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Article

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

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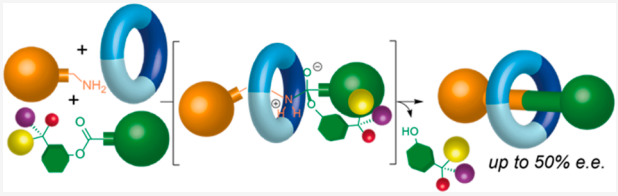
ABSTRACT: We report a one-step enantioselective synthesis of mechanically planar chiral [2]rotaxanes. Previous studies of such molecules have generally involved the separation of enantiomers from racemic mixtures or the preparation and separation of diastereomeric intermediates followed by post-assembly 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 pseudoenantiomeric 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 substitution[10] 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 pseudorotaxane 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.

Metal-free active template reactions have recently been developed in which rotaxanes[13] are spontaneously assembled under kinetic control in a single step by combining a primary amine, electrophile, and crown ether[14] 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).

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 the amine

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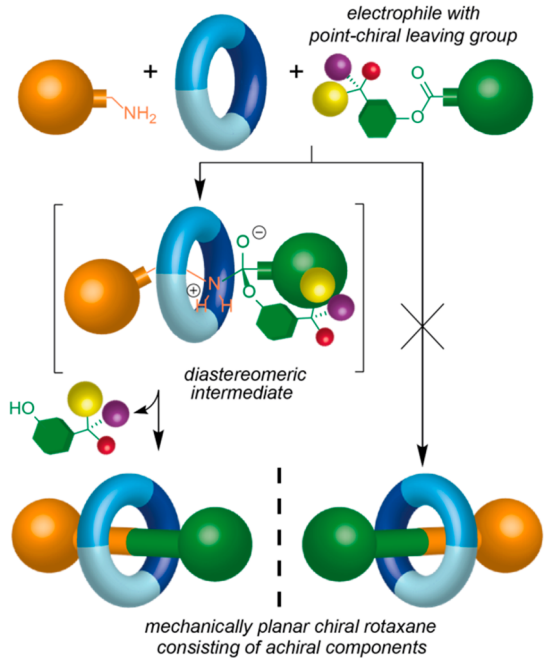


Figure 1. Enantioselective synthesis of mechanically planar chiral rotaxanes through metal-free active template *N*-acylation using a macrocycle lacking rotational symmetry and an electrophile with a point-chiral leaving group.

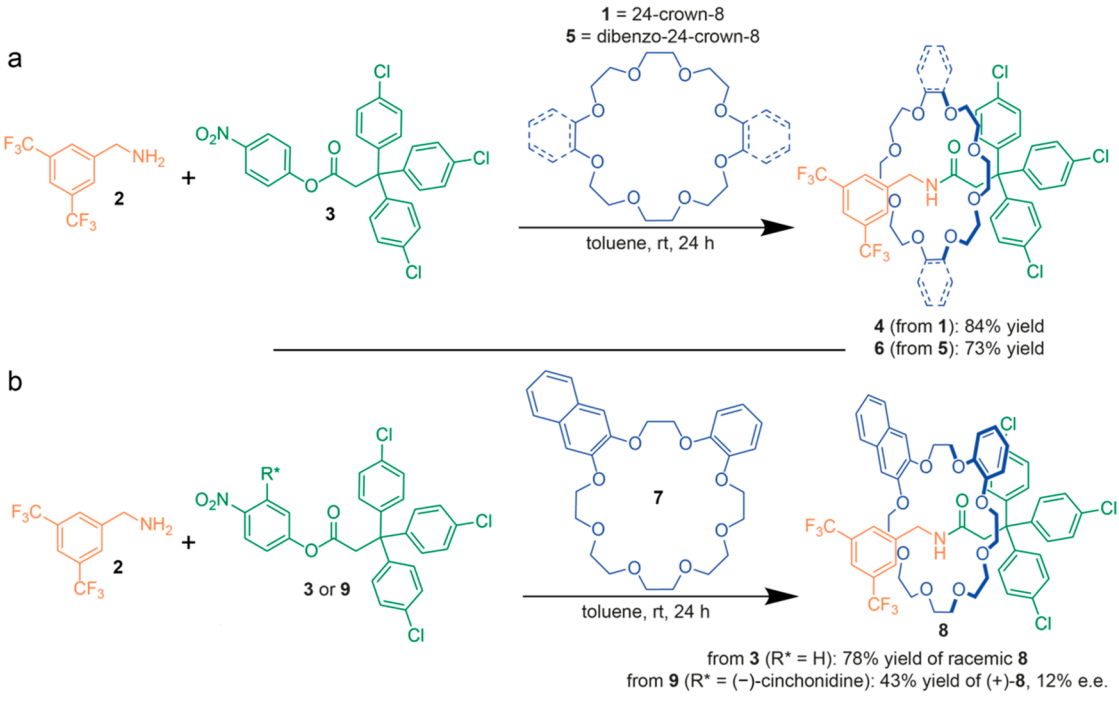
to the activated ester.[15] The nitro-phenol ester used in the reaction of **1**, **2**, and **3** thus provides an opportunity for a chiral directing group to be incorporated into the leaving group that could interact with a rotationally unsymmetrical macrocycle in the transition state (Figure 1).[16]

