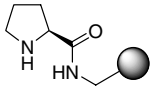
Different silica gel containing ionic liquid tails (3-methylimidazolium motif) have been synthesized with the aim of making the recycling process easier. In this way, the ionic liquid media containing proline (30 mol %) was adsorbed to the modified silica, catalyzing the reaction of acetone

18a (27.2 equiv) and *p*-nitrobenzaldehyde **17a** at 25 °C. Compound **19a** was obtained after one day of reaction in 83% yield and 48% ee.[187] As in the previous media, the amount of aldol condensation by-product was important and the system could be recycled threefold without important variations on the results. The modification of the ionic liquid structure had an important effect on the enantioselectivity, with the best anion and cation partner being BF_4 and 1-*n*-butyl-3-methylimidazolium, respectively.[187b]

Inorganic layered double hydroxides (LDH) have been used as a heterogeneous support for proline.[188] These systems consist of stacks of positively charged mixed metal hydroxide layers that require the presence of interlayer anions to maintain the overall charge neutrality, with anions being proline in these cases. When a Mg–Al–NO_3 LDH system was used as a support for (*S*)-proline and used as a catalyst (1 mol %) in the reaction between acetone **18a** (27.2 equiv) and benzaldehyde in acetone/heptane (1:4, v:v), the corresponding product **19** was obtained with a good chemical yield (95%) but poor enantioselectivity (6%).[188a] The related system derived from Mg–Al–CO_3 LDH showed better behavior reaching up to 94% ee when 35 mol % of proline was charged in the system.[188b]

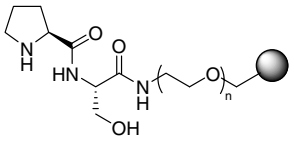
Instead of the above inorganic cationic support, an organic cationic polymer has been introduced in order to immobilize proline. Poly(diallyldimethylammonium) salts were a cationic polymer in which proline could be adsorbed and used as a catalyst (15 mol %) for the reaction between acetone **18a** (30 equiv) and benzaldehyde to give the expected aldol product with moderate results (53–59% yield and 66–69% ee), independent of the molecular mass of the support as well as its anionic counterion (Cl, BF_4, or PF_6). The polymeric system could be recycled sixfold without losing enantioselectivity.[189]

Not only the amino acid proline but also its derivatives have been introduced into different supports to facilitate their recovery and reuse. For instance, a polystyrene resin with an amino group terminal has been coupled to proline, affording the corresponding amide **57i**.[190] This polymeric catalyst (20 mol %) has been tested in the aldol reaction between acetone **18a** (68 equiv) and aliphatic aldehydes, rendering the expected products **19** with good results (55–100% yield and 54–86% ee, compare with Table 5). The immobilized catalyst could be recovered up to threefold and reused with important detrimental effect on the results.

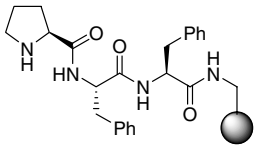


57i

Different peptides with an N-terminal proline have been attached to a PEG–polystyrene resin and tested for the aldol reaction. Among all the compounds tested, resin **148** emerged as the best catalyst (13 mol %) in the reaction between acetone (160 equiv) and *p*-nitrobenzaldehyde **17a** at −25 °C, yielding the expected compound **19a** (98%, 82% ee, compare with entry 2 in Table 8), with the removal of PEG-linker (dipeptide directed bound to the aminopolystyrene resin) lessening the results (**19a**: 26%, 60% ee).[191] The use of tripeptide directly bonded to the resin **149** did not produce any important advantage.[192]

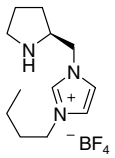


148



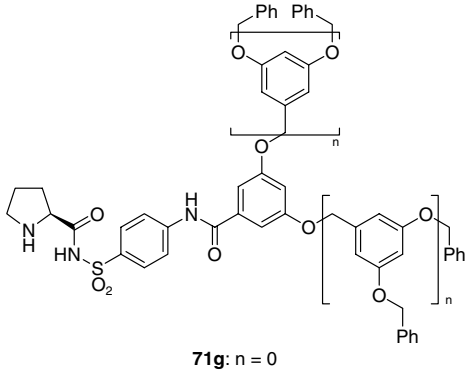
149

Different prolinamines have incorporated the ionic liquid motif to improve the initial reaction conditions. From the results obtained, imidazolium derivative **150** gave the best results. The reaction between cyclohexanone or cyclopentanone (10 equiv) with aromatic aldehydes in the presence of water (100 mol %) and acetic acid (5 mol %), and catalyzed by **150** (20 mol %) gave *anti*-**19** or *syn*-**19**, respectively, with good yields (66–92%), moderate diastereoselectivities (0–66%), and poor enantioselectivities (5–63%), with the catalyst being recovered and reused sixfold, obtaining similar enantiomeric excesses but lower yields and diastereoselectivities.[193]



150

The attachment of proline sulfonimide to a Fréchet dendritic support has been more successful.[194] Compounds **71g–i** (10 mol %) have been tested as catalysts in the reaction between cyclohexanone **18c** (2 equiv) and *p*-nitrobenzaldehyde **17a** in pure water as solvent at 25 °C over one day, affording isomer *anti*-**19e** with excellent results (86–92% yield, 94–98% de, and 98–99% ee), with the second generation catalyst **71h** ($n = 1$) providing the best results.

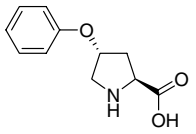


71g: n = 0
71h: n = 1
71i: n = 2

The results obtained are better than those using simple **71a** (*anti*-**19e**: 66%, 94% de, and 97% ee), which can be explained on the basis of the hydrophobic effect of the dendritic wedges. Improved results were obtained by increasing the amount of the source of the nucleophile, with the reaction times being longer for aliphatic and aromatic aldehydes without electron-withdrawing groups.

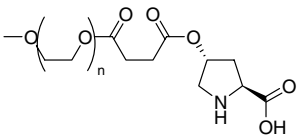
Catalyst **71h** was recovered by precipitation using an *n*-hexane/ethyl acetate mixture and reused fivefold without detrimental effect on the results.[194]

Without any kind of doubt, the 4-hydroxyproline motif has been the most used scaffold to be anchored onto different supports, owing to the presence of an easily modifiable hydroxy group. Thus, compound **78k** has been included in β-cyclodextrin to form a catalytic system (10 mol %), after being suspended in acetone **18a** (68 equiv) at room temperature, promoting the aldol reaction with different aromatic aldehydes.[195] Compounds **19** were obtained with good results (76–90% yield and 71–83% ee) after several hours (16–72 h). The catalytic **78k**-β-cyclodextrin system was recovered by simple filtration and reused fourfold with a slight deterioration of the chemical yield but maintaining the enantioselectivity.

