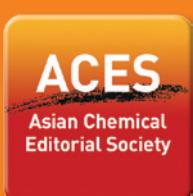


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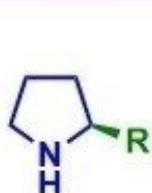
WILEY-VCH

Proline-derived Long-aliphatic-chain Amphiphilic Organocatalysts (PDLACAOs) for Asymmetric Reactions in Aqueous Media

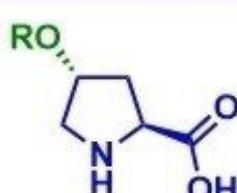
Erika Alarcón-Matus, Cuauhtémoc Alvarado,* Nancy Romero-Ceronio, Erika M. Ramos-Rivera, and Carlos E. Lobato-García^[a]

A tribute to Dr. Ángel Guzmán.

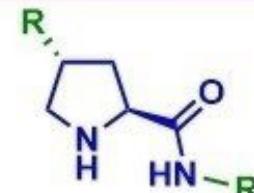
PDLACAOs



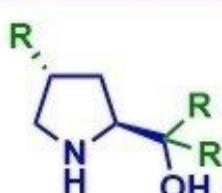
I. Pyrrolidine-type



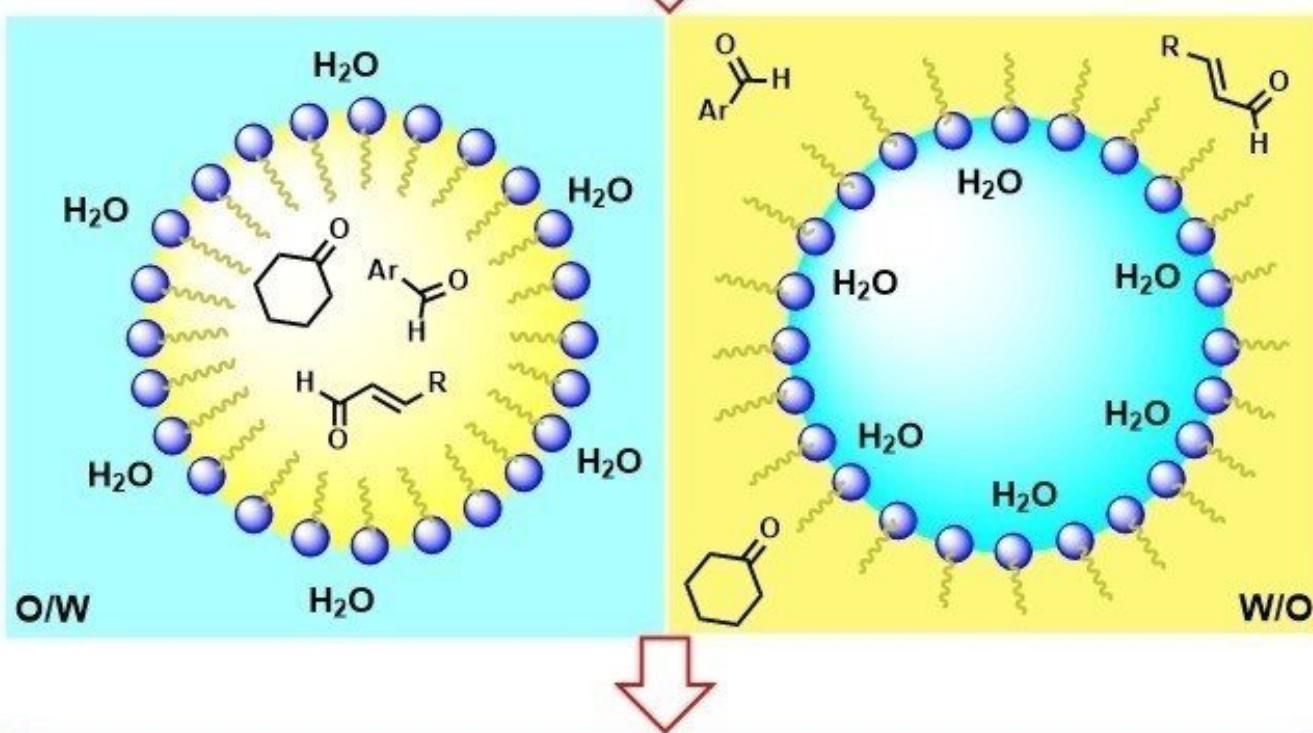
II. Proline-type



III. Prolinamide-type



IV. Prolinol-type



Cross-aldo reaction

Michael-Aldol Tandem Reaction

Cascade Reactions

Michael Addition Reaction

Mannich Reaction

Abstract: Herein, a specialized review of the origin and state of the art of proline-derived long-aliphatic-chain amphiphilic organocatalysts (PDLACAOs) and their use in asymmetric organic reactions in aqueous media (water, brine, and sea

water), including in water and in the presence of water, is presented. The reactions in which they have been evaluated and the most important mechanisms are discussed.

1. Introduction

Typically, when conducting an organic reaction, a large amount of organic solvent is used. Thus, solvents are the main waste product of any organic reaction. Moreover, most organic solvents are volatile, flammable, toxic and expensive. Therefore, strategies for the reduction or restriction of their use are being applied, and neat, solvent-free reactions, solid-state reactions (mechanochemistry), and reactions that use water as the reaction medium are being developed in accordance with green chemistry^[1] and the atom economy guidelines.^[2] According to Hayashi, "water is an environmentally friendly, safe medium, which avoids the problems of pollution".^[3] Sharples claims that "water has the advantages of high specific heat and inductive capacity, unique redox stability and in addition, it is a nonexhaustible resource".^[4] Due to these notorious advantages, many organic/inorganic reactions that use water as the reaction medium have been developed.^[5]

Prior to the advent of amphiphilic long-chain organocatalysts, when an asymmetric organic reaction was conducted using aqueous media or a mixture of aqueous media/organic solvents, the typical approach was to use transition-metal complexes. Unfortunately, the main problem with their use is their contamination of the organic products and the environment.^[3g] The use of emulsifying agents and transition-metal complexes is a common issue. A vast array of reactions, such as Sonogashira, Still, Heck, Susuki-Miyaura, and methatesis, among others, have been developed. For reactions of this type, due to the hydrophobic effect, the internal part of the micelle operates as a nanoreactor.^[3d,6]

Proline is a highly polar compound that can catalyse asymmetric aldol reactions in polar organic solvents with high enantioselectivity.^[7] However, when it was used for the same reaction in water, only the racemic mixture was obtained, as demonstrated by Barbas III.^[7b,8] Proline has been shown to be able to catalyse multicomponent reactions in water, thereby leading to the synthesis of heterocycles.^[9] It was until 2006, when Barbas III and Hayashi independently developed the first organocatalysts, that asymmetric aldol reactions could be conducted in the presence of water (Figure 1).^[3k,8c] Hayashi's catalysts were constructed from *trans*-4-hydroxy-L-proline, in which the hydroxyl moiety was substituted by diverse silicon-

based protective groups (**1a–1c**).^[8c] The same year, Barbas III described the first proline-derived long-aliphatic-chain amphiphilic organocatalyst (PDLACAO) **2**, with which the aldol reaction in water was conducted.^[8d] For the first time, one catalyst, namely, catalyst **2**, combined the best of two worlds: it was proline-derived and contained long amphiphilic hydrocarbon chains (Figure 1). Catalyst **2** was introduced by Barbas III in 2004 and used for the Michael addition reaction of cyclohexanone with either *p*-methoxy-*trans*- β -nitro styrene or its *o*-trifluoromethyl derivative in THF in the presence of water (up to 10%) with excellent stereoselectivities and moderate to satisfactory yields.^[10]

Important and interesting reviews have been conducted on organocatalysis under sustainable conditions, such as using water as a solvent, solvent-free conditions, mechanochemistry, polymer support, and using alternative energies such as microwave and ultrasonic irradiation.^[11] In these articles, all types of organocatalysts are discussed (proline-derived, thioureas, squaramides, and cinchone and cinchonine derivatives, among others),^[12] along with organometallic catalysts.^[13] An enormous diversity of proline-derived catalyst for aqueous and non-aqueous reactions has been designed, which includes PDLACAOs. The objective of this review is to describe the origin and state of the art of PDLACAOs and to follow their evolution from the report of the first catalyst by Barbas III in 2006 up to this year. The use of catalysts for asymmetric organic reactions in aqueous media (water, brine, and sea water) is examined, including in water and in the presence of water, along with the reactions in which they have been evaluated, and the most important mechanisms are discussed.

2. Classification of organic reactions using water

Prior to describing catalysts, to make the manuscript more comprehensible, the classification of and factors that affect organic reactions using water will be described. According to the number of phases, they are classified as one-phase reactions in-water and two-phase reactions a) in the presence of water

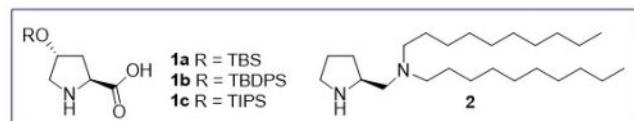


Figure 1. First amphiphilic organocatalysts.

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and b) on-water. According to Hayashi, during in-water reactions, the reactants that participate in the reaction are homogeneously dissolved.^[14] For reactions "in the presence of water" and "on water", it is possible to distinguish two phases by the formation of an emulsion, O/W or W/O, respectively. Hayashi defined reactions in the presence of water as "reactions that proceed in a concentrated organic phase with water being present as a second phase that influences the reaction in the organic phase". More quantitatively, Barbas III defined the direct aldol reaction in the presence of water as a procedure that uses a small amount of water (3–18 equiv.). In addition, Sharpless has defined on-water reactions as "a group of organic reactions that take place as an emulsion, the reactants are water insoluble, and in which the reaction rate acceleration is the same than in an organic solvent".^[6b]

3. Factors that affect reactions that uses water

Most amphiphilic organocatalysts that are described here are composed of an asymmetric pyrrolidine framework that contains a long amphiphilic chain. This chemical structure enables them to play three important roles in a reaction: catalyst, emulsifying agent, and asymmetric inducer. According to Li, "The chiral catalyst in emulsion significantly enhances the reactivity and stereoselectivity of the direct asymmetric aldol reactions, which can be attributed mainly to the larger interfacial surface area and uniformly distributed catalyst molecules in the interface of the emulsion droplets".^[15] Hence, the catalytic role of these novel amphiphilic chiral molecules in a reaction is more similar to an enzymatic process, which extends beyond the role of proline.^[16] Most reactions in which an amphiphilic organocatalyst participates can be included into the two-phase group; thus, they elapse as an emulsion inside a micelle. Therefore, it is important to identify the factors that

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affect emulsified reactions and micelles. These factors will be described next.

3.1. Hydrophobic Effect

Water is a highly polar compound and can form strong hydrogen bonds. Most organic compounds are hydrophobic and have low capacity for forming hydrogen bonds. Therefore, when an organic compound is added into water, it suffers from segregation, and it is forced to form aggregates, which are known as micelles. This is referred to as the hydrophobic effect. Typically, this phenomenon causes an increase in the reaction rate due to external pressure, and it might be modified in direct proportion to the quantity of water that is used. This effect could also be compared with reactions under pressure. Jorgensen has calculated that the hydrophobic component contributes to the reaction rates with a factor of approximately 10.^[3b,17] According to Coyne and Buttler, for reactions that occur inside micelles, "forced aggregates of organic reactants are raised in energy above their unaggregated ground states and are closer in energy to the activated complexes and transition states".^[18] In addition, the hydrophobic effect strongly influences the stereochemical outcome of reactions by favouring products from the most compact transition state and the common endo-cycloadditions in Diels-Alder and Huisgen cyclo-addition reactions.^[19]

3.2. Polarity Effect

The high polarity of water helps stabilize the transition states of aqueous organic reactions, as will be discussed in this manuscript. In addition, transition states occur in the aqueous phase, which is more polar than organic starting materials.^[20]

3.3. Hydrogen-Bonding Effect

As inside the active sites of enzymes, the hydrogen bond is the main stabilizing force of the transition state. The hydrogen bond is also posited to stabilize the transition states of organic reactions in water. In addition, the hydrogen bond is posited to diminish the energy of the frontier orbitals by reducing the electron density and the interorbital repulsion.^[18]

3.4. Micelles

A micelle is an aggregate with a hydrophobic core that functions as a nanoreactor and possess a hydrophilic external part that enables it to disperse in water. According to Sorrenti, "micellar environments are not just a soapy version of homogeneous catalysis, but micelles behave much more as nanoreactors characterized by unique features".^[21] An emulsifying agent must be present in a minimum concentration for the reaction to occur; this is known as the critical micelle

concentration (c.m.c.). Micelles are metastable aggregates with typical lifetimes of approximately 10^{-3} – 10^{-2} s;^[6b,22] therefore, their components are typically interchanged among them. The shapes of aggregates can change according to conditions such as the molecular structure, concentration and experimental conditions (such as spheres, ellipsoids, rods, and cylinders).^[23] The size of the amphiphilic chain is also important for both an emulsion and an organic reaction.

