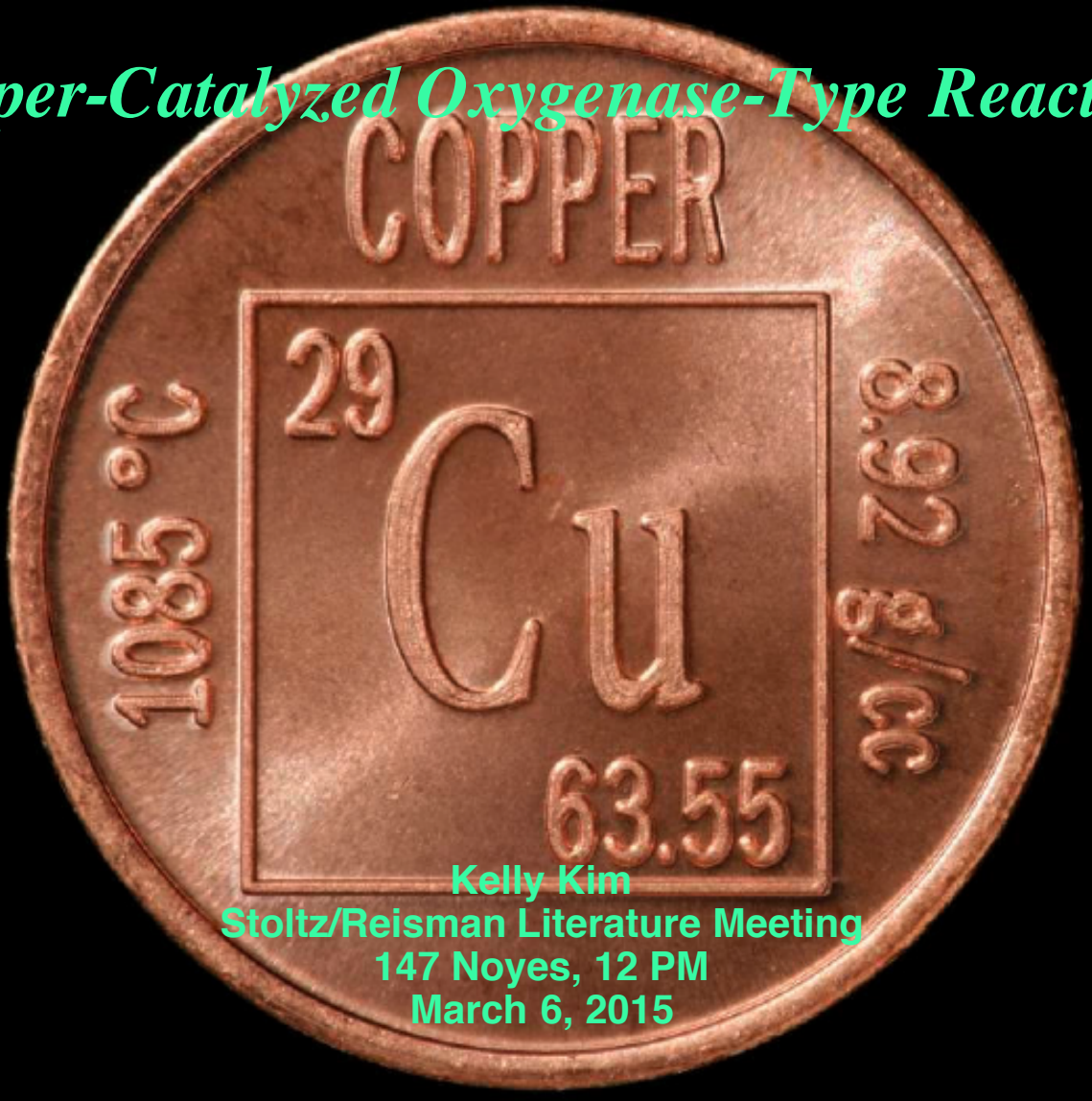
Copper-Catalyzed Oxygenase-Type Reactions



Kelly Kim

Stoltz/Reisman Literature Meeting
147 Noyes, 12 PM
March 6, 2015

Copper

29

Cu

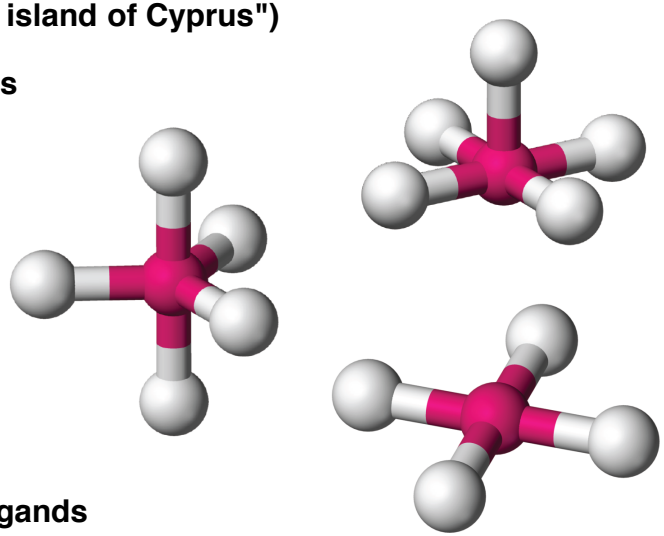
63.546

Group 11 metal

"Copper" comes from Latin "cuprum" ("from the island of Cyprus")

Used in human civilization for thousands of years

Found in the active sites of many enzymes

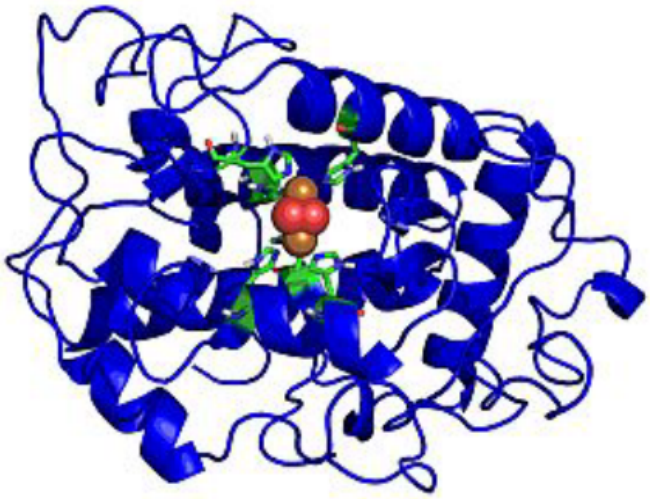


Electronic Configuration: $1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^1$

Cu(I) = d^{10} flexible geometry

Cu(II) = d^9 square planar, square-pyramidal, or trigonal-bipyramidal

Cu(III) = d^8 square planar, less common, stabilized by basic/anionic ligands



Stack, *Chem. Rev.* **2004**, *104*, 1013–1045.

Outline

I. Copper in enzymes and the reactions of different copper-dioxygen compounds

II. Use of copper-dioxygen catalysis in organic methodology

III. Applications of copper-dioxygen catalysis in total synthesis

IV. Summary

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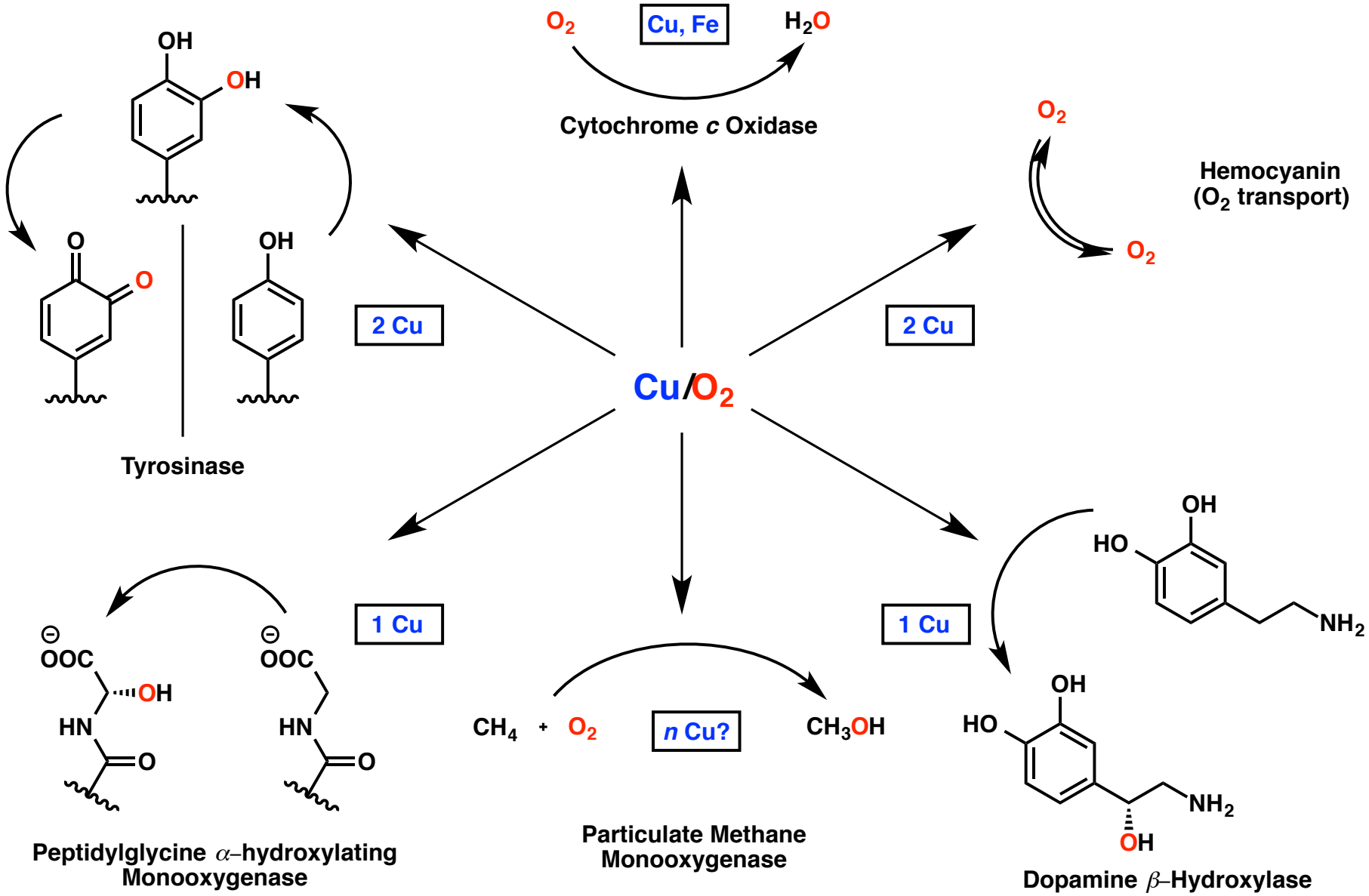
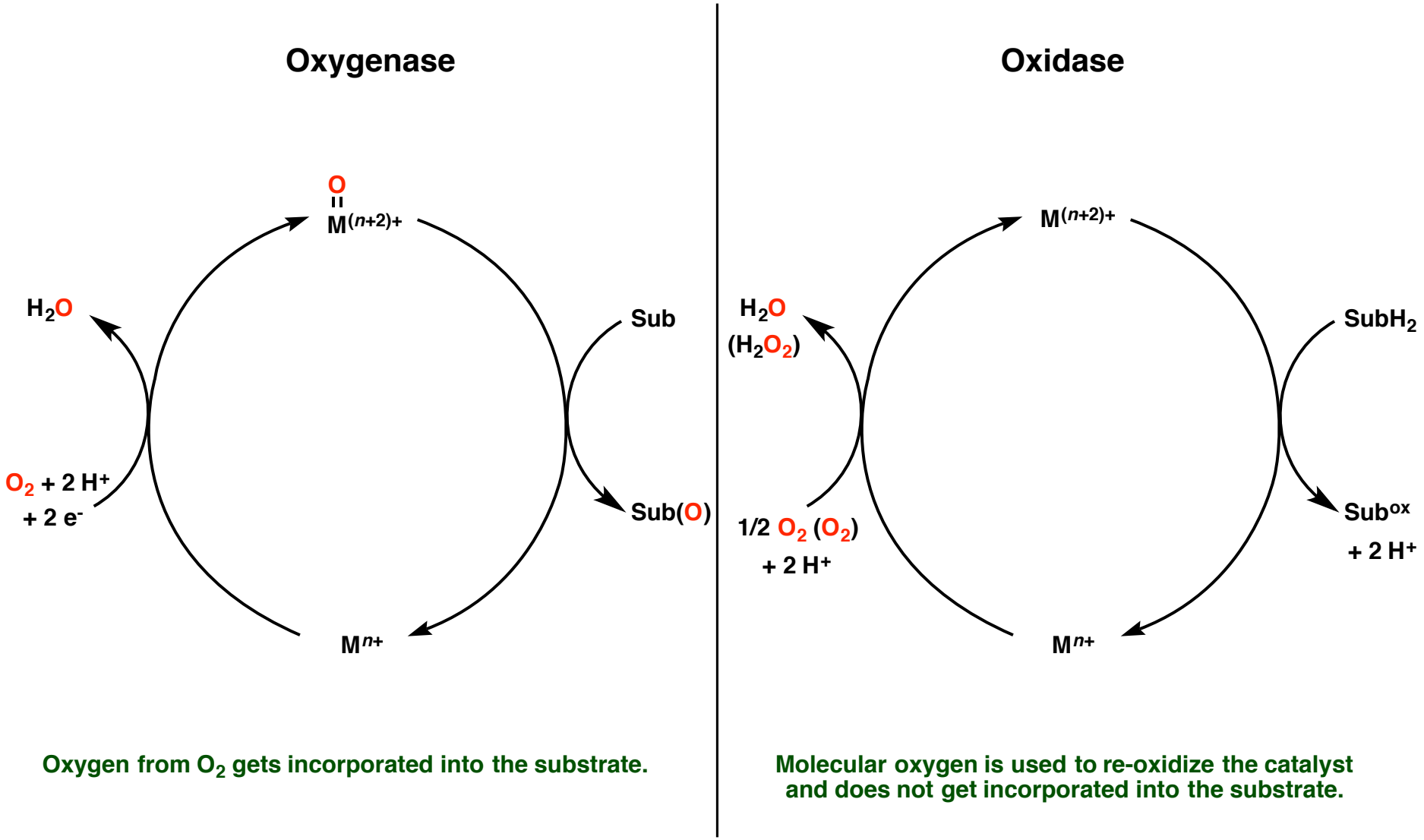
Copper in Biology: Enzymes



Solomon, *Angew. Chem. Int. Ed.* **2001**, *40*, 4570–4590. Stack, *Chem. Rev.* **2004**, *104*, 1013–1045.