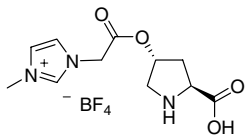


78k

The *trans*-4-hydroxyproline was anchored to a PEG-500 monomethyl ether polymer by means of a succinate spacer rendering catalyst **78l**. This catalyst (30 mol %) was used in the aldol reaction between acetone **18a** (68 equiv) and different aromatic and aliphatic aldehydes giving the expected compounds **19** in modest yield and enantioselectivities (8–81%, 59–98% ee), with the best chemical yield being obtained using DMSO as a solvent. The best enantioselectivity was obtained using DMF as a solvent. When α-hydroxyacetone **23a** (66 equiv) was used as the source of nucleophile in the reaction with cyclohexanecarboxaldehyde, the expected product *anti*-**24** ($R^1 = H$) was obtained in disappointing chemical yield (48%, 90% de, and 96% ee). The catalyst could be recovered by filtration and reused twice with a marginal variation.[196]



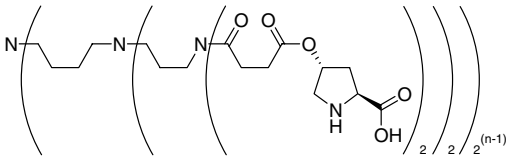
78l: n = *ca.* 110



78m

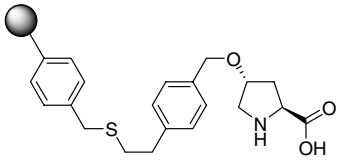
An ionic liquid motif has also been anchored to *trans*-4-hydroxyproline giving compound **78m**.[197] This catalyst (30 mol %) promoted the reaction between **18a** (27.2 equiv) and different aromatic and aliphatic aldehydes in DMSO/acetone (4:1, v:v), affording the expected products **19** (46–83% yield and 60–87% ee), with the catalyst being recycled up to threefold with comparable results. The reaction using pure acetone as solvent and source of nucleophile (136 equiv) gave even better results. A comparison of these results with those represented in Table 7 suggests that the ionic tail plays more than a supporting role in the catalytic cycle (see entry 7 in Table 7).

Commercially available diaminobutane poly(propyleneimine) dendrimers, containing different numbers of free amino groups (4, 8, 16, 32, and 64) on the surface of the structure, have been used as a homogenous support in the preparation of dendritic catalysts of type **78n**.[198] Among five dendrimers tested, second generation compound **78n** ($n = 2$) bearing eight α-amino acid units gave the best result. The reaction between acetone **18a** (27.2 equiv) with *p*-nitrobenzaldehyde **17a** in DMF/acetone (4:1, v:v) at 25 °C catalyzed by **78n** (6.5 mol %) gave the expected compound **19a** in moderate 61% yield and 65% ee, with the use of water compromising the enantioselectivity. The use of other generations gave better chemical yields but lower enantioselectivities. The lower enantioselectivity found for dendrimers of high generation was attributed to the so-called negative dendritic effect, which is caused by the steric hindrance between the proline units at the surface of nanomolecular compound.

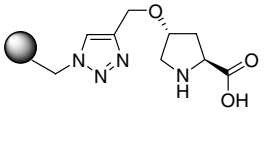


78n: n = 2

The *trans*-4-hydroxyproline motif has been incorporated into a resin following different synthetic strategies. The first example implied the co-polymerization of styrene with a styrylmethylmercapto derivative to form the polymer **78o**. The aldol reaction between cyclohexanone **18c** (5 equiv) with different aromatic aldehydes catalyzed by resin **78o** (10 mol %) in the presence of water (2 mol %) without solvent mainly gave isomers *anti*-**19** with good chemical yields (71–98%), diastereoselectivities (84–92% de), and excellent enantioselectivities (90–98% ee).[199] The resin could be recovered by simple filtration and reused fourfold with highly reproducible enantioselectivities but with a slightly decrease in yield.



78o

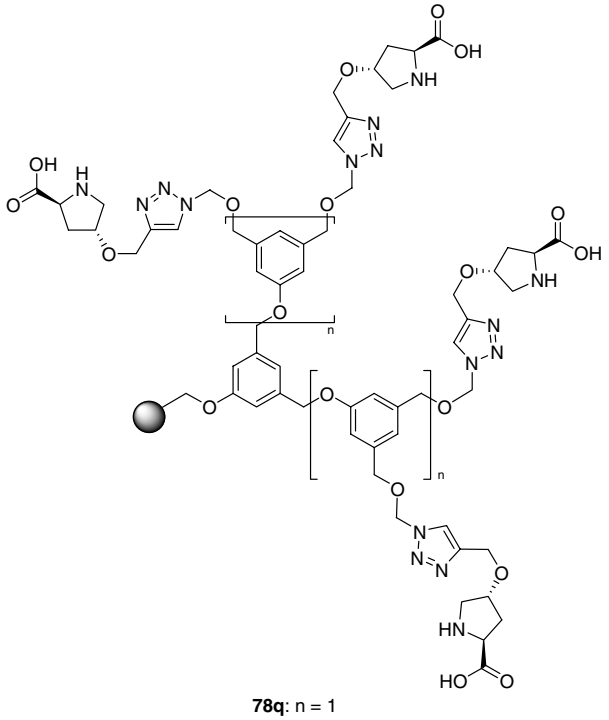


78p

The second general strategy of preparing a catalyst-modified resin is the modification of a commercially available resin. Consider **78p**, which was prepared from azide-substituted Merrifield resin through a 1,3-dipolar cycloaddition reaction with the corresponding *O*-propargyl hydroxyproline derivative.[200] The aldol reaction between alkyl ketones **18** (5 equiv) with different aromatic aldehydes catalyzed by resin **78p** (10 mol %) in the presence of water and poly(ethyleneglycol) dimethyl ether (DiMePEG-2000, 10 mol %) rendered the expected compounds **19** (70–97% yield, 64–94% de, and 93–97% ee). Resin **78p** could be reused threefold without detrimental results. The presence of water as a solvent was crucial to obtain good results, suggesting that the reaction took place at the interphase between polymer

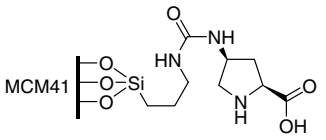
and the aqueous phase, with DiMePEG-2000 facilitating the diffusion of reagents from solvent to the resin interphase.

A long inert spacer is usually placed between the resin and the catalytic site of a reaction in order to minimize the negative influence of resin surface. This strategy has been followed in the preparation of system **78q**. The intercalation of a Fréchet dendritic support between the Wang resin and *trans*-4-hydroxyproline, following the aforementioned cycloaddition reaction permitted the synthesis of different dendritic resins. Among the three dendritic resins prepared, second generation compound **78q** emerged as the best catalytic system. In fact, the reaction between acetone **18a** (27.2 equiv) with *p*-nitrobenzaldehyde **17a** in DMSO/acetone (4:1, v:v) at 25 °C catalyzed by **78q** (30 mol %) gave the expected compound **19a** (90% yield and 84% ee), with lower generation systems giving lower enantioselectivities. The reuse of catalyst produced a sharp decrease in the chemical yield obtained for compound **19a**, while maintaining the enantioselectivity.[201]



