Molecular Machines for Catalysis

‡Lucy van Dijk, Michael J. Tilby, Robert Szpera, Owen A. Smith, Holly A. P. Bunce, Stephen P. Fletcher*

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA

*Corresponding author: stephen.fletcher@chem.ox.ac.uk

‡All authors contributed equally, in reverse alphabetical order.

Abstract

The past few decades have seen tremendous progress in the synthesis and operation of molecular systems capable of controlled mechanical movement. Here we review the use of molecular machines as catalysts for controlling chemical reactions. We highlight the various catalyst designs with a focus on how the mechanical motion is used to control catalysis with varying degrees of success. This review discusses the current challenges of designing effective catalysts, the scope and limitations of various systems, as well as future potential and aims for the field. Although it is difficult to predict which concepts will become most important as so much work is at the proof of concept level, it seems clear that molecular machines have the potential to significantly impact the field of catalysis.

1. Introduction

Nanotechnology is a mature discipline with many dozens of research institutes and journals dedicated to its study. However, some of the most popular visions of nanotechnology, and the subsequent revolutions they promise remain unrealized.[1,2] In particular, if and how molecular engineers will succeed in building nanoscale versions of the mechanical world for manufacturing purposes has been the subject of well publicised debate[3,4,5] and it is now widely accepted that molecular machines cannot simply mimic macroscopic designs.[6]

Molecular machine: a system in which a stimulus triggers the controlled motion of one molecular or submolecular component relative to another and potentially results in a net task (or work) being done.[7]

The use of molecular machines to do synthetic work is of course not a futuristic dream, but is fundamental to all biochemistry. Organisms use a great variety of ancient nanoscale machines to perform complex and intricate functions.[8] Biology can control directional movement of molecular motors and translate this into a wide range of functions from the movement of motor proteins to ATP synthesis.[9]

It has long been recognized that artificial nanoscale machines which emulate biological assemblies may give rise to many applications, but until recently progress was hindered by the sheer intractability of complex chemical systems. Great technical and conceptual advances in the last two decades now make it possible to produce 'large' systems capable of function, as highlighted by Jean-Pierre Sauvage, Fraser Stoddart and Ben Feringa's contributions to the design and synthesis of molecular machines for which they were awarded the 2016 Nobel Prize in Chemistry.[10,11,12]

The development of artificial molecular machines has a unique place in contemporary science. Besides historical and popular considerations, nano is unusual in that it often relies on science fiction to supply thought experiments and fodder for 'proofs of concept' experiments, and its leading scientists are generally comfortable to be seen to be having fun.[13]

Here we review efforts to develop molecular machines into functional assemblies that are capable of catalysing synthetic reactions. Catalysis is essential to modern manufacturing as it can increase the rate, reliability and efficiency of chemical processes. Catalysts can interconvert different types of energy (light, chemical) and use this energy to make or break chemical bonds. Learning how to harness the power of molecular machines to control catalytic function brings many challenges, but also holds great potential in the field of synthesis, and begins to address some long-awaited promises in nanotechnology.

Chemoselectivity: The preferential reaction of one functional group over another in a chemical reaction.[15]

Stereoselectivity: The preferential formation of one stereoisomer over another in a chemical reaction. If the stereoisomers are enantiomers, enantioselectivity applies (quantified by enantiomeric excess, e.e., or enantiomeric ratio, e.r.), if they are diastereomers, diastereoselectivity applies (quantified by diasteriomeric ratio, d.r.).[16]

We present an overview of innovations in using molecular machines as catalysts and discuss the concepts and principles emerging from the field. It is apparent that selectivity is a key challenge.[14] Perfectly selective switching of devices between 'on/off' states or between distinct catalytic functions has proven difficult to achieve. As with all catalysis, product chemo- and stereo-selectivity is also challenging. In addition, molecular machines must deal with kinetic factors that may

affect their use as catalysts. For example, once a product has been synthesised, it must be released from the machine introducing issues of product inhibition. In contrast to macroscopic objects, molecules are subject to diffusion and Brownian motion, complicating efforts to devise nanoscale 'assembly lines' where reacting molecules must pass from one catalytic site to the next.

If these obstacles can be overcome, molecular machines could offer vast synthetic utility beyond or complimentary to what is currently accessible through biological and small-molecule catalysis. Biology is incredibly efficient, but homochirality can restrict access to one enantiomer. Additionally, nature's repertoire of chemical reactions is somewhat limited despite what it manages to achieve with this set. In contrast, artificial catalysts can use building blocks which are not found in nature and may have unlimited potential. Organised assemblies of molecular machines with orthogonal responses to various stimuli could provide the opportunity to fabricate higher order, complex structures from a mixture of synthetic building blocks in a controlled series of 'one-pot' reactions.

Already illustrative examples of using molecular machines as catalysts are emerging, some of which are highlighted below in three core sections which have been grouped (albeit imperfectly) by the mechanical movement patterns associated with their design. Section 2, 'rotational switches', includes azobenzene-based switches and switches which involve bond rotations to control catalysis. Section 3 describes 'allosteric supramolecular catalysts' which generally open or close to mediate access to active sites, and section 4 illustrates 'rotaxanes' where movement about the interlocked components modifies the catalyst's architecture. Additionally, examples of more 'advanced molecular machines' where catalyst functions not normally seen in homo- or hetero-geneous systems are presented in section 5. This is followed by a brief discussion of the future challenges in the field and some concluding remarks in section 6. Though many other examples of molecular machines exist with alternative switching mechanisms and structures, including the operation of advanced materials,[7,17,18,19] here we will focus on systems most relevant to catalysis. We also explicitly focus this review on mechanical or 'machine-like' systems, where molecular movement of the components is a key aspect of control.

2. Rotational Switches

Perhaps the simplest mechanical systems capable of controlling catalysis are two-state switches. The operation of such switch-based catalysts can be classified into two broad categories. The first uses molecular motion to bring co-operative functional groups together to facilitate catalysis (Fig. 1a, left). The second strategy is to remove a blocking group from the catalytically active site to make it accessible to the substrate (Fig. 1a, right).

Molecular Switch: A molecule that can be reversibly shifted between two or more stable states. An important distinction between molecular 'switches' and 'motors' is that when switches return to their original state any mechanical work is undone. [7]

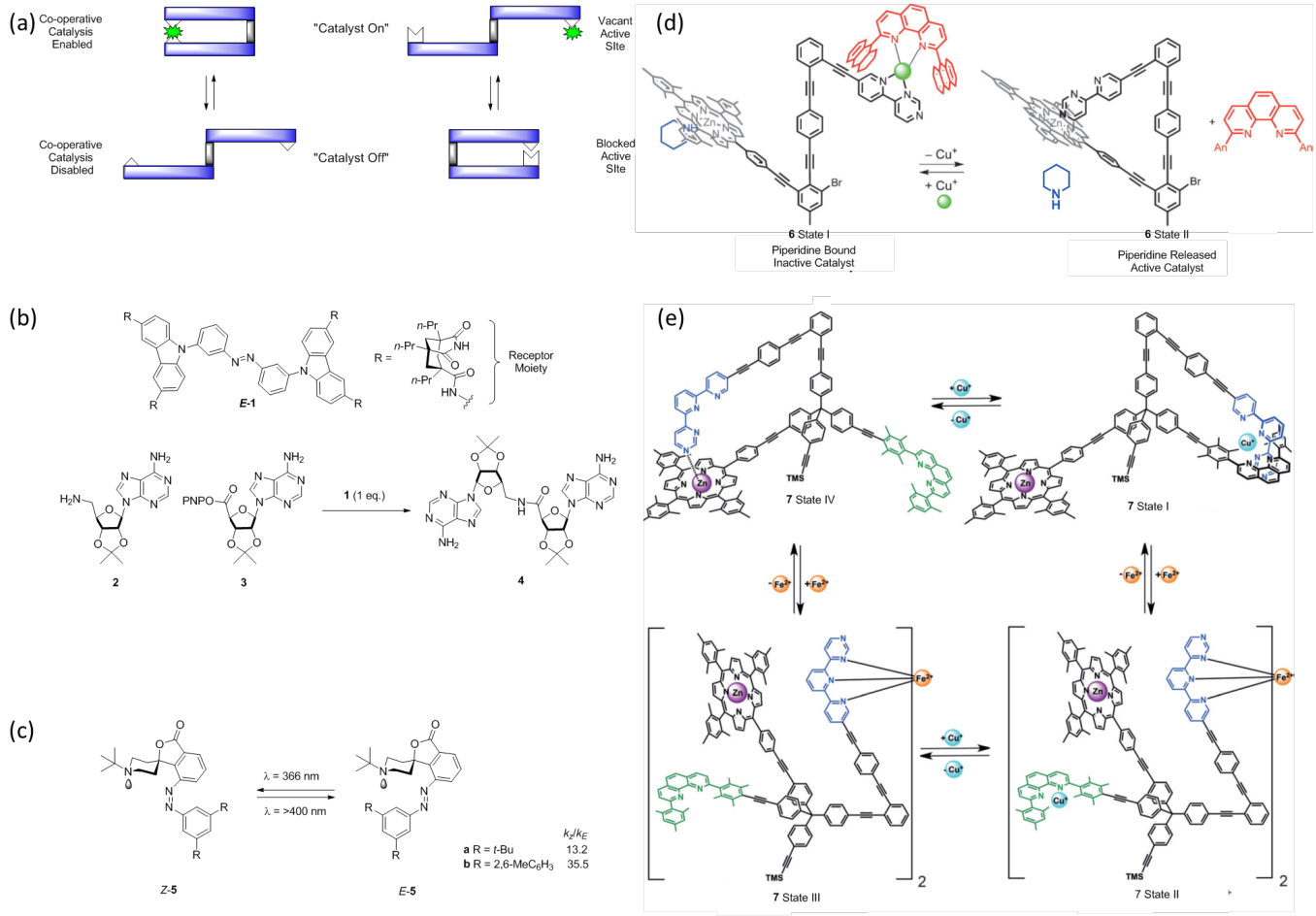

Figure 1. **(a)** Strategies used in two-state mechanically switchable catalysts. Left, moving two co-operative groups into close proximity turns the catalyst to the 'on' state. Right, moving two groups apart unblocks an active site to turns the catalyst 'on' **(b)** Rebek first demonstrated the use of an azobenzene switch, with more and less active geometries, as an amide bond forming catalyst.[24,25] Adapted with permission from REF. 25. **(c)** Photoswitchable catalysis mediated by (un)blocking a catalytically active tertiary amine.[27,28] Adapted with permission from REF. 27. **(d)** Use of a rotating arm to modulate catalytic activity through intramolecular (un)binding to a metal porphyrin. Adapted with permission from REF. 32. **(e)** A catalytically active molecular machine related to the example in part (d), which is capable of selectively switching between four states. Adapted with permission from REF. 36.

