Diarylprolinol derivatives in organocatalysis from another point of view: *structural aspects*

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Abstract

The synthesis of complex active molecules has afforded the search for new methods and new processes in organic synthesis. In this context, organic metal free catalysis has appeared as a powerful tool being complementary to metal catalysis in the field of asymmetric synthesis. The success of this methodology has been increasing in the last decade and the research for new organocatalytic systems as well as new applications has attracted the interest of many research groups. Among all organocatalysts, diarylprolinol derivatives have emerged as powerful scaffolds for asymmetric catalysis, proof of that is the huge number of publications reported using this kind of structure as catalysts. However, only in a few cases, different aspects of the catalysts structures and additional additives have been largely studied and a plausible explanation has been given. In this sense, this review treats to illustrate these important and scarce examples and to give a very general vision relating to the application of diarylprolinol derivatives in organocatalytic transformations from another point of view: *structural aspects*. The influence of catalyst structure, electronic effects, and the use of additives will be the aim of discussion and comment in this work.

Keywords

Catalysis, organocatalysis, α,α -diaryl-2-prolidinemethanol, α,α -diarylprolinol silyl ether, mechanism, additive, organocatalyst.

1. Introduction

Natural product synthesis and medicinal chemistry strongly depend on the development of new synthetic methodologies.[1] It is not an exaggeration to think that catalytic reactions are cornerstones in the design of future sustainable chemical processes.[2] In this context, organic catalysis has emerged as a powerful and efficient tool being complementary to metal-based catalysis in the field of asymmetric synthesis.[3] The success of this methodology has been increasing in the last decade and the research for new organocatalytic systems as well as new applications have attracted the interest of many research groups. Nowadays, the term asymmetric organocatalysis covers a wide range of organic processes and methodologies, providing efficient and environmentally friendly access to enantiomerically pure compounds including many drugs and bioactive natural products.[4]

Chiral secondary amines, and more recently chiral primary amines, have emerged as a privileged class of organocatalysts and play a fundamental role in a large variety of important transformations.[5, 6] Among these important structures, the amino acid proline[7] and the MacMillan's imidazolidinones[8] have become one of the most efficient organocatalysts. However, in the last years, diarylprolinol derivatives have appeared as a capable class of organocatalysts,[9] showing a remarkable generality compared with proline and imidazolidinones, which have displayed its efficiency in a great number of processes firstly focused on the α -, [10] β -, [11] and γ -functionalization[12] of carbonyl compounds, involving enamine, iminium-ion and dienamine activation or a combination of them.[13] Moreover, these catalysts have been also applied in diastereo- and enantioselective domino, one-pot, and multicomponent reactions.[14] Even when diphenylprolinol (*S*)-**1a** was synthesized in 1933 by Kapfhammer and Matthes,[15] it was not until 1987, when it found its first applications in asymmetric catalysis.[16, 17] Since then a great number of diarylprolinol derivatives have been reported on the literature, and some of them, such as diarylprolinol silyl ether derivatives **2a** and **2b**, have emerged as promising general catalysts in asymmetric synthesis (Fig. (1)).

Fig. (1). Representative α,α -diarylprolinol derivatives reported on the literature.[18]

Despite of this, it is rare to find studies where plausible explanations have been given about the different aspects of the catalyst structure, as well as, the effect of the additives. In this sense, this review illustrates just some representative examples of the application of diarylprolinol derivatives in catalytic transformations from another point of view: *structural aspects*. However, it is not our intention to be comprehensive and extensive since there is a remarkably large amount of literature concerning to this field and very interesting reviews previously reported.[9]

2. α,α -Diaryl-2-prolidinemethanol Derivatives

Although diaryl-2-prolidinemethanol derivatives have been used during long time, there are only a few studies on the structural requirements of the catalysts that can provide clues for further developments and for mechanistic interpretations of different processes.

It is remarkable in this context the work published by Lattanzi and co-workers.[19] They carried out an interesting screening of different diaryl-2-prolidinemethanol derivatives **1a-l** as catalysts for the asymmetric epoxidation of α,β -enones.[20, 21]

After their first publication about the catalytic asymmetric epoxidation of a broad variety of α,β -enones mediated by α,α -diphenyl-L-prolinol **1a** as a bifunctional organocatalyst,[22] they focused on the study of different steric and stereoelectronically modified α,α -diaryl-L-prolinols (Scheme 1, Table 1).

Scheme 1.

Table 1. Screening of catalysts **1a,c-h**, **5-7** to promote the asymmetric epoxidation of α,β -enone **8**.

