Enantioselective Organocatalysis: A Valuable Strategy for Chemical Synthesis

The rapid growth of organocatalysis over the last 10 years was fueled by the development of a small number of generic activation modes

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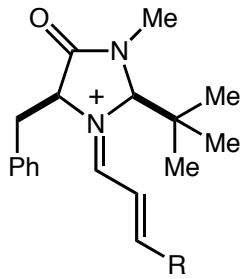
Organocatalysis ⟹ The rapid growth of organocatalysis over the last 10 years was fueled by the development of a small number of generic activation modes

Iminium catalysis Im



~50 new reactions

with Jorgensen, K. A.

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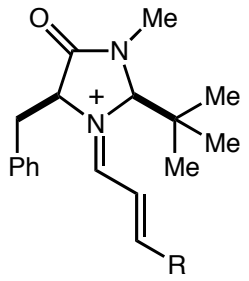

~50 new reactions

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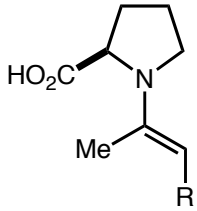
Enamine catalysis (En)



~20 new reactions

Hajos-Wiechert

⇒ Barbas-List

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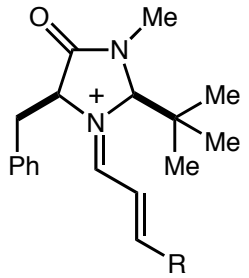

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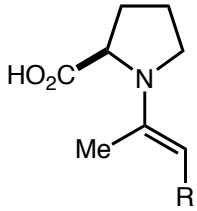

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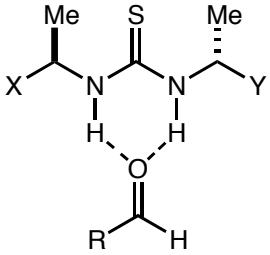
H-bond catalysis (H^+)



~30 new reactions

Jacobsen–Akiyama

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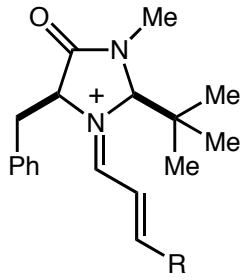

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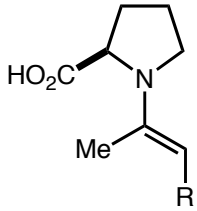

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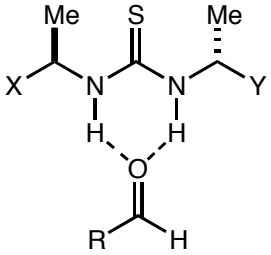

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Jacobsen–Akiyama

■ Last 10 years, organocatalysis has delivered many new asymmetric transforms (~150-200)

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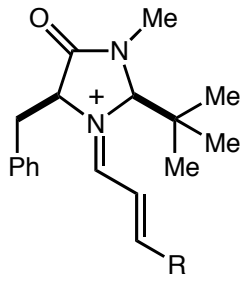

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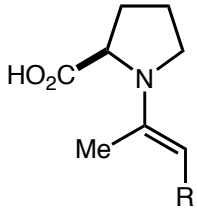

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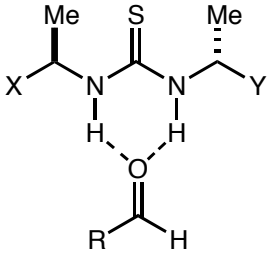

~30 new reactions

Jacobsen–Akiyama

- Last 10 years, organocatalysis has delivered many new asymmetric transforms (~150-200)
  - These 3 activation modes cover a large portion of the organocatalysis landscape

Organometallic Catalysis: Few Activation Concepts ⇨ *Many Powerful Reactions*

σ-bond insertion
C–C bond coupling

Suzuki
Negishi
Stille
Kumada
Fu

σ-bond insertion
C–N, S, O coupling

Buchwald
Hartwig

π-bond insertion

Noyori
Toste
Heck
Feringa
Krische

Lewis acid catalysis

Yates
Corey
Evans
Shibasaki
Mukaiyama

Olefin metathesis

Grubbs
Schrock
Hoveyda
Furstner

Atom transfer catalysis

Sharpless
Jacobsen
Shi
Doyle

■ Relatively few activation modes have resulted in literally thousands of new chemical reactions

Relatively Few Catalysis Activation Concepts ⟹ *Many Powerful Reactions*

Instead of focusing completely on the invention of individual catalytic reactions

using long-established activation modes

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Why don't we focus on the invention of new, useful catalytic activation modes?

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Design of an entirely new catalyst activation mode is extremely challenging

Relatively Few Catalysis Activation Concepts ⇨ *Many Powerful Reactions*

Instead of focusing completely on the invention of individual catalytic reactions using long-established activation modes

Why don't we focus on the invention of new, useful catalytic activation modes?

⇩

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OrganoSOMO catalysis

Photoredox organocatalysis

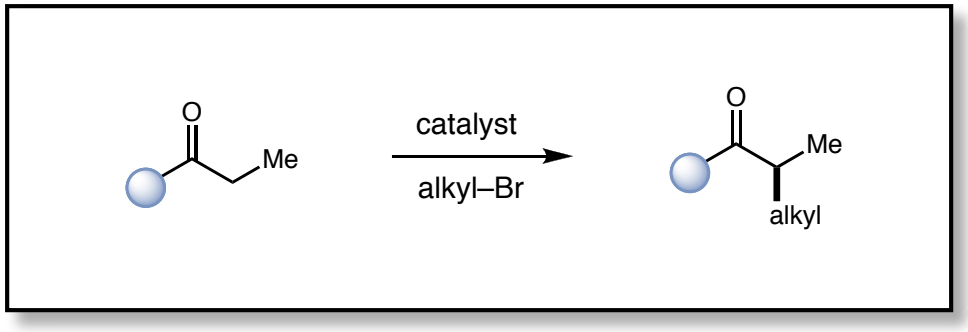
■ Two new modes of catalyst activation using organocatalysts

Relatively Few Catalysis Activation Concepts ⇨ *Many Powerful Reactions*

Photoredox organocatalysis

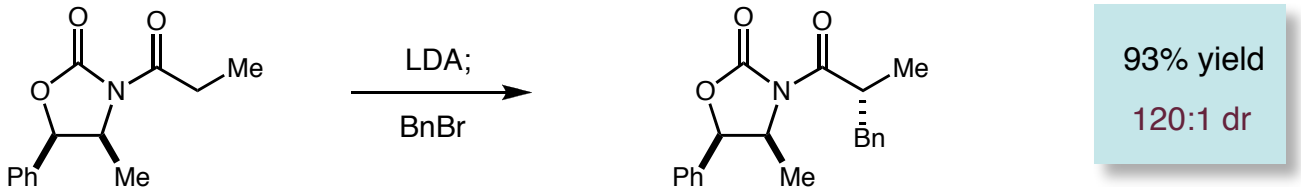
■ A new mode of organocatalytic activation

Holy Grails in Asymmetric Catalysis: Asymmetric α-Carbonyl Alyklation



Holy Grails in Asymmetric Catalysis: Enolate Alyklation

■ Chiral Auxiliary Controlled 1982, Evans, Meyers



93% yield

120:1 dr

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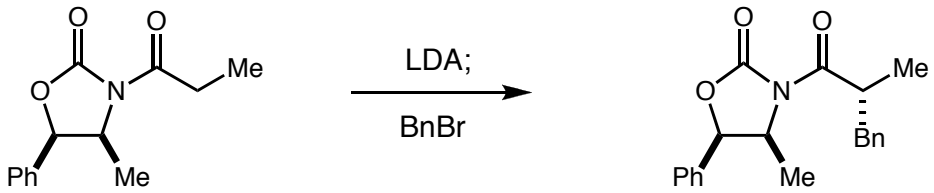

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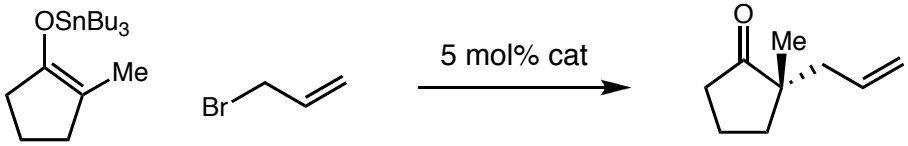
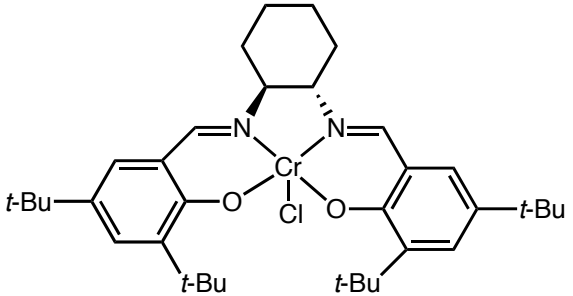
■ Catalytic Ketone Variant: Abby Doyle, Eric Jacobsen



84% yield

94% ee



salen catalyst

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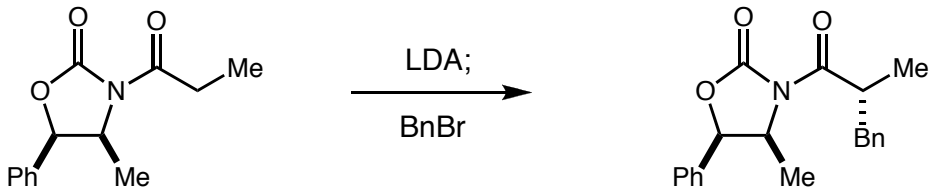

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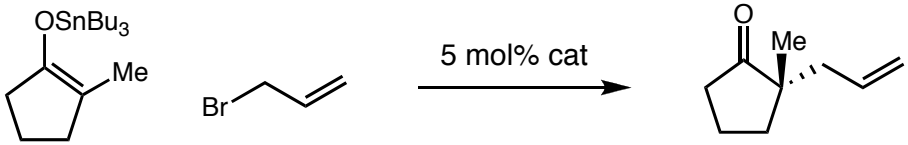

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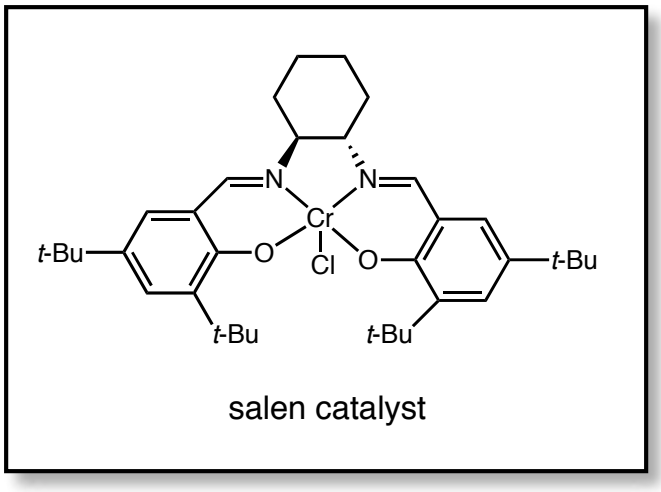


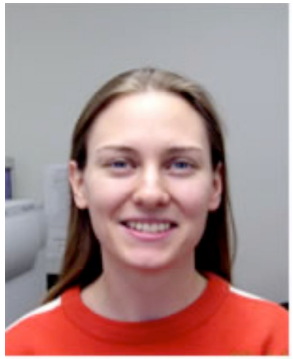
salen catalyst

■ **O'Donnell, Corey and Maruoka: glycine imine alkylation via PTC (seminal contributions)**

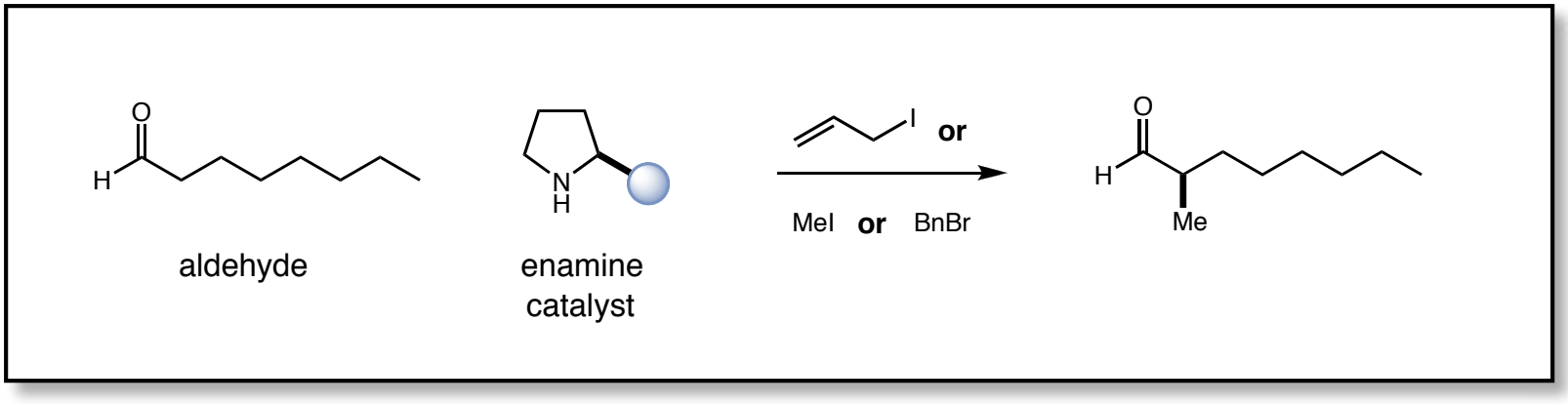
■ **Fu has also introduced an elegant enantioselective alkyl-halide alkylation reaction**

Can we use Enamine Catalysis to Solve Asymmetric Catalytic Carbonyl Alkylation

- **Teresa Beeson: 3rd Year Graduate Student**



- Initial idea: to perform asymmetric alkylation on aldehydes



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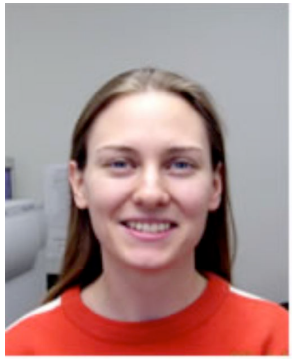

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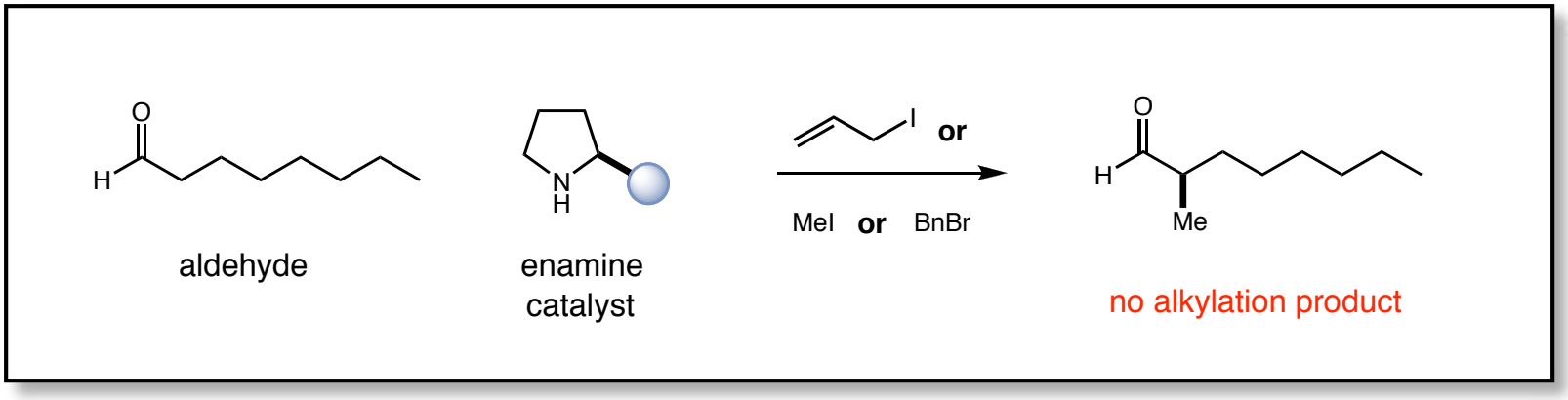
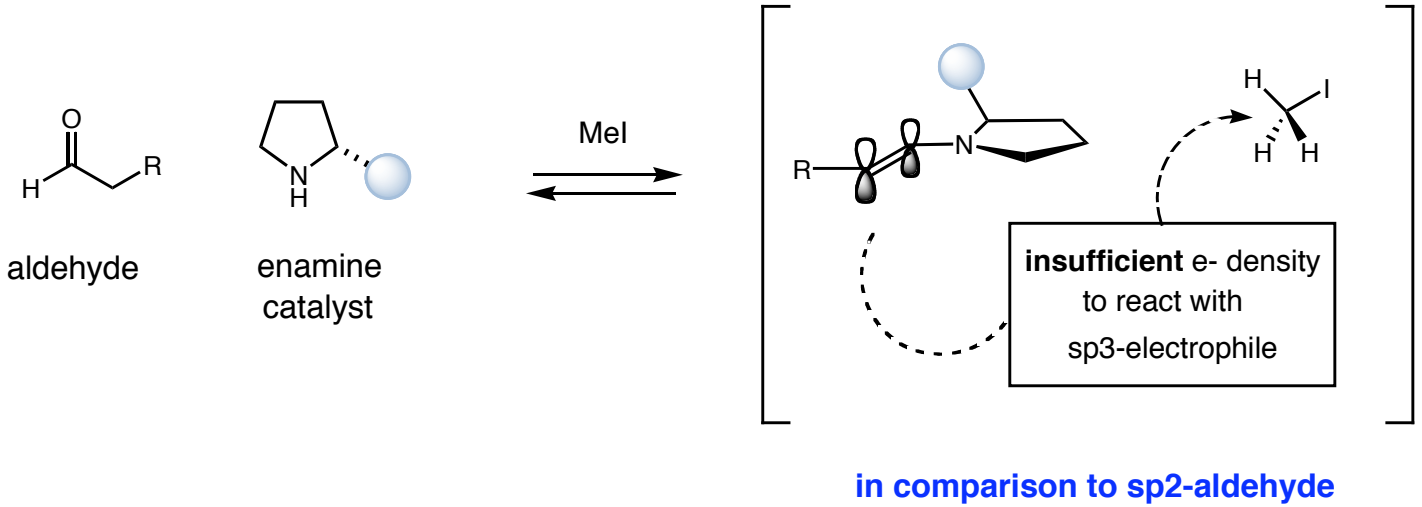


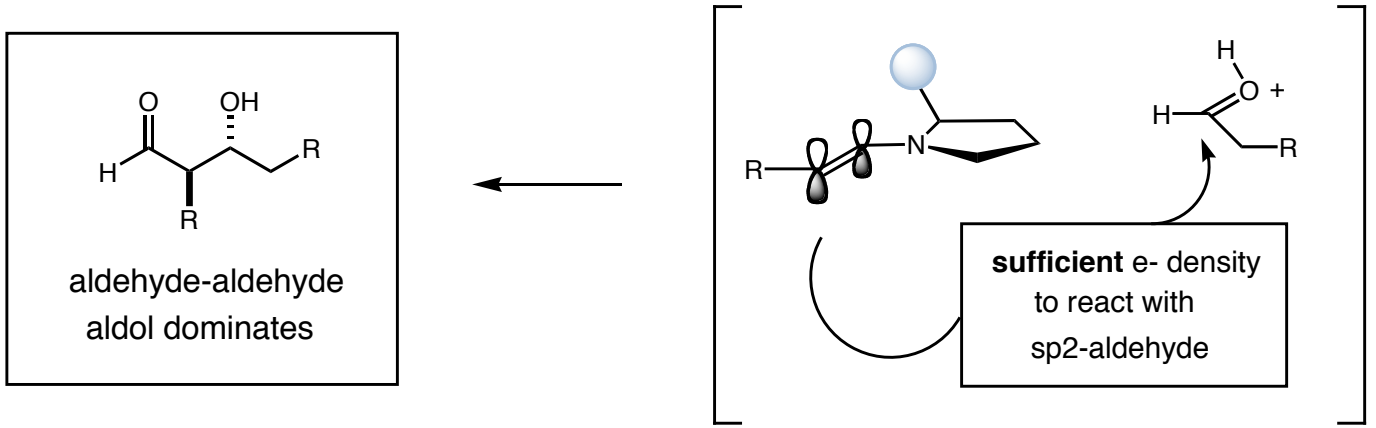
- Only products of aldehyde self dimerization were observed

Inherent Problems for Enamine Catalysis and Asymmetric Catalytic Alkylation

■ **Potential Issues for Enantioselective Alkylation using Enamine Catalysis**

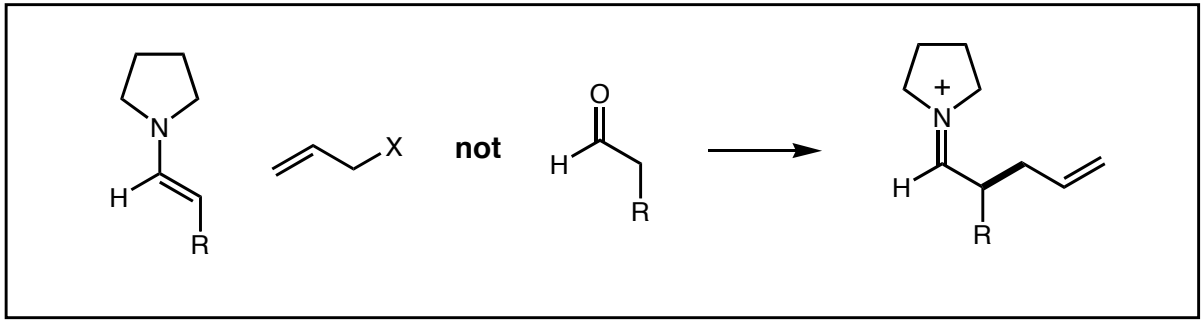


in comparison to sp2-aldehyde



■ **Intramolecular aldehyde alkylation can be accomplished (List and coworkers)**

Designing a New Organocatalytic Catalysis Concept: SOMO Catalysis



Trying to force a reaction to work within the confines
of a known catalysis concept or activation mode
(square peg, round hole)

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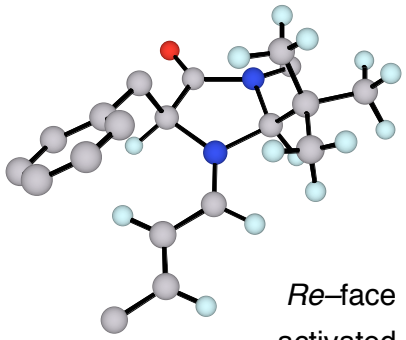
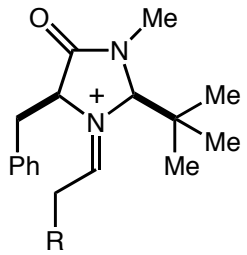


Re–face
activated

|||

iminium catalysis

LUMO–activation



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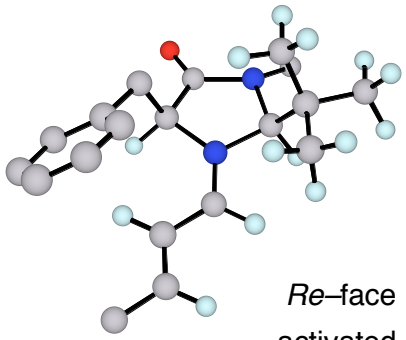

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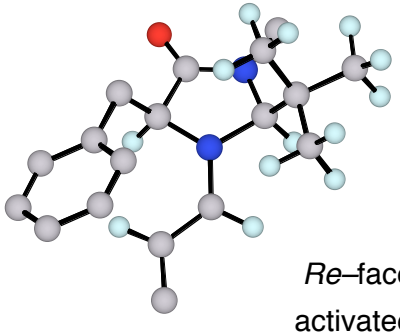

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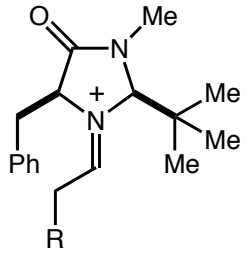
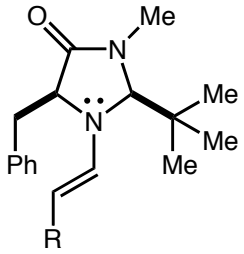


enamine catalysis

HOMO–activation



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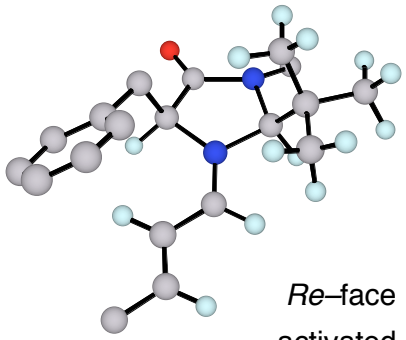

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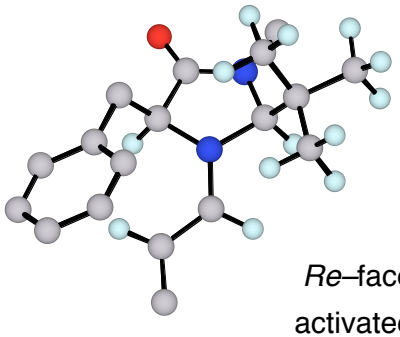

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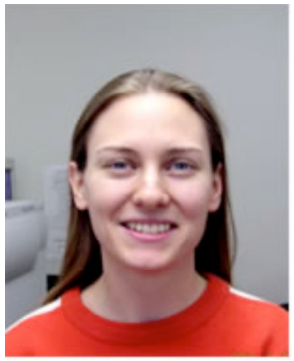

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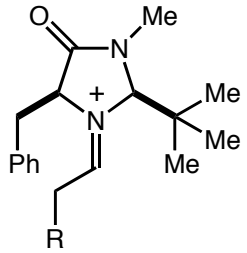

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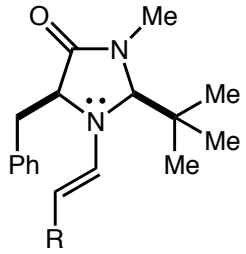

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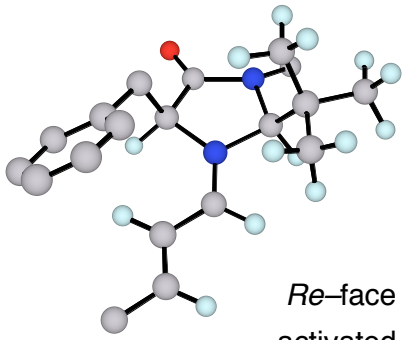

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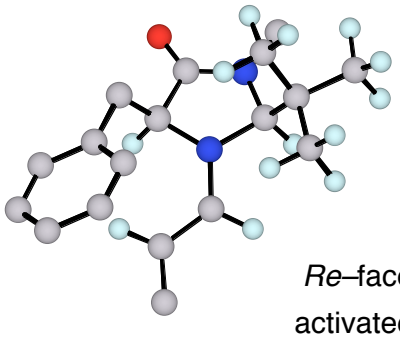

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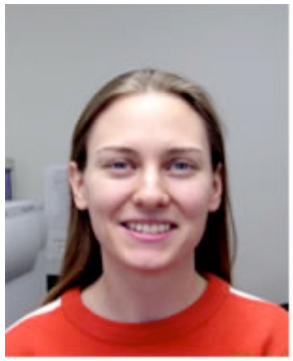

iminium catalysis

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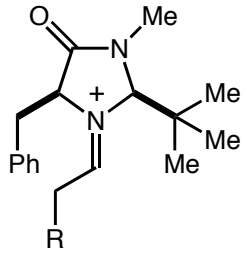
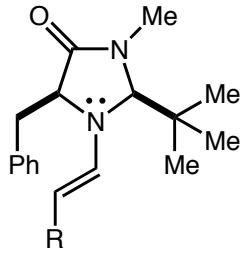


+2 e⁻

enamine catalysis

HOMO–activation



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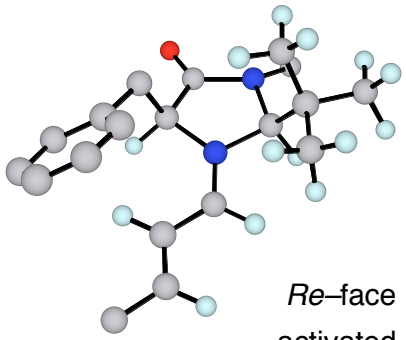

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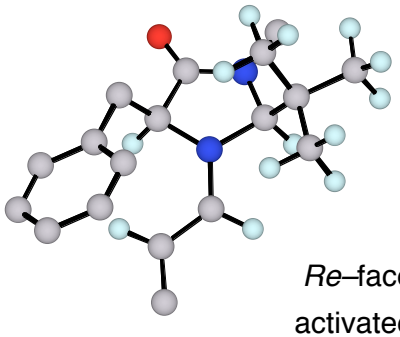

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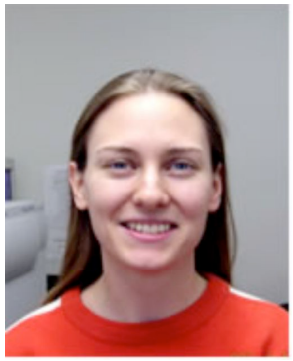

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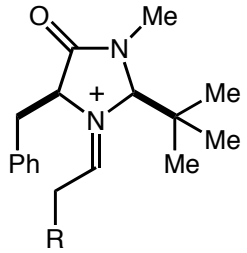

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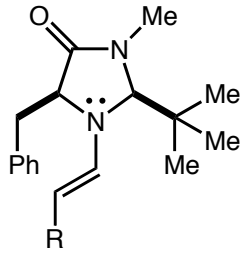
enamine catalysis

HOMO–activation

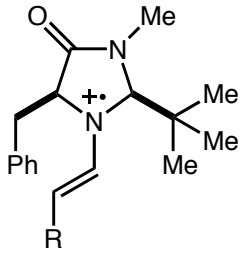


–1 e⁻

[oxid]

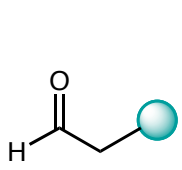
somo catalysis

SOMO–activation

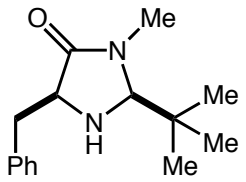


- Can we utilize the one electron species that lies between iminium and enamine catalysis

SOMO Catalysis: Potential Utility of New Catalysis Platform

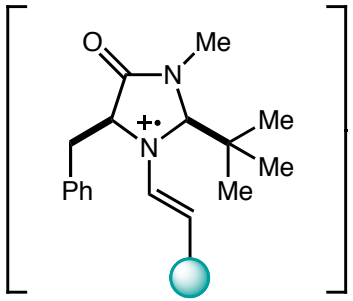


substrate



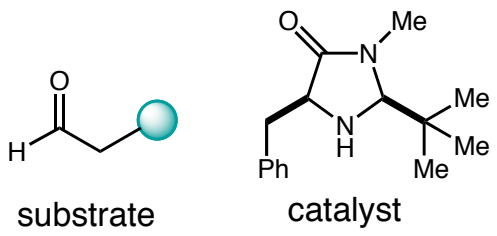
catalyst

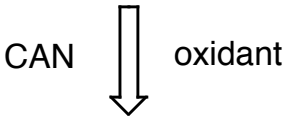
CAN ⇩ oxidant

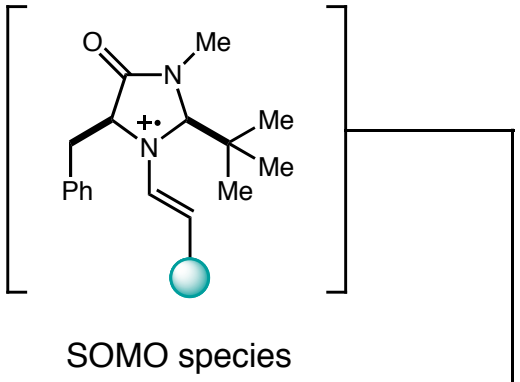


SOMO species

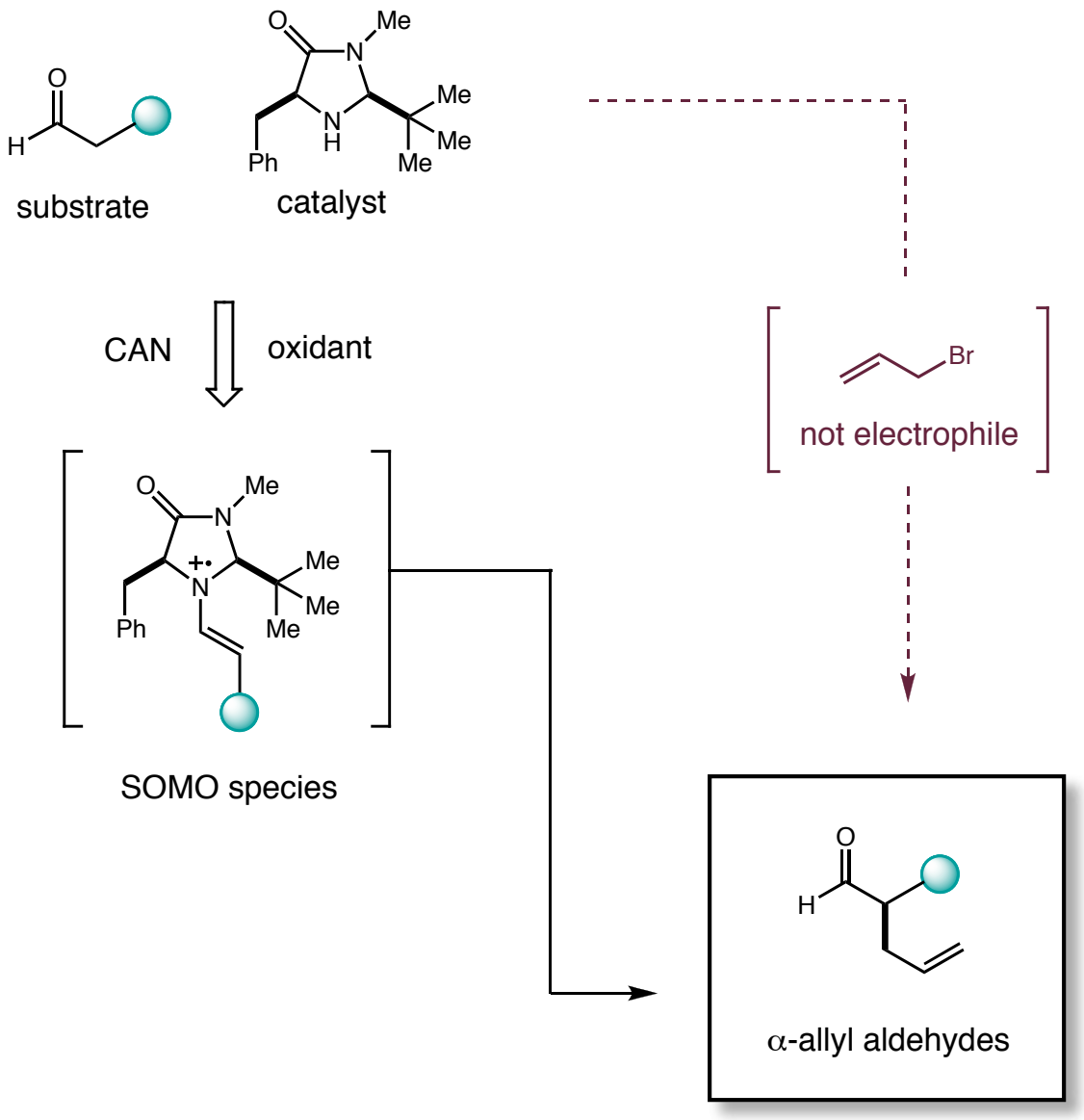
SOMO Catalysis: Potential Utility of New Catalysis Platform



