



## 7月文献汇报

# 金属催化的脱羧C-H官能团化

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日期：2019. 07. 28

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脱羧  $C_{sp^2}-H$  官能团化



脱羧  $C_{sp^3}-H$  官能团化



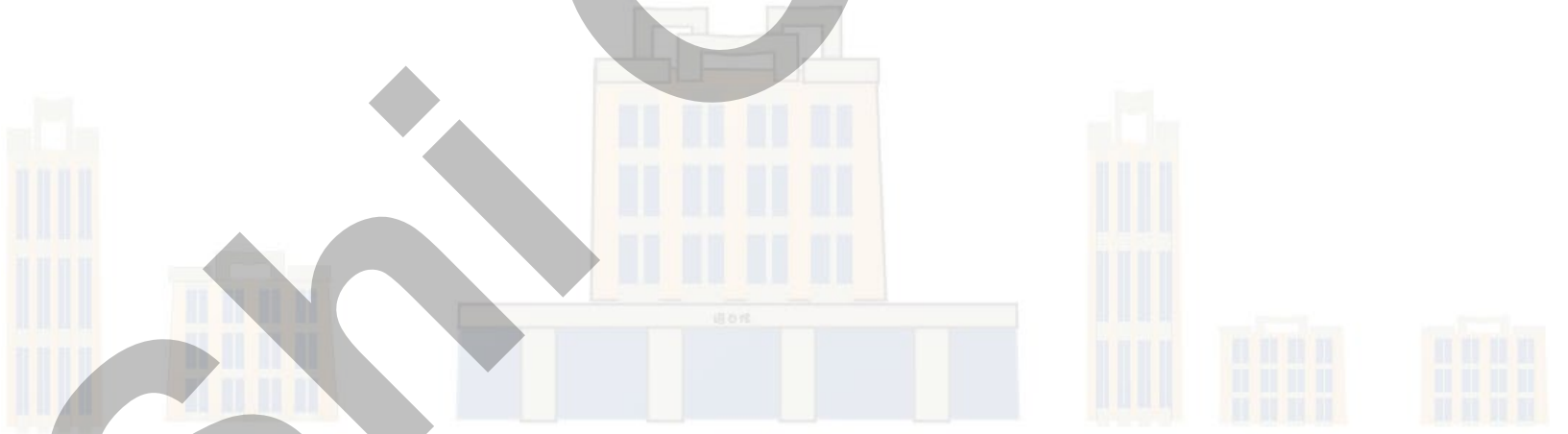
包含脱羧  $C-H$  键转换过程的其他反应



结论与展望



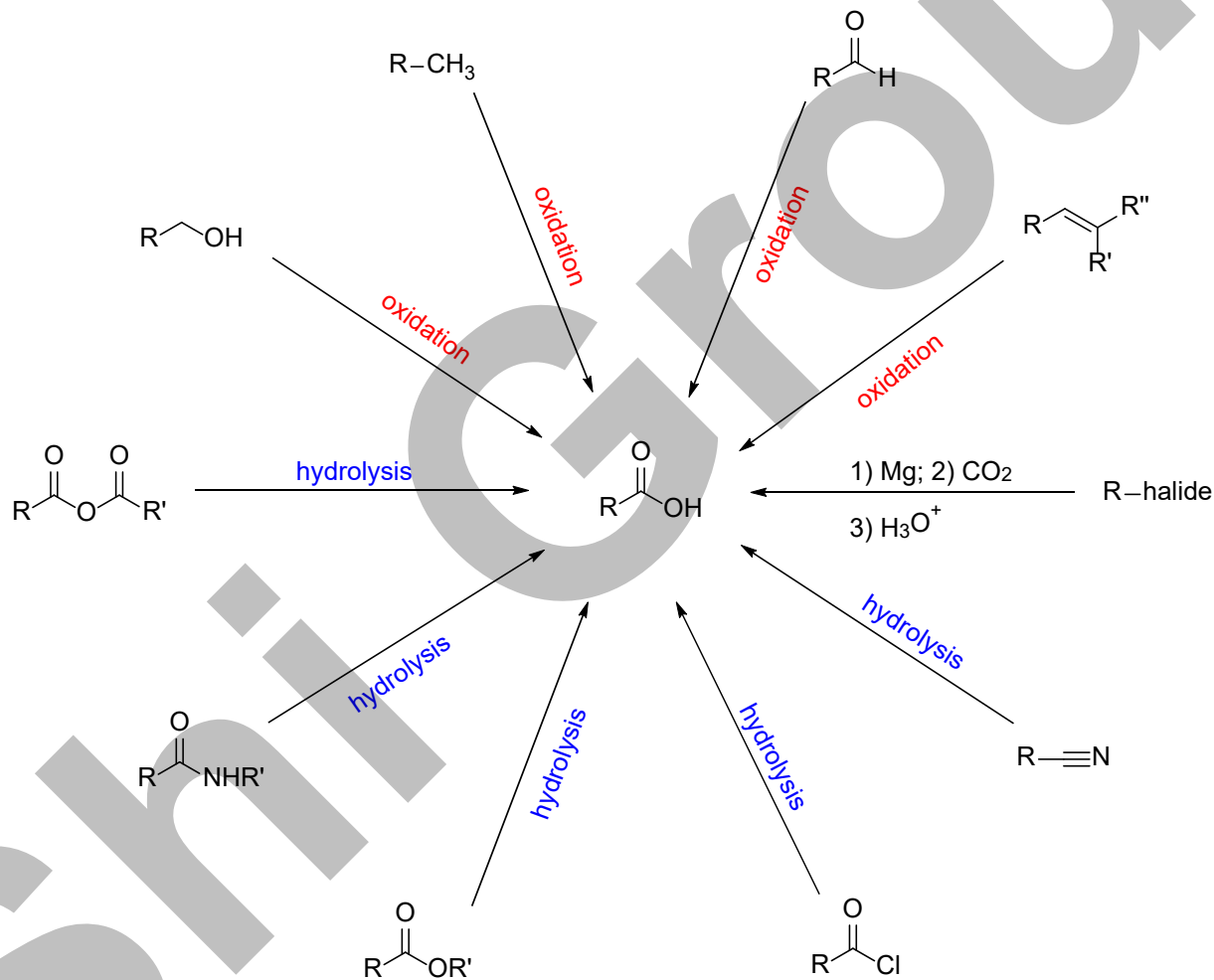
## 背景介绍



# 1 背景介绍



## 已知合成羧酸类物质的方法





## C-C键构建

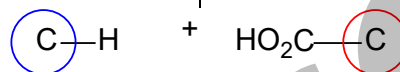
(a) direct C-H cross-coupling



(b) decarboxylative cross-coupling



oxidant

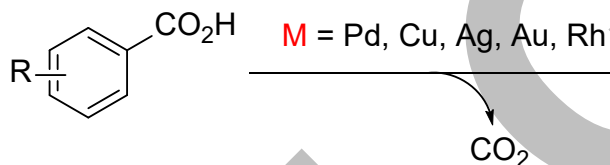


(c) decarboxylative C-H cross-coupling

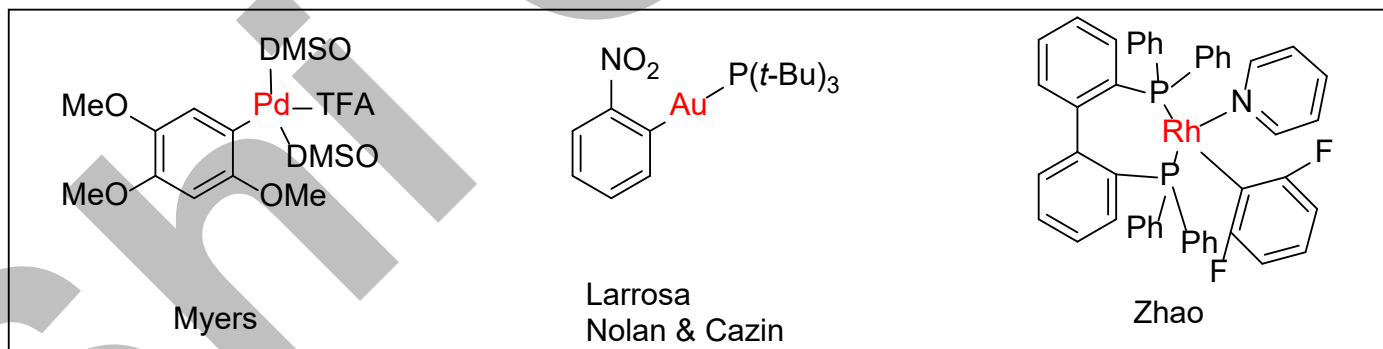
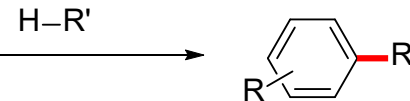


## 芳基金属物质形成与应用

(a) Decarboxylation



(b) C-H activation



Mannion, M. R. et al. *J. Am. Chem. Soc.* **2002**, 124, 11250.

Cornella, J. et al. *Chem. Commun.* **2009**, 7176.

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

Gooßen, L. J. et al. *Chem. Commun.* **2009**, 7173.

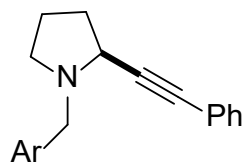
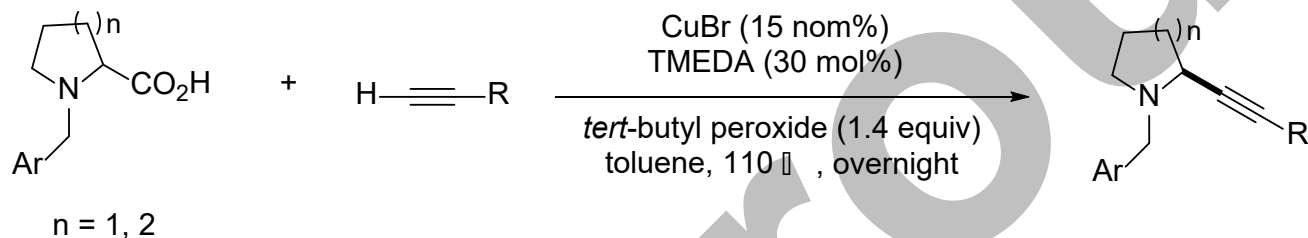


## 脱羧 $C_{sp}-H$ 官能团化

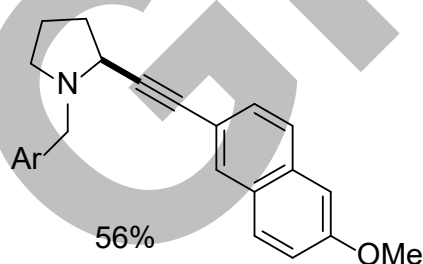
## 2 脱羧 C<sub>sp</sub>-H 官能团化



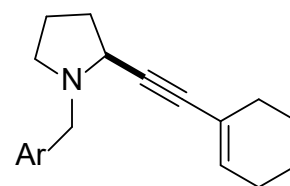
Cu催化的脱羧炔基化反应



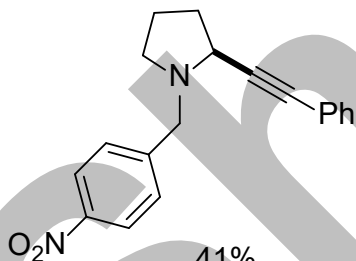
80%



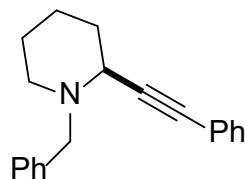
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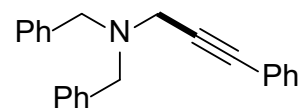
56%



41%



74%



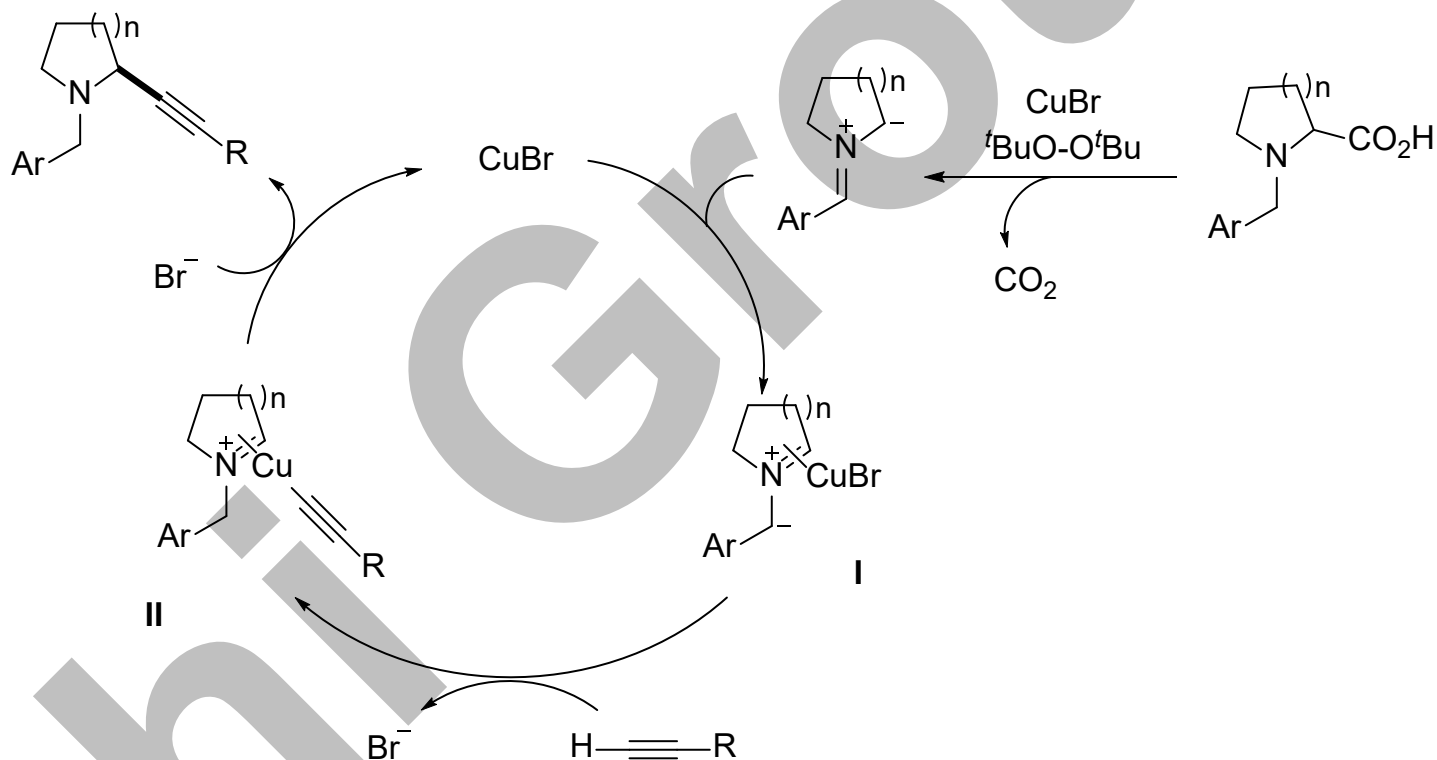
20%

Li, C. J. et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 792.

