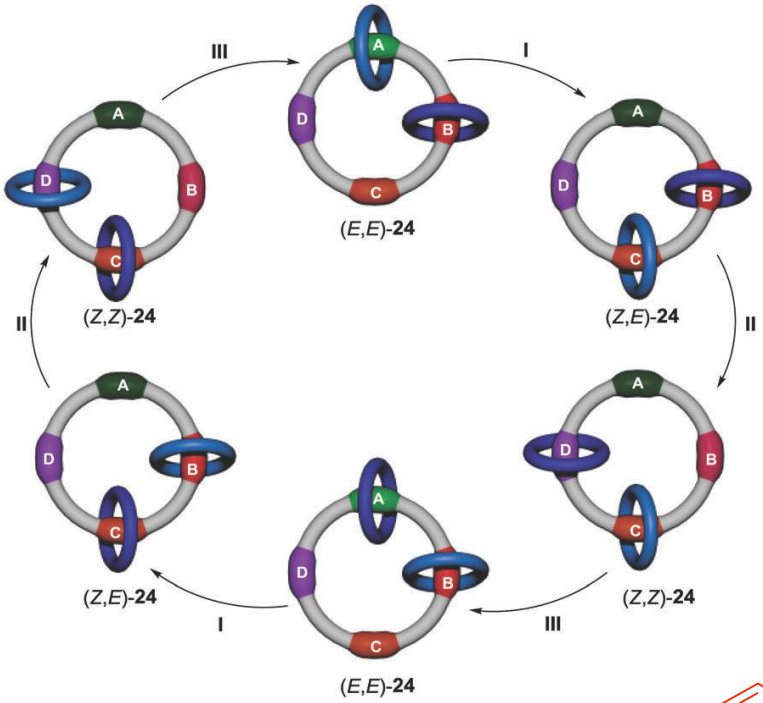
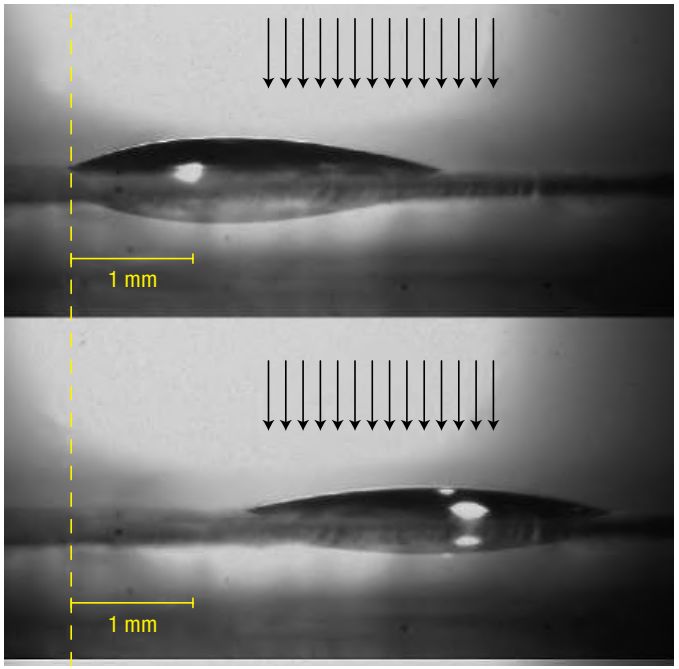
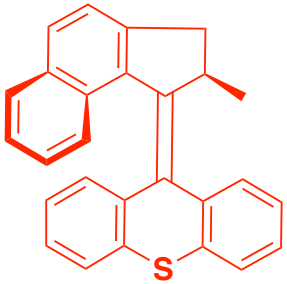
Molecular Motors, from Novelty to Function

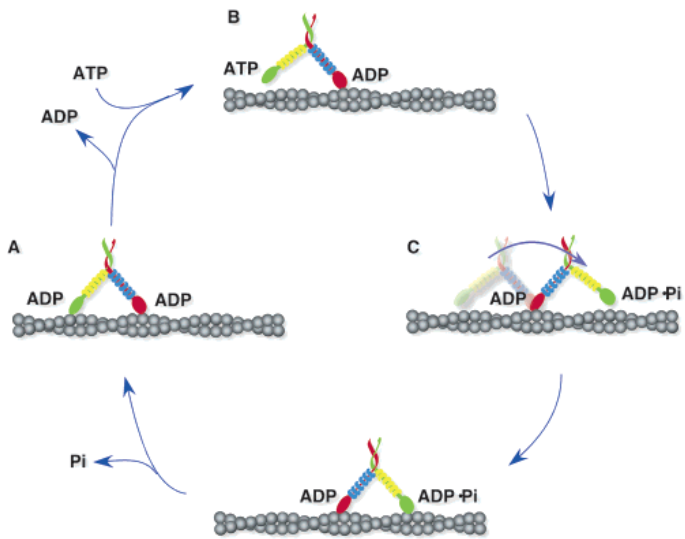




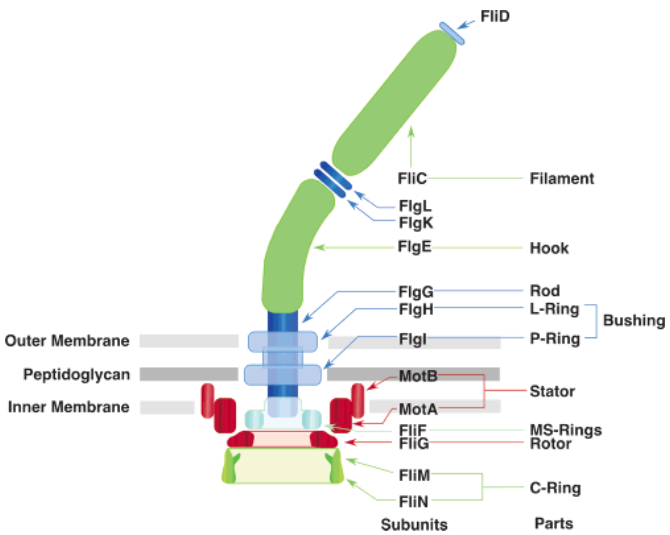


Soumitra Athavale
SED Group Meeting
20 February 2018

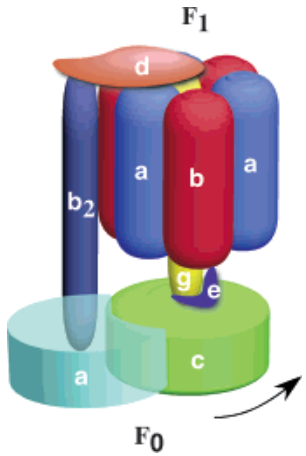
Motors as Indispensible Components of Life



Motor proteins



Bacterial flagella



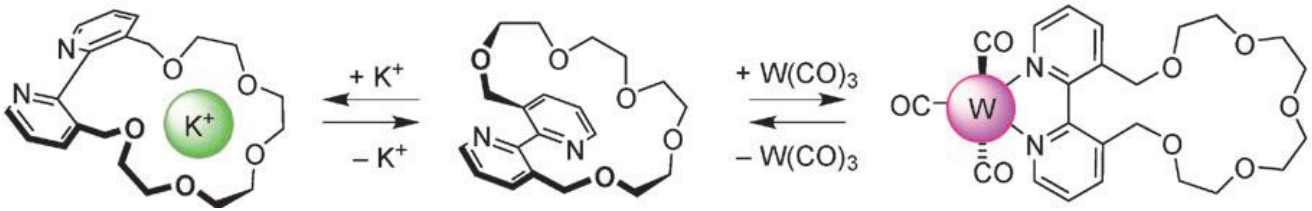
ATP synthase

Kinbara, K., Aida, T., *Chem Rev.,* 2005, 105, 1377.
Yoshida lab, https://www.youtube.com/watch?v=0y7n-vK1AJE

Inspiration from Proteins

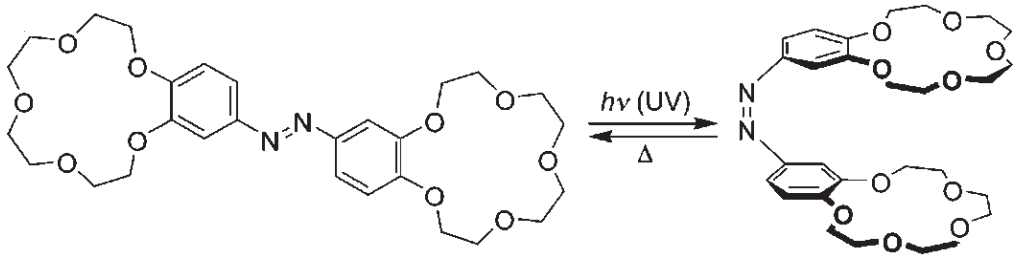
- Biological motors are complex multi-protein assemblies, optimized over millions of years of evolution.
- Although the exact mechanisms by which interacting components harness chemical energy and convert it into net macroscopic movement remain enigmatic, the ability of proteins to convert binding events and substrate reactions to changes in backbone conformation is central to the workings of complex biological machines.
- Indeed, stimuli induced conformational control is a hallmark of proteins and is utilized in all aspects of biochemical function.
- The field of molecular machines seems to have arisen from this desire to achieve controlled changes in the geometrical structure of designed compounds, especially with allostery.
- This would (ostensibly) be the first step towards building more complex structures which are structurally responsive to stimuli and exhibit machine-like or motor-like properties.

Examples from Supramolecular Chemistry
Stimuli induced conformational control



Preferred binding to Na^+

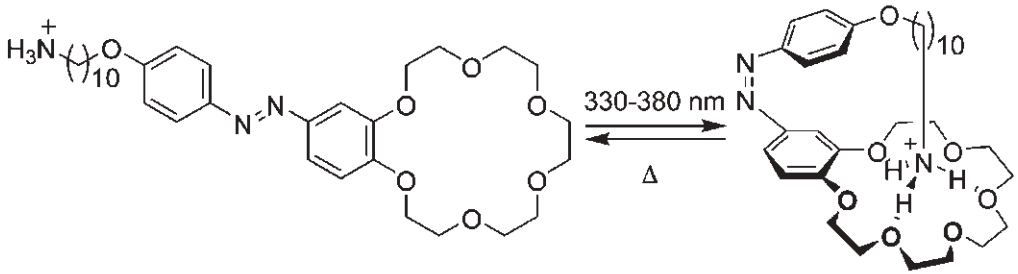
Rebek, 1979



Binds two Na^+

Binds one Rb^+

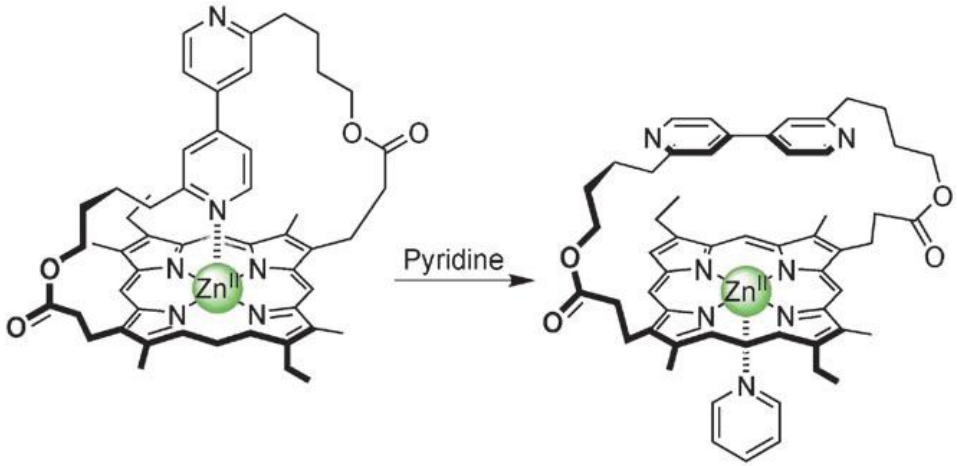
S. Shinkai, 1981
Photoresponsive 'molecular tweezers'



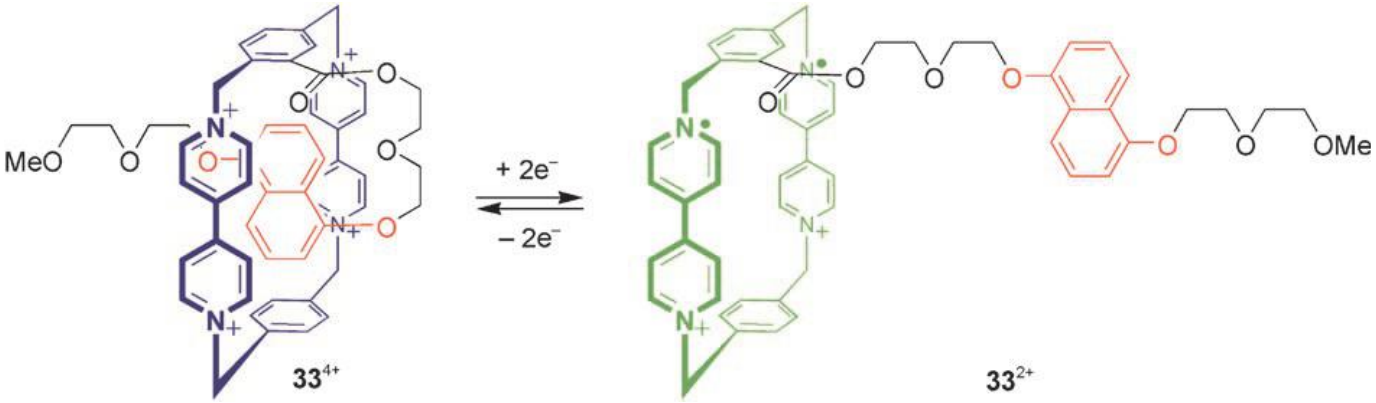
S. Shinkai, 1985
'tail-biting' crown ether

Erbas-Cakmak, S., Leigh, D. A., McTernan, C., Nussbaumer, A., *Chem. Rev.*, 2015, 115, 10081.

Examples from Supramolecular Chemistry



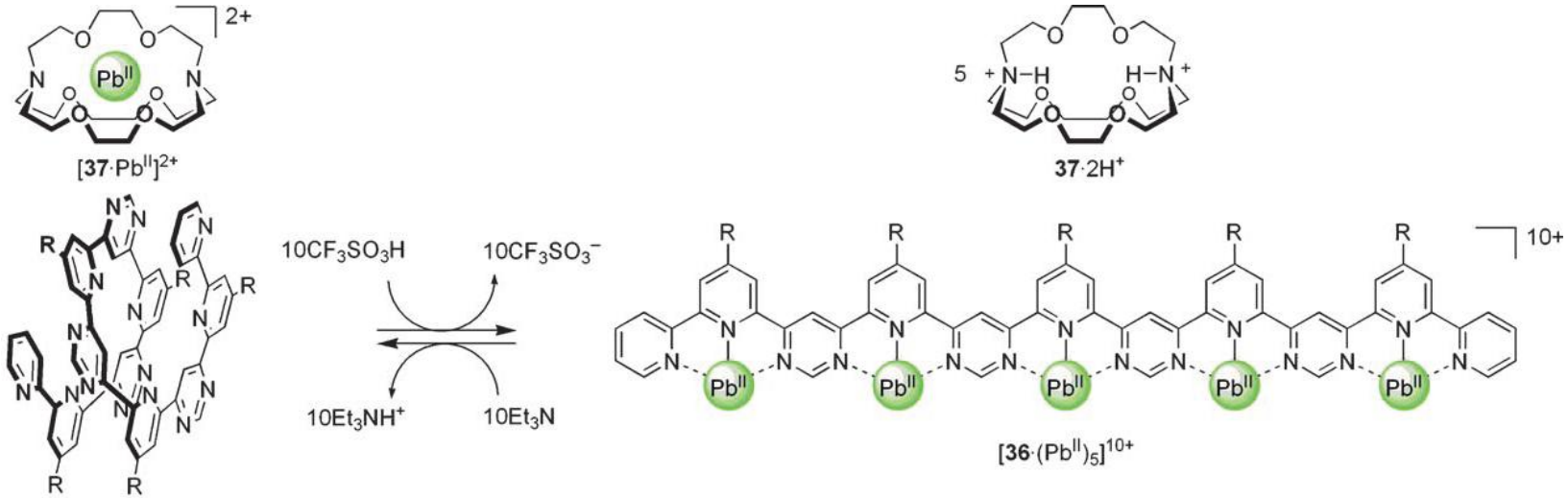
Sanders, 1984



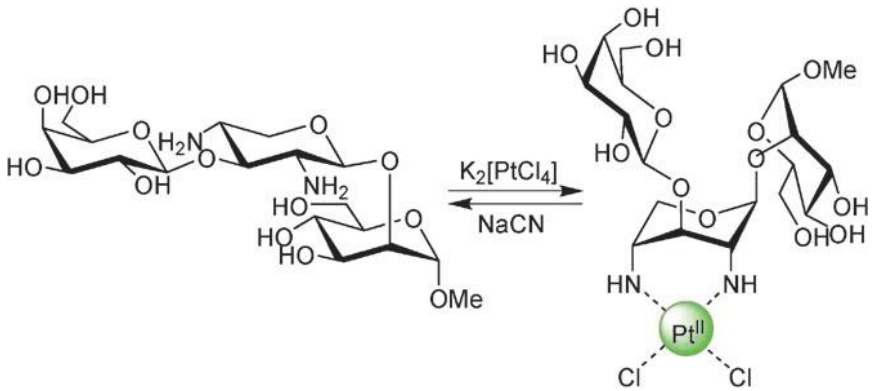
Stoddart and Williams, 1997

Erbas-Cakmak, S., Leigh, D. A., McTernan, C., Nussbaumer, A., *Chem. Rev.*, 2015, 115, 10081.

Examples from Supramolecular Chemistry



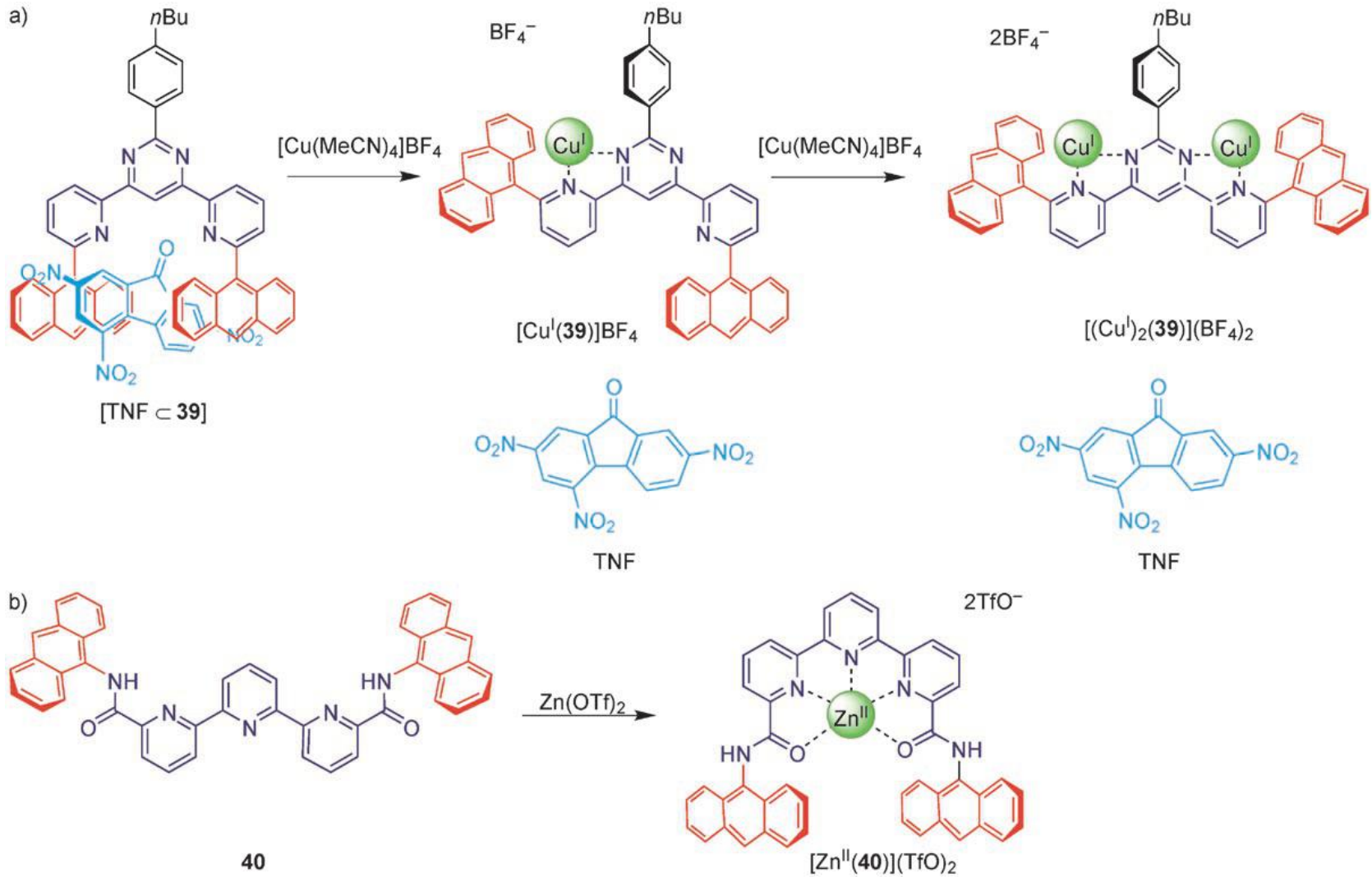
J.M. Lehn, 2002



Yuasa, 2004

Erbas-Cakmak, S., Leigh, D. A., McTernan, C., Nussbaumer, A., *Chem. Rev.,* 2015, 115, 10081.