Entry	Catalyst	t (h)	yield (%)	ee (%)
1	1a	94	72	75
2	1c	60	99	88
3	1d	87	60	77
4	1e	90	79	82
5	1f	90	48	78
6	1g	70	26	81
7	1h	65	85	76
8	5	97	14	63
9	6	140	22	23
10	7	46	27	-

From results shown in Table 1, is possible to remark some important ideas. The best reactivity and higher enantioselectivity were achieved with bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol (**1c**),[23] compared with the other catalysts (compare entry 2 with entries 1, 3-7). The presence of hindered phenyl rings in the catalyst seemed to be crucial for enantioselective induction since racemic product was obtained with catalyst **7** (entry 10). The electronic properties of the substituents on the phenyl ring also influenced the catalytic activity of the diaryl-2-pyrrolidinemethanols, and electron-donating groups enhanced the conversion to the epoxide, while electron-withdrawing substituents shown negative effect. Moreover, electronic character, steric size and the position of the groups on the phenyl ring were important in affecting the enantioselectivity. These results reinforced the mechanistic hypothesis proposed for this process involving the ionic pair made up of the *tert*-butyl hydroperoxide anion and the ammonium cation **10** as active species (Scheme 2). Indeed, catalysts with electron-donating substituents on the phenyl ring (**1c,e,h**) (entries 2, 4 and 7) were more efficient than unsubstituted **1a** (entry 1) and more active than electron-withdrawing substituted **1d,f,g**, favoring amine protonation by means of inductive or electronic effects (entries 3, 5 and 6), as expected.[24]

Another key factor, which could influence the catalytic activity, is the possible enhanced solubility of organocatalysts **1c,e,h** in the reaction solvent (entries 2, 4 and 7) compared with catalysts **1d,f,g** (entries

3, 5 and 6) which showed higher insolubility in the reaction media, as experimentally observed by the authors.

Scheme 2. Proposed mechanism for the catalytic cycle of epoxidation of α,β -unsaturated ketones **8** using catalyst **1a**.

In these reactions, the key role of the hydroxyl group in the catalyst is consistent with an intermolecular hydrogen-bonding interaction with the oxygen atom of the enone carbonyl group, which activates the enone towards 1,4-addition of the peroxy anion while directing and placing the partners in close proximity to react (Scheme 2, TS-11).[25] Indeed, the hydroxyl group was shown to be fundamental for the reactivity as well as for the asymmetric induction, since catalyst **1a** (entry 1) was more active and enantioselective than catalysts **5** and **6**,[26] (entries 8 and 9).

It is likely that an intramolecular hydrogen bonding in the ammonium cation **10**, between the oxygen of the hydroxyl group and the proximal +N-H group, might render the proton of the hydroxyl group more acidic. Consequently, it would be more susceptible to take part in an intermolecular hydrogen bonding with the oxygen of the carbonyl moiety, so activating the enone and providing the right orientation for the nucleophilic attack (Scheme 2). These data further confirm and generalize the hypothesis that the β -amino alcohol plays the role of a bifunctional catalyst according to the catalytic cycle proposed in Scheme 2,[20a] where *tert*-butyl hydroperoxide (TBHP) first would undergo deprotonation by the β -amino alcohol, which thus would generate the active catalytic species, ammonium **10**/*tert*-butyl peroxy anion ion pair. The hydroxyl group of the promoter then could activate and orientate *trans*-chalcone through hydrogen bonding with its carbonyl group for the nucleophilic 1,4-addition of the *tert*-butyl peroxy anion.

On the basis of the proposed catalytic cycle, the basicity of the amine and hydrogen bonding interactions would be fundamental in regulating the activity of the promoters.

Afterward and in order to gain more insight about the structure for the appropriate catalyst, the same group reported subsequent modifications of the diaryl-2-pyrrolidinemethanols, showing that fine modifications of the stereoelectronics of the substituents on the aryl moiety were also important to achieve higher efficiency in the same reaction (Scheme 3).[19b] In this context, they prepared new (*S*)-diaryl-2-pyrrolidenemethanol derivatives **1i-1l**, and checked them under the optimal conditions previously found for catalyst **1c**.

Scheme 3.

Table 2. Asymmetric epoxidation of α,β -enone **8** by catalysts **1a,c,i-l**.

Entry	Catalyst (%)	T (°C)	t (h)	yield (%)	ee (%)
1	1a (30)	r.t.	94	72	75
2	1c (20)	+4	112	90	91
3	1i (20)	+4	112	9	43
4	1j (20)	+4	86	37	86
5	1k (20)	+4	90	<5	-
6	1j (15)	+4	106	70	92
7	1l (10)	r.t.	110	93	89
8	1c (10)	r.t.	95	61	88

So, from this study is possible to remark that the type of substitution at the phenyl ring extremely affected the level of enantiocontrol. These results shown that *ortho*-type substitution was unfavorable in all respects, probably because of steric effect of the *ortho* substituents on the OH group, the activation via hydrogen bonding with the enone carbonyl moiety was avoided (entries 3 and 5). However, substitutions

at the *meta* positions proved to be crucial for catalyst performance. Small or major modifications of the nature of the substituents, with respect to the methyl group of **1c**, were detrimental (entries 4 and 6). In this respect, methyl substitution at the *meta* positions would seem to play a relevant role in the control of the enantioselectivity (compare entries 2 and 6 with 4). Catalyst **11** should have had improved activity with respect to **1c** due to the introduction of additional electron donating *p*-methoxy groups, however only had a comparable impact on enantioselectivity. A better comparison on catalysts activity can be gained by comparing the results obtained at 10 mol% loading, working at room temperature (entries 7-8). After similar reaction times, the epoxide was isolated in comparable ee, but a higher yield was achieved when catalyst **11** was used, as expected.

More recently, the same group has carried out a study to compare the influence of the member rings of the catalysts (Scheme 4).[19c] In this sense, the aromatic substitution pattern in catalyst **11** was maintained and the aliphatic ring was modified for the synthesis of cyclic catalysts **12** and **13**.

Scheme 4. Asymmetric epoxidation of α,β -enone **8** using catalysts **11**, **12** and **13**.

The results in Scheme 4 clearly showed that ring size is crucial and an important factor for the reaction to proceed and the pyrrolidine ring allowing the highest conversion and asymmetric induction (compare entry 1 with entries 2-3).

Whereas solvation effects are of reduced importance in the stabilization of charged and polar species when hexane is used as solvent, a more realistic idea on the basicity of secondary cyclic amines would be gained by considering the intrinsic basicity rather than the solution basicity.[27] As a result, meaningful differences in the basicities of the amines can be predicted by evaluation of the proton affinities as expected, being the four-membered ring amine the least basic.

3. α,α -Diarylprolinol Silyl Ether Derivatives

More recently α,α -diarylprolinol structures have been also considered as silyl ether derivatives, and a great number of articles have been published after the pioneering works by Jørgensen and Hayashi groups appeared in 2005.

α,α -Diarylprolinol silyl ether derivatives were used as catalysts for the first time in by Jørgensen group for the α -functionalization of aldehydes,[28] and simultaneously, by Hayashi and co-workers in the asymmetric Michael reaction of aldehydes and nitroalkenes.[29] Their works revealed the efficiency of these catalysts in terms of both reactivity and enantioselectivity and have attracted the attention from many other groups.

Taking as a representative example this first direct organocatalyzed enantioselective α -sulfenylation of aldehydes, we can see the influence of the structure of the reported catalysts (**2a-d**) in the process (Scheme 5, Table 3).[28a]

Scheme 5.

Table 3. Screening of different organocatalysts for the α -sulfenylation of aldehyde **14**.

Entry	Catalyst	yield (%)	ee (%)
1	17a	16	0
2	17b	30	25
3	6	56	52
4	1a	—	—
5	2a	90	77
6	2b	90	98
7	2c	73	90
8	2d	75	84
9 ^[a]	2b	90	96

10 ^[b]	2b	90	90
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^[a] After 1 h in the presence of LiClO₄ (30 mol%). ^[b] After 1 h in the presence of *o*-nitrobenzoic acid (10 mol%).

From the results summarized in Table 3, whereas L-proline (**17a**) was ineffective in this reaction (entry 1), the chiral pyrrolidine derivative **6** increased both the reactivity and enantioselectivity significantly (entry 3).[26a, 30] However, the authors observed a slow racemization of the product upon prolonged reaction times that also led to α,α -disulfenylation. To minimize such undesired interactions between the organocatalyst and the final product, the reaction was attempted in the presence of catalysts with an increased steric bulk (**1a** and **2a-d**). In the case of α,α -diphenyl-L-prolinol **1a** no reaction occurred (entry 4), probably as a result of the formation of the relatively stable and unreactive hemiaminals (**24** and **25**) that remove a significant amount of catalyst from the catalytic cycle (Scheme 6).[31, 32]

Scheme 6. Proposal of catalytic cycle with the formation of the unreactive hemiaminal species **24** and **25**.

Furthermore, the remarkable change of reactivity by trimethylsilyl protection of the free hydroxyl moiety of **1a** was explained by prevention of hemiaminal formation and the increased hydrophobicity of the corresponding protected diarylprolinol **2**, which improved the rate of enamine formation with aldehydes (entry 5). Additional improvements were also achieved through variation of the aryl substituents in the catalyst structure. The silylated L-prolinol derivatives **2b-d** with sterically demanding aryl substituents furnished the product **16** with high enantiomeric excess (entries 6-8),[33] but finally the fluorinated

derivative **2b** was identified as the best of these catalysts, as it gave product **16** in 90% yield and with 98% ee (entry 6). Nevertheless, in cases of slow conversion the turnover could be increased by adding salts such as LiClO₄ to the reaction mixture, with only a minor decrease in enantiomeric excess (entry 9). Protic acid (*o*-nitrobenzoic acid) was also tested in order to accelerate the reaction rate, but it led to a more pronounced loss of enantiomeric excess (entry 10).[34]

3.1. Effect of the Intermediate Geometry on the Control of Enantioselectivity

The implication of the intermediate structures on the stereoselection of α -, β -, and γ -functionalization of aldehydes using diarylprolinol silyl ether derivatives has been studied extensively.[28b, 32, 35]

The absolute configuration (*S*) of the final products in the previous process was in agreement with *Si*-face attack of the sulfur-centered electrophile on the *E*-conformation enamine intermediate **26b**. This one is energetically favored over the *Z*-conformation enamine intermediate **26a**, and on the other hand, the bulky substituent on the α -position of the pyrrolidine ring raises the energy of the *E*-conformation enamine intermediate **26c**. The *Re* face on the enamine intermediate **26b** is shielded effectively by the aryl and silyl substituents of the catalyst residue (Fig. (2)).

This hypothesis is confirmed by a model based on DFT calculations of the optimized enamine intermediates at the B3LYP/6-31G(d) level of theory.

Fig. (2). DFT-Calculated model of the optimized structures of the four different conformations enamine intermediates (**26a-d**) formed by aldehyde and catalyst. Ar = 3,5-(CF₃)₂-C₆H₃. The calculated values are ΔG (kcal/mol) relatives to **26b** (R = Me and *t*-Bu).[32e]

The free energies of the different enamine intermediates show that the enamines **Me-26b** (0 kcal/mol) and **Me-26c** (−0.1 kcal/mol) containing an *E* configuration of the double bond are more stable than the enamines **Me-26a** (1.9 kcal/mol) and **Me-26d** (5.6 kcal/mol) with a *Z* configuration (Fig. (2)). This difference in free energy originates from the steric repulsion between the methyl group and the protons adjacent to the nitrogen atom in the pyrrolidine ring. This is confirmed by an increase in relative free energy for enamine *t*Bu-**26a** and *t*Bu-**26d** compared to enamine *t*Bu-**26b** (7.5 and 12.1 kcal/mol, respectively) upon exchanging of the methyl group with the much more sterically demanding *tert*-butyl group. The calculations suggest that the two major enamine conformers present in a reaction mixture are the enamine intermediates (**26b** and **26c**).

The optimized geometries for enamine intermediate structures (**26a-d**) also show that one of the 3,5-di(trifluoromethyl)phenyl groups covers the *Re* face of the enamine. Clearly, the *Re* face of the nucleophilic enamine C-atom is like under an umbrella of the (TMSO)Ph₂C substituent, while the *Si* face is open (Fig. (2)).

In this context, interestingly the absolute configuration of the products (**27-36**) obtained using catalysts **2a-b** has been found to be identical for all of them (Figs. (3) and (4): α - and β -functionalization of carbonyl compounds, respectively). This is in agreement with all experimentally determined stereochemical courses of reactions and with the model proposed involving diarylprolinol silyl ether derivatives **2a-b** as organocatalyst.[9, 36]

Fig. (3). Stereochemistry in the formed final product (**27-31**) for some representative α -functionalization of carbonyl compounds using catalysts **2a-b**: C-Se bond formation (**27**),[37] C-N bond forming (**28**),[38] C-C bond forming (**29** and **31**),[39, 40] C-O bond forming (**30**).[41]

Fig. (4). Stereochemistry in the formed final product (**32-36**) for some representative β -functionalization of carbonyl compounds using catalysts **2a-b**: C-P bond forming reaction (**32**),[32c] C-O bond formation (**33**),[42] C-N bond formation (**34**),[32d] C-C bond formation (**35**),[43] C-S bond formation (**36**).[28c]

As in the case of the reactions proceeding through the formation of an enamine, DFT calculations have been also applied for those by an iminium mechanism, in order to explain the stereochemical outcome of the processes.[32c,d,f,35c] For example, computational studies carried out for the phosphorylation reaction to give product **32** (Fig. (4)) show that the nucleophile adds to the non-shielded *Re* face of the (*E*)-iminium-ion intermediate (*anti*-below), leading to the (*R*)-configuration of the product **32** through **TS-1**, which was calculated to have the lowest energy. Thereby, predicting the high enantioselectivity observed in the reaction (Fig. (5)).[32c]

Fig. (5). Intermediates used for the transition-state calculations. Calculated energies (ΔG (kcal/mol)) of the three DFT-optimized transition-states. Ar = 3,5-(CF₃)₂-C₆H₃.

