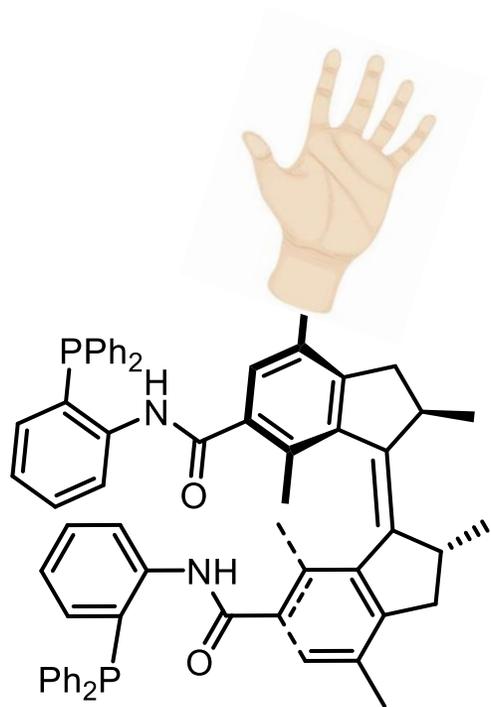
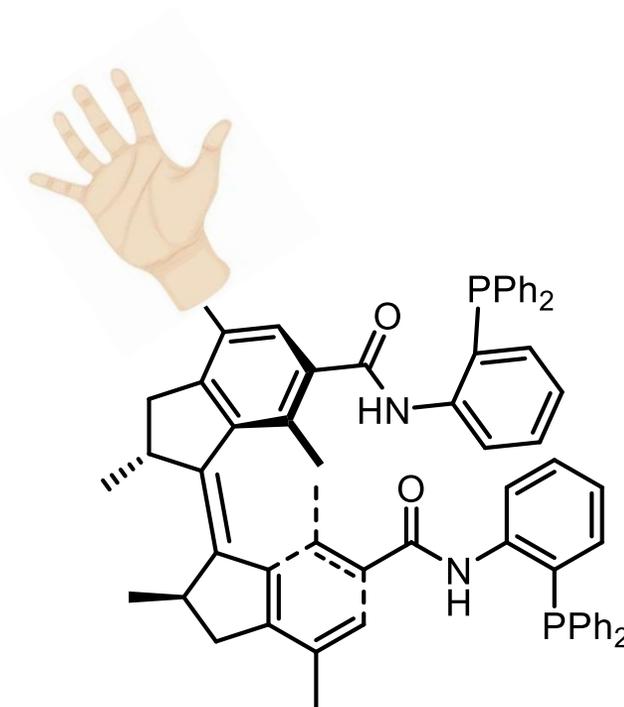
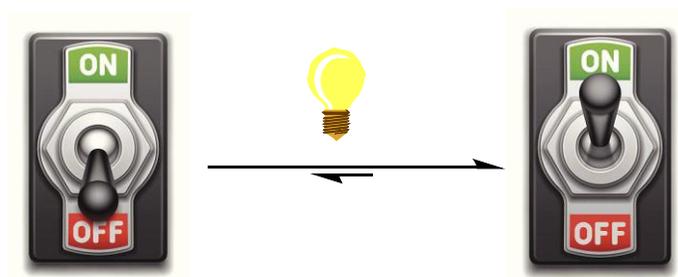


# Photoswitchable Catalysis



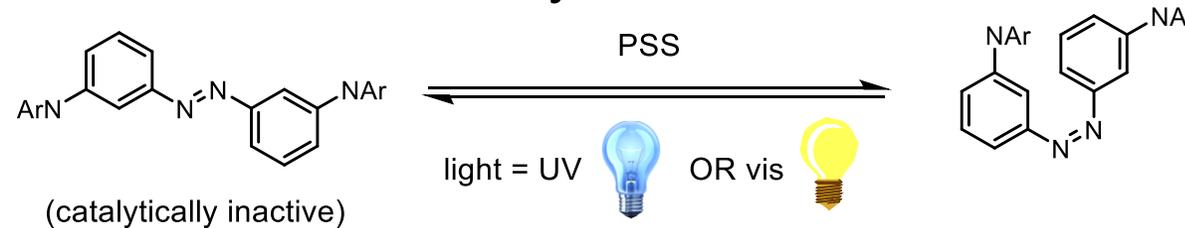
Casey Olen  
Denmark Group Meeting 2/15/22



# Outline

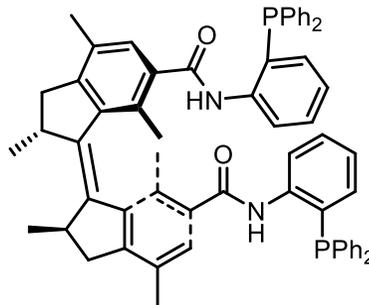
**Part 1:** Introduction and design principles for photoswitchable catalysis.

**Part 2:** “Simple” ON/OFF photoswitchable catalysis to control reaction rate based on *E/Z* isomerization and photocontrolled electrocyclization.



**Part 3:** Photoswitchable substrate selectivity development.

**Part 4:** Photoswitchable stereoselectivity, simple ON/OFF photoswitches and complex photoswitches based on unidirectional molecular motors.

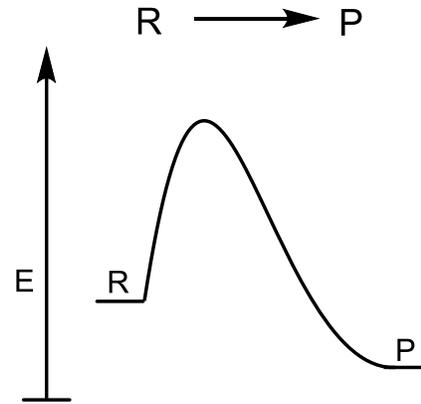


# Why Should We Care About Photoswitchable Catalysis?

## The way we usually do chemistry:

How can I make R and P conform to my theory of reactivity better?

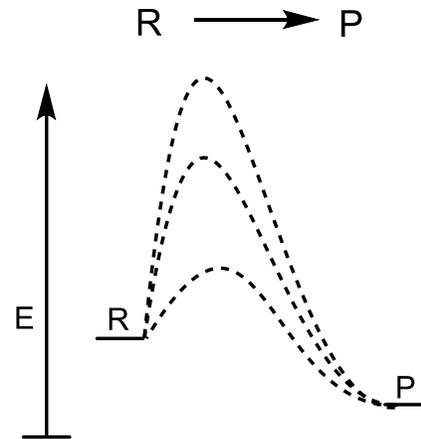
- Increase energy of R
- Introduce a catalyst
- Make catalyst, make R, run the reaction and pray



## How we could do it and how Nature does it:

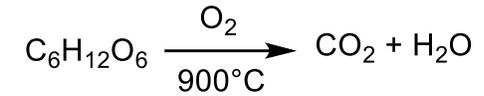
There are an infinite number of reaction coordinates from R to P. How can I use *in situ* switching to control which reaction coordinate is operative?

- Chemoswitches
- Electric field catalysis (my seminar)
- Photoswitches (this talk)

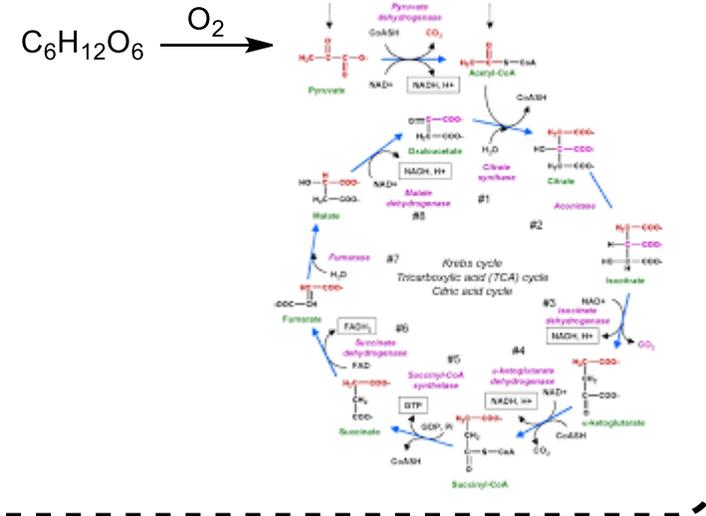


For example:

Human chemist glucose combustion:

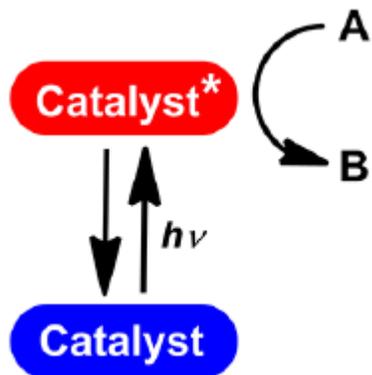


Nature's glucose combustion:

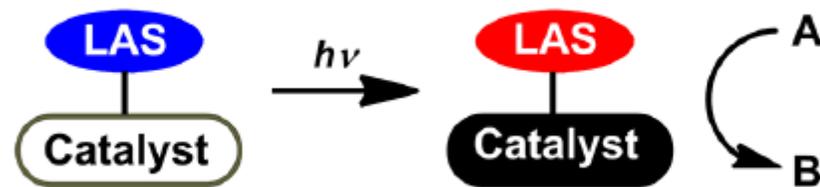


# Photoswitchable Catalysis Compared to Other Photochemical Methods

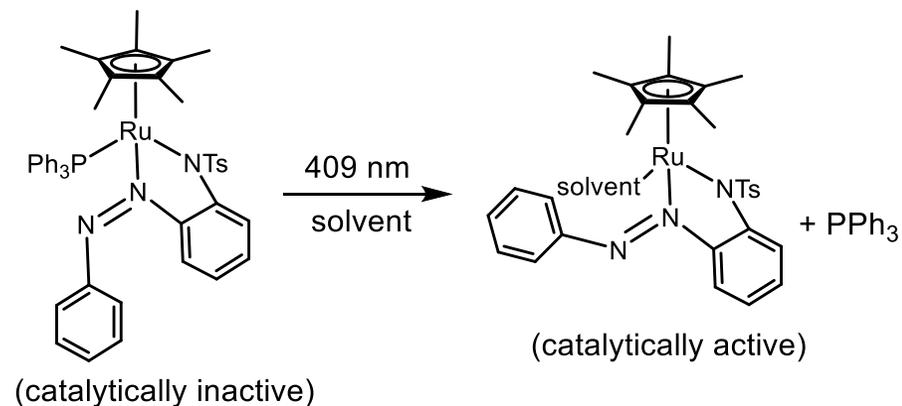
## Photo(redox)catalysis:



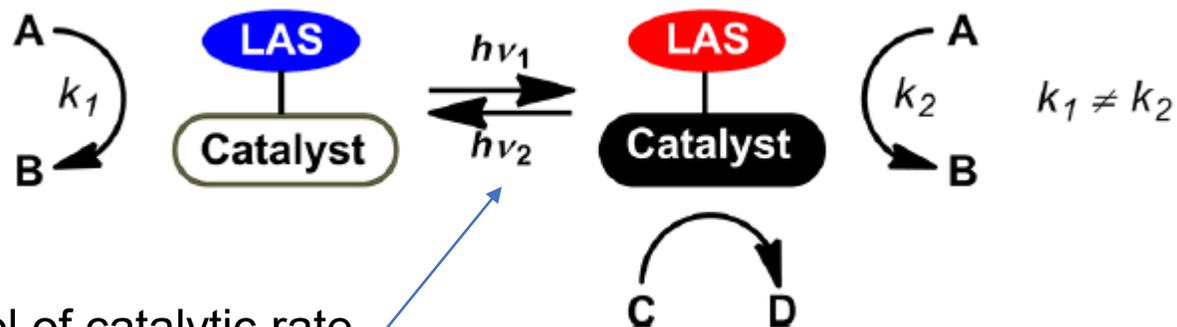
## Photocaged catalysis:



LAS = light-absorbing species



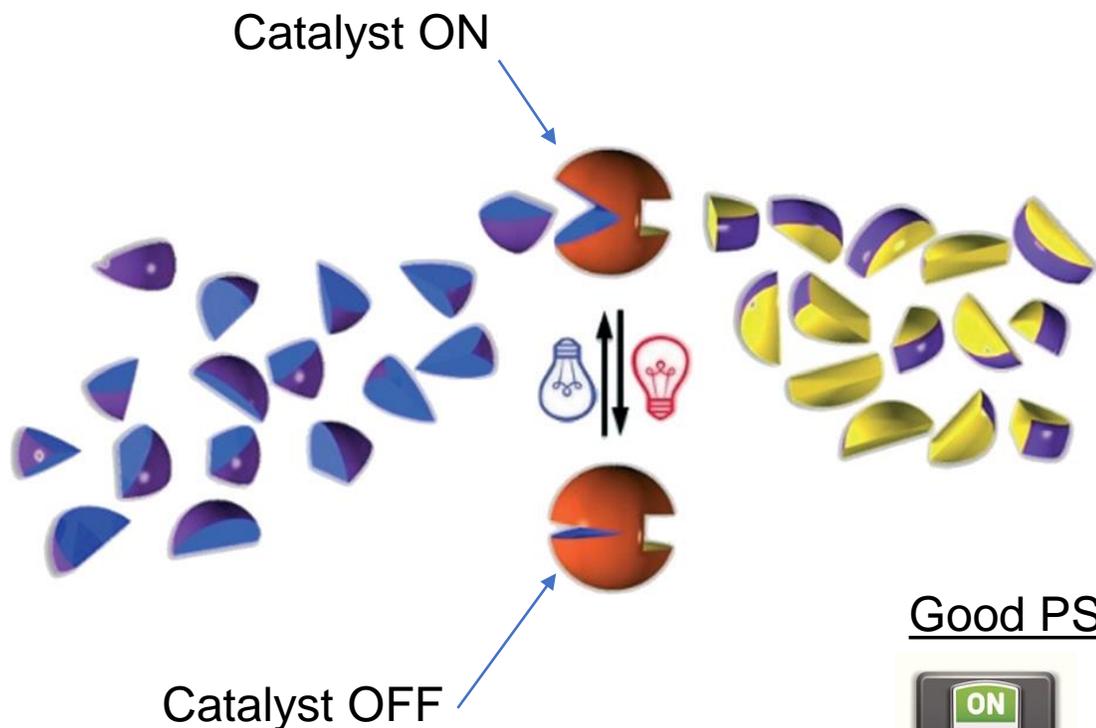
## Photoswitchable catalysis:



Reversible control of catalytic rate

# Simple Photoswitching: Binary ON/OFF Catalytic States

The simplest possible photoswitchable catalyst has binary ON and OFF states that can be interconverted with light:

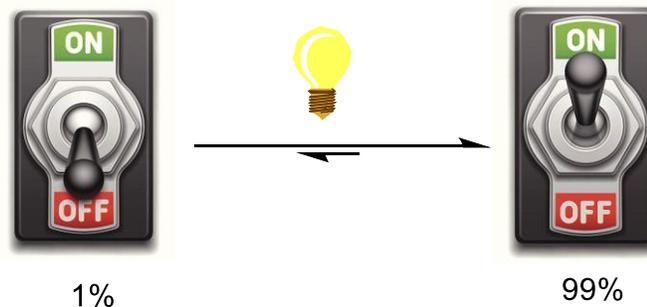


Useful terminology:

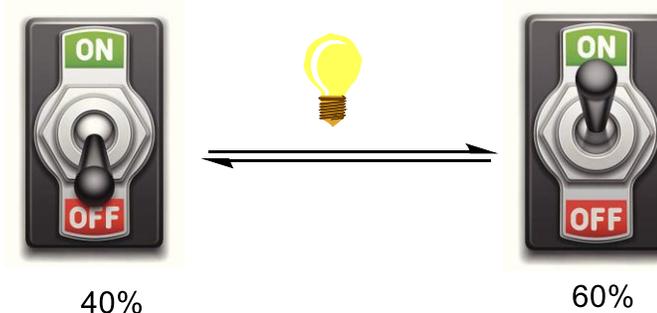
**Photochromism:** When absorbance properties change after exposure to light. Indicative of a light-induced change in electronic structure. Effective photoswitchable catalysts display significant photochromism.

**Photostationary State (PSS):** The equilibrium reached when a photochromic species is irradiated with a given wavelength of light. The best photoswitchable catalysts have a non-ground state PSS that can be accessed with full conversion.

Good PSS for photoswitching:



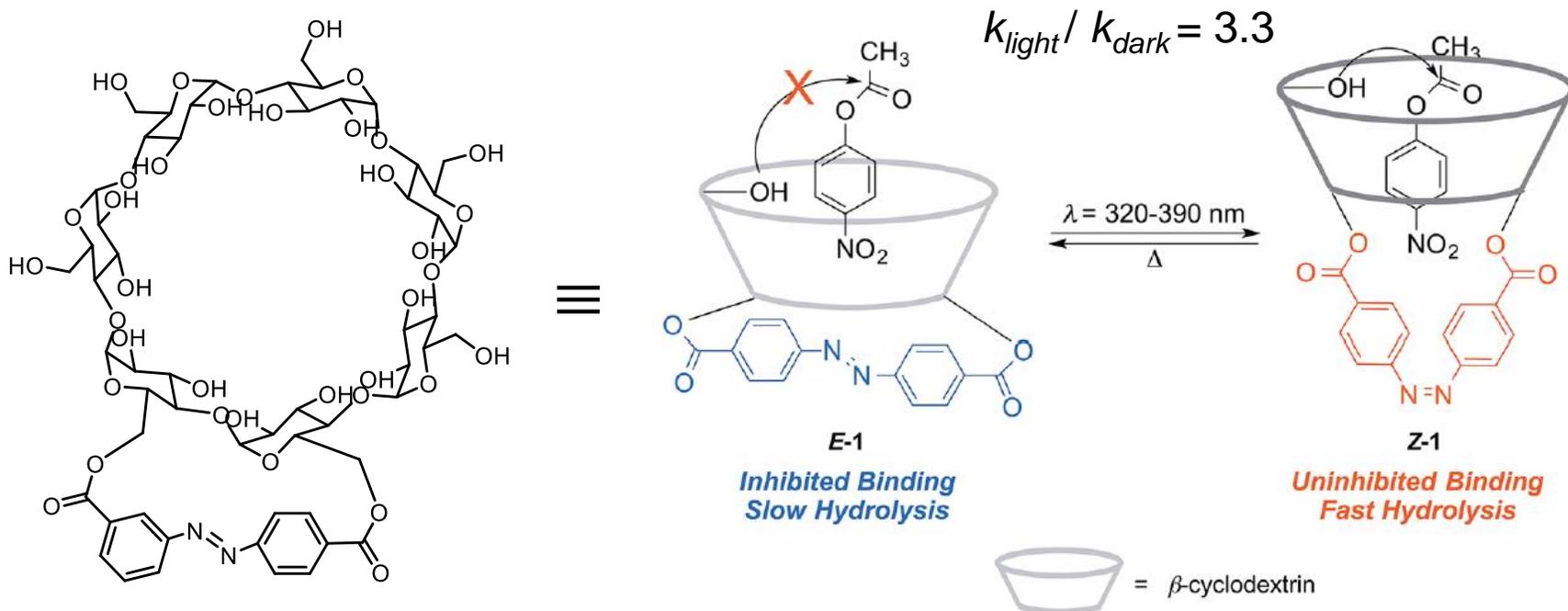
Bad PSS for photoswitching:



# Simple Photoswitching in Early Examples Based on *E/Z* Isomerization

What kind of systems can we think of that could make for a simple, binary photoswitchable catalyst?

