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Perspective

Triazole formation and the click concept in the synthesis of interlocked molecules

Abed Saady[1] and Stephen M. Goldup[1,2,*]

SUMMARY

The click concept, as originally discussed by Sharpless, Finn, and Kolb, is both powerful and simple. Kolb et al. suggested that in the search for functional molecules, chemists should focus on a small set of reactions that proceed in high yield under mild conditions and in high selectivity. Their proposal was that a relatively small number of such methodologies is sufficient to explore chemical space to solve problems in a range of disciplines, an idea pithily contained in their suggestion that chemists can obtain "diverse chemical function from a few good reactions." In this perspective, we discuss how these ideas are particularly relevant in the context of the synthesis and study of mechanically interlocked molecules (MIMs), which helps to explain why the best-known click reaction, the Cu-mediated alkyne-azide cycloaddition, was adopted so rapidly by the MIM community, and highlight that more explicit application of click concepts could help drive future progress.

INTRODUCTION

The truism that "chemistry is hard" is as relevant to high school students as it is to seasoned research leaders, although the former are perhaps more concerned with understanding foundational theories, whereas the latter are (hopefully!) referring to the challenges inherent in conducting novel research. In the context of synthetic chemistry, there are two obvious challenges: how to determine the "right" molecule to make and the best way to make it. In fact, these two questions are linked because the right molecule to make is the one that has the desired functions and properties and can be accessed efficiently. Indeed, there is often a balance to be struck between these two parameters because a "perfect" molecule that can only be made in milligram quantities is much less useful than a structure that can be accessed on process scale and performs adequately in the task; synthetic chemists are all too aware of the dangers inherent in letting the perfect become the enemy of the good.

In 2001, Sharpless, Finn, and Kolb reframed this challenge through the lens of what they christened "click" chemistry.[1] Their proposal was that chemists focused on functional molecules should, wherever possible, narrow the list of reactions they used to a set that were so simple that they effectively click molecular building blocks together like a child's construction toy. The requirements they proposed that such reactions must meet include high yield, broad scope, high chemoselectivity, high stereospecificity where this is a consideration, and high thermodynamic driving force to render bond formations functionally irreversible. In addition, they suggested that click reactions must also proceed under mild conditions (under air, using environmentally benign solvents, etc.) and the products be isolated without column chromatography. To a certain extent, the click concept is a re-expression of every synthetic chemist's preference for reactions that work well and are easy to perform!

THE BIGGER PICTURE

Challenges and opportunities:

- Rotaxanes and catenanes present synthetic challenges, which are partially compensated for by the flexibility chemists enjoy in designing the structure of mechanically interlocked targets. Thus, not unsurprisingly, there has always been a tendency to use bond-forming reactions that "just work," both in the mechanical bond-forming step and in the synthesis of precursors.
- This meant researchers working with interlocked molecules were well placed to adopt the copper-mediated alkyne-azide cycloaddition reaction, the archetypal example of "click" chemistry, for which Sharpless and Meldal were awarded the 2022 Chemistry Nobel Prize with Bertozzi.
- We highlight the impact this reaction and its variants have had on the synthesis of complicated and functional interlocked molecules, as well as suggest how a more explicit application of click concepts could help as the field pushes toward real-world applications, which require molecules to be both functional and accessible on a reasonable scale.

However, by clearly articulating what we mean by this, the authors provided a framework to evaluate new methodologies and strategies. Furthermore, reactions that meet the click requirements are particularly well suited to bio-orthogonal chemistry, reactions that are so simple and selective that they can take place in the complicated environment of a living cell.[2]

Sharpless and co-workers[1] highlighted several different processes that meet the click definition, but the reaction that most chemists think of when this concept is raised is the copper-mediated alkyne-azide cycloaddition (CuAAC) reaction reported independently by Sharpless,[3] and and Meldal,[4] which was subsequently extended to a copper-free strain-promoted variant (SP-AAC) by Bertozzi and coworkers.[5] Both owe their power to the high chemical potential of the alkyne and azide functional groups combined with their relative kinetic inertness under most conditions, which renders the triazole-forming reaction highly chemoselective. The discovery of these processes ultimately led to the 2022 Nobel Prize for Chemistry being awarded jointly to Sharpless, Meldal, and Bertozzi.[6]

In their original discussion of the click concept,[1] Sharpless and co-workers highlighted that the reactions that meet this requirement in synthetic chemistry produce molecules that are quite different from those found in natural systems; nature's building blocks are ultimately derived from CO_2, whereas those of the synthetic chemists are largely derived from the petrochemical industry. For this reason, the click concept is less easily applied to the synthesis of naturally occurring molecules than non-natural structures—most obviously, the triazole functional group produced in the archetypal CuAAC reaction is absent in natural products. Thus, the click concept, and specifically the CuAAC reaction, has had an oversized impact on the synthesis of non-natural products. Here, we discuss how click concepts and reactions, whether explicitly highlighted or not, have influenced the development of the chemistry of the mechanical bond. Although much of the article will be dedicated to syntheses of rotaxanes and catenanes that involve the formation of a triazole by the reaction of an alkyne with an azide, our aim is to highlight that future developments in the field can be accelerated by explicit inclusion of click concepts.

THE CLICK CONCEPT AND THE MECHANICAL BOND

The synthesis of mechanically interlocked molecules (MIMs)[7] can broadly be divided into two stages: the synthesis of the precursors and the formation of the final covalent bond that captures the interlocked structure. In both phases of the synthesis, the chemist has considerable freedom and motivation to select reactions that "just work," which means that MIM synthesis is well placed to take advantage of click concepts, although it should be noted that given the scale that such molecules are typically synthesized, the process requirements of click chemistry are less relevant.

First, in the synthesis of rotaxanes and catenanes, the structural requirements of the non-interlocked building blocks are only loosely defined. They must contain the motifs required to template the formation of the mechanical bond, and any functional groups present must not interfere with this, but if these requirements are satisfied, the only other obvious requirement is one of connectivity—catenanes require two macrocyclic components in the final product, whereas rotaxanes require a dumbbell-shaped component and one macrocycle. Thus, one can select the simplest possible reactions available to construct components with the required size and shape.

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Second, most syntheses rely on "passive" supramolecular templates in which non-covalent interactions are used to hold the building blocks in the required geometry for a final covalent bond formation to capture the interlocked structure. The non-covalent interactions that constitute the template must not be disrupted by the conditions of the final covalent bond formation. This also pushed and continues to push practitioners to make use of click-like reactions (high chemoselectivity, mild conditions) in the final covalent bond-forming step.

Third, the synthesis of catenanes inherently requires a macrocyclization event in the mechanical bond-forming step,[8] as does rotaxane formation when a clipping strategy is used, although this can be avoided by "stoppering" a pre-formed pseudorotaxane complex. Macrocyclization reactions are inherently hard to perform because they are slow (ring closure is a kinetically rare event) and so must usually be carried out at high dilution to avoid competitive intermolecular oligomerization reactions. This means that the functional groups involved in the macrocyclization reaction must not engage in side reactions under the conditions. Once again, click-like reactions are well suited to this task as they are highly chemoselective.

Finally, a corollary of the click requirement that reactions proceed with high driving force is that the bonds formed are functionally irreversible under most conditions. This is of particular benefit in the context of mechanically bonded structures, as reversible bond breaking could easily result in disassembly of the interlocked product, particularly if the non-covalent interactions that assembled the product are no longer present, either due to a change in the molecular environment (e.g., solvent) or removal of a component (e.g., metal ions).

