Improving Asymmetric Organocatalysts via Supramolecular Interactions

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Abstract: Since the rediscovery of proline as a catalyst in aldol reaction in 2000 by List, Barbas and Lerner and, soon after, the development of imonium catalysis by D. W. C. MacMillan, the emergence of Organocatalysis as an important instrument in Organic Synthesis is outstanding. Nowadays, one of the most important goals for chemist is the quest for new and more efficient catalysts. One emerging tool for improving existent organocatalysts consists in using additives which interact with the catalysts via supramolecular interactions such as hydrogen bonding. These interactions provide better catalysts in terms of activity and selectivity. The present review aims to cover and discuss the current evolution of this fast growing field.

Keywords: Organocatalysis, hydrogen bond, supramolecular interactions, enantioselective catalysis.

1. INTRODUCTION

Since the rediscovery of proline as a catalyst in aldol reaction in 2000 by List, Barbas and Lerner [1] and the development of imonium catalysis by D. W. C. MacMillan [2] soon after, the emergence of Organocatalysis [3] as an important tool in Organic Synthesis is outstanding (Fig. **1**). However, there are still a number of challenges and issues that lie ahead. Nowadays, most of the work of chemists is the elaboration of improved catalysts in terms of selectivity, efficiency or/and turnover ratio. This approach has been achieved by carefully and time consuming optimization of the catalyst. In this sense, the most common way is the design of modular ligands and/or the modification of previous catalysts. These built-up catalyst are designed by using high-yielding reactions with two or more simple generic components. For example, libraries of peptides and organocatalysts can be assembled together to form a new stock of organocatalysts with improved catalytic properties [4].

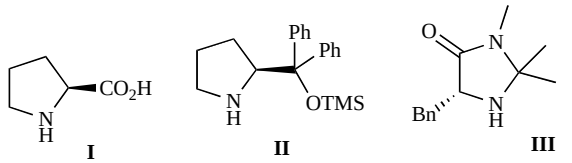

Fig. (1). Different organocatalysts.

Supramolecular Chemistry has become an emergent power in chemistry since the pioneering works of Lehn [5]. However, its use as a tailoring tool in the construction of catalysts is not common in Organic Chemistry. An exception is the work in the field of Organometallic Chemistry by Breit and coworkers. They have shown that the use of supramolecular interactions such as hydrogen bonds can improve an existent catalyst, reaching amazing results in enantioselective hydrogenation (Fig. **2**) [6].

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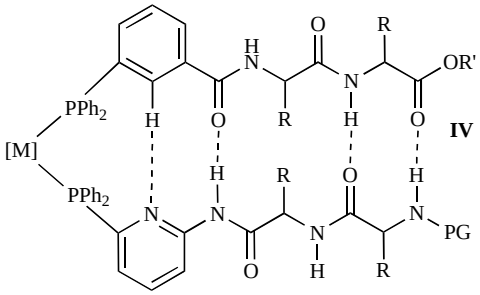

Fig. (2). Breit's supramolecular catalysts.

In the recent years, several research groups have studied the possibility of using non-covalent interactions in order to obtain new catalysts. Non-covalent bonds are formed very fast and quantitatively, offering the tantalizing possibility of using the potential simplicity of the supramolecular approach to build libraries of enantioselective catalysts. In particular, hydrogen bonding is one of the most dominant forces in molecular interaction and recognition in biological systems [7]. However, the design of organocatalysts which exploit this type of interactions as a tool to build complex scaffolds, has not been extensively used, probably due to the assumption that hydrogen bond is a much weaker interaction than covalent bond and it would be difficult to control the source of stereoselectivity. This perception has delayed the advancement in this area. In fact, only few research groups have recently implemented this new strategy. In this review, we have the aim to cover the last developments in the optimization of organocatalysts by supramolecular interactions with different additive stressing hydrogen bond donors [8].

