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A Chiral Macrocycle for the Stereoselective Synthesis of Mechanically Planar Chiral Rotaxanes and Catenanes

Shu Zhang,[=,1,2] Arnau Rodríguez-Rubio,[=1] Abed Saady,[1] Graham J. Tizzard,[1] Stephen M. Goldup*[,1]

[1]School of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK

[2]Current address: Institute of Advanced Materials, School of Chemistry and Chemical Engineering, and Jiangsu Province Hi-Tech Key Laboratory for Biomedical Research, Southeast University, Nanjing, 211189, China

*Correspondence and lead author: s.goldup@soton.ac.uk

[=]Denotes equal contribution - both authors have the right to list their name first on the CVs.

DEDICATION

The authors dedicate this article to Professor Sir Fraser Stoddart on the occasion of his 80th birthday.

SUMMARY (99 words)

Active-template auxiliary methodologies have previously been developed for the stereoselective synthesis of chiral interlocked molecules in which the mechanical bond provides the sole stereogenic unit. To date however, the covalent auxiliary has been included in the half-axle components (rotaxanes) or pre-macrocycle components (catenanes), and thus mechanically chiral rotaxane and catenane syntheses rely on different chiral components. Here we present a single, simple amino acid-derived macrocycle that mediates the formation of both catenanes and rotaxanes in excellent stereoselectivity. We demonstrate the flexibility of our approach through the stereoselective synthesis of all three isomers of a co-conformationally mechanically planar chiral [3]rotaxane.

Keywords: Catenanes, rotaxanes, chirality, stereoselective

INTRODUCTION

Enantiopure samples of "mechanically chiral" molecules,[1] rotaxanes and catenanes in which the mechanical bond provides the sole chirotopic stereogenic element have historically been produced by resolution of racemic samples[2] or unusual chiral building blocks,[3] both of which typically rely on preparative chiral stationary phase HPLC (CSP-HPLC) separation of the product or building blocks, respectively.[4] Although these methods have allowed preliminary studies on the properties of mechanically chiral molecules,[2f,g,3] the inherent limitations of CSP-HPLC has prevented more detailed studies of their applications.

To overcome this synthetic bottleneck, new stereoselective methods are required.[5] The first approach to this challenging goal was reported by Takata, Okamoto and co-workers in 2007 using a catalytic enantioselective kinetic resolution strategy; the acylation of a dynamic mixture of enantiomeric pseudorotaxanes gave rise to a small (~4% *ee*) but measurable stereoselectivity.[6] In 2020, Leigh and co-workers reported the synthesis of a mechanically planar chiral rotaxane in 50% *ee* using a substrate-controlled strategy in which a chiral leaving group was used to influence the configuration of the mechanical bond.[7] Kawabata and co-workers have reported the catalytic enantioselective kinetic resolution of a mechanically planar chiral rotaxane (>99% *ee* of unreacted starting material, 29% isolated yield).[8] Most recently, Zhu, Tian and co-workers reported the catalytic enantioselective desymmetrisation of rotaxanes containing a bilaterally symmetric macrocycle in up to 93% *ee*.[9]

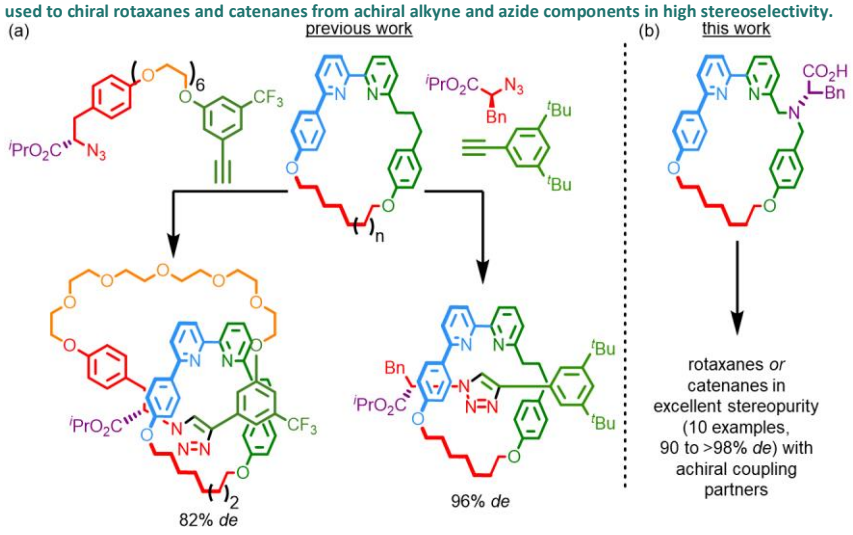
Our approach has been to focus on methods equivalent to chiral auxiliary strategies in covalent synthesis. In 2018, building on a previously reported non-stereoselective approach,[10] we disclosed the active template[11] Cu-mediated alkyne-azide cycloaddition (AT-CuAAC)[12] synthesis of mechanically planar chiral rotaxanes in up to 96% *ee* without separation of the intermediate diastereomers.[13] This approach was then extended using the same class of oriented bipyridine macrocycles[14] to a chiral interlocking auxiliary strategy.[15] We subsequently demonstrated an auxiliary approach to analogous chiral catenanes,[16] although

in this case a lower diastereoselectivity (*dr* = 2 : 1) was observed in the mechanical bond forming step which necessitated the separation of diastereomers prior to auxiliary cleavage. We have since extended our methodology to a highly stereoselective synthesis of a mechanically chiral catenane (82% *ee*) and a molecule containing an analogous co-conformational stereogenic unit (87% *ee*).[17] Most recently, we have extended our auxiliary approach to mechanically axially chiral catenanes and, in the process, identified an overlooked mechanically axial chiral rotaxane stereogenic unit.[18]

