Copper Catalyzed Aerobic Oxidative C-H Functionalizations

The Past —— Cu/O_2 ——→ The Future

2012/12/08

M1 Yohei Seki

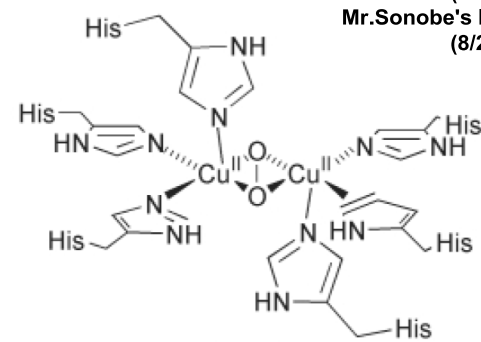
Contents

Contents

1-1. Copper

Hemocyanin

cf.Mr.Kimura's literature seminar
(4/13/2011)
Mr.Sonobe's literature seminar
(8/27/2012)



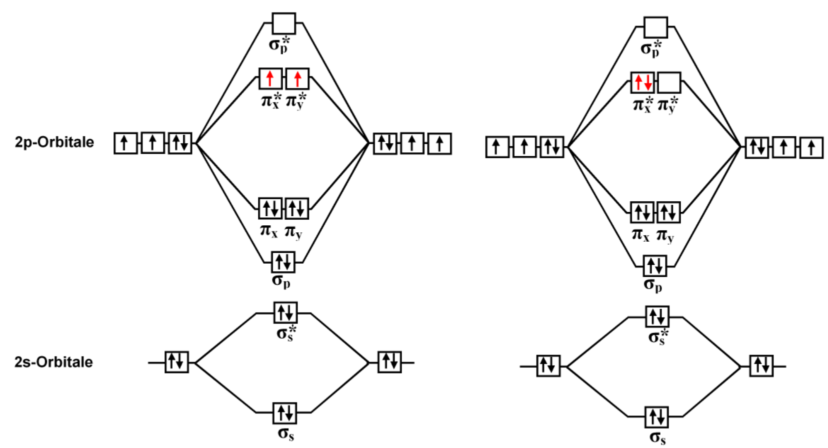
$d_{Cu\text{-}Cu}$ = 3.6 Å
$d_{O\text{-}O}$ = 1.49 Å

Copper active site of oxyhemocyanin

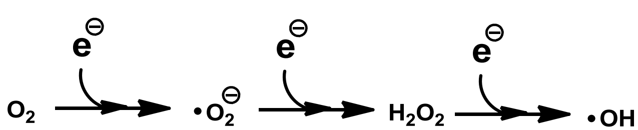
1. Atomic number **29**, in group **11**, and **first row transition metal**
2. **One s-orbital electron** on top of a filled d-electron shell
3. Oxidation states **+1**, **+2**, **+3**, **+4**
4. **Oxygen transportation**
5. **Essential trace element** in plants and animals

1-2. Oxygen

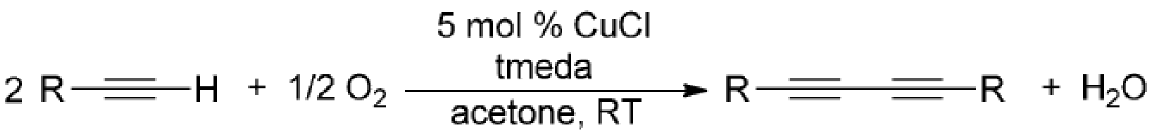
1. Atomic number 8, in group 16, and second row element
2. Triplet oxygen and singlet oxygen
3. Photosynthesis
4. 20.8% of the volume of air



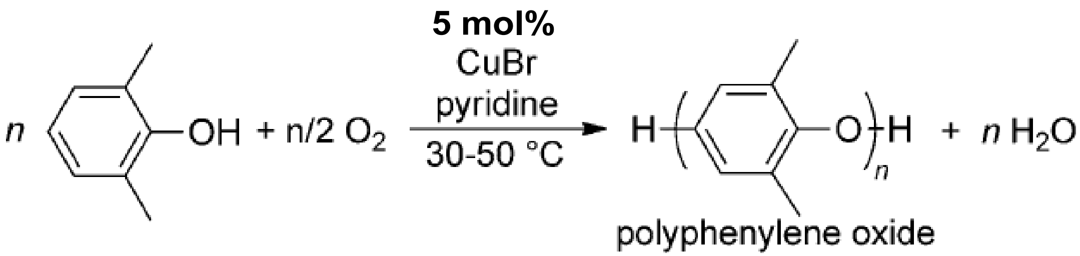
Reactive oxygen species



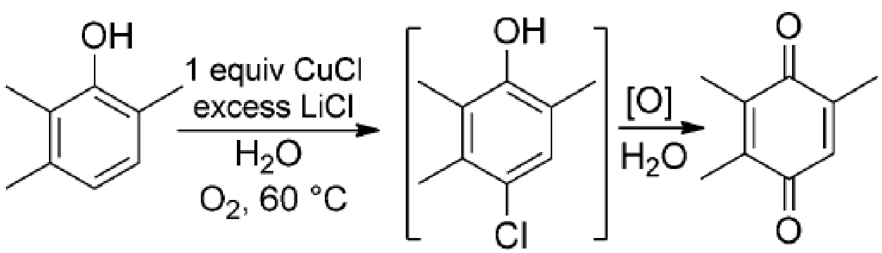
1-3. Cu/O2 system



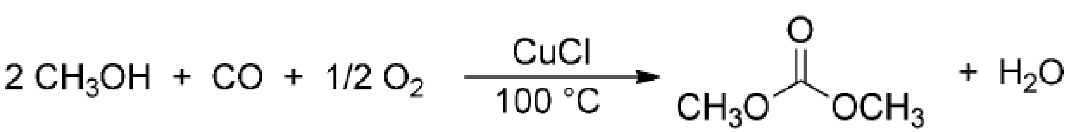
C. Glaser et al. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.



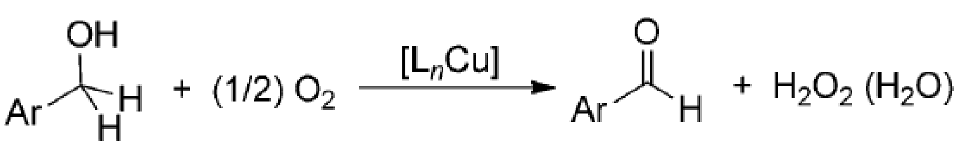
J.W. Eustance et al. *J. Am. Chem. Soc.* **1959**, *81*, 6335.



K. Takehira et al. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1522.



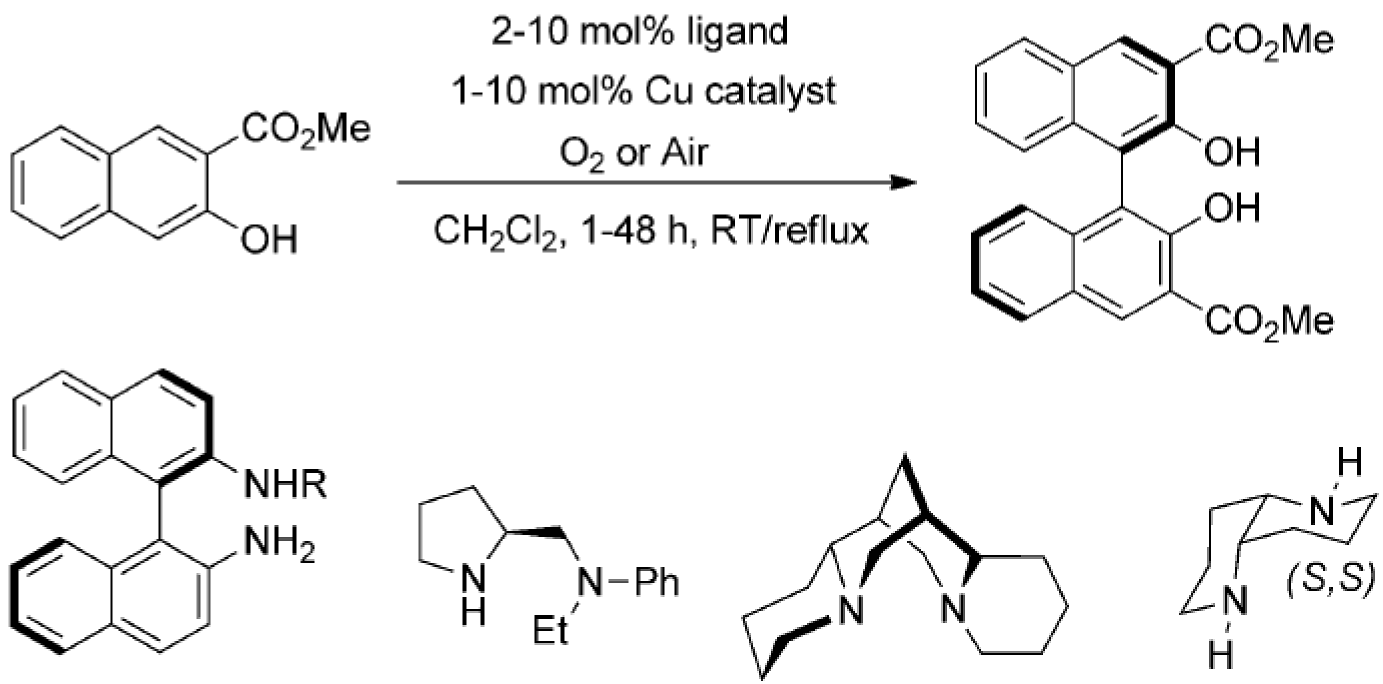
P. Rebora et al. *Ind. Eng. Chem. Prod. Res. Dev.* **1980**, *19*, 396.



C. S. Chou et al. *J. Am. Chem. Soc.* **1984**, *106*, 3374.
C. J. Urch et al. *Science* **1996**, *274*, 2044.
cf. Mr.Hashizume's literature seminar (7/2/2012)

Contents

2-1. Dimerization of naphthol derivative



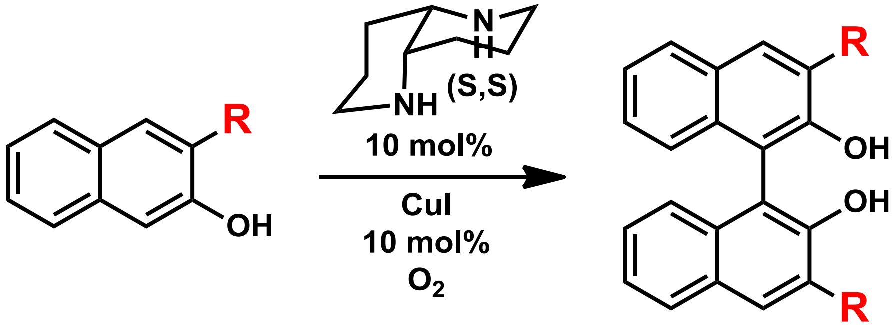
94% *ee*; 88% yield R = 3-pentyl — *Ha, 2004*

70% *ee*, 78% yield — *Nakajima, 1995*

47% *ee*, 38% yield — *Nakajima, 1999*

90-93% *ee*, 85% yield — *Kozlowski, 2001*

2-1. Dimerization of naphthol derivative



AM1 calculations showed HOMO energies (eV) of substrates with various R_1 groups.

HOMO energies (eV)

-H = -8.569
-COPh = -8.685
-COOMe = -8.735
$-PO(OMe)_2$ = -8.850
$-SO_2Ph$ = -8.926
$-NO_2$ = -9.133

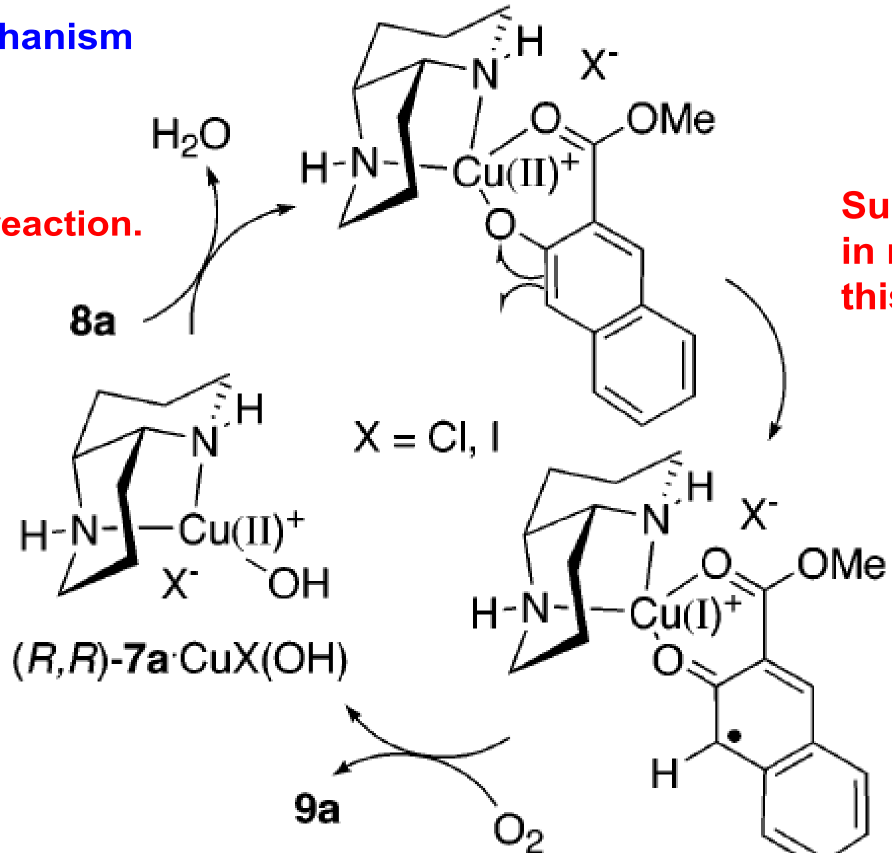
The reaction rates

M. C. Kozlowski et al. *J. Org. Chem.* **2003**, *68*, 5500.

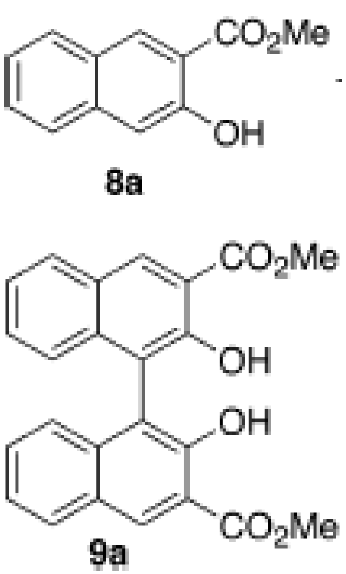
2-1. Dimerization of naphthol derivative

Possible mechanism

Water inhibited this reaction.



