Fundamentals and recent applications of visible light sensitized energy transfer ($E_n T$) for [2+2] and [4+2] cycloaddition

- Fundamentals
  - Definitions
  - Direct substrate excitation and why sensitization
  - Mechanisms of energy transfer
  - Photocatalyst and substrate considerations

- Applications
  - Photocatalytic olefin / olefin [2+2] cycloaddition
  - Photocatalytic olefin / carbonyl and olefin / oxime [2+2] cycloaddition (Paternò-Büchi type processes)
  - Photocatalytic dearomative [2+2] and [4+2] olefin / (hetero)arene cycloaddition
  - Enantioselective photocatalytic [2+2]
Reviews on energy transfer and sensitization:

Review on [2+2] photocycloaddition in general:

Reviews on Paternò-Büchi and aza Paternò-Büchi in general:

Reviews on olefin isomerization (site and E/Z):

Leading research groups (in no particular order):
– Yoon, UW-Madison
– Oderinde, BMS Princeton
– Xiao, CCNU, Wuhan
– Houk, UCLA
– Bach, TU München
– Glorius, Münster
– Gilmore, Münster
– Schindler, UMich
– Meggers, Marburg
– Baik, KAIST Daejeon
Definitions

- (Visible light) Photocatalysis:

  - Ground state catalyst
    \[ \rightarrow \text{(Visible) Light} \]
    \[ \rightarrow \text{Catalyst}^* \]
    \[ \rightarrow \text{Ground state catalyst, or catalyst intermediate} \]

- Photoredox catalysis:

  - Ground state catalyst
    \[ \rightarrow \text{Light} \]
    \[ \rightarrow \text{Catalyst}^* \]
    \[ \rightarrow \text{Oxidised or reduced catalyst} \]

- Energy transfer catalysis, or sensitization catalysis:

  - Ground state catalyst
    \[ \rightarrow \text{Light} \]
    \[ \rightarrow \text{Catalyst}^* \]
    \[ \rightarrow \text{Ground state catalyst} \]
Direct substrate excitation and why sensitization

- (Simplified) Jablonski diagram for direct substrate excitation:

\[ S_0 \text{ Ground state} \]
\[ S_1 \text{ Excited state} \]

\[ \text{Absorption} \]
\[ \text{Fluorescence} \]
\[ \text{Phosphorescence} \]

\[ \Delta E \text{ (Absorption and Emission)} \]
\[ = \text{Stokes shift} \]

- Taking into account vibrational states:

\[ S_0 \text{ Ground state} \]
\[ S_1 \text{ Excited state} \]

\[ \text{Non-radiative decay} \]
\[ \text{Absorption} \ S(0,0) \rightarrow S(1,3) \]
\[ \text{Fluorescence} \ S(1,0) \rightarrow S(0,0) \]
Mechanisms of energy transfer

- Förster energy transfer mechanism (Coulombic interaction), 1948:

  \[ k_{\text{ET}} = \left( \frac{R_0}{r} \right)^6 \frac{1}{\tau_D} \]

  \( R_0 = \text{Förster distance} = \text{distance for which energy transfer is 50\% (quantum) efficient} \)

  \( r = \text{Donor / Acceptor separation} \)

  \( \tau_D = \text{Donor fluorescence lifetime} \)

  We see that rate of EnT decreases by the inverse sixth power as distance between D and A increases.

- Longer range energy transfer, ca. 10 – 100 Å
Mechanisms of energy transfer

- Dexter energy transfer mechanism (exchange interaction), 1953:

\[ \begin{align*}
S_0 & \quad S_0 \\
S^1 & \quad S^1 \\
T_1 & \quad T_1
\end{align*} \]

\[ \begin{align*}
\text{Donor} & \quad \text{Acceptor} \\
\text{Light absorption} & \quad \text{ISC} \\
\text{Dexter energy} & \quad \text{transfer}
\end{align*} \]

- Rate (\( k_{\text{EnT}} \)) dependance described as:

\[ k_{\text{EnT}} = K \cdot J \cdot e^{-\frac{2R_{DA}}{L}} \]

\( K \) = Specific orbital interaction parameter
\( J \) = Spectral overlap integral
\( R_{DA}/L \) = Measure of distance between donor and acceptor (catalyst and substrate in this case)

- We see that rate of EnT decreases exponentially as distance between D and A increases.
- Negligible rate at distances greater than ~2 molecular diameters
- Thus, intimate physical contact and orbital overlap is required between substrate and catalyst for EnT to occur
- Short range energy transfer, ca. 5 – 30 Å
Photocatalyst considerations

a) Literature-known Photosensitizers

- Methylene blue
  - (32.0)
- \([\text{Ir}^{II}(\text{ppy})_2(\text{dtbpy})]^+\)
  - (49.2)
- \(\text{fac-}[\text{Ir}(\text{ppy})_3]\)
  - (58.1)
- Michler’s Ketone
  - (51.0)
- \(\text{fac-}[\text{Ir}(\text{dF-ppy})_3]\)
  - (63.5)

- \([\text{Ru}(\text{bpy})_3]^{2+}\)
  - (49.0)
- Riboflavin
  - (50.0)
- \([\text{Ir}^{III}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]^+\)
  - (61.8)
- Benzophenone
  - (69.1)
- Acetophenone
  - (74.0)
- Thioxanthone
  - (63.4)

All triplet energies are given in kcal mol\(^{-1}\).
Photocatalyst considerations

– State of the art in triplet photocatalyst design, Booker-Milburn and Elliot, 2020:

Photocatalyst considerations

State of the art in triplet photocatalyst design, Booker-Milburn and Elliot, 2020:

