Interlocking the Catalyst: Thread versus Rotaxane-Mediated Enantiodivergent Michael Addition of Ketones to β-Nitrostyrene.

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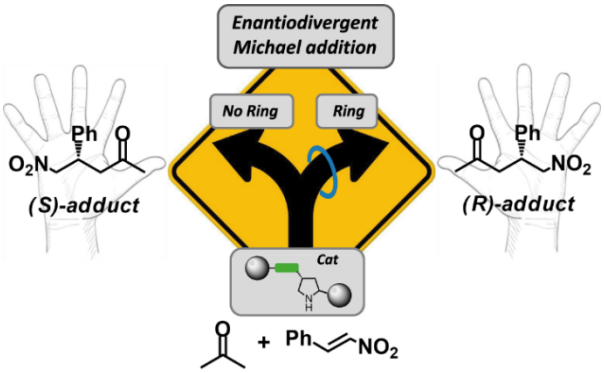
Supporting Information Placeholder



ABSTRACT: Fumaramide threads bearing one *L*-prolinamide fragment have been designed as templates for promoting the efficient formation of novel Leigh's [2]rotaxanes. Both threads and rotaxanes are shown to catalyze the asymmetric addition of ketones to β-nitrostyrene in an enantio and diastereoselective manner. Interestingly the enantioselective course of these processes is reversed simply by changing from thread to rotaxane as catalyst. DFT computations have allowed to rationalize the stereodivergence shown by the interlocked and non-interlocked catalysts.

One of the most challenging issues in asymmetric catalysis is to obtain the two possible enantiomers of the desired chiral products in a selected transformation.[1] Most of the chiral catalysts or ligands employed to access enantioenriched systems are generally obtained from natural sources as a unique enantiomer.[2] The synthesis of the alternative enantiomer of the catalyst is not an easy task, usually requiring several steps. To tackle this significant limitation, many researchers have approached to methods of enantio- and/or stereodivergent catalysis.[3] Enantiodivergent approaches involve a single enantiomer of the catalyst, which is able to catalyze a process and access both enantiomers of the desired final product just simply changing by the reaction conditions,[4] adding additives[5] or chemically tuning the catalyst structure.[6] Of particular interest is the recent design of switchable molecular machines enabled to catalyze a chemical transformation in stereodivergent fashions.[7]

In the last decades the synthesis and applications of mechanically interlocked molecules has received increased attention.[8] Owing to the particular properties that the mechanical bond endows to such systems,[9] they have become ideal candidates to be applied in different fields, remarking their use as catalysts[10] or ligands in metal-catalyzed processes.[11] Switchable rotaxane-based catalysts, able to change their catalytic activity (rate, chemoselective control, activation mode), are available.[12] Also specially selective, rigid and confined[13] interlocked systems have been designed, by which the chemo- or the enantioselectivity of a selected process is controlled and even enhanced due to the presence of the mechanical bond.[14]

Herein we describe the design and synthesis of a series of chiral prolinamide-based threads incorporating a fumaramide-ester template to allow their assembly into hydrogen-bonded [2]rotaxanes. The threads and the corresponding rotaxanes were employed as organocatalysts in the well-known asymmetric Michael addition of ketones to β-nitrostyrene,[15] aiming to detect remarkable alterations in their reactivity and/or selectivity due to the presence of the mechanical bond. Interestingly, a marked effect in the course of the process was found, enabling to obtain both possible enantiomers in an enantiodivergent approach just by picking either an interlocked or non-interlocked system as catalyst.

