Development, Mechanism and Application of Chan-Evans-Lam Reaction

Cuiwen Kuang

2017-04-24

Main reference:

Shannon S. Stahl et al. *J. Am. Chem. Soc.* **2009**, *131*, 5044.

Allan J. B. Watson et al. *J. Am. Chem. Soc.* **2017**, *139*, 4769.

OUTLINE

- Introduction of Chan-Evans-Lam Reaction
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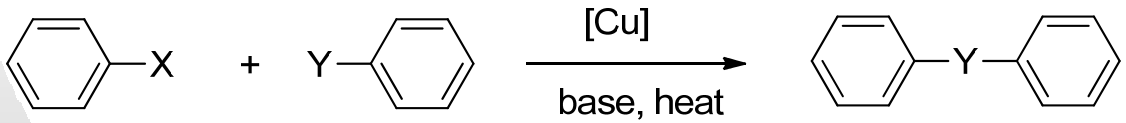
- Application of Chan-Evans-Lam Reaction
- Conclusion

Introduction of Chan-Evans-Lam reaction

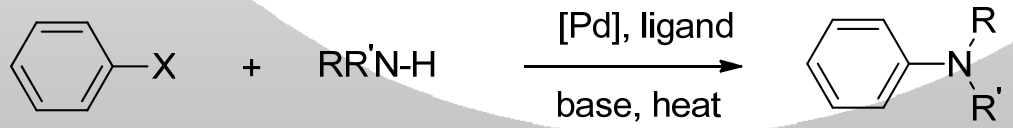
C-N coupling reaction

Ullmann 1903 and Goldberg 1906



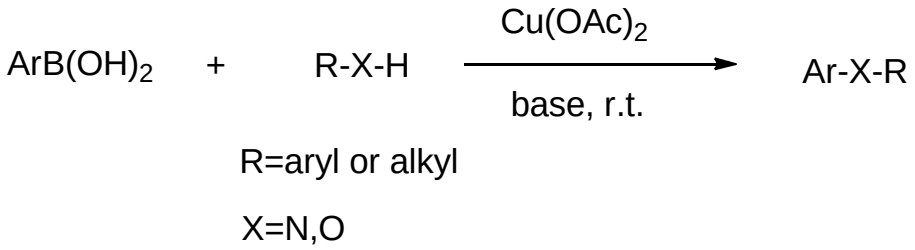
aryl halide phenol or arylamine

Buchwald-Hartwig coupling reaction



aryl halide

Introduction of Chan-Evans-Lam reaction



adventages of chan-evans-lam reacton:

1. Room temperature

2. Weak base.

3. Open to air

Evans' group found out about the discovery of copper-mediated O-arylation reaction on a National Organic Symposium poster presented by Chan and became interested in the reaction because of the importance of novel biaryl ether synthesis for vancomycin total synthesis.

-- Lam

D. M. T. Chan et al. *TetrahedronLett.* **1998**, *39*, 2933.

D. A. Evans et al. *Tetrahedron Lett.* **1998**, *39*, 2937 .

OUTLINE

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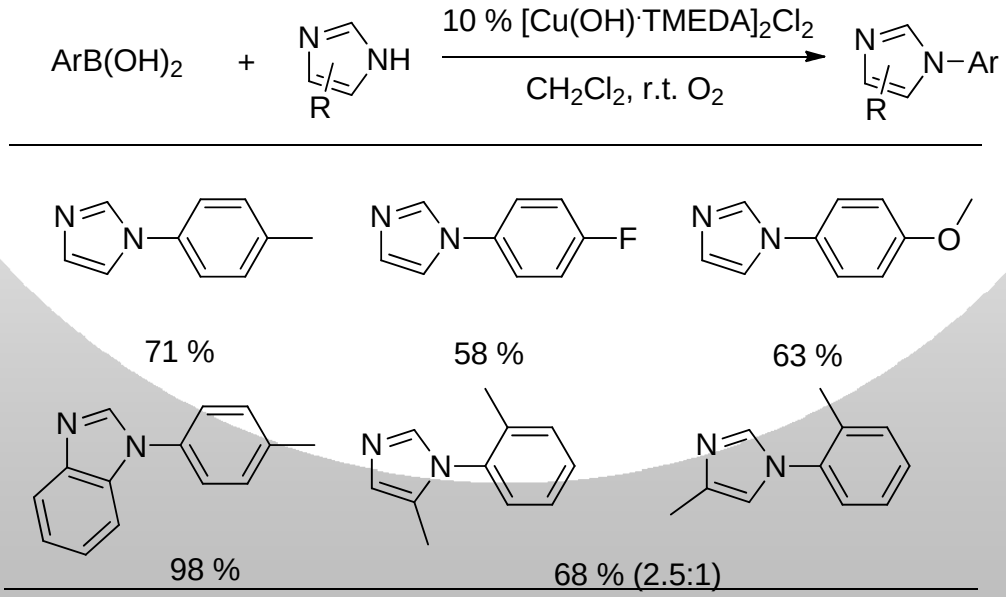
Development of Chan-Evans-Lam reaction

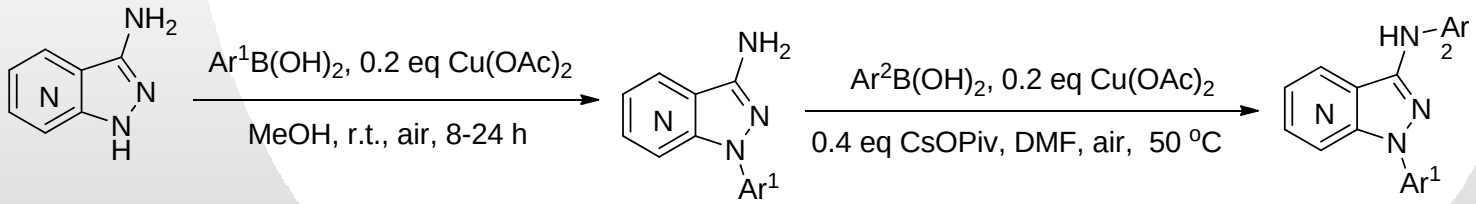
The first time to achieve the catalytic amount of copper