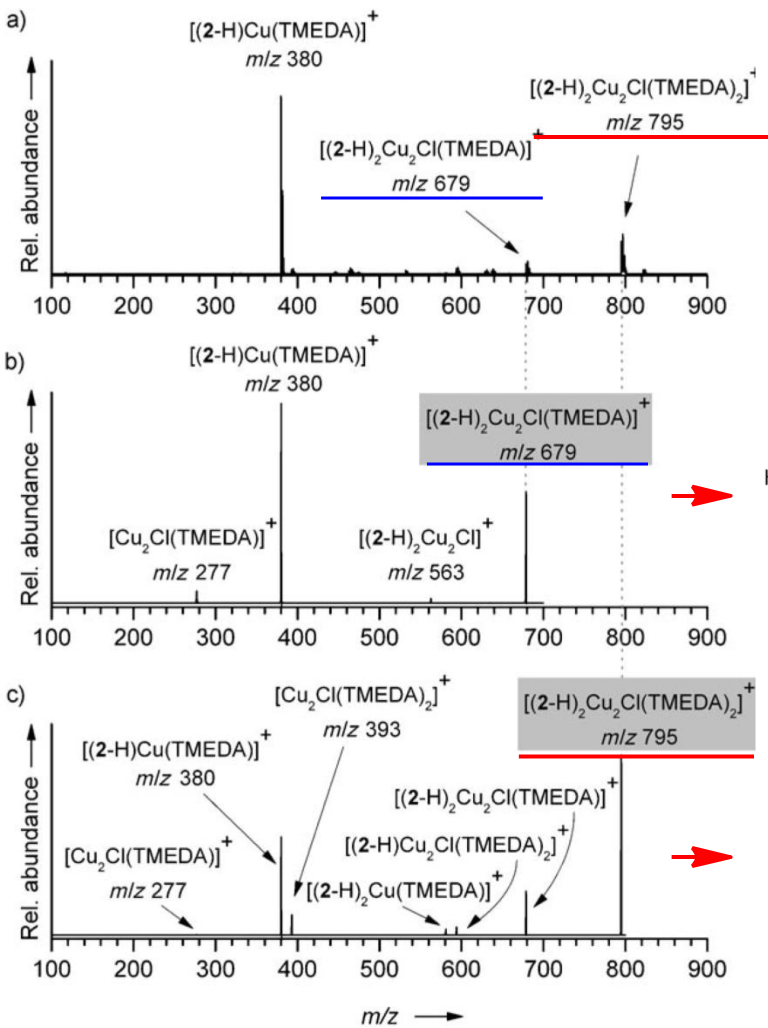
Substitution of EWG in naphthalene made this redox step slow.



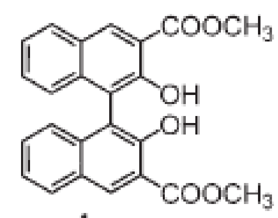
Lower yields were obtained with phosphine oxide substrate. Maybe, strong coordination between substrate and metal inhibited catalytic cycle?

M. C. Kozlowski et al. *J. Org. Chem.* **2003**, *68*, 5500.

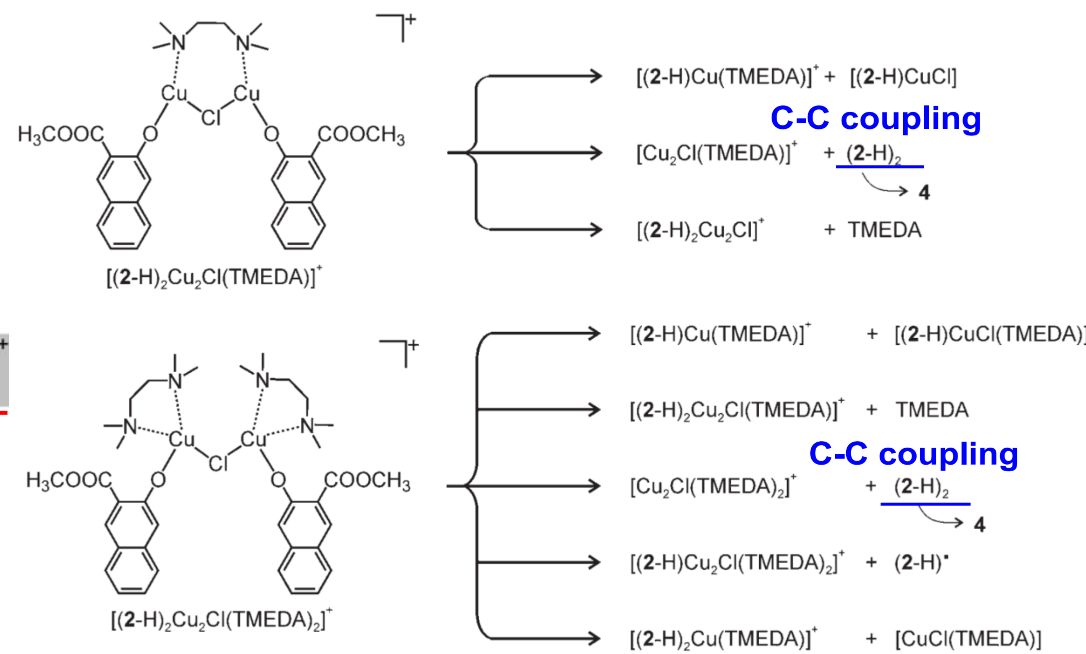
2-1. Dimerization of naphthol derivative



Gas-phase study with ESI mass (a) and CID spectrum (b, c)



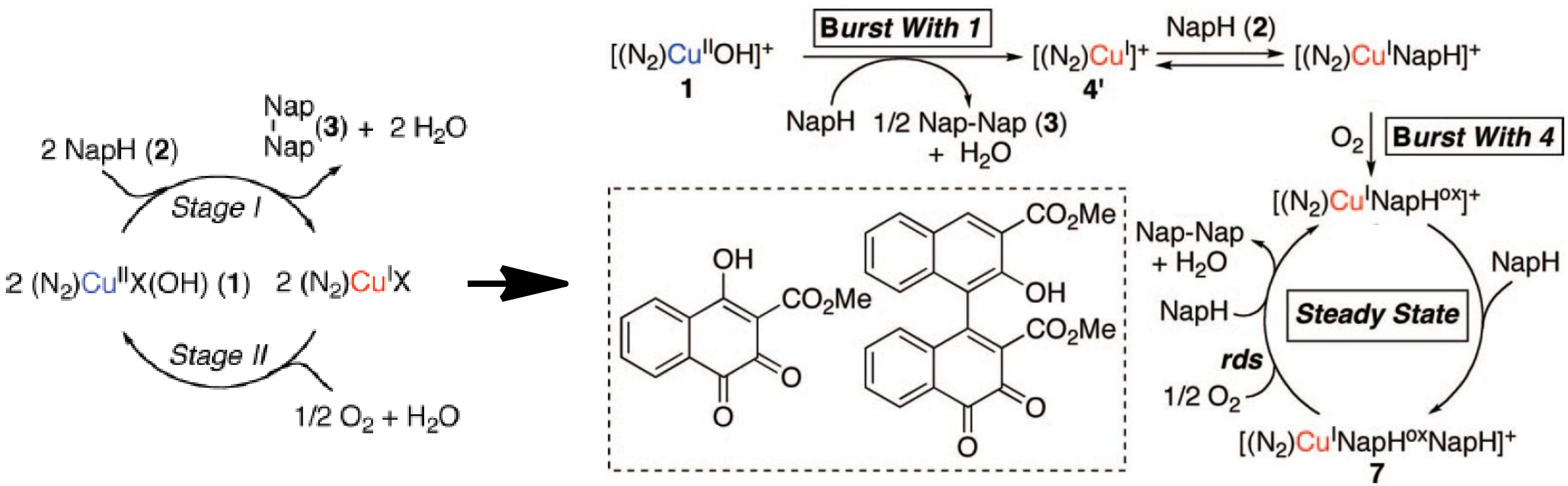
4



D. Schrcder et al. *Chem. Eur. J.* **2008**, *14*, 2180.

2-1. Dimerization of naphthol derivative

Possible mechanism

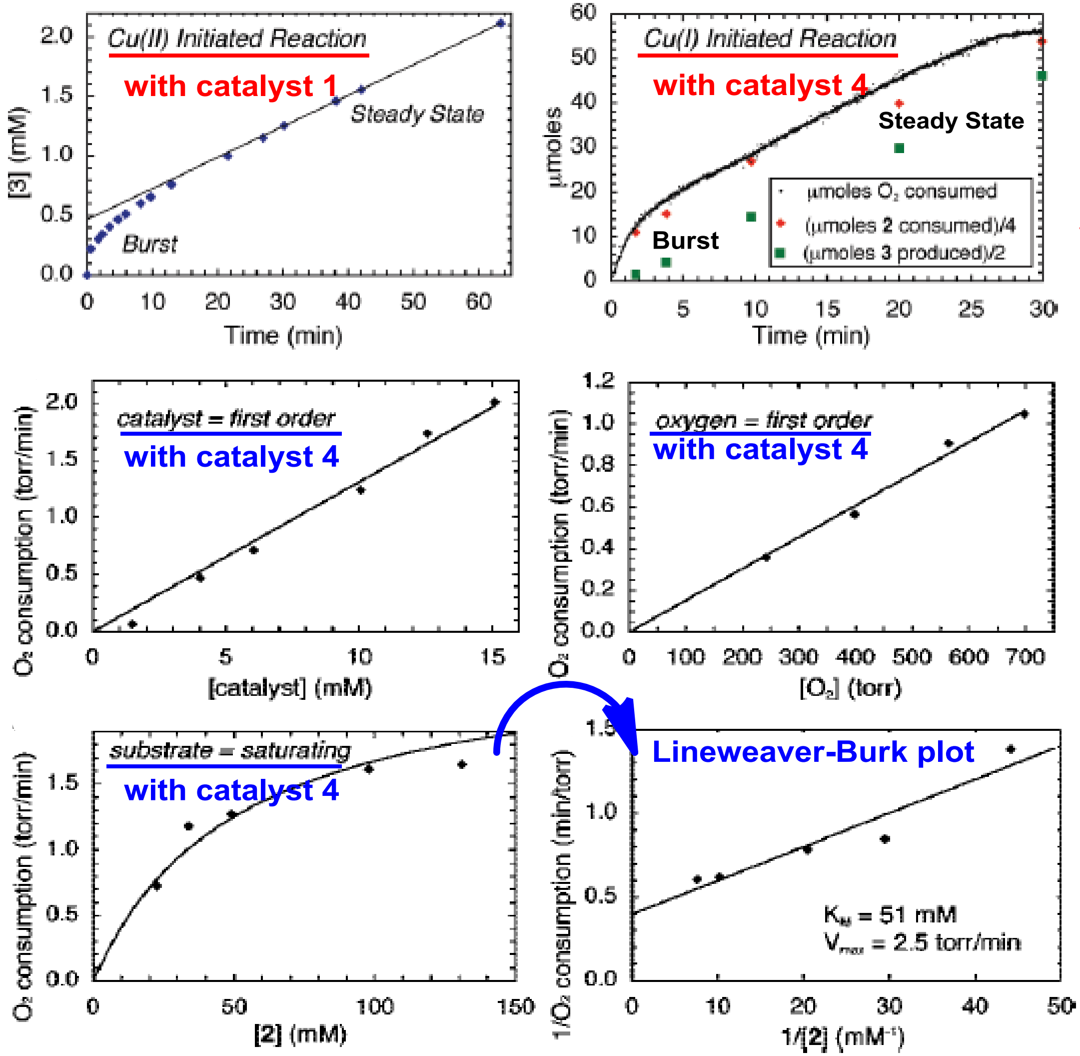


Isolated products

Cofactor NapH^{ox} and steady state catalyst 7 are not idetified.

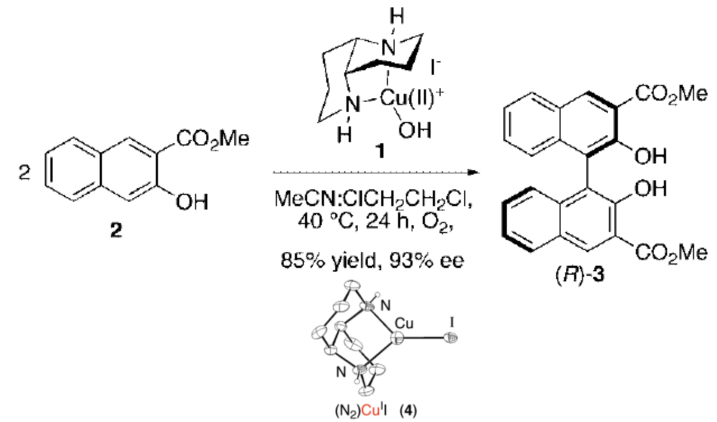
M. C. Kozlowski et al. *J. Am. Chem. Soc.* **2008**, *130*, 12232.