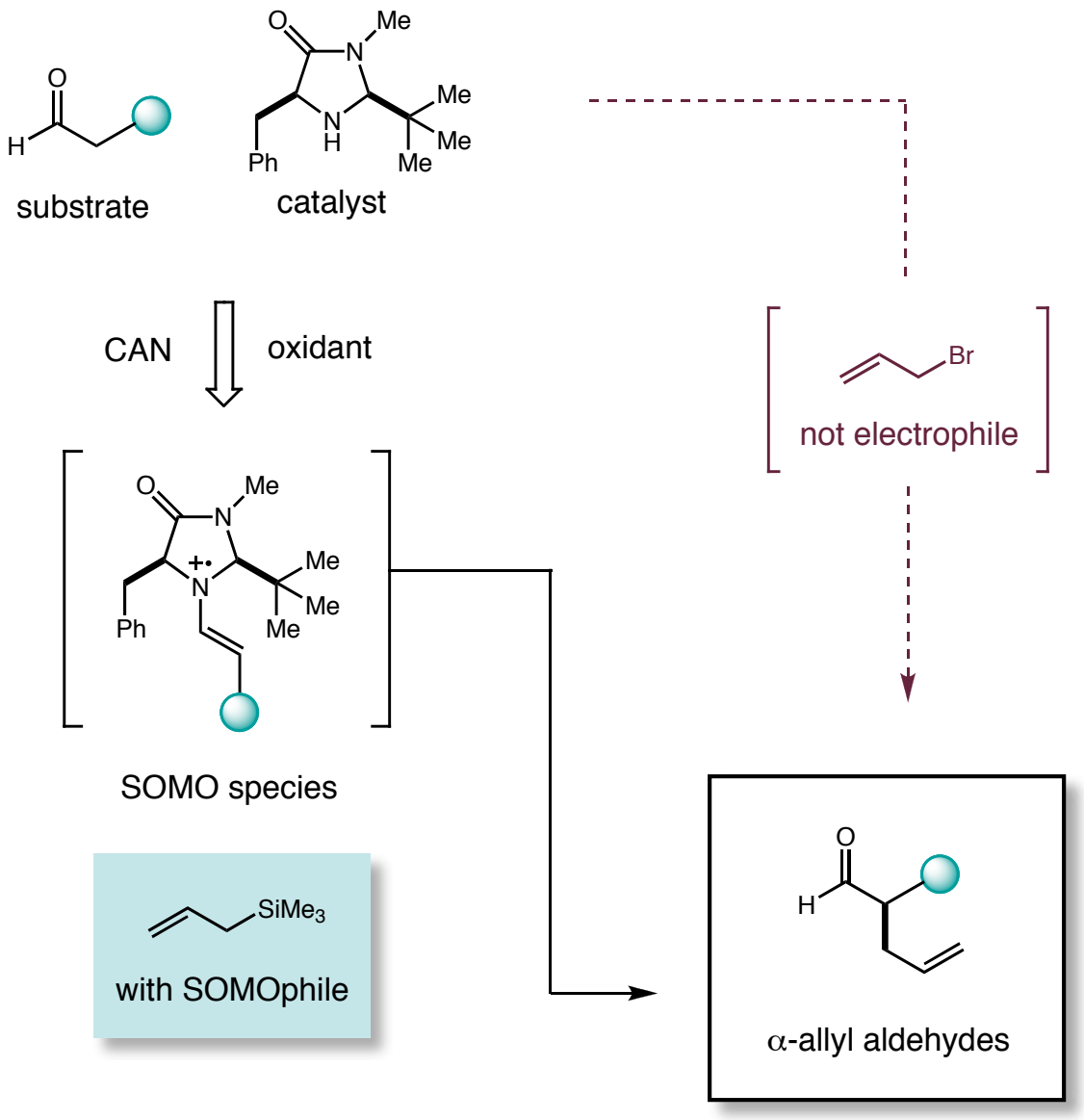




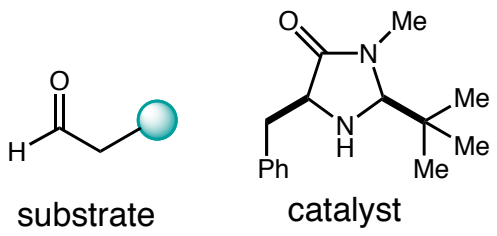
SOMO Catalysis: Potential Utility of New Catalysis Platform

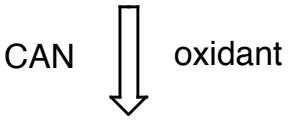


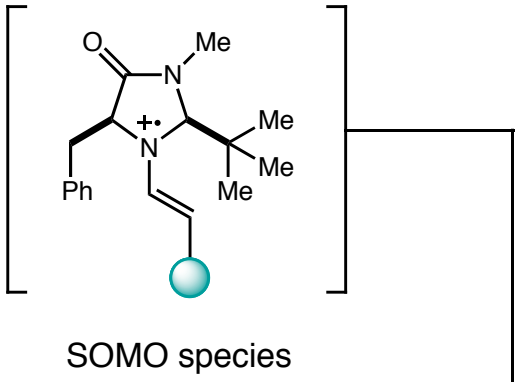
SOMO Catalysis: Potential Utility of New Catalysis Platform



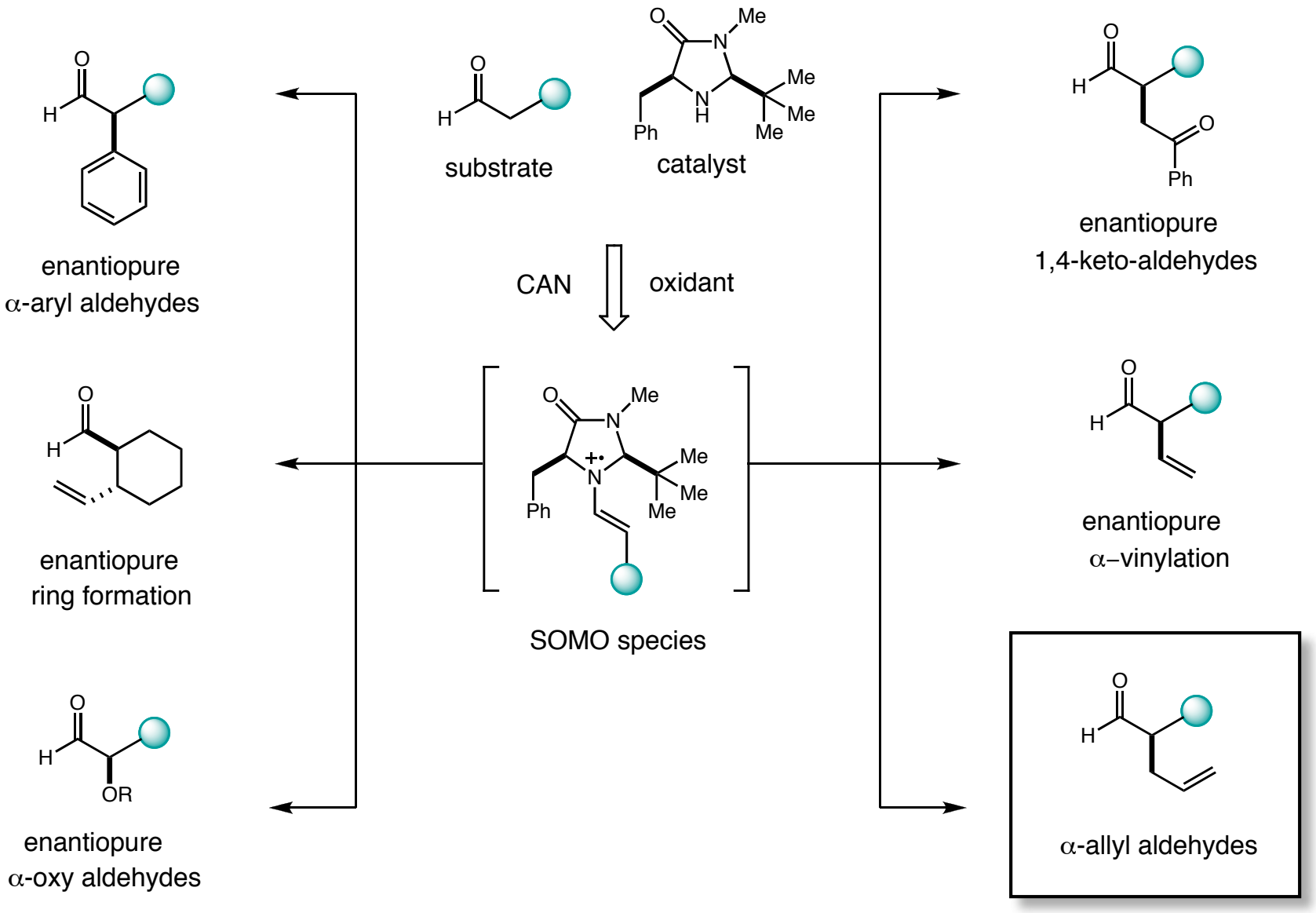
SOMO Catalysis: Potential Utility of New Catalysis Platform





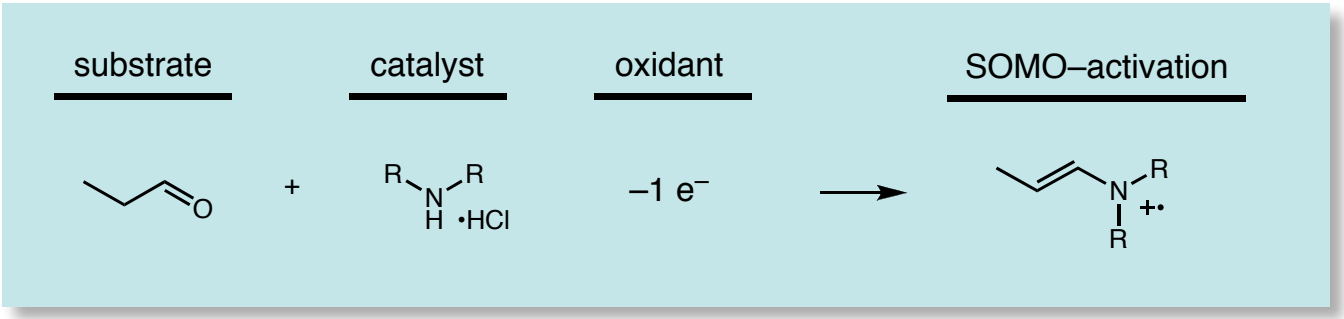


SOMO Catalysis: Potential Utility of New Catalysis Platform



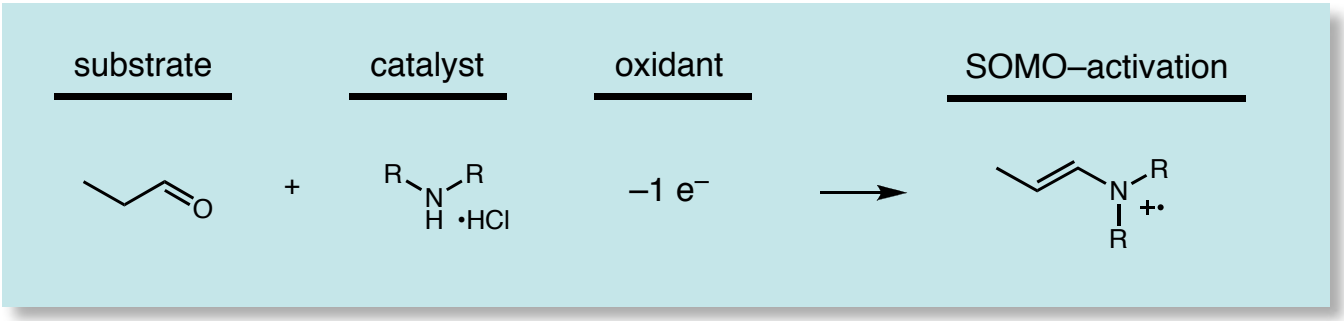
Designing a New Organocatalytic Catalysis Concept: SOMO Catalysis

- SOMO catalysis concept

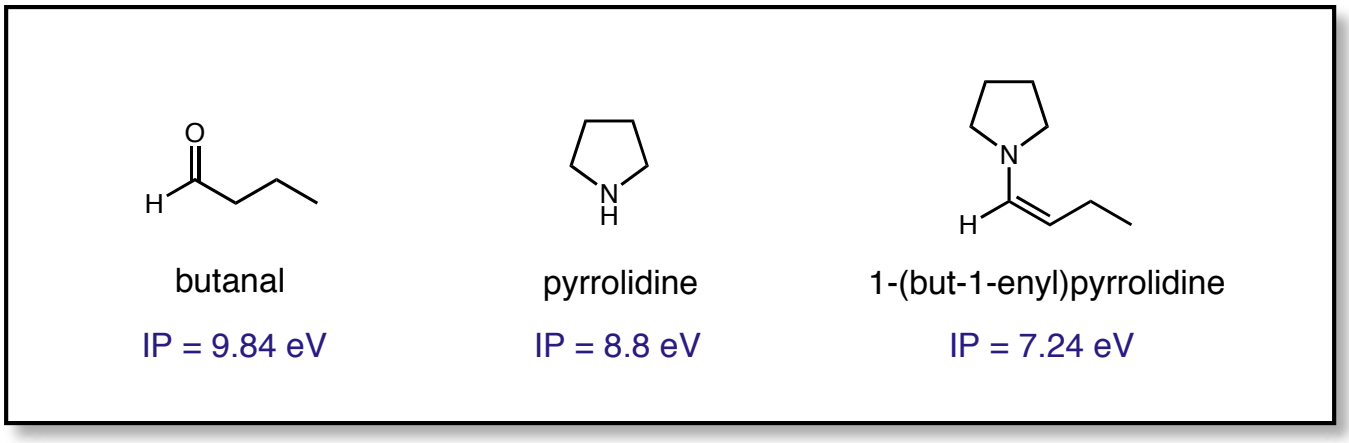


Designing a New Organocatalytic Catalysis Concept: SOMO Catalysis

- SOMO catalysis concept



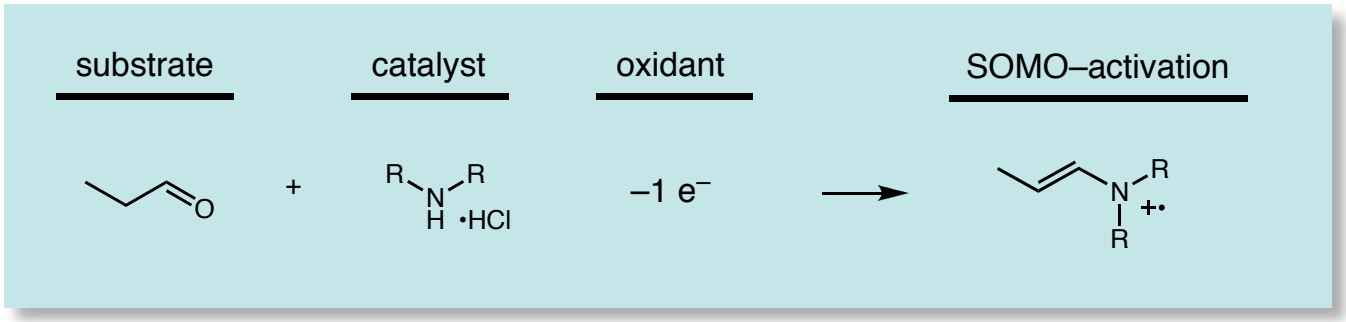
- Why will there be selective oxidation: oxidation potentials



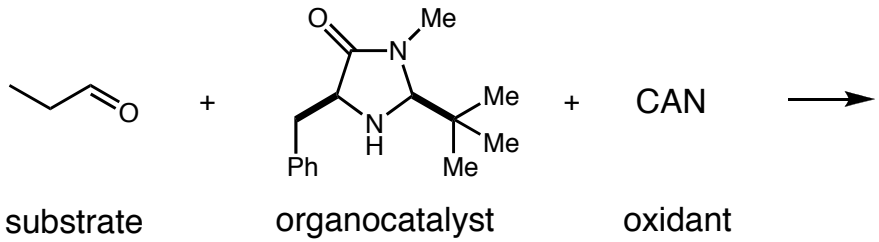
- Oxidant should selectively reract with transient enamine to generate radical iminium cation

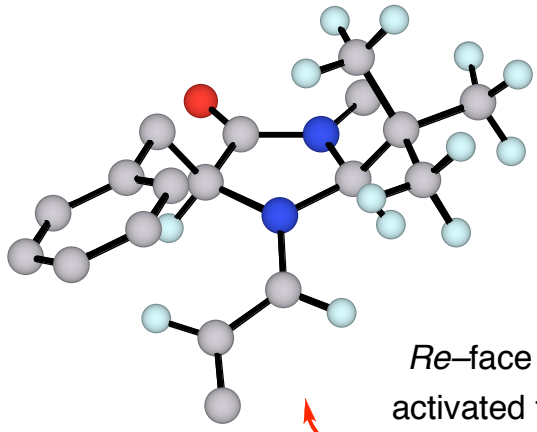
Designing a New Organocatalytic Catalysis Concept: SOMO Catalysis

- SOMO catalysis concept



- Requirements for enantioselectivity:
- Iminium geometry control
- α-carbon radical geometry control

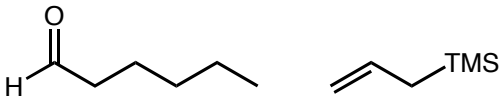




Re–face activated to SOMO nucleophiles

- Could this be a third general platform of induction for the imidazolidinone catalyst family

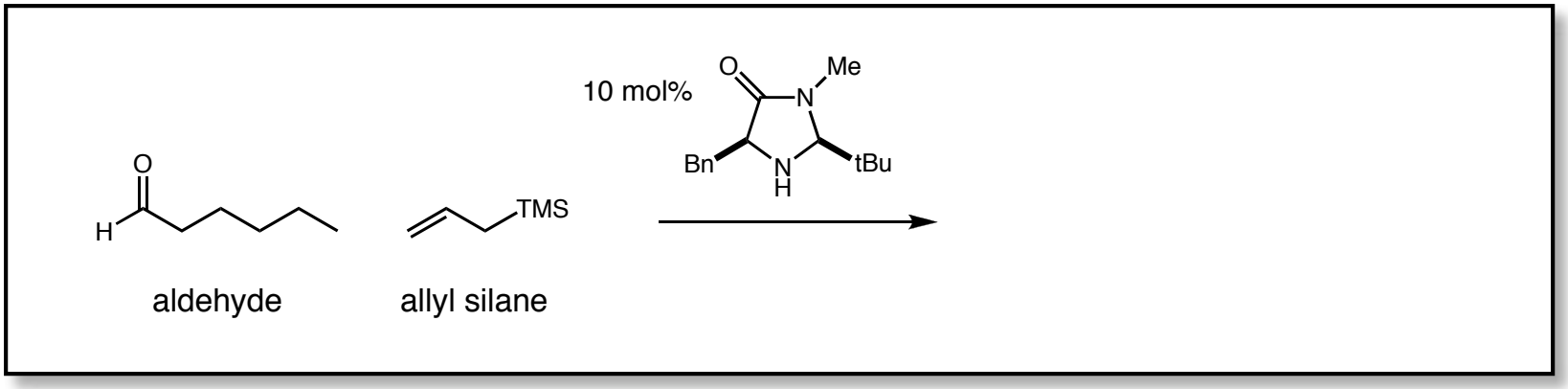
Studies to determine the utility of SOMO catalysis for aldehyde alkylation



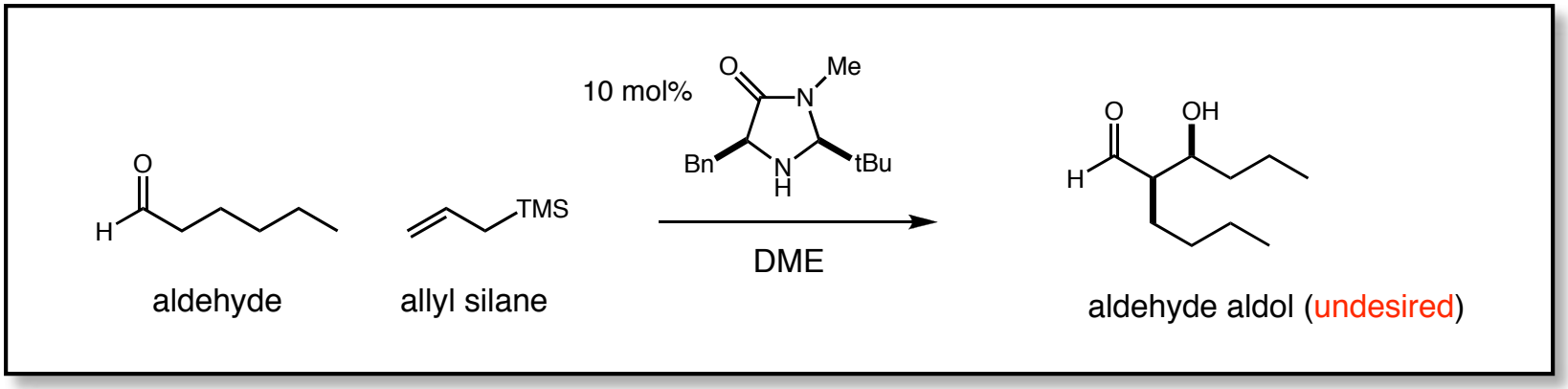
aldehyde

allyl silane

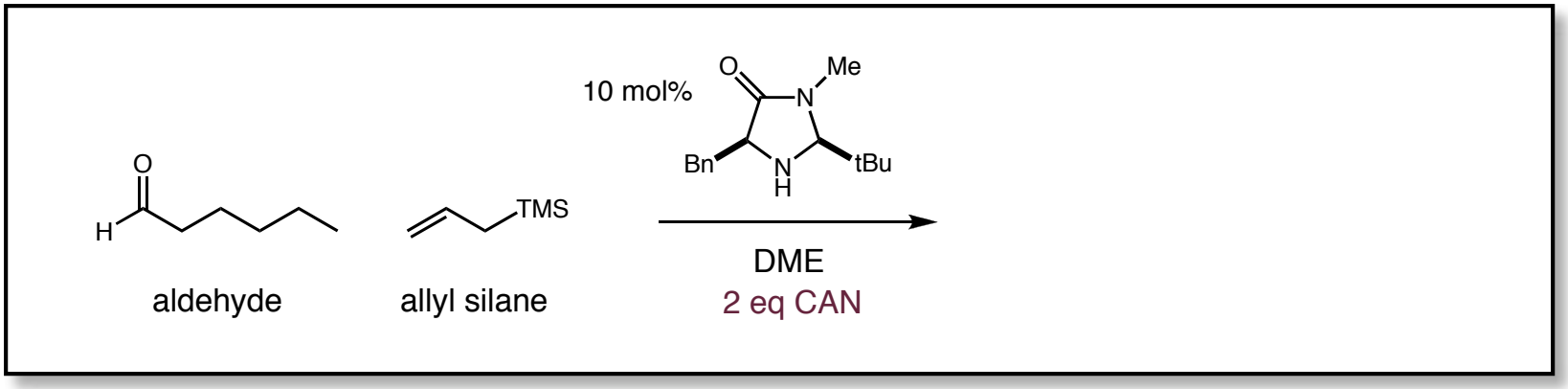
Studies to determine the utility of SOMO catalysis for aldehyde alkylation



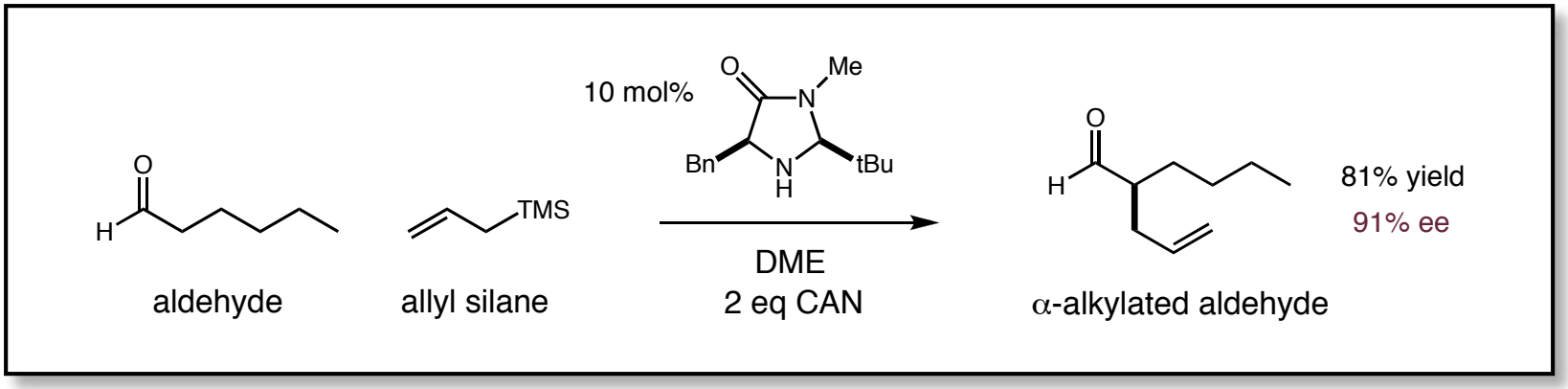
Studies to determine the utility of SOMO catalysis for aldehyde alkylation



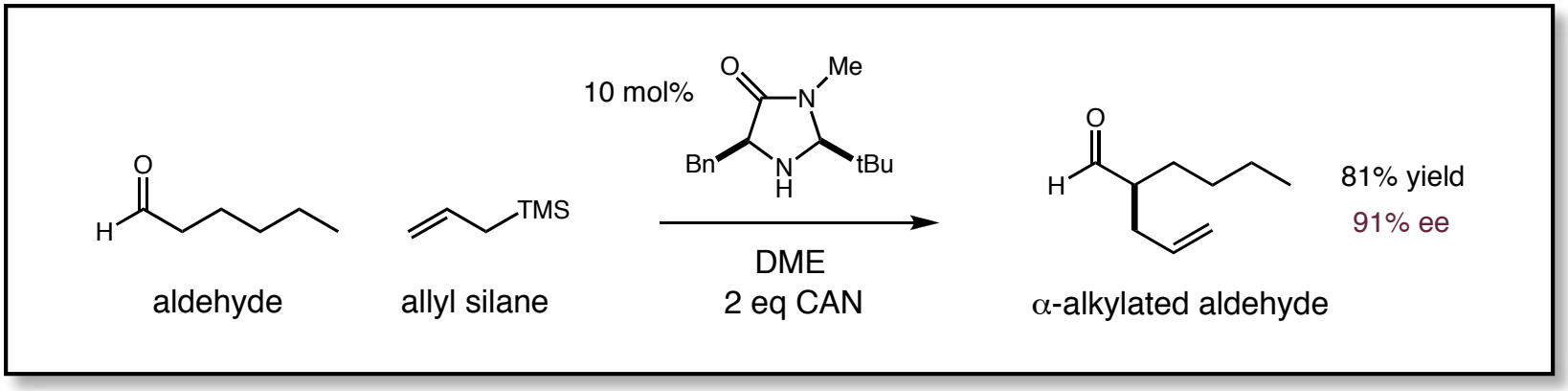
Studies to determine the utility of SOMO catalysis for aldehyde alkylation



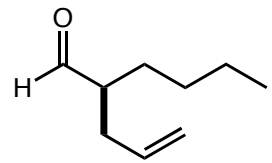
Studies to determine the utility of SOMO catalysis for aldehyde alkylation

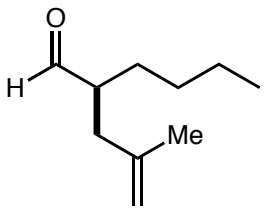


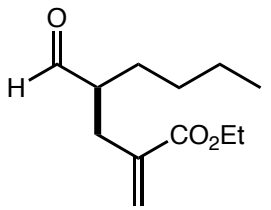
Studies to determine the utility of SOMO catalysis for aldehyde alkylation

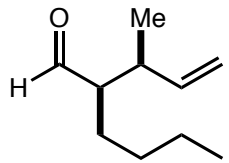


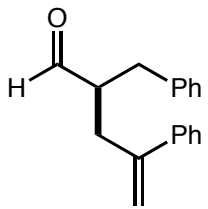
■ Varying the allylsilane and the aldehyde component

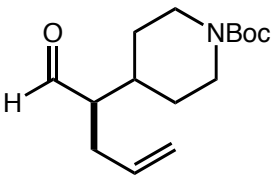

81% yield
91% ee


88% yield
91% ee


81% yield
90% ee


58% yield
94% ee

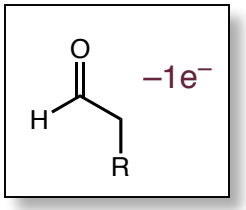

87% yield
90% ee

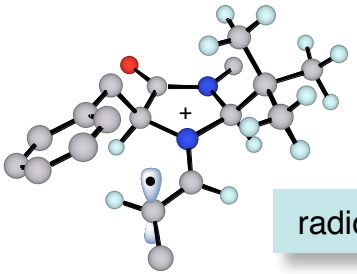

70% yield
93% ee

with Beeson, Masstrachio, Hong, Ashton, *Science*, **2007**, *316*, 582

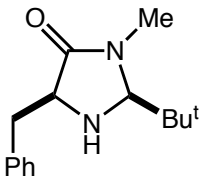
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

- OrganoSOMO Aldehyde Alkylation





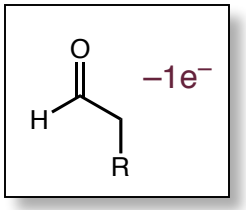
radical-cation ?

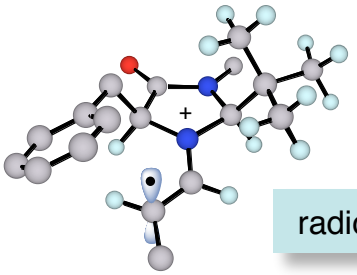


cat A

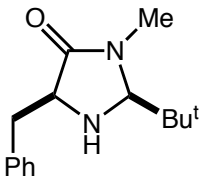
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation



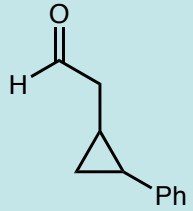


radical-cation ?



cat A

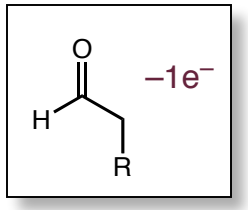
■ Mechanistic Evidence for radical cation

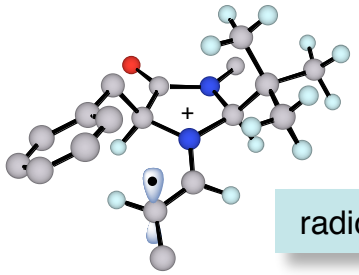


radical-clock substrate
used to detect
SOMO catalysis versus
enamine catalysis

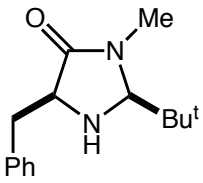
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation



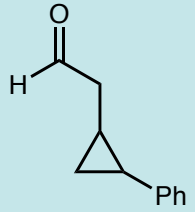


radical-cation ?

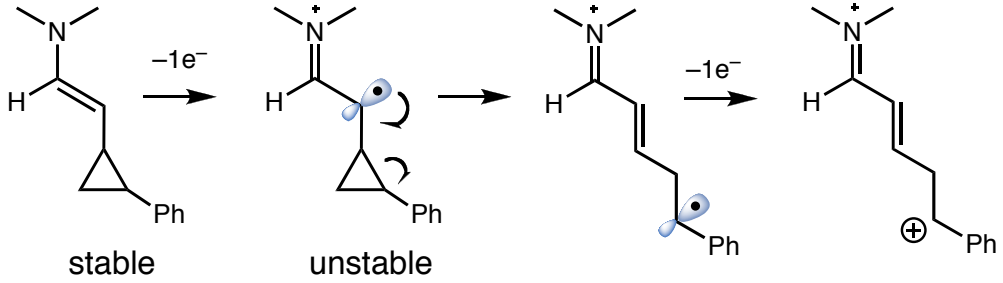


cat A

■ Mechanistic Evidence for radical cation



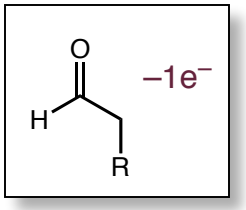
radical-clock substrate used to detect SOMO catalysis versus enamine catalysis

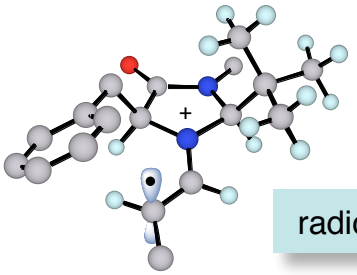


stable unstable

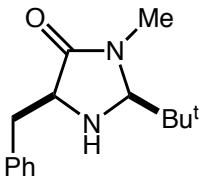
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation





radical-cation ?



cat A

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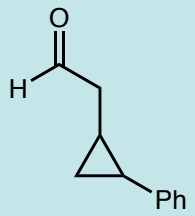
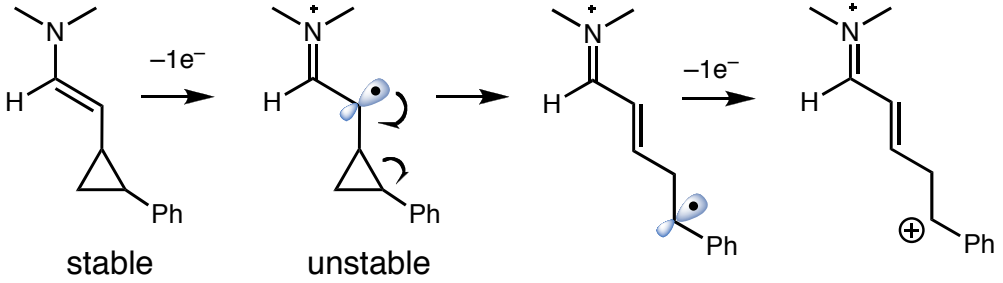
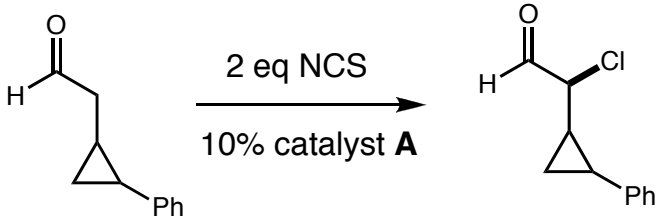


radical-clock substrate used to detect SOMO catalysis versus enamine catalysis



stable unstable

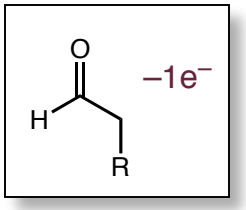
■ Enamine catalysis

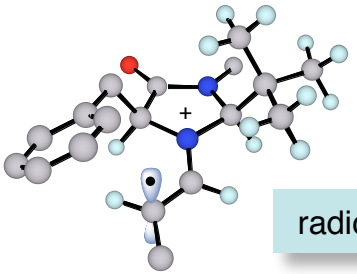


82 %

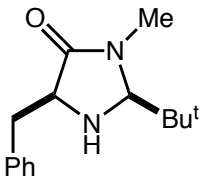
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation



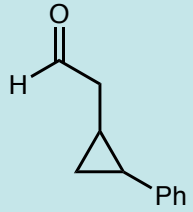


radical-cation ?