Oxygenase vs. Oxidase

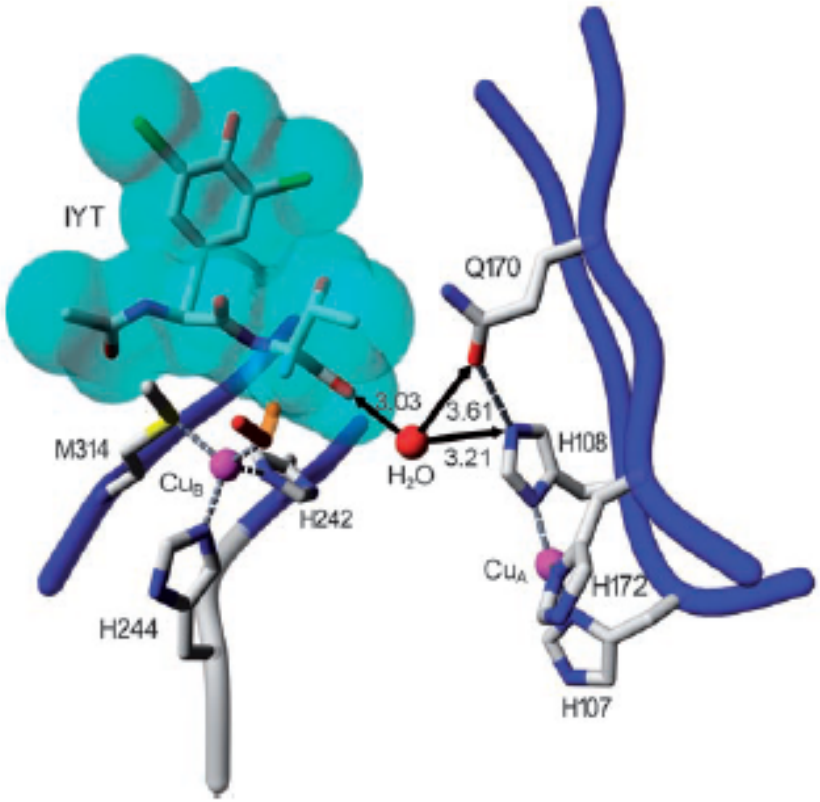


Oxygen from O_2 gets incorporated into the substrate.

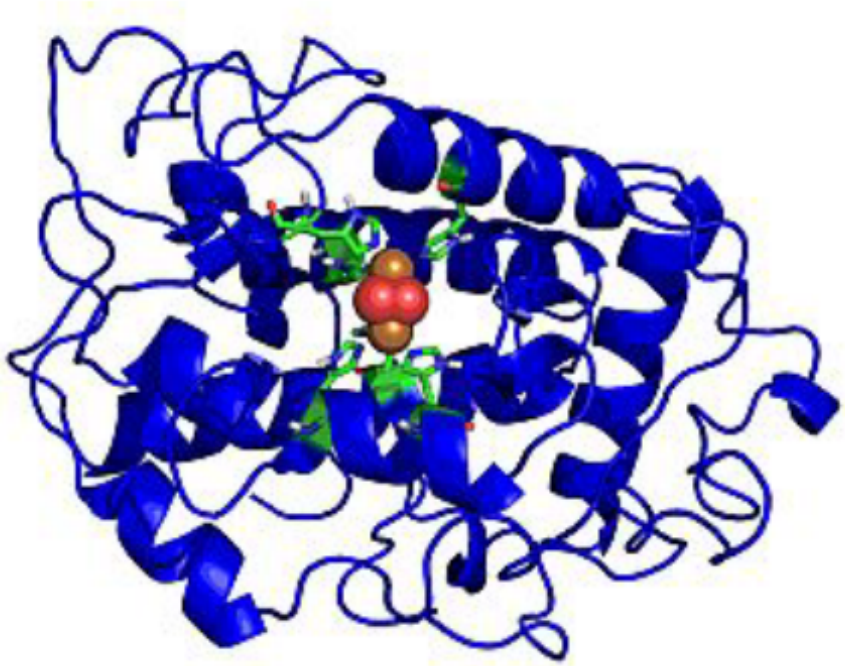
Molecular oxygen is used to re-oxidize the catalyst and does not get incorporated into the substrate.

Stahl, *Angew. Chem. Int. Ed.* **2004**, *43*, 3400–3420.

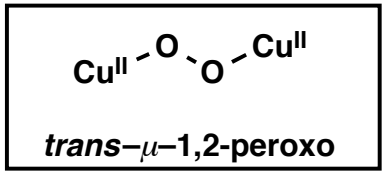
Dicopper-oxygen Cores in Oxygenase Enzymes



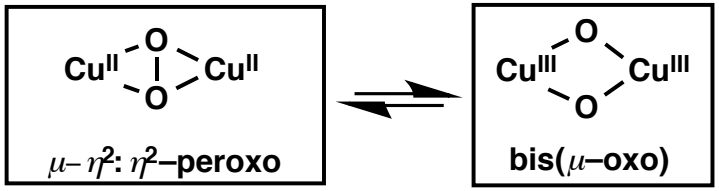
Peptidylglycine α–Hydroxylating Monooxygenase (PHM)



Tyrosinase (Tyr)



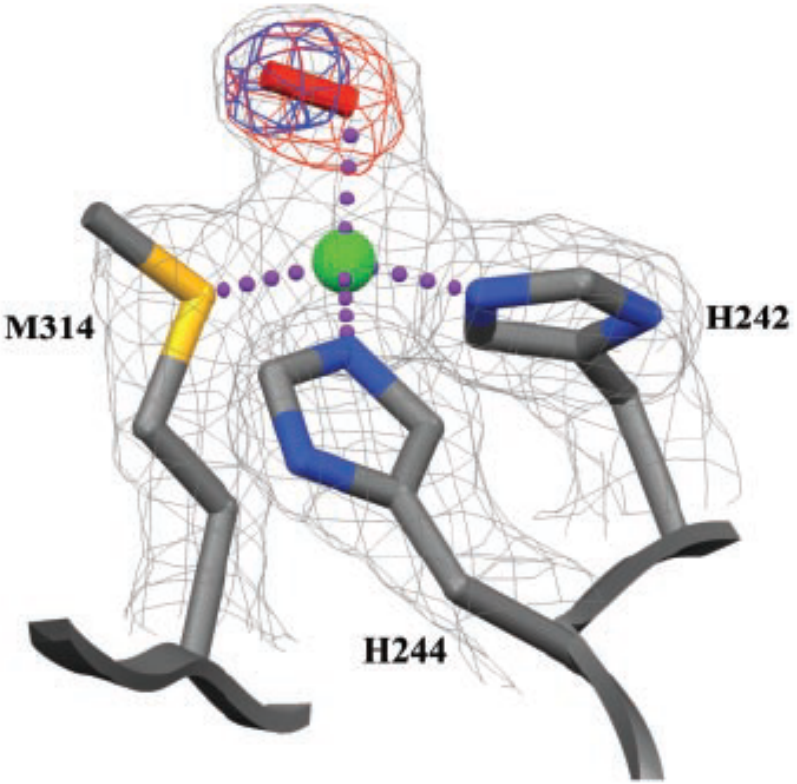
***trans*–μ–1,2-peroxo**



μ–η^2:η^2–peroxo **bis(μ–oxo)**

Adapted from Tuczek, *Angew. Chem. Int. Ed.* **2008**, *47*, 2344–2347.

Dicopper-oxygen Cores in Oxygenase Enzymes



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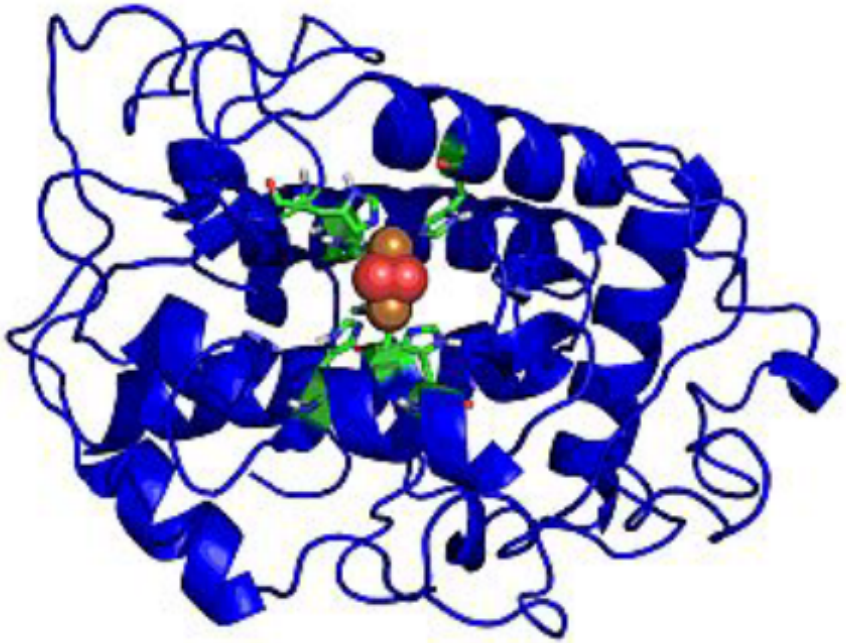
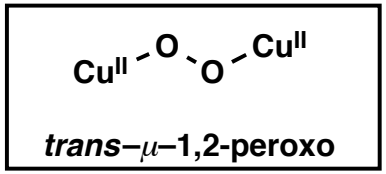
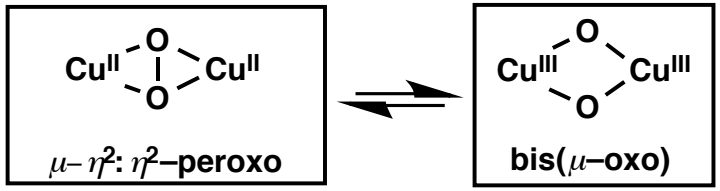


Tyrosinase (Tyr)



***trans*–μ–1,2-peroxo**

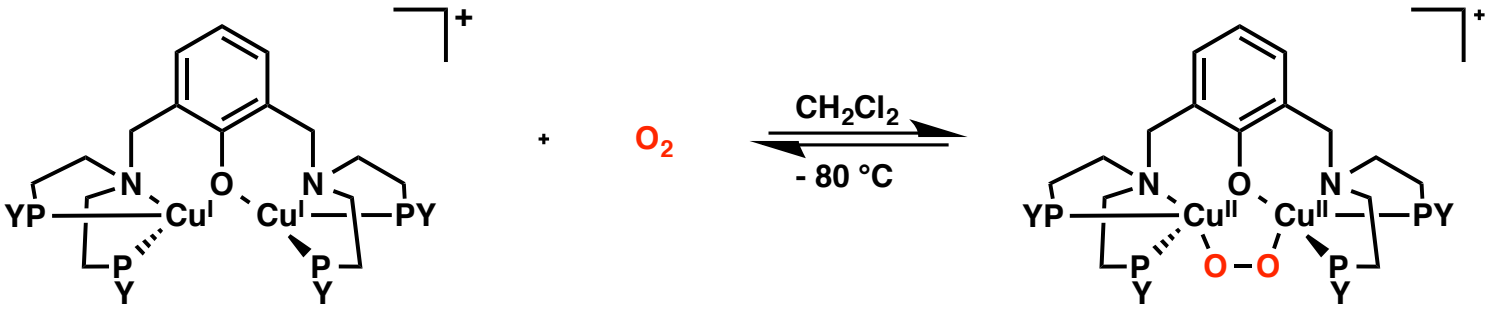


μ–η^2:η^2–peroxo

bis(μ–oxo)

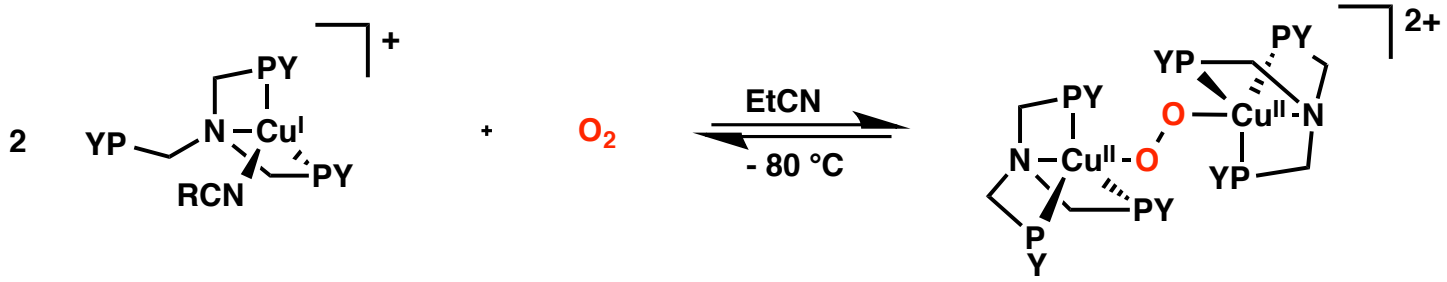
Adapted from Tuczek, *Angew. Chem. Int. Ed.* **2008**, *47*, 2344–2347.

