Photoredox Catalysis
Meet the Authors

David MacMillan  
Princeton University

Tehshik Yoon  
University of Wisconsin-Madison

Corey Stephenson  
University of Michigan
Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes
As we know from undergraduate organic chemistry, aldehydes and ketones react with secondary amines to form enamines, via iminium ions.

In the reaction below, however, the unsaturated aldehyde cannot form an enamine because the iminium ion generated by condensation with the cyclic secondary amine cannot lose a proton.

The iminium ion is highly reactive towards water and other nucleophiles.
Review: Organocatalysis

- If this condensation is done in the presence of a weak nucleophile – strong enough to attach the iminium but not strong enough to attach the aldehyde – an addition reaction takes place.

- This catalyst and strategy were invented by David MacMillan at the California Institute of Technology (now at Princeton) and was given the name “organocatalysis.”
In 2007, the MacMillan group introduced the concept of **SOMO-catalysis**, where SOMO = Singly Occupied Molecular Orbital. In this work, a mild oxidant (ceric ammonium nitrate, CAN) was used to oxidize the transient enamine to give the $3\pi$-electron radical cation (termed SOMO-activation). This strategy greatly expanded the scope of transformations possible with amine organocatalysis.

**SOMO-Catalysis**

- In 2007, the MacMillan group introduced the concept of **SOMO-catalysis**, where SOMO = Singly Occupied Molecular Orbital.
- In this work, a mild oxidant (ceric ammonium nitrate, CAN) was used to oxidize the transient enamine to give the $3\pi$-electron radical cation (termed SOMO-activation).

![Chemical reaction diagram](attachment:ChemicalDiagram.png)

- This strategy greatly expanded the scope of transformations possible with amine organocatalysis.
The MacMillan group first employed this strategy for the $\alpha$-allylation of aldehydes (mechanism shown below).
In an attempt to further expand the scope of amine organocatalyzed transformations, the MacMillan group hypothesized that they could merge organocatalysis and photoinduced electron-transfer catalysis. Their seminal work reported in 2008 described the merger of a cyclic secondary amine catalyst and Ru(bpy)$_3$Cl$_2$ for the alkylation of aldehydes.
Proposed Mechanism

- MacMillan’s proposed mechanism for the alkylation of aldehydes
In the prior SOMO-activation studies, the key step involves the addition of the radical cation to the allylsilane, which is termed the SOMOphile.

In this work, the role is reversed – the electron deficient radical reacts with the SOMOphilic enamine.

Reexamining the Proposed Mechanism

• Let’s take a closer look at the mechanism proposed by MacMillan

• One of the key steps in the photoredox cycle involves the single-electron transfer to $^{*}\text{Ru(bpy)}_3\text{Cl}_2$ from the $\alpha$-aminoradical intermediate (9)

• The proposed **closed** catalytic cycle requires the encounter of two low concentration intermediates

• As discussed in the prior lecture, *this mechanism would be improbable for quick reaction times with low catalysts loadings; therefore, a chain mechanism may be involved*
Revised Mechanism from Yoon

- This possibility was examined by Yoon and coworkers.
- They determined that the quantum yield ($\Phi$) for the reaction was 18, which can only be consistent with a chain mechanism.
- Their revised mechanism is shown below:

Chem. Sci. 2015, 6, 5426.
Using Kinetics to Improve the Reaction

- In the original report, MacMillan and coworkers used Stern–Volmer analysis to examine the quenching of *Ru(bpy)$_3$Cl$_2$.
- They determined that *only* the enamine quenched the emission of Ru(bpy)$_3$Cl$_2$, with $K_{SV} = 10 \text{ M}^{-1}$.
- Knowing $\tau_0 = 912 \text{ ns}$ in DMF, we can calculate the probability that the enamine quenches the excited state.

\[
K_q = \frac{K_{SV}}{\tau_0} = \frac{10 \text{ M}^{-1}}{912 \times 10^{-9} \text{ s}} = 1.1 \times 10^7 \text{ M}^{-1} \text{s}^{-1}
\]

\[
\% \text{ Ru(bpy)$_3^{3+}$ quenched by enamine} = \frac{K_q [\text{enamine}]}{\frac{1}{\tau_0} + K_q [\text{enamine}]} \times 100 \%
\]

\[
= \frac{(1.1 \times 10^7 \text{ M}^{-1} \text{s}^{-1})(0.016 \text{ M})}{(912 \times 10^{-9} \text{ s})^{-1} + (1.1 \times 10^7 \text{ M}^{-1} \text{s}^{-1})(0.018 \text{ M})}
\]

\[
= 15 \%
\]

Using Kinetics to Improve the Reaction

- From this low probability, Yoon and coworkers recognized that addition of a co-catalytic reductive quencher could improve the reaction.

- Let’s calculate the probability that \( \text{Ru(bpy)}_3\text{Cl}_2 \) is quenched by \( N,N\text{-dimethyl-}p\text{-toluidine (18)} \).

\[
\text{[Cl]} = 0.0017 \text{ M} \\
\%	ext{ Ru(bpy)}_3^{2+} \text{ quenched by 18} = \frac{(3.9 \times 10^8 \text{ m}^3\text{s}^{-1})(0.0017 \text{ M}) \times 100 \%}{(9.1 \times 10^{-5} \text{ s}^{-1}) + (1.1 \times 10^7 \text{ m}^3\text{s}^{-1})(0.0018 \text{ M}) + (3.9 \times 10^8 \text{ m}^3\text{s}^{-1})(0.0017 \text{ M})} = 34 \%
\]

- From this calculation, we can see why the reaction is more efficient with the addition of a co-catalytic quencher.
Efficient Visible-Light Photocatalysis of [2+2] enone cycloadditions
[2+2] Cycloadditions of Enones

• In the early 2000s, Nathan Bauld and Michael Krische from UT Austin demonstrated that the radical anions generated from biaryl bis(enones) could undergo [2+2] cycloaddition reactions.