First example of homogeneous, photoswitchable catalytic reactivity reported by Osa *et al* in an azobenzene-switchable cyclodextrin (1981):

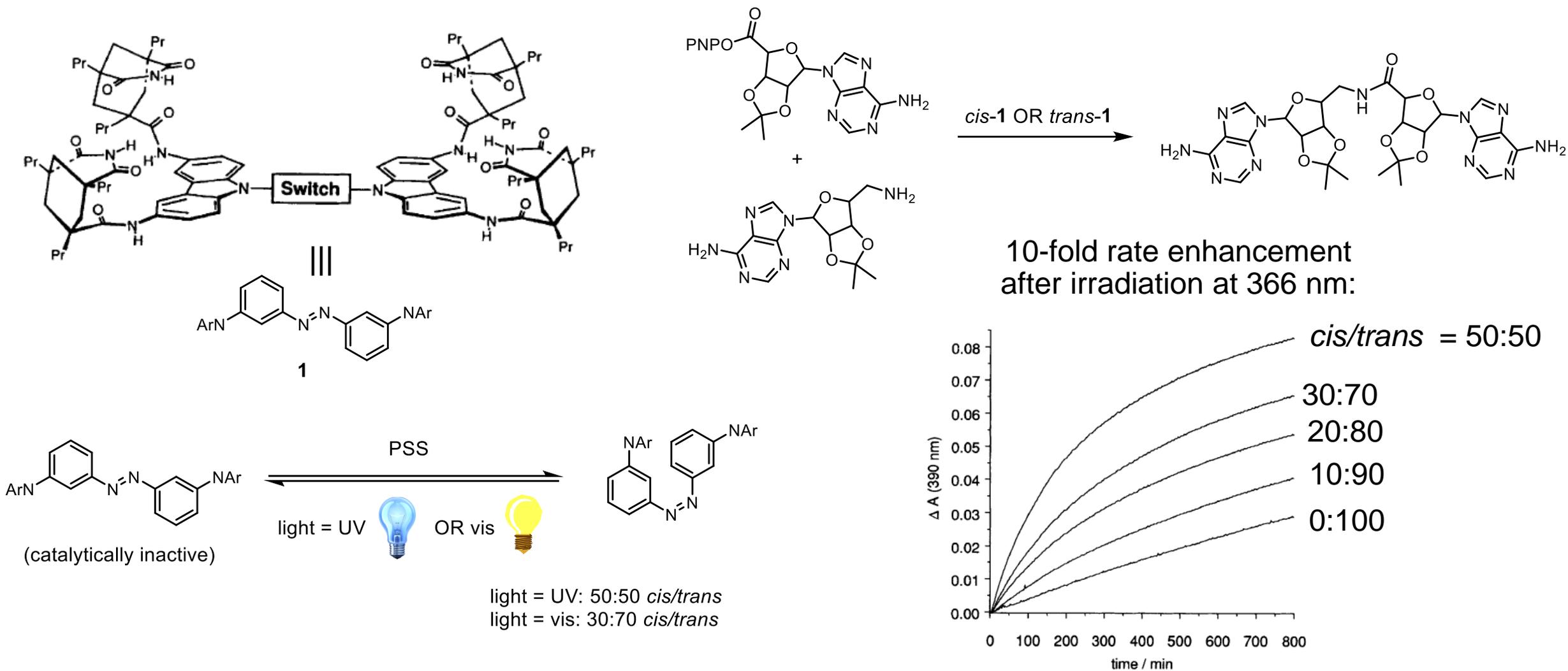


Photoswitching to **Z-1** increases the depth of the cyclodextrin cavity, permitting enhanced binding of the substrate and accelerating the reaction rate.

This system is far from ideal, and it may be generous to even call this a photoswitchable system. Maximum yields of **Z-1** did not exceed 50% in the PSS. **E-1** also competes with substrate binding, so ON/OFF control is poor.

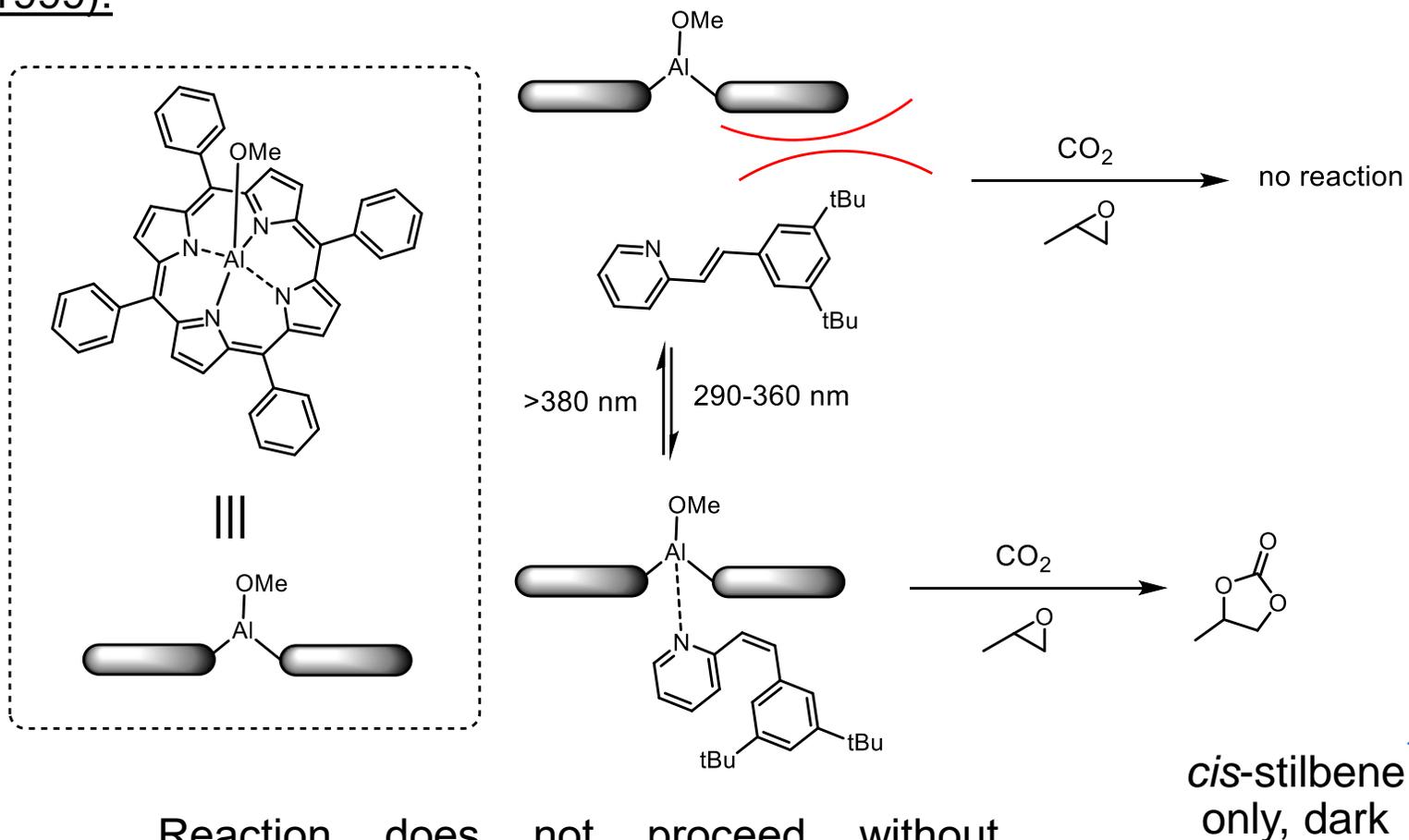
# Simple Photoswitching in Early Examples Based on *E/Z* Isomerization

Host-guest binding of nucleosides on a photoswitchable bis-carbazole system (Rebek, 1995):

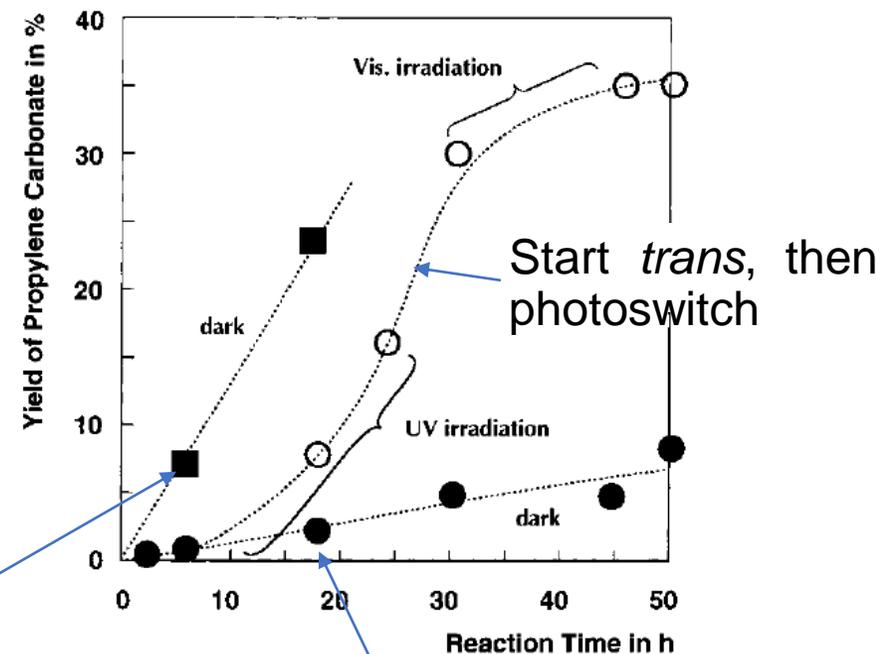


# Simple Photoswitching in Early Examples Based on *E/Z* Isomerization

Inoue *et al* develop a photoswitchable stilbene system for CO<sub>2</sub> capture and show *in situ* photoswitchable control (1999):



*In situ* photoswitching:

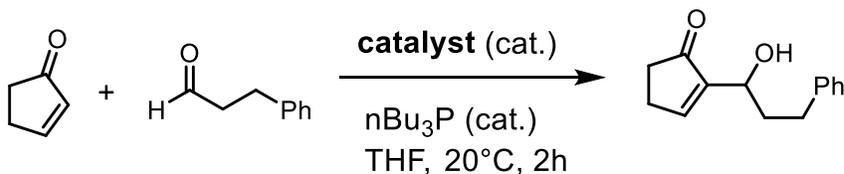
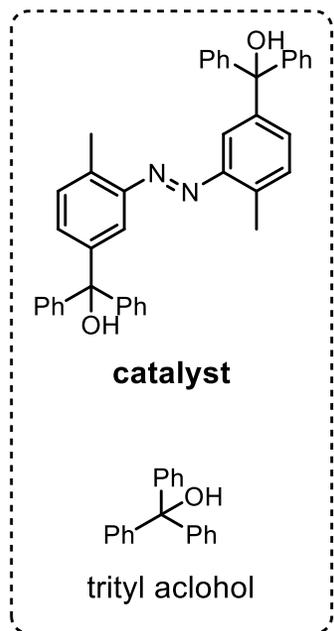


*cis*-stilbene only, dark

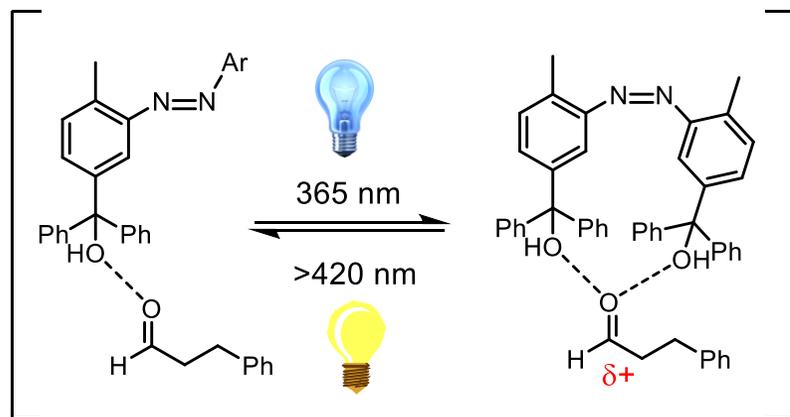
*trans*-stilbene only, dark

# Simple Photoswitching in MBH Reaction Based on *E/Z* Isomerization

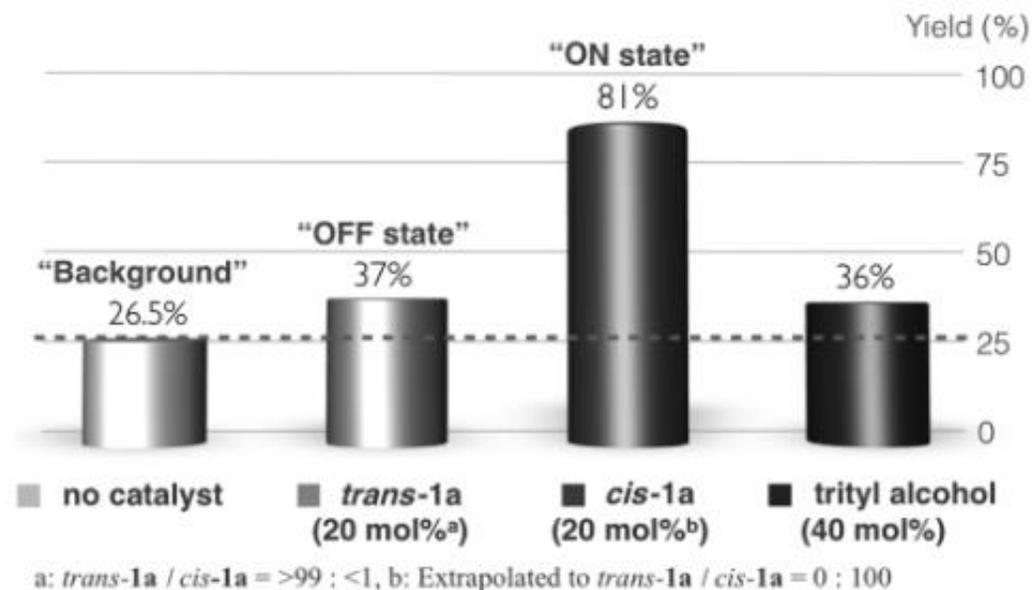
More modern example with photoswitchable azobenzene, cooperative acid catalysis (Kurahara, 2012):



Cooperative acid catalysis enabled by *trans/cis* isomerization of catalyst:



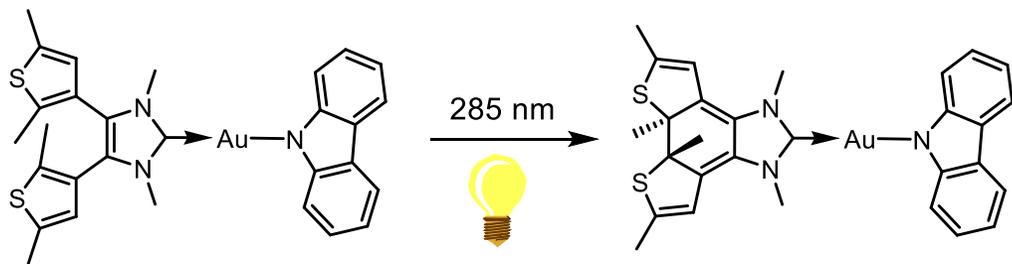
PSS at 95% *cis* azobenzene accessed by pre-irradiation before reaction



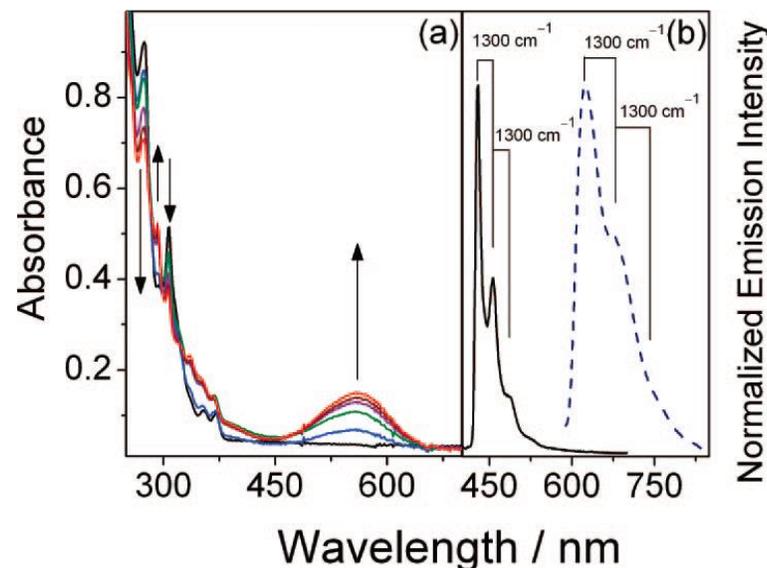
As we will soon see, incorporating bifunctional catalytic moieties on a photoswitchable scaffold is a powerful way to control reactivity.

# Photoswitching Dithienylethene-Functionalized *N*-heterocyclic Carbenes

Yam *et al* synthesized dithienylethene-containing *N*-heterocyclic carbenes in pursuit of photochromic metal complexes (2009):

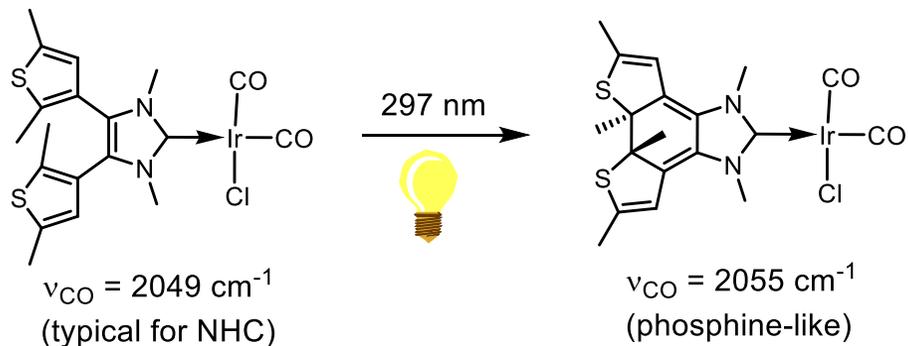


The dithienylethene NHC was also incorporated into Ag(I) and Pd(II) complexes, which displayed photochromism on irradiation at 200-300 nm.