Reactivity Differences between Dicopper-Oxygen Compounds

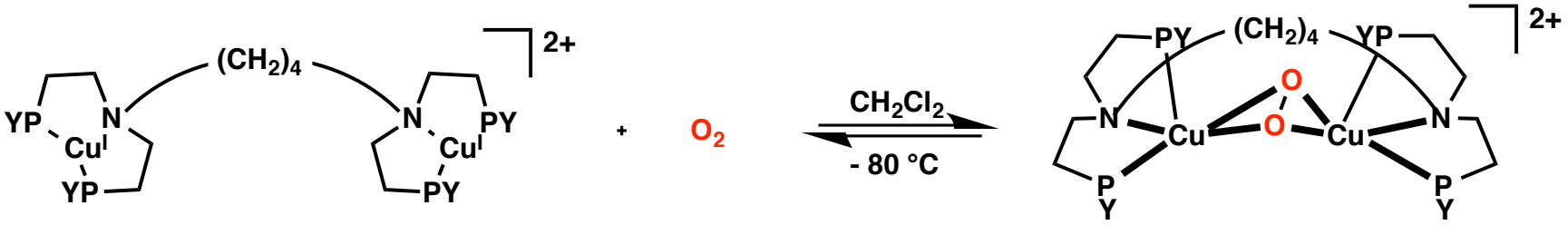


PY = 2-pyridyl

μ–phenoxo peroxo



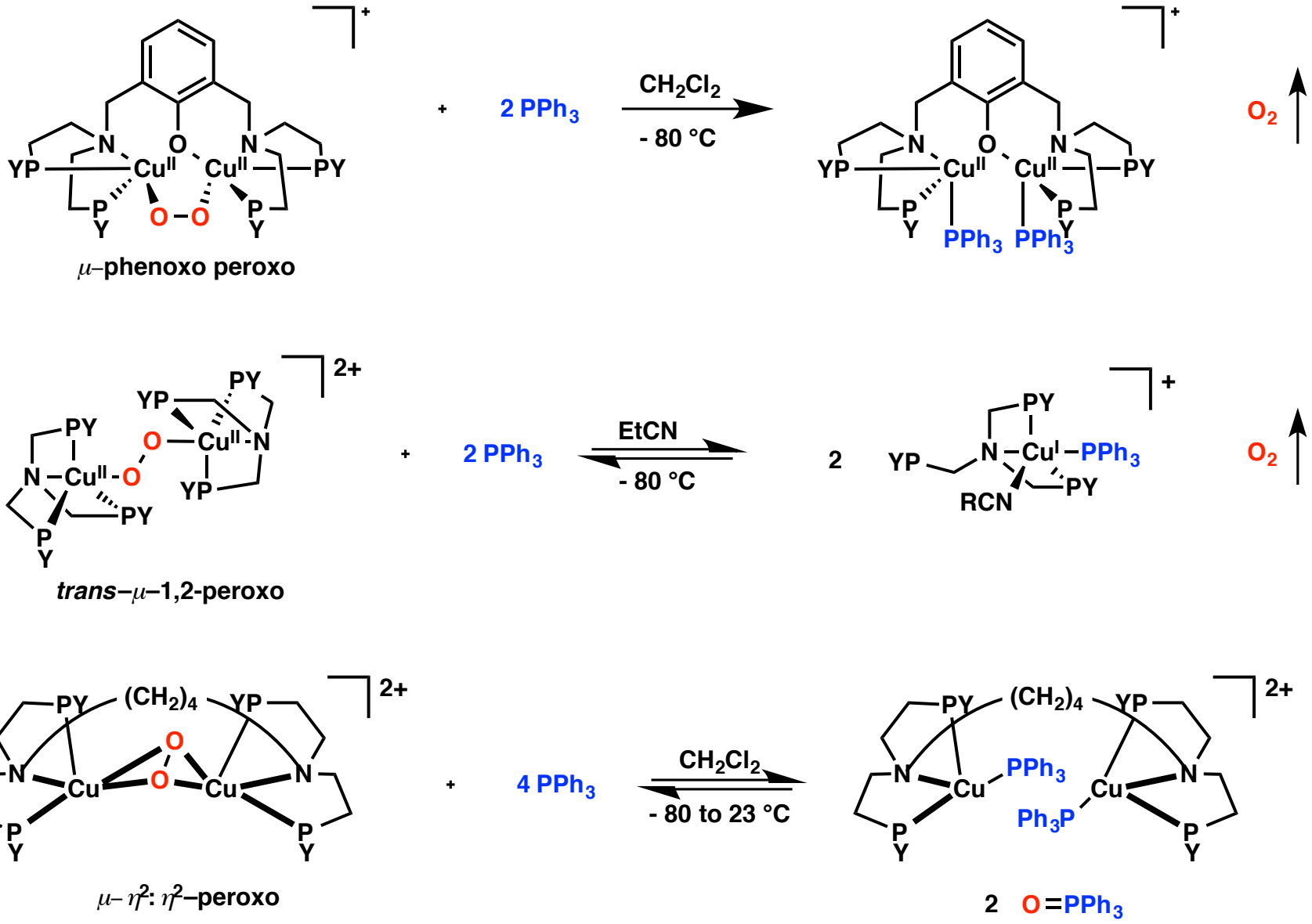
trans–μ–1,2-peroxo



μ– η^2: η^2–peroxo

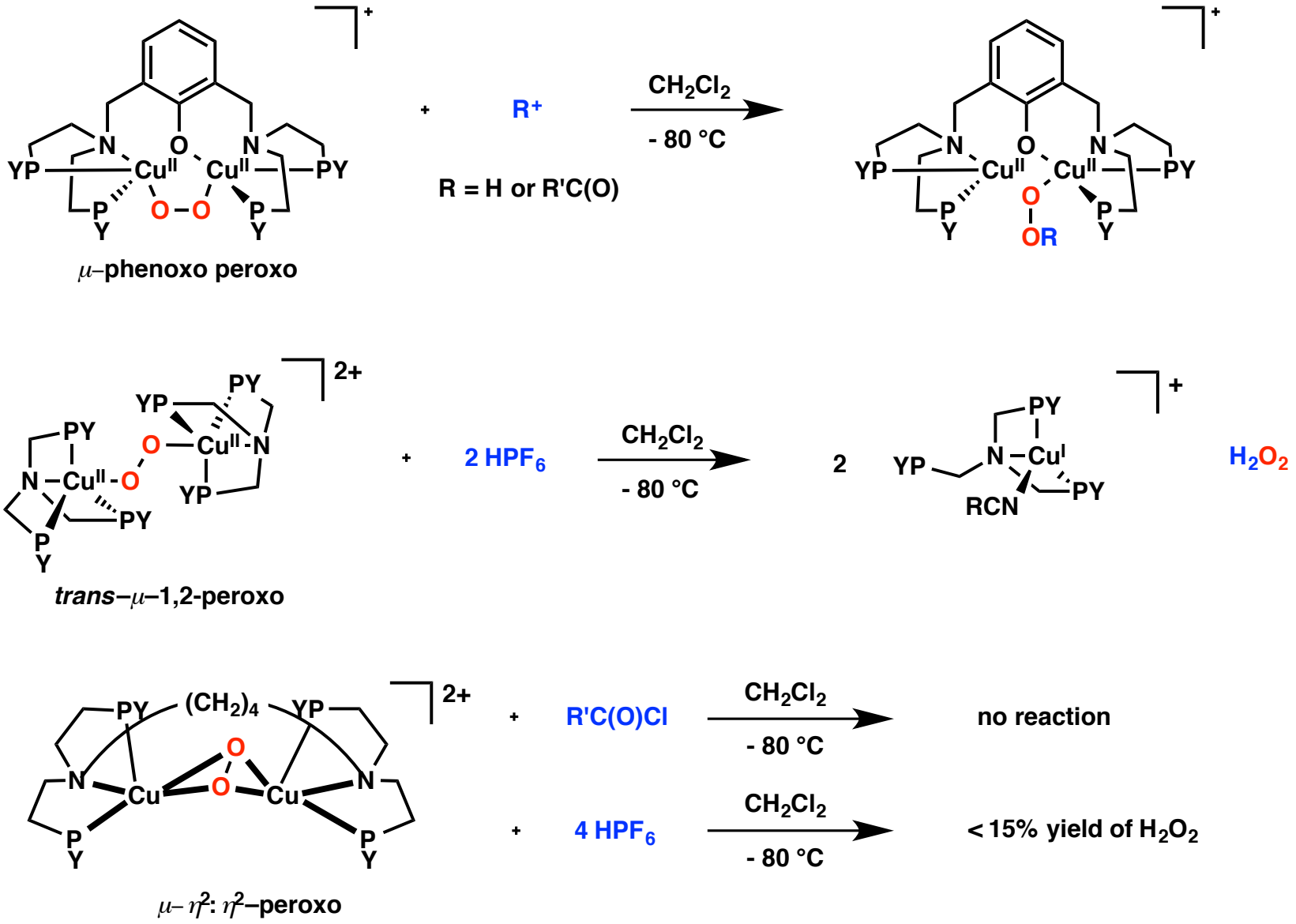
Karlin, *J. Am. Chem. Soc.* **1991**, *113*, 5322–5332. Tolman, *Chem. Rev.* **2004**, *104*, 1047–1076.

Reactivity Differences between Dicopper-Oxygen Compounds



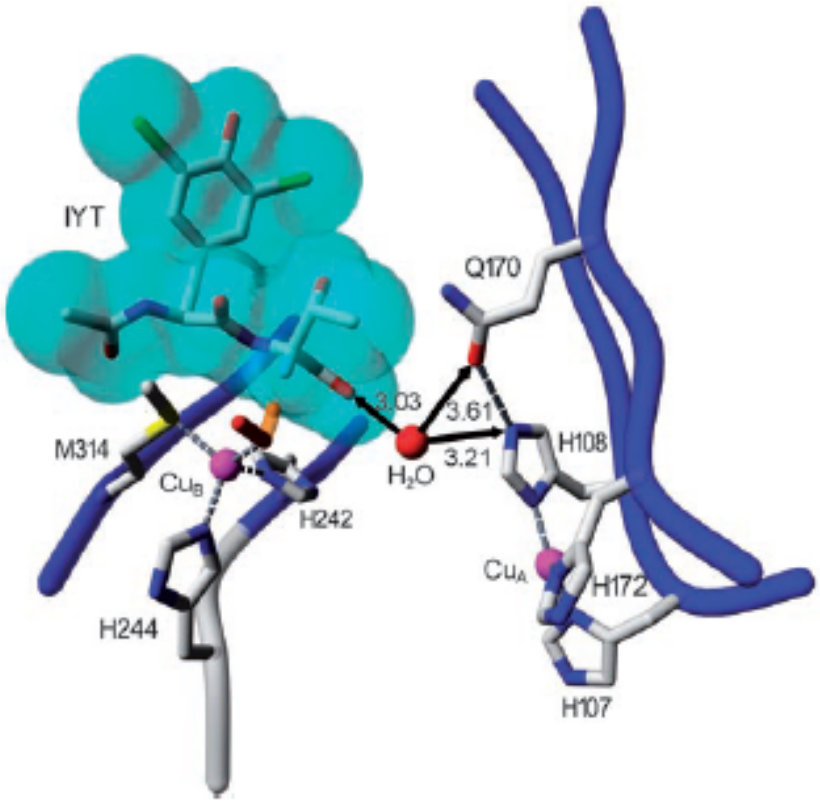
Karlin, *J. Am. Chem. Soc.* **1991**, *113*, 5322–5332. Tolman, *Chem. Rev.* **2004**, *104*, 1047–1076.

Reactivity Differences between Dicopper-Oxygen Compounds



Karlin, *J. Am. Chem. Soc.* **1991**, *113*, 5322–5332. Tolman, *Chem. Rev.* **2004**, *104*, 1047–1076.

Dicopper-oxygen Cores in Oxygenase Enzymes



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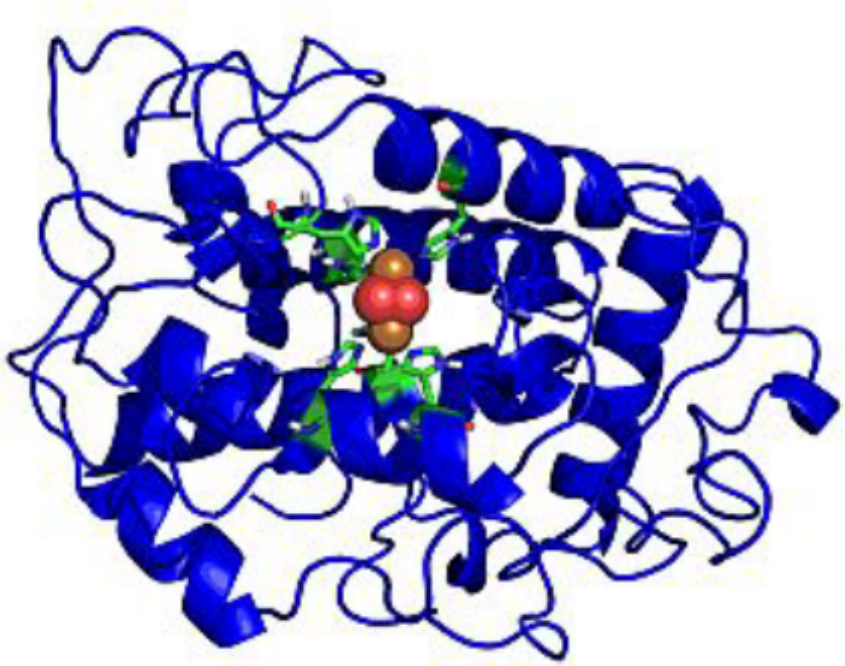

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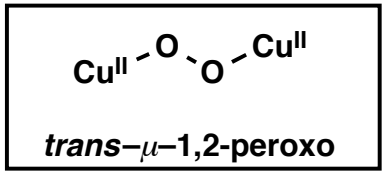
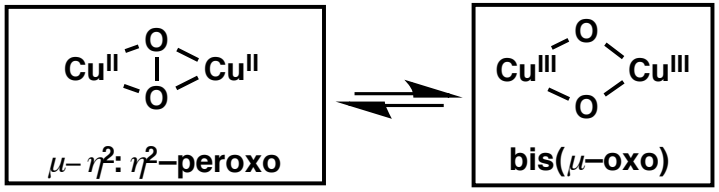


