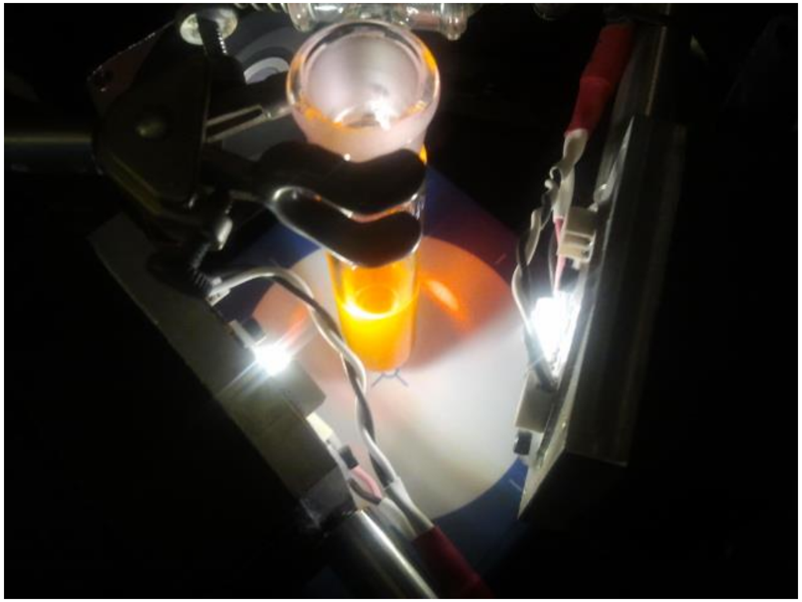
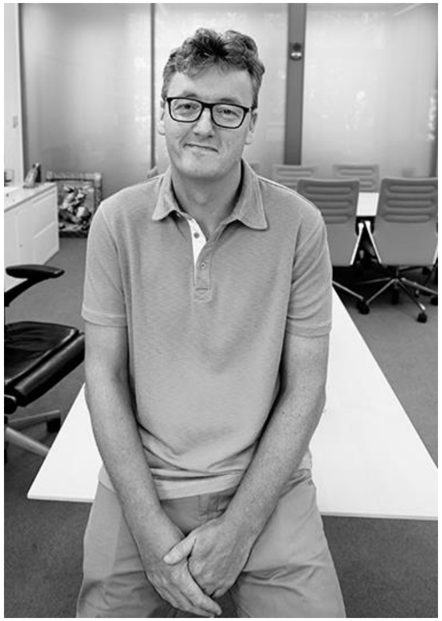
Photoredox Catalysis



CHEM 6420

Meet the Authors



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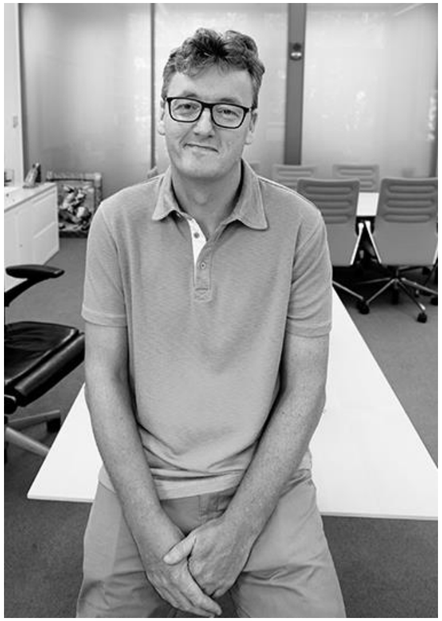
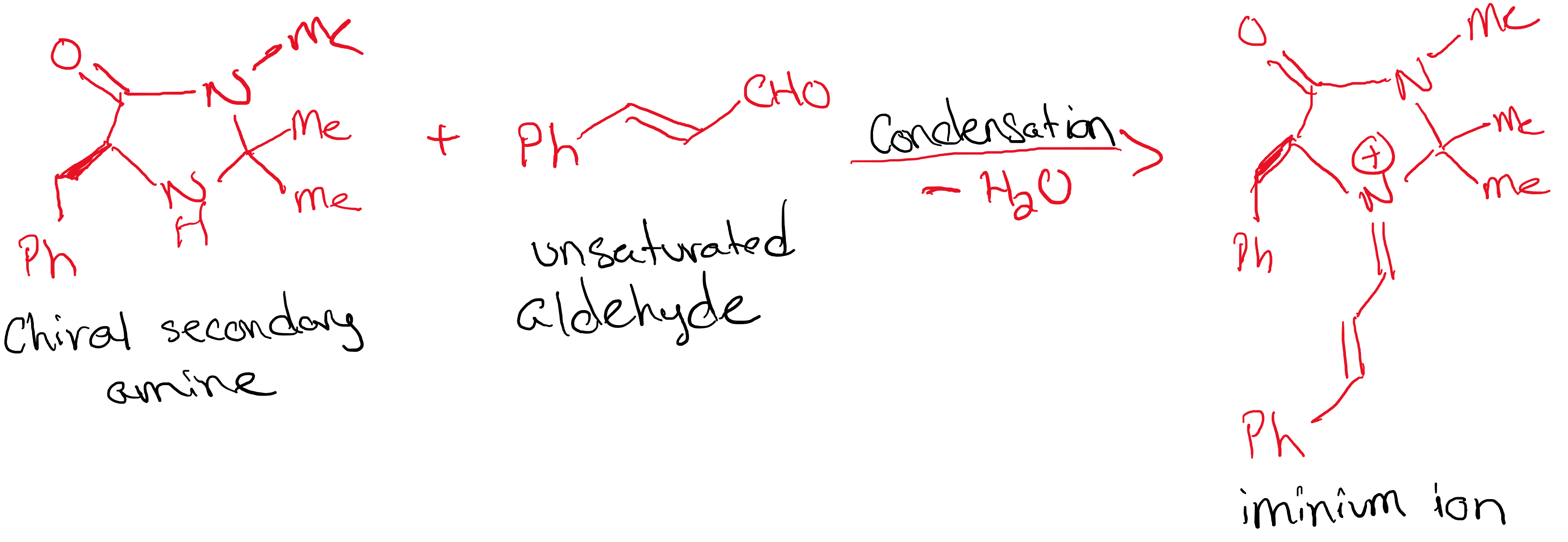


Merging Photeredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes

Review: Organocatalysis

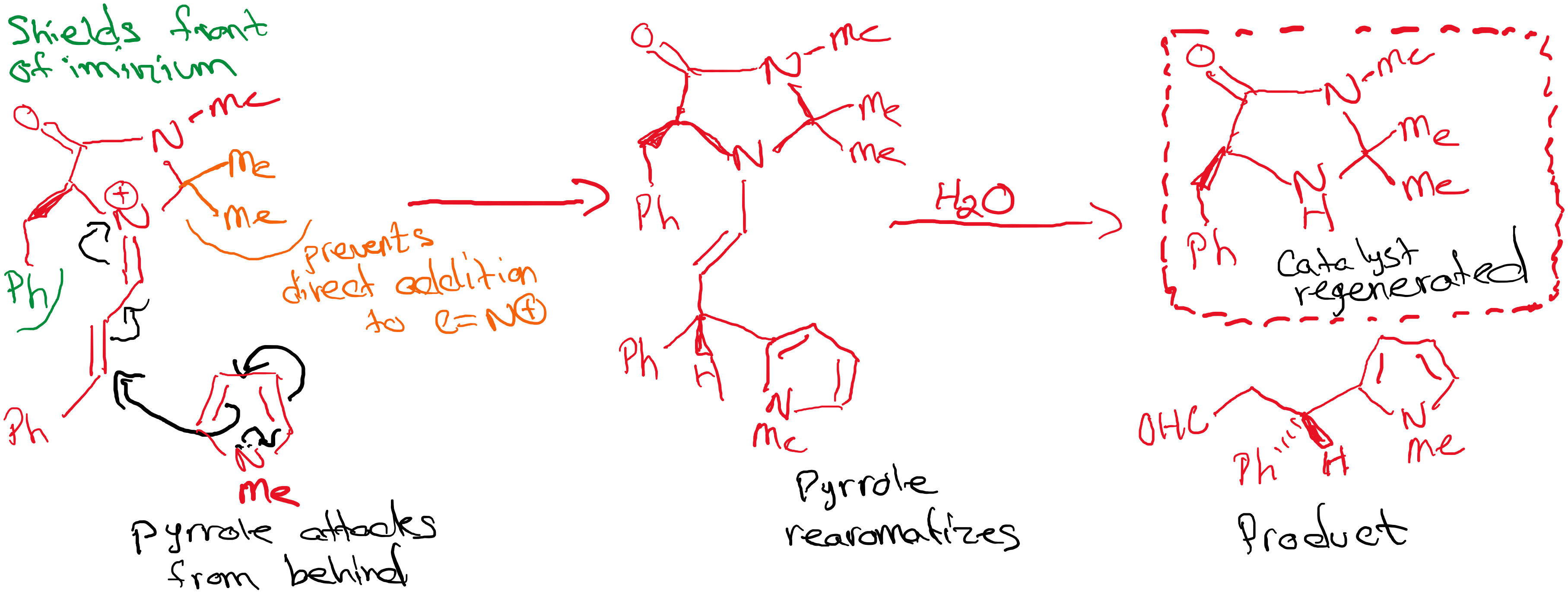
- As we know from undergraduate organic chemistry, aldehydes and ketones react with secondary amines to form enamines, via iminium ions
- In the reaction below, however, the unsaturated aldehyde cannot form an enamine because the iminium ion generated by condensation with the cyclic secondary amine cannot lose a proton



- The iminium ion is highly reactive towards water and other nucleophiles

Review: Organocatalysis

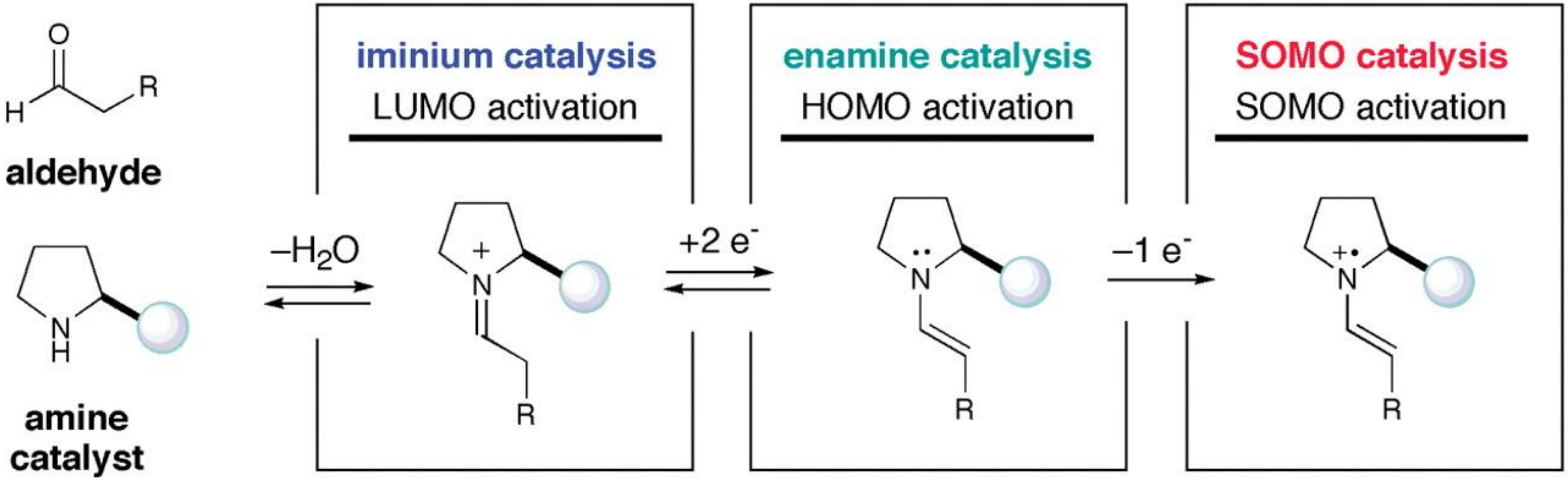
- If this condensation is done in the presence of a weak nucleophile – strong enough to attach the iminium but not strong enough to attach the aldehyde – an addition reaction takes place



- This catalyst and strategy were invented by **David MacMillan** at the California Institute of Technology (now at Princeton) and was given the name “organocatalysis”

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 3π-electron radical cation (termed SOMO-activation)

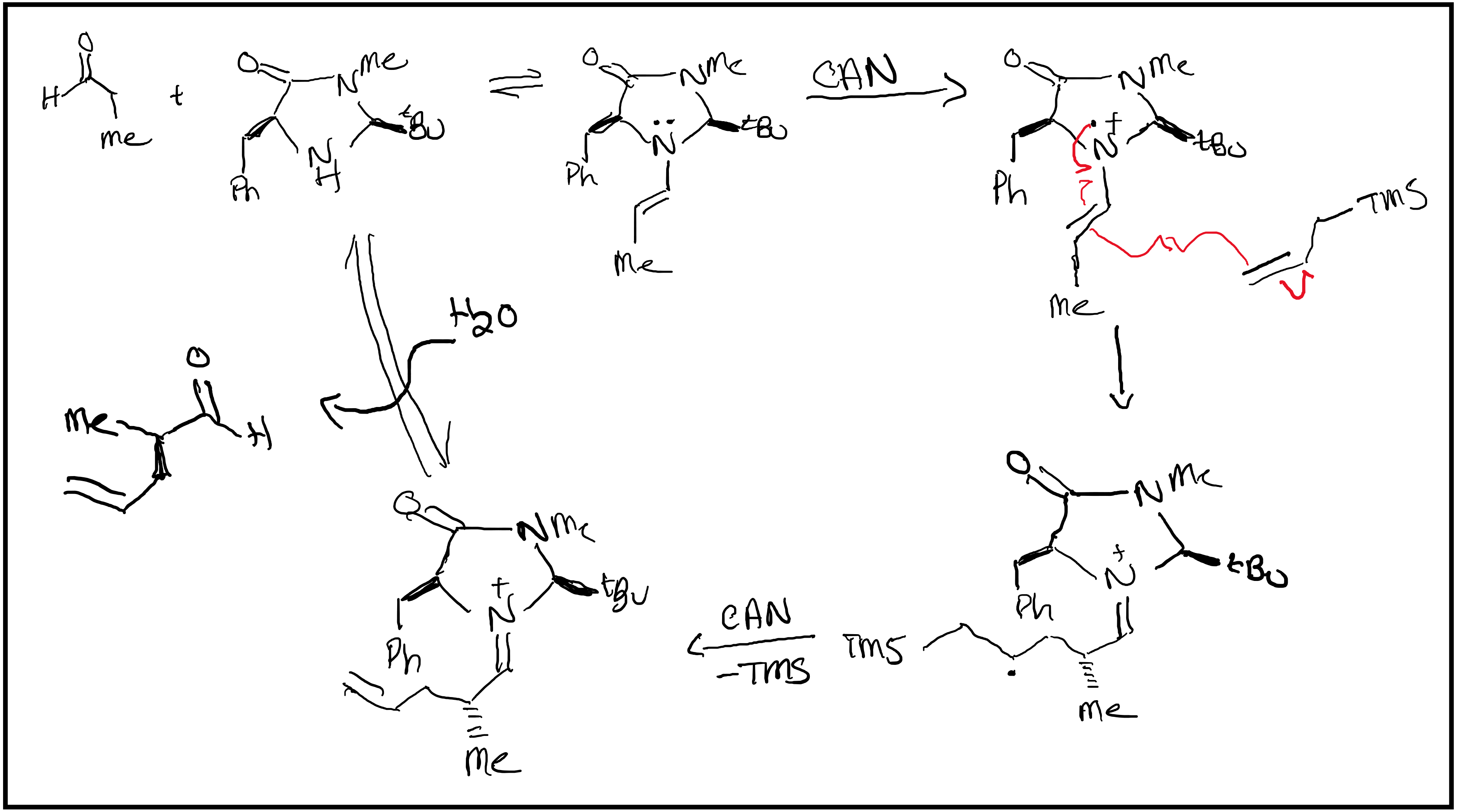


- This strategy greatly expanded the scope of transformations possible with amine organocatalysis

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

SOMO-Catalysis: Aldehyde α-Allylation

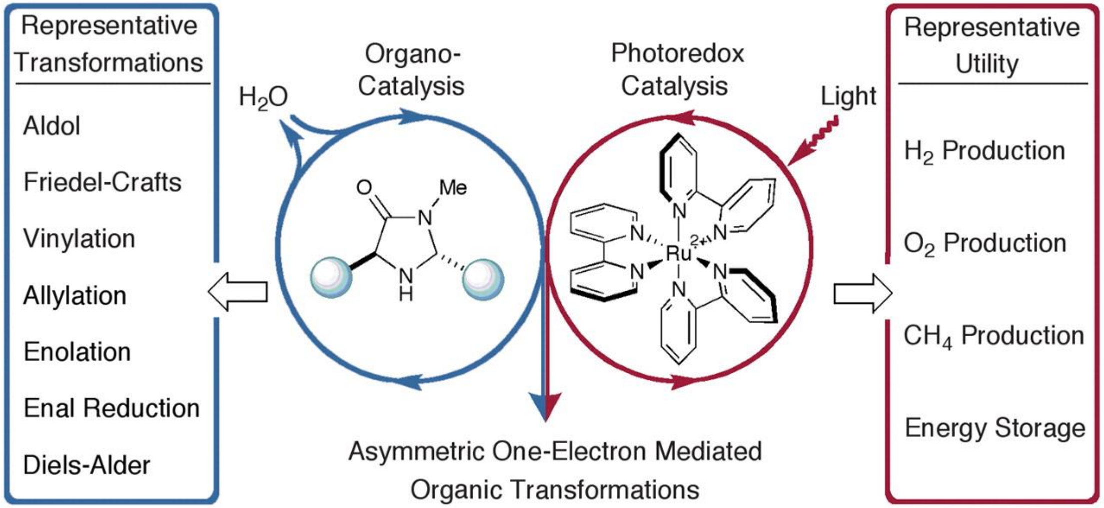
- The MacMillan group first employed this strategy for the α-allylation of aldehydes (mechanism shown below)

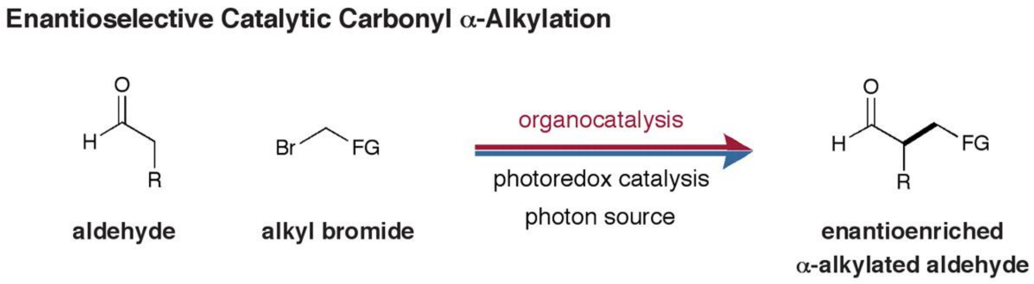


Science **2007**, *316*, 582

Merging Organo- and Photoredox Catalysis

- 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 $Ru(bpy)_3Cl_2$ for the alkylation of aldehydes

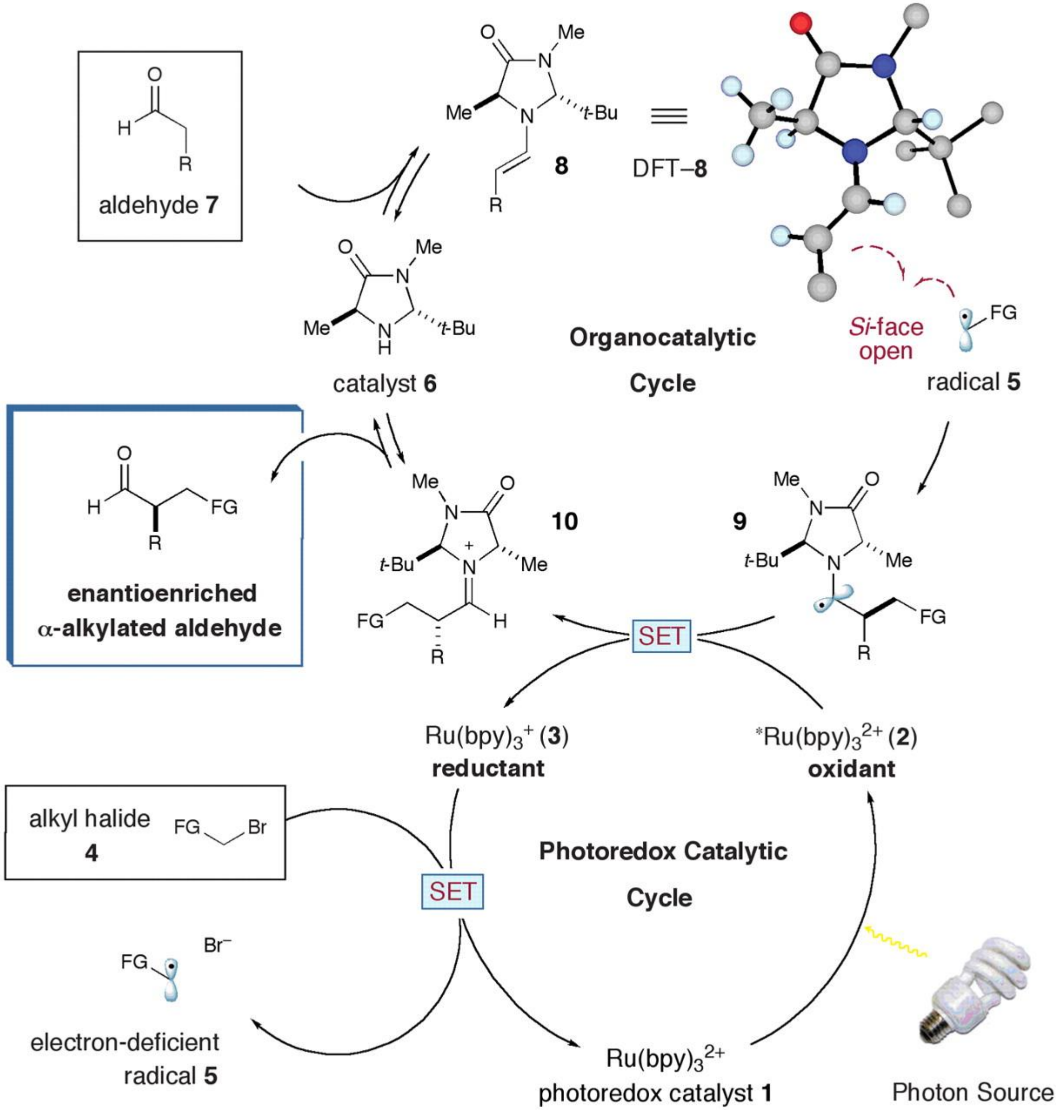




Science **2008**, *322*, 77.

Proposed Mechanism

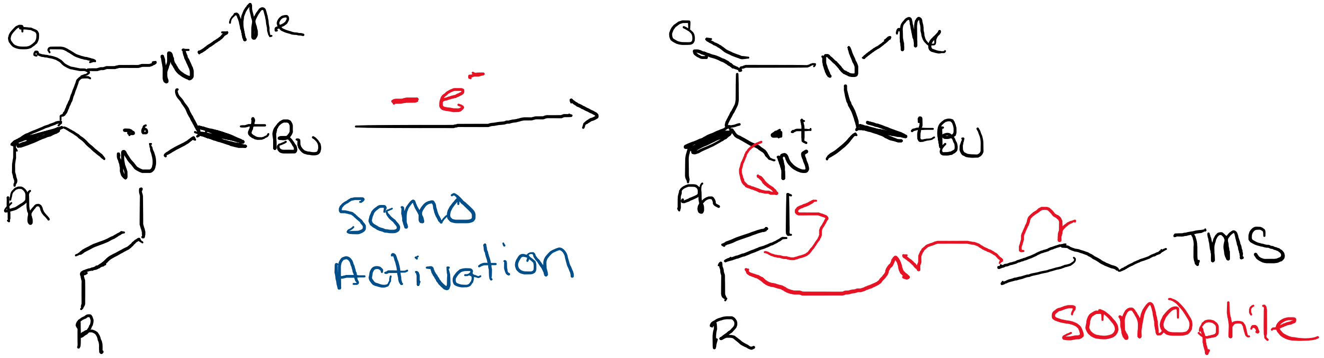
- MacMillan’s proposed mechanism for the alkylation of aldehydes



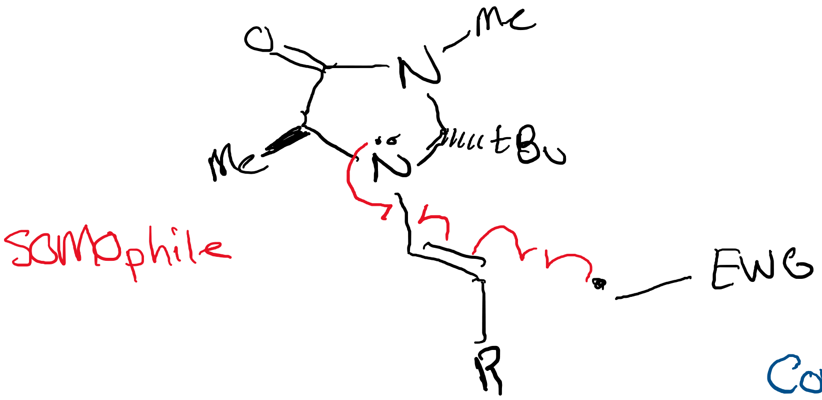
Science **2008**, *322*, 77.