Photochromism was demonstrated, but no catalytic applications were explored.

Bielawski *et al* empirically measure Tolman electronic parameters for a dithienylethene-NHC-ligated Ir complex (2011):

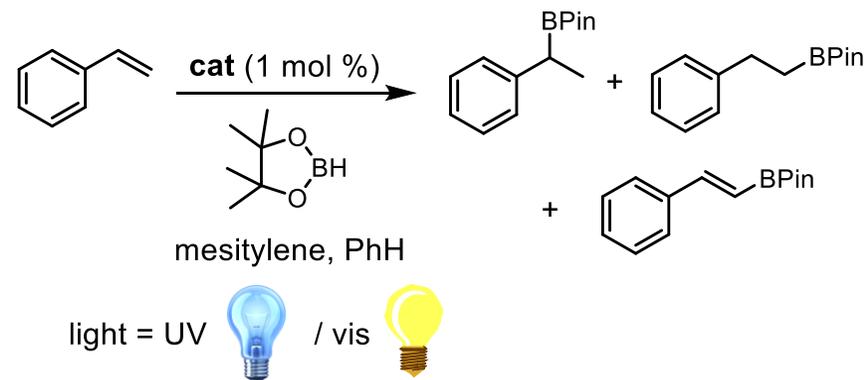
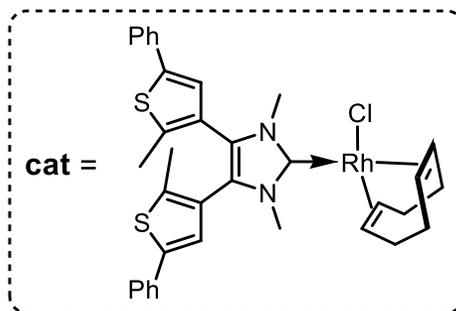
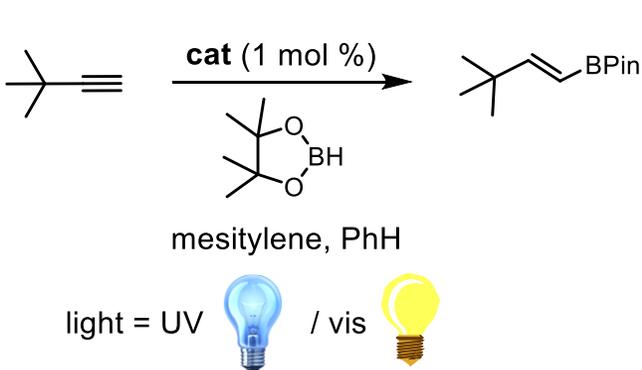


Ligand photocyclization decreases electron density on the metal center,

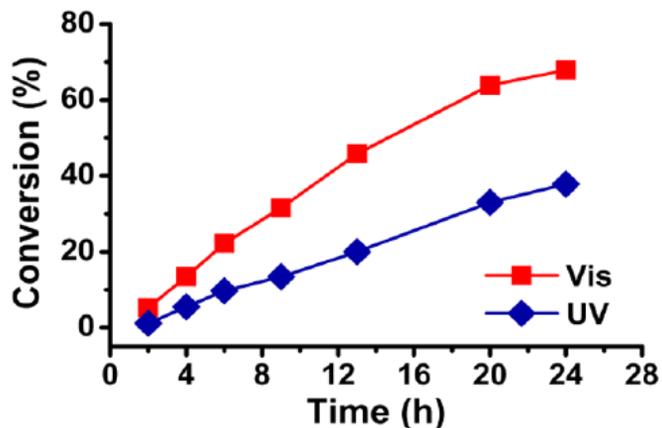
The dithienylethene-NHC ligand provides photoswitchable tunability of ligand electronic properties!

# Photoswitching Dithienylethene-Functionalized *N*-heterocyclic Carbenes

Photoswitchable NHC ligands for Rh-catalyzed hydroboration of alkenes and alkynes (2013):



Enhanced rate with visible light, slower with UV:

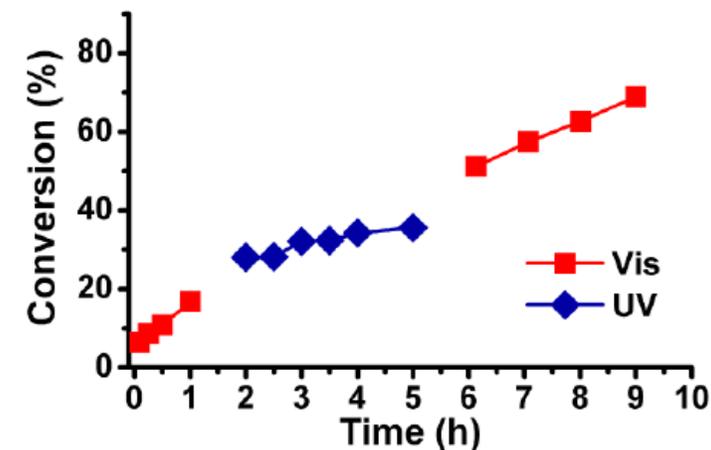


**Provide an explanation for the observed photoswitchable rate control.**

Hints:

- Light-dependent rate effect is seen regardless of alkyne/(substituted) styrene substrate
- What is the mechanism of Rh-catalyzed hydroboration?
- How do ligand electronics affect the RDS?

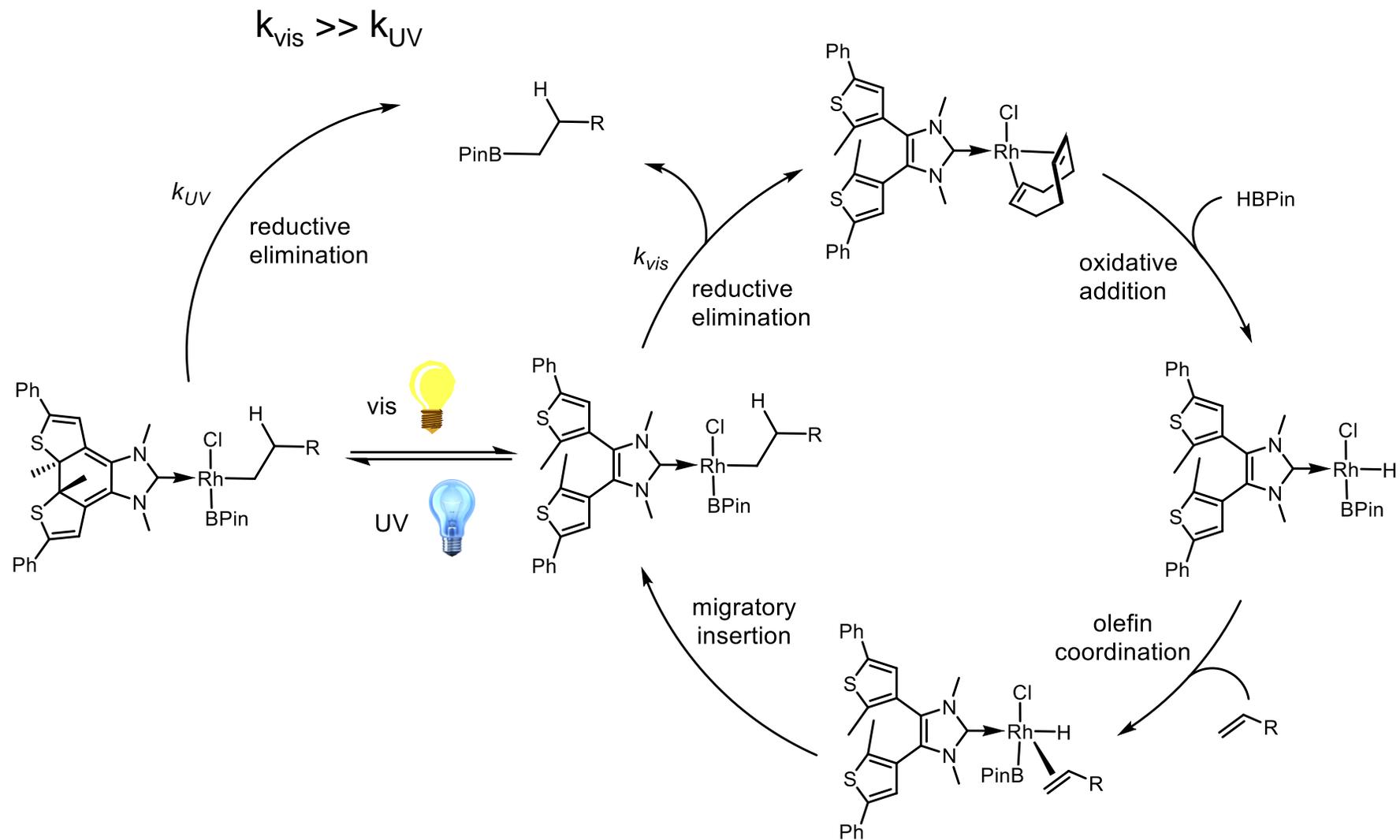
*In situ* ON/OFF photoswitching:



# Photoswitching Dithienylethene-Functionalized *N*-heterocyclic Carbenes

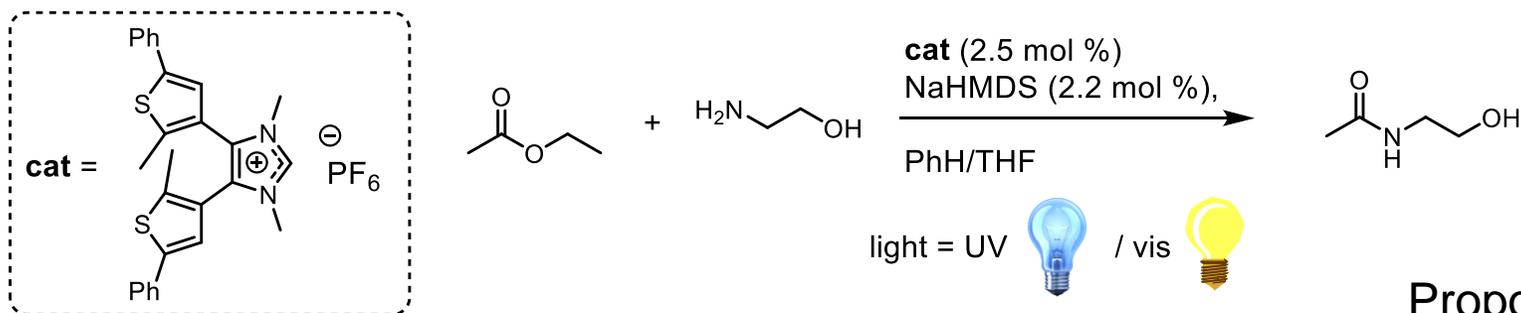
Photocyclization results in a more electron-deficient NHC ligand.

Reductive elimination is the rate-determining step, and is slower when the ligand is photocyclized.

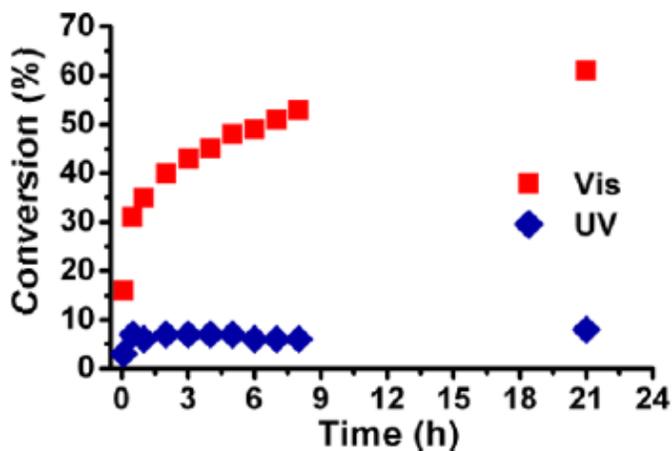


# Photoswitching Dithienylethene-Functionalized *N*-heterocyclic Carbenes

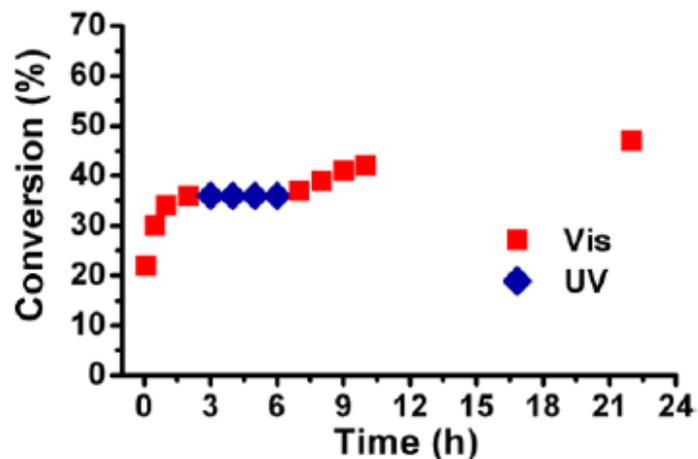
Bielawski *et al* also demonstrated *in situ* ON/OFF photoswitching using an NHC as an organocatalyst (2012):



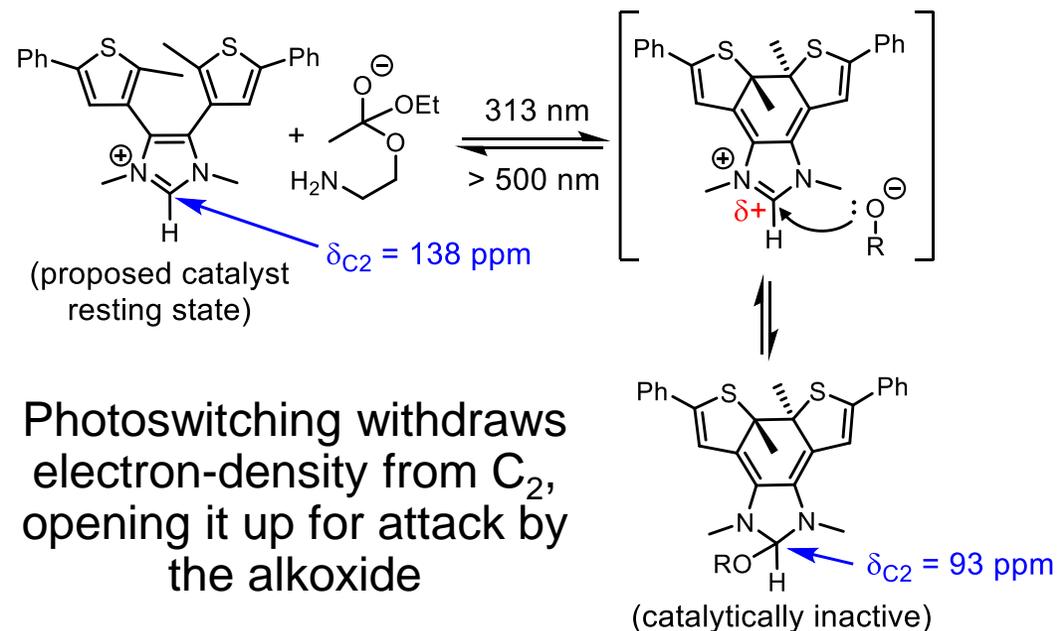
Rate control in two different continuously irradiated reactions:



*In situ* rate switching:



Proposed mechanism of catalyst deactivation:

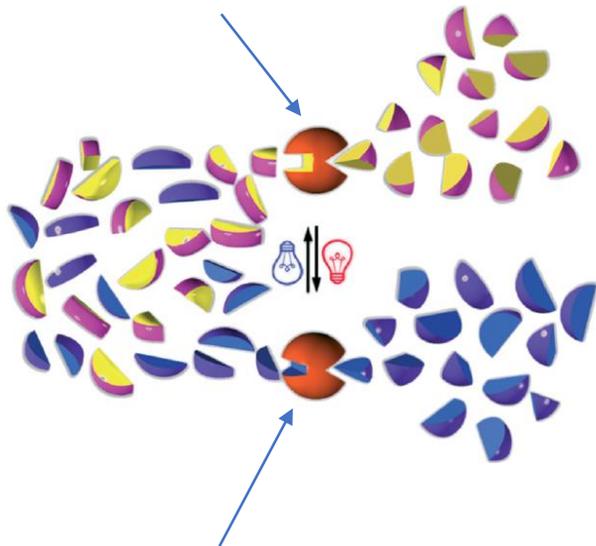


# Photoswitchable Substrate Selectivity is Underdeveloped with Big Potential

## Possibilities for photoswitchable substrate selectivity:

Switchable substrate selectivity  
(relatively unknown):

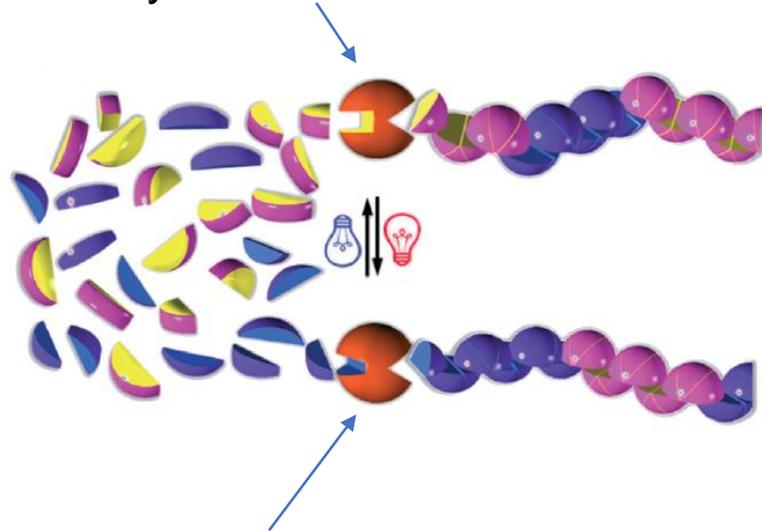
React substrate A



React substrate B

Switchable control over  
copolymerization:

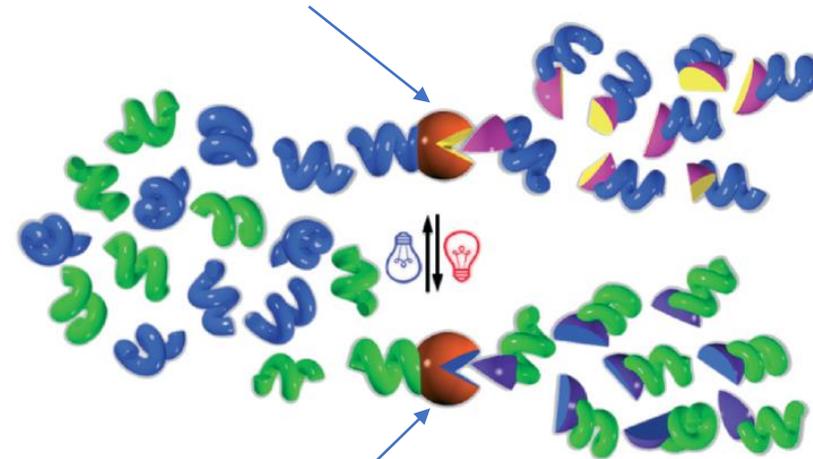
Polymerize monomer A



Polymerize monomer B

Switchable kinetic resolution  
(unknown):