***trans*–μ–1,2-peroxo**

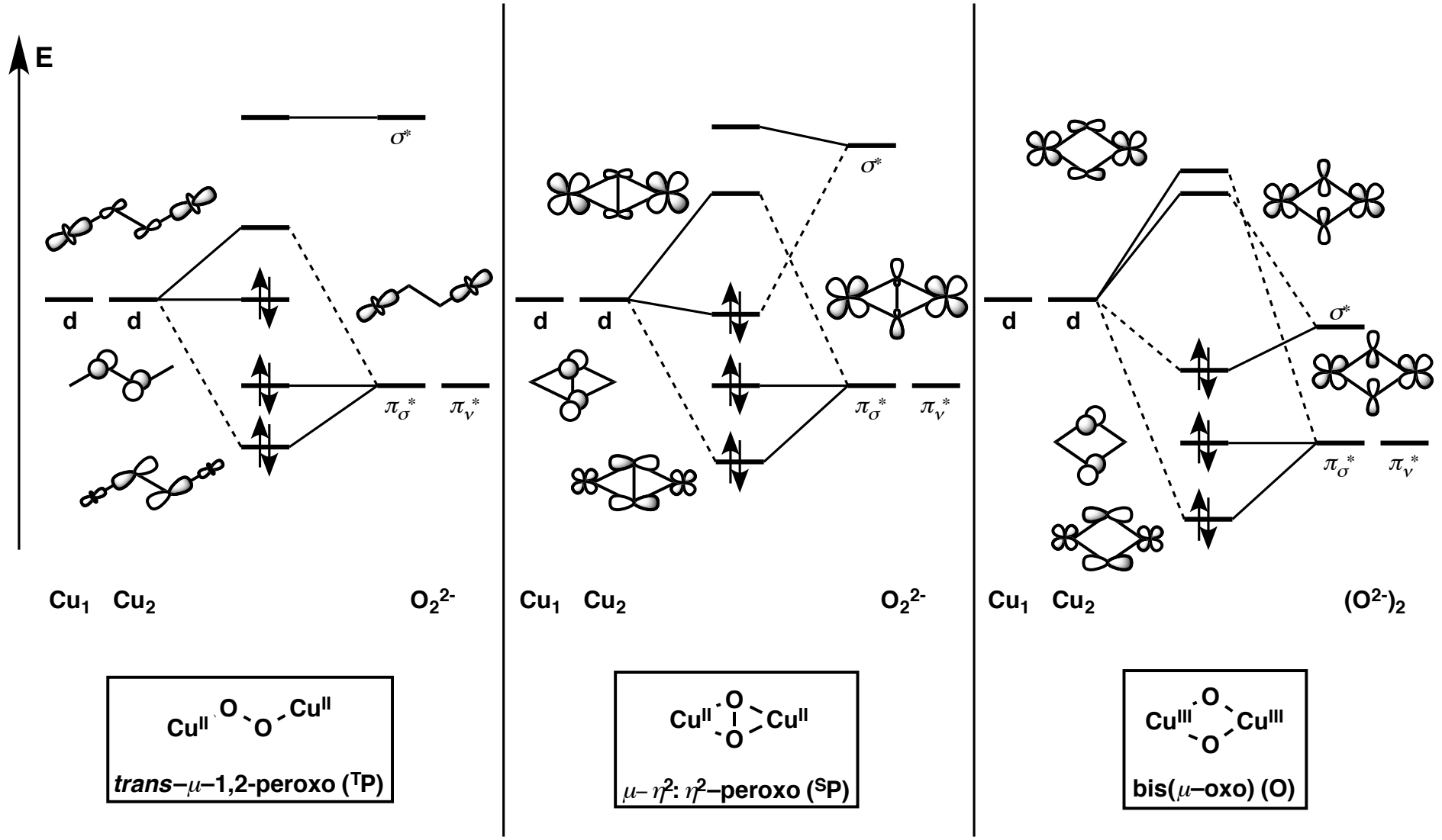
nucleophilic



electrophilic

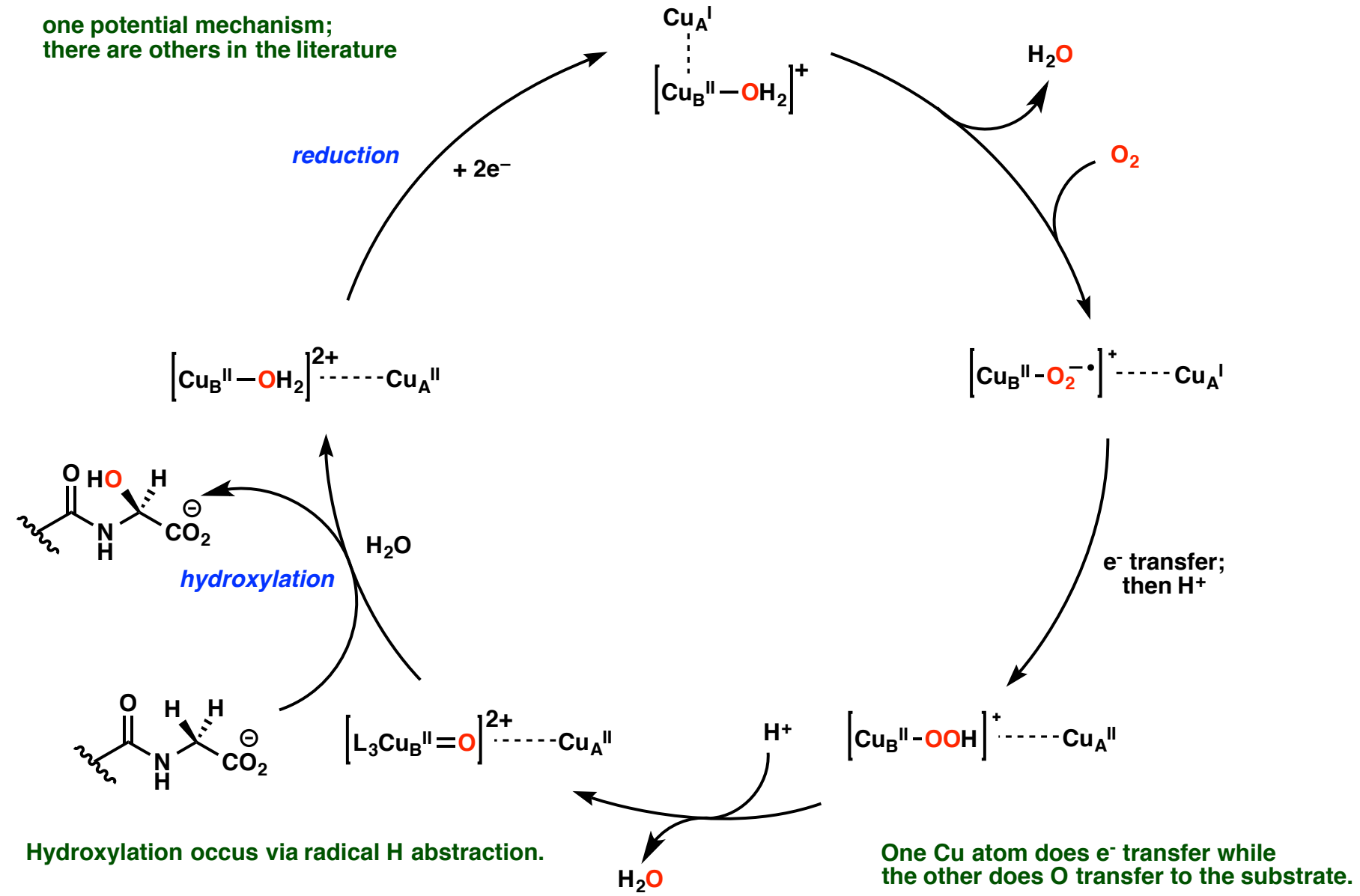
Adapted from Tuczek, *Angew. Chem. Int. Ed.* **2008**, *47*, 2344–2347.

Molecular Orbitals of Dioxygen-Dicopper Systems



Reproduced from Stack, *Chem. Rev.* **2004**, *104*, 1013–1045.

PHM Modification of Peptides

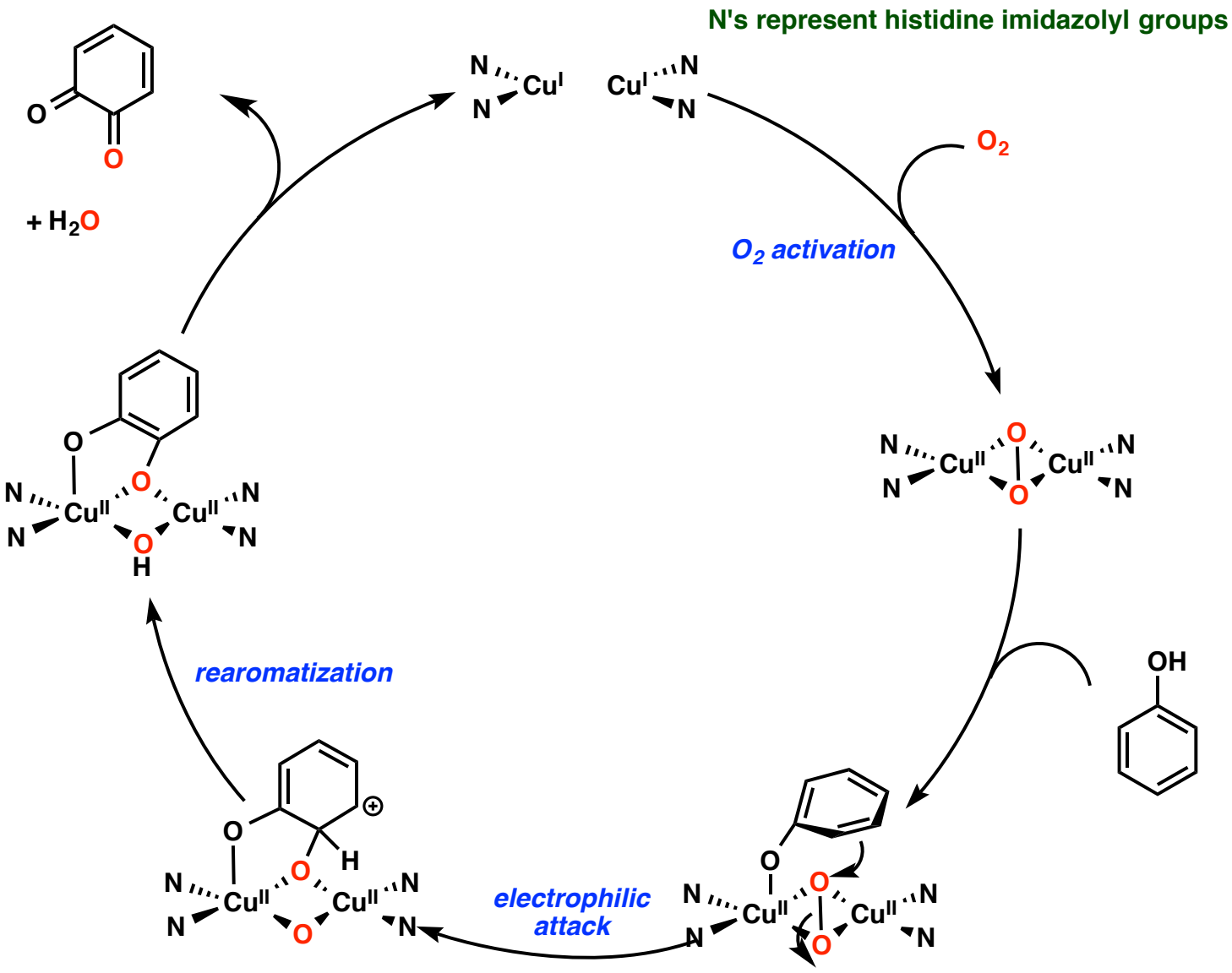


Hydroxylation occus via radical H abstraction.

One Cu atom does e⁻ transfer while the other does O transfer to the substrate.

Tuczek, *Angew. Chem. Int. Ed.* **2008**, *47*, 2344–2347.

Tyrosinase Oxidation of Phenols



Tolman, *Chem. Rev.* **2004**, *104*, 1047–1076.

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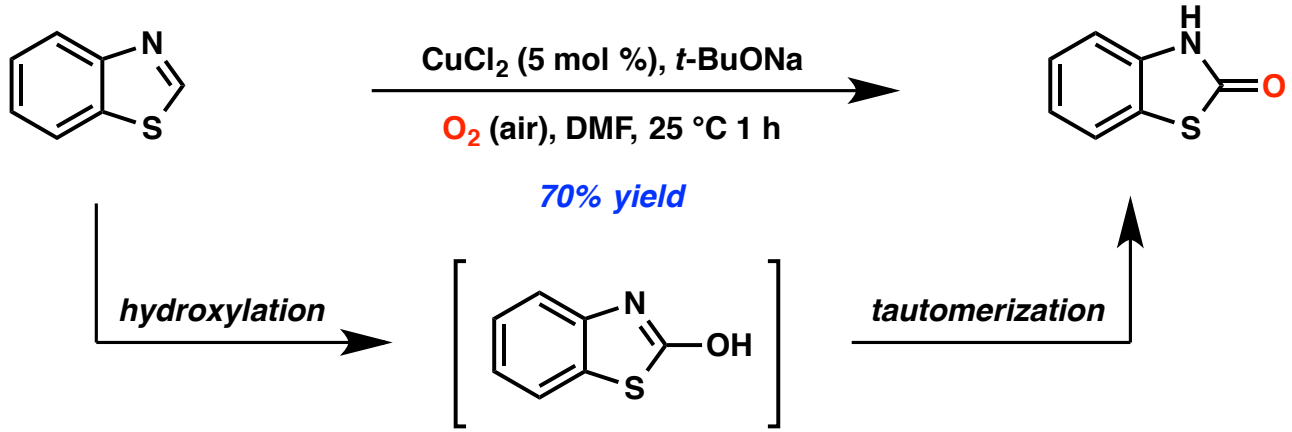
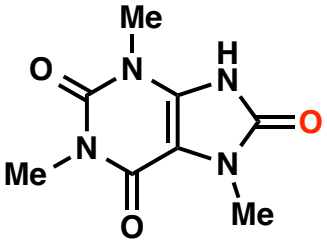
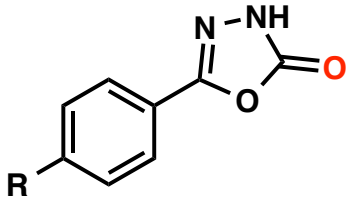
Oxidation of Electron-Deficient Arenes and Heteroarenes

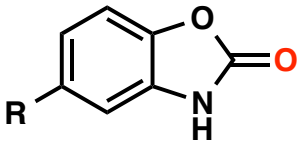




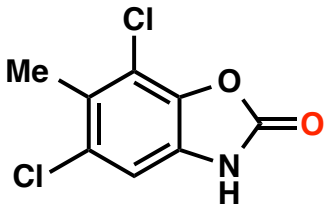
36%



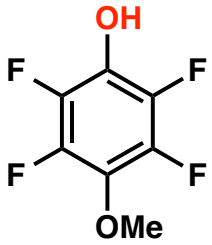
R = H (*84%*), Me (*84%*), OMe (*79%*), Cl (*37%*), Br (*76%*)



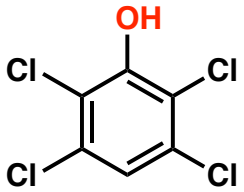
R = H (*73%*), Me (*67%*), *t*-Bu (*73%*), Cl (*51%*)



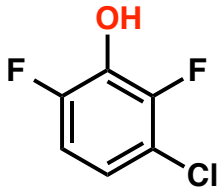
57%



68%



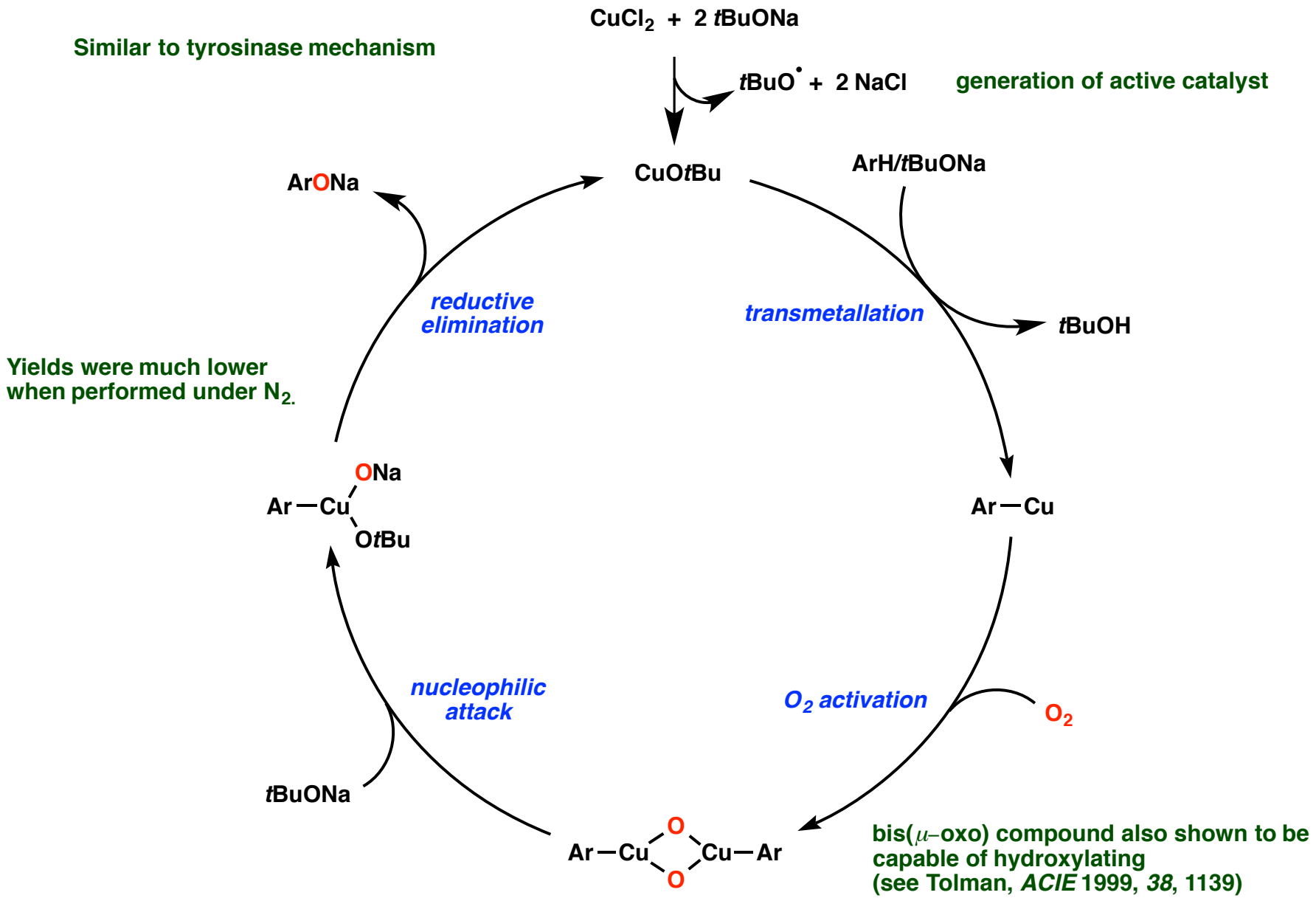
89%



58%

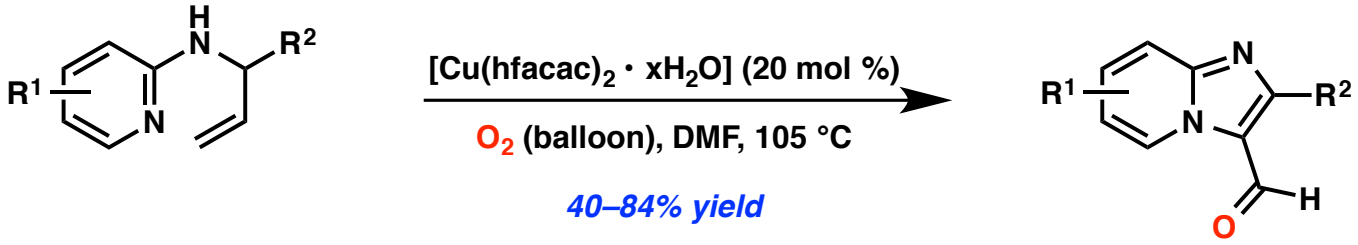
Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 4666–4670.