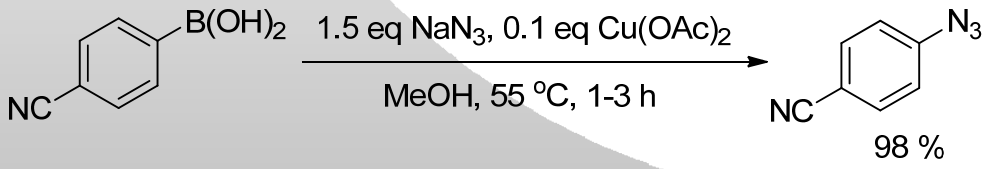


J. P. Collman and M. Zhong, *Org. Lett.*, **2000**, *2,* 1233.

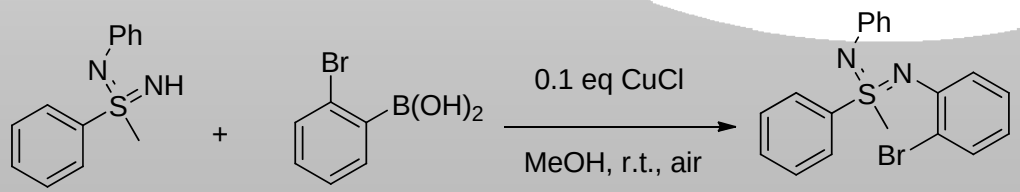
Development of Chan-Evans-Lam reaction

Selective Arylation





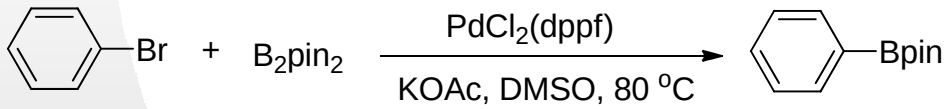
98 %



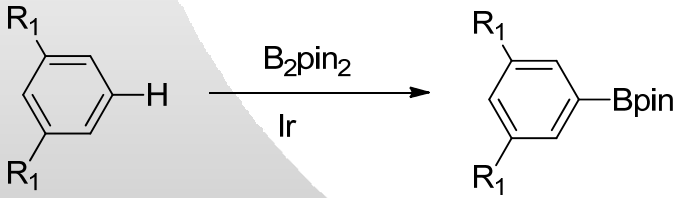
P. Das et al. *Chem. Commun.* **2014**, 50, 12911.
C. C. Aldrich et al. *Synlett*, **2010**, 9, 1441.
C. Bolm et al. *Org. Lett.*, **2013**, 15, 4277.

Development of Chan-Evans-Lam reaction

Miyaura Reaction (1995)