SOMO-Catalysis vs. Dual Organo- and Photoredox Catalysis

- 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



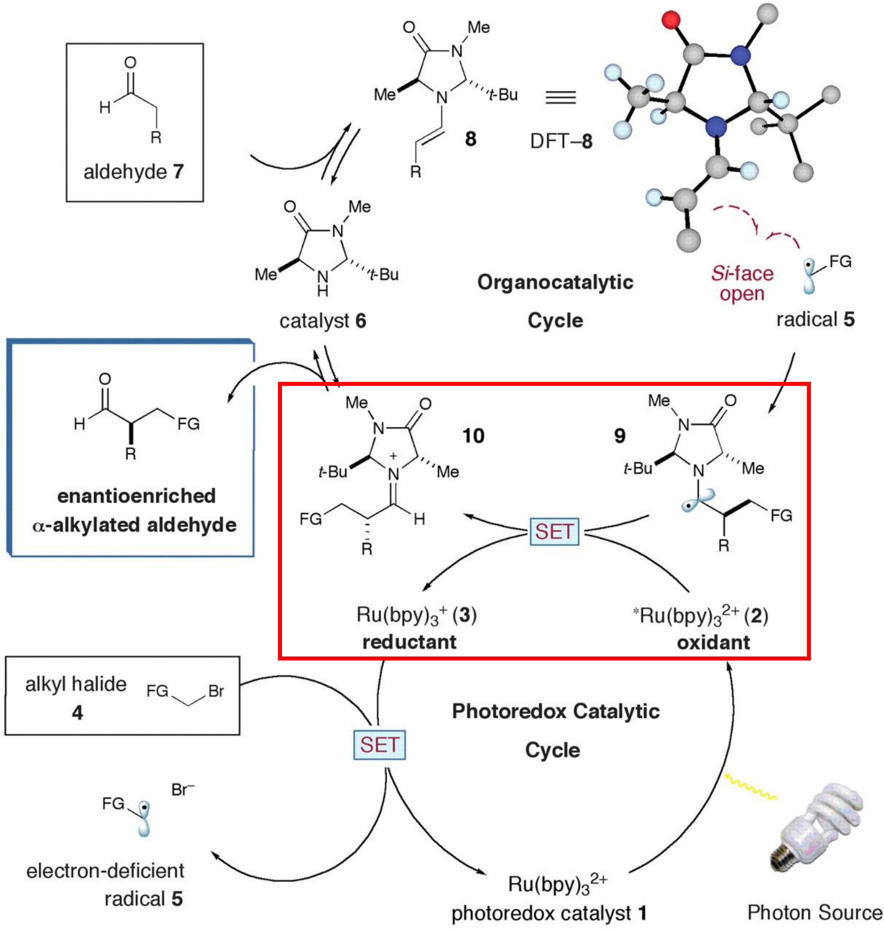
EWG = Electron-withdrawing group

Contrasting reactivity

Science **2007**, *316*, 582.; *Science* **2008**, *322*, 77.

Reexamining the Proposed Mechanism

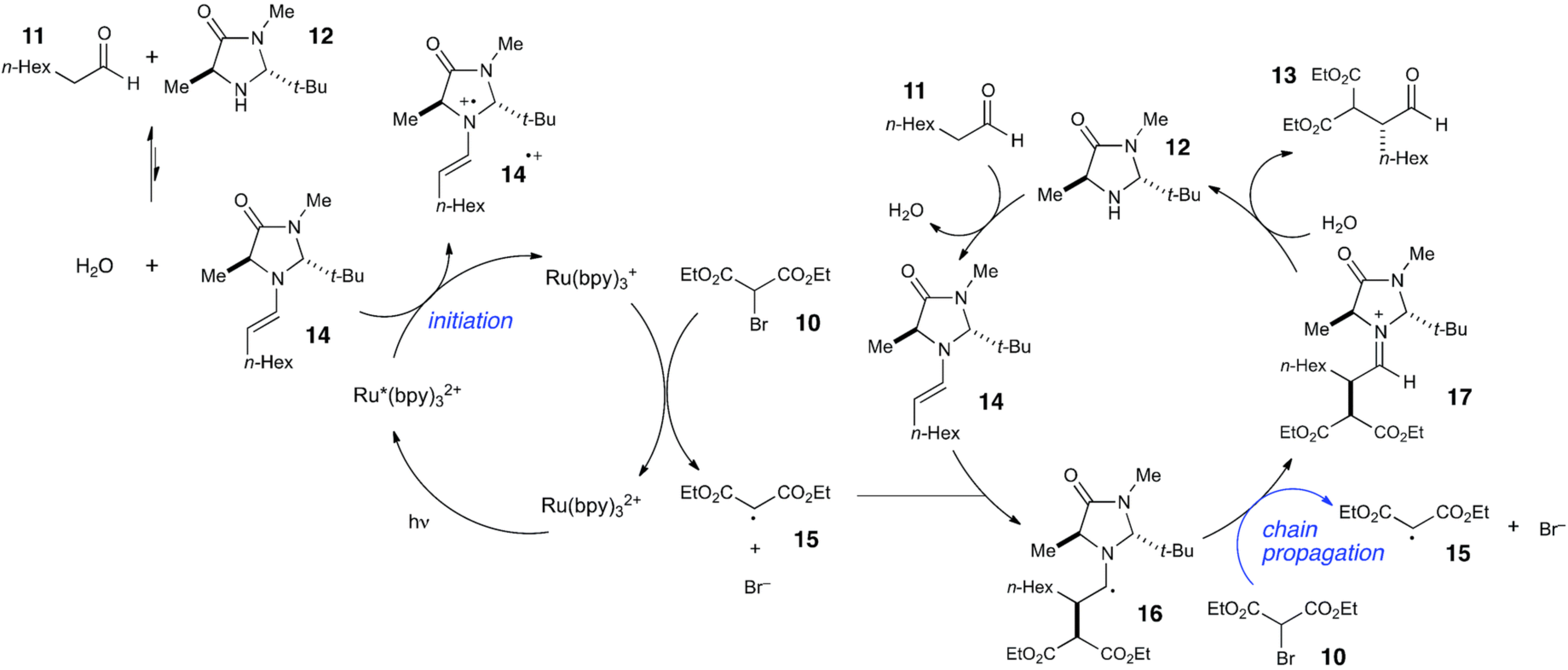
- Let’s take a closer look at the mechanism proposed by MacMillan
- One of the key steps in the photoredox cycle involves the single-electron transfer to *$Ru(bpy)_3Cl_2$ from the α-aminoradical intermediate (**9**)
- The proposed *closed* catalytic cycle requires the encounter of two low concentration 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*



Science **2008**, *322*, 77.

Revised Mechanism from Yoon

- This possibility was examined by Yoon and coworkers
- They determined that the quantum yield (Φ) 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 $^{*}Ru(bpy)_3Cl_2$
- They determined that *only* the enamine quenched the emission of $Ru(bpy)_3Cl_2$, with $K_{SV} = 10\ M^{-1}$
- Knowing $\tau_0 = 912$ ns in DMF, we can calculate the probability that the enamine quenches the excited state

$$k_q = \frac{K_{SV}}{\tau_0} = \frac{10\ M^{-1}}{(912 \times 10^{-9}\ s)} = 1.1 \times 10^{7}\ M^{-1} s^{-1}$$

$$\%\ {}^{3}Ru(bpy)_3^{2+}\ \text{Quenched by enamine} = \frac{k_q[\text{enamine}]}{\tau_0^{-1} + k_q[\text{enamine}]} \times 100\ \%$$

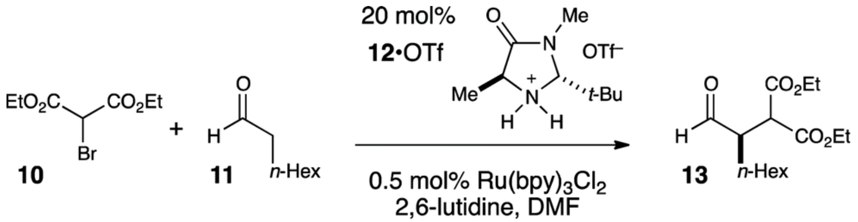
$$= \frac{(1.1 \times 10^{7}\ M^{-1} s^{-1})(0.018\ M)}{(912 \times 10^{-9}\ s)^{-1} + (1.1 \times 10^{7}\ M^{-1} s^{-1})(0.018\ M)} \quad \leftarrow \text{estimated by NMR}$$

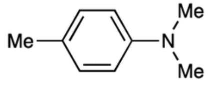
$$= 15\ \%$$

Science **2008**, *322*, 77.; *Chem. Sci.* **2015**, *6*, 5426.

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





18

$k_q = 3.9 \times 10^8\ M^{-1}\ s^{-1}$

	1 h
no additive	23% yield, 90% ee
+ 0.5 mol% **18**	89% yield, 88% ee

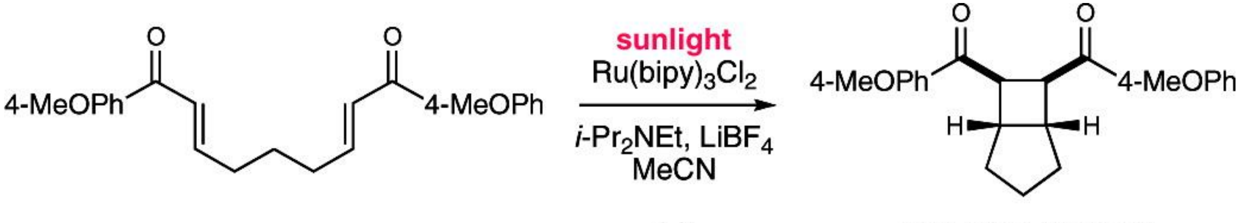
- Let's calculate the probability that $*Ru(bpy)_3Cl_2$ is quenched by *N,N*-dimethyl-*p*-toluidine (**18**)

$[18] = 0.0017\ M$

% $Ru(bpy)_3^{2+}$ Quenched by 18 $= \dfrac{(3.9 \times 10^8\ M^{-1}s^{-1})(0.0017\ M)}{(912 \times 10^{-9}\ s)^{-1} + (1.1 \times 10^7\ M^{-1}s^{-1})(0.018\ M) + (3.9 \times 10^8\ M^{-1}s^{-1})(0.0017\ M)} \times 100\ \%$

$= 34\ \%$

- From this calculation, we can see why the reaction is more efficient with the addition of a co-catalytic quencher

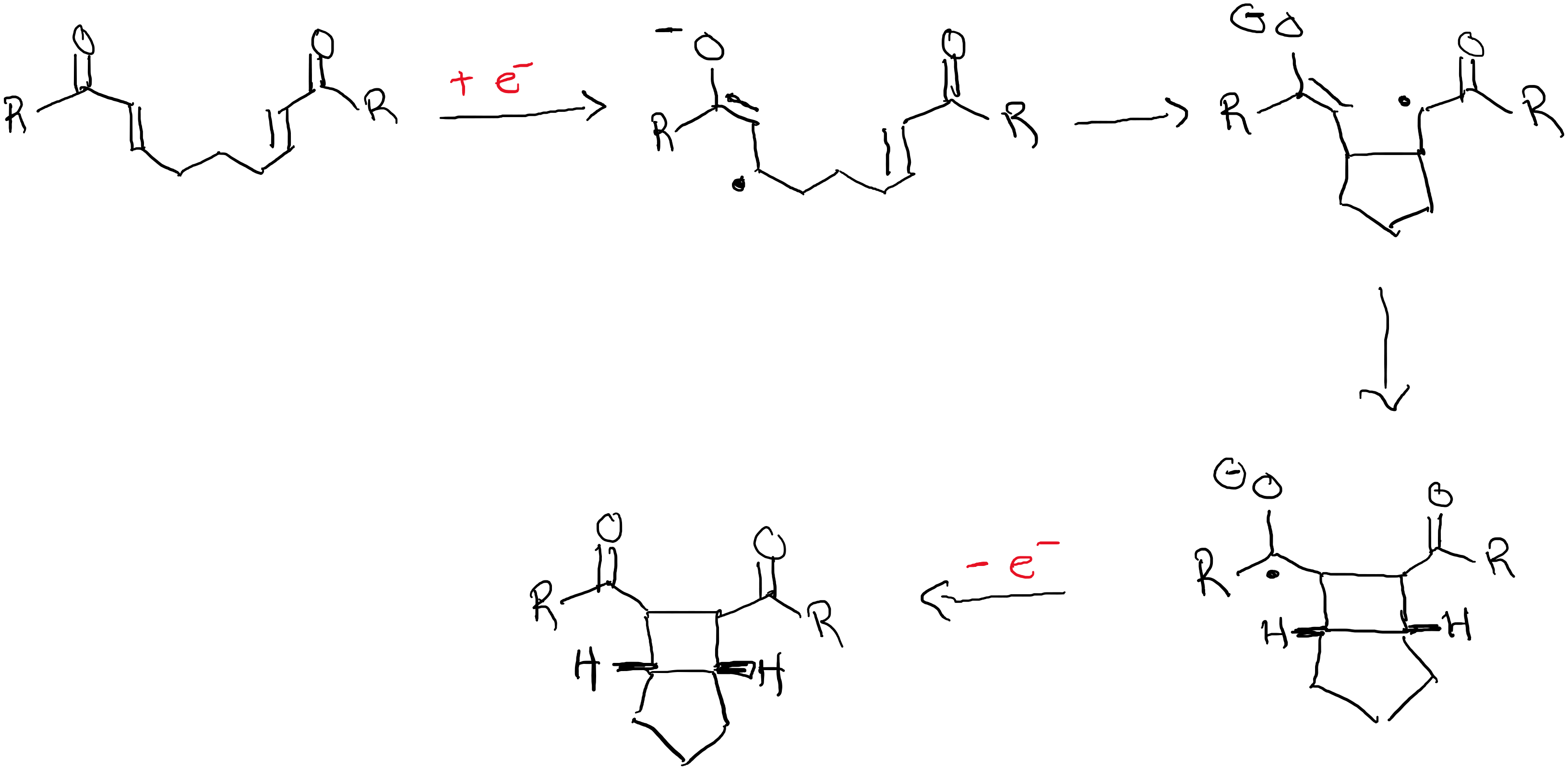


94% yield, 10:1 d.r.

Efficient Visible-Light Photocatalysis of [2+2] enone cycloadditions

[2+2] Cycloadditions of Enones

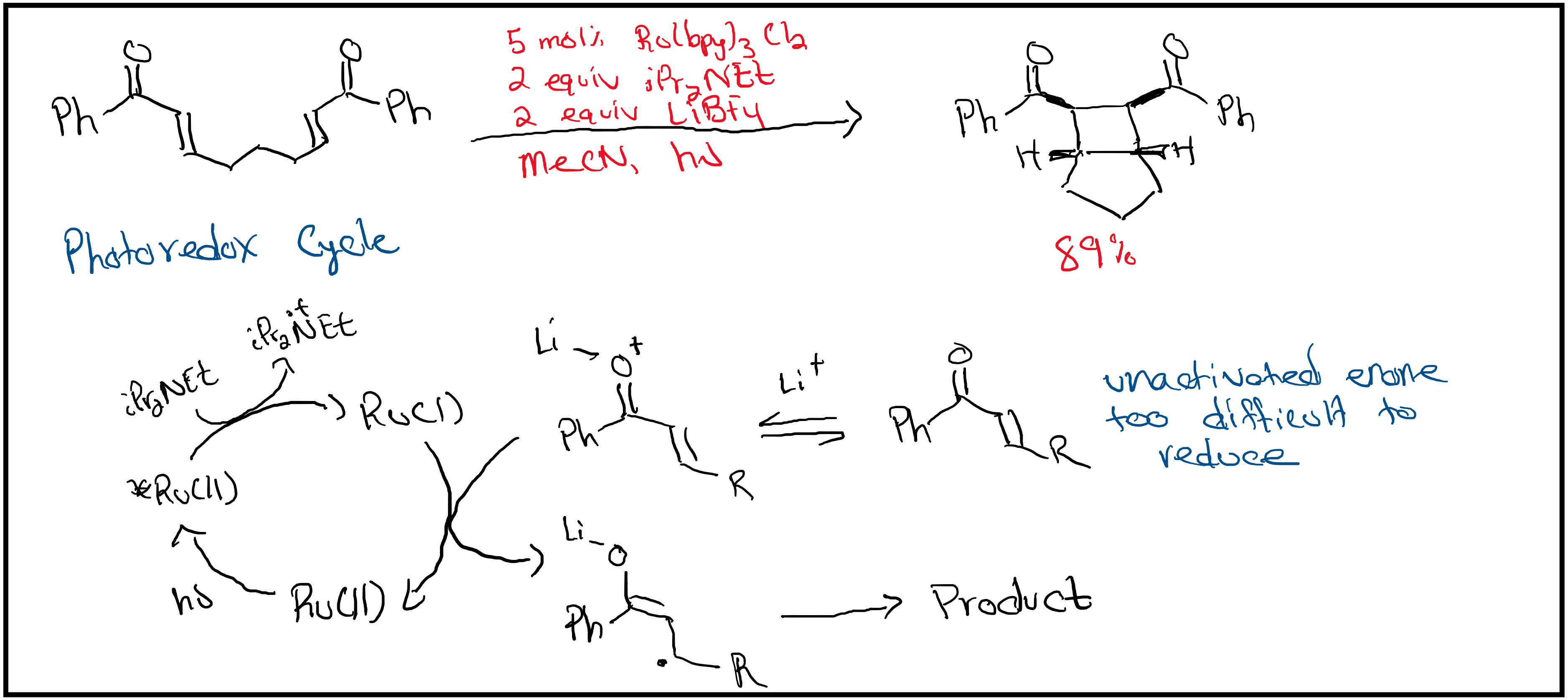
- In the early 2000s, Nathan Bauld and Michael Krische from UT Austin demonstrated that the radical anions generated from biaryl bis(enones) could undergo [2+2] cycloaddition reactions
- Their proposed mechanism is shown below:



J. Am. Chem. Soc. **2004**, *126*, 1634.

[2+2] Cycloadditions of Enones

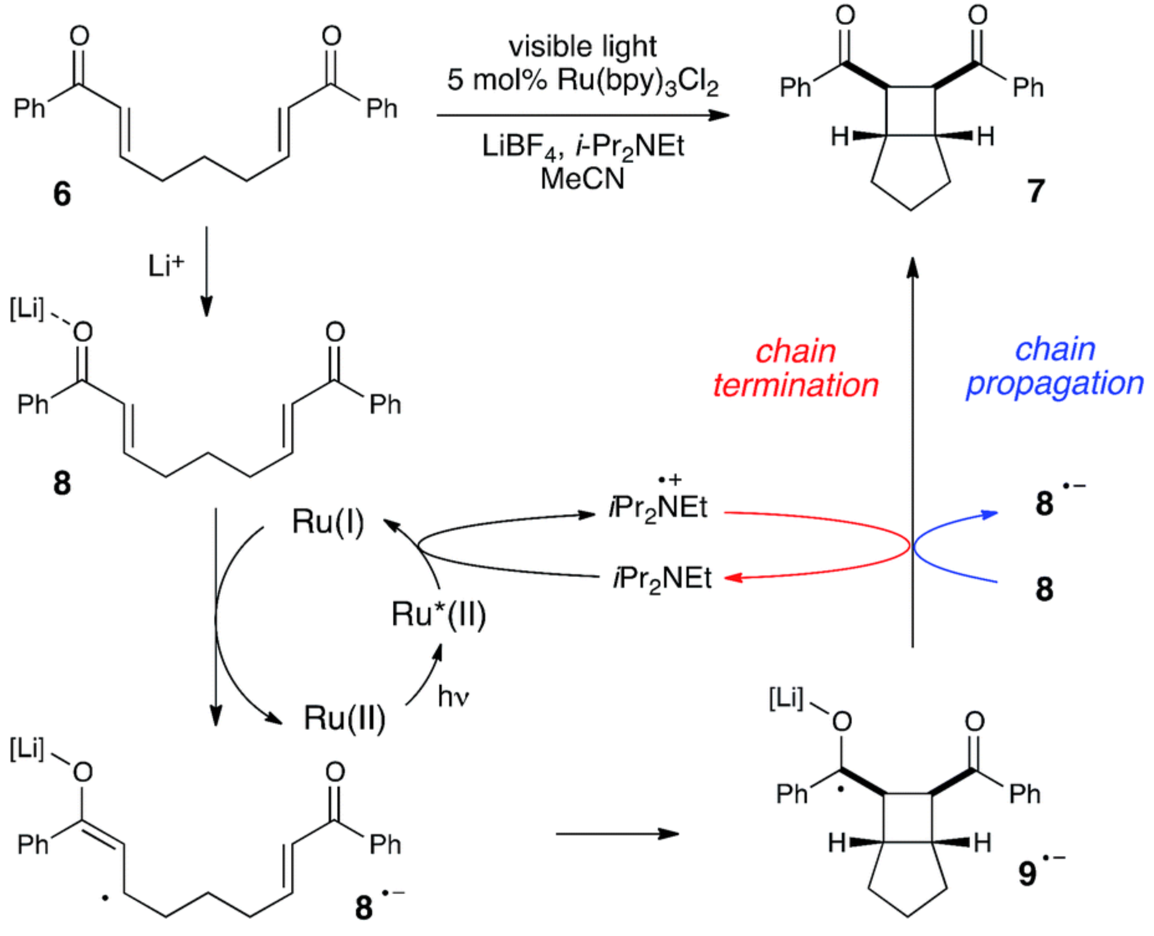
- In 2008, **Tehshik Yoon** and his group hypothesized that these radical anions could be generated using photoredox catalysis
- This was successfully accomplished using $Ru(bpy)_3Cl_2$ as the photocatalyst, *i*Pr_2NEt to reductively quench $*Ru(bpy)_3Cl_2$, and $LiBF_4$ as a Lewis acid to activate the enone towards reduction



J. Am. Chem. Soc. **2008**, *130*, 12886.

[2+2] Cycloadditions of Enones

- Years later, Yoon and coworkers calculated the quantum yield (Φ) of this reaction to be 77, which can only be consistent with a chain mechanism
- They proposed the revised mechanism shown below:



Chem. Sci. **2015**, *6*, 5426.

Stern–Volmer Analysis

- To provide evidence for their proposed mechanism, they used Stern–Volmer analysis to examine the excited state kinetics
- They determined that only $i\mathrm{Pr_2NEt}$ resulted in any luminescence quenching, with a $K_{SV} = 6.6\ \mathrm{M^{-1}}$
    - Indicates the proposed reductive quenching cycle is most probable
- As $\tau_0 = 855$ ns in MeCN, let's calculate the probability that $i\mathrm{Pr_2NEt}$ quenches $\mathrm{{}^*Ru(bpy)_2Cl_2}$

$[i\mathrm{Pr_2NEt}] = 0.2\ \mathrm{M}$

$$k_q(i\mathrm{Pr_2NEt}) = \frac{6.6\ \mathrm{M^{-1}}}{(855 \times 10^{-9}\ \mathrm{s})} = 7.9 \times 10^{6}\ \mathrm{M^{-1}s^{-1}}$$

$$\%\ \mathrm{{}^3Ru(bpy)_3^{2+}}\ \text{Quenched by } i\mathrm{Pr_2NEt} = \frac{(7.9 \times 10^{6}\ \mathrm{M^{-1}s^{-1}})(0.2\ \mathrm{M}) \times 100\ \%}{(855 \times 10^{-9}\ \mathrm{s})^{-1} + (7.9 \times 10^{6}\ \mathrm{M^{-1}s^{-1}})(0.2\ \mathrm{M})}$$

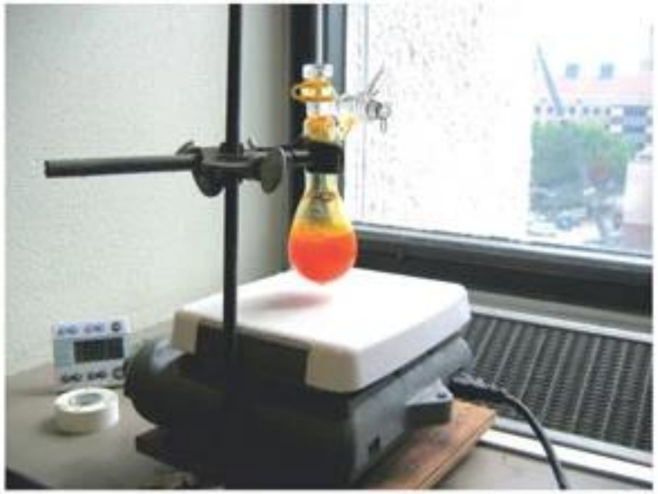
$= 57\ \%$

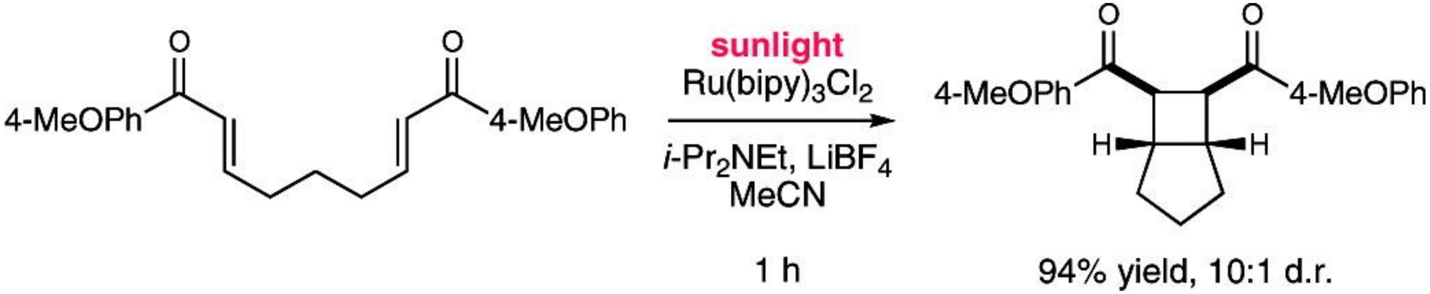
* No other terms in denominator as other reactants do not quench $\mathrm{{}^3Ru(bpy)_3^{2+}}$

Chem. Sci. **2015**, *6*, 5426.

