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Single-Step Enantioselective Synthesis of Mechanically Planar Chiral [2]Rotaxanes Using a Chiral Leaving Group Strategy

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Supporting Information Placeholder

ABSTRACT: We report a one-step enantioselective synthesis of mechanically planar chiral [2]rotaxanes. Previous studies of such molecules have generally involved the separation of enantiomers from racemic mixtures or the preparation and separation of diastereomeric intermediates followed by post-assembly modification to remove other sources of chirality. Here we demonstrate a simple asymmetric metal-free active template rotaxane synthesis using a primary amine, an activated ester with a chiral leaving group and an achiral crown ether lacking rotational symmetry. Mechanically planar chiral rotaxanes are obtained directly in up to 50% enantiomeric excess. The rotaxanes were characterized by NMR spectroscopy, high-resolution mass spectrometry, chiral HPLC, single crystal X-ray diffraction and circular dichroism. Either rotaxane enantiomer could be prepared selectively by incorporating pseudo-enantiomeric cinchona alkaloids into the chiral leaving group.

INTRODUCTION

Mechanical planar chirality arises in rotaxanes with achiral components when an unsymmetrical axle is threaded through a macrocycle lacking rotational symmetry (Figure 1).¹⁻⁴ Although lacking classical elements of chirality, studies on mechanically planar chiral rotaxanes suggest their asymmetry can be well expressed for applications.⁵⁻⁷ However, despite mechanically planar chiral rotaxanes being known for nearly 50 years, their enantioselective synthesis remains challenging.^{1d,8} Most studies on these systems rely on the separation of enantiomers from racemic mixtures by chiral stationary phase HPLC, limiting the scale of enantioenriched material that can readily be obtained.⁹

Goldup *et al.* have addressed this synthetic problem through a chiral auxiliary approach that forms intermediate diastereomeric rotaxanes having both point-chirality and mechanically planar chirality.^{10,11} Separation of these diastereomeric intermediates by flash chromatography, followed by removal of the point-chirality by either substitution¹⁰ or symmetrization,¹¹ afforded enantioenriched mechanically planar chiral rotaxanes. The only single-step synthesis of enantioenriched mechanically planar chiral rotaxanes to date used a chiral catalyst to resolve the interconverting enantiomers of a crown ether-ammonium pseudo-rotaxane by capping.¹² Despite attempts to optimize this method it produced rotaxanes in just 4% enantiomeric excess (e.e.). Here we report a simple, single-step, enantioselective synthesis of mechanically planar chiral rotaxanes that produces either enantiomer in up to 50% e.e..