At this point we note that, although such chiral catenanes have typically been referred to simply as "topologically" chiral, this label clearly makes no sense in the context of co-conformational stereochemistry. [19] Furthermore, we have recently demonstrated the synthesis of a catenane with the same stereogenic unit but whose stereochemistry is Euclidean.[20] For these reasons we have tentatively suggested that these stereogenic units of rotaxanes and catenanes be united under the single term "mechanically planar chiral"; we shall use this term throughout.

Although our published AT-CuAAC auxiliary strategies for the synthesis of mechanically planar chiral rotaxanes and catenanes rely on the same underlying concept, they use very different chiral building blocks because, to date, the chiral auxiliary has been included in the half-axle or pre-macrocycle component respectively, rather than the oriented bipyridine macrocycle[14] that mediates the AT-CuAAC reaction, and which is common to both syntheses (Figure 1a). Here we demonstrate a unified approach to these related mechanical stereogenic units by including an amino acid-derived chiral auxiliary in a readily available, oriented bipyridine macrocycle (Figure 1b). This very simple modification is both extremely efficient and extremely flexible, as we demonstrate below through the synthesis of mechanically planar chiral rotaxanes and catenanes in excellent stereopurity. To emphasize this point further, we applied this approach to the iterative synthesis of all three stereoisomers of a co-conformationally mechanically planar chiral [3]rotaxane.

Figure 1. Comparison between this work and our previous approaches to mechanically planar chiral rotaxanes and catenanes. (a) The same oriented bipyridine macrocycle can be used to make either chiral catenanes or rotaxanes using our AT-CuAAC approach but the auxiliary unit must be built into the alkyne or azide containing components. (b) The approach we present here allows the same chiral, oriented bipyridine macrocycle to be used to chiral rotaxanes and catenanes from achiral alkyne and azide components in high stereoselectivity.



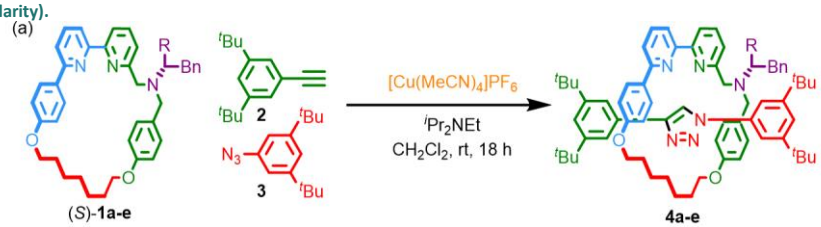
RESULTS AND DISCUSSION

Development of a chiral macrocycle for the synthesis of mechanically planar chiral rotaxanes. The AT-CuAAC reaction with small bipyridine macrocycles is thought to proceed by formation of a mono-metallic Cu^{I}-acetylide-azide complex[21] in which the metal ion is coordinated by the bipyridine unit of the macrocycle such that the azide and acetylide ligands are projected on opposite sides of the ring. This complex then reacts to generate a threaded Cu^{I}-triazolide[21a] before protonolysis of the Cu-C bond to generate the triazole product. Based on this mechanistic hypothesis, bipyridine macrocycle (*S*)-**1a** (Figure 2a) was designed and synthesized in which the chiral unit (>99% *ee*), derived from (*S*)-phenyl alanine methyl ester, is adjacent to the bipyridine moiety in the hope of maximizing the stereodifferentiation in the key bond forming step.

Pleasingly, the AT-CuAAC reaction of (*S*)-**1a** with alkyne **2** and azide **3** gave rise to mechanically planar chiral rotaxane **4a** in appreciable stereoselectivity (34% *de*, Figure 2a, entry 1), as judged by ^{1}H NMR analysis of the crude reaction product.[22] Macrocycle (*S*)-**1b** (>99% *ee*)[23] in which the methyl ester of (*S*)-**1a** was reduced to the primary alcohol, produced rotaxane **4b** in dramatically enhanced stereoselectivity (86% *de*, entry 2), whereas the corresponding silyl ether ([*S*]-**1c**) produced rotaxane **4c** in much lower selectivity (46% *de*, entry 3) and the corresponding acetoyl ester (*S*)-**1d** gave rotaxane **4d** with almost no stereoselectivity (18% *de*, entry 4). Carboxylic acid macrocycle (*S*)-**1e** (98% *ee*)[24,25] derived from (*S*)-**1a** by hydrolysis of the ester moiety, produced rotaxane **4e** as a single stereoisomer by ^{1}H NMR analysis (>98% *de*, entry 5). This excellent result was reinforced by reduction of **4e** to **4b**; the minor diastereomer could not be detected by ^{1}H NMR in either the crude or purified samples of **4b** obtained by this route.