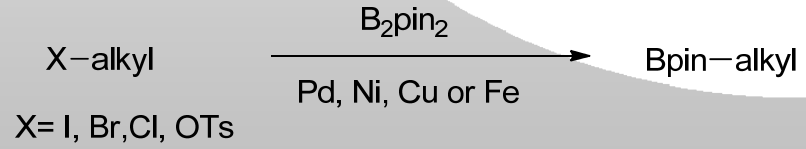


C-H Functionalization

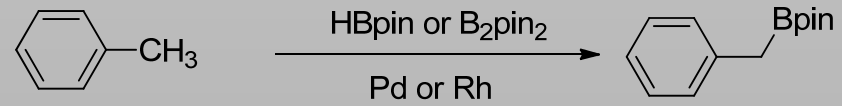


Synthesis of Aryl Boronate Esters

Cross-Coupling

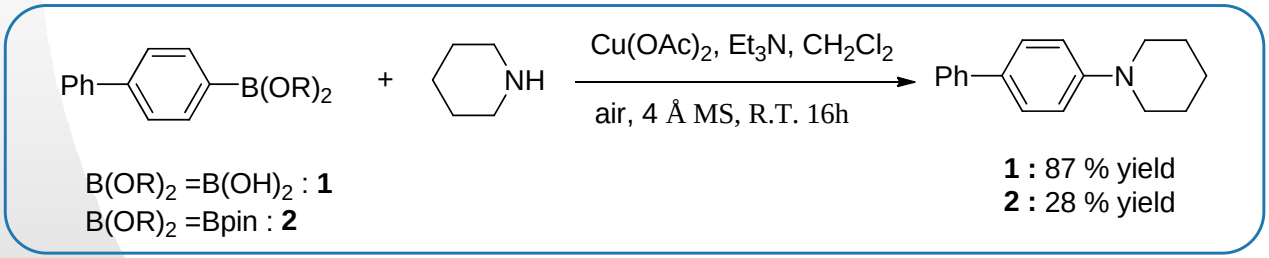


C-H Functionalization

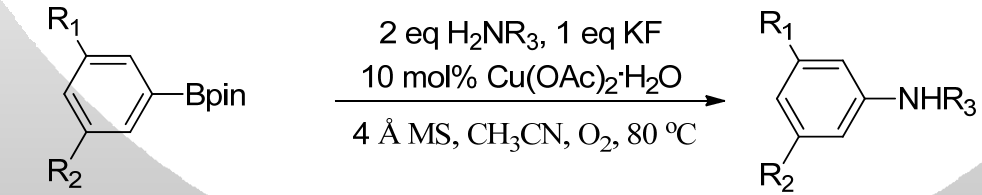


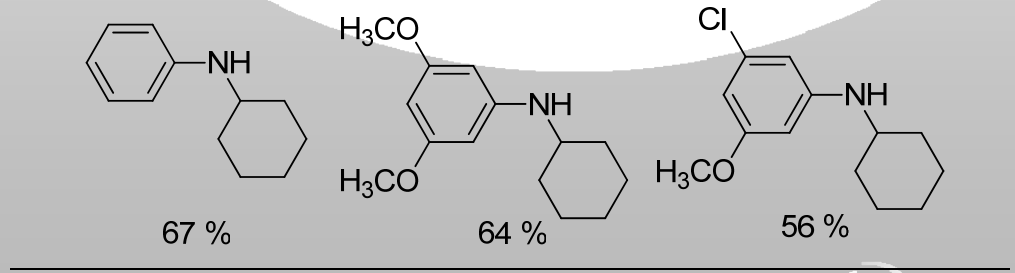
Synthesis of Alkyl Boronate Esters

Development of Chan-Evans-Lam reaction



Allan J. B. Watson et al. *J. Am. Chem. Soc.* **2017**, *139*, 476

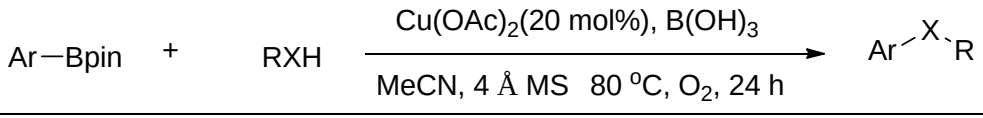


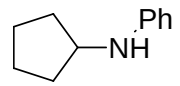


Only primary alkylamine

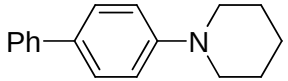
John F. Hartwig et al. *Org. Lett*. **2007**, *9*, 761.

Development of Chan-Evans-Lam reaction

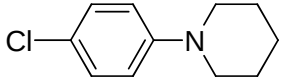




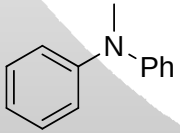
84 %



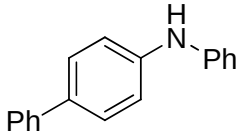
70 %



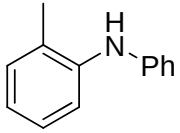
90 %



90 %



82 %

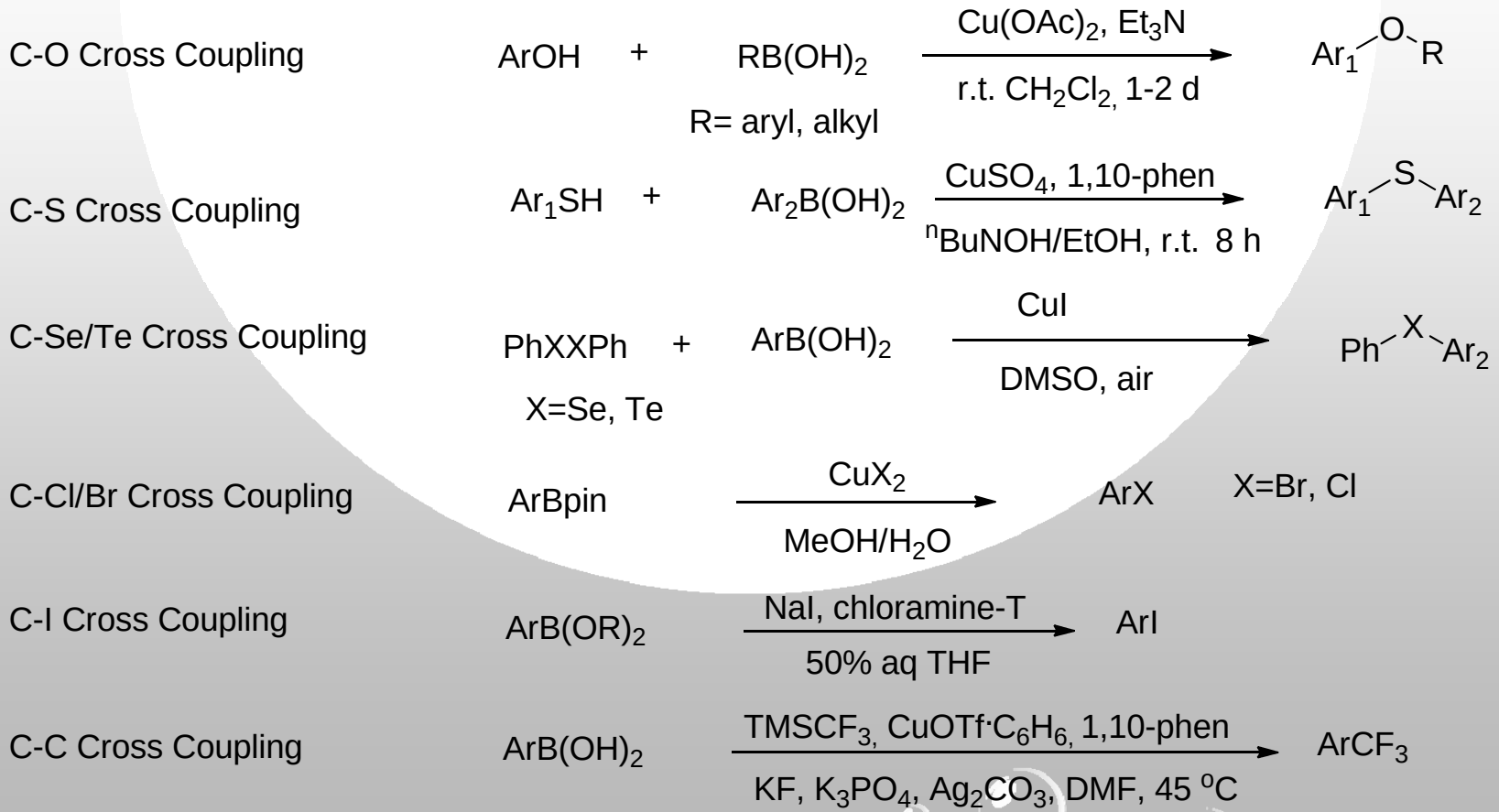


56 %

Remain problems：need heat, reaction time long related to arylboronic acid.

