A Chiral Interlocking Auxiliary Strategy for the Synthesis of Mechanically Planar Chiral Rotaxanes

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Abstract: We have serendipitously discovered a combination of reaction partners that function as a “chiral interlocking auxiliary” to both orientate a macrocycle and, effectively, load it onto a new axle. We demonstrate the potential of this finding through the synthesis of a number of targets in high enantiopurity, without separation of stereoisomers, including examples whose axles lack any functional groups that would allow their direct synthesis by other means, so called “impossible” rotaxanes. Intriguingly, by varying the order of bond forming steps, we can effectively choose which end of an axle the macrocycle is loaded onto, allowing the synthesis of both hands of a single target using the same reactions and building blocks.

Introduction

The ability of the covalent subcomponents in mechanically interlocked molecules (MIMs) to undergo large amplitude relative motion is perhaps the most well-appreciated consequence of the mechanical bond. However, threading covalent fragments through one another to generate MIMs can also lead to molecular stereochemistry that relies solely on the mechanical bond, allowing MIMs to display molecular chirality even when their covalent subcomponents themselves are achiral. The synthesis of such mechanically chiral molecules in enantiopure form has largely relied on the chiral stationary phase HPLC (CSP-HPLC) separation of a racemic mixture of products, which has limited the investigation of their properties.

Indeed, to date, only two direct enantioselective syntheses of mechanically planar chiral (MPC) rotaxanes, molecules in which the stereochemistry relies on the combination of an axle that lacks mirror planes perpendicular to its principle axis and a macrocycle whose only mirror planes lie parallel to the ring, have been reported. Takata and co-workers reported the formation of MPC enantiomers in 4.4% ee using the dynamic kinetic resolution of a pseudo-rotaxane precursor. More recently, Leigh and co-workers reported a direct enantioselective synthesis of MPC rotaxanes under substrate control in an impressive 50% ee using their organocatalytic active template reaction in conjunction with a chiral alcohol leaving group. Such direct enantioselective approaches are extremely attractive but, unless ~90% ee or higher can be achieved, the enantiomeric products still require CSP-HPLC separation for use in applications such as catalysis, sensing and materials science.

An alternative approach to enantiopure mechanically chiral MIMs that can circumvent the need for CSP-HPLC separation is to use a chiral auxiliary including an enantiopure fixed covalent stereogenic unit in the MIM structure gives rise to a mixture of diastereomers that differ in the configuration of the mechanical stereogenic unit as an unequal mixture. Where required, these diastereomers can be separated using standard synthetic techniques prior to removal of the covalent stereogenic unit to provide enantioenriched mechanically chiral products in which the mechanical bond provides the sole stereogenic unit. We have demonstrated this concept in the stereoselective synthesis of enantiopure MPC rotaxanes and related topologically chiral catenanes. However, although our auxiliary approach has allowed us to demonstrate the use of MPC rotaxanes in enantioselective Au-mediated catalysis, the diastereoselectivity of the key mechanical bond forming step can vary significantly with the same auxiliary depending on the coupling partners used. Furthermore, the separation of the mechanical epimers produced is far from simple or assured.
Here we report the serendipitous discovery of a structural motif that functions both as a chiral auxiliary, to select the orientation of a macrocycle on an axle, and an interlocking auxiliary, to effectively allow an oriented macrocycle to be threaded selectively onto an axle (Figure 1). We show that this “chiral interlocking auxiliary” approach allows the synthesis of MPC rotaxanes in excellent enantiopurity (92 - 99% ee), including so-called “impossible” rotaxanes and functionalized examples through late-stage diversification. Furthermore, by effectively selecting which end of an axle the macrocycle is threaded onto, we demonstrate the synthesis of both hands of a target using the same building blocks, highlighting an intrinsic link between mechanical motion and mechanical stereochemistry.