3.5. On-water effect

The rate of many reactions is speed up when they are performed on-water.^[3e,24] For example, during his studies with the Diels Alder reaction between cyclopentadiene and butanone, Breslow demonstrated that an aqueous suspension of the reaction was three-fold faster, than the neat reaction.^[24a] For on-water reactions, water is not used as solvent, but to generate an emulsion with insoluble, floating reactants. Heterogeneity is crucial for large rate enhancements, however, according to Sharpless,^[4] it is not the only cause. The answer lie in the unique chemistry between water and reactants at the oil-water interphase. Shen shown that approximately the 25% of surface water molecules at the interphase possess one dangling OH group (not H-bonded), protruding and preferentially oriented to the hydrophobic phase, while the other OH group remains H-bonded to water molecules.^[25] Protruding OHs are ready to catalyse reactions by forming H-bonds. Thus, whenever the transition state is more H-bonded to the surface water than are the reactants, an on-water acceleration can be anticipated. On the other hand, in a homogeneous solution, there is a H-bond network surrounding the reactants, and it has to be broken in order to OH groups be freed and useful for catalysis (Figure 2).^[26]

4. Classification of amphiphilic organocatalysts

To guide the discussion, catalysts are classified into four types according to their structure: I) pyrrolidine-type, II) proline-type, III) prolinamide-type and IV) prolinol-type (Figure 3). Additional important factors for this classification are as follows: a) PDLACAOs are constructed from two basic frameworks: (S)-proline, and (*trans*)-4-hidroxy-L-proline. b) The amphiphilic chain must be of at least 4-carbon length. c) The amphiphilic chain may be present at two locations: typically, by the carboxyl carbon when using the proline framework and on the hydroxyl of the 4-position when using the (*trans*)-4-hidroxy-L-proline framework. d) Sometimes, a heterocyclic moiety is inserted between the amphiphilic chain and the pyrrolidine framework, the most common of which are phenyl, imidazole and benzimidazole. e) The amphiphilic chain can also be tethered to distinct functional groups (amine, amide, and sulfonamide, among others). A similar classification was proposed by Gruttadaria and collaborators for proline-based amphiphilic organocatalysts.^[3i]

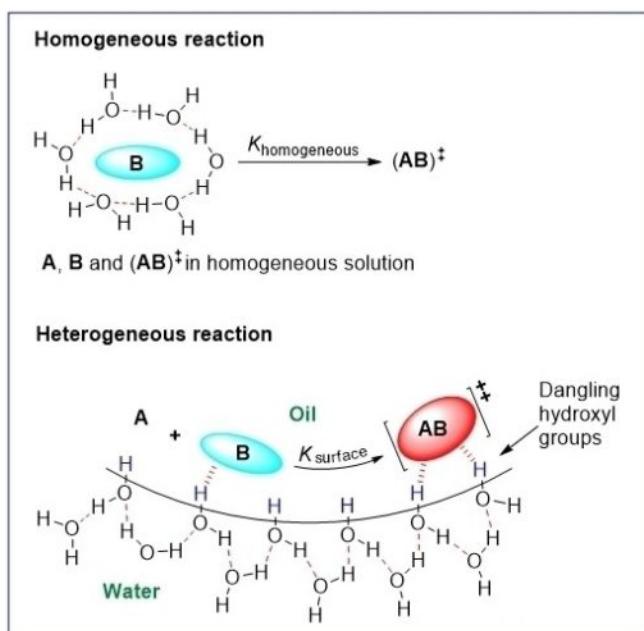


Figure 2. Homogeneous water reaction, and heterogeneous on-water reaction. On-water effect.

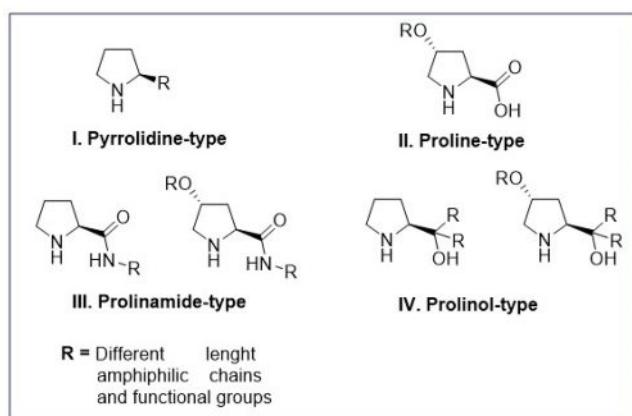


Figure 3. Classification of proline-derived long-aliphatic-chain amphiphilic organocatalysts (PDLACAOs).

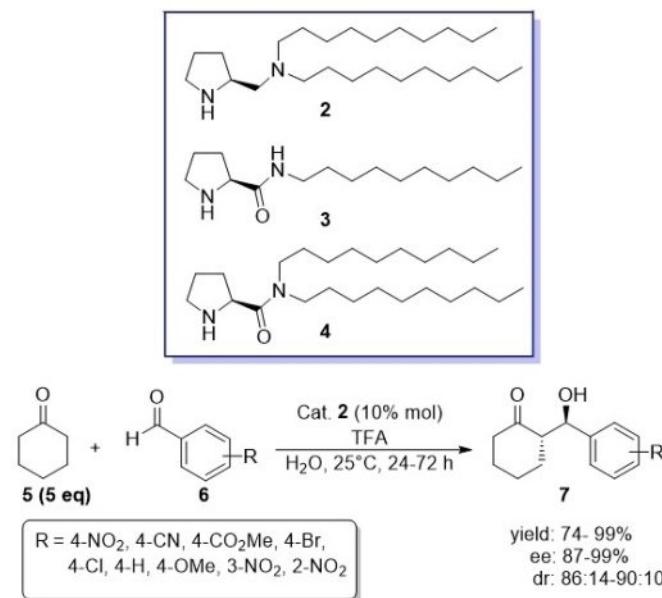
5. Type 1. Pyrrolidine-type organocatalysts

Pyrrolidine-derived long-aliphatic-chain amphiphilic organocatalysts (PDLACAOs) were the result of rational design, not chance, with nature as the guide. The group of Barbas III had been working with aldolases for a long time and knew that the catalytic sites of enzymes, where biological reactions occurred, were hydrophobic. In addition, it was also known that water inhibited the activity and chiral induction of common organocatalysts by interrupting ionic interactions and the formation of hydrogen bonds during the transition state.^[3b,d] Thus, a new class of organocatalysts was required for conducting asymmetric reactions in water. The first was catalyst **2**, as described above, in the seminal work by Barbas III and Mase.^[8d] Catalyst **2** is proline-derived and has a tertiary amine with two long

hydrophobic chains at position 2 of the pyrrolidine ring. The introduction of the hydrophobic chains was fundamental to the success of the catalyst, since this enabled it to form an emulsion in water. In the emulsion, an asymmetric organic reaction can occur with satisfactory selectivity since the organocatalyst forms a hydrophobic cavity, where the transition-state can be isolated from water.^[7a,8d,27]

Catalyst **2** was evaluated for the first cross-aldol reaction in water, which was developed by Barbas III (Scheme 1).^[8d] Cyclohexanone **5** and various aldehydes **6** were reacted in excess water (111 equiv.). Trifluoroacetic acid was used as an additive. Aldol products **7** were obtained in moderate to satisfactory yields (74–99%) and satisfactory to excellent enantiomeric excess (ee: 87–99%). Two additional amphiphilic organocatalysts, namely, **3** and **4**, were introduced in the same study, but catalyst **2** yielded the best results. After the success of this first catalyst, many reports have been presented, which we shall discuss.

During the same year, Barbas III and Mase proposed a general mechanism for the cross-aldol reaction in water.^[3k] In this reaction, in addition to the catalytic function of the amphiphilic organocatalyst **C**, it functions as an emulsifying agent. Thus, once in the emulsion, donor **D**, acceptor **A** and catalyst **C** can react. Initially, **D** reacts with the hydrophilic part of the catalyst **C** in the aqueous/organic interphase. An enamine intermediate **CD** forms, which is less water-soluble and, therefore, moves into the micelle core, where a reaction occurs with acceptor **A**. The formed imine intermediate **CDA** is positively charged and returns to the interphase, where it is hydrolysed by water, thereby releasing the aldol product **DA** inside the micelle core and enabling the catalyst **C** to resume the catalytic cycle (Figure 4). Figure 4 is a modification of the original figure that was published by Barbas.



Scheme 1. Asymmetric cross-aldol reaction of cyclohexanone with aldehydes in water using catalyst **2**, by Barbas III and Mase.

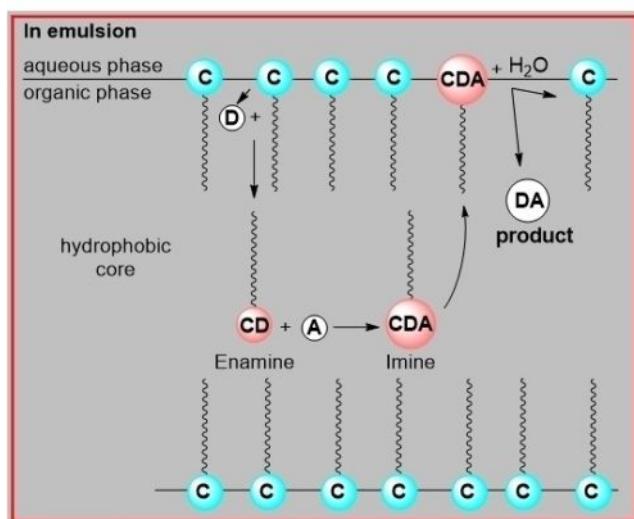
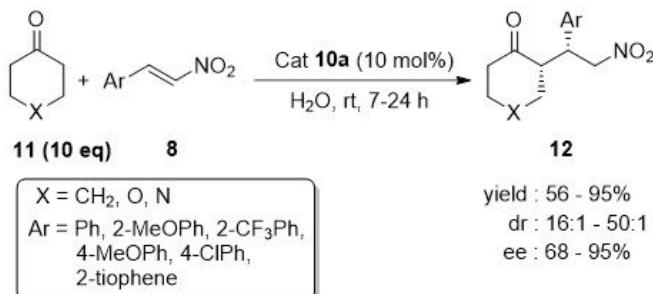
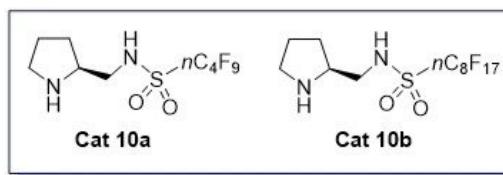


Figure 4. General mechanism for the cross-alcohol reaction in water that was proposed by Barbas III and Mase. Modified from the original.

Due to the success of catalyst **2** with the aldol reaction in water, it was further evaluated for the Michael reaction in water, brine and sea water by Barbas III in 2006^[8e] and for the crossed-aldol reaction in water in the presence of various surfactants by Mase in 2009.^[27a] The latter will be analysed in another section. For the Michael reaction, cyclohexanone **5** and various α,β -unsaturated nitroalkene acceptors **8** were used (Scheme 2). The best results were obtained using brine as the reaction medium. Catalyst **2** realized satisfactory performance for this reaction and yielded products **9** in regular to quantitative yields (57–99%) with satisfactory to excellent enantioselectivities (83–97%). Diverse non-cyclic ketones were also evaluated for this reaction with unsatisfactory results.

Two of the main problems with organocatalysts are their recyclability and high catalytic charge. Many of the catalysts that are reported here were synthesized with the objective of overcoming these problems. In 2006, Wang and collaborators reported the synthesis of two recyclable fluororous (*S*)-pyrrolidine sulfonamide catalysts **10a–b** and evaluated them for the Michael addition reaction between ketones **11** and aldehydes **6** to nitroolefins **8** in water (Scheme 3).^[28] The catalyst with the best performance was **10a**, with up to 95% yield, 50:1 diastereomeric ratio (dr) and 95% ee. These results were

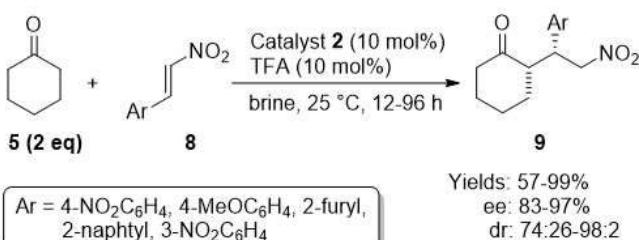


Scheme 3. Michael addition reaction in water using (*S*)-pyrrolidine sulfonamide catalysts **10a**, by Wang.

