中国科学技术大学
University of Science and Technology of China

Decarboxylative Cross Coupling

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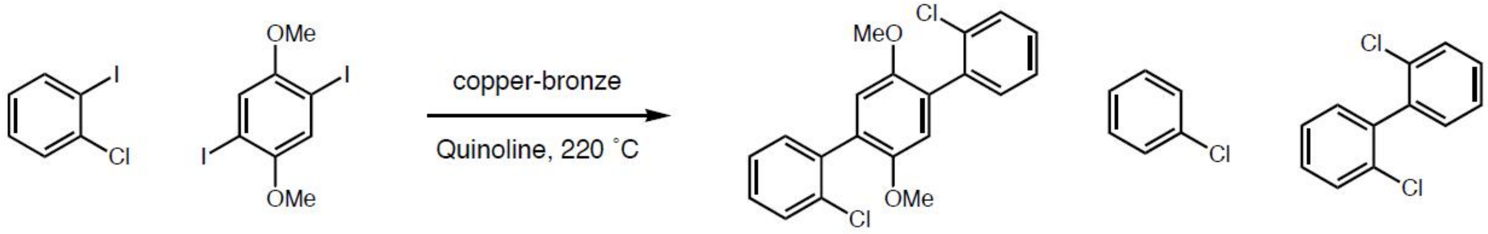
First Example

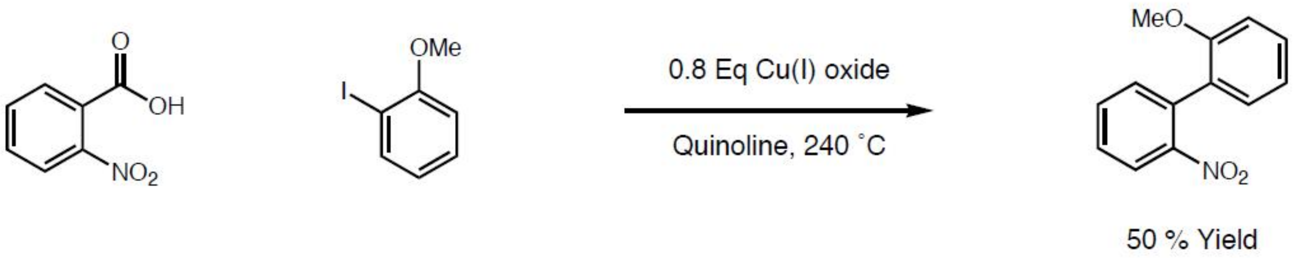
In 1958, Nilsson reported his findings regarding an Ullmann coupling.



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

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

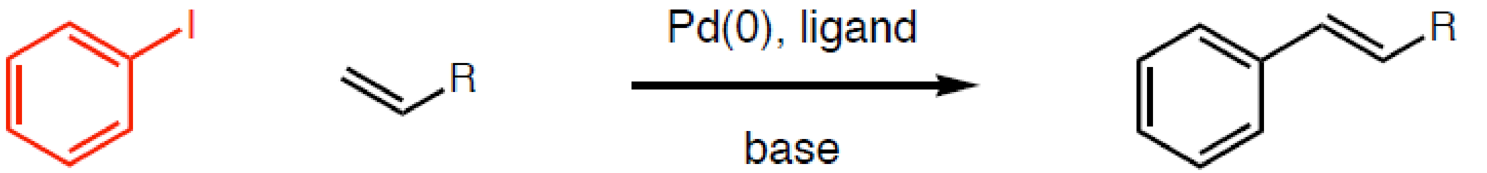
In 1966, Nilsson reported the first decarboxylative Ullmann coupling.



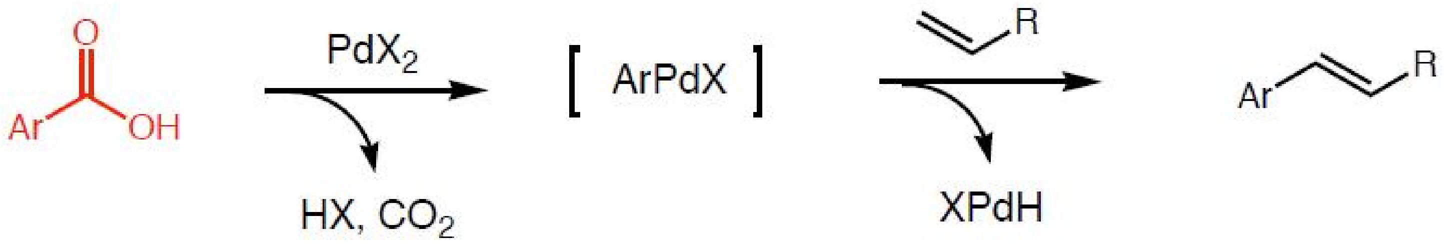
Nilsson, M. *Acta Chem. Scand.*, **1966**, *20*, 423-426.

Myers' Decarboxylative Heck Type Reaction

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

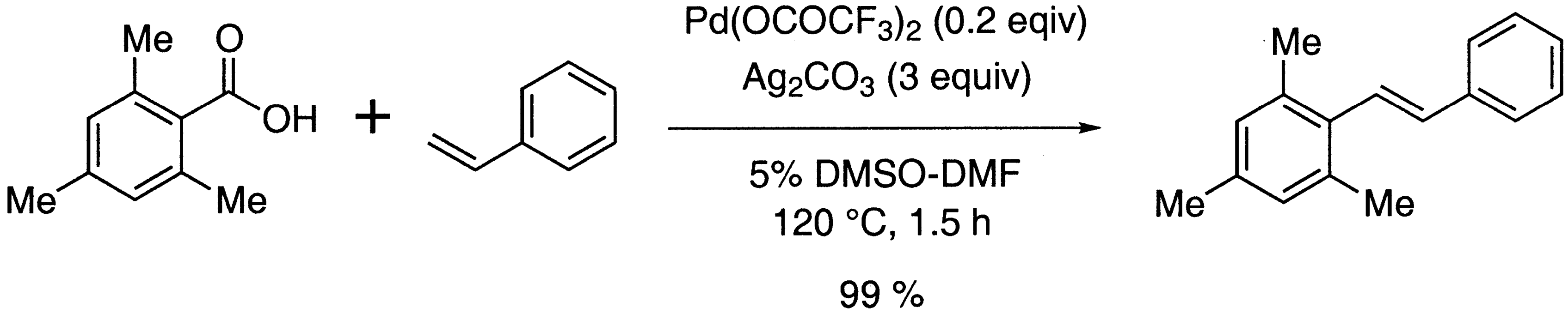


◆ In 2002, the Myers group reported a Heck reaction using benzoic acids.

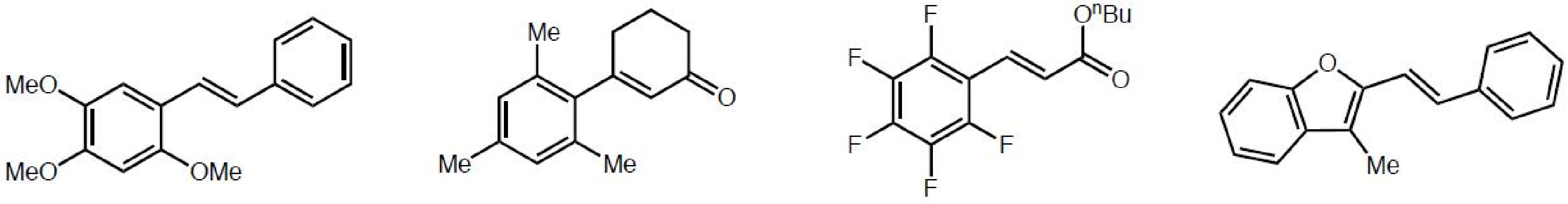


Myers, A. G. et al. *JACS*, **2002**, *124*, 11250-11251.

Myers' Decarboxylative Heck Type Reaction



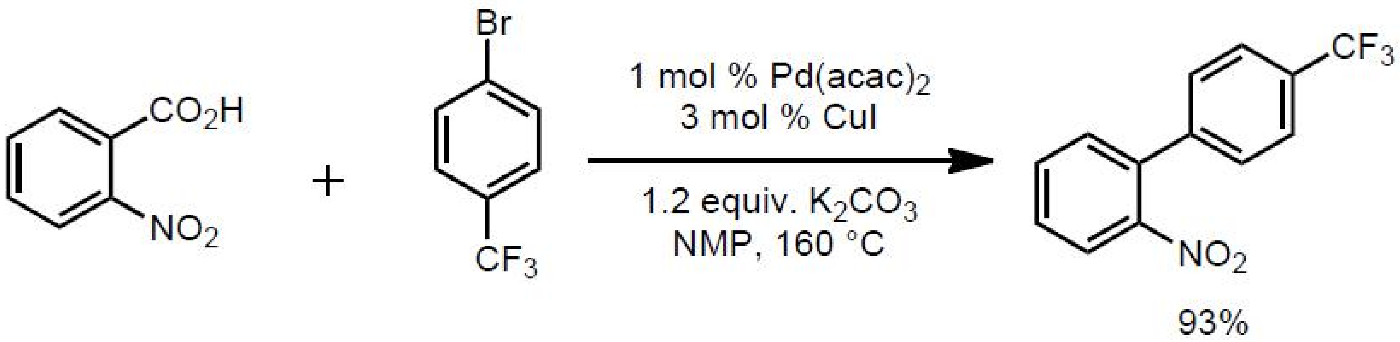
◆ **Electron-rich, -poor, and heteroaromatic acids are tolerated.**



91% Yield   61% Yield   66% Yield   90% Yield

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

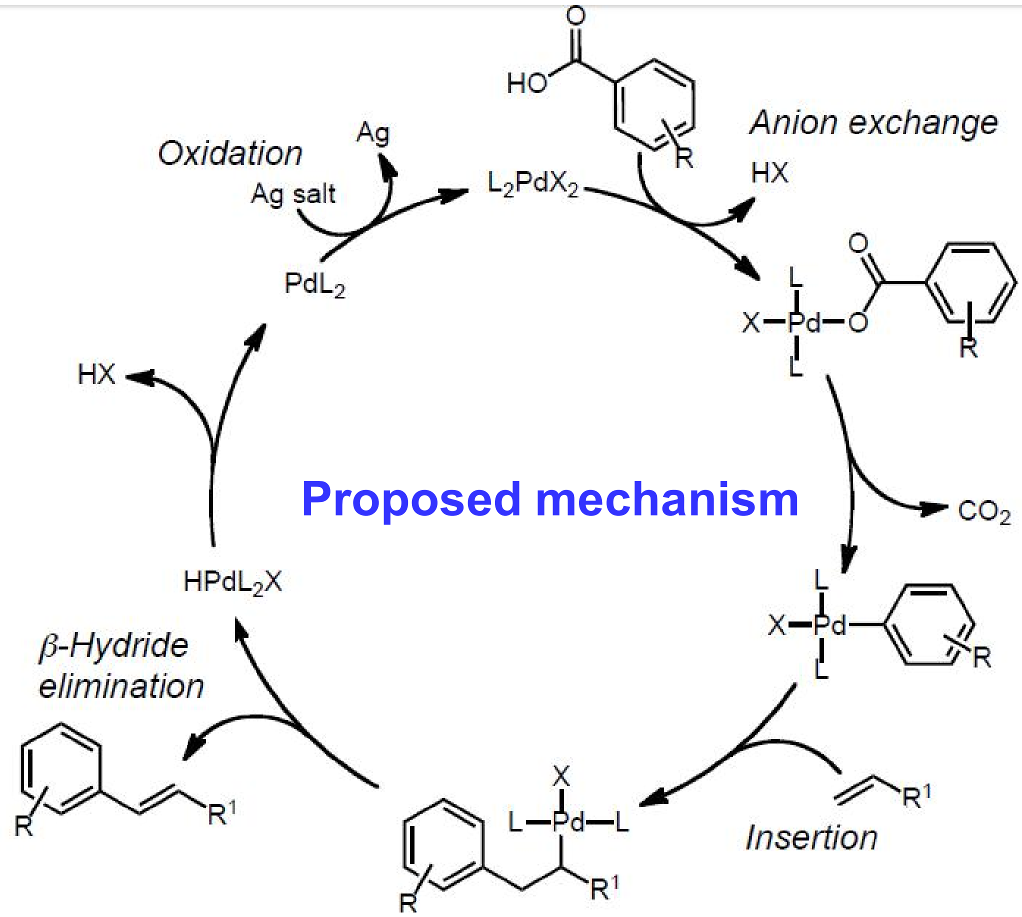
Decarboxylative Cross Coupling



Science **2006**, *313*, 662.

