Decarboxylative Cross-Coupling Chemistry

By definition, decarboxylative cross-coupling extrudes CO2 and forms C-C (or C-R) bond.

Tsuji-Trost type decarboxylative coupling / decarboxylative allylic alkylation.
Decarboxylative Tsuji-Trost Type Chemistry


\[
\text{MeCH} = \text{C(O)} - \text{OMe} + \text{Pd(OAc)}_2 / \text{PPh}_3 \rightarrow \text{MeCH} = \text{C(O)} - \text{OMe}
\]


- Tunge.

\[
\text{PhCH} = \text{C(Ph)} - \text{C} = \text{C(Ph)} + \text{Pd(PPh}_3)_4 \rightarrow \text{PhCH} = \text{C(Ph)} - \text{C} = \text{C(Ph)}
\]


- Stoltz.

\[
\text{MeCH} = \text{C(O)} - \text{OMe} + \text{Pd}_2(\text{dba})_3 \rightarrow \text{MeCH} = \text{C(O)} - \text{OMe}
\]

Stoltz JACS., 2004, 126, 15044-15045.

Decarboxyative Cross-Coupling Chemistry

- Cross-coupling chemistry typically requires a stoichiometric organometallic reagent.

\[
\text{R-M} + \text{X-R} \xrightarrow{\text{M}_x \text{catalyst}} \text{R-R'} + \text{M-X}
\]

- Acids can function in place of organometallic reagents in cross-coupling chemistry.

\[
\text{R-CO}_2 \text{H} + \text{X-R} \xrightarrow{\text{M}_x \text{catalyst}} \text{R-R'} + \text{H-X}
\]

- Acids can also replace aryl halides in Heck chemistry.

\[
\text{R-CO}_2 \text{H} + \text{R} \xrightarrow{\text{M}_x \text{catalyst}} \text{R-R'} + \text{H-X}
\]
The First Example of a Decarboxylative Cross-Coupling Reaction

- In 1958, Nilsson reported his findings regarding an Ullmann coupling.

- In 1966, Nilsson reported the first decarboxylative Ullmann reaction.

- This finding remained unelaborated for 35 years.

*...The reactive intermediate in the Ullmann reaction is likely to be an arylcopper.*


Andy Myers' Decarboxylative Heck-Type Reaction

- Typical Heck reactions couple aryl- or vinyl-halides with olefins.

Andy Myers' Decarboxylative Heck-Type Reaction

In 2002, the Myers group reported a Heck reaction using benzoic acids as halide surrogates.

Myers Decarboxylative Heck-Type Reaction

- The palladium system developed by the Myers group.

\[
\begin{align*}
\text{Ar}^+ \text{OH} & \quad \text{Ar}^+ \text{R} \\
1.0 \text{ Eq} & \quad 1.5 \text{ Eq} \\
\text{Pd} \left( \text{OTFA} \right)_2 & \quad 0.2 \text{ Eq} \\
\text{Ag}_2 \text{CO}_3 & \quad 3.0 \text{ Eq} \\
5\% \text{ DMSO} / \text{DMF} & \quad 120 \degree \text{C, } \text{<3 h} \\
\text{Ar}^+ \text{R} & \quad 18 \text{ examples}
\end{align*}
\]

- Electron-rich, -poor, and heteroaromatic acids are tolerated.

(My images or diagrams here)


Myers: Proposed Mechanism of Decarboxylative Heck

Myers: Mechanistic Studies


Myers: Mechanistic Studies

Myers: Heck-Type Arylation of Cyclic Enones

- In 2004, the Myers group published a Heck paper using cyclic enone substrates.

- Scope of the aromatic acid


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![Chemical Reaction](image)

- Scope of the cyclic α,β-unsaturated ketone.

![Scope Diagram](image)


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![Chemical Reaction](image)

- Scope of the cyclic α,β-unsaturated ketone.

