# Visible-light mediated photoredox and its application in dual catalysis

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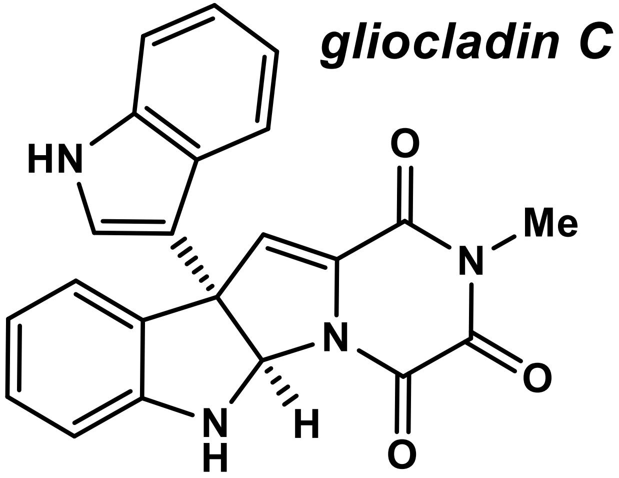
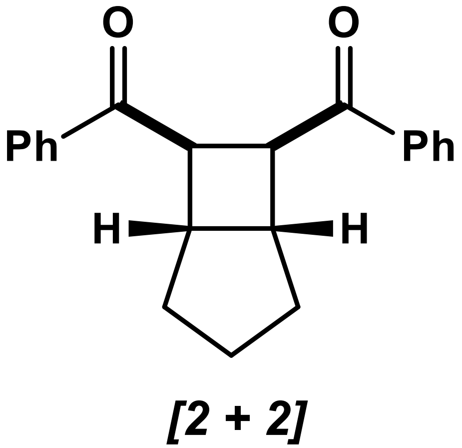
Synthesis Club
October 30th 2018

# Photoredox

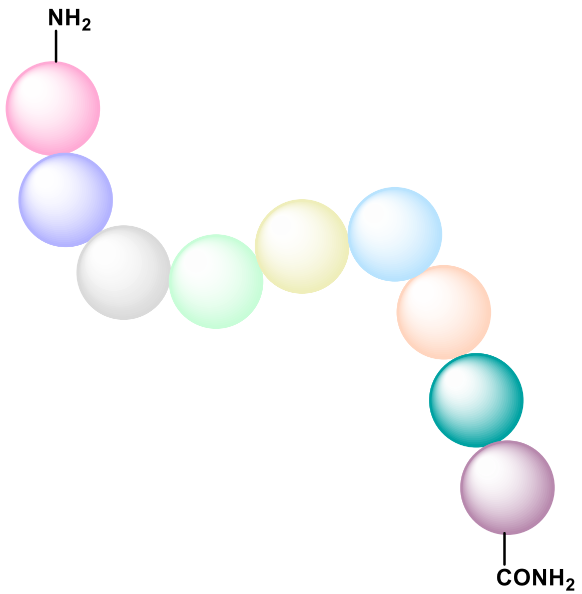
# Dual Catalysis Photoredox




Total Synthesis



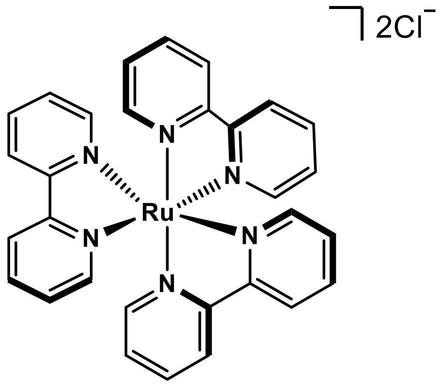

Enantioselective Cycloadditions




Chemical Biology

# General overview *What is photoredox?*

A form of catalysis where the input of energy is provided by visible light irradiation to produce target compounds through a redox-induced process




$Ru(bpy)_3Cl_2$

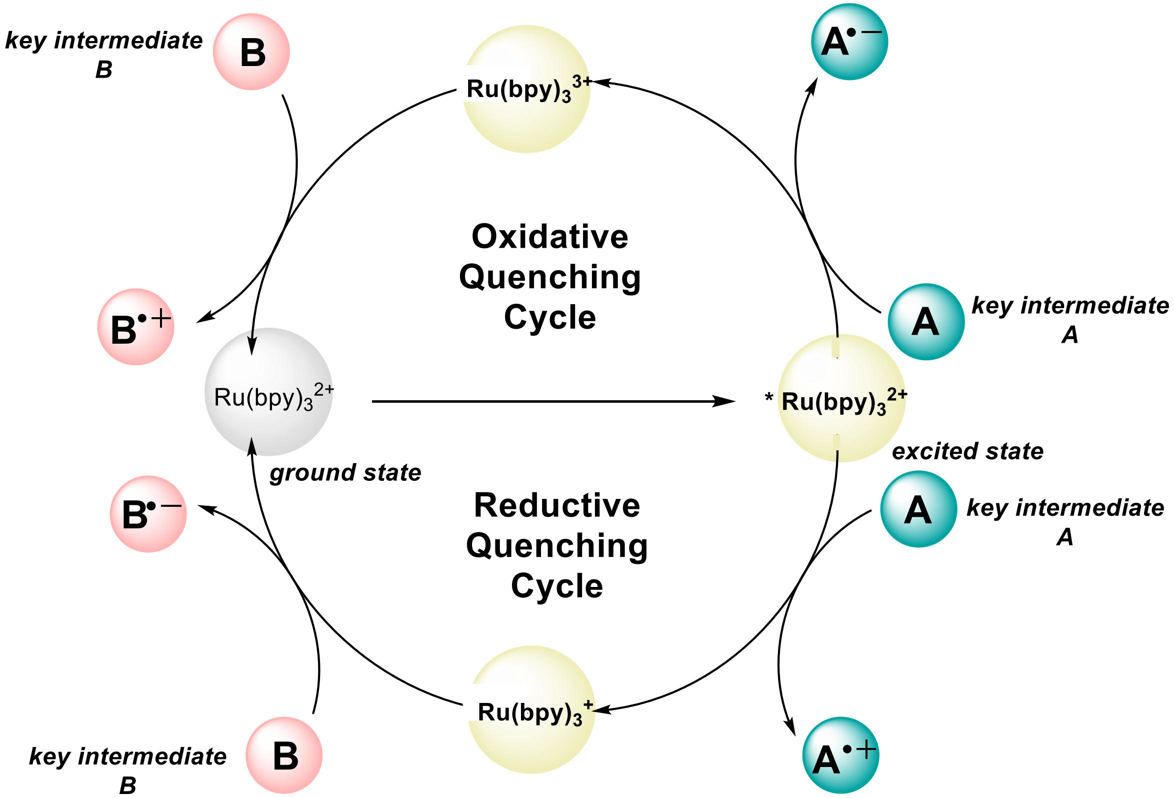
Typical photoredox catalyst

Allows access to excited (triplet) state through visible light irradiation → key intermediates

Two single electron transfer events

1) key intermediate **A** + excited photoredox catalyst (oxidative or reductive quench)

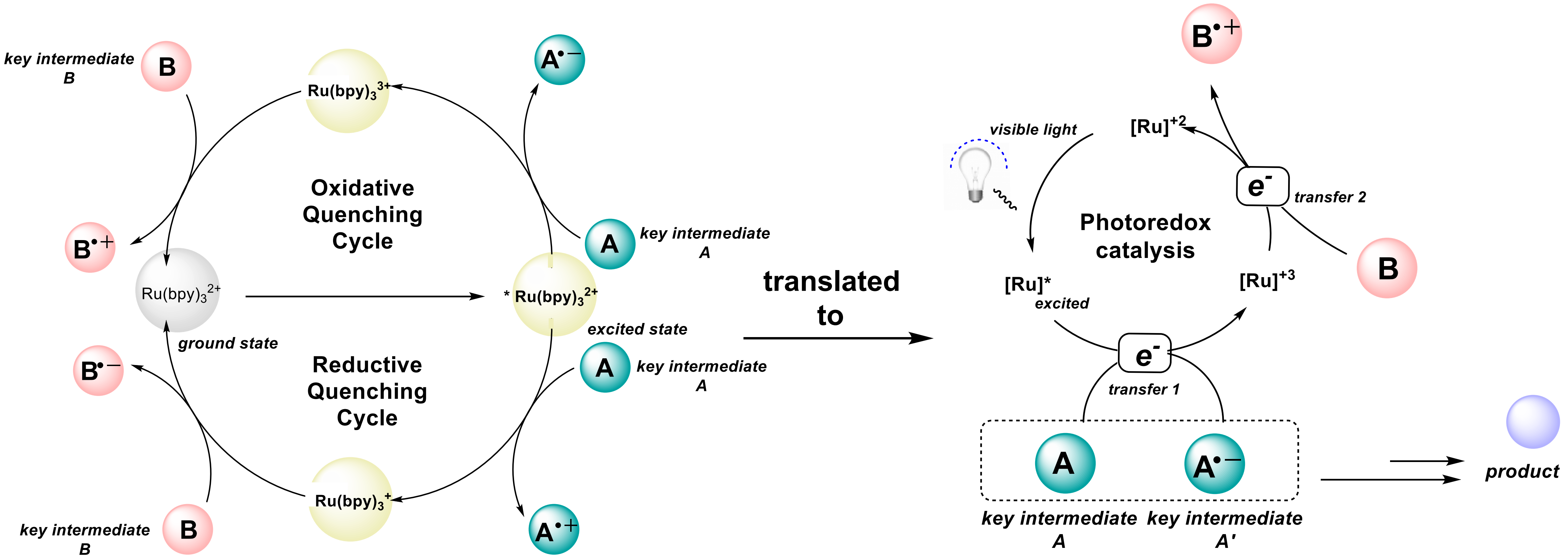
2) key intermediate **B** + oxidized or reduced photoredox catalyst → ground state






Stephenson, C. J. et. al. *Chem. Rev.* **2016**, 116, 9683.Glorius, F. et. al. *Chem. Soc. Rev.* **2018**, 47, 7190.Glorius, F. et. al. *Chem. Eur. J.* **2014**, 20, 3874. MacMillan, D. et. al. *Chem. Rev.* **2013**, 113, 5322.