a. Two-State Switches

Azobenzene derivatives have been widely exploited in switchable catalyst design[14,20] as the large geometrical changes between *E* and *Z* isomers can alter the catalytic site and therefore modulate the rate of reactions.[21,22,23] Seminal work by Würthner and Rebek demonstrates co-operative catalysis in amide bond formation between amino-adenosine **2** and an adenosine-derived activated ester **3** using azobenzene based switch **1** (Fig. 1b).[24,25] The catalyst possesses 3,6-diaminocarbazole derived 'scorpion receptors' which hydrogen bond to adenosine derivatives,[26] and its *Z* isomer provides rate enhancement *via* encouraging close proximity of the coupling partners. Irradiation at different wavelengths alters the photostationary state and ratio of *E*/*Z*-isomers. Pure *E*-isomer **1** has limited catalytic activity but a photostationary equilibrium mixture containing 50 % of the *Z*-isomer gave a rate enhancement of 10.5:1 relative to the uncatalysed reaction.

Photostationary state mixtures can be useful for switchable catalysis but may require constant irradiation to maintain the *E*/*Z* ratio and one isomer must be inactive, otherwise the catalyst cannot be fully switched off. Photoswitchable catalysts may also undergo thermal (or chemical) isomerisation leading to a mixture of isomers over time. Therefore, only catalysts with long thermal half-lives are suitable for practical applications unless the other isomer is completely inactive or the system is compatible with regular and easy to apply irradiation.

Active site blocking catalysts have been developed by Hecht *et al.* using conformationally restricted piperidines **5** (Fig. 1c). An equatorial *N*-*t*-Bu substituent minimises nitrogen inversion due to unfavourable 1,3-diaxial interactions in the other conformer. This forces substrates to approach from beneath the ring allowing reactions to occur when the catalyst is in its *Z*-isomer form. Upon isomerisation to the *E*-isomer, the nitrogen is sterically inaccessible slowing catalysis.[27,28] The rate of addition of nitroethane to *p*-nitrobenzaldehyde was increased 35.5 times upon switching

from the *E*- to *Z*-isomer. A related approach is to use hydrogen bonding to deactivate the catalytic site. Pericàs reported an azobenzene containing thiourea, which in the dark remains in the active *Z*-isomer and is effective for catalysing a Michael addition (96 % conversion, 18 h). Switching to the *E*-isomer under UV irradiation brings a hydrogen-bond accepting nitro group into close proximity with the thiourea, blocking the active site and lowering conversion (23 % conversion, 20 h).[29]

Leigh has described switchable organocatalysts capable of promoting highly enantioselective conjugate addition reactions, where the catalyst can be switched between 'on/off' states with high efficiency.[30] In this case quinine-derived squaramide units promote asymmetric addition. The reaction can be turned on and off by isomerisations mediated by various combinations of light, pH change and temperature, which cause a nitro group to block the catalytic site and shut down catalysis.

While azobenzene photoswitches operate using irradiation to switch from one state to another, it is also possible to control catalysis by using a combination of chemical reactivity and thermal free rotation about single C-C bonds to block or activate the catalytic moieties.

Allosteric Regulation: The regulation of a catalyst's structure, and catalytic activity, by the binding of a ligand at a site topologically distinct from the catalytically active site.[31]

Schmittel and co-workers developed a series of machines derived from rigid sp/sp^2 scaffolds that operate using a rotating 'arm', controlled by allosteric binding of Cu(I) ions, to modulate catalytic activity (Fig. 1d). An early demonstration of this design strategy was used to mediate a piperidine-catalysed Knoevenagel condensation.[32] A chain of events culminating in displacement of piperidine from zinc porphyrin **6** allows condensation to proceed (23 % yield, 30 min at 55 ^{o}C). The presence or absence of Cu(I) salts is used to control the placement of the pyridine-pyrimidine derived rotor which is either bound in an intermolecular copper complex or intramolecularly to the zinc porphyrin. When the rotating arm forms a Cu(I) complex with a phenanthroline derivative, piperidine binds to the zinc porphyrin and does not catalyse condensation. The catalytic cycle can be interrupted and restarted multiple times without loss of catalytic activity demonstrating the robustness of the system.

Subsequent publications on these metallo-regulated switches reported more mechanically and chemically sophisticated examples, such as the incorporation of additional catalytic functions and active states to increase the number of processes that can be facilitated. One system, related to that shown in Fig. 1d, is capable of catalysing two orthogonal chemical cycles. By taking advantage of the ligated copper species, formed by addition of a phenanthroline derivative, [3+2] cycloaddition between an alkyne and an azide can be promoted while Knoevenagel condensation is inhibited.[33] Incorporation of a zinc porphyrin can be used as a switchable photosensitizer for the *cis*- to *trans*-isomerisation of pyrimidyl-phenyl stilbenes. Irradiation for 30 minutes with the rotating arm displaced from the Zn centre produces a 72:28 *trans*:*cis* mixture but no isomerisation is observed when the rotating arm occupies the metal binding site.[34] Stilbene itself is inert to isomerisation suggesting that the *cis*-alkene must bind to the metal centre through nitrogen for isomerisation to occur. A unique demonstration of cooperative switching between two chemically interacting switches in a signalling network used Schmittel's metallo-regulated switches to catalyse a Michael addition.[35] While this system is very much a proof of principle, its successful operation over 3 cycles is remarkable considering how few nanoswitch catalysts can operate *in situ*.

b. <u>Multi-State Switches</u>

Multi-state switches are not limited to two modes of catalytic activity as they possess multiple switching states. In principle, this vastly increases the number of functions that can be performed by the same machine. Controlled switching between each of the catalytic states would enable the possibility of more elaborate sequences of reactions and sophisticated multi-step one-pot synthetic sequences, if rotational direction can be controlled and diffusion and reaction inhibition can be overcome.

The development of such rotors is not trivial, but a promising approach builds on Schmittel's metalloregulated machines that have been modified about the rotor-stator linker to accommodate additional arms (*c.f.* Figures 1d and 1e).[36] Redesign, from a 2,6-disubstituted benzene scaffold to tetrasubstituted carbon stator **7**, provides an extra switching state while introducing significant changes to the system's bond angles. The success of the system depicted in Fig. 1e illustrates that angle changes can be accommodated by elongating the length of the rotor. Here the rotating arm also features a tridentate ligand, resulting in a catalyst with four states. In State I, a copper atom is bound by the rotor and one of the stator arms, the structure is inactive for [3+2] cycloaddition chemistry. Upon addition of iron(II) ions, the tridentate rotor preferentially binds to iron, opening up free copper sites (State II) so that [3+2] click reactions can now be promoted. Sequential removal of Cu(I) and Fe(II) ions brings the catalyst to a resting state (State IV) which as before releases piperidine to catalyse the Knoevenagel condensation.

In practice, it was found that higher yields of both Click and Knoevenagel products were obtained after two cycles than during a single cycle. A third cycle was prevented by partial precipitation of the catalyst complex from the reaction mixture, which emphasises the challenge of switching catalyst machines *in situ* without loss of activity. In this system only two of the three arms on the stator contain a functional unit and the remaining site is simply occupied by a silyl protecting group, so even more sophisticated functional machines could be envisaged to arise from this scaffold.

In 2011, Feringa *et al*. demonstrated enantioselective Michael additions using photoswitchable catalysts based on the architecture of **8**.[37] Switching in these overcrowded alkene-based molecular motors is overall monodirectional and driven by a combination of photochemical *cis*/*trans* isomerisations followed by thermal helix inversions from (*M*,*M*) to (*P*,*P*) chirality (Fig. 2a). Overall, this yields a four-state switchable system, of which three are thermally stable at room temperature.

