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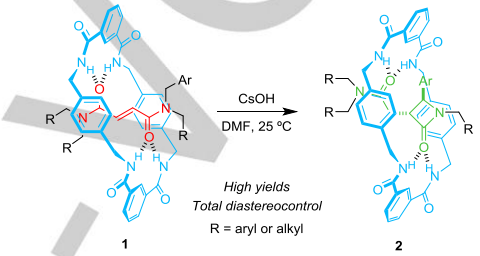
Enantioselective Formation of 2-Azetidinones by Ring-Assisted Cyclization of Interlocked *N*-(α-Methyl)benzyl Fumaramides

Alberto Martinez-Cuezva,*[a] Delia Bautista,[b] Mateo Alajarin,[a] and Jose Berna,*[a]

Abstract: The synthesis of optically active interlocked and non-interlocked 2-azetidinones by intramolecular cyclization of *N*-(α-methyl)benzyl fumaramide [2]rotaxanes is described. Two different strategies of asymmetric induction were tested in which the chiral group was located either proximal or distal to the reaction center of the thread. During these experiments, an interesting equilibration process inside the macrocyclic void occurred leading to the cyclization through the (α-methyl)benzyl carbon atom giving rise to *β*-lactams with a quaternary carbon atom in an enantio- and diastereocontrolled manner. This cyclization also proceeds in kinetically stable chiral pseudo[2]rotaxanes allowing further dethreading to provide enantioenriched 3,4-disubstituted *trans*-2-azetidinones. The stereochemical outcomes of the cyclizations inside and outside the macrocycle showed notorious differences.

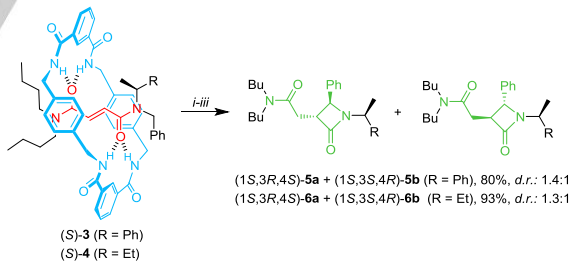
Nature has always been a source of inspiration for the scientific community. Many chemists have focused their efforts on mimicking the catalytic behavior of enzymes.[1] The increase of the reaction rates or the enhancement of the enantio- or diastereoselectivities of natural processes are feasible by the existence of active-site pockets constrained by the folding of the protein. Thus, synthetic compounds having a restricted void or matrix which could emulate the behavior of enzymes are highly demanding.[2] Besides the use of highly confined organocatalysts[3] or materials,[4] able to create the desirable rigid space for the stabilization of the corresponding transition states, self-assembled capsules,[5] molecular cages,[6] and macrocycles,[7] are in the spotlight. These tailor-suited systems can be easily tuned to enhance their catalytic features in a way similar to other enzymatic structures.[8,9] The chemical activity of mechanically interlocked molecules has been under intense study in recent years.[10,11] The presence of the mechanical bond[10a] infers particular chemical properties to these systems that have been applied as selective and/or switchable catalysts among others.[11]

Recently, we reported the intramolecular cyclization of *N*-benzyl fumaramide [2]rotaxanes **1** (Scheme 1).[12] In that work, we disclosed the role of the mechanical bond in a transformation which occurs in a regio- and diastereoselective manner giving interlocked 3,4-disubstituted *trans* 2-azetidinones **2** in high yields, in contrast with the less efficient conversion carried out outside the ring. The activating effect of the tetraamide macrocycle[13] in these processes markedly contrasts with the habitual steric shielding of the threaded functions,[10a,14] in this case promoting an unusual and disfavored 4-*exo*-*trig* ring closure. Herein we report our efforts for achieving carbon-to-carbon chirality induction from *N*-(α-methyl)benzyl substituents to the carbon atoms of the *β*-lactam ring and its implementation to the synthesis of enantioenriched 2-azetidinones.