**Figure 1.** The “chiral interlocking auxiliary” concept in the synthesis MPC rotaxanes

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**Results and discussion**

**Discovery of a potential chiral interlocking auxiliary motif**

We previously demonstrated that amino acid-derived azide 1 can be used to generate MPC rotaxanes in up to 96% ee using an active template copper-mediated alkyne-azide cycloaddition (AT-CuAAC)\(^1\) strategy.\(^2\) However, the stereoselectivity achieved with 1 varies considerably depending on the alkyne coupling partner used.\(^2\) During efforts to understand this problem, we compared the reaction of (S)-1 in the presence of macrocycle 2 with alkynes 3a and 3b, which differ in the steric hindrance around the acetylene moiety (Figure 2a). Alkyne 3a gave rise to rotaxane 4a in good yield but poor stereoselectivity (76% de), which could be assessed readily by \(^1\)H NMR analysis of the crude reaction product; two resonances were observed for triazole proton (H\(_{trz}\)) at 8.93 and 8.75 ppm which were attributable to the major and minor mechanical epimers respectively (Figure 2ai). Both resonances appear at higher ppm than the corresponding signal of the non-interlocked axle (\(\Delta\delta = 1.2\) ppm for the major isomer), presumably due to a C-H•••N H-bond between the bipyridine Ns and H\(_{trz}\), as commonly observed in similar systems.\(^20\),\(^21\),\(^22\),\(^23\) Pleasingly, reaction of o-Me acetylene 3b produced rotaxane 4b in good yield and a significantly enhanced stereoselectivity (\(\sim 95%\) de). Indeed, to assign the diastereoselectivity of the reaction, samples of rotaxane 4b had to be epimerized so that the \(^1\)H NMR resonances of the minor isomer could be identified (see ESI for full details).

Inspection of the \(^1\)H NMR spectrum of 4b (Figure 2a) led to two observations. Firstly, the resonance attributable to H\(_{trz}\) appears much closer to that of the same proton in the corresponding axle (Figure 2ai, \(\Delta\delta = 0.5\) ppm) than observed for rotaxane 4a. Secondly, the diastereotropic methylene ether protons H\(_{ether}\) appear as a well separated (\(\Delta\delta = 0.7\) ppm) pair of doublets in the \(^1\)H NMR spectrum of 4b, whereas in the case of 4a a much smaller separation was observed (\(\Delta\delta = 0.2\) ppm). This suggests that the mechanical stereochemistry of rotaxanes 4 is well expressed around the ether methylene unit (the same signals in the corresponding axles appear as a singlet) and that this effect is larger for 4b than 4a. In contrast, aliphatic protons associated derived from the azide component are more shielded in rotaxane 4a than 4b relative to the corresponding non-interlocked axle.
Figure 2. (a) Observation of the effect of an o-Me substituent on the diastereoselectivity of mechanical bond formation and the co-conformational bias in rotaxanes 4. (b) Partial 1H NMR of (i) the non-interlocked axle of rotaxane 4b, (ii) rotaxane 4b, (iii) rotaxane 4a, (iv) the non-interlocked axle of rotaxane 4a (colors and atom labels as in (a) with the exception of macrocycle protons which are shown in blue; correlations shown for protons H_{trz}, H_{ether} and aliphatic protons derived from the azide unit). (c) Solid state structure of 4b in sticks and spacefilling representations with selected intercomponent interactions indicated (substituted benzyl ether unit omitted for clarity, colors as in (a)).

\[\text{The absolute stereochemistry shown for rotaxanes 4 corresponds to the major isomer of 4b determined by x-ray diffraction analysis (S, S_{mp}), the major isomer of rotaxane 4a was not determined.}^{a}\text{Reagents and conditions: [Cu(MeCN)}_4]\text{PF}_6, \text{iPr}_2\text{EtN, CH}_2\text{Cl}_2, \text{rt, 16 h.}^{b}\text{Determined by 1H NMR analysis of the crude reaction products.}^{c}\text{Determined by 1H NMR analysis of the purified products.}

\text{Taken together, these observations are consistent with rotaxanes 4 existing as a mixture of rapidly exchanging co-conformations in which the bipyridine macrocycle is localized around either the triazole (4_{triazole}) or ether (4_{ether}) moiety of the axle (Figure 2a), presumably in both cases through C-H•••N H-bonds, augmented by other weak interactions (π-π, CH-π). Indeed, by comparing the difference in triazole chemical shifts of the corresponding non-interlocked axles and rotaxanes 4a (Δδ = 1.2 ppm) and 4b (Δδ = 0.5 ppm) with the maximum expected chemical shift difference (Δδ = ~2.3 ppm) were the triazole station fully occupied (estimated conservatively by considering that the 1H NMR signal attributable to the triazole proton of similar molecules in which the macrocycle is trapped around the triazole unit typically appear}
at >10 ppm), we estimate that 4a is slightly preferred (~55%) whereas 4b is favored significantly (~80%).