2. SUPRAMOLECULAR INTERACTIONS WITH CHIRAL ADDITIVES

In 2006, Shan and coworkers developed an intriguing approximation for the improvement of proline in aldol reaction [9]. In the past decade, L-proline has become one of the most attractive molecules in Green Chemistry, but there are still some issues that need to be solved, such as poor solubility of proline in common organic solvents or parasitic secondary reactions, etc… In this sense, Shan and coworkers disclosed that the addition of chiral diols could offer benefits in terms of efficiency and stereoselectivity in aldol reactions catalyzed by simple proline. Indeed, when chiral diols like

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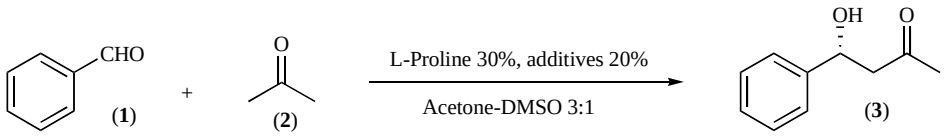
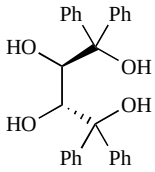
Table 1. Aldol Reaction Reported by Shan



Entry	Additive	Yield (%)	ee (%)
1	none	43	72
2	(R)-BINOL **(+)-4**	52	91
3	(S)-BINOL **(-)-4**	52	94
4	Rac-BINOL **4**	50	70
5	 **(5)**	40	94

BINOL (**4**) or tartrate derivatives (**5**) were used as additives, the reaction afforded higher yields and enantioselectivities, as it is shown in Table **1**. Surprisingly, the use of *R* or *S* BINOL did not affect the stereochemical outcome of the reaction. Despite this, when racemic BINOL was used, the enantioselectivity of the reaction dramatically decreased (entry 4, Table **1**). On the other hand, when racemic proline was used as catalyst, very poor chiral induction was observed, even with enantiopure diols were employed as additives.

On the basis of these results, the authors attributed the chiral induction in aldol reaction to the chirality of proline. Probably, the additives only enhanced the chiral inductive ability of proline by the formation of a chiral supramolecular system through hydrogen bonding interaction. They proposed a supramolecular interaction between diol, proline and reactants as it is shown in Fig. (**3**).

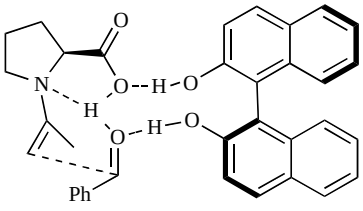


Fig. (3). Suggested transition state for aldol reaction.

In 2008, Zhao and coworkers design a modularly designed organocatalytic assemblies as organocatalysts for the direct nitro-Michael addition [10]. In this approach, they proposed that ionic interactions could be applied for the self-assembly of different units. In order to prove this concept, Zhao used simple proline as primary organocatalyst, which interacts with a second unit of catalysts, concretely a tertiary amine, carrying on a thiourea moiety. These two units in the reaction mixture will undergo an acid-base reaction between the carboxylic acid and the tertiary amine, leading an ammonium salt. Ionic interactions between the ammonium and the carboxylate should cause these two modules to self assemble [11] affording a new organocatalyst, incorporating the proline reaction center and a stereocontroling moiety (Fig. **4**).

In order to demonstrate the power of this approximation, they tested several self assembled organocatalysts in the direct nitro-Michael addition of ketones to nitrostyrenes. The authors reported that those improved organocatalysts rendered the addition product in high yields and excellent diastereo- and enantioselectivities, as it is shown in Fig. (**5**). Remarkably, the stereoinduction of the reaction is determined by the nature of the aminoacid in the assembled organocatalysts. As a result, L-proline and L-phenylglicine gave the desired adducts with opposite enantioselectivity.

