Facial Selectivity in Mechanical Bond Formation: Axially Chiral Enantiomers and Geometric Isomers from a Simple Prochiral Macrocycle

Andrea Savoini,[1,2‡] Peter Gallagher,[1,2‡] Abed, Saady,[1,2] John R. J. Maynard,[1] Patrick W. V. Butler,[1] Graham Tizzard,[1] and Stephen M. Goldup[1,2,*]

[1]Chemistry, University of Southampton, University Road, Southampton, SO17 1BJ.

[2]School of chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K.

[‡]These authors contributed equally.

ABSTRACT: In 1971, Schill recognized that a prochiral macrocycle encircling an oriented axle led to geometric isomerism in rotaxanes. More recently, we identified an overlooked chiral stereogenic unit in rotaxanes that arises when a prochiral macrocycle encircles a prochiral axle. Here we show that both stereogenic units can be accessed using equivalent strategies, with a single weak stereo-differentiating interaction sufficient for reasonable stereoselectivity. Using this understanding, we were able to demonstrate the first direct enantioselective (70% *ee*) synthesis of a mechanically axially chiral rotaxane.

▪ INTRODUCTION

Early in the development of the chemistry of the mechanical bond,[1] Schill recognized that when a macrocycle containing a prochiral center such that its faces are distinguishable encircles an axle with distinguishable ends, the rotaxane can exist as distinct geometric isomers even though the individual components are stereochemically trivial.[2] Although molecules that correspond to the type 1[3] mechanical geometric isomers (MGI-1) of rotaxanes have been reported, the vast majority where the mechanical bond provides the sole stereogenic unit[4] are constructed from calixarenes[5,6] or similar macrocycles[7] whose facial dissymmetry arises from the fixed cone-shaped conformation of the threaded ring.[8] In these cases, facial dissymmetry is expressed over the whole macrocycle, which has been shown to lead to stereoselective formation of the corresponding rotaxanes. However, to our knowledge, the only MGI-1 rotaxanes in which a single covalent prochiral center differentiates the faces of the ring,[9] as envisaged by Schill, were reported by Bode and Saito,[10] where no stereoselectivity was reported.

More recently,[11] we identified that when a facially dissymmetric macrocycle encircles a prochiral axle an overlooked mechanically axially chiral (MAC)[12] stereogenic unit arises that is analogous to that of catenanes identified by Wasserman and Frisch over 60 years earlier.[13] Having made this observation, we demonstrated that such molecules can be synthesized using a diastereoselective co-conformational chiral auxiliary[14] active template[15] Cu-mediated alkyne-azide cycloaddition (AT-CuAAC[16,17]) approach with a ring whose facial dissymmetry arises from a single prochiral sulfoxide unit.

If we consider a schematic AT-CuAAC retrosynthesis of MGI-1 isomers (Figure 1a) and MAC enantiomers (Figure 1b), in which the axle is divided into two half-axle components that couple through the macrocycle in the forward synthesis, the common challenge involved in the stereoselective synthesis of both becomes obvious; we must control which face of the macrocycle is oriented towards which half-axle component in the mechanical bond forming step.

Here, by re-examining our stereoselective synthesis of MAC rotaxanes, we identify that a single H-bond between the sulfoxide unit and one of the two half-axle components plays a key role in the reaction outcome. We use this understanding to develop a stereoselective approach to rotaxane MGI-1 isomers, which can be extended directly to their catenane counterparts. Finally, we apply our understanding to the direct synthesis of MAC rotaxanes without the need to produce diastereomeric intermediates.

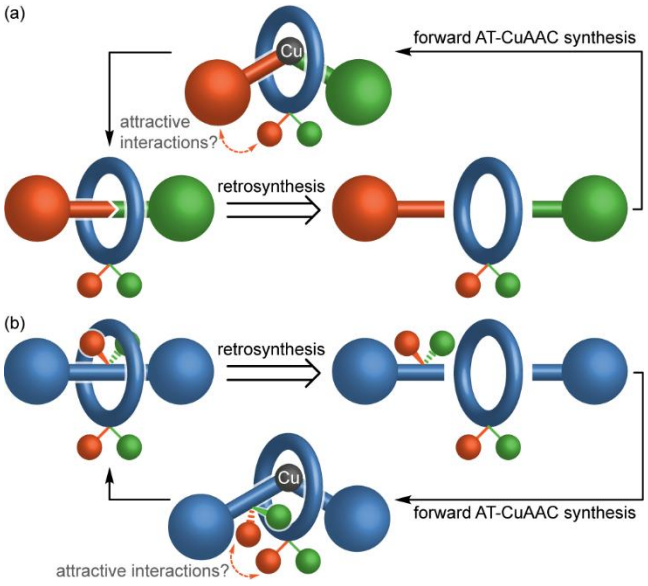
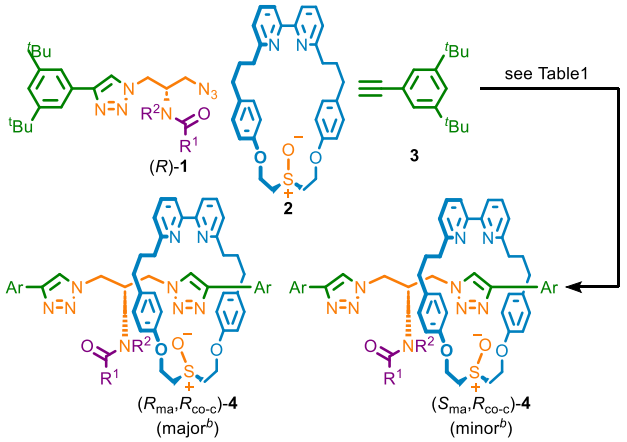


Figure 1. Schematic active template retrosyntheses of the mechanical (a) type 1 geometric isomers and (b) axially chiral enantiomers of rotaxanes highlighting the need to control of facial selectivity in the mechanical bond forming step and the potential for attractive interactions between one face of the macrocycle and one of the half-axles to provide this control.

