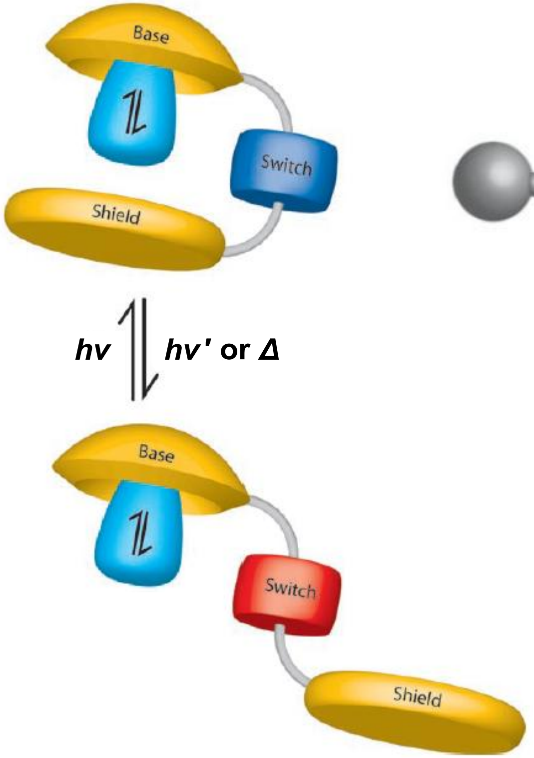
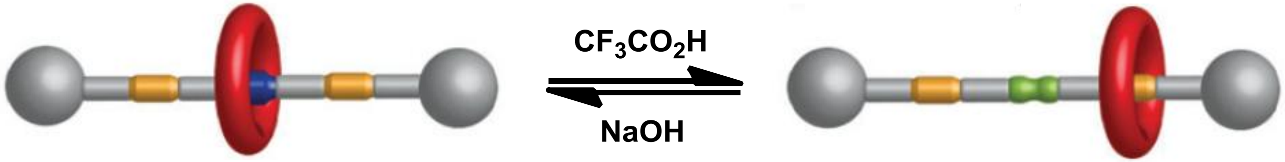
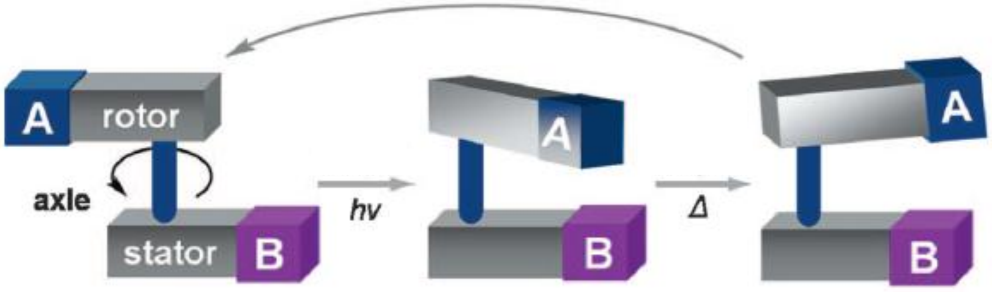
Switchable catalysis





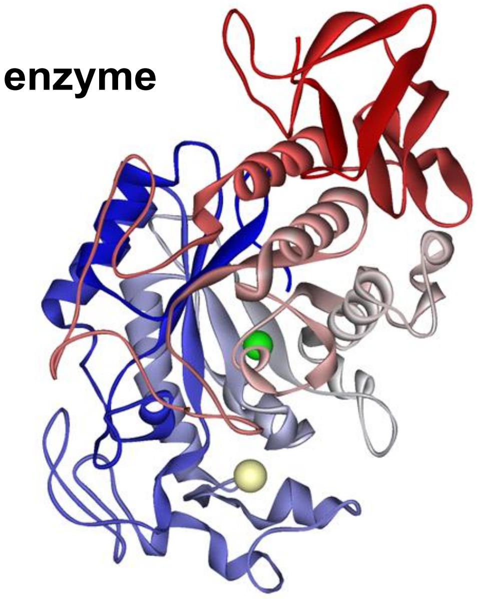


Literature Seminar
Yuya Morita (M2)
2013/7/1

Contents

1. Introduction

Enzymes catalyze a wide variety of biochemical reactions that occur in living organisms. Compared to man-made, chemical catalysts, enzymes frequently exhibit superior performance.



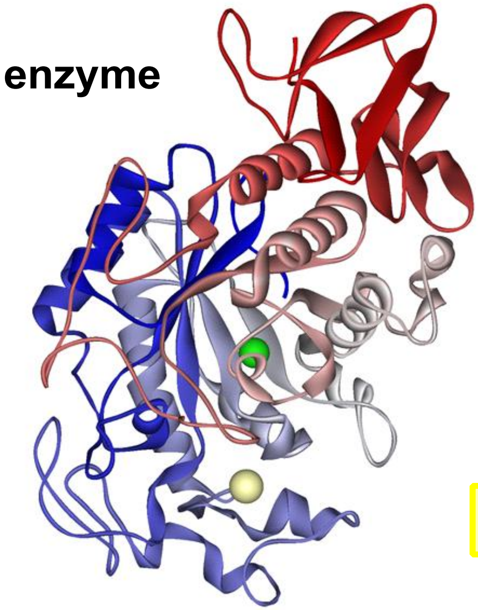
1) rate enhancement
2) reaction specificity
3) activity under moderate conditions
4) capacity for regulation

three-dimensional structure and elegant regulation by conformational changes though **allosteric regulator**

Structures that mimic enzyme reactivity have been pursued by an active field of researchers for decades with the goals of...

- **developing synthetically useful catalysts inspired by enzymes**
- **understanding fundamental questions with regard to mechanisms of enzyme action**

for the development of a "smart" catalysts



In order to realize **stimulus-responsive control** of **chemical catalysis** in artificial molecular catalysts, it is critical to exploit the features of **conformational flexibility** like enzymes do.

⟹ **catalysts for organic synthesis**

facile preparation of each product enantiomer individually

From a chemist's viewpoint, it certainly constitutes an appealing idea to be able to temporally and spatially modulate any given catalyst's activity and selectivity.

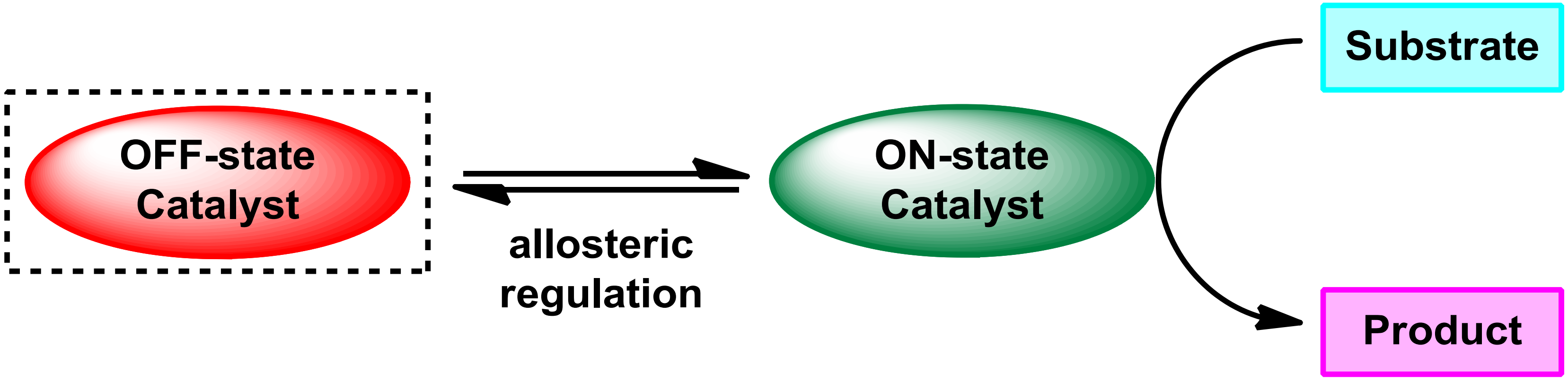
⇓

Switchable Catalysts

Switchable Catalysts

In the living cell, uncountable reactions occur in parallel. To ensure that all these processes proceed without interfering with one another, these operations must be controlled, their function must be switchable, and the switching must be reversible.

U. Lüning, *Angew. Chem. Int. Ed.* **2012**, *51*, 8163



Switchable Catalysts

prerequisites

- in situ reversibility between ON and OFF state
- high ON/OFF ratio of reactivity
- a significant population of the desired catalyst species

allosteric effectors

small molecules
pH (proton)
ion (anion, metal)
temperature
light

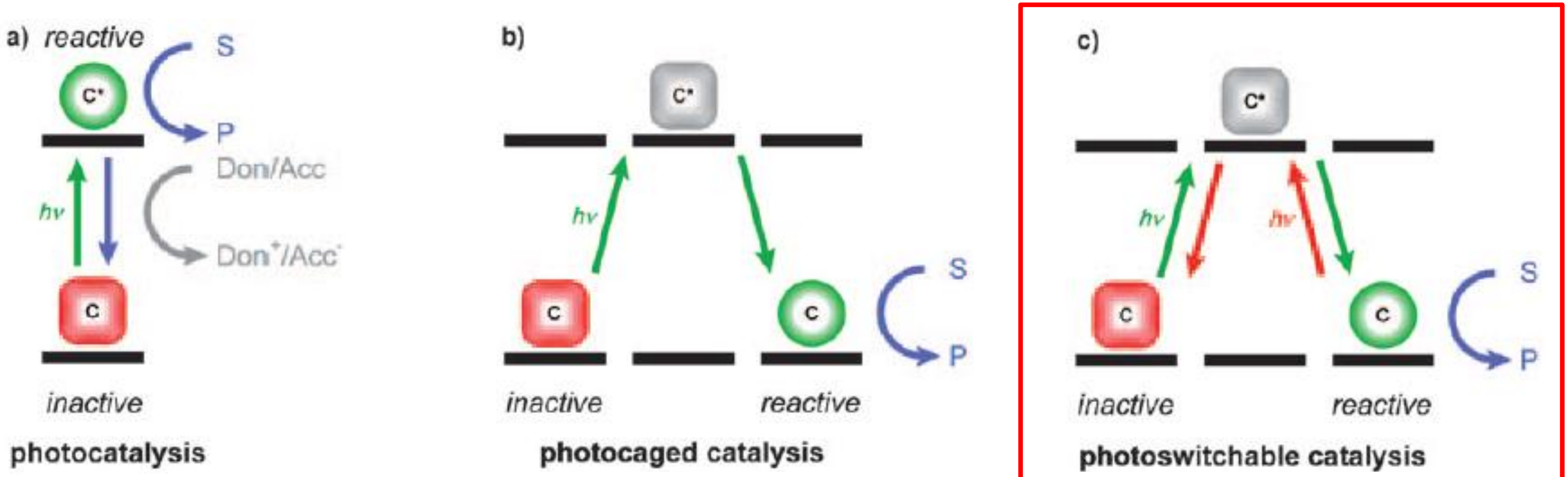
possible regulation

reactivity
chemoselectivity
regioselectivity
stereoselectivity

2. Photoswitchable Catalysts

Light is perhaps the most advantageous stimulus as it is a noninvasive stimulus that can be conveniently manipulated by modern optics, potentially enabling the setup of highly parallel processes.

general approaches towards photocontrol of catalytic activity



- transient excited state is reactive
- stoichiometric use of photons

- irreversibly generate the catalytically active species

- reversibly toggle between their inactive and reactive forms

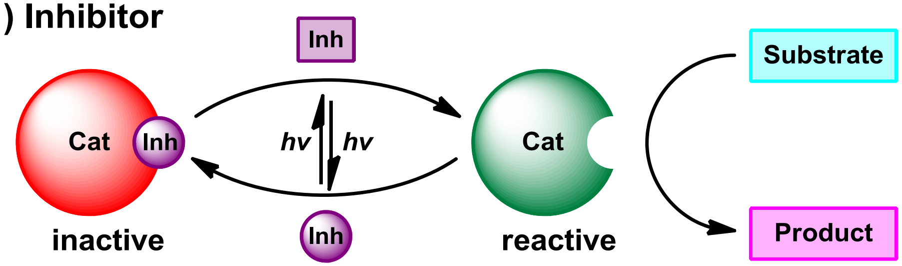
Photocontrolled thermal catalysis (b and c) is clearly an appealing yet challenging concept that offers great potential for the realization of smart catalysts.

S. Hecht, *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 5054

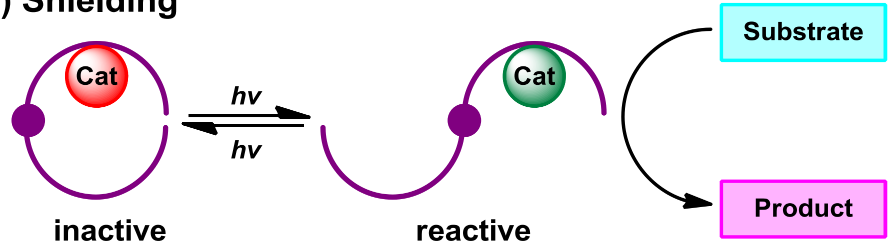
The design of photoswitchable catalysts

- in order to realize a reversible process, **photochromic moieties** have to be incorporated into the catalyst system
- two different light stimuli reversibly shuttle the catalytic system between an **active ON state** and an **inactive OFF state**.

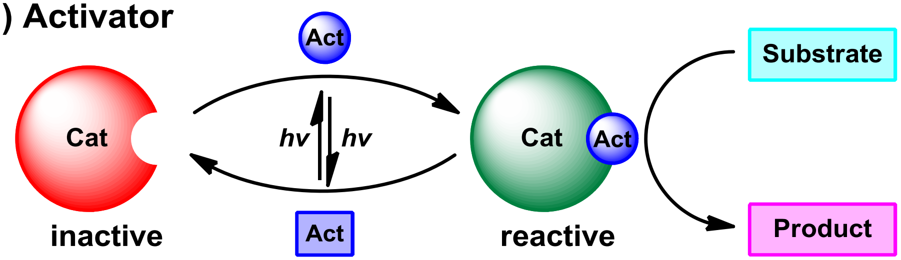
1) Inhibitor



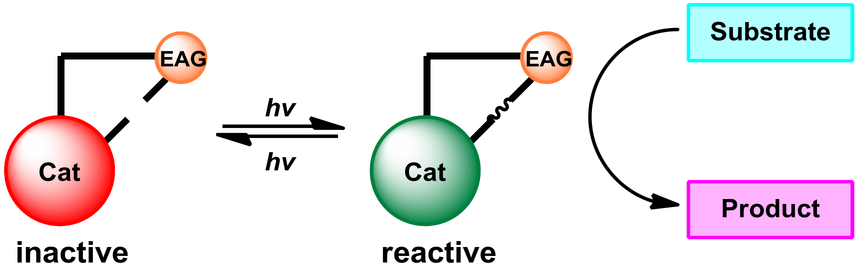
4) Shielding



2) Activator

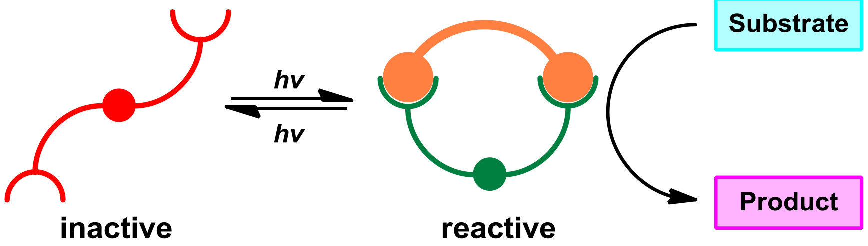


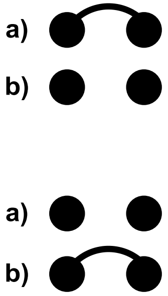
5) Electronic effects



(EAG; electronically active group)

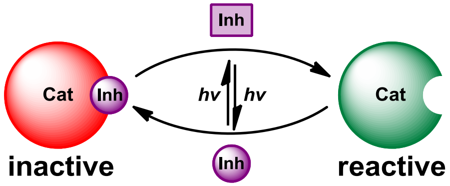
3) Template





1, 2) intermolecular interaction of a suitable photochromic additive
3, 4) direct incorporation of the photochrome into the catalyst framework
5) manipulation of the electronic nature

2-1. Inhibitor

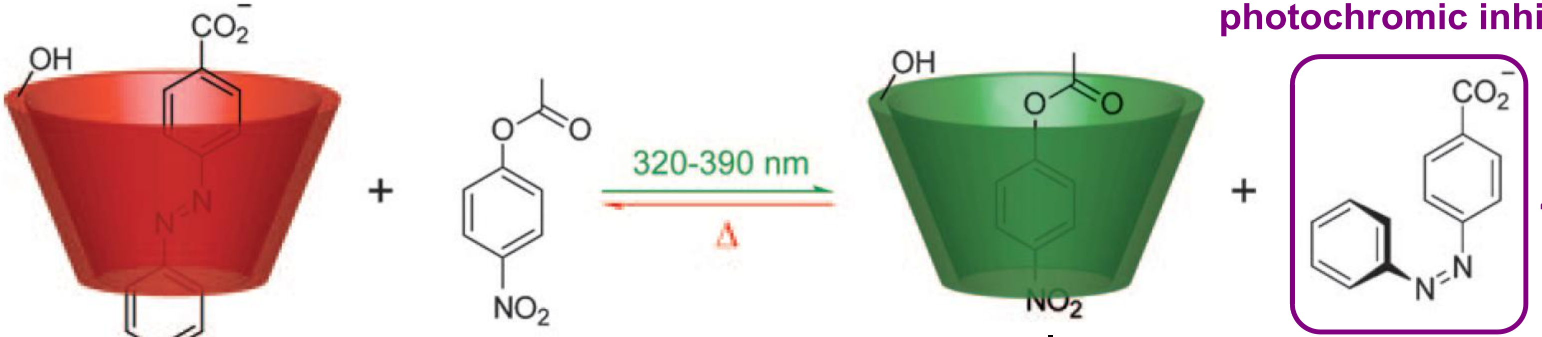


A. Ueno, *et al. J. Chem. Soc. Chem. Commun.* **1980**, 837

Photoregulation of Catalytic Activity of β-Cyclodextrin by an Azo Inhibitor

The first example of a photoswitchable catalyst system was described as early as in 1980.

photochromic inhibitor

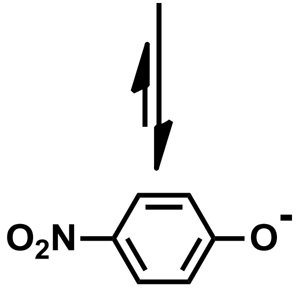


Z-isomer does not fit into **β-CD**

sustrate

inhibiting

not inhibiting

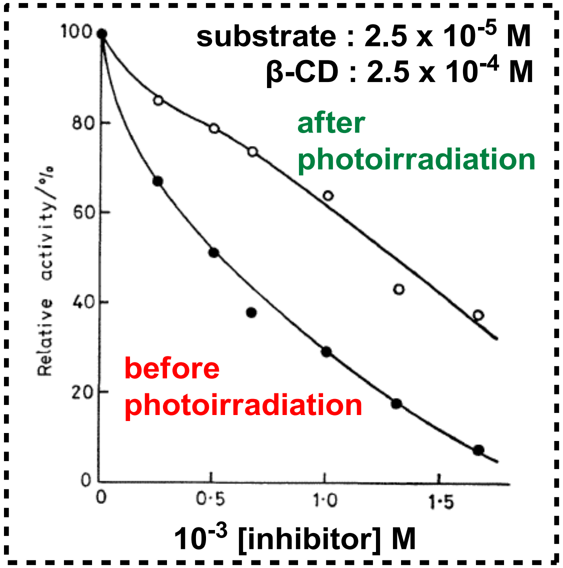


product

β-CD provides a host for the hydrophobic aryl residue of the ester

⇓

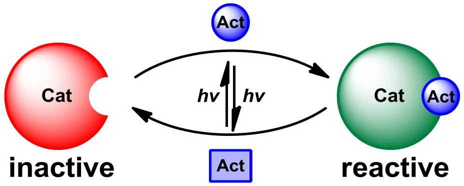
facilitates nucleophilic attack from one of the nearby peripheral OH groups



drawbacks

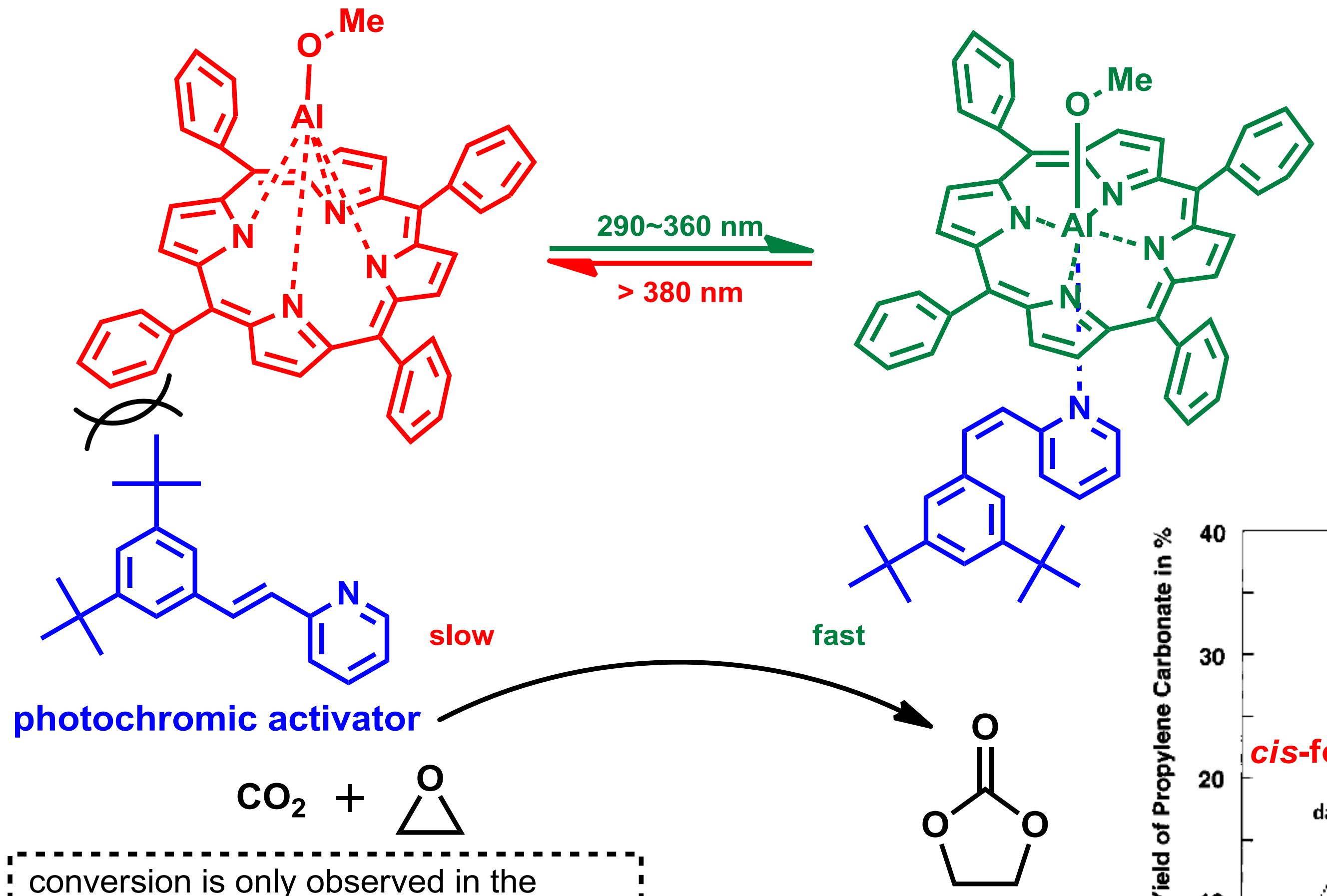
- The system does not provide turnover.
  (excess amont of β-CD and inhibitor is needed)
- The regulation is not satisfactory.

