

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

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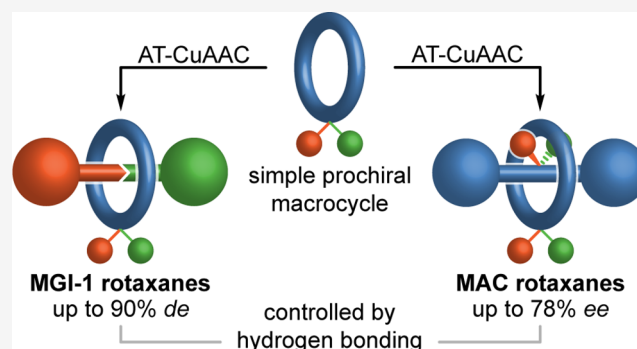


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**ABSTRACT:** In 1971, Schill recognized that a prochiral macrocycle encircling an oriented axle led to geometric isomerism in rotaxanes. More recently, we identified an overlooked chiral stereogenic unit in rotaxanes that arises when a prochiral macrocycle encircles a prochiral axle. Here, we show that both stereogenic units can be accessed using equivalent strategies, with a single weak stereodifferentiating interaction sufficient for moderate to excellent stereoselectivity. Using this understanding, we demonstrated 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,<sup>1</sup> 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.<sup>2</sup> Although molecules that correspond to the type 1<sup>3</sup> mechanical geometric isomers (MGI-1) of rotaxanes have been reported, the vast majority where the mechanical bond provides the sole stereogenic unit<sup>4</sup> are constructed from calixarenes<sup>5</sup> or similar macrocycles<sup>6</sup> whose facial dissymmetry arises from the fixed cone-shaped conformation of the threaded ring.<sup>7</sup> The same is true of the corresponding catenane stereogenic unit first reported by Gaeta and Neri.<sup>8</sup> In these cases, facial dissymmetry is expressed over the whole macrocycle, which has been shown to lead to the 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,<sup>9</sup> as envisaged by Schill, were reported by Bode and Saito,<sup>10</sup> where no stereoselectivity was reported.

More recently,<sup>11</sup> we identified that when a facially dissymmetric macrocycle encircles a prochiral axle, an overlooked mechanically axially chiral (MAC)<sup>12</sup> stereogenic unit arises that is analogous to the MAC stereogenic unit of catenanes identified by Wasserman and Frisch over 60 years earlier.<sup>13</sup> Having made this observation, we demonstrated that such molecules can be synthesized using a diastereoselective co-conformational chiral auxiliary<sup>14</sup> active template<sup>15</sup> Cu-

mediated alkyne–azide cycloaddition (AT-CuAAC)<sup>16,17</sup> 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 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 toward which half-axle component in the mechanical bond-forming step.

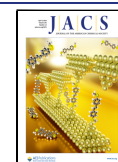
Here, by re-examining our stereoselective synthesis of MAC rotaxanes, we identify that a single H-bond between the sulfoxide unit and one of the two half-axle components appears to play a key role in the reaction outcome. We use this understanding to develop a stereoselective approach to rotaxane MGI-1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

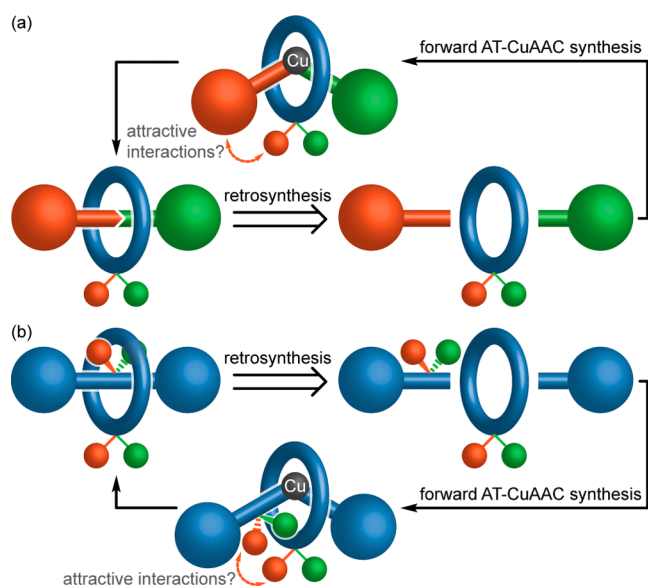
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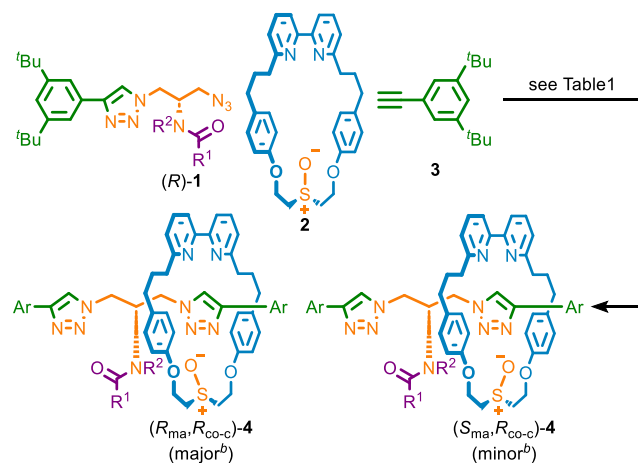
**Figure 1.** Schematic active template retrosyntheses of the mechanical (a) type 1 geometric isomers and (b) axially chiral enantiomers of rotaxanes, highlighting the need to control facial selectivity in the mechanical bond-forming step and the potential for attractive interactions between one face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