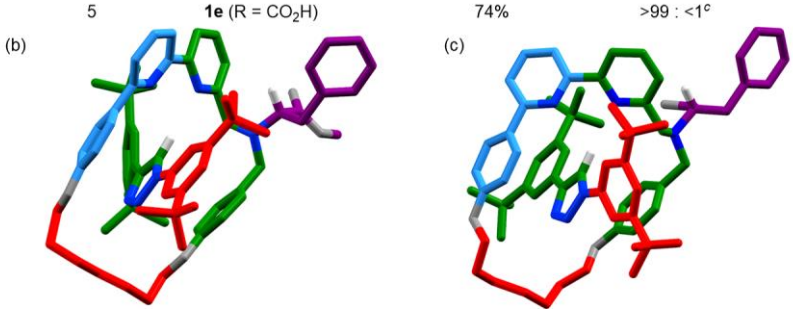
Figure 2. (a) Synthesis of diastereomeric rotaxanes 4. Solid-state structures of (b) of (S,R_{mp})-4a and (c) (S,S_{mp})-4b (colours as in (a) with the exception of O [grey], N [dark blue] and H [white]; majority of H omitted for clarity).

(a)



Entry	Macrocycle	Yield	(S,S_{mp}) : (S,R_{mp})[a]
1	**1a** (R = CO_2Me)	72%	33 : 67[c]
2	**1b** (R = CH_2OH)	78%	92 : 8[c]
3	**1c** (R = $CH_2OTBDMS$)	70%[b]	73 : 27[d]
4	**1d** (R = CH_2OAc)	83%[b]	59 : 41[d]
5	**1e** (R = CO_2H)	74%	>99 : <1[c]

(b) (c)



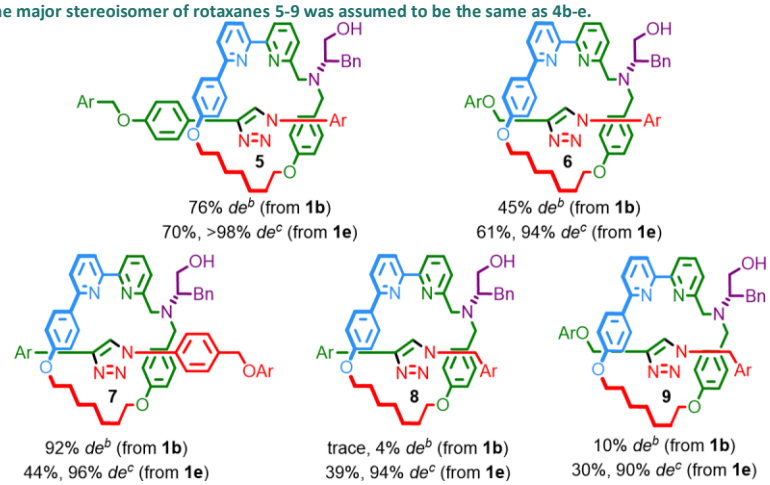
Reagents and conditions: (S)-**1** (1 equiv.), **2** (2 equiv.), **3** (2 equiv.), $[Cu(MeCN)_4]PF_6$ (0.92 equiv.), $^{i}Pr_2EtN$ (4 equiv.), CH_2Cl_2, rt, 18 h. [a]Stereolabel refers to the product after conversion to **4b** for comparison by ^{1}H NMR. [b]Isolated yield after conversion of the crude reaction product to **4b** (see ESI for details). [c]Determined by ^{1}H NMR analysis of the crude reaction product. [d]Determined by ^{1}H NMR analysis after conversion of the crude reaction product to **4b** (see ESI for details).

The relative stereochemistry of the major stereoisomers of rotaxanes **4** were compared by conversion of **4a**, **4c**, **4d** and **4e** to alcohol rotaxane **4b** for analysis by ^{1}H NMR. Whereas samples of rotaxane **4b** derived from macrocycles **1b**-**e** were found to be contain the same major diastereomer, macrocycle (*S*)-**1a** gives rise to the opposite major mechanical epimer. Crystals grown from a sample of **4b** (84% *de*) produced from macrocycle (S)-**1b** were analyzed by single crystal x-ray diffraction (SCXRD) and found to contain (S,S_{mp})-**4b** (Figure 2c). Crystals grown from a sample of **4a** (>98% *de*) derived from (*S*)-**1e** were found by SCXRD to contain the same relative orientation of the macrocycle and axle (Figure 2b), albeit the absolute stereochemistry is assigned (S,R_{mp})-**4a** (see ESI section S9 for a detailed discussion on the assignment of mechanical stereogenic units). Based on these corroborating data, macrocycles **1b**-**e** produce rotaxanes **4b**-**e** with the same relative orientation of axle and macrocycle, corresponding to the (S,S_{mp}) diastereomer of rotaxane **4b**, whereas (*S*)-**1a** selectively produces **4a** with the opposite relative orientation of axle and macrocycle.

Substrate scope of macrocycles (*S*)-1b and (*S*)-1e. Previously we have found that the diastereoselectivity of the AT-CuAAC reaction is highly dependent on the steric demand of the alkyne and azide components[13] to the point where a chiral auxiliary that is highly stereoselective (96% *de*) with one coupling partner, is entirely unselective with another substrate.[26] Although this issue can be overcome using our recently introduced chiral interlocking auxiliary approach,[15] macrocycles **1** would represent a complementary approach if they were suitable for the synthesis of a range of targets. Thus, we briefly investigated how substrate structure affected the diastereoselectivity of the reactions mediated by macrocycles (*S*)-**1b** and (*S*)-**1e** (Figure 3).

