Chem

CellPress

Perspective

Strategies for the Synthesis of Enantiopure Mechanically Chiral Molecules

John R. J. Maynard,[1] Stephen M. Goldup[1,2]*

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

[2]Lead Contact

*Correspondence: s.goldup@soton.ac.uk

SUMMARY

Mechanically interlocked molecules, such as rotaxanes and catenanes, are composed of two or more covalent subcomponents threaded through one another such that they cannot be separated without breaking a covalent bond. This arrangement can allow the covalent subcomponents to undergo large amplitude relative motion, and this property of the mechanical bond has been widely exploited in the design and synthesis of molecular machines. Another less well-known property of the mechanical bond is that it can give rise to chirotopic stereogenic units that do not rely on covalent stereogenic elements. Although the study of such "mechanically chiral" molecules is expanding, their synthesis in enantiopure form remains challenging. In this perspective we review the strategies available, highlighting key examples along the way, and suggest future areas for development.

Chirality, Rotaxanes, Catenanes, Stereoselective, Synthesis

INTRODUCTION

The synthesis of mechanically interlocked molecules (MIMs),[1] such as rotaxanes and catenanes, has progressed a long way since the first reports by Wasserman and Harrison.[2] Key to this success has been the development of template-directed methods,[3] pioneered by Sauvage[4] and Stoddart,[5] in which the precursors to the interlocked structure are organised relative to one another in space through non-covalent interactions such that, when a final covalent bond is formed, the components are permanently entangled, resulting in a mechanical bond. This passive template strategy has since been expanded to an "active" form in which the endotopic functionality of a macrocycle is able to mediate the formation of a new covalent bond; since bond formation takes place faster through the cavity of the ring than anywhere else in solution, this "active template"[6] results in threaded products and so can be used for mechanical bond formation under kinetic control.

These synthetic breakthroughs have paved the way for the application of MIMs in a range of areas,[7] and primarily as components of molecular machines,[8] for which Stoddart and Sauvage were awarded the Nobel Prize in 2016, alongside Feringa who developed covalent molecular motors,[9] where the ability of mechanically bonded components to undergo large amplitude relative motion is key to their function. However, applications of another unusual property of the mechanical bond, the ability to give rise to chirotopic stereogenic units *in the absence of covalent stereochemistry*,[10] are much less well developed than might be expected, particularly given the ubiquitous application of covalent stereochemistry in chemistry more generally. The dearth of applications of such chiral MIMs is almost certainly because their synthesis in enantiopure form remains challenging, despite these molecules being first discussed in the 1960s[11] and the first enantiopure examples being disclosed in the 1990s.

In this perspective we will discuss the synthesis of enantioenriched and enantiopure chiral interlocked molecules organised according to the classes of synthetic strategy typically discussed in covalent synthesis. Along the way we will discuss key examples of each strategy, attempt to highlight future directions and comment on recent applications of mechanically chiral molecules, with the aim of inspiring further research. To begin, we will briefly outline the broad classes of stereogenic elements that can arise due to the mechanical bond.

STEREOCHEMISTRY FROM THE MECHANICAL BOND

Chiral MIMs can be generated by incorporating covalent chirotopic stereogenic units into any of the sub-components, and this approach has been applied to develop chiral catalysts,[12] hosts,[13] and systems for materials applications.[14] The strategies for the synthesis of such molecules are identical to those used for the synthesis of chiral covalent molecules, with the added requirement of mechanical bond formation, and we will not discuss these systems further. Instead we will focus on systems in which the mechanical bond itself provides a chirotopic stereogenic unit,[10] which can arise in several ways, which we introduce briefly below based on categories we have proposed previously.[10a] For a more detailed discussion, including how to assign the absolute stereochemistry in such systems, we direct the interested reader to our recent comprehensive review on the topic.[10a]

Unconditional Mechanical (Topological) Chirality (Fig 1A)

A [2]catenane composed of two fully symmetrical macrocycles is, on average (*vide infra*), achiral. However, the topological isomer of a [2]catenane with two crossing points, the Solomon link (Fig 1Ai), is chiral regardless of the covalent structure of the rings.[15] Similarly, a cyclic [3]catenane (Fig 1Aii) in which all the rings are mutually interlocked also displays unconditional topological chirality.[16] Such stereogenic units, which rely on the pattern of crossing points between components, are topological in nature[17] because one enantiomer cannot be deformed into the other as long as no bond is allowed to pass through another, even if the components are allowed to deform in an arbitrary manner.[18] In contrast, covalent stereogenic units are not topological but Euclidean as relaxing the three dimensional properties of the system, for instance permitting the bond angles of a tetrahedral stereocentre to deform, allows the two enantiomeric configurations to be exchanged.

Conditional Mechanical Chirality (Fig 1B)

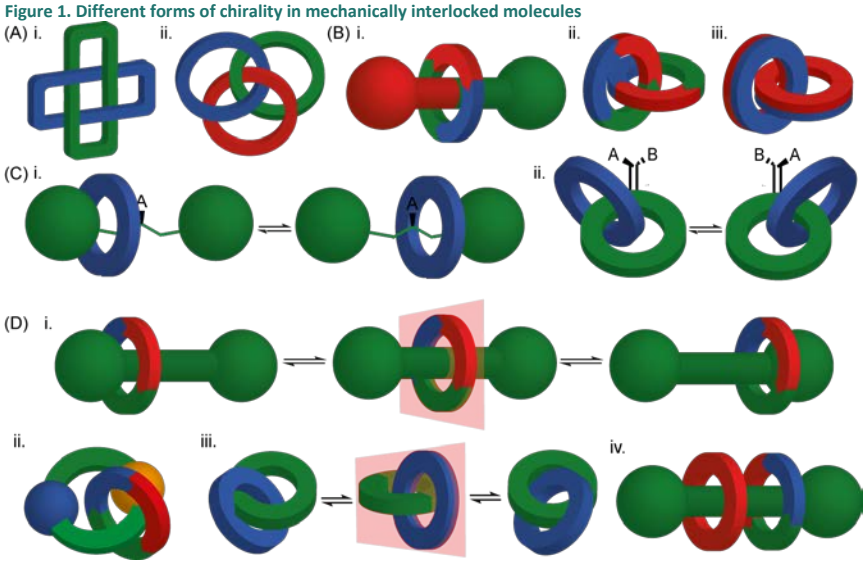
The chirotopic stereogenic unit of conditionally mechanically chiral rotaxanes and catenanes arises as a result of the underlying symmetry of the achiral covalent sub-components and the restrictions the mechanical bond places on their relative orientations. Archetypal examples of conditionally mechanically chiral molecules are mechanically planar chiral [2]rotaxanes (Fig 1Bi) and topologically chiral [2]catenanes (Fig 1Bii), which are composed of so-called "oriented" macrocycles that are desymmetrised by an unsymmetrical axle or a second oriented ring respectively, and axially chiral [2]catenanes (Fig 1Biii), the result of combining two macrocycles with distinct faces. The stereochemistry of axially chiral catenanes is Euclidian whereas that of mechanically planar chiral rotaxanes and topologically chiral [2]catenanes is not.[19]

Co-Conformational Chirality (Fig 1 C,D)

Even when conditional or unconditional mechanical stereochemistry are absent, mechanical motion can give rise to co-conformational chirality; the position of one component relative to the other, their co-conformation, can lead to desymmetrization of the molecule. Co-conformational chirality can arise in two distinct ways. Firstly, the position of a mechanically bonded component can act to desymmetrize a prochiral covalent unit in the other (Fig 1C) for which we have suggested the term "co-conformationally covalently chiral".[10a,20] Any covalent stereogenic unit (e.g. stereogenic centre [Fig 1Ci], axis [Fig 1Cii] or plane [not shown]) can be desymmetrised in this manner in either a rotaxane or catenane structure. Secondly, the position of one sub-component can alter the symmetry of the system such that a mechanical stereogenic unit arises, for which we have suggested the term "co-conformationally mechanically chiral" (Fig 1D).[10a] For example, an oriented ring on a symmetrical axle (Fig 1Di) can give rise to an achiral co-conformer, in which the ring coincides with the axle mirror plane, and enantiomeric pairs of co-conformations when the macrocycle is displaced either side of centre of the axle. In this manner, co-conformational equivalents can be constructed of conditional mechanical stereogenic units (e.g. Fig1Dii). In addition, a co-conformational mechanically helically chiral stereogenic unit arises even in the most symmetrical [2]catenane when the rings are not perfectly perpendicular to one other (Fig 1Diii).

Unlike unconditional and conditional mechanical stereogenic units, co-conformational stereochemistry can be dynamic or static, depending on the barrier to mechanical motion. Indeed, installing groups to restrict movement can "lock" the stereochemistry and enable enantiomer separation. Similarly, the presence of additional interlocked components, for example a second macrocycle in a [3]rotaxane (Fig 1Div), can prevent co-conformational exchange and so lead to static co-conformational stereogenic units.