▪ RESULTS AND DISCUSSION

Effect of conditions and substrate structure in the synthesis of MAC rotaxanes 4. Previously,[11] we found that the AT-CuAAC reaction of azide (*R*)-**1a**, macrocycle **2**, and alkyne **3** gave rotaxanes (R_{ma},$R_{co\text{-}c}$)[18]-**4a** (major) and (S_{ma},$R_{co\text{-}c}$)-**4a** (minor), which have the same static co-conformational covalent configuration (set by the configuration of **1a** and static because the NHBoc unit is too large to allow shuttling) and opposite mechanical axial configuration, in 50% *de* (Scheme 1; Table 1, entry 1). The solid-state structure obtained by single crystal x-ray diffraction (SCXRD) of an analogous catenane[11] contained a close contact between the polarized NH of the carbamate unit and the O atom of the sulfoxide unit, which suggested that an H-bond between these groups may play a role in the observed stereoselectivity.[19]

Scheme 1. Synthesis of rotaxanes **4**[a]



[a]Reagents and conditions (see also Table 1): (*R*)-**1** (1.1 equiv.), **2** (1 equiv.), **3** (1.1 equiv.), $[Cu(CH_3CN)_4]PF_6$ (0.96 equiv.), $^iPr_2NEt$ (2 equiv.). [b]Determined by SCXRD for **1a**[11] and **1d** (Figure 1); **1b**, **c** and **e** are presumed. Ar = 3,5-di-^{t}Bu-C_6H_3.

Table 1. Effect of reaction conditions and substrate on the AT-CuAAC diastereoselective synthesis of rotaxanes **4**

Entry	Substrate	Conditions	Selectivity[a]
1	**1a** (R^1 = OtBu, R^2 = H)	CH_2Cl_2, rt	50% *de*
2	**1a** (R^1 = OtBu, R^2 = H)	EtOH, rt	14% *de*
3	**1b** (R^1 = Me, R^2 = H)	CH_2Cl_2, rt	36% *de*
4	**1c** (R^1 = CCl_3, R^2 = H)	CH_2Cl_2, rt	48% *de*
5	**1d** (R^1 = CF_3, R^2 = H)	CH_2Cl_2, rt	70% *de*
6	**1d** (R^1 = CF_3, R^2 = H)	EtOH, rt	16% *de*
7	**1e** (R^1 = CF_3, R^2 = Me)	CH_2Cl_2, rt	10% *de*
8	**1a** (R^1 = OtBu, R^2 = H)	CH_2Cl_2, –40 °C	72% *de*
9	**1a** (R^1 = OtBu, R^2 = H)	CH_2Cl_2, –78 °C	80% *de*
10	**1d** (R^1 = CF_3, R^2 = H)	CH_2Cl_2, –40 °C	82% *de*
11	**1d** (R^1 = CF_3, R^2 = H)	CH_2Cl_2, –78 °C	70% *de*

[a]Determined by ^{1}H NMR analysis of the crude reaction product.

To test this proposal, we first compared the outcome of the reaction performed in CH_2Cl_2 and EtOH, the latter being a more competitive H-bonding solvent and found that the stereoselectivity was reduced to 14% *de* (entry 2). Furthermore, the reactions of azides **1b-d** to give rotaxanes **4b-d** (entries 3-5) proceeded with selectivities that paralleled the polarization of the N-H unit; trifluoro acetamide **1d** produced rotaxane **4d** in the highest selectivity (70% *de*), followed by trichloroacetamide **1c** (48% *de*) then acetamide **1b** (36% *de*). The SCXRD structure of the major isomer of **4d** (Figure 2) revealed the same (R_{ma},$R_{co\text{-}c}$) configuration as **4a** with an NH•••O H-bond observed between the amide NH and sulfoxide units. Methylated trifluoroacetamide rotaxane **4e** was produced in 10% *de* (entry 6), which suggests that there is some inherent facial bias between the azide and alkyne half-axles in the AT-CuAAC reaction of **2**.

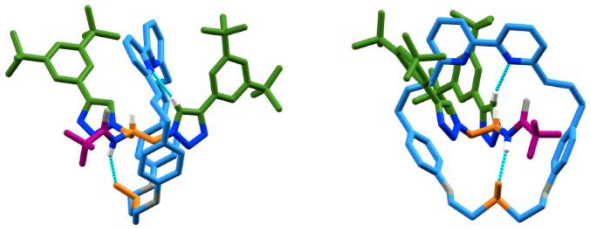
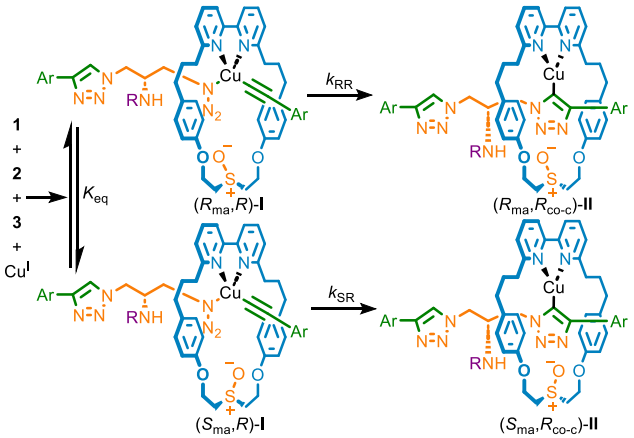


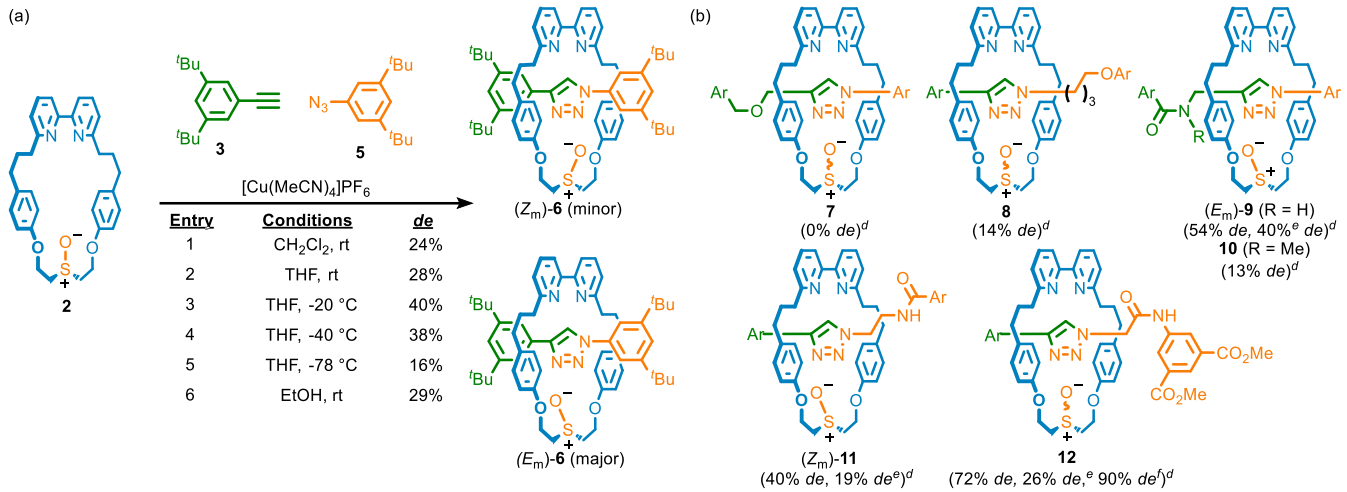
Figure 2. SCXRD structure of [R_{ma},$R_{co\text{-}c}$]-**4d** (major isomer) with key intercomponent interactions highlighted. Colors as in Scheme 1, including the sulfoxide (SO) moiety to highlight the differentiation of the macrocycle faces, except N [dark blue], O [grey], H [white]). Majority of H omitted.

