ACS Catalysis

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Rotaxane Catalysts

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INTRODUCTION

Rotaxanes are molecules composed of one or more macrocycles threaded onto one or more axles that bear bulky stoppers to prevent the macrocycles from slipping off.[1] The first syntheses of rotaxanes were reported in 1967 by Schill and Zollenkopf,[2] using multistep synthesis, and by Harrison and Harrison,[3] through a statistical approach, both of which gave very modest yields of the interlocked products. The properties of rotaxanes have attracted many groups, including ourselves, to build on those early reports and contribute to the development of strategies for assembling them on a preparative scale,[4,5] facilitating their study for a range of potential applications.[6−16] Accordingly, rotaxanes lie at the heart of many designs for molecular machines, including rotors,[6] muscles,[7] switches,[8] motors,[9] and shuttles,[10] and they are able to perform distinct tasks[11] including information storage,[12] mechanical work,[13] fluorescence switching,[14] the control of binding events,[15] and the controlled-release of guest molecules.[16]

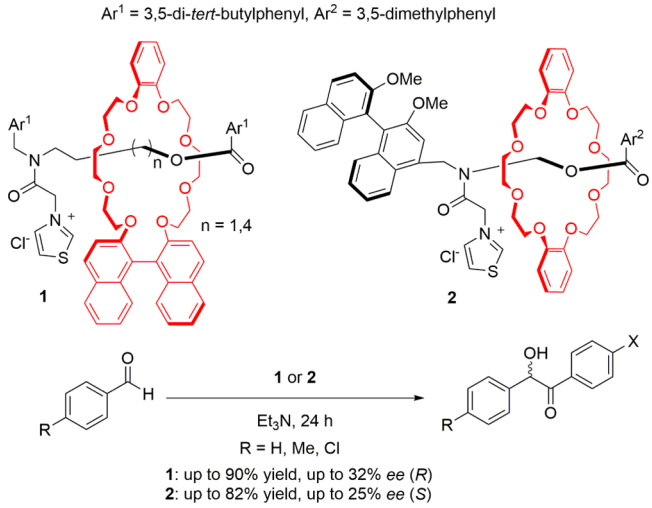
Supramolecular catalysis[17] is a growing area that is benefiting from developments in both supramolecular chemistry and homogeneous catalysis. In the past decade, rotaxanes have been combined with catalytic units to take advantage of the dynamics and/or chemical environment provided by the mechanical bonding of the components. In this Viewpoint, we outline and discuss the state-of-the-art in rotaxane catalysts, grouping systems by the type of catalysis performed (employing metal ions or organocatalysis) and their different modes of operation (for example as switchable or processive catalysts). We conclude by considering future outlooks for the field.

CATALYTIC MOTIFS ON ROTAXANE SCAFFOLDS

The first rotaxane catalysts and their application in asymmetric benzoin condensations were reported by Takata and colleagues in 2004 (Scheme 1).[18] A chiral binaphthyl unit in the macrocycle (**1**) or in the thread (**2**) of a rotaxane induced modest stereoselectivity in reactions mediated by a thiazolium salt moiety in the axle (Scheme 1). Rotaxane catalyst **2** was found to generate higher enantioselectivities in the reaction than the noninterlocked thread counterpart, indicating that the rotaxane macrocycle enhances the stereoselectivity of the catalyzed reaction.

In 2010, Berná and co-workers described a [2]rotaxane (**3**) that catalyzes an ester bond forming reaction that also results in a change in the position of the ring on the rotaxane axle (Scheme 2).[19] The two-station rotaxane **3** acts as an organocatalyst through a cyclic pathway involving translocation of the ring between the azodicarboxamide and succinic amide ester stations. Triphenylphosphene attack on the azodicarboxamide station displaces the macrocycle to give **3**-PPh_3, which can then catalyze a Mitsunobu reaction to give an ester and the reduced hydrazo-rotaxane **3**-H. Reoxidation with bis(acetoxy)-iodobenzene regenerates rotaxane **3**. The second binding site

Scheme 1. Asymmetric Benzoin Condensation Catalyzed by Chiral Rotaxanes



on the rotaxane thread is necessary for efficient catalysis: using a single-binding-site azodicarboxamide rotaxane (where the macrocycle cannot translocate), the reaction proceeded in poor yield as the macrocycle blocks reaction of the azo group with the triphenylphosphene.