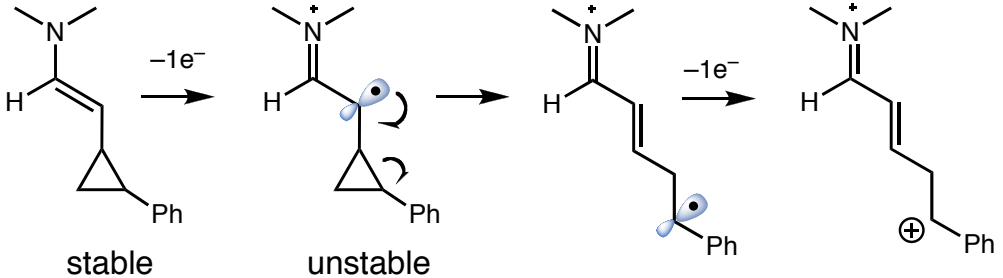


cat A

■ Mechanistic Evidence for radical cation

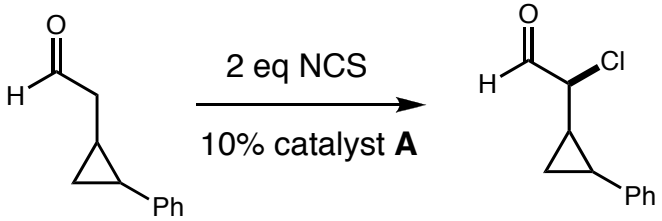


radical-clock substrate used to detect SOMO catalysis versus enamine catalysis



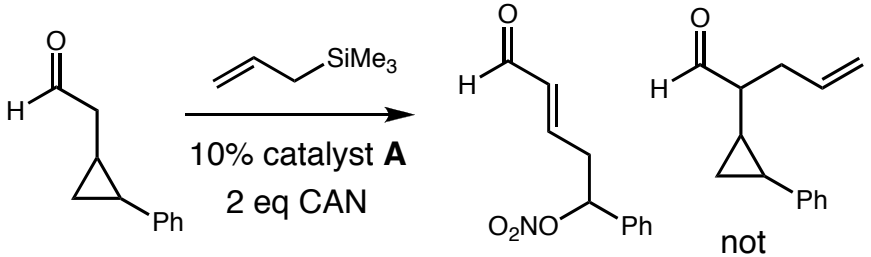
stable unstable

■ Enamine catalysis



82 %

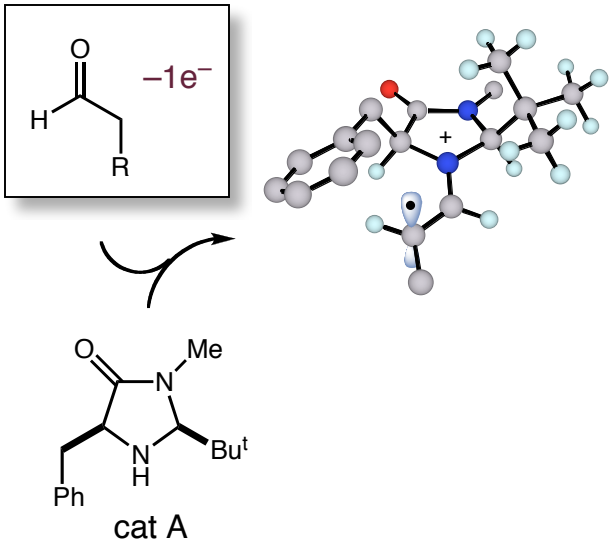
■ SOMO catalysis



68 % not observed

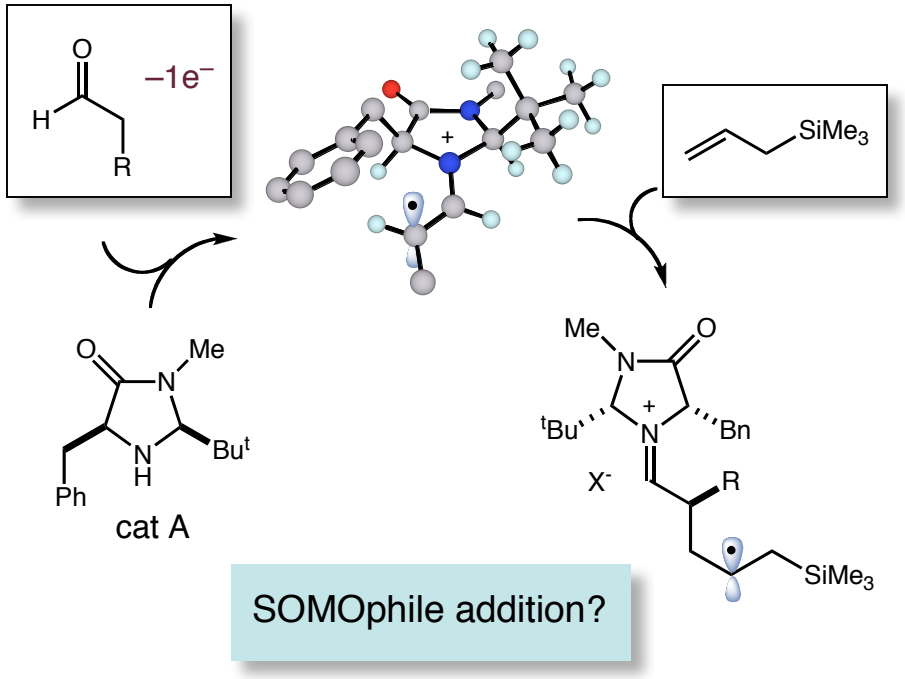
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

- OrganoSOMO Aldehyde Alkylation



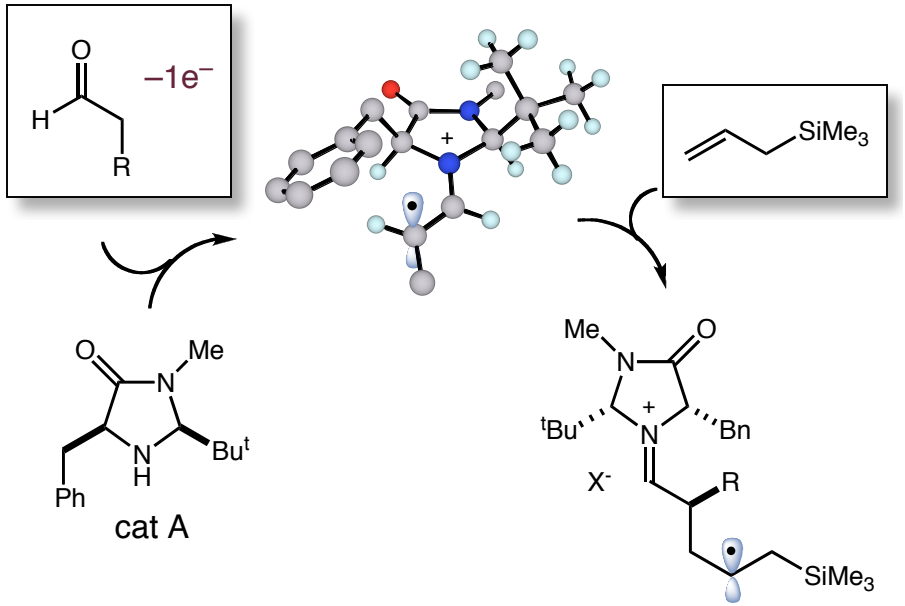
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation

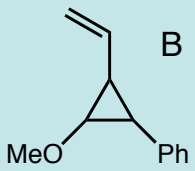


Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation



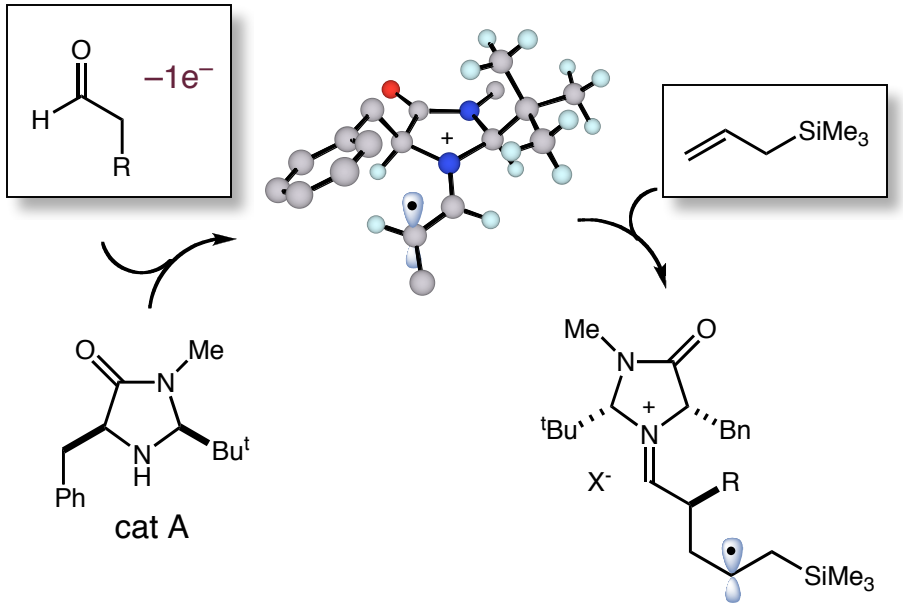
■ Newcombe radical vs cation discrimination



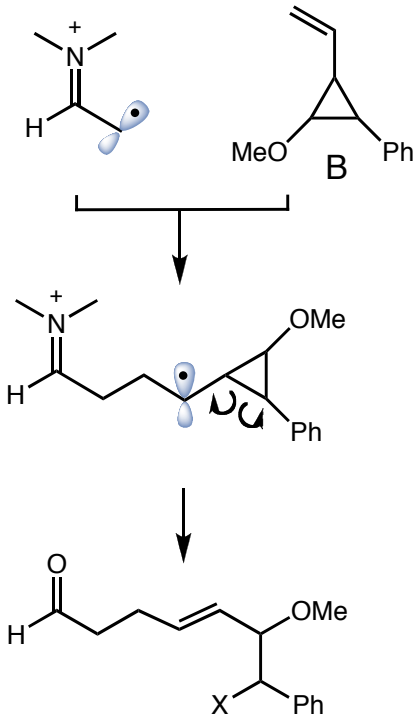
Newcombe: to detect
$2e^-$ π-addition pathway
versus
$1e^-$ SOMOphile addition

Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

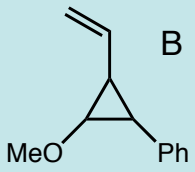
■ OrganoSOMO Aldehyde Alkylation



■ Test for SOMOphile



■ Newcombe radical vs cation discrimination



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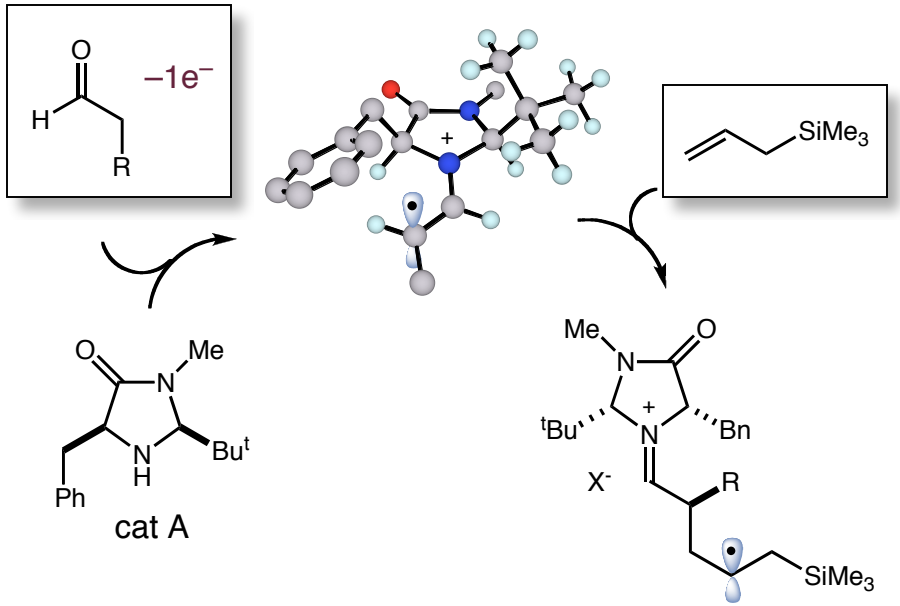
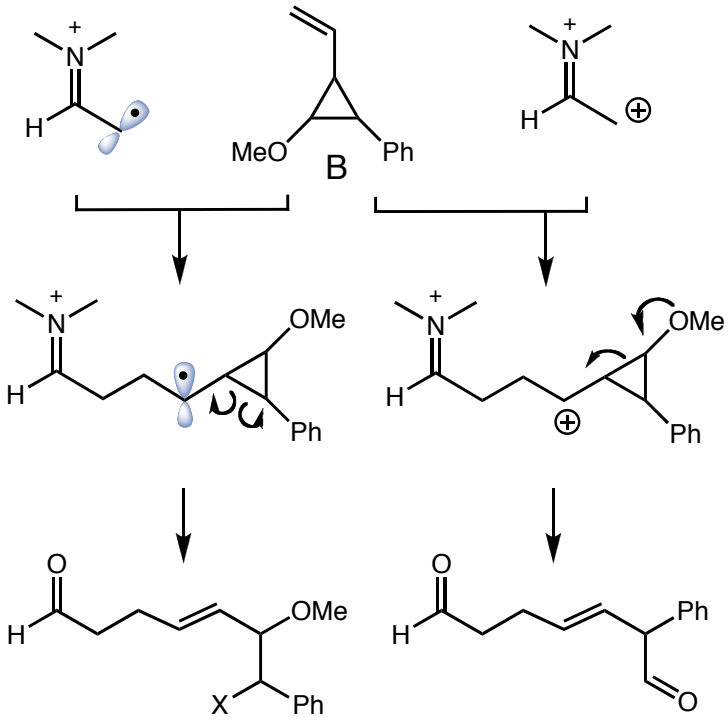
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

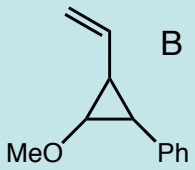
■ OrganoSOMO Aldehyde Alkylation



■ Test for SOMOphile



■ Newcombe radical vs cation discrimination



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$2e^-$ π-addition pathway
versus
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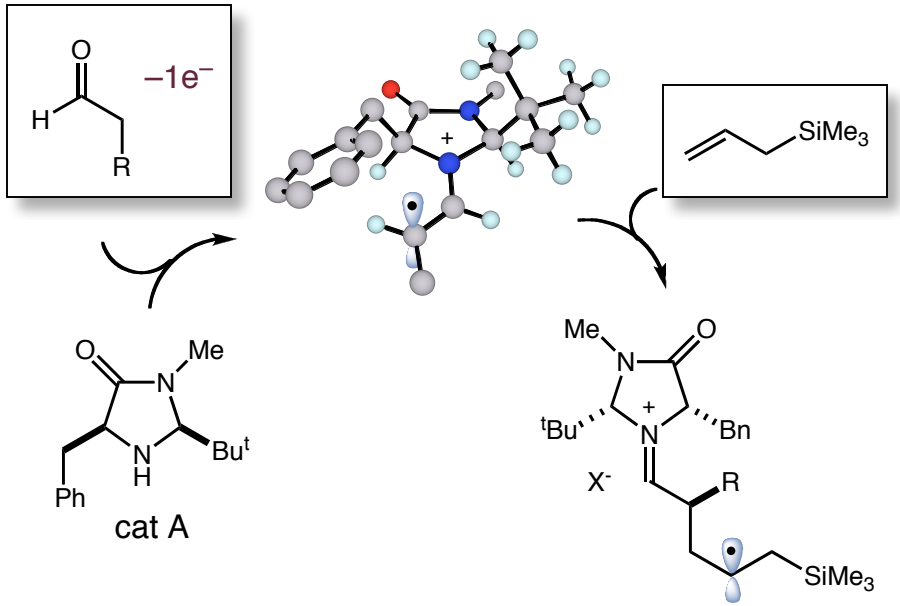
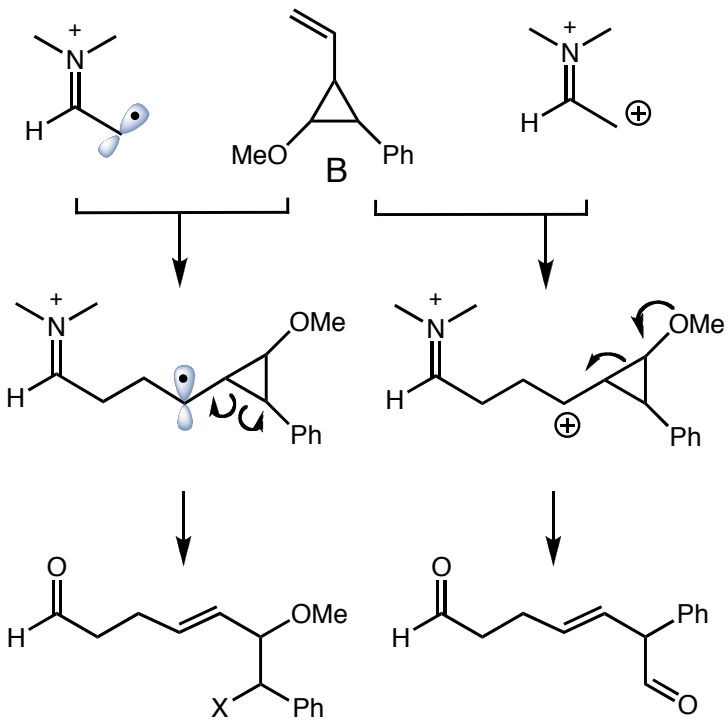
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

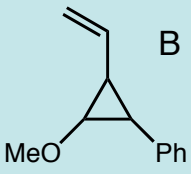
■ OrganoSOMO Aldehyde Alkylation



■ Test for SOMOphile



■ Newcombe radical vs cation discrimination



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versus
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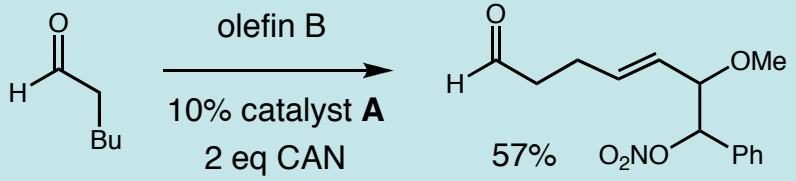
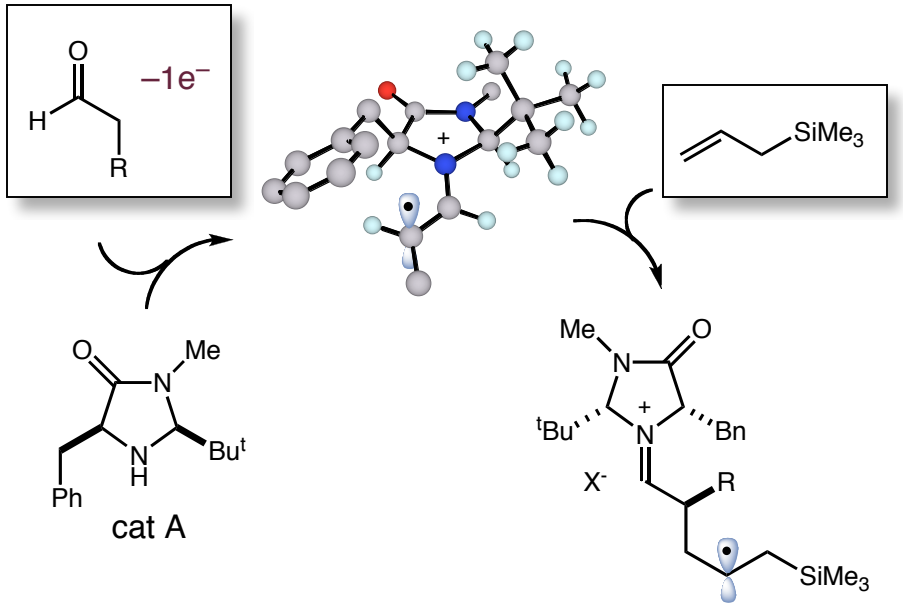


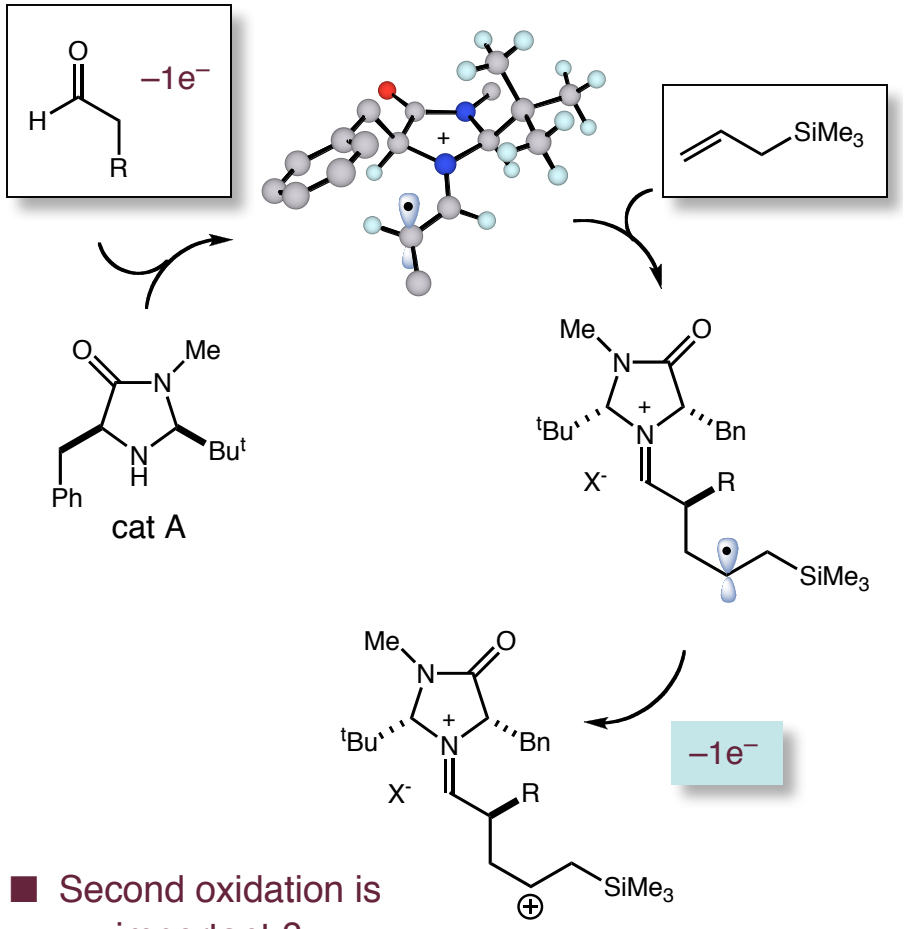
Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation



Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

- OrganoSOMO Aldehyde Alkylation

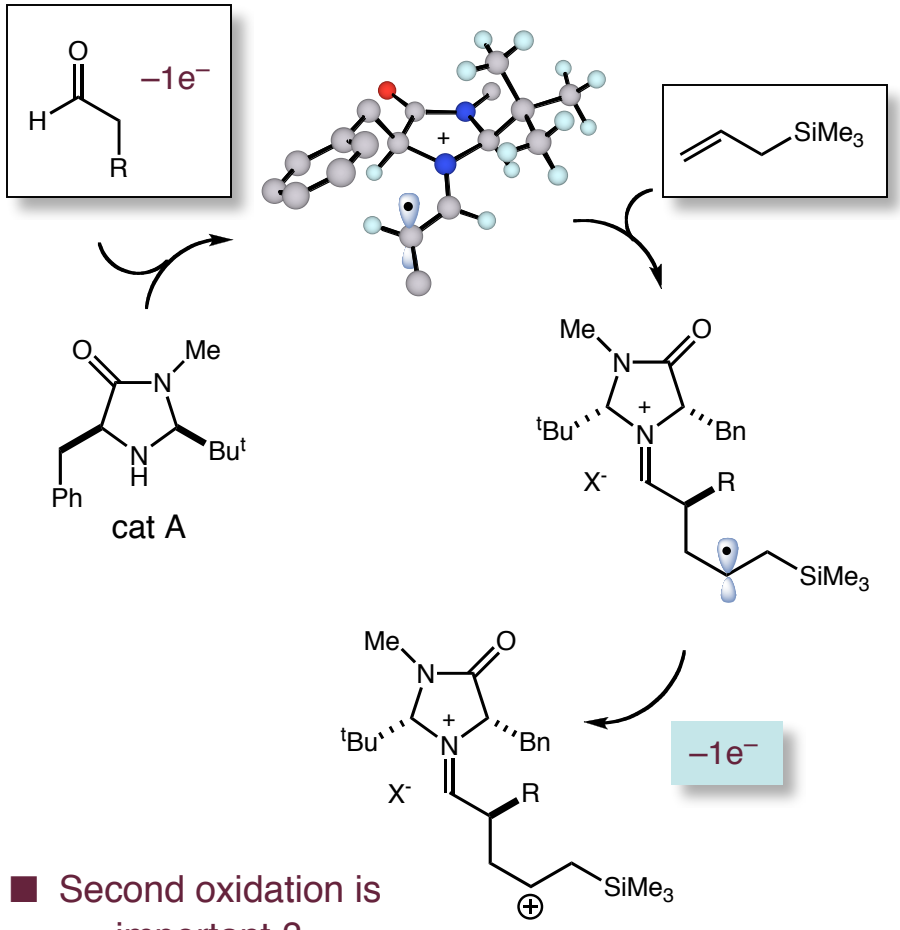


- Second oxidation is important ?

- This catalytic cycle would require 2 oxidation events

Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

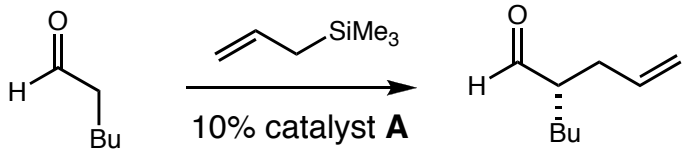
■ OrganoSOMO Aldehyde Alkylation



■ Second oxidation is important ?

■ This catalytic cycle would require 2 oxidation events

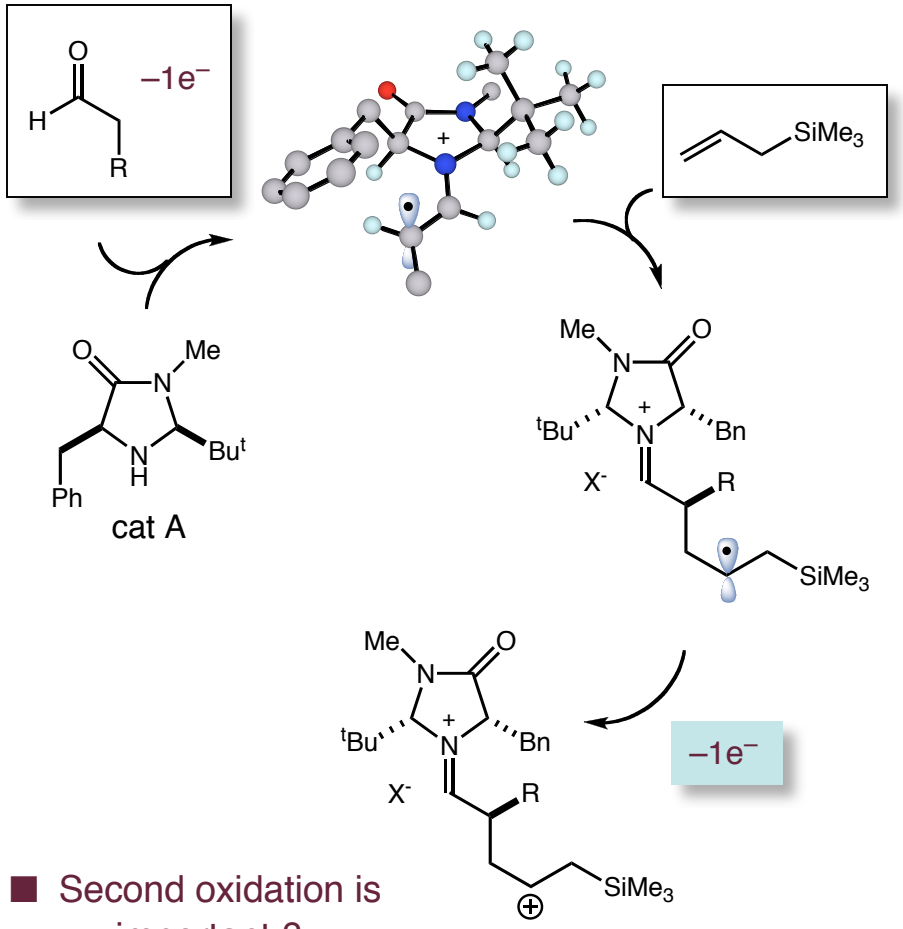
■ Test for second oxidation



X eq CAN	% Yield
1.0	37%
1.5	61%
2.0	88%
3.0	87%

Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation



■ Second oxidation is important ?

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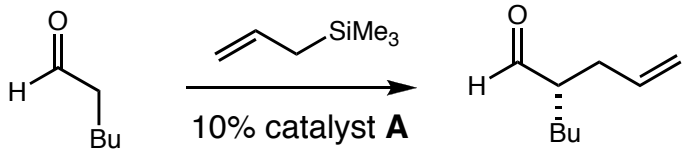
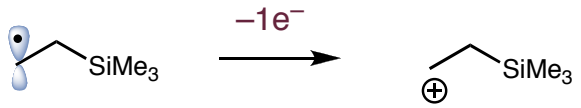
■ Test for second oxidation



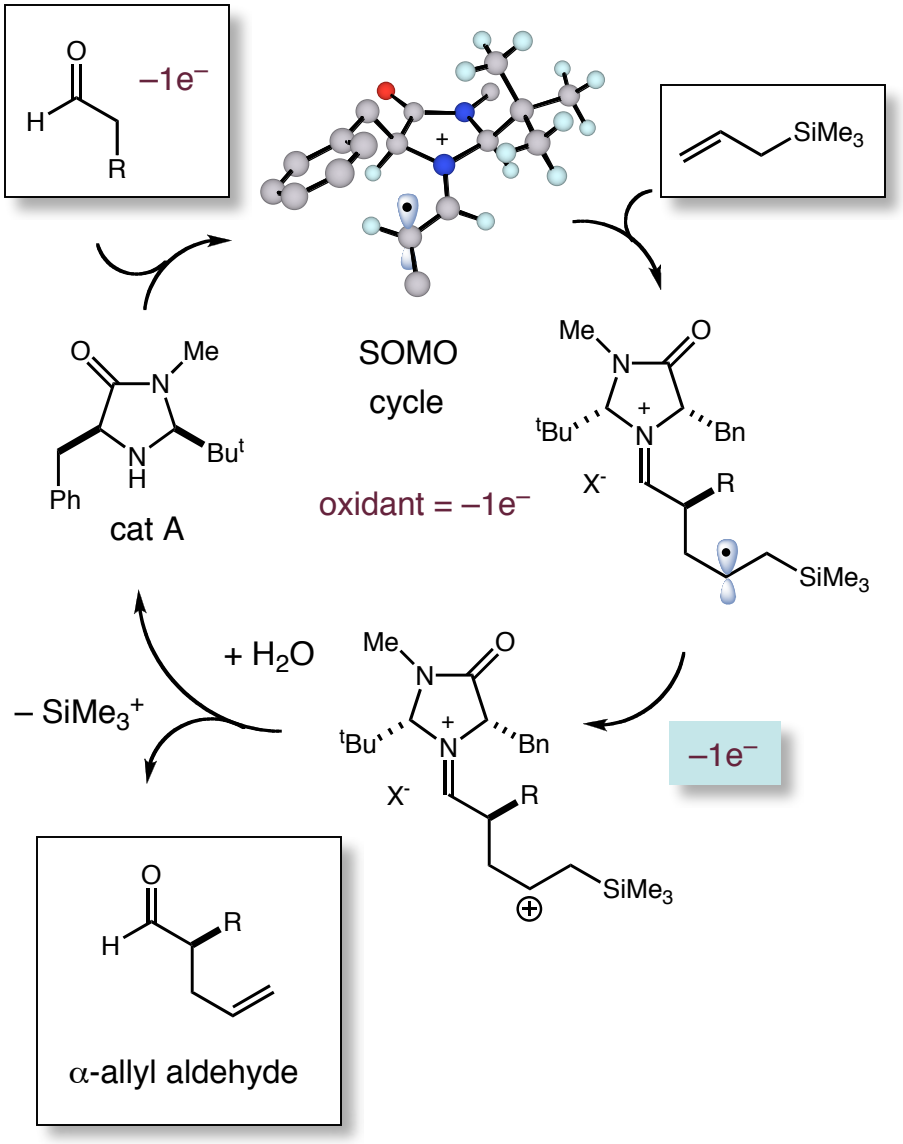
X eq CAN	% Yield
1.0	37%
1.5	61%
2.0	88%
3.0	87%

■ β-silyl radical readily oxidized



Enantioselective OrganoSOMO Catalysis: Possible Catalytic Cycle

■ OrganoSOMO Aldehyde Alkylation

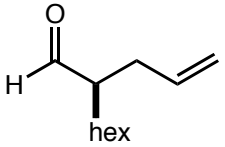


SOMO activation strategy is useful for a variety of organocatalytic reactions

Aldehyde α-allylation

Science **2007**, *316*, 582

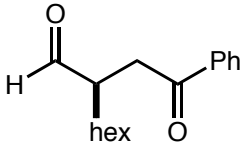
ACIE **2010**, asap (Flowers)



91% ee

Aldehyde α-enolation

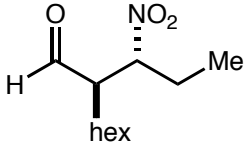
JACS **2007**, *129*, 7004



90% ee

β-Nitro-α-alkyl aldehyde

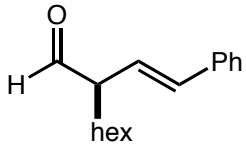
JACS **2009**, *131,* 11332



91% ee

Aldehyde α-vinylation

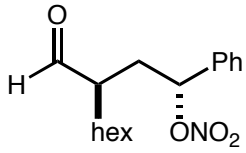
JACS **2008**, *130,* 398



94% ee

Olefin carbo-oxidation

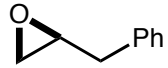
JACS **2008**, *130,* 16494



96% ee

α-Chlorination/epoxidation

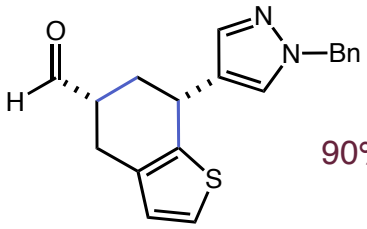
ACIE **2009**, *48,* 5121



94% ee

Cascade Cycloaddition

JACS **2010**, *132*, asap



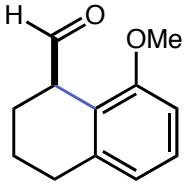
90% ee

Intramolecular α-arylation

JACS **2009**, *131,* 11640

JACS **2009**, *131,* 2086 (Nicolaou)

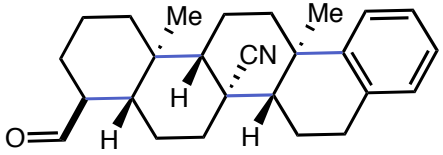
JACS **2010**, *132*, 6001 (Houk)