<table>
<thead>
<tr>
<th>entry</th>
<th>TX</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; &lt;sup&gt;a&lt;/sup&gt; (nm)</th>
<th>E&lt;sub&gt;T (Meas.)&lt;/sub&gt; &lt;sup&gt;d&lt;/sup&gt; (kJ/mol)</th>
<th>E&lt;sub&gt;T&lt;/sub&gt; /kcal/mol</th>
<th>τ&lt;sub&gt;T&lt;/sub&gt; &lt;sup&gt;h&lt;/sup&gt;</th>
<th>Φ&lt;sub&gt;ISC&lt;/sub&gt; &lt;sup&gt;i&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,3′-MeOTX</td>
<td>354</td>
<td>298&lt;sup&gt;e&lt;/sup&gt;</td>
<td>71.3</td>
<td>862 ± 40 ns</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>3,3′-FTX</td>
<td>362</td>
<td>289&lt;sup&gt;e&lt;/sup&gt;</td>
<td>69.1</td>
<td>456 ± 25 ns</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>3-MeOTX</td>
<td>367</td>
<td>283&lt;sup&gt;e&lt;/sup&gt;</td>
<td>67.7</td>
<td>867 ± 50 ns</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>4</td>
<td>3-FTX</td>
<td>370</td>
<td>282&lt;sup&gt;e&lt;/sup&gt;</td>
<td>67.5</td>
<td>520 ± 25 ns</td>
<td>0.83</td>
</tr>
<tr>
<td>5</td>
<td>TX (R/R′ = H)</td>
<td>380</td>
<td>274&lt;sup&gt;e&lt;/sup&gt;</td>
<td>65.6</td>
<td>760 ± 30 ns</td>
<td>0.76&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>1′TX (R′ = H, R = 2-′Pr)</td>
<td>385</td>
<td>266&lt;sup&gt;e&lt;/sup&gt;</td>
<td>63.6</td>
<td>880 ± 50 ns</td>
<td>0.86</td>
</tr>
<tr>
<td>7</td>
<td>2-FTX</td>
<td>388</td>
<td>261&lt;sup&gt;e&lt;/sup&gt;</td>
<td>62.4</td>
<td>585 ± 20 ns</td>
<td>0.81</td>
</tr>
<tr>
<td>8</td>
<td>4-MeOTX</td>
<td>385</td>
<td>263&lt;sup&gt;e&lt;/sup&gt;</td>
<td>62.9</td>
<td>1.8 ± 0.3 µs</td>
<td>0.70</td>
</tr>
<tr>
<td>9</td>
<td>2-MeOTX</td>
<td>399</td>
<td>242&lt;sup&gt;f&lt;/sup&gt;</td>
<td>57.9</td>
<td>1.7 ± 0.6 µs</td>
<td>0.83</td>
</tr>
<tr>
<td>10</td>
<td>2-F,2′-MeOTX</td>
<td>408</td>
<td>235&lt;sup&gt;f&lt;/sup&gt;</td>
<td>56.2</td>
<td>1.2 ± 0.2 µs</td>
<td>0.62</td>
</tr>
<tr>
<td>11</td>
<td>2,2′-MeOTX</td>
<td>415</td>
<td>231&lt;sup&gt;f&lt;/sup&gt;</td>
<td>55.3</td>
<td>863 ± 60 ns</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Substrate considerations

b) Selected Substrates

[Diagram showing various substrates with their respective values in parentheses]

General mechanism for sensitized [2+2] photocycloaddition

- General mechanism for sensitized olefin / olefin [2+2] photocycloaddition:

![Mechanism Diagram]

- EnT
- PC*
- hv
- PC
- ISC
- C–C bond formation
- 5-exo-trig
- Radical recombination
- C–C bond formation
Photocatalytic olefin / olefin [2+2] cycloaddition
Photocatalytic olefin / olefin [2+2] cycloaddition

- Norbornadiene / quadricyclene isomerization.
- Investigated as a photo-chemical energy storage system.
- Recognised as the earliest visible light photocatalytic energy transfer process:

\[
\text{[Ru(bpy)_3]Cl}_2 \text{ catalyst}
\]

\[
\text{MeCN, visible light, rt.}
\]

56% conversion

\[ E_T = \sim 47-50 \text{ kcal/mol} \]

**Table I. Half-Wave Oxidation and Reduction Potentials of 4 and 5**

<table>
<thead>
<tr>
<th>compound</th>
<th>( E_{1/2}^{\text{ox}}, \text{V}^a )</th>
<th>( E_{1/2}^{\text{red}}, \text{V}^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.82</td>
<td>-1.39</td>
</tr>
<tr>
<td>5</td>
<td>1.76</td>
<td>&lt; -2.4</td>
</tr>
</tbody>
</table>

\(^a\) Measured in acetonitrile; potentials are relative to SCE.

**Table II. Limiting Quantum Yields for Triplet-Sensitized Conversion of 4 to 5**

<table>
<thead>
<tr>
<th>sensitizer</th>
<th>( \lambda_{\text{excit.}}, \text{nm} )</th>
<th>( \phi_{\text{lim, sec}}^a )</th>
<th>( E_T, \text{ kcal (} \phi_T)) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru(bpy)_3 (^2+)</td>
<td>546</td>
<td>0.06 ± 0.01 (^b)</td>
<td>47 (^c) (1.0) (^d)</td>
</tr>
<tr>
<td>9-fluorenone</td>
<td>436</td>
<td>0.15 ± 0.01 (^e)</td>
<td>53.3 (^f) (0.93) (^g)</td>
</tr>
<tr>
<td>biacetyl</td>
<td>436</td>
<td>0.11 ± 0.01 (^k)</td>
<td>56.3 (^j) (1.0) (^i)</td>
</tr>
<tr>
<td>thioxanthone</td>
<td>405</td>
<td>&lt;0.3 (^m)</td>
<td>65.5 (^l) (1.0) (^j)</td>
</tr>
</tbody>
</table>

\(^a\) Triplet-state energy (efficiency of forming triplet state).
\(^b\) Corrected for incomplete quenching of sensitizer. \(^c\) Reference 13.
\(^d\) Reference 12. \(^e\) Obtained from intercept of plot of \( \phi^{-1} \) vs. [4]^{-1}.
\(^f\) Reference 25a. \(^g\) Reference 25b. \(^h\) Measured under conditions of complete sensitizer quenching. \(^i\) Reference 25d. \(^j\) Reference 25c.
Photocatalytic olefin / olefin [2+2] cycloaddition

– Xiao 2012.
  –Dimerization of 3-ylidene oxindoles via sensitized [2+2] cycloaddition:

\[
\begin{align*}
\text{R}_2\text{O}_2\text{C} & \quad \text{N} \\
\text{CO}_2\text{R} & \quad \text{N}
\end{align*}
\]

2 mol\% [Ru(bpy)$_3$]Cl$_2$, DMF, visible light

21 examples
67–91\% yields
All d.r. >19:1

– Select examples:

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Me} & \quad 83\% \\
\text{Br} & \quad \text{EtO}_2\text{C} & \quad 92\% \\
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Et} & \quad 87\%
\end{align*}
\]
Photocatalytic olefin / olefin [2+2] cycloaddition

- Yoon 2012.
  - Intramolecular [2+2] photocycloaddition of styrenes and olefins:

\[
\text{Ar} \equiv \begin{array}{c}
\text{X} \\
\text{R}_1
\end{array} + \begin{array}{c}
\text{X} \\
\text{R}_2
\end{array} \rightarrow \begin{array}{c}
\text{X} \\
\text{R}_1
\end{array}
\]

\[
\text{1 mol\% } [\text{Ir(dF(CF}_3\text{)}_ppy)_2(\text{dtbbpy})]\text{PF}_6
\]

DMSO, Blue LED, rt.