## 2 脱羧 C<sub>sp</sub>-H 官能团化



Cu催化脱羧炔基化的机理研究



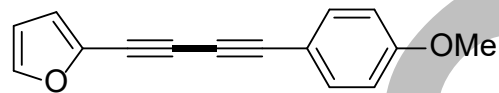
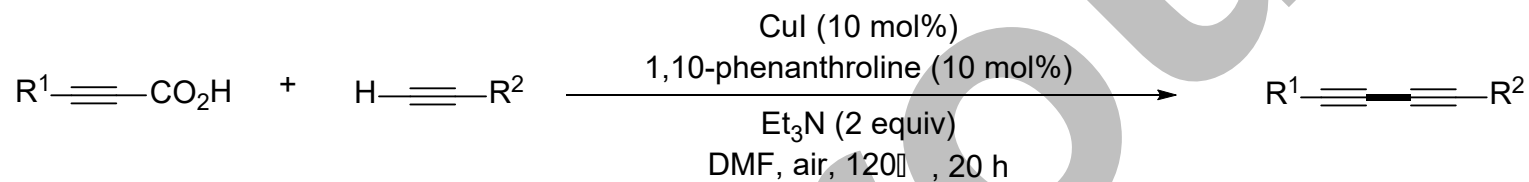
Li, C. J. et al. *Angew. Chem., Int. Ed.* **2009**, 48, 792.



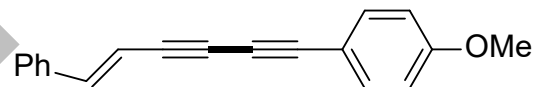
## 2 脱羧 C<sub>sp</sub>-H 官能团化



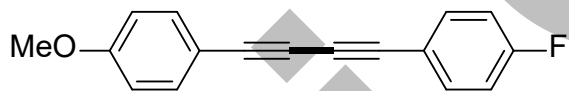
Cu催化合成共轭二炔



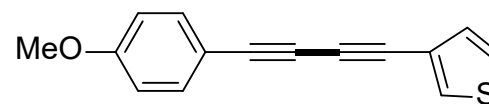
33%



47%



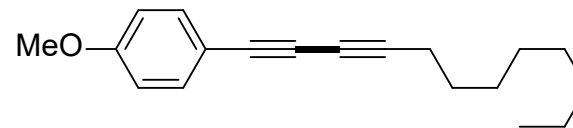
47%



46%



36%



32%

# Cadiot-Chodkiewicz





脱羧  $C_{sp^2}$ -H 官能团化

脱羧  
 $C_{sp^2}-H$   
官能化

非螯合辅助

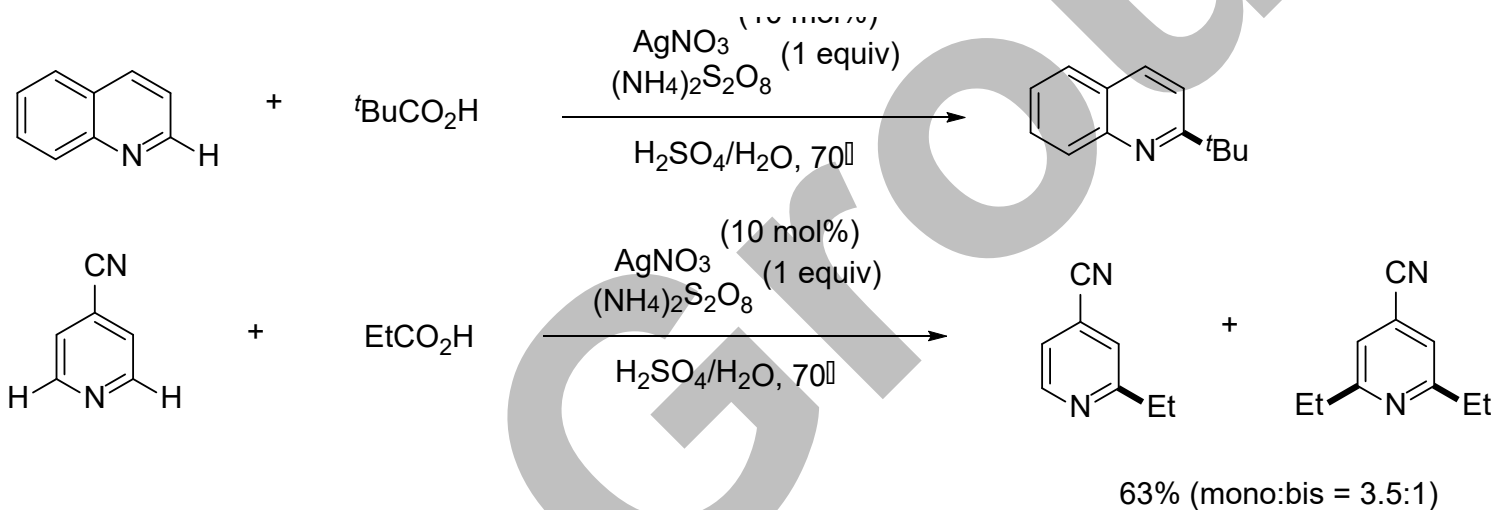
- 3.1. 异戊二烯C-H键官能团化
- 3.2. 苯环C-H键官能团化
- 3.3. 酰基C-H键官能团化

螯合辅助

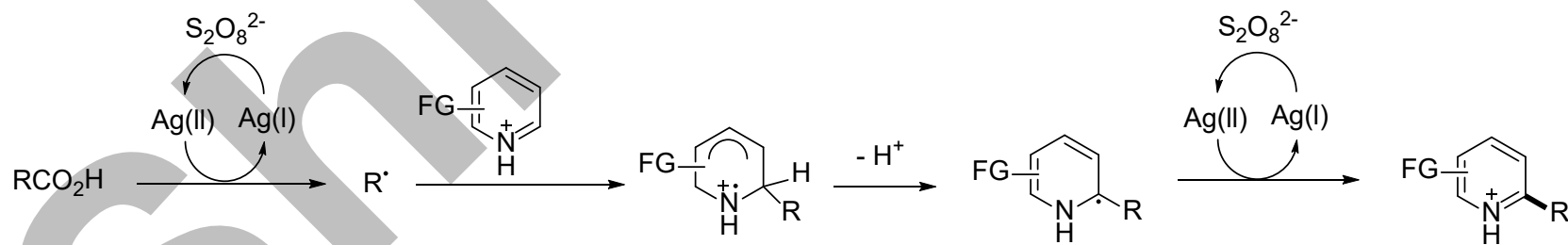
- 3.4. 脱羧C-H键芳基化
- 3.5. 脱羧C-H键酰化
- 3.6. 脱羧C-H键炔基化/环化

### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的烷基化

Ag催化的喹啉和4-氰基吡啶的烷基化反应



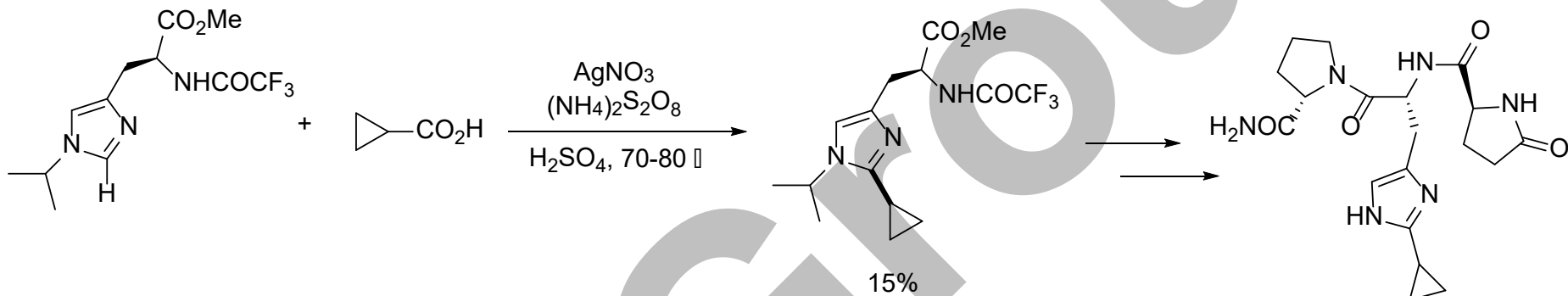
可能的亲核自由基加成质子化吡啶的机理 (Minisci反应)



### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的烷基化



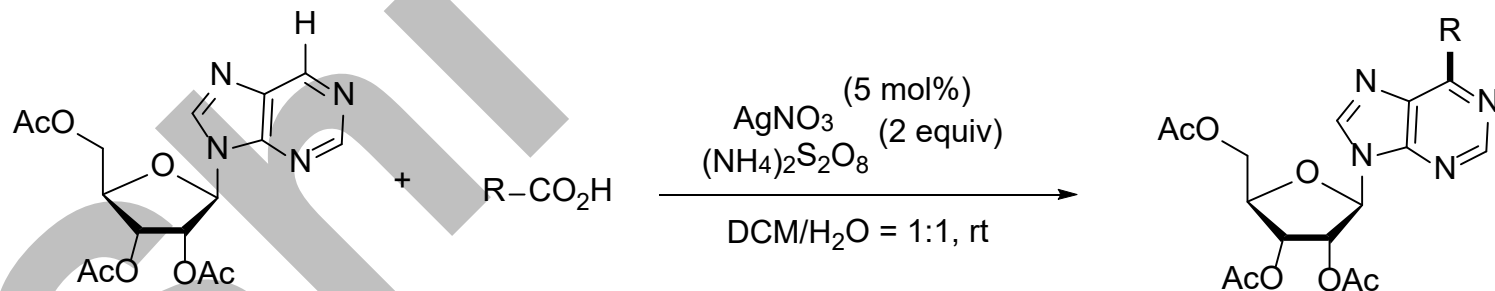
促甲状腺激素释放激素受体2有效激活剂前体的制备



Jain, R. et al. *J. Heterocycl. Chem.* **2008**, *45*, 1603.



Ag催化的嘌呤核苷烷基化反应

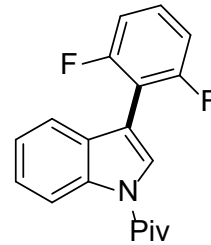
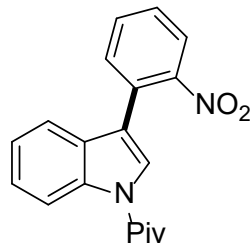
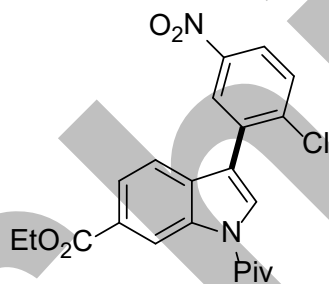
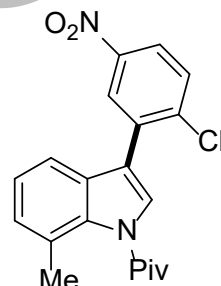
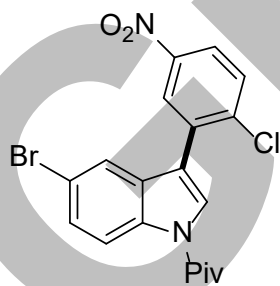
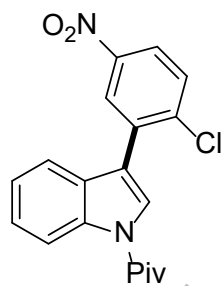
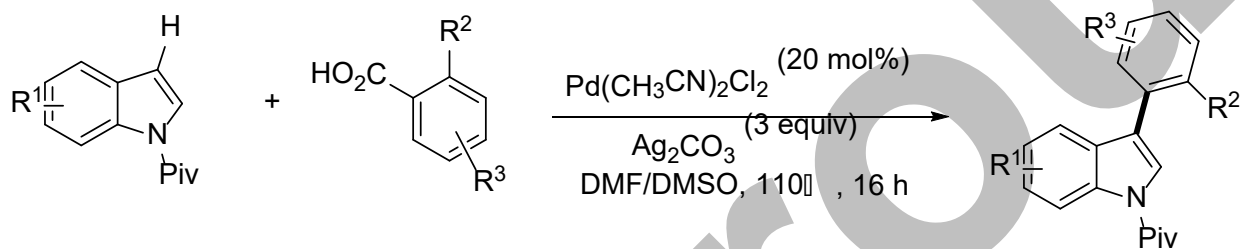


Guo, H. M. et al. *Org. Lett.* **2014**, *16*, 444.

### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的芳基化



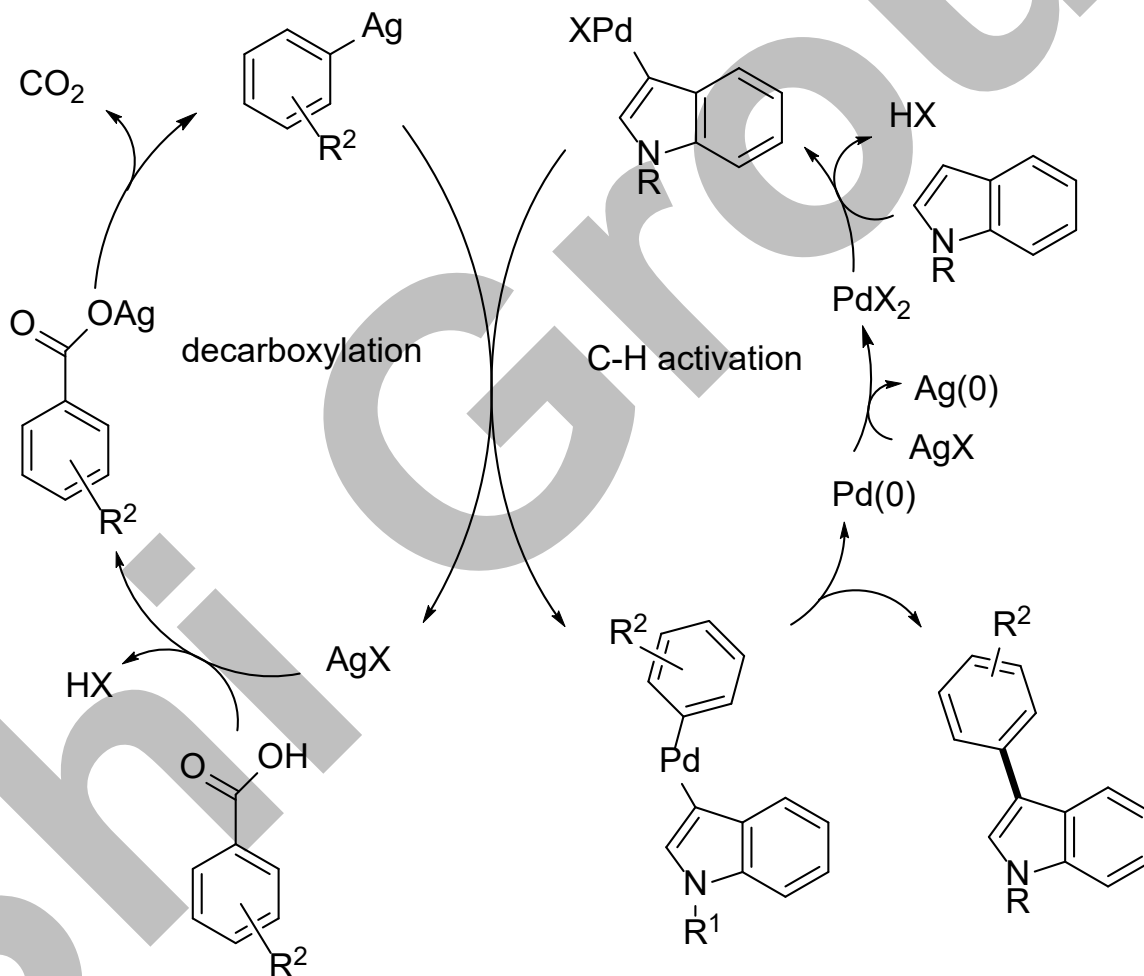
#### 吲哚的脱羧C3-H芳基化



### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的芳基化



#### 吲哚的脱羧C3-H芳基化反应机理

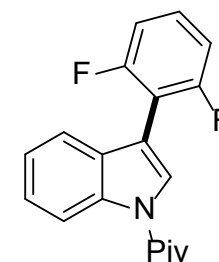
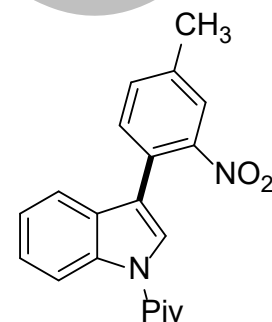
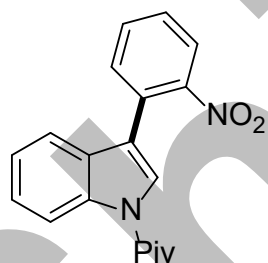
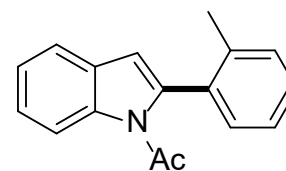
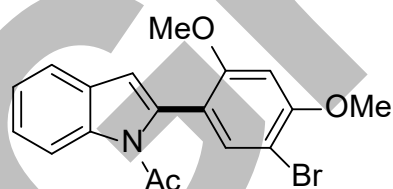
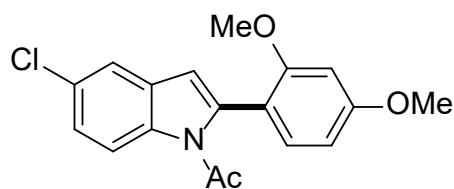
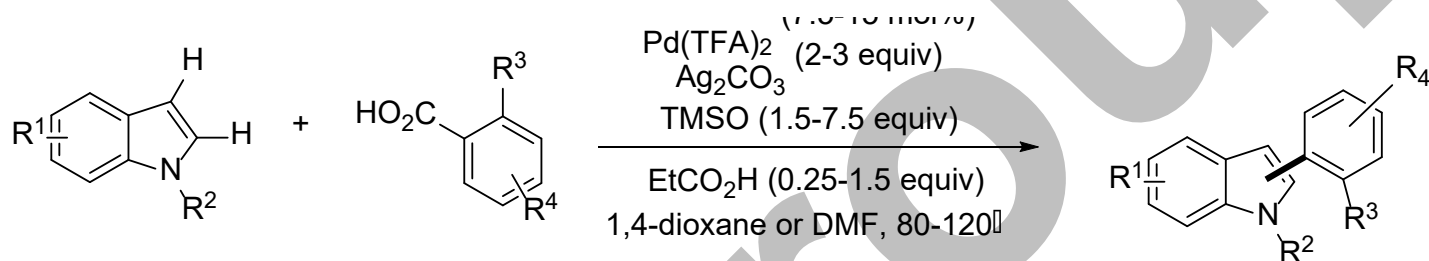




### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的芳基化



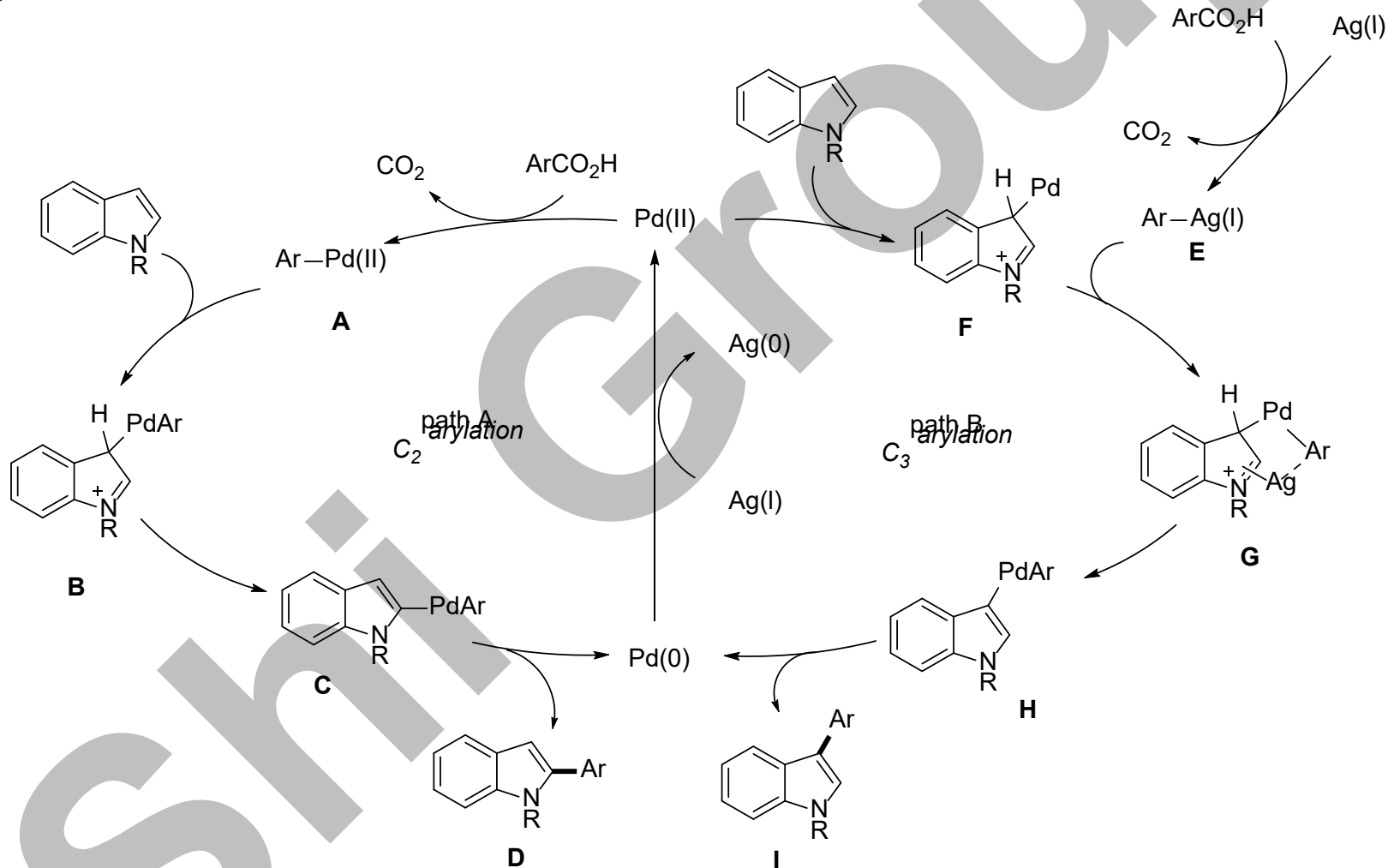
Pd催化的吲哚的区域选择性C-H芳基化



### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的芳基化

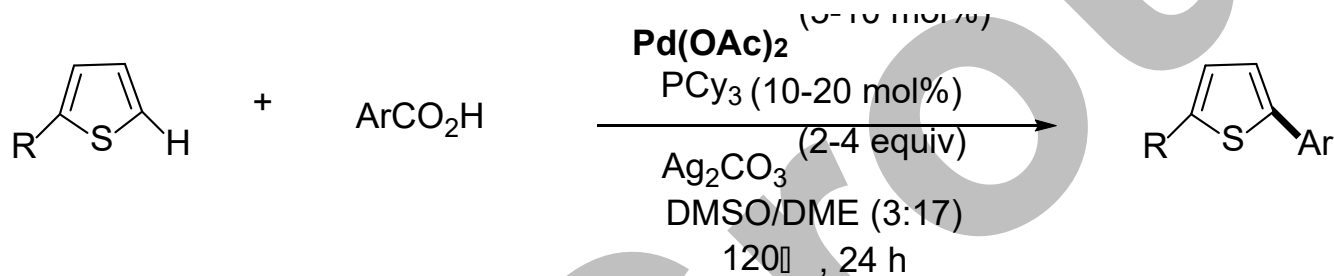


Pd催化的区域选择性C-H芳基化的提出机理



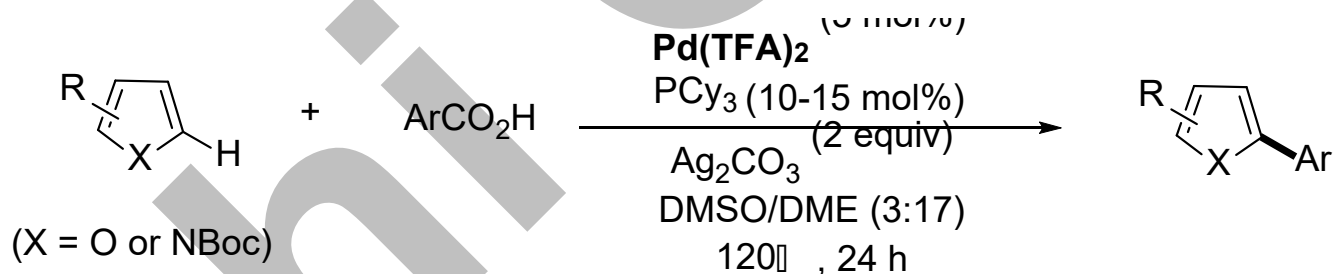
### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的芳基化

#### Pd催化的噻吩的C-H芳基化



Su, W. et al. *Angew. Chem., Int. Ed.* **2012**, 51, 227.

#### Pd催化的呋喃C-H芳基化

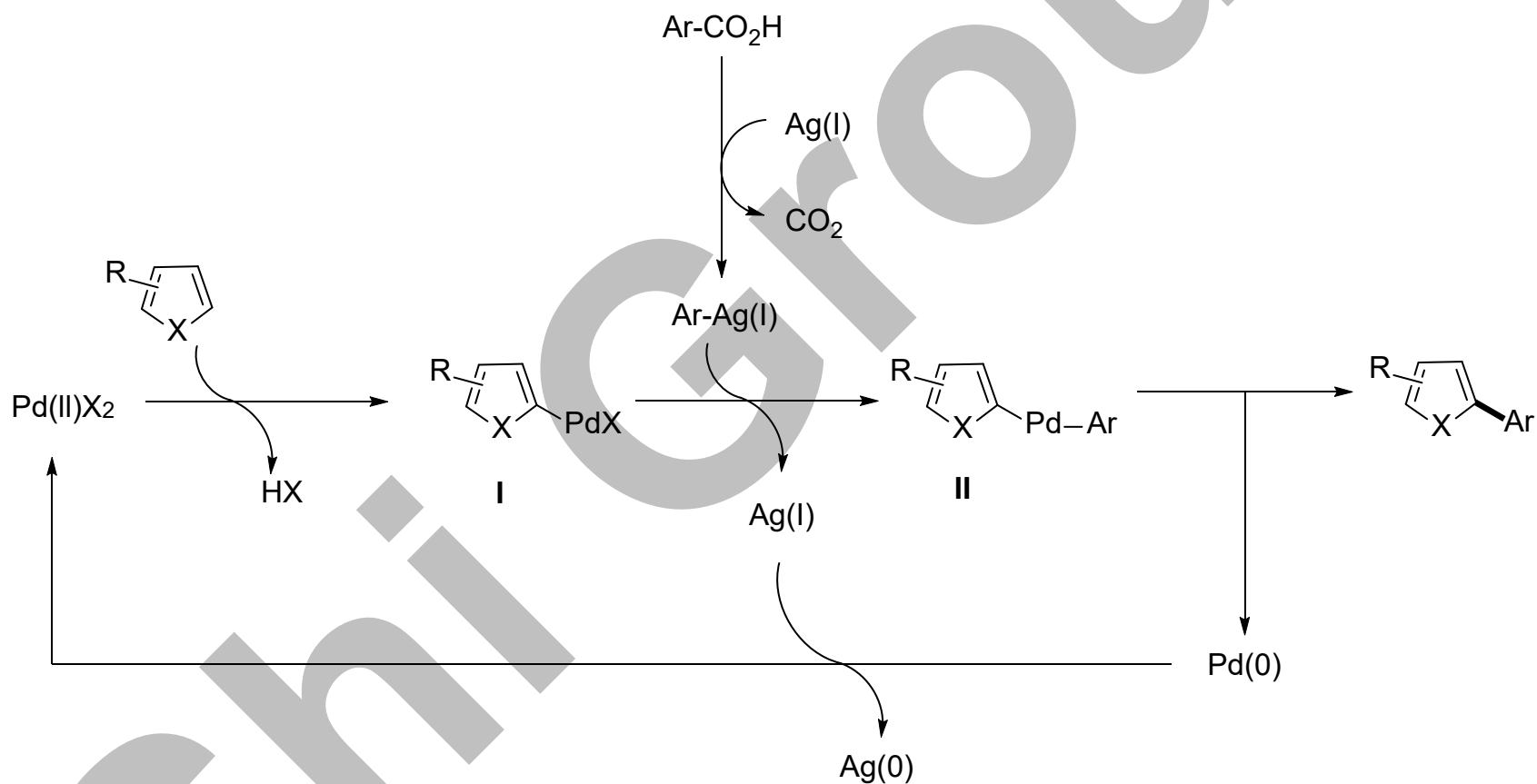


Su, W. P. et al. *Eur. J. Org. Chem.* **2014**, 2014, 4230.

### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的芳基化



Pd催化噻吩和呋喃脱羧C-H芳基化的机理

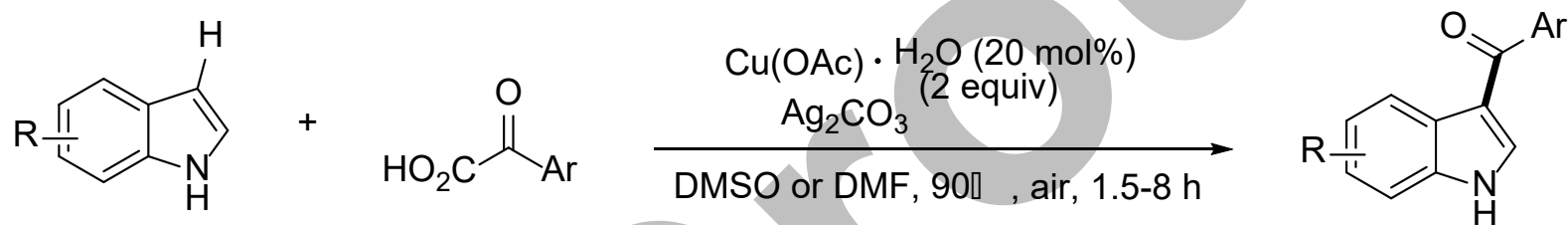


Su, W. P. et al. *Eur. J. Org. Chem.* **2014**, 2014, 4230.