These considerations are evident in Stoddart and co-workers' early report of molecular shuttle **1**;[9] all of the key steps in the synthesis of **1** are simple alkylation/silylation reactions, including the pyridine alkylation reaction that captures the interlocked structure (Figure 1A). Indeed, Stoddart and co-workers were early proponents of the idea of simple, modular approaches to interlocked molecules, as exemplified in their "molecular meccano" series of articles,[10] a reference to a popular children's construction toy.[11] More generally, for the reasons outlined above, many syntheses of MIMs rely on click-type reactions, such as amide (**2**[12]), urea (**3**[13]), carbamate (**4**[14]), or S_N2-type (**5**[15]) bond formations, or cycloaddition (**6**[16]) reactions to capture the interlocked structure (Figure 1B).

This is of course not to say that MIM chemists only use click reactions! Pd-mediated (e.g., Sonagashira, Suzuki) and other metal-mediated (e.g., Glaser) coupling reactions are often used in the synthesis of MIM precursors, particularly in the context of metal-templated mechanical bond formation.[17] Although these are not click-like in terms of their simplicity, scope, environmental burden, etc., they typically work extremely well with suitable substrates and do not introduce reactive or polar functional groups into the molecule, allowing the molecular design to remain relatively simple. Similarly, ring-closing alkene metathesis is often used in the final macrocyclization step, which, although not click-like (indeed, the reaction is reversible, which has been used to allow mechanical bond formation under thermodynamic control[18]), benefits from the fact that the alkene moieties are otherwise unreactive, allowing high yields of macrocyclic products to be obtained.[19]

The rapid adoption of the CuAAC click reaction in MIM synthesis

Based on the above it should be obvious that MIM synthesis was well placed to take advantage of the archetypal CuAAC click reaction when it appeared. Thus, it should

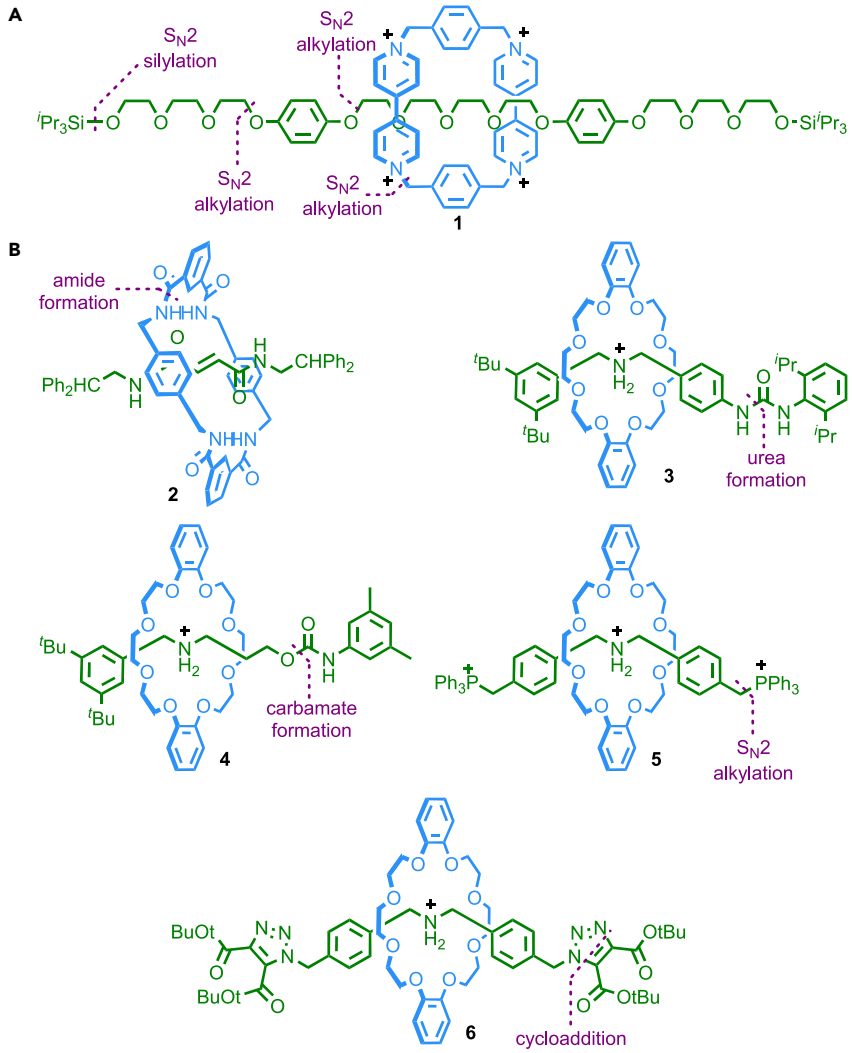

Figure 1. Early examples of MIMs that make use of click-like reactions in their synthesis

(A) An early molecular shuttle in which most key bonds were formed using click-like reactions (key disconnections labeled).

(B) Examples of early MIMs that make use of click-like reactions in the final step that captures the mechanical bond (key disconnections labeled).

come as no surprise that this new process was incorporated into the MIM chemist's toolbox relatively quickly after the first reports in 2002.[3,4] There are now far too many examples of interlocked structures for which the CuAAC reaction plays a key role in their synthesis to review here. In 2007, when Stoddart and co-workers reviewed this emerging area,[20] they highlighted that ~12 examples had appeared in the year since the first report of MIM synthesis[21] using the CuAAC reaction. Three years later, when Leigh and Hänni reviewed the field again,[22] they highlighted ~30 examples, and the figure will stand far, far higher now.[23] It is fair to say that the CuAAC reaction is now ubiquitous in MIM synthesis, which is noteworthy in itself—not many reactions go from being new and exciting to being as accepted as amide bond formation in such a relatively short period! Instead of providing a comprehensive overview of these applications, we will highlight selected examples that demonstrate how and why this situation has come about.