It is interesting to note that catalyst (*S*)-**2b** and L-proline (**17a**), which have identical absolute configuration, promote the formation of products with the opposite stereochemistry in the cases, for

instance, of α -amination reaction[44] (Fig. (6)), and Mannich[45] or aldol reaction,[46] (Fig. (6)). This fact is explained by the different nature of the transition states involved for each catalyst: (A) hydrogen bond approach for L-proline (**17a**), and (B) steric control approach for catalyst (S)-**2b** (Fig. (6)).

Fig. (6). Transition state models for the α -amination of aldehydes catalyzed by: (A) L-proline (**17a**) and (B) catalyst (S)-**2b**.

The mechanism for the proline-enamine intermediate has been investigated by computational studies mainly by Houk and co-workers[47] showing that the proton from the carboxylic acid group in the proline determines the stereochemical outcome of the reaction. The hydrogen bonding in the transition state directs the electrophile approach from the above to the *Re* face of the enamine intermediate, and hence yields the final product with *R* configuration (Fig. (7)).

Fig. (7). Transition state models for proline-catalyzed Mannich and aldol reactions.

Continuing with the discussion of the general stereochemical outcome of the reactions involving α,α -diarylprolinol silyl ether derivatives, while the absolute configuration of the products is very consistent in the cases of enamine or iminium-ion activation,[9] it has been found that the γ -functionalization of the α,β -unsaturated aldehydes apparently proceeded with a stereoselectivity opposed to this tendency (Fig. (8)).

Fig. (8). Observed configuration of α -, β -, and γ -functionalized products using α,α -diarylprolinol silyl ether derivatives as catalyst.

In a pioneering work on dienamine catalysis, Jørgensen and co-workers developed the γ -amination of α,β -unsaturated aldehydes **37** (Scheme 7), who encouraged by this interesting observation, carried out detailed studies about the mechanism of this reaction.[12e]

Scheme 7. γ -Amination reaction of α,β -unsaturated aldehydes **37** via dienamine activation.

Thus, computational and experimental investigations indicate that this reaction might be the result of a [4+2]-cycloaddition reaction between the diethyl azodicarboxylate (DEAD, **38**) and the chiral dienamine **41a** formed *in situ* with the catalyst (*S*)-**2b**. Finally, the formed aminated intermediates **42a** and **42f** could easily be hydrolyzed to give the γ -aminated product **39** and to release the catalyst (*S*)-**2b** (Fig. (9)).

Fig. (9). Intermediates and reaction paths calculated for the asymmetric electrophilic γ -amination of α,β -unsaturated aldehydes. The numbers below the intermediates are the energies relative to $(E,s\text{-}trans,E)\text{-}41a$ calculated by B3LYP/6-31G(d) and for the numbers in italics by B3LYP/6-31G(d)-(CPCM)/B3LYP/6-31G(d).

The authors optimized first the structure of the four different intermediates **41a** shown in Fig. (9) at the B3LYP/6-31G(d) level of theory. Furthermore, they located the transition states for the three different types of reaction paths outlined for the amination of the four dienamines **41a**, leading to a total of six transition states, two each for the α - (TS6a,b) and γ - (TS5a,b) amination reaction pathways and two for the Diels–Alder [4+2]-cycloaddition reaction path (TS4a,b). The transition state TS4b for the reaction between DEAD (**38**) and dienamine $(E,s\text{-}cis,E)\text{-}41a$ in a concerted Diels–Alder reaction pathway leading to (*R*)-product, was calculated to have the lowest energy, even more than the transition state for direct γ -addition TS5b, showing a preference for this Diels–Alder reaction path.

3.2. Effect of Catalyst Structure on the Enantioselectivity of the Reaction

The effect of the structure of the aromatic groups of the catalyst on the enantiomeric excess of the final product has been also investigated by Jørgensen group for the α -sulfenylation of 3-methyl butanal (**14**) (Scheme 5, Table 4).[28a, 32b]

Table 4. Relation between Taft's E_s values of the aromatic substituents of (*S*)-**2a-c** and enantioselectivity in the α -sulfonylation of 3-methyl butanal (**14**).

Cat. (<i>S</i>)- 2a $R = H$	Cat. (<i>S</i>)- 2b $R = CF_3$	Cat. (<i>S</i>)- 2c $R = CH_3$
Taft's E_s values	0	-2.40	-1.24
ee (%)	77	98	90

It was found that the enantiomeric excess increased moving from the simple diphenylprolinol **2a** to 3,5-dimethyl **2c** and 3,5-ditrifluoromethyl **2b** derivatives, indicating that the electronic properties of the *R*-groups in the catalyst did not have effect on the enantiomeric excess. Taft's E_s values (steric substituent constants),[48] are in approximately linear correlation with the optical activity of the products (Table 4). The size of CF_3 is relatively large, in the order of $Me < i\text{-Pr} < CF_3 < t\text{-Bu}$ and, hence, in sharp contrast to the small van der Waal radius of fluorine.[49] This supports that the asymmetric induction observed with catalyst **2b** completely relies on selective enamine conformation and steric shielding.

Other interesting reaction in organic synthesis is the catalytic asymmetric epoxidation. The same group published the first examples of asymmetric organocatalytic epoxidation of α,β -unsaturated aldehydes **43**, using hydrogen peroxide and catalyst **2b**. [50] Later, Córdova and co-workers also devised the direct asymmetric epoxidation of α,β -unsaturated aldehydes **43**, [51] and among different catalysts screened, catalyst **2a** showed, in this case, better reaction rate, yield and selectivity (Scheme 8, Table 5, entry 3).

Scheme 8.

Table 5. Screening of some catalysts in the direct asymmetric epoxidation of cinnamaldehyde (**43**).

Entry	Catalyst	t (h)	Conversion	dr	ee (%)
1	1a ^[a]	16	43	5:95	-22
2	7 ^[b]	3	6	80:20	-60
3	2a ^[b]	2	91	93:7	97
4	2d ^[b]	3	55	93:7	98
5	45 ^[b]	3	40	81:8	68
6	17a ^[a]	24	<1	n.d.	n.d.
7	17a ^[a,c]	16	79	60:40	-36
8	46 ^[b,d]	3	28	48:52	12
9	46 ^[b,e]	18	55	96:4	12

^[a] 30 mol% catalyst. ^[b] 10 mol% catalyst and 1.2 equiv. H₂O₂. ^[c] 0.8 equiv. TEA added. ^[d] Reaction run in H₂O:EtOH (1:1). ^[e] Reaction run in dioxane.

A general plausible mechanism for the amine-catalyzed asymmetric epoxidation reaction of α,β -unsaturated aldehydes is depicted in Scheme 9. The reaction takes place via the familiar formation of an iminium-ion intermediate **47** between the catalyst **2** and the α,β -unsaturated aldehyde **43**. Thus, the epoxide **44** can be obtained via nucleophilic attack of the peroxide to the electrophilic β -carbon of intermediate **47**, leading to an enamine intermediate **48** which attacks the electrophilic peroxygen atom, followed by hydrolysis of the iminium-ion intermediate **49**. Notoriously, this mechanism is different to that previously illustrated by Lattanzi and co-workers in Scheme 2, where a non-covalent activation is proposed.

Scheme 9. Mechanistic proposal for the organocatalytic epoxidation of α,β -unsaturated aldehydes **43**.

Based on the proposed catalytic cycle, the remarkable change of reactivity by TMS protection of the diarylprolinol **1a** was explained by prevention of amination with the substrate (**50**) or the product (**51**) (Scheme 8, Table 5, compare entries 1, 3 and 4). The same effect is observed comparing catalysts **7** and **45** (Scheme 8, Table 5, compare entries 2 and 5). The beneficial hydrophobic effect also explains the acceleration of the reaction by improving the rate of iminium-ion intermediate formation. Additionally, the high enantioselectivity observed with catalysts **2a** and **2d** is possible due to stabilization of the configuration of the iminium-ion intermediate, as well as efficient shielding of the *Si*-face of the chiral iminium-ion and enamine intermediates by the bulky aryl groups via plausible intermediates **47** and **48**, respectively. The stabilization of the enamine intermediate **48** is supported by the high *trans*-selectivity of the asymmetric epoxidation reactions with **2a** and **2d**.