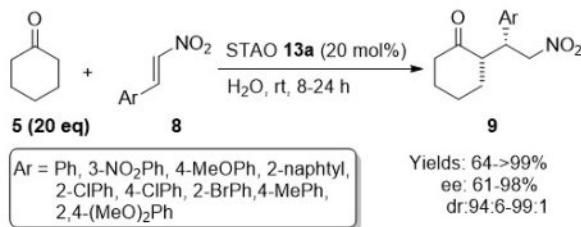
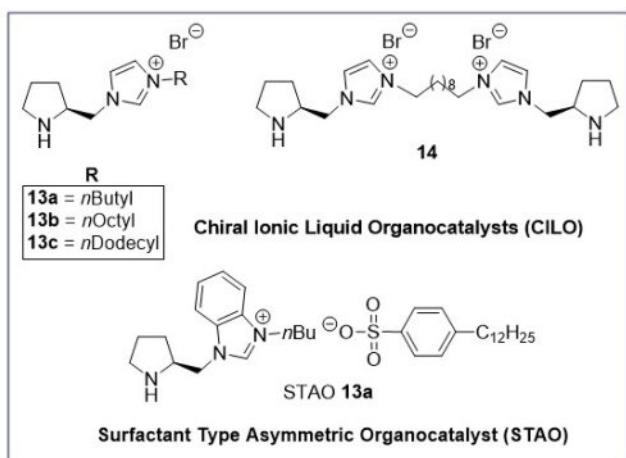
explained by the steric bulk of the longer fluorous alkyl chain in **10b**. Catalyst **10a** was recovered from the reaction mixture via fluorous solid-phase extraction (>90%) and shown to be recycled up to six times with observable decreases in yield (70%) and dr (11:1), in contrast to ee, which remained almost unchanged (89%). Nonanal and 3-methylbutanal were also used as donors with regular results for the former (98% yield, 81% ee, 4:1 dr) and low yield (60%) and satisfactory ee (86%) for the latter.

Inspired by the substantial success of organocatalysts in inducing enantioselectivity and in chiral ionic liquids (CILs), Luo and Cheng created a new type of asymmetric organocatalysts by combining both concepts (Scheme 4).^[29] At that time, CILs were employed as chiral-resolution agents, chiral solvents, and chiral additives.^[30] Unfortunately, only chiral additives induced a moderate enantioselectivity for selected reactions.^[31] In contrast, organocatalysts were unable to catalyse organic reactions in water. However, the salts of Br and BF₄ of the newly created CIL-organocatalysts successfully catalysed the asymmetric Michael addition reaction of cyclohexanone with diverse aldehydes in neat conditions. Months later, CIL-organocatalysts **13a–c** with various long alkyl chains on the imidazole moiety, along with the tweezer-type CIL-organocatalyst **14**, were tested for the Michael reaction in water with unsatisfactory results by the same authors.^[29] Then, CIL-organocatalyst **13a** was combined with sodium dodecylbenzenesulfonate (DBS); this new combination of CIL-organocatalyst-surfactant was referred to as a surfactant-type asymmetric organocatalyst (STAO). STAO **13a** catalysed the asymmetric Michael addition of cyclohexanone **5** with various aromatic nitroalkenes **8** in water. Products **9** were obtained with yields from regular to quantitative (64–>99%), enantiomeric excesses from moderate to excellent (61–98%) and excellent diastereomeric ratios (94:6–99:1).

Catalyst **10a**, which was reported by Wang (Scheme 3), was tested in the asymmetric cross-aldol reaction of diverse ketones (mainly cyclohexanone **5**) and aldehydes **6** in water, thereby



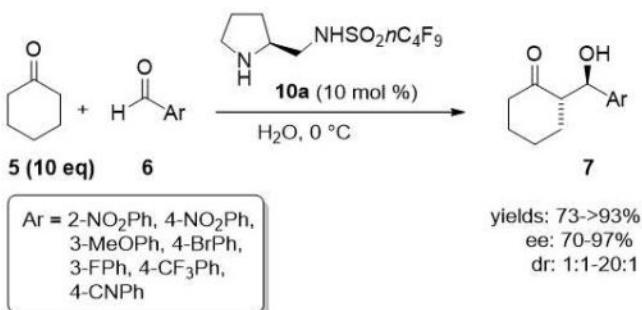
Scheme 2. Michael addition reaction in brine using catalyst **2**, by Barbas III.



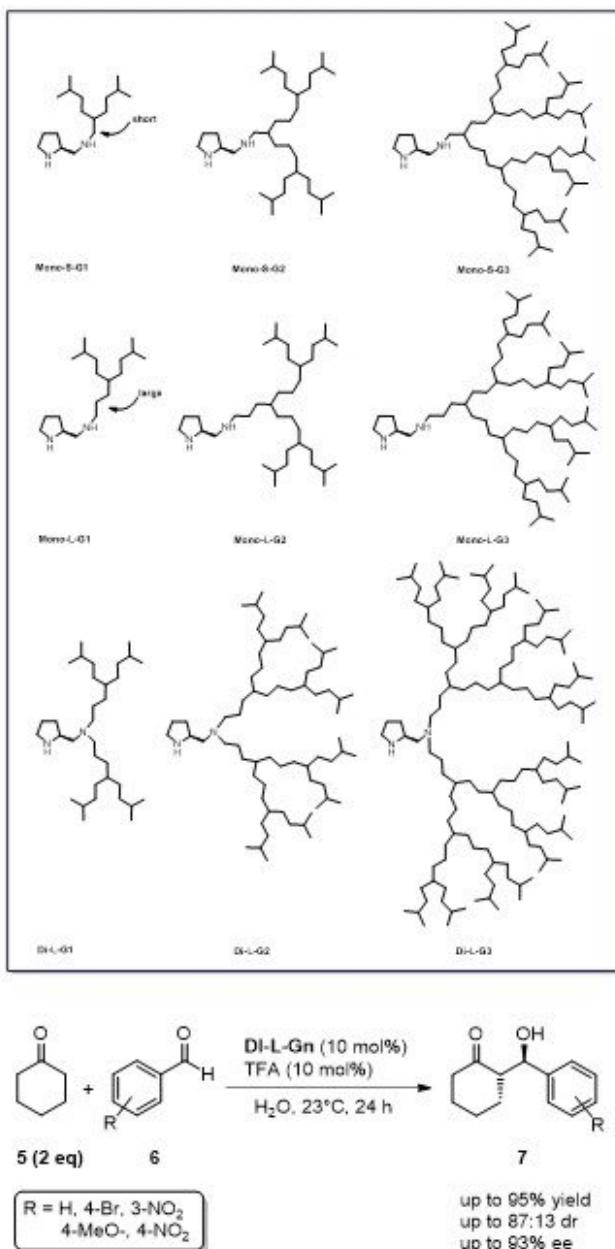
Scheme 4. Michael addition reaction in water using STAO 13a.

expanding its applicability (Scheme 5).^[32] Aldol products **7** were obtained in 73–93% yields, 70–97% ee, and 1:1–>20:1 dr. Among the donors that were employed, cyclopentanone **15** and two aliphatic aldehydes were included. The stereochemical outcome for aliphatic aldehydes was satisfactory, while cyclopentanone **15** yielded the worst results (70% ee, 1:1 dr). Catalyst **10a** was shown to be recycled up to seven times with no loss in activity.

With catalyst **2**, Barbas III showed that the incorporation of surfactant appendages (alkyl chains) onto the pyrrolidine framework obviated the necessity of adding an external surfactant to the reaction media. Via this approach, a catalyst could form micelles and catalyse organic reactions in water. However, no studies had been conducted regarding the effects of the size and shape of the surfactant appendages on the micelle formation efficiency and the catalyst properties. Thereby, an

Scheme 5. Cross-aldol reaction in water using recyclable fluorous (*S*)-pyrrolidine sulfonamide organocatalyst **10a**, by Wang.

interesting combination, namely, supramolecular chemistry-organocatalysis dendron-pyrrolidine (CADO), was reported for the first time in 2009 with this objective by Chow and Lo.^[33] CADO were classified into three series according to the number of dendrons and spacers (s=short, L=large) they contained: Di-L-Gn, Mono-L-Gn and Mono-S-Gn. CADO were tested in asymmetric aldol and Michael addition reactions in water (Scheme 6). The Aldol reaction was conducted using cyclopentanone **15** and cyclohexanone **5** as donors, while various aromatic aldehydes **6** were used as acceptors. Although adducts with cyclopentanone **15** were obtained in yields of up to 93 %, the stereochemical outcome was unsatisfactory (dr: 36:64–69:31, ee: 7–86%). Fortunately, these results facilitated the selection of the Di-L-Gn series as the series with the highest



Scheme 6. Cross-aldol reaction using dendron catalyst series Di-L-Gn.

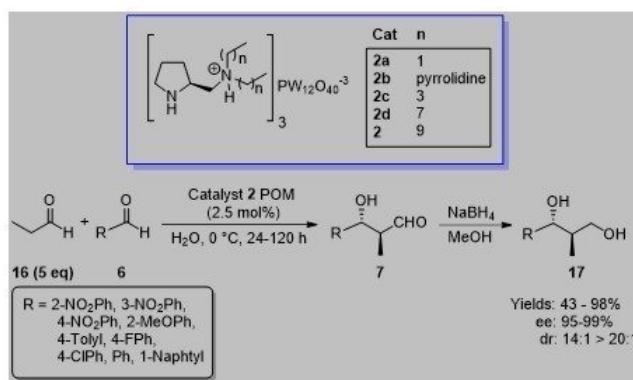
activity, which is presumably because it helps to obtain the best emulsion, and the two bulky dendron groups enable superior steric shielding. Thus, Di-L-G1 and Di-L-G2 produced the best enantiomeric excess (93%) and Di-L-G1 produced the best yield (95%), while Di-L-G1 and Di-L-G2 produced the best diastereomeric relationship (87:13). In addition, catalyst 2 (Figure 1) was tested under the same conditions as CADO, and results demonstrated better catalytic properties for CADO. Interestingly, catalysts in the Di-L-Gn series formed stable emulsions (even within one hour without stirring), which proved to be important for the reaction to proceed. Such emulsions had to be formed prior to the addition of the starting materials; otherwise, the product conversion and yields were very low. Further studies on the series Di-L-Gn, cyclohexanone 5 and diverse aldehydes 6 were conducted.

Afterwards, the three series of catalysts were evaluated in the asymmetric Michael addition reaction in water, with similar results to those for the aldol reaction. For this report, cyclohexanone and diverse Michael acceptors were used. The Di-L-Gn catalyst series again showed the best stereo differentiation properties, with diastereomeric relationships of up to 4:96 (anti/syn) and enantiomeric excess of up to 89%. Finally, catalysts Di-L-G2 and Di-L-G3 were shown to be recycled up to 5 times without substantial losses in activity (yield: 82–87%, dr: 6:94–9:91, ee: 80–84% for Di-L-G2 and yield: 78–81%, dr: 6:94–9:91, ee: 81–84% for Di-L-G3).

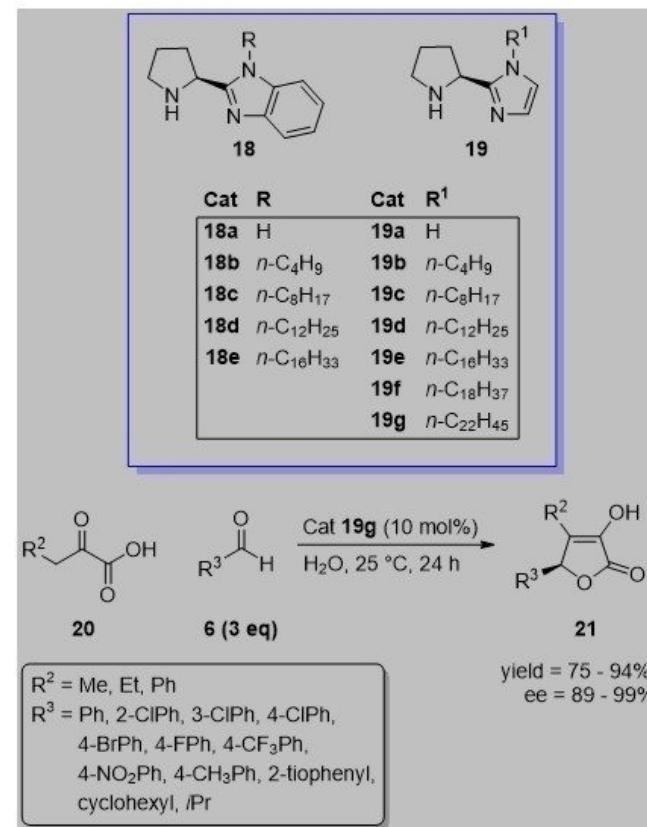
As part of the continuous efforts to develop new chiral emulsion organocatalytic systems, during the years 2011–2019, Professor Li published five interesting articles regarding pyrrolidine-based catalysts, which will be described below.^[23,34] The group had been working with quaternary ammonium polyoxometalates (POMs) as surfactant-type catalysts for the oxidation of organic molecules.^[35] POMs had already been used by Luo for the aldol reaction as a chiral catalyst support in a biphasic system with satisfactory results.^[36] Thus, in 2011, Li prepared the organic salts of catalysts 2, 2a–d with polyoxometalate acid ($H_3PW_{12}O_{40}$, POM) with the objectives of facilitating the formation of micelles and obtaining catalysts with a higher recyclability. Catalysts were evaluated for the asymmetric cross-aldol reaction in the presence of water (Scheme 7).^[34a] Among the evaluated catalysts, catalyst 2 in

combination with POM realized the best performance. The reaction was realized by using propionaldehyde 16 as a nucleophile and various aromatic aldehydes 6 as electrophiles. It was found that the most suitable amount of water for the reaction was 9 equivalents, while 5 equivalents of propionaldehyde 16 were used. Reduced adducts 17 were obtained in regular to excellent yields, along with excellent enantiomeric and diastereomeric excesses. The authors conducted a study with a light microscope image that showed the importance of forming a stable emulsion for the reaction. During the study, it was shown that catalysts with a short alkyl chain 2a and 2b were not able to form an emulsion and, therefore, produced low yields. Catalysts 2c and 2d produced unstable emulsions, whereas catalyst 2 with the longest alkyl chain produced the most stable emulsion and the best results in terms of yields and stereomeric excesses. Finally, it was shown that catalyst 2-POM could be recycled three times without loss in activity or selectivity.