## RESULTS AND DISCUSSION

**Effect of the Conditions and Substrate Structure in the Synthesis of MAC Rotaxanes 4.** Previously,<sup>11</sup> we found that the AT-CuAAC reaction of azide (*R*)-**1a**, macrocycle **2**, and alkyne **3** gave rotaxane diastereomers ( $R_{\text{ma}}, R_{\text{co-c}}$ )-**4a** (major) and ( $S_{\text{ma}}, R_{\text{co-c}}$ )-**4a** (minor) in 50% *de* (Scheme 1 and Table 1, entry 1). These products have the same conformational covalent configuration<sup>19</sup> (set by the configuration of **1a**) but opposite mechanical axial configuration. They are separable because the steric bulk of the NHBoc group prevents the epimerization of the covalent stereocenter by shuttling of the macrocycle between triazole-containing compartments. The solid-state structure obtained by single-crystal X-ray diffraction (SCXRD) of an analogous catenane<sup>11</sup> 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.<sup>20</sup>

To test this proposal, we first compared the outcome of reactions performed in  $\text{CH}_2\text{Cl}_2$  and EtOH, the latter being a more competitive H-bonding solvent, and found that the stereoselectivity was indeed 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; trifluoroacetamide **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 ( $R_{\text{ma}}, R_{\text{co-c}}$ ) configuration as that of **4a**, with an  $\text{NH}\cdots\text{O}$  H-bond observed between the amide NH and sulfoxide units. Methylated trifluoroacetamide rotaxane **4e** was produced in 10% *de* (entry 6), which, although consistent with the key role of the  $\text{NH}\cdots\text{O}$  H-bond, suggests that there is some inherent facial bias between the azide and alkyne half-axes in the AT-CuAAC reactions of **2**.

## Scheme 1. Synthesis of Rotaxanes 4<sup>a</sup>

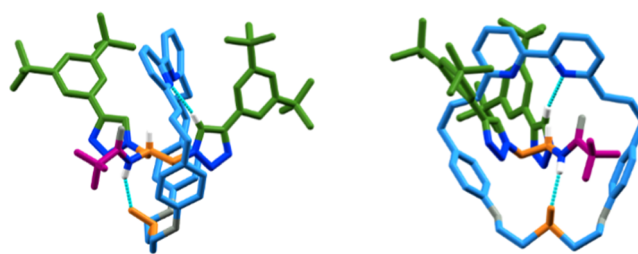


<sup>a</sup>Reagents and conditions (see also Table 1): (*R*)-**1** (1.1 equiv), **2** (1 equiv), **3** (1.1 equiv),  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$  (0.96 equiv),  $i\text{Pr}_2\text{NEt}$  (2 equiv). <sup>b</sup>Determined by SCXRD for **1a**<sup>11</sup> and **1d** (Figure 1); **1b**, **c**, and **e** are presumed. Ar = 3,5-di-*t*-Bu- $\text{C}_6\text{H}_3$ .

**Table 1. Effect of the Reaction Conditions and Substrate on the AT-CuAAC Diastereoselective Synthesis of Rotaxanes 4**

entry	substrate	conditions	selectivity <sup>a</sup>
1 <sup>11</sup>	<b>1a</b> ( $R^1 = \text{O}^t\text{Bu}$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , rt	50% <i>de</i>
2	<b>1a</b> ( $R^1 = \text{O}^t\text{Bu}$ , $R^2 = \text{H}$ )	EtOH, rt	14% <i>de</i>
3	<b>1b</b> ( $R^1 = \text{Me}$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , rt	36% <i>de</i>
4	<b>1c</b> ( $R^1 = \text{CCl}_3$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , rt	48% <i>de</i>
5	<b>1d</b> ( $R^1 = \text{CF}_3$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , rt	70% <i>de</i>
6	<b>1d</b> ( $R^1 = \text{CF}_3$ , $R^2 = \text{H}$ )	EtOH, rt	16% <i>de</i>
7	<b>1e</b> ( $R^1 = \text{CF}_3$ , $R^2 = \text{Me}$ )	$\text{CH}_2\text{Cl}_2$ , rt	10% <i>de</i>
8	<b>1a</b> ( $R^1 = \text{O}^t\text{Bu}$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , $-40^\circ\text{C}$	72% <i>de</i>
9	<b>1a</b> ( $R^1 = \text{O}^t\text{Bu}$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , $-78^\circ\text{C}$	80% <i>de</i>
10	<b>1d</b> ( $R^1 = \text{CF}_3$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , $-40^\circ\text{C}$	82% <i>de</i>
11	<b>1d</b> ( $R^1 = \text{CF}_3$ , $R^2 = \text{H}$ )	$\text{CH}_2\text{Cl}_2$ , $-78^\circ\text{C}$	70% <i>de</i>

<sup>a</sup>Determined by  $^1\text{H}$  NMR analysis of the crude reaction product.