25 examples
64–90% yields
d.r. 1:1 to >10:1

- Select examples:

- 89%, d.r. >10:1
- 71%, d.r. >10:1
- 80%, d.r. 7:1
- 90%, d.r. >10:1
- 89%, d.r. >10:1
- 76%, d.r. 5:1

Photocatalytic olefin / olefin [2+2] cycloaddition

- Yoon 2012.
- Total synthesis of (±)-cannabiorcycloic acid:

\[
\begin{align*}
\text{EtO}_2C\text{Me}\text{OH} + \text{OHCMe} & \xrightarrow{1 \text{ mol% } \text{[Ir(dF(CF}_3)ppy}_2(\text{dtbbpy})]\text{PF}_6} \text{DMSO, Blue LED, rt.}\nonumber \\
& \quad \rightarrow \text{EtO}_2C\text{Me}\text{OH} \quad \text{54\%} \\
& \quad \rightarrow \text{LiOH, 60 °C} \quad \text{97\%} \\
\end{align*}
\]

Photocatalytic olefin / olefin [2+2] cycloaddition

- Yoon 2012.
- Switchable selectivity through partitioning between electron transfer and energy transfer pathways:

\[
[Ru(bpz)_3]^{2+}:
\]

\[
[Ir(dF(CF_3)ppy)_2(dtbbppy)]^{+}:
\]

Scheme 1. Proposed Mechanism

Photocatalytic olefin / olefin [2+2] cycloaddition

Yoon 2014.
- Intramolecular [2+2] photocycloaddition of 1,3-dienes:

\[
\text{1 mol\% } [\text{Ir(dF(CF}_3\text{)}_3\text{ppy})_2(\text{dtbbpy})]PF_6 \to \text{conversion to product.}
\]

DMSO, Blue LED, rt.

18 examples
71–98% yields
d.r. 1:1 to >10:1

- Select examples:

- 95%, d.r. 3:1
- 81%, d.r. >10:1
- 98%, d.r. 2:1
- 92%, d.r. 2:1

Photocatalytic olefin / olefin [2+2] cycloaddition

- Yoon 2014.
- Total synthesis of (±)-epiraikovenal:

\[
\text{CHO} \quad \text{Me} \quad \text{Me} \\
\text{Me} \quad \text{CHO} \quad \begin{aligned} \text{AllylP(O)(OEt)}_2 \\ \text{BuLi} \end{aligned} \quad 84\% \\
\text{Me} \quad \text{Me} \quad \text{Me} \\
\begin{aligned} \text{Me} \quad \text{CHO} \\ \text{Me} \quad \text{Me} \quad \text{Me} \\ \text{OHC} \quad \text{OH} \end{aligned} \quad \begin{aligned} \text{1 mol}\% \text{[Ir(dF(CF}_3)ppy)_2(dtbbpy)]PF}_6 \\ \text{DMSO, Blue LED, rt.} \end{aligned} \quad 98\% \\
\text{Grubbs-II} \quad \begin{aligned} \text{Me} \\ \text{Me} \\ \text{Me} \quad \text{CHO} \quad \text{OH} \\ \text{Me} \quad \text{H} \quad \text{H} \quad \text{Me} \\ \text{H} \quad \text{H} \quad \text{Me} \quad \text{Me} \\
\end{aligned} \quad 42\%
Photocatalytic olefin / olefin [2+2] cycloaddition

  - Intramolecular crossed-addition [2+2] photocycloaddition of styryl / aryl vinyl ketones:

\[
\text{R} \quad \text{O} \quad \text{R} \\
1 \text{ mol}\% \quad [\text{Ir(}d\text{F(CF}_3\text{)}_3\text{ppy})_2(\text{dtbbpy})]\text{PF}_6 \\
\text{CH}_2\text{Cl}_2, \quad \text{White LED, rt.}
\]

- Select examples:

  - 96%
  - 77%
  - 83%, d.r. 2:1
  - 94%
Photocatalytic olefin / olefin [2+2] cycloaddition

- Computational study reveals the source of crossed-addition selectivity:

\[ \text{1 mol\%} \ \text{[Ir(dF(CF}_3\text{ppy)}_2(\text{dtbbpy})]}\text{PF}_6 \ \text{CH}_2\text{Cl}_2, \ \text{White LED, rt.} \]

20 examples
38–96% yields

Photocatalytic olefin / olefin [2+2] cycloaddition

- Jaimson 2020.
- Total synthesis of (±)-Sceptrin:

\[
\text{NHBOc} \quad \text{Cy}_2\text{BH}, \text{HBPin} \quad \text{THF, 50 °C} \quad \text{Cy}_2\text{B} - \text{NHBOc}
\]

\[
5 \text{ mol% Pd(PPh}_3)_2\text{Cl}_2 \quad \text{K}_2\text{CO}_3, \text{ THF / H}_2\text{O, 80 °C} \quad 63\%, \text{ two steps}
\]

\[
\text{Br} \quad \text{NHBoc}
\]

\[
1.8 \text{ mol% [Ir(dF(CF}_3)_ppy)_2(dtbbpy)]PF}_6 \quad 0.5 \text{ M MeOH} \quad \text{Blue LED, rt.}
\]

- Prior efforts to this molecule from Birman, Baran, and Chen required 11-25 steps.
Photocatalytic carbonyl / olefin [2+2] cycloaddition
Photocatalytic carbonyl / olefin [2+2] cycloaddition

– Schindler and Yoon 2020.
– Visible-light photosensitized Paternò-Büchi reaction of aryl glyoxalates and olefins.
– Schindler:

\[
\begin{align*}
\text{Ar} & \text{CO}_2 \text{R}_1 + \text{R}_2 & \xrightarrow{1 \text{ mol} \% \text{ [Ir(dF(CF}_3)ppy)_2(dtbbpy)]PF}_6 \text{ MeCN, Blue LED, rt.}} & 15 \text{ examples} \\
& & & 46–99{\%} \text{ yields}
\end{align*}
\]

– Select examples:

- \( \text{O} \text{Ph} \text{CO}_2 \text{Me} \) 68%, r.r. 4:1
- \( \text{O} \text{Ph} \text{CO}_2 \text{Et} \) 65%, d.r. 6:1
- \( \text{O} \text{H} \text{O} \text{Ph} \text{CO}_2 \text{Me} \) 64%, r.r. >20:1

– Yoon:

\[
\begin{align*}
\text{Ar} & \text{CO}_2 \text{R}_1 + \text{R}_2 & \xrightarrow{1 \text{ mol} \% \text{ [Ir(dF(CF}_3)ppy)_2(dtbbpy)]BAr}^F \text{ PhMe, Blue LED, rt.}} & 24 \text{ examples} \\
& & & \sim90{\%} \text{ yields}
\end{align*}
\]

– Select examples:

- \( \text{O} \text{Ph} \text{CO}_2 \text{Me} \) 98%
- \( \text{O} \text{H} \text{O} \text{Ph} \text{CO}_2 \text{Et} \) 46%
- \( \text{O} \text{S} \text{H} \text{O} \text{Ph} \text{CO}_2 \text{Et} \) 56%

Photocatalytic carbonyl / olefin [2+2] cycloaddition

- Schindler and Yoon 2020.
  - Yoon also demonstrates Norrish type-2 energy transfer reactivity:

\[
1 \text{ mol\% } [\text{Ir(dF(CF}_3\text{)ppy)}_2\text{(dtbbpy)}]\text{PF}_6
\]
MeCN, Blue LED, rt.

8 examples
52–97% yields

- Select examples:

\[
\begin{array}{c}
\[
\text{MeCO}_2\text{Me}
\end{array}
gr
\]

97%

\[
\begin{array}{c}
\[
\text{Br} \text{CO}_2\text{Me}
\end{array}
gr
\]

80%

Photocatalytic carbonyl / olefin [2+2] cycloaddition

- Schindler and Yoon 2020.
- ... And partitioning between energy transfer and electron transfer reactivity:

Scheme 1. Divergent Outcomes of Triplet Sensitization and Photoredox Reactions of Benzoylformate Esters

Photocatalytic oxime / olefin [2+2] cycloaddition
Photocatalytic oxime / olefin [2+2] cycloaddition

  – Intramolecular oxime / olefin [2+2] photocycloaddition:

\[
\text{Ar} = \text{O, CH}_2, \text{NTs}
\]

\[
0.5 \text{ mol}\% \ [\text{Ir}((\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6
\]

THF, Blue LED, rt.

21 examples
39–99% yields
d.r. 1.6:1 to >20:1

– Select examples:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>98%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>95%</td>
<td>2.5:1</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>74%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>42%</td>
<td>7:1</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>39%</td>
<td>&gt;4:1 exo/endo &gt;20:1</td>
</tr>
</tbody>
</table>

Photocatalytic oxime / olefin [2+2] cycloaddition

- Schindler 2019.
  - Optimization and mechanistic support:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Z/E ratio</th>
<th>Yield</th>
<th>d.r.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)</td>
<td>1:1.3</td>
<td>96%</td>
<td>91%^a</td>
</tr>
<tr>
<td>2</td>
<td>18a</td>
<td>1:1.3</td>
<td>96%</td>
<td>90%^a</td>
</tr>
<tr>
<td>3</td>
<td>18b</td>
<td>1:1.1</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18c</td>
<td>2:6</td>
<td>62%</td>
<td>13:1</td>
</tr>
<tr>
<td>5</td>
<td>18d</td>
<td>0:1</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

Conditions: Reactions were performed with 0.25 mM substrate and 0.5 mM Ir(ppy)$_2$(dtbbpy) in THF (0.01 M) at ambient temperature under blue LED (427 nm) for 6 h.

^aee:ee ratio (d.r.) was determined by $^1$H NMR from the crude reaction mixture

- Reaction performed on gram scale

**Mechanistic hypothesis for visible light-enabled Aza Paterno-Büchi reaction**

**a** Stem-volmer quenching studies

**b** Stereocconvergence of Aza Paterno-Büchi reaction

**c** Oxime E/Z isomerisation during course of reaction

Photocatalytic oxime / olefin [2+2] cycloaddition

  – Intermolecular [2+2] photocycloaddition between 2-isoxazoline-3-carboxylates and unactivated olefins:

\[
\begin{align*}
\text{R}_1 \text{O} & \quad \text{R}_2 \quad \text{N} \\
& \quad \text{R}_3 \quad \text{R}_4 \quad \text{O} \\
\text{R}_1 \text{O} & \quad \text{R}_2 \quad \text{N} \\
& \quad \text{R}_3 \quad \text{R}_4 \quad \text{O}
\end{align*}
\]

0.2–2.0 mol% Ir(dFppy)\textsubscript{3} MeCN, Blue LED, rt.

40 examples
52–99% yields
d.r. 1:1 to >20:1

– Select examples:

\begin{align*}
\text{Boc} & \quad \text{EtO}_2C & \quad \text{EtO}_2C & \quad \text{CO}_2Et \\
96\%, \text{ d.r. } 3:1, \text{ r.r. } >20:1 \\
\text{n-Hex} & \quad \text{EtO}_2C & \quad \text{EtO}_2C & \quad \text{N-Boc} \\
96\%, \text{ d.r. } 3:1, \text{ r.r. } 18:1 \\
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
70\% \\
\text{AcO} & \quad \text{EtO}_2C & \quad \text{EtO}_2C & \quad \text{Me} & \quad \text{Me} \\
87\%, \text{ d.r. } 1:1, \text{ r.r. } >20:1
\end{align*}
Photocatalytic oxime / olefin [2+2] cycloaddition

  – Intermolecular [2+2] photocycloaddition between 2-isoxazoline-3-carboxylates and unactivated olefins.

– Stereochemical model:

\[ \text{Triplet energy transfer} \]

\[ \text{N–O cleavage:} \]

Photocatalytic dearomative $[2+2]$ and $[4+2]$ cycloaddition
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
- Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

- In optimization studies, authors note two products arising from this substrate, either of which can be selected for based on photocatalyst and solvent selection:

![Chemical Structures]

<table>
<thead>
<tr>
<th>Photocatalyst</th>
<th>Solvent</th>
<th>A (%)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ir(ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>MeCN</td>
<td>67</td>
<td>30</td>
</tr>
<tr>
<td>[Ir(ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>1,4-dioxane</td>
<td>45</td>
<td>53</td>
</tr>
<tr>
<td>[Ir(ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>1,2-DCE</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>[Ir(ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>MeOH</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>MeCN</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>1,2-DCE</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td>[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>1,4-dioxane</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., JACS, 2018, 140, 8624-8528.
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
- Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

**Question:** Can you provide me with a mechanism for the appearance of the second product?

![Chemical Structures]

**Optimal photocatalyst:**

\[\text{[Ir(ppy)$_2$(dtbbpy)]PF$_6$}\]

PC \( E_T = 49.2 \text{ kcal/mol} \)

**Optimal photocatalyst:**

\[\text{[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$}\]

PC \( E_T = 60.1 \text{ kcal/mol} \)
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
- Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

- **Answer:** Sequential sensitized [2+2] cycloaddition, sensitized cyclobutylmethyl ring opening / recombination

![Chemical diagram showing the photocatalytic process](image)
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
  - Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

  \[
  \text{MeOH, Blue LED, rt.}
  \]
  \[
  \text{Dioxane, Blue LED, rt.}
  \]

  - Select examples:

<table>
<thead>
<tr>
<th>Example</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., JACS, 2018, 140, 8624-8528.
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
  - Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition.

- Stern Volmer and reaction timecourse studies reveal source of reaction selectivity:

\[
\begin{align*}
1a & \quad \text{1 mol\% } [\text{Ir(ppy)}_2(\text{dtbbpy})]\text{PF}_6 \quad \text{MeOH, Blue LED, rt.} \\
2a & \quad \text{PC } E_T = 59.8 \text{ kcal/mol} \\
3a & \quad \text{PC } E_T = 55.9 \text{ kcal/mol}
\end{align*}
\]

\[
\begin{align*}
1a & \quad \text{1 mol\% } [\text{Ir(dF(CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6 \quad \text{Dioxane, Blue LED, rt.} \\
3a & \quad \text{PC } E_T = 60.1 \text{ kcal/mol}
\end{align*}
\]
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
  - Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition.
  - Stern Volmer and reaction timecourse studies reveal source of reaction selectivity:

![Chemical structures and reaction pathways](image)

1a

\[ \text{Me} \quad \text{O} \]

1 mol% [Ir(ppy)\(_2\)(dtbbpy)]PF\(_6\)
MeOH, Blue LED, rt.

2a

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

\[ E_T = 59.8 \text{ kcal/mol} \]

PC \[ E_T = 49.2 \text{ kcal/mol} \]

1a

3a

\[ \text{Me} \quad \text{O} \]

1 mol% [Ir(dF(CF\(_3\))ppy)\(_2\)(dtbbpy)]PF\(_6\)
Dioxane, Blue LED, rt.

\[ E_T = 55.9 \text{ kcal/mol} \]

\[ E_T = 60.1 \text{ kcal/mol} \]

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., JACS, 2018, 140, 8624-8528.
Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

– Intramolecular indole C3-tethered olefin dearomative cycloaddition:

\[
\text{4 mol\% [Ir(dF(CF}_3\text{)ppy})_2(dtbbpy)]PF}_6 \\
\text{CH}_2\text{Cl}_2 / \text{MeCN (3:1)} \\
\text{Blue LED, rt., 24-48 h.}
\]

27 examples
27–99% yields

– Select examples:

95%
91%
66%
98%
81%
50%
Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

  - Intramolecular indole C2-tethered olefin dearomative cycloaddition:

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{X} & \quad \text{N} \text{Bn, NH, O, S, CH}
\end{align*}
\]

2 mol% Ir(dFppy)$_3$
0.05 M MeCN
Blue LED, rt.

35 examples
29–97% yields

- Select examples:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>97%</td>
</tr>
<tr>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>97%</td>
</tr>
<tr>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>85%</td>
</tr>
<tr>
<td><img src="image4.png" alt="Compound 4" /></td>
<td>82%</td>
</tr>
<tr>
<td><img src="image5.png" alt="Compound 5" /></td>
<td>95%</td>
</tr>
<tr>
<td><img src="image6.png" alt="Compound 6" /></td>
<td>95%</td>
</tr>
</tbody>
</table>
Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

Oderinde, M. S. and co-workers, JOC, 2021, 86, 1730-1747.

Select examples:

- 2 mol% [Ir(dF(Me)ppy)₂(dtbbpy)]PF₆
- 0.10 M MeCN, Blue LED, rt.
- 77 examples
- 22–95% yields

**Examples:**

- 90%, d.r. 1:1
- 87%, d.r. 7:1
- 75%, d.r. 8:1
- 62%, d.r. 6:1
- 90%, d.r. 6:1
Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

- Oderinde, 2021.
- Extension to intermolecular indole / olefin dearomative cycloaddition:
- Scale up:

\[
\begin{align*}
\text{100 g} & \quad \text{3.0 equiv.} \\
\text{5 L Batch reactor} & \quad \text{107 g} \\
\text{78 % yield} & \quad \text{d.r. >20:1}
\end{align*}
\]
Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

  - A rare example of Gd-photocatalysis for energy transfer:

  $$\text{Indole + Olefin} \rightarrow \text{Product}$$

  4 mol% Gd(OTf)$_3$
  CH$_2$Cl$_2$ / MeCN (1:1)
  Blue LED, rt., 12 h.

  54 examples
  45–98% yields

- Select examples:

  - 84%, >95:5 r.r.
  - 89%, 92:8 r.r.
  - 97%, >95:1 r.r.
  - 57%, >95:5 r.r.
  - 45%, 80:20 r.r.

Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

  - Dearomatization in 3-substituted indoles with isoprene:

  
  ![Reaction Scheme](image)

  10 mol% Gd(OTf)$_3$
  5.0 equiv. MeCN
  0.1 M CH$_2$Cl$_2$
  Blue LED, rt., 12 h.

  6 examples
  58–85% yields

- Select examples:

  ![Select Examples](image)

  70%, d.r. 3:1
  76%, d.r. 3:1

Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

  – A rare example of Gd-photocatalysis for energy transfer:

\[
\text{Indole} + \text{Olefin} \xrightarrow{4 \text{ mol\% Gd(OTf)}_3, \text{Blue LED, rt., 12 h.}} \text{Product}
\]

\[
\text{Indole} + \text{Olefin} \xrightarrow{10 \text{ mol\% Gd(OTf)}_3, \text{Blue LED, rt., 12 h.}} \text{Product}
\]

– **Question:** Can you provide me with a mechanism for these transformations?
Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

- Proposed mechanism of transformation:

![Diagram of proposed mechanism](image)

**Figure 4.** Proposed divergent reaction pathways following [2+2] photocycloaddition/ring-expansion sequence.
Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

- Mechanistic support:

Figure 5. a) UV/Vis absorption spectra of 1a/[Gd] (1:1, 1.0 mM) in CH$_3$CN. b) Job plot analysis (absorbance as a function of $\chi$, that is, the molar fraction of 1a). c) Isolation of a side product 8 as an indicator for intermediate A. d) Probing the intermediate A through the photosensitised isomerization.
Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

- Glorius, 2019.
  
  - Intramolecular [4+2] cycloaddition of C2-tethered pyridine olefins:

  **Conditions A:**
  1. 1.5 mol% PS–[Ir(dF(CF\textsubscript{3})ppy\textsubscript{2}(bpy))]PF\textsubscript{6}
  2. 0.1 M Me\textsubscript{2}CO, Blue LED, rt

  **Conditions B:**
  1. 20 mol% benzil
  2. 0.1 M Me\textsubscript{2}CO, Blue LED, rt

  44 examples
  22–97% yields

- Select examples:

  ![Chemical structures](image)

  - 94%, d.r. 3.5:1
  - 71%, d.r. 1.2:1
  - 97%, d.r. 2:1
  - 86%, d.r. 3.4:1

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

– Interestingly use of a recyclable polymer supported photocatalyst:

![Diagram of photocatalyst synthesis]

Figure 2. Synthesis of an Immobilized Iridium Photocatalyst

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

Glorius, 2019.

Mechanistic support:

A. Kinetic profile using E-4a as substrate

B. Stern-Volmer plots

EnT

C2-Minisci addition

R

Ar

Ir(III), Blue LED

C

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

- Photocatalytic dearomative intermolecular [4+2] cycloaddition between quinolines or isoquinolines and olefins:

**Conditions A:**
2 mol% \([\text{Ir}(\text{dF(CF}_3)_2\text{ppy})_2(\text{dtbbpy})]\)PF$_6$
HFIP, Blue LED, rt

**Conditions B:**
2 mol% \([\text{Ir}(\text{dF(CF}_3)_2\text{ppy})_2(\text{dtbbpy})]\)PF$_6$
1.25 equiv. BF$_3$OEt$_2$
CH$_2$Cl$_2$, Blue LED, rt

83 examples
28–99% yields

- Select examples:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield (%)</th>
<th>r.r.</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>64%</td>
<td>r.r. &gt;19:1, d.r. 4:1</td>
<td></td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>67%</td>
<td>r.r. 94:6, d.r. &gt;19:1</td>
<td></td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>40%</td>
<td>r.r. 9:1, d.r. &gt;19:1</td>
<td></td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>46%</td>
<td>r.r. &gt;19:1, d.r. 94:6</td>
<td></td>
</tr>
</tbody>
</table>

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

- Photocatalytic dearomative intermolecular [4+2] cycloaddition between quinolines or isoquinolines and olefins:

Photocatalytic Asymmetric [2+2] Cycloaddition
Different modes of enantioinduction have thus far been explored.

1. Coordination / Complexation induced triplet state energy lowering:

2. Chiral photocatalyst with recognition motif for substrate:

- Direct (UV)
- Sensitized (visible)
Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Bach, 2013.
- A chiral Lewis acid promotes triplet state energy lowering in a UV-light mediated intramolecular [2+2] cycloaddition:

$$\begin{align*}
\text{50 mol\% chiral oxazaborolidine} \\
\text{CH}_2\text{Cl}_2, 366 \text{ nm UV, } -70 \degree \text{C}
\end{align*}$$

9 examples
41–87% yields
81–90% ee

- Select examples:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>81%</td>
<td>88% ee</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>83%</td>
<td>82% ee</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>84%</td>
<td>90% ee</td>
</tr>
</tbody>
</table>

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Bach, 2013.
- A chiral Lewis acid promotes triplet state energy lowering in a UV-light mediated intramolecular [2+2] cycloaddition:

\[
\begin{align*}
\text{50 mol\% chiral oxazaborolidine} \\
\text{CH}_2\text{Cl}_2, 366 \text{ nm UV, } -70 ^\circ \text{C}
\end{align*}
\]

- 9 examples
- 41–87\% yields
- 81–90\% ee

- Bathochromic shift upon Lewis acid / substrate coordination:

\[
\begin{align*}
\text{Ar} &= \text{m-xylyl}
\end{align*}
\]
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

- Bach, 2014.
  - A xanthone sensitizer incorporating a hydrogen bond recognition motif allows for visible-light driven (>400 nm) enantioselective [2+2]:

\[
\begin{align*}
X = \text{CH}_2, \text{O}, \text{NTs} \\
10 \text{ mol}\% \text{ chiral xanthone} \\
\text{PhCF}_3, \text{ White LED, } -25 \degree \text{C} \\
\rightarrow \\
\text{8 examples} \\
\text{82–95\% yields} \\
\text{87–94\% ee}
\end{align*}
\]

- Select examples:

\[
\begin{align*}
\text{86\%, 92\% ee} & \quad \text{79\%, 88\% ee} & \quad \text{95\%, 87\% ee}
\end{align*}
\]

**Figure 3.** Mechanistic model for sensitization and enantioface differentiation in the complex 1-7. The unshaded arrow indicates the approach of the tethered alkene onto the excited quinolone double bond.

**Figure 1.** UV/Vis spectra of 1 (\(\lambda = 0.5 \text{ mW}\)) and 7 (\(\lambda = 0.5 \text{ mW}\)) in trifluorotoluene (PhCF\(_3\)).
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

- Bach, 2016.
  - Extension to an intermolecular regime:

  10 mol% chiral xanthone
  PhCF₃, 420 nm, −25 ºC

  15 examples
  44–94% yields
  80–95% ee

- Select examples:
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinoxalinone and Olefins

- First enantioselective visible-light photocatalytic intermolecular [2+2] cycloaddition for azetidine synthesis. Use of the same hydrogen-bond recognition xanthone sensitizer:

\[
\begin{align*}
10 \text{ mol% chiral xanthone} \\
1,2\text{-DCE, 420 nm, } -25^\circ\text{C}
\end{align*}
\]

16 examples
50–99% yields
73–96% ee

- Select examples:

- 99%, 94% ee
- 99%, 89% ee
- 50%, 96% ee
- 90%, 73% ee

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

  - Enantioselective intermolecular [2+2] cycloaddition enabled by substrate triplet state energy lowering catalysis:

\[
\text{2.5 mol\% } [\text{Ru(bpy)}_3(\text{PF_6})_2] \\
\text{15 mol\% (S,S)-t-Bu-PyBox} \\
\text{10 mol\% Sc(OTf)_3} \\
\text{iPrOAc/MeCN (3:1), White CFL, rt.}
\]

12 examples
66–86% yields
83–98% ee
d.r. 2:1 – 4:1

- Select examples:

\[
\begin{align*}
\text{84\%, 93\% ee, d.r. 3:1} \\
\text{82\%, 94\% ee, d.r. 3:1} \\
\text{82\%, 85\% ee, d.r. 4:1} \\
\text{84\%, 92\% ee, d.r. 2:1}
\end{align*}
\]
Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Enantioselective intermolecular [2+2] cycloaddition enabled by substrate triplet state energy lowering catalysis:

**B This work:** Lewis acid catalyzed energy transfer

**Fig. 4.** Computational and experimental evidence for a Lewis acid-promoted decrease in triplet energy ($E_\gamma$). (A) Experimental (exp) and calculated (calc) $S_0$–$T_1$ gaps for 2’-hydroxychalcone 2 and its Sc(III) complex. (B) Experimental near-IR emission data for 2’-hydroxychalcone 2 in the absence (black) and presence (red) of Sc(OTf)$_3$. The emission is partially quenched in the presence of oxygen (blue).

<table>
<thead>
<tr>
<th></th>
<th>$E_\gamma$ (exp)</th>
<th>$E_\gamma$ (calc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2’-H. Chalcone</td>
<td>54 kcal/mol</td>
<td>51 kcal/mol</td>
</tr>
<tr>
<td>2’-H. Chalcone + Oxygen</td>
<td>33 kcal/mol</td>
<td>32 kcal/mol</td>
</tr>
</tbody>
</table>

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins


- Extension to styrene substrates in enantioselective [2+2] photocycloaddition:

\[
\text{[Ru(bpy)}_3\text{](PF}_6\text{)}_2 \quad 15 \text{ mol\% (S,S)-t-Bu-PyBox} \\
10 \text{ mol\% Sc(OTf)}_3 \quad \\
iPrOAc/MeCN (3:1), \text{ White CFL, rt.}
\]

- 32 examples
- 77–95\% yields
- 85→99\% ee
- d.r. 1:1 – >10:1

- Select examples:

\[
\begin{align*}
&\text{OH} & \text{O} & \text{Ar}_1 \\
&\text{Ph} & + & \text{Ar}_2 \\
&\text{R} & + & \text{Ar}_2
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{O} \\
\text{Ar}_1 & \text{Ph} & \text{OH} & \text{O} \\
\text{Ph} & + & \text{Ar}_2 & \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \text{Ph} & \text{OH} & \text{O} \\
\text{Ph} & + & \text{Ph} & \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{O} \\
\text{Ph} & \text{OH} & \text{O} & \text{Ph} \\
\text{Ph} & + & \text{Ph} & \text{Ph}
\end{align*}
\]

88\%, >99\% ee, d.r. 2:1
94\%, 96\% ee, d.r. >10:1
94\%, 96\% ee, d.r. 2:1
18\%, 17\% ee, d.r. 2:1
Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Application to the total synthesis norlignan:

![Chemical structures and reaction conditions]

1.5 equiv.

2.5 mol% \([\text{Ru(bpy)}_3\text{(PF}_6)_2]\)
38 mol% (S,S)-t-Bu-PyBox
32 mol% Sc(OTf)_3
iPrOAc/MeCN (3:1), White CFL, rt.

80%, e.e. 94%, d.r. 3:1

10 mol% Rockphos-Pd-G3
1.0 equiv. Cs_2CO_3
5.0 equiv. MeOH, PhMe, 90 ºC

91%

i) NH_3, MeOH/THF
ii) NaOCl, THF

63%

63

Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

- A chiral Ir photocatalyst with a hydrogen-bonding motif induces asymmetry in an intramolecular [2+2]:

\[
1 \text{ mol% } \Delta-[\text{Ir(F}_3\text{CF}_3\text{ppy})_2\text{(ppyN–H)}]BAr^F
\]

\[
\text{CH}_2\text{Cl}_2 / \text{Pentane (1:1), Blue LEDs, } -78 \, ^\circ\text{C}
\]

13 examples
82–>98% yields
20–91% ee

- Select examples:

>98%, 91% ee
93%, 90% ee
98%, 20% ee
86%, 68% ee
98%, 3% ee
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

- A chiral Ir photocatalyst with a hydrogen-bonding motif induces asymmetry in an intramolecular [2+2]:
- Photocatalyst optimization:

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Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Maleimide

– Yoon and Baik, 2019.
– A later publication from these groups explored intermolecular asymmetric [2+2] cycloaddition between quinolinones and maleimide.
– This work revealed an unexpected order of events in energy transfer leading to optically enriched products.

\[
\text{1 mol\% } \Delta \text{Ir(F}_2\text{CF}_3\text{ppy)}_2\text{(MeOpypzN–H)}\text{BARF} \\
\text{CH}_2\text{Cl}_2, \text{Blue LEDs, } -78 \degree \text{C}
\]

21 examples
14–99% yields
7–99% ee

– Select examples:

\[
\text{R = iPr} \quad 82\%, 97\% \text{ ee} \\
\text{R = nBu} \quad 14\%, 7\% \text{ ee} \\
\text{R = Me} \quad 30\%, 70\% \text{ ee}
\]

\[
\text{67\%, 99\% ee} \\
\text{99\%, 99\% ee, d.r. 6:1} \\
\text{74\%, 51\% ee}
\]
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Maleimide

– Yoon and Baik, 2019.
– A later publication from these groups explored intermolecular asymmetric [2+2] cycloaddition between quinolinones and maleimide.
– This work revealed an unexpected order of events in energy transfer leading to optically enriched products.

