Photoswitchable Catalysis

Casey Olen
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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:

Human chemist glucose combustion:

\[ \text{C}_6\text{H}_{12}\text{O}_6 \xrightarrow{\text{O}_2, 900^\circ\text{C}} \text{CO}_2 + \text{H}_2\text{O} \]

Nature's glucose combustion:

\[ \text{C}_6\text{H}_{12}\text{O}_6 \xrightarrow{\text{O}_2} \]

\[ \text{C}_6\text{H}_{12}\text{O}_6 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]
Photoswitchable Catalysis Compared to Other Photochemical Methods

**Photo(redox)catalysis:**

![Diagram of photo(redox)catalysis](image)

**Photocaged catalysis:**

![Diagram of photocaged catalysis](image)

**Photoswitchable catalysis:**

![Diagram of photoswitchable catalysis](image)

LAS = light-absorbing species
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:**

1% ON

Bad PSS for photoswitching:

40% OFF

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):

$k_{\text{light}} / k_{\text{dark}} = 3.3$

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):

\[
\text{cis/trans} = 50:50
\]

10-fold rate enhancement after irradiation at 366 nm:

\[
\frac{\Delta A (360 \text{ nm})}{\text{time / min}}
\]

Simple Photoswitching in Early Examples Based on $E/Z$ Isomerization

Inoue et al develop a photoswitchable stilbene system for CO$_2$ capture and show *in situ* photoswitchable control (1999):

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**Diagram:**

In *in situ* photoswitching:
- cis-stilbene only, dark
- trans-stilbene only, dark

Reaction does not proceed without additional $N$-coordination to the Al center

**Graph:**

- Yield of propylene carbonate in %
- Reaction Time in h
- Vis. irradiation
- UV irradiation
- dark

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Simple Photoswitching in MBH Reaction Based on $E/Z$ Isomerization

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

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

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

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.

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.

Bielawski et al. Organometallics. 2013, 32, 3121–3128
Bielawski et al also demonstrated *in situ* ON/OFF photoswitching using an NHC as an organocatalyst (2012):

\[
\text{cat} = \begin{array}{c}
\text{Ph} \\
\text{S} \\
\text{S} \\
\text{N} \\
\text{N} \\
\text{PF}_6
\end{array}
\]

Rate control in two different continuously irradiated reactions: 

*In situ* rate switching:

- UV
- Vis

**Proposed mechanism of catalyst deactivation:**

Photoswitching withdraws electron-density from C\(_2\), opening it up for attack by the alkoxide.
Photoswitchable substrate selectivity is underdeveloped compared to other research in this area.

**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

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

\[
\text{cat-H: } R = H \\
\text{cat-NO}_2: R = \text{NO}_2
\]

\(cis\text{-cat-NO}_2\) 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.
Development of a Zn-salicylaldimine 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):

\[
\text{OEt} \quad + \quad \text{PhH} \quad \xrightarrow{X \ (10 \text{ mol} \%) \ \text{irradiation} = Y} \quad \text{PhH} \quad + \quad \text{PhH}
\]

\[\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}\]

\(X = \text{open}, \ Y = \text{none}: \ 30\% \ \text{ee trans}, \ 50\% \ \text{ee cis}, \ 55:45 \ \text{dr}\)

\(X = \text{open}, \ Y = \text{PSS at 313 nm}: \ 11\% \ \text{ee trans}, \ 37\% \ \text{ee cis}, \ 70:30 \ \text{dr}\)

\(X = \text{closed}, \ Y = \text{none}: \ 5\% \ \text{ee trans}, \ 5\% \ \text{ee cis}, \ 63:37 \ \text{dr}\)

Only 23% \textbf{closed} in the PSS, attributed to strong stabilizing effect of chelation in the \textbf{open} form.

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

\((R)\)-ON

\((S)\)-ON

Photoswitching the sense of enantioinduction is \textit{much} harder than simply switching ON/OFF.

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:

\[
\text{MeO-SH} + \text{O} \xrightarrow{\text{2 (0.3 mol %) CD}_2\text{Cl}_2, -15^\circ\text{C}} \text{ArS} \text{-O} 
\]

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

Catalyst design strategy:

Red-shift step 1

\[
(P,P)\text{-trans-2} \quad 312 \text{ nm, } 20^\circ\text{C} \quad (99\%)
\]

Blue-shift step 2

\[
(M,M)\text{-trans-2} \\
(M,M)\text{-cis-2} \quad 312 \text{ nm, } -60^\circ\text{C} \quad (81\%) \\
(P,P)\text{-cis-2} \quad 70^\circ\text{C} \quad (76\%)
\]

First-Generation Molecular Motor for Catalytic Thiol Additions to Eneones

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

\[
\text{MeO} - \text{SH} + \text{C} = \text{C} \rightarrow \text{ArS}^* \\
\text{CD}_2\text{Cl}_2, -15^\circ\text{C}, 15\text{ h}
\]

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

Distal catalytic functionality renders **trans-2 ineffective**.

\(\text{Switch ON}\)  \(\text{Switch R/S}\)  \(\text{OFF}\)

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, leading to a mixture of diastereomers.

Testing switchable phosphines in Heck arylation:

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:

Poor photoswitchability with the Trost-type substitution, bad candidate for photoswitchable catalysis!

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:

Applying the ambidextrous ligand in a palladium catalyzed desymmetrization reaction:

Excellent enantioselectivity is demonstrated for both pseudo-enantiomeric forms of $L_2$.

In this case, $(P,P)$-trans-$L_2$ 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):**

**Bisphosphine molecular motor ligand (2015):**

Long spacer, low selectivity

Short spacer, ee > 86%

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.

Switching from the \((M,M)\) form to the \((P,P)\) form is feasible, but not reversible.

The Pd catalyst is unstable to prolonged UV irradiation.

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Second generation molecular motors with tricylic stator and asymmetric rotor:

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

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:

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

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

Conformers of Stable state (S):

Conformers of Metastable state (MS):

Atropisomerization processes of Stable (left) and Metastable states (right)

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:
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):

Blue-shift in 420 nm PSS indicates reverse photoswitch:

Good photoswitching from (R,P,S\textsubscript{a})-1 to pseudo-enantiomeric (R,M,R\textsubscript{a})-1

Not a great reverse photoswitch
In situ Photoswitchable enantioselective catalysis using the BINOL-derived second-generation molecular motor:

Light on/off Δee up to 113% (best case Δee = 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.

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

R = H, OH

Tuning dithienylethene-based ligands:

Investigated on a platinum complex

Reported photoswitchable differential binding for Ni and Zn porphyrin complexes:

Reported bimetallic complexes with photochromic properties:

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:

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:

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

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).
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!