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# Optimizing the Structure of 4-Dialkylamino-α,α-diarylprolinol Ethers as Catalysts for the Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes in Water

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We optimized the structure of a new family of chiral diarylprolinol-type organocatalysts with improved performances in conjugate addition reactions performed in water and proceeding under the iminium activation manifold. The principles behind the catalyst design were, firstly, the incorporation of a tertiary amino group at the 4-position of the pyrrolidine scaffold, which can facilitate the reaction by providing a basic site that favors deprotonation of the pronucleophile, and, secondly, a bulky diaryltrialkylsilyloxymethyl group maintained at the 2-position to control the iminium ion geometry and to provide the required steric bias for face stereoselection. The nature of this 4-dialkylamino group and the relative 2,4-configuration was optimized and the resulting catalyst proved its efficiency in the catalytic enantioselective cyclopropanation of α,β-unsaturated aldehydes using water as the reaction solvent. Moreover, the reaction was studied by computational methods, which indicated that the overall transformation proceeded through a cascade Michael/α-alkylation sequence, in which the first iminium-mediated Michael addition reaction was the rate-determining step and also the step at which stereochemical information was transferred from the catalyst to the products.

## Introduction

The development of more environmentally acceptable chemical processes has led to increased interest in both academic and industrial research. In particular, replacing the commonly used volatile organic compounds by solvents with lower vapor pressures or by liquids that are believed to be more environmentally benign has been a field of remarkable activity in the last few years. Especially, the use of water as the solvent has received substantial attention,[1] not only because of its inherent friendliness towards environment but also owing to the fact that it is the cheapest and most widely available solvent. In this sense, aminocatalysis, which is known as the ability of primary or secondary amines to promote an organic transformation through the reversible formation of azomethine intermediates such as iminium ions or enamines, constitutes a privileged manifold for developing processes that can take place in water because of the compatibility of the catalysts and the reactive intermediates that participate in the catalytic cycle towards aqueous media and ambient oxygen. Moreover, aminocatalytic processes have demonstrated their high level of performance in reactions that involve functionalization of carbonyl compounds with exceptional levels of regio- diastereo- and enantiocontrol. In addition, the ability of these catalysts to promote tandem or domino reactions that combine different transformations in a single manipulation leading to a high degree of molecular complexity in a fast and reliable way and starting from simple starting materials is another positive aspect related to aminocatalysis and to the environmental benefits associated to these domino processes.

In this sense, several chiral primary and secondary amines have been designed and employed in different transformations by using an aqueous environment, mostly focused on reactions such as the aldol, Mannich, Michael, or other related ones that proceed under enamine activation.[2] In this sense, the main tendency in the catalyst design has focused on the introduction of long hydrophobic alkyl side chains in the catalyst structure. The concept behind this design is based on the fact that aggregation of the organocatalyst with the hydrophobic reagents participating in the Michael reaction reduces the contact between these reagents and bulk water as the reaction proceeds, therefore, the reagents behave as if they were dissolved in an organic solvent.[3] Alternatively, the use of catalysts with improved solubility in water achieved by introducing perfluorinated alkyl side chains[4] or lateral quaternary ammonium moieties[5] on their structure has also been explored and also several surfactant-type organocatalysts have been found to efficiently catalyze several of these reactions in water with excellent results.[6] Other authors have focused on the development of recyclable chiral amine catalysts that can also be used in aqueous media, such as modified chiral ionic liquid-type organocatalysts[7] and some examples of chiral secondary amines attached to solid supports[8] or incorporated into dendrimeric structures.[9]

On the other hand, and as previously mentioned, although a wide variety of such modified catalysts have been developed

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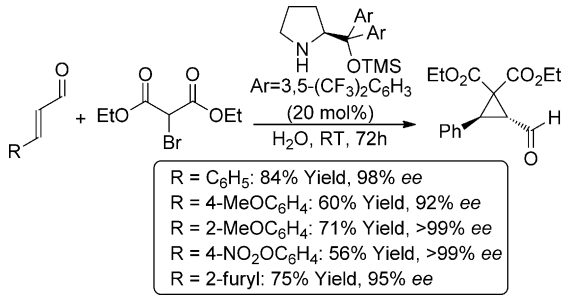
to promote reactions under the enamine activation manifold, only a few examples based on the iminium activation approach as the operating organocatalytic activation mechanism in an organic reaction proceeding in an aqueous medium have been reported in the recent literature.[10] Moreover, and despite the fact that the iminium activation manifold is an outstanding platform for developing cascade processes,[11] only a few examples that proceed in water as the reaction solvent have been reported up to date.[12] In particular, our group has demonstrated in a preliminary way (Scheme 1) that the enantioselective




**Scheme 1.** "In water" organocatalytic enantioselective cyclopropanation of enals developed by our group.

cyclopropanation of α,β-unsaturated aldehydes with diethyl bromomalonate can be performed by using an *O*-TMS protected α,α-diarylprolinol derivative as the catalyst in a reaction involving a cascade sequence that consists of an initial Michael reaction under iminium activation followed by intramolecular α-alkylation under enamine catalysis.[12a] We have also demonstrated that, although other methodologies require the incorporation of one equivalent of a Brønsted base to quench the HBr formed as the reaction proceeds forward,[13] performing the reaction in water led to the formation of the final cyclopropanes in good yields and stereoselectivities without the need of such an stoichiometric additive, which, on the other hand, is known to lead to undesired side-reactions.[13i]

However, this methodology reported in our preliminary study suffered from a very important drawback, associated to the need of an important excess of α,β-unsaturated aldehyde reagent (three-fold excess with respect to ethyl bromomalonate) to obtain good yields of the final cyclopropanation product. This requirement resulted in a problematic situation when we tried to conduct the reaction on a larger scale because the reaction mixture appeared as an emulsion and not as a homogeneous solution and could not be properly stirred. For this reason, we decided to synthesize a modified version of the initial diarylprolinol catalyst aiming to identify a new structurally related chiral secondary amine with improved performances in this reaction if working in a purely aqueous environment.