Figure 1. Different forms of chirality in mechanically interlocked molecules

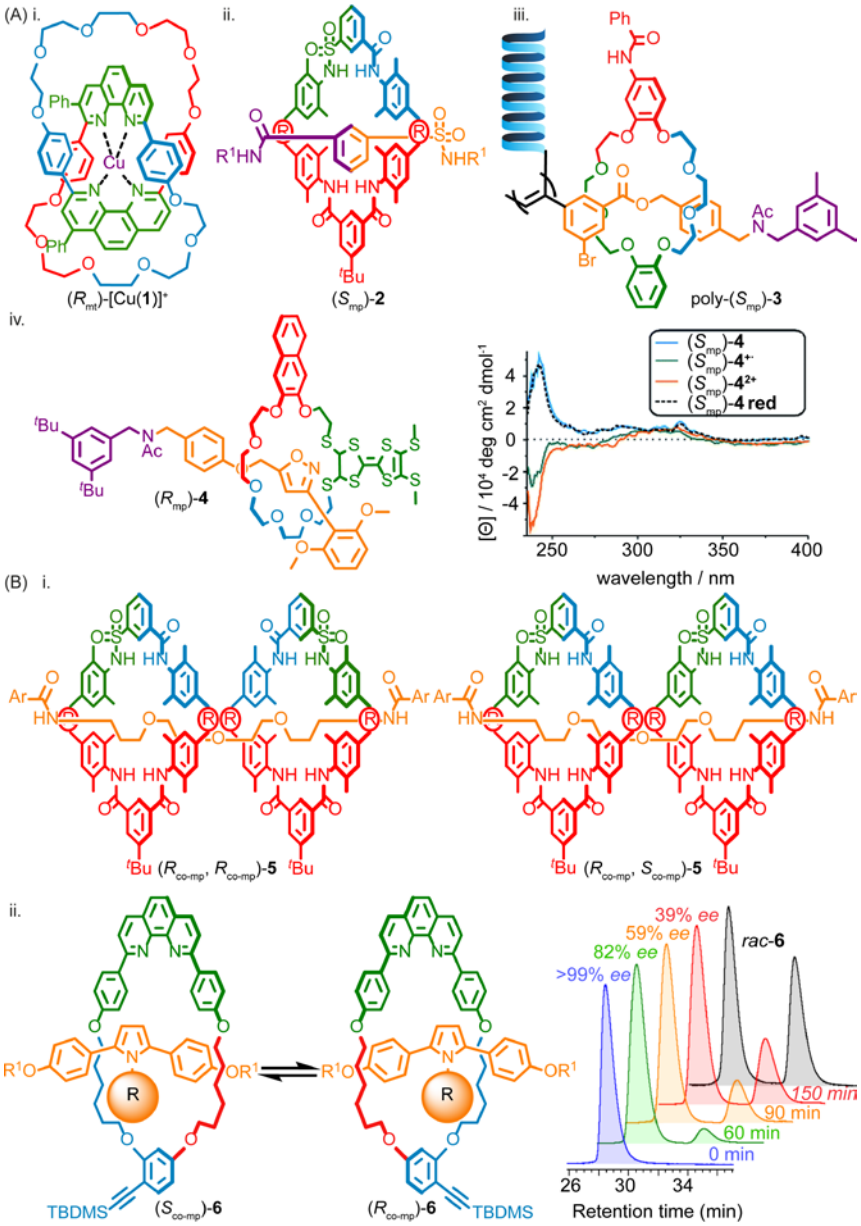


(A) Unconditional topologically chiral molecules: i. a Solomon link and ii. a cyclic [3]catenane.
(B) Conditionally mechanically chiral molecules: i. a mechanically planar chiral [2]rotaxane, ii. a topologically chiral [2]catenane and iii. an axially chiral [2]catenane.
(C) Co-conformationally covalently chiral molecules: i. enantiomeric co-conformations of a covalent centrally chiral [2]rotaxane, ii. enantiomeric co-conformations of a covalently axially chiral [2]catenane.
(D) Co-conformationally mechanically chiral molecules: i. two enantiomers and the achiral form of a co-conformationally mechanically planar chiral [2]rotaxane, ii. a co-conformationally topologically chiral catenane iii. the mechanically helically chiral co-conformations of a [2]catenane, iv. a co-conformationally mechanically planar chiral [3]rotaxane.

RESOLUTION OF ENANTIOMERS

One of the oldest methods in organic synthesis for producing enantiopure samples of chiral molecules is to synthesise a racemic/scalemic mixture and separate the enantiomers. To date, the only separation method applied to MIMs is chiral stationary phase HPLC (CSP-HPLC). This approach is attractive as a simple racemic synthesis followed by CSP-HPLC can yield enantiomerically pure samples and is applicable to any mechanical stereogenic element. However, the cost of preparative scale CSP-HPLC columns can be prohibitive, and their limited capacity limits the scale of such separation. Nevertheless, CSP-HPLC was integral to the birth of the field, with the first examples of enantiopure topologically chiral catenanes and mechanically planar chiral rotaxanes produced in this way; in 1988, Sauvage, Okamoto and co-workers separated the enantiomeric Cu^{I} complexes of catenane **1** (Fig 2Ai),[21] and in 1997, Vögtle, Okamoto and co-workers separated the enantiomers of rotaxane **2** (Fig 2Aii).[22] In both cases, crystal structures were not obtained and so the absolute stereochemistry could not be assigned. The enantiomers were instead designated as (+)/(-) on the basis of their optical rotation. Following on from these initial studies, several conditionally mechanically chiral molecules have been successfully separated using CSP-HPLC, including examples with prototypical applications. Takata and co-workers reported polyactylene **3** based on a mechanically planar chiral [2]rotaxane monomer in which the helicity of the polymer was controlled by the mechanical stereochemistry of the side chains (Fig 2Aiii).[23] More recently, Schalley and co-workers reported mechanically planar chiral [2]rotaxane **4** containing an oriented tetrathiafulvalene functionalised macrocycle that acts as an electrochemical chiroptical switch (Fig 2Aiv).[24]

Figure 2. Mechanically Chiral Molecules Separated Using CSP-HPLC



(A) Conditionally mechanically chiral molecules separated using CSP-HPLC: i. Savage's topologically chiral catenane **1**, ii. Vogtle's mechanically planar chiral rotaxane **2** (R = 1,1-cyclohexyl, R^1 = 4-C_6H_4-trityl). iii. Takata's mechanically planar chiral polyacetylene **3** in which the mechanical stereochemistry dictates the polymer helicity. iv. Schalley's mechanically planar chiral rotaxane **4** that displays redox-controlled chiroptical properties.

(B) Co-conformationally chiral molecules separated using CSP-HPLC: i. chiral and *meso* stereoisomers of co-conformationally mechanically planar chiral rotaxane **5** (Ar = 4-$C_6H_4CH_2O$-4-C_6H_4-trityl); (ii) co-conformationally mechanically planar chiral [2]rotaxane **6** and its time-dependent racemization (assessed by CSP-HPLC) through macrocycle shuttling (R = 4-C_6H_4-4-C_6H_4-cy, R^1 = $(CH_2)_6CR_3$).

Resolution is clearly applicable to molecules containing static mechanical stereogenic units if conditions for the separation can be identified. However, the application of CSP-HPLC to co-conformationally chiral molecules requires that the enantiomers do not interconvert on the timescale of the separation. The first separation of a co-conformationally chiral molecule, [3]rotaxane **5** (Fig 2Bi),[25] in which two oriented macrocycles encircle a centrosymmetric axle, was reported by Vögtle and co-workers. Rotaxane **5** can be formed as three stereoisomeric co-conformations; a pair of enantiomeric structures ($R_{co\text{-}mp}$,$R_{co\text{-}mp}$)-**5** and ($S_{co\text{-}mp}$,$S_{co\text{-}mp}$)-5 (not shown) and a *meso* form, ($R_{co\text{-}mp}$,$S_{co\text{-}mp}$)-**5**, which are unable to interconvert due to the inability of the macrocycles to pass each other on the axle.[26] Thus, rotaxane **5** is stereochemically static

despite the isomers technically being related by co-conformational motion. The first separation of a stereodynamic co-conformationally chiral molecule was reported by Saito and co-workers.[27] The rate of exchange between the enantiomeric co-conformations of mechanically planar chiral [2]rotaxane **6** (Fig 2Bii) was controlled by the size of the substituent on the central pyrrole moiety. Large substituents slowed the shuttling sufficiently for the isomers to be separated and the authors studied the rate of racemisation of the separated enantiomers. More recently, Takata and co-workers separated the co-conformational mechanical planar enantiomers of a [2]rotaxane in which a bulky tertiary amine station provided the barrier to racemisation.[28] Whereas in the case of **6**, the achiral co-conformation in which the macrocycle occupies the centre of the axle is always unstable, in the example reported by Takata, protonation of the bulky tertiary amine resulted in an achiral co-conformation in which the macrocycle encircled the central ammonium station.

The above examples demonstrate the value of CSP-HPLC separations in preliminary studies of mechanically chiral molecules. However, this approach is necessarily limiting due to the prohibitive cost of obtaining and maintaining a preparative CSP-HPLC system and the scale on which such separations can be carried out. For this reason, as mechanically chiral MIMs move towards applications in a range of areas, synthetic methods that remove the need for CSP-HPLC purification are required and these will be discussed in the following sections. Alternatively, other resolution techniques, such as crystallisation of diastereomeric salts, that have been very successful in covalent synthesis but yet to be applied in the synthesis of chiral MIMs, could prove useful for resolution of racemic MIMs on larger scale.

ENANTIOPURE MIMS FROM ENANTIOPURE STARTING MATERIALS

In organic synthesis, making enantiopure molecules using enantiopure starting materials includes a range of strategies, from so called "chiral pool" approaches, through chiral derivatisation to allow separation of diastereomers, to stereoselective synthesis under substrate control. In the following sections we will outline the history and applications of each of these strategies in the synthesis of mechanically chiral molecules.

"Chiral pool" approaches to enantiopure interlocked molecules

The term "chiral pool" typically refers to strategies that start from readily available chiral molecules (amino acids, sugars etc) whose stereogenic units remain embedded within the final product. Here we use it more broadly to include any synthetic strategy that starts from an enantiopure starting material whose covalent stereogenic unit is directly transferred to the product, albeit subtly changed. Although the synthesis of enantiopure MIMs containing covalent stereogenic units typically starts from covalent fragments in which these units are already embedded, given that the co-conformational and mechanical stereogenic units arise from the mechanical bond alone, it may not be immediately obvious how such a strategy can be applied in these cases.

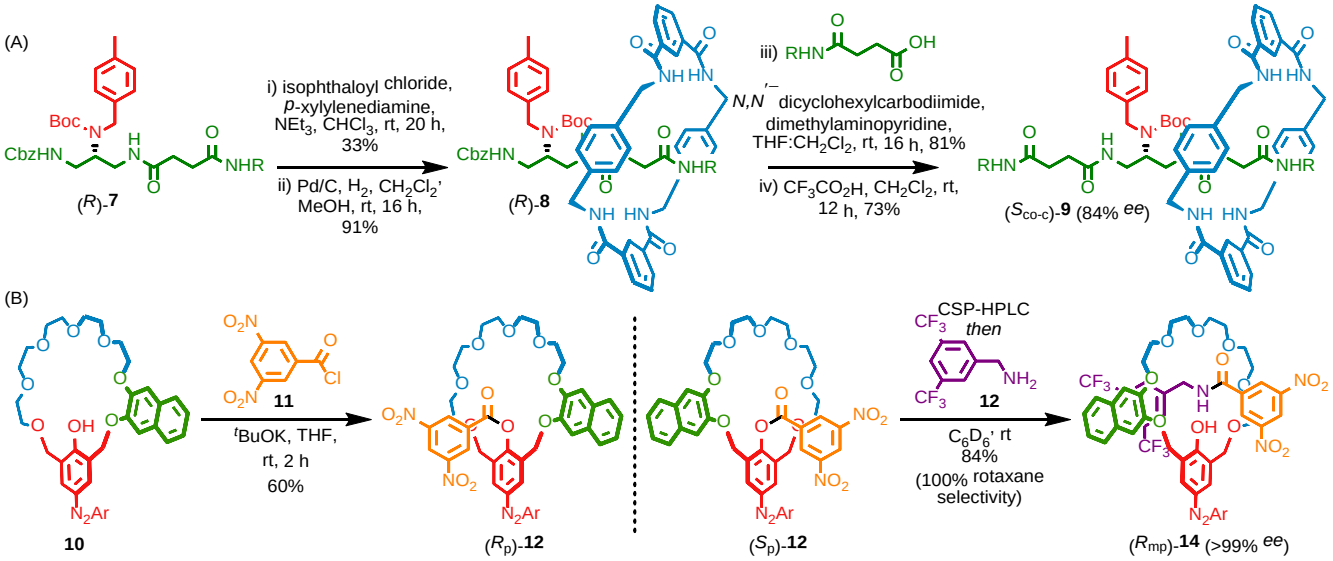
The most straightforward class of chiral MIMs to envisage synthesising using a chiral pool approach are those containing co-conformational covalent stereogenic units; the stereochemistry of these molecules relies on the mechanical desymmetrisation of a covalent prochiral unit and thus the problem is simplified to how to introduce the mechanically bonded component selectively around the correct enantiotopic substituent. This in turn suggests such molecules can be made by starting from a chiral fragment whose covalent structure becomes symmetrised once the synthesis is complete. Leigh and co-workers have developed this approach for the synthesis of co-conformationally covalent point chiral rotaxanes,[29] including rotaxane **9**, which was subsequently applied as an enantioselective catalyst.[29c] The synthesis of **9** (Figure 3A), in which the central benzylic substituent prevents the exchange of co-conformational enantiomers, makes use of an asparagine-derived chiral building block in which the terminal amines are differentiated that is subsequently elaborated to key intermediate (*R*)-**7**. Mechanical bond formation gives rotaxane (*R*)-**8** that contains a covalent stereocentre. Subsequent symmetrisation of the axle component gives rise to rotaxane ($S_{co\text{-}c}$)-**9**. This chiral pool approach is suitable for any co-conformational covalently chiral interlocked rotaxane or catenane, although it has so far only been applied in the case of rotaxanes containing prochiral stereocentres.