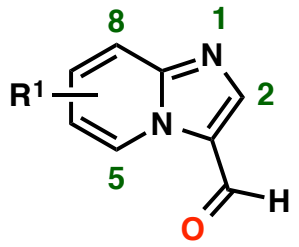
Oxidation of Electron-Deficient Arenes and Heteroarenes



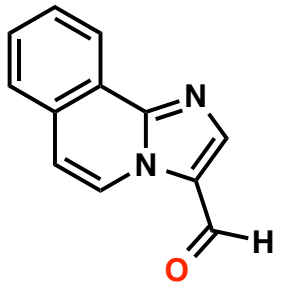
Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 4666–4670.

Dehydrogenative Aminooxygenation: Formyl-Substituted N-Heterocycles

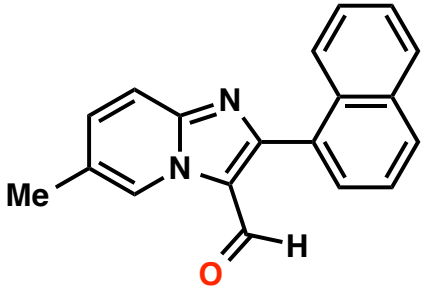




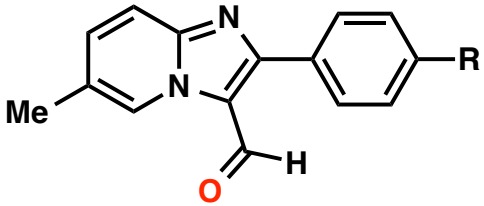
R = H (*70%*), 8-Me (*71%*), 6-Me (*51%*), 5-Me (*48%*), 6-Cl (*51%*)



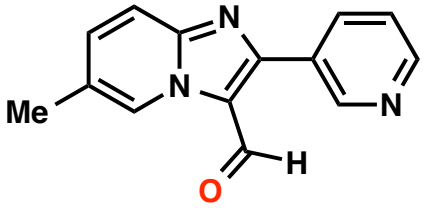
84%



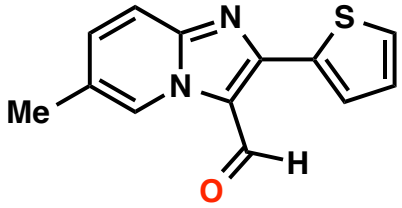
64%



R = OMe (*66%*), Me (*77%*), F (*70%*), CN (*42%*), COOMe (*56%*)



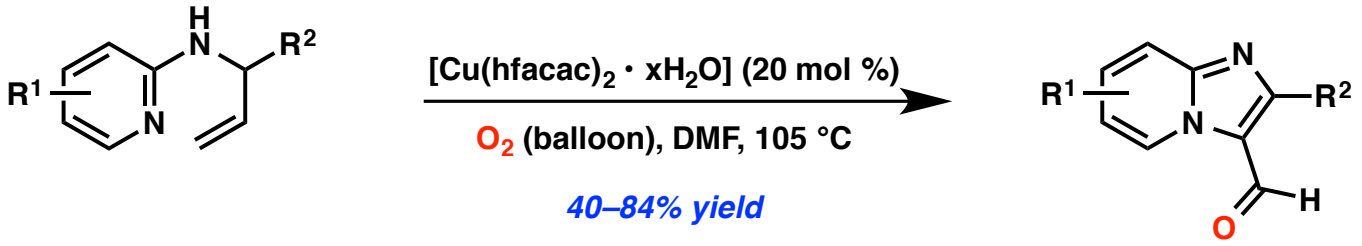
40%

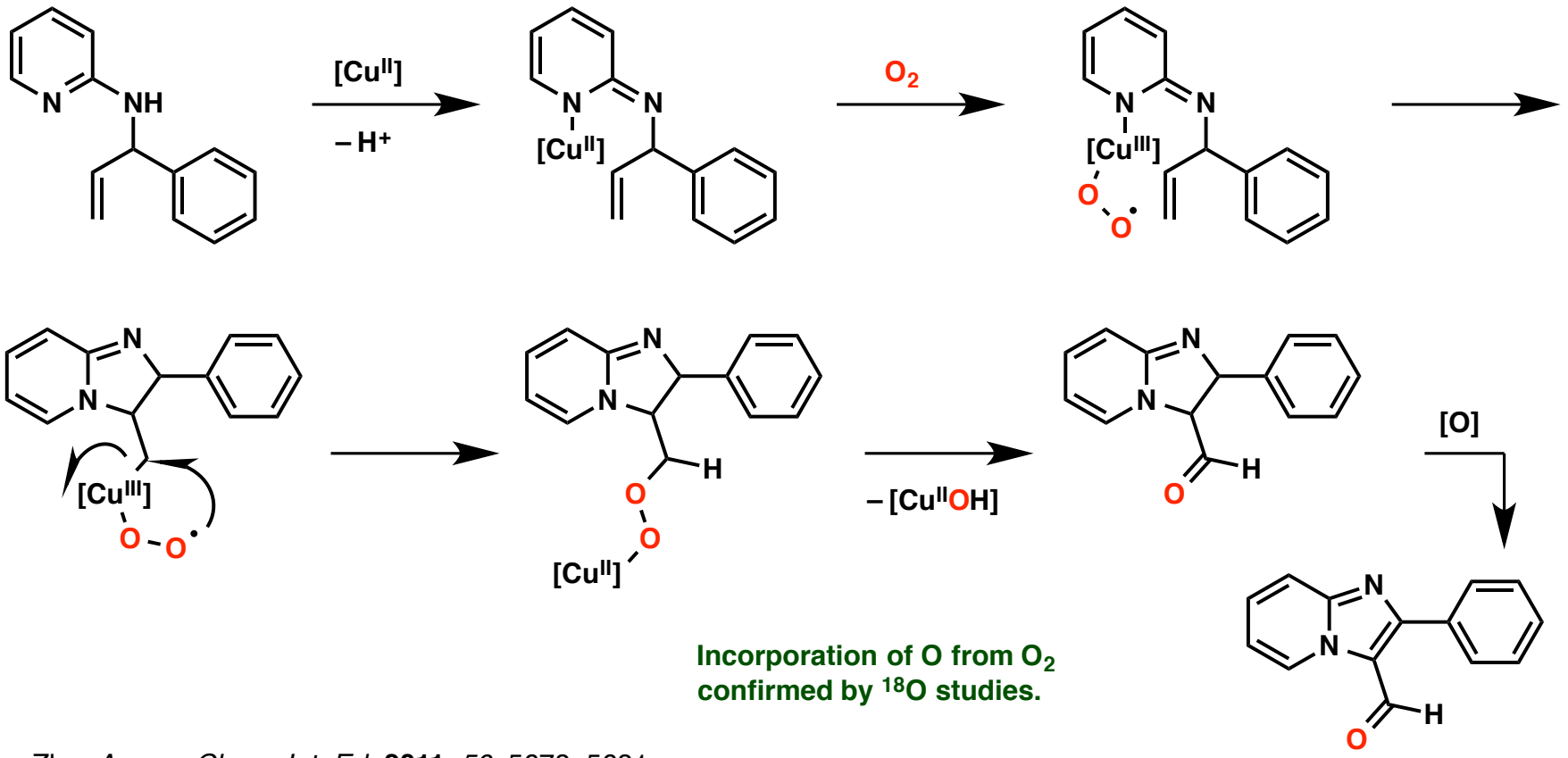


46%

Zhang; Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678–5681.

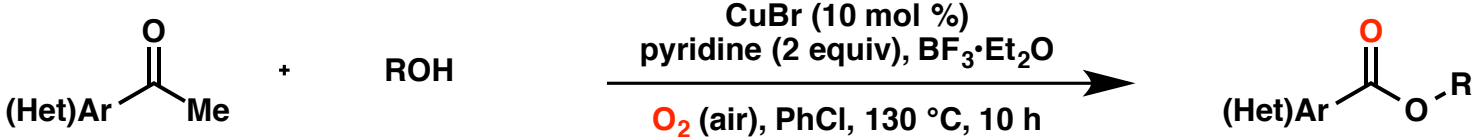
Dehydrogenative Aminooxygenation: Formyl-Substituted N-Heterocycles



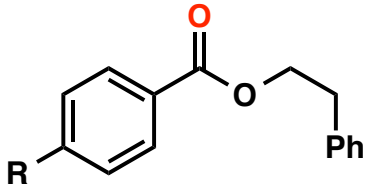


Zhang; Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678–5681.

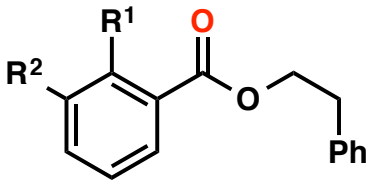
Synthesis of Esters from Ketones: Selective C(CO)–C(alkyl) Cleavage



45–82% yield

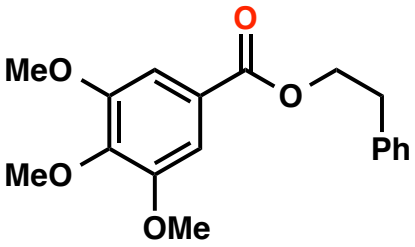


R = Ph *(82%)*, OMe (*81%*), Me (*66%*), ^{t}Bu (*75%*), F (*72%*), Cl (*73%*), Br (*78%*), NO_2 (*81%*), CN (*71%*), CF_3 (*78%*), SO_2Me (*59%*)

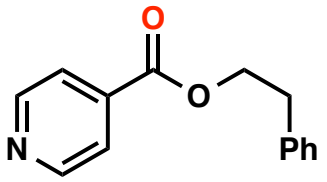


R^1 = H, R^2 = OMe (*78%*), NO_2 (*66%*), Br (*71%*)

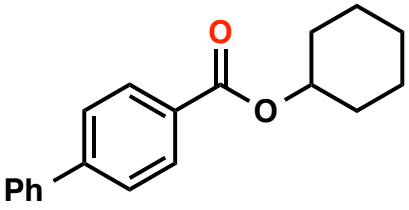
R^1 = Br, R^2 = H (*53%*)