Starting from macrocycle (*S*)-**1b**, rotaxanes **5** and **6**, which are derived from alkyne precursors less sterically bulky than alkyne **2**, and rotaxane **7**, derived from a less sterically bulk aryl azide than **3**, were produced in reasonable stereochemical purity (76%, 45% and 92% *de* respectively as judged by ^{1}H NMR analysis of the crude reaction products). If instead macrocycle (*S*)-**1e** was employed, after reduction of the crude reaction product,[24] rotaxanes **5**, **6** and **7** were produced in significantly enhanced diastereomeric purity (>98%, 94% and 96% *de* respectively), and reasonable isolated yield. Both macrocycles produced the same major stereoisomer of the product. Based on this, and the similarity between the observed stereoselectivity with (*S*)-**1e** in the synthesis of rotaxane **4e**, we tentatively assign the major stereoisomers produced to have the same relative orientation of axle and macrocycle, as shown.

Figure 3. Rotaxanes 6-9 derived from macrocycles 1b and 1e.[a] The relative orientation of axle and macrocycle in the major stereoisomer of rotaxanes 5-9 was assumed to be the same as 4b-e.



76% *de*[b] (from **1b**)
70%, >98% *de*[c] (from **1e**)

45% *de*[b] (from **1b**)
61%, 94% *de*[c] (from **1e**)

92% *de*[b] (from **1b**)
44%, 96% *de*[c] (from **1e**)

trace, 4% *de*[b] (from **1b**)
39%, 94% *de*[c] (from **1e**)

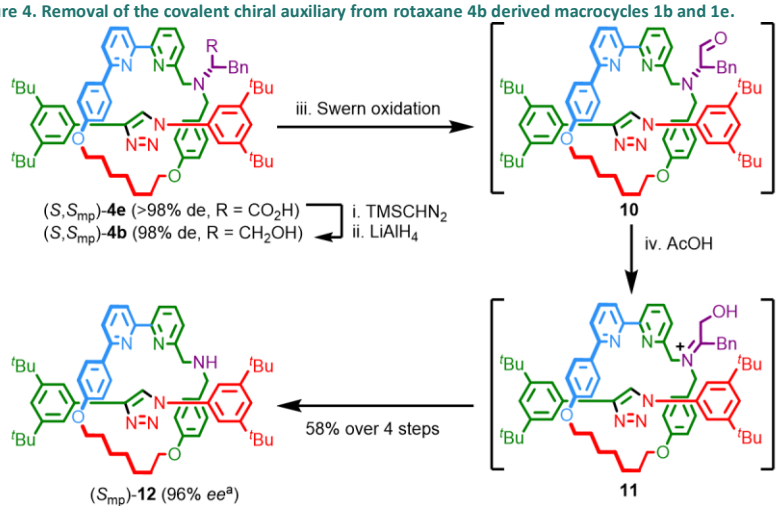
10% *de*[b] (from **1b**)
30%, 90% *de*[c] (from **1e**)

[a]Rotaxanes **5**-**9** were produced from (*S*)-**1b** or (*S*)-**1e** under the conditions shown in Figure 2a (except **8** and **9** which were synthesized in $CHCl_3$-EtOH (1 : 1)) with subsequent reduction of the crude AT-CuAAC reaction product in the case of (*S*)-**1e** (see ESI for further details). [b]Determined by ^{1}H NMR analysis of the crude AT-CuAAC reaction product. [c]Determined by ^{1}H NMR analysis of the crude reaction product after reduction. Ar = 3,5-di-^{t}Bu-C_6H_3.

Initial attempts to use a benzylic azide substrate under the same conditions failed; only trace amounts of rotaxane **8** could be detected by reaction with (*S*)-**1b** or (*S*)-**1e**. When the reaction solvent was replaced with $CHCl_3$-EtOH (1 : 1), which has previously been employed in AT-CuAAC synthesis of catenanes, [27] rotaxane **8** was produced from (*S*)-**1e** in high selectivity (94% *de*) and moderate isolated yield (39%). The same reaction with macrocycle (*S*)-**1b** still resulted in low conversion and stereoselectivity (<5%, ~4% *de*). Finally, rotaxane **9**, which is produced by reacting propargylic and benzyl azide half axles, was produced in low yield (30%) after a difficult purification but with excellent stereoselectivity (90% *de*), whereas macrocycle (*S*)-**1b** resulted in much lower stereoselectivity (10% *de*). Based on these preliminary results, the stereoselectivities of reactions involving macrocycle (*S*)-**1e** are remarkably unaffected by the steric demand of the alkyne and azide substrates, particularly when compared with our previously reported auxiliary methods.

Auxiliary removal from rotaxane 4e. Having shown that macrocycles **1** can be used to stereoselectively form [2]rotaxanes, and in particular that macrocycle (*S*)-**1e** has broad scope in terms of the steric demand of the alkyne and azide components, we turned to demonstrating the removal of the covalent stereogenic unit (Figure 4). Pleasingly, reduction of (S,S_{mp})-**4e** (>98% *de*) to (S,S_{mp})-**4b** (98% *de*)[24] over two steps, followed by oxidation under Swern conditions gave corresponding α-amino aldehyde **10**, which was not isolated but instead subjected to acidic conditions to give rotaxane (S_{mp})-**12**, presumably *via* tautomerisation to corresponding iminium **11** and subsequent hydrolysis.[16] CSP-HPLC analysis of the product of this sequence confirmed that the diastereopurity of (S,S_{mp})-**4e** was cleanly converted to enantiopurity of the final products, allowing for the enantiopurity of macrocycle (*S*)-**1e** (98% *ee*[24]); rotaxane (S_{mp})-**5** was formed in 96% *ee* from (S,S_{mp})-**4e** (>98% de).