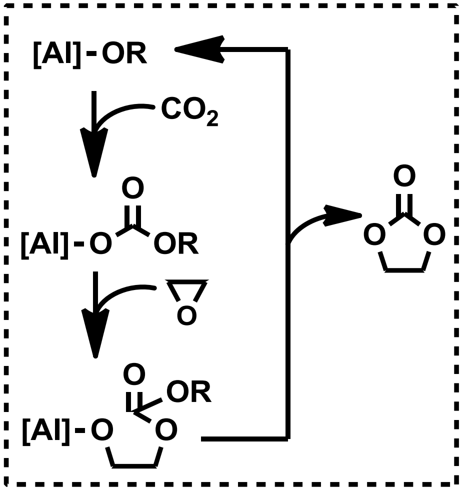
2-2. Activator



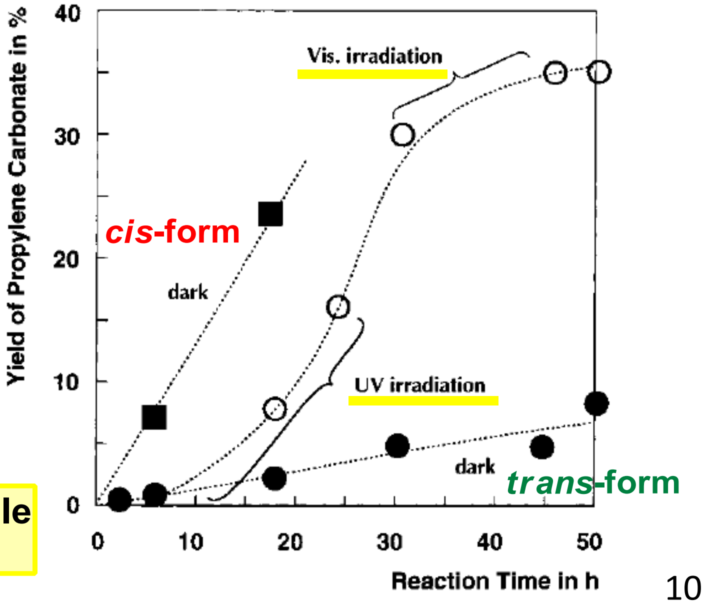
S. Inoue, *et al. J. Am. Chem. Soc.* **1999**, *121*, 2325

Photoresponsive Molecular Switch to Control Chemical Fixation of CO_2



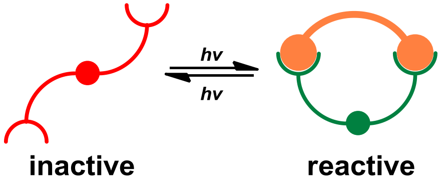


conversion is only observed in the
presence of axial nitrogen-based ligands



O demonstrates photoswitchable ability of this system !!

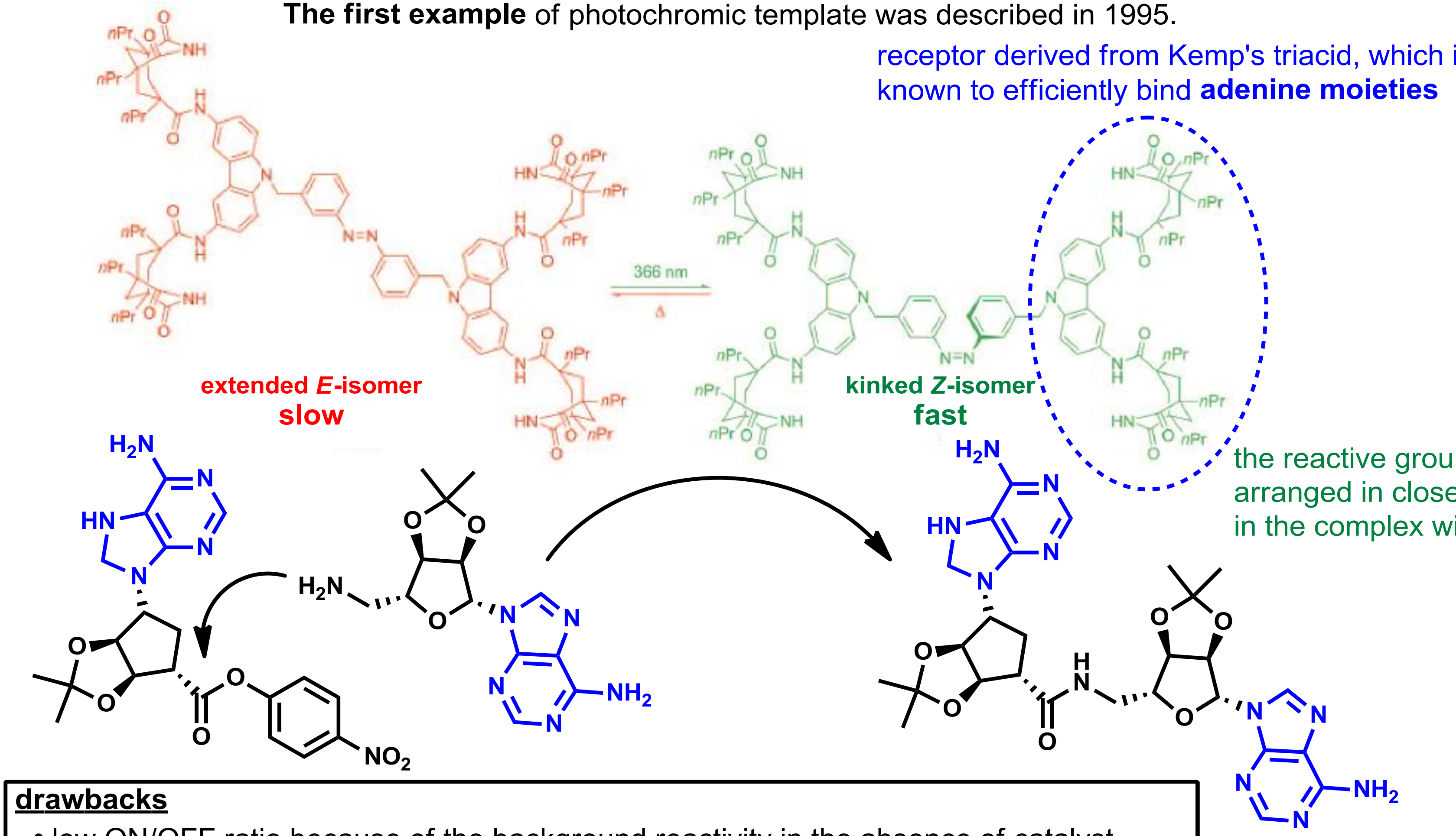
2-3. Template



J. Rebek, Jr., *et al. Angew. Chem. Int. Ed.* **1995**, *34*, 446

Light-Switchable Catalysis in Synthetic Receptors

The first example of photochromic template was described in 1995.



receptor derived from Kemp's triacid, which is known to efficiently bind **adenine moieties**

extended *E*-isomer
slow

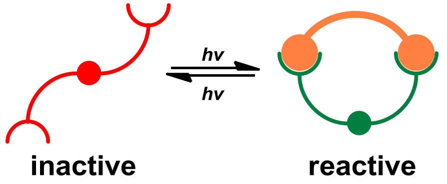
kinked *Z*-isomer
fast

the reactive groups are arranged in close proximity in the complex with *Z*-isomer

drawbacks

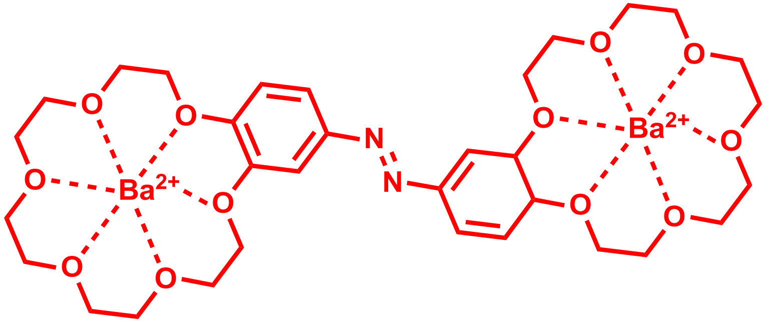
- low ON/OFF ratio because of the background reactivity in the absence of catalyst
- low efficiency of isomerization (ca. 50% *Z*-isomer) because of the carbazole absorption
- reactants have to be equipped with adenine residues
- **product inhibition** (equimolar amount of catalyst is needed)

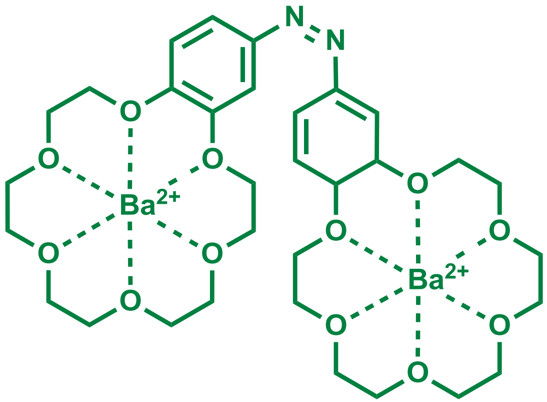
2-3. Template

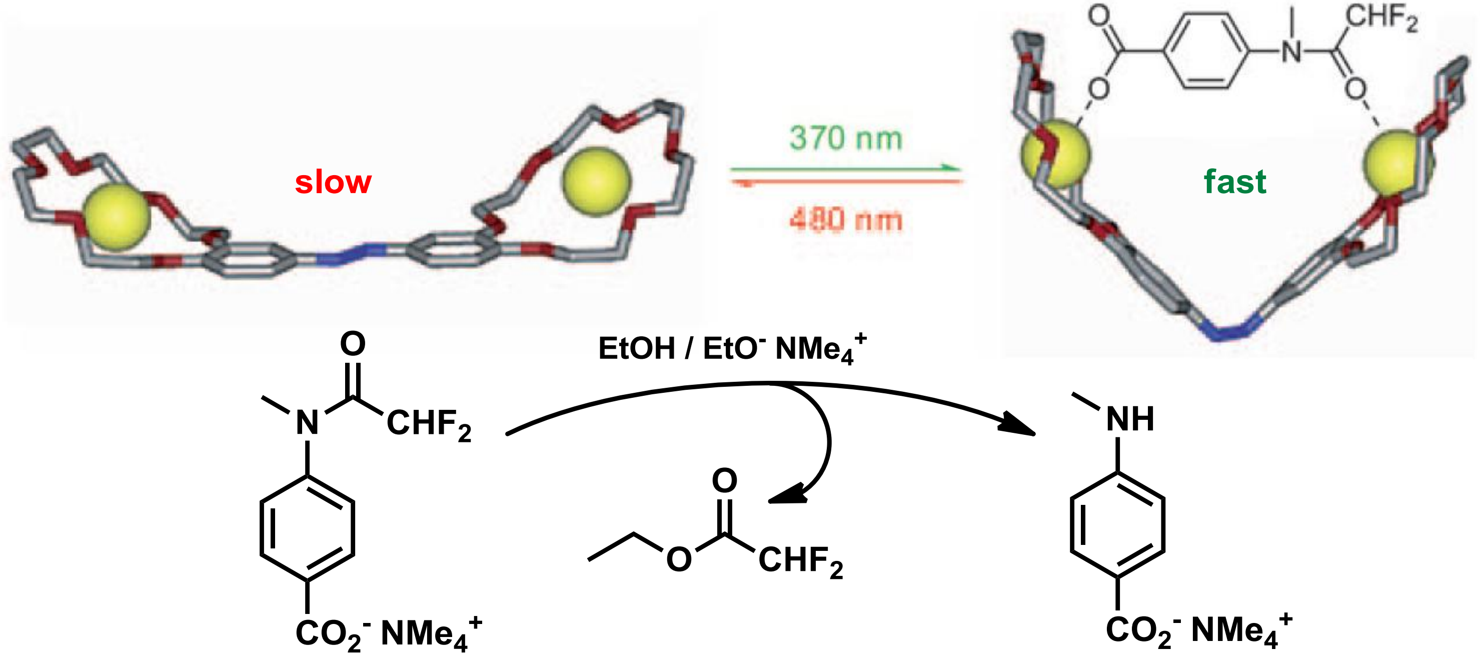


R. Cacciapaglia, *et al. J. Am. Chem. Soc.* **2003**, *125*, 2224

The Bis-Barium Complex of a Butterfly Crown Ether as a Phototunable Supramolecular Catalyst

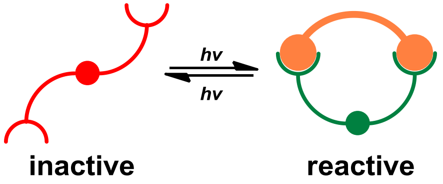


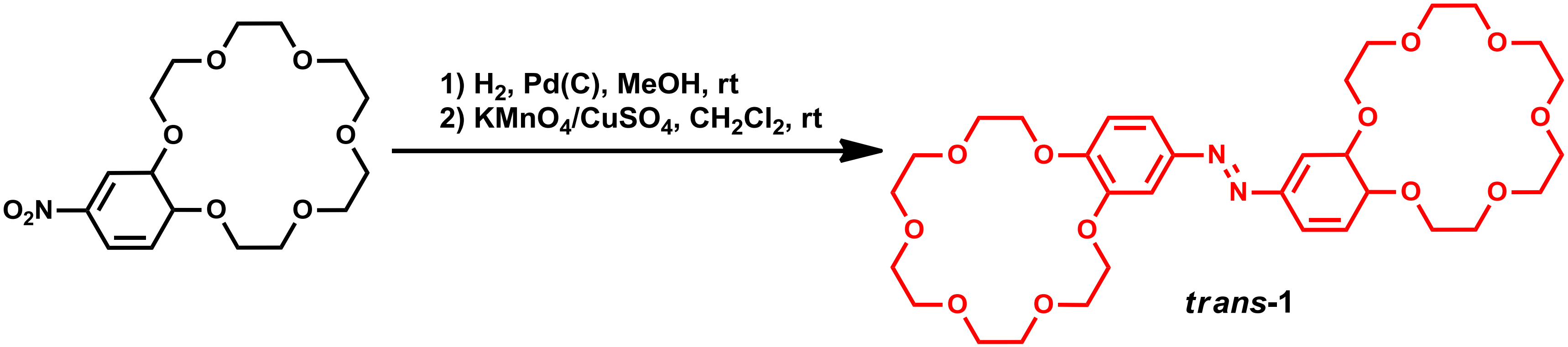




2-3. Template

R. Cacciapaglia, *et al. J. Am. Chem. Soc.* **2003**, *125*, 2224





1) H_2, Pd(C), MeOH, rt
2) $KMnO_4/CuSO_4$, CH_2Cl_2, rt

***trans*-1**

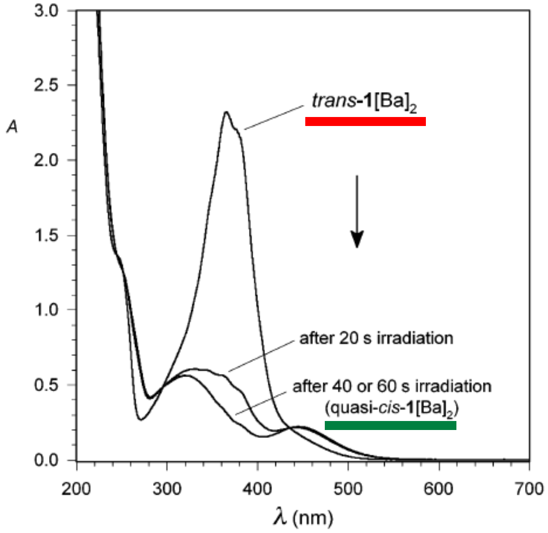


Figure 2. UV−vis spectra of 0.10 mM *trans*-**1**·[Ba]$_2$ before and after irradiation at 370 nm.

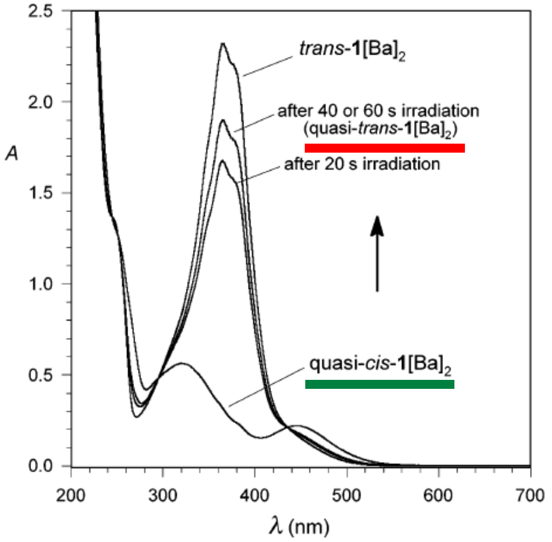


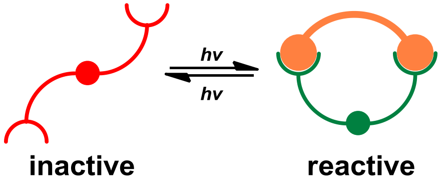
Figure 3. UV−vis spectra of 0.10 mM quasi-*cis*-**1**·[Ba]$_2$ before and after irradiation at 480 nm. The spectrum of 0.10 mM *trans*-**1**·[Ba]$_2$ is shown for comparison.

Irradiation at 370 nm leads to
quasi-*cis*-1[Ba]$_2$ (*cis* / *trans* = 95 / 5)

Irradiation at 480 nm leads to
quasi-*trans*-1[Ba]$_2$ (*cis* / *trans* = 19 / 81)

relatively high efficient and fast interconvertibility of photostationary states !!

2-3. Template



R. Cacciapaglia, *et al. J. Am. Chem. Soc.* **2003**, *125*, 2224

Table 1. Catalysis of the Basic Ethanolysis of Anilides **2** and **3** in EtOH−CH_3CN (65/35 v/v) at 25 °C[a]

substrate	additive (0.10 mM)	k_{obs}[b] (s^{-1})	k_{rel}
2	none	3.93×10^{-5}	1
	trans-**1**·$[Ba]_2$	1.09×10^{-2}	280
	quasi-*trans*-**1**·$[Ba]_2$	1.84×10^{-2}	470
	quasi-*cis*-**1**·$[Ba]_2$	4.89×10^{-2}	1240
3	none	1.85×10^{-6}	1
	trans-**1**·$[Ba]_2$	4.26×10^{-4}	230
	quasi-*trans*-**1**·$[Ba]_2$	7.82×10^{-4}	420
	quasi-*cis*-**1**·$[Ba]_2$	2.36×10^{-3}	1280

[a] Experiments carried out on 0.025 mM substrate solutions in the presence of 1.00 mM Me_4NOEt. [b] Clean first-order time dependence was observed in all cases. Error limits are on the order of ±5%.

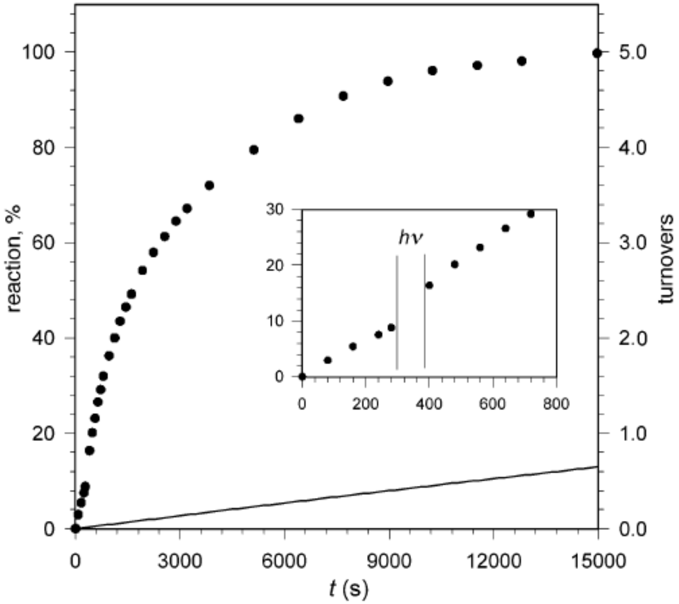


Figure 5. Turnover catalysis with product inhibition in the ethanolysis of a 5-fold molar excess of **3** in the presence of 5.00 mM $EtONMe_4$ and 0.10 mM *trans*-**1**·$[Ba]_2$ irradiated at 370 nm for 40 s after 5 min from the start. The line represents the background ethanolysis. The inset shows the early stages of the reaction.

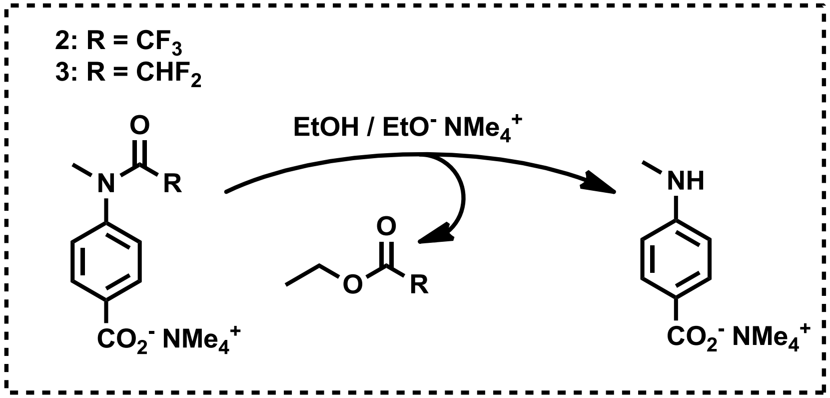
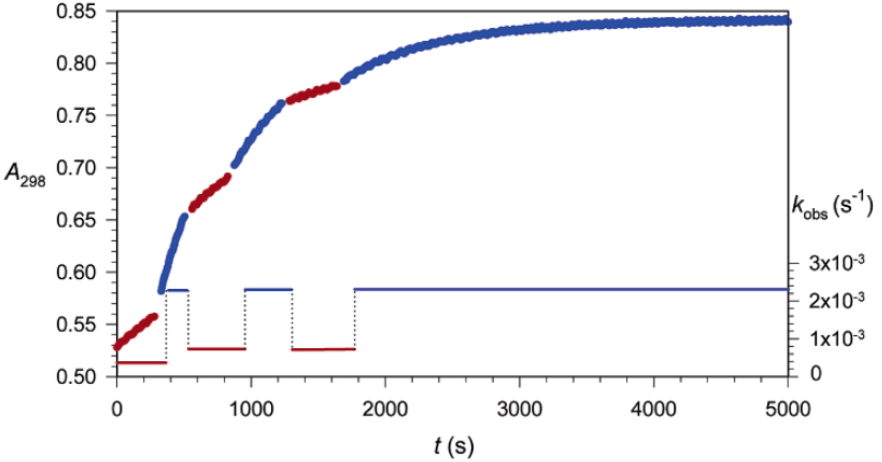


Figure 8. Basic ethanolysis of **3**. Repeated photoconversion into quasi-cis-**1**•$[Ba]_2$ and quasi-trans-**1**•$[Ba]_2$ were obtained upon alternate irradiation at 370 or 480 nm for 40 s. Specific rates are reported on the right-hand ordinate axis.