React substrate A

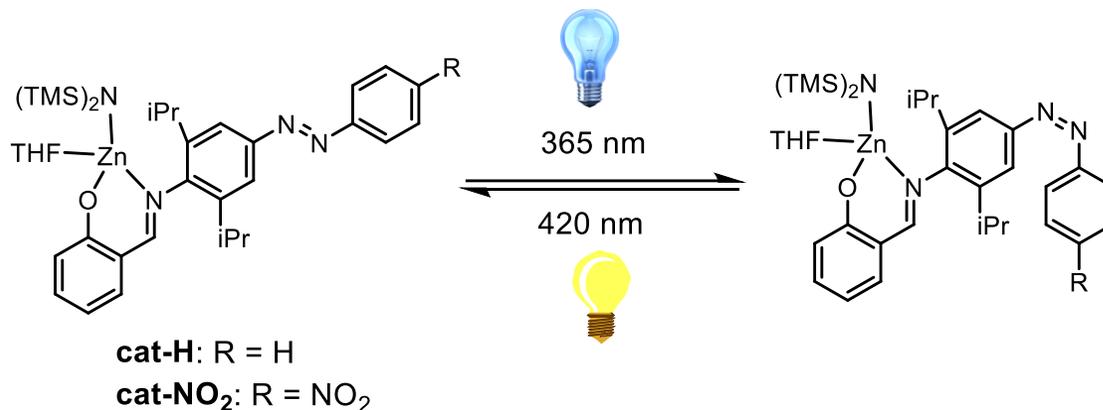


React *ent*-substrate A

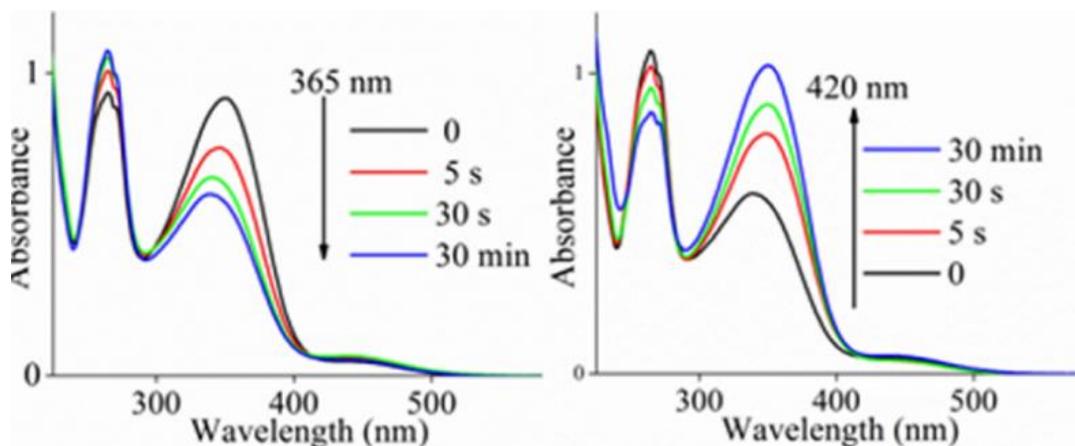
Photoswitchable substrate selectivity is especially underdeveloped compared to other research in this area.

# Photoswitchable Substrate Selectivity in Ring-Opening Polymerization

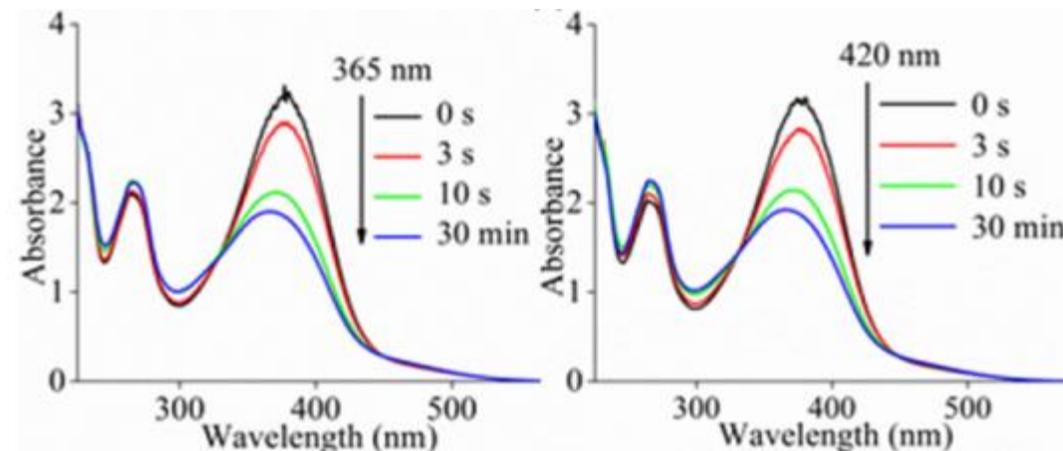
Development of a Zn-salicylaldimine complex for a photoswitchable ring-opening polymerization catalyst (Chen, 2019):



Switchable photochromism for **cat-H**:



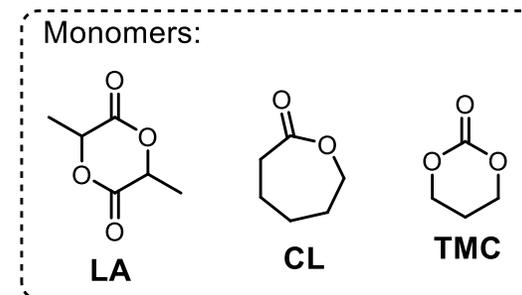
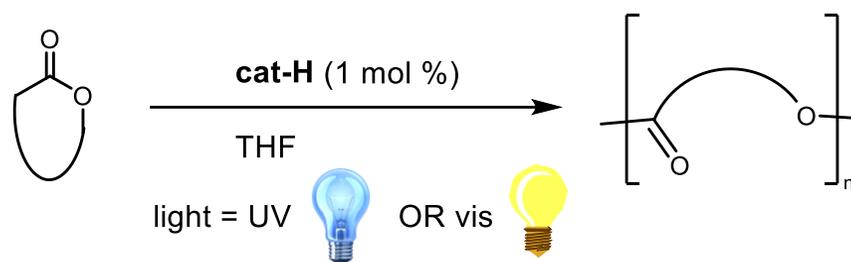
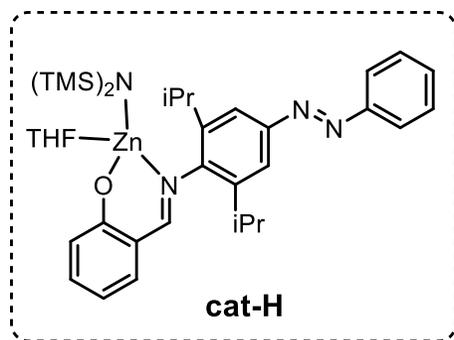
**cis-cat-NO<sub>2</sub>** does not display differential UV/visible light photochromism:



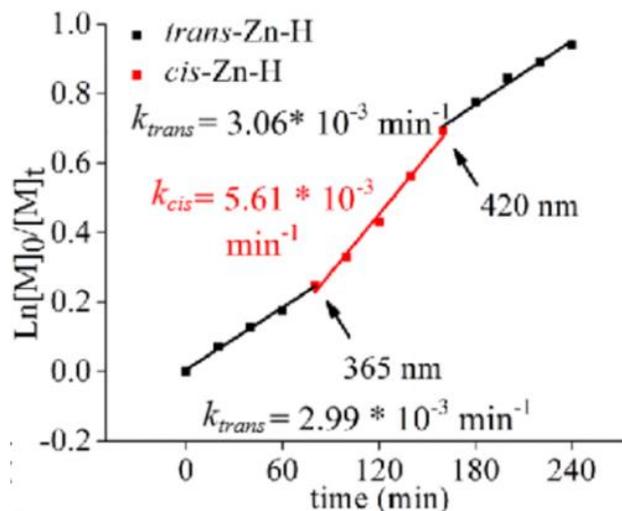
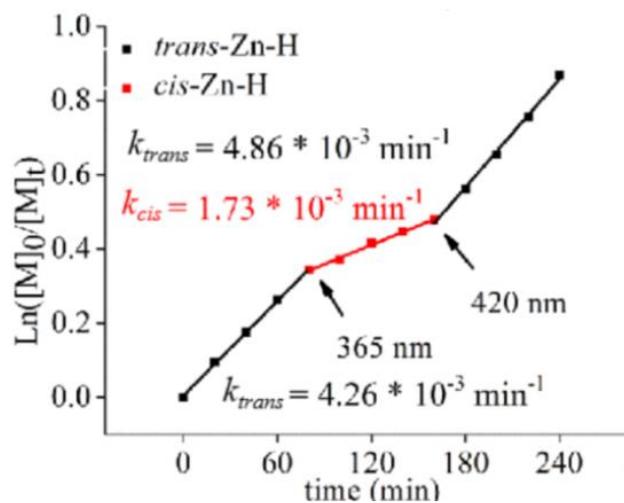
The catalyst can be switched ON but not OFF. This is more like a photocaged catalyst and not a good photoswitch.

# Photoswitchable Substrate Selectivity in Ring-Opening Polymerization

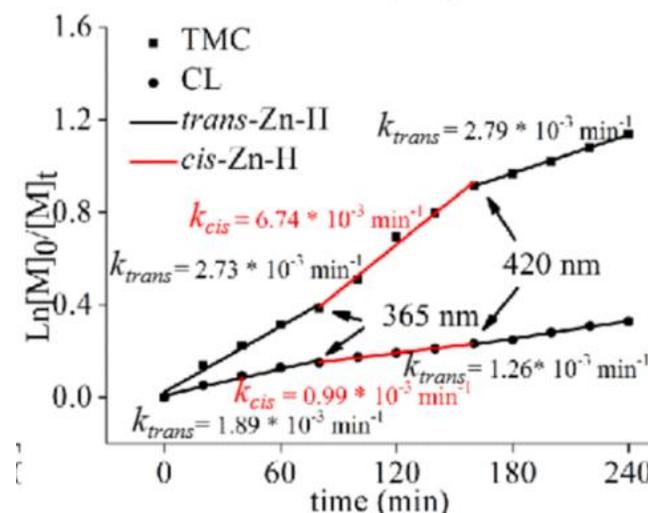
Development of a Zn-salicylaldehyde complex for a photoswitchable ring-opening polymerization catalyst (Chen, 2019):



Photoswitching ON/OFF polymerization of **LA** and **TMC**:



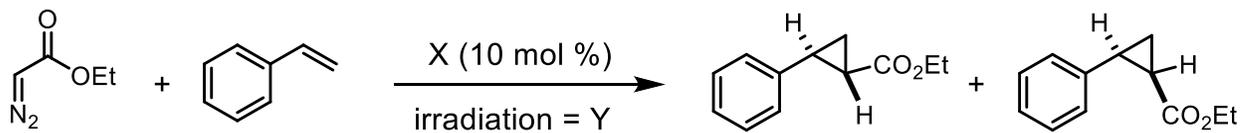
Attempted photoswitchable copolymerization of **TMC** and **CL**:



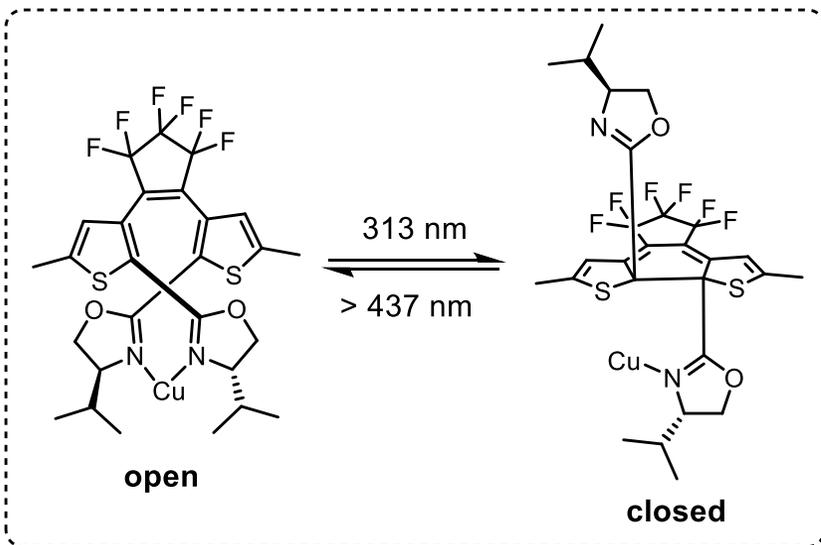
Dark gives 32% **CL** in copolymer.  
365 nm light gives 26% **CL** in copolymer.

# Photoswitchable Stereoselectivity: Moving Beyond ON/OFF Photoswitches

The first example of a photoswitchable stereoselectivity effect was demonstrated with a simple ON/OFF photoswitch in a Cu-bisoxazoline system (Branda, 2005):

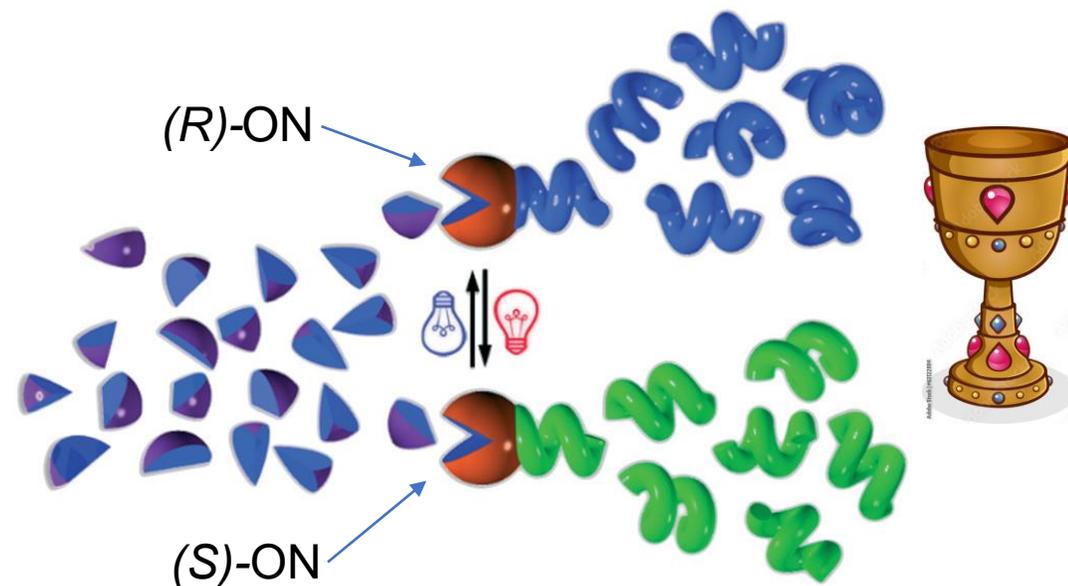


X = **open**, Y = none: 30% ee *trans*, 50% ee *cis*, 55:45 dr  
X = **open**, Y = PSS at 313 nm: 11% ee *trans*, 37% ee *cis*, 70:30 dr  
X = **closed**, Y = none: 5% ee *trans*, 5% ee *cis*, 63:37 dr



Only 23% **closed** in the PSS, attributed to strong stabilizing effect of chelation in the **open** form.

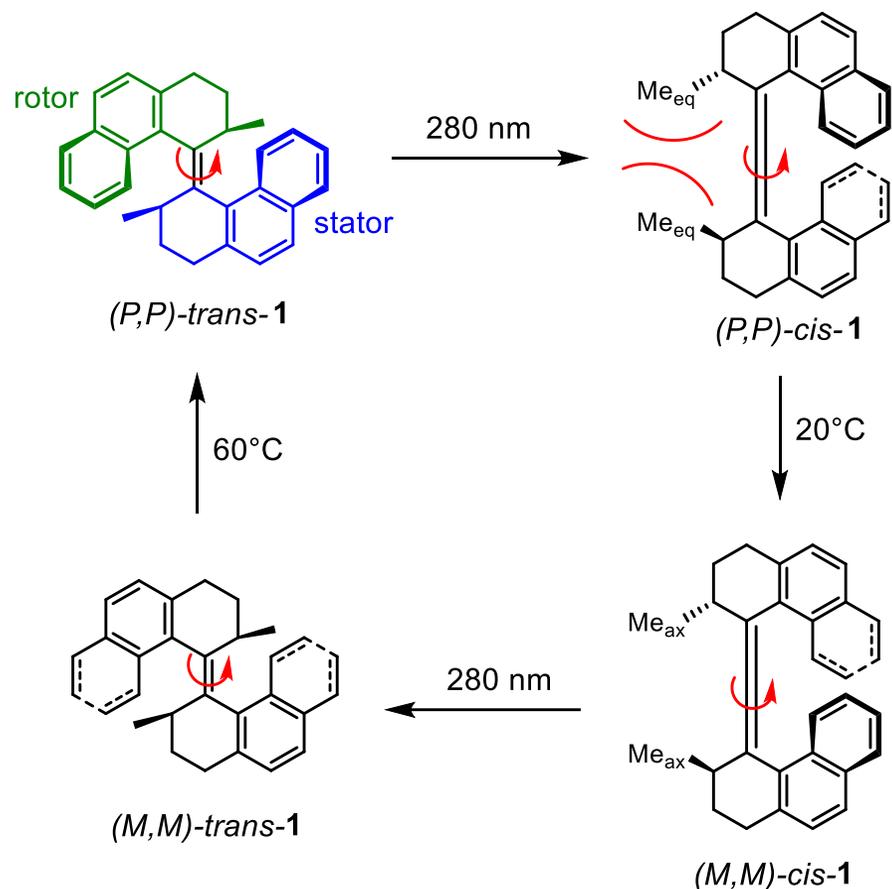
The “holy grail” stereochemical photoswitch is a **photoswitchable ambidextrous catalyst**, one that produces enantiomeric products depending on irradiation conditions:



Photoswitching the sense of enantioinduction is *much* harder than simply switching ON/OFF.