• Their proposed mechanism is shown below:

[2+2] Cycloadditions of Enones

- In 2008, Tehshik Yoon and his group hypothesized that these radical anions could be generated using photoredox catalysis.
- This was successfully accomplished using Ru(bpy)$_3$Cl$_2$ as the photocatalyst, $i$Pr$_2$NET to reductively quench *Ru(bpy)$_3$Cl$_2$, and LiBF$_4$ as a Lewis acid to activate the enone towards reduction.
[2+2] Cycloadditions of Enones

- Years later, Yoon and coworkers calculated the quantum yield ($\Phi$) of this reaction to be 77, which can only be consistent with a chain mechanism.

- They proposed the revised mechanism shown below:

\[ \text{Ligand} \rightarrow \text{Ru}^0 \rightarrow \text{Ru}^{\text{II}} \rightarrow \text{Ru}^{\text{III}} \rightarrow \text{Product} \]

\[ \text{Chain Termination} \quad \text{Chain Propagation} \]

Chem. Sci. 2015, 6, 5426.
To provide evidence for their proposed mechanism, they used Stern–Volmer analysis to examine the excited state kinetics. They determined that only iPr$_2$NEt resulted in any luminescence quenching, with a $K_{SV} = 6.6 \text{ M}^{-1}$. This indicates the proposed reductive quenching cycle is most probable. As $\tau_0 = 855 \text{ ns}$ in MeCN, let’s calculate the probability that iPr$_2$NEt quenches *Ru(bpy)$_2$Cl$_2$.

\[
\frac{[\text{iPr}_2\text{NEt}]}{[\text{iPr}_2\text{NEt}]} = 0.2 \text{ m}
\]

\[
k_q(\text{iPr}_2\text{NEt}) = \frac{6.6 \text{ m}^{-1}}{(855 \times 10^{-9} \text{s})} = 7.9 \times 10^6 \text{ m}^{-1} \text{s}^{-1}
\]

\[
\frac{\% \text{ *Ru(bpy)$_3$}^{2+} \text{ quenched}}{\text{by iPr}_2\text{NEt}} = \frac{(7.9 \times 10^6 \text{ m}^{-1} \text{s}^{-1})(0.2 \text{ m})}{(855 \times 10^{-9} \text{s})^{-1} + (7.9 \times 10^6 \text{ m}^{-1} \text{s}^{-1})(0.2 \text{ m})} \times 100 \%
\]

\[
= 57 \%
\]

* No other terms in denominator as other reactants do not quench *Ru(bpy)$_3$.$^{2+}$
Use of Sunlight

- The reaction could also be efficiently promoted on gram scale using sunlight.

![Chemical reaction diagram](image)

This reaction was published in *J. Am. Chem. Soc.* 2008, 130, 12886.
Electron-Transfer Photoredox Catalysis: Development of a Tin-Free Reductive Dehalogenation Reaction
Reductive Dehalogenations

- One of the most common precursors to carbon radicals are alkyl halides.
- Reductive dehalogenation ($\text{C–X} \rightarrow \text{C–H}$) is typically accomplished using tin reagents, such as tributyltin hydride.

\[
\text{Initiation} \quad \text{Bu}_3\text{Sn} - \text{H} \quad \xrightarrow{\text{h2}} \quad \text{Bu}_3\text{Sn}^+ + \text{H}^+
\]

\[
\text{Propagation} \quad \text{Bu}_3\text{Sn} \quad \xrightarrow{\text{H–SnBu}_3} \quad \text{MeO} - \text{Bu}_3\text{Sn}^+ + \text{BrSnBu}_3
\]
Reductive Dehalogenation

- Typically, reductive dehalogenations with H–SnBu$_3$ are initiated with AIBN.

Example Reaction:

\[
\begin{align*}
\text{CN} & \quad \text{N} = \text{N} \quad \text{CN} \\
\triangle & \rightarrow 2 \times \text{CN} & + & \text{N} = \text{N} \\
\text{CN} & \quad \text{H} & \quad \text{SnBu}_3 \rightarrow \text{CN} & \quad \text{Bu}_3\text{Sn}^+ \\
\end{align*}
\]
The Tin Problem

- Tributyltin hydride, as well as other tributyltin-based compounds, are well-documented to be toxic, especially to marine life.

- Tributyltin has been demonstrated to cause impairments to growth, development, reproduction, and survival of many marine species.

- As these toxic effects can occur with extremely low levels of tributyltin, and tributyltin can persist in the environment for long periods of time, a major focus has been developing tin-free radical reactions to help eliminate tributyltin waste from the environment.
Tin-Free Reductive Dehalogenation

- **Corey Stephenson** and coworkers determined two separate conditions for photoredox-catalyzed reductive dehalogenations.
- Both conditions utilize Ru(bpy)$_3$Cl$_2$ as the photocatalyst.
- The first set of conditions use a combination of $i$Pr$_2$NEt and formic acid (HCOOH), and the second set of conditions utilize a combination of $i$Pr$_2$NEt and Hantzsch ester (3).

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$i$Pr$_2$NEt (2 equiv), HCOOH (2 equiv), Ru$^{2+}$ (5 mol %), 24 h</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>$i$Pr$_2$NEt (10 equiv), HCOOH (10 equiv), Ru$^{2+}$ (2.5 mol %), 4 h</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N (10 equiv), HCOOH (10 equiv), Ru$^{2+}$ (5 mol %), 24 h</td>
<td>20$^b$</td>
</tr>
<tr>
<td>4</td>
<td>$i$Pr$_2$NEt (2 equiv), 3 (1.1 equiv), Ru$^{2+}$ (2.5 mol %), 4 h</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>$i$Pr$_2$NEt (10 equiv), HCOOH (10 equiv), Ru$^{2+}$ (1 mol %), 4 h</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>$i$Pr$_2$NEt (10 equiv), HCOOH (10 equiv), Ru$^{2+}$ (0.05 mol %), 4 h</td>
<td>75$^c$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after purification by chromatography on SiO$_2$. $^b$ 25% conversion. $^c$ Reaction conducted on a 2.0 g (4.6 mmol) scale.
• Let’s examine the proposed mechanism for the conditions using iPr$_2$NEt and Hantzsch ester

* Hydrogen atom transfer (HAT) step can also occur from 3$^+$. 
Where does the Hydrogen Come From?

- For the conditions utilizing $i\text{Pr}_2\text{NEt}$ and HCOOH, the origin of the hydrogen-atom in the product is slightly unclear.
- Performing deuterium labeling studies using either DCO$_2$D and DCO$_2$H led to the same 4:1 distribution of H:D products.