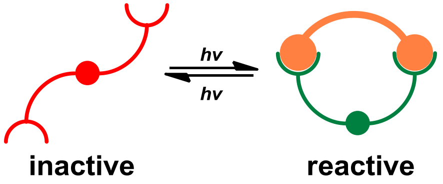
The activity of the catalyst is repeatedly photoswitched !!

drawbacks

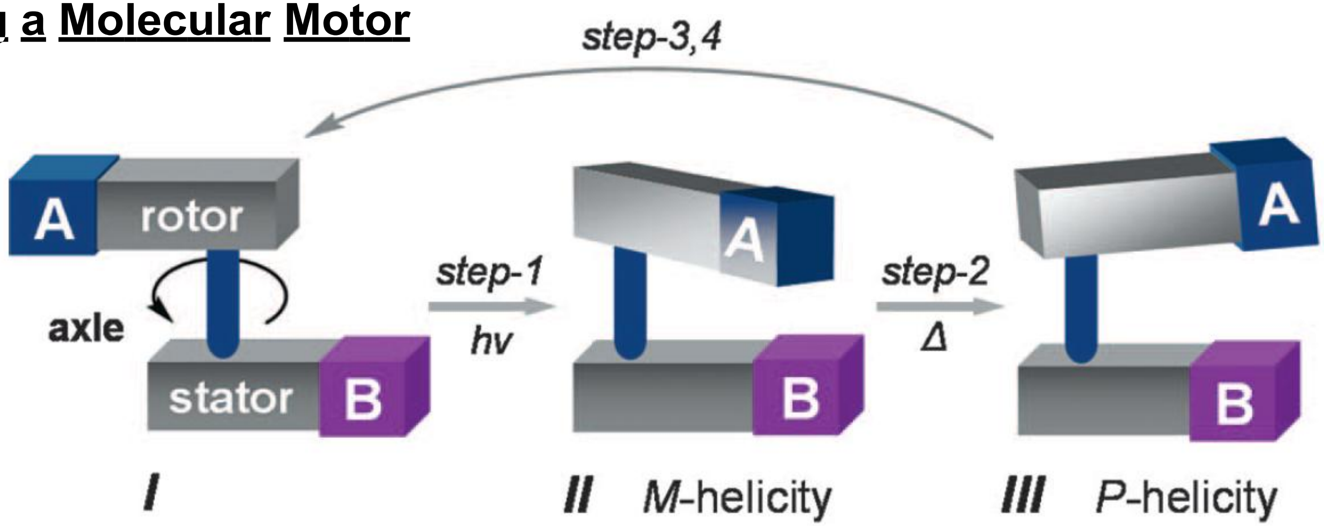
- narrow substrate scope
- low ON/OFF ratio
- **product inhibition** (equimolar amount of catalyst)

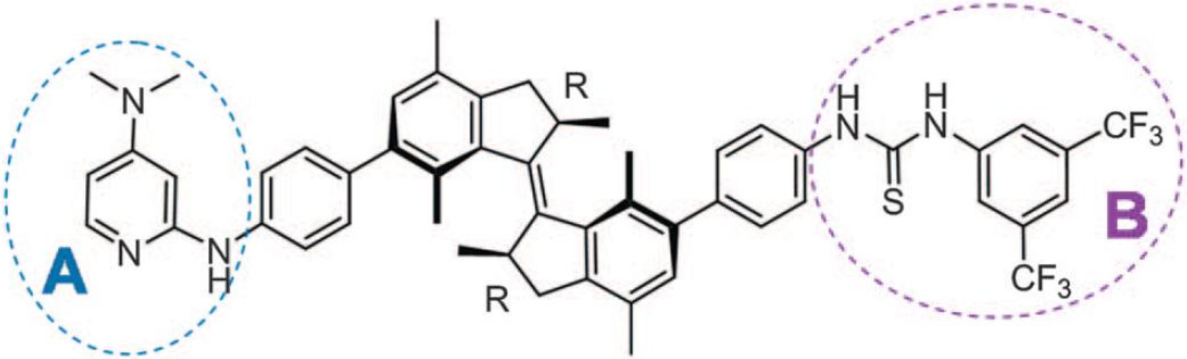
2-3. Template

B. L. Feringa, *et al. Science* **2011**, *331*, 1429



Dynamic Control of Chiral Space in a Catalytic Asymmetric Reaction Using a Molecular Motor





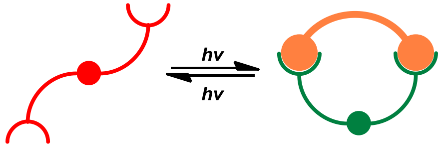
(2*R*,2'*R*)-(*P*,*P*)-*trans*-**1**

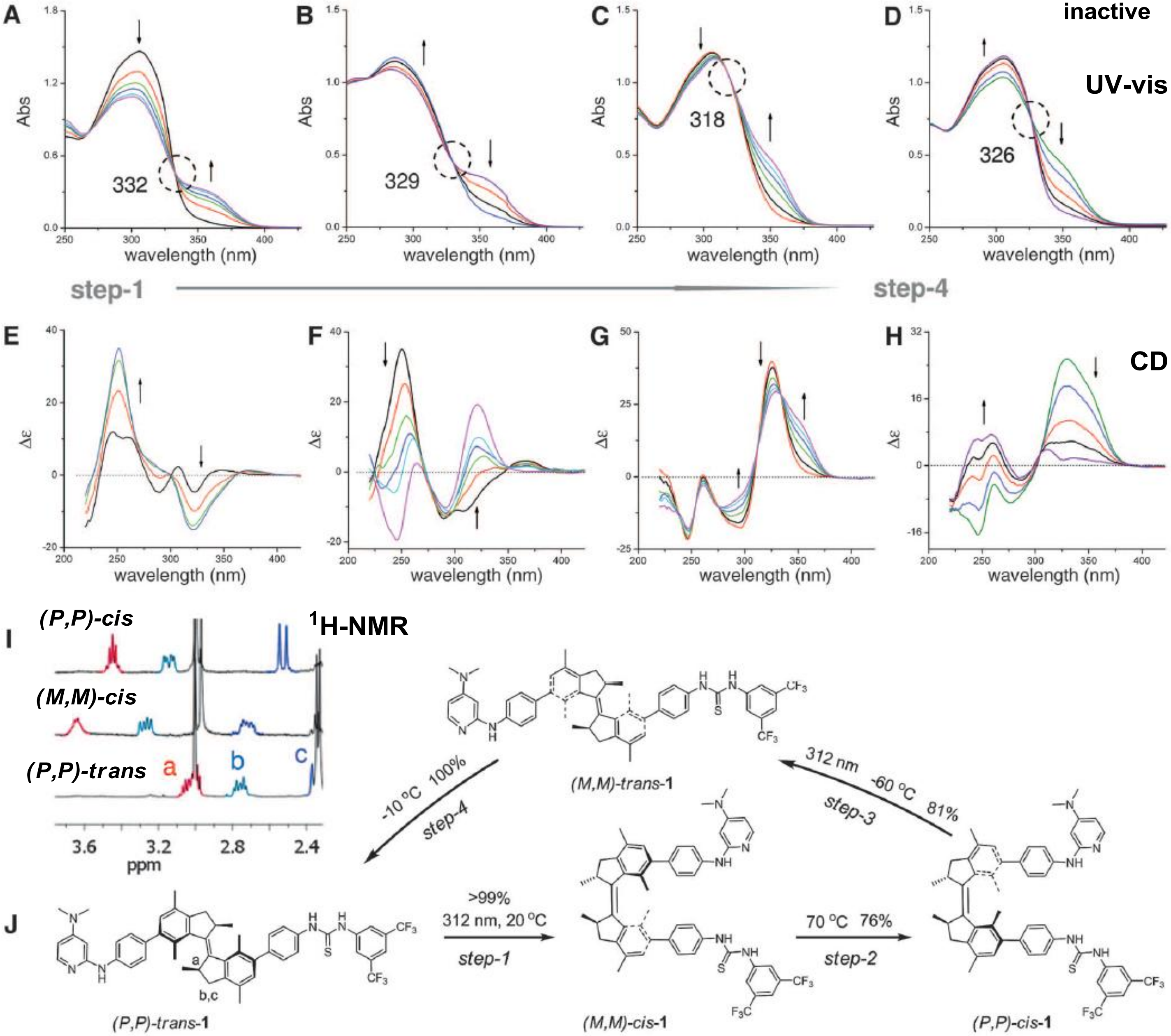
A and B can cooperate to form a **bifunctional organocatalyst** when in proximity ro each other

this catalyst allows for exquisite control over not only catalyst activity but also **stereoselectivity**

2-3. Template

B. L. Feringa, *et al. Science* **2011**, *331*, 1429





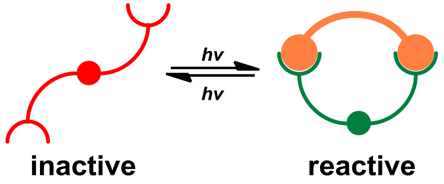
UV-vis spectra

CD spectra

^{1}H-NMR

2-3. Template

B. L. Feringa, *et al. Science* **2011**, *331*, 1429



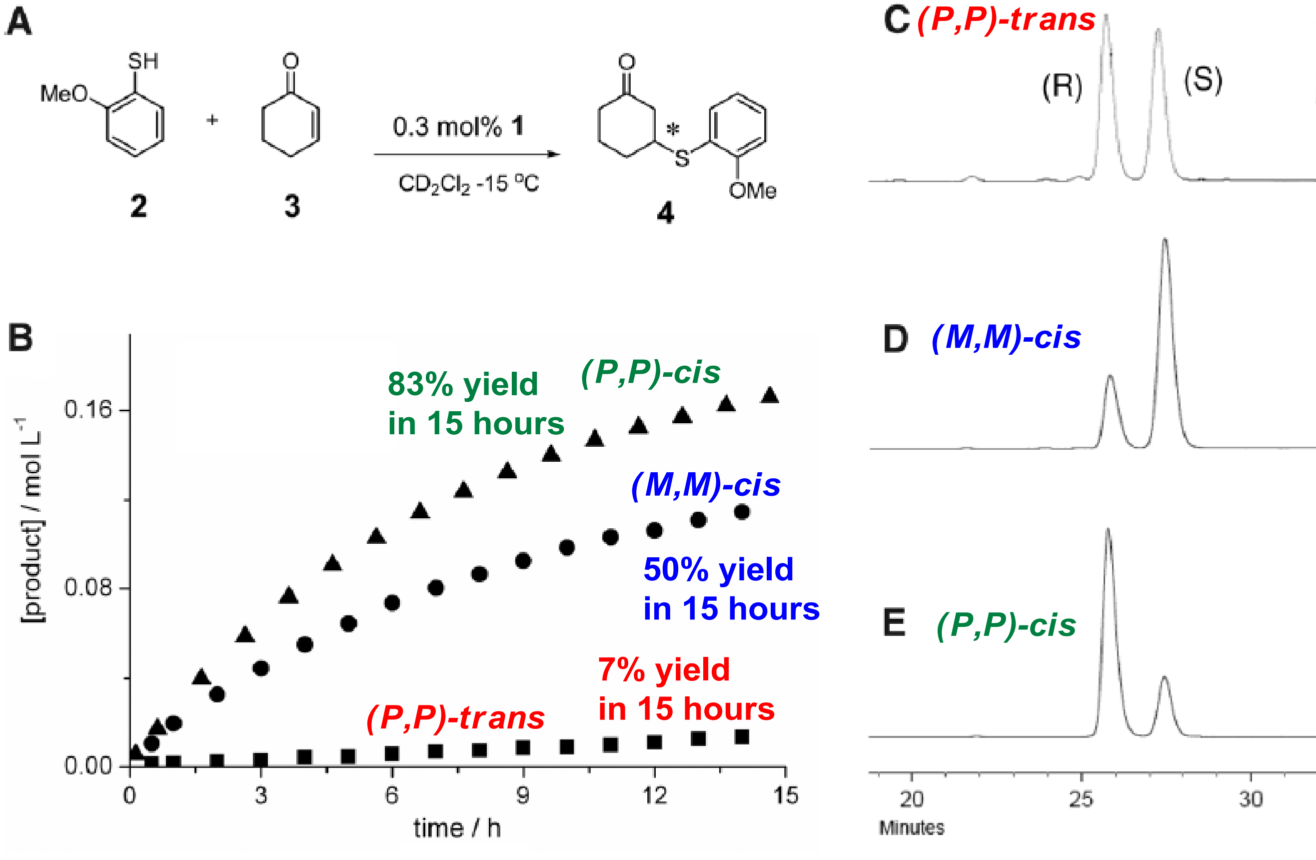
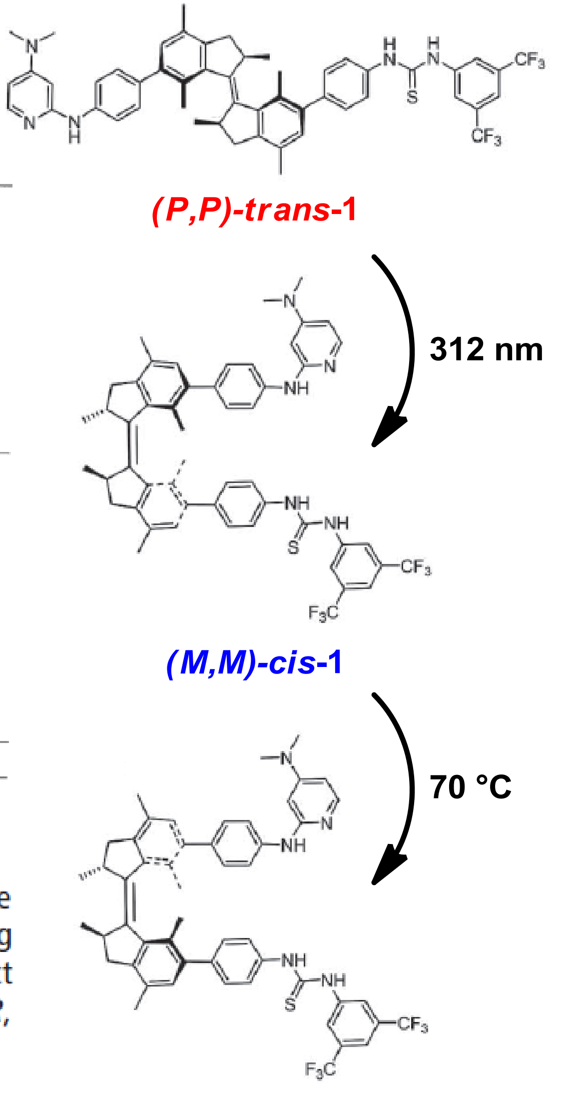


Fig. 3. Catalytic performance of compound **1** for the Michael addition of **2** (0.2 M) to **3** (0.2 M) to give chiral adduct **4**. (**A**) Reaction scheme and conditions. (**B**) Reaction kinetics followed by measuring product formation with in situ ^{1}H-NMR spectroscopy. (**C** to **E**) Chiral HPLC traces of the reaction product **4** using catalyst (*P*,*P*)-*trans*-**1** (e.r., *S*/*R*, 49/51), (*M*,*M*)-*cis*-**1** (e.r., *S*/*R*, 75/25), and (*P*,*P*)-*cis*-**1** (e.r., *S*/*R*, 23/77), respectively.

a catalyst loading is as low as 0.3 mol% !!



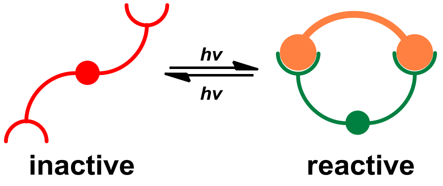
***(P,P)-trans*-1**

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

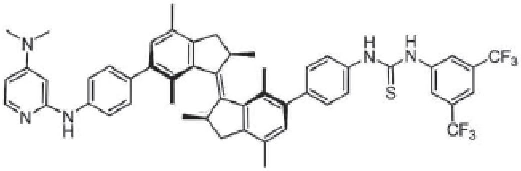
***(P,P)-cis*-1**

2-3. Template

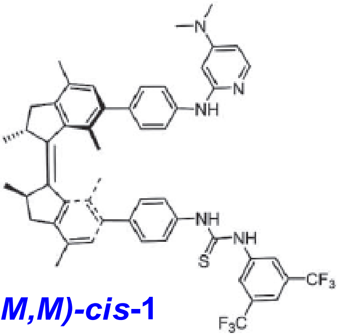
B. L. Feringa, *et al. Science* **2011**, *331*, 1429



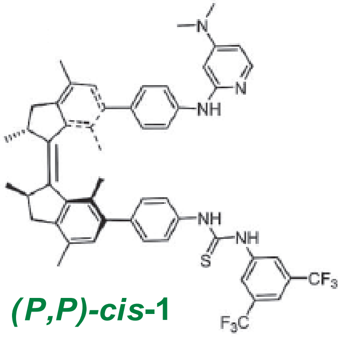
no cooperative effect is possible



***(P,P)-trans*-1**



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



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

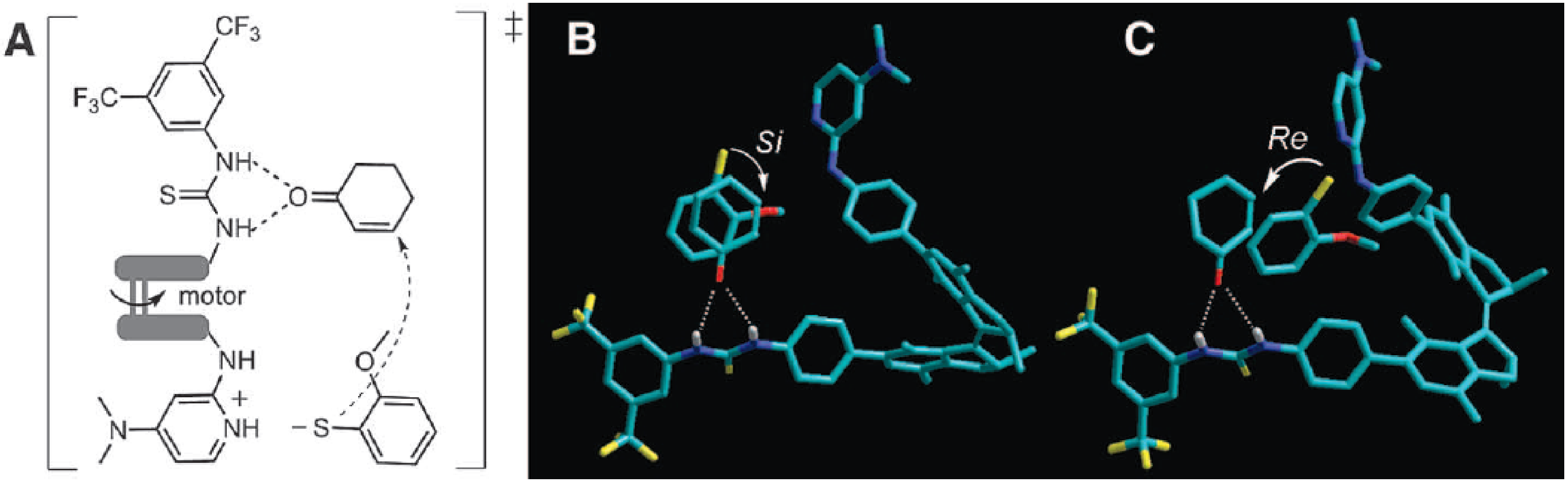
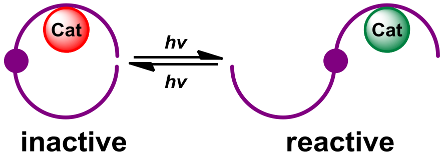
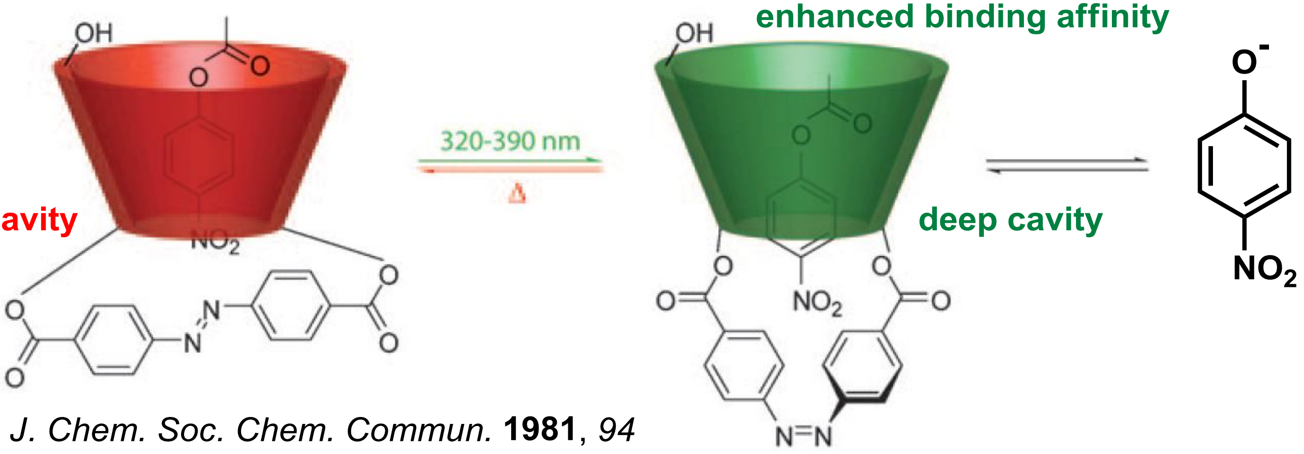


Fig. 4. Proposed ternary complex (**A**) involved in the mechanism of thiol addition to enone catalyzed by **1** and the energy-minimized structures for the asymmetric Michael addition (B and C) obtained using Hyperchem 8.0 (RM1). (**B**) Catalyst (*2R,2′R*)-(*M,M*)-*cis*-**1**; thiol addition to the Si face is favored (marked with arrow) to give the product (*S*)-**4**. (**C**) Catalyst (*2R,2′R*)-(*P,P*)-*cis*-**1**; thiol addition to the Re face is favored to give the product (*R*)-**4**. In the trans isomer (not shown), the catalytic units are pointed antiparallel to each other, precluding bifunctional activation.

2-4. Shielding



The development of photoswitchable catalysts based on β-CDs by Ueno and co-workers was complemented by covalently linking the photochromic azobenzene with the catalytically active macrocycle.



