Organic Molecules, Photoredox, and Catalysis

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What is Photoredox Catalysis

Oxidation

Catalyst → Catalyst*

Reduction
Transition Metal Catalysts

- $\text{Ru(bpy)}_3^{3+}$
  - $\lambda_{max} = 452 \text{ nm}$
  - $E_{\text{red}} = 1.29 \text{ V}$
  - $E_{\text{red}} = -1.33 \text{ V}$

- $\text{Ir(ppy)}_3^{3+}$
  - $\lambda_{max} = 375 \text{ nm}$
  - $E_{\text{red}} = 0.77 \text{ V}$
  - $E_{\text{red}} = -2.19 \text{ V}$

Organic Catalyst

- eosin$Y^-$
  - $\lambda_{max} = 539 \text{ nm}$
  - $E_{\text{red}} = 0.78 \text{ V}$
  - $E_{\text{red}} = -1.06 \text{ V}$

- eosin$Y^{3-}$

- Similar range of reduction potentials
- $\text{Ru(bpy)}_3^{3+}$ 104 $/g$
- $\text{Ir(ppy)}_3^{3+}$ 1300 $/g$
- eosin$Y^-$ 1 $/g$

Why Photoredox?

• Facilitates unique/exotic bond construction
• Occurs under mild conditions
• Orthogonal to polar or two electron processes
• Tunable catalysts
• Excited state regulates reactivity
• Redox neutral processes allow catalytic use of external oxidants and reductants
Photoredox Functionalizing Untapped Reactivity

Occurs for electron rich alkenes:

\[
\text{EDG} \quad \text{O}_2 \quad \text{Sensitizer} \quad \text{EDG} \quad x \ 2
\]

No reaction for electron deficient alkenes:

\[
\text{EWG} \quad \text{O}_2 \quad \text{Sensitizer} \quad \text{EWG} \quad x \ 2
\]

Solution:

\[
\text{Ph} \quad \text{Mes-Acr BF}_4 \ (5 \text{ mol}\%) \quad \text{Ph} \quad x \ 2
\]

Photoredox Functionalizing Untapped Reactivity

Photophysical Process

- Absorption
- Decay
- ISC
- PET
- Cage escape
- Back electron transfer
- $S_1$ vs $T_1$
Absorption and Types of Decay

- **Absorption** of a photon causing an electron to excite from the ground state ($S_0$) to the singlet excited state ($S_1$)

- **Radiative decay** - Loss of radiation in the form of a photon. $S_1$ to $S_0$ is called fluorescence

- **Non-radiative decay** (Interconversion): loss of energy as heat/ vibrations/ and rotations.

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Inter System Crossing (ISC) and Electron Transfer

ISC:

- ISC is a radiationless spin relaxation from $S_1$ to the triplet $T_1$ and is a forbidden process.
- Transition from $T_1$ to $S_0$ is a forbidden process.
- Relaxation from $S_1$ to ground state $S_0$ is an allowed transition.
- A reductant can donate an electron to the excited substrate.
- This transfer causes the formation of a radical ion pair.

Photochemical Electron Transfer (PET)

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Cage Escape and Back Electron Transfer (BET)

- Cage Escape - The process of solvation and separation of a radical ion pair into free ions
- Only possible if the excited state has a long lifetime
- BET - The decay of an excited electron back to the ground state of the reductant
- BET causes no net reaction between the photocatalyst and the reductant

Outline - Photocatalyst Design

- Photophysical Properties
  - pH
  - Quantum Yield
  - Free Rotor Effect
  - Heavy Atom Effect
  - Donor-Acceptor Catalysts

Methods
pH Effects on Absorption

- Isomer A and B are not catalytically active species and do not absorb in the visible light region.
- pH is often neglected when catalytic species are reported in the literature and can drastically effect the absorption of a catalyst.