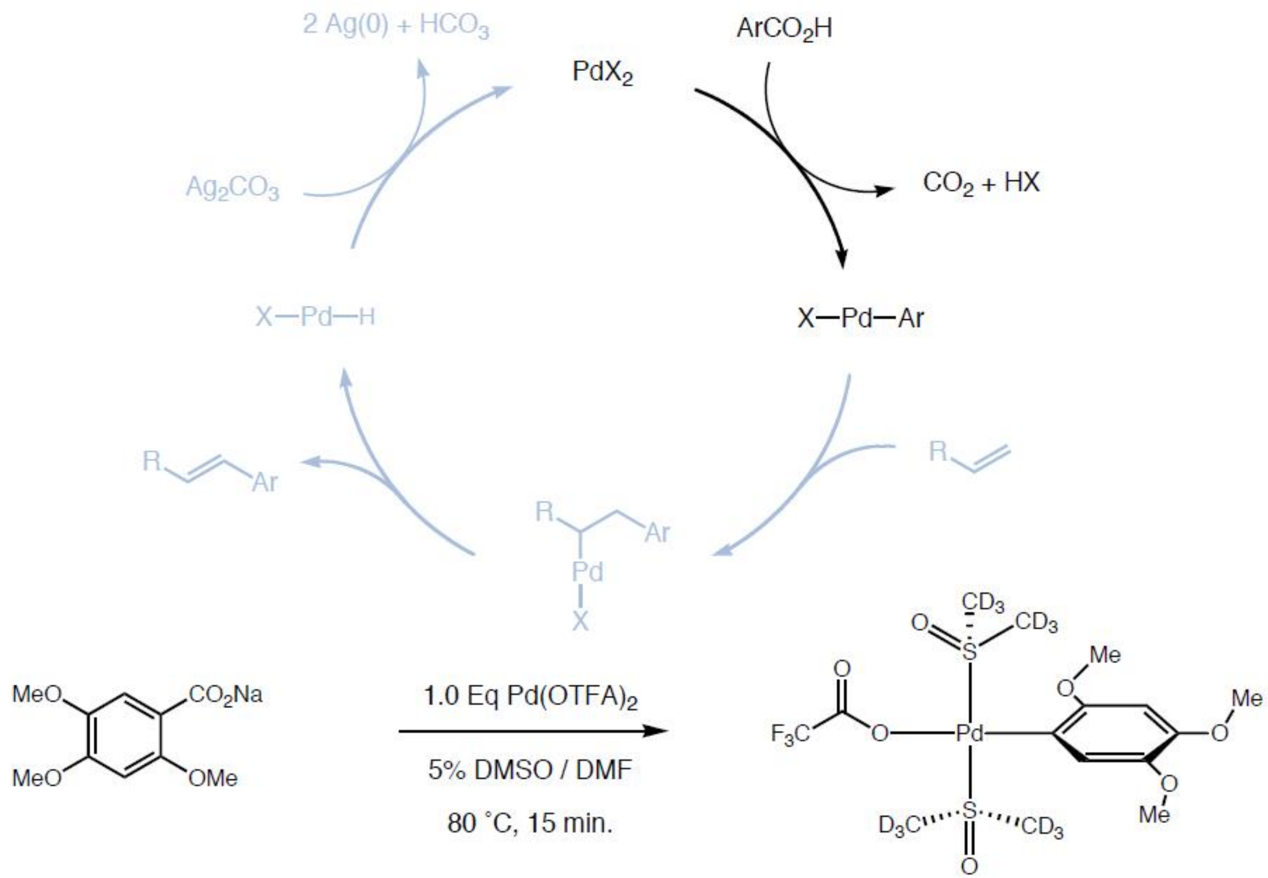
- ◆ **Bimetallic catalyst system-Pd/Cu**
- ◆ **Lower temperature**
- ◆ **Higher yield---practical industrial application**

Mechanistic Studies



JACS 2005, 127, 10323.

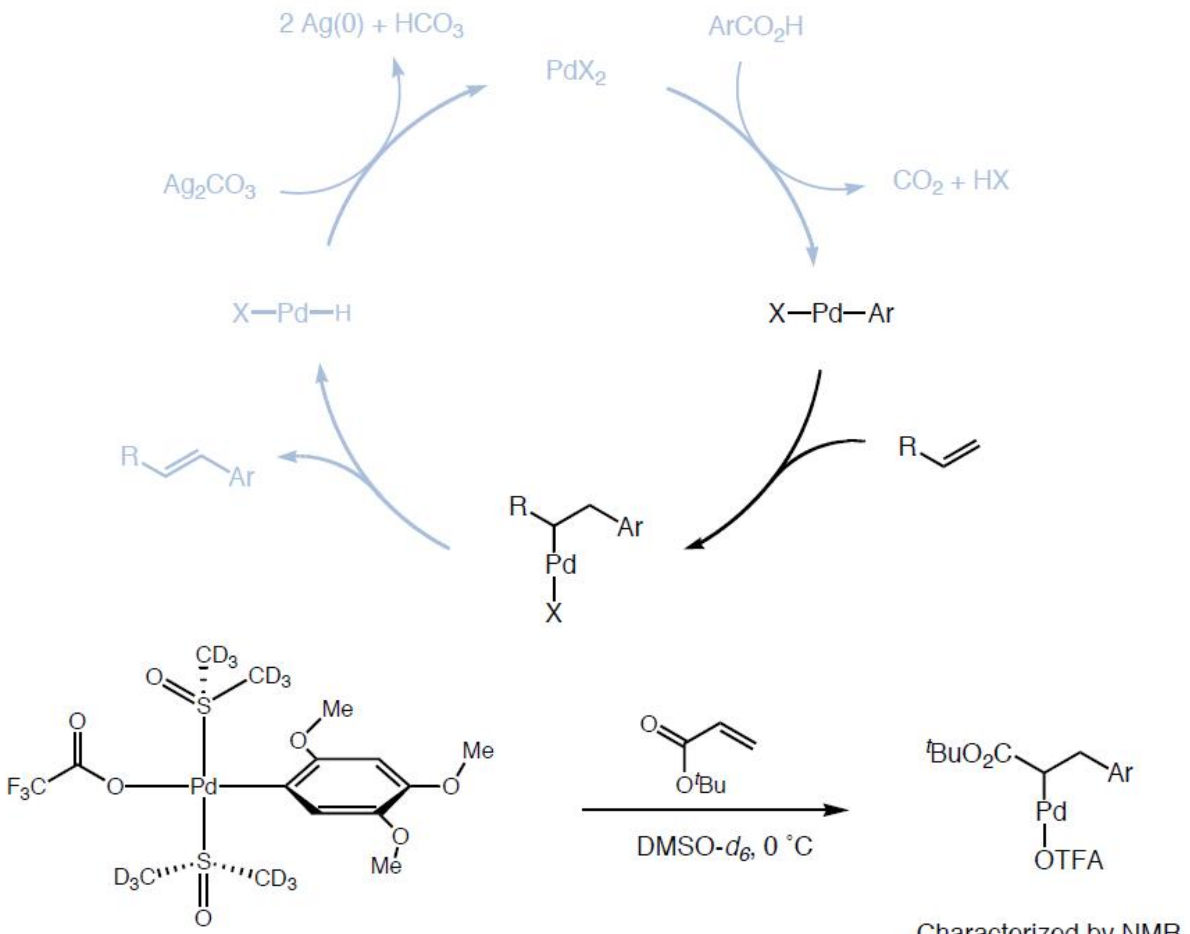
Mechanistic Studies



Confirmed by crystal structure

JACS 2005, 127, 10323.

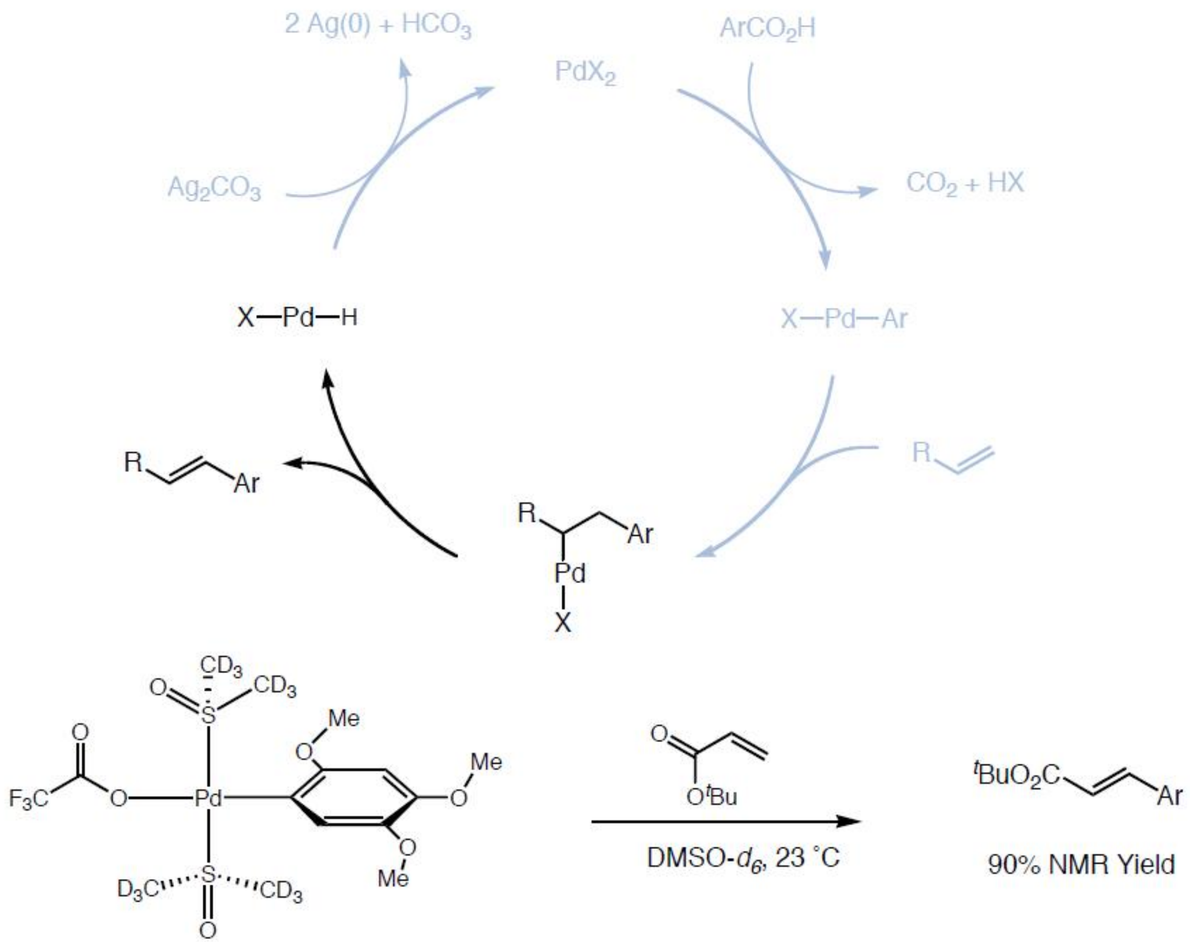
Mechanistic Studies



Characterized by NMR

JACS 2005, 127, 10323.