Examples from Supramolecular Chemistry



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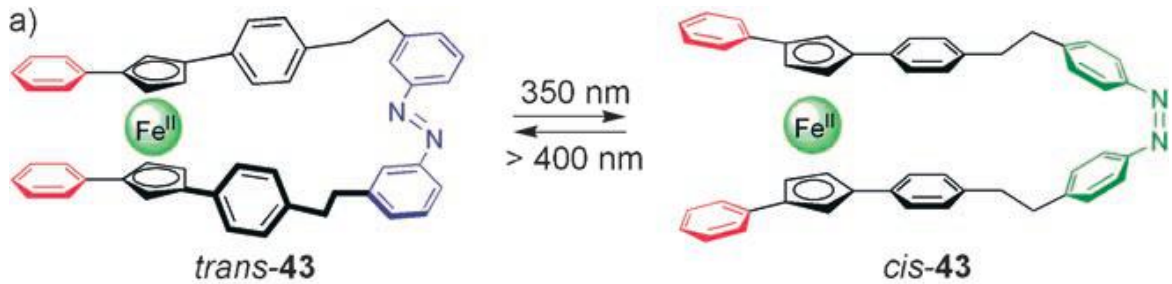
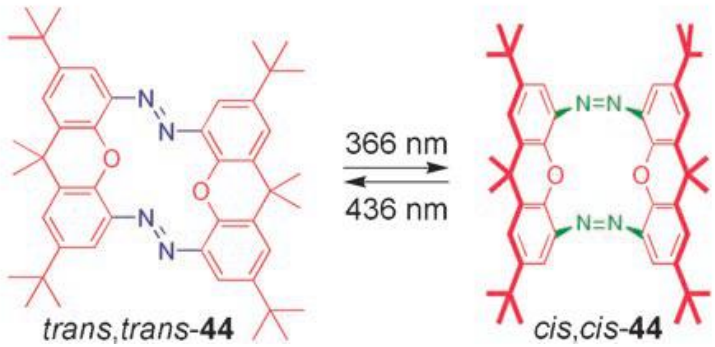


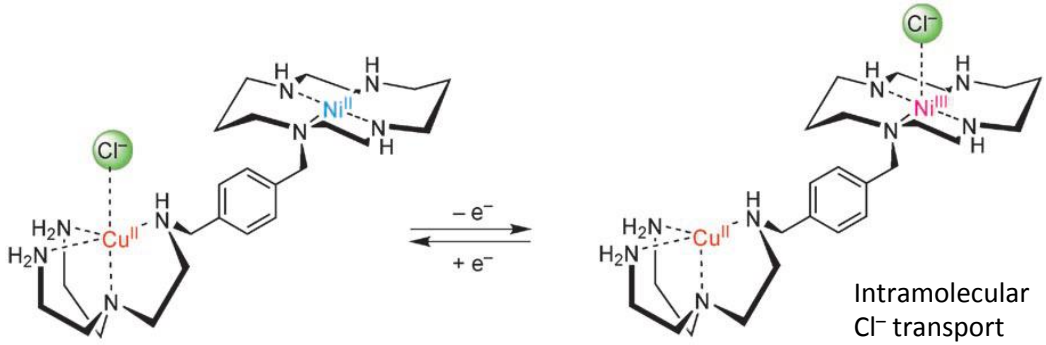
49° angle change of the phenyl arms

Aida, 2003
Molecular scissors



~90° angle between the xanthene units

Tamaoki, 2004
Molecular hinge



Intramolecular Cl^- transport

Zambarbieri, 1999

Erbas-Cakmak, S., Leigh, D. A., McTernan, C., Nussbaumer, A., *Chem Rev.,* 2015, 115, 10081.

Machines (switches, tweezers, shuttles, motors……)

- Since the 1970s, imaginatively designed molecules incorporating binding motifs from supramolecular chemistry or isomerically labile groups has resulted in a plethora of compounds that can undergo a change in structure upon a specific stimulus.

- All of these are collectively and loosely referred to as molecular machines.

- Formally, a *molecular machine* 'is a system in which a stimulus triggers the controlled motion of one molecule or submolecular component relative to another, potentially resulting in a net task being performed'.

- A *molecular switch* 'is a type of machine in which the change in relative positions of the components influences a system as a function of the state of the switch.' (when the switch is returned to its original state, any mechanical work performed by the earlier switching will be undone)

- A molecular motor 'is a machine in which the change in relative positions of the components influences a system as a function of the trajectory of its components.' Such machines can be used to progressively drive systems away from equilibrium and perform work.

- *Most molecular machines are molecular switches and not motors.*

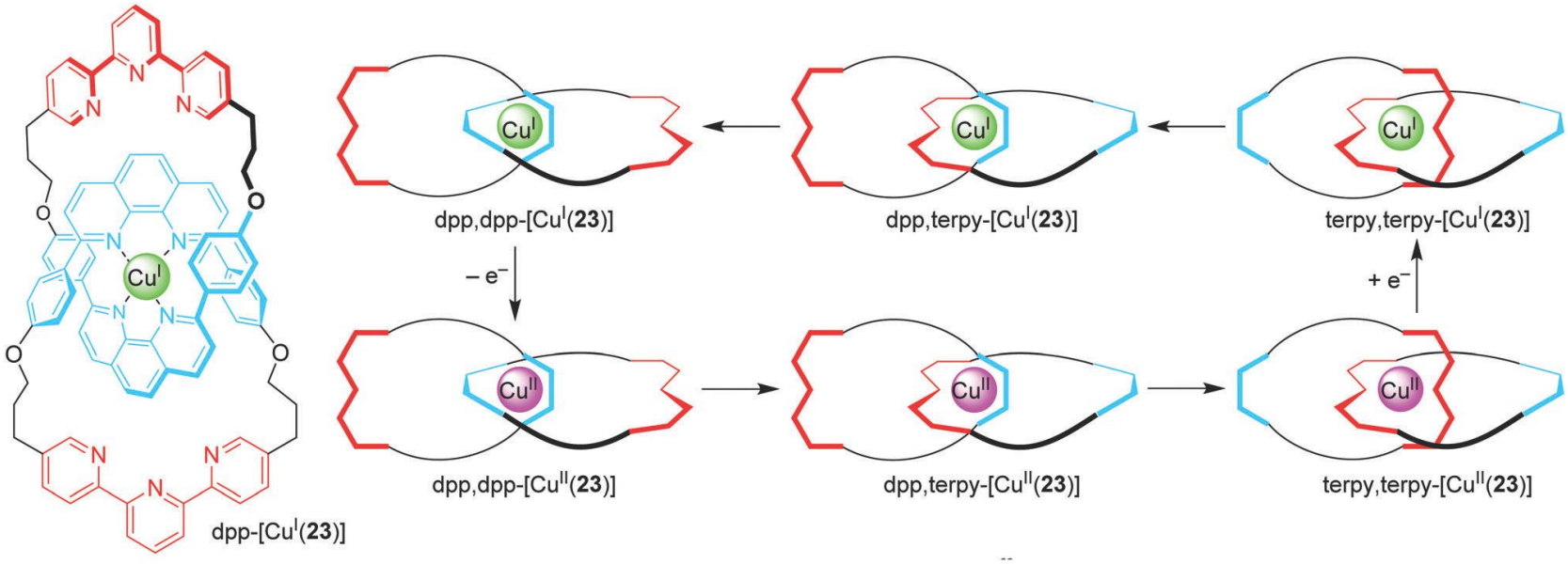
Chatterjee M. N., Kay E. R., Leigh D. A., J. Am. *Chem Soc.,* 2006, 128, 4058.
Feringa, B. L., Leigh, D. A. *et al*., *Chem. Soc. Rev.,* 2017, 46, 2592.

Molecular motors

- A true molecular motor should have fuelled, directional and repetitive motion without undoing any mechanical work that has been performed.
- For this, the system must work away from equilibrium.
- "The challenge of designing molecular motors lies not with producing motion at the molecular level, but in controlling the directionality of movement."

Chatterjee M. N., Kay E. R., Leigh D. A., J. Am. *Chem Soc.,* 2006, 128, 4058.
Feringa, B. L., Leigh, D. A. *et al*., *Chem. Soc. Rev.,* 2017, 46, 2592.

Catenane Classics



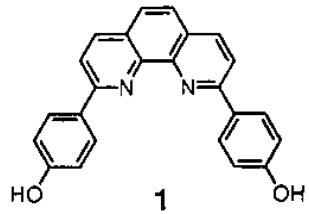
- Catenane **23** consists of a *bpy* and *terpy* sites and a bound Cu(I) ion with a preferred coordination number of 4>5>6

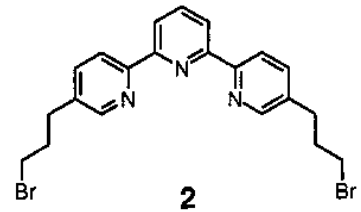
- Electrochemical oxidation to Cu(II) results in a change in preferred coordination (6>5>4) to give octahedral, *terpy* binding.

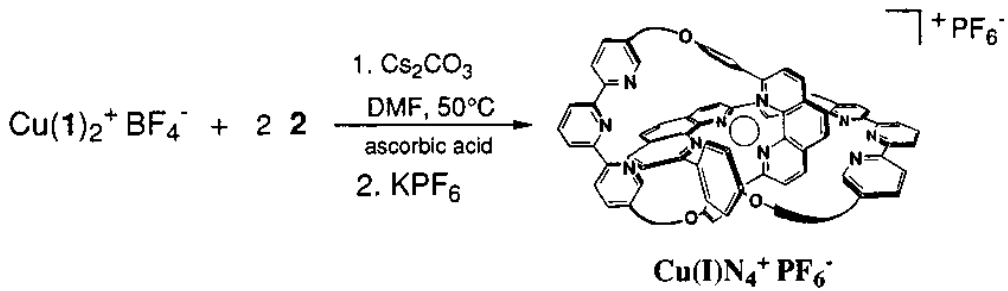
- Intermediate Cu(I)N_5 and Cu(II)N_5 species were detected by UV-vis spectroscopy. CV traces showed transitions consistent with the proposed pathway.

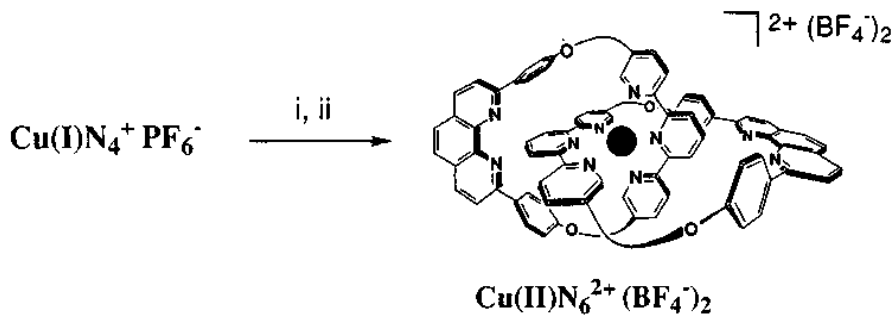
Cardenas, D. J., Livoreil, A., Sauvage J.P., *J. Am. Chem Soc.,* 1996, 118, 11980.
Feringa, B. L., Leigh, D. A. *et al*., *Chem. Soc. Rev.,* 2017, 46, 2592.

Catenane Classics







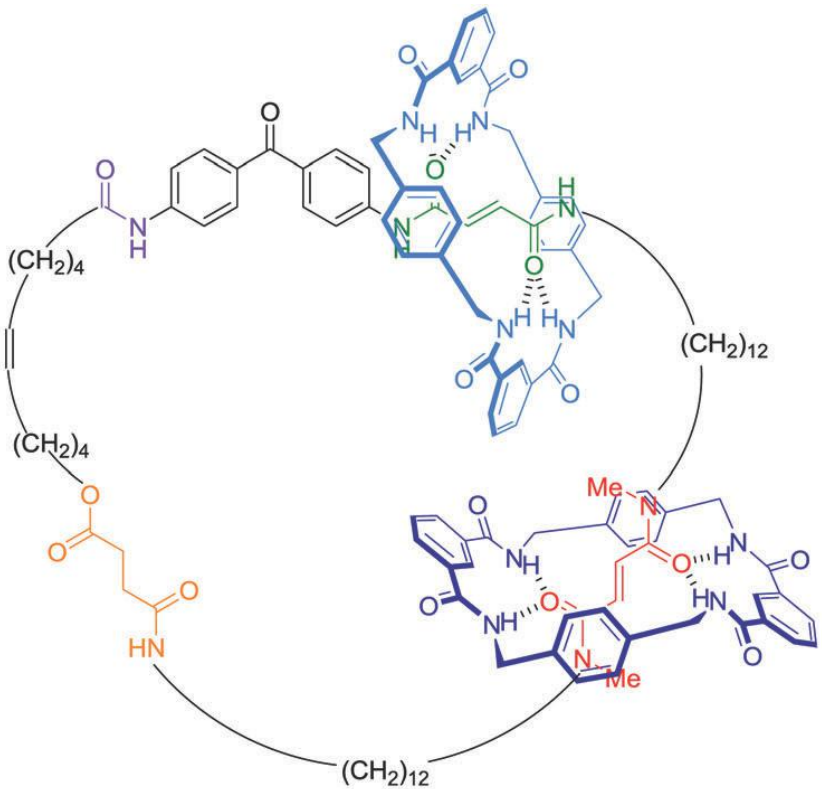


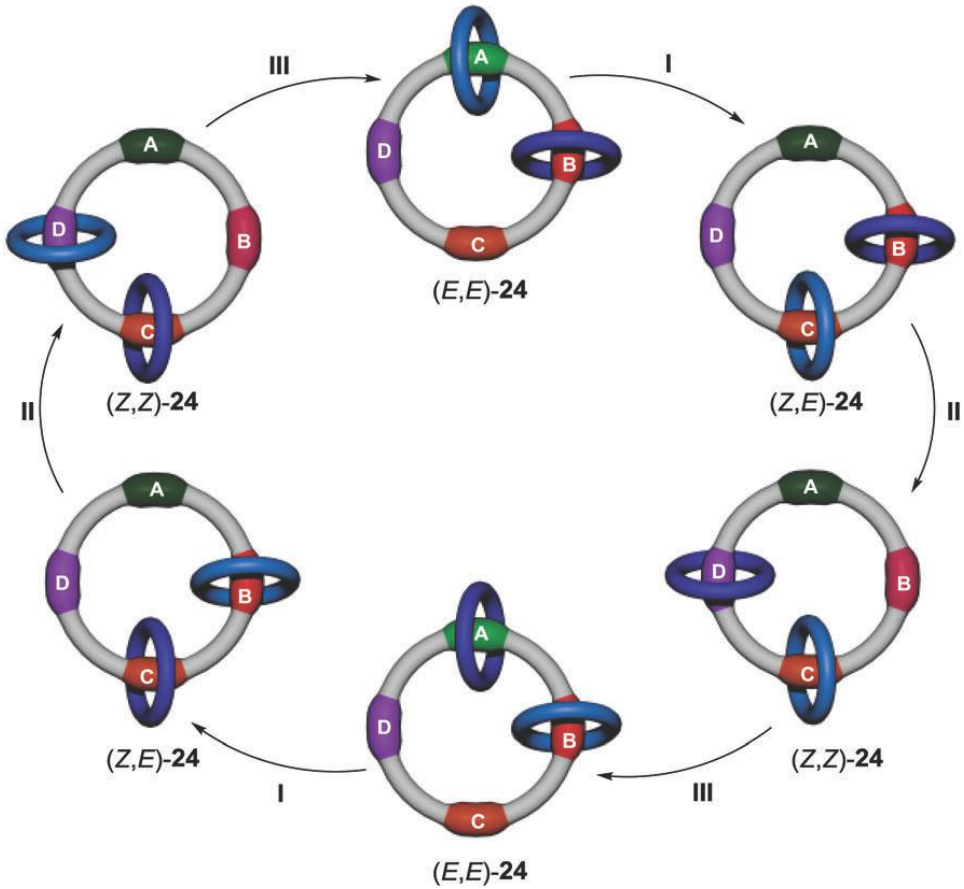
(i) KCN, MeCN-H_2O, 23°C, 15h, 80%. (ii) $Cu(BF_4)_2$, MeCN-CH_2Cl_2, 23°C, 15 h, 83%.

Thus, Sauvage's catenane showed rotary movement, albeit non-directional upon a reversible redox transformation.

Cardenas, D. J., Livoreil, A., Sauvage J.P., *J. Am. Chem Soc.,* 1996, 118, 11980.