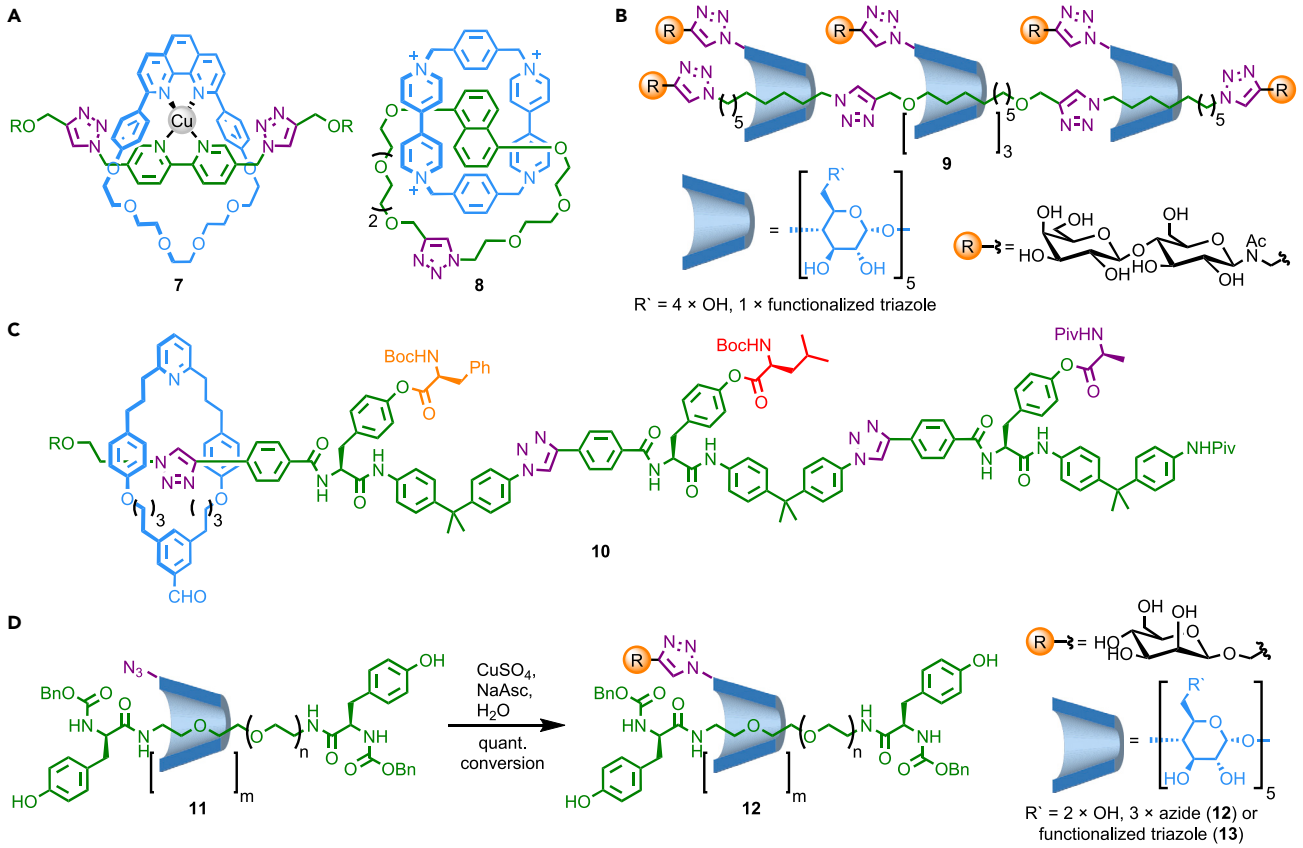

Figure 2. MIMs that demonstrate the synthetic utility of the CuAAC reaction

(A) Early examples of MIMs in which the CuAAC reaction was used to capture the mechanical bond (R = -4-C_6H_4-C(4-^{t}Bu-C_6H_4)).

(B) Lactose-functionalized oligorotaxane **9** synthesized using the CuAAC reaction under aqueous conditions.

(C) Synthesizing molecular machine precursor **10** whose building blocks are constructed using a highly convergent CuAAC strategy (R = -4-C_6H_4-C(4-^{t}Bu-C_6H_4)).

(D) Highly functionalized polyrotaxane **12** produced by post-synthetic modification of polyrotaxane **11**.

Mild, chemoselective reactions lead to high yields in the final mechanical bond-forming step

The mild, chemoselective nature of the CuAAC reaction was the first feature to be highlighted to the field. Sauvage and co-workers demonstrated its use in the synthesis of rotaxanes[21] using their seminal Cu-phenanthroline template strategy.[24] They noted that the CuAAC reaction allowed the synthesis of structures such as **7** (Figure 2A) in which the metal-binding units were less hindered, which were formed in low yields using other stoppering reactions as the templating interactions were easily disrupted. The mild conditions of the CuAAC reaction helped avoid this. Just two months later, Stoddart reported the synthesis of rotaxanes,[25] and soon after catenanes (e.g., **8**),[26] using the CuAAC reaction in conjunction with their iconic viologen "blue box" macrocycle. They highlighted explicitly that this reaction "not only renders the simple [MIMs] much more accessible, but it also provides the opportunity to prepare respectable quantities of more exotic mechanically interlocked compounds," paving the way for their applications. They were entirely correct; at this stage, the CuAAC reaction is one of the most widely used reactions to capture the mechanical bond in the stoppering approach to rotaxanes.

The CuAAC reaction under aqueous conditions for the synthesis of MIMs

Organic solvents are typically used in MIM synthesis, but being able to carry reactions out the CuAAC reaction under aqueous conditions is particularly advantageous when making use of highly hydrophilic precursors or using the hydrophobic effect to template mechanical bond formation. This benefit, which is particularly relevant when considering the synthesis of biologically relevant MIMs, was also demonstrated early in the adoption of the CuAAC reaction by MIM chemists. In 2007,[27] Brown and co-workers used the CuAAC reaction to cyclize a DNA single strand functionalized on one end by an alkyne and the other with an azide. The triazole-linked cyclic oligonucleotide produced was then hybridized with a second azide/alkyne-functionalized single strand, and the CuAAC reaction used to efficiently close this second ring. Helix formation between the circular and linear components is expected to result in a catenane with multiple crossing points; a fully entwined precursor would contain six crossing points, but the authors propose, based on molecular modeling, that a triply entwined product is more likely. Soon after,[28] Fort and co-workers demonstrated the synthesis of lactose-functionalized oligo- and poly-rotaxanes (e.g., **9**, Figure 2B) by co-oligomerization of bis-alkyne and bis-azide-functionalized cyclodextrin-based pseudorotaxanes.

High-yielding CuAAC reactions allow the synthesis of complicated structures

In the construction of the non-interlocked precursors for MIM synthesis, the high efficiency of the CuAAC reaction and the chemically benign nature of the triazole formed are clearly a boon. This is perhaps most starkly demonstrated in the synthesis of rotaxane **10**,[29] a precursor to a molecular machine that carries out the synthesis of a simple peptide oligomer. The synthesis of **10** (Figure 2C) requires 19 linear steps, three of which are CuAAC reactions (one in its active-template[30] modification,[31] see below). Given the length of the synthetic sequence, the high yield of the CuAAC reaction was essential to the production of this ground-breaking molecular machine.

Post-synthetic modification is an efficient method for late-stage diversification of functional molecules, but the small quantities that MIMs are usually produced in means that this strategy is only effective when the reaction used is extremely efficient, making the CuAAC an excellent option where applicable.[32,33] For example, Yui and Hyun synthesized polyrotaxanes (e.g., **11**, Figure 2D) based on cyclodextrin macrocycles functionalized with one, two, or three azide units.[34] Subsequent CuAAC reactions with different propargyl functionalized mannose (**12**) or phosphorylcholine units gave rise to densely functionalized polyrotaxanes bearing these biological ligands. Importantly, the authors report quantitative conversion of the azide moieties under extremely mild conditions, even when very high molecular weight polyethylene glycol axes (20,000 $gmol^{-1}$) were used.

MIM structures in which the triazole plays a functional role

Although one of the key advantages of the CuAAC reaction is that the triazole moiety formed is chemically unreactive, it can act as a ligand for metal ions[35] or as a hydrogen bonding donor, an effect that is enhanced further by alkylation to give the corresponding triazolium moiety, which also engages in charge-charge or charge-dipole interactions. These features, combined with its ease of installation, make the triazole functional group useful in the synthesis and operation of functional MIMs.