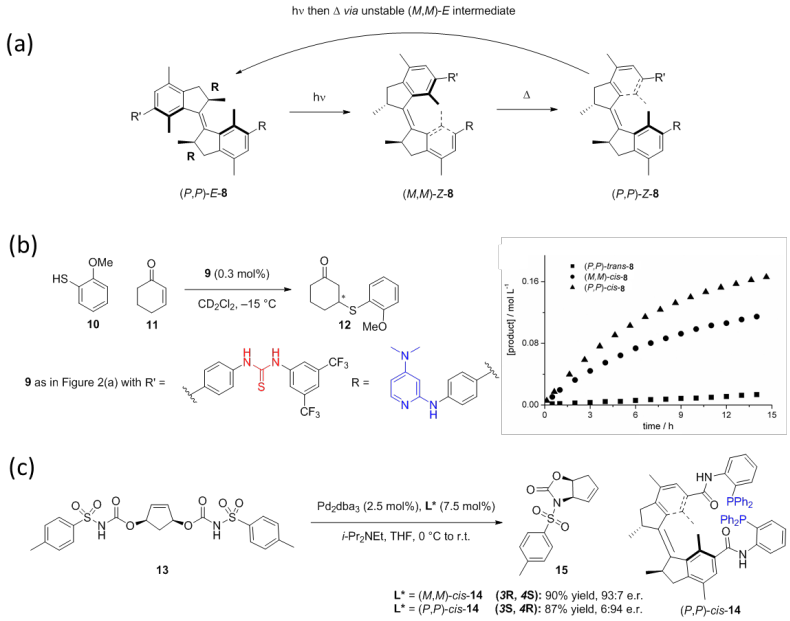

Figure 2. **(a)** Monodirectional switching between thermally stable states of Feringa's overcrowded alkene based catalyst. Adapted with permission from REF. 37. **(b)** The relative rates of formation for the enantioselective addition of 2-methoxythiophenol to cyclohexenone for the different switchable isomers as determined by *in situ* ^{1}H NMR spectroscopy.[38] Adapted with permission from REF. 37. **(c)** The application of both *cis* ligand **L*** isomers to the enantioselective desymmetrisation of **13**. Adapted with permission from REF. 41.

The close proximity of thiourea and Brønsted basic DMAP moieties in the two *cis*-states of **9** allows bifunctional catalysis with the chiral architecture controlling enantioselectivity in the Michael addition of **10** to **11** to yield **12**. In the *trans*-isomer, significant separation of the functional groups reduces the rate of product formation and affords no stereocontrol, this serves as the catalyst off state. Modest enantioselectivity was observed for both *cis*-isomers with the (*M*,*M*)-*cis* configuration giving an e.r. of 75:25 compared to an e.r. of 23:77 obtained with the (*P*,*P*)-*cis* isomer (Fig. 2b). Subsequently, a modified catalyst lacking the phenyl spacer proved capable of catalysing enantioselective 1,2-addition of nitromethane to trifluoromethylketones.[38] Both *cis*-configurations of this modified catalyst gave good yields (>90 %) and respectable e.r.s, with the (*M*,*M*)-*cis* configuration giving higher enantioselectivity (up to 86:14 e.r.). The higher enantioselectivity observed was attributed to the catalytic arms being closer to the *pseudo*-enantiomeric core of the modified catalyst.

Ideally, asymmetric ligands based on molecular machines would allow access to both enantiomers of a compound in pure form by simply switching the catalyst. This would reduce the synthetic effort required to make both enantiomers of a ligand, and in principle allow the design of more sophisticated reaction sequences. Likely inspired by Trost's use of bidentate phosphine ligands in the Pd-catalysed desymmetrisation of **13** (Fig. 2c),[39,40] photoswitchable bisphosphine ligands (*P*,*P*)-*cis*-**14** and (*M*,*M*)-*cis*-**14** were devised. The design involves replacement of the bifunctional organocatalysts in the rotor described above with phosphines, and this system is highly effective in the desymmetrisation of **13** to give either enantiomer of **15** with high ee.[41] Despite the high enantioselectivities observed with the pure ligand in either catalytic state, it has proven challenging to switch stereochemistry during a reaction. Complexation to the metal ion can hinder switching,[42] and in this example, the ligands could not be switched *in situ* as the catalyst was not stable to the switching conditions. Due to their widespread use in metal catalysis, the development of switchable phosphine ligands would be important, and strategies that allow *in situ* switching of metal-ligand complexes would be most welcome.

3. Allosteric Supramolecular Catalysts

Allosteric regulation of enzymes is common in biology.[31] Catalytic activity of artificial molecular machines can similarly be modulated by smaller molecules acting as allosteric effectors, interacting with distal sites and changing oligomeric states[43] or conformations.

Allosteric supramolecular catalysts rely on a variety of structural motifs but generally operate by the same principles seen in the switches and rotors above; either by moving sites together in a cooperative fashion or exposing a catalytic site by moving a steric blocker.

a. Macrocyclic Allosteric Machines

Metal atoms in organometallic macrocycles provide sites for both catalytic activity and allosteric binding. Such macrocycles are often synthesised by self-assembly.[44] This approach uses metal centres with well-defined coordination geometries producing rigid structures. The Weak Link Approach (WLA) synthetic strategy is employed to obtain the necessary conformational flexibility to allow switching between different states.[45]

The WLA uses a metal centre with bidentate ligands that have a hemilabile component which can be displaced by a reversible binder. This serves as the allosteric effector which induces molecular motion resulting in a closed, semi-open or open conformation. Generally, in the closed conformation, the active site of the machine is not readily accessible to the reactants resulting in an 'off' state or a slowed reaction rate.

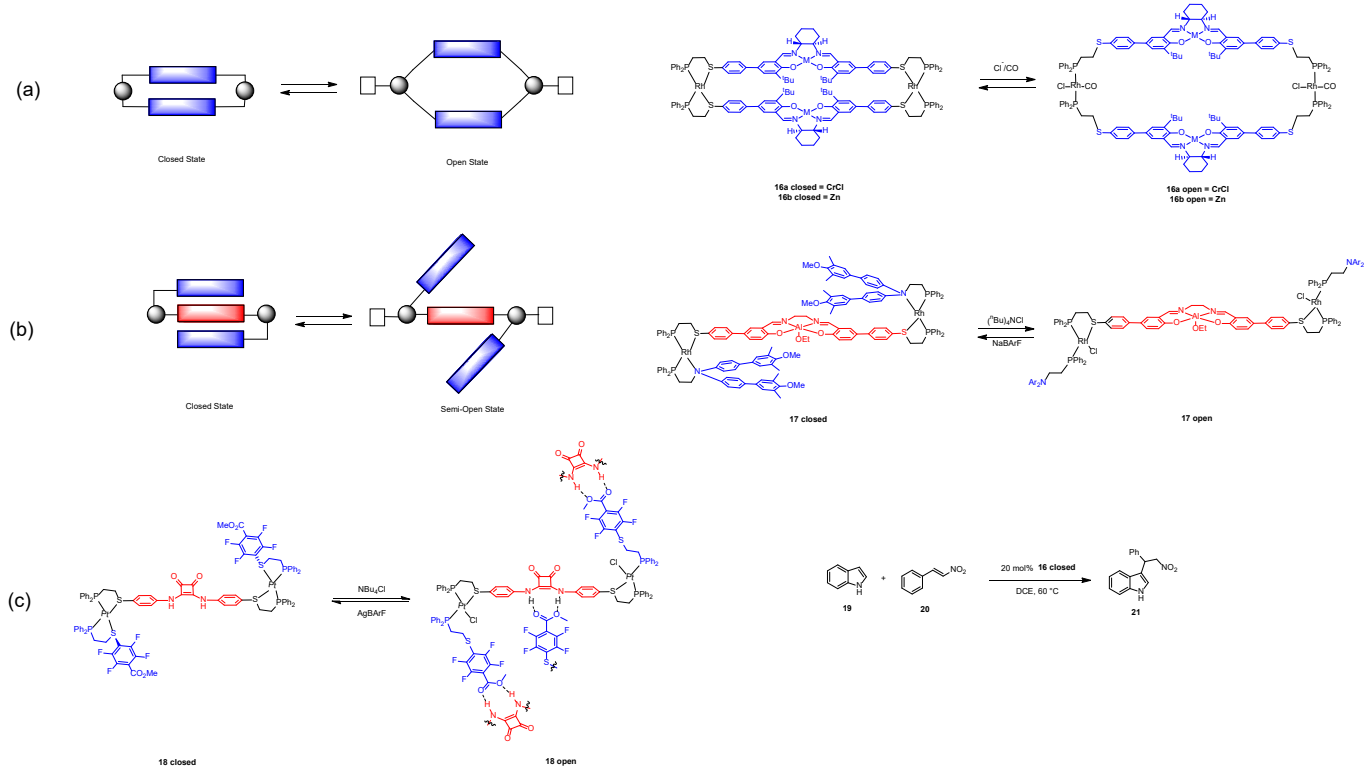

Figure 3. **(a)** Schematic of the general principle of macrocyclic allosteric machines and an example of initial work showing a macrocyclic molecular machine which catalyses an epoxide opening. Adapted with permission from REF. 46. **(b)** Schematic representing Triple layer complexes (TLC) as molecular machines and the first triple layer catalyst which was shown to control a living polymerisation reaction. Adapted with permission from REF. 52. **(c)** An example of a triple layer complex that incorporates a squaramide catalyst, this machine functions by controlling the state of oligomerisation. Adapted with permission from REF. 53.

Macrocyclic machines constructed by the WLA consist of two metal hinges connected by rigid spacers (Fig. 3a). The rigid spacer is covalently linked to the metal hinges *via* bidentate ligating sites. When the hemilabile ligands are bound to the hinge, the two rigid spacers are in close proximity resulting in the closed state. The first functional macrocycle constructed with this method used rhodium metal hinges.[45] A rigid spacer containing an aryl group is bound to the hinge *via* phosphorus and a hemilabile oxygen component. The closed state is stabilised by the square planar *cis* geometry at rhodium and π-π stacking between the spacers. The open state can be induced *via* addition of CO which acts as an allosteric effector by displacing the weakly bound oxygen, causing the rigid spacers to move apart.