Su, W. et al. *Angew. Chem., Int. Ed.* **2012**, 51, 227. 20

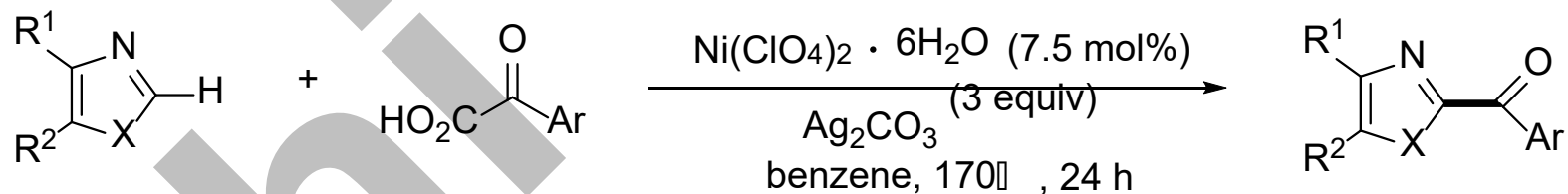
### 3.1. 异戊二烯C-H键官能团化---杂芳烃C-H键的酰化

#### Cu催化的吲哚C3-H酰化反应



Zhang, Z. et al. *Org. Biomol. Chem.* **2014**, 12, 1721.

#### Ni催化的唑类C-H酰化

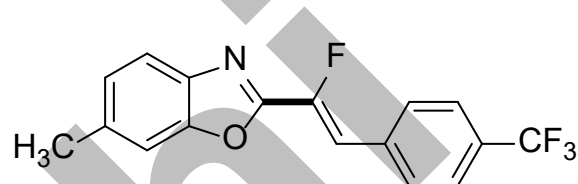
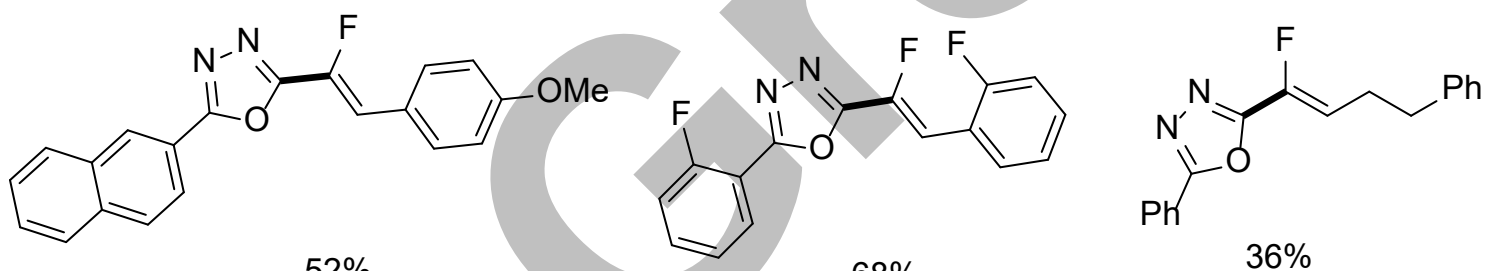
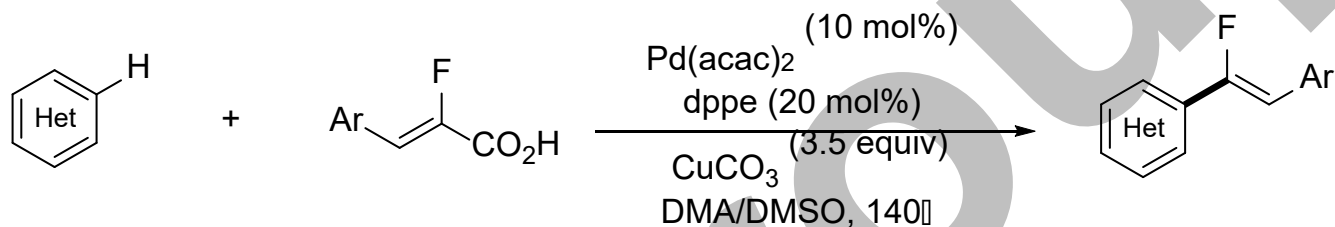


Ge, H. et al. *Chem. Eur. J.* **2014**, 20, 7241.

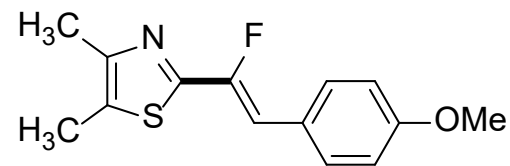
### 3.1. 异戊二烯C-H键官能团化---异戊二烯C-H键的烯基化



Pd/Cu介导的异构芳烃脱羧氟代烯基化




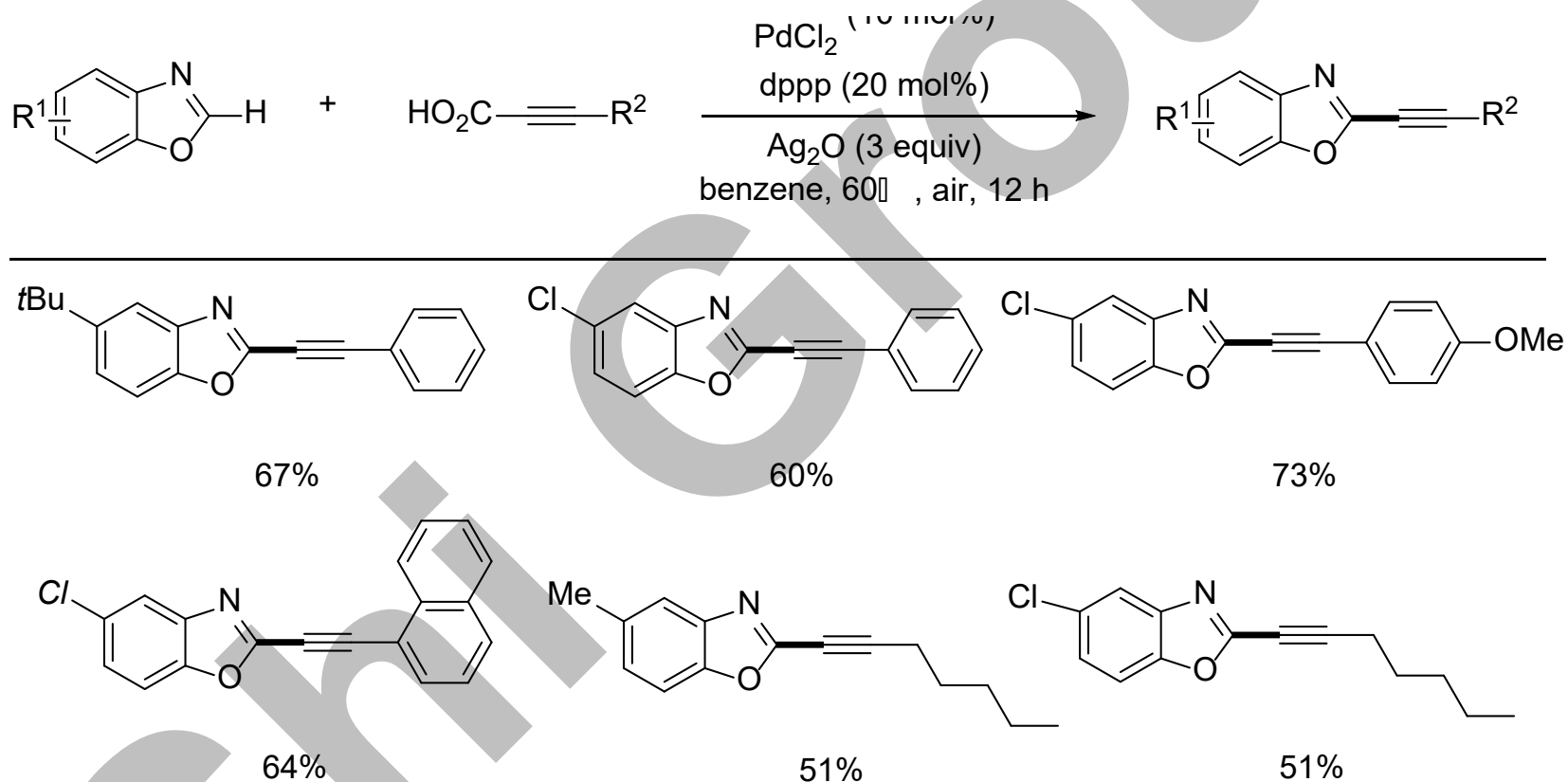
DMSO as solvent



(10 mol%) as catalyst  
Pd(TFA)<sub>2</sub>  
dioxane/DMSO as solvent

### 3.1. 异戊二烯C-H键官能团化---异戊二烯C-H键的炔基化

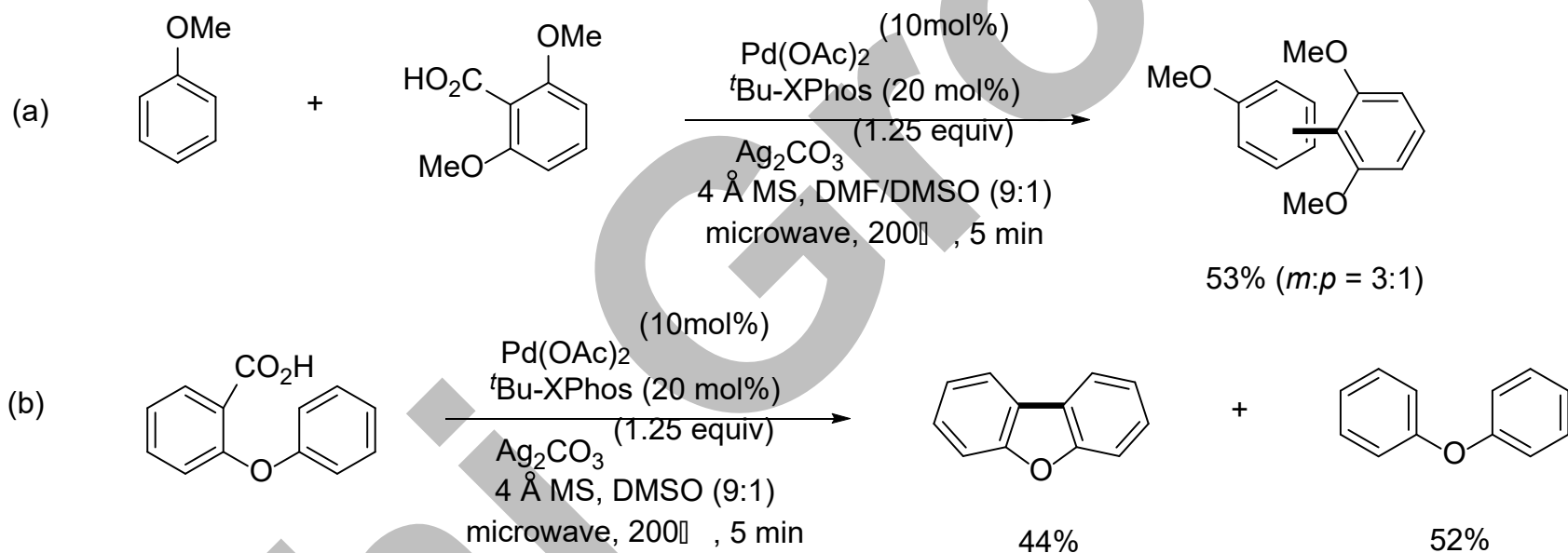
 Pd催化的苯并恶唑的脱羧炔基化反应



## 3.2. 苯环C-H键官能团化



Pd催化的(a)分子间和(b)分子内脱羧芳基化反应



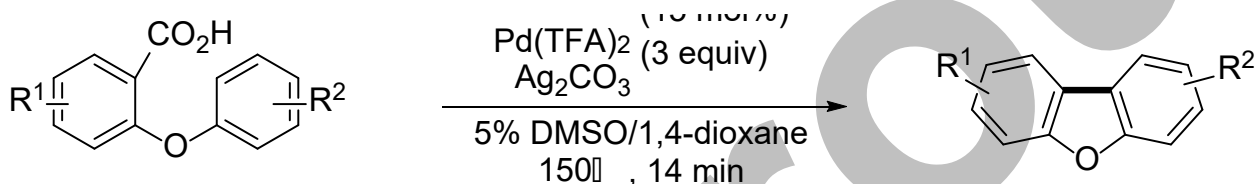
Crabtree, R. H. et al. *Chem. Commun.* **2008**, 6312.



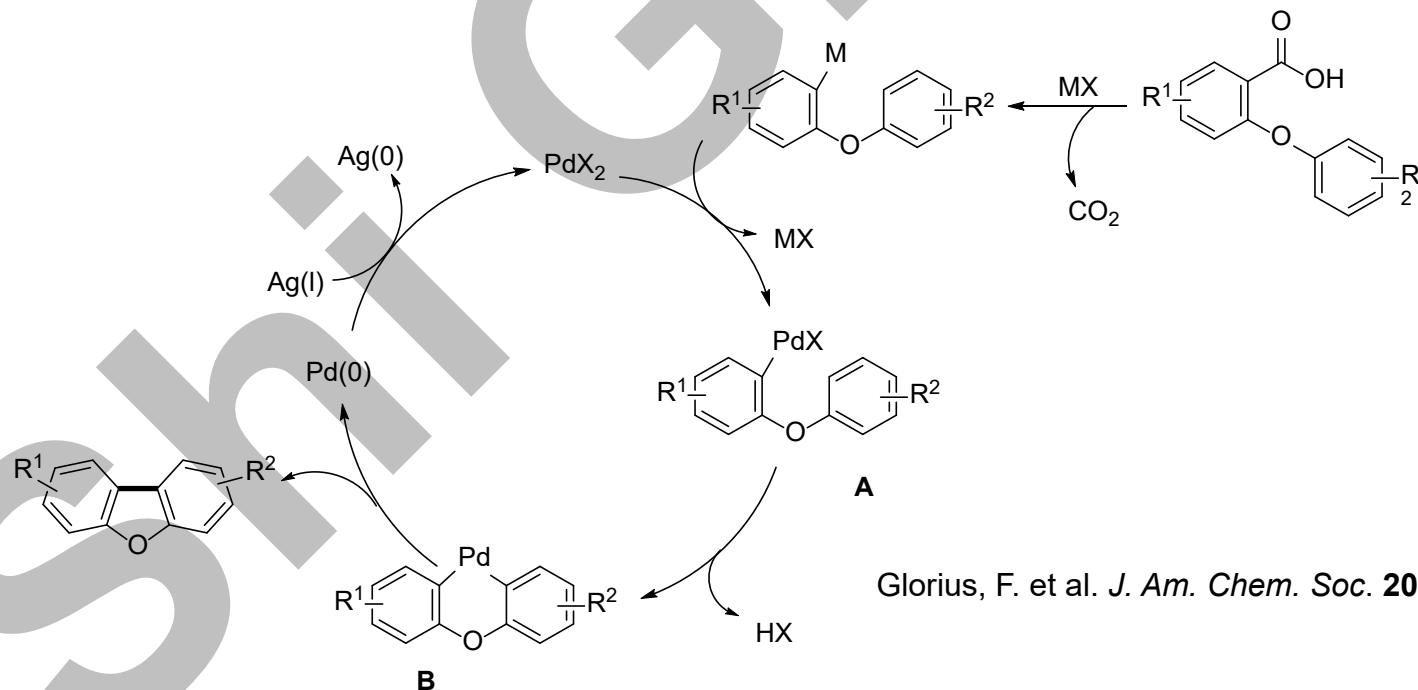
## 3.2. 苯环C-H键官能团化



Pd催化的分子内脱羧芳基化反应



Pd催化的2-苯氧基苯甲酸分子内脱羧芳基化的机理

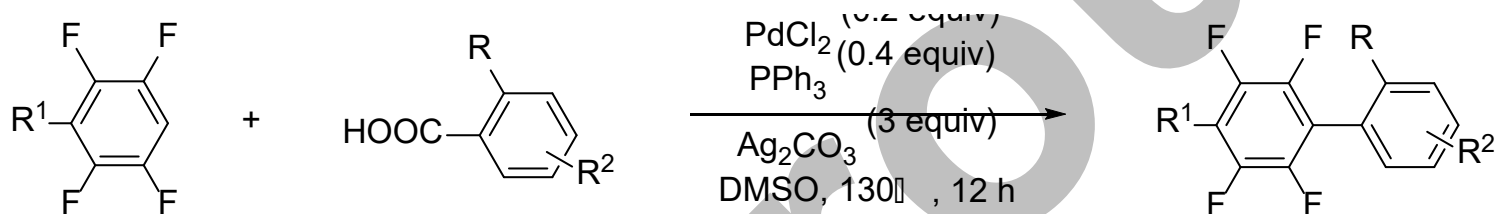


Glorius, F. et al. *J. Am. Chem. Soc.* **2009**, *131*, 4194.