The observed difference in co-conformational preference is presumably due to steric clash between the o- Me substituent and the ring which disfavors H-bonding to Htrz. The solid-state structure of 4b obtained through single crystal x-ray diffraction analysis (Figure 2c) is consistent with this proposal as, although the 4b trizole co-conformation was found in the solid state, the observed C-H...N contacts are much longer than those in other otherwise similar systems (C-H...N = 2.6 and 3.0 vs 2.5 and 2.7 Å). The space filling representation of the solid-state structure also emphasizes the sterically crowded nature of the triazole station as the macrocycle is seen to be buttressed on one side by the sterically crowded covalent stereogenic center and on the other by the o-Me substituent of the aryl unit. The solid-state structure of 4b also allowed us to assign the absolute stereochemistry of the major isomer to be (S,Smp)-4b.

An “interlocking auxiliary”, as introduced by Leigh and Leigh and co-workers and recently extended by Coutrot, is a unit that facilitates mechanical bond formation but from which the macrocycle can then be shuttled away from readily to a “receiver” region of the axle, before the interlocking auxiliary unit is removed. The combination of azide 1 with an o-Me aromatic alkyne appears to meet the requirements of both a chiral auxiliary (high stereoselectivity) and interlocking auxiliary (weak non-covalent interactions with the functional group produced) and so could combine these functions as a “chiral interlocking auxiliary”.

Demonstration of the chiral interlocking auxiliary concept

To validate our hypothesis, we investigated the AT-CuAAC reaction of o-Me alkyne 5a with azide (S)-1 and macrocycle 2 with the intention of shuttling the macrocycle onto the unhindered triazole unit prior to removing the chiral interlocking auxiliary to generate rotaxane 8. AT-CuAAC coupling of 5a with (S)-1 and 2 gave rotaxane 6 in excellent isolated yield (80%). 1H NMR analysis of 6 (Figure S49) suggests that, as expected, the macrocycle is significantly displaced from the hindered triazole; the triazole proton appears at relatively low chemical shift (δ = 7.60 ppm) and the diastereotopic benzylic methylene protons appear as a well separated pair of doublets (Δδ = 0.58 ppm). We were unable to ascertain the diastereoselectivity of the reaction at this stage as only one set of signals could clearly be observed.

The PMB protecting group was removed to give rotaxane 7 in which the ring is free to shuttle to the unhindered triazole. Reaction with TMSCHN2 “stopped” the new axle, trapping the macrocycle over the receiver unit. Finally, addition of K2CO3 and MeOH removed the auxiliary fragment to give a crude reaction product containing rotaxane 8 and macrocycle 2 in a 96 : 4 ratio, as judged by 1H NMR analysis of the crude reaction mixture (Figure S56), suggesting that as expected the macrocycle is significantly displaced towards the unhindered triazole unit in of rotaxane 7 under the reaction conditions. Overall, rotaxane 8 was isolated in 65% yield over 3 chemical steps from 6 (52% from 5a). Alternatively, starting from carboxylic acid half-axle 5b, rotaxane 7 could be produced directly from the AT-CuAAC coupling and converted to rotaxane 8 in 61% yield over 3 chemical steps from 5b without isolation of the intermediate structures. CSP-HPLC analysis of the samples of rotaxane 8 produced using our chiral interlocking auxiliary revealed an enantiopurity of 94% ee, suggesting that the initial AT-CuAAC coupling proceeds in ~94% de. Given that the para substituent of the acetylene moiety appears not to strongly influence the diastereoselectivity of the process (both 4b and 8 are produced with similar stereopurity), it is reasonable to assume the orientation of the macrocycle on the axle is the same in both cases. Thus, we tentatively assign the dominant configuration of 8 to be (Smp)-8 and by extension, the intermediates to be (S,Smp)-6, (S,Smp)-7.
Figure 3. (a) A chiral interlocking auxiliary synthesis of MPC rotaxane \( (S_{mp})-8 \) using an esterification stoppering strategy.\(^a\) (b) A chiral interlocking auxiliary synthesis of MPC rotaxane \( (S_{mp})-10 \) using a cross-coupling stoppering strategy.\(^b\) (c) A chiral interlocking auxiliary synthesis of phosphine oxide-containing MPC rotaxane \( (S_{mp})-12 \).\(^c\)