It is less obvious how such an approach can be applied to conditionally mechanically chiral molecules in which the stereochemistry arises solely from the mechanical stereogenic unit. However, Hirose and co-workers' approach, which makes use of atropisomeric phenolate esters, broadly fits the definition of chiral pool, although the key starting materials are produced by

CSP-HPLC.[30] The first key step in Hirose's synthesis of rotaxane **14** (Fig 3B), an enantioselective host for phenylglycinol, is the acylation of macrocycle **10** that contains an endotopic phenol unit with half-axle component **11** to give a racemic mixture of atropisomeric products (R_p)-**12** and (S_p)-**12** in which the ester unit cannot rotate through the plane of the ring. CSP-HPLC separation of **12** and reaction with amine half axle **13** gives rise to enantiopure mechanically planar chiral rotaxanes **14**. Thus, in the key mechanical bond forming step, the covalent planar chiral stereogenic unit is converted to a mechanical planar stereogenic unit. Unfortunately, the absolute stereochemistry of the products was not determined.

Given the challenge of identifying suitable chiral pool strategies, it is perhaps unsurprising that only two stereogenic units arising from the mechanical bond have been produced using this approach. Although the link between covalent and co-conformational covalent stereogenic units is relatively intuitive, Hirose's methodology clearly demonstrates a link between covalent and mechanical stereogenic units that is not widely appreciated, suggesting that other similar strategies should be possible, particularly if the covalent chiral starting materials can be accessed using catalytic enantioselective processes rather than CSP-HPLC.

Figure 3. Chiral pool approaches to Co-Conformationally and Mechanically Chiral Molecules



(A) Leigh's symmetrisation approach to co-conformationally covalently chiral [2]rotaxane organocatalyst ($S_{co\text{-}c}$)-**9** (R = $CH_2CH(Ph)_2$).
(B) Hirose's "chiral pool" approach to mechanically planar chiral [2]rotaxane (R_{mp})-**14** via pre-rotaxane (S_p)-**12** (Ar = 2,4-di-NO_2-C_6H_3).

Chiral derivatisation for the synthesis of mixed covalently/mechanically chiral molecules

Including covalent stereogenic units in the structure of a mechanically or co-conformationally chiral molecules can be exploited to drive a self-assembly processes towards the selective formation of one of the possible diastereomers, bias a co-conformational stereogenic unit or enable the separation of mechanical epimers without the use of CSP-HPLC. Although often not explicitly discussed as such, this chiral derivatisation strategy is by far the most common method for the synthesis of enantiopure mechanically and co-conformationally chiral molecules.

All the benefits of chiral derivatisation strategies to access mechanically and co-conformationally chiral molecules were demonstrated in the syntheses of cyclodextrin-based MIMs in the 1990s. Cyclodextrin (CD) macrocycles, cyclic oligomers of D-glucose, are oriented and thus MIMs based on CDs can express conditional mechanical chirality, although this is often overlooked; articles tend to focus on the facial dissymmetry of the conically shaped macrocycles. When the threaded complex between α-CD (**12**) and an ammonium guest was stoppered, Kaifer and Isnin observed the formation of two diastereomers of rotaxane **13**.[31] The authors later reported the diastereoselective (3 : 2) formation of (D,R_{mp})-**13** (Fig 4 Ai, D refers to the covalent stereochemistry of the glucose units) and its separation from the minor product (D,R_{mp})-**13** (not shown) by reversed phase preparative TLC.[32] This report is, to our knowledge, the first stereoselective synthesis and separation of mechanically planar chiral rotaxanes using

a chiral derivatisation strategy. In 1995, Stoddart and co-workers demonstrated a similar approach to the synthesis and separation of topologically chiral [2]catenanes **14** and highlighted the nature of this stereogenic unit, although in this case no stereoselectivity was observed.[33] Anderson and co-workers later reported the formation of a CD-based [2]rotaxane as a single mechanical epimer.[34]

Moving beyond static stereogenic units, Anderson and co-workers reported the stereoselective synthesis of co-conformationally chiral [3]rotaxane **15** and [2]rotaxane **16** (Fig 4Aiii).[35] Stoppering of the host-guest complexes formed between a bis-diazonium salt and α-CD produced rotaxanes **15** and **16**, both of which contain a centrosymmetric axle and so express co-conformational mechanical planar chirality. ^{1}H NMR NOE analysis showed that **15** formed as a single static co-conformational stereoisomer with the macrocycles in a head-to-head orientation, corresponding to a ($R_{co\text{-}mp}$,$R_{co\text{-}mp}$,D) configuration. Similar analysis of [2]rotaxane **16** revealed that the ring preferentially resided with the narrow rim of the CD ring interacting with the stopper unit, corresponding to the ($R_{co\text{-}mp}$,D) stereoisomer and demonstrating that the covalent stereochemistry of the macrocycle can bias the dynamic co-conformational mechanical planar chiral stereogenic unit.

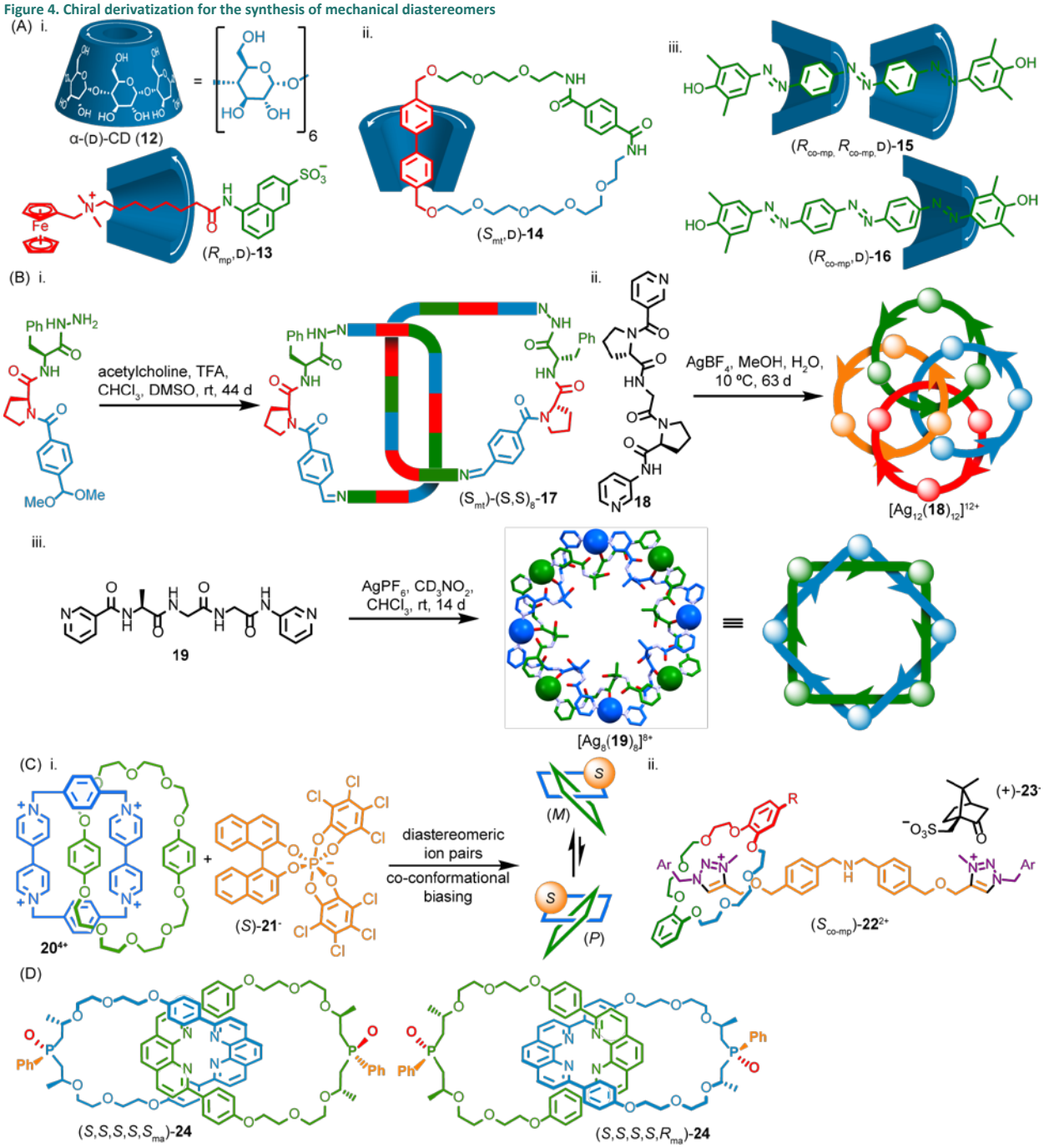
The stereoselectivity observed in the formation of mechanically and co-conformationally chiral CD-based interlocked molecules is presumed to arise due to the relative stabilities of stereoisomeric host-guest precursors and can thus be considered an example of thermodynamic control, albeit the final covalent bond forming reaction that traps the mixture takes place under kinetic control. When mechanical bond formation itself takes place under thermodynamic control, extremely high levels of stereoselectivity can be observed. Sanders and co-workers reported the stereoselective synthesis of topologically chiral catenane **17** as a single stereoisomer from a dynamic library composed of chiral acetal/acylhydrazine monomers in the presence of acetylcholine, although the major diastereomer was not identified (Fig 4Bi).[36] Sanders and co-workers also reported the diastereoselective formation of a Solomon link under dynamic control, this time using disulphide bond formation, although again, the major stereoisomer was not assigned.[37] Later, Gagne and co-workers,[38] and Trabolsi and co-workers[39] reported the stereoselective self-assembly of [2]catenanes from chiral building blocks, including the absolute stereochemistry of a crystallized product by comparison with a covalent stereogenic unit as an internal reference.