98% ee

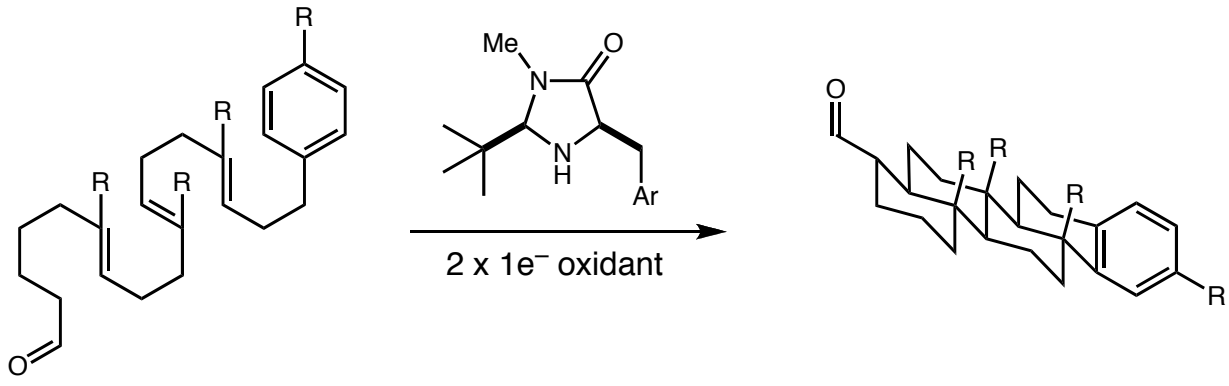
Polyene cyclization

JACS **2010**, *132*, 5027



92% ee

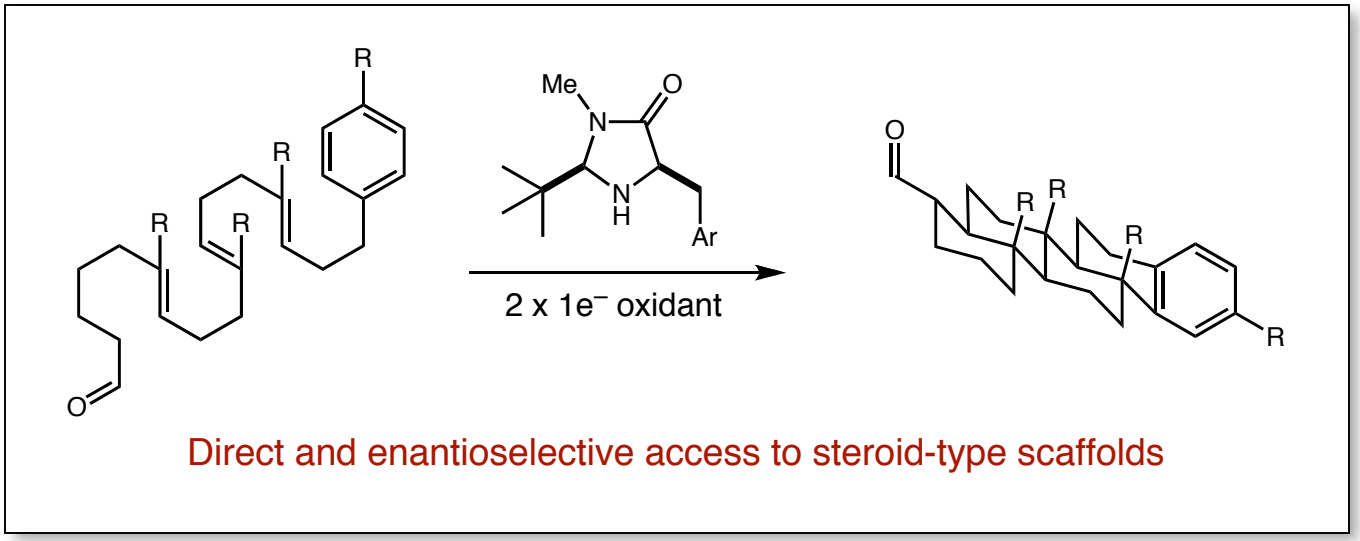
Multiple Radical Bond Formations

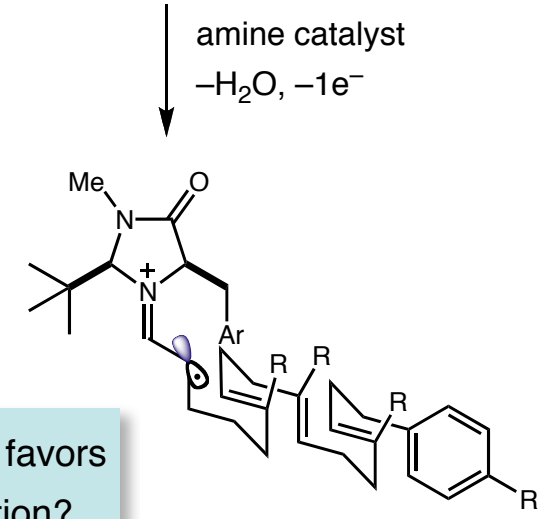


Direct and enantioselective access to steroid-type scaffolds

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Multiple Radical Bond Formations

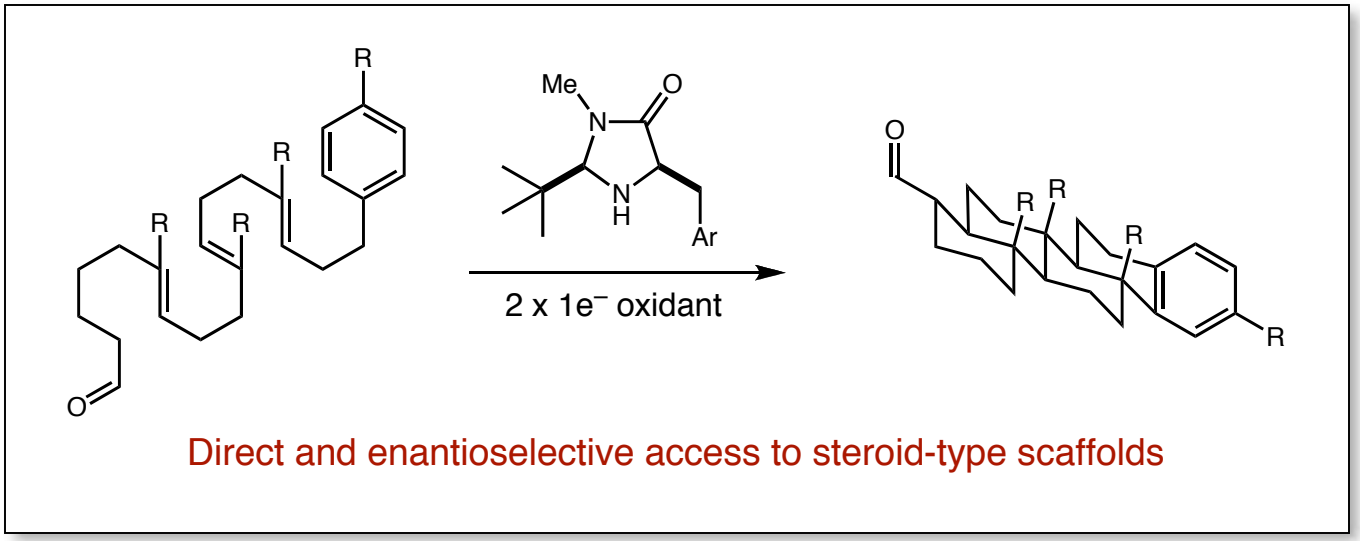


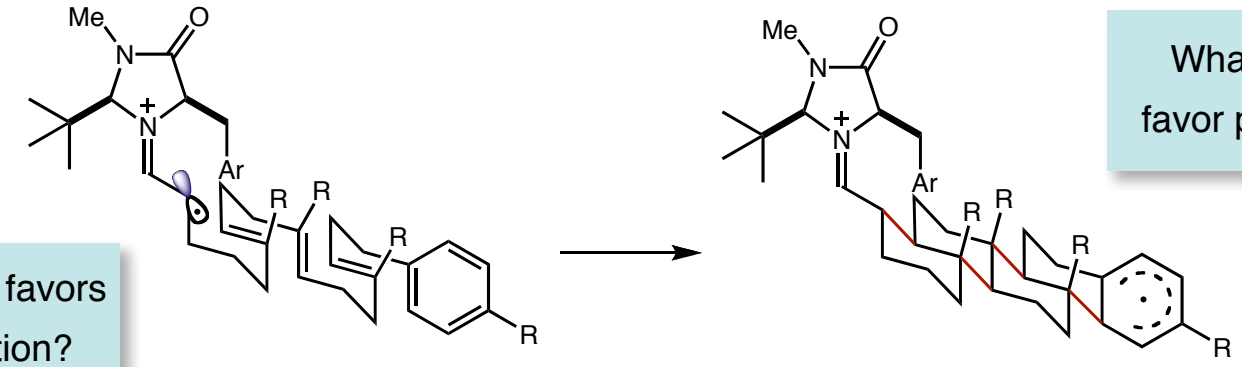


What oxidant favors polycyclization?

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Multiple Radical Bond Formations



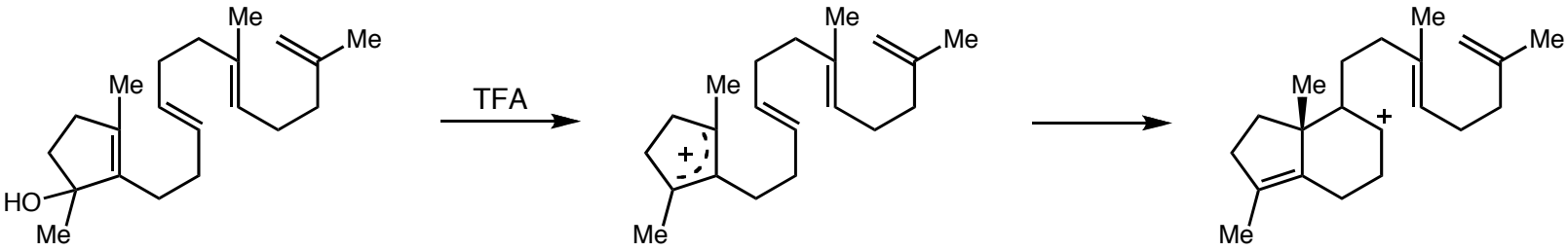


What oxidant favors polycyclization?

What substituents favor polycyclization?

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

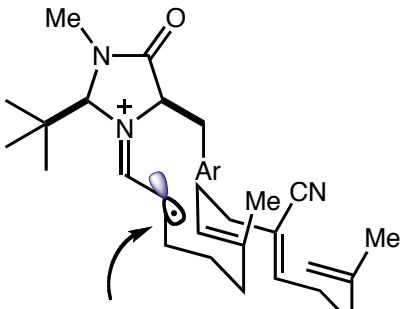
Radical vs. Cation Propagating Species in Polycyclization



Propagating species is carbocation: electron rich double bonds favor cyclization

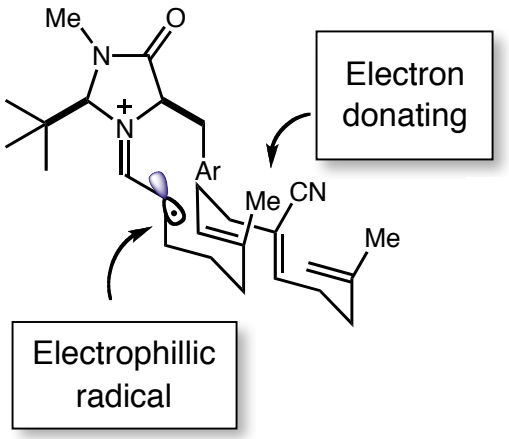
Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994.

Radical vs. Cation Propagating Species in Polycyclization



Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Radical vs. Cation Propagating Species in Polycyclization



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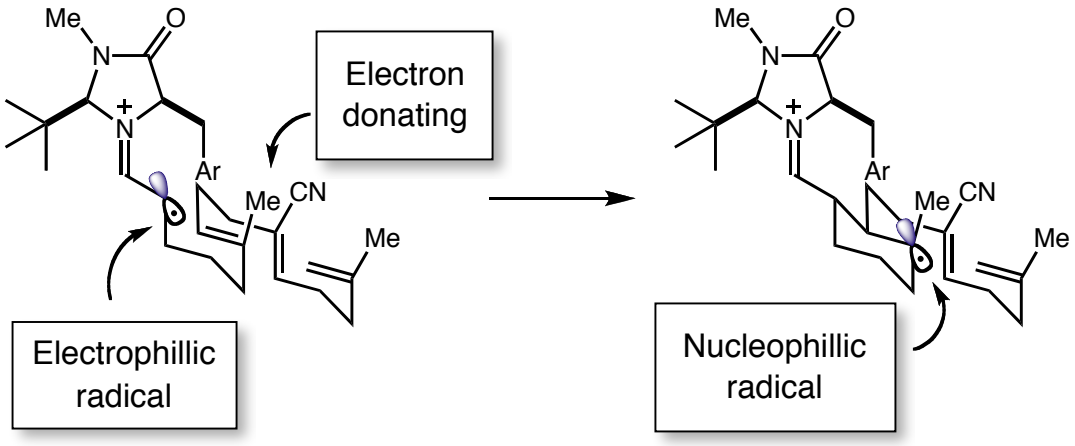
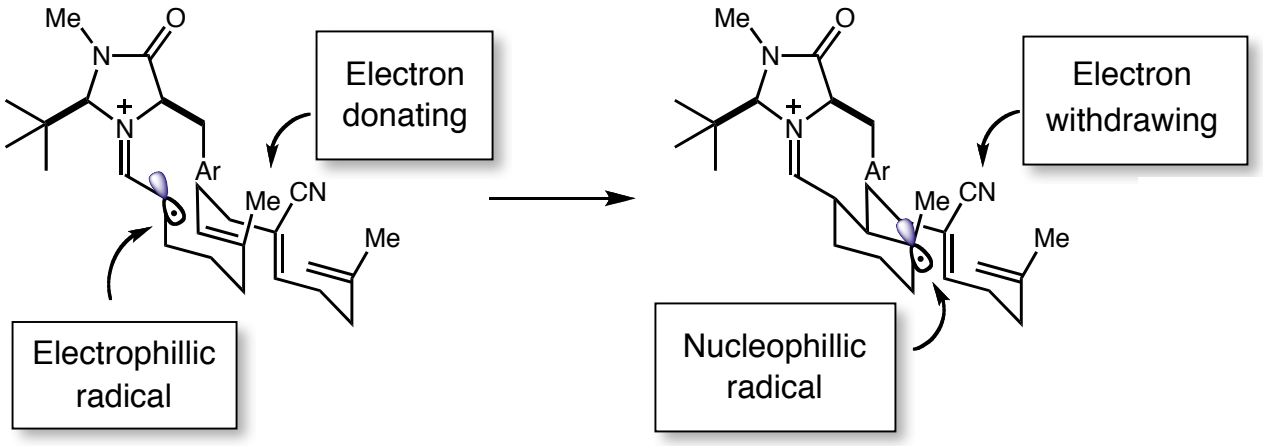


Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Radical vs. Cation Propagating Species in Polycyclization



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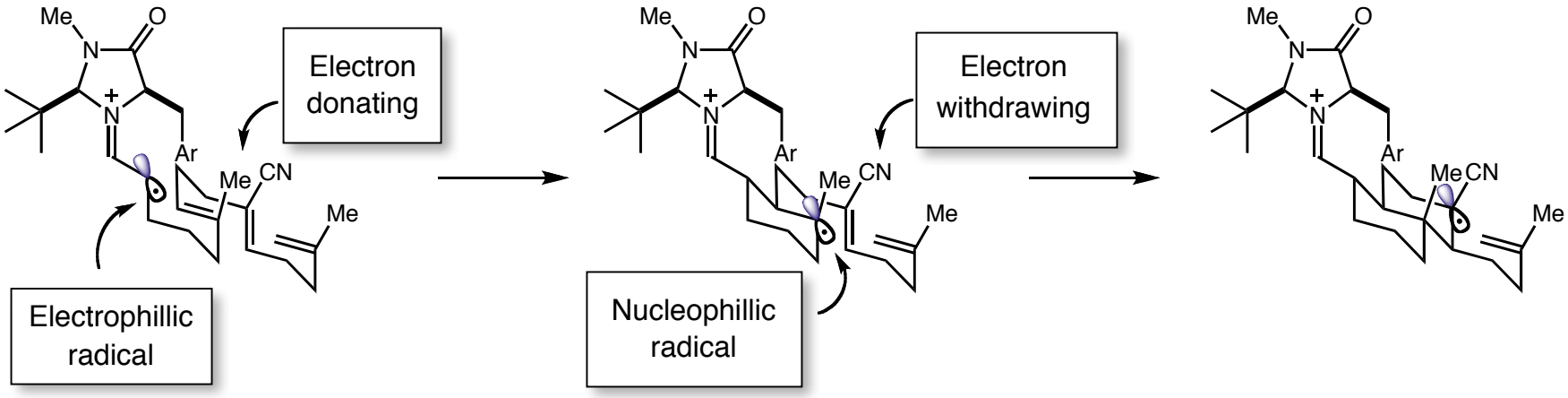
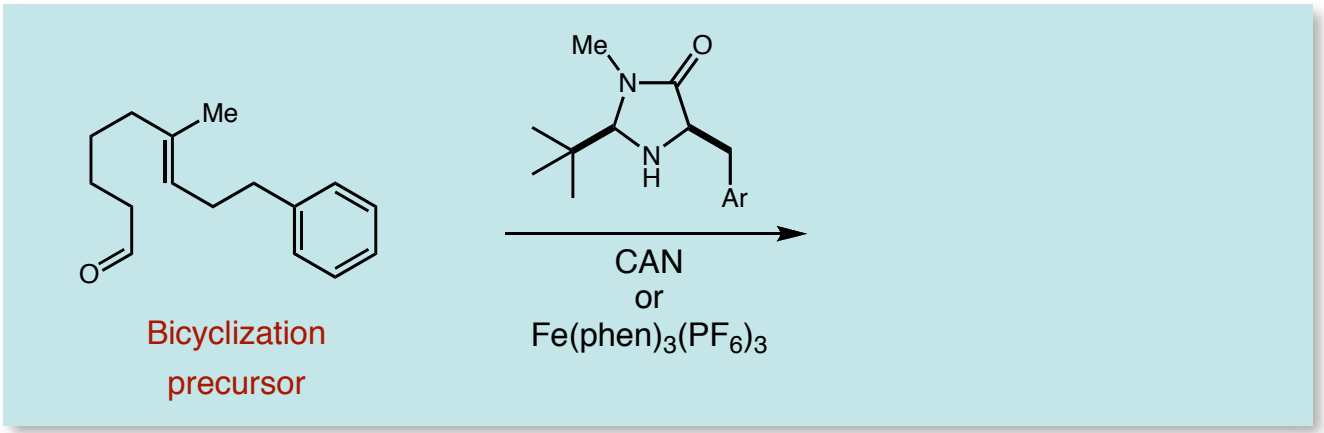
Radical vs. Cation Propagating Species in Polycyclization



Propagating species is radical: alternating polarity favors cyclization

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Competition with Premature Radical Oxidation



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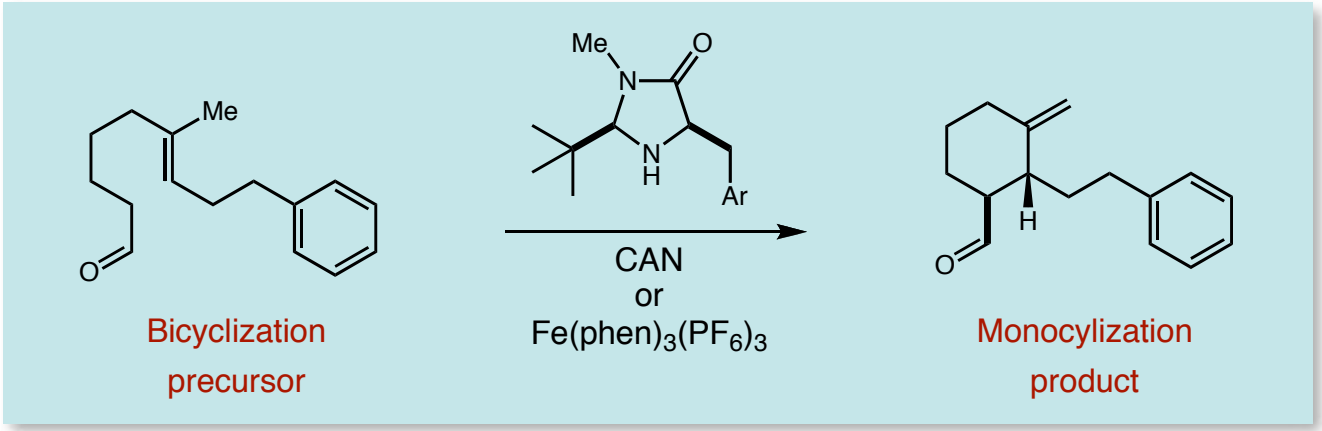
Competition with Premature Radical Oxidation



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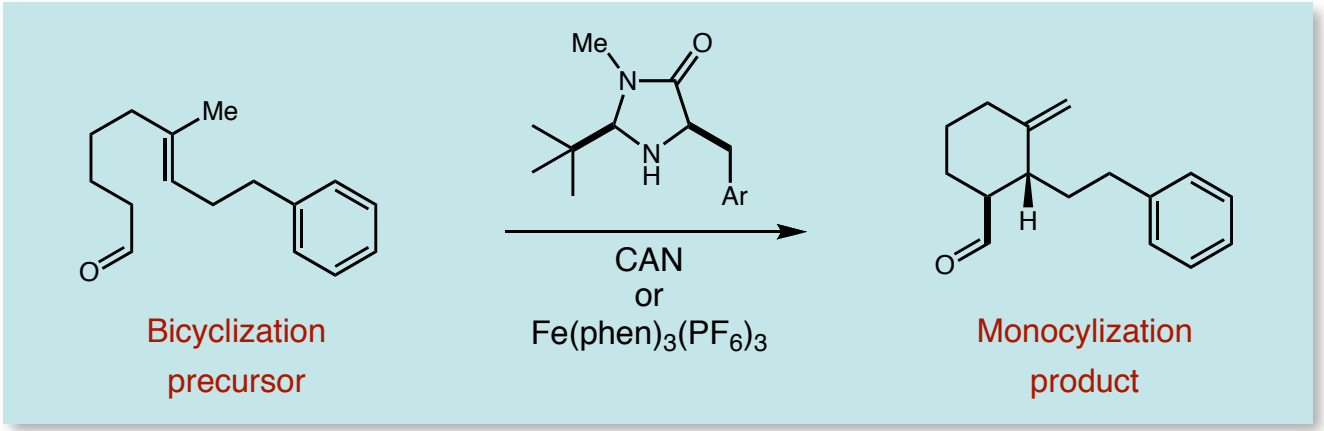
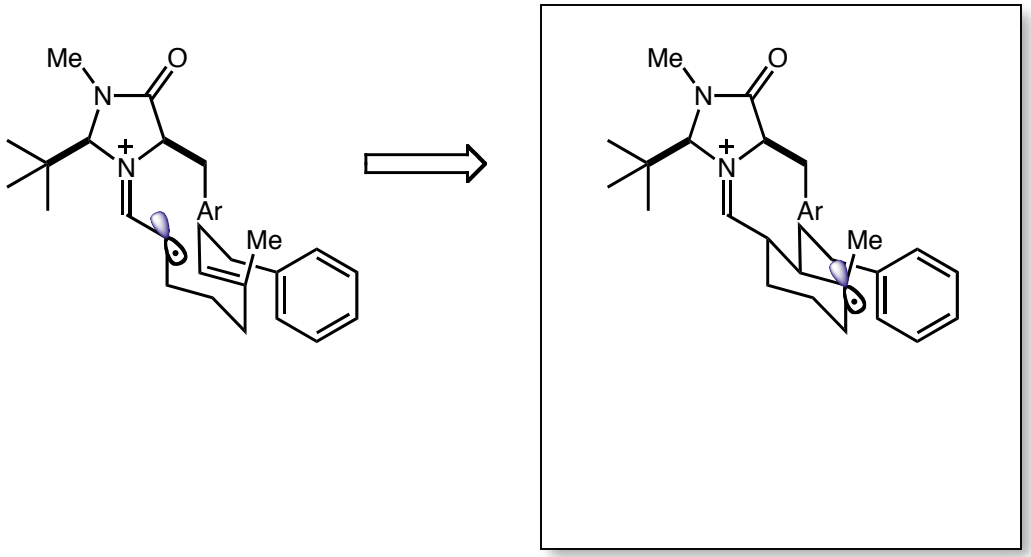
Competition with Premature Radical Oxidation





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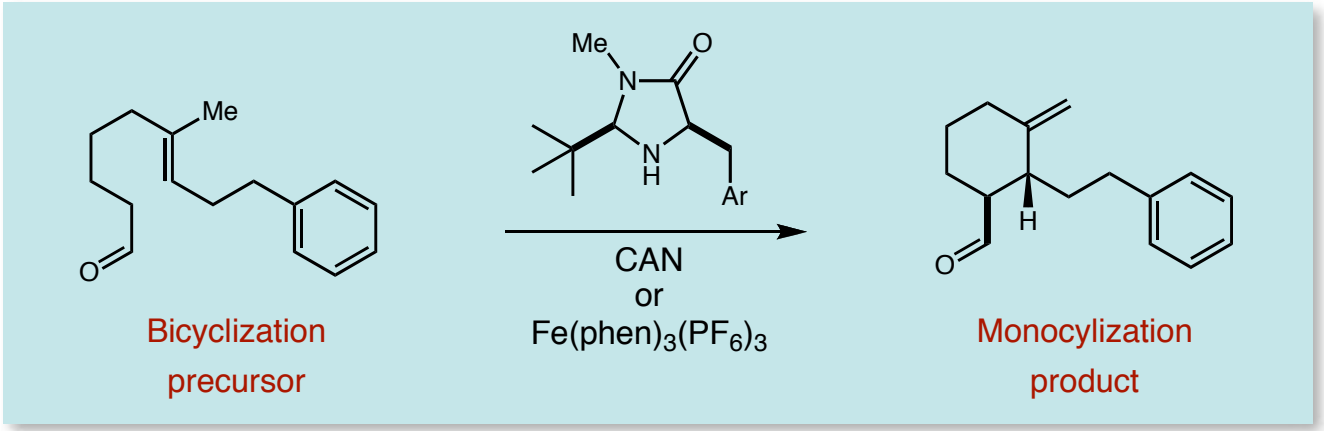
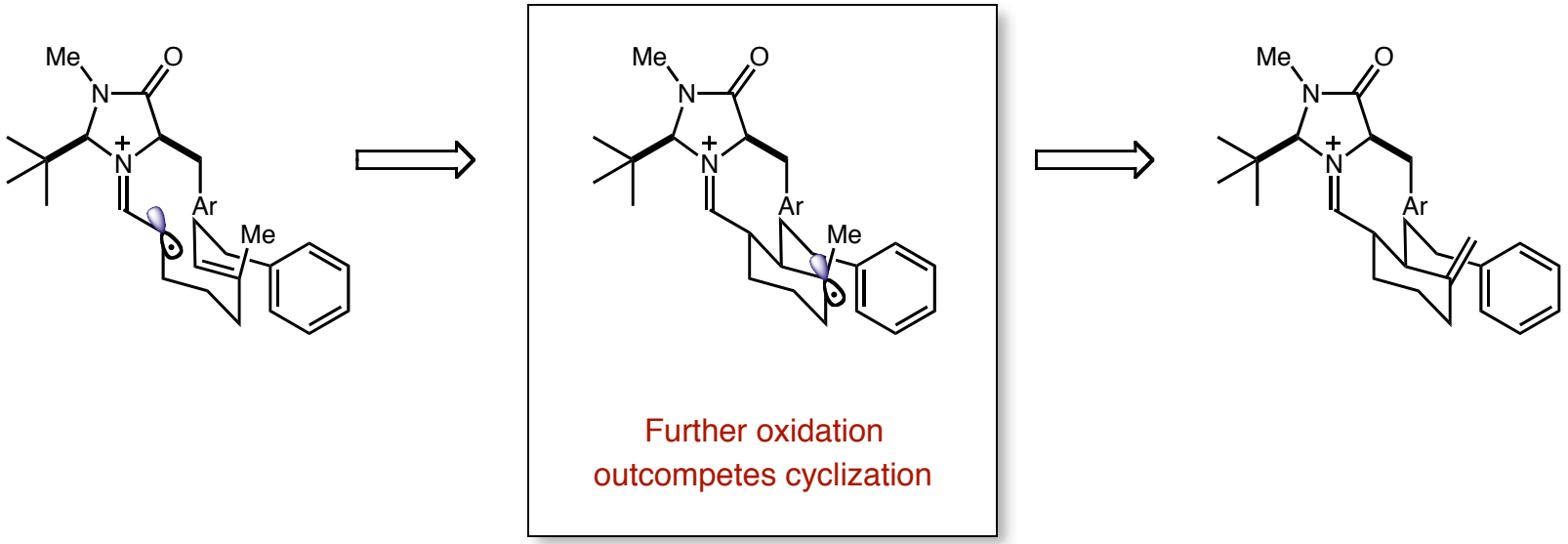
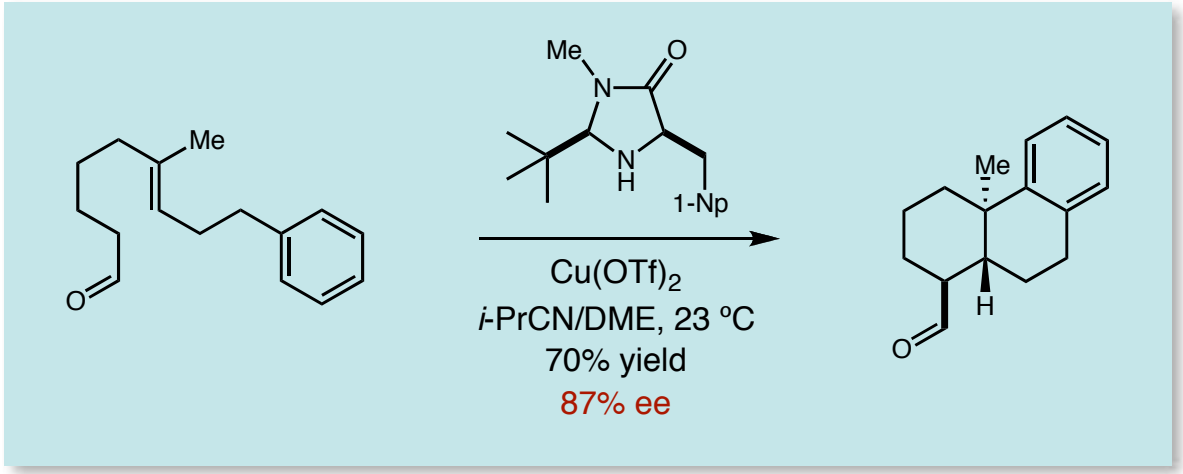
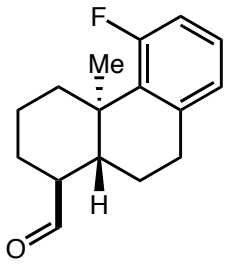




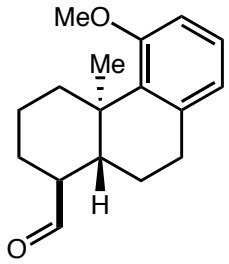
Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Copper Oxidant Allows for Efficient Bicyclization

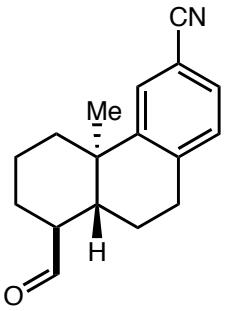




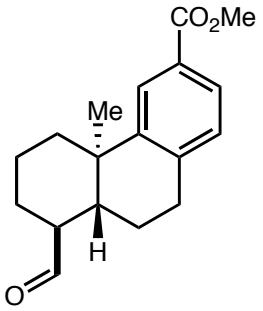
65% yield
90% ee



75% yield
88% ee



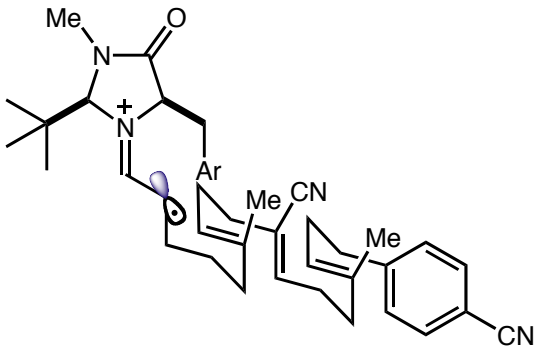
74% yield
88% ee



77% yield
87% ee

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

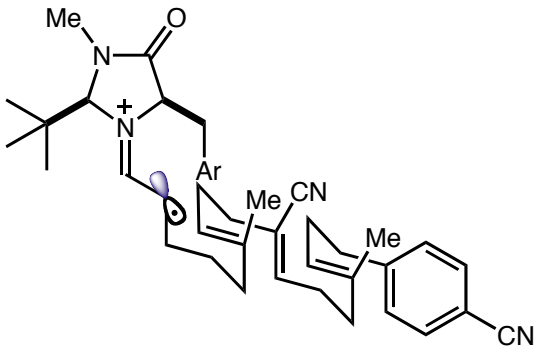
Alternating Polarity of Olefins Allows for Multicyclization



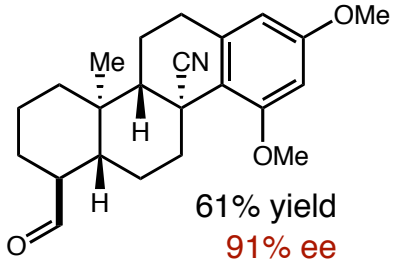
Will alternating polarity enable multicyclization?

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Alternating Polarity of Olefins Allows for Multicyclization



Will alternating polarity enable multicyclization?



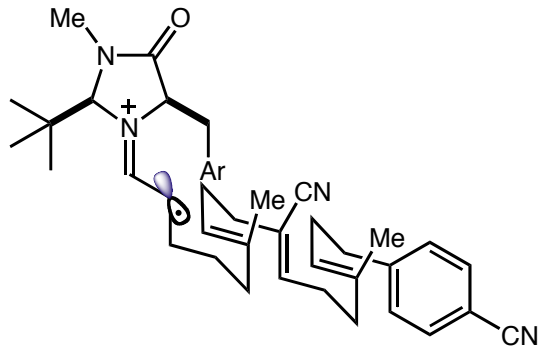
61% yield

91% ee

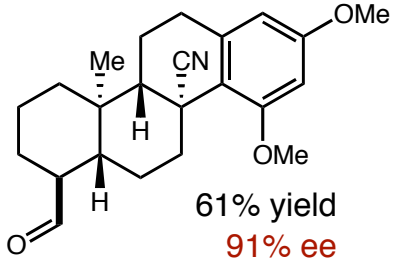
Tricyclization

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Alternating Polarity of Olefins Allows for Multicyclization

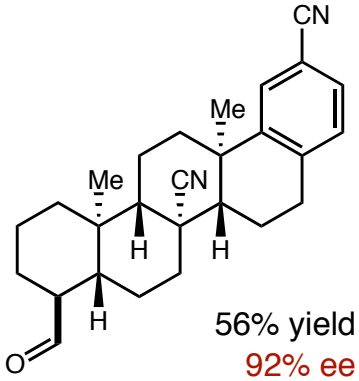


Will alternating polarity enable multicyclization?



61% yield
91% ee

Tricyclization

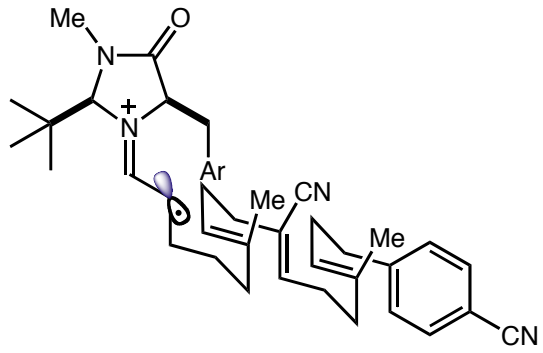


56% yield
92% ee

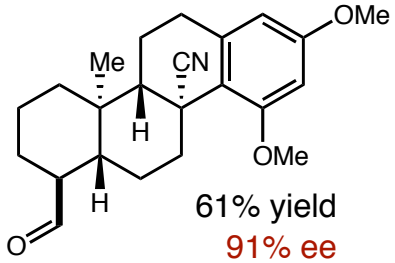
Tetracyclization

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Alternating Polarity of Olefins Allows for Multicyclization

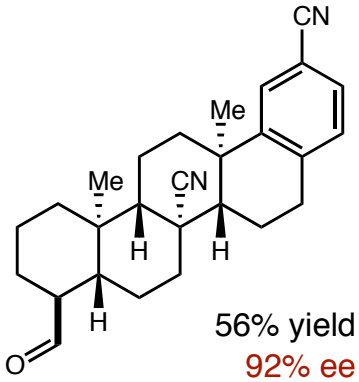


Will alternating polarity enable multicyclization?



