

**Visible Light Photoredox Catalysis in Organic  
Chemistry  
~Toward Green & Efficient Reactions~**

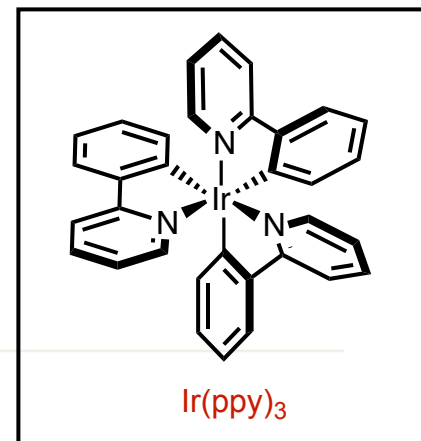
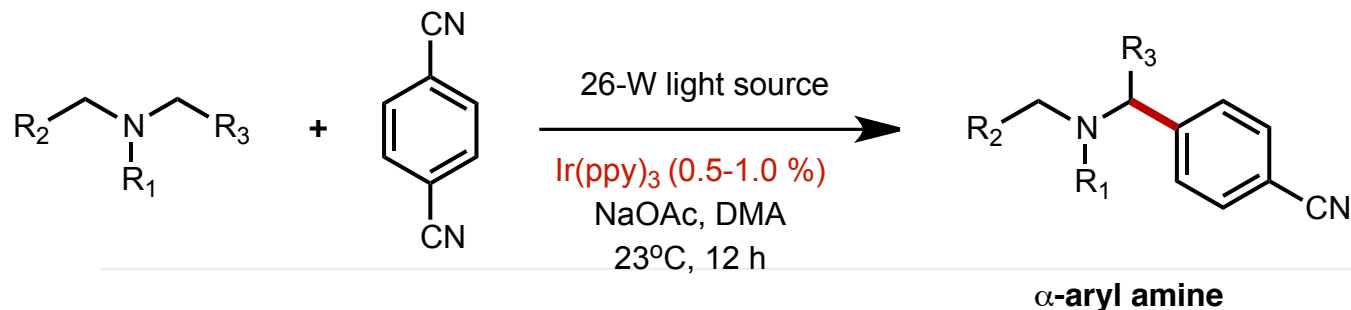
**DAMITH PERERA**

**DEPARTMENT OF CHEMISTRY**

**MICHIGAN STATE UNIVERSITY**

**18 JANUARY, 2012**

# Photoredox Reaction: A Most Recent Example

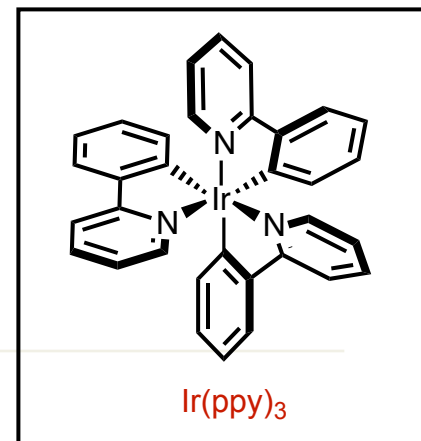
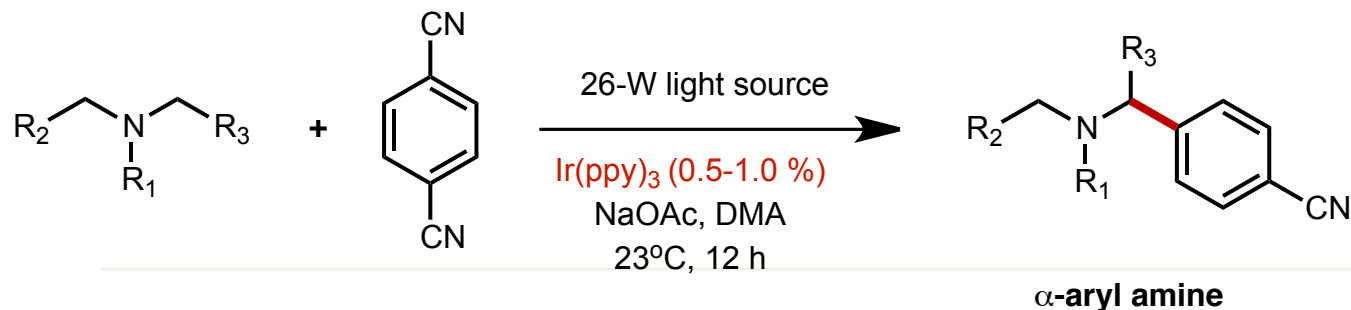


“Discovery of an alpha-Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity”

McNally, A.; Prier, C. K.; MacMillan, D. W. C.

*Science* **2011**, *334*, 1114-1117.

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“Discovery of an alpha-Amino C–H Arylation Reaction Using the Strategy of  
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# Serendipity

- Serendipity: Fortunate Discoveries by Accident
- Serendip, a former name for [Sri Lanka](#) + -ity.
- In Science:

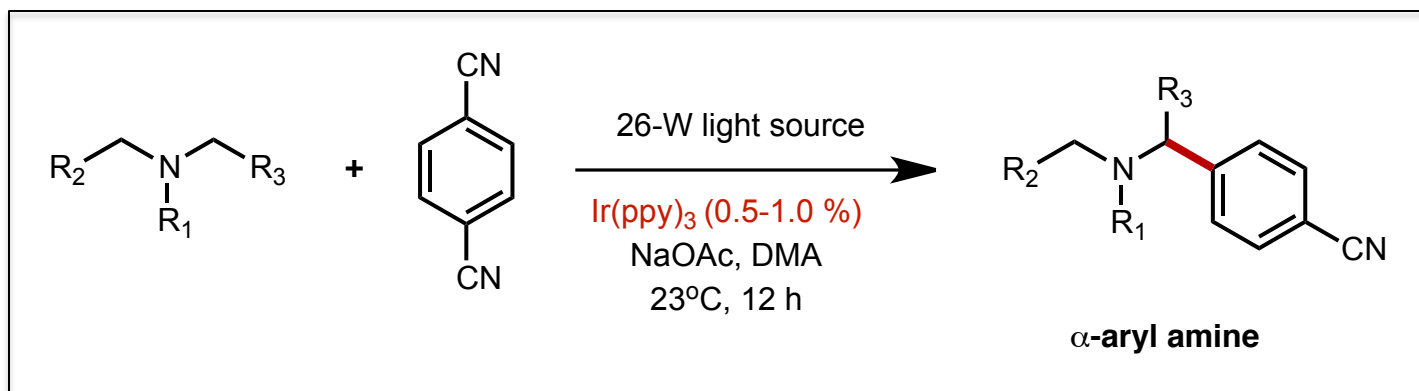
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“ It is true that my discovery of LSD was a chance discovery, but it was the outcome of planned experiments and these experiments took place in the framework of systematic pharmaceutical, chemical research. It could better be described as serendipity ”

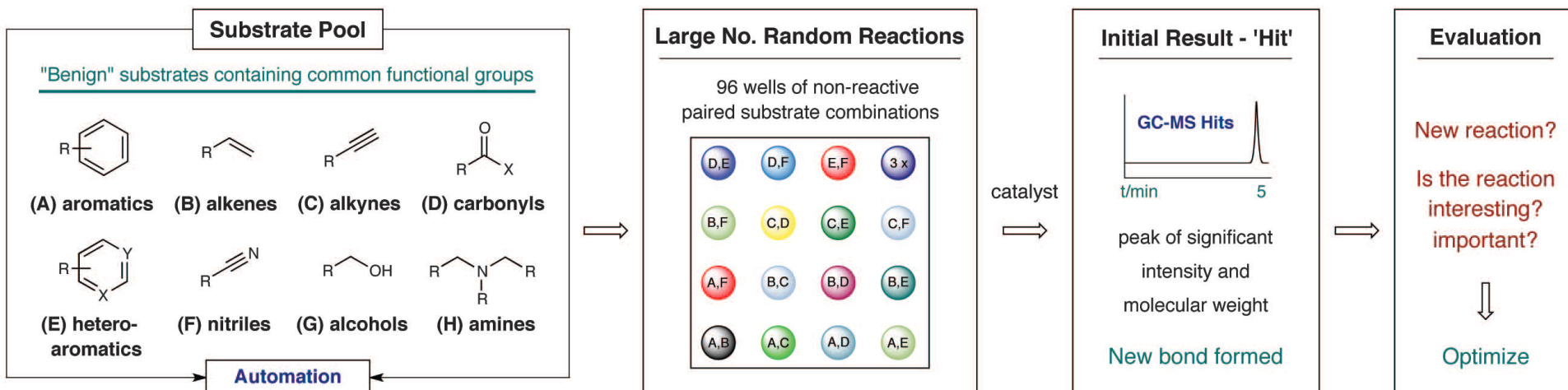
- *Albert Hofmann*

- Discovery of penicillin (Alexander Fleming) & cisplatin (Barnett Rosenberg)

# Accelerated Serendipity



Reaction discovery via accelerated serendipity: High-throughput combination and evaluation of benign substrates and catalysts



Choice of Catalysis: Photoredox Catalysis

# Why Photoredox Catalysis?



Visible Light (43% of Solar Energy): Readily available, clean and renewable.

An attractive “reagent” for organic synthesis

- Potential byproducts are minimized
- Atom economical
- Mild alternative to traditional methods
- Environmentally friendly

**Problem:** Many organic molecules are unable to absorb visible light requiring highly specialized energy sources for traditional photochemistry

**Solution:** Photoredox catalysis

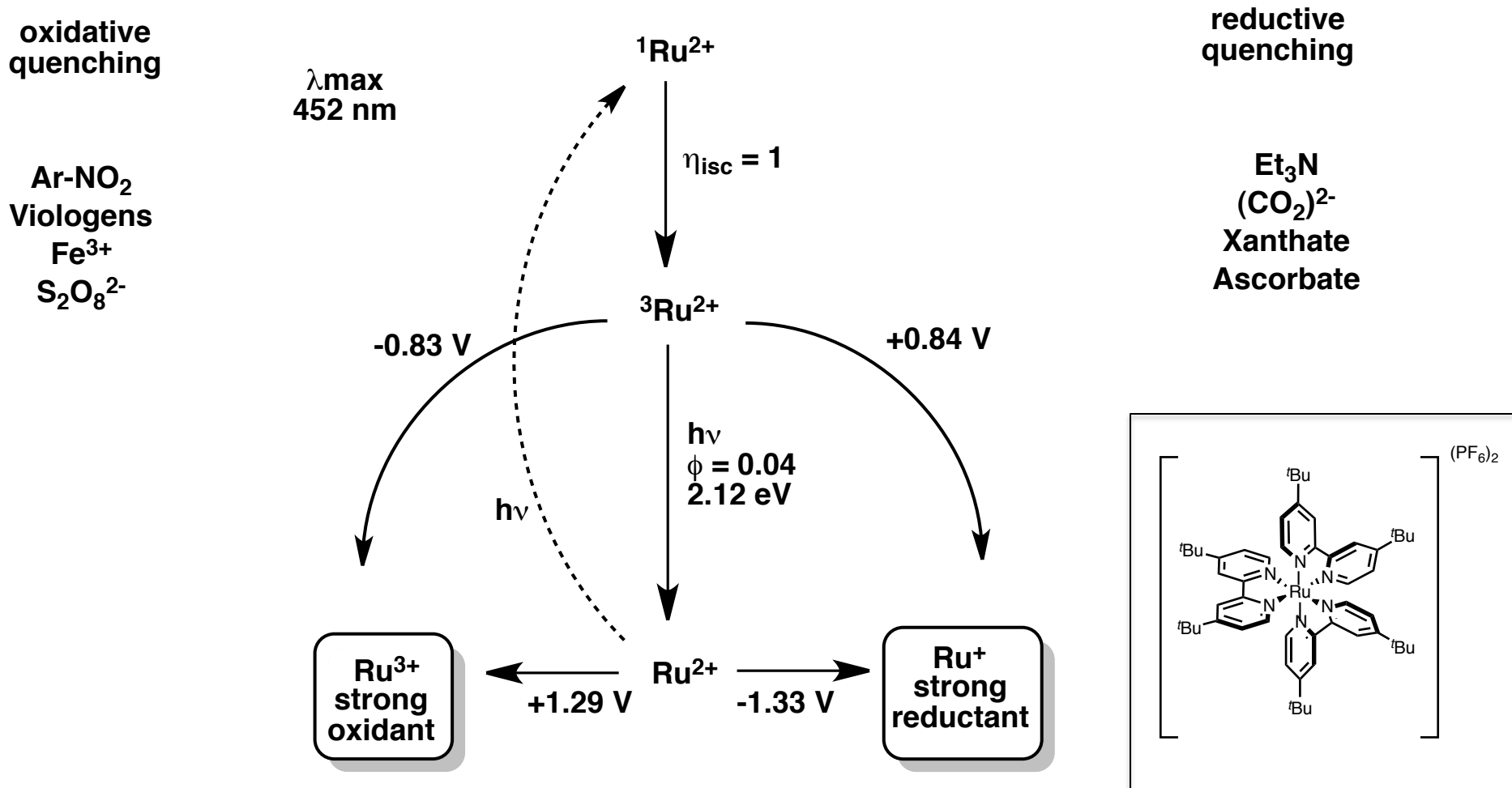
For an early discussion of visible light in photochemical reactions see Ciamician, G. *Science* **1912**, *36*, 385–394.

# Why Photoredox Catalysis?

“It is a relatively young and emerging field in organic synthesis that has recently delivered a variety of powerful bond-forming processes”

*-David MacMillan*

# Basics of Photoredox Catalysis



Oxidative and Reductive quenching photoredox cycles of  $[\text{Ru}(\text{bpy})_3]^{2+}$

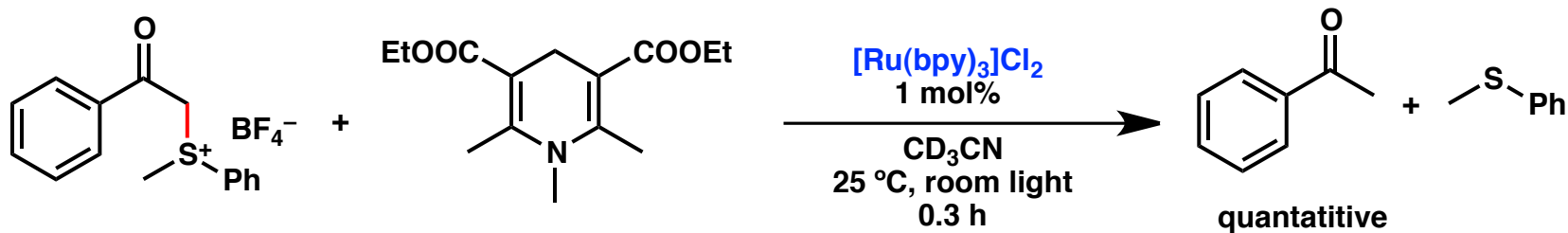
Teply, F. *Collect. Czech. Chem. Commun.* **2011**, 76, 859.

Narayanam, J. M. R.; Stephenson, C. R. *J. Chem. Soc. Rev.* **2011**, 40, 102.



# History of Photoredox Catalysis

Kellogg



1978

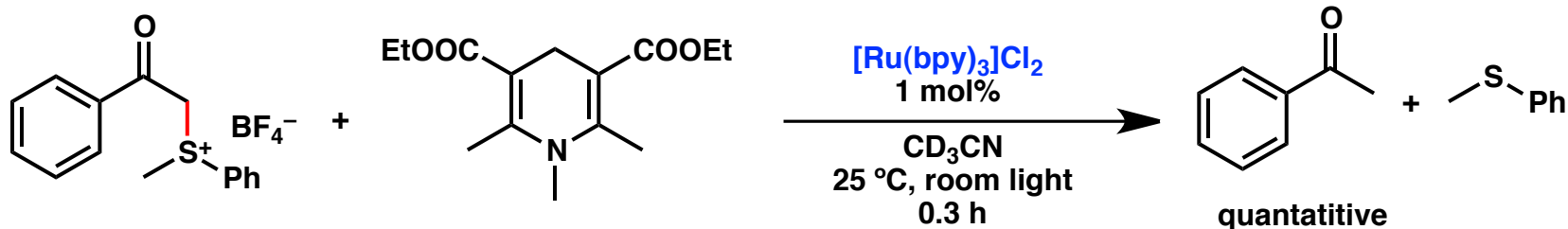
1984

2003

2008

# History of Photoredox Catalysis

Kellogg



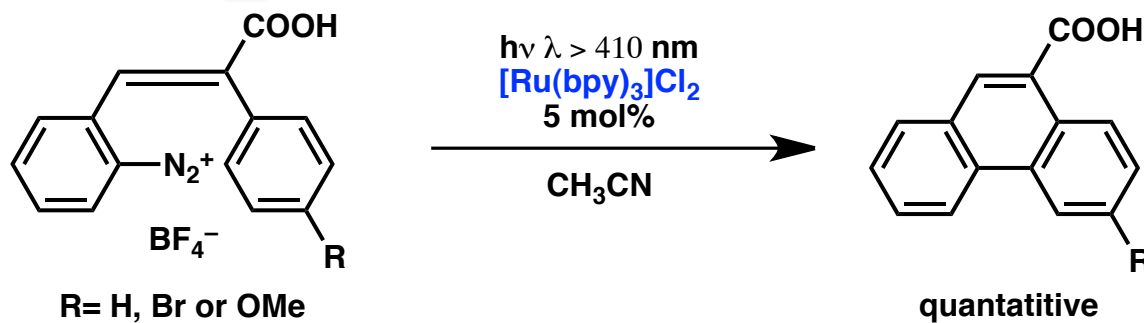
1978

1984

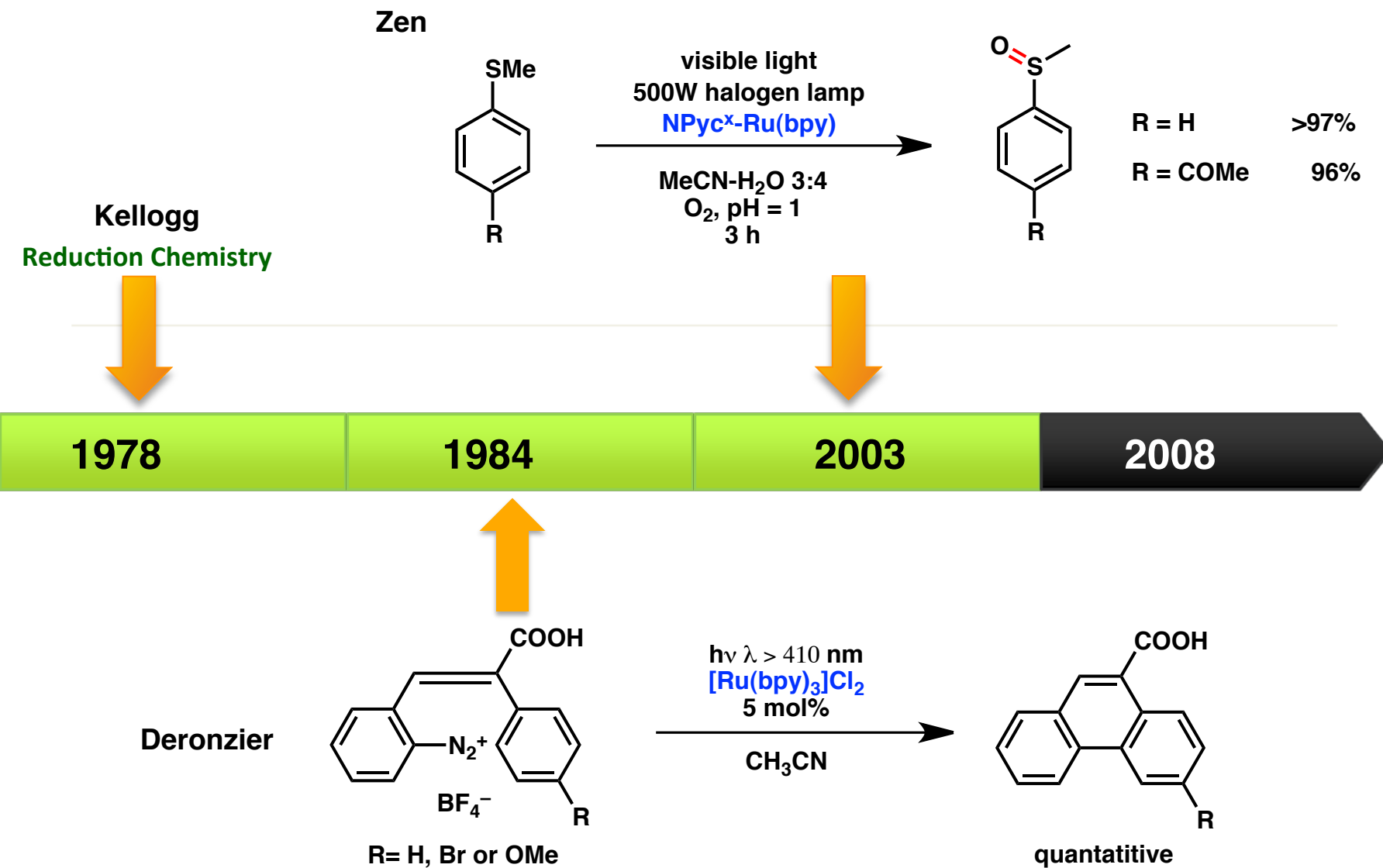
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2008

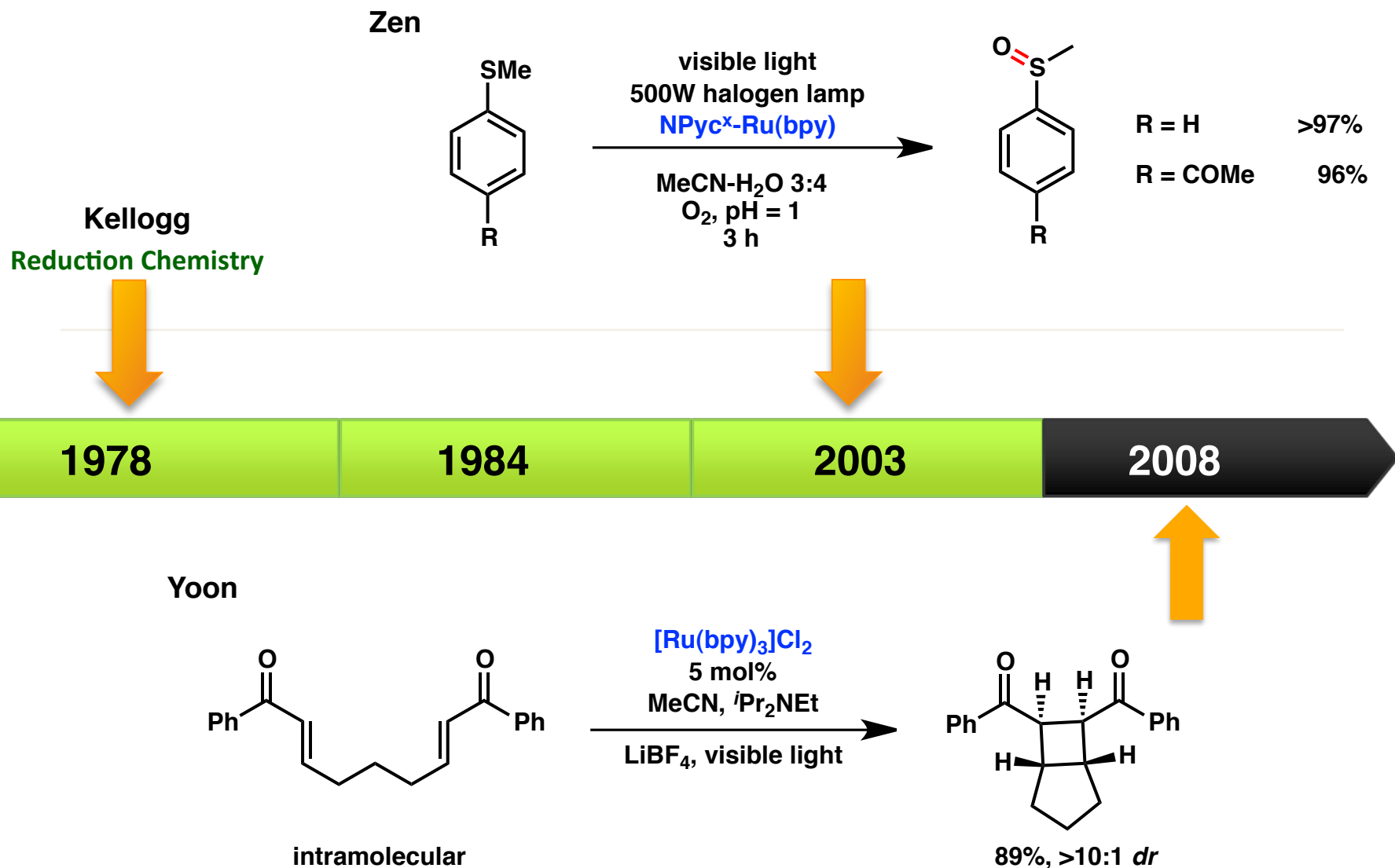
Deronzier



# History of Photoredox Catalysis

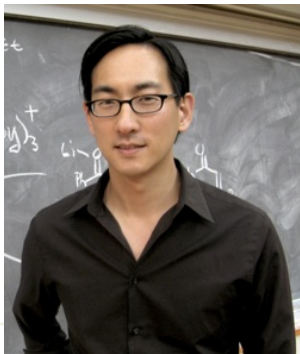


# History of Photoredox Catalysis



# Pioneers in Photoredox Catalysis

2008 Onwards



**Tehshik P. Yoon**  
University of Wisconsin



**David MacMillan**  
Princeton University



**Corey R. J. Stephenson**  
Boston University

... and others

# Outline

## ❖ $\alpha$ -Amino C-H Oxidation to:

C-C bond formation

C-N bond formation

C-P bond formation

## ❖ Transformations:

C-O to C-X

C-X to C=O

C-B to C-O

C-X to C-H

Tandem Reactions

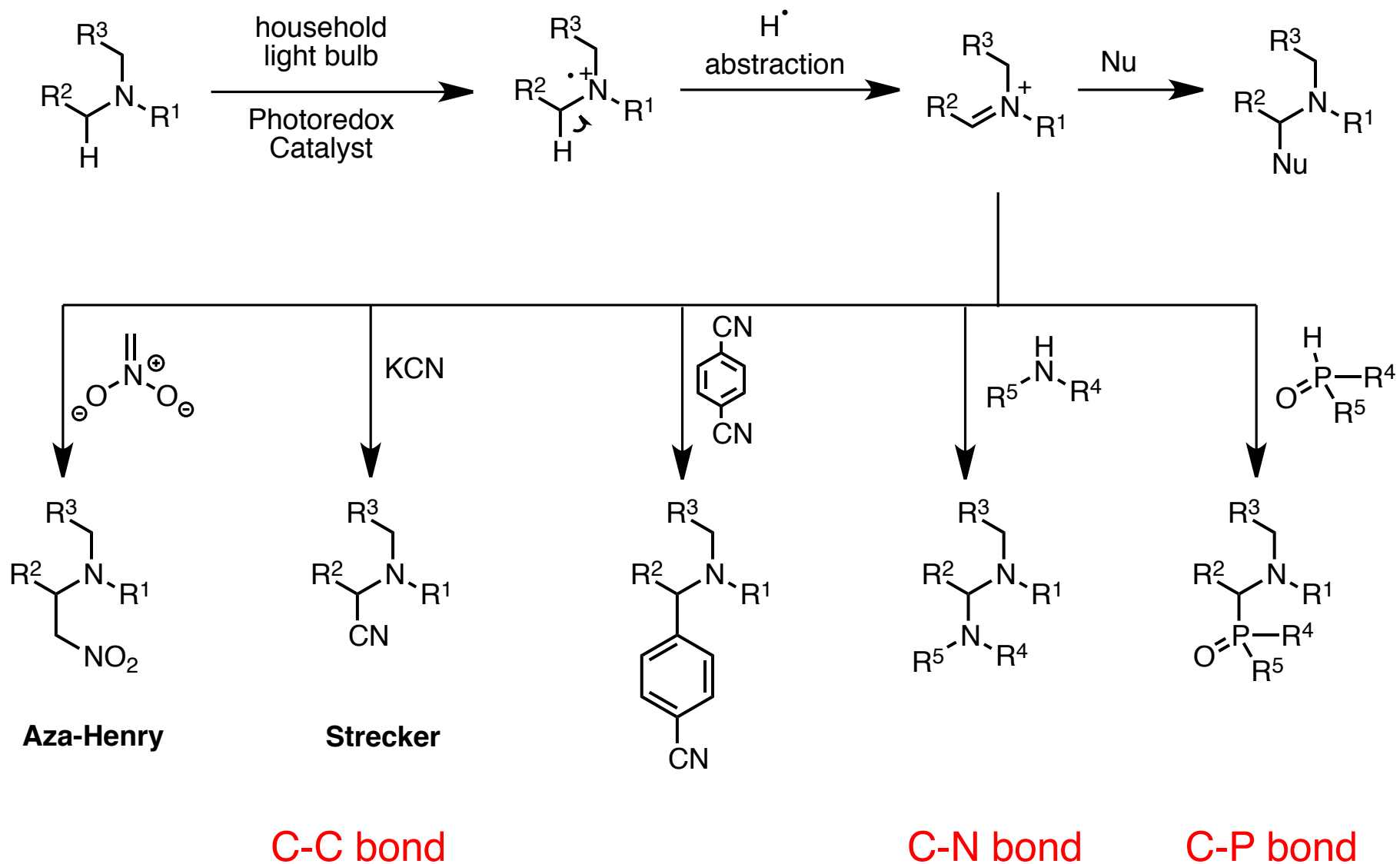
## ❖ Applications:

Trifluoromethylation of Drugs

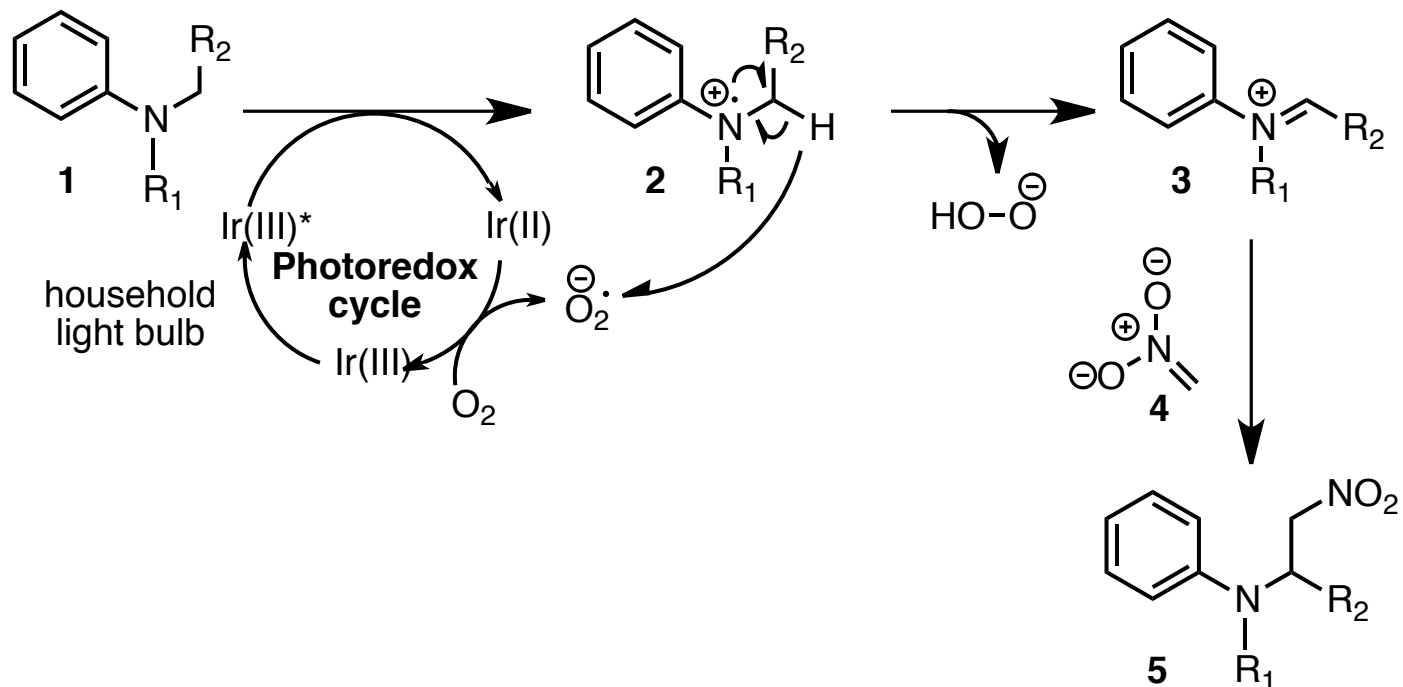
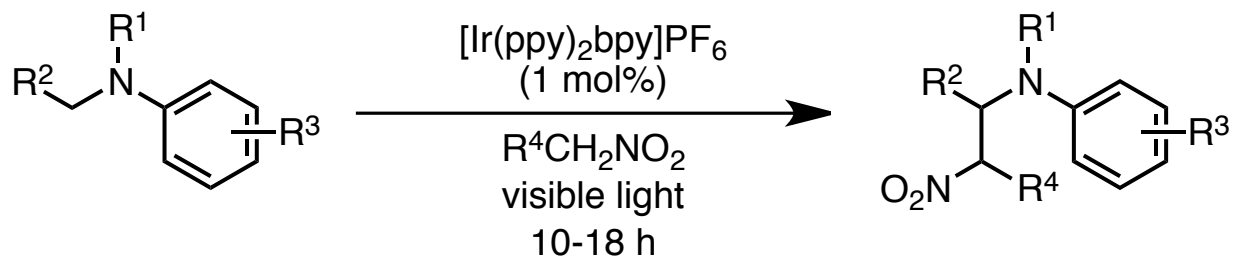
Total Synthesis

## ❖ Future Developments

# The Catalytic Oxidation of $\alpha$ -Amino C-H Bonds

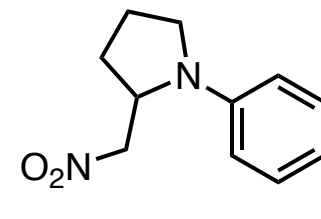
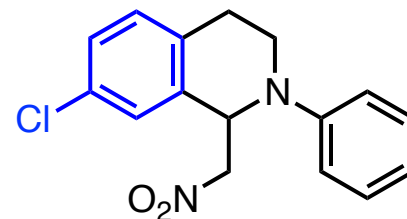
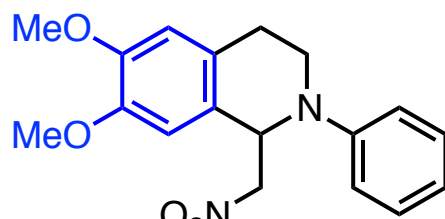
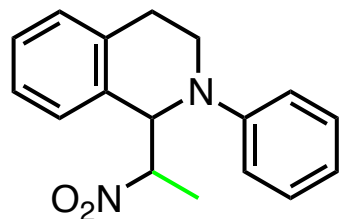
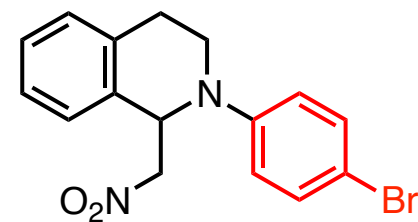
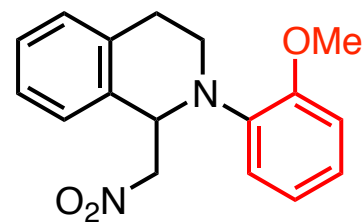
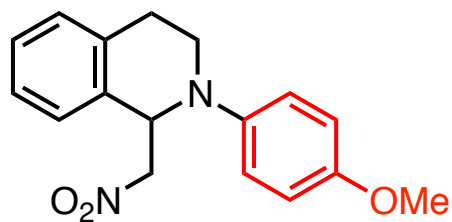
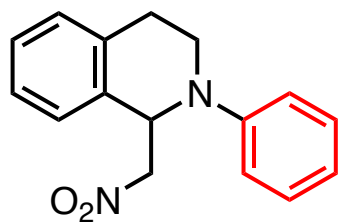
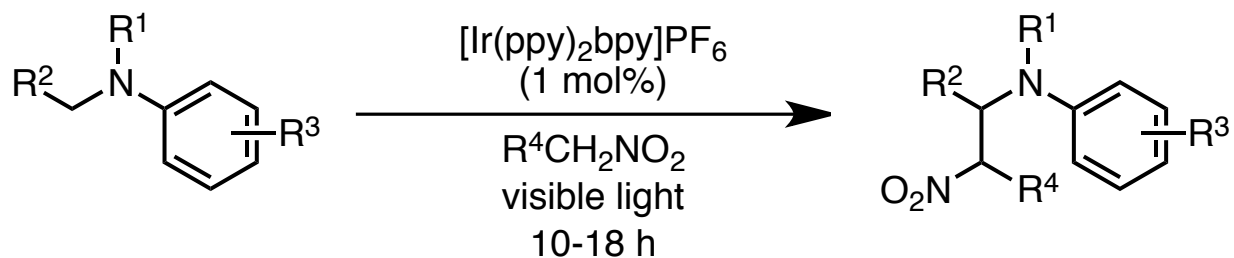


# Oxidative Aza-Henry Reaction

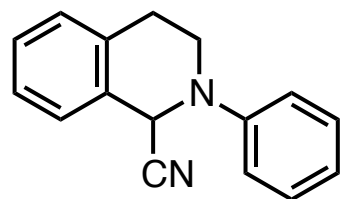
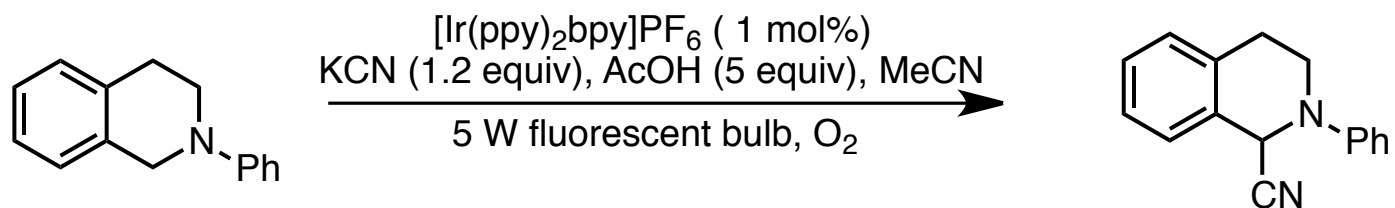




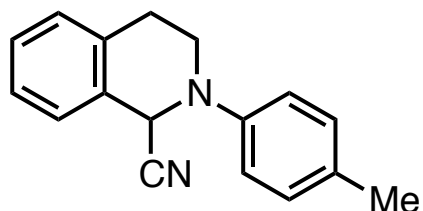
# Oxidative Aza-Henry Reaction



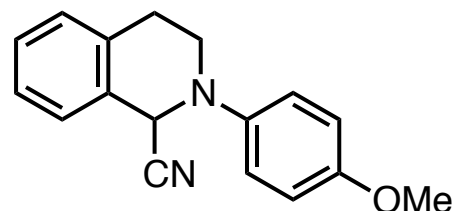
# Oxidative Strecker Reaction



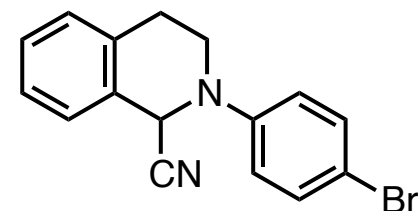
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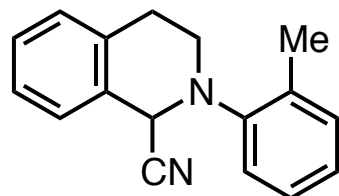
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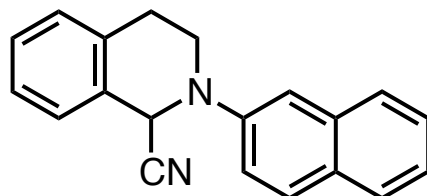
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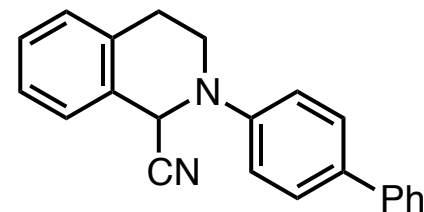
82%



76%

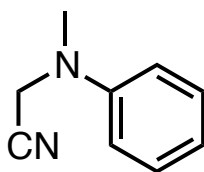
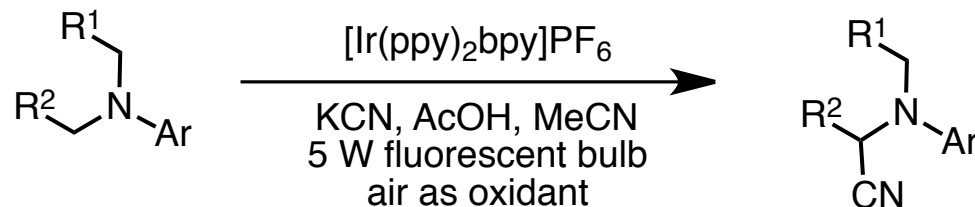


88%

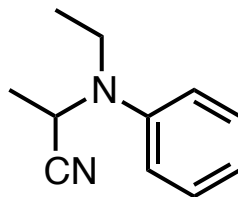


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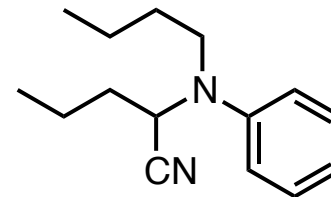
# Oxidative Strecker Reaction: Aniline Derivatives



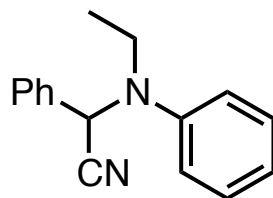
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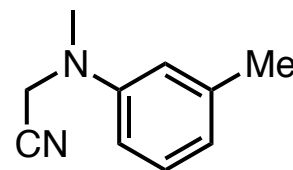
74%



78%

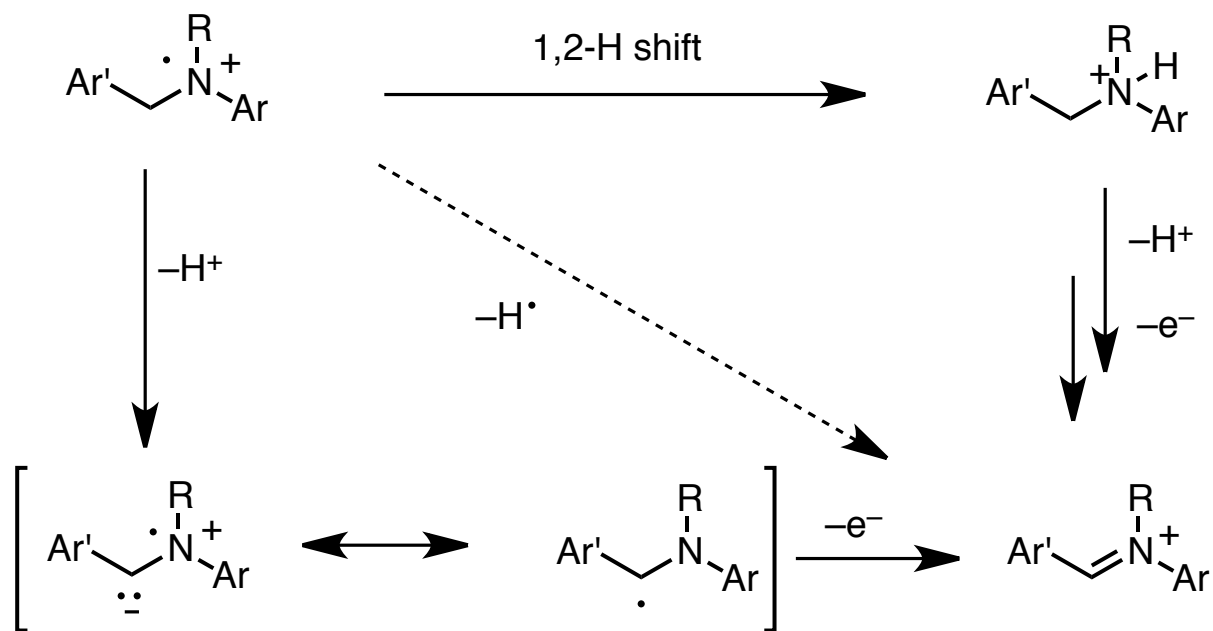
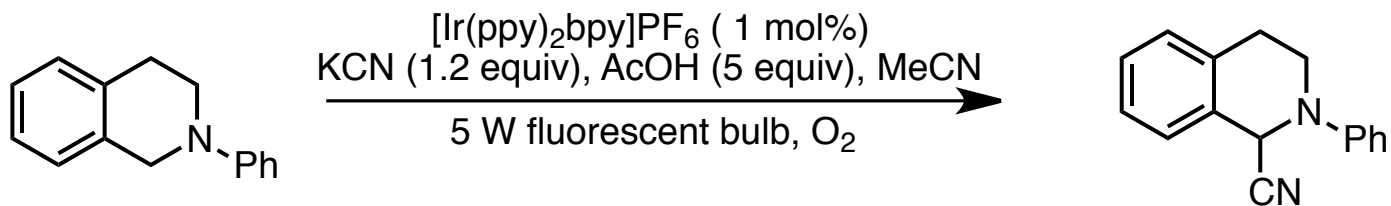


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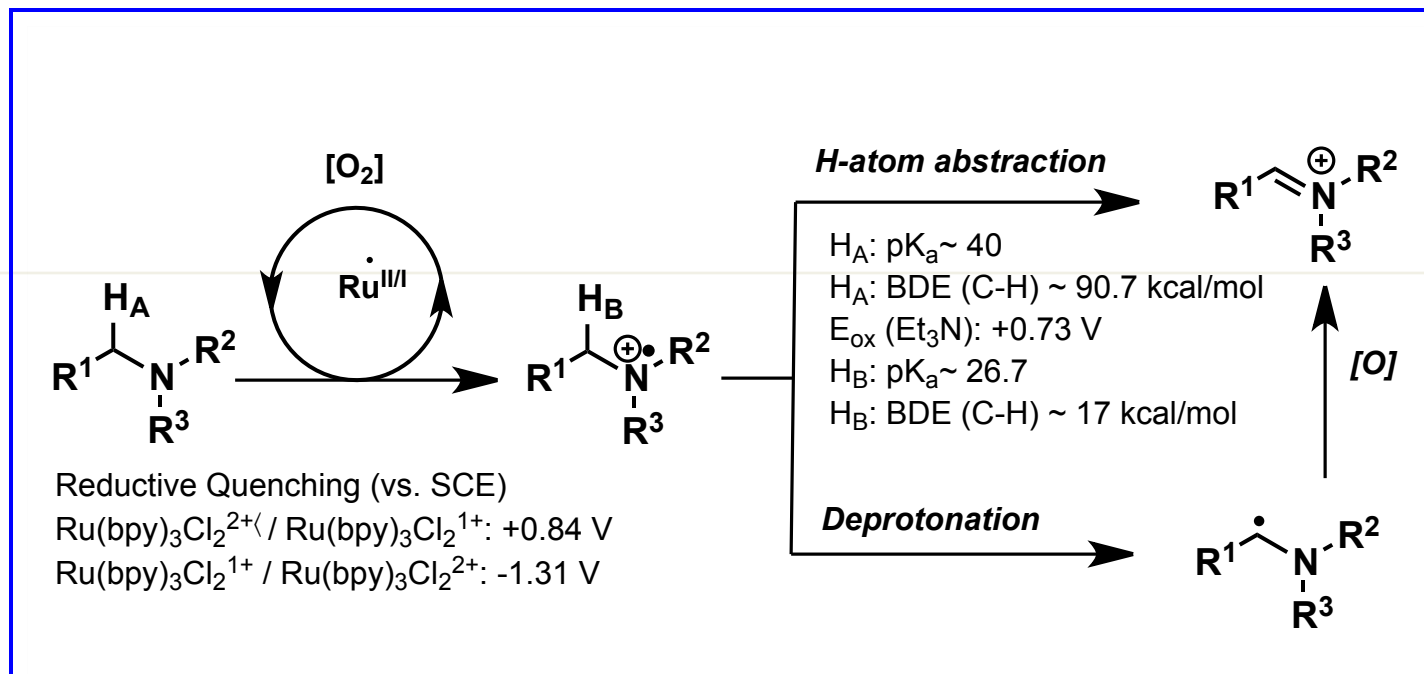


70%

# Proposed Mechanism

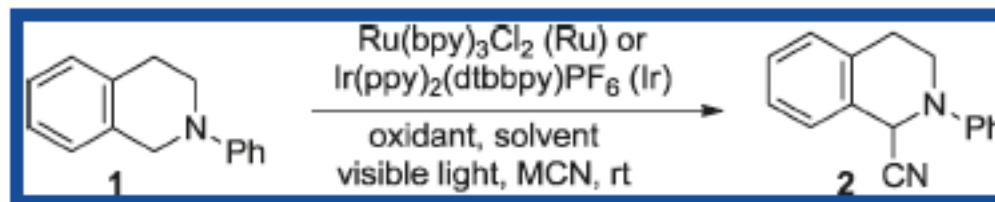


# Oxidant: Oxygen vs BrCCl<sub>3</sub>



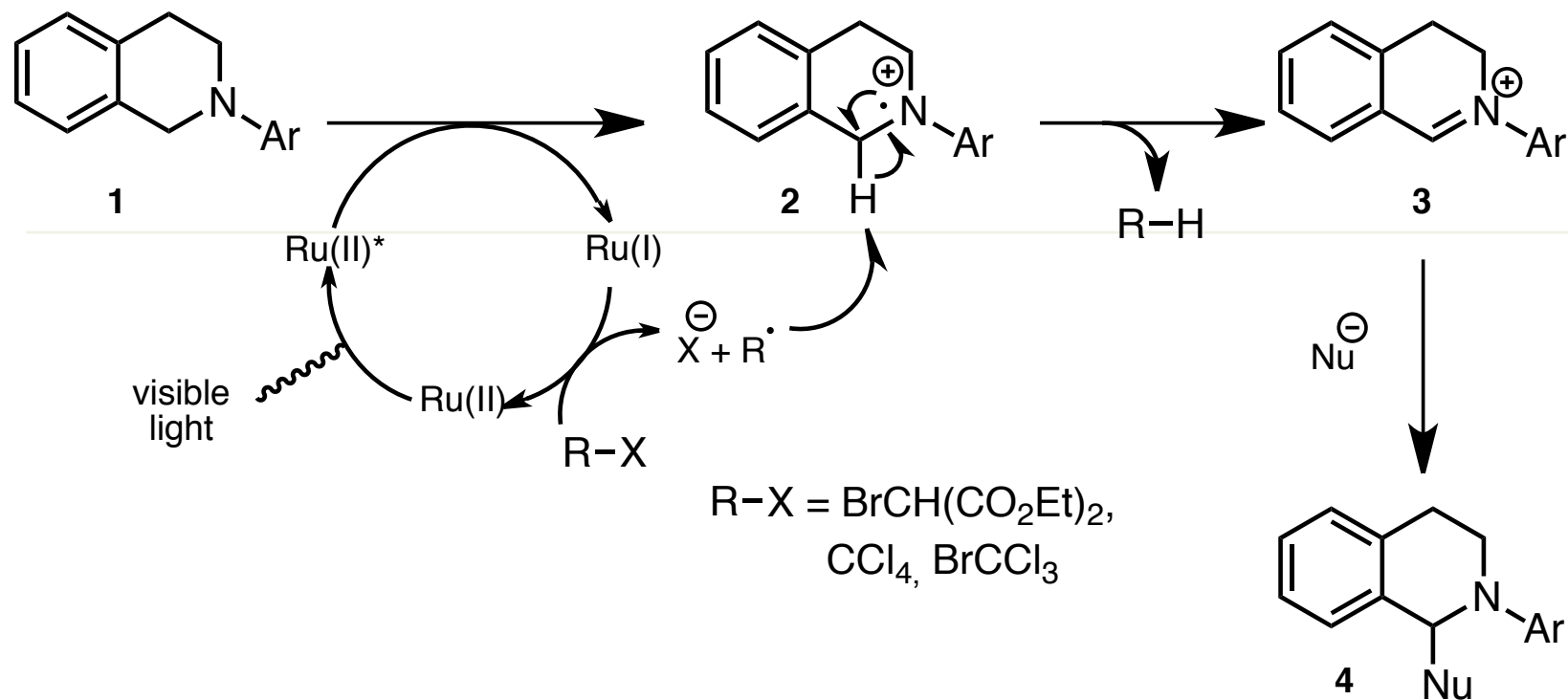
# Oxidant: Oxygen vs BrCCl<sub>3</sub>

Table 1. Optimization of Iminium Ion Formation



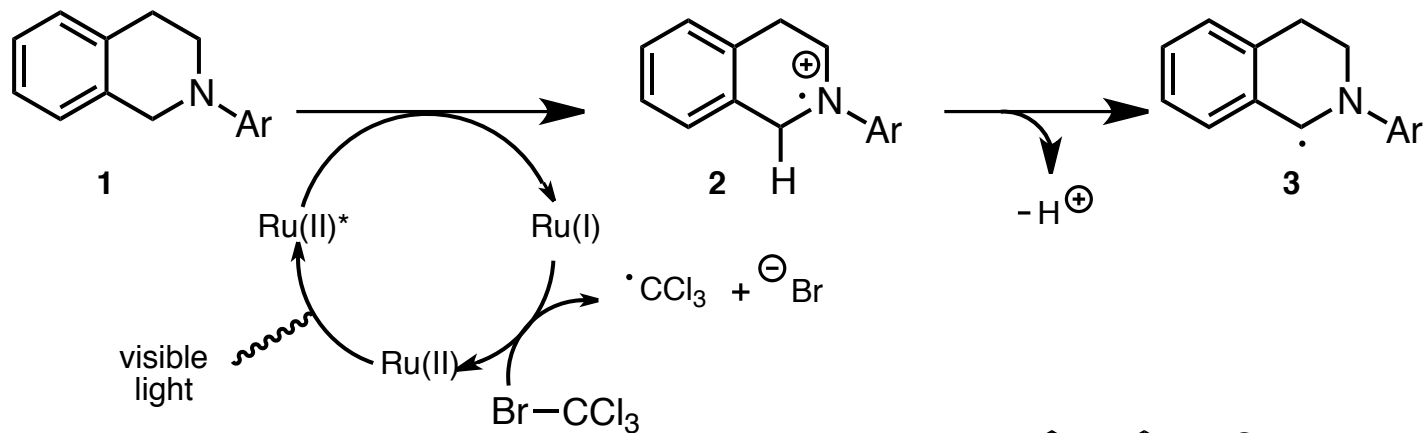
| entry | conditions  | yield <sup>a</sup> |
|-------|---|--------------------|
| 1     | Ir (1 mol %), EtO <sub>2</sub> CCH <sub>2</sub> Br (3 equiv), DMF, white light, NaCN (5 equiv)                          | 36                 |
| 2     | Ru (1 mol %), (EtO <sub>2</sub> C) <sub>2</sub> CHBr (3 equiv), DMF, blue LEDs, NaCN (5 equiv)                          | 95                 |
| 3     | Ru (1 mol %), CCl <sub>4</sub> :DMF (1:1), blue LEDs, NaCN (5 equiv)  | 36                 |
| 4     | Ru (1 mol %), CCl <sub>4</sub> (3 equiv), CH <sub>3</sub> CN, blue LEDs, NaCN (5 equiv)                                 | 53                 |
| 5     | Ru (1 mol %), BrCCl <sub>3</sub> (3 equiv), DMF, blue LEDs, NaCN (5 equiv)  | 60                 |
| 6     | Ru (1 mol %), BrCCl <sub>3</sub> (3 equiv), DMF, blue LEDs then <i>no light</i> , NaCN (5 equiv)                        | 85                 |
| 7     | Ru (1 mol %), BrCCl <sub>3</sub> (3 equiv), DMF, blue LEDs then <i>no light</i> , Bu <sub>4</sub> NCN (5 equiv)         | 17                 |
| 8     | Ru (1 mol %), BrCCl <sub>3</sub> (3 equiv), THF, blue LEDs then <i>no light</i> , NaCN (5 equiv)                        | NR                 |
| 9     | Ru (1 mol %), BrCCl <sub>3</sub> (3 equiv), THF/H <sub>2</sub> O (2:1), blue LEDs then <i>no light</i> , NaCN (5 equiv) | 83                 |