RESULTS AND DISCUSSION

Development of an Enantioselective Rotaxane 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 of a mechanically planar rotaxane product.

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



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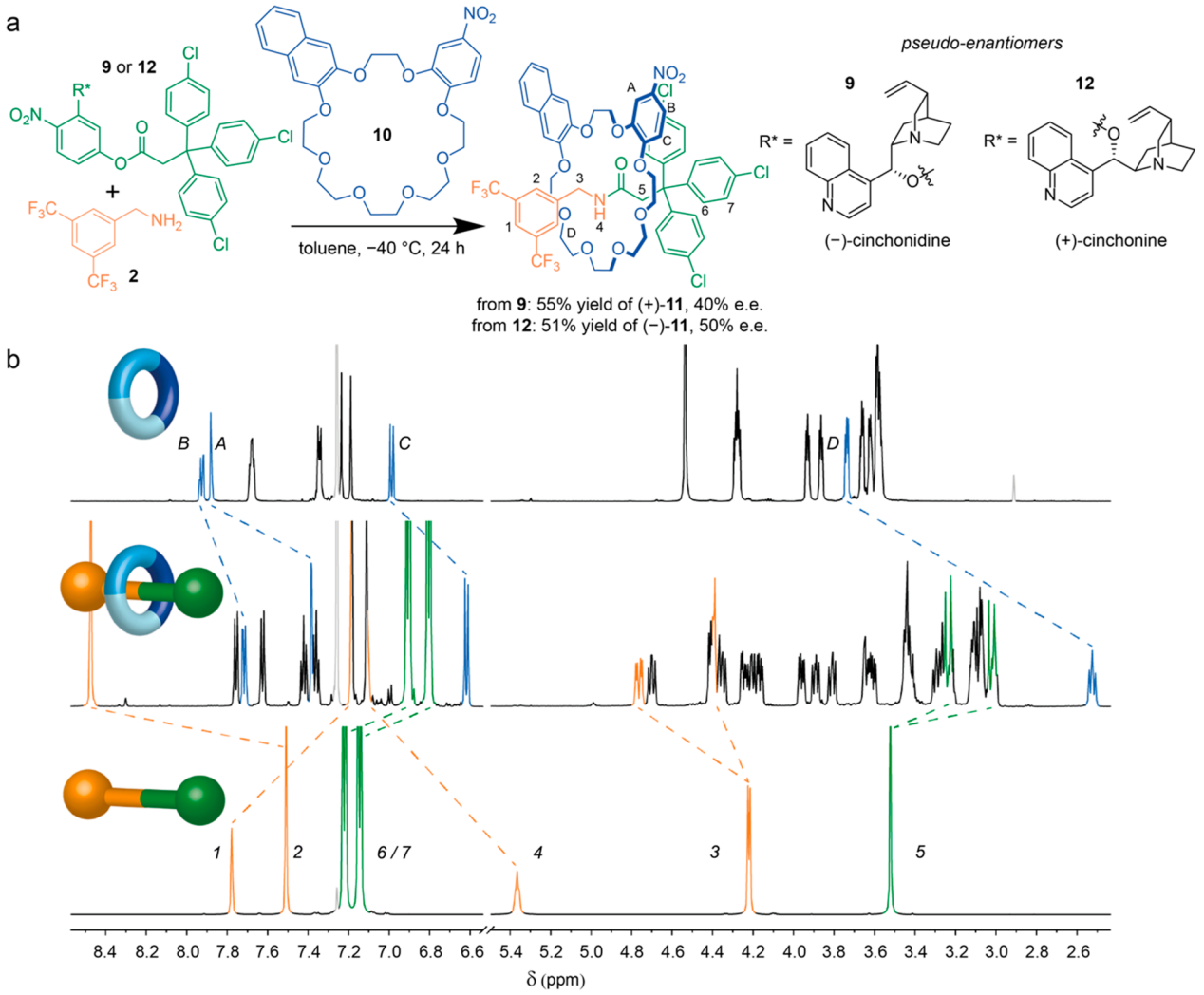