78q: n = 1

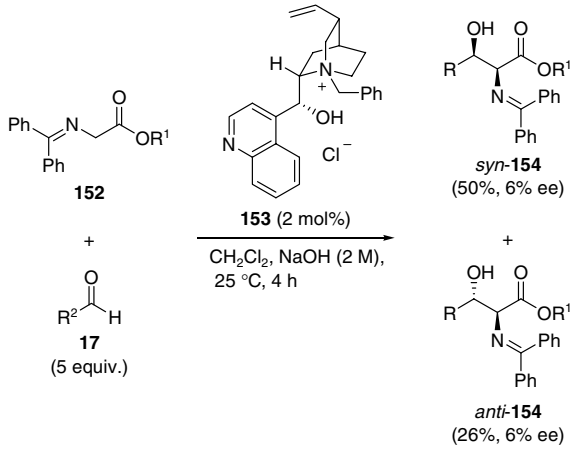
The *cis*-4-aminoproline motif has been incorporated into different mesoporous and lamellar siliceous materials with different topologies and tested in the aldol reaction between α-hydroxyacetone **23a** (29.2 equiv) and aliphatic and aromatic aldehydes. The best results were obtained with catalyst **151** (20 mol %) in DMSO/**23a** (1.6:1, v:v) at room temperature, to afford aldol products **24** ($R^1 = H$) with moderate to good results (55–60% yield, 16–90% de, and 70–99% ee), with the alternative use of microwave decreasing only the reaction times from 1 to 3 days to 10–30 min. Surprisingly, aliphatic aldehydes afforded the expected *anti*-**24** isomer as the main product of the reaction, while the reaction with benzaldehyde afforded the corresponding *syn*-**24** isomer (see Schemes 7 and 21).[202]



151

6. Phase-transfer catalysis

Enantioselective phase-transfer catalysis (PTC) is a generally useful alternative for the synthesis of many chiral compounds. This strategy has been extensively used in alkylation, epoxidation, conjugate addition, and related processes, with the use of chiral ammonium salts being the typical transfer agent.[203] However, the related aldol process has been scarcely investigated. The reaction of glycine derivatives **152** with different aldehydes **17** using cinchonidium salt **153** as a catalyst (Scheme 37) was the first example of this type of reaction.[204] However, this initial example was clearly disappointing; a nearly 1:1 diastereomeric mixture of **154** with very low enantiomeric excess for the case of using hydrocinnamaldehyde [$R^2 = (CH_2)_2Ph$] was reported. The great importance of β-hydroxy-α-amino acids for the pharmaceutical industry has meant that efforts were further focused in this process.

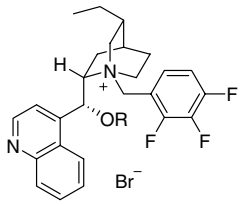


152 + **17** (5 equiv.) → **153** (2 mol%), CH_2Cl_2, NaOH (2 M), 25 °C, 4 h → *syn*-**154** (50%, 6% ee) + *anti*-**154** (26%, 6% ee)

Scheme 37.

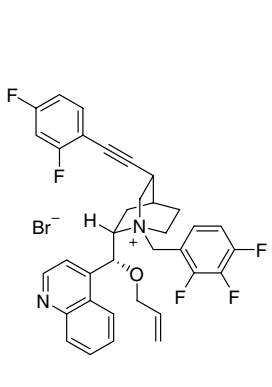
Cinchonidium salts of type **155** were further assayed as catalysts.[205] Whereas the reaction with alcohol derivative **155a** gave a practically negligible enantioselectivity, the reaction when using catalyst **155b** (17 mol %), an excess of aldehyde (4 equiv) and *tert*-butyliminotri(pyrrolidino)phosphorane as organic base (1.7 equiv) gave the expected products **154** with moderate results (34–78% yield, 0–14% de, and 52–83% ee for *syn*-**154**). The iminic aldol products **154** were very unstable to chromatography during isolation and, therefore, were transformed by hydrolysis of the imine and acylation to the more stable amide derivative. While smaller amounts of catalyst **155b** afforded the aldol product with the same enantioselectivity but with lower yield, the use of a smaller amount of phosphazene base gave a lower

yield but higher enantiomeric excess. Aldehydes with aromatic rings provided better results, with those bearing neutral or poor electron-withdrawing groups giving the best enantioselectivities. Catalyst **155b** has been also used as a catalyst in the aldol reaction between α-alkoxy acetophenone derivatives using sodium hydroxide as base.[206] However, the enantiomeric excess for the direct aldol reaction never exceeded 22%.

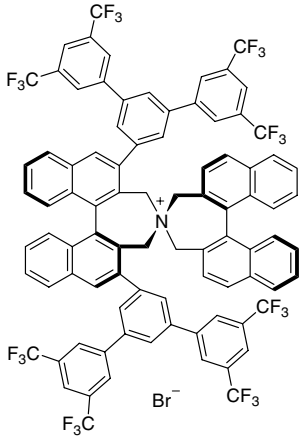


155a: R = H
155b: R =CH_2=$CHCH_2$

The more elaborate catalyst **156** (17 mol %) was used under similar conditions to those previously mentioned using *tert*-butyliminotri(pyrrolidino)phosphorane (2.5 equiv) as an organic base to give compounds **154** with similar results (38–86% yield, 0–82% de, and 2–43% ee for *anti*-**154**) but with the *anti*-**154** isomer being the major product in many cases.[207]



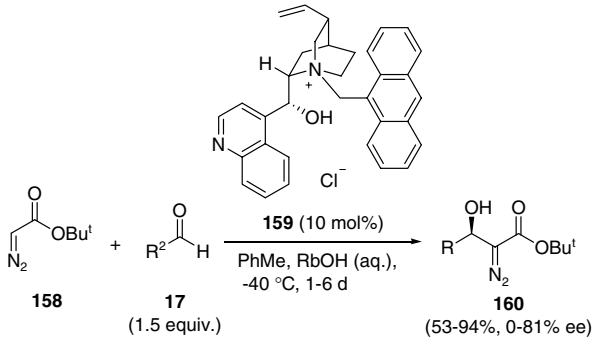
156



157

A real breakthrough occurred when ammonium salt **157** was introduced in this process, since the reaction of glycinate **152** ($R^1 = Bu^t$) and aliphatic aldehydes (2 equiv) could be performed in the presence of only 2 mol % of catalyst and using 1% aqueous NaOH and toluene at 0 °C, affording in short reaction times, the expected product **154** with good chemical yields and diastereoselectivities (39–84% and 33–95%, respectively). Furthermore, excellent enantioselectivities for the main isomer *anti*-**154** (80–98% ee) were obtained.[208] The diastereoselectivity ratio reversed with the reaction time, with the enantiomeric excess of *anti*-**154** decreasing, while that of *syn*-**154** remained unchanged. These facts were attributed to the existence of a retro-aldol process in which the chiral catalyst played an important role. In order to minimize this retro-aldol process, the amount of aqueous base should be decreased, adding inorganic salts (NH_4Cl) to control the pH of the overall process.