# Proposed Mechanism - First Hypothesis

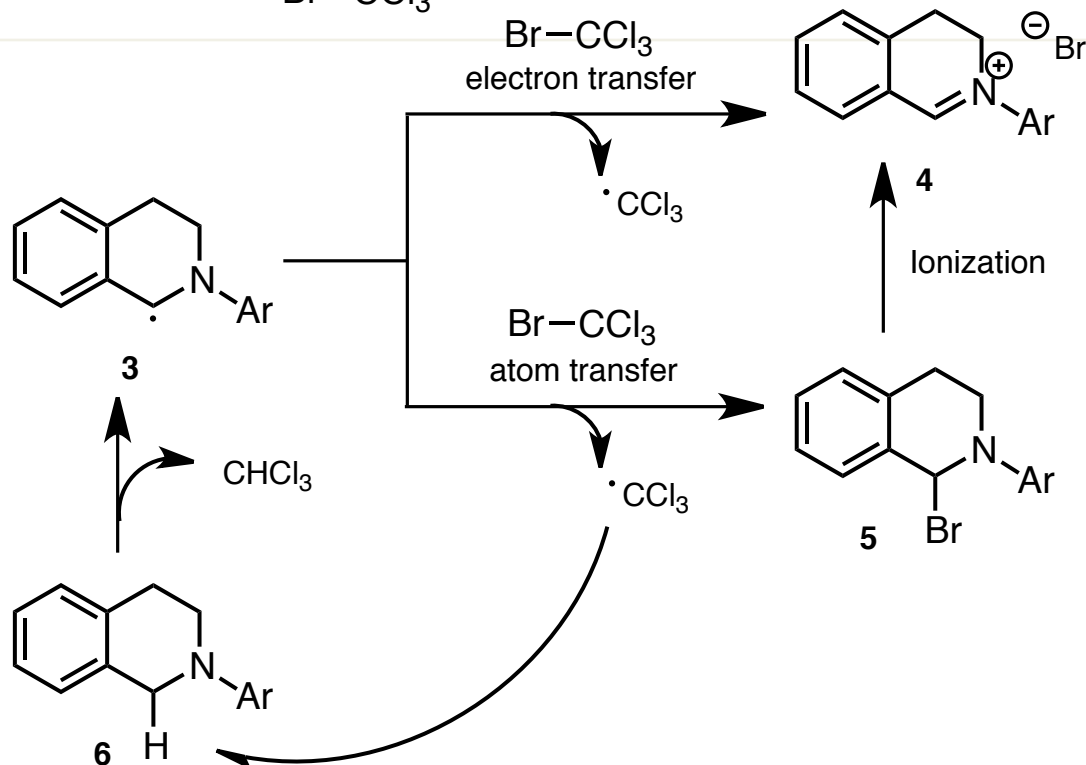


# Proposed Mechanism – Second Hypothesis

Initiation

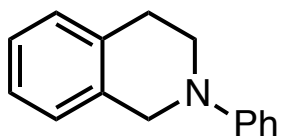


Propagation



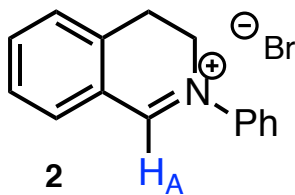


# Reactive Intermediate – Iminium ion

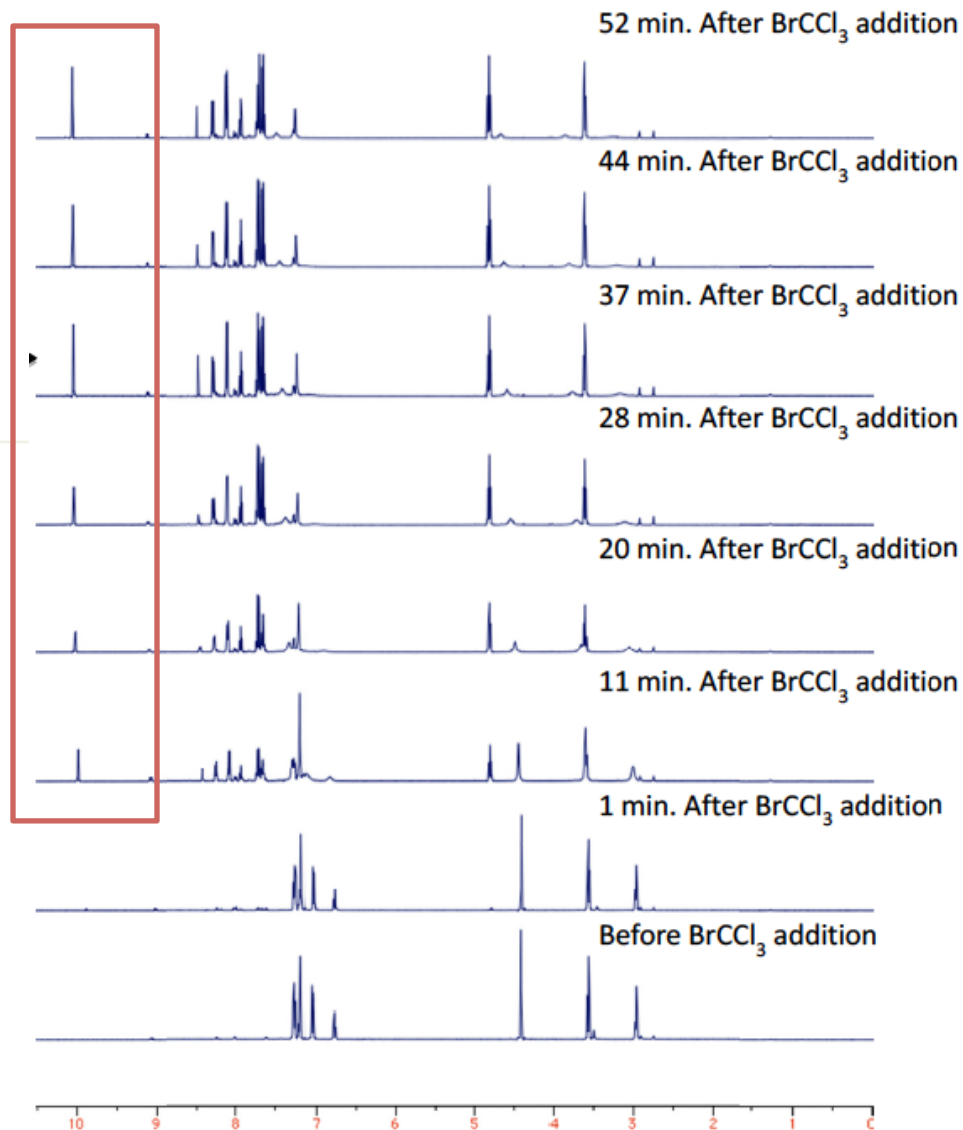


1

Ru(bpy)<sub>3</sub>Cl<sub>2</sub> (1 mol%)  
DMF, visible light, 1.5 h  
BrCCl<sub>3</sub> (3 equiv)

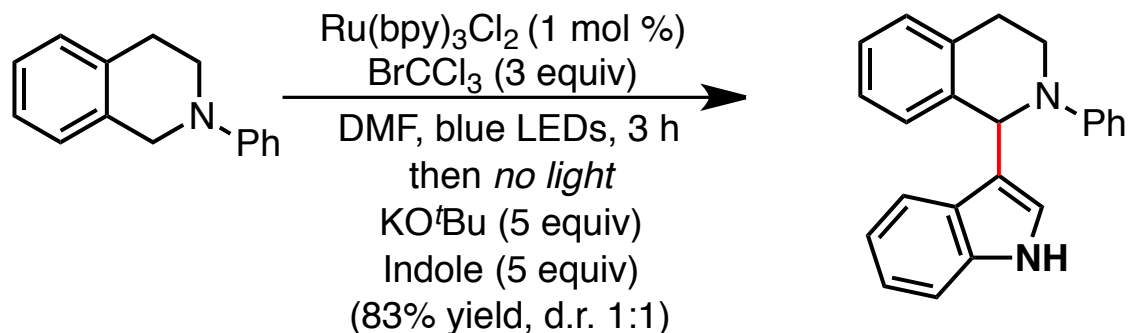
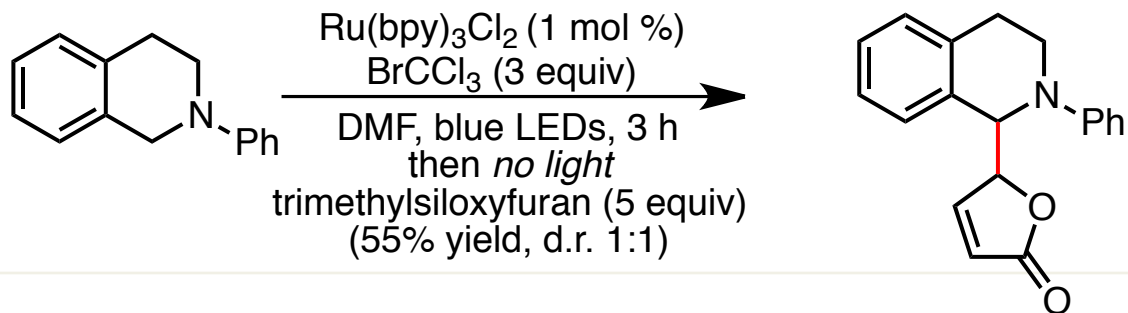


2

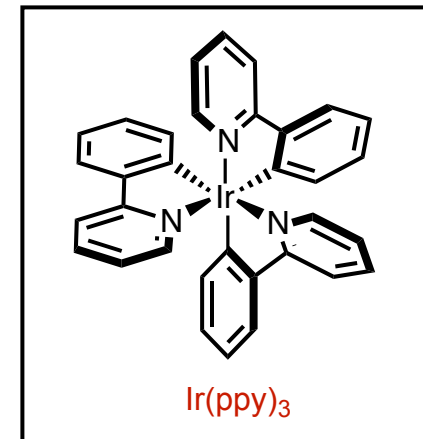
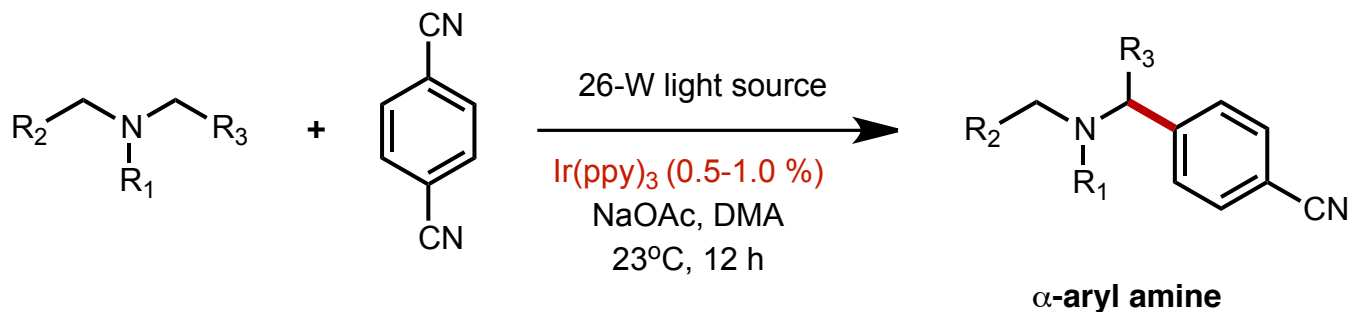


# Trapping of Iminium With Other Nucleophiles

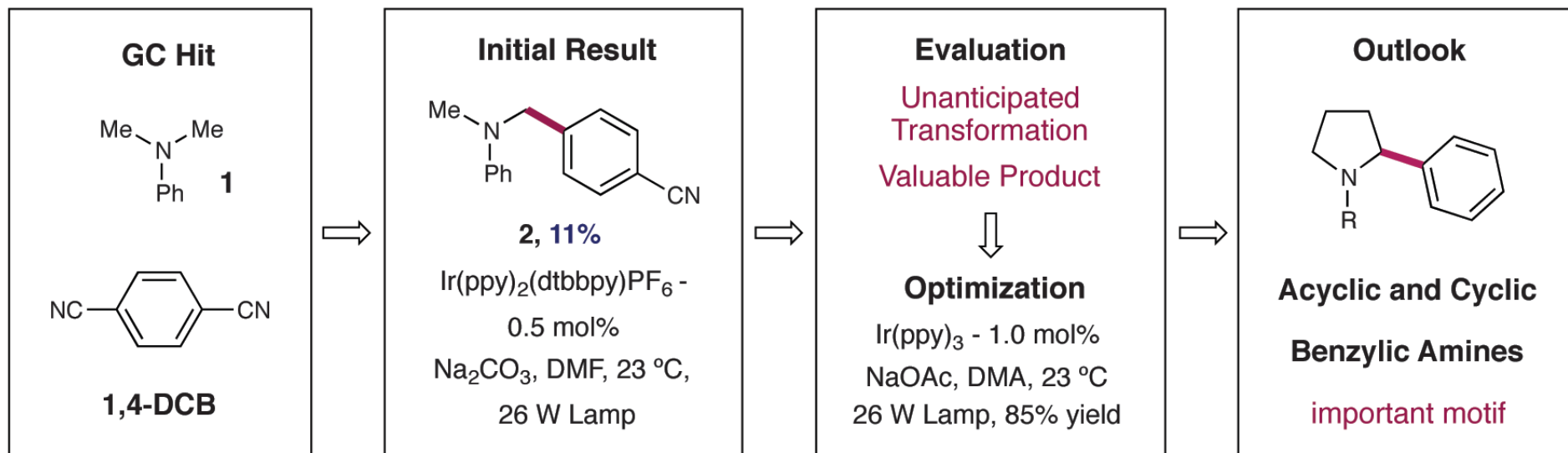
## Trapping of iminium intermediates



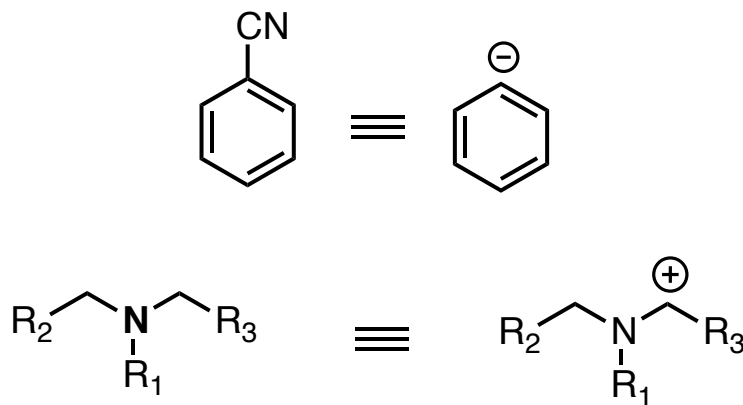
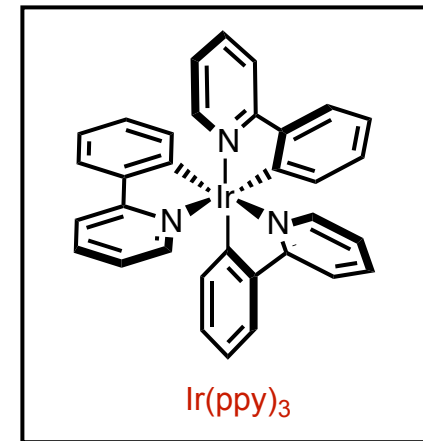
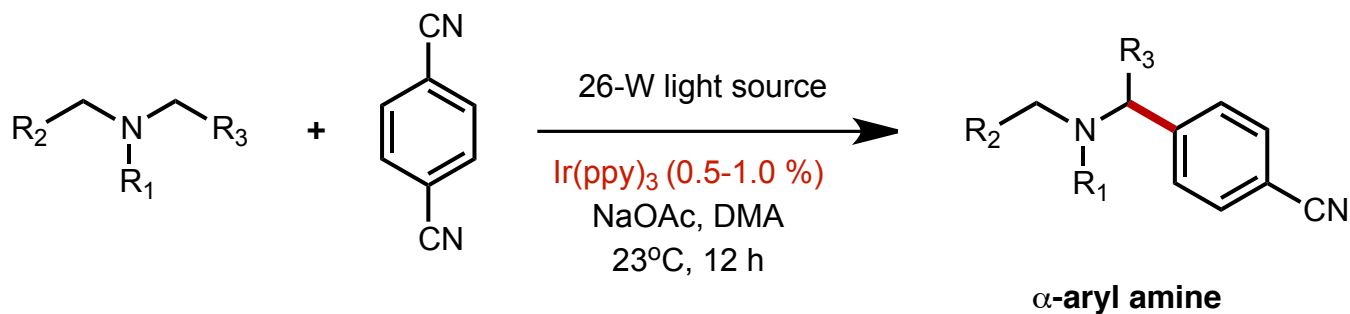
# $\alpha$ -Amino Arylation



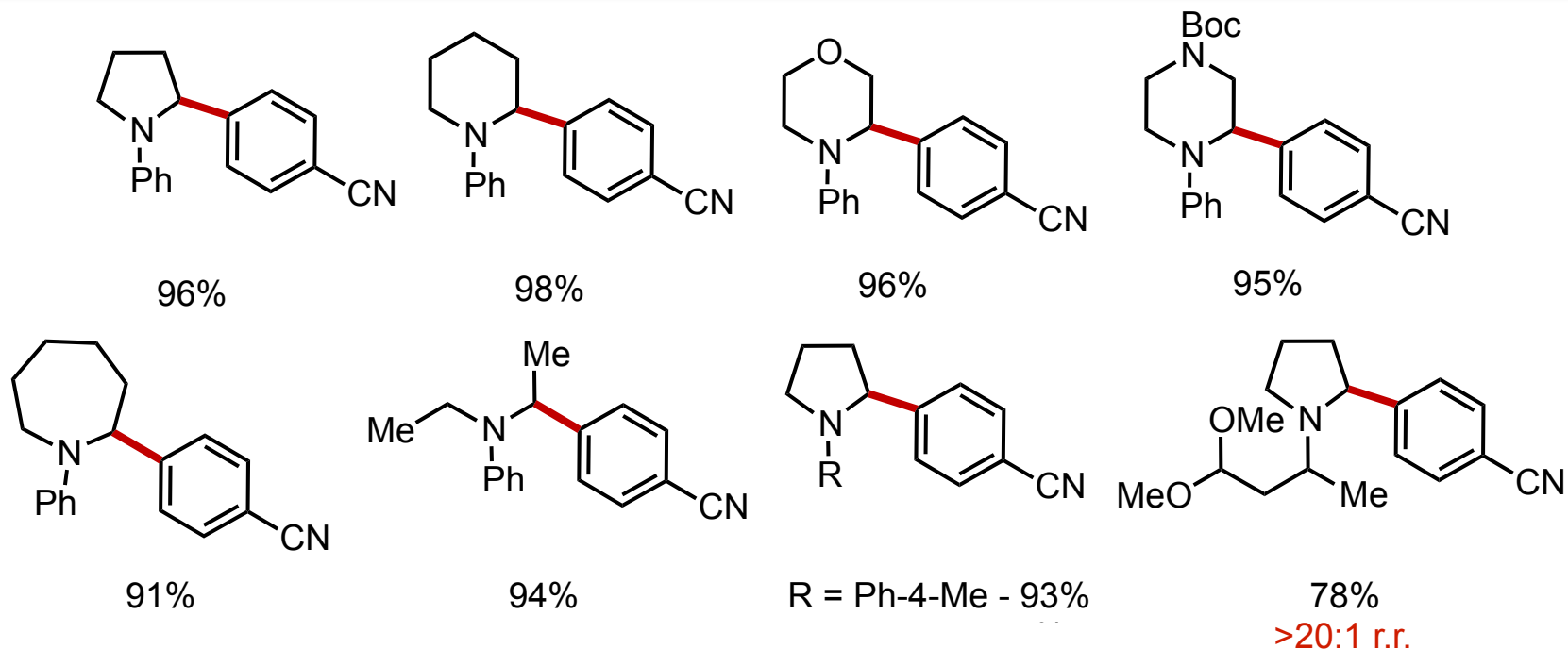
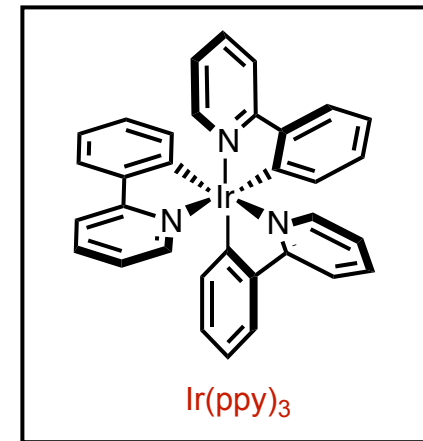
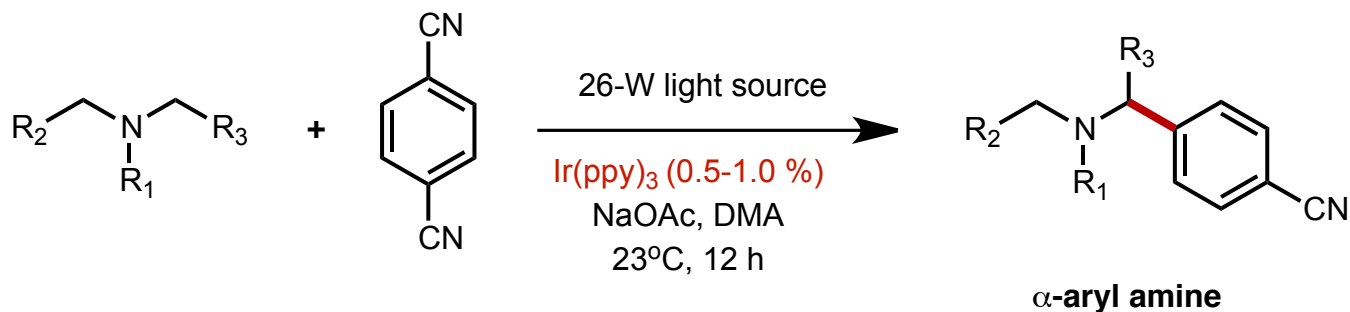
## Accelerated Serendipity: GC Hit, Initial Result, Reaction Evaluation, Optimization and Outlook



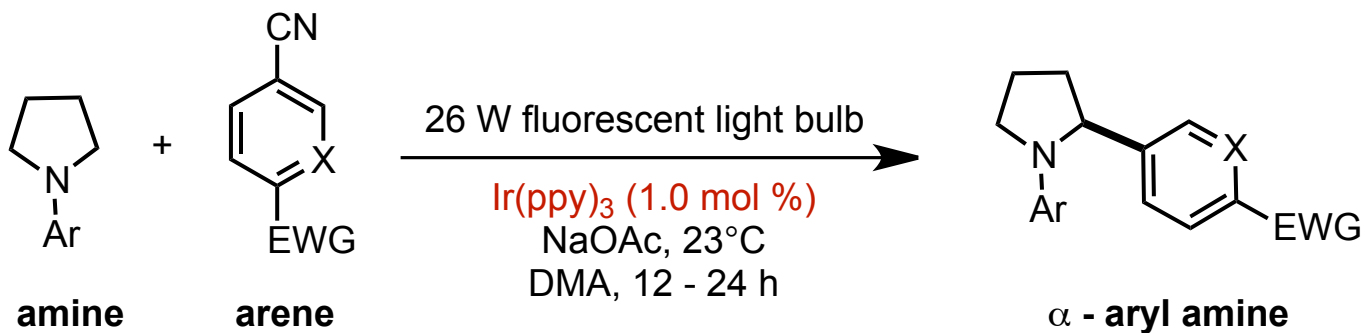
# $\alpha$ -Amino Arylation



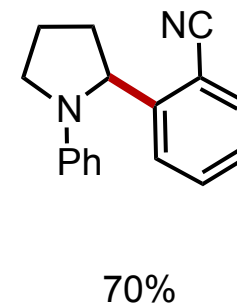
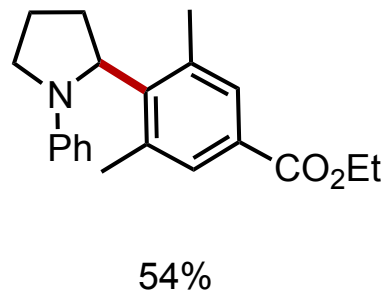
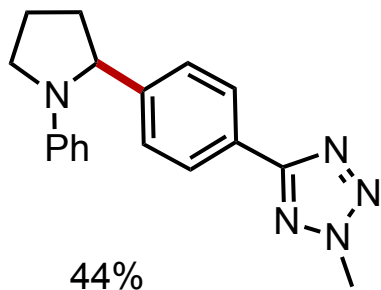
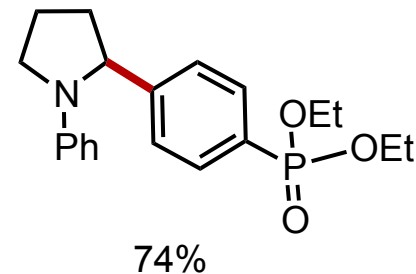
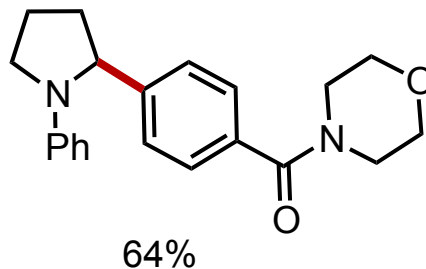
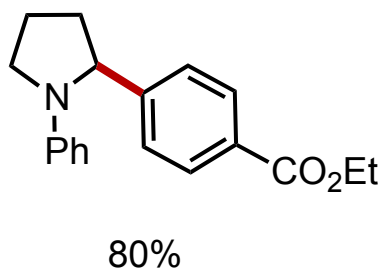
# Structural Scope



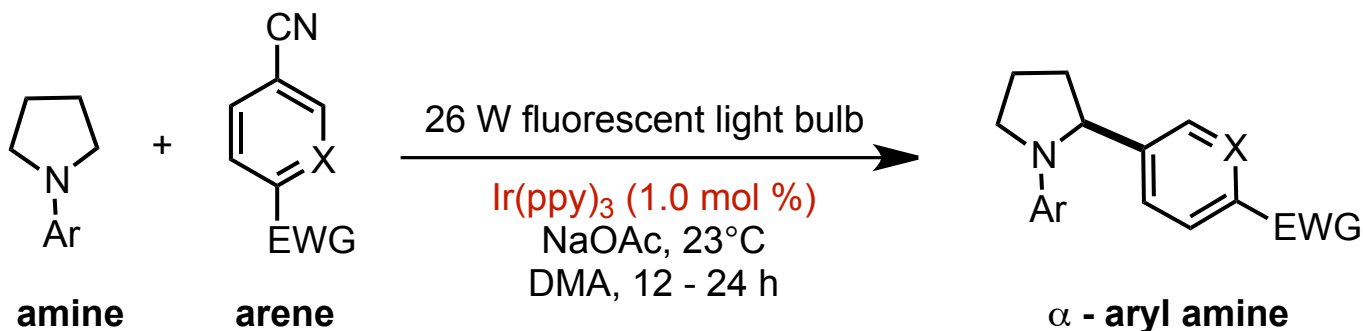
# Structural Scope



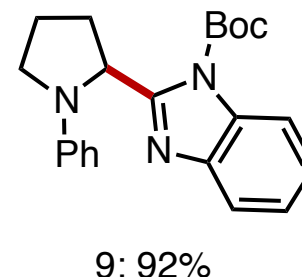
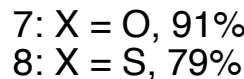
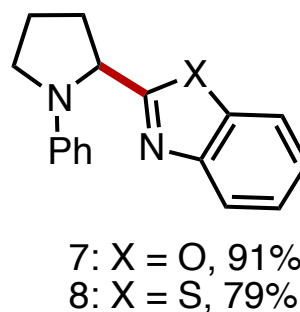
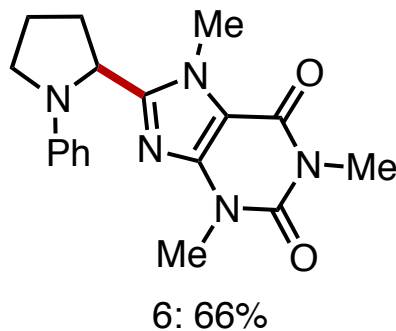
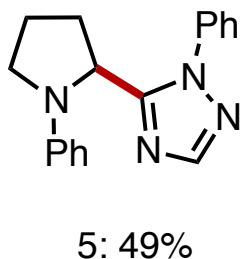
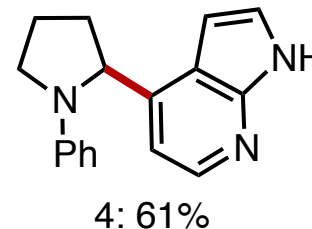
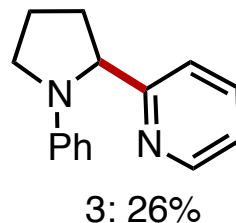
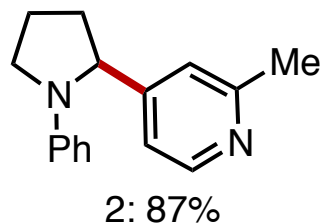
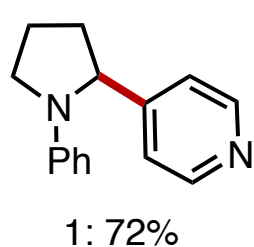
## Electron-deficient arenes