2-1. Dimerization of naphthol derivative



1. Steady state followed initial burst of product formation.
2. Formation of product 3 was not observed until the oxygen-uptake burst, but substrate 2 was consumed in the burst.

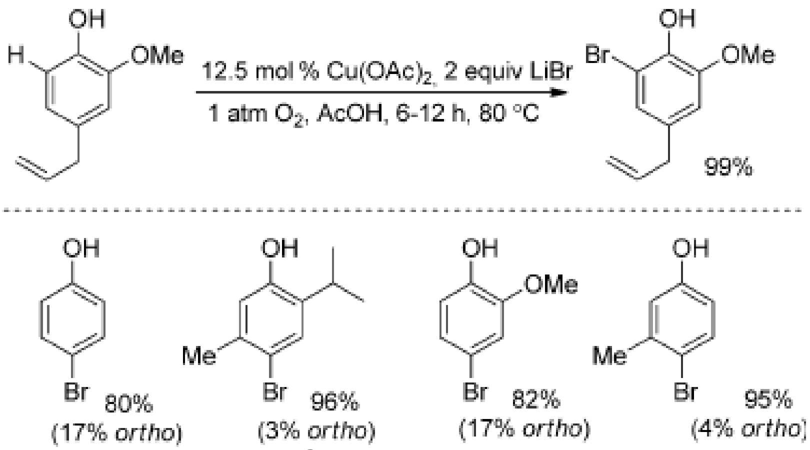
First-order dependencies of catalyst 4, O_2 and the saturation dependence on the substrate 2 was observed.



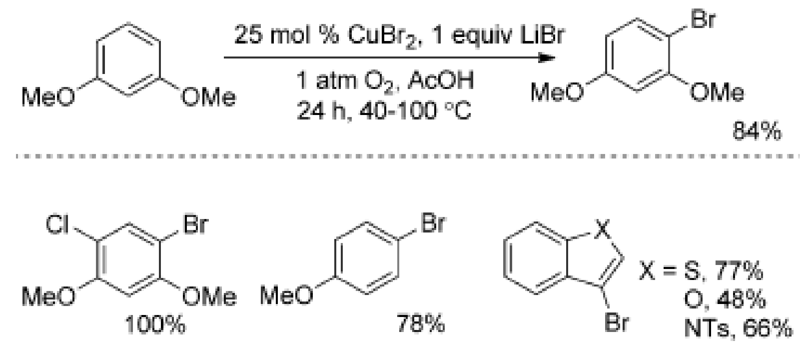
M. C. Kozlowski et al. *J. Am. Chem. Soc.* **2008**, *130*, 12232.

2-2. Chlorination and bromination of arene

Bromination

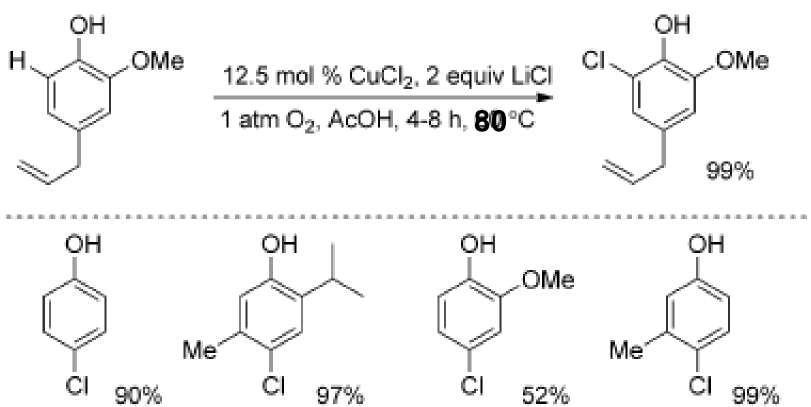


E. V. Gusevskaya et al. *Tetrahedron Lett.* **2007**, *48*, 6401.

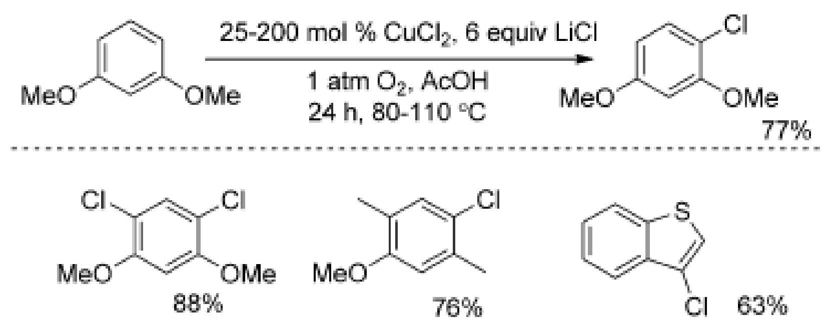


S. S. Stahl. *Chem. Commun.* **2009**, 6460.

Chlorination



E. V. Gusevskaya et al. *Chem. Commun.* **2006**, 209.

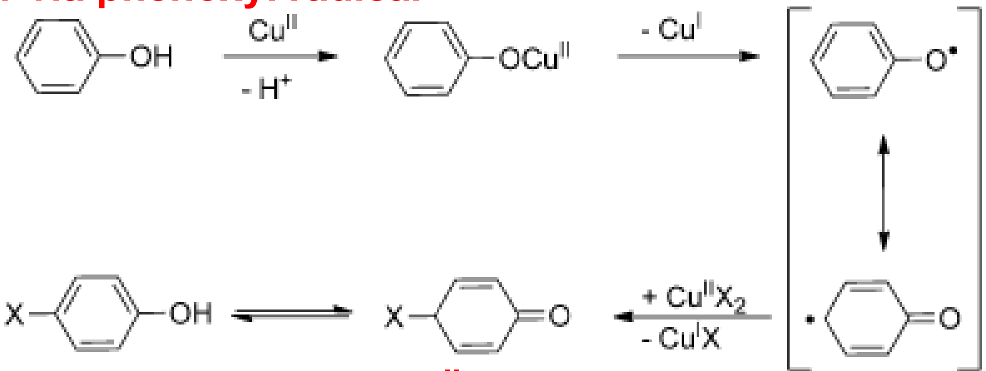


S. S. Stahl. *Chem. Commun.* **2009**, 6460.

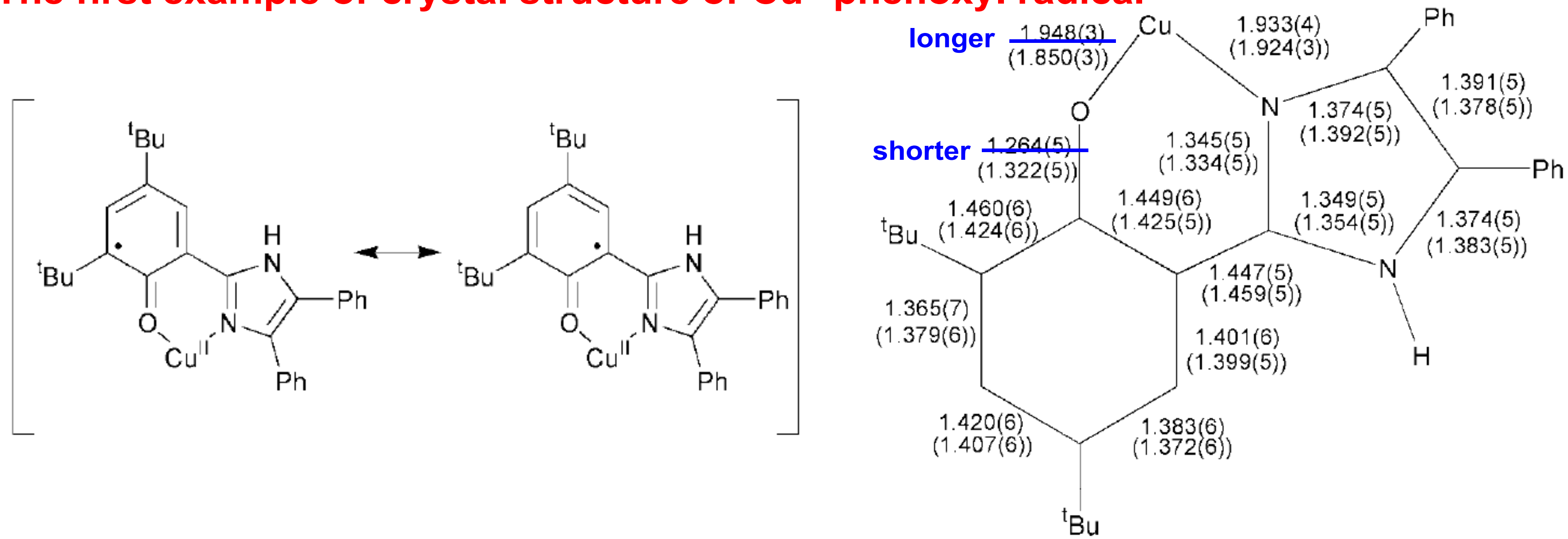
2-2. Chlorination and bromination of arene

Possible mechanism

Single-electron transfer via phenoxyl radical

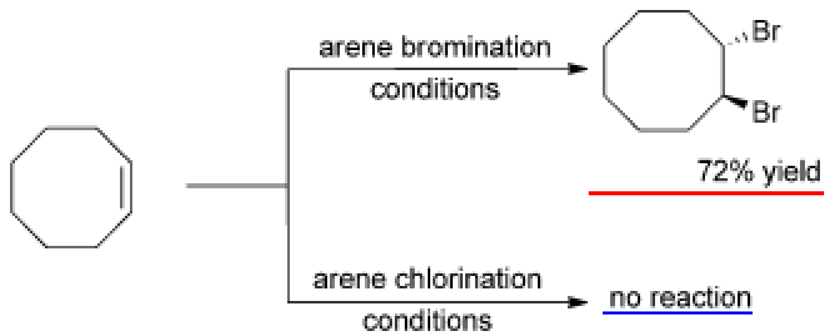


The first example of crystal structure of Cu^{II}-phenoxyl radical



Gavin Whittaker and Claire Wilson et al. *Chem. Commun.* **2001**, 1824.

2-2. Chlorination and bromination of arene



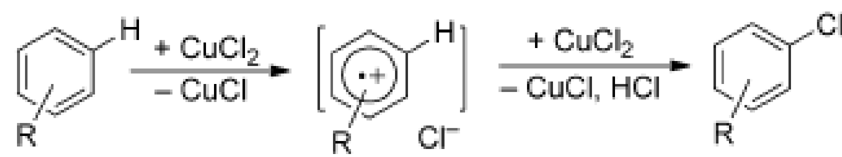
Possible mechanism

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

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

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

$$Ar{-}H + HBr + 1/2\,O_2 \longrightarrow Ar{-}Br + H_2O \quad (4)$$

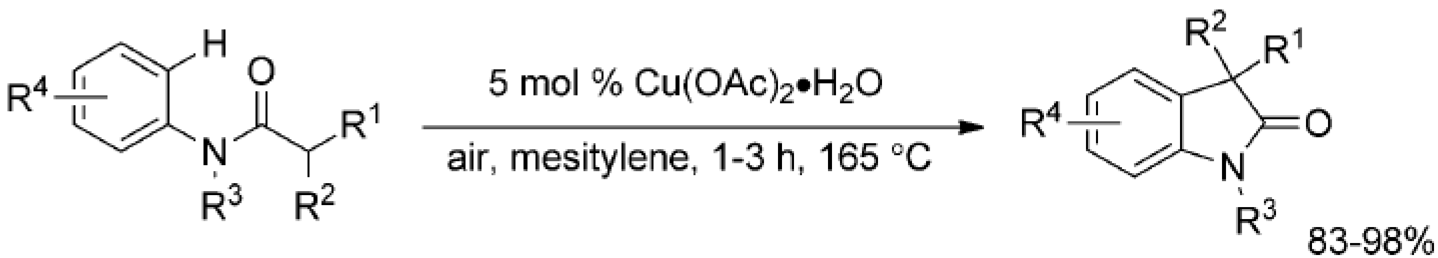


The bromination reaction turn red-brown in color on heating, possibly implicating the formation of molecular bromine in solution.

Without aryl-OH, reaction proceeded. So, direct complexation of the arene to Cu^{II} can not be required.

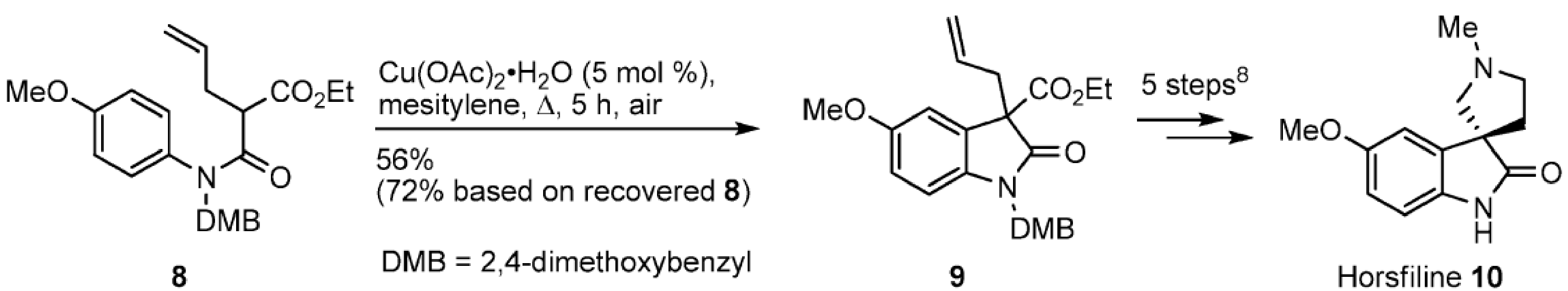
S. S. Stahl. *Chem. Commun.* **2009**, 6460.

