Stereocontrol in the Synthesis of β-Lactams Arising from the Interlocked Structure of Benzylfumaramide-Based Hydrogen-Bonded [2]Rotaxanes

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Abstract: β-Lactams are highly valuable compounds due to their antibiotic activity. Among the number of well-established methodologies for building this privileged scaffold, our research group settled on a novel synthetic approach for their preparation. This Account focuses on our latest progress in the synthesis of these compounds through a novel base-promoted intramolecular cyclization of benzylfumaramide-based rotaxanes. The mechanical bond plays a significant role in the process by activating the cyclization inside the macrocycle void, avoiding the formation of by-products and fully controlling the diastereoselectivity. Further investigations on this transformation led to the formation of enantioenriched 2-azetidinones. The cyclization of enantiopure interlocked α-methylbenzylfumaramides allows the formation of two new stereogenic centers in the lactamic four-member ring, one of them a quaternary carbon, keeping the initial configuration of the chiral group of the starting material.

Key words: Mechanical Bonding, Cyclization, Stereoselectivity, β-lactams, Macrocycles

1 Introduction

1.1 Mechanically Interlocked Molecules and Applications

Mechanically interlocked molecules (MIMs) have attracted enormous attention from the scientific community over the last decades.[1] Among the different types of MIMs rotaxanes are privileged scaffolds formed by at least one macrocycle that encircles a thread with bulky groups at its ends.[2] In these compounds the mechanical bond limits the relative motions of the entwined components.[3] This feature has been exploited, for instance, in the building of rotaxane-based switches in which the translational ring motion can be controlled by external stimuli.[4] This control has also allowed the design of functional molecular systems, such as sensors,[5] responsive materials,[6] or drug delivery systems,[7] among others. The precise organization and control of the interlocked components are important aims in the building of artificial molecular machinery. The relevance of this fascinating area was rewarded by the Royal Swedish Academic of Science with the Nobel Prize of Chemistry 2016 to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa for "*the design and synthesis of molecular machines*".[8]

Nowadays the development of applications of mechanically interlocked systems in several scientific areas is being vigorously studied, underlining their current use in catalysis,[9] a field that is growing but still with a limited number of reported examples to date. Diverse approaches have been explored, such as the use of interlocked systems as ligands in metal-catalyzed processes[10] or as organocatalysts themselves.[11] Most of the examples are based on the ability of the systems in modulating/switching their catalytic activity as a response to an external stimulus, due to the change of the relative position of the sterically demanding macrocycle.

1.2 Chemical Stabilization of the Mechanical Bond

One of the most common effects of the mechanical bond observed in rotaxanes lies on the kinetic stabilization of the threaded functionalities when they are located inside the macrocyclic cavity.[12] Due to the steric hindrance exerted by the surrounding mechanically linked macrocycle these functions are shielded, decreasing their reaction rates in different transformations, or even precluding them (Figure 1). This effect is a great advantage if the functionality is unstable or very reactive.[13] By taking advantage of this stabilization of the encapsulated functionalities different applications have been developed. As an example the encapsulation of azo- and cyanine-derived dyes enhanced their stability to environmental degradation pathways, increasing at the same time their fluorescence.[14] Smith and co-workers have also demonstrated that squaraine dyes, systems unstable under biological conditions, were stabilized by an

interlocked polyamide macrocycle and maintain their high fluorescence in the deep red and near infrared.[15]

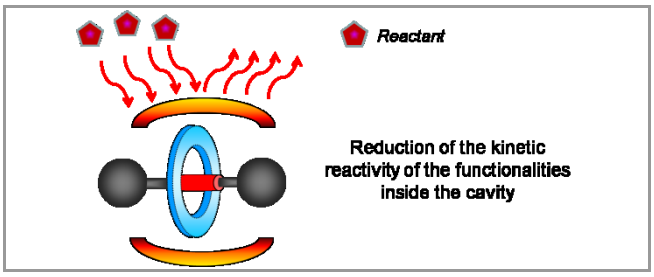


Figure 1 Common mechanical bond stabilization of the functionalities inside the macrocycle void in [2]rotaxanes.

