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Stereodivergent Macrocyclization in Dynamic Chiral Confinement

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The absolute and relative configurations of a macrocyclic natural product bearing multiple chirality have a crucial influence on its physical and biological properties. Nevertheless, their preparation with full stereocontrol remains largely unexplored in synthetic community. Here, we show a stereodivergent macrocyclization under dynamic chiral confinement in which the stepwise chirality switching of a chiral space directs complete stereocontrol. To confine a substrate in a dynamic chiral space, we used a chiral capsule enclosing a substrate which is collectively switchable in the chirality in response to external stimuli, but their conformations are firmly fixed by subsequent self-assembly. The consecutive chirality switching enables the confined reactions of an enclosed achiral substrate to sequentially install diverse chirality on a macrocycle product with full stereocontrol in a single pot operation, thus changing only a sequence of physical stimuli enables access to a remarkable stereodivergence in a macrocyclization process.

Introduction

Complex macrocycles bearing multiple chirality are commonly encountered structural motifs in biologically active natural products and pharmaceuticals.[1] The stereochemical configuration in addition to the conformational rigidity of a closed ring structure has a decisive impact on its properties.[2] Nevertheless, their synthesis faces a formidable challenge to induce chirality during a ring-closing event.[3] Although confinement into a chiral space has been reported to generate enantiomeric macrocycles,[4] the multiple chirality induction with full stereocontrol remains a substantial challenge. The multiple chirality induction with controlled stereoselectivity requires the combination of an enantioselective reaction with a controlled diastereoselective step, which cannot be achieved with fixed single systems without structural changes.[5] Thus, an important goal would be the construction of dynamic systems from a single framework that can sequentially dictate the configuration of stereoisomers in response to external stimuli.[6] Such systems could perform consecutive steps to generate complex chiral molecules with multiple chirality induction in a single pot. To address this challenge, we envisioned that locking a linear substrate into a dynamic chiral capsule would allow access to the control of stereoselectivity in macrocyclization through multi-step sequences of chirality switching. The switching of capsule chirality would be accompanied by concurrent switching with the encapsulated substrate in the chiral conformation.[7] Thus, the first step chemical reaction of the substrate locked in the chiral capsule would generate a chiral intermediate with controlled enantioselectivity by chirality switching of the capsule. Upon completing the enantioselective reaction, a subsequent ring-closing reaction would induce additional chirality associated with rotationally-restricted ring closure.[8] The stereoselectivity in a ring closing process of an enantiomeric intermediate formed in the first-step reaction could be controlled through consecutive chirality switching, thus achieving stereodivergence in macrocyclization.

Results and Discussion

Our strategy to achieve stereodivergence in a macrocyclization integrates a confined reaction and consecutive chirality switching. For chiral confinement of a linear substrate, we used aromatic amphiphile **1** forming a switchable chiral capsule upon enclosing a hydrophobic linear substrate in aqueous environments (Figure 1a).[9] Upon addition of linear substrate **2** into a solution of host molecule **1** (50 μM, methanol/water = 6.0 : 4.0 v/v) at a mole ratio of 1 : 2, (**2**⊂**1**$_2$), the circular dichroism (CD) spectra showed the induction of a negative Cotton effect (Figure 2b), corresponding to *P*-chirality (Supplementary section 2.4). Subsequently, the capsule (**2**⊂**1**$_2$) self-assembles into a robust 2D sheet structure (Supplementary Figure S13c), enabling the encapsulated linear substrate to adopt a fixed chiral conformation. The capsule chirality in the sheet assembly can be inverted from kinetically-trapped *P*-chirality to thermodynamically stable *M*-chirality upon sonication (Figure 2b & Supplementary Figure S13). When heated to 45 °C and then cooled to room temperature, the CD signal recovers the negative Cotton effect (Supplementary Figure S34). Thus, the key feature of the capsule induced by substrate trapping is the stimuli-responsive control over chirality by sonication (*P*- to *M*-chirality) or heat-treatment (*M*- to *P*-chirality).