Perhaps the most impressive examples of chiral derivatisation in the stereoselective synthesis of mechanically chiral catenanes under thermodynamic control have been reported by Fujita and co-workers[40] beginning in 2016 with the report of a metallo[41] [4]catenane. Catenane $[Ag_{12}(\mathbf{18})_{12}]^{12+}$, formed by the self-assembly of twelve equivalents of short peptide **18** and twelve Ag^+ cations, crystallised from the reaction mixture over nine weeks (Fig 4Bii).[40a] Single crystal x-ray diffraction (SCXRD) revealed $[Ag_{12}(\mathbf{18})_{12}]^{12+}$ to be composed of four oriented macrocycles linked together to generate a tetra-interlocked structure with twelve crossing points that expresses unconditional topological chirality. In addition, the rings themselves are oriented, resulting in conditional topological stereogenic units. Strikingly, the interplay between these topological stereogenic units and the fixed covalent stereocentres of **18** resulted in the formation of $[Ag_{12}(\mathbf{18})_{12}]^{12+}$ as a single diastereomer. Fujita and co-workers have since extended this approach to the formation of a number of different complex knotted and interlocked structures, including [2]catenane $[Ag_8(\mathbf{19})_8]^{8+}$ that contains four crossing points and thus corresponds to an 8^21 link (Fig 4Biii).[40d] Once again, this structure expresses both conditional and unconditional topological chirality but crystallizes as a single stereoisomer due to the covalent stereochemistry of building block **19**.

Returning to the biasing of dynamic stereogenic units, the dynamic co-conformational mechanical helical chiral stereogenic unit of catenanes is unusual in that i) it can be expressed in all catenanes regardless of their covalent structure and ii) to our knowledge, there is no equivalent static mechanical stereogenic unit. Stoddart and co-workers described the biasing of this stereogenic unit in otherwise achiral catenane $\mathbf{20}^{4+}$ using non-covalent interactions (Fig 4Ci);[42] in the presence of chiral phosphate anion **21**, two sets of signals corresponding to catenane **20** were observed in a ~2 : 1 ratio, which were interpreted to arise as a result of a biased equilibrium between diastereomeric ion pairs. To our knowledge this is the first example of the biasing of a co-conformational stereogenic unit using non-covalent interactions alone, a strategy that remains under-explored. It has since been demonstrated that co-conformational mechanical helical stereogenic units can be biased by including covalent stereogenic units within the structure of [2]catenanes.[43] Indeed, such biasing is almost certainly present in all

[2]catenanes containing covalent stereogenic units, whether it is recognised or not. More recently, Credi and co-workers demonstrated the biasing of the co-conformational mechanical planar chiral stereogenic unit; cationic [2]rotaxane **22**$^{2+}$ gave rise to an 85 : 15 mixture of diastereomers in the presence of chiral anionic guest **23** (Fig 4Cii).[44]

Figure 4. Chiral derivatization for the synthesis of mechanical diastereomers



(A) Mechanical diastereomers based on α-CD (**12**) rings: i. Kaifer's CD-based mechanically planar chiral [2]rotaxane **13** (major stereoisomer). ii. One isomer of Stoddart's topologically chiral catenane **14**. iii. Anderson's co-conformational [3]rotaxane **15** and [2]rotaxane **16** (major diastereomers).
(B) Topologically chiral molecules assembled under thermodynamic control: i. Sanders topologically chiral [2]catenane **17** (arbitrary stereochemistry shown). ii. Fujita's tetra-interlocked metallo [4]catenane $[Ag_{12}(\mathbf{18})_{12}]^{12+}$ that expresses conditional and unconditional topological chirality. iii. Fujita's metallo [2]catenane $[Ag_8(\mathbf{19})_8]^{8+}$ that contains four crossing points ($8^2 1$ link) and expresses both conditional and unconditional topological chirality.

(C) Biasing of co-conformational stereogenic units using non-covalent interactions: i. A diastereomeric ion pair-based on a helically chiral co-conformation of Stoddart's cationic catenane **20**$^{4+}$ and chiral phosphate anion **21**$^{-}$. ii. A diastereomeric ion pair based on Credi's co-conformationally mechanically planar chiral rotaxane **22** and camphor sulfonate (**23**) (R = CH_2-3-pyrenyl).
(D) Separation of mechanical stereoisomers: Marinetti's axially chiral catenanes **24** that could be separated by HPLC.

Finally, we return to the use of chiral derivatisation to allow the separation of mechanical stereoisomers. On the one hand, the very need for separation is a limitation when compared to stereoselective self-assembly under thermodynamic control. Conversely separability can become essential if mechanical bond formation takes place under kinetic control and/or the stereoselectivity of an assembly process is not perfect. However, unless the diastereoisomerism is well-expressed in the physical properties of the products this is a challenge and examples, outside of the context of CD-based interlocked molecules (*vide supra*), are relatively rare. For example, although Vogtle and co-workers explored the use of enantiopure sugars [45] and topologically chiral knots [46] as stoppering units for rotaxanes, the diastereomeric mixtures formed were not separated. However, using this approach Marinetti and co-workers demonstrated the first, and to our knowledge only, synthesis of an enantiopure mechanically axially chiral [2]catenane (Fig 4D). [47] [2]catenane **24** was produced using an enantiopure covalent building block as a 1 : 1 mixture of mechanically axially chiral diastereomers. Separation of the mechanical epimers was achieved using normal-phase HPLC to give enantiopure samples of both stereoisomers.

Chiral derivatisation is clearly an extremely powerful and arguably under-appreciated method to access enantiopure mechanically chiral molecules. The key practical disadvantage of this approach is that the covalent stereogenic units that direct the synthesis remain in the product, which is problematic when trying to assess the benefits of mechanical stereochemistry in an application. However, once these benefits are established, it seems likely that most chiral MIMs for applications in, for example, catalysis will be single diastereomers rather than enantiomers as their synthesis, purification and analysis is inherently simpler. Similarly, the biasing of co-conformational stereogenic units to stereoselectively produce diastereomeric host-guest complexes, as in the case of catenane **20** and rotaxane **22** seems a promising route to new enantioselective sensing applications for MIMs. Indeed, the presence of dynamic co-conformational stereogenic units has often been overlooked in previously described systems this remains an area ripe for exploitation.

Chiral auxiliary and substrate control for the synthesis of chiral MIMs where the mechanical bond provides the sole stereogenic unit

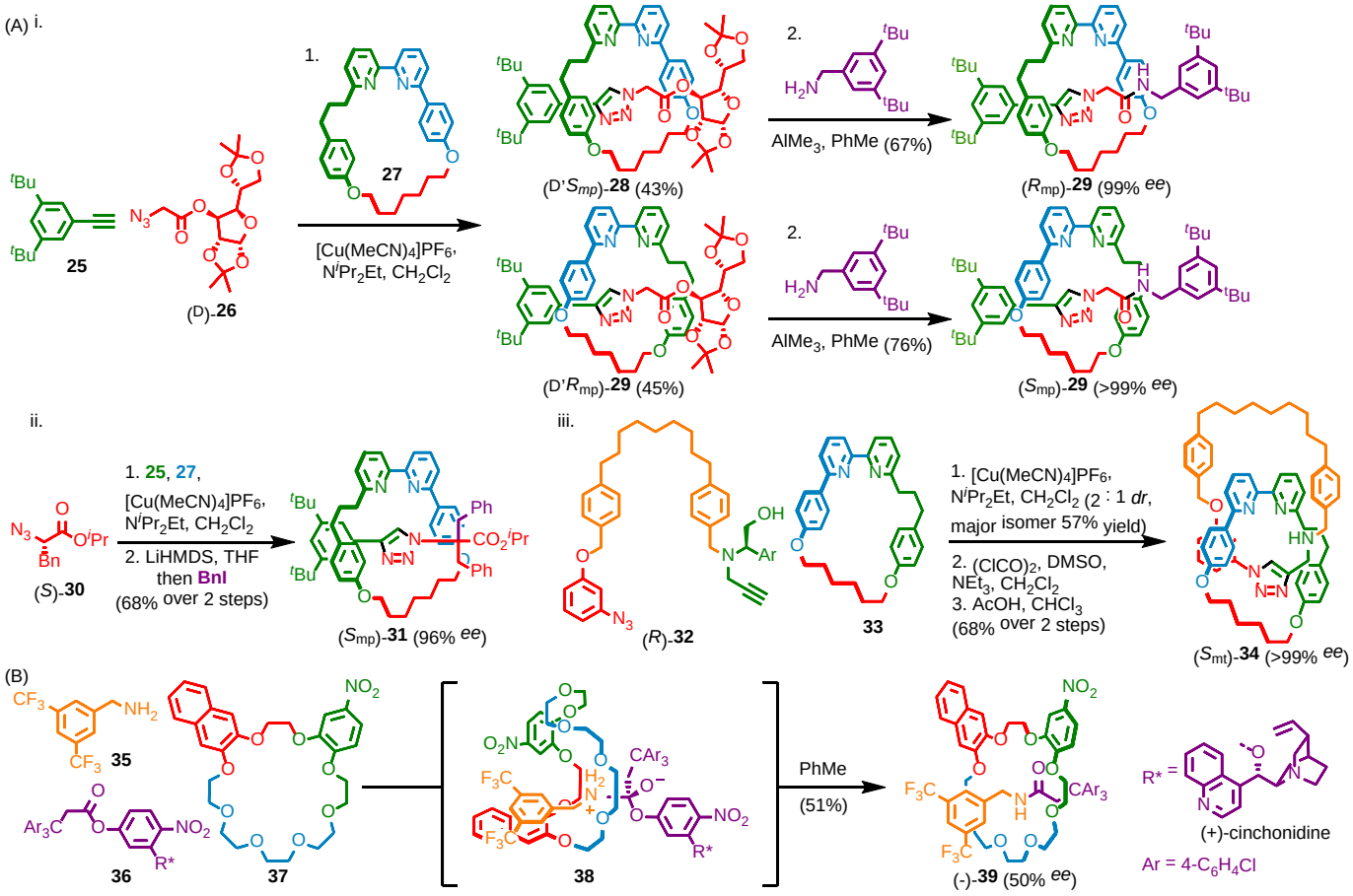
As alluded to above, it is desirable to investigate the potential application of mechanical stereogenic units using molecules in which the mechanical bond provides the only source of stereochemical information; for example, were a catalyst containing mechanical and covalent stereochemistry to prove effective, it would be hard to distinguish the role of the different stereogenic units. [48] In order to facilitate the push to identify applications of mechanically chiral molecules, without the need for CSP-HPLC separation of their enantiomers, strategies that rely on covalent stereochemistry in the building blocks that is not retained in the final products have recently been developed and will be discussed below.

Chiral auxiliary strategies are one way to achieve this. A chiral auxiliary is broadly speaking, an enantiopure fragment that is included in the molecule in the key bond forming step and is then removed to yield the target compound. [49] Chiral auxiliary methodologies are common in synthetic organic chemistry, where they are used to impart stereoselectivity on key bond formations and allow the separation of the desired diastereomer from unwanted stereoisomers using non-chiral techniques, but are less explored in the context of mechanically bonded molecules. Here, for simplicity, we use a slightly expanded definition of chiral auxiliary approach to include any synthesis in which mechanical epimers are separated and the covalent stereochemistry removed to yield enantiopure mechanical enantiomers in which the mechanical bond provides the sole stereogenic unit.

