Crown Ether Active Template Synthesis of Rotaxanes**

Fielden, Stephen d. p.

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Fielden, SDP 2023, 'Crown Ether Active Template Synthesis of Rotaxanes**', *ChemSystemsChem*.
https://doi.org/10.1002/syst.202300048

[Link to publication on Research at Birmingham portal](#)

ChemSystemsChem

Concept
doi.org/10.1002/syst.202300048

**Chemistry
Europe**
European Chemical
Societies Publishing

www.chemsystemschem.org

Crown Ether Active Template Synthesis of Rotaxanes**

Stephen D. P. Fielden*[a]

Rotaxanes are interlocked molecules that consist of a macrocycle encircling a stoppered thread. The ability to control relative component positions makes rotaxanes ideal building blocks for constructing functional and responsive molecular machines. Despite the potential of rotaxanes, their challenging synthesis limits their application. One approach to construct rotaxanes is to use an active template synthesis, where a reaction that forms the thread is accelerated in the cavity of a macrocycle. An emerging method of active template synthesis that exploits the ability of crown ether macrocycles to accelerate simple organic reactions is discussed herein. Crown ether active template synthesis (CEATS) permits the rapid and simple synthesis of rotaxanes containing a wide range of functionality. Integrating rotaxane formation with chemical reaction networks has permitted the construction of molecular machines. The simplification of rotaxane synthesis will facilitate their widespread study and application.

1. Introduction

The 2016 Nobel Prize in Chemistry was awarded for the design and synthesis of molecular machines. The Nobel Committee noted: *'A substantial part of the progress made towards molecular machinery has its roots in the emergence of interlocked molecular assemblies based on mechanical bonds.'*[1] Studies of rotaxanes, interlocked molecules consisting of a macrocycle encircling a stoppered thread, currently dominate this field.[2] Whilst the constituent components of a rotaxane cannot be separated without breaking a covalent bond, their relative positions can be controlled using a range of stimuli. This makes rotaxanes a useful class of molecules and has enabled their application as pumps,[3] switchable catalysts[4] and electronic components.[5]

Crown ethers are one of the most commonly found macrocycles in rotaxanes. This is primarily because they form strong complexes, pseudo-rotaxanes, by hydrogen bonding/π stacking to templates containing a variety of functional groups, including secondary ammonium, urea, pyridinium and amidinium.[2] These complexes can be capped to produce rotaxanes in high yields (Figure 1a). For example, dibenzo-24-crown-8 **1** threads onto **2**-H·PF$_6$ to form an interlocked complex (Figure 1b). This is transformed to [2]rotaxane **3**-H·PF$_6$ by a Sonogashira coupling.[6] This example, along with other passive template syntheses, relies on the covalent capture of a thermodynami-cally stable complex. Building components with recognition elements that enable strong binding often requires many synthetic steps.[7] However, once the rotaxane has formed, it is sometimes possible to switch off the recognition between the crown ether and thread (e.g., by use of a pH responsive ammonium group),[8] providing a method to develop stimuli-responsive rotaxanes (Figure 1c).

In this concept article, a recently discovered method to form rotaxanes, crown ether active template synthesis (CEATS), is presented. CEATS exploits the acceleration of reactions within the cavities of crown ethers. This removes the need to form thermodynamically favoured complexes between the precursor components, thereby simplifying their synthesis. Instead, just mixing a suitable primary amine, crown ether and electrophile in a non-polar solvent is sufficient for spontaneous rotaxane assembly. CEATS therefore permits rotaxanes to be accessed from simple starting materials using routine organic reactions. In turn, these rotaxanes can be further manipulated by simple transformations. The ability to integrate rotaxane synthesis with chemical reaction networks is already proving of great use to Systems Chemists, who aim to explore how generating complexity in supramolecular systems can lead to unusual behaviour. The simplicity of CEATS means that rotaxanes are now easily accessible to all chemists. This will help to bring rotaxanes to the forefront of research across the chemical sciences.

[a] Dr. S. D. P. Fielden
School of Chemistry
University of Birmingham
Edgbaston, Birmingham B15 2TT, United Kingdom
E-mail: s.fielden@bham.ac.uk

2. Development of Crown Ether Active Template Synthesis

Active template synthesis exploits reactions that are accelerated when the macrocycle and thread precursor components of a rotaxane are in close proximity (Figure 2a). The key to an effective active template reaction is therefore the stabilisation of a transition state in the cavity of a macrocycle, with a rotaxane formed as a kinetic product. Hence, whilst passive template approaches can be regarded as operating under

ChemSystemsChem

Concept
doi.org/10.1002/syst.202300048

Chemistry Europe
European Chemical
Societies Publishing

thermodynamic control, active template reactions proceed under kinetic control.[9] The most commonly used mode of active template synthesis uses the Cu[I] catalysis of the azide-alkyne Huisgen cycloaddition within a macrocyclic cavity (Figure 2b).[10] This reaction has been used to construct molecular synthesisers,[11] chiral rotaxanes[12] and interlocked oligomers.[13] It should be noted that there are examples where both passive and active methods can be combined, such as cooperative capture rotaxane synthesis,[14] which requires cucurbituril macrocycles to accelerate the *metal-free* azide-alkyne Huisgen cycloaddition whilst also binding strongly to spectator ammonium groups[15] and cyclodextrin macrocycles.