The second paper was published in 2012 and describes the synthesis of chiral isotetronic acid derivatives 21 in water (Scheme 8).^[23] This issue was examined again in 2019 by Li.^[34d] With this objective, two series of pyrrolidine-type catalysts were designed: the first with a benzoimidazole motif 18a–e and the second an imidazole 19a–g. Both bearing alkyl chains of various lengths. For the synthesis of isotetronic acid derivatives 21, α -ketoacids 20, aromatic aldehydes 6 and aliphatic



Scheme 7. Asymmetric cross-aldol reaction in the presence of water using catalysts 2 and polioxometalate acid, by Li.



Scheme 8. Synthesis of isotetronic acids 21 in water using catalyst 19g, by Li.

aldehydes were used. The reactions were conducted in water, and the best results in terms of yields and ee were obtained by employing catalyst **19g**. This reaction is highly enantioselective (89–99%). Studies of catalyst recovery and/or recyclability were not conducted.

Typically, when conducting a reaction in water, the starting materials are water-insoluble. For this reaction, α -ketobutyric acid is water-soluble; therefore, a special reaction mechanism in which reaction occurs in the interphase was proposed by the authors (Figure 5). First, the hydrophilic part of the catalyst (pyrrolidine-imidazol moiety) reacts with α -ketobutyric acid to generate an enamine. Second, an aldehyde from the interior of the micelle is trapped by the enamine to produce the isotetronic acid product. The formed adduct is distributed either inside or outside the micelle according to its solubility. The introduction of heterocycles into the catalyst, due to their basicity, helps stabilize the transition state by forming an acid-base interaction between the acid group in **20** and one of the heteroatom's nitrogen atoms. Water is claimed to have an important role in the reaction conversion and enantioselective induction because when the reaction was conducted in its absence, both of them diminished (chloroform, conversion: 18% and ee: 75%). To evaluate their mechanism model, according to which the reaction should proceed on the interphase, the authors conducted fluorescence microscopy studies. In such studies, the best catalysts were able to form emulsions, and they were mainly distributed on the surfaces of emulsion

droplets; therefore, the reaction should proceed on the interphase.

In a third paper (2014), Li described a new series of pyrrolidine-based catalysts that were combined with a mercapto imidazole moiety **22a–f** (Scheme 9).^[34b] The catalysts were used for the Michael addition reaction of cyclohexanone **5** and tetrahydro-4H-pyran-4-one to various nitroolefins **8** in water. The reaction elapsed with regular to excellent yields, satisfactory to excellent diastereomeric relationship, and regular to excellent enantiomeric excesses. Although catalysts **22c**, **22e** and **22f** showed satisfactory performances for this reaction, catalyst **22d** realized the best performance by forming the most stable emulsion. Studies of catalyst recovery and/or recyclability were not conducted.

Later in the same year, Li's group evaluated catalysts **22a–f** for the synthesis of 2-hydroxy-9-oxo-bicyclo[3.3.1]nonanes **25** in water from cyclohexanone **5** and β,γ -unsaturated α -keto esters **24** (Scheme 10).^[34c,37] The reaction of compounds **5** and **24** had been already studied by three research groups for the production of chiral [3.3.1]bicycles,^[38] chiral alcohols^[39] and chiral fused dihydropyrans via 3+3 annulation, aldol reaction and hetero-Diels-Alder reaction, respectively.^[16] In this new approach, although most catalysts **22b–f** realized satisfactory performance, the catalyst with the best activity was **22e**. Thus, bicyclo nonanes **25** were obtained via a 3+3 tandem annulation reaction (Michael-Aldol sequence) in satisfactory to excellent yields with highly satisfactory overall ee. Inspiration for the creation of catalysts **22a–f** was obtained from Lin, who originally attempted to introduce the sulfone functional group onto his catalysts instead of a sulfur atom. Lin posited that the oxygen of the sulfone functionality should provide a hydrogen bond with water and, thus, improve the reactivity and stereo-selectivity of the Michael reaction, which they were testing.^[40] For catalysts **22a–f**, an imidazole group performed that function instead. Studies of catalyst recovery and/or recyclability were not conducted.

To explain the obtention of bicyclo nonanes **25**, the transition state that is illustrated in Figure 6 was proposed. Initially, carbonyl oxygen in position 1 of α -ketoester tethers to the imidazole moiety of the catalysts by hydrogen-bond. Via this mechanism, (*E*)-enamine can attack the 4-position of the α -ketoester from the rear side; therefore, the stereochemistry can

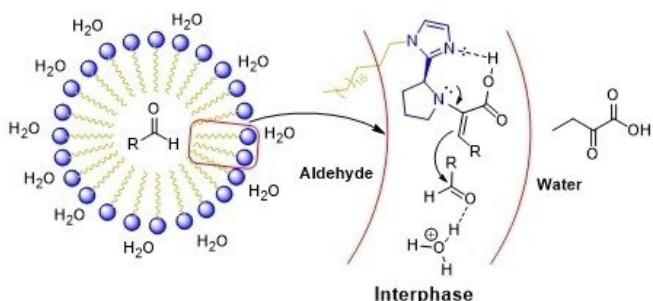
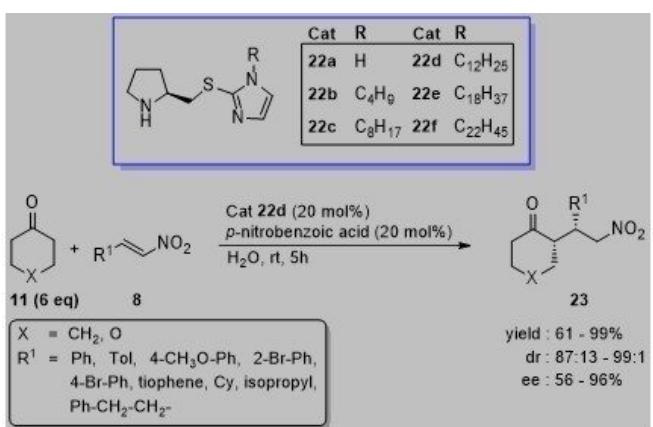
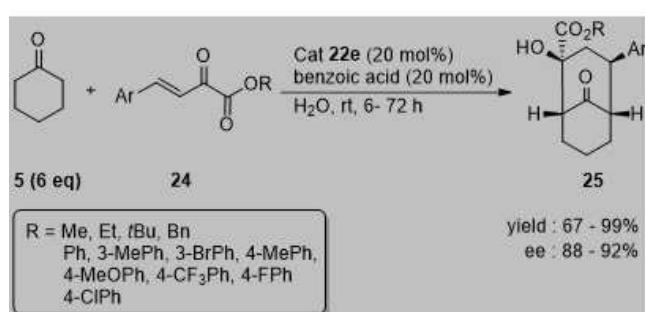


Figure 5. Reaction model for the synthesis of isotetronic acid derivatives that was proposed by Li.



Scheme 9. Michael addition reaction using catalyst **22d**, by Li.



Scheme 10. Synthesis of 2-hydroxy-9-oxo-bicyclo[3.3.1]nonanes **25** in water, using catalyst **22e**.



Figure 6. Most favoured TS for the synthesis of 2-hydroxy-9-oxo-bicyclo[3.3.1]nonanes 25.

be justified. Again, the presence of the imidazole in the catalyst is supported.

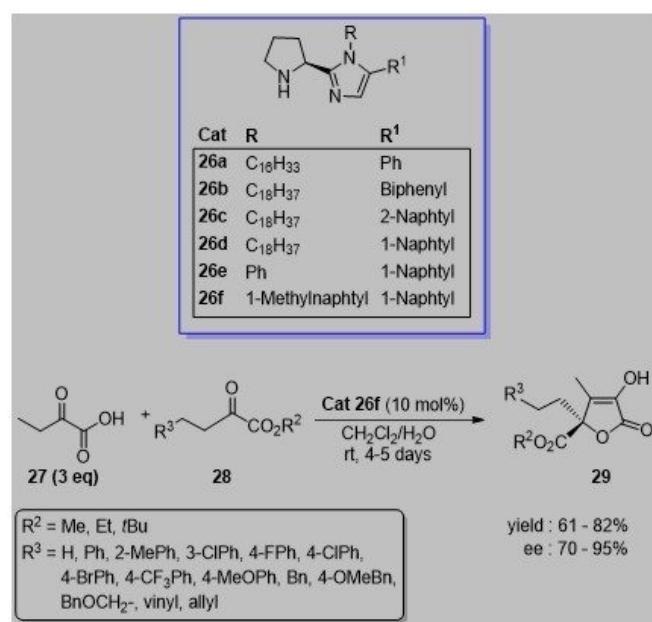
The last article in the series was published in the previous year, as already discussed. It considers the synthesis of isotetronic acids 29 that have a quaternary centre (QC) in the 5-position of the lactam ring (Scheme 11).^[34d] Water was used as the reaction medium for the synthesis of the QC-isotetronic acids 29. This cascade reaction was challenging because α -ketobutyric acid 27 and α -ketoesters 28 are of similar nucleophilicity and, thus, 4 products could be obtained. Therefore, the catalyst to be employed should be able to control the chemo- and stereoselectivities. Initially, catalyst 19g (Scheme 8), which was applied for the synthesis of isotetronic acid, was evaluated with negative results.^[23] Hence, a new set of catalysts

26a-f with substituents at the 5- and N-positions of the imidazole ring were synthesized to fit the reaction. All catalysts 26a-f realized satisfactory chemoselectivity control by producing adduct 29 as the main product in satisfactory yields. Unfortunately, only catalyst 26f realized satisfactory control of the chirality; hence, the obtained stereoselectivity depended strongly on the type of substituent at the 5-position of the imidazole ring.

Theoretical results that were obtained via DFT helped establish the transition state (TSI) of minimum energy to explain the stereochemistry of the reaction (Figure 7). Since the reaction proceeds in water, a strongly ionic, zwitterionic intermediate is proposed to form between the catalyst and the α -ketoacid (in blue). This intermediate can be stabilized by water. Once the intermediate has formed, α -ketoester can be activated by the acidic proton of the N atom on the 3-position of the imidazole moiety. The *anti*-enamine attacks the *Re*-face of ketoester, thereby producing QC-isotetronic acid with the *R* configuration. When *anti*-enamine attacks the *Si*-face of ketoester (TSII), steric hindrance is generated between the ketoester and the catalyst, thereby increasing the transition energy by 4.3 kcal/mol. Further studies that explain the chemoselectivity are discussed in the supporting information (SEI) of the corresponding article.

6. Type II. Proline-type organocatalysts

The first series of proline-type organocatalysts 31a-f was described by Hayashi in 2006. These combined proline-surfactant catalysts are interesting because the proline molecule is intact and, therefore, they are bifunctional. For these catalysts, the hydroxyl group of 4-hydroxyproline can be easily esterified or etherified with a long alkyl chain group. Catalysts 31a-f were designed and applied for the direct asymmetric cross-aldol reaction of aldehydes in the presence of water (Scheme 12).^[41] According to an evaluation of their catalytic activity, 31c performed the best by producing most diols 17 with high enantioselectivity (up to 99%) and diastereoselectivity (>20:1). Yields ranged from moderate to high. Catalysts 30a and 30b were also tested for this reaction and showed



Scheme 11. Synthesis of QC-isotetronic acids using catalyst 26f, by Li.

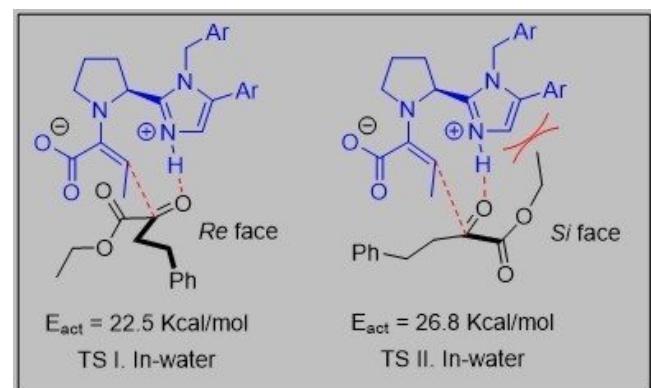
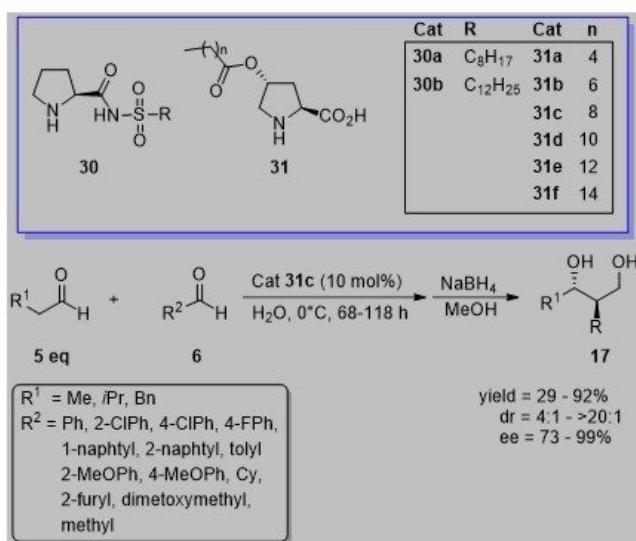


Figure 7. Energy transition states for the synthesis of QC-isotetronic acids in water.