2-3. Cyclization of anilides to give oxindole



R^1 = EWG (CO_2R, CN, Ph)
R^2 = alkyl, allyl
R^3 = Me, Bn
R^4 = EWG or EDG

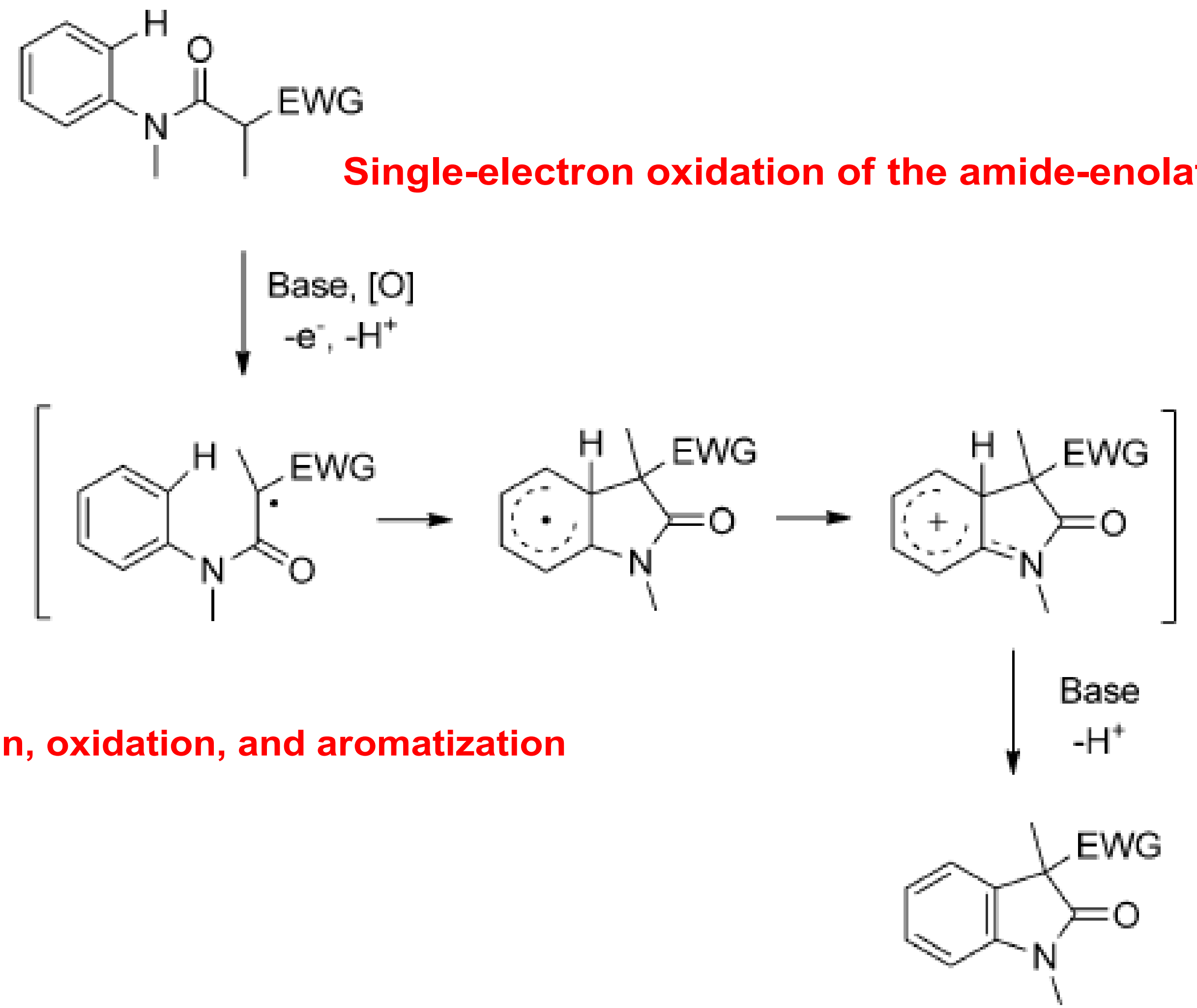
Application to the synthesis of anticancer, analgesic oxindole alkaloid Horsfine 10



[8]Barry M.Trost et al. *Org. Lett.* **2006**, *8*, 2027.
R. J. K. Taylor et al. *Org. Lett.* **2010**, *12*, 3446.

2-3. Cyclization of anilides to give oxindole

Possible mechanism



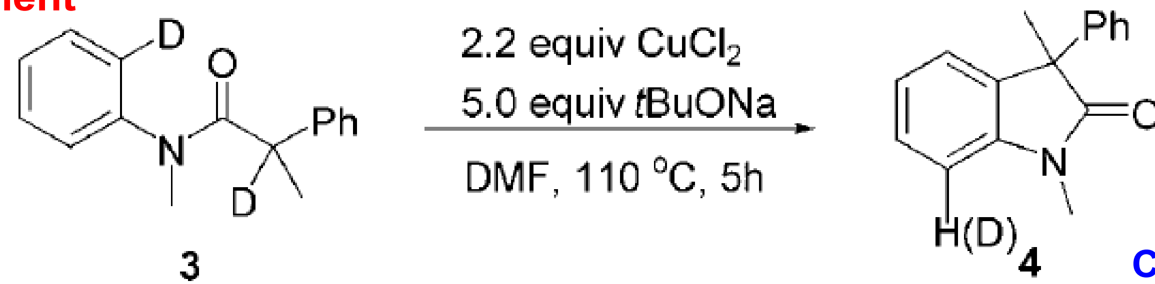
Single-electron oxidation of the amide-enolate moiety by Cu^{II}

Cyclization, oxidation, and aromatization

E. P. K┘ndig et al. *Angew. Chem. Int. Ed.* **2009**, *121*, 1664.

2-3. Cyclization of anilides to give oxindole

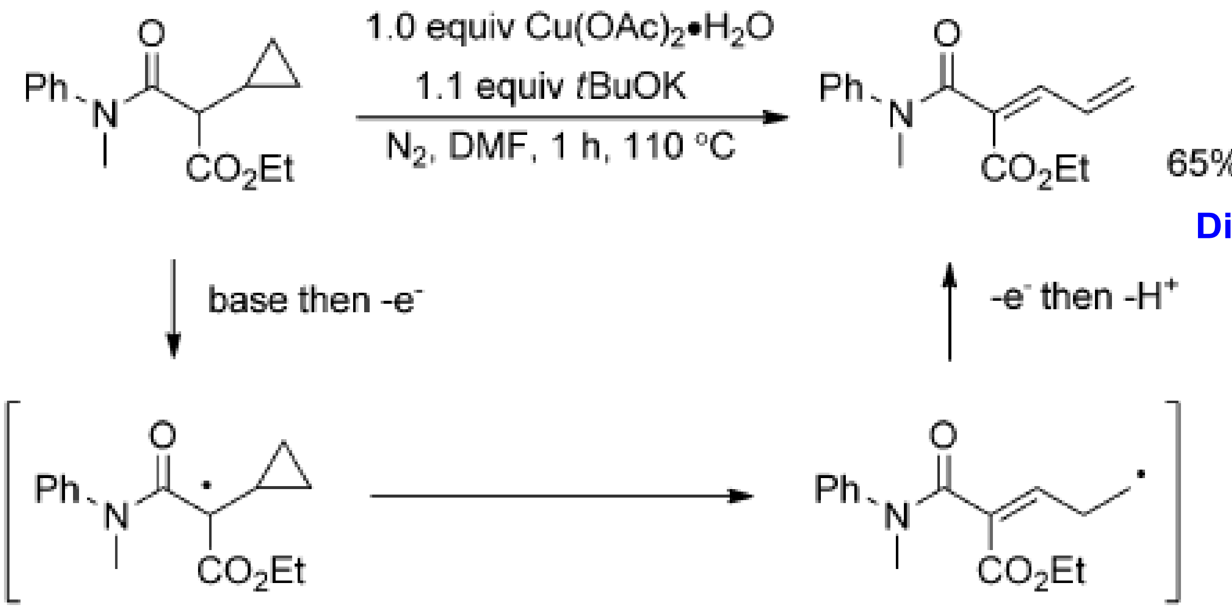
Labeling experiment



$K_D/K_H = 0.8$

Csp^2-H bond breaking is not involved in the rate-determining step.

Radical-mediated cyclopropane scission

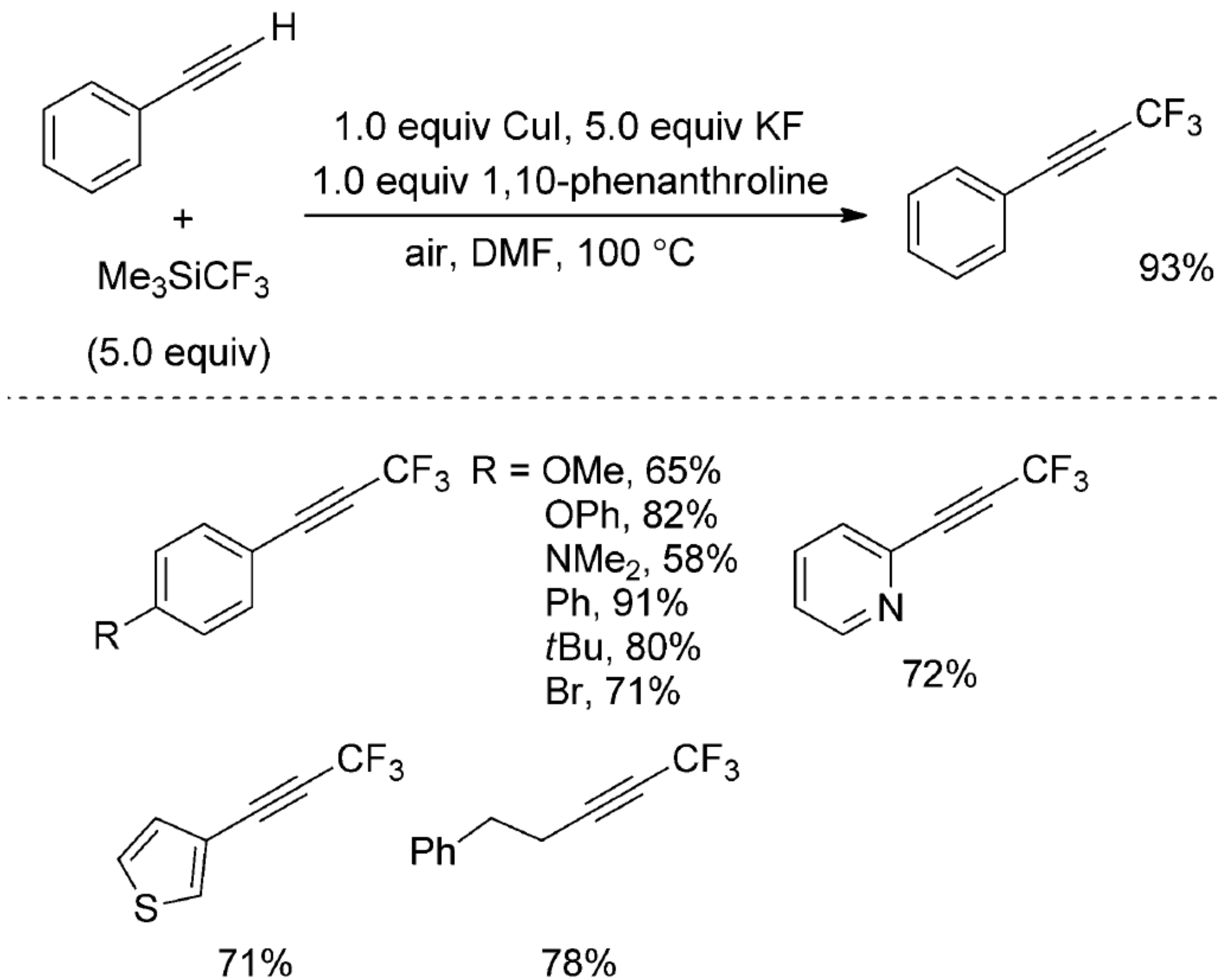


Diene was obtained.

E. P. K┘ndig et al. *Angew. Chem. Int. Ed.* **2009**, *121*, 1664.
R. J. K. Taylor et al. *Chem. Commun.* **2009**, 3249.