Several examples of MIM synthesis in which a pre-formed triazole unit is involved in the templating interaction have been reported. In 2009, Beer and co-workers reported that an alkylated triazole can be used as part of the binding motif in their

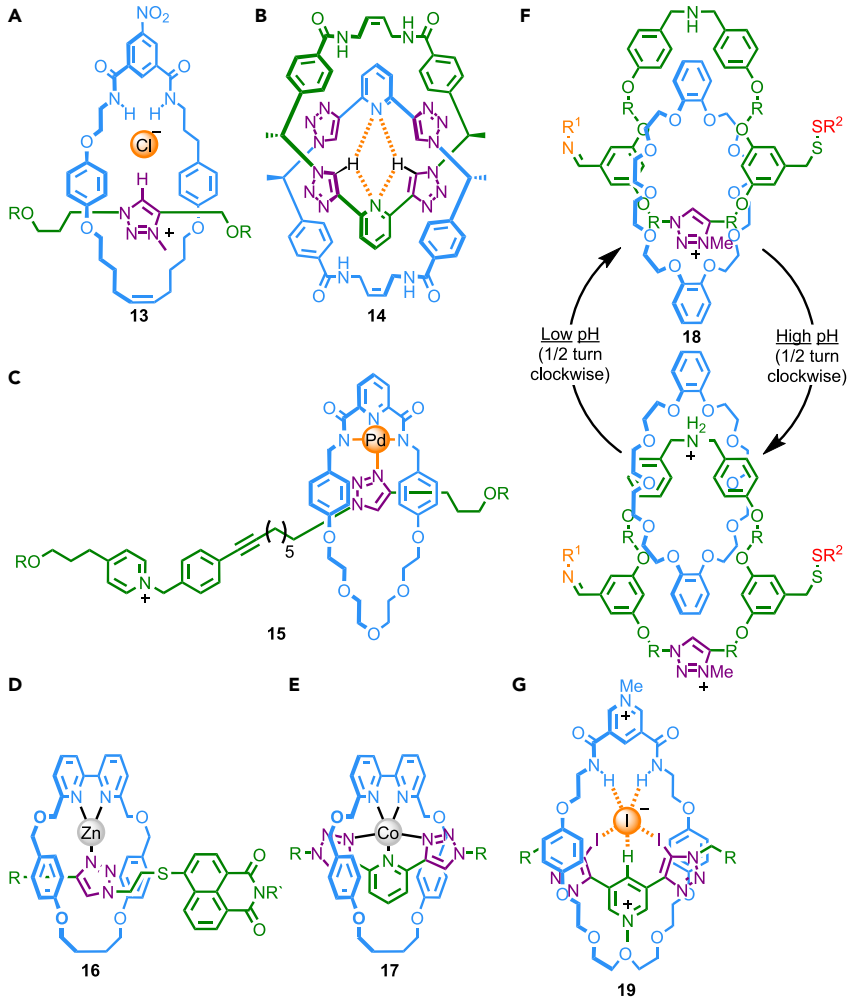

Figure 3. The non-covalent interactions presented by the triazole functional group and its derivatives in functional MIMS

(A) Rotaxane **13**, which relies on an anion-templated motif that includes a methyl triazolium unit for its synthesis (R = -4-C_6H_4-C(4-^{t}Bu-C_6H_4)).

(B) Catenane **14** formed after trapping a bis-triazole pyridine dimer using RCM (one set of H-bonds responsible for dimer formation highlighted).

(C) A rotaxane molecular switch in which a triazole-Pd interaction stabilizes one of the co-conformational states.

(D) Stimuli-responsive rotaxane **16** that produces a fluorescent switch on with Zn^{II} in the cavity.

(E) Rotaxane single-ion magnet **17** in which triazole-Co^{II} coordination is a key part of the binding motif.

(F) Catenane molecular motor **18** for which one of the stations in a methyl triazolium unit (R = $(CH_2)_3$, R^1 = NH-3,5-di-^{t}Bu-benzoyl, and R^2 = 2,5-di-Me-benzyl).

(G) Halogen-bonding anion host rotaxane **19** in the iodotriazole unit is a key factor in affinity and selectivity (R = permethyl β-cyclodextrin).

anion-templated synthetic methodology;[36] rotaxane **13** was produced after RCM of a mixture of the corresponding triazolium axle, bis-alkene pre-macrocycle, and tetra butyl ammonium chloride (Figure 3A). Similarly, Gunnlaugsson and co-workers reported that the triazole units of bis-triazole pyridine moieties engaged in a symmetrical hydrogen bonding interaction and demonstrated that this interaction, combined with a ring-closing alkene metathesis reaction to capture the interlocked structure, could be used to construct chiral homocatenanes (e.g., **14**, Figure 3B).[37]

The triazole moiety has also been used as ligand in metal-responsive MIMs. Lusby and co-workers demonstrated molecular shuttle **15** in which the triazole moiety acts as a ligand for Pd^{II} in one of the shuttled states (Figure 3C).[38] In a slightly different application, Goldup, Watkinson, and co-workers demonstrated that the triazole unit could be part of the binding motif in the development of MIM-based selective metal ion sensors—rotaxane **16** selectively responds to Zn^{II} over other divalent transition metal ion by producing a fluorescent switch on output upon binding (Figure 3D).[39] More generally, Goldup, Roessler, Crespo, and co-workers built on a previous demonstration that the mechanical bond could be used to access coordination environments that are inaccessible to their non-interlocked counterparts[40] to develop rotaxane-based Co^{II} field-dependent single-ion magnets—the triazole moieties of **17** are key components of the metal-binding motif (Figure 3E).[41]

The hydrogen-bond-donating nature of the triazolium ring allowed it to be used by Coutrot as a station in a crown-ether-based molecular switch,[42] a feature that was subsequently elaborated by Leigh and co-workers to generate molecular motors (Figure 3F). When the amine unit of **18** is protonated, the corresponding ammonium unit is a better station than the triazolium, but deprotonation causes the macrocycle to shuttle to this moiety. By controlling the path of shuttling, the authors were able to demonstrate directed motion over a cycle of low pH –> high pH –> low pH.[43] Beer and co-workers extended the use of triazolium moieties as functional supramolecular units to the use of iodotriazoles as halogen bond donors in MIMs.[44] Iodotriazole rotaxane **19** binds anions in water much more strongly than its H-bond donor triazole analog with a significant selectivity for iodide as this anion is a better halogen bond acceptor (Figure 3G).

Conclusions

From the above, it should be obvious that the CuAAC reaction took off so quickly in the synthesis of MIMs precisely because of its status as the archetypal click reaction. The field was poised to adopt this approach in part because of the structural flexibility its practitioners typically adopt—the only requirement is that the molecule can be made and that it achieves the desired function. This, combined with the sometimes-beneficial properties of the triazole moiety formed, have allowed the CuAAC reaction to become the reaction of choice in MIM synthesis.

COPPER-FREE ALKYNE-AZIDE CYCLOADDITION REACTIONS FOR THE SYNTHESIS OF MIMS—COOPERATIVE CAPTURE

The CuAAC reaction has its non-metal-mediated counterpart in the SP-AAC developed by Bertozzi and co-workers.[5] Although the latter has been used to stopper a pseudorotaxane by Hoogenboom and co-workers,[45] another Cu-free triazole-forming reaction that meets the definition of a click reaction is much more commonly used in the synthesis of interlocked molecules.