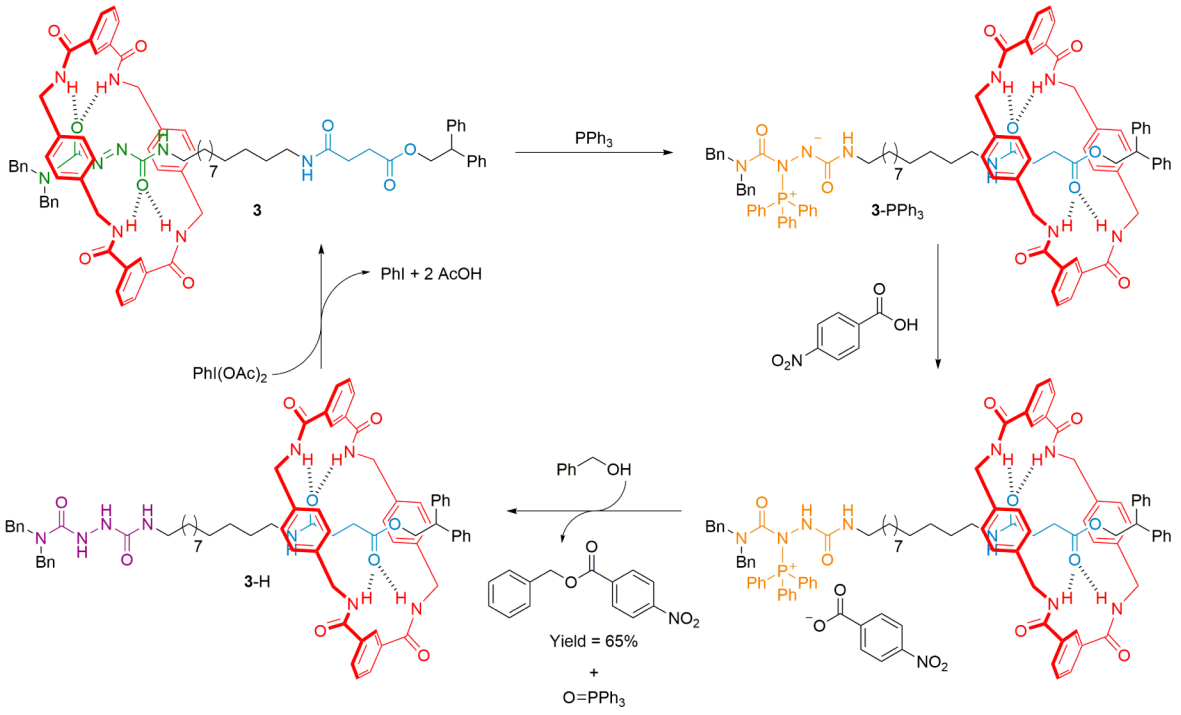
Loeb, Stephan, and colleagues have used the sterically crowded environment of an amine group encapsulated within a rotaxane to develop a novel frustrated Lewis pair for the activation of hydrogen. (Scheme 3).[20] Exposing a mixture of rotaxane **4** and a boron Lewis acid to H_2 led to formation of the protonated rotaxane **4**-H and the corresponding borohydride anion in good yields, consistent with heterolytic activation of H_2 (Scheme 3). The steric hindrance created by the rotaxane architecture is essential to generate the frustrated Lewis pair: when the corresponding free thread counterpart was employed, no activation of H_2 was observed, affording exclusively the classical Lewis acid−base adduct. Although the rotaxane system is not catalytic, it shows the useful effect an interlocked architecture can have on reactivity.

Nishibayashi and colleagues have investigated the use of rotaxane ligands in palladium catalysis.[21] Chiral [2]pseudorotaxane rhodium complex **5** was shown to promote the hydrogenation of enamides in excellent yields and with high enantioselectivies (Scheme 4). Fan and co-workers later employed a pseudorotaxane tridentate rhodium complex as a catalyst in similar reactions achieving similar yields but lower enantiomeric excesses.[22] These systems illustrate the potential of interlocked

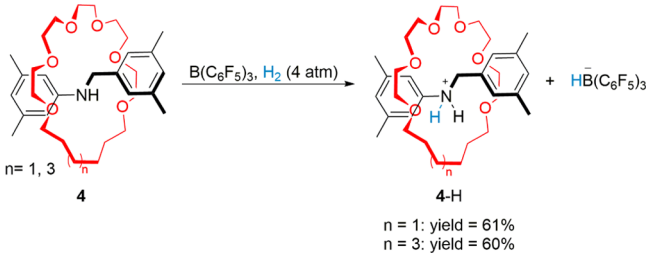
Received: September 6, 2014
Published: November 3, 2014

   dx.doi.org/10.1021/cs5013415 | ACS Catal. 2014, 4, 4490−4497

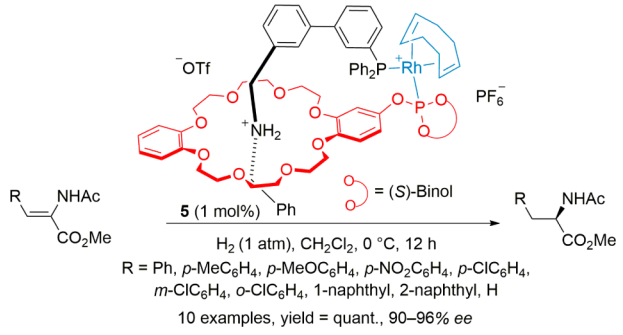
Scheme 2. Mitsunobu Ester Formation Catalyzed by a Molecular Shuttle Catalyst (3)



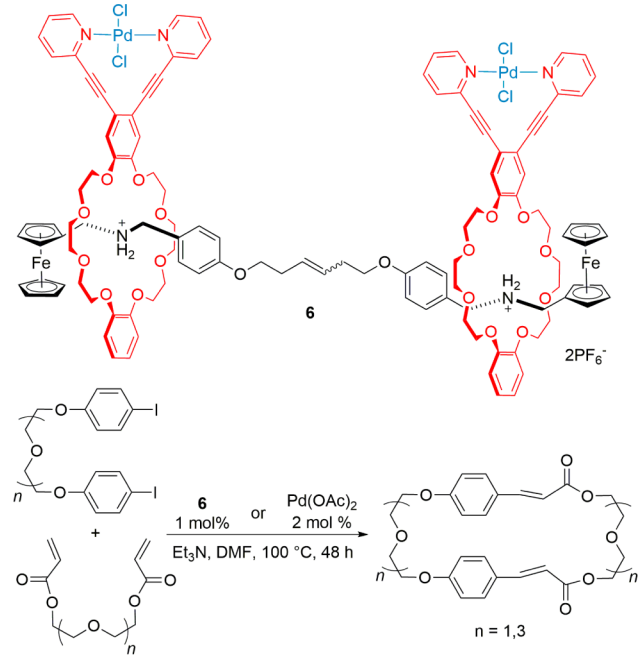
Scheme 3. Heterolytic Activation of H_2 Using a Rotaxane (4) as a Frustrated Lewis Base



Scheme 4. Enantioselective Hydrogenation of Enamides Using a [2]Pseudorotaxane Rhodium Complex (5)



Scheme 5. [3]Rotaxane Dinuclear Palladium Catalyst (6) for a Mizoroki–Heck Ring Closure Reaction



n = 1: Yield (macrocycle:polymer): catalyst **6** = 45:28; $Pd(OAc)_2$ = 32:28

n = 3: Yield (macrocycle:polymer): catalyst **6** = 62:14; $Pd(OAc)_2$ = 54:10

structures in metal catalysis, demonstrating that some chiral pseudorotaxane complexes can provide superior activity and chiral induction to simple macrocyclic systems.

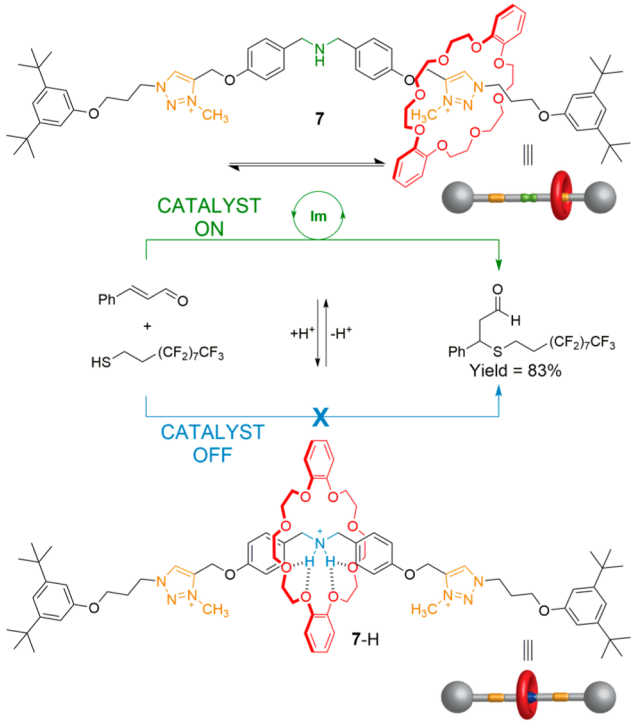
Osakada and co-workers employed a dinuclear palladium [3]rotaxane catalyst (**6**) in the Mizoroki–Heck reaction (Scheme 5).[23] Catalyst **6** afforded more macrocyclic products, as opposed to linear polymers, in the reaction than were formed when using $Pd(OAc)_2$. The authors propose that the mobility of the macrocyclic components of the rotaxane allows the Pd centers to adopt positions that are an optimal distance apart to promote macrocyclization. Although **6** only displays modest improvement over the noninterlocked catalyst, the result nevertheless demonstrates the potential of rotaxane architectures to preorganize reactive groups to favor a particular reaction outcome.