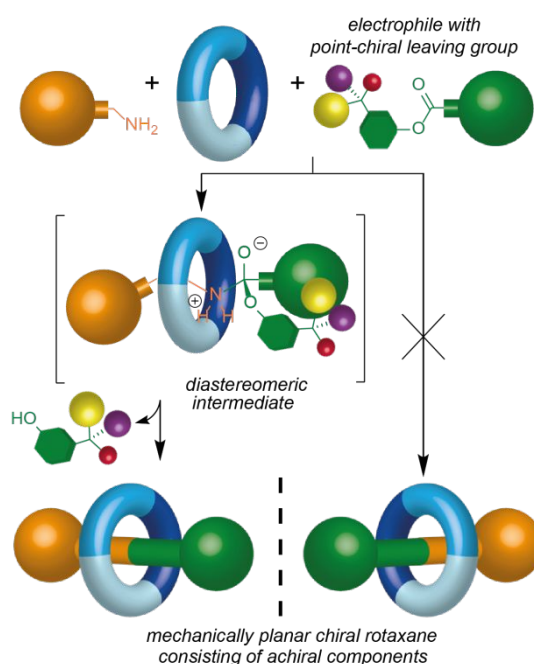
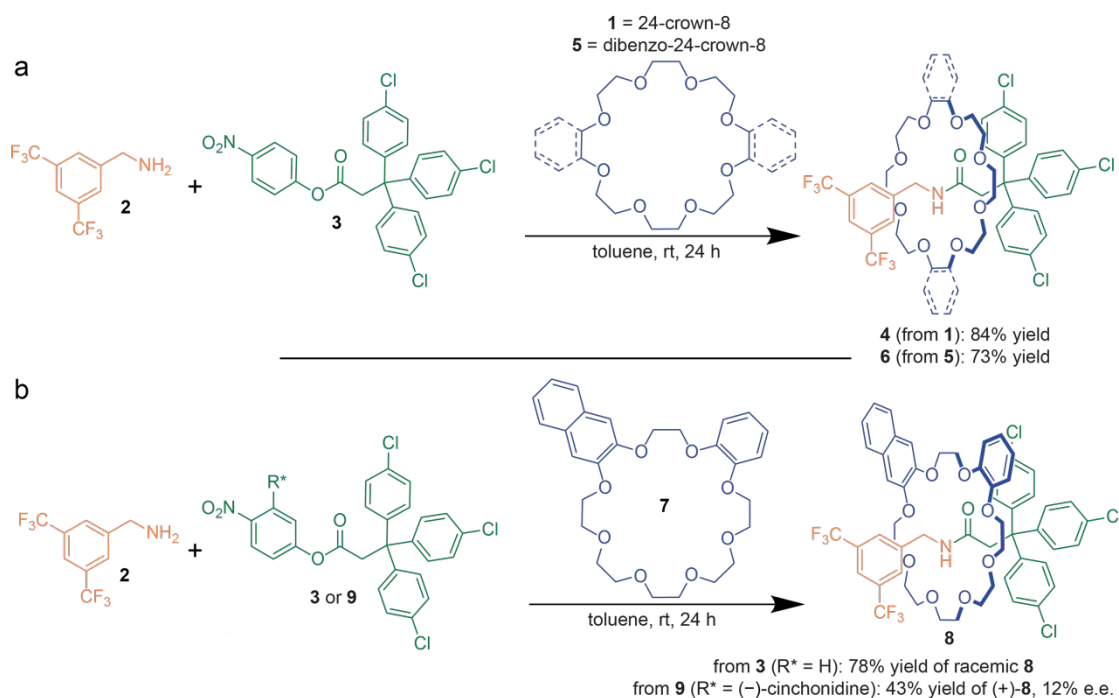


Figure 1. Enantioselective synthesis of mechanically planar chiral rotaxanes through metal-free active template *N*-acylation using a macrocycle lacking rotational symmetry and an electrophile with a point-chiral leaving group.

Metal-free active template reactions have recently been developed in which rotaxanes¹³ are spontaneously assembled under kinetic control in a single step by combining a primary amine, electrophile and crown ether¹⁴ in apolar solvents. Crown ethers stabilize the transition states of various nucleophilic substitution reactions through the cavity by C-H hydrogen bonding, thereby favoring the formation of rotaxanes over the unthreaded axle. Different reactions, amines and leaving groups result in different degrees of accelerated reaction through the ring, affording different rotaxane:thread selectivities. We chose crown ether-stabilized *N*-acylation for the present study (Scheme 1), as this active template reaction often results in a particularly high ratio of rotaxane:thread.¹⁴ This suggested the reaction might be tolerant of the additional functionality necessary in the macrocycle (to break rotational symmetry) and axle building blocks (to provide a chiral leaving group).

Scheme 1: (a) Achiral rotaxane synthesis by active template *N*-acylation using rotationally symmetrical crown ethers. (b) Racemic and unoptimized enantioselective synthesis of a mechanically planar chiral rotaxane.



An example of an active template *N*-acylation is the reaction of 24-crown-8 **1**, primary amine **2** and electrophile **3** in toluene at room temperature, producing amide [2]rotaxane **4** in 84% yield (Scheme 1a).^{14b} The rate determining step of crown ether catalyzed *N*-acylation reactions is the collapse of the tetrahedral intermediate formed on addition of an amine to the activated ester.¹⁵ The nitrophenol ester used in the reaction of **1**, **2** and **3** thus provides an opportunity for a chiral directing group to be incorporated into the leaving group that could interact with a rotationally unsymmetrical macrocycle in the transition state (Figure 1).¹⁶

RESULTS AND DISCUSSION

Development of an enantioselective synthesis

To establish that functionalized crown ethers could take part in the active template reaction, amine **2** and activated ester **3** were treated with commercially available dibenzo-24-crown-8 **5** in toluene, yielding the corresponding [2]rotaxane **6** in 73% yield (Scheme 1a). However, although the rotaxane axle is unsymmetrical, dibenzo-24-crown-8 (**5**) is D_{2h} symmetric and so rotaxane **6** is achiral.¹ Macrocycle **7**, containing two different aromatic rings, lacks rotational symmetry (it has C_{1h} symmetry, alternatively referred to as C_s). Reaction of **7** with **2** and **3** furnished racemic mechanically planar chiral rotaxane **8** in 78% yield (Scheme 1b). The enantiomers of **8** could be separated by chiral stationary phase HPLC (see Supporting Information).