## 3.2. 苯环C-H键官能团化



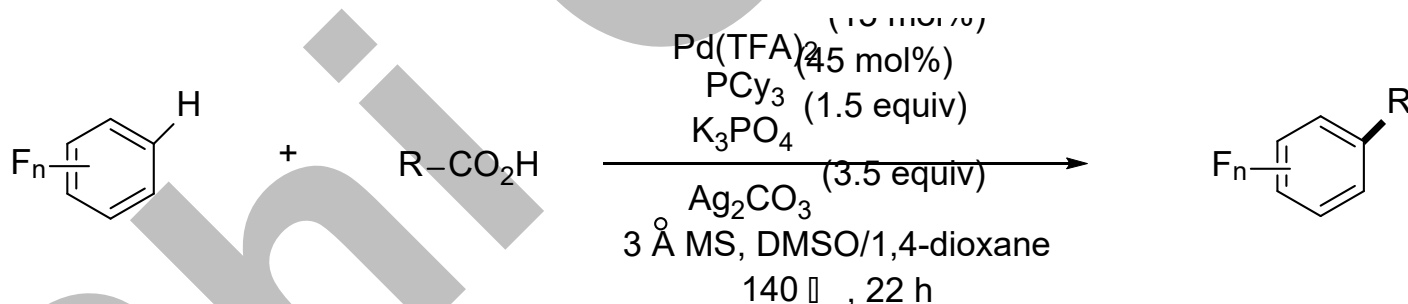
Pd催化聚氟苯与苯甲酸的脱羧芳基化反应



Tan, Z. et al. *Org. Lett.* **2010**, 12, 1564.



Pd催化的氟代芳烃与羧酸的脱羧反应

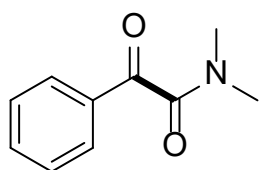
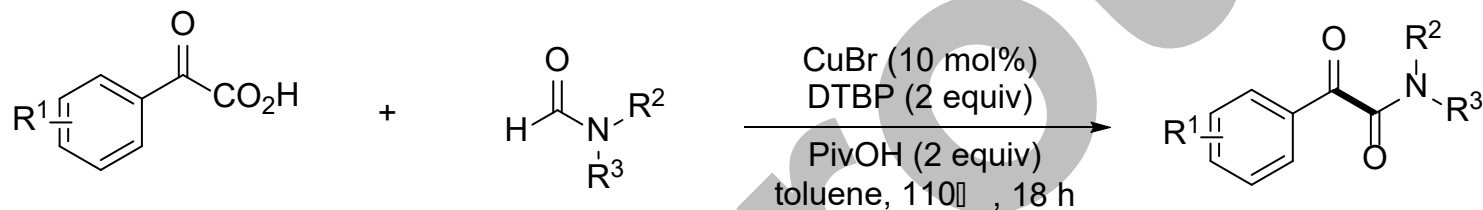


Su, W. et al. *J. Org. Chem.* **2011**, 76, 882.

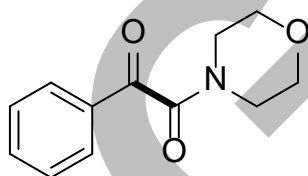
### 3.3. 酰基C-H键官能团化



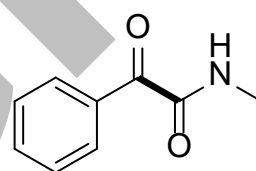
甲酰胺和 $\alpha$ -氧代羧酸的脱羧交叉偶联合成 $\alpha$ -酮酰胺



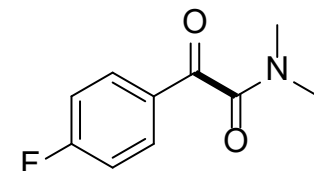
81%



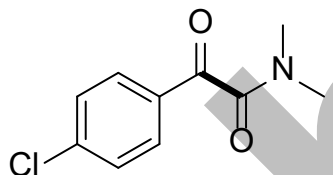
85%



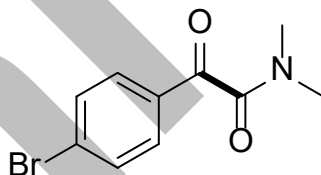
61%



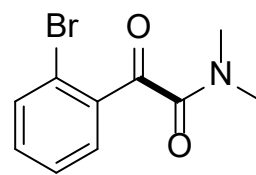
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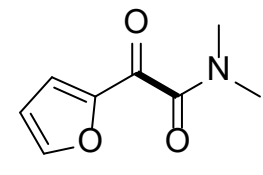
85%



82%



68%



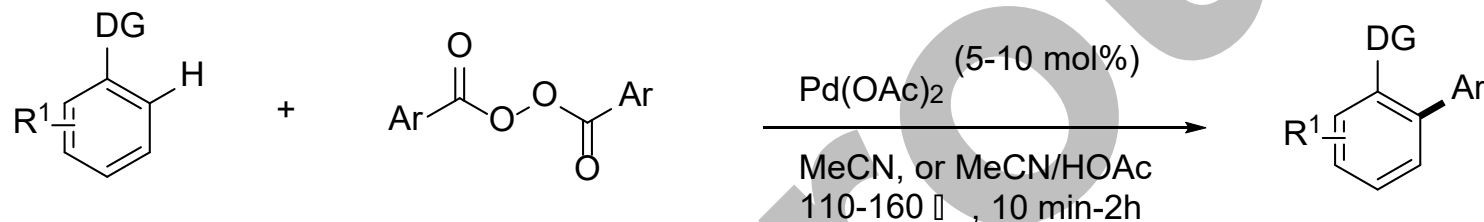
51%

Wang, L. et al. *Chem. Commun.* **2013**, 49, 3640.

## 3.4. 脱羧C-H键芳基化



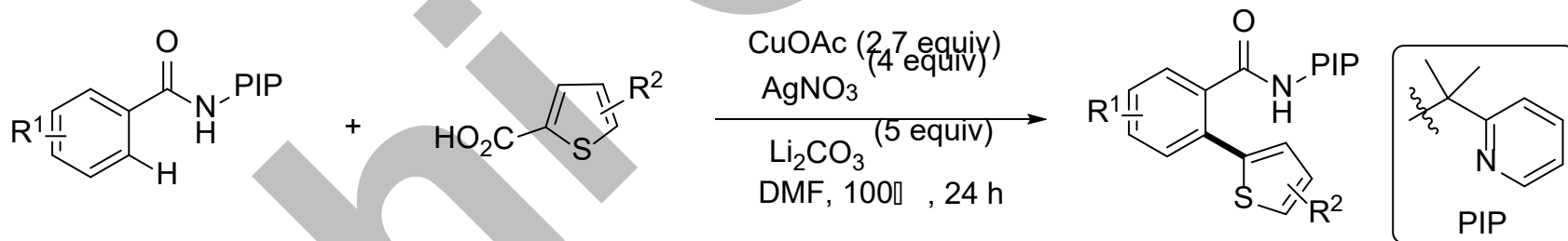
Pd催化的脱羧C-H芳基化与酰基过氧化物作为芳基化试剂



Yu, W. Y. et al. *Org. Lett.* **2009**, *11*, 3174.



用2-噻吩羧酸进行Cu / Ag催化的C-H芳基化

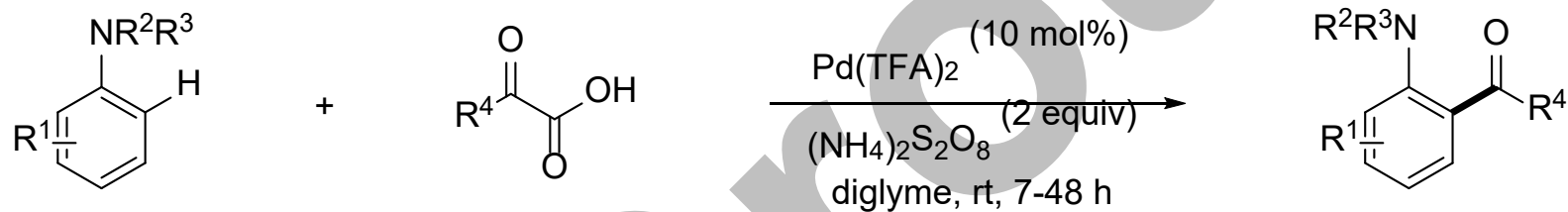


Shi, B. F. et al. *Org. Lett.* **2015**, *17*, 3338.

## 3.5. 脱羧C-H键酰化



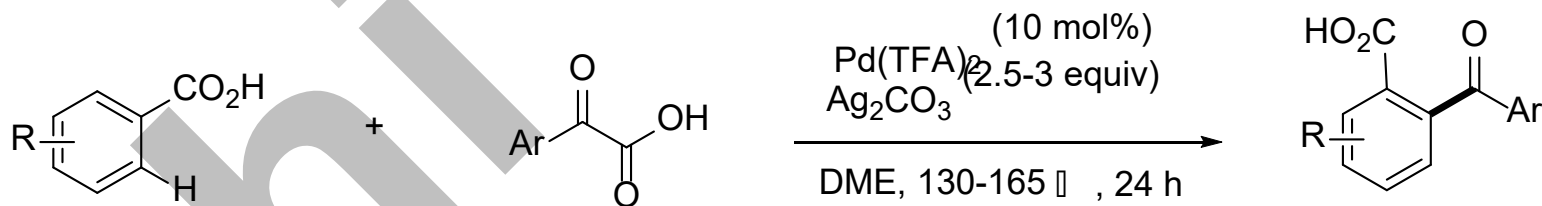
室温下Pd催化的苯胺类与 $\alpha$ -氧代羧酸的脱羧酰化反应



Ge, H. et al. *J. Am. Chem. Soc.* **2010**, *132*, 11898.



Pd催化的苯甲酸脱羧酰化反应

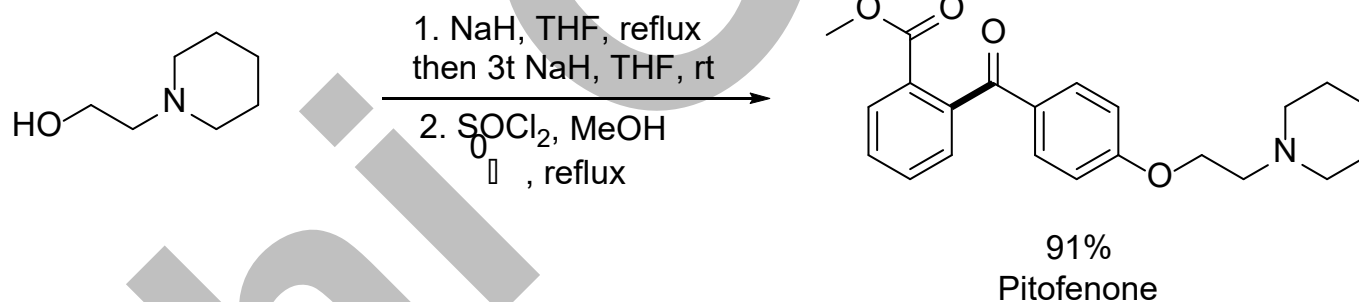
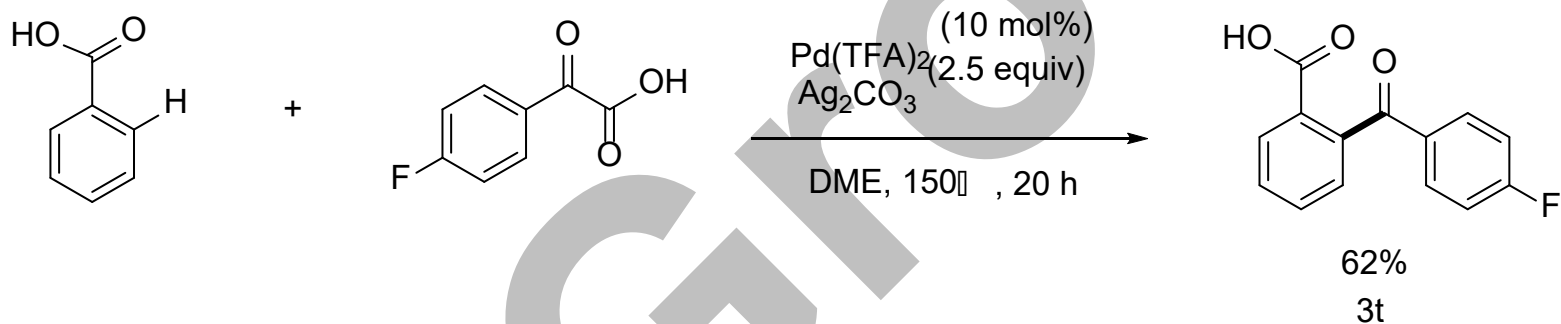


Ge, H. et al. *Org. Lett.* **2013**, *15*, 2930.

## 3.5. 脱羧C-H键酰化



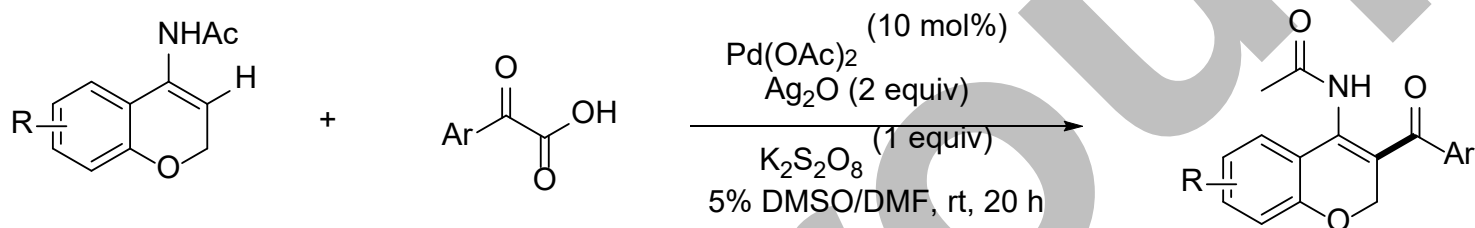
药物Pitofenone合成



Ge, H. et al. *Org. Lett.* **2013**, *15*, 2930.