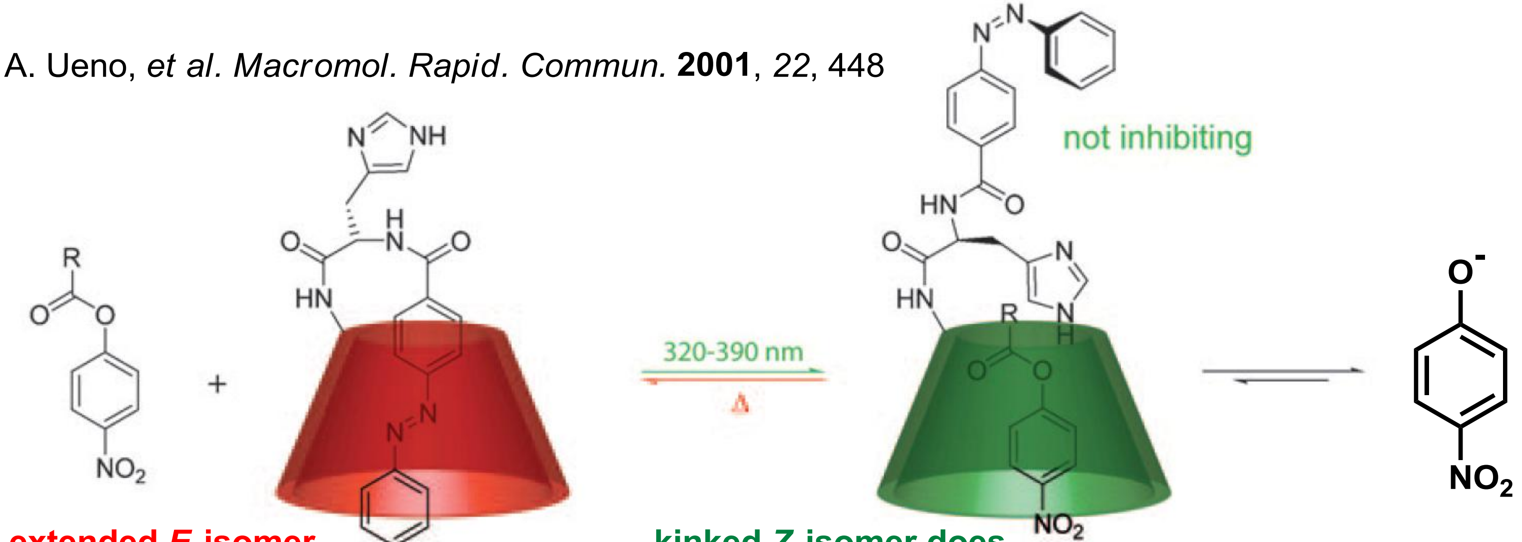
enhanced binding affinity

shallow cavity

deep cavity

A. Ueno, *et al. J. Chem. Soc. Chem. Commun.* **1981**, *94*

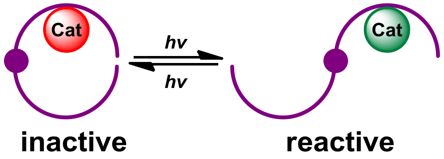
A. Ueno, *et al. Macromol. Rapid. Commun.* **2001**, *22*, 448



extended *E*-isomer occupies the cavity

inhibiting

kinked *Z*-isomer does not fit into the cavity

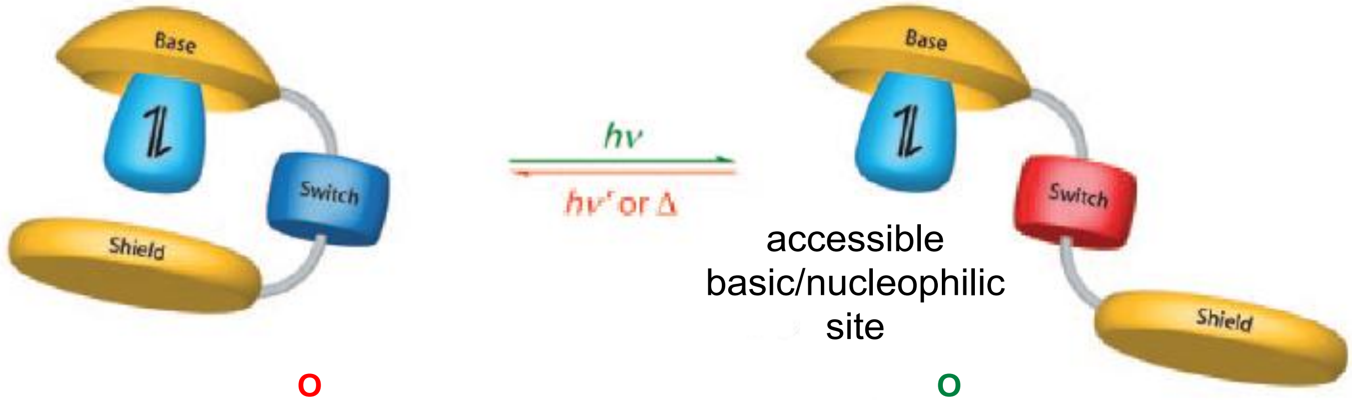


2-4. Shielding

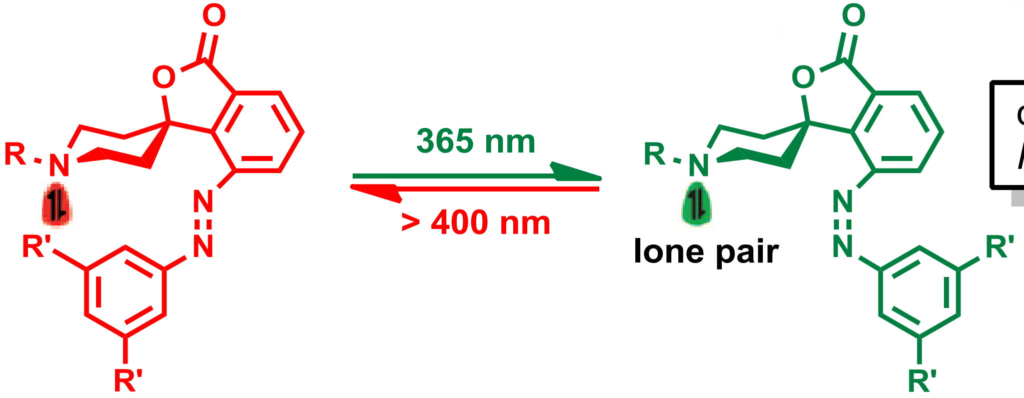
S. Hecht, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 5968

Photoswitching of Basicity

While previous two examples are based on photocontrolled steric shielding of the substrate binding site, another approach followed by Heckt's group is the **photocontrolled shielding of the active site**.



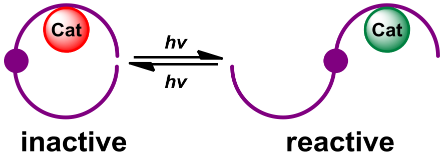
accessible
basic/nucleophilic
site



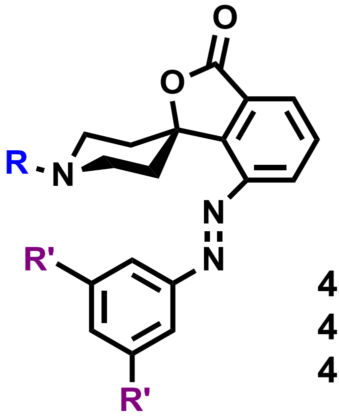
conformationally restricted
N-alkylated piperidine base

- the preference of the piperidine ring to adopt a **chair conformation** with the *N*-alkyl substituent in an **equatorial** position
- the **spiro junction** enables the rigid and **orthogonal** positioning of the photochromic azobenzene moiety

2-4. Shielding



S. Hecht, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 5968



R : conformational fixation

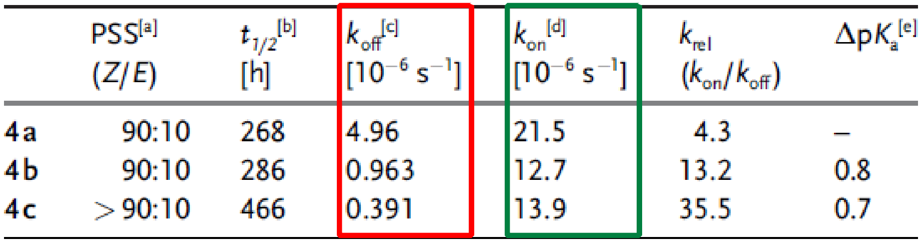
R' : steric-shielding capability

4a R = Me, R' = *t*Bu

4b R = *t*Bu, R' = *t*Bu

4c R = *t*Bu, R' = 2,6-$Me_2C_6H_3$

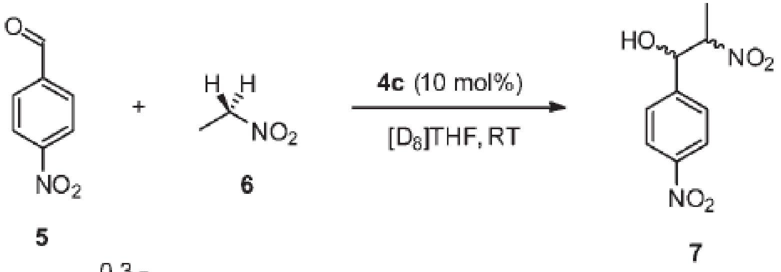
Table 1: Photochemical, kinetic, and thermodynamic data for the piperidine bases 4a–c.



	PSS[a] (*Z*/*E*)	$t_{1/2}$[b] [h]	k_{off}[c] [10^{-6} s^{-1}]	k_{on}[d] [10^{-6} s^{-1}]	k_{rel} (k_{on}/k_{off})	ΔpK_a[e]
4a	90:10	268	4.96	21.5	4.3	–
4b	90:10	286	0.963	12.7	13.2	0.8
4c	>90:10	466	0.391	13.9	35.5	0.7

[a] Photostationary state (PSS) obtained by irradiation at 365 nm. [b] Half-life of the *Z* isomer, measured at 20 °C. [c] Rate constant of Henry reaction using pure *E* isomer (Figure 3). [d] Rate constant of Henry reaction extrapolated to 100% *Z* isomer (Figure 3). [e] Difference of pK_a values, i.e. $pK_a(PSS) - pK_a(E)$, obtained from titration with trifluoromethanesulfonic acid using Neutral Red as reference base.

Performance of the photoswitchable base in Henry reaction



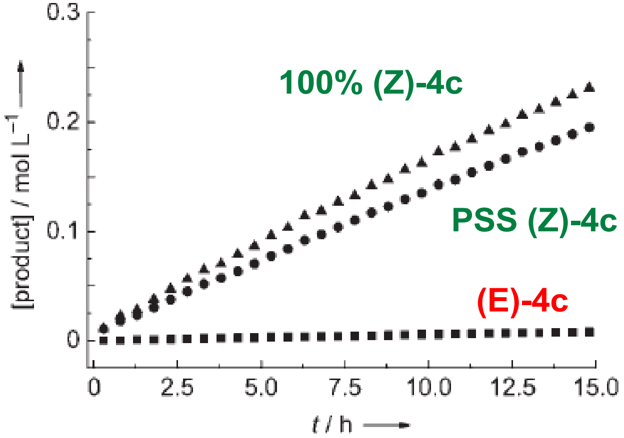
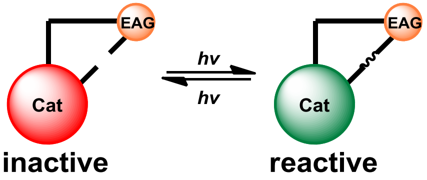


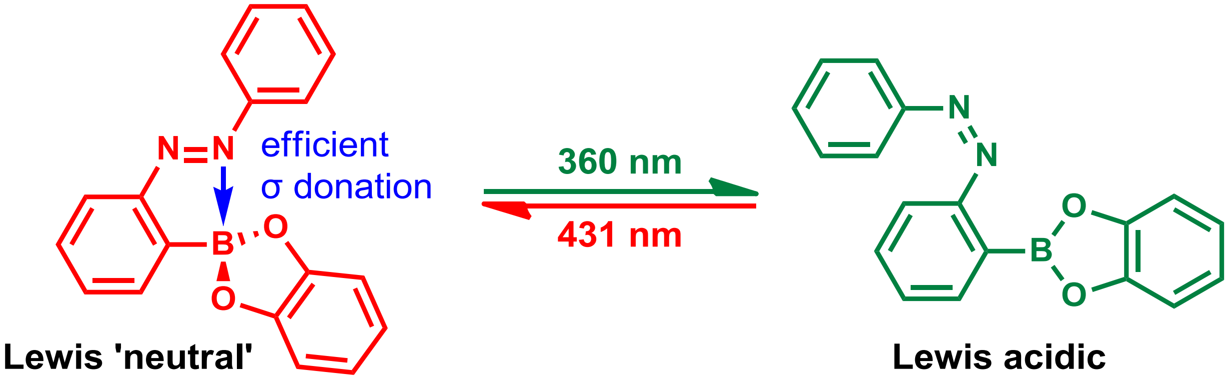
Figure 3. Performance of the photoswitchable piperidine **4c** in its two switching states as general base catalyst for the Henry reaction of **5** with **6** to give **7**: ■ (*E*)-**4c**, ● (*Z*)-**4c** in the photostationary state with residual (*E*)-**4c**, ▲ extrapolation to 100% (*Z*)-**4c** with a correction for the thermal (*Z*)-**4c**→(*E*)-**4c** back reaction. Reaction conditions: catalyst (10 mol%), 4-nitrobenzaldehyde (0.40 M, 1 equiv), nitroethane (12 equiv), [D_8]THF, 25 °C.

Although this example illustrates the power of structure-based optimization, the system suffers from the low intrinsic activity of the piperidine lead structure, which limits the general scope of the catalyst system and the attainable ON/OFF ratios.

2-5. Electronic effects

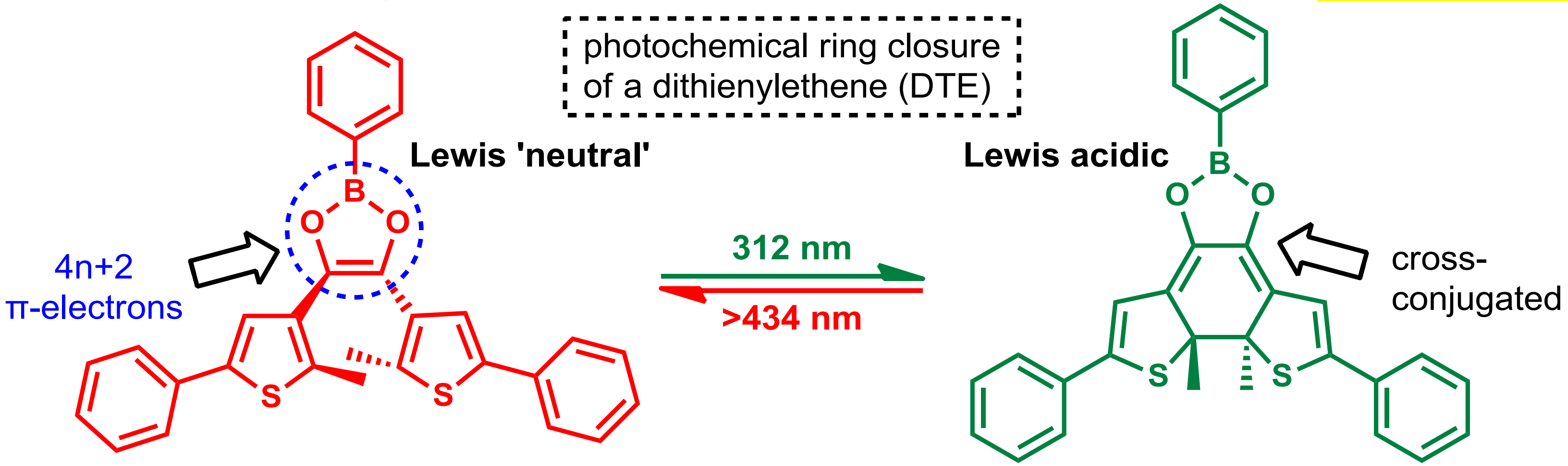


T. Kawashima, *et al. Org. Lett.* **2005**, *7*, 3909



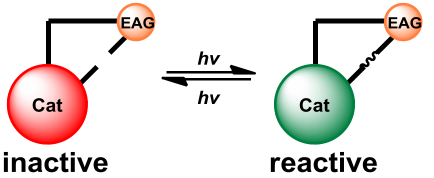
feasibility of electronic modulation

N. R. Branda, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 5034


photochemical ring closure of a dithienylethene (DTE)

Neither Kawashima’s nor Branda’s system have been used as photoswitchable Lewis acids to control any chemical transformation…

2-5. Electronic effects



C. W. Bielawski, *et al. J. Am. Chem. Soc.* **2012**, *134*, 12693

Photoswitchable N-Heterocyclic Carbene Organocatalysts

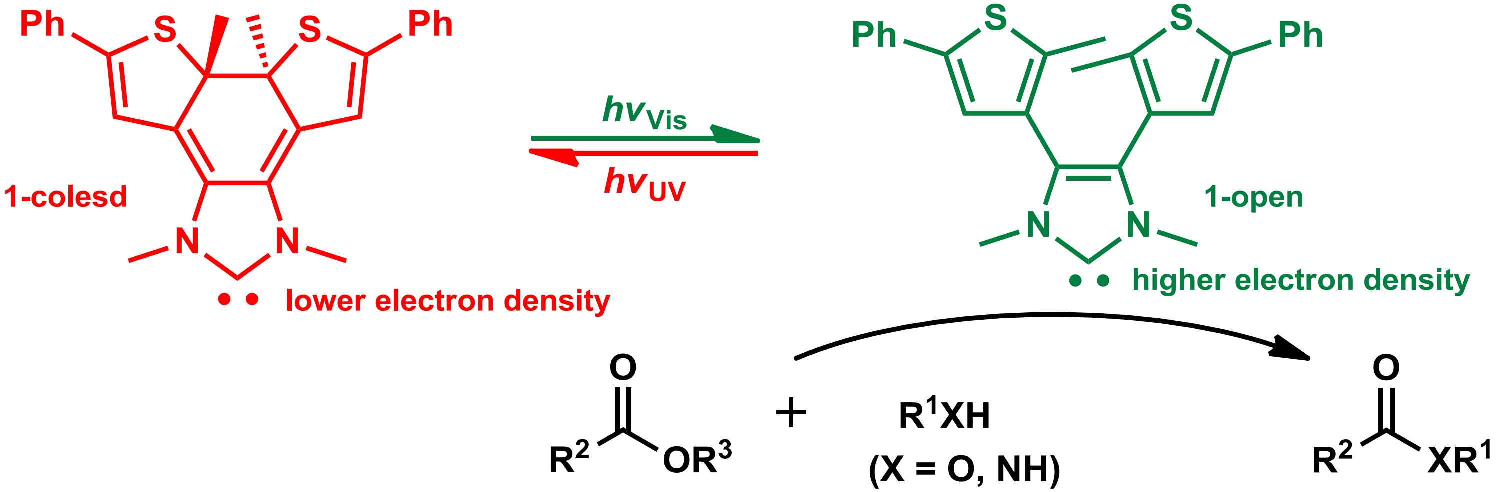


Figure 1.

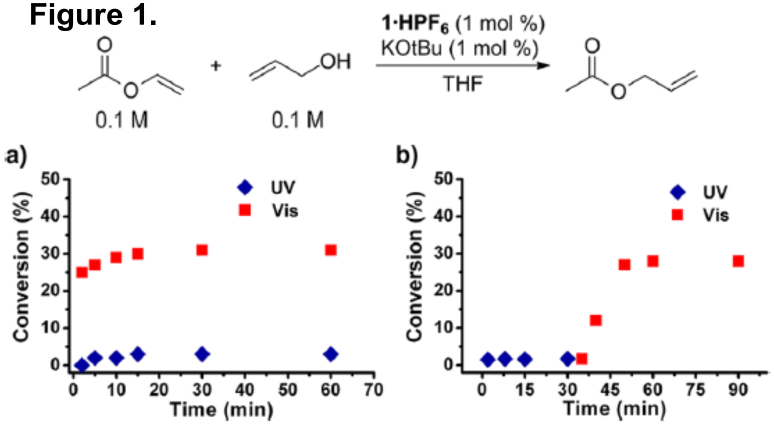
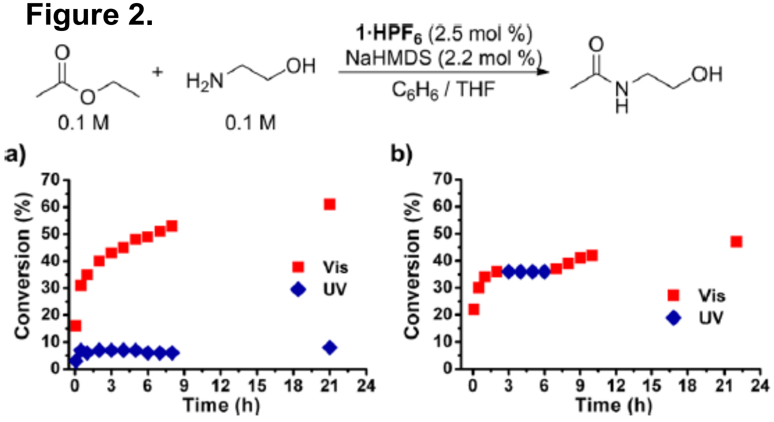


Figure 2.

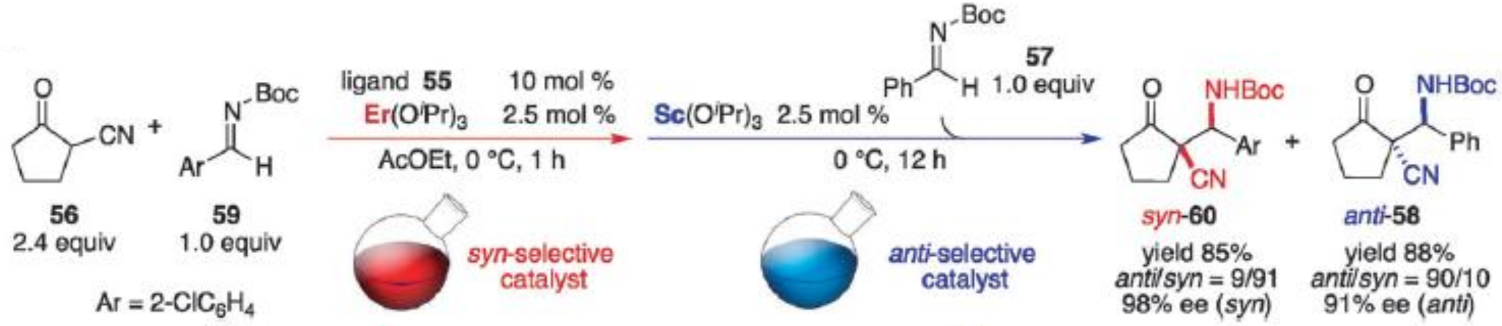


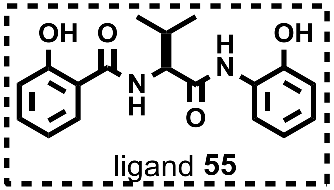
The activity of the NHC organocatalyst was remotely tuned via exposure to UV and visible light. This is rare example of a photoswitchable catalyst that operates via the remote photomodulation of its electronic structure.

3. Metal-Cation-Switchable Catalysts

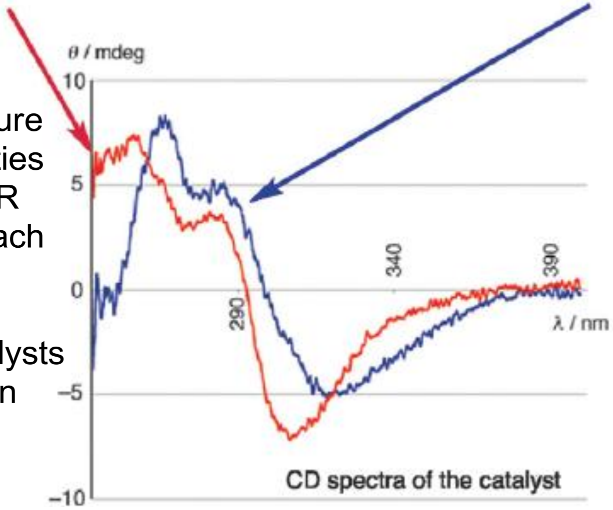
M. Shibasaki, *et al. J. Am. Chem. Soc.* **2009**, *131*, 3779

Diastereoswitching of catalytic asymmetric Mannich-type reaction





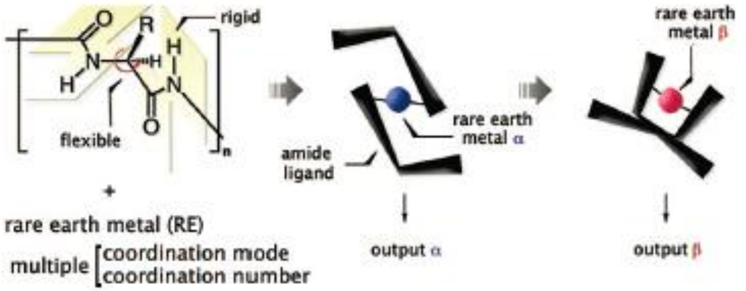
ligand **55**



CD spectra of the catalyst

Although the dynamic nature and paramagnetic properties of the Er^{3+} hampered NMR analysis, CD spectra of each catalyst produced distinct patterns, suggesting that chiroptically different catalysts were formed depending on the rare earth metal used.

