

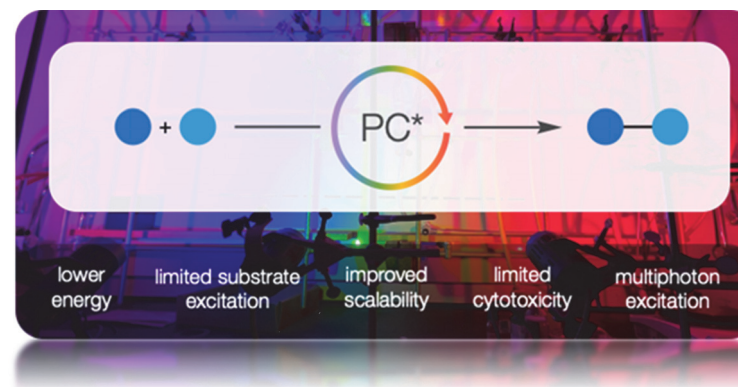
Red-Shifting Blue Light Photoredox Catalysis for Organic Synthesis: A Graphical Review

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Abstract Photoredox catalysis has revolutionized synthetic chemistry in recent decades. However, the field has traditionally used high-energy blue/ultraviolet light to activate chromophores. High-energy irradiation is associated with several drawbacks (e.g., activation of sensitive functional groups, undesired metal-ligand homolysis, background activation of molecules, and poor penetration), which has led researchers to develop alternative systems with lower energy deep red (DR) or near-infrared (NIR) light. This graphical review provides a concise overview of photophysical principles relevant to photoredox catalysis. Several applications that benefit from low-energy irradiation, such as large-scale batch reactions, photodynamic therapy, biological labeling, and multi-photon excitation are reviewed.

Key words photoredox catalysis, deep red and near-infrared light, cross-coupling, reaction engineering, photodynamic therapy, photoaffinity labeling, proximity labeling, multiphoton excitation

Photoredox catalysis has emerged as a transformative tool in synthetic chemistry, carving out complementary pathways to established reactions as well as novel modes of substrate and catalyst activation for new chemistry. Indeed, photoredox catalysis has reinvigorated radical chemistry with its ability to access open-shell species under catalytic conditions. The merger of transition-metal-catalyzed cross-coupling with photoredox catalysis ('metallaphotoredox catalysis') has emerged as a powerful alternative for other cross-coupling-based technologies, with Ni catalysts featuring prominently. Metallaphotoredox catalysis has been especially transformative in how chemists approach C(sp²)-C(sp³) bond formation, where feedstock aliphatic

coupling partners are used in place of organometallic nucleophiles. Furthermore, the ability to deliver energy in the form of light with pinpoint control defined by lasers has led to the patterning of materials using photoredox catalysts. Lastly, an emerging application uses photoredox catalysis to impact and probe biological systems.

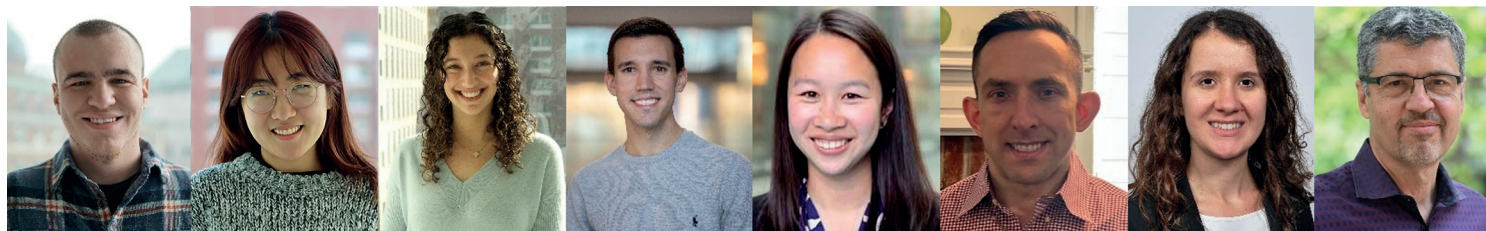
The most commonly employed photoredox catalysts (PCs) absorb a photon of visible light, largely in the region of 380–450 nm (translating to approximately 63–70 kcal/mol), to access the singlet excited state. However, the high-energy light needed for photoredox catalysis can be problematic as several common functional groups can be directly photoexcited at these wavelengths. Indeed, control experiments sometimes indicate that the photoredox catalyst itself plays a minor role and that direct substrate excitation, or more commonly the intermediacy of electron donor-acceptor complexes, are responsible for the observed reactivity. Furthermore, catalytically generated intermediates may be directly photoexcited leading to productive chemistry or destructive side reactions.

With Ir- and Ru-derived photocatalysts, the singlet excited state initially accessed after excitation is extremely short-lived, decaying to the triplet within 10 ps via intersystem crossing (ISC). Triplet energies vary by catalyst structure: the Ir(ppy)₃ singlet is 70 kcal/mol while the triplet is 60 kcal/mol. For Ru(bpy)₃, those figures are 63 and 46 kcal/mol for the singlet and triplet excited states, respectively. From the triplet excited state, single-electron transfer (SET) and energy transfer (ET) steps can take place, which have largely defined the broad reactivity accessible within photoredox catalysis. Aside from the inherent waste associated with using 63 kcal/mol light (blue) to access a 46 kcal/mol excited state (red), the triplet energies matter for two interrelated fundamental reasons: they correspond to the energy potential that can be conveyed to the target molecule (ET steps), and they correlate with the oxidizing and reducing potential of the photocatalyst (SET steps), with numbers estimated from the Rehm-Weller equation. Thus, there has been emerging interest in developing technologies by which photoredox catalysis can use low energy deep red (DR) or near-infrared (NIR) light (specifically in the visible range of 660–730 nm) to access the same, or novel, excited state chemistry accessible with blue and purple light.