Next, we investigated the structure and location for an effective chiral leaving group in the electrophile. Preliminary screening studies identified nitrophenol ester **9**, in which the chiral information stems from an *O*-alkylated cinchonidine unit adjacent to the nitro-group (Scheme 1b). This electrophile was reactive under the rotaxane-forming conditions despite the introduction of the deactivating electron-donating ether linkage. Combining **2**, **7** and **9** in a 1:1:1 stoichiometry in toluene at room temperature afforded rotaxane **8** in 43% yield (Scheme 1b). Under similar conditions, electrophiles based on alkyl (thio)esters or with the cinchonidine unit positioned at the ortho position of the nitrophenol ring were either unreactive or generated less rotaxane (see Supporting Information). HPLC analysis of rotaxane **8** (isolated by

flash chromatography) obtained from electrophile **9** revealed that the (+) enantiomer (determined by polarimetry) had been formed in 12% e.e., confirming that a point-chiral leaving group was able to induce enantioselectivity in a mechanically planar rotaxane.

Increasing the electronic difference between the two aromatic substituents within the macrocycle improved the enantioselectivity of the active template reaction. Macrocycle **10**, with a nitro group on the catechol unit (see Supporting Information for its synthesis), afforded rotaxane (+)-**11** in 23% e.e. at room temperature, which increased to 40% e.e. (55% yield) when the rotaxane-forming reaction was performed at -40°C (Figure 2a). Lowering the reaction temperature beyond -40°C did not result in further improvements in enantioselectivity.¹⁷

The opposite enantiomer of the rotaxane, (–)-**11**, could be selectively accessed using electrophile **12**, derived from (+)-cinchonine, a pseudo-enantiomer of cinchonidine (see Supporting Information for synthesis).¹⁸ Combining **2**, **10** and **12** at -40°C gave rotaxane (–)-**11** in 50% e.e. and 51% yield. (Figure 2a). The difference in enantioenrichment is a consequence of electrophiles **9** and **12** being diastereomers rather than true enantiomers.

Characterization of rotaxanes

Comparison of the ^1H NMR spectra of macrocycle **10**, rotaxane **11**, and the unthreaded axle (see Supporting information for synthesis) in CDCl_3 at 298 K (Figure 2b) confirmed the interlocked structure of **11**. The geminal protons of the crown ether display twice the number of environments in rotaxane **11** as in unthreaded **10** due to desymmetrization of the two macrocycle faces upon rotaxane formation, while H_3 and H_5 of the axle (hydrogen labeling shown in Figure 2a), which are situated either side of the amide group, display strong diastereotopic splitting ($\Delta\delta = 0.39$ and 0.22 ppm respectively) within the chiral environment of rotaxane **11**, but not in the corresponding achiral non-interlocked axle. Upfield shifts of H_6 and H_7 ($\Delta\delta = -0.32$ and -0.34 ppm) in the threaded axle and H_A , H_B and H_C ($\Delta\delta = -0.49$, -0.21 and -0.37 ppm) of the nitrocatechol unit of the threaded macrocycle result from π - π interactions involving these moieties. These intercomponent interactions may play a role in rigidifying the transition state of the

collapsing tetrahedral intermediate. The large downfield shift of the amide N-H proton H_4 ($\Delta\delta = +1.74$ ppm) in **11** is indicative of intercomponent hydrogen bonding between the amide and the glycol chain of the macrocycle. An upfield shift of H_D ($\Delta\delta = -1.29$ ppm) results from hydrogen bonding with the amide oxygen atom.^{14b}