This indicates that $i\text{Pr}_2\text{NEt}$ is likely the major source of the H-atom (pathway B).

Meet the Authors

David MacMillan  
Princeton University

Abigail Doyle  
Princeton University

Gary Molander  
University of Pennsylvania

Vladimir Gevorgyan  
UT Dallas
Transition-Metal Catalyzed Cross-Coupling Reactions

• Transition metal catalyzed cross-coupling reactions are among the most utilized methods to form C–C and carbon–heteroatom bonds in organic chemistry.

• These reactions have gained such importance in both academia and industry that in 2010, the Nobel Prize in Chemistry was awarded to Richard Heck, Ei-ichi Negishi, and Akiro Suzuki for their pioneering work in Pd-catalyzed cross-couplings.
One of the most widely used cross-coupling reactions are Suzuki–Miyaura Couplings.

These can be described as a transition-metal catalyzed C–C bond forming reaction between an organic halide (vinyl or aryl) or triflate and a boronic acid or ester.
Catalytic Cycle

- The catalytic cycle of Suzuki–Miyaura Couplings consists of three key steps:
  1. Oxidative addition
  2. Transmetalation
  3. Reductive elimination
Oxidative Addition

- The first step in the catalytic cycle is **oxidative addition**
- Oxidative addition can be described as a transition metal atom inserts itself into a $\sigma$ bond
- The oxidation state of the metal is raised by two, for example M(0) to M(II), which is the result of the metal having two extra ligands bearing a formal negative charge (similar to the process for the formation of Grignard reagents)

\[
\text{M}(0) + \text{Ar}_1 \xrightarrow{\text{oxidative addition}} \text{M}(II) + \text{Ar}_1
\]
The next step is known as **transmetalation**, where the nucleophile \( R^1 \) is transferred from the organometallic reagent to the transition metal and the counterion moves in the opposite direction.

For Suzuki–Miyaura couplings, additional base (ethoxide or hydroxide) is typically required to accelerate the transmetalation step.
Reductive Elimination

• Most reactions that occur around a transition metal are reversible, and so the reverse of oxidative addition, known as reductive elimination, provides a simple route for the release of neutral organic products from a complex.

• The general mechanism shows M(II) going to M(0), releasing X–Y and forming a new X–Y $\sigma$ bond.
Heck Reaction

- The **Heck reaction** couples an alkene with an organic halide or triflate ($R^1-X$) to form a new alkene.
- The $R^1$ group can be aryl, vinyl, or any alkyl group **without $\beta$-hydrogens on an sp$^3$ carbon atom**.
The $\beta$-Hydride Elimination Problem

- C(sp$^3$)–X bond is more electron-rich than the C(sp$^2$)–X
  - Oxidative addition slower for alkyl halides vs. aryl/vinyl halides
- Alkyl-M complexes are highly reactive due to absence of stabilizing interactions with $d$-orbitals of M
- Thermodynamically favorable $\beta$-hydride elimination leads to formation of olefinic side products
- Slow elimination of cross-coupled product from the catalyst increases probability for side reactions
  - Ar-Ar > Ar-alkyl > alkyl-alkyl
Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis
Cross-Coupling Reactions

- The cross-coupling methods previously discussed are highly effective for C(sp²)–C(sp²) cross-coupling

- However, extension to C(sp³) centers have proven challenging because of:
  - Lower rates of oxidative addition
  - Lower rates of transmetalation
  - The tendency of alkylmetallic intermediates to undergo β-hydride elimination

*Traditional Cross-Coupling: Two-Electron Transmetalation*

- high activation energy
- rate-limiting step of most Suzuki cross-couplings
- requires stoichiometric base, high temperature
- transmetalation rate:
  - \( C_{sp} > C_{sp2} > C_{sp3} \)
The Molander group recognized that one of the key limitations of traditional cross-coupling methods for C(sp^3)-coupling is the rate-limiting transmetalation step.

For traditional two-electron transmetalation, the reactivity is inversely proportional to the heterolytic C–B bond strength, predisposing C(sp^3) nucleophiles for failure in cross-coupling reactions.

They envisioned that developing a new activation mode based on single-electron transfer chemistry would be a more efficient strategy.

Trends in homolytic C–B bond strength dictate that this strategy would exhibit reactivity complimentary to traditional cross-coupling, and now favors C(sp^3) nucleophiles.

Science 2014, 345, 433.
The proposed mechanism for the Molander group’s single-electron transmetalation strategy is shown below:

**Photoredox Cross-Coupling: Single-Electron Transmetalation**

- low activation energy
- reactivity dictated by measurable redox potentials
- requires no base or heat
- SET rate: $C_{sp3} > C_{sp2} > C_{sp}$
Why Nickel?

• Ni also has a number of readily available oxidation states commonly invoked in catalysis
• Similar to Pd, Ni(0)/Ni(II) catalytic cycles are widespread, but easy accessibility of Ni(I) and Ni(III) allows for different modes of reactivity and radical mechanisms
• Other key differences between Ni and Pd are highlighted in the table below

<table>
<thead>
<tr>
<th>Nickel</th>
<th>Palladium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ni(0)/Ni(I)/Ni(II)/Ni(III)</strong></td>
<td><strong>Pd(0)/Pd(II)</strong></td>
</tr>
<tr>
<td>Smaller atomic radius</td>
<td>Larger atomic radius</td>
</tr>
<tr>
<td>Less electronegative</td>
<td>More electronegative</td>
</tr>
<tr>
<td>Harder</td>
<td>Softer</td>
</tr>
<tr>
<td>Facile oxidative addition</td>
<td>Facile reductive elimination</td>
</tr>
<tr>
<td><strong>Radical pathways more accessible</strong></td>
<td></td>
</tr>
</tbody>
</table>
Reaction Scope