Employment of deep red or near-infrared light is extremely attractive. The relatively low energy associated with these wavelengths (35–40 kcal/mol) is unlikely to photoexcite any common functional groups. Red light also penetrates materials and tissues in ways that higher energy light does not. Indeed, the 600–800 nm window is known as the ‘phototherapeutic window.’ Emerging chemical biology applications of photoredox catalysis are more likely to benefit from lower wavelength excitation, avoiding cytotoxicity associated with high-energy light. For example, thymidine cross-links occur when cells are exposed to 400 nm light. Furthermore, within the context of photoaffinity labeling, the use of lower energy light mitigates background activation of organic molecules, thereby truly enabling spatiotemporal control in labeling only at the localized site of a red-light-absorbing photocatalyst. Nevertheless, the successful translation of photoredox catalysis into regions of lower energy light is still nascent. The direct excitation of a photocatalyst from its singlet ground state (S_0) to

its triplet excited state (T_1), a step mediated by spin-orbit coupling (SOC), would eliminate the wasteful energy loss associated with ISC ($S_1 \rightarrow T_1$), enabling productive photocatalysis even with lower energy light. As such, our lab has identified a class of Os-based photocatalysts, as heavy atoms such as Os, Pd, and Pt are commonly incorporated to induce strong SOC and facilitate the spin-forbidden $S_0 \rightarrow T_1$ excitation, that unlock DR and NIR photoredox catalysis. The development of new transition-metal-based photoredox catalysts, as well as red-light-absorbing organic dyes (e.g., methylene blue and fluorescein), will prove pivotal as the field shifts to red-light photoredox catalysis for applications such as batch-scale reactions and photoaffinity labeling. This review highlights the various approaches and fundamental photophysical concepts at play in red-shifting blue light photoredox catalysis.

Biographical Sketches



from left to right

Logan R. Beck studied chemistry and mathematics at the University of Colorado Boulder (CU Boulder, B.A. 2019). While there, he researched photoinduced organocatalyzed atom transfer radical polymerization in the lab of Prof. Garret M. Miyake. He then transferred to the groups of Prof. Niels H. Damrauer and Prof. Tarek Sammakia, where he worked on the synthesis of organic chromophore dimers for singlet fission. After completing his undergraduate studies, he moved to Columbia University for his Ph.D. to work under Prof. Tomislav Rovis. His graduate research focuses on developing photoredox catalysis using deep red and near-infrared light.

Katherine A. Xie studied chemistry and psychology at Cornell University (B.A. 2018), where she conducted undergraduate research in the lab of Prof. Thomas Cleland. She then worked with Prof. Kwanghun Chung at the Massachusetts Institute of Technology on developing chemical methods of tissue preservation. In 2020, she joined the group of Prof. Tomislav Rovis at Columbia University, where she is currently pursuing doctoral research on photoredox catalysis with low-energy light.

Samantha L. Goldschmid earned her B.A. in chemistry from Johns Hopkins University in 2019, where she worked with Prof. V. Sara Thoi on designing new homogeneous catalysts for electrochemical carbon dioxide reduction. She then worked with Dr. Jared DeCoste at the U.S. Army Combat Capabilities Development Command Center developing materials for photocatalytic nerve agent decontamination. In 2020, she joined the group of Prof. Tomislav Rovis at Columbia

University, where her doctoral research focuses on utilizing low-energy light to develop new synthetic methods and tools.

Stavros K. Kariofillis earned his B.S. in biochemistry from Lafayette College in 2013, where he worked with Prof. Roxy Swails on developing new water-soluble catalysts for cross-coupling. As an undergraduate student, he also worked with Prof. Melanie Sanford at the University of Michigan studying the organometallic properties and reactivity of copper(I)-difluoromethyl complexes. He received his Ph.D. from Princeton University as an NSF Graduate Research Fellow under the guidance of Prof. Abigail Doyle, including a year at UCLA as a Visiting Graduate Researcher, where his research focused on methodology development within nickel/photoredox catalysis. In 2022, he joined the lab of Prof. Tomislav Rovis at Columbia University as a postdoctoral researcher, where he is developing new platforms for red-light-mediated protein labeling.

Candice L. Joe studied chemistry at Haverford College and earned her B.Sc. in 2008. She received her Ph.D. from Boston College under the guidance of Prof. Kian Tan in 2014 and then moved to Princeton University to complete her postdoctoral studies with Prof. Abigail Doyle. In 2016, she joined the Process Chemistry department at Bristol Myers Squibb in New Brunswick, NJ as a member of the Catalysis Group.

Trevor C. Sherwood earned his B.S. in chemistry at Rensselaer Polytechnic Institute in 2008 working with Prof. Robert J. Linhardt on the synthesis of carbohydrates. He then earned his Ph.D. in 2013 in the laboratory of Prof. Scott A. Snyder

at Columbia University, where he completed the total syntheses of alkaloid and polyphenolic natural products. In 2013, Trevor joined the Bristol Myers Squibb Discovery Chemistry Immunology group in Princeton, NJ.

Melda Sezen-Edmonds is a Principal Scientist in the Chemical Process Development department at Bristol Myers Squibb in New Brunswick, NJ. Before joining Bristol Myers Squibb in 2018, she received her Ph.D. in chemical engineering from Princeton University working with Prof. Lynn Loo, and her B.S. in chemical and biological engineering from Koç University (Turkey).

Tomislav Rovis was born in Zagreb in the former Yugoslavia but was largely raised in Southern Ontario, Canada. Following his undergraduate studies at the University of Toronto, he earned his Ph.D. at the same institute in 1998 under the direction of Prof. Mark Lautens. From 1998–2000, he was an NSERC postdoctoral fellow at Harvard University with Prof. David A. Evans. In 2000, he began his independent career at Colorado State University and was promoted in 2005 to associate professor and in 2008 to professor and John K. Stille Chair in Chemistry. His group’s accomplishments have been recognized by a number of awards including an NSF CAREER award and a Roche Excellence in Chemistry award. He has been named a GlaxoSmithKline Scholar, an Amgen Young Investigator, an Eli Lilly Grantee, an Alfred P. Sloan Fellow, a Monfort Professor at Colorado State University, a Fellow of the American Association for the Advancement of Science, a Katritzky Young Investigator in Heterocyclic Chemistry, and an Arthur C. Cope Scholar. In 2016, he moved to Columbia University, where he served as the Samuel Latham Mitchill Professor of Chemistry.