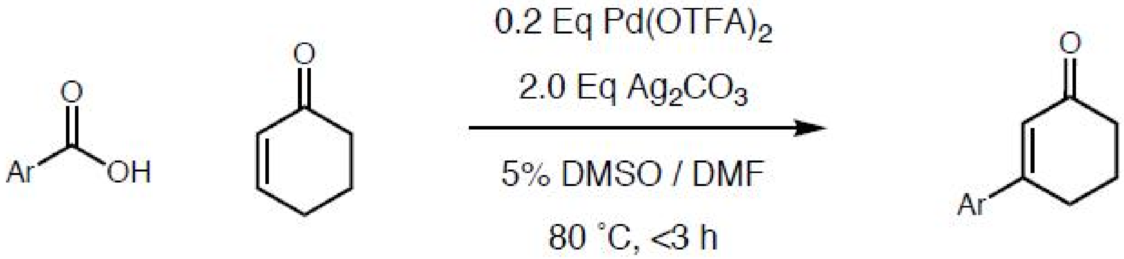
Mechanistic Studies



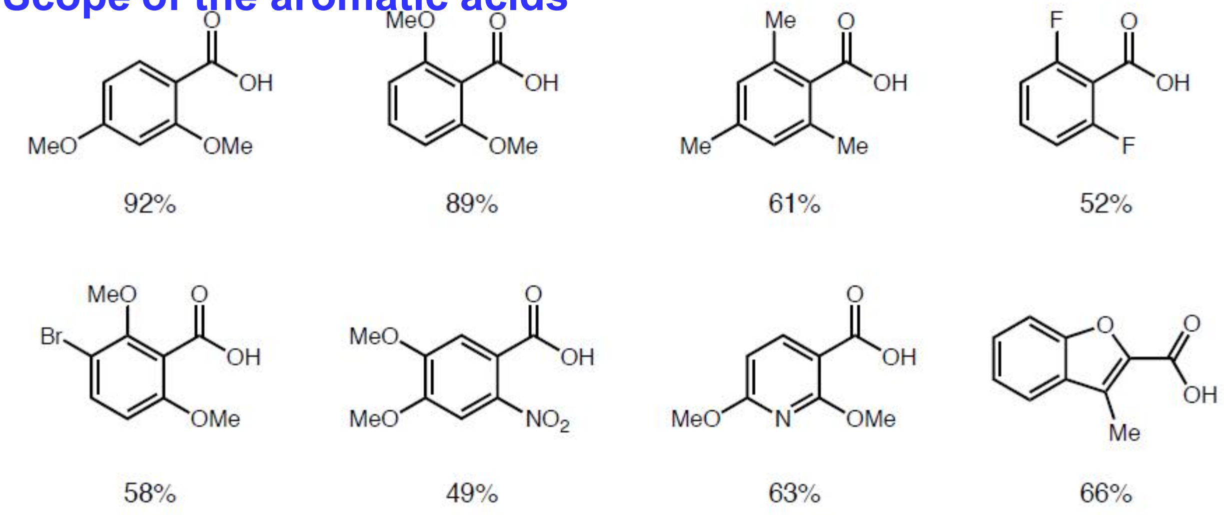
JACS 2005, 127, 10323.

Decarboxylative Cross Coupling

Cyclic enone as substrates



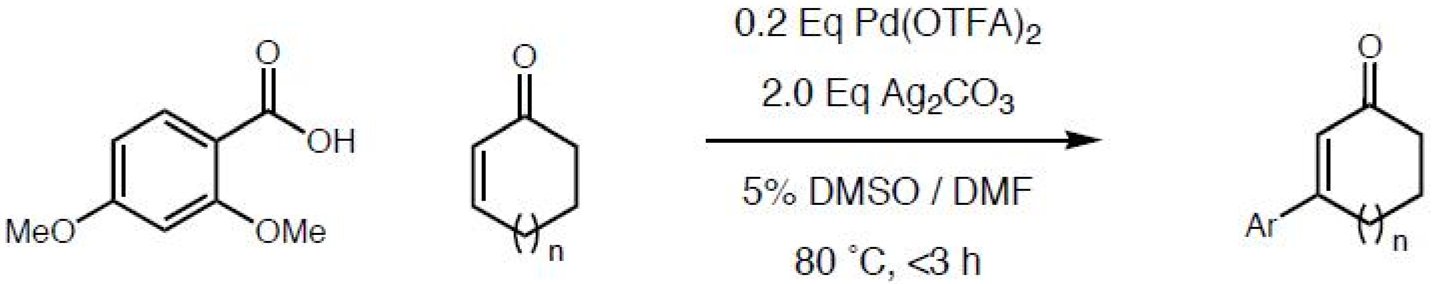
Scope of the aromatic acids

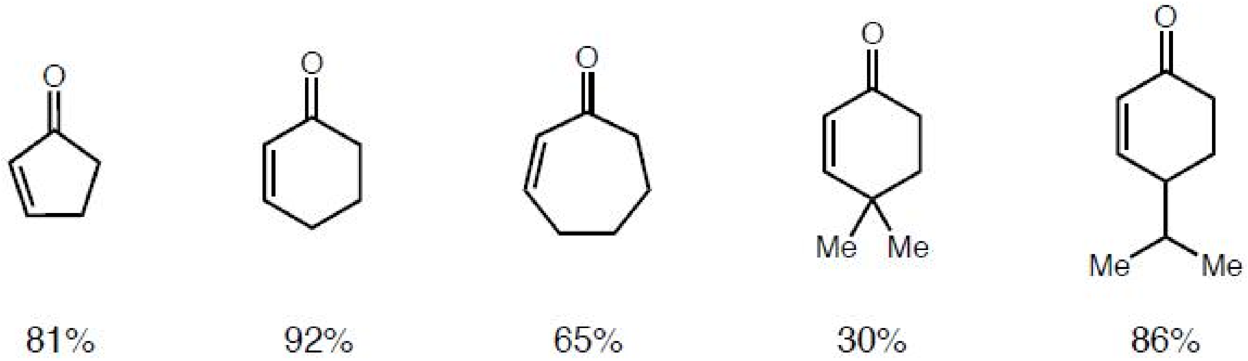


Org. Lett. ***2004**, 6, 433*

Decarboxylative Cross Coupling

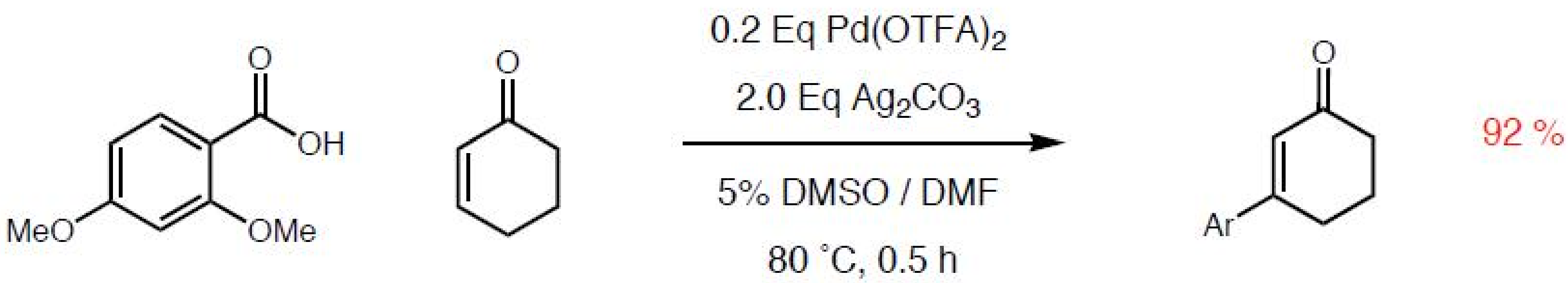
Cyclic enone as substrates



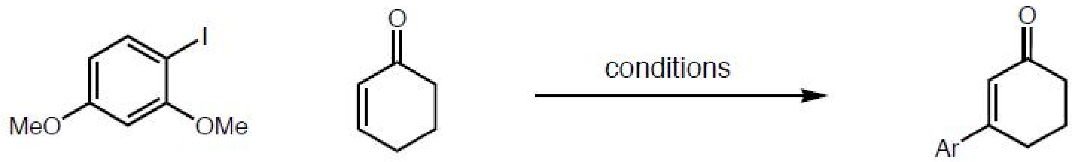


Org. Lett. 2004, 6, 433

Decarboxylative Cross Coupling



Compare to traditional coupling methods

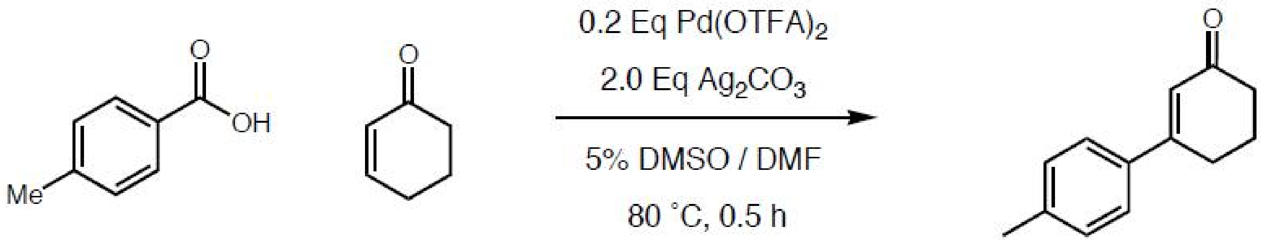


Pd(OAc)$_2$ (0.1)	Pd(OAc)$_2$ (0.1)	Pd(OAc)$_2$ (0.2)
NaOAc (2.0), Bu$_4$NCl (1.0)	NaHCO$_3$ (3.0), Bu$_4$NCl (1.0)	NaHCO$_3$ (3.0), Bu$_4$NCl (1.0)
DMF, 80 ˚C, 22 h	DMF, 80 ˚C, 17 h	DMF, 80 ˚C, 16 h
29%	55%	59%

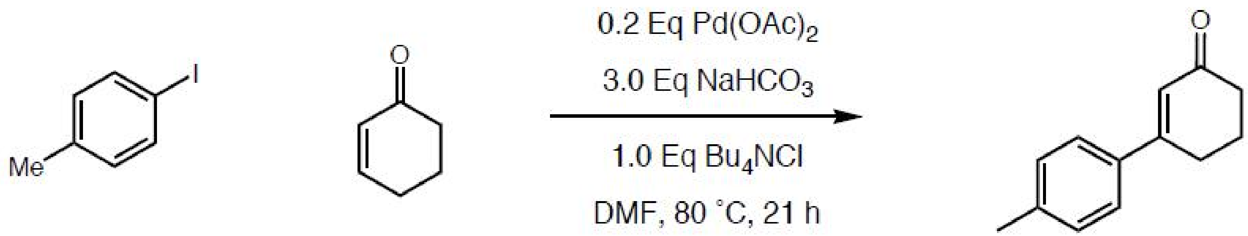
***Org. Lett.* 2004, 6, 433**

Decarboxylative Cross Coupling

Ortho-substitution is required



0%



100%

Biaryl Synthesis via Decarboxylative Coupling

Tradition biaryl synthesis use organometallic reagents

$$\text{Ar-M} \quad + \quad \text{X-Ar} \xrightarrow{\text{catalyst}} \text{Ar-Ar} \quad + \quad \text{M-X}$$

M=SnR_3, BR_3, ZnX, etc

X=halide, OTf, etc

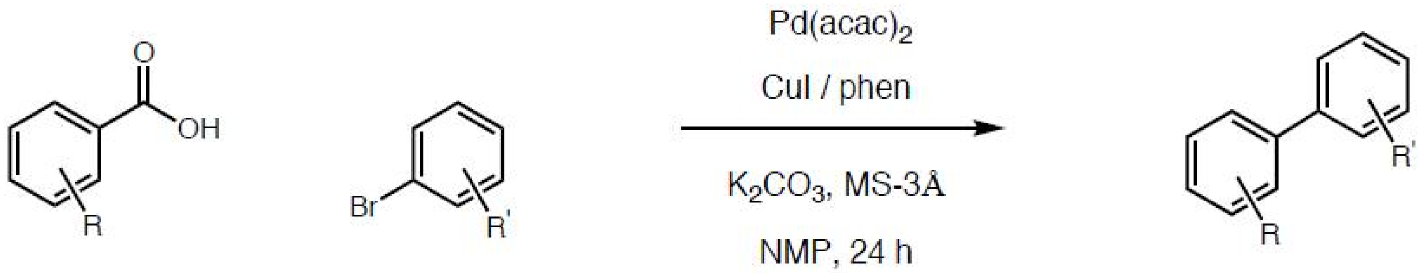
Decarboxylative biaryl coupling reaction use aromatic acids as substrates

$$\text{Ar-COOH} \quad + \quad \text{X-Ar} \xrightarrow{\text{catalyst}} \text{Ar-Ar} \qquad \text{H-X}$$