## Results and Discussion

The key aspects of our catalyst design are shown in Figure 1 and rely on the incorporation of a tertiary amine moiety at the 4-position of the diarylprolinol skeleton. This would allow us

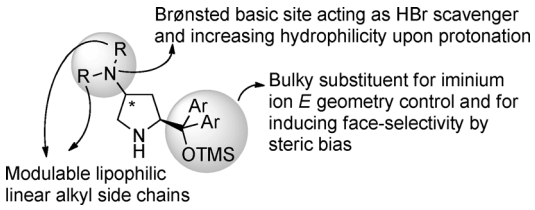
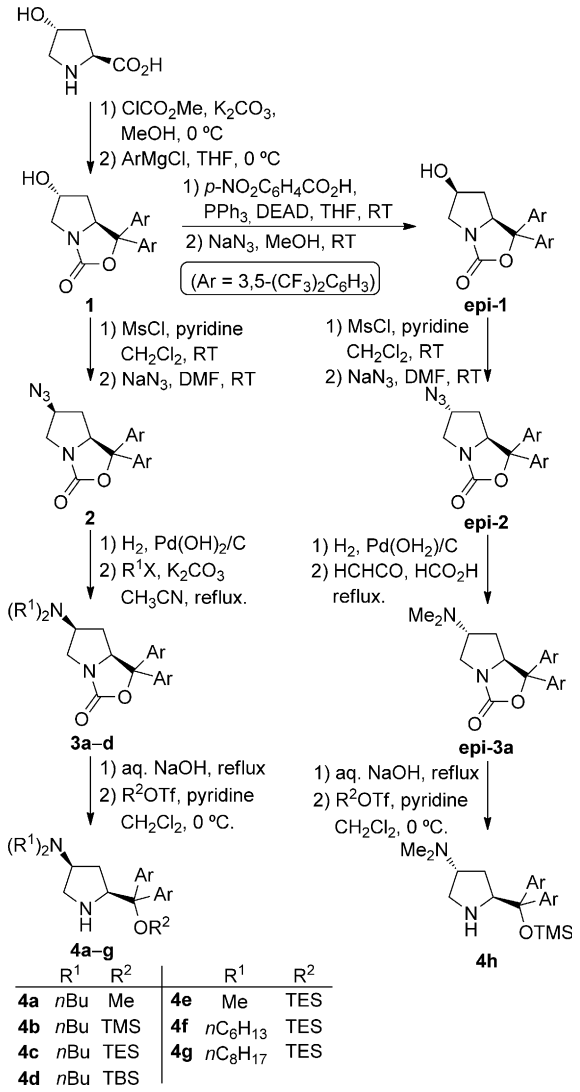



**Figure 1.** Relevant features associated to the catalyst design.

the modulation of the ability of the catalyst to form micellar aggregates in disperse aqueous solutions by means of introducing linear alkyl side chains of different lengths at the nitrogen atom. In addition, the presence of this additional Brønsted basic site would also cooperate in the reaction because it affords a slightly basic initial reaction medium that could facilitate activation of the bromomalonate by assisting its deprotonation. Moreover, as it was also expected that the reaction medium would become increasingly acidic as the reaction moved towards completion because of the continuous generation of HBr eliminated after the intramolecular α-alkylation step, it was also envisaged that protonation of the tertiary amine site would result in a catalyst architecture with improved ambiphilic character. On the other hand, the bulky diaryl(trialkylsilyloxy)methyl group at the 2-position of the pyrrolidine structure was maintained as key element for achieving stereocontrol, because it was known that these types of diarylprolinol-based catalysts control the iminium ion geometry (preferential formation of *E* iminium ion), and also because of their performance in exerting a very effective degree of stereoinduction during the conjugate addition step by blocking one of the diastereotopic faces of the Michael acceptor through steric bias.[14] It has also to be pointed out that the incorporation of the additional 4-dialkylamino substituent at the catalyst scaffold results in an additional stereogenic center with potential implications in the performance of the new catalyst in terms to stereocontrol and, therefore, the influence of the configuration of this stereocenter is another issue that has to be studied in order to identify the best catalyst architecture.

The synthesis of this family of highly modular catalysts was performed according to the synthetic pathway shown in Scheme 2, by starting from the commercially available and cheap reagent *trans*-4-hydroxyproline. The synthesis begins with the esterification and N-carbamoylation of the starting material followed by reaction with the required aryl Grignard reagent, which led to the formation of bicyclic adduct **1** in good yield without the need to previously protect the secondary hydroxy group of the starting 4-hydroxyproline. Next, the amino functionality was installed by initial mesylation followed by nucleophilic displacement by the azide anion (taking place with no epimerization) and subsequent hydrogenation and N-alkylation with a set of alkyl halides. Finally, a family of different catalysts **4a–g** was obtained by hydrolysis and a final O-silylation (or O-methylation) step. In addition, diastereomeric *cis*-configured catalyst **4h** was prepared as representative model for studying the influence of the relative stereochemistry of the two stereocenters present at the catalyst structure starting



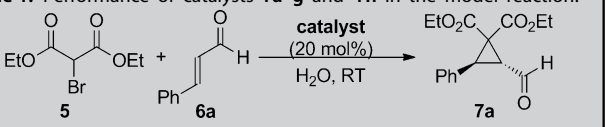

| | $R^1$ | $R^2$ | | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **4a** | *n*Bu | Me | **4e** | Me | TES |
| **4b** | *n*Bu | TMS | **4f** | $nC_6H_{13}$ | TES |
| **4c** | *n*Bu | TES | **4g** | $nC_8H_{17}$ | TES |
| **4d** | *n*Bu | TBS | | | |

**Scheme 2.** Synthesis of catalysts **4a–h**. The *N*-methylation for the synthesis of **3a** and the final O-methylation step for the synthesis of catalyst **4a** were performed by using a modified procedure (see the Supporting Information).

from **1**. In this sense, *trans*-configured derivative **4h** was prepared from **1** by standard Mitsunobu inversion followed by the same set of transformations as used before for converting **1** into **4**.

With this family of different catalysts in hand, we proceeded to evaluate their performance in the projected cyclopropanation reaction using the reaction between cinnamaldehyde and diethyl bromomalonate as a model system (Table 1). In all cases we applied the conditions initially set up by us in our preliminary report, which involve the use of 20 mol% of catalyst in water as the only solvent and using a 3:1 ratio of diethyl bromomalonate to cinnamaldehyde. We started by evaluating the nature of the protecting group at the oxygen atom maintaining a common di-*n*-butylamino group as 4-substituent of the α,α-diarylprolinol architecture and keeping a 2,4-*cis* relative configuration for all cases (entries 1–4). As it can be seen in Table 1, this O-protecting group had little influence on the yield of the reaction and also all these catalysts **4a–d** furnished

**Table 1.** Performance of catalysts **4a–g** and **4h** in the model reaction.[a]



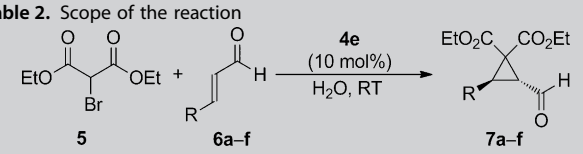

| Entry | Catalyst | Yield [%][b] | *dr*[c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | **4a** | 88 | >19:1 | 80 |
| 2 | **4b** | 85 | >19:1 | 92 |
| 3 | **4c** | 85 | >19:1 | 93 |
| 4 | **4d** | 82 | >19:1 | 94 |
| 5 | **4e** | 94 | >19:1 | 96 |
| 6 | **4f** | 75 | >19:1 | 93 |
| 7 | **4g** | 75 | >19:1 | 88 |
| 8 | **4h** | 99 | >19:1 | 86 |
| 9 | **4e**[e] | 94 | >19:1 | 96 |
| 10 | **4e**[f] | 36 | >19:1 | 84 |
| 11 | **4e**[e,g] | 93 | >19:1 | 96 |