Crown ethers are ideal candidates for use in an active template approach because their properties are well understood and many are commercially available. It has been known for several decades that glymes and crown ethers catalyse a variety of simple chemical reactions involving amines, including ester aminolysis (Figure 3a),[16–18] nucleophilic aromatic substitution[19] and, more recently, ring-opening polymerisation of *N*-carboxyanhydrides.[20] Catalysis in these reactions occurs because the crown ether forms hydrogen bonds with the zwitterionic tetrahedral intermediate that forms upon nucleophilic attack by an amine (Figure 3a). This facilitates proton transfer from the ammonium moiety to the leaving group, which accelerates collapse of the tetrahedral intermediate (the rate determining step). The possibility of using this mode of reaction acceleration for rotaxane formation was first demonstrated by Hirose and co-workers,[21] who showed that aminolysis of pre-rotaxane **4**, a crown ether attached to a stopper via a phenolic ester linkage, produced rotaxane **5** with high selectivity over non-interlocked thread (Figure 3c).[22] Given that the selectivity of rotaxane over non-interlocked thread formation increased when solvent polarity was decreased, it is likely that the crown ether motif accelerates amide formation. Dethreading of such rotaxanes, which consist of a thread containing an amide unit only, is thermodynamically favourable but inhibited when bulky stoppers are present. With smaller stoppers, spontaneous disassembly was observed.[23]

In a more recent report of metal-free active template rotaxane synthesis, Leigh and co-workers reported stabilisation
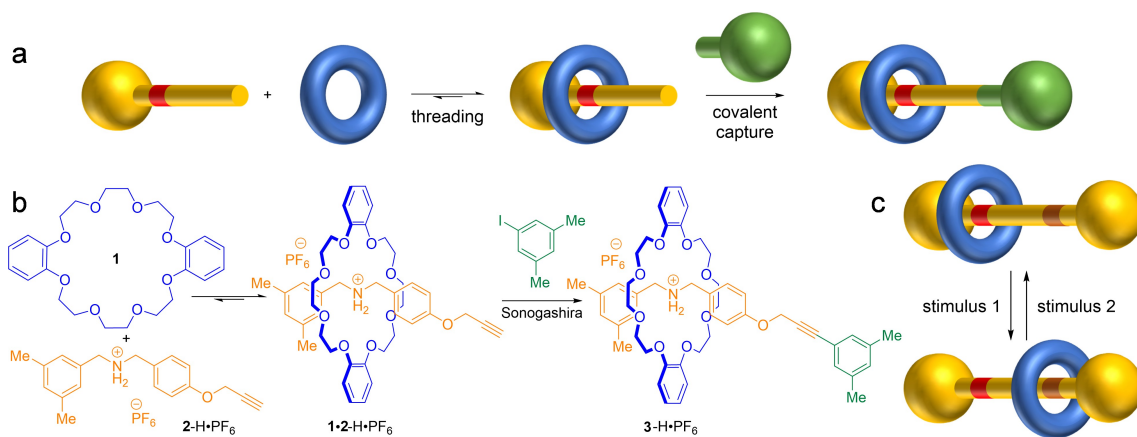
of the S_N2 substitution between primary amine nucleophile **6** and cyclic sulfate electrophile **7** by bifunctional macrocycle **8**, resulting in the formation of zwitterionic rotaxane **9** (Figure 3c).[24] The presence of both hydrogen bond donating (pyridyl-2,6-dicarboxyamide) and accepting (oligoethylene glycol) groups within macrocycle **8** allowed it to stabilise developing charges in the S_N2 transition state. Control studies using modified macrocycles showed that: (1) rotaxane still formed, albeit in lower yield, if the hydrogen bond donating amides were replaced with esters in the macrocycle and (2) no rotaxane formed if the hydrogen bond accepting oligoethylene glycol group was removed but the amides remained. Therefore, it can be deduced that an oligoethylene glycol chain alone could accelerate the S_N2 substitution. In turn, this suggested that unfunctionalized crown ethers may be able to form rotaxanes by stabilising the transition state of the S_N2 substitution.

This indeed turned out to be the case. During my PhD studies in the Leigh group, we demonstrated that simply mixing primary amine **6**, bromide **10** and 24-crown-8 **11** in toluene results in the formation of rotaxane **12**-H·Br in 48% yield (Figure 4a).[25] Given that crown ether **11** binds to amine **6** very weakly (32 ± 2 M^{-1}), it was clear that rotaxane formation was only possible because the crown ether bound to, and hence stabilised, the S_N2 transition state; rotaxane **12**-H·Br formed as a kinetic product. The reaction requires the use of primary amines. Other nucleophiles, such as thiols, alcohols and anilines do not result in rotaxane formation. It was also determined that 24-crown-8 **11** has the optimum 'Goldilocks' cavity size for maximising rotaxane yield. Other alkylating reagents were found to be compatible with the reaction (Figure 4b). For example, rotaxane **15** could be accessed by conjugate addition of amine **13** to α,β-unsaturated amide **14** (the aza-Michael reaction). Rotaxane **15** is formed as a neutral molecule (which is then protonated during purification). This means that the strong crown-ether ammonium binding found in the zwitterionic intermediate is removed in the product due to rapid tautomerization. The lack of strong intercomponent interactions in rotaxane **15** further demonstrates how CEATS operates under kinetic control – it would not be possible to make neutral **15** directly from non-interlocked precursors using a passive template approach.