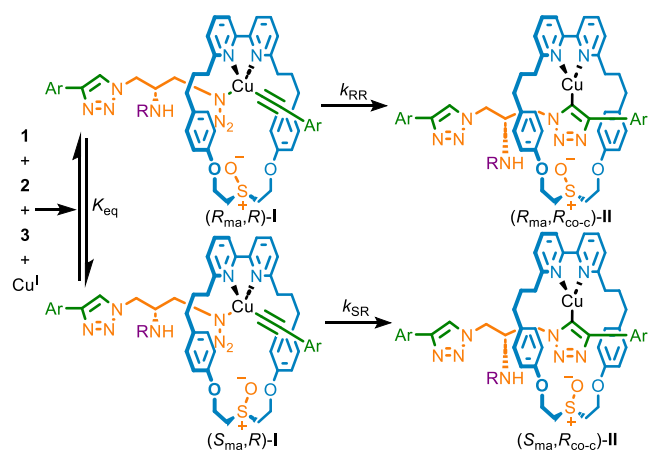


**Figure 2.** SCXRD structure of  $[(R_{\text{ma}}, R_{\text{co-c}})\text{-4d}$  (major isomer), with key intercomponent interactions highlighted. Colors as in Scheme 1, including the sulfoxide (SO) moiety to highlight the differentiation of the macrocycle faces, except N [dark blue], O [gray], and H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

The effect of the 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  $-40^\circ\text{C}$  (entry 8) and  $-78^\circ\text{C}$  (entry 9) increased the observed selectivity, that for **4d** was higher at  $-40^\circ\text{C}$  (entry 10) and then fell at  $-78^\circ\text{C}$  (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,<sup>21</sup> which include an

equilibrium between diastereomeric azide/acetylide complexes I, followed by irreversible formation of the corresponding triazolides II (Scheme 2).<sup>22</sup> The observed stereoselectivity is thus a composite function of the pre-equilibrium step ( $K_{\text{eq}}$ ) and the relative rates ( $k_{\text{RR}}$ ,  $k_{\text{SR}}$ ) 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.<sup>23</sup>

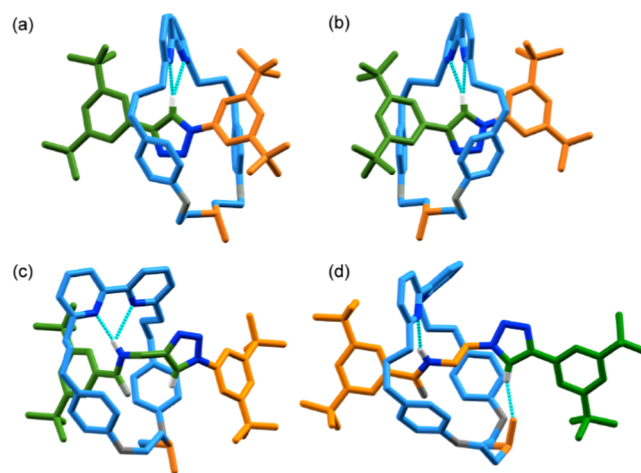
### Scheme 2. Proposed AT-CuAAC Mechanism Highlighting Pre-Equilibrium and Kinetic Resolution Steps



**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.

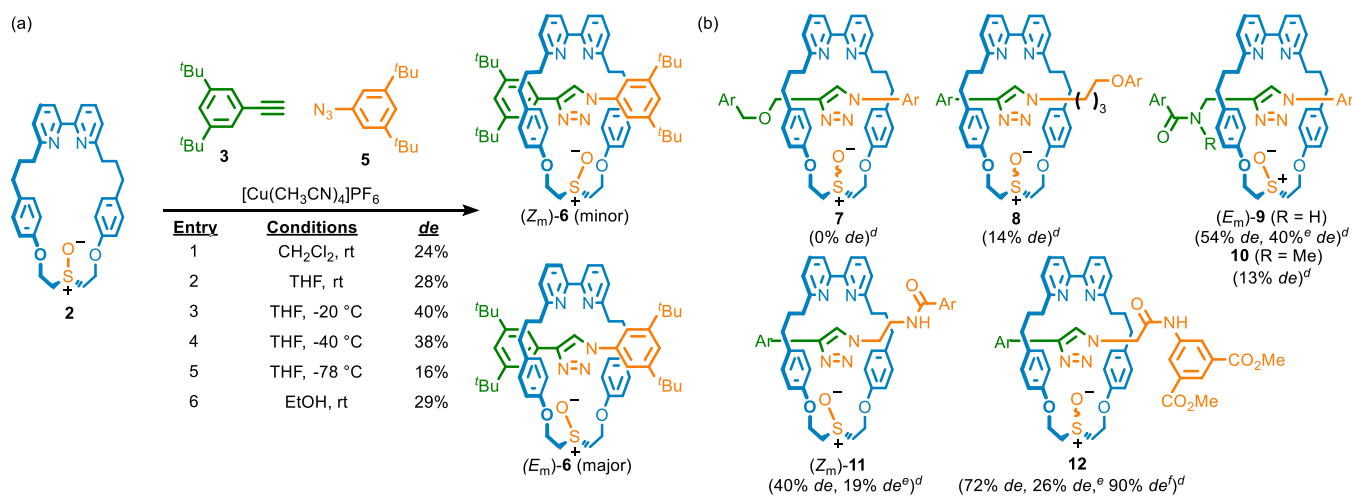
Intrigued by the small but measurable stereoselectivity observed in the formation of 4e, which cannot arise due to the proposed stereodifferentiating NH...O interaction, we exam-