[a] The reaction was conducted with an aliquot (0.125 mmol) of **5** and a threefold excess of **6a** in the presence of the catalyst (20 mol%) in water (1 mL) at room temperature. [b] Yield of pure product after flash column chromatography. [c] Diastereomeric ratio determined by NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis after reduction to the corresponding primary alcohol (see Experimental Section). [e] 10 mol% of catalyst was employed. [f] 5 mol% of catalyst was employed. [g] Reaction performed by using a 1:1.2 ratio of **5** and **6a**.

similar levels of enantiocontrol with the only exception of the O-methyl derivative **4a** that furnished cyclopropane **7a** at a moderate 80% *ee* (entry 1). We therefore decided to use the triethylsilyl substituent as the most convenient O-protecting group in terms of better stability towards hydrolysis and we next evaluated the role played by the alkyl groups placed at the tertiary amine moiety. In this sense, we observed that the smallest dimethylamino group at the 4-position of the catalyst (catalyst **4e**) led to a notable improvement in the yield of the reaction, also observing that it proceeded with slightly higher enantioselectivity (entry 5). Importantly, if the length of these alkyl chains was increased, the performance of the catalysts decreased notably (entries 6 and 7). The influence of the relative configuration of the two stereocenters at the catalysts was also evaluated by observing that the *trans*-2,4-disubstituted analogue of **4e** performed very well in terms of catalytic activity but led to the formation of the final cyclopropane adduct with a somewhat lower degree of enantiocontrol (entry 8).

Once catalyst **4e** had been identified as the most effective architecture for this transformation, we also found that the catalyst loading could be lowered down to 10 mol% without significantly affecting the results (entry 9) but if the reaction was conducted by using 5 mol% of **4e**, the yield dropped down drastically. Remarkably, we also found that the good performance of this catalyst in water also enabled us to perform the reaction by using a 1:1.2 ratio of cinnamaldehyde and diethyl bromomalonate, which resulted in an important improvement with respect to the original conditions reported. Finally, it should be pointed out that in all the reactions evaluated, the final cyclopropane adducts were formed as single diastereoisomers, as NMR analysis of the crude reaction mixtures indicated.

**Table 2.** Scope of the reaction




| Entry | R | Product | Yield [%][a] | *dr*[b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | Ph | **7a** | 93 | >19:1 | 97 |
| 2 | 2-$CH_3OC_6H_4$ | **7b** | 83 | >19:1 | >99 |
| 3 | 4-$CH_3OC_6H_4$ | **7c** | 80 | >19:1 | 94 |
| 4 | 4-$NO_2C_6H_4$ | **7d** | 60 | >19:1 | >99 |
| 5 | 4-$FC_6H_4$ | **7e** | 70 | >19:1 | 93 |
| 6 | 2-furyl | **7f** | 83 | >19:1 | >99 |

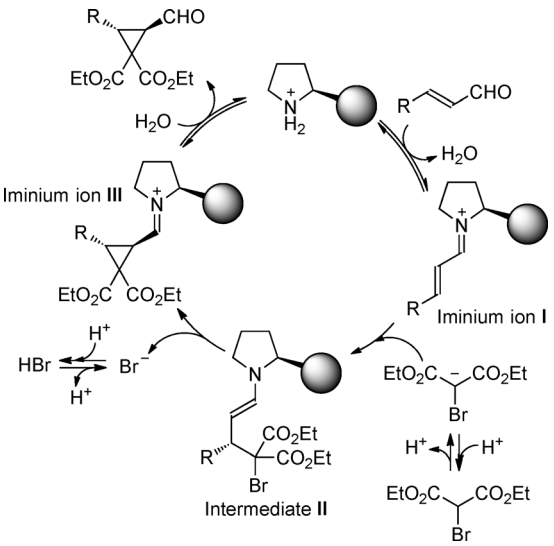
[a] Yield of pure product after column chromatography purification. [b] Determined by NMR analysis of crude reaction mixture. [c] Determined by HPLC analysis after reduction to the corresponding primary alcohol (see the Supporting Information).

With these notably improved reaction conditions in hand, we proceeded to study the scope of the reaction with respect to the possibility of using other α,β-unsaturated aldehydes as substrates (Table 2). As it can be seen in this table, all enals **6a–f** tested performed well in the reaction regardless of the electronic nature of the β-substituent which includes the reaction using electron-rich (entries 2 and 3) and electron-poor (entries 4 and 5) substrates. Moreover, heteroaryl substituents were also tolerated (entry 6). In all cases the yields were high, the formation of one single diastereoisomer was observed, and the final cyclopropanation products were obtained in higher than 90% *ee* It should be pointed out that all these adducts were found to be somewhat unstable compounds and, therefore, they were subjected to reduction under standard conditions ($NaBH_4$, MeOH, 0 °C) to obtain the more stable primary alcohols that were isolated and fully characterized. At this point, we additionally found the conditions for the HPLC separation of both enantiomers using chiral stationary phase HPLC columns. Therefore, *ee* determinations were performed at this stage.

### Mechanistic aspects

We also decided to study the reaction using computational tools to unveil the most relevant aspects associated to the reaction pathway and to the factors that govern the stereoselectivity. We assumed a catalytic cycle as shown in Scheme 3, in which the reaction would start by the activation of the enal by the catalyst through iminium ion formation which should be followed by a Michael addition step with diethyl bromomalonate (with the participation of the corresponding enolate) generating an enamine intermediate, and this would subsequently undergo intramolecular α-alkyation reaction and final hydrolysis that would release the product and would account for catalyst turnover.

For the first study of the energetic profile of the reaction we decided to perform our calculations by using the more structurally simple *O*-TMS α,α-diphenylprolinol chiral catalyst for the reaction between cinnamic aldehyde and dimethyl bromomalonate. Accordingly, we started by calculating the energies of the two possible diastereomeric *Z* and *E* iminium salts that could be eventually formed after the condensation reaction between the catalyst and cinnamaldehyde. As in other studies, the *E* iminium ion (*E*)-**I** was 5.02 kcal mol$^{-1}$ more stable than the corresponding *Z* iminum ion (*Z*)-**I** (Figure 2).




**Scheme 3.** Proposed catalytic cycle for the enantioselective cyclopropanation of α,β-unsaturated aldehydes with diethylbromomalonate catalyzed by a chiral secondary amine.