Figure 4. Removal of the covalent chiral auxiliary from rotaxane 4b derived macrocycles 1b and 1e.

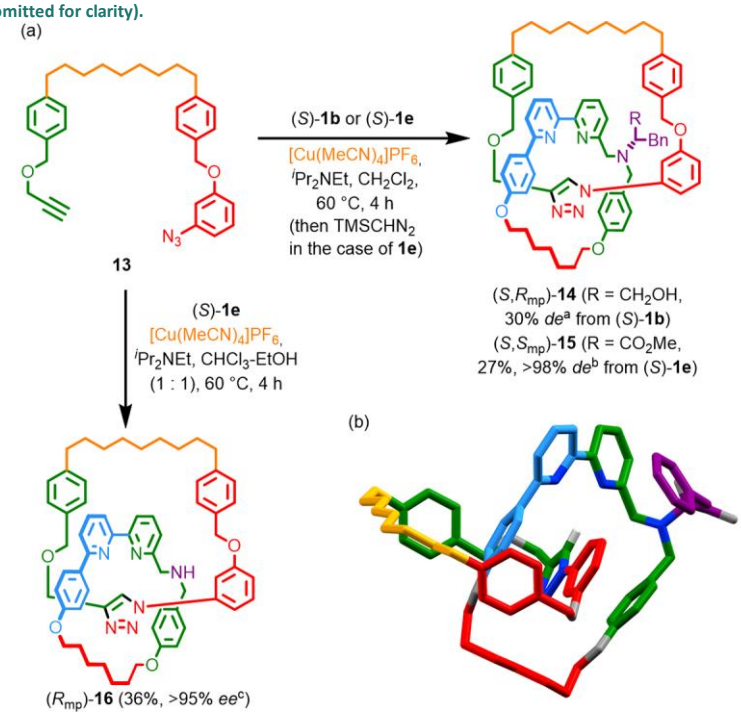


Reagents and conditions: i. $TMSCHN_2$, THF-MeOH (1 : 1), rt, 18 h. ii. $LiAlH_4$, THF, 0 °C to rt, 4 h. iii. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 C to rt. iv. AcOH, $CHCl_3$, rt, 18 h. [a]Determined by CSP-HPLC analysis.

Synthesis of a mechanically planar chiral catenane. Having demonstrated the application of macrocycles (*S*)-**1** in the synthesis of rotaxanes, we turned to their application in the synthesis of a mechanically planar chiral catenane (Figure 5a). Reaction of alkyne/azide pre-macrocycle **13** mediated by macrocycle (*S*)-**1b** under AT-CuAAC catenane forming conditions[27] gave catenane **14** in moderate stereoselectivity (30% *de*). When macrocycle (*S*)-**1e** was used with subsequent esterification, corresponding catenane **15** was obtained as a single diastereomer (>98%[22] *de*) as judged by ^{1}H NMR analysis of the crude reaction product and purified material. Pleasingly, a sample of *rac*-**15** (*% *de*) obtained by performing the same synthesis with *rac*-**1e,** produced crystals suitable for SCXRD analysis. The solid state structure obtained (Figure 5b), contained the *rac*-(S,S_{mp}) diastereomer of catenane, which allows us to assign the product of the reaction with (*S*)-**1e** as (S,S_{mp})-**15**. Reduction of a sample of (S,S_{mp})-**15** gave (S,R_{mp})-**14** (note the formal inversion of stereolabel, see ESI section S9) in 94% *de*,[24] which was isolated as a single diastereomer (>98%[22] *de*) as judged by ^{1}H NMR. Comparison of this material with that produced from (*S*)-**1b** allowed us to assign the major stereoisomer from the latter as

(S,R_{mp})-**14**. Thus, once again, macrocycles **1b** and **1e** are shown to form the mechanical bond with the same relative orientation of azide and alkyne components as for rotaxanes **4b**-**e**.

Figure 5. (a) Stereoselective synthesis of catenanes 14, 15 and 16. (b) Solid-state obtained from catenane 15 synthesized from *rac*-1e (colours as in (a) with the exception of O [grey], N [dark blue] and H [white]; majority of H omitted for clarity).



Reagents and conditions: (S)-**1** (1 equiv.), **13** (1.1 equiv.), $[Cu(MeCN)_4]PF_6$ (1 equiv.), $^iPr_2EtN$ (4 equiv.), CH_2Cl_2 (**14** and **15**) or $CHCl_3$-EtOH (1 : 1, **16**), 60 °C, 4 h (then $TMSCHN_2$, THF-MeOH (1 : 1), rt, 18 h for **1e**). [a]Determined by ^1H NMR analysis of the crude reaction product. [b]The minor diastereomer could not be detected by ^1H NMR analysis of either the crude or purified products. [c]Determined by CSP-HPLC analysis.

