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EDGE ARTICLE

# Enhancing the Selectivity of Prolinamide Organocatalysts by the Mechanical Bond in [2]Rotaxanes

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The synthesis of a pair of modulable interlocked prolinamides and their use as organocatalyts in three different enamine-activated processes is reported. A diacylaminopyridine moiety was incorporated into the thread for directing the [2]rotaxane formation further allowing the association of complementary small molecules. The rotaxane-based systems were tested as organocatalysts in asymmetric enamine-mediated processes, unveiling a significantly improved catalytic ability if compared with the non-interlocked thread. The presence of an electron-withdrawing nitro group at the macrocyclic counterpart helps to achieve high conversions and enantioselectivities. These systems are able to interact with *N*-hexylthymine as cofactor to form supramolecular catalysts displaying a divergent catalytic behaviour. The presence or not of the cofactor controls the chemoselectivity in competitive reactions.

## 1. Introduction

Asymmetric organocatalysis has become a powerful tool for the synthesis of sophisticated molecules starting from easily available starting materials.[1] In this arena, (*S*)-proline was found to be a promising catalyst for asymmetric aldol transformations,[2,3] and consequently the development of catalytic scaffolds bearing this privileged moiety is still a hot topic.

During the last decades the interest of the scientific community in the synthesis and study of mechanically interlocked molecules (MIMs) has undergone a huge evolution.[4] Within the range of applications of rotaxanes, the most frequently employed MIMs, those devoted to the study of their chemical reactivity, for example their use as organocatalysts[5] or ligands in metal catalysed transformations,[6] are lately capturing the attention of the chemists. In this regard, switchable rotaxane-based catalysts, able to change their catalytic activity (ON/OFF, enantio- or diastereoselectivity alterations, diverse activation modes) are of high interest.[7] In general, the macrocycle inhibits the catalysis when located over the catalytic active site.[8] As a result, the non-interlocked threads are more reactive than the corresponding interlocked systems, although displaying poorer selectivities. In contrast, the more rigid and confined interlocked catalysts[9] oftentimes afford higher diastereo- or enantioselectivities.[10] In this line, we have demonstrated that the location of a polyamide ring close to a pyrrolidine active site of an interlocked catalyst switches the enantioselective course of a process, generating both possible enantiomers of the final products via an enantiodivergent approach.[11] Recently, Leigh and coworkers reported a controlled dynamic switching allowing the enantioselectivity of a rotaxane-catalyzed reaction to be reversed, and thus highlighting the importance of the position of the ring with regard to the catalytic active site.[12]

Having in mind the potential of mechanically interlocked architectures for acting as catalysts,[13] herein we have designed a series of chiral prolinamide-based rotaxanes bearing a diacylaminopyridine (DAP) moiety as template,[14] ready to be used as organocatalysts (Figure 1).[15] The election of the DAP function as a binding site might enable these systems to modulate their activity by the interaction with complementary molecules, such as *N*-hexylthymine acting as a supramolecular co-catalyst.[16,17] Furthermore, we postulated that the proximity of the macrocycle to the catalytic active site (pyrrolidine core, Fig. 1, green circle) and its restricted translational motion between the bulky groups (Fig. 1, grey circle) could influence the course of the studied processes with unforeseeable trends. The position of the ring near the active site would generate a restricted dynamic chiral pocket allowing that the selectivity of a catalytic process could result amplified. In this context, the effect of the strength of the interaction between the interlocked components on the catalytic behaviour has been also studied by varying the acidity the NH of the isophthalamide units through the incorporation of different substituents[18] on the macrocycle (Fig. 1, blue circle).

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic and mass spectrometry data for all new compounds.