Linear substrate **2** features an aliphatic ketone spacer with reactive aromatic end groups for S_NAr reaction, which is a macrocyclization precursor for the synthesis of chiral cyclo-

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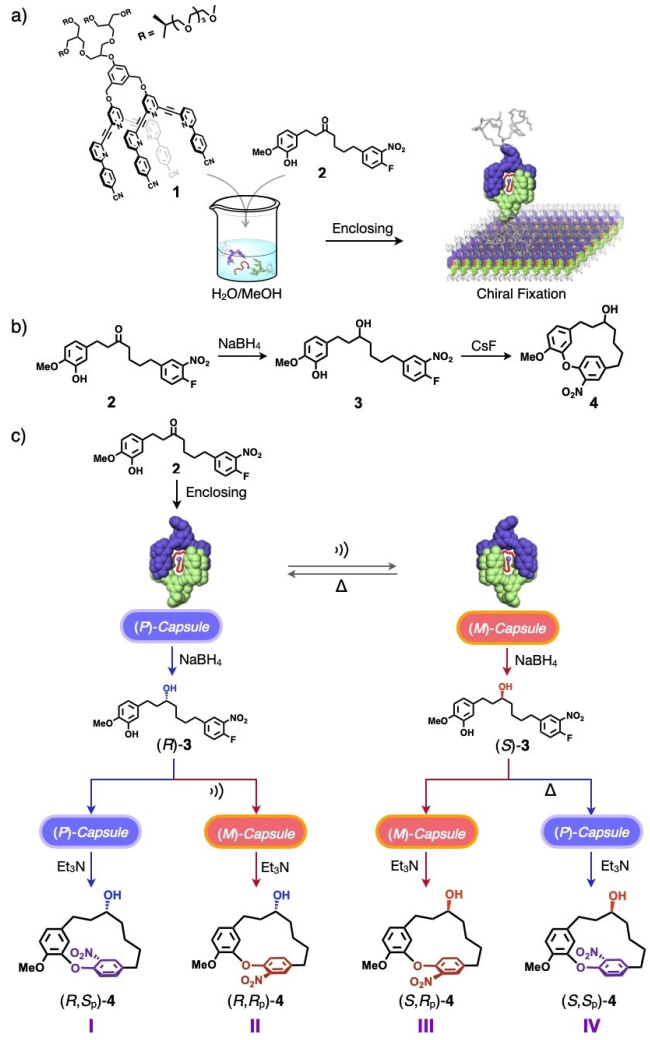

Figure 1. Stereodivergent macrocyclization in dynamic chiral capsule
(a) Schematic representation of the formation of capsule assembly. Linear substrate **2** is enclosed by host molecule **1** at a 1:2 mole ratio in methanol-water solution (6:4, v/v), forming a chiral capsule of which chirality is fixed through subsequent self-assembly process. (b) Conventional synthesis of **4** starting from a linear substrate, generating a macrocycle with a lack of stereoselectivity. (c) Stereodivergent synthesis of **4** starting from linear substrate **2** under switchable chiral confinement, producing any one of four stereoisomers of macrocycle **4** bearing double chirality by selecting the sequence of external stimuli among four pathways (I, II, III, and IV). The switch state of the capsule (*P* or *M*) dictates sequentially the configuration of the stereocenter and planar chiral configuration in the macrocycle.