Catenane Classics-Directional Rotation

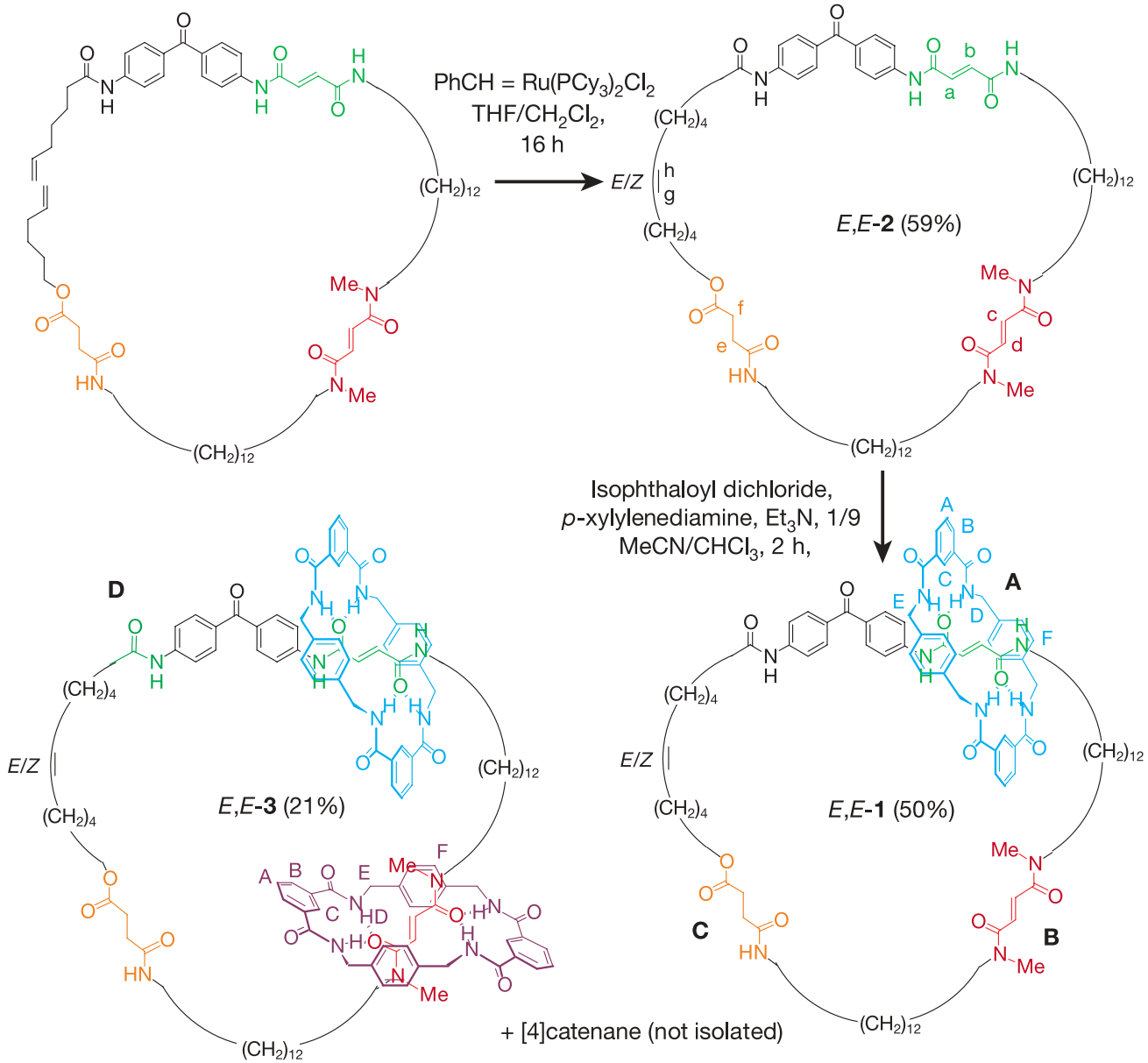




- Binding stations A, B, C and D with relative affinities for the benzylic amide macrocycles A>B>C>D
- Aplication of stimuli I, II and III in this order results in a net clockwise movement of the macrocycles
- I: 350nm, DCM, 5 min, 67%. II: 254nm, 20 min, 50%. III: heat, 100 ^{o}C, 24 h, quant OR cat ethylenediamine, 50 ^{o}C, 48h, 65% OR cat Br_2, 400-670nm, -78 ^{o}C, 10 min, quant

Leigh, D. A., Wong, J., Dehez, F., Zerbetto, F., *Nature,* 2003, 424, 174

Catenane Classics-Directional Rotation



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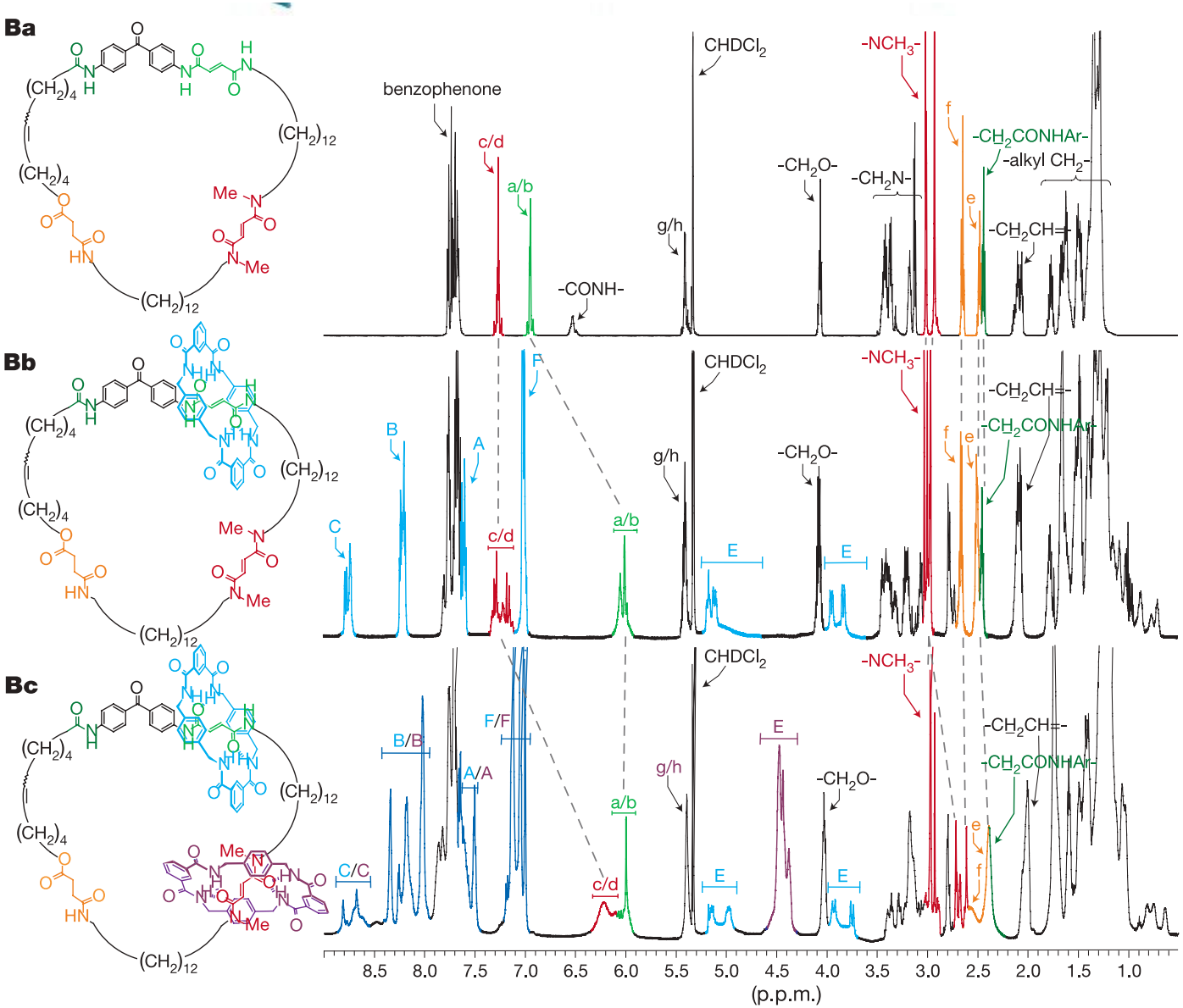
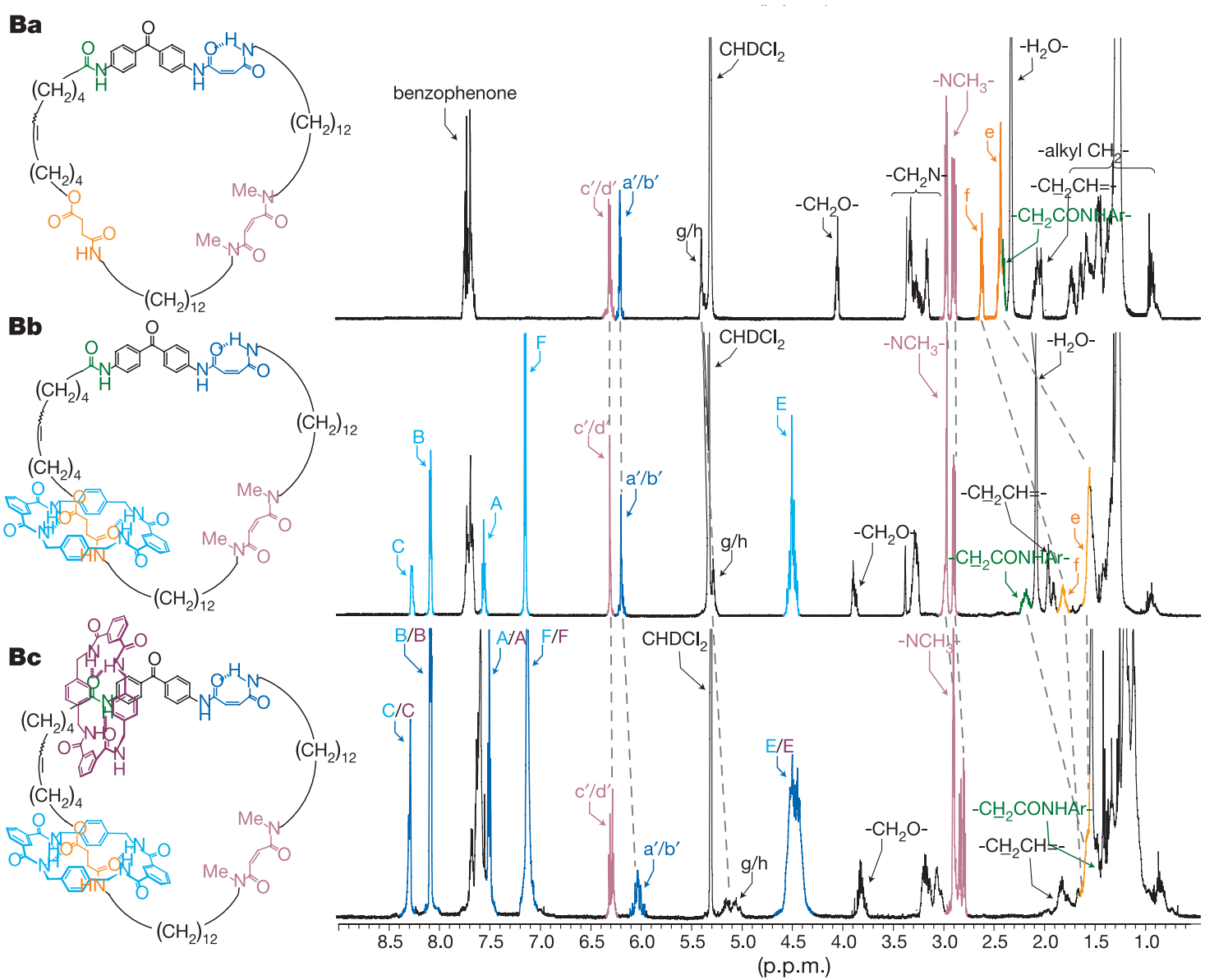
Catenane Classics-Directional Rotation



- Binding is characterized by the signature shielding of the station protons

Leigh, D. A., Wong, J., Dehez, F., Zerbetto, F., *Nature,* 2003, 424, 174

Catenane Classics-Directional Rotation



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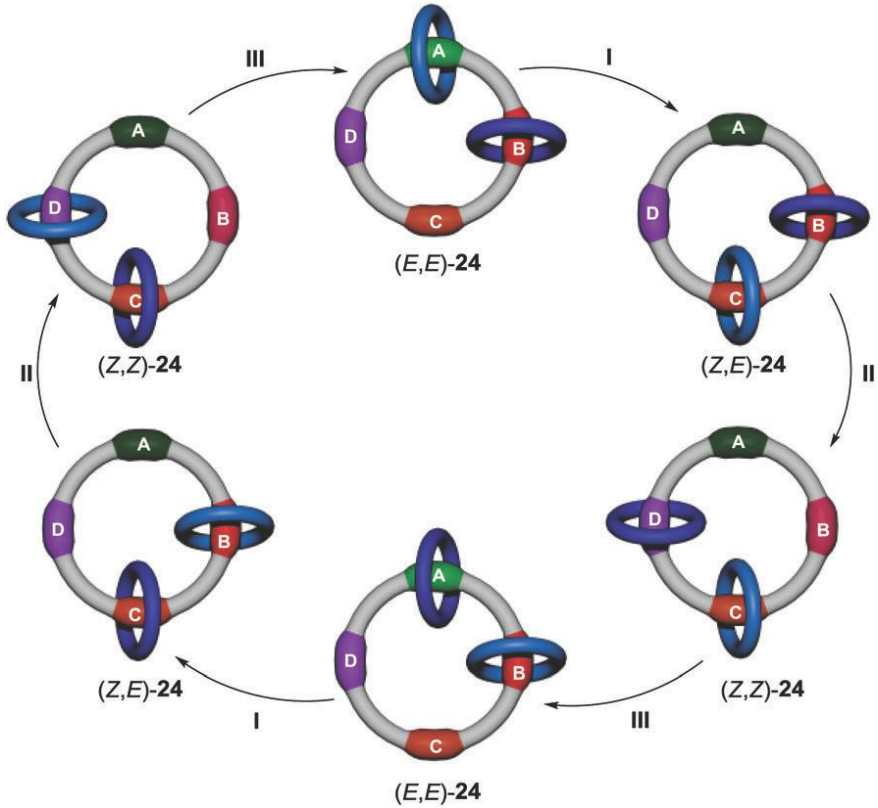
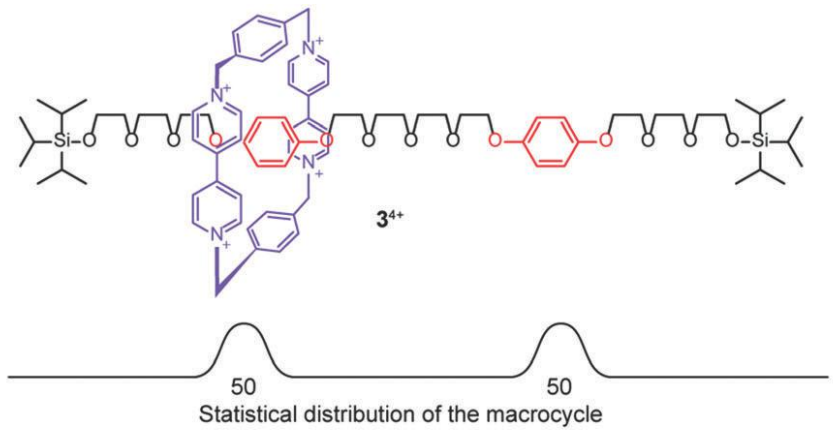


- Binding kinetics guarantees unidirectional motion
- Model, symmetrical 2-station [2]-rotoxanes with separation of 12 carbon atoms were synthesized and energy barriers for shuttling determined by VT-NMR
- Barriers were: A,B: 16 kcal, C: 11 kcal, D:<8 kcal and A',B' << 8kcal
- Thus, at 298 K, movement from A/B to another station is 4000 times slower than movement from C, and 10^6 times slower than movement from D.
- The catenane motor thus, ultimately harnesses Brownian motion of the macrocycles on the track to direct net unidirectional motion.

Leigh, D. A., Wong, J., Dehez, F., Zerbetto, F., *Nature,* 2003, 424, 174

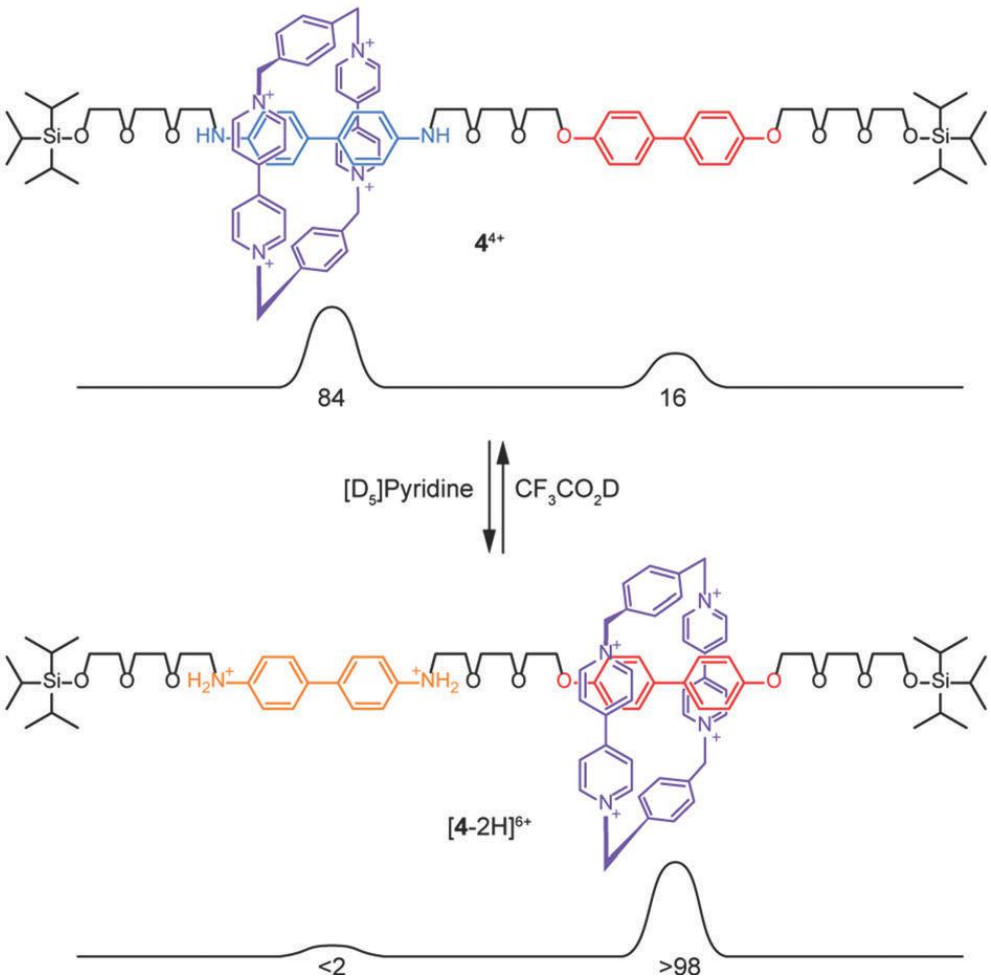
Rotoxane Classics



- First molecular shuttle by Stoddart with the remark "insofar as it becomes possible to control the movement of one molecular component with respect to the other in a [2]-rotoxane, the technology for building 'molecular machines' will emerge."

Anelli, P. L., Spencer, N., Stoddart, J.F, *J. Am. Chem Soc.,* 1991, 113, 5131.
Bissell, R., Cordova, E., Kaifer, A., Stoddart, J. F., *Nature*, 1994, 369, 133.
Feringa, B. L., Leigh, D. A. *et al*., *Chem. Soc. Rev.,* 2017, 46, 2592.

Rotoxane Classics



- First molecular shuttle by Stoddart with the remark "insofar as it becomes possible to control the movement of one molecular component with respect to the other in a [2]-rotoxane, the technology for building 'molecular machines' will emerge."
- Incorporation of two distinct stations allows stimuli induced shuttling of the macrocycle.
- To extract useful work however, the shuttle should operate in a far-from-equilibrium state.

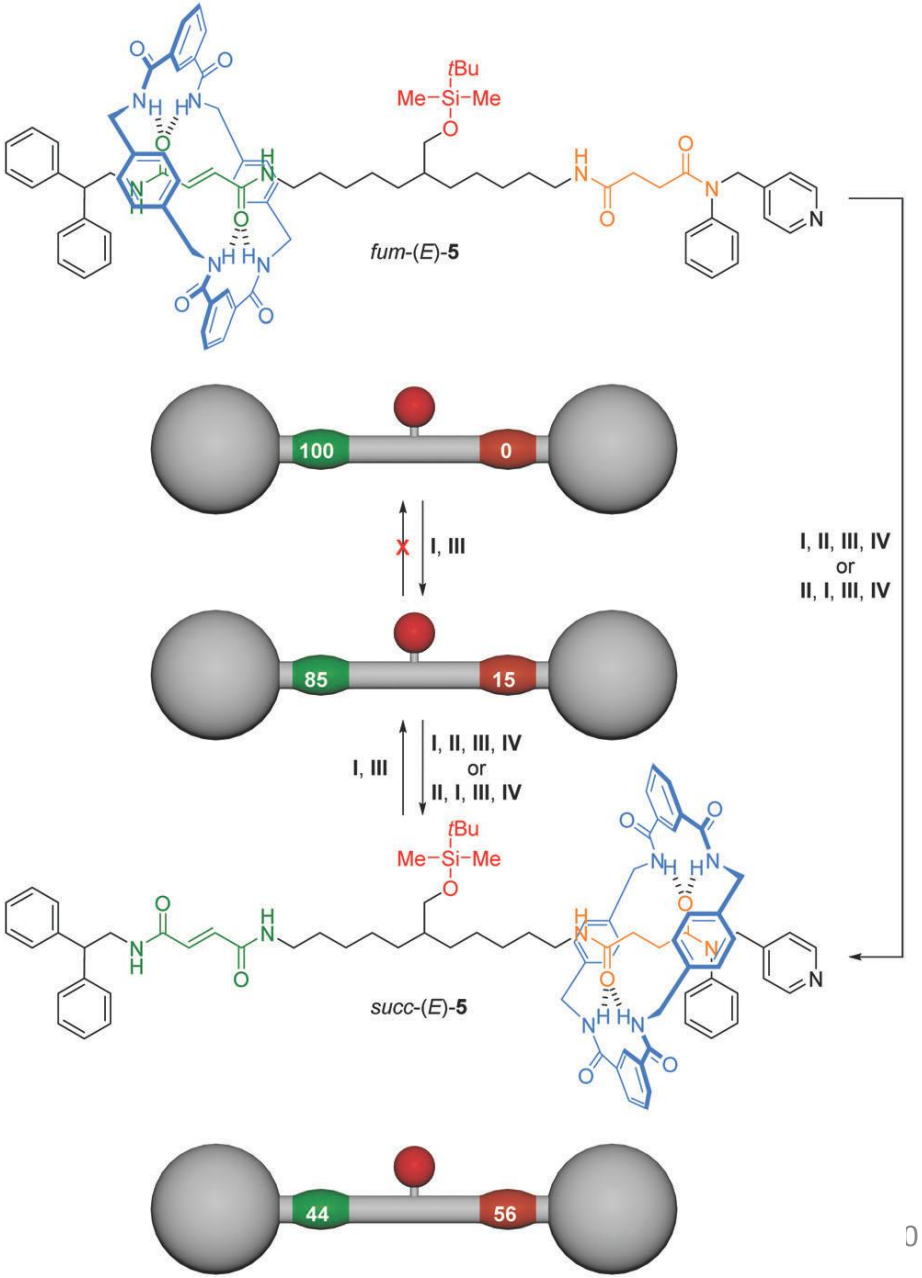
Anelli, P. L., Spencer, N., Stoddart, J.F, *J. Am. Chem Soc.,* 1991, 113, 5131.
Bissell, R., Cordova, E., Kaifer, A., Stoddart, J. F., *Nature*, 1994, 369, 133.
Feringa, B. L., Leigh, D. A. *et al*., *Chem. Soc. Rev.,* 2017, 46, 2592.

Rotoxane Classics-Directional Ratcheted Movement

- Leigh reported the first rotoxane incorporating a ratchet mechanism to maintain a non-equilibrium occupancy of the macrocycle on the two stations.

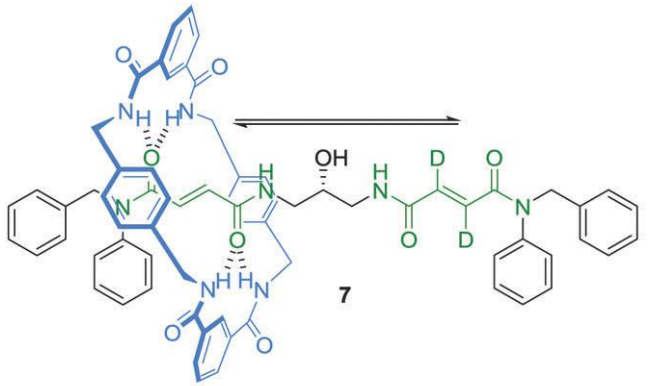
- I: desilylation
- II: E to Z photoisomerization
- III: resilylation
- IV: Z to E thermal isomerization

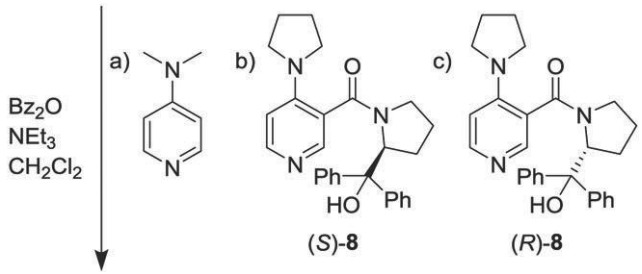
- The machine is not a simple switch but also not quite a molecular motor, since repetitive cycles are not possible.

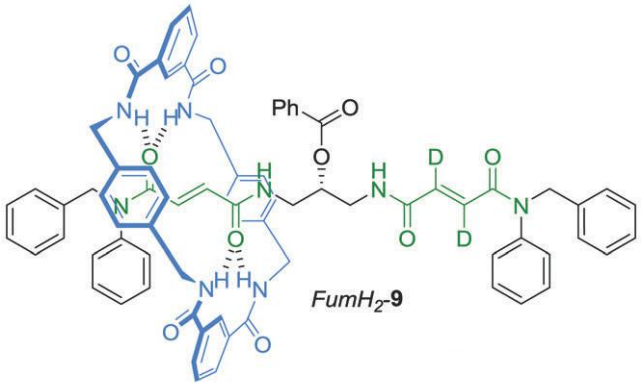


Chatterjee, M., Kay, E., Leigh, D .A, *J. Am. Chem Soc.,* 2006, 128, 4058.

Rotoxane Classics-Directional Ratcheted Movement







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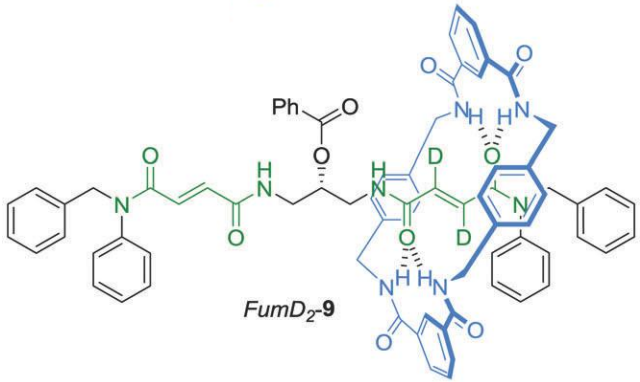


- The two stations on the rotoxane can be desymmetrized by using a chiral amine for benzoylation.
- Essentially a DKR.
- The free energy difference in the two diastereomeric transition states is translated to a non-equilibrium Brownian distribution of the macrocycle on the two stations.

Conditions	Catalyst	Product Distribution (±3%) *Fum*H_2-**9**:*Fum*D_2-**9**
(a)	DMAP	50:50
(b)	(*S*)-**8**	33:67
(c)	(*R*)-**8**	67:33

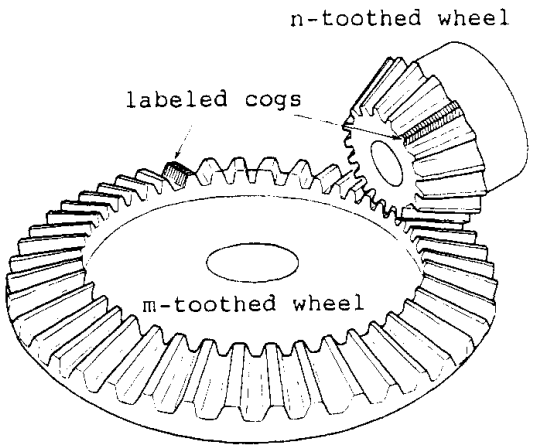
Alvarez-Perez, M., Goldup, S., Leigh, D .A, Slawin, A., *J. Am. Chem Soc.,* 2008, 130, 1836.

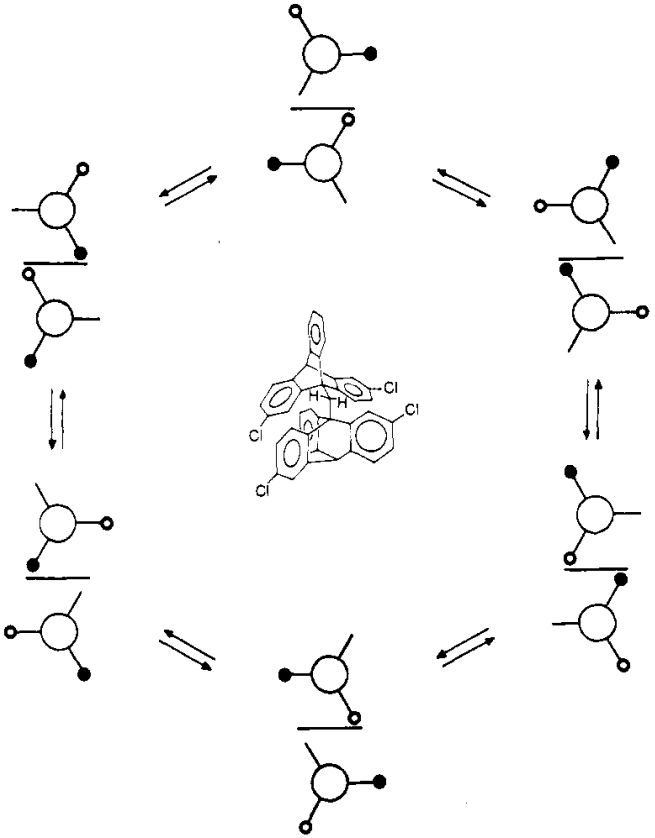
Recap

- A *molecular machine* 'is a system in which a stimulus triggers the controlled motion of one molecule or submolecular component relative to another, potentially resulting in a net task being performed'.
- The chemical literature has extensive examples wherein a binding or isomerization event results in a conformational/geometrical change in the molecular components.
- To make a bonafide molecular motor, a repetitive, fuelled movement away from equilibrium is necessary. Attaining unidirectional motion is the critical challenge to achieve this objective.
- Such motion has been demonstrated in the ingenious design of catenanes and some rotoxanes by a partitioning of random Brownian motion by chemical or physical constraints.
- Although fascinating, these systems remain highly engineered.

Rotation Along Single and Double Bonds

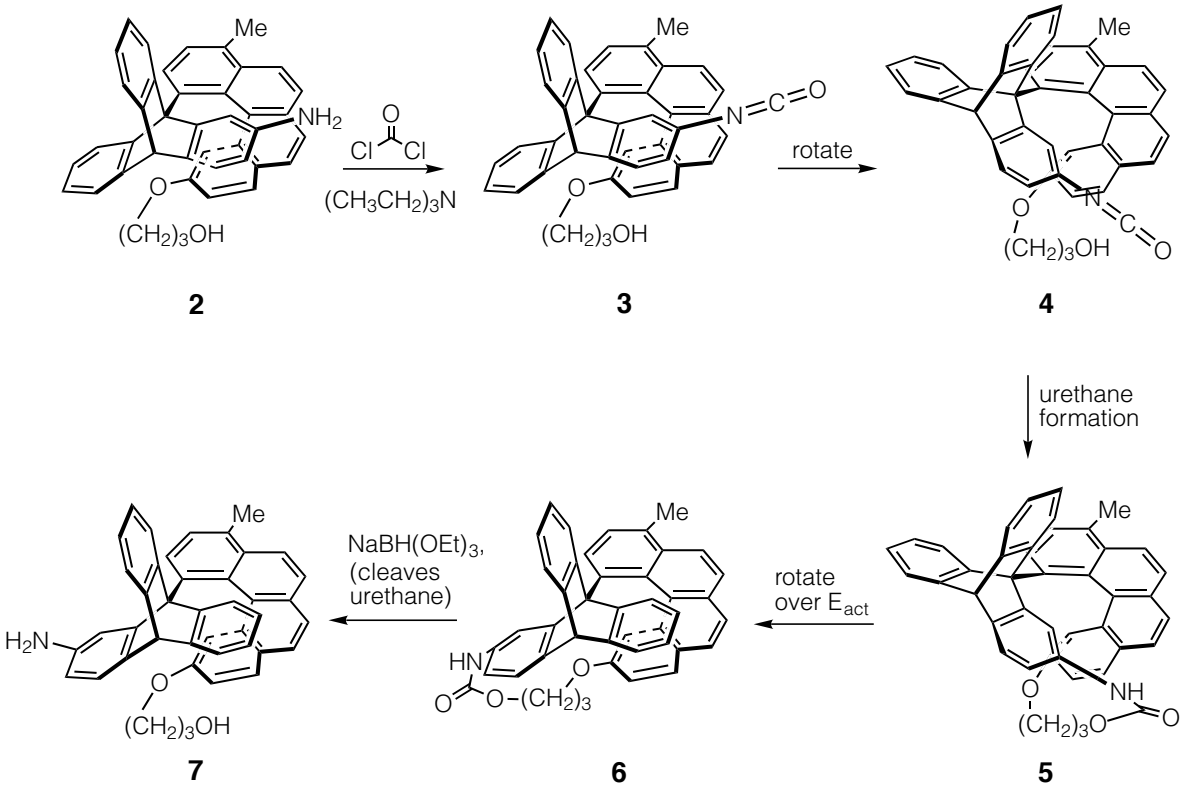
- Rotation around a single bond is the most conceptually simple, repetitive circular motion.
- Although direct control over such a rotation is not possible, restricted rotation around hindered single bonds can lead to correlated movement.
- Disrotatory movement in triptycene derivatives (a molecular bevel gear) was first explored by Mislow and Iwamura.

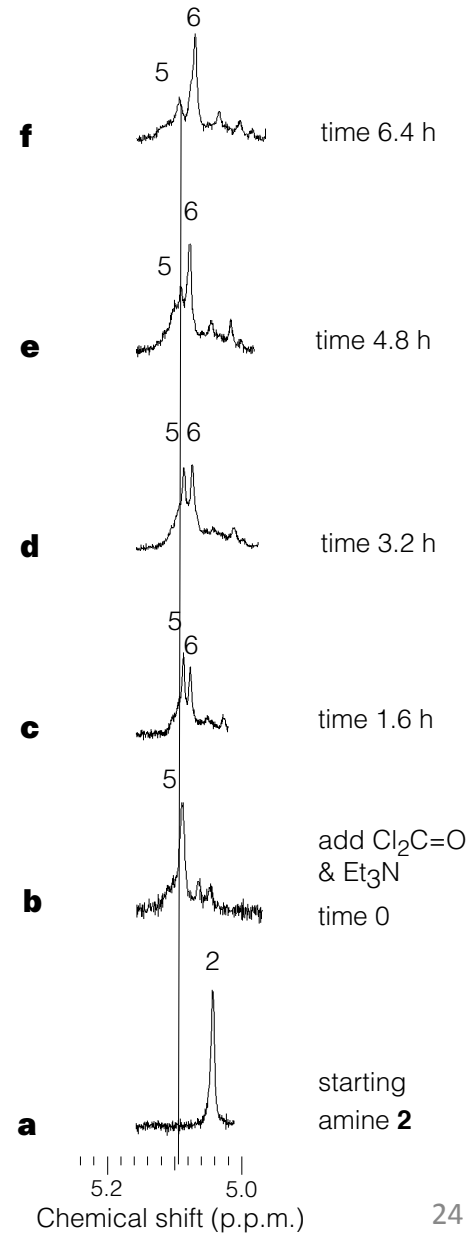




Iwamura, H., Mislow, K., *Acc. Chem. Res.*, 1988, 21, 175.

Directional Rotation Along Single Bonds

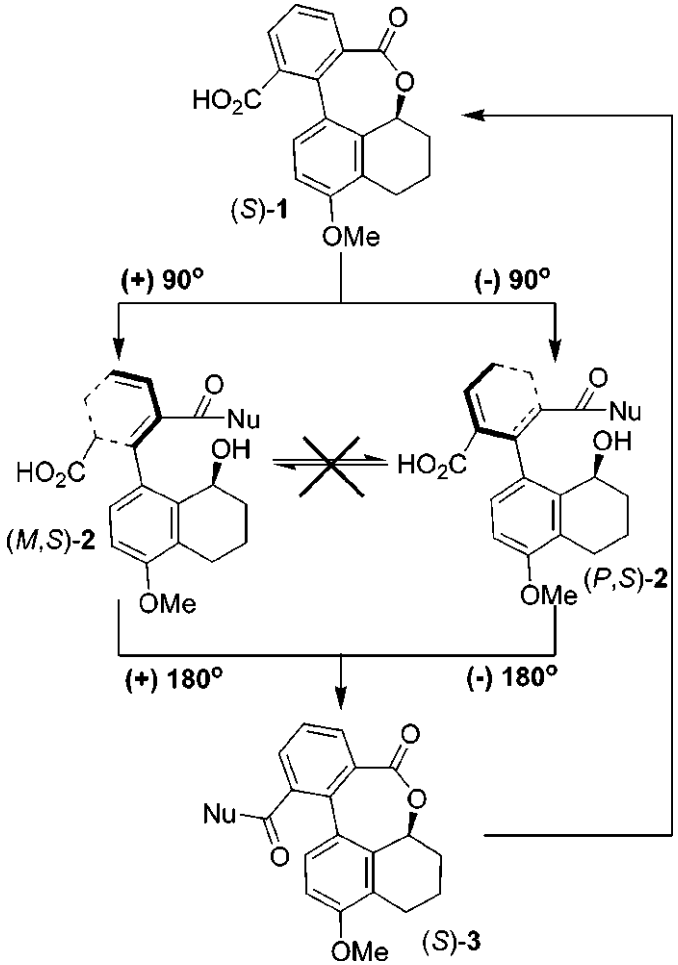


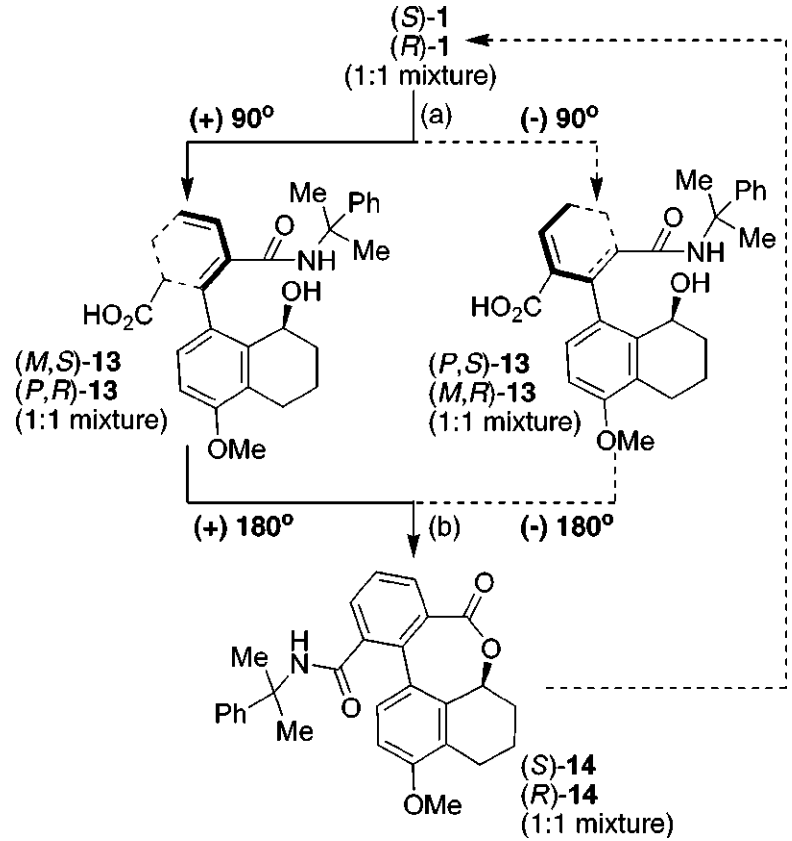


- Direct rotation in **2** has a barrier of ~25kcal/mol and is slow at room temperature (several days).
- The chemical energy of carbonyl dichloride is utilized to reduce the energy barrier for clockwise rotation. A non-repeatable, directional 120° rotation is achieved.
- Treatment of **7** with $COCl_2$ leads rapidly to **6** but not to **5.**

Kelly, T., De Silva, H., Silva, R., *Nature,* 1999, 401, 150.

Directional Rotation Along Single Bonds



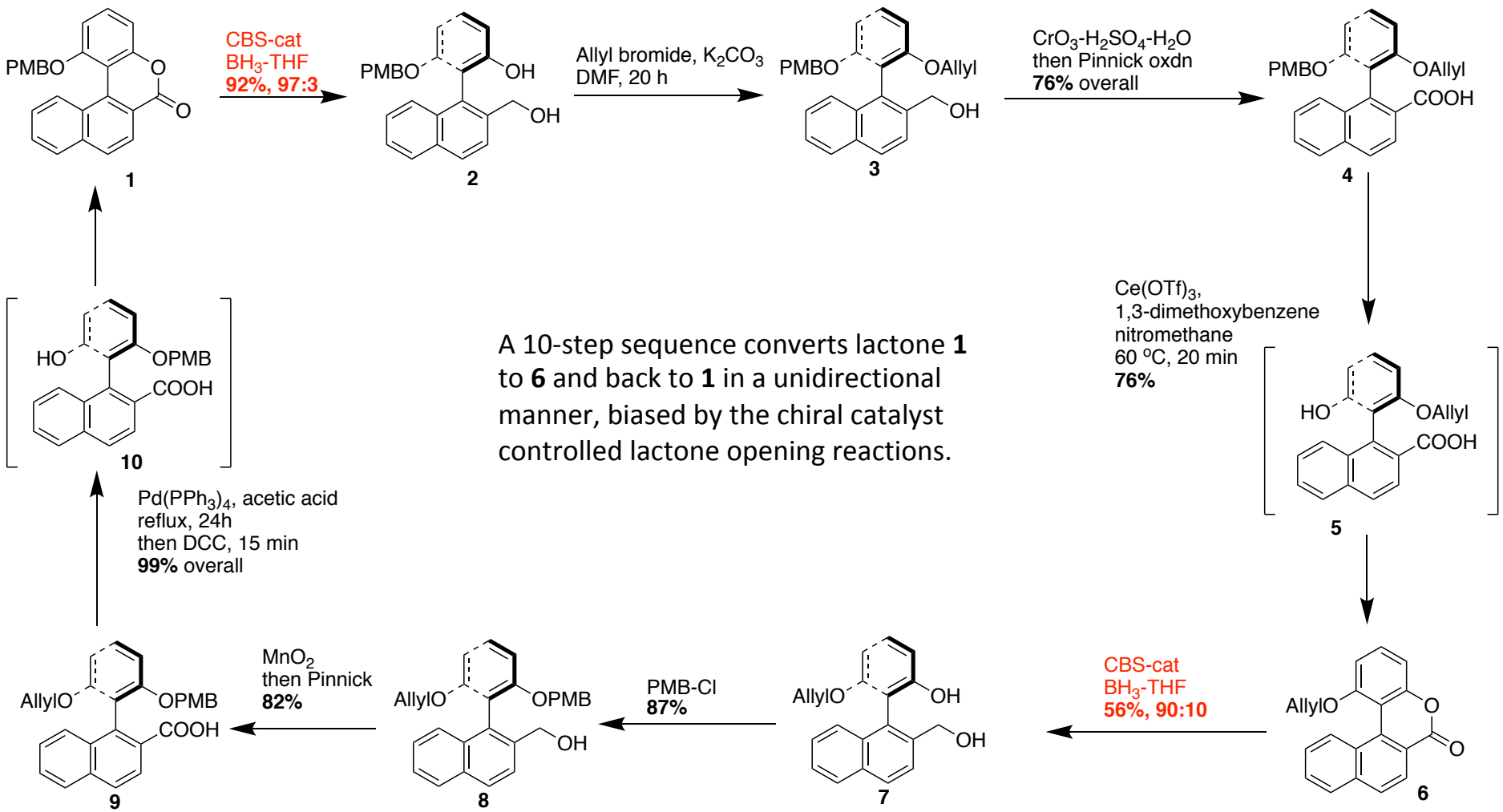


[a] Conditions used: (a) $PhC(CH_3)_2NH_2$, $AlMe_3$, CH_2Cl_2, reflux; (b) DCC, DMAP, DMAP·HCl, $CHCl_3$, reflux.

- If the nucleophilic lactone opening of **1** is diastereospecific, subsequent relactonization to give **3** must inherently proceed through a directional rotation of the biaryl.
- Studies with the racemate **1** are consistent with this hypothesis.

Dahl, B., Branchaud, B., *Org. Lett.*, 2006, 8, 5841.

Directional 360º Rotation Along Single Bonds

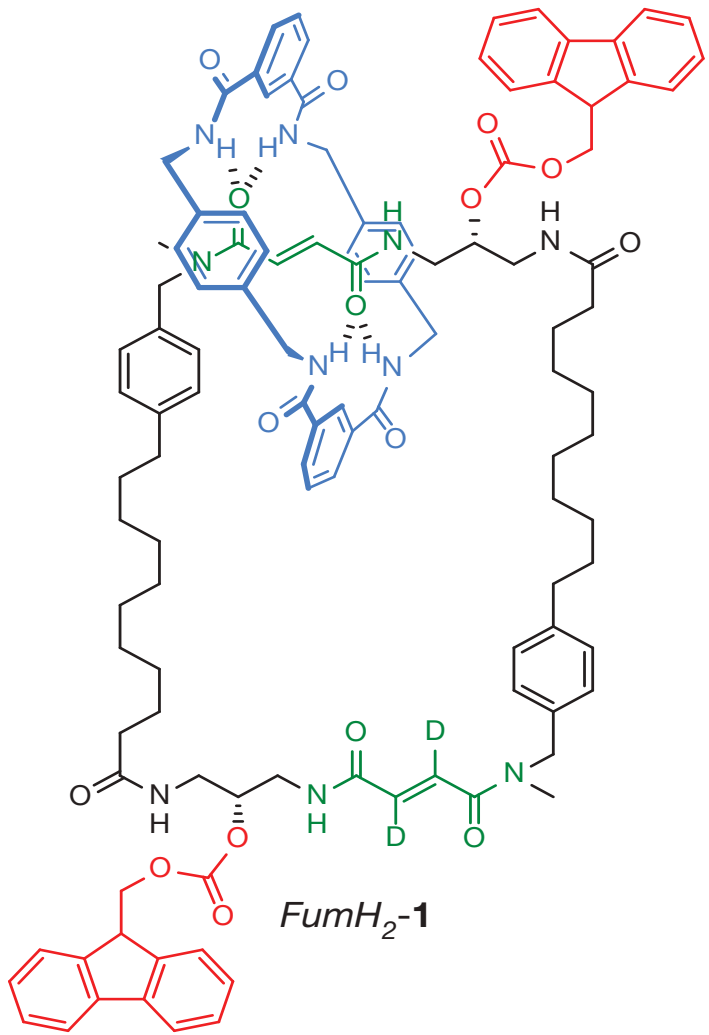


A 10-step sequence converts lactone **1** to **6** and back to **1** in a unidirectional manner, biased by the chiral catalyst controlled lactone opening reactions.

First demonstration of a chemically driven 360º unidirectional rotation by Feringa.

Fletcher, S., Dumur, F., Pollard, M., Feringa, B. L., *Science,* 2005, 310, 80.

Group Problem

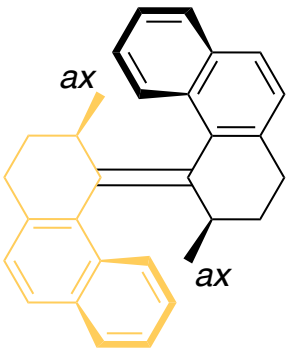


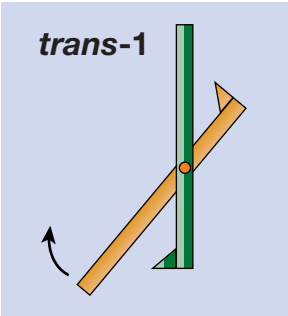
FumH$_2$-**1**

- The treatment of Catenane **1** with excess $KHCO_3$, excess Fmoc-Cl and a *bulky* amine base in DCM results in an autonomous, *Fmoc fuelled* directional clockwise movement of the macrocycle.
- What are the kinetic constraints necessary for this operation to occur and how does it occur?

Group Problem-Solution

Light Driven Motors



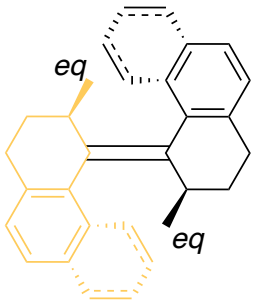


(R,R)-(P,P)-*trans-**1*** ΔE = ~0 kJ/mol

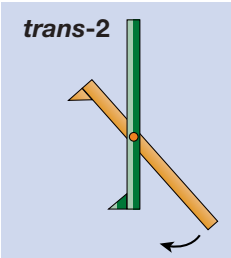
The extraordinary molecule **1** has the following stereochemical features:

1. Thermally stable but photochemically interconvertible olefin isomerism.
2. P, *P* or *M, M* helicity.
3. Fixed configurations at the stereogenic centers.
4. Conformational flexibility of the cycloalkane rings resulting in the adoption of pseudoaxial or equatorial orientations of the methyl groups.

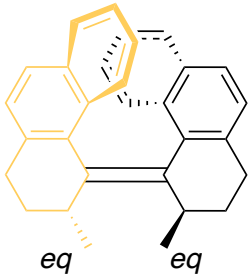
This can result in 3 other isomers:



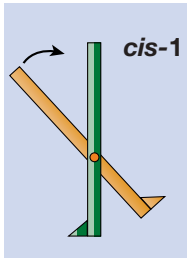
(R,R)-(M,M)-*trans-**1***



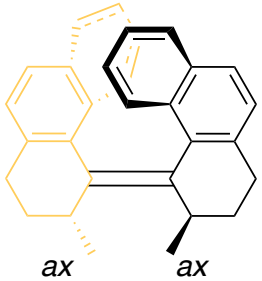
ΔE = + 35.9 kJ/mol



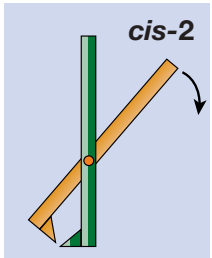
(R,R)-(M,M)-*cis-**1***



ΔE = 46 kJ/mol



(R,R)-(P,P)-*cis-**1***

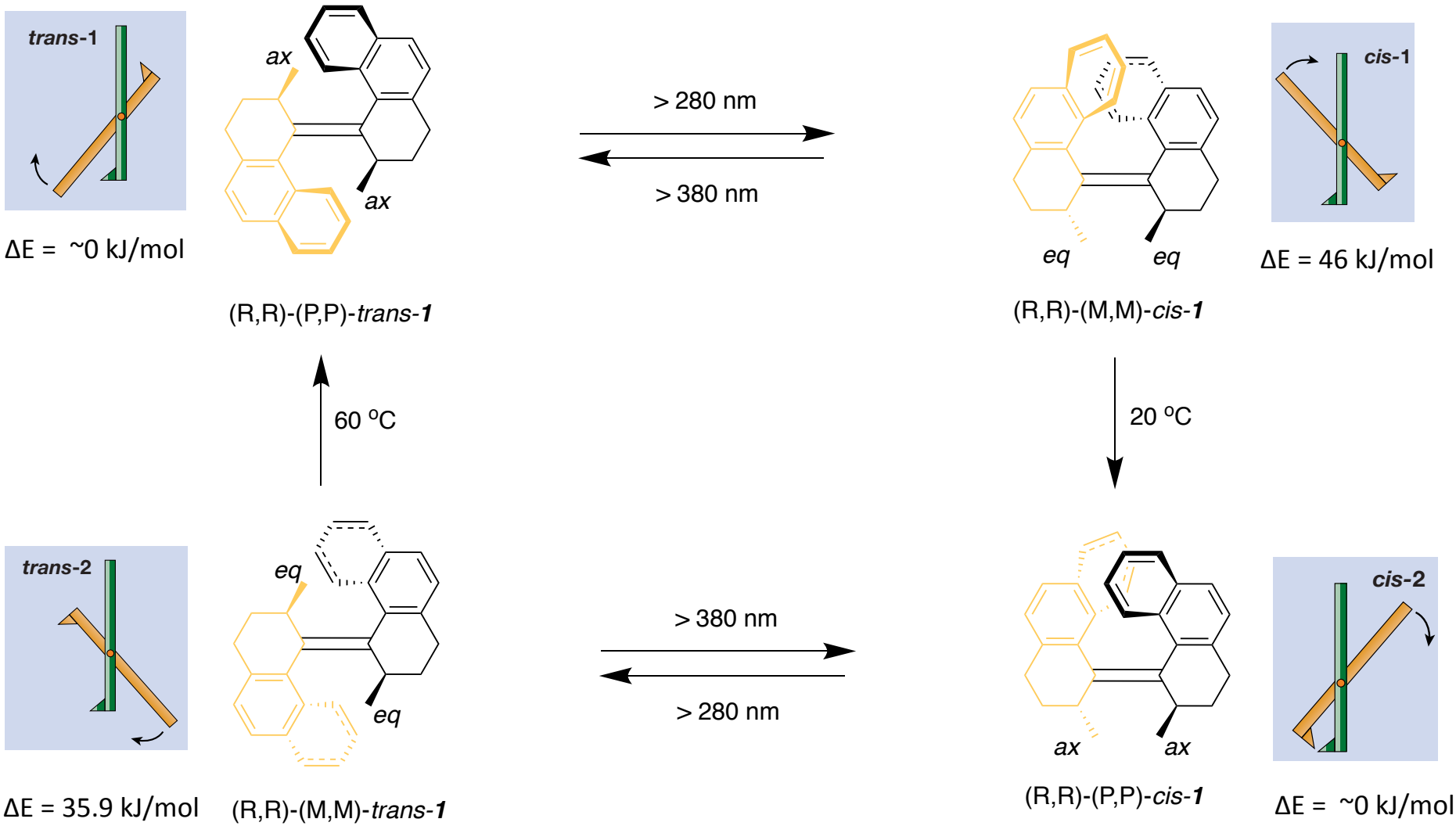


ΔE = ~0 kJ/mol

The orientation of the methyl groups is linked to the helicity of the molecule. Pseudoequatorial orientation in the (M,M) helix results in a high steric cost (MOPAC93-AM1 calculations.

Koumura, N., Zijistra, R., van Delden, R., Harada, N., Feringa, B. L., *Nature,* 1999, 401, 152.
Davis, A., *Nature,* 1999, 401, 120.

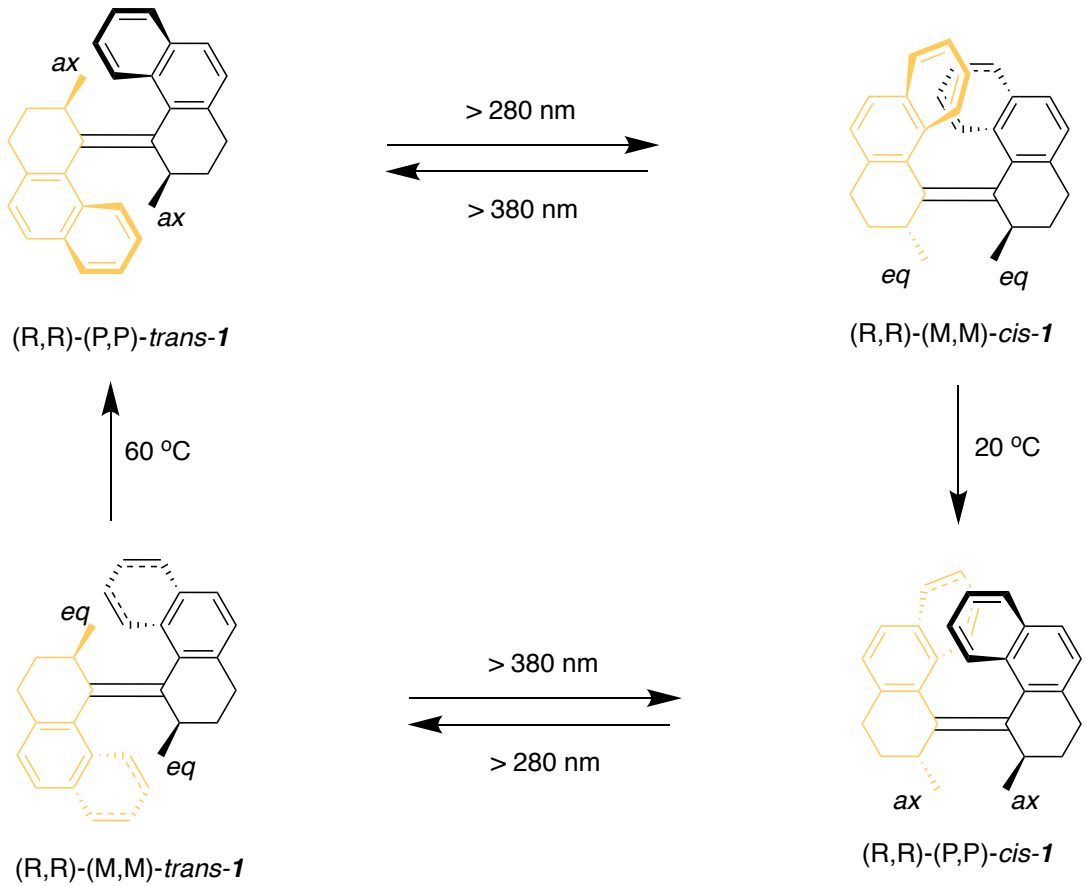
Light Driven Motors

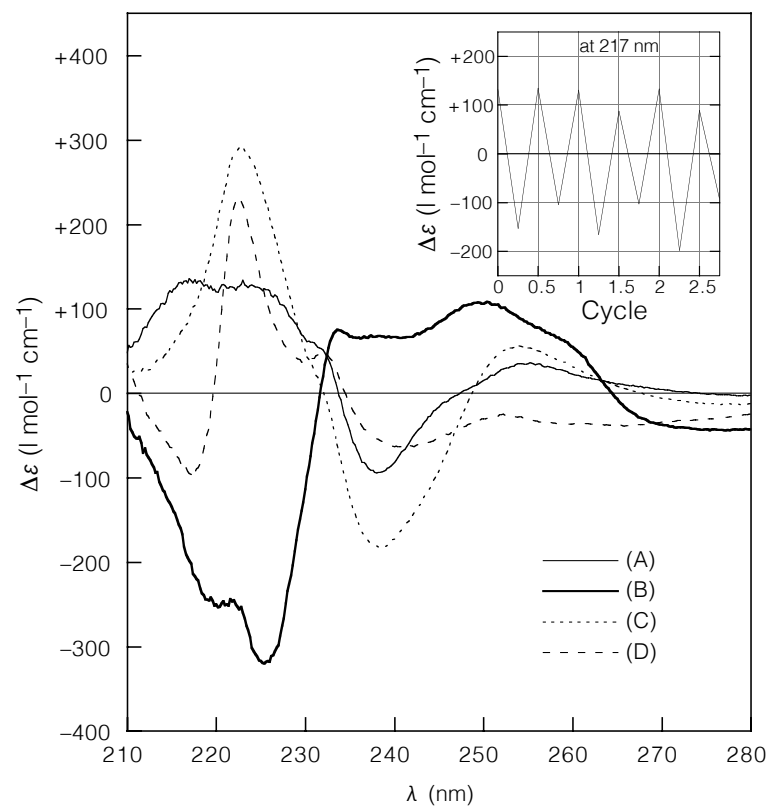


A unidirectional rotation is achieved by two cycles of photochemical alkene isomerization followed by a thermal relaxation.

Koumura, N., Zijistra, R., van Delden, R., Harada, N., Feringa, B. L., *Nature,* 1999, 401, 152.

Light Driven Motors

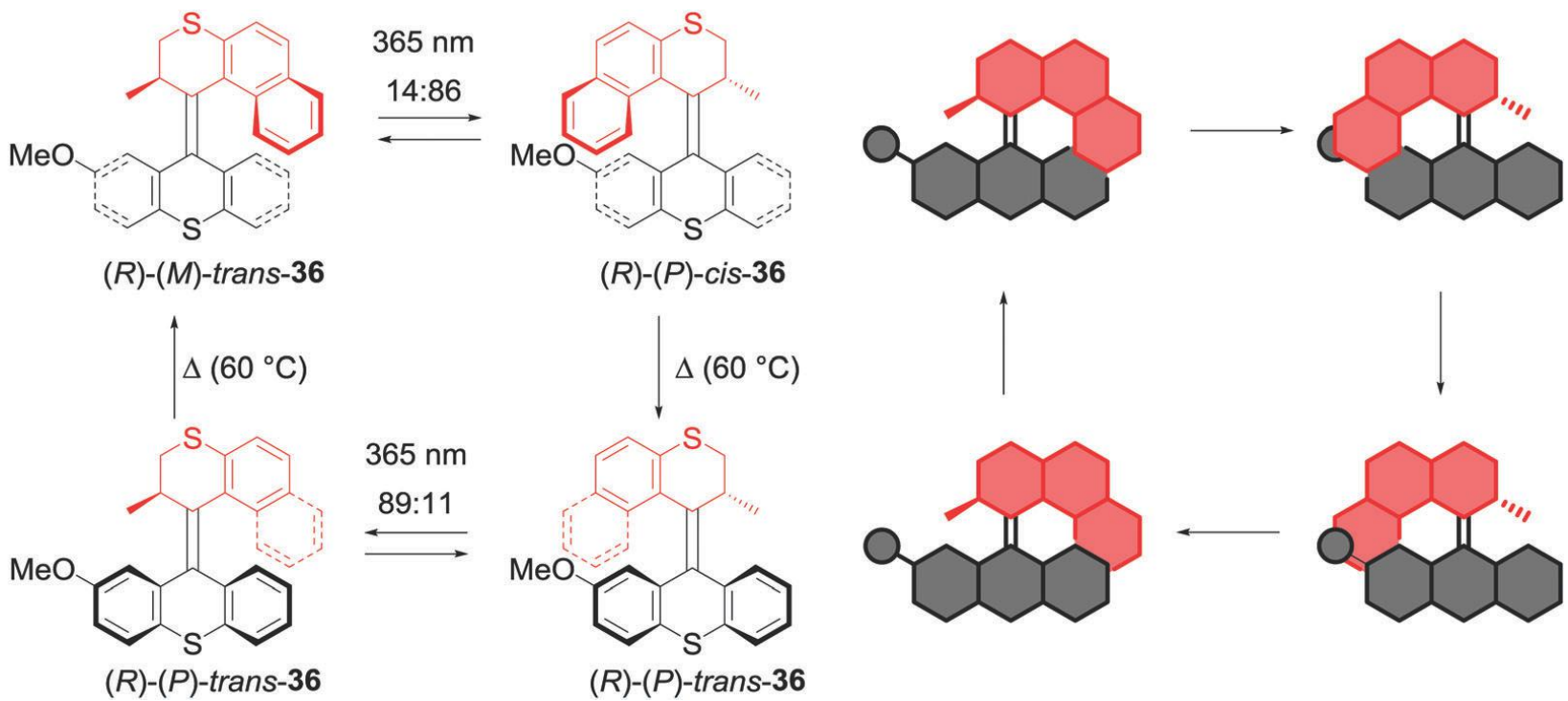




- Each intermediate is isolable and characterized by NMR, UV, CD and chiral HPLC.
- The thermal relaxation steps are irreversible.
- If the molecule is irradiated at >280 nm at 60 °C, a continuous unidirectional motion results.
- The mechanism arises from a beautiful interplay between the dynamic helical chirality and the fixed point chirality of the stereogenic centres.

Koumura, N., Zijistra, R., van Delden, R., Harada, N., Feringa, B. L., *Nature,* 1999, 401, 152.

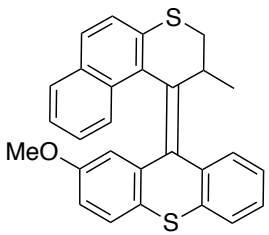
Light Driven Motor, 2nd Generation



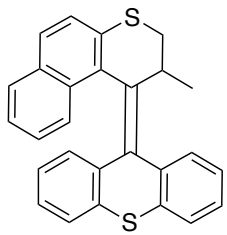
- A simplified structure with a single stereogenic centre is sufficient for unidirectional motion.
- The thermal relaxation barriers (thermal helix inversion, THI) in both cycles are roughly the same, resulting in a uniform motion.
- In general, the efficiency or speed of rotation is dependent upon the THI barriers.

Koumura, N., Geertsema, E., Meetsma, A., Feringa, B. L., *J. Am. Chem. Soc.*, 2000, 122, 12005.

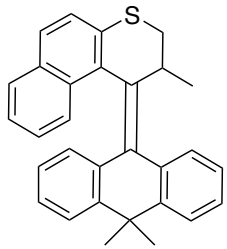
Optimizing the 2nd-gen Motor



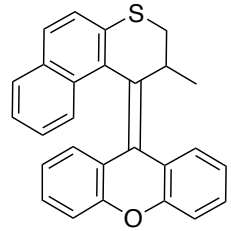
184 h



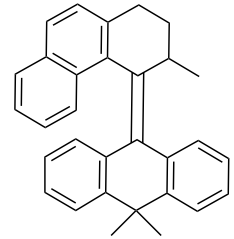
215 h



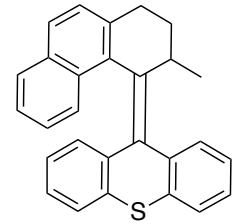
233 h



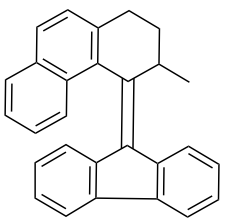
26.3 h



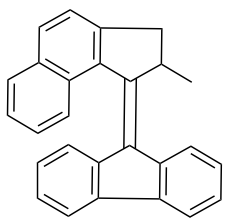
2.01 h



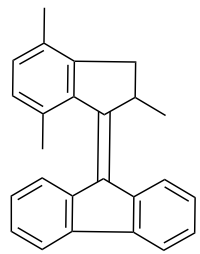
0.67 h



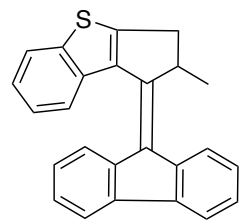
1400 years



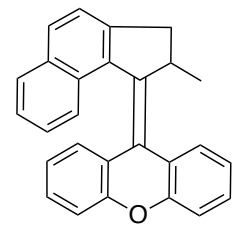
3.2 min



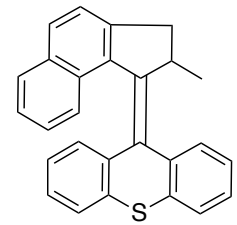
15 s



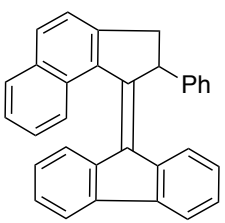
70 ms



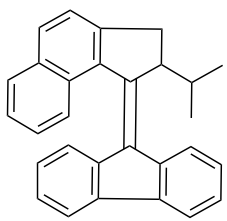
2.8 us



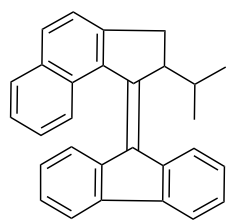
110 ns



9.8 min



1.5 min

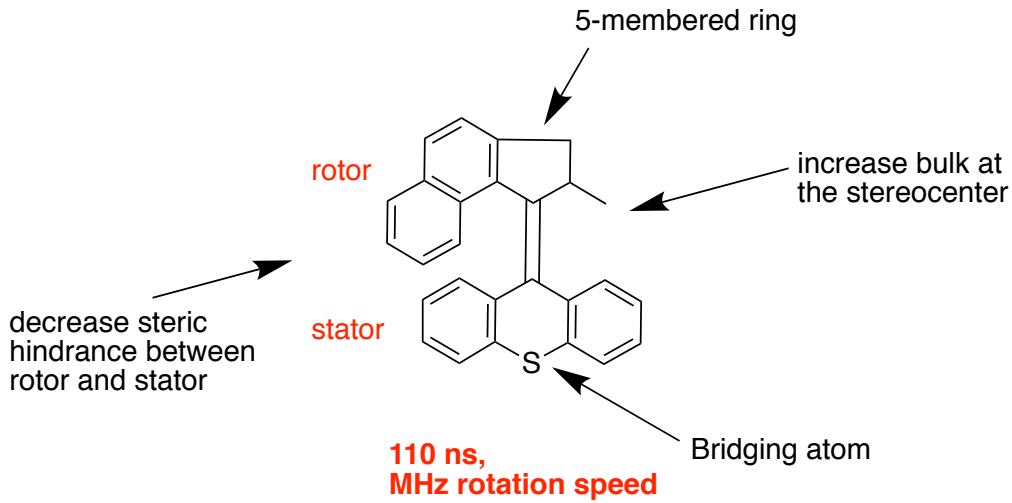


5.7 ms

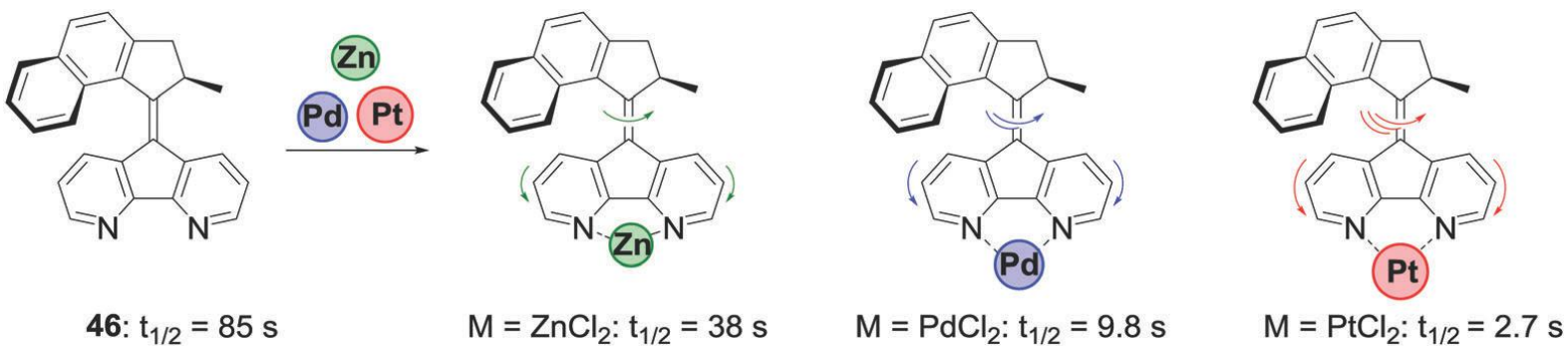
- Half lives of the metastable excited isomer.
- Inversely proportional to the rate of thermal relaxation and thus to the rotational speed.
- Generally well predicted by DFT calculations, but a clear trend is not obvious.

Klok, M. *et al., J. Am. Chem. Soc.,* 2008, 130, 10484.
Vicario, J., Walko, M., Meetsma, A., Feringa, B. L.*, J. Am. Chem. Soc.,* 2006, 128, 5127.
Vicario, J., Meetsma, A., Feringa, B. L.*., Chem. Commun.,* 2005, 5910.
Koumura, N., Geertsema, E., van Gelder, M., Meetsma, A., Feringa, B. L.*, J. Am. Chem. Soc.,* 2002, 124, 5037.

Optimizing the 2nd-gen Motor

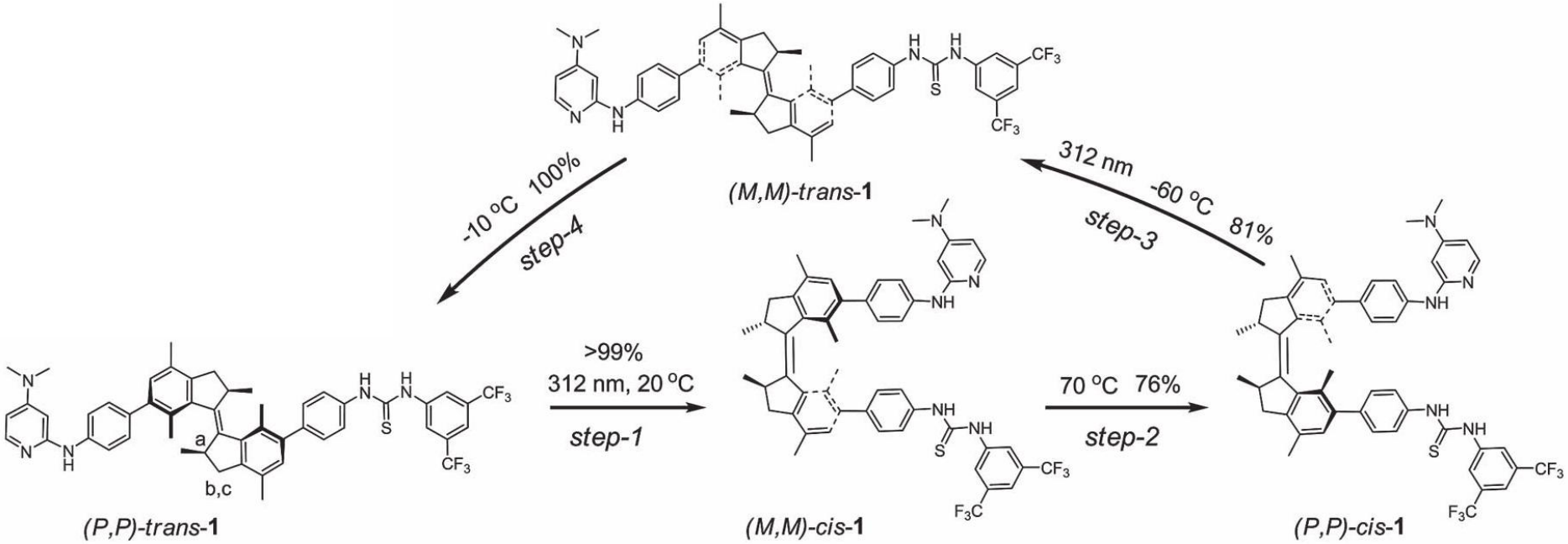


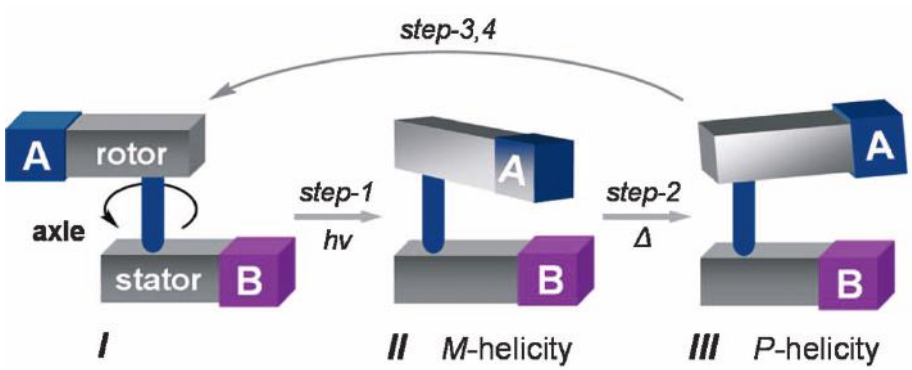
Allostery controlled rotation frequency



Faulkner, A., van Leeuwen, T., Feringa, B. L., Wezenberg, S., *J. Am. Chem. Soc.,* 2016, 138, 13597.

Applications – Photoswitchable Catalysts

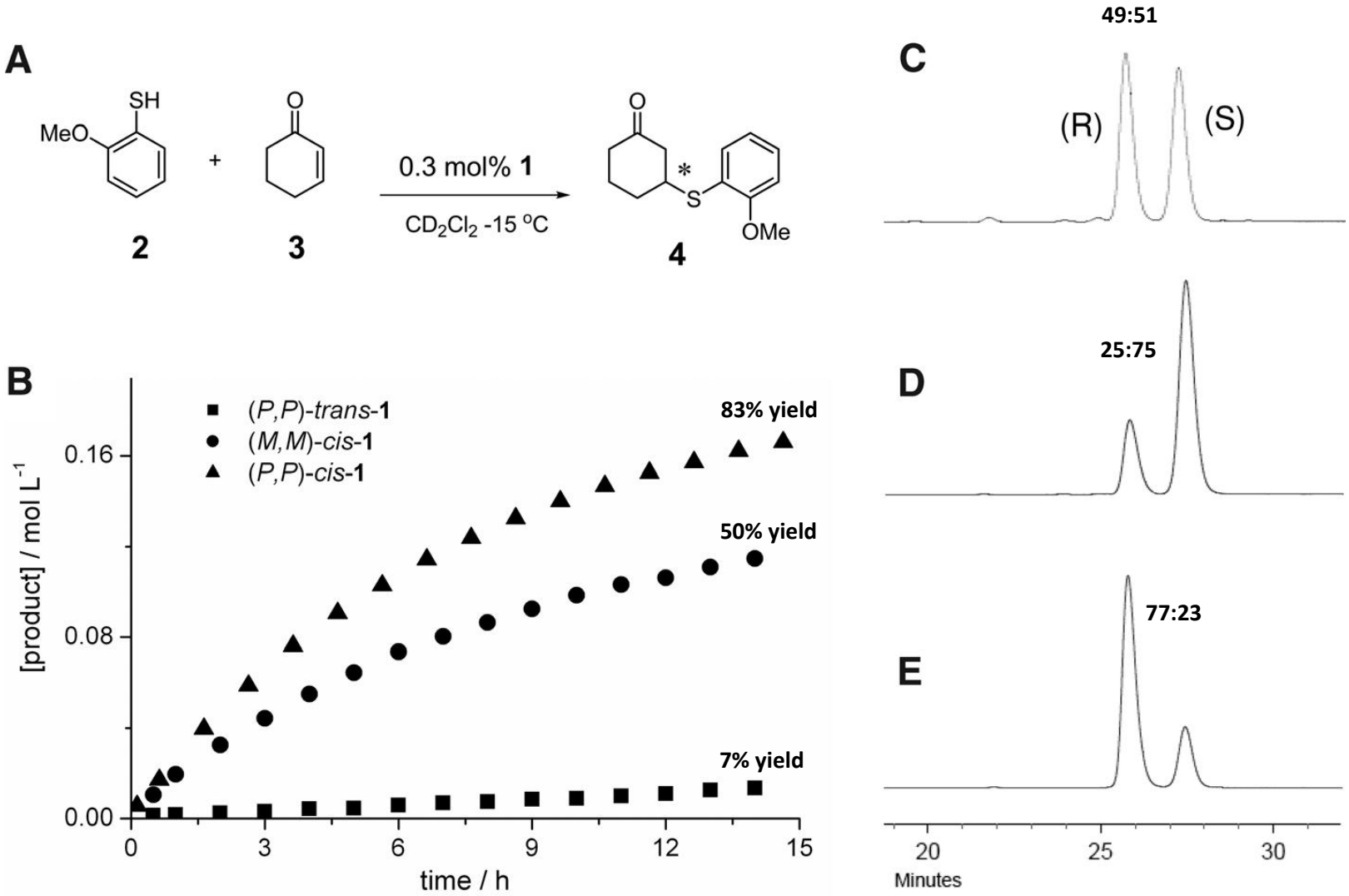




Molecular motor with functionalized rotor and stator which can form a bifunctional organocatalyst pair when brought in proximity

Wang, J., Feringa, B. L., *Science.,* 2011, 331, 1429.

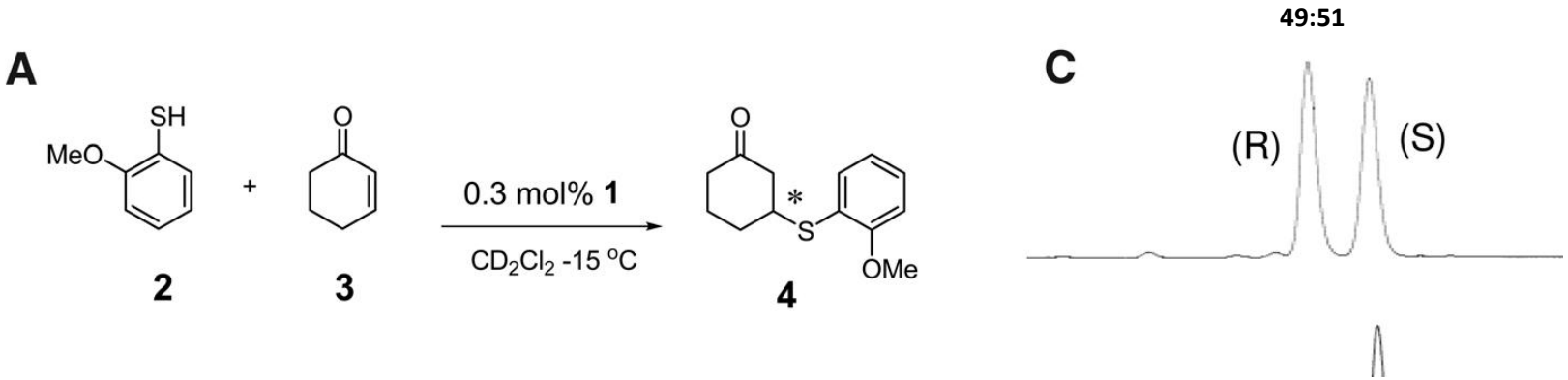
Applications – Photoswitchable Catalysts

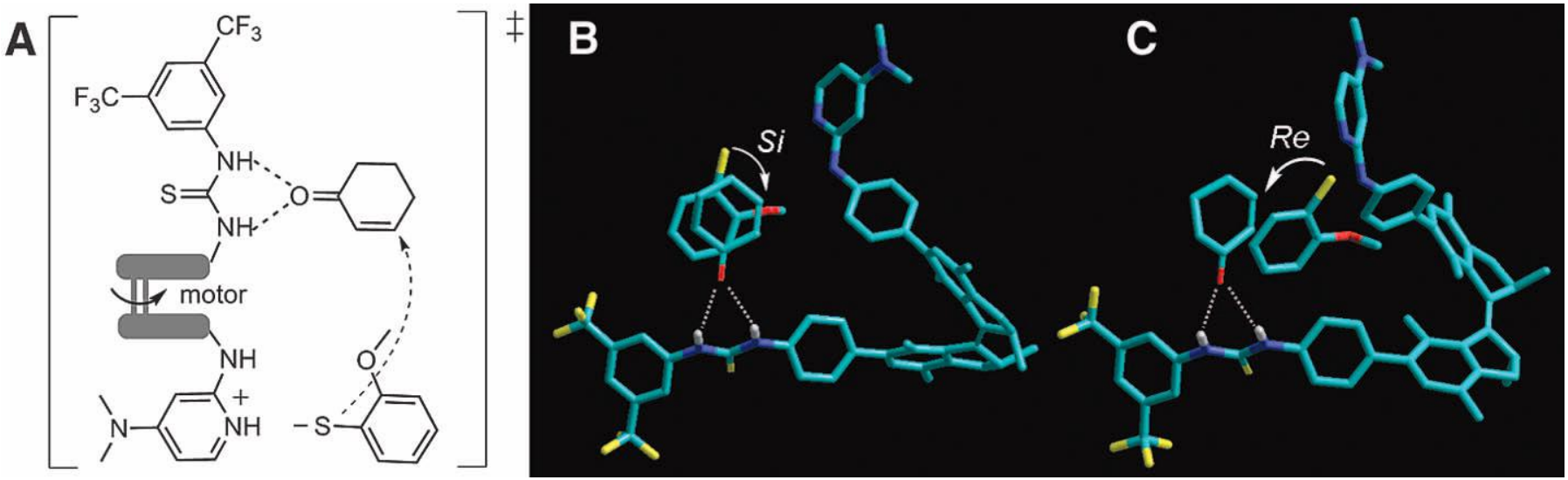


Control of catalytic activity as well as enantioselectivity can be achieved through selection of the appropriate rotary state of the catalyst. In-situ conversion of (P,P)-trans-1 to (M,M)-cis-1 was also demonstrated.

Wang, J., Feringa, B. L., *Science.,* 2011, 331, 1429.

Applications – Photoswitchable Catalysts





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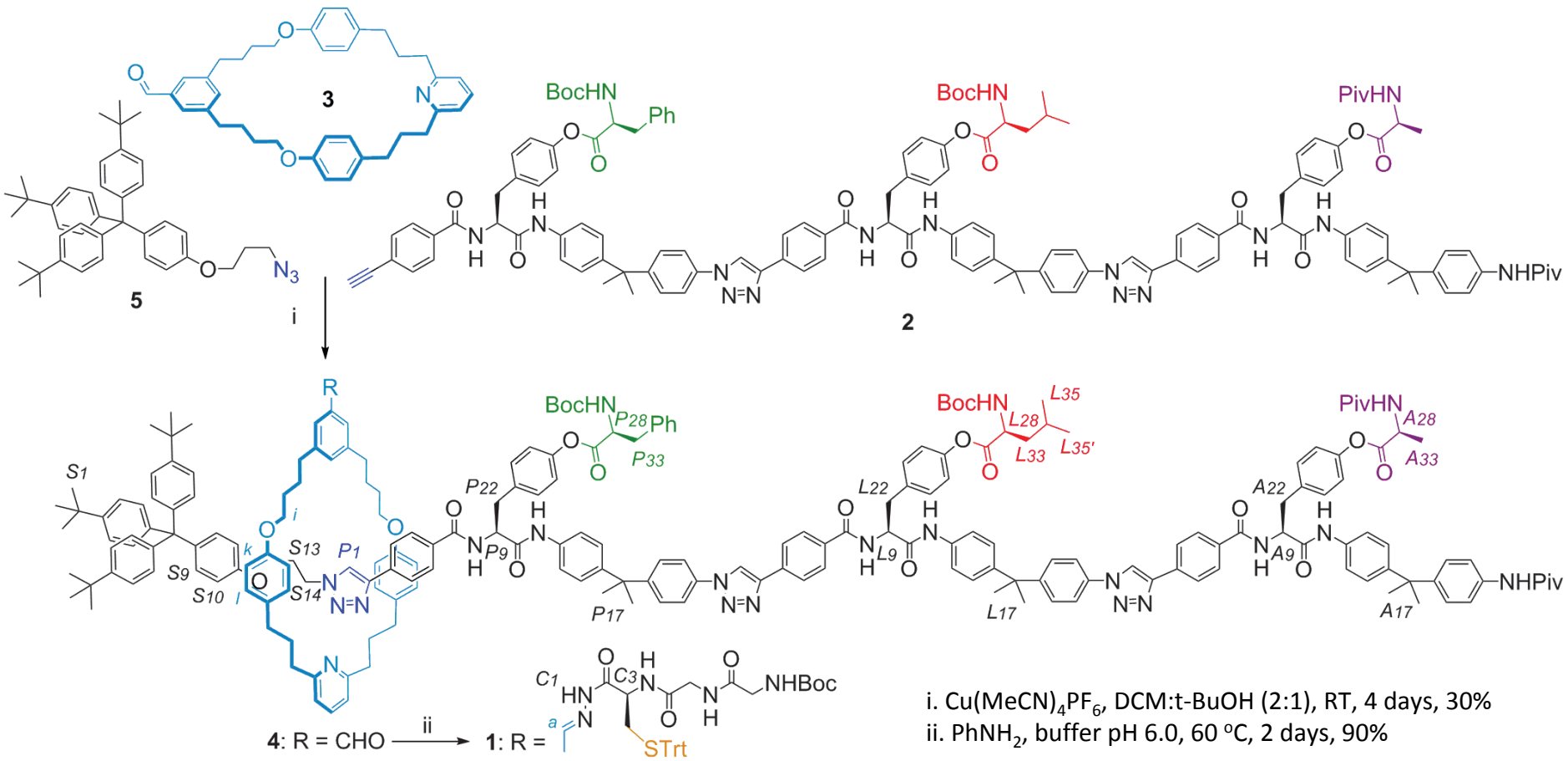
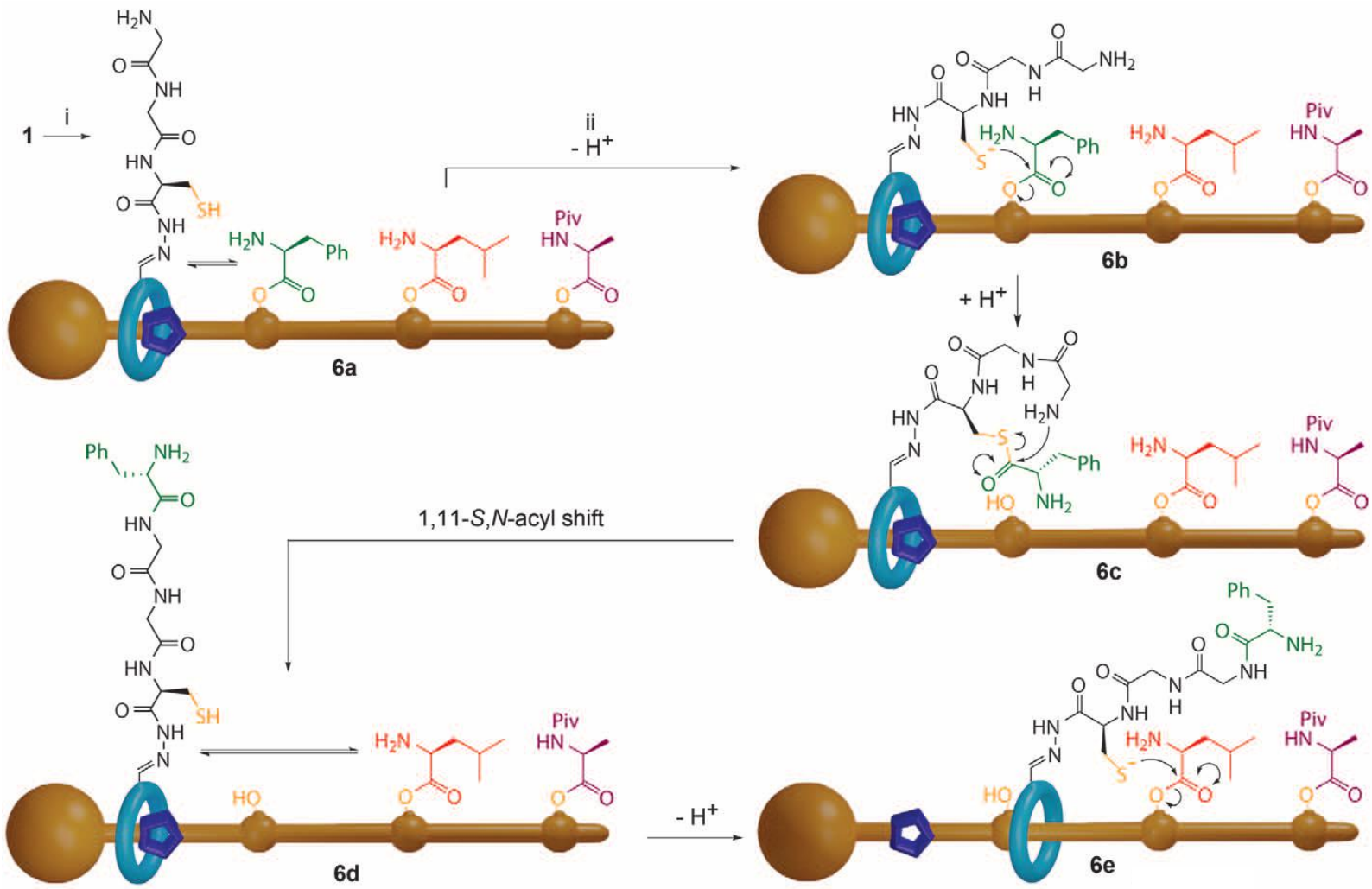
Applications – Artificial Ribozyme Mimic



Rotoxane **1** with pre-attached amino-acyl esters and a macrocycle shuttle is poised for peptide synthesis.

Leigh, D. A, *et al.*, *Science,* 2013, 339, 189.

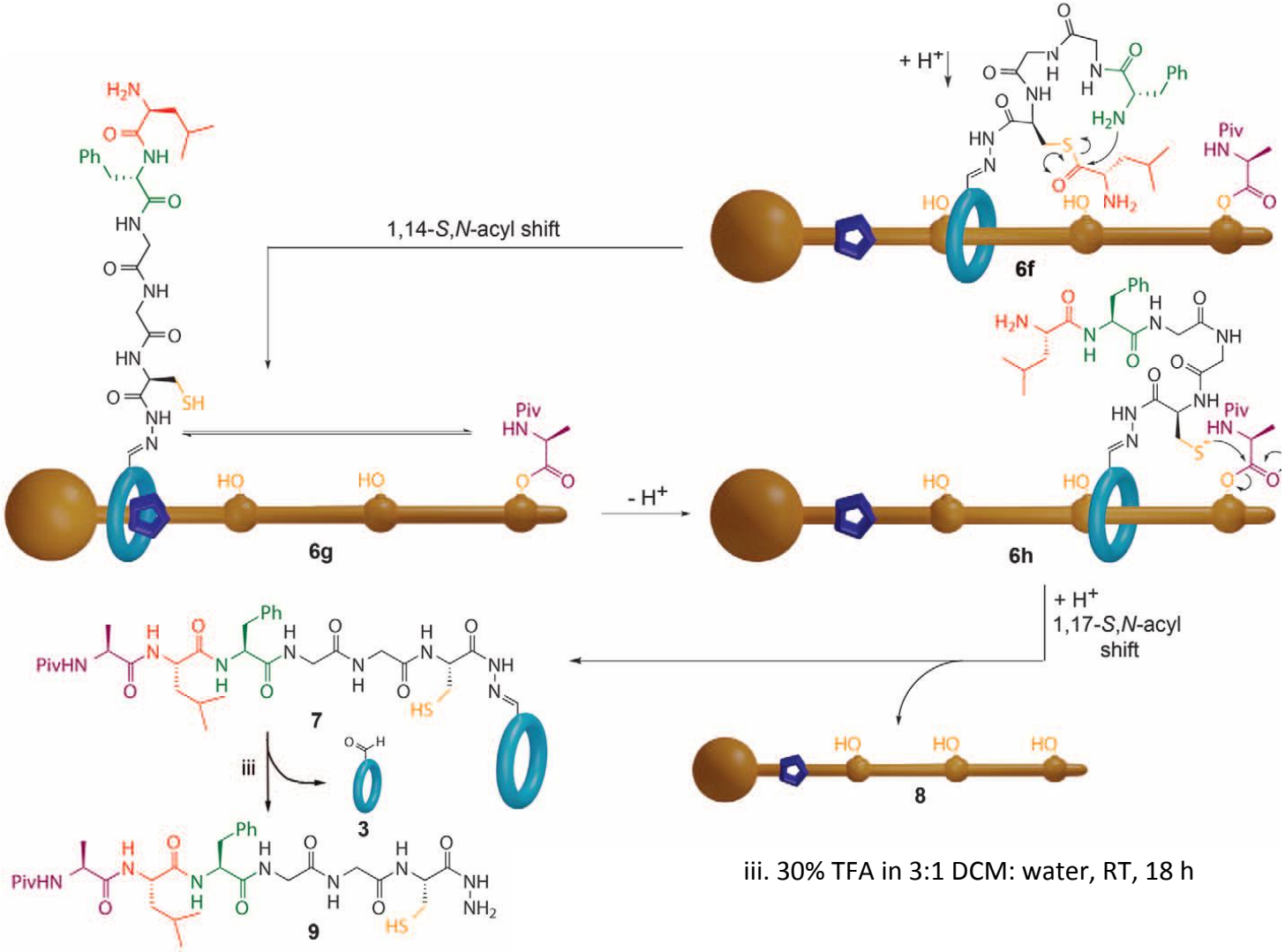
Applications – Artificial Ribozyme Mimic



i. 20% TFA in DCM, RT, 2 h, 100%%
ii. DIPEA, $P(CH_2CH_2COOH)$ in 3:1 MeCN:DMF, 60 °C, 36 h

Leigh, D. A, *et al.*, *Science,* 2013, 339, 189.

Applications – Artificial Ribozyme Mimic

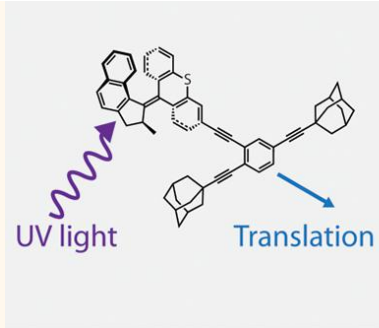


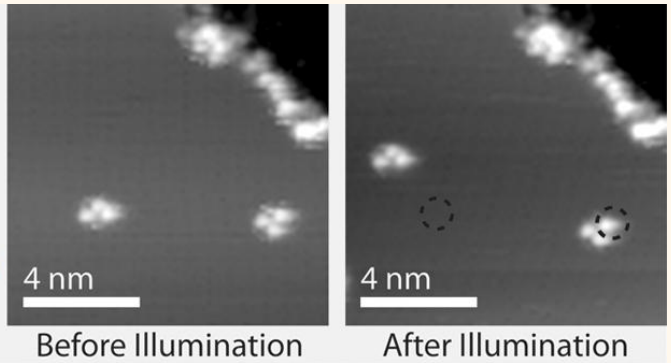
iii. 30% TFA in 3:1 DCM: water, RT, 18 h

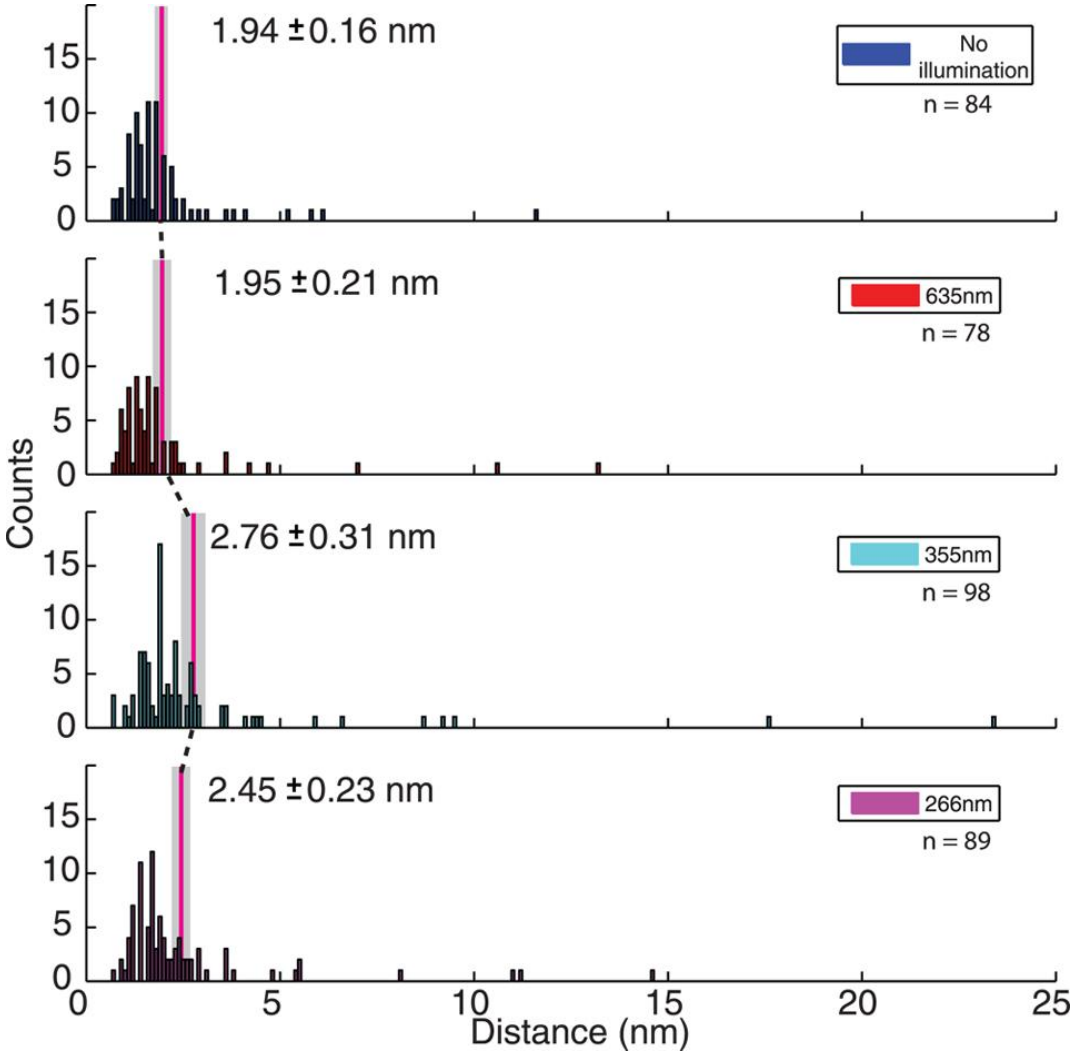
At the end of 36 h, only **8** and **9** are detected by HPLC and MS. A single peptide fragment corresponding to the expected sequence is detected after hydrazone deprotection. Thus, this highly modular molecular machine can be designed to autonomously perform iterative tasks in synthesis.

Leigh, D. A, *et al.*, *Science,* 2013, 339, 189.

Applications – A 'Nano-roadster'



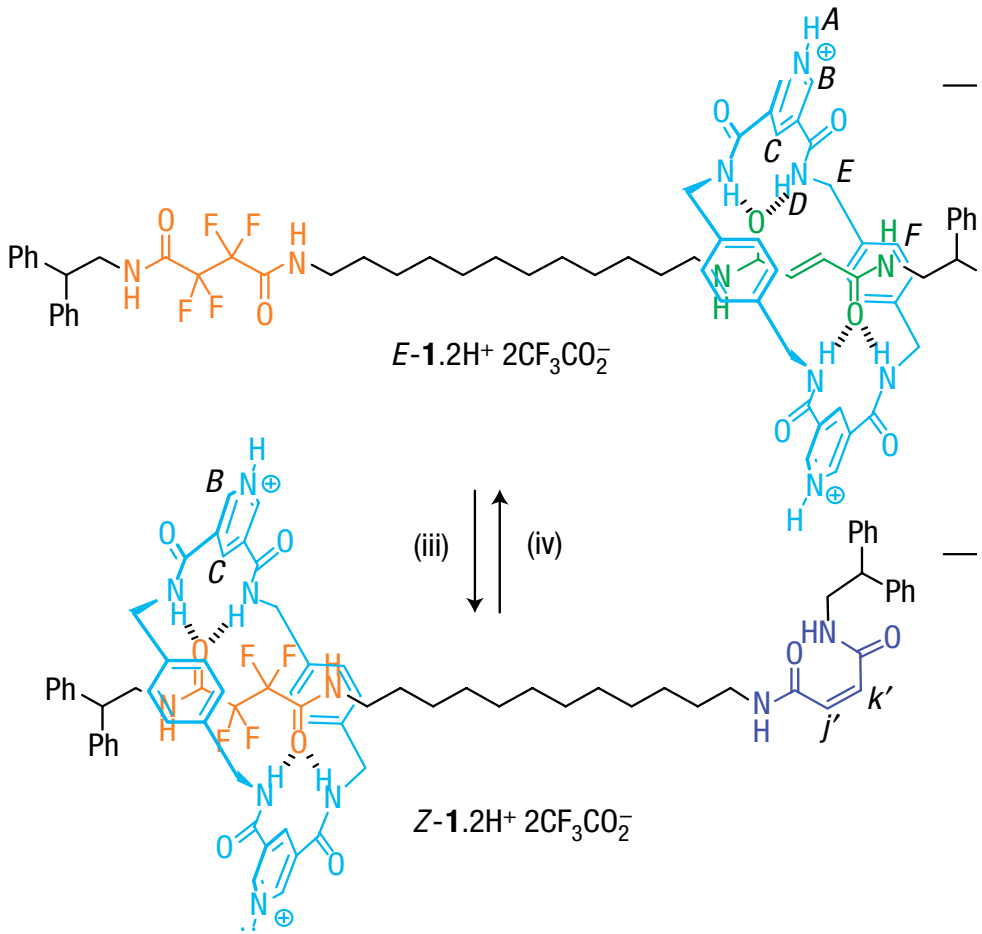




Molecules deposited on Cu(111) surface and STM imaged at 161K.
Light illumination results in greater diffusion movement of individual roadsters

Tour, J., Grill, L. *et al.*, *ACS Nano,* 2016, 10, 10945.

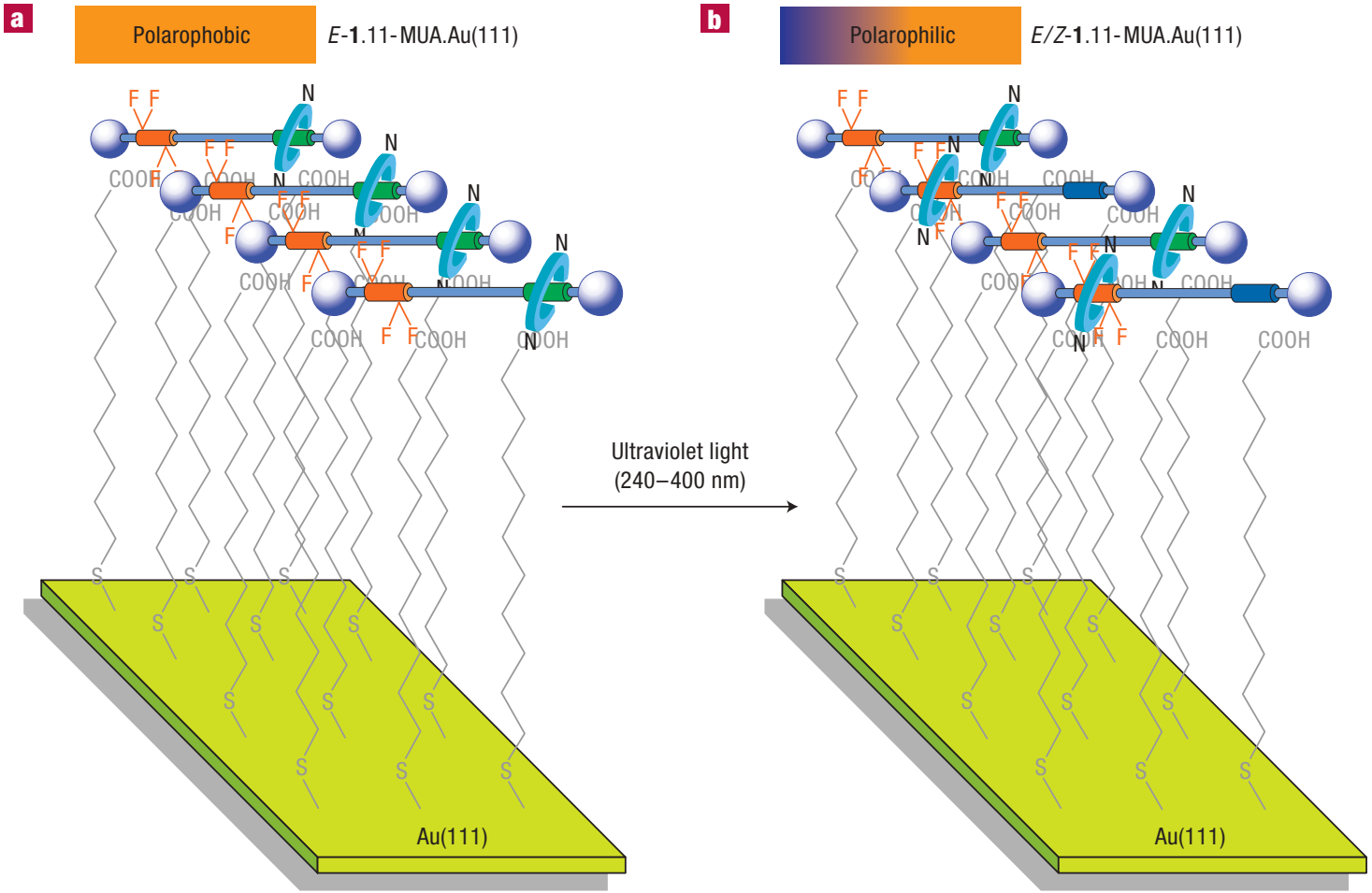
Applications – Macroscopic Transport



Shuttling of the macrocycle from the fumaramide station results in shielding of the fluorinated maleimide leading to an increased polarophilicity of the surface.

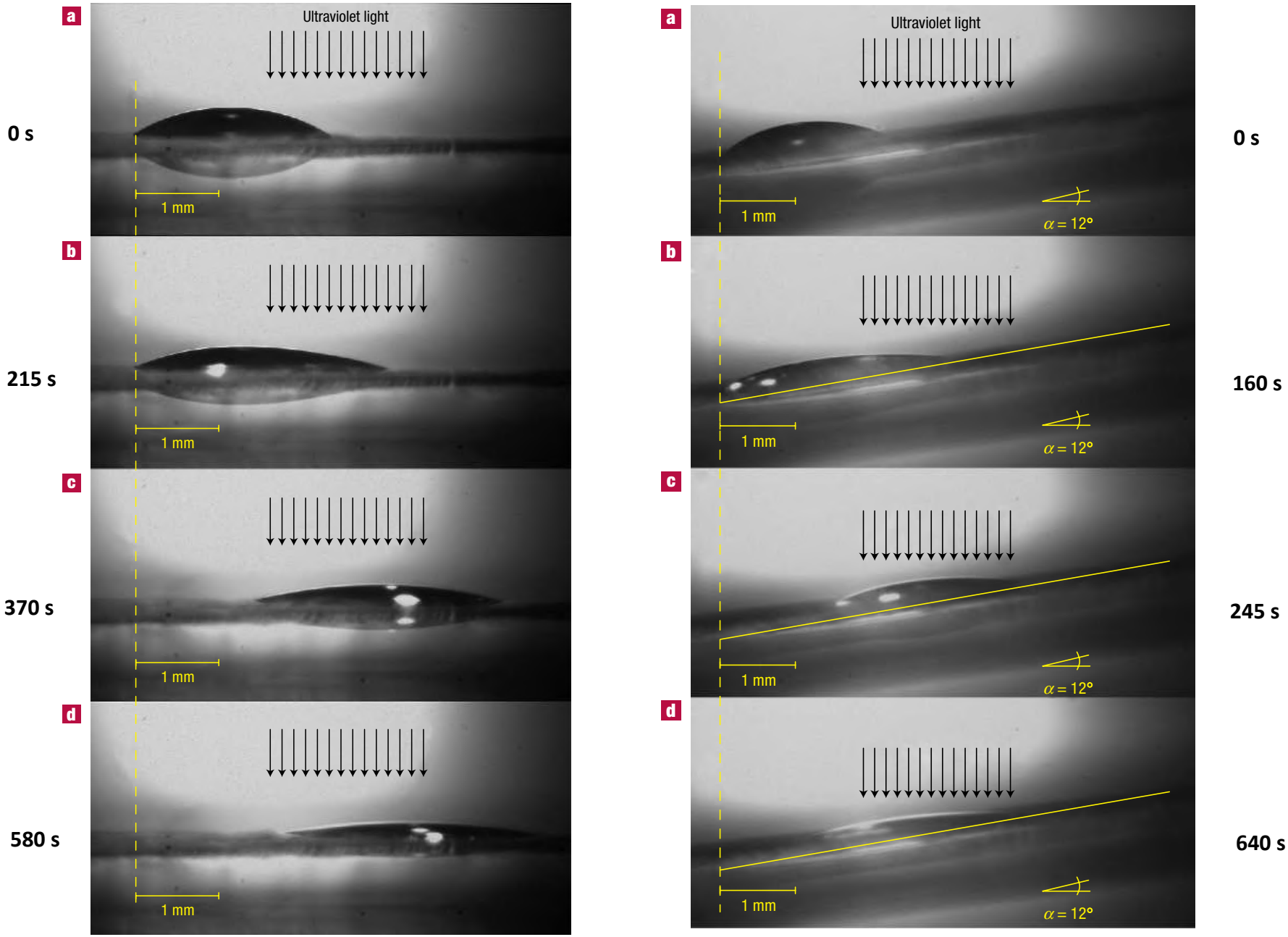
Berna, J., Leigh, D. A., Lubomska, M., Mendoza, S., Perez, E., Rudolf, P., Teobaldi, G., Zerbetto, F., *Nat. Mat.,* 2005, 4, 704.

Applications – Macroscopic Transport



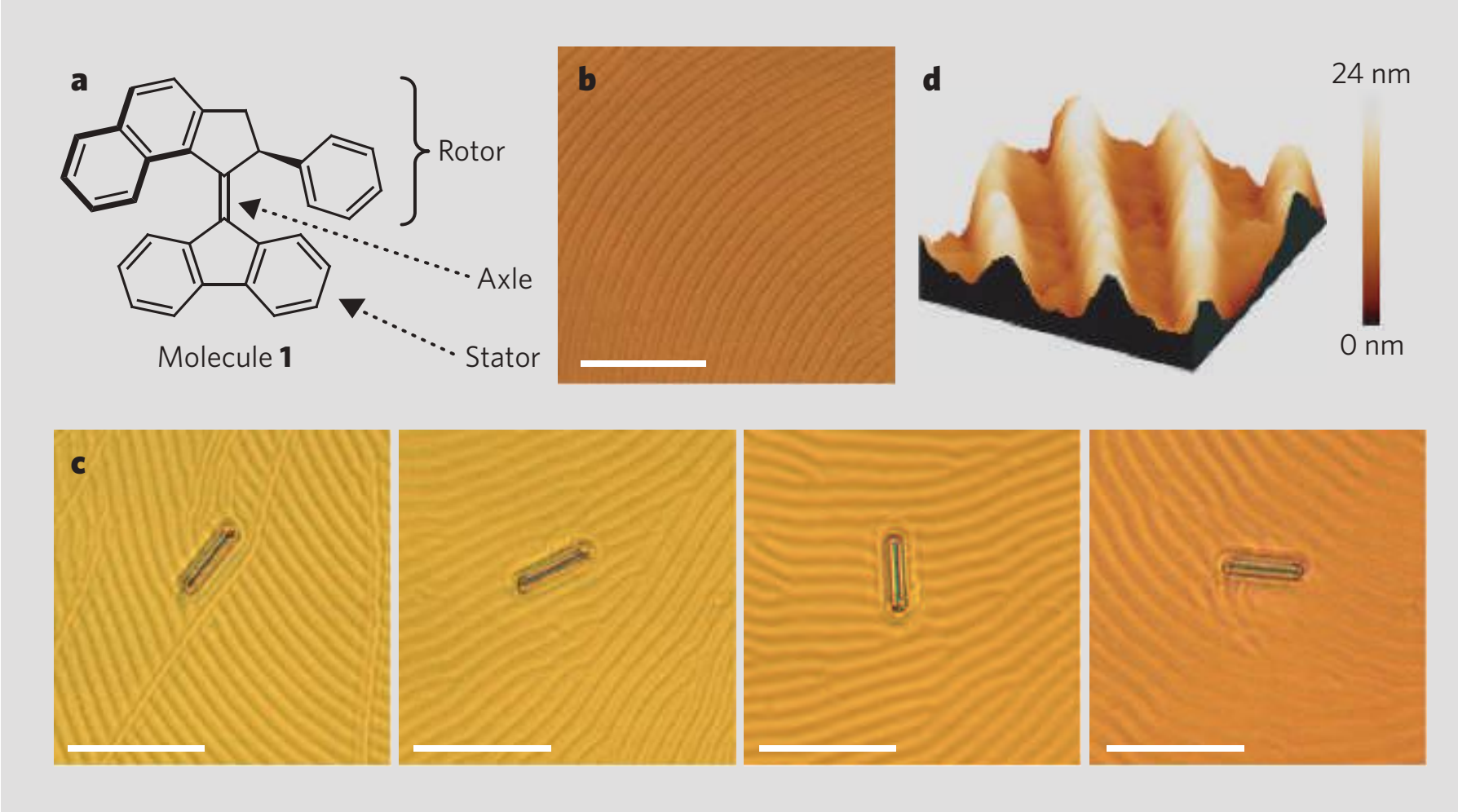
Shuttling of the macrocycle from the fumaramide station results in shielding of the fluorinated maleimide leading to an increased polarophilicity of the surface.

Berna, J., Leigh, D. A., Lubomska, M., Mendoza, S., Perez, E., Rudolf, P., Teobaldi, G., Zerbetto, F., *Nat. Mat.,* 2005, 4, 704.



Movement of a 1.25 uL drop of diiodomethane on mica coated rotoxane upon UV irradiation.

Applications – Macroscopic Movement

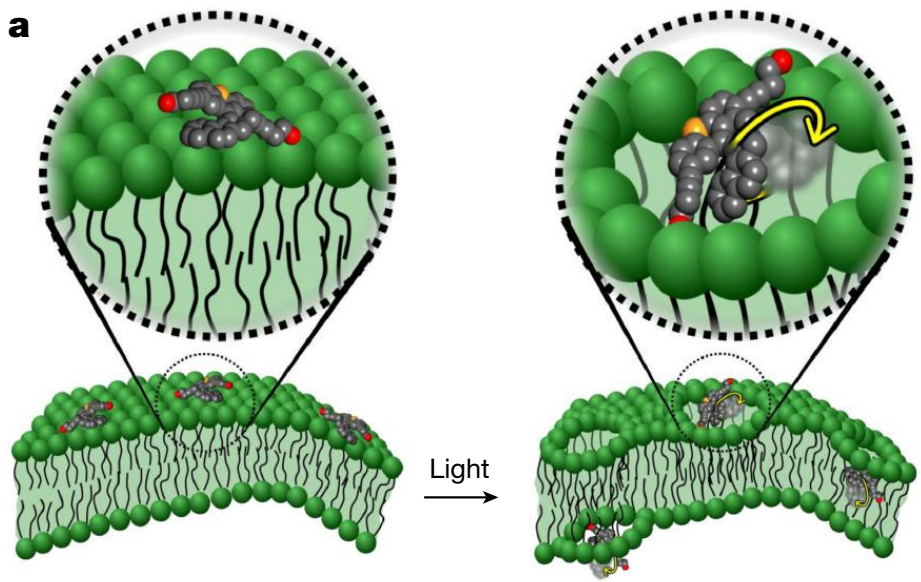


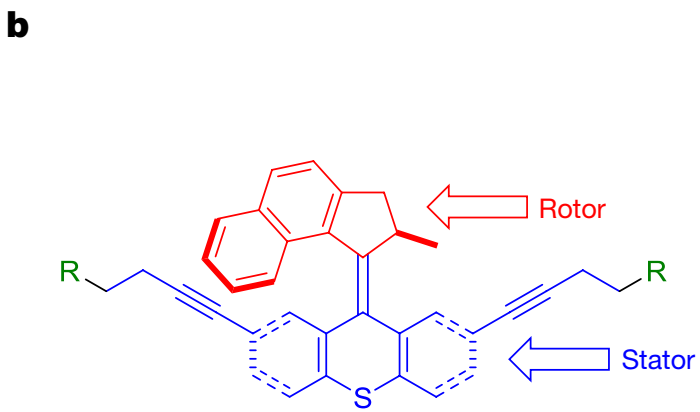
Doping of **1** (1 wt %) on a cholesteric liquid crystal film results in a surface polygonal fingerprint dependent on the helicity of the rotor. Thus, upon motor activation, the surface reorganizes in a clockwise fashion.

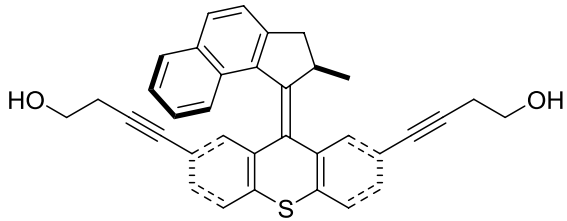
Scale bar = 50 um, images at 15s interval after irradiation. Effect continues for ~10 min after which the reverse movement is seen due to a second helical inversion by thermal relaxation

Feringa, B. L. *et al.*, *Nature,* 2006, 440, 163.

Applications – Cytotoxic Warheads







3

Best candidate. Efficient insertion into the membrane.
Fast motor rotation (~2-3 MHz).

Motor arms can be functionalized by membrane targeting peptides. Upon UV irradiation, mechanical disruption of the membranes results in perforation and cell death.

Tour, J. M. *et al.*, *Nature,* 2017, 548, 567.

Summary

- Molecular machines exemplify the confluence of synthetic design and function.
- To make a bonafide molecular motor, a repetitive, fuelled movement away from equilibrium is necessary. Attaining unidirectional motion is the critical challenge to achieve this objective.
- Early work in supramolecular chemistry involving molecular switches, catenanes and rotoxanes led to fascinating examples of controlled directional motion in these systems.
- Feringa's discovery of overcrowded alkene based, light activated motors was a landmark in the field. The mechanism involves a beautiful interplay between the dynamic helical chirality and the fixed point chirality of the stereogenic centres.
- Molecular motors now have reliable structural deign principles and the focus in the last decade has shifted to demonstrating utility.
- To this end, impressive proof of principle applications have been reported and many exciting advances are expected in the future.

Nobel Prize in Chemistry, 2016

Photo: A. Mahmoud
Jean-Pierre Sauvage
Prize share: 1/3

Photo: A. Mahmoud
Sir J. Fraser Stoddart
Prize share: 1/3

Photo: A. Mahmoud
Bernard L. Feringa
Prize share: 1/3

The Nobel Prize in Chemistry 2016 was awarded jointly to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa *"for the design and synthesis of molecular machines"*.

https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2016/press.html

Nobel Prize in Chemistry, 2016

"2016's Nobel Laureates in Chemistry have taken molecular systems out of equilibrium's stalemate and into energy-filled states in which their movements can be controlled. In terms of development, the molecular motor is at the same stage as the electric motor was in the 1830s, when scientists displayed various spinning cranks and wheels, unaware that they would lead to washing machines, fans and food processors. Molecular machines will most likely be used in the development of things such as new materials, sensors and energy storage systems."

https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2016/press.html

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Important Reviews

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   Kay, E., Leigh, D. A., Zerbetto, F., *ACIE*, 2007, 46, 72.
3. Artificial Molecular Motors
   Kassem, S., van Leeuwen, T., Lubbe, A., Wilson, M., Feringa, B. L., Leigh, D. A., , *Chem. Soc. Rev.,* 2017, 46, 2592.
4. Making Molecular Machines Work
   Browne, W., Feringa, B. L., *Nat. Nanotechnol.,* 2006, 1, 25.

Individual articles as referenced in the slides.