These systems have been employed in many bimetallic catalysed reactions as the rigid spacers can be modified to contain different catalytically active moieties.[46,47,48,49,50] Anionic allosteric binders can also be used to produce an open state which allows pre-organisation of reactants in close proximity to each other resulting in catalysis. This

strategy is effectively used in a metal-salen-catalysed epoxide opening of cyclohexene oxide with azidotrimethylsilane catalysed by **16** (Fig. 3a).[46] This system was compared to a monomeric Cr(III)-salen analogue. Under the reaction conditions the open state of the macrocyclic molecular machine gave 68 % ee (compared to 12 % ee) and a 20-fold increase in rate.

These macrocycle machines have been employed as molecular sensors for allosteric effectors such as chloride anions.[47] When the effector switches the machine on, an acyl transfer reaction between acetic anhydride and pyridyl carbinol is accelerated by the bimetallic Zn(II)-salen active site, producing acetic acid which is detected using a pH-probe. This concept has been extended by using the acetate by-product as the allosteric effector, leading to autocatalysis of the reaction.[50] When linked with a pH-sensitive fluorophore probe, this establishes a system that mimics the PCR process with exponential signal amplification.

Thus far, these systems are limited to reactions requiring bimetallic catalysts. Also, in many examples, the machine cannot be entirely switched off as the catalytic site is merely less accessible to the reagents in the closed state. These limitations need to be addressed if macrocycle allosteric molecular machines are to extend beyond proof of concept experiments.

b. Triple Layer Complexes

Triple layer complexes (TLC), first developed by Mirkin in 2006,[51] consist of three rigid spacers which can be switched from a closed to semi-open state *via* allosteric binding to a metal hinge (Fig. 3b). In contrast to the macrocycles above, these TLC now use two different bidentate ligands, producing a heteroligated complex, which allows selective dissociation of the weaker binding heteroatom.

In the context of catalysis, the exterior rigid spacers are normally chemically inert and in the closed state block a single active site on the central rigid spacer. To further demonstrate how molecular machines could function like allosteric enzymes, Mirkin *et al*. produced an Al-salen derived TLC catalyst **17** for the living polymerisation of ε-caprolactone (Figure 3(b)).[52] Polymer growth and molecular weight could be controlled by the on/off switching of the catalyst, highlighting potential applications in material synthesis.

In principle, a wide range of catalysts could be incorporated into the TLC catalytic site. Mirkin produced a squaramide-based TLC hydrogen bond donor organocatalyst **18** which catalyses the Michael addition of indole **19** to nitrostyrene **20** (Fig. 3c).[53] In contrast to previous examples, the catalytically active state is the closed state. Oligomers form in the semi-open state by hydrogen bonding between the squaramide and the exterior rigid spacers blocking the catalytic site, which produces negligible amount of product after 24 h (turnover frequency of 1.74×10^{-6} s^{-1}). When closed, the molecular machine exists as a monomer due to steric and geometric constraints preventing intermolecular hydrogen bonding allowing approximately a 21.5-fold increase in turnover frequency (3.47×10^{-5} s^{-1}). This can also be considered a biomimetic approach as many enzymes are known to produce active species by oligomer dissociation.[43]

c. Allosteric Molecular Tweezers

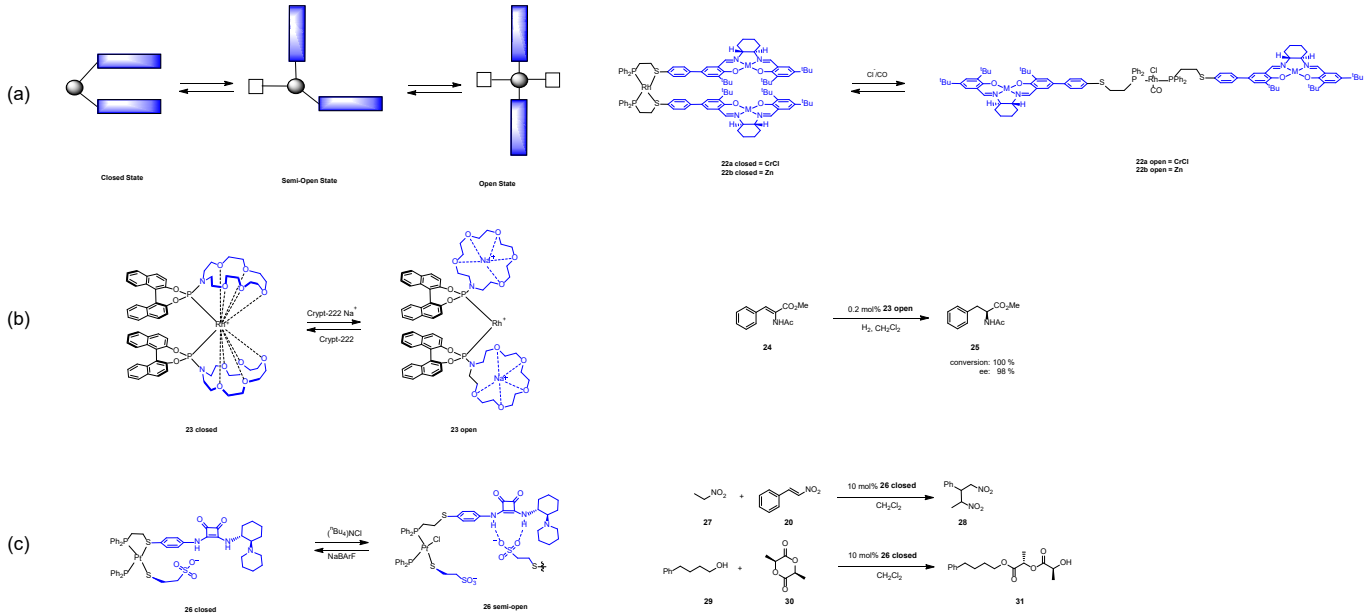

Figure 4. **(a)** Schematic of a molecular tweezer activated by an allosteric effector and an example of a molecular tweezer constructed via the WLA. Adapted with permission from REF. 58. **(b)** A molecular tweezer complex with a catalytically active rhodium hinge. Adapted with permission from REF. 59. **(c)** A molecular tweezer which incorporates a bifunctional catalyst, the switching from the on to off state is controlled by the degree of oligomerisation and a simultaneous protonation. Adapted with permission from REF. 60.

Generally allosteric molecular tweezers contain a central node, to which allosteric effectors can bind. In the closed state, the two exterior ligands are close in geometric proximity (Fig. 4a). The addition of allosteric effectors increases conformational flexibility resulting in a semi-open or open state. The differences between bimetallic tweezer complexes and macrocycle allosteric machines should be noted.[46] There is no bimetallic active site in the open state of the tweezer complex, therefore it is switched off when open. Also, the tweezer complexes generally exhibit improved solubility in organic solvents and tend to have enhanced rates of reaction and enantioselectivity.

Jacobsen demonstrated that metal-salen complexes can catalyse asymmetric epoxide ring openings.[54,55] Structural and kinetic studies identified that this occurs through a bimetallic mechanism.[56] Enhanced reactivity was observed by linking the salen units via a dendrimer allowing cooperative catalysis.[57] Mirkin's tweezer catalyst **22** furthers these findings by showing that the supramolecular system has a greater activity in both the open and closed state compared to a monomeric salen catalyst (Fig 4a).[58] This was demonstrated by the reaction of cyclohexene oxide with azidotrimethylsilane, the closed state gives better initial enantioselectivity than the open state, and at low concentrations (0.14×10^{-3} M) the closed state is more enantioselective than the open state or monomeric salen species (49 % ee compared to 21 % ee). This potentially results from solvent interference in the selectivity determining transition state in the monomeric and open species, while the closed state's consistent selectivity over the concentration range arises due to predefined alignment which promotes cooperativity. Overall this demonstrates that molecular machines may have the ability to retain selectivity over a range of conditions due to the rationally designed active site, and illustrates that they can also be used as probes to study the mechanism of catalytic reactions.

An alternative approach is to use cations as allosteric effectors. For example, Fan has developed a tweezer (Fig. 4b) based on a rhodium complex featuring aza-crown ether modified phosphoramidite ligands **23**.[59] In the closed state the aza-crown ethers bind to cationic rhodium, causing the catalyst to be switched off. Addition of Na^+ switches the catalyst on by interacting with the crown ether moieties and causing dissociation from rhodium. This rhodium centre is then available to catalyse asymmetric hydrogenation of dehydroamino acid **24**, giving 100 % conversion and ee values of 92-98 %, and demonstrating that the hinge can also be used as the active catalytic centre.

Molecular tweezers have also been extended to incorporate bifunctional catalysts that contain two different ligands on the metal hinge **26**.[60] In this case, one ligand contains a squaramide hydrogen bond donor and a tertiary amine Lewis base component, whilst the other ligand controls the degree of oligomerisation with a charged sulfonate group, similar to Mirkin's previous work.[53,61] In the semi-open state intermolecular ligand-ligand interactions prevail and the bifunctional catalyst has limited activity. However, in the rigid closed state, the charged sulfonate group

prevents oligomerisation with the hydrogen bond donor hence the active site can readily catalyse reactions. This machine has been shown to catalyse both Michael additions of nitroethane **27** to nitrostyrene **20** and the ring opening of lactone **25**. The fact that this machine is capable of promoting two different reactions shows a degree of versatility not normally seen with other molecular machines. It should also be noted that these machines actually exhibit improved activity over the standard free ligand bifunctional catalysts, potentially indicating the need to control oligomerisation in catalyst design and again providing mechanistic insight into benchmark catalytic processes.