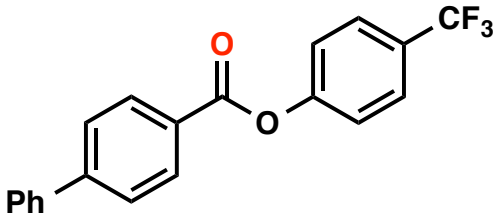
80%



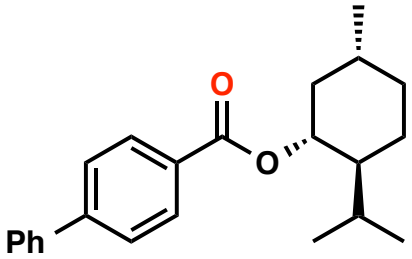
73%



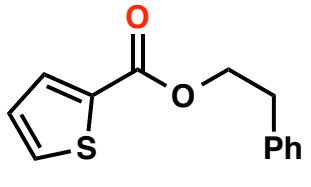
62%



45%



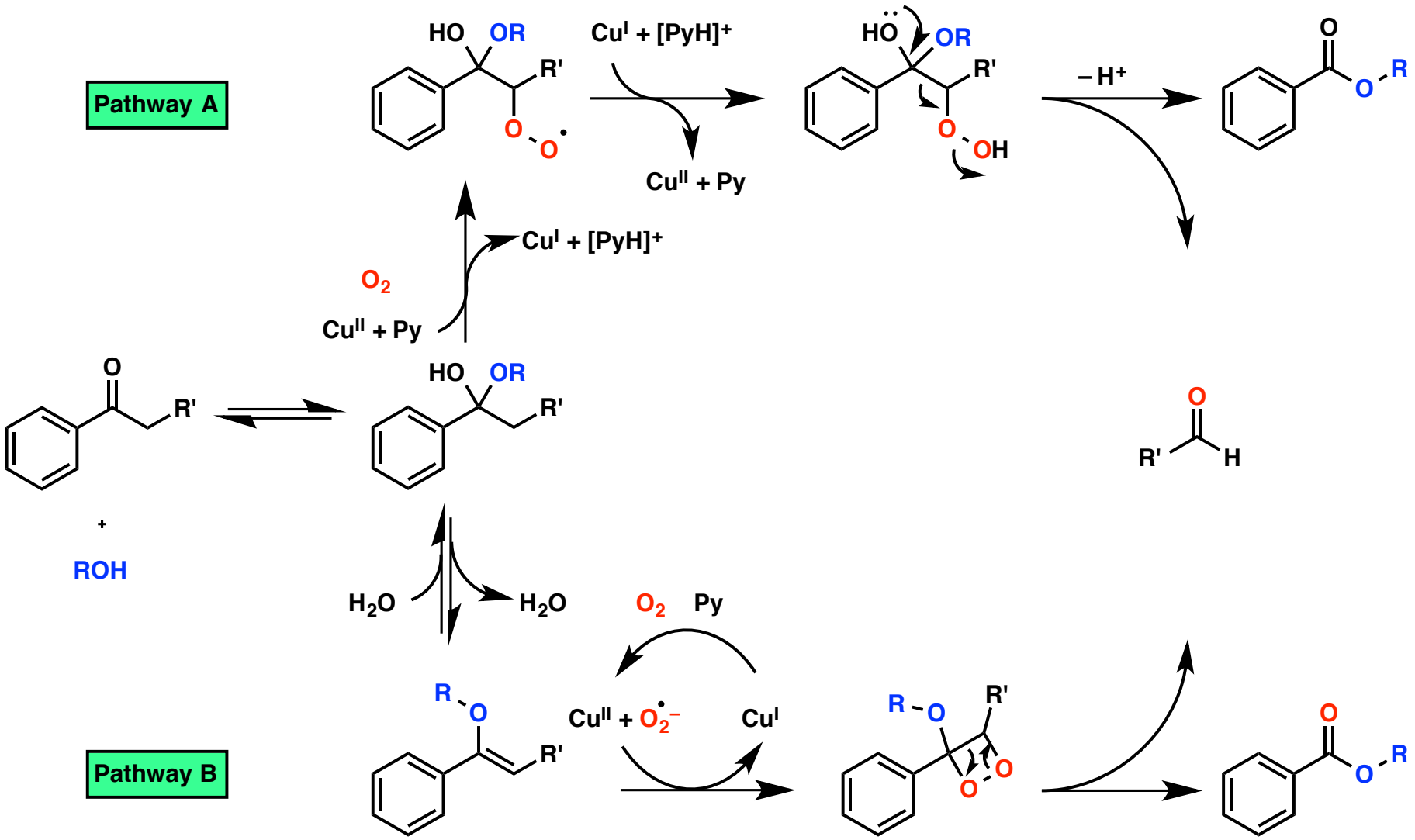
57%



52%

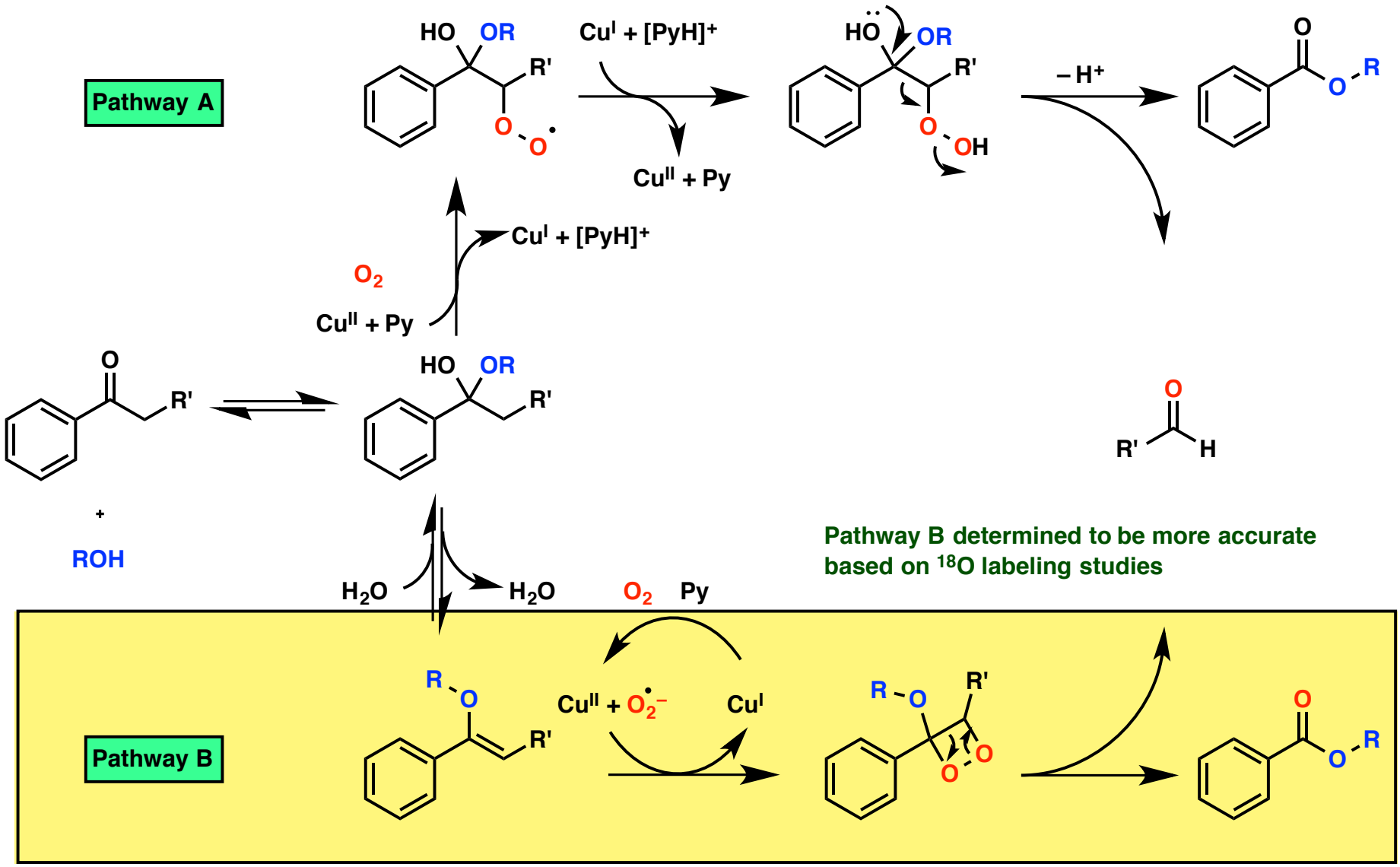
Jiao, *J. Am. Chem. Soc.* **2014**, *136*, 14858–14865.

Synthesis of Esters from Ketones: Selective C(CO)–C(alkyl) Cleavage



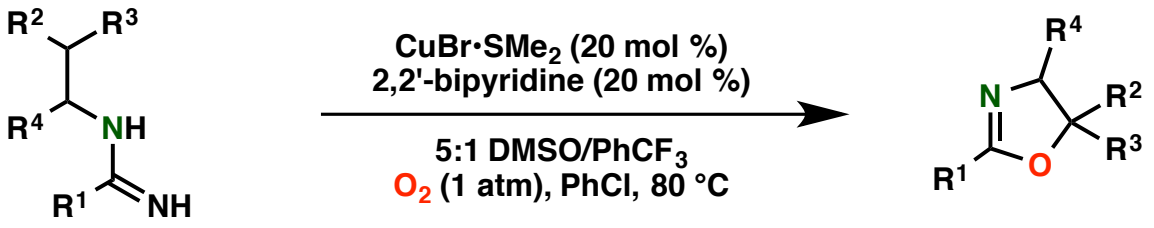
Jiao, *J. Am. Chem. Soc.* **2014**, *136*, 14858–14865.

Synthesis of Esters from Ketones: Selective C(CO)–C(alkyl) Cleavage

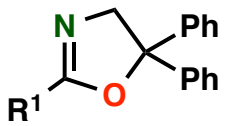


Jiao, *J. Am. Chem. Soc.* **2014**, *136*, 14858–14865.

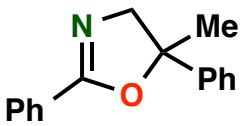
Amidine-Directed Aliphatic C–H Oxygenation



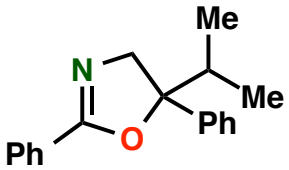
9–83% yield



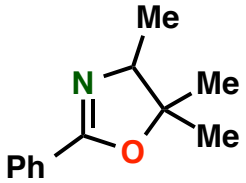
R^1 = 4-Br-C_6H_4 (*83%*)
2-napthyl (*79%*)
2-thienyl (*55%*)
isopropyl (*52%*)



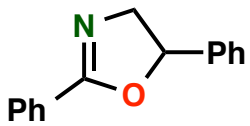
72%



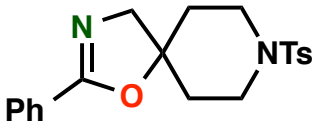
70%



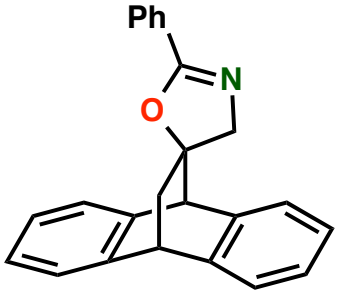
56%



9%



41%



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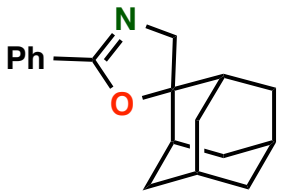

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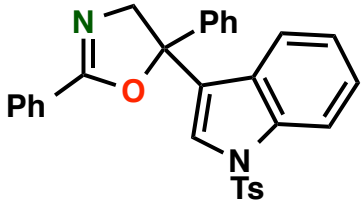
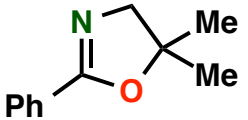


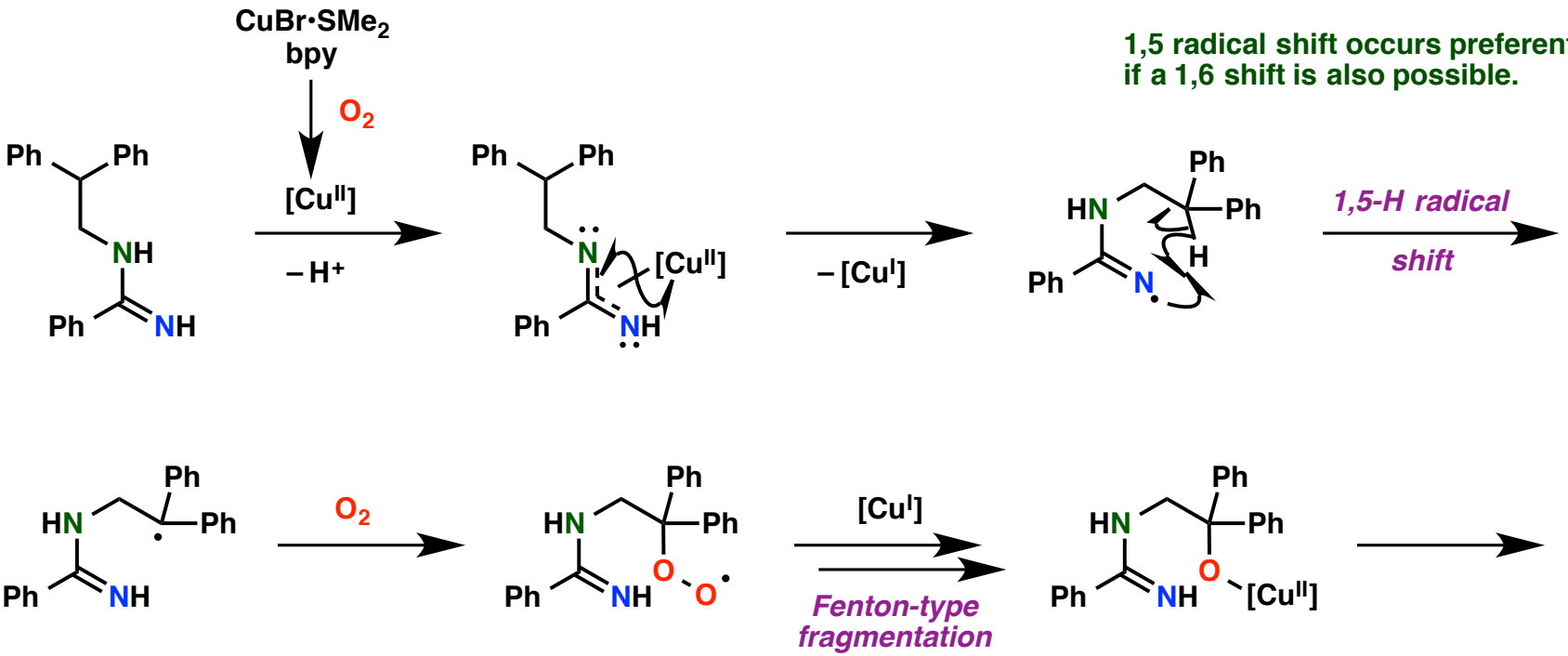
59%



39%

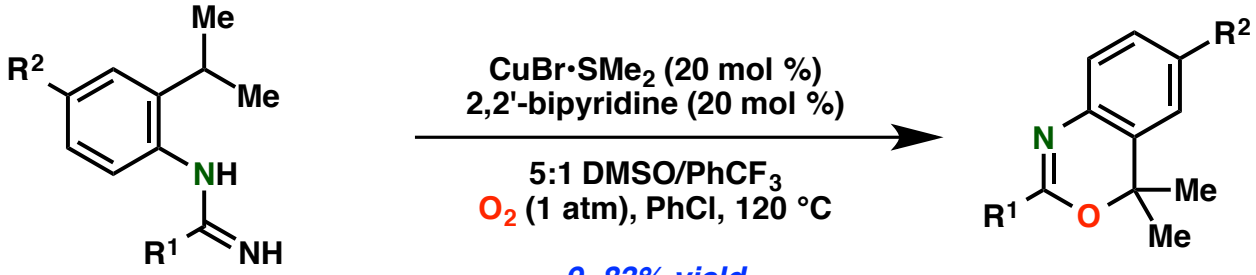
Chiba, *J. Am. Chem. Soc.* **2012**, *134*, 11980–11983.

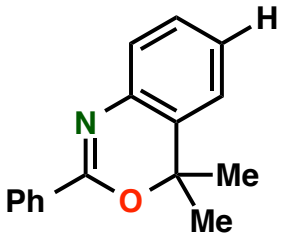
Amidine-Directed Aliphatic C–H Oxygenation



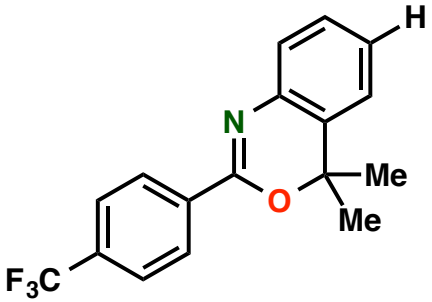
Chiba, *J. Am. Chem. Soc.* **2012**, *134*, 11980–11983.

Amidine-Directed Aliphatic C–H Oxygenation





67%



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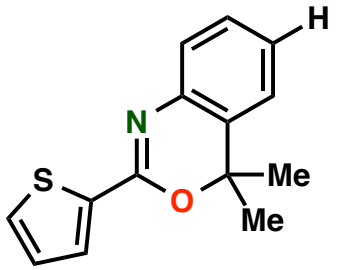
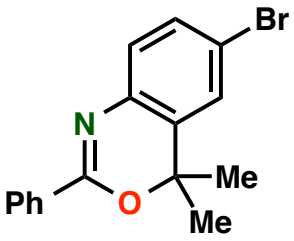


42%



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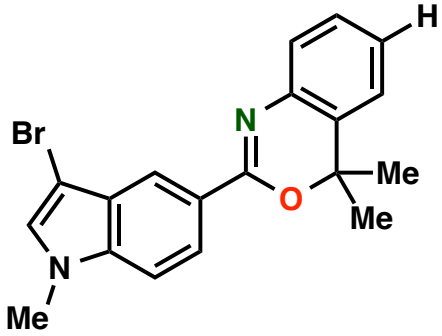
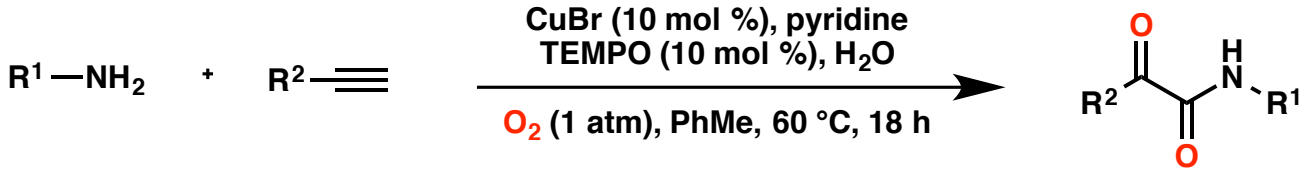
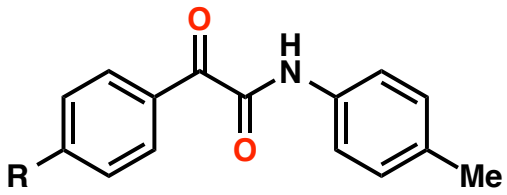


65%

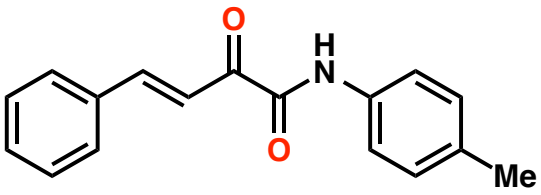
Chiba, *J. Am. Chem. Soc.* **2012**, *134*, 11980–11983.