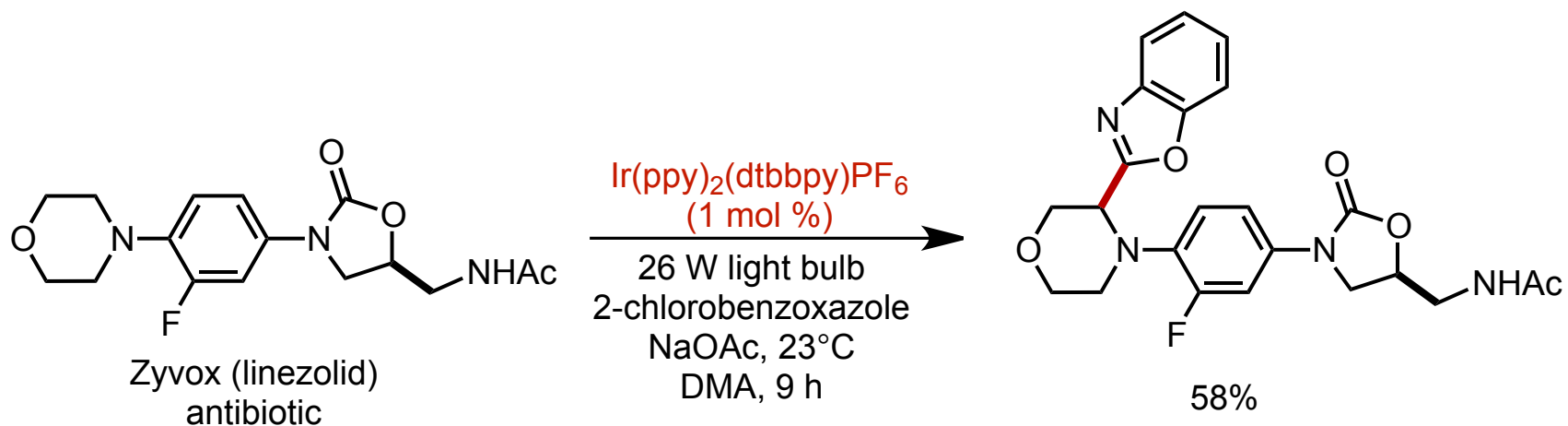
# Structural Scope



## Electron-deficient heteroatomics

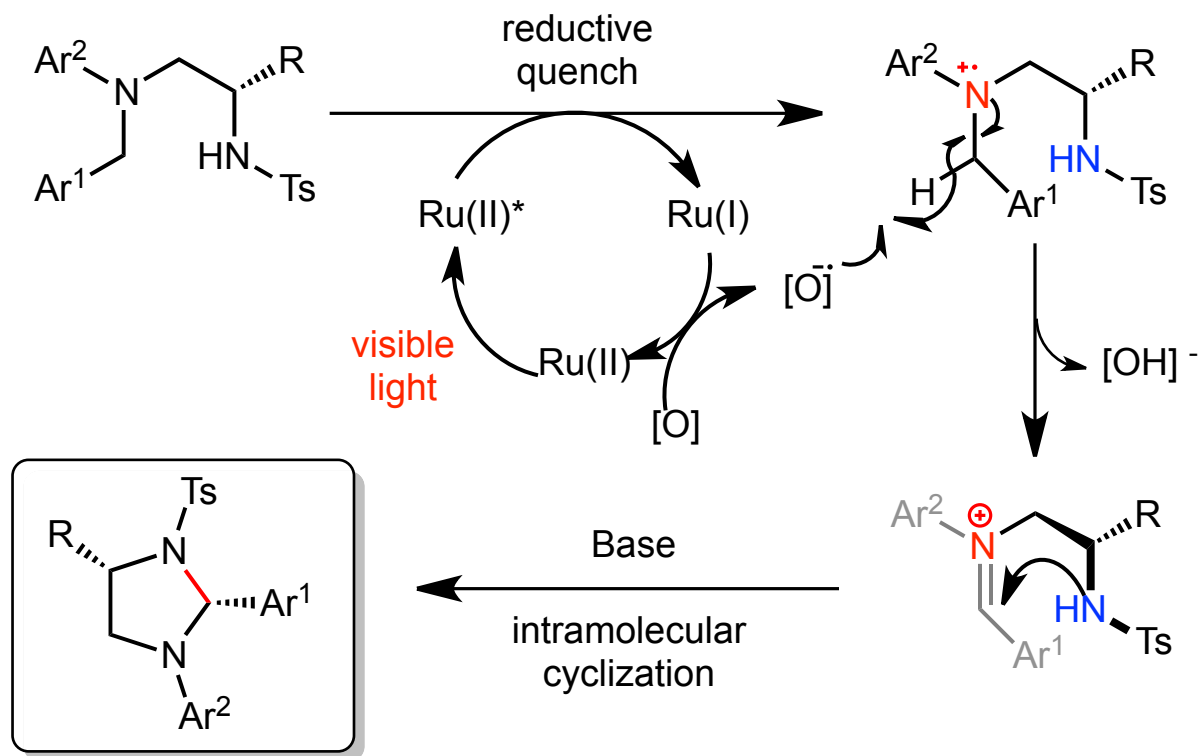
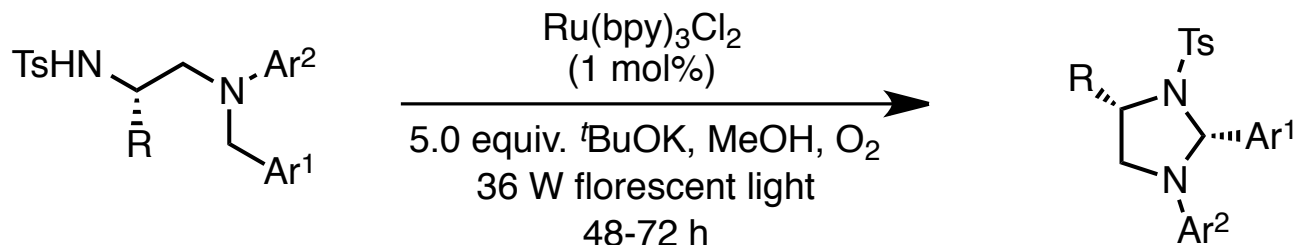


# Photoredox Arylation of Pharmaceuticals

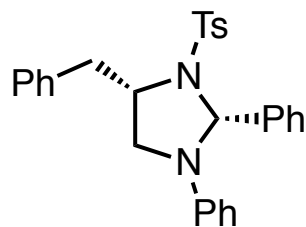
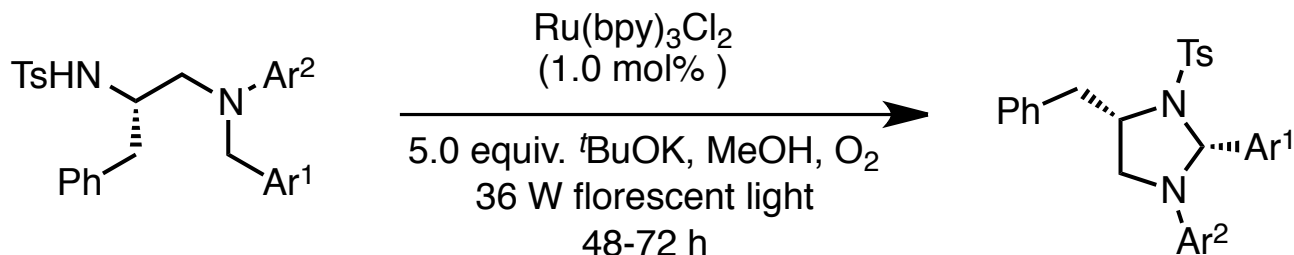




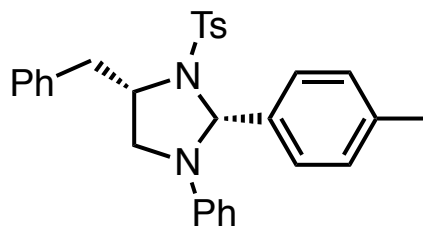
# Intramolecular C-N bond formation via photoredox



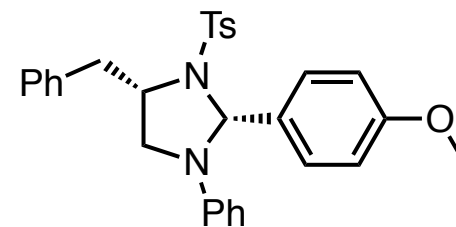
# Intramolecular C-N bond formation via photoredox



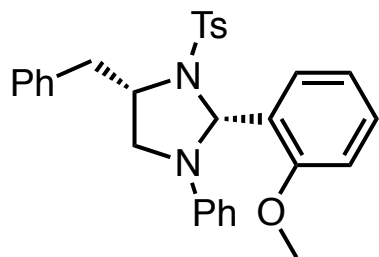
92%  
dr 10:1



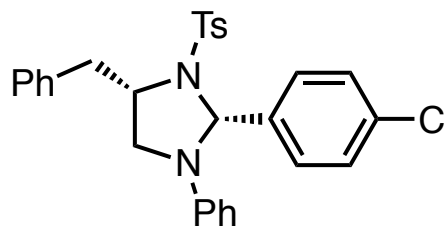
93%  
dr > 19:1



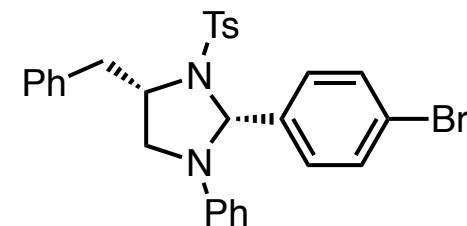
90%  
dr > 19:1



92%  
dr > 19:1

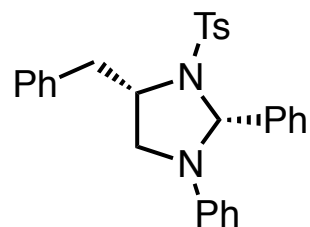
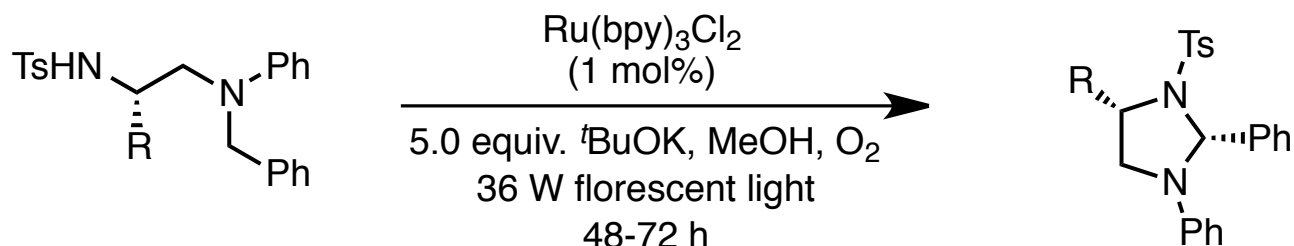


92%  
dr > 19:1

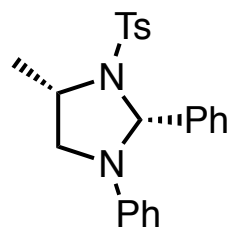


92%  
dr 8:1

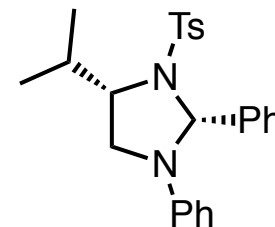
# Intramolecular C-N bond formation via photoredox



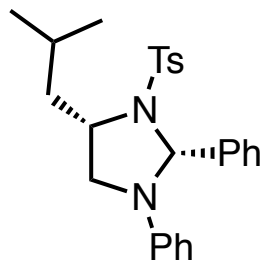
92%  
*dr* 10:1



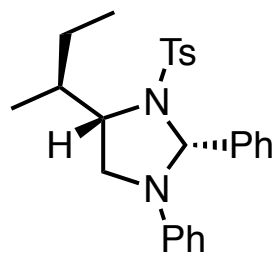
92%  
*dr* > 19:1



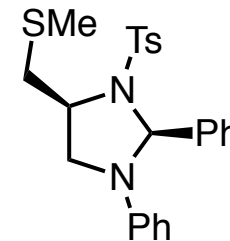
89%  
*dr* 3:1



94%  
*dr* > 19:1

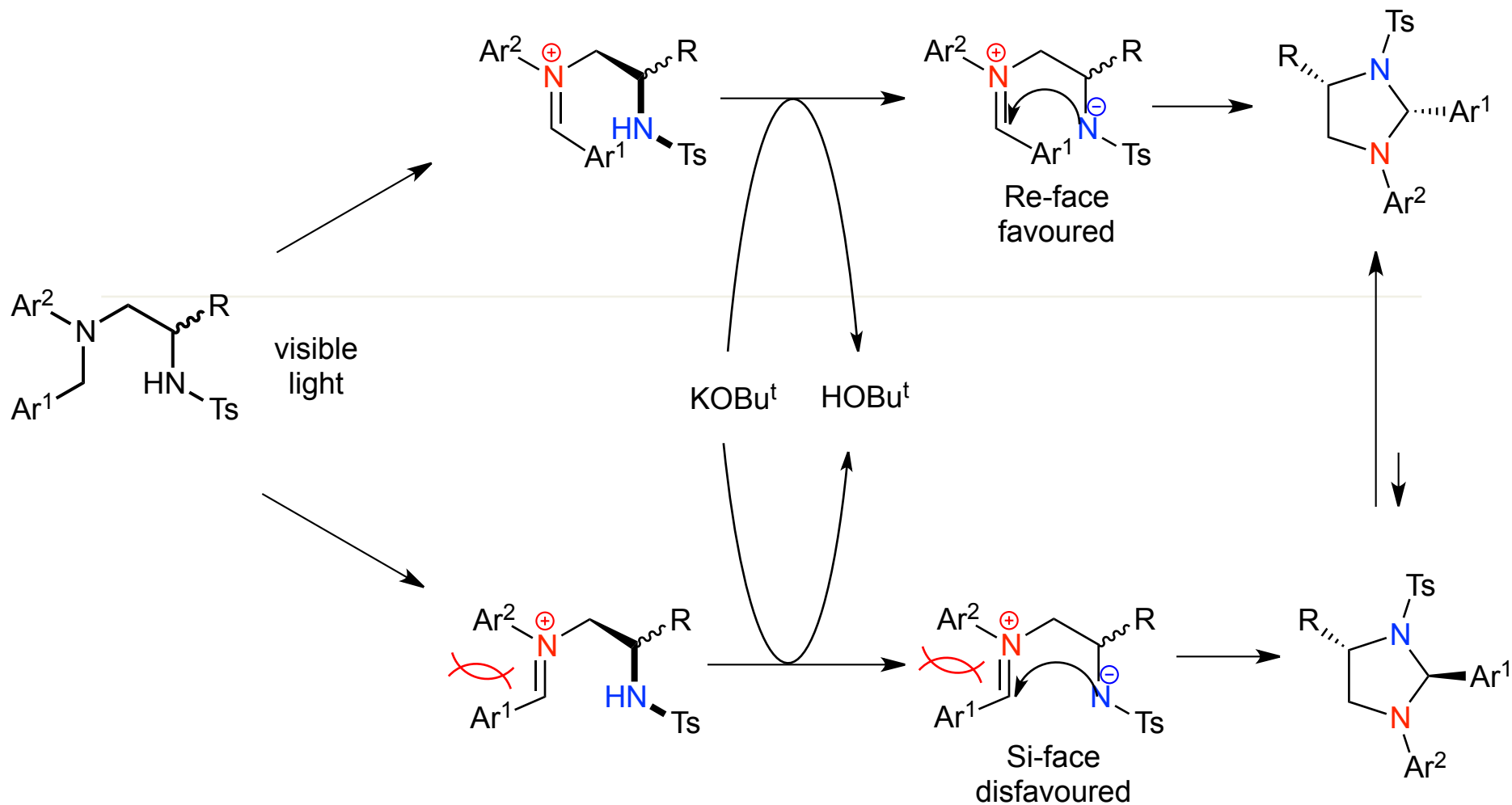


90%  
*dr* 2:1

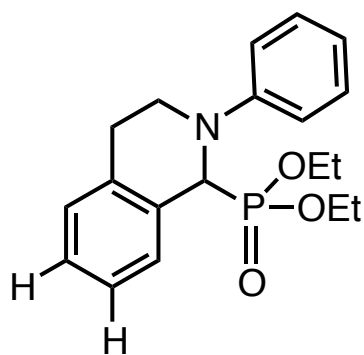
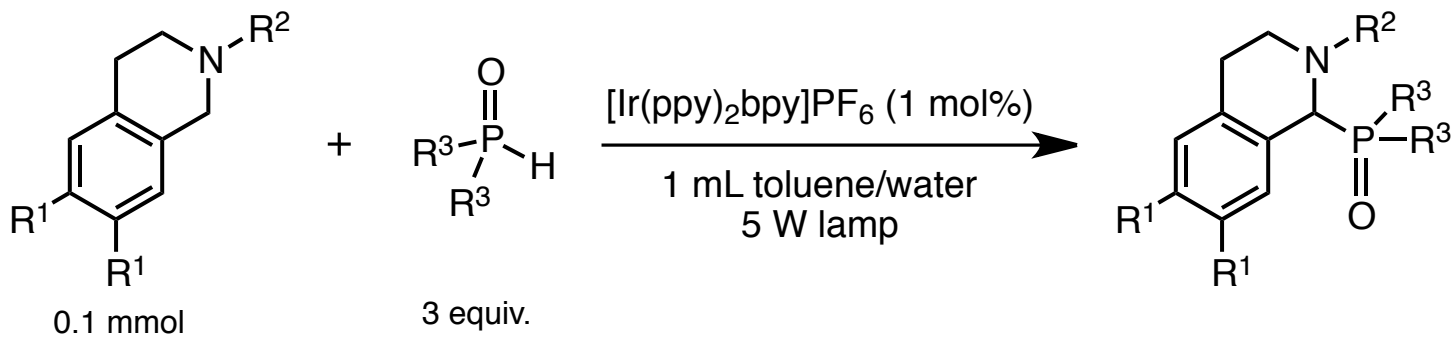


45%  
*dr* 3:1

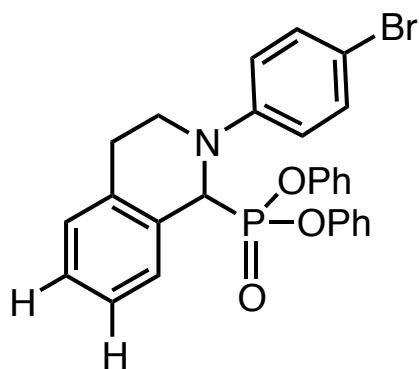
# Proposed Stereochemical Pathways



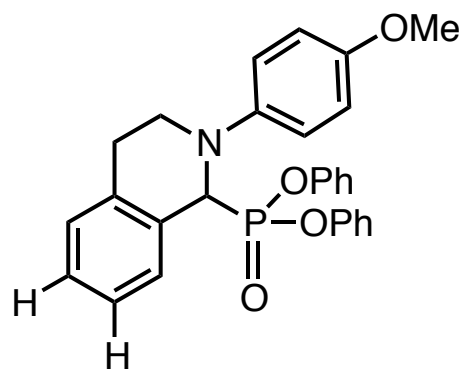
# Photoredox catalyzed C–P bond forming reactions



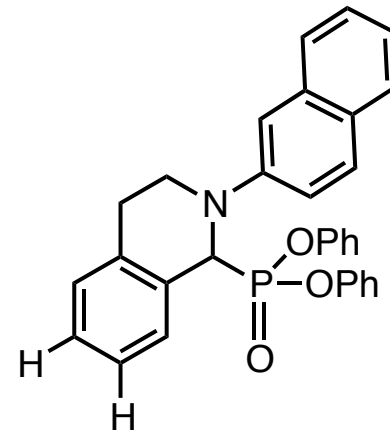
89%



90%



72%



73%

# Outline

❖  $\alpha$ -Amino C-H Oxidation to:

C-C bond formation  
C-N bond formation  
C-P bond formation

❖ Transformations:

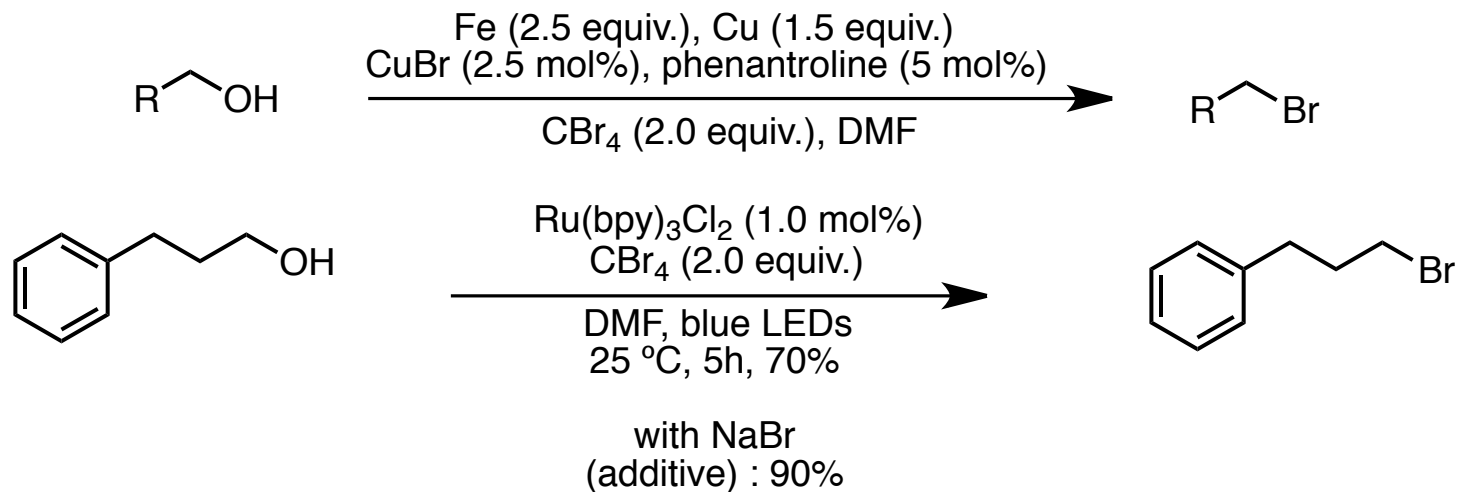
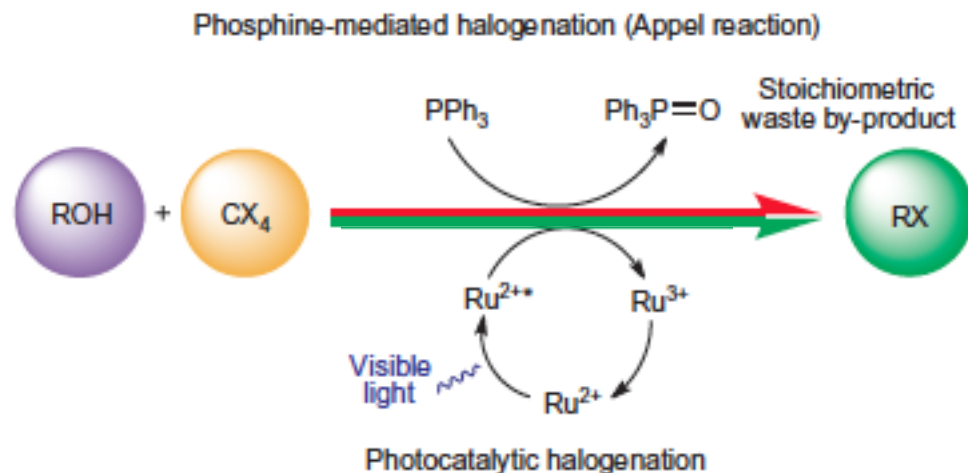
C-O to C-X  
C-X to C=O  
C-B to C-O  
C-X to C-H  
Tandem Reactions

❖ Applications:

Trifluoromethylation of Drugs  
Total Synthesis

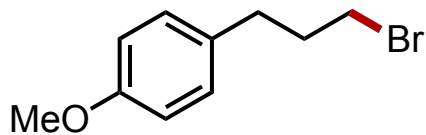
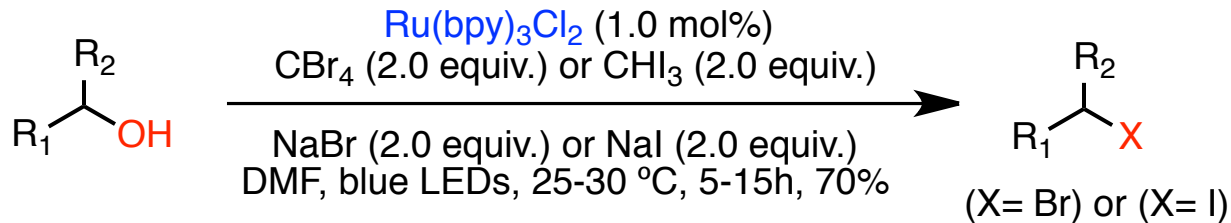
❖ Future Developments

# Photocatalytic Alcohol Activation

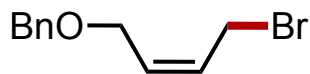


Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2011**, *3*, 140-145.  
Le´onel, E., Paugam, J. P.; Ne´de´lec, J.-Y. *J. Org. Chem.* **1997**, *62*, 7061.