Scheme 1. CsOH-catalyzed intramolecular cyclization of interlocked *N*-benzyl fumaramides

To this end we first prepared enantioenriched pseudo-[2]rotaxanes **3** and **4** bearing a single stereogenic carbon at one of the *N*-substituents of the thread.[15,16,17] When these species were submitted to a one-pot CsOH-catalyzed cyclization-dethreading process,[12] the non-interlocked *trans*-β-lactams **5** and **6** were obtained in good yields although in a disappointing low diastereomeric ratios (1.3-1.4:1 approx.) (Scheme 2).[18]



Scheme 2. One-pot synthesis of the *β*-lactams **5** and **6**. Reaction conditions: i) CsOH, DMF, 25 °C; ii) HCl 1 M; iii) 100 °C, 24 h.

Unfortunately, placing the stereogenic carbon proximal to the benzylic carbon atom involved in the cyclization, both at the same fumaramide N atom, prevented an effective chirality induction. We next moved to the alternative distal approach, that is locating the chiral inductor at the other terminus of the fumaramide. Thus we next assayed the [2]rotaxane **7** bearing a *N,N*-dibenzyl-*N´,N´*-bis((*R*)-1-phenylethyl)fumaramide as thread incorporating a C_2-chiral asymmetric inductor (Scheme 3). First, the CsOH-promoted cyclization of **7** was carried out at room temperature (Scheme 3, conditions i) affording a discouraging 1.6:1 mixture of two diastereoisomers, *trans* **9a** and **9b**. Surprisingly, when the reaction was carried out at a rather higher temperature (120 ºC) **7** yielded a completely different product in high yield, the rotaxane **10**, as resulting from the cyclization of the thread through one of the chiral carbon atoms. Rotaxane **10** was obtained as a single diastereoisomer in a

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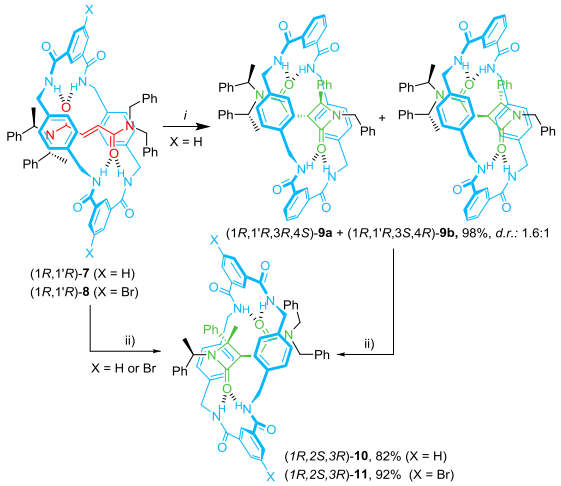
process involving the formation of a tetrasubstituted stereogenic center from a trisubstituted one.[15b] The product **10** also formed by heating the diastereomeric mixture **9** at the same temperature (Scheme 3, conditions ii) in the presence of the base.



Scheme 3. Synthesis of *trans* β-lactams **9-11**. Reaction conditions i) CsOH (1 equiv.), DMF, 25 °C, 12 h; ii) CsOH (1 equiv.), DMF, 120 °C, 2 h.

We determined the absolute configuration of the chiral centers of the dibromo analogous **11**, directly obtained in 92 % yield by a CsOH-promoted cyclization of the corresponding interlocked fumaramide **8** (see Scheme 3) by single-crystal X-ray diffraction analysis (see Figure 1, CCDC: 1830131). The structure of **11** unveiled that the cyclization, in which a quaternary carbon is formed, occurred with retention of the configuration at the reacting chiral stereocenter.[15b,19,20]

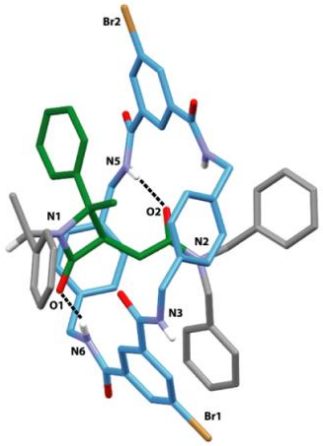
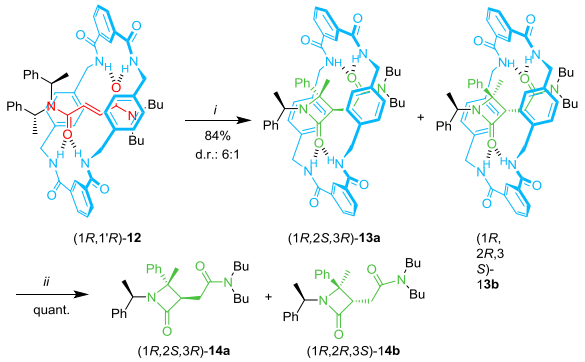


Figure 1. X-Ray structure of the [2]rotaxane **11**. Intramolecular hydrogen-bond lengths [Å] (and angles [deg]): O2HN5 2.09 (165); O1HN6 1.93 (166).