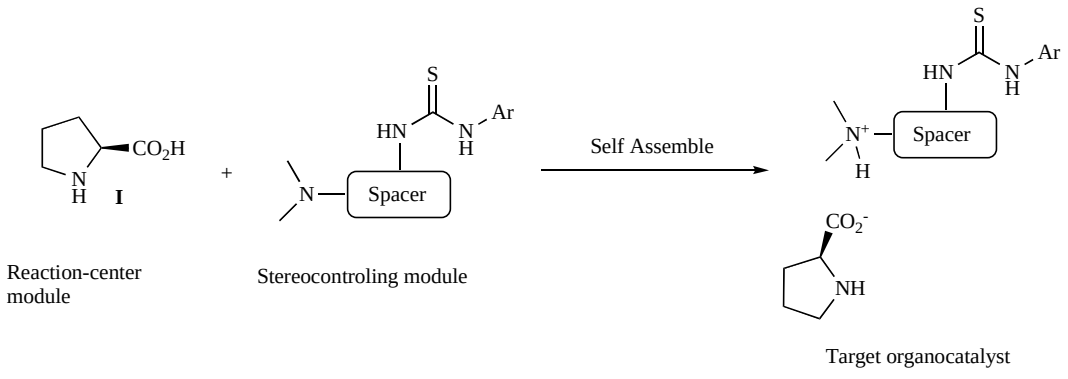


Fig. (4). Zhao Organocatalyst.

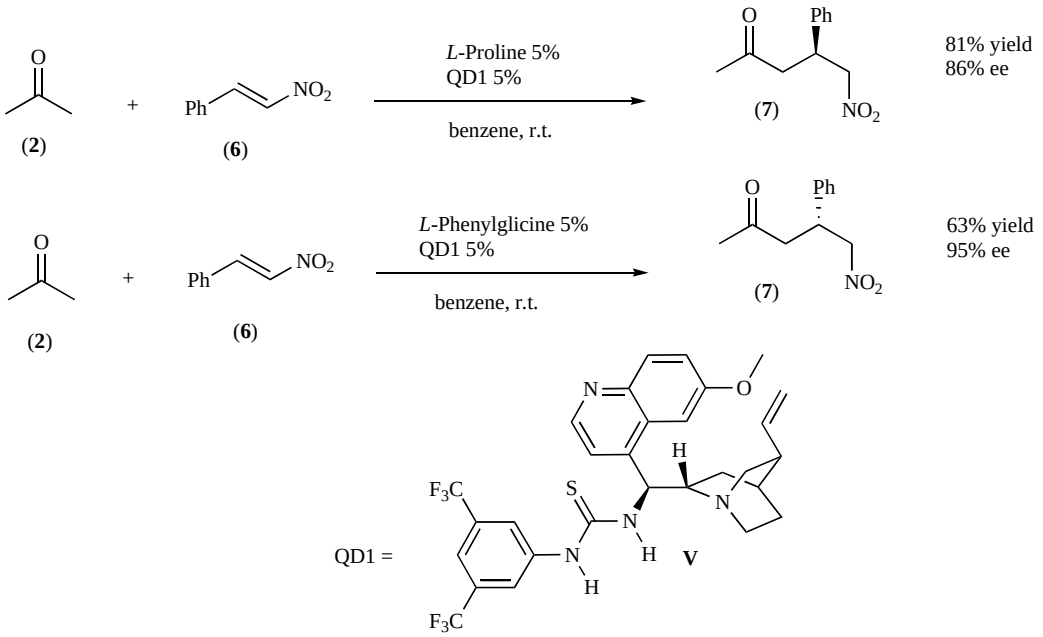


Fig. (5). Michael Addition catalyzed by assembled organocatalysts reported by Zhao.

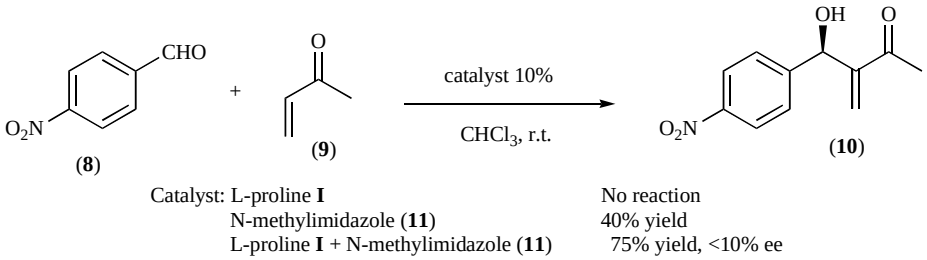


Fig. (6). Miller's MBH reaction catalyzed by proline and imidazole.