Quantum Yield

\[ \phi = \frac{\text{# molecules that undergo specific chemical process}}{\text{# photons of light absorbed}} \]

- Quantum Yield is an indicator of a processes efficiency
- Quantum yield is usually measured in terms of relative rates to different processes and can be misleading
- Example: both of these have the same quantum yield but vastly different rates of fluorescence. The rate of ISC for pyrene-3-carboxaldehyde is also much faster then benzene.

\[ \begin{align*}
\text{Benzene} & \quad \Phi=0.2 \\
\text{Pyrene-3-carboxaldehyde} & \quad \Phi=0.2, \ k_f=1\times10^8 \\
\end{align*} \]


Free Rotor Effect

- Addition of substituents with many degrees of rotational/vibrational freedom increases the efficiency of internal conversion.
- The substitution of a simple alkyl group can drastically effect the quantum yield of a catalyst.

\[
\Phi_I = 0.29 \quad \Phi_I = 0.011
\]


Why the bromines?

- Significant numbers of efficient photocatalysts contain multiple heavy atoms such as bromine or iodine.
- Heavy atoms lead to an increased population of the T$_1$ state
- This increase is due to Spin Orbit Coupling and is called the heavy atom effect

Donor-Acceptor Electron Transfer

- Efficient photocatalysts have charge separation or areas of high and low electron density separated by a lack of conjugation
- These donor-acceptor pairs facilitate electron transfer due to Marcus Theory

A New Organic Photoredox Catalyst

Acr⁺-Mes
- Strong absorption band at $\lambda=430$nm
- Strong donor-acceptors regions
- Catalyst’s excited state possesses high oxidation potential
- Reduced catalyst participates in further single electron transfer
- Mix between $S_1$ and $T_1$ state
- Commercially available 1g/$170

Acr⁺-Mes Photochemical Applications

Photophysical Properties

Catalyst Design

Methods

Aryl C-H Functionalization

Anti-Markovnikov Hydrofunctionalization

[3+2] Cyclizations

Polar Radical Crossover additions

Decarboxilative Functionalization
Anti-Markovnikov Alkene Hydrofunctionalization
Anti-Markovnikov Hydroetherification

\[
\begin{align*}
R_1 & \quad R_2 & \quad \text{Z}(=\text{CH}_2)_n \\
\text{Mes-Acr BF}_4^- (5 \text{ mol%}) & \quad \text{PhCH(CN)}_2 (1.0 \text{ equiv.}) & \quad 450\text{nm LEDs} \\
& \quad \text{DCE (0.5M), 23} \degree \text{C} & \\
\end{align*}
\]

Selected Examples:

- 60% Yield
- 41% Yield, 5:1 d.r.
- 68% Yield, 2.5:1 d.r.
- 46% Yield, 1.2:1 d.r.

Mechanism

Intramolecular Anti-Markovnikov Hydroamination

Intramolecular Hydroamination:

\[
\text{Me}\quad\text{H}\quad\text{Me} \quad\text{Ph}\quad\text{Me}\quad\text{Ph}
\]

\[
\text{Me}\quad\text{TsN}\quad\text{H}
\]

\[
\text{Mes-ACr}^+\text{BF}_4^- (5 \text{ mol%})
\]

\[
\text{PhSH} (20 \text{ mol%})
\]

\[
\text{450nm LEDs}
\]

\[
\text{DCE, 23 °C}
\]

70% Yield
3:1 d.r.

72% Yield
12:1 d.r.

54% Yield

79% Yield

Intermolecular Anti-Markovnikov Hydroamination

Intermolecular Hydroamination:

\[
\text{Ph} = \text{Me} + \text{H} \quad \text{Mes-Acr BF}_4^- (5 \text{ mol\%}) \\
\text{Ph} = \text{Me} + \text{N} \quad \text{Mes-Acr BF}_4^- (5 \text{ mol\%}) \\
\text{OMe} = \text{Me} + \text{N} \quad \text{Mes-Acr BF}_4^- (5 \text{ mol\%})
\]