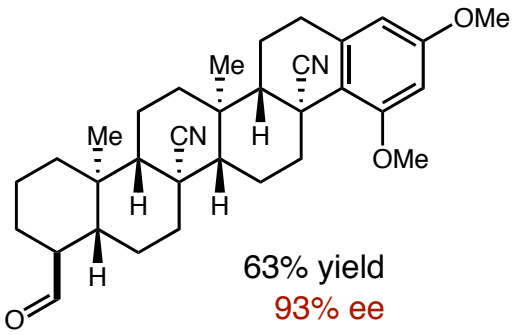
61% yield
91% ee

Tricyclization



56% yield
92% ee

Tetracyclization

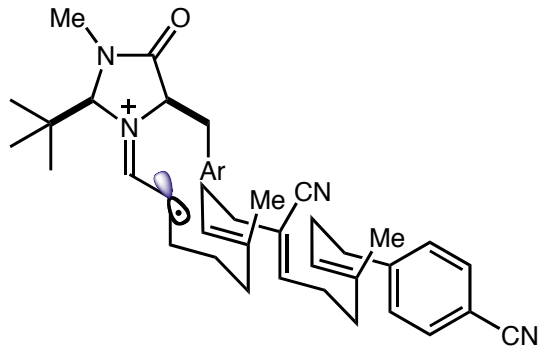


63% yield
93% ee

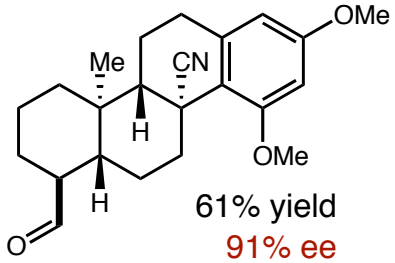
Pentacyclization

Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Alternating Polarity of Olefins Allows for Multicyclization

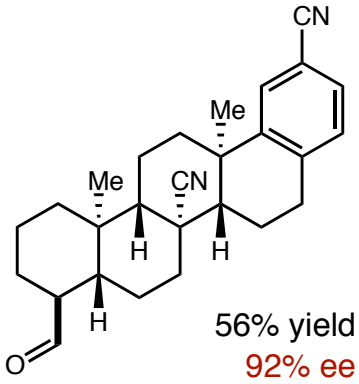


Will alternating polarity enable multicyclization?



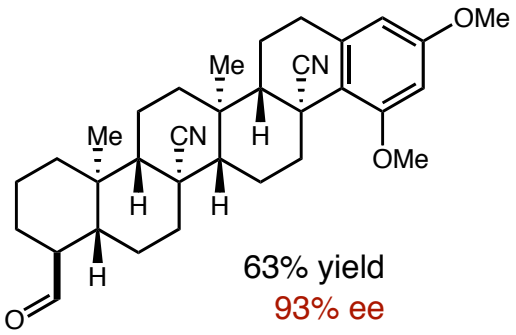
61% yield
91% ee

Tricyclization



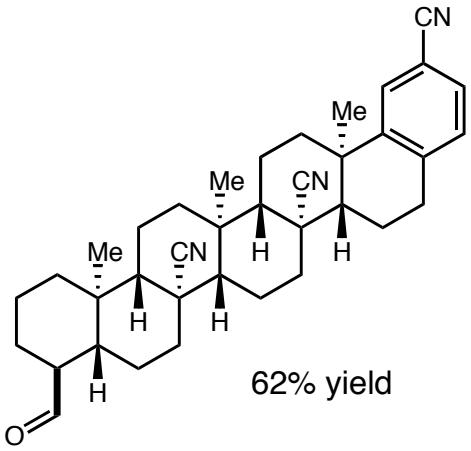
56% yield
92% ee

Tetracyclization



63% yield
93% ee

Pentacyclization



62% yield

Hexacyclization

- 6 new C–C bonds
- 11 contiguous stereocenters
- 5 all-carbon quaternary stereocenters
- 92% yield per bond formation

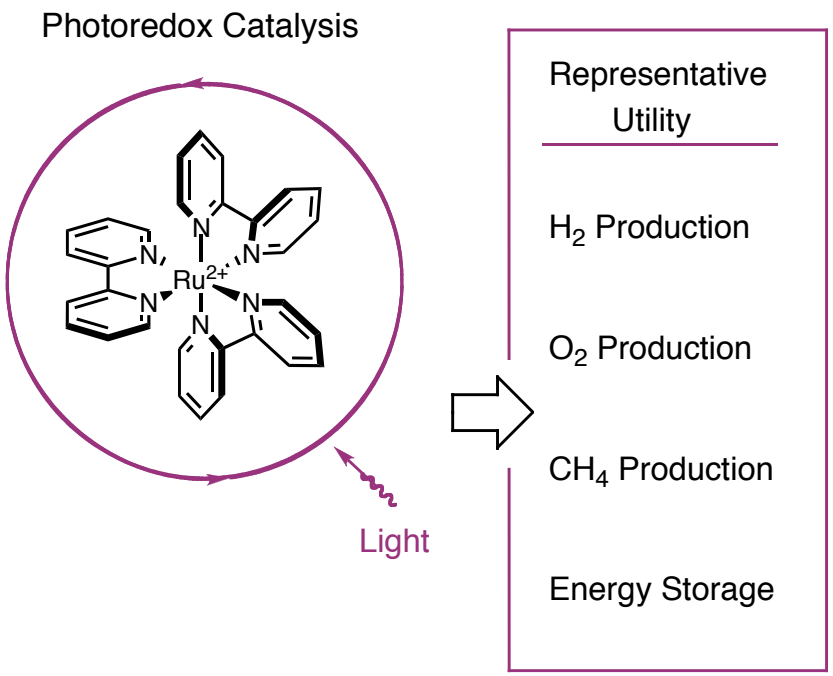
Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

Relatively Few Catalysis Activation Concepts ⇨ *Many Powerful Reactions*

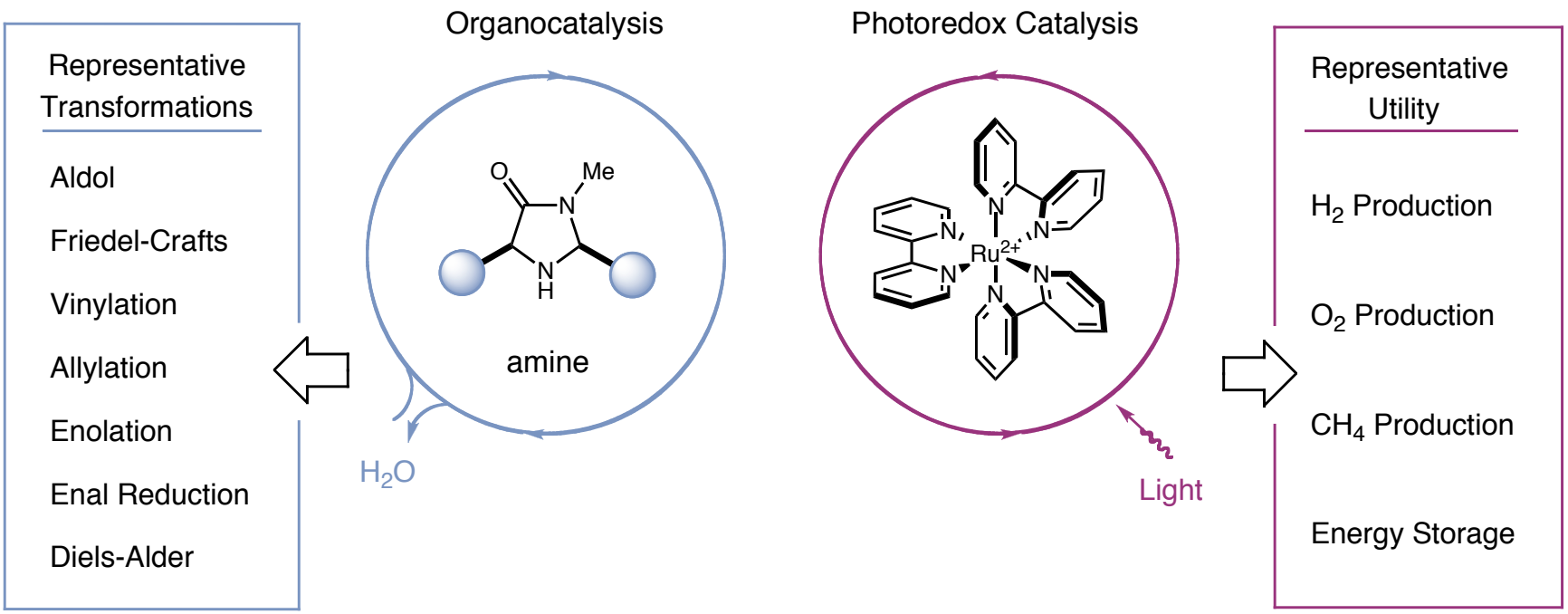
Photoredox organocatalysis

■ A new mode of organocatalytic activation

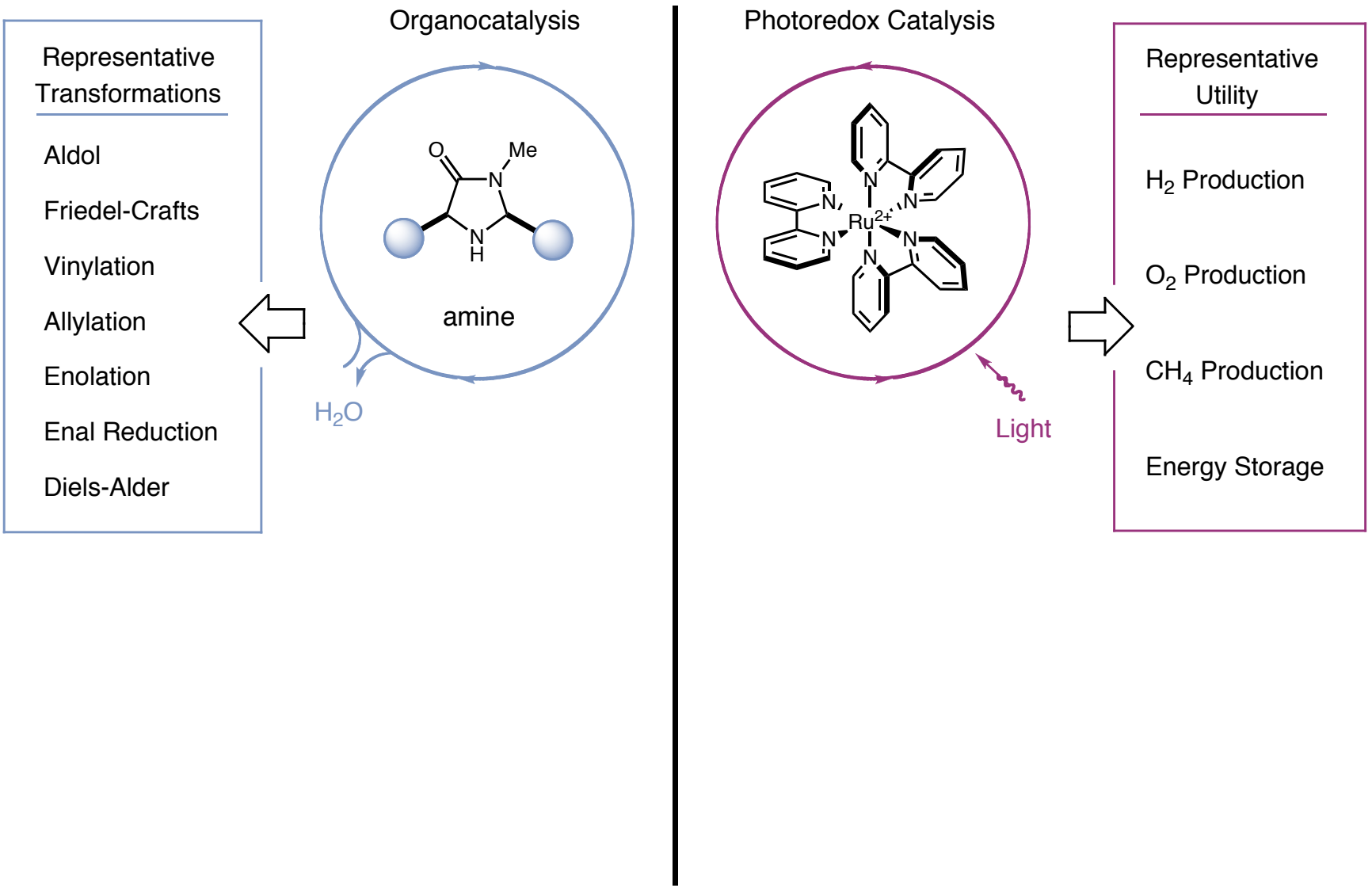
The Utility of Merging Different Catalysis Areas: New Catalytic Bond Constructions



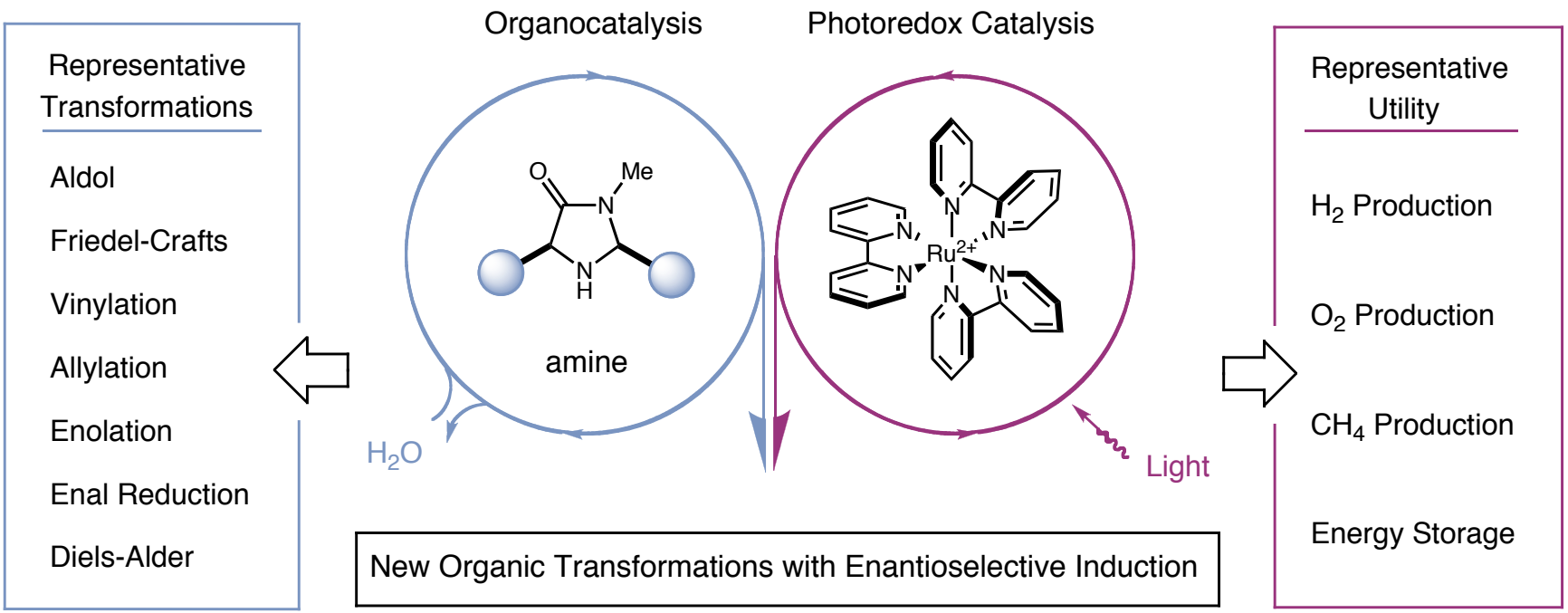
The Utility of Merging Different Catalysis Areas: New Catalytic Bond Constructions



The Utility of Merging Different Catalysis Areas: New Catalytic Bond Constructions

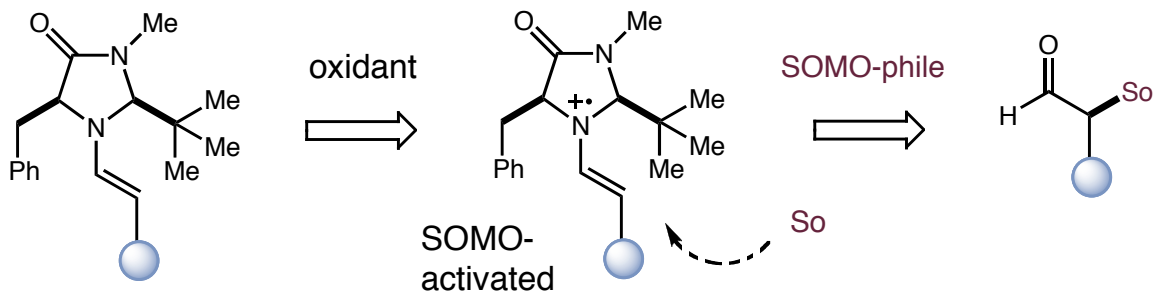


The Utility of Merging Different Catalysis Areas: New Catalytic Bond Constructions

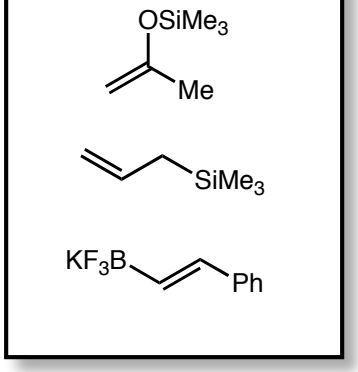


How can we use Photoredox Catalysis to Enable Aldehyde α-Alkylation

- SOMO catalysis, activated species reacts with electron rich π-systems



SOMO-philes =



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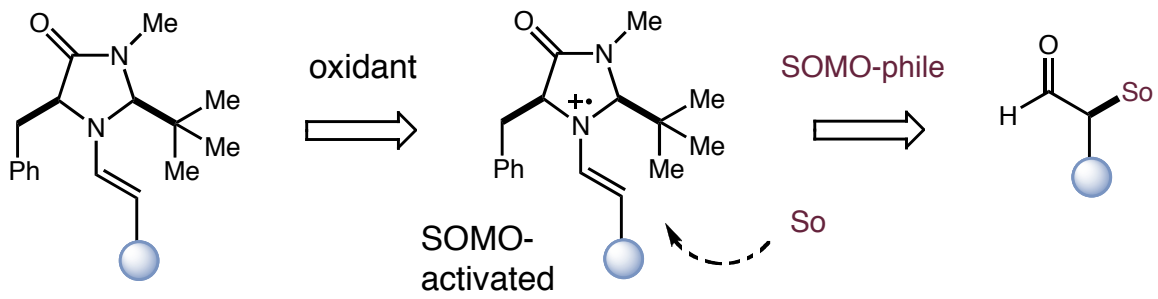
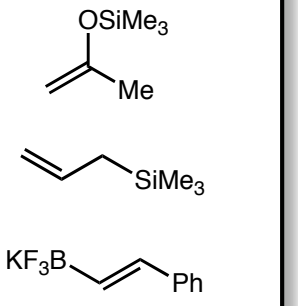
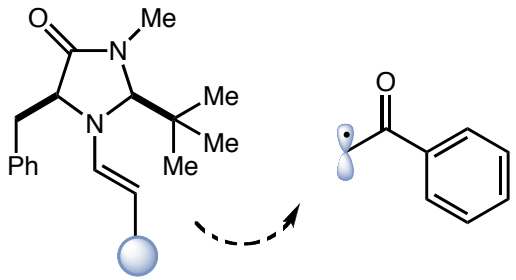


SOMO-philes =



- Can we electronically reverse the role of the catalyst

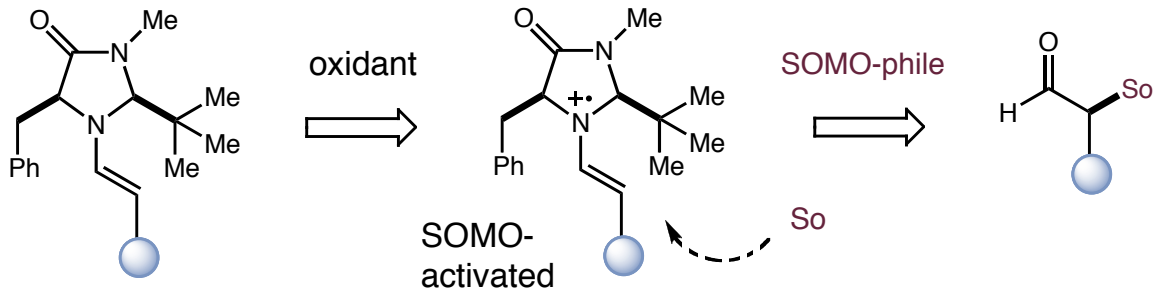


enamine (SOMO-phile)

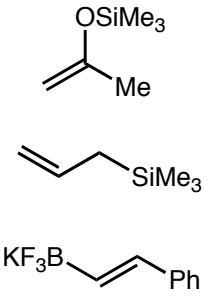
SOMO-activated (α-acyl radical)

How can we use Photoredox Catalysis to Enable Aldehyde α-Alkylation

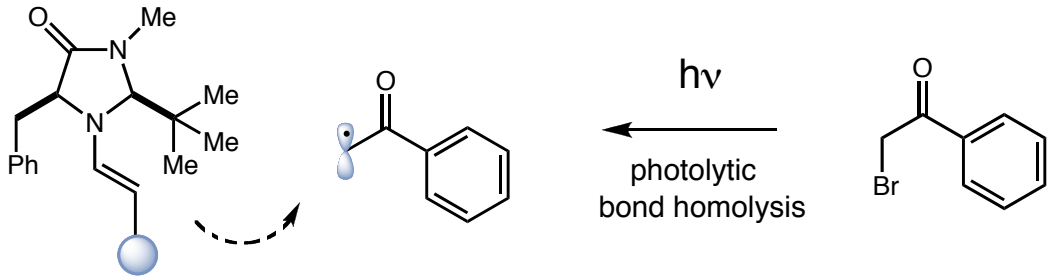
- SOMO catalysis, activated species reacts with electron rich π-systems



SOMO-philes =



- Can we electronically reverse the role of the catalyst

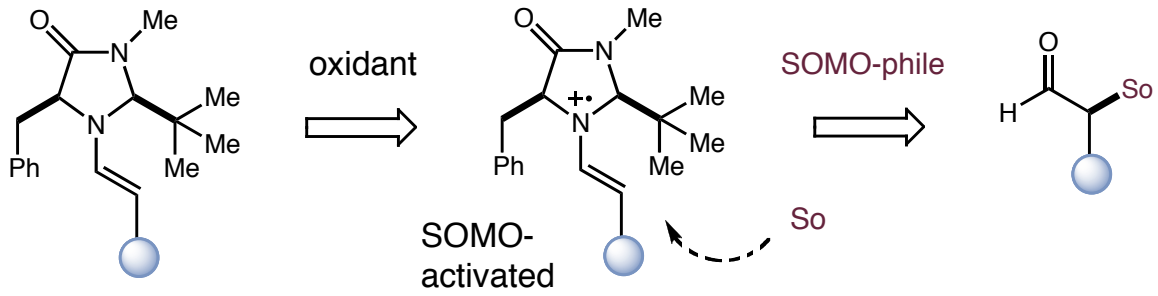


enamine
(SOMO-phile)

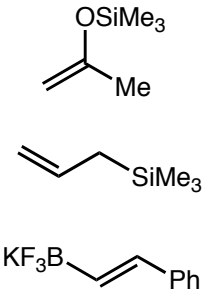
SOMO-activated
(α-acyl radical)

How can we use Photoredox Catalysis to Enable Aldehyde α-Alkylation

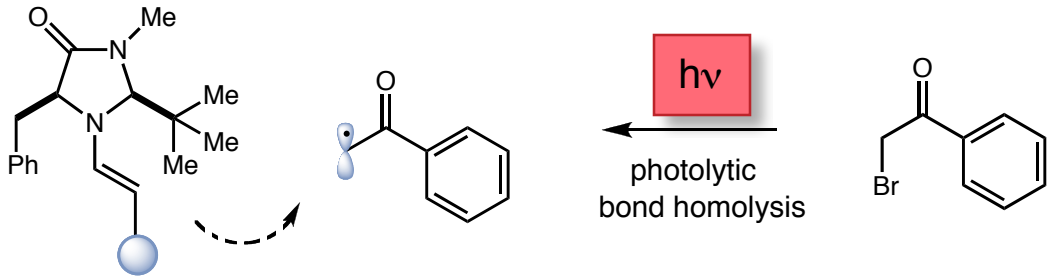
■ SOMO catalysis, activated species reacts with electron rich π-systems



SOMO-philes =



■ Can we electronically reverse the role of the catalyst



enamine
(SOMO-phile)

SOMO-activated
(α-acyl radical)

How can we use Photoredox Catalysis to Enable Aldehyde α-Alkylation

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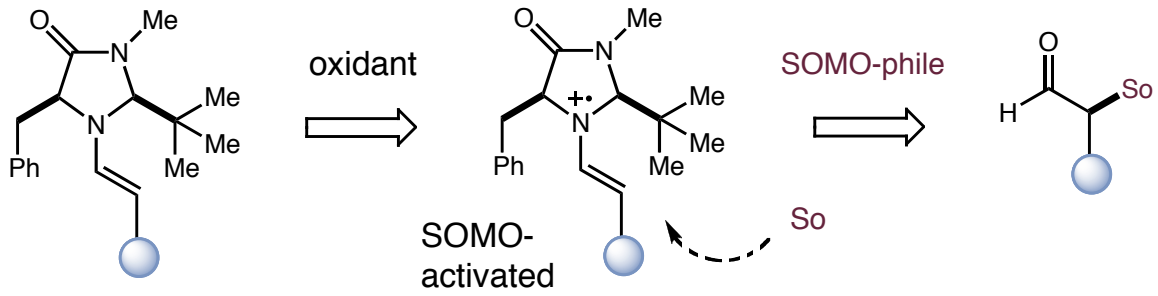
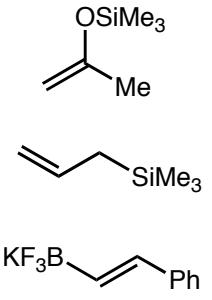
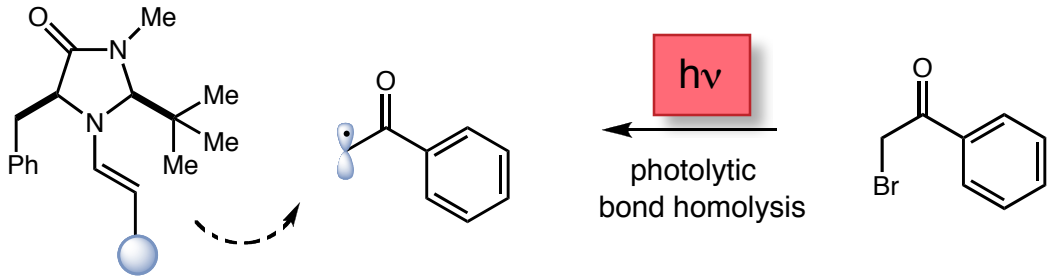


SOMO-philes =



- Can we electronically reverse the role of the catalyst

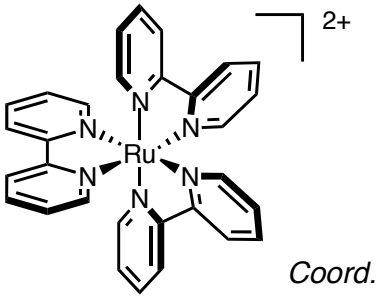


enamine
(SOMO-phile)

SOMO-activated
(α-acyl radical)

hν = photobox!

Ru(bpy)$_3$: A Versatile and Extensively Utilized Photredox Catalyst

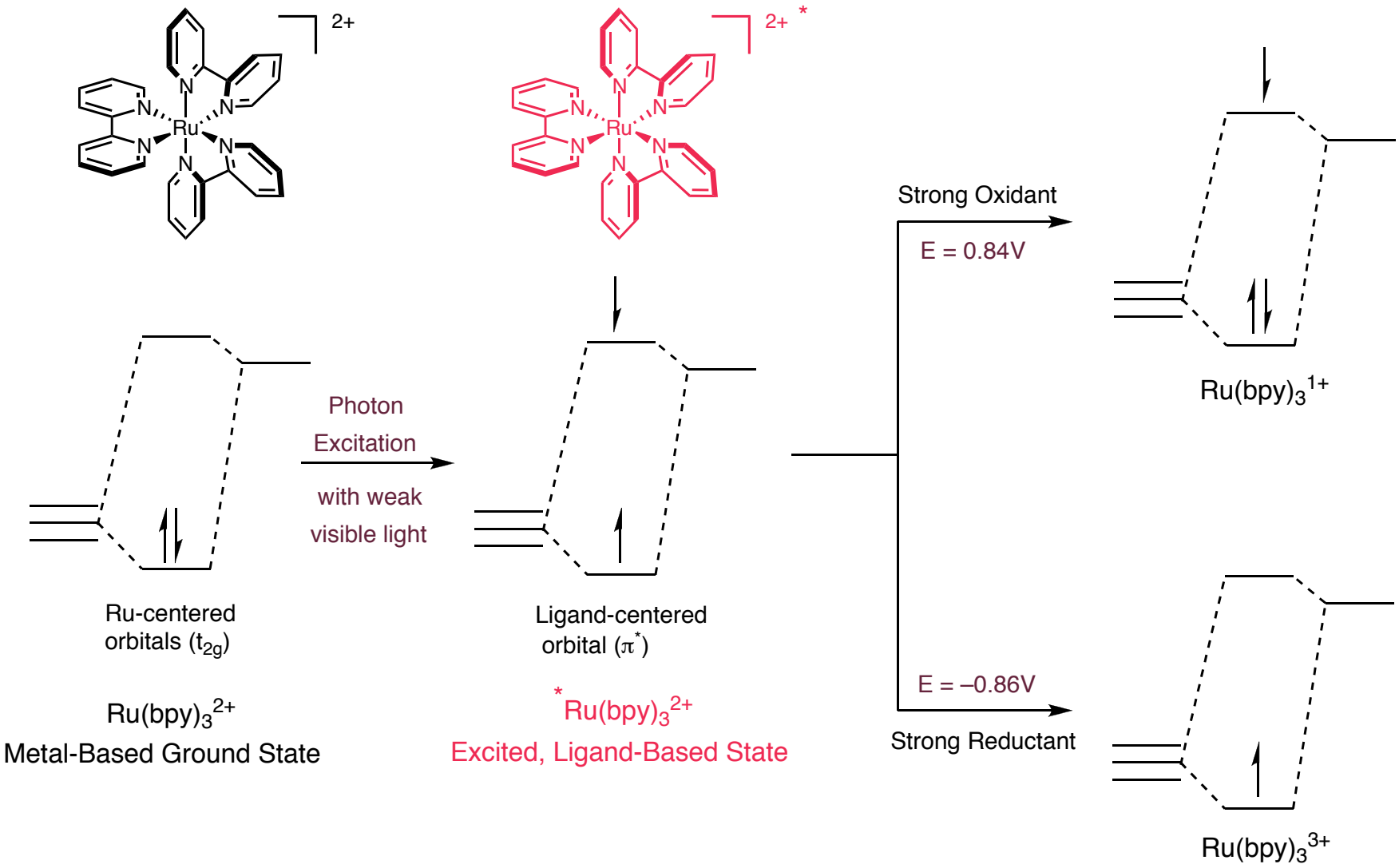


$Ru(bpy)_3X_2$

Coord. Chem. Rev. **1982**, *46*, 159.

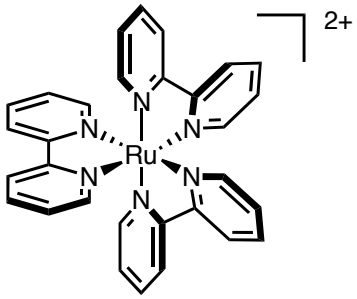
- **Visible MLCT absorption at 452 nm (weak visible light)**
- **Long-lived excited state (~ 620ns)**
- **High quantum yield (~0.05 - H_2O/298K)**
- **Effective excited state oxidant and reductant**
- **Used extensively as electron transfer catalyst**
- **Inexpensive ($38/g - Strem 2008)**

Ru(bpy)$_3$: Electronic Properties that Enable Photredox Catalysis



Balzani, A. J. V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zewelsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.

