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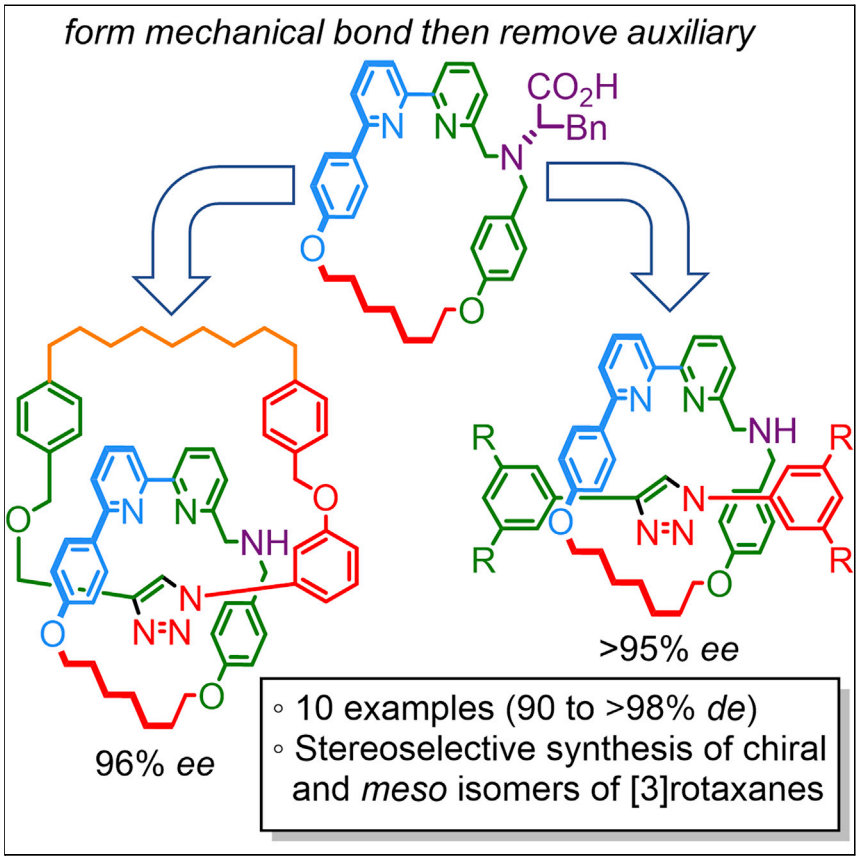

Mechanically chiral molecules are chiral due to interlocking of achiral covalent subcomponents. They are under investigation in catalysis, materials chemistry, and sensing, but their synthesis remains challenging. We report a simple chiral macrocycle that allows the synthesis of both rotaxanes and catenanes in excellent diastereopurity. Subsequent removal of the covalent chiral auxiliary unit gives rise to the corresponding product in excellent enantiopurity. This flexible approach even allows the synthesis of more complicated structures with multiple interlocked components.

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Highlights

Diastereoselective synthesis of rotaxanes and catenanes using a chiral macrocycle

Very general approach: 10 products with 90 to >98% de

Auxiliary removal gives mechanically planar chiral products in high ee

Applicable to structurally complex targets: synthesis of [3]rotaxanes stereoisomers

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A chiral macrocycle for the stereoselective synthesis of mechanically planar chiral rotaxanes and catenanes

Shu Zhang,[1,3,4] Arnau Rodríguez-Rubio,[1,3] Abed Saady,[1] Graham J. Tizzard,[1] and Stephen M. Goldup[1,2,5,*]

SUMMARY

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.

INTRODUCTION

Enantiopure samples of "mechanically chiral" molecules,[1–4] rotaxanes, and catenanes in which the mechanical bond provides the sole chirotopic stereogenic element have historically been produced by resolution of racemic samples[5–11] or unusual chiral building blocks,[12] both of which typically rely on preparative chiral stationary phase high-performance liquid chromatography (CSP-HPLC) separation of the product or building blocks.[13–16] Although these methods have allowed preliminary studies on the properties of mechanically chiral molecules,[10–12] the inherent limitations of CSP-HPLC have prevented more detailed studies of their applications.

