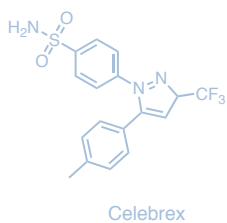
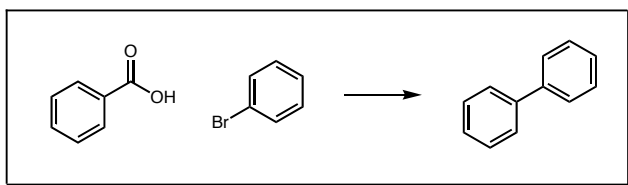
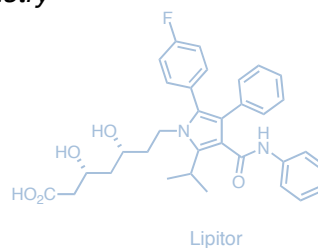
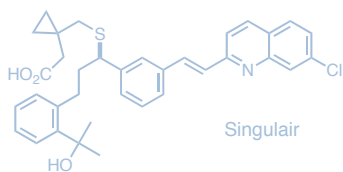
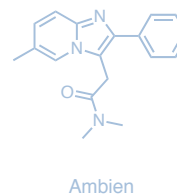


Decarboxylative Cross-Coupling Chemistry



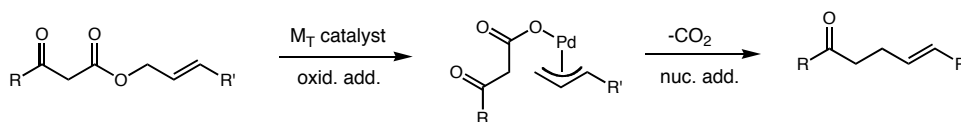
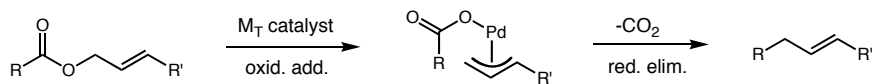
Nathan Jui
MacMillan Group Meeting
February 12, 2008



Boudoin, O. *Angew.*, **2007**, *46*, 1373-1375.

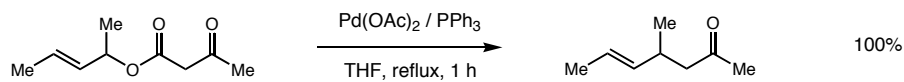
Decarboxylative Cross-Coupling Chemistry

- By definition, decarboxylative cross-coupling extrudes CO_2 and forms C-C (or C-R) bond.
- Tsuji-Trost type decarboxylative coupling / decarboxylative allylic alkylation.



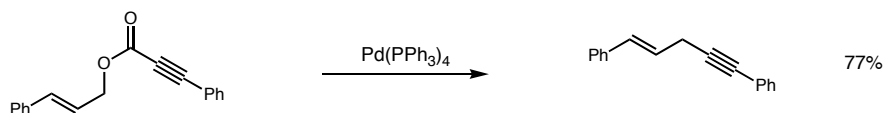
Decarboxylative Tsuji-Trost Type Chemistry

- Initial report of reactivity Tsuji 1980 (palladium-catalyzed Carroll rearrangement).



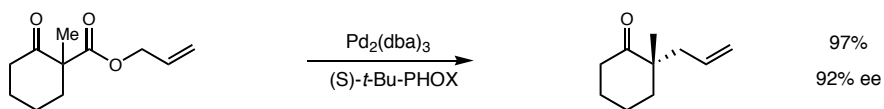
Tsuji *Tett. Lett.*, **1980**, *21*, 3199-3202.

- Tunge.



Tunge *JACS.*, **2005**, *127*, 13510-13511.

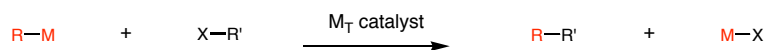
- Stoltz.



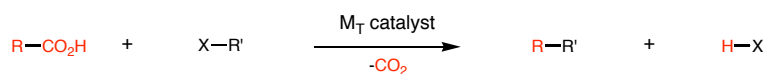
Stoltz *JACS.*, **2004**, *126*, 15044-15045.

Decarboxylative Cross-Coupling Chemistry

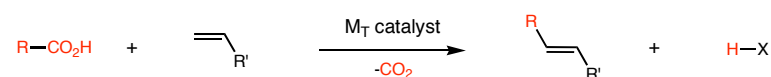
- Cross-coupling chemistry typically requires a stoichiometric organometallic reagent.



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

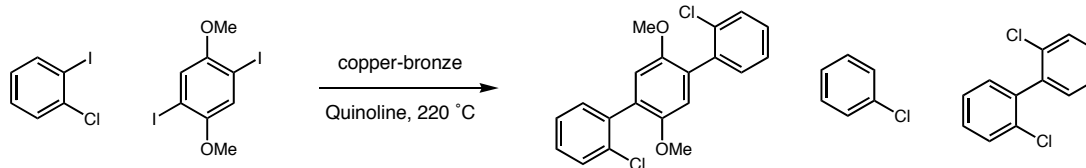


- Acids can also replace aryl halides in Heck chemistry.



The First Example of a Decarboxylative Cross-Coupling Reaction

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

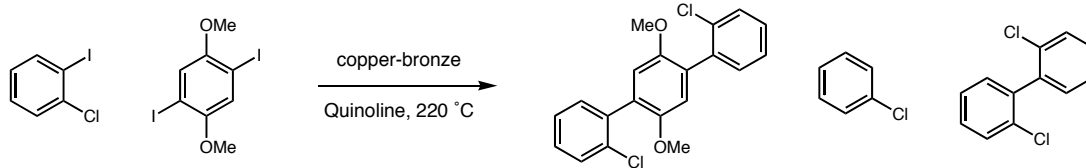


"...The reactive intermediate in the Ullmann reaction is likely to be an arylcopper."

Nilsson, M. *Acta Chem. Scand.*, **1958**, *12*, 537-546.

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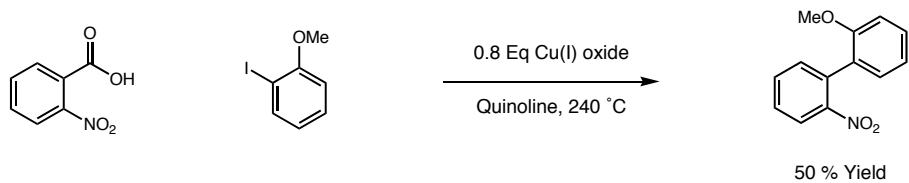
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"...The reactive intermediate in the Ullmann reaction is likely to be an arylcopper."