How can we use Photoredox Catalysis to Enable Single Electron Pathways

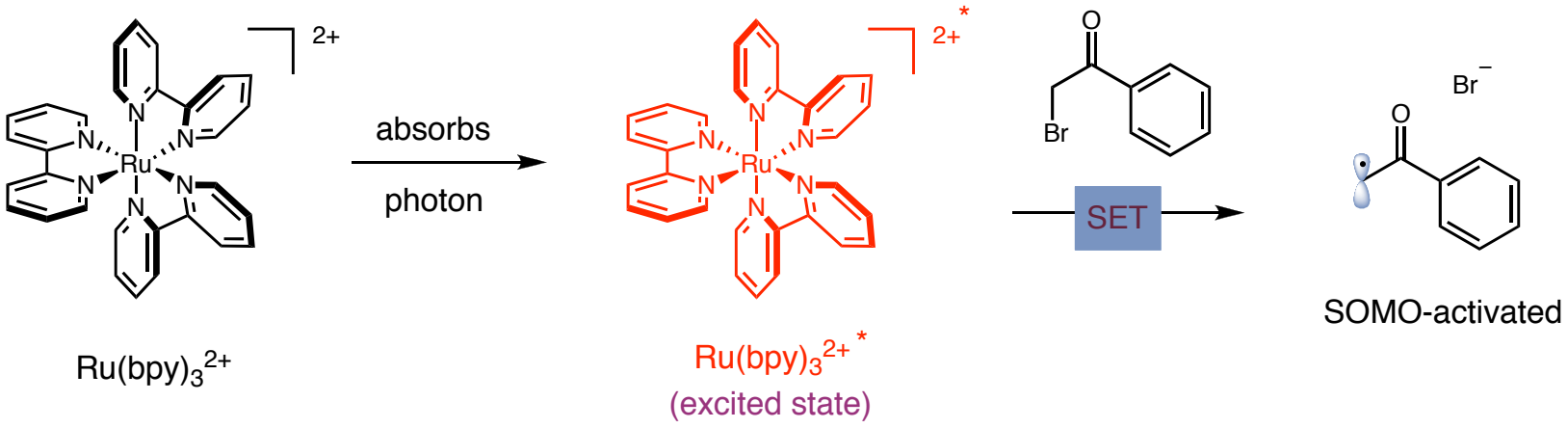


$Ru(bpy)_3^{2+}$

15W

Fluorescent bulb

How can we use Photoredox Catalysis to Enable Single Electron Pathways

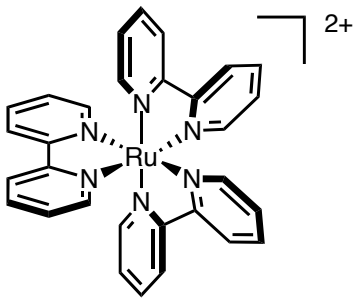


15W

Fluorescent bulb

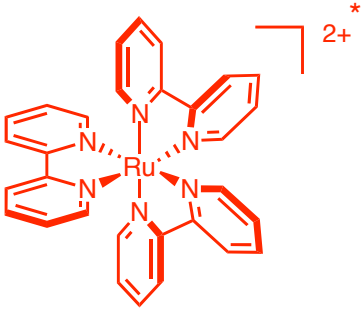
SET = single electron transfer

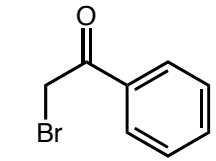
How can we use Photoredox Catalysis to Enable Single Electron Pathways



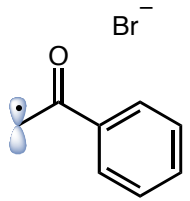
absorbs

photon





SET



SOMO-activated

$Ru(bpy)_3^{2+}$

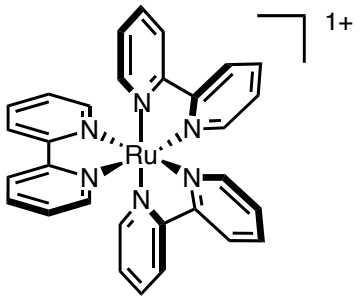
$Ru(bpy)_3^{2+*}$

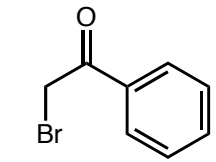
(excited state)

SET

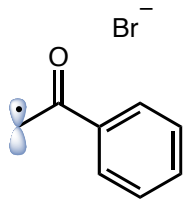
15W

Fluorescent bulb





SET

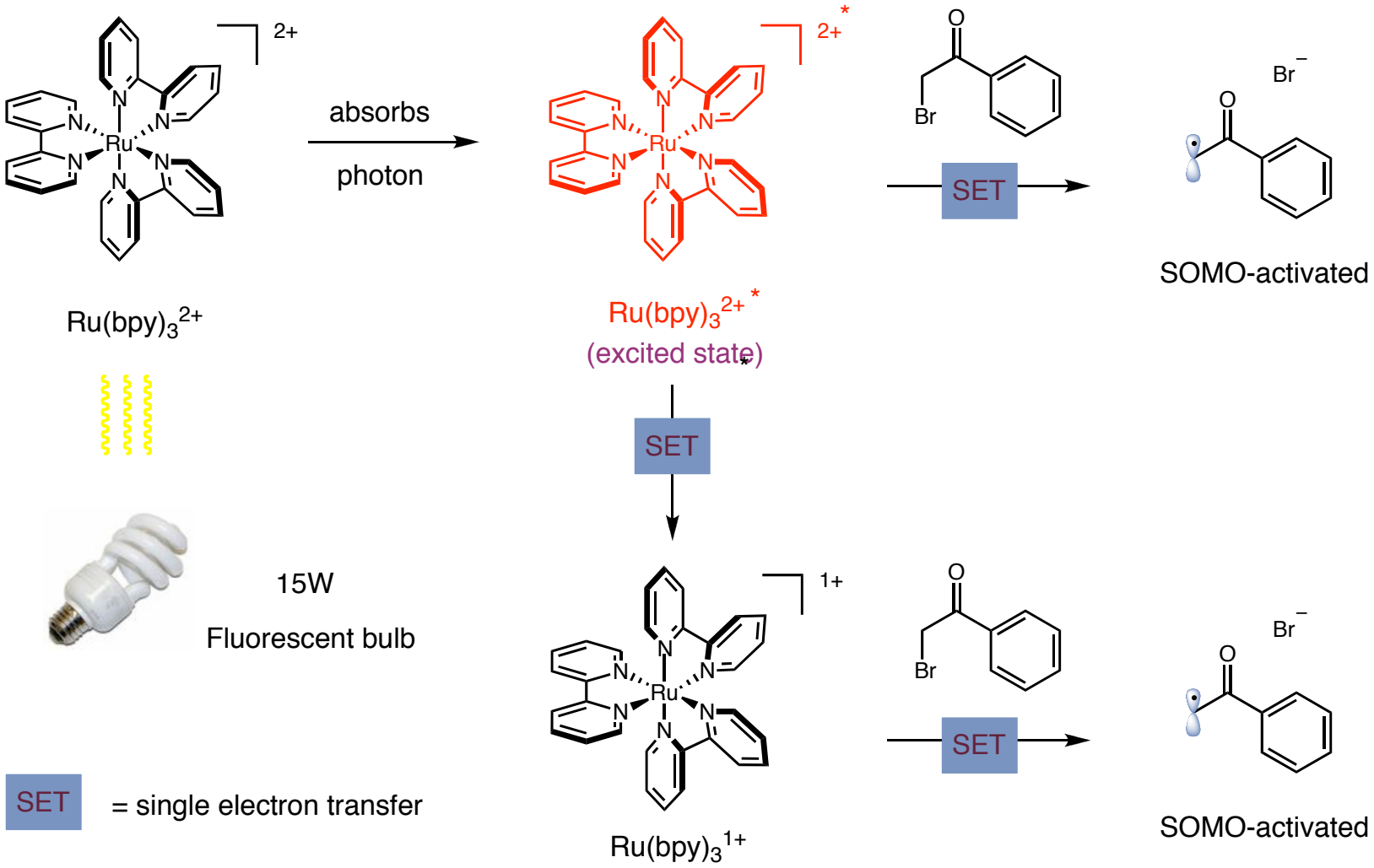


SOMO-activated

SET = single electron transfer

$Ru(bpy)_3^{1+}$

How can we use Photoredox Catalysis to Enable Single Electron Pathways



■ Using a household 15W light bulb with Ru(bpy) ⟹ highly reactive one-electron species

Photoredox Catalytic

Cycle

$Ru(bpy)_3^{2+}$
photoredox catalyst **1**

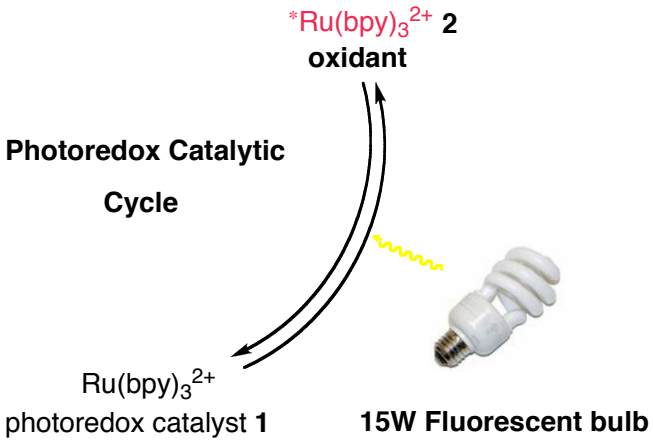
Merging Enantioselective Organocatalysis and Photoredox Catalysis

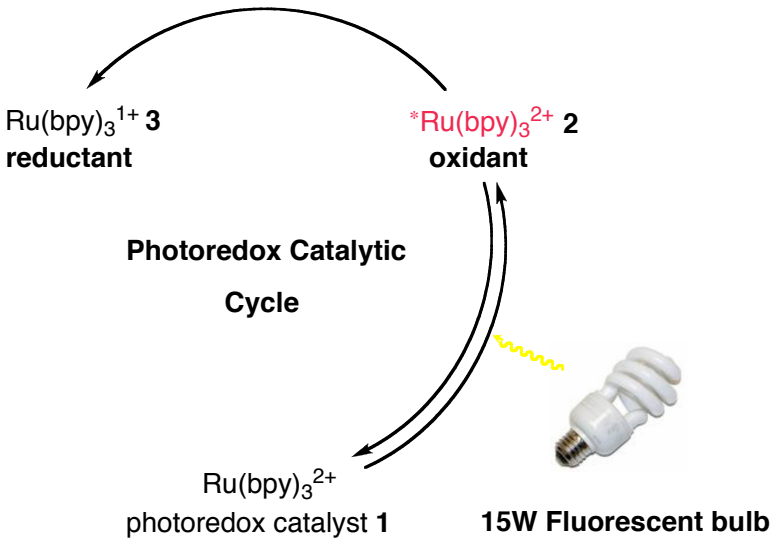
Photoredox Catalytic Cycle

$Ru(bpy)_3^{2+}$
photoredox catalyst **1**

15W Fluorescent bulb

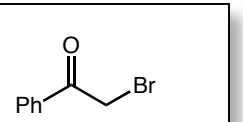
Merging Enantioselective Organocatalysis and Photoredox Catalysis

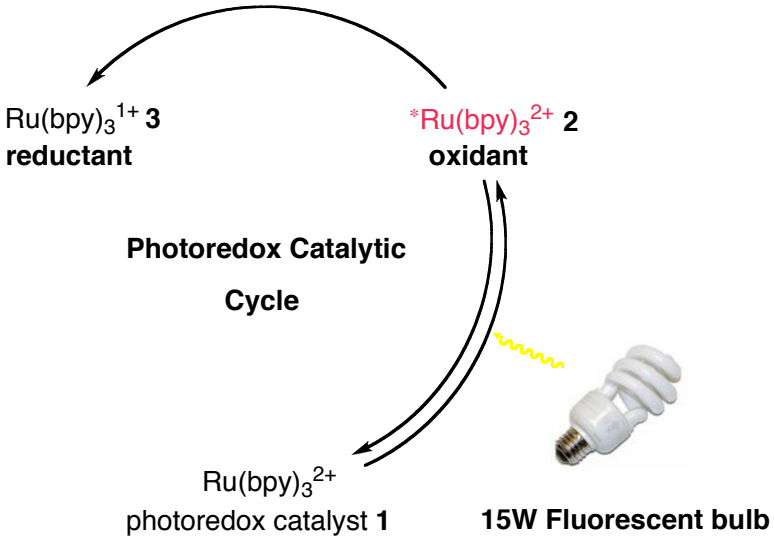



Ru(bpy)3 1+ 3
reductant
*Ru(bpy)3 2+ 2
oxidant
Photoredox Catalytic
Cycle
Ru(bpy)3 2+
photoredox catalyst 1
15W Fluorescent bulb

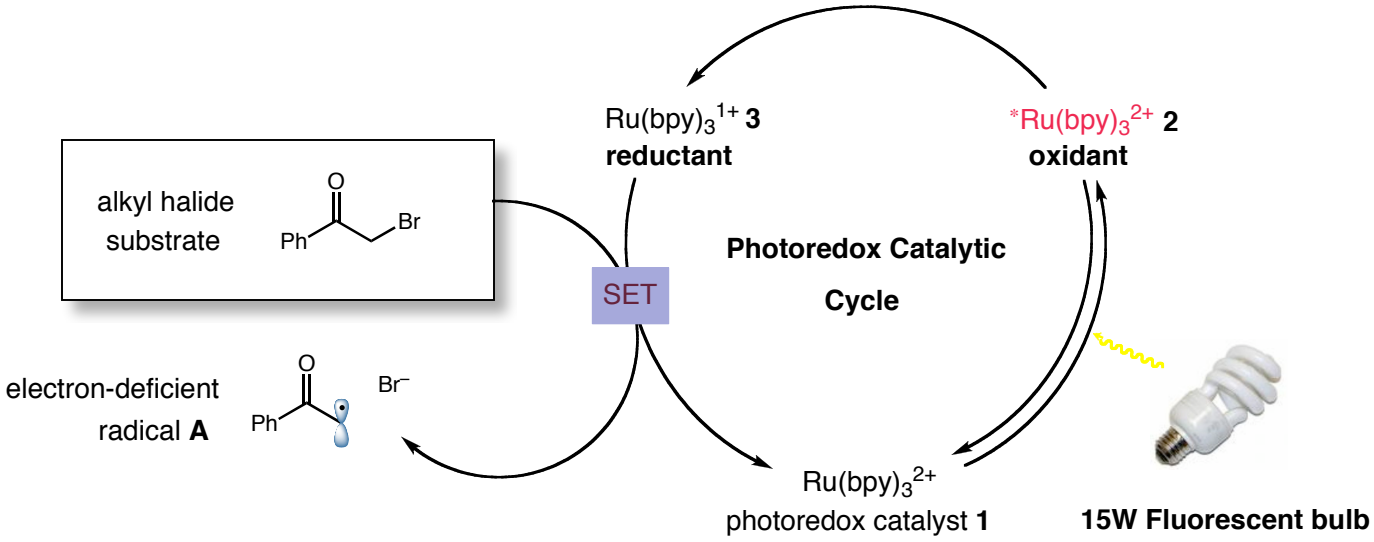
Merging Enantioselective Organocatalysis and Photoredox Catalysis

alkyl halide substrate

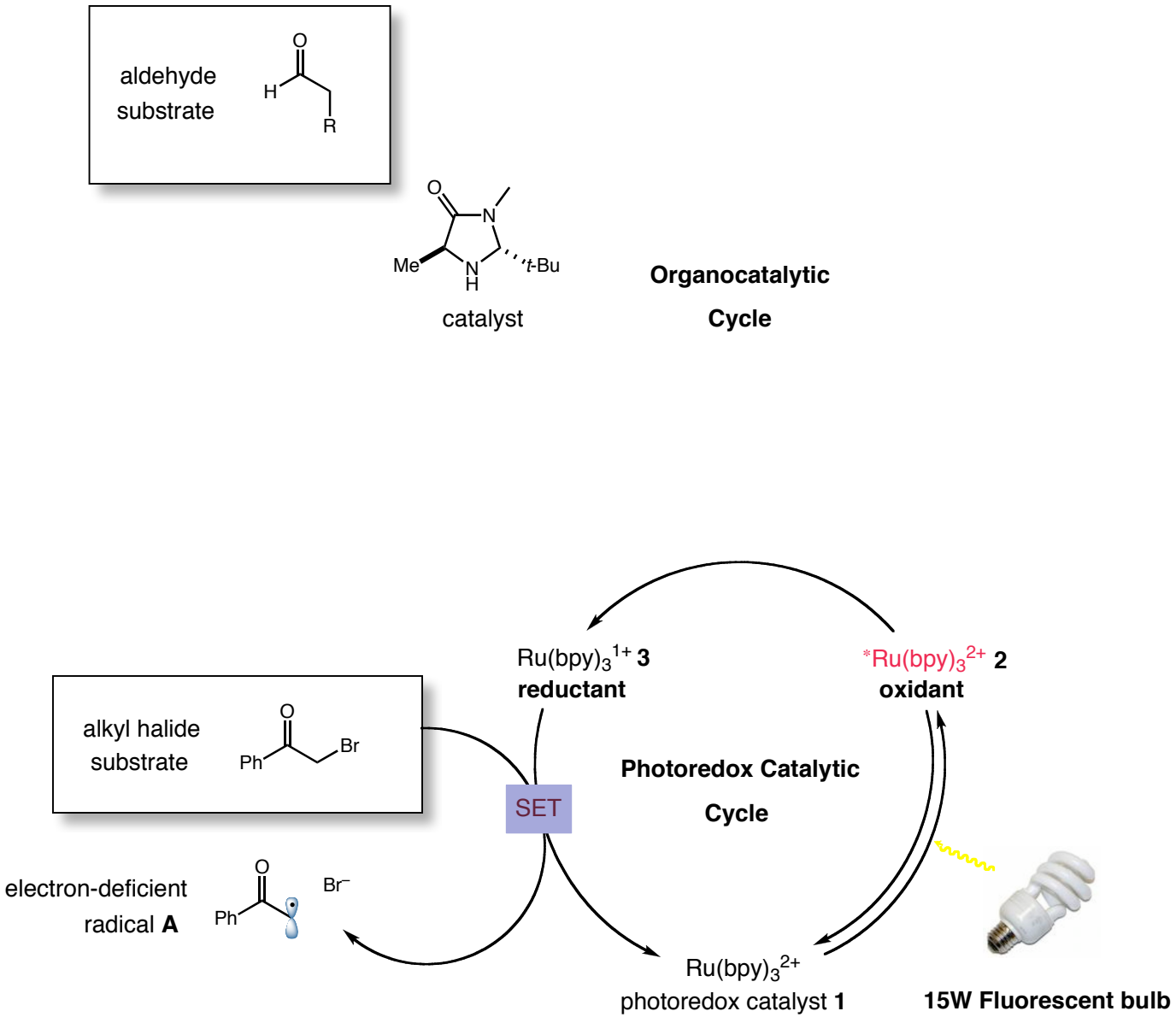




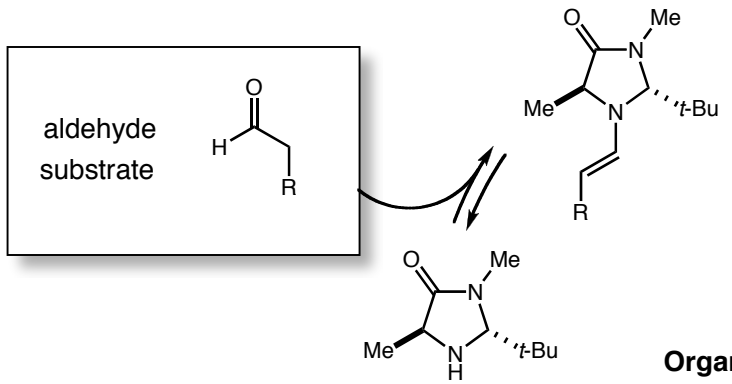
Merging Enantioselective Organocatalysis and Photoredox Catalysis

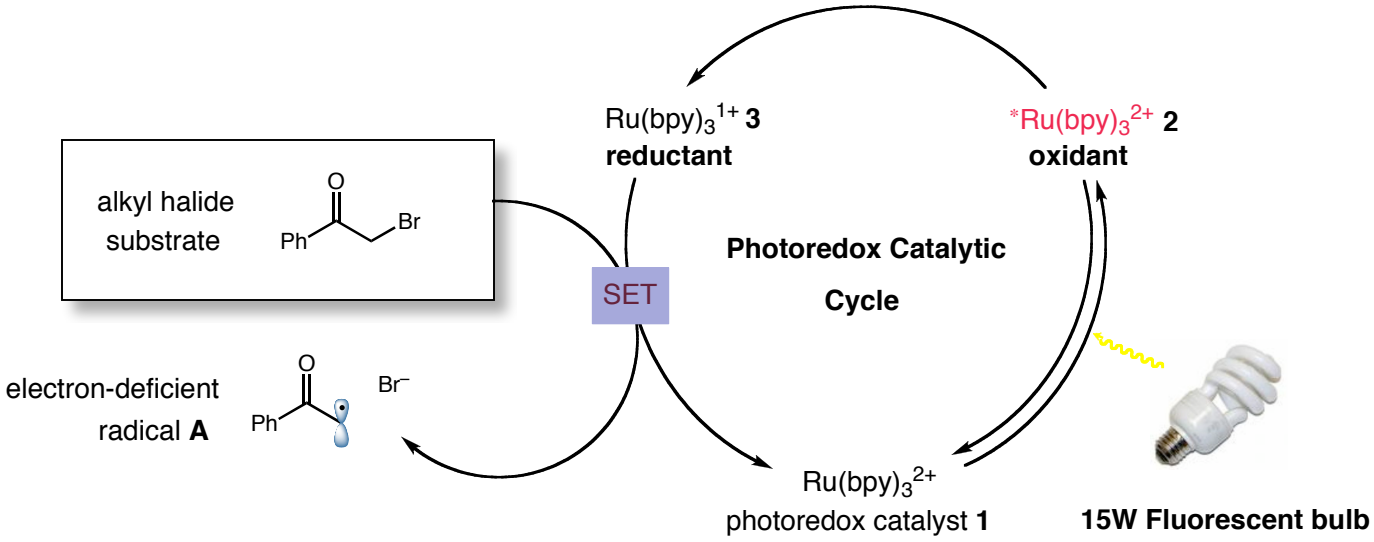


Merging Enantioselective Organocatalysis and Photoredox Catalysis

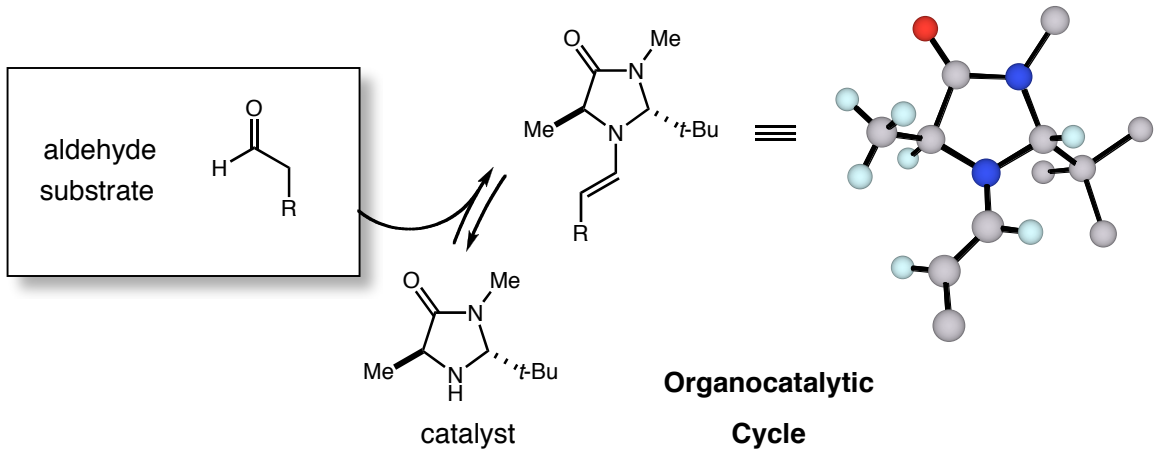


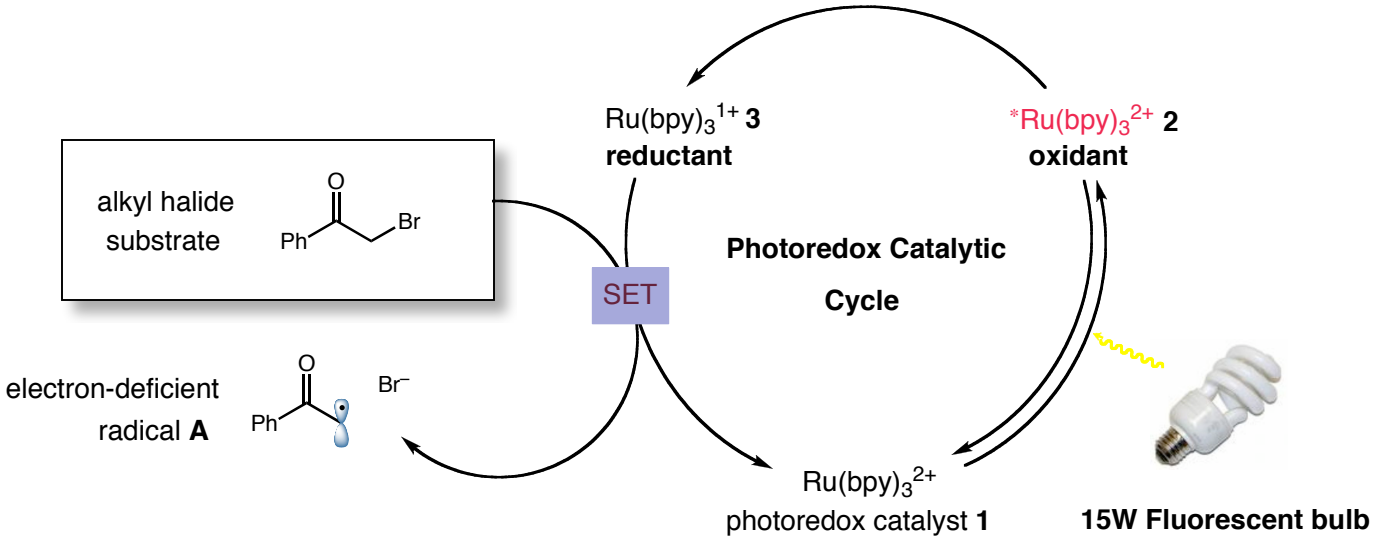
Merging Enantioselective Organocatalysis and Photoredox Catalysis



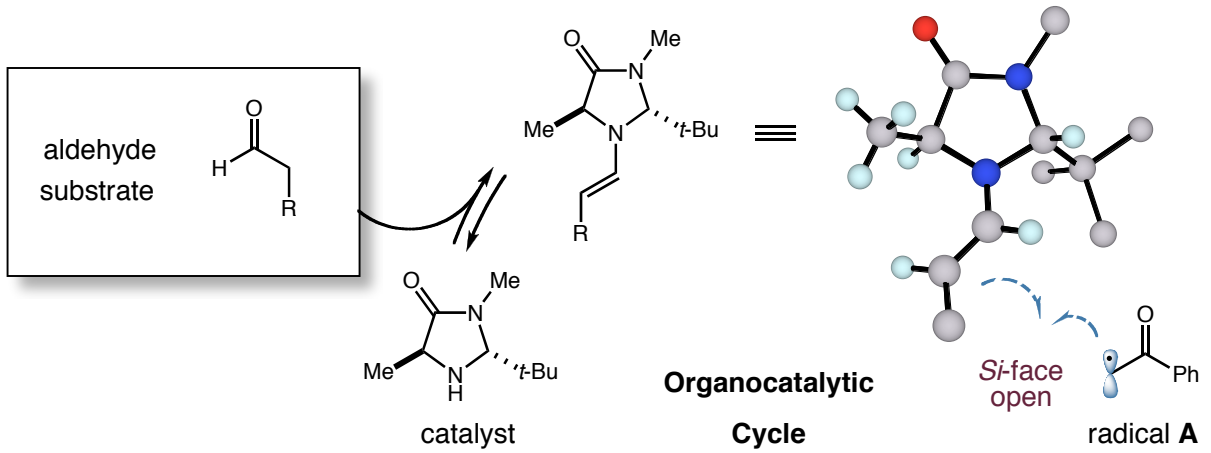


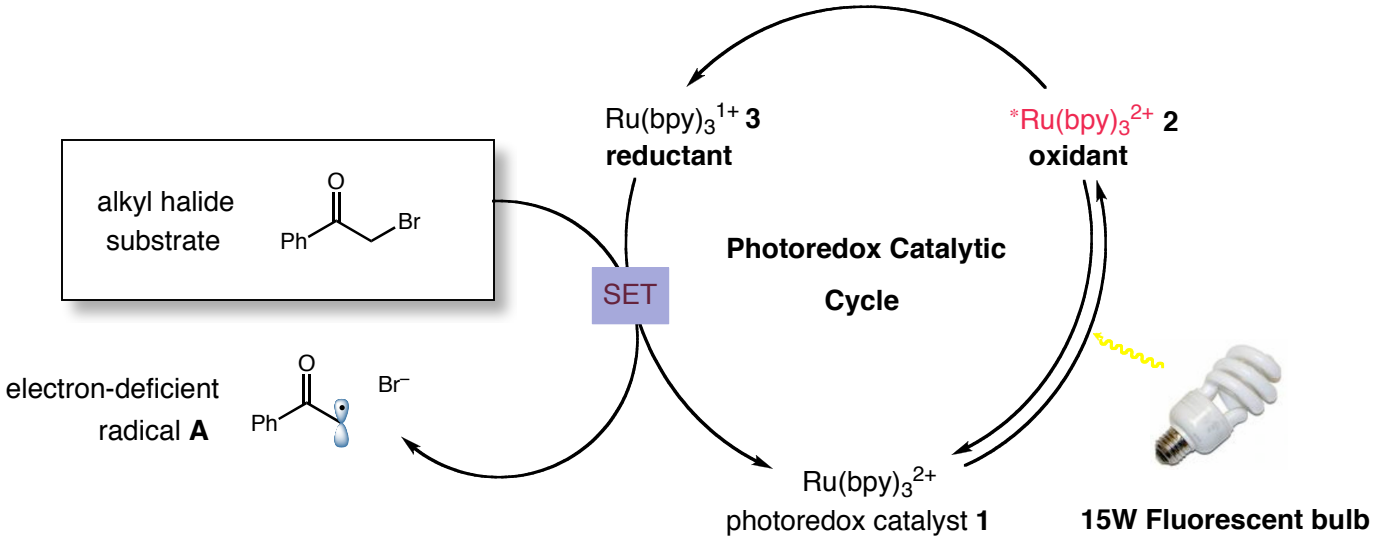
Merging Enantioselective Organocatalysis and Photoredox Catalysis



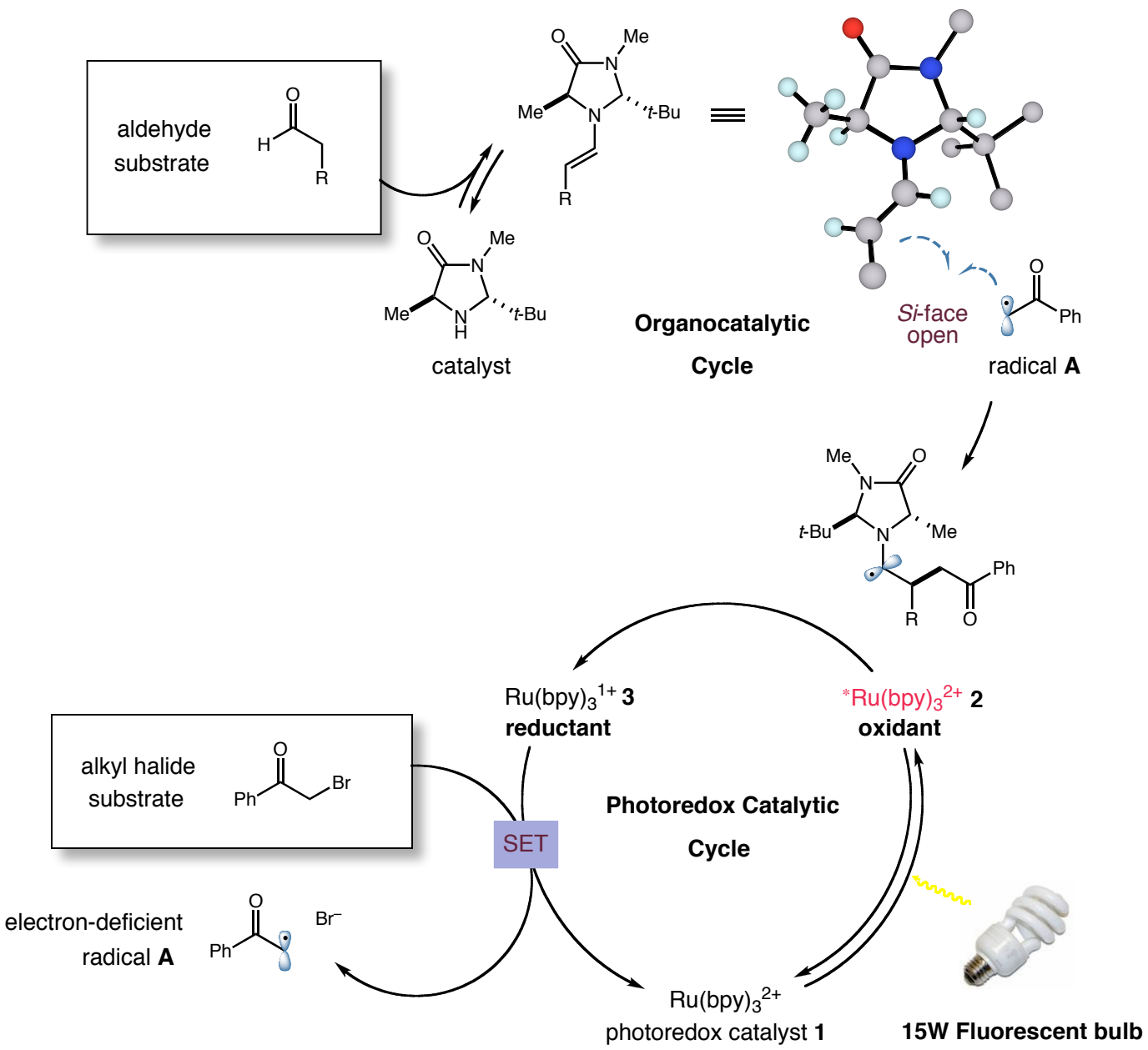


Merging Enantioselective Organocatalysis and Photoredox Catalysis

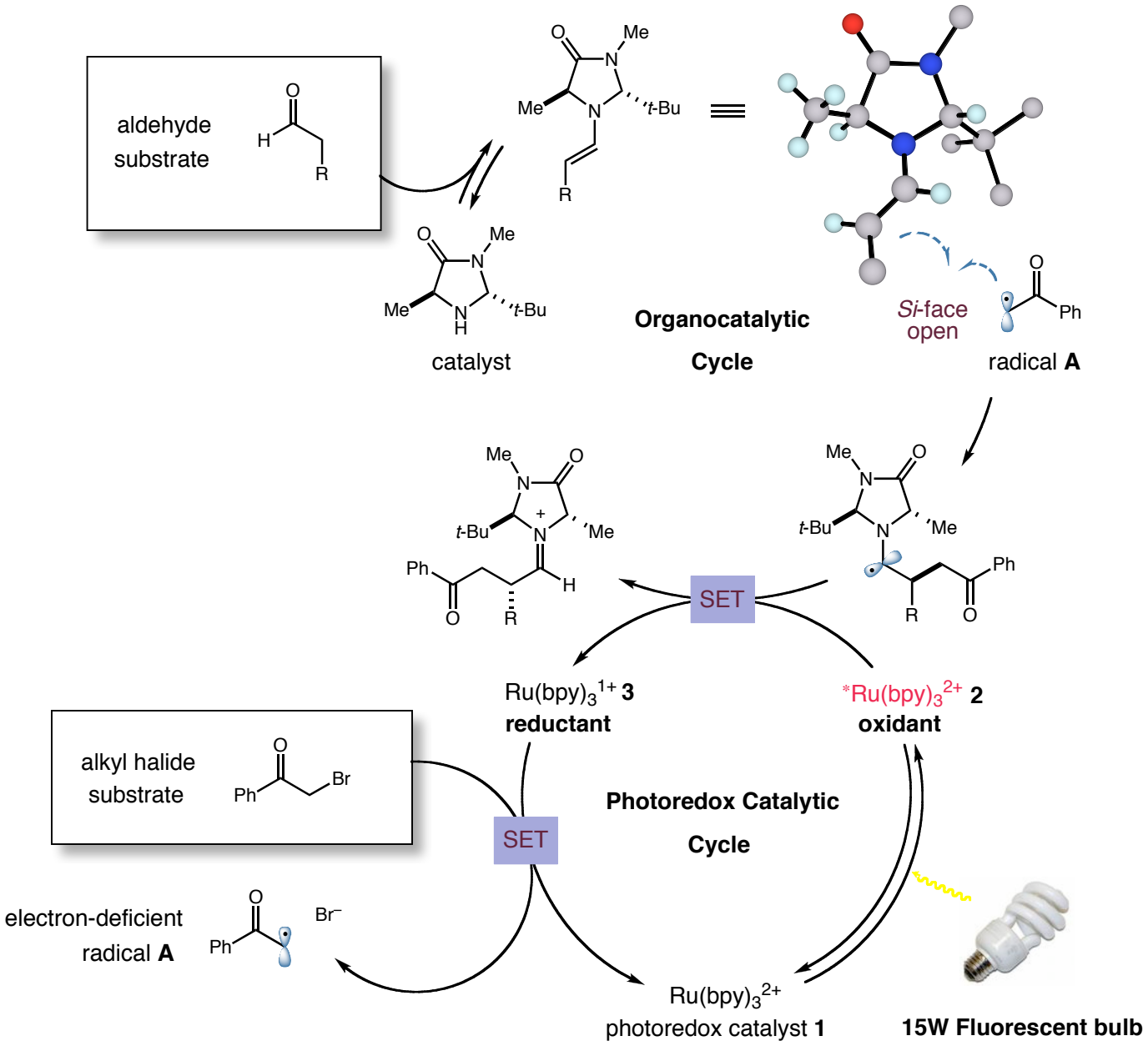




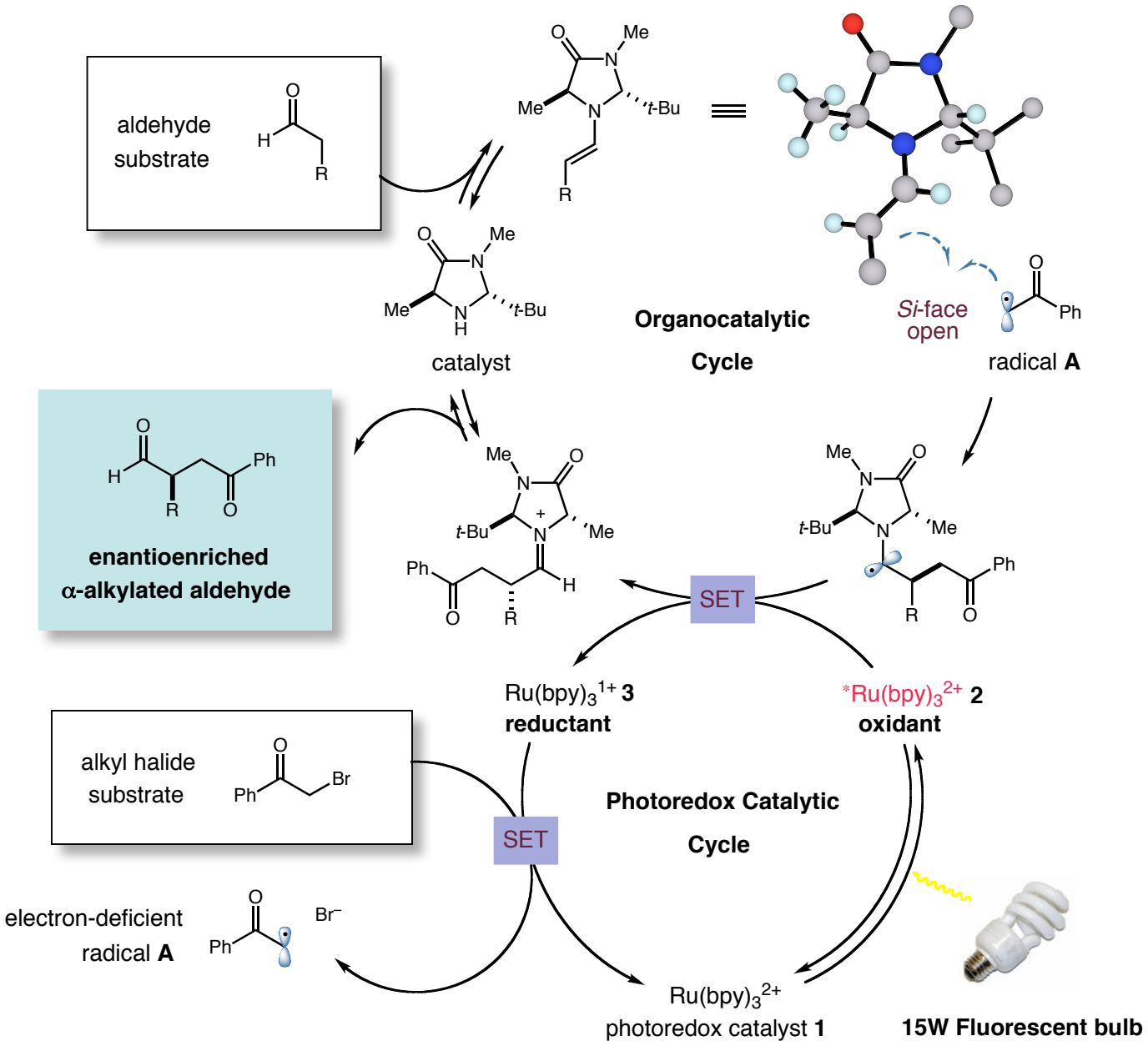
Merging Enantioselective Organocatalysis and Photoredox Catalysis



