XU LAB
Innovation through Catalysis

北京大學
PEKING UNIVERSITY

XU GROUP
Department of Chemistry, Peking University

Selected Weekly Literature Presentations

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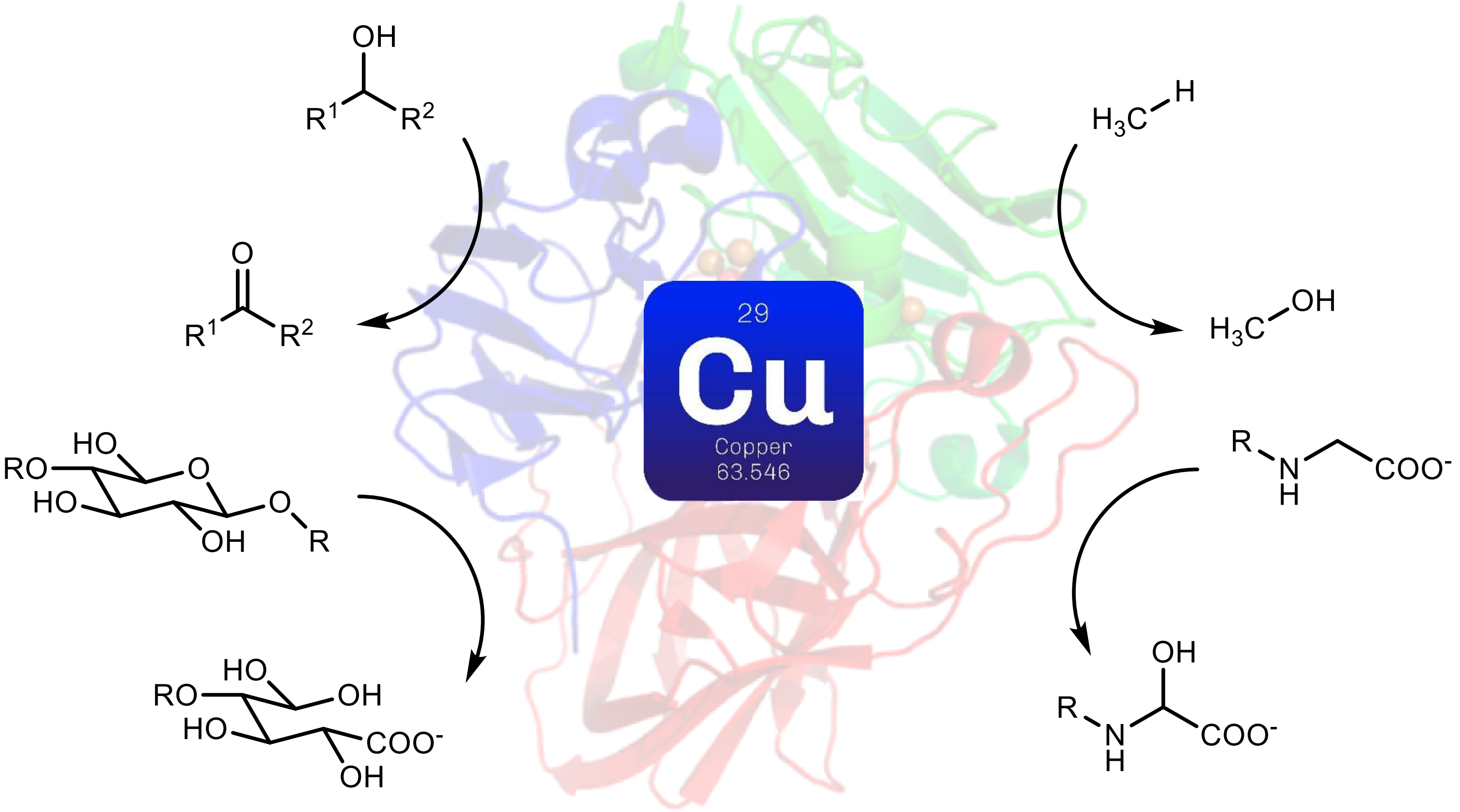
These slides contain personal interpretations and may include errors or subjective views.

Copper Catalyzed Hydroxylation of C(sp^3)-H Bonds: Biochemistry and Small Molecule Emulations



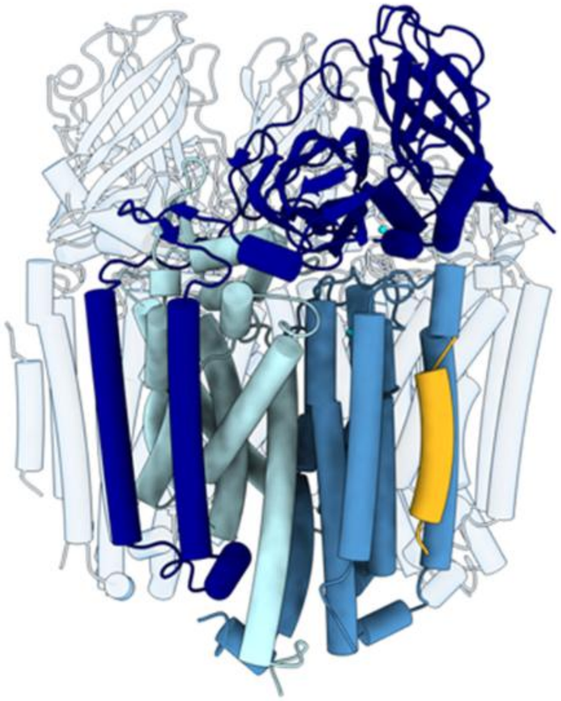
Presenter: Xiuan Chen

Advisor: Prof. Yan Xu

2026.4.18

Outline

- Introduction: Cu in biology
- Copper-dependent monooxygenases: case studies on two enzymes
- Small molecule emulation
- Application



What will NOT be covered

- Radical relay chemistry
- Fenton-like reactions

Outline

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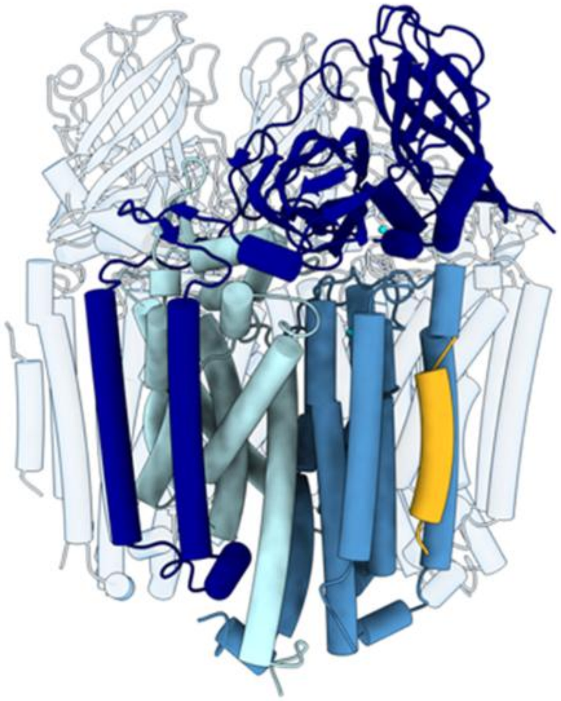
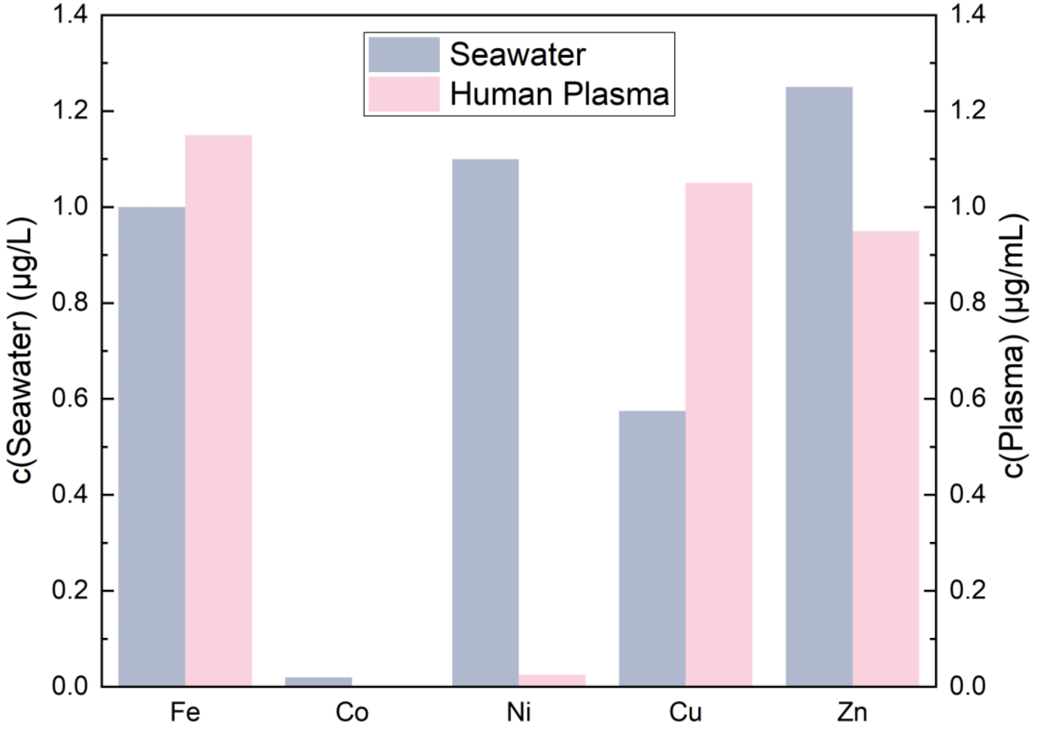
- Application

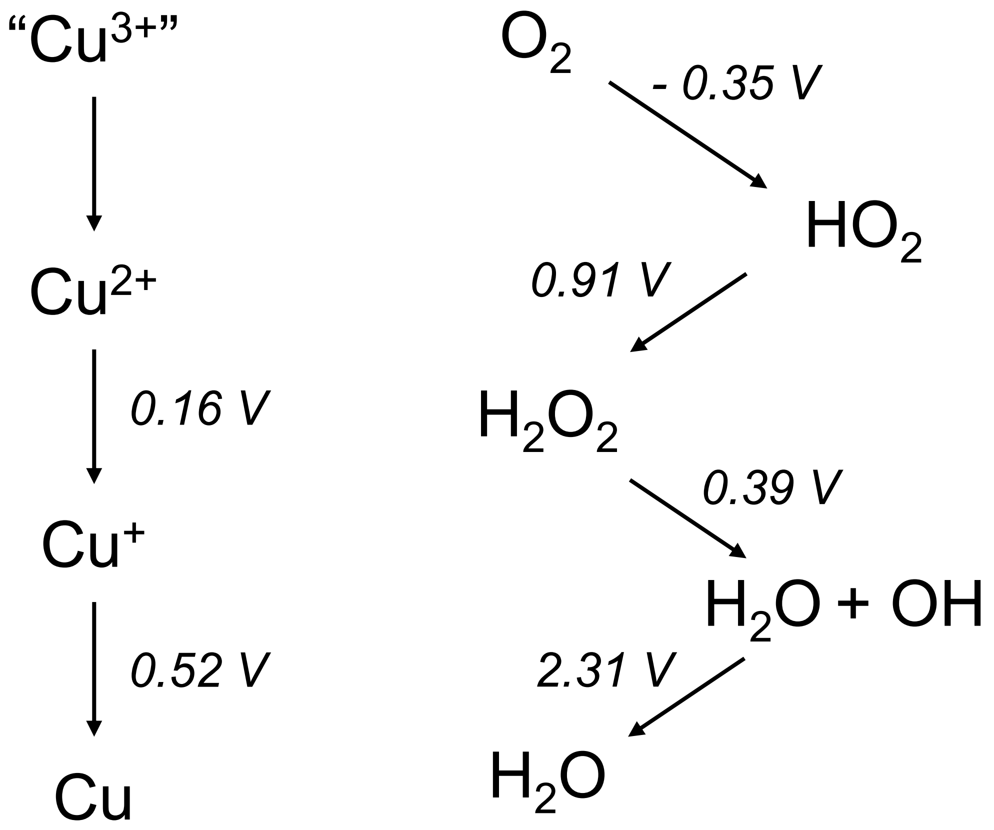


Copper in biology

Element Abundance of Selected TM



Redox potential under physiological conditions

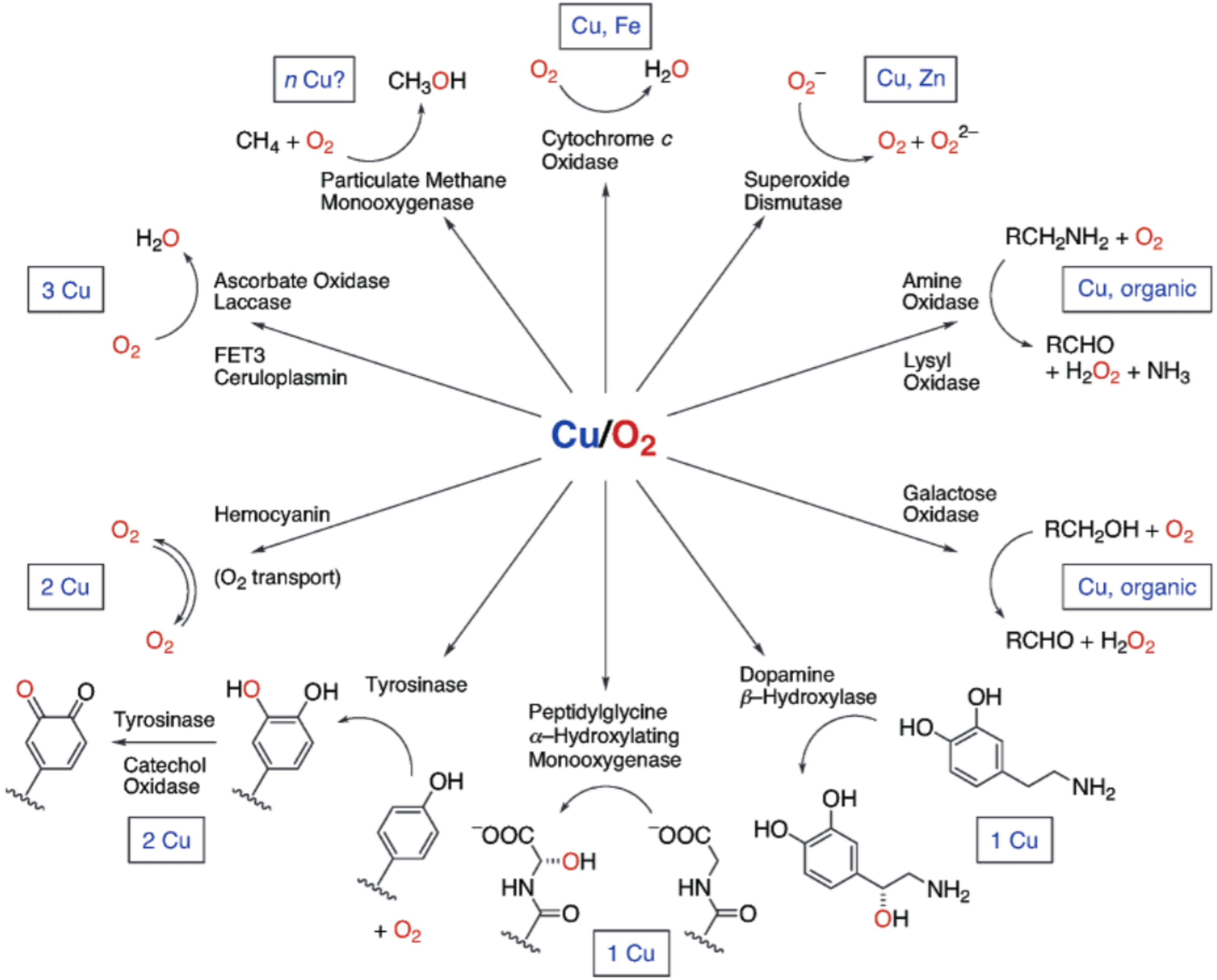


13.1: Biological Significance of Metals. *ChemLibreTexts*; LibreTexts
标准电极电位数据手册. 科学出版社, **1991**.
Sawyer, D. T. Oxygen Chemistry; Oxford University Press: Oxford, U.K., **1991**.
Bounds, P. L. *et al.* Free Radical Biol. Med. **2010**, *49*, 317.

Copper in biology

rich redox behavior of Cu & Cu clusters

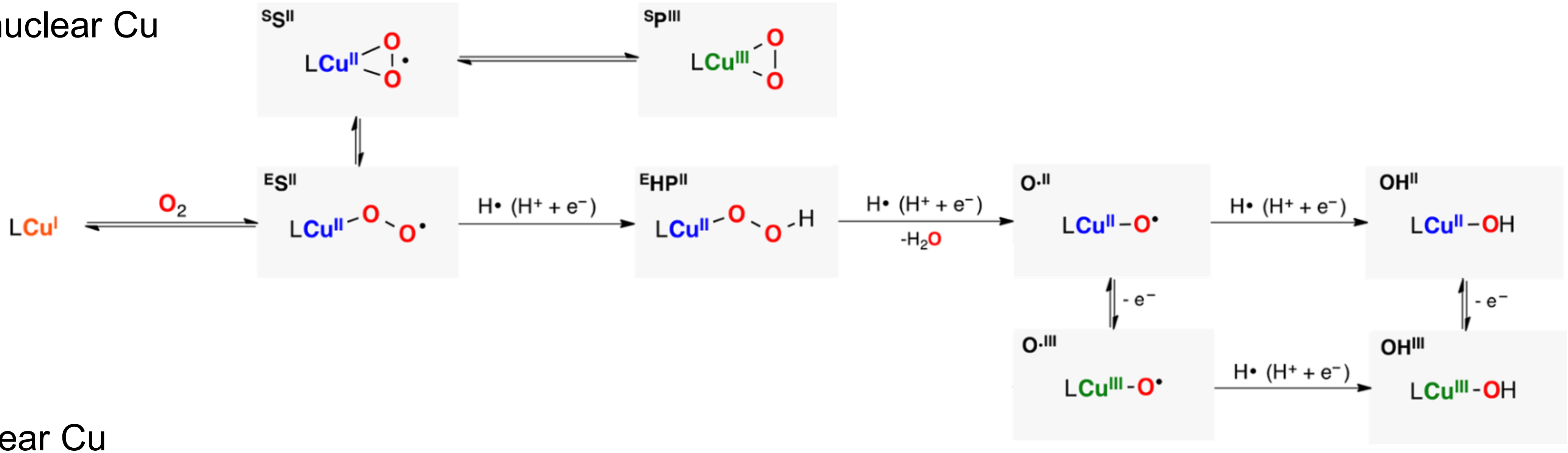
necessity of metal for O_2 activation



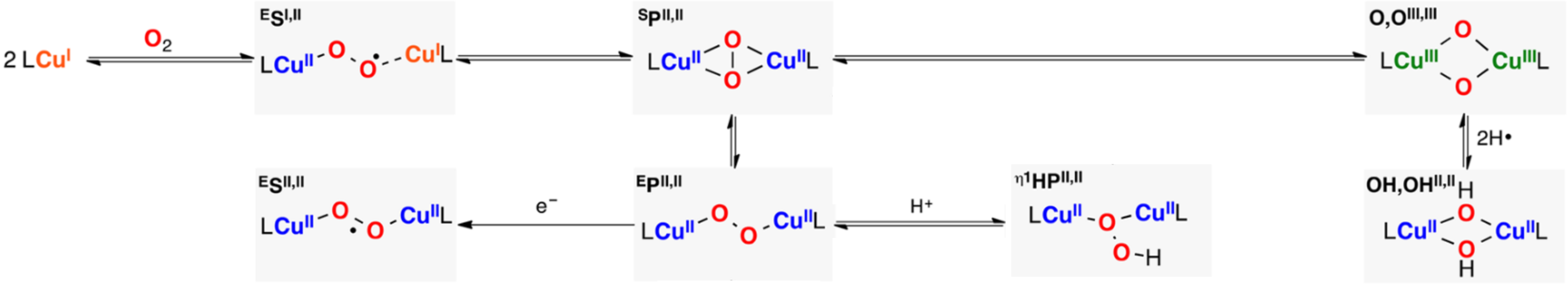
Stack, T. D. P. *et al. Chem. Rev.* **2004**, *104* (2), 1013–1046.