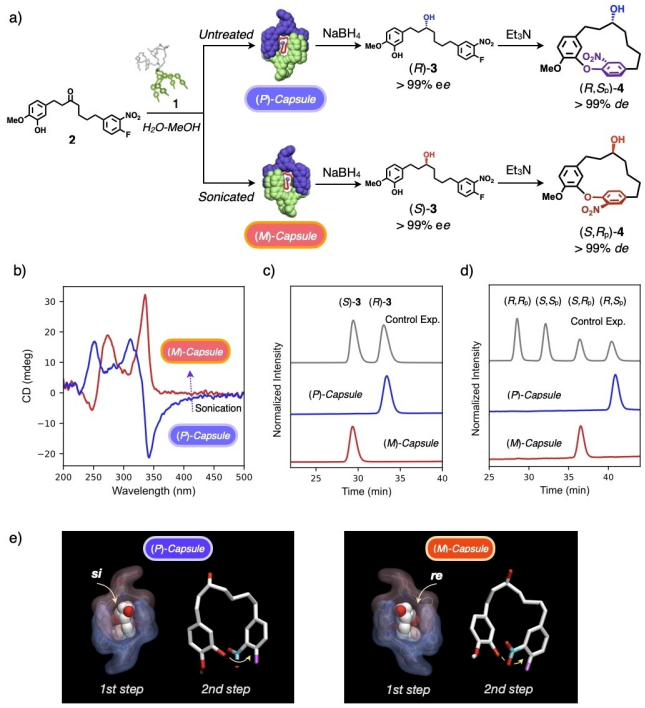

Figure 2. Synthesis of enantiomeric macrocycles
(a) Scheme of one-pot two-step sequential reactions to synthesize enantiomers of **4** in *P*/*M* capsules where *P*-capsule generates (***R***,***S***$_p$)-**4** while *M*-capsule generates (***S***,***R***$_p$)-**4**. (b) CD spectra of untreated and sonicated solution. The untreated solution exhibits a negative. Cotton effect, while the solution shows a positive Cotton effect after sonication, indicating sonication-driven chirality switching of capsule from *P* to *M*. (c) Chiral HPLC traces of **3** obtained by hydrogenation of **2** in the absence of **1** (top), and in the **2**⊂**1**$_2$ sheet assembly of the untreated (middle) and sonicated (bottom) solutions. (d) Chiral HPLC traces of **4** obtained by S_NAr macrocyclization of **3** in the absence of **1** (top), and in the **3**⊂**1**$_2$ sheet assembly of the untreated (middle) and sonicated (bottom) solutions. (e) Optimized chiral conformations of **2** and **3** in the chiral capsule by theoretical calculations. In the *P*-capsule (left), hydride attack to the *si* face is favored to generate **3** with the (*R*)-configuration and then the phenol addition to an atropisomeric conformer of the 2-nitro-3-fluorophenyl group is favored to yield macrocycle **4** with (S_p)-planar chiral configuration consistent with the experimental observation. While the *M*-capsule (right) holds an opposite chiral conformation of the substrate to yield the enantiomeric macrocycle **4** with the (*S*)-stereocenter and (R_p)-planar chiral configuration through two step sequential reactions.

phanes that are structural motifs found in a wide range of biologically active natural products with a medicinal activity.[8,10] Considering chiral transfer from the capsule,[4b,11] hydrogenation of ketone under chiral confinement would generate an enantioselective hydroxy product because of the preferred spatial orientation of one prochiral face over the other toward a nucleophile. In addition, macrocyclization of the aromatic groups would induce planar chirality due to the restricted rotation of the *m*-nitrophenyl group. Thus, a two-step sequential reaction of the substrate under chiral confinement, first enantioselective hydrogenation of the ketone and then macrocyclization, would generate a macrocyclic product bearing two disparate chirality (Figure 1c, pathway I). To corroborate enantioselective hydrogenation of the ketone group in the first step, we added $NaBH_4$ to the untreated solution of **2**⊂**1**$_2$-capsule with *P*-chirality at ambient conditions (Figure 2a). The hydrogenation under chiral confinement in the capsule assembly solution affords a pure enantiomer (*R*-form) of **3** with enantiomeric excess (*ee*) of > 99% with quantitative conversion within 1 hr (Figure 2c). It is worth noting that the CD signal of the sheet solution remains unchanged even after hydrogenation of the substrate, suggesting that the first hydrogenation does not influence on the capsule chirality (Supplementary Figure S28, blue curve).

This result stimulated us to consider that a subsequent macrocyclization in a one-pot would add additional chirality to the macrocycle skeleton. To confirm the formation of a diastereomeric macrocycle in a sequential one-pot process, we

added subsequently a base (Et_3N) to the capsule solution of (*R*)-**3** for S_NAr macrocyclization (Figure 2a). The amine catalyzed reaction generates a cyclized product with planar chirality (S_p) induction with superb diastereoselectivity (*de* >99%) with nearly quantitative conversion (Figure 2d & Supplementary Table S2), demonstrating that the capability of the capsule in the chirality induction during a macrocyclization event does not be compromised by the first step enantioselective reaction. This result illustrates that the two-step sequential reactions of the substrate under chiral confinement can generate a macrocycle product bearing double chirality including a stereocenter and planar chirality in a one-pot process without the need of the intermediate separation and purification.

