Copper-Catalyzed Aerobic Oxidative C-H Functionalizations

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Reporter: Weiyu Yin (殷韦玉)

Date: 2013-04-08

Content

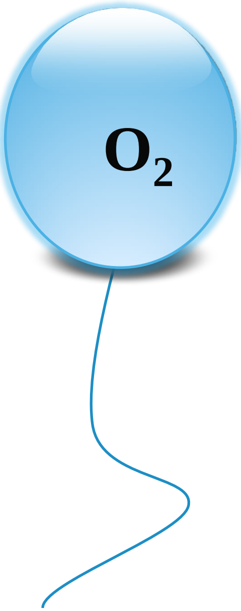
- Introduction
- C-H Oxidation Initiated by Single-Electron Transfer(SET)
- C-H Oxidation that Resemble Organometallic Reactions
- High-Valent Organometallic Copper
- Summary and Outlook
- Acknowledgement

Main ref.: Stahl, *Angew. Chem. Int. Ed*. **2011**, *50*, 11062 – 11087

Introduction

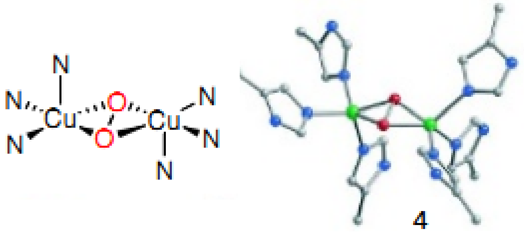
- Selective Oxidation and Oxidative CH functionalization
- Oxidants: TBHP, Oxone, DDQ, IBX, O_2…

wind



- Abundance,
- Low cost,
- Environmentally friendly byproduct(H_2O),
- Potential industrial prospects

Drawback: Poor selectivity



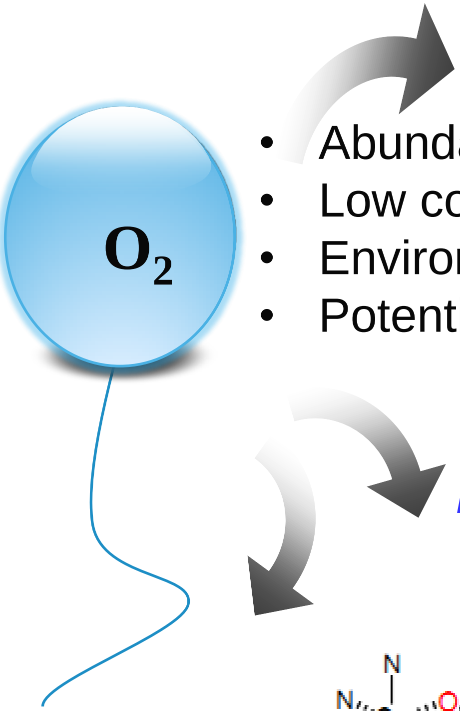
Metalloenzyme intermediate

Tolman, *Nature*, **2008**, *455*, 333 – 340

Introduction

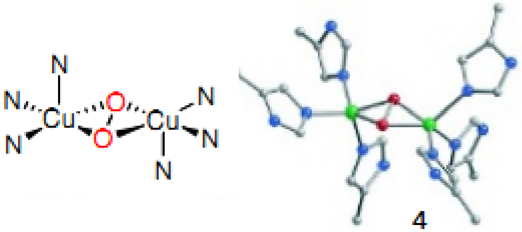
- Selective Oxidation and Oxidative CH functionalization
- Oxidants: TBHP, Oxone, DDQ, IBX, O_2…

wind



- Abundance,
- Low cost,
- Environmentally friendly byproduct(H_2O),
- Potential industrial prospects

High selectivity



Metalloenzyme intermediate

Tolman, *Nature*, **2008**, *455*, 333 – 340

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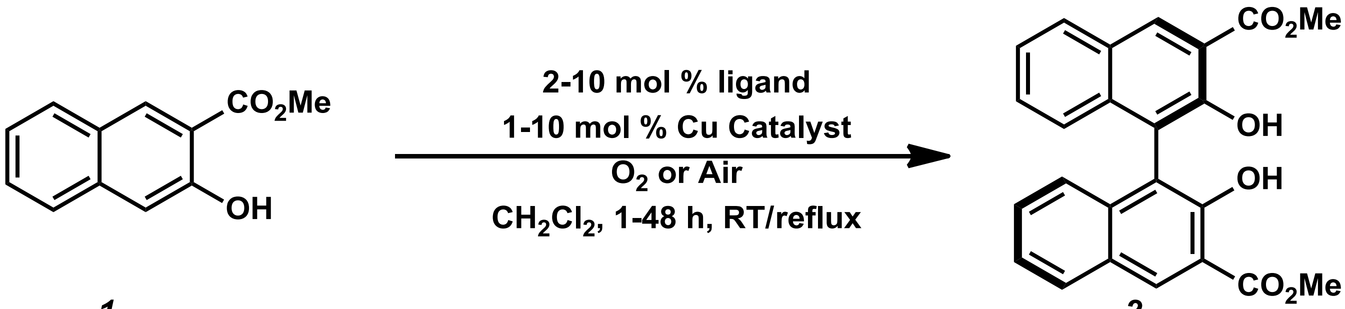
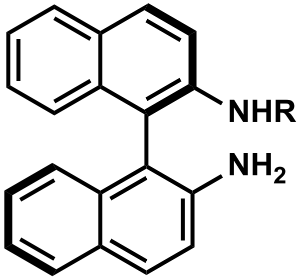
Homocouplings of naphthol derivative



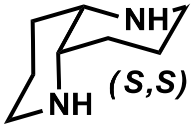
2-10 mol % ligand
1-10 mol % Cu Catalyst
O_2 or Air
CH_2Cl_2, 1-48 h, RT/reflux

1 *2*



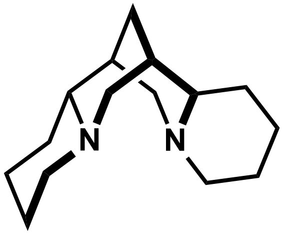
94% ee, 88% yiled
R = 3-pentyl

Ha, 2004



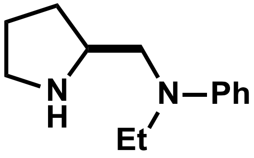
90-93% ee, 85% yiled

Kozlowski, 2001



47% ee, 38% yiled

Nakajima, 1999



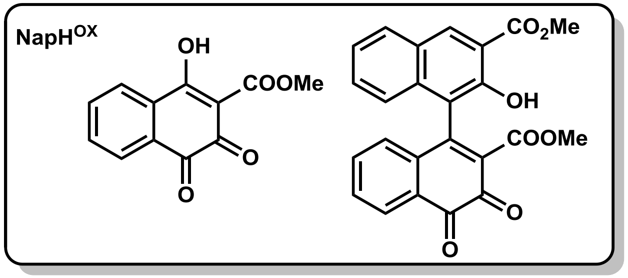
70% ee, 78% yiled

Nakajima, 1995

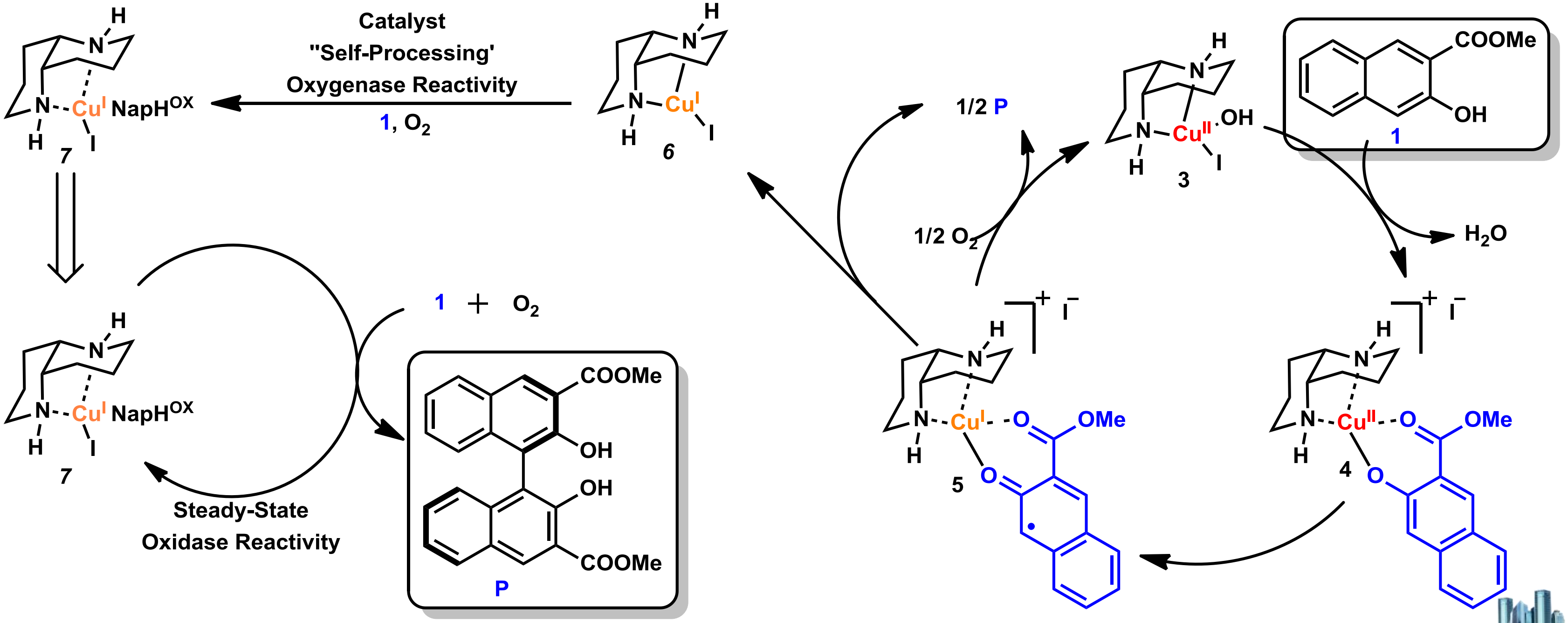
[1] Ha, *Tetrahedron*. **2004**, *60*, 9037 – 9042
[2] Kozlowski, *Org. Lett.* **2001**, *3*, 1137 – 1140
[3] Nakajima, *J. Org. Chem.* **1999**, *64*, 2264 – 2271
[4] Nakajima, *Tetrahedron Lett.* **1995**, *36*, 9519 – 9520

Homocouplings of naphthol derivative

Implicate a striking similarity between this synthetic catalyst system and certain biological copper oxidases, such as copper amine oxidases(CAOs)



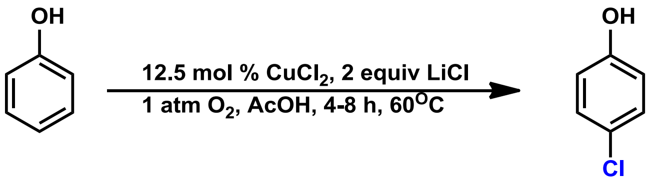
Proposed Mechanism:



[1] Kozlowski, *J. Org. Chem.* **2003**, *68*, 5500 – 5511

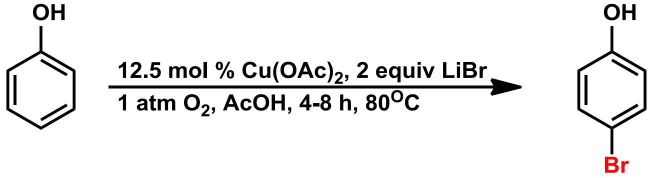
[2] Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 12232 – 12233

Bromination and Clorination of Arenes



8 9

90% GC yield

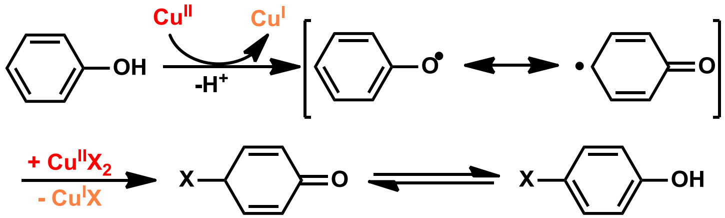


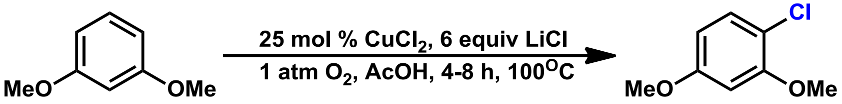
8 10

75% GC yield

para : ortho = 80 : 17

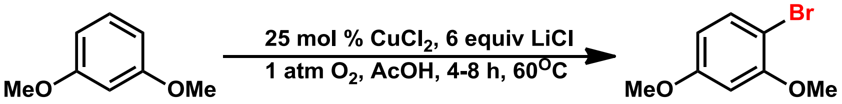
Proposed Mechanism:





11 12

77% yield



11 13

84% yield

Proposed Mechanism:

$$2\,CuBr_2 \longrightarrow 2\,CuBr + Br_2 \qquad (1)$$

$$Ar\text{-}H \quad Br_2 \longrightarrow Ar\text{-}Br + HBr \qquad (2)$$

$$2\,CuBr + 2\,HBr + 1/2\,O_2 \longrightarrow 2\,CuBr_2 + H_2O \qquad (3)$$

$$Ar\text{-}H + HBr + 1/2\,O_2 \longrightarrow 2\,CuBr + H_2O \qquad (4)$$

[1] Gusevskaya, *Chem. Commun.* **2006**, 209 –211
[2] Gusevskaya, *Appl. Catal. A* . **2006**, *309*,122 – 128.
[3] Gusevskaya, *Tetrahedron Lett.* **2007**, *48*, 6401 – 6404.
[4] Stahl, *Chem. Commun*. **2009**, 6460 – 6462.