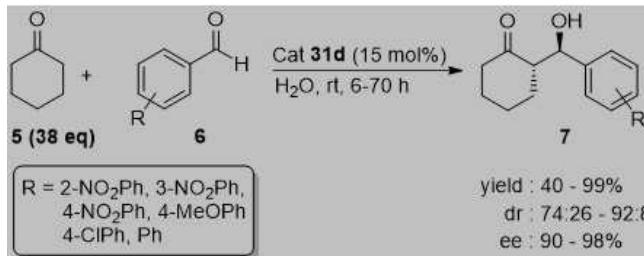


Scheme 12. Cross-aldo reaction using catalyst 31c, by Hayashi.

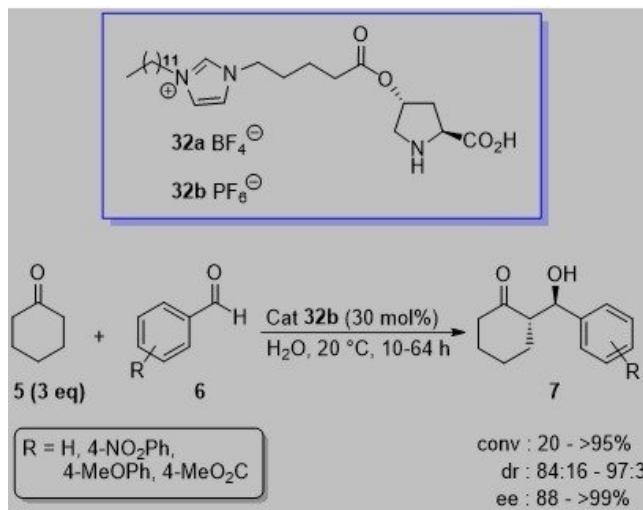
satisfactory performances in terms of enantioselectivity (95-96%); unfortunately, the obtained yields were also low (16-17%). The authors explained that the best results were obtained with catalysts 31a-f since they could form emulsions during the reaction, whereas catalysts 30a-b could not. Studies of catalyst recovery and/or recyclability were not conducted.

One year later, catalysts 31c and 31d and a new catalyst with a long alkyl chain (n=16) 31g were used by professor Li for the cross-aldo reaction of cyclohexanone 5 with diversely substituted aldehydes 6 in water (Scheme 13).^[15] Aldol adducts 7 were obtained in low to highly satisfactory yields with satisfactory diastereomeric relationships and satisfactory to excellent enantiomeric excess. An optical microscopy image of emulsion droplets showed that both catalysts 31c and 31d could form metastable emulsions, although catalyst 31d showed the best performance. The authors suggest that "a metastable O/W emulsion can be obtained when the ratio of the catalyst to cyclohexanone is optimized". Studies of catalyst recovery and/or recyclability were not conducted.

In 2008, a long-chain, ionic-liquid, proline-based catalyst that carried an imidazolium cation 32b was reported by Zlotin (Scheme 14).^[42] According to him, "recoverability is a characteristic feature of amphiphilic organocatalysts containing ionic



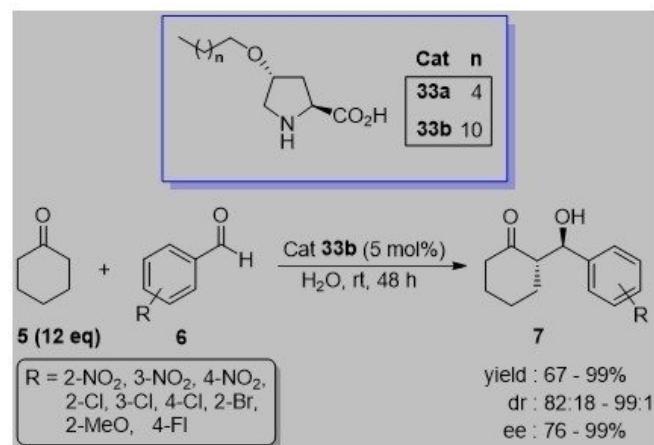
Scheme 13. Aldol synthesis using catalyst 31d by Li.



Scheme 14. Cross-aldo reaction that is catalysed by long-chain, ionic-liquid, proline-based catalyst 32b, by Zlotin.

liquid fragments". With this in mind, catalyst 32b was designed and used for the cross-aldo reaction of cyclohexanone 5, cyclopentanone 15 and diverse aldehydes 6 in the presence of water. The reactions proceeded with low to satisfactory yields, satisfactory to highly satisfactory diastereomeric relationship, and highly satisfactory to excellent ee. This catalyst has the advantage of recoverability, and it was proved that it can be used at least five times without loss of activity.

The last study of 2008 was reported by Fu.^[43] The synthesis of two new proline-based catalysts 33a and 33b that carry long alkyl chains via ether bonds was presented (Scheme 15). Catalysts of this type have the advantage of chemical stability compared with the esterified catalysts that carry an organic acid in the same position. These catalysts were evaluated for the direct aldol reaction of cyclic and aliphatic ketones with various aldehydes in water. When using cyclohexanone 5 as the nucleophile and catalyst 33b, aldol adducts 7 were obtained with regular to excellent yields, satisfactory to excellent



Scheme 15. Cross aldol reaction in water using catalyst 33b, by Lu.

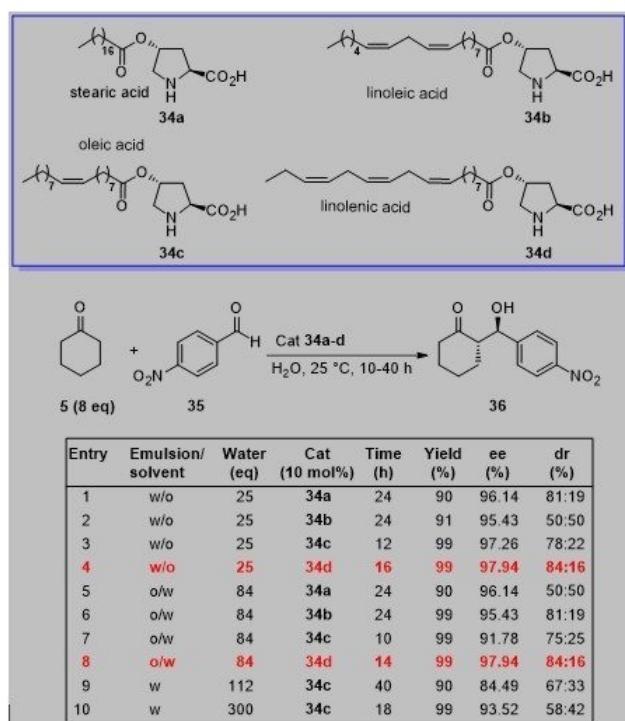
diastereomeric ratios and satisfactory to excellent enantiomeric excesses. However, when acetone was used as the nucleophile, the results were poor (yield: 61–92% and ee: 58–84%). These findings were attributed to the ability of cyclohexanone to form a metastable emulsion with water, which acetone was unable to do. Interestingly, the authors found that the configuration of the aldol centre could vary according to the quantity of water that was added to the reaction medium when acetone was employed as the nucleophile. Studies of catalyst recovery and/or recyclability were not conducted.

In 2013, catalyst **31d** (Scheme 12) was evaluated for the asymmetric Mannich reaction between *N*-PMP-protected aminoglyoxylate and cyclohexanone **5** in the presence of water^[44] with discouraging results, low to regular yields (49–61%), zero to regular dr (50:50–75:25) and regular to satisfactory ee (72–83%). The same catalyst was also evaluated for the Cascade Mannich-type/intramolecular cyclization of *N*-PMP-protected aminoglyoxylate with an aqueous solution of tetrahydro-2H-pyran-2,6-diol with satisfactory ee and dr but very low yields (4–18%). Studies of catalyst recovery and/or recyclability were not conducted.

The last article regarding compounds of this type was published by Soni and Patel in 2019.^[45] In this interesting report, the authors demonstrated that in addition to hydrophobicity, the structure and conformation of the catalytic framework enabled high stereo-induction. Four new catalysts **34a–d** were synthesized, which were all based on trans-4-hydroxy-L-proline, which was esterified with various fatty acids that contained 18-carbon alkyl chains and from zero to three *cis*-alkenes, respectively (Scheme 16). The catalysts were evaluated for the

aldol reaction between cyclohexanone **5** and 4-nitrobenzaldehyde **35** in the presence of water and in water. In Scheme 16, it is shown that these four catalysts **34a–d** realized excellent performances for this reaction, and catalyst **34d**, which carries a linolenic acid chain with three double bonds, yielded the best results in the shortest time. Studies of catalyst recovery and/or recyclability were not conducted.

The excellent yields and stereochemical results that were realized by catalyst **34d** were explained by the presence of double bonds in the alkyl chain. Double bonds can help to stabilize both micelles in an emulsion and the position of the acceptor site of the aldehyde during transition state. In the case of micelles, the presence of double bonds helps stabilize the movement of alkyl chains, and they enable the formation of π - π interactions between alkyl chains, which contributes to the micelle stability. The stereochemical outcome is explained by the control of steric and electronic factors. The double bonds play a strategic role in this matter since they restrict the mobility of the catalyst structure, which, hence, can form a hydrophobic pocket. The authors claim that the formation of the hydrophobic pocket is important because it can act as an enzyme-like active-site and facilitate the chiral induction of the aldol adduct. Indeed, the more double bonds there are, the better the stabilization of the hydrophobic pocket. A chiral pocket is more likely to form during in-water reactions due to the dilution effect and the possibility of the formation of two phases. In Figure 8, a proposed transition state is illustrated, with the amphiphilic cavity surrounding the acceptor aldehyde. Electronic CH- π interactions that occur between catalyst double bonds and aromatic hydrogens of the aldehyde make an important contribution to the formation and stability of the chiral pocket. The formation of the cavity was supported by DFT studies.



Scheme 16. Cross-aldol reaction in the presence of water and in water using catalysts **34a–d**, by Soni and Patel.

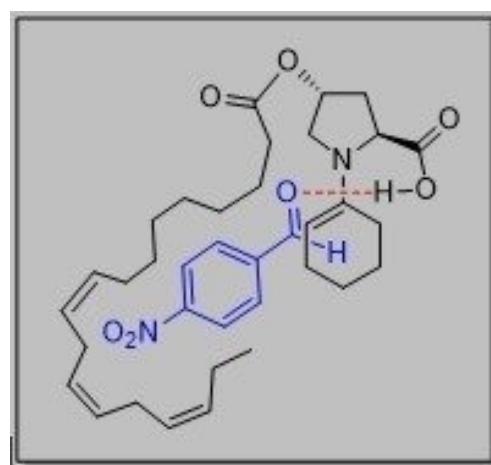
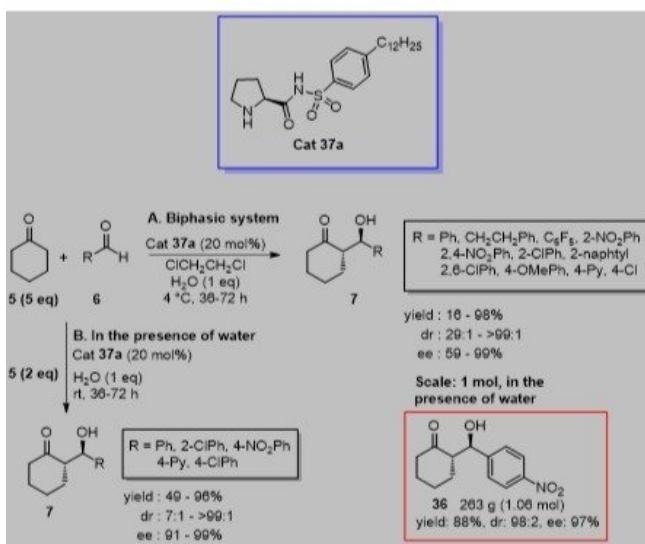


Figure 8. Proposed transition state (Houk-List model) for the cross-aldol reaction using catalyst **34d**, by Soni and Patel.