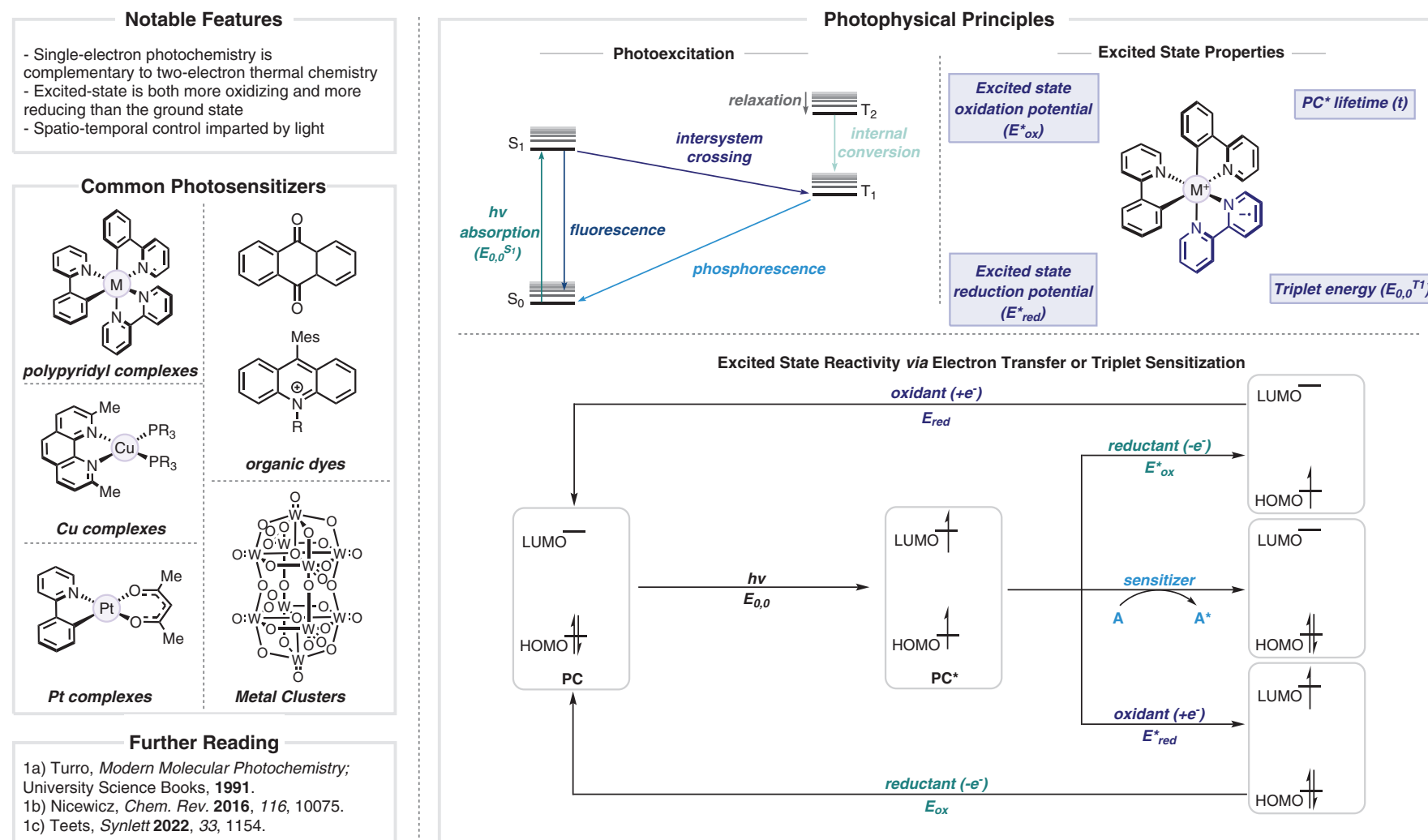
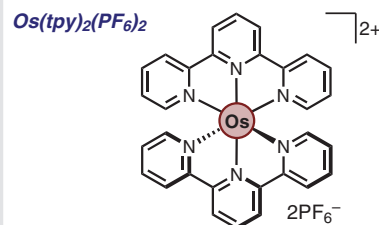


Figure 1 Overview of photophysical principles of photoredox catalysis^{1a-c}

Notable Features

- Enhanced penetration through biological tissue
- Lower extinction coefficient imparts batch scalability of photochemical reactions
- Lower energy light enhances functional group tolerance and decreases unwanted side reactivity

PC Structures

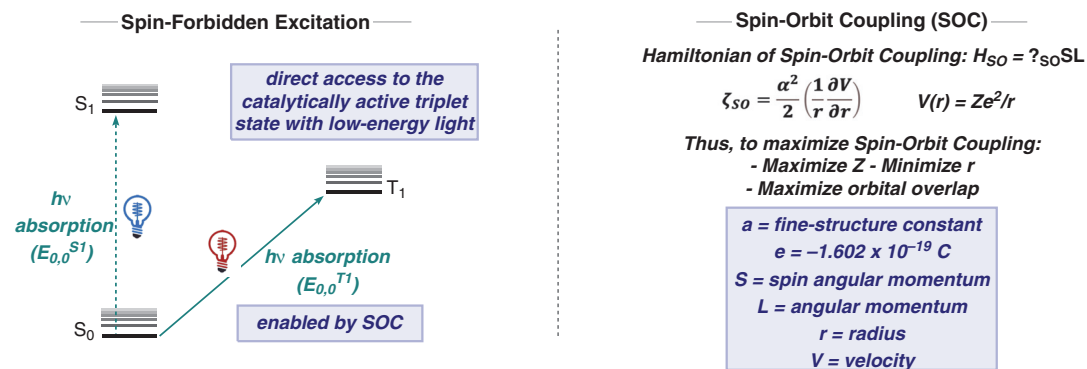


Other PC structures: *vide infra*

Further Reading

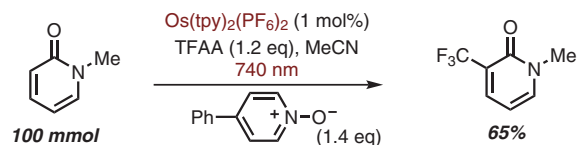
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NIR Photoredox Catalysis via Direct Excitation



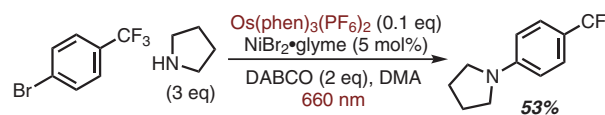
Selected Examples: Direct Excitation of Photocatalyst with NIR/DR light

Trifluoromethylation



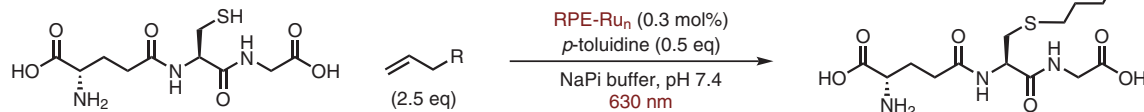
2a) Joe, Rovis, *ACS Cent. Sci.* **2020**, *6*, 2053.

Metallaphotoredox Catalysis



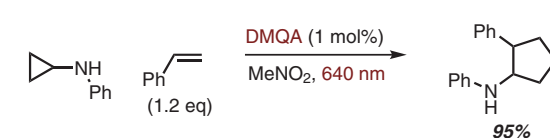
2a) Joe, Rovis, *ACS Cent. Sci.* **2020**, *6*, 2053.

Thiol-Ene Reaction



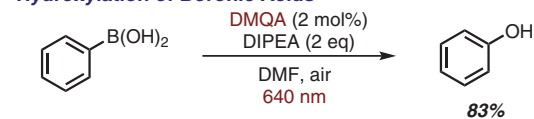
2c) Schlau-Cohen, *Chem* **2022**, *8*, 174.