Proposed Mechanism-- Electrophilic bromination pathway

A

$$2\,CuBr_2 \longrightarrow 2\,CuBr + Br_2 \qquad (1)$$

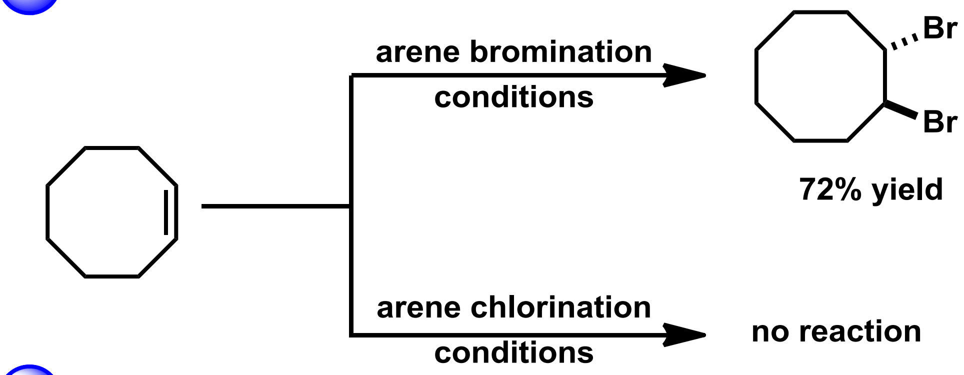
$$Ar\text{-}H \quad Br_2 \longrightarrow Ar\text{-}Br + HBr \qquad (2)$$

$$2\,CuBr + 2\,HBr + 1/2\,O_2 \longrightarrow 2\,CuBr_2 + H_2O \qquad (3)$$

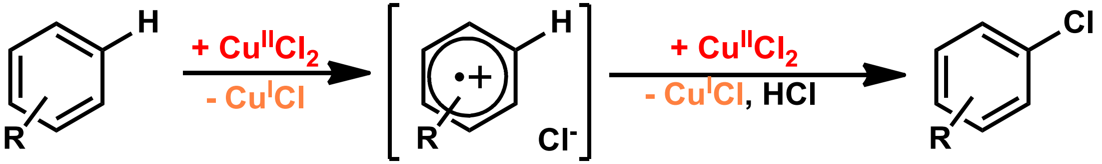
$$Ar\text{-}H + HBr + 1/2\,O_2 \longrightarrow 2\,CuBr + H_2O \qquad (4)$$

'The bromination reaction turn red-brown in color upon heating'

B



C

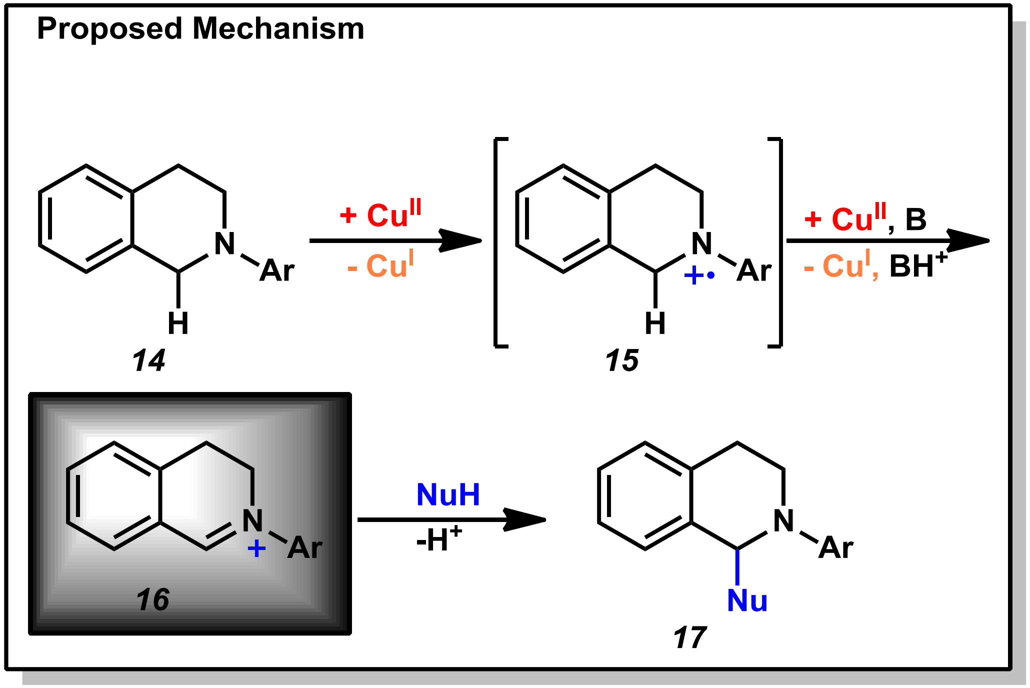


'Direct complexation of the arene to Cu(II) does not appear to be required for halogenation to proceed'

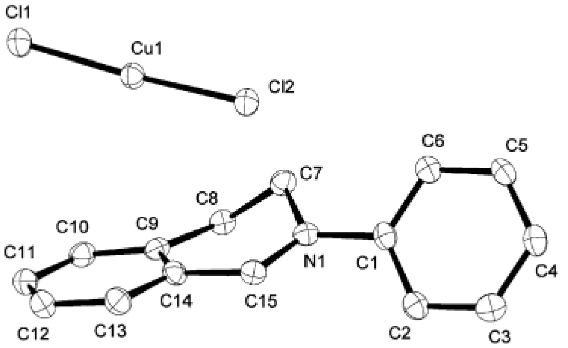
Stahl, *Chem. Commun*. **2009**, 6460 – 6462.

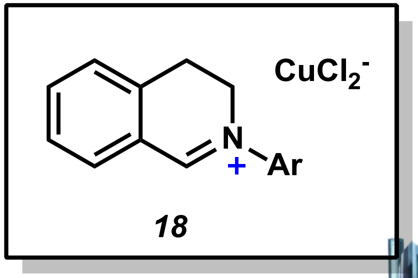
α-Functionalization of Tertiary Amines

- ✓ Cross Dehydrogenative Coupling reaction
- ✓ Typical Oxidants: TBHP or DDQ



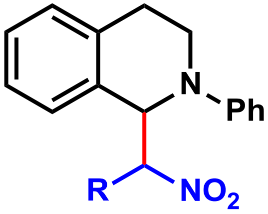
Proposed Mechanism





Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106 – 8109.

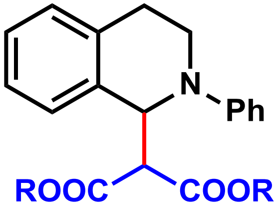
α-Functionalization of Tertiary Amines



19

R = H, 90%

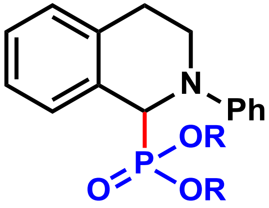
Li, 2007



20

R = Me, 82%

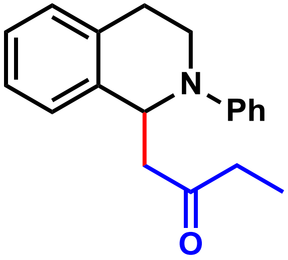
Li, 2009



21

R = Me, 90%

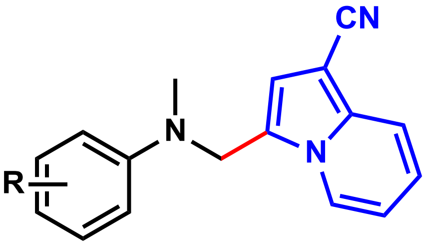
Li, 2009



22

62%

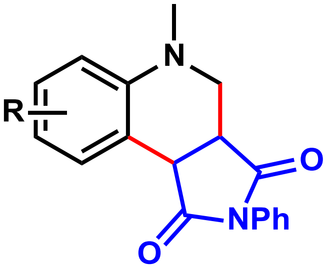
Guo, 2009



23

R = *t*-Bu, 90%

Zhang, 2011



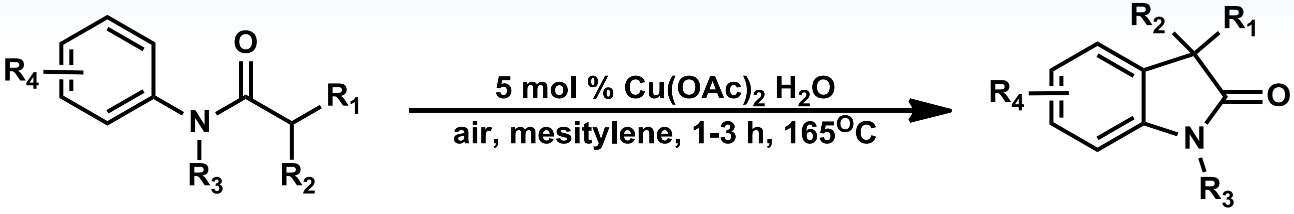
24

R = *t*-Bu, 78%

Miura, 2011

[1] Li, *Green Chem*. **2007**, *9*, 1047 – 1050
[2] Li, *Synlett.* **2009**, 138 –142
[3] Li, *Chem. Commun*. **2009**, 4124 – 4126
[4] Guo, *Chem. Commun.* **2009**, 953 – 955
[5] Zhang, *J. Org. Chem.* **2011**, *76*, 1759 – 1766
[6] Miura, *J. Org. Chem.* **2011**, *76*, 6447 – 6451

Reactions of Amide-Enolates



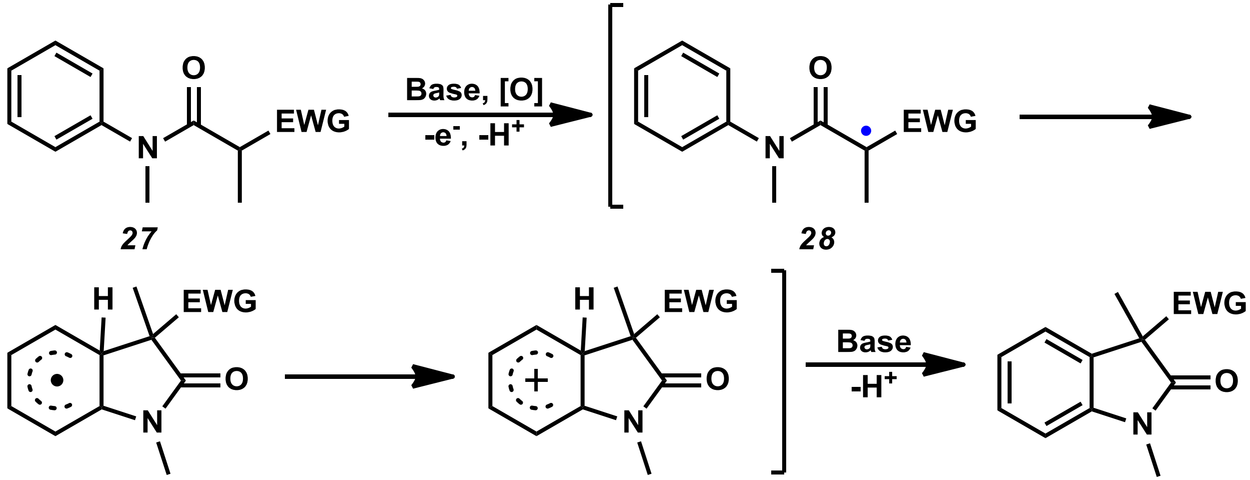
25

26

83-98%

R_1 = CO_2R, CN, Ph; R_2 = alkyl, allyl; R_3 = Me, Bn; R_4 = EWG or EDG

Proposed Mechanism:

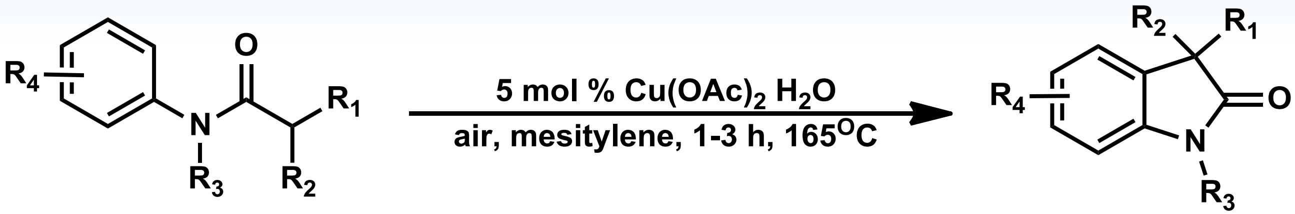


27 ***28***

29 ***30*** ***31***

[1] Taylor, *Org. Lett*. **2010**, *12*, 3446 – 3449
[2] Kündig, *Angew. Chem. Int. Ed*. **2009**, *48*, 1636 – 1639
[2] Taylor, *Chem. Commun*. **2009**, 3249 – 3251