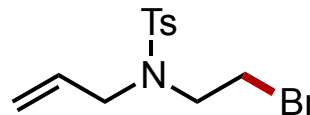
# Photocatalytic Alcohol Activation: Substrate Scope



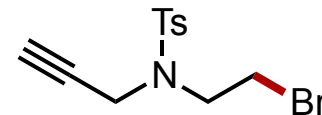
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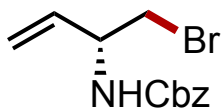
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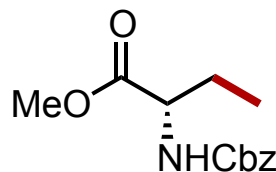
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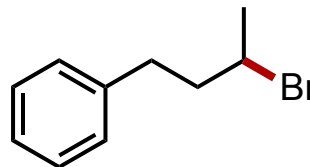
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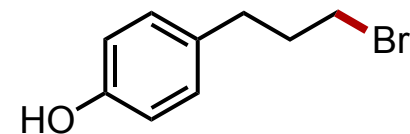
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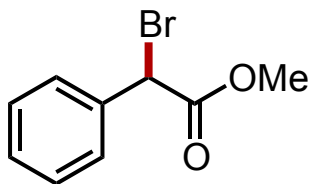
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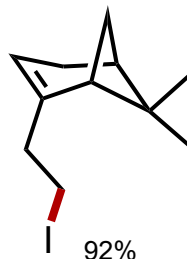
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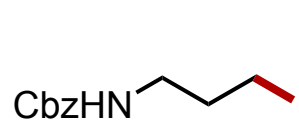
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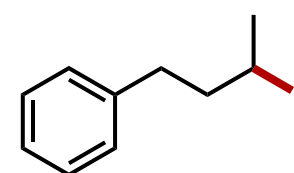
86%



92%



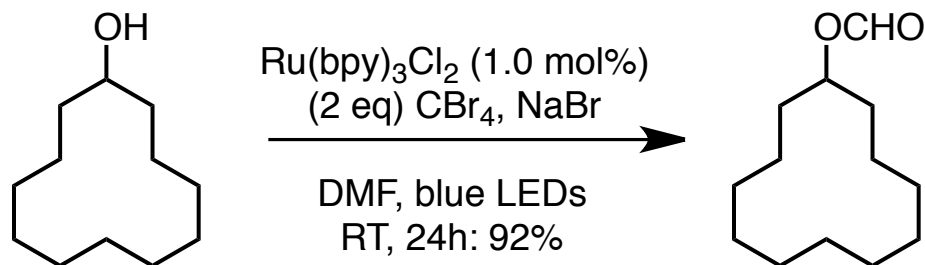
95%



75%

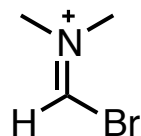


# Mechanistic Investigations



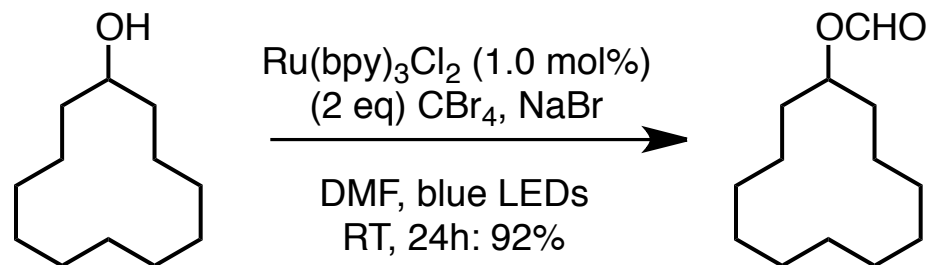
Observations: Premature quenching primary alcohols leads to formate-ester side products

Hypothesis: DMF is involved in the transformation via in-situ formation of a Vilsmeier-Haak type reagent



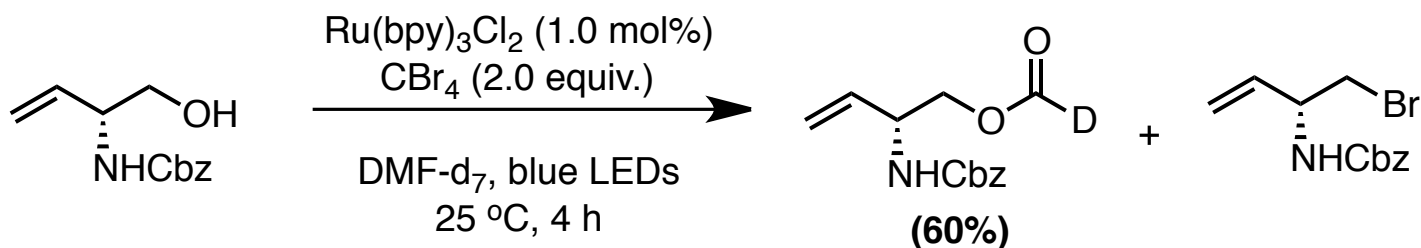
Vilsmeier-Haak reagent

# Mechanistic Investigations

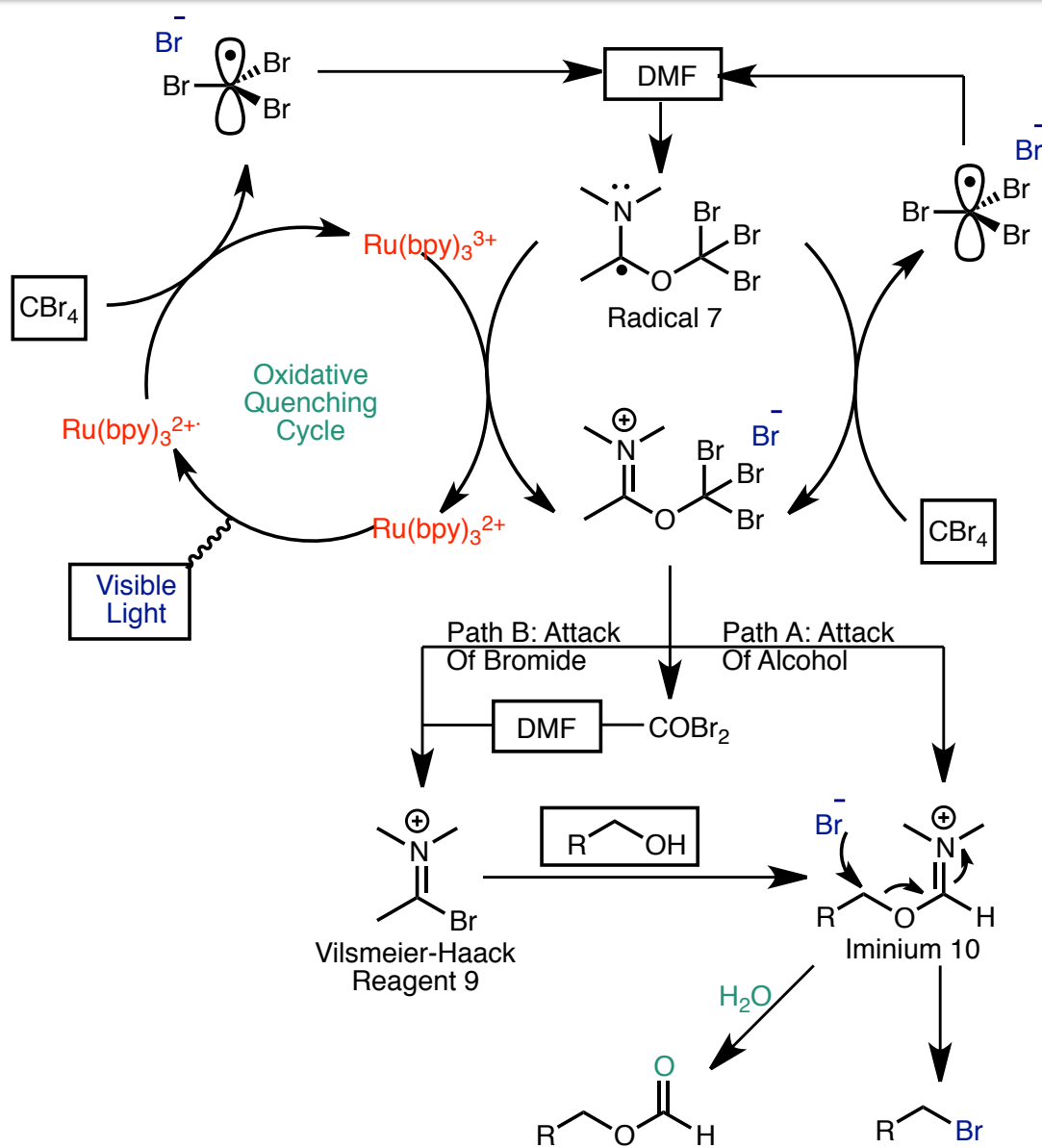


Observations: Premature quenching primary alcohols leads to formate-ester side products

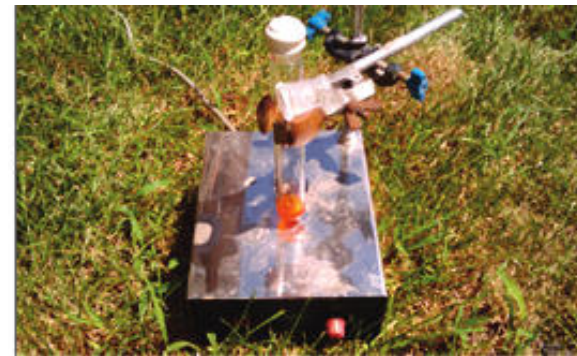
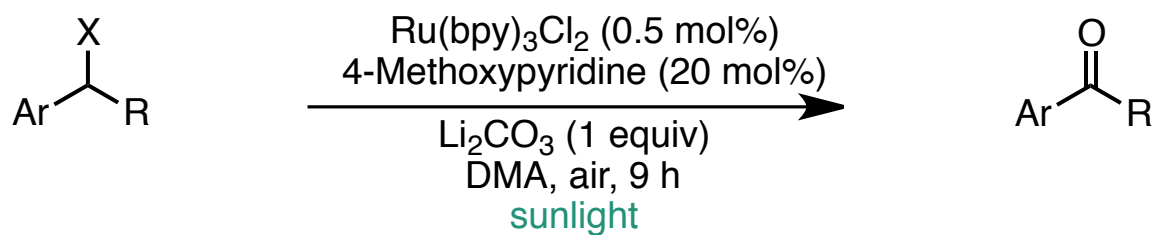
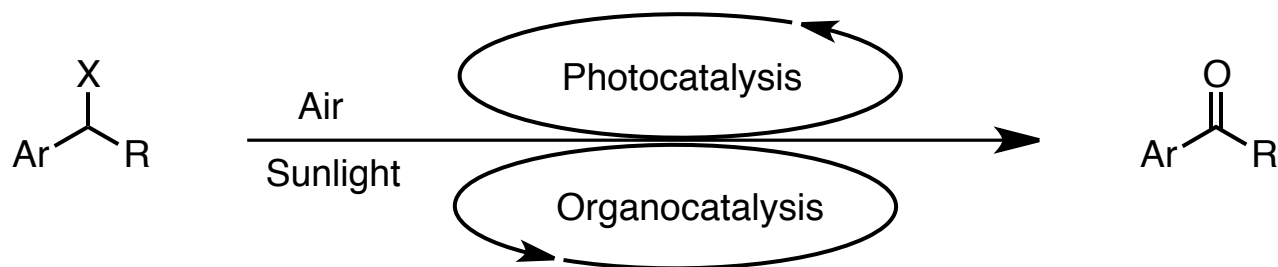
Hypothesis: DMF is involved in the transformation via in-situ formation of a Vilsmeier-Haak type reagent



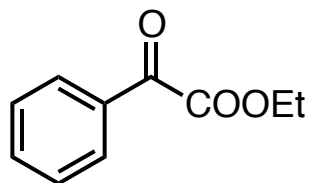
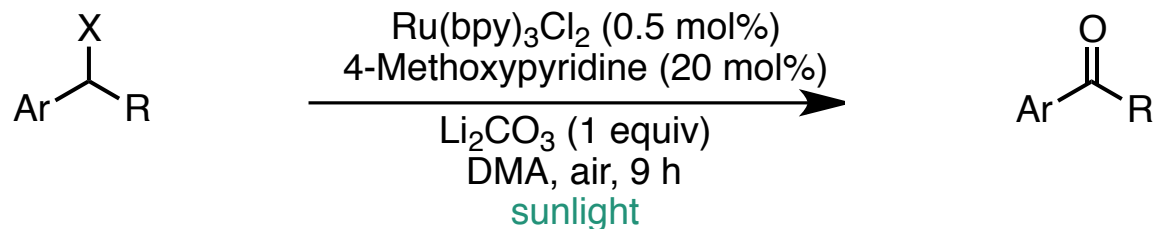
# Mechanistic Investigations



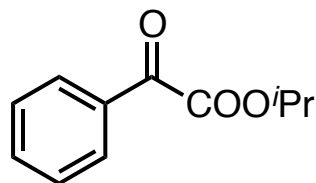
# Aerobic Oxidation of Benzyl Halides



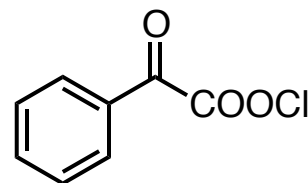
# Aerobic Oxidation of Benzyl Halides



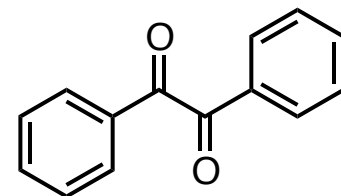
X=Br, 75%



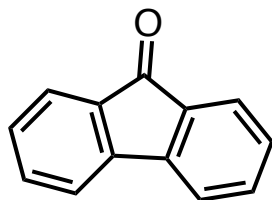
X= Br, 83%



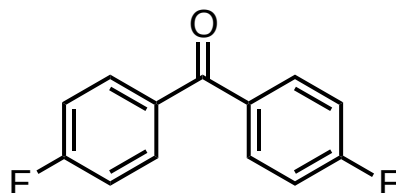
X= Br, 85%



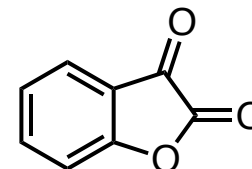
X= Cl, 81%  
X= Br, 81%



X= Br, 56%

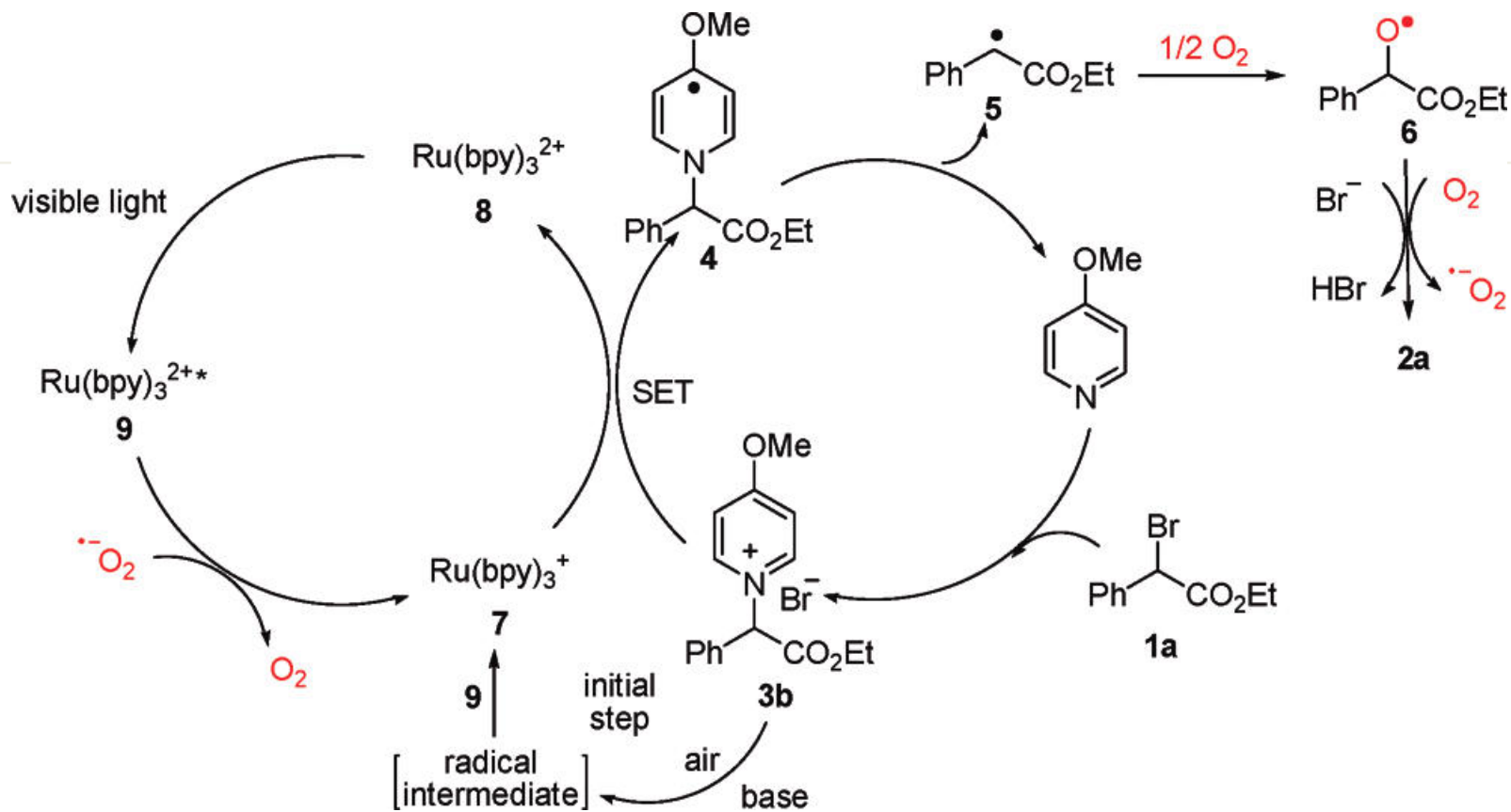
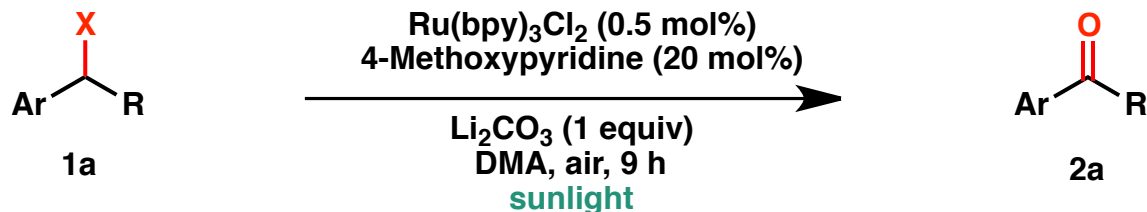


X= Cl, 39%

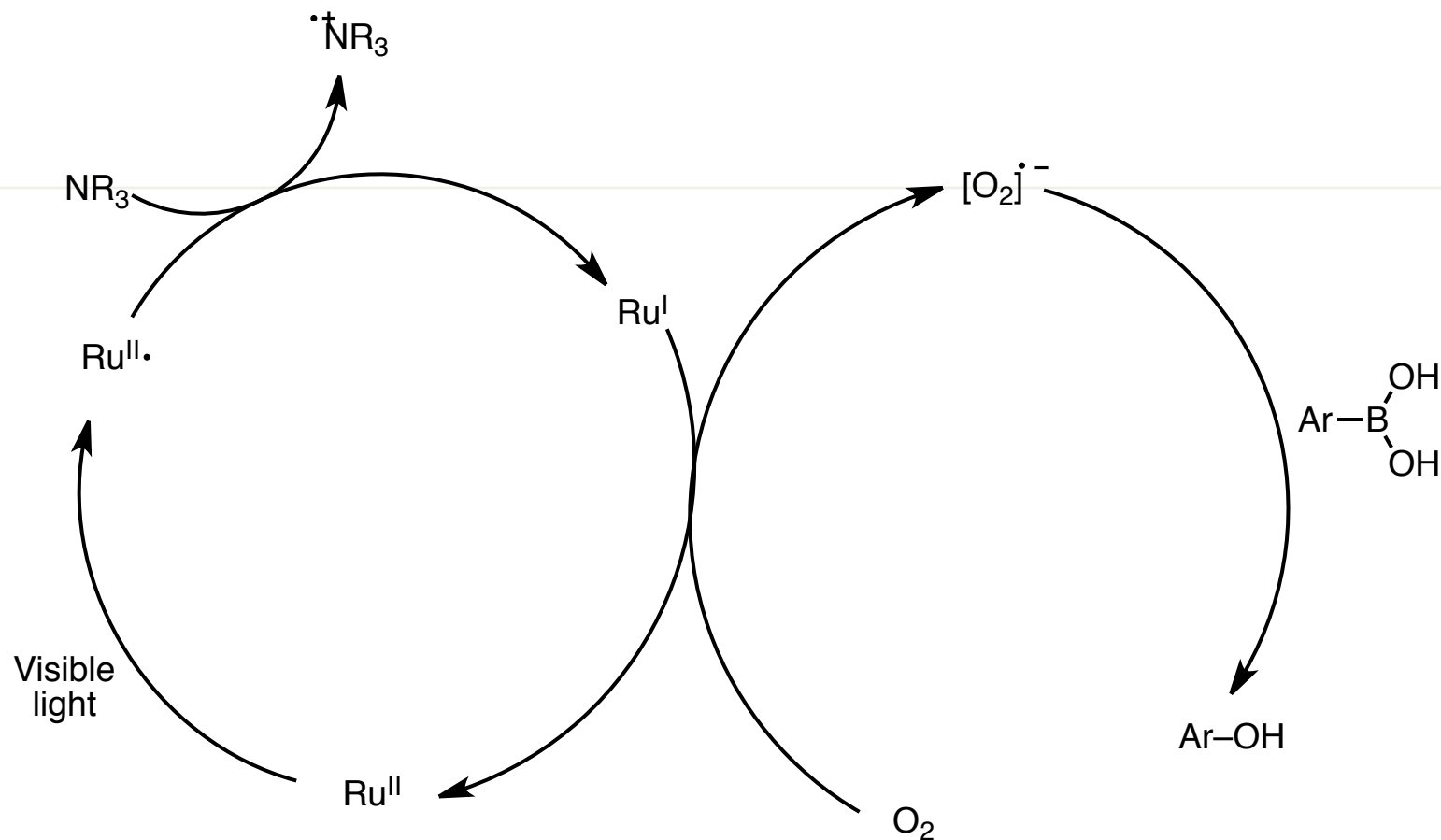
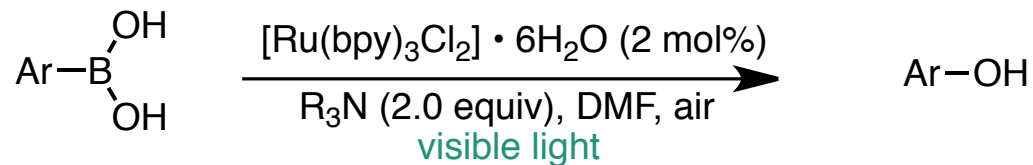


X= Br, 0%

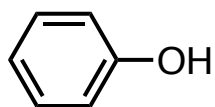
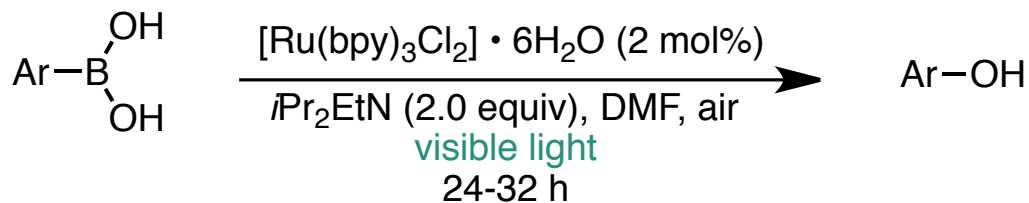
# Aerobic Oxidation of Benzyl Halides



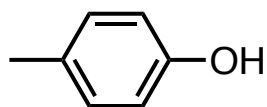
# Photoredox Hydroxylation of Arylboronic Acids



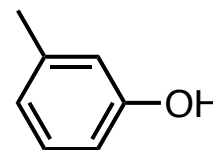
# Photoredox Hydroxylation of Arylboronic Acids



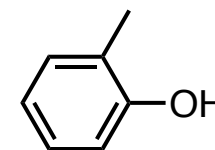
81%



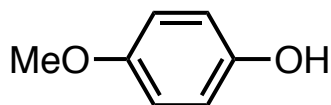
94%



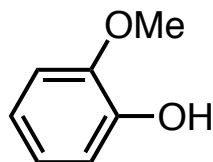
91%



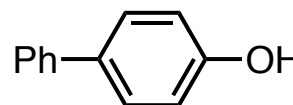
72%



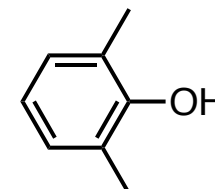
93%



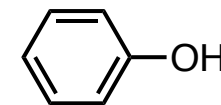
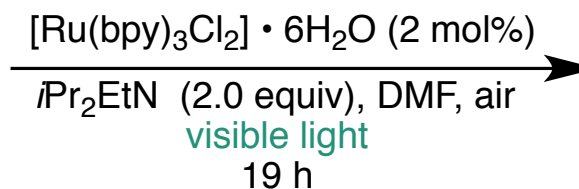
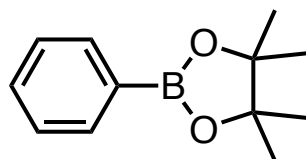
72%



94%



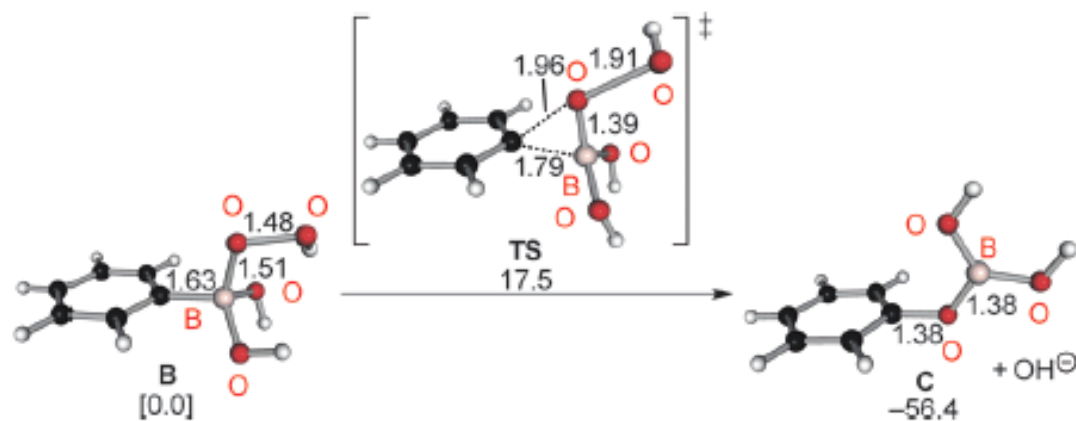
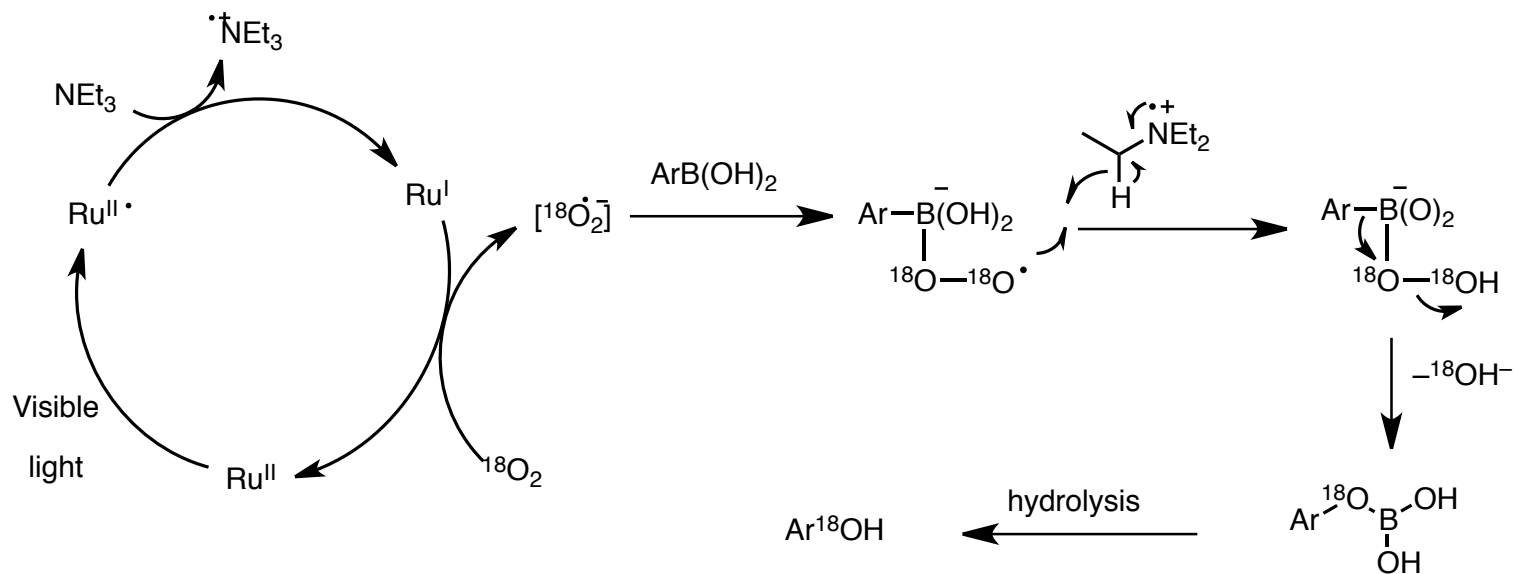
69%