Aromatic aldehydes have been successfully used as electrophiles in the enantioselective PTC-aldol process using, as source of nucleophile, diazo ester derivatives **158** and cinchonidium salt catalyst **159** (Scheme 38). From all the bases tested RbOH provided the best results, with the electronic character of the substituent of the aldehyde strongly influencing the enantiomeric excess. The aromatic aldehydes with a strong electron-donor substituent gave racemic mixtures of compounds **160**. The reaction with aliphatic aldehydes gave moderate results except in the case of pivalaldehyde ($R^2 = Bu^t$ in **17**), which reached 81% enantioselectivity.[209]



158 **17** (1.5 equiv.) **159** (10 mol%), PhMe, RbOH (aq.), -40 °C, 1-6 d → **160** (53-94%, 0-81% ee)

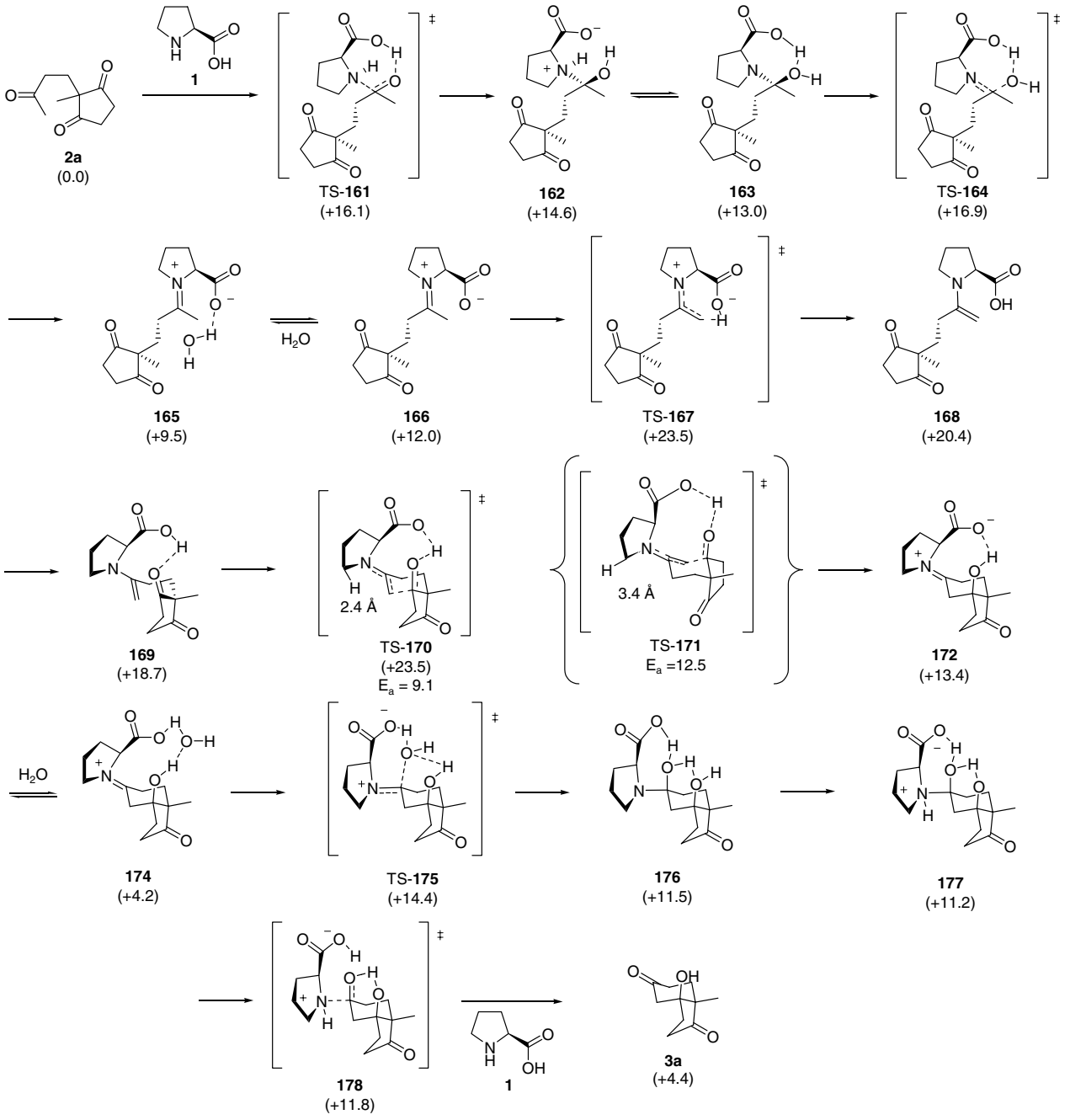
Scheme 38.

7. Mechanistic studies

A great effort has been carried out in order to elucidate the possible mechanism of the reaction catalyzed by proline-type derivatives and in this section will try to summarize the latest results.

7.1. Intramolecular reactions

Initial experiments seemed to show that the intermolecular aldol reaction of triketones **2** catalyzed by (*S*)-proline **1** presented a small dilution effect,[210a] and a small non-linear effect,[210c,d] and therefore the initially proposed mechanism involved the presence of two proline molecules, one forming the enamine nucleophile and the other being a proton relay.[210b] The recent careful repetition of those experiments showed that there is no dilution or non-linear effect.[211] These facts, together with the observation of ^{18}O-incorporation in the final product[212] when the reaction was carried out in the presence of ^{18}O-enriched water meant the initial mechanism was abandoned. Computational calculations not only of the transition-state[213] but also of all possible different steps of the process[214] gave a fuller picture (Scheme 39). Among the initial possible pathways there was once which involved the presence of two proline molecules in the transition state that did not fit with the current experimental data, since the protonated enamine intermediates reduce the nucleophilic character of intermediates and the key transition state has a relatively higher energy (+29.0 kcal/mol). The most likely mechanism pathway involves the formation of enamine **168**, which is the truly nucleophile. The starting carbonyl compound **2a** reacts



Scheme 39. Proposed pathway of the proline-catalyzed cyclization of **2a** with the values of solvation energies (kcal/mol) in DMSO in parentheses.

with the nitrogen atom of proline to afford a zwitterionic iminium intermediate **166**, which after an intramolecular deprotonation gives the nucleophilic enamine **168**. The enhanced nucleophilicity of the enamine C=C bond together with the activation of the carbonyl electrophile in intermediate **169** by the carboxylic acid constitutes the basis of the mechanism, with many steps being equilibria or reversible processes. The transformation **168** to **172** is the rate-determining step. Four possible transition states (two chair and boat like structures) for forming six-membered ring were located and analyzed, with the chair transition states TS-**170** and TS-**171** being lower in energy. In both transition states, the hydrogen bonding of the carboxylic acid proton to the forming alkoxide oxygen provides charge stabilization, with distances being similar. However, the energy barrier to the formation of TS-**170** is 3.4 kcal/mol lower than the barrier to formation of alternative TS-**171** ($E_a = 12.5$ kcal/mol). The extra stabilization of the former transition state is due to intramolecular hydrogen bonding and forces the iminium double bond out of planarity in TS-**171**, which in turn means that conformational restraints are imposed by the hydrindanone ring system. There exits a favorable electrostatic interaction between the α-hydrogen of the nitrogen in the pyrrolidine ring with the oxygen atom of reactive carbonyl group, which contributes to the lower energy of TS-**170** than TS-**171**, with these distances being