Contents

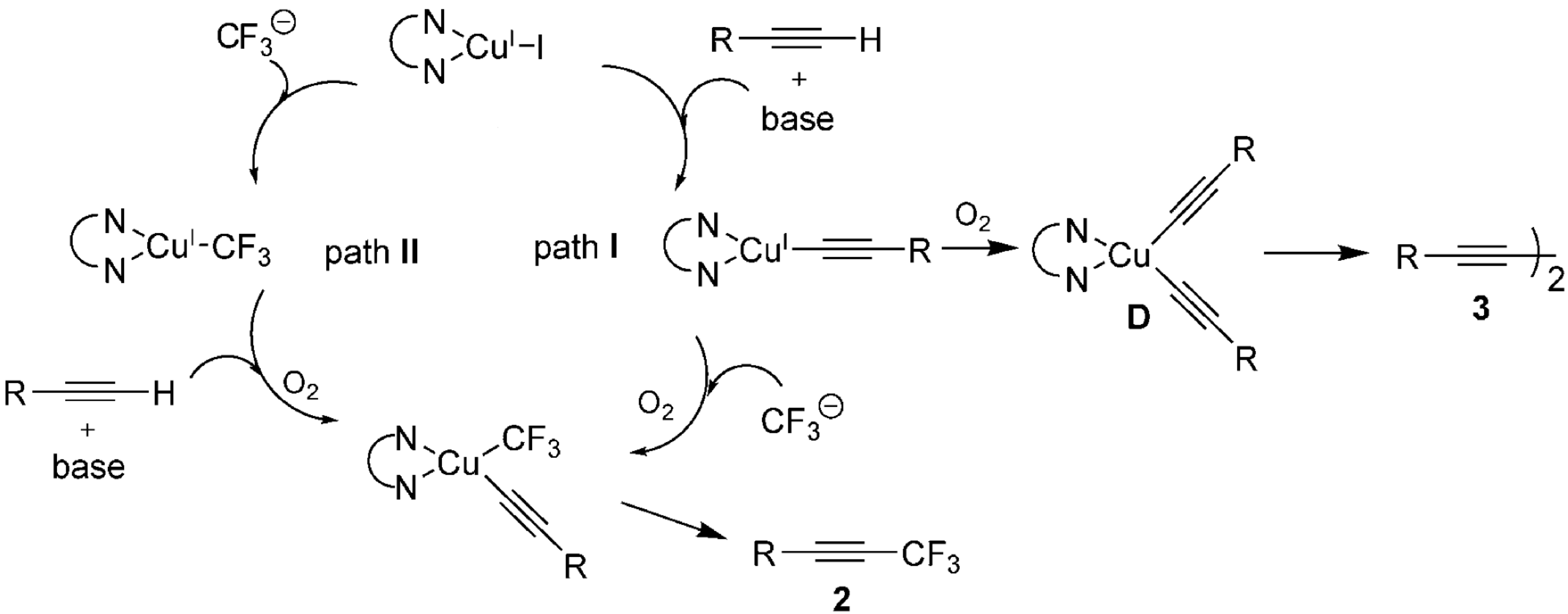
3-1. Oxidative trifluoromethylation of terminal alkyne



F.-L. Qing et al. *J. Am. Chem. Soc.* **2010**, *132*, 7262.

3-1. Oxidative trifluoromethylation of terminal alkyne

Pregenerated $CuCF_3$, Phen, 5 eq of CF_3 sauces were effective for this reaction.

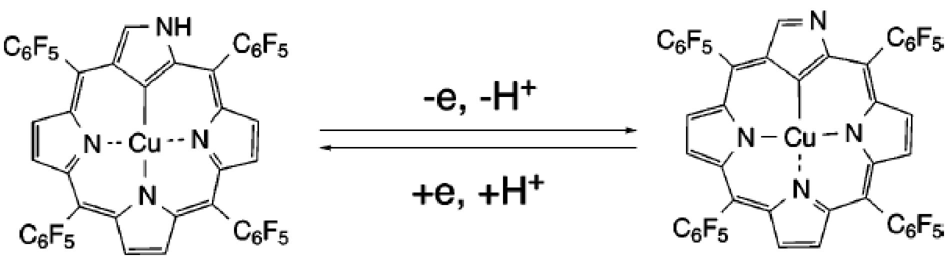


When air was replaced with O_2, the reaction was completely inhibited and only 3 was generated.

F.-L. Qing et al. *J. Am. Chem. Soc.* **2010**, *132*, 7262.

Contents

4-1. Mechanism of formation of Cu(Ⅲ) species



1, Cu(II) **2, Cu(III)**

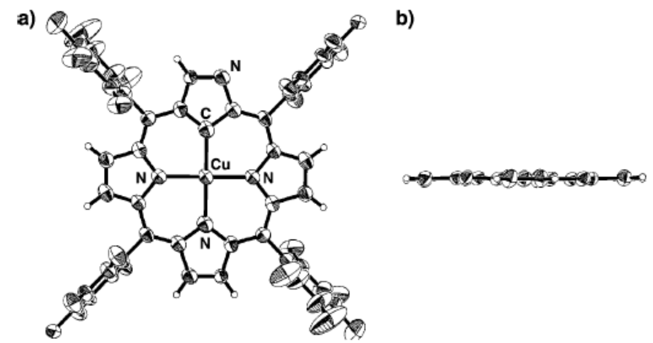


Figure 2. X-ray single-crystal structure of **2**: (a) top and (b) side views. Meso substituents are omitted for clarity in the side view. The thermal ellipsoids were scaled to the 30% probability levels. Due to the disorder of the nitrogen at a confused pyrrole ring, one of the eight possible forms is shown.

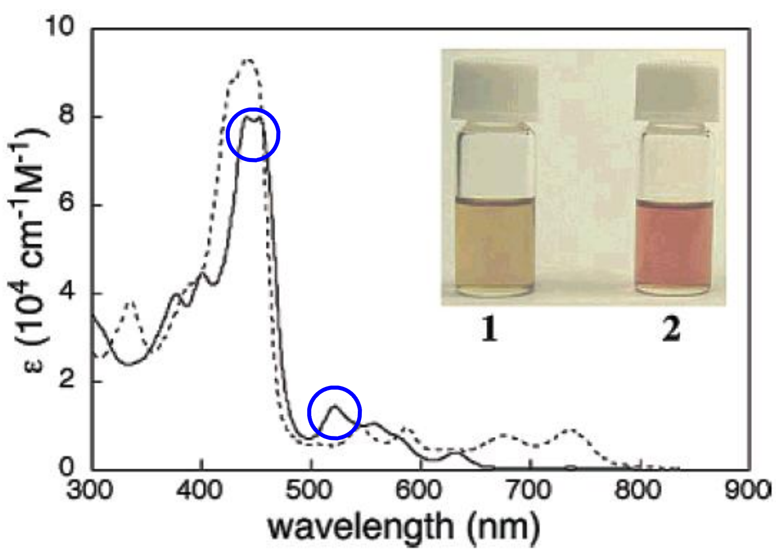


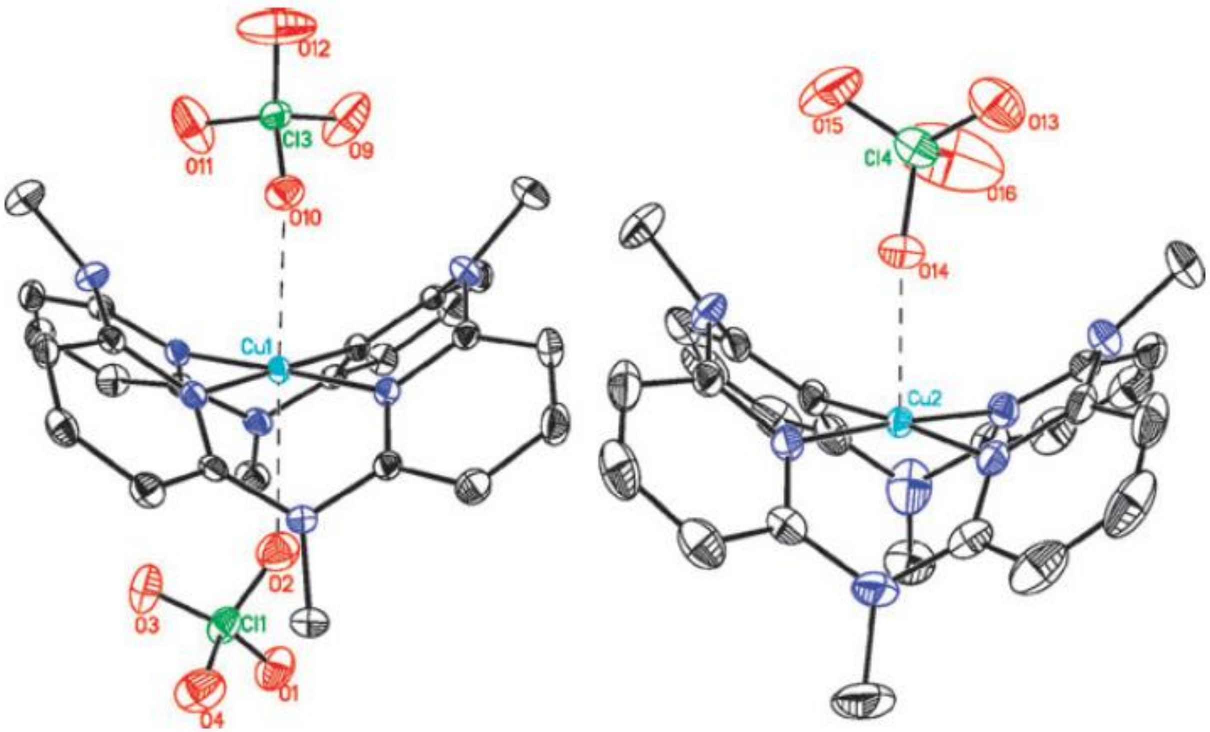
Figure 1. UV/vis absorption spectra and the naked colors of the solutions (inset) of **1** (dotted line, left) and **2** (solid line, right) in CH_2Cl_2.

1. When the Cu^{II} complex was treated with 1.5 eq of DDQ in $CHCl_3$ the solution changed from yellowish-brown to red.

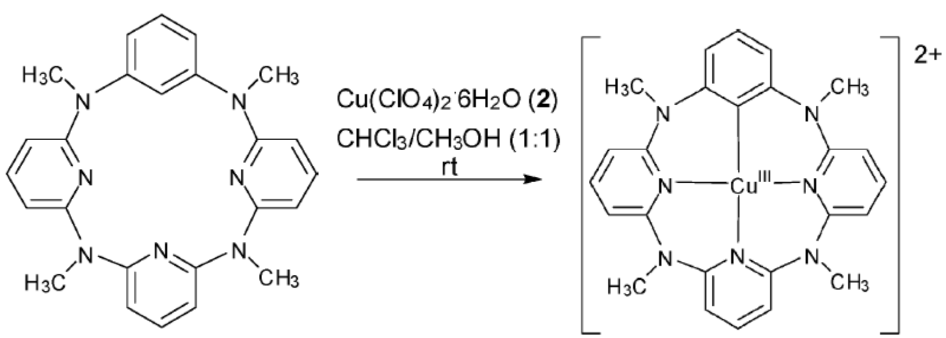
2. The reverse reaction was accomplished by the reaction of Cu^{III} with *p*-toluenesulfonylhydrazide.

H. Furuta et al. *J. Am. Chem. Soc.* **2003**, *125*, 11822.

4-1. Mechanism of formation of Cu(Ⅲ) species



Cu^{III} was coordinated by six ligands(left) or five ligands(right).



1

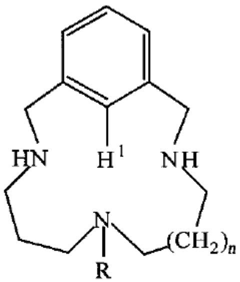
2 ClO_4^-
3

Entry	**1**/mmol	**2**/mmol	Conditions	Time/min	**3** (%)[a]
1	0.1	0.1	Aerobic	15	54
2	0.1	0.1	Aerobic	60	76
3	0.1	0.15	Aerobic	15	92
4	0.1	0.15	Aerobic	60	99
5	0.1	0.15	Anaerobic	15	34
6	0.1	0.15	Anaerobic	60	60

[a] Isolated yield.

M.-X. Wang et al. *Chem.Commun.* **2009**, 2899 .

4-1. Mechanism of formation of Cu(Ⅲ) species



L1: R = H n = 0
L2: R = Me n = 1
L3: R = H n = 1

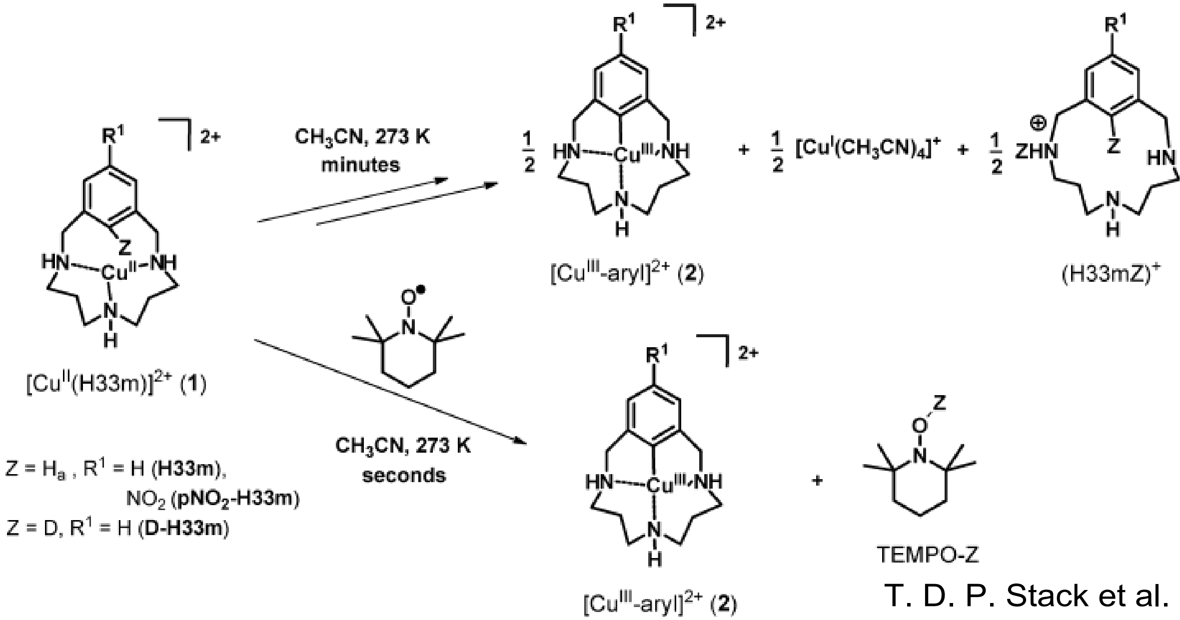
$$2\,[Cu^{II}L](X)_2 \xrightarrow[298\,K]{MeCN} [Cu^{III}L'](X)_2 + [Cu^{I}(LH)](X)_2$$

L = L1, L2, L3
X = ClO_4^-, $CF_3SO_3^-$

1•X_2: L1'
2•X_2: L2'
3•X_2: L3'

Disproportionation of Cu^{II} occured.