R-BF₃K Scope

<table>
<thead>
<tr>
<th>R</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>PhMe</td>
<td>89% (97%)</td>
</tr>
<tr>
<td>Me</td>
<td>PhMe</td>
<td>82%</td>
</tr>
<tr>
<td>14</td>
<td>PhF₂</td>
<td>99%</td>
</tr>
<tr>
<td>15</td>
<td>PhF₂</td>
<td>70%</td>
</tr>
<tr>
<td>16</td>
<td>PhMeO₂C</td>
<td>94%</td>
</tr>
<tr>
<td>17</td>
<td>PhMeO₂C</td>
<td>75%</td>
</tr>
<tr>
<td>18</td>
<td>PhF₃CO</td>
<td>97%</td>
</tr>
<tr>
<td>19</td>
<td>PhMe</td>
<td>72%</td>
</tr>
<tr>
<td>20</td>
<td>PhMe</td>
<td>86%</td>
</tr>
</tbody>
</table>

Ar-Br Scope

<table>
<thead>
<tr>
<th>Ar</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCF₃</td>
<td>21</td>
<td>79%</td>
</tr>
<tr>
<td>PhMe</td>
<td>22</td>
<td>75%</td>
</tr>
<tr>
<td>PhOMe</td>
<td>23</td>
<td>90%</td>
</tr>
<tr>
<td>PhCHO</td>
<td>24</td>
<td>81%</td>
</tr>
<tr>
<td>PhCO₂Me</td>
<td>25</td>
<td>56%</td>
</tr>
<tr>
<td>PhMe</td>
<td>26</td>
<td>63%</td>
</tr>
<tr>
<td>PhOH</td>
<td>27</td>
<td>96%</td>
</tr>
<tr>
<td>PhNHAc</td>
<td>28</td>
<td>63%†</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>29</td>
<td>75%</td>
</tr>
<tr>
<td>PhCN</td>
<td>30</td>
<td>90%</td>
</tr>
<tr>
<td>PhCF₃</td>
<td>31</td>
<td>65%</td>
</tr>
<tr>
<td>PhMe</td>
<td>32</td>
<td>65%</td>
</tr>
<tr>
<td>PhMe</td>
<td>33</td>
<td>57%</td>
</tr>
<tr>
<td>PhMe</td>
<td>34</td>
<td>96%</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>35</td>
<td>73%‡</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>36</td>
<td>72%</td>
</tr>
<tr>
<td>PhSCHO</td>
<td>37</td>
<td>58%</td>
</tr>
<tr>
<td>PhS₅NH₂</td>
<td>38</td>
<td>54%</td>
</tr>
<tr>
<td>PhS₅O</td>
<td>39</td>
<td>56%</td>
</tr>
<tr>
<td>PhPh</td>
<td>40</td>
<td>61%</td>
</tr>
</tbody>
</table>

* Reaction performed on 1.0 g (5.5 mmol) ArBr with 1 mol % 4, 1.5 mol % Ni(COD)₂, and 1.5 mol % dtbbpy.
† Reaction performed with 3 mol % 4, 5 mol % Ni(COD)₂, and 5 mol % dtbbpy.
‡ 55% isolated pure, 18% isolated as mixture with bromide starting material

Science 2014, 345, 433.
To highlight the differences between single-electron transmetalation and that of traditional cross-coupling, they performed a competition experiment between C(sp$^3$) and C(sp$^2$) nucleophiles.

Using this protocol, no C(sp$^2$)–C(sp$^2$) coupling was observed.

---

*Science* 2014, 345, 433.
Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes
Cross-Coupling Precursors

- Traditional organometallic cross-coupling methods typically involve the coupling of an aryl or vinyl halide with one of the following:

<table>
<thead>
<tr>
<th>Aryl or vinyl boronic acid</th>
<th>Zinc halides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stannanes</td>
<td>Grignard fragments</td>
</tr>
</tbody>
</table>

- Aryl or vinyl boronic acid: Used for Suzuki Couplings
- Stannanes: Used for Stille Couplings
- Zinc halides: Used for Negishi Couplings
- Grignard fragments: Used for Kumada Couplings
• The Doyle and MacMillan groups questioned whether the merger of photoredox and nickel catalysis could deliver a mechanism in which feedstock chemicals that contain common yet nontraditional leaving groups (C(sp³)–COOH and C(sp³)–H bonds) could serve as useful coupling partners.
Proposed Mechanism

- The proposed mechanism for the cross-coupling of carboxylic acids and aryl halides is shown below:
**Reaction Scope**

Boc-Pro-OH + aryl halide $\xrightarrow{1}$ 1 mol% photocatalyst 1, 10 mol% NiCl$_2$-glyme, 15 mol% dtbbpy, Cs$_2$CO$_3$, DMF, 26 W CFL light, 23 °C $\rightarrow$ (±)-benzylic amine

---

**Catalyst Combination**

---

### iodoarenes $X = I$

- (±)-10 78% yield
- (±)-11 65% yield
- (±)-12 74% yield
- (±)-13 77% yield

### bromoarenes $X = Br$

- (±)-14 86% yield
- (±)-15 90% yield
- (±)-16 75% yield
- (±)-17 87% yield
- (±)-18 88% yield
- (±)-19 85% yield
- (±)-20 82% yield
- (±)-21 67% yield
- (±)-22 60% yield

---

**chloroarenes $X = Cl$**
Reaction Scope

\[ \text{amino acid} \rightarrow \text{product} \]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cbz-Pro-OH</td>
<td>(±)-25</td>
<td>93%</td>
</tr>
<tr>
<td>Boc-Pip-OH</td>
<td>(±)-26</td>
<td>82%</td>
</tr>
<tr>
<td>Boc-Morph-OH</td>
<td>(±)-27</td>
<td>61%</td>
</tr>
<tr>
<td>Boc-Val-OH</td>
<td>(±)-28</td>
<td>72%</td>
</tr>
<tr>
<td>Boc-Trp(Boc)-OH</td>
<td>(±)-29</td>
<td>83%</td>
</tr>
<tr>
<td>R = CO₂Bn</td>
<td>(±)-30</td>
<td>77%</td>
</tr>
<tr>
<td>R = SMe</td>
<td>(±)-31</td>
<td>83%</td>
</tr>
<tr>
<td>Boc-N-Me-Leu-OH</td>
<td>(±)-32</td>
<td>91%</td>
</tr>
<tr>
<td>Tetrahydro-2-furoic acid</td>
<td>(±)-33</td>
<td>82%</td>
</tr>
</tbody>
</table>
Reaction Scope

• By starting with a dimethylaniline, single-electron oxidation leads to an α-amino radical, which can be cross-coupled with aryl halides using dual photoredox/nickel catalysis.