To overcome this synthetic bottleneck, new stereoselective methods are required.[17] Takata, Okamoto, and co-workers reported the first approach to this challenging goal in 2007 by using a catalytic enantioselective kinetic resolution strategy; the acylation of a dynamic mixture of enantiomeric pseudorotaxanes gave rise to a small (~4% enantiomeric excess [ee]) but measurable stereoselectivity.[18] In 2020, Leigh and co-workers reported the synthesis of a mechanically planar chiral rotaxane in 50% ee by using a substrate-controlled strategy in which a chiral leaving group was used to influence the configuration of the mechanical bond.[19] 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).[20] Most recently, Zhu, Tian, and co-workers reported the catalytic enantioselective desymmetrization of rotaxanes containing a bilaterally symmetric macrocycle in up to 93% ee.[21]

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

THE BIGGER PICTURE

Thanks to the efforts of synthetic organic chemists over the last century, the synthesis of chiral small molecules has progressed significantly, which has facilitated their study in a range of areas from medicine to materials science. By contrast, the synthesis of chiral mechanically interlocked molecules, structures that are formed by threading one molecule through another, remains challenging. This is at least in part because such structures are extremely challenging to make—until 2014, the only way to access them was by using chiral stationary phase HPLC. We have developed auxiliary methods to access chiral catenanes and rotaxanes, but in each case, the source of covalent chiral information was in a reaction component bespoke to the particular synthesis. Here, we present a chiral macrocycle that can be used to make both chiral catenanes and rotaxanes in excellent stereoselectivity. The efficiency of this approach opens significant structural space for further investigation.

approach,[22] we disclosed the active template[23,24] Cu-mediated alkyne-azide cycloaddition (AT-CuAAC)[25–27] synthesis of mechanically planar chiral rotaxanes in up to 96% ee without separation of the intermediate diastereomers.[28] This approach was then extended, using the same class of oriented bipyridine macrocycles,[29] to a chiral interlocking auxiliary strategy.[30] We subsequently demonstrated an auxiliary approach to analogous chiral catenanes,[31] although in this case, a lower diastereoselectivity (diastereomeric ratio [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).[32] Most recently, we have extended our auxiliary approach to mechanically axially chiral catenanes and, in the process, identified an overlooked mechanically axially chiral rotaxane stereogenic unit.[33]

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.[34] Furthermore, we have recently demonstrated the synthesis of a catenane with the same stereogenic unit but whose stereochemistry is Euclidean.[35] 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 in the oriented bipyridine macrocycle[29] that mediates the AT-CuAAC reaction, 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.

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[36–38] 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[36] 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*)-phenylalanine 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% diastereomeric excess [de]; Figure 2A, entry 1), as judged by ^{1}H NMR analysis of the crude

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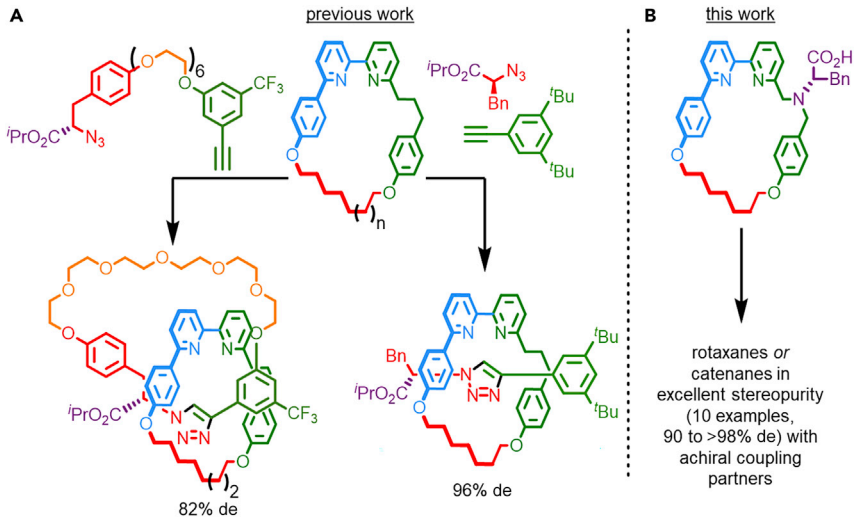


Figure 1. Comparison between this work and our previous approaches to mechanically planar chiral rotaxanes and catenanes