ined the AT-CuAAC coupling between macrocycle 2, and half-axes 3 and 5, neither of which contain a directing group. At rt in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 3a, entry 1), geometric isomers ( $E_{\text{m}}$ )-6 and ( $Z_{\text{m}}$ )-6 were formed 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.<sup>24</sup> Analysis of the separated isomers of 6 by SCXRD allowed their absolute stereochemistry to be determined (Figure 3a,b). 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 solvent was comparable to THF (entry 6).<sup>25</sup>



**Figure 3.** (a) Solid-state structures of (a) ( $Z_{\text{m}}$ )-6, (b) ( $E_{\text{m}}$ )-6, (c) ( $Z_{\text{m}}$ )-9, and (d) ( $E_{\text{m}}$ )-11 with key intercomponent interactions highlighted. Colors as in Scheme 1, including the sulfoxide (SO) moiety to emphasize the macrocycle faces, except for O (gray), N (dark blue), and H (white). The majority of H was omitted for clarity.

### Scheme 3. AT-CuAAC Synthesis of Rotaxane Geometric Isomers of Type 1. (a) Effect of Conditions on the Formation of Rotaxanes 6.<sup>a</sup> (b) Effect of the Half-Axle Structure, on the Stereoselectivity of Mechanical Bond Formation with Macrocyclic 2.<sup>b,c</sup>



<sup>a</sup>Reagents and conditions: 2 (1 equiv), 3 (1.1 equiv), 5 (1.1 equiv), [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> (0.96 equiv), <sup>i</sup>Pr<sub>2</sub>EtN (2 equiv). <sup>b</sup>Synthesized in THF at rt (Scheme 3a, entry 2) unless otherwise stated. <sup>c</sup>Stereochemistry of the major isomer indicated where determined. <sup>d</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction product. <sup>e</sup>Synthesized in EtOH. <sup>f</sup>Synthesized at -40 °C in THF. Ar = 3,5-di-<sup>t</sup>Bu-C<sub>6</sub>H<sub>3</sub>.

Although the selectivities observed in the formation of **4e** and **6** are consistent with some inherent facial bias between the azide and alkyne half-axes in the mechanical bond-forming step, when a propargylic alkyne was employed with aryl azide **5** to generate rotaxane **7**, no stereoselectivity was observed (Scheme 3b). In contrast, the reaction of an alkyl azide and aryl acetylene **3** to give rotaxane **8** proceeded in an appreciable stereoselectivity (14% *de*). Thus, although it is clearly possible to achieve low selectivities in the AT-CuAAC reactions of **2** in the absence of obvious directing interactions, this is highly substrate-dependent, and its origins are unclear at this time.<sup>26</sup>

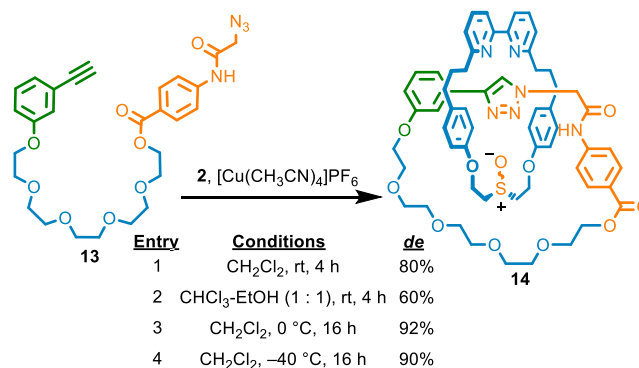
Returning to our H-bonding-directed approach, when a propargylic amide was reacted with **2** to give **9**, significantly improved stereoselectivity (54% *de*) was obtained, which was reduced in EtOH (40% *de*). The corresponding *N*-methyl amide gave rise to rotaxane **10** in low selectivity (13% *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 **12**, whose amide NH is expected to be more polarized than that of **11**, was produced in good selectivity (72% *de*) at rt, which was improved (90% *de*) when the same reaction was conducted at  $-40\text{ }^{\circ}\text{C}$ . 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*).

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 $\cdots$ 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<sup>11</sup> this interaction in the solid-state structures of both diastereomers of epimeric MAC catenanes even though, in principle, in one diastereomer, the S–O bond could be expected to project away from the NH unit, which is possible due to the flexible nature of macrocycle **2**. The major isomers of rotaxanes **9** and **11** determined by SCXRD (Figure 3c,d, 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 $\cdots$ O interaction appears able to direct the synthesis of MGI-1 isomers, the major product depends on the detailed structure of the half-axes used.<sup>27</sup> We also note that whereas an NH $\cdots$ O interaction is observed in the SCXRD structure of **4d**, in the case of **9** and **11**, this is replaced by an NH $\cdots$ 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 intramolecular 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 polarized 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)<sup>28</sup> to give **14** with good stereocontrol (80% *de*, entry 1). The same reaction in  $\text{CHCl}_3$ -EtOH gave reduced selectivity (60% *de*, entry 2), whereas performing the

reaction at  $0\text{ }^{\circ}\text{C}$  in  $\text{CH}_2\text{Cl}_2$  increased the selectivity (92% *de*, entry 3). Lowering the temperature further ( $-40\text{ }^{\circ}\text{C}$ ) 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**<sup>a</sup>