dx.doi.org/10.1021/cs5013415 | ACS Catal. 2014, 4, 4490–4497

SWITCHABLE ROTAXANE CATALYSTS

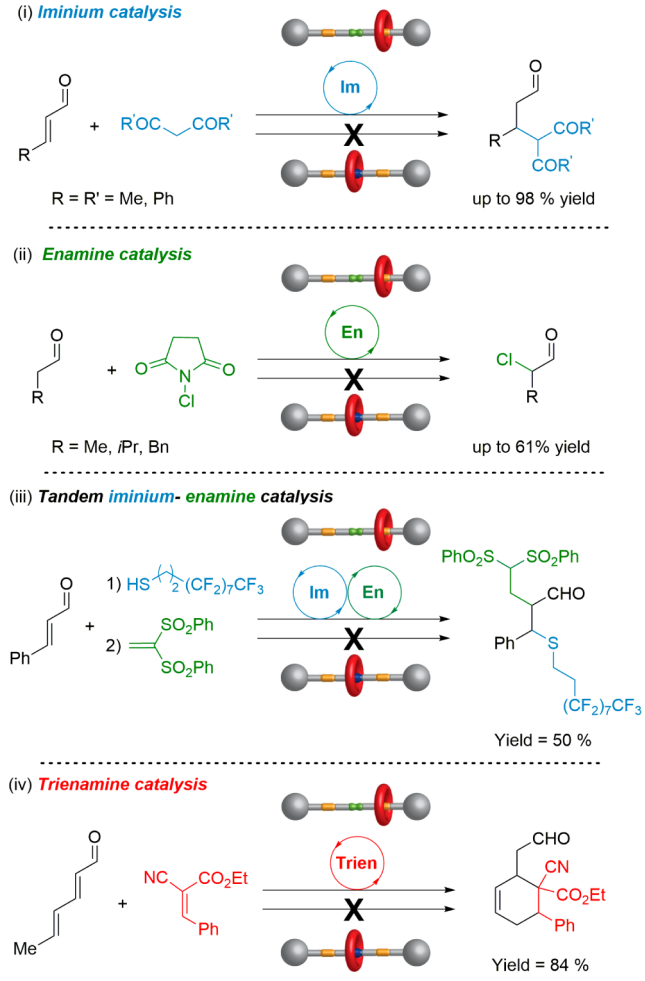
Nature controls enzymatic synthesis through a variety of trigger-induced effects.[24] This has inspired the development of a class of synthetic rotaxane catalysts where an external stimulus can be used to turn "on" or "off" the catalytic activity of the system.[25] Rotaxane **7** consists of a dibenzo-24-crown-8 macrocycle, a dibenzylamine/ammonium moiety which serves as the catalytic unit, and a triazolium ring (Scheme 6). The organocatalytic group can be concealed or revealed, and its activity switched "on" and "off", by the well-defined acid/base-promoted translocation of the macrocycle on the thread. When the rotaxane is protonated, the macrocycle preferentially interacts with the ammonium unit (a better station than the triazolium ring) concealing it, and the system is in its "off" state (Scheme 6, bottom). When the secondary amine is not protonated, the triazolium ring is the preferred binding site for the macrocycle, and so the amine group is exposed and available for catalysis (Scheme 6, top). Switchable rotaxane catalyst **7** was able to very effectively control the rate of the Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde (Scheme 6).

Scheme 6. Controlling the Rate of Michael Addition Using a Switchable Rotaxane Catalyst (7)



In Scheme 6, rotaxane **7** catalyzes the Michael addition through iminium ion activation. However, secondary amines can also act as catalysts through other activation mechanisms.[26] One of the interesting potential applications of switchable catalysts would be to use them to react selectively with particular building blocks within a pool of potential reactants. By switching on and off various types of catalyst in different orders it may then prove possible to carry out sequences of reactions, generating different products from the common building block pool. To accomplish this, it is necessary to establish the different types of reactions and activation modes that are promoted by any particular switchable catalyst. Furthermore, the masking of an axle site in a rotaxane is an intrinsically fluxional process. The dynamic nature of binding interactions and molecular level motions means that for some of the time even in the "off" state the catalytic group of a switchable rotaxane will be exposed and available to participate in reactions. Accordingly rotaxane **7** has been investigated both for its ability to catalyze a variety of reaction types through different organocatalyst activation modes and for its effectiveness in switching "off" catalytic activity (Scheme 7).[27]

Scheme 7. Scope of Switchable Rotaxane Organocatalyst 7 through Different Activation Mechanisms

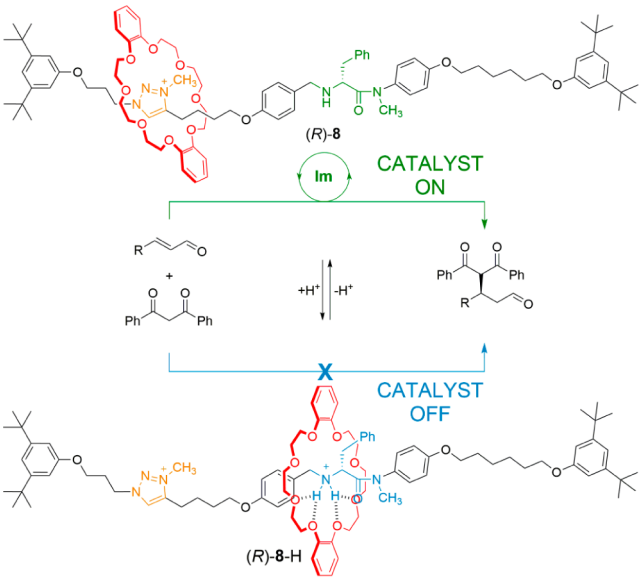


The "on-state" of the rotaxane shows excellent catalytic activity (often 95–98% yields) in the β-functionalization of carbonyl compounds with C- or S-nucleophiles through iminium activation, although the "off-state" of the reaction also promotes the most facile of these transformations to a lesser degree (Scheme 7, i). The "on-state" of the rotaxane is somewhat less effective (40–61% conversions) at promoting nucleophilic addition or substitution reactions via enamine catalysis, but the switching is more effective, with the "off-state" of the catalyst showing no detectable catalytic activity in these reactions (Scheme 7, ii). The rotaxane catalyst is even able to promote tandem iminium–enamine reaction sequence with high efficiency (Scheme 7, iii) and the Diels–Alder reaction of a dienal through a trienamine activation pathway (Scheme 7, iv).