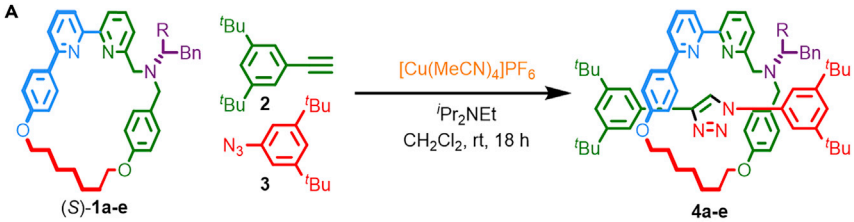
(A) The same oriented bipyridine macrocycle can be used to make either chiral catenanes or rotaxanes using our AT-CuAAC approach, but the auxiliary unit must be built into the alkyne or azide containing components.

(B) The approach we present here allows for the same chiral, oriented bipyridine macrocycle to be used to chiral rotaxanes and catenanes from achiral alkyne and azide components in high stereoselectivity.

reaction product.[39] Macrocycle (*S*)-**1b** (>99% ee),[40] in which the methyl ester of (*S*)-**1a** was reduced to the primary alcohol, produced rotaxane **4b** in dramatically enhanced stereoselectivity (86% de; Figure 2A, entry 2), whereas the corresponding silyl ether ([*S*]-**1c**) produced rotaxane **4c** in much lower selectivity (46% de; Figure 2A, entry 3), and the corresponding acetoyl ester (*S*)-**1d** gave rotaxane **4d** with almost no stereoselectivity (18% de; Figure 2A, entry 4). Carboxylic acid macrocycle (*S*)-**1e** (98% ee),[41,42] derived from (*S*)-**1a** by hydrolysis of the ester moiety, produced rotaxane **4e** as a single stereoisomer by ^{1}H NMR analysis (>98% de, Figure 2A, 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.

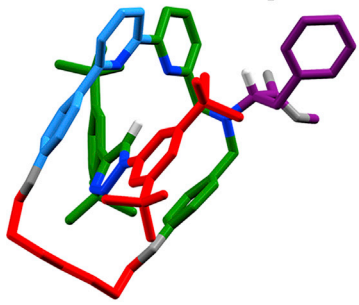
The relative stereochemistries of the major stereoisomers of rotaxanes **4** were compared by conversion of **4a** and **4c–4e** to alcohol rotaxane **4b** for analysis by ^{1}H NMR. Whereas samples of rotaxane **4b** derived from macrocycles **1b–1e** were found to contain the same major diastereomer, 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 supplemental information section S9 for a detailed discussion on the assignment of mechanical stereogenic units). According to these corroborating data, macrocycles **1b–1e** produce rotaxanes **4b–4e** 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.

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



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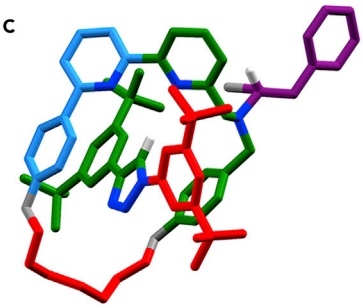

Figure 2. The effect of marocycle 1 structure on the stereoseletivity of the AT-CuAAC reaction

(A) Synthesis of diastereomeric rotaxanes **4**.

(B and C) Solid-state structures of (B) (S,R_{mp})-**4a** and (C) (S,S_{mp})-**4b** (colors as in A, with the exception of O [gray], N [dark blue], and H [white]; majority of H omitted for clarity).

Reagents and conditions: (*S*)-**1** (1 equiv), **2** (2 equiv), **3** (2 equiv), $[Cu(MeCN)_4]PF_6$ (0.92 equiv), $^iPr_2EtN$ (4 equiv), CH_2Cl_2, room temperature (RT), 18 h.

[a]Stereolabel refers to the product after conversion to **4b** for comparison by ^1H NMR.

[b]Isolated yield after conversion of the crude reaction product to **4b** (see supplemental information for details).

[c]Determined by ^1H NMR analysis of the crude reaction product.

[d]Determined by ^1H NMR analysis after conversion of the crude reaction product to **4b** (see supplemental information for details).