As allosteric tweezer complexes can be heteroligated[62,63,64,65] they can incorporate a variety of catalytically active sites. This presents the opportunity to develop systems with two different catalysts for orthogonal reactions or tandem processes. Fan's studies indicate that it is important to consider the role the metal plays as this can be a site for reactivity, and there is a report of a WLA where a metal hinge also acts as a redox centre to control catalytic activity.[66]

In summary, allosteric effectors may be used in a variety of catalytic molecular machines functioning *via* a range of mechanisms. The WLA has provided a modular approach to the synthesis of allosteric supramolecular machines. Their synthetic practicality (air stability, solubility etc.) provides the opportunity for widespread applications. By using alternative hinges and spacers the scope of these machines may be greatly increased presenting possibilities for applications in artificial sensors, electronics and material science.

4. Rotaxanes

Mechanical bonding: results from interlocked molecular architecture. Mechanically interlocked molecules cannot be separated without breaking covalent bonds.

Rotaxanes are a valuable platform for the development of molecular machines, and have found application in the construction of many molecular devices including switches, logic gates, sensors, and nanovalves.[67] The interlocked rotaxane scaffold possess various features which are pertinent to catalysis, including the ability to switch states in response to external stimuli,[68,69,70,71] and the unique steric environment about the mechanical bond.[71,72]

The most widely reported mechanism for switching the catalytic state of a rotaxane is by translocation of the macrocycle along the axis to reveal and conceal different binding sites (Fig. 5a). Macrocycle translocation can be induced by reversible modification of binding sites on the axle, changing the macrocycle's affinity to that site. Binding site modification can be achieved by various external stimuli, including pH change,[68,69,73,74,75] irradiation with light,[70] or use of additives.[76] Encapsulation of a binding site by the macrocycle blocks access of reactants to the site, and so any catalytic activity of the site is switched off.

Two broad classes of switchable rotaxane catalysts have emerged; bistate unifunctional and bistate bifunctional. Bistate unifunctional rotaxanes can switch between two states, of which only one is catalytically active. These systems therefore switch between 'on/off' states. Bistate bifunctional rotaxanes can be switched between two different catalytically active states (see 'bifunctional systems' subsection). Although this review focuses on rotaxanes as switchable catalysts, we also highlight two relevant non-switchable systems (defined as unistate unifunctional) which highlight important features of rotaxane catalysts. These are discussed along with bistate unifunctional systems in the first subsection, 'unifunctional systems'. Other reviews have covered rotaxanes as unistate unifunctional catalysts and as ligands more comprehensively.[77,7879]

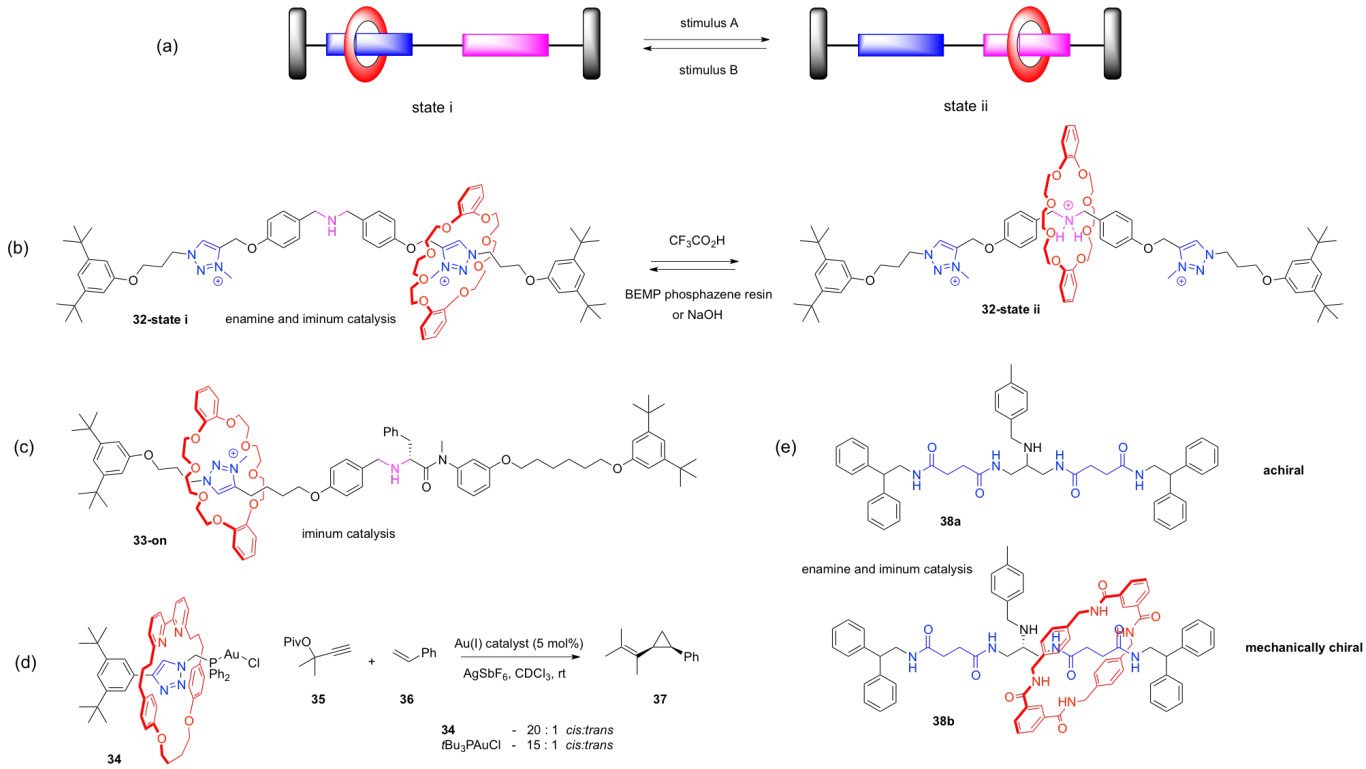

Figure 5. **(a)** Switchable rotaxane with two binding sites. Stimulus A modifies the pink binding site to increase its affinity for the macrocycle, inducing macrocycle translocation. Stimulus B reverses the effect of stimulus A, and the macrocycle returns to bind the blue site. **(b)** A pH switchable bistate unifunctional rotaxane catalyst reported by the Leigh group. Adapted with permission from REF. 69. **(c)** A chiral bistate unifunctional rotaxane catalyst reported by the Leigh group. Adapted with permission from REF. 73. **(d)** A co-factor switchable rotaxane reported by the Goldup group. Adapted with permission from REF. 71. **(e)** A mechanically point chiral unistate unifunctional rotaxane reported by the Leigh group. Adapted with permission from REF. 72.

a) Unifunctional Systems

In 2012, Leigh and co-workers described a bistate unifunctional rotaxane with a secondary amine catalytic site, and a triazolium alternate binding site.[69] With the amine protonated, the crown ether macrocycle encapsulates the ammonium cation, inhibiting catalytic activity (**32**-state ii, Fig. 5b). Addition of base forms the free amine, and the macrocycle then preferentially binds the triazolium ring leaving the amine available to perform organocatalysis (**32**-state i, Fig. 5b). This rotaxane catalyst can perform enamine catalysis for aldehyde α-functionalization, iminium catalysis for Michael additions and Diels-Alder reactions with α,β-unsaturated aldehydes.[74] For the Michael addition of a thiol to an α,β-unsaturated aldehyde, *in situ* switching between **32**-state ii and **32**-state i was demonstrated. The reagents were stirred with **32**-state ii ('off' state) for 48 hours with no product formation, but after a base wash to switch the catalyst to **32**-state i ('on' state), the product was obtained in almost quantitative yield after 1 hour.[69]

Leigh and co-workers subsequently investigated the chemoselectivity of rotaxane **32** in its 'on/off' states. In order for switchable rotaxane catalysts to find practical applications, such systems must display high efficiency in promoting or suppressing reactions in different states. Binding of the rotaxane macrocycle to sites on the axle is an intrinsically fluxional process, so that even in the formal 'off' state, the catalytically active site will be exposed for short periods.[74] However, **32**-state ii was generally efficient in suppressing catalytic activity, with only the most facile reaction, sulfa-Michael addition, proceeding to an observable extent.

The Leigh group have also reported chiral bistate unifunctional rotaxane **33**, with an axle bearing a *d*-phenylalanine derived secondary amine (Fig. 5c).[73] Again, the catalyst state could be manipulated by changing the pH. Impressive e.r.s of up to 94:6 could be obtained in Michael additions of 1,3-diketones to α,β-unsaturated aldehydes, comparable to those observed using a commercially available Jørgensen–Hayashi catalyst. The acyclic nature of this switchable rotaxane catalyst is interesting, as many chiral organocatalysts rely on conformationally rigid cyclic architectures to achieve high levels of stereocontrol. In this case, the mechanical bond of the rotaxane has little influence on the enantioselectivity of the reaction, as the non-interlocked axle affords similar e.r.s to the interlocked system. Nonetheless, the presence of the macrocycle in the rotaxane allows the catalytic activity to be switched 'off', which can't be achieved for the non-interlocked system.