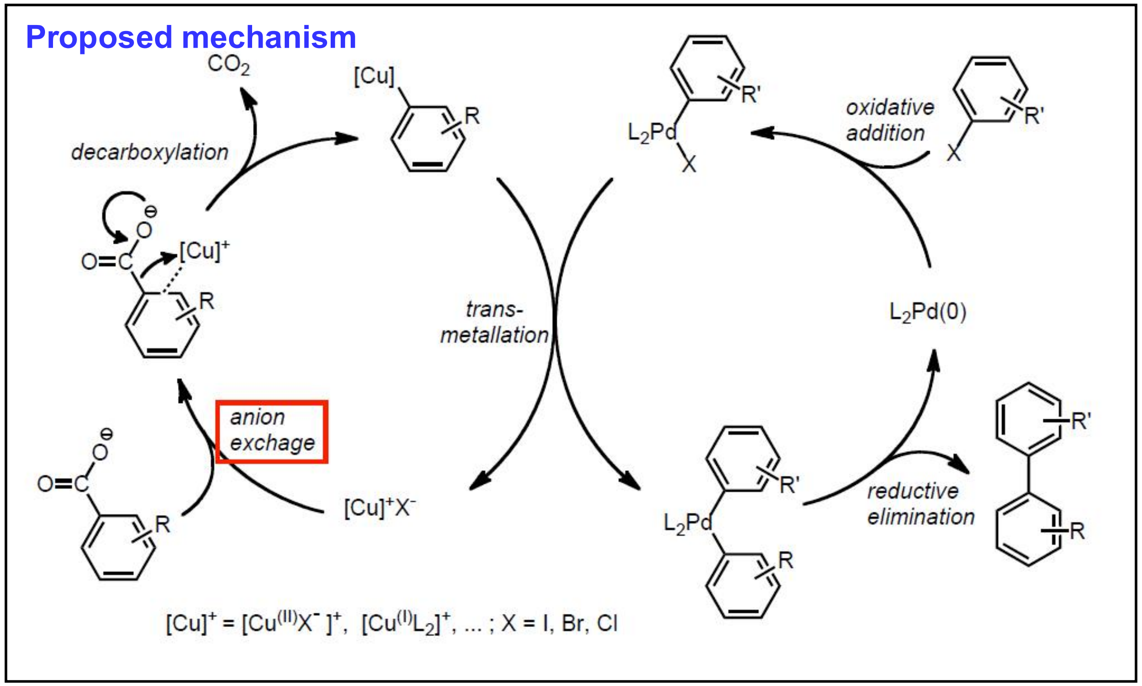
X=halide, OTf, etc

Biaryl Synthesis via Decarboxylative Coupling

In 2006, Gooβen reported bimetallic catalyst for decarboxylative baryl synthesis

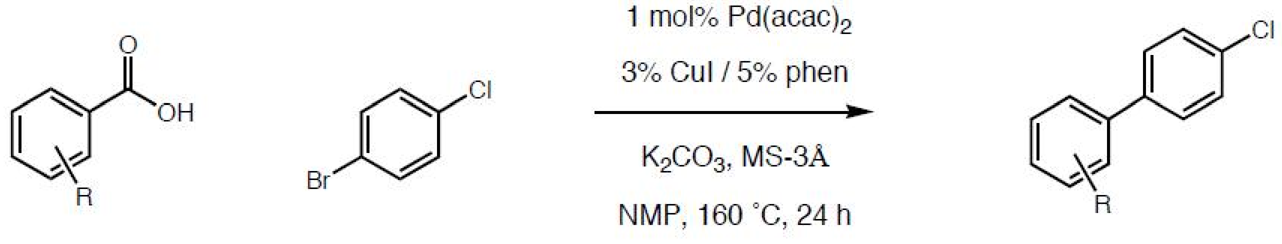


***Science* 2006, 313, 662**

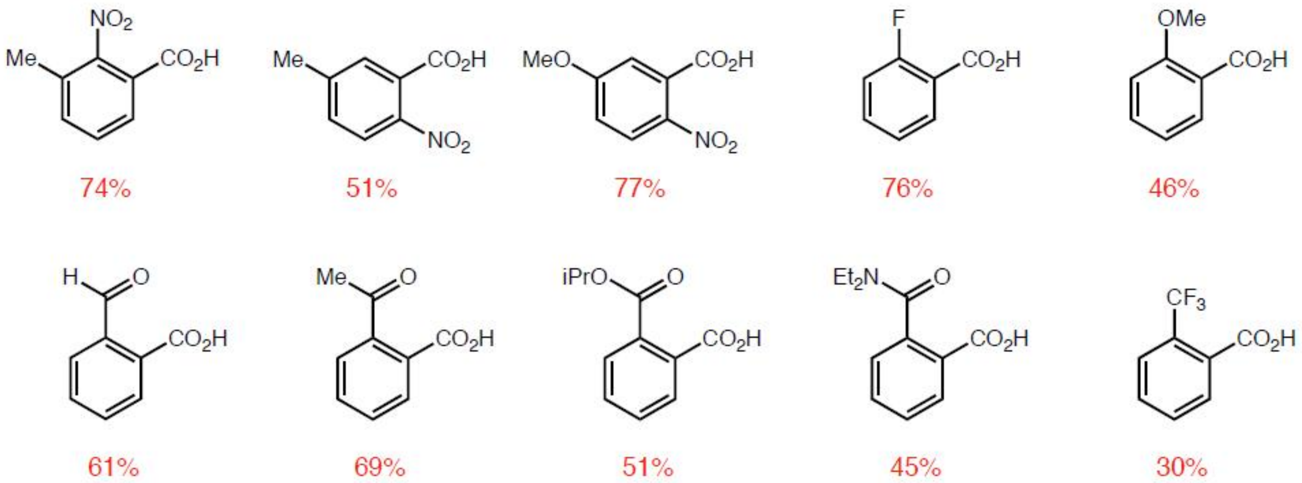


Biaryl Synthesis via Decarboxylative Coupling

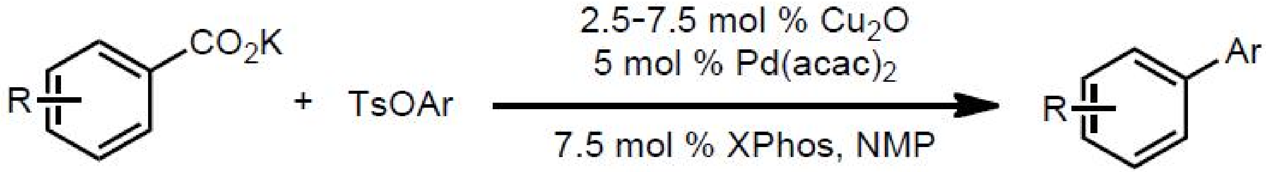
Follow Up Work



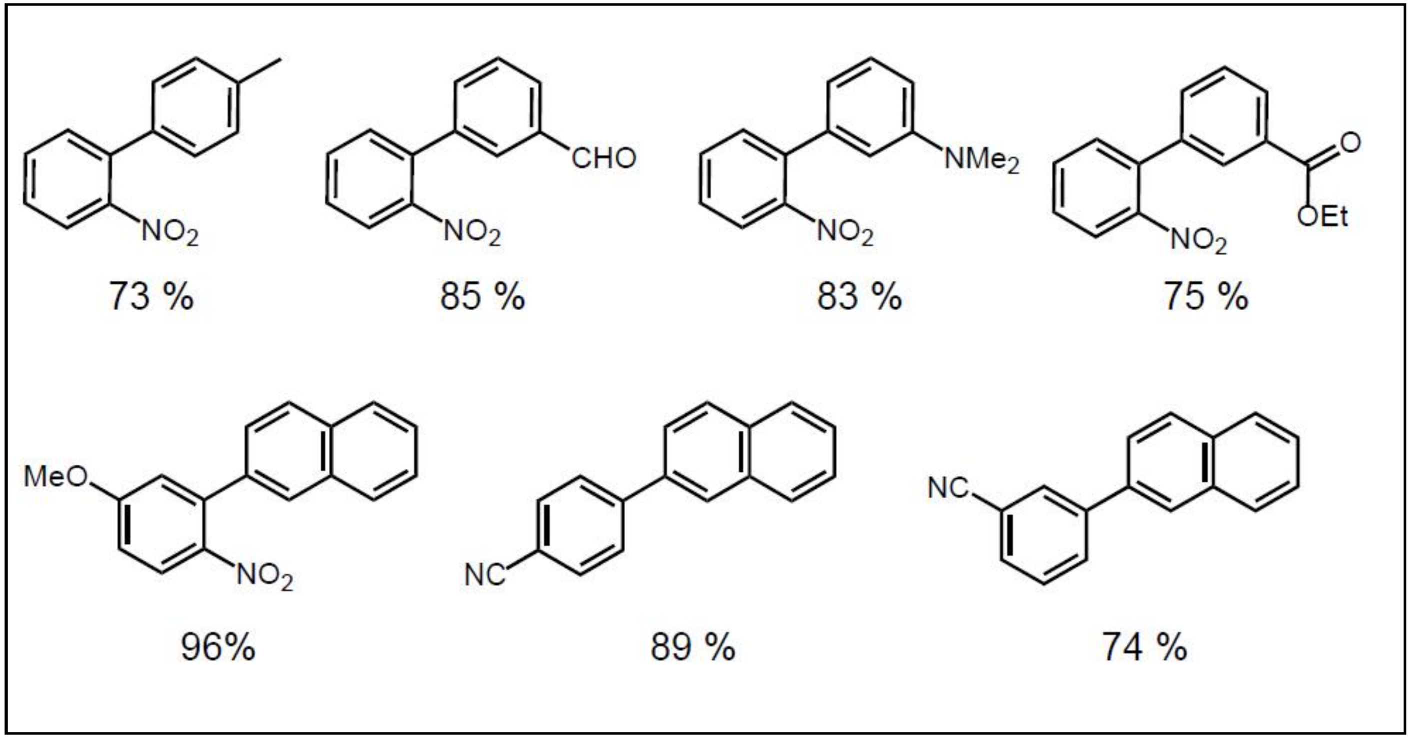
JACS 2007, 129, 4824



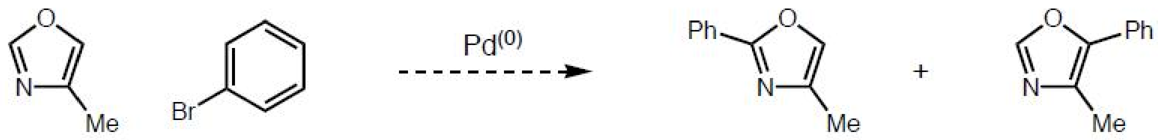
Decarboxylative Cross Coupling

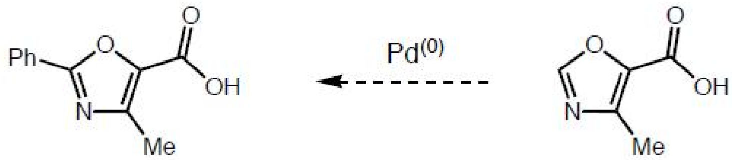


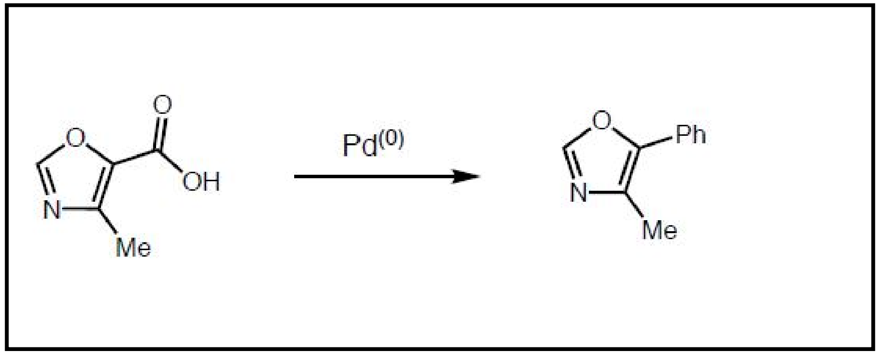
Angew. Chem. Int. Ed. **2008**, *47*, 3100