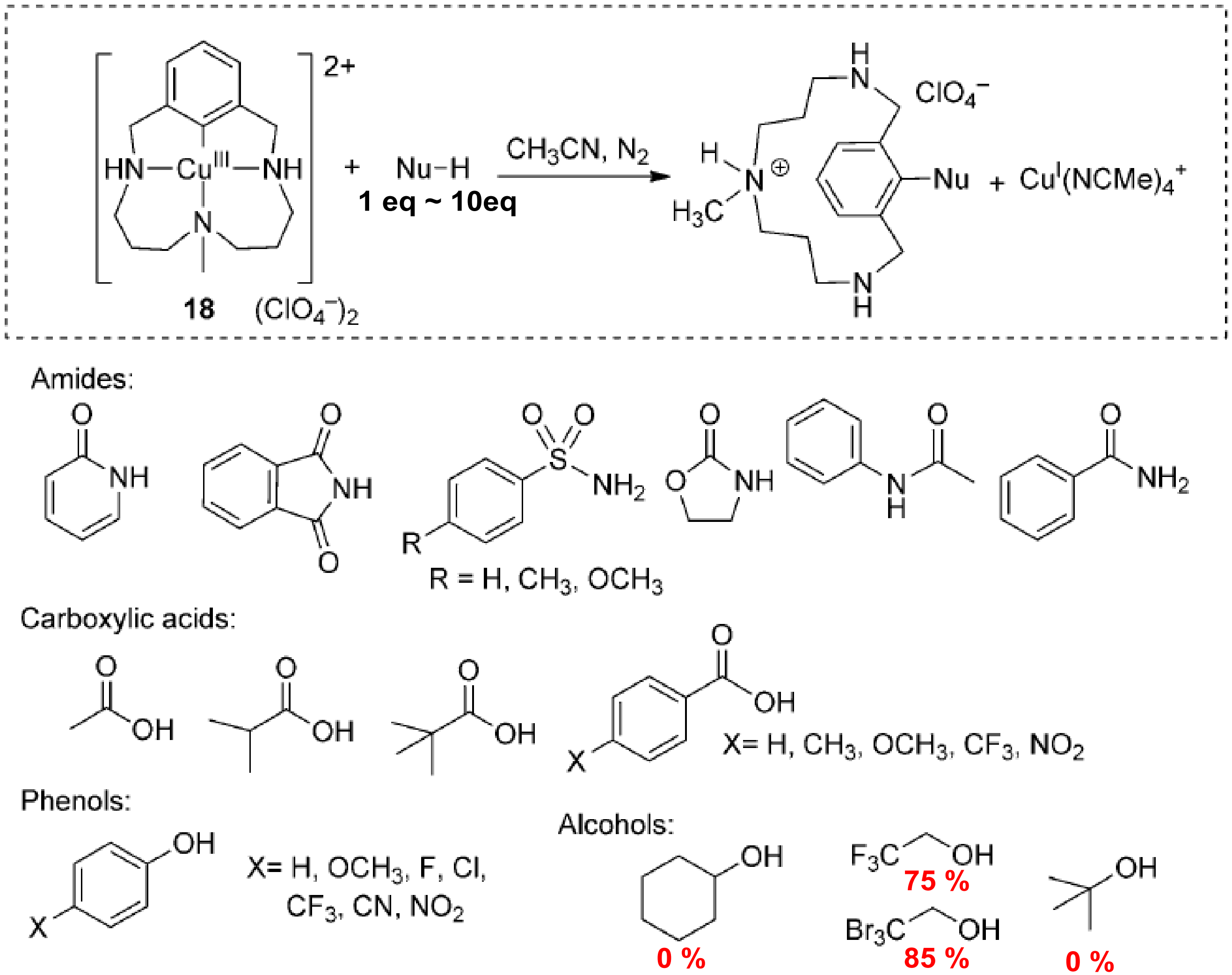
T. D. P. Stack et al. *Angew. Chem.* **2002**, *114*, 3117.



Concerted proton-coupled electron transfer (PCET) occured.

T. D. P. Stack et al. *J. Am. Chem. Soc.* **2010**, *132*, 12299.

4-2. Reactivity of Cu(Ⅲ) species

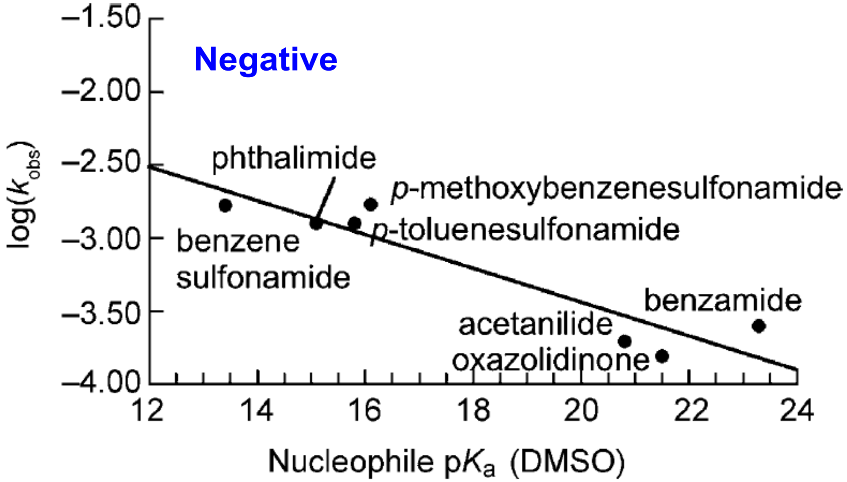


Aliphatic alcohols were less ractive.

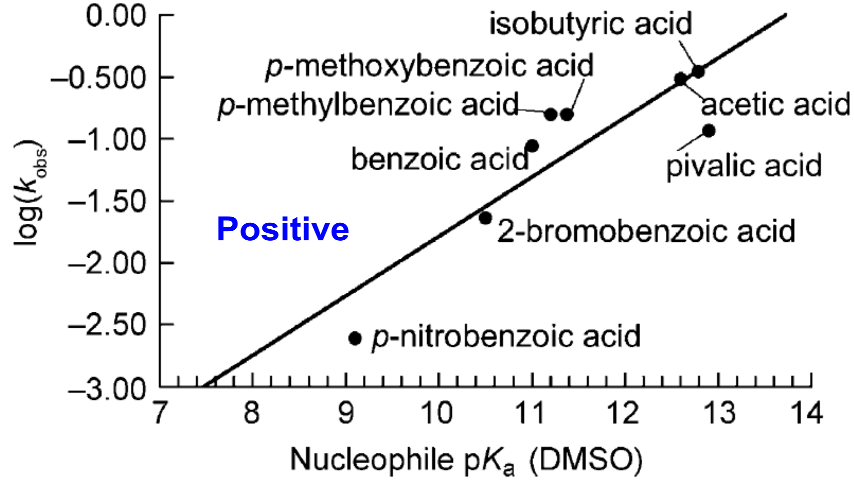
S. S. Stahl et al. *Chem. Eur. J.* **2011**, *17*, 10643.

4-2. Reactivity of Cu(Ⅲ) species

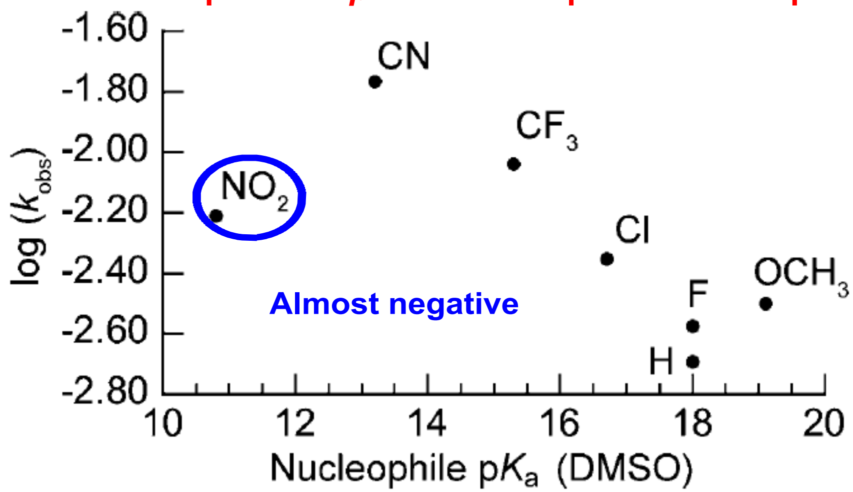
Bronsted plot with nitrogen nucleophile



Bronsted plot with carboxylic acid nucleophile



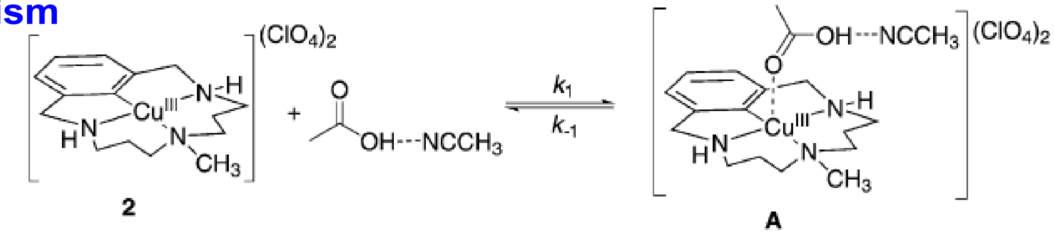
Bronsted plot with *p*-substituted phenol nucleophile



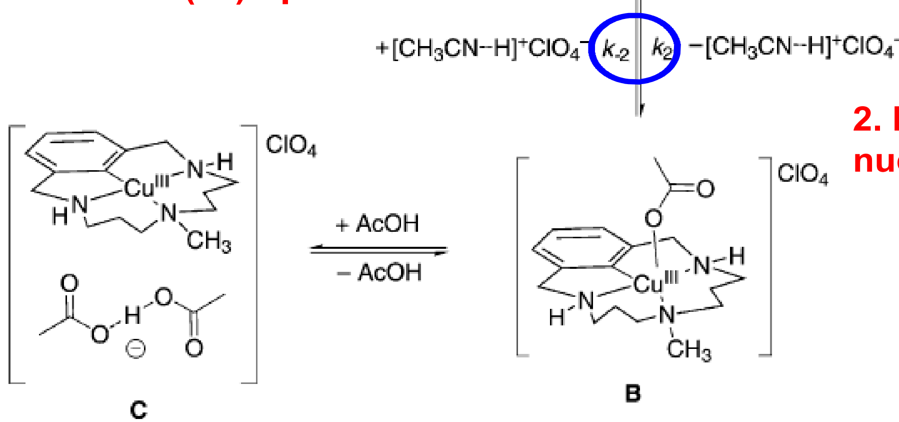
S. S. Stahl et al. *Chem. Eur. J.* **2011**, *17*, 10643.

4-2. Mechanism of Reaction of Cu(Ⅲ) species

Possible mechanism

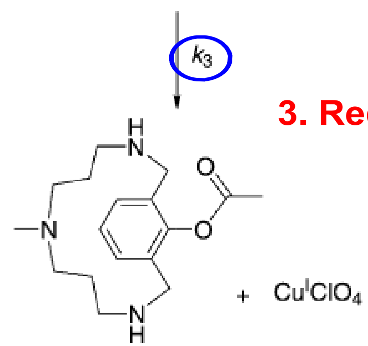


1. Pre-equilibrium formation of Cu(Ⅲ) species



2. Deprotonation of coordinated nucleophile

Dissociation of coordinated nucleophile



3. Reductive elimination

The rate-limiting step for different nucleophiles

Negative bronsted plot

↓

The rate-limiting deprotonation

Positive bronsted plot

↓

The rate-limiting reductive elimination

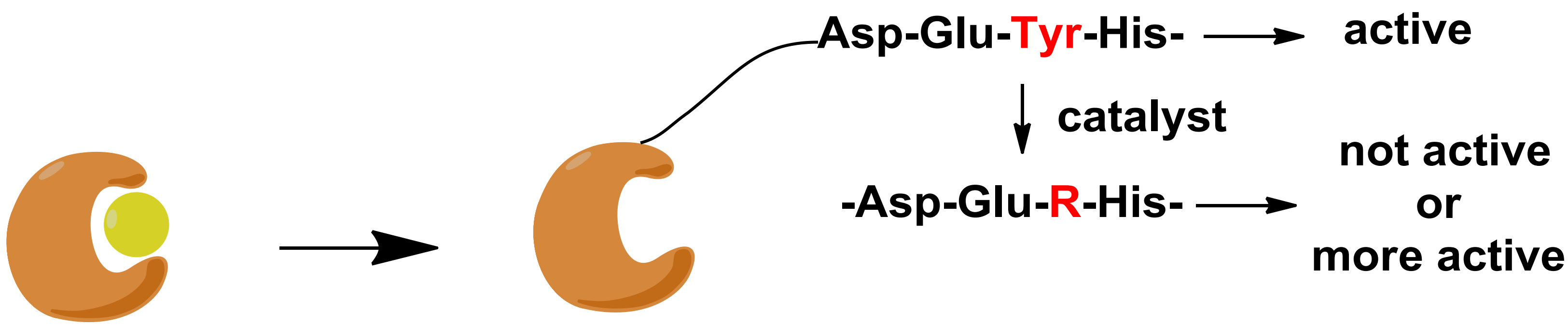
S. S. Stahl et al. *Chem. Eur. J.* **2011**, *17*, 10643.