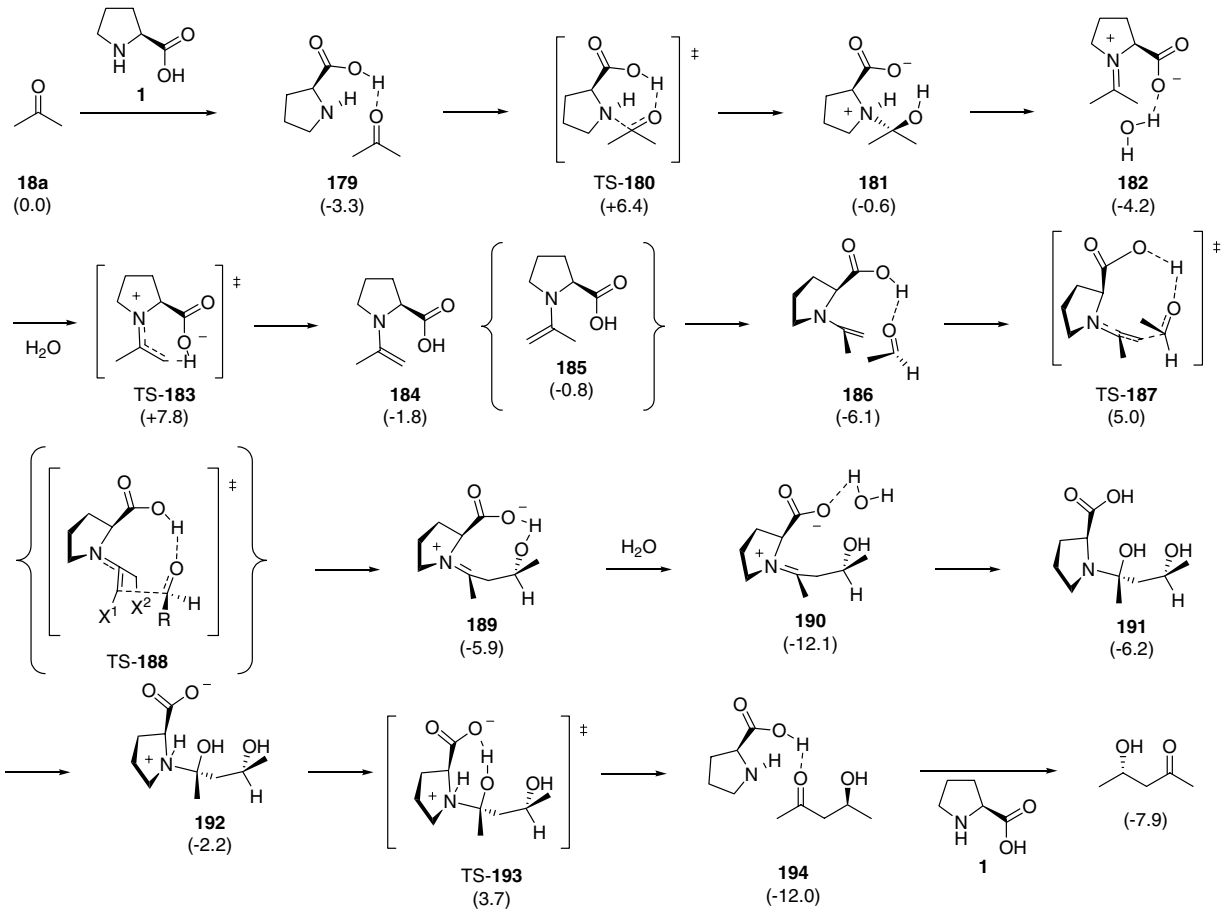
2.4 Å and 3.4 Å, respectively. All these facts mean that the transition state **170** is preferred over alternative TS-**171** and it is also the stereochemistry-determining step of the reaction. After the formation of C–C bond, the hydrolysis intermediate **172** is achieved in a series of easy steps that leads to the release of aldol product **3a** and recovery of catalyst. These steps are analogous, but in reverse order, to those at the beginning corresponding to the formation of zwitterionic iminium intermediate **166**, with the most difficult step being, as expected, the nucleophilic attack of water TS-**175**. This step will compete with the reversal of C–C bond forming step TS-**170** at a low concentration of water, which has an important significance on the obtained enantiomeric excesses.

The important role of the iminium planarity has been further checked with other systems such as *cis*- and *trans*-4,5-methanoprolines,[215] in which the energy required for the *trans*-stereoisomer to achieve the necessary planar iminium arrangement in the corresponding aldol transition state is responsible for its poorer catalytic activity and with other pyrrolidine derivatives as well.[216]

7.2. Intermolecular reactions

The initial computational calculation of all the possible different steps of the intermolecular reaction process[217] showed a similar profile to the intramolecular one (Scheme 40). The process starts with acetone **18a** complexation by proline **1** to form very stable species when the calculations were carried out under gas-phase conditions. However, the stability of **179** is not so high under DMSO conditions. The formation of enamine **184** follows the expected steps. At this point, different authors gave alternative pathways. The original study implies the complexation of this *syn*-conformer (active methylene group relative to carboxylic acid one) in a *cis*-mode, to form intermediate **186**, which through transition state **187** gives zwitterionic intermediate **189**, giving catalyst **1** and the expected aldol product after the usual steps.

In this initial pathway, the enamine formation is the rate-determining step with the asymmetric transition step having a similar energetic level. Alternatively, the *anti*-conformer **185** has been presented as the correct pathway, since the energetic difference between both possible enamine conformers is only 1 kcal/mol and rotation around the single C–N bond could take place very easily.[218] In fact, when the quantum mechanical calculation of the possible transition states for the reaction with acetone (**18a**: $X^1 = X^2 = H$) or cyclohexanone [**18c**: X^1–$X^2 = (CH_2)_3$] with acetaldehyde, benzaldehyde, or isobutyraldehyde were reevaluated,[219] in all cases, the transition state with lower calculated energy was of type TS-**188** (*anti*-enamine, *re*-car-



Scheme 40. Proposed pathway of the proline-catalyzed intermolecular aldol between acetone (**18a**) and acetaldehyde with the values of solvation energies (kcal/mol) in DMSO in parentheses.

bonyl and carboxylic activation or *cis*-mode), which implied the C–N bond rotation prior to the reaction with the electrophile. The stability of this transition state was attributed, as above, to the favorable hydrogen bonding interaction between α-hydrogen of the nitrogen in the pyrrolidine ring with the oxygen of the reactive carbonyl group.

An electrospray ionization mass spectrometry study showed that, in general, the above reaction profile is true, since intermediates of type **181**, **185** (**184**), **189**, and **192** could be detected either as the protonated specie or as the sodium complex.[220]

Whereas further calculations for amide **56** corroborated this hypothesis,[82b] the initial calculation results for the case of tetrazole **76** were unconcluded.[122b] However, a further study showed that although the related *anti*-enamine intermediate had only 0.37 kcal/mol more than the corresponding *syn*-conformer (compare with conformers **184** and **185**), the corresponding transition state (*anti*-enamine, *re*-carbonyl and tetrazole activation, compare with TS-**188**) was 1.99 kcal/mol more stable than any other possibilities, concordant with previous calculations.[221] Moreover, similar calculation studies for alanine **126** as catalysts again showed the initial formation of the corresponding *syn*-conformer, which rotates to the *anti*-one, with the postulated more stable transition stated being related with TS-**188**.[222] Finally, it should be pointed out that these calculation studies have permitted the in silico prediction of the enantioselectivity level of different bicyclic proline analogues.[223]

In addition to all aforementioned calculations in order to describe the possible pathway, an alternative process has been postulated.[224] This new hypothetic pathway goes through the formation of the corresponding heterocyclic oxazolidinone by reaction of proline **1** and ketone **18** (clearly detected by NMR studies, see Fig. 2), and not through the zwitterionic iminium of type **182**. The deprotonation process gives the expected *syn*-conformer **184**, which reacts in a *trans*-mode (with respect to the carboxylic group) with the corresponding electrophilic carbonyl compound. In a simultaneous process, one oxygen atom of carboxylic acid moiety reacts to regenerate the initial oxazolidinone ring.