Decarboxylative Cross Coupling

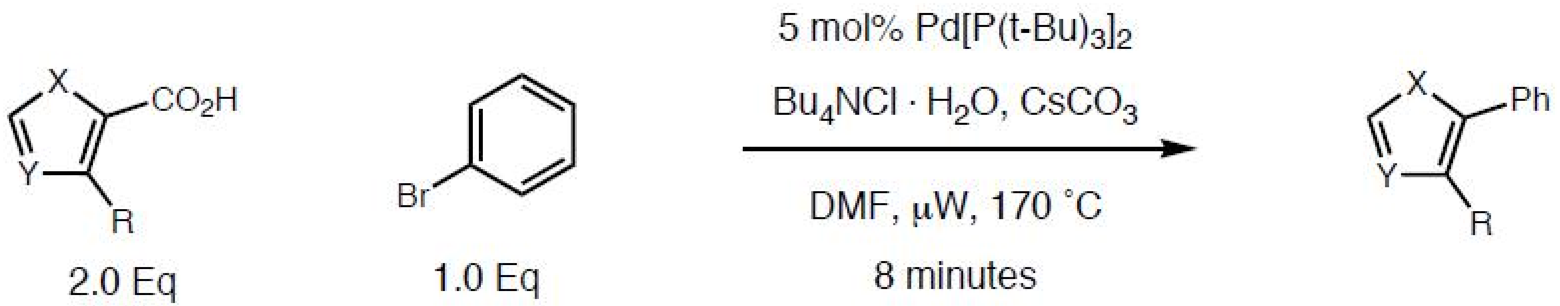


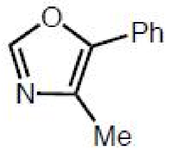




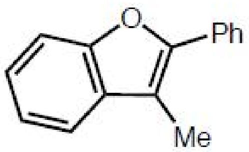
JACS 2006, 128, 11350

Decarboxylative Cross Coupling

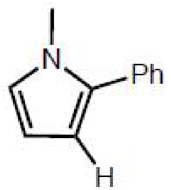




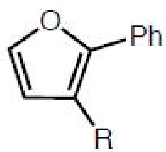
74%



86%

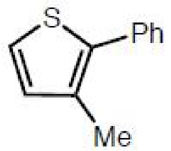


88%

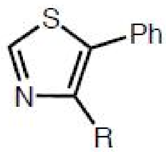


R = Me, 86%

R = H, 41%



63%



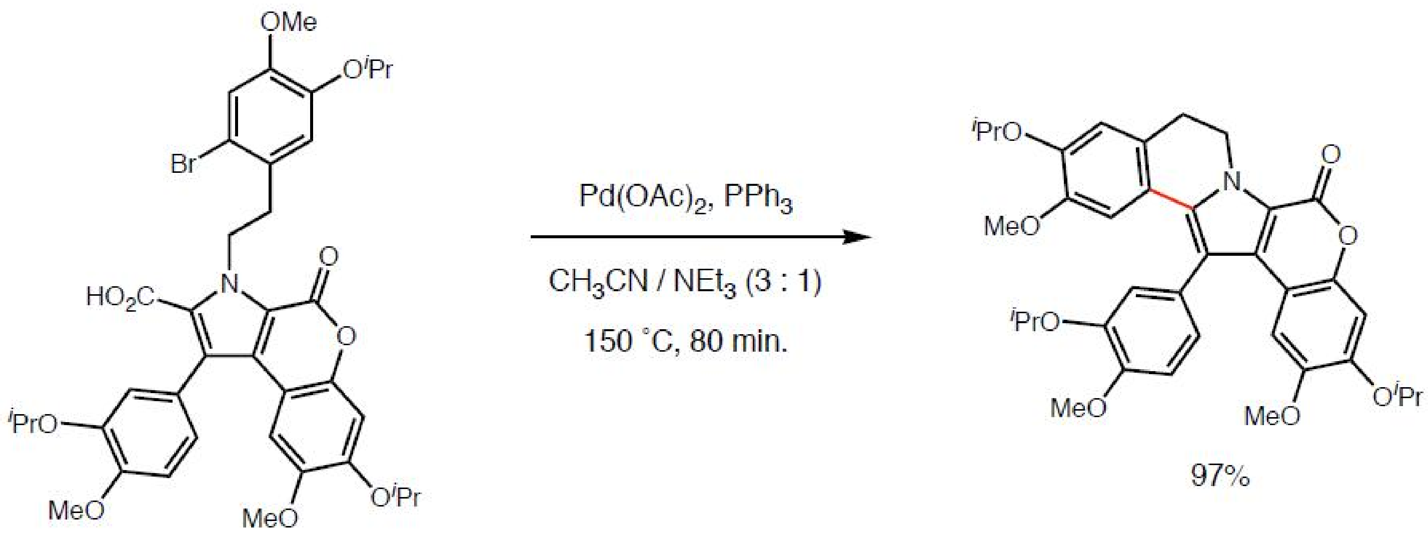
R = Me, 74%

R = H, 23%

JACS 2006, 128, 11350

Decarboxylative Cross Coupling

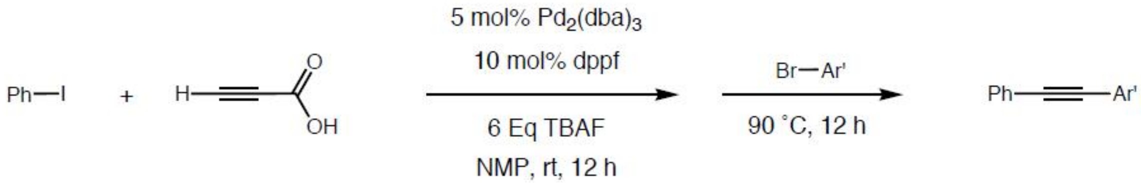
Synthesis of Lamellarin L.

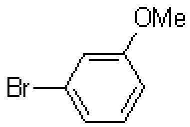
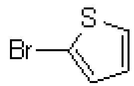
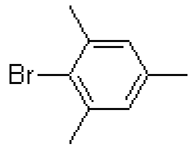
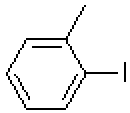
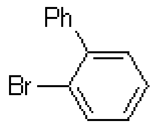
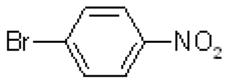
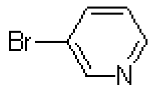


Chem. Eur. J. 2000, 6, 1147.

Decarboxylative Cross Coupling

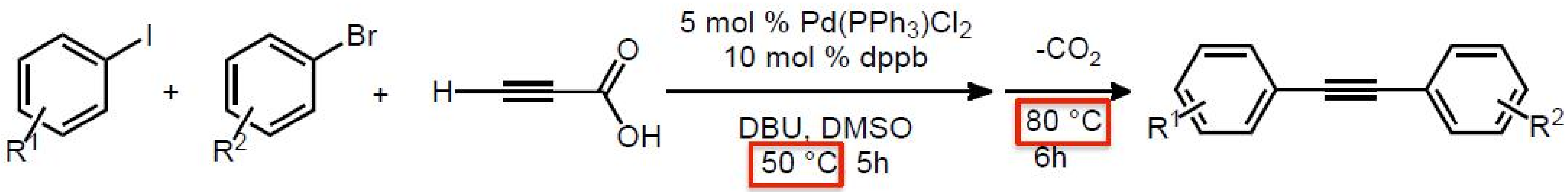
Potential for Combination with other Coupling Methods



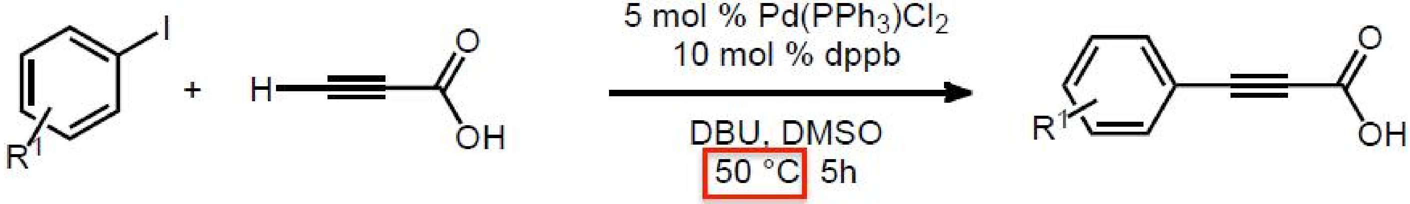
Ar-I	Ar-Br	yield (%, isol.)	Ar-I	Ar-Br	yield (%, isol.)
Ph—I		48	Ph—I		61
Ph—I		91			81
Ph—I		62	Ph—I		69

Decarboxylative Cross Coupling

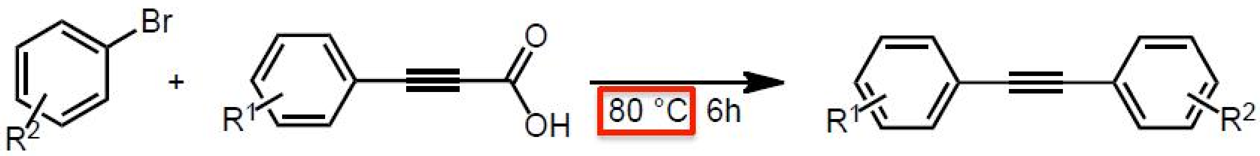
One-pot---combination of Sonogashira coupling and decarboxylative coupling