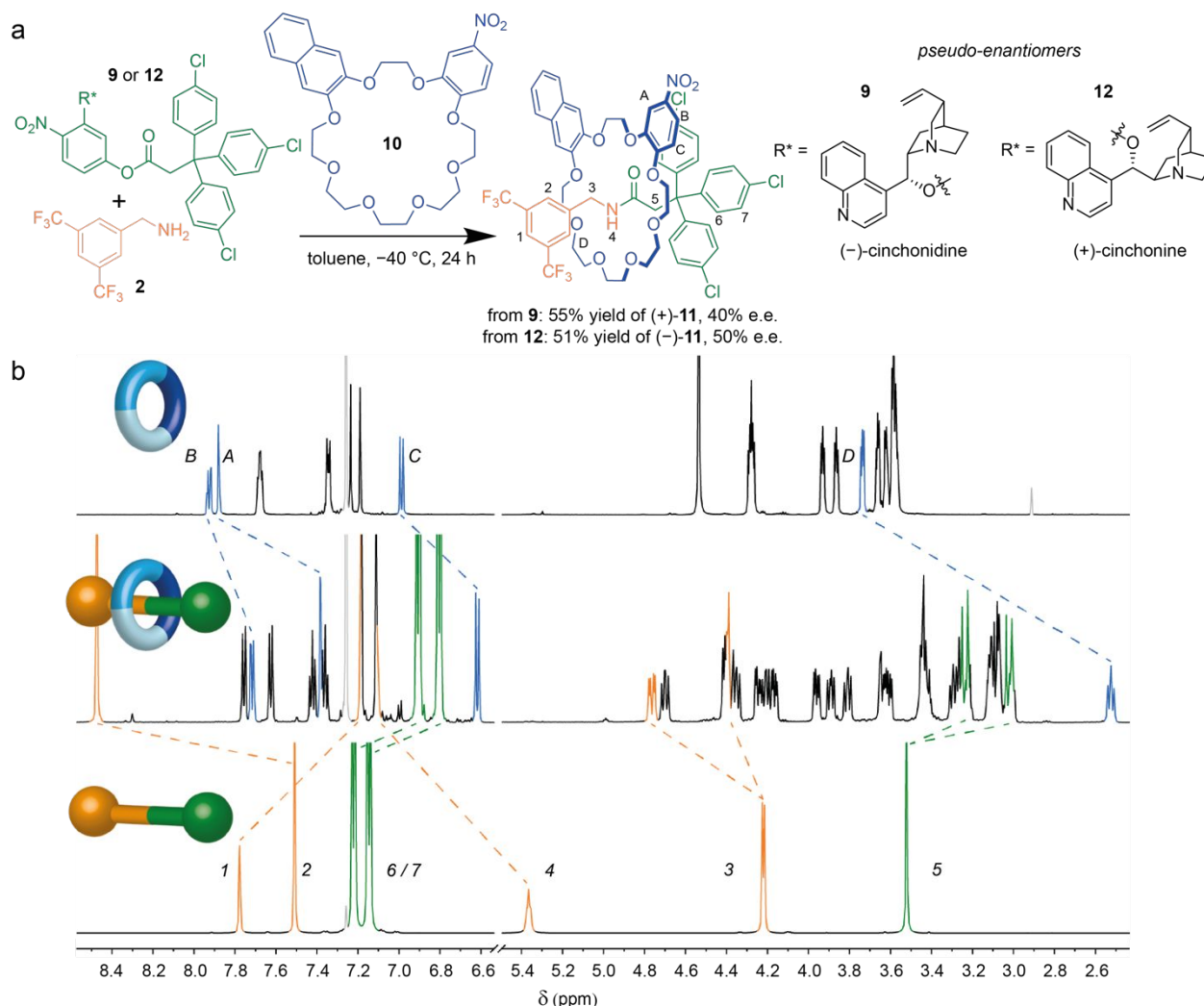


Figure 2. (a) Enantioselective synthesis of mechanically planar chiral rotaxane **11**. Reaction conditions: 2 equiv. of amine **2**, 1 equiv. each of electrophile and crown ether **10**; toluene, [0.14M], -40 °C, 24 h. (b) Partial ¹H NMR spectra (600 MHz, CDCl₃, 295 K) of macrocycle **10** (top), rotaxane **11** (middle) and the corresponding unthreaded axle (bottom).