We initially intended to remove the chiral auxiliary from catenane **15** using the same sequence as for rotaxane **4e**. However, fortuitously, we first attempted the same reaction with macrocycle (*S*)-**1e** using a $CHCl_3$-EtOH solvent mix (1 : 1). Remarkably, we found that under these conditions, not only does mechanical bond formation proceed efficiently, but the auxiliary is also removed from the product to directly give catenane (R_{mp})-**16** in high stereoselectivity (>95% *ee*).[28] Although extremely convenient, the process by which the auxiliary cleaves under these conditions is unclear. Attempts to apply this method in the case of macrocycle **1e** alone or rotaxane **4e** gave a complex mixture of products in which the desired cleavage product is a minor component (see ESI section S8). Nonetheless, these results demonstrate that macrocycle **1e** can be used for the stereoselective synthesis of mechanically planar chiral catenanes. The auxiliary can then be removed either in a stepwise manner, as with rotaxane **4e**, or in a single step under some circumstances, as here.

Application of macrocycle 1e to the synthesis of co-conformationally mechanically planar chiral [3]rotaxanes. In addition to being able to use macrocycle **1e** to synthesise both mechanically planar chiral rotaxanes and catenanes in high enantiopurity, a particular advantage of placing the chiral auxiliary on the bipyridine macrocycle, rather than in alkyne or azide component, is that it is now possible to target more complicated chiral interlocked structures in a concise manner. In 1999, Vogtle and co-workers reported co-conformationally mechanically planar chiral [3]rotaxanes in which the axle component is bilaterally symmetric.[29] Such molecules can be formed as either a pair of C_2-symmetric enantiomers or as an achiral meso C_{2v} diastereomer, depending on the relative orientation of the two rings (Figure 6a). Although Vogtle and co-workers were able to use CSP-HPLC to partially separate the mixture stereoisomers produced in an unselective manner, to our knowledge, this is the only reported example in which the mechanical bond provides the sole stereogenic unit.[30]

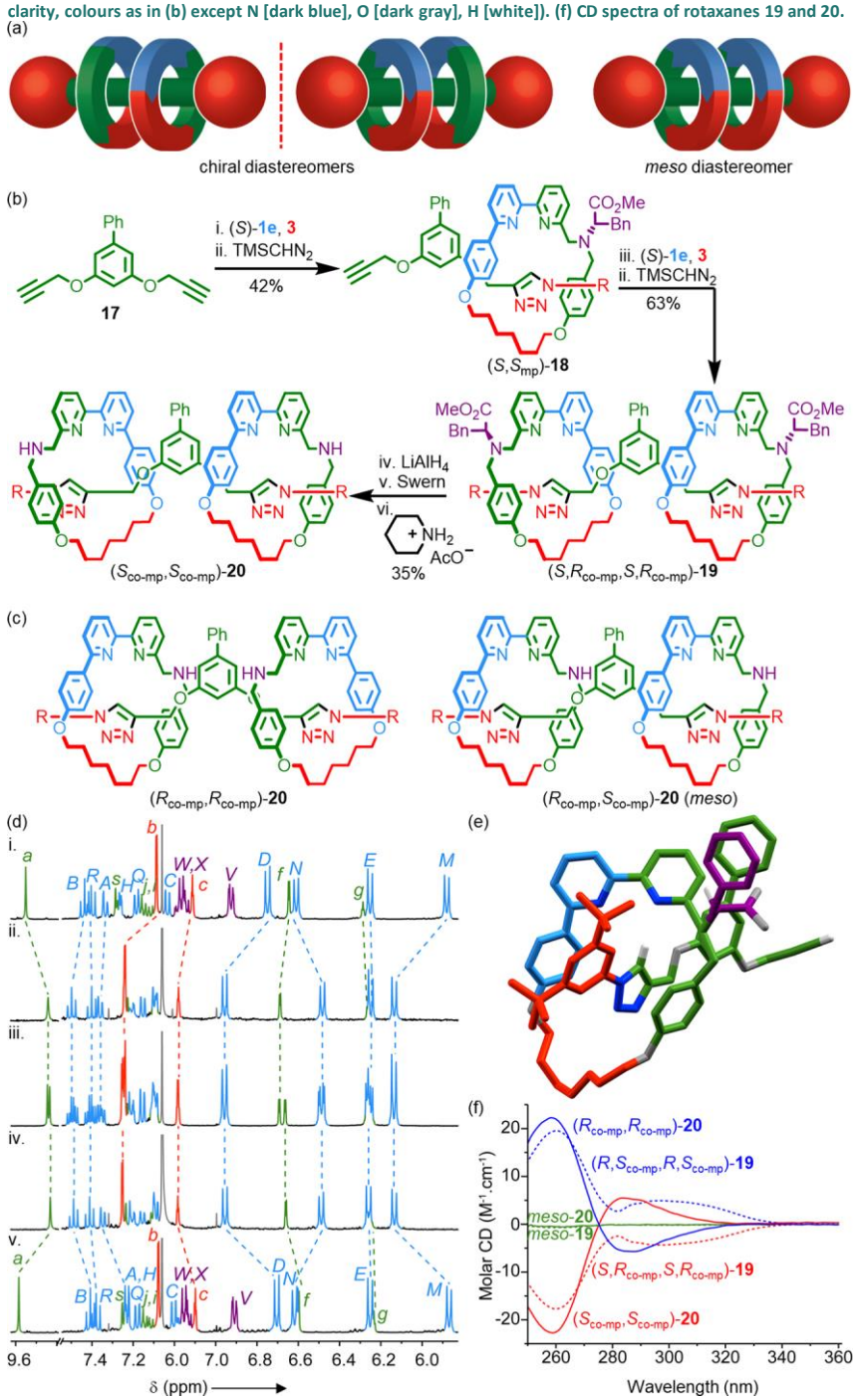
To address this unsolved challenge, we synthesised [3]rotaxanes **19** in a stepwise manner from bis-alkyne **17** *via* [2]rotaxane **18** using two sequential AT-CuAAC reactions. We envisaged we should obtain a chiral diastereomer by using the same stereoisomer of macrocycle **1e** in both steps (i.e. (*S*)-**1e** [Figure 6b] or (*R*)-**1e** [not shown]) or the *meso* product if the first coupling was carried out with (*S*)-**1e** and the second with (*R*)-**1e** (not shown). In keeping with the results above, the stereoselectivity in the first AT-CuAAC step to give [2]rotaxanes **18** was high (93 : 7 *dr*), which was further improved after purification (96 : 4 *dr*). SCXRD analysis of the carboxylic acid derivative of rotaxane **18** produced directly from (*S*)-**1e** (Figure 6e) allowed us to assign the absolute stereochemistry of the product as (S,S_{mp})-**18**.