Merging Enantioselective Organocatalysis and Photoredox Catalysis

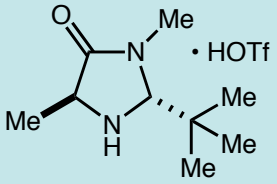


Merging Enantioselective Organocatalysis and Photoredox Catalysis

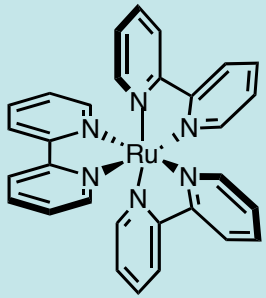


Merging Photoredox and Enantioselective Organocatalysis: Initial Results

Catalyst Combination



organocatalyst **A** (20 mol%)



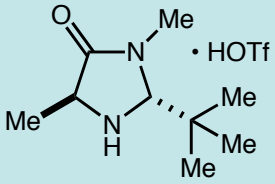
$Ru(bpy)_3Cl_2$ **B** (0.5 mol%)

Photon Source

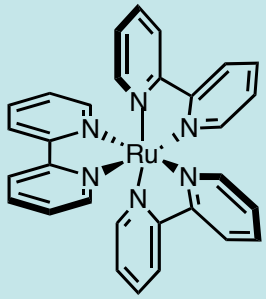
15 W fluorescent light bulb

Merging Photoredox and Enantioselective Organocatalysis: Initial Results

Catalyst Combination



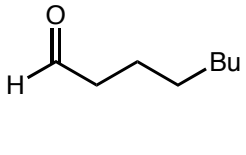
organocatalyst **A** (20 mol%)



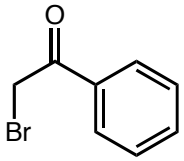
$Ru(bpy)_3Cl_2$ **B** (0.5 mol%)

Photon Source

15 W fluorescent light bulb



octanal



α-bromoketone

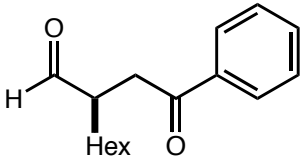
fluorescent light

organocatalyst **A**

$Ru(bpy)_3Cl_2$ **B**

2,6-lutidine, DMF,

23 °C



enantioenriched

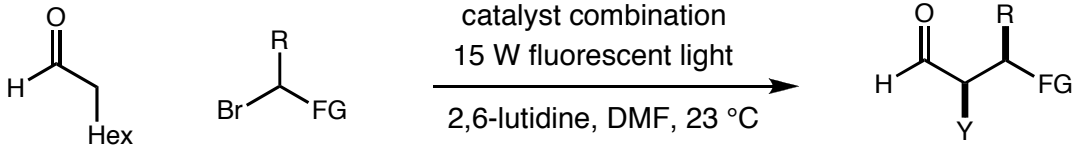
α-alkylated aldehyde

84% yield

96% ee

preliminary experiments revealed that the asymmetric tandem catalysis mechanism was possible

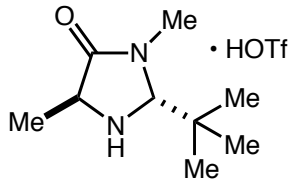
Photoredox and Organocatalysis: Bromocarbonyl Scope



octanal

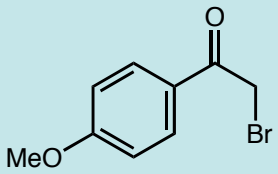
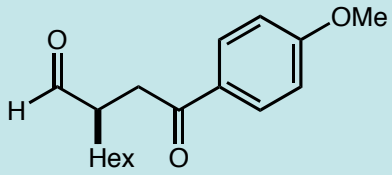
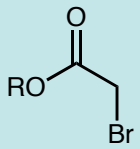
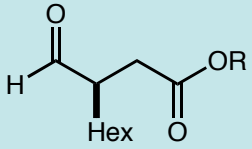
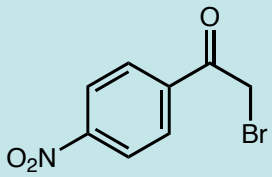
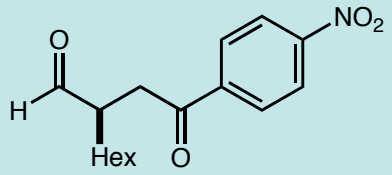
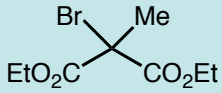
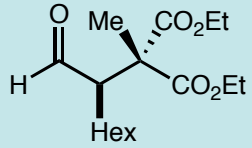
racemic α-bromocarbonyl

enantioenriched α-alkylated aldehyde



20 mol% catalyst

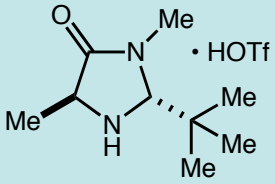
0.5 mol% $Ru(bpy)_3Cl_2$

α-bromocarbonyl	alkylation product	α-bromocarbonyl	alkylation product
			
	87% yield, 96% ee		80% yield, 92% ee
			
	84% yield, 95% ee		80% yield, 88% ee

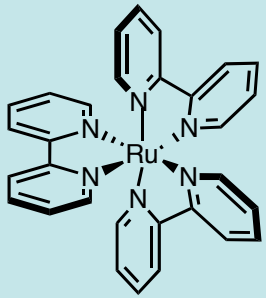
A variety of alkylation substrates can be used that are outside the realm of 2e pathways

Merging Photoredox and Enantioselective Organocatalysis: Initial Results

Catalyst Combination



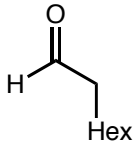
organocatalyst **A** (20 mol%)



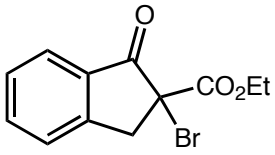
$Ru(bpy)_3Cl_2$ **B** (0.5 mol%)

Photon Source

15 W fluorescent light bulb



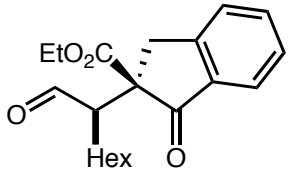
octanal



racemic
α-bromoketone

fluorescent light

organocatalyst **A**
$Ru(bpy)_3Cl_2$ **B**
2,6-lutidine, DMF,
23 °C

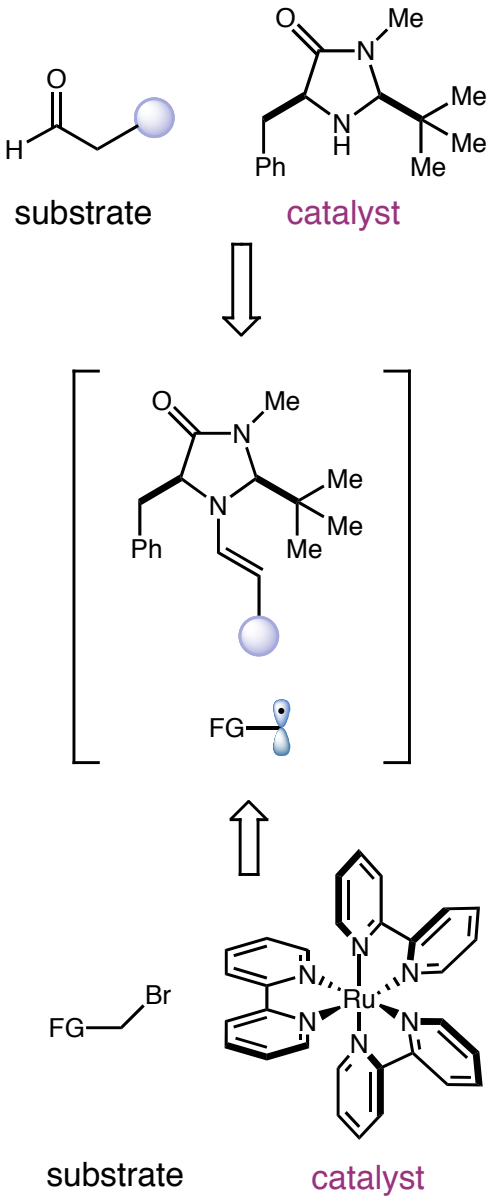


enantioenriched
α-alkylated aldehyde

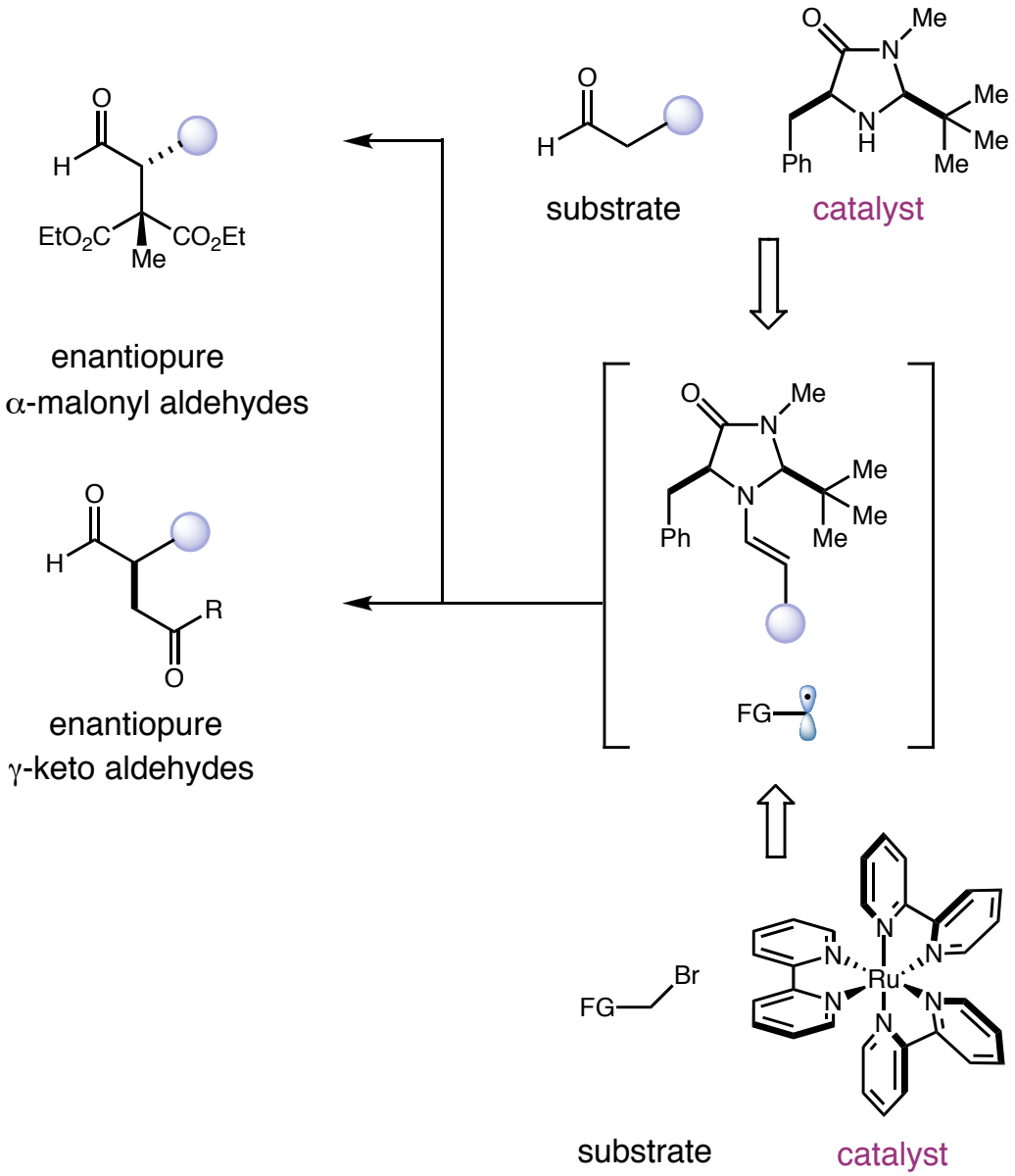
70% yield,
5:1 dr, 99% ee

with David Nicewicz, *Science*, **2008**, *3*, 77 (published online Thurs, Sept 4th)

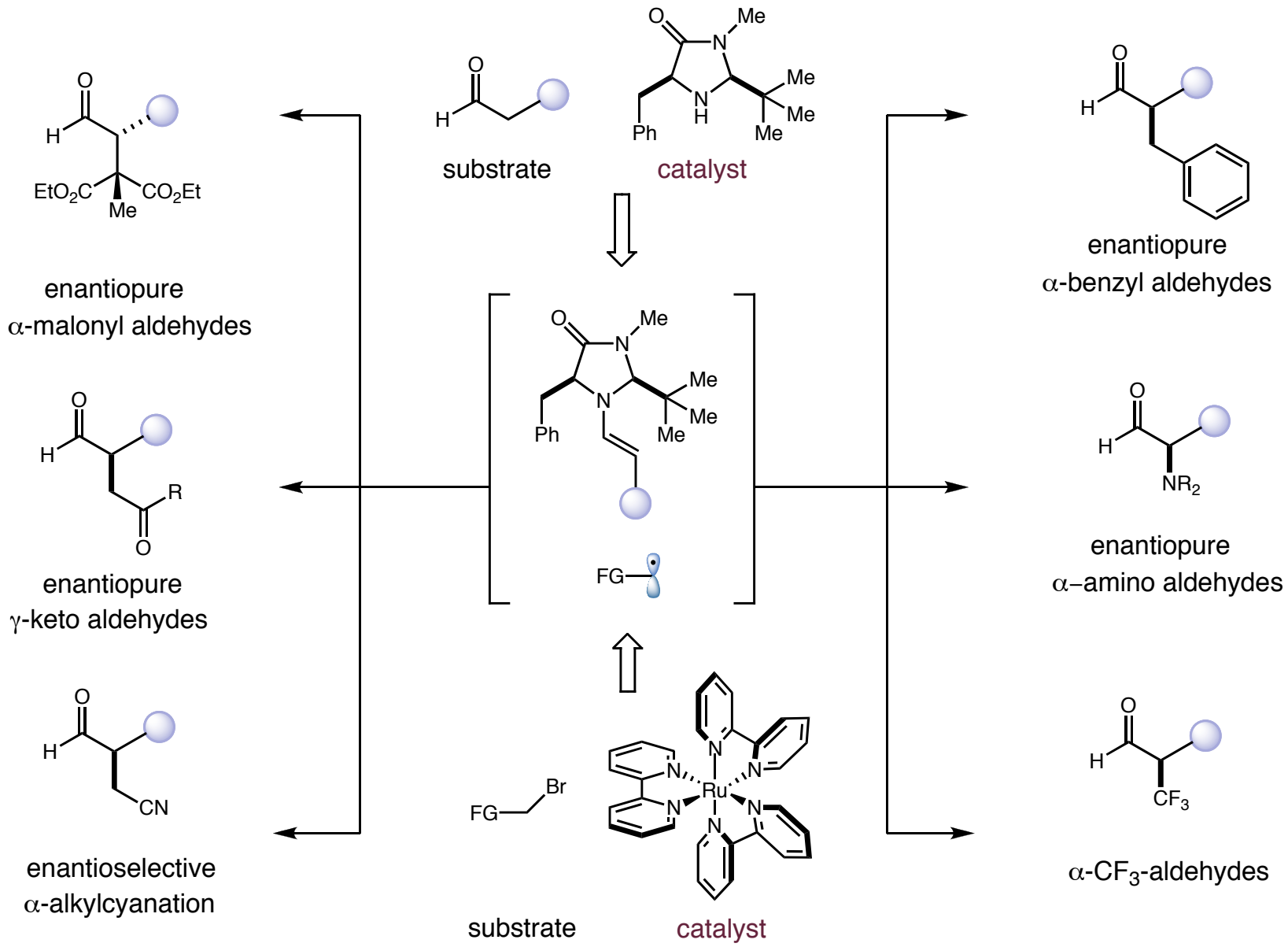
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



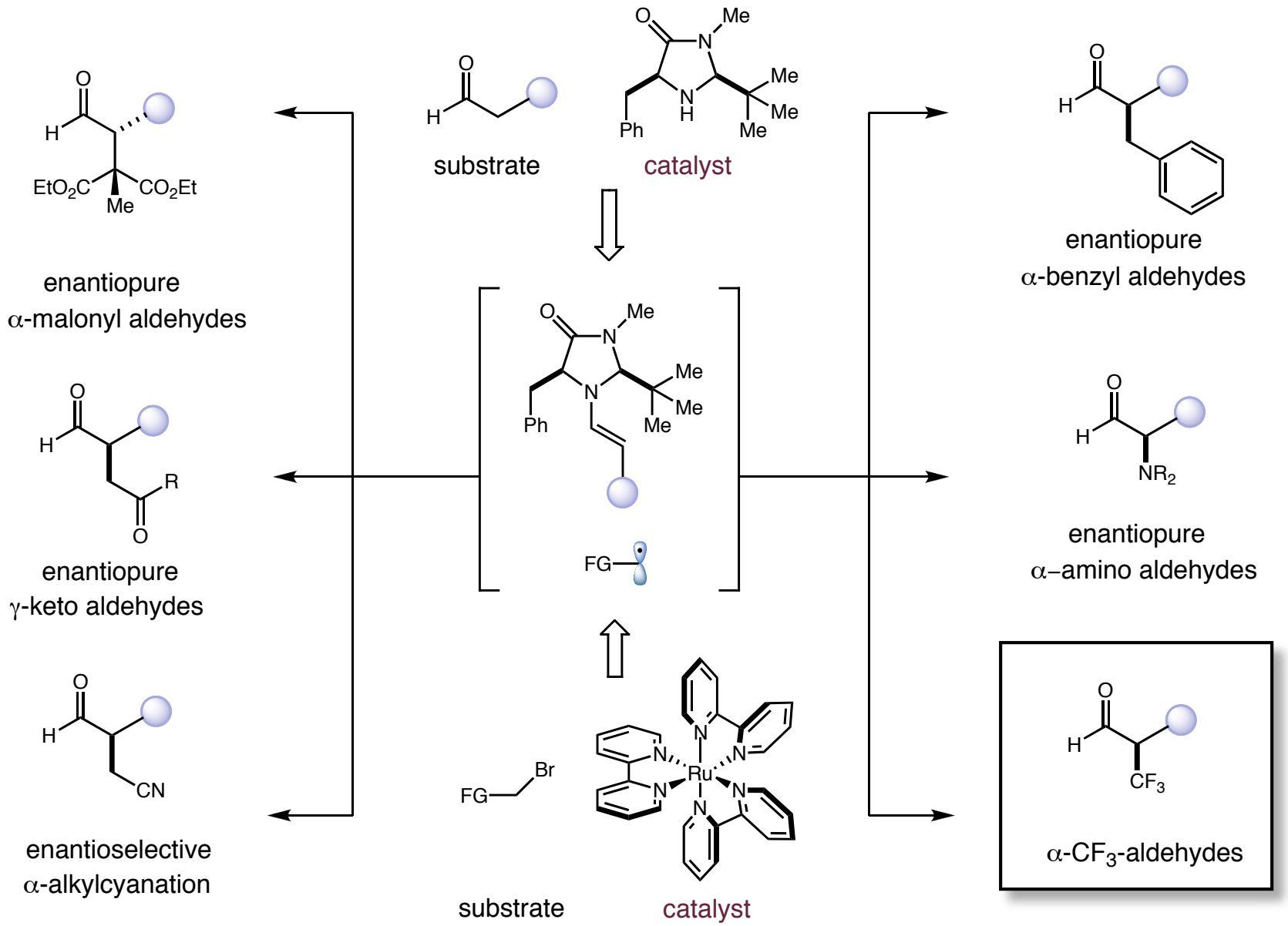
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



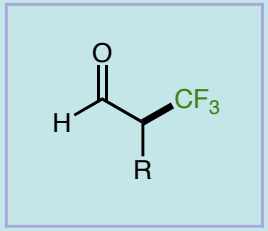
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



Photoredox Organocatalysis: Potential Utility of New Catalysis Platform

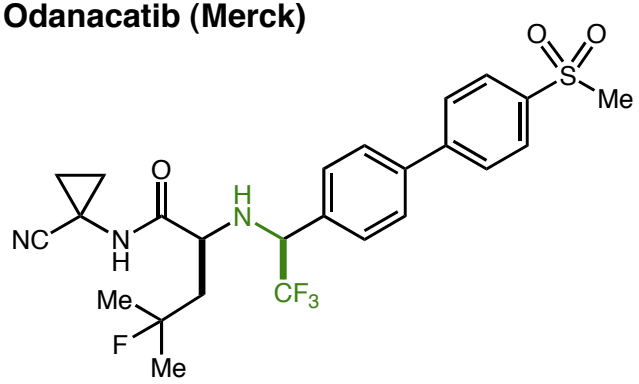


Merging Photoredox and Organocatalysis: α-Perfluoroalkylation

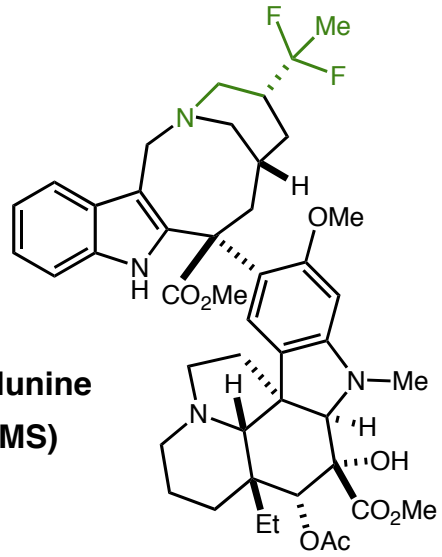


- Versatile synthon for medicinal agent synthesis
- Enhance potency, elevate lipophilicity and/or improve metabolic stability
- No known catalytic routes to α-formyl CF_3

Odanacatib (Merck)

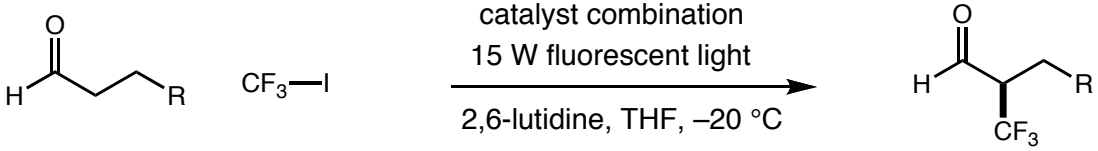


Vinflunine (BMS)



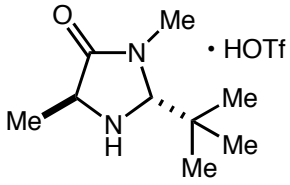
Enantioselective α-perfluoralkylation of formyl could provide new entry to pharmacaphores

Photoredox and Organocatalysis: Trifluoromethylation



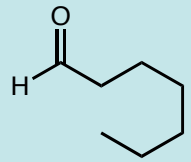
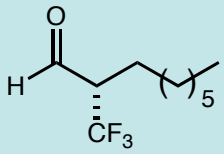
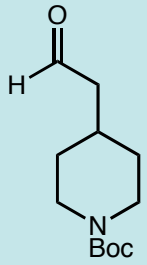
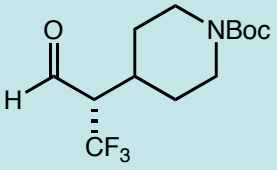
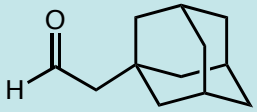
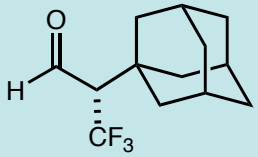
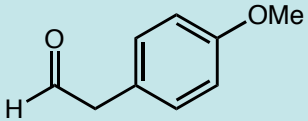
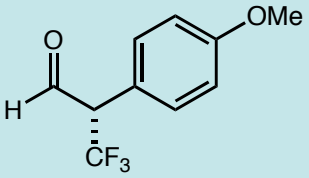
aldehyde trifluoromethyl iodide

enantioenriched
α-trifluoromethylation



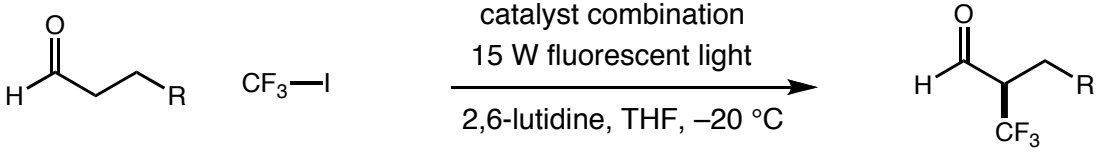
20 mol% catalyst

0.5 mol% $Ir(ppy)_2bpy$

aldehyde	trifluoromethylation product	aldehyde	trifluoromethylation product
	 79% yield, 99% ee		 70% yield, 98% ee
	 73% yield, 90% ee		 61% yield, 93% ee

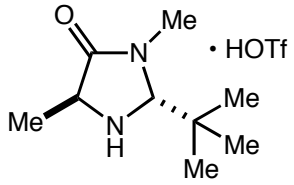
with Nagib, Scott, *JACS*, **2009**, *131*, 10875

Photoredox and Organocatalysis: Trifluoromethylation



aldehyde trifluoromethyl iodide

enantioenriched
α-trifluoromethylation



20 mol% catalyst

0.5 mol% $Ir(ppy)_2bpy$

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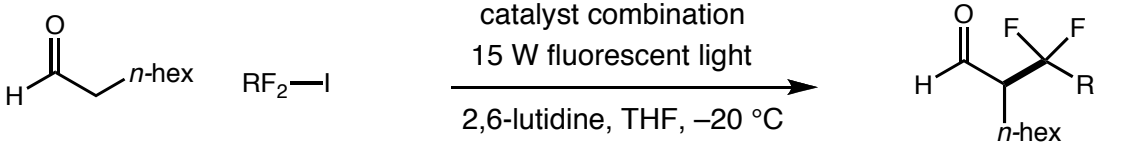
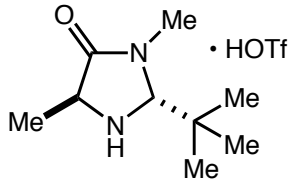
Photoredox and Organocatalysis: perfluoroalkylation



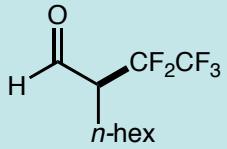
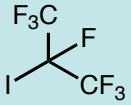
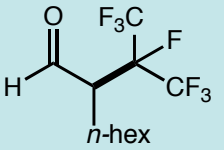
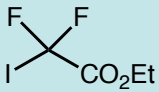
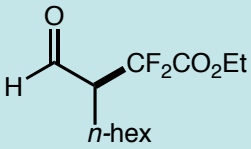
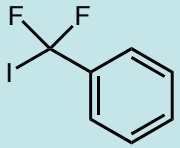
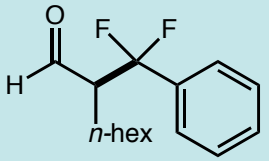
aldehyde fluoroalkyl iodide

enantioenriched α-perfluoroalkylation



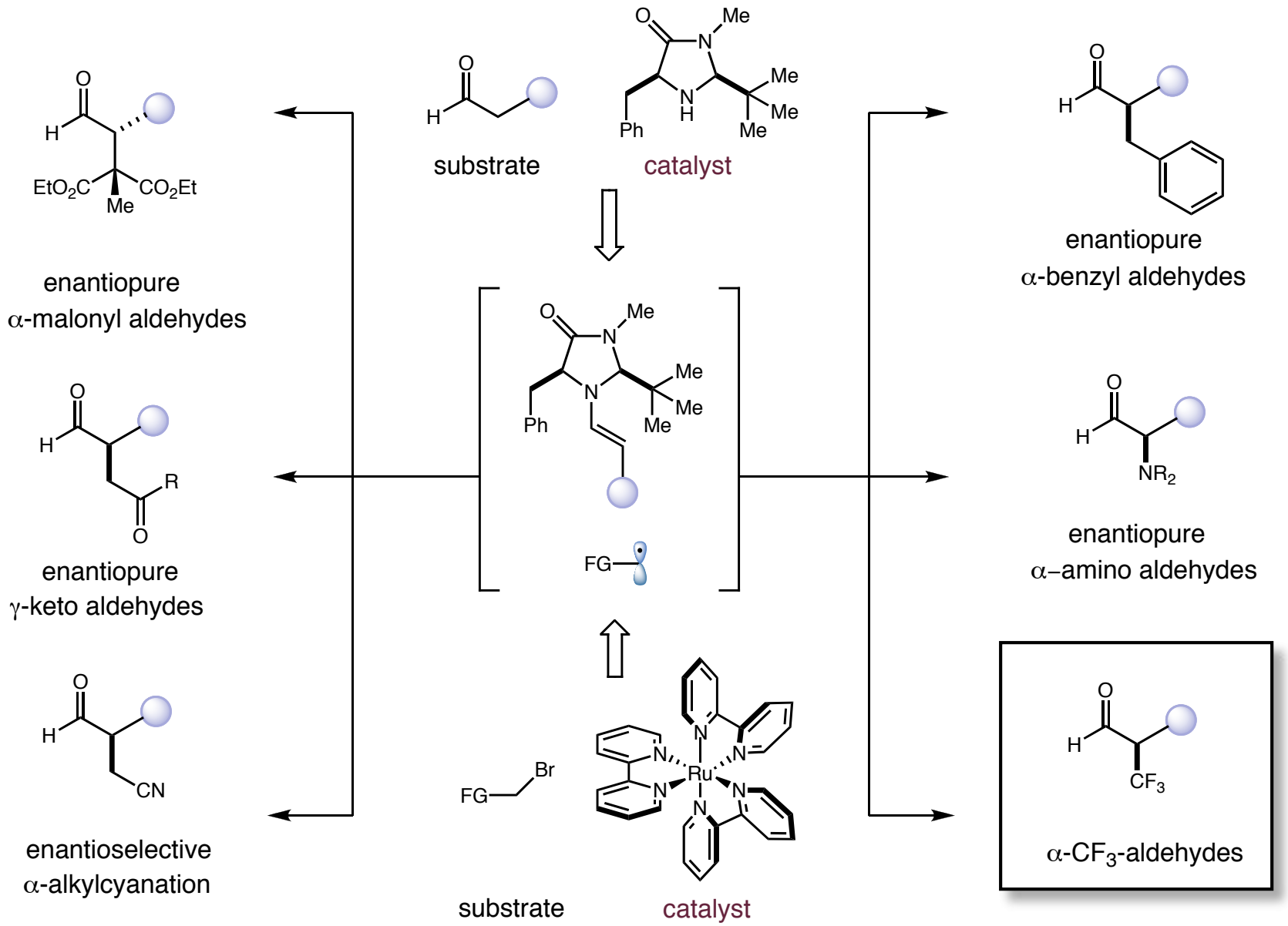
20 mol% catalyst

0.5 mol% $Ir(ppy)_2bpy$

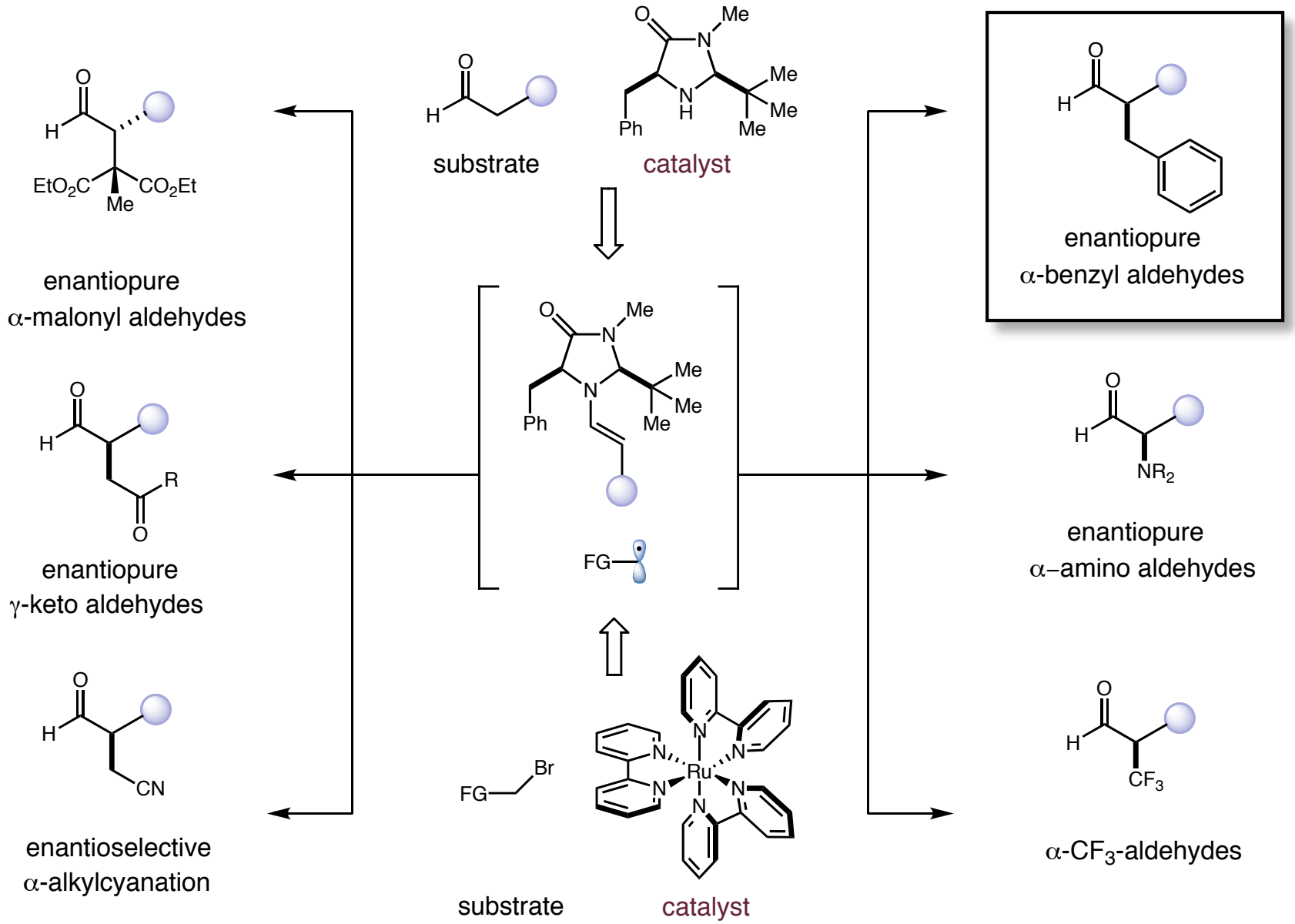
RF_n–I	fluoroalkylation product	RF_n–I	fluoroalkylation product
$I—CF_2CF_2$	 73% yield, 96% ee		 72% yield, 98% ee
	 89% yield, 99% ee		 85% yield, 98% ee

with Nagib, Scott, *JACS*, **2009**, *131*, 10875

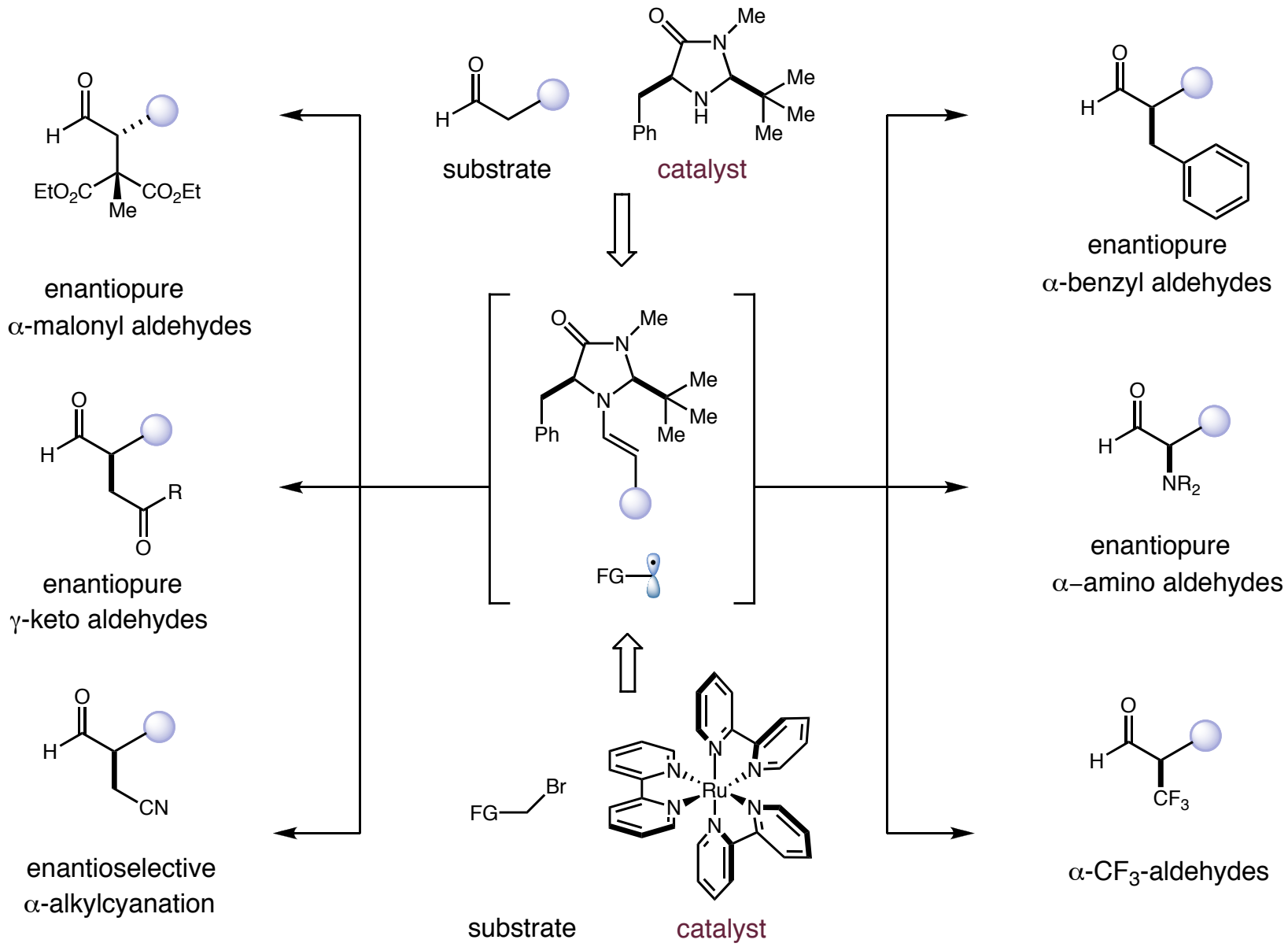
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