The effect of temperature on the stereoselectivity of the reactions of **1a** and **1d** was more complicated. Whereas reducing the reaction temperature in the synthesis of **4a** from rt (entry 1), to –40 °C (entry 8), to –78 °C (entry 9) increased the observed selectivity, that for **4d** was higher at –40 °C (entry 10) and then fell at –78 °C (entry 11). We suggest that this slightly counterintuitive observation can be rationalized in broad terms by considering that the AT-CuAAC reaction takes place over several steps,[20] which include an equilibrium between diastereomeric azide/acetylide complexes **I** followed by irreversible formation of the corresponding triazolides **II** (Scheme 2).[21] The observed stereoselectivity is thus a composite function of the pre-equilibrium step (K_{eq}) and the relative rates (k_{RR}, k_{SR}) at which intermediates **I** progress to triazolides **II**. The effect of temperature on the reaction to produce **4d** suggests the pre-equilibrium and kinetic resolution steps respond differently to changes in temperature, resulting in the observed behavior.[22]

Scheme 2. Proposed AT-CuAAC mechanism highlighting pre-equilibrium and kinetic resolution steps



Scheme 3. AT-CuAAC synthesis of rotaxane geometric isomers of type 1. (a) Effect of conditions on the formation of rotaxanes **6**.[a] (b) Effect of half-axle structure on the stereoselectivity of mechanical bond formation with macrocycle **2**.[b,c]



[a]Reagents and conditions: **2** (1 equiv.), **3** (1.1 equiv.), **5** (1.1equiv.), $[Cu(MeCN)_4]PF_6$ (0.96 equiv.), $^iPr_2EtN$ (2 equiv.). [b]Synthesized in THF at rt (Scheme 3a, entry 2) unless otherwise stated. [c]Stereochemistry of the major isomer indicated where determined. [d]Determined by ^1H NMR analysis of the crude reaction product. [e]Synthesized in EtOH. [f]Synthesized at –40 °C in THF. Ar = 3,5-di-^{t}Bu-C_6H_3.

Stereoselective synthesis of MGI-1 rotaxanes. Having demonstrated that a single H-bond between the sulfoxide unit and one of the incoming half-axle components appears to be important in the synthesis of rotaxanes **4**, we turned our attention to the synthesis of analogous rotaxanes expressing the MGI-1 stereogenic unit.

Intrigued by the small but measurable stereoselectivity observed in the formation of **4e**, which cannot arise due to the proposed stereo-differentiating NH•••O H-bond, we examined the AT-CuAAC coupling between macrocycle **2** and aryl alkyne **3** and aryl azide **5** half-axles, neither of which contain a directing group, at rt in CH_2Cl_2 (Scheme 3a, entry 1), which gave geometric isomers (E_m)-**6** and (Z_m)-**6** in low but significant stereoselectivity (24% *de*), confirming that the AT-CuAAC reactions of **2** are not only biased by the H-bond identified in the case of rotaxanes **4**.[23] Analysis of the separated isomers of **6** by SCXRD allowed their absolute stereochemistry to be determined (Figure 3a, 3b).

Replacing the solvent with THF marginally improved the selectivity (28% *de*, entry 2), as did lowering the reaction temperature to –20 °C (40% *de*, entry 3) but, as with **4d**, reduced selectivity was observed at lower temperatures (entries 4 and 5). Using EtOH as a reaction solvent was comparable to THF (entry 6).[24] Interestingly, when a propargylic alkyne was employed with **5** in THF to generate rotaxane **7**, no stereoselectivity was observed (Scheme 3b), whereas the reaction of an alkyl azide and **3** to give rotaxane **8** proceeded in low stereoselectivity (14% *de*). This suggests that steric hindrance associated with the coupling partners plays a role in determining facial selectivity in the AT-CuAAC reactions of **2**, as has previously been observed in the synthesis of mechanical planar chiral rotaxanes,[25] although the precise origin of the stereocontrol observed in these simple systems remains unclear.

Returning to our H-bonding-directed approach, when instead a propargylic amide was reacted with **2** to give **9**, a significantly improved stereoselectivity (54% *de*) was obtained, which was reduced in EtOH (40% *de*). The corresponding *N*-methyl amide gave rise to rotaxane **10** in low selectivity (13% *de*). The AT-CuAAC coupling of **3** and an alkyl azide bearing a simple amide gave rotaxane **11** in moderate stereoselectivity (40% *de*), which was reduced in EtOH (19% *de*). Thus, the amide can be placed in either coupling partner. Finally, rotaxane **13**, whose amide NH is expected to be more polarized than that of **12** was produced in good selectivity (72% *de*) at rt, which was improved (90% *de*) when the same reaction was conducted at –40 °C. Reducing the temperature further did not improve the observed stereocontrol and led to a slow reaction. Replacing the reaction solvent with EtOH once again led to reduced selectivity (26% *de*).