The overall picture of this simple process is still more complicated due to the partial solubility of α-amino acids in the reaction media.[225] The crystallization of racemic mixtures can lead to three different types of crystals. The most common situation is the formation of a racemate-crystal, in which both enantiomers are included in the unit cell by symmetry. More strange is the case of the conglomerate-crystal, in which a physical mixture of both enantiomerically pure crystals is obtained. The last possibility is the solid-solution-crystal, in which the enantiomers are randomly distributed. However, there is no practical method for predicting whether a given compound will form a crystal of a concrete type. Thus, for example, a large non-linear effect was observed when proline was solved in chloroform in the presence of small quantities of ethanol.[226] The initial enantiomeric excess was 10% and after triturating in the above solvent mixture, the enantiomeric excess reached up to 99%, with the highly selective dissolution of one enantiomer being caused not by a simple extraction of the excess enantiomer, but by the following dissolution and recrystallization mechanism. In this context, the use of a co-solvent could modify the expected crystal structure for the racemic mixture, and therefore change this non-linear effect.

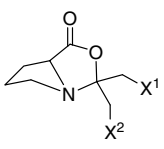


Figure 2.

Under certain conditions it was found that proline with different enantiomeric excesses catalyzed the intermolecular aldol reaction with the same enantioselectivity. The phase study of this process showed that proline formed two solid phases at equilibrium (conglomerate-crystals), and according to the phase rules when three different phases are in equilibrium, all parameters of the system are fixed; the name for this point being eutectic. At this stage, whatever the initial mixture of both enantiomers will render always the same composition for the solved proline.[227] The concentration of the excess enantiomer at the eutectic point depends on the solvent and temperature, even on the presence of doping agents,[228] and closely corresponds to the solubility of the pure enantiomer. However, the solid-solution equilibrium is not always reached for many reactions and so the expected eutectic conditions could not be applied. For instance, α-amino acid proline during this transient period has a higher solubility than equilibrium conditions, which could modify the enantioselectivity of the aldol reaction. This high proline solution concentration under non-equilibrium conditions has been explained as a function of the higher solubility of conglomerate-crystals at the eutectic point to the enantiopure phase than racemate-crystals.[229] All these anomalies could disorientate the most simple interpretation for a non-linear effect as a result of two or more chiral molecules acting in the transition state.[230]

8. Applications to the synthesis of biologically active products

The enantioselective direct aldol reaction, especially the intramolecular version of this process, has been extensively used for the synthesis of biologically active compounds with a wide range of interest. In this section some representative examples of the use of this methodology to the synthesis of complicated natural products and other compounds with relevant biological activities are compiled.

8.1. Intramolecular reactions

The intramolecular aldol reaction catalyzed by α-amino acids, generally proline **1** and phenylalanine **115**, have been

used as powerful tools for the construction of chiral bicyclic frameworks, through the aldol condensation process, used in turn as starting materials for the asymmetric construction of natural products.

Bicyclic aldol product **3a** (R = Me, $n = 1$ in Table 1), coming from the aldol cyclization of triketone **2a**, has been used as a starting material in the synthesis of brexane derivatives.[231] However, bicyclic ketone **4a** and its enantiomer have been more used as the starting material for different natural product synthesis. For example, sesquiterpenes, punctantin A **195**,[232] coraxeniolide A **196**,[233] and taxol (partial synthesis)[234] used compound **4a** as a starting material. It should be pointed out that for compound **196** the corresponding *ent*-**4a** was the correct enantiomer used, as well as in the partial preparation of sesterterpenoide variecolin.[235] Besides these examples, steroids are probably the family of natural products which have used the most extensive compound **4a** in their preparation, as is the case of estrone **197**[236] and derivatives,[237] vitamin D_3 **198** and analogues,[238] cardenolides, and 5β-lanosterol derivatives,[239] the aglycon part of cardiac glycosides,[240] and unnatural *ent*-cholesterol **199** (Chart 1).[241]

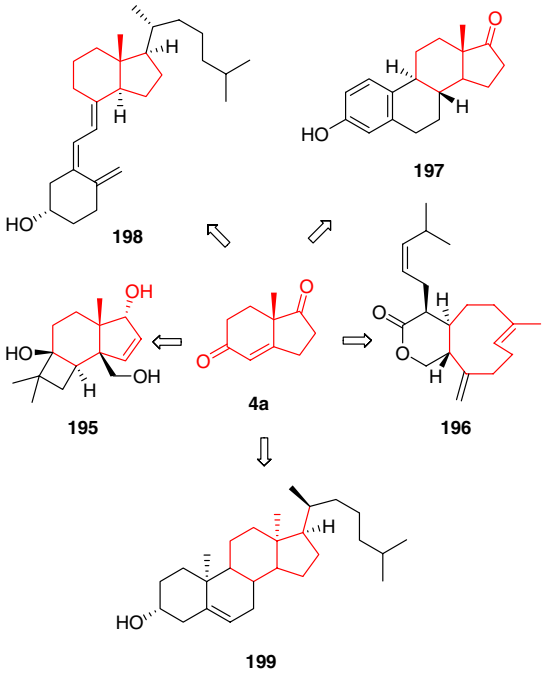


Chart 1. Natural products prepared from **4a**.

Among these bicyclic compounds **4** and **114**, the Wieland–Miescher ketone **4b** (R=Me, $n = 2$) has been extensively used in the synthesis of natural terpenes. Thus, natural sesquiterpenes[242] such as albicanol **200**,[243] (+)-pallescensin A **201**,[244] and (+)-avarol **202**[245] have been synthesized starting from **4b** (Chart 2).

The total synthesis of chiral indolic diterpene derivatives[246] and (−)-paspaline **203**[247] has been also accomplished starting from ketone **4b**, with other diterpenes possessing interesting biological properties[248] such as plaquetet aggregation inhibitor activity,[249] anti-inflammatory agent activity,[250] and cytotoxic activities, such as taxol **204**[251] and structurally related diterpenes[252] using the same ketone as the reagent.

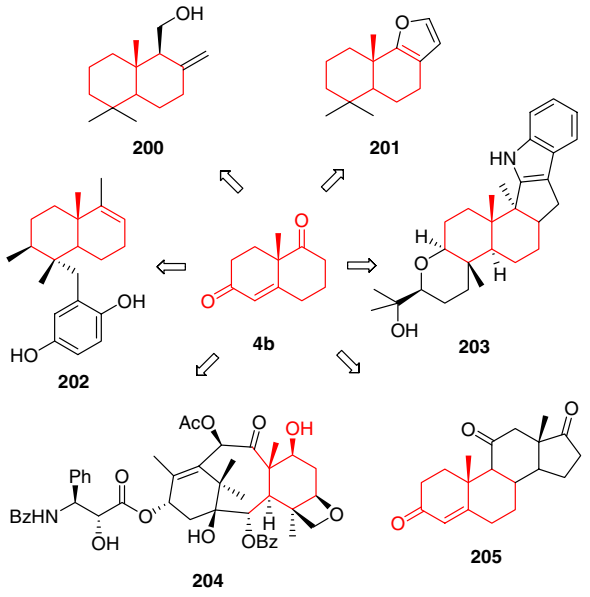


Chart 2. Natural products prepared from **4b**.