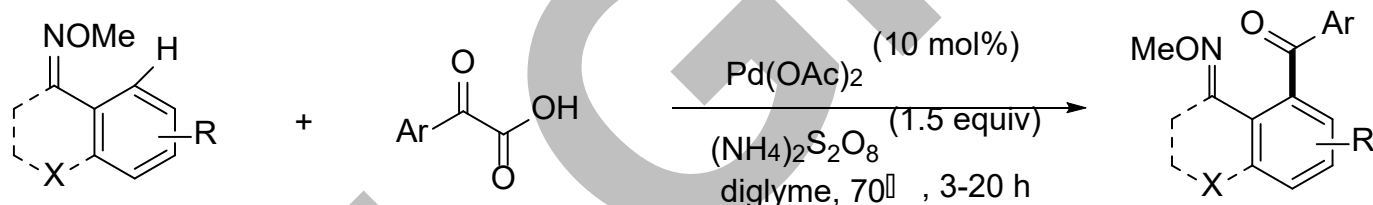
## 3.5. 脱羧C-H键酰化

### ☰ Pd催化的环酰胺与 $\alpha$ -氧代羧酸的脱羧酰化反应



Duan, X. H. et al. *Org. Lett.* **2012**, *14*, 4358.

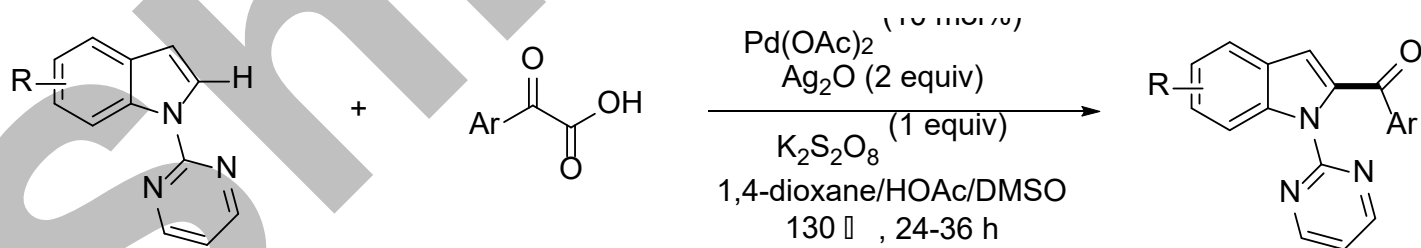
### ☰ Pd催化的脘的脱羧酰化反应



(X = C or O)

Kim, I. S. et al. *Chem. Commun.* **2013**, *49*, 925.

### ☰ Pd催化吡啶C2-的脱羧酰化

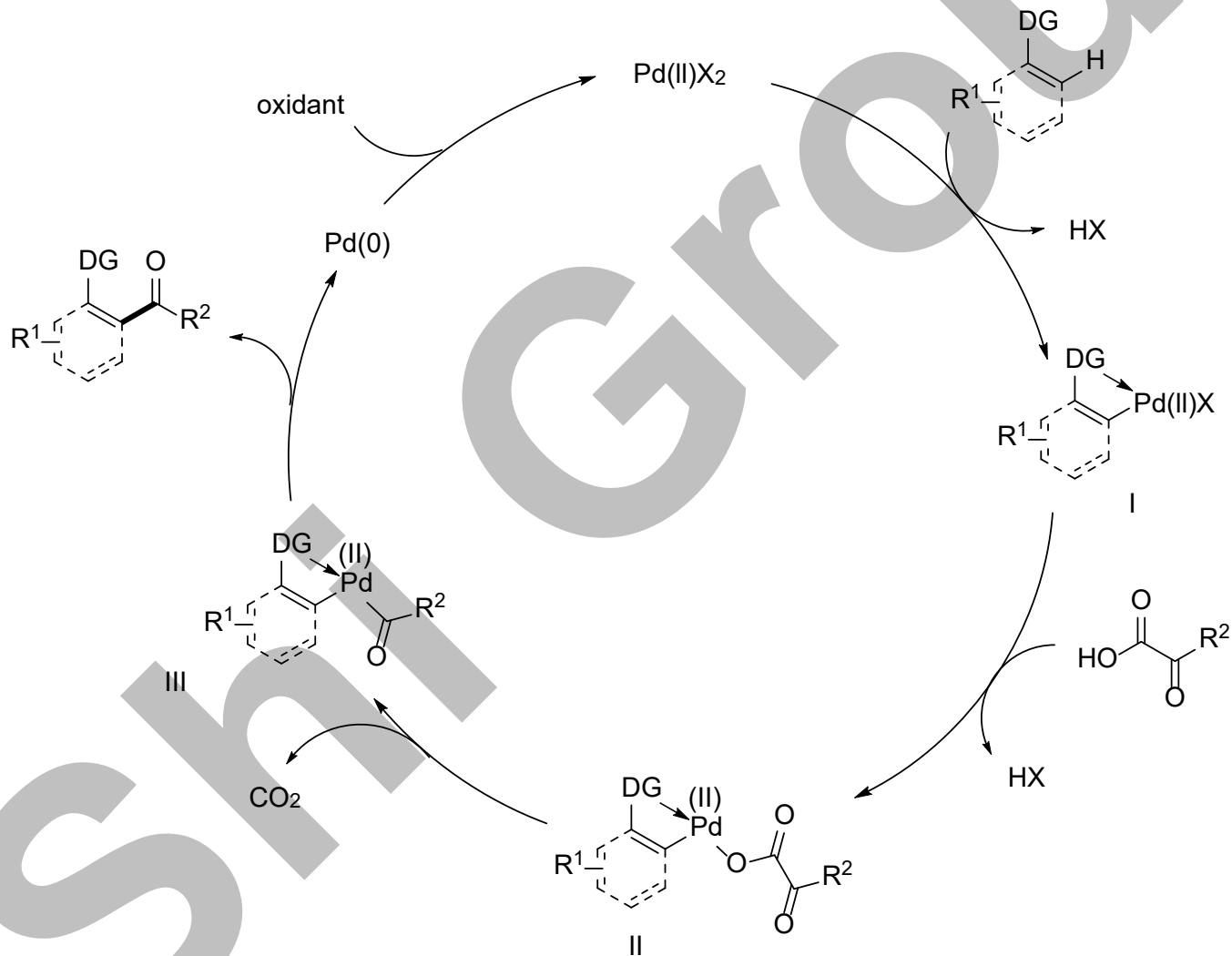


Zhu, C. et al. *Chem. Commun.* **2013**, *49*, 2933.

## 3.5. 脱羧C-H键酰化



Pd催化的脱羧C-H酰化反应的一般反应途径

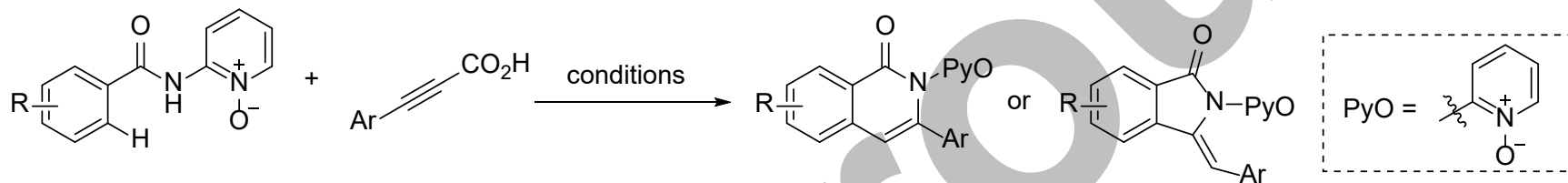




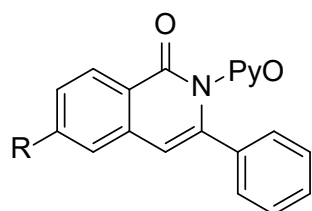
## 3.6. 脱羧C-H键炔基化/环化



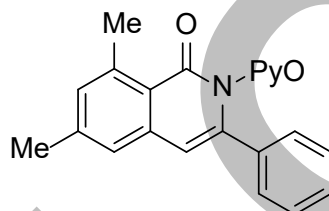
Co催化脱羧C-H炔基化/环化串联反应形成异喹啉酮和异吲哚酮



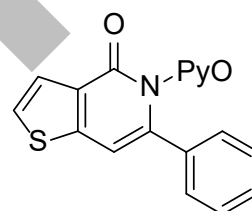
**Condition A:**  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  (10 mol%),  $\text{Ag}_2\text{O}$  (5 mol%),  $\text{NaOPiv} \cdot \text{H}_2\text{O}$  (2 equiv), 80 °C, TFE



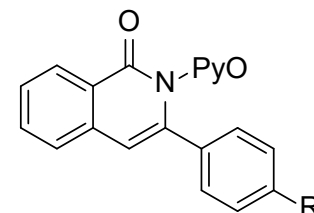
R = Br, 76%  
R = I, 88%



35%

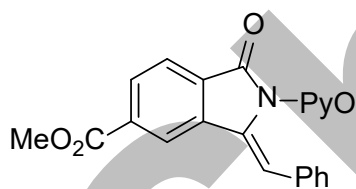


47%

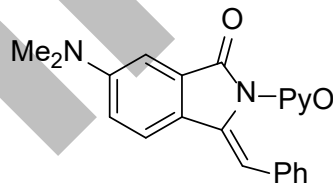


R = CN, 34%  
R = CO<sub>2</sub>Me, 44%

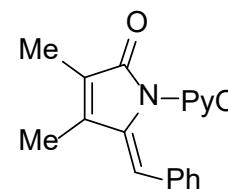
**Condition B:**  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  (10 mol%),  $\text{Ag}_2\text{O}$  (1.5 equiv),  $\text{Na}_2\text{CO}_3$  (2 equiv), 100 °C, DMF



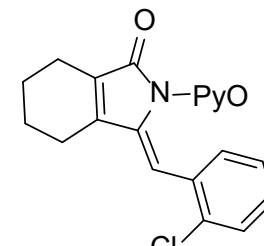
50%



77%



24%



26%  
%

小结:

脱羧  
 $C_{sp^2}-H$   
官能化

非螯合辅助

- 3.1. 异戊二烯C-H键官能团化
- 3.2. 苯环C-H键官能团化
- 3.3. 酰基C-H键官能团化

螯合辅助

- 3.4. 脱羧C-H键芳基化
- 3.5. 脱羧C-H键酰化
- 3.6. 脱羧C-H键炔基化/环化

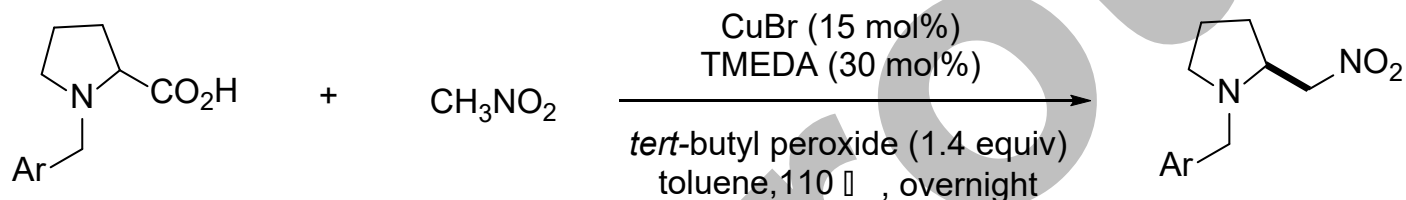


脱羧  $C_{sp^3}$ -H 官能团化

## 4 脱羧 C<sub>sp</sub><sup>3</sup>-H 官能团化



Cu催化硝基甲烷与 $\alpha$ -氨基酸的脱羧烷基化反应



Ar = Ph, 86%

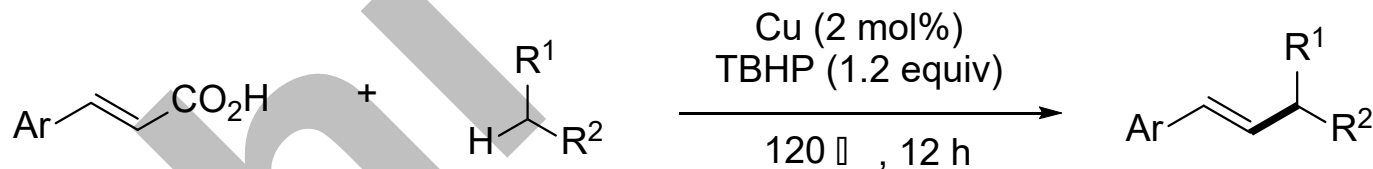
Ar = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 58%

Ar = *m*-ClC<sub>6</sub>H<sub>4</sub>, 67%

Li, C. J. et al. *Angew. Chem., Int. Ed.* **2009**, 48, 792.



Cu催化的sp<sup>3</sup> C-H键脱羧烯烃化反应

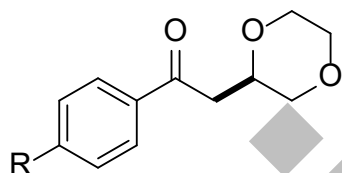
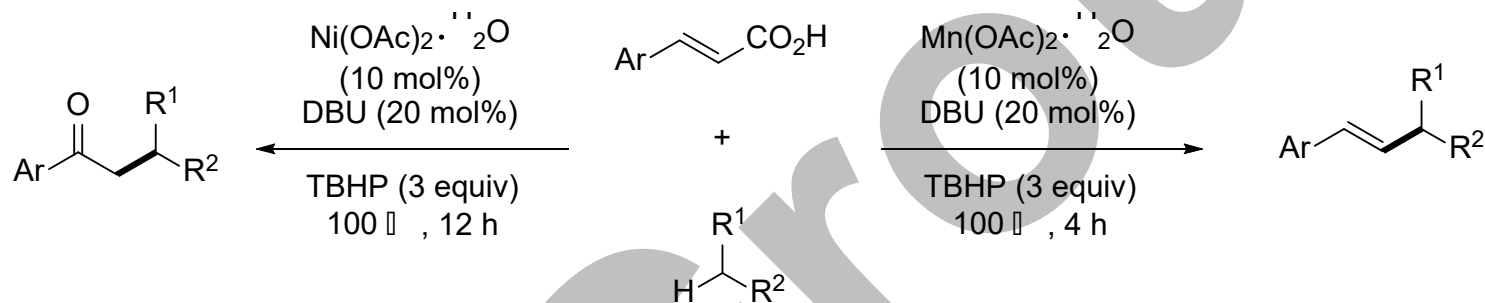


Liu, Z. Q. et al. *Chem. Sci.* **2012**, 3, 2853.

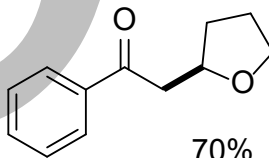
# 4 脱羧 C<sub>sp</sub><sup>3</sup>-H 官能团化



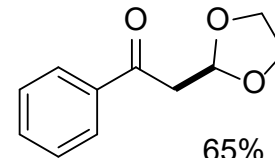
Ni和Mn催化的芳基乙烯基羧酸与环醚的脱羧交叉偶联



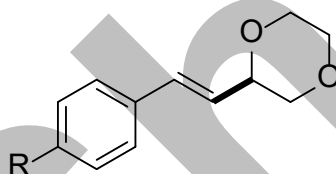
R = Me, 81%  
R = Cl, 70%  
R = Br, 65%  
R = OMe, 87%



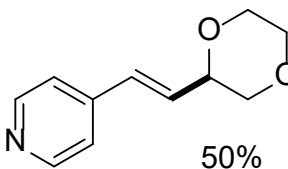
70%



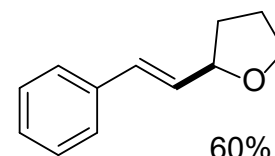
65%



R = Me, 80%  
R = Cl, 70%  
R = Br, 65%  
R = OMe, 80%



50%



60%

Wen, J. L. et al. *Sci. Rep.* **2014**, *4*, 7446.