7. Type III. Prolinamide-type organocatalysts

With the objective of solving the problems of solubility and availability for various enantiomers of most organocatalysts that were encountered at that time,^[8c,17a,32,46] Carter and Yang designed the first long-chain prolinesulfonamide-type organocatalyst **37a** in 2008 (Scheme 17). Catalyst **37a** is a combination of components of STAO catalysts **13a–c** (Scheme 4) with the sulfonic acid attached to the carbonyl group of the pyrrolidine framework by a sulfonamide bond, and it does not have an ionic character. Catalyst **37a** was easily obtained in satisfactory overall yield via a three-step procedure from *N*-cbz-L-proline and *p*-dodecylsulfonyl chloride.^[47] During the years 2008–2010, a series of 7 articles were published by Carter and Yang for the evaluation of catalyst **37a** in aldol,^[46a–c,48] Mannich,^[49] Robinson,^[50] and [2 + 2]-cycloaddition^[51] reactions and for the synthesis of a natural product, namely, lycopodine.^[52] The Robinson and [2 + 2]-cycloaddition reactions were performed in the absence of water and are outside the scope of this review; the same applies to the synthesis of lycopodine. However, the use of catalyst **37a** in the absence of water is an example of its improved solubility with respect to proline and its potential application in aqueous, non-aqueous, or mixed reactions.

When evaluating catalyst **37a** for the cross-aldol reaction, the authors showed that it performed well in a biphasic system A (dichloroethane/water) and in the presence of water B (Scheme 17). For the biphasic system (dichloroethane-water), the reaction proceeded with up to 98% yield, >99:1 dr and 99% ee. The results were similar for in the presence of water reactions. The in the presence of water methodology has several advantages regarding the biphasic process; for instance, it is free of organic solvents, it is conducted at room temperature, only two equivalents of the nucleophile are used (whereas 5 eq. are used in the biphasic system), and highly importantly, it could be scaled up to 1 mol with only 2% catalyst and highly satisfactory results. Catalyst was recovered



Scheme 17. Cross-aldol reaction using catalyst **37a**, by Carter and Yang.

in a 60% yield by crystallization. These results were supported in a subsequent publication (2010) by the same authors.^[48]

In addition, a thorough study of transition states via DFT was included.^[48] The most stable transition state, namely, the "TS-Anti-Re" state (the lowest in energy), is illustrated in Figure 9. To explain the strong stereochemistry that is realized with catalyst **37a**, the authors consider the formation of nonclassical hydrogen bonds among sulfonamide oxygens, the hydrogen from the aldehydic functional group and the hydrogens from the cyclohexyl enamine. Transition state TS *Syn-Si* is less stable than TS *Anti-Re* because there is no interaction between the aldehydic hydrogen and the sulfonamide oxygen. In addition, steric hindrance could arise between the phenyl aldehydic ring and the sulfonamide moiety of the catalyst.

In 2009, same authors assessed the activity of catalyst **37a** for the Mannich reaction with dichloroethane in the presence of water (Scheme 18).^[49] The reaction was conducted with preformed aldimine **38** using acetone, cyclohexanone and tetrahydro-4*H*-thiopyran-4-one as donors. The yields for products **39a–c** ranged from regular to highly satisfactory, ee was

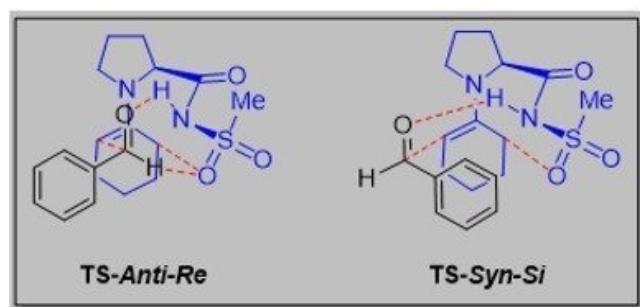
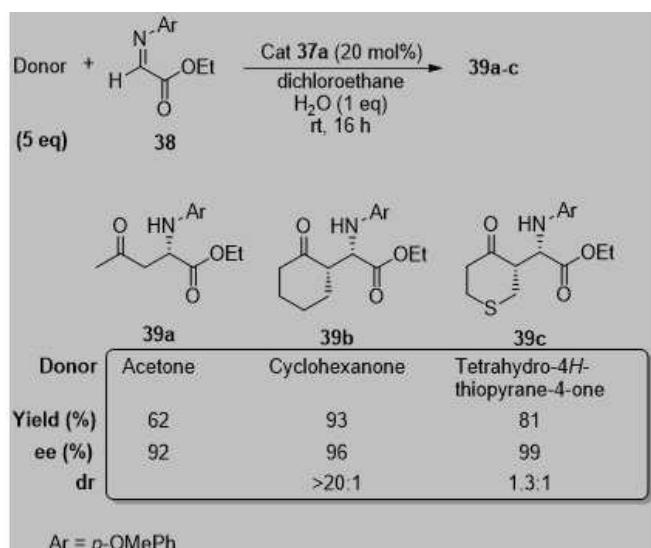


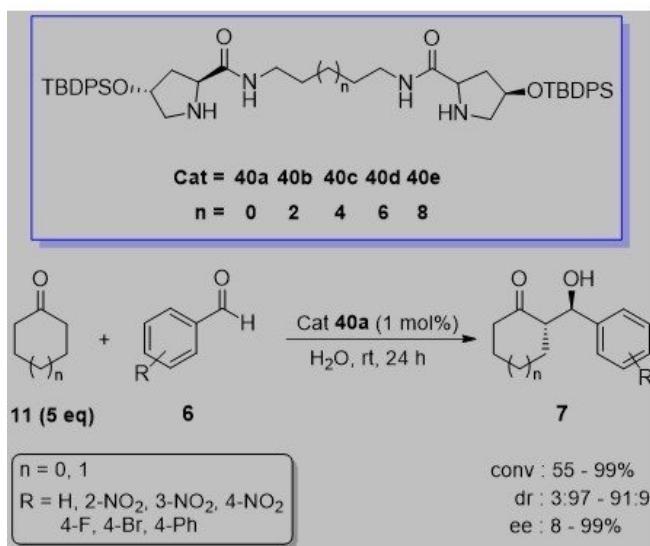
Figure 9. Transition states for the TS-Anti-Re $\Delta G_{MP2/\infty} = 0.1$ (0.0 with solvation correction) major enantiomer and TS-Anti-Si $\Delta G_{MP2/\infty} = 4.5$ (3.7 with solvation correction) minor enantiomer for the cross-aldol reaction using catalyst **37a**, by Carter and Yang.



Scheme 18. Mannich reaction in the presence of water using catalyst **37a**, by Carter and Yang.

high for the three ketones, and dr was from almost equal to satisfactory. Studies of catalyst recovery and/or recyclability were not conducted.

A series of five C₂-symmetric diprolinamide organocatalysts **40a–e** were introduced by Henderson and Delaney in 2011–2013 (Scheme 19).^[53] These catalysts were reported in three publications, which present their evaluation for the cross-aldol reaction in water. By this time, it was known that the incorporation of two proline units into one scaffold helped increase yields and improve the stereochemical outcome of organic reactions.^[54] Therefore, catalysts **40a–e** were synthesized with this objective. In addition, the authors posited that proline units could operate synergistically and/or individually and increase the catalytic activity. Catalyst **40b** (*n*=2) was the first of the series to be synthesized (2011), via a 4-step procedure with 57% overall yield,^[53b] while the remaining four catalysts were introduced in 2013. From the series, catalyst **40a**, which has the shortest alkyl chain (*n*=0), showed the highest activity.^[53c] Hence, Scheme 19 only presents the results for catalyst **40a**. Overall, the best results were obtained when cyclohexanone **5** was used as the nucleophile; the results that were obtained using cyclopentanone **15** were not satisfactory in most cases, and the *syn*-adducts were favoured when using this ketone. In their studies, the authors also showed that the reaction could be affected by the type of ions that were present in the aqueous phase and demonstrated that the best reaction medium for the reaction was deionized or Millipore-treated water, although the procedure also could be conducted with tap water in the presence of EDTA.^[53b] Remarkably, aldol that was synthesized from cyclohexanone **5** and pentafluorobenzaldehyde was obtained in quantitative yield with very high optical purity in 72 h (>99/1, anti/*syn*, 90% ee). The load of catalyst **40a** was diminished to an extremely low value (0.1 mol%), thereby yielding a turnover number of 1000. Studies of catalyst recovery and/or recyclability were not conducted.



Scheme 19. Cross-aldol reaction in water using catalyst **40a**, by Henderson and Delaney.

A transition state for the reaction was proposed by the authors, in which prolinamide units are in close proximity and can cooperate each other *via* hydrogen bonding effects or a steric mechanism. In addition, it is posited that one of the prolinamide moieties could act as a directing group and that the catalyst can form a chiral pocket (Figure 10).

Cationic amphiphilic catalysts **41a–b** (as their TFA salts) that carry a guanidine motif were reported by Jimeno in 2015 (Scheme 20) and assessed for the cross-aldol reaction in water.^[55] Since the guanidine group is known for its strong

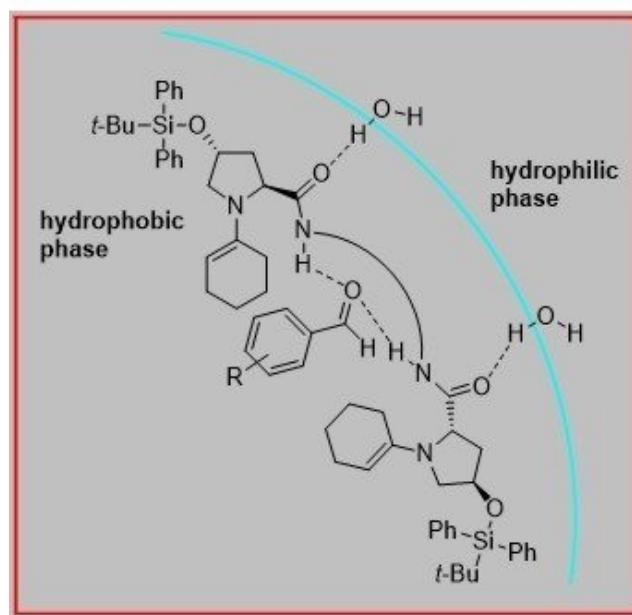
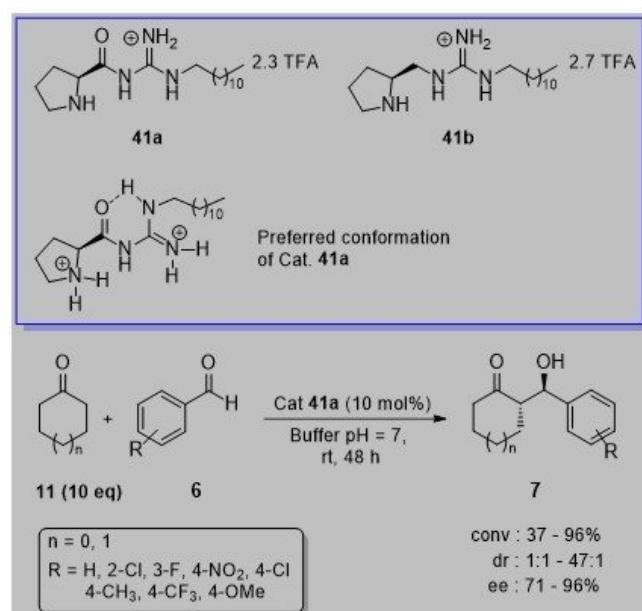


Figure 10. Proposed transition state for the cross-aldol reaction in water using catalyst **40a**, by Henderson and Delaney.

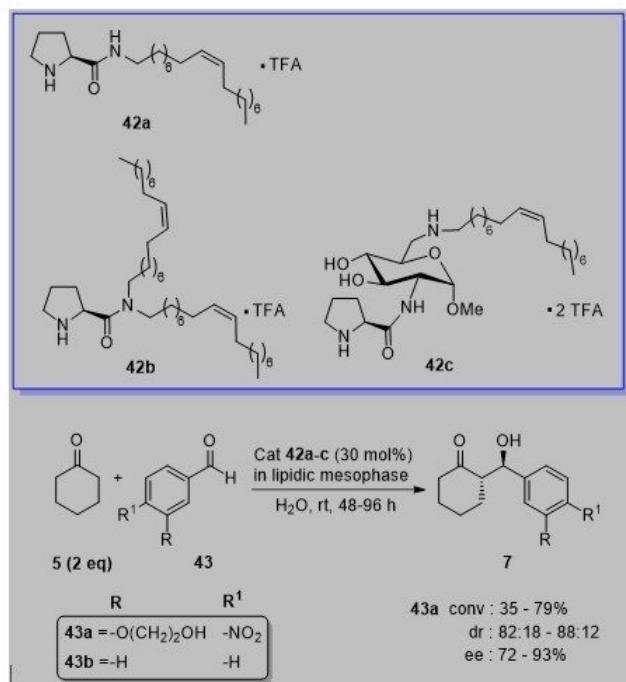


Scheme 20. Cross-aldol reaction in water using catalyst **41a**, by Jimeno.

hydrogen bond properties, it was integrated into these catalysts with the objective of enabling them to bond a vast range of functional groups, such as nitro, carbonyl, or carboxylate.^[54] Catalyst **41a** showed the highest activity during the optimization studies; the authors attribute this to the structural rigidity that the catalyst can adopt, which is conferred by the hydrogen bond between carbonyl and guanidine groups. This conformation was supported by ¹H NMR and by DFT theoretical studies. The results demonstrate that when using cyclohexanone **5** as a nucleophile, almost top values for conversion, dr and ee were attained for the aldol product **7**. In contrast, cyclopentanone **15** resulted again a poor nucleophile since the worst results were obtained when it was employed. Cyclooctanone was used as a nucleophile as well, with regular results (conv: 55%, dr: 4:1, ee: 75%). Studies of catalyst recovery and/or recyclability were not conducted.