Reactions of Amide-Enolates


5 mol % $Cu(OAc)_2$ H_2O

air, mesitylene, 1-3 h, 165^{O}C

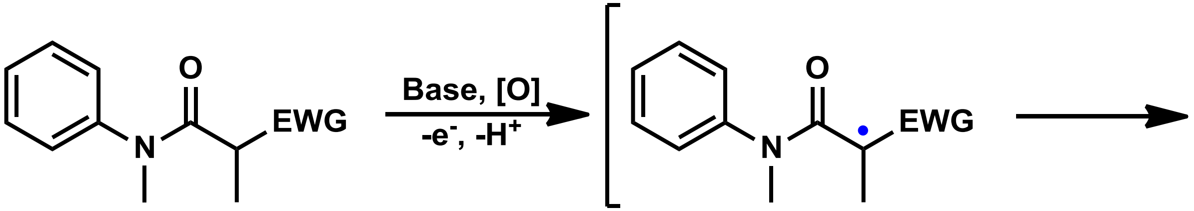
25

26

83-98%

R_1 = CO_2R, CN, Ph; R_2 = alkyl, allyl; R_3 = Me, Bn; R_4 = EWG or EDG

Proposed Mechanism:

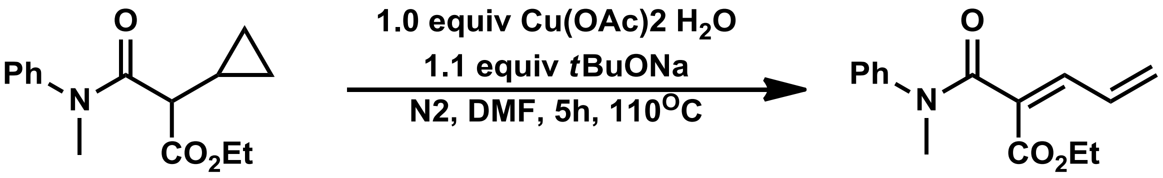

Base, [O]

-e$^-$, -H$^+$

27

28

Radical probe experiment:


1.0 equiv Cu(OAc)2 H_2O

1.1 equiv *t*BuONa

N2, DMF, 5h, 110^{O}C

29

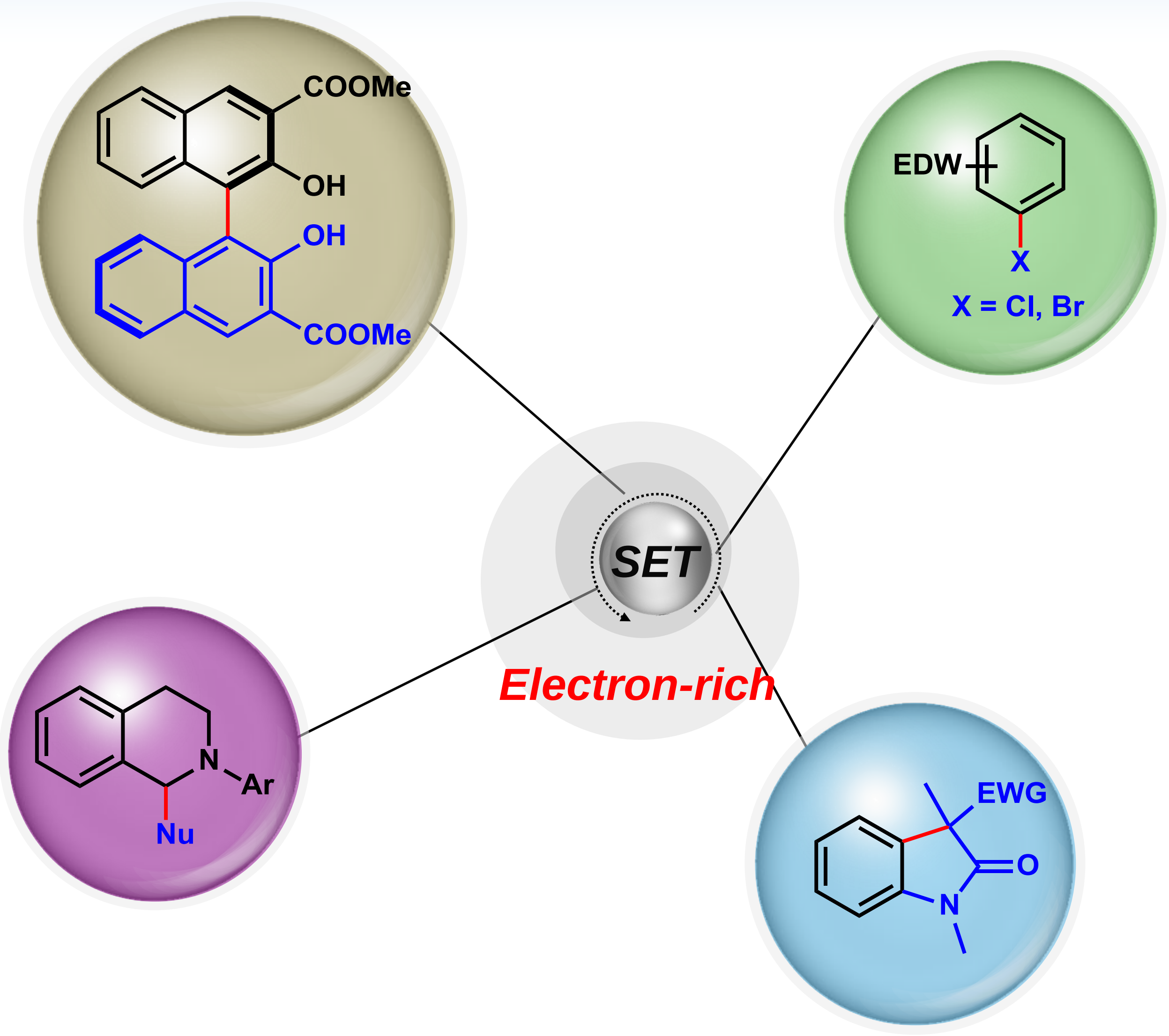
30

[1]Taylor, *Org. Lett*. **2010**, *12*, 3446 – 3449

[2]Kündig, *Angew. Chem. Int. Ed*. **2009**, *48*, 1636 – 1639

[2]Taylor, *Chem. Commun*. **2009**, 3249 – 3251

Summary



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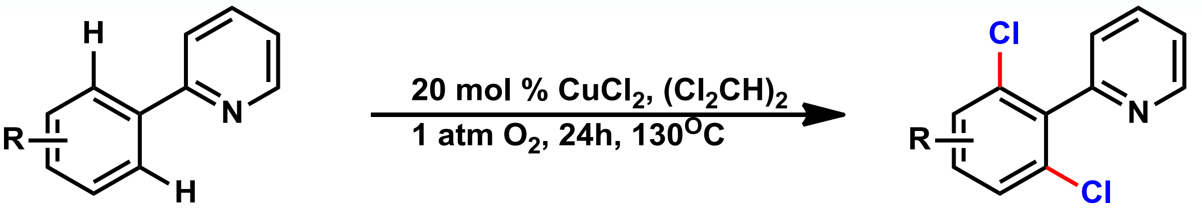
Chelate-Directed C-H Oxidation Reactions



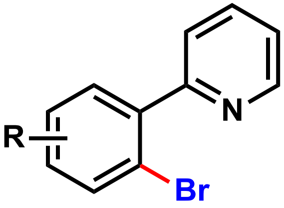
31

32

R = OMe, 93%

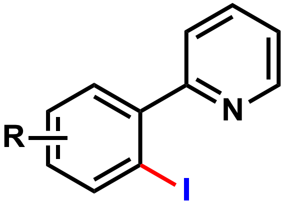
R = CF_3, 20%

Cu(II) mediated diverse CH functionazation



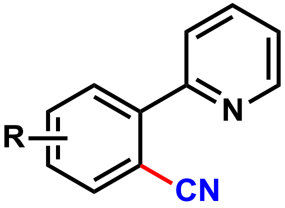
33

65%



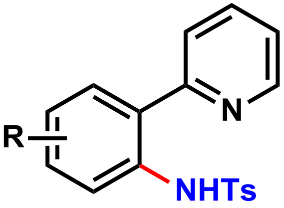
34

61%



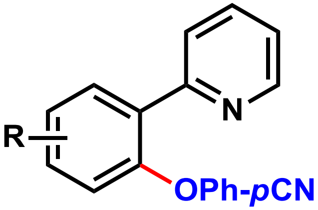
35

42-67%



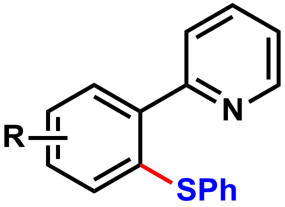
36

74%



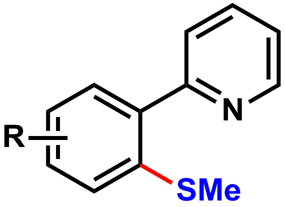
37

35%



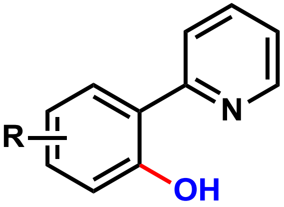
38

40%



39

51%

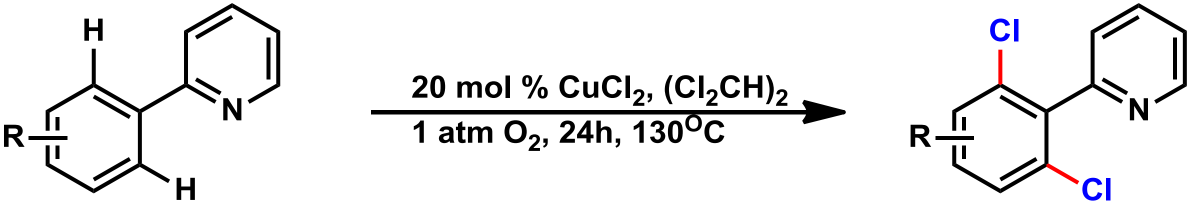


40

67%

Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790 – 6791

Chelate-Directed C-H Oxidation Reactions



31

32

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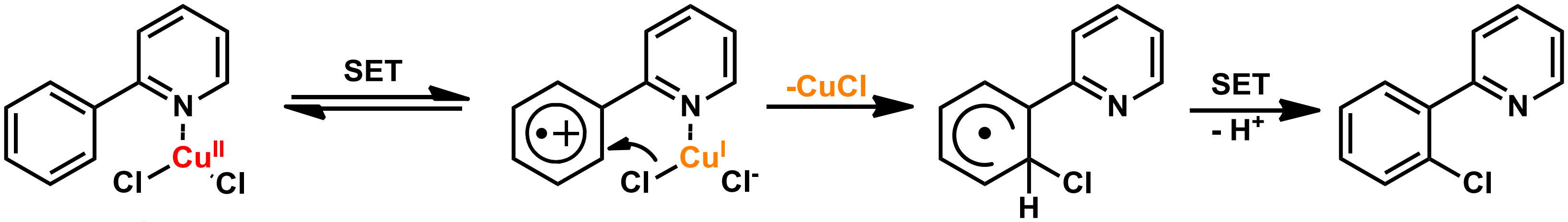
R = CF_3, 20%

Proposed Mechanism:



41

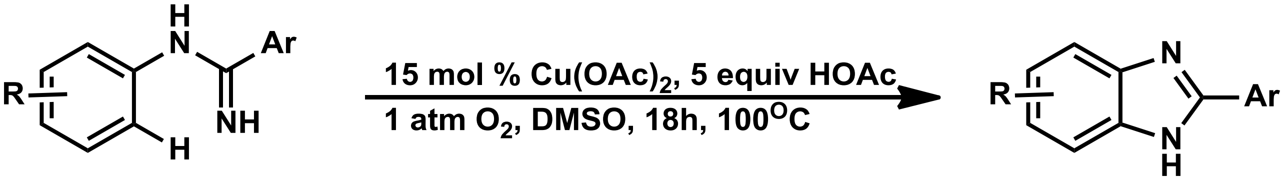
42

43

44

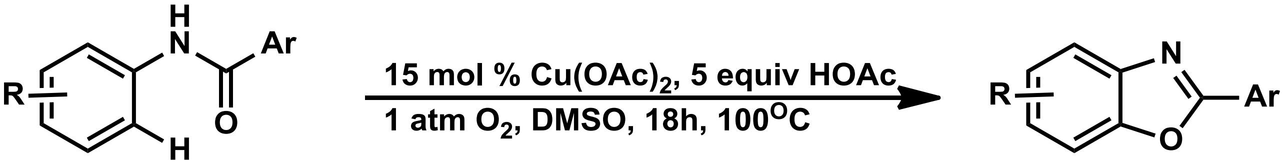
Yu, *J. Am. Chem. Soc*. **2006**, *128*, 6790 – 6791

Oxidative Annulation Reactions



45

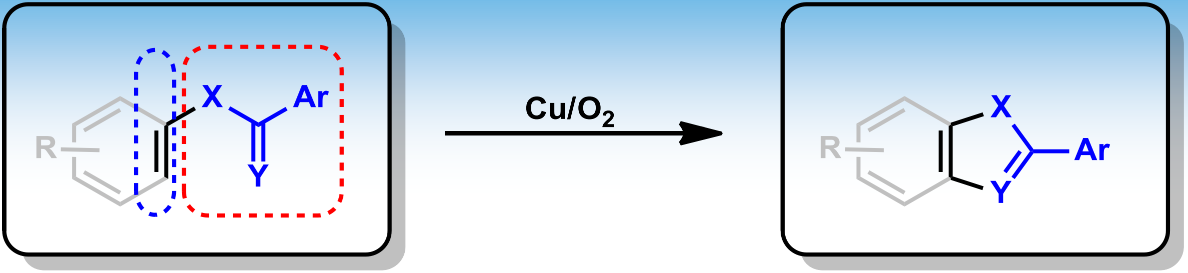
46
68-89%

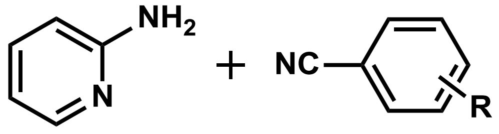


47

48
42-92%

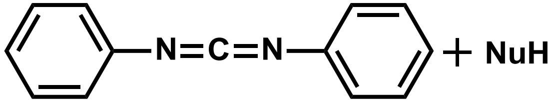
[1] Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 1932 – 1934
[2] Nagasawa, *Angew. Chem. Int. Ed*. **2008**, *47*, 6411 – 6413