• The net reaction is a direct C–H, C–X cross-coupling reaction.
Visible Light-Induced Room-Temperature Heck Reaction of Functionalized Alkyl Halides with Vinyl Arenes/Heteroarenes
Owing to the difficulty of cross-coupling alkyl halides, limited examples of alkyl-Heck reactions exist.

**Intramolecular Alkyl-Heck Reactions (Fu, Alexanian)**


**Literature Precedent**

**Intermolecular Alkyl-Heck Reactions (Alexanian, Zhou)**

\[
\begin{align*}
\text{Cyclohexyl}^\text{I} + \text{Ph} & \quad \xrightarrow{5 \text{ mol}\% \text{ Pd(dppf)Cl}_2, 2 \text{ equiv Cy}_2\text{NMe}} \quad \text{PhCF}_3, 110 ^\circ \text{C, 14 h}} \\
& \quad \text{84%} \\
\text{Cyclohexyl}^\text{I} + \text{Ph} & \quad \xrightarrow{5 \text{ mol}\% \text{ Pd(PPh}_3)_4, \text{7 mol}\% \text{ dppf}} \quad \text{Cy}_2\text{NMe, Lil, PhCF}_3, 110 ^\circ \text{C, 36 h}} \\
& \quad \text{78%}
\end{align*}
\]


Current Drawbacks

- The prior Heck reactions of alkyl halides suffer from various drawbacks, which includes the need for high reaction temperatures.

- These high temperatures result in the erosion of stereocontrol during the reaction, and limits the reaction scope (low functional group tolerance).

- The Gevorgyan lab proposed that a possible solution to these drawbacks could be to employ a visible-light induced, room-temperature Heck reaction:
  - Access to substrates which are inaccessible through traditional methods.
  - Milder conditions will allow for greater stereochemical control.
  - Milder conditions will allow for a broader reaction scope; greater functional group tolerance.
Optimization of Reaction Conditions

\[ \text{Catalyst (10 mol\%) + Ligand (20 mol\%)} \]

\[ \text{3 equiv Base} \]

Conditions, PhH, 12 h

---

<table>
<thead>
<tr>
<th>No.</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Cond.</th>
<th>Yield(^{[b]}) ([%]) (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{[c]})</td>
<td>Pd(OAc)(_2)</td>
<td>L</td>
<td>iPr(_2)NMe</td>
<td>120 °C</td>
<td>traces</td>
</tr>
<tr>
<td>2(^{[c]})</td>
<td>Pd(dppf)Cl(_2)</td>
<td>–</td>
<td>Cy(_2)NMe</td>
<td>100 °C</td>
<td>35 (5:1)</td>
</tr>
<tr>
<td>3(^{[d]})</td>
<td>Pd(PPh(_3))(_2)Cl(_2) (5 mol%)</td>
<td>xantphos (10 mol%)</td>
<td>Cs(_2)CO(_3)</td>
<td>100 °C</td>
<td>0</td>
</tr>
<tr>
<td>4(^{[e]})</td>
<td>Pd(PPh(_3))(_4) (35 mol%)</td>
<td>–</td>
<td>K(_2)CO(_3)</td>
<td>100 °C</td>
<td>10 (1:0)</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh(_3))(_4)</td>
<td>–</td>
<td>Cs(_2)CO(_3)</td>
<td>RT, blue LED</td>
<td>35 (56(^{[f]})) (30:1)</td>
</tr>
<tr>
<td>6</td>
<td>Pd(dppf)Cl(_2)</td>
<td>–</td>
<td>Cy(_2)NMe</td>
<td>RT, blue LED</td>
<td>traces</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)(_2)</td>
<td>dppf</td>
<td>iPr(_2)NMe</td>
<td>RT, blue LED</td>
<td>traces</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)(_2)</td>
<td>L</td>
<td>iPr(_2)NMe</td>
<td>RT, blue LED</td>
<td>traces</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)(_2)</td>
<td>xantphos</td>
<td>Cs(_2)CO(_3)</td>
<td>RT, blue LED</td>
<td>85 (49:1)</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)(_2)</td>
<td>xantphos</td>
<td>Cs(_2)CO(_3)</td>
<td>up to 110°C</td>
<td>traces</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)(_2)</td>
<td>xantphos</td>
<td>Cs(_2)CO(_3)</td>
<td>RT, dark</td>
<td>traces</td>
</tr>
<tr>
<td>12</td>
<td>–</td>
<td>xantphos</td>
<td>Cs(_2)CO(_3)</td>
<td>RT, blue LED</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Standard conditions: 1a 0.1 mmol scale, PhH 0.25 M, 120 °C or 34 W blue LED. \(^{[b]}\) GC-MS yield and ratio. \(^{[c]}\) PhCF\(_3\) as solvent. \(^{[d]}\) DCE as solvent. \(^{[e]}\) PhMe as solvent. \(^{[f]}\) THF as solvent.
Scope of Alkenes

Conditions: 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol Pd(OAc)$_2$, 0.1 mmol xantphos, 1.5 mmol Cs$_2$CO$_3$, PhH (0.25 M), 34 W blue LED, rt.
Scope of Alkyl Iodides

**Conditions I:** 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol Pd(OAc), 0.1 mmol xantphos, 1.5 mmol Cs$_2$CO$_3$, PhH (0.25 M), 34 W blue LED, rt.

- $G = \text{Bpin}, X = I$: 70%$^b$
- $X = \text{Br}$: 80%$^b$
- $R = \text{SnBu}_3$: 71%$^c$
- $R = \text{NPhthl}, X = I$: 73%$^b$
- $X = \text{Br}$: 59%$^b$
- $R = \text{OPiv}$: 76%$^c$
- $R = \text{P(O)(OEt)}_2$: 58%$^a$
- $R = \text{Ts}$, $X = I$: 61%$^a$
- $X = \text{Br}$: 39%$^b$
- $R = \text{GeMe}_3$: 68%$^a$

- $97\% (E:Z = 10:1)^a$

**Conditions II:** 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol xantphos Pd G3, 1 mmol $i$Pr$_2$NEt, PhH (0.25 M), 34 W blue LED, rt.