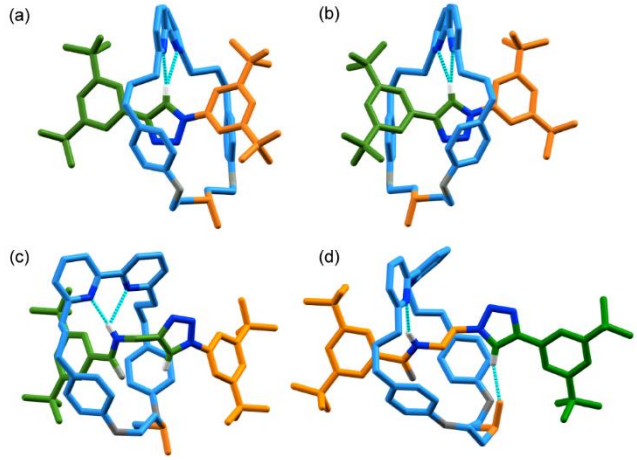


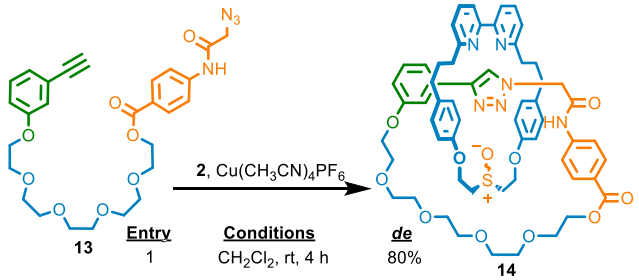
Figure 3. (a) Solid state structures of (a) (Z_m)-**6**, (b) (E_m)-**6**, (c) (Z_m)-**9** and (d) (E_m)-**11** with key intercomponent interactions highlighted. Colors as in Scheme 1, including the sulfoxide (SO) moiety to emphasize the macrocycle faces, except O (grey), N (dark blue), H (white). Majority of H omitted for clarity.

As in the case of rotaxanes **4**, the high selectivity observed in the synthesis of **9**, **11** and **12** is consistent with the key role of an NH•••O interaction between the macrocycle and half-axle in controlling the facial selectivity in the AT-CuAAC reactions of macrocycle **2**. However, we previously observed[11] this interaction in the solid-state structures of both diastereomers of epimeric MAC catenanes due to the

flexible nature of macrocycle **2**. The major isomers of rotaxanes **9** and **11** determined by SCXRD (Figure 3c and 3d respectively) highlight the importance of this flexibility; although both were formed selectively, counterintuitively the ring is oriented in opposite directions with respect to the amide in the major diastereomer of each. Thus, although the NH•••O interaction appears able to direct the synthesis of MGI-1 isomers, the major product depends on the detailed structure of the half-axles used.[26] We also note that whereas an NH•••O interaction is observed in the SCXRD structure of **4d**, in the case of **9** and **11** this is replaced by an NH•••N interaction between the amide proton and one of the bipyridine N atoms, with the SO unit instead interacting with the polarized C-H of the triazole moiety in an inter- or intra-molecular manner respectively, presumably because the NH unit is geometrically accessible to the macrocycle in rotaxanes **9** and **11** whereas it is not in the case of **4d**.

Stereoselective synthesis of an MGI catenane. Having established that a polarised NH unit appears sufficient to control the synthesis of MGI-1 rotaxanes with macrocycle **2**, we briefly investigated whether the same approach could be applied to the related isomers of catenanes. Pre-macrocycle **13**, which contains an activated amide unit analogous to that of **12**, reacted with **2** under our AT-CuAAC catenane-forming conditions (Scheme 4)[27] to give **14** with good stereocontrol (80% *de*, entry 1). The same reaction in $CHCl_3$-EtOH gave reduced the selectivity (60% *de*, entry 2) whereas performing the reaction at 0 °C in CH_2Cl_2 increased the selectivity (92% *de*, entry 3). Lowering the temperature further (–40 °C) had no significant effect (90% *de*, entry 4). Thus, unsurprisingly given the similarity of their stereogenic units, MGI-1 rotaxanes and MGI catenanes can be made with good stereocontrol using equivalent strategies.

Scheme 4. Stereoselective synthesis of catenane **14**.[a]



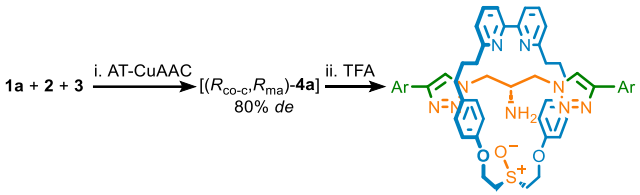
Entry	Conditions	*de*
1	CH_2Cl_2, rt, 4 h	80%
2	$CHCl_3$-EtOH (1 : 1), rt, 4 h	60%
3	CH_2Cl_2, 0 °C, 16 h	92%
4	CH_2Cl_2, -40 °C, 16 h	90%

[a]Reagents and conditions: **13** (2 equiv.) was added over the time stated using a syringe pump to **2** (1 equiv.), $[Cu(MeCN)_4]PF_6$ (0.97 equiv.), $^{i}Pr_2EtN$ (4 equiv.).

Direct enantioselective synthesis of MAC rotaxanes. Finally, we returned to apply our findings to the stereoselective synthesis of the enantiomers of MAC rotaxanes. In our original report we separated the diastereomers of epimeric rotaxanes **4a** before removing the Boc group to generate rotaxane **15** (Scheme 5) in which the MAC stereogenic unit is the only fixed source of stereochemistry. This was necessary as the AT-CuAAC reaction only proceeded in 50% *de*; given that the ultimate purpose of developing methodologies to produce stereochemically complex mechanically interlocked molecules is ultimately so they can then be applied to solve chemical problems, for example in sensing[28] or catalysis,[29] for which they must be available in high stereopurity, in our original report this was a necessary step.

Trivially, our optimized conditions for the diastereoselective formation of **4a** (Table 1, entry 9) removes the need for the separation of the MAC epimers and so allows the synthesis of highly enantioenriched samples of rotaxane **15** in a two-step, one-pot manner (Scheme 5); AT-CuAAC coupling of (*R*)-**1a** followed by TFA-mediated removal of the Boc group gave rotaxane (R_{ma})-**15** in good stereoselectivity (+78% *ee*) in agreement with that observed for **4a** (80% *de*). The same reaction with (*S*)-**1a** gave (S_{ma})-**5** (77% *ee*).

Scheme 5. Two-step, one-pot synthesis of enantioenriched MAC rotaxanes **15**[a]



[a]Reagents and conditions: i. **1a** (1.1 equiv.), **2** (1 equiv.), **3** (1.1 equiv.), $[Cu(CH_3CN)]PF_6$ (0.96 equiv.), $^{i}Pr_2NEt$ (2 equiv.), CH_2Cl_2, 16 h; ii. TFA, CH_2Cl_2, –78 °C to rt, 6 h. [b]Determined by analytical CSP-HPLC. Ar = 3,5-di-^{t}Bu-C_6H_3.

