Copper-Catalyzed Aerobic Oxidative C-H Functionalizations

Supervisor: Prof. Yong Huang

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, O₂...

- Abundance,
- Low cost,
- Environmentally friendly byproduct (H₂O),
- Potential industrial prospects

Drawback: Poor selectivity

Metalloenzyme intermediate

Introduction

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

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

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
Homocouplings of naphthol derivative

\[ \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \]
\[ \text{OH} \quad \text{OH} \]

2-10 mol % ligand
1-10 mol % Cu Catalyst

\[ \text{O}_2 \text{ or Air} \]
\[ \text{CH}_2\text{Cl}_2, 1-48 \text{ h, RT/reflux} \]

1

2

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

90-93% ee, 85% yield

47% ee, 38% yield

70% ee, 78% yield

Ha, 2004
Kozlowski, 2001
Nakajima, 1999
Nakajima, 1995

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. **Catalyst**
   - "Self-Processing" Oxygenase Reactivity
   - 1, O₂

2. **Steady-State Oxidase Reactivity**
   - 1 + O₂

3. **1/2 P**
   - 1/2 O₂
   - H₂O

4. **Step 5**
   - 5

5. **Step 6**
   - 6

6. **Step 7**
   - 7

References:

**Bromination and Chlorination of Arenes**

![Chemical reactions and mechanisms]

**Proposed Mechanism:**

1. 
   
   ![Reaction mechanism diagram]

   Proposed reaction steps:
   - 2 CuBr₂ → 2 CuBr + Br₂
   - Ar-H + Br₂ → Ar-Br + HBr
   - 2 CuBr + 2 HBr + 1/2 O₂ → 2 CuBr₂ + H₂O
   - Ar-H + HBr + 1/2 O₂ → 2 CuBr + H₂O

**References:**

Proposed Mechanism-- Electrophilic bromination pathway

A

\[ 2 \text{CuBr}_2 \rightarrow 2 \text{CuBr} + \text{Br}_2 \] (1)

\[ \text{Ar-H} + \text{Br}_2 \rightarrow \text{Ar-Br} + \text{HBr} \] (2)

\[ 2 \text{CuBr} + 2 \text{HBr} + \frac{1}{2} \text{O}_2 \rightarrow 2 \text{CuBr}_2 + \text{H}_2\text{O} \] (3)

\[ \text{Ar-H} + \text{HBr} + \frac{1}{2} \text{O}_2 \rightarrow 2 \text{CuBr} + \text{H}_2\text{O} \] (4)

‘The bromination reaction turn red-brown in color upon heating’

B

\[ \text{arene bromination conditions} \rightarrow \text{72\% yield} \]

C

\[ \text{H} \]

\[ \text{+ Cu}^{II}\text{Cl}_2 - \text{Cu}^{I}\text{Cl} \]

\[ \text{Cl}^- \]

\[ \text{+ Cu}^{II}\text{Cl}_2 - \text{Cu}^{I}\text{Cl}, \text{HCl} \]

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

α-Functionalization of Tertiary Amines

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

α-Functionalization of Tertiary Amines

Reactions of Amide-Enolates

![Chemical structure and reaction scheme]

$\text{R}_1 = \text{CO}_2\text{R}, \text{CN}, \text{Ph}; \text{R}_2 = \text{alkyl}, \text{allyl}; \text{R}_3 = \text{Me}, \text{Bn}; \text{R}_4 = \text{EWG or EDG}$

Proposed Mechanism:

1. Base, [O]
2. $-e^-, -H^+$
3. Formation of intermediate 28
4. Base, $-H^+$

Reactions of Amide-Enolates

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

Proposed Mechanism:

Radical probe experiment:

Summary

Electron-rich

SET
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
Chelate-Directed C-H Oxidation Reactions

\[ \text{R} \quad \text{H} \quad \text{H} \]

20 mol % CuCl₂, (Cl₂CH)₂
1 atm O₂, 24h, 130°C

\[ \text{R} \quad \text{Cl} \quad \text{H} \]

R = OMe, 93%
R = CF₃, 20%

Cu(II) mediated diverse CH functionalization

33
R - Br
65%

34
R - I
61%

35
R - CN
42-67%

36
R - NHTs
74%

37
R - OPh-pCN
35%

38
R - SPh
40%

39
R - SMe
51%

40
R - OH
67%

Chelate-Directed C-H Oxidation Reactions

Oxidative Annulation Reactions


Punniyamurthy, Org. Lett. 2011, 13, 1194 – 1197

Hetero-Functionalization of Terminal Alkynes

\[
\begin{align*}
\text{R} \equiv \text{H} + \text{H} - \text{N} \rightarrow & \text{R} \equiv \text{N} \\
60 & \rightarrow 61 & 20 \text{ mol } \% \text{ CuCl}_2, 2.0 \text{ equiv pyridine} \\
& 2.0 \text{ equiv Na}_2\text{CO}_3, 1\text{ atm O}_2, \text{ toluene} & 4h, 70^\circ\text{C} \\
& \rightarrow \text{R} \equiv \text{N} \\
60 & \rightarrow 62 & \end{align*}
\]

\[
\begin{array}{ccc}
\text{Ph} \equiv \text{N} & \text{CO}_2\text{Me} & \text{Ph} \equiv \text{N} \\
63 & 89\% & 64 & 78\% & 65 & 78\%
\end{array}
\]