3. SUPRAMOLECULAR INTERACTIONS WITH ACHIRAL ADDITIVES

The first example with achiral additives to improve existing catalysts was reported by S. J. Miller in 2006 [12]. Miller and coworkers studied the Morita-Baylis-Hillman (MBH) reaction of methyl vinyl ketone (MVK) with different aldehydes catalyzed by proline. It was demonstrated that when *N*-methyl-imidazoline was added as co-catalyst, the conversion and enantioselectivity of the reaction improved dramatically, as it is ilustrated in Fig. (**6**).

However, the first real example of improved organocatalyst by supramolecular interaction with achiral additives was reported by M. L. Clarke in 2007 [13]. In this work, Clarke disclosed that achiral additives bearing hydrogen bond donors such as pyridinones (**B**) could strongly associate with amidonaphtyridines (**A**) in apolar solvents, as shown in Fig. (**7**). This association was previously reported by Kelly *et al.* to template a S_N2 reaction [14].

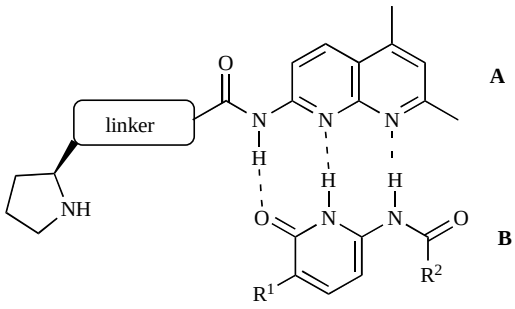


Fig. (7). Supramolecular assembled organocatalyst proposed by Clarke.

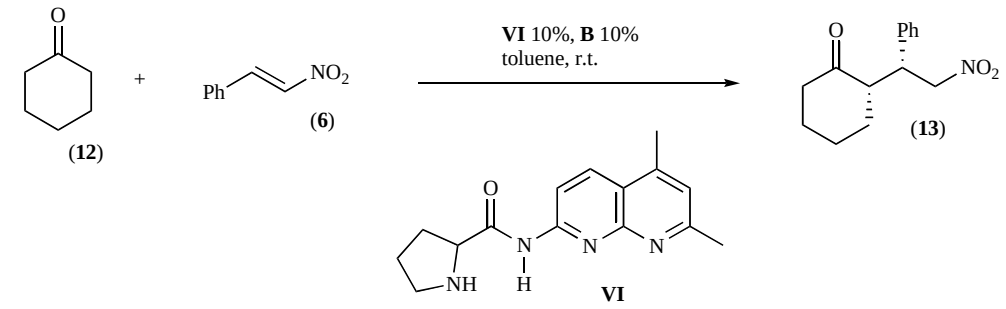
Clarke and coworkers chose the enantioselective Michael addition of ketones to nitrostyrenes as a test reaction. This reaction is a well-known and potentially useful organocatalytic reaction nowadays, but it is not efficiently catalyzed by proline. They showed that the assembly of pyridinones with amidonaphtyridines increases dramatically the enantioselectivity of this reaction. Moreover, it was demonstrated that this complex could be easily prepared as well could be adjustable to the requirements of the reactions under study.

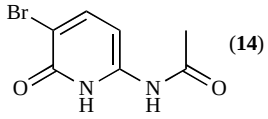
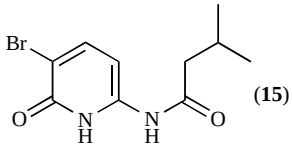
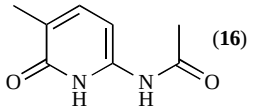
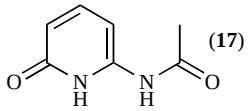
As it is shown in Table **2**, when (*S*)-ProNap is used on its own, the reaction is efficiently catalyzed, but products are obtained in almost racemic form. Gratifyingly, the addition of different pyridinones increases the enantioselectivity up to 79% (entry 5; Table **2**).

In 2008, Schreiner and coworkers described the use of Schreiner's thiourea as an efficient cocatalyst in the alcoholysis of styrene oxides [15]. In this paper Schreiner used the cooperative combination of mandelic acid and a Schreiner's thiourea. The resulting catalytic system renders the alcoholysis of styrene oxides in high conversions.