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[28] to the point where a chiral auxiliary that is highly stereoselective (96% de) with one coupling partner is entirely unselective with another substrate.[43] Although this issue can be overcome using our recently introduced chiral interlocking auxiliary approach,[30] 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 ^1H NMR analysis of the crude reaction products). If instead macrocycle (*S*)-**1e** was employed, after reduction of the crude reaction product,[41] rotaxanes **5**, **6**, and **7** were produced in significantly

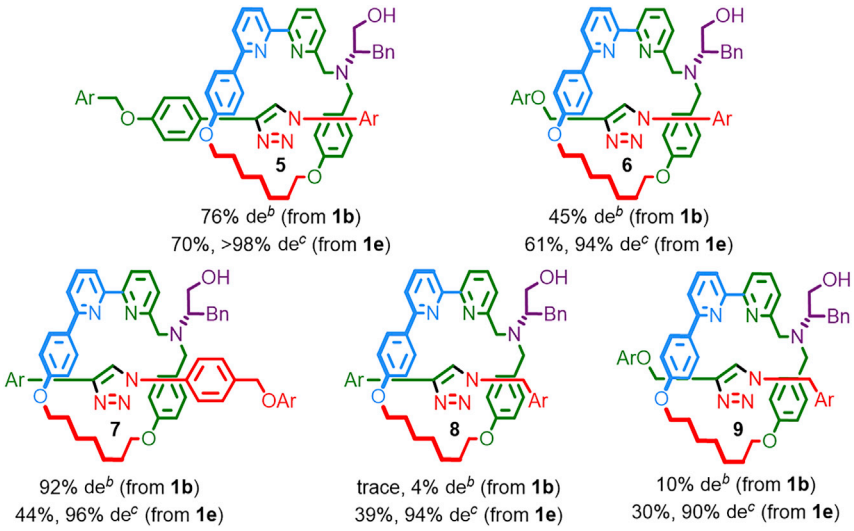

Figure 3. Rotaxanes 6–9 derived from macrocycles 1b and 1e[a]

[a]The relative orientation of axle and macrocycle in the major stereoisomer of rotaxanes **5**–**9** was assumed to be the same as **4b**–**4e**. 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 supplemental information 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.

enhanced diastereomeric purity (>98%, 94%, and 96% de, respectively) and reasonable isolated yield. Both macrocycles produced the same major stereoisomer of the product. On the basis of 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.

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,[44] 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% and ~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**

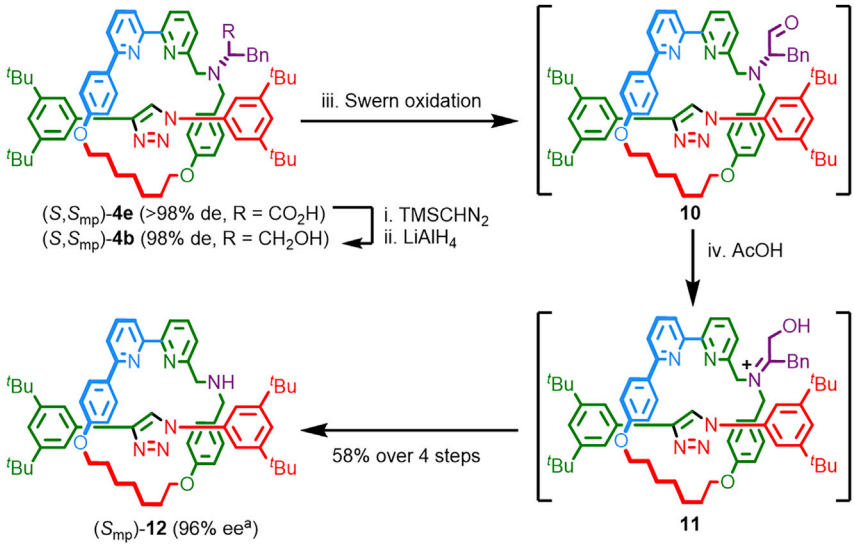

Figure 4. Removal of the covalent chiral auxiliary from rotaxane 4b derived macrocycles 1b and 1e

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.

(>98% de) to (S,S_{mp})-**4b** (98% de)[41] 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 tautomerization to corresponding iminium **11** and subsequent hydrolysis.[31] 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[41]); rotaxane (S_{mp})-**5** was formed in 96% ee from (S,S_{mp})-**4e** (>98% de).