The facile switch between *P*- and *M*-capsules by sonication encouraged us to consider the control of stereoselectivity in multiple chirality induction because the substrate inside undergoes concurrent chirality switching in its enantiomeric conformer.[9] Consequently, two-step sequential reactions of **2** after sonication would afford an enantiomeric macrocycle of (S,R_p)-**4** (Figure 1c, pathway III). To implement the chirality switching of the capsule into enantiocontrol in a macrocyclization process, two-step sequential reaction was performed with the capsule solution after sonication (Figure 2a). Upon sonication, indeed, the CD signal at longer wavelengths was inverted from the negative minimum to a strong positive Cotton effect (Figure 2b), indicative of chirality switching from *P*- to *M*-chirality. Similar to that of an untreated condition, the first hydrogenation affords enantiopure **3**, but with an inversion in absolute configuration (*S*-enantiomer) (Figure 2c). After completing the hydrogenation, the subsequent reaction of (*S*)-**3** upon addition of an amine base produces an enantiomeric macrocycle, (S,R_p)-**4** with an opposite configuration at the stereocenter and inverted planar chirality without the loss of enantiopurity and conversion (Figure 2d & Supplementary Table S3).

These observations in combination with control experiments indicate that the confinement in the chiral interior directs the linear substrate to hold a folded chiral conformation with preferred prochiral faces of the carbonyl group and favored spatial orientation of *m*-nitrophenyl group. Indeed, calculations showed that linear substrate **2** enclosed in the chiral interior of (*P*)-capsule holds a folded conformation with more open *si*-face than *re*-face of the prochiral ketone group and preferential atropisomeric conformer of the nitrophenyl group (Figure 2e). Thus, the hydride nucleophile in the first step attacks preferentially to the *si*-face to give **3** with the (*R*) stereocenter and then the subsequent S_NAr reaction is favored to generate macrocycle **4** with the (S_p) configuration, consistent with experimental observations. While the (*M*)-capsule brings the substrate to hold an inverted chiral conformation with sterically-hindered *si*-face of prochiral ketone and flipping of the nitrophenyl group which explains the control of stereoselectivity in double chirality induction by sonication-driven switching.

The respective diastereomers of (R,S_p)-**4** and (S,R_p)-**4** could be obtained by subsequent chirality switching after completing the first-step enantioselective hydrogenation (Figure 1c, pathways II & IV). While preserving the absolute configurations formed in the first step reaction, the chirality switching of the capsule would trigger flipping of the nitrophenyl group, thus the subsequent macrocyclizations can generate diastereomeric macrocycles. When completed the first-step reaction in the untreated solution generating **3** with the (*R*) stereocenter, the solution was subsequently subjected to sonication to trigger chirality switching from *P*- to *M*-capsules (Figure 3a & Supplementary section 3.1). Indeed, the CD signal was inverted from the negative minimum to a positive Cotton effect upon