Nilsson, M. *Acta Chem. Scand.*, **1958**, *12*, 537-546.

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

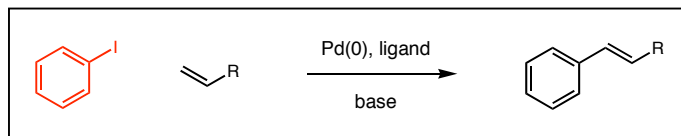


Nilsson, M. *Acta Chem. Scand.*, **1966**, *20*, 423-426.

- This finding remained unelaborated for 35 years.

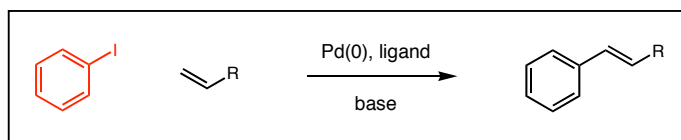
Andy Myers' Decarboxylative Heck-Type Reaction

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

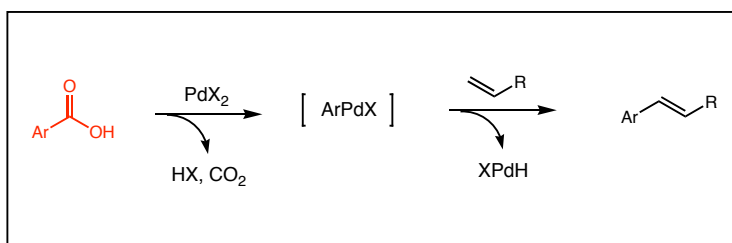


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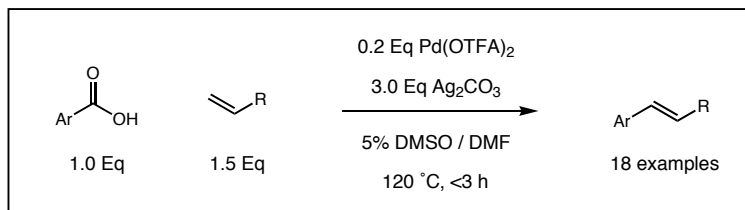


- In 2002, the Myers group reported a Heck reaction using benzoic acids as halide surrogates.

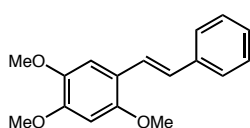


Myers Decarboxylative Heck-Type Reaction

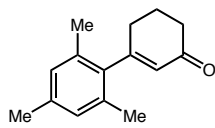
- The palladium system developed by the Myers group.



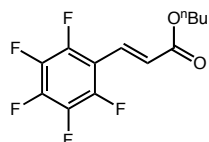
- Electron-rich, -poor, and heteroaromatic acids are tolerated.



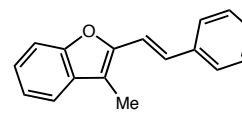
91% Yield



61% Yield



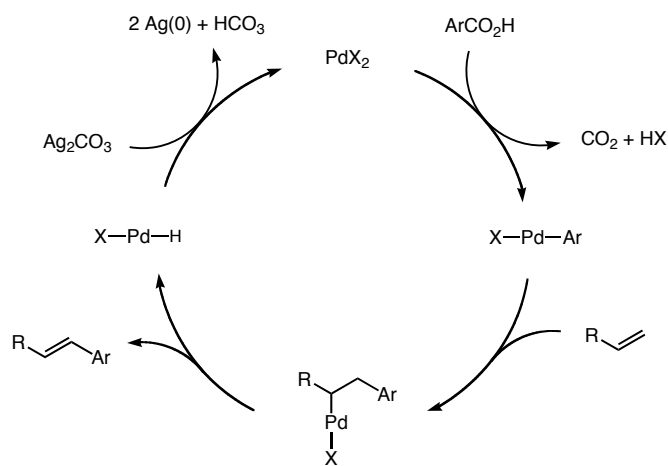
66% Yield



90% Yield

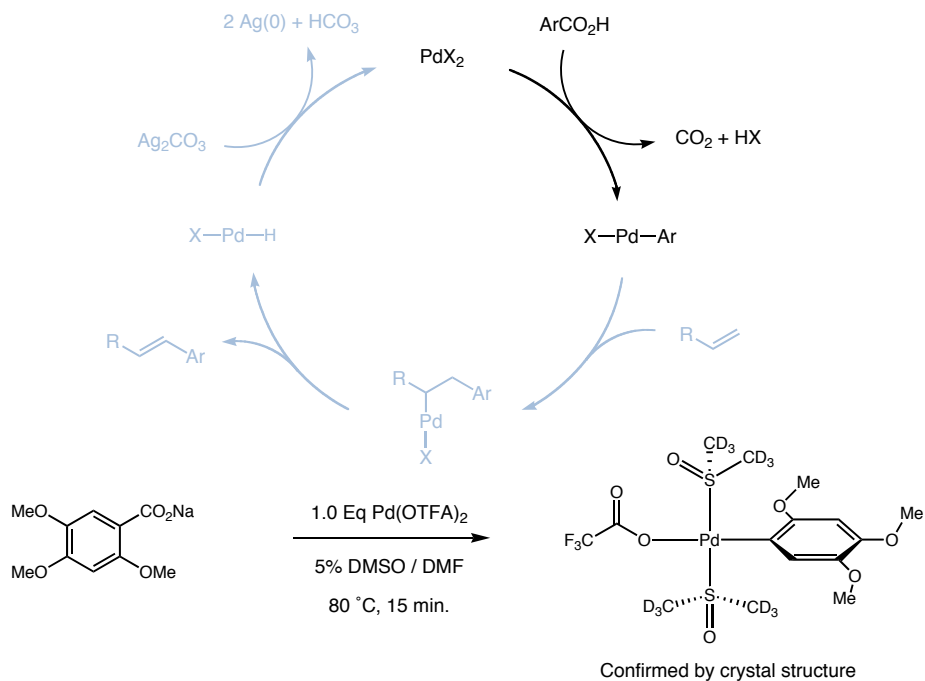
Myers, A. G. et al. *JACS*, **2002**, *124*, 11250-11251.