Enantioenriched samples of rotaxane **11** (40% e.e. for the (+) enantiomer and 50% e.e. for the (-) enantiomer) were compared by circular dichroism (Figure 3a). The CD spectra of the mechanically planar chiral rotaxane enantiomers are symmetrical in terms of curve shape and have exciton couplings of opposite sign with maxima at 243 nm. The difference in intensity (normalized for absorption) of the spectra in Figure 3a corresponds to the difference in enantioenrichment of the samples.

Although we were unable to obtain high quality single crystals of **11**, single crystals of a racemic sample of **13** suitable for analysis by X-ray diffraction were grown by slow evaporation of an isopropanol/hexane solution of **13** (Figure 3b). Rotaxane **13** contains the same macrocycle as **11** and an axle derived from amine **2** and a different acyl stopper. The X-ray crystal structure of **13** (Figure 3c), containing both rotaxane enantiomers in the unit cell,

shows similar intercomponent interactions to those observed by ¹H NMR for **11** in solution (Figure 2b). Hydrogen bonds are present between an oxygen of the macrocycle glycol chain and the amide hydrogen atom of the axle and between the amide oxygen and a macrocycle C-H hydrogen atom (analogous to H_D in **11**).¹⁴ The di(alkoxy)naphthalene ring of the macrocycle and bis(trifluoromethyl)benzene unit of the axle π -stack (Figure 3d, closest centroid-centroid distance = 3.67 Å),¹⁹ with the nitro-catechol moiety positioned so as to cover one face of the amide group. A similar arrangement in the transition state of the active template reaction would orient the macrocycle with respect to the axle building blocks such that one mechanically planar chiral enantiomer would be favored over the other.

Origin of enantioselectivity

A preliminary indication of the origin of chiral transduction in these systems comes from the relative energies of the tetrahedral

intermediates preceding (+)- and (–)-**11**, calculated at PM6 level²⁰ using the Gaussian 09 software package²¹ (Supporting Information and Figure 4). The collapse of similar tetrahedral intermediates has previously been shown^{15a} to be the rate determining step for the glyme catalysis of ester aminolysis. Following the Hammond postulate, the differences between the diastereomeric tetrahedral intermediates to (+)- and (–)-**11** from **9** and **12** may resemble those between the transition states. The lowest energy intermediate calculated for both pseudo-enantiomeric leaving groups featured an (*S*) stereocenter adjacent to the ammonium unit, but with the macrocycle orientation inverted for the two pseudo-enantiomers (Figure 4), meaning changing between the leaving groups of **9** and **12** favors the formation of a different enantiomer of **11**, as observed experimentally. The somewhat surprising indication that the two chiral leaving groups both favor an (*S*)-tetrahedral intermediate may reflect why the pseudo-enantiomers do not generate equal and opposite e.e.'s in the active template reaction. The non-covalent interactions in the intermediate (e.g. the stacking of the electron-rich naphthalene unit with the electron-poor aryl group of the nucleophile, and the hydrogen bonding to the glycol oxygens to the H-N atoms) are reminiscent of those present in the X-ray crystal structure of rotaxane **13**.

Also consistent with the stacking of the electron-rich naphthalene unit with the electron-poor aryl group of the nucleophile providing the driving force for organization of the transition state is the experimental evidence that decreasing the electron-density of the other aromatic ring of the macrocycle increases the enantio-selectivity of rotaxane formation (i.e. 12% e.e. for (+)-**8**; 40% e.e. for (+)-**11**). The less electron-rich the catechol ring is, the less it competes with the naphthalene group for π -stacking with the bis(trifluoromethyl)benzylamine and so the greater the enantiodiscrimination in the transition state.