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[44] 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%[39] de), as judged by ^{1}H NMR analysis of the crude reaction product and purified material. Pleasingly, a sample of *rac*-**15** (>99% 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, allowing 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 supplemental information section S9 for a detailed discussion) in 94% de,[41] which was isolated as a single diastereomer (>98%[39] 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**–**4e**.

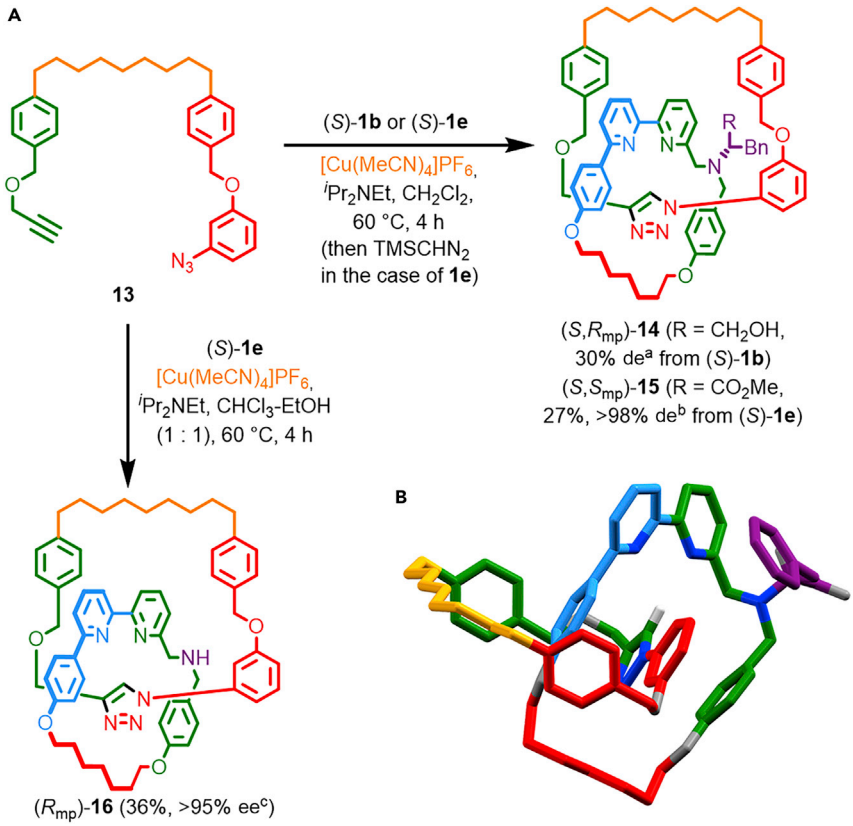

Figure 5. The application of macrocycles 1b and 1e in the synthesis of mechanically planar chiral catenanes

(A) Stereoselective synthesis of catenanes **14**–**16**.

(B) Solid-state obtained from catenane **15** synthesized from *rac*-**1e** (colors as in A, with the exception of O [gray], 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), $^{i}Pr_2EtN$ (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** by using the same sequence as for rotaxane **4e**. However, fortuitously, we first attempted the same reaction with macrocycle (*S*)-**1e** by 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).[45] 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 supplemental information section S8 for a more detailed discussion). 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.