2 Literature Methods for 4-*Exo-trig* Ring Closures of Benzylfumaramides for the Synthesis of β-Lactams

β-Lactams are highly valuable compounds containing a unique scaffold responsible of its bioactivity.[16] Since the discovery of penicillin, which contains an azetidin-2-one backbone, and its extended use in medicine as an antibiotic drug, many researchers have been stimulated to synthesize and study these four-membered heterocycles and surrogates (Figure 2).[17]

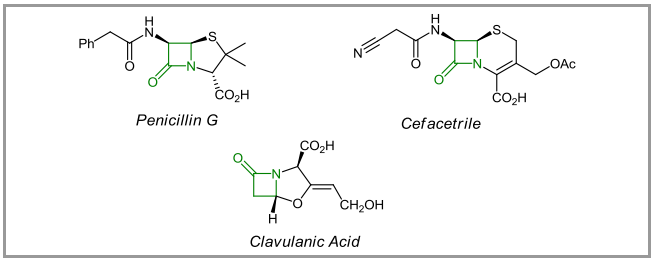
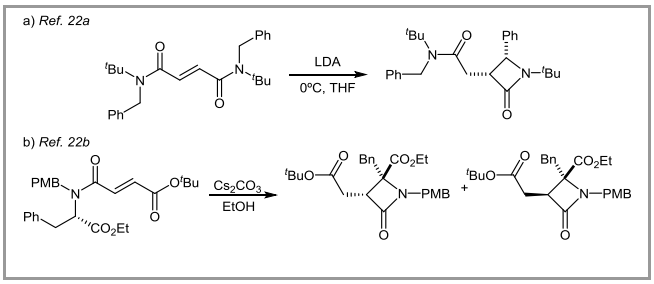


Figure 2 Selected examples of antibiotics containing a β-lactam core (in green).

One the most employed and straightforward method for β-lactam preparation is the Staudinger reaction, having the huge advantage of the use of readily available starting materials.[18] A much less-extended approach to access 2-azetidinones is based on the 4-exo-*trig* intramolecular cyclization of benzylfumaramides.[19] Clayden *et. al* reported a cyclization of benzylfumaramides to solely afford the corresponding *cis*-β-lactams following a lithium-mediated process (Scheme 1a). Some years after Kawabata described an intramolecular addition of axially chiral enolates, generated from amino acids, to provide a *cis* and *trans* mixture of β-lactams in an enantioselective fashion (Scheme 1b).



Scheme 1 Reported synthesis of β-lactams through 4-exo-*trig* cyclizations of benzylfumaramides.

3 Our First Encounter with Interlocked β-Lactams

3.1 An Unexpected Result in our Laboratory

During our research program in the synthesis and application of hydrogen-bonded (HB) [2]rotaxanes having the Leigh's tetraamide ring[20] we serendipitously found an interesting reactivity of a benzylfumaramide axis. A simple polyamide macrocycle allowed not only a cyclization inside its void to proceed, but also enhanced its reaction rate, a rather unusual event in HB rotaxanes (Figure 3).[21a]

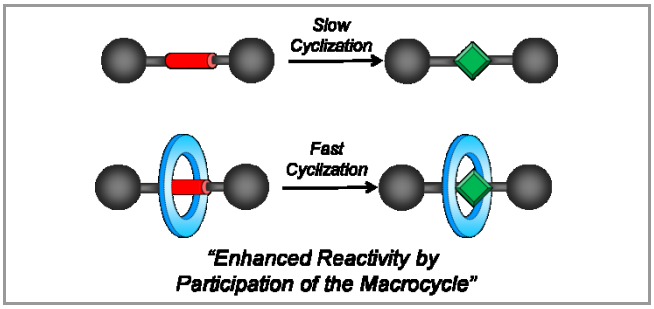
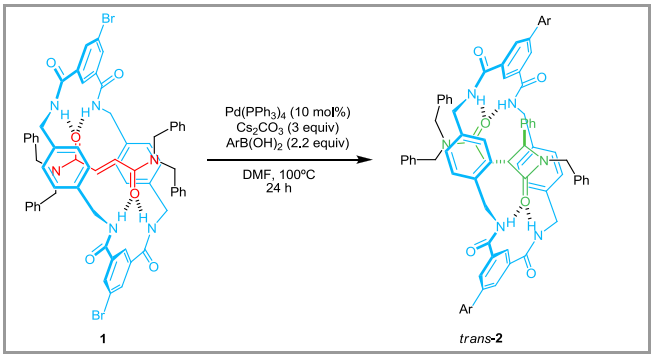


Figure 3 Enhancement of the reactivity of interlocked functionalities activated by a polyamide macrocycle in [2]rotaxanes.

Our initial findings were discovered during the derivatization of the macrocyclic counterpart via palladium-catalyzed cross-coupling reactions (Scheme 2). The presence of bromo substituents at the 5-position of the isophthalamide units of the ring in the fumaramide-based rotaxane **1** would allow a straightforward arylation reaction with arylboronic acids or esters following a Suzuki-Miyaura protocol. Among the broad range of catalytic conditions reported in bibliography for these processes[22] we initially assayed this transformation employing catalytic amounts of $Pd(PPh_3)_4$ as palladium source, cesium carbonate as base and the suitable boronic acid/ester in DMF at a temperature of 100 ºC for 24 hours. Surprisingly not only the expected cross-coupling process occurred, but also we observed a complete vanishing of the initial fumaramide double bond when the product was analyzed by ^{1}H NMR

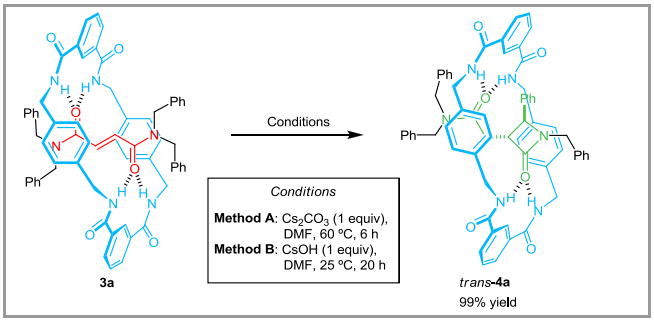
spectroscopy. A deeper NMR study and a structural elucidation of one of the final products **2** by X-ray diffraction analysis revealed the formation of an azetidinone core inside the macrocyclic void. Moreover, these transformations proceeded quantitatively and in a total diastereocontrolled manner, only yielding the *trans* isomers. The efficiency of this ring-closure from a fumaramide derivative and the scarce number of related reactions in the chemical literature[19] prompted us to further explore this process.



Scheme 2 Initial conditions for the one-step protocol Suzuki cross-coupling reaction and intramolecular cyclization of rotaxane **1**

3.2 Finding the Optimal Reaction Conditions

Having obtained this captivating preliminary result, we were intrigued by this diastereoselective intramolecular cyclization reaction that occurred inside the macrocyclic counterpart. In order to reveal how this process takes place we started by discarding some components from the catalytic system. In fact, the base (Cs_2CO_3, 1 equivalent) is the sole reactant needed for efficiently promoting the desired cyclization process employing the rotaxane **3a** as model substrate, analogue to compound **1** but without the bromo substituents (Scheme 3). The reaction proceeds at lower temperatures (60 ºC), entailing the full conversion to the interlocked lactam *trans*-**4a** as a single diastereoisomer in a short period of time (Scheme 3, Method A).



Scheme 3 Base-promoted intramolecular cyclization of model rotaxane **3a**

X-ray analysis of a single crystal of **4a** confirmed its interlocked structure and the *trans* configuration of the azetidinone ring (Figure 4). The hydrogen-bonding interactions between the new thread and the macrocycle, as a result of three intramolecular hydrogen bonds, can also be seen.

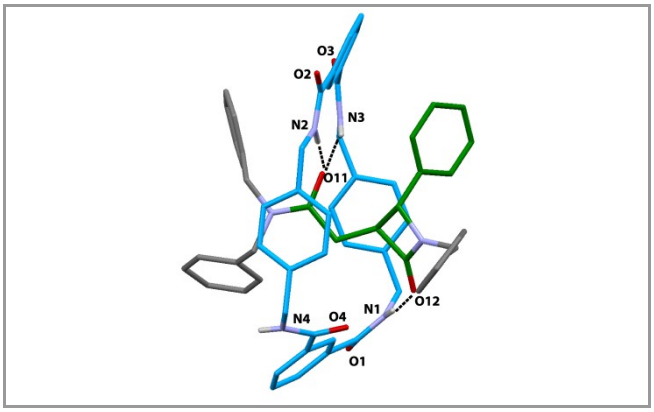


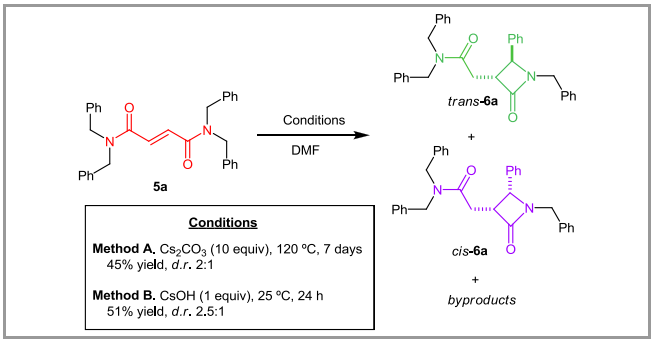
Figure 4 X-ray structure of the [2]rotaxane *trans*-**4a**. Intramolecular hydrogen bond lengths [Å] (and angles [deg]): O11HN2, 2.42 (161.6); O11HN3, 2.23 (176.0); O12HN1, 1.85 (166.3)

We screened a wide range of solvents and bases. Only highly polar solvents, such as DMF or DMSO, were suitable for this transformation. Interestingly other carbonates (Na_2CO_3 or K_2CO_3) under identical conditions did not promote the cyclization. The higher solubility exhibited by the cesium base should be in the root of this result. Stronger bases such as hydroxides (NaOH, KOH or CsOH) also induced the cyclization even at room temperature, in less than 6 hours and in quantitative yield (Scheme 3, Method B). At this point CsOH was selected as base for the study of the scope of this transformation. It is important to mention that this process also occurs in the presence of catalytic amounts of base (CsOH or Cs_2CO_3), although longer reaction times and temperatures are required to achieve good conversions.