Recently Berná and co-workers disclosed a photoswitchable bistate unifunctional rotaxane,[70] in which the state of the catalyst could be controlled by irradiation with different wavelengths of light. In the 'on' state, a

photoisomerisable olefinic station exists as the *E*-stereoisomer, allowing the macrocycle to bind to it, and leaving the catalytically active station unhindered. Upon photoirradiation, isomerisation to the *Z*-stereoisomer induces translocation of macrocycle switching the catalyst 'off'. In the 'on' state, the sulfide motif exerts modest diastereocontrol in a Baylis-Hilman reaction between an aldehyde and yne-one, with d.r.s up to 80:20. Conversely, reduced yields and no diastereocontrol were observed with the rotaxane in the 'off' state. Although photoswitchable rotaxane catalysts haven't been widely reported, they could prove useful in systems where reactants are acid or base labile and incompatible with pH switching.

The Berná group have also reported a unistate unifunctional rotaxane system which undergoes chemically induced macrocycle translocation while promoting Mitsunobu esterifications.[76] The axle hosts a macrocycle which moves from, then returns to, its original position during the overall process. Although this system doesn't have a formal 'off' state, it demonstrates the potential of chemically induced macrocycle translocation, a switching mode far less explored than pH changes.

The Goldup group have reported a unique approach to switchable rotaxane catalysis, which relies on catalytically innocent cofactors to manipulate a rotaxane based phosphine-gold complex **34** (Fig. 5d).[71] Goldup and co-worker's approach is distinct from the systems described above as state switching doesn't result from macrocycle translocation. Instead, addition of co-factors disrupts the stabilizing interactions of the macrocyclic nitrogens with the Au^+ (formed by chloride abstraction), switching the catalyst 'on'. The rotaxane then catalyses a cyclopropanation between propargylic alcohol **35** and styrene **36** (Fig. 5d).[71] While achieving high stereocontrol in Au(I) mediated transformations is typically difficult due to the metals linear coordination geometry, the unique steric environment of the rotaxane-gold complex afforded diastereomeric ratios of 20:1 compared to 15:1 obtained with P^tBu_3. When the reaction was performed with the non-interlocked axle, the diastereoselectivity dropped to 13:1, demonstrating the steric influence of the mechanical bond.[64] It is worth noting that the non-interlocked phosphine was susceptible to oxidation, while the rotaxane stabilizes the phosphine. Different cofactors were found to induce different diastereoselectivities, which is attributed to the different co-conformations they induce between the macrocycle and thread, akin to the allosteric modulation of enzymes. This presents a new supramolecular approach of using cofactors to modulate catalyst activity and selectivity. Development of this concept to allow modulation of chemo- and enantioselectivity could prove particularly interesting.

The mechanical bonding in rotaxanes has been exploited to induce chirality in individually achiral threads and macrocycles. In unistate unifunctional rotaxane **38** prepared by the Leigh group,[72] incorporation of a bulky benzylamine group on the central carbon of the thread prohibits shuttling of the macrocycle between the two succinamide stations. The prochiral central carbon of the thread is therefore rendered point chiral in the rotaxane due to desymmetrization by the macrocycle (Fig. 5e). This rotaxane was shown to afford modest enantioselectivities in iminium and enamine catalysis, with e.r.s of up to 71:29 obtained in some benchmarking reactions. Although this system features no switching, it does suggest intriguing possibilities of developing novel machines where mechanical (pseudo)chirality can be switched and use to control the outcome of chemical reactions.

b) Bifunctional Systems

Bistate bifunctional systems have two distinct active sites, of which only one is revealed at any given time whilst the other is concealed by the macrocycle. The Leigh group have reported such a system,[68] containing a squaramide hydrogen bond donor site in addition to a secondary amine site (Fig. 6a). This switchable rotaxane is capable of selective activation of either an α,β-unsaturated aldehyde **40** when the secondary amine catalyst is switched 'on' (**39**-state Ii), or β-nitrostyrene **20** when the hydrogen bonding catalyst is switched 'on' (**39**-state IIii). The Leigh group have shown that from a three-component mixture containing **40**, **20**, and **41**, that either Michael adduct **42** or **43** can be obtained with excellent chemoselectivity. The product promoted by the catalytic site which is switched 'off' is detected only in trace amounts. [68] The Leung group subsequently reported a similar bifunctional rotaxane containing both thiourea and secondary amine active sites. [75] Leung and co-workers demonstrated that *in situ* catalyst state switching is possible, so that the product being formed from the reactant pool can be changed mid-reaction.[75] Control experiments conducted in both the Leigh and Leung groups using only the rotaxane axle without the interlocked macrocycle gave poor chemoselectivity. For both the Leigh and Leung systems, catalyst state switching is induced *via* pH control.

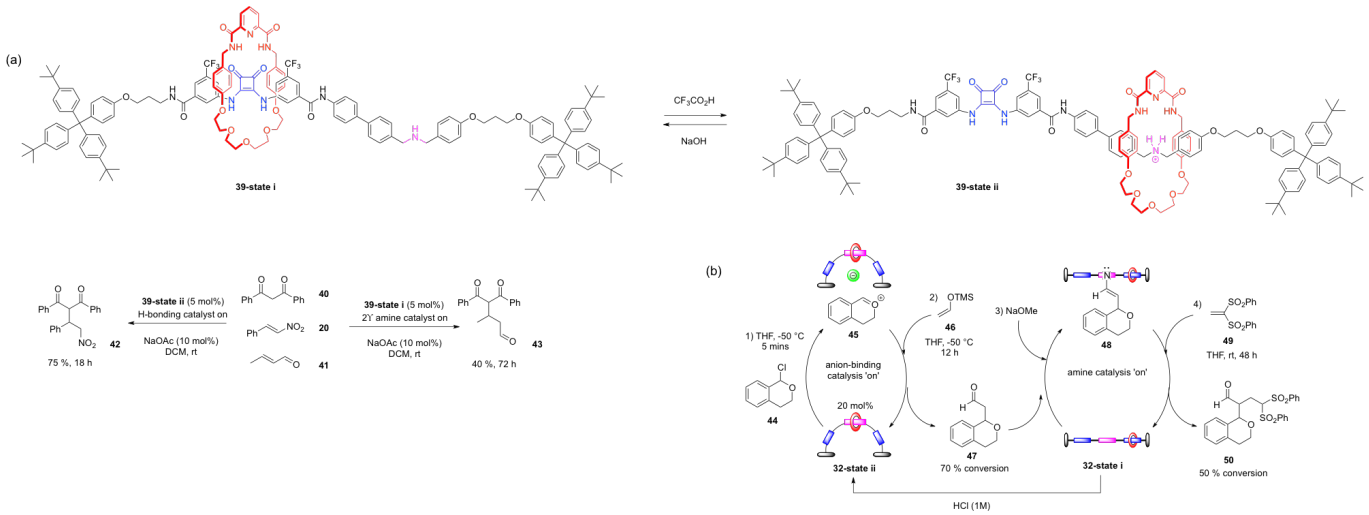

Figure 6. **(a)** Bistate bifunctional rotaxanes separately reported by the Leigh and Leung groups can selectively activate either a β-nitrostyrene or an α,β-unsaturated aldehyde to undergo Michael additions.[68,75] Adapted with permission from REF. 68. **(b)** Tandem anion binding, enamine catalysis, with *in situ* catalyst state switching, to generate to C-C bonds.[74] Adapted with permission from REF. 80.

Recently Leigh and co-workers reported that the aminocatalysis 'off' state in rotaxane **32** (**32**-state ii)[69] actually corresponds to an 'on' state for anion binding catalysis.[80] With the central secondary ammonium station encapsulated by the macrocycle, the two triazolium rings of the axle are conveniently poised to bind chloride and bromide anions. Cooperative action of the two triazolium moieties is required for effective halide abstraction, therefore anion binding is inhibited when the macrocycle binds one of the triazolium sites. The synthetic utility of this anion binding was demonstrated in promoting formation of oxonium **45** from activated alkyl halide **44**, and its subsequent reaction with nucleophile **46**. The Leigh group demonstrated that tandem anion binding – enamine catalysis was possible by switching the rotaxane catalytic state *in situ*, enabling the formation of two carbon-carbon bonds in a single pot (Fig. 6b). After **32**-state ii catalyses the formation of aldehyde **47**, **32**-state i then catalyses nucleophilic addition to Michael acceptor **49** via enamine catalysis, to afford **50**. As the first example of tandem reactivity exploiting both catalytic modes of a bifunctional rotaxane, this report suggests that such rotaxane systems may have an exciting future.

Together these studies demonstrate the excellent chemoselectivity of switchable rotaxane catalysts in selecting individual reactions from complex substrate mixtures. It would appear that there is enormous potential for catalyst systems where a single product can be selected from a pool of reactants. This is certainly one of the most exciting prospects for the future of switchable rotaxane catalysis. Looking forward, the ability to prepare complex molecules by controlling the order of multiple reactions in one pot through catalyst state manipulation would be particularly impressive.

5. Advanced Molecular Machines

The examples in this section showcase the most advanced machine-like systems, which are somewhat disparate but provide exciting proof-of-concepts for reactivity manifolds not normally seen in homogeneous or heterogeneous catalysis. These machines mimic biological processes and macroscopic manufacturing methods, and represent the first nano-scale 'assembly line'-like processes with molecular machines, in contrast to mechanical movement controlling reactivity *via* turning 'on' or 'off' catalytic sites. The following examples highlight very adventurous research that will likely drive the field of molecular machines in fascinating new directions.

a. Processive Molecular Machines

Catalysis by synthetic molecular machines is inevitably compared to that by enzymes, nature's switchable macromolecular catalysts. Biological systems provide long-term goals in terms of the levels of efficiency and selectivity that can be achieved. Additionally, nature is generally capable of chemistry that differs tremendously from that seen in the artificial systems described above. Understanding and mimicking biochemical processes provides inspiration for scientists to create novel biomimetic machines and devices, such as molecular assembly lines, which will ultimately lead to the development of new concepts and understanding as well as novel chemical methods.