One of the main problems that are encountered with organocatalysts is their low recoverability. To overcome this problem, they have been tethered to various heterogeneous supports, e.g., polymers,^[57] cloth,^[58] and mesoporous silica.^[59] Keeping this objective in mind, in 2018, Landau reported three prolinamide-type catalysts **42a–c** that carry long amphiphilic oleylamine chains (Scheme 21).^[60] The catalysts were synthesized and incorporated into two lipidic mesophases: liquid cubic phases (LCPs) and cubosomes (LCPs give rise to cubosomes after dispersion via ultrasonication in water). The obtained LCPs and cubosomes were assessed for the cross-aldol reaction of cyclohexanone and aldehydes in phosphate buffer solution (PBS).

According to the authors, "LCPs are gel-like, liquid crystalline biomaterials that form spontaneously upon mixing water



Scheme 21. Cross-aldol reaction using lipidic mesophases (LCPs and cubosomes), by Landau.

and lipid molecules in a well-defined composition and temperature range given by the phase diagram".^[61] Advantageously, LCPs and cubosomes are stable structures that can be recovered from the reaction medium. The basic structure of the LCPs and cubosomes is illustrated in Figure 11. It is formed by a curved lipid bilayer of monoolein and the corresponding catalyst **42a–c** with an inner channel of tuneable diameter. Basic structures can adopt different three-dimensional arrangements and, thus, form LCPs and cubosomes. Organic reactions are claimed to occur in the lipid-water interphase of the lipidic mesophases; hence, they are also regarded as nanoreactors.

After a careful selection of the components for the LCPs and cubosomes (catalysts **42a–c** 5% and monoolein 95%) and after identifying the optimal reaction conditions, namely, catalytic loading of 30%, PBS 0.1 M as the reaction medium, room temperature and a reaction time of 48–96 h, LCPs and cubosomes of catalysts **42a–c** were tested for the cross-aldol reaction in PBS (the buffer is necessary for the lipidic mesophase stability). Cyclohexanone was used as nucleophile, and two aldehydes, namely, hydrophilic **43a** and hydrophobic **43b**, were used as electrophiles (Scheme 21). Thus, LCPs and cubosomes of catalyst **42a** showed the highest activities, while those for catalyst **42c** were the lowest. In Scheme 21, only the results for aldehyde **43a** are presented since, unfortunately, after 72 h of aldehyde **43b** reaction within LCPs and cubosomes of cat **42b**, only 8% conversion to the aldol products **7** was detected. This is a limitation of the methodology with lipidic mesophases, as aldehydes should travel via the inner channels of LCPs and/or cubosomes for the reaction to occur. Therefore, hydrophilic aldehydes are necessary for producing satisfactory results. Importantly, LCPs and cubosomes were recycled 5 times with no loss in terms of the results.

Many chiral supramolecular structures, such as nanotubes, nanorods, and nanocages, have been developed and utilized as catalysts.^[62] Various of these supramolecular structures can be obtained via chiral self-assembly. Depending on their composition, amphiphilic organocatalysts can behave as self-assembled

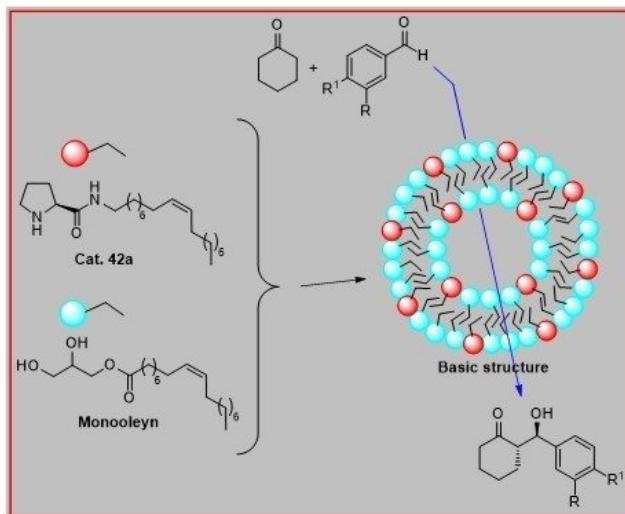


Figure 11. Lipidic mesophase basic structure.

dynamic systems and form supramolecular structures. Thus, Liu and Zhang reported a couple of studies in which the formation of supramolecular structures using long-chain, proline-containing, amphiphilic dipeptides was described.^[63] In the first of these studies (2012), a set of four amphiphilic catalysts that contained a dipeptide of L-tryptophan-L-proline **44a-d** were reported (Figure 12).^[63a] The catalysts were evaluated for the cross-alcohol reaction in water using cyclohexanone **5** and 2-NO₂-benzaldehyde. The catalyst with the best performance was **44b** (yield: 87%, ee: 90%). Unfortunately, despite promising results with this catalyst, neither the scope nor the diastereomeric relationship was reported. Via scanning electron microscopy (SEM), the authors found that depending on the solvent, catalyst **44b** was used for organization into two supramolecular structures: nanospheres in water and nanofibers in a mixture of water-dimethylsulfoxide (DMSO). Studies of catalyst recovery and/or recyclability were not conducted.

In their second article (2018),^[63b] Liu and Zhang reported two dipeptide catalysts: **45a**, which is an homochiral catalyst that contains 4-hydroxy-L-proline-L-glutamic acid, and **45b**, which is an heterochiral catalyst that contains 4-hydroxy-L-proline-D-glutamic acid. Both catalysts possess a dodecylamine amphiphilic tail, and it was shown that they could self-assemble into chiral nanofibers. According to the authors, "glutamide was employed for the construction of the nanofibers, because this unit was found to have a strong self-assembly capacity" (Figure 12).^[64] Nanofibers of catalysts **45a** and **45b** were prepared by adding them to pure acetonitrile or by using THF or CHCl₃ as cosolvents. The obtained nanofibers were inside organogels, which were evaluated for the cross-alcohol reaction of cyclic ketones **11** and aldehydes **6** in the presence of water. Such organogels showed low catalytic activity. Therefore, the solvent of organogels was air-dried and corresponding xerogels were obtained. Then, the catalytic activity of the xerogels was assessed in the presence of water for the described reaction, and the one composed of catalyst **45a** realized the best performance. When using **45a**-xerogel and six-membered cyclohexanones **5**, aldol products **7** were obtained in up to 97% yield, up to 96:4 dr, and up to 95% ee (Scheme 22). Surprisingly, the best ee (>99%) was realized when cyclopentanone was used as a nucleophile; none of the other studied catalysts attained this value. **45a**-Xerogel was reused six times, obtaining aldol adducts in high yields and 92% ee

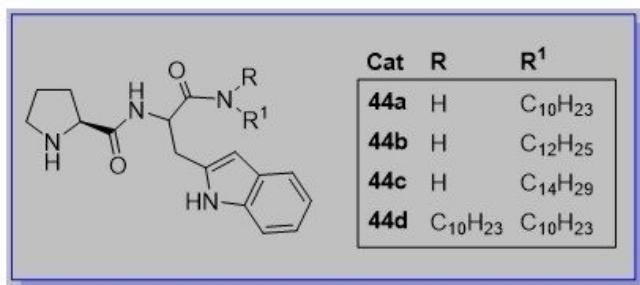
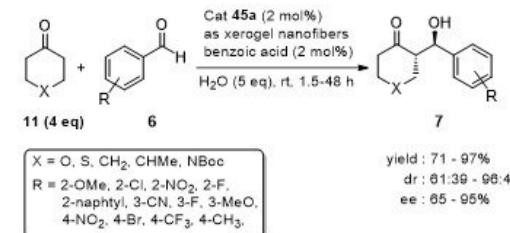
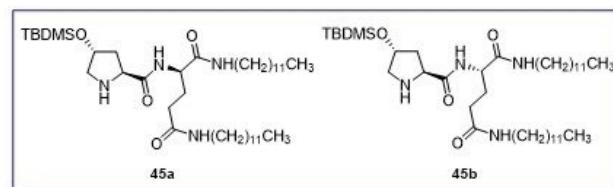


Figure 12. L-Tryptophan-L-proline amphiphilic self-assembled organocatalysts **44a-b**, by Liu and Zhang.



Scheme 22. Cross-alcohol reaction in the presence of water using xerogels of catalysts **45a-b**, by Liu and Zhang.

overall. Importantly, when the catalytic loading of **45a**-xerogel was diminished to 0.3 mol%, aldol adducts **7** were obtained in satisfactory yields and 86% ee.

The excellent results that were obtained with **45a**-xerogel were explained as follows: Dipeptide **45a** is self-assembled into multilayer nanofibers, the strong positive supramolecular chirality of which is guided by L-glutamic acid. Proline remains on the fibre surface (where the aldol reaction is conducted) and controls the molecular chirality. Indeed, it is posited that the supramolecular and molecular chiralities of **45a**-xerogel act synergistically and produce aldol products in excellent yields and stereoselectivities (Figure 13). In the case of xerogel **45b**, it is posited that the chirality of the aldol product was lower due to the less efficient collective chirality of the fibre.

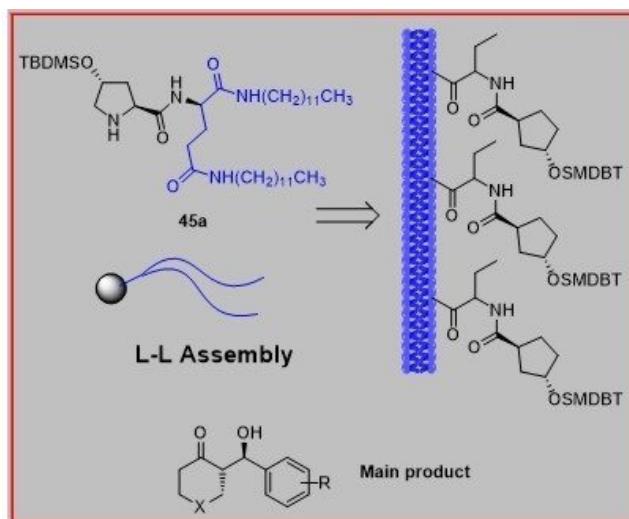
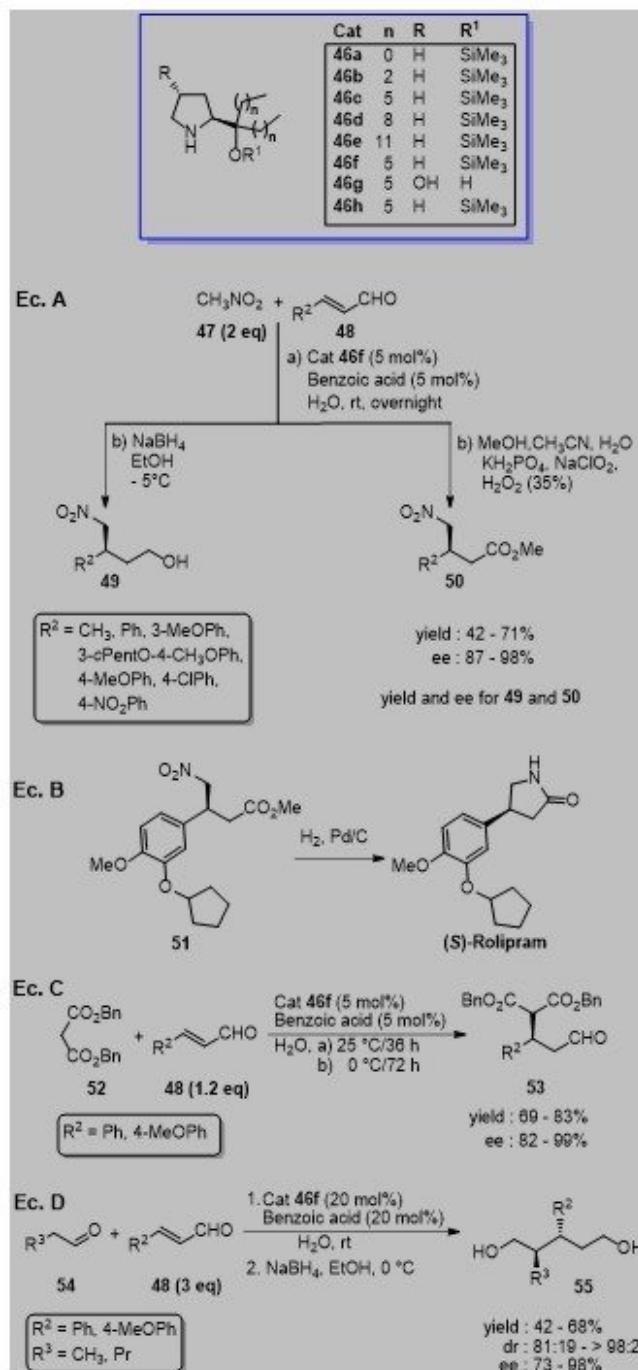


Figure 13. Structure of **45a**-xerogel self-assembly, by Liu and Zhang.