In 1983, Mock and co-workers observed that cucurbituril-6 (CB6, **20**, Figure 4), a hexameric cyclic glycouril oligomer, accelerates the Huisgen cycloaddition reaction between alkynes and azides bearing proximal ammonium units, a reaction later dubbed the CB-mediated alkyne-azide cycloaddition (CB-AAC) reaction.[46] The ammonium units are essential because these polarized functional groups interact with the dipoles of the carbonyl groups that line the portals of the CB, leading to co-inclusion of the substrates within the barrel-shaped macrocycle. Steinke and co-workers later demonstrated that the CB-AAC reaction could be used to synthesize rotaxanes[47] and polyrotaxanes[48] effectively when the ammonium unit was substituted with a bulky stopper. The same reaction has since been applied by Au-Yeung to the synthesis of catenanes.[49]

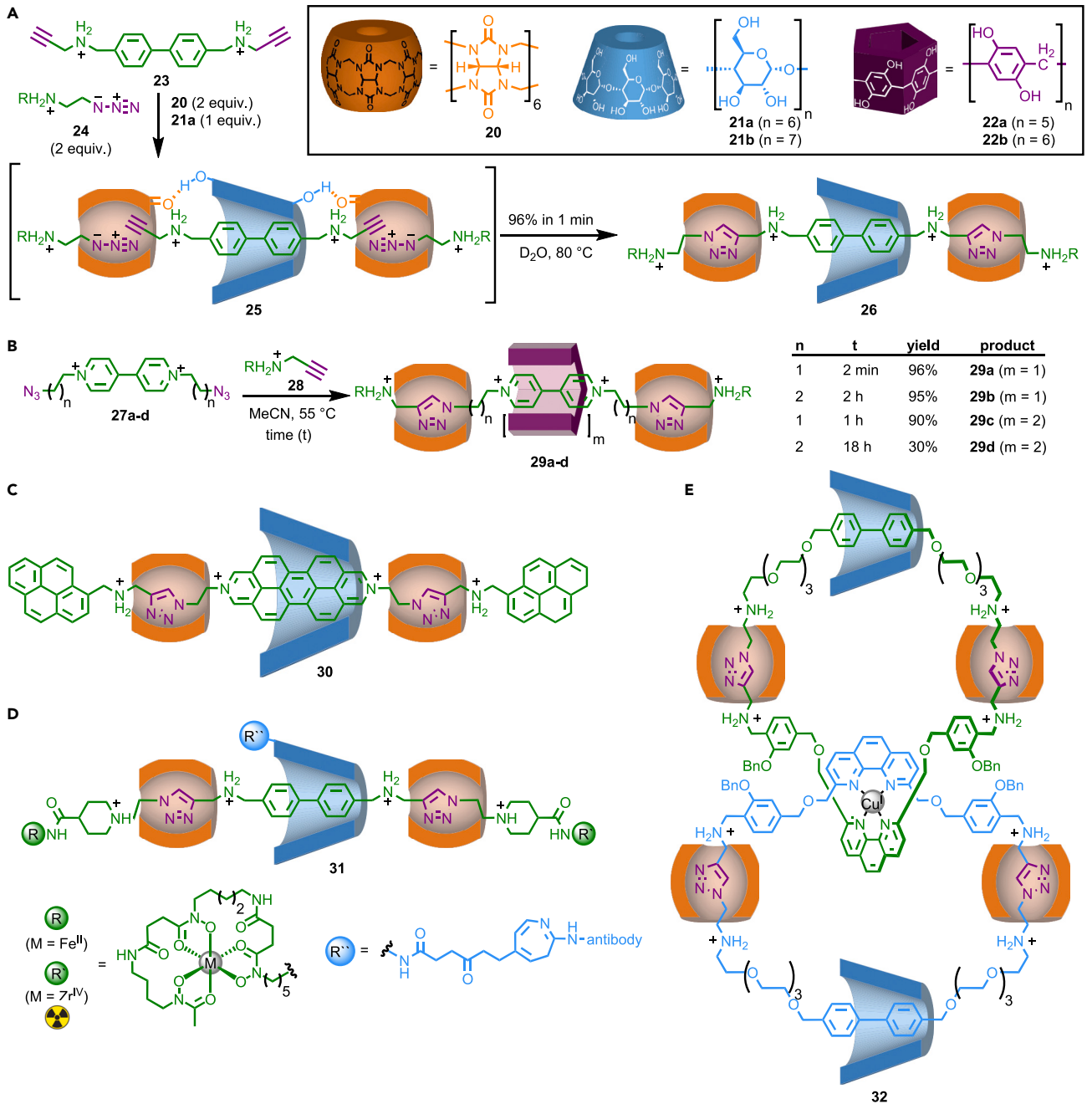

Figure 4. The cooperative capture approach (CC-AAC) for the synthesis of catenanes and rotaxanes

(A) The CC-AAC reaction between 23 and 24 mediated by macrocycles **20** and **21** via proposed intermediate **25** (key H-bonding interactions between macrocycles indicated) to give rotaxanes **26**.

(B) The effect of substrate structure on the product distribution in the CC-AAC reaction mediated by P5A (**22a**).

(C) Stimuli-responsive fluorescent rotaxane **30** synthesized using the CC-AAC reaction.

(D) A targeted rotaxane-based radiotracer synthesized using the CC-AAC reaction.

(E) [8]catenane **32** assembled in a single step using the CC-AAC reaction.

Although the CB-AAC reaction for the synthesis of rotaxanes proceeds in reasonable yield, Stoddart and co-workers' "cooperative capture"[50] AAC (CC-AAC) reaction, in which a second macrocycle that can hydrogen bond to the carbonyl units of the CB6 ring is included in the reaction mixture, approaches the click ideal in terms of

specificity, rate, and reaction conditions. In their first report of CC-AAC approach,[51] Stoddart and co-workers showed that combining CB6 with cyclodextrin (CD) macrocycles (**21**), cyclic oligomers of glucose, in a 2:1 ratio ensured that the reaction between bis-alkyne **23** and azide **24** (2 equivalents) yielded corresponding hetero[4]rotaxane **26** quantitatively in only 1 min (Figure 4A). Both β-CD (**21a**) and γ-CD (**21b**) macrocycles, which differ in the number of glucose units, were suitable for the reaction. In contrast, although the same reaction, when the CD ring was omitted, produced the corresponding [3]rotaxane through the CB-AAC reaction, it was not complete even after 1 week. The relatively high reaction temperature used in this first report was necessitated by the low solubility of azide **24** in water.

The authors rationalized the spectacular rate enhancement observed under CC-AAC conditions by noting that the hydrogen bonding interactions between the CB6 and CD rings preorganize the substrates to favor the desired reaction; in proposed intermediate **25**, the alkyne and azide moieties are bound within the CB6 rings due to dipole-dipole interactions, and the biphenyl of the bis-alkyne is included within the CD ring due to the hydrophobic effect, allowing the ensemble to be stabilized by the H-bond network between macrocycles (Figure 4A). Thus, the requirements for a successful CC-AAC synthesis is for the substrates to interact favorably with the macrocycles and the macrocycles to interact favorably with one another through H-bonding.

The authors demonstrated that this principle was general by replacing the β-CD ring with Ogoshi's[52] phenolic pillararene macrocycles (**22**), cyclic oligomers of hydroquinone, the OH groups of which can also engage in H-bonding with CB6 (Figure 4B).[53] Interestingly, whereas the pentamer, P5A (**22a**), produced corresponding [4]rotaxane **29** in 96% in 2 min, with hexamer P6A (**22b**) the yield of [4]rotaxane was much lower (38%). The authors rationalized this observation by noting that the CB6 and P6A rings suffer from a size mismatch; indeed, crystallographic analysis of a CB6-P6A [4]rotaxane revealed that only 4 of the possible 6 H-bonds were observed.

The pillararene modification of the CC-AAC synthesis has both advantages and disadvantages. On the positive side, it is much more tolerant of substrate structure than the parent CB-AAC reaction, which relies on the use of ethylammonium azides and propargyl ammonium substrates, and the CC-AAC reaction with CD rings, both of which fail when the distance between the alkyne and azide functional groups and the ammonium unit is varied. In contrast, the P5A-mediated CC-AAC reaction still proceeds well (95%) when 3 methylene units separate the azide and the charged N of the viologen unit, and when four methylenes are used, the corresponding [5]rotaxane containing two P5A units is formed in excellent (90%) yield (Figure 4B). The challenge in these reactions arises due to the difference in solubility between the P5A and CB6 rings, the former of which is soluble in polar organic media and the latter in water. This problem can be solved by preforming the CB complex of one of the reaction substrates in water followed by anion metathesis with a lipophilic counteranion, which results in an organic-soluble complex that can then be employed in the CC-AAC reaction in MeCN.