![Scope Diagram](image)

Myers: Heck-Type Arylation of Cyclic Enones

- Advantage of decarboxylative Heck: electron rich arene substrates.

- Same reaction using traditional conditions is challenging.

Myers: Heck-Type Arylation of Cyclic Enones

- Disadvantage of decarboxylative Heck: ortho-substitution is needed.

- 'Traditional' Heck conditions form product in quantitative yield.

Biaryl Synthesis via Decarboxylative Coupling

- Traditional biaryl couplings use stoichiometric organometallic reagents.

\[
\begin{array}{c}
\text{Ar}^1 \text{M} & \text{X} \text{Ar}^2 & \text{M}_{\text{cat.}} & \text{Ar}^1 \text{Ar}^2 & \text{M} \text{X} \\
\text{M} = \text{SnR}_3, \text{BR}_3, \text{ZnX}... & \text{X} = \text{halide}, \text{OTf}... \\
\end{array}
\]

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\end{array}
\]

- Decarboxylative biaryl coupling reactions utilize aromatic acid as organometallic surrogate.

\[
\begin{array}{c}
\text{Ar}^1 \text{COOH} & \text{X} \text{Ar}^2 & \text{M}_{\text{cat.}} & \text{Ar}^1 \text{Ar}^2 & \text{H} \text{X} \\
\text{X} = \text{halide}, \text{OTf}... & \text{X} \text{CO}_2 \\
\end{array}
\]

Baudoin, O. Angew., 2007, 46, 1373-1375.
Biaryl Synthesis via Decarboxylative Coupling: Gooßen

In 2006, Gooßen reported a bimetallic system for decarboxylative biaryl synthesis.

![Chemical structure and reaction scheme](image)

Proposed mechanism.

**Biaryl Synthesis via Decarboxylative Coupling: Gooßen**

- System catalytic in palladium and copper.

  ![Chemical Reaction Diagram](image)

  1 mol% Pd(acac)$_2$
  3% Cul / 5% phen
  K$_2$CO$_3$, MS-3Å
  NMP, 160 °C, 24 h

- Scope of the aromatic acid.

  ![Aromatic Acid Chart](chart)

Biaryl Synthesis via Decarboxylative Coupling: Gooßen

- System stoichiometric in copper.

\[
\begin{align*}
\text{System stoichiometric in copper.} \\
\text{2 mol\% Pd(acac)\textsubscript{2}} \\
\text{1.2 Eq Cul / bipy} \\
\text{K\textsubscript{2}CO\textsubscript{3}, MS-3\AA} \\
\text{NMP, 160 °C, 24 h}
\end{align*}
\]

- Scope of the aromatic acid.

\[
\begin{align*}
\text{Scope of the aromatic acid.} \\
\text{57\%} \\
\text{79\%} \\
\text{97\% (42)} \\
\text{62\%}
\end{align*}
\]

\[
\begin{align*}
\text{55\% (34)} \\
\text{91\% (0)} \\
\text{42\% (0)} \\
\text{41\% (0)}
\end{align*}
\]


Biaryl Synthesis via Decarboxylative Coupling: Gooßen

- System catalytic in palladium and copper.

\[
\begin{align*}
\text{System catalytic in palladium and copper.} \\
\text{1 mol\% Pd(acac)\textsubscript{2}} \\
\text{3\% Cul / 5\% phen} \\
\text{K\textsubscript{2}CO\textsubscript{3}, MS-3\AA} \\
\text{NMP, 160 °C, 24 h}
\end{align*}
\]

- Summary of the aryl bromide scope.

\[
\begin{align*}
\text{Summary of the aryl bromide scope.} \\
\text{77\%} \\
\text{91\%} \\
\text{68\%} \\
\text{53\%}
\end{align*}
\]

Boehringer Ingelheim group was trying to do C-H activation of oxazoles.

They postulated that regioselectivity would be dictated by the presence of a blocking group.