Inspired by previous studies that detail the acceleration of ester aminolysis by crown ethers, the utilization of CEATS to access rotaxanes containing just an amide functional group in the thread was also demonstrated. Electron deficient electrophiles are required for the reaction to proceed at room temperature. For example, amine **16** reacts with 24-crown-8 **11** and nitrophenol ester **17** to give rotaxane **18** (Figure 5a).[26] This reaction was found to be particularly selective towards rotaxane formation over non-interlocked thread ($>100:1$ selectivity). It was also possible to produce rotaxane **19** by ligating two peptide fragments in the presence of a crown ether (Figure 5c). The ability to incorporate crown ethers into specific positions within peptide sequences may be useful for protecting certain linkages from enzymatic degradation or for controlling secondary structure.[27]

Stephen Fielden completed his undergraduate studies at the University of Oxford. He then undertook PhD studies with Professor David Leigh at the University of Manchester. Part of his PhD work included developing the general applicability of CEATS. He was awarded the 2019 Thesis Prize from the RSC MASC group. After a postdoctoral position in the same group he moved to the group of Professor Rachel O'Reilly at the University of Birmingham to contiue his postdoctoral research. He is currently a Leverhulme Early Career Fellow at the University of Birmingham. His research interests span supramolecular chemistry, molecular machines and non-equilibrium polymer nanotechnology.

ChemSystemsChem

Concept
doi.org/10.1002/syst.202300048

**Chemistry
Europe**
European Chemical
Societies Publishing

Figure 1. (a) Rotaxane synthesis using a passive template, illustrated by the threading and capping protocol. The macrocycle and half-thread form a stable interlocked pseudo-rotaxane, which then reacts to produce a [2]rotaxane. (b) An example of a passive template rotaxane synthesis using crown ether **1** and ammonium half thread **2**-H·PF$_6$.[6] (c) Stimuli can be used to control the relative positions of the macrocycle and thread in a rotaxane.
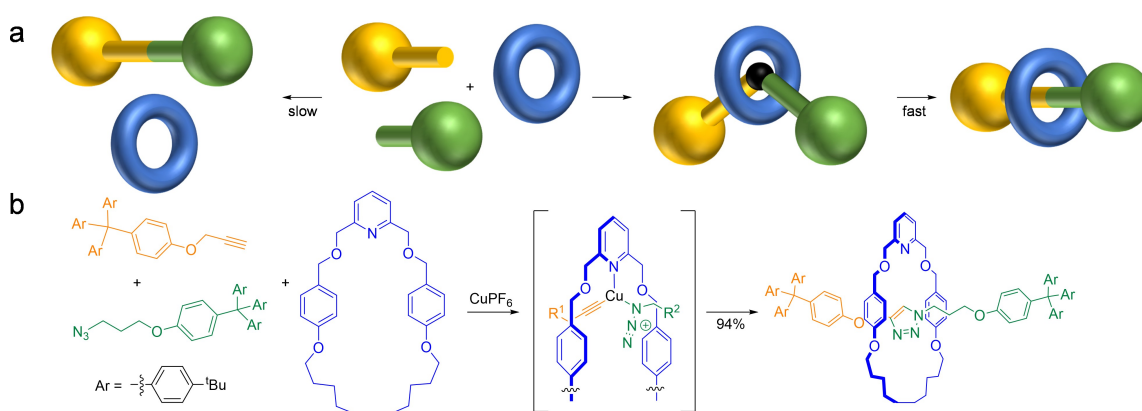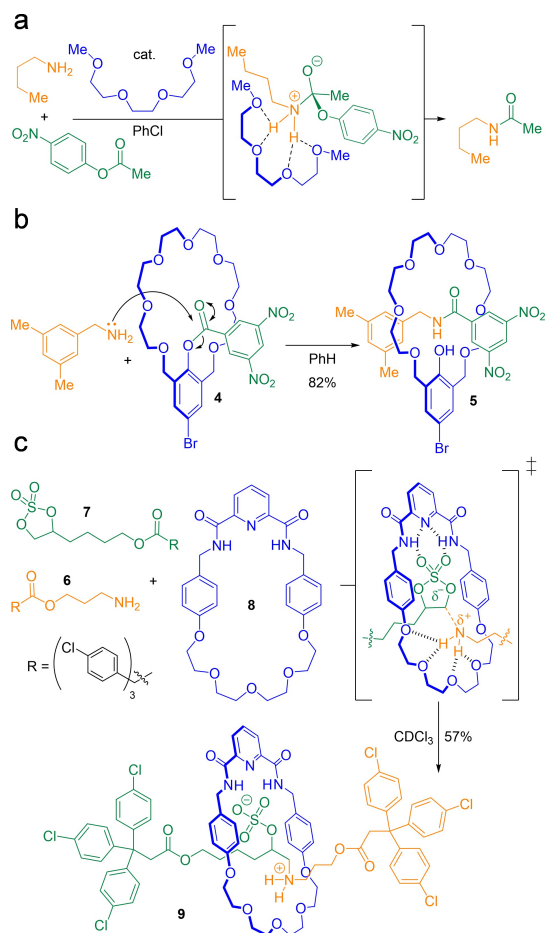