Recently, Demir and coworkers have used Schreiner's thiourea [16] as a useful host-guest complex with proline in order to enhance its catalytic properties [17]. As it is commonly known, proline presents some important drawbacks such as poor solubility in common organic solvents and parasitic reactions that make difficult the use of low catalyst loadings. Proline could react with aldehydes to furnish the bicyclic product **18** via 1,3 polar cycloaddition, as illustrated in Fig. (**8**) [18]. It is noteworthy that the rate of this reaction is strongly affected by the polarity of the solvent, for example in DMSO the reaction becomes competitive in comparison with the

Table 2. Michael Addition to Nitrostyrenes Reported by Clarke



Entry	B	Yield (%)	D.r.	ee (%)
1	none	87	15:1	15
2	 (**14**)	82	31:1	47
3	 (**15**)	74	33:1	34
4	 (**16**)	59	41:1	35
5	 (**17**)	63	58:1	79

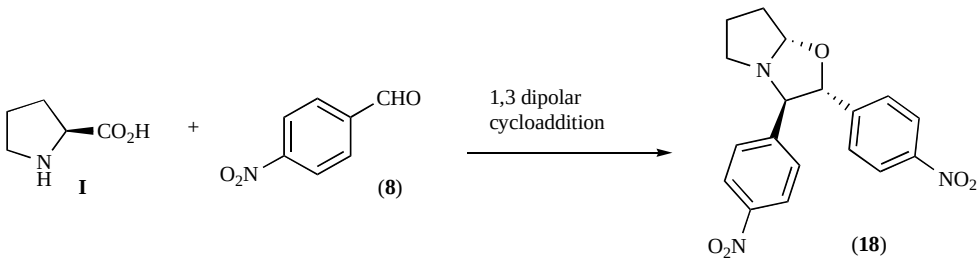


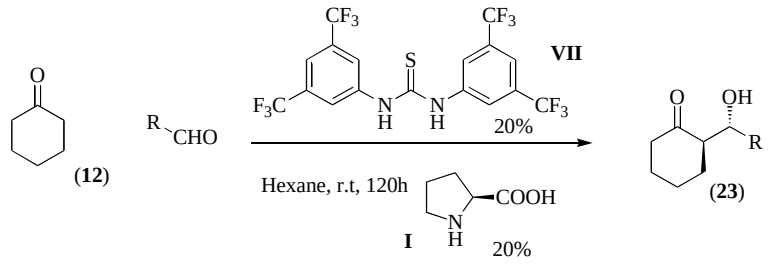
Fig. (8). Parasitic reaction of proline.

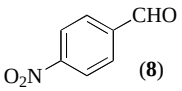
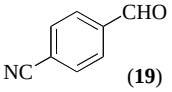
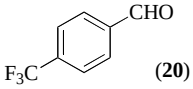
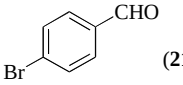
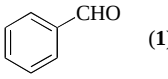
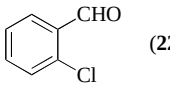
aldol reaction. In order to reduce this side reaction, apolar solvents such as toluene or chloroform could be used. However, the low solubility of proline in these solvents makes this solution not realistic.

In this sense, Demir and coworkers realized that solubility of proline can be increased by the addition of hydrogen bond donors such as Schreiner's thiourea (**VII**). They explained this fact due to the formation of host-guest complex between the carboxylic acid moiety of proline and thiourea. This kind of interaction has been extensively studied in the literature. In 2007, Moran and coworkers carry out a study about host-guest interactions between hydrogen-bond donors and carbonyl moieties. In that study, they demonstrated that the strongest interactions are achieved with thiourea as hydrogen bond donor [19].