# First-Generation Molecular Motor for Catalytic Thiol Additions to Eneones

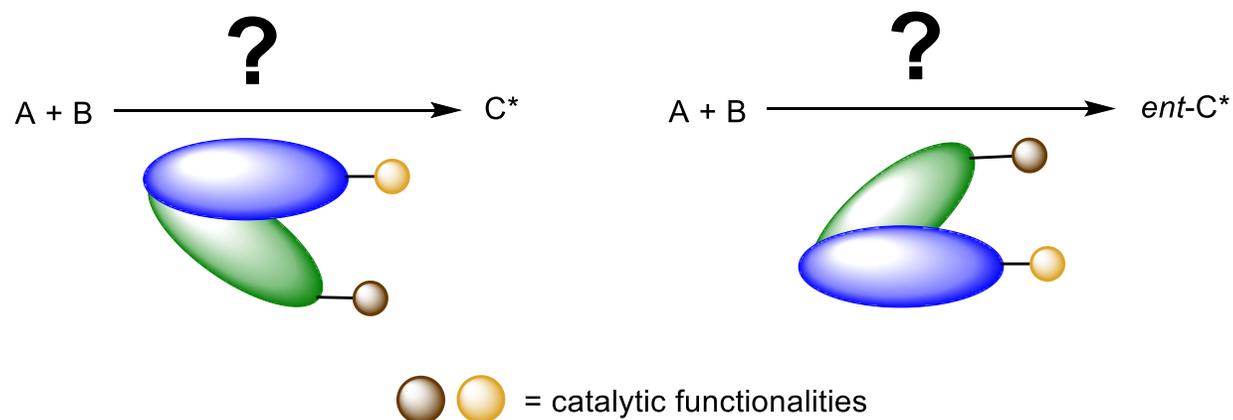
Feringa *et al* previously demonstrated a unidirectional molecular motor powered by sequential photochemical-thermal isomerization events (1999):



Clockwise rotation is determined by the configuration of the Me-bearing stereocenters.

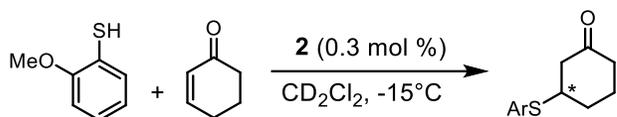
Intermediate inversion of helical chirality; Both pseudo-enantiomeric  $(P,P)$  and  $(M,M)$  helices can be accessed by appropriate choice of photoswitch or thermal isomerization.

Can we use this observation to design an ambidextrous catalyst that can be switched to produce enantiomeric products?



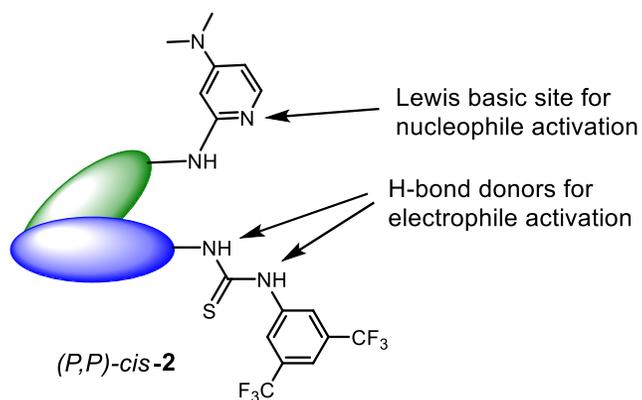
# First-Generation Molecular Motor for Catalytic Thiol Additions to Eneones

Consider a Michael reaction:

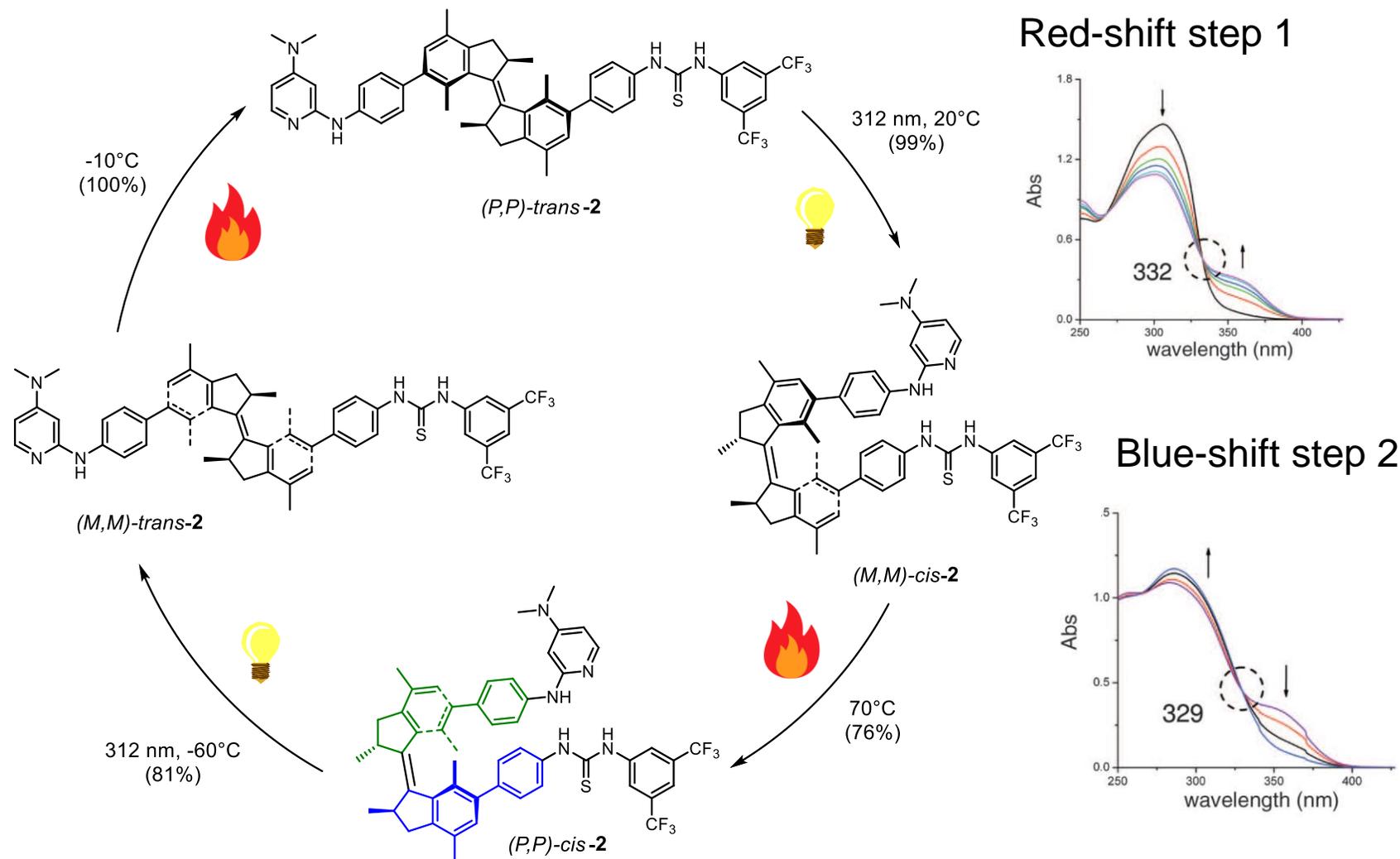


We need both enantiomers of the product tomorrow and we cannot make *ent*-**2**. Is it possible?

Catalyst design strategy:

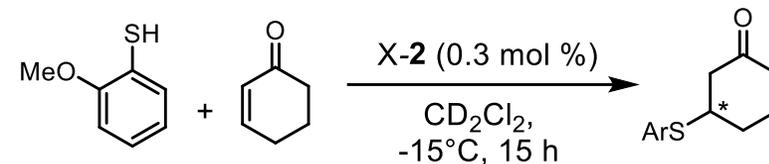
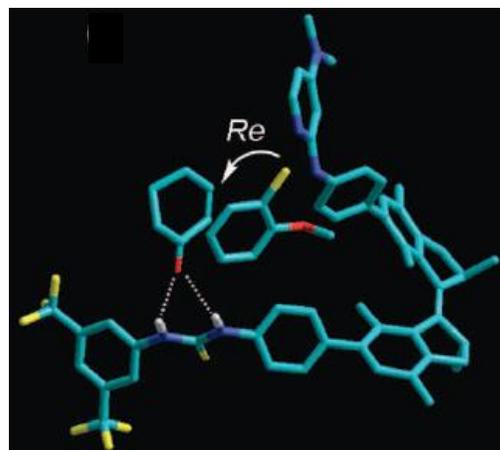
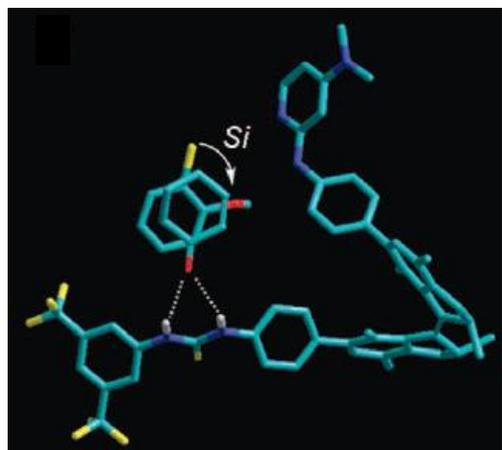
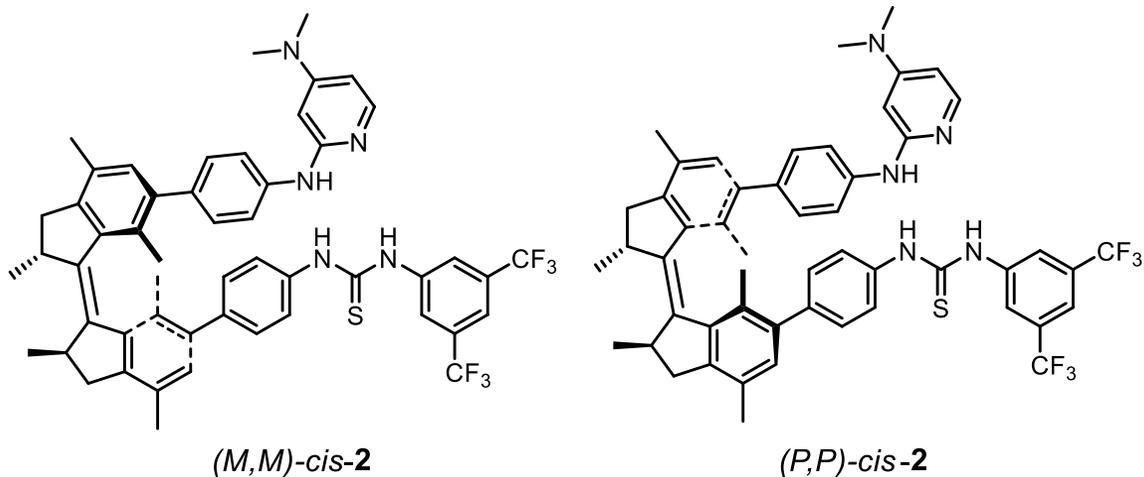


New molecular motor design and verification of rotary cycle:

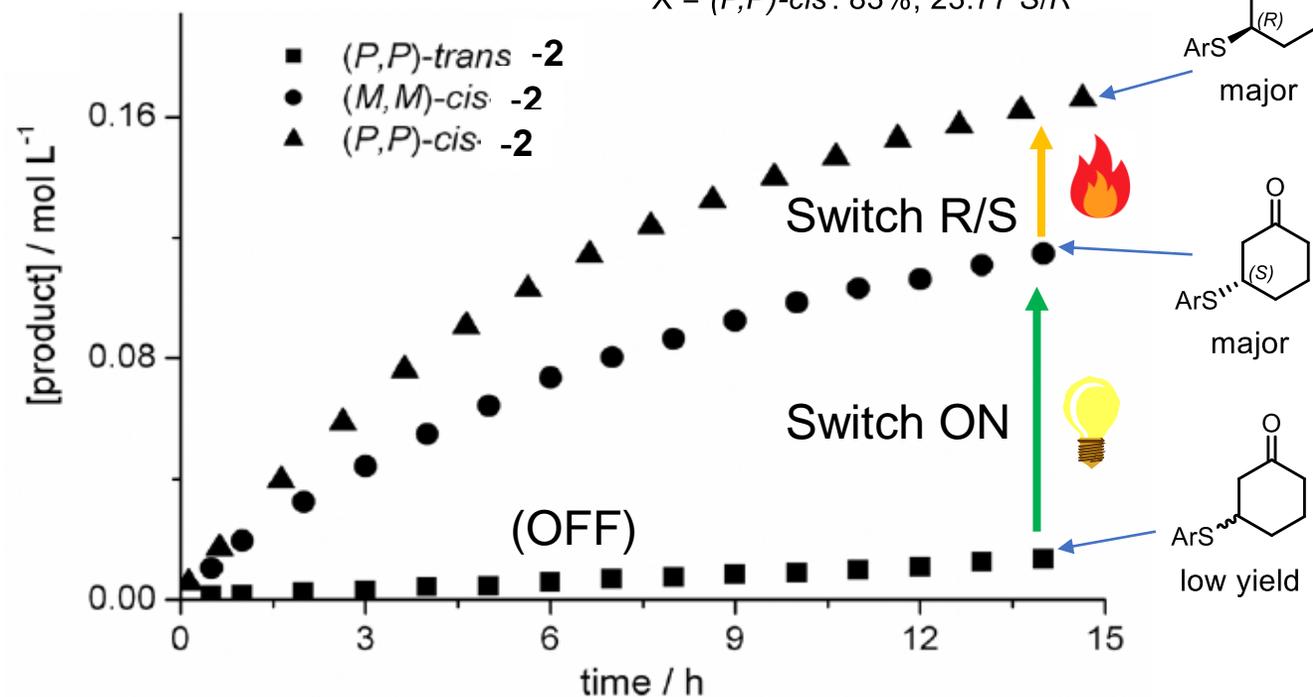


# First-Generation Molecular Motor for Catalytic Thiol Additions to Eneones

Stable pseudo-enantiomeric morphologies and effective catalytic activity make for a **photoswitchable ambidextrous catalyst**.



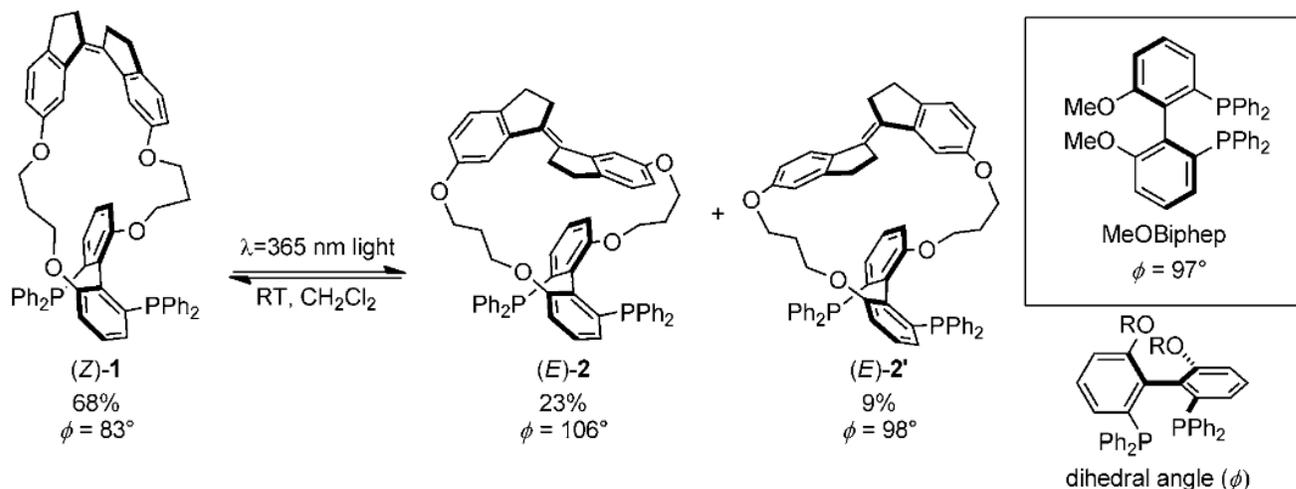
X = (P,P)-*trans*: 7%, 49:51 S/R  
X = (M,M)-*cis*: 50%, 75:25 S/R  
X = (P,P)-*cis*: 83%, 23:77 S/R



Distal catalytic functionality renders *trans*-2 ineffective.

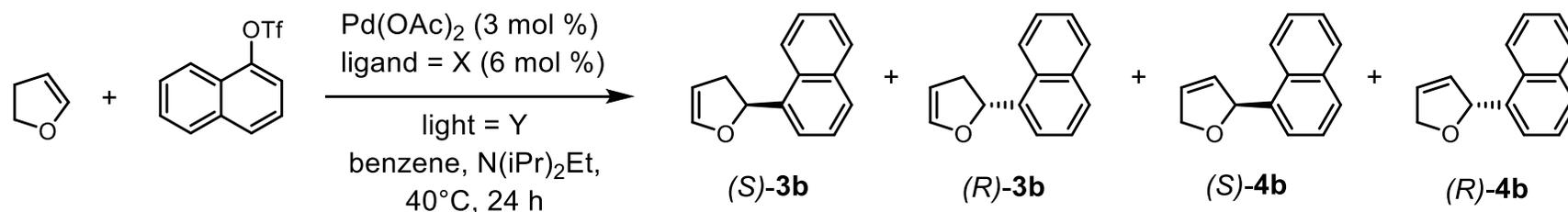
# Photoswitchable Tuning of Bisphosphine Bite Angle Inspired by Feringa

Incorporating a Feringa-like photoswitch into the backbone of a bisphosphine ligand (Craig, 2014):



No incorporation of central chirality on molecular motor precludes central-to-helical chirality transfer, leads to a mixture of diastereomers.

Testing switchable phosphines in Heck arylation:



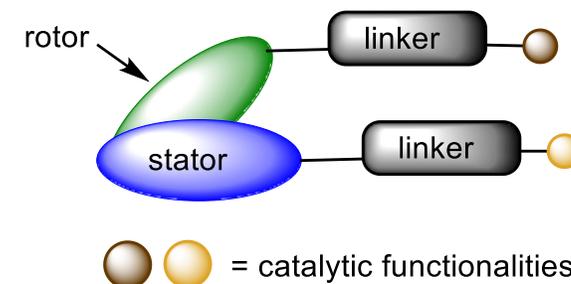
ligand = MeOBiphep, light = none: 79:21 **3b/4b**, 54% ee (S)-3b  
ligand = (Z)-1, light = none: **72:28 3b/4b**, 60% ee (S)-3b  
ligand = (E)-2, light = none: **88:12 3b/4b**, 13% ee (S)-3b  
ligand = (E)-2, light = 365 nm: 85:15 **3b/4b**, 42% ee (S)-3b

Also explored Tsuji allylations, but the ligand bite angle had little effect on ee (93% vs. 91%).