The CC-AAC reaction genuinely approaches the click ideal set out by Sharpless and co-workers[1] in that it is highly selective and proceeds to give the desired product rapidly and in exceptionally high yield, and can even be conducted in water. Indeed, in their first report,[51] Stoddart and co-workers showed that it could be used to produce high molecular weight polyrotaxanes in a single step with up to 64 rings encircling the axle—a result that highlights the efficiency of the CC-AAC reaction. Given this, it is unsurprising that several applications of this methodology have been

reported for the synthesis of complicated products with interesting properties, selected examples of which are discussed below, have been reported; indeed, if anything, the CC-AAC reaction seems under-used given its potential.

Stoddart and co-workers synthesized fluorescent rotaxane **30** (Figure 4C) using the CC-AAC reaction mediated by CB6 and γ-CD and showed that the fluorescent output of **30** was altered by the presence of the encircling rings.[54] Specifically, the rings encircling the axle controlled the aggregation of the fluorescent axle, resulting in a higher quantum yield of the interlocked product. This effect could be reversibly enhanced by the inclusion of the stopper units within additional CD rings, resulting in a stimuli-responsive luminescent response. More recently, Holland and d'Orchymont have made use of the CC-AAC reaction to assemble mechanically interlocked radiotracers such as **31** (Figure 4D)[55–57] in which the mechanical bond is used to link the metal-binding moiety and the targeting unit. In addition to providing a new way to assemble the radiotracer components efficiently, the mechanical bond was shown to alter the degradation pathways of the radiotracer, offering a new way to alter the pharmacokinetic properties of these important species. It is noteworthy that the CC-AAC reaction remains efficient even when the CD ring is functionalized—the same authors recently reported an extended reaction scope study in which they also probed the mechanism of the CC-AAC process.[58] Finally, the CC-AAC reaction is particularly suited to the synthesis of structurally complicated rotaxanes and catenanes, as demonstrated by Au Yeung and co-workers in the synthesis of an [8]catenane **37** in 72% yield (Figure 4E).[59] Not only is the high yield of the product noteworthy, but the CC-AAC conditions also do not interfere with the Cu-phenanthroline template.

Conclusions

Although the CB-AAC reaction has been used to synthesize both rotaxanes and catenanes, the CC-AAC modification is far more efficient, allowing access to complicated, functionalized, interlocked molecules rapidly and in high yield. Although both are limited to CB6 macrocycles and substrates bearing a charged group near to the azide and alkyne functional groups, the ability to assemble interlocked molecules in water in high yield has obvious potential as attention turns to the biological applications of MIMs, as shown by Holland and d'Orchymont.

CLICK REACTIONS AND ACTIVE TEMPLATES—THE AT-CuAAC REACTION AND BEYOND

In addition to passive template strategies, so-called "active-template" strategies have been developed.[30] The latter differ from the former in that they are examples of kinetic templating; the interactions that organize the subcomponents also accelerate the bond-forming reaction, meaning that this takes place faster through the cavity of the macrocycle than anywhere else in solution, resulting in the interlocked product.

The first such active-template reaction was reported by Leigh and co-workers in 2006.[31] They used pyridine-containing macrocycle **33** in which the N donor projects into the cavity to bind a Cu^{I} ion to mediate the CuAAC reaction between half axles **34** and **35** (Figure 5A). The authors showed that not only does this active-template CuAAC (AT-CuAAC) reaction yield target rotaxane **36** in good yield with one equivalent of all of the components, but that the yield, based on macrocycle **33**, can be increased to essentially quantitative when an excess of half axles was used. The loading of Cu^{I} could also be reduced to 20 mol % without a significant reduction in yield. Neither of these changes would be possible using a traditional passive

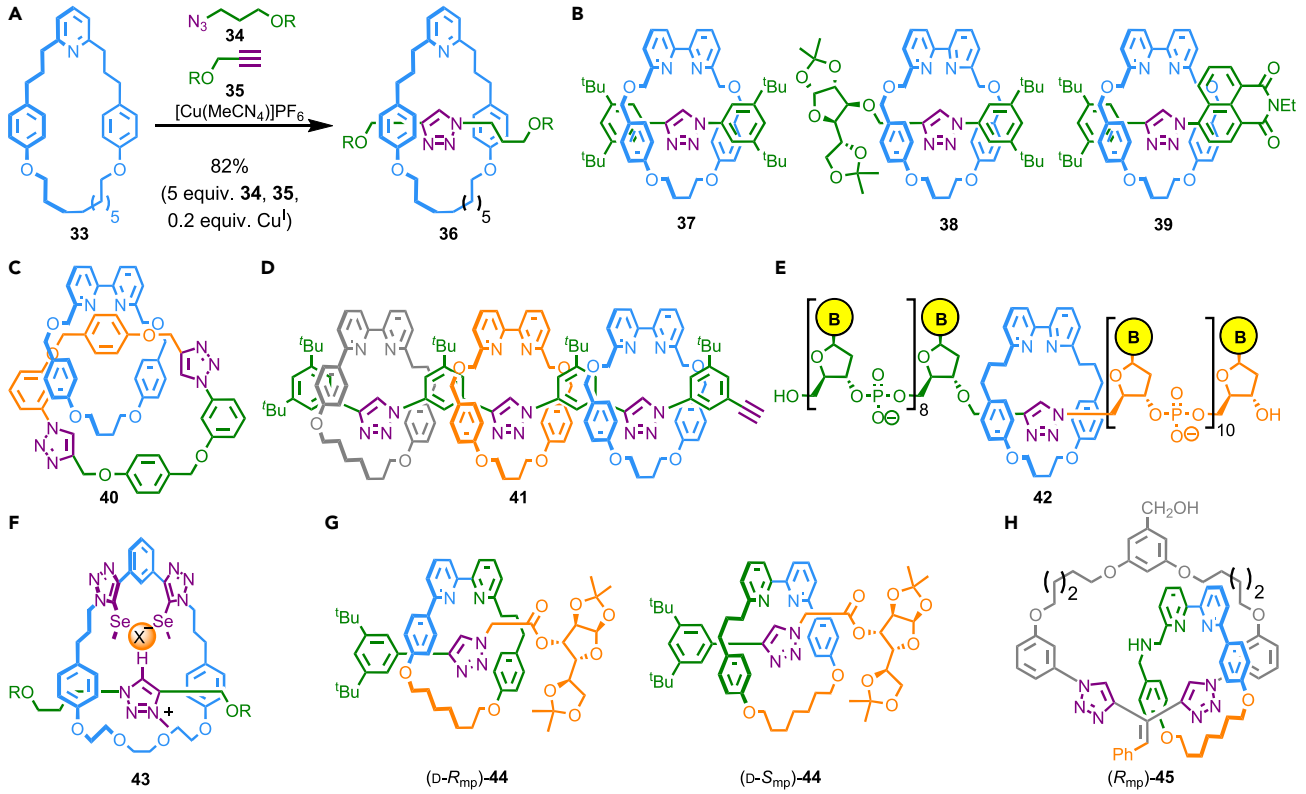

Figure 5. The active-template CuAAC (AT-CuAAC) in MIM chemistry

(A) Leigh's first AT-CuAAC synthesis (R = -4-C_6H_4-C(4-^{t}Bu-C_6H_4)) using substoichiometric Cu^I.