Hetero-Functionalization of Terminal Alkynes

20 mol % CuCl₂, 2.0 equiv pyridine
2.0 equiv Na₂CO₃, 1 atm O₂, toluene
4h, 70°C

Proposed Mechanism:

Hetero-Functionalization of Terminal Alkynes

$$\text{R} = \text{Ph}$$

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$^\circ$C

78 → 79

71%

80

56%

81

51%

Homo & Cross-Coupling Reactions of Arenes

\[ \begin{align*}
\text{78} & \quad \text{1 mol % } \text{CuCl}_2, \text{ 1.2-1.5 equiv base} \\
& \quad \text{1 atm O}_2, \text{ THF, 1-2h, 0-50}^\circ\text{C} \\
\text{79} & \quad \text{71%}
\end{align*} \]

\[ \begin{align*}
\text{82} & \quad \text{HN}^\text{Ph} \quad \text{HN}^\text{Me} \\
& \quad \text{20 mol % } \text{Cu(OAc)}_2, \text{ 40 mol % } \text{PPh}_3 \\
& \quad \text{1 atm O}_2, \text{ xylene, 140}^\circ\text{C, 24 h} \\
\text{84} & \quad \text{X = S, 81%; = O, 71%; = NMe, 51%} \\
&Mori, 2009
\end{align*} \]

\[ \begin{align*}
\text{85} & \quad \text{H} = \text{C} = \text{O} \\
& \quad \text{30 mol % } \text{CuCl}_2, \text{ 30 mol % } \text{1,10-phenanthroline} \\
& \quad \text{15 mol % DDQ, 3.0 equiv tBuOLi} \\
& \quad \text{1 atm O}_2, \text{ MDSO, 4h, 40}^\circ\text{C} \\
\text{87} & \quad \text{R = Me, 72%; R = CF}_3, \text{ 60%} \\
& \quad Hong, 2010
\end{align*} \]

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

89
Osuka, 2000

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!
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

enantioselectivity (93% ee) as 1. Furthermore, treatment with molecular oxygen converts 4 into 1. In the absence of the naphthol substrate 2, O2-uptake measurements reveal a 4/O2 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 O₂, MeCN, 40 °C. (B) Kinetic time course for the OBC with catalyst 4. (Blue) Actual O₂ uptake; (red) μmols [2] consumed divided by 4; (green) μmols [3] formed divided by 2. Conditions: [2] = 151 mM, [4] = 10 mM, pO₂ = 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 CuII 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 O₂ (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, pO₂ normalized to 849 Torr. (B) Dependence on initial O₂ pressure: [2] = 190 mM, [4] = 10 mM. (C) Dependence on substrate 2 concentration: [4] = 13 mM, pO₂ 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 [O₂] (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.\textsuperscript{7} We speculate that the combination of NapH^{Ox} with the

\textit{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**

<table>
<thead>
<tr>
<th>entry</th>
<th>anion source</th>
<th>solvent</th>
<th>product X</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>Br₂CHCHBr₂</td>
<td>Br, 1f</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>I₂</td>
<td>ClCH₂CH₂Cl</td>
<td>I, 1g</td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td>TMSCN</td>
<td>MeCN</td>
<td>CN, 1h</td>
<td>42%</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>MeNO₂</td>
<td>CN, 1h</td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td>TsNH₂</td>
<td>MeCN</td>
<td>TsNH₂, 1i</td>
<td>74%</td>
</tr>
<tr>
<td>6</td>
<td>p-CN-PhOH</td>
<td>MeCN</td>
<td>p-CN-PhO, 1j</td>
<td>35%</td>
</tr>
<tr>
<td>7</td>
<td>PhSH</td>
<td>DMSO</td>
<td>PhS, 1k</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>MeSSMe</td>
<td>DMSO</td>
<td>MeS, 1l</td>
<td>51%</td>
</tr>
<tr>
<td>9</td>
<td>H₂O</td>
<td>DMSO</td>
<td>OH, 1b</td>
<td>22%</td>
</tr>
</tbody>
</table>