The first successful[50] chiral auxiliary synthesis of a mechanically chiral MIM, albeit in 1 : 1 *dr*, was reported by Goldup and co-workers using enantiopure sugar-based alkyne **25** as a coupling partner in an active template Cu-mediated alkyne-azide cycloaddition (AT-CuAAC)[51] reaction (Fig 5Ai). Diastereomeric products **28** could be separated, characterised by SCXRD, and the sugar unit removed without cleaving the mechanical bond, giving access to the separated enantiomers of rotaxane **29** with known configuration in excellent enantiopurity. [52] Goldup and co-workers have since demonstrated an improved auxiliary synthesis (Fig 5Aii) using chiral azide

(*S*)-**30**, which achieves a *dr* of 98 : 2 in the mechanical bond forming step and thus allows access to enantiopure mechanically planar chiral rotaxane (S_{mp})-**31**, if the diastereomers are separated prior to symmetrisation of the auxiliary stereocentre, or enantioenriched products (96% *ee*) if the separation step is omitted.[53] Unfortunately the stereoselectivity of reactions using chiral azide **30** showed a strong dependence on the alkyne coupling partner with less sterically hindered alkynes resulting in lower stereoselectivity (*dr* = ~3 : 1), a result that was rationalised through computational modelling. Despite this limitation, the same group have since used their approach in the synthesis of a mechanically planar chiral rotaxane ligand for enantioselective catalysis.[54] A similar auxiliary strategy has also been applied to the stereoselective synthesis (2 : 1 in the mechanical bond forming step) of topologically chiral catenane **34** by employing a pendant chiral auxiliary on the oriented macrocycle precursor **32** (Fig 5Aiii).[55] These results suggest that auxiliary strategies can provide an efficient route to mechanically chiral molecules that lack any covalent stereogenic units but there is clearly room for improvement in both the generality and stereoselectivity of these reactions.

Figure 5. Chiral auxiliary and direct enantioselective approaches to mechanically chiral molecules



(A) i. Goldup's synthesis of rotaxane **29** *via* separable diastereomers **28**. ii. Goldup's stereoselective synthesis of rotaxane (S_{mp})-**32** (96% ee) without separation of the intermediate diastereomers using chiral azide (*S*)-**30**. iii. Goldup's chiral auxiliary synthesis of catenane **34** by cyclisation of alkyne/azide (S_{mt})-**33** and subsequent removal of the pendant chiral group (Ar = 4-C_6H_4OMe).
B) Leigh's direct enantioselective synthesis of rotaxane **39** through the stereoselective displacement of the chiral leaving group of ester **36**.

More recently, Leigh and co-workers reported an enantioselective synthesis of mechanically planar chiral rotaxanes in up to 50% *ee* using a modification of their metal-free active template approach.[56] The reaction of activated ester half-axle **36**, the leaving group of which was functionalised with a bulky chiral cinchonidine substituent, with primary amine half-axle **35** mediated by oriented macrocycle **37**, resulted in direct formation of enantioenriched samples

(50% *ee*) of mechanically planar chiral rotaxane **39** (Fig 5B).[57] The authors suggested, based on molecular modelling, that the stereoselectivity is a consequence of selective formation of one of the four possible stereoisomeric tetrahedral intermediates **38**, which is organised by π-π stacking between the naphthalene unit of the macrocycle and the electron deficient substituent of the amine. Based on this modelling, although they were not able to get absolute confirmation, the authors tentatively assign the major product as shown.

The development of advanced strategies to access mechanically and co-conformationally chiral MIMs where the mechanical bond provides the sole stereogenic unit is still in its infancy. The use of substrate control in the mechanical bond forming step clearly has potential and the two general strategies, chiral auxiliary and direct stereoselective formation of the mechanical bond each have advantages and disadvantages. Direct stereoselective mechanical bond formation removes the need for separation of diastereomers and cleavage of an auxiliary, which dramatically simplifies the synthesis and increases its efficiency. However, unless the product is formed in very high *ee* (>95%), preparative CSP-HPLC will be required to allow application of the products in catalysis, sensing and materials. Chiral auxiliary strategies allow the separation of diastereomeric products and can lead to high diastereoselectivity, giving access to highly enantioenriched products in reasonable yields, but require more synthetic steps and current strategies suffer from limited substrate scope. Given how recent these developments are, however, it seems likely that both strategies will improve significantly in the coming years and will play key roles in developing the applications of chiral MIMs. Finally, although the majority of reports focus on mechanically planar chiral rotaxanes, there is clearly a need to extend such approaches to the synthesis of other mechanical and co-conformational stereogenic units.

CATALYTIC ENANTIOSELECTIVE APPROACHES

Despite the intense interest in enantioselective catalytic routes to chiral natural products, pharmaceuticals, agrochemicals, and ligands, reports of catalytic enantioselective approaches to the mechanical stereogenic units have been limited. Depending on the stereogenic unit targeted, three distinct categories of potential catalytic enantioselective approaches can be envisaged: direct catalytic enantioselective mechanical bond formation, post-synthetic desymmetrization, and dynamic kinetic resolution (DKR).

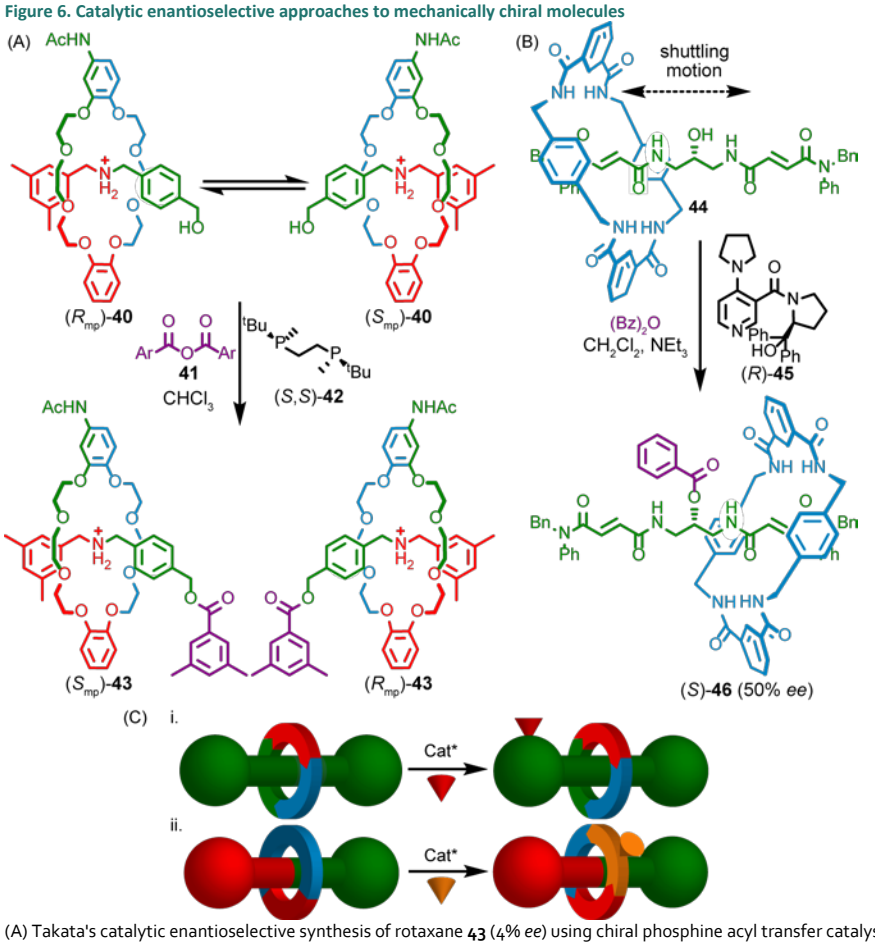
In 2007, Takata and co-workers demonstrated the first and only example of the direct catalytic enantioselective synthesis of a mechanically chiral molecule.[58] The approach relies on the stereoselective acylation of enantiomeric threaded host-guest complexes **40** whose stereochemistry arises as a result of the orientation of a macrocycle threaded onto an ammonium-containing half-axle and is thus directly analogous to the mechanically planar chiral stereogenic unit. When the acylation of the host-guest complex by benzoate ester **41** is mediated by chiral phosphine nucleophile (*S*,*S*)-**42**, one enantiomer of **40** reacts selectively, giving rise to an enantioenriched product **43**. Since this corresponds to a dynamic kinetic resolution (DKR) process, the maximum yield and stereoselectivity of the reaction are both 100% but, unfortunately, rotaxane **43** was obtained in only 4% *ee*.

The only example of the catalytic enantioselective synthesis of a co-conformationally chiral molecule was reported by Leigh and co-workers.[29a] Rotaxane **44** exists as a racemic mixture of co-conformationally covalently chiral enantiomers due to the prochiral stereocentre of the axle. Benzoylation of the alcohol moiety catalysed by *N*,*N*-dimethylamino pyridine (DMAP) results in a racemic mixture of static co-conformational enantiomers as the benzoyl group blocks the passage of the macrocycle. When chiral catalyst **45** is used in place of DMAP, an enantioenriched (50% *ee*) mixture of rotaxanes ($S_{co\text{-}c}$)-**46** is produced. In this case, the major enantiomer could be identified using a "chiral pool" synthesis, as for rotaxane **9**. The authors identified that this DKR process corresponds to an information ratchet mechanism as the mechanical state of the rotaxane is dictated by the kinetics of the gating process in the different co-conformations.[59]

The relative lack of catalytic enantioselective approaches to mechanically chiral molecules is almost certainly a consequence of the technical and theoretical challenge of implementing strategies from covalent chemistry in the context of interlocked molecules. Perhaps the most obvious and potentially fruitful way to address this challenge would be to focus on the catalytic enantioselective desymmetrisation of mechanically prochiral molecules (Fig 6c). For example, [2]rotaxanes based on either a C_{2v} macrocycle and an axle in which the two ends are differentiated (Fig 6Ci), or in which the macrocycle is oriented but the axle is centrosymmetric (Fig Cii) could be converted to enantioenriched mechanically planar chiral [2]rotaxanes by catalytic enantioselective desymmetrisation of the macrocycle or axle respectively. Similar strategies could be envisaged for any static conditional mechanical stereogenic unit. In the case

of co-conformational stereogenic units, a similar desymmetrisation process could be envisaged, although if the stereogenic unit is dynamic, DKR processes in which the desymmetrisation event traps the product in a specific enantiomeric co-conformation, as demonstrated for rotaxane **43**, are particularly attractive. As with direct enantioselective processes under substrate control (*vide supra*), if the products are to be used in applications such as catalysis, it is essential that they are produced in good to excellent (>90%) stereoselectivity, otherwise chiral separation will still be required.