Contents

5-1. Innovative method of remedy

Mechanism of medicinal action

Classical

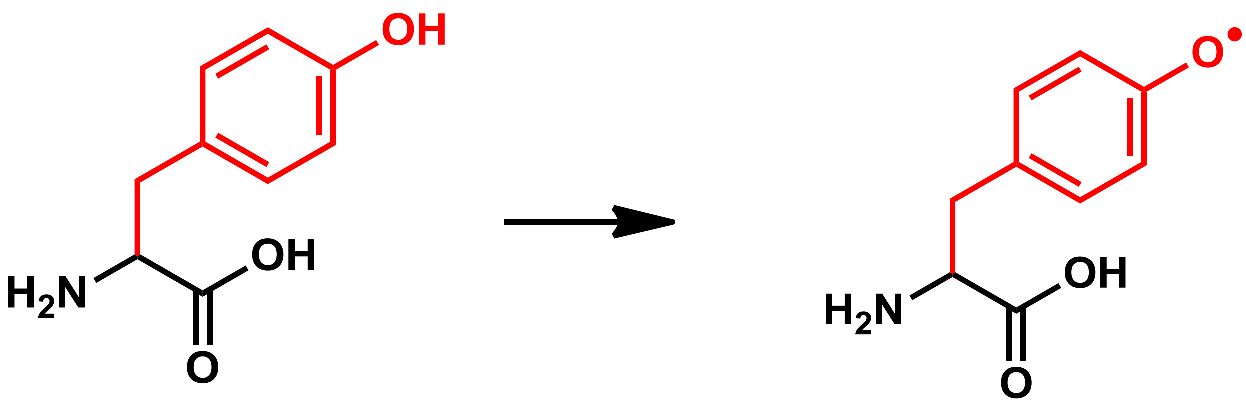


Host-Guest complex

Artificial transformation of amino acid by catalyst

Does it become a curative medicine ?

5-2. Target residue = Tyrosine



1. One of the 22 amino acids

2. Phosphorylation target
by protein kinases

3. Precursors to hormones,
alkaloids, pigments...and so on

1. Production by
myeloperoxidase (MPO)

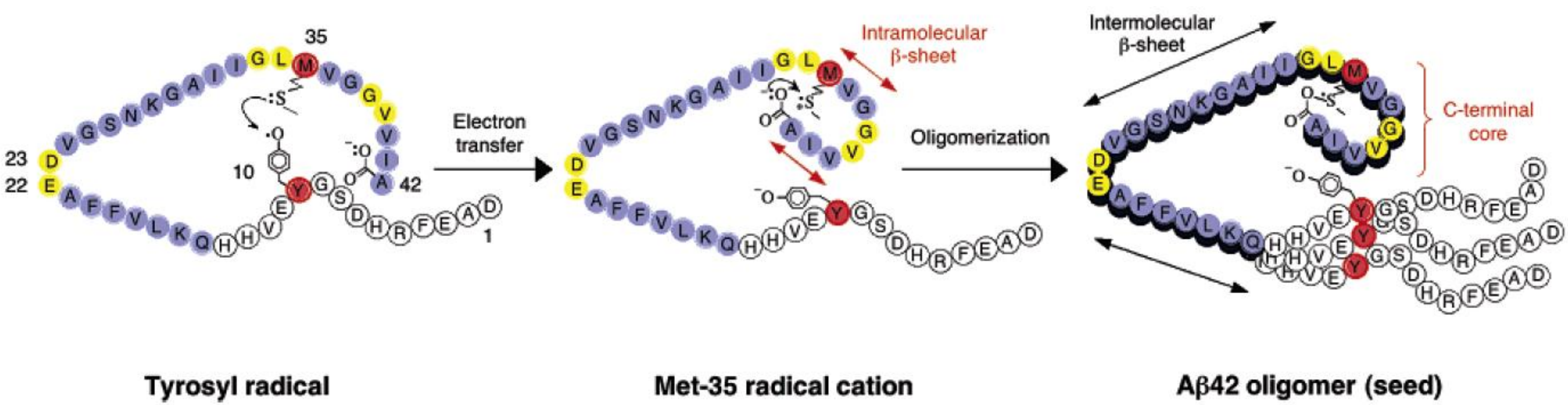
2. Alzheimere's disease
K. Irie et al. *J. Am. Chem. Soc.* **2005**, *127*, 15168.

5-3. Tyrosyl radical ～Alzheimer‘s disease～

Possible mechanism

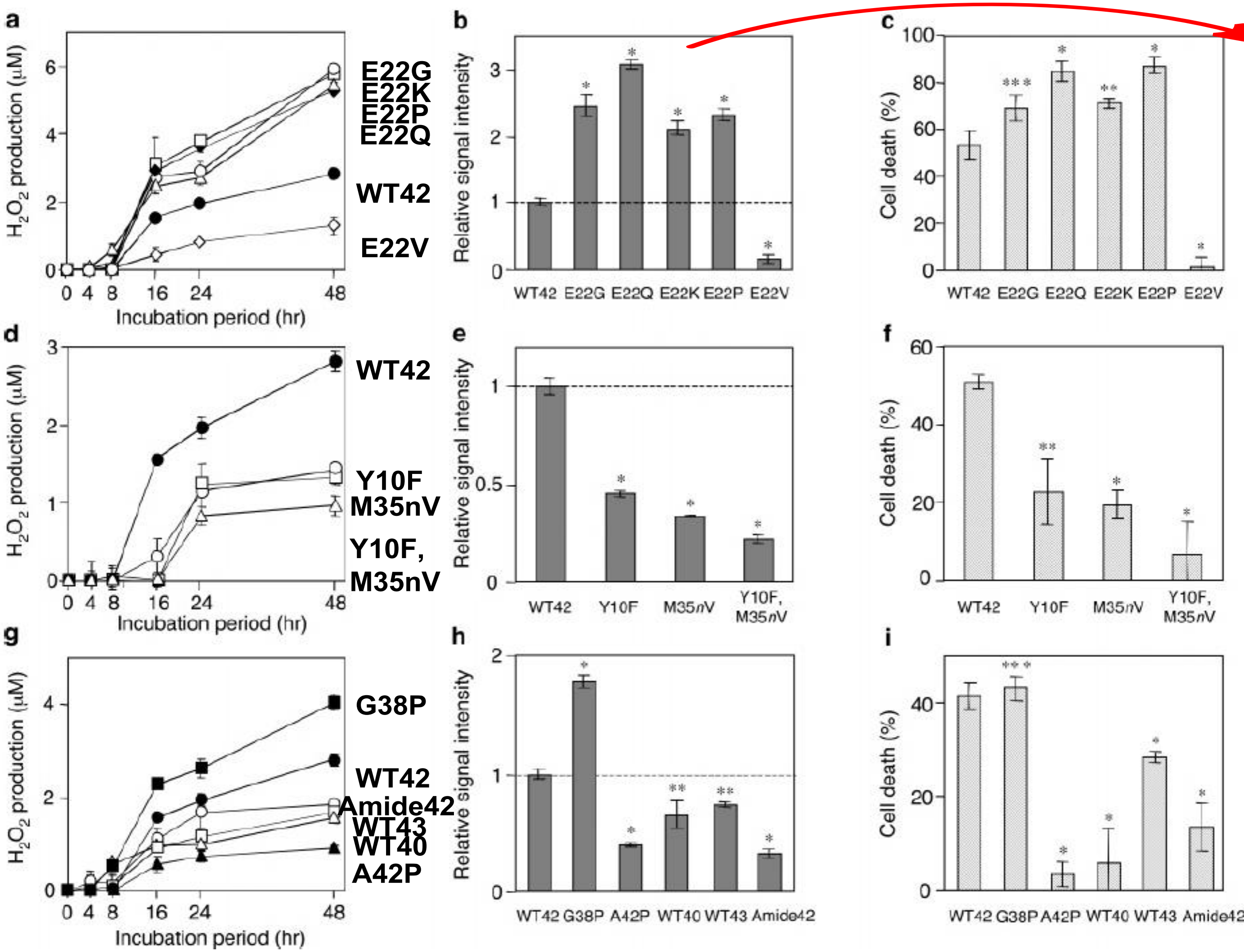
$$A\beta42 + O_2 \xrightarrow[\text{reducing agents}]{Cu^{2+}} A\beta42/Cu^{+} + O_2^{\bullet -}$$

$$\xrightarrow{H_2O} \quad A\beta42(\text{Tyr10-O}^{\bullet}),\ A\beta42(\text{Met35-S}^{\bullet +}) + H_2O_2 \text{ (neurotoxic)} \longrightarrow \text{aggregation, neurotoxicity}$$



K. Irie et al. *J. Am. Chem. Soc.* **2005**, *127*, 15168.

5-3. Tyrosyl radical ～Alzheimer‘s disease～



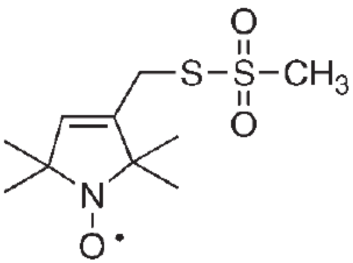
ESR spectra of Aβ42 mutants

Production of hydrogen peroxide and radicals by Aβ42 mutants along with neurotoxicity in vivo.

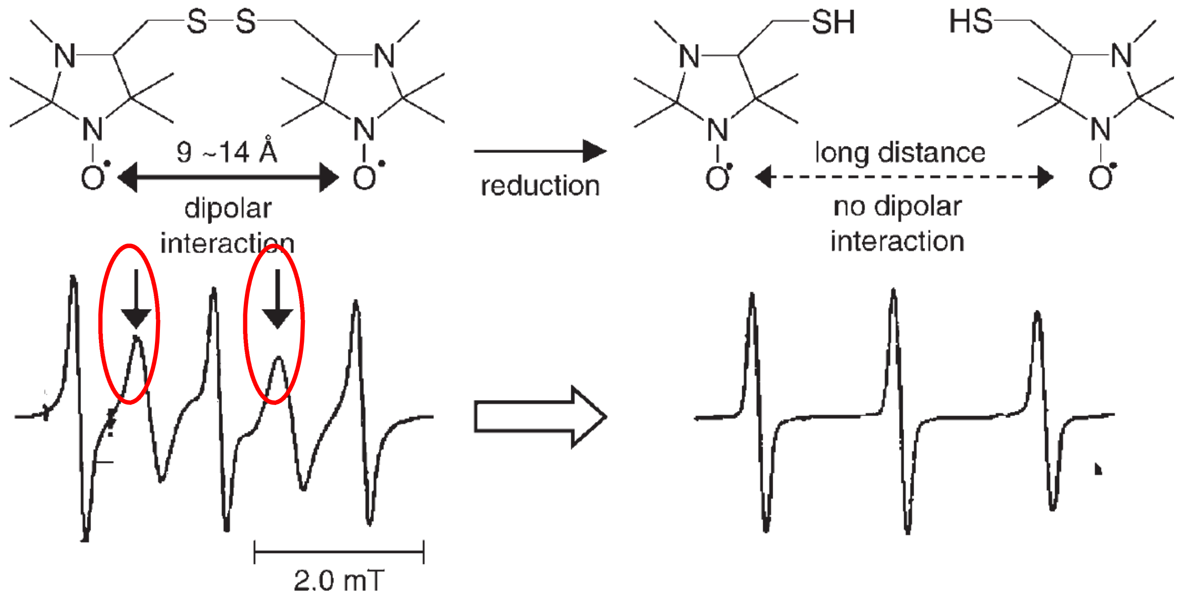
WT = Wild Type

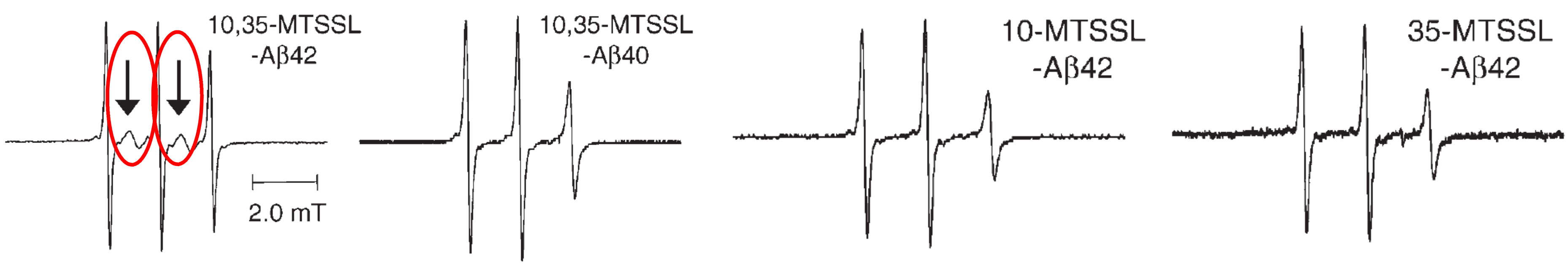
K. Irie et al. *J. Am. Chem. Soc.* **2005**, *127*, 15168.