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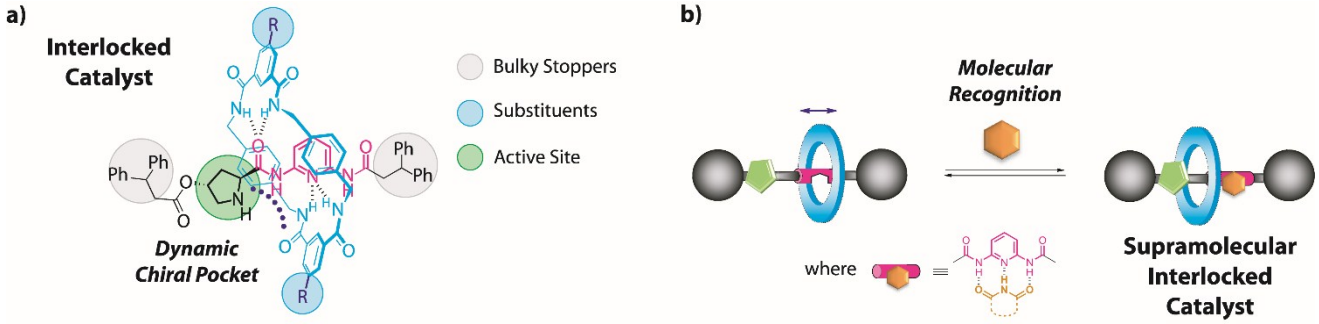
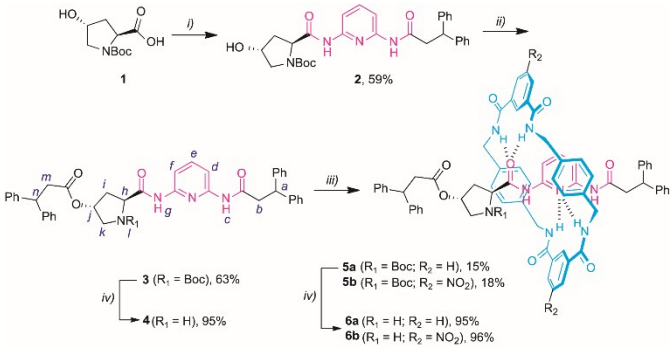



**Fig. 1** Design of: a) an interlocked DAP-based organocatalyst and, b) the formation of its hydrogen-bonding supramolecular complex.

## 2. Results and discussion

### 2.1 Synthesis of the mechanically interlocked DAP-based prolinamides

We started the synthesis from the commercially available Boc protected *trans*-4-hydroxy-*L*-proline **1** (Scheme 1). The amidation reaction between **1** and *N*-(6-aminopyridin-2-yl)-3,3-diphenylpropanamide (**S1**),[14a] in the presence of ethyl chloroformate and $Et_3N$, yielded compound **2** in 59% yield. Then, the esterification of **2** with 3,3-diphenylpropanoyl chloride provided the protected thread **3** in moderate yield. The corresponding Leigh-type [2]rotaxanes **5a,b** were readily obtained by carrying out a five-component reaction with *p*-xylylenediamine and the suitable isophthaloyl chloride ($R_2$ = H or $NO_2$) (see ESI† for further details).[19] A Boc deprotection of the resulting prolinamides afforded the thread **4** and the rotaxanes **6a,b** (in only 3 and 4 synthetic steps, respectively), which can be directly tested as organocatalysts.




**Scheme 1** Synthesis of DAP-based non-interlocked and interlocked catalysts **4** and **6a-b**. Reaction conditions: i) ethyl chloroformate, $Et_3N$, THF, 0 °C; then addition of *N*-(6-aminopyridin-2-yl)-3,3-diphenylpropanamide **S1**; 25 °C, overnight; then reflux for 3 h; ii) 3,3-diphenylpropanoyl chloride, $Et_3N$, $CH_2Cl_2$, 25 °C, overnight; iii) *p*-xylylenediamine, isophthaloyl dichloride, $Et_3N$, $CHCl_3$, 25 °C, 4 h; iv) TFA, $CHCl_3$, overnight. Experimental procedures can be found in the ESI†.