\(^a\)Reagents and conditions: i. \([Cu(MeCN)]PF_6\), \( \text{Pr}_2\text{EtN}, \text{CH}_2\text{Cl}_2\), rt, 16 h (80%); ii. TFA, \( \text{CH}_2\text{Cl}_2\), rt, 16 h; iii. TMSCHN\(_2\) (2.0 M in hexanes), MeCN, rt, 16 h then MeOH, K\(_2\)CO\(_3\), rt, 3 h (65% over two steps, 94% ee). \(^b\)Reagents and conditions: i. \([Cu(MeCN)]PF_6\), \( \text{Pr}_2\text{EtN}, \text{CH}_2\text{Cl}_2\), rt, 16 h (89%); ii. PhC\(_6\)H\(_5\), PdCl\(_2\)(PPh\(_3\))\(_2\), Cul, \( \text{Pr}_2\text{NH}\), 110 °C, 16 h (94%); iii. K\(_2\)CO\(_3\), MeOH, \( \text{CH}_2\text{Cl}_2\), rt (87%, 96% ee). \(^c\)Reagents and conditions: i. \([Cu(MeCN)]PF_6\), \( \text{Pr}_2\text{EtN}, \text{CH}_2\text{Cl}_2\), rt, 16 h (85%); ii. PhB(OH)\(_2\), Pd(OAc)\(_2\), PPh\(_3\), K\(_2\)PO\(_4\), H\(_2\)O, THF, 80 °C, 16 h (93%, 79 : 21 mixture of co-conformations); iii. K\(_2\)CO\(_3\), MeOH, \( \text{CH}_2\text{Cl}_2\), rt, 16 h (70%, 98% ee).

A key advantage of the chiral interlocking auxiliary concept is that, if the azide and o-Me aryl acetylene units are conserved, other details of the structure and reaction sequence can be varied without significantly altering the outcome of the process. For example, if the protected ester functional group of \( 5a \) is replaced by a bromine atom, a similar sequence can be performed in which the stoppering step is achieved using a Pd\(^0\) mediated cross coupling; reaction of acetylene \( 9 \) with macrocycle \( 2 \) and azide \( (S)-1 \) followed by Sonogashira coupling and transesterification to remove the interlocking auxiliary, gave rise to rotaxane \( (S_{mp})-10 \), once again in similarly excellent yield over 3 steps (73%) and enantiopurity (92% ee). Similarly, it is relatively trivial to alter the structure of the receiver portion of the axle. Reaction of acetylene \( 11 \) with \( (S)-1 \) and macrocycle \( 2 \), followed by Suzuki cross coupling and cleavage of the auxiliary unit by transesterification, gave MPC phosphine oxide \( 12 \) in 60% overall yield and excellent enantiopurity (98% ee).
Examination of the samples of rotaxanes 10 and 12 immediately after auxiliary cleavage by $^1$H NMR revealed that the latter contained a lower ratio of the desired product to non-interlocked macrocycle 2 (96 : 4 vs 80 : 20 respectively; Figure S108). We cautiously assign this observation to the differing ratio of co-conformations in the corresponding precursor prior to Pd$^0$ mediated cross-coupling. Indeed, whereas in the case of rotaxanes (S,S$\text{mp})$-4 and (S,S$\text{mp}$)-7 it was not possible to directly observe the co-conformational ratio by $^1$H NMR as they were in fast exchange compared with the $^1$H NMR timescale, the Br substituent of the AT-CuAAC products of 9 and 11 prior to cross coupling is sufficiently bulky to slow the process of co-conformational exchange. $^1$H NMR analysis revealed signals consistent with an 80 : 20 ratio of receiver : auxiliary co-conformations in the case of the product derived from 11, whereas in the case of the intermediate derived from 9 only trace amounts of a second co-conformation were observed (>95 : <5).

Synthesis of “impossible” MPC rotaxanes using a chiral interlocking auxiliary strategy

**Figure 4.** Synthesis of “impossible” MPC rotaxanes. (a) Rotaxanes (S$\text{mp}$)-13-15 synthesized using the esterification stoppering approach. (b) Late-stage diversification of rotaxane (S,S$\text{mp}$)-17 to give MPC rotaxanes (S$\text{mp}$)-18-20 through a Pd$^0$-mediated stoppering approach.