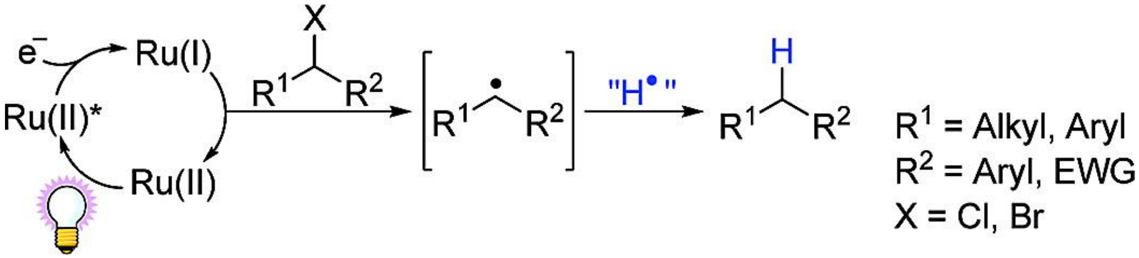
Use of Sunlight

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





J. Am. Chem. Soc. **2008**, *130*, 12886.



Electron-Transfer Photoredox Catalysis: Development of a Tin-Free Reductive Dehalogenation Reaction

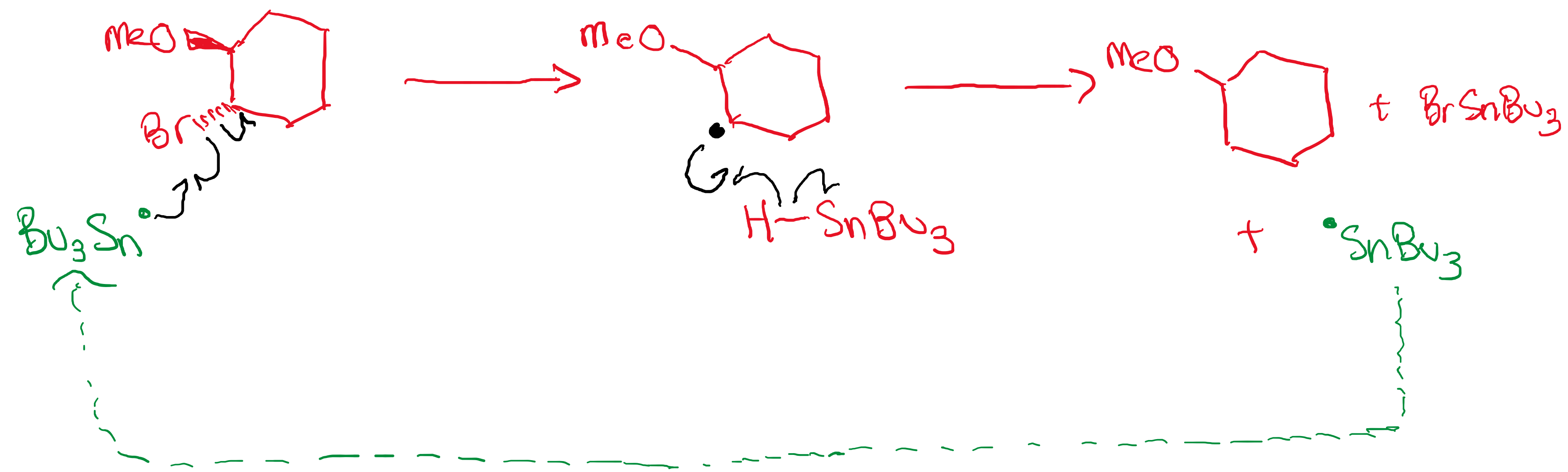
Reductive Dehalogenations

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

Initiation

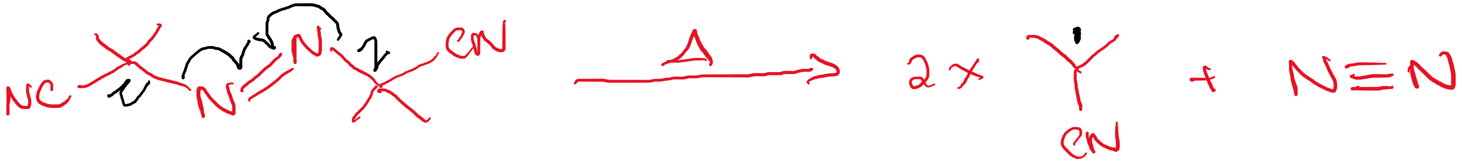
$$Bu_3Sn-H \xrightarrow{h\nu} Bu_3Sn^{\bullet} + H^{\bullet}$$

Propagation

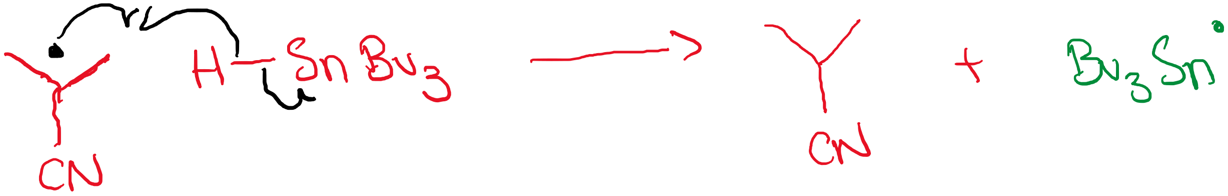


Reductive Dehalogenation

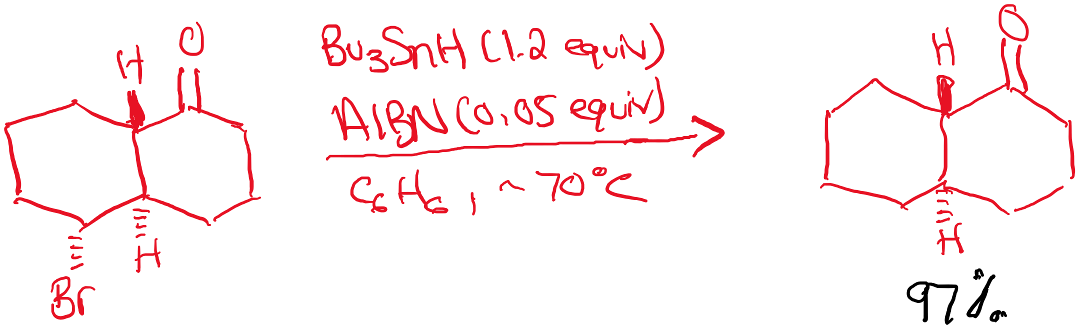
- Typically, reductive dehalogenations with H–$SnBu_3$ are initiated with AIBN



AIBN



Example Reaction



The Tin Problem

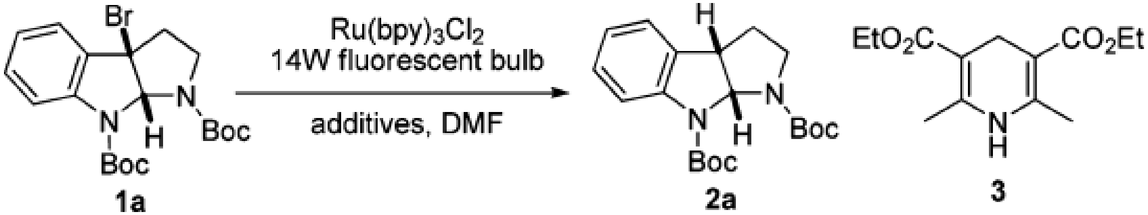
- Tributyltin hydride, as well as other tributyltin-based compounds, are well-documented to be toxic, *especially to marine life*

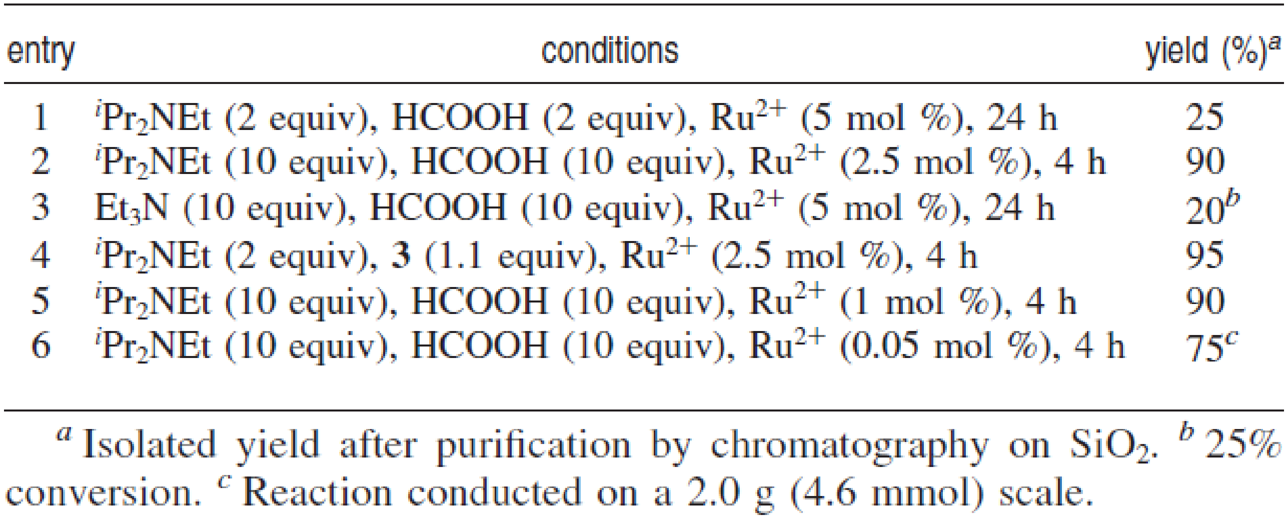
- Tributyltin has been demonstrated to cause impairments to growth, development, reproduction, and survival of many marine species

- 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**)





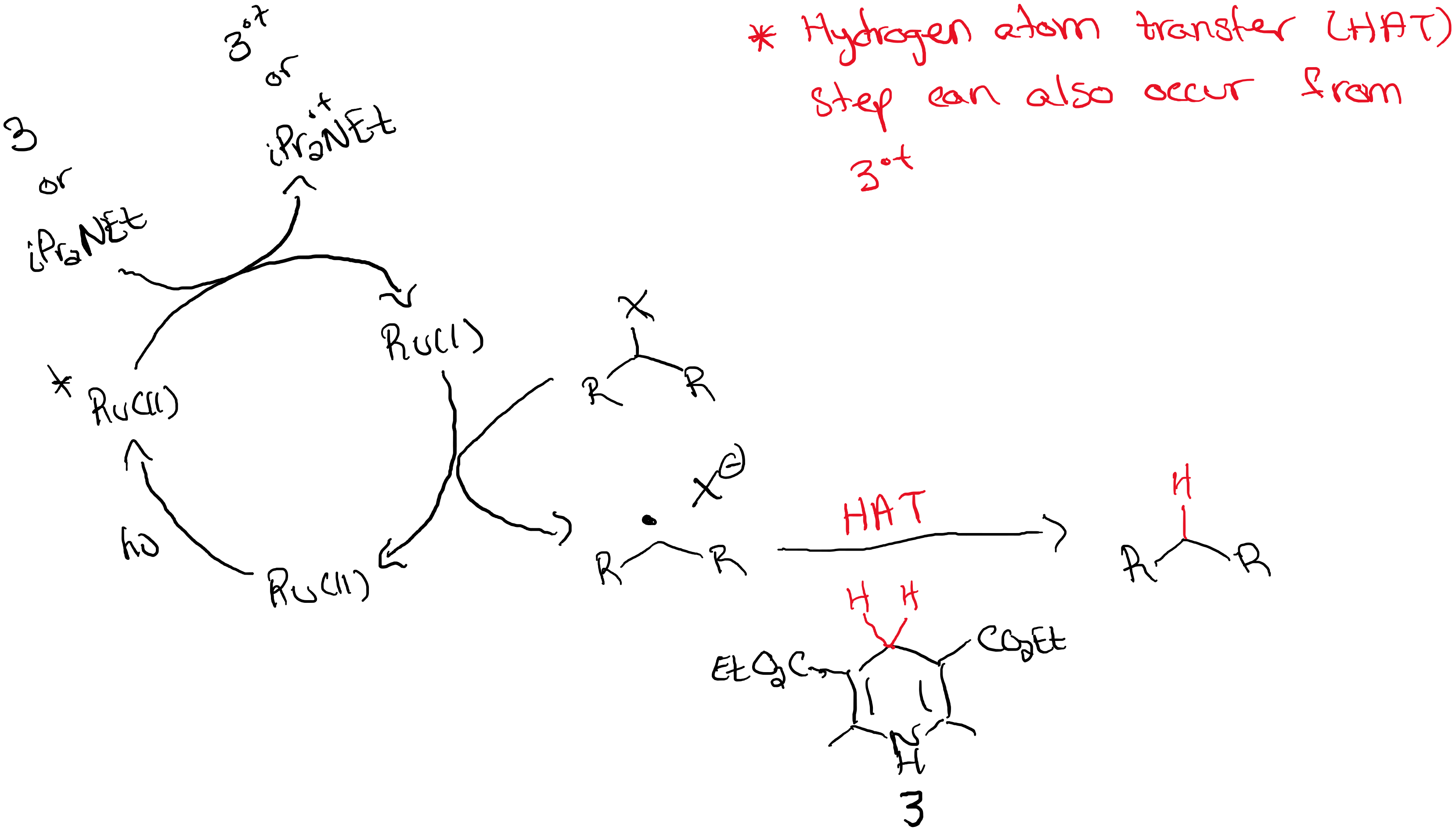
entry	conditions	yield (%)[a]
1	^{i}Pr$_2$NEt (2 equiv), HCOOH (2 equiv), Ru^{2+} (5 mol %), 24 h	25
2	^{i}Pr$_2$NEt (10 equiv), HCOOH (10 equiv), Ru^{2+} (2.5 mol %), 4 h	90
3	Et$_3$N (10 equiv), HCOOH (10 equiv), Ru^{2+} (5 mol %), 24 h	20[b]
4	^{i}Pr$_2$NEt (2 equiv), **3** (1.1 equiv), Ru^{2+} (2.5 mol %), 4 h	95
5	^{i}Pr$_2$NEt (10 equiv), HCOOH (10 equiv), Ru^{2+} (1 mol %), 4 h	90
6	^{i}Pr$_2$NEt (10 equiv), HCOOH (10 equiv), Ru^{2+} (0.05 mol %), 4 h	75[c]

[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.

J. Am. Chem. Soc. **2009**, *131*, 8756.

Proposed Mechanism

- Let’s examine the proposed mechanism for the conditions using *i*Pr_2NEt and Hantzsch ester

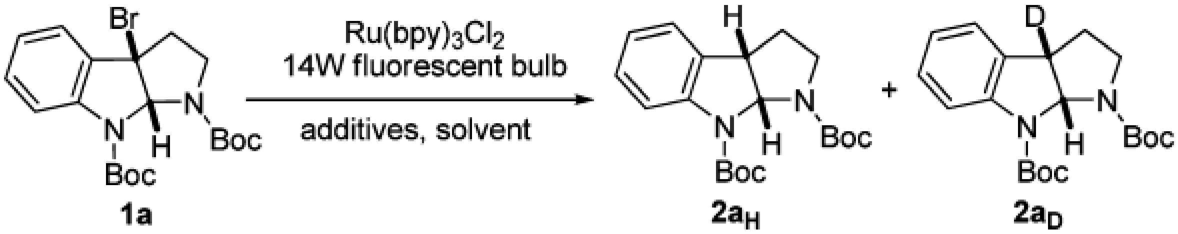


* Hydrogen atom transfer (HAT) step can also occur from $3^{\bullet+}$

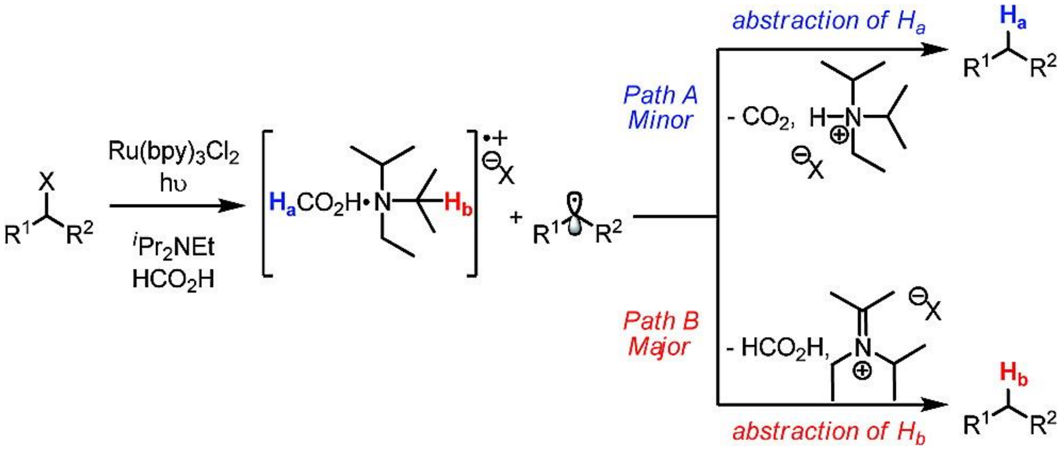
J. Am. Chem. Soc. **2009**, *131*, 8756.

Where does the Hydrogen Come From?

- For the conditions utilizing *i*Pr_2NEt and HCOOH, the origin of the hydrogen-atom in the product is slightly unclear
- Performing deuterium labeling studies using either DCO_2D and DCO_2H led to the same 4:1 distribution of H:D products

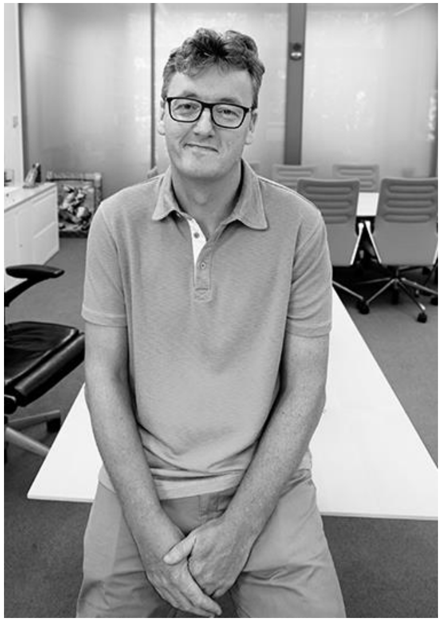


- This indicates that *i*Pr_2NEt is likely the major source of the H-atom (pathway B)



J. Am. Chem. Soc. **2009**, *131*, 8756.

Meet the Authors



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Abigail Doyle
Princeton University

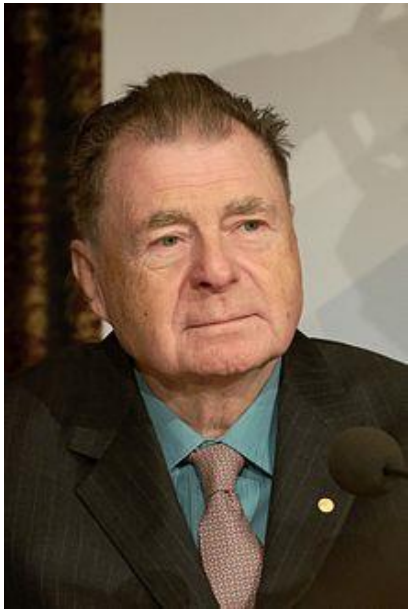
Gary Molander
University of Pennsylvania

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



Richard Heck

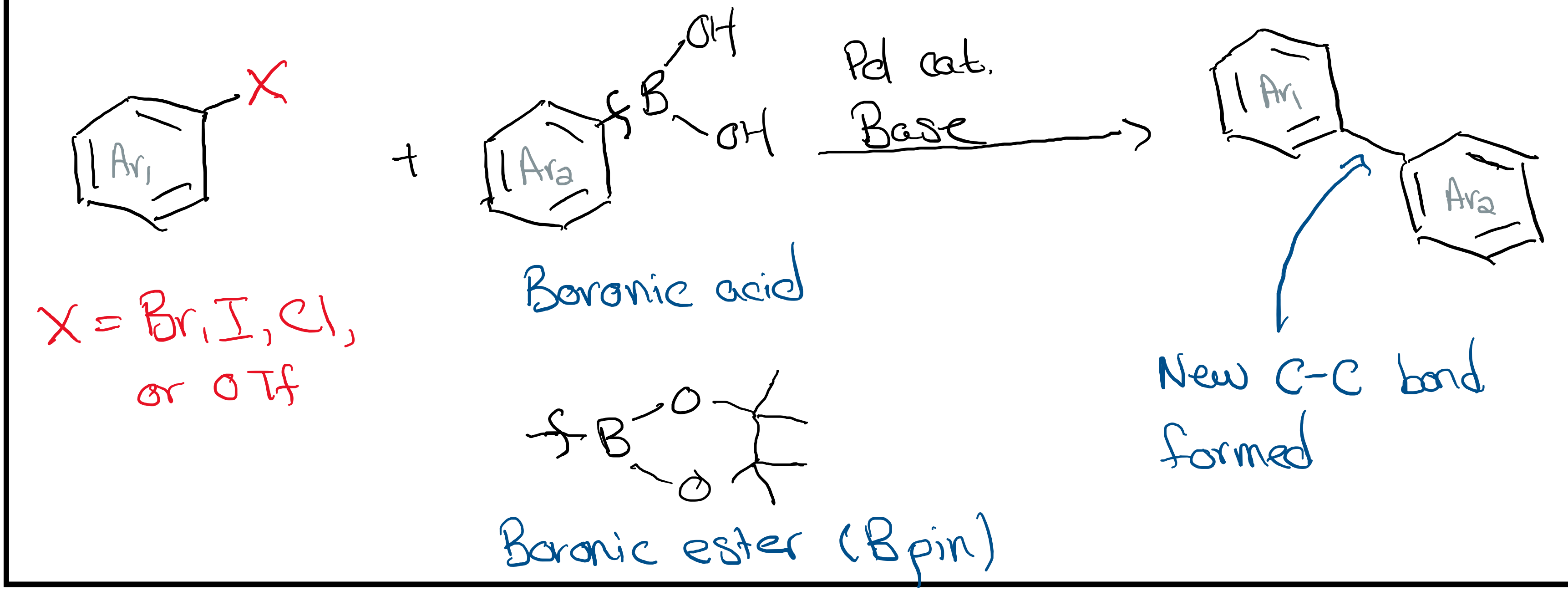
Ei-ichi Negishi

Akiro Suzuki

Suzuki–Miyaura Coupling

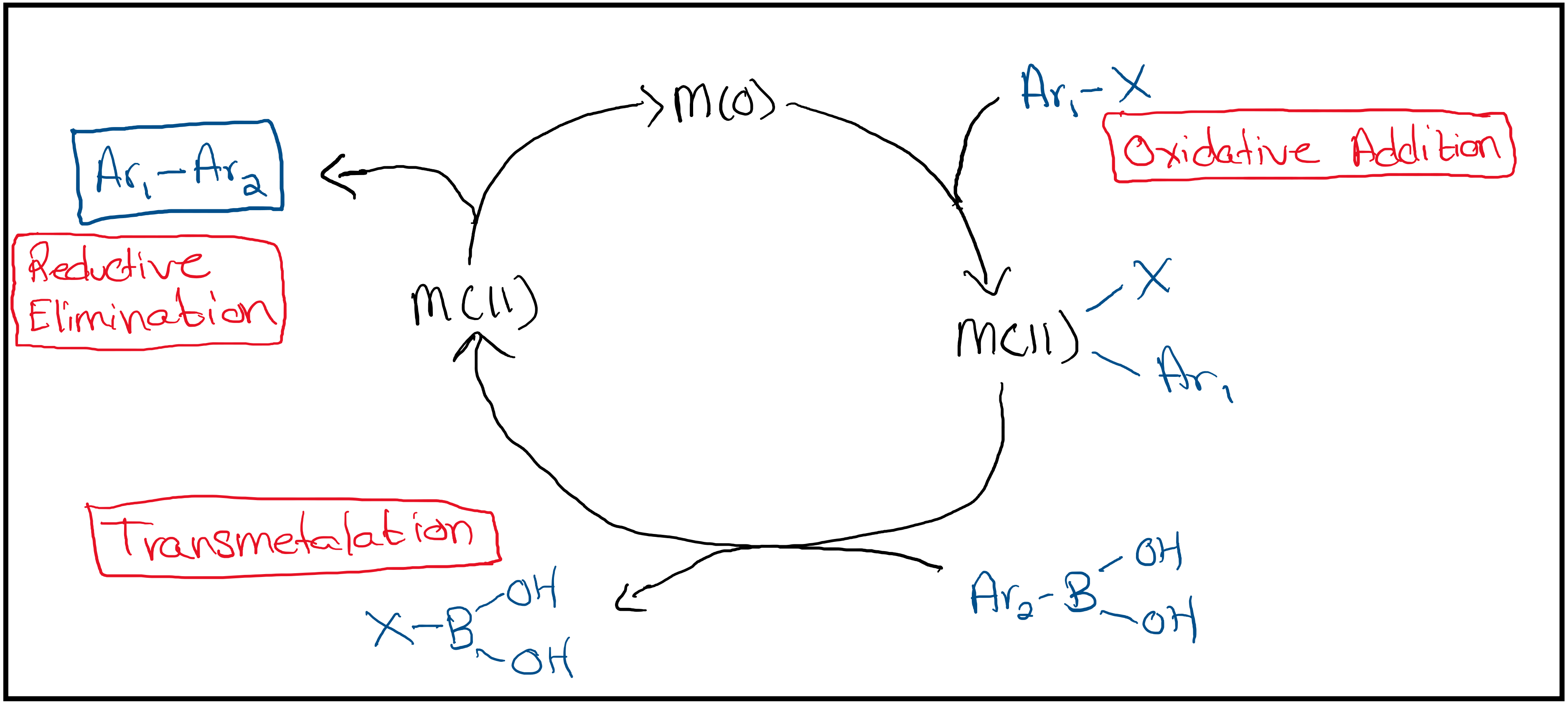
- One of the most widely used cross-coupling reactions are Suzuki–Miyaura Couplings

- 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



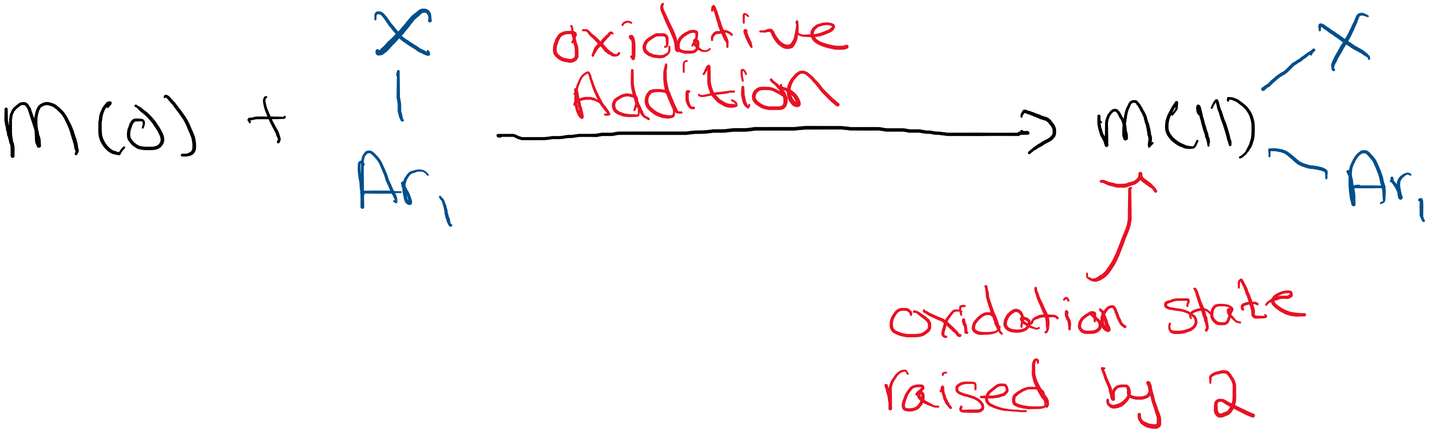
Catalytic Cycle

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



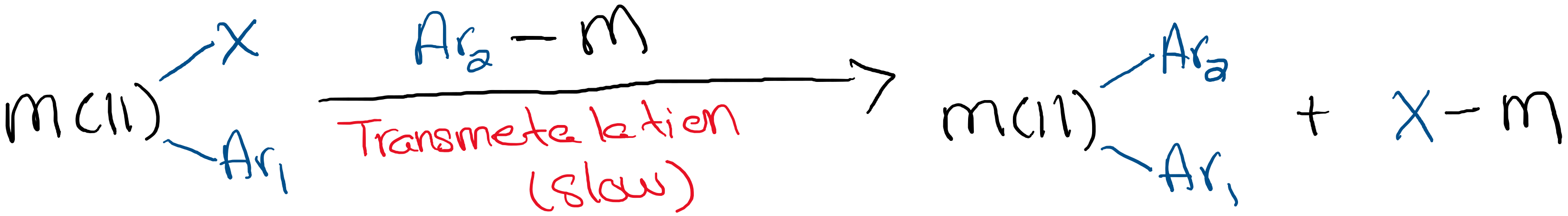
Oxidative Addition

- The first step in the catalytic cycle is oxidative addition
- Oxidative addition can be described as a transition metal atom inserts itself into a σ 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)