Figure 6. Catalytic enantioselective approaches to mechanically chiral molecules



(A) Takata's catalytic enantioselective synthesis of rotaxane **43** (4% *ee*) using chiral phosphine acyl transfer catalyst (*S*,*S*)-**42** (Ar = 2,4-di-^{t}Bu-C_6H_3)
(B) Leigh's dynamic kinetic resolution of co-conformationally covalently chiral rotaxane **44** with chiral acyl transfer catalyst 45 to give rotaxane **46** in 50% *ee*.
(C) Schematic of desymmetrisation approaches to mechanically planar chiral [2]rotaxanes: i. Desymmetrisation of a centrosymmetric axle. ii. Desymmetrisation of a bilaterally symmetrical macrocycle.

CONCLUSIONS

As demonstrated above, despite the potential for mechanically interlocked molecules to display stereochemistry as a result of the mechanical bond being identified over half a century ago, the synthesis of such species in enantiopure form remains in its infancy. Of the various strategies discussed, CSP-HPLC remains the dominant method by sheer number of examples, presumably thanks to the simplicity of the synthetic requirements it imposes; if a racemic mixture of the target can be produced, which is now relatively easy with modern synthetic methods, and if they can be separated, again, thanks to huge progress in CSP-HPLC over the last decades, this is likely to be possible. However, the technical requirements this approach imposes can be challenging, particularly if the properties and applications of such MIMs are to be investigated; the cost of preparative scale CSP-HPLC columns is prohibitive for many research groups, as is the scale such separations can be achieved on. As alluded to above, other resolution strategies, most obviously the formation of diastereomeric salts with chiral counterions, should be investigated as these are typically highly scalable, albeit the correct combination of cation and anion is hard to predict *a priori.*

Chiral pool techniques are attractive but the range of stereogenic units these can be applied to appears relatively small; they are particularly suited to co-conformational covalently chiral molecules. However, based on Hirose's work, other unusual forms of covalent stereochemistry might be applicable, but this remains underexplored. Conversely, the use of covalent stereochemistry to bias the formation of mixed mechanical/covalent chiral diastereomers under thermodynamic control appears promising and has been extremely successful in terms of the stereoselectivities achieved. And of course, even when the stereoselectivity is less than perfect, the diastereomeric nature of the products can allow their separation using standard technique, although it is hard to predict if this will be possible beforehand. Indeed, in many cases, the mechanical stereogenic unit of mixed covalent/mechanical stereoisomers has been overlooked as the resulting diastereoisomerism was poorly expressed in the molecule's physical properties.

Of course, it is desirable to produce molecules in which the mechanical stereogenic unit is the only source of stereochemistry, particularly if their benefits and applications are to be investigated. Chiral auxiliary, substrate directed stereoselectivity and catalytic asymmetric methods all hold up the promise of being able to efficiently produce these systems without the need for CSP-HPLC separations. However, all current methods have limitations. Chiral auxiliary methods developed to date have relatively narrow substrate scope and the need for multiple steps (mechanical bond formation and diastereomer separation, followed by auxiliary cleavage under relatively harsh conditions) limits the generality of these approaches. Conversely, the enantioselective methods developed to date using substrate control or chiral catalysts do not meet the requirement of high stereoselectivity to avoid the need for CSP-HPLC separation to yield enantiopure products.

In the last decades, and particularly more recently, great strides have been taken towards being able to make mechanically chiral molecules to order, the essential challenge that we must overcome to be able to make them "useful" (or at least work out what they might be useful for). One way in which work in this area could be accelerated further is through the use of computational modelling to identify promising auxiliaries, substrates and catalysts to achieve high stereoselectivity in the formation of the chiral MIM. Indeed, Goldup and Leigh both employed modelling to rationalise *post hoc* the outcome of their auxiliary and substrate-controlled reactions respectively, suggesting such systems, despite their complexity, are amenable to computational analysis. Similarly, it would clearly be beneficial if researchers with experience of working in more traditional enantioselective synthesis would bring their expertise to bear on the problem. Indeed, this Perspective is specifically structured to make the field more accessible and so encourage them to take up the challenge! Combining the skills of synthetic supramolecular chemists and those versed in the enantioselective synthesis of complex covalent structures would undoubtedly accelerate progress.

Finally, we began this article by highlighting the general lack of applications of chiral MIMs where the stereochemistry arises due to the mechanical bond. Indeed, Leigh's co-conformationally chiral organocatalyst,[29c] Hirose's mechanically planar chiral sensor for chiral guests,[30] and Goldup's mechanically planar chiral rotaxane ligand for enantioselective gold catalysis[54] remain the only direct prototypical applications to date. However, many properties of chiral MIMs have been identified that may lead to applications, including the ability of co-conformational stereogenic units to be biased by non-covalent interactions which could lead to new types of sensor,[42,44] particularly when combined with the large CD response of some chiral MIMs;[22] the switchable chiroptical properties of interlocked molecules which could be used in new materials;[23,24,52,60,61] and coming full circle, enantioselective host-guest chemistry which might lead to new supports for CSP-HPLC.[30] Indeed, chiral MIMs have potential applications in any area where chiral covalent structures are currently used if it can be proven that a mechanical stereogenic unit can bring significant benefits. If these applications are to be developed, and others identified, it is obvious that new synthetic methods to access structurally diverse chiral MIMs are required and all the strategies described above will have their part to play in this campaign. In the short term, methods that can produce molecules where the mechanical bond provides the sole stereogenic unit are particularly desirable as only in these cases can the key role of the mechanical stereochemistry be unambiguously demonstrated. Moving beyond prototypes, in the longer term the synthesis of such chiral MIMs must be made easier so that their synthetic costs do not outweigh the benefits that mechanical stereogenic units might bring.[62] This challenge may be easier than it appears because, once the utility of these unique stereogenic units has been demonstrated, catalysts, sensors and materials containing a mixture of mechanical and covalent stereogenic units, which are inherently easier to access, are almost

certainly going to be the systems that find viable applications, significantly lowering the barrier to genuine applications. Given the growing interest in mechanically chiral molecules and the increasing sophistication of the chemistry used to access them, we see a bright future for the wide range of stereogenic units that can be created in mechanically bonded systems.

ACKNOWLEDGMENTS

S.M.G thanks the European Research Council (Consolidator Grant Agreement no. 724987) and Leverhulme Trust (ORPG-2733) for funding. S.M.G. is a Royal Society Wolfson Research Fellow.

AUTHOR CONTRIBUTIONS

S.M.G. and J.R.J.M. conceived, wrote and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES AND NOTES

1 Bruns, C. J. & Stoddart, J. F. *The Nature of the Mechanical Bond: From Molecules to Machines*. (Wiley, 2016).
2 (a) Wasserman, E. The Preparation of Interlocking Rings: A Catenane1. *J. Am. Chem. Soc.* **82**, 4433-4434 (1960). (b) Harrison, I. T. & Harrison, S. Synthesis of a stable complex of a macrocycle and a threaded chain. *J. Am. Chem. Soc.* **89**, 5723-5724 (1967).
3 Reviews: (a) Beves, J. E., Blight, B. A., Campbell, C. J., Leigh, D. A. & McBurney, R. T. Strategies and Tactics for the Metal-Directed Synthesis of Rotaxanes, Knots, Catenanes, and Higher Order Links. *Angew. Chem. Int. Ed.* **50**, 9260-9327 (2011). (b) Lewis, J. E. M., Beer, P. D., Loeb, S. J. & Goldup, S. M. Metal ions in the synthesis of interlocked molecules and materials. *Chem. Soc. Rev.* **46**, 2577-2591 (2017).
4 Dietrich-Buchecker, C. O., Sauvage, J. P. & Kintzinger, J. P. Une nouvelle famille de molecules : les metallo-catenanes. *Tetrahedron Lett.* **24**, 5095-5098 (1983).
5 Ashton, P. R., Goodnow, T. T., Kaifer, A. E., Reddington, M. V., Slawin, A. M. Z., Spencer, N., Stoddart, J. F., Vicent, C. & Williams, D. J. A [2] Catenane Made to Order. **28**, 1396-1399 (1989).
6 Reviews: (a) Crowley, J. D., Goldup, S. M., Lee, A. L., Leigh, D. A. & McBurney, R. T. in *Chem. Soc. Rev.* Vol. 38 1530-1541 (2009). (b) Denis, M. & Goldup, S. M. The active template approach to interlocked molecules. *Nat. Rev. Chem.* **1**, 0061 (2017).
7 Reviews on applications of interlocked molecules: (a) Neal, E. A. & Goldup, S. M. Chemical consequences of mechanical bonding in catenanes and rotaxanes: Isomerism, modification, catalysis and molecular machines for synthesis. *Chem. Commun.* **50**, 5128-5142 (2014). (b) Leigh, D. A., Marcos, V. & Wilson, M. R. Rotaxane Catalysts. *ACS Catal.* **4**, 4490-4497 (2014). (c) Xue, M., Yang, Y., Chi, X., Yan, X. & Huang, F. Development of Pseudorotaxanes and Rotaxanes: From Synthesis to Stimuli-Responsive Motions to Applications. *Chem. Rev.* **115**, 7398-7501 (2015). (d) Mayumi, K., Ito, K. & Kato, K. *Polyrotaxane and Slide-Ring Materials in Monographs in Supramolecular Chemistry*. (Royal Society of Chemistry, 2015). (e) Lewis, J. E. M., Galli, M. & Goldup, S. M. Properties and emerging applications of mechanically interlocked ligands. *Chem. Commun.* **53**, 298-312 (2016). (f) Bąk, K. M., Porfyrakis, K., Davis, J. J. & Beer, P. D. Exploiting the mechanical bond for molecular recognition and sensing of charged species. *Mater. Chem. Front.* **4**, 1052-1073 (2020). (g) Martinez-Cuezva, A., Saura-Sanmartin, A., Alajarin, M. & Berna, J. Mechanically Interlocked Catalysts for Asymmetric Synthesis. *ACS Catal.*, 7719-7733 (2020).
8 Reviews on molecular machines: (a) Coskun, A., Banaszak, M., Astumian, R. D., Stoddart, J. F. & Grzybowski, B. A. Great expectations: can artificial molecular machines deliver on their promise? *Chem. Soc. Rev.* **41**, 19-30 (2012). (b) Erbas-Cakmak, S., Leigh, D. A., McTernan, C. T. & Nussbaumer, A. L. Artificial Molecular Machines. *Chem. Rev.* **115**, 10081-10206 (2015). (c) Aprahamian, I. The Future of Molecular Machines. *ACS Cent. Sci.* **6**, 347-358 (2020). (d) Heard, A. W. & Goldup, S. M. Simplicity in the Design, Operation, and Applications of Mechanically Interlocked Molecular Machines. *ACS Cent. Sci.* **6**, 117-128 (2020).
9 (a) Sauvage, J. P. From Chemical Topology to Molecular Machines (Nobel Lecture). *Angew. Chem. Int. Ed.* **56**, 11080-11093 (2017). (b) Stoddart, J. F. Mechanically Interlocked Molecules (MIMs)-Molecular Shuttles, Switches, and Machines (Nobel Lecture). *Angew. Chem. Int. Ed.* **56**, 11094-11125 (2017). (c) Feringa, B. L. The Art of Building Small: From Molecular Switches to Motors (Nobel Lecture). *Angew. Chem. Int. Ed.* **56**, 11060-11078 (2017).
10 Reviews: (a) Jamieson, E. M. G., Modicom, F. & Goldup, S. M. Chirality in rotaxanes and catenanes. *Chem. Soc. Rev.* **47**, 5266-5311 (2018). (b) Evans, N. H. Chiral Catenanes and Rotaxanes: Fundamentals and Emerging Applications. *Chem. Eur. J.* **24**, 3101-3112 (2018). (c) Pairault, N. & Niemeyer, J. in *Synlett* Vol. 29 689-698 (2018). (d) Nakazono, K. & Takata, T. Mechanical Chirality of Rotaxanes: Synthesis and Function. *Symmetry* **12** (2020).
11 Frisch, H. L. & Wasserman, E. Chemical Topology. *J. Am. Chem. Soc.* **83**, 3789-3795 (1961).
12 Examples of covalent chiral rotaxane catalysts: (a) Tachibana, Y., Kihara, N. & Takata, T. Asymmetric benzoin condensation catalyzed by chiral rotaxanes tethering a thiazolium salt moiety via the cooperation of the component: can rotaxane be an effective reaction field? *J. Am. Chem. Soc.* **126**, 3438-3439 (2004). (b) Blanco, V., Leigh, D. A., Marcos, V., Morales-Serna, J. A. & Nussbaumer, A. L. A switchable [2]rotaxane asymmetric organocatalyst that utilizes an acyclic chiral secondary amine. *J. Am. Chem. Soc.* **136**,