49 ***50***

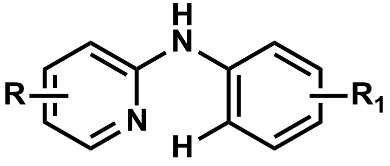
Nagasawa, 2009



51 ***52***

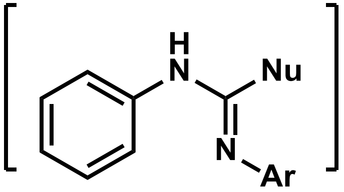
NuH: Alcohol or Amine

Bao, 2010



53

Zhu, 2010



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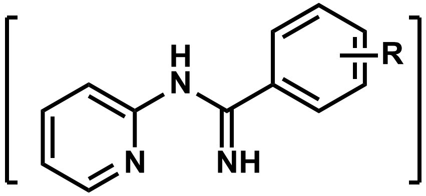
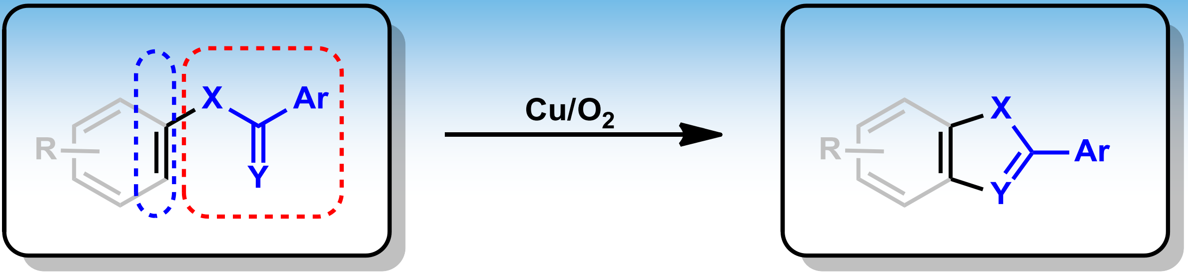
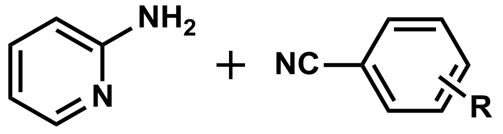


56

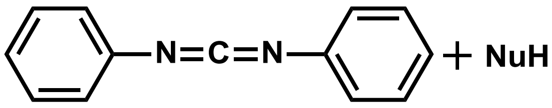
[1] Nagasawa, *J. Am. Chem. Soc.* **2009**, *131*, 15080 – 15081
[2] Bao, *Adv. Synth. Catal.* **2010**, *352*, 2905 – 2912
[3] Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217 – 13219
[4] Punniyamurthy, *Org. Lett.* **2011**,*13*, 1194 – 1197
[5] Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678 – 5681





49 *50*

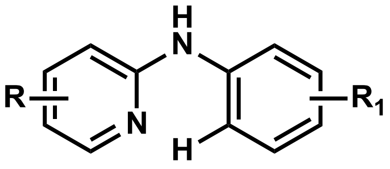
Nagasawa, 2009



51 *52*

NuH: Alcohol or Amine

Bao, 2010



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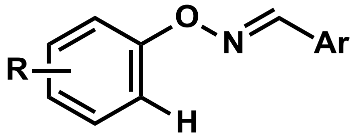
Zhu, 2010



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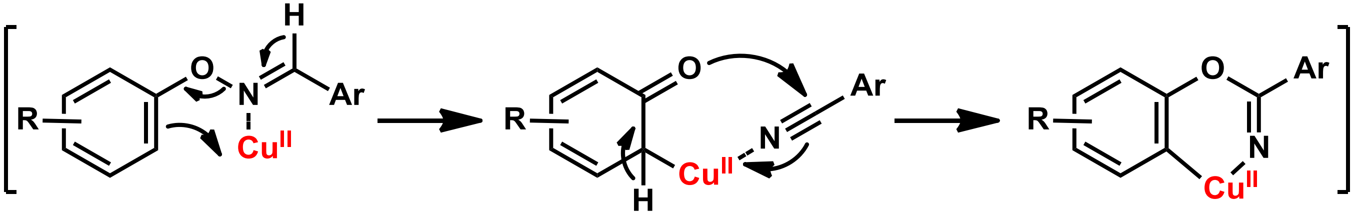
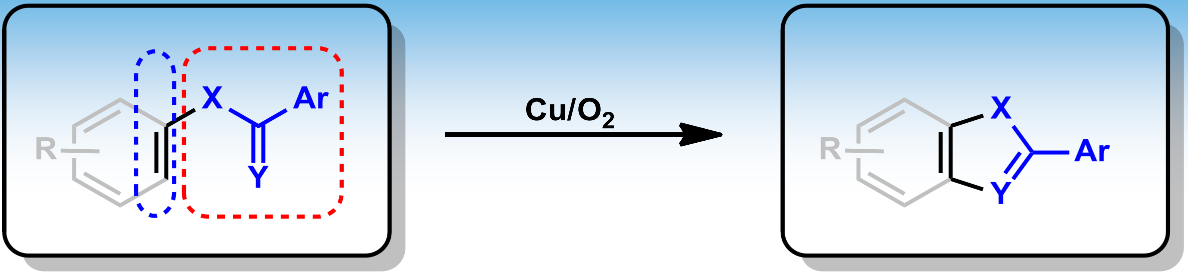
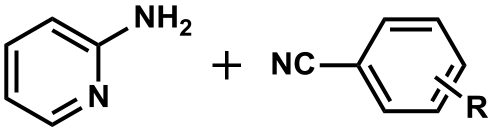
Punniyamurthy, 2011



57 *58* *59*

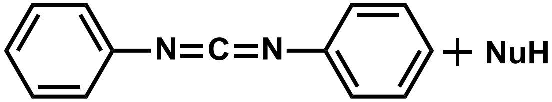
[1] Nagasawa, *J. Am. Chem. Soc.* **2009**, *131*, 15080 – 15081
[2] Bao, *Adv. Synth. Catal.* **2010**, *352*, 2905 – 2912
[3] Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217 – 13219
[4] Punniyamurthy, *Org. Lett.* **2011**,*13*, 1194 – 1197
[5] Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678 – 5681





49 **50**

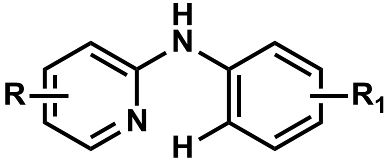
Nagasawa, 2009



51 **52**

NuH: Alcohol or Amine

Bao, 2010



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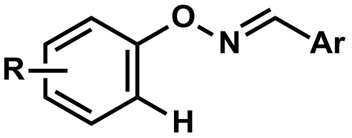
Zhu, 2010



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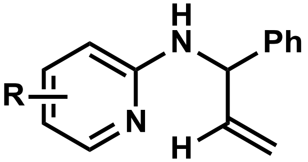
Punniyamurthy, 2011



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Zhu, 2011

[1] Nagasawa, *J. Am. Chem. Soc.* **2009**, *131*, 15080 – 15081
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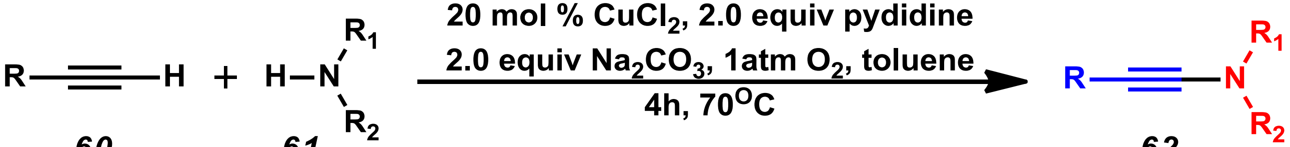
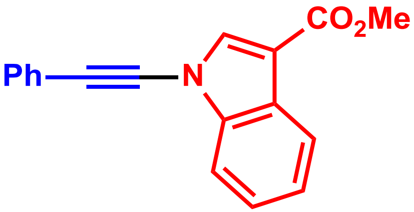
[3] Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217 – 13219
[4] Punniyamurthy, *Org. Lett.* **2011**,*13*, 1194 – 1197
[5] Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678 – 5681

Hetero-Functionalization of Terminal Alkynes



60 *61* *62*



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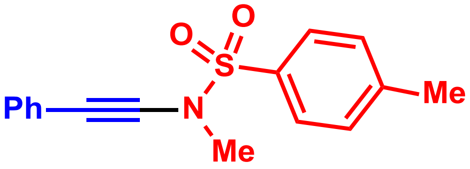
89%



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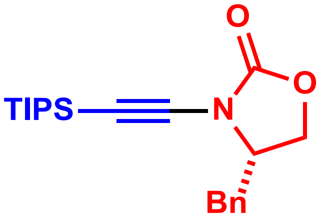

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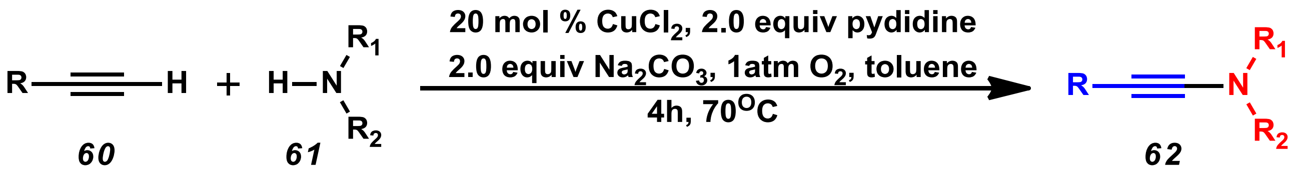
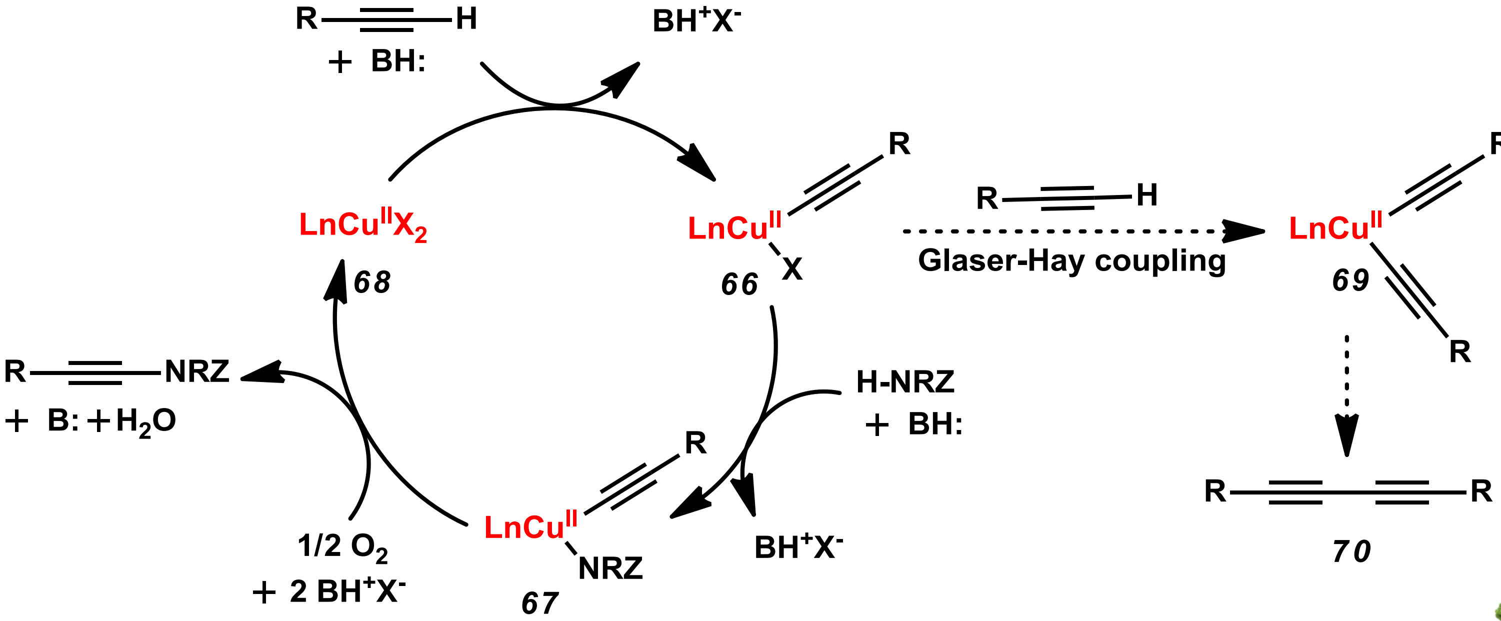
Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833 – 835