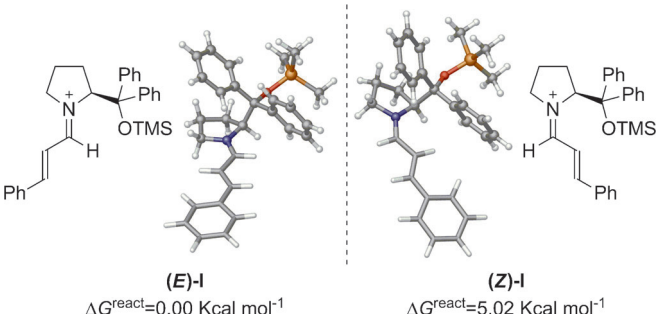



**Figure 2.** Main geometrical features and $\Delta G^{react}$ values of the iminium ion (*Z*)-**I** and (*E*)-**I** obtained at the B3LYP/6-31G(d) level of theory using the PCM model.

We next proceeded to calculate the transition states associated to the initial Michael reaction that leads to the formation of enamine intermediate **II** (Figure 3). We observed that the approach of the bromomalonate reagent to this *E*-iminium ion (*E*)-**I** through its less hindered face resulted in a transition state (TS-**1a**) significantly lower in energy than the transition state corresponding to the reaction through its most hindered face (TS-**1b**). The latter reaction would eventually result in the formation of the final product with the opposite absolute configuration at the stereogenic center that was formed in this initial step ($\Delta G^{\neq} = 12.20$ and 16.35 kcal mol$^{-1}$, respectively). We also calculated the energy of the transition state associated to the

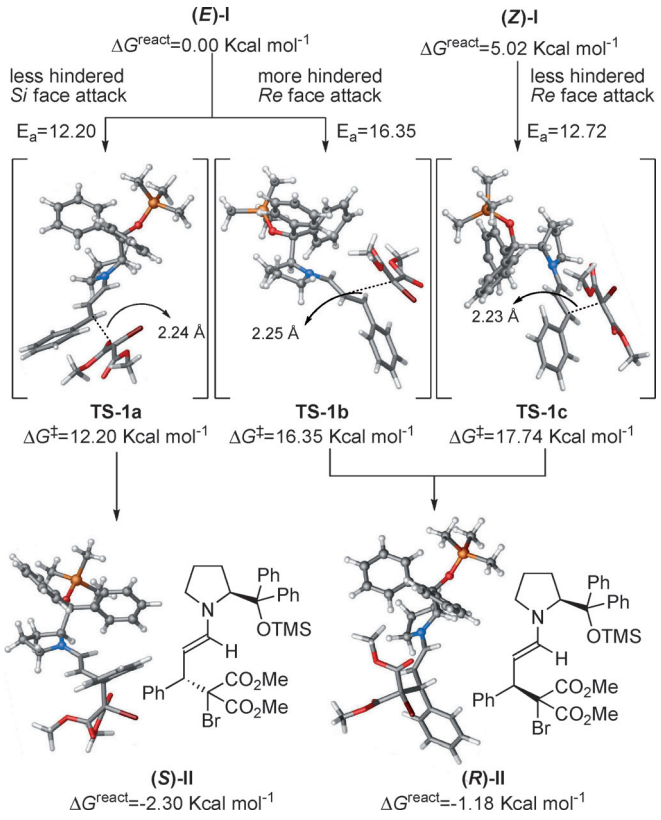



**Figure 3.** Optimized transition states for the Michael addition to (*E*)-**I** and (*Z*)-**I** and optimized structures and $\Delta G^{react}$ values for enamines **II**. Activation energies are given in kcal mol$^{-1}$.

conjugate addition of the bromomalonate reagent to the iminium ion (*Z*)-**I** through its less hindered face (TS-**1c**), which would also lead to the formation of the final product with the opposite configuration at the Michael-generated stereocenter to that obtained experimentally (enamine intermediate (*R*)-**II**), and this transition state was also higher in energy ($\Delta G^{\neq}$ = 17.74 kcal mol$^{-1}$) than the two transition states of the reactions involving the *E*-iminium ion TS-**1a** and TS-**1b**. However, interestingly, the calculated activation energy ($E_a$) was comparable to the activation barrier needed to reach (*R*)-**II** ($\Delta\Delta G^{\neq}$ = 12.72 kcal mol$^{-1}$ for the formation of (*R*)-**II** through the participation of iminium ion (*Z*)-**I** versus $\Delta\Delta G^{\neq}$ = 12.20 kcal mol$^{-1}$ for the formation of (*S*)-**II** through participation of iminium ion (*E*)-**I**).

We next analyzed the subsequent intramolecular α-alkylation step involving $S_N2$-type reaction between the nucleophilic enamine moiety and the alkyl bromide. (Figure 4). At this point, four different situations could be taken into account. The first two arise if starting from the enamine intermediate (*S*)-**II** and consist of a direct $S_N2$ reaction (TS-**2a**-*trans*) or a $S_N2$ reaction after a 180° turn in the C–C bond created in the previous step (TS-**2a**-*cis*) to afford the desired cyclopropane with a (2*R*,3*S*)-configuration or a (2*R*,3*R*)-configuration, respectively. In the same way, the intermediate (*R*)-**II** could undergo the reaction through the same two channels (TS-**2b**-*trans* and TS-**2b**-*cis*) generating the (2*S*,3*R*)- or (2*S*,3*S*)-configured cyclopropanes, respectively. As it can be seen in Figure 4, the formation

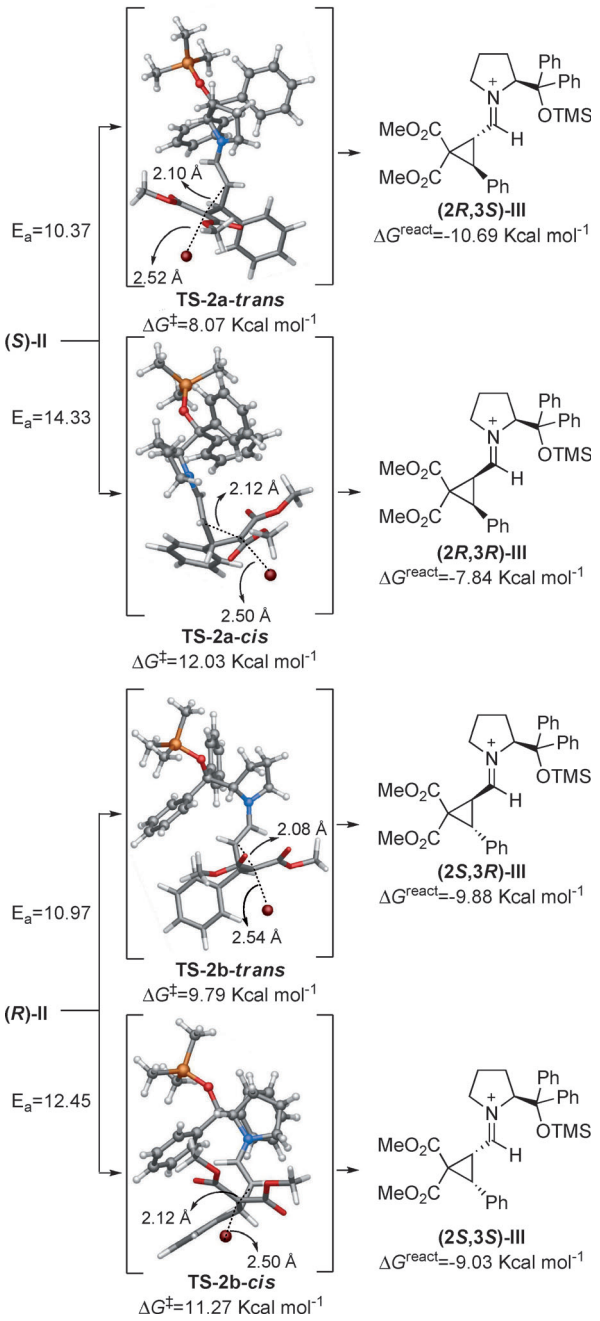



**Figure 4.** Optimized transition states for the $S_N2$ reaction step and $\Delta G^{react}$ values for intermediates **III**. Activation energies are given in kcal mol$^{-1}$.