Figure 2. (a) The active template strategy. The covalent capture reaction is accelerated within a macrocyclic cavity. (b) An example of active template synthesis of a rotaxane using the Cu^I catalysed click reaction.[10]

CEATS was found to be applicable to a wide range of electrophiles,[26] permitting access to a variety of neutral rotaxanes *via* the formation of (thio)urea, carbamate, sulfonamide, phosphinamide or phosphoramidate threads (Figure 5d). In addition, rotaxanes could be formed by nucleophilic aromatic substitution. Many of these functional groups had not previously been incorporated into crown ether rotaxanes. Therefore, CEATS opens the door to access rotaxanes with unprecedented properties. For example, terminal phosphoramidates, as found in rotaxane **20**, selectively form covalent bonds with serine proteases.[28] This could be potentially exploited to develop a new switching mechanism; steric crowding upon protein binding may cause the crown ether to shuttle away from a phosphoramidate unit. Alternatively, the sulfonamide unit in rotaxane **21** could be used as a synthetic handle to further functionalise the thread.[29] Another possible application could use the crown ether ring to modify the catalytic activity of a thiourea thread, as found in rotaxane **22**. This would build on a previous report detailing the control of a rotaxane thiourea catalyst by transient activation with a chemical reaction network.[30]

CEATS has been used to access rotaxanes with a wide variety of functionality. This is because a large scope of electrophiles is compatible with CEATS, including highly reactive acid chlorides and isocyanates.[26] However all reported CEATS reactions to date use an amine nucleophile containing a R-CH$_2$-NH$_2$ moiety. Clearly this means steric crowding around the reacting amine center must be minimized to allow the crown ether to bind strongly to the transition state. Future work should focus on gaining deeper mechanistic understanding of CEATS reactions with the view to widening nucleophile scope.

3. Applications of Crown Ether Active Template Synthesis

CEATS has been used to synthesise rotaxanes with properties that differ to those made from a passive template approach. The thread and macrocycle components of rotaxanes formed using CEATS are often only weakly bound (but kinetically locked). The lack of strong stabilising intercomponent inter-

ChemSystemsChem

Concept
doi.org/10.1002/syst.202300048

Chemistry Europe
European Chemical
Societies Publishing

Figure 3. Progress towards CEATS (a) Acceleration of ester aminolysis by triglyme.[16] (b) Formation of rotaxane **4** by aminolysis of pre-rotaxane **5**.[22] (c) Rotaxane synthesis using bifunctional macrocycle **8**, which stabilises the developing charges during the S_N2 substitution of **6** and **7**.[24]

groups of the thread. Rotaxanes made using CEATS therefore often display interactions between functional groups that are not normally observed in solution or the solid state. For example, the crown ether of rotaxane **18** can accept hydrogen bonds from the amide N–H unit of the thread (Figure 5b). Similarly, situating a crown ether proximal to an amine within a rotaxane greatly increases the basicity of the latter.[31] Weak intercomponent binding also permits rapid shuttling of a macrocycle along the length of a thread.[32]

CEATS operates when a crown ether stabilises the transition state of a thread-forming reaction. If the rotaxane product is chiral, one enantiomer can be formed selectively if the transition state that proceeds it is diastereomeric. This is the case if the crown ether lacks rotational symmetry and the electrophile is chiral. A diastereomeric relationship implies the transition states have different free energies, so one enantiomer of the rotaxane product will form faster than another.

It was therefore possible to use CEATS to synthesise mechanically chiral rotaxanes[33] (whereby chirality arises due to the interlocking of achiral components) enantioselectively. This was demonstrated by the reaction of amine **16**, crown ether **23** and enantiopure ester **24** (Figure 6). The corresponding mechanically planar chiral[34] rotaxane (−)-**25** was formed in 50% enantiomeric excess (e.e.). It was proposed that π-stacking between the macrocycle naphthalene unit and the electron deficient bis(trifluoromethyl)phenyl ring of the thread stabilised the transition state, whilst the face of approach of the electrophile was determined by its chirality. Recently, post-synthetic catalytic desymmetrization of a range of rotaxanes formed by CEATS provided an alternative route to enantioenriched (>90% e.e.) mechanically planar chiral rotaxanes.[35]