Myers: Proposed Mechanism of Decarboxylative Heck



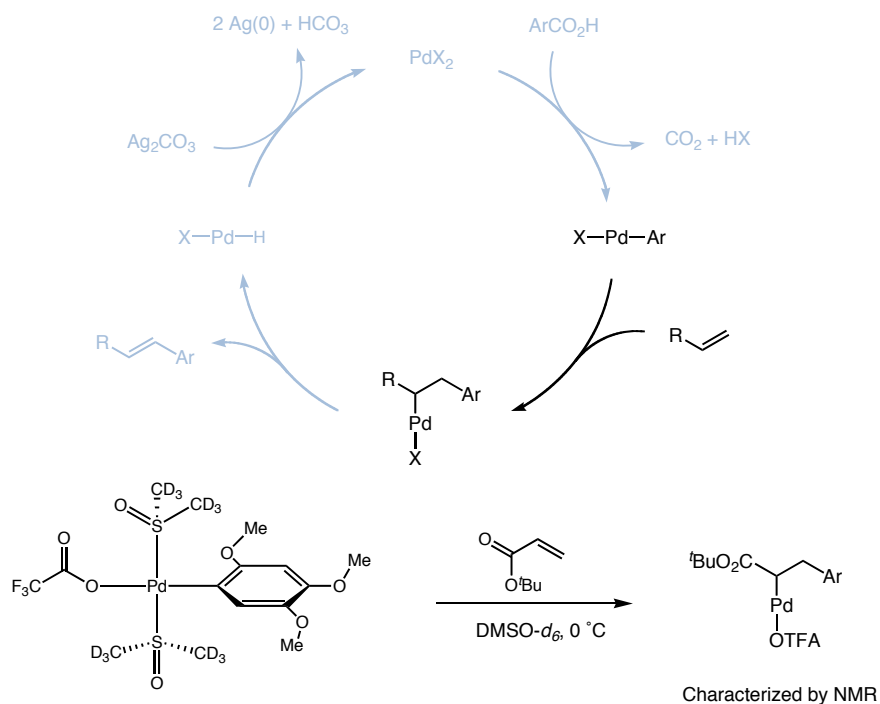
Myers, A. G. et al. *JACS*, **2005**, *127*, 10323-10333.

Myers: Mechanistic Studies



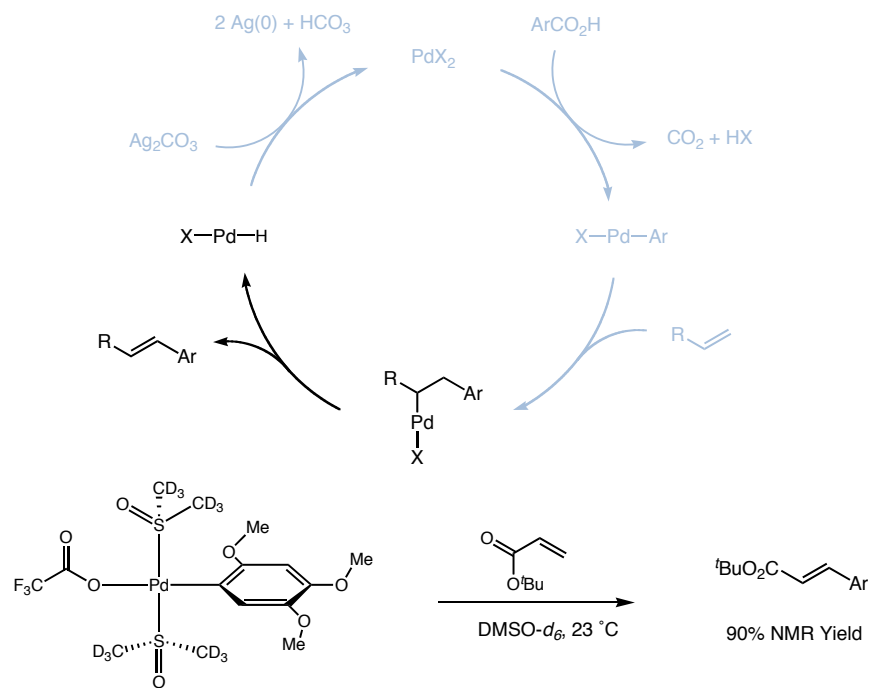
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Myers: Mechanistic Studies



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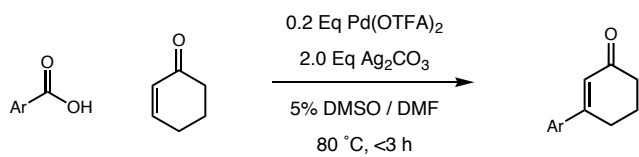
Myers: Mechanistic Studies



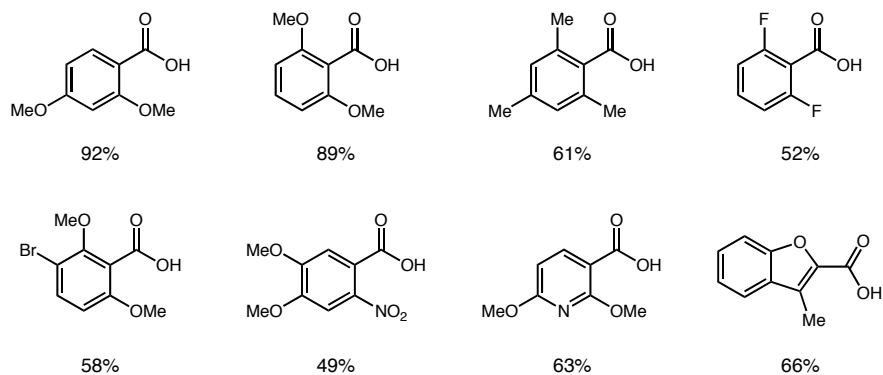
Myers, A. G. et al. *JACS*, **2005**, *127*, 10323-10333.