Figure 2. (a) Enantioselective synthesis of mechanically planar chiral rotaxane **11**. Reaction conditions: 2 equiv of amine **2**, 1 equiv each of electrophile and crown ether **10**, toluene, [0.14 M], −40 °C, 24 h. (b) Partial ^{1}H NMR spectra (600 MHz, $CDCl_3$, 295 K) of macrocycle **10** (top), rotaxane **11** (middle) and the corresponding unthreaded axle (bottom).

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 pseudoenantiomer 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 ^{1}H 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 significant diastereotopic splitting ($\Delta\delta$ = 0.39 and 0.22 ppm respectively) within the chiral environment of rotaxane **11** which, as would be expected, is absent for 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 $\pi-\pi$ 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 upshield shift of H_D ($\Delta\delta$ = −1.29 ppm) results from hydrogen bonding with the amide oxygen atom.[14b]

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

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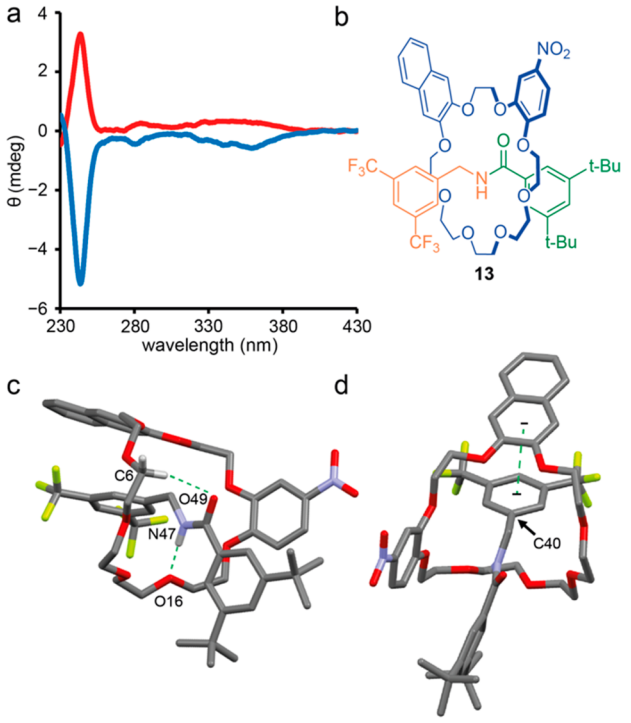

Figure 3. (a) Circular dichroism spectra (1.0×10^{-4} M, CH_2Cl_2, 298 K) of (+)-**11** (red) and (−)-**11** (blue), baseline corrected. (b) Chemical structure of racemic rotaxane **13**. (c) X-ray crystal structure of racemic rotaxane **13**, side-on view showing intercomponent hydrogen bonds (in green). Hydrogen bond lengths: N47H—O16, 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.