The reversibility of these cyclizations allows to rationalize the conversion of **9** into **10** (see Scheme S5). Thus, by increasing the temperature, the ring opening of the kinetically controlled product, β-lactams **9**, should occur through a retro-Michael addition[21] followed by a second cyclization for leading to the thermodynamically most stable interlocked β-lactam **10**. The different stability of **9** and **10** is tentatively attributed to the dissimilar repulsive non-bonding interactions between their interlocked components, more severe in **10** having a bis(α-methylbenzyl)amino stopper than in **9** with a less sterically demanding dibenzylamino group. Nevertheless, the cyclizations leading to **10** and **11** are noticeable by involving one of the more substituted benzylic carbon atoms of the thread as well by its stereochemical course (retention of configuration).[15e,22] We proposed some mechanistic proposals accounting for this latter aspect which are based on our previous assumption concerning the anchimeric assistance of the surrounding macrocycle.[12] Thus, it might be explained by a rapid deprotonation/cyclization with a concurrent disconnection of the assistant-ring precluding the racemization at the chiral center[23] (Fig. S2, cycle A) or the regioselective insertion of a stabilized carbene in the C-H bond of a trisubstituted chiral carbon atom[24] (Fig. S2, cycle B). Other alternative explanations based on radical pathways[25] were also envisaged although seemed unlikely as result of our experiments with TEMPO or in absence of light conditions (see Schemes S6 and S7).

In order to release the β-lactams[26] from the interlocked architecture we next replaced the dibenzylamino stopper of the starting rotaxane **7** by a dibutylamino one for decreasing the kinetic stability of the final interlocked ensemble, thus exploring the reactivity of the pseudo[2]rotaxane **12** with a (*E*)-*N,N*-dibutyl-*N´,N´*-bis((*R*)-1-phenylethyl)fumaramide as thread. This structural modification excludes the possibility of using the previous reaction conditions (120 ºC, DMF) due to the quick dethreading of the fumaramide outside the ring. After an optimization of the reaction conditions, the cyclization was carried out at the lowest temperature allowing the β-lactam formation to occur (65 °C) inside the macrocycle and in the presence of an excess of base (5 equiv) (Scheme 4). After 4 hours, two *trans* diastereoisomers were obtained in a 6:1 ratio, both as single enantiomers. In this case, the cyclization of the thread occurred with a substantial percentage (15%) of configurational inversion at the reacting stereocenter still with a complete *trans* selectivity. We reasoned that the presence of the less sterically-demanding two *n*-butyl groups of the thread would allow a relative displacement of the macrocycle away from the reactive center to decrease the steric congestion near the bulky C_2 chiral inductor thus proving the critical role of the ring not only in the reactivity but also in the stereoselectivity. Rotaxanes **13** were dethreaded by heating at 120 ºC in DMF solution to quantitatively yield the corresponding *trans* β-lactams **14**.



Scheme 4. Cyclization of the interlocked fumaramide **12** and synthesis of *trans* β-lactams **14**. Conditions: i) CsOH (5 equiv.), DMF, 65 °C, 4 h; ii) DMF, 120 °C, 4 h. The absolute configurations of the chiral carbons of **13** and **14** were assigned by comparison with those of **11**.

