Palladium-Catalyzed Decarboxylative $sp^3$–$sp^3$ Coupling of Nitrobenzene Acetic Esters

Enantioselective Addition of Activated Terminal Alkynes to 1–Acylypyridinium Salts Catalyzed by Cu-Bis(oxazoline) Complexes

Antoinette E. Nibbs
Short Literature Presentation
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Palladium-Catalyzed Decarboxylative $sp^3$–$sp^3$ Coupling of Nitrobenzene Acetic Esters

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Nitroarenes

- Important intermediates in the synthesis of polymers, azo dyes, and pharmaceuticals
- Decarboxylative coupling
  - Reactions occur under neutral conditions
  - Reactions avoid the use of reagents necessary for transmetalation
- Catalysis of the decarboxylative coupling of sp\(^3\)-hybridized carbons is still a challenge
**Synthetic Challenges of sp³–sp³ couplings**

- Current methods require stoichiometric quantities of organometallic reagents

![Chemical reaction diagram](image)

Previous Work

Pd-catalyzed decarboxylative benzylic coupling of nitrogen-containing heteroaromatics with allyl electrophiles

Allylation/aza cope rearrangement

Did not translate to more general benzylic couplings

New method for the decarboxylative coupling of nitrobenzene acetic esters

![Chemical diagram showing the reaction pathway]

- Oxidative addition
- Reductive elimination

53%, dr > 95:5
Standard Conditions for o- and p-nitrophenyl Acetic Esters

- Catalyst and Ligand Screening
  - Pd(0), rac-BINAP, dppe, dppf

- Temperature
  - Ambient vs heating

- Findings
  - rac-BINAP as the most selective ligand for benzylic allylation
**Substrate Scope**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Ph</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>R = OEt</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conditions: 0.3 mmol substrate, 0.0075 mmol Pd2dba3, 0.015 mol rac-BINAP, 3 mL toluene, 100 °C, 1-3 h

- Terminally unsubstituted allyl esters gave clean conversion
- Functional group tolerance
- No products from enolate allylation
- Addition of methoxy substituents

*The fact that α-mono and α-α disubstituted p-nitrophenyl acetic esters undergo “facile decarboxylation” indicates that decarboxylation must precede C-C bond formation!!!*
Decarboxylative Coupling of o-nitrophenyl Acetic Esters

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate" /></td>
<td><img src="image2.png" alt="Product" /></td>
<td>no product or degradation of starting material</td>
</tr>
</tbody>
</table>

Conditions: 0.3 mmol substrate, 0.0075 mmol Pd$_2$dba$_3$, 0.015 mol rac-BINAP, 3 mL toluene, 100 °C, 1-3 h

- limited to α-monosubstituted substrates
- $p$-nitrophenyl decarboxylation can be achieved
Alkyl-Substituted Allyl Groups

<table>
<thead>
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<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>

Conditions: 0.3 mmol substrate, 0.0075 mmol Pd$_2$dba$_3$, 0.015 mol rac-BINAP, 3 mL toluene, 100 °C, 1-3 h

elimination due to basicity of benzylic anion?
### Dinitroarene Substrates

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image1" alt="Product 1" /></td>
<td>&lt;5%</td>
</tr>
<tr>
<td><img src="image2" alt="Substrate 2" /></td>
<td><img src="image2" alt="Product 2" /></td>
<td>95%</td>
</tr>
<tr>
<td><img src="image3" alt="Substrate 3" /></td>
<td><img src="image3" alt="Product 3" /></td>
<td>26%</td>
</tr>
</tbody>
</table>

Conditions: 0.3 mmol substrate, 0.015 mmol Pd(PPh₃)₄, 3 mL toluene, room temp, 1-3 h

Rate of reaction increases with increased stability of benzylic anion – rate limiting step is decarboxylation
Utility in Pharmaceutical Synthesis

- reduction to anilines
- decarboxylative coupling can be followed by reductive cyclization to afford dihydroquinolones or quinolines

1. 2.5 mol % Pd$_2$dba$_3$ / 5 mol % (rac)-BINAP
2. Zn, HCl

1. 2.5 mol % Pd$_2$dba$_3$ / 5 mol% (rac)-BINAP
2. SnCl$_2$, •H$_2$O, MeOH
Conclusion

- Development of a new method for catalytic sp$^3$–sp$^3$ decarboxylative coupling of nitrobenzene acetic esters
- Neutral reaction conditions
- Does not require organometallic reagents for transmetallation
- Functional group tolerance
- Decarboxylative coupling of o-nitrophenyl acetic esters limited to α-monosubstituted substrates
- Alkyl substituted allyl electrophiles lead to competing elimination, which can be remedied somewhat by dinitroarenes (stabalization of benzylic anion)
Enantioselective Addition of Activated Terminal Alkynes to 1-Acylpyridinium Salts Catalyzed by Cu-Bis(oxazoline) Complexes

Sun, Zhankui; Yu, Shouyun; Ding, Zuoding; Ma, Dawei
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry
**Synthesis of Piperdine Units**

- Stereoselective synthetic strategies include nucleophilic substitution, reductive amination, reduction of pyridines, cycloadditions
- Asymmetric attack of nucleophiles onto activated pyridines to afford dihydropyridines

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most studies are focused on using chiral pyridine substrates

only **one** example of a catalytic asymmetric reaction
Catalytic Enantioselective Reissert Reaction of Pyridine Derivatives

\[
\begin{align*}
&\text{Et}_2\text{AlCl (5 or 10 mol %)} \\
&10 \text{ mol \% ligand} \\
&T\text{MScN (2 equiv)} \\
&R'\text{OCOC}\text{Cl (1.4 equiv)} \\
&\text{CH}_2\text{Cl}_2, -60 ^\circ\text{C}
\end{align*}
\]

**Model Studies**

- Less bulky ligands gave best selectivities
- Optimized base (\(i\)-Pr\(_2\)NPr-\(n\))
- Optimized solvent (CH\(_2\)Cl\(_2\))
- N-substituents affect reaction
- Excess amount of starting materials required
- Catalyst loading

\[ \text{N} \text{O} \text{N} \text{R} \text{L1: } \text{R}=\text{Ph} \text{L2: } \text{R}=\text{Bn} \text{L3: } \text{R}=\text{Me} \text{L4: } \text{R}=\text{CH}_2\text{CH}_2 \text{L5: } \text{R}=\text{H} \]

\[ \begin{align*}
\text{N} \text{O} \\
\text{R} \text{L} \\
\text{N} \text{O}
\end{align*} \]
Variation of 1-Alkynes

- Propiolate/ynone modifications
- Reactivity of inactivated 1-alkynes

The carbonyl group adjacent to the alkyne moiety is essential for the enantioselectivity of the addition!
Recent Developments

Black, D.; Beveridge, R.; Arndsten, B. *JOC*, **2008**, ASAP.

\[
\begin{align*}
\text{Pyridine} + \text{ester} + \text{alkyne} & \xrightarrow{5\% \text{ CuCl, 5.5\% chiral L}} \\
& \text{–78 °C, 14h, } i\text{-Pr}_2\text{NEt} \\
& \text{up to 92\% yield, 84\% ee}
\end{align*}
\]
Comparative Analysis

The carbonyl group adjacent to the alkyne moiety is NOT essential for the enantioselectivity of the addition!
Mechanism

\[ \text{Mechanism} \]

\[
\text{Pyridine} + \text{Acetyl chloride} + \text{Alkyne} \rightarrow \text{Product}
\]

5 mol% CuCl, 5.5 mol% chiral L, \(-78^\circ\text{C}, 14\text{h}\)

up to 92% yield, 84% ee

the carbonyl group adjacent to the alkyne moiety is NOT essential for the enantioselectivity of the addition!
Conclusion

- Development of first catalytic asymmetric addition of 1-alkynes to 1-acylpyridinium salts
- C3-carbonyl group is NOT necessary for good enantioselectivity

\[
\begin{align*}
\text{Pyridinium salt} & \quad + \quad \text{Alkyne} \\
\text{Cul, ligand, base} & \quad \text{solvent, } -78 \degree C, 15 \text{ h} \\
\text{Product} & \quad \text{R} = \text{Me, i-Bu, Bn}
\end{align*}
\]