During solid-phase peptide synthesis, amines are often protected as carbamates using an Fmoc (fluorenylmethyloxycarbonyl) group.[36] This protecting group is labile under basic conditions. Protecting amine **16** with an Fmoc group in the presence of 24-crown-8 **11** generates carbamate rotaxane **26** (Figure 7a).[26] Subsequent deprotection regenerates amine **16** and releases crown ether **11** back into solution. Leigh and
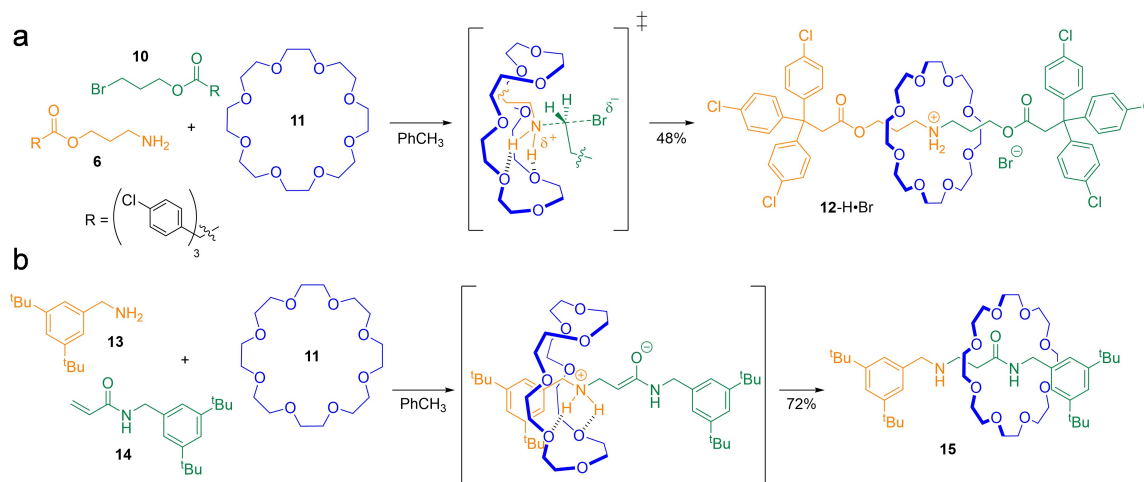
actions means confining a macrocycle in such a way is thermodynamically disfavoured. In order to reduce free energy, the macrocycle can form weak interactions with functional


Figure 4. The realisation of CEATS using amine alkylation.[25] (a) 24-crown-8 **11** stabilises the transition state of the S_N2 reaction between **6** and **10**. (b) 24-crown-8 **11** also stabilises the transition state of the aza-Michael reaction between **13** and **14** to give amine rotaxane **15**.
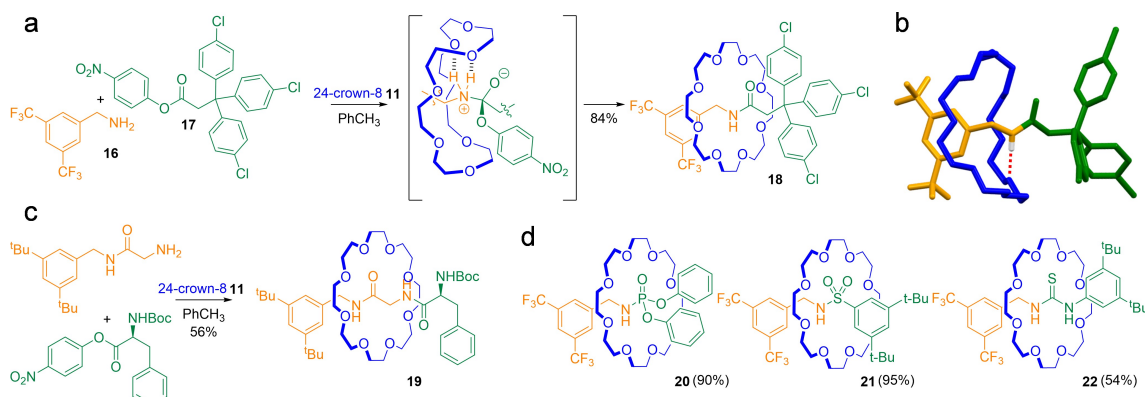
Figure 5. Rotaxane synthesis by amine acylation. (a) Formation of rotaxane **18** in high yield by crown-ether mediated ester aminolysis.[26] (b) Crystal structure of **18**, with a crown ether-amide hydrogen bond shown by a red dotted line.[26] (c) Synthesis of rotaxane **19** by ligation of two peptide derivatives.[25] (d) Examples of other rotaxanes synthesised by amine acylation. Yields of rotaxane forming reactions are shown in parentheses.[26]
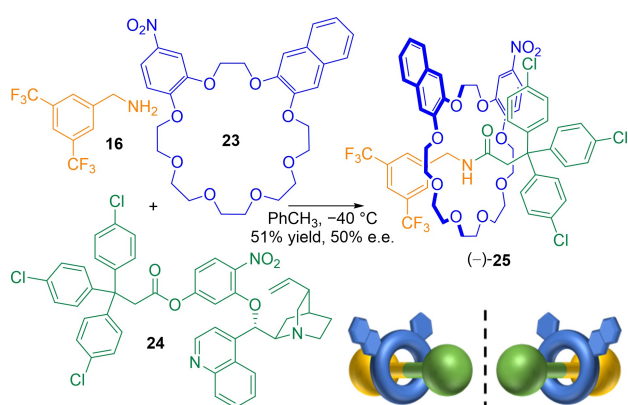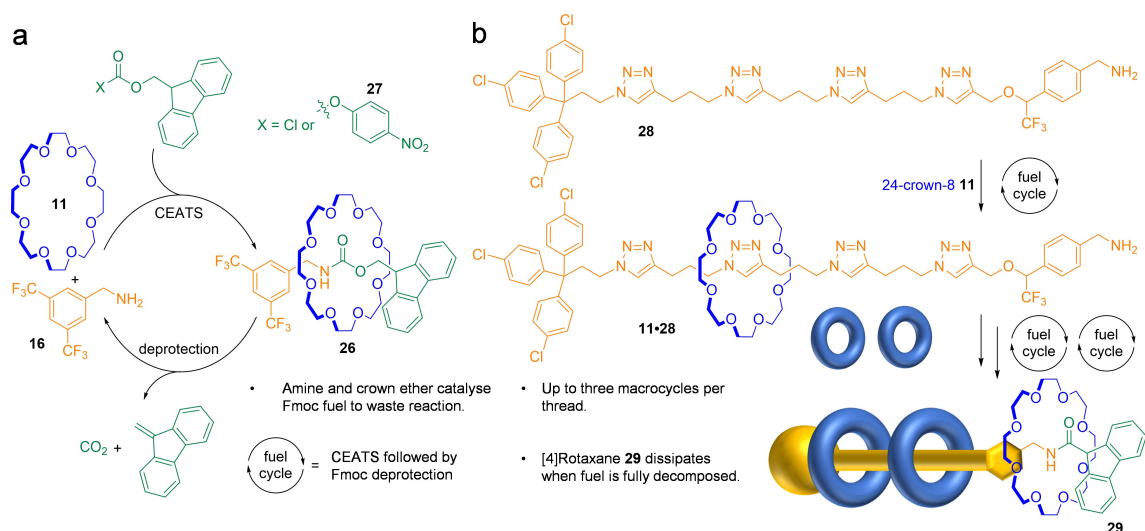