Chiral amines employed as asymmetric organocatalysts are usually cyclic,[28] but pyrrolidine rings form perched, rather than threaded, complexes with crown ethers of the size present in rotaxane **7**, which is not conducive for rotaxane formation.

dx.doi.org/10.1021/cs5013415 | ACS Catal. 2014, 4, 4490–4497

Scheme 8. Controlling the Rate and Stereoselectivity of Michael Addition Using a Switchable Rotaxane Asymmetric Catalyst (8)



R	Conversion (%)[a]	er
Me	60	90:10
Et	70	94:6
*n*Pr	65	93:7

[a]Conversions determined by ^{1}H NMR after 24 h

However, a switchable asymmetric organocatalytic system has been developed that uses a simple acyclic secondary amine housed within a rotaxane architecture (Scheme 8). The acyclic chiral secondary amine promotes an asymmetric Michael addition with stereochemical control comparable to, or better than, commercial cyclic amine organocatalysts at the expense of a slower rate of conversion.[29]

PROCESSIVE ROTAXANE CATALYSTS

A processive catalyst performs several rounds of catalysis before dissociating from the substrate, as exemplified by the ribosome, DNA polymerases and exonucleases.[30] This is different to the mode of action of most heterogeneous and homogeneous catalysts for which distributive catalysis is the norm (i.e., the catalyst dissociates from the substrate after each catalytic event). Nature often employs rotaxane-like architectures to ensure processivity, the threaded structure meaning that a cyclic component must move progressively along a track without dethreading. These biological catalysts are inspiring the development of synthetic systems with similar properties.

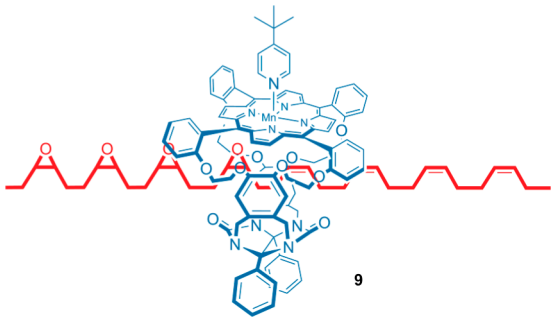
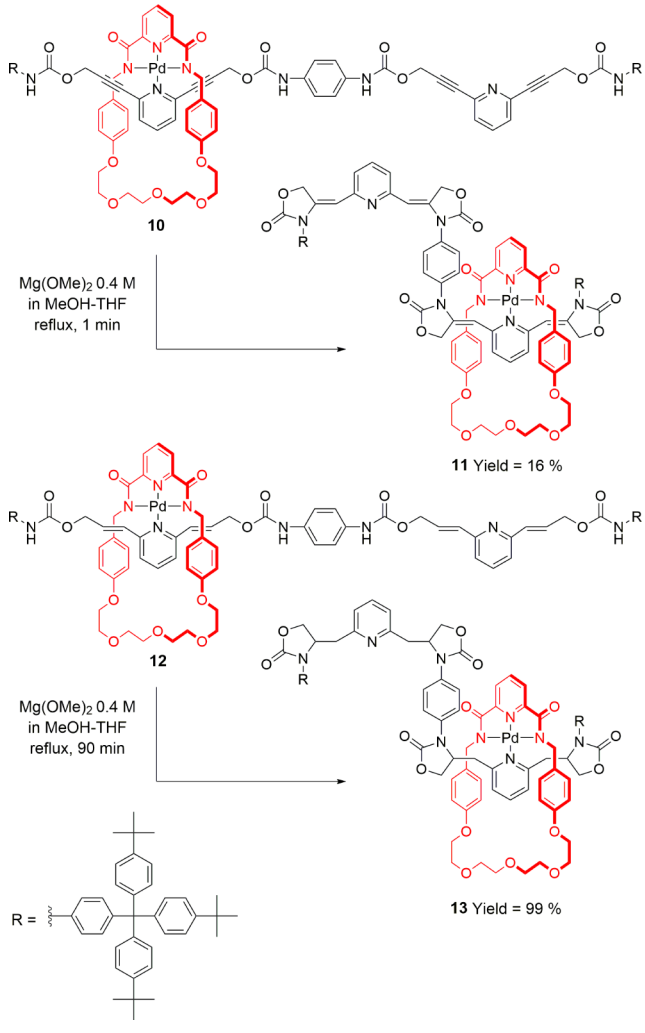


Figure 1. Randomly processive epoxidation of polybutadiene by a threaded macrocyclic manganese porphyrin catalyst.