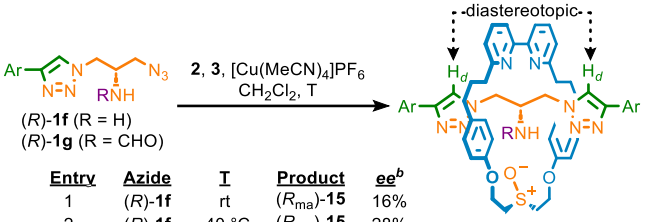
More excitingly, the high stereoselectivity observed in the AT-CuAAC reaction of azides **1** bearing a polarized NH presents the opportunity for the direct synthesis of MAC rotaxanes without the need for first forming separable co-conformational diastereomers; if the N substituent is too small to trap the macrocycle in one triazole-containing compartment, the only fixed stereochemistry in the product is provided by the MAC stereogenic unit.

The reaction of primary amine-containing azide (*R*)-**1e** with macrocycle **2** and alkyne **3** at rt gave MAC rotaxane **15** directly but in low stereoselectivity (16% *ee*, Scheme 6, entry 1), which increased when the reaction was performed at –40 °C (28% *ee*, entry 2) and improved further still at –78 °C (42% *ee*, entry 3). CSP-HPLC analysis of a sample of rotaxane (R_{ma})-**15** produced from (*R*)-**1a** (Scheme 5) and comparison with the same product from (*R*)-**1f** confirmed that the latter also produces (R_{ma})-**15** as the major product (Figure 4a).

When instead formamide-containing azide (*R*)-**1g** was reacted with **2** and **3**, even at rt rotaxane **16**[30] was obtained in reasonable stereopurity (57% *ee*, entry 3), which was improved further at –40 °C (67% *ee*, entry 4). Conducting this reaction at –78 °C reduced the observed stereoselectivity (59% *ee*, entry 5), suggesting that, as with azide **1d**, the pre-equilibrium and kinetic resolution steps result in an unusual temperature dependence. CSP-HPLC analysis of a sample of rotaxane **16** produced by formylation of a sample of rotaxane (R_{ma})-**15** of known stereopurity and comparison

with the same compound produced from (*R*)-**1g** confirmed that the latter produces (R_{ma})-**16** as the major stereoisomer. When (*S*)-**1g** was reacted instead (S_{ma})-**16** was produced (70% *ee*, entry 6). The solid-state structure of **6** obtained by SCXRD (Figure 2b) did not display the expected intermolecular NH•••O H-bond; instead, the same interaction was found to occur in an intermolecular fashion within the unit cell.

Scheme 6. Direct synthesis of enantioenriched mechanically axially chiral rotaxanes **15** and **16**[a]



Entry	Azide	T	Product	ee[b]
1	(*R*)-**1f**	rt	(R_{ma})-**15**	16%
2	(*R*)-**1f**	-40 °C	(R_{ma})-**15**	28%
3	(*R*)-**1f**	-78 °C	(R_{ma})-**15**	42%
4	(*R*)-**1g**	rt	(R_{ma})-**16**	57%
5	(*R*)-**1g**	-40 °C	(R_{ma})-**16**	67%
6	(*R*)-**1g**	-78 °C	(R_{ma})-**16**	59%
7	(*S*)-**1g**	-40 °C	(S_{ma})-**16**	70%

[a]Reagents and conditions: i. **1** (1.1 equiv.), **2** (1 equiv.), **3** (1.1 equiv.), [Cu(CH$_3$CN)]PF$_6$ (0.96 equiv.), ^{i}Pr$_2$NEt (2 equiv.), CH$_2$Cl$_2$, 16 h. [b]Determined by analytical CSP-HPLC.

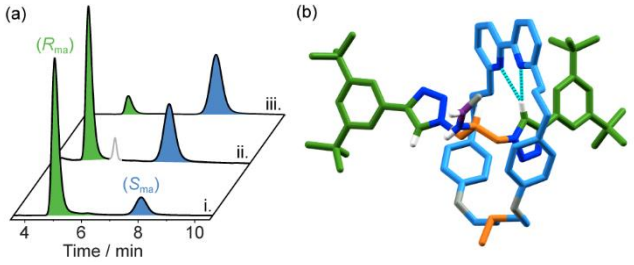


Figure 4. (a) CSP-HPLC analysis of: i. (R_{ma})-**16** (67% *ee*) produced from (*R*)-**1g**; ii. (R_{ma})-**16** (21% *ee*) produced from (R_{ma})-**15** (21% ee; minor impurity highlighted in grey), and iii. (S_{ma})-**16** (70% *ee*) produced from (*S*)-**1g**. (b) Solid state structure of *rac*-**16**, in which the N-H•••O bond between the SO unit and the amide is intermolecular (colors as in Scheme 6, including the sulfoxide (SO) moiety to highlight the differentiation of the macrocycle faces, except N [dark blue], O [grey], H [white]).

The different co-conformational behaviors of **4a**, **15** and **16** are clear from analysis of their respective ^{1}H NMR spectra. Diastereomers (R_{ma},$R_{co\text{-}c}$)-**4a** and (S_{ma},$R_{co\text{-}c}$)-**4a** are separable species; heating a mixture diastereomers **4a** resulted in no change in their ratio (Figure S47), confirming that the macrocycle cannot shuttle between the two compartments due to the large NHBoc unit. In contrast, the diastereotopic triazole resonances H$_d$ of amine rotaxane **15** appear as two sharp singlets at 298 K, indicating that diastereomeric co-conformations (R_{ma},$R_{co\text{-}c}$)-**5** and (S_{ma},$R_{co\text{-}c}$)-**5** are in fast exchange on the ^{1}H NMR timescale through rapid shuttling of the macrocycle between the two triazole-containing compartments (Figure S190). The same resonances for formylated rotaxane **16** are broad at 298 K, although once again only two signals are observed (Figure S200). This observation is consistent with (R_{ma},$R_{co\text{-}c}$)-**16** and (S_{ma},$R_{co\text{-}c}$)-**16** exchanging on the ^{1}H NMR timescale, albeit more slowly than (R_{ma},$R_{co\text{-}c}$)-**15** and (S_{ma},$R_{co\text{-}c}$)-**15**, in keeping with the larger steric bulk of the formamide group of **6**. Accordingly, increasing the temperature resulted in sharpening of the two resonances corresponding to H$_d$ (Figure S211).