Figure 6. Enantioselective synthesis of mechanically planar chiral rotaxane (−)-**25** by CEATS.[33]
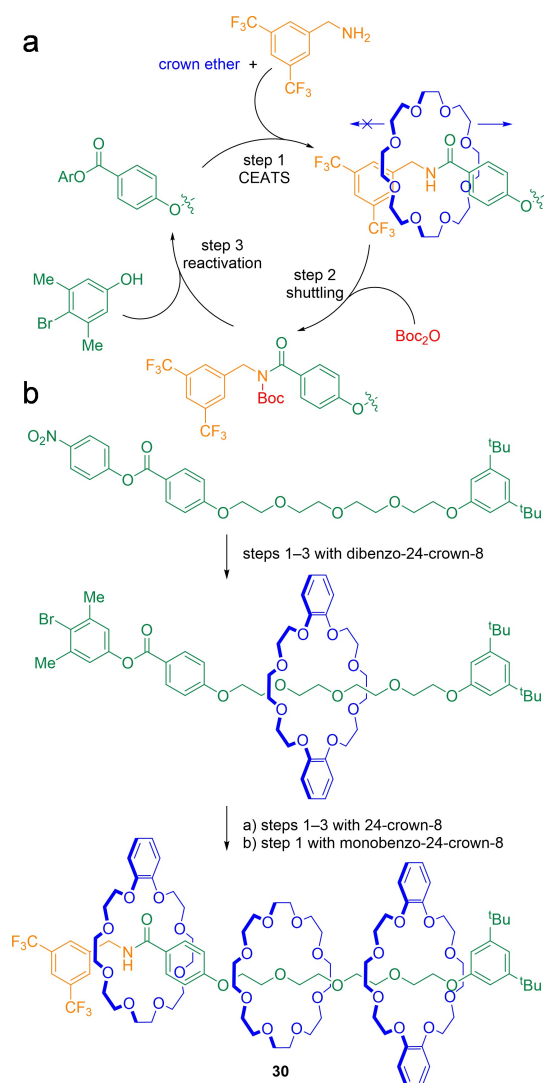
consists of an amine reactive site connected to a stoppered collection thread via a steric speed bump (to slow macrocycle shuttling). Threading of crown ether **11** onto **28** is thermodynamically unfavourable and does not occur in the absence of **27**. The pump operates by an information ratchet mechanism; Fmoc protection is accelerated by CEATS to favour rotaxane formation, whilst Fmoc deprotection is faster when the macrocycle(s) is situated on the collection thread (as this reduces steric crowding around the carbamate).

Hence, combining **11**, **27** and **28** under basic conditions leads to the spontaneous formation of [4]rotaxane **29** *via* three pumping cycles. When the fuel source is exhausted, this molecule spontaneously disassembles to regenerate **28**.

CEATS has also been incorporated into the design of pump that uses transamidation to enable sequence specific threading of crown ether derivatives.[38] In this design, which also operates via an information ratchet mechanism, crown ethers accelerate ester aminolysis and thus thread irreversibly onto a collection thread (Figure 8a). Cumulative uptake of crown ethers is

co-workers studied how energy released by the decomposition of Fmoc electrophile **27** can be used to fuel catalytically driven rotaxane pump **28** (Figure 7b).[37] This molecular machine

Figure 7. Catalysis-driven molecular pump **27**. (a) Fuel cycle based on CEATS used to drive macrocycles onto a thread. (b) Pump **28** and operation.[37]

ChemSystemsChem

Concept
doi.org/10.1002/syst.202300048

Chemistry Europe
European Chemical
Societies Publishing

Figure 8. A molecular pump based on transamidation.[38] (a) Reaction cycle that employs CEATS to drive macrocycles irreversibly onto a thread. (b) Synthesis of [4]rotaxane **30** formed using a sequence specific pumping mechanism.

possible by reactivating the amide functional group via carbamate formation and nucleophilic displacement with an electron deficient phenol. Employing this reaction cycle with three different crown ethers permitted the sequence selective formation of [4]rotaxane isomer **30** (Figure 8b). When synthesising **30** it was impossible both for (1) loaded macrocycles to dethread back into solution or (2) more than one of the same macrocycle to load onto a thread. However, the slow background reaction between an amine and activated pump without crown ether acceleration meant a small amount of amide formation did not result in the capture of a macrocycle. These rotaxane side products, which were missing macrocycles, were removed by chromatography after each CEATS reaction.