- amide-based ligands possess reasonable rigidity (planar amide) and conformational flexibility (α-carbon)
- rare earth metals have multiple coordination modes and coordination numbers

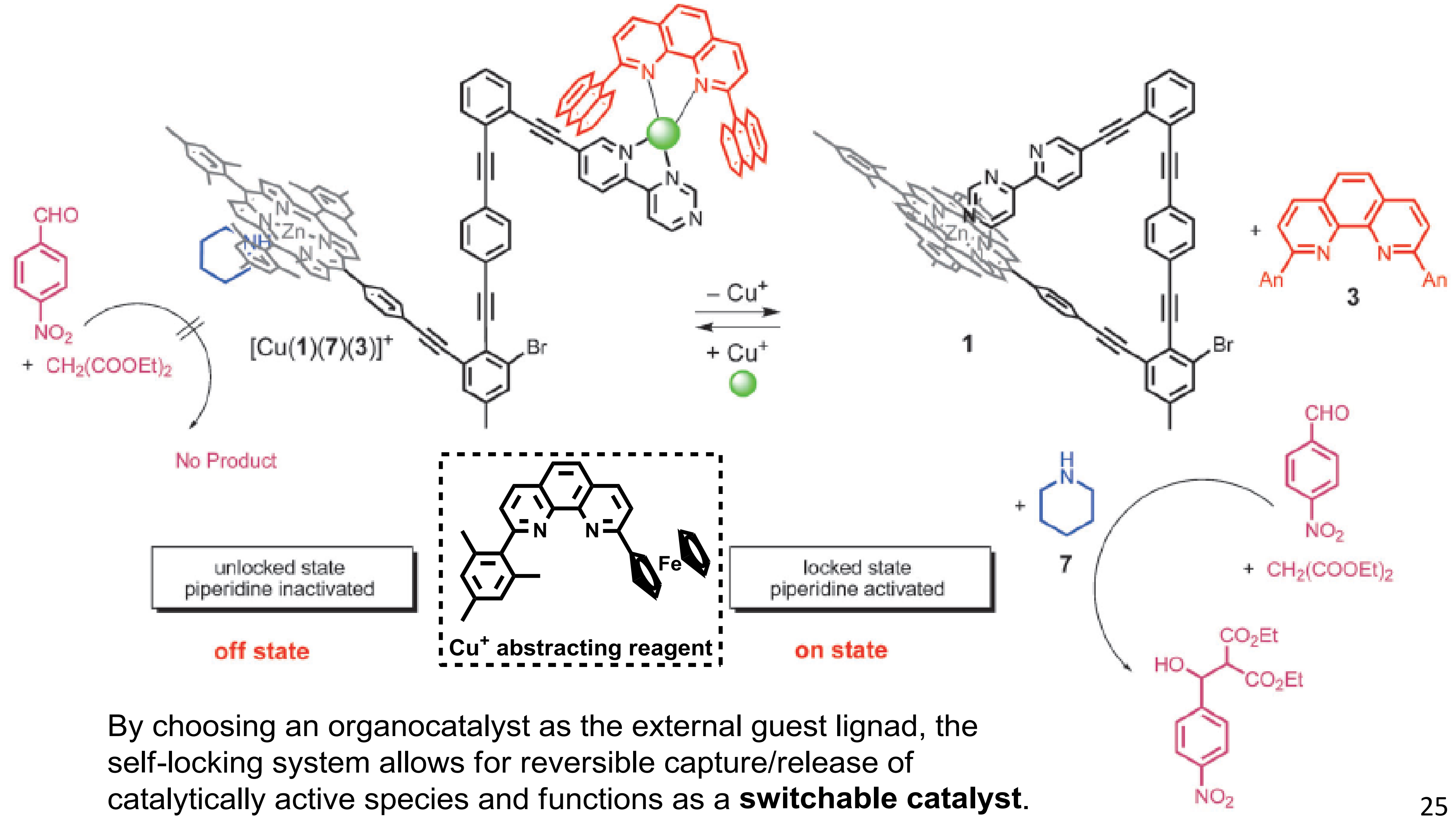


Unfortunately, the change in the stereoselevtivity was **only unidirectional** and **a reversible switching system remains to be developed**.

3. Metal-Cation-Switchable Catalysts

M. Schmittel, *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 3832

Self-locking system for reversible capture/release of an organocatalyst

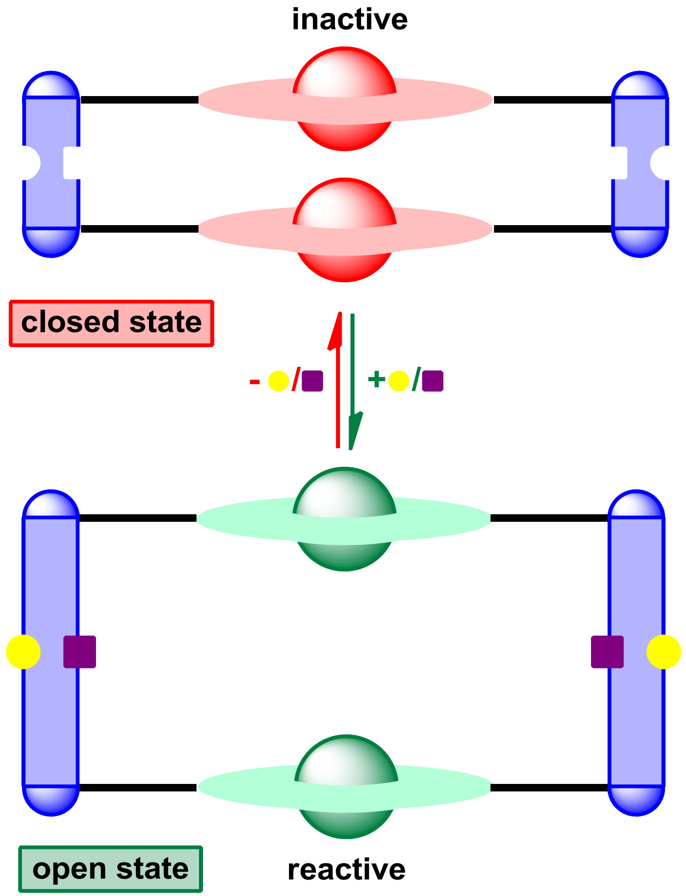


By choosing an organocatalyst as the external guest lignad, the self-locking system allows for reversible capture/release of catalytically active species and functions as a **switchable catalyst**.

4. Supramolecular approaches

Supramolecular approaches display a distinct three-dimensional architecture through noncovalent interactions, while a reasonable degree of conformational freedom remains to allow modification of its three-dimensional shape in response to specific signals.

4-1. Layered Systems



inactive

closed state

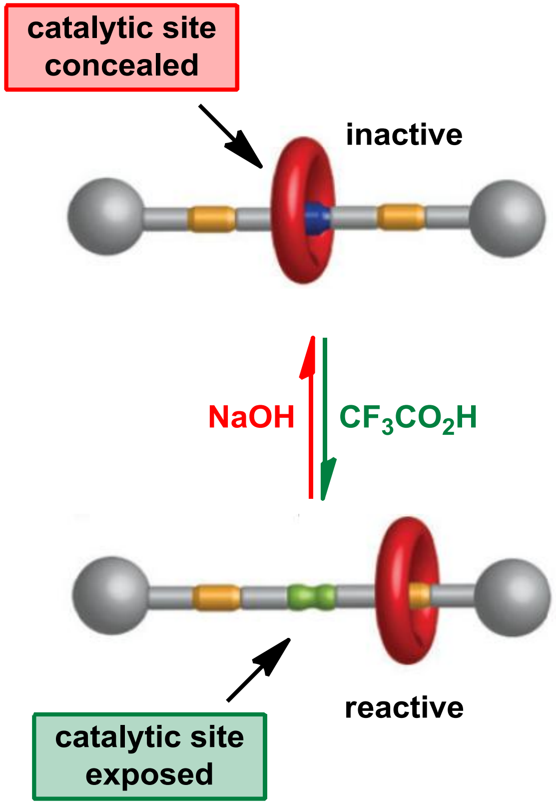
- ●/■

+ ●/■

open state

reactive

4-2. Rotaxanes



catalytic site concealed

inactive

NaOH

CF_3CO_2H

reactive

catalytic site exposed

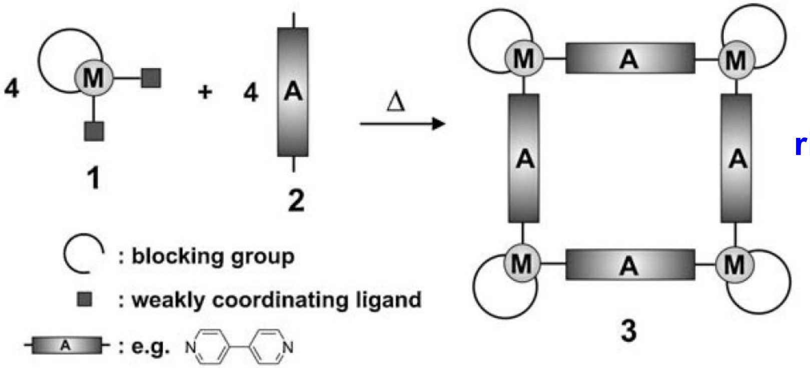
4-1-1. Layered Systems - Introduction

C. A. Mirkin, *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 114

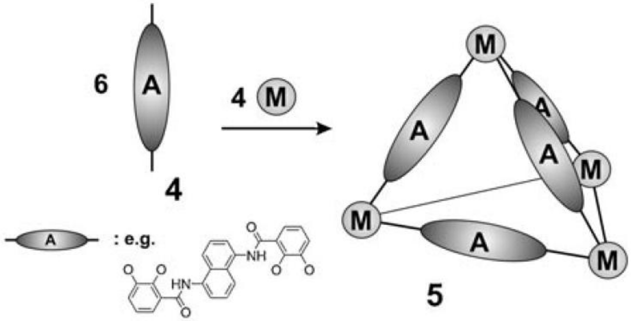
Supramolecular Coordination Assembly Approaches

directional-bonding approach (DBA)

M : for example, Pd^{II}, Pt^{II}



rigid



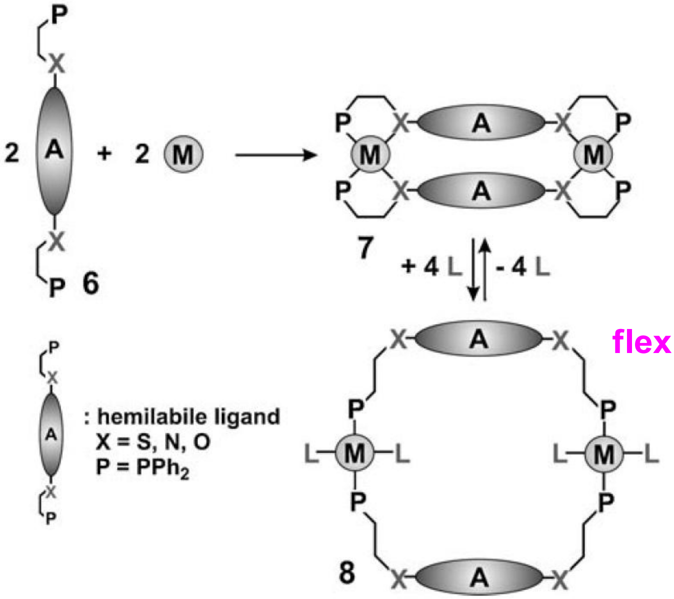
rigid

symmetry-interaction approach (SIA)

M : for example, Ga^{III}, Fe^{III}, Al^{III}

weak-link approach (WLA)

M : for example, Rh^{I}, Pd^{II}, Cu^{I}, Ir^{I}



flexible

reversible in situ modification

(charges and counterions are not shown)

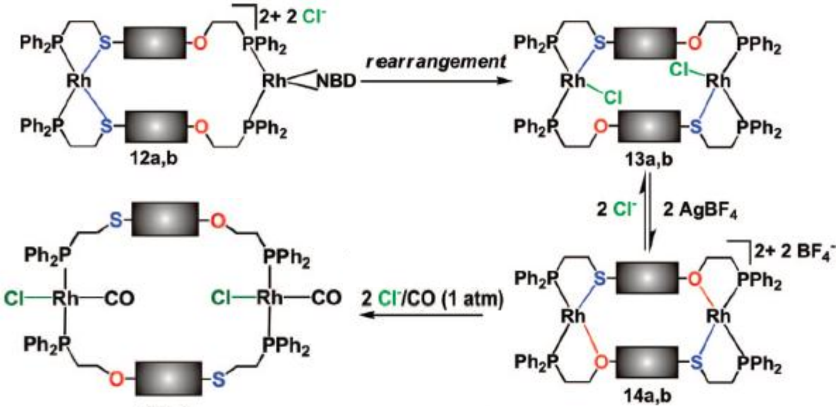
Structures formed through these supramolecular approaches can exhibit catalytic activities reminiscent of enzymes in terms of catalytic acceleration by proximity effects in cages, discrimination between different isomers of a substrate, and regulation in terms of catalytic activity and selectivity.

4-1-1. Layered Systems - Introduction

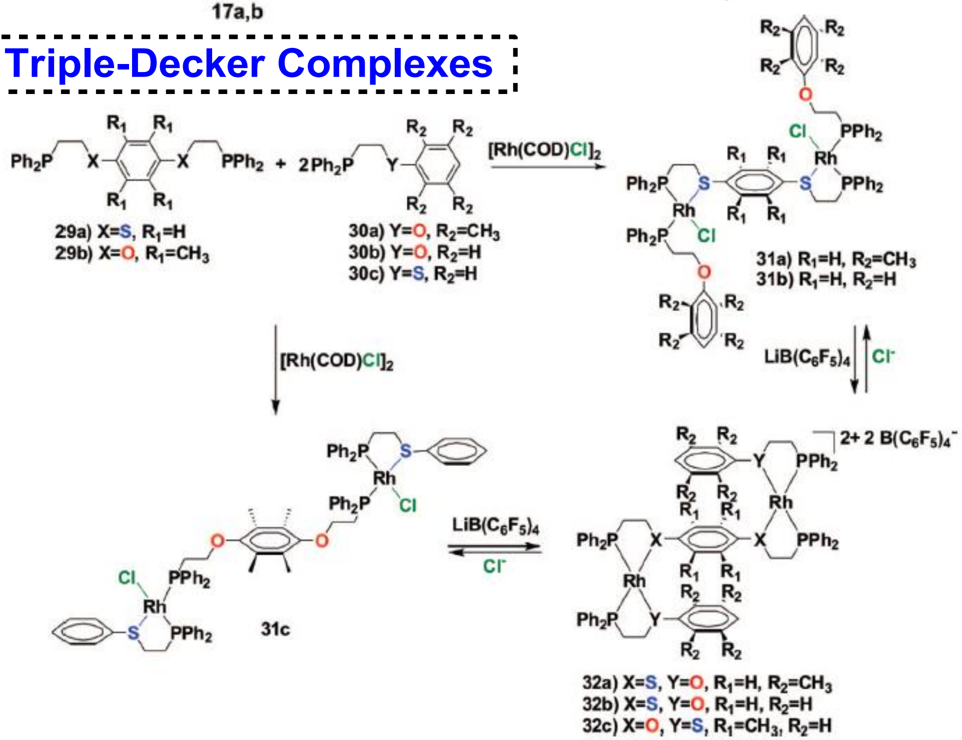
Heteroligated Complexes via Halide-Induced Ligand Rearrangement (HILR)

C. A. Mirkin, *et al. Acc. Chem. Res.* **2008**, *41*, 1618

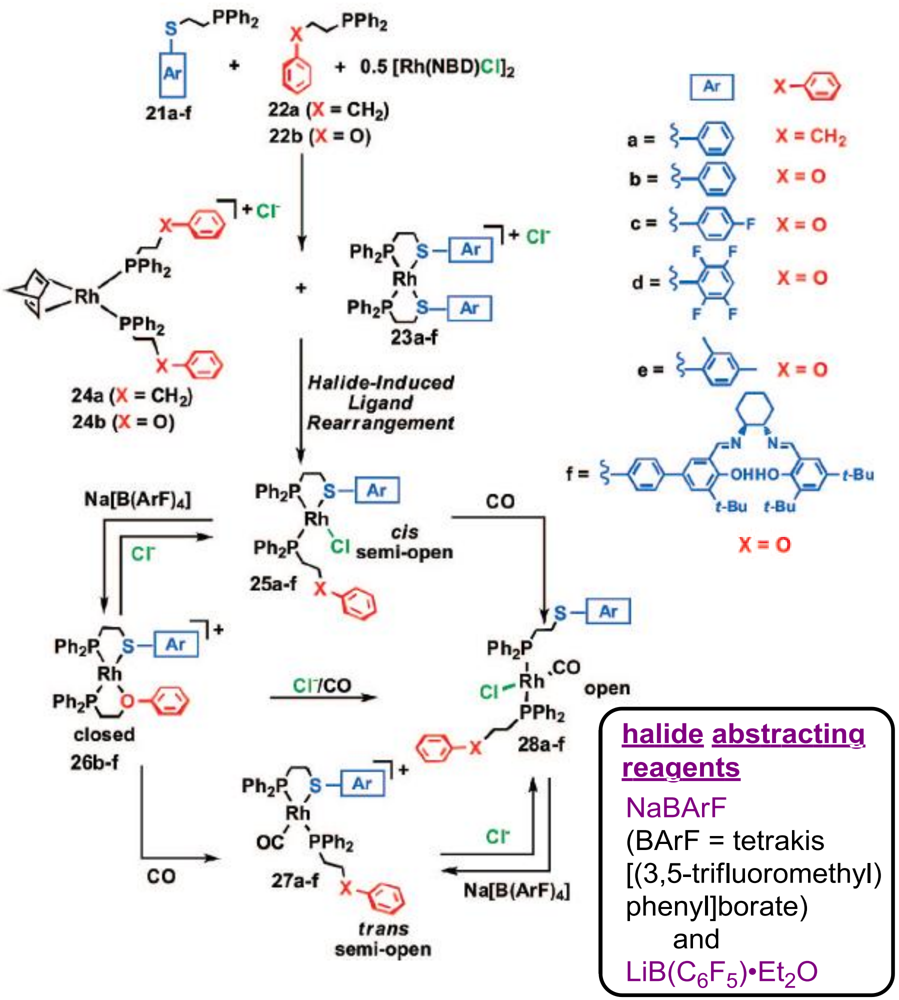
Macrocyclic Complexes



Triple-Decker Complexes



Tweezer Complexes

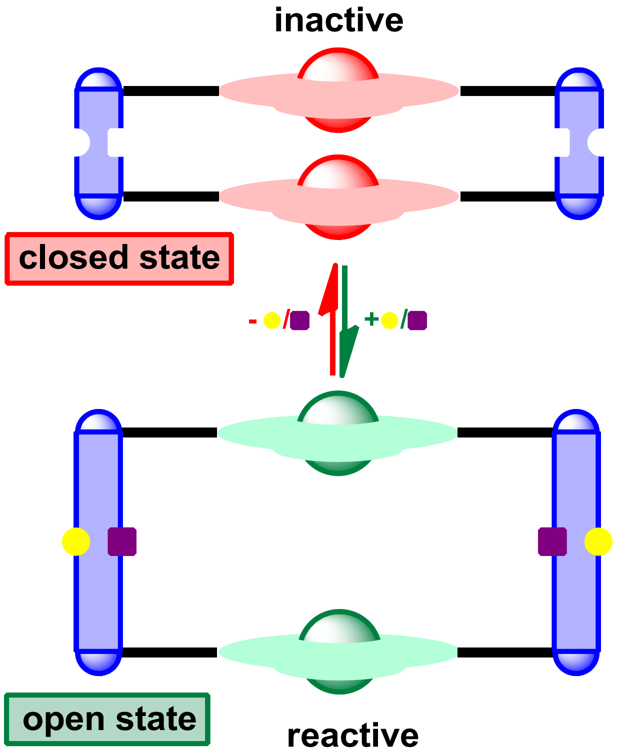


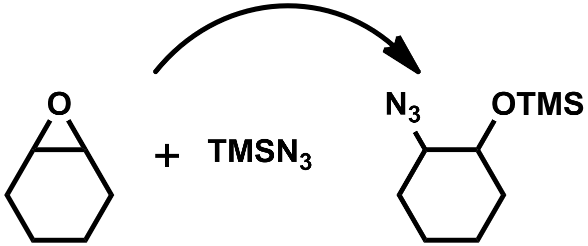
halide abstracting reagents

NaBArF
(BArF = tetrakis [(3,5-trifluoromethyl) phenyl]borate)
and
$LiB(C_6F_5) \cdot Et_2O$

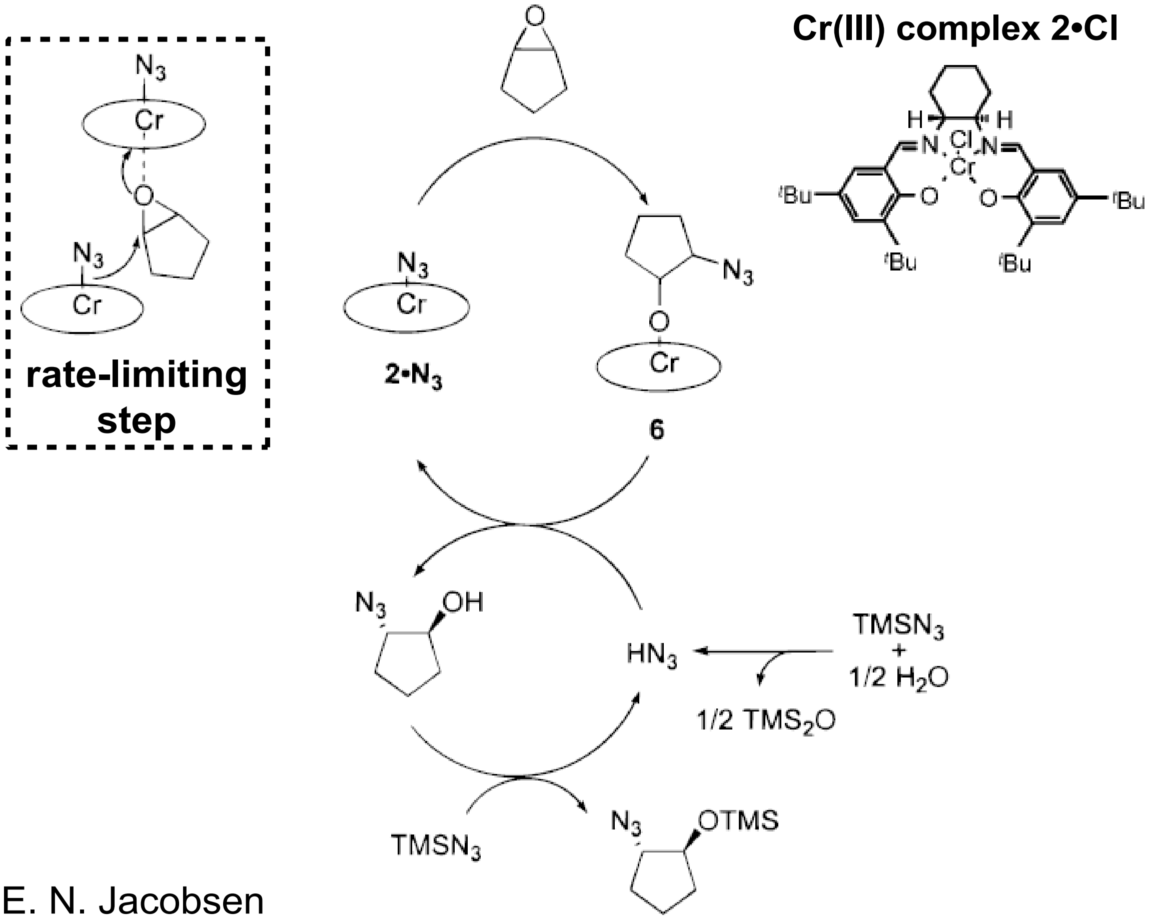
4-1-2. Macrocycle Approach

C. A. Mirkin, *et al. J. Am. Chem. Soc.* **2003**, *125*, 10508





This reaction was selected because of its demonstrated **bimetallic mechanism** that requires two metal-salen monomeric catalyst to activate both the electrophile (epoxide) and the nucleophile (azide).