- $53^a$
- $56^b$
- $80^a$

**Conditions III:** 0.25 mmol scale, 1 equiv. halide, 4 equiv. styrene, 6 equiv. Cs$_2$CO$_3$, PhH (0.0625 M).

- $64^a$
- $87^a$
- $79^a$
- $76^a$

$^a$Conditions I: 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol Pd(OAc), 0.1 mmol xantphos, 1.5 mmol Cs$_2$CO$_3$, PhH (0.25 M), 34 W blue LED, rt.  
$^b$Conditions II: 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol xantphos Pd G3, 1 mmol $i$Pr$_2$NEt, PhH (0.25 M), 34 W blue LED, rt.  
$^c$Conditions III: 0.25 mmol scale, 1 equiv. halide, 4 equiv. styrene, 6 equiv. Cs$_2$CO$_3$, PhH (0.0625 M).
• The Gevorgyan group performed a series of mechanistic experiments which provided evidence for a radical mechanism.

\[ \text{TMS-} \text{I} \quad + \quad \text{allyl} \quad \xrightarrow{1 \text{ equiv TEMPO}} \quad \text{TMS-} \text{allyl} \quad + \quad \text{adduct} \quad (0\%) \quad + \quad \text{products} \quad (42\%) \quad \text{(NMR yield)} \]

\[ \text{TMS-} \text{I} \quad + \quad \text{cyclopropene} \quad \xrightarrow{\text{Conditions I}} \quad \text{TMS-} \text{cyclopropene} \quad + \quad \text{adduct} \quad \text{(59\%)} \quad \text{Only observed product} \]

• Stern-Volmer Analysis demonstrated that iodomethyltrimethyl silane quenched the excited state of Pd(PPh\textsubscript{3})\textsubscript{4}.
Their proposed mechanism is shown below:

i. SET from \( \text{Pd}(0) \) to alkyl iodide
ii. Radical addition to styrene
iii. \( \beta \)-hydride elimination
Meet the Authors

J. C. (Tito) Scaiano
University of Ottawa

David Nicewicz
UNC Chapel Hill

Garret Miyake
Colorado State University
In 2012, Xiao and coworkers reported an electrochemical-mediated oxidative hydroxylation of arylboronic acids. The mechanism proceeds through a nucleophilic superoxide radical, which is generated by the one-electron reduction of molecular oxygen. Their proposed mechanism is shown below:

Oxidative Hydroxylation of Arylboronic Acids

- Xiao and coworkers hypothesized that the superoxide radical anion could be produced using a reductive quenching photoredox cycle.
- Their proposed mechanism for their Ru(bpy)$_3$Cl$_2$-photocatalyzed transformation is shown below:

![Chemical mechanism diagram]

Oxidative Hydroxylation of Arylboronic Acids

• The system developed by Xiao and coworkers suffers from several drawbacks:

1) Long irradiation times required to achieve synthetically useful yields
   • Hypothesized to be from slow reductive quenching by the amine

2) \( \text{Ru(bpy)}_3\text{Cl}_2 \) is extremely expensive ($73/g)

• Scaiano and coworkers envisioned that an overarching solution to both of these drawbacks would be to employ an inexpensive photocatalyst that is known to undergo fast reductive quenching by amines
In 2013, Scaiano and coworkers proposed that Methylene Blue, an inexpensive organic dye ($2.25/g), could be utilized as a photocatalyst for reductive quenching photoredox cycles.

**Photochemical Properties**
- Absorption $\lambda_{\text{max}}$: 665 nm
- $\epsilon = 90,000 \text{ M}^{-1}\text{cm}^{-1}$
- Triplet Energy: 1.50 eV
- $\Phi_T = 0.52$
- Triplet $\tau_0$ (MeCN): 32 $\mu$s
- Triplet Transient $\lambda_{\text{max}}$: 420 nm
- Triplet $\epsilon = 11,000 \text{ M}^{-1}\text{cm}^{-1}$

**Redox Properties**
- $E_{1/2}^{\text{red}}$ (MB$^+/\text{MB}^-$) = -0.47 V vs. SCE
- $E_{1/2}^{\text{ox}}$ (*MB$^+/\text{MB}^*$) = 0.97 V vs. SCE

To test this hypothesis, they chose to examine the oxidative hydroxylation of arylboronic acids.
In order to determine the origin of this difference in observed reactivity, the excited state kinetics for Methylene Blue and Ru(bpy)$_3$Cl$_2$ were analyzed in detail.

The results are shown in the table below:

<table>
<thead>
<tr>
<th>Quencher</th>
<th>Methylene Blue</th>
<th>Ru(bpy)$_3$Cl$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPr$_2$NEt</td>
<td>$2.44 \times 10^8$</td>
<td>$6.21 \times 10^6$</td>
</tr>
<tr>
<td>Phenylboronic acid</td>
<td>$1.34 \times 10^8$</td>
<td>$3.72 \times 10^6$</td>
</tr>
<tr>
<td>Phenol</td>
<td>$5.81 \times 10^5$</td>
<td>$6.68 \times 10^5$</td>
</tr>
<tr>
<td>O$_2$</td>
<td>$2.46 \times 10^9$</td>
<td>$2.97 \times 10^9$</td>
</tr>
</tbody>
</table>

**J. Am. Chem. Soc. 2013, 135, 13286.**
Methylene Blue vs. Ru(bpy)$_3$Cl$_2$

- Since the first step in the catalytic cycle is the quenching of $^3$PC by $i$Pr$_2$NEt, we can use the $k_q$ values from the previous slide to calculate the probability of this event (under initial reaction conditions) for each photocatalyst.

\[
\text{% Triplet Quenching by } i\text{Pr}_2\text{NEt under initial reaction conditions =} \frac{100 \% \times k_{q}^{iPr_2NEt}[iPr_2NEt]}{\tau_0^{-1} + k_{q}^{iPr_2NEt}[iPr_2NEt] + k_{q}^{PhB(OH)_2}[PhB(OH)_2] + k_{q}^{O_2}[O_2]}
\]

Photocatalyst

- Methylene Blue: 85 %
- Ru(bpy)$_3$Cl$_2$: 20 %

*Reaction with $^3$MB is 4.25 times more favorable than the corresponding reaction with $^3$Ru(bpy)$_3$Cl$_2$*
Mechanistic Insights from Excited State Kinetics

- When following the progress of the reaction over time, we can see that the reaction has an induction period.
- This is caused because of competitive non-productive quenching of $^3$MB by phenylboronic acid.
- As the reaction proceeds and phenylboronic acid is consumed, the rate of the reaction increases.