4. Summary and Outlook

The last few years have seen the emergence of crown ether active template synthesis (CEATS), a facile protocol to access rotaxanes. This method exploits the ability of crown ethers to accelerate elementary organic reactions, such as S_N2 substitutions, ester aminolysis and Fmoc protection. The strengths of this approach lie in its versatility and simplicity; as a case in point, rotaxane **26** was made by combining three commercially available reagents (crown ether **11**, amine **16** and Fmoc-Cl) with base in toluene.[26] Rotaxanes can be formed from a variety of electrophiles to produce threads containing unfamiliar functional groups. Unlike passive template syntheses, there is no need to integrate strong binding interactions into the rotaxane structure. In this regard, CEATS is already[39] proving to be a 'supramolecular late-stage functionalisation methodology'[40] – where a primary amine or electrophilic group on a complex molecule (or assembly) can be used as a handle for rotaxane formation. For Systems Chemists, the ability to integrate chemical reaction networks (including transient Fmoc protection and transamidation) with rotaxane (dis)assembly provides an exciting opportunity to develop responsive nanotechnology and transient materials, as exemplified by the realisation of autonomous and sequence specific molecular pumps. I anticipate that CEATS will prove an enabling technique for developing ever more sophisticated molecular machinery and accessing hitherto unexplored dynamic molecular architectures.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: supramolecular chemistry · rotaxanes · chemical reaction networks · crown ethers

[1] O. Ramström, "Scientific Background on the Nobel Prize in Chemistry 2016", can be found under https://www.nobelprize.org/prizes/chemistry/2016/press-release/, **2016** (accessed 29/09/23).
[2] C. J. Bruns, J. F. Stoddart, in *The Nature of the Mechanical Bond: From Molecules to Machines*, John Wiley & Sons, Inc., Hoboken, **2017**, vol. 1.
[3] J. S. W. Seale, Y. Feng, L. Feng, R. D. Astumian, J. F. Stoddart, *Chem. Soc. Rev.* **2022**, *51*, 8450–8475.
[4] C. Kwamen, J. Niemeyer, *Chem. Eur. J.* **2021**, *27*, 175–186.
[5] P. Wu, B. Dharmadhikari, P. Patra, X. Xiong, *Nanoscale Adv.* **2022**, *4*, 3418–3461.
[6] J.-B. Giguère, D. Thibeault, F. Cronier, J.-S. Marois, M. Auger, J.-F. Morin, *Tetrahedron Lett.* **2009**, *50*, 5497–5500.
[7] A. W. Heard, S. M. Goldup, *ACS Cent. Sci.* **2020**, *6*, 117–128.
[8] P. R. Ashton, R. Ballardini, V. Balzani, I. Baxter, A. Credi, M. C. T. Fyfe, M. T. Gandolfi, M. Gómez-López, M. V. Martínez-Díaz, A. Piersanti, N. Spencer, J. F. Stoddart, M. Venturi, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 11932–11942.
[9] M. Denis, S. M. Goldup, *Nat. Chem. Rev.* **2017**, *1*, 0061.

ChemSystemsChem

Concept

doi.org/10.1002/syst.202300048

Chemistry Europe
European Chemical
Societies Publishing

[10] V. Aucagne, K. D. Hanni, D. A. Leigh, P. J. Lusby, D. B. Walker, *J. Am. Chem. Soc.* **2006**, *128*, 2186–2187.

[11] B. Lewandowski, G. De Bo, J. W. Ward, M. Papmeyer, S. Kuschel, M. J. Aldegunde, P. M. Gramlich, D. Heckmann, S. M. Goldup, D. M. D'Souza, A. E. Fernandes, D. A. Leigh, *Science* **2013**, *339*, 189–193.

[12] M. A. Jinks, A. de Juan, M. Denis, C. J. Fletcher, M. Galli, E. M. G. Jamieson, F. Modicom, Z. Zhang, S. M. Goldup, *Angew. Chem. Int. Ed.* **2018**, *57*, 14806–14810.

[13] J. E. M. Lewis, J. Winn, L. Cera, S. M. Goldup, *J. Am. Chem. Soc.* **2016**, *138*, 16329–16336.

[14] X. Hou, C. Ke, J. Fraser Stoddart, *Chem. Soc. Rev.* **2016**, *45*, 3766–3780.

[15] W. L. Mock, T. A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5302–5308.

[16] J. C. Hogan, R. D. Gandour, *J. Org. Chem.* **1991**, *56*, 2821–2826.

[17] J. C. Hogan, R. D. Gandour, *J. Org. Chem.* **1992**, *57*, 55–61.

[18] N. Basilio, L. Garcia-Rio, J. C. Mejuto, M. Perez-Lorenzo, *J. Org. Chem.* **2006**, *71*, 4280–4285.

[19] N. Basilio, L. García-Río, Á. Peña-Gallego, M. Pérez-Lorenzo, *New J. Chem.* **2012**, *36*, 1519–1526.