Processive: When a catalyst remains attached to the substrate and performs multiple rounds of catalysis before dissociation.[81]

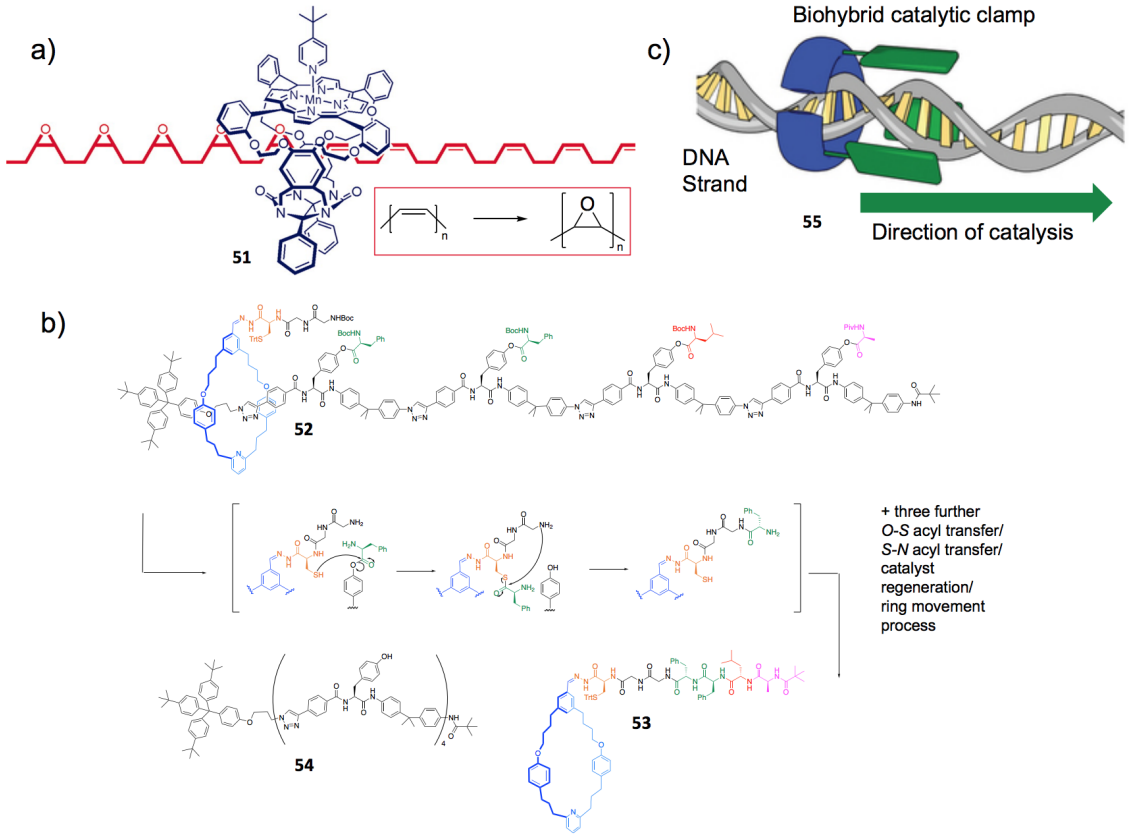

Figure 7. **(a)** A catalytically active rotaxane capable of repeated oxidation of polybutadiene *via* an 'active site' type catalysis. Adapted with permission from REF.85. **(b)** Peptide synthesis from a pre-loaded sequence of amino acids using a ribosome mimicking molecular machine. Adapted with permission from REF.89. **(c)** Biohybrid catalyst with switchable directionality as well as switchable processive/distributive catalysis. Adapted with permission from REF.97.

Rowen and Nolte's early example of a catalytically active rotaxane was inspired by processive enzymes,[81] such as T4 DNA polymerase holoenzyme[82] and λ-exonucleoase,[83] which bind to biopolymers and perform several catalytic iterations in sequence along the substrate before dissociation. The artificial system consists of a polybutadiene track threaded through a macrocyclic Mn(III) porphyrin complex to form a *pseudo*-rotaxane **51**, (Fig. 7a).[84] Upon addition of an oxidant (PhIO/NaOCl) a Mn(V) species is formed which can epoxidise olefins along the polymer thread. A bulky *tert*-butylpyridine ligand binds the outside of the porphyrin ring ensuring only olefins inside the macrocycle's cavity are oxidised. This is reminiscent of the operation of an enzyme active site.

Further kinetic and thermodynamic studies identified that oxidation occurs randomly along the polymer due a mismatch between the slow oxidation rate and fast catalyst movement along the polymer.[85] Continued developments of this system[86,87,88] include modifications with additional substituents on the porphyrin ring to replace the bulky ligand and prevent catalyst decomposition. In addition, the spacer between the porphyrin and glycoluril group has been elongated to increase the flexibility of the macrocycle and decrease the rate of catalyst movement. Modulation of the catalyst has the potential to better match the rates of oxidation and catalyst movement and produce a truly sequential processive artificial molecular machine.

A processive artificial molecular machine developed by the Leigh group,[89] is able to synthesise peptides using native chemical ligation and a mechanism which mimics nature's ribosome. The rotaxane based system **52**, (Fig. 7b), consists of a ring featuring a modified amino acid arm with a cysteine residue and a terminal glycylglycine amine group. The axle has a stopper and bears a preloaded sequence of boc protected amino acids that prevent the ring from moving freely along the chain. Following removal of the boc protecting groups, the native chemical ligation process is able to synthesize peptides from the amino acids presented along the track. The synthesis follows the pre-organised sequence along the backbone *via* several rounds of O-S/S-N acyl transfers. To release the completed peptide from **53**, the macrocycle is removed *via* hydrolysis. Overall the system can couple up to four amino acids from a predetermined sequence.[90] The machine is currently limited to sequencing about ten amino acids[91] due to increasing difficulty of S-N acyl transfer. Loaded amino acids cannot interfere with acylation steps[92] and after one peptide has been sequenced the information contained on the axis is destroyed.[93] Nevertheless, this is an elegant proof of concept that mimics the ribosome while synthesizing peptides in the non-natural direction (from the N to C terminus), demonstrating that artificial machines can achieve processes not known in nature.

It is likely that a diverse range of chemical transformations can be conducted with processive rotaxane catalysis. Palladium systems have been developed by the Takata group.[94] Here the rotaxane ring contains palladium which promotes hydroamination of an unsaturated linear axis. These studies suggest a number of intriguing possibilities, including long-range chirality transfer from the macrocyclic ring backbone[95,96] and the potential to access a diverse range of new polymers which may be selectively synthesised *via post*-polymerization modification.

Distributive: the most common mode of operation for homogeneous and heterogeneous catalysis where conversion occurs at a single site before dissociation of the catalyst.[97]

A biohybrid molecular machine which functions as a detachable rotaxane has been developed **55**, (Fig. 7c).[97] A manganese maleimide-functionalised porphyrin was conjugated to a gp45 'clamp protein'. This clamp-like biohybrid can cause oxidation events to occur at the end of an AAA nucleotide sequence on a DNA backbone. The catalytic clamp can either function in a sequential or random motion depending on the addition of an octapeptide molecular 'switch'. The octapeptide protein can close the ring structure of the gp45 protein hence preventing binding to DNA, allowing only distributive catalysis to occur. The directionality of procession can be restricted by using a 'clamp-loader complex' so that the clamp and complex associate, and load together onto the DNA at a preferential binding site, such as a nick in one strand of the double stranded DNA. The complex is immobile, remains at the loading site, and therefore blocks the clamp from sliding in one direction along the DNA, but the clamp is free to slide in the other direction. Although somewhat complex, this system demonstrates the ability to control processive catalysis and highlights the possibility of using biohybrid molecular machines to alter biopolymers.

b. Molecular transporters

Molecular machines have been used to induce movement of materials on the macroscopic scale and even to transport macroscopic solid objects or liquid droplets in proof of principle applications.[98,99,100] This section discusses the use of machines to manipulate molecules in a controlled fashion at the nano-scale. If properly harnessed, the ability to control the movement or transport of small molecules could have potentially transformative applications in catalysis and synthesis. Whilst these machines are not necessarily performing new catalytic reactions, the realization of the components of molecular assembly lines is an exciting new development, and as seen below it is possible to achieve complementary stereochemical outcomes to those seen in traditional chemistry.

A rotaxane based transporter developed by Credi *et al*. is capable of carrying cargo down a track and then releasing it.[101] The system consists of a ring that undergoes pH controlled shuttling between two different recognition sites. The cargo is a ruthenium complex which is loaded on the ring *via* a tether. Uptake and unloading of the cargo operates *via* orthogonal stimuli to the shuttling using photo-dissociation, allowing for fine, step-wise control. A limitation of this system is that reloading cargo after dissociation is not possible.