Sonogashira coupling

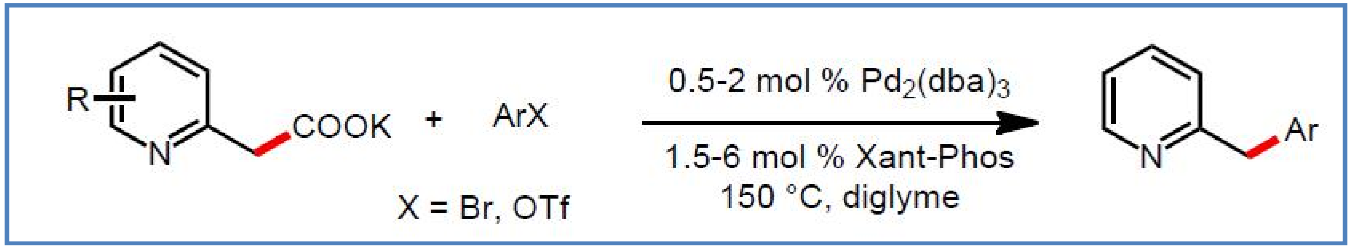


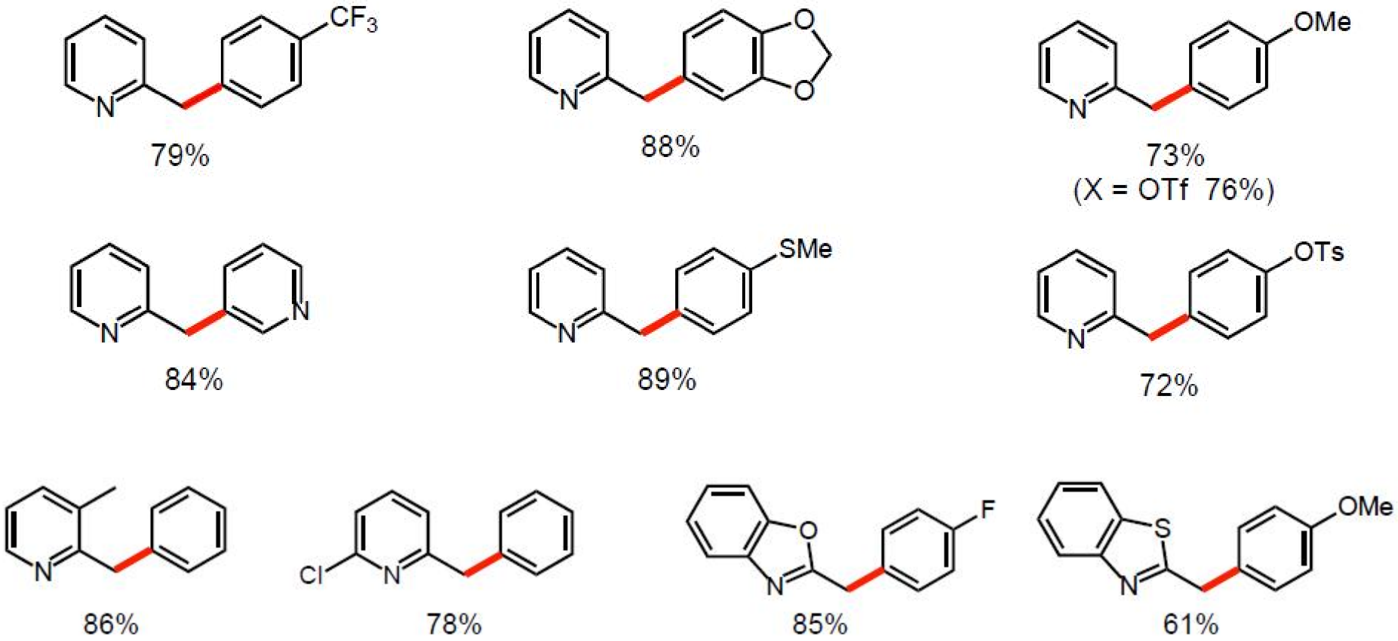
Decarboxylative coupling



J. Org. Chem. ***2010****, 75, 6244.*

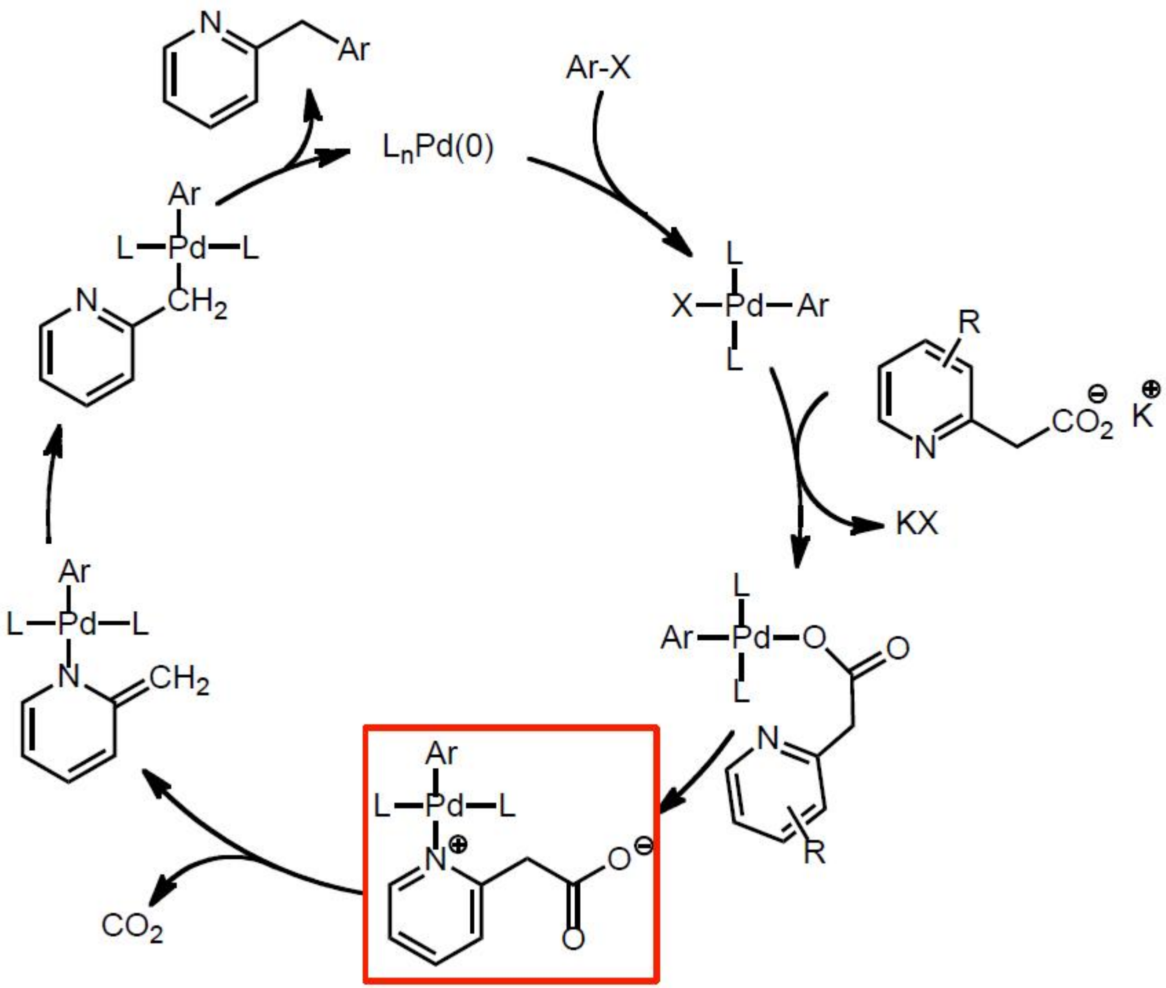
Decarboxylative Cross Coupling





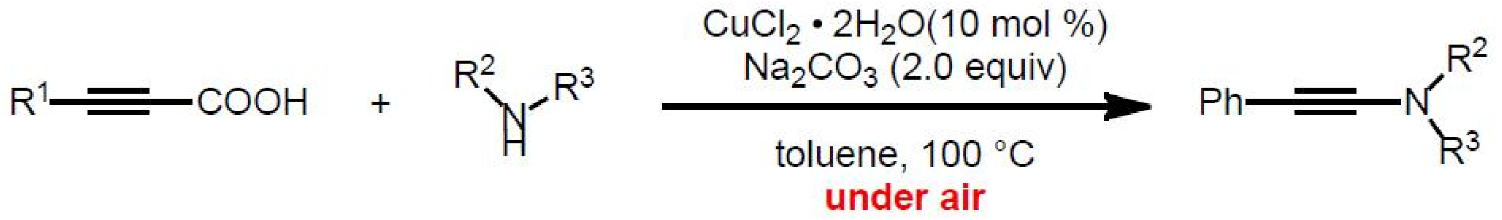
JACS 2010, 132, 14391

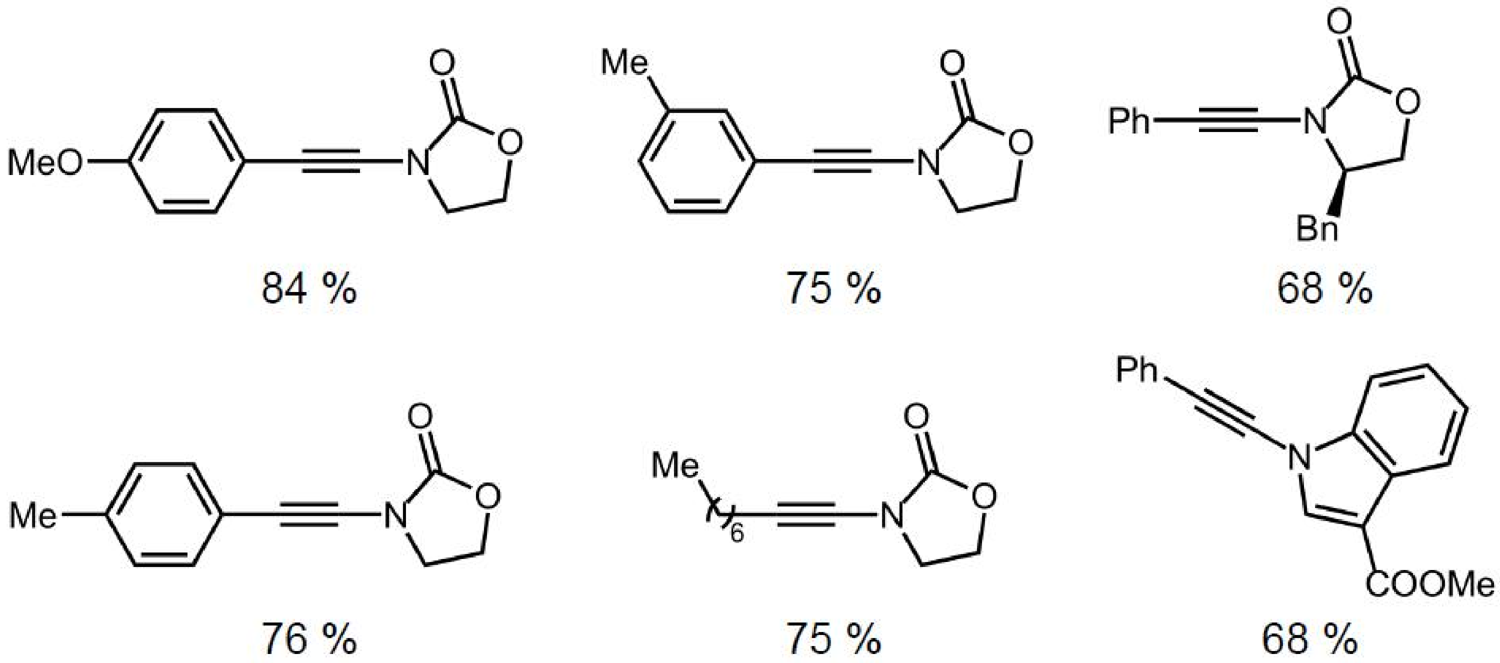
Decarboxylative Cross Coupling



JACS 2010, 132, 14391

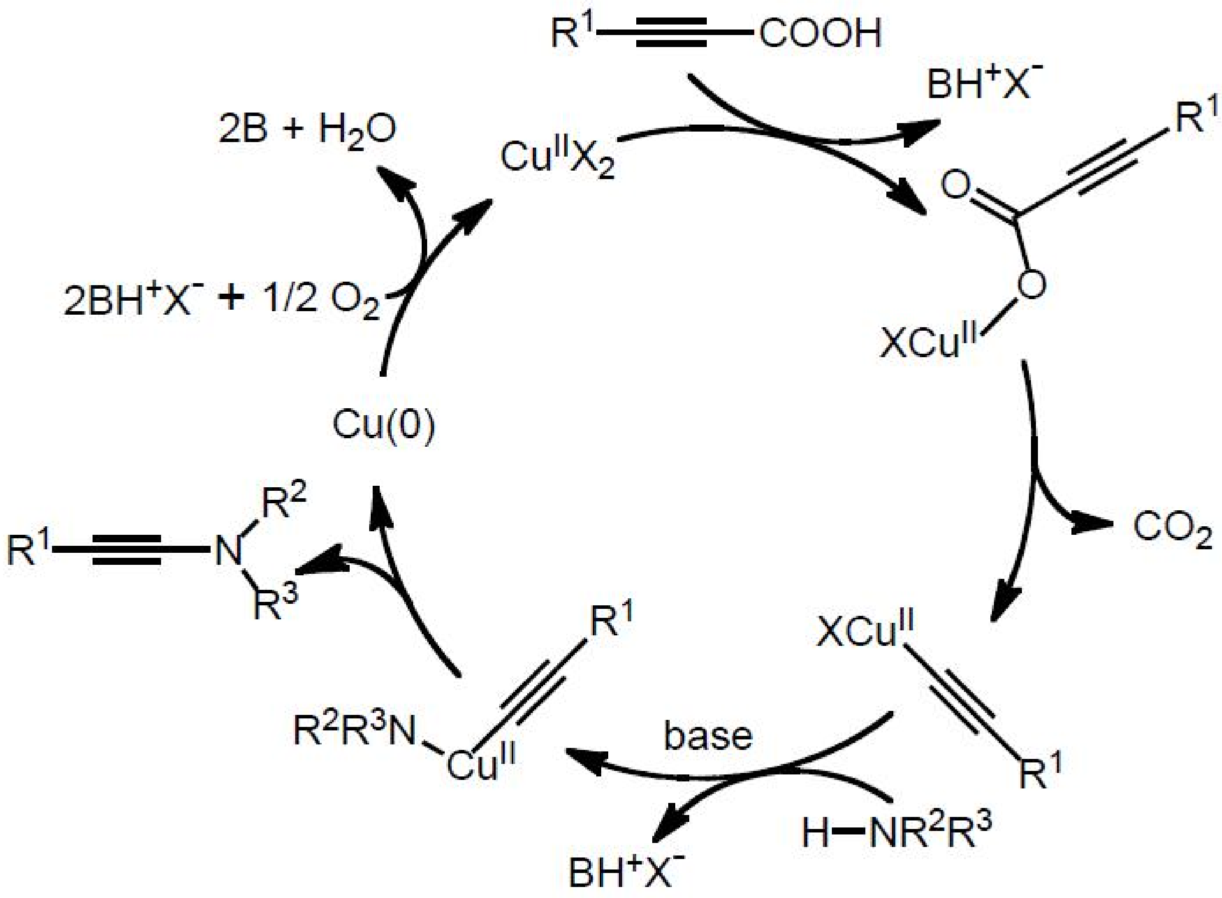
Decarboxylative Cross Coupling



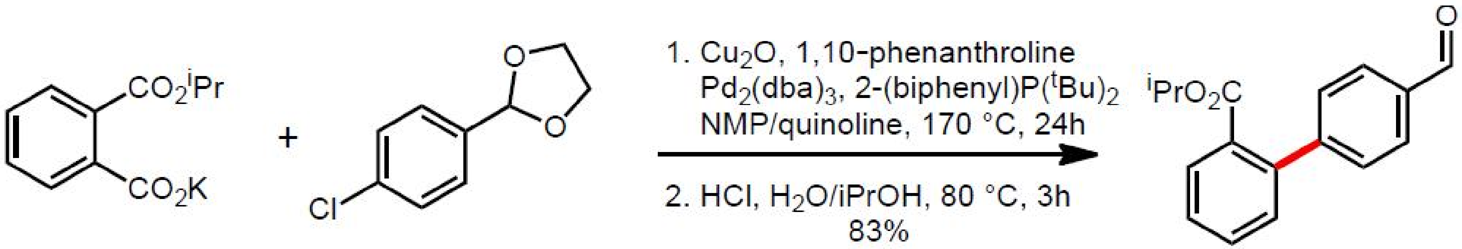