of the (2*R*,3*S*)-**III** product is favored in terms of energy ($\Delta\Delta G^{\neq}$ = 10.37 kcal mol$^{-1}$ versus $\Delta\Delta G^{\neq}$ = 14.33, 10.97, and 12.45 kcal mol$^{-1}$), which also agrees with the experimental observation.

These calculated data also indicated that, for the preferred pathway which generates iminium ion (2*R*,3*S*)-**III** through intermediate (*S*)-**II**, the activation energy associated to the first step of the cascade (the Michael reaction) was higher than the one required for the subsequent intramolecular $S_N2$ reaction ($\Delta\Delta G^{\neq}$ = 12.20 kcal mol$^{-1}$ and 10.37 kcal mol$^{-1}$, respectively). This also indicated that this first Michael reaction was indeed

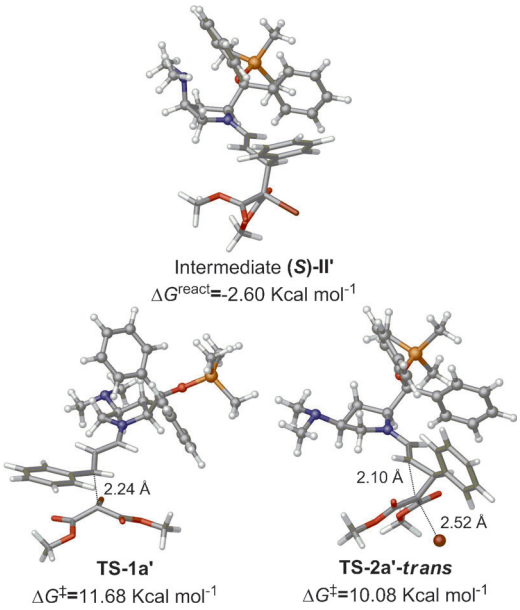



**Figure 5.** Optimized transition states for the Michael addition and intramolecular alkylation reaction TS-**1a**′ and TS-**2a**′-*trans* and optimized structure, and $\Delta G^{react}$ value for enamines (*S*)-**II**′ in the **4e**-catalyzed reaction.

the rate-limiting step of the process (and also irreversible as we envisioned in the catalytic cycle in Scheme 3). Additionally, it was the step at which the stereochemical information was transferred from the catalyst to the product. In this sense, our calculations also indicated that the eventual formation of the opposite enantiomer to the one experimentally observed should occur most probably through the attack of the bromomalonate reagent to the iminium ion intermediate (*Z*)-**I** and not as a consequence of poor face stereodiscrimination of the *O*-TMS α,α-diarylprolinol catalyst.

Finally, we also calculated the energetic profile for the reaction by using the newly designed organocatalyst **4e** (Figure 5). These calculations indicated that the initial Michael reaction step was slightly more exothermic than the parent reaction using the simpler *O*-TMS-α,α-diphenylprolinol and also that lower activation energy barriers were required for both the rate-limiting initial Michael reaction ($\Delta\Delta G^{\neq} = 11.68$ kcal mol$^{-1}$) and also for the subsequent intramolecular $S_N2$-type reaction ($\Delta\Delta G^{\neq} = 7.47$ kcal mol$^{-1}$). These data are also in agreement with the higher activity of catalyst **4e** compared to the activity of the *O*-TMS-protected α,α-diphenylprolinol catalyst used in our previous work.

## Conclusion

We showed that incorporating a 4-dimethylamino group in the structure of *O*-TMS-α,α-diarylprolinol results in an aminocatalyst with improved abilities to catalyze the enantioselective cyclopropanation of α,β-unsaturated aldehydes with diethyl bromomalonate in water. A computational study also indicated that the reaction proceeded through a cascade Michael/intramolecular α-alkylation process, in which the initial Michael reaction is the rate-determining step and also the moment at which stereochemistry is placed. The catalyst belongs to a novel class of catalysts that are active in reactions in aqueous media, involving activation of enals through iminium ion formation. The activity results are in contrast to that of most of the other related structures reported, which have been exclusively employed in reactions under enamine activation. Thus, this novel catalyst structure may pave the way for its application in other related transformations.

## Experimental Section

### General methods

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for $^1$H and $^{13}$C, respectively. Chemical shifts ($\delta$) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for $^1$H NMR, $CDCl_3$, 77.0 ppm for $^{13}$C NMR). IR spectra were measured in a PerkinElmer 1600 apparatus and only characteristic bands are given. Mass spectra were recorded on a Waters micromass GCT spectrometer by using electronic impact (EI, 70 eV). Analytical thin-layer chromatography was performed by using precoated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by UV irradiation or phosphomolibdic acid. Melting points were measured in a Büchi B-540 apparatus and were uncorrected. Optical rotations were measured on a PerkinElmer 241 polarimeter. The enantiomeric excesses (*ee*) of the products were determined by chiral stationary phase HPLC in a Waters 2695 with a Waters 2998 photodiode array detector and by using the indicated chiral column and conditions in each case. Analytical-grade solvents and commercially available reagents were used without further purification. Silica gel (Silica gel 60, 230–400 mesh, Merck) was employed for flash column chromatography.