Cu-O_2 interactions

- Mononuclear Cu



- Dinuclear Cu



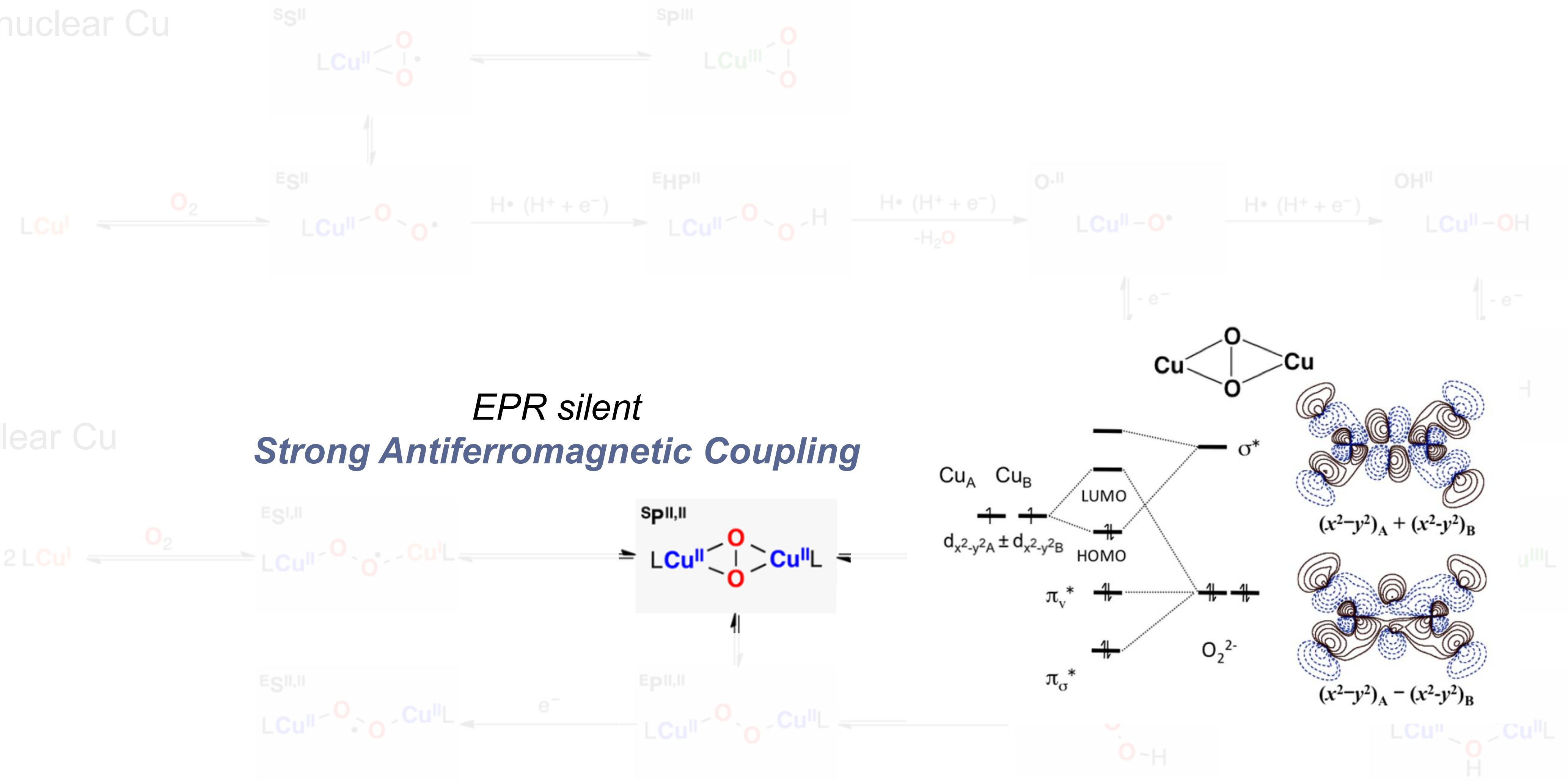
Garcia-Bosch, I. *et al.* *Chem. Rev.* **2019**, *119* (4), 2954–3031.

Cu-O_2 interactions

- Mononuclear Cu
- Dinuclear Cu

EPR silent

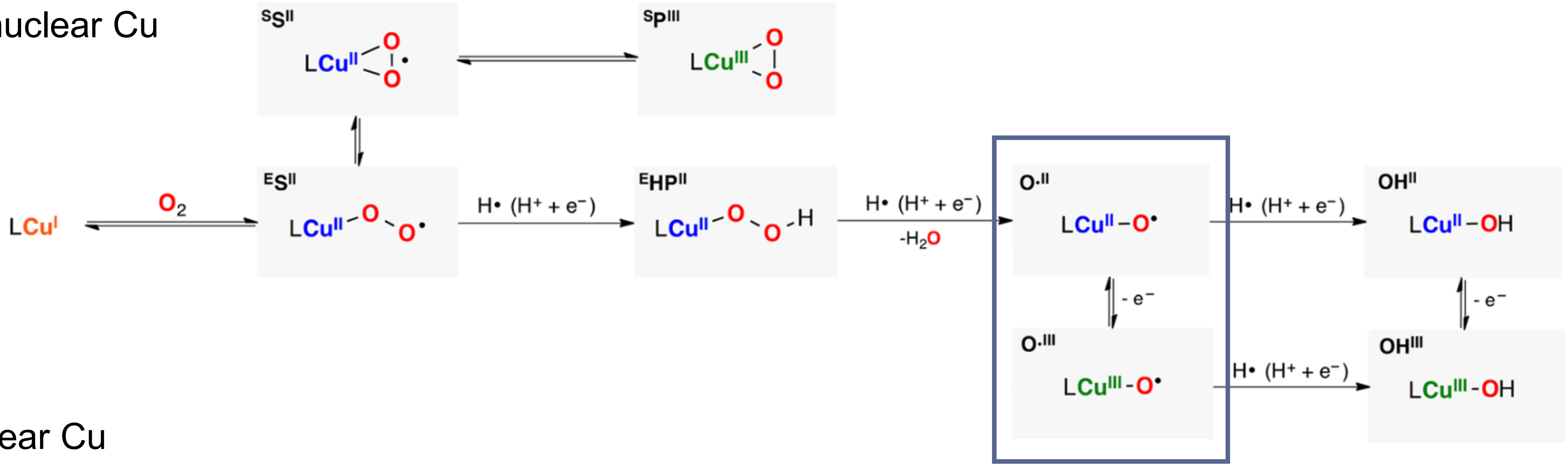
Strong Antiferromagnetic Coupling



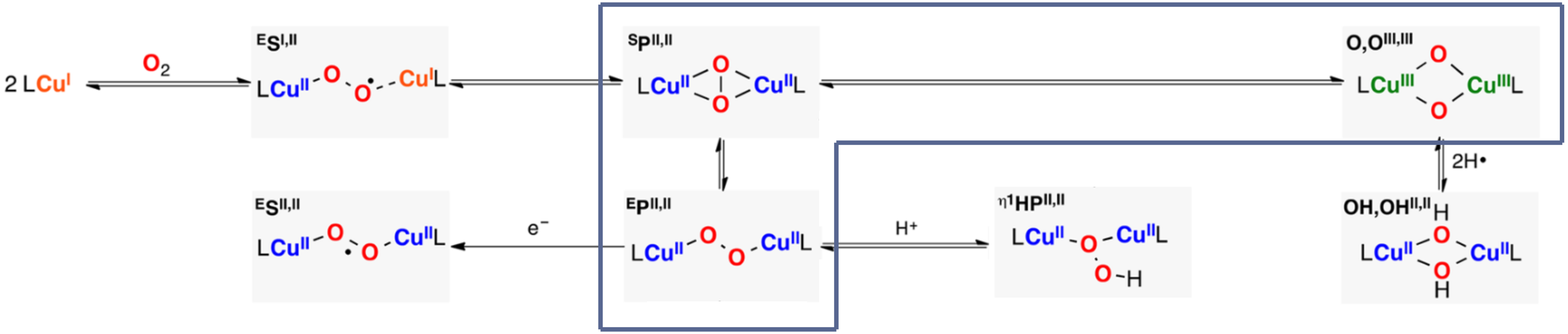
Garcia-Bosch, I. *et al. Chem. Rev.* **2019**, *119* (4), 2954–3031.
Solomon, E. I. *et al. Chem. Rev.* **2014**, *114* (7), 3659–3853.

Cu-O_2 interactions

- Mononuclear Cu

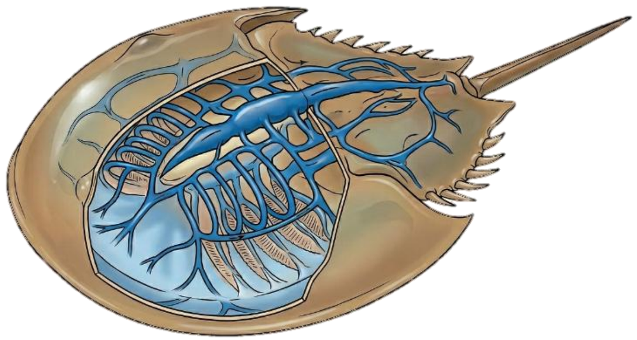


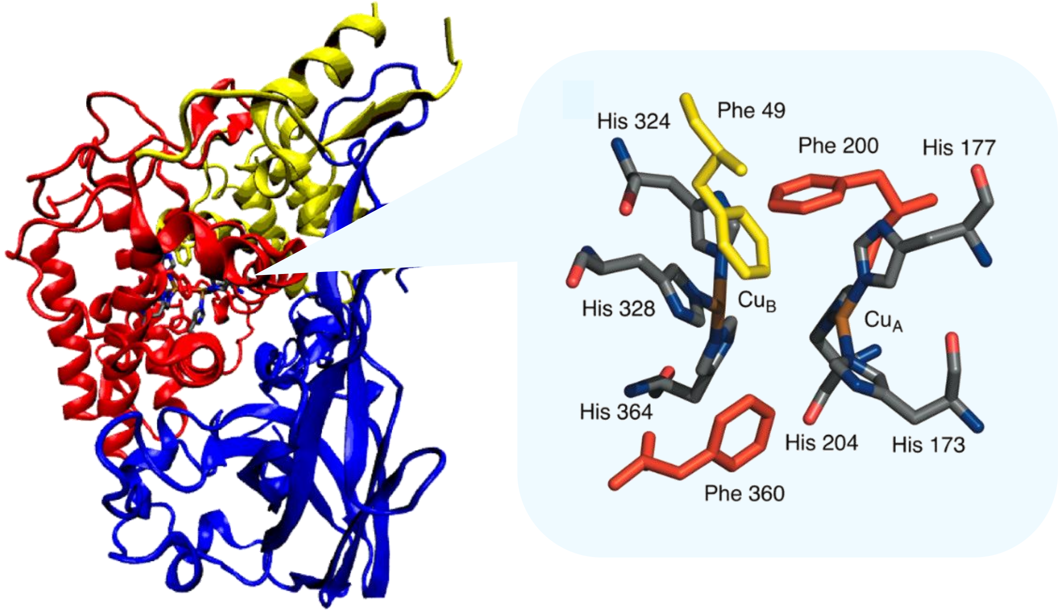
- Dinuclear Cu



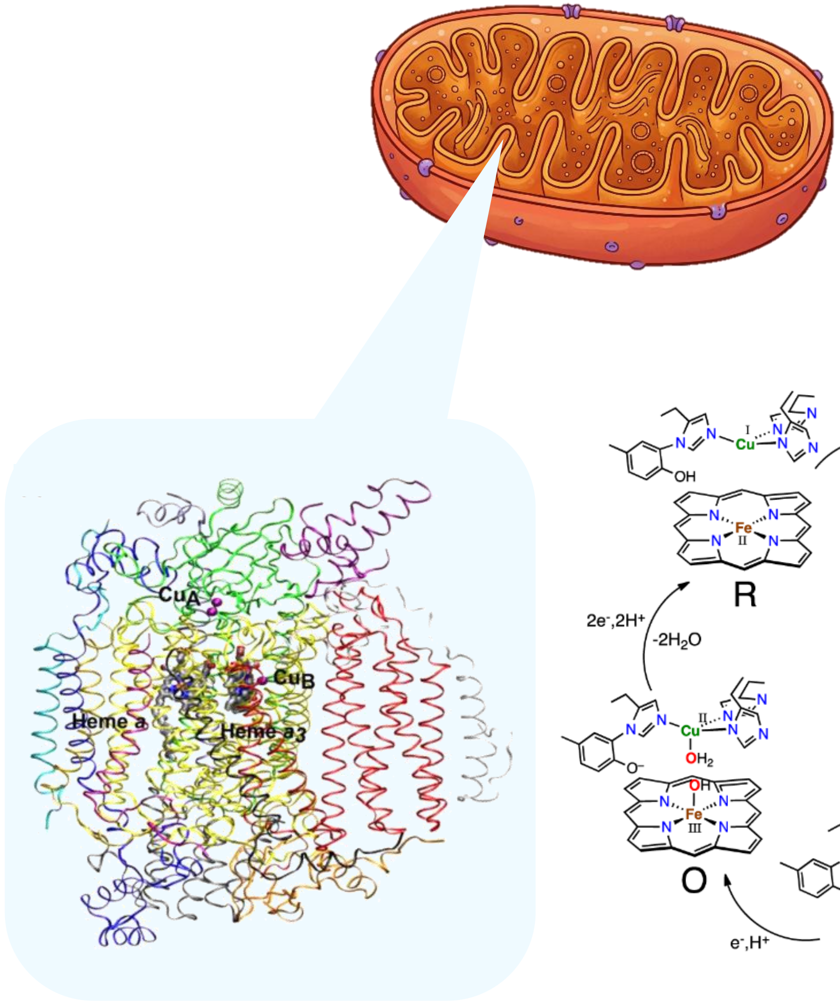
Garcia-Bosch, I. *et al. Chem. Rev.* **2019**, *119* (4), 2954–3031.

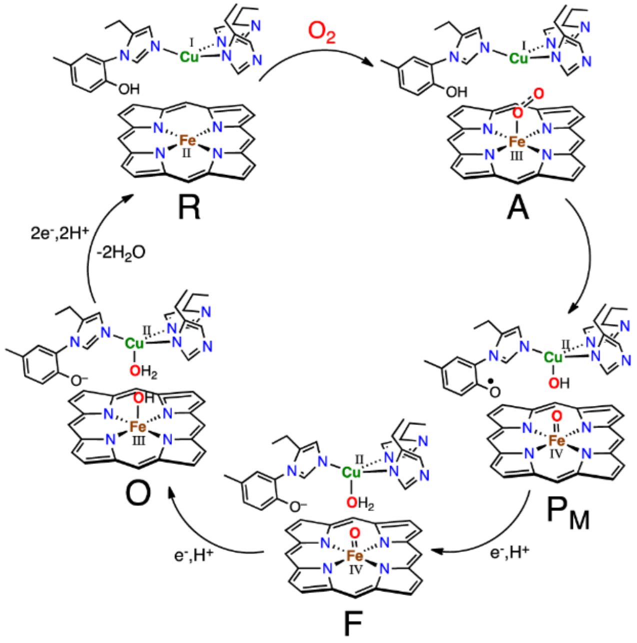
Copper in biology





*Hemo**cyanin** from Limulus polyphemus*





Cytochrome C oxidase (Complex IV)

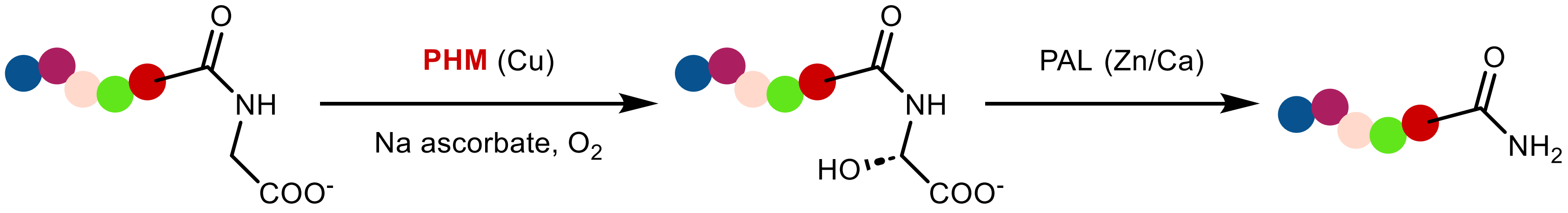
Solomon, E. I. *et al. Chem. Rev.* **2014**, *114* (7), 3659–3853.