4905-4908 (2014). (c) Xu, K., Nakazono, K. & Takata, T. Design of Rotaxane Catalyst for O -Acylative Asymmetric Desymmetrization of meso -1,2-Diol Utilizing the Cooperative Effect of the Components. *Chem. Lett.* **45**, 1274-1276 (2016). (d) Mitra, R., Zhu, H., Grimme, S. & Niemeyer, J. Functional Mechanically Interlocked Molecules: Asymmetric Organocatalysis with a Catenated Bifunctional Bronsted Acid. *Angew. Chem. Int. Ed.* **56**, 11456-11459 (2017). (e) Martinez-Cuezva, A., Marin-Luna, M., Alonso, D. A., Ros-Niguez, D., Alajarin, M. & Berna, J. Interlocking the Catalyst: Thread versus Rotaxane-Mediated Enantiodivergent Michael Addition of Ketones to beta-Nitrostyrene. *Org. Lett.* **21**, 5192-5196 (2019). (f) Dommaschk, M., Echavarren, J., Leigh, D. A., Marcos, V. & Singleton, T. A. Dynamic Control of Chiral Space Through Local Symmetry Breaking in a Rotaxane Organocatalyst. *Angew. Chem. Int Ed.* **58**, 14955-14958 (2019). (g) Calles, M., Puigcerver, J., Alonso, D. A., Alajarin, M., Martinez-Cuezva, A. & Berna, J. Enhancing the selectivity of prolinamide organocatalysts using the mechanical bond in [2]rotaxanes. *Chem. Sci.* **11**, 3629-3635 (2020). (h) Pairault, N., Zhu, H., Jansen, D., Huber, A., Daniliuc, C. G., Grimme, S. & Niemeyer, J. Heterobifunctional Rotaxanes for Asymmetric Catalysis. *Angew. Chem. Int Ed.* **59**, 5102-5107 (2020).

13 Examples of covalent chiral rotaxane sensors: (a) Mitra, R., Thiele, M., Octa-Smolin, F., Letzel, M. C. & Niemeyer, J. A bifunctional chiral [2]catenane based on 1,1'-binaphthyl-phosphates. *Chem. Commun.* **52**, 5977-5980 (2016). (b) Lim, J. Y. C., Marques, I., Felix, V. & Beer, P. D. Enantioselective Anion Recognition by Chiral Halogen-Bonding [2]Rotaxanes. *J. Am. Chem. Soc.* **139**, 12228-12239 (2017). (c) Lim, J. Y. C., Marques, I., Felix, V. & Beer, P. D. A Chiral Halogen-Bonding [3]Rotaxane for the Recognition and Sensing of Biologically Relevant Dicarboxylate Anions. *Angew. Chem. Int. Ed.* **57**, 584-588 (2018).

14 (a) Ishiwari, F., Fukasawa, K., Sato, T., Nakazono, K., Koyama, Y. & Takata, T. A rational design for the directed helicity change of polyacetylene using dynamic rotaxane mobility by means of through-space chirality transfer. *Chem. Eur. J.* **17**, 12067-12075 (2011). (b) Ishiwari, F., Nakazono, K., Koyama, Y. & Takata, T. Rational control of a polyacetylene helix by a pendant rotaxane switch. *Chem. Commun.* **47**, 11739-11739 (2011). (c) Suzuki, S., Ishiwari, F., Nakazono, K. & Takata, T. Reversible helix–random coil transition of poly(m-phenylenediethynylene) by a rotaxane switch. *Chem. Commun.* **48**, 6478-6478 (2012). (d) Inouye, M., Hayashi, K., Yonenaga, Y., Itou, T., Fujimoto, K., Uchida, T. A., Iwamura, M. & Nozaki, K. A doubly alkynylpyrene-threaded [4]rotaxane that exhibits strong circularly polarized luminescence from the spatially restricted excimer. *Angew. Chem. Int. Ed.* **53**, 14392-14396 (2014). (e) David, A. H. G., Casares, R., Cuerva, J. M., Campana, A. G. & Blanco, V. A [2]Rotaxane-Based Circularly Polarized Luminescence Switch. *J. Am. Chem. Soc.* **141**, 18064-18074 (2019).

15 Examples: Pentecost, C. D., Chichak, K. S., Peters, A. J., Cave, G. W. V., Cantrill, S. J. & Stoddart, J. F. A Molecular Solomon Link. *Angew. Chem. Int. Ed.* **46**, 218-222 (2007). (b) Prakasam, T., Lusi, M., Elhabiri, M., Platas-Iglesias, C., Olsen, J. C., Asfari, Z., Cianferani-Sanglier, S., Debaene, F., Charbonniere, L. J. & Trabolsi, A. Simultaneous self-assembly of a [2]catenane, a trefoil knot, and a Solomon link from a simple pair of ligands. *Angew. Chem. Int. Ed.* **52**, 9956-9960 (2013). (c) Schouwey, C., Holstein, J. J., Scopelliti, R., Zhurov, K. O., Nagornov, K. O., Tsybin, Y. O., Smart, O. S., Bricogne, G. & Severin, K. Self-Assembly of a Giant Molecular Solomon Link from 30 Subcomponents. *Angew. Chem. Int. Ed.* **53**, 11261-11265 (2014). (d) Beves, J. E., Danon, J. J., Leigh, D. A., Lemonnier, J.-F. & Vitorica-Yrezabal, I. J. A Solomon Link through an Interwoven Molecular Grid. *Angew. Chem. Int. Ed.* **54**, 7555-7559 (2015).

16 Examples: (a) Lincheneau, C., Jean-Denis, B. & Gunnlaugsson, T. Self-assembly formation of mechanically interlocked [2]- and [3]catenanes using lanthanide ion [Eu(III)] templation and ring closing metathesis reactions. *Chem. Commun.* **50**, 2857-2860 (2014). (b) Wood, C. S., Ronson, T. K., Belenguer, A. M., Holstein, J. J. & Nitschke, J. R. Two-stage directed self-assembly of a cyclic [3]catenane. *Nat. Chem.* **7**, 354-358 (2015). (c) Zhu, R., Lubben, J., Dittrich, B. & Clever, G. H. Stepwise halide-triggered double and triple catenation of self-assembled coordination cages. *Angew. Chem. Int. Ed.* **54**, 2796-2800 (2015). (c)

17 Walba, D. M. Topological stereochemistry. *Tetrahedron* **41**, 3161-3212 (1985).

18 The unconditional mechanical stereochemistry of MIMs is similar to that found in knotted structures: Fielden, S. D. P., Leigh, D. A. & Woltering, S. L. Molecular Knots. *Angew. Chem. Int. Ed.* **56**, 11166-11194 (2017).

19 Indeed cyclisation of the axle of a mechanically planar chiral rotaxane gives rise to a topologically chiral cateane so the stereogenic units are clearly related, However, it is

important to note that rotaxanes are by definition topologically trivial as arbitrary deformation of the ring can allow it to escape over the stoppers.

20 Leigh and co-workers suggest the term "mechanically point chiral" to describe this stereogenic unit. We prefer to emphasize the covalent co-conformational nature of this stereogenic unit as it has a direct bearing on the synthetic strategies that can be adopted, as demonstrated here.

21 Mitchell, D. K. & Sauvage, J. P. A Topologically Chiral [2]Catenand. *Angew. Chem. Int. Ed.* **27**, 930-931 (1988).

22 Yamamoto, C., Okamoto, Y., Schmidt, T., Jager, R. & Vogtle, F. Enantiomeric resolution of cycloenantiomeric rotaxane, topologically chiral catenane, and Pretzel-shaped molecules: Observation of pronounced circular dichroism. *J. Am. Chem. Soc.* **119**, 10547-10548 (1997).

23 Ishiwari, F., Nakazono, K., Koyama, Y. & Takata, T. Induction of Single-Handed Helicity of Polyacetylenes Using Mechanically Chiral Rotaxanes as Chiral Sources. *Angew. Chem. Int. Ed.* **56**, 14858-14862 (2017).

24 Gaedke, M., Witte, F., Anhäuser, J., Hupatz, H., Schröder, H. V., Valkonen, A., Rissanen, K., Lützen, A., Paulus, B. & Schalley, C. A. Chiroptical inversion of a planar chiral redox-switchable rotaxane. *Chem. Sci.* **10**, 10003-10009 (2019).

25 Schmieder, R., Hübner, G., Seel, C. & Vögtle, F. The First Cyclodiasteromeric [3]Rotaxane. *Angew. Chem. Int. Ed.* **38**, 3528-3530 (1999).

26 To our knowledge only one example of a [3]rotaxane in which the rings can pass one another on the axle has been reported: Zhu, K., Baggi, G. & Loeb, S. J. Ring-through-ring molecular shuttling in a saturated [3]rotaxane. *Nat. Chem.* **10**, 625-630 (2018).

27 Mochizuki, Y., Ikeyatsu, K., Mutoh, Y., Hosoya, S. & Saito, S. Synthesis of Mechanically Planar Chiral rac-[2]Rotaxanes by Partitioning of an Achiral [2]Rotaxane: Stereoinversion Induced by Shuttling. *Org. Lett.* **19**, 4347-4350 (2017).

28 Fumitaka, I. & Toshikazu, T. Rotaxanes with Dynamic Mechanical Chirality: Systematic Studies on Synthesis, Optical Resolution, Racemization, and Chiral-Prochiral Interconversion. (2019).