We investigated the ring location over the thread in rotaxane **6a**. The comparison of the $^1$H NMR spectra of thread **4** and rotaxane **6a** recorded in $CDCl_3$ showed that the signals of the pyridine ring ($H_d$, $H_e$ and $H_f$, see lettering in Scheme 1), are shifted to higher field in **6a** as a result of the binding with the benzylic amide macrocycle. However, the magnitude of this shifting is slightly smaller (see ESI†, Table S1) than in other DAP-based rotaxanes[14] pointing out that the ring could be rather interacting with other hydrogen bonding motifs of the thread. Indeed, the nearby of the five-membered ring to the encircled DAP unit of **6a** causes the concomitant shifting of the $^1$H NMR signals of the pyrrolidine core indicating that the macrocycle also keeps close to the active site, structurally defining a dynamic chiral pocket.

The DAP function is able to interact with neutral molecules, such as barbiturates, flavins or thymine derivatives, via a recognition process by forming a complementary DAD–ADA hydrogen bonding network.[20] At this point, we reasoned that the DAP unit in **6** could enable the formation of a supramolecular complex with a suitable guest inducing the translation of the ring to the proline ester frame (see Fig 2). In this regard, we next explored the ability of rotaxanes **6** to interact with *N*-hexylthymine (**T**) by calculating the association constant of the formed 1:1 complex.[14a] We probed that the presence of this cofactor is able to compete with the ring for the DAP unit at the thread. Titration $^1$H NMR experiments ($CD_2Cl_2$, 298 K) showed that **6a,b** are able to bind **T** with similar association constants of ~ 20 $M^{-1}$ through the DAP unit (see ESI†, Fig. S2-5). For further proving this weak association we carried out $^1$H PGSE (Pulsed Gradient Spin Echo) diffusion measurements on solutions of **T** and **6b** in $CDCl_3$ at 298 K, revealing a 8% decrease of the D coefficient of the thymine derivative as a consequence of its complexation with the rotaxane (see ESI†, Tables S7-8).

Note that the association constants of **6·T** are lower than in other reported similar complexes[14] being the proline fragment

the only differential structural fragment. For further information, we computed the **6a·T'** (with T' = $N^1$-methylthymine) supramolecular aggregate at DFT level (Figure 2) in which the ring simultaneously interacts with the ester and the amino group of the pyrrolidine core (see ESI†). The formation of only two out of three possible H-bonds between the DAP and a thymine units, probably to favour aromatics interactions with the nearby diphenylmethyl stopper, gives also account of the moderate strength of this interaction. It must be noted that the estimated magnitude of the association constanta of **6·T** are in the same order to that obtained for the free thread **4** (22 $M^{-1}$) (see ESI†, Fig S6-7), reinforcing the idea of the disturbing effect of the proximal five-membered ring to the H-Bonding DAD array.

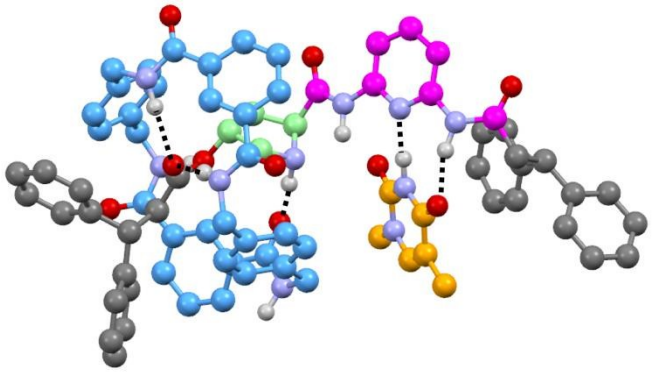
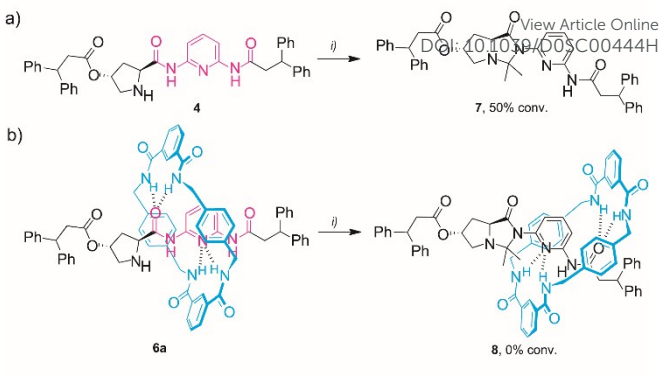


**Fig. 2** Computed minimum-energy co-conformer of the supramolecular complex **6a·T'** (with T' = $N^1$-methylthymine) at the M06/cc-pVDZ theoretical level.