Outline

- Introduction: Cu in biology
- Copper-dependent monooxygenases: case studies on two enzymes
  - *Peptidylglycine Monooxygenase (PHM)*
  - *particulate Methane Monooxygenase (pMMO)*
- Small molecule emulation
- Application

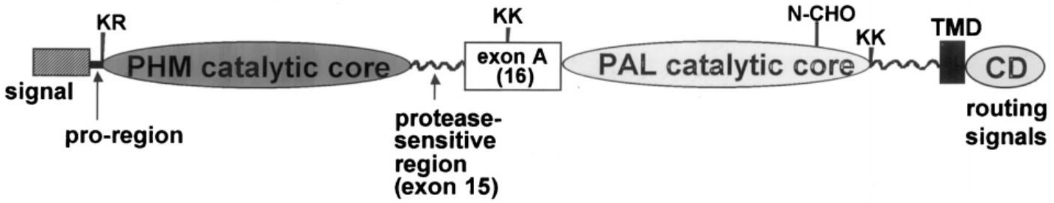
Peptidylglycine Monooxygenase

- ***C-terminal amidation*** of peptides for normal biological function

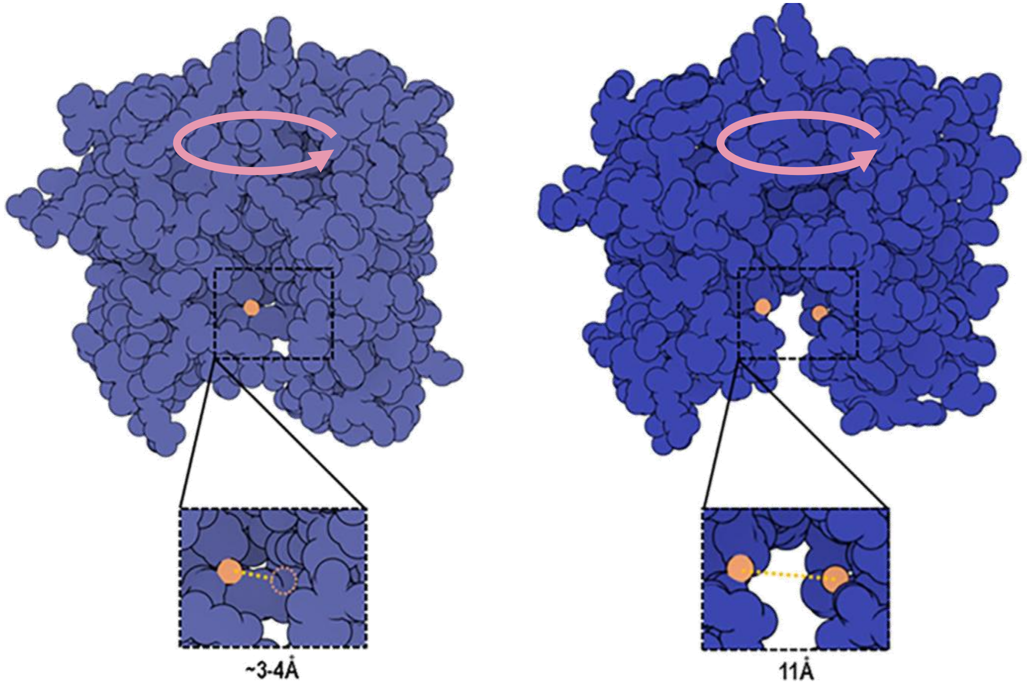


Dysfunction causes:
altered behavior
abnormal neurotransmission
inability of temp. stabilization

both enzymes translated onto one peptide chain then proteolyzed during PTM



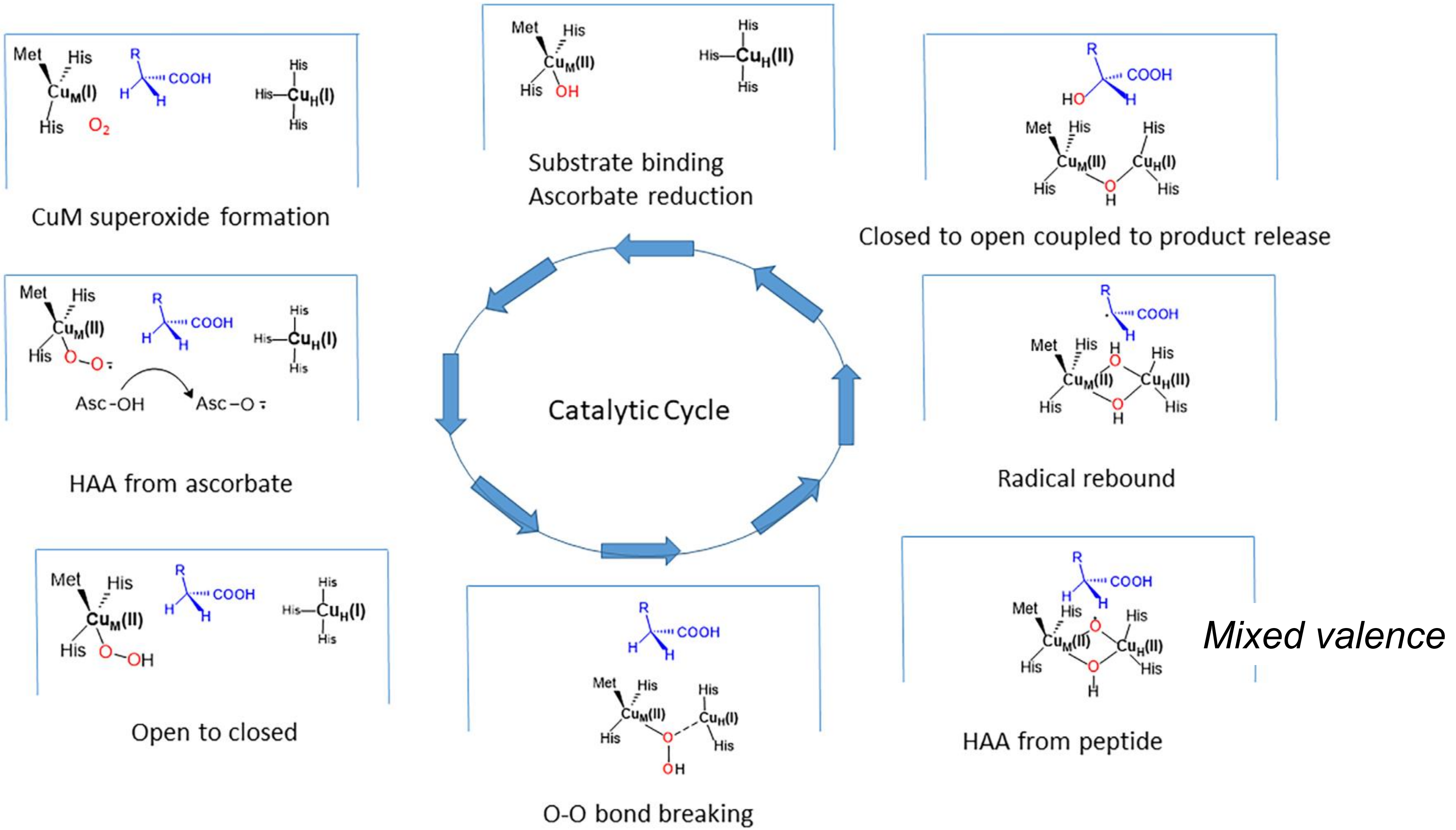
*close-open transformation of **PHM***



Amzel L. M. *et al. Cell. Mol. Life Sci.* **2000**, *57* (8), 1236–1259.
Mains, R. E. *et al. British J Pharmacology* **2022**, *179* (13), 3306–3324.

Peptidylglycine Monooxygenase

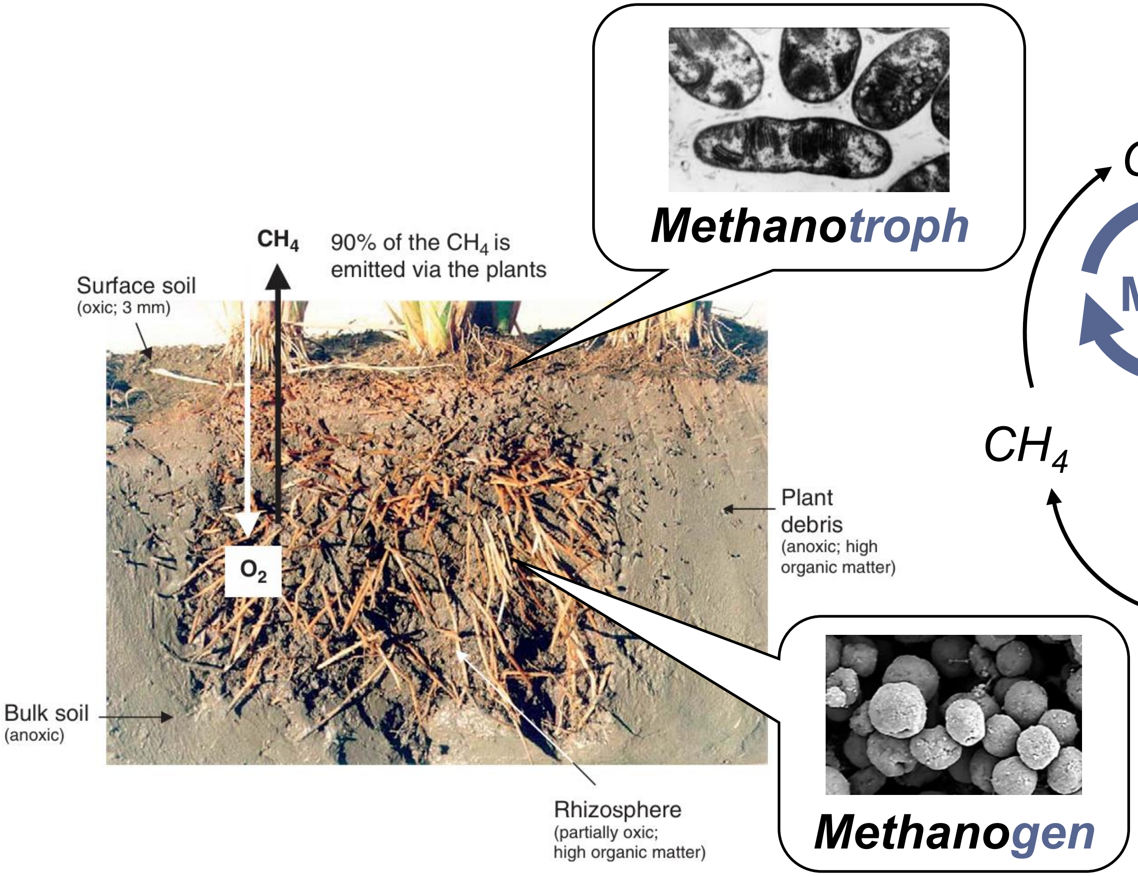
- Proposed mechanism

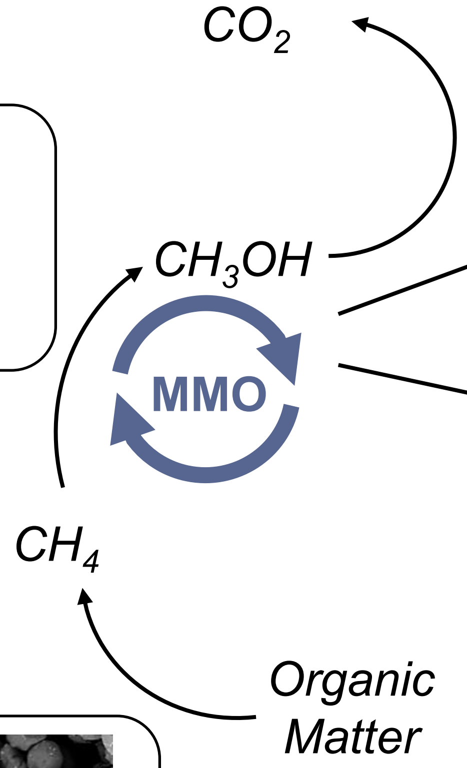


Wang, B. *et al. J. Am. Chem. Soc.* **2019**, *141* (50), 19776–19789.
Blackburn, N. J. *et al. J. Am. Chem. Soc.* **2024**, *146* (8), 5074–5080.

particulate Methane Monooxygenase

- ***Methanotroph***: discovered in 1905





not always present & working

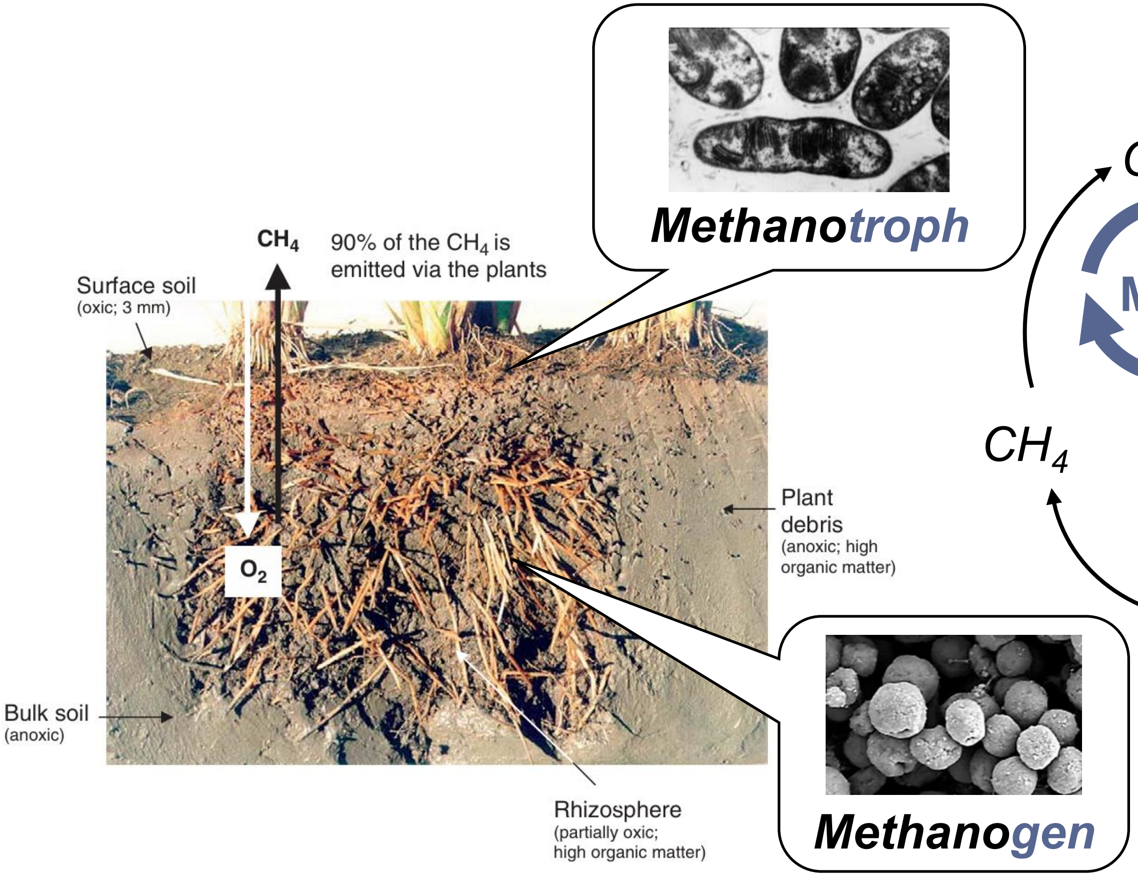
soluble MMO: di-iron center

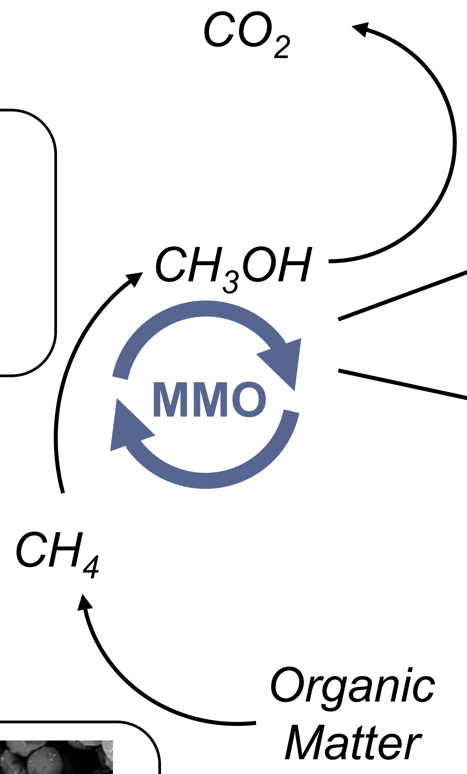
membrane-bound particulate MMO

Conrad, R. *Advances in Agronomy*; Elsevier, 2007; Vol. 96, pp 1–63.

particulate Methane Monooxygenase

- ***Methanotroph***: discovered in 1905





not always present & working

soluble MMO: di-iron center

membrane-bound particulate MMO

Active Site??

Fe?

di-Cu?

mono-Cu?

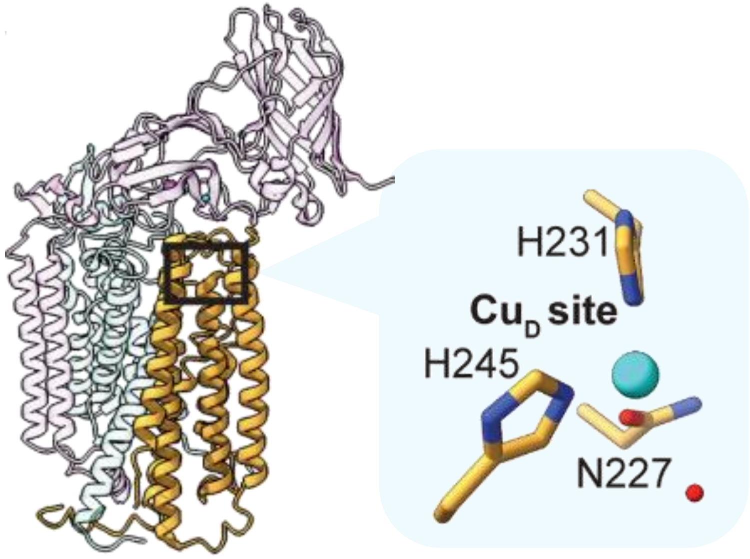
tri-Cu?

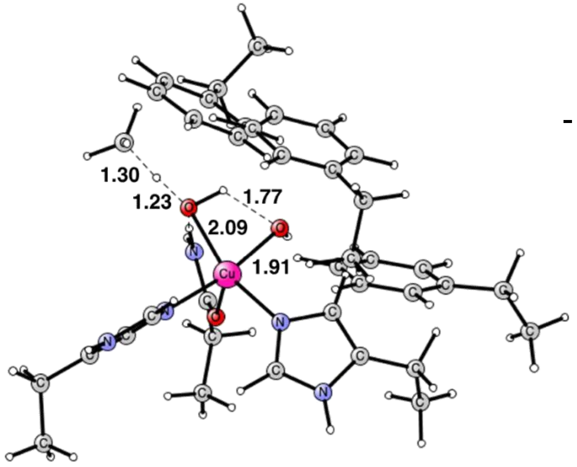
Which Cu site?

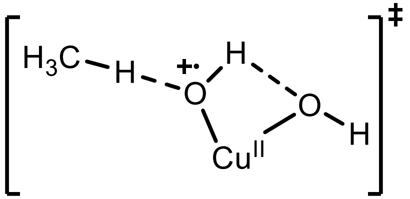
Conrad, R. *Advances in Agronomy*; Elsevier, 2007; Vol. 96, pp 1–63.
Ross, M. O.; Rosenzweig, A. C. *J Biol Inorg Chem* **2017**, *22* (2–3), 307–319.
Rosenzweig, A. C. *et al. Chem. Rev.* **2024**, *124* (3), 1288–1320.

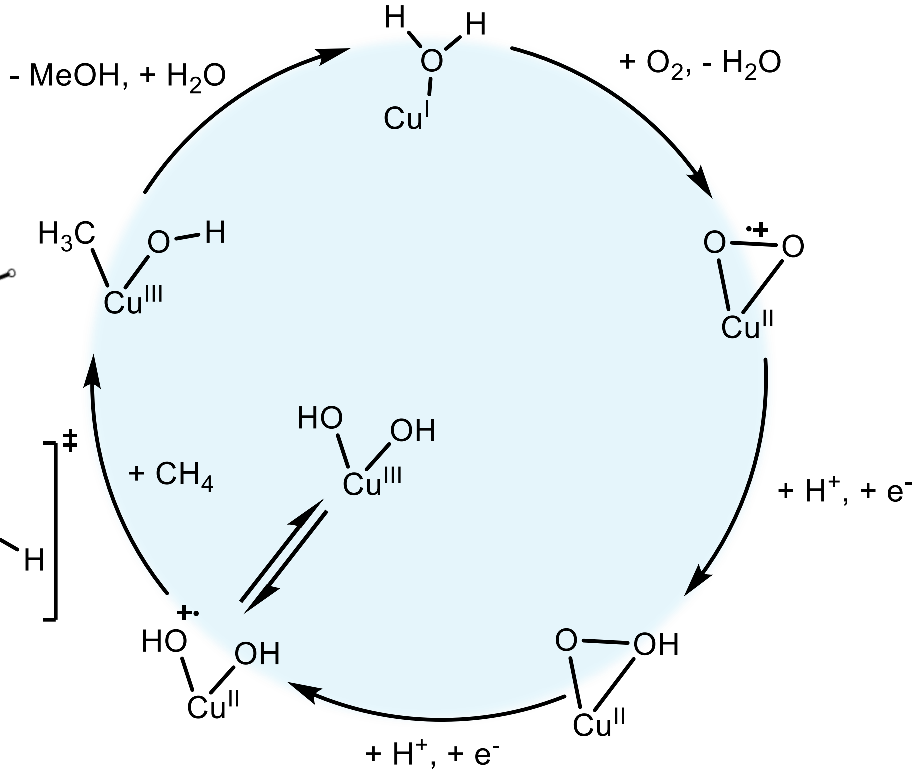
particulate Methane Monooxygenase

- A monocopper mechanism at Cu_D site









BDE** (CH_3—H) = **105 kJ/mol

Siegbahn, P. E. M. *J. Phys. Chem. B* **2024**, *128* (24), 5840–5845.
Rosenzweig, A. C. *et al. Science* **2022**, *375* (6586), 1287–1291.