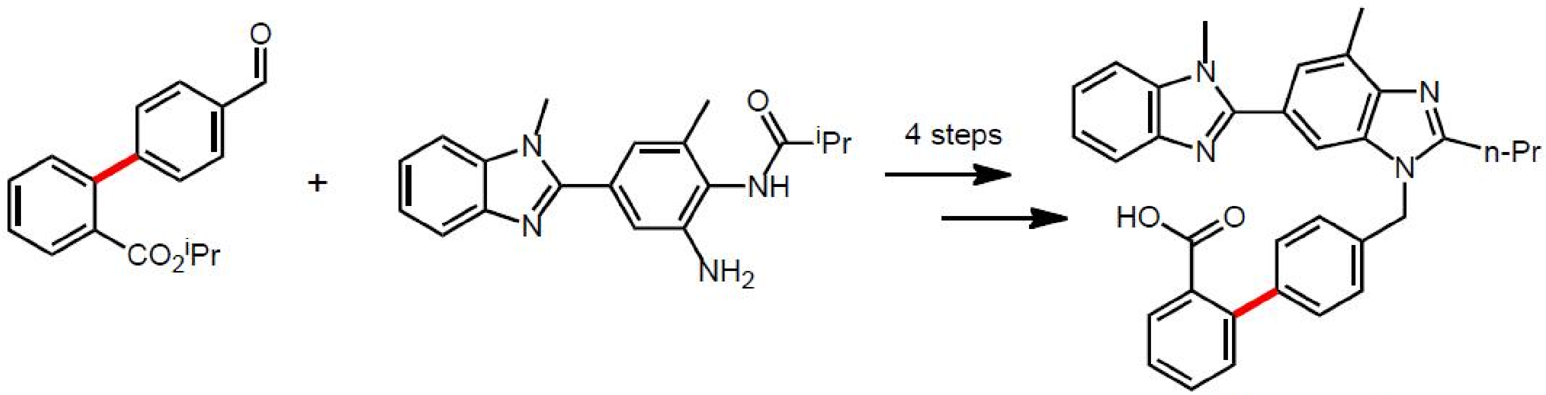
Org. Lett. 2010, 12, 2000

Decarboxylative Cross Coupling



Synthesis of Telmisartan （替米沙坦）





Telmisartan

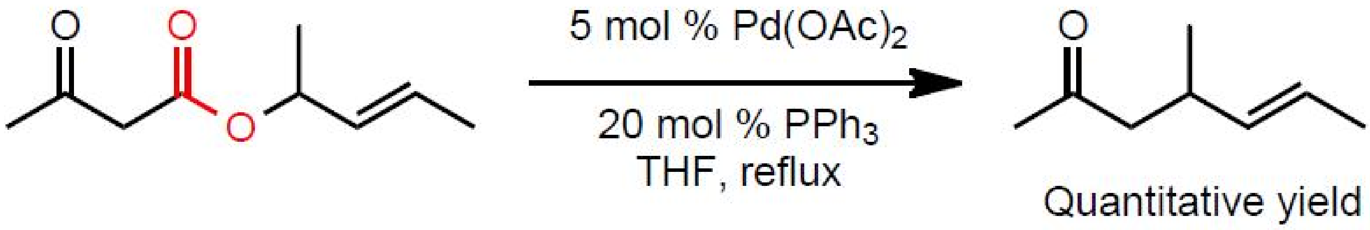
35% overall yield

J. Org. Chem. ***2008****, 73, 8631*

Intramolecular Decarboxylative Coupling

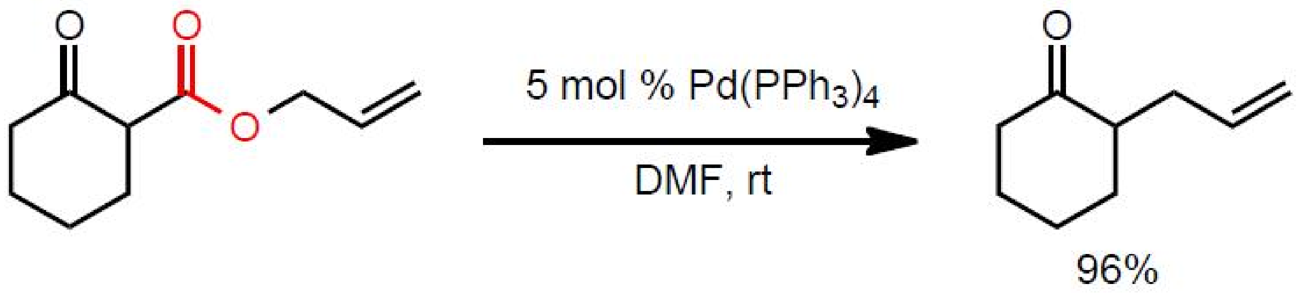
Pd catalyzed decarboxylative allylic alkylation

Tsuji :



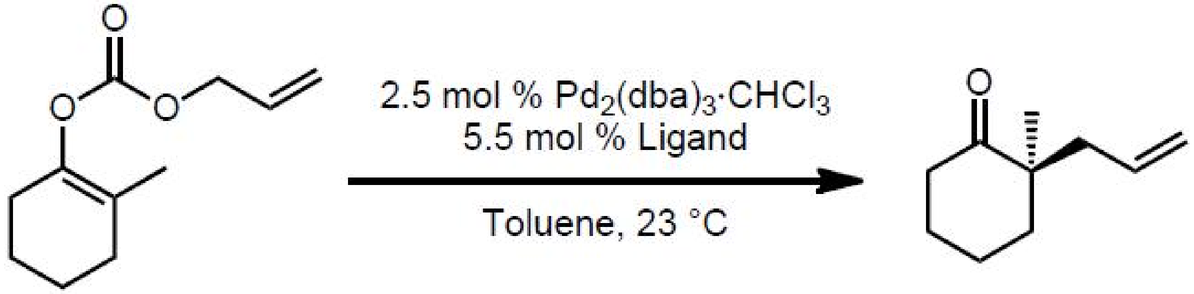
Tetrahedron Lett. **1980**, *21*, 3199.

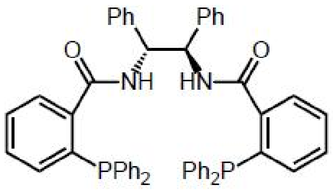
Saegusa :