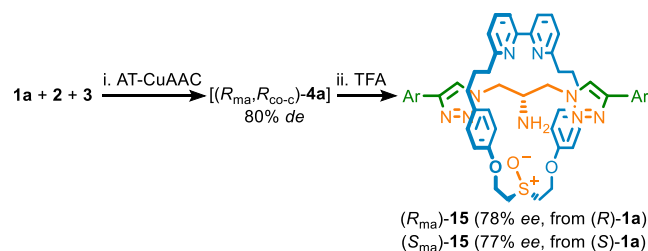


<sup>a</sup>Reagents and conditions: **13** (2 equiv) was added over the time stated using a syringe pump to **2** (1 equiv),  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$  (0.97 equiv),  $^i\text{Pr}_2\text{EtN}$  (4 equiv).

#### 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,<sup>11</sup> 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*; the ultimate purpose of developing methodologies to produce stereochemically complex mechanically interlocked molecules is so that they can then be investigated in applications such as sensing<sup>29</sup> or catalysis,<sup>30</sup> for which they must be of high stereopurity.

#### Scheme 5. Two-Step, One-Pot Synthesis of Enantioenriched MAC Rotaxanes **15**<sup>a,b</sup>



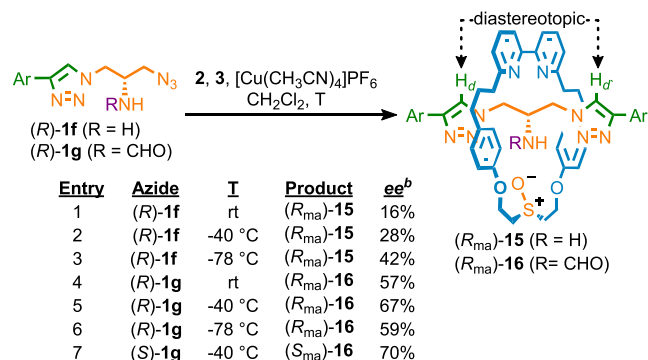
<sup>a</sup>Reagents and conditions: i. **1a** (1.1 equiv), **2** (1 equiv), **3** (1.1 equiv),  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$  (0.96 equiv),  $^i\text{Pr}_2\text{EtN}$  (2 equiv),  $\text{CH}_2\text{Cl}_2$ , 16 h; ii. TFA,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^{\circ}\text{C}$  to rt, 6 h. <sup>b</sup>Determined by analytical CSP-HPLC. Ar = 3,5-di-*t*Bu-C<sub>6</sub>H<sub>3</sub>.

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*<sub>ma</sub>)-**15** in good stereoselectivity (78% *ee*) in

agreement with that observed for **4a** (80% *de*). The same reaction with (*S*)-**1a** gave (*S*<sub>ma</sub>)-**5** (77% *ee*).

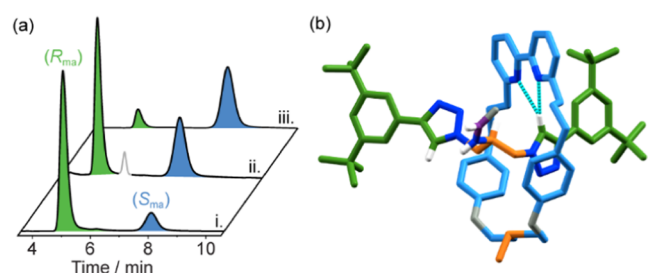
More excitingly, the high stereoselectivity observed in the AT-CuAAC reaction of azides **1** bearing a polarized NH presents the opportunity for the direct synthesis of MAC rotaxanes without the need for first forming separable co-conformational diastereomers; if the N substituent is too small to trap the macrocycle in one triazole-containing compartment, the only fixed stereochemistry in the product is provided by the MAC stereogenic unit. Thus, 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  $-40\text{ }^{\circ}\text{C}$  (28% *ee*, entry 2) and improved further still at  $-78\text{ }^{\circ}\text{C}$  (42% *ee*, entry 3). CSP-HPLC analysis of a sample of rotaxane (*R*<sub>ma</sub>)-**15** produced from (*R*)-**1a** (Scheme 5) and comparison with the same product from (*R*)-**1f** confirmed that the latter also produces (*R*<sub>ma</sub>)-**15** as the major product (Figure 4a).

### Scheme 6. Direct Synthesis of Enantioenriched Mechanically Axially Chiral Rotaxanes **15** and **16**<sup>a</sup>



<sup>a</sup>Reagents and conditions: i. **1** (1.1 equiv), **2** (1 equiv), **3** (1.1 equiv), [Cu(CH<sub>3</sub>CN)]PF<sub>6</sub> (0.96 equiv), <sup>i</sup>Pr<sub>2</sub>EtN (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 16 h.