3.3 Elucidating the Effects of the Mechanical Bond

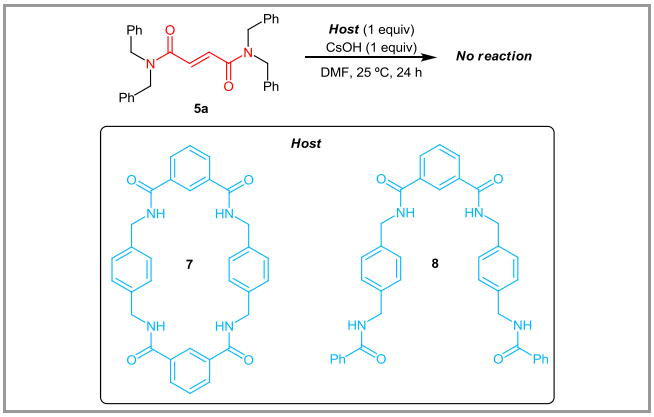
Once the optimal reaction conditions were settled, we wondered what would be the reactivity of the reactivity of the unthreaded tetrabenzylfumaramide **5a** in comparison with that of **3a** (Scheme 4). We observed a complete lack of reactivity of **5a** versus Cs_2CO_3 at 60 ºC. Higher temperatures, longer reaction times and a large excess of base were required to achieve a moderate conversion of this fumaramide, giving rise to a complex mixture of *trans* and *cis* lactams **6a** in low yield together with a number of byproducts (Scheme 4, Method A). The use of CsOH as base triggered the desired cyclization of thread **5a** at room temperature, although a longer period of time was required when compared with rotaxane **3a**. Again

a mixture of diastereoisomers of **6a** was obtained along with some byproducts (*d.r.* 2.5:1, *trans:cis*) (Scheme 4, Method B).



Scheme 4 Base-promoted intramolecular cyclization of thread **5a** under two different conditions (A or B)

To further study the effect of the mechanical bond in this transformation we decided to carry out the cyclization of the free thread **5a** in the presence of different polyamide derivatives that could act as hosts or receptors (Scheme 5). Thus, we tested the non-interlocked macrocycle **7** and its opened surrogate **8**, both of which could competitively interact with the thread by hydrogen bonding, potentially altering the course of the process. When submitted both independent experiments under the optimal conditions we did not observed any transformation, recovering the initial thread **5a** without modification. We explained these results by the fact that the base is probably reacting with the most acidic hydrogens, i.e. the hydrogen of the amide functions of receptors **7** and **8**, quenching it and preventing any further deprotonation of the benzyl groups. In fact, the addition of 5 equivalents of CsOH drives the formation of a nearly equal distribution of *trans* and *cis* lactams **6a** observed before (Scheme 4), confirming this hypothesis.



Scheme 5 Base-promoted intramolecular cyclization of thread **5a** in the presence of polyamide hosts.

The presence of the mechanical bond in rotaxane **3a** is thus the origin of its enhanced reactivity towards the formation of the new azetidinone skeleton in the presence of base. A series of significant effects over the reactivity are observed when the macrocycle encircled the fumaramide thread:

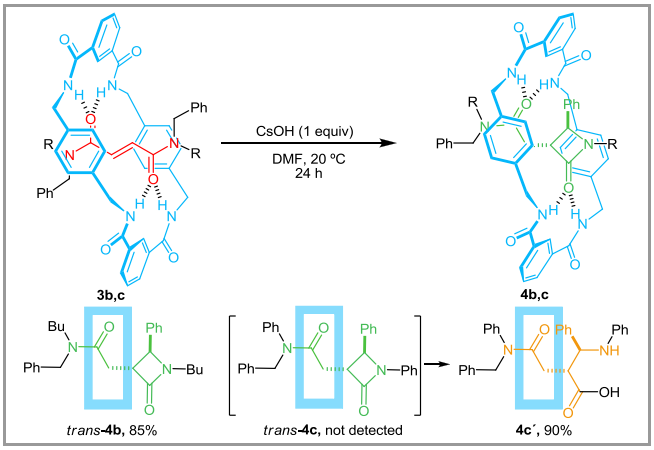
1- Acceleration of the cyclization process. There is a marked activation when the macrocycle surrounded the thread.