Nolte, Rowan, and co-workers have demonstrated processive catalysis for the epoxidation of polybutadiene using a synthetic system that employs a catalytically active manganese porphyrin-containing macrocycle threaded on to a polybutadiene thread (**9**, Figure 1).[31,32] Using PhIO to oxidize the Mn ion incorporated within the threaded macrocycle, epoxidation of polybutadiene to polybutadieneepoxide occurs with high stereoselectivity: 80:20 *trans*/*cis*. However, when using a Mn-porphyrin catalyst without a binding cavity the opposite stereoselectivity was observed (20:80 *trans*/*cis*), highlighting the steric demand on the reaction occurring inside the macrocycle cavity. After thorough investigations into the mechanism of threading and diffusion of the macrocycle along the polymeric thread, the authors were able to conclude that the rate of diffusion of the macrocycle along the thread is much greater than the rate of epoxidation.[31b,33] In other words, the catalyst does not act in a sequentially processive fashion, rather it rapidly traverses the length of the polymeric thread randomly reacting or not with alkene groups it encounters. Expanding the cavity size of the macrocycle by using longer spacer groups allowed the rate of macrocycle shuttling to be adjusted.[34]

Takata's group has reported a macrocyclic Pd catalyst that can successively promote the cyclo-isomerization of propargyl (**10**) or allyl (**12**) urethane groups within a thread (Scheme 9).[35]

Scheme 9. Successive Catalytic Cyclo-isomerization of Propargyl (10) or Allyl (12) Urethane Groups within a Thread by a Macrocyclic Pd Catalyst



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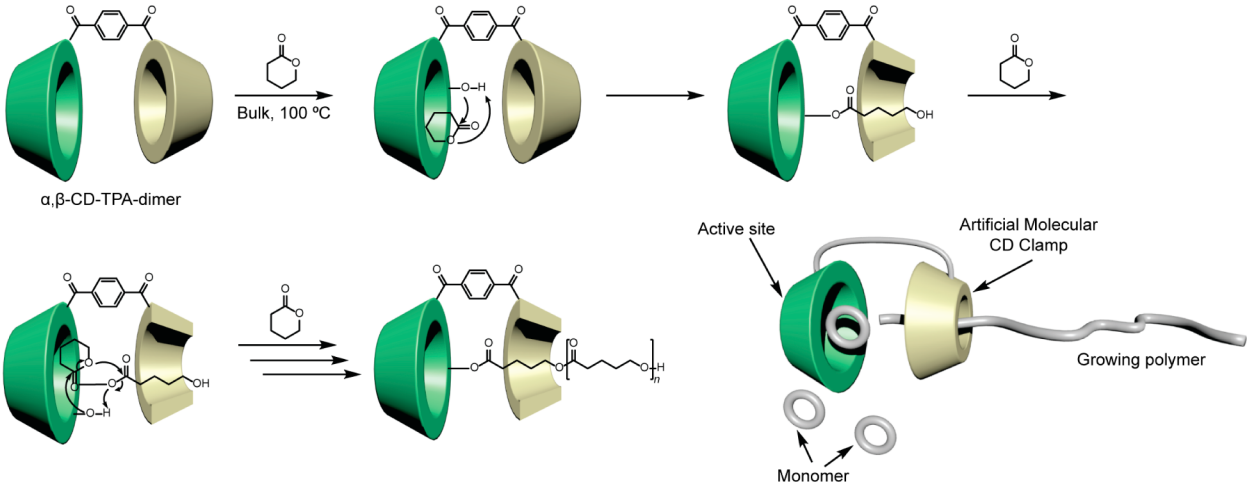
Scheme 10. Polymerization of δ-VL Initiated by an α,β-CD-TPA-Dimer



The reactions were shown to occur exclusively inside the cavity of the macrocycle. The reaction of macrocycle with a stoppered thread gave no isomerization product, although other permutations (stoppered thread with an acyclic Pd complex or unstoppered thread with the Pd macrocycle) afforded product.

As an extension of an early report,[36] Harada and co-workers have described a particularly interesting cyclodextrin (CD) dimer system that acts as an artificial molecular clamp that can polymerize cyclic esters in the absence of cocatalysts or solvents (Scheme 10).[37] Ring opening polymerization of δ-valerolactone (δ-VL) by a CD dimer consisting of α- and β-CDs connected by a terephthalamide (TPA) spacer gave poly(δ-VL) with M_n = 11 000. A mixture of α- and β-CDs displayed low polymerization activity under the same conditions. Studies suggest that the β-CD moiety of the dimer acts as the active site, binding a δ-VL monomer and catalyzing its incorporation into the polymer chain, whereas the α-CD unit threads the growing polymer chain ensuring that addition of the monomer only occurs to one end of the chain (Scheme 10). Studies into the length of the linker showed that if it was too short then monomer recognition was hampered, although if it was too long, then the CD dimer was no longer able to effectively clamp the growing polymer chain.

Recently Nolte, Rowan, and colleagues designed a biohybrid catalyst in which a small molecule catalyst was grafted onto a mutant of gp45—a T4 bacteriophage DNA clamp protein (Figure 2a).[38] The trimeric clamp protein contains a cysteine residue on each monomer unit that acts as a tether for the manganese porphyrin catalyst (Figure 2b). Incubation of supercoiled DNA plasmid with the catalytic clamp in the presence of an oxygen donor resulted in oxidation at sites containing three consecutive adenosine residues.