A. J. B. Watson et al. *J. Am. Chem. Soc.* **2017**, *139*, 4769.

Development of Chan-Evans-Lam reaction



P. Y. S. Lam et al. *SYNTHESIS* **2011**, *6*, 0829–0856.

Development of Chan-Evans-Lam reaction

summary

Adventages of CEL reaction

- Mild condition
- Cheap copper catalyst
- Good to excellent yield
- Diverse Substrate scope

OUTLINE

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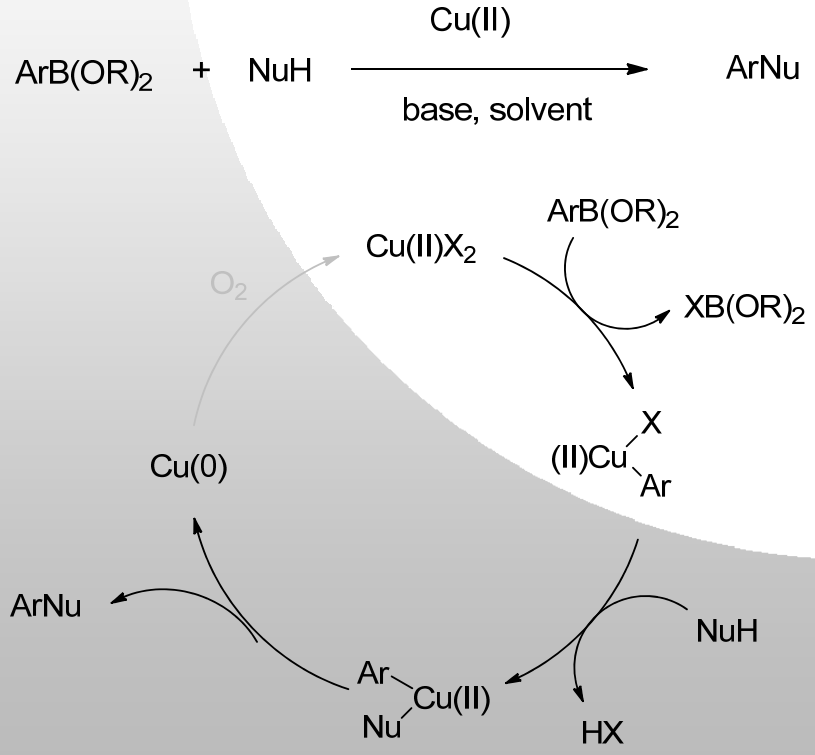
Mechanism of Chan-Evans-Lam reaction

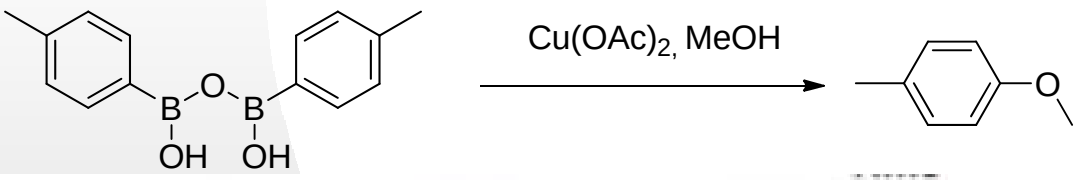
The first generation

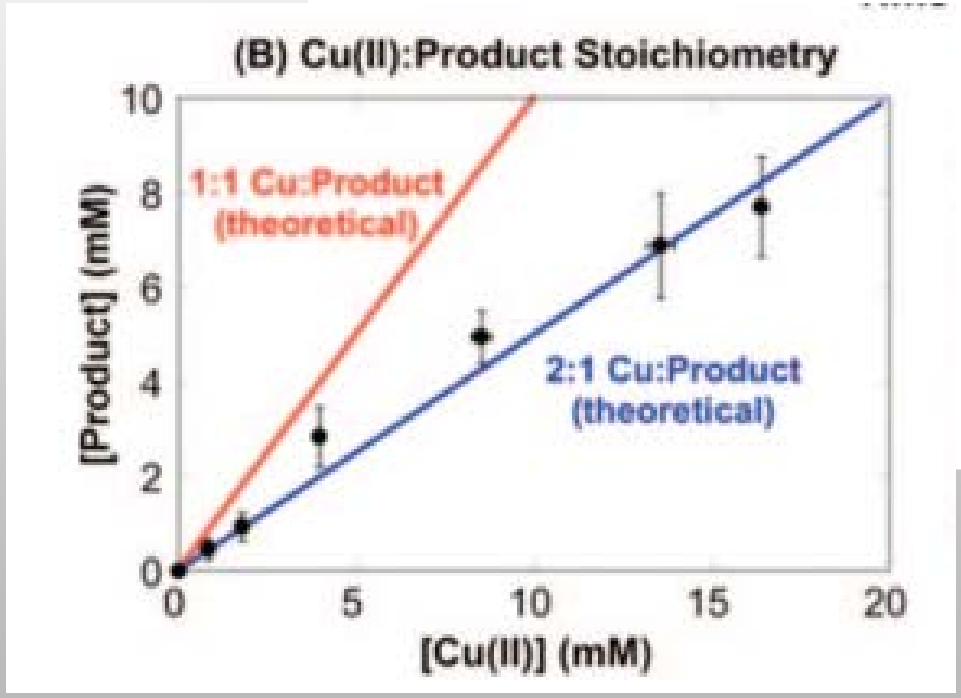


Base on facts:
1eq Cu(II) can achieve the reaction.
Referring to Pd catalytic cycle and Ullmann reaction.

Mistakes:
The reaction is open to air, O_2 can be oxidant to recycle the copper.