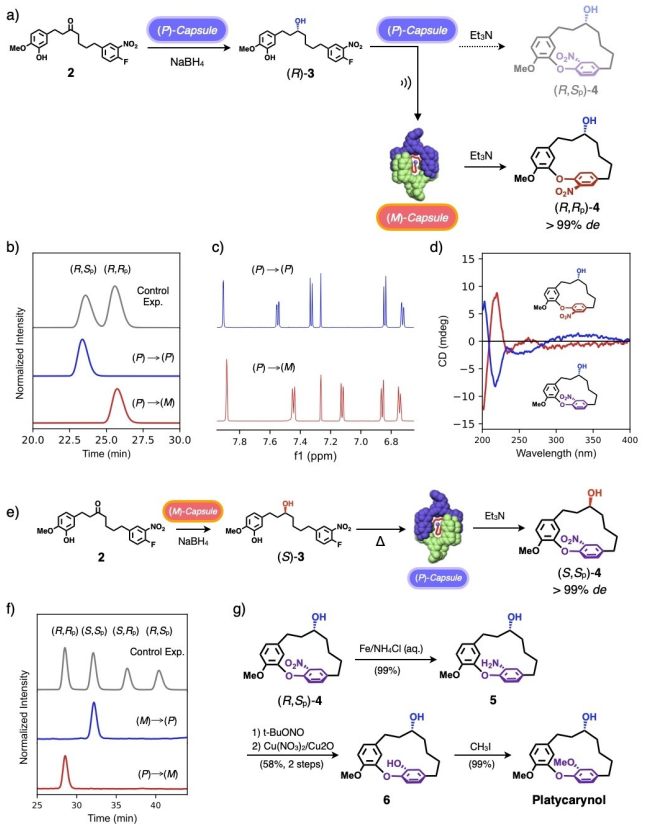

Figure 3. Synthesis of diastereomeric macrocycles
(a) Scheme of two-step sequential reactions with capsule chirality switching (*P* to *M*) after completing the first step hydrogenation to afford (***R,R*****$_p$**)-**4**. The *R* stereocenter is induced in the first step hydrogenation in *P*-capsule. Subsequently, the chirality of capsule is switched to *M* upon sonication, thereby resulting in R_p planar chirality of the macrocycle product in the second step. (b) Reverse phase HPLC traces of **4** obtained after completing two-step sequential reactions of **2** in the absence of **1** (top), and in the **2**⊂**1**$_2$ sheet assembly of the untreated solution (middle) and the sonicated solution after completing the first step hydrogenation in (*P*)-capsule (bottom). (c) Partial ^{1}H-NMR spectra of (***R,S*****$_p$**)-**4** obtained from *P*-capsule (blue curve) and (***R,R*****$_p$**)-**4** (red curve) obtained from the sonicated solution (*M*-capsule) after completing the first step hydrogenation in (*P*)-capsule. (d) CD spectra of (***R,S*****$_p$**)-**4** (blue curve) and (***R,R*****$_p$**)-**4** (red curve). (e) Scheme of two-step sequential reactions with capsule chirality switching (*M* to *P*) by heat-treatment after completing the first step hydrogenation to produce (***S,S*****$_p$**)-**4**. The *S*-stereocenter is induced in the first step hydrogenation in *M*-capsule. Subsequently, the chirality of capsule is switched to *P* by heat-treatment, thereby resulting in S_p planar chirality of product in the second step. (f) Chiral HPLC traces of **4** obtained after macrocyclization by two-step reactions of **2** in the absence of **1** (top), and in the **2**⊂**1**$_2$ sheet assembly of the sonicated solution (*M*-capsule) for the first step and then heat-treatment (*P*-capsule) for the second step (middle), and the untreated solution (*P*-capsule) for the first step and then sonicated solution (*M*-capsule) for the second step (bottom). (g) Synthesis of platycarynol using (***R,S*****$_p$**)-**4** obtained from two-step reactions of **2** in untreated solution of **2**⊂**1**$_2$ sheet assembly (*P*-capsule).

sonication without interfering the formation of the 2-D sheet assembly (Supplementary Figure S28), thus suggesting that the stereocenter does not have any noticeable influences on the collective switching capability of the capsule. To confirm the diastereoselective planar chirality induction, the S_NAr macrocyclization of (*R*)-**3** generated in the *P*-capsule was performed by sequential addition of Et_3N after sonic-ation to convert into *M*-capsule. The reaction generates a clean macrocycle product (R,R_p)-**4** with near perfect diasteroselectivity, as determined by analytical HPLC (Figure 3b) and chiral HPLC (Figure 3f). Appearance of a pure single peak at an unidentical retention time to (R,S_p)-isomer in both analytical and chiral HPLC traces demonstrates that the subsequent chirality switching after the enantioselective reaction dictates absolute configuration in a macrocyclization. ^{1}H-NMR spectrum obtained from the sonicated solution after completing the first step reaction shows a single species with disparate chemical shifts of the aromatic protons (Figure 3c), confirming the formation of a diastereomer of (R,S_p)-**4**. To investigate the diastereomeric nature, both the diastereomers were subjected to CD experiments in $CDCl_3$ solution (Figure 3d). The CD spectrum of (R,R_p)-**4** shows opposite Cotton effect signals to (R,S_p)-macrocycle, but with a non-mirror image, further supporting that the macrocycle isomer generated after subsequent switching into *M*-capsule has a diastereomeric relationship with that formed in the untreated solution.