▪ CONCLUSIONS

In conclusion, we have demonstrated that type 1 rotaxane mechanical geometric isomers and mechanically axially chiral enantiomers can be obtained by controlling facial selectivity in an AT-CuAAC synthesis. Specifically, we show that an H-bonding interaction between a prochiral macrocycle and a functional group unsymmetrically disposed in the corresponding half-axle (rotaxane synthesis) or pre-macrocycle (catenane synthesis) is sufficient to control the reaction outcome. The high selectivity observed with optimized substrates allowed us to design a direct enantioselective synthesis of mechanically axially chiral rotaxanes, only the second[31a] example of a direct stereoselective synthesis of a mechanically chiral molecule and the first of this recently identified stereogenic unit. To date, type 1 mechanical geometric isomers of rotaxanes based on calixarenes and similar cone-shaped macrocycles,[5,6b,7d,e] as well as structures expressing combinations of mechanical and covalent stereochemistry[4h] have been investigated as components of molecular switches and motors. Here we have demonstrated that such isomerism can be expressed and controlled in much simpler macrocycles, opening new motifs for study. Similarly, mechanically planar chiral molecules, for which stereoselective methods are known,[14,25,31] have been investigated as enantioselective sensors,[28] catalysts,[29] and chiroptical switches.[32] With methodological concepts now in hand to efficiently synthesize their mechanically axially chiral cousins in high stereopurity, we eagerly anticipate the chemical applications to which molecules containing this stereogenic unit will soon be put.

ASSOCIATED CONTENT

Supporting Information. Procedures and full characterization data (NMR, MS, CD, SCXRD, HPLC as appropriate) for all novel compounds and supplementary discussion.

AUTHOR INFORMATION

Corresponding Author

*s.m.goldup@bham.ac.uk

Author Contributions

‡These authors contributed equally.

ACKNOWLEDGMENT

SMG thanks the ERC (Agreement no. 724987) for funding and the Royal Society for a Wolfson Research Fellowship (RSWF\FT\180010). A. Saady thanks the Council for Higher Education-Israel for a personal fellowship. AS thanks the Royal Society and University of Birmingham for funding. PG thanks the University of Southampton and the University of Birmingham for funding.

▪ REFERENCES

(1) Bruns, C. J.; Stoddart, J. F., *The Nature of the Mechanical Bond: From Molecules to Machines*. Wiley: 2016.

(2) Schill, G., *Catenanes, Rotaxanes and Knots*. Academic Press: New York, 1971.

(3) We have recently identified a second form of rotaxane geometric stereochemistry and so have proposed that these are disambiguated by the addition of the type 1/2 label: Gallagher, P.; Savoini, A.; Saady, A.; Goldup, S. M. *ChemRxiv* **2023**, DOI: 10.26434/chemrxiv-2023-60b2b.

(4) The stereochemistry of rotaxanes and catenanes whose macrocycle contains one or more covalent stereogenic centre in the main chain (e.g., as found in cyclodextrin rings) and whose axle/second ring respectively are oriented can be fully described by a covalent stereodescriptor and either a mechanical planar stereolable or mechanical geometric stereolabel. We prefer the mechanically planar description as, in the case of catenanes, this typically although not always[31g] refers to a topological source of stereochemistry, one of the unusual properties of such systems. For selected examples of structures that conform to this class of molecule see: (a) Armspach, D.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Godi, A.; Moore, C. P.; Prodi, L.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Wear, T. J.; Williams, D. J., Catenated Cyclodextrins. *Chem. Eur. J.* **1995,** *1* (1), 33. (b) Craig, M. R.; Hutchings, M. G.; Claridge, T. D. W.; Anderson, H. L., Rotaxane-encapsulation enhances the stability of an azo dye, in solution and when bonded to cellulose. *Angew. Chem. Int. Ed.* **2001,** *40* (6), 1071. (c) Wang, Q. C.; Ma, X.; Qu, D. H.; Tian, H., Unidirectional threading synthesis of isomer-free [2]rotaxanes. *Chem. Eur. J.* **2006,** *12* (4), 1088. (d) Bruns, Exploring and Exploiting the Symmetry-Breaking Effect of Cyclodextrins in Mechanomolecules. *Symmetry* **2019,** *11* (10), 1249. (e) Makita, Y.; Kihara, N.; Takata, T., Synthesis and kinetic resolution of directional isomers of [2]rotaxanes bearing a lariat crown ether wheel. *Supramol. Chem.* **2021,** *33* (1-2), 1. (f) Schroder, H. V.; Zhang, Y.; Link, A. J., Dynamic covalent self-assembly of mechanically interlocked molecules solely made from peptides. *Nat. Chem.* **2021,** *13* (9), 850. (g) Lopez-Leonardo, C.; Saura-Sanmartin, A.; Marin-Luna, M.; Alajarin, M.; Martinez-Cuezva, A.; Berna, J., Ring-to-Thread Chirality Transfer in [2]Rotaxanes for the Synthesis of Enantioenriched Lactams. *Angew. Chem. Int. Ed.* **2022,** *61* (39), e202209904. (h) Liu, E.; Cherraben, S.; Boulo, L.; Troufflard, C.; Hasenknopf, B.; Vives, G.; Sollogoub, M., A molecular information ratchet using a cone-shaped macrocycle. *Chem* **2023,** *9* (5), 1147.