### Synthesis of catalyst 4e

(6*R*,7a*S*)-1,1-bis[3,5-bis(trifluoromethyl)phenyl]-6-hydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (**1**): Methyl chloroformate (22.4 mL, 0.289 mol) was dropwise added to a suspension of *trans*-4 L-hydroxyproline (17.21 g, 0.138 mol) and $K_2CO_3$ (18.0 g, 0.138 mol) in MeOH (70 mL) at 0 °C. The mixture was stirred at this temperature for 8–10 h, after which the solvent was removed under reduced pressure. The obtained solid was redissolved in $CH_2Cl_2$ and washed with water. The aqueous layer was then extracted with $CH_2Cl_2$ (2×25 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered. After the removal of the solvent (2*S*,4*R*)-dimethyl 4-hydroxypyrrolidine-1,2-dicarboxylate, was isolated as a yellowish solid (27.83 g, 0.137 mol, quantitative). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 4.42–4.35 (m, 2H), 3.67–3.52 (m, 7H), 3.47–3.30 (m, 2H), 2.40–2.13 (m, 1H), 2.03–1.93 ppm (m, 1H). $^{13}$C NMR ($CDCl_3$, 75.4 MHz) (*denotes minor rotamer signals): $\delta$ = 173.2, 173.1*, 155.6, 155.3*, 69.6, 68.8, 57.8, 57.5*, 54.9, 54.4*, 52.7, 52.6*, 38.9, 38.2* ppm. Anal. calcd. for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.59; H, 6.68; N, 6.95. Next, a solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (14.9 mL, 0.086 mol) in THF (15 mL) was dropwise added to a suspension of Mg (2.1 g, 0.086 mol) in dry THF (25 mL) at 0 °C. The mixture was stirred at reflux for 1 h and then it was allowed to reach RT, after which a solution of (2*S*,4*R*)-dimethyl 4-hydroxypyrrolidine-1,2-dicarboxylate (5.01 g, 0.025 mol) in dry THF (15 mL) was dropwise added at 0 °C. The mixture was heated to reflux for 2 h and it was afterwards poured into an $NH_4Cl$ ice bath and filtered. The mixture was then

extracted with EtOAc (3×20 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered. After the removal of the solvent, the obtained solid was purified through flash chromatography (hexane/EtOAc 6: 4) to yield **1** as a brownish solid (9.50 g, 0.017 mol, 67%). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.99 (s, 2H), 7.92 (s, 1H), 7.90 (s, 1H), 7.87 (s, 2H), 4.97 (dd, 1H, $J$ = 11.5, 4.7 Hz), 4.64–4.62 (m, 1H), 4.12 (dd, 1H, $J$ = 12.8, 5.5 Hz), 3.26 (d, 1H, $J$ = 12.8 Hz), 2.03 (bs, 1H), 1.81 (dd, 1H, $J$ = 13.0, 4.7 Hz), 1.22 ppm (ddd, 1H, $J$ = 13.0, 11.5, 5.2 Hz). $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 158.8, 144.2, 141.4, 132.8 (q, $J_{CF}$ = 33.8 Hz), 132.7 (q, $J_{CF}$ = 34.0 Hz), 125.8 (d, $J_{CF}$ = 2.4 Hz), 125.4 (d, $J_{CF}$ = 2.4 Hz), 123.5–123.4 (m, 1C), 122.9–122.8 (m, 1C), 122.8 (q, $J_{CF}$ = 273.3 Hz), 122.7 (q, $J_{CF}$ = 272.8 Hz), 83.5, 71.0, 67.1, 56.7, 39.2 ppm. Anal calcd. for $C_{22}H_{13}F_{12}NO_3$: C, 46.58; H, 2.31; N, 2.47. Found: C, 46.67; H, 2.21; N, 2.30. MS (70 eV) *m/z* (%): 567 (6, $M^+$), 548 (21), 478 (58), 439 (15), 369 (22), 241 (27), 213 (21). FTIR: $\tilde{\nu}$ = 3459 (OH st), 1759 (C=O st) cm$^{-1}$. $[\alpha]_D^{20}$: +104.9 ($c$ = 1.0, $CH_2Cl_2$). M.p.: 75–78 °C (hexanes/EtOAc 8:2).

(6*S*,7a*S*)-6-azido-1,1-bis[3,5-bis(trifluoromethyl)phenyl]-tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (**2**): Pyridine (197 μL, 2.317 mmol) was added to a solution of **1** (730 mg, 1.287 mmol) in dry $CH_2Cl_2$ (60 mL). The reaction mixture was cooled to 0 °C and methanesulfonyl chloride (108 μL, 2.317 mmol) was dropwise added. The solution was stirred for 6 h at RT and the reaction was then quenched with $H_2O$ (30 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3×20 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered. The removal of the solvent afforded (6*R*,7a*S*)-1,1-bis[3,5-bis(trifluoromethyl)phenyl]-3-oxohexahydropyrrolo[1,2-*c*]oxazol-6-yl methanesulfonate as colorless oil after flash column chromatography purification (hexanes/EtOAc 6:4). (807 mg, 1.248 mmol, 97%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (s, 2H), 7.94 (s, 1H), 7.91 (s, 1H), 7.89 (s, 2H), 5.34–5.29 (m, 1H), 4.91 (dd, 1H, $J$ = 11.4, 4.6 Hz), 4.30 (dd, 1H, $J$ = 13.9, 6.1 Hz), 3.52 (d, 1H, $J$ = 13.9 Hz), 3.09 (s, 3H), 2.14 (dd, 1H, $J$ = 14.0, 4.6 Hz), 1.41 ppm (ddd, 1H, $J$ = 14.0, 11.4, 5.6 Hz). $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 158.5, 143.9, 140.9, 132.8 (q, $J_{CF}$ = 33.8 Hz), 132.7 (q, $J_{CF}$ = 34.0 Hz), 125.9 (d, $J_{CF}$ = 2.9 Hz), 125.5 (d, $J_{CF}$ = 2.9 Hz), 123.5–123.4 (m, 1C), 122.9–122.8 (m, 1C), 122.8 (q, $J_{CF}$ = 273.0 Hz), 122.7 (q, $J_{CF}$ = 273.2 Hz), 83.7, 79.3, 66.8, 54.3, 38.7, 37.1 ppm. Anal. calcd. for $C_{23}H_{15}F_{12}NO_5S$: C, 42.80; H, 2.34; N, 2.17. Found: 42.88; H, 2.42; N, 2.05. MS (70 eV) *m/z* (%): 646 (32, $[M+H]^+$), 627 (25), 626 (100), 603 (15) 602 (60), 506 (81) 439 (17). FTIR: $\tilde{\nu}$ = 1769 cm$^{-1}$ (C=O st). $[\alpha]_D^{20}$: +106.2 ($c$ = 1.0, $CH_2Cl_2$). M.p.: 95–97 °C (hexane/EtOAc 8:2). Next, this compound (993 mg, 1.539 mmol) was dissolved in DMF (30 mL) and sodium azide (300 mg, 4.617 mmol) was added at once. The mixture was stirred at 70 °C for 8–10 h, after which water (20 mL) was added and the mixture was extracted with $Et_2O$ (2× 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2×20 mL), brine (2×20 mL), and $H_2O$ (2×20 mL), dried over anhydrous $Na_2SO_4$, and filtered. Compound **2** was isolated as a white solid (911 mg, 1.538 mmol, quantitative) after the removal of the solvent and was found to be analytically pure by NMR spectroscopy. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.96 (s, 2H), 7.93 (s, 2H), 7.85 (s, 2H), 4.83–4.62 (m, 1H), 4.43–4.14 (m, 1H), 3.88 (dd, 1H, $J$ = 12.7, 3.4 Hz), 3.46 (dd, 1H, $J$ = 12.7 Hz, 6.6 Hz), 2.31–2.21 (m, 1H), 1.40–1.17 ppm (m, 1H). $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 158.3, 144.2, 140.9, 132.88 (q, $J_{CF}$ = 33.7 Hz), 132.86 (q, $J_{CF}$ = 34.0 Hz), 125.8 (d, $J_{CF}$ = 2.6 Hz), 125.7 (d, $J_{CF}$ = 2.8 Hz), 123.8–123.3 (m, 1C), 123.3–122.8 (m, 1C), 122.72 (q, $J_{CF}$ = 273.2 Hz), 122,67 (q, $J_{CF}$ = 273.4 Hz), 84.1, 67.4, 60.8, 52.7, 35.4 ppm. HRMS: Calcd. for $[C_{22}H_{13}F_{12}N_2O_2]^+$: 565.0785 ($[M+H]^+-N_2$); found: 565.0791. MS (70 eV) *m/z* (%): 479 (18), 478 (40), 369 (18), 192 (26), 257 (65), 213 (31), 188 (14), 187 (10), 174 (15), 149 (12), 148 (70), 130 (28), 95 (13), 76 (17), 67 (100). FTIR: $\tilde{\nu}$ = 2112 cm$^{-1}$ ($N_3$ st), 1758 (C=O st). $[\alpha]_D^{20}$: −155.9 ($c$ = 1.0, $CH_2Cl_2$). M.p.: 119–122 °C (hexane/EtOAc 8:2).