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 ^{1}H 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(alkoxyl)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 the PM6 level[20] using the Gaussian 09 software package[21] (Supporting Information and Figure 4). The collapse of similar tetrahedral intermediates has

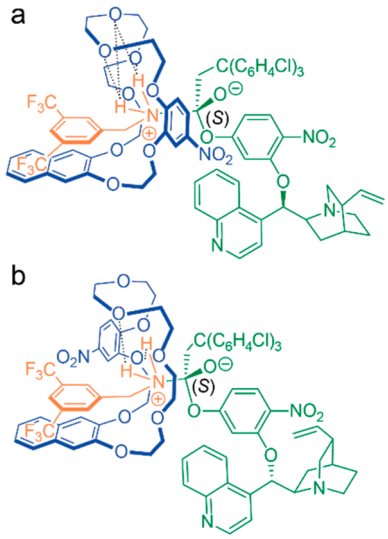

Figure 4. Tentative rationale for the transfer of chirality from Euclidean point-chirality (of the leaving group) to mechanical planar chirality (of the rotaxane). The lowest energy tetrahedral intermediates were modeled (see Supporting Information) using (a) electrophile **9** or (b) electrophile **12**. The di(alkoxyl)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 pseudoenantiomeric 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.

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 pseudoenantiomeric leaving groups featured an (*S*) stereocenter adjacent to the ammonium unit, but with the macrocycle orientation inverted for the two pseudoenantiomers (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 pseudoenantiomers do not generate equal and opposite e.e.'s in the active template reaction. The noncovalent 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 of the glycol oxygens to the H—N atoms) are reminiscent of those present in the X-ray crystal structure of rotaxane **13**.

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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 enantioselectivity 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.

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*-acylation. Pseudoenantiomeric cinchona alkaloids allow either rotaxane enantiomer to be accessed. X-ray crystallography and molecular modeling 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 designs[23] of molecular machinery.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c03447.

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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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Bruns, C. J.; Stoddart, J. F. *The Nature of the Mechanical Bond: From Molecules to Machines*; John Wiley & Sons: Hoboken, NJ, 2017. (b) Jamieson, E. M. G.; Modicom, F.; Goldup, S. M. Chirality in rotaxanes and catenanes. *Chem. Soc. Rev.* **2018**, *47*, 5266−5311. (c) Evans, N. H. Chiral catenanes and rotaxanes: Fundamentals and emerging applications. *Chem. - Eur. J.* **2018**, *24*, 3101−3112. (d) Nakazono, K.; Takata, T. Mechanical chirality of rotaxanes: Synthesis and function. *Symmetry* **2020**, *12*, 144.

(2) If a prochiral or meso thread is incorporated into a rotaxane, then chirality can arise from the position of the ring on the axle. See: (a) Alvarez-Pérez, M.; Goldup, S. M.; Leigh, D. A.; Slawin, A. M. Z. A chemically-driven molecular information ratchet. *J. Am. Chem. Soc.* **2008**, *130*, 1836−1838. (b) Cakmak, Y.; Erbas-Cakmak, S.; Leigh, D. A. Asymmetric catalysis with a mechanically point-chiral rotaxane. *J. Am. Chem. Soc.* **2016**, *138*, 1749−1751. (c) 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.* **2019**, *58*, 14955−14958.

(3) Mechanical planar chirality can also result from confinement of an unsymmetrical macrocycle to one side of a nonprochiral axle possessing D_{nh} symmetry. See: (a) 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.* **2017**, *19*, 4347−4350. (b) 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.* **2019**, *141*, 9129−9133.