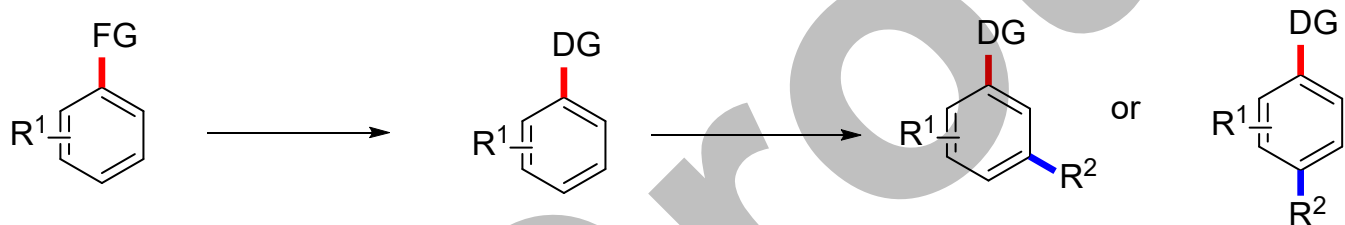
包含脱羧 C-H 键转换过程的其他反应

# 5.1 羧基作为邻位C-H键官能团化的无痕导向基团

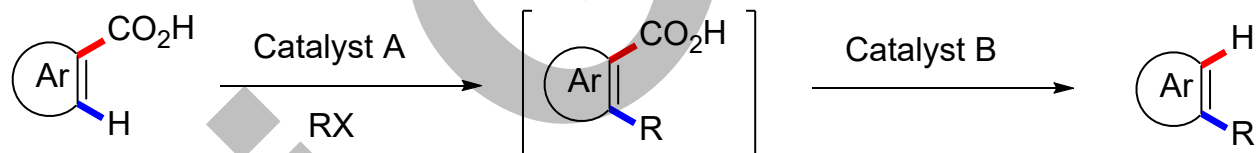


不同途径的间、对位芳香族C-H官能团化

(a) Directed *meta* and *para* aromatic C-H functionalization



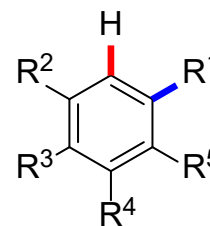
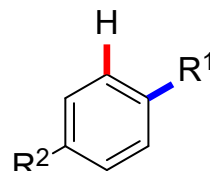
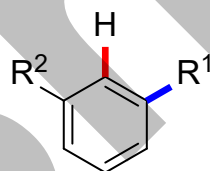
(b) Carboxyl group as a traceless directing group for aromatic C-H functionalization



*C-H functionalization*

*decarboxylation*

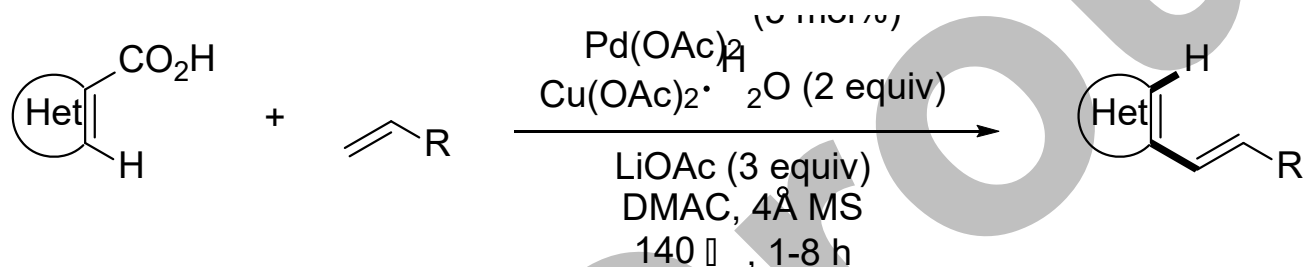
products:



## 5.1 羧基作为邻位C-H键官能团化的无痕导向基团



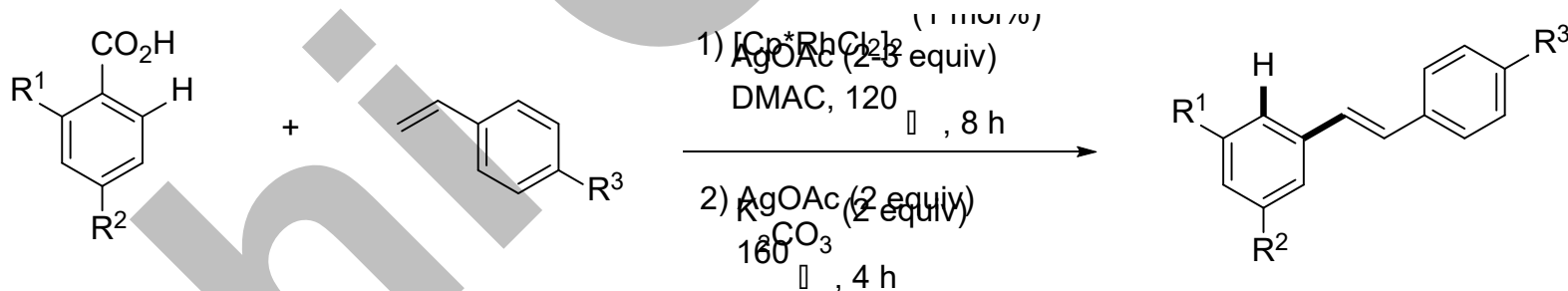
由可去除的羧基指导的杂环化合物的乙烯基化



Miura, M. et al. *Org. Lett.* **2008**, 10, 1159.



通过苯甲酸的邻位烯基化和脱羧，得到二苯乙烯



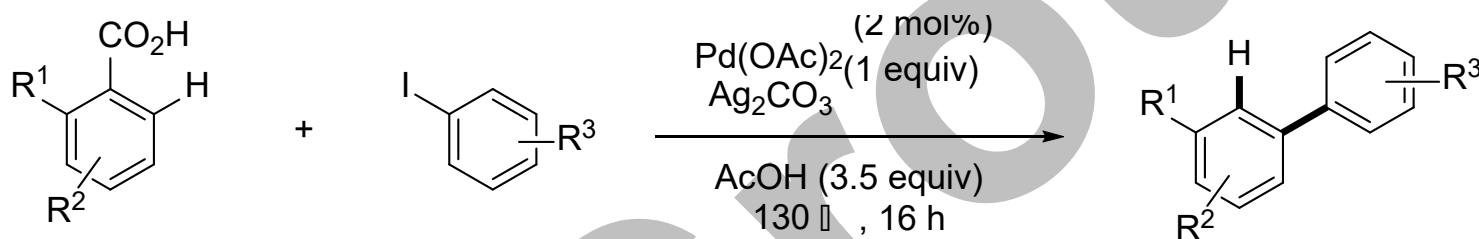
Miura, M. et al. *Org. Lett.* **2010**, 12, 5776.



## 5.1 羧基作为邻位C-H键官能团化的无痕导向基团



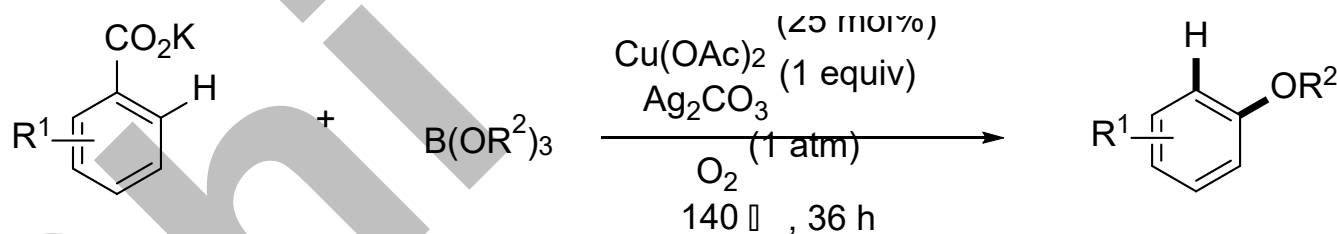
羧基作为无痕导向基团在常规的间位选择上直接芳构化应用



Larrosa, I. et al. *Angew. Chem., Int. Ed.* **2011**, 50, 9429.



羧酸盐基团作为无痕导向基团在C-H烷氧基化合成芳基醚中的应用

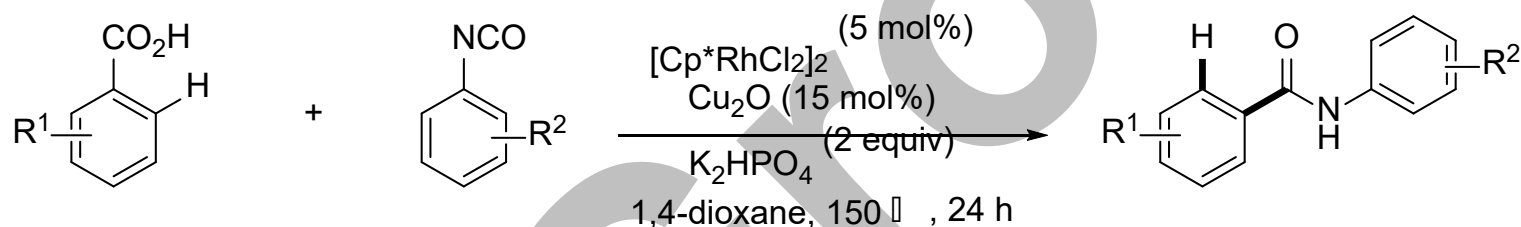


Gooßen, L. J. et al. *Angew. Chem., Int. Ed.* **2013**, 52, 2959.

## 5.1 羧基作为邻位C-H键官能团化的无痕导向基团



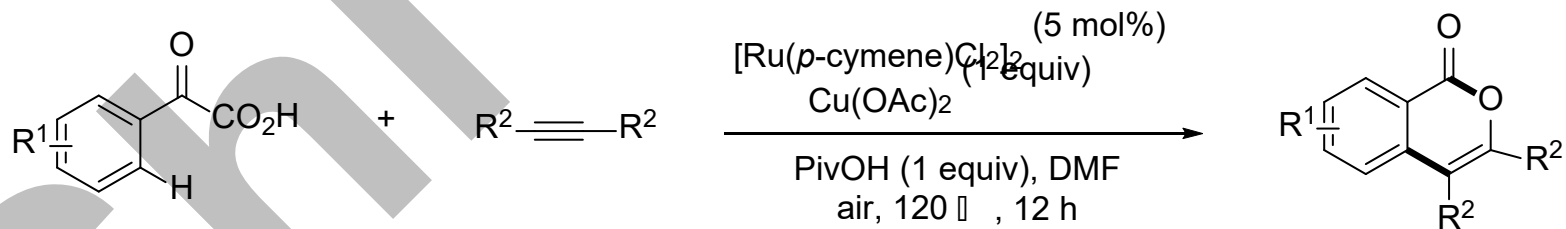
羧基作为无痕导向基团在C-H酰胺化合成N-芳基苯甲酰胺中的应用



Li, C. J. et al. *Chem. Eur. J.* **2015**, *21*, 1900.



羧基作为无痕导向基团用于C-H交叉偶联/环化 $\alpha$ -酮基羧酸与内炔烃的应用

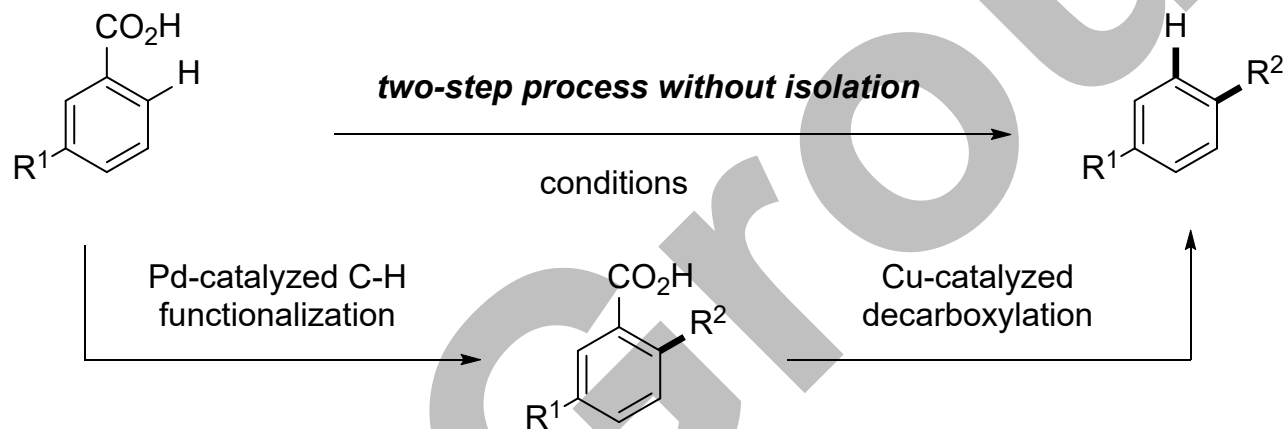


Wang, L. et al. *Chem. Eur. J.* **2015**, *21*, 1904.

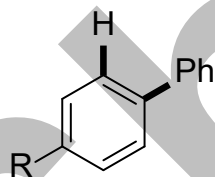
## 5.1 羧基作为邻位C-H键官能团化的无痕导向基团



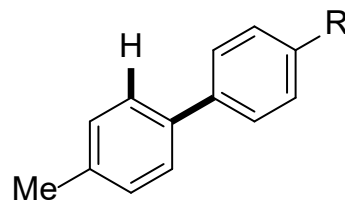
使用羧基作为无痕导向基团的间位取代的苯甲酸的对位-C-H键官能团化



**Arylation with iodobenzenes**, conditions: 1)  $\text{Pd}(\text{OAc})_2$  (2 mol%),  $\text{Ag}_2\text{CO}_3$  (0.56 equiv),  $\text{K}_2\text{CO}_3$  (0.5 equiv), AcOH, 120 °C, 24 h; 2)  $\text{Cu}_2\text{O}$  (5 mol%), 1,10-phenanthroline (10 mol%), NMP/quinoline (3/1), 170 °C, 24 h;



R = Ph, 80%  
R =  $\text{CF}_3$ , 55%  
R = Br, 60%  
R = OH, 78%



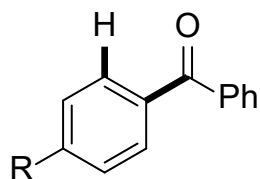
R = OMe, 80%  
R = F, 85%  
R = Cl, 81%

Zhang, Y. et al. *Synlett* **2016**, 27, 277.