A system functioning entirely by chemical stimuli has been developed by Leigh, **56**.[102] The machine transports small molecules *via* a central hydrazone rotary switch (Fig. 8a). Initially the transporter arm is not locked in a given conformation and reagents that promote kinetically controlled disulfide formation attach the arm to the cargo. Cargo movement is controlled by pH, which switches the *E/Z* hydrazine geometry from **57** to **58**, and the cargo can be released *via* reduction of the disulfide bond, **59**. This elegant system is capable of performing transportation in forward or reverse directions and all of the operations can be accomplished in 'one-pot'.

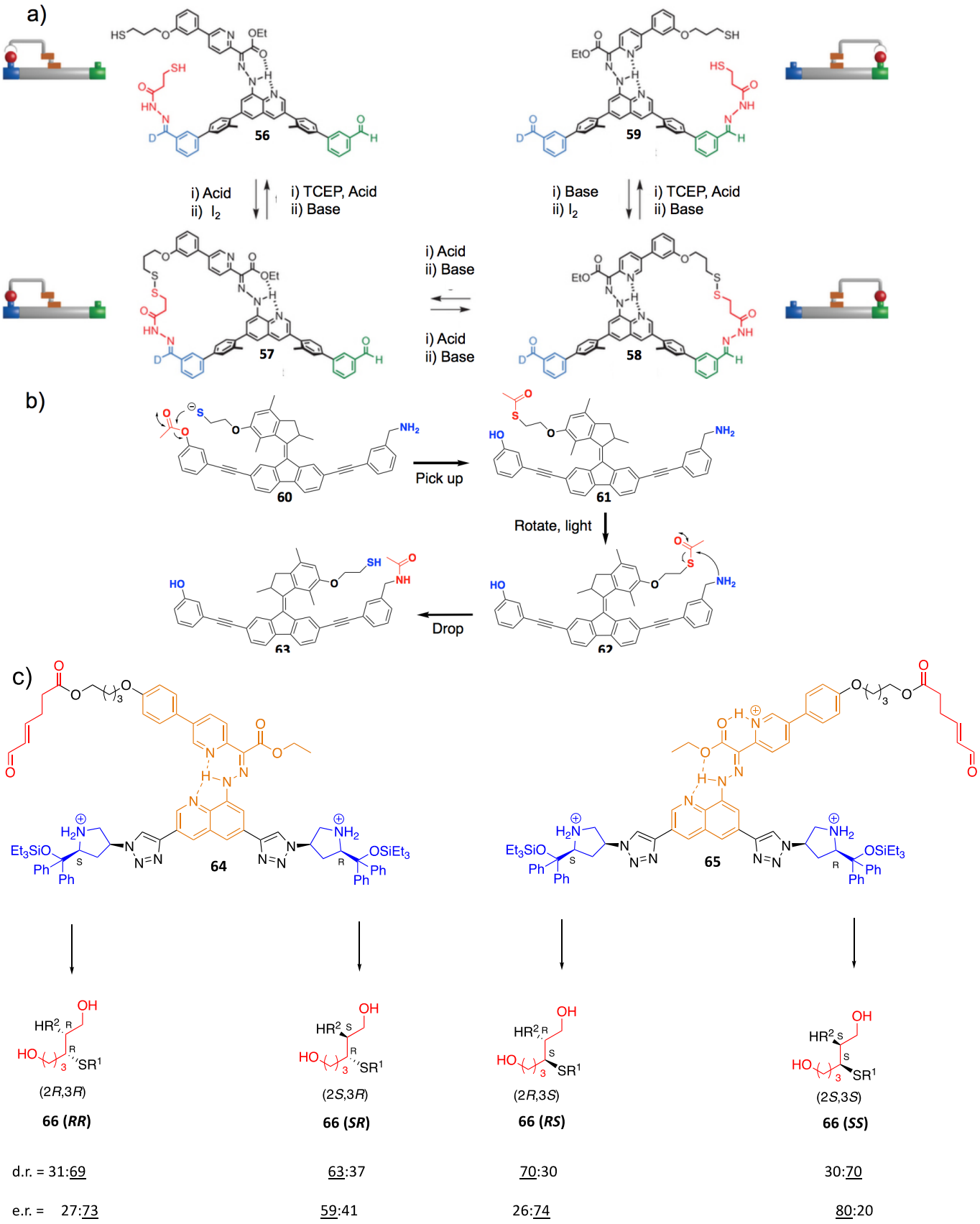

Figure 8. **(a)** Structure of molecular machine and cargo with switchable arm capable of rotating to transport small molecules. Adapted with permission from REF.102. (b) A light driven molecular transporter capable of moving an acyl group between two sites. Adapted with permission from REF.103. **(c)** A stereodivergent machine capable of synthesizing d.r.s not achievable by conventional means. Adapted with permission from REF.104.

A transporter device developed by the Feringa group **60**, (Fig. 8b)[103] has a number of important chemical differences. Loading of cargo is accomplished by acetylation of a thiol group located on a rotor, and the rotation of the arm from **61** to **62** is light driven, rather than driven by chemical means. Although this particular design uses irreversible O- to N-transfer to move the acyl group and give **63**, there does not appear to be a fundamental reason why more sophisticated light driven devices could not be designed for reversible transportation. The development of controlled photoisomerisation reactions can be tricky, and here the photostationary state ratio of **61**:**62** is ~1:5, but light is a 'non-invasive reagent' and the authors point out that the use of light may provide advantages in control, in space and time, for the construction of nano-scale assembly lines.[103]

A major recent advance described by the Leigh group is a molecular machine capable of stereodivergent synthesis so that it can selectively produce an excess of any of the four possible isomers in a molecule containing two stereogenic centres (Fig. 8c).[104] A hydrazone rotary switch controls cargo-arm movement and position by pH (*c.f.* **64** and **65**), and the system features two prolinol silyl ethers of opposite handedness, which promote bond-forming reactions. Through careful manipulation after each step in the 'one-pot' sequence, the machine can produce an enriched mixture of any diastereomer of **66**, including the *anti* diastereoisomers not selectively accessible by conventional iminium-enamine catalysis. Whilst diastereoselectivities (typically 3:7 d.r.) and enantioselectivities (18-60 % ee) are modest, this catalyst can access new products not accessible by traditional synthesis methods.

Stereodivergent synthesis: A synthetic approach capable of producing all of the possible stereoisomers of a molecule selectively.

Overall these molecular transporters demonstrate the use of various stimuli to allow the uptake, movement and release of small molecule-cargo. With further development, these have the potential to become functional nanomaterials capable of new and selective chemistry at the nano-scale level. There appears to be significant opportunities to desymmetrise these systems for stereoselective applications, especially if future work enables molecular assembly lines to use many machines in concurrence or in sequence. In particular, the ability to access products unavailable by other means indicates the potential of molecular machines to be far more than academic curiosities.

6. Conclusions and Future Challenges

Synthetic systems capable of mimicking biological machines are now moving beyond proof-of-concept experiments so that relatively sophisticated reactions can be catalysed. However, it is still difficult to imagine precisely which concepts and designs will allow the leap forward to make these machines broadly useful or rival natural processes.

Particularly in asymmetric catalysis, there are many opportunities. As seen in Fig. 2c, molecular rotors can now induce enantioselectivities rivalling those seen with traditional bisphosphine ligands, and the mechanical bonding of achiral threads to macrocycles can also induce chirality (Fig. 5e). In both systems asymmetry is derived from key structural features of the catalyst; the helical chirality of the rotor and the point chirality of the rotaxane, and the use of the inherent stereochemistry of the machine as the origin of asymmetry (as opposed to incorporating a chiral active site) is fascinating in terms of molecular design. This suggests that this field may ultimately yield many new concepts in stereochemistry and catalysis, and that these systems may be able to catalyse asymmetric reactions that are currently not possible.

In catalysis, ligand design and reaction optimisation still remains difficult and chance, intuition and systematic screening often play an important role in reaction discovery. New successful reactions now benefit substantially from multiple generations of ligands that have been developed, and "privileged ligands" often re-emerge as being especially useful.[105, 106] Although synthesis has advance tremendously, and the complexity of machines that can now be built is astounding, being able to generate multiple iterations of a catalyst-machine for screening is likely difficult due to their synthetic and operational complexity. If highly active and specific catalysts are a genuine research goal, then the design of ligand/machine platforms that are modular and easy to synthesize would facilitate the development of "privileged machines" (like enzymes) that are capable of efficiently catalysing multiple processes.

A reoccurring theme in the operation of nano-machines is that the environment and forces important at the macroscopic level are fundamentally different than those at the molecular scale. The design of 'nano-production line' like processes, where different catalysts can be used in sequence is hindered by diffusion, which is simply too fast for that to be realistic. Cascade and multistep sequences are possible, but as of now rely on promoting orthogonal reactions, rather than funnelling of a substrate down a production line. Strategies to address or harness diffusion would be an important advance, and may complement the emerging strategy of moving a substrate between different activating sites (Fig 8).

Finally, our inability to observe how these machines actually work is almost certainly limiting the further development of catalyst-machines. Workhorse methods such as X-ray crystallography and NMR spectroscopy are useful for measuring structure, resting states and equilibrium concentrations but are limited in their ability to measure solution dynamics and far-from-equilibrium systems. As the movement of molecular machines is highly

complex, which factors control catalysis, even in well-studied conventional systems, is often only poorly understood. As a consequence, detailed mechanistic and structure/reactivity relationship studies may have a profound impact on the field, especially if techniques capable of high spatial and temporal resolution are used.

Overall, molecular machines provide the opportunity to extend into chemical space inaccessible to both biological systems and conventional chemistry. It is anticipated that these studies will lead to many exciting future concepts and applications and, at the very least, the development and discovery of new tools for synthesis.

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