2- Full control of the regio- and diastereoselectivity of the final azetidinone. Starting from the interlocked system only one of the two possible diastereoisomers (*trans*) of the formed β-lactam is observed. In contrast mixture of the *cis* and *trans* isomers are detected when the free thread is employed.

3- Protection of the lactam moiety against decomposition, which is unstable in basic media. The macrocycle notably reduces the chemical reactivity of the lactam core, which is very reactive in basic media towards hydrolysis.

4 Diastereoselective Synthesis of Interlocked and non-Interlocked β-Lactams

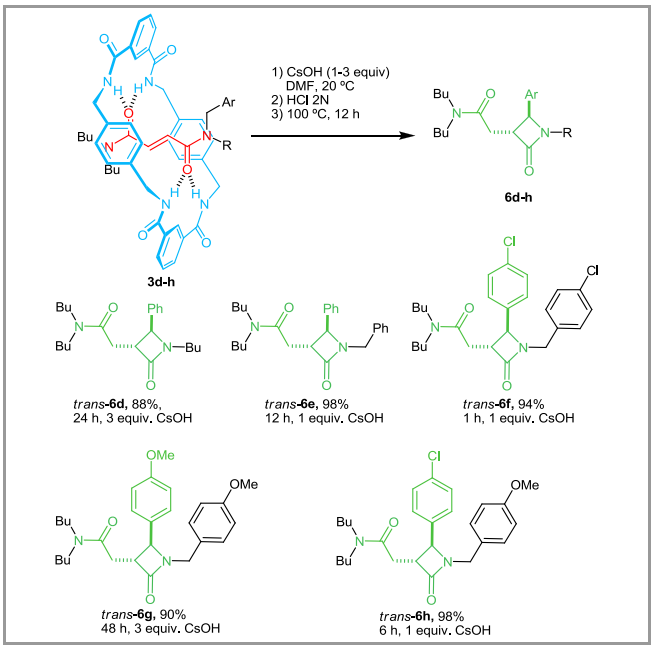
The base-catalyzed cyclization of interlocked fumaramides was expanded to other starting materials by varying the groups attached at the ends of the threads. CsOH was selected as base due to its higher activity, being able to carry out this process at room temperature. Only one benzyl group is required to obtain the desired products. Thus, rotaxanes **3b** and **3c**, having butyl or phenyl groups at both nitrogens, respectively, were fully converted into the corresponding *trans* lactams **4b-c** (Scheme 6). In the case of rotaxane **3c**, with a *N*-phenyl substituent, the expected lactam *trans*-**4c** could not be isolated. Instead the interlocked 3-(phenylamino)propanoic acid derivative **4c'** resulting from the lactam ring opening[23] was identified.



Scheme 6 CsOH-promoted intramolecular cyclization of rotaxanes **3b-c**. For clarity, the ring in lactams **4** is represented by a blue rectangle.

Having in mind the high interest for azetidinone derivatives, we focused our attention in carrying out this transformation with the *kinetically stable*

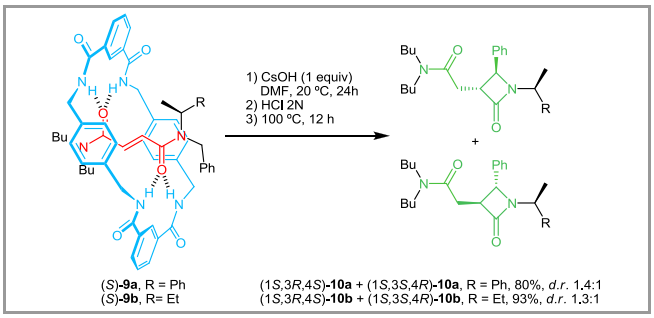
pseudorotaxanes[24] **3d-h** which, after a dethreading step,[25] would generate the liberated four-membered cyclic guest as a unique diastereoisomer (Scheme 7). With this aim a one-pot three-step procedure was carefully designed. First a CsOH-catalyzed cyclization reaction was carried out, followed by a neutralization step to avoid the decomposition of the free lactam in basic media. The subsequent thermal dethreading at high temperature (100 ºC) of the resulting reaction mixture allowed for the isolation of the non-interlocked lactams **6d-h** in high yields. This procedure allowed the presence of a wide range of substituents on the threads. One amide group was substituted with two *n*-butyl chains, having the appropriate size to provide an enough mechanical stability at room temperature and an easy dethreading under thermal conditions. The incorporation of only one benzyl group on the starting interlocked thread, as in **3d**, is enough to efficiently obtain the corresponding lactam *trans*-**6d**. However, in this later case 3 equivalents of base are required to obtain high yields thus increasing the speed of the process consequently avoiding the undesired dethreading of the starting material. Importantly the substituents on the benzyl groups drastically influence the cyclization rates. Thus electron-donating substituents, such as a methoxy group at the *para* position of the benzyl group (in **3g**), slowed down the process, whereas an inductively electron-withdrawing one, such as chloro (in **3f**), speeded it up, achieving a complete conversion in less than one hour. Interestingly, when both different substituted benzyl groups (with chloro and methoxy subtituents) are present at same time on the interlocked fumaramide, such as in **3h**, only one of the two possible lactams (*trans*-**6h**) was obtained, the one in which the *p*-chlorobenzyl group attack the olefin and form the new C-C bond.