It is important to remark that the absolute configuration obtained in the final product of this process using catalysts **2a,d** is opposite to that observed by Lattanzi in her works on epoxidation of α,β -unsaturated ketones using α,α -diaryl-2-prolidinemethanol derivatives **1** as catalysts (Schemes 1 and 3).[19, 22, 52] But on the other hand, it is in agreement with the regular tendency for catalysts **2**, i.e., the stereochemistry is obtained as above explained. In the case of L-proline (**17a**), opposite facial attack occurs on the peroxygen by the plausible transition state depicted in Fig. (10), that results in formation of *ent*-**44**. [53]

Fig. (10). Pausible transition state when L-proline (**17a**) is used as catalyst.

Other interesting α,α -prolinol silyl ether derivatives reported in the literature are **3a,b** (OTES) and **4a,b** (OTBS) (Fig. (1)). These catalysts have also been emerged as feasible and promising catalysts affording good similar enantioselectivities than **2a,2b** (OTMS) in several processes,[54] but sometimes with worst reactivity maybe because the reaction becomes slower as the silyl substituent becomes bulkier. Only in a few cases, catalysts **3** and **4** have shown better results than the corresponding TMS protected partner (**2**), where the presence of a bulkier silyl moiety led to higher enantioselectivities and reactivities.[55]

3.3. Effect of Additives on the Reactivity of the Reaction

Several works have shown that carefully chosen acidic[56] or basic[57] co-catalysts or additives can enhance pyrrolidine- or imidazolidinone-catalyst activity.[58] Here we want to show a few representative examples, where the appropriate election of the additives was decisive for the success of the process, in order to illustrate the possible role played by these species.[59]

In this context, Christmann and co-workers reported a strong correlation between the pK_a value of mild carboxylic acids and the reaction rate,[60] observed on the cyclization of tethered α,β -unsaturated carbonyl compounds **52** via dienamine catalysis (Scheme 10, Table 6).[12j]

Scheme 10. Cyclization of tethered α,β -unsaturated carbonyl compounds **52** via dienamine catalysis.

Table 6. Screening of different co-catalysts in the cyclization of tethered α,β -unsaturated carbonyl compound **52**.

Entry	Co-catalyst	pK _a	t (h)	ee (%)
1	None	-	144	80 ^[a]
2	AcOH	4.76	12	82
3	<i>p</i> -MeO-C ₆ H ₄ CO ₂ H	4.47	12	84
4	C₆H₅CO₂H	4.20	3	90
5	<i>p</i> -Cl-C ₆ H ₄ CO ₂ H	3.99	4	88
6	<i>p</i> -NO ₂ -C ₆ H ₄ CO ₂ H	3.44	22	86

^[a] 50% conversion.

In this case, the acid of choice was the C₆H₅CO₂H, which afforded the best results in terms of reactivity and enantioselectivity (entry 4). The co-catalyst could be involved in a complex enamine-iminium-dienamine equilibrium, but it may also play a role in the activation of the dienophile/Michael acceptor, taking into account the mechanism proposed for this reaction (Scheme 10).

The same group observed in an enantioselective organocatalytic Rauhut–Currier-type cyclization of tethered α,β -unsaturated carbonyl compounds **54** catalyzed by (*S*)-**2a**, that the use of acetic acid as an additive led to a considerable increase in the reaction rate without impairing the enantioselectivity [3 h (57% yield, 89% ee) *versus* 72 h (60% yield, 88% ee)] (Scheme 11).[121] It is conceivable that acetic acid assists in the formation of the carbon-carbon bond in the cyclization step, by activating the Michael acceptor of the dienamine intermediate **55**.

Scheme 11. Crossed intramolecular Rauhut–Currier-type reactions via dienamine activation.

Córdova and co-workers also found that the efficiency and enantioselectivity of the catalyst **2a** were significantly improved by the addition of an organic acid in the α -aminomethylation of aldehydes.[61] In

this sense, acetic acid gave the best results with respect to conversion and enantioselectivity of the reaction. Since the addition of achiral alkali cations had been shown previously by Adolfsson and co-workers to increase the enantioselectivity of small peptide catalyzed asymmetric transformations,[62] the authors decided to investigate the possibility of using this positive additive effect on this process (Scheme 12, Table 7).[63]

Scheme 12.

Table 7. Screen of different alkali salts in α -aminomethylation of aldehyde **14**.