Hetero-Functionalization of Terminal Alkynes

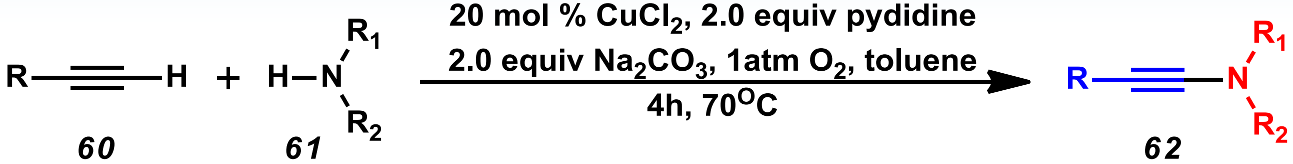


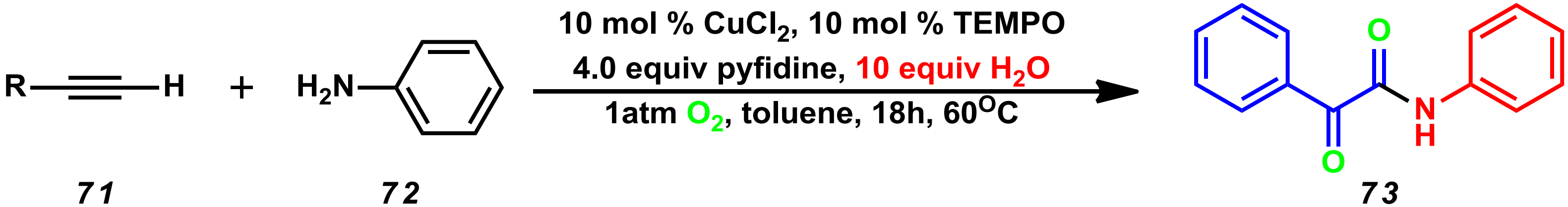
Proposed Mechanism:



Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833 – 835

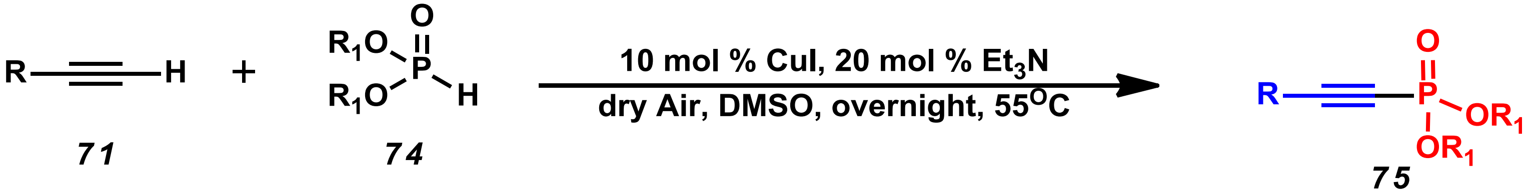
Hetero-Functionalization of Terminal Alkynes





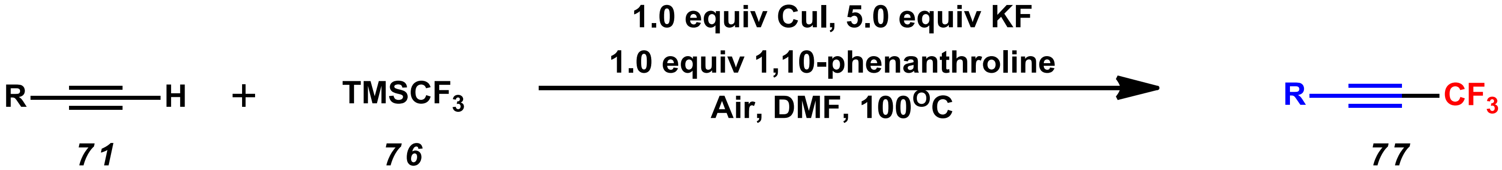
90%

Jiao, 2009



R = Ph, 93%

Han, 2009

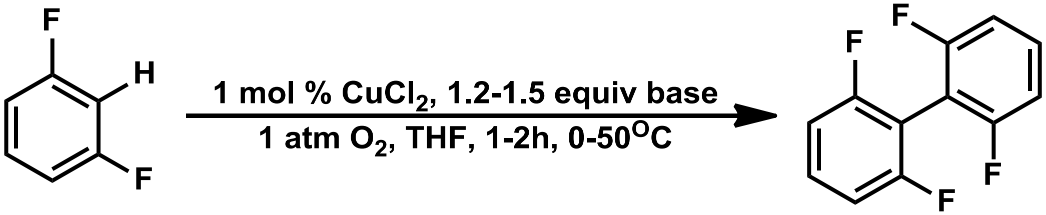


R = Ph, 93%

Qing, 2010

[1] Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833 – 835
[2] Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 28 – 29
[3] Han, *J. Am. Chem. Soc.* **2009**, *131*, 7956 – 7957
[4] Qing, *J. Am. Chem. Soc.* **2010**, *132*, 7262 – 7263

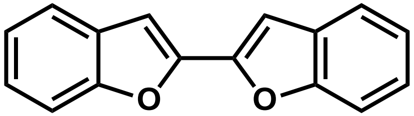
Homo & Cross-Coupling Reactions of Arenes



78

79

71%



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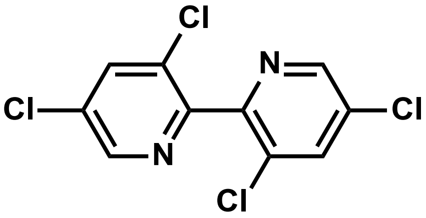

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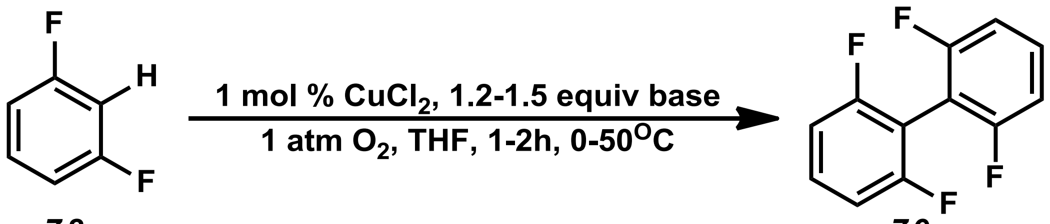
51%

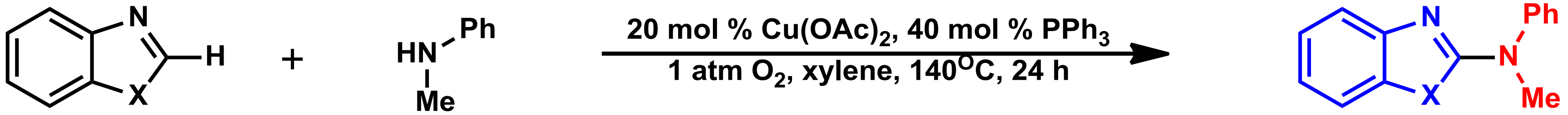
[1] Daugulis, *J. Am. Chem. Soc.* **2009**, *131*, 17052 – 17053

Homo & Cross-Coupling Reactions of Arenes



78 ***79***

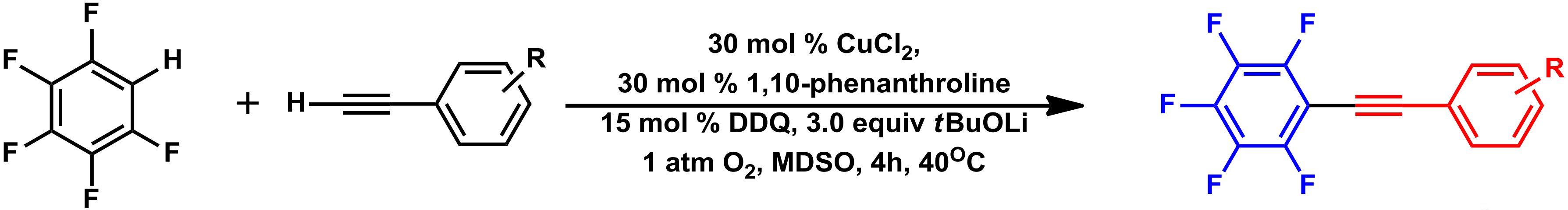
71%



82 ***83*** ***84***

X = S, 81%; = O, 71%; = NMe, 51%

Mori, 2009



85 ***86*** ***87***

R = Me, 72%; R = CF_3, 60%

Hong, 2010

[1] Daugulis, *J. Am. Chem. Soc.* **2009**, *131*, 17052 – 17053

[2] Mori, *Org. Lett*. **2009**, *11*, 1607 – 1610

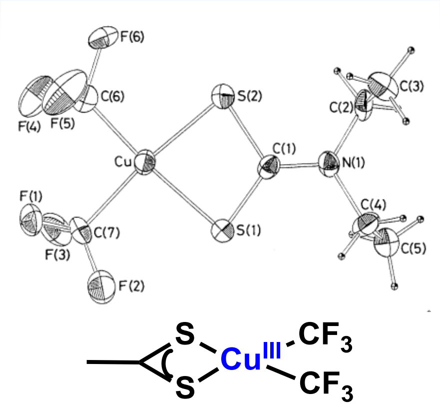
[3] Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522 – 2523

Content

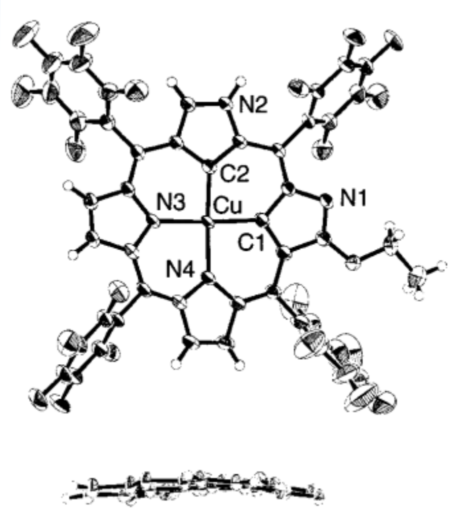
- Introduction
- C-H Oxidation Initiated by Single-Electron Transfer(SET)
- C-H Oxidation that Resemble Organometallic Reactions
- High-Valent Organometallic Copper
- Summary and Outlook
- Acknowledgement

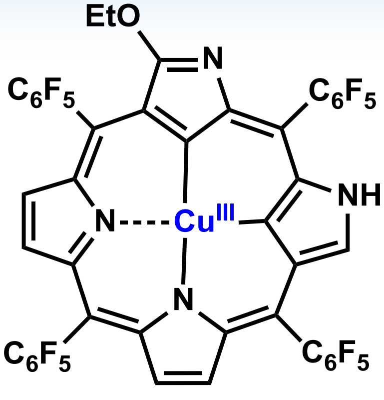
Main ref.: Stahl, *Angew. Chem. Int. Ed*. **2011**, *50*, 11062 – 11087

High-valent organometallic copper



88
Burton, 1989





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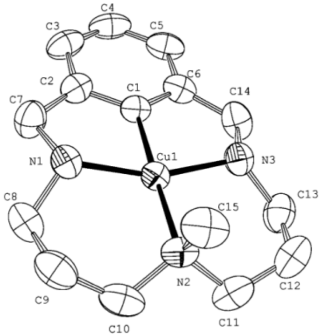
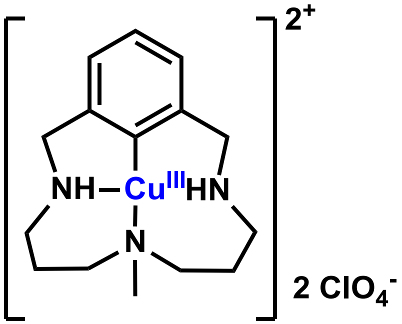
Osuka, 2000





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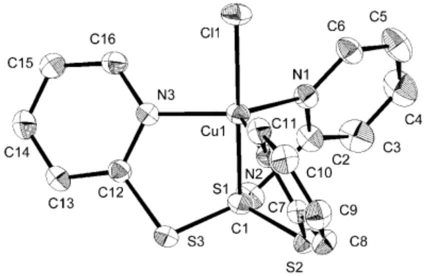
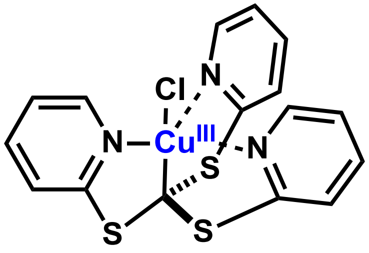
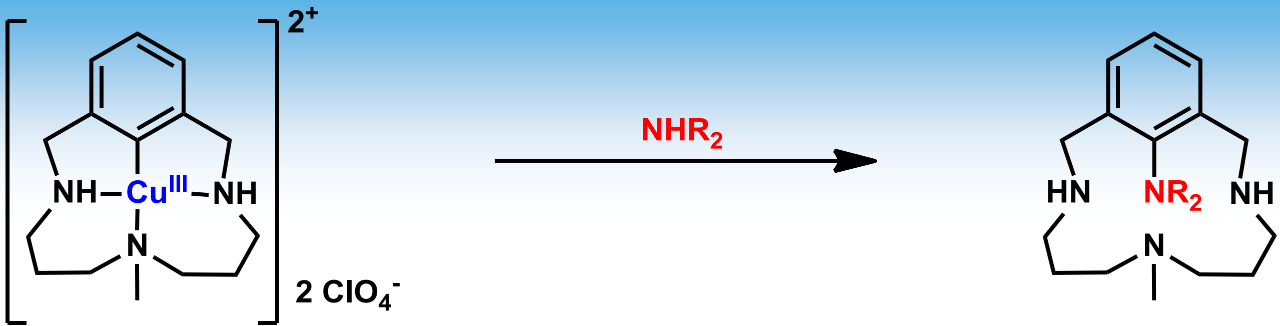
Stack, 2002