Scheme 7 One-pot CsOH-promoted cyclization-dethreading protocol starting from pseudorotaxanes **3d-h**

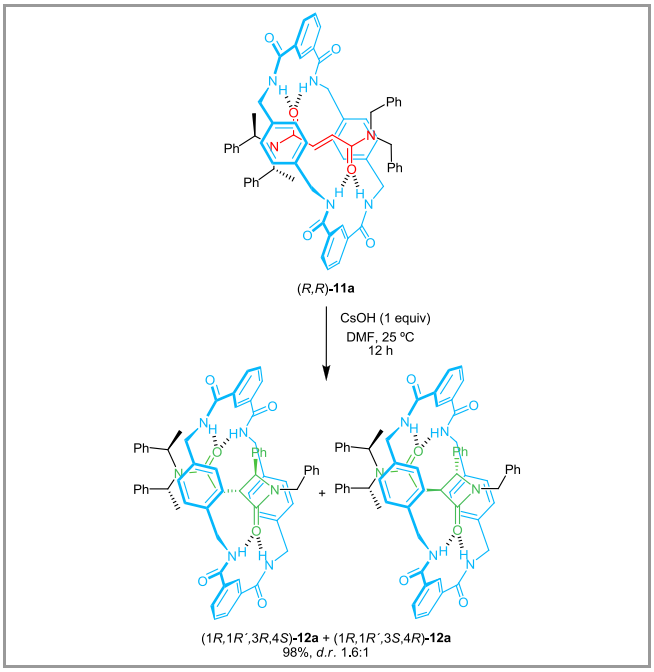
5 Asymmetric Cyclization of Enantiopure Interlocked Fumaramides

The efficiency of the CsOH-promoted cyclization of interlocked fumaramides prompted us to further explore the use of this methodology in the synthesis of enantioenriched lactams.[21b] As a first approach we envisioned that the incorporation of chiral inductors into the thread could control the configuration of the new chiral centers in the final substituted azetidinone core. Thus we synthesized the enantiopure fumaramide rotaxanes **9a,b**, having a α-(methyl)benzyl[26] and *sec*-butyl groups, respectively, as chiral inductors, connected to the same amide group bearing the benzyl group which will trigger the cyclization (Scheme 8). Unpleasantly, when submitted under the optimized one-pot protocol previously described in Scheme 7, a mixture of diastereisomeric lactams **10a,b** in a poor 1.4:1ratio was isolated. Both enantiopure lactams are *trans* and not observing the formation of *cis* derivatives. Thus the employed chiral groups are shown to be unable of efficiently controlling the diastereoselectivity of the process towards the formation of a single *trans* isomer **10**.



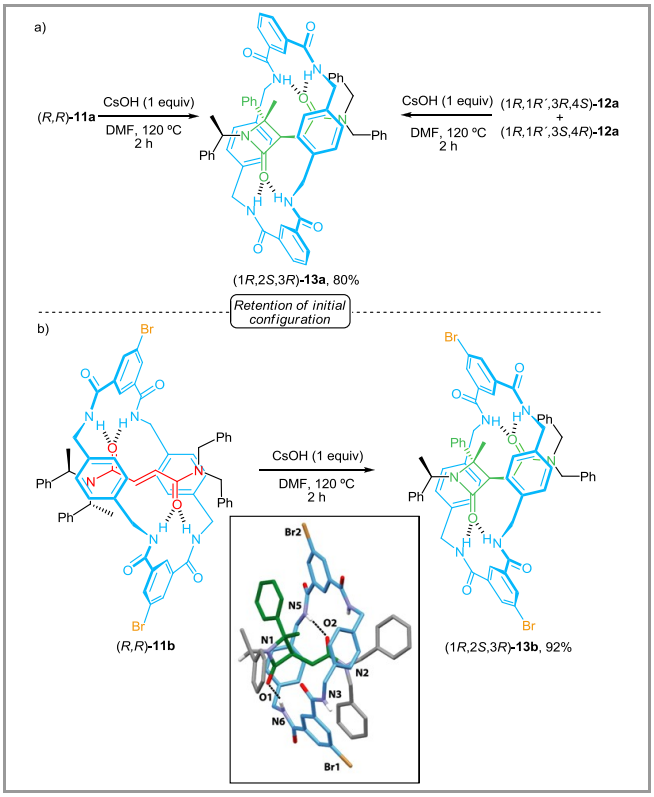
Scheme 8 One-pot CsOH-promoted cyclization-dethreading protocol for pseudorotaxanes **9a,b**