After the second coupling step, [3]rotaxanes **19** were isolated in high diastereopurity (≥94% *de* for the chiral and *meso* diastereomers)[31] as judged by ^{1}H NMR analysis. Circular dichroism (CD) analysis of the product of coupling (S,S_{mp})-**18** with macrocycle (*S*)-**1e** (Figure 6f) revealed a strong Cotton effect, consistent with the chiral nature of the expected product diastereomer. The same product derived from coupling (*R*)-**1e** in both steps produced a mirror image CD response, consistent with its expected enantiomeric nature. If instead (S,S_{mp})-**18** was coupled with (*R*)-**1e** the product did not exhibit a significant CD response.[32] Combined with the absolute stereochemistry determined by SCXRD of (S,S_{mp})-**18**, this allowed us to assign the three products obtained as chiral diastereomers (S,$R_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-**19** (Figure 6b) and (R,$S_{co\text{-}mp}$,R,$S_{co\text{-}mp}$)-**19** (not shown), and *meso* diastereomer (R,$S_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-**19** (not shown). In keeping with this assignment, the ^{1}H NMR spectrum of proposed *meso* diastereomer, (R,$S_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-**19** (Figure 6di), is distinct from that of the chiral diastereomers (e.g., (S,$R_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-**19**, Figure 6dv).

Attempts to remove the auxiliary units from rotaxane (S,$R_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-**19** using the sequence described above for rotaxane **4b** (reduction, Swern oxidation then AcOH) led to a complex mixture of products that included the corresponding non-interlocked bipyridine macrocycle, suggesting that the axle component is not stable to the reaction conditions. When the acetic acid salt of piperidine was used in place of AcOH to catalyse the cleavage of the auxiliary unit (Figure 6b), the reaction mixture slowly evolved to produce rotaxanes **20**, presumably *via* hydrolysis of a piperidine enamine, without significant decomposition. Using this sequence, ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20** (Figure 6b) ($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-**20** and ($R_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20** (*meso*) (Figure 6c) were isolated in excellent stereopurity (96%, 94% and 90% *de* respectively) and reasonable yield.

Analysis of the different stereoisomers of rotaxanes **20** by ^{1}H NMR (Figure 6d) and CD (Figure 5f) revealed the expected features. The structures assigned as enantiomers ($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-**20** and ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20** produced the same ^{1}H NMR spectra (*e.g.*, Figure 6civ) and mirror image CD spectra whereas the sample assigned as *meso* diastereomer ($R_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20** was distinct by ^{1}H NMR (Figure 6dii) and produced no significant CD signal.[32] A mixture of rotaxane **20** stereoisomers produced by direct reaction of bis-alkyne **17** with two equivalents of azide **3** and the analogous amine macrocycle lacking the chiral auxiliary contained both diastereomers in a 1 : 1 ratio, as judged by ^{1}H NMR (Figure 6diii), produced no CD signal and contained three species with different retention times by CSP-HPLC in a ~ 1 : 1 : 2 ratio, consistent with a statistical mixture of ($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-**20**, ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20** and ($R_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20**. HPLC analysis of the stereoenriched samples of rotaxanes **20** revealed peaks with the expected retention times, albeit their absolute stereopurity could not be determined by CSP-HPLC due to the broad peaks obtained and the overlap of the peaks associated with ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20** and ($R_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20**. However, the high diastereopurity of the products at all steps of the synthesis, combined with the strong CD response of the chiral diastereomers and the qualitative appearance of the CSP-HPLC chromatogram confirms they are highly stereoenriched.

Figure 6. (a) Cartoon representations of co-conformationally mechanically planar chiral [3]rotaxane diastereomers. (b) Synthesis of ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-20 by iterative AT-CuAAC coupling of bis-alkyne 17 with macrocycle (*S*)-1e and subsequent cleavage of the auxiliary. (c) [3]Rotaxane diasteromers ($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-20 and ($R_{co\text{-}mp}$,$S_{co\text{-}mp}$)-20 (*meso*) derived by iterative coupling with (*R*)-1e twice or (*S*)-1e then (*R*)-1e respectively. (c) Partial ^{1}H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of i. *meso*-19, ii. *meso*-20, iii. 1 : 1 mixture of *rac*-($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-20 and *meso*-20, iv. ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-20, v. (S,$R_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-19 (colours as in (b) except macrocycle in blue, auxiliary in purple). (e) Solid-state structure of the carboxylic acid derivative of (S,S_{mp})-18 (majority of H omitted for clarity, colours as in (b) except N [dark blue], O [dark gray], H [white]). (f) CD spectra of rotaxanes 19 and 20.