For the first time, Demir and coworkers showed that proline forms a host-guest supramolecular assembly with Schreiner's thiourea. Moreover, this new proline-thiourea complex exhibit higher solubility and reactivity than proline itself. The authors proved the potential of this new catalyst system in the direct aldol reaction of cyclohexanone with aromatic aldehydes. Aldol reaction, as it is well-known, presents important drawbacks when simple proline is used as catalyst. In this case, the diastereoselectivity of the reaction is around 2:1 as shown in Table **3**, and the enantioselectivity is moderate. However, when thiourea is used as additive,

Table 3. Aldol Reaction Reported by Demir and Coworkers



Entry	Aldehyde	Yield (%)	D.r.	ee (%)
1	 (**8**)	96	92:8	>99
2	 (**19**)	79	93:7	99
3	 (**20**)	93	94:6	99
4	 (**21**)	87	90:10	99
5	 (**1**)	79	88:12	98
6	 (**22**)	83	94:6	99

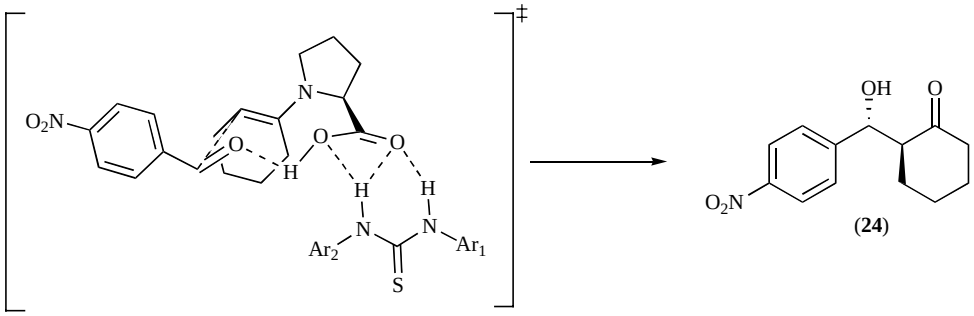


Fig. (9). Reported Transition state for the aldol reaction using proline and Schreiner's thiourea as catalysts.

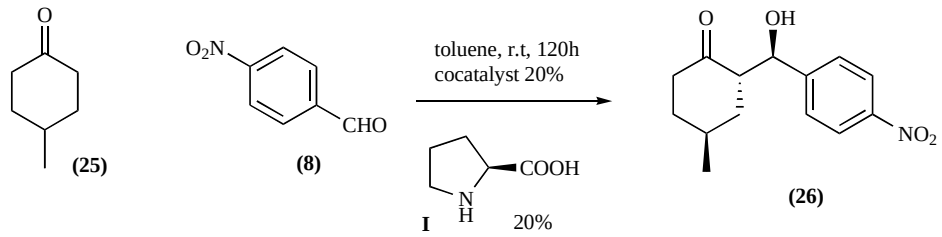
the efficiency of this reaction is dramatically enhanced. It means, thiourea not only benefits the yield of the reaction, but also increases the diastereoselectivity up to 25:1, achieving enantiomeric excesses of 99%.

Demir *et al.* justify this increased efficiency in terms of stereoselectivity through interactions in the transition state, as it is shown in Fig. (**9**).

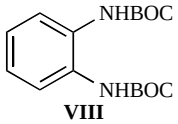
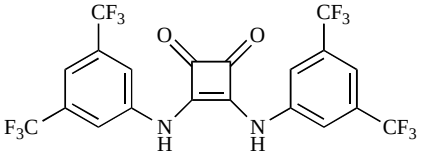
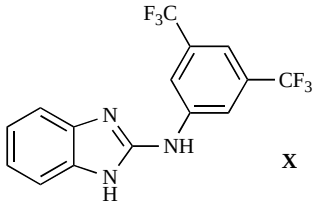
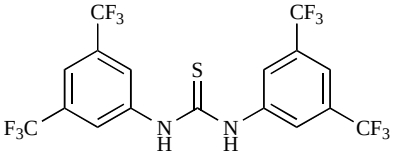
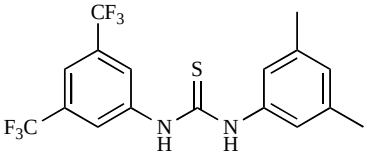
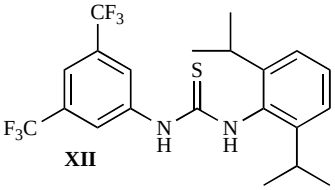
The authors also disclosed that this interaction could work with other aminoacids such as tryptophane. However, the results are slightly worse than using proline.

Soon after, Rios and coworkers, inspired by the pioneering work of Demir, applied the same strategy for the desymmetrization of 4-substituted cyclohexanones [20]. In this work, they studied the interaction between different hydrogen bond donors and proline.