Entry	Additive	Solvent	Conversion (%)	ee (%)
1	None	DMF	80	78
2	NaCl	DMF	>95	72
3	LiCl	DMF	>95	90
4	LiBr	DMF	>95	96
5	LiI	DMF	>95	88
6	LiClO ₄	DMF	96	74
7	LiOAc	DMF	>95	75
8	NH ₄ Cl	DMF	90	66
9	LiBr	CH ₃ CN	>95	75
10	LiBr	NMP	96	58
11	LiBr	<i>i</i> -PrOH	68	58
12	LiBr	CHCl ₃	86	37

It was found that the addition of alkali salts increased the rate of the reactions. Moreover, lithium halide salts (LiCl, LiBr, LiI) significantly increased the enantioselectivity of this process (entries 3-5). This positive effect was plausibly due to the higher Lewis acidity of the lithium halide salts as compared to LiClO₄ and LiOAc, which did not increase the enantioselectivity of the reaction (entries 6-7). In addition,

lithium with its higher Lewis acidity was the cation of choice, as NaCl did not improve the enantioselectivity of the reaction (entry 2). Moreover, the highest enantioselectivity for the solvents tested was achieved using LiBr in DMF (entry 4), which also suggested that the solubility of the lithium halide salts may be important.

A feasible explanation about the role displayed by the additive is shown in Fig. (11), where the authors represent a proposed transition state model **60** to account the configuration obtained in the final products **59** of this **2a**-catalyzed reaction.

Fig. (11). Proposed transition state model **60** for α -aminomethylation of aldehyde **14**.

In accordance, the *Re*-face of the chiral enamine is approached by the aminomethyl ether **57** via a plausible six-membered transition state **60**. The proton from the acetic acid or lithium cation possibly stabilizes the proposed transition state by activation of the methoxy leaving group of **57**.

Furthermore, the same group screened different additives in the first direct organocatalytic asymmetric domino oxa-Michael-aldol condensation reaction to optimize the reaction conditions with catalyst **2a** and finding that the addition of a substoichiometric amount of an organic acid (20 mol%) increased the enantioselectivity and efficiency of the reaction (Scheme 13).[64]

From the results obtained in this process, they decided that the best trade-off between reactivity and enantioselectivity to investigate and extend this asymmetric domino oxa-Michael-aldol reaction would be to use 2-nitrobenzoic acid as the additive and toluene as the solvent (37% conv (16 h), 88% ee), compared with other results and overall compared with the result in absence of additive (10% conv (16 h), 9% ee).

Scheme 13. Domino oxa-Michael-aldol reaction.

In agreement with the mechanism reaction proposed for this reaction in Scheme 14, the authors gave a plausible explanation about the role and the positive effect afforded by using of additive. In this way, the addition of a substoichiometric amount of an organic acid reasonably accelerates the catalytic domino reaction by providing a Brønsted acid, which would activate the benzaldehyde moiety towards the intramolecular 6-exo-trig aldol condensation (63). In addition, the organic acid would stabilize the iminium-ion intermediate (47) and consequently push the equilibrium towards the oxa-Michael addition.

Scheme 14. A plausible reaction pathway for an asymmetric tandem oxa-Michael-aldol condensation reaction catalyzed by **2a**.

However and even when the use of additives is not well understood so far, they are used very frequently being crucial for the success of a great number of procedures. Further studies in order to clarify their role should be performed by the authors.

4. Conclusion

With the development, in the last years, of catalytic asymmetric methodologies directed to the preparation of biologically active molecules, organocatalysis has appeared as a powerful tool being complementary to transition metal-based catalysis in the field of asymmetric synthesis. Among other important structures

diarylprolinol derivatives have appeared as a promising class of organocatalysts which have displayed its efficiency in a great number of processes. This review has been focused on a few selected and representative examples relating to the application of diarylprolinol derivatives in catalytic transformations. A general vision concerning some structural features of these catalysts such as ring size (a), substitution in the chiral carbon (b), substitution on the rings of the bulky substituent (c), protection of the hydroxyl function (d), and the use of external additives (e) has been illustrated (Fig (12)).

Fig. (12). Structural features of diarylprolinol derivatives as organocatalysts.

The influence of these modifications on the final results of the organocatalytic processes could be summarized as follows:

- (a) The size of the aliphatic ring seems to be crucial for the success of the process related with the basicity of the secondary amines, being the five member ring the most efficient one in general.
- (b) The bulky substitution on the chiral carbon atom is decisive in the stereoselective control of such processes by using hydrogen bond or steric control approaches. Thus, in some cases, it is possible to afford the products with the opposite absolute configuration for the same reaction.
- (c) and (d) In a more specific manner, the substituents on the rings (R) of the catalyst and the protection of the hydroxyl function (R') seem to play an important role in the enantioselectivity of the process related with steric factors.
- (e) The use of different additives (HA) could be decisive for the enhancement of the reaction rate, but their influence in the enantioselective outcome cannot be discarded.

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