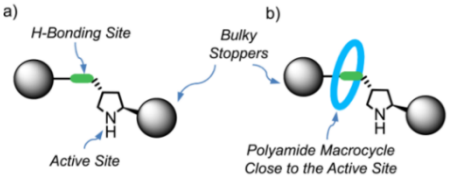
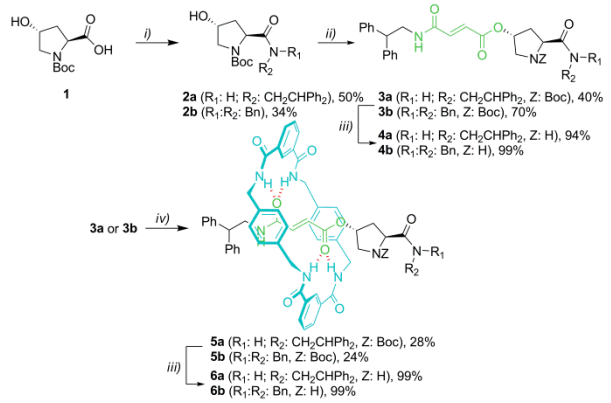


Figure 1. Catalyst design: a) Non-interlocked prolinamide as thread; b) Interlocked prolinamide with a polyamide ring.

Having in mind the elegant reported works describing the utilization of interlocked species as enhanced catalysts or ligands, especially those in which the mechanical bond participates in the stabilization of the transition states,[16] we designed a pair of interlocked prolinamides (Figure 1). These systems incorporate bulky groups at the end of their threads which avoid the disassembly of the mechanically interlocked compound. Both bear a fumaric fragment as a suitable template able to ring around the hydrogen-bonded polyamide macrocycle. The relative position of the macrocycle and the active site of the prolinamide backbone is crucial in this design. The ring should be spatially close to the catalyst active site in order to better control and stabilize the transition states of putative processes by shielding one of the two faces where the substrates can react and creating a more restricted pocket. Importantly this space should be large enough to allow the substrates interact with the prolinamide, without inhibiting the reaction or the catalyst turnover.

To approach this goal, we synthetized two prolinamide-based rotaxanes differing in the degree of substitution at the amide N atom (secondary or tertiary amide) (Scheme 1). Starting from the commercially available protected *trans*-4-hydroxy-*L*-proline **1** the synthesis of the corresponding *N*-Boc-protected threads **3a,b** was accomplished. First, an amidation reaction was carried out employing the suitable amine (2,2-diphenylethylamine for **2a** or dibenzylamine for **2b**) in the presence of the coupling system EDCI/HOBt. Then, an esterification reaction between (*E*)-4-(2,2-diphenylethylamino)-4-oxobut-2-enoic acid (**S1**) and fragments **2a**/**2b** provided the corresponding protected threads **3a,b**, which can be deprotected in the presence of TFA to afford the catalytically active threads **4a,b**.

Scheme 1. Synthesis of prolinamide-based threads 4a,b and rotaxanes 6a,b.[a]

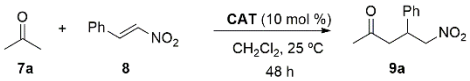


[a]Reaction conditions: *i*) EDCI, HOBt, amine (2,2-diphenylethylamine or dibenzylamine), DIPEA, CH_2Cl_2, 25 °C, overnight; *ii*) (*E*)-4-((2,2-diphenylethyl)amino)-4-oxobut-2-enoic acid (**S1**), EDCI, DMAP, CH_2Cl_2, 25 °C, overnight; *iii*) TFA, $CHCl_3$, overnight; *iv*) *p*-xylylenediamine, isophthaloyl chloride, Et_3N, $CHCl_3$, 25 °C, 4h.

Both threads **3a,b** own an amido-ester function which has been previously utilized as hydrogen-bond acceptor in the synthesis of polyamide-based rotaxanes although with a moderate templating ability.[17] The [2]rotaxanes **5a,b** were obtained in reasonable yields (24-28%) by a five-component reaction with *p*-xylylenediamine and isophthaloyl chloride in the presence of Et_3N (see Supporting Information). Finally, Boc deprotection of compounds **5a-b** in the presence of TFA yielded the prolinamide-based rotaxanes **6a-b** quantitatively. An exhaustive ^{1}H NMR analysis of thread **4a** and rotaxane **6a** allowed us to acquire a precise idea about the relative position of the macrocycle along the thread (Fig. S1). By comparison with reported examples,[18] the displacement of the proton signals of the thread after rotaxanation indicates that the ring is located over the fumaramide binding unit. In this scenario, the active site of the pyrrolidine core remains available to participate in asymmetric reactions catalyzed by the cyclic secondary amine. The photoisomerization of **6a** afforded the maleamide-based system *Z*-**6a** enabling its use as catalyst (see SI for further details).