(4) For examples of other stereochemical consequences of threading, see: (a) Fuller, A.-M. L.; Leigh, D. A.; Lusby, P. J. Sequence isomerism in [3]rotaxanes. *J. Am. Chem. Soc.* **2010**, *132*, 4954−4959. (b) Talotta, C.; Gaeta, C.; Qi, Z.; Schalley, C. A.; Neri, P. Pseudorotaxanes with self-sorted sequence and stereochemical orientation. *Angew. Chem., Int. Ed.* **2013**, *52*, 7437−7441. (c) La Manna, P.; Talotta, C.; Gaeta, C.; Soriente, A.; De Rosa, M.; Neri, P. Threading of an inherently directional calixarene wheel with oriented ammonium axles. *J. Org. Chem.* **2017**, *82*, 8973−8983. (d) Cui, J.-S.; Ba, Q.-K.; Ke, H.; Valkonen, A.; Rissanen, K.; Jiang, W. Directional shuttling of a stimuli-responsive cone-like macrocycle on a single-state symmetric dumbbell axle. *Angew. Chem., Int. Ed.* **2018**, *57*, 7809−7814. (e) Zheng, L.-S.; Cui, J.-S.; Jiang, W. Biomimetic synchronized motion of two interacting macrocycles in [3]rotaxane-based molecular shuttles. *Angew. Chem., Int. Ed.* **2019**, *58*, 15136−15141. (f) Ng, A. W. H.; Yee, C.-C.; Au-Yeung, H. Y. Radial hetero[5]-catenanes: peripheral isomer sequences of the interlocked macrocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 17375−17382.