To monitor the extent of oxidation and determine the mode of catalysis (processive or distributive) the authors developed an elegant probe for oxidation using atomic force microscopy (AFM). Oxidation of the plasmid DNA generates an aldehyde that can then react with a biotin derivative of an aldehyde-reactive probe. Treatment with streptavidin results in the protein binding to the biotinylated sites and the large bulk created by the streptavidin–biotin interaction marks the sites of oxidation and renders them "visible" by AFM. Clusters of streptavidin labels were observed by AFM, indicating a processive catalysis mode of action (Figure 2c). A random distribution along the thread would be expected if only distributive

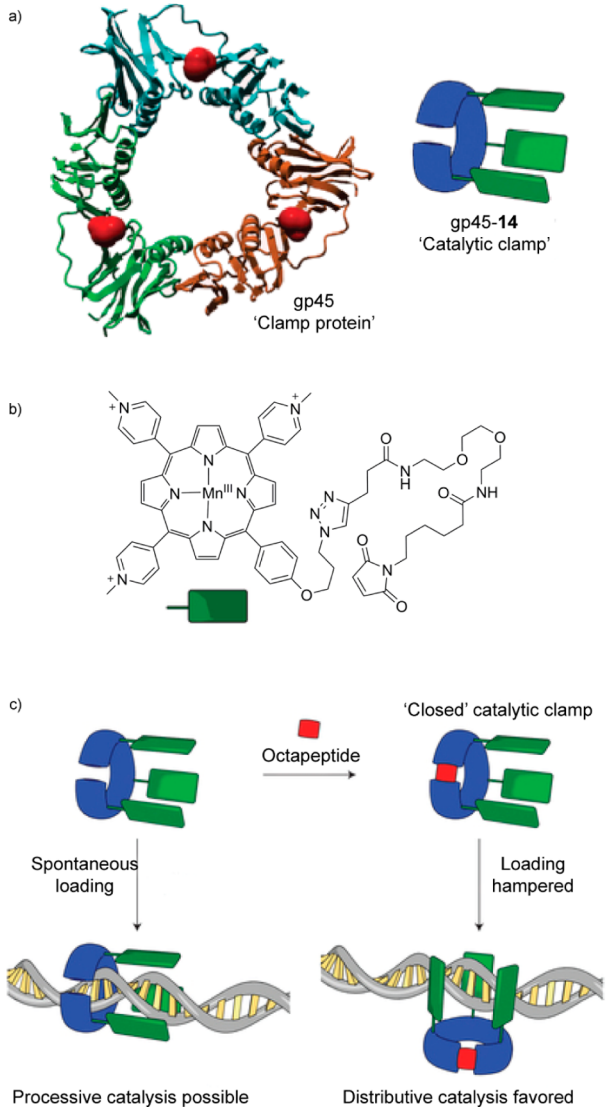
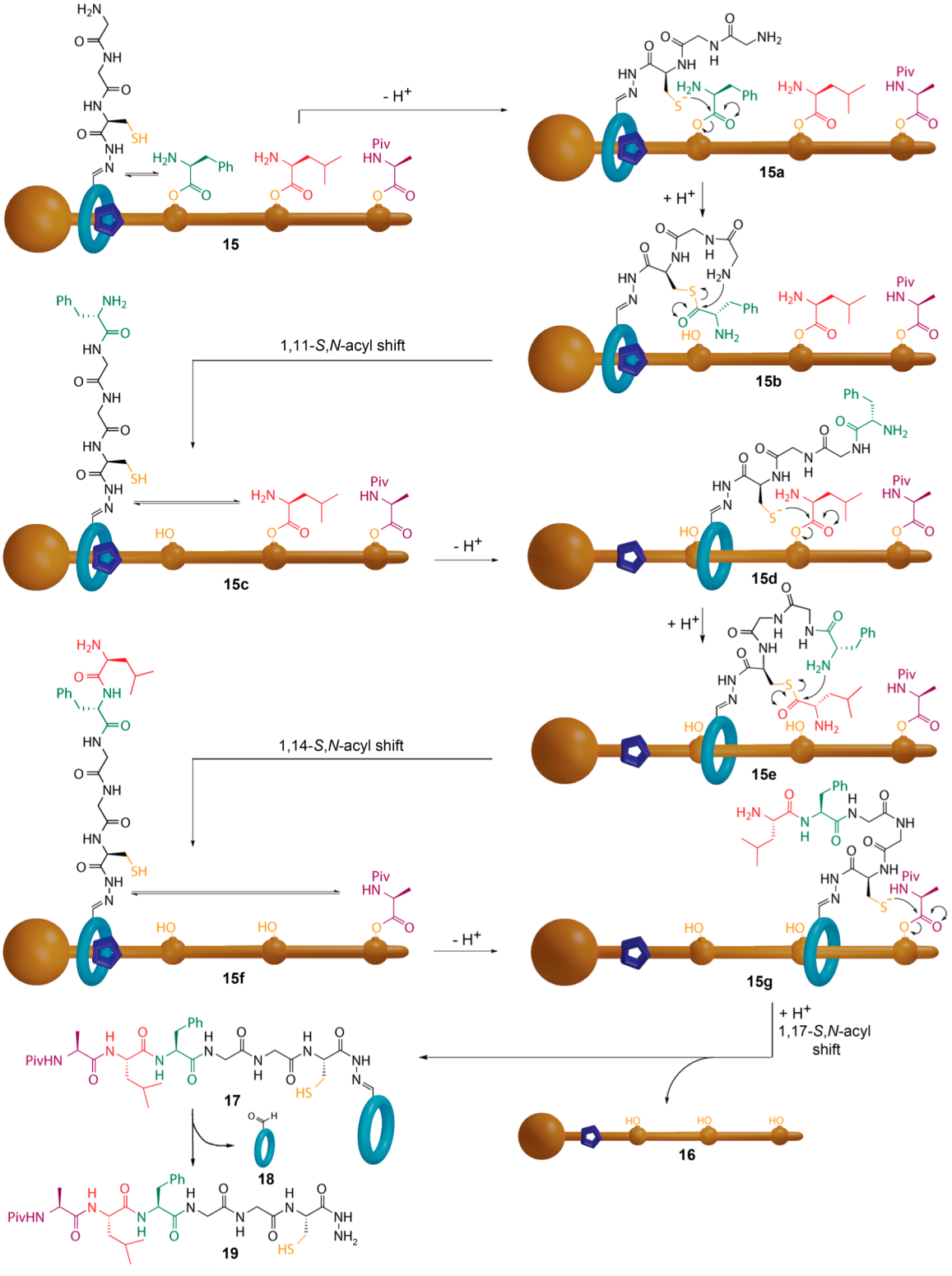