Myers: Heck-Type Arylation of Cyclic Enones

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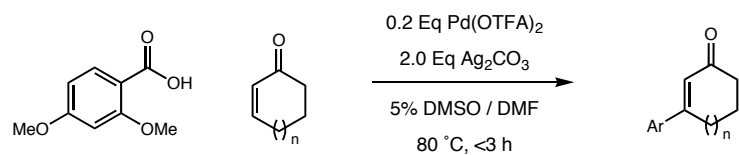
- Scope of the aromatic acid



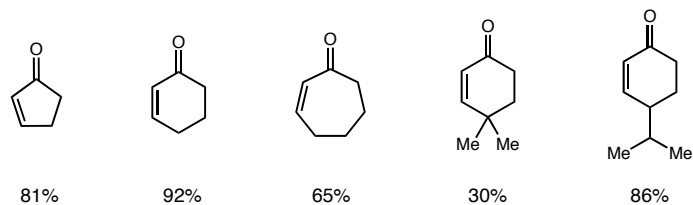
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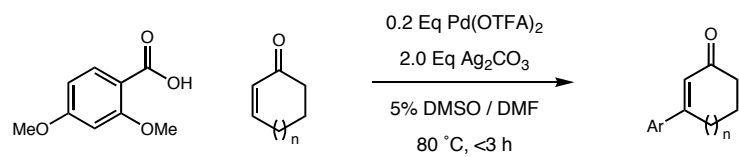
- Scope of the cyclic α,β -unsaturated ketone.



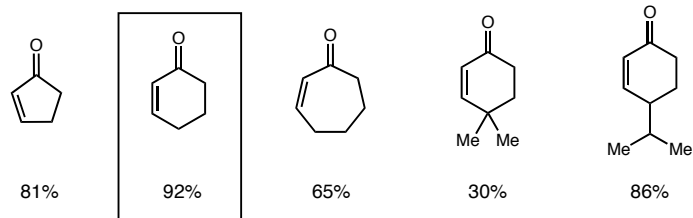
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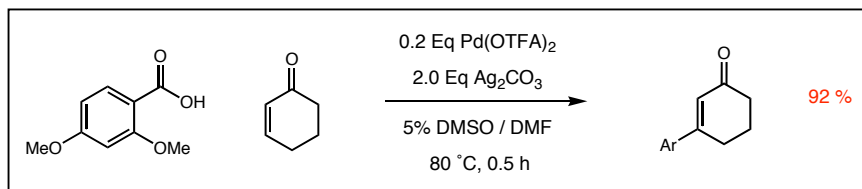
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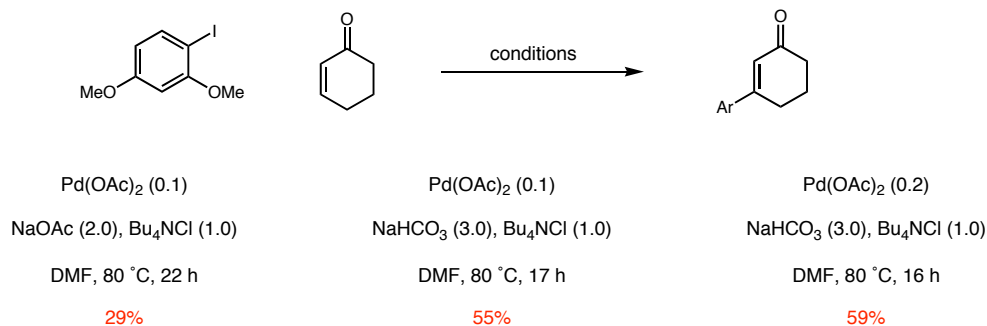
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Myers: Heck-Type Arylation of Cyclic Enones

- Advantage of decarboxylative Heck: electron rich arene substrates.



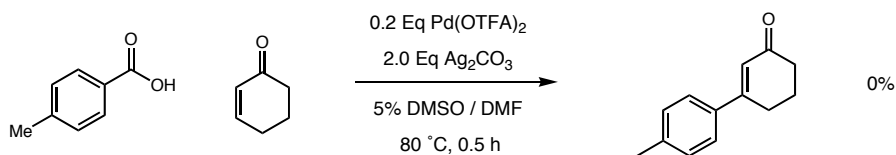
- Same reaction using traditional conditions is challenging.



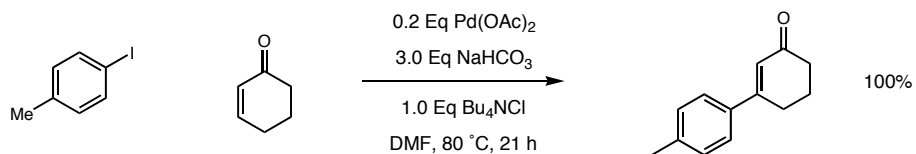
Myers, A. G. et al. *Org. Lett.*, **2004**, 6, 433-436.

Myers: Heck-Type Arylation of Cyclic Enones

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



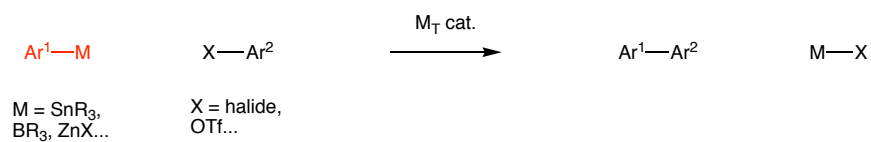
- 'Traditional' Heck conditions form product in quantitative yield.



Myers, A. G. et al. *Org. Lett.*, **2004**, 6, 433-436.

Biaryl Synthesis via Decarboxylative Coupling

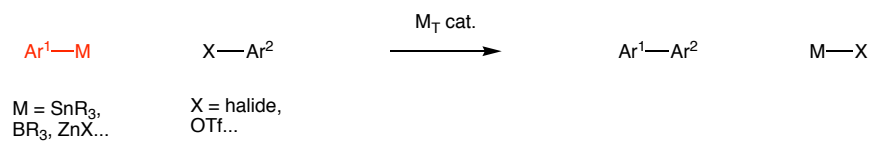
- Traditional biaryl couplings use stoichiometric organometallic reagents.



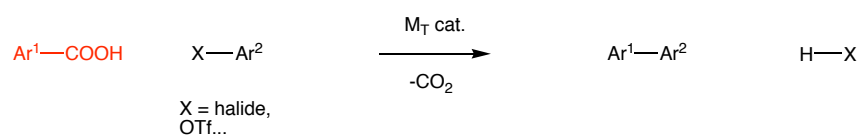
Baudoin, O. *Angew.*, **2007**, 46, 1373-1375.

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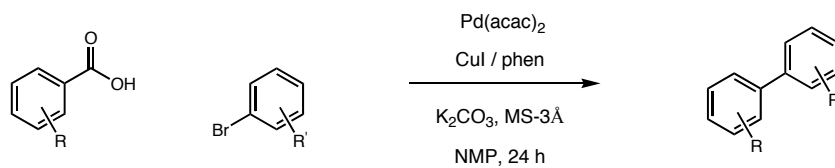
- Decarboxylative biaryl coupling reactions utilize aromatic acid as organometallic surrogate.