To corroborate full stereocontrol by selectively producing a remaining (S,S_p)-diastereomer of macrocycle **4** (Figure 1c, pathway IV), the *M*-capsule solution was subjected to heat treatment to switch into a *P*-capsule upon completion of the first step hydrogenation (Figure 3e & Supplementary section 3.2). The subsequent macrocyclization of (*S*)-**3** upon heat-treatment produces (S,S_p)-**4** with opposite planar chirality to the stereoisomer obtained without heat-treatment with excellent diastereoselectivity (Figure 3f). This result illustrates that stepwise chirality switching can sequentially dictate the absolute and relative configurations of stereoisomers. Thus, the stereoselectivity in a sequential process can be fully controlled by physical stimuli applied in each step. Taken together, all four of the possible stereoisomers can be readily accessed in nearly quantitative conversions (> 96% conv.), and superb enantio- (> 99% *ee*) and diastereoselectivity (> 99% *de*) through proper choice of only switching pathways without any structural modification or any change in reaction condition (Figure 4). From these observations, it is remarkable that the combination of dynamic switching and robust confinement enables inducing multiple chirality in a macrocyclization event in a single pot operation with full stereocontrol with substantial precision and efficiency, which cannot be achieved by fixed confinement systems. The highly efficient performance of the capsule could be attributed to consecutive chirality switching without noticeable fatigue and robust chirality fixation by subsequent self-assembly.

Our strategy to achieve full stereocontrol in the synthesis of chiral macrocycles can be highly useful for the facile synthesis of complex natural products bearing multiple chirality which is critical for biological activity. As an example, the macrocycle

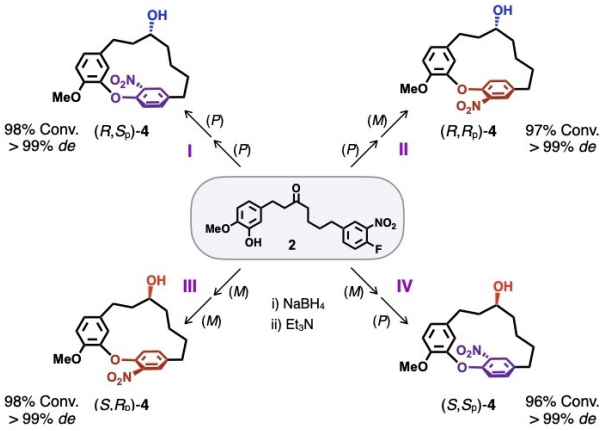

Figure 4. Selective formation of stereoisomeric macrocycles through different pathways. A switching pathway (I, II, II, and IV) directs the highly selective formation of any possible stereoisomer of macrocycle 4 in one pot sequential reactions in $2\subset1_2$ sheet assembly. The reagents and conditions for each step are the same across all pathways. The pathways differ in whether external stimuli for chirality switching are applied or not, and the order in which the external stimuli are applied within a pathway.

generated from this process can be readily converted into natural product platycarynol which has therapeutic potential including anticancer activity.[10a,12] To prove our strategy for easy access to bioactive natural products, we selected the (R,S_p)-diastereomer to synthesize platycarynol with the identical absolute configurations (Figure 3g). The nitro group of (R,S_p)-**4** was converted into amino compound **5** by hydrogenation. After converting into hydroxy compound **6**, subsequent methylation with CH_3I was carried out to afford a macrocycle product (57% overall yield) with the spectral data consistent with reported natural platycarynol.[10a] This result suggests that a broad range of bioactive natural macrocycles bearing multiple chirality would be easily accessible through a stereodivergent macrocyclization using our dynamic confinement strategy.

Conclusions

The incorporation of dynamic switching into confined reactions, as delineated here, provides access to achieving a remarkable level of stereodivergence in a single pot macrocyclization process. Only a simple change in the sequence of physical stimuli directs the selective formation of any possible stereoisomer of a macrocycle bearing multiple chirality. We anticipate that our dynamic confinement strategy provides access to the facile synthesis of complex natural products bearing multiple chirality, applicable to a wide range of biological targets.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[13–18]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Full stereodivergence · Dynamic confinement · Chiral macrocyclization · Multiple chirality induction · Chirality switching

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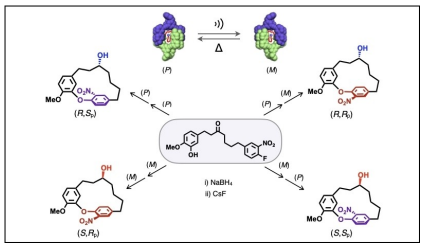
RESEARCH ARTICLE

Full stereodivergence in a macrocyclization event can be achieved by implementing a dynamic chirality switching into robust confinement using a repeatedly switchable chiral capsule. The consecutive chirality switching enables the confined reactions of an enclosed achiral substrate to sequentially install multiple chirality with full stereocontrol by changing only a sequence of physical stimuli.



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