(1.5 equiv) 450nm LEDs DCE, 23 °C

72% 81% Yield 4:1 (N\textsubscript{1}/N\textsubscript{2}) 83%

Anti-Markovnikov Hydrofluoronation

HF addition:

\[
\begin{align*}
\text{Mes-Me}_2\text{PhA}^+\text{tr BF}_4 (5 \text{ mol}\%) \quad &\text{4-(NO}_2\text{)C}_6\text{H}_4\text{SH (25 mol\%) } \\
\text{NET}_3^+\text{HF (1.0-2.0 equiv.)} \quad &\text{450nm LEDs} \\
\text{CHCl}_3/\text{TFE (9:1), 23 °C} \end{align*}
\]

75% Yield  
85% Yield  
65% Yield  
34% Yield

Anti-Markovnikov Hydrochloronation

HCl Addition:

\[
\begin{align*}
\text{Mes}\text{-}Acr BF}_4^- (2.5 \text{ mol\%}) & \quad 4\text{-}(\text{MeO})C_6H_4\text{SH} (20 \text{ mol\%}) \\
\text{CHCl}_3/\text{TFE} (2.5:1), \ 23 \ ^\circ\text{C}
\end{align*}
\]

Anti-Markovnikov Hydrofunctionalization

Intermolecular Hydrocarboxylation:

\[ \begin{align*}
R_1 & \quad + \\
R_2 & \quad \text{Mes-Acr}^+ \text{BF}_4^- (5 \text{ mol}%) \\
\text{PhSH} (20 \text{ mol}%) \\
2.6 - \text{lutidine} (25 \text{ mol}%) \\
\text{450nm LEDs} \\
\text{DCE, 23 °C} \\
\end{align*} \]

\[ R_2 \quad R_3 \quad \text{H} \quad \text{O} \quad \text{R}_4 \quad \text{O} \quad \text{R}_4 \]

Hydrotrifluoromethylation:

\[ \begin{align*}
\text{Ar} & \quad \text{R}_2 \\
\text{Ar} & \quad + \\
\text{F}_3\text{C}^- \text{SO}_3\text{Na} & \quad (1.5 \text{ equiv.}) \\
\text{Mes-Acr}^+ \text{BF}_4^- (2.5 \text{ mol}%) \\
\text{PhSH} (1.0 \text{ equiv}) \\
\text{450nm LEDs} \\
\text{CHCl}_3/\text{TFE} (9:1), 23 °C \\
\end{align*} \]

\[ \begin{align*}
\text{Ar} & \quad \text{H} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{Ar} & \quad \text{CF}_3 \\
\end{align*} \]


Polar Radical Crossover Additions

- Aryl C-H Functionalization
- Anti-Markovnikov Hydrofunctionalization
- Formal [3+2] Cycloadditions
- Decarboxilative Functionalization
- Polar Radical Crossover Additions
Group Question

Provide a reasonable mechanism, and a stereochemical rationale for the formation of the syn and anti products. Finally, indicate which will be the major product.

Mechanism

Group Question Answer

Decarboxylative Functionalization

Aryl C-H Functionalization

Anti-Markovnikov Hydrofunctionalization

Formal [3+2] Cycloadditions

Polar Radical Crossover additions

Decarboxilative Functionalization
Hydrodecarboxylation

\[
\text{Mes-Acr BF}_4^+ (1 \text{ mol}) \\
\text{Bis(4-chlorophenyl) disulfide (10 mol}) \\
\text{2,6-lutidine (20 mol}) \\
\text{450nm LEDs} \\
\text{DCE, 23 °C}
\]

Selected examples

- Ph-NHBoc: 99% Yield
- Me-NHCbz: 82% Yield
- Me-OH-NHCbz: 90% Yield
- Cbz: 91% Yield

Hydrodecarboxylation

Fluorination

Decarboxylative Fluorination:

\[ R \cdot \text{CO}_2\text{H} \xrightarrow{\text{Mes-Acr BF}_4 (1 \text{ mol\%}) \atop \text{Selectfluor (2.0 equiv)} \atop \text{Cs}_2\text{CO}_3 (1.0 \text{ equiv})} 23 \text{ W CFL} \atop \text{DCE, 23 } ^\circ\text{C}} R \cdot \text{F} \]