Biaryl Synthesis via Decarboxylative Coupling: Forgione & Bilodeau

- Boehringer Ingelheim group was trying to do C-H activation of oxazoles.

![Chemical reaction diagram]

- They postulated that regioselectivity would be dictated by the presence of a blocking group.

![Chemical reaction diagram]


Forgione & Bilodeau: Heteroaromatic Decarboxylative Biaryl Synthesis

- The optimized reaction conditions are useful for many heteroaromatic acids.

<table>
<thead>
<tr>
<th>![Chemical structure]</th>
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<tbody>
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</tbody>
</table>

Forgione & Bilodeau: Heteroaromatic Decarboxylative Biaryl Synthesis

- The optimized reaction conditions are useful for many heteroaromatic acids.

\[
\begin{align*}
\text{Carboxylic Acid} & \quad 5 \text{ mol}\% \ Pd[P(t-Bu)\text{Cl}_2] \quad \text{Bu}_4\text{NCl} \cdot \text{H}_2\text{O} \cdot \text{CsCO}_3 \\
\text{Bromine Compound} & \quad \text{DMF, \(\mu\text{W, 170 }^\circ\text{C}\)} \\
\text{Product} & \quad 8 \text{ minutes} \\
\end{align*}
\]

- Electron-rich, -poor, and heteroaromatic bromides also work (66-85% yield).


Proposed Mechanism of Heteroaromatic Acid Coupling

- Biproduct of reaction using 2-furancarboxylic acid could shed light on the mechanism.

**Proposed Mechanism of Heteroaromatic Acid Coupling**

- Biproduct of reaction using 2-furancarboxylic acid could shed light on the mechanism.

![Mechanism Diagram]


**Synthesis of Lamellarin L**

- In 2000, Steglich et al. used similar chemistry to forge the final bond in Lamellarin L.

![Synthesis Diagram]

Optimized system uses 30 mol % palladium and arsine ligand.

![Chemical Reaction](image)

Scope of the aromatic acid.


Summary of Decarboxylative Biaryl Syntheses

Gooßen system is ideal for electron-poor benzoic acids.

![Chemical Reaction](image)

Forgione / Bilodeau system for heteroaromatic acids.

![Chemical Reaction](image)

Becht system is best for electron-rich benzoic acids.

![Chemical Reaction](image)
Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee

- Standard syntheses of unsymmetrically substituted diaryl alkynes utilize protected acetylenes.

![Chemical diagram showing the reaction of M with Ar to form A', followed by cross-coupling to produce A'].

- Propionic acid as TMS-acetylene substitute in a one-pot diaryl alkyne synthesis protocol.

![Chemical diagram showing the reaction of COOH with Ar to form an intermediate, which then reacts with Ar' to produce A'].


Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee

- Diaryl alkyne synthesis system developed by Lee group.

![Chemical diagram showing the reaction of Ph-I and H- with 5 mol% Pd(dba)_3, 10 mol% dppf, 6 Eq TBAF, NMP, rt, 12 h, Br-Ar', 90°C, 12 h to produce Ph-Ar'].

**Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee**

- Diaryl alkyne synthesis system developed by Lee group.

![Chemical reaction diagram]

- Aryl bromide scope.


---

Summary of Decarboxylative Cross-Coupling Chemistry

- Acids can be used (in some cases) as organometallic reagent surrogates.

\[
\begin{align*}
&\text{Ar}^\text{M} \quad \leftrightarrow \quad \text{ArCO}_2\text{H} \\
&\text{ArCH}_2^\text{M} \quad \leftrightarrow \quad \text{ArCH}_2\text{CO}_2\text{H} \\
&R\equiv^\text{M} \quad \leftrightarrow \quad R\equiv\text{CO}_2\text{H}
\end{align*}
\]

- Acids can also function as replacements for aryl (and potentially vinyl) halides.

\[
\begin{align*}
&\text{Ar}^\text{I} \quad \leftrightarrow \quad \text{ArCO}_2\text{H}
\end{align*}
\]