[3+2] Cycloaddition



2d) Gianetti, *Synlett* **2022**, *33*, 1194.

Hydroxylation of Boronic Acids



2e) Gianetti, *J. Am. Chem. Soc.* **2020**, *142*, 12056.

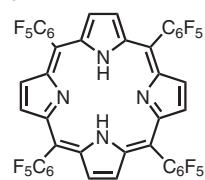
Figure 2 Overview of spin-forbidden excitation to access photoredox catalysis with NIR/DR light^{1a,2a-k}

Notable Features

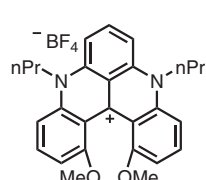
- Deep red and near-infrared photocatalysis can be merged with transition-metal catalysis similarly to higher energy blue and purple light paradigms
- Applications to cross-coupling and polymer synthesis have emerged and continue to be developed further

Photocatalysts from Examples

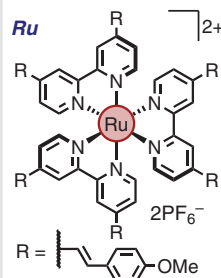
Por



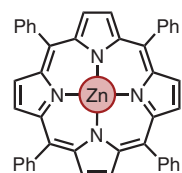
DMQA



Ru



Zn

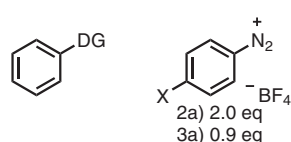


Further Reading

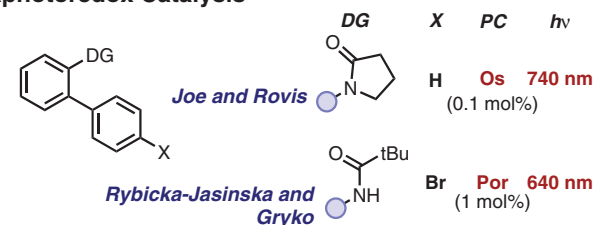
- Additional synthetic applications for DR/NIR:
 3e) Gianetti, *J. Org. Chem.* **2021**, *86*, 10640.
 3f) Cormier, Goddard, *Chem. Sci.* **2021**, *12*, 6964.
 An additional example of deep red light used for nickel metallaphotoredox C–N coupling:
 3g) Rovis, *J. Am. Chem. Soc.* **2022**, *144*, 22409.

Examples of Metallaphotoredox Catalysis

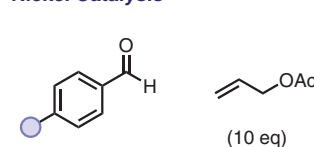
Palladium Catalysis



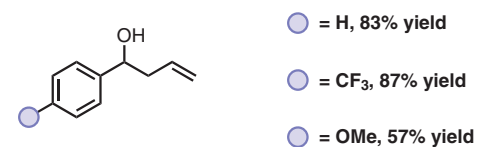
- 2a) Joe, Rovis, *ACS Cent. Sci.* **2020**, *6*, 2053.
 3a) Rybicka-Jasinska, Gryko, *ACS Org. Inorg. Au* **2022**, *2*, 422.



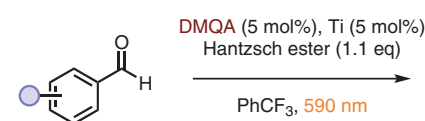
Nickel Catalysis



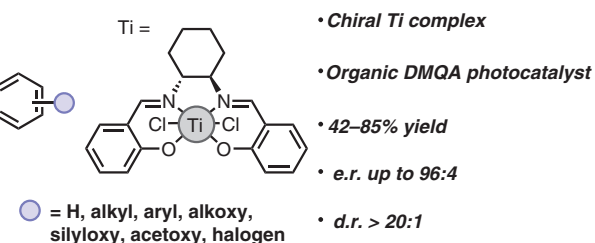
- 3b) Turro, Sun, *Nat. Commun.* **2022**, *13*, 2288.



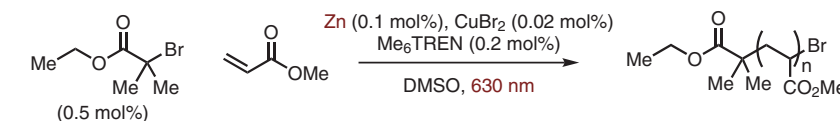
Titanium Catalysis



- 3c) Fermi, Gualandi, Cozzi, *Chem. Sci.* **2022**, *13*, 5973.



Copper-Catalyzed Polymerization



- 3d) Matyjaszewski, *ACS Macro. Lett.* **2022**, *11*, 376.

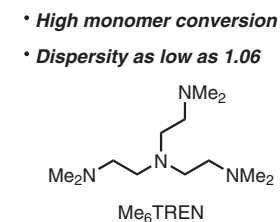


Figure 3 Selected metallaphotoredox applications of NIR/DR photocatalysis^{2a,3a–g}

Some Engineering Considerations for Scale Up

Reaction

- Solvent
- Concentration
- Photosensitizer/ photocatalyst
- Starting material
- Temperature

Radiation

- Light source wavelength
- Light source intensity
- Quantum yield of desired reaction
- Absorbance of reaction components
- Sensitivity of reaction components to light

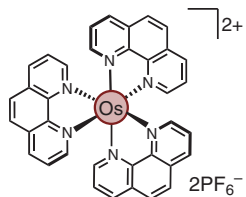
Reactor

- Light distribution
- Photon flux
- Reactor material
- Mixing/heat transfer
- Chemical compatibility
- Cost

Notable Features

- Blue light is strongly absorbed by the photocatalyst and the intensity decays to zero at shorter path lengths
- Red light can penetrate deeper into a reactor, as dictated by the Beer–Lambert law