(B) Examples of sterically hindered [2]rotaxanes available using the AT-CuAAC reaction with small bipyridine macrocycles.

(C) Multicomponent catenane **40** synthesized using the AT-CuAAC reaction under pseudo-high dilution conditions.

(D) [4]rotaxane **41** containing three different macrocycles synthesized in high yield using an iterative AT-CuAAC approach.

(E) Oligonucleotide rotaxane **42** synthesized using the AT-CuAAC reaction in water (B = DNA base).

(F) Chalcogen bonding rotaxane **43** that acts as a host for anions synthesized using the ring triazole moieties as ligands for Cu^I (R = -4-C_6H_4-C(4-^{t}Bu-C_6H_4)).

(G) Mechanically epimeric rotaxanes **44** that differ in the configuration of the mechanical bond that could be separated by simple flash chromatography (the "mp" suffix refers to the mechanically planar chiral stereogenic unit; D refers to the configuration of glucose that was used to produce the chiral acetonide stopper).

(H) Mechanically planar chiral catenane **45** in which an exocyclic double bond defines the orientation of one of the macrocycles synthesized stereoselectively using the AT-CuAAC reaction.

template—the nature of the active-template approach allows it to function with substoichiometric template and allows macrocycles involved in "failed" coupling steps to be recycled by reaction with additional half axle components.

As might be expected, the AT-CuAAC reaction inherits many of the advantages associated with the parent click reaction. Goldup and co-workers demonstrated that, when smaller bipyridine-based macrocycles are used, the approach shows broad substrate scope (e.g., 37–39, Figure 5B) and that yields can approach quantitative in some cases.[60] Over a series of articles, Goldup and co-workers optimized the process to be rapid, suitable for a range of macrocycle sizes and structures (albeit all within the bipyridine series),[61] and proceed in a variety of solvents including under aqueous conditions.[62] Increasing the reaction rate allowed the AT-CuAAC reaction to be used to produce catenanes,[63] including examples assembled from multiple components (e.g., **40**, Figure 5C), under pseudo-high dilute conditions, in excellent yield. The high yield possible in each mechanical bond-forming step was

showcased in the iterative synthesis of oligorotaxanes, including an example with three different macrocycles arranged along a single axle (**41**, Figure 5D).[64]

Given these advantages, unsurprisingly, the AT-CuAAC reaction has been used for the synthesis of a number of structurally complicated MIMs and functional targets. Leigh and co-workers[29] used it as the final mechanical bond-forming step in the synthesis of rotaxane **10** and later analogs. Goldup and co-workers used the AT-CuAAC reaction to synthesize sensors for both anions[65] and cations[39] (e.g., **16**) and triazole-based mechanically chelating ligands, as well as the synthesis of DNA-based rotaxanes under aqueous conditions (e.g., **42**, Figure 5E).[66] Beer and co-workers have used various Cu-binding motifs to synthesize interlocked molecules using the AT-CuAAC reaction as hosts for anions that incorporate triazolium (H-bond donor), iodotriazole (halogen bond donor),[67,68] and selenotriazole (chalcogen bond donor)[69] in their anion binding pocket (e.g., **43**, Figure 5F).

A particular advantage of the active-template approach is that it, in principle, allows the synthesis of sterically congested interlocked products; in contrast to passive template approaches, active-template reactions do not require the formation of a thermodynamically favored threaded intermediate, which is disfavored by steric congestion, only that the path from starting material to the threaded product be kinetically accessible. The AT-CuAAC reaction is particularly well suited to this application as the thermodynamic driving force for the conversion of the alkyne and azide substrates to the corresponding triazole is extremely high, and the proposed Cu-acetylene-azide first intermediate of the reaction does not incur the same steric congestion as the product. Applying the Hammond postulate, the high driving force suggests that the transition state for the reaction will be "early" and so starting material-like in terms of steric congestion, which, combined with the high overall driving force that renders triazole formation functionally irreversible under synthetic conditions, allows the synthesis of sterically congested products.

This feature was demonstrated by Goldup and co-workers[60] in their exploration of the effect of macrocycle size and substrate scope; rotaxane **37** (Figure 5B) was produced in essentially quantitative yield with only one equivalent of all reaction components, despite the sterically congested nature of the structure. The benefit of such "small" MIMs is that they effectively maximize the effect of the mechanical bond—it is a simple thought experiment to realize that effect of the mechanical bond on the properties of catenanes composed of infinitely large rings will be negligible and very large in the case of molecules composed of very small rings. This principle is important when considering chemical applications of MIMs, for example, as multivalent hosts or ligands for which preorganization is important.

Goldup and co-workers have taken advantage of this feature to develop syntheses of mechanically chiral molecules—structures that are chiral solely as a result of the mechanical bond[70,71]—that rely on the formation of mixed covalent-mechanical diastereomer intermediates. In their first reported example, rotaxane **44** (Figure 5G), which contains both a mechanically planar chiral and several covalent stereogenic units, was produced as an equimolar mixture of diastereomers that could be separated by flash chromatography.[72] Subsequent removal of the covalent stereochemistry by aminolysis with an achiral amine gave rise to the first enantiopure mechanically planar chiral rotaxanes produced without recourse to chiral stationary phase high-performance liquid chromatography (HPLC) during their synthesis. It is important to note that the use of flash chromatography to separate the diastereomers of **44** was only possible because the diastereomerism was well expressed, which the

authors attributed to the sterically crowded nature of the structure—although mixed covalent-mechanical diastereomers had been reported previously, their separation was either not attempted or required HPLC.[70] The same group later demonstrated that, with suitably designed substrates, it was possible to form the mechanical bond diastereoselectively using the AT-CuAAC reaction, which suggests that the covalent stereochemistry and incipient mechanical stereogenic unit interact to affect the kinetics of the available diastereomeric AT-CuAAC pathways. This approach has allowed the stereoselective synthesis of mechanically planar chiral[73–78] and mechanically axially chiral[79] catenanes and rotaxanes. In one recent example to stand for all, mechanically planar chiral catenane **46** in which the stereogenic unit arises due to the sequence of atoms in the bipyridine macrocycle and a trisubstituted exocyclic double bond in the triazole-containing ring was synthesized in 98% diastereomeric excess (*de*) in the mechanical bond-forming step (Figure 5H).[80]

Our discussion of the active-template approach has focused on the AT-CuAAC reaction, partly because of the focus of this article on click reactions but also because it is the most widely applied, precisely because of its click-like qualities of generality and high yield. However, it should be noted that other covalent bond-forming reactions have been demonstrated in an active-template modification.[30] Of particular note in our discussion of click concepts are the crown-ether-mediated organocatalytic active-template reactions developed by Leigh and co-workers,[81] many of which are modifications of reactions that meet some if not all click requirements. All examples make use of the tendency of neutral amines to interact weakly with crown-ether rings, which both increases the polarization of the N-H bond and stabilizes the transition states of reactions in which the nitrogen acts as a nucleophile. Thus, when the amine and electrophile are paired such that they react with one another slowly in the absence of the crown ether (i.e., the amine should be relatively electron deficient and so only weakly nucleophilic and the electrophile should not be activated), in the presence of the crown ether, the reaction takes place through the cavity to produce the corresponding rotaxane.