# “Templated” thinking towards photoredox




“conceptual perspective”

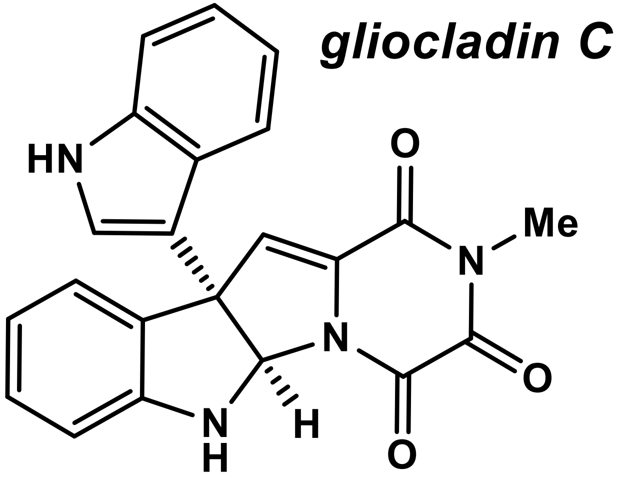
“mechanistic perspective” (for oxidative quenching)



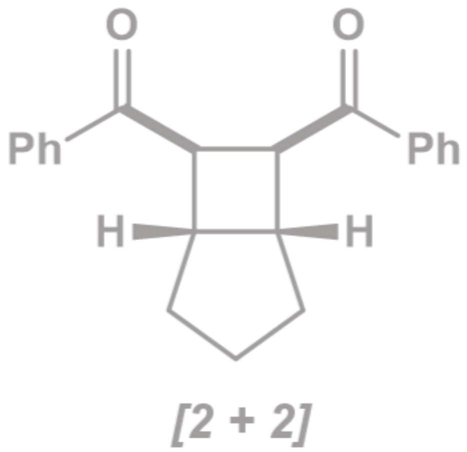
Stephenson, C. J. et. al. *Chem. Rev.* **2016**, 116, 9683. Glorius, F. et. al. *Chem. Soc. Rev.* **2018**, 47, 7190. Glorius, F. et. al. *Chem. Eur. J.* **2014**, 20, 3874. MacMillan, D. et. al. *Chem. Rev.* **2013**, 113, 5322.

# Photoredox

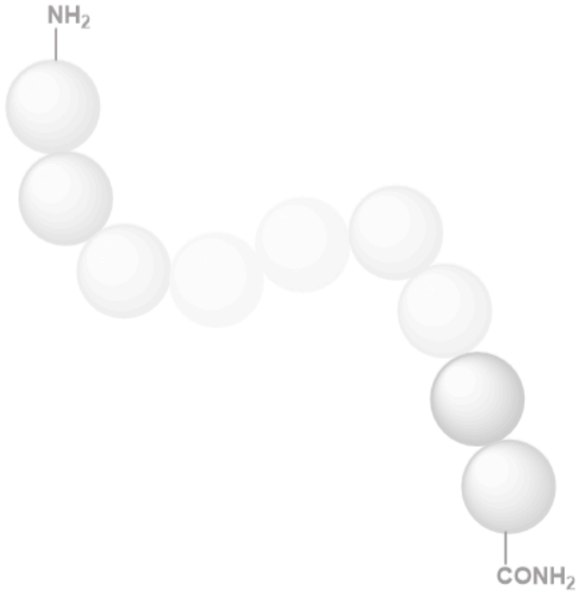
# Dual Catalysis Photoredox




*Total Synthesis*

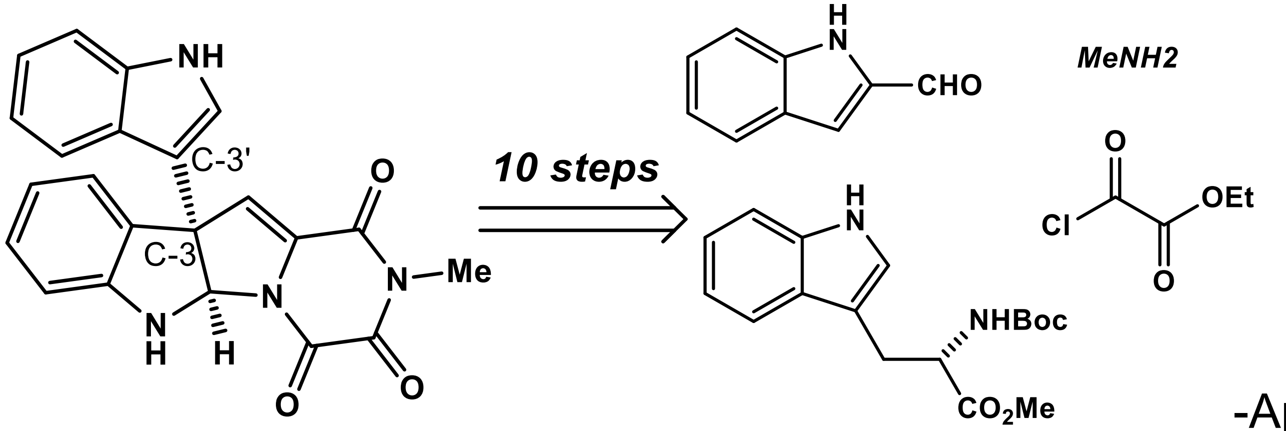



*Enantioselective Cycloadditions*




*Chemical Biology*

# (+)-Gliocladin C Background, Retrosynthesis and Considerations




***gliocladin C***

***retrosynthetic analysis***

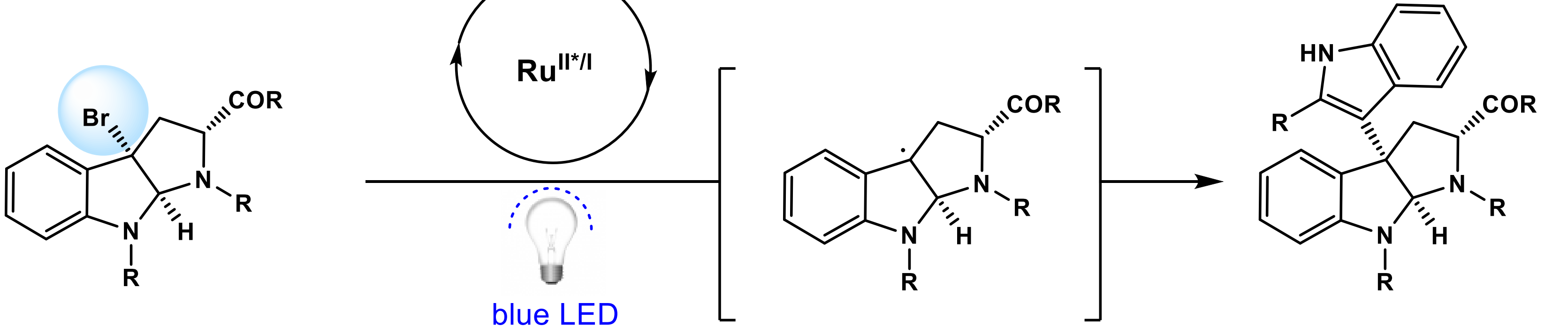
- Derived as a subclass of molecules under the hexahydropyrroloindolines alkaloids

- Broad range of biological activity: cytotoxicity against lymphocytic leukemia cell lines and antibacterial activity

-Approaches to the synthesis of bispyrroloindoline dimers achieved by Overman and Govek (C3-C7’), Baran and coworkers (C3-N1’), and Rainier and Espejo (C3-N1’)

**Key Bond Construction**

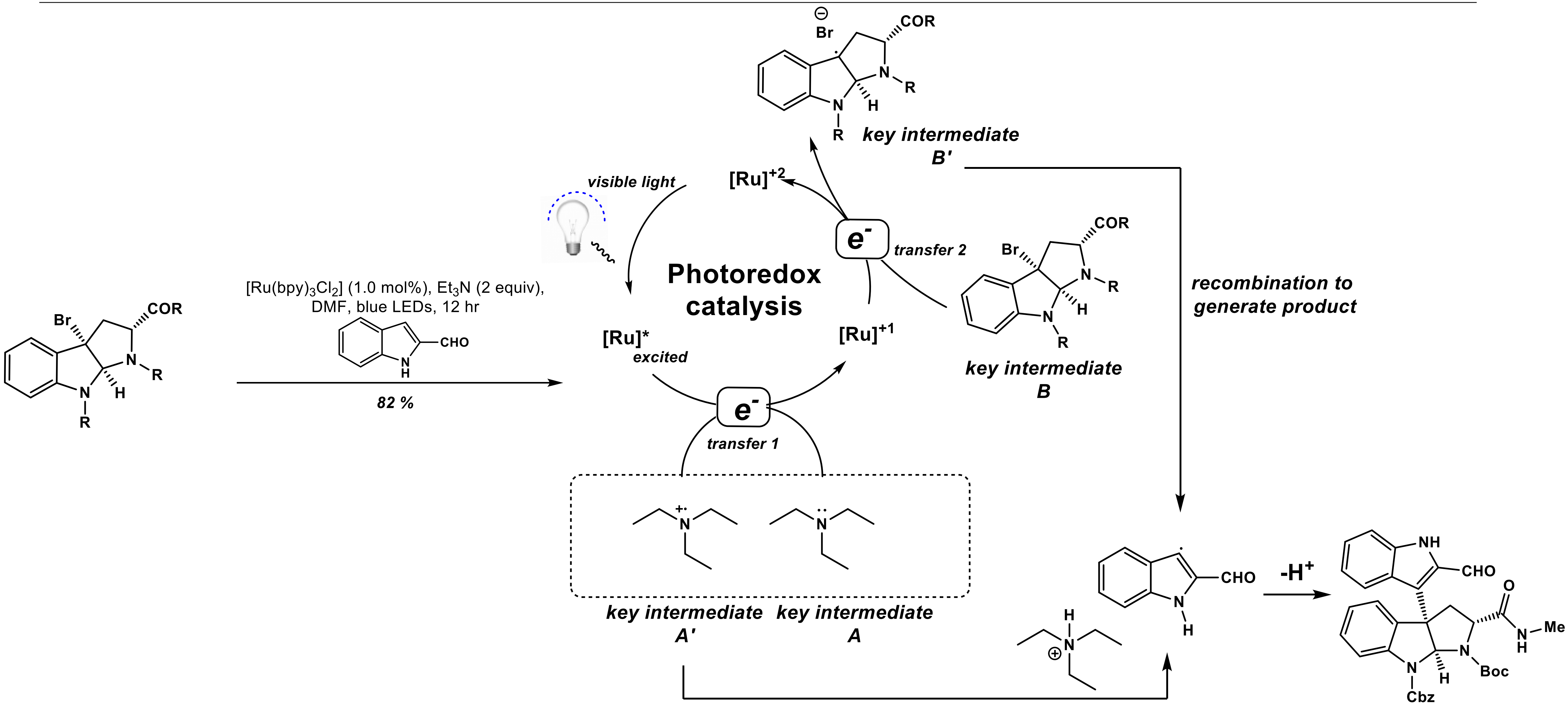
gliocladin C viewed as a *key intermediate* for the preparation of other C3-C3’ bispyrroloindoline alkaloids



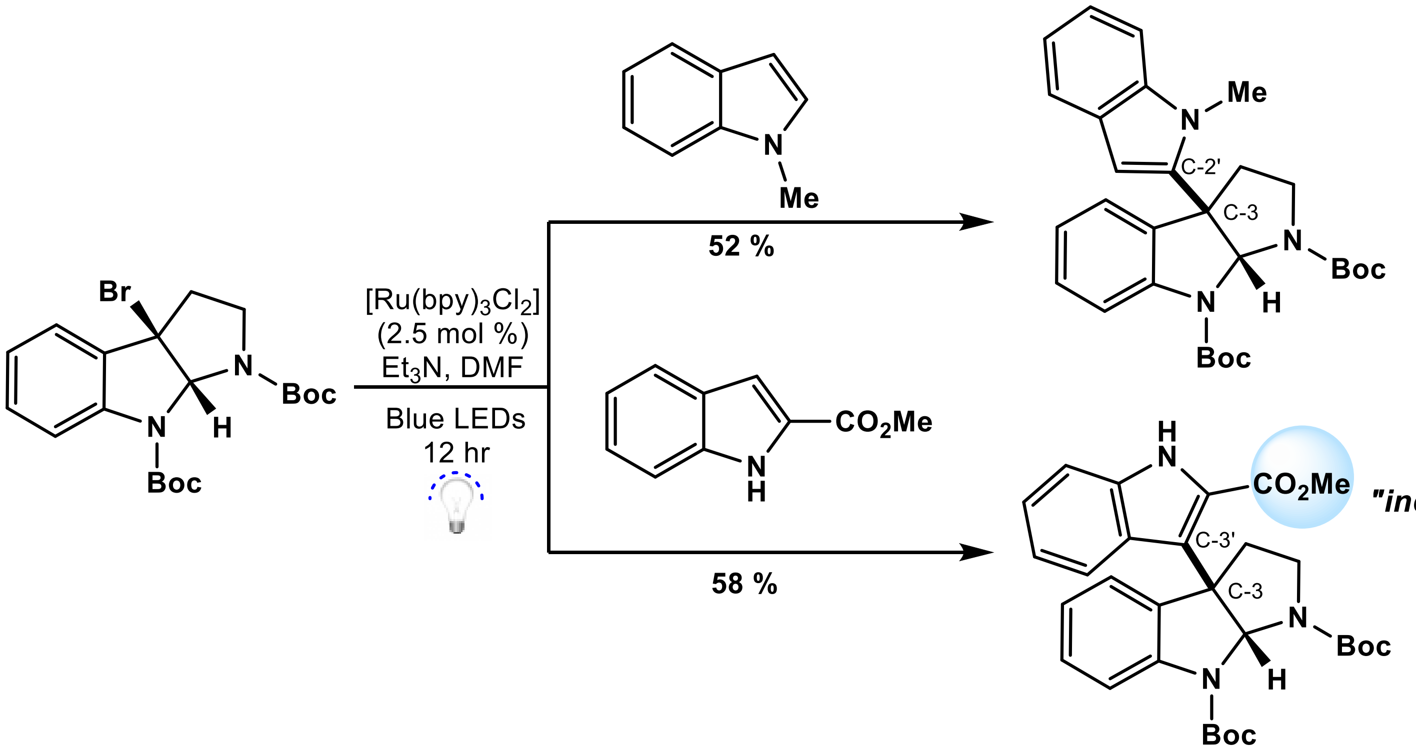


Baran, P. S. et. al. *J. Am. Chem. Soc.* **2008**, *130*, 10886. Govek, S. P.; L. E. Overman; et.al. *J. Am. Chem. Soc.* **2001**, *123*, 9468
Stephenson, C. J. et. al. *Angew. Chem. Int. Ed.* **2011**, *50*, 9655.Rainier, J. D. et. al. *J. Am. Chem. Soc.* **2008**, *130*,12894.Overman, L. E. et. al. *Org. Lett.* **2007**, *9*, 339.

# Proposed photoredox catalytic cycle

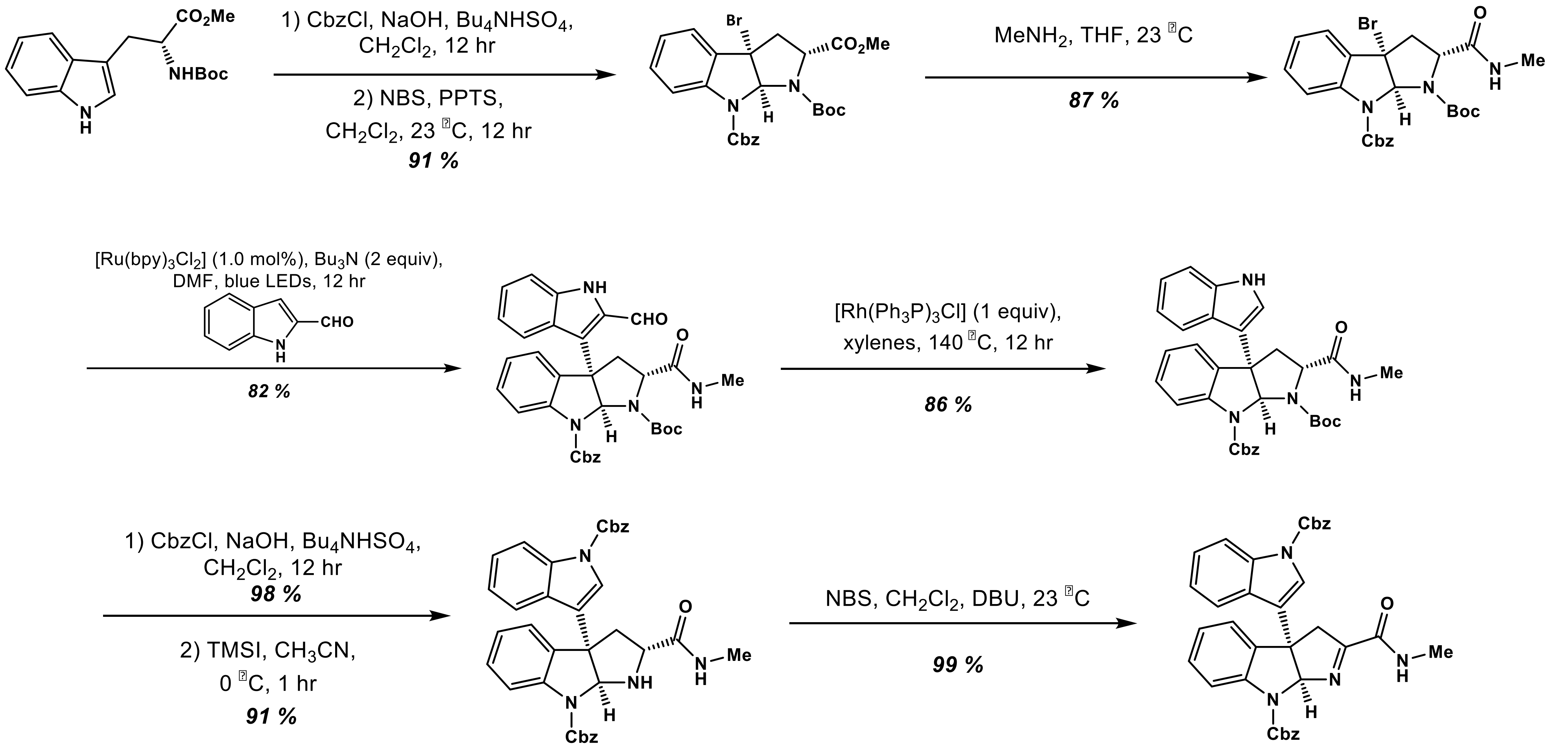


# Enabling selective access to bisindoles *via* photoredox



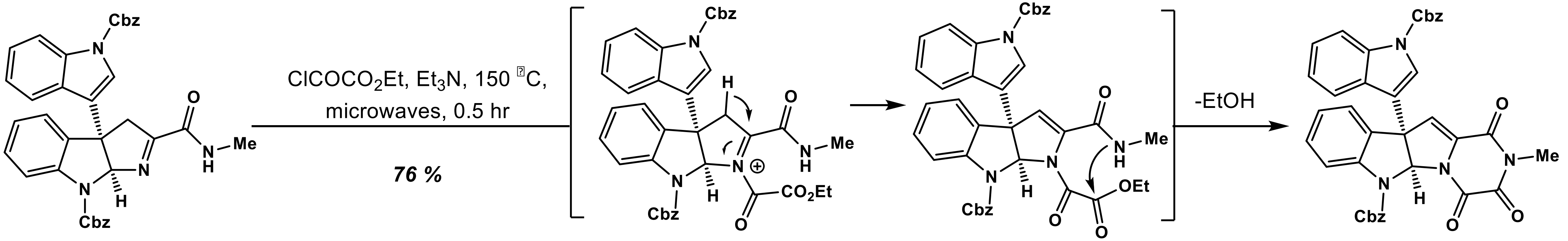

***C-2' blocking***
***"induced" substitution at C-3***

# Forward synthesis



# Forward synthesis

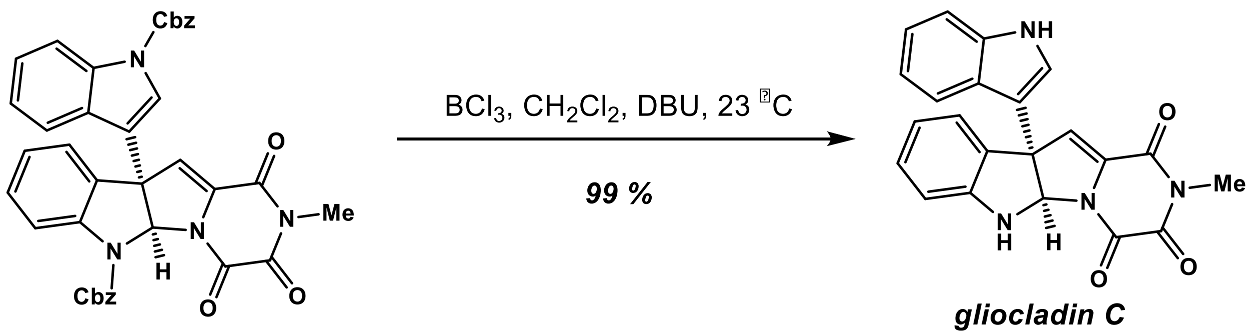
## inspiration from Woodward: acylation/elimination of cyclic oxime ethers






Woodward, R. B. et. al. *J. Org. Chem.* **1979**, *44*, 2487.