The quassin triterpene family[253] and meroterpenes with cholesterol acyltransferase inhibitor activity[254] are examples in which ketone **4b** has used as a starting material, as well as in different steroids,[255] including (+)-adrenosterone **205**,[255d] and the oxytetracyclic core of the potent antibiotic platensimycin.[256]

Different analogous Wieland–Miescher ketones have also been employed in the synthesis of a great amount of natural products. For instance, bicyclic ketone **114a** or *ent*-**114a** has served as starting chiral material in the synthesis of different sesquiterpenes,[257] exhibiting relevant pharmacological activities, or quinine sesquiterpene derivatives,[258] such as popolohuanone E **206**, which has a potent cytotoxicity activity.[259] Diterpenes from the clerodane family,[260] as well as the core of antibiotic terpentecin,[261] and chapecoderin A **207**[262] from the labdane family have been easily prepared following the above strategy. From the family of triterpenes, synthetic terpene 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid **208**,[263] allelochemical brevione B **209**,[264] and partial analogous of the antimalarial agent bruceantin[265] were prepared as above and as depicted in Chart 3.

Chiral bicyclic compound **114d** has served as the common starting point in the synthesis of several natural products (Chart 4), such as (+)-cyclomyltaylane-5α-ol **210**[266] and diterpene (+)-norrisolide **211**, which is employed by molluscans as a chemical defense,[267] as well as in the partial synthesis of antibiotic and antitumor agent GKK1032A_2.[268]

Other bicyclic compounds of type **114** have been used as convenient reagents in syntheses of different steroids,[269] terpenes,[270] and antibiotics.[271]

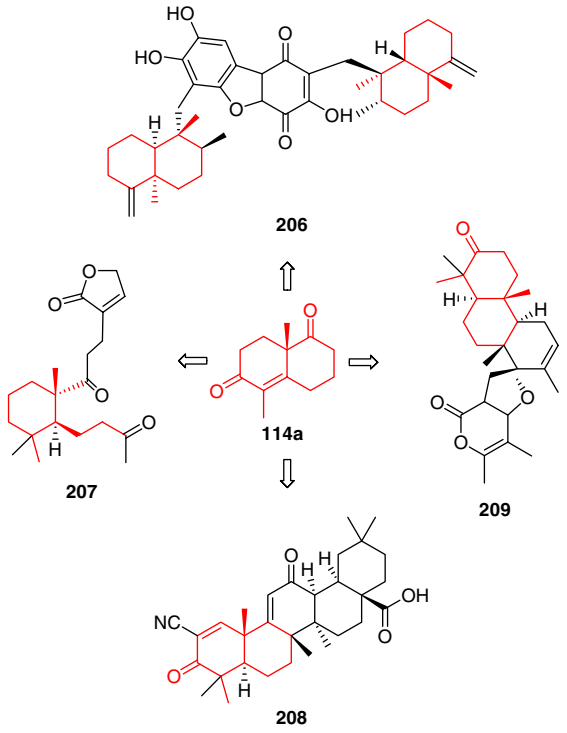


Chart 3. Natural products prepared from **114a**.

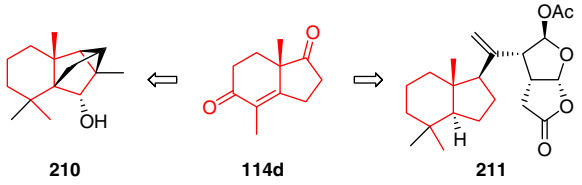
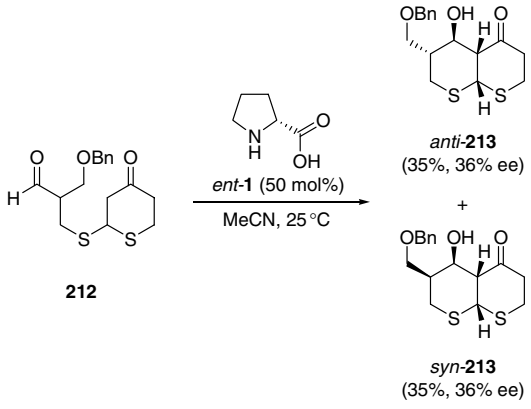


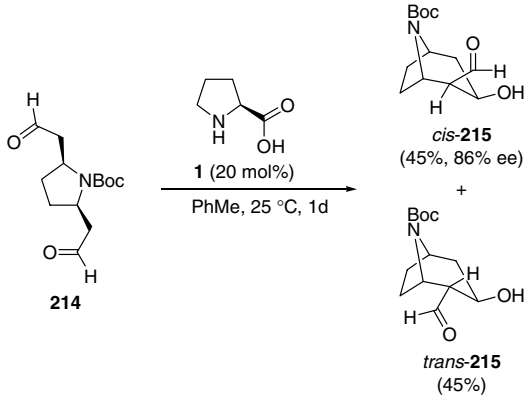
Chart 4. Natural products prepared from **114d**.

Not only have bicyclic compounds **4** and **114** shown their potential in natural product synthesis but the use of this direct intramolecular aldol reaction has given results, which are very appropriate for the construction of crucial chiral frameworks in turn used in the total synthesis of some interesting natural products. Historically, the total synthesis of macrolide antibiotic erythromycin was a landmark in the enantioselective synthesis of natural products, showing the great potential of enantioselective organocatalyzed aldol reaction. In the synthesis of the aforementioned antibiotic, one of the key step was the cyclization of compound **212**, which was accomplished by reaction with (*R*)-proline *ent*-**1**, giving a 1:1 mixture of two diastereoisomers **213** (Scheme 41). Besides the obvious aldol process, the reaction also implied a retro-Michael and Michael processes forcing the formation of only one of the two possible absolute configurations for the thioketal moiety.[272] The isomer *syn*-**213** could be isolated and recrystallized to reach an enantiomeric excess higher than 99%, being used as starting material in further steps of the synthesis.

This approach was also applied to the challenging enantioselective synthesis of the tropane ring skeleton of cocaine (Scheme 42). In this case, the 6-(enolexo)-*exo*-trig desym-



Scheme 41.



Scheme 42.

metrization processes of compound *meso*-**214** in toluene gave an inseparable 1:1 mixture of isomers **215**.[273] The benzylation of the alcohol permitted the isolation of both isomers by HPLC, with *cis*-**215** isomer being used in the synthesis of unnatural (+)-cocaine. This reaction represents the first example of an intramolecular proline-catalyzed aldol reaction generating aza-bridged bicyclic structures.

A similar strategy, in this case of diastereoselective aldol-catalyzed chiral aza-spiro keto aldehyde has been used in the preparation of the azaspirane core of immunosuppressant FR 901483 with moderate success.[274]

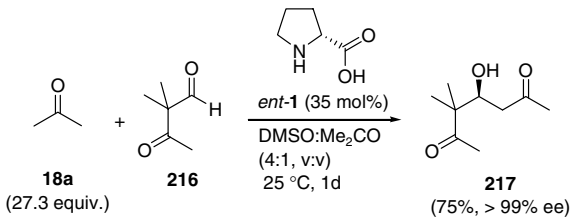
8.2. Intermolecular reactions

The organocatalyzed intermolecular aldol reaction has been less used, as it was expected, in the enantioselective synthesis of compounds with biological interest. However, the high level of selectivity obtained was similar to the previous section and, as it will be shown, the potential utility of this process is very important.

8.2.1. Ketones as source of nucleophile

8.2.1.1. Aldehydes as electrophiles. Epothilones A–D display taxotere-like anticancer activity, with their syntheses being very valuable. A recent approach to their partial

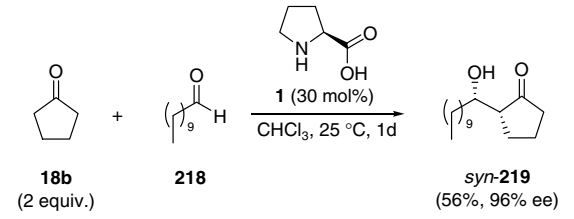
synthesis involved the preparation of the corresponding C1–C6 ketoacid synthon. The asymmetric key step in the synthesis of this acid allowed the aldol reaction between acetone **18a** and ketoaldehyde **216** to give compound **217** as just only one enantiomer (Scheme 43). Further intramolecular aldol condensation gave the corresponding 2-cyclohexenone derivative and degradative oxidation gave the expected (3*S*)-3-hydroxy-4,4-dimethyl-5-hexanoic acid.[275]



Scheme 43.

A diastereoselective approach of this reaction has also been used in the construction of steroid brassinolide side chain using *tert*-butyl(dimethyl)silyloxy acetone **23b** as the source of nucleophile.[276]

The natural oviposition attractant pheromone of *Culex* mosquito, (−)-(5*S*,6*S*)-6-acetoxyhexadecan-5-olide, which transmits the West Nile virus was obtained through the aldol reaction depicted in Scheme 44. The results were good, even the diastereomeric excess, which reached up to 70% (compare with those in Table 2). The acylation of the hydroxyl moiety and Baeyer–Villiger oxidation afforded the expected pheromone.[277a] 2-Pentyl-1,3-dithiane-2-carboxaldehyde has been proposed as the alternative aldehyde partner, giving similar results in a longer synthetic process.[277b] The Baeyer–Villiger oxidation of *syn*-**219** and radical dehydroxylation gave the corresponding chiral 5-hexadecanolide, which is the pheromone isolated from oriental hornet *Vespa orientalis*.[278]

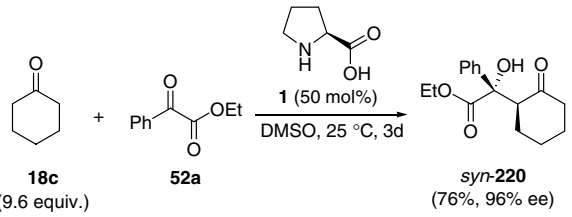


Scheme 44.

Sphingoids are long chain aminodiols and triol bases presented in sphingolipids, which are important membrane constituents. Their synthesis have been accomplished by the reaction of cyclic ketone **31** with pentadecanal catalyzed by proline **1** (30 mol %) at 25 °C, affording the corresponding aldol product *anti*-**32** with an excellent result (49% yield, 99% de, and 95% ee, compare with those in Table 3). The subsequent diastereoselective amino reduction and deprotection rendered the expected product.[279] A similar diastereoselective approach permitted the synthesis of carbasugar 1-*epi*-(+)-MK7607[280] and ulosonic acid precursors.[281]

The dynamic kinetic resolution of compound *rac*-**33** by reaction with ketone **29** (2 equiv), catalyzed in this case by tetrazole derivative **76**, in wet DMSO afforded the expected product **34** in 75% yield and more than 98% ee (compare with Scheme 10). Compound **34** was converted, after radical dehydroxylation and reductive desulfurization, into the corresponding ethylene ketal of natural serricornin, a beetle sex pheromone.[282]

8.2.1.2. Ketones as electrophiles. Oxybutynin (ditropan) is a widely prescribed muscarinic receptor antagonist for the treatment of urinary frequency, urgency, and urge incontinence. Recently, its partial synthesis has been accomplished by the aldol reaction between cyclohexanone **18c** and ethyl phenylglyoxylate **52a** catalyzed by proline (Scheme 45, compare with Schemes 12 and 18). The reduction of ketone, dehydration of the secondary alcohol formed, hydrogenation of the double C–C bond and hydrolysis, gave the corresponding quaternary α-hydroxy-acid, which is the main constituent of the aforementioned pharmaceutical.[283]



Scheme 45.

A tertiary alcohol group is also presented in convolutamyne A, which is an alkaloid isolated from Floridian marine bryozoan *Amathia convolute*. The synthesis of this compound was carried out by the aldol reaction of acetone **18a** with 4,6-dibromoisatin ($R^1 = 4,6\text{-}Br_2$ and $R^2 = H$ in **91**) catalyzed by peptide **92** under similar conditions to those reported in Scheme 30. The corresponding expected product of type **93** could be isolated in a practical quantitative yield and 68% ee, with the enantiomeric excess reaching up to >99% by a recrystallization process.[284]

8.2.2. Aldehydes as source of nucleophile. The auto-aldol reaction of α-(benzyloxy)acetaldehyde ($R = OCH_2Ph$ in **44**), using (*R*)-proline *ent*-**1** and under similar reaction conditions to those reported in Scheme 15, gave the corresponding diastereoisomer *anti*-**45** in 78% yield and 98% ee.[285] This intermediate was further transformed into the required glycoside for the total synthesis of natural products brasoside and littoralisone.

The cross-aldol reaction between propionaldehyde **20a** ($R^1 = Me$ in Table 4) and *p*-nitrobenzaldehyde **17a**, to give the corresponding compound *anti*-**43** (>88% yield, 88% de, and 99% ee), has been used as the asymmetric key step in the synthesis of trichostatin A, which is a potent and specific histone deacetylase inhibitor.[286] A similar protocol

was employed in the synthesis of prelactone B. In this case, the process started with the aldol reaction between propionaldehyde (**20a**, $R^1 = Me$ in Table 4) and an excess isobutyraldehyde (4 equiv, $R^2 = Pr^i$ in Table 4) catalyzed by proline (10 mol %) to give the expected product *anti*-**43** (98% de and 99% ee). The final diastereoselective Mukaiyama aldol reaction followed by lactonization gave the expected product.[287]

9. Conclusions and outlook

Although organocatalysis is a venerable resource for the synthesis of chiral compounds,[288] it is only after the discovery of the Robinson annulation catalyzed by simple α-amino acids in the seventies of previous century that it was envisioned as a useful tool, together with its blossoming at the beginning of this century with the introduction of the intermolecular aldol reaction, as was presented in this review.

Whereas simple intramolecular molecular aldol reactions (Robinson annulations) and even intermolecular processes using ketones as a source of nucleophile and aldehydes as electrophiles, have been extensively studied, other intramolecular reactions, such as enolexo-*exo*-trig processes, or intermolecular reactions, using either ketones as electrophiles or aldehydes as electrophiles, are scarcely investigated, with reactions using aldehydes as the source of the nucleophile and ketones as electrophiles having a testimonial presence. Also the use of less reactive ketones, such as 3-pentanone, α,β-unsaturated ketones, even alkyl aryl ketones in the typical aldol reaction with aldehydes remains unexplored. Therefore, other new catalysts different from pyrrolidine derivatives, as well as reaction conditions, should be developed in order to fill these gaps, as well as to make possible the use of other sources of nucleophile such esters, amides, and their thio and amino derivatives, probably with the phase-transfer catalysis being also an adequate approach to solve these problems.

In general and with some exceptions, any organocatalyzed process is viewed as a green approach to the synthesis of a compound. Therefore, the organocatalytic aldol reaction will be used profitably by industry in the near future.

Acknowledgments

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