Mechanism of Chan-Evans-Lam reaction





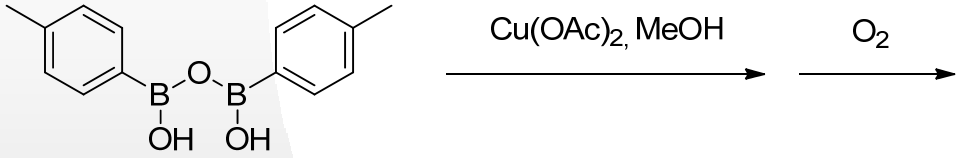
Conclusion

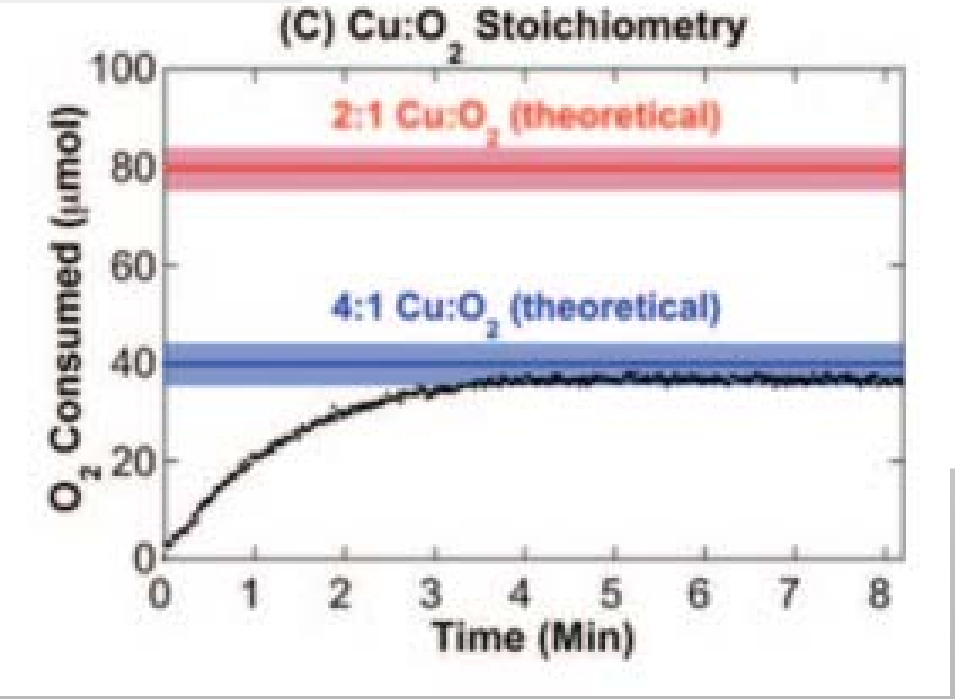
Product :Cu(II)=1 :2

$$2\ Cu^{II}X_2 + ArB(OR)_2 + MeOH \longrightarrow 2\ Cu^{I}X + ArOMe$$

S. S. Stahl et al. *J. Am. Chem. Soc.* **2009**, *131*, 5044.

Mechanism of Chan-Evans-Lam reaction

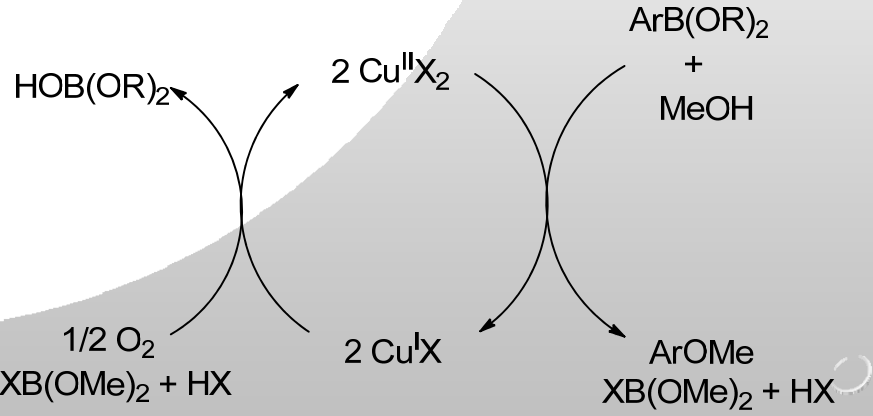




Conclusion

Product： Cu(II)=1： 2

Cu： O_2=4： 1



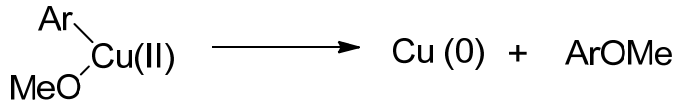
S. S. Stahl et al. *J. Am. Chem. Soc.* **2009**, *131*, 5044.

Mechanism of Chan-Evans-Lam reaction

Without O_2, how is Cu(II) converted to Cu(I) ?

Possible Pathway

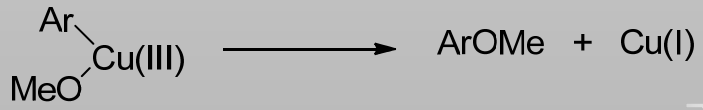
(A) Reductive Elimination From Cu(II)

(i) 

(ii) Cu (0) + Cu(II) ⟶ 2 Cu(I)

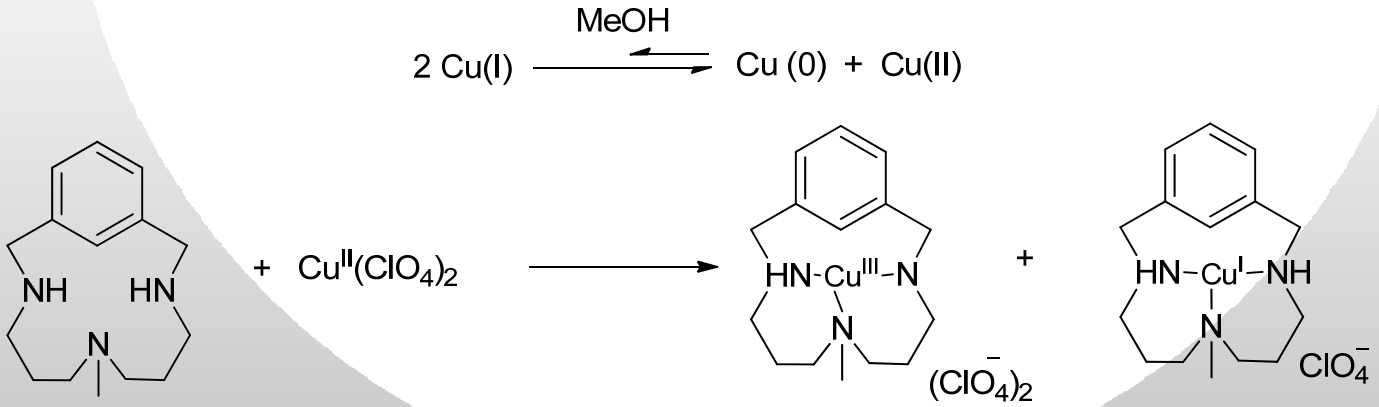
(B) Reductive Elimination From Cu(III)

(i) 

(ii) 

S. S. Stahl et al. *J. Am. Chem. Soc.* **2009**, *131*, 5044

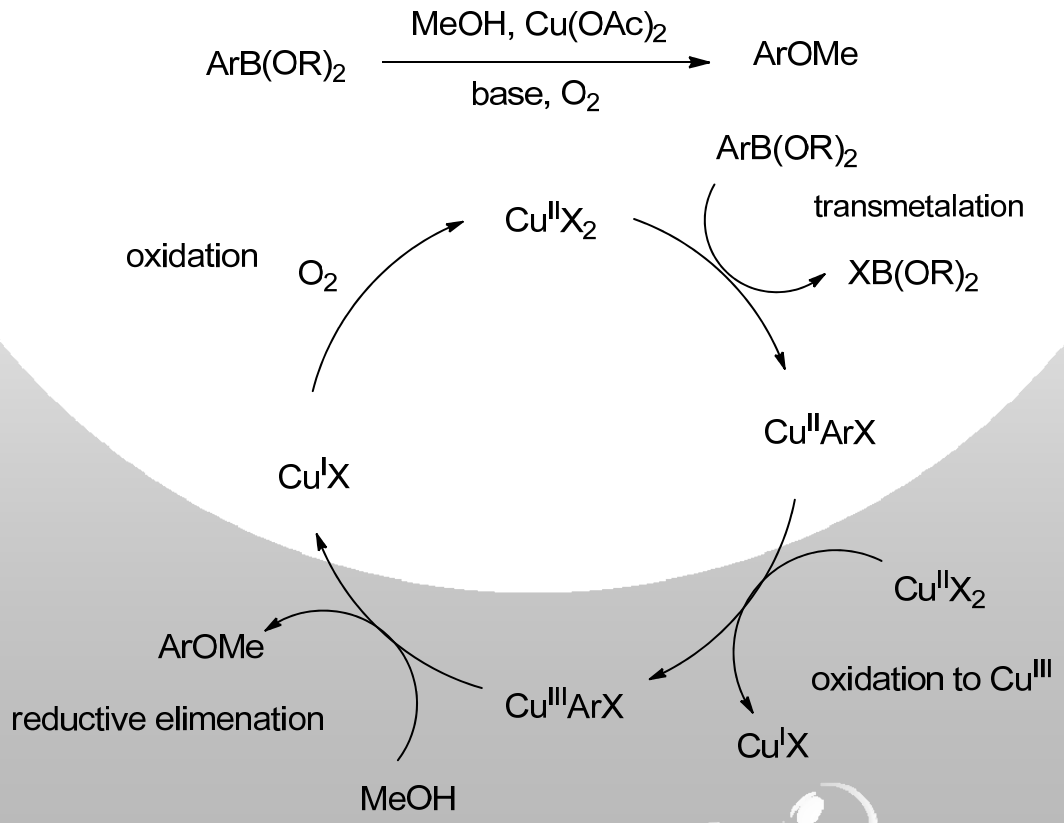
Mechanism of Chan-Evans-Lam reaction



T. D. P. Stack et al. *Angew. Chem. Int. Ed.* **2002**, *41*,

In favor of the pathway B

Mechanism of chan-evans-lam reaction



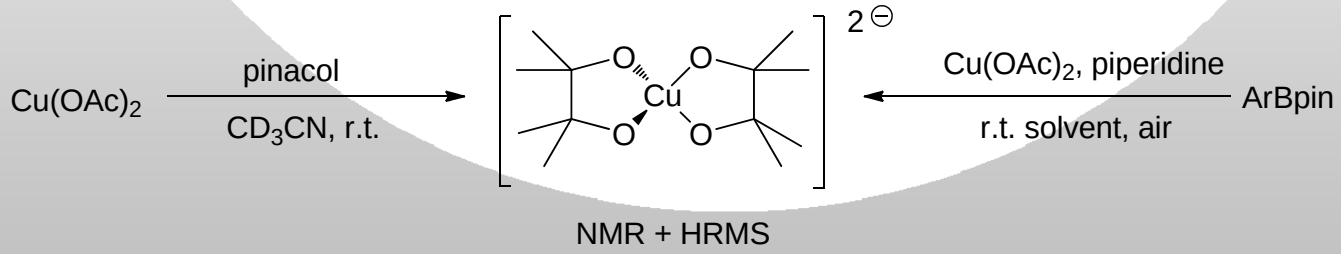
S. S. Stahl et al. *J. Am. Chem. Soc.* **2009**, *131*, 5044

Mechanism of Chan-Evans-Lam reaction

Although the cycle is accomplished, there are remain some questions.

1. Why the reactivity of ArBpin is lower than $ArB(OH)_2$.

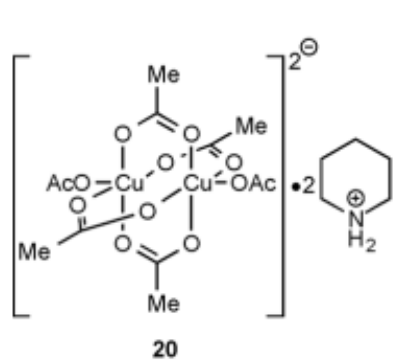
2. Addition of Et_3N can accelerate the reaction rather the addition of AcOK/AcOH Inhibit the reaction.



Detected in both isolated sample and reaction mixture

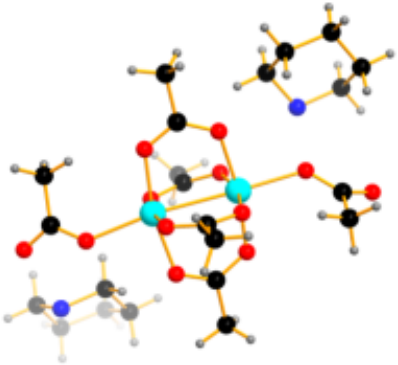
A. J. B. Watson et al. *J. Am. Chem. Soc.* **2017**, *139*, 4769

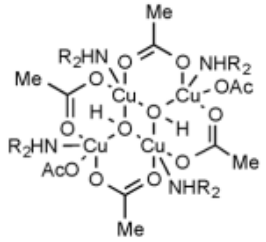
Mechanism of Chan-Evans-Lam reaction



20

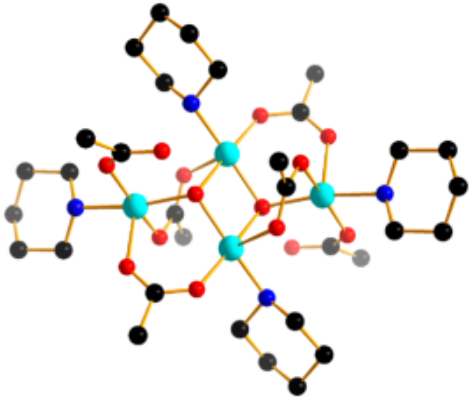
≡



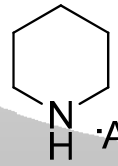


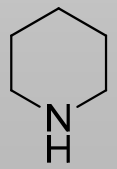
21

≡



Inactive complex **active complex**

$[Cu(OAc)_2]\cdot 2H_2O$ +  $\cdot AcOH$ — MeCN, 48 h; 0 °C then 20 °C → **20** less effective

$[Cu(OAc)_2]\cdot 2H_2O$ +  — PhMe; air, r.t. 10 min → **21** active

A. J. B. Watson et al. *J. Am. Chem. Soc.* **2017**, *139*, 4762

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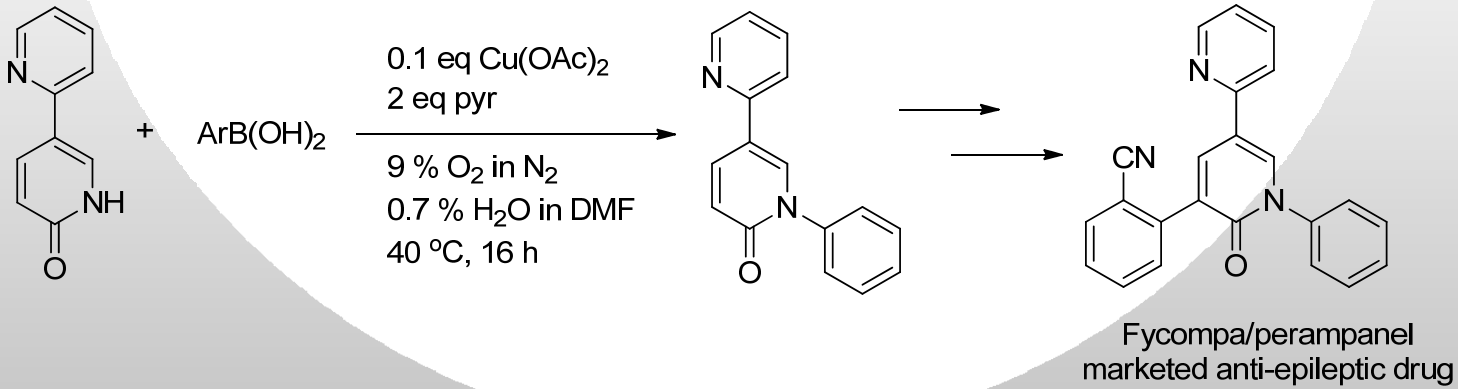
Application of Chan-Evans-Lam reaction

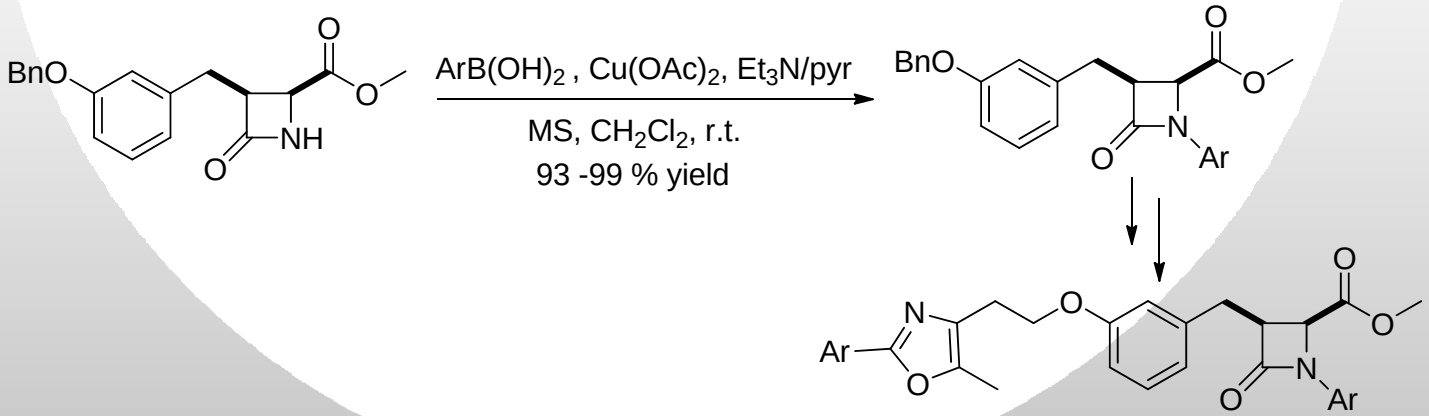
As of January 2014, there are 613 patents since its discovery(1998)