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- Introduction: Cu in biology
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  - Baran-Schönecker method
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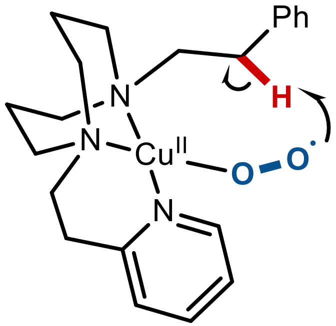
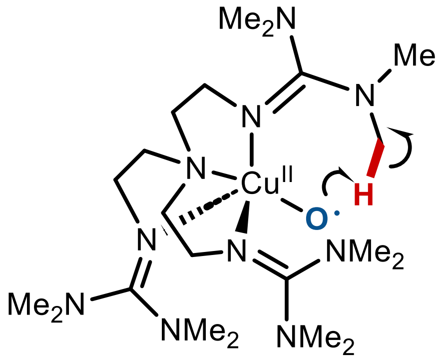
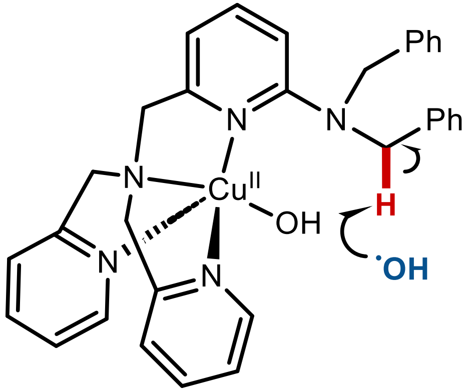
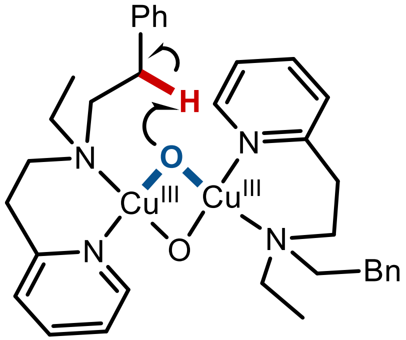
Ligand Oxidation on Cu Complexes

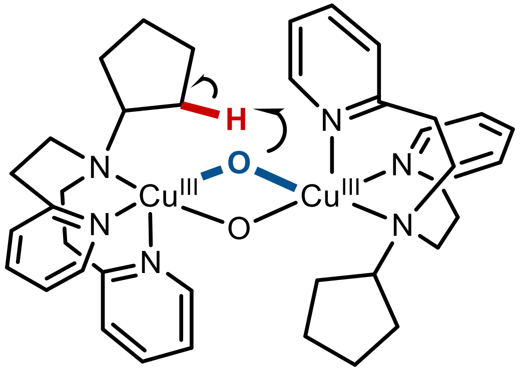
Mononuclear complexes









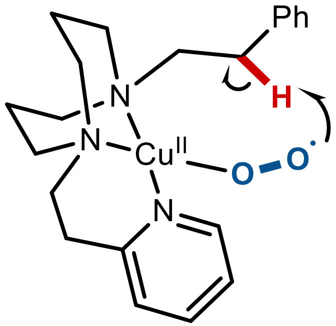


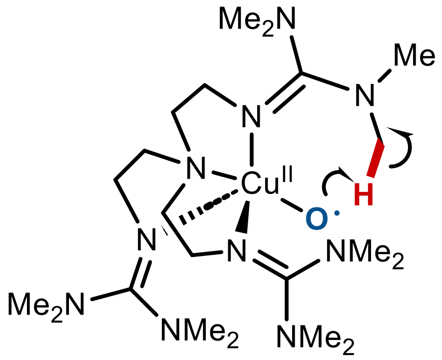
Dinuclear complexes

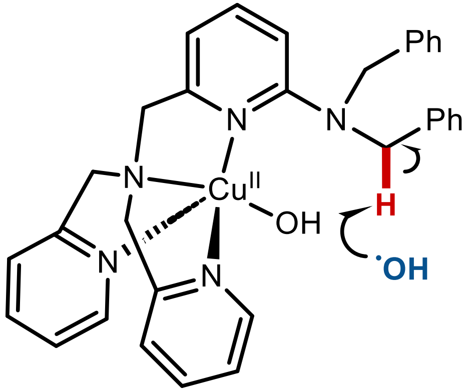
Karlin, K. D. *et al. Angew. Chem. Int. Ed.* **2008**, *47* (1), 82–85.
Itoh, S. *et al. J. Am. Chem. Soc.* **2009**, *131* (8), 2788–2789.
Réglier, M. *et al. Eur. J. Inorg. Chem.* **2000**, *2000* (2), 393–398.
Fukuzumi, S. *et al. Angew. Chem. Int. Ed.* **2000**, *39* (2), 398–400.
Fukuzumi, S. *et al. J. Am. Chem. Soc.* **1998**, *120* (12), 2890–2899.

Ligand Oxidation on Cu Complexes

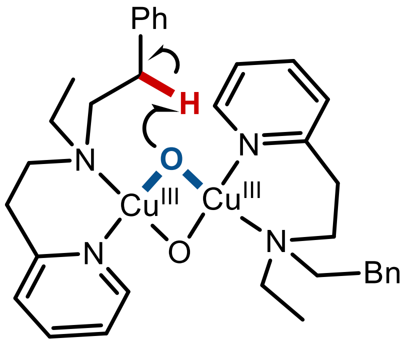
Mononuclear complexes

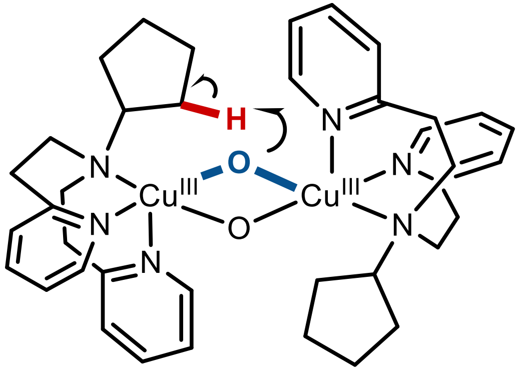






C-H hydroxylated products not readily cleavable from ligand/DG





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Réglier, M. *et al. Eur. J. Inorg. Chem.* **2000**, *2000* (2), 393–398.
Fukuzumi, S. *et al. Angew. Chem. Int. Ed.* **2000**, *39* (2), 398–400.
Fukuzumi, S. *et al. J. Am. Chem. Soc.* **1998**, *120* (12), 2890–2899.

Outline

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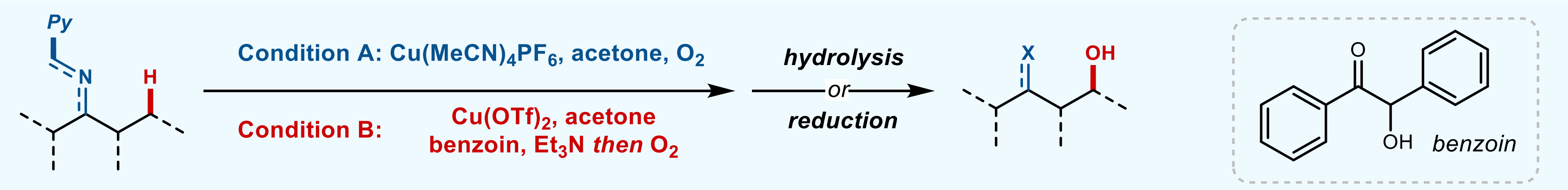
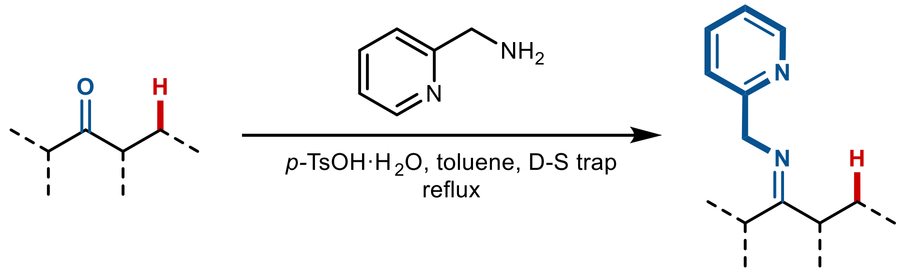
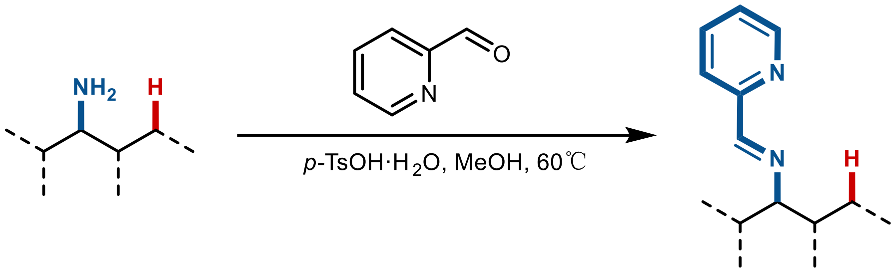
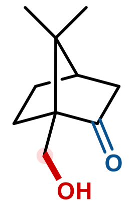
Discovery



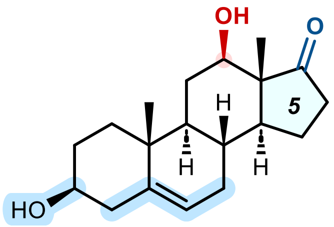
yield: *from ketone/amine*
in parentheses: [O] step only



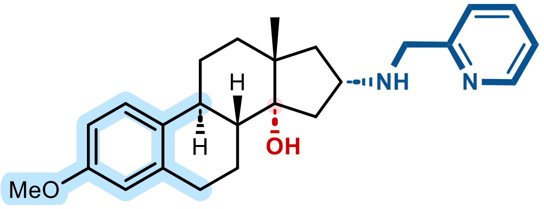




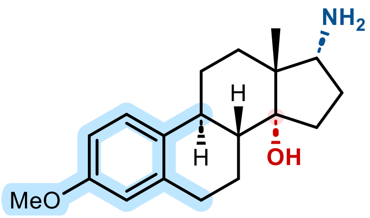
A: 17.4% (31%)
B: 2.2% (4%)



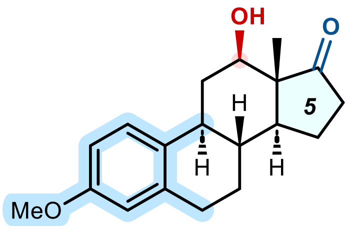
A: 17.4% (20%)
B: 30.5% (35%)



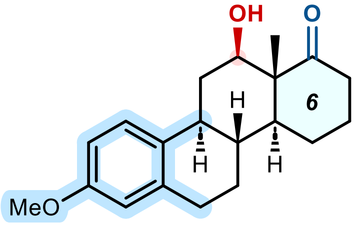
A: 12% (18%)



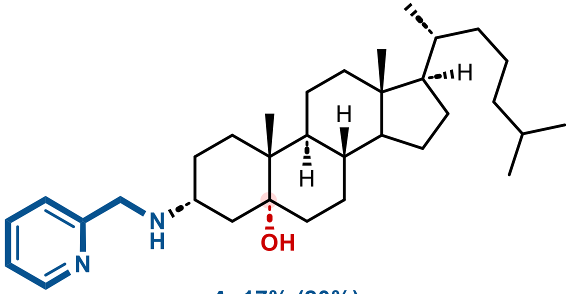
A: 37% (46%)



B: 43.5% (50%)



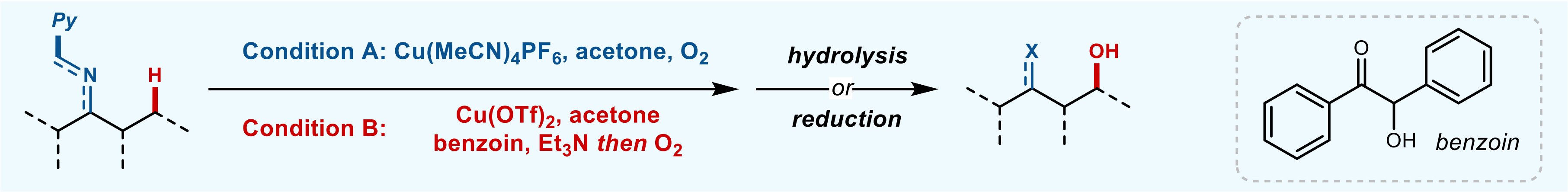
A: 15.6% (18%)
B: 9.6% (11%)

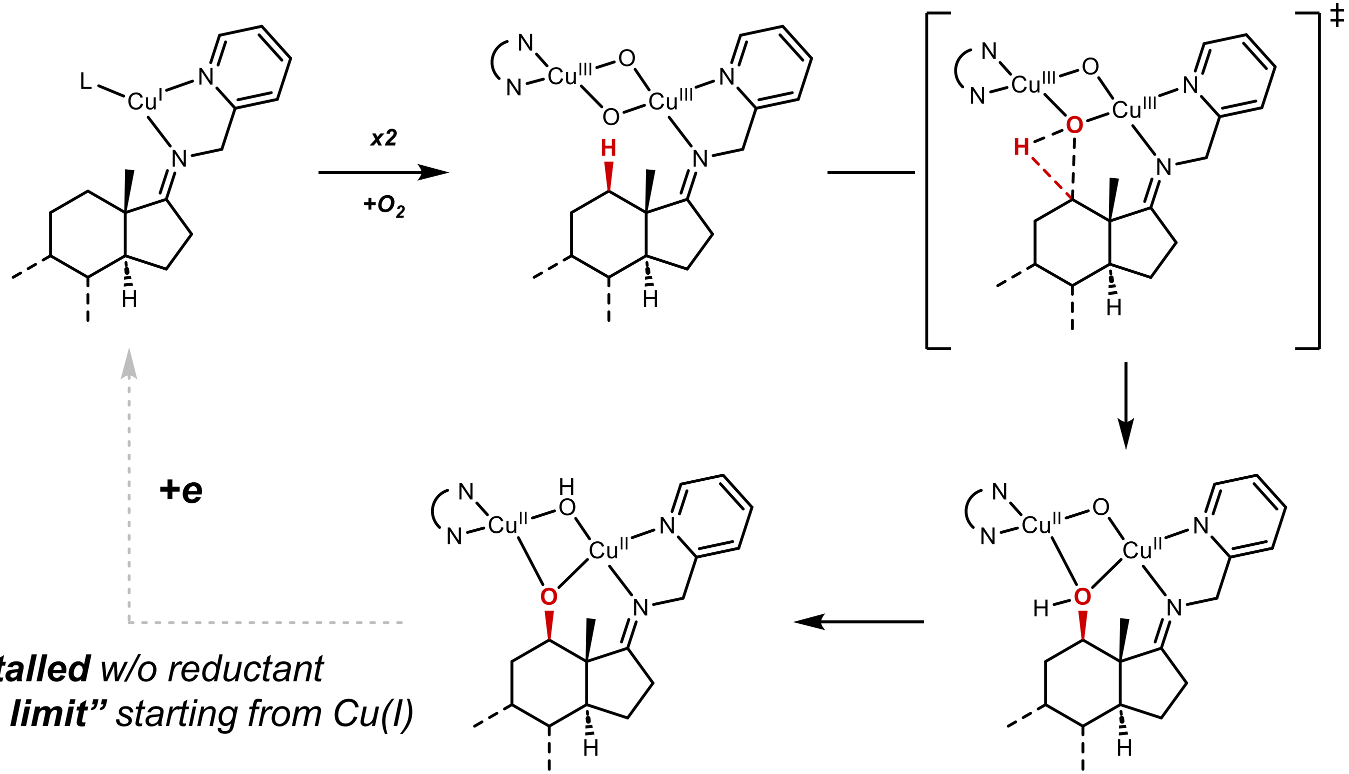


A: 17% (20%)

Schönecker, B *et al. Angew. Chem. Int. Ed.* **2003**, *42* (28), 3240–3244; *Tetrahedron* **2005**, *61* (1), 103–114; *Chem. Eur. J.* **2004**, *10*, 6029 – 6042

Mechanism postulation

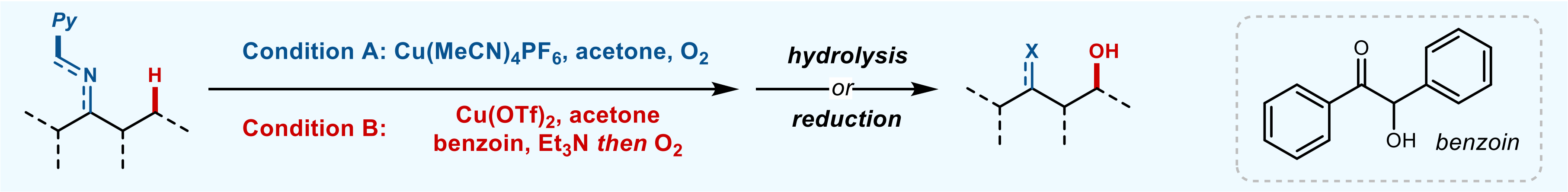


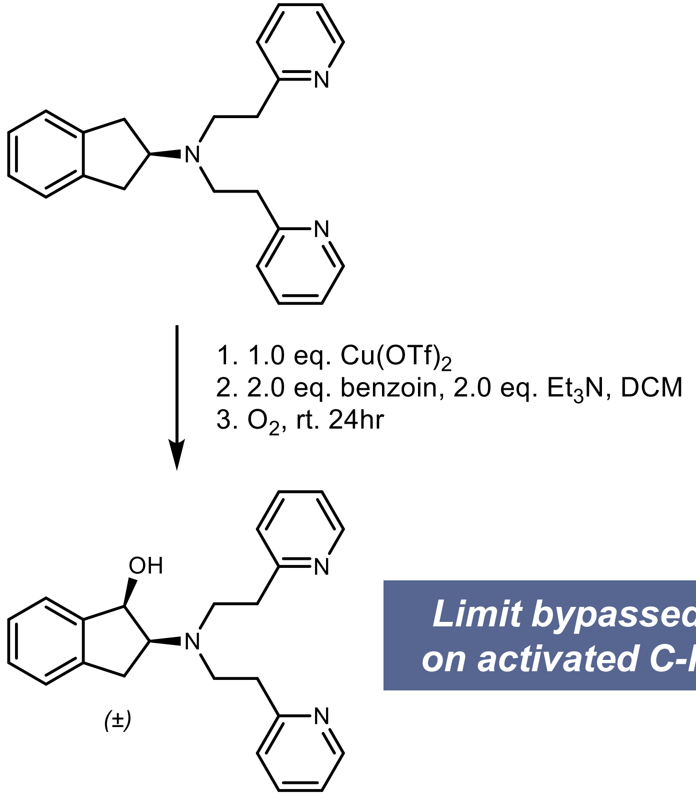


Stalled *w/o reductant*
a ***"50% limit"*** *starting from Cu(I)*

Schönecker, B *et al. Tetrahedron* **2005**, *61* (1), 103–114. Holthausen, M. C. *et al. Angew Chem Int Ed* **2003**, *42* (48), 5961–5965.