Table 4. Desymmetrization Aldol Reaction Reported by Rios *et al*.



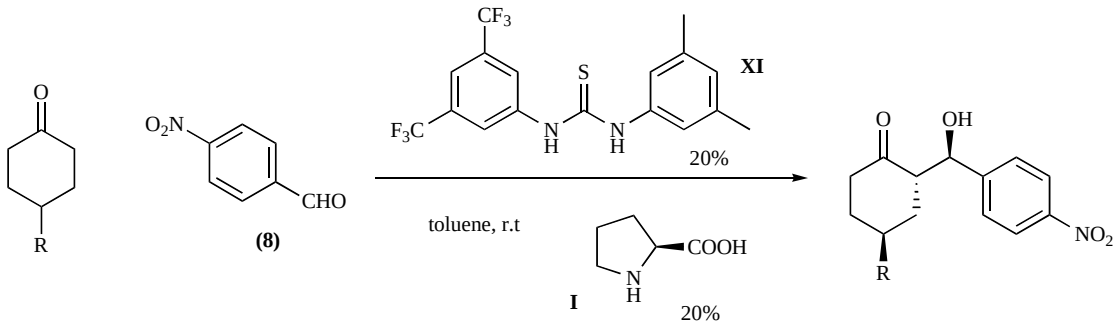
(25) **(8)** **I** **(26)**

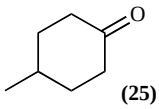
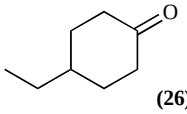
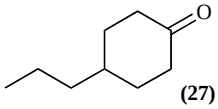
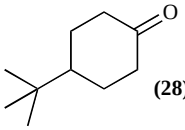
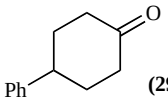
Entry	Cocatalyst	Conversion (%)	D.r.	ee (%)
1	-	0	-	-
2	 **VIII**	50	14:1:0:0	87
3	(+)-BINOL **(+)-4**	traces	-	-
4	 **IX**	traces	-	57
5	 **X**	70	4:1:0:0	94
6	 **VII**	75	7:1:0:0	99
7	 **XI**	90	10:1:0:0	99
8	 **XII**	53	5:1:0:0	99

BOC-protected diamines, benzoimidazoles, squaramides and thioureas were employed as hydrogen bond donors. The best results were obtained with thioureas as additives. Surprisingly, simple benzoimidazoles improved the performance of proline itself affording good diastereo- and enantioselectivities (Table **4**). Interestingly, 3,5-dimethyl thiourea **XI** gave the best results for the desymmetrization reaction, rendering the product in good yields and in very good diastereo- and enantioselectivities. On the other hand, Schreiner's thiourea and different substituted thioureas gave slightly worse results in terms of diastereo- and enantioselectivity (Table **4**).

The authors demonstrated the scope of the reaction by desymmetrizating different 4-substituted cyclohexanones and using dif-

Table 5. Desymmetrization of Different 4-substituted Cyclohexanones



Entry	Ketone	Product	Yield (%)	D.r.	ee (%)
1	 **(25)**	**3a**	85	10:1:0:0	99
2	 **(26)**	**3b**	65	11:2:0:0	94
3	 **(27)**	**3c**	80	4:1:0:0	96
4	 **(28)**	**3d**	69	7:2:1:0	97
5	 **(29)**	**3e**	83	11:2:0:0	97

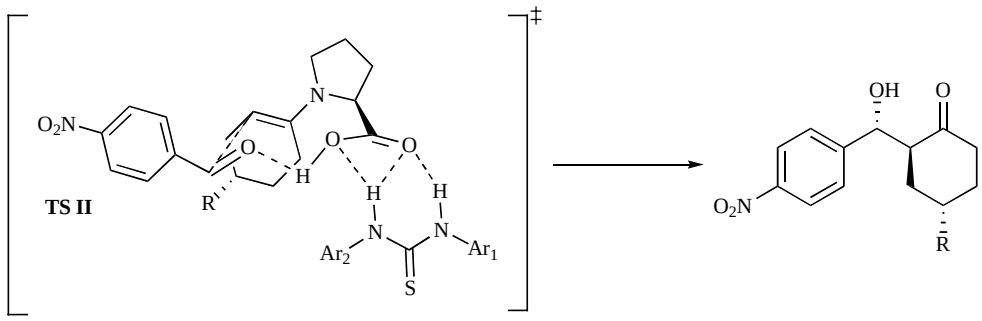


Fig. (10). Transition state proposed for the desymmetrization reaction.

ferent aldehydes. In all the examples the results were excellent as it is shown in Table **5**.