Selected Examples:

- 82% Yield
- 98% Yield
- 55% Yield
- 51% Yield

Formal [3+2] Cycloadditions
Formal [3+2] Cycloaddition for Pyrrole Synthesis

\[
\begin{align*}
N & \quad R_2 \quad + \quad \text{EWG} \\
\text{R}_1 \quad \text{EWG} & \quad \text{Mes-Acr}^+\text{BF}_4^- (5 \text{ mol}%) \\
& \quad \text{450nm LEDs} \\
& \quad \text{DCE, 23 °C}
\end{align*}
\]

Selected examples:

- **MeO**
  - 91% Yield
- **Cl**
  - 85% Yield
- **Bu**
  - 76% Yield
- **Ph**
  - 65% Yield

Proposed Mechanism

Oxazole Synthesis via Azirine–Aldehyde Cycloaddition

\[
\text{Mes-Acr}^+\text{BF}_4^- \; (5 \, \text{mol}\%)
\]
\[
2 \, \text{equiv} \text{Li}_2\text{CO}_3
\]
\[
7 \, \text{W} \; 450\text{nm LEDs}
\]
\[
4\AA \, \text{MS}, \text{DCE}, 23^\circ\text{C}
\]

Selected examples:

- Cl-Ph-N=O-Ph
  - 73\% Yield
- Ph-MeO-N=O-Ph
  - 59\% Yield
- Ph-N=O-Ph
  - 53\% Yield
- Ph-N=O-Ph
  - 56\% Yield
- Ph-N=O-Ph
  - 36\% Yield
- Ph-N=O-Ph
  - 74\% Yield

Aryl C-H Functionalization

- Aryl C-H Functionalization
- Anti-Markovnikov Hydrofunctionalization
- Formal [3+2] Cycloadditions
- Polar Radical Crossover additions
- Decarboxilative Functionalization
Arene C-H Amination

\[
\text{MeO-} + \text{NR}_2'\text{H} \quad \text{(1.25 - 2.0 equiv)} \quad \text{Mes-t-Bu}_2\text{PhAc}^+\text{BF}_4^- (5 \text{ mol%}) \\
\text{O}_2, \text{TEMPO (20 mol%)} \quad \text{455nm LEDs} \\
\text{DCE, 33°C} \quad \Rightarrow \text{MeO-} \quad \text{NR}_2'
\]

Selected Examples:

- **99% Yield**
  - MeO- \text{9H}- \text{N} \quad \text{(Boc)}_2\text{N} \quad 4:1 \text{ p:o}

- **85% Yield**
  - MeO- \text{9H}- \text{N} \quad \text{Me} \quad 5:1 \text{ p:o}

- **52% Yield**
  - MeO- \text{9H}- \text{N} \quad \text{(Boc)}_2\text{N} \quad \text{CO}_2\text{Me} \quad 5:1 \text{ p:o}

Mechanism

Arene Cyanation

\[
\begin{align*}
\text{R} & \quad \text{TMSCN (1.5 equiv)} + \\
& \quad \text{Mes-t-Bu}_2\text{PhAcr BF}_4 (5 \text{ mol}\%) \\
& \quad \text{O}_2 \\
& \quad \text{MeCN/ pH 9 Buffer 10:1} \\
& \quad 455\text{nm LEDs}
\end{align*}
\]

43\% Yield
48\% Yield
51\% Yield A:B 1:1.3
39\% Yield

Conclusion

- Organic photoredox catalysis is an expanding field
- Many privileged catalytic scaffolds other than the acridinium family exist
- Applications towards oxidation, reduction, C-H functionalization, and decarboxylative functionalization have been discovered
- New dual catalytic systems should be developed to enable enantioselective catalysis
- Increased oxidation and reduction potentials are necessary for the discovery of new types of synthetic disconnections
References

Reviews


Books


Questions?