### 2.2 Background reactivity of the thread 4 and rotaxane 6a in the presence of acetone

A characteristic scenario found in enamine-type transformations catalysed by pyrrolidine-based systems is the catalyst deactivation due to undesirable side reactions. The formation of cyclic species obtained by the intramolecular attack of the corresponding enamine to various side groups of the catalyst, such as secondary amides or carboxyl groups, is often reported.[21] The presence of such relatively stable species generally result in a decreasing of the reaction rate (low conversion) and selectivity (low e. r.). This is why, we monitored the stability of thread **4** and rotaxane **6a** in the presence of an excess of acetone (Scheme 2). We found that after 48 h, around 50% of the thread **4** was consumed, affording the cyclic imidazolidone **7** (Scheme 2a and Figure S8). Importantly, compound **7**, easily isolable and characterised by HRMS (ESI+), showed a moderate stability in solution. After 72 h in $CDCl_3$ at room temperature, 70% conversion of **7** into the initial thread **4** was observed, releasing free acetone (ESI†, Fig. S9). In stark contrast, rotaxane **6a** remained completely unaffected when submitted to the same reaction conditions as the mechanical bond precludes the formation of the undesired cyclic byproduct **8** (Scheme 2b).




**Scheme 2** Formation of the imidazolidone derivative of: a) thread **4**; b) rotaxane **6a**. Reaction conditions: i) acetone (20 equiv.), $CDCl_3$ (0.025 M), 25 °C, 2 days. Full experimental procedures can be found in the ESI†.

### 2.3 Catalytic activity of the interlocked prolinamides

Once the DAP-based rotaxanes **6** were assembled, we decided to explore their aptitude as organocatalysts by comparing its activity with that of the free thread **4**. For this study we chose three enamine-type transformations: aldol reactions between acetone and *p*-nitrobenzaldehyde[22] or phenylglyoxylic acid,[23] and the Michael addition of acetone to β-nitrostyrene (Fig. 3).[24] Testing the activity of *N*-hexylthymine as cofactor was also planned.

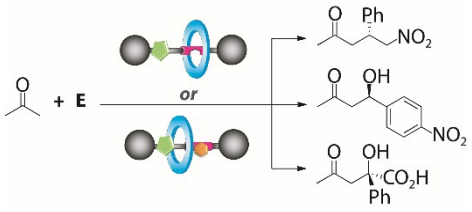



**Fig. 3** Selected enamine-type processes studied in this work.

#### 2.3.1 Asymmetric Michael addition of acetone to β-nitrostyrene

After a short optimization of the reaction conditions (see ESI†, Tables S2-3), we decided to use dichloromethane as solvent, as it should allow the establishment of intercomponent hydrogen bonds between the thread and the macrocycle, thus precluding a random ring motion in the interlocked structures. As we expected, thread **4** showed to be inactive (Table 1, entry 1). This lack of reactivity was attributed to the formation of the inactive cyclic imidazolidone **7**, which can be easily formed attending to the large molar excess of acetone (ratio acetone:**4**, 100:1). In contrast moderate conversions were achieved when rotaxanes **6a,b** were used, although affording adduct **9** in poor e.r. (Table 1, entries 2-3).

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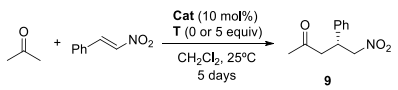
**Table 1.** Organocatalyzed Michael addition of acetone with β-nitrostyrene.[a]




| entry | cat | T | % Conv[b] | e. r.[c] |
|---|---|---|---|---|
| 1 | **4** | NO | < 5 | -:- |
| 2 | **6a** | NO | 55 | 57:43 |
| 3 | **6b** | NO | 28 | 54:46 |
| 4 | **4** | YES | 17 | 57:43 |
| 5 | **6a** | YES | 85 | 78:22 |
| 6 | **6b** | YES | 95 | 91:9 |
| 7 | - | YES | 0 | 0 |

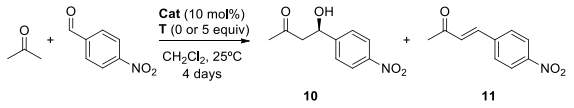
[a] Reaction conditions: acetone (0.25 mmol), β-nitrostyrene (0.025 mmol), catalyst (10 mol%), *N*-hexylthymine (0 *or* 0.125 mmol), $CH_2Cl_2$ (100 µL), 25 °C, 5 days. [b] Determined by $^1$H NMR from the crude reaction. [c] e. r. determined by HPLC using a Daicel ChiralPak AS-H column.

Interestingly, the presence of up to 5 equivalents of *N*-hexylthymine (**T**) in the reaction media positively altered the course of the process (Table 1, entries 4-6; see ESI† for further details, Table S5) whereas other complementary cofactors (barbital and non-alkylated thymine) did not promote similar pronounced changes (see ESI†, Table S4). It must be noted that the reaction carried out in the presence of **T** without catalyst was fully unproductive (Table 1, entry 7). In the case of thread **4**, a slight increase of the conversion towards adduct **9** was detected (Table 1, compare entries 1 and 4), although it was practically unselective (57:43 e.r.). Probably, the presence of **T** in the reaction media precludes the formation of **7** rising up the productivity of **4** in the formation of **9**. In contrast, the more constrained rotaxanes **6** showed both better activity and selectivity. It is important to highlight that the enhancement of the catalytic behaviour of the interlocked systems compared with the free thread is a rather uncommon effect, as the macrocycle usually inhibits or reduced the activity of the functionalities settled inside or near its cavity.[25] Note that the major reason of this overall outcome could lie on the inhibition of **4** by the substrate (see Scheme 2). Remarkably, rotaxane **6b**, with nitro groups at the macrocycle, resulted to be the best catalyst, achieving nearly full conversion and remarkably increasing the enantiomeric ratio to 91:9 e.r. of the adduct **9** instead of the poor e.r. in the absence of **T** (Table 1, compare entries 3 and 6). Note that the acidity of the amide NH protons of the macrocycle in **6b** is slightly increased by the electron-withdrawing $NO_2$ groups. In this scenario it seems reasonable that an intermolecular hydrogen-bonding interaction macrocycle-electrophile could be established, where the ring acts as a second activation site, likewise a bifunctional catalyst.[26] This performance is noteworthy: catalyst **6b**, that initially is a poorly active and completely unselective system, is converted in an enhanced supramolecular catalyst **6b·T** upon addition of the complementary cofactor. Additional control experiments (see ESI†, Table S6) carried out using as catalyst the non-interlocked macrocycle, alone or in combination with **4** and/or **T**, supported the need of the mechanical bond to obtain good activities and selectivities during the considered Michael addition.

### 2.3.2 Asymmetric aldol reaction of acetone with *p*-nitrobenzadehyde

In this reaction thread **4** displayed again extremely poor activity, showing a low conversion towards adduct **10** and moderate enantioselectivity (Table 2, entry 1), which is in agreement with the undesired but favourable formation of the imidazolidone **7**. Moreover, a high amount of enone[27] **11**, formed in the competitive condensation pathway, was also observed (ratio **10**:**11**, 50:50). Remarkably, higher conversions were obtained when the rotaxanes **6a,b** were used and, more importantly, almost avoiding the formation of the enone **11** (Table 2, entries 2-3).

**Table 2.** Organocatalyzed aldol reaction of acetone with *p*-nitrobenzaldehyde.[a]




| entry | cat | T | % Conv[b] | 10 : 11[c] | e. r.[d] |
|---|---|---|---|---|---|
| 1 | **4** | NO | 14 | 50 : 50 | 76 : 24 |
| 2 | **6a** | NO | 58 | 91 : 9 | 76 : 24 |
| 3 | **6b** | NO | 60 | 100 : 0 | 88 : 12 |
| 4 | **4** | YES | 76 | 83:17 | 62:38 |
| 6 | **6b** | YES | 78 | 91 : 9 | 70:30 |

[a] Reaction conditions: acetone (0.25 mmol), *p*-nitrobenzaldehyde (0.025 mmol), catalyst (10 mol%), *N*-hexylthymine (0 *or* 0.125 mmol), $CH_2Cl_2$ (100 µL), 25 °C, 4 days. [b] Determined by $^1$H NMR from the crude reaction. [c] Ratio **10**:**11** was determined by $^1$H NMR analysis. [d] e. r. determined by HPLC using a Daicel ChiralPak AS-H column.

As in prior results, the nitro-containing rotaxane **6b** was the best catalyst, improving the conversion to adduct **10** (60%), the chemoselectivity (enone **11** was not detected) and the enantioselectivity (88:12 e. r.) of the process (Table 2, entry 3). The presence of the mechanical bond apparently creates a well-defined chiral environment where the enamine intermediate is located, inside which the new C-C bond forming reaction occurs, generating enantioenriched products with higher selectivities.

In this transformation the addition of thymine as cofactor was unfruitful, lowering the enantiomeric ratios, although displaying a slight increase of the conversion (Table 2, entries 4-6). Apparently, in this reaction the activating interaction macrocycle-electrophile is better stablished in the initial rotaxane than in the thymine-cofactoring state.

### 2.3.3 Asymmetric aldol reaction of acetone with phenylglyoxylic acid

Finally, thread **4** and rotaxanes **6** showed to be highly active catalysing this second aldol reaction (Table 3, entries 1-3). The great activity showed by thread **4** in this case could probably be explained by the establishment of hydrogen-bonded interactions between the acid group of the electrophile and the basic nitrogen atom of the pyridine.[23a,28]

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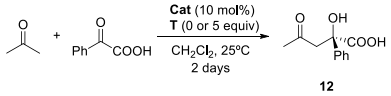
As in previous examples, the selectivity showed by thread **4** was lower than those shown by the constrained rotaxanes, again rotaxane **6b** giving the best results (almost full conversion and a high 92:8 e.r. for aldol **12** after 48 hours). When thymine **T** is present the e. r. decreased (Table 3, entry 5).

**Table 3.** Organocatalyzed aldol reaction of acetone with phenylglyoxylic acid.[a]



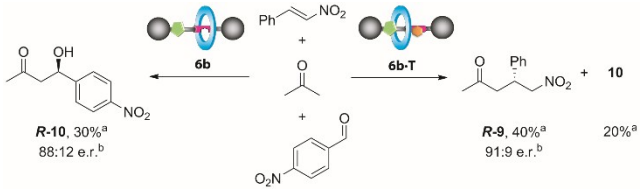

12

| entry | cat | T | % Conv[b] | e.r.[d] |
|---|---|---|---|---|
| 1 | **4** | NO | 93 | 75:25 |
| 2 | **6a** | NO | 54 | 89:11 |
| 3 | **6b** | NO | 85 | 92:8 |
| 4 | **4** | YES | 100 | 60:40 |
| 5 | **6b** | YES | 38 | 72:28 |

[a] Reaction conditions: acetone (0.25 mmol), phenylglyoxylic acid (0.025 mmol), catalyst (10 mol%), *N*-hexylthymine (0 *or* 0.125 mmol), $CH_2Cl_2$ (100 µL), 25 °C, 2 days. [b] Determined by $^1$H NMR from the crude reaction. [d] e. r. determined by HPLC using a Daicel ChiralPak AS-H column. For analytic reasons, the adduct **12** was derivatized to its methyl ester (ESI†).