Formation of α–Ketoamides from Terminal Alkynes





R = H (*77%*), Me (*67%*), F (*71%*)
Br (*56%*), OMe (*63%*), Et (*70%*)



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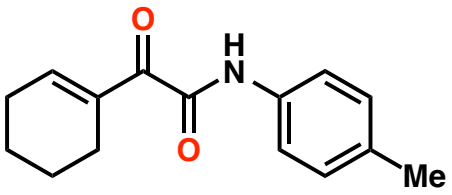
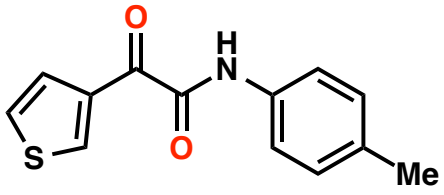
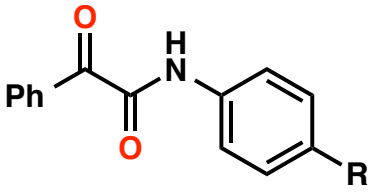


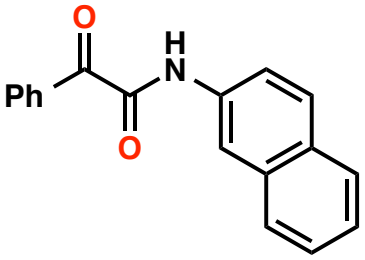
24%



64%



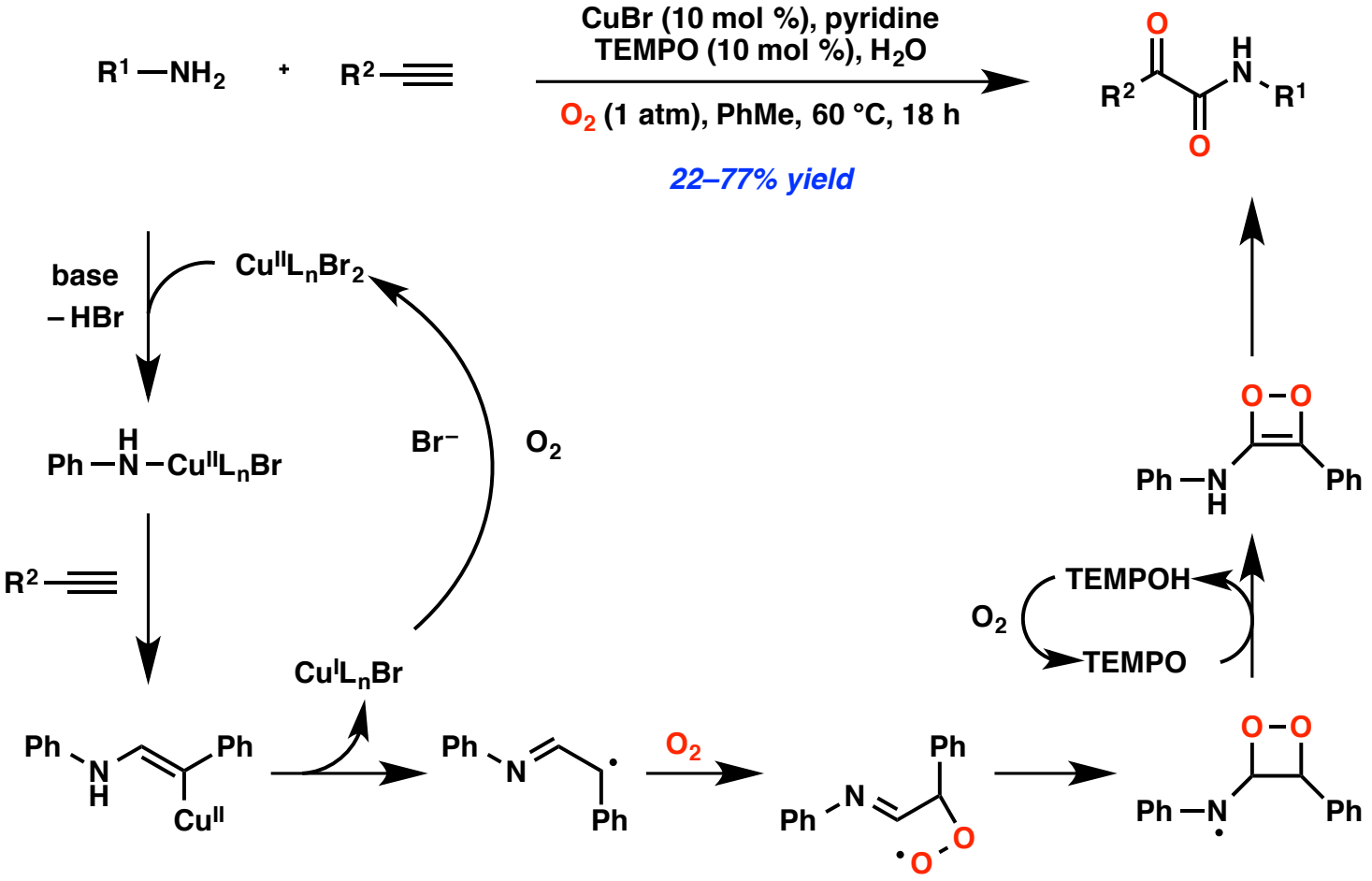
R = H (*47%*), Me (*77%*), OCF_3 (*36%*)
OMe (*77%*), F (*47%*), Cl (*41%*),
Br (*32%*), CO_2Et (*22%*)



51%

Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 28–29.

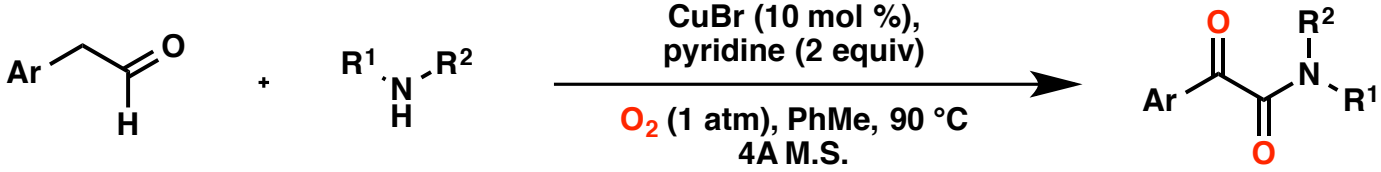
Formation of α–Ketoamides from Terminal Alkynes



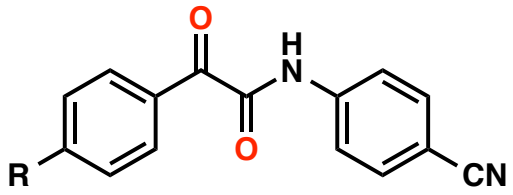
Incorporation of O from O_2 confirmed by ^{18}O studies.

Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 28–29.

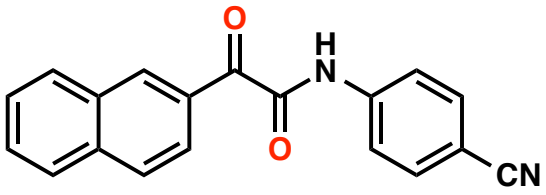
Formation of α–Ketoamides from Aryl Acetaldehydes



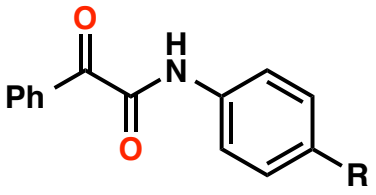
35–90% yield



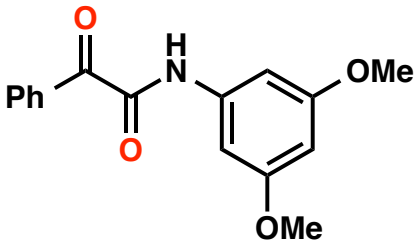
R = H (*82%*), Me (*77%*), F (*84%*)
Br (*75%*), OMe (*83%*), Cl (*78%*)



75%



R = CN (*82%*), CO_2Et (*60%*),
CF_3 (*70%*) NO_2 (*90%*),
OCF_3 (*52%*)



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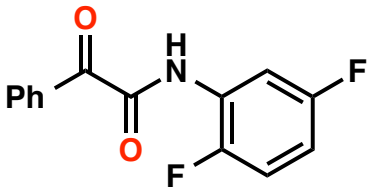
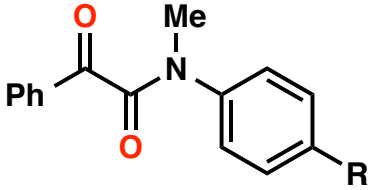
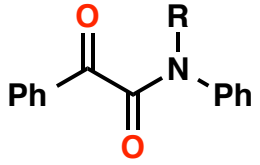


90%



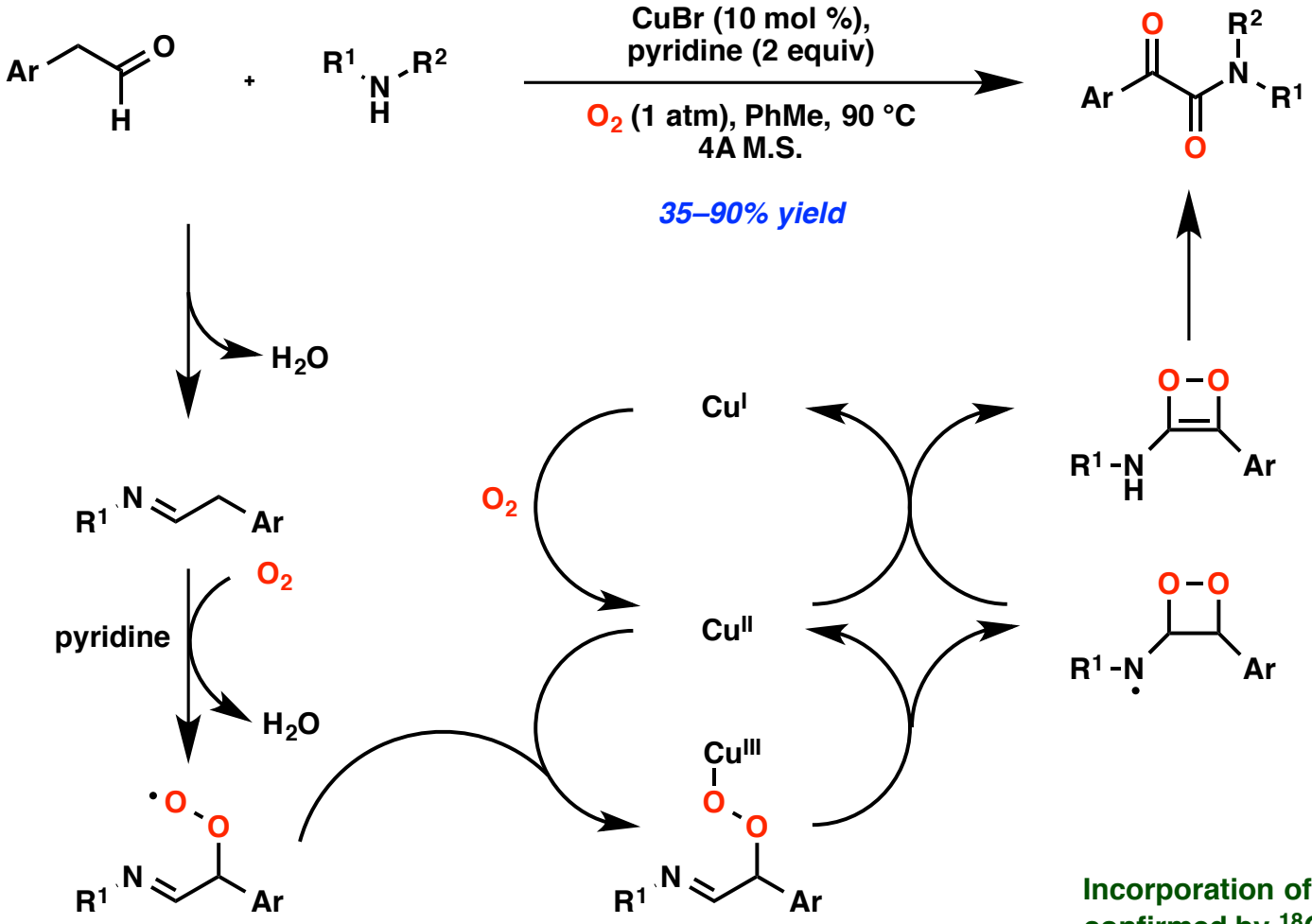
R = H (*65%*)
Cl (*60%*)
Me (*41%*)



R = Et (*40%*)
$PhCH_2$ (*56%*)
Ph (*36%*)

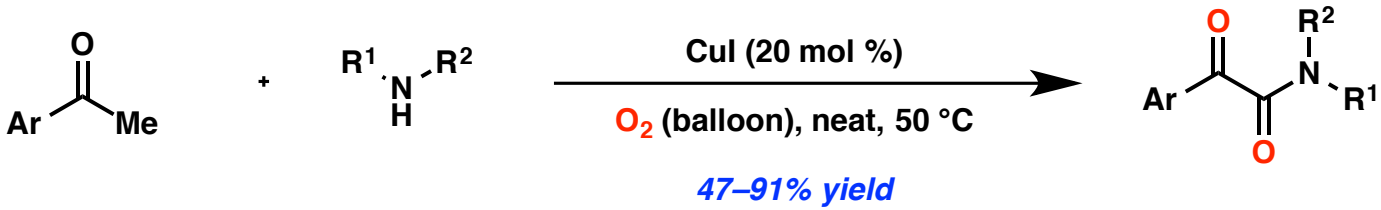
Jiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 11088–11092.

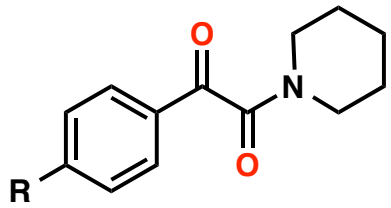
Formation of α–Ketoamides from Aryl Acetaldehydes



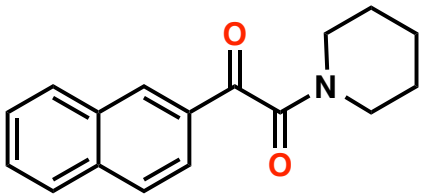
Jiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 11088–11092.