(6*S*,7a*S*)-1,1-bis[3,5-bis(trifluoromethyl)phenyl]-6-(dimetylamino)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (**3a**): A solution of **2** (888 mg, 1.568 mmol) in MeOH was shaken under $H_2$ (90 psi) atmosphere for 10–12 h in the presence of $Pd(OH_2)$ (44 mg, 5% wt). Afterwards, the solution was filtered through a Celite path and the solvent was removed, affording (6*S*,7a*S*)-6-amino-1,1-bis[3,5-bis(trifluoromethyl)phenyl]tetrahydropyrrolo-[1,2-*c*]oxazol-3(1*H*)-one as a brownish solid (849 mg, quantitative). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.97 (s, 2H), 7.91 (s, 1H), 7.88 (s, 1H), 7.87 (s, 2H), 4.68 (dd, 1H, $J$ = 9.4, 6.4 Hz), 3.90–3.69 (m, 1H), 3.51–3.43 (m, 2H), 2.07 (ddd, 1H, $J$ = 12.3, 6.4, 6.2 Hz), 1.34 (bs, 2H), 0.97 ppm (ddd, 1H, $J$ = 12.3, 9.4, 7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 159.1, 144.6, 141.5, 132.8 (q, $J_{CF}$ = 33.8 Hz), 132.6 (q, $J_{CF}$ = 34.0 Hz), 125.9 (d, $J_{CF}$ = 3.5 Hz), 125.8 (d, $J_{CF}$ = 3.5 Hz), 123.8–123.1 (m, 1C), 122.9–122.3 (m, 1C), 122.8 (q, $J_{CF}$ = 273.3 Hz), 122.7 (q, $J_{CF}$ = 272.9 Hz), 83.9, 68.2, 55.6, 52.8, 39.2 ppm. HRMS: Calcd. for $[C_{22}H_{15}F_{12}N_2O_2]^+$: 567.0942 ($[M+H]^+$); found: 567.0950. MS (70 eV) *m/z* (%): 567 (100, $[M+H]^+$), 566 (7, $M^+$), 548 (20), 549 (80) 523 (29). FTIR (cm$^{-1}$): 3468, 3459 ($NH_2$ st), 1764 (C=O st). $[\alpha]_D^{20}$: −116.5 ($c$ = 1.0, MeOH). M.p.: 123–125 °C (hexanes/EtOAc 8:2). Next, this compound (200 mg, 0.35 mmol) was dissolved in MeOH (20 mL) and aqueous formaldehyde (37%) (1.2 mL, 15.9 mmol) and formic acid (306 μL, 8.1 mmol) were added. The solution was stirred at reflux for 10–12 h and then 6 M NaOH (15 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3×15 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered. After the removal of the solvent, the obtained oil was purified through flash chromatography (hexane/EtOAc 4:6) and the product **3a** was isolated as a white solid (190 mg, 0.33 mmol, 94%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.95 (s, 2H), 7.91 (s, 2H), 7.85 (s, 2H), 4.65 (dd, 1H, $J$ = 11.4, 5.4 Hz), 3.67 (dd, 1H, $J$ = 11.5, 6.9 Hz), 3.47 (dd, 1H, $J$ = 11.5, 8.0 Hz), 3.21–3.01 (m, 1H), 2.15 (s, 6H), 1.90–180 (m, 1H), 1.19–1.04 ppm (m, 1H). $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 158.2, 144.5, 141.3, 132.8 (q, $J_{CF}$ = 33.8 Hz), 132.7 (q, $J_{CF}$ = 33.9 Hz), 125.8 (d, $J_{CF}$ = 3.0 Hz), 125.5 (d, $J_{CF}$ = 3.0 Hz), 123.9–123.1 (m, 1C), 123.0–122.6 (m, 1C), 122.8 (q, $J_{CF}$ = 273.1 Hz), 122.7 (q, $J_{CF}$ = 273.1 Hz), 83.5, 68.1, 66.9, 50.3, 43.7, 33.9 ppm. HRMS: Calcd. for $[C_{24}H_{19}F_{12}N_2O_2]^+$: 595.1255 ($[M+H]^+$); found: 595.1257. MS (70 eV) *m/z* (%): 598 (40, $[M+H]^+$), 581 (56), 566 (10), 549 (60), 523 (29), 126 (25), 112 (14). FTIR: $\tilde{\nu}$ = 1749 cm$^{-1}$ (C=O st). $[\alpha]_D^{20}$: −122.0 ($c$ = 1.0, $CH_2Cl_2$). M.p.: 78–80 °C (hexane/EtOAc 8:2).