### 2.4 Exploring the activity of the catalyst 6b in competitive experiments

Catalyst **6b** clearly works under two different regimes in the studied processes, either uncomplexed or complexed with *N*-hexylthymine forming the supramolecular interlocked catalyst **6b·T**. Thus, we envisioned that the addition or not of the cofactor **T** could influence on the distribution rate between the final adducts when two electrophiles are simultaneously present. Therefore, we carried out competitive experiments by adding *p*-nitrobenzaldehyde (1 equiv.) and β-nitrostyrene (1 equiv.) to acetone (1.5 equiv.) in the presence of catalyst **6b** (10 mol%), with or without **T** (Scheme 3).




**Scheme 3** Michael *versus* aldol addition of acetone using rotaxane **6b** as catalyst in the presence or not of *N*-hexylthymine (**T**). Reaction conditions: *p*-nitrobenzaldehyde (1 equiv.), *trans*-β-nitrostyrene (1 equiv.), acetone (1.5 equiv.), catalyst **6b** (10 mol%), *N*-hexylthymine (5 equiv., *if required*), $CH_2Cl_2$ (0.25 M), 25 °C, 5 days.[a] Determined by $^1$H NMR from the crude reaction. [b] e. r. determined by HPLC using a Daicel ChiralPak AS-H column.

After 5 days, we observed the formation of the aldol adduct **10** (30%), with only traces of the Michael adduct **9** (<5%) when **T** was not added. In contrast, the chemoselectivity become reversed in the presence of **T**, preferently forming the Michael adduct **9** (40%), (rate **9**:**10**, 2:1) (see ESI†, Figure S10). Importantly, the isolated adducts **9** and **10** maintained the enantiomeric ratios previously obtained in the individual experiments.

## 3. Conclusions

In summary, we have synthesized a series of chiral mechanically interlocked diacylaminopyridine-based prolinamides in a straightforward manner (only 4 synthetic steps). Their catalytic activity was modulated by complexation with a complementary DAD array (*N*-hexylthymine), forming a supramolecular catalyst. Importantly, the presence of the flexible and, at the same time, bulky isophthalamide ring improves the ability of the interlocked systems as catalysts if compared with the free thread, by creating a dynamic chiral pocket. As a result, the mechanical bond overrides the formation of inactive species that inhibits the catalysis, thus enhancing the overall catalytic activity of the interlocked systems. This remarkable behaviour differs from the considerably lower catalytic activity showed by previously reported rotaxane-based catalysts when compared with their non-interlocked threads. In our interlocked catalysts the benzylic amide macrocycle shows not only a shielding effect but also an activating role. The presence of electron-withdrawing groups attached to the macrocycle, which increases the acidity of the NH amide groups, is beneficial for the outcomes of the assayed reactions, usually increasing the conversion and enantioselectivities. The addition or not of an external cofactor to the reaction media allows to switch the chemoselectivity in competitive experiments. All these facts allow this versatile system to work in two dissimilar regimes, being an effective catalyst in three different enamine-type processes.

These results highlight that the employment of mechanically interlocked molecules as catalysts could open exciting paths in the field of asymmetric catalysis thus making a contribution to the design of new systems that could tackle challenging transformations.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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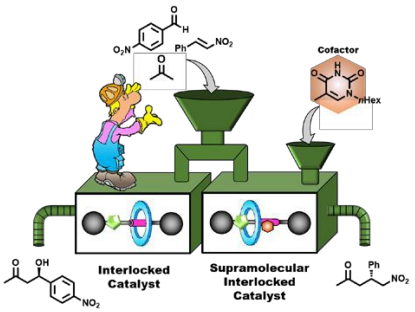


The mechanical bonding and the cofactor assembly in interlocked prolinamide-based organocatalysts upgrade enamine-type transformations by increasing their yields and enantio- and chemoselectivities.