---

In comparison, the probability of quenching of $^3\text{Ru(bpy)}_3\text{Cl}_2$ by $i\text{Pr}_2\text{NEt}$ decreases slightly as the reaction progresses.

This should be expected; as a reagent is consumed, its concentration in the reaction decreases, and since reagent concentrations impact quenching probability, we would also expect the probability of triplet quenching to decrease.

---

**J. Am. Chem. Soc. 2013, 135, 13286.**
• The proposed mechanism for the oxidative hydroxylation of arylboronic acids photocatalyzed by Methylene Blue is shown below.

\[
\text{O}_2^• + \text{MB} \rightarrow \text{MB}^• \quad \text{hv} \\
\text{MB}^• + \text{O}_2 \rightarrow \text{MB}^{2•} \\
\text{MB}^{2•} + \text{arylboronic acid} \rightarrow \text{hydroxylation product} \\
\]

\[
\begin{align*}
k_1 &= 2.4 \times 10^8 \text{ M}^{-1}\text{s}^{-1} \\
k_2 &= 5.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1} \\
k_3 &= 2.9 \times 10^8 \text{ M}^{-1}\text{s}^{-1} \\
k_4 &= < 10^8 \text{ s}^{-1} \\
\end{align*}
\]
Direct Catalytic Anti-Markovnikov Hydroetherification of Alkenols
Markovnikov’s Rule

• Let’s examine the electrophilic addition of HBr to an alkene

• When HBr reacts as an electrophile, it is attacked at H, losing Br⁻

• Electrophilic addition of a proton to an alkene results in a carbocation, which reacts rapidly with the Br⁻ just formed

• Overall, HBr adds across the alkene
Markovnikov’s Rule

• For unsymmetrical alkenes, product is dictated by which of the possible carbocation intermediates is the most stable

\[
\text{Ph} = \underset{\text{H}}{\longrightarrow} \text{Br} \quad \rightarrow \quad \text{Ph} = \underset{\text{+}}{\longrightarrow} \text{Br}
\]

• **Markovnikov’s rule**: The hydrogen ends up attached to the carbon of the double bond that has more hydrogens to start with

\[
\text{Ph} \quad \underset{\text{X}}{\longrightarrow} \quad \text{Ph} \quad \underset{\text{+}}{\longrightarrow} \quad \text{Ph} \quad \underset{\text{Br}}{\longrightarrow}
\]

\[
\text{unstable primary carbocation. Not formed.}
\]
While there are a vast number of examples of direct addition of heteroatom nucleophiles to alkenes to give Markovnikov products, comparatively few examples exist that provide anti-Markovnikov selectivity. David Nicewicz and coworkers proposed that single-electron oxidation of alkenes to their respective radical-cations may provide a general way to access anti-Markovnikov selectivity for a range of heteroatom nucleophiles with unactivated alkenes.

\[ \text{R} \overset{-e^-}{\rightarrow} [\text{R} \text{C} \text{C}]^{+} \overset{H-\text{OR}'}{\leftrightarrow} \text{R} \overset{-H^+}{\rightarrow} \text{R}-\text{OR'} \overset{\text{Favored}}{\rightarrow} \text{R} \overset{\text{Anti-Markovnikov}}{\rightarrow} \text{R}-\text{OR'} \]

In order to photocatalytically generate radical cations from alkenes, Nicewicz and coworkers chose to utilize the commercially available 9-mesityl-10-methylacridinium ion (Acr\(^{+}\)-Mes) developed by Fukuzumi and coworkers in 2010.

The photocatalyst is a linked electron donor-acceptor system, with acridinium acting as the electron acceptor and mesityl moiety acting as the electron donor.

The excited state of Acr\(^{+}\)-Mes possesses a long lifetime (27 µs in MeCN) and a high excited state energy (2.37 eV) which is extremely oxidizing.

\[ E_{1/2}(3\text{Mes}^{+*}-\text{Acr}^{*}/\text{Mes}-\text{Acr}^{*}) = 2.08 \text{ V vs. SCE} \]
Anti-Markovnikov Hydroetherification of Alkenols

• The proposed mechanism for their transformation is shown below:

[Diagram of the mechanism]

\[ \text{coupled to oxidation of 11} \]

\[ +e^- \]

\[ \text{Ph} \]

\[ \text{NC} \]

\[ \text{CN} \]

\[ \text{Ph} \]

\[ \text{CN} \]

\[ \text{Ph} \]

\[ \text{Ph} \]

\[ \text{H-atom donor} \]

\[ \text{H-Atom Transfer} \]

\[ \text{coupled to reduction of 13} \]

\[ -e^- \]

\[ \text{450 nm LEDs} \]

\[ \text{photoredox catalyst} \]

\[ \text{SET} \]

\[ \pm H^+ \]

\[ \text{Redox Couple} \]

\[ \text{Proton Transfer} \]

\[ \text{Single Electron Transfer} \]

\[ \text{J. Am. Chem. Soc. 2012, 134, 18577.} \]
**Reaction Scope**

![Chemical structures and reaction conditions](attachment:image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenol</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Structure 1" /></td>
<td><img src="" alt="Product 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Structure 2" /></td>
<td><img src="" alt="Product 2" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="" alt="Structure 3" /></td>
<td><img src="" alt="Product 3" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="" alt="Structure 4" /></td>
<td><img src="" alt="Product 4" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="" alt="Structure 5" /></td>
<td><img src="" alt="Product 5" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="" alt="Structure 6" /></td>
<td><img src="" alt="Product 6" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="" alt="Structure 7" /></td>
<td><img src="" alt="Product 7" /></td>
</tr>
<tr>
<td>8</td>
<td><img src="" alt="Structure 8" /></td>
<td><img src="" alt="Product 8" /></td>
</tr>
</tbody>
</table>