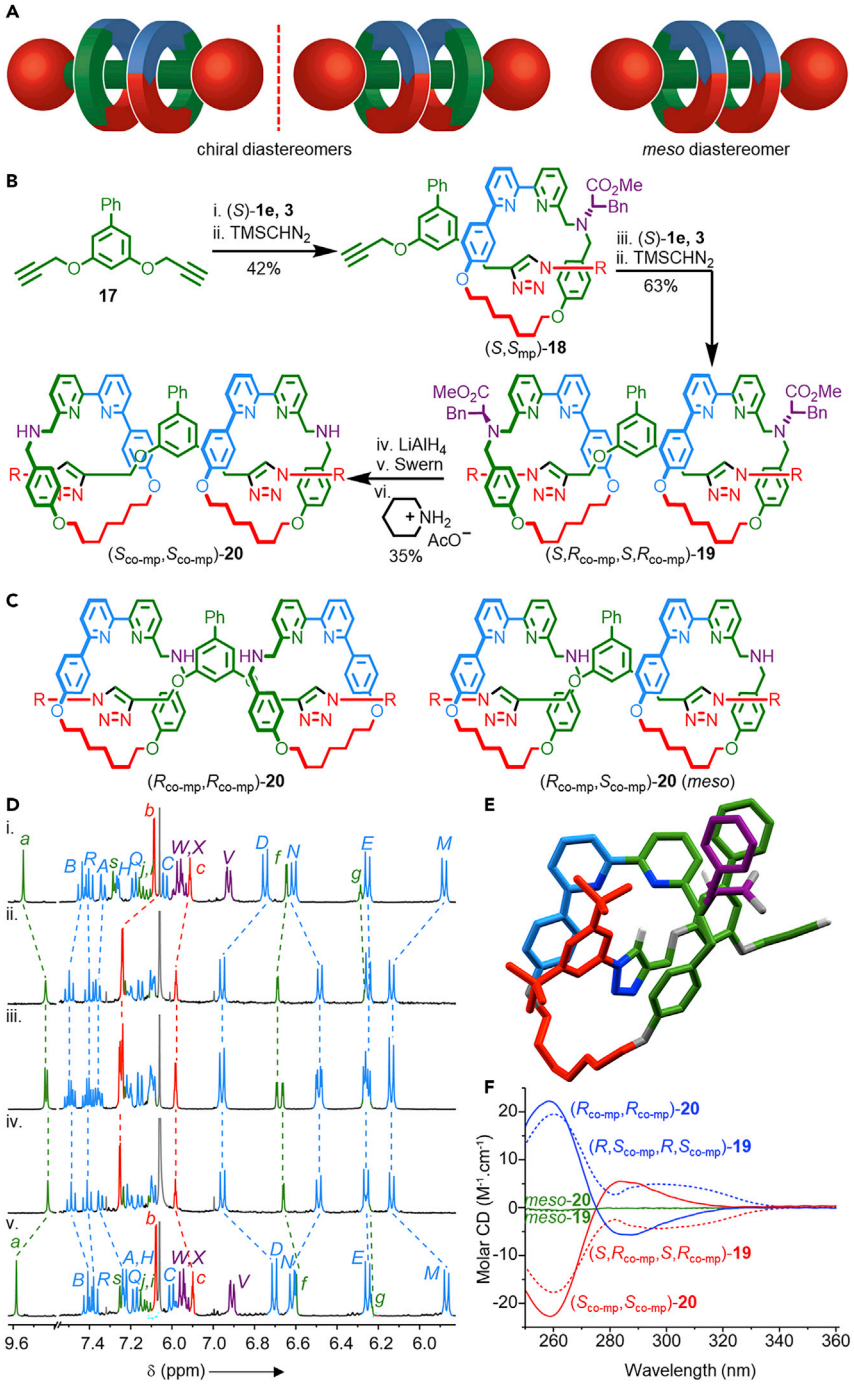

Figure 6. The structure, synthesis and analysis of co-conformationally mechanically planar chiral rotaxanes

(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 and with (*S*)-**1e** and then (*R*)-**1e**, respectively.

(D) Partial ^{1}H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of (Di) *meso*-**19**, (Dii) *meso*-**20**, (Diii) 1:1 mixture of *rac*-($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-**20** and *meso*-**20**, (Div) ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**20**, and (Dv) (S,$R_{co\text{-}mp}$,S,$R_{co\text{-}mp}$)-**19** (colors as in B except macrocycle in blue and auxiliary in purple).

Figure 6. *Continued*

(E) Solid-state structure of the carboxylic acid derivative of (S,S_{mp})-**18** (majority of H omitted for clarity, colors as in B except N [dark blue], O [dark gray], and 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.

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 synthesize 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, Vögtle and co-workers reported co-conformationally mechanically planar chiral [3]rotaxanes in which the axle component is bilaterally symmetric.[46] 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 Vögtle and co-workers were able to use CSP-HPLC to partially separate the mixture of stereoisomers produced in an unselective manner, to the best of our knowledge, this is the only reported example in which the mechanical bond provides the sole stereogenic unit.[47]

To address this unsolved challenge, we synthesized [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),[48] 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.[49] 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** by 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 catalyze 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, we isolated ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**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) 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 6Div) 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.[49] A mixture of rotaxane **20** stereoisomers produced by direct reaction of bis-alkyne **17** with 1 equiv of azide **3** and the analogous amine macrocycle lacking the chiral auxiliary containing 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 an ~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.