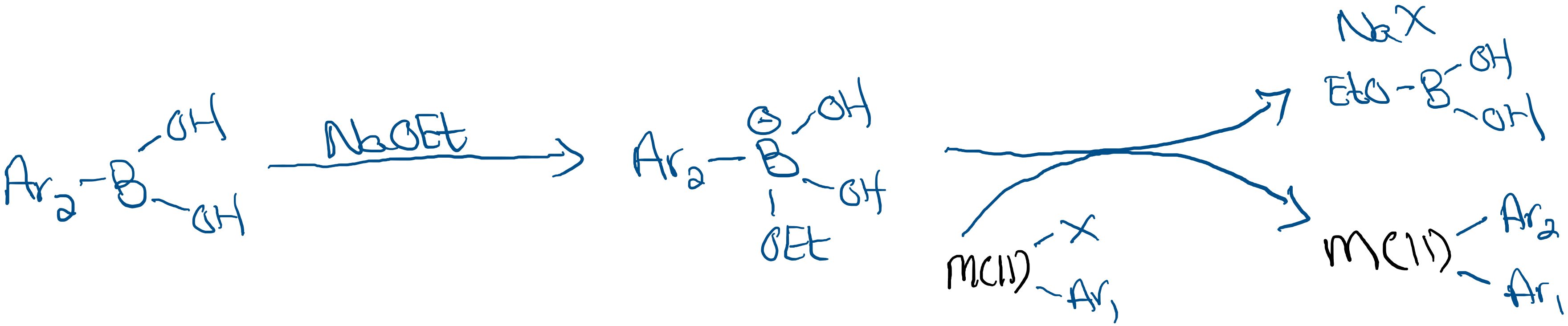


Transmetalation

- 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



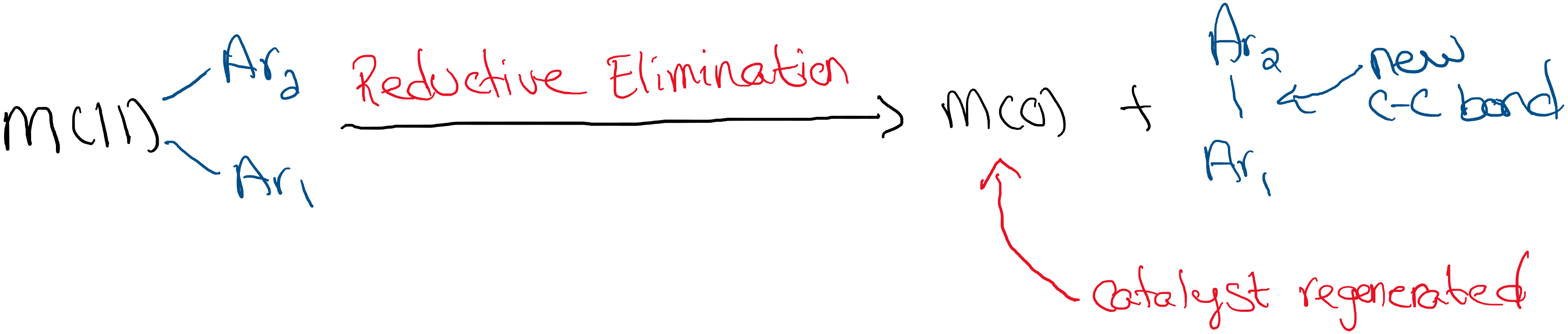
- For Suzuki–Miyaura couplings, additional base (ethoxide or hydroxide) is typically required to accelerate the transmetalation step



Reductive Elimination

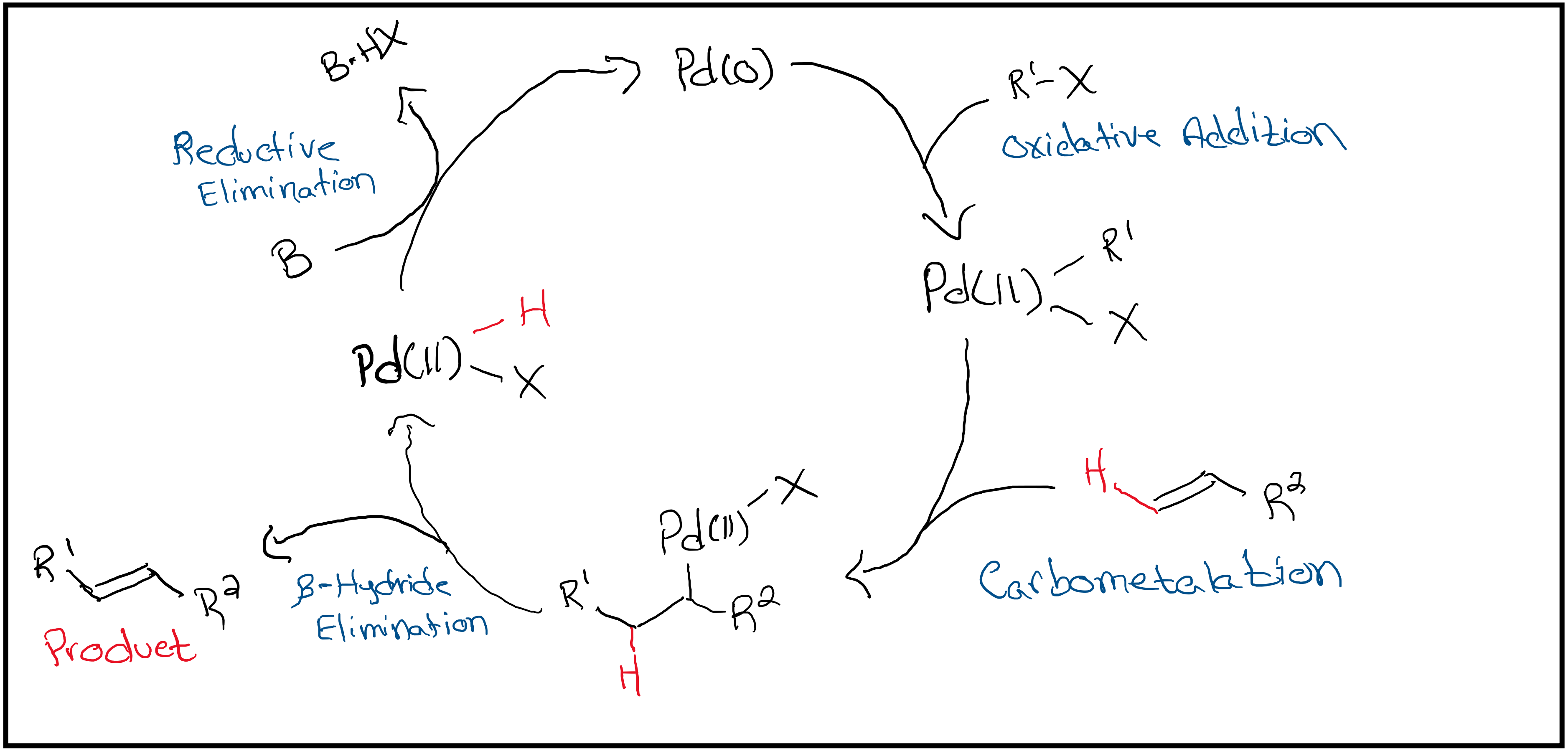
- Most reactions that occur around a transition metal are reversible, and so the reverse of oxidative addition, known as reductive elimination, provides a simple route for the release of neutral organic products from a complex

- The general mechanism shows M(II) going to M(0), releasing X–Y and forming a new X–Y σ bond

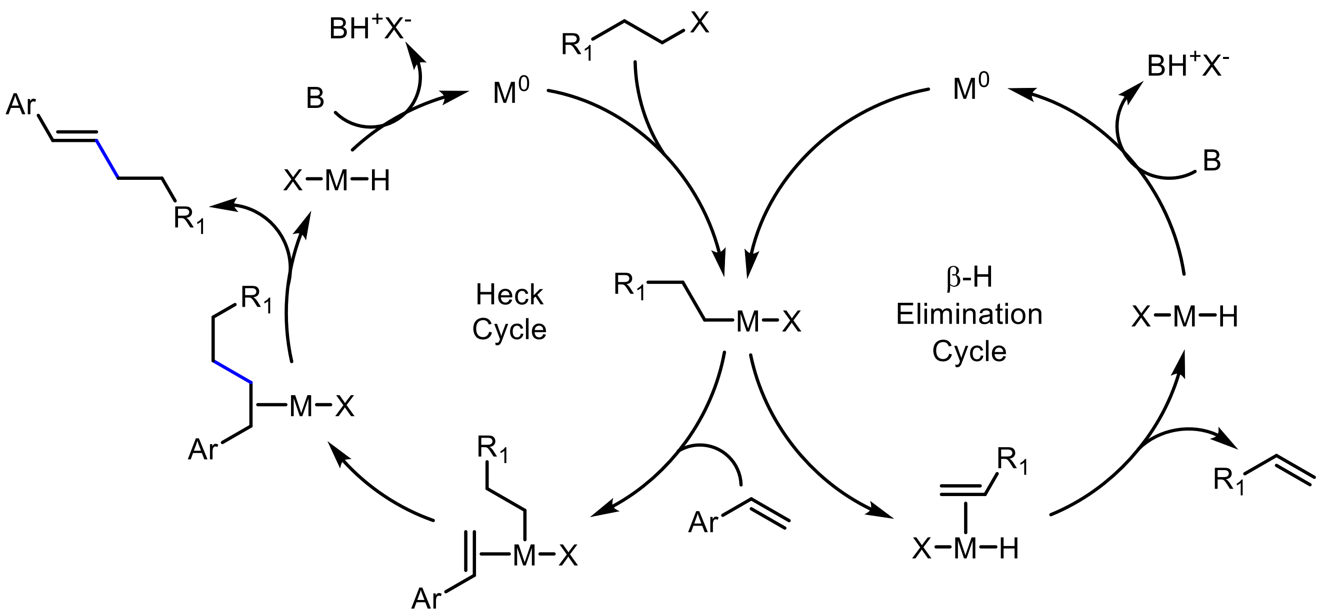


Heck Reaction

- 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 β-hydrogens on an sp^3 carbon atom



The β-Hydride Elimination Problem



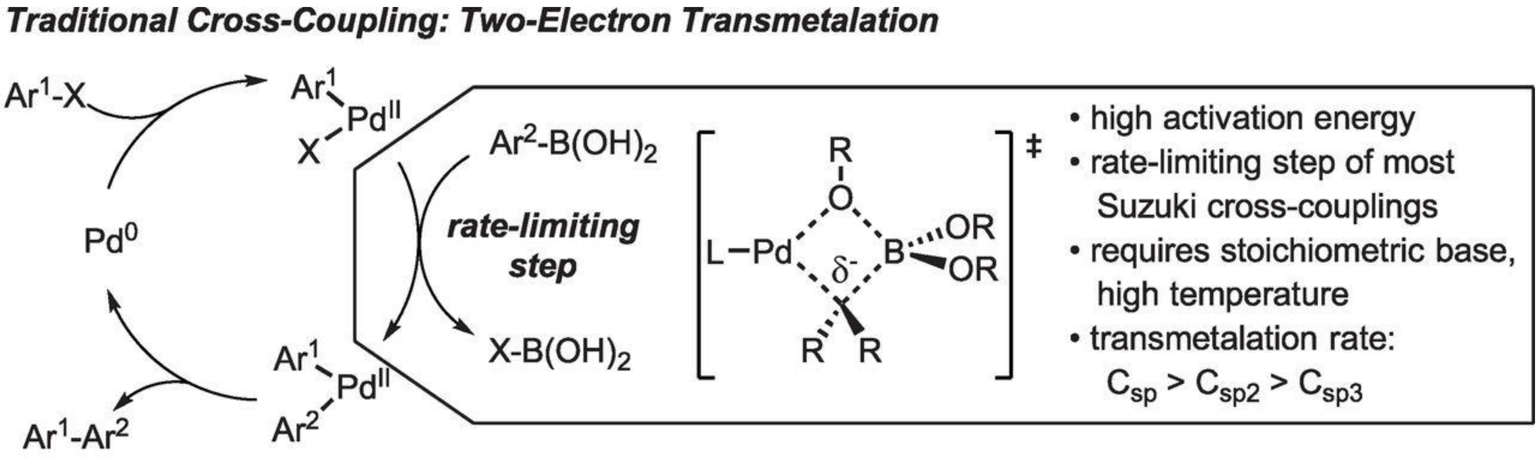
- C(sp^3)–X bond is more electron-rich than the C(sp^2)–X
  - Oxidative addition slower for alkyl halides vs. aryl/vinyl halides
- Alkyl-M complexes are highly reactive due to absence of stabilizing interactions with *d*-orbitals of M
- Thermodynamically favorable β-hydride elimination leads to formation 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 $C(sp^2)–C(sp^2)$ cross-coupling

- However, extension to $C(sp^3)$ 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: $C_{sp} > C_{sp2} > C_{sp3}$

Science **2014**, *345*, 433.

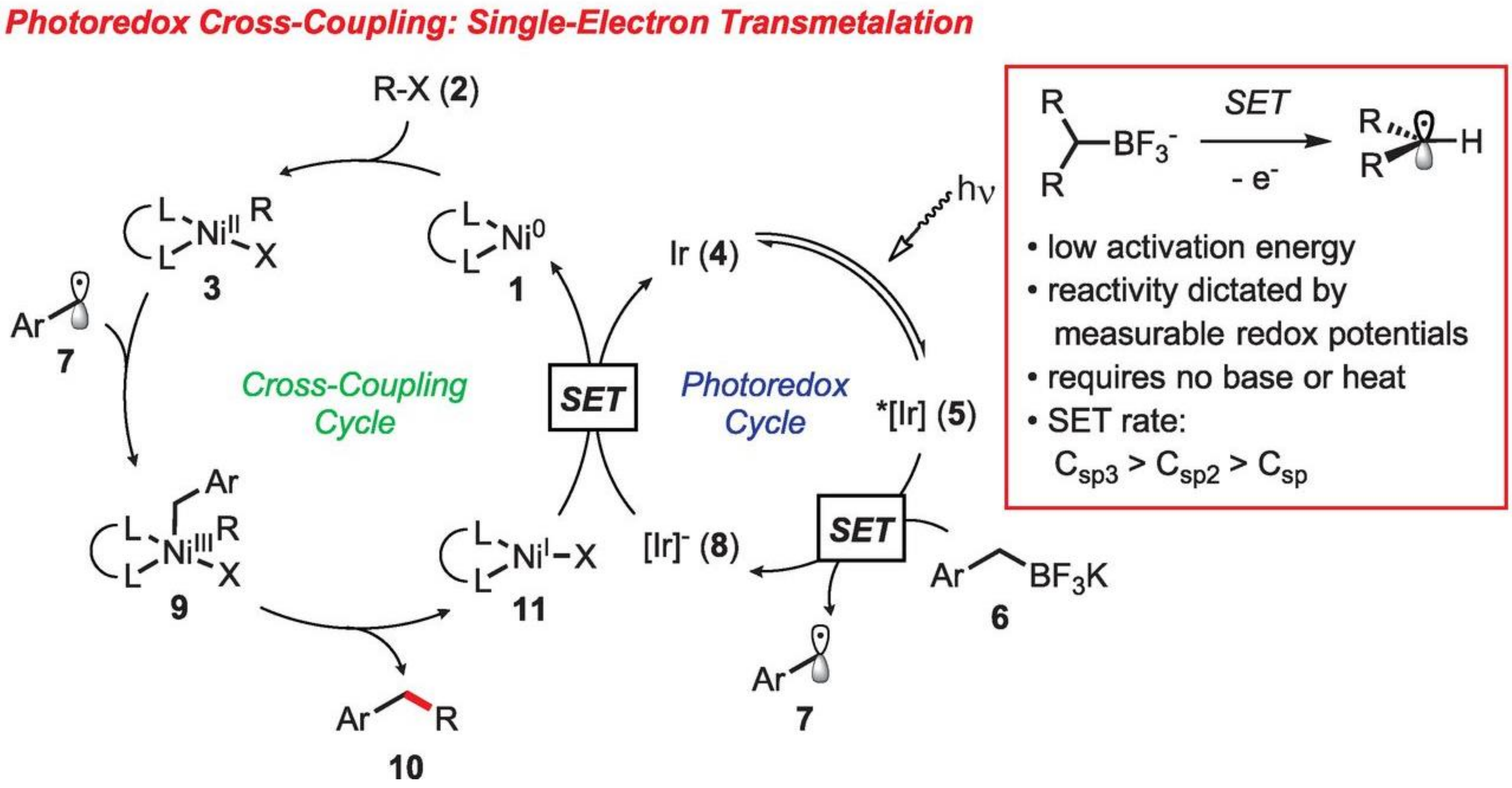
Single-Electron Transmetalation

- 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.

Single-Electron Transmetalation

- The proposed mechanism for the Molander group’s single-electron transmetalation strategy is shown below:



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

Science **2014**, *345*, 433.

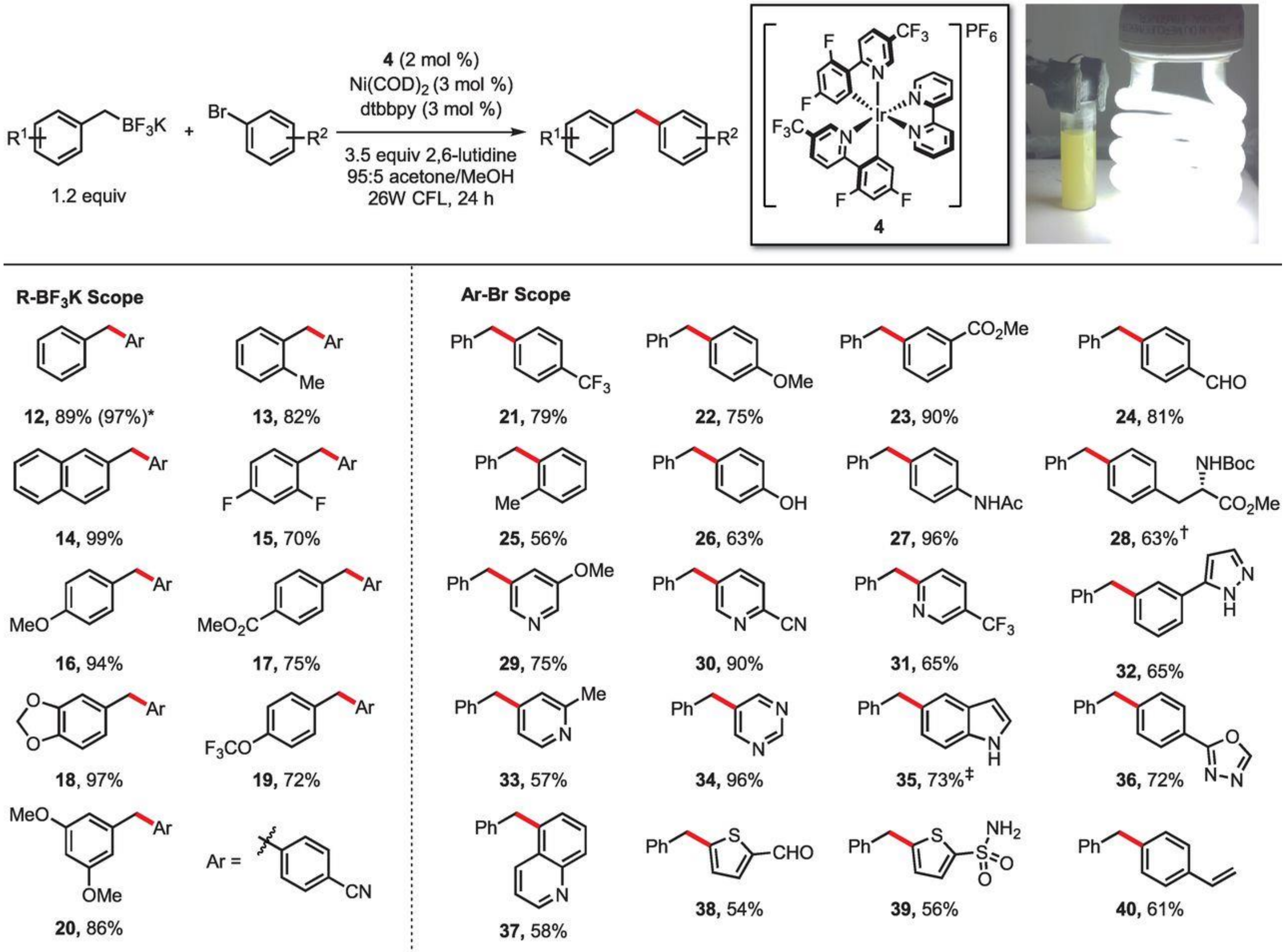
Why Nickel?

- 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

Nickel	**Palladium**
Ni(0)/Ni(I)/Ni(II)/Ni(III)	Pd(0)/Pd(II)
Smaller atomic radius	Larger atomic radius
Less electronegative	More electronegative
Harder	Softer
Facile oxidative addition	Facile reductive elimination
Radical pathways more accessible	

Nature **2014**, *509*, 299.

Reaction Scope



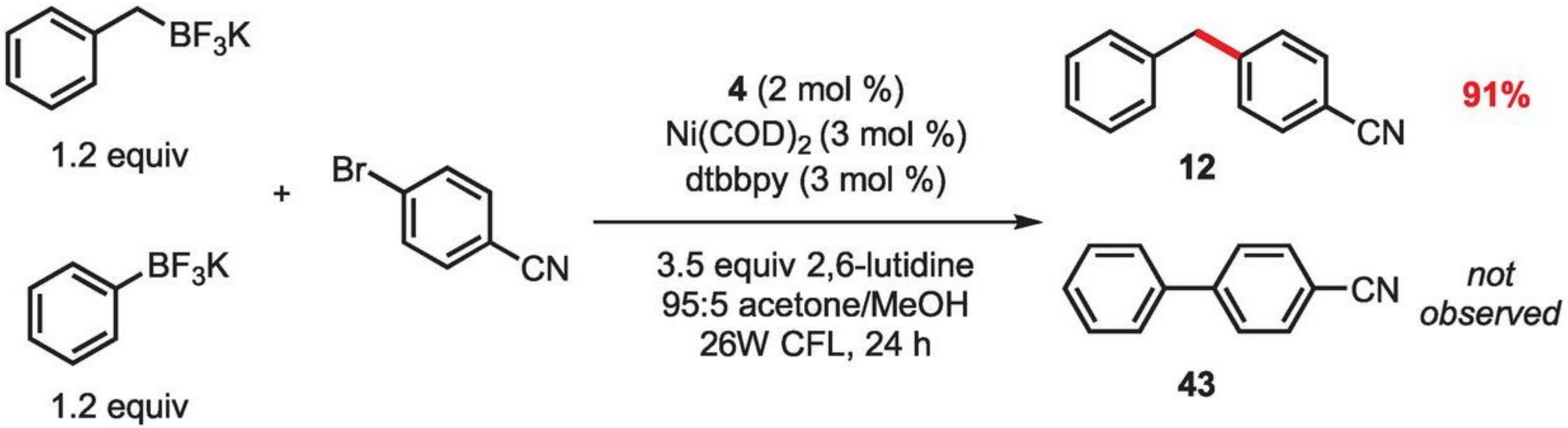
* Reaction performed on 1.0 g (5.5 mmol) ArBr with 1 mol % **4**, 1.5 mol % Ni(COD)$_2$, and 1.5 mol % dtbbpy. † Reaction performed with 3 mol % **4**, 5 mol % Ni(COD)$_2$, and 5 mol % dtbbpy. ‡ 55% isolated pure, 18% isolated as mixture with bromide starting material

Science **2014**, *345*, 433.

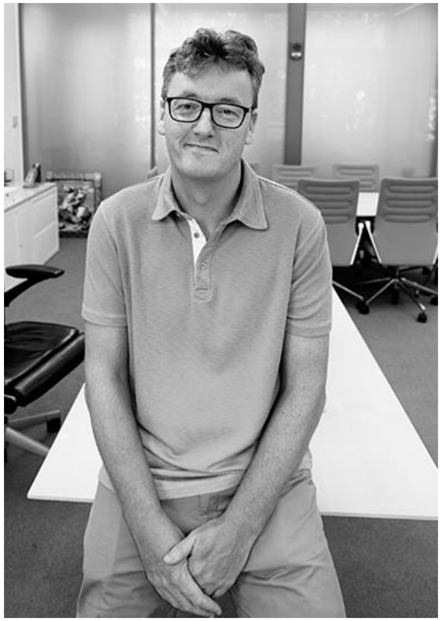
Complimentary Reactivity

- 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.