(5) Selected examples: (a) Arduini, A.; Ciesa, F.; Fragassi, M.; Pochini, A.; Secchi, A., Selective synthesis of two constitutionally isomeric oriented calix[6]arene-based rotaxanes. *Angew. Chem. Int. Ed.* **2005,** *44* (2), 278. (b) Arduini, A.; Bussolati, R.; Credi, A.; Faimani, G.; Garaudee, S.; Pochini, A.; Secchi, A.; Semeraro, M.; Silvi, S.; Venturi, M., Towards controlling the threading direction of a calix[6]arene wheel by using nonsymmetric axles. *Chem. Eur. J.* **2009,** *15* (13), 3230. (c) Pierro, T.; Gaeta, C.; Talotta, C.; Casapullo, A.; Neri, P., Fixed or invertible calixarene-based directional shuttles. *Org. Lett.* **2011,** *13* (10), 2650. (d) Arduini, A.; Bussolati, R.; Credi, A.; Secchi, A.; Silvi, S.; Semeraro, M.; Venturi, M., Toward directionally controlled molecular motions and kinetic intra- and intermolecular self-sorting: threading processes of nonsymmetric wheel and axle components. *J. Am. Chem. Soc.* **2013,** *135* (26), 9924. (e) Ciao, R.; Talotta, C.; Gaeta, C.; Margarucci, L.; Casapullo, A.; Neri, P., An oriented handcuff rotaxane. *Org. Lett.* **2013,** *15* (22), 5694. (f) Zanichelli, V.; Ragazzon, G.; Arduini, A.; Credi, A.; Franchi, P.; Orlandini, G.; Venturi, M.; Lucarini, M.; Secchi, A.; Silvi, S., Synthesis and Characterization of Constitutionally Isomeric Oriented Calix[6]arene-Based Rotaxanes. *Eur. J. Org. Chem.* **2016,** *2016* (5), 1033. (g) La Manna, P.; Talotta, C.; Gaeta, C.; Soriente, A.; De Rosa, M.; Neri, P., Threading of an Inherently Directional Calixarene Wheel with Oriented Ammonium Axles. *J. Org. Chem.* **2017,** *82* (17), 8973. (h) Bazzoni, M.; Andreoni, L.; Silvi, S.; Credi, A.; Cera, G.; Secchi, A.; Arduini, A., Selective access to constitutionally identical, orientationally isomeric calix[6]arene-based [3]rotaxanes by an active template approach. *Chem. Sci.* **2021,** *12* (18), 6419. (i) Cera, G.; Arduini, A.; Secchi, A.; Credi, A.; Silvi, S., Heteroditopic Calix[6]arene Based Intervowen and Interlocked Molecular Devices. *Chem. Rec.* **2021,** *21* (5), 1161. (j) Andreoni, L.; Bonati, F. C.; Groppi, J.; Balestri, D.; Cera, G.; Credi, A.; Secchi, A.; Silvi, S., Selective enhancement of organic dye properties through encapsulation in rotaxane orientational isomers. *Chem. Commun.* **2023,** *59* (33), 4970.

(6) (a) Gaeta, C.; Talotta, C.; Mirra, S.; Margarucci, L.; Casapullo, A.; Neri, P., Catenation of calixarene annulus. *Org. Lett.* **2013,** *15* (1), 116. (b) Zanichelli, V.; Dallacasagrande, L.; Arduini, A.; Secchi, A.; Ragazzon, G.; Silvi, S.; Credi, A., Electrochemically Triggered Co-Conformational Switching in a [2]catenane Comprising a Non-Symmetric Calix[6]arene Wheel and a Two-Station Oriented Macrocycle. *Molecules* **2018,** *23* (5), 1156.

(7) Selected examples: (a) Xue, M.; Su, Y. S.; Chen, C. F., Isomeric squaraine-based [2]pseudorotaxanes and [2]rotaxanes: synthesis, optical properties, and their tubular structures in the solid state. *Chem. Eur. J.* **2010,** *16* (28), 8537. (b) Xia, Y.-X.; Xie, T.; Han, Y.; Chen, C.-F., Triptycene-derived calix[6]arene analogues: synthesis, structure and complexation with paraquat derivatives. *Org. Chem. Front.* **2014,** *1* (2). (c) Wang, H. X.; Meng, Z.; Xiang, J. F.; Xia, Y. X.; Sun, Y.; Hu, S. Z.; Chen, H.; Yao, J.; Chen, C. F., Guest-dependent directional complexation based on triptycene derived oxacalixarene: formation of oriented rotaxanes. *Chem. Sci.* **2016,** *7* (1), 469. (d) Cui, J. S.; Ba, Q. K.; Ke, H.; Valkonen, A.; Rissanen, K.; Jiang, W., Directional Shuttling of a Stimuli-Responsive Cone-Like Macrocycle on a Single-State Symmetric Dumbbell Axle. *Angew. Chem. Int. Ed.* **2018,** *57* (26), 7809. (e) Li, K. A.; Wang, Z.; Xie, C. D.; Chen, T.; Qiang, H.; Liu, Y. A.; Jia, X. S.; Hu, W. B.; Wen, K., Unidirectional complexation of pillar[4]arene[1]benzoquinoneoxime with alkyl alcohols. *Org. Biomol. Chem.* **2019,** *17* (20), 4975.

(8) (a) Li, K. A.; Wang, Z.; Xie, C. D.; Chen, T.; Qiang, H.; Liu, Y. A.; Jia, X. S.; Hu, W. B.; Wen, K., Unidirectional complexation of pillar[4]arene[1]benzoquinoneoxime with alkyl alcohols. *Org. Biomol. Chem.* **2019,** *17* (20), 4975. (b) Wang, X.; Gan, Q.; Wicher, B.; Ferrand, Y.; Huc, I., Directional Threading and Sliding of a Dissymmetrical Foldamer Helix on Dissymmetrical Axles. *Angew. Chem. Int. Ed.* **2019,** *58* (13), 4205.

(9) For a detailed discussion of facial dissymmetry in interlocked structures see ref. 11.

(10) Saito, F.; Bode, J. W., Synthesis and stabilities of peptide-based [1]rotaxanes: molecular grafting onto lasso peptide scaffolds. *Chem. Sci.* **2017,** *8* (4), 2878.

(11) Maynard, J. R. J.; Gallagher, P.; Lozano, D.; Butler, P.; Goldup, S. M., Mechanically axially chiral catenanes and noncanonical mechanically axially chiral rotaxanes. *Nat. Chem.* **2022,** *14* (9), 1038.

(12) (a) Jamieson, E. M. G.; Modicom, F.; Goldup, S. M., Chirality in rotaxanes and catenanes. *Chem. Soc. Rev.* **2018,** *47* (14), 5266. (b) Pairault, N.; Niemeyer, J., Chiral Mechanically Interlocked Molecules - Applications of Rotaxanes, Catenanes and Molecular Knots in Stereoselective Chemosensing and Catalysis. *Synlett* **2018,** *29* (6), 689. (c) Evans, N. H., Chiral Catenanes and Rotaxanes: Fundamentals and Emerging Applications. *Chem. Eur. J.* **2018,** *24* (13), 3101.

(13) Frisch, H. L.; Wasserman, E., Chemical Topology. *J. Am. Chem. Soc.* **1961,** *83*, 3789.

(14) Maynard, J. R. J.; Goldup, S. M., Strategies for the Synthesis of Enantiopure Mechanically Chiral Molecules. *Chem* **2020,** *6* (8), 1914.

(15) Denis, M.; Goldup, S. M., The active template approach to interlocked molecules. *Nat. Rev. Chem.* **2017,** *1* (8), 0061.

(16) Aucagne, V.; Hanni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B., Catalytic "click" rotaxanes: a substoichiometric metal-template pathway to mechanically interlocked architectures. *J. Am. Chem. Soc.* **2006,** *128* (7), 2186.