**Notes:**
- Catalyst 2 (5 mol %)
- 0.5 equiv PhCH(CN)_2
- 450 nm LEDs
- DCE [0.5 M], 23 °C

**Results:**
- 80% yield
- 60% yield
- 82% yield
- 77% yield
- 68% yield
- 46% yield

**Details:**
- **Entry 1:**
  - $E_{\nu} = +1.26 \text{ V}$
- **Entry 2:**
  - $E_{\nu} = +1.69 \text{ V}$
- **Entry 3:**
  - $E_{\nu} = +1.41 \text{ V}$
- **Entry 4:**
  - $E_{\nu} = +1.95 \text{ V}$
- **Entry 5:**
  - $E_{\nu} = +1.98 \text{ V}$
- **Entry 6:**
  - $E_{\nu} = +2.10 \text{ V}$  
  - $> 5:1 \text{ E:Z}$
- **Entry 7:**
  - $E_{\nu} = +1.30 \text{ V}$
- **Entry 8:**
  - $E_{\nu} = +1.88 \text{ V}$
- **Entry 7:**
  - $77\% \text{ yield}$
- **Entry 8:**
  - $68\% \text{ yield}$
- **Entry 3:**
  - $46\% \text{ yield}$

**Reference:**

Markovnikov vs. Anti-Markovnikov Selectivity

- In order to emphasize the unique regioselectivity of this process, Nicewicz and coworkers performed direct comparisons of alkene reactivity with cation radicals or Bronsted acids.

The second example is intriguing as the tetrahydropyran product was obtained via the radical cation method from a 6-endo cyclization despite a more kinetically favorable 5-exo pathway being available.

\[ \text{Condition A: 1.0 equiv 1, benzene, 80 °C} \]
\[ \text{Condition B: 2 (5 mol %), 0.5 equiv 3, 450 nm LEDs, DCM, 23 °C} \]
\[ \text{Condition C: TfOH, DCM, 23 °C} \]

Organocatalyzed Birch Reduction Driven by Visible Light
The **Birch reduction** is a dissolving metal reduction of aromatic rings.

Below is the reaction of benzene with Li in liquid ammonia to give an unconjugated diene:

When Li is dissolved in ammonia, it gives an intense blue solution. This is the color of solvated electrons.

Group 1 metals (like Li and Na) ionize to give Li\(^+\) or Na\(^+\) and e\(^-\)(NH\(_3\))\(_n\)

\[
\text{Li} \quad \text{Fast} \rightarrow \text{Li}^\oplus + e^\oplus[NH_3]^\ominus \quad \text{Slow} \rightarrow \text{NH}_2 + H \rightarrow \frac{1}{2} \text{H}_2
\]
Birch Reduction of Arenes

• Since reducing NH$_3$ to NH$_2^-$ and H$_2$ is quite slow, better electron acceptors will be preferentially reduced.

• Our benzene example will follow the mechanism outlined below:
Birch Reduction of Arenes

- What if we have substituents on the aromatic ring?

  - **Electron-withdrawing groups promote ipso, para Birch reductions**
  - **Electron-donating groups promote ortho, meta Birch reductions**

  ![Electron-withdrawing example](image)

  ![Electron-donating example](image)
Birch Reduction of Arenes

- Electron-withdrawing groups stabilize electron density at the \textit{ipso} and \textit{para} positions while electron-donating groups stabilize ortho and meta electron density.
Organocatalyzed Birch Reduction Driven by Visible Light

• Classic Birch reductions involve the use of dangerous reagents and challenging reaction conditions

• The harsh conditions also limits the functional group compatibility

• Photochemical Birch reductions of arenes with visible light have remained elusive due to the requirement from strong reducing potentials (−3.42 V vs. SCE), while the high triplet energy of benzene (3.6 eV) prevents triplet energy sensitization

• As the mechanism for the classical Birch reaction involves solvated electrons, Garret Miyake and coworkers hypothesized that solvated electrons could be generated photochemically

• You may remember this process as trivial electron transfer
The simple two-step mechanism for trivial electron transfer is shown below:

\[
D + h\nu \rightarrow *D \rightarrow D^\bullet + e^\bullet_{solv}
\]

\[
e^\bullet_{solv} + A \rightarrow A^{*-}
\]

- In this case, the “emitted” species is an electron, which immediately becomes surrounded by solvent to yield a “solvated electron” \(e^\bullet_{solv}\).
- The electron is then “absorbed” by a suitable acceptor to form a radical anion \(A^{*-}\).
- Eq 10 is the primary photochemical process termed \textit{photoionization}, which may involve a transient excited state (*D).
- Nearly all molecules undergo photoionization when they absorb a photon whose energy \((E = h\nu)\) exceeds the ionization potential of a molecule in solution.
- Lasers can produce very high [photons] that are absorbed by D. The [photons] can be so high that *D can then absorb a second photon to cause photoionization.
Miyake and coworkers envisioned that consecutive photoinduced electron transfer system could be employed to access solvated electrons.

The system, as shown below, involves generating the radical anion (one-electron reduced form) of the photocatalyst, which is then excited and photoionized.

\[ \text{Organocatalyzed Birch Reduction Driven by Visible Light} \]

---

\[ \text{J. Am. Chem. Soc. 2020, 142, 13573.} \]
**Reaction Scope**

**a General Reaction Conditions**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>51%</td>
</tr>
</tbody>
</table>

**b Photoredox Catalyzed Birch Reduction**

- **1**: 70%, 52%, 10 mmol scale
- **2**: 62%
- **3**: 51%
- **4**: 48%
- **5**: 24%
- **6**: 63%
- **7**: 40%
- **8**: 38%
- **9**: 32%
- **10**: 48%
- **11**: 80%
- **12**: 71%
- **13**: 47%
- **14**: 38%
- **15**: 75%
- **16**: 72%
- **17**: 82%
- **18**: 40%

**Conditions**

- PC (0.75-1.25 mol%)  
- NMe₂OH (10 eq)  
- MeOH/AmylOH  
- 405 nm LED  
- Ambient temperature  
- 96-144 h
Their proposed mechanism for the organocatalyzed Birch reduction is shown below: