Highly Enantioselective 6π Photoelectrocyclizations Engineered by Hydrogen Bonding

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Introduction

Highly Enantioselective 6π Photoelectrocyclizations Engineered by Hydrogen Bonding

Wesley B. Swords,† Hanna Lee,‡ Yerin Park, Franco Llamas, Kazimer L. Skubi, Jiyong Park, Ila A. Guzei, Mu-Hyun Baik,* and Tehshik P. Yoon*

Abstract: Photochemical electrocyclization reactions are valued for both their ability to produce structurally complex molecules and their central role in elucidating fundamental mechanistic principles of photochemistry. We present herein a highly enantioselective 6π photoelectrocyclization catalyzed by a chiral [68]photoretrodiene. This transformation was successfully realized by engineering a strong hydrogen-bonding interaction between a pyrazole moiety on the catalyst and a basic imidazolyl ketone on the substrate. To shed light on the origin of stereoselection, we conducted a comprehensive investigation combining experimental and computational mechanistic studies. Results from density functional theory calculations underscore the crucial role played by the prochirality and the transannularity of the photoelectrocyclization process as well as the steric demand in the subsequent [4,4]-6π shift step. Our findings not only offer valuable guidance for developing chiral photocatalysts but also serve as a significant reference for achieving high levels of enantioselectivity in the 6π photoelectrocyclization reaction.

Mu-Hyun “Mookie” Baik

• Vordiplom (BS), Heinrich-Heine Universität Düsseldorf (1991-1995)
• PhD, UNC Chapel Hill (Cynthia K. Schauer) (1995-2000)
• Postdoc, Columbia (Richard A. Friesner) (2002-2005)
• Faculty at KAIST since 2015
• Former faculty at Indiana University, 2003-2015
• Computational chemistry, focusing on the mechanism of organometallic catalysts
• Seeks to predict new catalysts

Tehshik Yoon

• MS, CalTech (Erick M. Carreira) (1996-1998)
• Faculty at UW Madison since 2005
• Methodology-driven, specializing in the controlled synthesis of complex molecules via photochemistry
Context

Thermal: 6π disrotatory

Bergman, Trauner, & co-workers (2010)

Photochemical
Chapman & co-workers (1968)

Gong, Meggers, & co-workers (2015)

Thermal: 6π disrotatory


Bergman, Trauner, & co-workers (2010)

Photochemical
Chapman & co-workers (1968)

Gong, Meggers, & co-workers (2015)
Previous Photocatalytic Electrocyclizations

Bach & co-workers (2017)

\[
\begin{array}{c}
\text{thioxanthone (50 mol\%)} \\
\text{Cu(ClO}_4\text{)}_2 (50 \text{ mol\%)} \\
3 (60 \text{ mol\%)} \\
\text{blue LED}
\end{array}
\]

\[
\begin{array}{c}
\text{1} \\
\text{chiral ligand}
\end{array}
\]

\[
\begin{array}{c}
\text{thioxanthone} \\
\text{57\% yield} \\
30\% \text{ ee}
\end{array}
\]

Paton, Smith, & co-workers (2017)

\[
\begin{array}{c}
\text{Ir(Fppy)}_3 (1 \text{ mol\%)} \\
\text{blue LED} \\
\pm 5 \\
94\% \text{ yield}
\end{array}
\]

Paton, Smith, & co-workers (2022)

\[
\begin{array}{c}
\text{Ir((5-CF}_3\text{)(4'-t-Bu)ppy)}_3 (1 \text{ mol\%)} \\
\text{Sc(OTf)}_3 (25 \text{ mol\%)} \\
7 (25 \text{ mol\%)} \\
\text{blue LED}
\end{array}
\]

\[
\begin{array}{c}
\text{6} \\
\text{chiral ligand}
\end{array}
\]

\[
\begin{array}{c}
\text{7} \\
\text{95\% yield} \\
90\% \text{ ee}
\end{array}
\]

Baik, Yoon, & co-workers (2023)

\[
\begin{array}{c}
\text{chiral [Ir] photocatalyst} \\
\text{blue LED}
\end{array}
\]

\[
\begin{array}{c}
\text{8} \\
\text{90\% \text{ ee}}
\end{array}
\]

\[
\begin{array}{c}
\text{•strong hydrogen bond} \\
\text{•chiral photocatalyst} \\
\text{•high ee (>90\%)}
\end{array}
\]

Edtmüller, V.; Pöthig, A.; Bach, T. Tetrahedron 2017, 73, 5038
Reaction Optimization

<table>
<thead>
<tr>
<th>entry</th>
<th>modification</th>
<th>yield</th>
<th>d.r.</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>57%</td>
<td>6:1</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2</td>
<td>29%</td>
<td>3:1</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>17%</td>
<td>3:1</td>
<td>53%</td>
</tr>
<tr>
<td>4</td>
<td>20 ºC</td>
<td>60%</td>
<td>8:1</td>
<td>73%</td>
</tr>
<tr>
<td>5</td>
<td>-40 ºC</td>
<td>58%</td>
<td>5:1</td>
<td>96%</td>
</tr>
<tr>
<td>6</td>
<td>1 mol% Λ-PC</td>
<td>39%</td>
<td>5:1</td>
<td>74%</td>
</tr>
<tr>
<td>7</td>
<td>0.01 M</td>
<td>55%</td>
<td>7:1</td>
<td>82%</td>
</tr>
<tr>
<td>8</td>
<td>in air</td>
<td>&lt;5%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>dark</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>no Λ-PC</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>(Z)-9</td>
<td>84%</td>
<td>8:1</td>
<td>91%</td>
</tr>
<tr>
<td>13</td>
<td>11 instead of 9</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>12 instead of 9</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>13 instead of 9</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

• Λ-PC serves both as a photosensitizer and as a chiral ligand to enhance enantioselectivity
• Presence of a *carbamate* (with Boc or Fmoc) is required for the reaction to work
  • The PC can only transfer the energy to the substrate with a carbamate
  • Cyclized product from tertiary amine 12 decomposes
• Triplet energies based on calculations:
  • carbamate: 50.9 kcal·mol⁻¹
  • secondary amine: 53.4 kcal·mol⁻¹
  • ether: 54.0 kcal·mol⁻¹

• Presence of the *imidazole* (NMI) allows for hydrogen bonding between Λ-PC and the substrate
  • Binding of the substrate to the photocatalyst post energy transfer promotes the enantioselectivity

Substrate Scope

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>71%</td>
<td>93%</td>
<td>8:1</td>
</tr>
<tr>
<td>14</td>
<td>48%</td>
<td>82%</td>
<td>3:1</td>
</tr>
<tr>
<td>15</td>
<td>62%</td>
<td>93%</td>
<td>10:1</td>
</tr>
<tr>
<td>16</td>
<td>49%</td>
<td>89%</td>
<td>5:1</td>
</tr>
<tr>
<td>17</td>
<td>9%</td>
<td>74%</td>
<td>9:1</td>
</tr>
<tr>
<td>18</td>
<td>89%</td>
<td>96%</td>
<td>1:1:1</td>
</tr>
<tr>
<td>19</td>
<td>55%</td>
<td>96%</td>
<td>2.5:1</td>
</tr>
<tr>
<td>20</td>
<td>81%</td>
<td>97%</td>
<td>2:1</td>
</tr>
<tr>
<td>21</td>
<td>76%</td>
<td>93%</td>
<td>1:1:1</td>
</tr>
<tr>
<td>22</td>
<td>71%</td>
<td>96%</td>
<td>10:1</td>
</tr>
<tr>
<td>23</td>
<td>56%</td>
<td>94%</td>
<td>12:1</td>
</tr>
<tr>
<td>24</td>
<td>82%</td>
<td>93%</td>
<td>10:1</td>
</tr>
</tbody>
</table>

Incompatible Substrates

A) Reaction profile monitoring the concentrations of (E) & (Z) olefin starting materials, as well as cis & trans products

B) Stern-Volmer plot, showing quenching of Λ-PC via both alkene isomers

• likely through energy transfer (oxidation & reduction potentials of Λ-PC are too low to perform either redox process)

Testing the reaction without NMI

\[
\begin{align*}
\text{substrate} & \xrightarrow{\text{standard conditions}} \text{product} \\
\text{79% yield} & \quad 37\% \text{ ee, 4:1 d.r.}
\end{align*}
\]

• In the absence of NMI, reduced hydrogen bonding interaction between substrate and Λ-PC results in lower ee

Performing [2+2] cycloaddition

\[
\begin{align*}
\text{substrate} & \xrightarrow{\text{standard conditions}} \text{product} \\
\text{-20 °C} & \quad 76\% \text{ yield} \\
& \quad 78\% \text{ ee, 1:1 d.r.} \\
\text{-65 °C} & \quad 82\% \text{ yield} \\
& \quad 91\% \text{ ee, 2:1 d.r.}
\end{align*}
\]

• The presence of NMI in enone 28 performs with relatively good ee (up to 91% ee at -65 °C) in the [2+2] cycloaddition

Proposed Mechanism

hv, intersystem crossing (ISC), triplet excited-state energy transfer (TEET)

6π electrocyclization

reverse intersystem crossing (RISC)

[1,4] hydride shift

Computational Studies

• Viable encounter complexes A and B, with their respective free energies (kcal·mol⁻¹)

• 6π electrocyclization energy diagram, differentiating both profiles for the formation of (S,S) and (R,S) diastereomers
**Concluding Remarks**

Baik, Yoon, & co-workers (2023)

- Effective method to access indoline scaffolds with high ee, and reasonable to high yield on a variety of substrates
- Photocatalyst serves two important purposes:
  - Chiral ligand (effectuated through hydrogen bonding)
  - Photosensitizer which performs an energy transfer to the substrate
- Considerations from this method:
  - NMI (or potentially another strong H-bond donor) is required to achieve high ee
  - Carbamate is required for the reaction to work (incompatible with secondary amine and ether, and tertiary amine decomposes)