Moyano and Rios disclosed that the use of thiourea improved the catalysts in terms of solubility, increasing the acidity of the carboxylic acid of proline and stabilizing the transition state previously described by Houk [21] and Demir. The transition state of the desymmetrization is illustrated in Fig. (**10**) where is clearly showed the absolute configuration of desymmetrization product obtained.

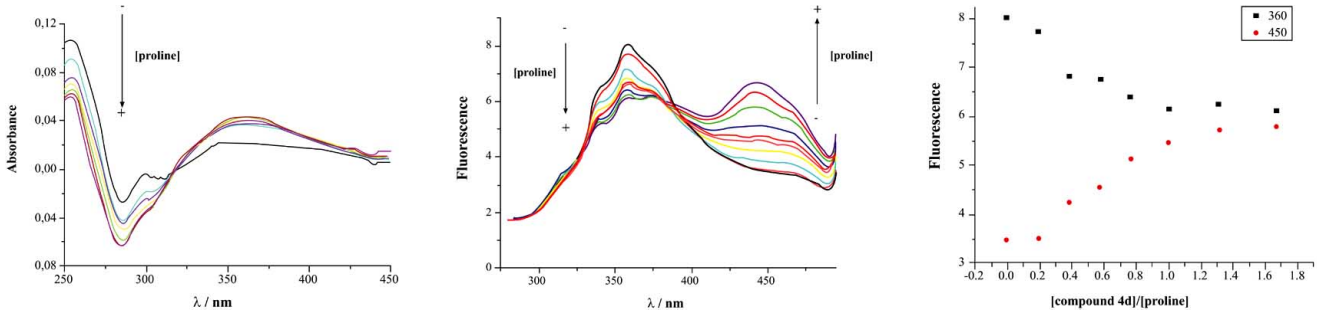


Fig. (11). (a) (left) UV spectra **(b)** (center) fluorescence spectra for proline/**4f** mixtures. **(c)** (right) Job plot at λ=360 nm (▪) and 445 nm (●)dd a descriptive label of the figure here.

The substituent in 4-position of ketone has to be in opposite face than the aldehyde in order to avoid steric interactions.

As they explain in their work, spectroscopical studies about the interaction of proline and different hydrogen bond donors were done in order to investigate the stoichiometry between additives and proline in $CHCl_3$. They recorded both the UV and fluorescence spectra of the additive **XI** with different amounts of proline. As shown in graphics **11a** and **11b** (Fig. **11**), UV spectrum of compound **XI** shows a slight blue-shift to 360 nm, an absorbance increase at 360 nm and an isosbestic point around 310 nm with increasing concentration of proline was observed. These spectral features suggest a ground-state complex between thiourea and proline. Since the UV spectra did not show large enough differences to calculate the stoichiometry of the complex, fluorescence spectroscopy was used to evaluate this interaction. The addition of increasing amounts of proline to a solution of **XI** lead to a decrease of the fluorescence signal at 360 nm and cause an increase at 445 nm. A Job plot [22] with these two λ showed the formation of a stable 1:1 complex between proline and compound **XI** (Fig. **11**, graphic **c**).

4. CONCLUSIONS

The examples described above have nicely demonstrated the power of supramolecular interactions in order to improve existent organocatalysts. This new type of tailored catalysts has demonstrated its utility in Michael reaction and in direct aldol reaction catalyzed by simple proline. The beauty of this new approach is the easy modification of catalysts by simple mixing the right hydrogen bond donors with the right organocatalysts.

From the standpoint of sustainable chemistry, the simplicity of this new methodology makes it an intriguing new tailoring tool, which is expected to grow and develop as a real alternative to the existent catalysts.

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