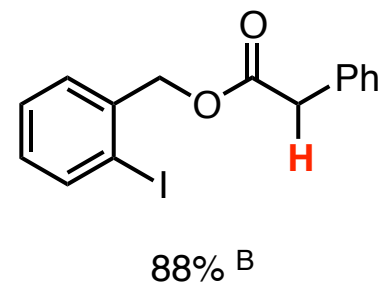
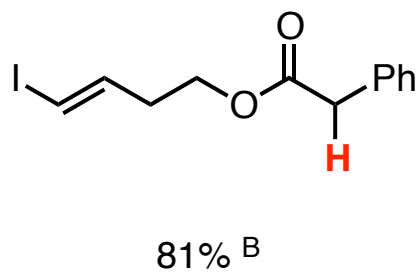
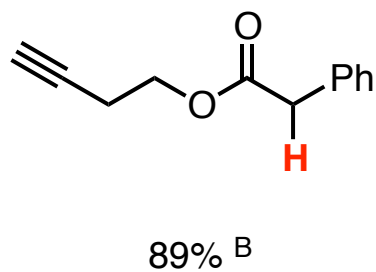
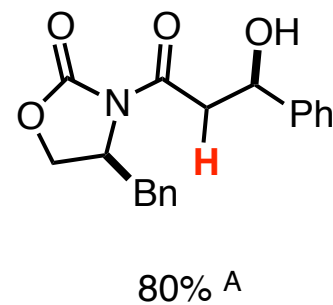
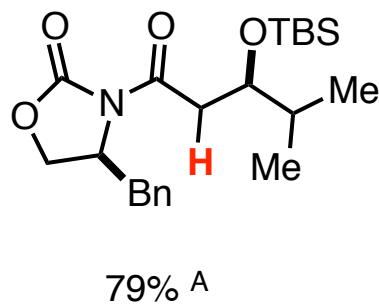
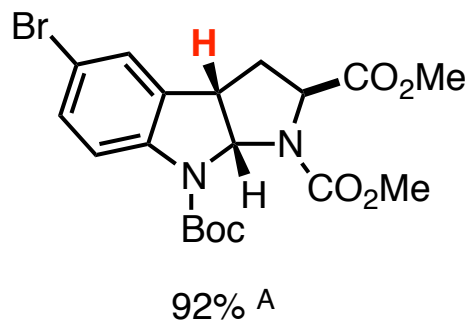
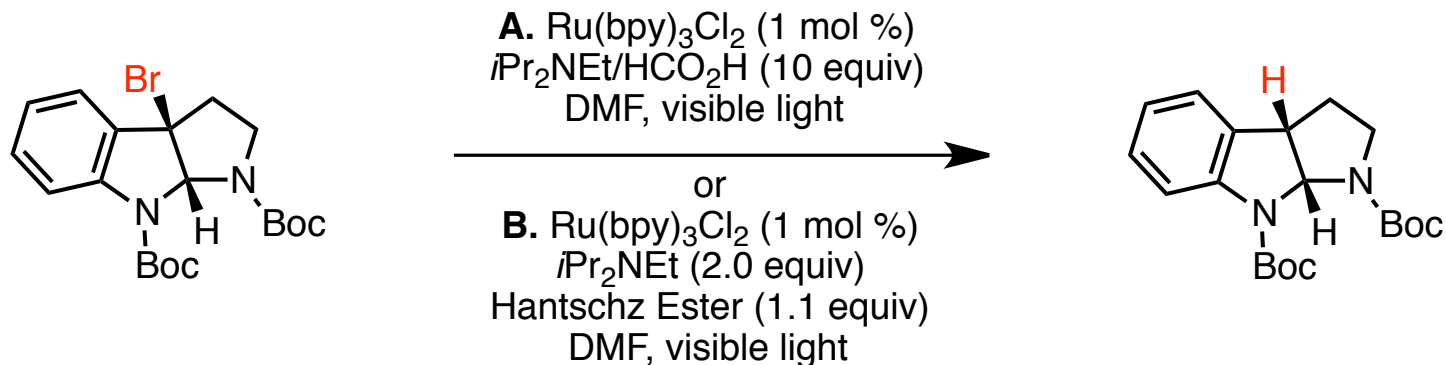
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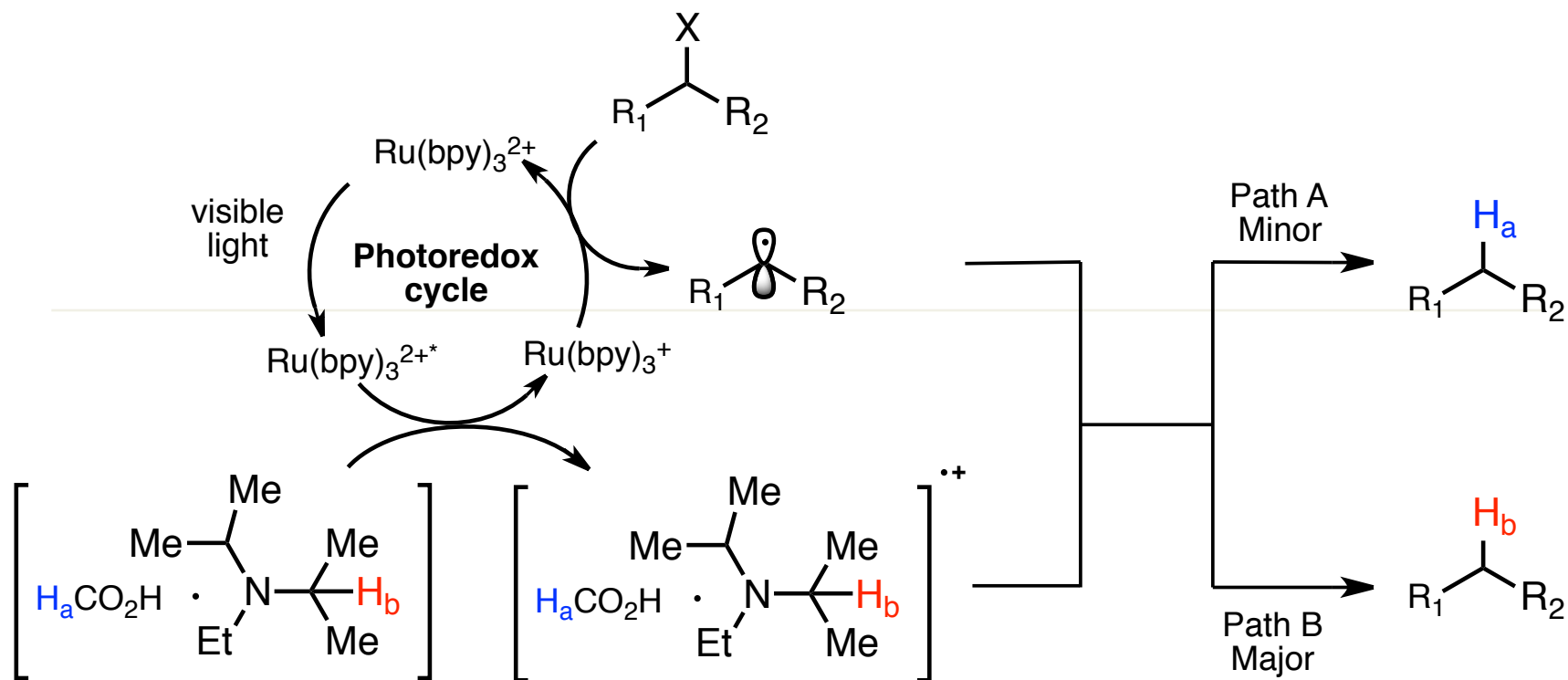
# Mechanistic Insight



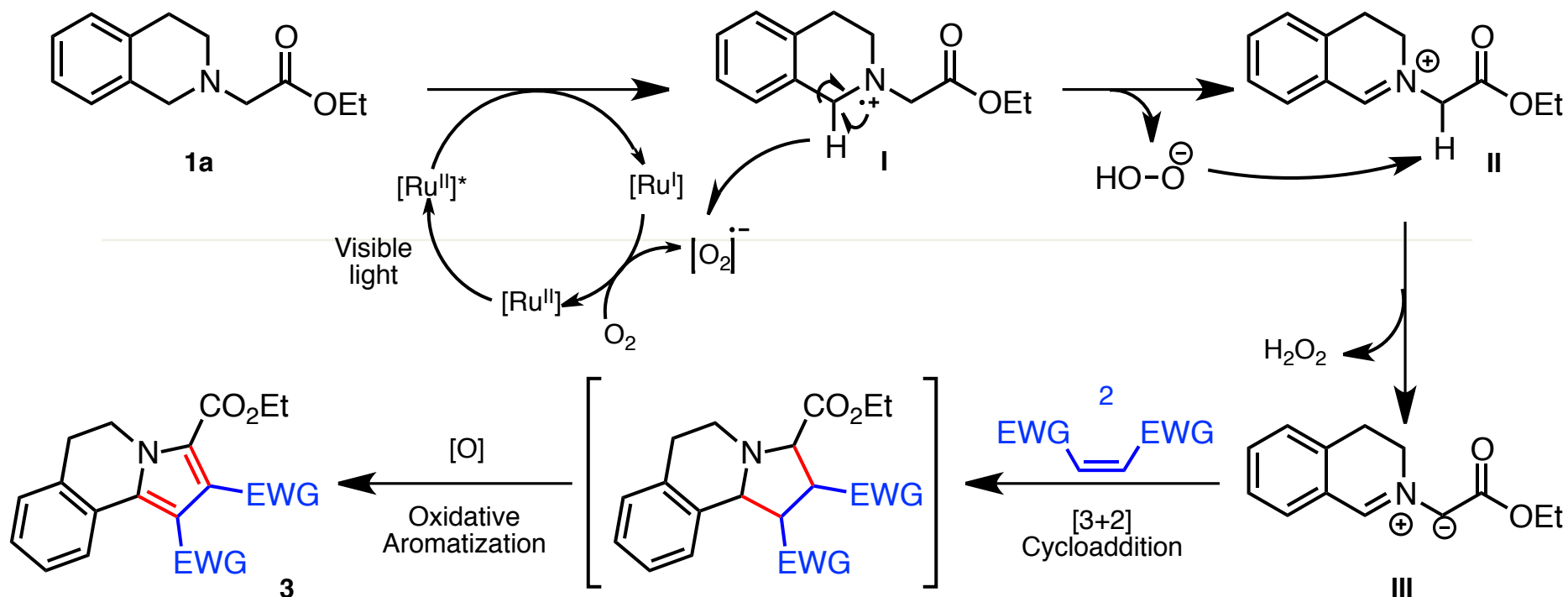
# Photoredox-mediated reductive dehalogenation



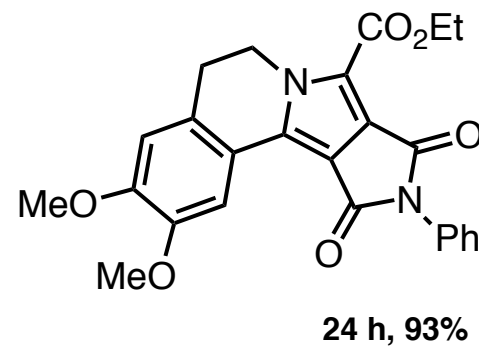
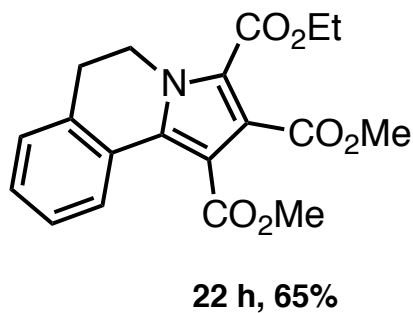
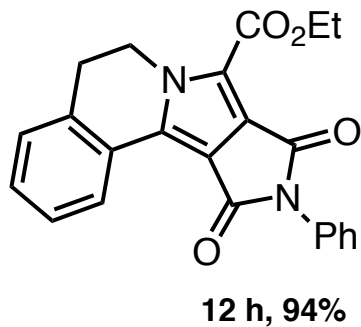
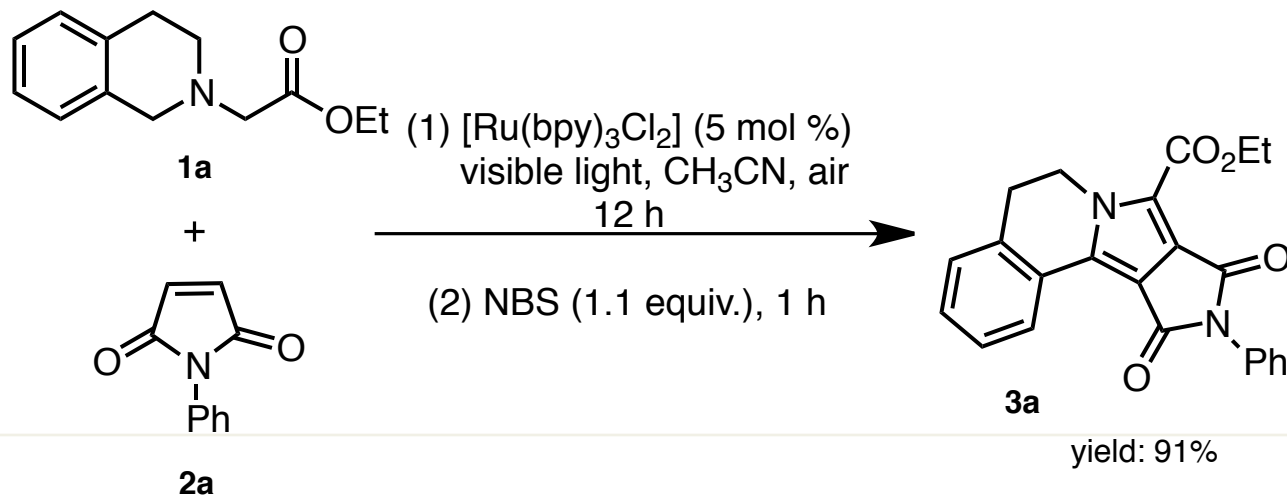
# Mechanism



# Photoredox [3+2] Cycloaddition/Aromatization

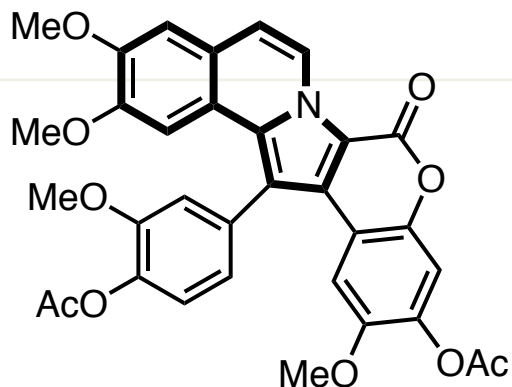


# Photoredox [3+2] Cycloaddition/Aromatization



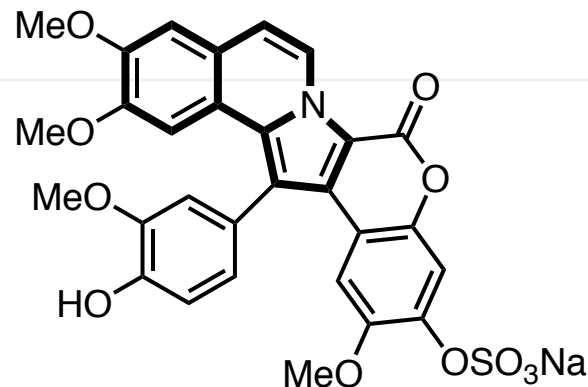
# Photoredox [3+2] Cycloaddition/Aromatization

- Lamellarin alkaloids, a new family of marine natural products
- Contain a pyrrolo[2,1-a]isoquinoline core



**lamellarin D triacetate**

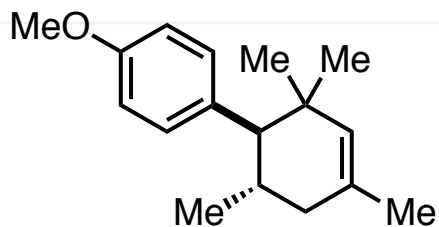
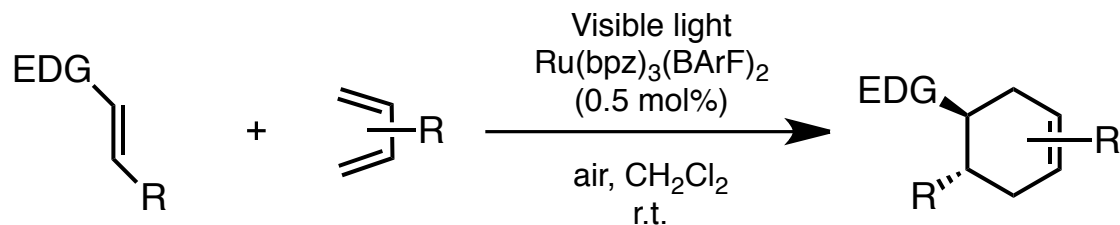
Inhibitor of human topoisomerase I



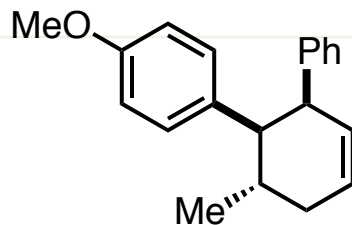
**lamellarin 20-sulfate**

Inhibition of HIV integrase

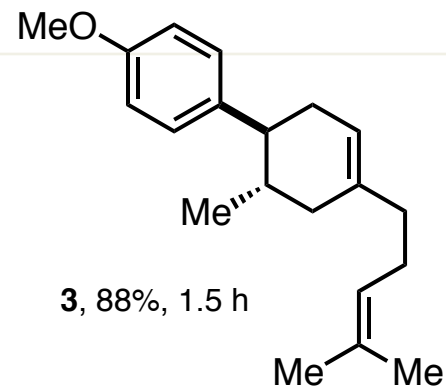
# Radical Cation Diels-Alder Cycloadditions



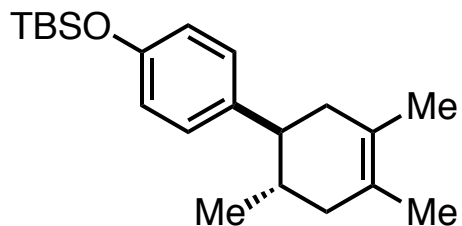
1, 91%, 2 h



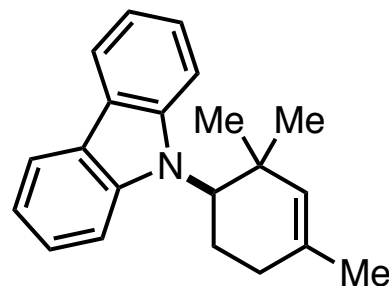
2, 72%, 20 h  
>10:1 *endo:exo*



3, 88%, 1.5 h

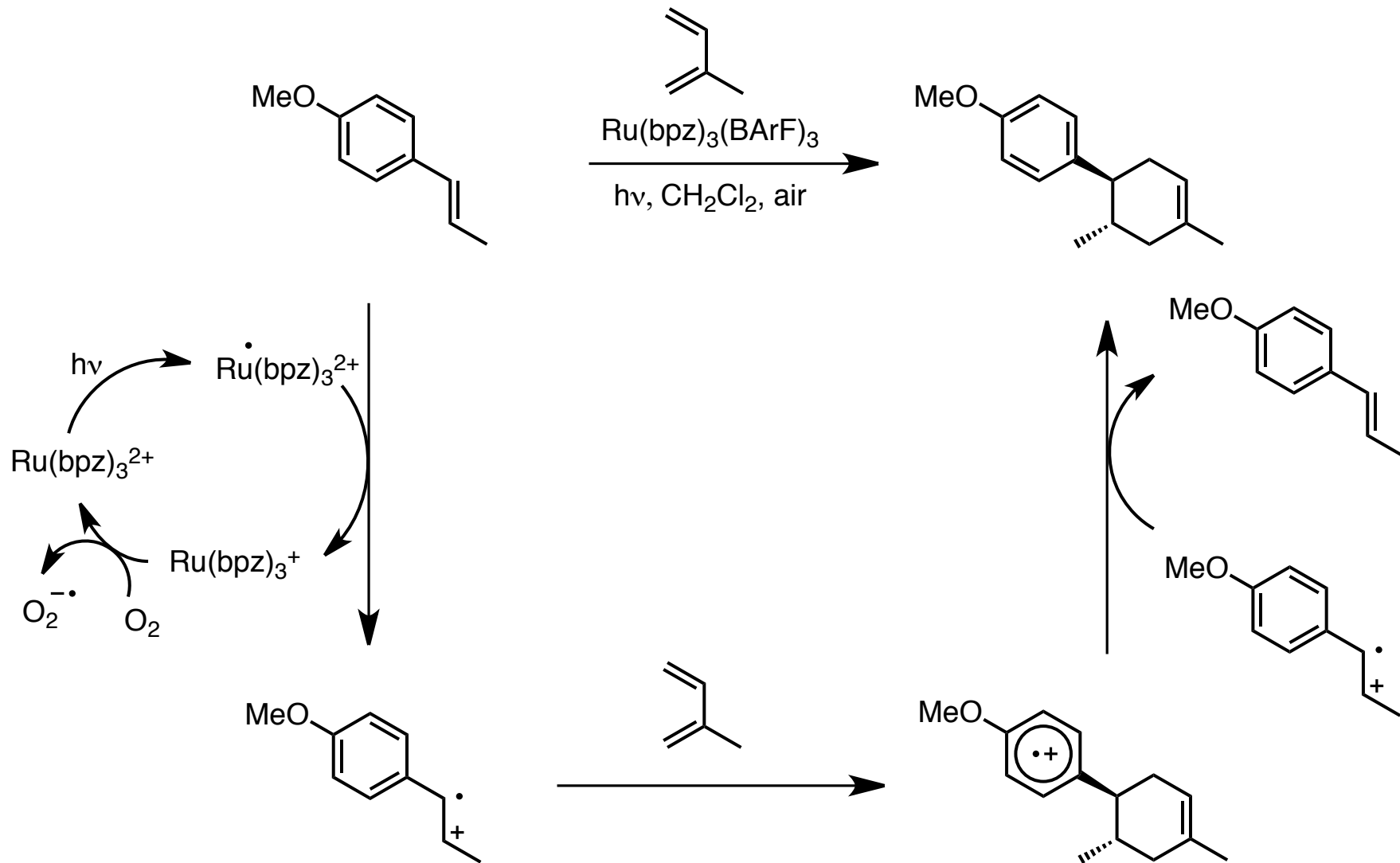


4, 77%, 4 h



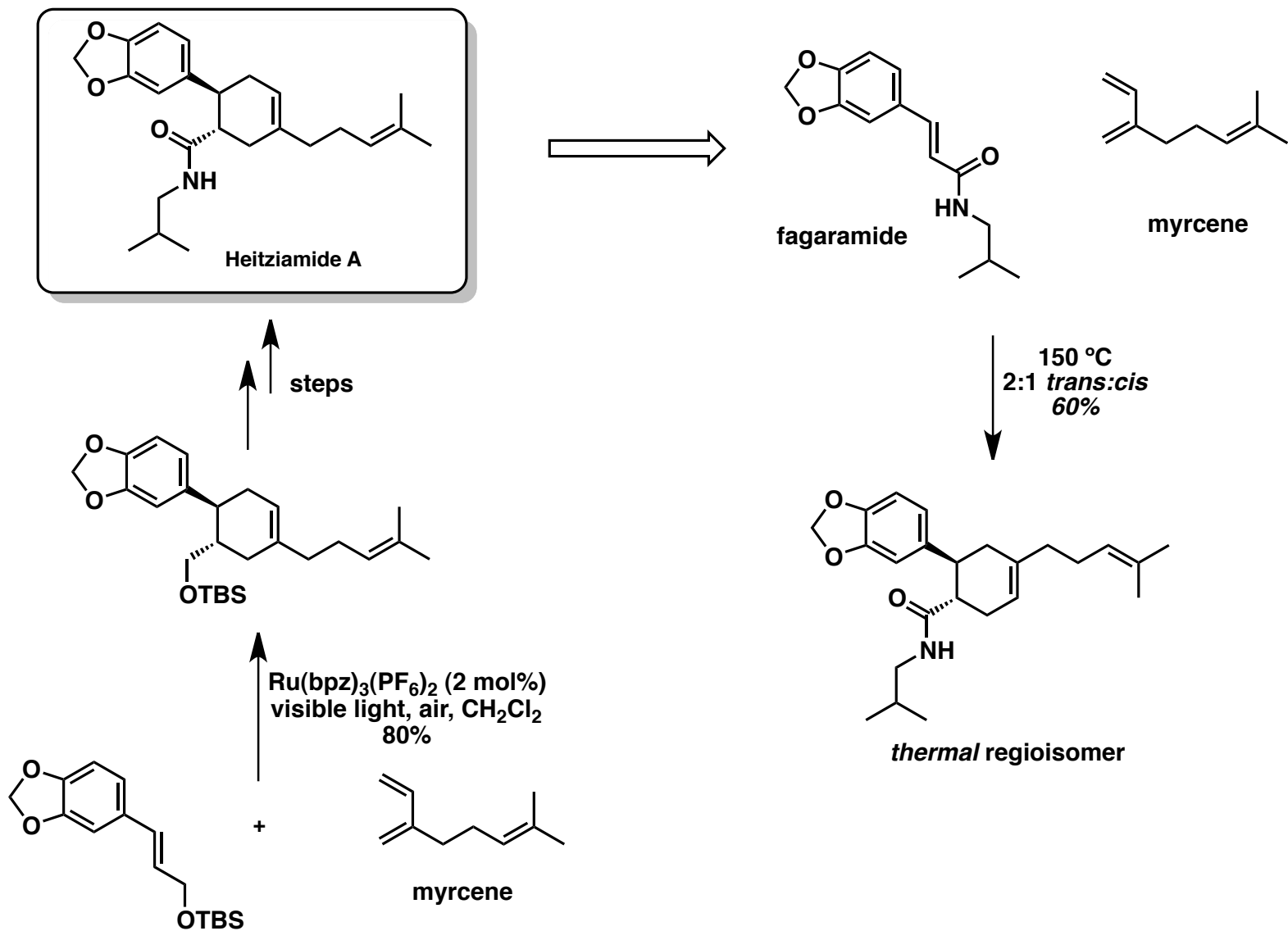
5, 65%, 24 h

# Radical Cation Diels-Alder Cycloadditions

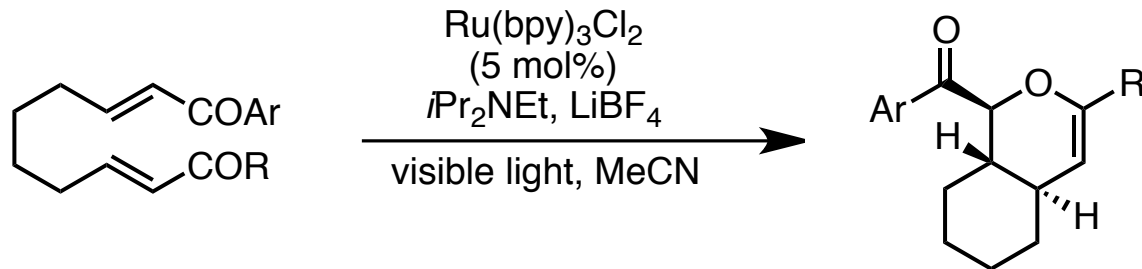


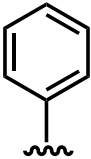
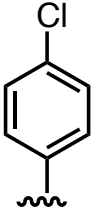

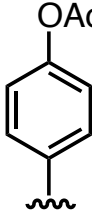
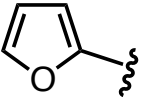
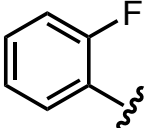
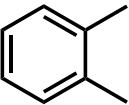