Baudoin, O. *Angew.*, **2007**, 46, 1373-1375.

Biaryl Synthesis via Decarboxylative Coupling: Gooßen

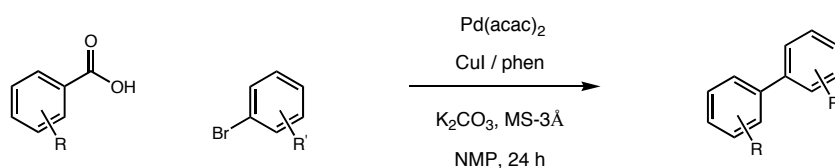
- In 2006, Gooßen reported a bimetallic system for decarboxylative biaryl synthesis.



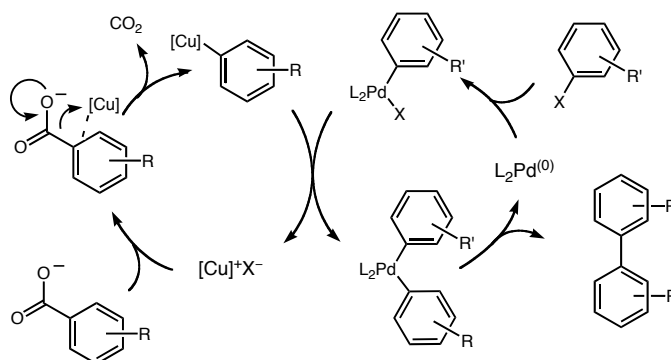
Gooßen, L. J. et al. *Science*, **2006**, 313, 662-664.

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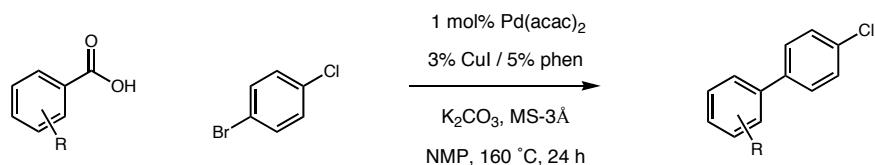
- Proposed mechanism.



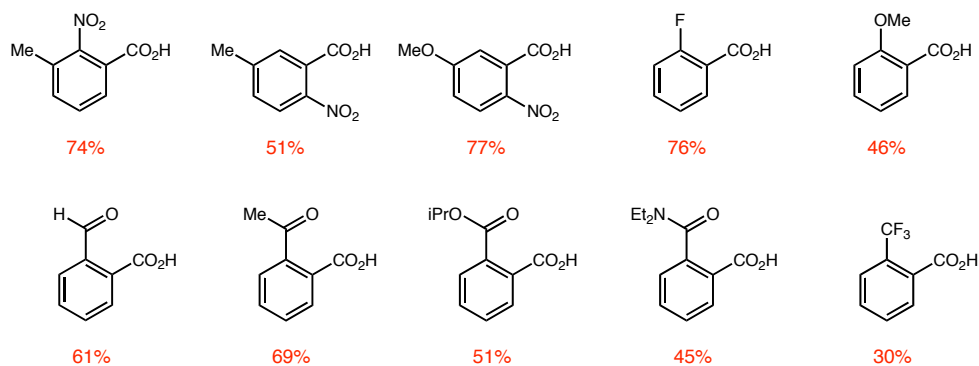
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Biaryl Synthesis via Decarboxylative Coupling: Gooßen

- System catalytic in palladium and copper.



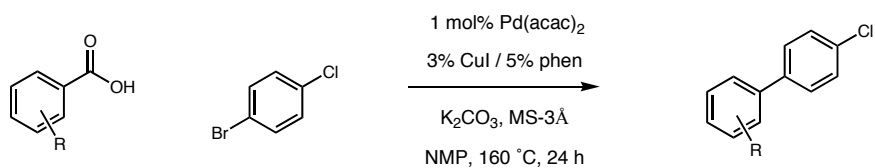
- Scope of the aromatic acid.



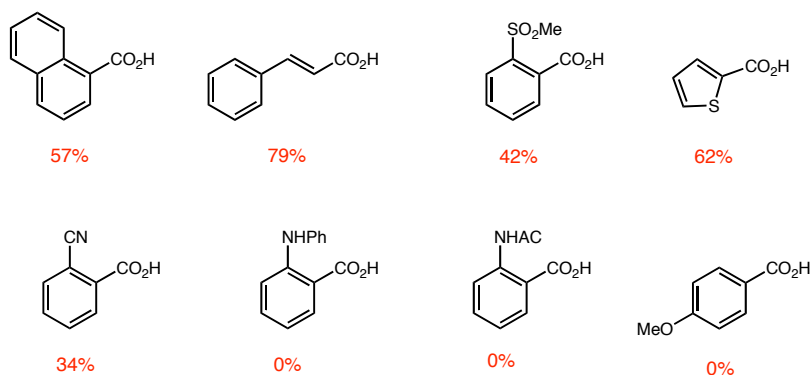
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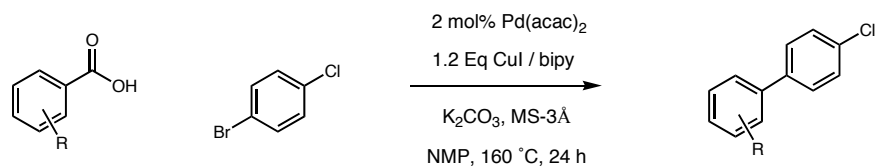
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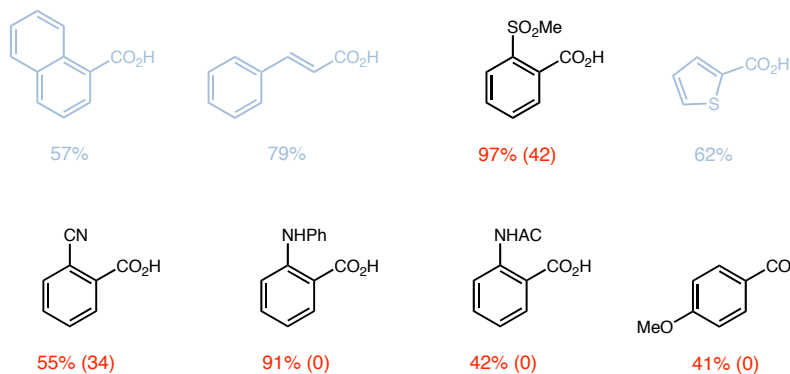
Gooßen, L. J. et al. *JACS.*, **2007**, *129*, 4824-4833.