(2*S*,4*S*)-2-[bis[3,5-bis(trifluoromethyl)phenyl]triethylsilyl-oxy]methyl-4-dibutylaminopyrrolidine, (**4e**): 4 M NaOH (1.4 mL, 5.7 mmol) was added to a solution of **3a** (340 mg, 0,572 mmol) in MeOH (30 mL) and stirred at reflux for 12 h. Then $H_2O$ (20 mL) was added and the mixture was extracted with EtOAc (1×20 mL) and with $CH_2Cl_2$ (2× 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and after filtration the removal of the solvent afforded (2*S*,4*S*)-2-[bis[3,5-bis(trifluoromethyl)phenyl]-hydroxymethyl]-4-(dimethylamino)pyrrolidine as colorless oil (300 mg, 0,572 mmol, quantitative). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.08 (s, 2H), 8.00 (s, 2H), 7.74 (s, 2H), 4.53 (dd, 1H, $J$ = 9.0, 3.5 Hz), 3.28 (d, 1H, $J$ = 11.9 Hz), 2.92 (dd, 1H, $J$ = 11.9, 4.7 Hz), 2.61–2.41 (m, 1H), 2.28 (s, 6H), 1.88 (ddd, 1H, $J$ = 14.0, 9.0, 5.0 Hz), 1.66 ppm (d, 1H, $J$ = 14.0 Hz). $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 149.1, 148.6, 131.9 (q, $J_{CF}$ = 33.2 Hz), 131.7 (q, $J_{CF}$ = 33.2 Hz), 126.6 (d, $J_{CF}$ = 3.1 Hz), 125.8 (d, $J_{CF}$ = 3.3 Hz), 123.3 (q, $J_{CF}$ = 272.8 Hz), 123.2 (q, $J_{CF}$ = 272.8 Hz), 121.3–120.8 (m, 2C), 77.4, 65.5, 63.6, 50.6, 42.7, 32.4 ppm. HRMS: Calcd. for $[C_{23}H_{21}F_{12}N_2O]^+$: 569.1462 ($[M+H]^+$). Found: 569.1456. MS (70 eV) *m/z* (%): 525 (60, $[M+H]^+$), 468 (11), 435 (32), 220 (18), 113

(100), 73 (16), 71 (10), 68 (46). FTIR: $\tilde{\nu}=3335\ cm^{-1}$ (OH st). $[\alpha]_D^{20}$: −16.9 ($c=1.0$, $CH_2Cl_2$). Next, this compound (300 mg, 0.573 mmol) was solved in dry $CH_2Cl_2$ (20 mL), and pyridine (115 μL, 1.432 mmol) and TESOTf (259 μL, 1.146 mmol) were added at 0 °C. The reaction mixture was stirred for 12 h at this temperature, after which it was quenched with $H_2O$ (15 mL). The mixture was extracted with $CH_2Cl_2$ (3×15 mL) and the combined organic fractions were dried over anhydrous $Na_2SO_4$ and filtered. The solvent was removed and the residue was purified trough flash column chromatography (hexane/EtOAc 8:2), isolating **4e** as a colorless oil (305 mg, 0.447 mmol, 78%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta=8.10$ (s, 2H), 7.92 (s, 2H), 7.71 (s, 2H), 4.31 (dd, 1H, $J=10.0$, 6.5 Hz), 3.16–2.89 (m, 1H), 2.68–2.47 (m, 1H), 2.35–2.11 (m, 1H), 2.07 (s, 6H), 2.04–1.87 (m, 1H), 1.79 (bs, 1H), 1.20–1.02 (m, 1H), 0.84 (t, 9H), 0.46–0.02 ppm (m, 6H). $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta=147.5$, 145.7, 131.6 (q, $J_{CF}=33.4$ Hz), 130.8 (q, $J_{CF}=33.3$ Hz), 128.9 (d, $J_{CF}=2.7$ Hz), 128.5 (d, $J_{CF}=2.5$ Hz), 123.4 (q, $J_{CF}=272.7$ Hz), 123.1 (q, $J_{CF}=272.8$ Hz), 122.0–121.9 (m, 1C), 121.8–121.6 (m, 1C), 82.0, 67.1, 64.2, 51.0, 44.2, 33.1, 6.8, 6.2 ppm. HRMS: Calcd. for $[C_{29}H_{35}F_{12}N_2OSi]^+$: 683.2327 ($[M+H]^+$); found: 683.2315. MS (70 eV) *m/z* (%): 478 (16), 435 (36), 113 (100), 73 (18), 71 (10), 68 (46). FTIR: $\tilde{\nu}=3352\ cm^{-1}$ (NH st). $[\alpha]_D^{20}$: −5.7 ($c=1.0$, $CH_2Cl_2$).

### Cyclopropanation reaction: General procedure

The starting α,β-unsaturated aldehyde (0.150 mmol) was added to a mixture of catalyst **4e** (0.013 mmol) and water (1 mL) under vigorous stirring. The mixture was cooled down to 0 °C and after 30 min, diethylbromalonate (0.125 mmol) was added at once. The reaction was stirred until TLC analysis indicated complete consumption of the malonate. Next, the mixture was extracted with $CH_2Cl_2$ (3×1 mL) and the combined organic layers were dried, the solvent was removed, and the mixture was purified through flash column chromatography (hexane/EtOAc 8: 2).

(2*R*,3*S*)-diethyl 2-formyl-3-phenylcyclopropane-1,1-dicarboxylate, (**7a**): The cyclopropane **7a** was prepared according to the general procedure after 7 d by using *trans*-4-fluorocinnamaldehyde (19.8 μL, 0.150 mmol), diethyl bromomalonate (92%, 22,9 μL, 0.125 mmol) and the catalyst **4e** (6.9 mg, 0.0125 mmol). The product **7a** was isolated after flash chromatography purification as a colorless oil (33.7 mg, 0.116 mmol, 70%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta=9.45$ (d, 1H, $J=4.7$ Hz), 7.58–7.40 (m, 5H), 4.58–4.15 (m, 2H), 3.92 (q, 2H, $J=7.0$ Hz), 3.82 (d, 1H, $J=7.4$ Hz), 3.37 (dd, 1H, $J=7.4$, 4.7 Hz), 1.30 (t, 3H, $J=7.0$ Hz), 0.93 ppm (t, 3H, $J=7.0$ Hz). $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta=196.0$, 166.0, 164.5, 132.2, 128.5, 128.4, 128.0, 62.4, 61.9, 44.7, 38.1, 35.2, 14.0, 13.6 ppm. The other spectroscopic and physical properties matched with those reported in the literature.[12a]

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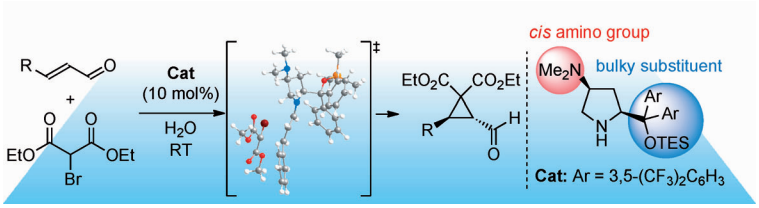


**Be water my friend:** A new family of chiral diarylprolinol-type organocatalysts with improved performances in conjugate addition reactions in water and proceeding under the iminium activation manifold were studied. Once the optimized catalyst structure had been found, it proved its efficiency in the catalytic enantioselective cyclopropanation of α,β-unsaturated aldehydes using water as the only reaction medium.

*J. I. Martínez, E. Reyes, U. Uria, L. Carrillo, J. L. Vicario**

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**Optimizing the Structure of 4-Dialkylamino-α,α-diarylprolinol Ethers as Catalysts for the Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes in Water**