Afterwards we decided to explore the outcome of the cyclization by positioning the chiral inductors and the benzyl group on different amide groups of the substrate (Scheme 9). With this aim, the cyclization of the rotaxane (*R*,*R*)-**11a**, having a fumaramide thread with two benzyl and two α-methylbenzyl groups, was carried out. But this assay provided a mixture of *trans* diastereoisomers of the lactams **12a** still with a poor selectivity (*d.r.* 1.6:1).



Scheme 9 CsOH-promoted cyclization of rotaxanes (*R*,*R*)-**11a**

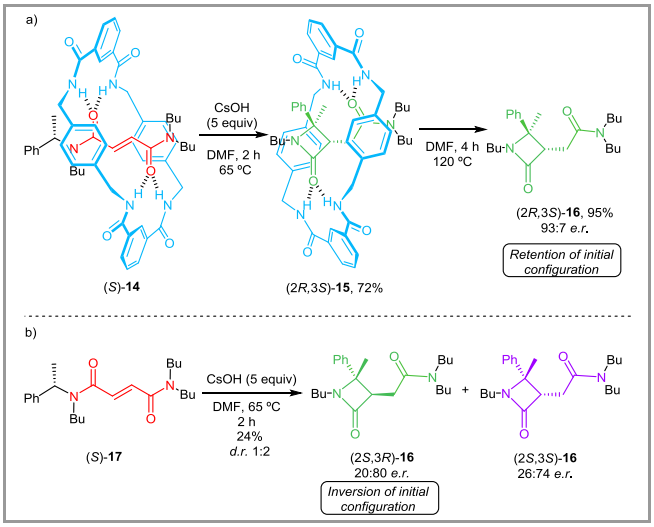
The bulkiness of the stoppers in rotaxane **11a** precludes the disassembly of its components through a thermal deslipping process. So we decided to carry out the transformation at higher temperatures, looking for a change in the diastereomeric ratio by increasing the mobility of the macrocycle (Scheme 10). Surprisingly, the reaction at 120 ºC afforded a new product, rotaxane **13a**, in high yield. Instead of the expected attack of one benzyl group to form the azetidinone core, the cyclization through one of the chiral carbon atoms of the α-methyl groups occurred. The rotaxane **13a** was obtained as a unique diastereoisomer forming a new tetrasubstituted stereogenic center from a trisubstituted one.[27] It is worthy to highlight that the heating at the same temperature of the diastereomeric mixture **12a** in the presence of base led to the same compound **13a**. (Scheme 10a). We were able to elucidate the structure by X-ray diffraction analysis of a single crystal of the rotaxane **13b**, analog to **13a**, but with two bromo substituents at the macrocycle (Scheme 10b). The analysis of the structure discloses the interlocked nature of the system and also the *trans* configuration of the substituents on the lactam core of the thread. Moreover the structure reveals that the cyclization process occurred with retention of the initial configuration of the methylbenzyl groups.[28,29]



Scheme 10 Diastereo- and enantioselective synthesis of interlocked lactams: a) **13a**; b) **13b**, with its X-ray structure (inset). Intramolecular hydrogen-bond lengths [Å] (and angles [deg]): O2HN5 2.09 (165); O1HN6 1.93 (166)

Finally, we decided to test the reactivity of rotaxane (*S*)-**14**, having just one α-methylbenzyl group able to react (Scheme 11). In this particular case we wondered if the presence of only one chiral carbon atom is efficient enough for achieving a high enantiocontrolled cyclization (Scheme 11a). Note that rotaxane **14**, with three butyl and one α-methylbenzyl groups as stoppers, is prone to undergo a dethreading reaction at high temperatures,required to efficiently promote the cyclization through the tertiary carbon on the methylbenzyl group. Thus a careful screening of the reaction temperature was carried out, finding that at least 60 ºC are necessary to achieve good conversions towards the formation of the threaded lactam **15**, avoiding the disassembly of its interlocked

components. The presence of an excess of base (5 equiv.) increases the cyclization rate. The thermal extrusion of the free lactam *trans*-**16** and the later analysis by chiral-phase HPLC revealed that a highly enantioselective cyclization had occurred (93:7 e.r.), assuming that it proceed with retention of the initial configuration by comparison with the initial results obtained for rotaxanes **13a,b**.