# Heitziamide A: A Case for Photoredox D.A.

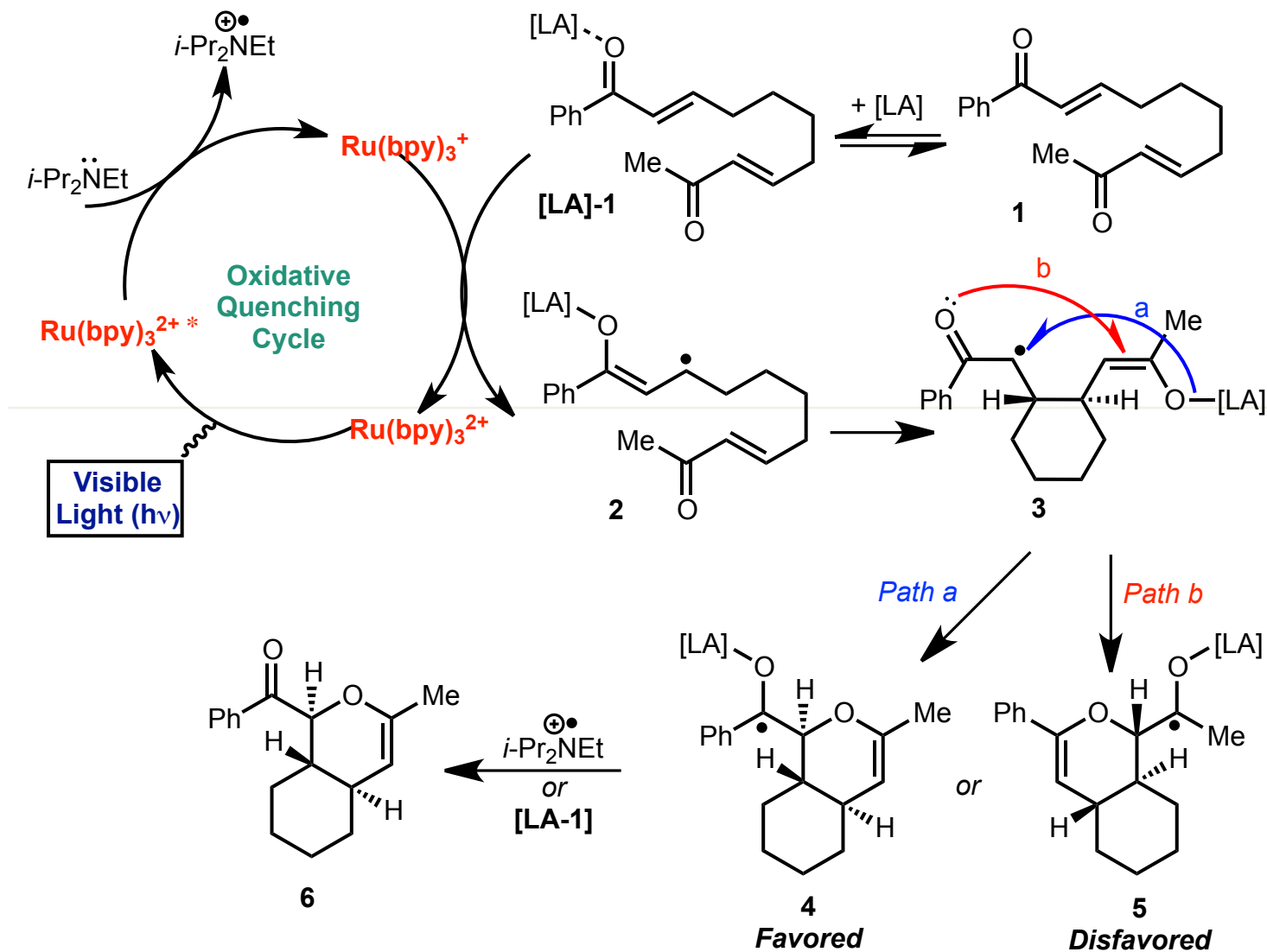


# Radical Anion Hetero-Diels-Alder Cycloadditions

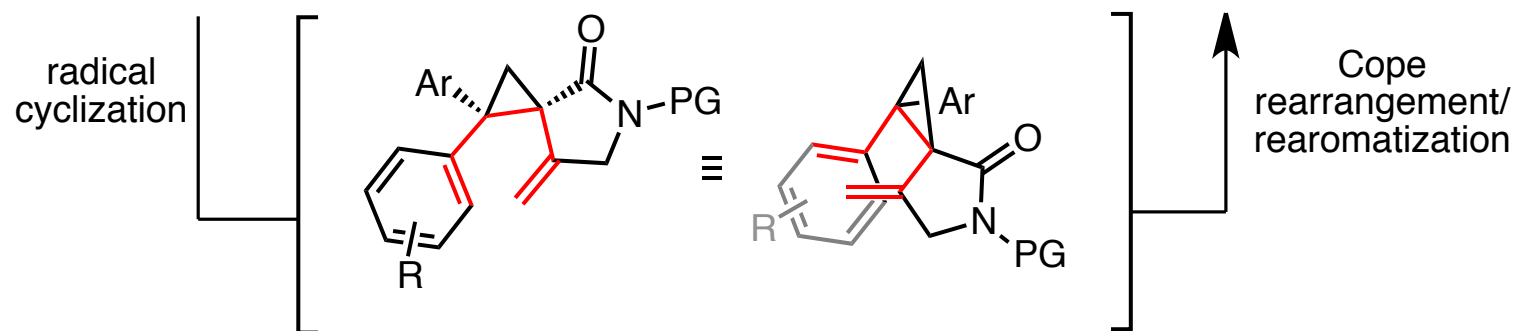
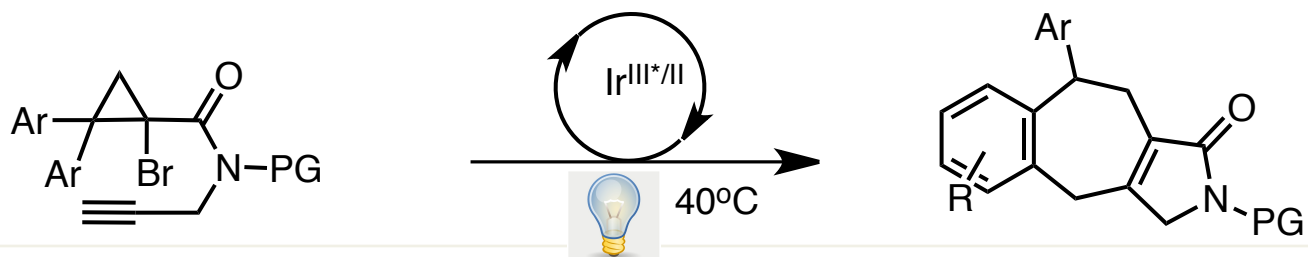


|          |   |  |  |  |
|----------|---|--|--|--|
| Ar = R = | <br>86 % | <br>70%   | <br>83% | <br>76% |
|          | <br>77%  | <br>84% | <br>6%  |  |
|          | Ar= Ph R= $\text{CH}_2\text{OBn}$<br>76%  | Ar= Ph R= <i>t</i> -Bu<br>12%  |  |  |

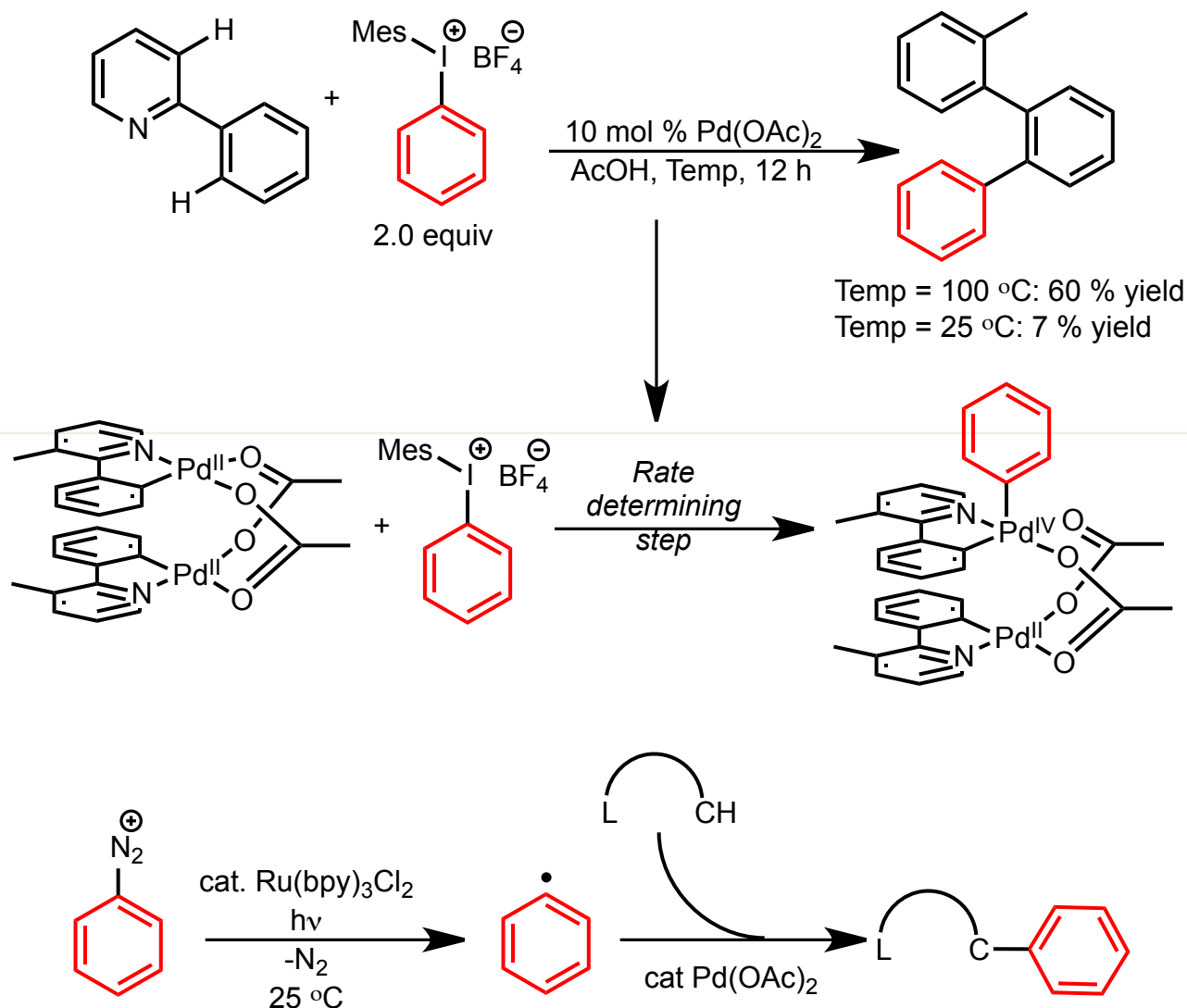
# Mechanism



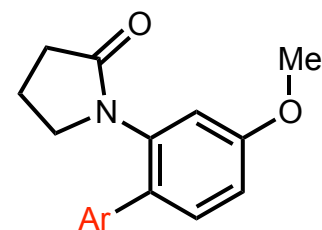
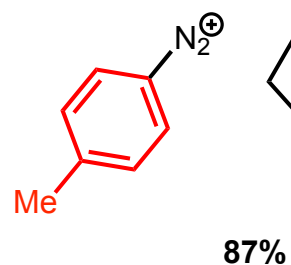
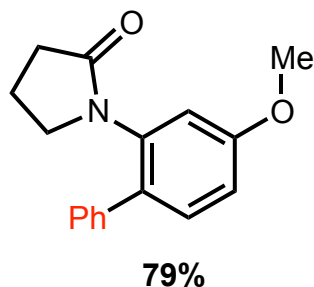
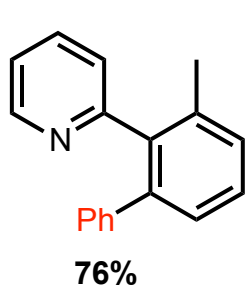
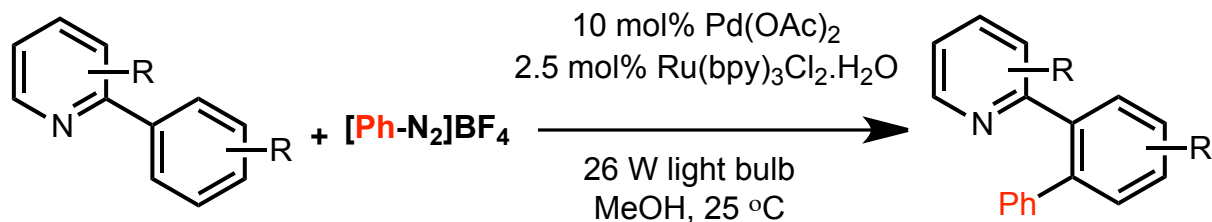
# Photoredox Radical Cyclization/Cope



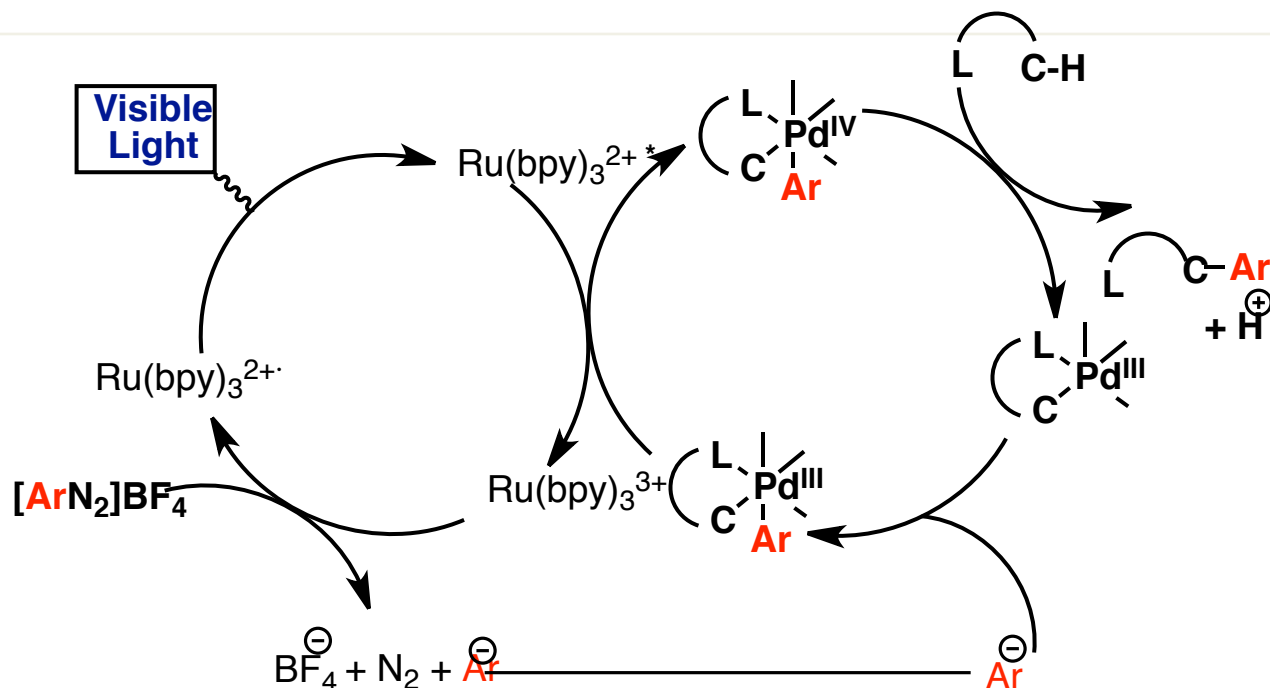
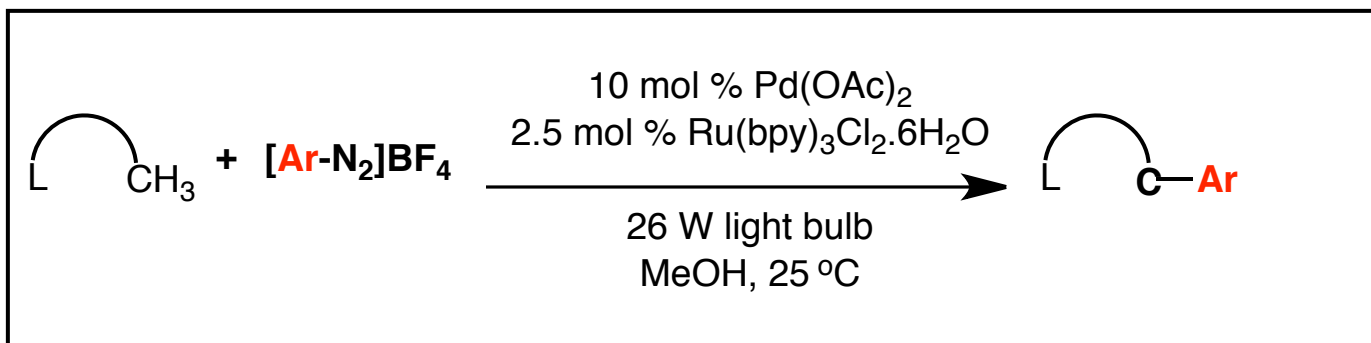
# Combining Photoredox with Transition Metals



# Combining Photoredox with Transition Metals



# Mechanism



# Outline

❖  $\alpha$ -Amino C-H Oxidation to:

C-C bond formation

C-N bond formation

C-P bond formation

❖ Transformations:

C-O to C-X

C-X to C=O

C-B to C-O

C-X to C-H

Tandem Reactions

❖ Applications:

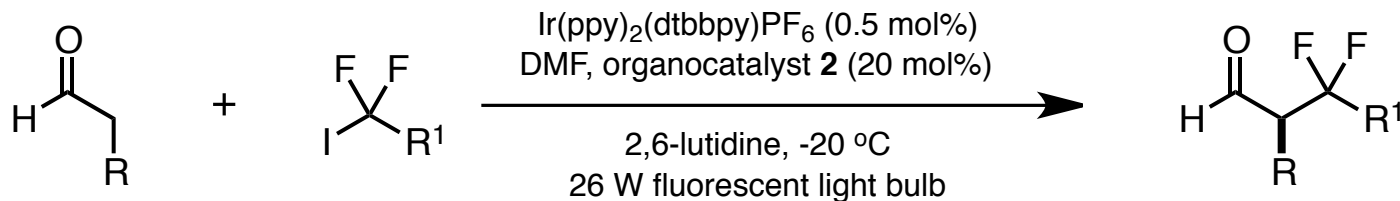
Trifluoromethylation of Drugs

Total Synthesis

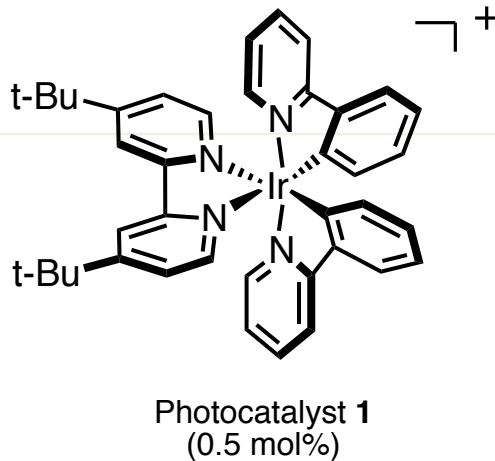
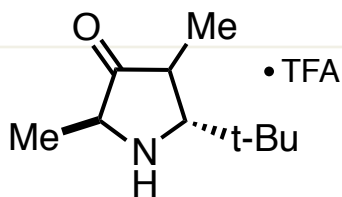
❖ Future Developments



# Trifluoromethylation of Aldehydes



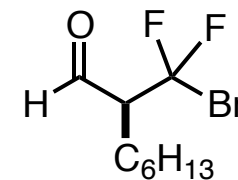
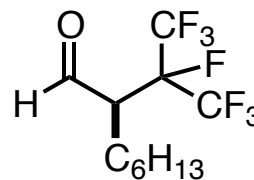
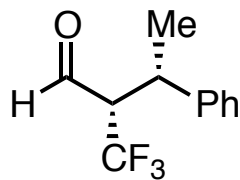
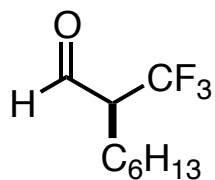
## Catalyst Combination



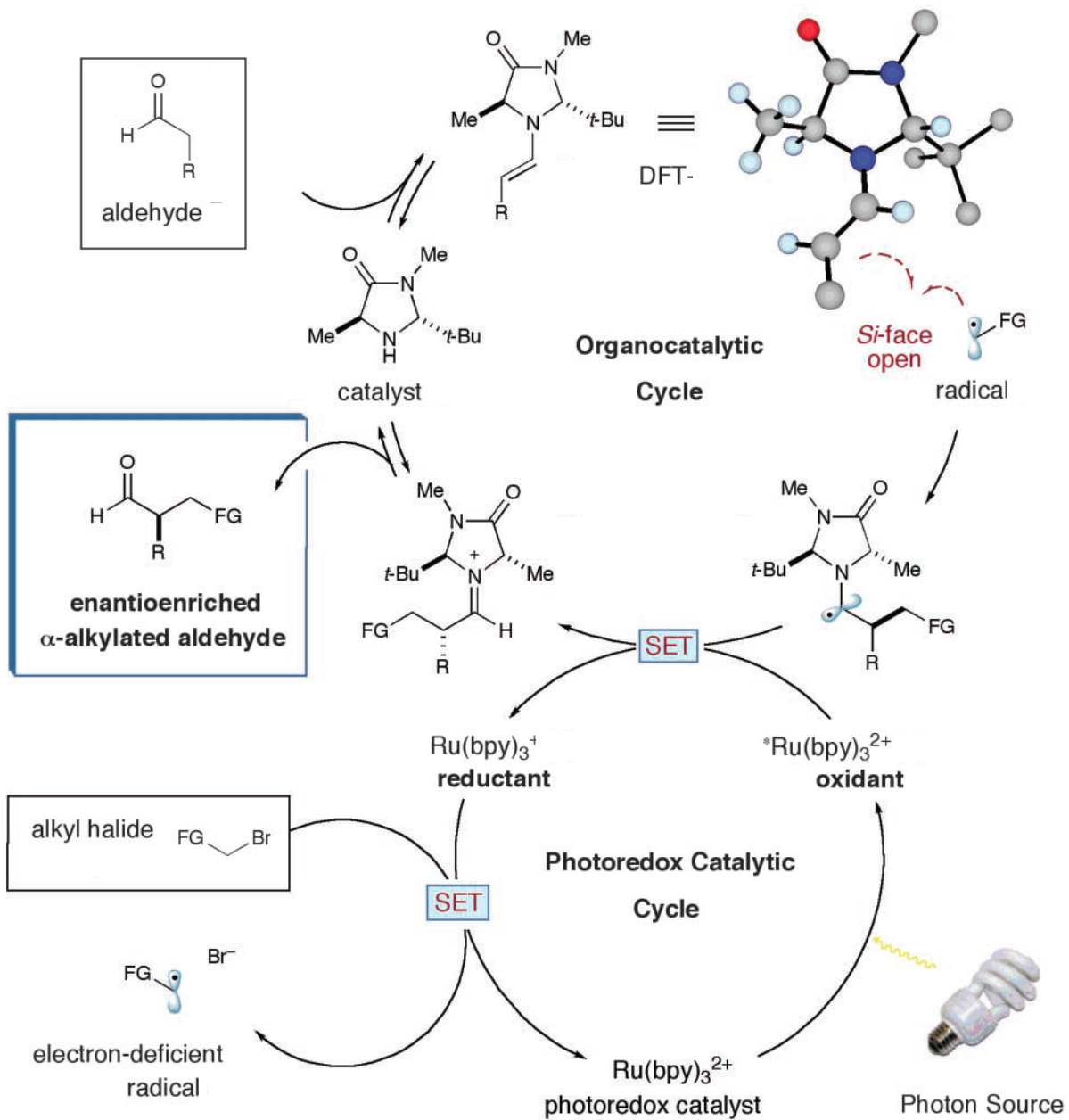
## Photon Source



26 W fluorescent light bulb

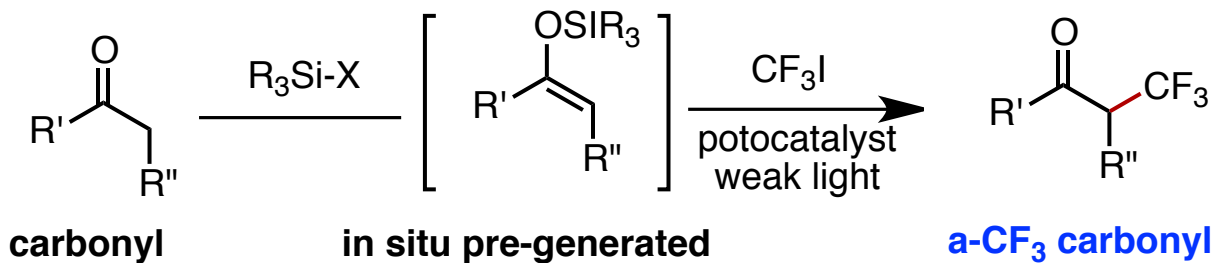
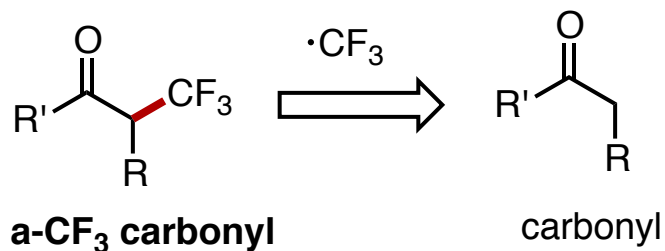


# Mechanism

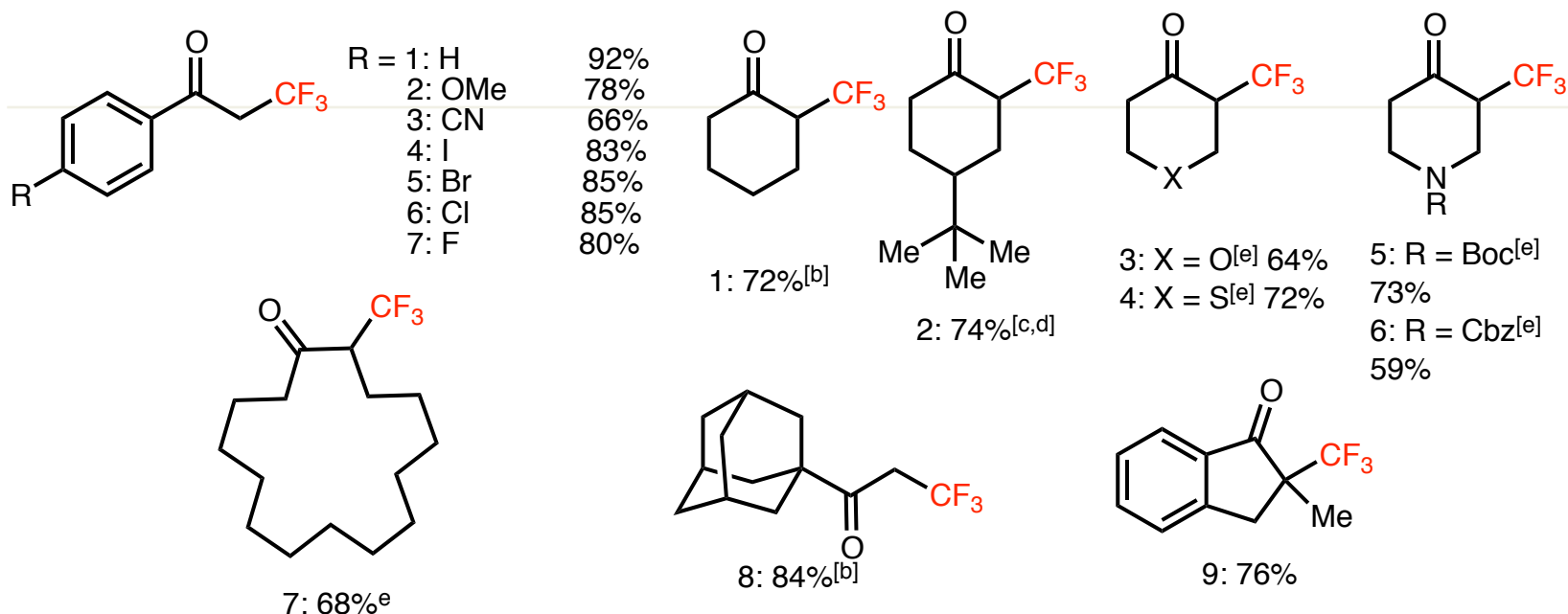
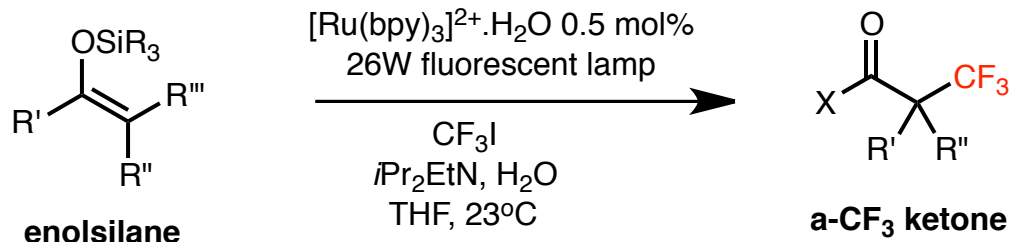


# Synthesis of $\alpha$ -Trifluoromethyl Carbonyl Compounds

Access to novel  $\text{CF}_3$  synthons

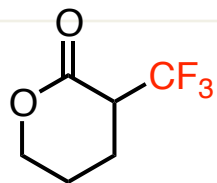
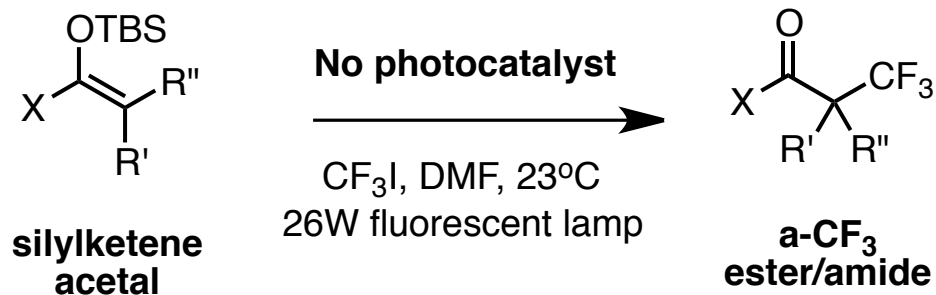


# Trifluoromethylation of Ketone Silylenol Ethers

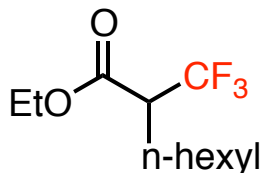


[a] Yield of isolated product; SiR = TIPS unless otherwise noted. [b] TES ether employed. [c] TBS ether employed. [d] 2.2:1 d.r. [e] With NaHCO<sub>3</sub> in MeCN and TES ether.