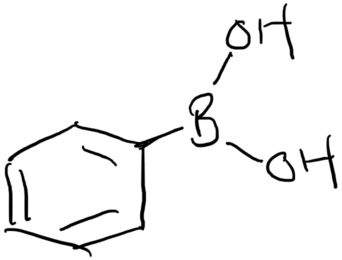


Merging Photeredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes

Cross-Coupling Precursors

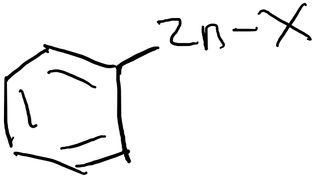
- Traditional organometallic cross-coupling methods typically involve the coupling of an aryl or vinyl halide with one of the following:

Aryl or vinyl boronic acid



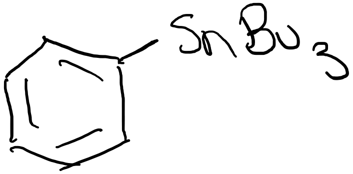
Used for Suzuki Couplings

Zinc halides



Used for Negishi Couplings

Stannanes



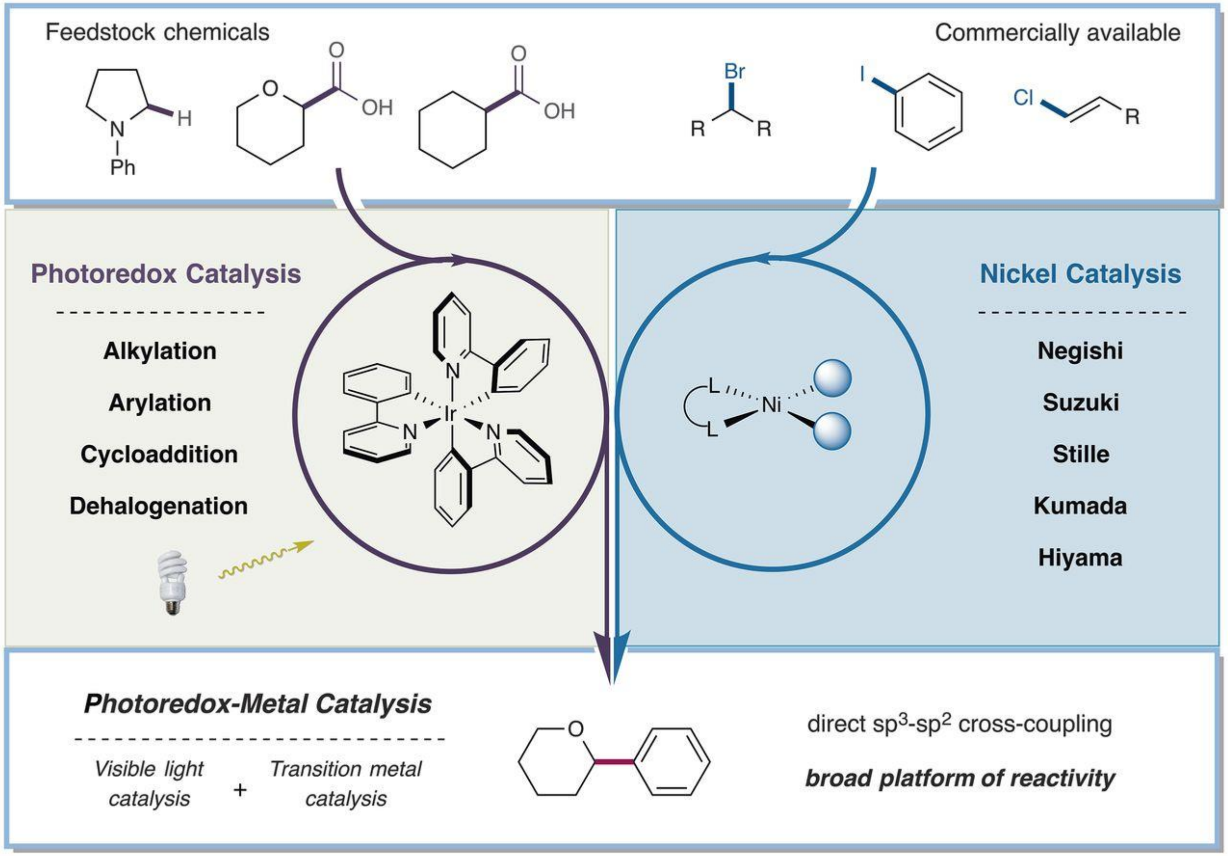
Used for Stille Couplings

Grignard fragments

Used for Kumada Couplings

Merging Photoredox with Nickel Catalysis

- 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(sp^3)–COOH and C(sp^3)–H bonds) could serve as useful coupling partners



Feedstock chemicals

Commercially available

Photoredox Catalysis

Alkylation

Arylation

Cycloaddition

Dehalogenation

Nickel Catalysis

Negishi

Suzuki

Stille

Kumada

Hiyama

Photoredox-Metal Catalysis

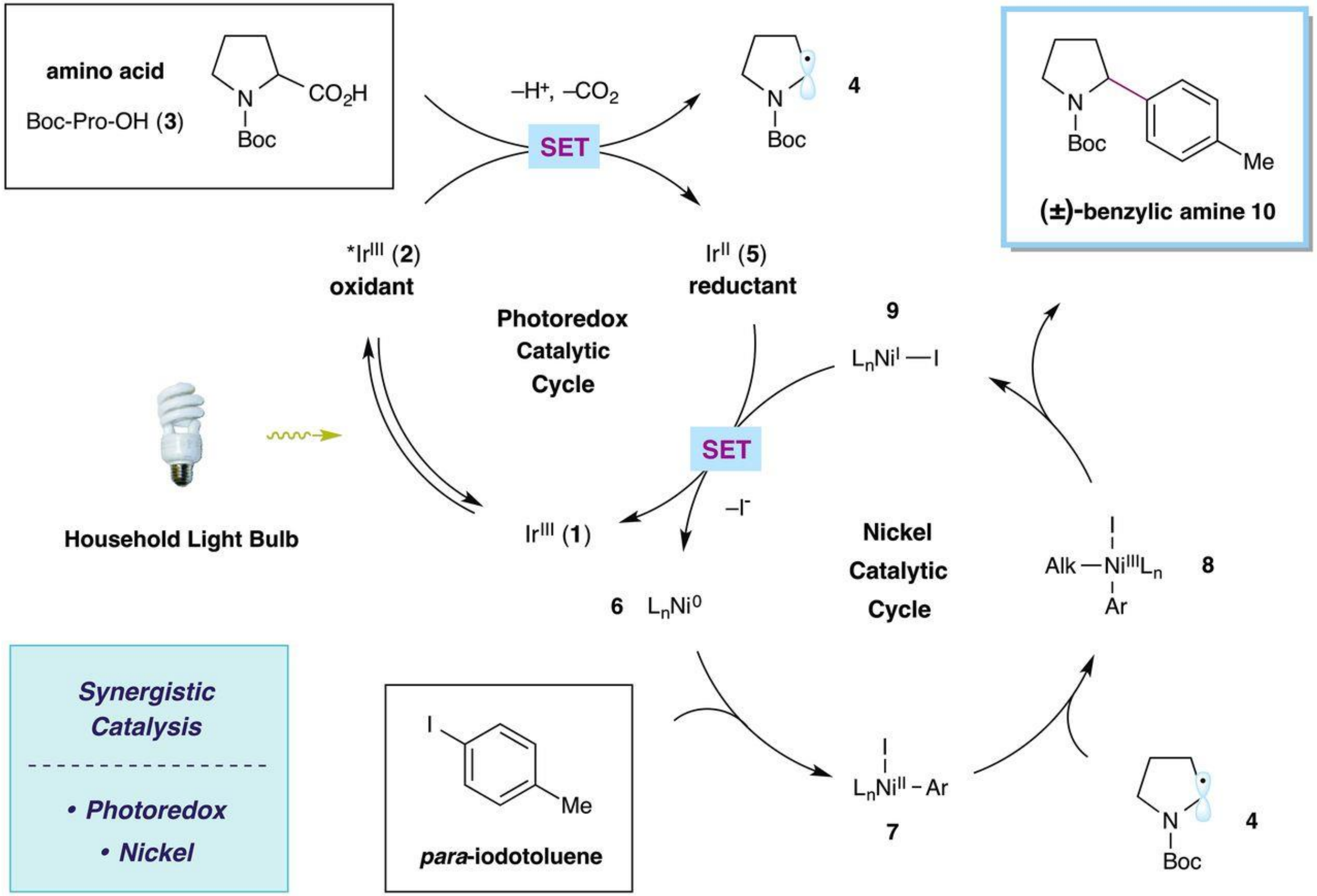
Visible light catalysis + *Transition metal catalysis*

direct sp^3-sp^2 cross-coupling

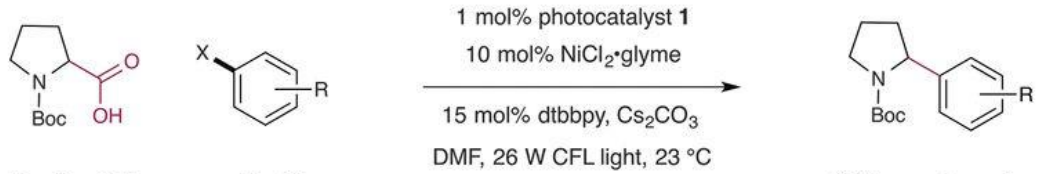
broad platform of reactivity

Proposed Mechanism

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



Reaction Scope



1 mol% photocatalyst **1**

10 mol% $NiCl_2$•glyme

15 mol% dtbbpy, Cs_2CO_3

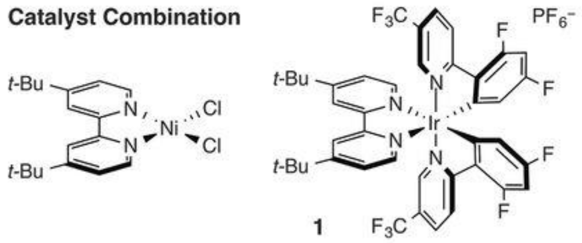
DMF, 26 W CFL light, 23 °C

Boc-Pro-OH

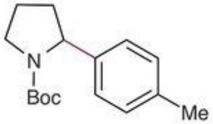
aryl halide

(±)-benzylic amine

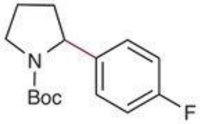
Catalyst Combination



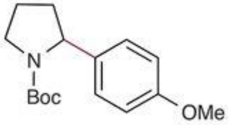
iodoarenes X = I



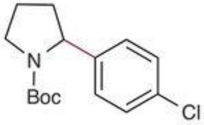
(±)-**10** 78% yield



(±)-**11** 65% yield

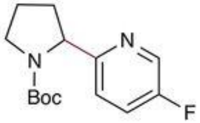


(±)-**12** 74% yield

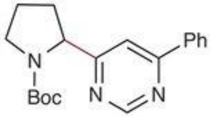


(±)-**13** 77% yield

chloroarenes X = Cl

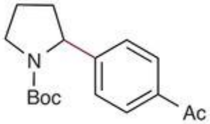


(±)-**23** 64% yield

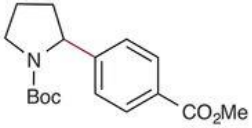


(±)-**24** 65% yield

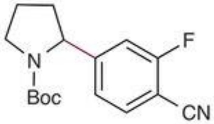
bromoarenes X = Br



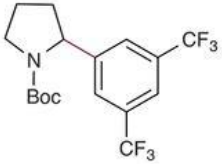
(±)-**14** 86% yield



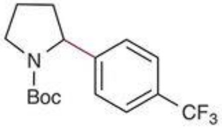
(±)-**15** 90% yield



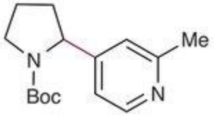
(±)-**16** 75% yield



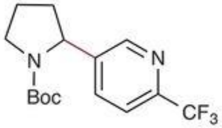
(±)-**17** 87% yield



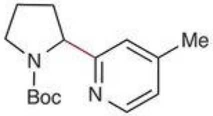
(±)-**18** 88% yield



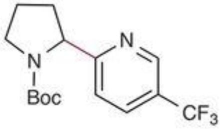
(±)-**19** 85% yield



(±)-**20** 82% yield

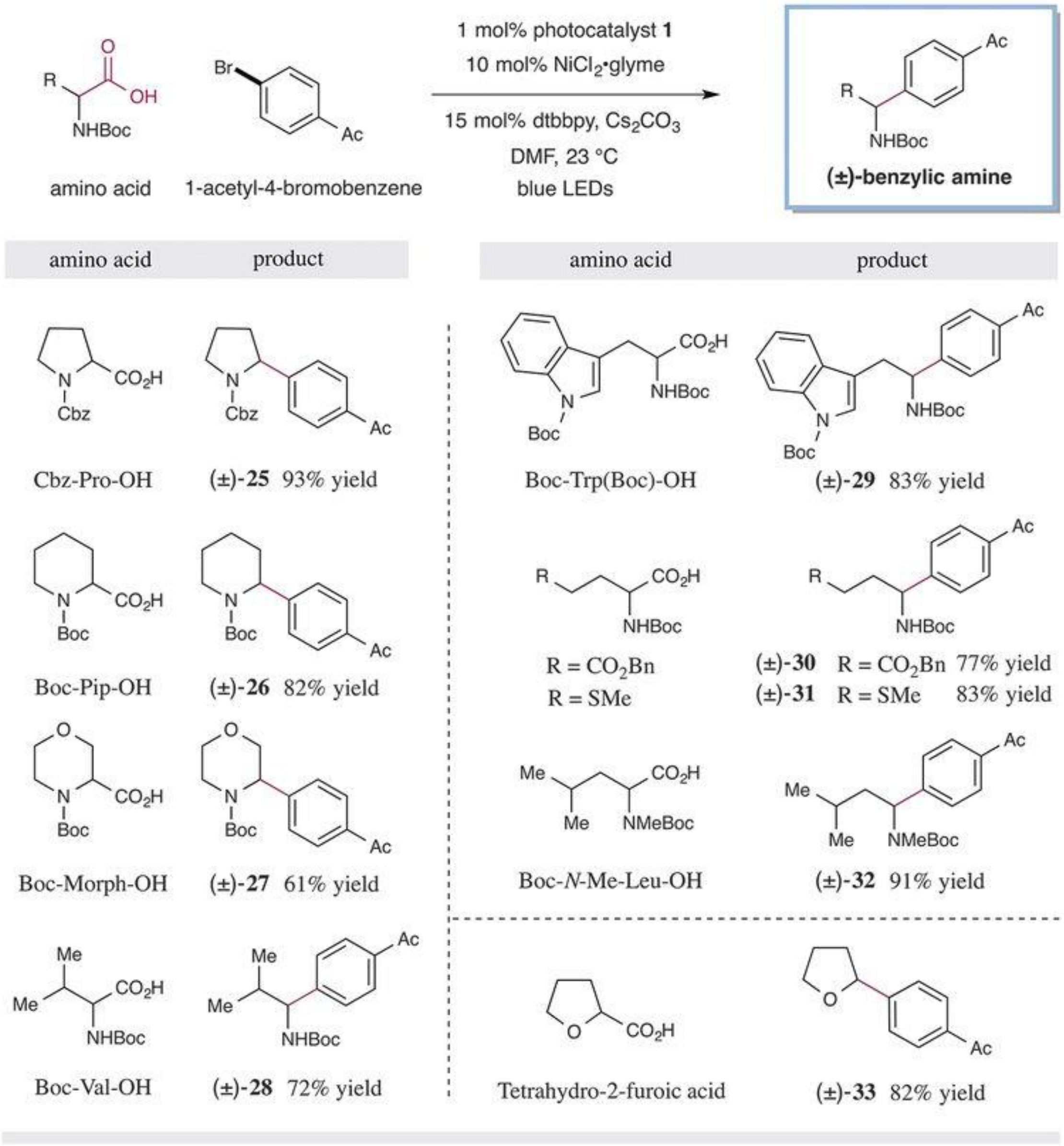


(±)-**21** 67% yield



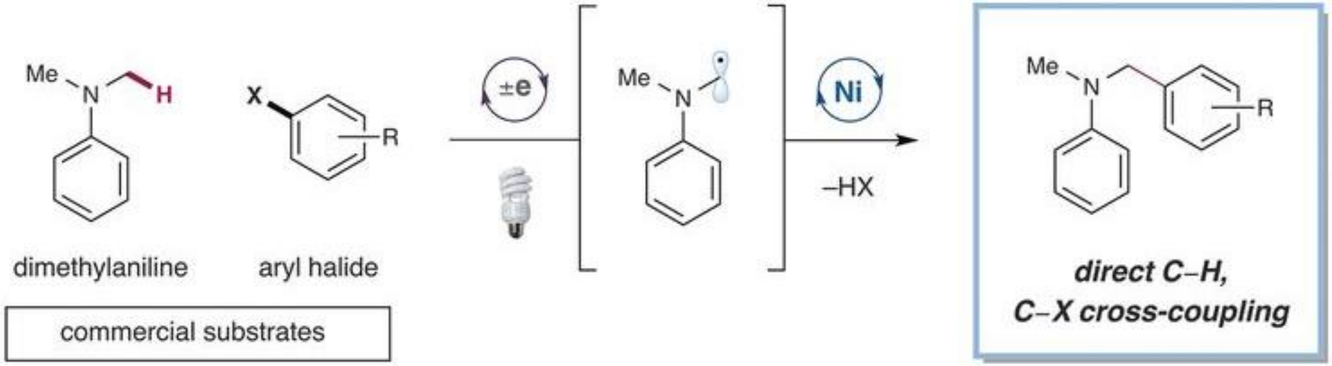
(±)-**22** 60% yield

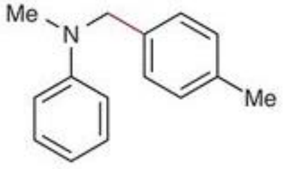
Reaction Scope



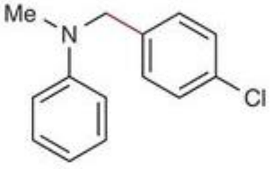
Reaction Scope

- 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

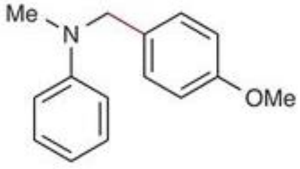




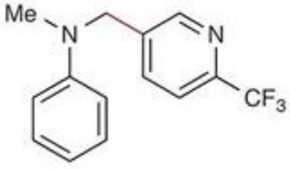
34 84% yield



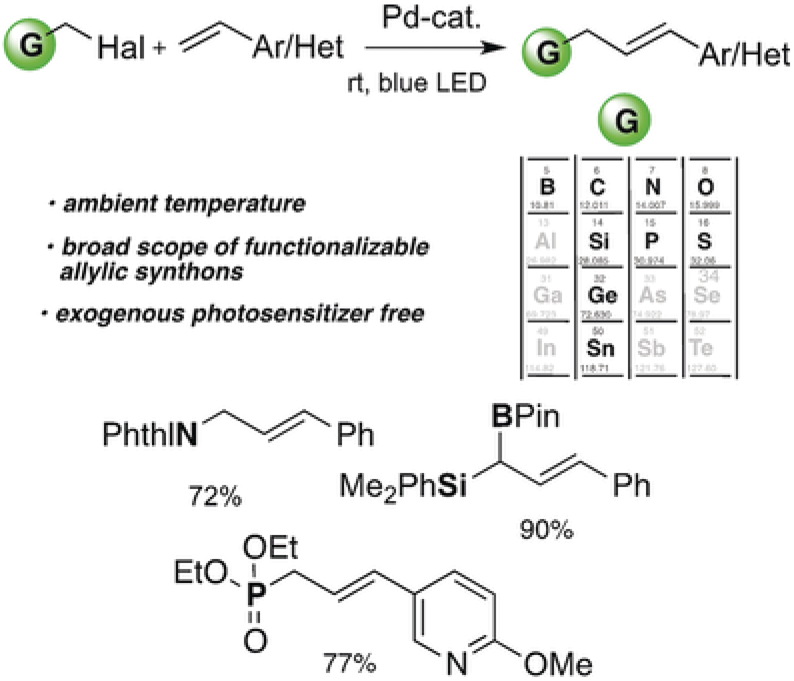
35 72% yield



36 93% yield



37 60% yield[†]



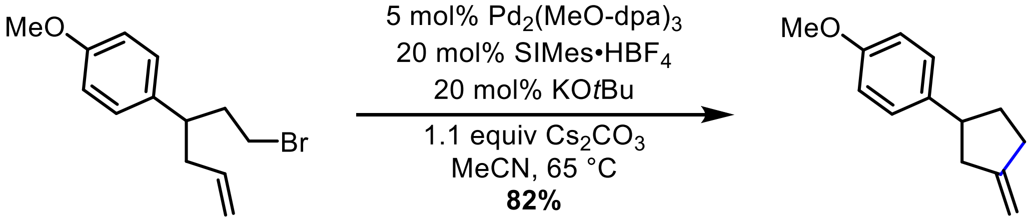
- *ambient temperature*
- *broad scope of functionalizable allylic synthons*
- *exogenous photosensitizer free*

Visible Light-Induced Room-Temperature Heck Reaction of Functionalized Alkyl Halides with Vinyl Arenes/Heteroarenes

Literature Precedent

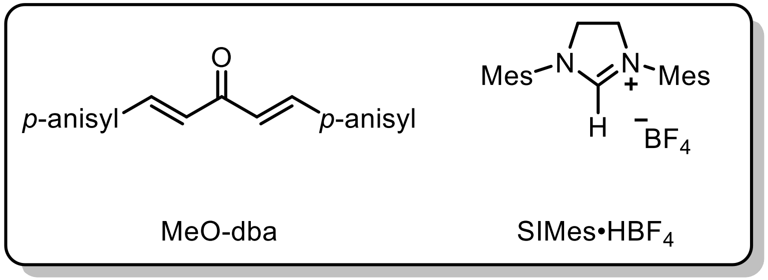
- Owing to the difficulty of cross-coupling alkyl halides, limited examples of alkyl-Heck reactions exist

Intramolecular Alkyl-Heck Reactions (Fu, Alexanian)



5 mol% $Pd_2(MeO\text{-}dpa)_3$
20 mol% SIMes•HBF_4
20 mol% KO*t*Bu

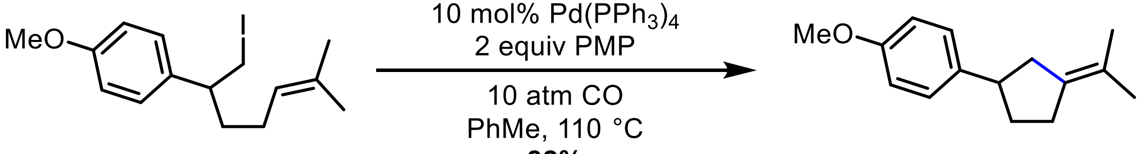
1.1 equiv Cs_2CO_3
MeCN, 65 °C
82%



MeO-dba

SIMes•HBF_4

Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.*, **2007**, *129*, 11340.



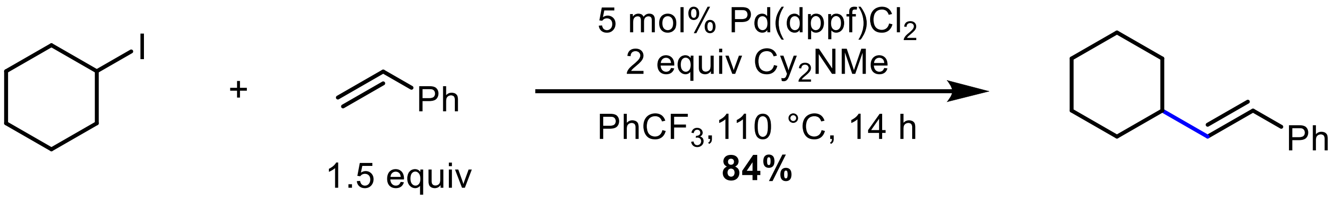
10 mol% $Pd(PPh_3)_4$
2 equiv PMP

10 atm CO
PhMe, 110 °C
82%

Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.*, **2011**, *133*, 20146.

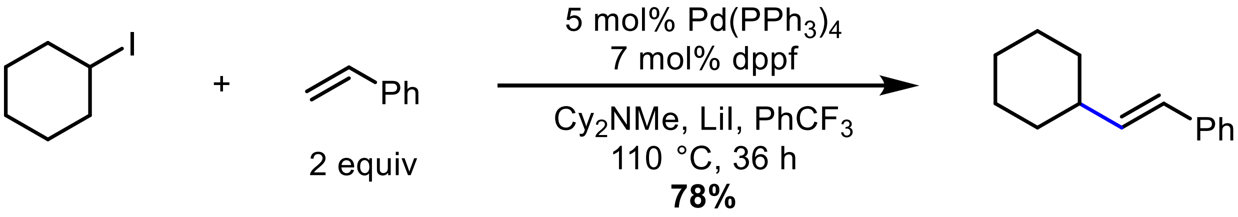
Literature Precedent

Intermolecular Alkyl-Heck Reactions (Alexanian, Zhou)



5 mol% $Pd(dppf)Cl_2$
2 equiv Cy_2NMe
$PhCF_3$,110 °C, 14 h
84%

McMahon, C. M.; Alexanian, E. J. *Angew. Chem. Int. Ed.*, **2014**, *53*, 5974.



5 mol% $Pd(PPh_3)_4$
7 mol% dppf
Cy_2NMe, LiI, $PhCF_3$
110 °C, 36 h
78%

Zou, Y.; Zhou, J. *Chem. Commun.*, **2014**, *50*, 3725.