Figure 2. Biohybrid catalyst capable of DNA oxidation. (a) Crystal structure of mutant gp45 protein and cartoon representation of the conjugate catalytic clamp. (b) Porphyrin catalyst. (c) The catalytic clamp can spontaneously load onto DNA, but in the presence of an octapeptide, the loading is hindered. Adapted with permission from ref 38. Copyright 2013 Nature Publishing Group.

dx.doi.org/10.1021/cs5013415 | ACS Catal. 2014, 4, 4490–4497

Scheme 11. Sequential Peptide Synthesis Using a Rotaxane-Based Molecular Machine (15). Reprinted with Permission from Ref 39. Copyright 2013 American Association for the Advancement of Science



oxidation was occurring which, in fact, is observed upon addition of an octapeptide that hampers loading of the clamp (Figure 2c). The principle of grafting synthetic catalysts onto biological systems is clearly a promising strategy for developing novel and productive catalyst systems.

A processive artificial rotaxane-based molecular machine was recently described that successively adds amino acids to a growing peptide chain (Scheme 11).[39] The macrocycle moves along a thread derivatized with amino acid phenolate esters, picking up the groups that block its path and linking them together through successive native chemical ligation reactions to form a new peptide oligomer. The sequence of the product corresponds to the order of the building blocks on the original track.

dx.doi.org/10.1021/cs5013415 | ACS Catal. 2014, 4, 4490−4497

The machine (**15**) comprises a thread that contains amino acid building blocks attached via phenolic ester linkages and a macrocycle bearing both a cysteine residue and an amine site capable of receiving the amino building blocks from successive native chemical ligation reactions. The amino acid residues on the track act as barriers for the macrocycle, ensuring that the macrocycle can only pass after cleavage of each phenolic ester in turn (**15**−**15c**−**15f**−**16**/**17**). As the macrocycle moves along the thread the cysteine thiolate group detaches the next available amino acid phenolic ester to form the corresponding thioester (**15a**−**15b**). The amino acid is transferred to the amine elongation site via an S−N acyl shift (**15c**), simultaneously regenerating the catalytic thiolate group (**15d**). This process continues with each successive amino acid barrier (**15e**−**15f**−**15g**) before the macrocycle slips off the thread with the newly formed single-sequence peptide chain attached (**17**). Hydrolysis liberates the newly formed peptide (**19**) from the macrocycle (**18**). Tandem mass spectrometry confirmed high sequence integrity in the peptide synthesized by the molecular machine.

A key step in the synthesis of molecular machine **15** is the rotaxane formation step using "active metal template"[5] chemistry to ensure that the track does not contain residual binding sites for the macrocycle which would retard its movement during the machine's operation. Preforming a short rotaxane synthon, followed by elongation of the thread, provides an effective route to machines threaded onto more extended oligomer tracks.[40]

FUTURE OUTLOOK

Although the field is still in its infancy, the distinct properties imparted by rotaxane architectures are proving to have a series of unique and useful applications in catalysis:

(i) Rotaxanes can be effective scaffolds for homogeneous (metal ion and organic) catalysis, with the dynamic properties and transient or persistent encapsulation of moieties possible with these architectures able to influence the rate and/or stereochemical outcome of different catalyzed reactions. We can expect many more examples of such systems in the future, exploiting the potential of the rotaxane framework to position reactive groups and/or substrates in optimal arrangements for catalysis.

(ii) Switchable rotaxane catalysts can be used to switch "on" or "off" a variety of reaction types and have the potential to control which building blocks in a mixture react together, the order in which building blocks react, the chemo- and regioselectivity of reactions and the outcome of one-pot tandem reaction sequences.

(iii) The intrinsic association of components within a rotaxane means that the ring can move along a track without detaching and exchanging with others in the bulk. As in biology, this special spatial arrangement can be exploited to ensure processivity in catalysis. The foundations have been laid for the development of artificial molecular machines that can accomplish sequence-specific synthesis, an unsolved general problem of contemporary polymer science.[41]

The particular combination of supramolecular chemistry and catalysis provided by rotaxane architectures, offers great potential for advanced functions that are difficult or impossible to achieve in other ways.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the EPSRC for funding.

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