Scheme 1. Intramolecular vs Intermolecular Enantioselective [2 + 2] Photoreactions Using Enantiopure Chiral Ir Sensitizers

Scheme 2. Control Experiments Show That Intermolecular Cycloaddition of 1x with Maleimide Outcompetes Intramolecular Cyclization

Scheme 4. Proposed Mechanism for Enantioselective Intermolecular [2 + 2] Photocycloaddition
Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Chiral-at-Rh complex coordination to a 2-acrolyl imidazole / pyrazole allows for enantioselective intermolecular [2+2]:

\[ \text{2 mol\% } \Delta\text{-}[\text{RhL}_2(\text{MeCN})_2]PF_6 \]
\[ \text{Me}_2CO, \text{Blue LED, rt.} \]

- Select examples with 2,3-dimethylbutadiene:

- 93%, 96% ee, d.r. 10:1
- 72%, 99% ee, d.r. 9:1
- 84%, 96% ee, d.r. 6:1
- 72%, 95% ee, d.r. 8:1
- 95%, 99% ee, d.r. >20:1

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

Meggers, 2017.

Chiral-at-Rh complex coordination to a 2-acrolyl imidazole/pyrazole allows for enantioselective intermolecular [2+2]:

$$\text{Me}_2\text{CO, Blue LED, rt.}$$

25 examples
66–99% yields
88–99% ee
d.r. 6:1 → 20:1

Select examples with other olefins:

66%, 97% ee, d.r. 9:1
97%, 99% ee, d.r. 6:1
94%, 99% ee, d.r. >20:1
96%, 99% ee, d.r. >20:1

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

– Mechanistic support:


Figure 4. Proposed mechanism. ISC = intersystem crossing.
Photocatalytic Asymmetric Dearomative [2+2] Cycloaddition of Benzofurans and Olefins

Meggers and Baik, 2018.

Chiral at Rh coordination to a 2-acylpyrazole benzofuran produces a photoactive complex:

i) 2 mol% $\Delta$-[RhL$_2$(MeCN)$_2$]PF$_6$ in CH$_2$Cl$_2$, Blue LED, rt., 18 h.

ii) LiCl, Et$_3$N, MeOH

20 examples
60–88% yields
73–99% ee
d.r. 2.5:1 – >20:1

Select examples:

- 76%, 98% ee, 12.1:1 d.r., 11.8:1 r.r
- 74%, 96% ee, 11.1:1 d.r., 9.1:1 r.r
- 91%, 99% ee

Photocatalytic Asymmetric Dearomative [2+2] Cycloaddition of Benzofurans and Olefins

- Meggers and Baik, 2018.
- Chiral at Rh coordination to a 2-acylpyrazole benzofuran produces a photoactive complex:

**Figure 3.** Proposed catalytic cycle.
Photocatalytic Asymmetric Dearomative [2+2] Cycloaddition of Benzofurans and Olefins

- Meggers and Baik, 2018.
- Chiral at Rh coordination to a 2-acylpyrazole benzofuran produces a photoactive complex:

![Chemical reaction diagram]

**Figure 5.** Asymmetric dearomatization with (E)- and (Z)-β-methylstyrrene. For the reaction at −30 °C, 5 W blue LEDs were employed (see the Supporting Information for the setup) and reaction time was 60 h. The absolute configuration of a derivative of 6a was determined by X-ray crystallography. The relative configuration of its diastereoisomer 6a’ was determined by NMR studies.

Photocatalytic Asymmetric [2+2] Cycloaddition of eneiminium ions and olefins

- Bach 2018 and Bach, Wenger 2020
- Iminium ions of unsaturated carbonyl compounds lead to triplet state energy lowering and thereafter asymmetric [2+2] photocycloaddition:

\[
\text{Pyrrolidine} \quad \text{NH}_4\text{PF}_6 \quad \text{PhMe, 110°C} \quad 57\%
\]

\[
\text{[Ir(dF(CF}_3)ppy)_2(bpy)]PF}_6 \quad \text{MeCN, 420 nm, rt.} \quad \text{i) 2.5 mol%} \quad 75\%
\]

\[
\text{NaOH, H}_2\text{O} \quad \text{ii) NaOH, H}_2\text{O}
\]

\( (+) \)

**Scheme 1.** Schematic energy diagram for the singlet (S) and triplet (T) states of \( \alpha,\beta \)-unsaturated carbonyl compounds I and the respective eneiminium ions II.

**Scheme 3.** Intramolecular iridium-catalyzed [2+2] photocycloaddition of eneiminium ions 8.
Photocatalytic Asymmetric [2+2] Cycloaddition of eneiminium ions and olefins

– Bach 2018 and Bach, Wenger 2020
– Iminium ions of unsaturated carbonyl compounds lead to triplet state energy lowering and thereafter asymmetric [2+2] photocycloaddition:

Scheme 4. Formation of eneiminium ion 11 and its ruthenium-catalyzed [2+2] photocycloaddition to 2,3-dimethylbutadiene (d.r. = diastereomeric ratio).

Figure 2. [2+2] Photocycloaddition products obtained by the reaction of eneiminium ion 11 with different olefins (λ = 457 nm, catalyst: 2.5 mol% Ru(bpy)$_3$(PF$_6$)$_2$ in MeCN).
Photocatalytic Asymmetric [2+2] Cycloaddition of eneiminium ions and olefins

- Bach 2018 and Bach, Wenger 2020
- Iminium ions of unsaturated carbonyl compounds lead to triplet state energy lowering and thereafter asymmetric [2+2] photocycloaddition:

**Scheme 5.** Enantioselective ruthenium-catalyzed [2+2] photocycloaddition of eniminium ion 17 (Ar = 3,5-bis(trifluoromethyl)phenyl; TDS = tert-hexyldimethylsilyl) to cyclobutane 12a.

**Scheme 8.** Formation of enantioenriched compound 3aa from cinnamonic aldehyde (6a) under catalytic conditions.
Summary

– Photosensitization, or energy transfer catalysis promotes a broad range of different modes of [2+2] and [4+2] cycloaddition.

– Olefins, carbonyls, oximes, and arenes have been shown to undergo sensitization.

– Two general modes of inducing enantiocontrol in photocatalytic [2+2] have thus far been explored:
  – Triplet state energy lowering in the presence of a chiral catalyst
  – Chiral photocatalyst coordination to a substrate prior to energy transfer

– Current limitations in the methodology involve accessing substrates with higher triplet state energies.
  – This may soon be lifted with the recent development of a family of near-UV absorbing high triplet energy xanthone dyes.

– Other types of energy transfer processes can be promoted:
  – Alkene isomerization
  – Bond homolysis processes for N- and C-centered radical generation, for example