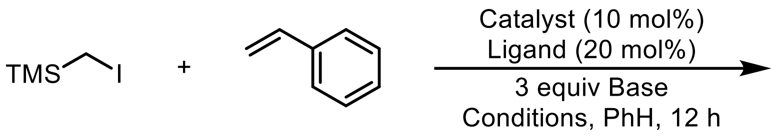
Current Drawbacks

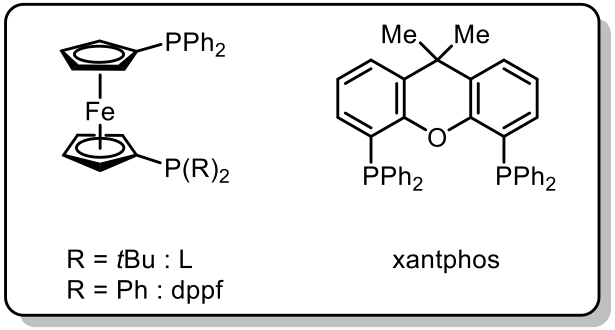
- The prior Heck reactions of alkyl halides suffer from various drawbacks, which includes the need for high reaction temperatures

- 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

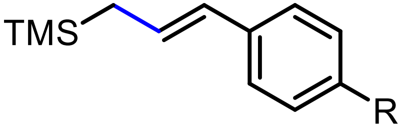




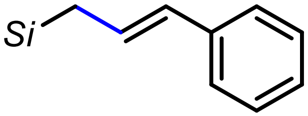
No.	Catalyst	Ligand	Base	Cond.	Yield[b] [%] (*E*:*Z*)
1[c]	$Pd(OAc)_2$	L	*i*Pr_2NEt	120 °C	traces
2[c]	$Pd(dppf)Cl_2$	–	Cy_2NMe	100 °C	35 (5:1)
3[d]	$Pd(PPh_3)_2Cl_2$ (5 mol %)	xantphos (10 mol %)	Cs_2CO_3	100 °C	0
4[e]	$Pd(PPh_3)_4$ (35 mol %)	–	K_2CO_3	100 °C	10 (1:0)
5	$Pd(PPh_3)_4$	–	Cs_2CO_3	RT, blue LED	35 (56[f]) (30:1)
6	$Pd(dppf)Cl_2$	–	Cy_2NMe	RT, blue LED	traces
7	$Pd(OAc)_2$	dppf	*i*Pr_2NEt	RT, blue LED	traces
8	$Pd(OAc)_2$	L	*i*Pr_2NEt	RT, blue LED	traces
9	**$Pd(OAc)_2$**	**xantphos**	**Cs_2CO_3**	**RT, blue LED**	**85 (49:1)**
10	$Pd(OAc)_2$	xantphos	Cs_2CO_3	up to 110 °C	traces
11	$Pd(OAc)_2$	xantphos	Cs_2CO_3	RT, dark	traces
12	–	xantphos	Cs_2CO_3	RT, blue LED	0

[a] Standard conditions: **1 a** 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

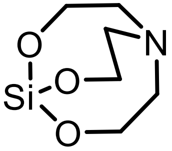


R = H, X = I: 88%
X = Br: 55%
R = OMe: 82%
R = F: 73%
R = CN: 80%
R = CO_2Me: 89%
R = Br: 59%

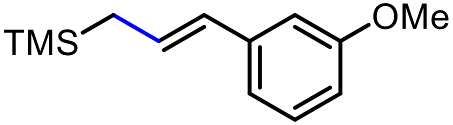


Si = $S(OEt)_3$: 65%

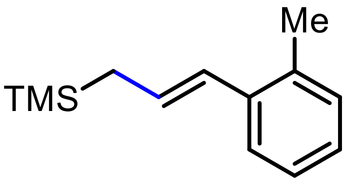
Si =



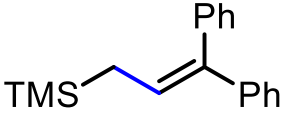
: 62%



83%



72%



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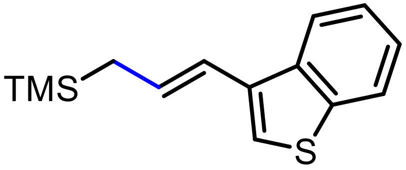
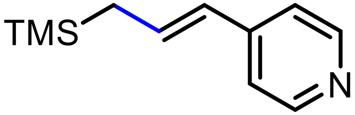
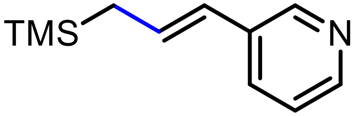


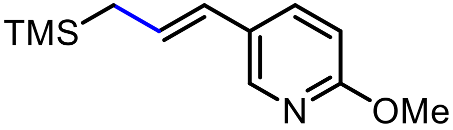
58%



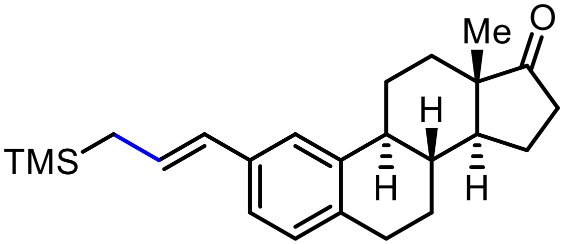
59%



71%



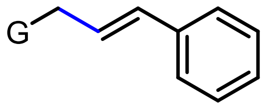
84%



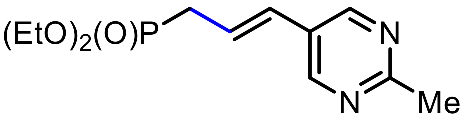
81%

Conditions: 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol $Pd(OAc)_2$, 0.1 mmol xantphos, 1.5 mmol Cs_2CO_3, PhH (0.25 M), 34 W blue LED, rt.

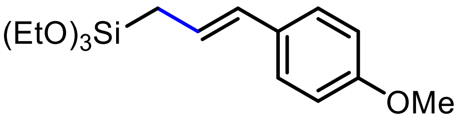
Scope of Alkyl Iodides



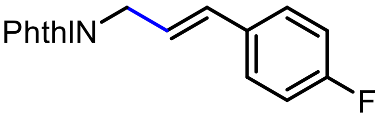
G = Bpin, X = I: 70%[b]
X = Br: 80%[b]
R = $SnBu_3$: 71%[c]
R = NPhthl, X = I: 73%[b]
X = Br: 59%[b]
R = OPiv: 76%[c]
R = $P(O)(OEt)_2$: 58%[a]
R = Ts, X = I: 61%[a]
X = Br: 39%[b]
R = $GeMe_3$: 68%[a]



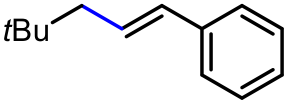
53%[a]



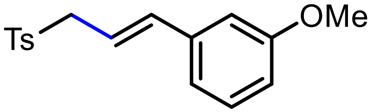
64%[a]



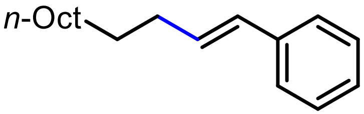
56%[b]



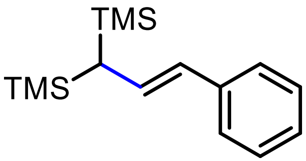
87%[a]



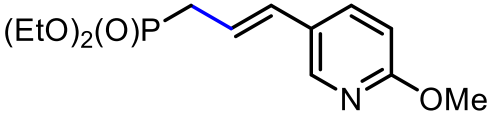
80%[a]



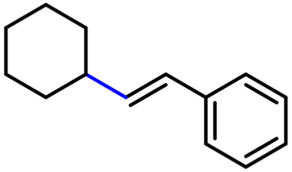
79%[a]



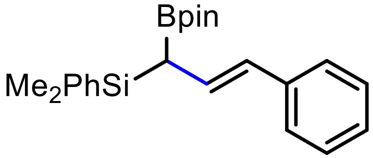
97% (*E*:*Z* = 10:1)[a]



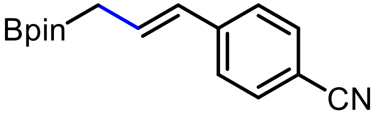
77%[a]



76%[a]



90%[a]

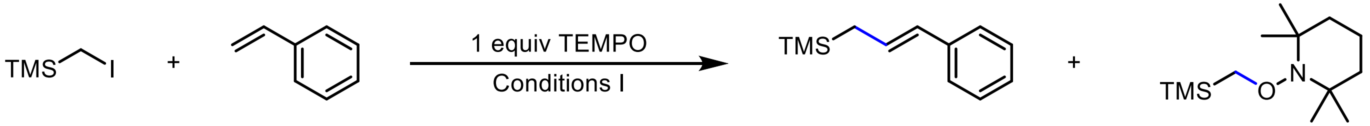


78%[b]

[a] **Conditions I:** 0.75 mmol halide, 0.5 mmol styrene, 0.05 mmol Pd(OAc), 0.1 mmol xantphos, 1.5 mmol Cs_2CO_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_2NEt, 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_2CO_3, PhH (0.0625 M).

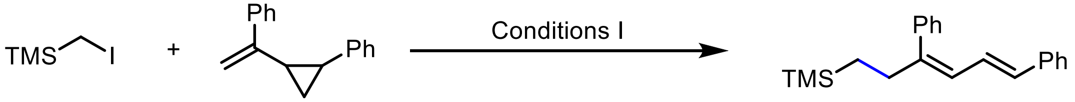
Mechanistic Studies

- The Gevorgyan group performed a series of mechanistic experiments which provided evidence for a radical mechanism



0%

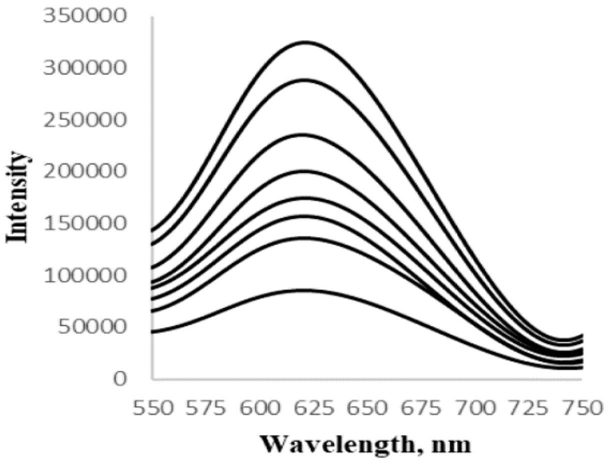
42%
(NMR yield)

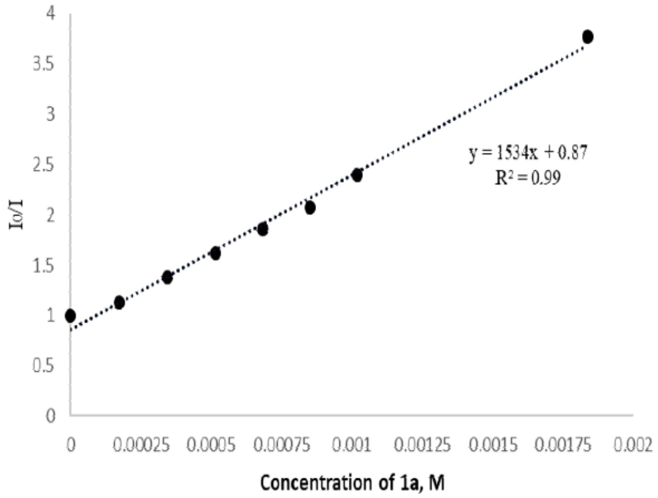


- Consistent with radical mechanism

59%
Only observed product

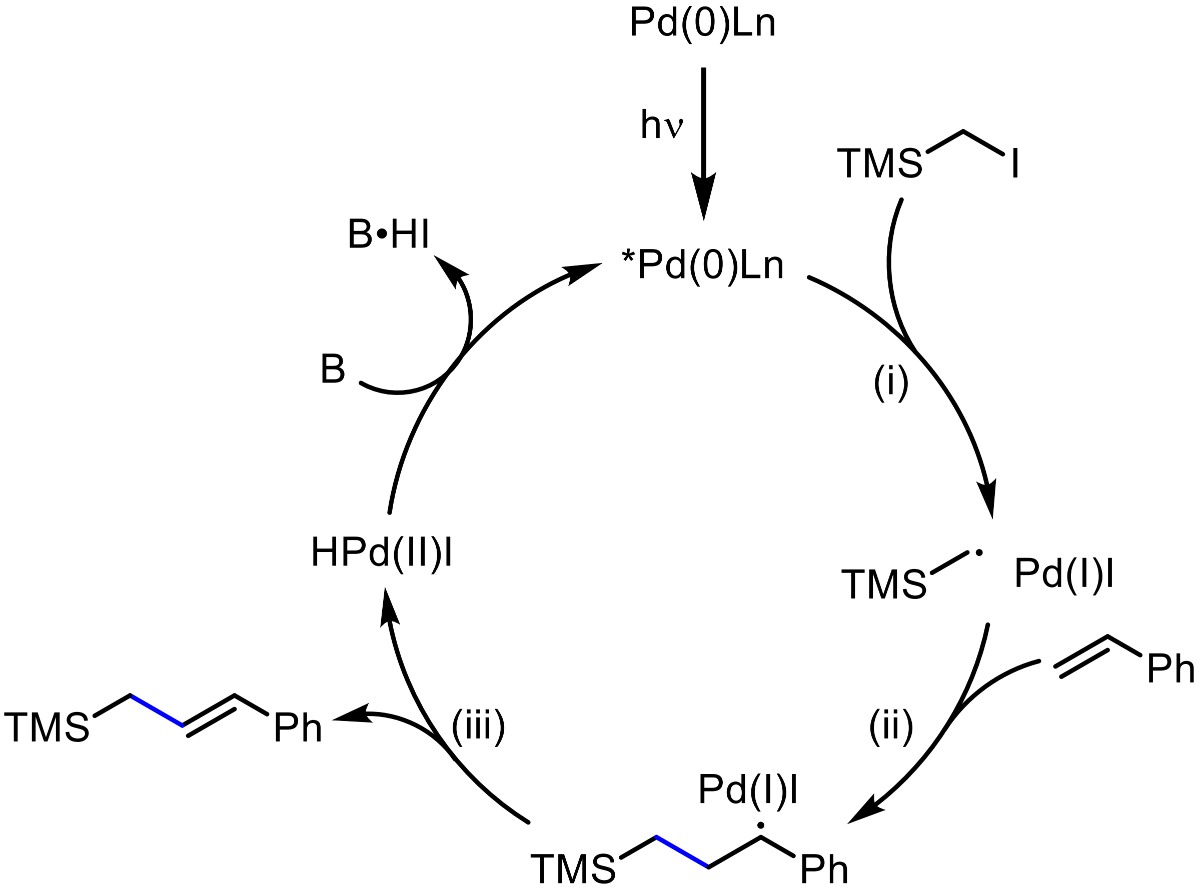
- Stern-Volmer Analysis demonstrated that iodomethyltrimethyl silane quenched the excited state of $Pd(PPh_3)_4$





Proposed Mechanism

- Their proposed mechanism is shown below:



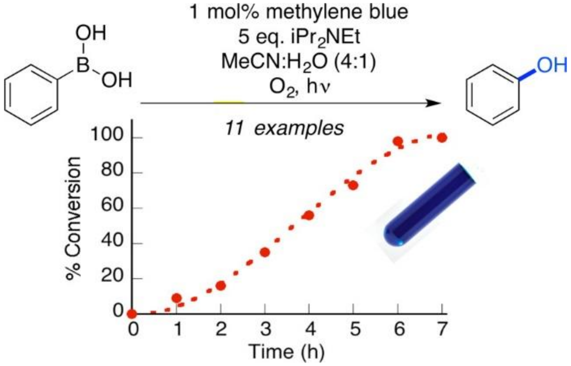
i. SET from *Pd(0) to alkyl iodide
ii. Radical addition to styrene
iii. β-hydride elimination

Meet the Authors

J. C. (Tito) Scaiano
University of Ottawa

David Nicewicz
UNC Chapel Hill

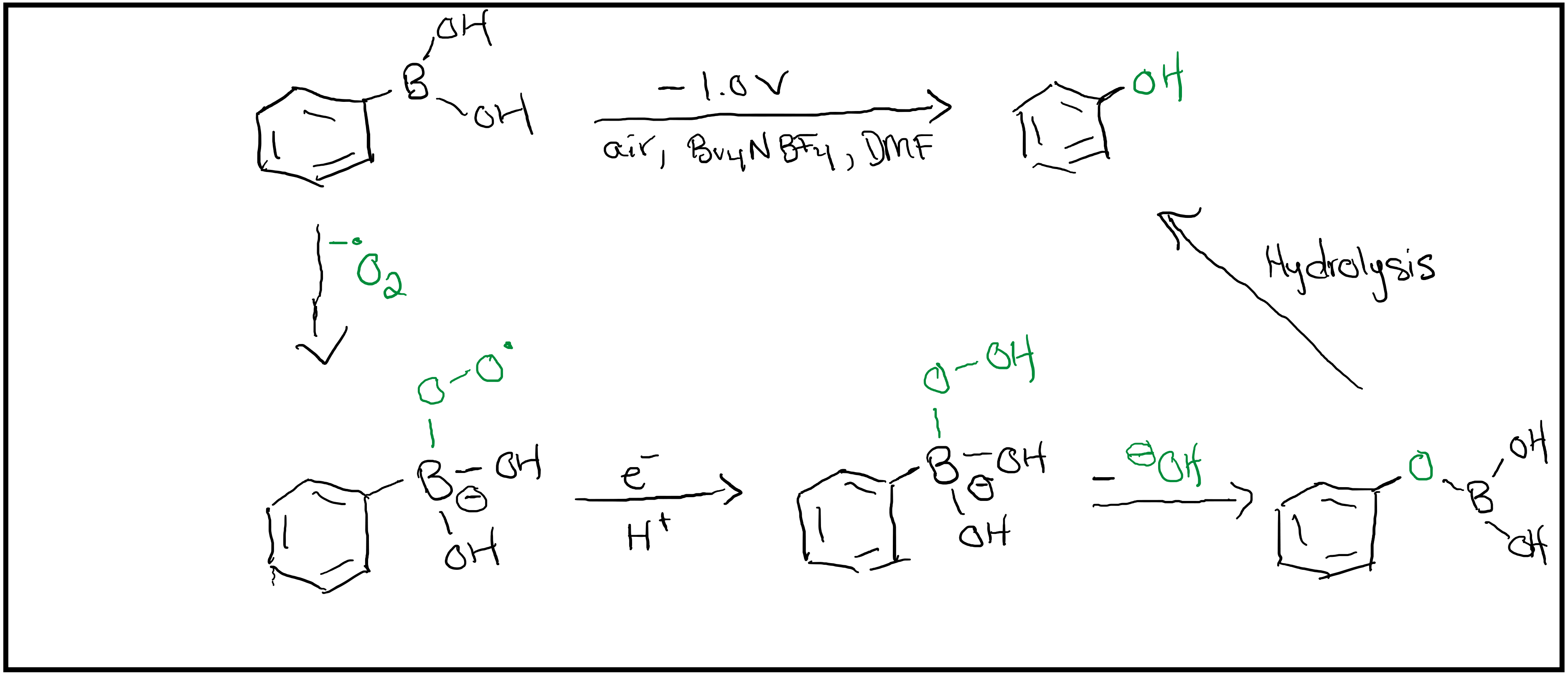
Garret Miyake
Colorado State University



Mechanistic Insights and Kinetic Analysis for the Oxidative Hydroxylation of Arylboronic Acids by Visible Light Photoredox Catalysis: A Metal-Free Alternative

Oxidative Hydroxylation of Arylboronic Acids

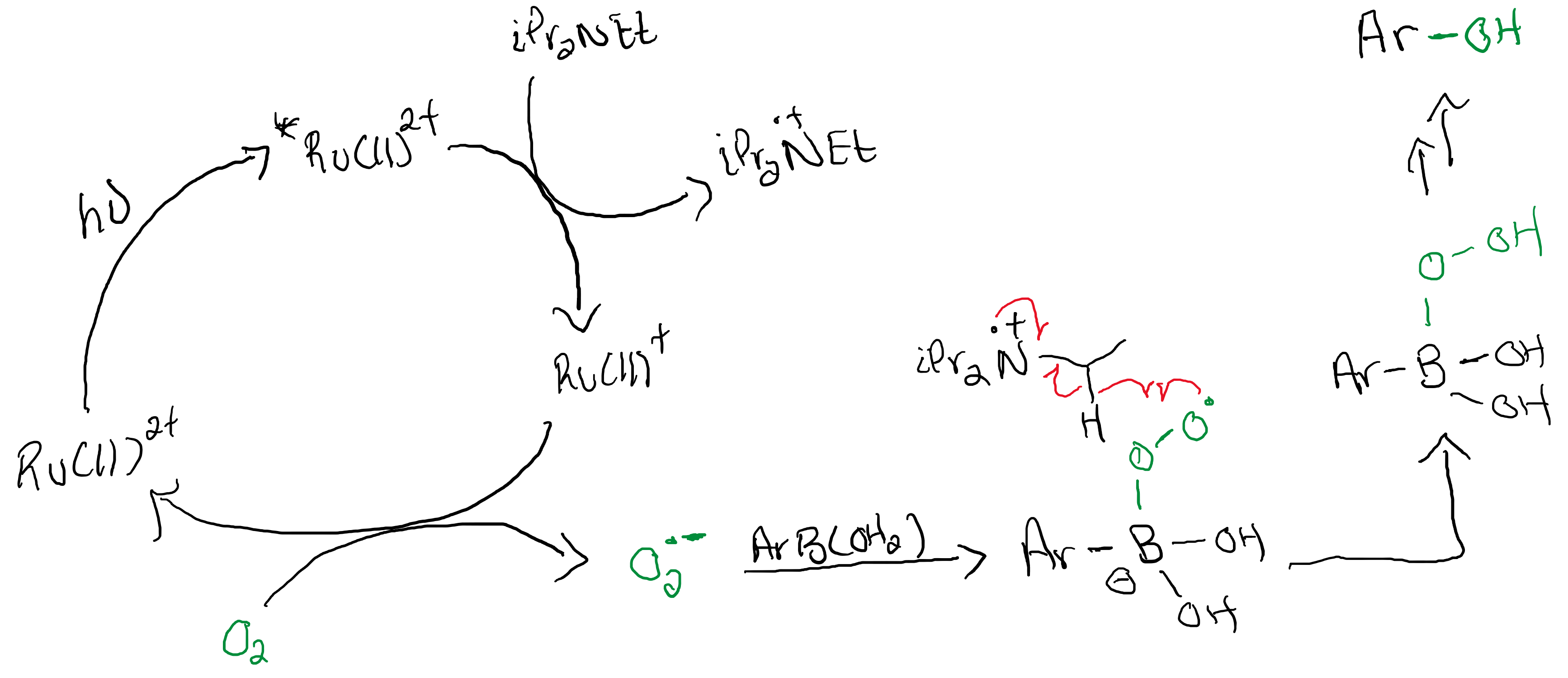
- In 2012, Xiao and coworkers reported an electrochemical-mediated oxidative hydroxylation of arylboronic acids
- The mechanism proceeds through a nucleophilic superoxide radical, which is generated by the one-electron reduction of molecular oxygen
- Their proposed mechanism is shown below:



Chem. Commun. **2012**, *48*, 7203.

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:



Angew. Chem. Int. Ed. **2012,** *51*, 784.

Oxidative Hydroxylation of Arylboronic Acids

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

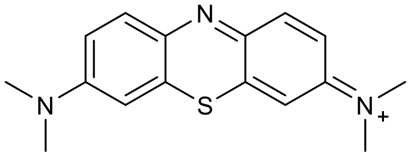
1) Long irradiation times required to achieve synthetically useful yields
    - Hypothesized to be from slow reductive quenching by the amine

2) $Ru(bpy)_3Cl_2$ 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

Methylene Blue

- 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



MB

Photochemical Properties

Absorption λ_{max}: 665 nm

ε = 90,000 $M^{-1}cm^{-1}$

Triplet Energy: 1.50 eV

Φ_T = 0.52

Triplet τ_0 (MeCN): 32 μs

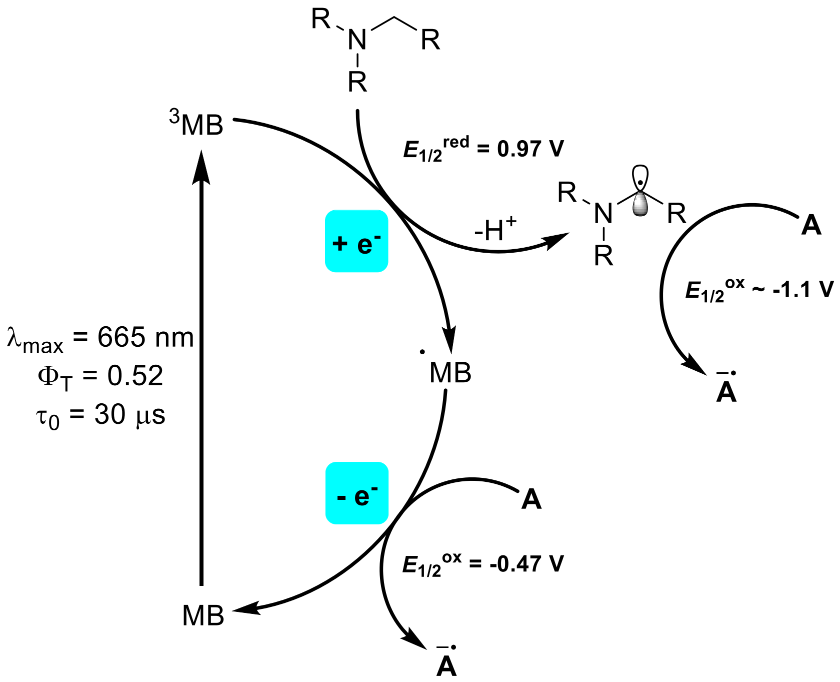
Triplet Transient λ_{max}: 420 nm

Triplet ε = 11,000 $M^{-1}cm^{-1}$

Redox Properties

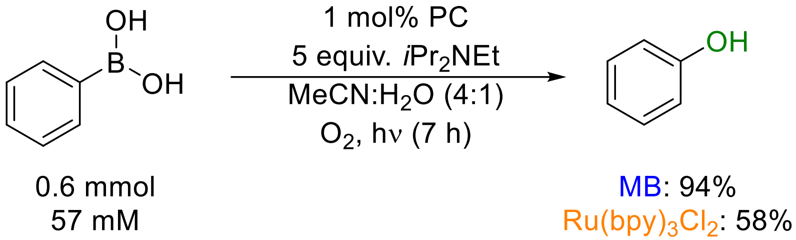
$E_{1/2}$ ($MB^+/MB^\bullet$) = -0.47 V vs. SCE

$E_{1/2}$ ($^*MB^+/MB^\bullet$) = 0.97 V vs. SCE



- To test this hypothesis, they chose to examine the oxidative hydroxylation of arylboronic acids

Methylene Blue vs. $Ru(bpy)_3Cl_2$



- In order to determine the origin of this difference in observed reactivity, the excited state kinetics for Methylene Blue and $Ru(bpy)_3Cl_2$ were analyzed in detail
- The results are shown in the table below:

	Triplet Quenching: k_q ($M^{-1}s^{-1}$)	
Quencher	Methylene Blue	$Ru(bpy)_3Cl_2$
iPr$_2$NEt	2.44×10^8	6.21×10^6
Phenylboronic acid	1.34×10^8	3.72×10^6
Phenol	5.81×10^5	6.68×10^5
O_2	2.46×10^9	2.97×10^9

J. Am. Chem. Soc. **2013,** *135*, 13286.

Methylene Blue vs. $Ru(bpy)_3Cl_2$

- Since the first step in the catalytic cycle is the quenching of ^3PC by *i*Pr_2NEt, we can use the k_q values from the previous slide to calculate the probability of this event (*<u>under initial reaction conditions</u>*) for each photocatalyst

% Triplet Quenching by *i*Pr_2NEt under initial reaction conditions =

$$\frac{100\,\% \times k_q^{iPr_2NEt}[iPr_2NEt]}{\tau_0^{-1} + k_q^{iPr_2NEt}[iPr_2NEt] + k_q^{PhB(OH)_2}[PhB(OH)_2] + k_q^{O_2}[O_2]}$$

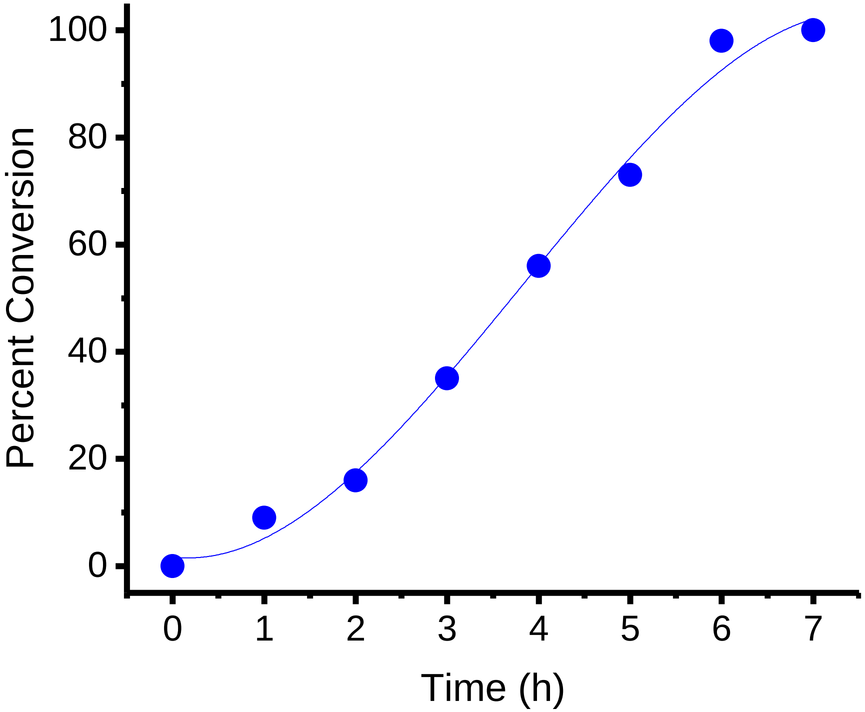
Photocatalyst	
Methylene Blue	85 %
$Ru(bpy)_3Cl_2$	20 %