J. Am. Chem. Soc. **1980**, *102*, 6381.

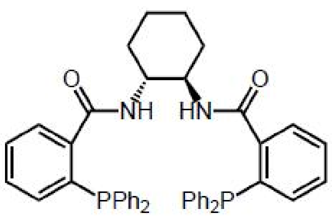
Decarboxylative Cross Coupling





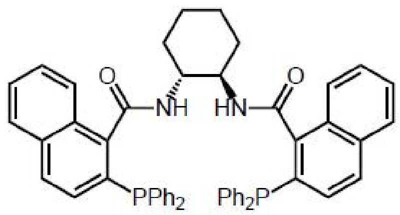
(*R*,*R*)-**L2**

73%， 61% ee



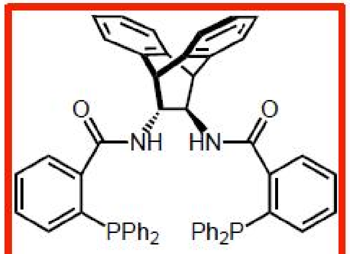
(*R*,*R*)-**L1**

73%， 31% ee



(*R*,*R*)-**L3**

85%， 60% ee

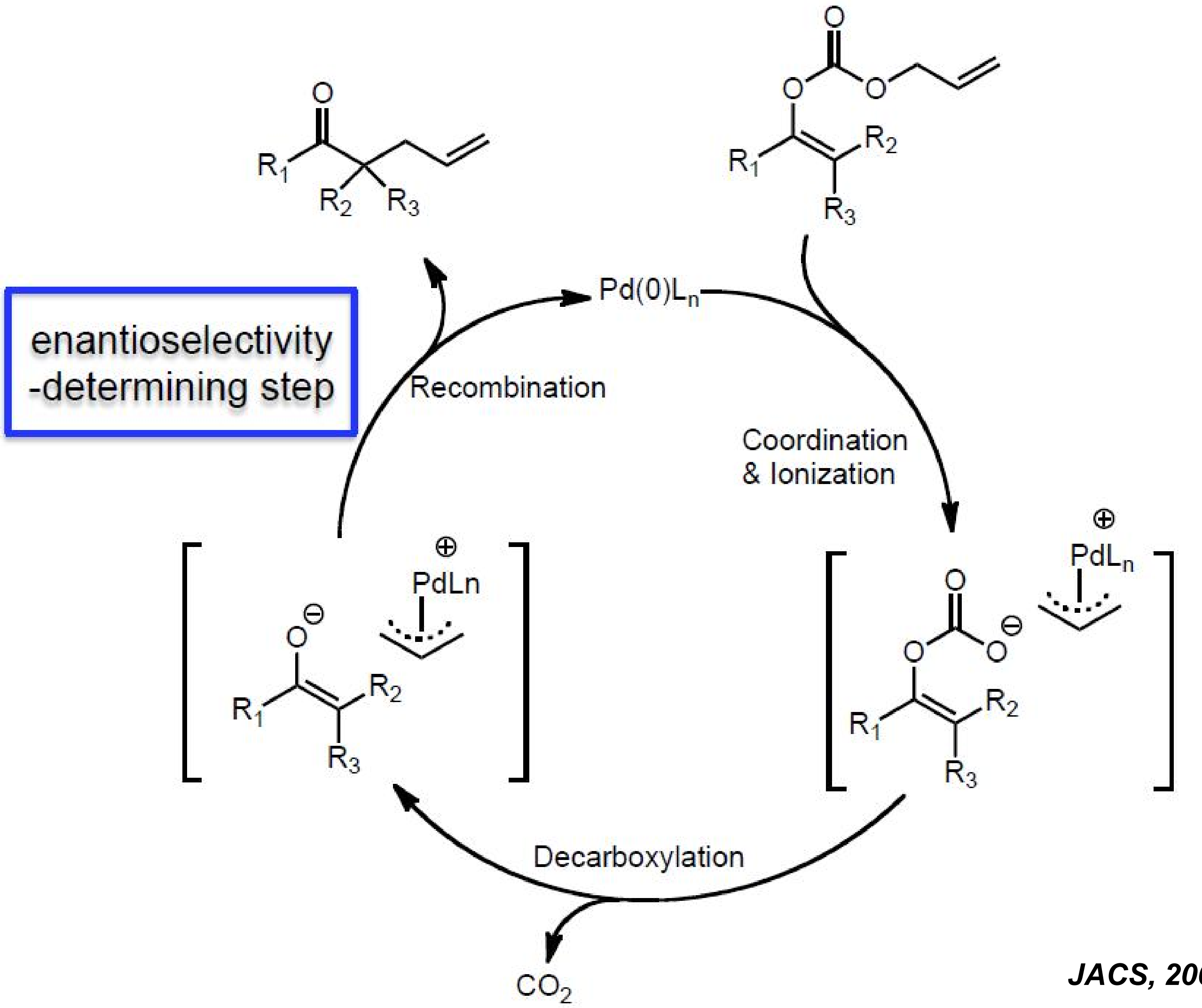


(*R*,*R*)-**L4**

88%， 85% ee

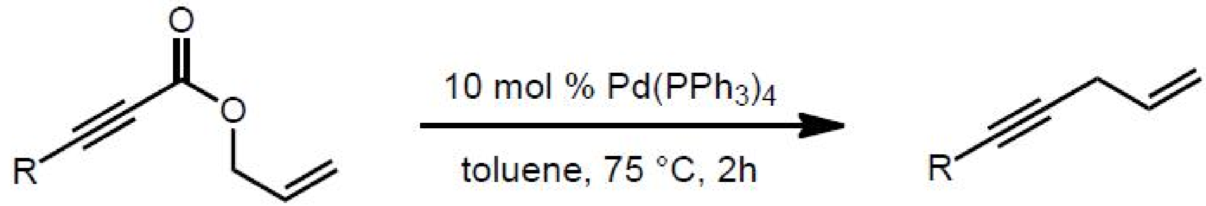
JACS, 2009, 131, 18343.

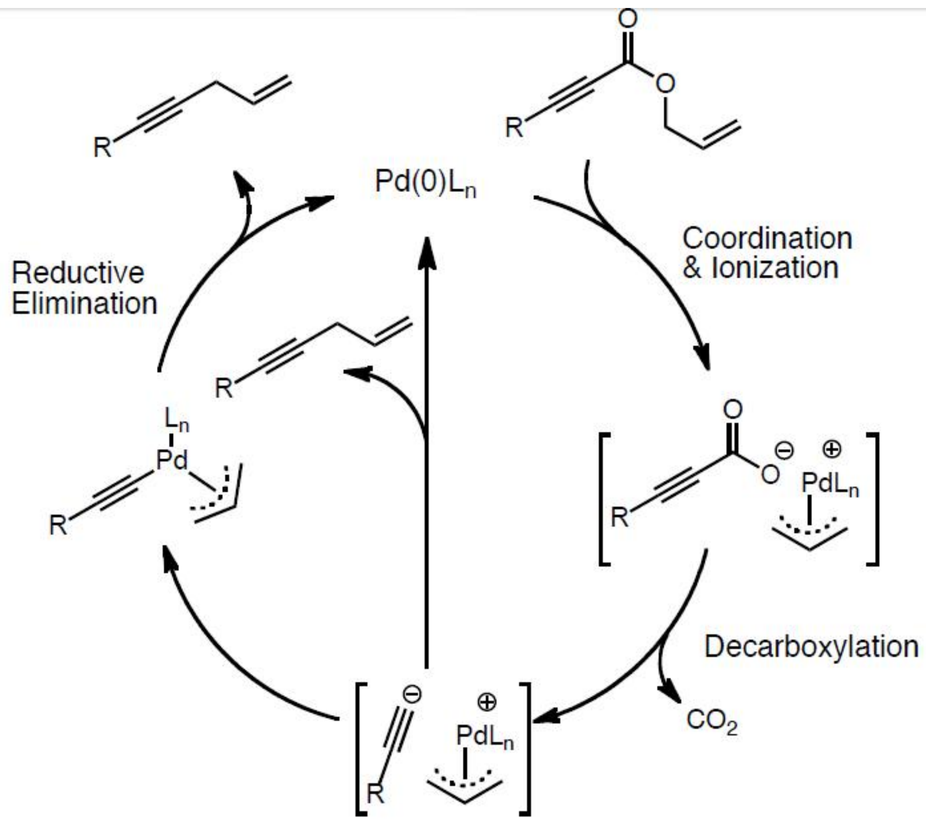
Decarboxylative Cross Coupling



JACS, 2009, 131, 18343.

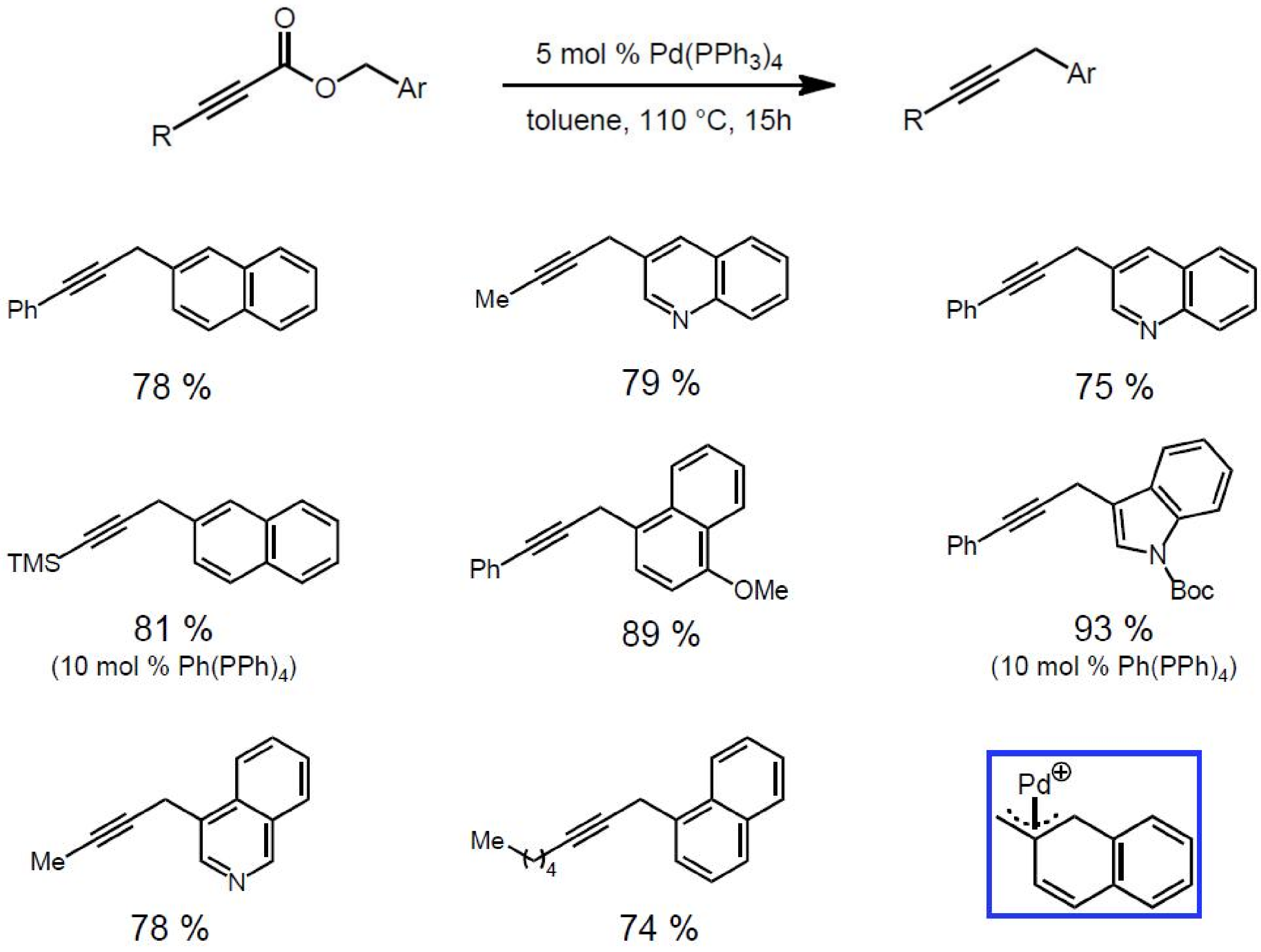
Decarboxylative Cross Coupling





JACS, 2005, 127, 13510.

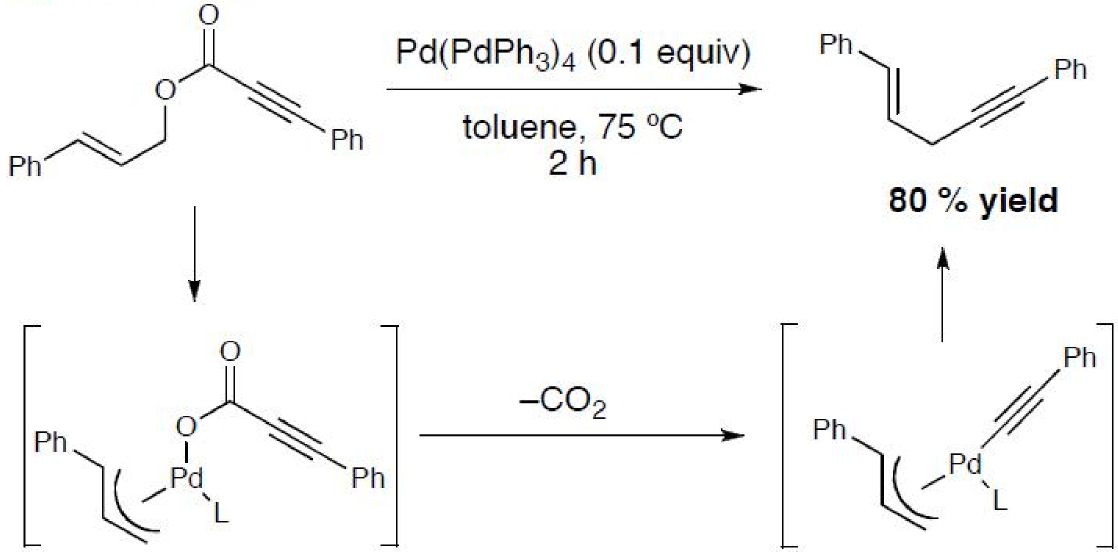
Decarboxylative Cross Coupling



JACS, 2010, 132, 9280

Decarboxylative Cross Coupling

Intramolecular



Intermolecular