(17) Saady, A.; Goldup, S. M., Triazole formation and the click concept in the synthesis of interlocked molecules. *Chem* **2023,** *9* (8), 2110.

(18) The suffix "ma" indicates that the label refers to the mechanical axial stereogenic unit. The suffix "co-c" indicates that the stereochemical label refers to the co-conformational covalent stereogenic unit.[11]

(19) We note that the previously reported SCXRD structure of minor diastereomer (*S*ma,*R*co-c)-**4a**[11] contains the same interaction but in this case it occurs intermolecularly between neighboring molecules in the unit cell, as observed for **4d** (Figure 2).

(20) (a) Neal, E. A.; Goldup, S. M., Competitive formation of homocircuit [3]rotaxanes in synthetically useful yields in the bipyridine-mediated active template CuAAC reaction. *Chem. Sci.* **2015,** *6* (4), 2398. (b) Neal, E. A.; Goldup, S. M., A Kinetic Self-Sorting Approach to Heterocircuit [3]Rotaxanes. *Angew. Chem. Int. Ed.* **2016,** *55* (40), 12488. (b) Modicom, F.; Jamieson, E. M. G.; Rochette, E.; Goldup, S. M., Chemical Consequences of the Mechanical Bond: A Tandem Active Template-Rearrangement Reaction. *Angew. Chem. Int. Ed.* **2019,** *58* (12), 3875.

(21) Winn, J.; Pinczewska, A.; Goldup, S. M., Synthesis of a rotaxane Cu(I) triazolide under aqueous conditions. *J. Am. Chem. Soc.* **2013,** *135* (36), 13318.

(22) We note that our results cannot rule out that either K_{eq} or $k_{SS}/_{SR}$ depends on a large negative entropy of reaction or activation respectively, which may also account for the unexpected temperature dependence of the AT-CuAAC reaction.

(23) The subscript is intended to indicate the mechanical origin of the stereochemistry. For a detailed discussion of how the mechanical stereogenic unit is assigned in such systems, see ESI section 8.

(24) Other combinations of solvent and temperature did not improve the reaction stereoselectivity. See ESI section 9 for further details.

(25) (a) Jinks, M. A.; de Juan, A.; Denis, M.; Fletcher, C. J.; Galli, M.; Jamieson, E. M. G.; Modicom, F.; Zhang, Z.; Goldup, S. M., Stereoselective Synthesis of Mechanically Planar Chiral Rotaxanes. *Angew. Chem. Int. Ed.* **2018,** *57* (45), 14806. (b) de Juan, A.; Lozano, D.; Heard, A. W.; Jinks, M. A.; Suarez, J. M.; Tizzard, G. J.; Goldup, S. M., A chiral interlocking auxiliary strategy for the synthesis of mechanically planar chiral rotaxanes. *Nat. Chem.* **2022,** *14* (2), 179.

(26) Unfortunately, we were unable to determine the absolute stereochemistry of rotaxane **10** as crystals suitable for SCXRD analysis were not forthcoming.

(27) Lewis, J. E. M.; Modicom, F.; Goldup, S. M., Efficient Multicomponent Active Template Synthesis of Catenanes. *J. Am. Chem. Soc.* **2018,** *140* (14), 4787.

(28) Hirose, K.; Ukimi, M.; Ueda, S.; Onoda, C.; Kano, R.; Tsuda, K.; Hinohara, Y.; Tobe, Y., The Asymmetry is Derived from Mechanical Interlocking of Achiral Axle and Achiral Ring Components - Syntheses and Properties of Optically Pure [2]Rotaxanes. *Symmetry* **2018,** *10* (1), 20.

(29) Heard, A. W.; Goldup, S. M., Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis. *Chem* **2020,** *6* (4), 994.

(30) ^{1}H NMR analysis of **16** confirmed that the ring is able to shuttle past the formamide unit. See ESI section 11.

(31) (a) Denis, M.; Lewis, J. E. M.; Modicom, F.; Goldup, S. M., An Auxiliary Approach for the Stereoselective Synthesis of Topologically Chiral Catenanes. *Chem* **2019,** *5* (6), 1512. (c) Tian, C.; Fielden, S. D. P.; Perez-Saavedra, B.; Vitorica-Yrezabal, I. J.; Leigh, D. A., Single-Step Enantioselective Synthesis of Mechanically Planar Chiral [2]Rotaxanes Using a Chiral Leaving Group Strategy. *J. Am. Chem. Soc.* **2020,** *142* (21), 9803. (c) Imayoshi, A.; Lakshmi, B. V.; Ueda, Y.; Yoshimura, T.; Matayoshi, A.; Furuta, T.; Kawabata, T., Enantioselective preparation of mechanically planar chiral rotaxanes by kinetic resolution strategy. *Nat. Commun.* **2021,** *12* (1), 404. (d) Li, M. F.; Chia, X. L.; Tian, C.; Zhu, Y., Mechanically planar chiral rotaxanes through catalytic desymmetrization. *Chem* **2022,** *8* (10), 2843. (e) Rodriguez-Rubio, A.; Savoini, A.; Modicom, F.; Butler, P.; Goldup, S. M., A Co-conformationally "Topologically" Chiral Catenane. *J. Am. Chem. Soc.* **2022,** *144* (27), 11927. (f) Zhang, S.; Rodríguez-Rubio, A.; Saady, A.; Tizzard, G. J.; Goldup, S. M., A chiral macrocycle for the stereoselective synthesis of mechanically planar chiral rotaxanes and catenanes. *Chem* **2023,** *9* (5), 1195. (g) Pairault, N.; Rizzi, F.; Lozano, D.; Jamieson, E. M. G.; Tizzard, G. J.; Goldup, S. M., A catenane that is topologically achiral despite being composed of oriented rings. *Nat. Chem.* **2023,** *15* (6), 781.

(32) (a) Gaedke, M.; Witte, F.; Anhauser, J.; Hupatz, H.; Schroder, H. V.; Valkonen, A.; Rissanen, K.; Lutzen, A.; Paulus, B.; Schalley, C. A., Chiroptical inversion of a planar chiral redox-switchable rotaxane. *Chem. Sci.* **2019,** *10* (43), 10003. (b) Wang, Y.; Gong, J.; Wang, X.; Li, W. J.; Wang, X. Q.; He, X.; Wang, W.; Yang, H. B., Multistate Circularly Polarized Luminescence Switching through Stimuli-Induced Co-Conformation Regulations of Pyrene-Functionalized Topologically Chiral [2]Catenane. *Angew. Chem. Int. Ed.* **2022,** e202210542.