<sup>b</sup>Determined by analytical CSP-HPLC. Ar = 3,5-di-<sup>t</sup>Bu-C<sub>6</sub>H<sub>3</sub>.



**Figure 4.** (a) CSP-HPLC analysis of i. (*R*<sub>ma</sub>)-**16** (67% *ee*) produced from (*R*)-**1g**; ii. (*R*<sub>ma</sub>)-**16** (21% *ee*) produced from (*R*<sub>ma</sub>)-**15** (21% *ee*; minor impurity highlighted in gray), and iii. (*S*<sub>ma</sub>)-**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 [gray], and H [white]). The majority of H was omitted for clarity.

When instead formamide-containing azide (*R*)-**1g** was reacted with **2** and **3**, even at rt rotaxane **16**<sup>31</sup> was obtained in reasonable stereopurity (57% *ee*, entry 3), which was improved further at  $-40\text{ }^{\circ}\text{C}$  (67% *ee*, entry 4). Conducting this reaction at  $-78\text{ }^{\circ}\text{C}$  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*<sub>ma</sub>)-**15** of known stereopurity and comparison with the same compound produced from (*R*)-**1g** confirmed that the latter produces (*R*<sub>ma</sub>)-**16** as the major stereoisomer. When (*S*)-**1g** was reacted instead, (*S*<sub>ma</sub>)-**16** was produced (70% *ee*, entry 6). The solid-state structure of **16** obtained by SCXRD (Figure 4b) 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.

The different co-conformational behaviors of **4a**, **15**, and **16** are clear from the analysis of their respective <sup>1</sup>H NMR spectra. Diastereomers (*R*<sub>ma</sub>,*R*<sub>co-c</sub>)-**4a** and (*S*<sub>ma</sub>,*R*<sub>co-c</sub>)-**4a** are separable species; heating a mixture of 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<sub>d</sub><sup>32</sup> of amine rotaxane **15** appear as two sharp singlets at 298 K, indicating that diastereomeric co-conformations (*R*<sub>ma</sub>,*R*<sub>co-c</sub>)-**15** and (*S*<sub>ma</sub>,*R*<sub>co-c</sub>)-**15** are in fast exchange on the <sup>1</sup>H NMR timescale through rapid shuttling of the macrocycle between the two triazole-containing compartments (Figure S190). The same resonances for formamide rotaxane **16** are broad at 298 K, although once again, only two signals are observed (Figure S200). This observation is consistent with (*R*<sub>ma</sub>,*R*<sub>co-c</sub>)-**16** and (*S*<sub>ma</sub>,*R*<sub>co-c</sub>)-**16** exchanging on the <sup>1</sup>H NMR timescale, albeit more slowly than (*R*<sub>ma</sub>,*R*<sub>co-c</sub>)-**15** and (*S*<sub>ma</sub>,*R*<sub>co-c</sub>)-**15**, in keeping with the larger steric bulk of the formamide group of **16**. Accordingly, increasing the temperature resulted in the sharpening of the two resonances corresponding to protons H<sub>d</sub> (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 contained in one of the two half-axes (rotaxane synthesis) or unsymmetrically disposed in the corresponding pre-macrocycle structure (catenane synthesis) appears to be sufficient to control the reaction outcome. Although the focus of our discussion has been on reaction stereoselectivities, it should be noted that, as is typically the case for AT-CuAAC reactions mediated by bipyridine macrocycles,<sup>33</sup> all of the interlocked structures reported were obtained in good to excellent isolated yield (50–90%, see the SI for details). The high selectivity observed with optimized substrates allowed us to design a direct enantioselective synthesis of mechanically axially chiral rotaxanes, only the second<sup>34a</sup> 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,<sup>5,8b,6d,e</sup> as well as structures expressing combinations of mechanical and covalent stereochemistry<sup>4h</sup> 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 up new motifs for study. Similarly, mechanically planar chiral molecules, for which

stereoselective methods are known,<sup>14,26,34</sup> have been investigated as enantioselective sensors,<sup>29</sup> catalysts,<sup>30</sup> and chiroptical switches.<sup>35</sup> 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

### Data Availability Statement

Characterization data for reported compounds is available from the University of Birmingham UBIRA eData repository at <https://doi.org/10.25500/edata.bham.00001077>.

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c14329>.

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

### Accession Codes

CCDC 2303663, 2307076, and 2307119–2307122 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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## ■ 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: Savoini, A.; Gallagher, P. R.; Saady, A.; Goldup, S. M. The Final Stereogenic Unit of [2]Rotaxanes: Type 2 Geometric Isomers. *J. Am. Chem. Soc.* **2024**, DOI: 10.1021/jacs.3c14594.
- (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 stereolabel or mechanical geometric stereolabel. We prefer the mechanically planar description as, in the case of catenanes, this typically although not always<sup>34g</sup> 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.; Stoddart, J. F. Catenated Cyclodextrins. *Chem. - Eur. J.* **1995**, *1* (1), 33–55. (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), 1071–1074. (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), 1088–1096. (d) Bruns, C. J. Exploring and Exploiting the Symmetry-Breaking Effect of Cyclodextrins in Mechanomolecules. *Symmetry* **2019**, *11* (10), No. 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), 1–7. (f) Schröder, H. V.; Zhang, Y.; Link, A. J. Dynamic covalent self-assembly of mechanically interlocked molecules solely made from peptides. *Nat. Chem.* **2021**, *13* (9), 850–857. (g) Lopez-Leonardo, C.; Saura-Sanmartin, A.; Marin-Luna, M.; Alajarin, M.; Martinez-Cueva, A.; Berna, J. Ring-to-Thread Chirality Transfer in [2]-Rotaxanes for the Synthesis of Enantioenriched Lactams. *Angew. Chem., Int. Ed.* **2022**, *61* (39), No. 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), 1147–1163.
- (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), 278–281. (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), 3230–3242. (c) Pierro, T.; Gaeta, C.; Talotta, C.; Casapullo, A.; Neri, P. Fixed or invertible calixarene-based directional shuttles. *Org. Lett.* **2011**, *13* (10), 2650–2653. (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), 9924–9930. (e) Cio, R.; Talotta, C.; Gaeta, C.; Margarucci, L.; Casapullo, A.; Neri, P. An oriented handcuff rotaxane. *Org. Lett.* **2013**, *15* (22), 5694–5697. (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), 1033–1042. (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), 8973–8983. (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), 6419–6428. (i) Cera, G.; Arduini, A.; Secchi, A.; Credi, A.; Silvi, S. Heteroditopic Calix[6]arene Based Intervoven and Interlocked Molecular Devices. *Chem. Rec.* **2021**, *21* (5), 1161–1181. (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), 4970–4973.

(6) 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), 8537–8544. (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), 140–147. (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 oxalixarene: formation of oriented rotaxanes. *Chem. Sci.* **2016**, *7* (1), 469–474. (d) Cui, J. S.; Ba, Q. K.; Ke, H.; Valkonen, A.; Rissanen, K.; Jiang, W. Directional Shuttling of a Stimuli-Responsive Cone-Like Macrocyclic on a Single-State Symmetric Dumbbell Axle. *Angew. Chem., Int. Ed.* **2018**, *57* (26), 7809–7814. (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), 4975–4978.

(7) (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), 4975–4978. (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), 4205–4209.

(8) (a) Gaeta, C.; Talotta, C.; Mirra, S.; Margarucci, L.; Casapullo, A.; Neri, P. Catenation of calixarene annulus. *Org. Lett.* **2013**, *15* (1), 116–119. (b) Zanichelli, V.; Dallacassagrande, 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 Macrocyclic. *Molecules* **2018**, *23* (5), No. 1156.

(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), 2878–2884.

(11) Maynard, J. R. J.; Gallagher, P.; Lozano, D.; Butler, P.; Goldup, S. M. Mechanically axially chiral catenanes and nonconventional mechanically axially chiral rotaxanes. *Nat. Chem.* **2022**, *14* (9), 1038–1044.

(12) (a) Jamieson, E. M. G.; Modicom, F.; Goldup, S. M. Chirality in rotaxanes and catenanes. *Chem. Soc. Rev.* **2018**, *47* (14), 5266–5311. (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), 689–698. (c) Evans, N. H. Chiral Catenanes and Rotaxanes: Fundamentals and Emerging Applications. *Chem. - Eur. J.* **2018**, *24* (13), 3101–3112.

(13) Frisch, H. L.; Wasserman, E. Chemical Topology. *J. Am. Chem. Soc.* **1961**, *83*, 3789–3795.

(14) Maynard, J. R. J.; Goldup, S. M. Strategies for the Synthesis of Enantiopure Mechanically Chiral Molecules. *Chem* **2020**, *6* (8), 1914–1932.

(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), 2186–2187.

(17) Saady, A.; Goldup, S. M. Triazole formation and the click concept in the synthesis of interlocked molecules. *Chem* **2023**, *9* (8), 2110–2127.

(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.<sup>11</sup>

(19) We note that others have referred to such co-conformational covalent stereochemistry as “mechanical point chirality” (Cakmak, Y.; Erbas-Cakmak, S.; Leigh, D. A. Asymmetric Catalysis with a Mechanically Point-Chiral Rotaxane. *J. Am. Chem. Soc.* **2016**, *138* (6), 1749–1751.). We introduced the co-conformational covalent description<sup>12a</sup> as it is more precise and information rich; it highlights that the stereogenic unit arises due to desymmetrization of a covalent pro-stereogenic unit and that these stereoisomers can in principle be converted by co-conformational movement. One of the reviewers of this manuscript suggested the term “co-configurational isomers” might be more useful and clearer for a nonexpert. We hesitate to adopt it here as changes in nomenclature should be properly discussed and put in the wider context of the field. However, we wanted to give credit to our anonymous reviewer for this intriguing suggestion and will consider its use in future.

(20) We note that the previously reported SCXRD structure of minor diastereomer ( $S_{ma}, R_{co-c}$ )-**4a**<sup>11</sup> contains the same interaction but in this case it occurs intermolecularly between neighboring molecules in the unit cell, as observed for **4d** (Figure 1).

(21) (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), 2398–2404. (b) Neal, E. A.; Goldup, S. M. A Kinetic Self-Sorting Approach to Heterocircuit [3]Rotaxanes. *Angew. Chem., Int. Ed.* **2016**, *55* (40), 12488–12493. (c) 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), 3875–3879.