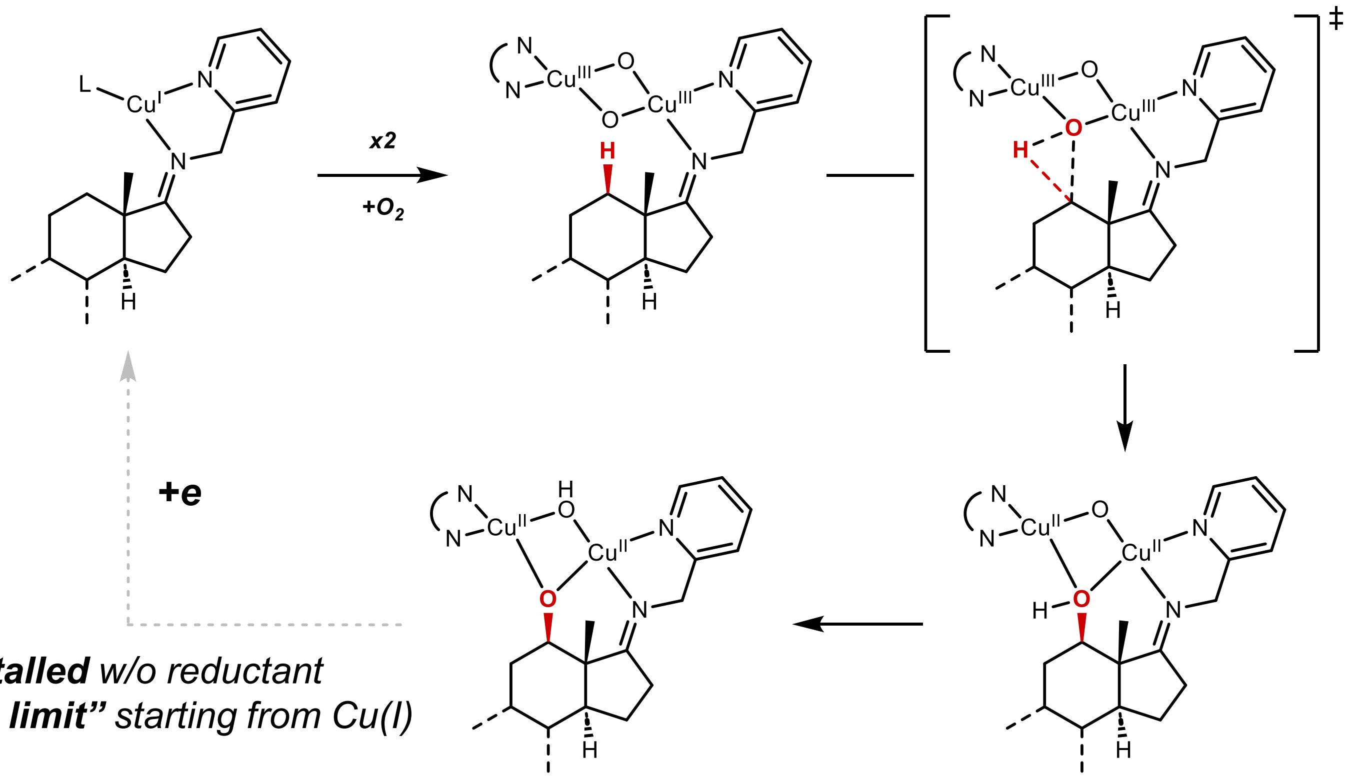
Mechanism postulation





Limit bypassed on activated C-H

quantitative yield



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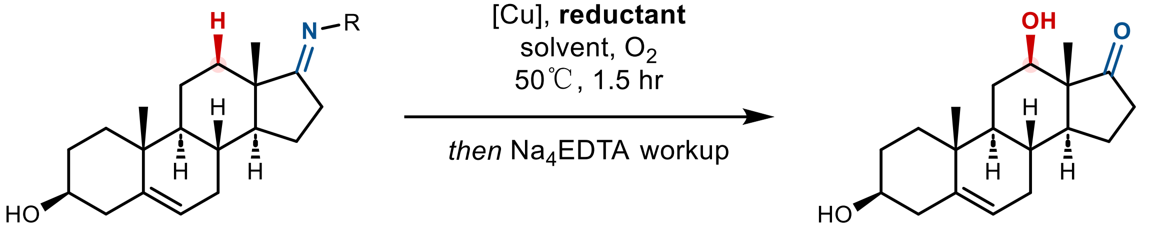
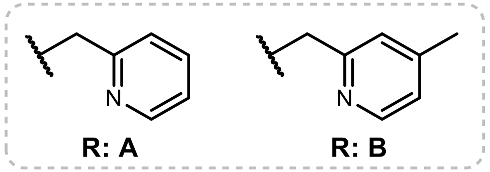
Baran’s modification

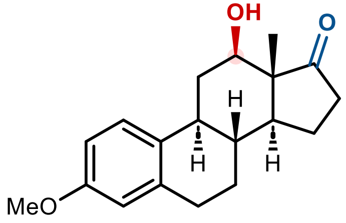




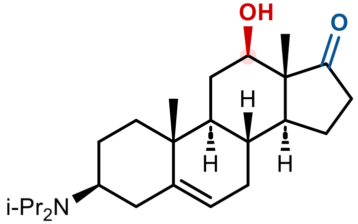
[Cu]	Red.	Solv.	R	Yield%
Cu(I)	None	0.02 M acetone	A	45%
Cu(I)	benzoin/Et_3N	0.02 M acetone	A	21%
Cu(I)	**Na ascorbate**	0.02 M acetone	A	67%
Cu(I)	**Na ascorbate**	0.15 M ace/MeOH 1:1	A	66%
Cu(I)	**Na ascorbate**	0.15 M ace/MeOH 1:1	B	90%
Cu(II)	**Na ascorbate**	0.15 M ace/MeOH 1:1	B	68%

Cu(I) = $Cu(MeCN)_4PF_6$; Cu(II) = $Cu(OTf)_2$, 2.0 eq. reductant

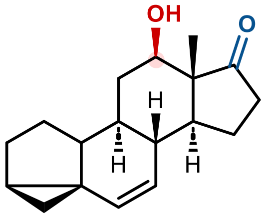
All yields here starting from imine



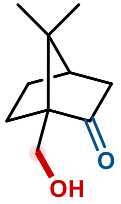
*from Cu(I): **62%***
*from Cu(II): **64%***



*from Cu(I): **32%***
*from Cu(II): **68%***



*from Cu(I): **40%***
*from Cu(II): **2%***

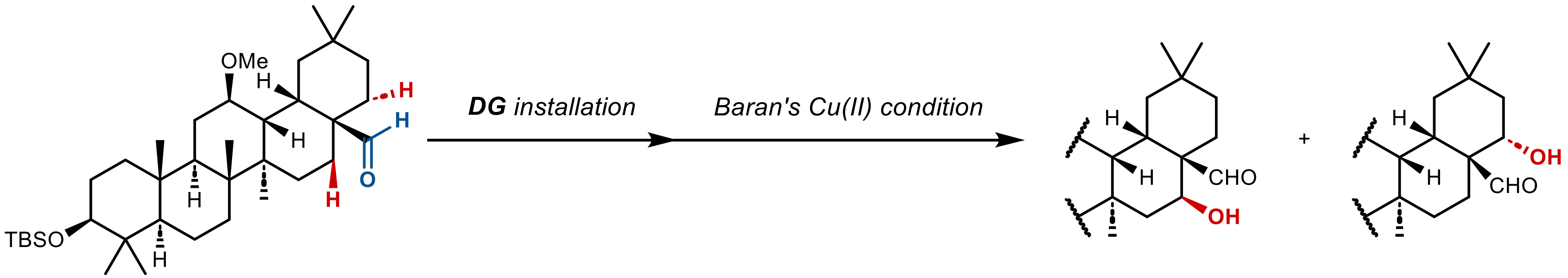


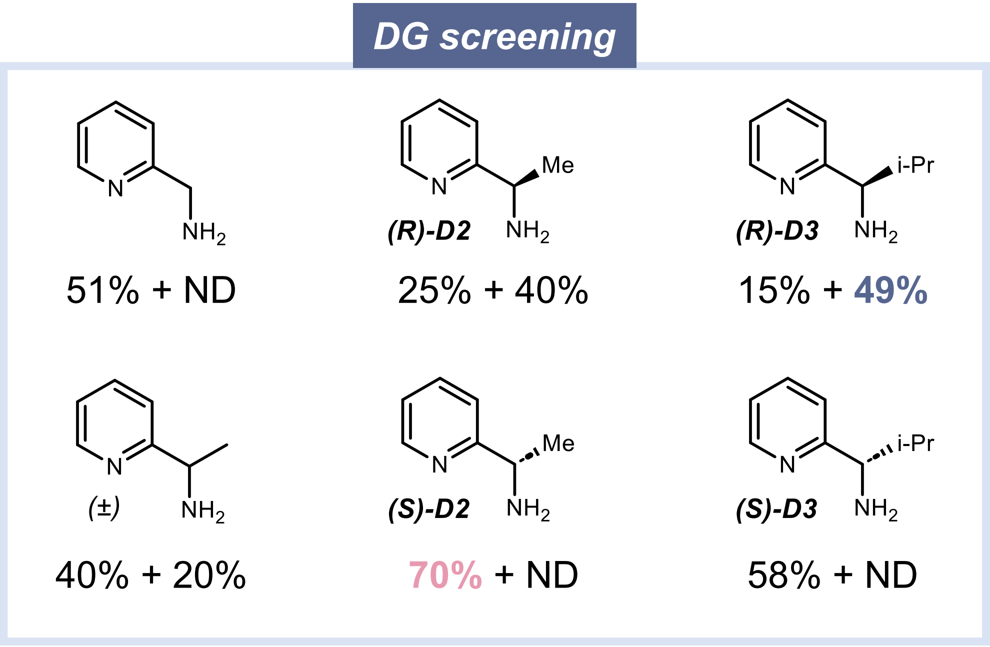
extra [Cu] & red. used
6 hr instead of 1.5 hr
DG-A used

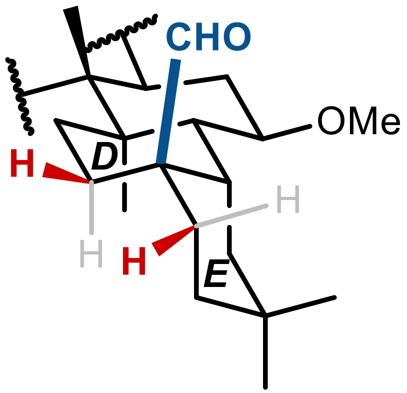
*from Cu(I): **94%***
*from Cu(II): **87%***

Baran, P. S. *et al.* *J. Am. Chem. Soc.* **2015**, *137* (43), 13776–13779.

Local desymmetrization through DG design



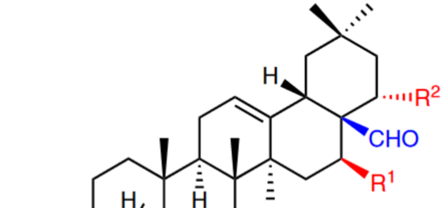




Yu, B. *et al. Nat Commun* **2020**, *11* (1), 4371.

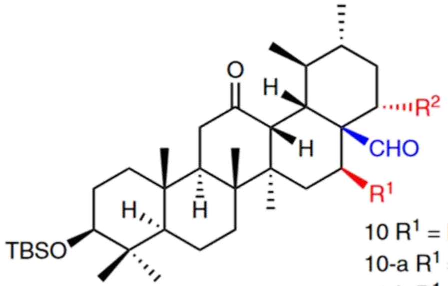
Local desymmetrization through DG design

- Selected Scope (*brsm* yield in parentheses)



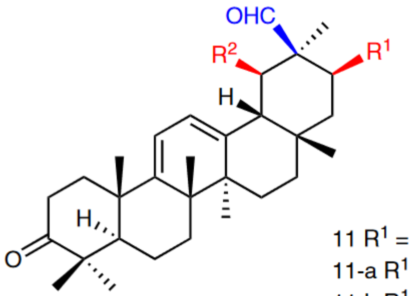
6 $R^1 = R^2 = H$
6-a $R^1 = OH, R^2 = H$
6-b $R^1 = H, R^2 = OH$

Entry	DG	6-a	6-b
1a	D2(R)	N.D.	47% (83%)
1b	D2(S)	65%	N.D.
1c	D3(R)	N.D.	53% (90%)
1d	D3(S)	92%	N.D.



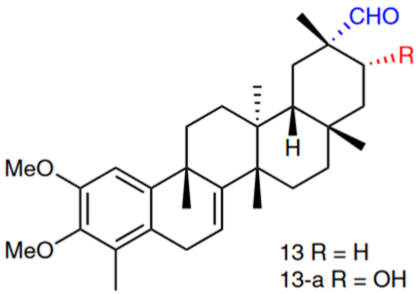
10 $R^1 = R^2 = H$
10-a $R^1 = OH, R^2 = H$
10-b $R^1 = H, R^2 = OH$

Entry	DG	10-a	10-b
5a	D2(R)	N.D.	65%
5b	D2(S)	75%	N.D.
5c	D3(R)	N.D.	94%
5d	D3(S)	73%	N.D.



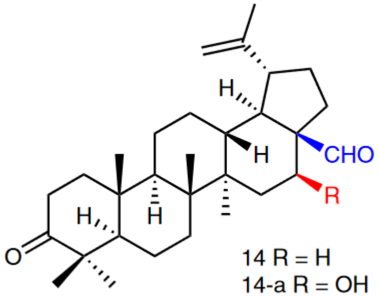
11 $R^1 = R^2 = H$
11-a $R^1 = OH, R^2 = H$
11-b $R^1 = H, R^2 = OH$

Entry	DG	11-a [X-ray]	11-b [X-ray]
6a	D2(R)	N.D.	42%
6b	D2(S)	71%	N.D.
6c	D3(R)	N.D.	46%
6d	D3(S)	89%	N.D.



13 R = H
13-a R = OH

Entry	DG	13-a
8a	D2(R)	47%
8b	D2(S)	69%
8c	D3(R)	47%
8d	D3(S)	80%



14 R = H
14-a R = OH

Entry	DG	14-a
9a	D2(R)	53%
9b	D2(S)	96%
9c	D3(R)	75%
9d	D3(S)	98%

Yu, B. *et al. Nat Commun* **2020**, *11* (1), 4371.

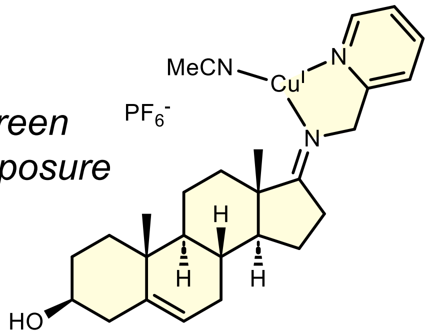
Outline

- Introduction: Cu in biology
- Copper-dependent monooxygenases: case studies on two enzymes
- Small molecule emulation
    - Baran-Schönecker method
    - Mechanism revision and further optimization
- Application

Is it *really* through $[Cu_2O_2]$?

- Reaction of well-defined complexes under **extremely dilute** conditions *($[Cu]$ = 4mM)*

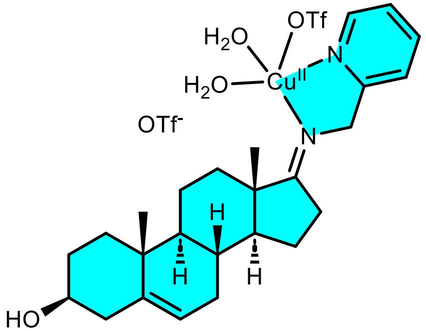
instant green upon O_2 exposure



S-Cu^I

[O]	Temp	Time	Yield%
O_2	0 ℃	6 h	46%
O_2	20 ℃	6 h	**57%**
O_2	50 ℃	6 h	**77%**
5 eq. H_2O_2	20 ℃	0.5 h	**66%**

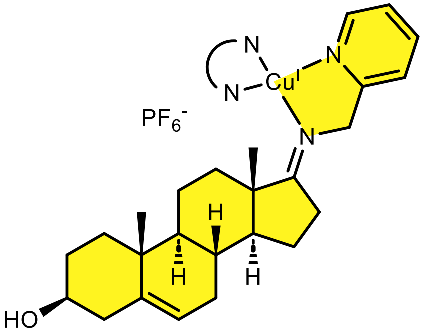
50% limit can be surpassed w/o reductant



S-Cu^II

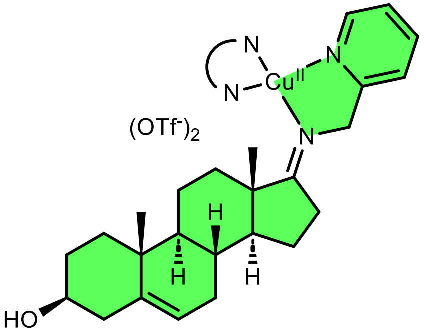
[O]	Temp	Time	Yield%
O_2	50 ℃	6 h	2%
5 eq. H_2O_2	20 ℃	0.5 h	43%

Cu(II) inactive towards O_2 but active towards H_2O_2



S_2-Cu^I

[O]	Temp	Time	Yield%
O_2	20 ℃	6 h	0%
O_2	50 ℃	6 h	0%
5 eq. H_2O_2	20 ℃	0.5 h	38%



S_2-Cu^II

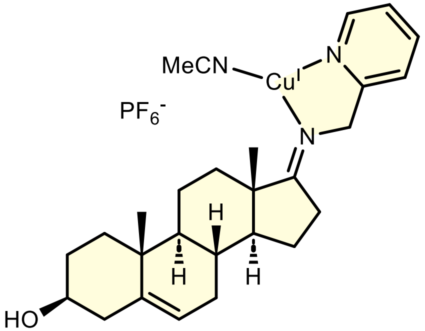
[O]	Temp	Time	Yield%
O_2	50 ℃	6 h	10%
5 eq. H_2O_2	20 ℃	0.5 h	53%

L_2Cu not active

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

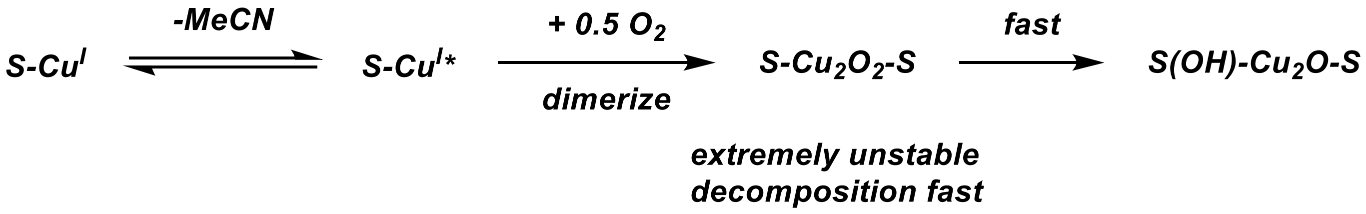
Is it *really* through $[Cu_2O_2]$?