*With 1 equiv of Cu(OAc)₂, air, solvent, 130 °C, 24 h. At 100 °C, 8 h. With 1 equiv of CuF₂. Difunctionalized products (10–20%) were also obtained.*
Scheme 31. Proposed mechanisms considered for benzoxazole/benzoimidazole formation.
Scheme 7. Plausible mechanism.
Scheme 1. Proposed Mechanism for the Direct Transformation

\[
\text{Ph-NH}_2 + \text{Ph-} \rightarrow \text{O}_2 (1 \text{ atm}) \xrightarrow{\text{standard conditions}} \text{Ph-CONHPh}
\]
Scheme 1. Proposed Reaction Path

Ph$_3$C$_3$P(O)(OiPr)$_2$ + H$_2$O

$\text{Ph- \equiv \equiv + CuI}$

$\text{1a + base}$

$\text{Ph- \equiv \equiv Cu}$

$\text{Ph- \equiv \equiv Cu}$

$\text{O$_2$}$

$\text{Ph- \equiv \equiv \equiv \equiv Ph}$

$\text{1a + O$_2$}$

$\text{Ph- \equiv \equiv Cu}$

$\text{O$_2$}$

$\text{Ph- \equiv \equiv \equiv \equiv Ph}$

$\text{(OiPrO)$_2$P(O)H}$

$\text{2a}$

$\text{(OiPrO)$_2$P(OH)}$

$\text{2a'}$

$\text{5}$

$\text{(OiPrO)$_2$P(OH)}$

$\text{6}$

$\text{Ph- \equiv \equiv \equiv \equiv Ph}$

$\text{7}$
**Scheme 1.** Plausible Reaction Pathways for Trifluoromethylation

![Diagram showing the reaction pathways](image-url)
**Scheme 4.** Bases Employed in Dimerization

Base 1  \( i\text{PrMgCl}^+\text{LiCl} + \text{tetramethylpiperidine (1:1.1) } \)

Base 2  Base 1 + ZnCl\(_2\) (1:0.25)

Base 3  Dicyclohexylamine + \( i\text{PrMgCl}^+\text{LiCl} + \text{ZnCl}_2\) (1.1:1:0.25)

Base 4  Base 1 + ZnCl\(_2\) (1:0.5)
Hetero-Functionalization of Terminal Alkynes and Electron Deficient Heteroarenes

1. Reaction 1:
   \[ R\equiv H + R\text{O}\text{P}O\text{H} \xrightarrow{10 \text{ mol} \% \text{ CuI}, 20 \text{ mol} \% \text{ Et}_3\text{N}} \text{ dry Air, DMSO, overnight, 55}\degree\text{C} \rightarrow R\equiv \text{P}OR_1 \]
   R = Ph, 93%
   Mori, Org. Lett. 2009, 11, 1607 – 1610

2. Reaction 2:
   \[ R\equiv H + \text{TMS}C\text{F}_3 \xrightarrow{1.0 \text{ equiv CuI}, 5.0 \text{ equiv KF}} \text{ Air, DMF, 100}\degree\text{C} \rightarrow R\equiv C\text{F}_3 \]
   R = Ph, 93%
   Han, 2009

3. Reaction 3:
   \[ \text{X}H + \text{HN}^\text{Ph} \xrightarrow{20 \text{ mol} \% \text{ Cu(OAc)}_2, 40 \text{ mol} \% \text{ PPh}_3} \text{ 1 atm O}_2, \text{xylene, 140}\degree\text{C, 24 h} \rightarrow \text{Ph} \]
   X = S, 81%;
   = O, 71%;
   = NMe, 51%
   Mori, 2009

Summary

Chelated-Directed C-H Oxidation Reactions

\[ \text{31} \xrightarrow{20 \text{ mol} \% \text{CuCl}_2, (\text{Cl}_2\text{CH})_2} \text{Cl} \xrightarrow{1 \text{ atm} \text{O}_2, 24\text{h}, 130^\circ\text{C}} \text{32} \]

Oxidative Annulation Reactions

\[ \text{45} \xrightarrow{15 \text{ mol} \% \text{Cu(OAc)}_2, 5 \text{ equiv HOAc}} \xrightarrow{1 \text{ atm} \text{O}_2, \text{DMSO}, 18\text{h}, 100^\circ\text{C}} \text{46} \]

68-89%

Hetero-Functionalization of Terminal Alkynes

\[ \text{60} + \text{61} \xrightarrow{20 \text{ mol} \% \text{CuCl}_2, 2.0 \text{ equiv pyridine, 2.0 equiv Na}_2\text{CO}_3} \xrightarrow{1 \text{ atm} \text{O}_2, \text{toluene}, 4\text{h}, 70^\circ\text{C}} \text{62} \]

Homo & Cross-Coupling Reactions of Arenes

\[ \text{78} \xrightarrow{1 \text{ mol} \% \text{CuCl}_2, 1.2-1.5 \text{ equiv base}} \xrightarrow{1 \text{ atm} \text{O}_2, \text{THF}, 1-2\text{h}, 0-50^\circ\text{C}} \text{79} \]

71%