Formation of α–Ketoamides from Aryl Methyl Ketones





R = H (*88%*), Me (*79%*), NO_2 (*91%*), Br (*76%*), OMe (*61%*), Cl (*82%*), CN (*74%*), *n*-hexyl (*64%*)



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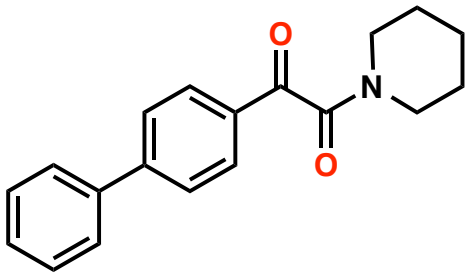
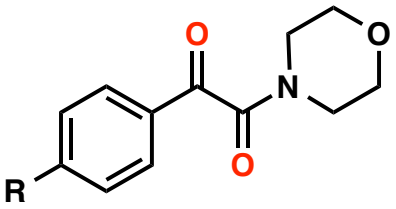
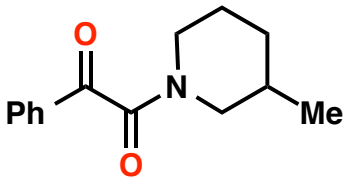


47%



R = H (*70%*), Cl (*62%*)



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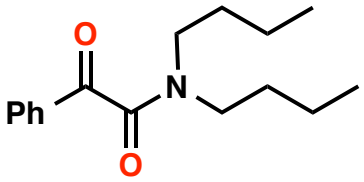

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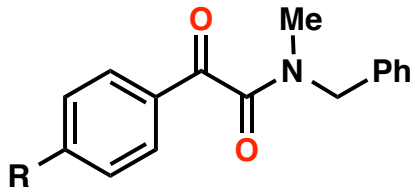
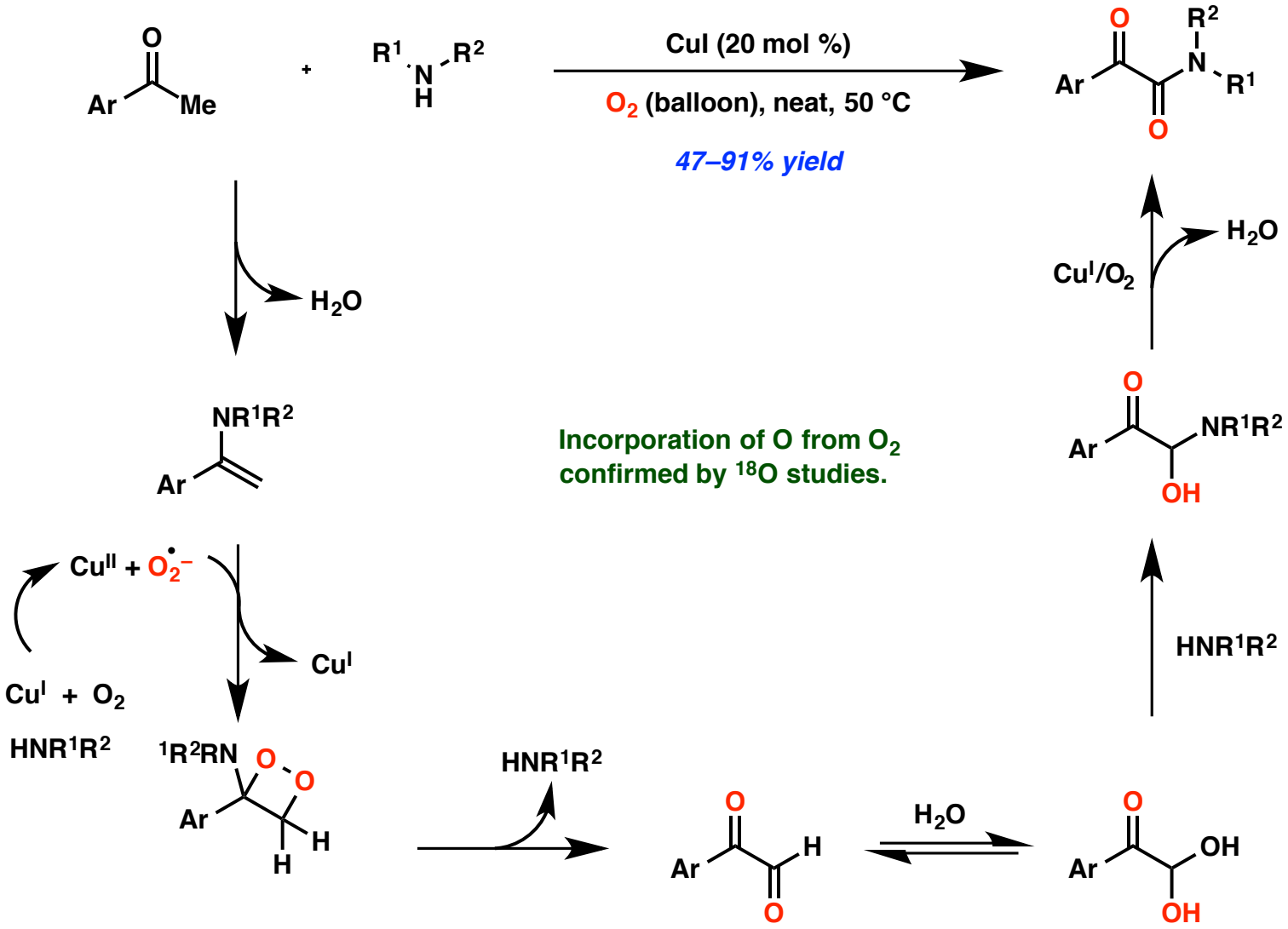


R = H (*74%*), NO_2 (*82%*), Cl (*76%*)

Ji, *Chem. Sci.* **2012**, *3*, 460–465.

Formation of α–Ketoamides from Aryl Methyl Ketones



Ji, *Chem. Sci.* **2012**, *3*, 460–465.

Outline

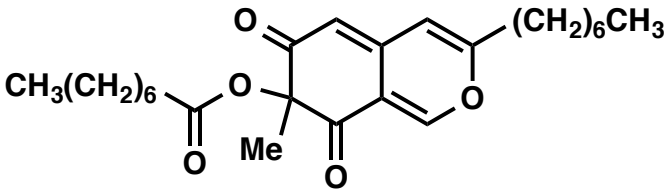
I. Copper in enzymes and the reactions of different copper-dioxygen compounds

II. Use of copper-dioxygen catalysis in organic methodology

III. Applications of copper-dioxygen catalysis in total synthesis

IV. Summary

Application in Total Synthesis: The Azaphilones



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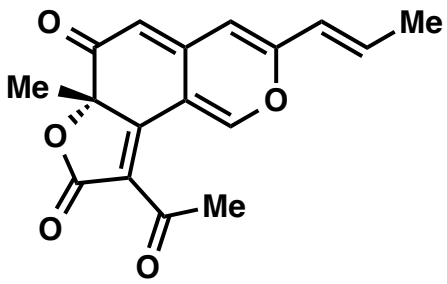
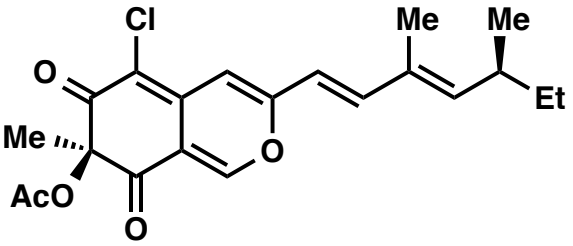
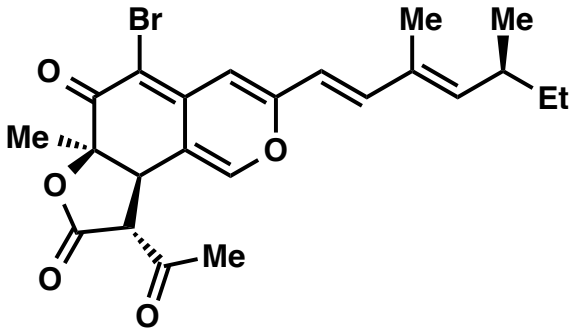


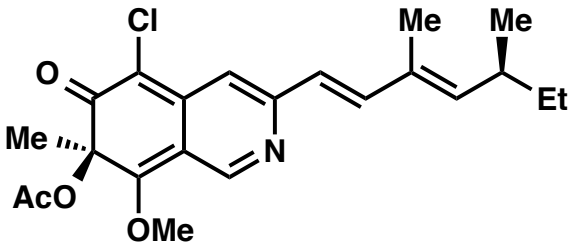
trichoflectin



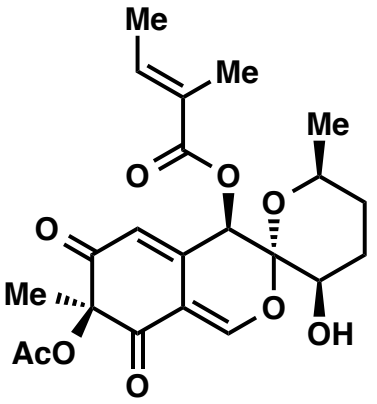
sclerotiorin



5-bromoochrephilone



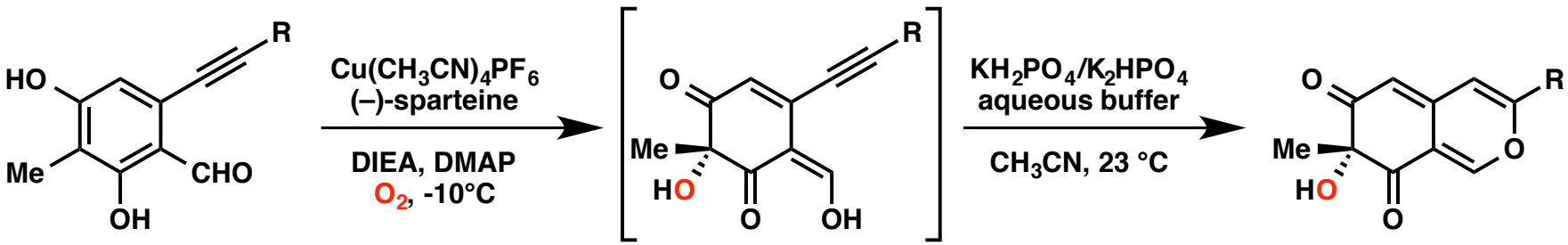
8-*O*-methylsclerotiorinamine

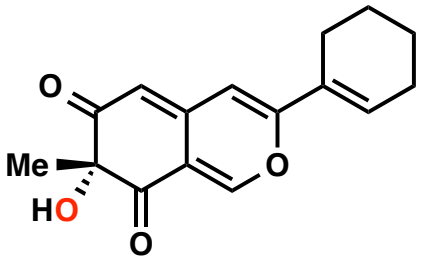


daldinin

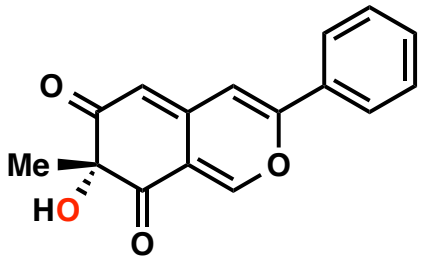
Porco, Jr. *Angew. Chem. Int. Ed.* **2004**, *43*, 1239–1243.

Application in Total Synthesis: The Azaphilones

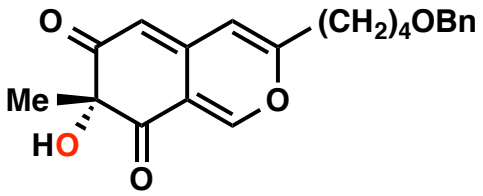




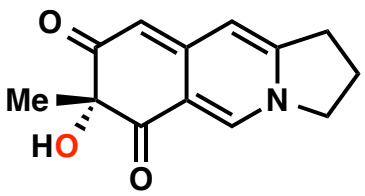
71% yield
96% ee



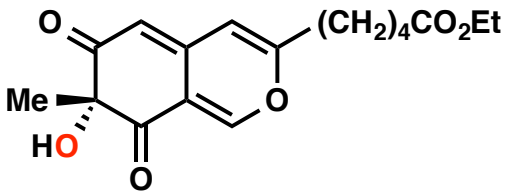
64% yield
95% ee



68% yield
97% ee



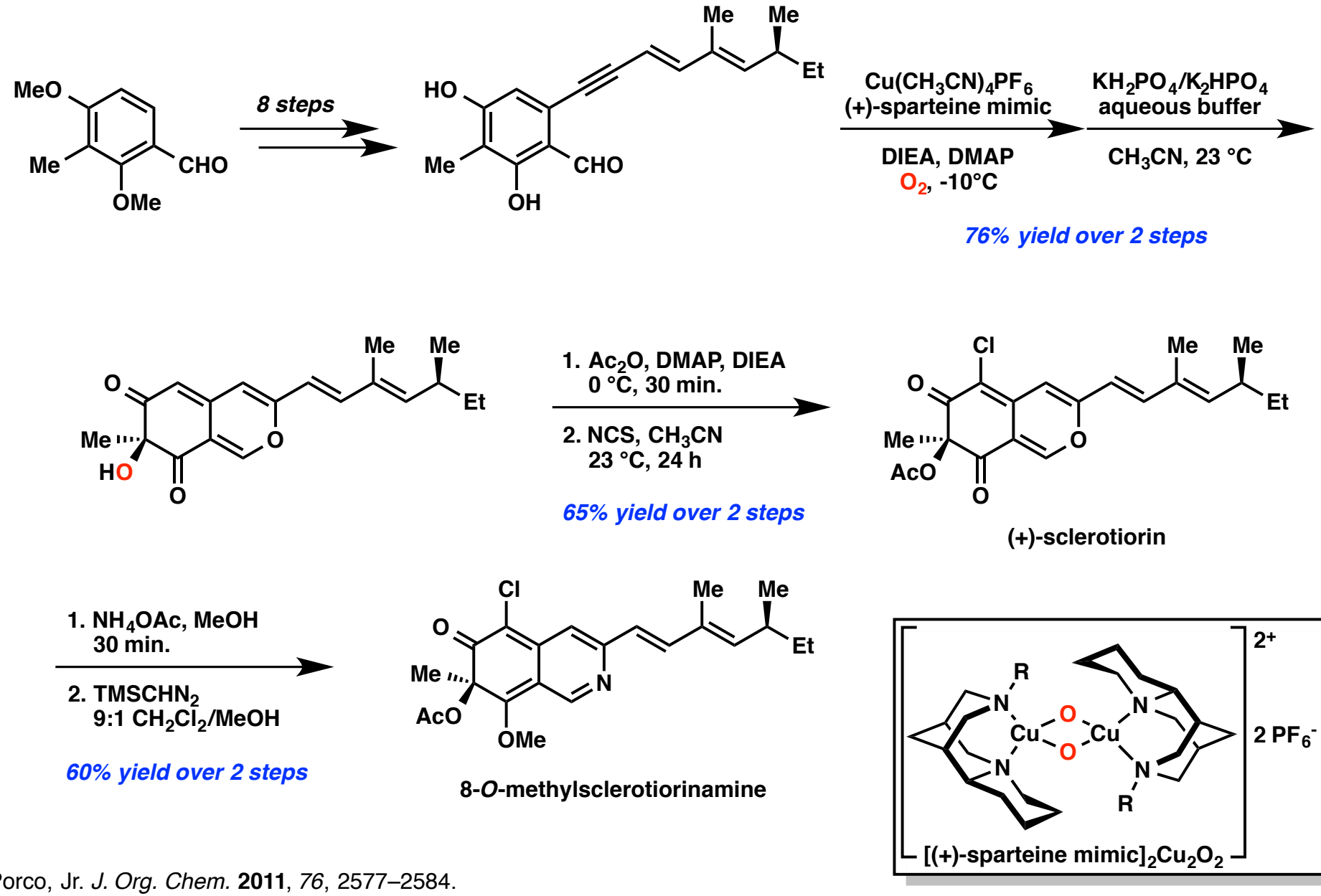
44% yield
97% ee



72% yield
97% ee

Porco, Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343.

Application in Total Synthesis: The Azaphilones



Porco, Jr. *J. Org. Chem.* **2011**, *76*, 2577–2584.

Summary

Copper plays an important role in biochemistry and many other fields.

Dioxygen-copper compounds make up the active sites of several important enzymes.

The structure of the dioxygen-dicopper core influences a catalytic system's reactivity.

Copper-catalyzed reactions with molecular oxygen can also effect many useful transformations in synthetic organic chemistry.