91
Takui, 2006

[1] Burton, *J. Chem. Soc. Chem. Commun.* **1989**, 1633–1634
[2] Osuka, *J. Am. Chem. Soc.* **2000**, *122*, 803–807
[3] Stack, *Angew. Chem. Int. Ed*. **2002**, *41*, 2991–2994
[4] Takui, *Angew. Chem. Int. Ed*. **2006**, *45*, 7611–7614



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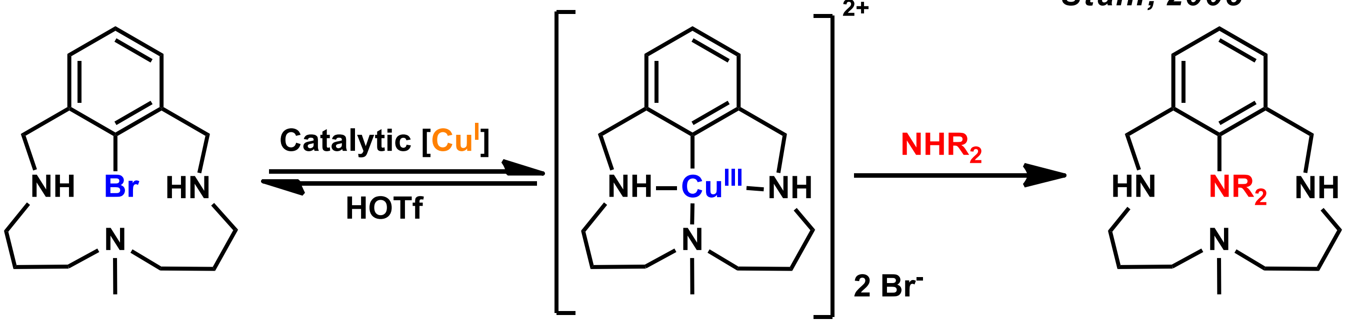
92

Stahl, 2008



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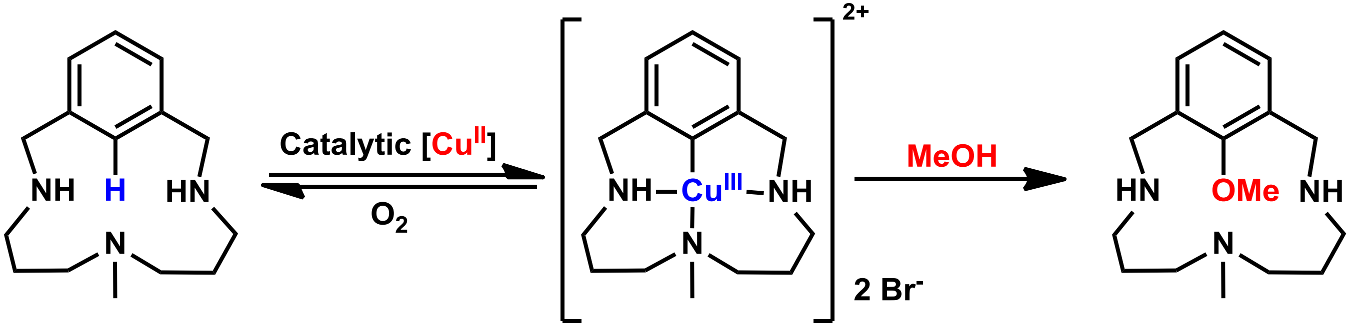
Detected by ultraviolet-visible(UV) and NMR spectroscopy

92

Ribas, 2010



95

94

Detected by UV spectroscopy

96

Stahl, 2010

[1] Stahl, *J. Am. Chem. Soc*. **2008**, *130*, 9196–9197
[2] Ribas, *Chem. Sci.* **2010***, 1*, 326–330
[3] Stahl, *J. Am. Chem. Soc*. **2010**, *132*, 12068–12073

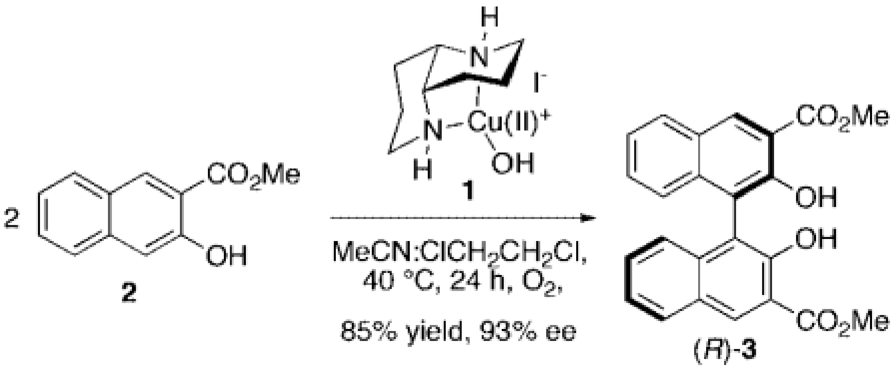
Summary and Outlook

- C-H Oxidation Initiated by Single-Electron Transfer(SET)
- C-H Oxidation that Resemble Organometallic Reactions
- High-Valent Organometallic Copper

Acknowledgement

- Prof. Yong Huang
- All the Professors in SCBB
- All members in E203
- Everyone here

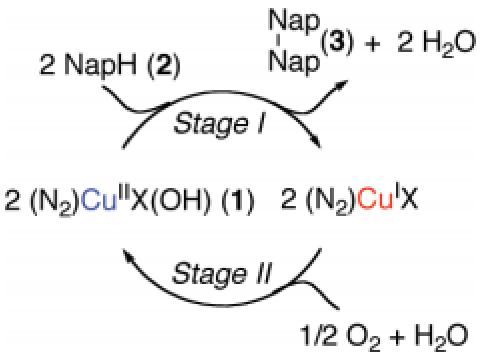
Thank You !

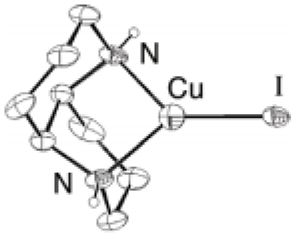


(1)

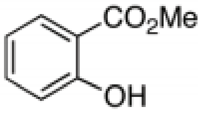
Product **3** forms in a 1:2 ratio with respect to the copper concentration, indicating that **1** serves as a one-electron oxidant.

Scheme 1. Hypothetical "Ping-Pong" Mechanism for Copper-Catalyzed Aerobic Oxidative Biaryl Coupling





$(N_2)Cu^{I}I$ (**4**)



5

enantioselectivity (93% ee) as **1**. Furthermore, treatment with molecular oxygen converts **4** into **1**. In the absence of the naphthol substrate **2**, O_2-uptake measurements reveal a **4**/O_2 stoichiometry of 4:1 with or without unreactive substrate analogue **5**. Although

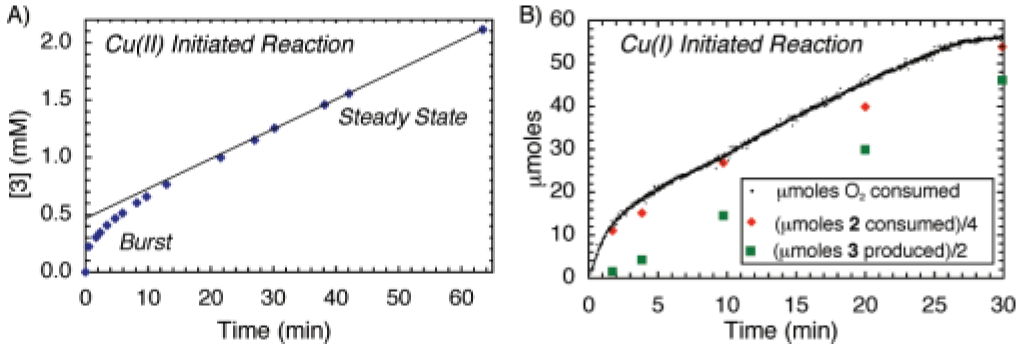


Figure 1. (A) Kinetic time course for product (**3**) formation in the OBC with catalyst **1** from HPLC. Conditions: [**2**] = 94 mM, [4-biphenyl phenyl ether] = 23 mM, [**1**] = 2 mM, atmospheric O_2, MeCN, 40 °C. (B) Kinetic time course for the OBC with catalyst **4**. (Blue) Actual O_2 uptake; (red) *µ*mols [**2**] consumed divided by 4; (green) *µ*mols [**3**] formed divided by 2. Conditions: [**2**] = 151 mM, [**4**] = 10 mM, pO_2 = 840 Torr, [4-biphenyl phenyl ether] = 42 mM, 6 mL of MeCN, 40 °C. Concentrations of **2** and **3** determined by GC.

continuous gas manometry. When the reaction was initiated with Cu^{II} complex **1**, the time course (Figure 1A) revealed an initial burst of product formation followed by slower steady-state turnover. The burst reflects stoichiometric oxidation of the substrate by **1**, resulting in formation of ~0.5 equiv of product. The slower steady-state rate suggests that the chemistry of OBC (Stage I, Scheme 1)

is not rate determining and points to reoxidation of the catalyst by O_2 (Stage II, Scheme 1) as the rate-determining step.

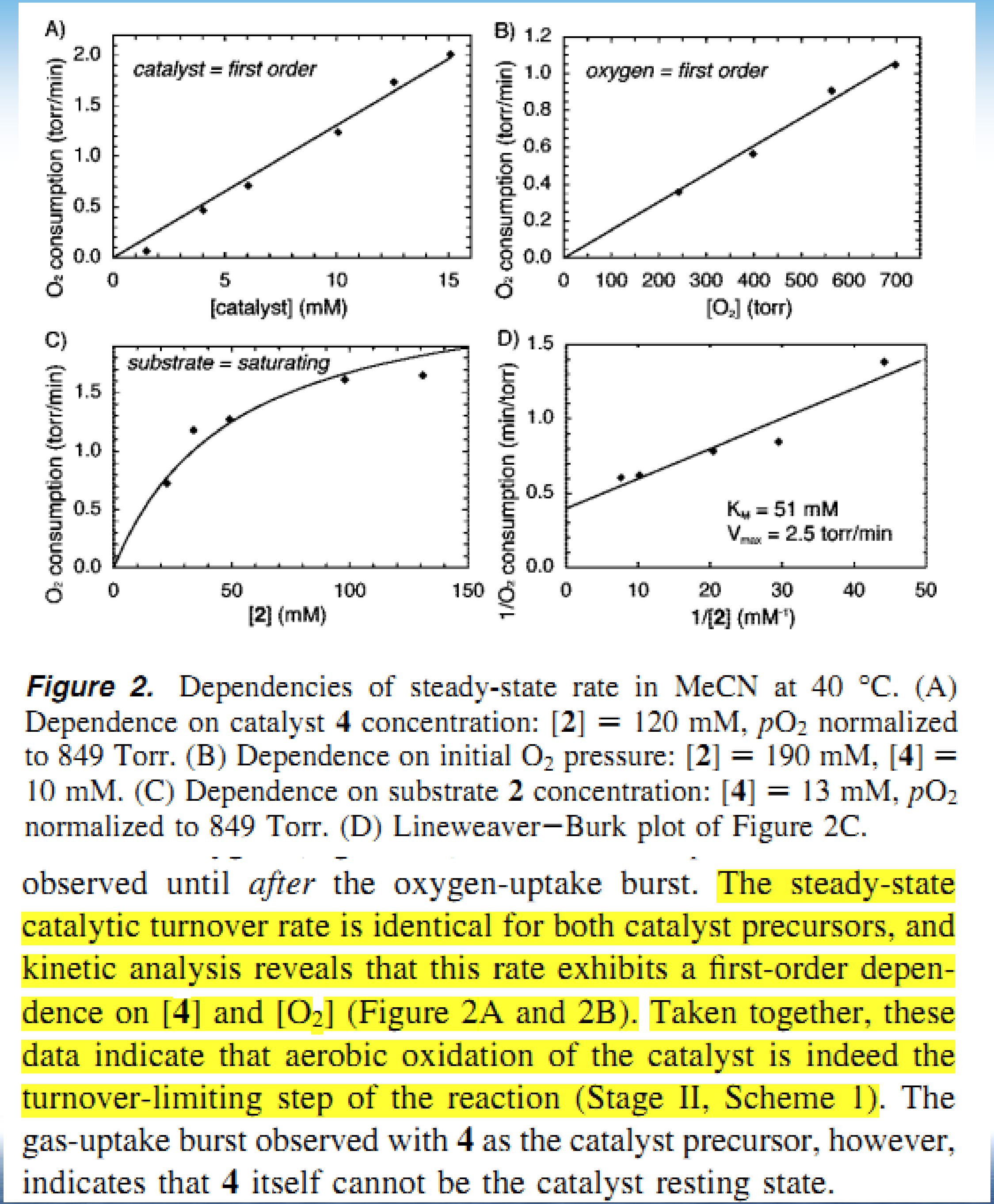
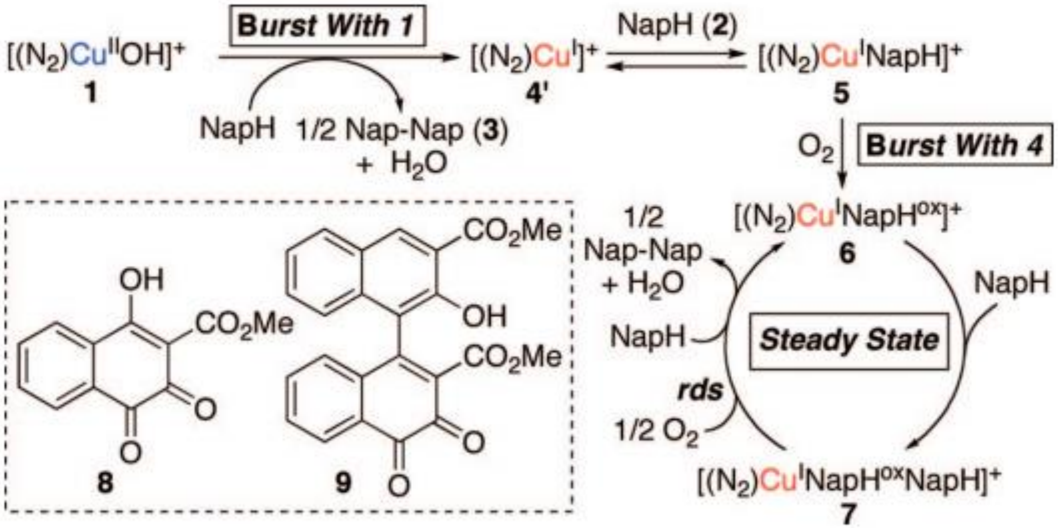