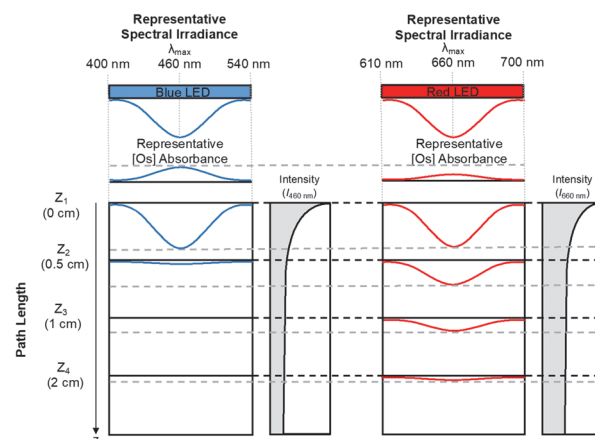
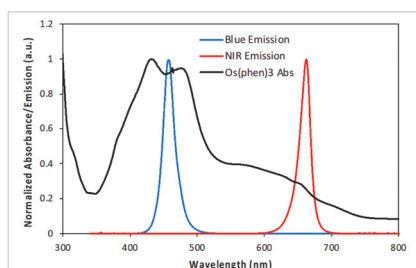
Application to $\text{Os}(\text{phen})_3(\text{PF}_6)_2$



$$\epsilon(460 \text{ nm}) = 15200 \text{ M}^{-1}\text{cm}^{-1}$$

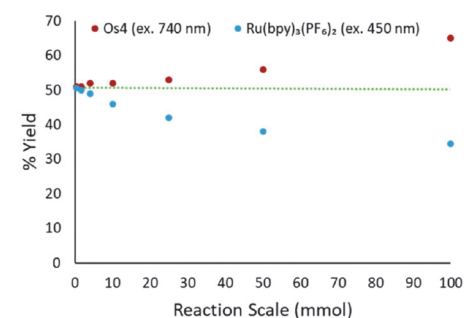
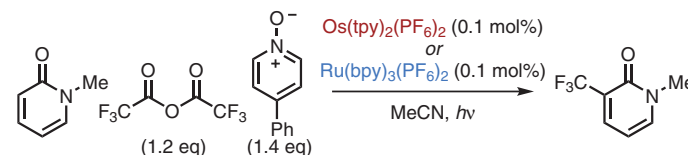
$$\epsilon(660 \text{ nm}) = 3200 \text{ M}^{-1}\text{cm}^{-1}$$

- Lower ϵ in red region
- Further penetration into reaction mix



4a) Sezen-Edmonds, *Org. Process Res. Dev.* **2020**, *24*, 2128.

Wavelength Impact on Yield



2a) Joe, Rovic, *ACS Cent. Sci.* **2020**, *6*, 2053.

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- 4b) Corcoran, *Angew. Chem. Int. Ed.* **2020**, *59*, 11964.
- 4c) Scaiano, *Acc. Chem. Res.* **2016**, *49*, 1320.
- 4d) Wolf, *Org. Biomol. Chem.* **2016**, *14*, 9088.
- 4e) Loubiere, *Chem. Eng. Process.* **2016**, *104*, 120.
- 4f) Edwards, *Nat. Commun.* **2020**, *11*, 804.

Figure 4 Engineering principles for scale-up^{2a,d,4a–f}

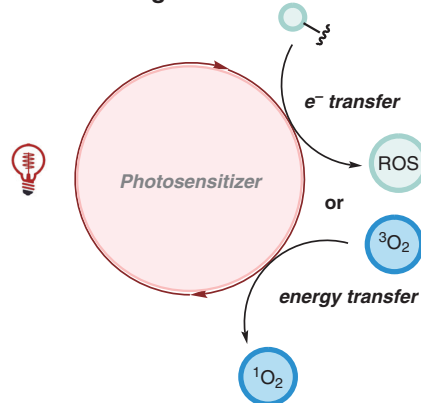
Notable Features

- Spatiotemporal control, high photocytotoxicity, and improved tissue penetration in photodynamic therapy (PDT) and photouncaging

Further Reading

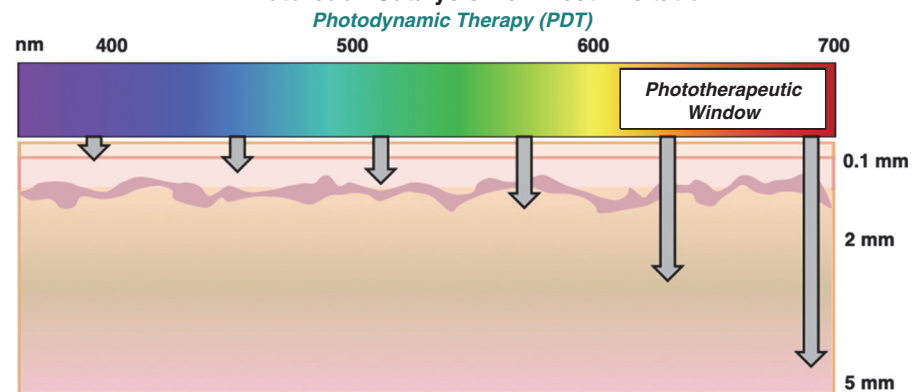
- 5d) Arnaut, *Coord. Chem. Rev.* **2016**, 325, 67.
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 5f) Gasser, *Acc. Chem. Res.* **2017**, 50, 2727.
 5g) McFarland, *Chem. Rev.* **2019**, 119, 797.
 5h) Gunnlaugsson, *Chem. Soc. Rev.* **2017**, 46, 7706.
 5i) Lo, *Inorg. Chem.* **2019**, 58, 2231.
 5j) Sadler, *Nat. Chem.* **2019**, 11, 1041.
 5k) Alabugin, *Photochem. Photobiol.* **2019**, 95, 722.
 5l) Peng, *J. Am. Chem. Soc.* **2018**, 140, 14851.
 5m) Han, *J. Am. Chem. Soc.* **2016**, 138, 14586.

Biological Mechanism



Design principle: low-energy light excitation of photosensitizer to generate cytotoxic reactive oxygen species (ROS) or singlet oxygen with applications in cancer treatment

NIR Photoredox Catalysis via Direct Excitation

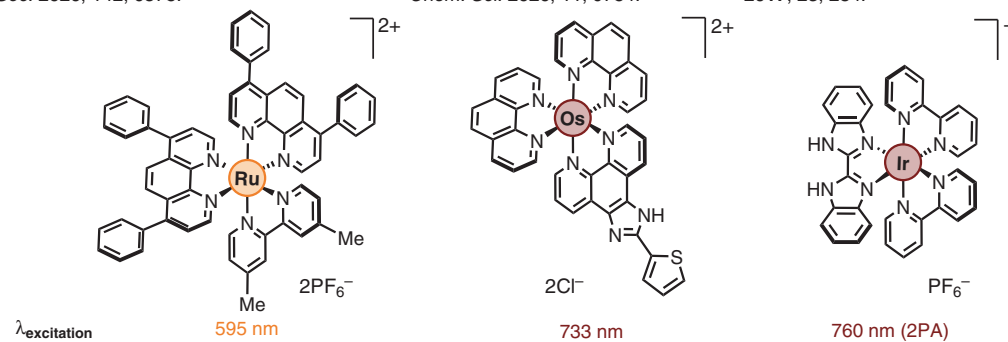


DR/NIR Photosensitizers

5a) Spingler, Ciofini, Gasser, *J. Am. Chem. Soc.* **2020**, 142, 6578.