Biaryl Synthesis via Decarboxylative Coupling: Gooßen

- System stoichiometric in copper.



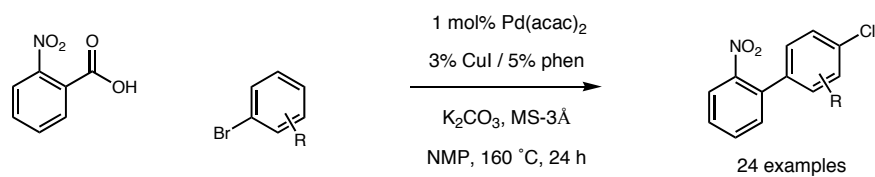
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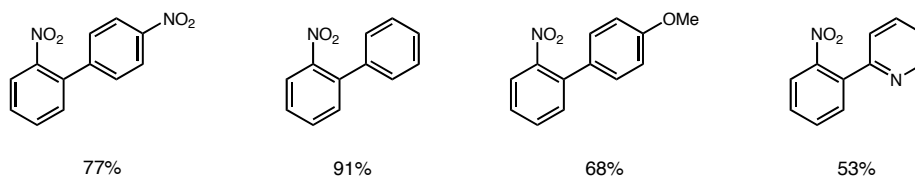
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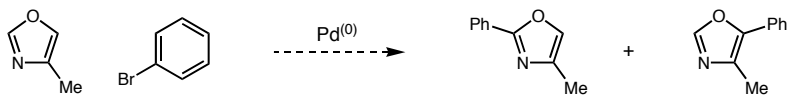
- Summary of the aryl bromide scope.



Gooßen, L. J. et al. *JACS.*, **2007**, *129*, 4824-4833.

Biaryl Synthesis via Decarboxylative Coupling: Forgione & Bilodeau

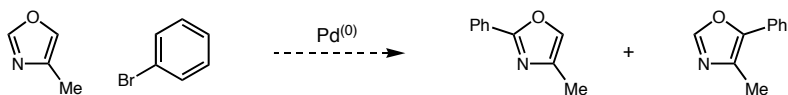
- Boehringer Ingelheim group was trying to do C-H activation of oxazoles.



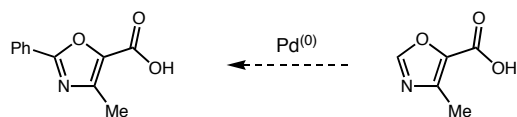
Forgione, P.; Bilodeau, F. et al. *JACS.*, **2006**, *128*, 11350-11351.

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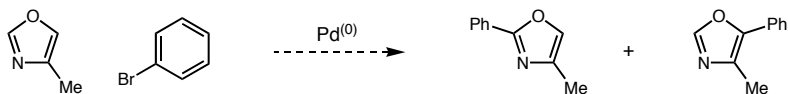
- They postulated that regioselectivity would be dictated by the presence of a blocking group.



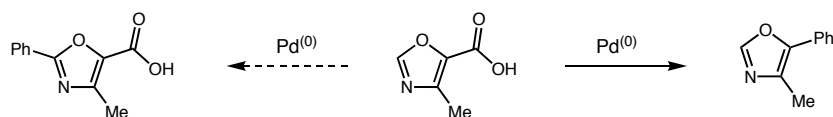
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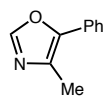
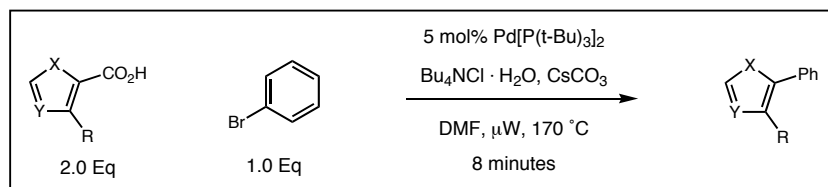
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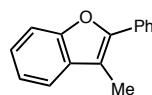
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Forgione & Bilodeau: Heteroaromatic Decarboxylative Biaryl Synthesis

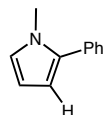
- The optimized reaction conditions are useful for many heteroaromatic acids.



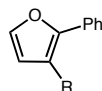
74%



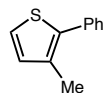
86%



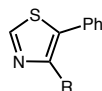
88%



R = Me, 86%
R = H, 41%



63%

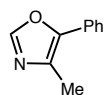
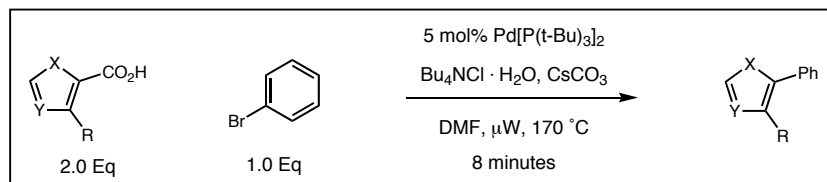


R = Me, 74%
R = H, 23%

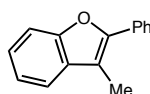
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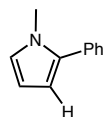
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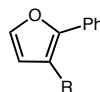
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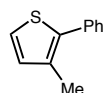


88%

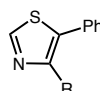


R = Me, 86%

R = H, 41%



63%



R = Me, 74%

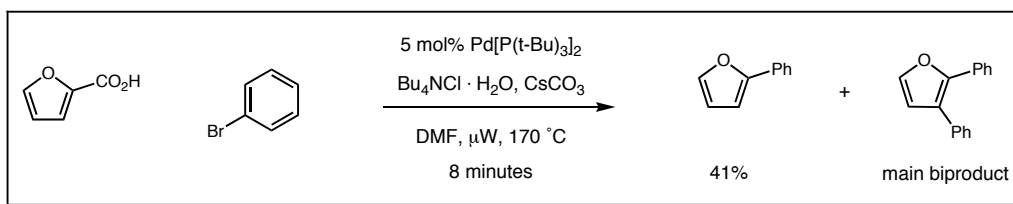
R = H, 23%

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

Forgione, P.; Bilodeau, F. et al. *JACS.*, **2006**, *128*, 11350-11351.