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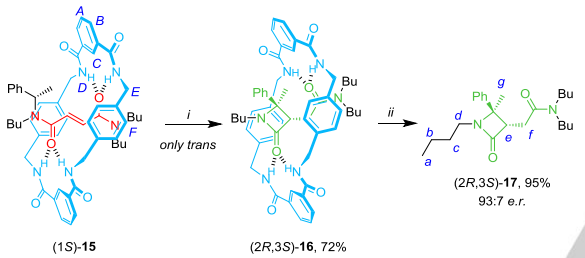
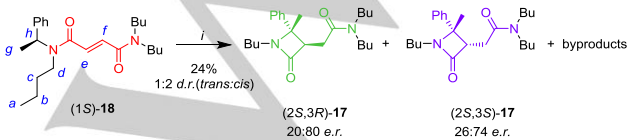
We next removed one of the two α-methylbenzyl groups of **12** in order to minimize the displacement of the ring away from the reactive center of the fumaramide and, more importantly, for checking if the retention of the configuration at the reactive chiral carbon is efficient enough for achieving a highly stereocontrolled cyclization in a case in which the only stereocenter is the reacting one. Therefore we assayed the intramolecular cyclization in the pseudorotaxane **15**, with three *n*-butyl and one (*S*)-α-methylbenzyl groups as stoppers at the fumaramide thread. A solution of **15** in DMF was heated in the presence of an excess of base at 65 °C allowing its cyclization to diastereoselectively provide the interlocked *trans* β-lactam **16** in 72% yield (Scheme 5, conditions i).[27] The free *trans*-β-lactam **17** was quantitatively obtained after the habitual dethreading process (Scheme 5, conditions ii).[28] Pleasantly, chiral HPLC analysis of lactam **17** revealed that a highly enantioselective cyclization had occurred (**17**, 93:7 e.r.). It is important to remark that this level of stereocontrol is achieved at a relatively high temperature.



Scheme 5. Enantioselective synthesis of β-lactam **17**. Reaction conditions: i) CsOH (5 equiv.), DMF, 65 °C, 2 h; ii) DMF, 120 °C, 4 h.

Figure 2 displays the stacked plot of the ^{1}H NMR spectra of the chiral fumaramide **18**, the rotaxane **15**, the interlocked *trans* β-lactam **16** and the *trans* β-lactam **17**. The comparison of the spectra of the thread **18**, as a 2:1 mixture of rotamers at 298 K in $CDCl_3$, and the rotaxane **15** disclosed the interlocked nature of this latter species and the stabilization of the less sterically crowded rotamer of the thread.[29] Interestingly, the splitting of signals of the macrocycle (light blue) of **15** is ascribed to the magnetically inequivalent isophthalamide units due to the asymmetry of the thread **18**. After cyclization, the corresponding interlocked *trans* β-lactam **16** is obtained as a single diastereoisomer (green). Comparison of the spectra of the rotaxane **16** and the non-interlocked **17**, resulting from the thermal dethreading step, shows a substantial shielding of the signals of the β-lactam core (H_e and H_f, green).

In stark contrast, the cyclization of the non-interlocked fumaramide **18** under identical conditions required a significant extension of the reaction time (6 h) to finally give a mixture of the two *cis* and *trans* diastereoisomers (2:1 d.r.) in very low yield (24%) accompanied by a number of byproducts (Scheme 6). A quick inspection of the ^{1}H NMR spectra of the mixture of lactams in Figure 2e shows the *cis* diastereoisomer as the major product



Scheme 6. Intramolecular cyclization of the α-methylbenzyl fumaramide **18**. Reaction conditions: i) CsOH (5 equiv.), DMF, 65 °C, 2 h; ii) DMF, 120 °C, 4 h.