[20] Y. Xia, Z. Song, Z. Tan, T. Xue, S. Wei, L. Zhu, Y. Yang, H. Fu, Y. Jiang, Y. Lin, Y. Lu, A. L. Ferguson, J. Cheng, *Nat. Commun.* **2021**, *12*, 732.

[21] The first synthesis of a small molecule crown ether [2]rotaxane by Busch and co-workers may have operated by an active template approach, although the chemical structure of the thread makes this difficult to prove, see: A. G. Kolchinski, D. H. Busch, N. W. Alcock, *J. Chem. Soc. Chem. Commun.* **1995**, 1289–1291. Hiratani and coworkers subsequently reported a rotaxane synthesis by double aminolysis of a crown ether diester. The possibility of the crown ether accelerating rotaxane formation was not discussed, see: K. Hiratani, J.-i. Suga, Y. Nagawa, H. Houjou, H. Tokuhisa, M. Numata, K. Watanabe, *Tetrahedron Lett.* **2002**, *43*, 5747–5750.

[22] K. Hirose, K. Nishihara, N. Harada, Y. Nakamura, D. Masuda, M. Araki, Y. Tobe, *Org. Lett.* **2007**, *9*, 2969–2972.

[23] K. Hirose, Y. Nakamura, Y. Tobe, *Org. Lett.* **2009**, *11*, 145–147.

[24] G. De Bo, G. Dolphijn, C. T. McTernan, D. A. Leigh, *J. Am. Chem. Soc.* **2017**, *139*, 8455–8457.

[25] S. D. P. Fielden, D. A. Leigh, C. T. McTernan, B. Perez-Saavedra, I. J. Vitorica-Yrezabal, *J. Am. Chem. Soc.* **2018**, *140*, 6049–6052.

[26] C. Tian, S. D. P. Fielden, G. F. S. Whitehead, I. J. Vitorica-Yrezabal, D. A. Leigh, *Nat. Commun.* **2020**, *11*, 744.

[27] S. R. Beeren, C. T. McTernan, F. Schaufelberger, *Chem* **2023**, *9*, 1378–1412.

[28] U. R. Haedke, S. C. Frommel, F. Hansen, H. Hahne, B. Kuster, M. Bogyo, S. H. Verhelst, *ChemBioChem* **2014**, *15*, 1106–1110.

[29] P. S. Fier, S. Kim, K. M. Maloney, *J. Am. Chem. Soc.* **2019**, *141*, 18416–18420.

[30] C. Biagini, S. D. P. Fielden, D. A. Leigh, F. Schaufelberger, S. Di Stefano, D. Thomas, *Angew. Chem. Int. Ed.* **2019**, *58*, 9876–9880.

[31] M. J. Power, D. T. J. Morris, I. J. Vitorica-Yrezabal, D. A. Leigh, *J. Am. Chem. Soc.* **2023**, *145*, 8593–8599.

[32] V. N. Vukotic, K. Zhu, G. Baggi, S. J. Loeb, *Angew. Chem. Int. Ed.* **2017**, *56*, 6136–6141.

[33] C. Tian, S. D. P. Fielden, B. Perez-Saavedra, I. J. Vitorica-Yrezabal, D. A. Leigh, *J. Am. Chem. Soc.* **2020**, *142*, 9803–9808.

[34] E. M. G. Jamieson, F. Modicom, S. M. Goldup, *Chem. Soc. Rev.* **2018**, *47*, 5266–5311.

[35] M. Li, X. L. Chia, C. Tian, Y. Zhu, *Chem* **2022**, *8*, 2843–2855.

[36] R. Behrendt, P. White, J. Offer, *J. Pept. Sci.* **2016**, *22*, 4–27.

[37] S. Amano, S. D. P. Fielden, D. A. Leigh, *Nature* **2021**, *594*, 529–534.

[38] L. Binks, C. Tian, S. D. P. Fielden, I. J. Vitorica-Yrezabal, D. A. Leigh, *J. Am. Chem. Soc.* **2022**, *144*, 15838–15844.

[39] Z. Peng, P.-P. Jia, X.-Q. Wang, X.-L. Zhao, H.-B. Yang, W. Wang, *Research Square preprint* **2023**, DOI: 10.21203/rs.3.rs-2597765/v1.

[40] J. Börgel, T. Ritter, *Chem* **2020**, *6*, 1877–1887.

CONCEPT

Crown ether active template synthesis (CEATS) is a recently developed method for accessing rotaxanes using kinetic control. This makes it possible to produce thermodynamically disfavored rotaxanes by coupling their assembly with simple chemical reactions. CEATS has provided access to rotaxanes containing a wide variety of functionality and can be used as a mechanism to drive molecular pumps.

crown ether active template synthesis
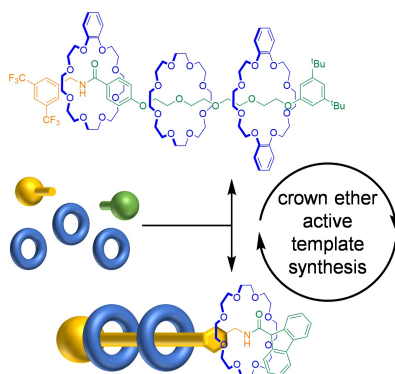
Dr. S. D. P. Fielden*

1 – 8

Crown Ether Active Template Synthesis of Rotaxanes