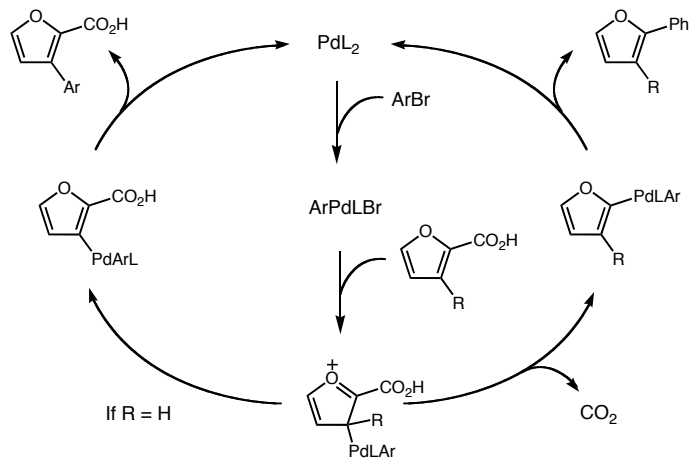
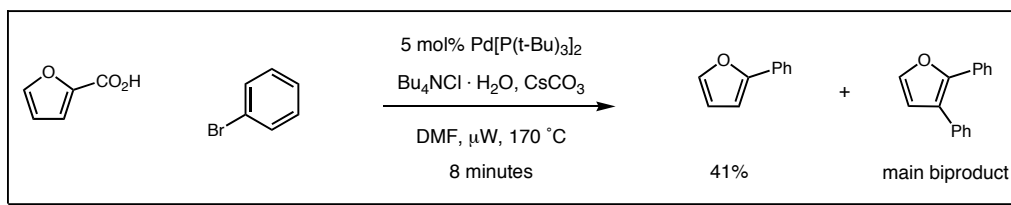
Proposed Mechanism of Heteroaromatic Acid Coupling

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



Proposed Mechanism of Heteroaromatic Acid Coupling

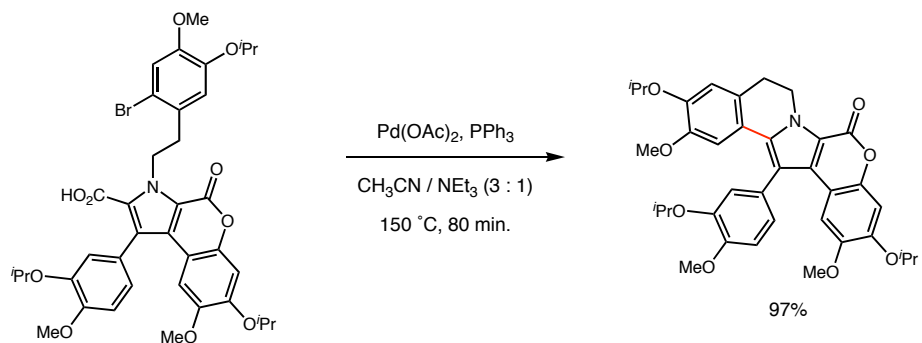
- Biproduct of reaction using 2-furancarboxylic acid could shed light on the mechanism.



Forgione, P.; Bilodeau, F. et al. *JACS.*, **2006**, *128*, 11350-11351.

Synthesis of Lamellarin L

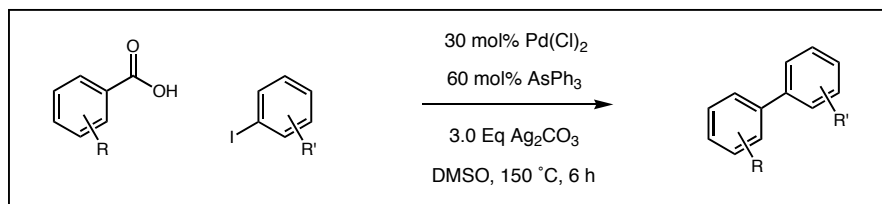
- In 2000, Steglich et al. used similar chemistry to forge the final bond in Lamellarin L.



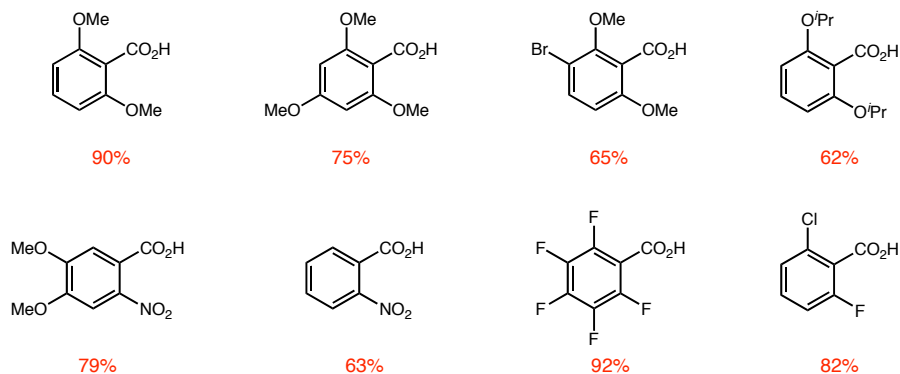
Steglich, W.; Peschko, C.; Winkhofer, C. *Chem. Eur. J.*, **2000**, *6*, 1147-1151.

Biaryl Synthesis via Decarboxylative Coupling: Becht

- Optimized system uses 30 mol % palladium and arsine ligand.



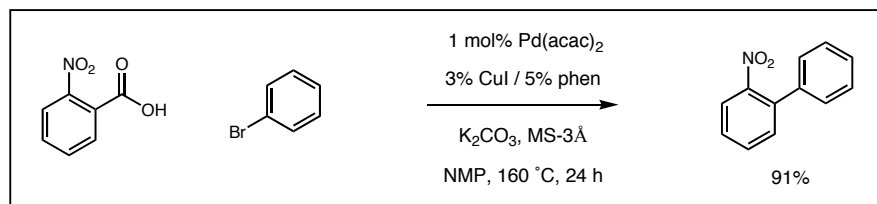
- Scope of the aromatic acid.