29 (a) Alvarez-Pérez, M., Goldup, S. M., Leigh, D. A. & Slawin, A. M. Z. A chemically-driven molecular information ratchet. *J. Am. Chem. Soc.* **130** (2008). (b) Carlone, A., Goldup, S. M., Lebrasseur, N., Leigh, D. A. & Wilson, A. A Three-Compartment Chemically-Driven Molecular Information Ratchet. *J. Am. Chem. Soc.* **134**, 8321-8323 (2012). (c) Cakmak, Y., Erbas-Cakmak, S. & Leigh, D. A. Asymmetric Catalysis with a Mechanically Point-Chiral Rotaxane. *J. Am. Chem. Soc.* **138**, 1749-1751 (2016).

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

31 Isnin, R. & Kaifer, A. E. Novel class of asymmetric zwitterionic rotaxanes based on .alpha.-cyclodextrin. *J. Am. Chem. Soc.* **113**, 8188-8190 (1991).

32 Isnin, R. & Kaifer, A. E. A new approach to cyclodextrin-based rotaxanes. *Pure Appl. Chem.* **63**, 495-498 (1993).

33 Armspach, D., Ashton, P. R., Ballardini, R., Balzani, V., Godi, A., Moore, C. P., Prodi, L., Spencer, N., Stoddart, J. F., Tolley, M. S., Wear, T. J., Williams, D. J. & Stoddart, J. F. Catenated Cyclodextrins. *Chem. Eur. J.* **1**, 33-55 (1995).

34 Craig, M. R., Hutchings, M. G., Claridge, T. D. W. & Anderson, H. L. Rotaxane-Encapsulation Enhances the Stability of an Azo Dye, in Solution and when Bonded to Cellulose. *Angew. Chem. Int. Ed.* **40**, 1071-1074 (2001).

35 Craig, M. R., Claridge, T. D. W., Anderson, H. L. & Hutchings, M. G. Synthesis of a cyclodextrin azo dye [3]rotaxane as a single isomer. *Chem. Commun.*, 1537-1538 (1999).

36 Lam, R. T. S., Belenguer, A., Roberts, S. L., Naumann, C., Jarrosson, T., Otto, S. & Sanders, J. K. M. Amplification of Acetylcholine-Binding Catenanes from Dynamic Combinatorial Libraries. *Science* **308**, 667 (2005).

37 Ponnuswamy, N., Cougnon, F. B., Pantos, G. D. & Sanders, J. K. Homochiral and meso figure eight knots and a Solomon link. *J. Am. Chem. Soc.* **136**, 8243-8251 (2014).

38 Chung, M.-K., White, P. S., Lee, S. J. & Gagné, M. R. Synthesis of Interlocked 56-Membered Rings by Dynamic Self-Templating. *Angew. Chem. Int. Ed.* **48**, 8683-8686 (2009).

39 Prakasam, T., Lusi, M., Nauha, E., Olsen, J. C., Sy, M., Platas-Iglesias, C., Charbonniere, L. J. & Trabolsi, A. Dynamic stereoisomerization in inherently chiral bimetallic [2]catenanes. *Chem. Commun.* **51**, 5840-5843 (2015).

40 (a) Sawada, T., Yamagami, M., Ohara, K., Yamaguchi, K. & Fujita, M. Peptide [4]Catenane by Folding and Assembly. *Angew. Chem. Int. Ed.* **55,** 4519-4522 (2016). (b) Sawada, T., Saito, A., Tamiya, K., Shimokawa, K., Hisada, Y. & Fujita, M. Metal-peptide rings form highly entangled topologically inequivalent frameworks with the same ring- and crossing-numbers. *Nat. Commun.* **10,** 921 (2019). (c) Sawada, T., Inomata, Y., Shimokawa, K. & Fujita, M. A metal-peptide capsule by multiple ring threading. *Nat. Commun.* **10,** 5687 (2019). (d) Inomata, Y., Sawada, T. & Fujita, M. Metal-Peptide Torus Knots from Flexible Short Peptides. *Chem* **6,** 294-303 (2020).

41 It is a matter of debate whether M-L bonds should be considered covalent, in which case structures such as $[Ag_{12}(\mathbf{18})_{12}]^{12+}$ and $[Ag_8(\mathbf{19})_8]^{8+}$ are mechanically interlocked, or non-covalent, in which case they should be considered as catenane-like coordination complexes. This distinction is not clear, and we have elected to treat them as interlocked for the purposes of this discussion.

42 Vignon, S. A., Wong, J., Tseng, H. R. & Stoddart, J. F. in *Org. Lett.* Vol. 6 1095-1098 (2004).

43 Hori, A., Akasaka, A., Biradha, K., Sakamoto, S., Yamaguchi, K. & Fujita, M. Chirality induction through the reversible catenation of coordination rings. *Angew. Chem. Int. Ed.* **41,** 3269-3272 (2002). Yamamoto, M., Takeuchi, M. & Shinkai, S. Oligosaccharide binding to a boronic-acid-appended phenanthroline·Cu(I) complex which creates superstructural helicates and catenates. *Tetrahedron* **58,** 7251-7258 (2002).

44 Corra, S., de Vet, C., Groppi, J., La Rosa, M., Silvi, S., Baroncini, M. & Credi, A. Chemical On/Off Switching of Mechanically Planar Chirality and Chiral Anion Recognition in a [2]Rotaxane Molecular Shuttle. *J. Am. Chem. Soc.* **141,** 9129-9133 (2019).

45 Schmidt, T., Schmieder, R., Muller, W. M., Kiupel, B. & Vogtle, F. Chiral amide rotaxanes with glucose stoppers - Synthesis, chiroptical properties and wheel-axle interactions. *Eur. J. Org. Chem.* **1998,** 2003-2007 (1998).

46 Lukin, O., Kubota, T., Okamoto, Y., Schelhase, F., Yoneva, A., Müller, W. M., Müller, U. & Vögtle, F. Knotaxanes - Rotaxanes with knots as stoppers. *Angew. Chem. Int. Ed.* **42,** 4542-4545 (2003).

47 Theil, A., Mauve, C., Adeline, M.-T., Marinetti, A. & Sauvage, J.-P. Phosphorus-Containing [2]Catenanes as an Example of Interlocking Chiral Structures. *Angew. Chem. Int. Ed.* **45,** 2104-2107 (2006).

48 For a related example in the context of pseudorotaxane see: Hattori, G., Hori, T., Miyake, Y. & Nishibayashi, Y. Design and preparation of a chiral ligand based on a pseudorotaxane skeleton: application to rhodium-catalyzed enantioselective hydrogenation of enamides. *J. Am. Chem. Soc.* **129,** 12930-12931 (2007).

49 Eliel, E., Wilen, S. & Mander, L. *Stereochemistry of Organic Compounds*. (John Wiley and Sons, Inc., 1994).

50 For previous attempts to develop auxiliary syntheses see: (a) Mobian, P., Banerji, N., Bernardinelli, G. & Lacour, J. Towards the stereoselective synthesis of inherently chiral pseudorotaxanes. *Org Biomol Chem* **4,** 224-231 (2006). (b) Glen, P. E., O'Neill, J. A. T. & Lee, A.-L. Synthesis of a C1-symmetric Box macrocycle and studies towards active-template synthesis of mechanically planar chiral rotaxanes. *Tetrahedron* **69,** 57-68 (2013).

51 (a) Aucagne, V., Berna, J., Crowley, J. D., Goldup, S. M., Hanni, K. D., Leigh, D. A., Lusby, P. J., Ronaldson, V. E., Slawin, A. M., Viterisi, A. & Walker, D. B. Catalytic "active-metal" template synthesis of [2]rotaxanes, [3]rotaxanes, and molecular shuttles, and some observations on the mechanism of the cu(i)-catalyzed azide-alkyne 1,3-cycloaddition. *J. Am. Chem. Soc.* **129,** 11950-11963 (2007). (b) Lahlali, H., Jobe, K., Watkinson, M. & Goldup, S. M. Macrocycle Size Matters: "Small" Functionalized Rotaxanes in Excellent Yield Using the CuAAC Active Template Approach. *Angew. Chem. Int. Ed.* **50,** 4151-4155 (2011).

52 Bordoli, R. J. & Goldup, S. M. An efficient approach to mechanically planar chiral rotaxanes. *J. Am. Chem. Soc.* **136,** 4817-4820 (2014).

53 Jinks, M. A., de Juan, A., Denis, M., Fletcher, C. J., Galli, M., Jamieson, E. M. G., Modicom, F., Zhang, Z. & Goldup, S. M. Stereoselective Synthesis of Mechanically Planar Chiral Rotaxanes. *Angew. Chem. Int. Ed.* **57,** 14806-14810 (2018).

54 Heard, A. W. & Goldup, S. M. Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis. *Chem* **6,** 994-1006 (2020).

55 Denis, M., Lewis, J. E. M., Modicom, F. & Goldup, S. M. An Auxiliary Approach for the Stereoselective Synthesis of Topologically Chiral Catenanes. *Chem* **5,** 1512-1520 (2019).

56 (a) De Bo, G., Dolphijn, G., McTernan, C. T. & Leigh, D. A. [2]Rotaxane Formation by Transition State Stabilization. *J. Am. Chem. Soc.* **139,** 8455-8457 (2017). (b) Fielden, S. D.

P., Leigh, D. A., McTernan, C. T., Perez-Saavedra, B. & Vitorica-Yrezabal, I. J. Spontaneous Assembly of Rotaxanes from a Primary Amine, Crown Ether and Electrophile. *J. Am. Chem. Soc.* **140**, 6049-6052 (2018). (c) Tian, C., Fielden, S. D. P., Whitehead, G. F. S., Vitorica-Yrezabal, I. J. & Leigh, D. A. Weak functional group interactions revealed through metal-free active template rotaxane synthesis. *Nat. Commun.* **11**, 744 (2020).

57 Tian, C., Fielden, S. D. P., Pérez-Saavedra, B., Vitorica-Yrezabal, I. J. & Leigh, D. A. Single-Step Enantioselective Synthesis of Mechanically Planar Chiral [2]Rotaxanes Using a Chiral Leaving Group Strategy. *J. Am. Chem. Soc.* (2020).

58 Makita, Y., Kihara, N., Nakakoji, N., Takata, T., Inagaki, S., Yamamoto, C. & Okamoto, Y. in *Chem. Lett.* Vol. 36 162-163 (2007).

59 Wilson, M. R., Solà, J., Carlone, A., Goldup, S. M. S. M., Lebrasseur, N. & Leigh, D. A. D. A. An autonomous chemically fuelled small-molecule motor. *Nature* **534**, 235-240 (2016).

60 Tai, T. Y., Liu, Y. H., Lai, C. C., Peng, S. M. & Chiu, S. H. Absolute Configurations of Topologically Chiral [2]Catenanes and the Acid/Base-Flippable Directions of Their Optical Rotations. *Org. Lett.* **21**, 5708-5712 (2019).

61 Gell, C. E., McArdle-Ismaguilov, T. A. & Evans, N. H. Modulating the expression of chirality in a mechanically chiral rotaxane. *Chem. Commun.* **55**, 1576-1579 (2019).

62 Heard, A. W. & Goldup, S. M. Simplicity in the Design, Operation, and Applications of Mechanically Interlocked Molecular Machines. *ACS Cent. Sci.* **6**, 117-128 (2020).