(22) Winn, J.; Pinczewska, A.; Goldup, S. M. Synthesis of a rotaxane Cu(I) triazolide under aqueous conditions. *J. Am. Chem. Soc.* **2013**, *135* (36), 13318–13321.

(23) We note that our results cannot rule out that either  $K_{eq}$  or  $k_{SS}/k_{SR}$  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.

(24) 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 SI Section 8.

(25) Other combinations of solvent and temperature did not improve the reaction stereoselectivity. See SI Section 9 for further details.

(26) (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), 14806–14810. (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), 179–187.

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

(28) Lewis, J. E. M.; Modicom, F.; Goldup, S. M. Efficient Multicomponent Active Template Synthesis of Catenanes. *J. Am. Chem. Soc.* **2018**, *140* (14), 4787–4791.

(29) 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), No. 20.

(30) Heard, A. W.; Goldup, S. M. Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective. *Catalysis. Chem.* **2020**, *6* (4), 994–1006.

(31) <sup>1</sup>H NMR analysis of **16** confirmed that the ring is able to shuttle past the formamide unit. See [SI Section 11](#).

(32) The <sup>1</sup>H spectra of rotaxanes **15** and **16** are extremely complicated because the mechanical bond renders any nuclei not related by single bond rotation (e.g., the <sup>t</sup>Bu groups of the axle unit) magnetically inequivalent; for example, all of the methylene protons flanking the amine unit in the axle are magnetically inequivalent. For this reason, when assigning the <sup>1</sup>H NMR spectra of these molecules (see the [SI](#)), we took the decision to assign different letters to carbon atoms (and the associated protons) whose equivalence is lifted by the mechanical bond and reserved prime notation to differentiate diastereotopic geminal protons. Thus, although the triazole protons of rotaxanes **15** and **16** are labelled in [Scheme 6](#) as H<sub>d</sub> and H<sub>d'</sub> in accordance with standard practice for diastereotopic signals to aid an intuitive understanding of the diagram, they are assigned as H<sub>d</sub> and H<sub>h</sub> in their characterization data.

(33) For recent examples of functionalized and functional molecules synthesized in good to excellent yield using the AT-CuAAC reaction mediated by bipyridine macrocycles see: (a) Zhang, Z.; Tizzard, G. J.; Williams, J. A. G.; Goldup, S. M. Rotaxane PtII-complexes: mechanical bonding for chemically robust luminophores and stimuli responsive behaviour. *Chem. Sci.* **2020**, *11* (7), 1839–1847. (b) Acevedo-Jake, A.; Ball, A. T.; Galli, M.; Kukwikila, M.; Denis, M.; Singleton, D. G.; Tavassoli, A.; Goldup, S. M. AT-CuAAC Synthesis of Mechanically Interlocked Oligonucleotides. *J. Am. Chem. Soc.* **2020**, *142* (13), 5985–5990. (c) Cirulli, M.; Salvadori, E.; Zhang, Z. H.; Dommett, M.; Tuna, F.; Bamberger, H.; Lewis, J. E. M.; Kaur, A.; Tizzard, G. J.; van Slageren, J.; Crespo-Otero, R.; Goldup, S. M.; Roessler, M. M. Rotaxane Co(II) Complexes as Field-Induced Single-Ion Magnets. *Angew. Chem., Int. Ed.* **2021**, *60* (29), 16051–16058. (d) Rajamalli, P.; Rizzi, F.; Li, W.; Jinks, M. A.; Gupta, A. K.; Laidlaw, B. A.; Samuel, I. D. W.; Penfold, T. J.; Goldup, S. M.; Zysman-Colman, E. Using the Mechanical Bond to Tune the Performance of a Thermally Activated Delayed Fluorescence Emitter. *Angew. Chem., Int. Ed.* **2021**, *60* (21), 12066–12073. (e) Maynard, J. R. J.; Galmes, B.; Stergiou, A. D.; Symes, M. D.; Frontera, A.; Goldup, S. M. Anion-pi Catalysis Enabled by the Mechanical Bond. *Angew. Chem., Int. Ed.* **2022**, *61* (12), No. e202115961. (g) Saady, A.; Malcolm, G.; Fitzpatrick, M.; Pairault, N.; Tizzard, G.; Mohammed, S.; Tavassoli, A.; Goldup, S. M. A Platform Approach to Cleavable Macrocycles for the Controlled Disassembly of Mechanically Caged Molecules. *Angew. Chem., Int. Ed.* **2024**, No. e202400344.

(34) (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), 1512–1520. (b) 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), 9803–9808. (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), No. 404. (d) Li, M. F.; Chia, X. L.; Tian, C.; Zhu, Y. Mechanically planar chiral

rotaxanes through catalytic desymmetrization. *Chem* **2022**, *8* (10), 2843–2855. (e) Rodríguez-Rubio, A.; Savoini, A.; Modicom, F.; Butler, P.; Goldup, S. M. A Co-conformationally "Topologically" Chiral Catenane. *J. Am. Chem. Soc.* **2022**, *144* (27), 11927–11932. (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), 1195–1207. (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), 781–786.

(35) (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), 10003–10009. (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**, *61*, No. e202210542.