- Reaction of well-defined complexes under **extremely dilute** conditions *([Cu] = 4mM)*



S-Cu^I

under previous dinuclear proposal

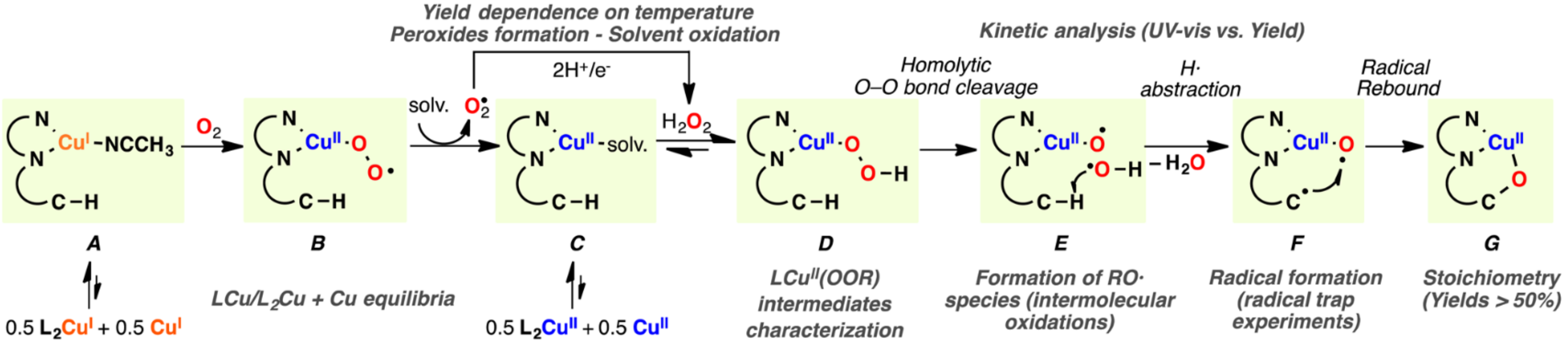


cannot explain such temperature sensitivity

[O]	Temp	Time	Yield%
O_2	0 ℃	6 h	46%
O_2	20 ℃	6 h	57%
O_2	50 ℃	6 h	77%

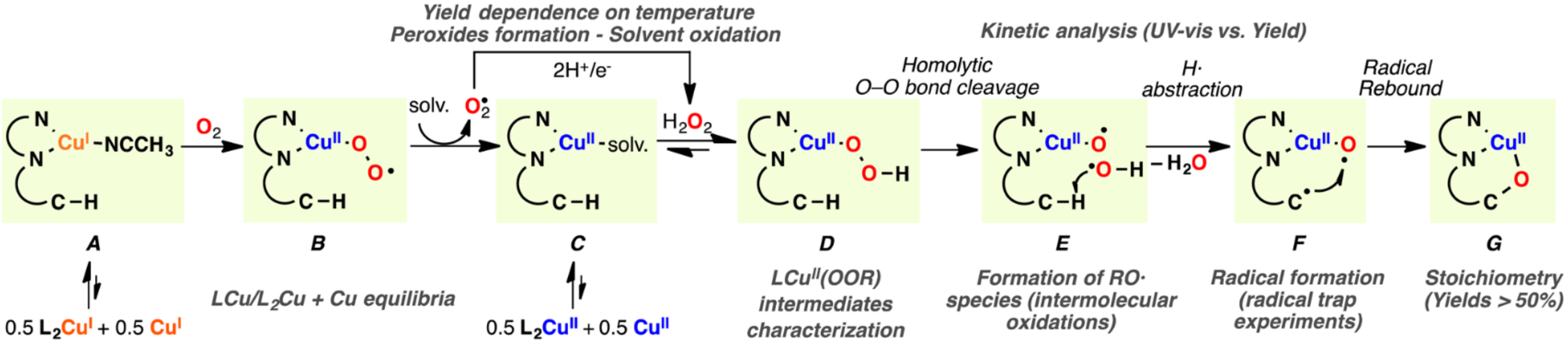
*yield **sensitive to temperature***
under long reaction time

new mechanism



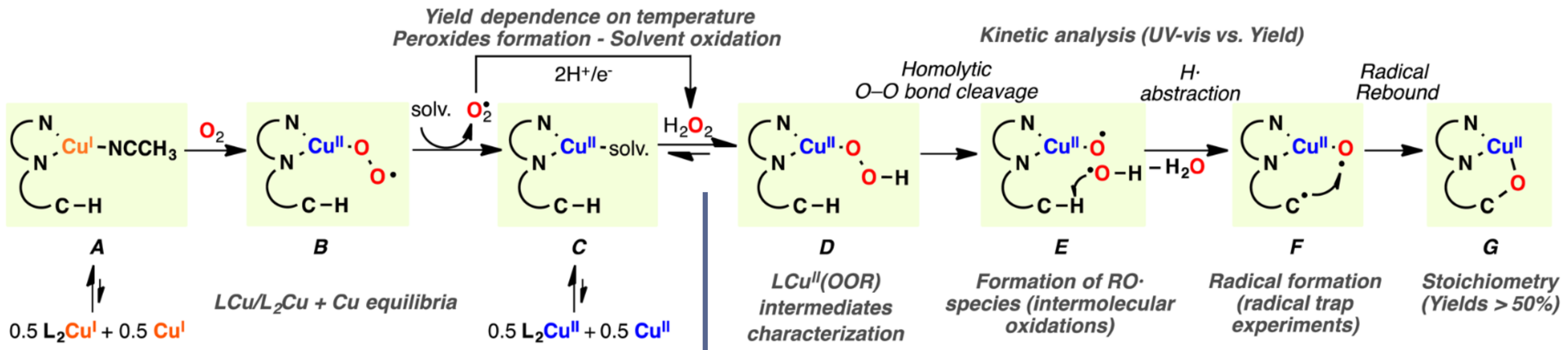
Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

The Monocopper Mechanism



Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation



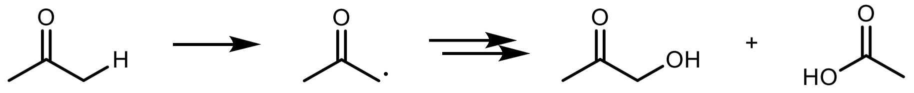
Question: main species in solution

Determined via NMR to be mononuclear

Question: source of H_2O_2

Low temp: disproportionation, $2HO_2 = H_2O_2 + O_2$

High temp: solvent oxidation by HO_2



pdts confirmed by GC-MS

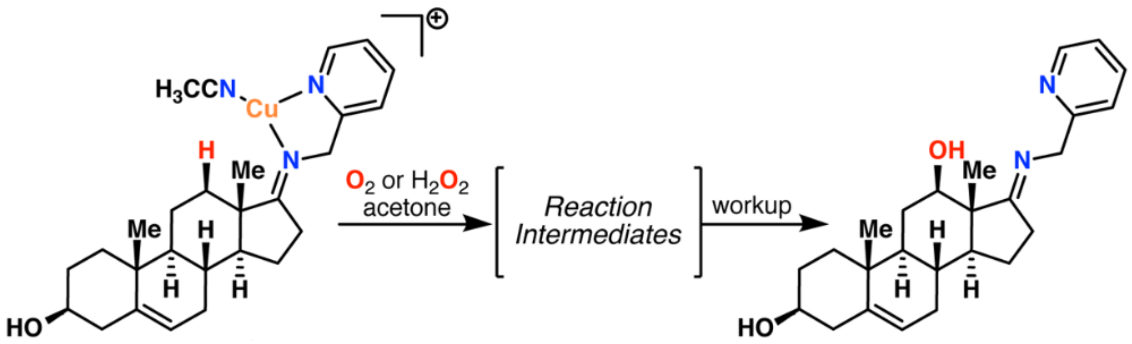
solvents prone to peroxidation give higher yields

toluene/benzene low yield due to sequestering

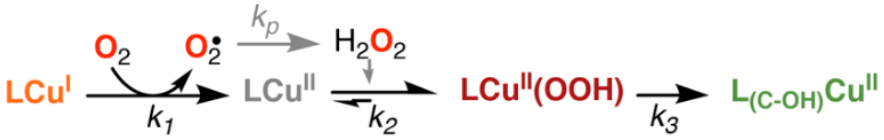
Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

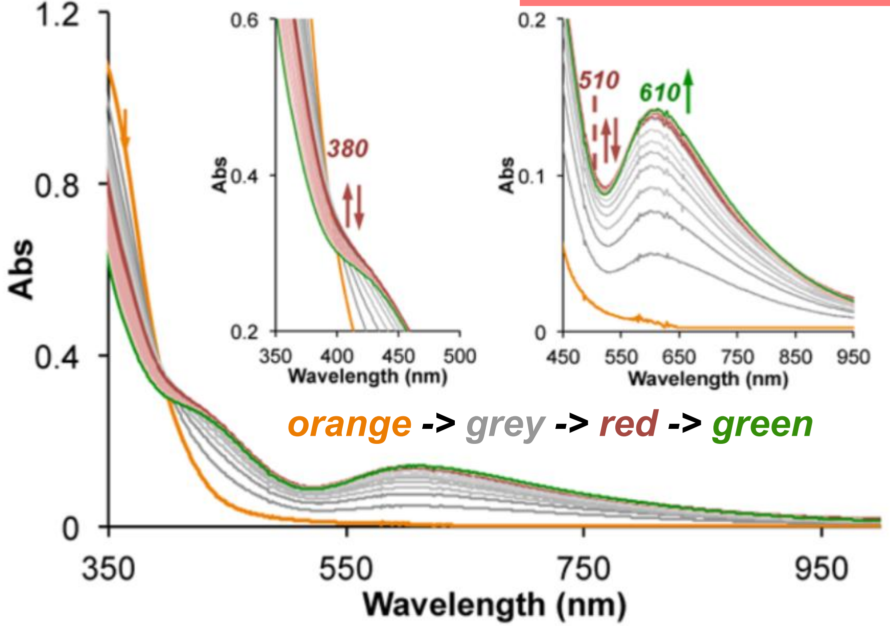
Question: prove intermediacy of Cu(II)-OOH

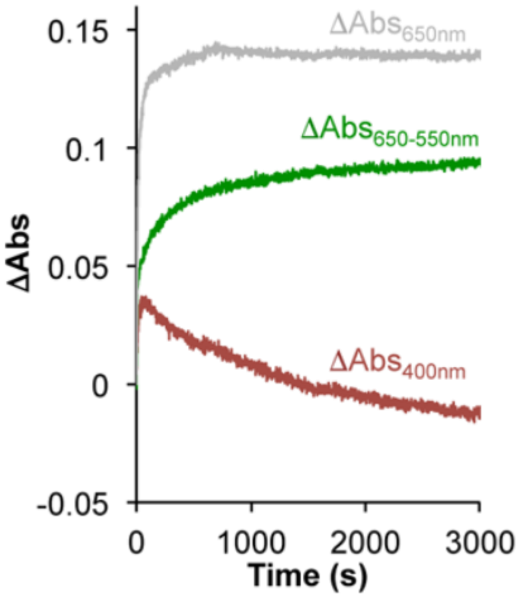


O_2 as oxidant

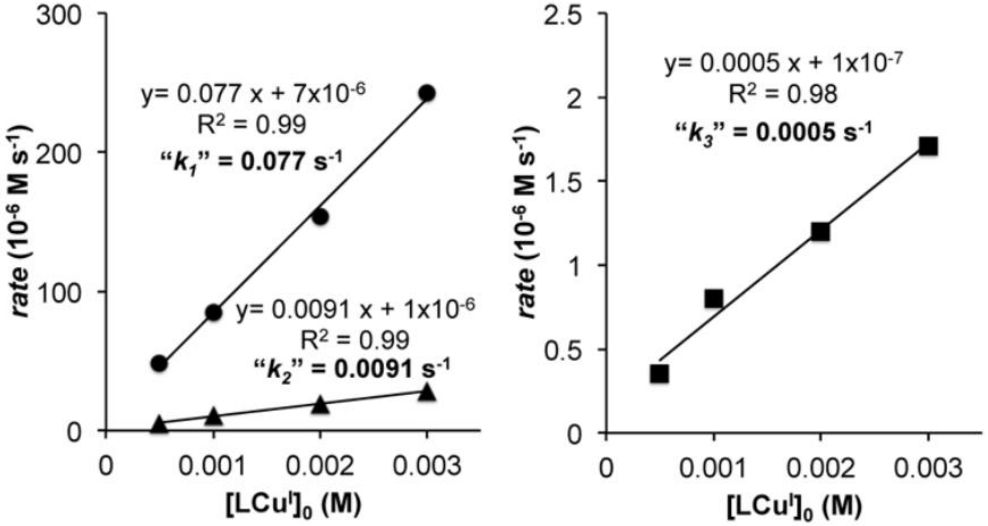


Intermediacy of 2 species





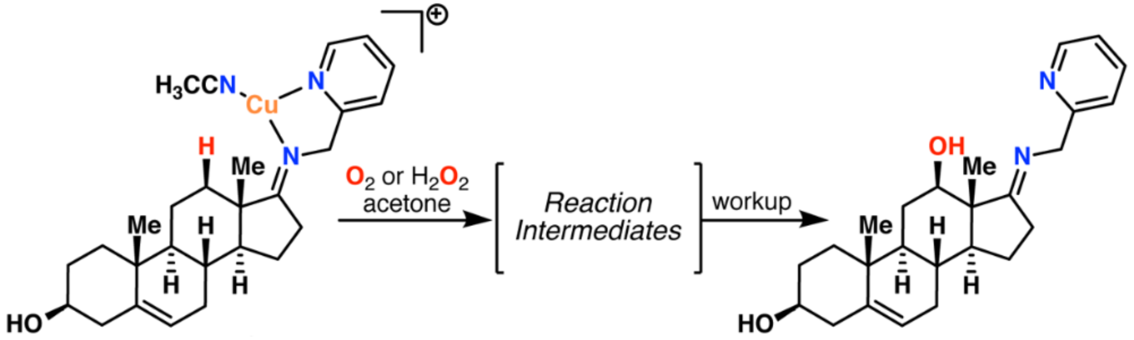
1st order wrt. [Cu]



Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

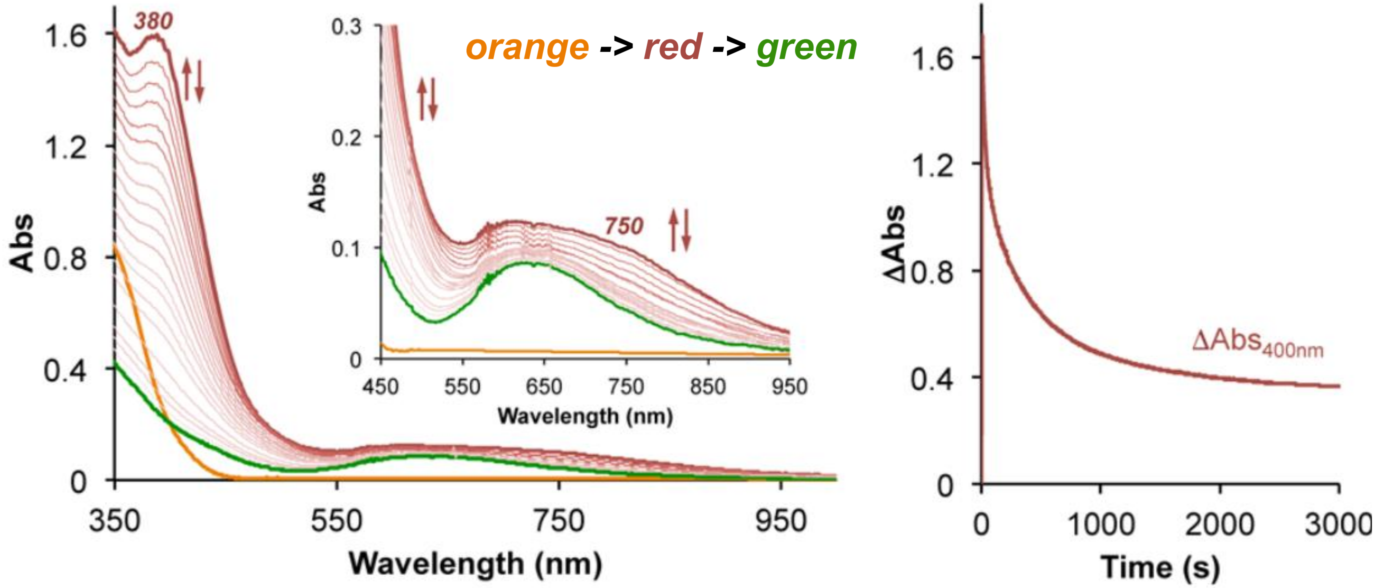
Experimental & spectral validation

Question: prove intermediacy of Cu(II)-OOH

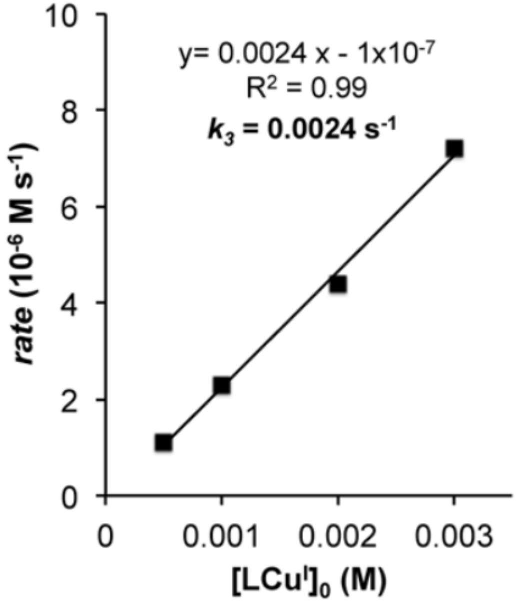


large excess H_2O_2 as oxidant

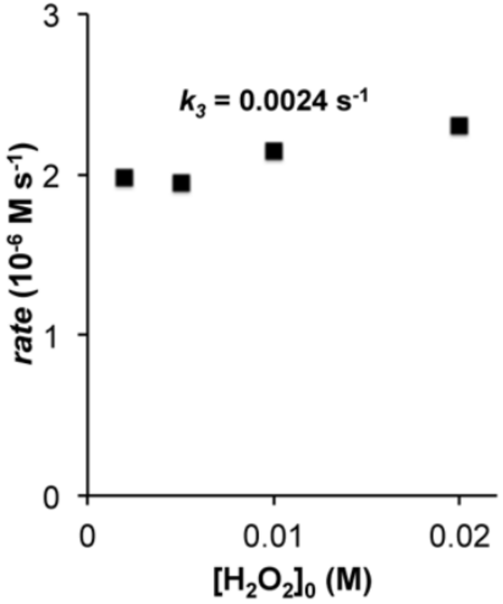
Intermediacy of 2 species



1st order wrt. [Cu]



0th order wrt. [H_2O_2]