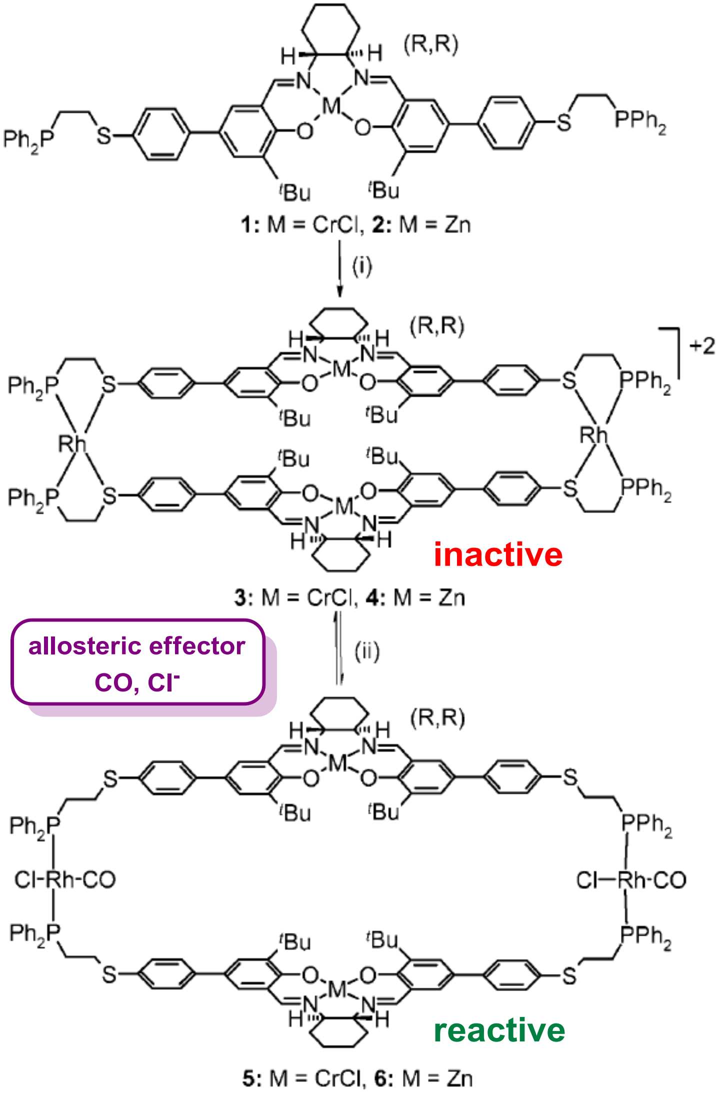


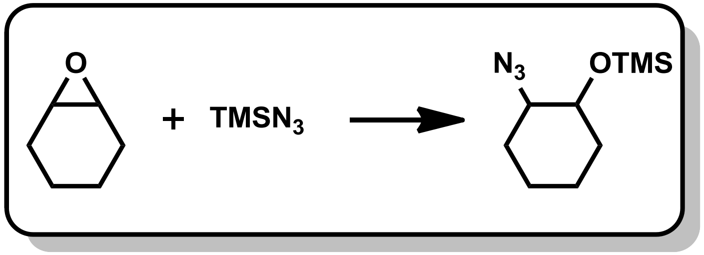
E. N. Jacobsen
Acc. Chem. Res. **2000**, *33*, 421

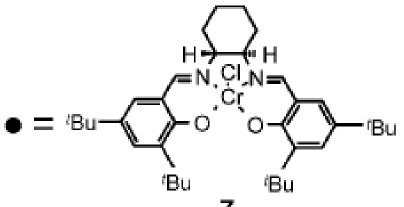
4-1-2. Macrocycle Approach

C. A. Mirkin, *et al. J. Am. Chem. Soc.* **2003**, *125*, 10508

This work represented **the first demonstration** of an allosteric catalyst made possible through supramolecular coordination chemistry.







7

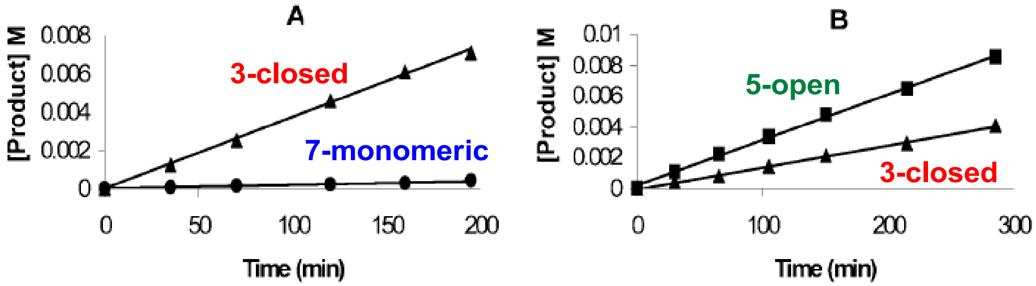
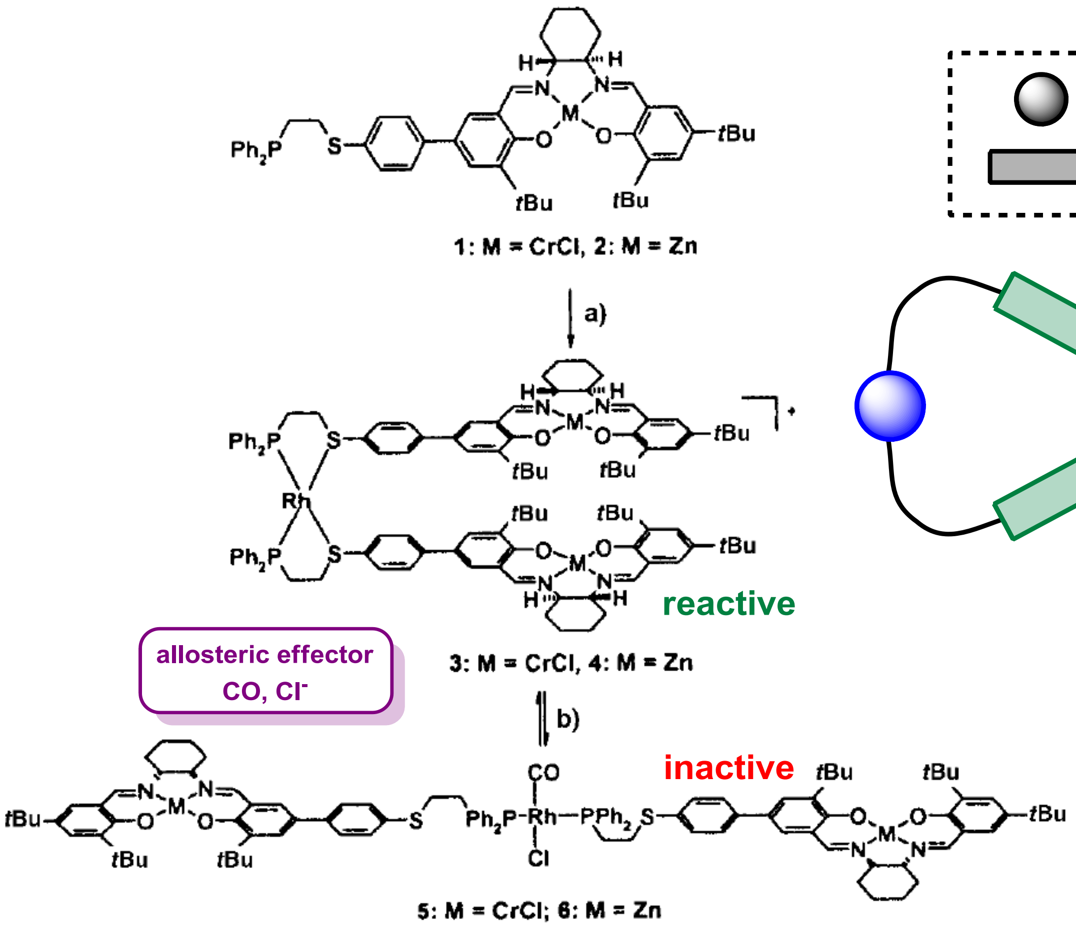


Figure 2. Graph A: Initial rate kinetics for the ring opening of cyclohexene oxide by TMSN$_3$ catalyzed by **3** (▲) (2.6 mM) and a monomeric Cr(III)-salen complex **7** (●) (5.2 mM) in benzonitrile at room temperature. The catalyst concentrations are the same with respect to Cr(III). Graph B: Initial rate kinetics for the ring opening of cyclohexene oxide by TMSN$_3$, as catalyzed by **3** (▲) and **5** (■) each at 2.6 mM, in benzonitrile/pyridine at room temperature.

[a] Counterions are BF$_4^-$. Reagents and solvents: (i) Rh(norbornadiene)$_2$BF$_4$, CH$_2$Cl$_2$; (ii) PPNCl/CO, benzonitrile; **3** and **4** may be synthesized from **5** and **6**, respectively, by the removal of CO in vacuo or by N$_2$ purge.

4-1-3. Molecular Tweezers

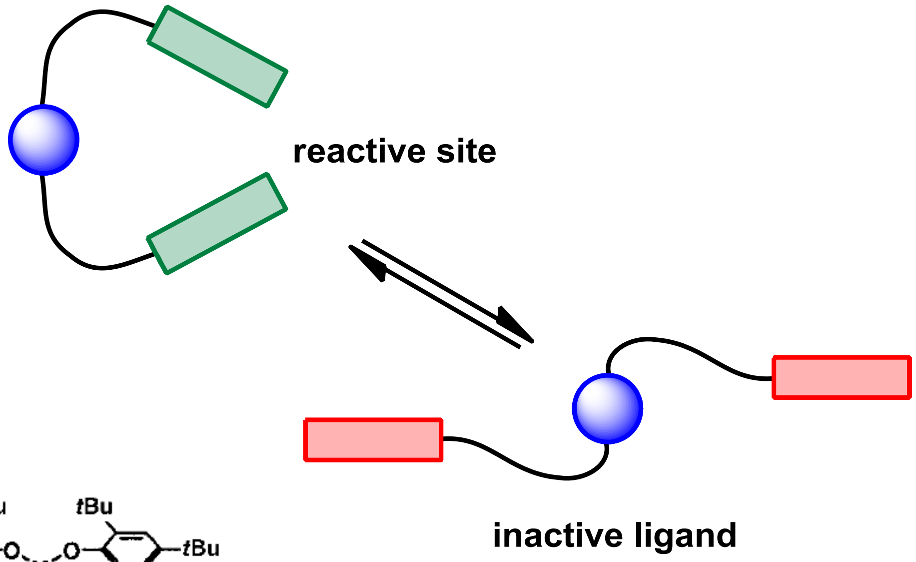
C. A. Mirkin, *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 5503



Scheme 2. Synthesis of the allosteric tweezer complexes. Counterions are BF_4^-. All cyclohexyl salen backbones have (*R*,*R*) stereochemistry. Reagents and solvents; a) $[Rh(NBD)_2]BF_4$, CH_2Cl_2; b) PPNCl/CO (PPNCl = bis(triphenylphosphoranylidene)ammonium chloride); **3** and **4** may be synthesized from **5** and **6**, respectively, by the removal of CO in vacuo or by purging with N_2.

● **Structural transition-metal center**

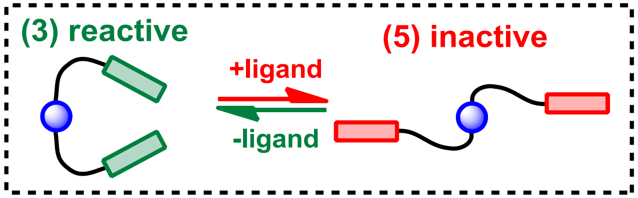
▬ **Catalytic transition-metal center**

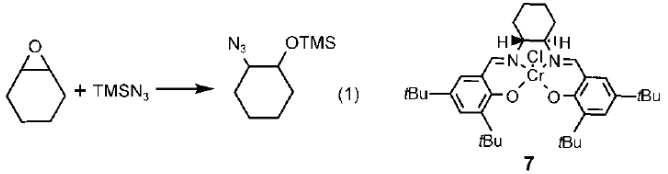


This dramatic change in shape was expected to generate a larger allosteric effect than the related macrocyclic analogue!

4-1-3. Molecular Tweezers

C. A. Mirkin, *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 5503



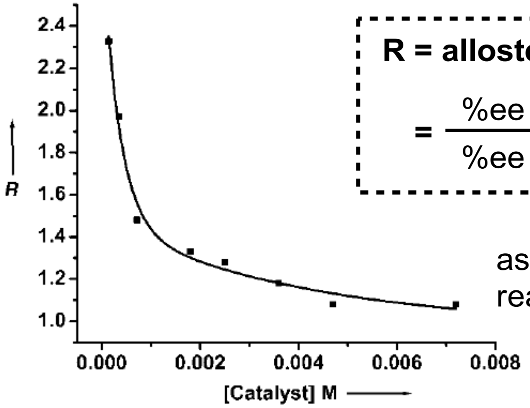


Entry	Catalyst	[Catalyst] M 1×10^{-3}	% *ee* of product[b]
1	**3**	7.2	80
2	**5**	7.2	74
3	**7**	7.2	26
4	**3**	4.7	80
5	**5**	4.7	73
6	**3**	3.6	79
7	**5**	3.6	68
8	**7**	3.6	12
9	**3**	2.5	77
10	**5**	2.5	60
11	**3**	1.8	72
12	**5**	1.8	54
13	**3**	0.72	65
14	**5**	0.72	44
15	**3**	0.36	63
16	**5**	0.36	32
17	**3**	0.14	49
18	**5**	0.14	21

[a] All reactions were performed at room temperature in THF. [b] % *ee* of 1-azido-2-(trimethylsiloxy)cyclohexane was determined by chiral GC.

increased solubility
(in comparison with the macrocycle)
⇩
greater ranges of catalyst concentration

Figure 1. The allosteric effect expressed in terms of selectivity

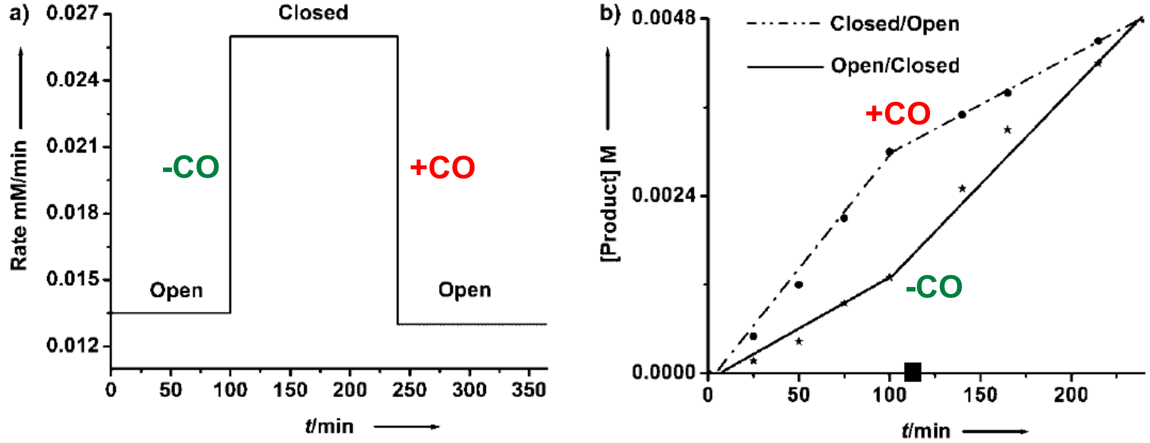


R = allosteric selectivity ratio

$$= \frac{\%\text{ee of the product formed by using } \mathbf{3}}{\%\text{ee of the product formed by using } \mathbf{5}}$$

as the catalyst concentration is increased the reaction would become more intermolecular

Figure 2. In situ reversibility of the catalysis

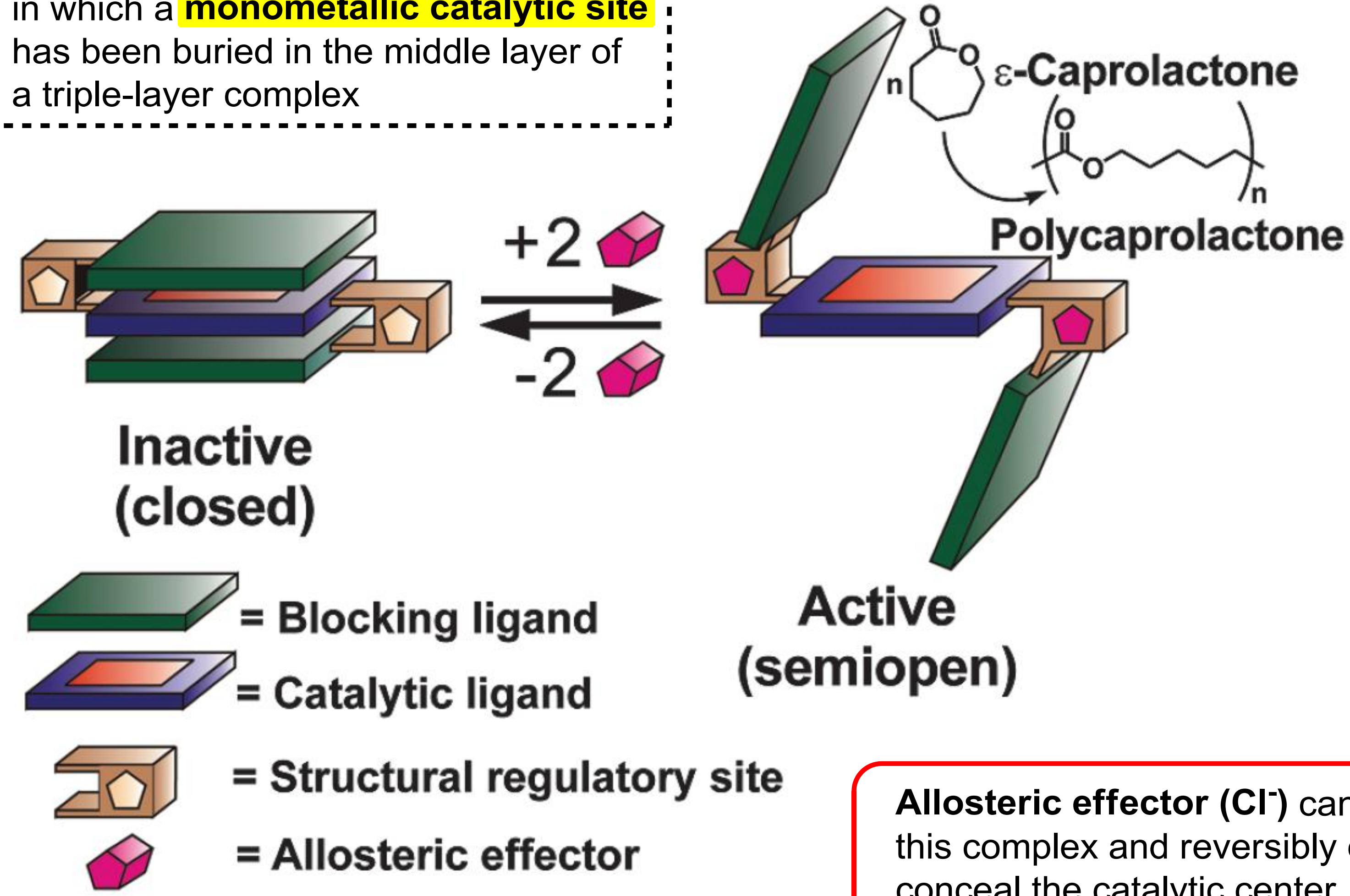


The ability to reversibly convert from **3** to **5** in situ by CO saturation and CO desaturation of a solution containing Cl$^-$ ions were shown.

4-1-4. Triple-Layer Catalysts

C. A. Mirkin, *et al. Science* **2010**, *330*, 66

an allosteric spramolecular structure in which a **monometallic catalytic site** has been buried in the middle layer of a triple-layer complex

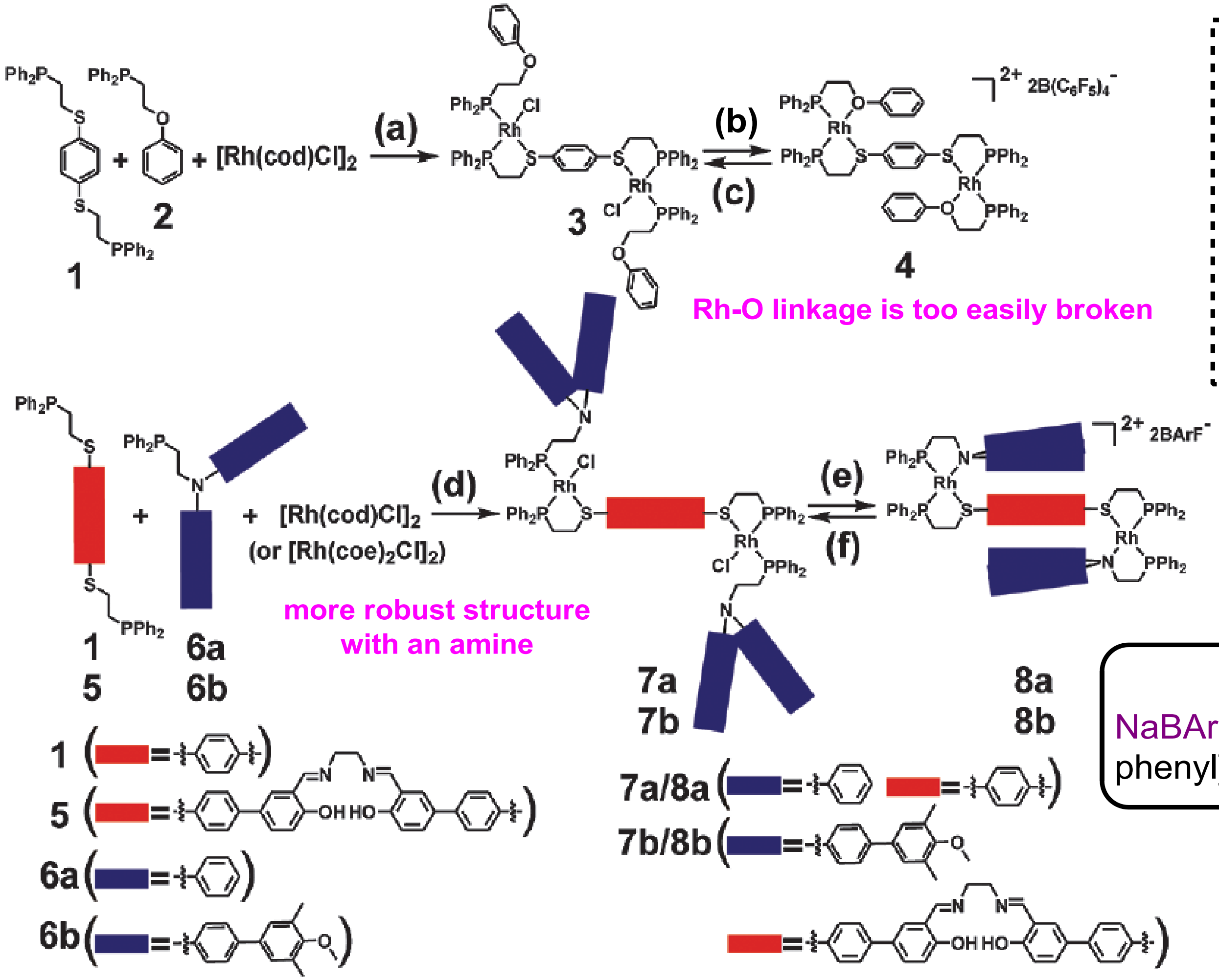


Allosteric effector (Cl^-) can open and close this complex and reversibly expose and conceal the catalytic center.