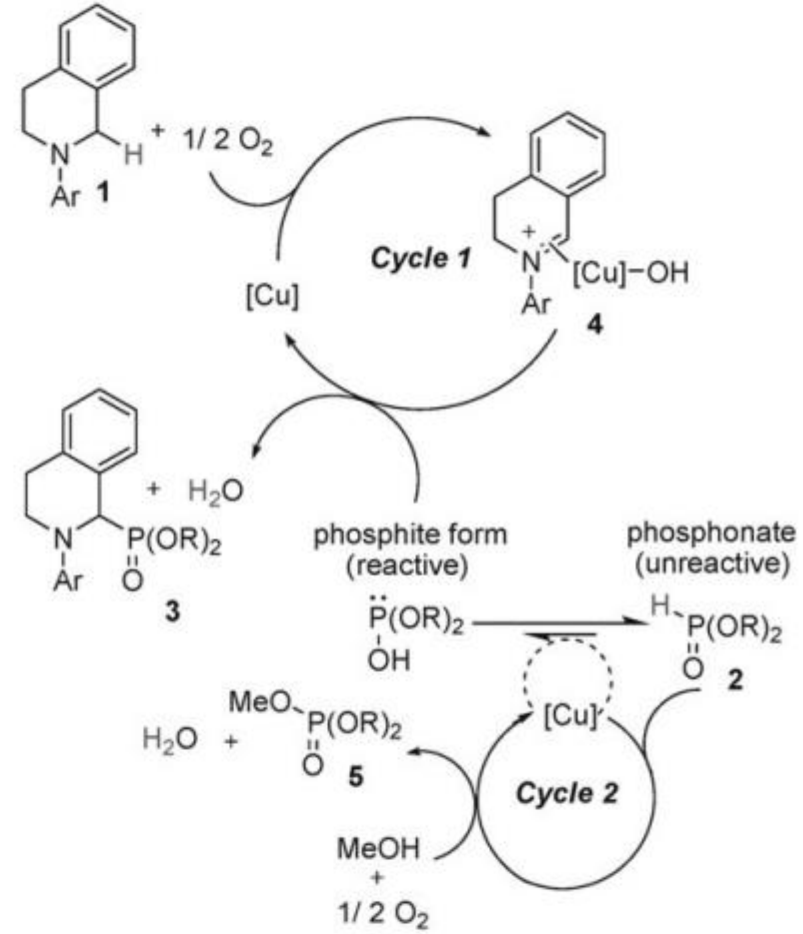
Figure 2. Dependencies of steady-state rate in MeCN at 40 °C. (A) Dependence on catalyst **4** concentration: [**2**] = 120 mM, pO_2 normalized to 849 Torr. (B) Dependence on initial O_2 pressure: [**2**] = 190 mM, [**4**] = 10 mM. (C) Dependence on substrate **2** concentration: [**4**] = 13 mM, pO_2 normalized to 849 Torr. (D) Lineweaver−Burk plot of Figure 2C.

observed until *after* the oxygen-uptake burst. The steady-state catalytic turnover rate is identical for both catalyst precursors, and kinetic analysis reveals that this rate exhibits a first-order dependence on [**4**] and [O_2] (Figure 2A and 2B). Taken together, these data indicate that aerobic oxidation of the catalyst is indeed the turnover-limiting step of the reaction (Stage II, Scheme 1). The gas-uptake burst observed with **4** as the catalyst precursor, however, indicates that **4** itself cannot be the catalyst resting state.

the burst phase is complete. During steady-state turnover, substrate **2** is converted exclusively into product **3** (Figure 1B). These results suggest selective *oxidase* reactivity arises from enlistment of a cofactor, **NapH^{OX}**, formed in a catalyst “self-processing” event analogous to that characterized in biological catalysts, such as amine oxidases.[7] We speculate that the combination of **NapH^{OX}** with the

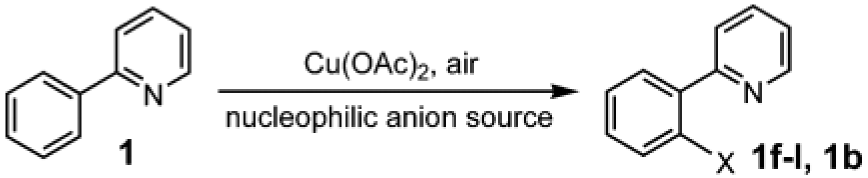
Scheme 2. “Sequential” Mechanism for Copper-Catalyzed Aerobic OBC Consistent with the Kinetic Data





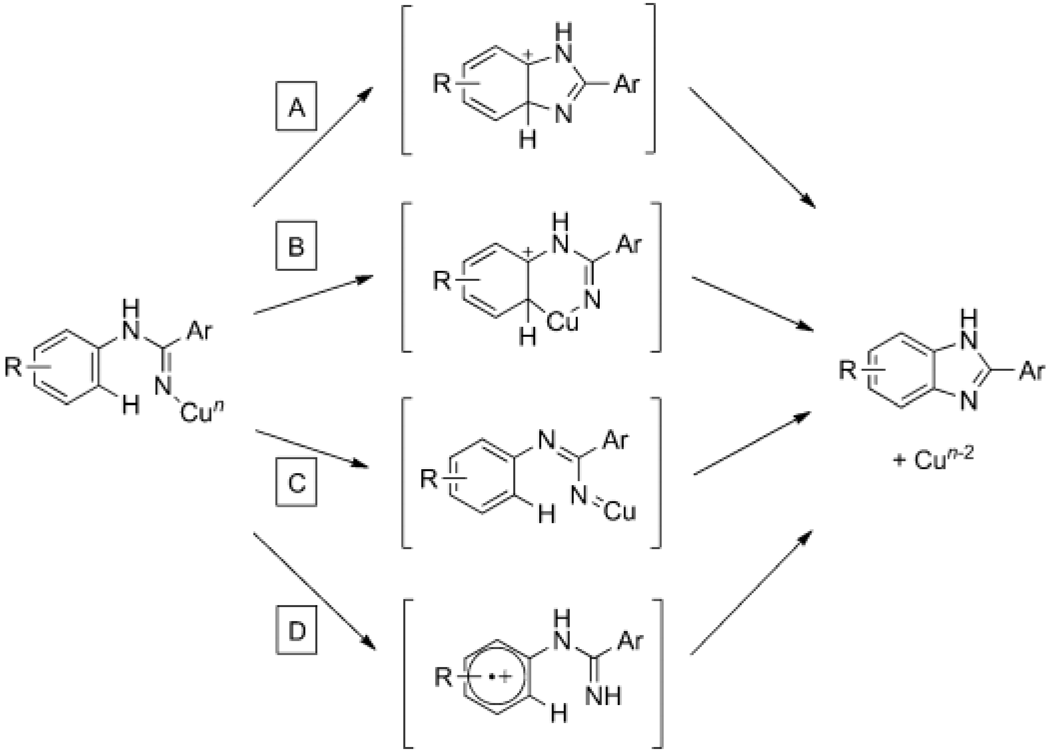
Scheme 2 A tentative mechanism for the oxidative phosphonation reaction.

Table 2. Cu(II)-Mediated Diverse C−H Functionalizations[a]

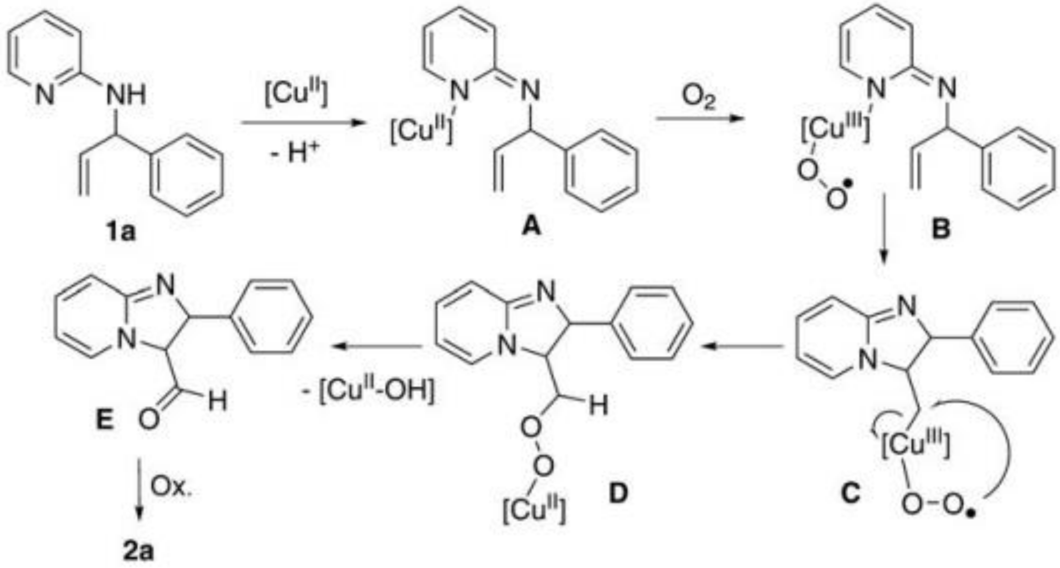


entry	anion source	solvent	product (X)	yield
1	−	$Br_2CHCHBr_2$	Br, **1f**	65%[d]
2	I_2	$ClCH_2CH_2Cl$	I, **1g**	61%[b,d]
3	TMSCN	MeCN	CN, **1h**	42%
4	−	$MeNO_2$	CN, **1h**	67%
5	$TsNH_2$	MeCN	TsNH, **1i**	74%
6	*p*-CN-PhOH	MeCN	*p*-CN-PhO, **1j**	35%
7	PhSH	DMSO	PhS, **1k**	40%
8	MeSSMe	DMSO	MeS, **1l**	51%[d]
9	H_2O	DMSO	OH, **1b**	22%[c]

[a] With 1 equiv of Cu(OAc)$_2$, air, solvent, 130 °C, 24 h. [b] At 100 °C, 8 h. [c] With 1 equiv of CuF$_2$. [d] Difunctionalized products (10−20%) were also obtained.

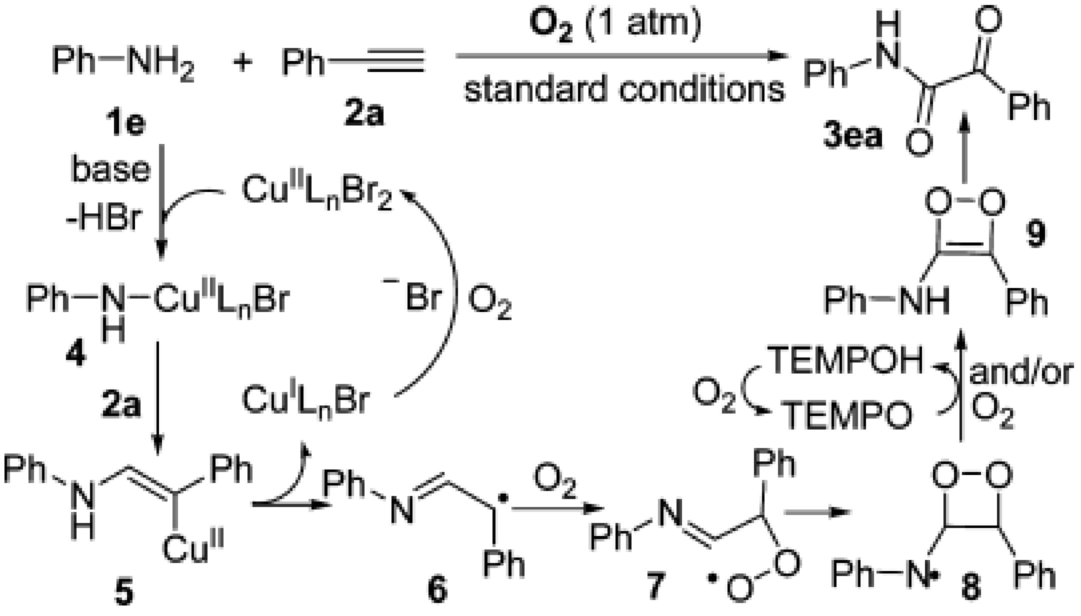


Scheme 31. Proposed mechanisms considered for benzoxazole/benzimidazole formation.