At this point we were intrigued by the behavior of our systems[19] as chiral catalysts in the asymmetric Michael addition of different ketones **7** to β-nitrostyrene **8**. Initially, we assayed dichloromethane as non-competitive solvent, in which the hydrogen-bonding network between the thread and the macrocycle in the interlocked systems should remain intact. The presence of an acid as additive,[20] commonly employed in this enamine-mediated transformations, other solvents and temperature were also tested (see Tables S1-S4). Thus, we assayed the reaction between acetone **7a** and β-nitrostyrene **8** in the presence of catalytic amounts (10 mol %) of the corresponding threads **4** and rotaxanes **6** (Table 1). Thread **4b** and rotaxane **6b** having a tertiary amide attached to the pyrrolidine core notably showed higher activities when compared with **4a** and **6a** (with a secondary amide attached to the pyrrolidine core), obtaining 100% conversion to the Michael adduct **9a** in 2 days (Table 1, compare entries 1-2 and 3-4).

Table 1. Asymmetric Michael reaction between acetone 7a and β-nitrostyrene 8.[a]



Entry	Catalyst	Conversion (%)[b]	e. r.[c]	Config.
1	**4a**	59	**69**:31	*S*
2	**6a**	57	26:**74**	*R*
3	**4b**	100	**75**:25	*S*
4	**6b**	100	29:**71**	*R*
5[d]	**4b**	100	**72**:28	*S*
6[d]	**6b**	100	27:**73**	*R*
7	**5b**	0	-	-

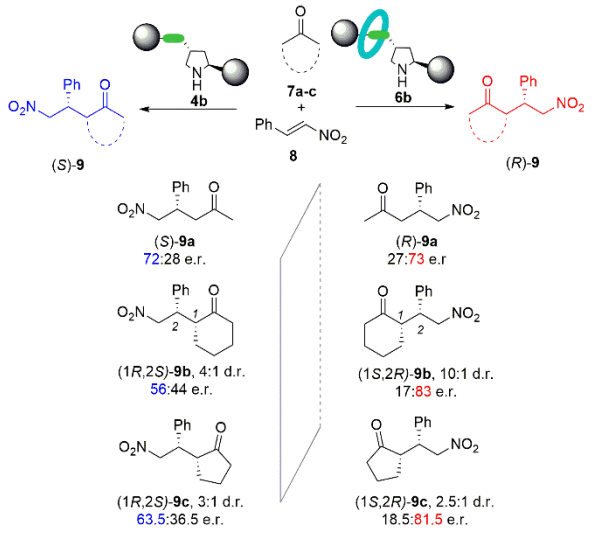
[a]Reaction conditions: nitrostyrene **8** (0.025 mmol), acetone **7a** (0.25 mmol), CH_2Cl_2 (100 μL) and catalyst (10 mol %) were stirred at 25 °C for 48 h. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC. [d]Reaction conducted in the presence of 10 mol % of *p*-nitrobenzoic acid.

The lower conversions obtained with the systems **4a** and **6a** could be due to the formation of a stable imidazolidinone

intermediate by reaction of the enamine with the nitrogen of the pendant amide group, dramatically slowing down the reaction rates.[19] The use of *p*-nitrobenzoic acid as additive slightly increases the e. r. when **6b** is employed (Table 1, entry 6). As we expected, the reaction with the Boc-protected **5b** was unproductive, further proving the active participation of the secondary amine as catalytic site in the deprotected systems (Table 1, entry 7).