(5) 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.* **2017**, *56*, 14858−14862.
(6) Kameta, N.; Nagawa, Y.; Karikomi, M.; Hiratani, K. Chiral sensing for amino acid derivative based on a [2]rotaxane composed of an asymmetric rotor and an asymmetric axle. *Chem. Commun.* **2006**, 3714−3716.
(7) Heard, A.; Goldup, S. M. Synthesis of a mechanically planar chiral rotaxane ligand for enantioselective catalysis. *Chem.* **2020**, *6*, 994−1006.
(8) Glen, P. E.; O'Neill, J. A. T.; Lee, A.-L. Synthesis of a C_1-symmetric Box macrocycle and studies towards active-template synthesis of mechanically planar chiral rotaxanes. *Tetrahedron* **2013**, *69*, 57−68.
(9) (a) Yamamoto, C.; Okamoto, Y.; Schmidt, T.; Jäger, R.; Vögtle, F. Enantiomeric resolution of cycloenantiomeric rotaxane, topologically chiral catenane, and pretzel-shaped molecules: Observation of pronounced circular dichroism. *J. Am. Chem. Soc.* **1997**, *119*, 10547−10548. (b) Schalley, C. A.; Beizai, K.; Vögtle, F. On the way to rotaxane-based molecular motors: Studies in molecular mobility and topological chirality. *Acc. Chem. Res.* **2001**, *34*, 465−476. (c) Kameta, N.; Hiratani, K.; Nagawa, Y. A novel synthesis of chiral rotaxanes via covalent bond formation. *Chem. Commun.* **2004**, 466−467. (d) 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* **2018**, *10*, 20. (e) Gell, C. E.; McArdle-Ismaguilov, T. A.; Evans, N. H. Modulating the expression of chirality in a mechanically chiral rotaxane. *Chem. Commun.* **2019**, *55*, 1576−1579. (f) 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.* **2019**, *10*, 10003−10009.
(10) Bordoli, R.; Goldup, S. M. An efficient approach to mechanically planar chiral rotaxanes. *J. Am. Chem. Soc.* **2014**, *136*, 4817−4820.
(11) 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.* **2018**, *57*, 14806−14810.
(12) Makita, Y.; Kihara, N.; Nakakoji, N.; Takata, T.; Inagaki, S.; Yamamoto, C.; Okamoto, Y. Catalytic asymmetric synthesis and optical resolution of planar chiral rotaxane. *Chem. Lett.* **2007**, *36*, 162−163.
(13) De Bo, G.; Dolphijn, G.; McTernan, C. T.; Leigh, D. A. [2]Rotaxane formation by transition state stabilization. *J. Am. Chem. Soc.* **2017**, *139*, 8455−8457.
(14) (a) Fielden, S. D. P.; Leigh, D. A.; McTernan, C. T.; Pérez-Saavedra, B.; Vitorica-Yrezabal, I. J. Spontaneous assembly of rotaxanes from a primary amine, crown ether and electrophile. *J. Am. Chem. Soc.* **2018**, *140*, 6049−6052. (b) 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.* **2020**, *11*, 744.
(15) (a) Hogan, J. C.; Gandour, R. D. Structural requirements for glyme catalysis in butylaminolysis of aryl acetates in chlorobenzene. Identification of -$OCH_2CH_2OCH_2CH_2OCH_2CH_2O$- as the optimal subunit for catalysis. *J. Org. Chem.* **1991**, *56*, 2821−2826. (b) Basilio, N.; García-Río, L.; Mejuto, J. C.; Pérez-Lorenzo, M. A. New reaction pathway in the ester aminolysis catalyzed by glymes and crown ethers. *J. Org. Chem.* **2006**, *71*, 4280−4285.
(16) Chiral leaving groups have previously been employed in asymmetric substitution reactions. See: Lepore, S. D.; Mondal, D. Recent advances in heterolytic nucleofugal leaving groups. *Tetrahedron* **2007**, *63*, 5103−5122.
(17) Heller, D.; Buschmann, H.; Scharf, H.-D. Nonlinear temperature behavior of product ratios in selection processes. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1852−1854.
(18) *Cinchona alkaloids in synthesis and catalysis: Ligands, immobilization and organocatalysis*; Eui Song, C., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2009.
(19) (a) Hunter, C. A.; Sanders, J. K. M. The nature of $\pi-\pi$ interactions. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534. (b) Riwar, L.-J.; Trapp, N.; Kuhn, B.; Diederich, F. Substituent effects in parallel displaced $\pi-\pi$ stacking interactions: Distance matters. *Angew. Chem., Int. Ed.* **2017**, *56*, 11252−11257.
(20) Stewart, J. J. P. Optimization of parameters for semiempirical methods V. Modification of NDDO approximations and application to 70 elements. *J. Mol. Model.* **2007**, *13*, 1173−1213.
(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision D.01; Gaussian, Inc.; Wallingford, CT, 2013.
(22) (a) Lim, J. Y. C.; Marques, I.; Félix, V.; Beer, P. D. A chiral halogen-bonding [3]rotaxane for the recognition and sensing of biologically relevant dicarboxylate anions. *Angew. Chem., Int. Ed.* **2018**, *57*, 584−588. (b) 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.* **2020**, *4*, 1052−1073.
(23) (a) Fu, X.; Zhang, Q.; Rao, S.-J.; Qu, D.-H.; Tian, H. One-pot synthesis of a [c2]daisy-chain-containing hetero[4]rotaxane via a self-sorting strategy. *Chem. Sci.* **2016**, *7*, 1696−1701. (b) Rao, S.-J.; Zhang, Q.; Mei, J.; Ye, X.-H.; Gao, C.; Wang, Q.-C.; Qu, D.-H.; Tian, H. One-pot synthesis of hetero[6]rotaxane bearing three different kinds of macrocycle through a self-sorting process. *Chem. Sci.* **2017**, *8*, 6777−6783. (c) Chen, S.; Wang, Y.; Nie, T.; Bao, C.; Wang, C.; Xu, T.; Lin, Q.; Qu, D.-H.; Gong, X.; Yang, Y.; Zhu, L.; Tian, H. An artificial molecular shuttle operates in lipid bilayers for ion transport. *J. Am. Chem. Soc.* **2018**, *140*, 17992−17998. (d) Zheng, X.; Zhang, Y.; Cao, N.; Li, X.; Zhang, S.; Du, R.; Wang, H.; Ye, Z.; Wang, Y.; Cao, F.; Li, H.; Hong, X.; Sue, A. C.-H.; Yang, C.; Liu, W.-G.; Li, H. Coulombic-enhanced hetero radical pairing interactions. *Nat. Commun.* **2018**, *9*, 1961. (e) Li, W.-J.; Wang, W.; Wang, X.-Q.; Li, M.; Ke, Y.; Yao, R.; Wen, J.; Yin, G.-Q.; Jiang, B.; Li, X.; Yin, P.; Yang, H. B. Daisy chain dendrimers: Integrated mechanically interlocked molecules with stimuli-induced dimension modulation feature. *J. Am. Chem. Soc.* **2020**, *142*, 8473−8482.

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