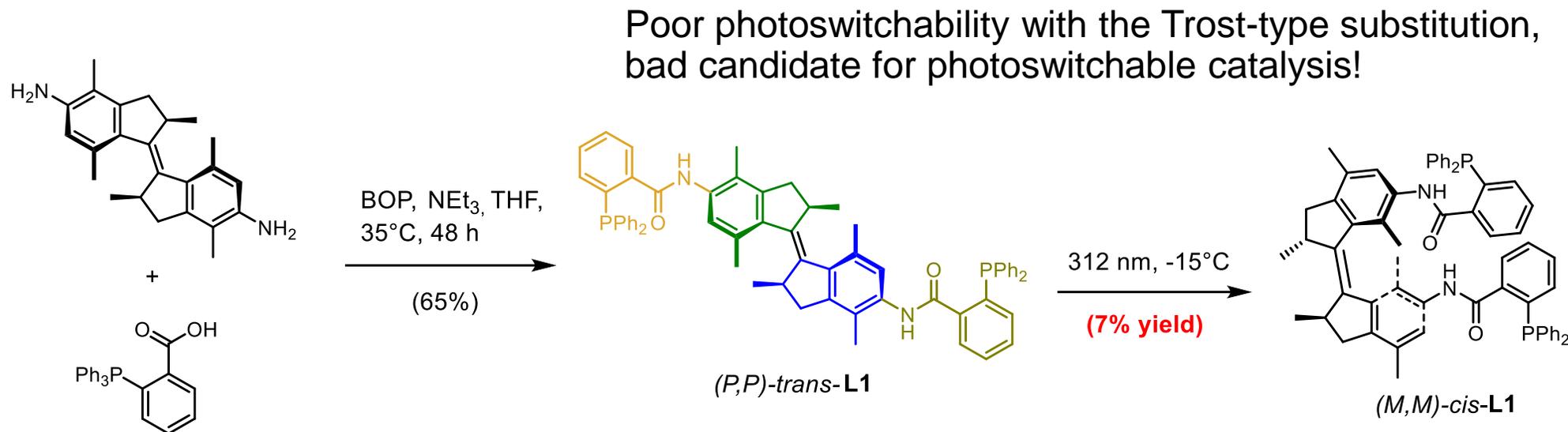
# First-Generation Molecular Motor for Switchable Bis-Phosphine Ligands

Feringa's 2011 work outlines a general scaffold for photoswitchable, ambidextrous catalysts based on unidirectional molecular motors.

How can we use this technology for different types of catalysis? Can we make a photoswitchable, ambidextrous *ligand* for transition metal catalysis?

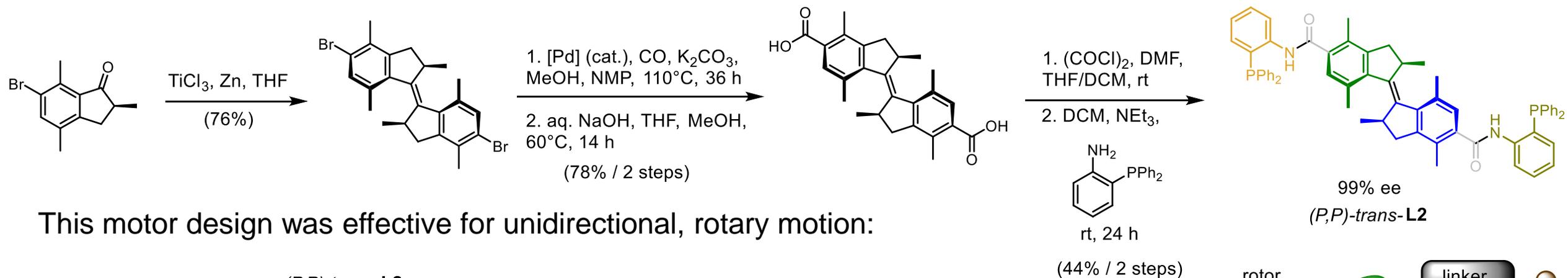


Incorporating Trost-type ligands in a unidirectional molecular motor:

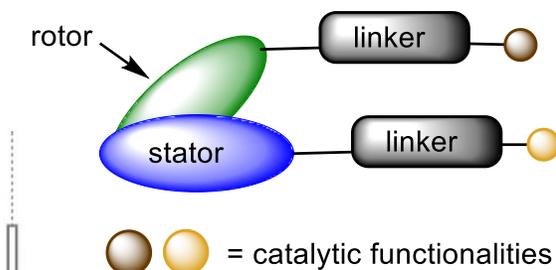
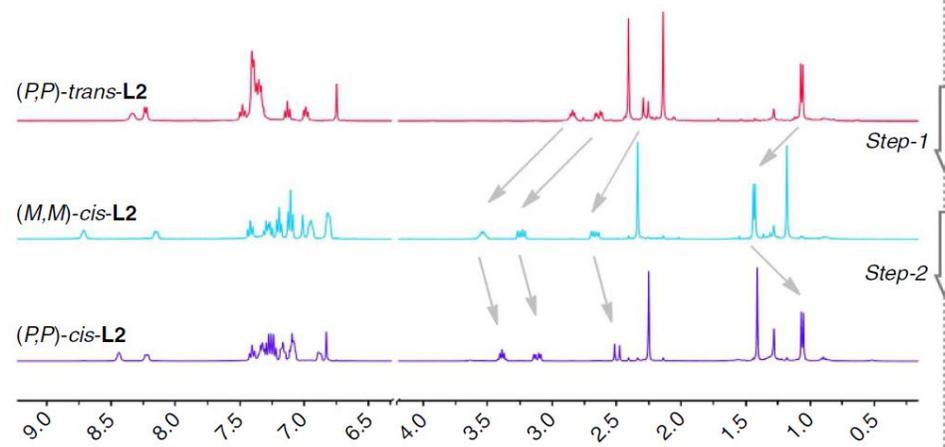
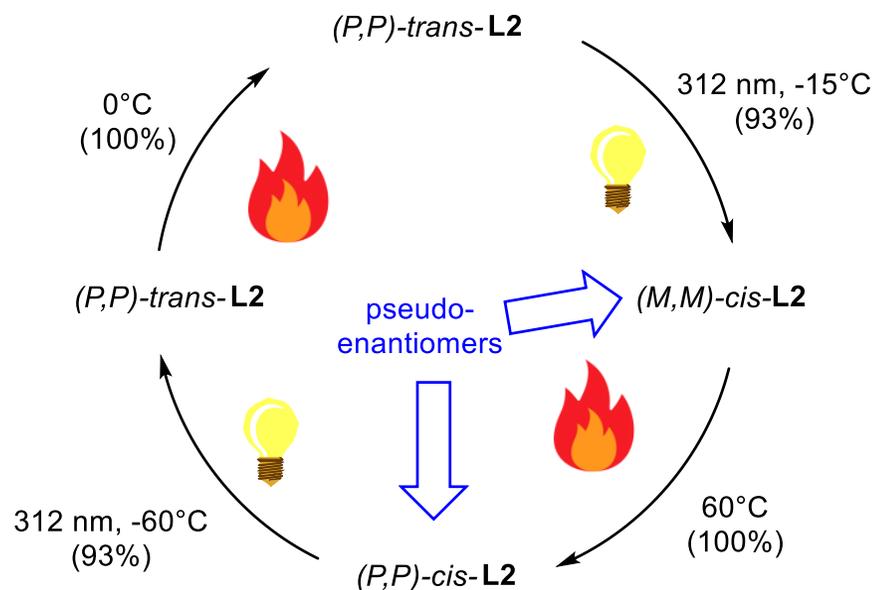


# First-Generation Molecular Motor for Switchable Bis-Phosphine Ligands

Redesigning the molecular motor to incorporate a Trost-like bisphosphine ligand:

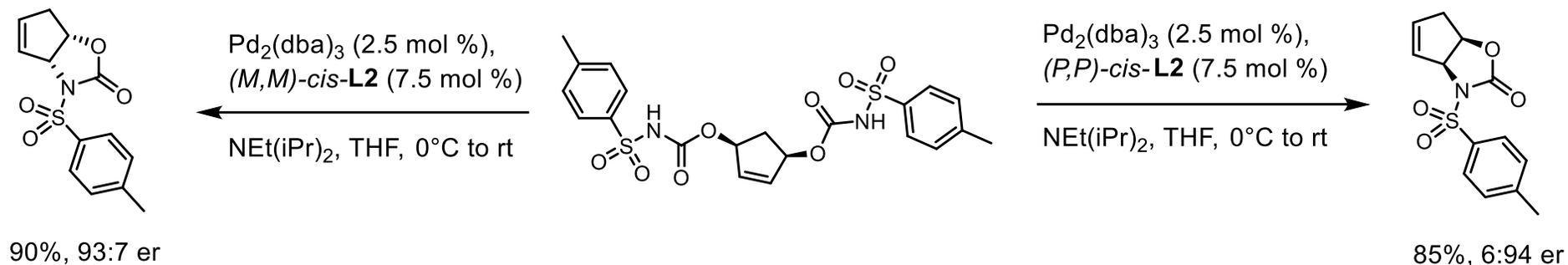


This motor design was effective for unidirectional, rotary motion:



# First-Generation Molecular Motor for Switchable Bis-Phosphine Ligands

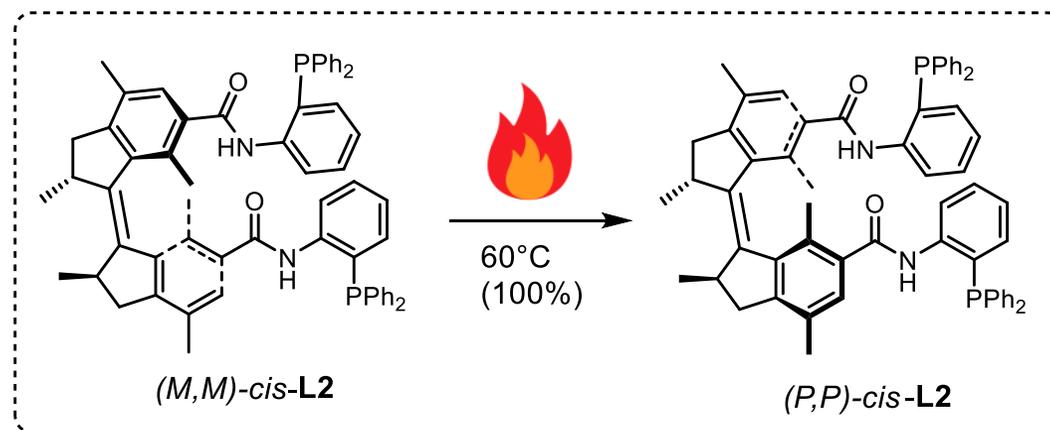
Applying the ambidextrous ligand in a palladium catalyzed desymmetrization reaction:



Excellent enantioselectivity is demonstrated for both pseudo-enantiomeric forms of **L2**.

In this case,  $(P,P)\text{-trans-L2}$  gave 65% yield, with expectedly poor enantioinduction at 53:47 er.

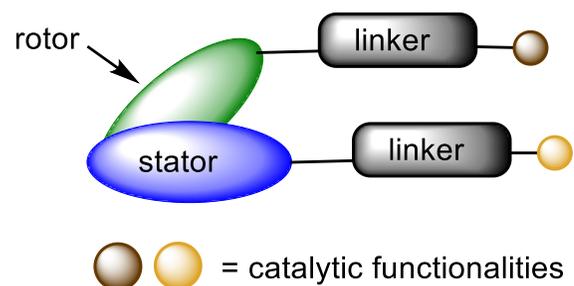
Is it possible to switch enantioselectivity *in situ*? In this case, attempted *in situ* UV photoisomerization led to degradation of the catalytic Pd complex and low selectivity.



# Lessons Learned from Feringa's First Generation Molecular Motor

Unidirectional molecular motors have *intrinsic pseudo-enantiomeric forms* in their rotary cycle, making them prime candidates for ambidextrous, photoswitchable catalysts.

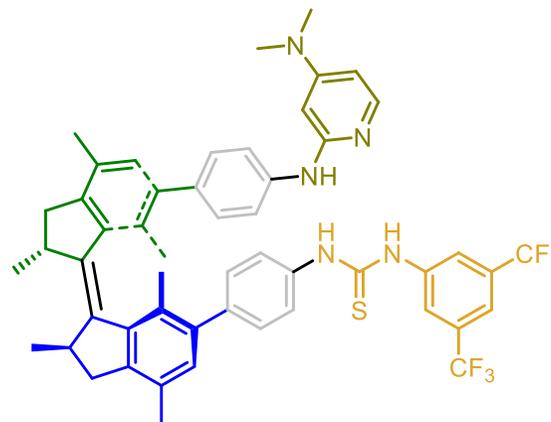
Feringa's pioneering 2011 work achieved only moderate to low enantiomeric excess (ee ~50%) in a thiol Michael addition. What design principles should we consider to optimize an ambidextrous, photoswitchable catalyst?



## Design goals:

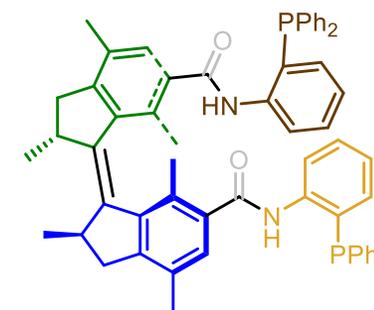
- high control over rotary motion of motor
- shorter is better for the linker, places catalytic functionality closer to helix, better stereocontrol
- the active catalytic species must be stable to the photo/thermal isomerization conditions required to power the motor

## Lewis base/H-bond donor molecular motor catalyst (2011):



Long spacer, low selectivity

## Bisphosphine molecular motor ligand (2015):



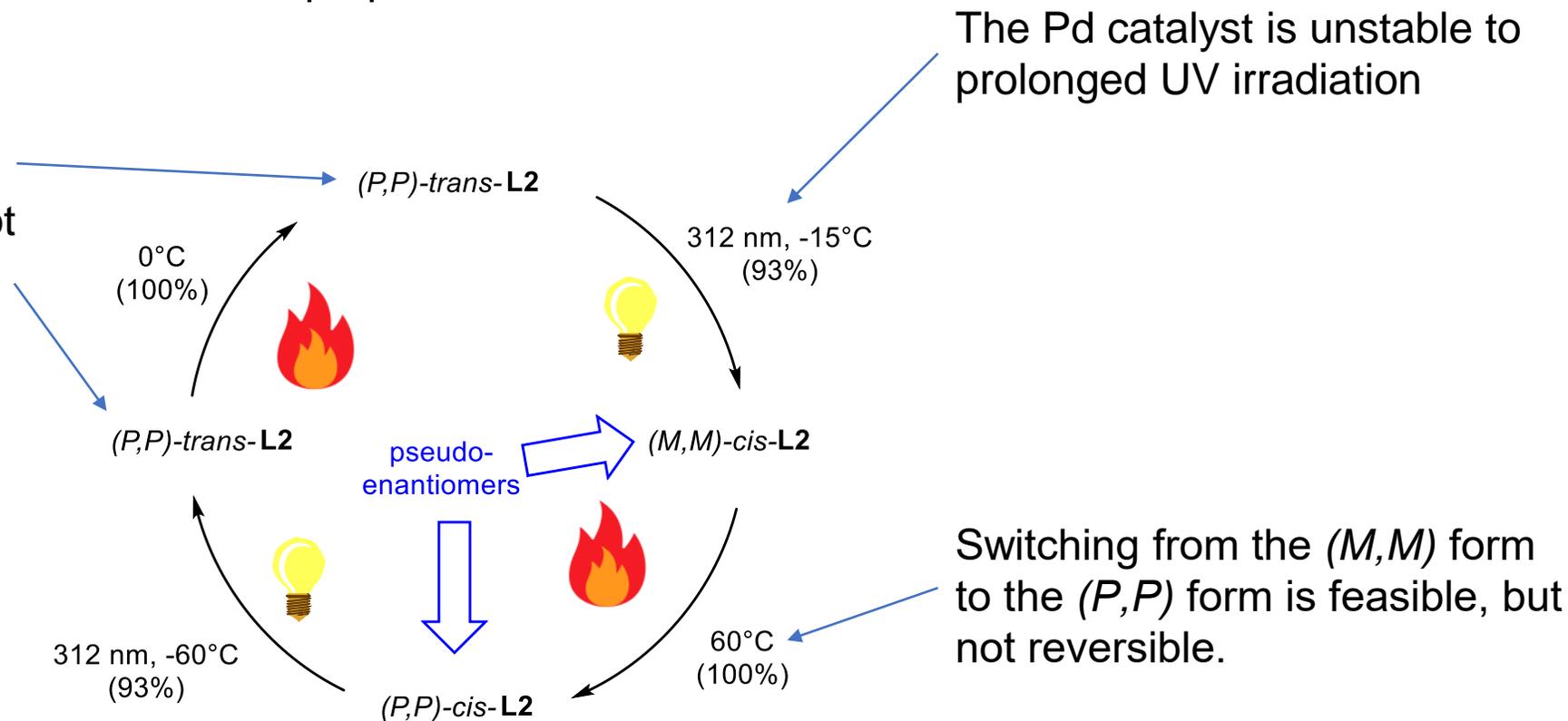
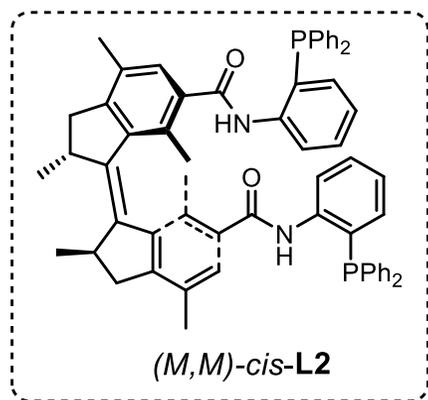
Short spacer, ee > 86%

# Lessons Learned from Feringa's First Generation Molecular Motor

Ideally, switching the molecular motor could be accomplished *in situ*, obviating the need for preparing the isomeric forms of the molecular motor separately.