5b) Cameron, Alberto, McFarland, *Chem. Sci.* **2020**, 11, 9784.

5c) Weinstein, Bryant, *Chem. Eur. J.* **2017**, 23, 234.



Hypoxic Photouncaging

2b) Kim, Peng, *J. Am. Chem. Soc.* **2022**, 144, 163.

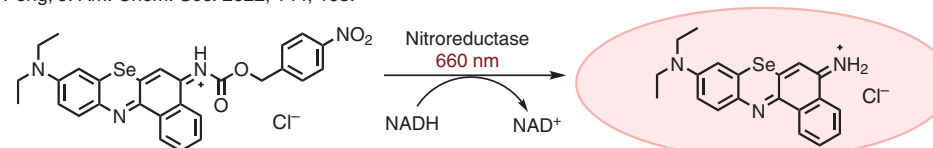


Figure 5 Use of DR/NIR photoredox catalysis for biological applications^{5a-m}

Notable Features

- Low-energy light in photoredox catalysis can be harnessed using multi-photon excitation, metal–organic frameworks (MOFs) and/or biological co-catalysts
- Provides alternative pathways to upconversion and SFE for catalyst activation with DR/NIR light

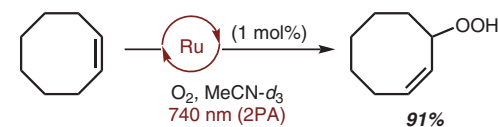
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 6d) Ceroni, *Phys. Chem. Chem. Phys.* **2018**, *20*, 8071.
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 6f) Chao, *J. Am. Chem. Soc.* **2022**, *144*, 4091.
 6g) Hu, *J. Am. Chem. Soc.* **2022**, *144*, 17604.
 6h) Qian, *Nat. Commun.* **2013**, *4*, 2719.
 6i) König, *Science* **2014**, *346*, 725.
 6j) Wilson, *Photochem. Photobiol.* **2007**, *83*, 1441.
 6k) Lakowicz, *Inorg. Chem.* **1997**, *36*, 5548.
 6l) Yang, *ChemCatChem* **2020**, *12*, 4185.
 6m) Malval, *J. Chem. Phys. Lett.* **2020**, *11*, 6487.

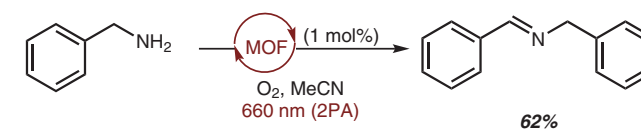
Low-Energy Photoredox Catalysis

Multi-photon Excitation

3b) Turro, Sun, *Nat. Commun.* **2022**, *13*, 2288.



6a) Duan, *ACS Catal.* **2019**, *9*, 422.



Biological Co-catalysis

2c) Schlaue-Cohen, *Chem* **2022**, *8*, 174.

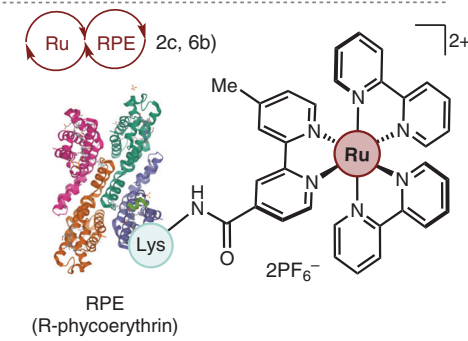
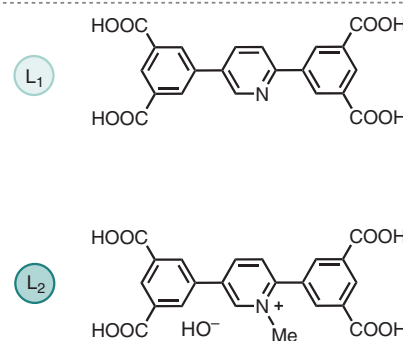
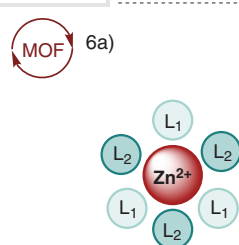
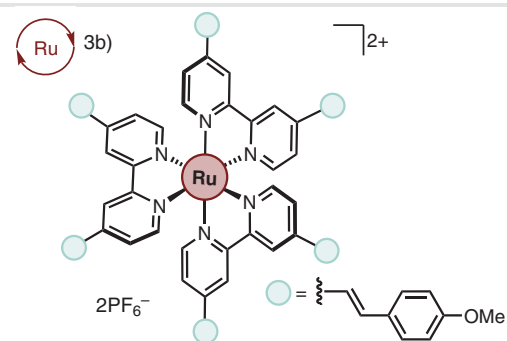
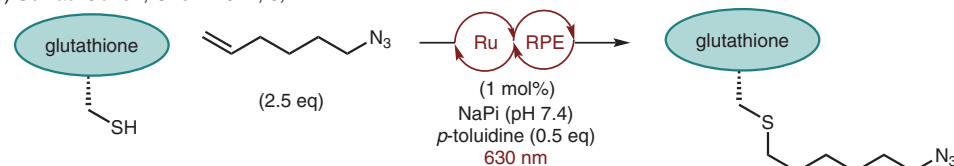
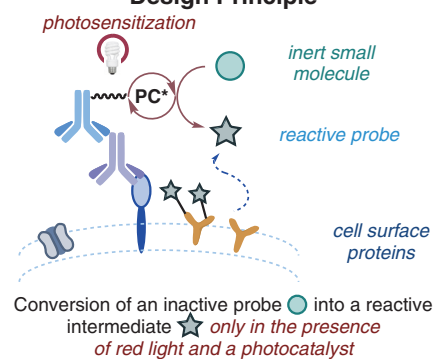


Figure 6 Use of DR/NIR photoredox catalysis through multiphoton excitation^{2c,6a-n}

Notable Features

- Enhanced penetration through biological tissue
- Lower energy light enables targeted and localized activation of a substrate only in the presence of light and a photosensitizer, in addition to enhancing functional group compatibility