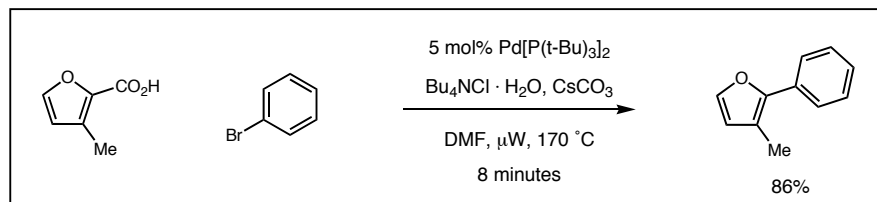
Becht, J.-M. et al. *Org.Lett.*, **2007**, 9, 1781-1783.

Summary of Decarboxylative Biaryl Syntheses

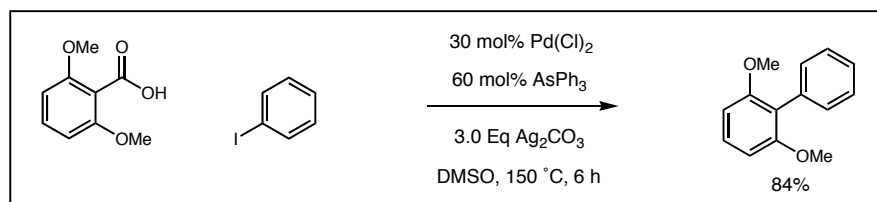
- Gooßen system is ideal for electron-poor benzoic acids.



- Forgione / Bilodeau system for heteroaromatic acids.

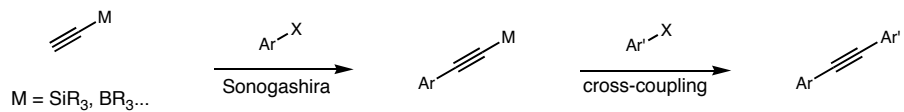


- Becht system is best for electron-rich benzoic acids.

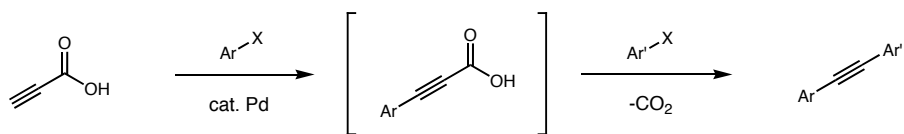


Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee

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



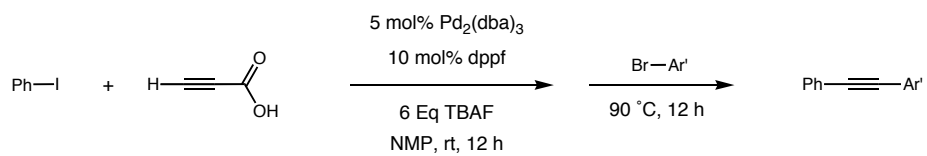
- Propiolic acid as TMS-acetylene substitute in a one-pot diaryl alkyne synthesis protocol.



Lee, S. et al. *Org.Lett.*, ASAP.

Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee

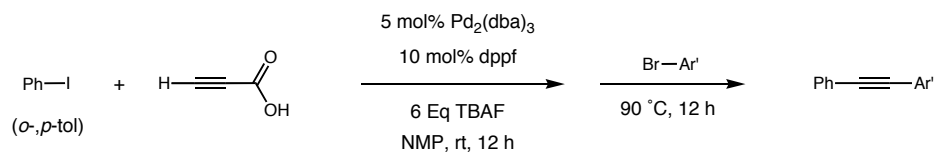
- Diaryl alkyne synthesis system developed by Lee group.



Lee, S. et al. *Org.Lett.*, ASAP.

Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee

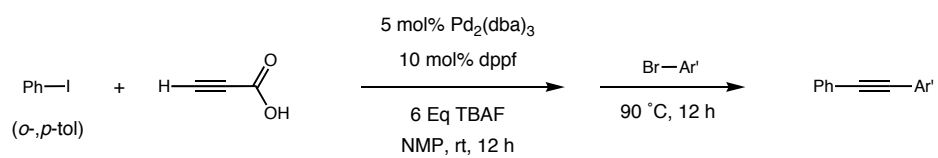
- Diaryl alkyne synthesis system developed by Lee group.



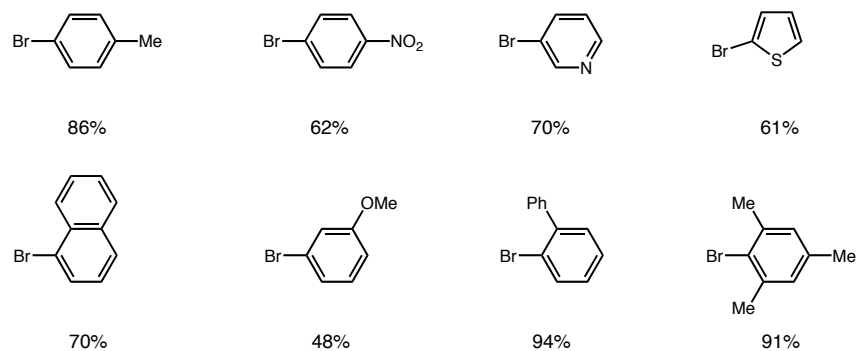
Lee, S. et al. *Org.Lett.*, ASAP.

Decarboxylative Non-Symmetrical Diaryl Alkyne Synthesis: Lee

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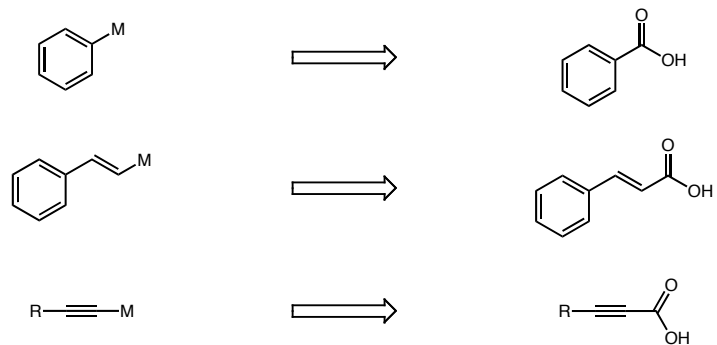
- Aryl bromide scope.



Lee, S. et al. *Org.Lett.*, ASAP.

Summary of Decarboxylative Cross-Coupling Chemistry

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



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