The first such organocatalytic active template was reported in 2017 and concerned the nucleophilic attack of an amine to a cyclic sulfate mediated by a crown-ether macrocycle modified to interact with both substrates to produce rotaxanes of the form of **49** (Figure 6A).[82] Later reports have made use of simple crown ethers, including commercially available examples (e.g., **50**, Figure 6B), to mediate the formation of rotaxanes through amine alkylation,[83] acylation, carbamate, urea, sulfonamide, and phosphoramide formation.[81] All but the amine alkylation reaction would qualify as click reactions (high driving force, highly selective, can be carried out under simple conditions with simple purification) in their non-active template guise, and, indeed, the products are mostly formed in high isolated yield. Even amine alkylation, which in its non-active-template guise fails the click test due to the potential for over-alkylation, proceeds highly selectively because this side reaction is suppressed by the mechanical bond in the product.

Given its recent introduction, there are relatively fewer applications of these active-template crown-ether-mediated amine functionalization reactions. That said, Leigh and co-workers used this reaction as a component of an autonomous chemically driven molecular pump,[84] and a modification of this strategy could be used synthetically to iteratively pump macrocycles onto an axle to produce oligorotaxanes (e.g., **51**, Figure 6C).[85] They also demonstrated the direct enantioselective synthesis of mechanically planar chiral rotaxane **55** through the use of an acyl donor (**54**) bearing a chiral leaving group (Figure 6D).[86] Most recently, Tian, Zhu, and co-workers used

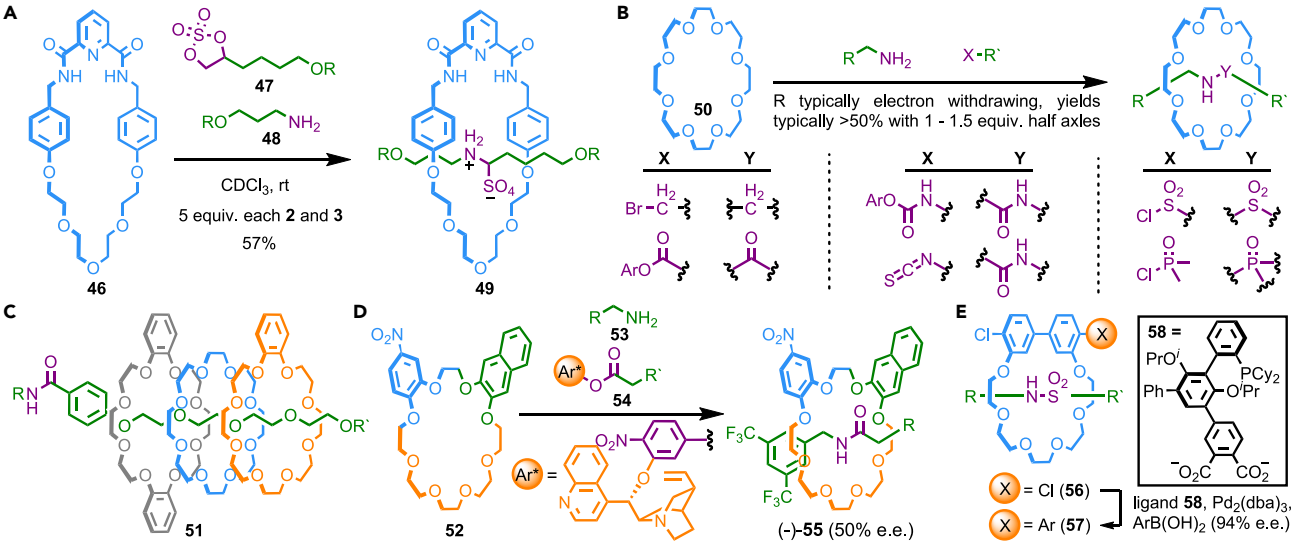

Figure 6. Organocatalytic active-template reactions that rely on crown-ether-amine interactions to mediate click-type processes

(A) The first reported organocatalytic active-template reaction (R = $C(O)CH_2C(4\text{-}Cl\text{-}C_6H_4)$).

(B) Examples of the wide variety of amine functionalization active-template reactions mediated by simple crown-ether macrocycles.

(C) Hetero[4]rotaxane **51** synthesized using an iterative amide formation active-template pumping protocol (R = $CH_2(3,5\text{-}di\text{-}CF_3C_6H_3$, R' = 3,5-di-tBu-$C_6H_3$)).

(D) The single step synthesis of mechanically planar chiral amide rotaxane **55** using a chiral leaving group active-template strategy (R = $CH_2(3,5\text{-}di\text{-}CF_3C_6H_3$), R' = $C(4\text{-}C_6H_4Cl)_3$).

(E) The enantioselective catalytic desymmetrization of rotaxane **556** synthesized using an active-template amide forming reaction (R = $CH_2(3,5\text{-}di\text{-}CO_2H\text{-}C_6H_3$), R' = 3,5-di-$CF_3C_6H_3$).

these reactions to produce prochiral rotaxanes (e.g., **56**) that could be enantioselectively desymmetrized to yield mechanically planar chiral rotaxanes in up to 94% enantiomeric excess (ee) (Figure 6E).[87]

Conclusions

The AT-CuAAC approach inherits many of the click advantages of the parent Nobel prize-winning reaction; it has broad substrate scope, often proceeds in very high yield, and can even take place in water. It has been used to make functional molecules and complicated structures that would be very hard to access in other ways. More generally, active-template modifications of other click reactions, such as amine acylation, have begun to emerge. Although active-template reactions based on other reactions have been reported, it seems sensible to suggest that click-type processes are particularly well suited to active-template modifications, as long as they can be directed through the cavity of a macrocycle.

CONCLUSIONS—FUTURE DIRECTIONS FOR CLICK REACTIONS IN THE SYNTHESIS OF MIMS

As discussed above, chemists working on the synthesis of interlocked molecules were well placed to adopt click concepts and the archetypal CuAAC reaction itself given the structural flexibility of the targets under consideration. As a consequence, triazole motifs are now ubiquitous in MIM chemistry, where they are installed to facilitate the synthesis of MIM precursors, in the mechanical bond-forming step itself or as functional motifs in their own right. Variations on the CuAAC reaction, most prominently, the copper-free cooperative capture (CC-AAC) and the active-template CuAAC (AT-CuAAC) reactions, are also having a significant impact on the variety and quantities of MIMs that can be readily synthesized.

The drive to make the synthesis of MIMs as efficient as possible is linked to the development of applications of catenanes and rotaxanes—if such large molecules are to be genuinely useful, their synthesis must be streamlined to maximize the cost-benefit relationship.[88] This is important given that MIMs have been proposed to be useful in a range of areas, including materials science,[89] catalysis,[90] and biology,[91] as well as components of molecular machines,[92] but they will never achieve their potential if they are only available in vanishingly small quantities.

To aid this transition, the discussion above suggests that "click" concepts could be considered more explicitly in the synthesis of functional catenanes and rotaxanes—although the CuAAC reaction has been wholeheartedly adopted and many "old" click reactions (such as amide, urea, and carbamate formation) are widely used in the field, there are limited examples of more recently identified click processes such as the thiol-ene and nitrile oxide cycloaddition reactions; although these reactions are widely used in materials science,[93,94] they remain relatively rare in the synthesis of MIMs.[95–100] The rapid success of the CuAAC reaction suggests that there are other click processes waiting in the wings to facilitate the synthesis of functional MIMs and thus their progress toward being truly useful molecules.

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AUTHOR CONTRIBUTIONS

S.M.G. and A.S. planned the manuscript, prepared the text, and commented on final drafts.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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