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 the best of our knowledge that this has been achieved. However, improvements remain to be made. First, the structural origin of the high stereoselectivity is unclear, although it is striking that the most effective macrocycles, **1b** and **1e**, both present an acidic oxygen functional group, suggesting that H bonding or metal coordination may be important.[50] Second, although it is possible to remove the auxiliary unit, the sequence (esterification, reduction, oxidation, tautomerization, 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[23,24]—and perhaps also passive template methodologies[51]—that allows for 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[43] and sensing[12] and as chiroptical switches,[52–54] together with their chiroptical properties[55–57] and unusual stereochemistry,[58] 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.m.goldup@bham.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 contact.

Data and code availability

Raw characterization data are available from the University of Southampton data repository (https://doi.org/10.5258/SOTON/D2493). The accession numbers for the solid-state structure of rotaxanes **4a**, **4b**, and **S20**; catenane *rac*-**15**; and macrocycle *rac*-**1e** are CCDC: 2207367, 2207368, 2207370, 2207369, and 2207366, respectively. Any additional information required for reanalyzing the data reported in this paper is available from the lead contact upon request.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2023.01.009.

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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** and obtained single crystals of **4b** for SCXRD analysis. A.R.-R. completed these investigations, synthesized rotaxanes **8** and **9**, and obtained single crystals of **4a** and **15** for SCXRD analysis. A.R.-R. and A.S. synthesized rotaxanes **20**. A.S. obtained single crystals of **18** for SCXRD analysis. A.R.-R. led the preparation of the supplemental information 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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39. Diastereoselectivity was assessed using the relative integration of pairs of equivalent protons (typically the triazole protons) of the major and minor diastereomers.[22,28,30–33,35] The GSD peak integration function of MestReNova (11.0.4, Mestrelab Research S.L.) was used throughout rather than a simple sum integration as this allowed a consistent approach even when the peaks of interest were close in chemical shift. Where possible, more than one pair of peaks was used and the average value obtained reported. All values are reported as-measured, except where signals corresponding to the minor diastereomer could not be observed, for which the dr is assigned as >99:<1 as signals corresponding to ~1% of the major diastereomer were routinely detectable. We note that the precise de value obtained with a given macrocycle/axle combination is less important than whether the reaction is highly selective or not given that the molecules presented are not functional targets in their own right. The approach taken here clearly establishes this key information in a systematic manner. See the general experimental information section of the supplemental information for a more detailed discussion.

40. The minor enantiomer was not detected (Figure S29).

41. Phenylalanine ester derivatives can suffer from epimerisation. Although we did not observe this in the synthesis of macrocycle 1a, after hydrolysis and re-esterification[42] 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.

42. Macrocycle (*S*)-**1e** was synthesized 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[41] on the actual enantiopurity of **1e**.

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47. Cyclodextrin-based [3]rotaxanes that contain both covalent and co-conformational mechanical planar chiral stereogenic units have been synthesized selectively: Craig, M.R., Claridge, T.D.W., Anderson, H.L., and Hutchings, M.G. (1999). Synthesis of a cyclodextrin azo dye [3]rotaxane as a single isomer. Chem. Commun. *16*, 1537–1538. https://doi.org/10.1039/a902494h.

48. ($S,R_{co\text{-}mp},S,R_{co\text{-}mp}$)-19 was isolated in 98% de. Two signals that could correspond to the minor diastereomer of ($R,S_{co\text{-}mp},R,S_{co\text{-}mp}$)-19 were observed by ^{1}H NMR analysis, integration of which indicated 94% de or 96% de, the lower value of which is reported here. Similarly, two signals were observed for the minor diastereomer of ($R,S_{co\text{-}mp},S,R_{co\text{-}mp}$)-19 and give rise to either 94% or 98% de. On this basis, we cannot comment on any matched or mismatched stereoselectivity in the second coupling step.

49. 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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