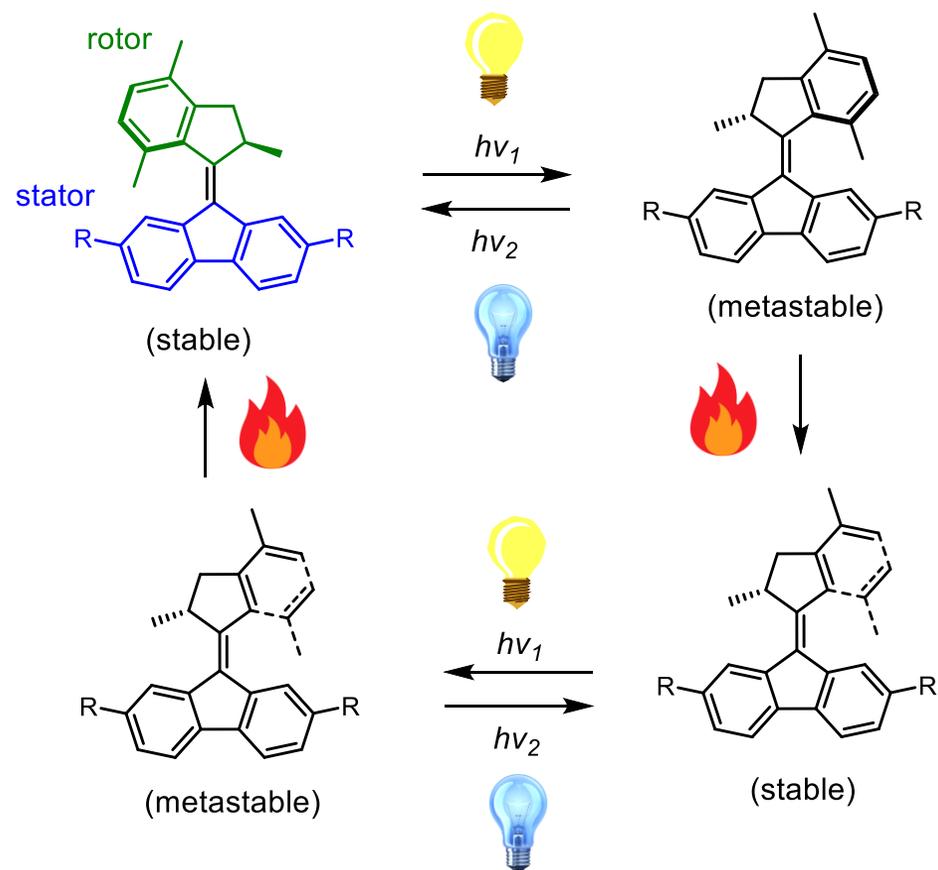
The first-generation motor is unsuitable for this purpose:

Switching from *(M,M)* back to *(P,P)* requires passing through the *trans* isomers, which do not provide good enantioinduction

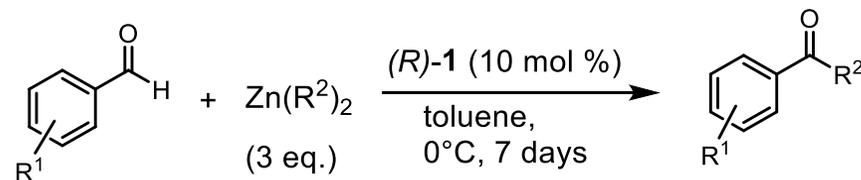


# Second Generation Molecular Motor for Catalytic Diethylzinc Additions

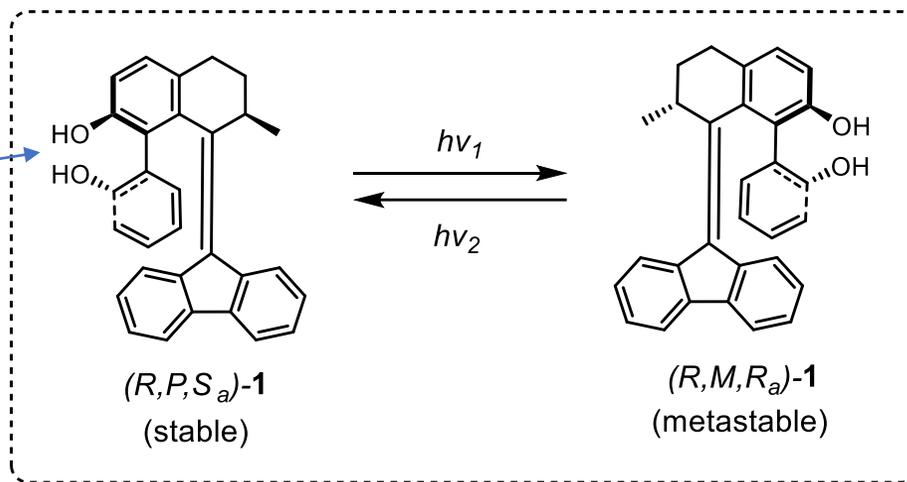
Second generation molecular motors with tricyclic stator and asymmetric rotor:



A BINOL-based ligand on a second generation molecular motor as a Zn chelator:



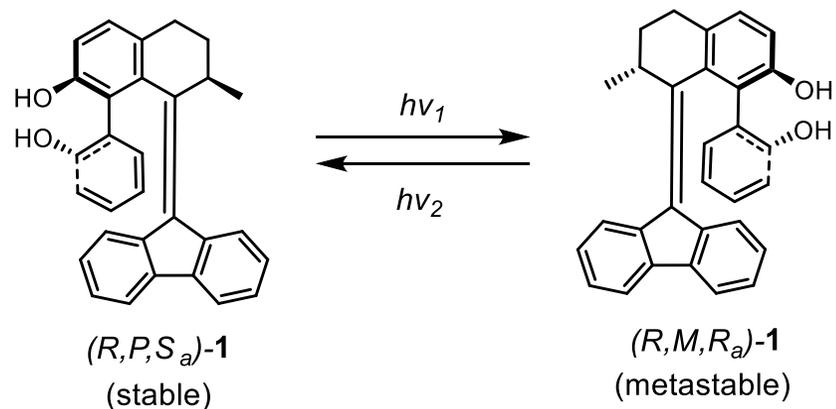
Bidentate coordination required for effective catalysis.



Second generation motors tends to have higher barriers for thermal inversion compared to the first generation. This allows switching directly between pseudo-enantiomeric forms through proper choice of temperature and light wavelength.

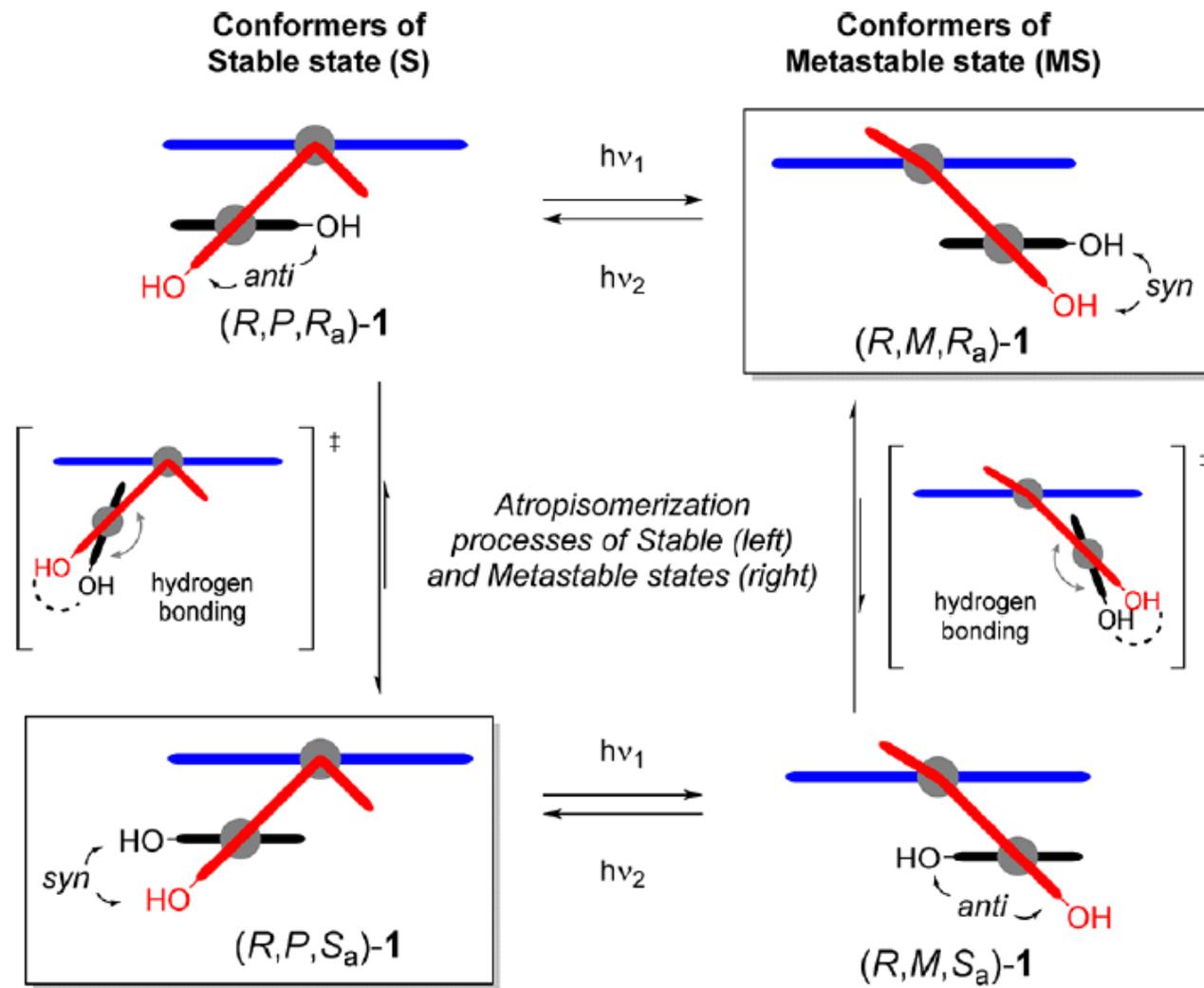
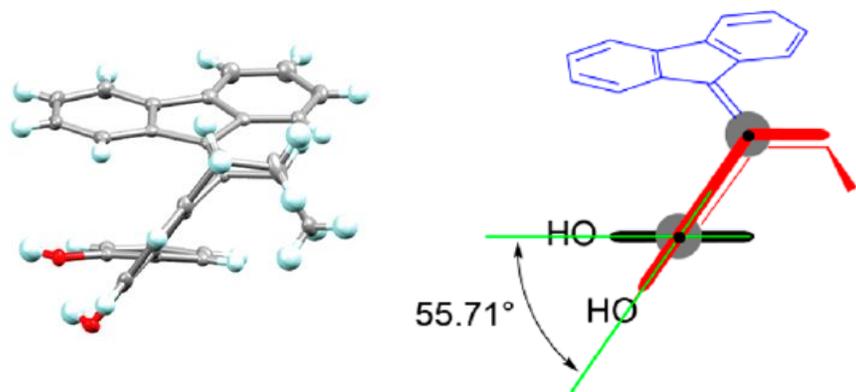
# A Closer Look At the Atropisomerism of the Second-Generation Motor

This is not a simple *E/Z* isomerization:



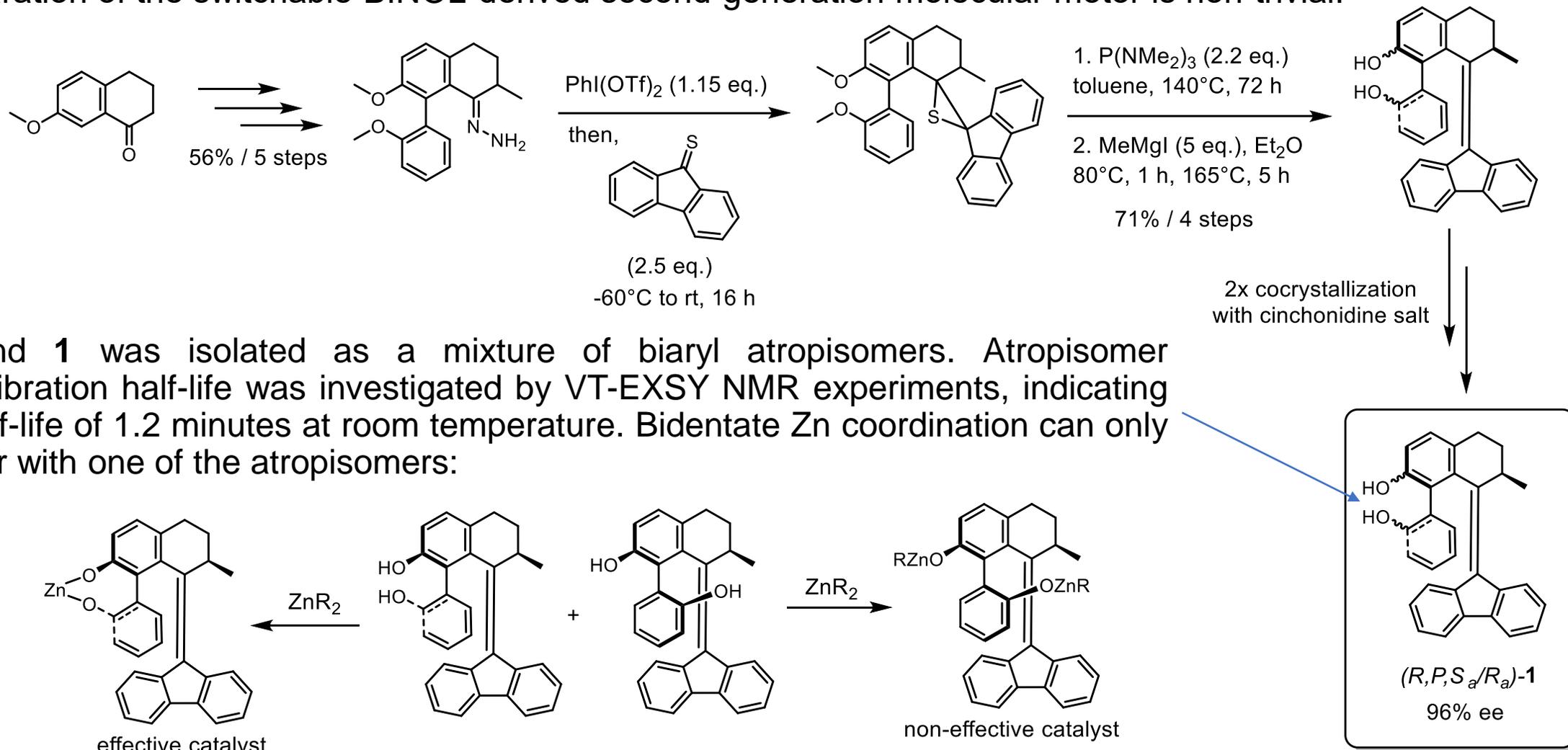
Central-to-helical-to-axial transfer of chirality!

ORTEP diagram of solid-state  $(R,P,S_a)$ -1:

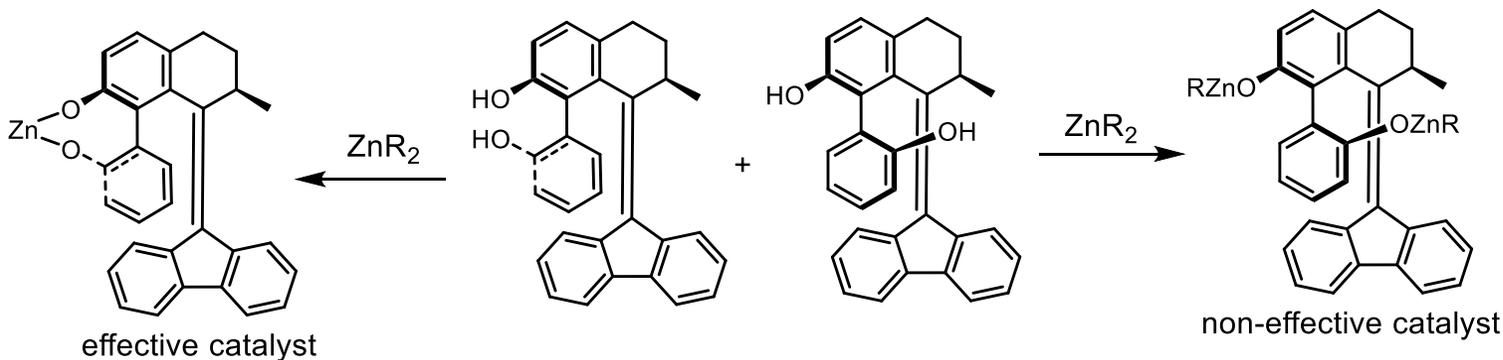


# Second Generation Molecular Motor for Catalytic Diethylzinc Additions

Preparation of the switchable BINOL-derived second-generation molecular motor is non-trivial:

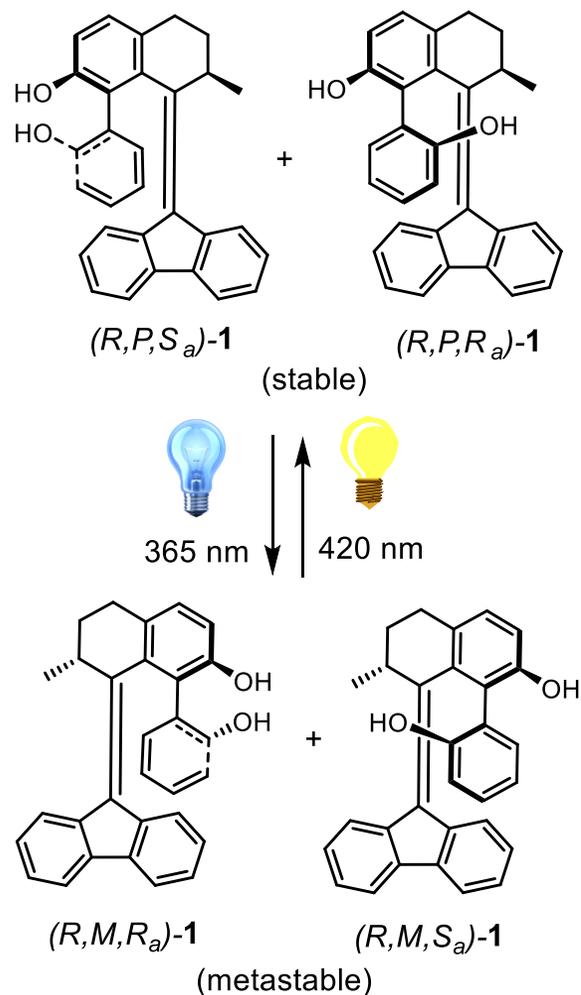


Ligand **1** was isolated as a mixture of biaryl atropisomers. Atropisomer equilibration half-life was investigated by VT-EXSY NMR experiments, indicating a half-life of 1.2 minutes at room temperature. Bidentate Zn coordination can only occur with one of the atropisomers:

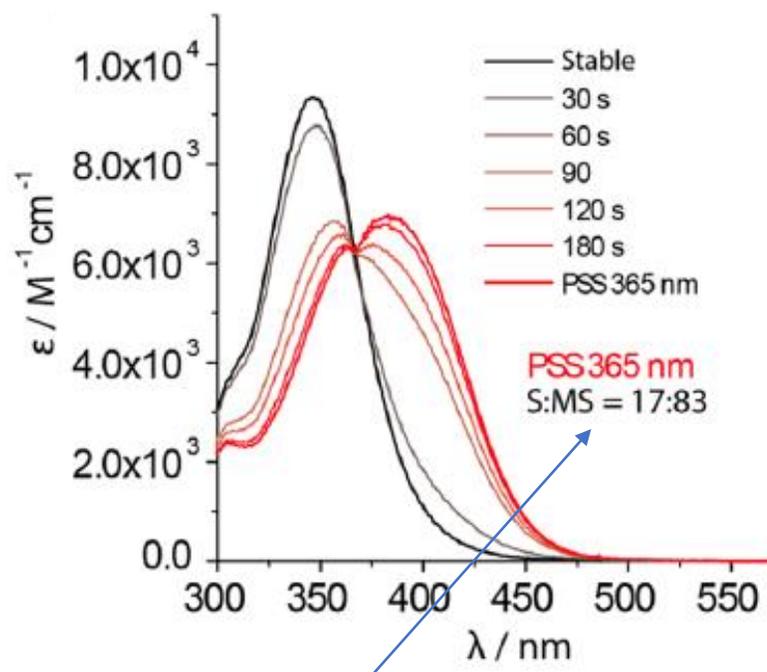


# Second Generation Molecular Motor for Catalytic Diethylzinc Additions

Testing photoswitchability of the BINOL-derived second generation molecular motor ligand:

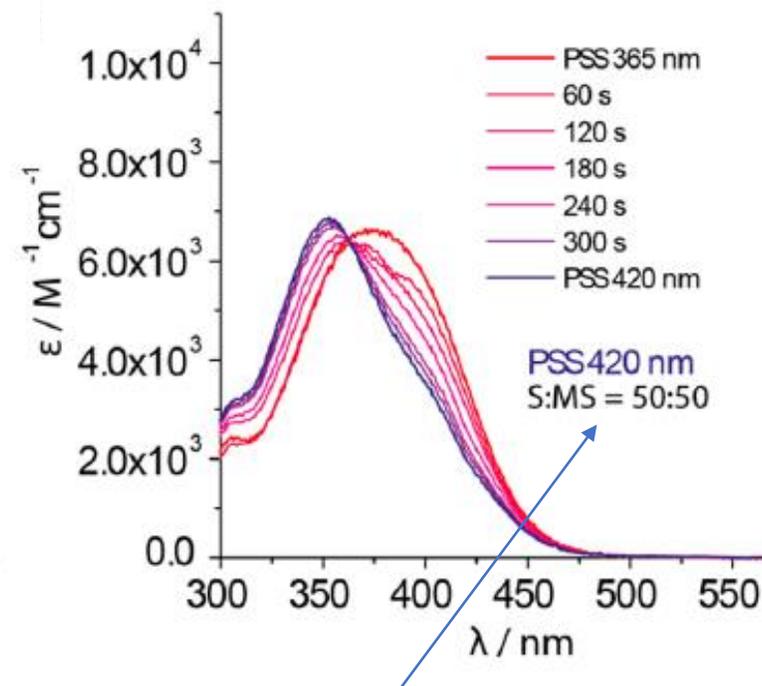


Red-shifted absorbance in 365 nm PSS indicates photoswitching to the metastable state (confirmed by HPLC):



Good photoswitching from  $(R,P,S_a)$ -1 to pseudo-enantiomeric  $(R,M,R_a)$ -1

Blue-shift in 420 nm PSS indicates reverse photoswitch:



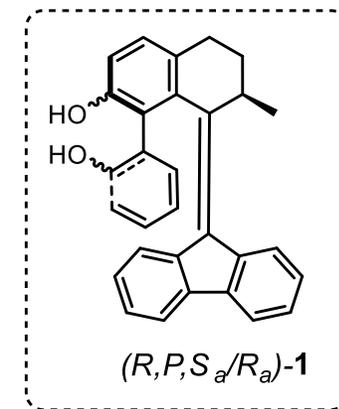
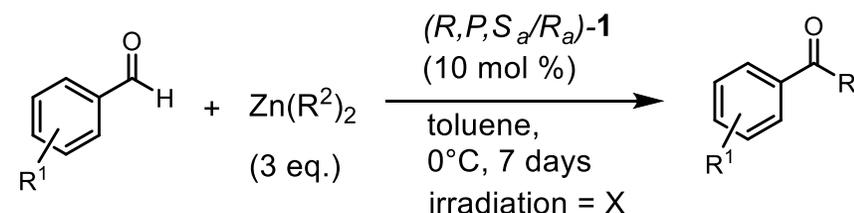
Not a great reverse photoswitch

# Second Generation Molecular Motor for Catalytic Diethylzinc Additions

## In situ Photoswitchable enantioselective catalysis using the BINOL-derived second-generation molecular motor:

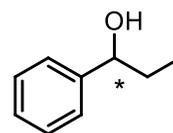
Light on/off  $\Delta ee$  up to 113% (best case  $\Delta ee = 200\%$ , full reversal of enantioselectivity).

No degradation or racemization was observed in the catalyst recovered from the reaction mixture, which could be recycled.

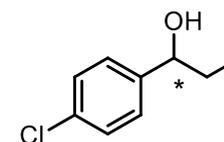


## How could this system be improved based on the discussed design principles?

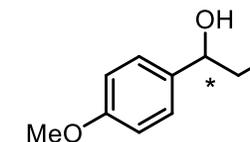
- More complete photoswitching- 17:83 is good not great.
- Approximate chelating groups to the helical axis- Perhaps hard in this system since it is already a small molecule. Reminder: helical chirality is the source of enantioinduction.



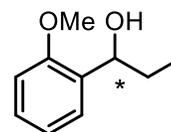
X = none: 86%, 68% ee (R)  
X = 365 nm: 80%, 45% ee (S)



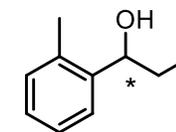
X = none: 80%, 35% ee (R)  
X = 365 nm: 80%, 24% ee (S)



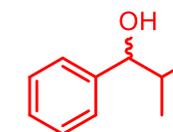
X = none: 37%, 40% ee (R)  
X = 365 nm: 76%, 55% ee (S)



X = none: 81%, 46% ee (R)  
X = 365 nm: 72%, 31% ee (S)



X = none: 58%, 48% ee (R)  
X = 365 nm: 79%, 50% ee (S)

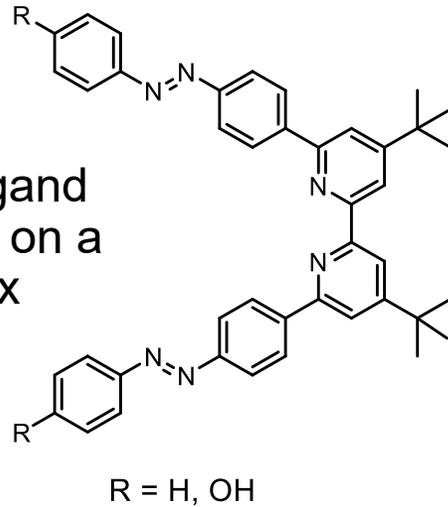


X = none: 40%, < 5% ee  
X = 365 nm: 57%, < 5% ee

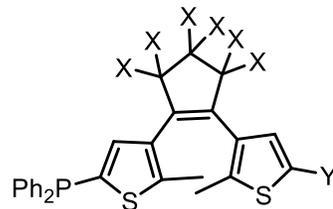
# Future Directions 1: The Low-Hanging Fruit

There are many reported photochromic ligands that have never been explored in photoswitchable metal catalysis:

Photocontrolled ligand exchange with bpy on a copper complex



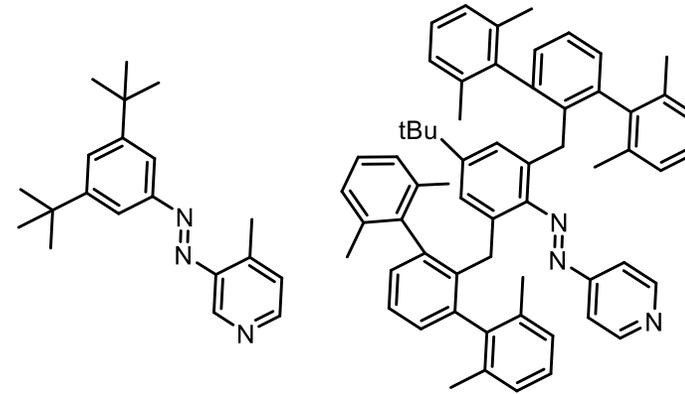
Tuning dithienylethene-based ligands:



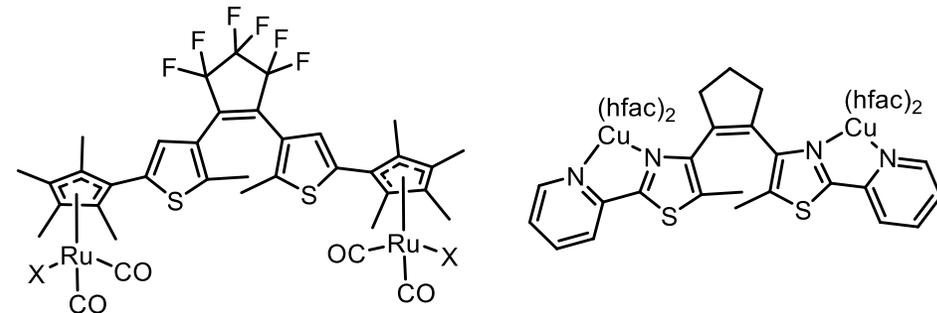
X = F/H, Y = Cl  
X = F/H, Y = Ph  
X = F/H, Y = C<sub>6</sub>H<sub>4</sub>(p-OMe)

Investigated on a platinum complex

Reported photoswitchable differential binding for Ni and Zn porphyrin complexes:

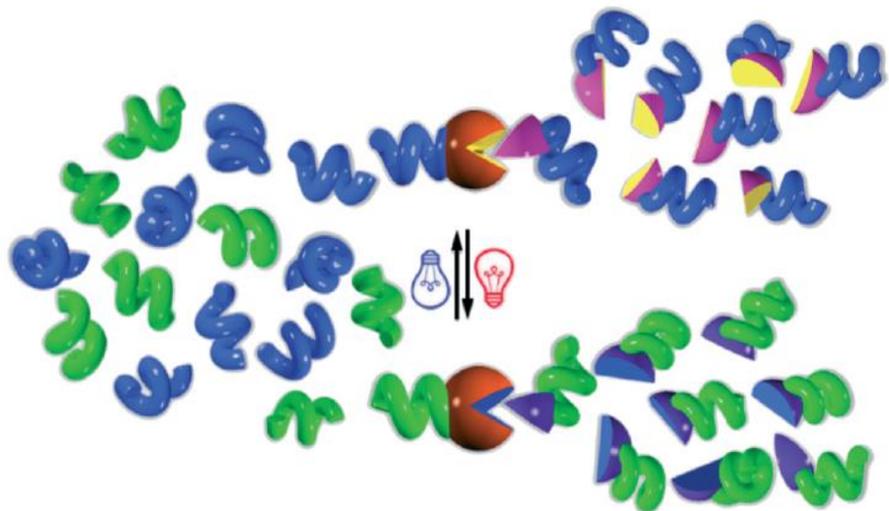


Reported bimetallic complexes with photochromic properties:

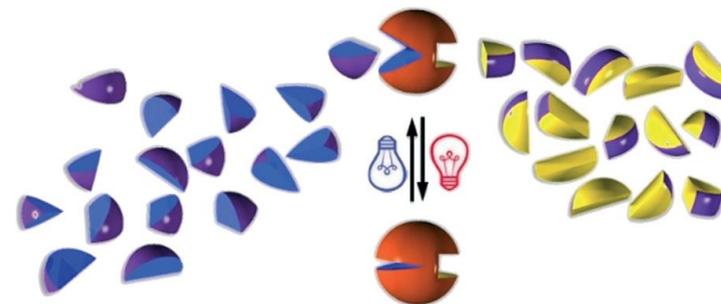


# Future Directions 2: Hard Unsolved Problems

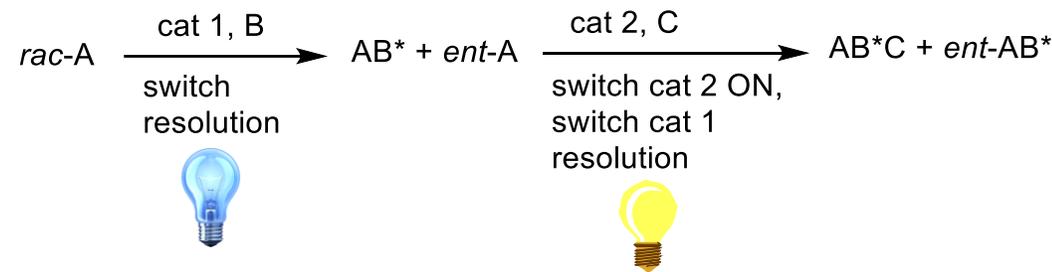
No examples of photoswitchable kinetic resolution:



Why would we want to do this anyway?  
Does it not defeat the purpose of kinetic resolution?



We could exploit tandem photoswitches to do multiple steps in one pot:

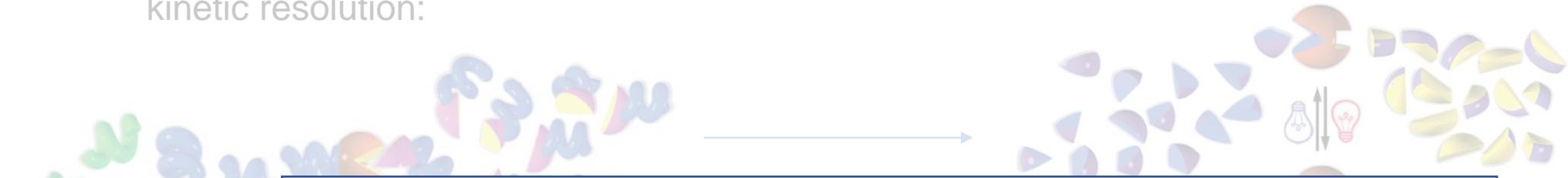


Tandem photo/chemo switches?

Pretty much everything past simple ON/OFF photoswitches is underdeveloped. The examples in this talk are at the cutting edge, but still crude compared to what we know is possible (i.e. in Nature).

# Future Directions 2: Hard Unsolved Problems

No examples of photoswitchable kinetic resolution:



*“To sum up, it is clear that we are enjoying the early days of a fascinating development. There are no rules established yet. However, the basic tools are provided, which is the ideal scenario for creative scientists to flourish.”*

Freixa, 2020

es to do

AB\*C + ent-AB\*

Why would we want to do this anyway?  
Does it not defeat the purpose of kinetic resolution?

switch resolution



switch cat 2 ON,  
switch cat 1 resolution

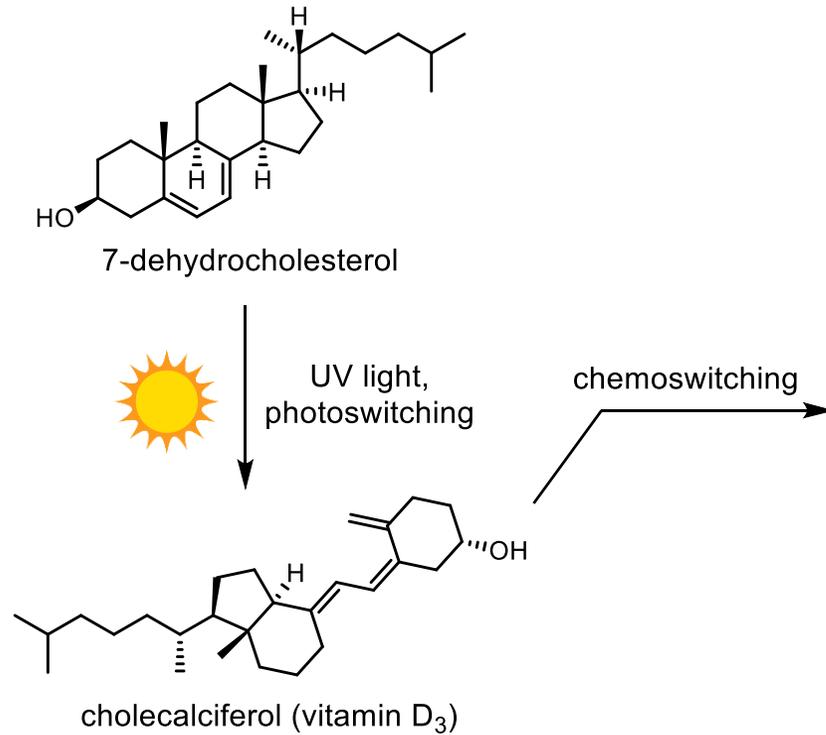


Tandem photo/chemo switches?

Pretty much everything past simple ON/OFF photoswitches is underdeveloped. The examples in this talk are at the cutting edge, but still crude compared to what we know is possible (i.e. in Nature).

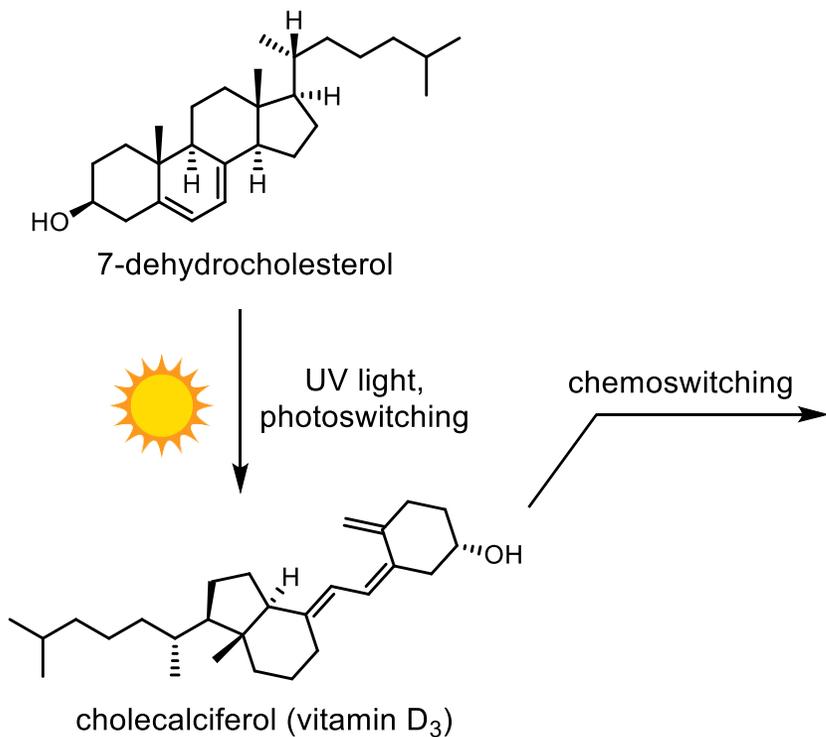
# Useful Reviews and an Inspiring Natural Tandem Photoswitch

Nature executes tandem photo/chemoswitching all the time. It is far from impossible!



# Useful Reviews and an Inspiring Natural Tandem Photoswitch

Nature executes tandem photo/chemoswitching all the time. It is far from impossible!



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Review

Directing Coupled Motion with Light: A Key Step Toward Machine-Like Function

Romain Costil,<sup>\*,†</sup> Mira Holzheimer,<sup>‡</sup> Stefano Crespi, Nadja A. Simeth, and Ben L. Feringa<sup>\*</sup>



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Photoswitchable catalysis using organometallic complexes

Cite this: *Catal. Sci. Technol.*, 2020, 10, 3122

Zoraida Freixa <sup>ab</sup>

FEATURE ARTICLE

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Photoswitchable catalysis based on the isomerisation of double bonds

Cite this: *Chem. Commun.*, 2019, 55, 6477

Ruth Dorel and Ben L. Feringa <sup>\*</sup>