4-1-4. Triple-Layer Catalysts

C. A. Mirkin, *et al. Science* **2010**, *330*, 66

Figure. The synthesis of triple-layer complexes with chemically tailorable layers through the choice of hemilabile ligand starting materials



Rh-O linkage is too easily broken

more robust structure with an amine

reagents and reaction conditions

(a) CH_2Cl_2, rt

(b) $LiB(C_6F_5)\cdot Et_2O$, CH_2Cl_2, rt

(c) $(^{n}Bu)_4NCl$, CH_2Cl_2, rt

(d) THF, rt

(e) NaBArF, CH_2Cl_2, rt

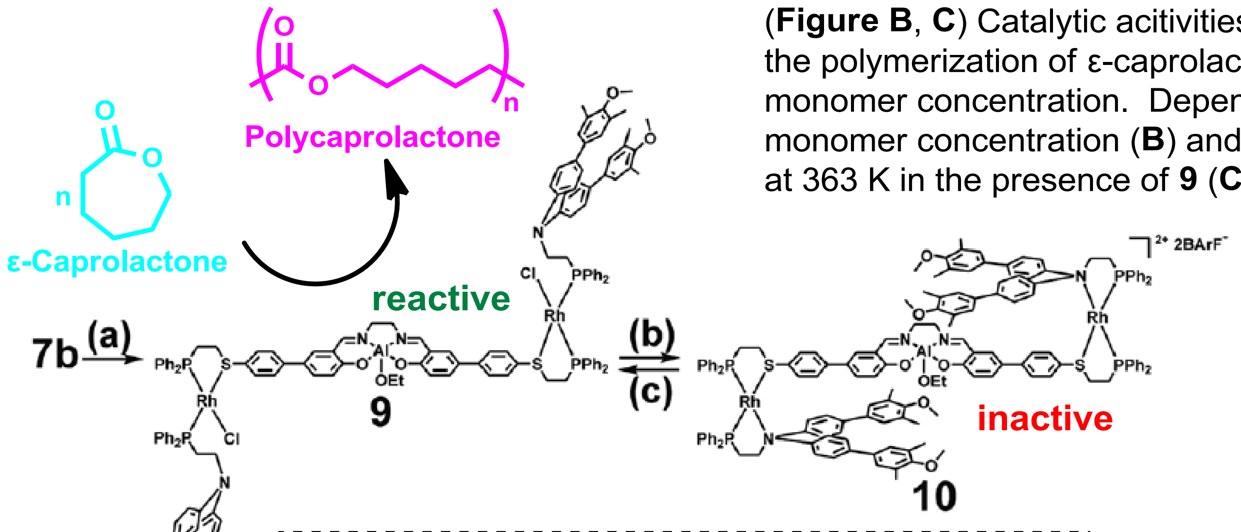
(f) $(^{n}Bu)_4NCl$, CH_2Cl_2, rt

halide abstracting reagents

NaBArF (BArF = tetrakis[(3,5-trifluoromethyl) phenyl]borate) and $LiB(C_6F_5)\cdot Et_2O$

4-1-4. Triple-Layer Catalysts

C. A. Mirkin, *et al. Science* **2010**, *330*, 66



(a) $AlEt_3$, toluene, 0°C→rt→80°C; EtOH, rt→80°C
(b) NaBArF, CH_2Cl_2, rt
(c) $(^nBu)_4NCl$ (CD_3CN can also be used), CH_2Cl_2, rt

(**Figure B**, **C**) Catalytic acitivities of compounds **9** and **10** with respect to the polymerization of ε-caprolactone as a function of temperature and monomer concentration. Dependence on temperature at 541 mM monomer concentration (**B**) and dependence on monomer concentration at 363 K in the presence of **9** (**C**).

catalyst concentration : 2.09 mM

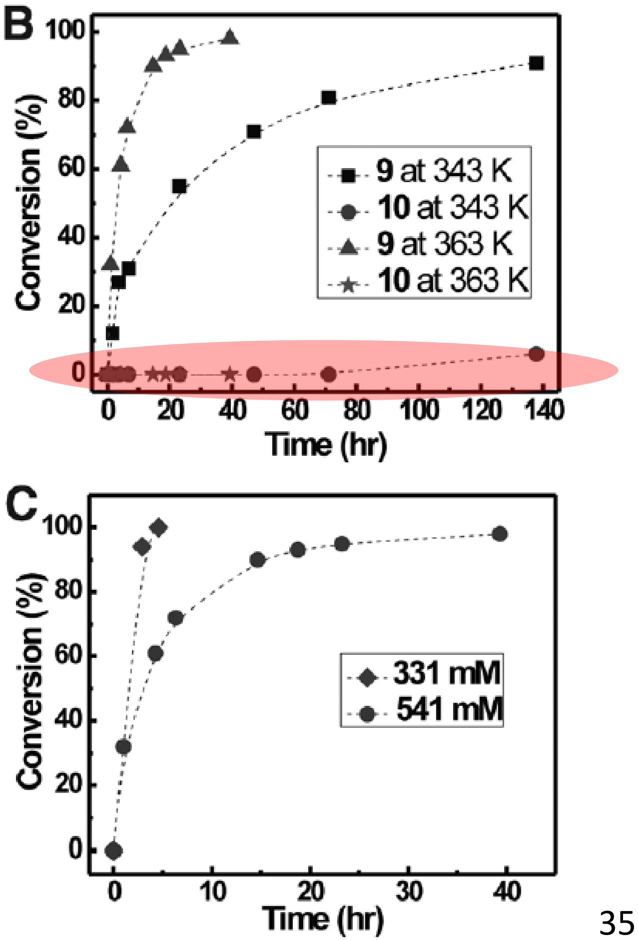


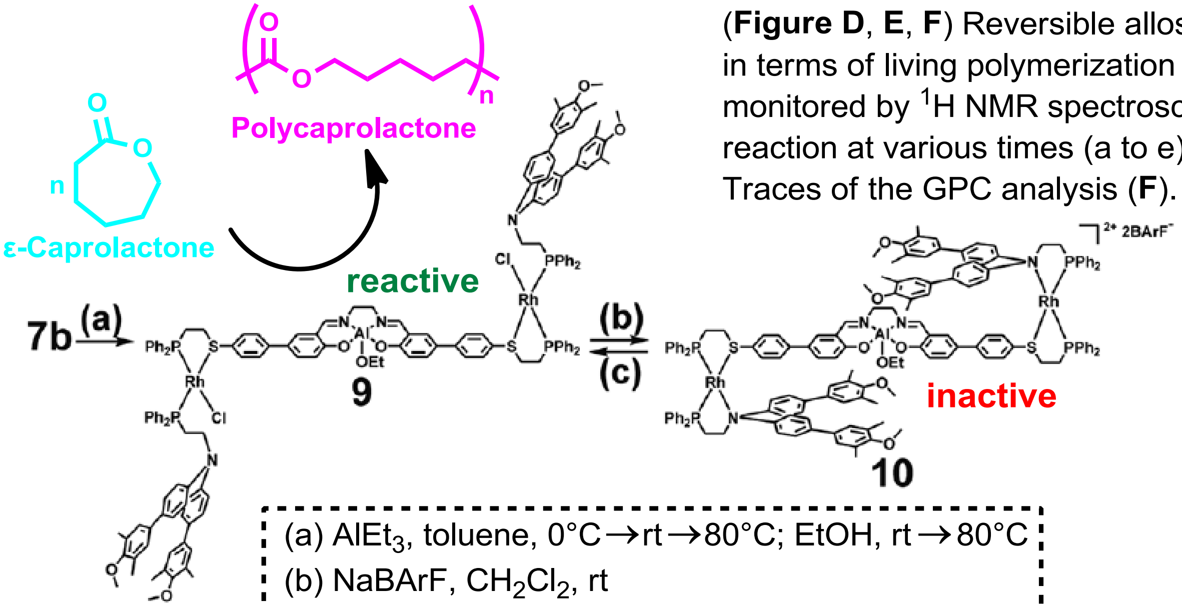
Figure B

semi-open compound **9** is active
closed compound **10** is initially almost completely inactive !!

(after abount 100 hours of catalysis, residual activity is observed (about 7% of **9**), which is caused by decomposition of **10**)

4-1-4. Triple-Layer Catalysts

C. A. Mirkin, *et al. Science* **2010**, *330*, 66



- (a) $AlEt_3$, toluene, 0°C→rt→80°C; EtOH, rt→80°C
- (b) NaBArF, CH_2Cl_2, rt
- (c) $(^nBu)_4NCl$ (CD_3CN can also be used), CH_2Cl_2, rt

(**Figure D**, **E**, **F**) Reversible allosteric regulation of the triple-layer complex in terms of living polymerization reaction. The formation of the product was monitored by ^1H NMR spectroscopy (**D**), and samples were taken from the reaction at various times (a to e) and analyzed by GPC for M_n and PDI (**E**). Traces of the GPC analysis (**F**).

(M_n = number average molecular weights)

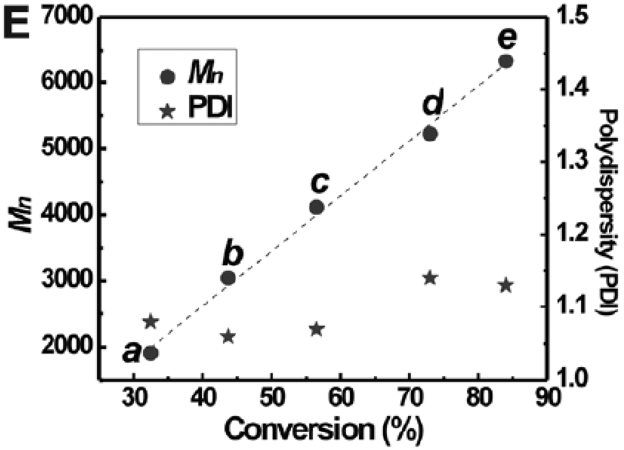
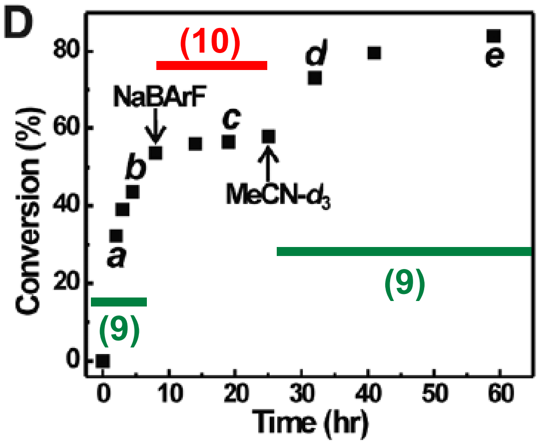


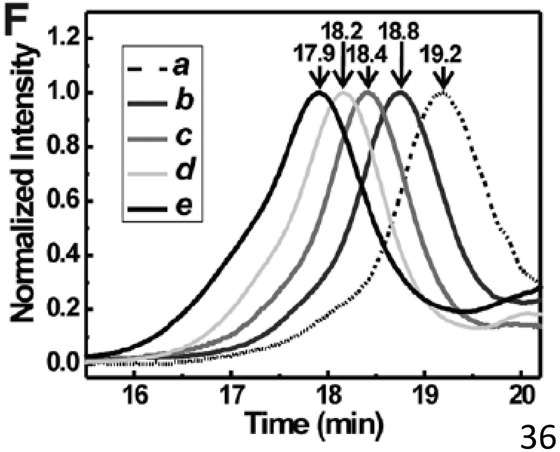
Figure D

As a proof-of-concept experiment, the catalyst was deactivated by addition of the Cl^- abstracting agent (NaBArF), and addition of acetonitrile reactivates the catalyst.

Figure E

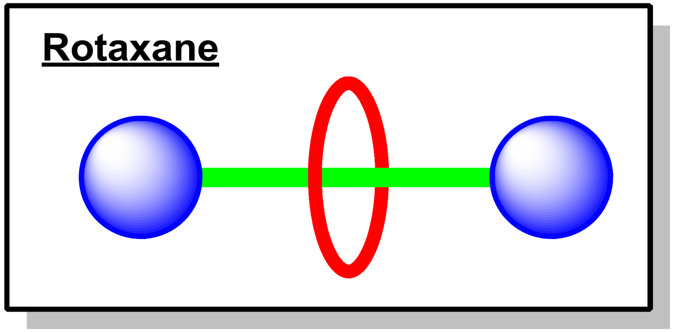
A linear relation between percentage of substrate conversion to product and M_n of the polymer was observed, which confirms that the catalyst maintains its catalytic activity during the allosteric regulation process.

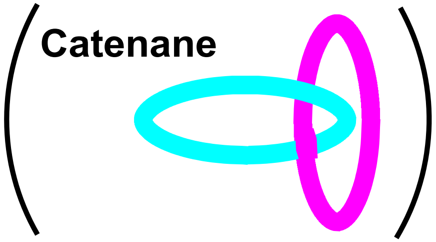


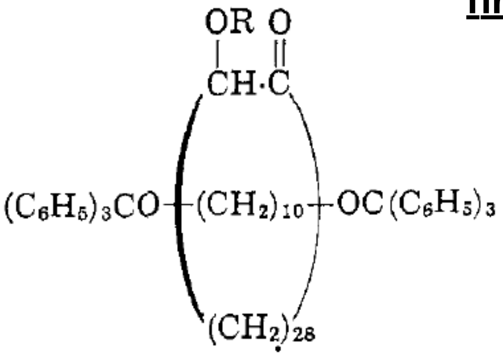


4-2-1. Syntheses of Rotaxanes

Mechanically interlocked molecular systems such as rotaxanes and catenanes have attracted increasing attention due to the unique bonding and structure and a prototype of molecular machines.







2, R = H
6, R = $CO(CH_2)_2CO_2$ resin

firstly synthesized rotaxane

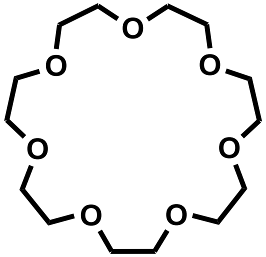
It depended on accidental formation from mixuture of "thread", "ring" and "stopper".
So the yield was very low...

S. Harrison, *et al.*
J. Am. Chem. Soc. **1967**, *89*, 5723

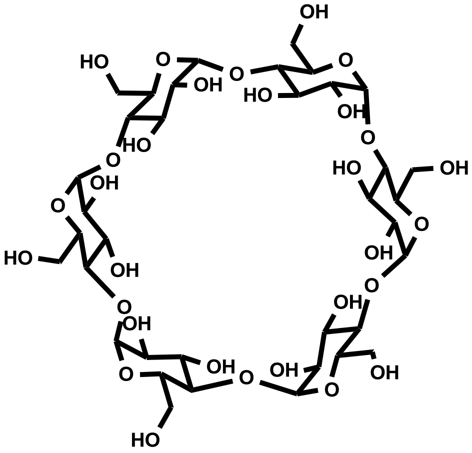
In the latter part of the 20th century

Some efficient syntheitic methodology were developed.

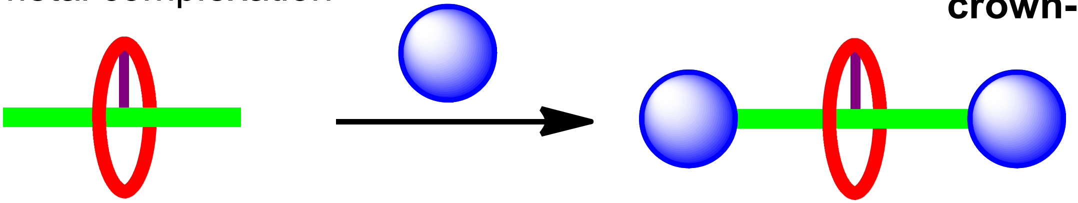
1) host-guest interaction
2) donor-acceptor interaction
3) hydrogen bond
4) metal complexation



crown-ether

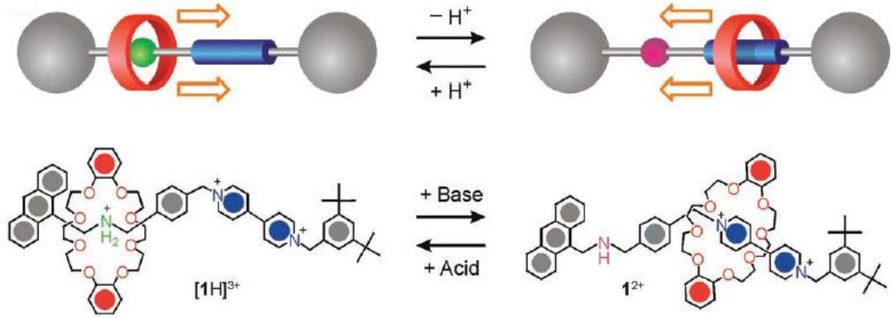


cyclodextrin



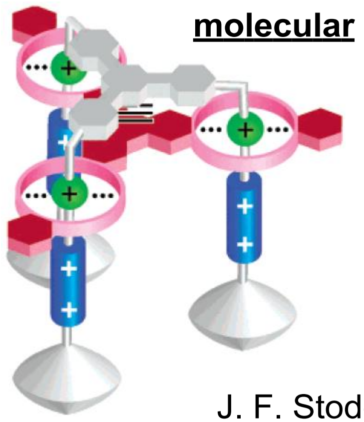
4-2-2. Application to Molecular Machines

molecular shuttle



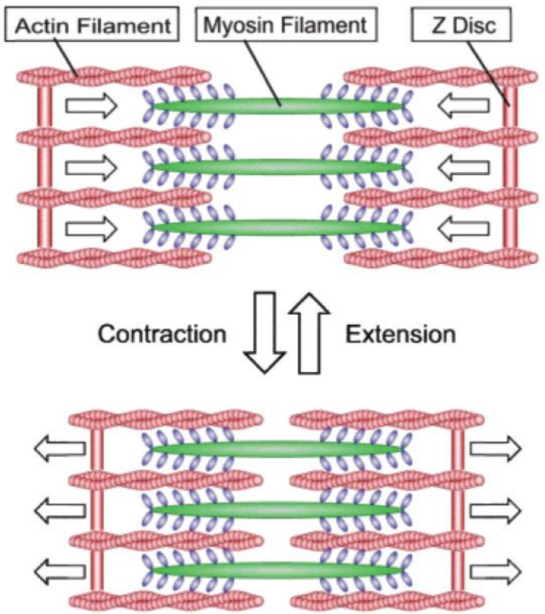
J. F. Stoddart, *et al. J. Am. Chem. Soc.* **1991**, *113*, 5131

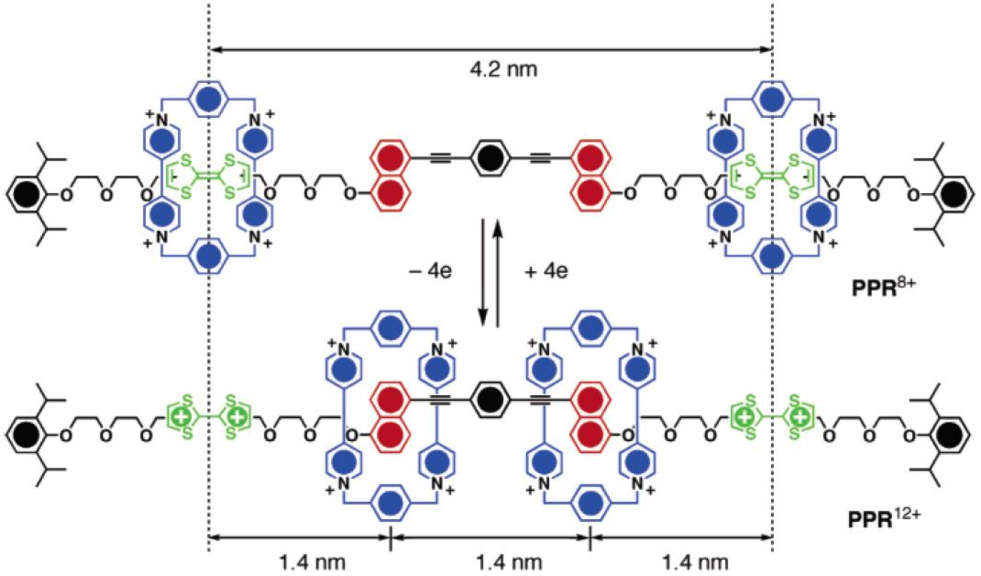
molecular elevator



J. F. Stoddart, *et al.*
J. Am. Chem. Soc. **2006**, *128*, 1489
Scienece **2004**, *303*, 1845

molecular muscle



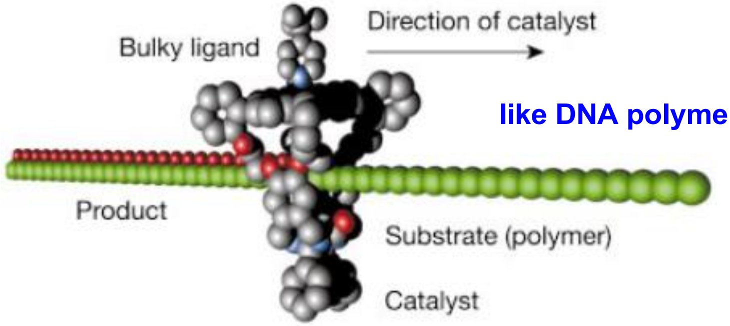


J. F. Stoddart, *et al. J. Am. Chem. Soc.* **2005**, *127*, 9745
J. -P. Sauvage, *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 3284