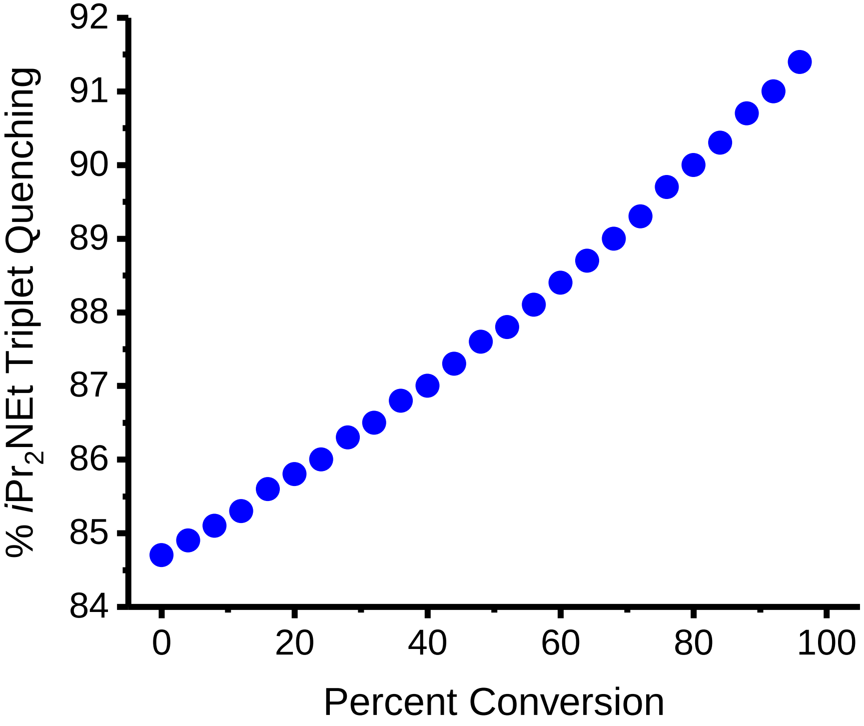
☆ Reaction with ^3MB is 4.25 times more favorable than the corresponding reaction with $^3Ru(bpy)_3Cl_2$

J. Am. Chem. Soc. **2013,** *135*, 13286.

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

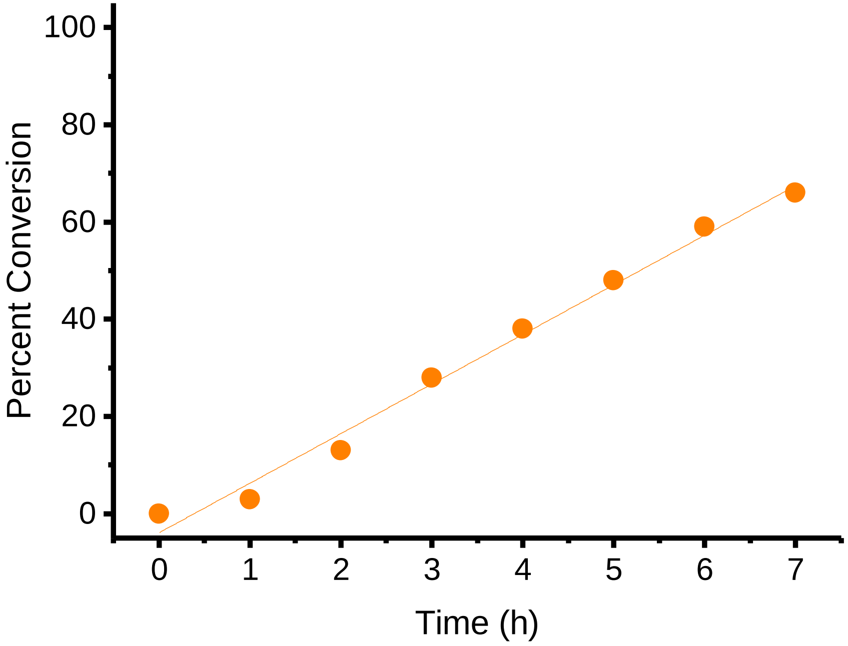


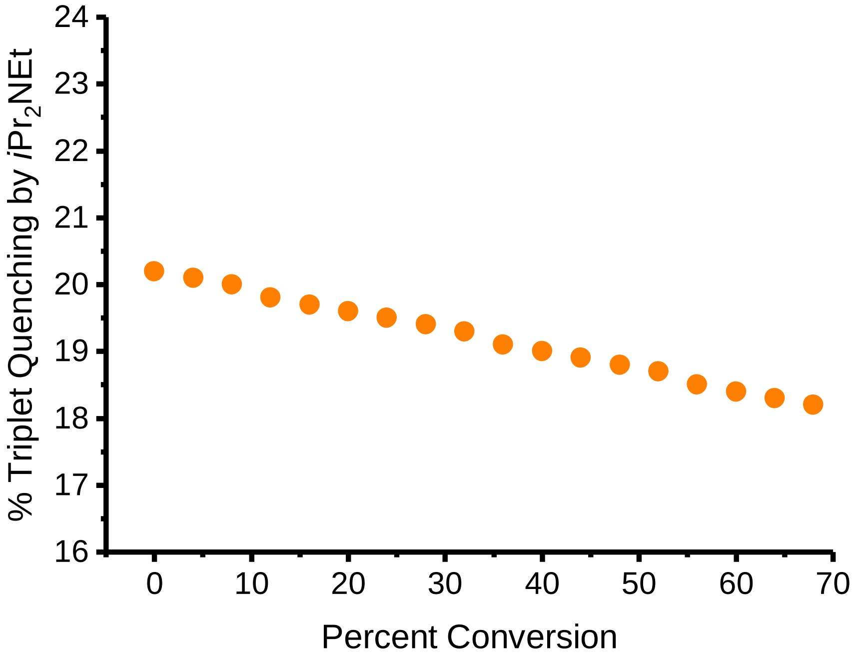


J. Am. Chem. Soc. **2013,** *135*, 13286.

Mechanistic Insights from Excited State Kinetics

- In comparison, the probability of quenching of $^3Ru(bpy)_3Cl_2$ by $i$$Pr_2NEt$ decreases slightly as the reaction progresses
- This should be expected; as a reagent is consumed, it's concentration in the reaction decreases, and since reagent concentrations impact quenching probability, we would also expect the probability of triplet quenching to decrease

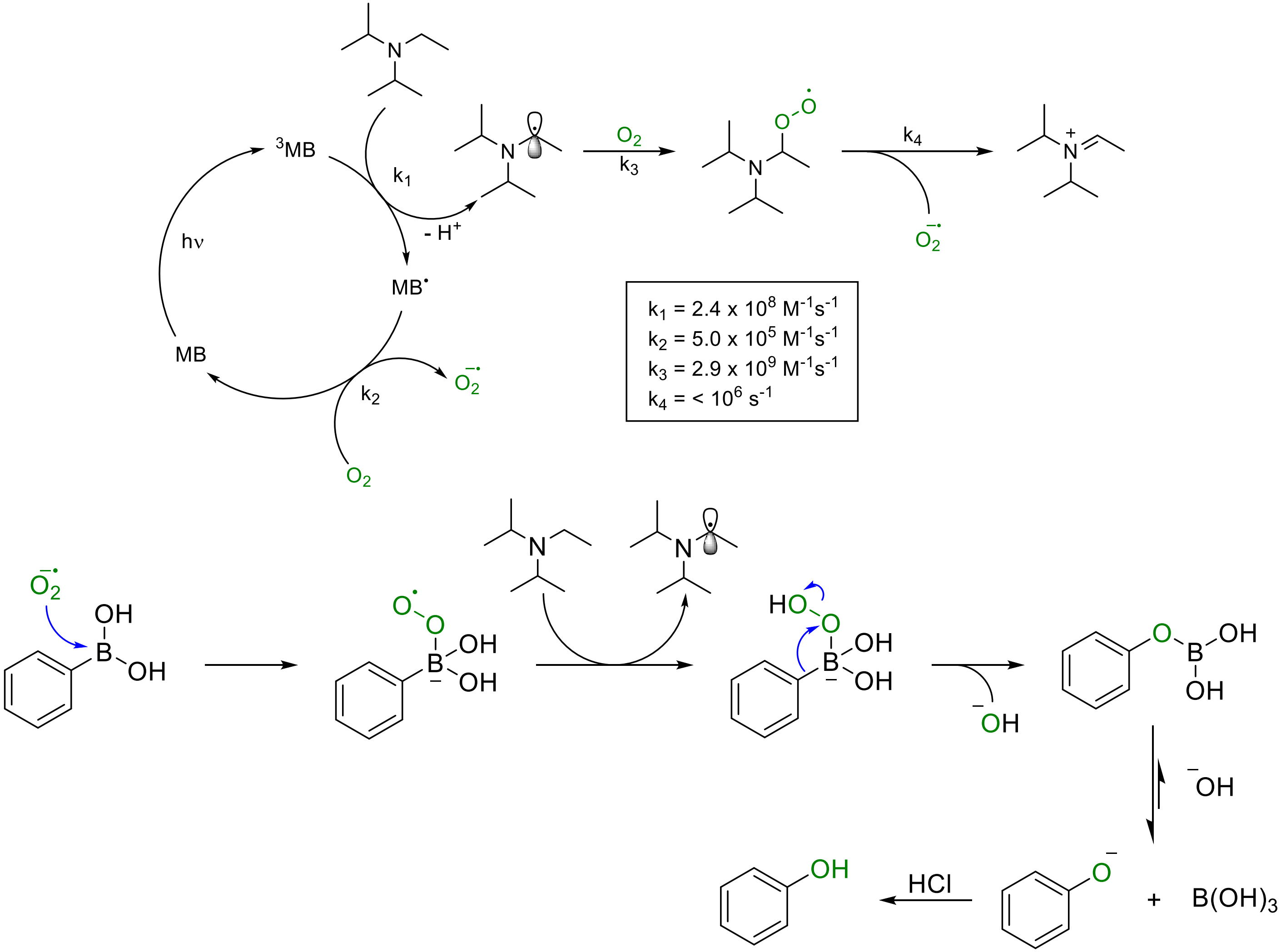




J. Am. Chem. Soc. **2013,** *135*, 13286.

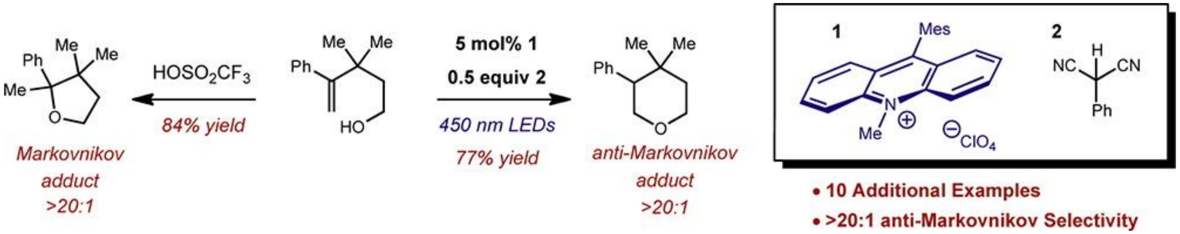
Proposed Mechanism

- The proposed mechanism for the oxidative hydroxylation of arylboronic acids photocatalyzed by Methylene Blue is shown below



$k_1 = 2.4 \times 10^8\ M^{-1}s^{-1}$
$k_2 = 5.0 \times 10^5\ M^{-1}s^{-1}$
$k_3 = 2.9 \times 10^9\ M^{-1}s^{-1}$
$k_4 = < 10^6\ s^{-1}$

J. Am. Chem. Soc. **2013,** *135*, 13286.



Direct Catalytic Anti-Markovnikov Hydroetherification of Alkenols

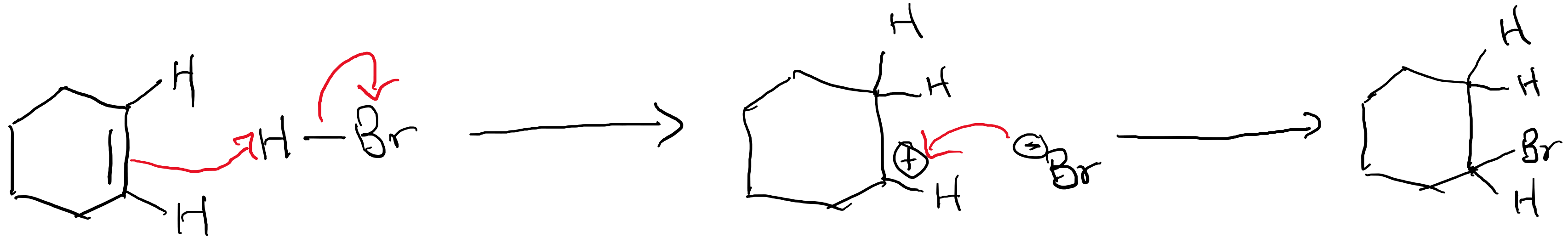
Markovnikov’s Rule

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

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

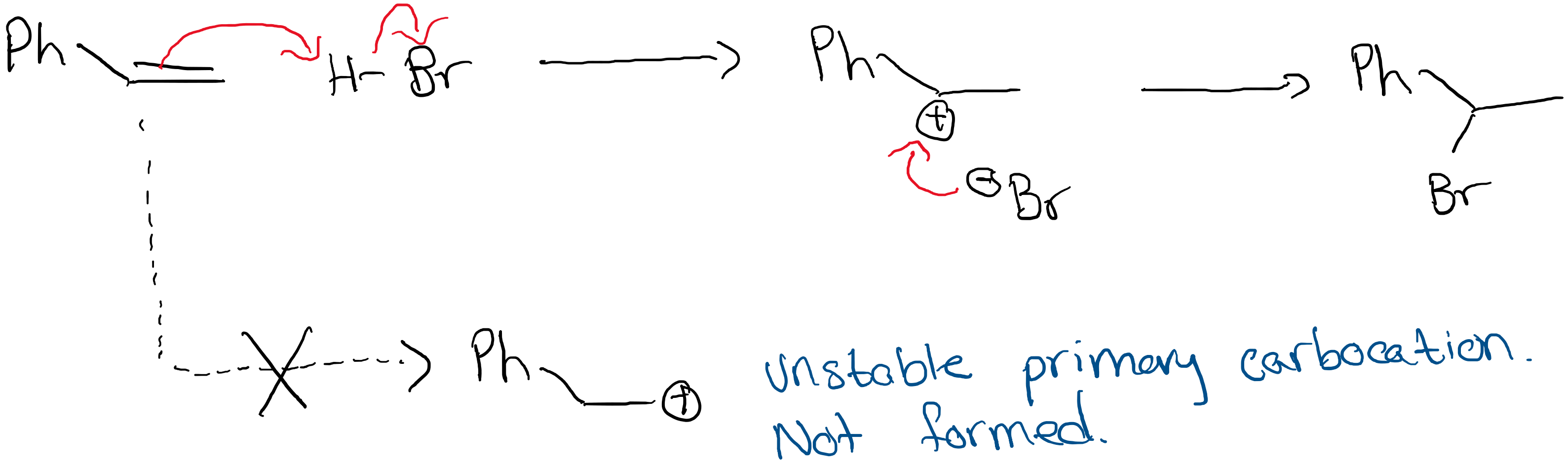
- Electrophilic addition of a proton to an alkene results in a carbocation, which reacts rapidly with the Br⁻ just formed

- 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

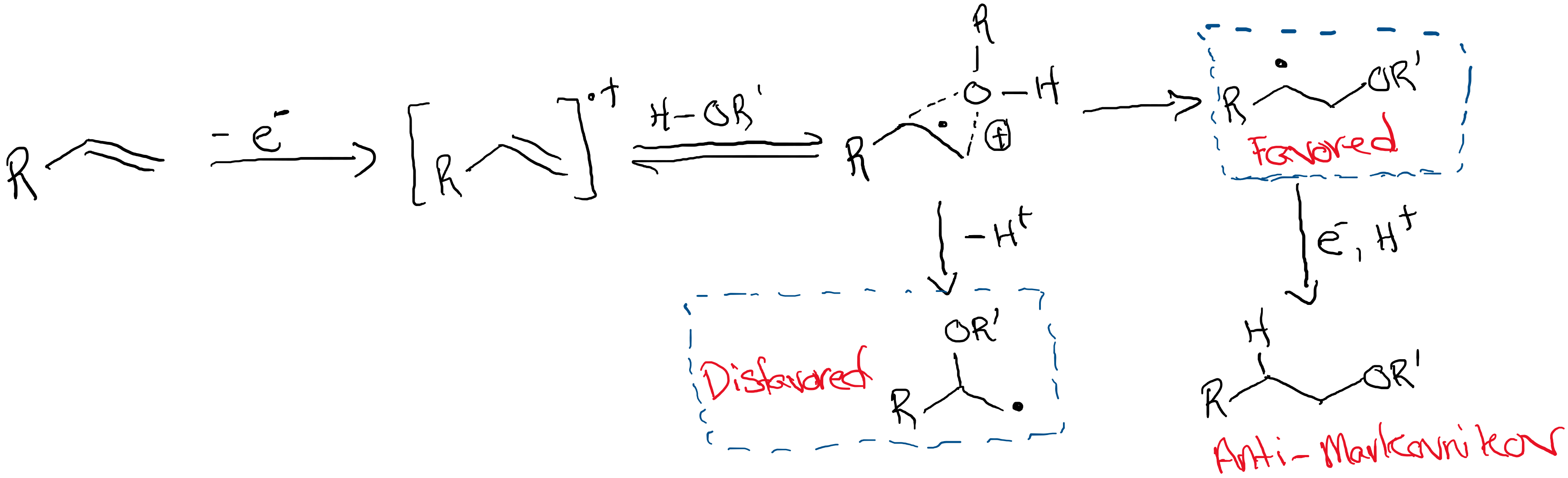


Unstable primary carbocation.
Not formed.

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

Anti-Markovnikov Hydroetherification of Alkenols

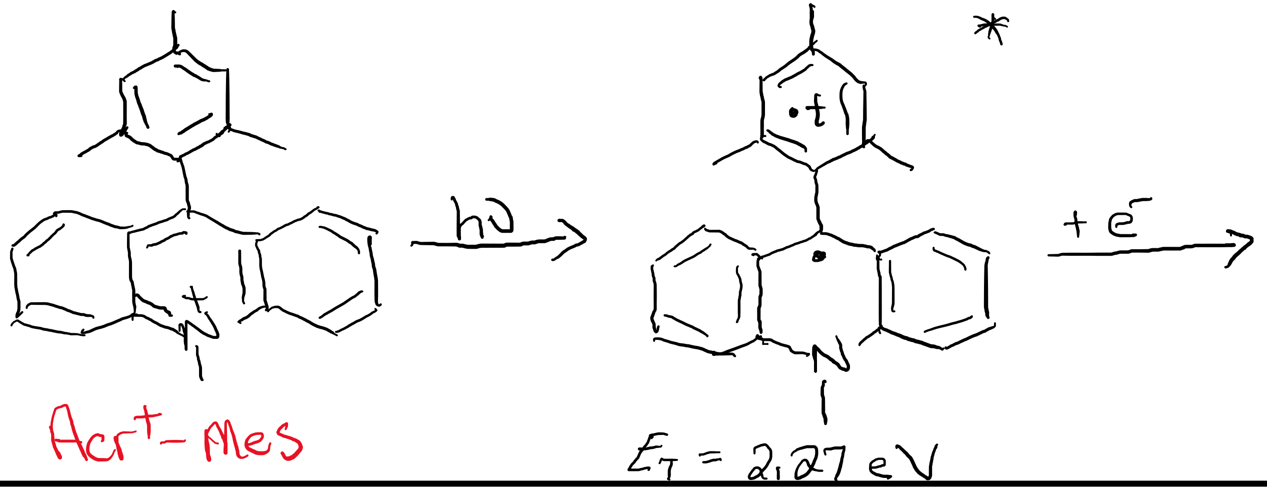
- While there are a vast number of examples of direct addition of heteroatom nucleophiles to alkenes to give Markovnikov products, comparatively few examples exist that provide anti-Markovnikov selectivity
- David Nicewicz and coworkers proposed that single-electron oxidation of alkenes to their respective radical-cations may provide a general way to access anti-Markovnikov selectivity for a range of heteroatom nucleophiles with unactivated alkenes



J. Am. Chem. Soc. **2012,** *134*, 18577.

Acridinium Photocatalysts

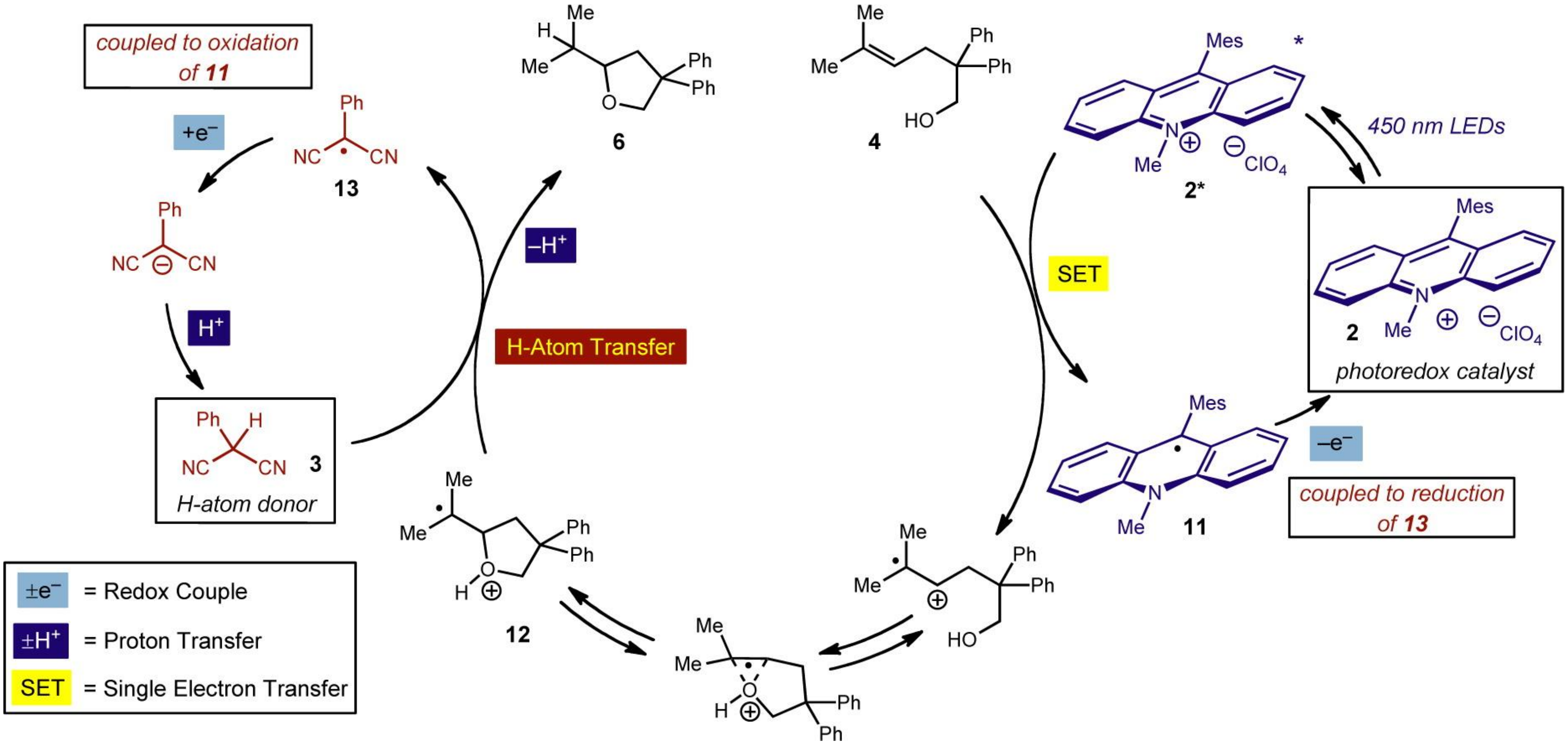
- In order to photocatalytically generate radical cations from alkenes, Nicewicz and coworkers chose to utilize the commercially available 9-mesityl-10-methylacridinium ion (Acr^+-Mes) developed by Fukuzumi and coworkers in 2010
- The photocatalyst is a linked electron donor-acceptor system, with acridinium 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
  - $^*E_{1/2}(^3\text{Mes}^{\bullet +}\text{-Acr}^{\bullet}/\text{Mes-Acr}^{\bullet}) = 2.08$ V vs. SCE



J. Am. Chem. Soc. **2004,** *126*, 1600.

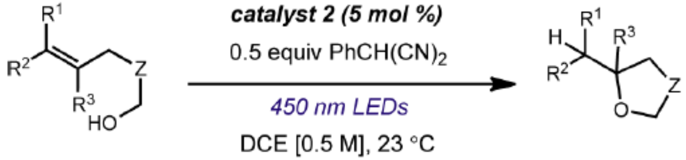
Anti-Markovnikov Hydroetherification of Alkenols

- The proposed mechanism for their transformation is shown below:



J. Am. Chem. Soc. **2012,** *134*, 18577.

Reaction Scope

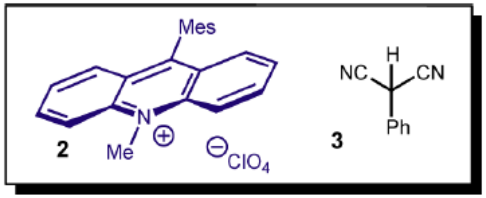


catalyst 2 (5 mol %)