![Chemical Structures](image)

Reagents and conditions: i. [Cu(MeCN)]$_2$PF$_6$, 1Pr$_2$EtN, CH$_2$Cl$_2$, rt, 16 h (99%); ii. PhCCH, PdCl$_2$(PPh$_3$)$_2$, CuI, 1Pr$_2$NH, 110 °C, 16 h, then aqueous work up, then MeOH, K$_2$CO$_3$, CH$_2$Cl$_2$, rt (58%, 94% ee); iii. PhB(OH)$_2$, Pd(OAc)$_2$, PPh$_3$, K$_2$PO$_4$, H$_2$O, THF, 80 °C, 16 h (aqueous work up), then MeOH, K$_2$CO$_3$, CH$_2$Cl$_2$, rt (61%, 98% ee); iv. PhB(OH)$_2$, Pd(OAc)$_2$, PPh$_3$, K$_2$PO$_4$, H$_2$O, THF, 80 °C, 16 h (aqueous work up), then MeOH, K$_2$CO$_3$, CH$_2$Cl$_2$, rt (61%, >98% ee)

The results above demonstrate that the combination of azide 1 and an o-Me aryl acetylene benzylic ester fragment can act as a chiral interlocking auxiliary. They also demonstrate, as in the synthesis of rotaxanes (S$\text{mp}$)-10 and (S$\text{mp}$)-12, that the structure of the receiver unit can significantly alter the efficiency of the shuttling process integral to this methodology. However, rotaxanes 8, 10 and 2 can all be synthesized directly using the AT-CuAAC reaction, albeit in racemic form, indeed that is how these samples were prepared for CSP-HPLC analysis. Given that one of the benefits of the interlocking
auxiliary concept is that it can allow access to targets that do not contain motifs that facilitate mechanical bond formation, we set out to explore the limits of our methodology through the synthesis of such so-called “impossible rotaxanes”, systems in which there is no significant interaction between axle and macrocycle.

Using a precursor analogous to alkyne 5a in which the triazole receiving unit is replaced with a simple alkyl bis-ether fragment gave rotaxane (S\textsubscript{mp})-13 (see ESI for full details). In this case the macrocycle is presumed to interact with the receiving unit through C-H•••N hydrogen bonds between the polarized ether protons and the bipyridine unit. Despite the comparatively weak nature of this interaction, \(^1\)H NMR analysis of the crude reaction mixture after transesterification revealed a 88 : 12 ratio of rotaxane (S\textsubscript{mp})-13 to macrocycle 2. Overall, rotaxane (S\textsubscript{mp})-13 was isolated in 52% yield and 94% ee over 4 steps.

To probe the effect of reducing the strength of the interactions between the receiving unit and the macrocycle further, we investigated the synthesis of rotaxane (S\textsubscript{mp})-14 in which the di-yne receiving unit presents no significant attractive interactions to the macrocycle at all. Surprisingly, the crude product mixture after transesterification revealed a ratio of (S\textsubscript{mp})-14 : 2 of ~2 : 3, suggesting that even in this case the receiving unit competes effectively for the macrocycle, allowing di-yne rotaxane (S\textsubscript{mp})-14 to be isolated in 24% overall yield and 94% ee after a challenging final purification.

Similarly, rotaxane (S\textsubscript{mp})-15, in which the macrocycle encircles a simple alkyl chain could be synthesized, albeit in a much lower isolated yield of just 11% in the final step, due in part to a challenging final purification and in part, based on the ratio of (S\textsubscript{mp})-15 : 2 : 3 in the crude product of transesterification, the co-conformational bias favoring the auxiliary unit. This could be improved when a phenolic ester link was used in place of the benzyl ester; in this case rotaxane (S\textsubscript{mp})-15 was isolated in 28% yield after transesterification to remove the auxiliary unit and (S\textsubscript{mp})-15 was the dominant species observed in the crude reaction mixture ((S\textsubscript{mp})-15 : 2 = 3 : 2). This suggests that the benzylc methylene acts as a competing station for the macrocycle through C-H•••N H-bonding, consistent with our previous observations in the case of 4b.

Finally, we extended our synthesis of impossible MPC rotaxanes by demonstrating the use of our Pd\(^{0}\)-mediated cross-coupling stoppering approach in the late-stage diversification of a common building block.\(^{28}\) Rotaxane (S,S\textsubscript{mp})-17 was synthesized from the corresponding alkyne block by reaction with macrocycle 2 and azide (S)-1 in excellent yield and subjected to a Sonagashira cross-coupling with phenyl acetylene to give conjugated rotaxane (S\textsubscript{mp})-18, Suzuki cross-coupling with PhB(OH)\(_2\) to produce (S\textsubscript{mp})-19, and Suzuki cross-coupling with pyrene-boronic acid to give rotaxane (S\textsubscript{mp})-20 all in good yield and enantiopurity (≥94% ee in all cases).

**Stereodivergent synthesis using a single set of building blocks**

As demonstrated above, our chiral interlocking auxiliary strategy notionally achieves the threading of a macrocycle onto an axle in a fixed orientation. Perhaps less obviously, the absolute configuration of the final product depends on which side of the receiver unit the interlocking auxiliary is tethered to. Thus, in theory, it is possible to synthesize both enantiomers of an MPC rotaxane using a single stereoisomer of the auxiliary by selecting which side the ring is threaded from.

To demonstrate this principle, we extended our chiral interlocking auxiliary approach to employ a direct aminolysis reaction as this avoids the need for a stoppering step to trap the macrocycle on the receiver region. Using this approach, rotaxane 22a was produced over two steps using a grafting reaction\(^{24,29}\) to replace the auxiliary unit. Precursor 21a was produced in 80% yield by reaction of the corresponding alkyne with azide 1 and macrocycle 2. The macrocycle in 21a is free to explore the length of the axle and, as expected, \(^1\)H NMR analysis (see ESI) suggested the preferred co-conformation is that in which the ring encircles the alkyl chain of the ester portion of the axle, presumably due to C-H•••N H-bonding interactions. Reaction of 21a with 3,5-di-\(^7\)Bu benzylamine (25a) gave rotaxane 22a in excellent selectivity for the interlocked product; a ratio of 84 : 16 (22a : 2) was observed by \(^1\)H NMR analysis of the crude...
amination of the products of these two sequences reveal mirror image spectra (the TMS unit gave half-axle 25b, a bond forming steps. grafting reaction.

**Figure 5.** (a) Chiral interlocking auxiliary synthesis of MPC rotaxanes (Smp)-22 using an aminolysis grafting reaction. (b) Synthesis of both enantiomers of rotaxane MPC 28 by varying the order of amide bond forming steps.

Reagents and conditions: 25a, CH2Cl2, 60 °C, 16 h (62%, 96% ee). Reagents and conditions: i. 26a or 26b, (S)-1, 2, [Cu(MeCN)3]PF6, Pr2EtN, CH2Cl2, rt, 16 h (78% for (S,Smp)-27a, 71% for (S,Smp)-27b); ii. 25b or 25a, CH2Cl2, 60 °C, 16 h (75%, 98% ee for (Smp)-28; 90%, 94% ee for (Rmp)-28).

Having developed this simple aminolysis approach, we turned our attention to synthesizing both enantiomers of rotaxane 28 by making use of common axle building blocks carboxylic acid 23, alkyne 24 and amines 25. Coupling of 23 with amine 25a followed by hydrolysis, ester formation and removal of the TMS unit gave half-axle 26a. AT-CuAAC coupling followed by aminolysis with amine 25b gave rotaxane 28. Conversely, if instead carboxylic acid 23 is coupled first with amine 25b and converted to AT-CuAAC precursor 26b, subsequent AT-CuAAC coupling and aminolysis by amine 25a gave rise to the opposite enantiomer of rotaxane 28. In keeping with this, circular dichroism (CD) and CSP-HPLC analysis the products of these two sequences reveal mirror image spectra (Figure 6a) and enantiopurities of ≥94% ee (Figure 6b) for each enantiomer.
Conclusions

In conclusion, we have demonstrated a chiral interlocking auxiliary strategy based on the combination of a simple $\alpha$-chiral azide and an $\omega$-Me-aromatic acetylene for the synthesis of MPC rotaxanes in which the mechanical bond provides the only stereogenic unit. This approach allows the synthesis of challenging MPC rotaxanes in excellent ($\geq 93\%$ ee) enantiopurity, including “impossible” rotaxanes where, for example, the macrocycle encircles a simple alkyl chain and, by employing a cross-coupling reaction as the stoppering step, late-stage diversification of a single rotaxane building block can be achieved. Finally, we demonstrate an unusual property of combining molecular motion and mechanical chirality, namely the potential to synthesize both hands of an MPC target using the same starting materials by controlling which end of the axle the macrocycle is effectively threaded on from. Given recent reports of applications of mechanically chiral molecules, and the increased interests in the applications of interlocked molecules in general, we anticipate that these findings will spur further developments in their study and application.

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