Design Principle



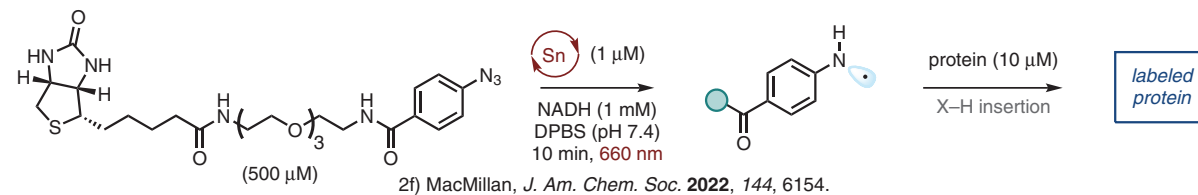
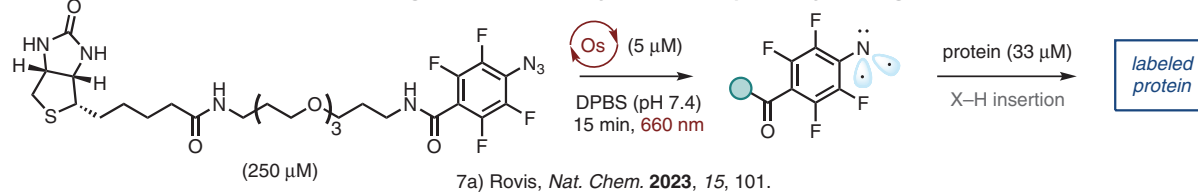
Further Reading

- 7c) Fox, *J. Am. Chem. Soc.* **2021**, *143*, 10793.
 7d) Yang, *J. Am. Chem. Soc.* **2022**, *142*, 17156.
 7e) Yoon, *Angew. Chem. Int. Ed.* **2020**, *59*, 8957.

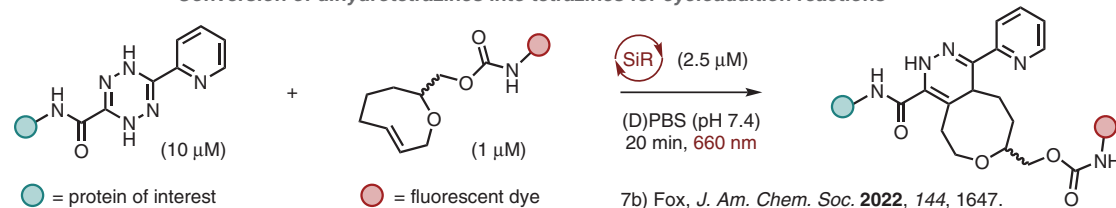
DR/NIR Photoredox Catalysis for Biological Applications

Labeling of Biomolecules

Accessing nitrenes and aminyl radicals for proximity labeling



Conversion of dihydrotetrazines into tetrazines for cycloaddition reactions



representative red-light-absorbing photocatalysts

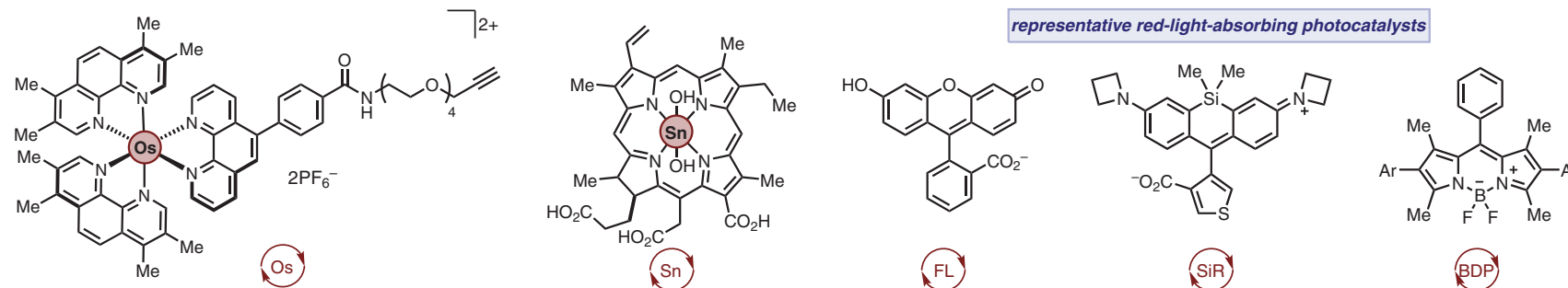
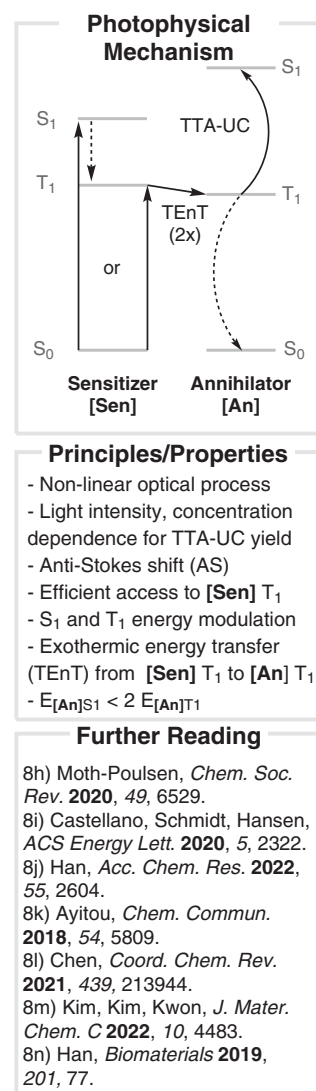
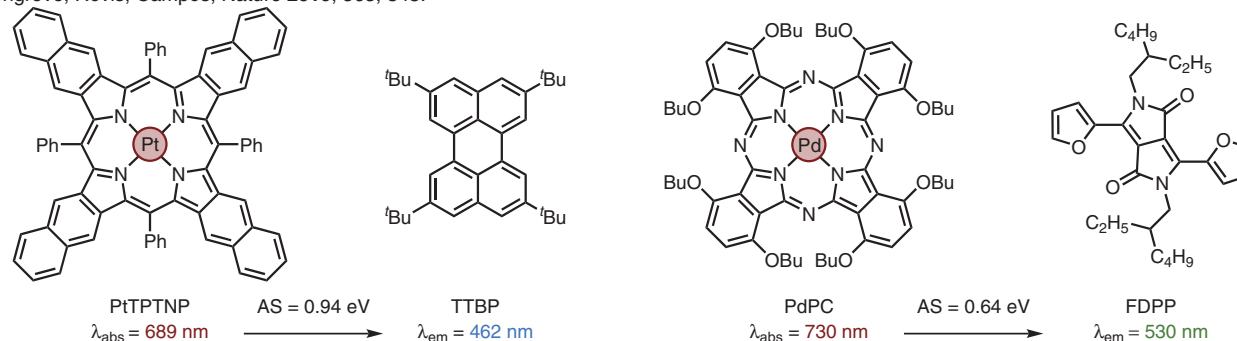
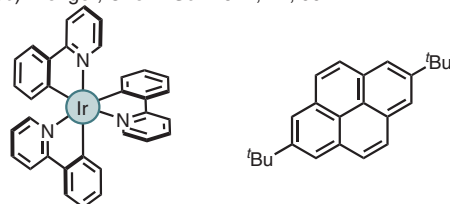
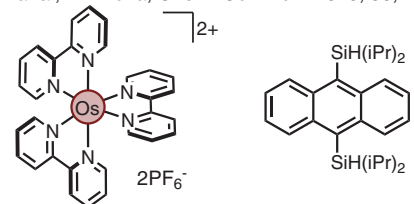
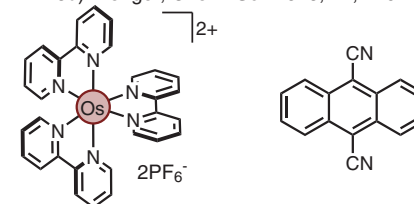
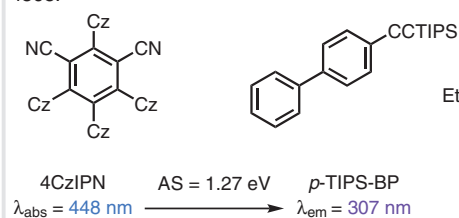
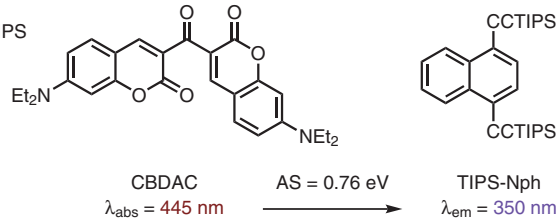
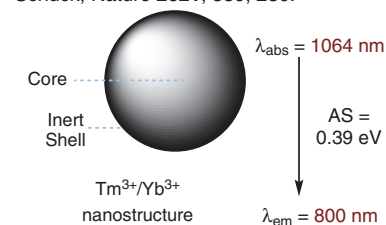