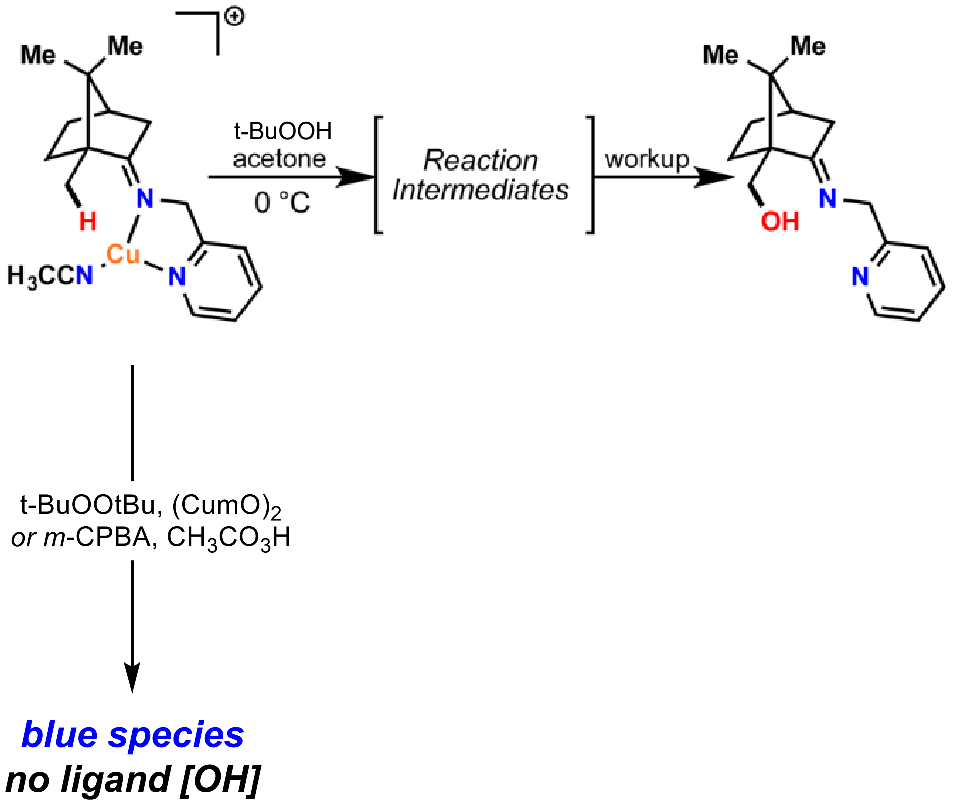


Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

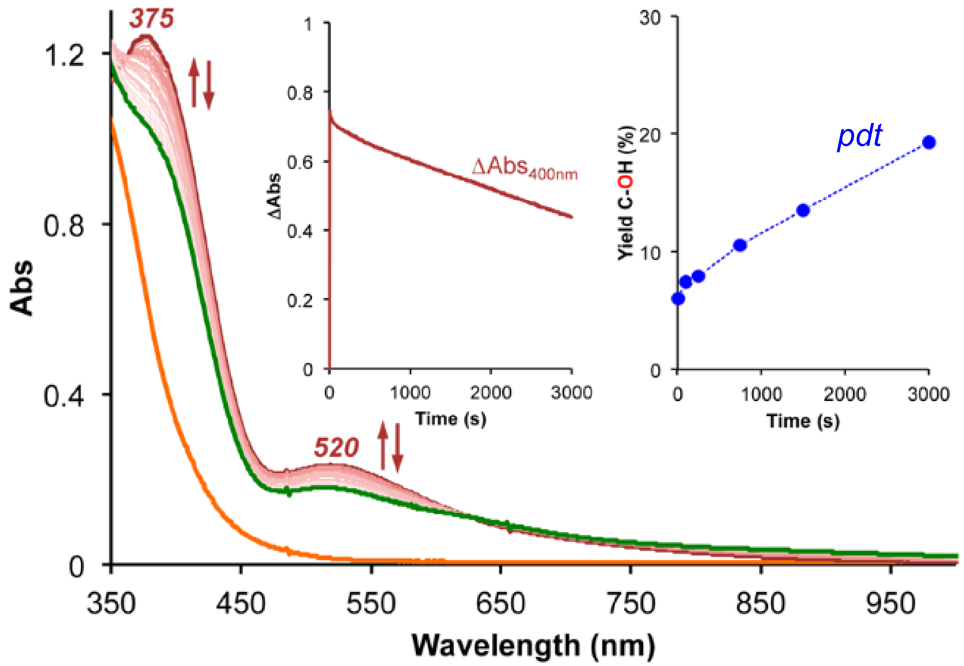
Experimental & spectral validation

Question: prove intermediacy of Cu(II)-OOH

- *Additional experiment:* **ROOH as oxidant**



Similar spectra shift w/ H_2O_2 and O_2 cases

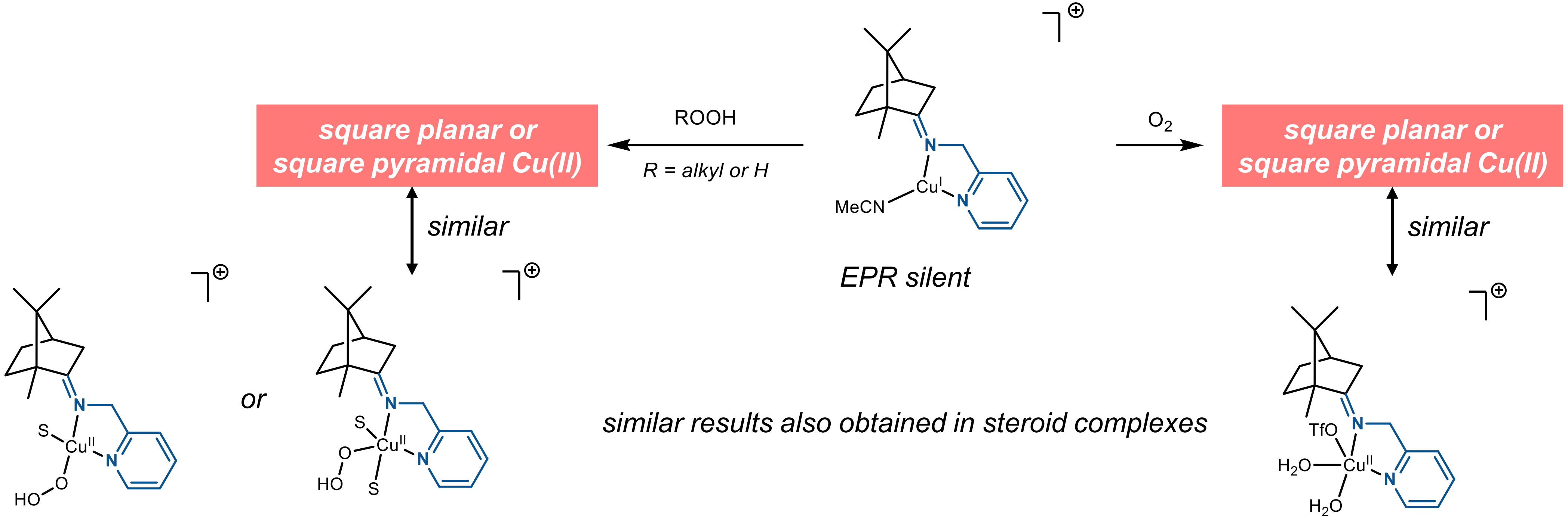


Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

Question: prove intermediacy of Cu(II)-OOH

- *EPR to confirm presence of relevant Cu species*

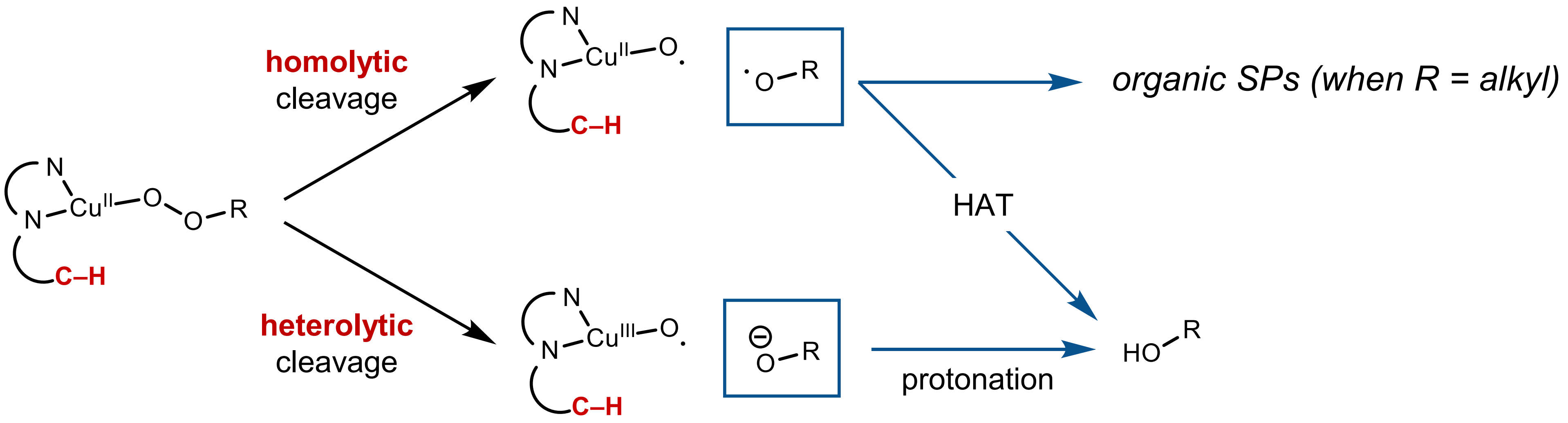


Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

Question: O-O cleavage mechanism & the HAT species

- *ROOH with **different HAT capabilities***



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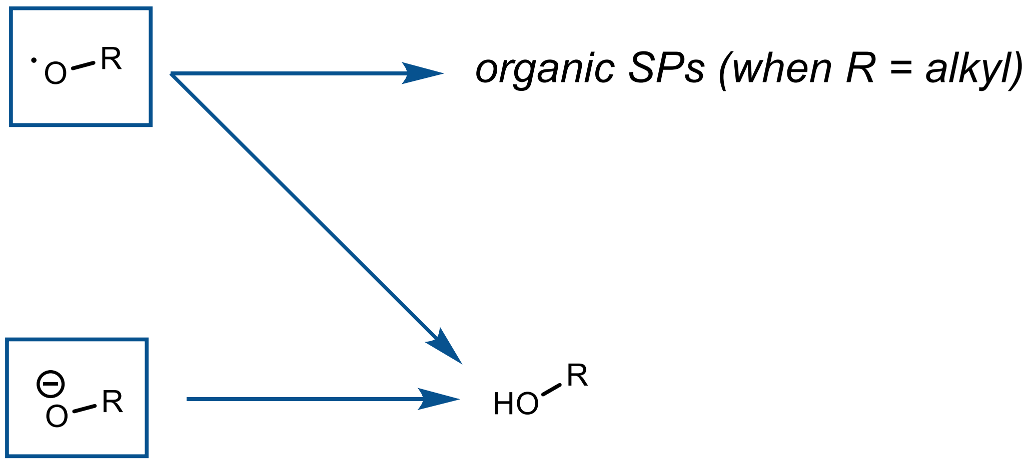
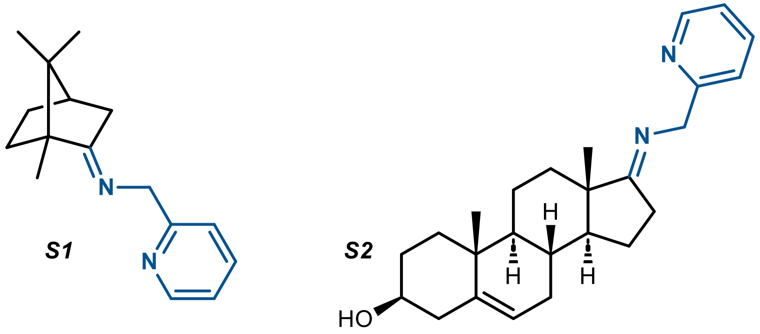
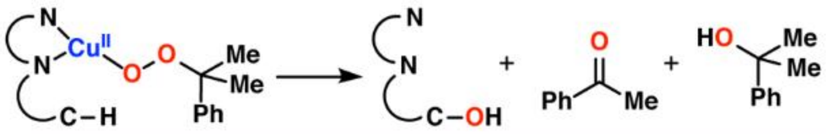






	Yield		
L = ***S1***, 20 °C	25%	28%	72%
0 °C	14%	17%	83%
–40 °C	8%	3%	97%
L = ***S2***, 20 °C	27%	26%	74%
0 °C	31%	7%	93%
–40 °C	36%	3%	96%

Homolysis of O–O bond in Cu^{II}–OOR involved

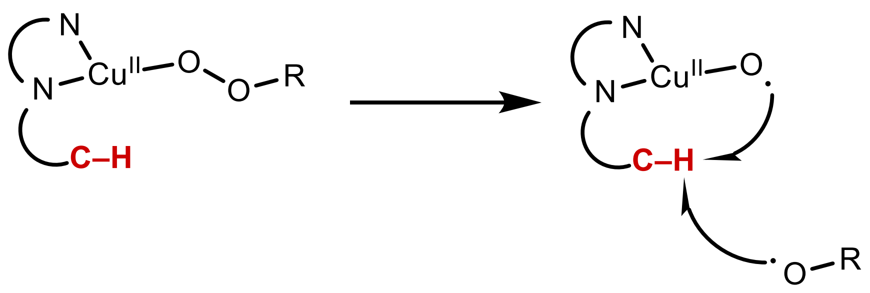
*consistent observation of SPs corresponding to **radical β-scission***

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

Question: O-O cleavage mechanism & the HAT species

- *ROOH with* ***different HAT capabilities***



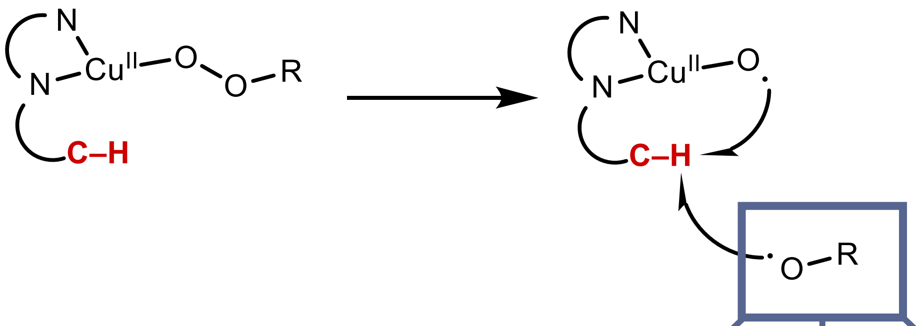
Cu(II)–O *for HAT or* ***O-radical*** *for HAT?*

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

Question: O-O cleavage mechanism & the HAT species

- *ROOH with* ***different HAT capabilities***



Cu(II)–O *for HAT or* ***O-radical*** *for HAT?*

HAT
(productive)

β-scission
(non-productive)

Cage escape
(non-productive) — *Oxidation of solvent or external substrates*

<u>Productive vs. non-productive pathways</u>

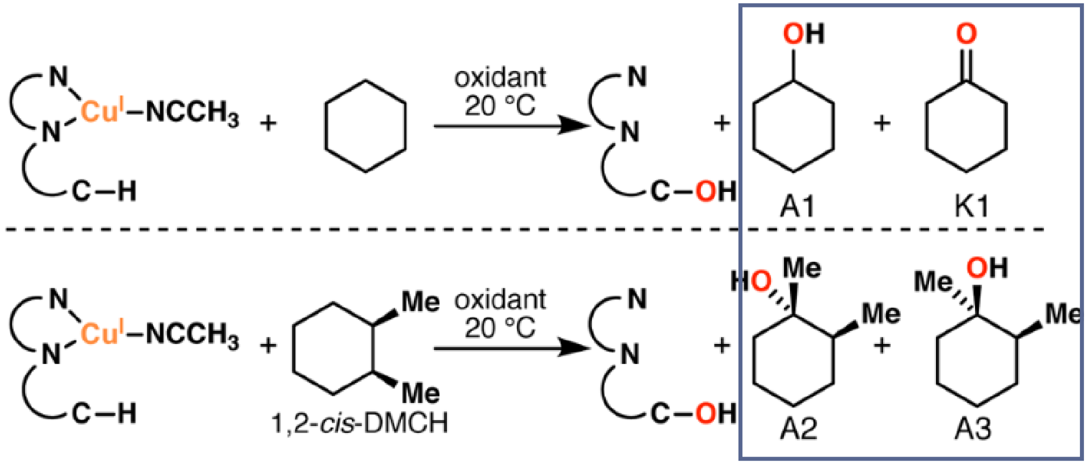
Dependence on RO• :	Dependence on C–H:
CumO•, *tBuO*• << HO•	**S1**: methyl **S2**: methylene
Stronger oxidant: higher yields	*Weaker C–H bond: higher yields*

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

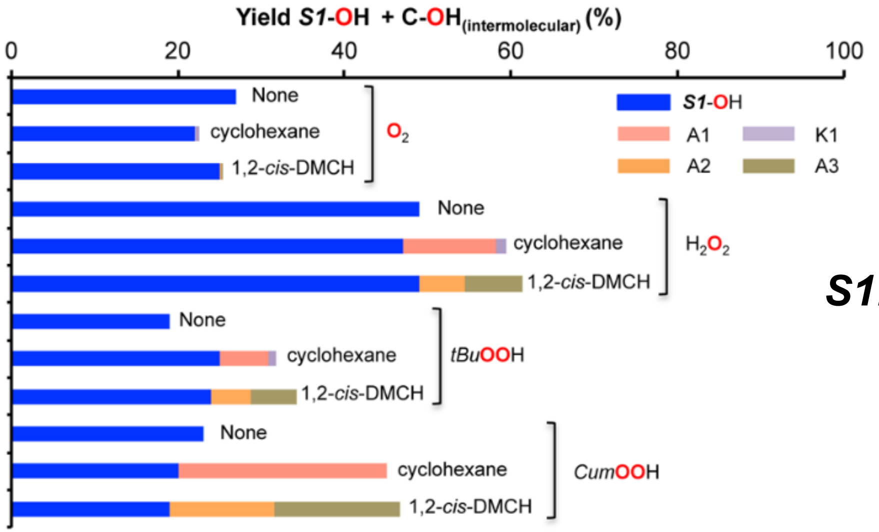
Experimental & spectral validation

Question: O-O cleavage mechanism & the HAT species

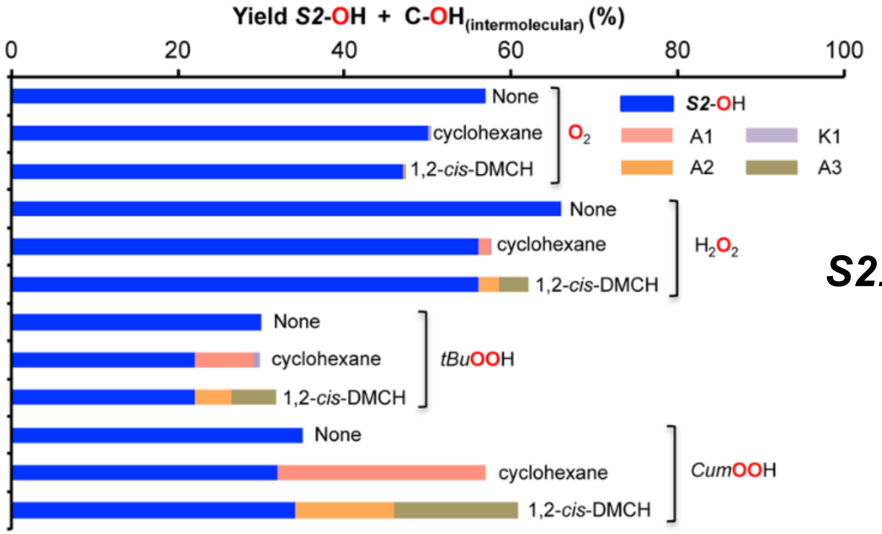
- *External substrate to test **cage escape** of radical*



formed only through escaped RO·



***S1**: primary C–H*



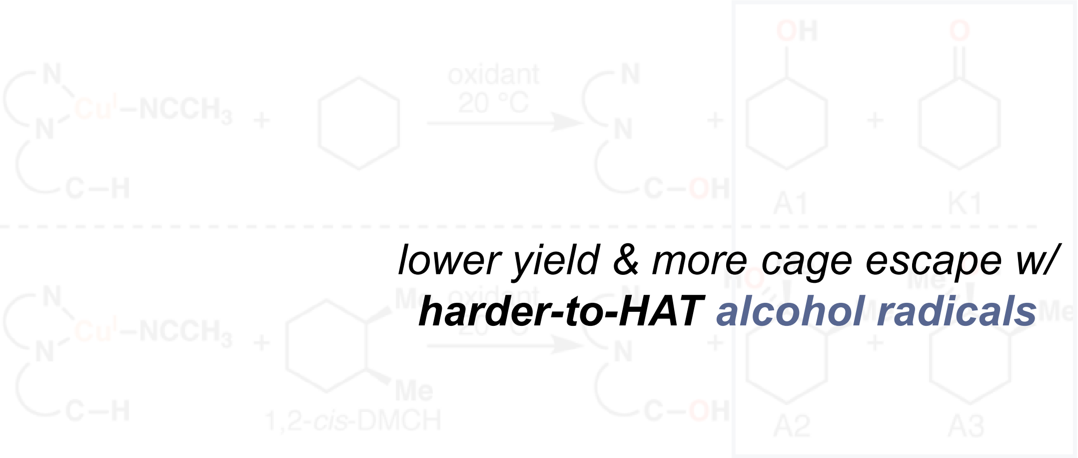
***S2**: secondary C–H*

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

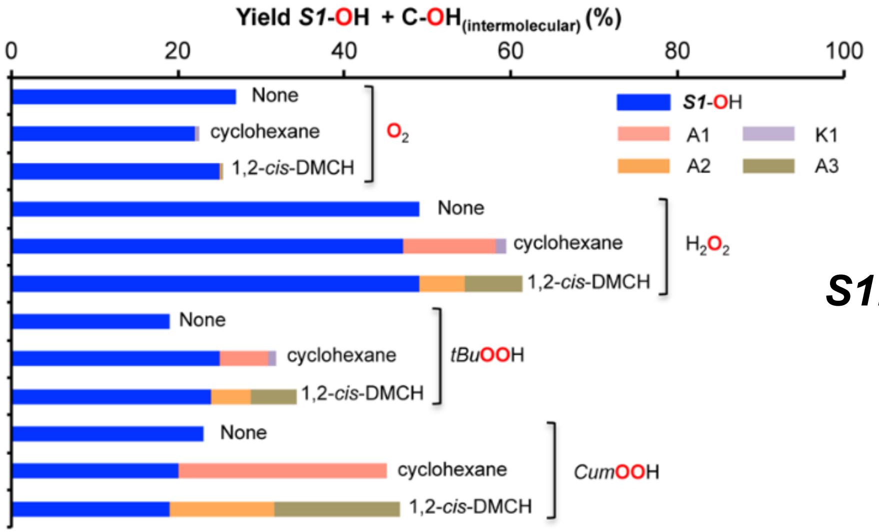
Question: O-O cleavage mechanism & the HAT species