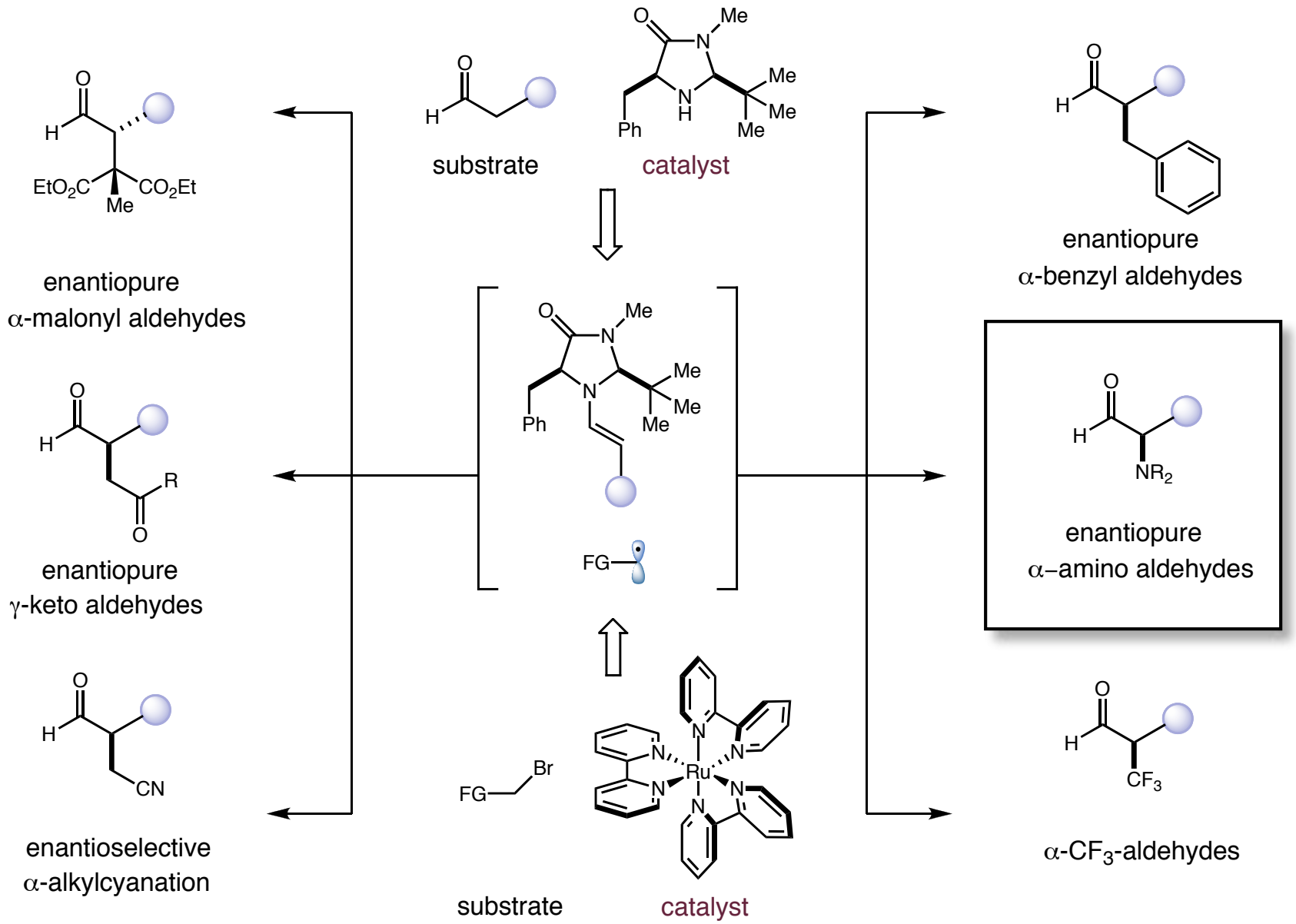
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



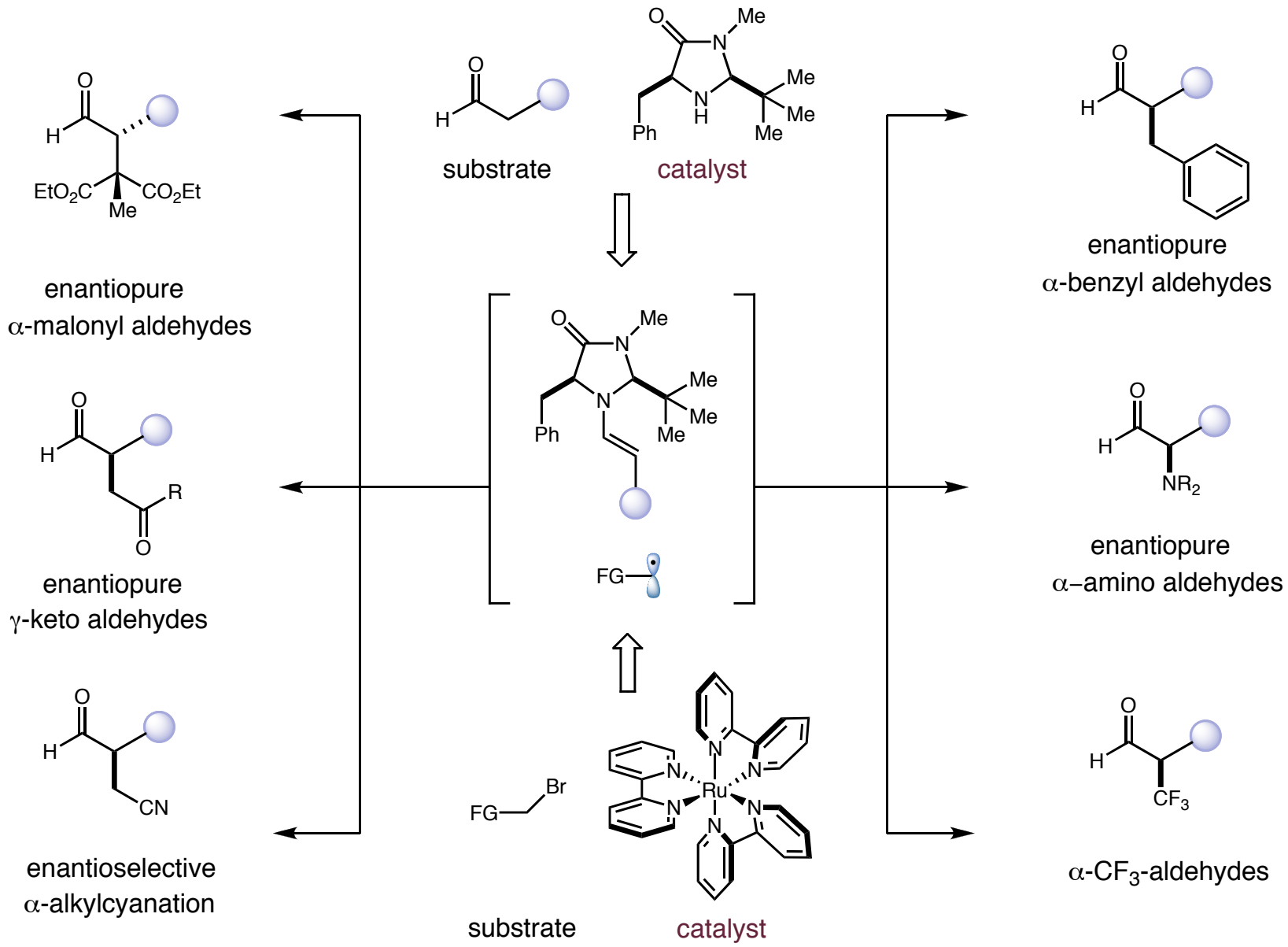
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



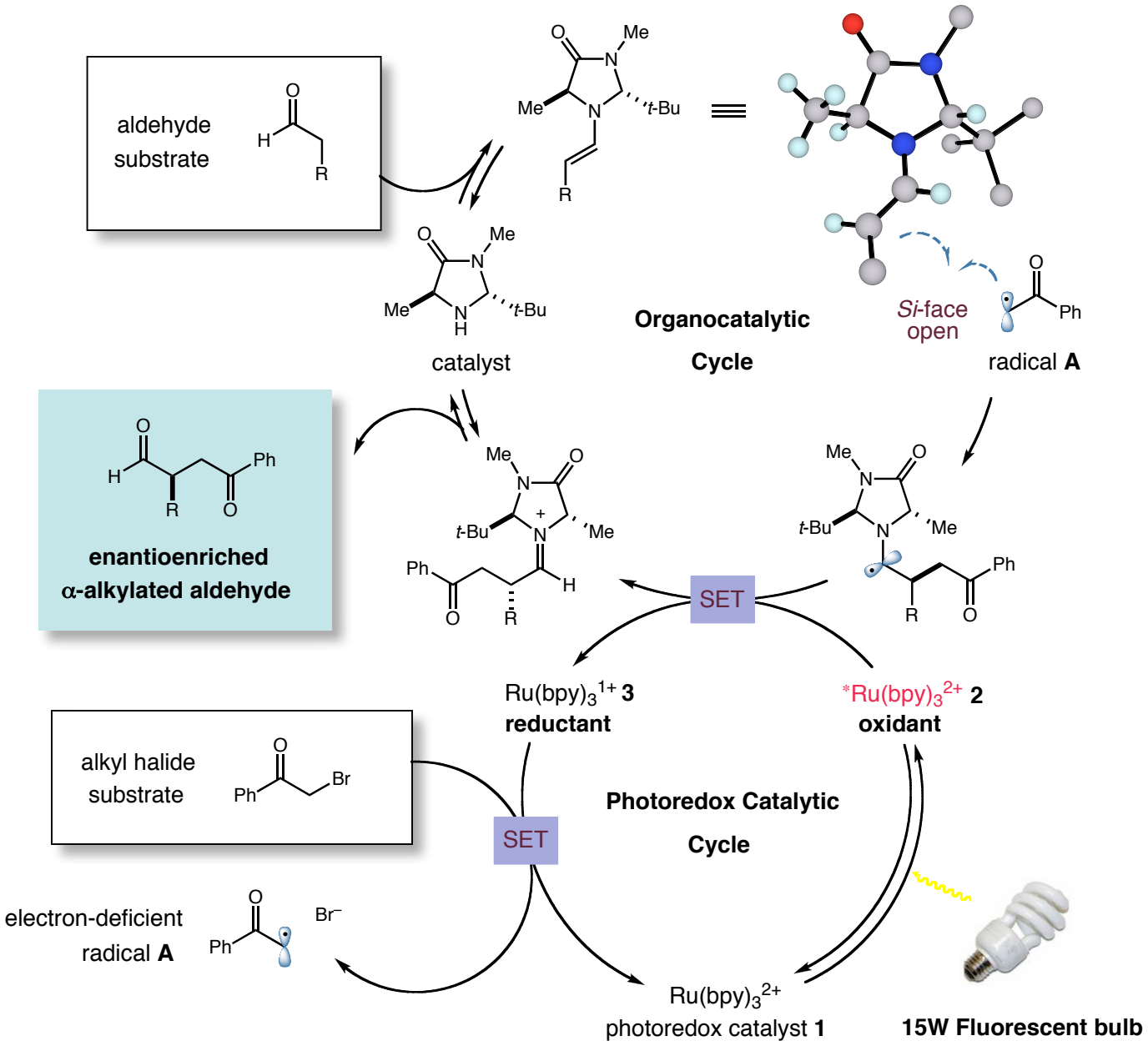
Photoredox Organocatalysis: Potential Utility of New Catalysis Platform



Photoredox Organocatalysis: Potential Utility of New Catalysis Platform

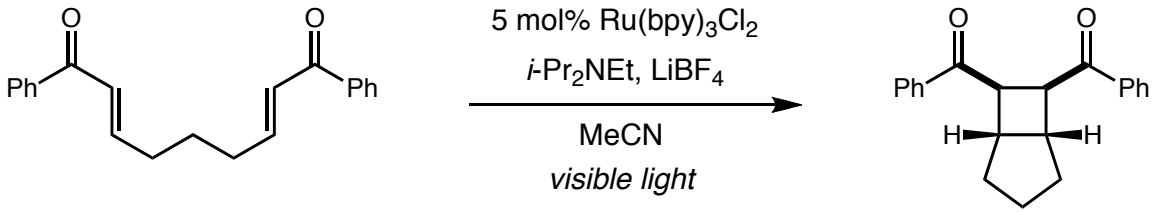


Merging Enantioselective Organocatalysis and Photoredox Catalysis



Photoredox Catalysis: New Directions for Organic Synthesis

■ Visible Light Photocatalysis of [2+2] Enone Cycloadditions



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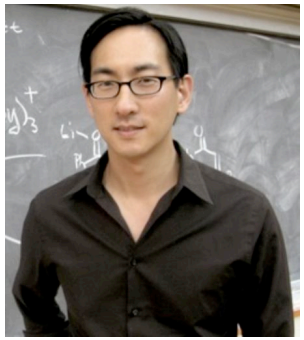

Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12866-12887.
J. Am. Chem. Soc. **2009**, *131*, 14604-14605.

Photoredox Catalysis: New Directions for Organic Synthesis

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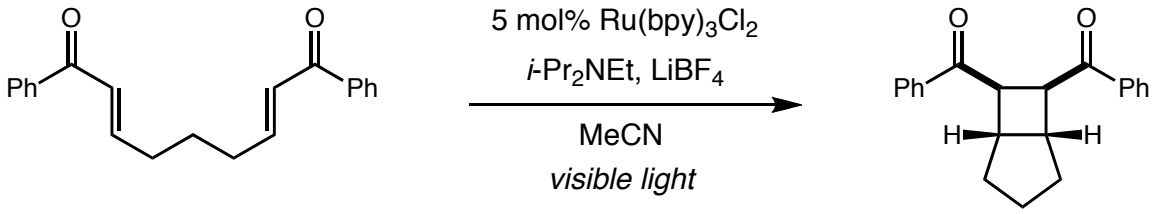

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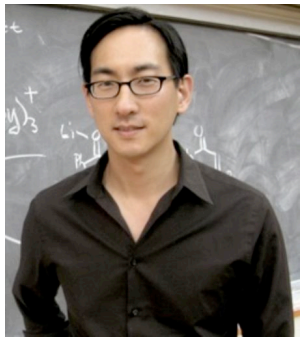
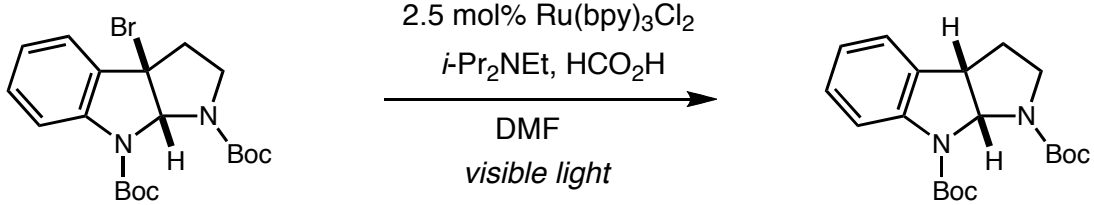


Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12866-12887.
J. Am. Chem. Soc. **2009**, *131*, 14604-14605.

■ Photoredox Catalysis: Hydro-dehalogenation of alkanes



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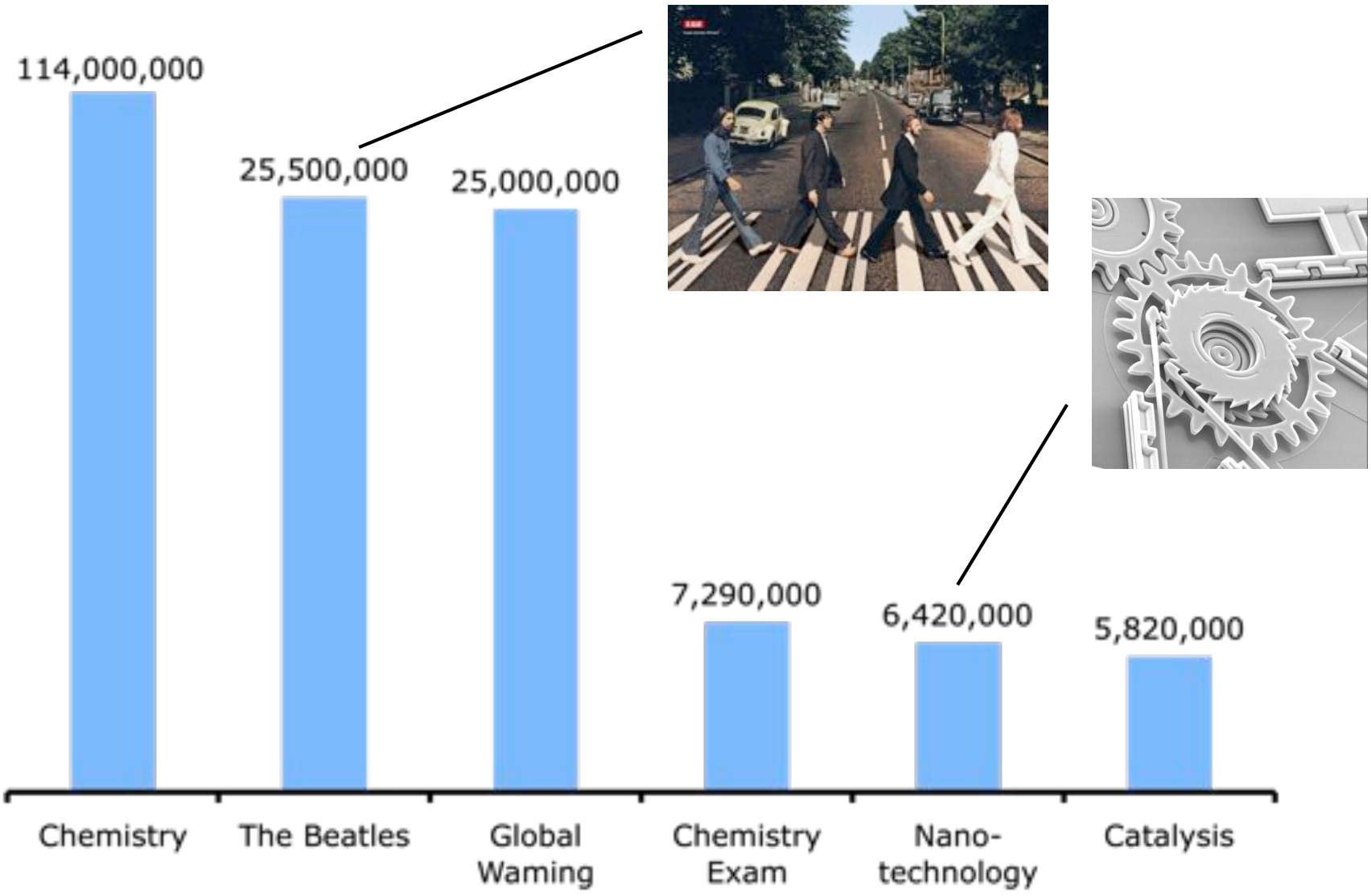
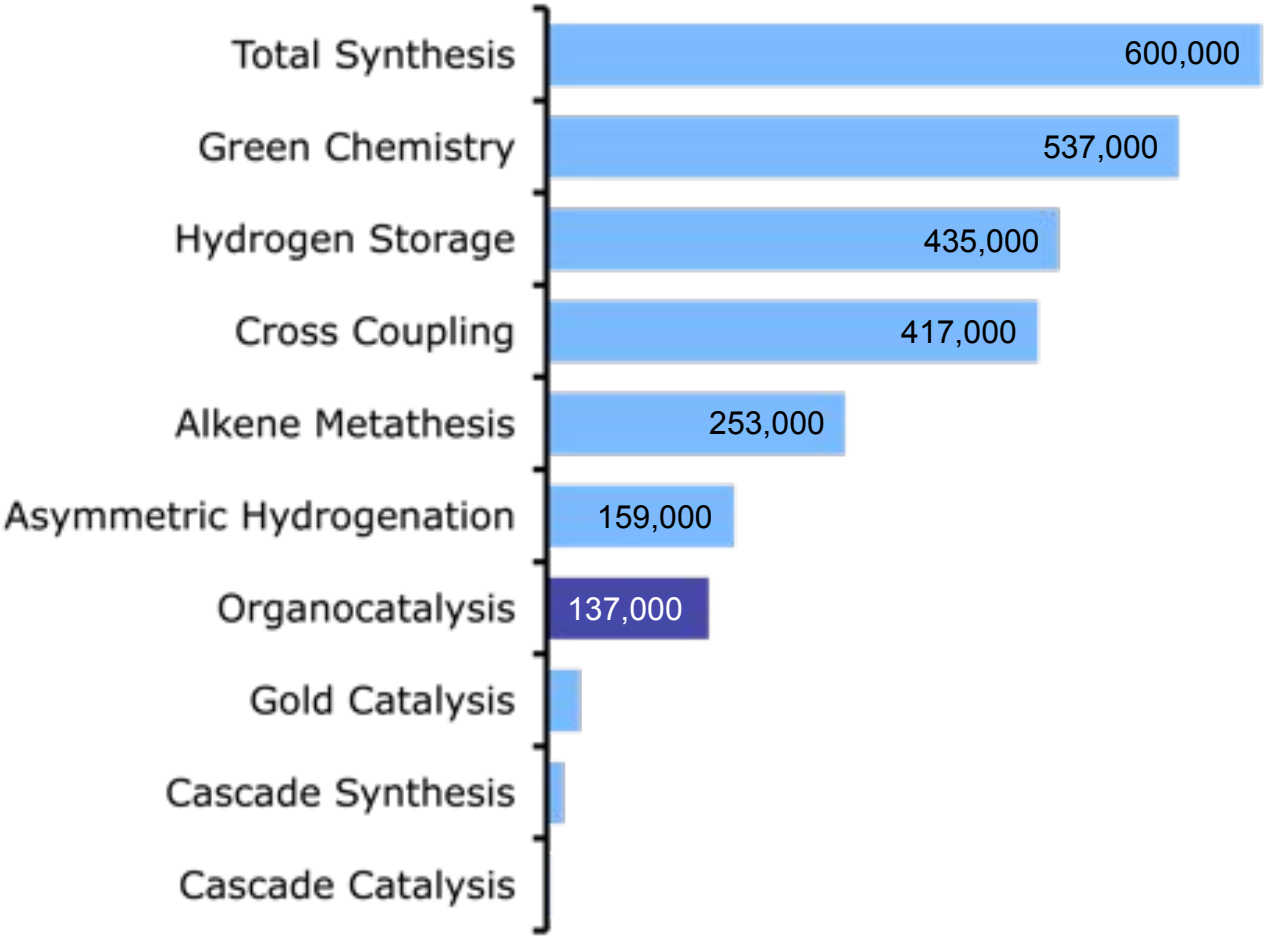
Stephenson, C. R. J. *J. Am. Chem. Soc.* **2008**, *130*, 12866-12887.

Putting Science, Catalysis and Organocatalysis in Context

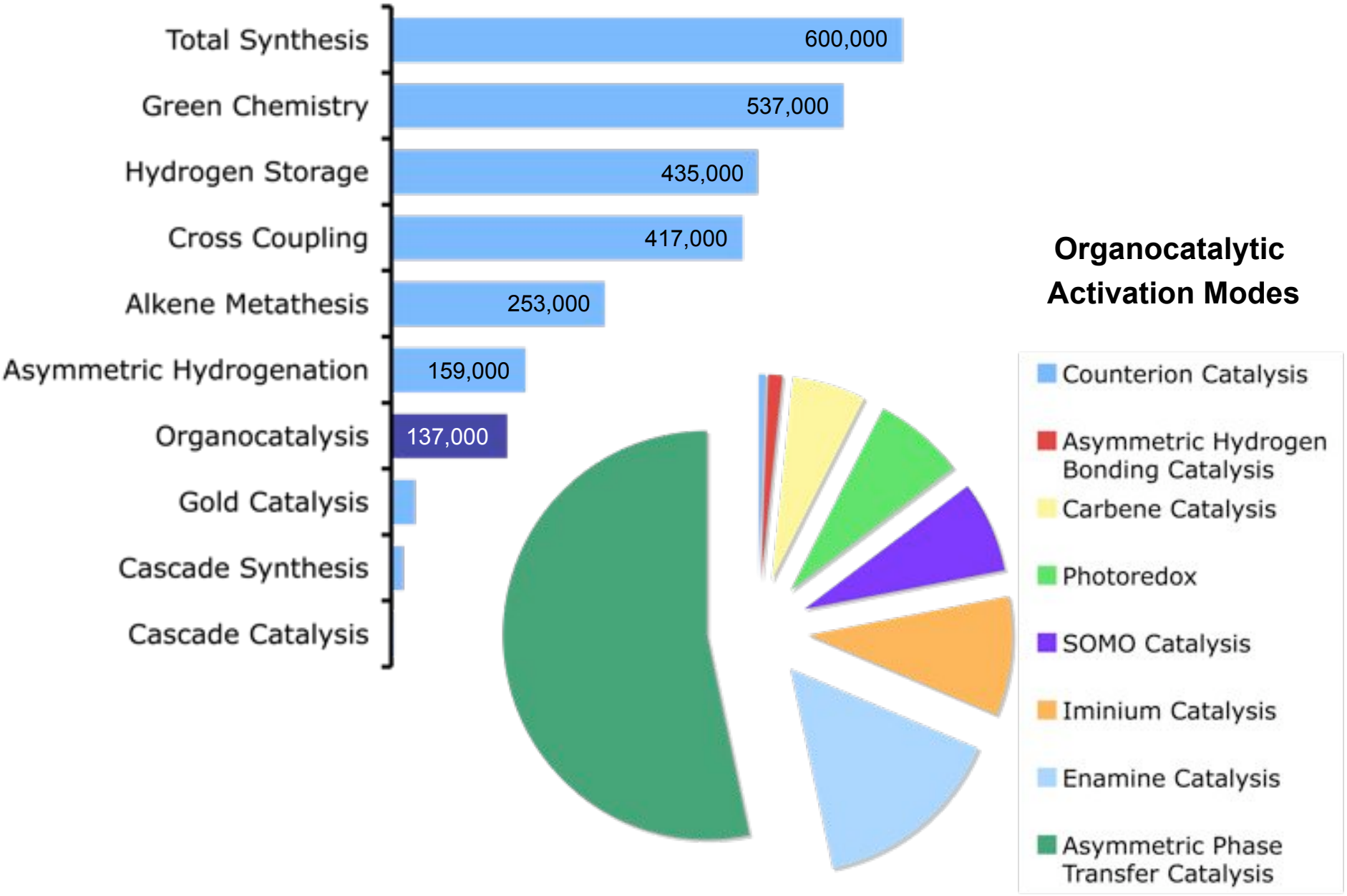
# of Hits for Google Keyword Search:



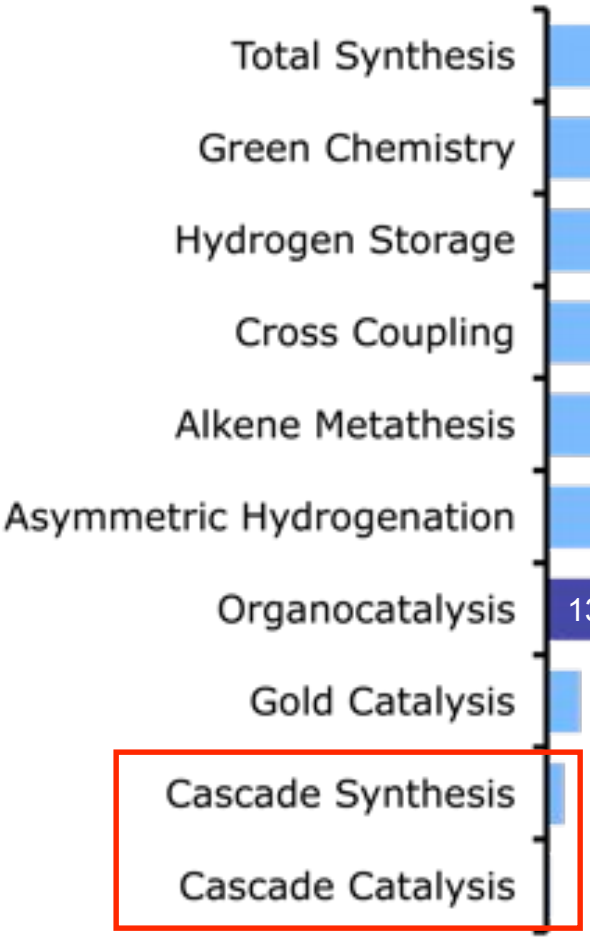
Overview of Chemistry Hot Topics – Google Hits



Overview of Chemistry Hot Topics – Google Hits

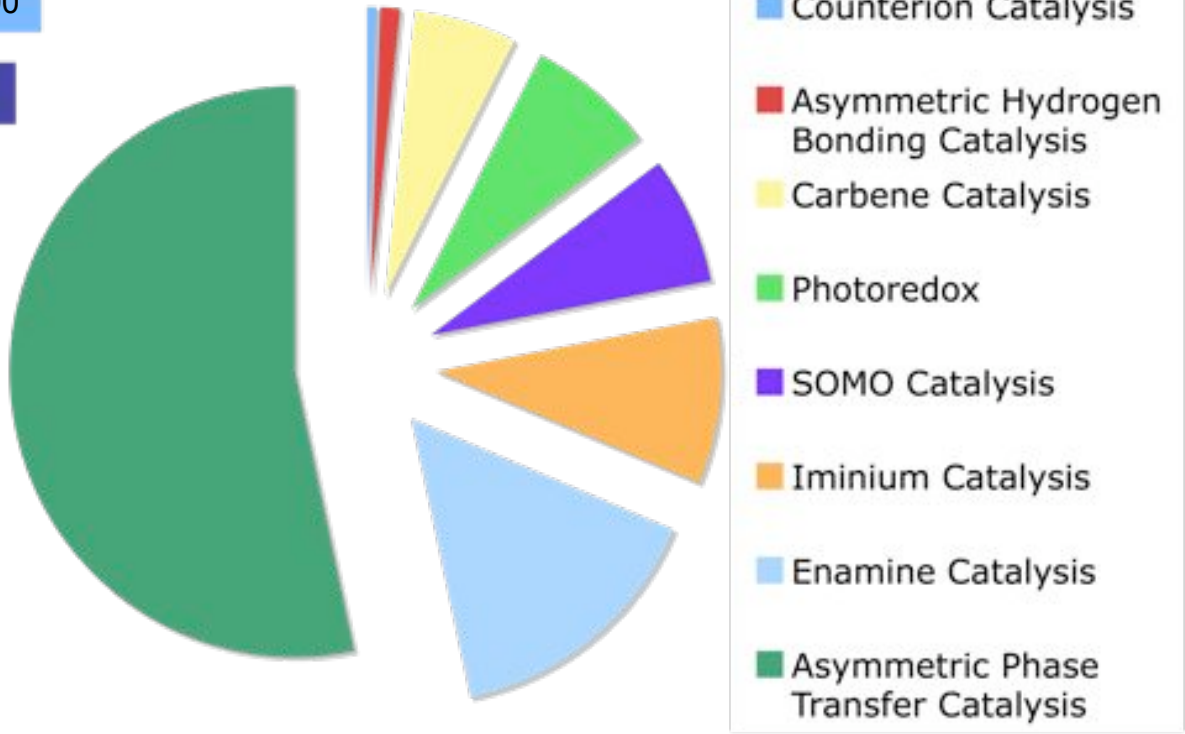


Overview of Chemistry Hot Topics – Google Hits



Emerging Important Areas

Organocatalytic Activation Modes



The early years: Berkeley

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Chris Borths	Jake Wiener
Vy Dong	Tehshik Yoon
Wendy Jen	Dr. Jeongbob Seo

Naiomi Anchor (UG)

MacMillan Group Caltech 2002

Joel Austin
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Sean Brown
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Dr. Chris Sinz
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Rebecca Wilson
Dr. Wenjing Xiao
Tehshik Yoon

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Dr. Kate Ashton
Teresa Beeson
Joe Carpenter
Diane Carrera
Dr. Jay Conrad
Dr. Tom Graham
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Dr. Pilar Garcia Garcia
Dr. J. B. Hong
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Nate Jui
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Phong Pham
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Katie Saliba
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Grace Wang
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Joe Carpenter
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Jae Won Lee
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Dr. Rebecca Grange
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Cottrell Scholar

Funding (pharmaceutical)