Reagents and conditions: i. (S)-**1e** (1 equiv.), **17** (1 equiv.), **3** (1 equiv.), $[Cu(MeCN)_4]PF_6$ (1 equiv.), $^iPr_2EtN$ (1 equiv.), $CHCl_3$-EtOH (1 : 1), rt, 1 h. ii. $TMSCHN_2$, THF-MeOH (1 : 1), rt, 18 h. iii. (S)-**1e** (1 equiv.), **3** (1 equiv.), $[Cu(MeCN)_4]PF_6$ (2 equiv.), $^iPr_2EtN$ (1 equiv.), $CHCl_3$-EtOH (1 : 1), rt, 1 h. iv. $LiAlH_4$, THF, 0 °C to rt, 4 h. v. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 C to rt. vi. piperidinium acetate, THF-H_2O (9 : 1), 70 °C, 5 days.

CONCLUSIONS

In conclusion, we have demonstrated that by placing a simple and readily removed amino acid derived chiral auxiliary on a bipyridine macrocycle we can prepare mechanically planar chiral rotaxanes and catenanes in which the mechanical bond provides the sole stereogenic unit in excellent enantiopurity. Importantly, our results suggest that macrocycle **1e** can produce interlocked products in excellent stereoselectivity even when the steric demand of the alkyne and azide substrates is reduced. The same relative disposition of alkyne and azide components was observed in the three examples that were characterized by SCXRD, which suggests that **1e** has a reliable preference in terms of the major stereoisomer produced. We demonstrated the flexibility of this approach through the stereoselective synthesis of all three stereoisomers of a co-conformationally mechanically planar chiral [3]rotaxane, the first time to our knowledge that this has been achieved. Improvements remain to be made, however. Firstly, the structural origin of the high stereoselectivity is unclear, although it is striking that the most effective macrocycles, **1b** and **1e**, both present and acidic oxygen functional group, suggesting that H-bonding or metal coordination may be important.[33] Secondly, although it is possible to remove the auxiliary unit, the sequence (esterification, reduction, oxidation, tautomerisation and hydrolysis) is somewhat cumbersome. We are now working to address this. These issues notwithstanding, our results suggest that it will be possible to design chiral macrocycles for use in the active template approach,[11] and perhaps also passive template methodologies,[34] that allow large families of mechanically chiral molecules to be prepared readily from simple, achiral building blocks. We anticipate that this will dramatically accelerate the investigation of mechanically chiral molecules in a range of applications at a time when their potential in catalysis,[26] sensing[3] and as chiroptical switches,[35] and their chiroptical properties[36] and unusual stereochemistry[37] is increasing.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact: Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Professor Stephen M. Goldup (s.goldup@soton.ac.uk).

Materials Availability: Full procedures for the synthesis of all novel compounds from commercially available materials are reported in the Supplemental Information. Requests for samples of any of the novel molecules reported here will be considered on a case-by-case basis by the Lead Author.

Data and Code Availability: Raw characterization data will be available upon publication through the University of Southampton data repository. The accession number for the solid-state structure of rotaxanes **4a**, **4b** and **S20**, catenane *rac*-**15**, and macrocycle *rac*-**1e** reported here are CCDC 2207367, 2207368, 2207370, 2207369 and 2207366 respectively. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

Supplemental Information: The supplemental Information includes experimental procedures and characterization data and analysis for all novel compounds and additional discussion.

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AUTHOR CONTRIBUTIONS

S.M.G. conceived the project and secured project funding. S.Z. designed macrocycle **1a** and carried out initial synthetic investigations with rotaxanes **4**, **5**-**7** and **12** and catenanes **14**-**16**. A.R.R. completed these investigations, synthesised rotaxanes **8** and **9** and obtained single crystals of **4a** and **15** for SCXRD analysis. A.R.R. and A.S. synthesised rotaxanes **20**. A.S. obtained single crystals of **18** for SCXRD analysis. A.R.R. led the preparation of the ESI and contributed to the stereochemical analysis of all products. G.J.T. collected and analyzed all SCXRD data reported. S.M.G. wrote the manuscript with input from all authors. All authors contributed to the reviewing and editing of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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(23) The minor enantiomer was not detected (Figure S29).
(24) Phenylalanine ester derivatives can suffer from epimerisation. Although we did not observe this in the synthesis of macrocycle **1a**, after hydrolysis and re-esterification[25] the stereopurity was slightly degraded (>99% *ee* to 98% *ee*). Thus, in cases where the interlocked product was esterified prior to stereochemical analysis (necessary as the carboxylic acid derivatives often exhibit broad ^{1}H NMR spectra) the value obtained represents a lower limit. Note that we are assuming that one diastereomer is not strongly thermodynamically preferred.
(25) Macrocycle (*S*)-**1e** was synthesised by hydrolysis of (*S*)-**1a**. Unfortunately we were unable to achieve separation of **1e** by analytical CSP-HPLC and so to determine its stereopurity we converted it back to **1a**. The *ee* determined is thus a lower limit[24] on the actual enantiopurity of **1e**.
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(32) Rotaxanes *meso*-**19** and *meso*-**20** contain small amounts (~2% and 5% respectively) of a chiral diastereomer, presumably in an inballanced ratio (*i.e.*, not 0% *ee*), which accounts for the small CD response observed.

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