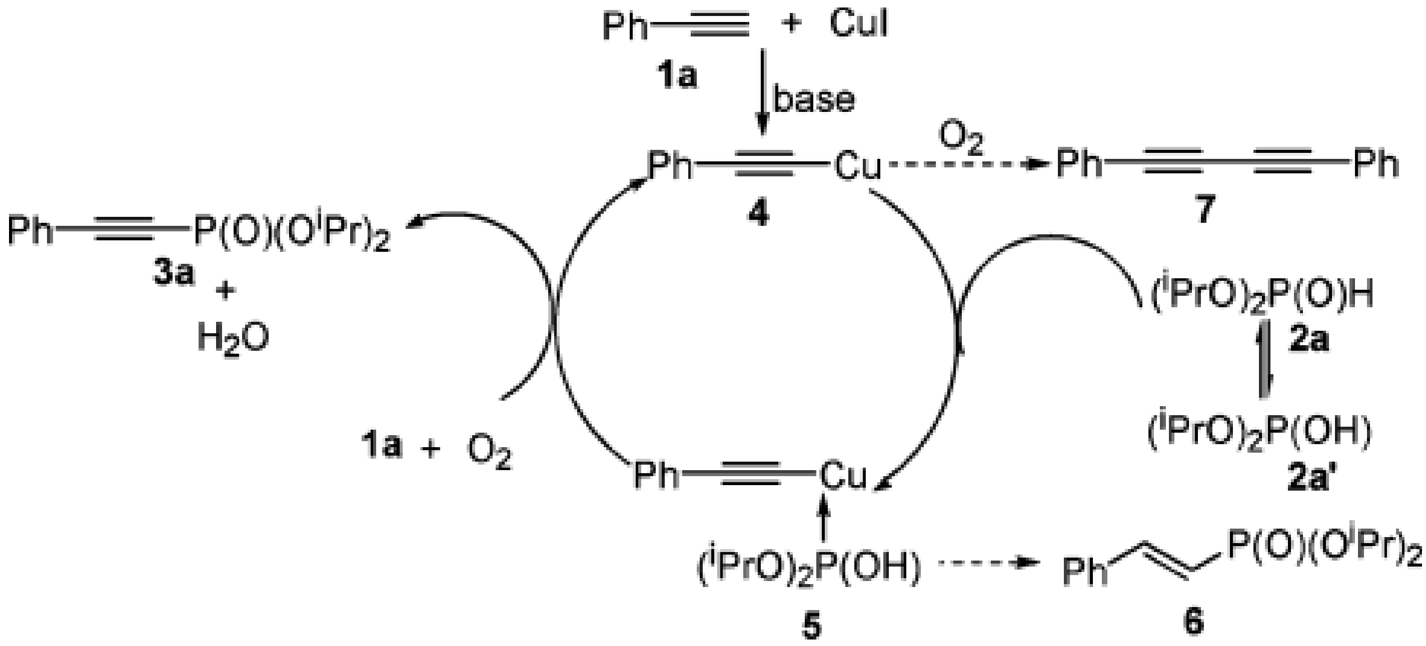


Scheme 7. Plausible mechanism.

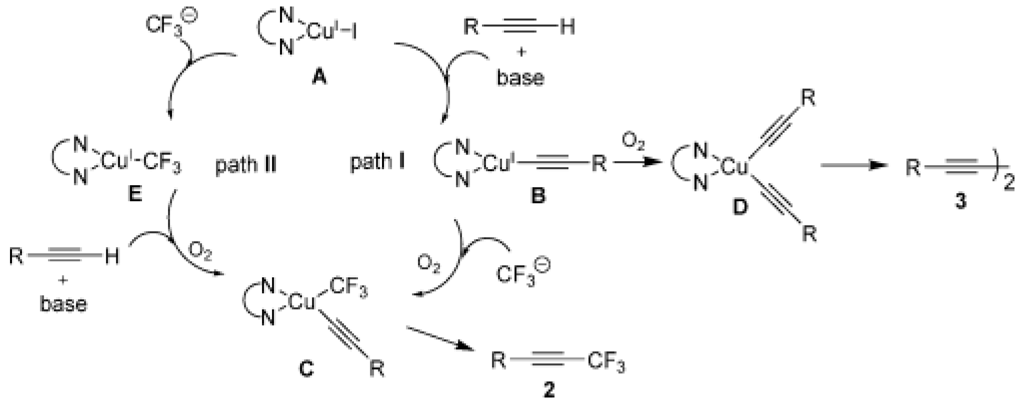
Scheme 1. Proposed Mechanism for the Direct Transformation

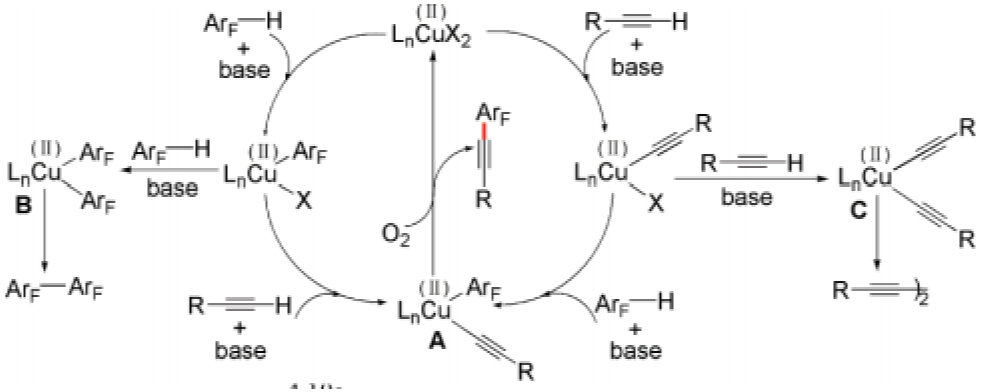


Scheme 1. Proposed Reaction Path



Scheme 1. Plausible Reaction Pathways for Trifluoromethylation

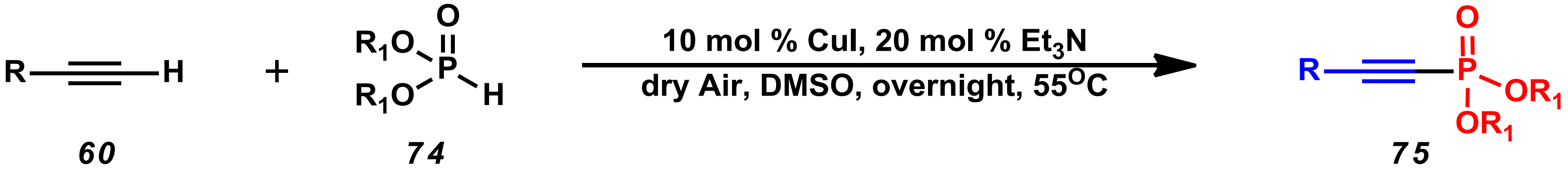



(II)
L$_n$CuX$_2$
Ar$_F$—H
+
base
R—≡—H
+
base
(II)
L$_n$Cu
Ar$_F$
Ar$_F$
B
Ar$_F$—H
base
(II)
L$_n$Cu
Ar$_F$
X
Ar$_F$
R
O$_2$
(II)
L$_n$Cu
R
X
R—≡—H
base
(II)
L$_n$Cu
R
R
C
Ar$_F$—Ar$_F$
R—≡—H
+
base
(II)
L$_n$Cu
Ar$_F$
A
R
Ar$_F$—H
+
base
R—≡—)$_2$

Scheme 4. Bases Employed in Dimerization

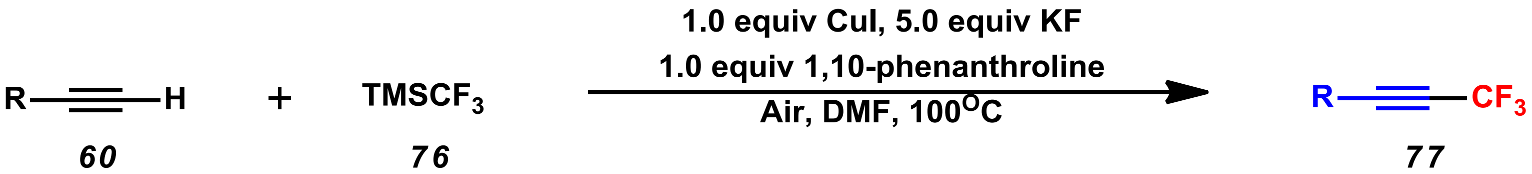
Base 1	*i*PrMgCl*LiCl + tetramethylpiperidine (1:1.1)
Base 2	Base 1 + $ZnCl_2$ (1:0.25)
Base 3	Dicyclohexylamine + *i*PrMgCl*LiCl + $ZnCl_2$ (1.1:1:0.25)
Base 4	Base 1 + $ZnCl_2$ (1:0.5)

Hetero-Functionalization of Terminal Alkynes and Electron Deficient Heteroarenes



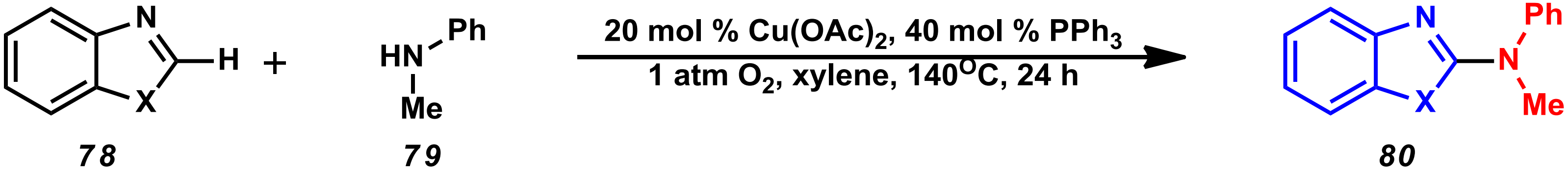
R = Ph, 93%

Han, 2009



R = Ph, 93%

Qing, 2010



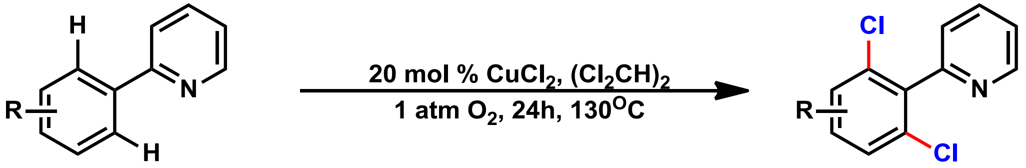
X = S, 81%;
= O, 71%;
= NMe, 51%

Mori, 2009

[3] Mori, *Org. Lett.* **2009**, *11*, 1607 – 1610

Summary

Chelated-Direacted C-H Oxidation Reactions

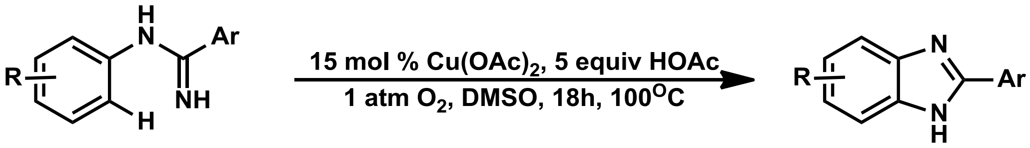


20 mol % $CuCl_2$, $(Cl_2CH)_2$

1 atm O_2, 24h, 130^{O}C

31 *32*

Oxidative Annulation Reactions



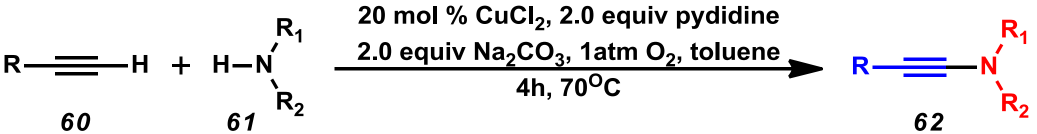
15 mol % $Cu(OAc)_2$, 5 equiv HOAc

1 atm O_2, DMSO, 18h, 100^{O}C

45 *46*

68-89%

Hetero-Functionalization of Terminal Alkynes



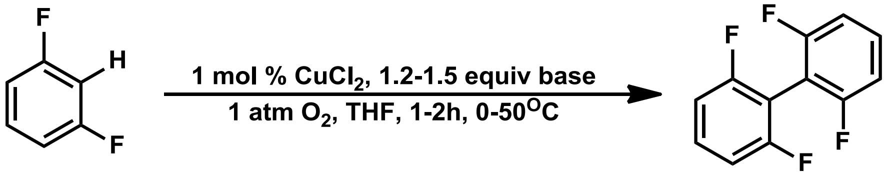
20 mol % $CuCl_2$, 2.0 equiv pydidine

2.0 equiv Na_2CO_3, 1atm O_2, toluene

4h, 70^{O}C

60 *61* *62*

Homo & Cross-Coupling Reactions of Arenes



1 mol % $CuCl_2$, 1.2-1.5 equiv base

1 atm O_2, THF, 1-2h, 0-50^{O}C

78 *79*

71%