The results obtained for acetone **7a** were extended to the use of cyclic ketones **7**, which are prochiral and thus lead to the formation of a second stereocenter in the process. The conjugate additions of cyclohexanone **7b** and cyclopentanone **7c** afforded the corresponding *syn* diastereoisomers as main products regardless of the catalyst employed, although in different diastereomeric ratios (Scheme 2). In the case of adduct **9b** the diastereoselectivity increased when the interlocked **6b** was the catalyst if compared with the unthreaded **4b** (Scheme 2, **6b**, 10:1 *vs* **4b**, 4:1 *d.r.*). In contrast the *d.r.* was almost not affected by the presence of the mechanical bond when cyclopentanone **7c** was used. More importantly, as initially occurred for adduct **9a**, we were able to obtain the two enantiomerically enriched *syn* diastereoisomers **9b-c** as major byproducts just by rotaxanation of the catalyst. To the best of our knowledge this is the first time that the presence or not of the mechanical bond at a catalyst backbone is able to control the enantioselective course of a process by accessing both enantiomers in an enantiodivergent fashion.

Scheme 2. Enantiodivergent Michael reaction of ketones 7a-c with β-nitrostyrene 8.[a-c]



[a]Reaction conditions: nitrostyrene **8** (0.025 mmol), ketone **7a-c** (0.25 mmol), CH_2Cl_2 (100 µL), *p*-nitrobenzoic acid (10 mol %) and catalyst **4b** or **6b** (10 mol %) were stirred at 25 °C for 48 h (complete conversion). [b]Diastereomeric ratio (*syn*:*anti*) determined by ^{1}H NMR. [c]Enantiomeric ratio of the *syn* diastereoisomer (major) determined by chiral HPLC.

In order to rationalize the stereodivergence shown by the interlocked and non-interlocked catalysts and its enantioselective outcomes, we performed a DFT study of the reactions using acetone (**7a**) as carbonyl reactant. For computational efficiency, we used as simplified models the enamine intermediates **4c'** and **6c'** in which methyl groups replace the stoppers of the experimental systems (Figure 2). The transition structures for the *Si*- and *Re*-attack of both thread-enamine **4c'** and rotaxane-enamine **6c'** over the two prochiral faces of (*E*)-β-nitrostyrene (**8**) were computed at PCM(dichloromethane)/wB97XD/cc-pVDZ theoretical level (Supp. Info.). The $TS_{4c'\cdot Si8}$ transition state for the addition of **4c'** to the *Si*-face of the nitrostyrene, leading to adduct (*S*)-**9a** was computed to be 7.0 kJ/mol lower in energy than $TS_{4c'\cdot Re8}$ leading to (*R*)-**9a** (*Re*-attack) (Figure 2a). The establishment of a hydrogen bond between the amide NH group and the nitro group (1.99 Å) stabilizes both TS structures bringing near the electrostatically complementary enamine and nitro N atoms ($d_{N\text{-}N}$ = 3.84 and 3.87 Å for $TS_{4c'\cdot Si8}$ and $TS_{4c'\cdot Re8}$, respectively). The *gauche* orientation between the phenyl group of the nitrostyrene and the double bond of the enamine moiety (Φ = -57.3°) in $TS_{4c'\cdot Si8}$ favours an optimal trajectory of the reactants[22] with a newly forming C-C bond distance *d* = 2.2 Å and following a Bürgi-Dunitz trajectory of θ = 107.5° very close to the ideal one.[23] In contrast, the *antiperiplanar* conformation (Φ = +2.0°) of $TS_{4c'\cdot Re8}$ showing a new forming C-C bond distance d = 2.00 Å counts with an approaching trajectory of the reactants θ = 114.4° far away from the optimal one.