# Summary




**hypothetical set up**

Synthesis of gliocladin C synthesized in 10 steps with a 30 % overall yield

Able to provide a rapid and scalable route to synthesize C3-C3’ bisindole alkaloid frameworks

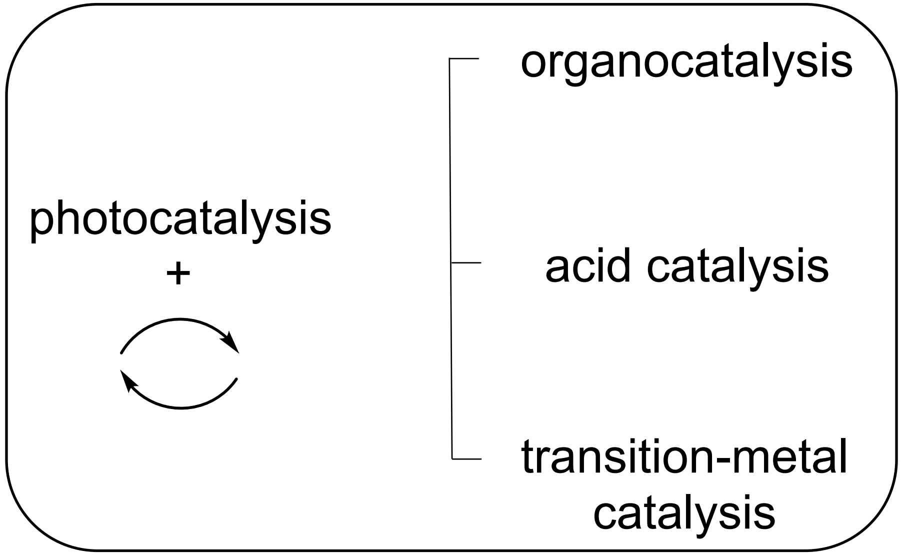
Synthetic designs based on photochemical transformations can be used to access complex natural products



Stephenson, R. J. et. al. *Org. Lett.* **2012**, *14*, 94

# Dual Catalysis Photoredox + Adjunct Catalysis

Single electron transfer “bridges the gap” between photoredox catalysis and adjunct catalysis



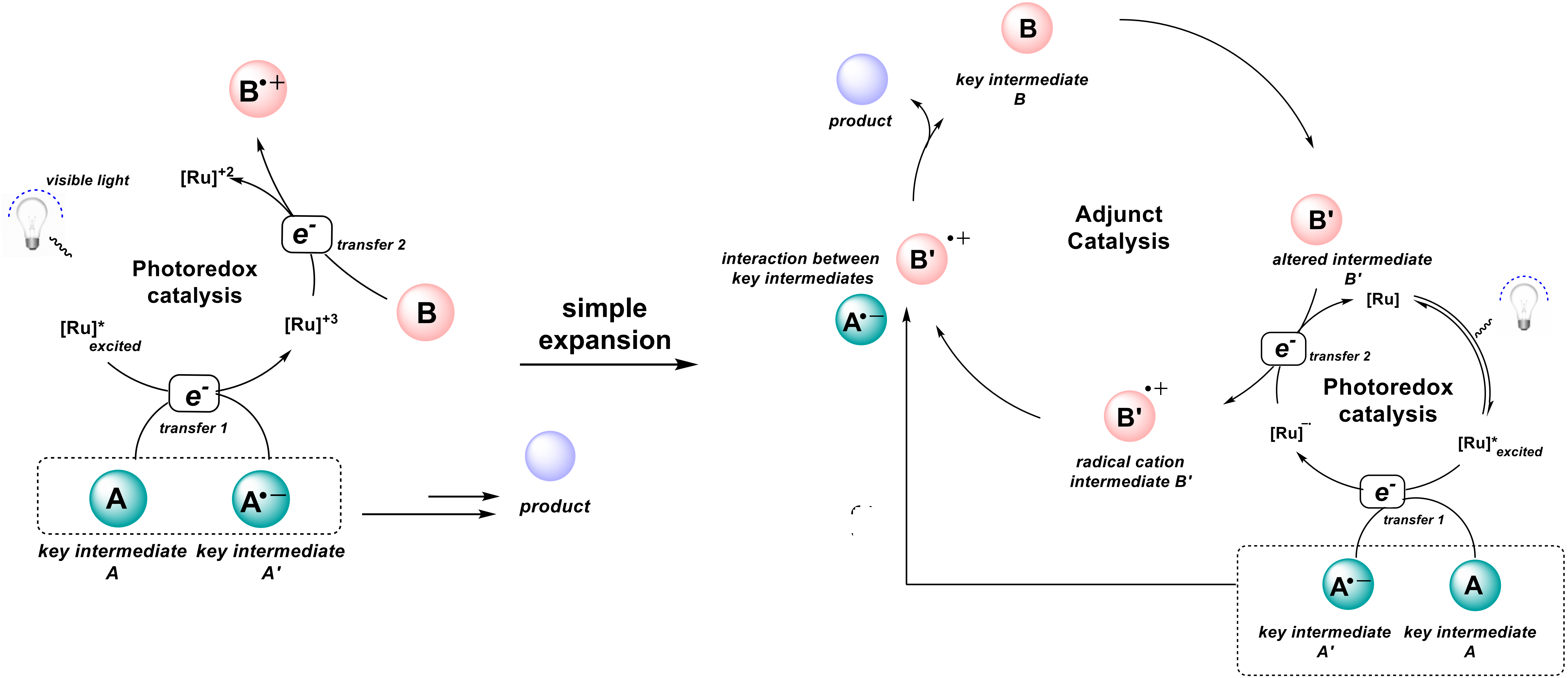

Organic radicals ( key intermediates ) delivered from photoredox activation are capable of engaging in “intercepting” catalytic cycles

Access to a wide range of previously inaccessible redox-neutral transformations that would be energetically unfeasible under non-irradiative conditions



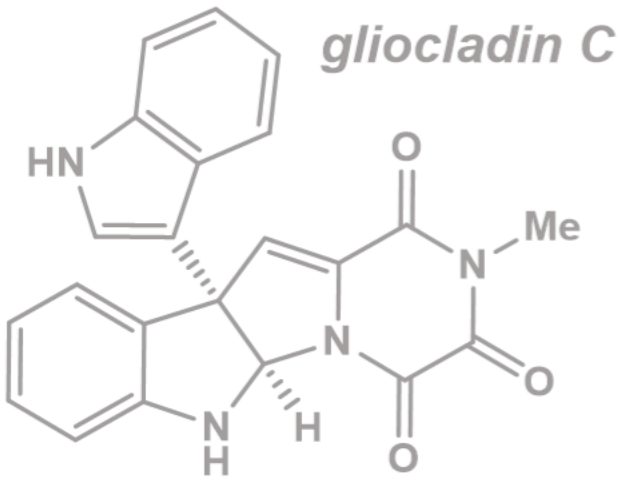
MacMillan, D. et. al. *Nature Rev.* **2017**, *1*, 52. Glorius, F. et. al. *Chem. Eur. J.* **2014**, *20*, 3874.

# “Templated” thinking towards photoredox dual catalysis

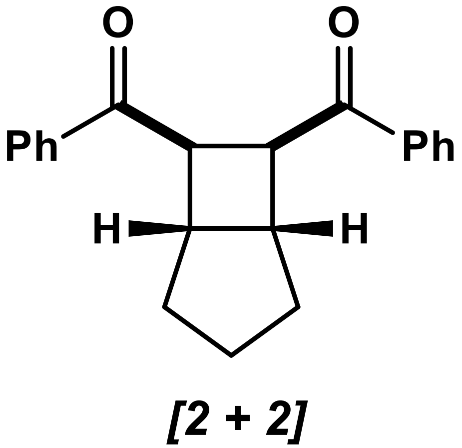


Photoredox

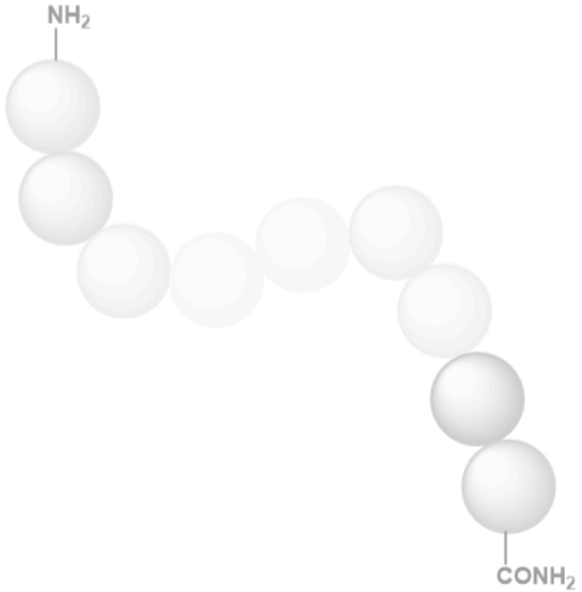
# Dual Catalysis Photoredox




*Total Synthesis*

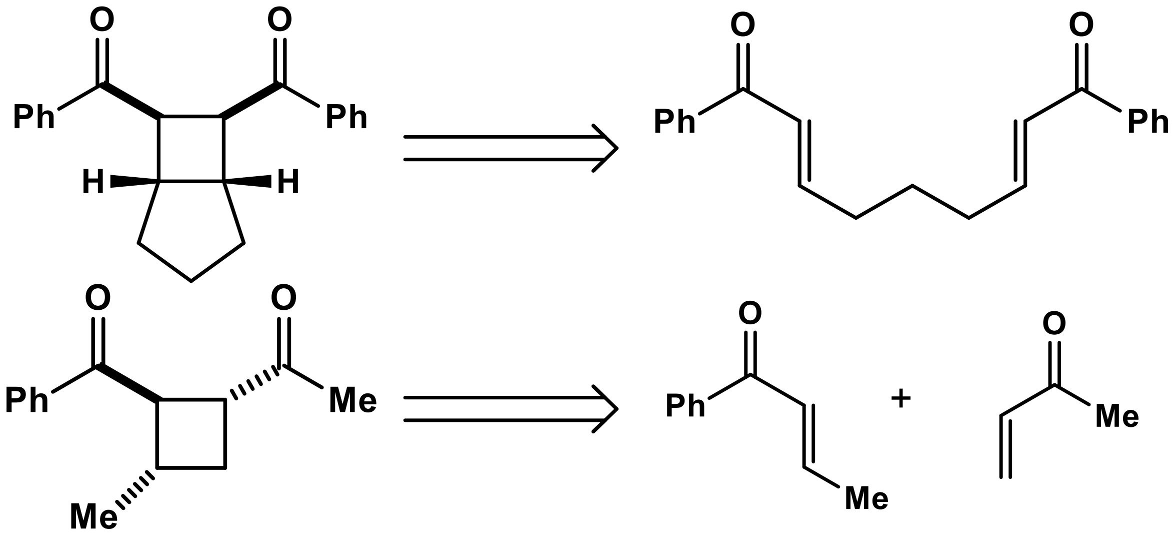



*Enantioselective Cycloadditions*




*Chemical Biology*

# Enantioselective cycloadditions Retrosynthesis, background and consideratio

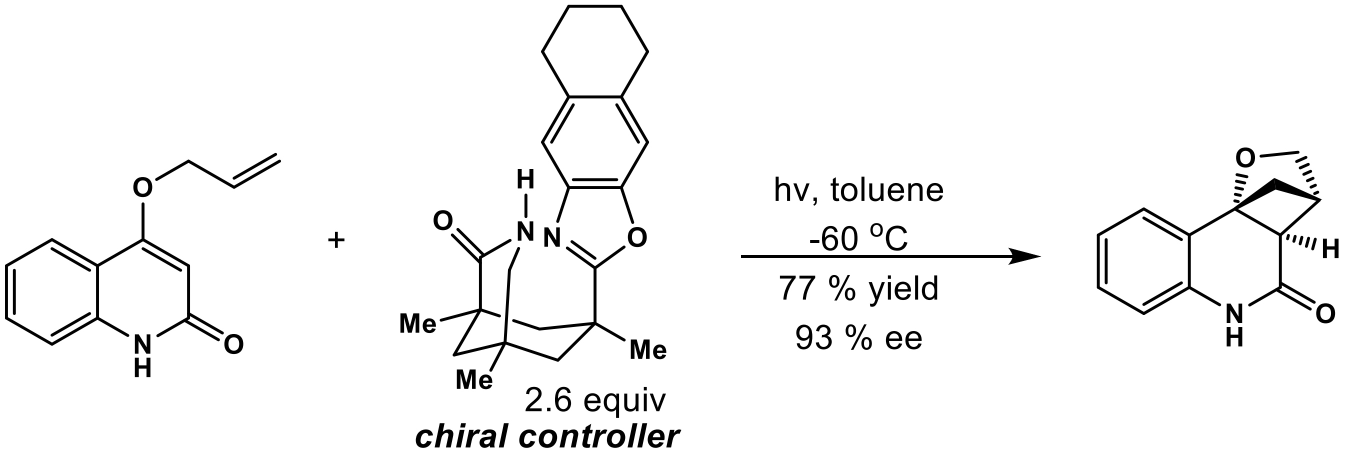


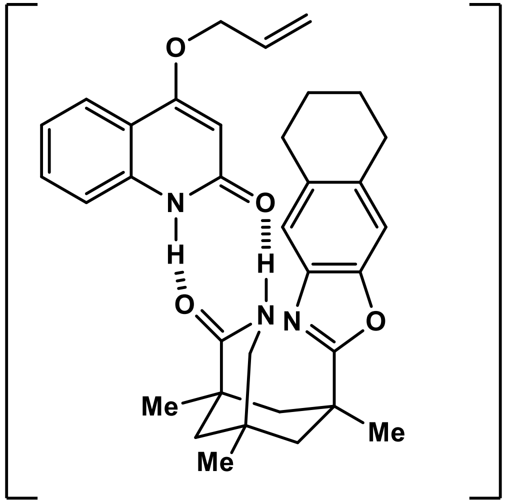

First highly enantioselective photoredox reactions emerged in early 2000's. Progress since then has been modest

Complex structural motifs enabled by photochemistry (cyclobutanes and oxetanes) remain challenging to prepare

The difficulty of enantioselective photoreactions lies within the challenge of managing racemic background photoreactions

Drawing inspiration from previous cases: work by Bach



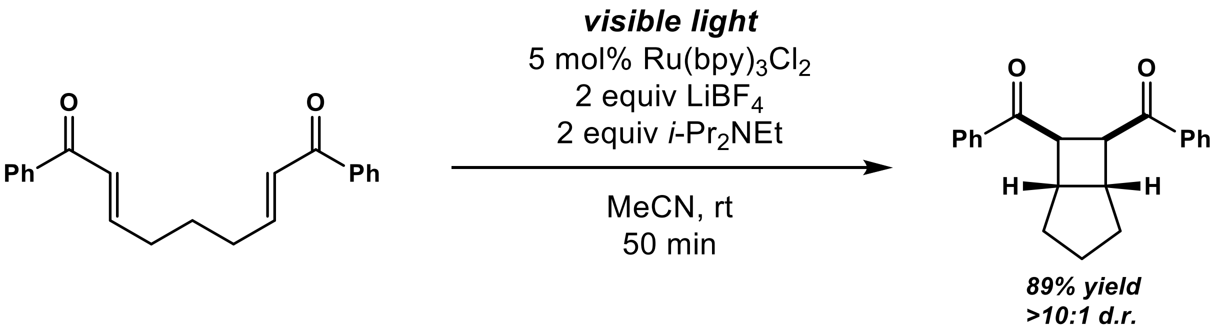

Based from these results: high enantioselectivity → selective activation of a catalyst-bound substrate

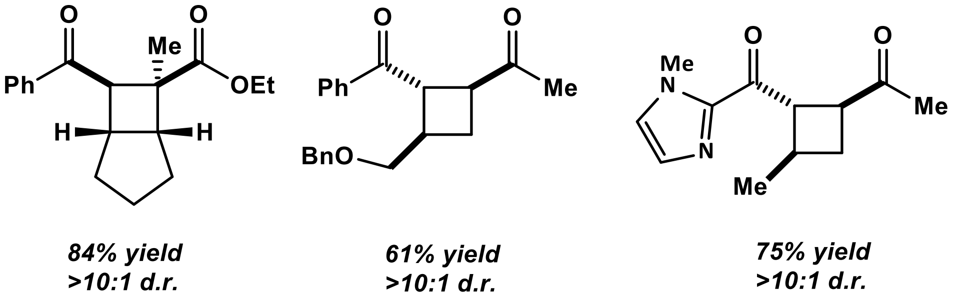


Yoon, T. P. et. al. *Science* **2016**, *354*, 6318. Yoon, T. P. et. al. *Acc. Chem. Res.* **2016**, *49*, 2307.

# [2 + 2] photocycloaddition

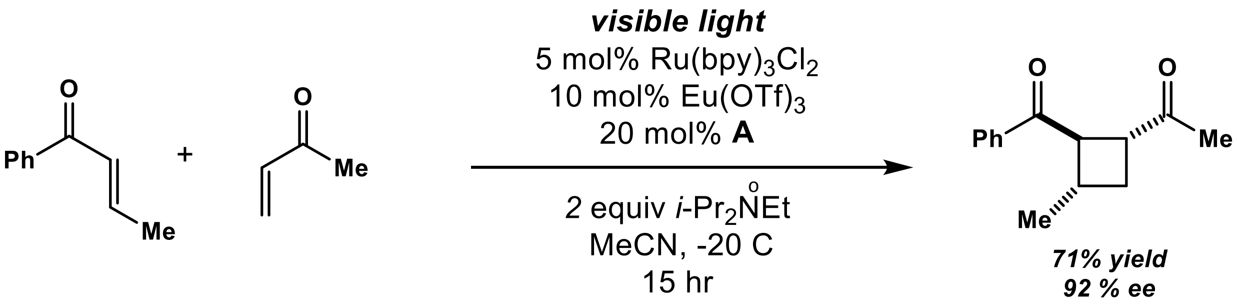
## Initial investigations

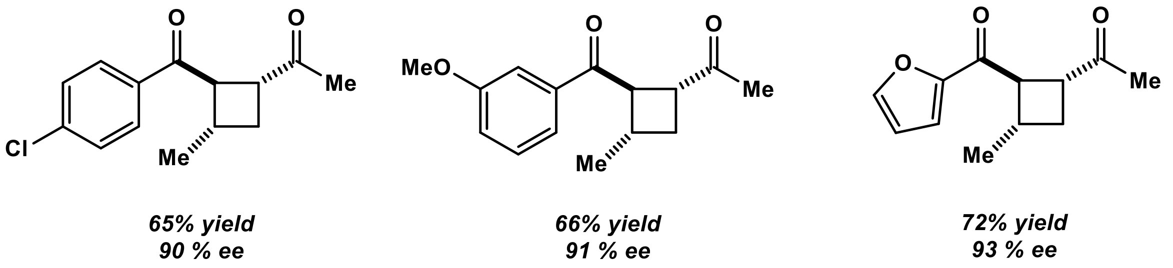


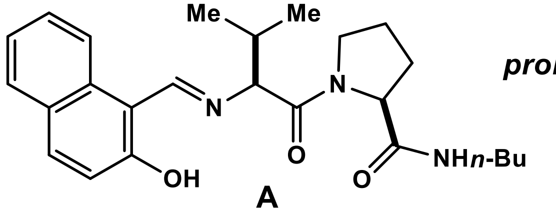




- -In the absence of photocatalyst → no reaction
- -Structure of Lewis acid catalyst is important
- -Concentration of Lewis acid catalyst did not affect enantioselectivity → no racemic background reaction

## Enhancing enantioselectivity



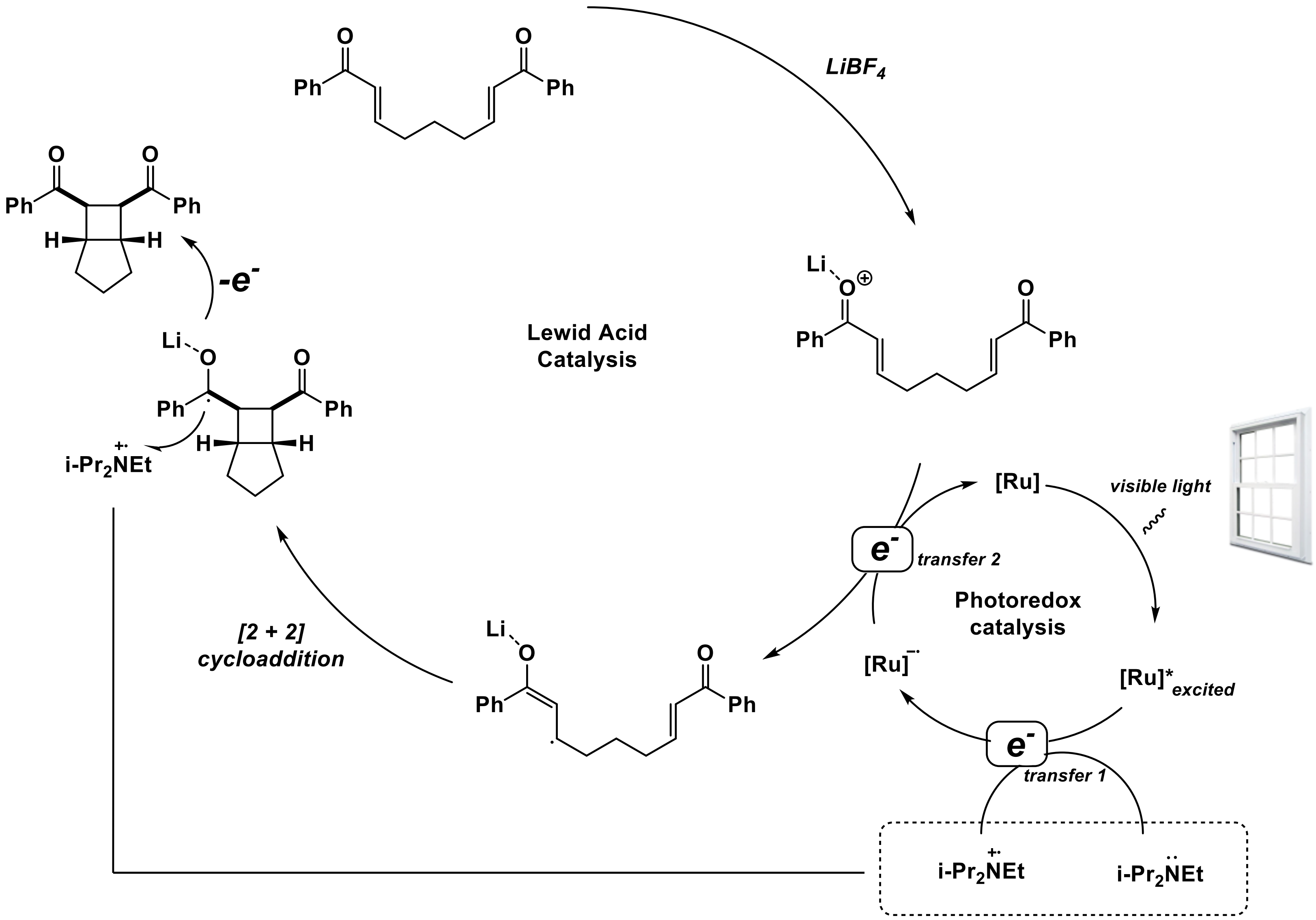



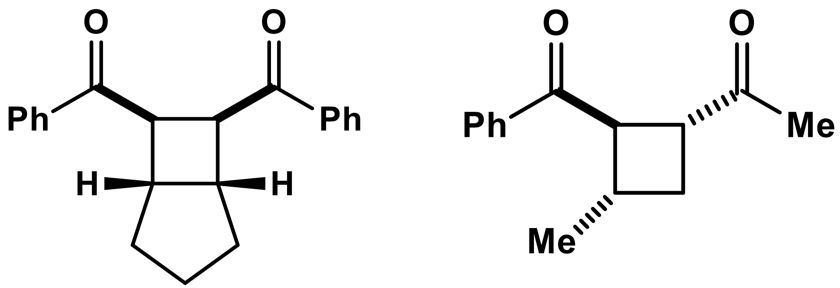

*proline-valine Schiff base ligand*

Yoon, T. P. et. al. Science **2014**, *344*, 392.

# Proposed lewis acid/photoredox catalytic cycle



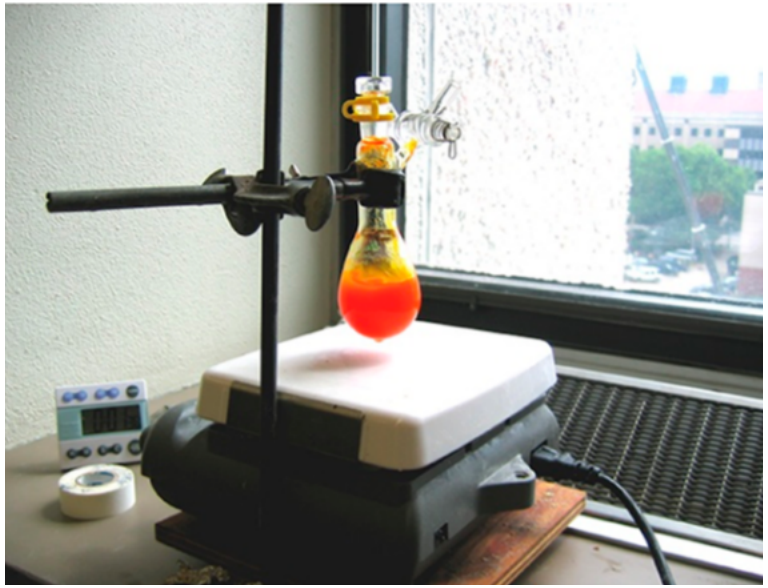
# Summary




Previous attempts to control the stereochemical outcome in photocatalytic reactions relied on single chiral photocatalyst

Relative and absolute stereochemistry of the [2 + 2] cycloadditions can be controlled through chiral Lewis acid catalyst and photocatalyst

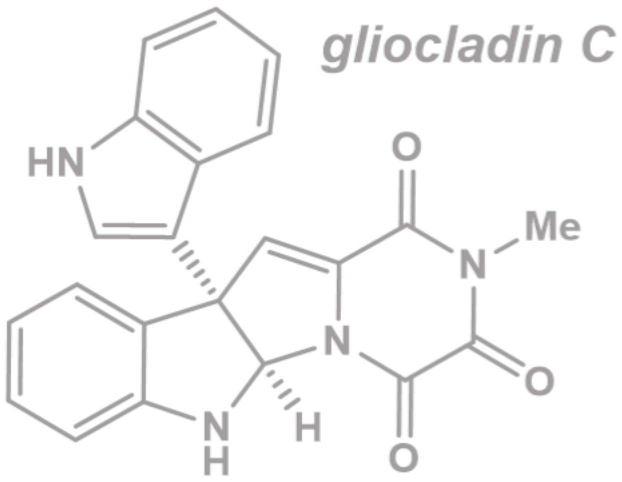
Catalytic photochemical control is feasible



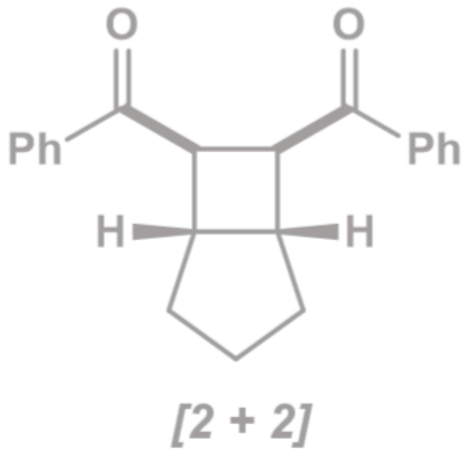
**actual set up**

# Photoredox

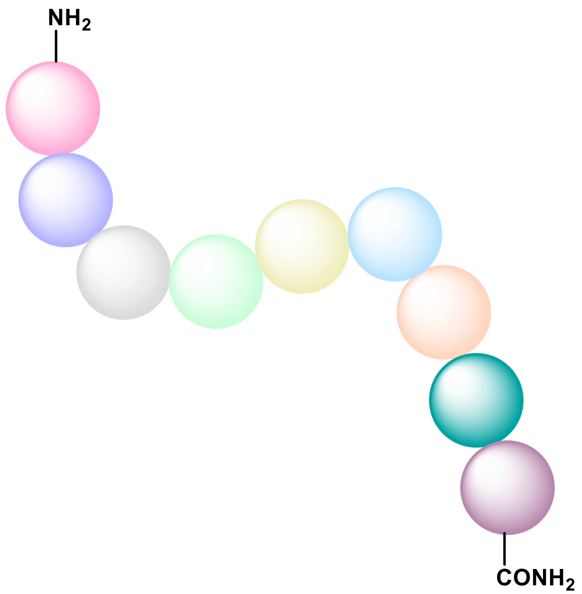
# Dual Catalysis Photoredox




Total Synthesis




Enantioselective Cycloadditions



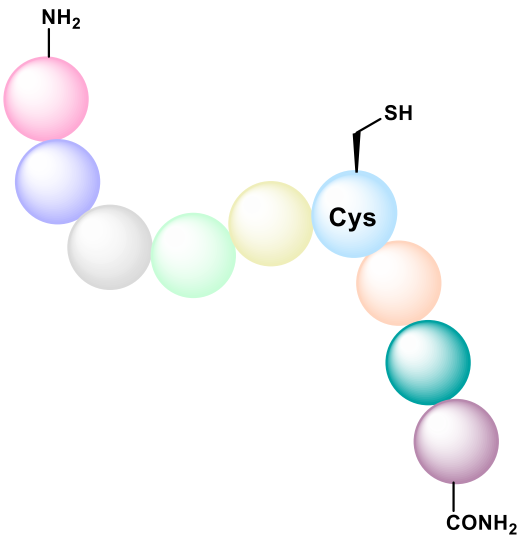

Chemical Biology

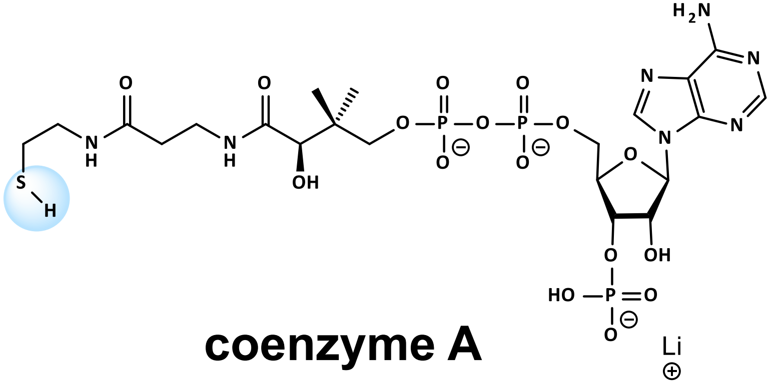
# Chemical Protein Synthesis Background and Considerations

Site-specific functionalization at native cysteine residues of unprotected peptides and biomolecules can be challenging

Although protecting groups allow for orthogonal functionalization, a method introducing thioarylation amongst unprotected peptides and biomolecules may simplify synthesis

Current strategies for C-S coupling (Ullmann) or nonmetal-catalyzed reactions (thiol-click arylations) for thioarylation are either limited in scope or provide incompatible reaction conditions



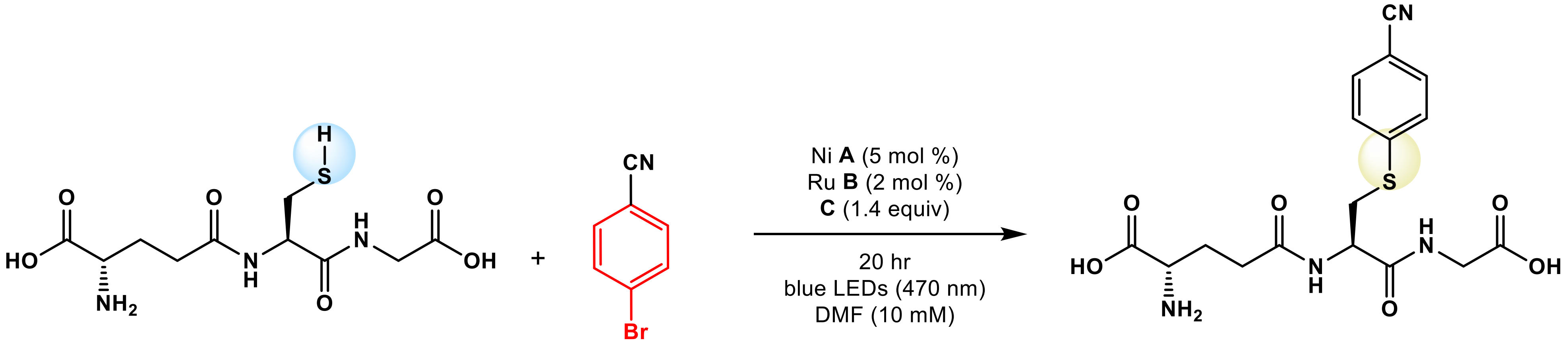




**coenzyme A**

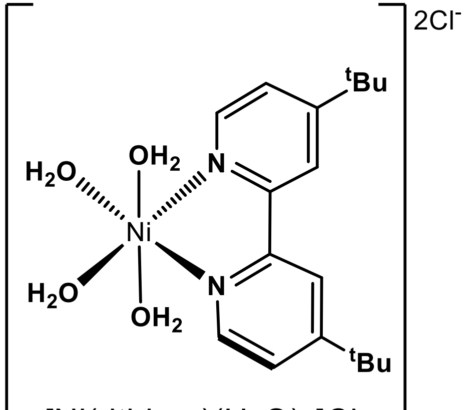


Molander, G. et. al. *Chem. Sci.* **2018**, *9*, 336.