Figure 7 Applications of DR/NIR photoredox catalysis for biological applications^{2f,7a-e}



Triplet-Triplet Annihilation Upconversion (TTA-UC)

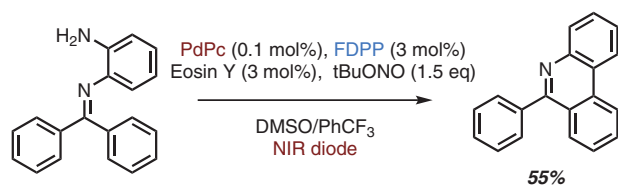
Selected Examples of Established Upconversion Systems

8a) Congreve, Rovis, Campos, *Nature* **2019**, *565*, 343.8b) Wenger, *Chem. Sci.* **2021**, *12*, 9922.8c) Yanai, Kimizuka, *Chem. Commun.* **2020**, *56*, 7017.8d) Wenger, *Chem. Sci.* **2023**, *14*, 149.8e) Kerzig, *J. Mater. Chem. C* **2022**, *10*, 4568.8f) Yanai, Kimizuka, *J. Mater. Chem. C* **2022**, *10*, 4558.8g) Suh, Bednarkiewicz, Cohen, Chan, Schuck, *Nature* **2021**, *589*, 230.Figure 8 Overview of current triplet-triplet annihilation upconversion technology^{8a-n}

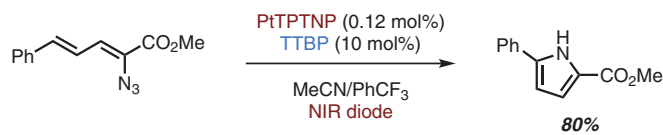
Selected Synthetic Examples of Triplet–Triplet Annihilation Upconversion

8a) Congreve, Rovis, Campos, *Nature* 2019, 565, 343.

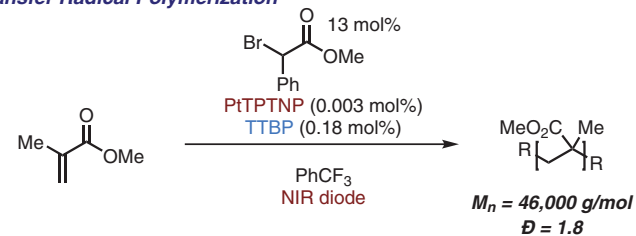
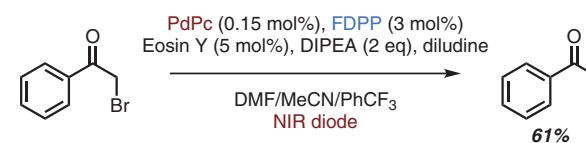
Radical Cyclization



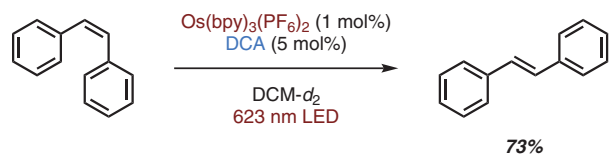
Vinyl Azide Sensitization



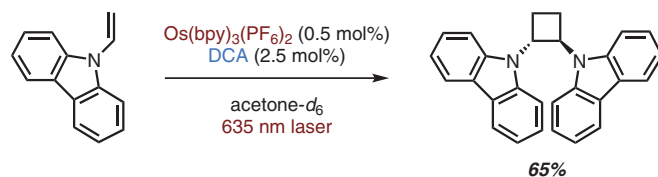
Atom Transfer Radical Polymerization

 α -Haloketone Reduction8d) Wenger, *Chem. Sci.* 2023, 14, 149.

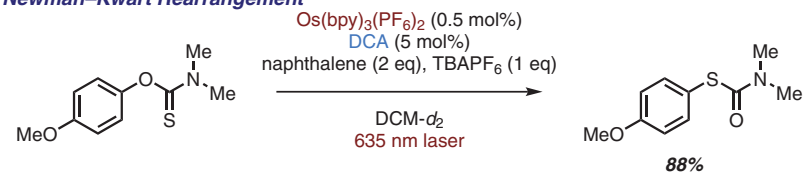
Alkene Isomerization



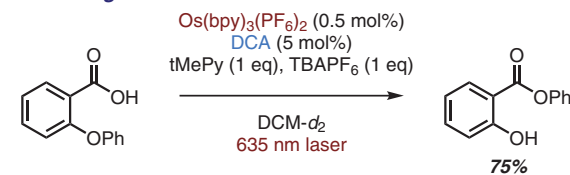
[2+2] Cycloaddition



Newman–Kwart Rearrangement



Ether-to-Ester Rearrangement

Figure 9 Applications of triplet–triplet annihilation upconversion to synthesis^{8a,d}

Conflict of Interest

The authors declare no conflict of interest.

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