Fycompa/perampanel
marketed anti-epileptic drug

A. Kayano and K. Nishiura, *U.S. Pat*. 8304548B2, Nov. 12, **2012.**

Application of Chan-Evans-Lam reaction

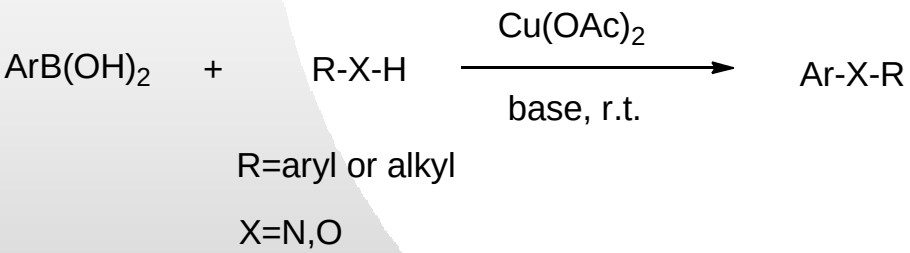


potent dual PPAR α/γ agonists
potential anti-diabetic agents

W. Wang and P. Devasthale et al. *Bioorg. Med. Chem. Lett*, **2008**, *18*, 1939.

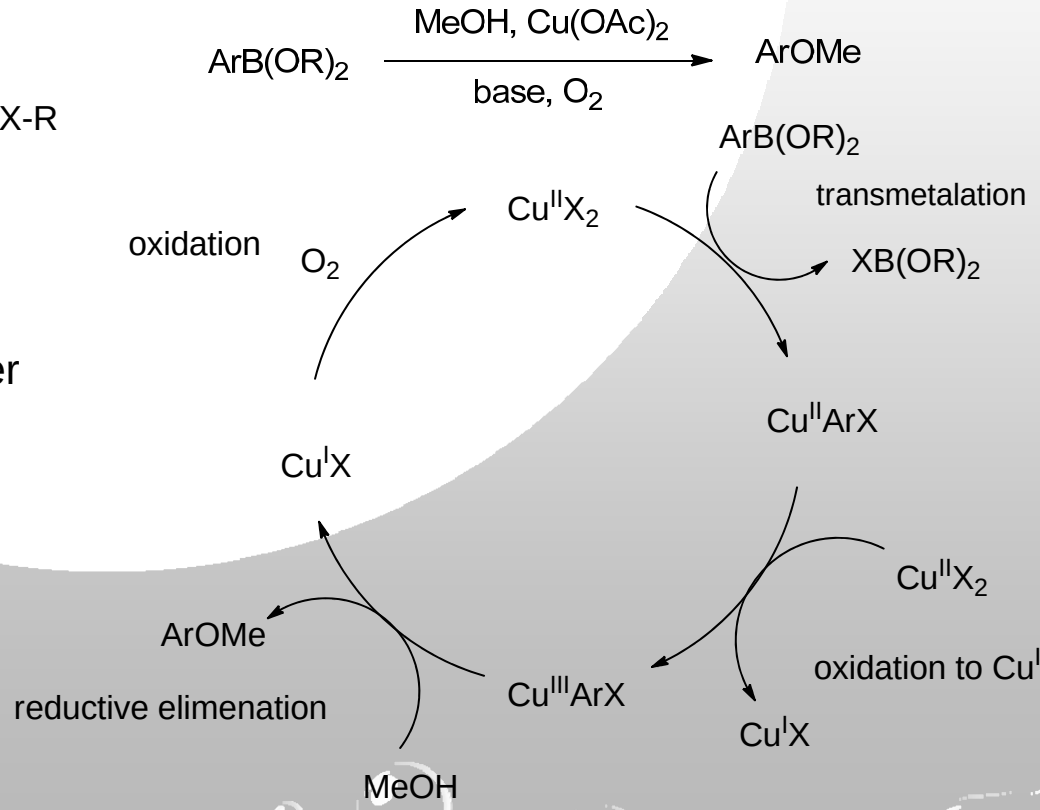
Conclusion

1. Development of Chan-Evans-Lam reaction



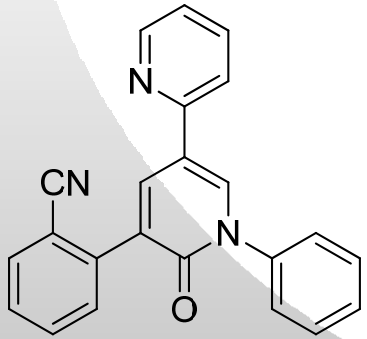
From equivalent to catalytic amount of copper
From boronic acid to boronate esters
From C-N/C-O bond to other bond

2. Mechanism of Chan-Evans-Lam reaction

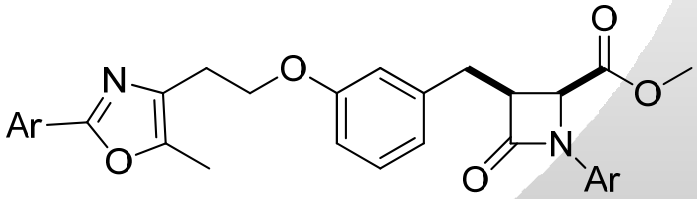


Conclusion

3. Application of Chan-Evans-Lam reaction



Fycompa/perampanel
marketed anti-epileptic drug



potent dual PPAR α/γ agonists
potential anti-diabetic agents

THANK YOU