0.5 equiv $PhCH(CN)_2$

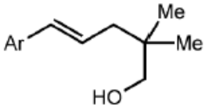
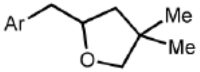
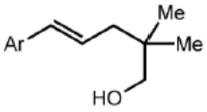
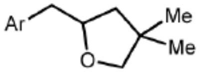
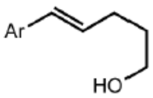
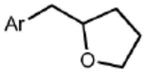
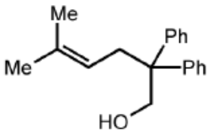
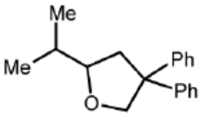
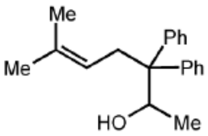
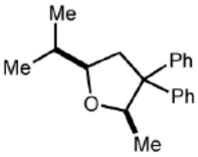
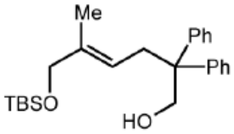
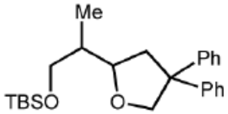
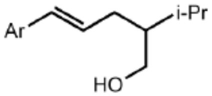
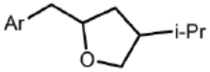
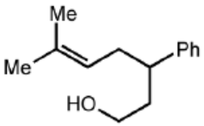
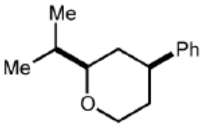
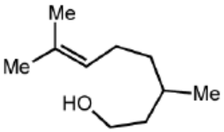
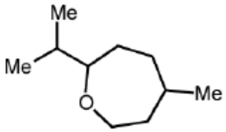
450 nm LEDs

DCE [0.5 M], 23 °C



2

3

Entry	Alkenol	Product
1	 Ar = 4-(MeO)C_6H_4 $E_{p/2}$ = +1.26 V	 *80% yield*
2	 Ar = 4-(Cl)C_6H_4 $E_{p/2}$ = +1.69 V	 *60% yield*
3	 Ar = 4-(MeO)C_6H_4 $E_{p/2}$ = +1.41 V	 *82% yield*
4	 $E_{p/2}$ = +1.95 V	 *77% yield*
5[b]	 $E_{p/2}$ = +1.98 V	 *41% yield* *5:1 d.r.*[c]
6[b]	 $E_{p/2}$ = +2.10 V *> 5:1 E:Z*	 *41% yield* *1.1:1 d.r.*[c]
7	 Ar = 4-(MeO)C_6H_4 $E_{p/2}$ = +1.30 V	 *77% yield* *1.8:1 d.r.*[c]
8[b]	 $E_{p/2}$ = +1.88 V	 *68% yield* *2.5:1 d.r.*[c]
9[b]	 $E_{p/2}$ = +1.92 V	 *46% yield* *1.2:1 d.r.*[c]

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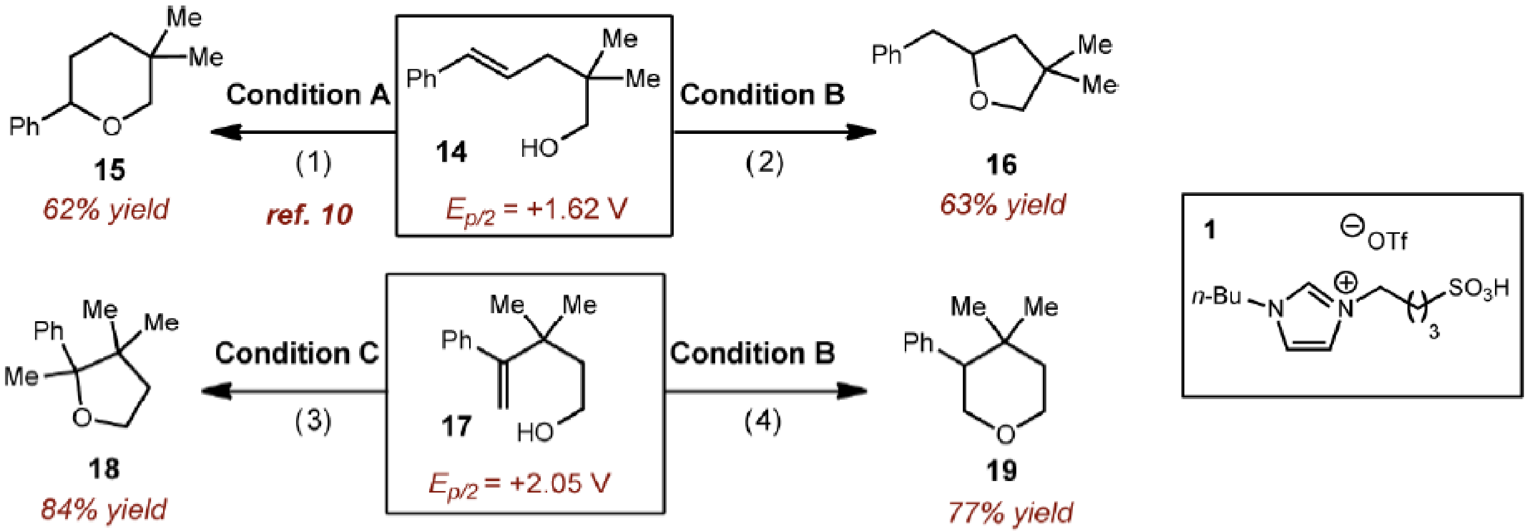
Markovninkov vs. Anti-Markovnikov Selectivity

- 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



Condition A: 1.0 equiv **1**, benzene, 80 °C
Condition B: **2** (5 mol %), 0.5 equiv **3**, 450 nm LEDs, DCM, 23 °C
Condition C: TfOH, DCM, 23 °C

- 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

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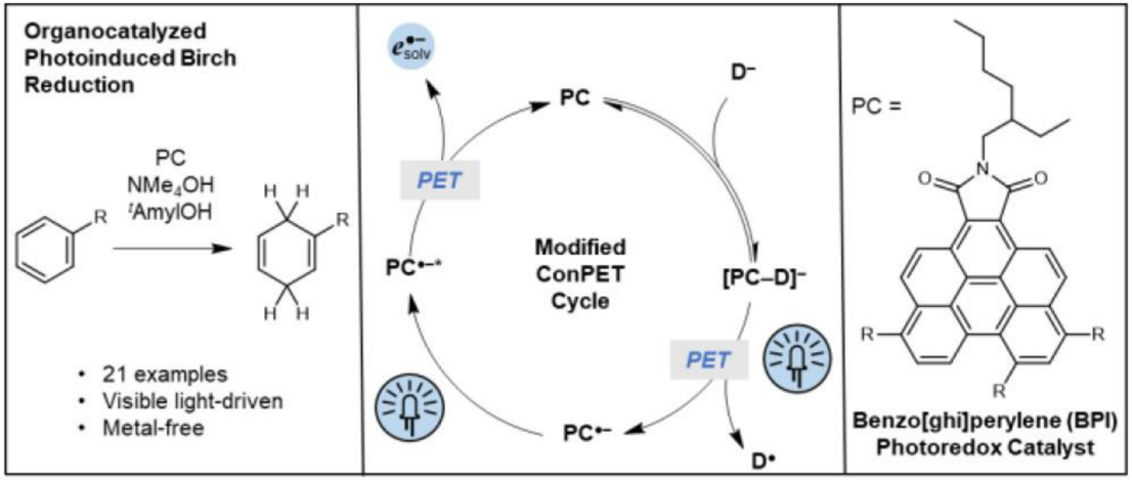
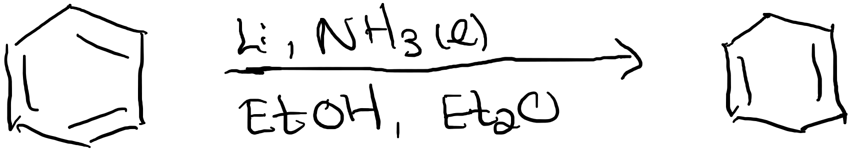


Organocatalyzed Birch Reduction Driven by Visible Light

Birch Reduction of Arenes

- 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



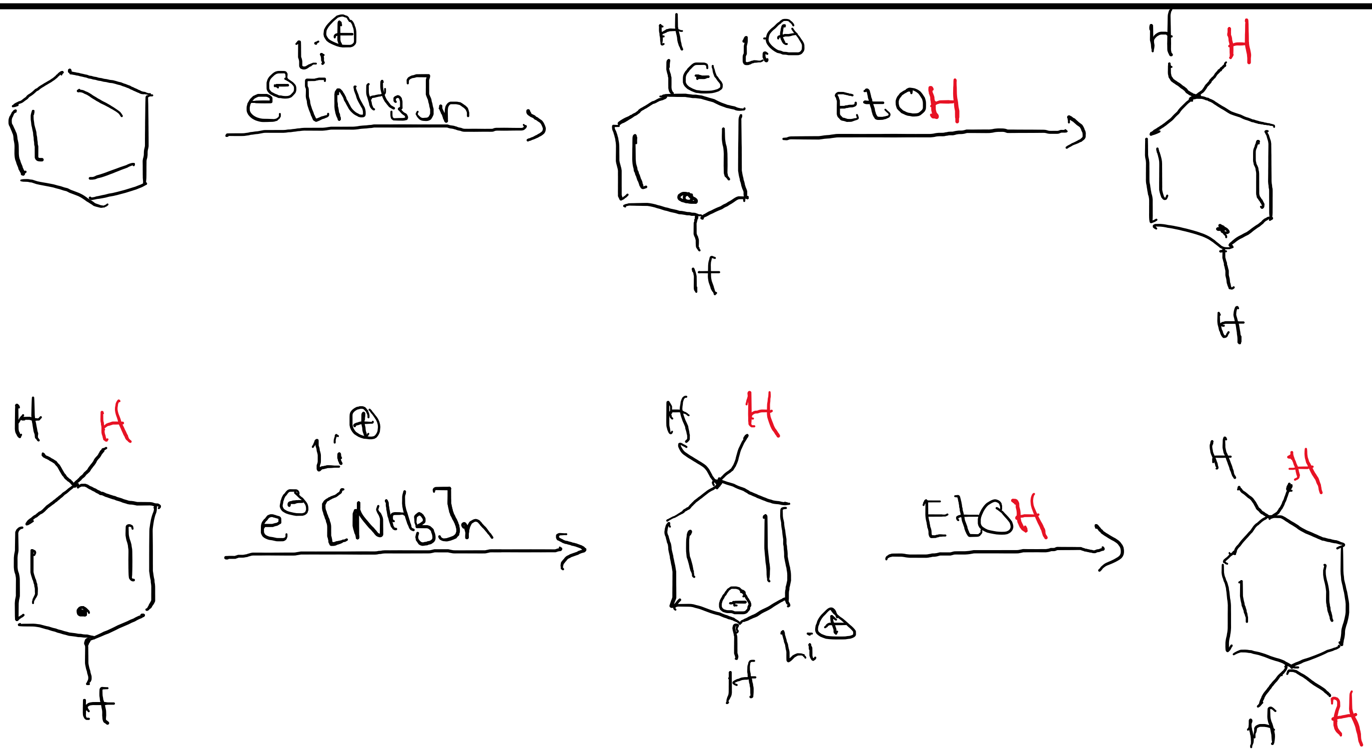
- When Li is dissolved in ammonia, it gives an intense blue solution. This is the color of solvated electrons
- Group 1 metals (like Li and Na) ionize to give Li^+ or Na^+ and $e^-(NH_3)_n$

$$Li \xrightarrow{\text{Fast}} Li^{\oplus} + e^{\ominus}[NH_3]_n \xrightarrow{\text{Slow}} {}^{\ominus}NH_2 + H \longrightarrow \tfrac{1}{2} H_2$$

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:

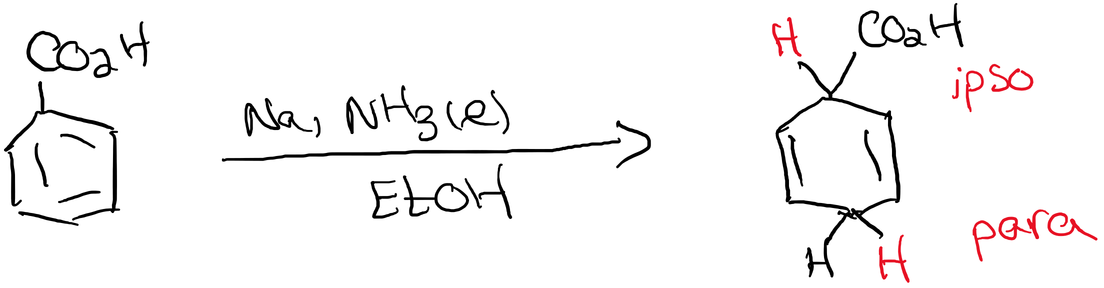


Birch Reduction of Arenes

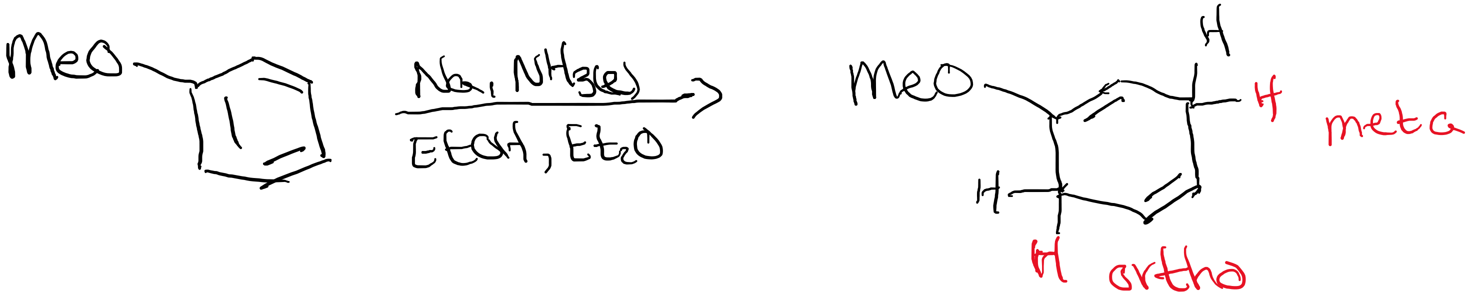
- What if we have substituents on the aromatic ring?

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

Electron-withdrawing

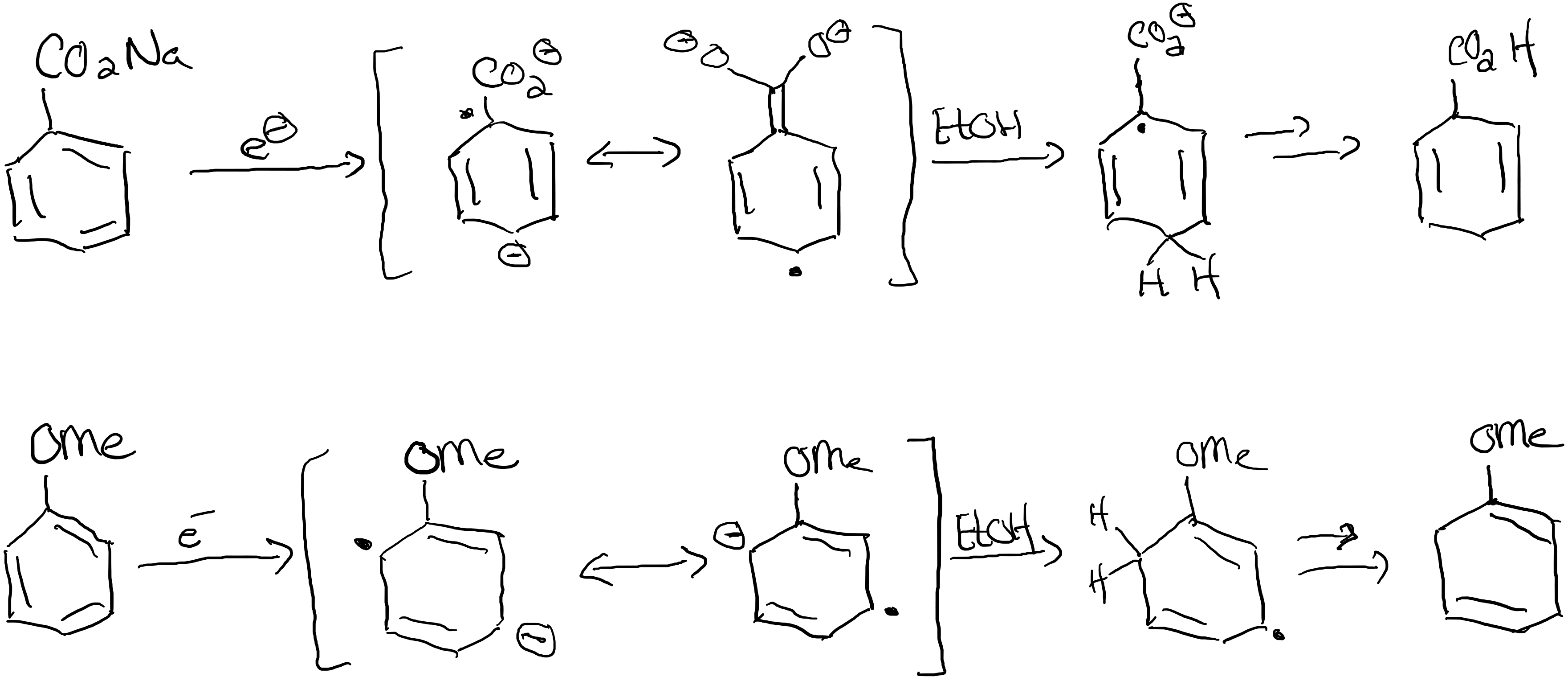


Electron-donating



Birch Reduction of Arenes

- Electron-withdrawing groups stabilize electron density at the *ipso* and *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*

“Trivial” Electron Transfer (From Chapter 7)

- The simple two-step mechanism for trivial electron transfer is shown below:

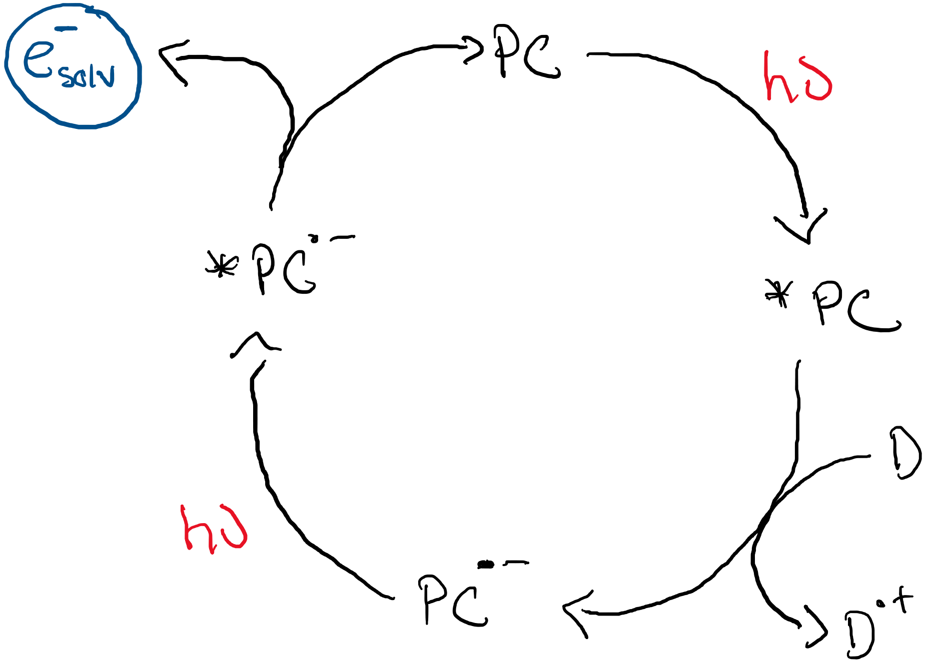
$$D + h\nu \rightarrow {}^{*}D \rightarrow D^{\bullet +} + e^{\bullet -}_{solv} \qquad (10)$$

$$e^{\bullet -}_{solv} + A \rightarrow A^{\bullet -} \qquad (11)$$

- 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 ($A^{\bullet -}$)
- Eq 10 is the primary photochemical process termed *photoionization*, which may involve a transient excited state (*D)
- Nearly all molecules undergo photoionization when they absorb a photon whose energy (E = hν) 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

Organocatalyzed Birch Reduction Driven by Visible Light

- 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



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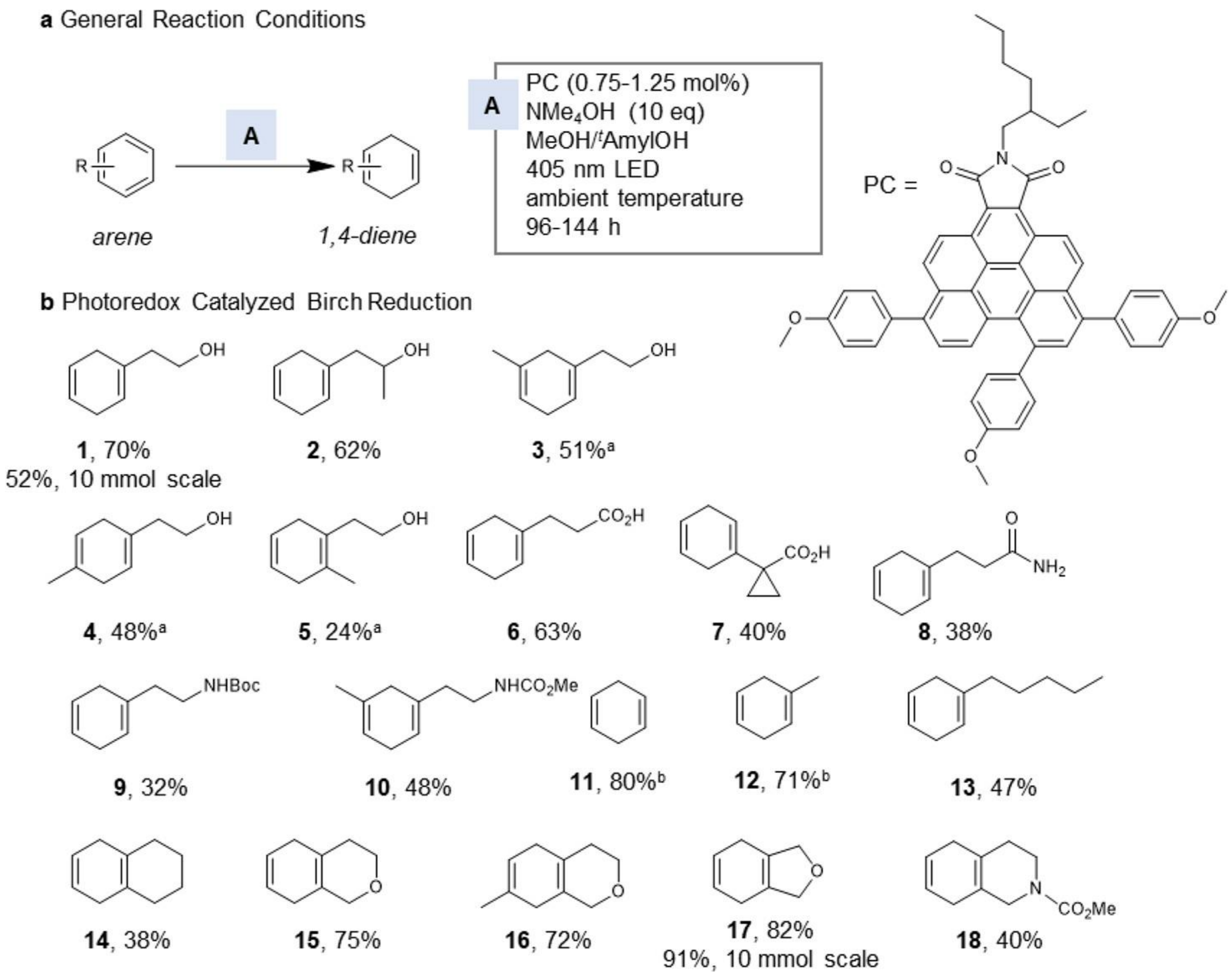
Reaction Scope



A

PC (0.75-1.25 mol%)
NMe_4OH (10 eq)
MeOH/^{t}AmylOH
405 nm LED
ambient temperature
96-144 h

b Photoredox Catalyzed Birch Reduction

1, 70%
52%, 10 mmol scale

2, 62%

3, 51%[a]

4, 48%[a]

5, 24%[a]

6, 63%

7, 40%

8, 38%

9, 32%

10, 48%

11, 80%[b]

12, 71%[b]

13, 47%

14, 38%

15, 75%

16, 72%

17, 82%
91%, 10 mmol scale

18, 40%

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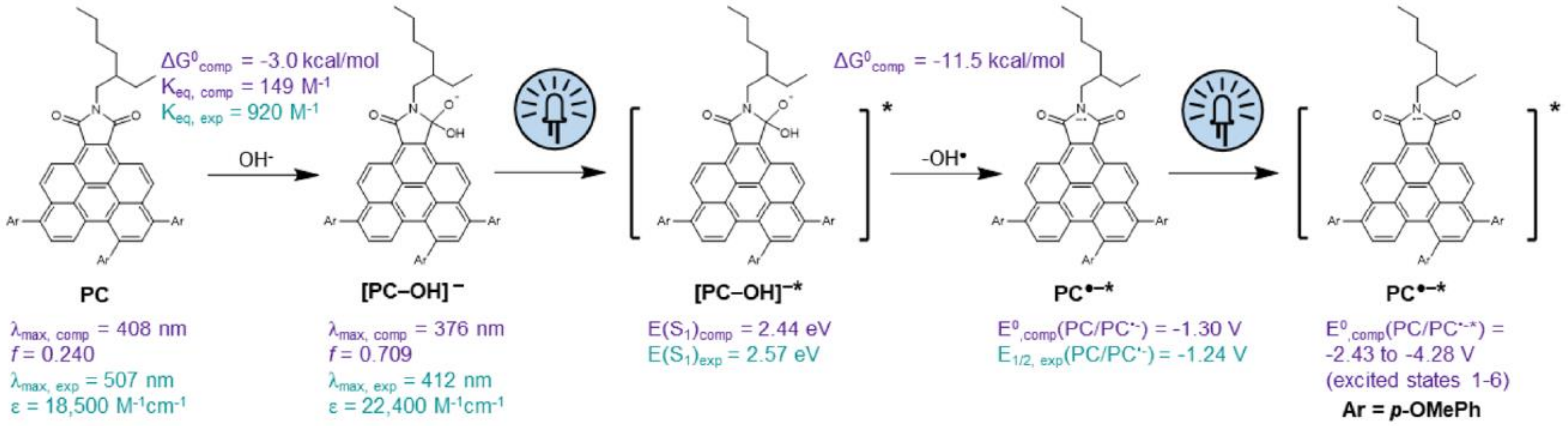
Organocatalyzed Birch Reduction Driven by Visible Light

- Their proposed mechanism for the organocatalyzed Birch reduction is shown below:

a Plausible Mechanism for Consecutive Photoinduced Electron Transfer



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