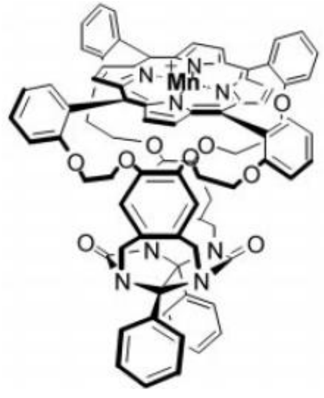
4-2-3. Application to Catalysts

Epoxidation of Polybutadiene by Topologically Linked catalyst

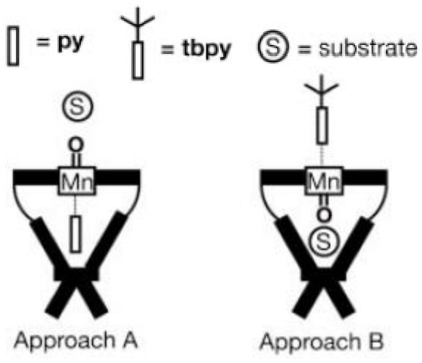
A. E. Rowan, *et al.* *Nature* **2003**, *424*, 915



like DNA polymerase



cavity containing porphyrin complex

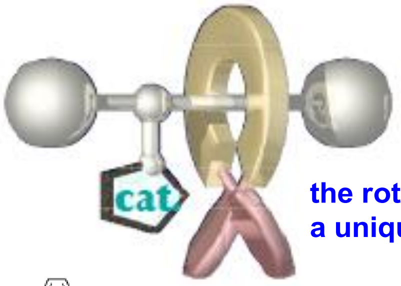


A) 'outside' mechanism
B) 'inside' mechanism

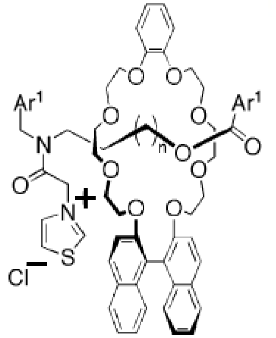
a rotaxane that mimics the ability of processive enzymes to catalyze multiple rounds of reaction while the polymer substrate stays bound

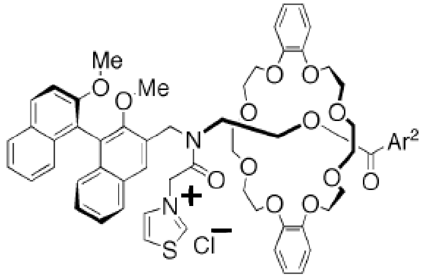
Asymmetric Benzoin Condensation Catalyzed by Chiral Rotaxanes

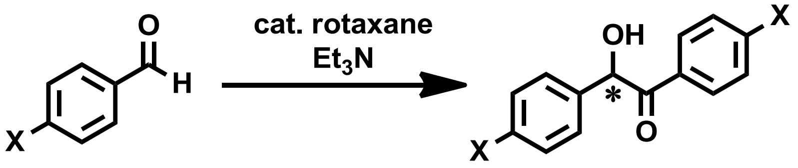
T. Takata, *et al.* *J. Am. Chem. Soc.* **2004**, *126*, 3438



the rotaxane structure gives a unique reaction field



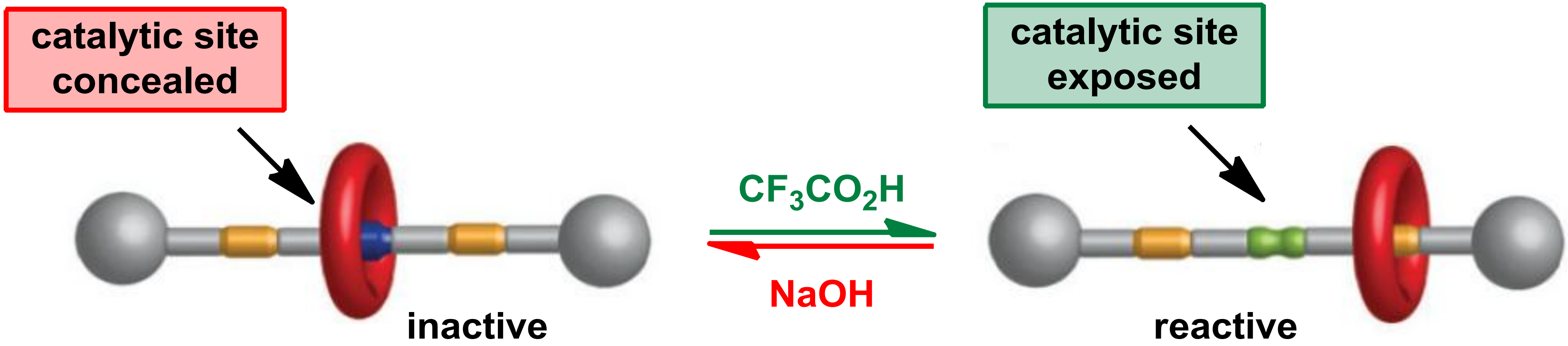




the rotaxane field made by mechanically linked wheel and axle components gives an unprecedented space for recognition and reaction

4-2-4. Rotaxane-Based Switchable Organocatalyst

D. A. Leigh, *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 5166



catalytic site concealed

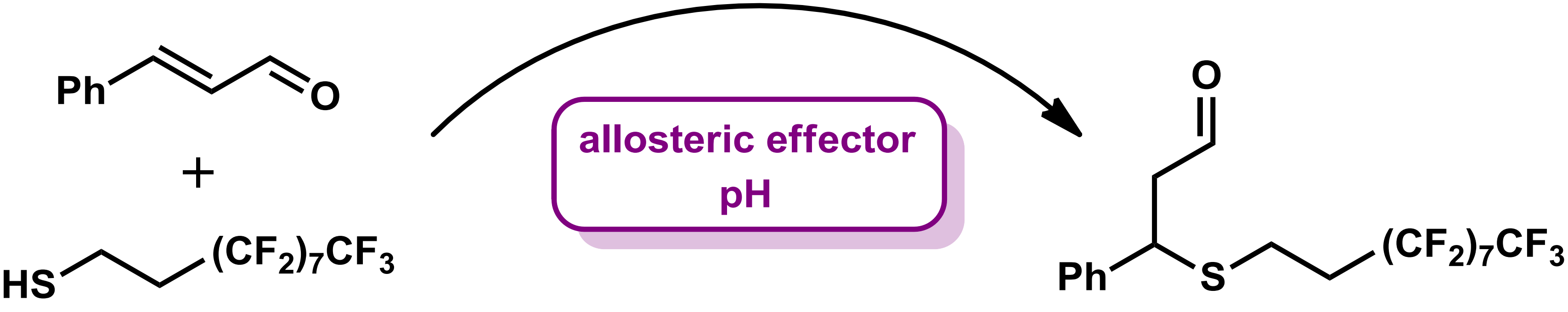
catalytic site exposed

CF_3CO_2H

NaOH

inactive

reactive

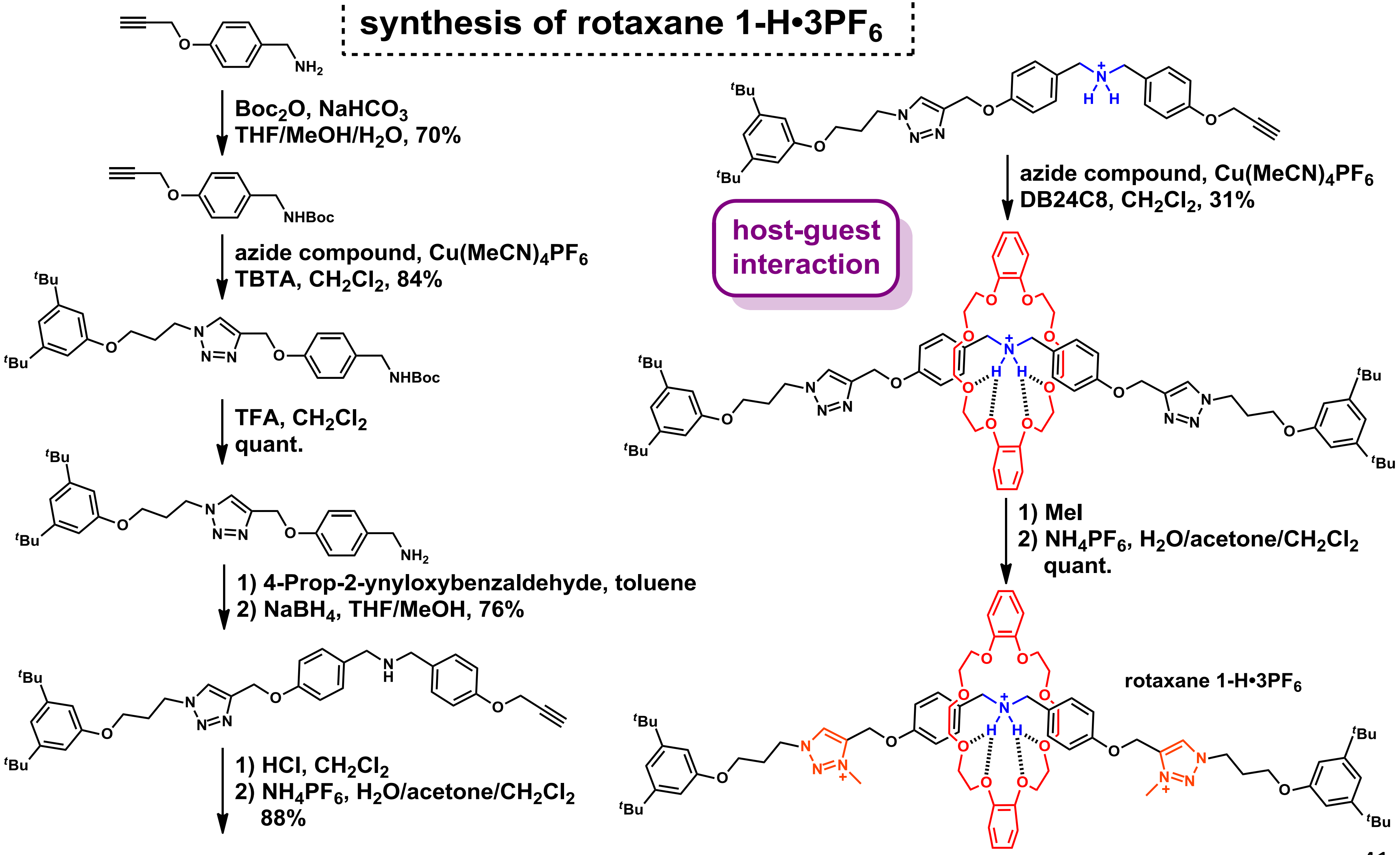


allosteric effector pH

4-2-4. Rotaxane-Based Switchable Organocatalyst

D. A. Leigh, *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 5166

synthesis of rotaxane 1-H•3PF$_6$



Boc$_2$O, NaHCO$_3$
THF/MeOH/H$_2$O, 70%

azide compound, Cu(MeCN)$_4$PF$_6$
TBTA, CH$_2$Cl$_2$, 84%

TFA, CH$_2$Cl$_2$
quant.

1) 4-Prop-2-ynyloxybenzaldehyde, toluene
2) NaBH$_4$, THF/MeOH, 76%

1) HCl, CH$_2$Cl$_2$
2) NH$_4$PF$_6$, H$_2$O/acetone/CH$_2$Cl$_2$
88%

azide compound, Cu(MeCN)$_4$PF$_6$
DB24C8, CH$_2$Cl$_2$, 31%

host-guest interaction

1) MeI
2) NH$_4$PF$_6$, H$_2$O/acetone/CH$_2$Cl$_2$
quant.

rotaxane 1-H•3PF$_6$

4-2-4. Rotaxane-Based Switchable Organocatalyst

D. A. Leigh, *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 5166

Figure 1. Acid-base switching of the position of the macrocycle in rotaxane

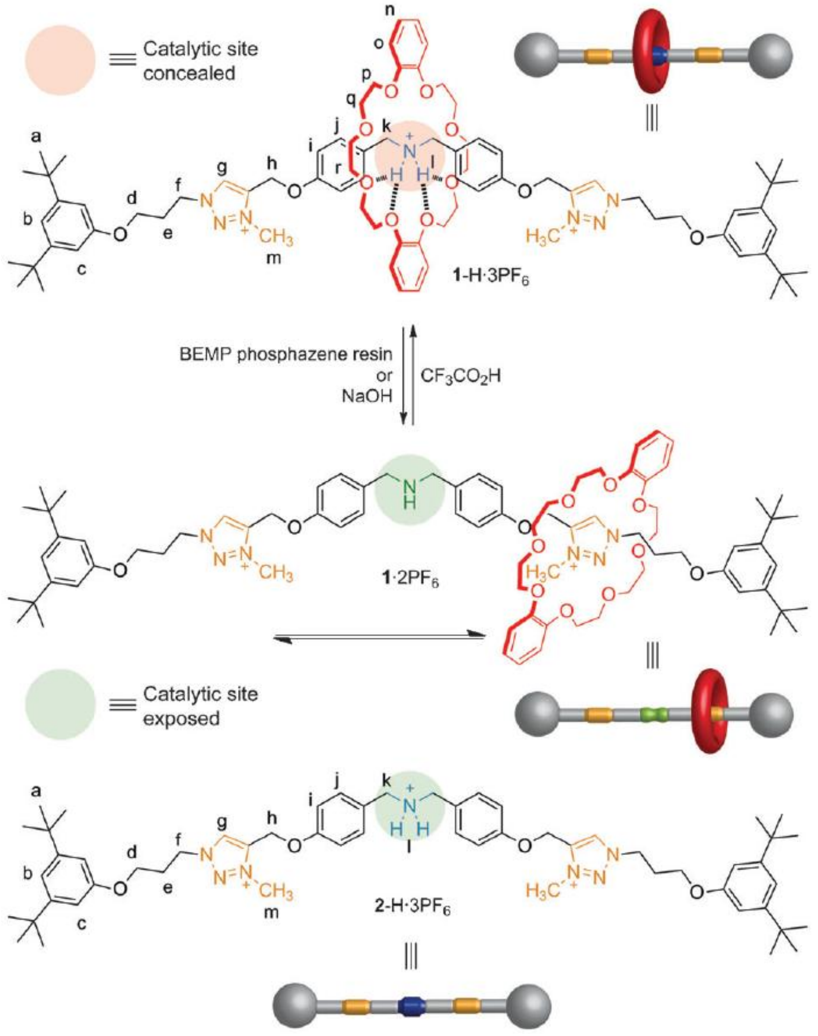
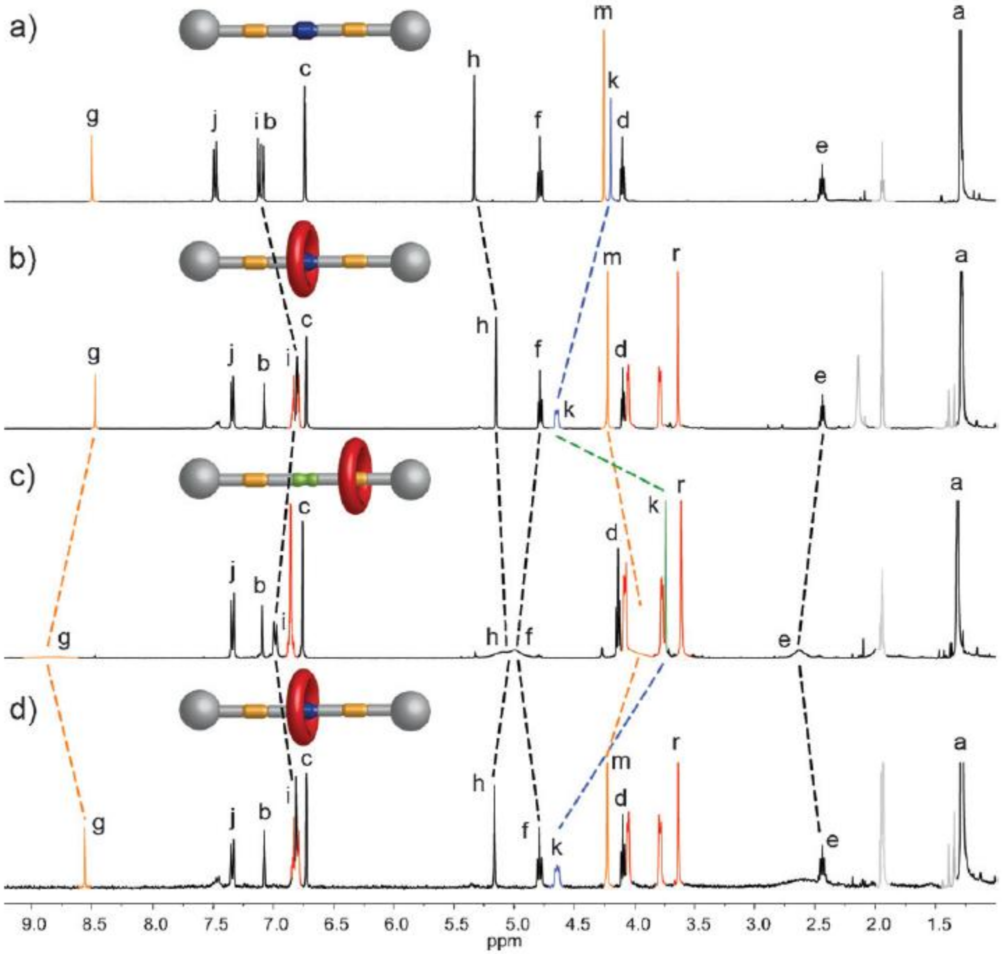


Figure 2. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K)

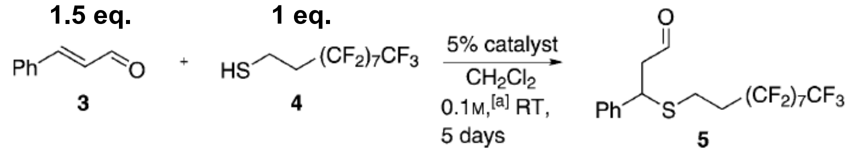


a) thread **2**-H•3PF$_6$ b) rotaxane **1**-H•3PF$_6$ c) rotaxane **1**-2PF$_6$ (338 K)
d) solution from (c) after addition of 1 eq. of CF_3CO_2H

4-2-4. Rotaxane-Based Switchable Organocatalyst

D. A. Leigh, *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 5166

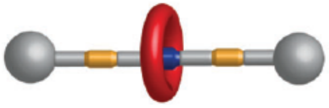
Michael addition of thiol **4** to *trans*-cinnamaldehyde **3**



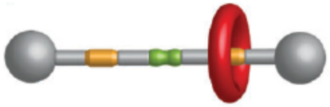
Entry	Catalyst	Yield[b]
1	no catalyst	no reaction
2	dibenzylamine	69%
3	**2**·2PF$_6$	30%
4	**2**-H·3PF$_6$	49%
5	**1**·2PF$_6$	83%
6	**1**-H·3PF$_6$	no reaction
7	**1**·2PF$_6$/**1**-H·3PF$_6$ + 10 min NaOH$_{(aq)}$ wash	66%[c]
8	no catalyst + 10 min NaOH$_{(aq)}$ wash	traces[d]

[c] yield after 10 min washing with 1 M NaOH$_{(aq)}$ and subsequent 1 h stirring at RT

rotaxane **1**-H•3PF$_6$

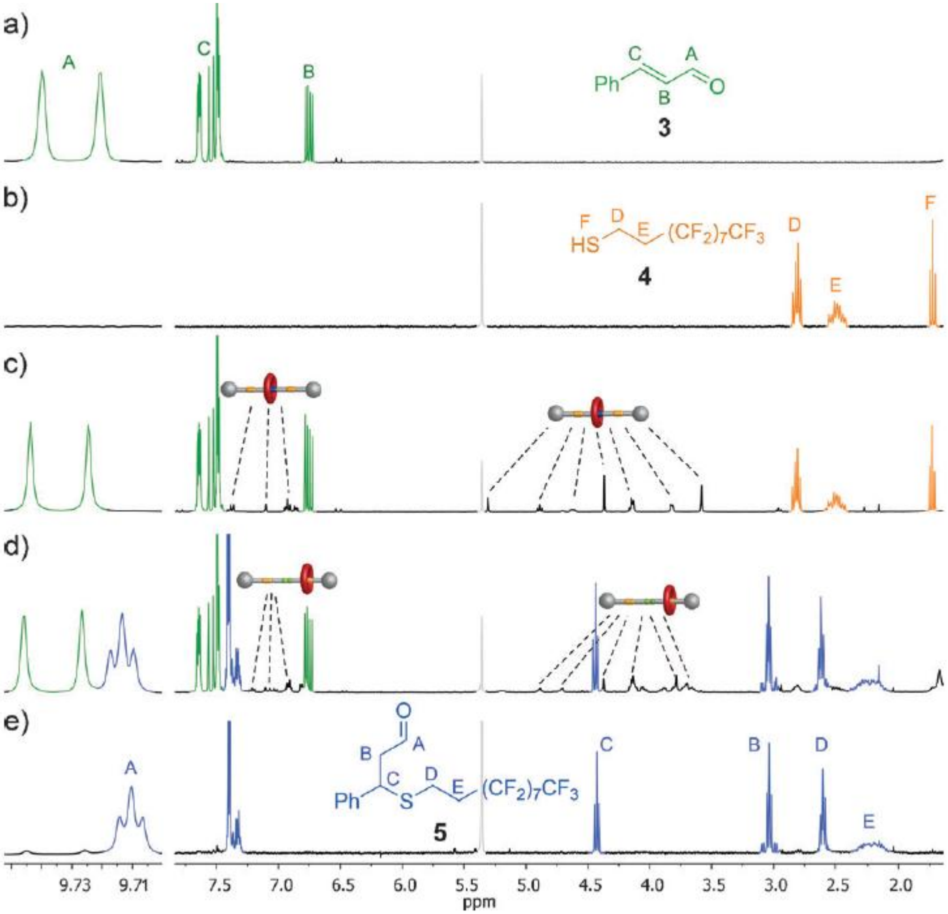


rotaxane **1**•2PF$_6$



thread **2**

Figure 3. 1H NMR spectra (400 MHz, CD_2Cl_2, RT)



a) *trans*-cinnamaldehyde **3**   b) tiol **4**

c) reaction mixture of **3** and **4** after 48 h stirring in the presence of 5 mol% of **1**-H•3PF$_6$

d) reaction mixture from (c) 1 h after deprotonation of **1**-H•3PF$_6$ with a 10 min wash with 1 M NaOH$_{(aq)}$ (residual **3** is the result of 1.5 eq being used to ensure complete consumption of **4**.

e) product **5**

5. Summary and Perspective

- Impressive and significant advances through **allosteric regulation** have led to the development of a number of **switchable catalysts** with multiple catalytic functions having adequate **temporal and spatial** resolution.

- For the practical application of switchable catalysts, the **low catalytic efficiency** and **the narrow scope of applicable reactions** are problematic so far.

- The goal of switchable catalysis is not only the mere enabling of a given chemical transformation but also the **complete control** over its outcome by developing suitable catalysts to dictate chemoselectivity, regioselectivity, and stereoselectivity of the reaction. Applying these features to **polymerization processes** would be particularly beneficial in this context.

- Furthermore these catalysts are not only advantageous for their utility in organic synthesis, but can also be applied to a much **broader field** such as materials and devices because these catalysts can produce multiple outputs from an intricate molecular ensemble.

Useful reviews

S. Hecht, *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 5054
C. A. Mirkin, *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 114
C. J. Hawker, *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 199
N. Kumagai.; M. Shibasaki. *Cat. Sci. Technol.* **2013**, *3*, 41

Other examples of switchable catalysts (not shown in slide)

N. R. Branda, *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 2019 (photoswitchable lignad)
C. A. Mirkin, *et al. J. Am. Chem. Soc.* **2005**, *127*, 1644 (layered system)
C. A. Mirkin, *et al. J. Am. Chem. Soc.* **2007**, *129*, 14182 (layered system)
K. Nagasawa, *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 9254 (solvent-control)
J. Rebek, Jr.,*et al. Angew. Chem. Int. Ed.* **2011**, *50*, 9400 (light-responsive cavitand)
N. R. Branda, *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 5431 (electronic effects)