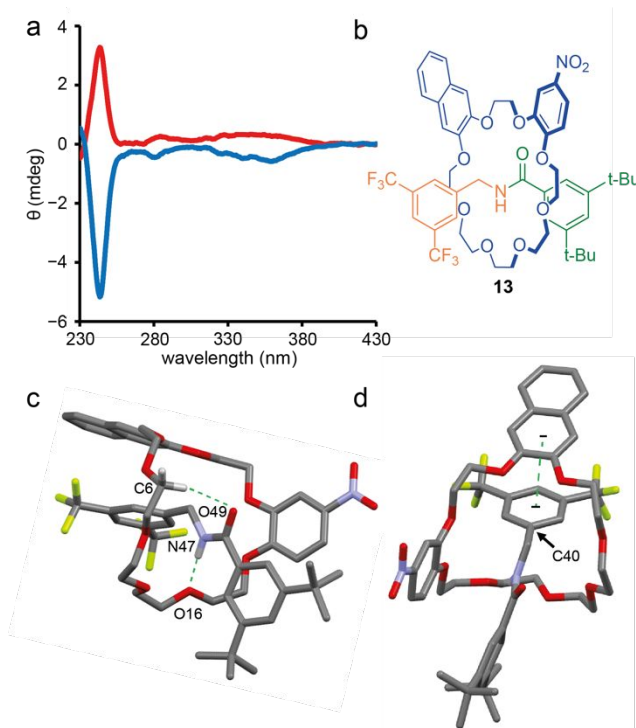


Figure 3. (a) Circular dichroism spectra (1.0×10^{-4} M, CH_2Cl_2 , 298 K) of (+)-**11** (red) and (–)-**11** (blue), baseline corrected. (b) Chemical structure of racemic rotaxane **13**. (c) X-Ray crystal structure of racemic rotaxane **13**, side-on view showing intercomponent hydrogen bonds (in green). Hydrogen bond

lengths: N47—HO16, 2.20 Å; O49—HC6, 2.63 Å. Hydrogen bond angles: N47—H—O16, 158.4°; O49—H—C6, 161.8°. (d) X-Ray crystal structure of **13** viewed along the axle showing π -stacking between the macrocycle 1,2-dihydroxynaphthalene and axle bis(trifluoromethyl)phenyl rings. Centroid-centroid distance, 3.67 Å. Angle described by C40 and centroids, 97.6°. Solvate molecules and other hydrogen atoms omitted for clarity.

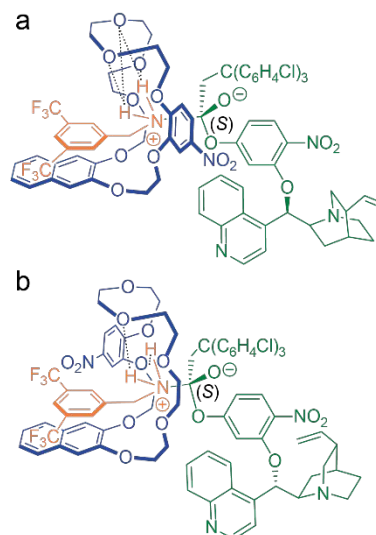


Figure 4. Tentative rationale for the transfer of chirality from Euclidean point-chirality (of the leaving group) to mechanical planar chirality (of the rotaxane). The lowest energy tetrahedral intermediates were modelled (see Supporting Information) using (a) electrophile **9** or (b) electrophile **12**. The di(alkoxy)naphthalene ring of the macrocycle and bis(trifluoromethyl)benzene unit originating from the nucleophile π -stack, causing the nitro-catechol ring to be positioned so as to cover one face of the tetrahedral center of the intermediate. This thermodynamically favored arrangement of components ensures the different handedness of the pseudo-enantiomeric leaving groups is well-expressed in the diastereomeric transition states, resulting in enantioselectivity in the mechanically planar chiral rotaxane product. Hydrogen bonds are indicated by black dotted lines.

CONCLUSIONS

The examples presented demonstrate that mechanically planar chiral rotaxanes can be directly accessed in up to 50% e.e. in a single synthetic step. The chirality of the point-chiral leaving group is transferred into mechanically planar chirality in the rotaxane through metal-free active template *N*-aminolysis. Pseudo-enantiomeric cinchona alkaloids allow either rotaxane enantiomer to be accessed. X-Ray crystallography and molecular modelling suggest that the origin of the enantioselectivity lies in π -stacking of an electron-rich aromatic ring on the macrocycle with an electron-poor aryl group originating from the nucleophilic axle building block. This positions the second aromatic ring of the macrocycle in an orientation that blocks one face of the electrophile. Simple methods for accessing enantioenriched mechanically planar chiral rotaxanes should improve their availability for investigation in applications such as asymmetric catalysis,⁷ chiral (bio)molecule sensing^{1,6,22} and novel designs²³ of molecular machinery.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXX. Experimental procedures, synthesis and characterization data, including circular dichroism,

chiral HPLC, NMR, MS, and X-ray crystallography data (PDF). Crystallographic data for **13** (CIF).

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Author Contributions

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Notes

The authors declare no competing financial interest.

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