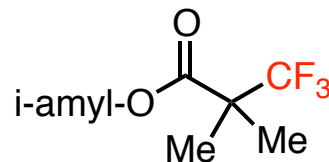
# Trifluoromethylation of Silylenolesters and Amides



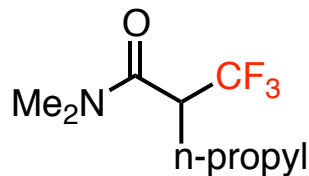
1: 85%



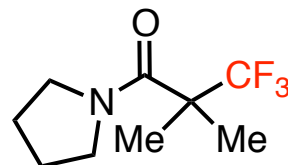
2: 86%



3: 74% [b,c]



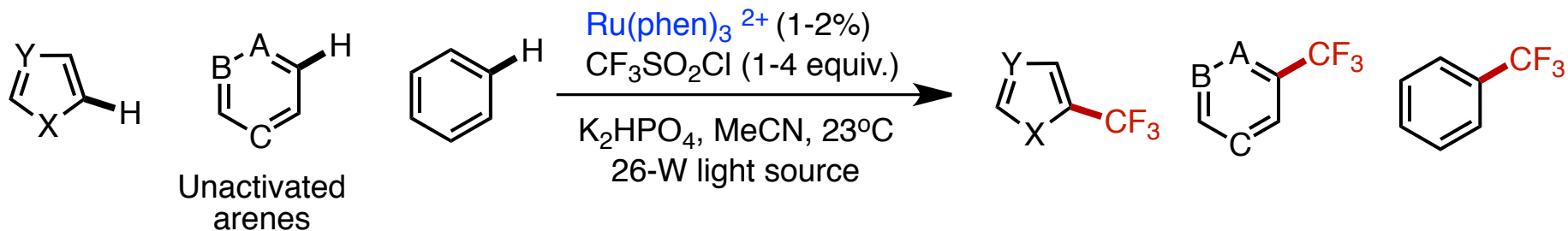
4: 76%



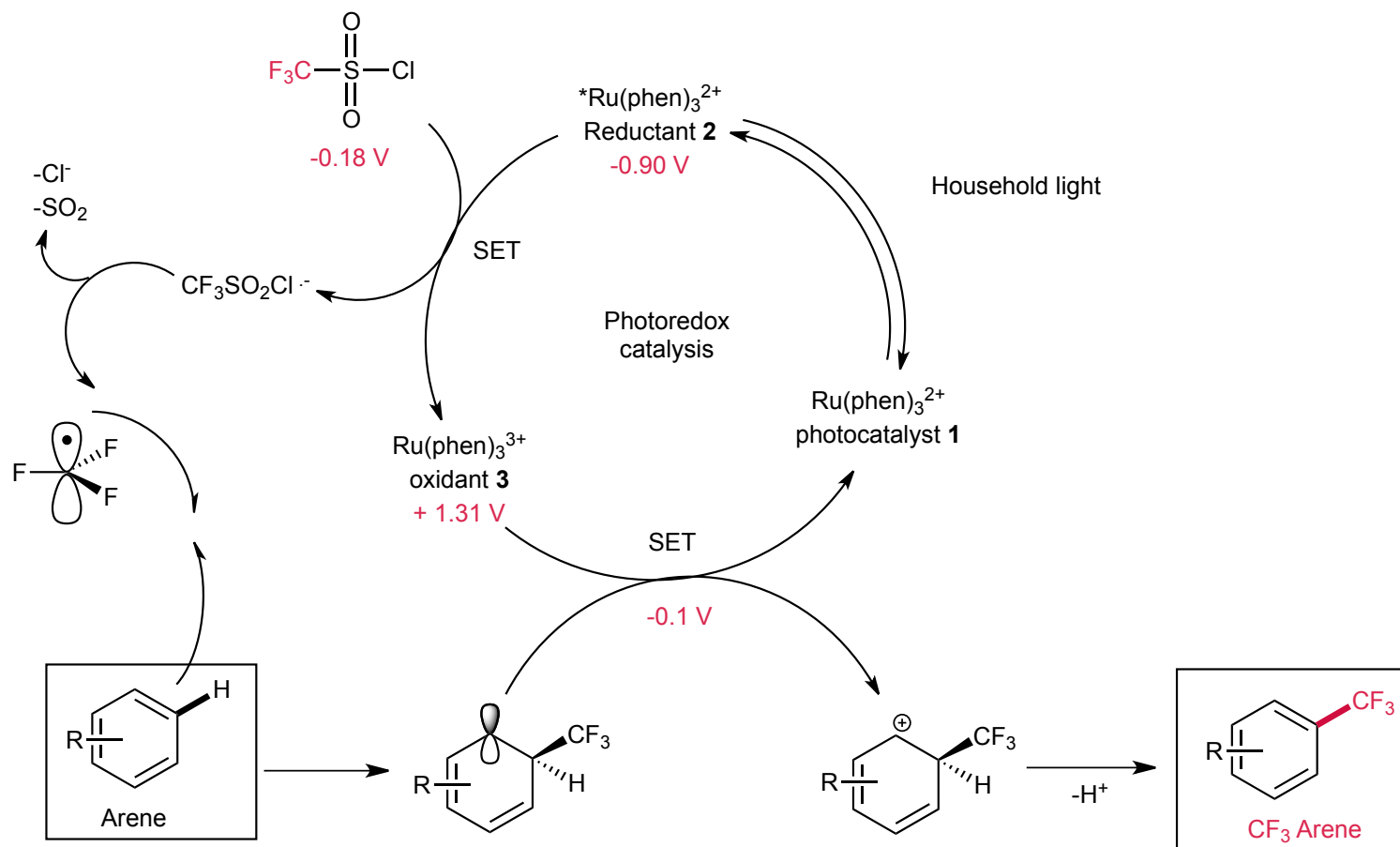
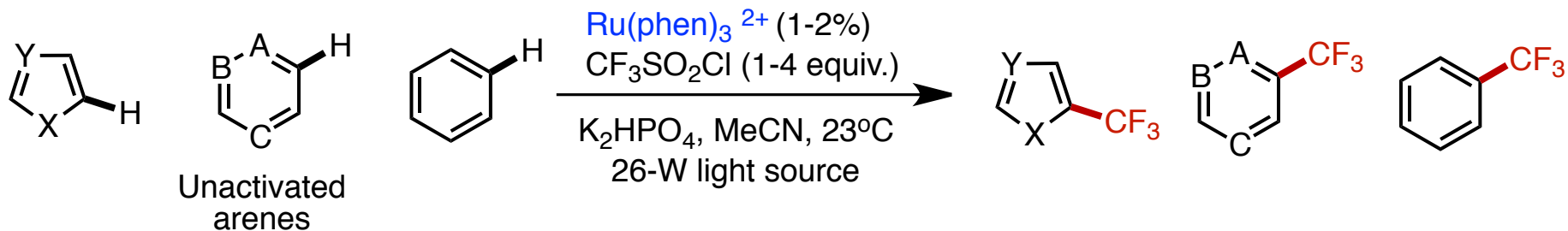
5: 84% [b]

[a] Yield of isolated products. [b] 0.5 mol % **1**. H<sub>2</sub>O, Et<sub>3</sub>N, isoamyl alcohol employed. [c] in MeCN.

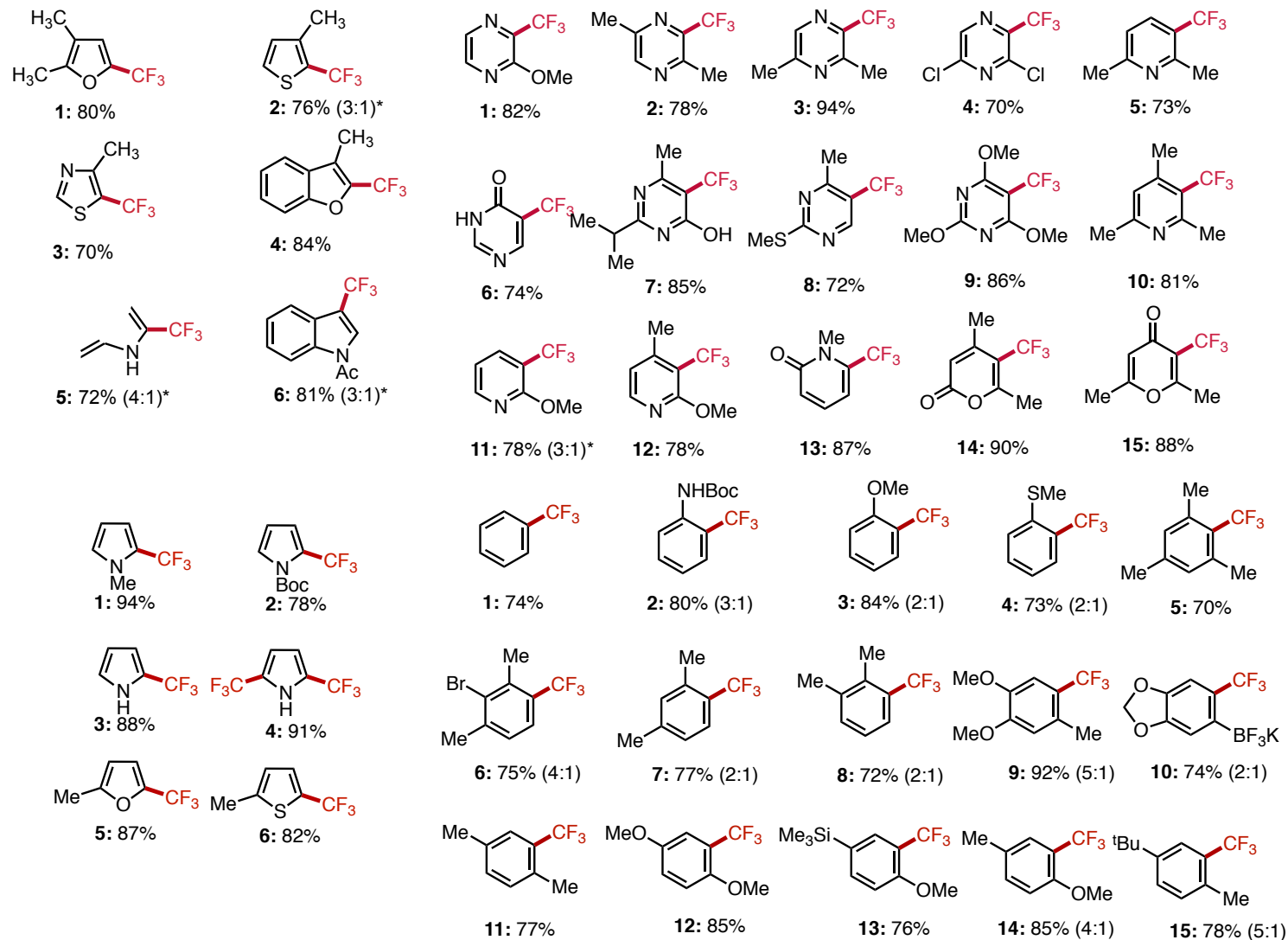
# Trifluoromethylation of Arenes and Heteroarenes



# Trifluoromethylation of Arenes and Heteroarenes



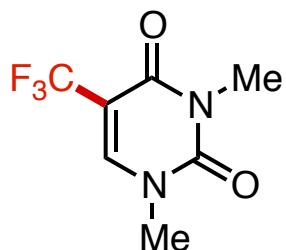
# Substrate Scope



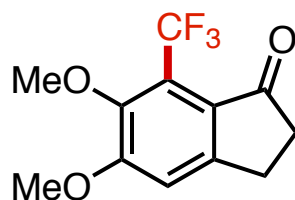


# Applications to Existing Drug Molecules

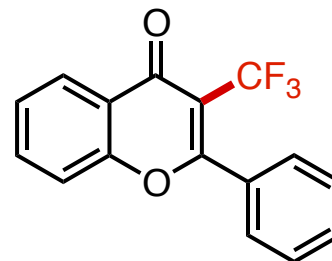
## Selectivity



DNA base analogue  
CF<sub>3</sub>-methyluracil  
92%

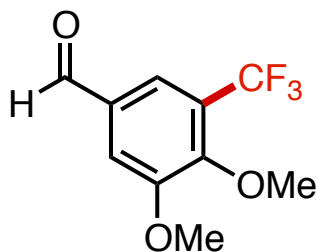


Anti-Alzheimer's  
CF<sub>3</sub>-Ariccept precursor  
94%

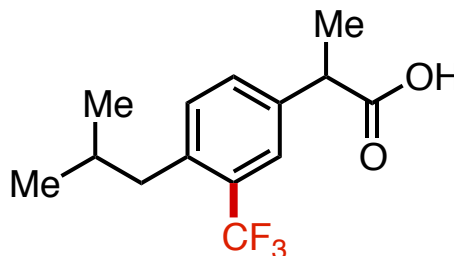


Vitamin P  
CF<sub>3</sub>-Flavone  
85%

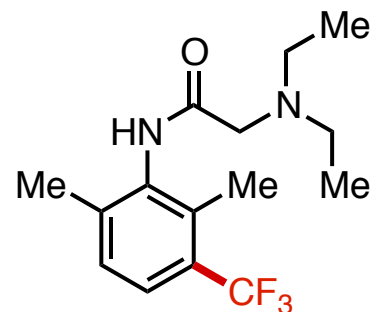
## Promiscuity



Flavorant (coffee/chocolate)  
CF<sub>3</sub>-methylvanillin  
82% (5:1)

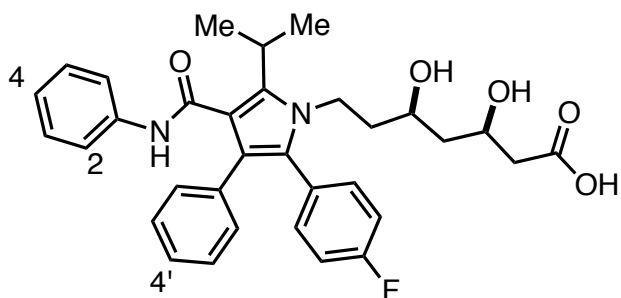


Anti-inflammatory  
CF<sub>3</sub>-ibuprofen  
78% (1.4:1)

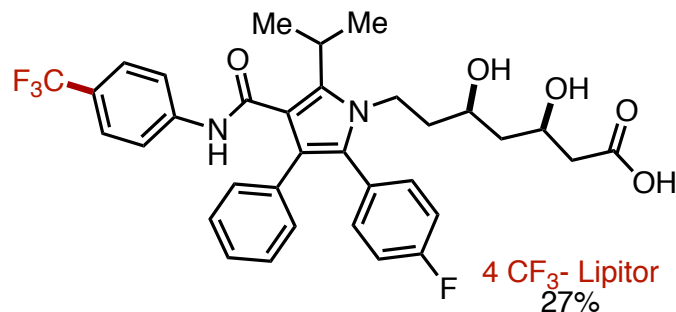


Anaesthetic, anti-arrhythmic  
CF<sub>3</sub>-lidocaine  
78% (2:1)

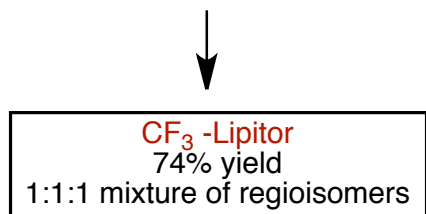
# Applications to Existing Drug Molecules



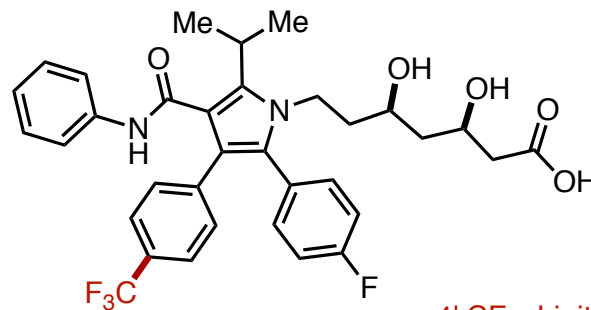
Cholesterol-lowering drug Lipitor



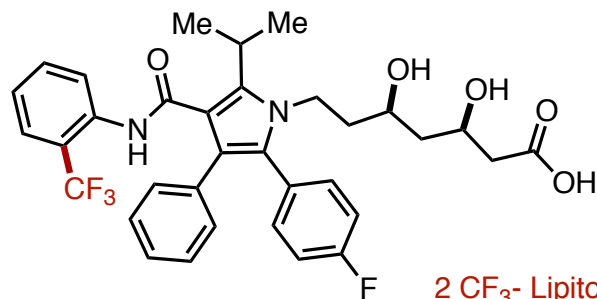
4 CF<sub>3</sub>- Lipitor  
27%



Seperation  
by SFC



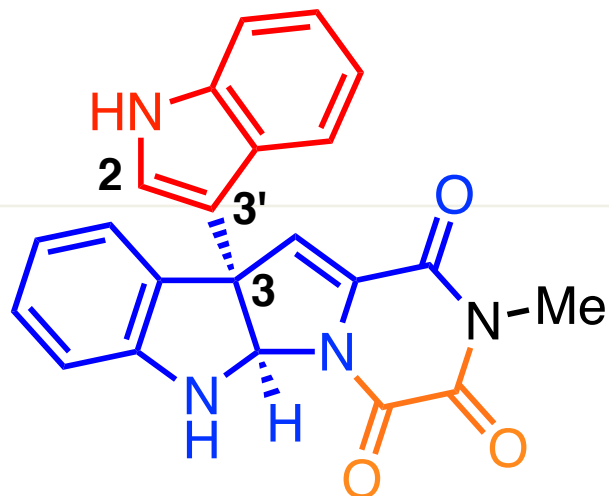
4' CF<sub>3</sub>- Lipitor  
27%



2 CF<sub>3</sub>- Lipitor  
25%

# Total Synthesis of (+)-Gliocladin C

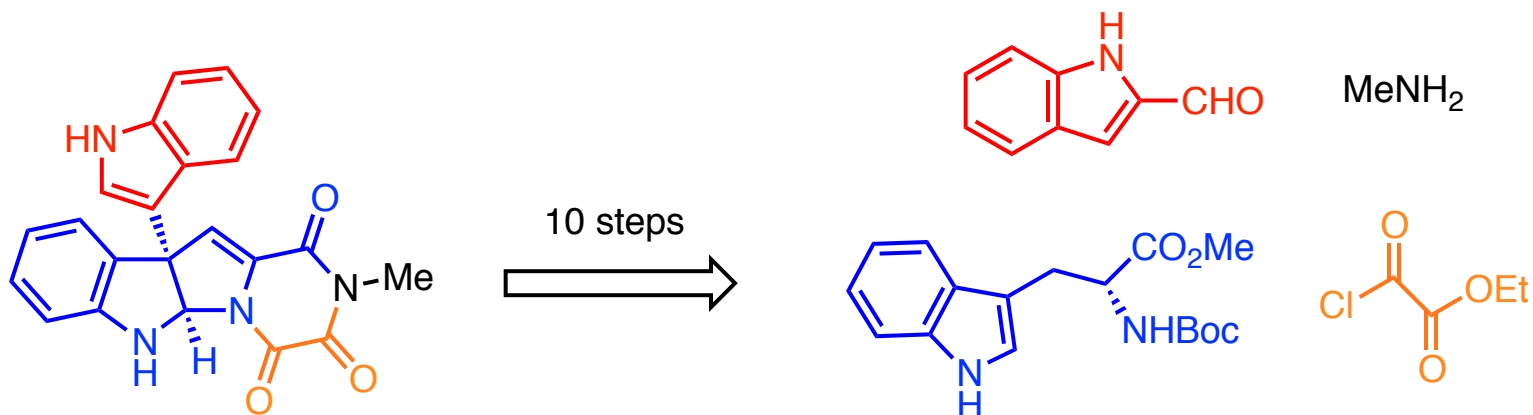
- C3–C3' indole alkaloids, contain the 3a-(3-indolyl) hexahydropyrrolo-[2,3-b]indole skeleton



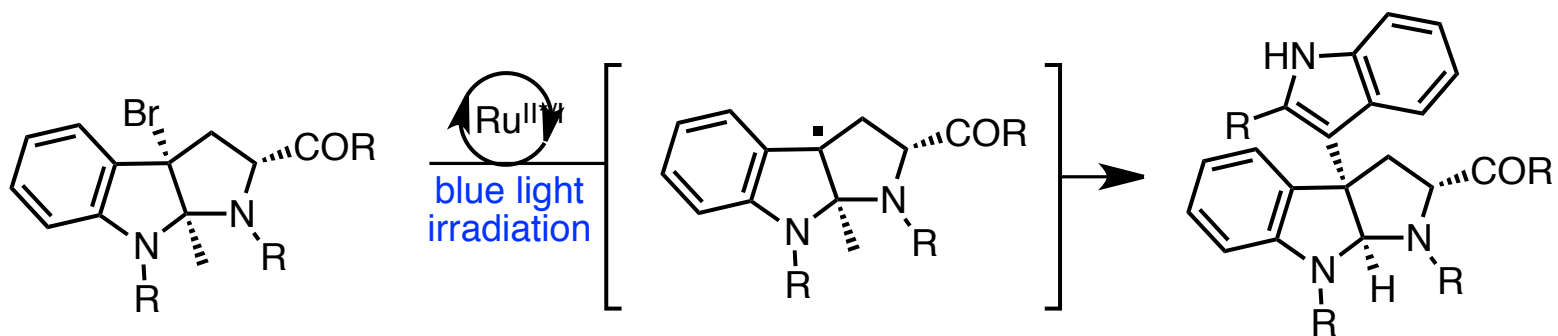
**Gliocladin C**

- Gliocladin C - cytotoxic against P-388 lymphocytic leukemia cell lines

# Total Synthesis of (+)-Gliocladin C



Commercially available starting materials



# Outline

❖  $\alpha$ -Amino C-H Oxidation to:

C-C bond formation

C-N bond formation

C-P bond formation

❖ Transformations:

C-O to C-X

C-X to C=O

C-B to C-O

C-X to C-H

Tandem Reactions

❖ Applications:

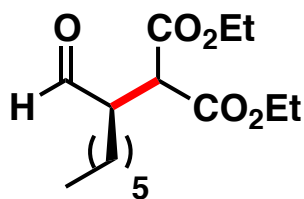
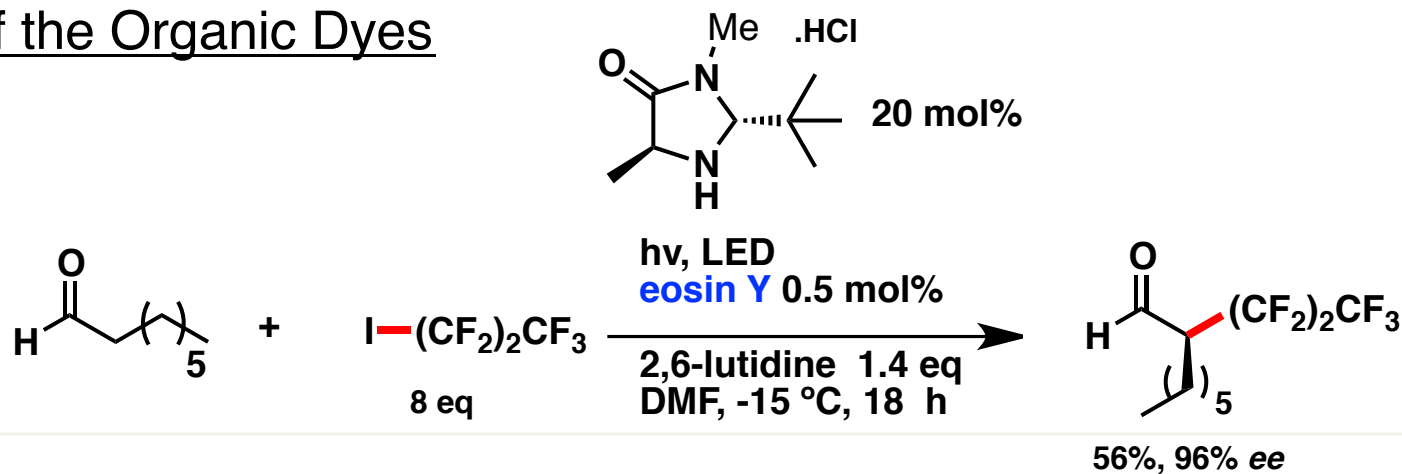
Trifluoromethylation of Drugs

Total Synthesis

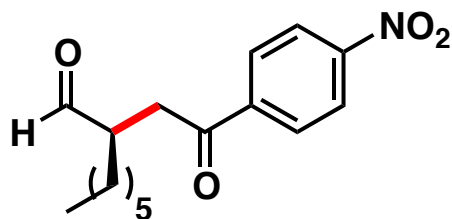
❖ Future Developments

# Future Developments

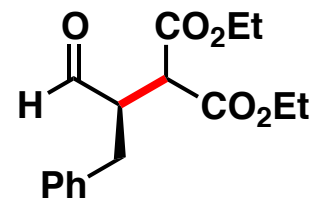
## Use of the Organic Dyes



85%, 88% ee

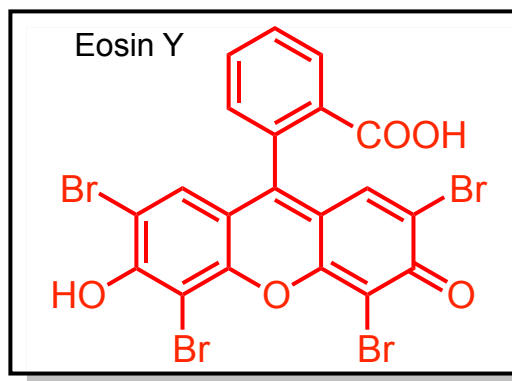
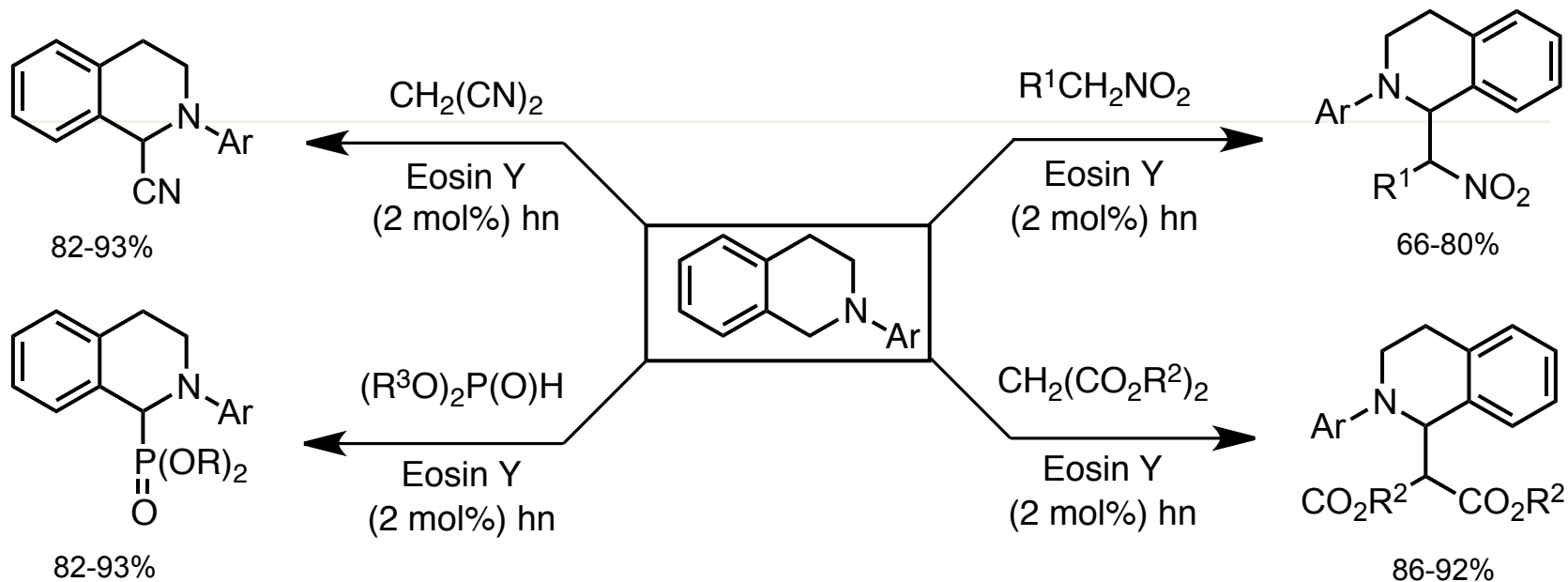


85%, 88% ee



85%, 88% ee

# Use of Organic Dyes



# Conclusions

- Generation of new C-C, C-N and C-P via  $\alpha$ -Amino C-H Oxidation and mild alternative to existing methods.
- Valuable functional group transformations.
- Applications in Drug discovery and Total synthesis.

“and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature”

Ciamician, G. *Science* **1912**, 36, 385–394.



# Acknowledgements

Dr. Maleczka

Dr. Borhan

## **The Maleczka group**

Luis, Rosario, Li, Fangyi, Peter, Susanne, Aaron and Hamid

Anil, Munmun, Salinda, Udayanga and Dilini

**Thank you all !!!**