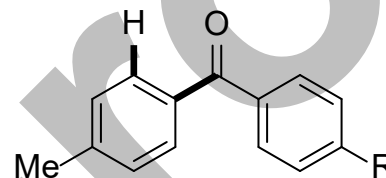
## 5.1 羧基作为邻位C-H键官能团化的无痕导向基团



**Benzoylation with benzoylformic acids**, conditions: 1) Pd(TFA)<sub>2</sub> (10 mol%), Cu<sub>2</sub>CO<sub>3</sub> (3 equiv), DME, 150-165 °C, 24-48 h; 2) Cu<sub>2</sub>O (5 mol%), 1,10-phenanthroline (10 mol%), NMP/quinoline (3/1), 170 °C, 24 h;

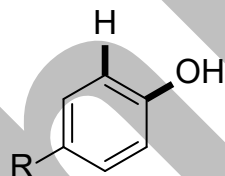


R = Ph, 75%  
R = CF<sub>3</sub>, 60%  
R = Br, 60%  
R = CO<sub>2</sub>Me, 55%

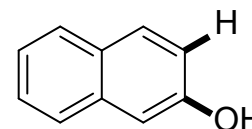


R = OMe, 70%  
R = F, 60%  
R = Cl, 50%

**Hydroxylation with oxygen**, conditions: 1) Pd(TFA)<sub>2</sub> (10 mol%), BQ (1 equiv), KOAc (2 equiv), DMAc, O<sub>2</sub> (1-5 atm), 115 °C, 15 h; 2) Cu<sub>2</sub>O (5 mol%), 1,10-phenanthroline (10 mol%), NMP/quinoline (3/1), 220 °C, 12 h;



R = F, 45%  
R = CF<sub>3</sub>, 88%  
R = Cl, 84%  
R = OMe, 70%



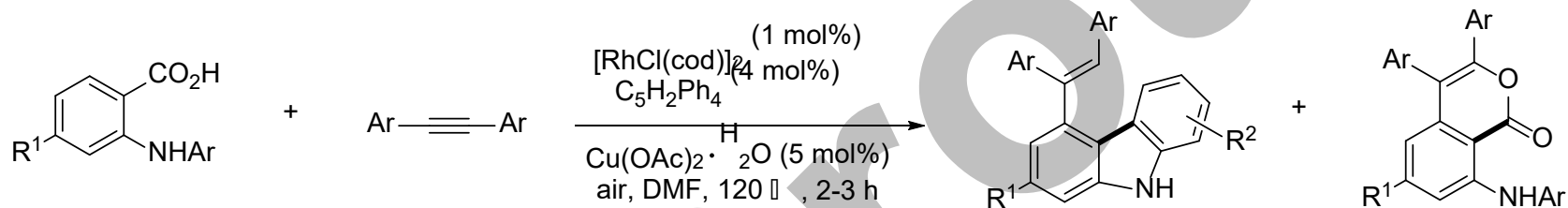
60%

Zhang, Y. et al. *Synlett* **2016**, 27, 277.

## 5.2 氧化脱羧和其他反应



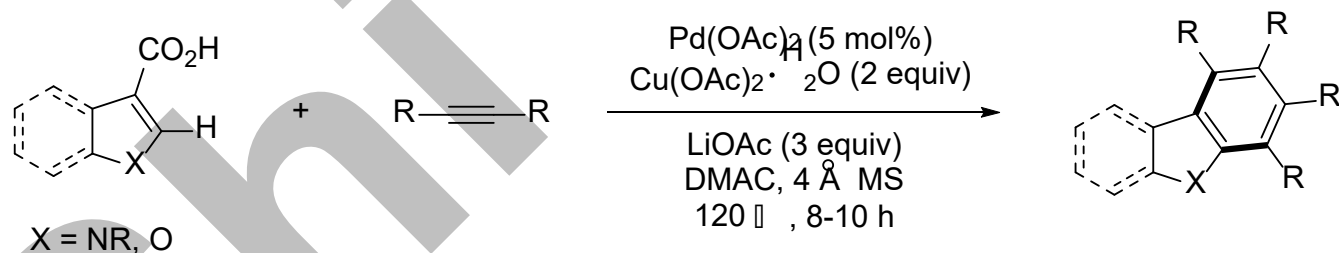
N-苯基邻氨基苯甲酸与炔烃的脱羧交叉偶联



Miura, M. et al. *J. Org. Chem.* **2009**, *74*, 3478.



杂环羧酸与炔烃的脱羧交叉偶联

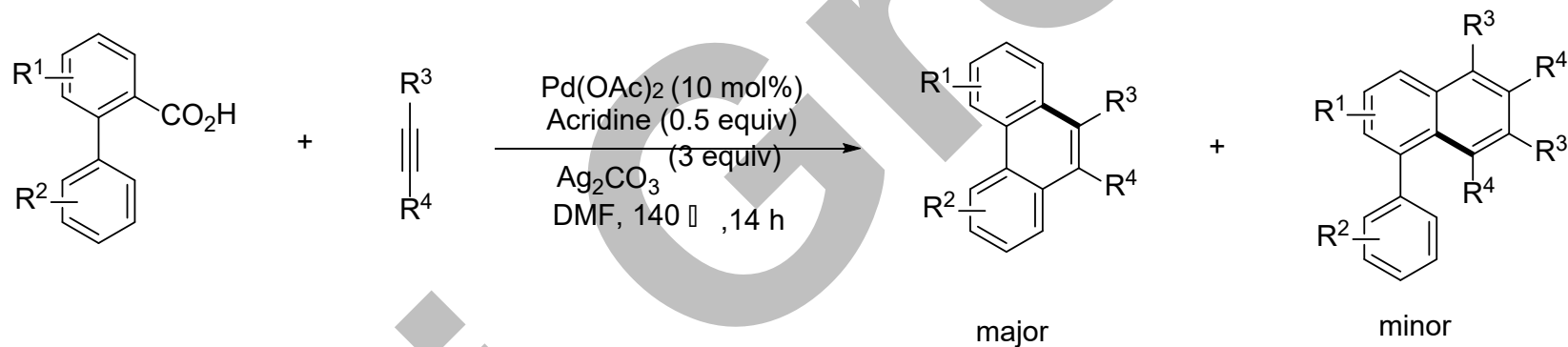


Miura, M. et al. *Org. Lett.* **2009**, *11*, 2337.

## 5.2 氧化脱羧和其他反应



钯催化的2-苯基苯甲酸与炔烃的分子间[4+2]环化

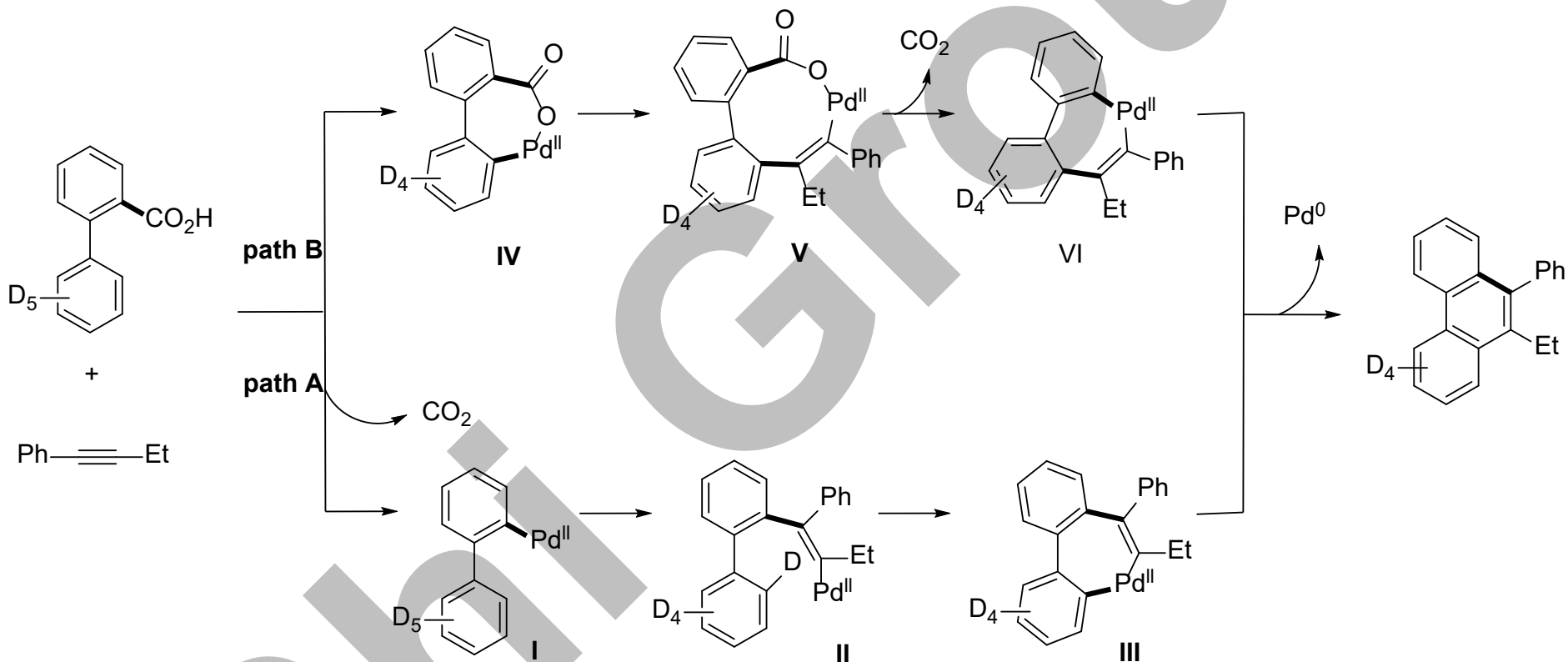


Glorius, F. et al. *J. Am. Chem. Soc.* **2010**, 132, 14006.

## 5.2 氧化脱羧和其他反应




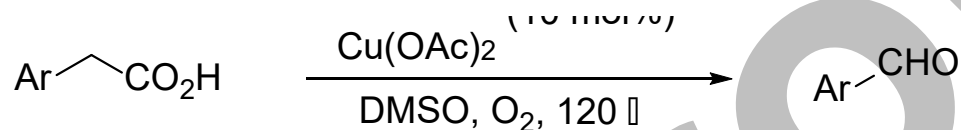
分子[4+2]环庚烷合成2-苯基苯甲酸的机理探讨




Glorius, F. et al. *J. Am. Chem. Soc.* **2010**, *132*, 14006.

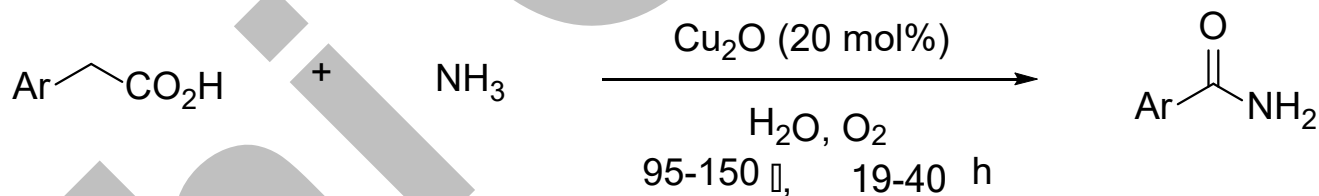
## 5.2 氧化脱羧和其他反应

 芳基乙酸脱羧氧化合成芳香醛



Song, Q. et al. *J. Org. Chem.* **2014**, 79, 1867.

 芳基乙酸脱羧氨氧化合成伯酰胺

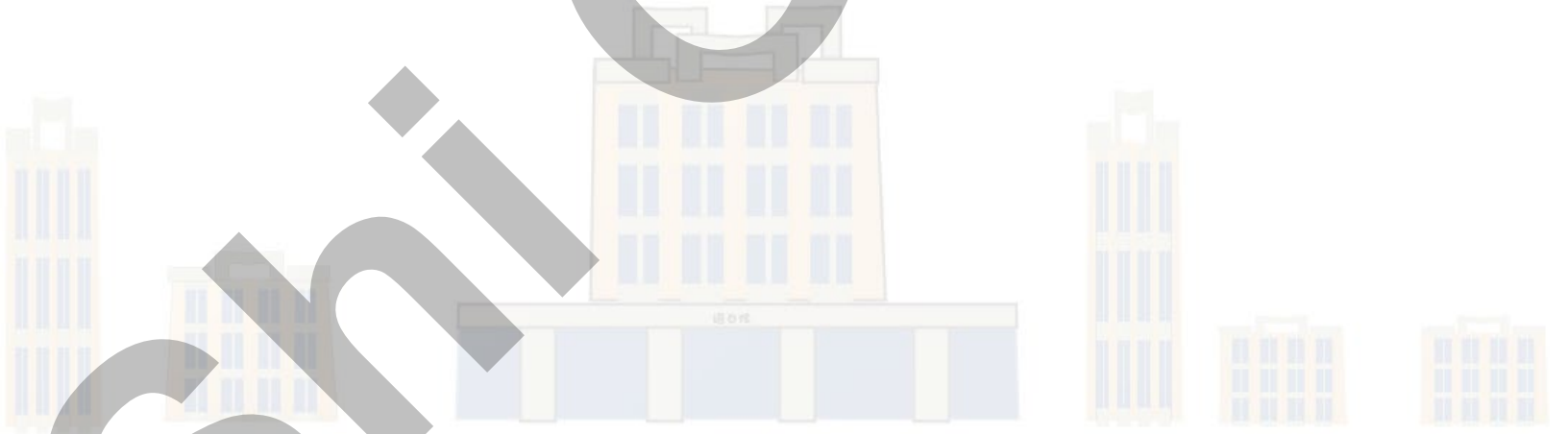


Song, Q. et al. *Org. Lett.* **2014**, 16, 624.



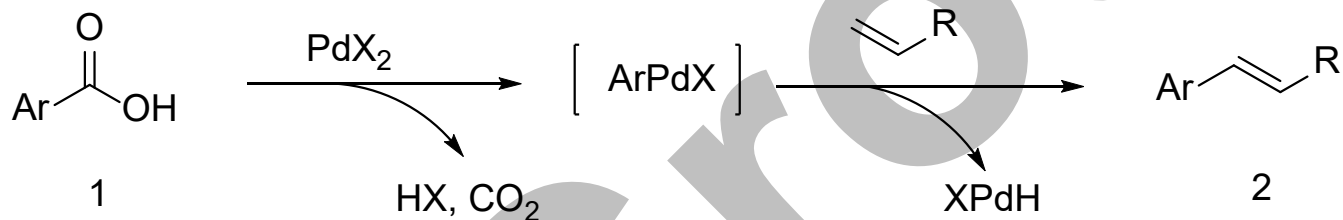


## 结论与展望

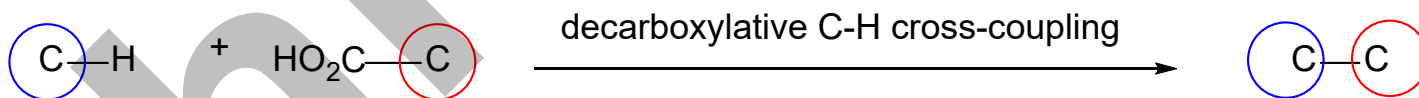


## 6 结论与展望

### 结论



Andrew G. Myers. et al. *J. Am. Chem. Soc.* **2002**, 124, 11250.



## 6 结论与展望

### 结论

1. 已建立的脱羧偶联反应通常反应温度 $>120^{\circ}\text{C}$ ;
2. 中性脱羧的脱羧偶联反应的芳基羧酸必须在邻位含有取代基;
3. 氧化脱羧不需要邻位取代基, 但是, 由于形成自由基中间体而显示出低选择性;

## 6 结论与展望

### 展望

1. 配体有望增强催化剂的催化活性，如引入一些双齿配体，可以促进部分双金属催化体系的转金属化，导致反应温度降低；
2. 是否可以利用导向基团辅助的C-H键官能团化反应，实现新的导向基团辅助的金属促进的脱羧模式；
3. 由于近几年的电化学、光化学的火热研究，开发更多的反应方法来进行脱羧C-H官能团化反应研究。

Thank you!