# Proof of Concept

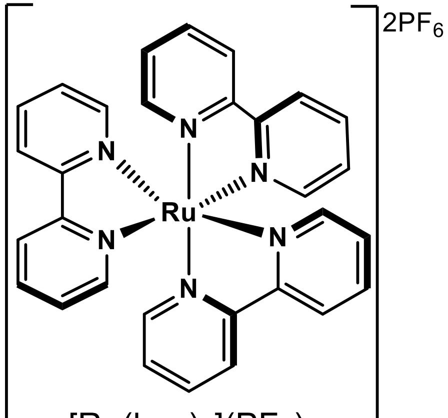



**glutathione**




$[Ni(dtbbpy)(H_2O)_4]Cl_2$

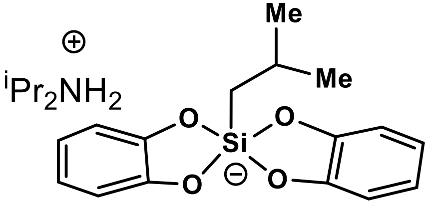
**A**




$[Ru(bpy)_3](PF_6)_2$

**B**

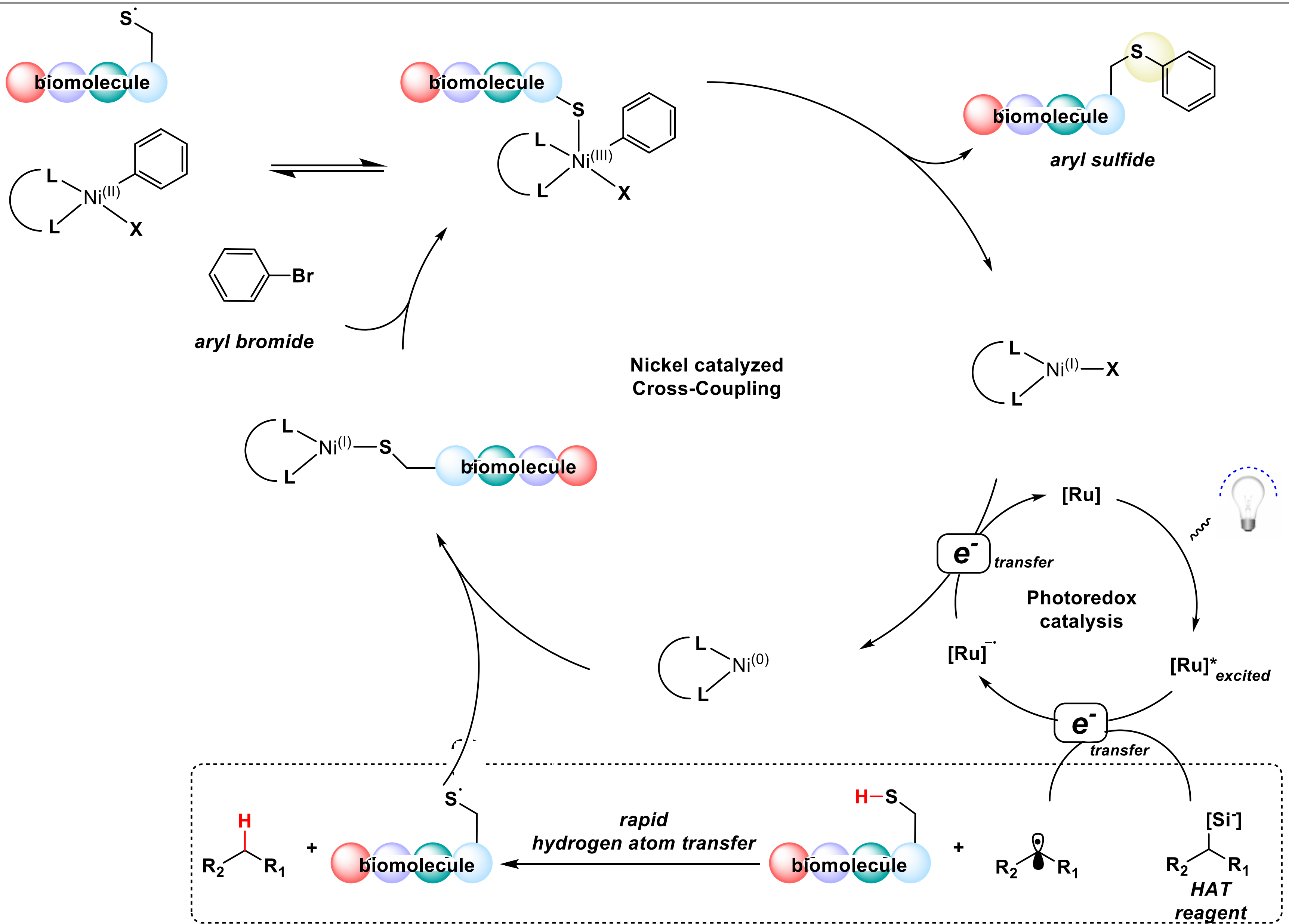
***HAT reagent***



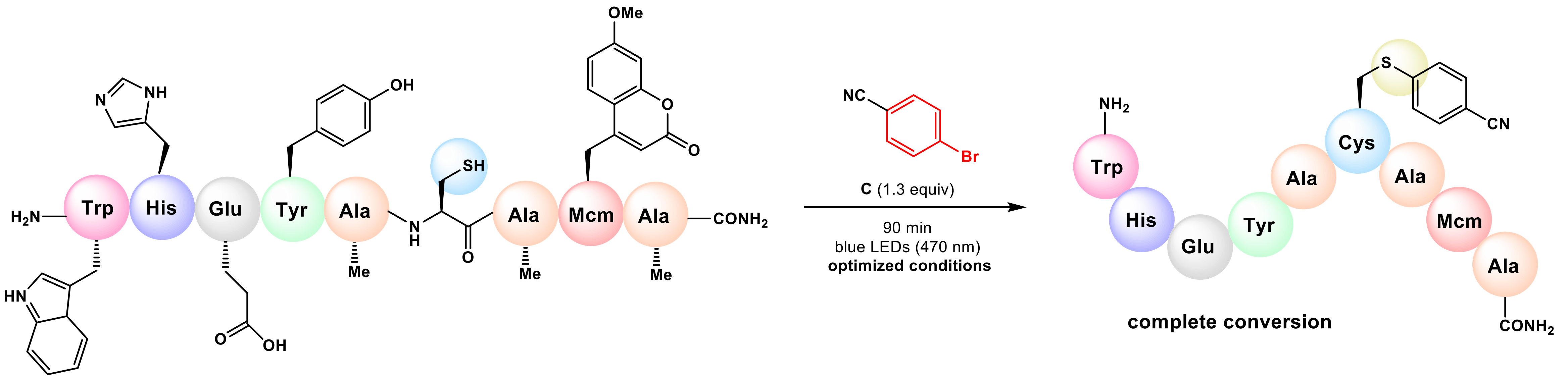

ammonium
*bis*(catechol) silicate

**C**

# Proposed Ni/photoredox catalytic cycle

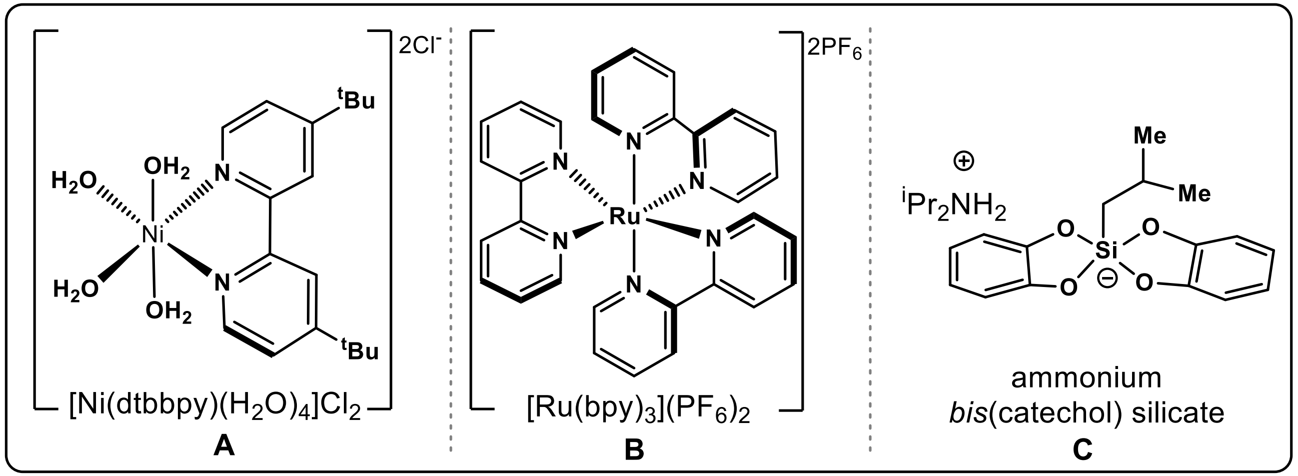


## globally unprotected peptide → successful C-S coupling against neighboring Xaa residues

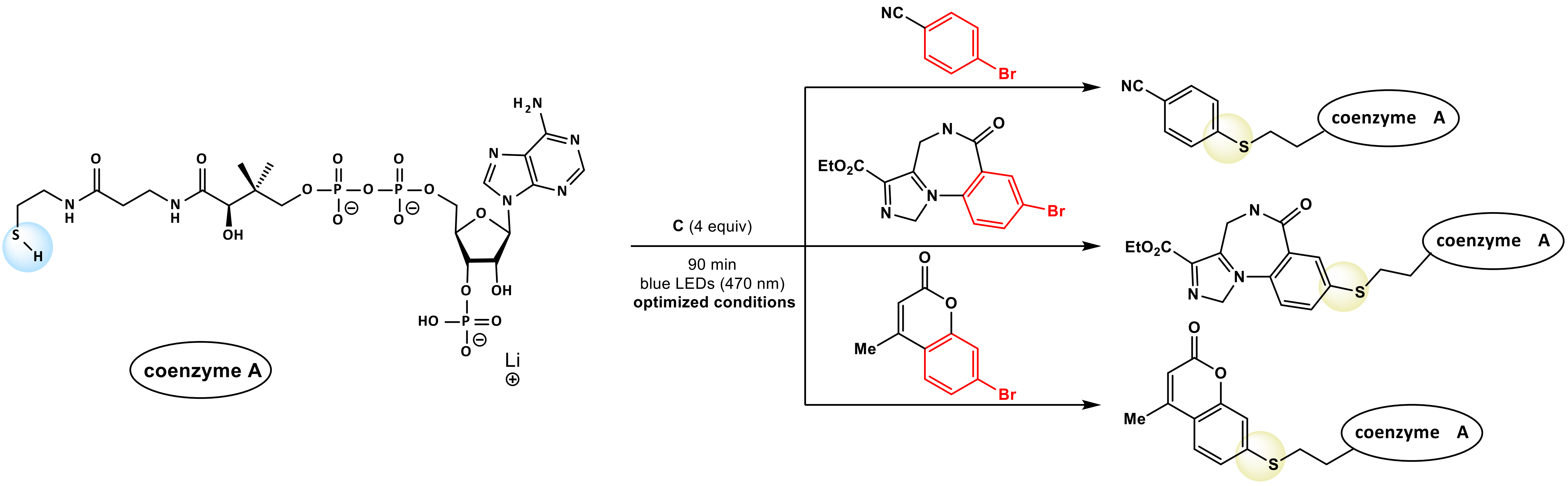



**optimized conditions**

ArBr (20 equiv)
Ni **A** (5 mol %)
Ru **B** (2 mol %)
DMF (10 mM)



**coenzyme A** → **ArBr derivatives** → **functionalized coenzyme A variants**

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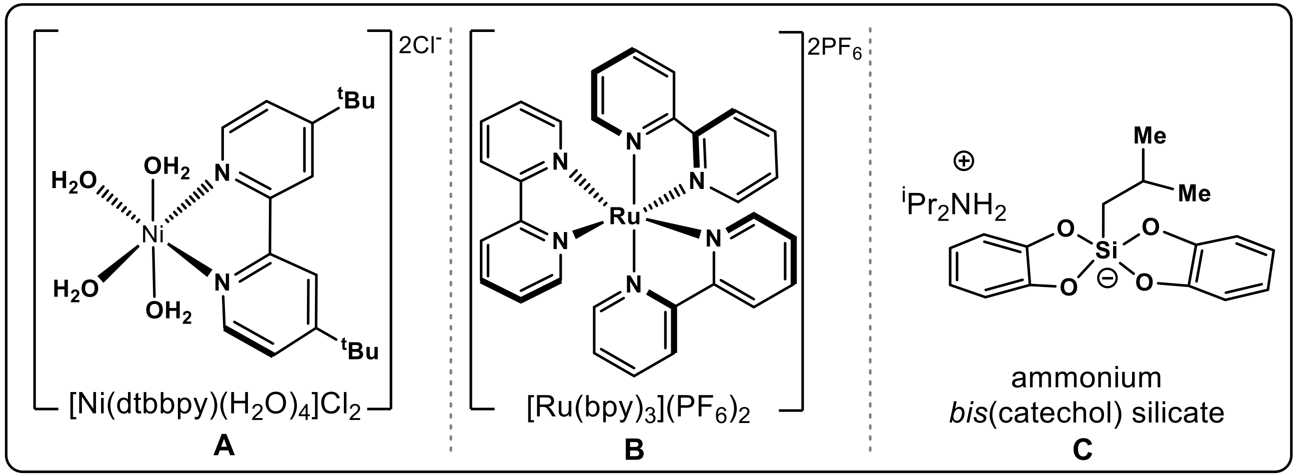
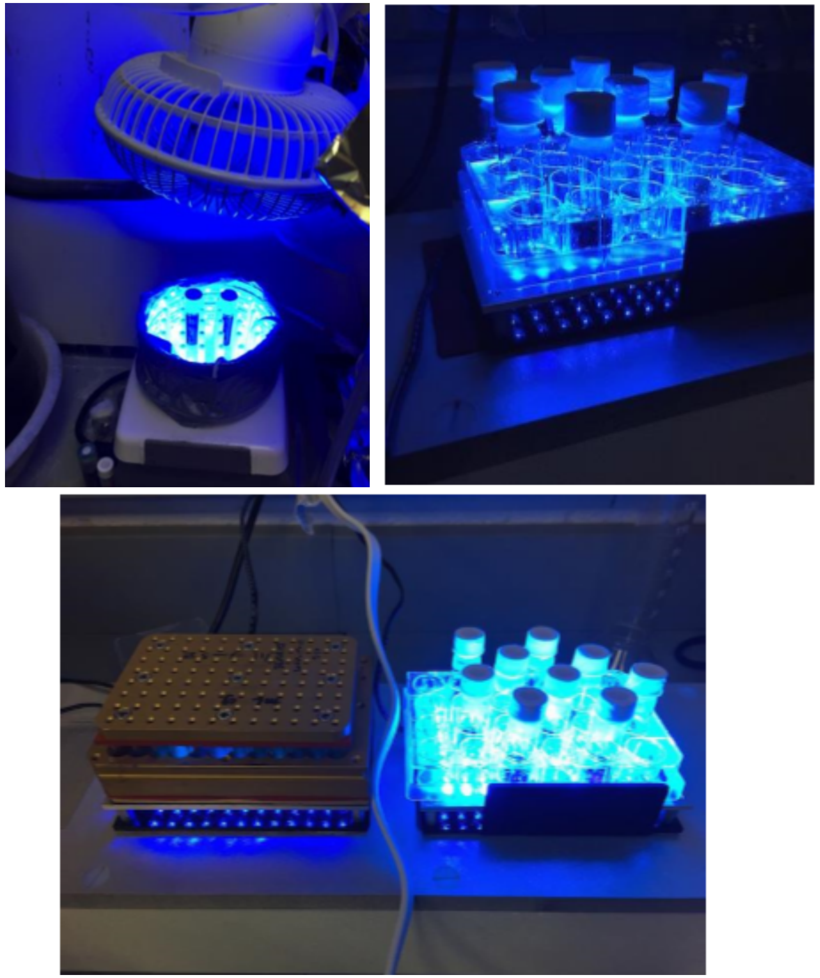


# Summary

Able to develop an efficient Ni/photoredox method to thioarylate unprotected peptides and biomolecules

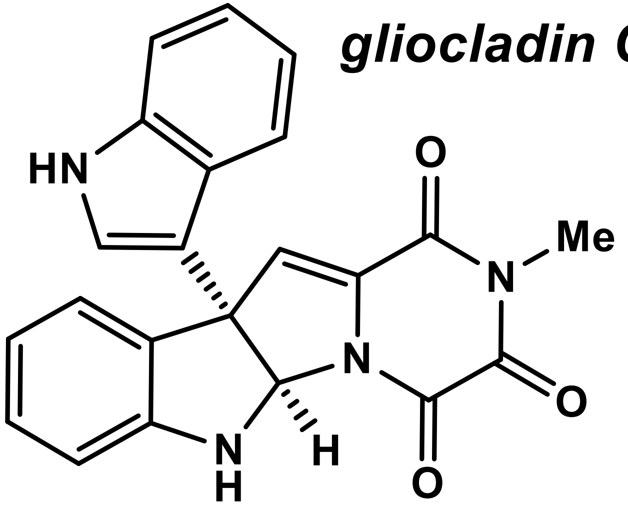
No requirement of transition-metal reagents needed, reaction set-up is straightforward and is scalable

Serves as another useful alternative to other approaches used for thioarylation (Pd- catalyzed cross-coupling reactions)

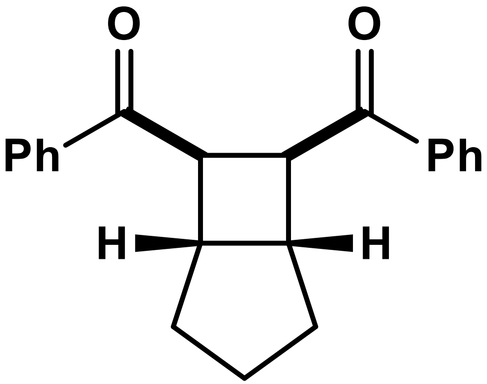


**actual set up**

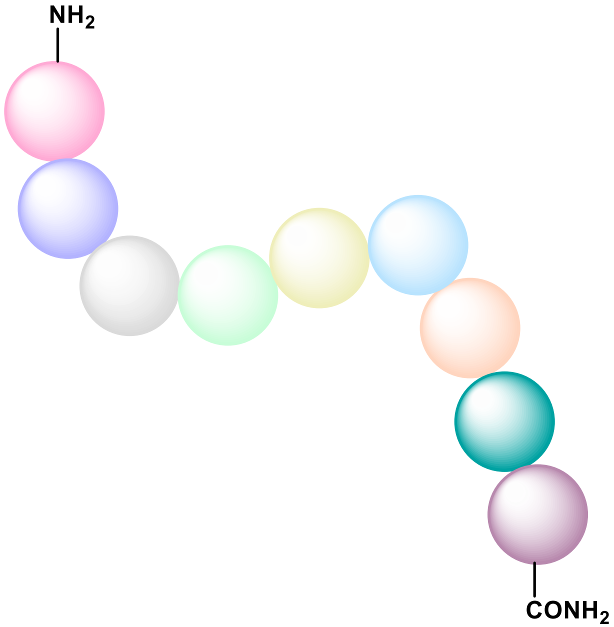
# Conclusion




*gliocladin C*




*[2 + 2]*




Photoredox catalysis and its application in dual catalysis is a powerful strategy that is widely applicable to many fields