5-3. Tyrosyl radical ～Alzheimer‘s disease～



MTSSL-Ms

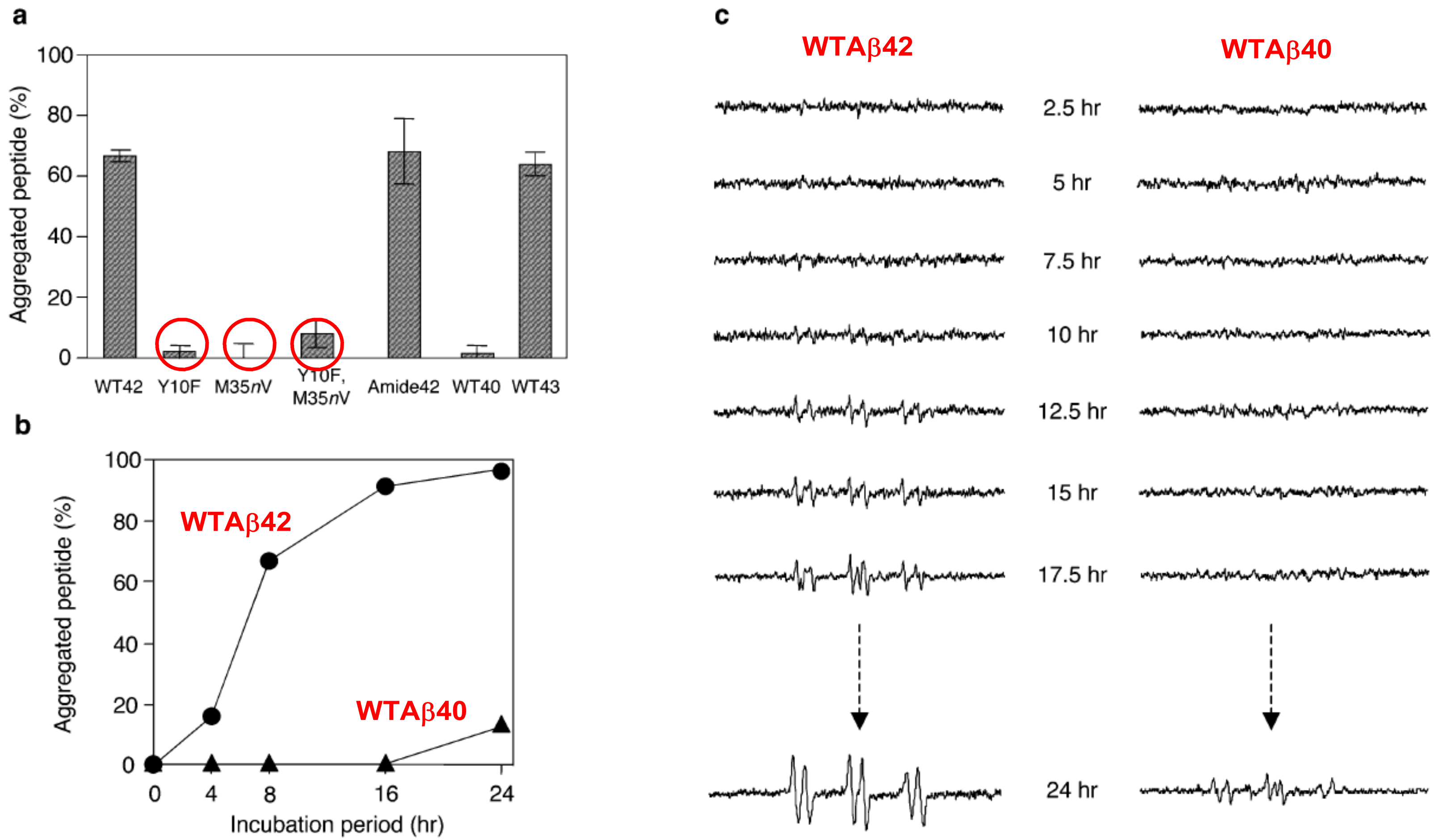




Tyr10 and Met35 are located within ~15Å.

K. Irie et al. *ChemBioChem* **2007**, *8*, 2308.

5-3. Tyrosyl radical ～Alzheimer‘s disease～



K. Irie et al. *J. Am. Chem. Soc.* **2005**, *127*, 15168.

5-3. Tyrosyl radical ～Alzheimer's disease～

1. Production of tyrosyl radical can be occured through Cu/O_2 in the presence of reducing agents.

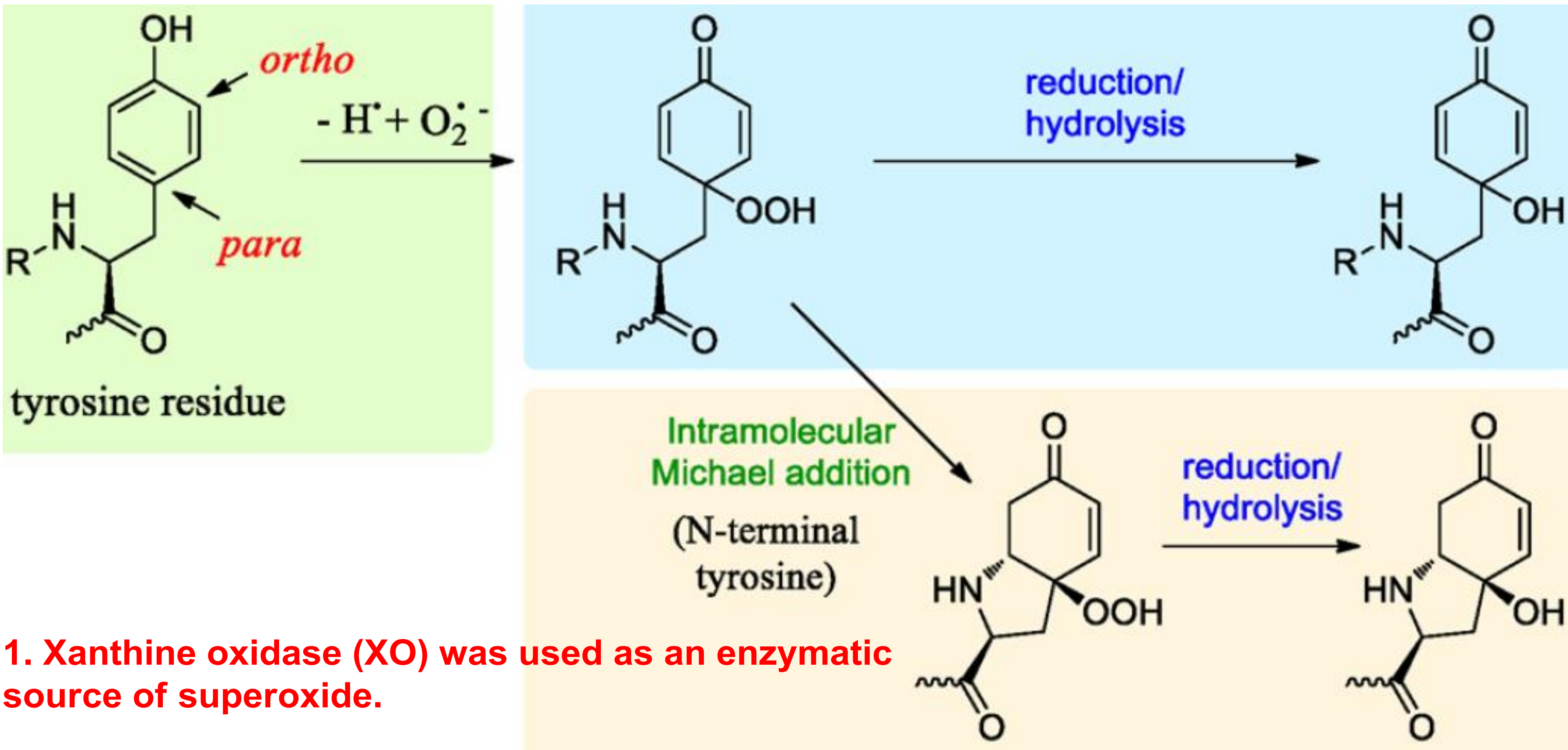
2. S-oxidized radical cation of Met-35 can be generated by the reduction of the tyrosyl radical at Tyr-10.

3. Interaction of the C-terminal carboxylate anion with the S-oxidized radical cation of Met-35 could be essential to the neurotoxicity of Aβ42.

↓

Application to artificial transformation of Tyr can be interesting.

5-4. Product of tyrosine oxidation



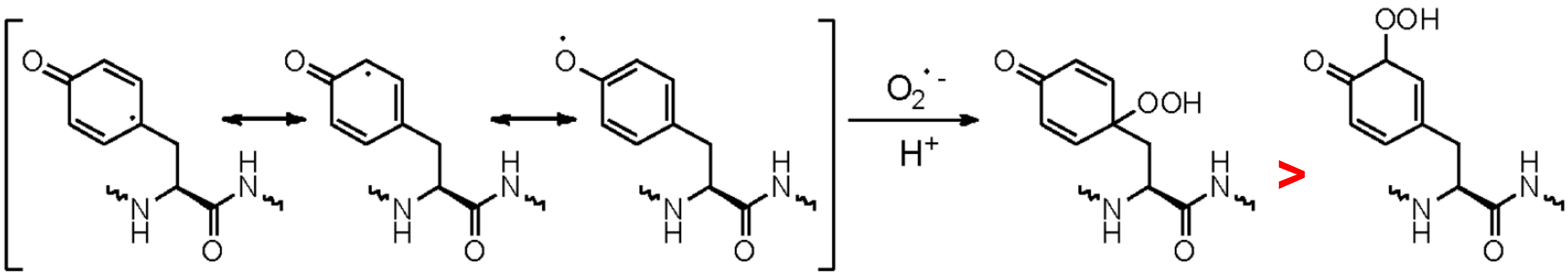
1. Xanthine oxidase (XO) was used as an enzymatic source of superoxide.

2. Horseradish peroxidase (HRP) was used as catalyst of formation of tyrosyl radical.

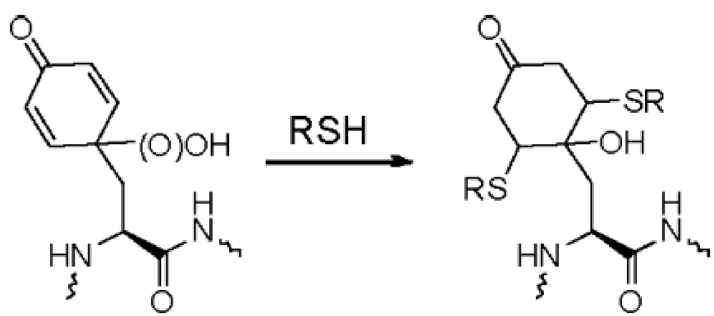
Ned A. Porter et al. *J. Am. Chem. Soc.* **2012**, *134*, 16773.

5-4-1. Proposed mechanism

Possible mechanism



This reaction is of interest due to its general novelty as well as to challenge steric hindrance and rearomatization stabilization.



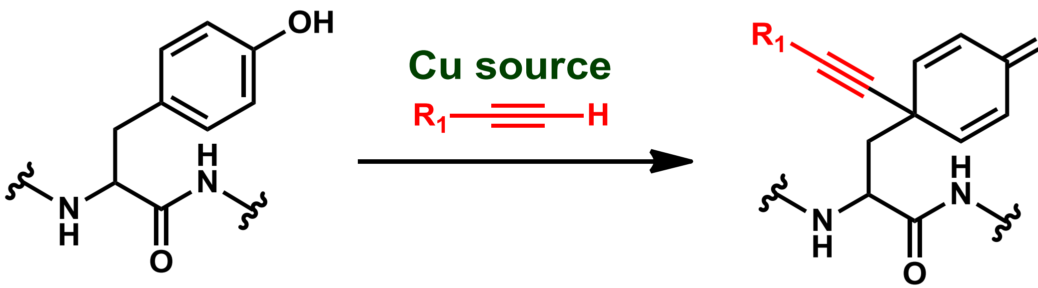
The formation of michael-type adducts with a number of nucleophiles such as cysteines.

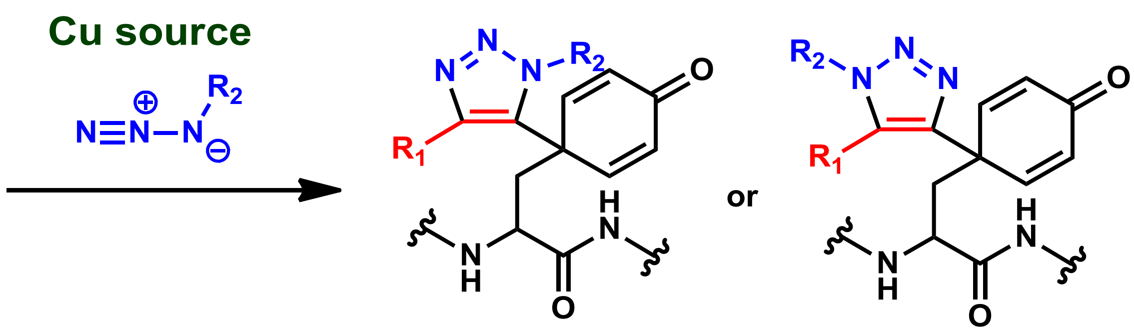
Manuscript in preparation

Ned A. Porter et al. *J. Am. Chem. Soc.* **2012**, *134*, 16773.

5-5. Application to artificial transformation of Tyr with Cu/O_2

Click chemistry





One-pot ligations can be achieved.

Ligations of *ortho* position, *O*-Alkynylation,
Michael-type addition...etc?

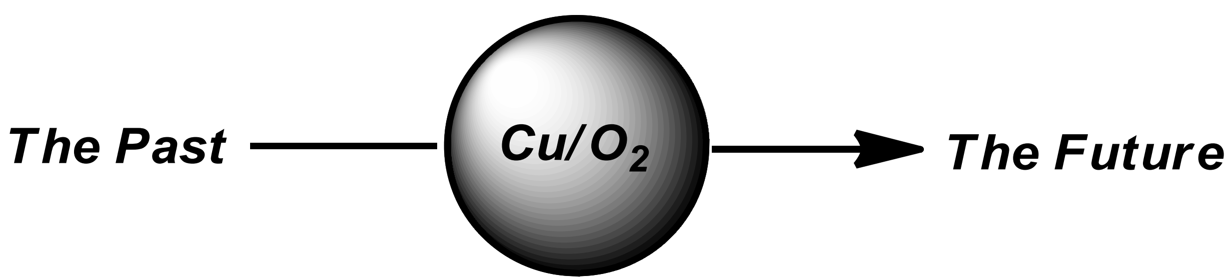
Contents

6. Summary

Cu catalyzed aerobic C-H oxidation reactions have been developed in recent years, and it also clarifies key challenges that lie ahead. This is because mechanistic understanding of these reactions were not completely elucidated.

↓

If this problem is solved, Cu catalyzed aerobic C-H oxidation reactions will be more interesting and application to reactions in body can be possible.



Reference

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"Copper-oxygen chemistry", kenneth D. Karlin, Shinobu Itoh

"最新ペプチド合成技術とその創薬研究への応用" 木曽 良明、向井秀仁