Scheme 11 Enantioselective synthesis of the non-interlocked lactams **16**: a) starting from rotaxane (*S*)-**14**; b) starting from thread (*S*)-**17**.

In stark contrast, the reaction of the non-interlocked thread (*S*)-**17** under the same reaction conditions gave a complex mixture of the two diastereoisomers, being the *cis*-**16** the main one (*d.r.* 1:2) together with a number of byproducts (Scheme 11b). The obtained yield for the mixture *cis*+*trans*-**16** was a poor 24 %. Interestingly, the chiral HPLC analysis of the *trans*-**16** showed that the main enantiomer formed in this reaction, (2*S*,3*R*)-**16**, is the opposite than the one obtained in the analogous cyclization occurring with the rotaxane **14,** (2*R*,3*S*)-**16**, (compare HPLC chromatograms shown in Figure 5). This result is in agreement with a cyclization of the isolated thread occurring with inversion of the configuration in the building of the new quaternary carbon of the lactam core.

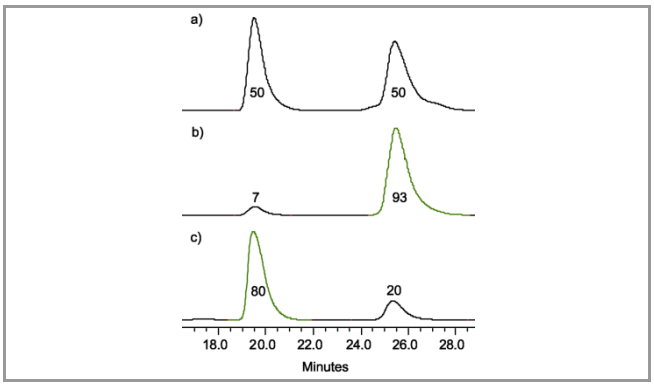


Figure 5 HPLC traces of: a) racemate of *trans*-**16**; b) enantioenriched (2*R*,3*S*)-**16** (7:93 e.r.); c) enantioenriched (2*S*,3*R*)-**16** (80:20 e.r.).

6 Conclusions

In this Account we describe the development of a novel synthetic approach for accessing chiral β-lactams, as a result of a serendipitous discovery. This unconventional methodology allows the isolation of interlocked and non-interlocked 2-azetidinones derivatives in high (quantitative) yields and in a total stereocontrolled manner. The base-promoted formal intramolecular Michael addition of α-benzylfumaramides occurs inside the cavity of the benzylic amide macrocycle, which activates and stereodirects the process.

Moreover, by following this approach a series of enantioenriched 2-azetidinones with two contiguous chiral centers, including a quaternary carbon, was obtained in a regio-, diastereo-, and enantiocontrolled manner. The presence of the encapsulating macrocycle forces to the formation of only one diastereoisomer (*trans*) in a confined space with a high enantioselectivity, the opposite to that found when the reaction was carried out with the naked thread.

This is an unprecedented, simple, and enantioselective cyclization that built enantioenriched β -lactams from straightforwardly accessible fumaramides. This methodology opens the door for future developments in syntheses of related compounds via macrocycle activation.

Acknowledgment

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Alberto Martinez-Cuezva was born in Burgos (Spain). He graduated in Chemistry at the Universidad de Burgos. In 2010, he completed his PhD at the same university working on the development of novel catalytic systems. He moved to the Max-Planck Institut für Kohlenforschung (Germany) to work as a Postdoctoral Researcher in the group of Prof. Benjamin List (2010-2013). During this time he focused in the synthesis of potential asymmetric organocatalysts. In 2013, he joined the Department of Organic Chemistry at Universidad de Murcia as a Postdoctoral Researcher (Marie-Curie and Juan de la Cierva Fellow). In 2018, he was awarded with a Ramón y Cajal contract. His research interests are focused on the synthesis of novel interlocked compounds oriented towards the development of new functional molecular machines, including their employment as advanced organocatalysts.

Carmen Lopez-Leonardo was born in Murcia (Spain). She received her BSc degree at the Universidad de Murcia, and her PhD at the same university working on the synthetic uses of iminophosphoranes. She moved to the Université Catholique de Louvain (Belgium) to work as a Postdoctoral NATO fellow in the group of Prof. Leon Ghosez. She returned to the Universidad de Murcia where she is currently Senior Lecturer in Organic Chemistry. Her research interests include organophosphorus compounds, supramolecular chemistry and mechanical bonds.

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