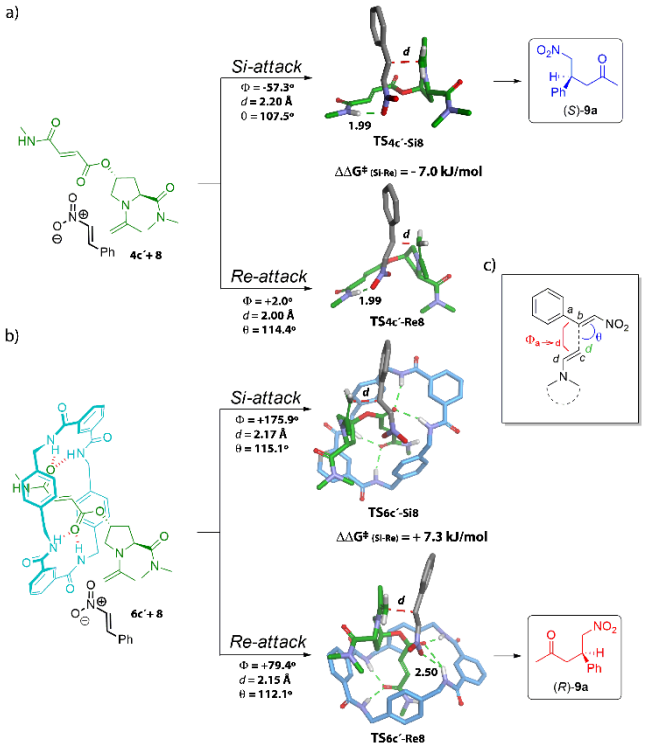


Figure 2. Nucleophilic attack of the enamine of: a) thread **4c'**; and b) rotaxane **6c'**, to the (*E*)-β-nitrostyrene (**8**). Energy differences, $\Delta\Delta G^{\ddagger}_{(Si\text{-}Re)}$, between the two respective TSs are shown in kJ/mol. Distances and angles are shown in Å and deg (°), respectively. c) Definition of *d*, θ and Φ.

With rotaxane **6c'** as catalyst, the addition over the *Re*-face of nitrostyrene is preferred by 7.3 kJ/mol with respect to the *Si*-attack (Figure 2b). This preference is mainly attributed to the NH···ONO hydrogen bond established in the *gauche* conformation (Φ = +79.4°) of $TS_{6c'\cdot Re8}$, involving now *one NH group of the ring*, which preorganizes the nucleophile-electrophile pairing ($d_{N\text{-}N}$ = 3.49 Å). In this structure, the length of newly forming C-C bond *d* = 2.15 Å and the approaching angle θ = 112.1° are close to the ideal ones. In stark contrast, *no hydrogen bonds* linking both reactants are

present in the computed TS for the *Si*-attack $TS_{\mathbf{6c'\cdot Si8}}$, showing an *antiperiplanar* orientation between the phenyl and enamine motifs (Φ = +175.9°), a d = 2.17 Å newly forming C-C bond distance and a θ = 115.1° approaching trajectory.

In conclusion, we have synthesized a series of interlocked and non-interlocked prolinamides and evaluated their catalytic activity in the Michael reaction between different ketones and β-nitrostyrene. Interestingly, the mechanical bond deeply affects the enantiocontrol of the process allowing an enantiodivergent synthesis of γ-nitroketones. Starting from the same chiral prolinamide backbone both enantiomers of the final products were accessed just by selecting the interlocked or non-interlocked catalysts. A DFT study shows that with the rotaxanes as catalysts, the macrocycle plays a crucial role by establishing a hydrogen bond with the electrophile in the TS thus favoring the attack of the nucleophile to the *Si* face of the nitrostyrene. By contrary, when the nude threads were employed the enantioselective courses of these processes are reversed as result of a different hydrogen bond between both reactants now involving the NH group of the thread. These examples could hopefully help to the future design of new interlocked catalysts by placing anchoring units for reactants in thread and ring, by mean of which the mechanical bond could be further exploited in the field of asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, NMR spectra, computational details and HPLC traces are available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest..

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