8. Type IV. Prolinol-type organocatalysts

For reactions that use organic solvents, diaryl prolinol silyl ethers have been widely used because they showed high reliability in terms of applicability and stereocontrol.^[65] By contrast, unprotected diaryl prolinols are unreliable and unpredictable as catalysts. This is attributed to the presence of free OH, which is a reactive group that could help realize stereocontrol by forming hydrogen bonds or react with the intermediate imine to form oxazolidines (Figure 14).^[66] By far, prolinol-type organocatalysts have been the least-studied amphiphilic organocatalysts for reactions that use water as the medium. Free OH could also be the reason since the silyl protective group is poorly resistant to water and, hence, OH could be easily freed in the media.

To the best of our knowledge, only four articles regarding this issue have been published, and they will be discussed next. Palomo and his group reported the first family of prolinol-type organocatalysts **46a–h** in 2007 (Scheme 23).^[22] The catalysts were built from L-proline or *trans*-4-hydroxy-L-proline. Hydroxyl groups for catalysts **46a–g** were protected with trimethylsilyl. According to the authors, the catalysts were conceived based on two main design elements: "a) the favourable role played by hydrophobic alkyl chains in water-compatible enamine-mediated catalysis,^[3b,8d,e] and b) the assumption that for effective control of iminium geometry and face shielding, a bulky group should be located near the nitrogen atom".^[67] The Michael addition reaction with pyrrolidine-type catalysts had already been reported by Barbas III^[8d] and Wang,^[28,32] hence, the catalysts that are reported here further contribute to the scope of amphiphilic organocatalysts for this reaction. Thereby, catalysts **46a–h** were synthesized and evaluated for the asymmetric Michael addition of four nucleophiles, namely, nitromethane **47** (Ec. A), malonic acid benzyl ester **52** (Ec. C) propanal **54a** and pentanal **54b** (Ec. D), to a series of α - β -unsaturated aldehydes **48**. Catalyst **46f** was the most active, and in Scheme 23, only the results that were obtained via its use will be presented. Although aldehydes of a modest scope were utilized for the catalyst **46f**, Michael adducts (**49**, **50**, **53** and **55**) were obtained with regular yields and up to 99% ee. Fortunately, the use of amphiphilic aldehydes (propanal **54a** and pentanal **54b**) also produced two chiral centre adducts **55** with excellent dr (81:19->98:2). Finally, one of the adducts (**51**) that were obtained via the addition of nitromethane was reduced, and (S)-Ropipram, which is a type IV phosphodiesterase inhibitor, was obtained (Ec. B).^[68] Thus, the possibility of enamine activation by amphiphilic catalyst **46f** and its



Scheme 23. Michael addition reactions in-water using catalyst **46f**, by Palomo.

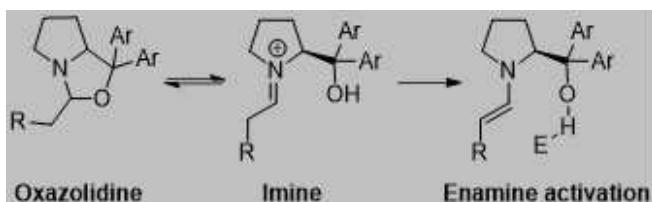
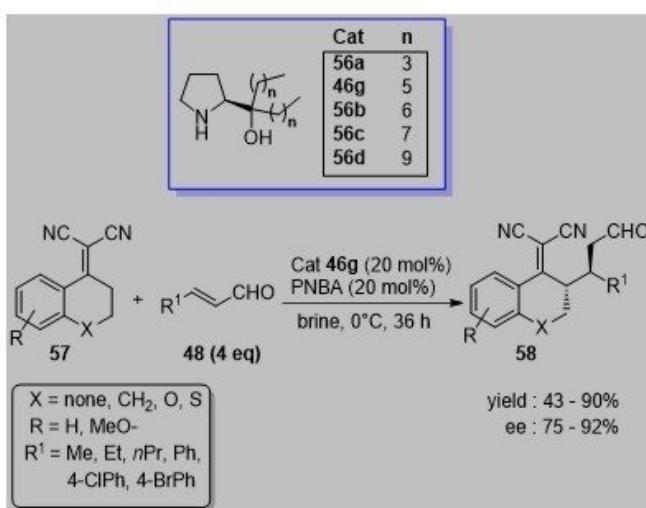


Figure 14. Oxazolidine formation in enamine activation.

important applications were demonstrated. Studies of catalyst recovery and/or recyclability were not conducted.

One year later, a complementary set of Palomo's catalysts, which included **46g** (Scheme 23), was reported by Loh (**56a–d**, Scheme 24).^[69] The hydroxyl group was left unprotected for the whole set. The catalysts were designed under the rationale that "dialkyl-(S)-prolinols with alkyl chains as hydrophobic groups should assemble with hydrophobic reactants in water and sequester the transition state from water and, therefore, high

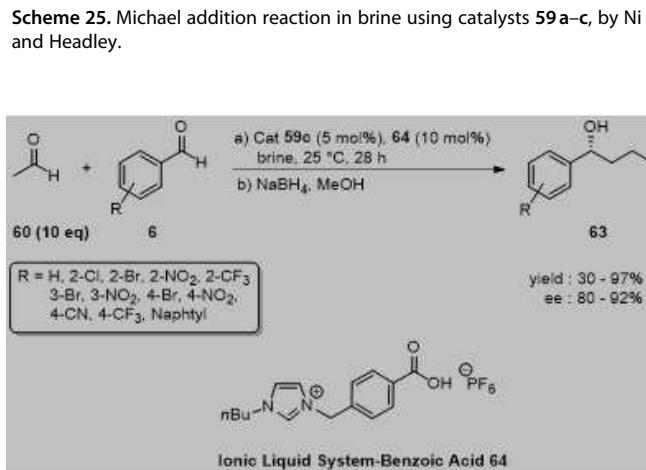
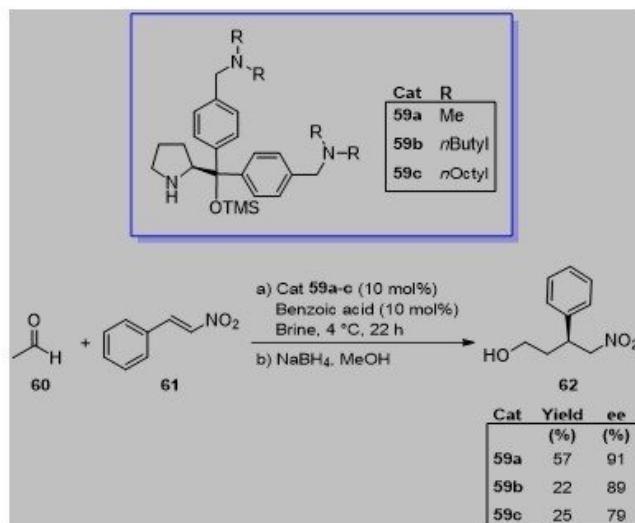


asymmetric induction may be achieved in water". The catalysts were evaluated for the Michael addition reaction of dicyanoolefins **57** to α,β -unsaturated aldehydes **48** in water. Dicyanoolefins **57** are important starting materials in the Michael reaction because their donor-acceptor properties enable multifunctional products with two vicinal tertiary carbon centres to be obtained.^[70] The reaction proceeded well in brine at 0°C using catalyst **46g**. The yields for products **58** ranged from low to highly satisfactory (43–90%), while ee fluctuated from satisfactory to highly satisfactory (75–92%). It was shown that ee could be improved by a single recrystallization from isopropanol (ee > 99%). The obtained results demonstrated that unprotected dialkyl prolinols are useful for catalysing organic reactions in water. Studies of catalyst recovery and/or recyclability were not conducted. Recently, a review of the use of protected and unprotected diarylprolinols in stereoselective catalysis with organic solvents has been published.^[66]

Ni and Headley published a couple of studies in 2012–2013 on a new class of long-chain diarylprolinol catalysts **59b–c**.^[71] These catalysts originated from previously reported water-soluble short-chain catalysts **59a**, with which Ni's group had been working and which were being used for Michael addition reactions in water.^[72] Originally, due to its solubility characteristics, catalyst **59a** was designed as a Brönsted salt with benzoic acid with the following objectives: a) promote the formation of enamine during reaction with donor, b) increase chemical yields and stereoselectivity, c) enhance the aqueous solubility, and d) provide easy recycling of catalysts. In the first article, the synthesis of catalysts **59a–c** and their evaluation for the Michael addition reaction of acetaldehyde **60** to nitroolefins **61** in brine were reported, whereas the second article reported the cross-alcohol reaction of acetaldehyde **60** to aromatic aldehydes in brine. The use of acetaldehyde **60** as a nucleophile is challenging due to its ambivalent nucleophile-electrophile chemical behaviour, which enables it to generate various side-products, e.g., via multi/poly-alcoholization, dehydration and

polymerization.^[73] Hence, acetaldehyde **60** could be selectively used. However, it had not yet been used for in-water reactions at that time. Scheme 25 presents the results for the Michael reaction in brine.^[71a] Unfortunately, for this reaction, the short-chain catalyst **59a** was the most active; hence, short chain catalysts can also realize satisfactory performance in water. Indeed, although a satisfactory ee (89%) was realized by using long-chain catalyst **59b**, it produced the Michael adduct **62** in very low yield (22%). Studies of catalyst recovery and/or recyclability were not conducted.

Finally, in the cross-Aldol reaction, catalyst **59c** was found to be the most active (Scheme 26).^[71b] A broad range of aldehydes were utilized in the presence of ionic liquid **64** as an additive. After NaBH₄ reduction of aldol adducts, alcohols **63** were obtained with low to excellent yields (30–97%) and ee of up to 92%. Studies of catalyst recovery and/or recyclability were not conducted.



9. Summary and Outlook

Since the seminal report by Barbas III on the use of the first amphiphilic long-chain organocatalyst for reactions in aqueous media in 2006, many catalysts have been described. Nowadays, the use of aqueous media for organic reactions is not as unusual as it was years ago. Important achievements have been realized with PDLACAOs, such as quantitative conversions of >99%, excellent stereochemical outcomes of ee > 99%, dr of up to 99:1, recyclability up to 7 times, and a catalytic charge of as low as 0.1% for some of the catalysts. These factors, along with the price, availability and/or ease of synthesis of each catalyst should be considered when selecting one of them for a reaction. The compounds with the highest recyclability, namely, ionic liquids, self-assembled xerogels and cubosomes, were the result of the combination of supramolecular chemistry, materials science and organic chemistry. Unfortunately, recoverability and/or recyclability studies, which are of utmost importance in the design of these catalysts, were not conducted for most of them. Such complex structures represent the state-of-the-art on PDLACAOs, although their future evolution might involve the development of enzyme-like structures with similar catalytic efficiency. According to the literature included herein, reactions with PDLACAOs occur in emulsions, and the better the emulsion, the better the conversion and stereochemical outcome. Moreover, a 4-carbon-long chain in the catalyst is the minimum requirement for the formation of a metastable emulsion. However, despite the important described achievements, this rising area of organocatalysis has large challenges to face, which involve a) the catalytic charge, b) the donor equivalents, c) the reaction scope, d) scaling up and e) the application of catalysts to the synthesis of natural products. From the analysis of the literature in this review, these challenges can be identified as follows: a) For the catalysts that were analysed here, the normal catalytic charge varied between 10–20%, which is too large compared with those of metal catalysts. In the worst cases, it was elevated to 30%, and in the best example, it was reduced to 1%. Catalyst **40a** was used with a catalytic charge of as low as 0.1%, which might open a path to the development of more efficient PDLACAOs. b) During reactions, the donor (or nucleophile) was typically used in a proportion that ranged from 5 to 10 fold with respect to the aldehyde acceptor, although 38 eq of the donor were used in an extreme case and two equivalents in the best cases. The donor is used as an emulsifying medium for these reactions, which leads to its use in large quantities. Therefore, novel methodologies that use a minor quantity of the donor should be developed. c) Amphiphilic catalysts have been applied mainly in the cross-aldol reaction and in the Michael addition reaction, but only one example of their application in the Mannich reaction is available (Scheme 18), which is a very narrow scope. d) To demonstrate their applicability at the industrial level, the utility of the catalysts must be demonstrated for large-scale reactions. However, most reactions that are described here are at 1-mmol scale, and only one example of an aldol reaction at 1-mol scale is presented. The same issue is identified when considering their application in the synthesis

of natural products: in the consulted literature, only one example is presented.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: organocatalysis in water · organocatalysis in the presence of water · amphiphilic organocatalysts · long-aliphatic-chain amphiphilic organocatalysts · proline-derived amphiphilic organocatalysts.

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