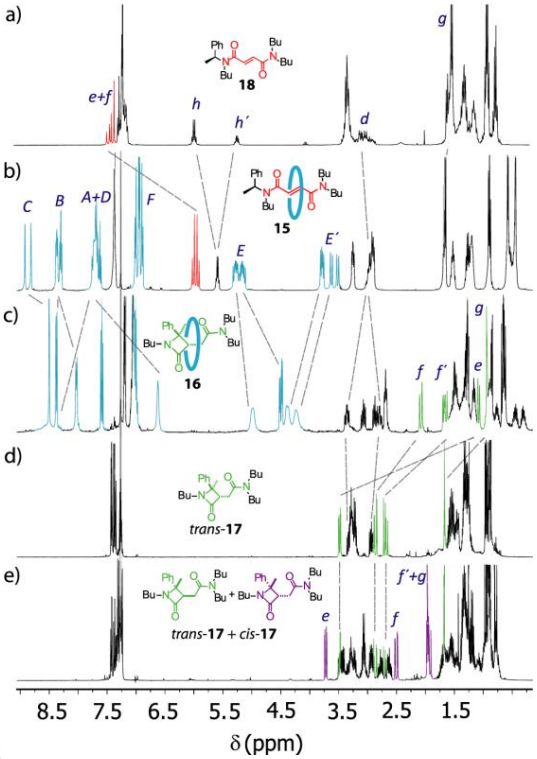


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of a) *N*-(α-methyl)benzylfumaramide **18**, b) *N*-(α-methyl)benzylfumaramide [2]rotaxane **15**, c) interlocked *trans* β-lactam **16**, d) *trans* β-lactam **17**, and e) *trans* and *cis* β-lactam **17** obtained by cyclization of thread **18**. Lettering as in Schemes 5 and 6.

(in purple) of the cyclization out of the ring, in sharp contrast with the *trans* selective cyclization occurring inside of the macrocycle. Chiral HPLC analysis of both diastereoisomers disclosed a discrete enantioselectivity (74:26 e.r. for *cis*-**17** and 80:20 e.r. for *trans*-**17**). Intriguingly, the sense of the enantioselection in the formation of *trans*-**17** is opposite to that operating inside the ring, the major (2*R*,3*S*) enantiomer in that case being now the minor one.

In summary, the base-catalyzed intramolecular cyclization of enantiopure α-methylbenzyl fumaramides occurring inside the cavity of a removable benzylic amide macrocycle, allows the synthesis of 2-azetidinones with two contiguous chiral centers, including a quaternary carbon, in a regio-, diastereo- and enantio- controlled manner. Similar processes are shown also to occur in non-interlocked fumaramides although under harsher reaction conditions. The scenario in which this reaction is carried out, inside or outside the ring cavity, deeply affect to the reactivity and the stereocontrol of the process in the former case avoiding the formation of one of the two possible cis/trans diastereoisomers. Furthermore, an unprecedented, simple and enantioselective cyclization yielding enantioenriched β–lactams from easily available fumaramides has been uncovered for the first time paving the way for future developments in related syntheses of these relevant compounds.

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Keywords: template synthesis • rotaxane • pseudorotaxane • supramolecular chemistry • stereoselectivity

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[17] The unconsumed enantiopure thread during the rotaxane formation is fully recovered during the isolation process enabling its re-utilization in ulterior preparations.

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[27] The same reaction conditions at 65 ºC did not promote an analogous cyclization of the pseudorotaxane **3** (Scheme 1), most probably because the retro-Michael reaction of the products *β*-lactams **5** did not occur (which required 120 ºC, see Scheme 3), thus precluding the further stereoselective cyclization through the *α*-methylbenzyl group.

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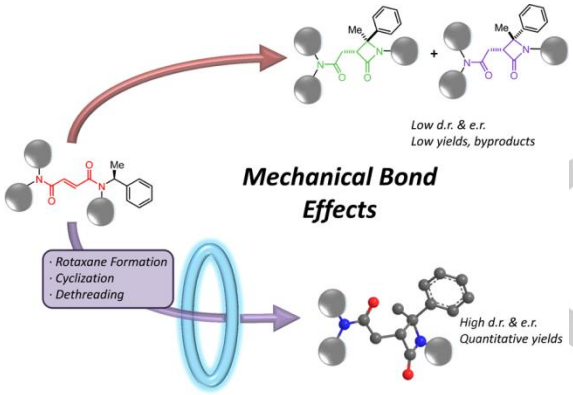

Mechanical Bond Effects. An unprecedented intramolecular cyclization through the (α-methyl)benzyl carbon atom of interlocked fumaramides gives rise to β-lactams with a quaternary carbon atom in an enantio- and diastereocontrolled manner. The stereochemical consequences of the cyclizations inside and outside the ring exhibited remarkable differences.

A. Martinez-Cuezva, D. Bautista, M. Alajarin, J. Berná,**

Page No. – Page No.

Enantioselective Formation of 2-Azetidinones by Ring-Assisted Cyclization of Interlocked *N*-(α-Methyl)benzyl Fumaramides