- *External substrate to test **cage escape** of radical*

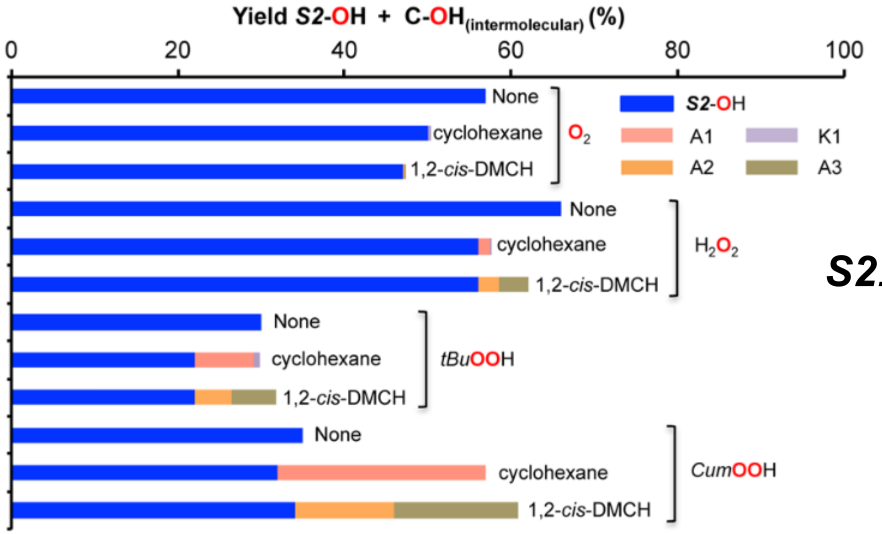


lower yield & more cage escape w/ ***harder-to-HAT alcohol radicals***

formed only through escaped RO·



***S1**: primary C–H*



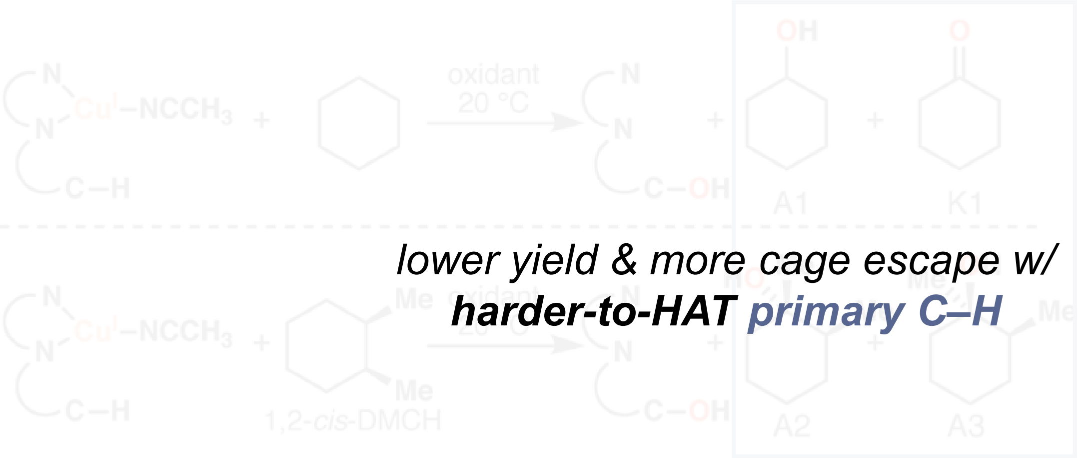
***S2**: secondary C–H*

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

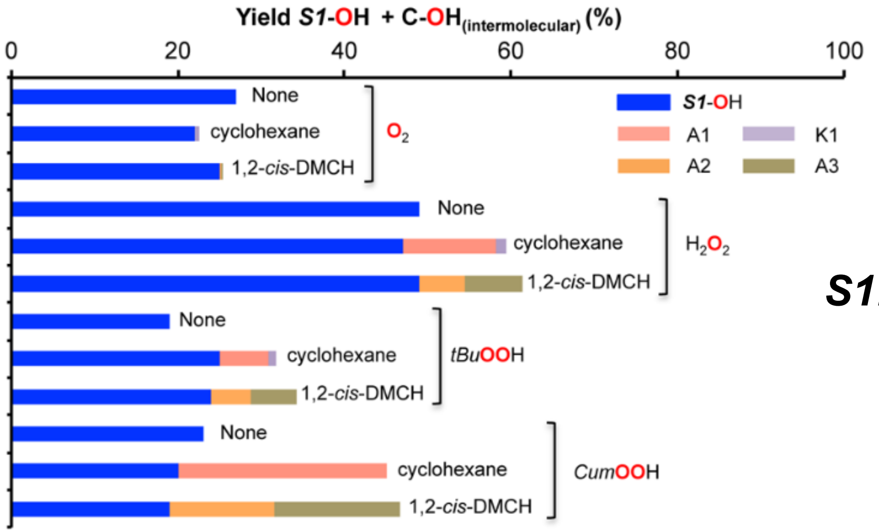
Question: O-O cleavage mechanism & the HAT species

- *External substrate to test **cage escape** of radical*

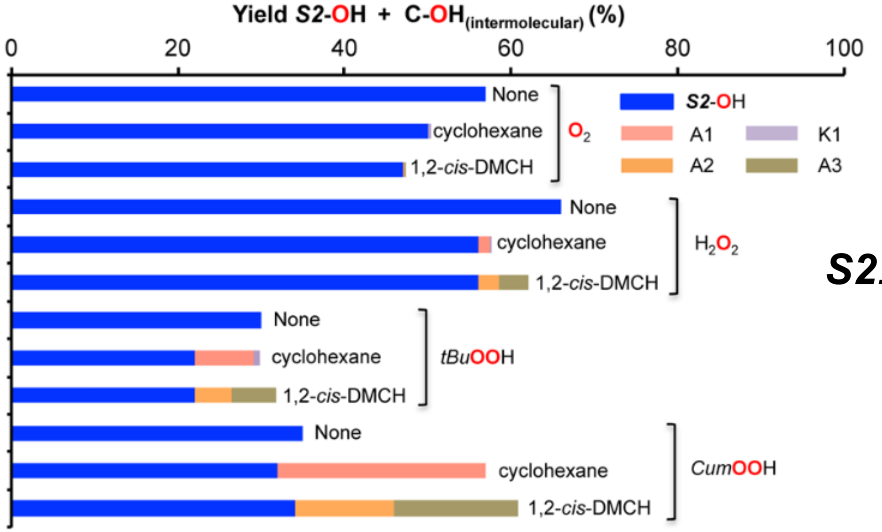


lower yield & more cage escape w/
***harder-to-HAT** primary C–H*

formed only through escaped RO·



***S1**: primary C–H*



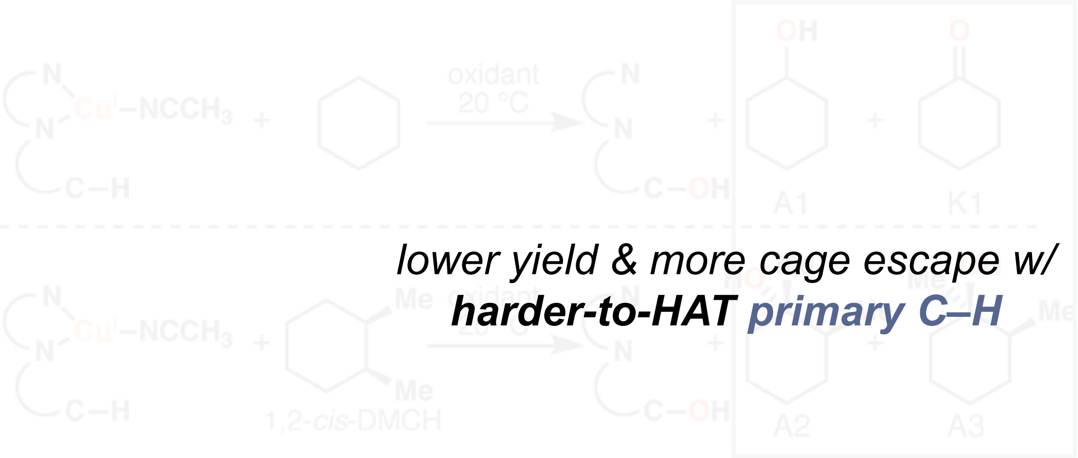
***S2**: secondary C–H*

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Experimental & spectral validation

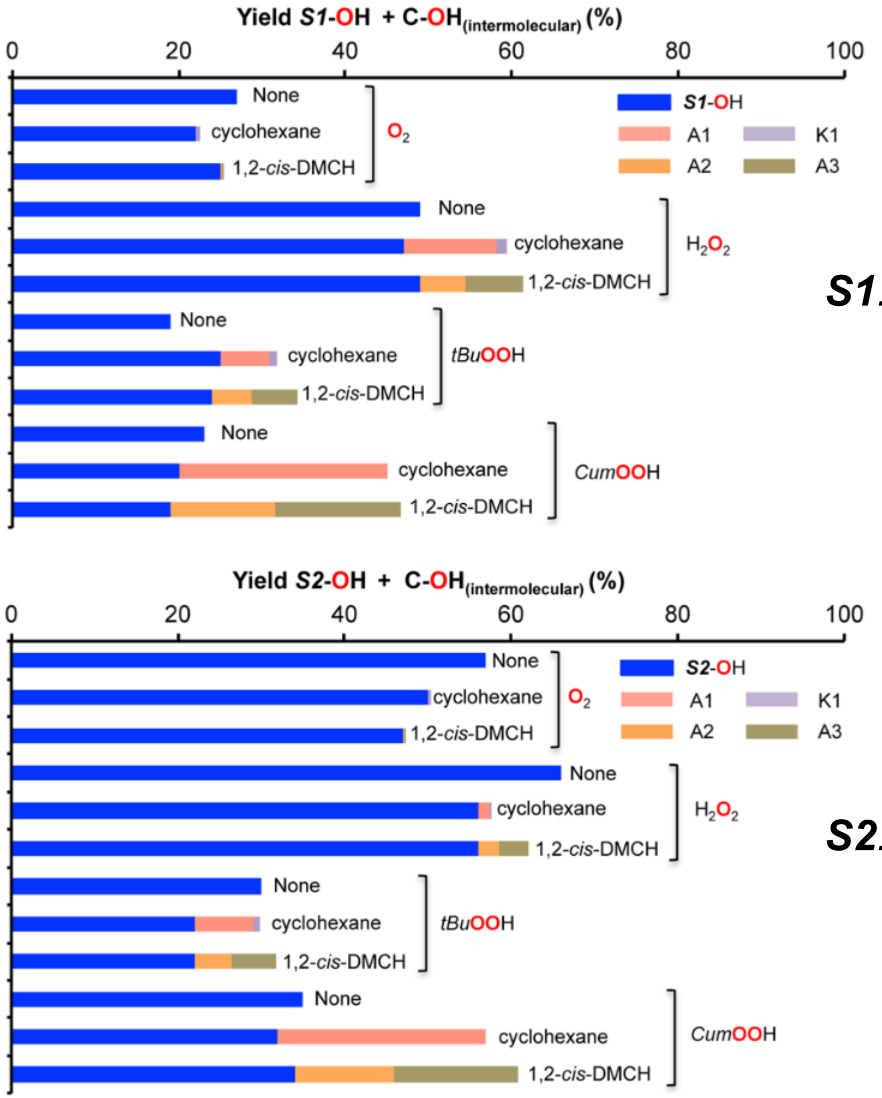
Question: O-O cleavage mechanism & the HAT species

- *External substrate to test **cage escape** of radical*



lower yield & more cage escape w/
***harder-to-HAT** primary C–H*

An OH or OR radical is the HAT species.



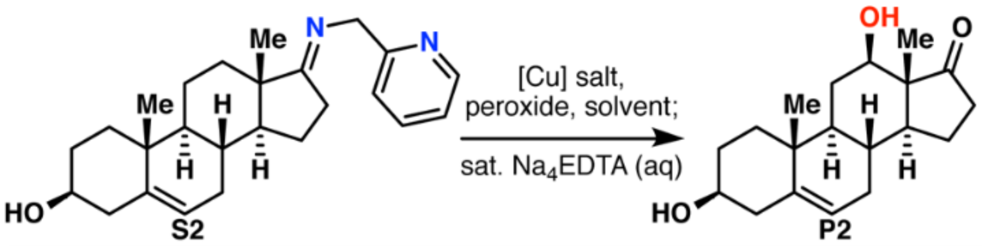
S1: *primary C–H*

S2: *secondary C–H*

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

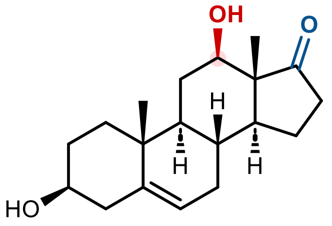
Improved condition

- *Scope: isolated yield (NMR yield), previous best condition given*

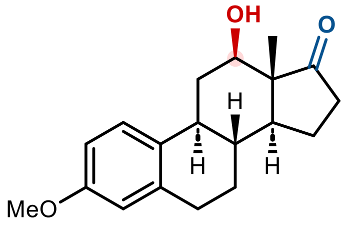


Entry	[Cu] salt[b]	Peroxide[c]	Solvent[d]	Time (min)	Yield (%)[e]	DHEA (%)
1	$Cu(OTf)_2$	H_2O_2	acetone	90	57	25
2	$Cu(OAc)_2·H_2O$	H_2O_2	acetone	90	25	49
3	$CuCl_2·2H_2O$	H_2O_2	acetone	90	0	98
4	$Cu(NO_3)_2·3H_2O$	H_2O_2	acetone	90	77	9
5	$Cu(NO_3)_2·3H_2O$	TBHP	acetone	120	0	100
6	$Cu(NO_3)_2·3H_2O$	TBHP/Et_3N	acetone	120	3.8	64
7	$Cu(NO_3)_2·3H_2O$	lauroyl peroxide	acetone	120	0	86
8	$Cu(NO_3)_2·3H_2O$	cumyl peroxide	acetone	120	0	59
9	$Cu(NO_3)_2·3H_2O$	H_2O_2	acetone/MeOH	90	87	13
10	$Cu(NO_3)_2·3H_2O$	H_2O_2	CH_2Cl_2	90	42	0
11	$Cu(NO_3)_2·3H_2O$	H_2O_2	THF	90	99	1
12	$Cu(NO_3)_2·3H_2O$	H_2O_2	1,4-dioxane	90	87	4

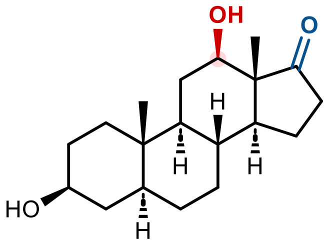
All: 1.1 eq. [Cu], 5.0 eq. [O], 0.2 M, r.t.



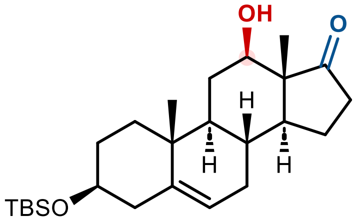
93% *(99%);* ***80% @ gram scale***
prev: 90% (Baran, Cu^{I})



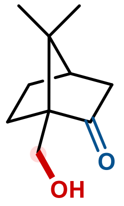
70%
prev: 64% (Baran, Cu^{II})



82%
prev: 80% (Baran, Cu^{I})



81% *(95%)*
prev: 52% (Baran, Cu^{I})

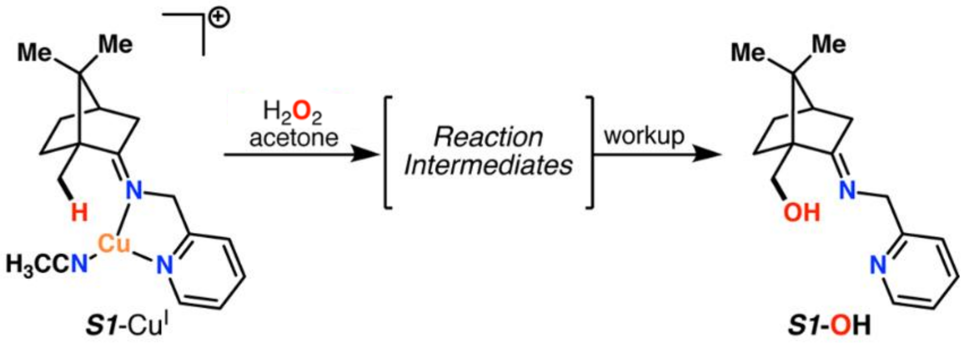


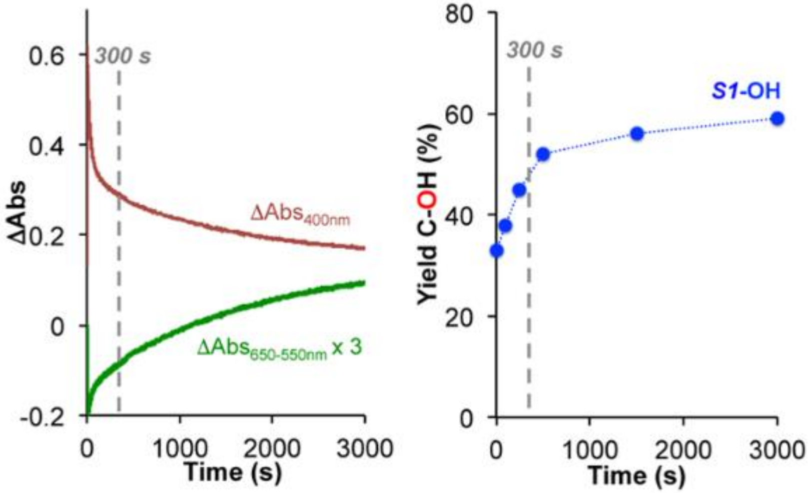
74% *(81%) (extra [O] & elevated temp)*
prev: 94% (Baran, Cu^{I})

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

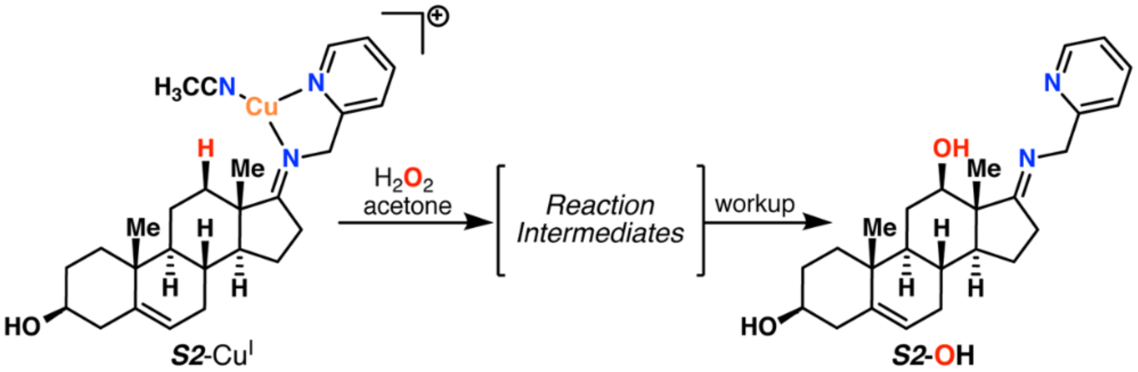
Or is it the whole picture?

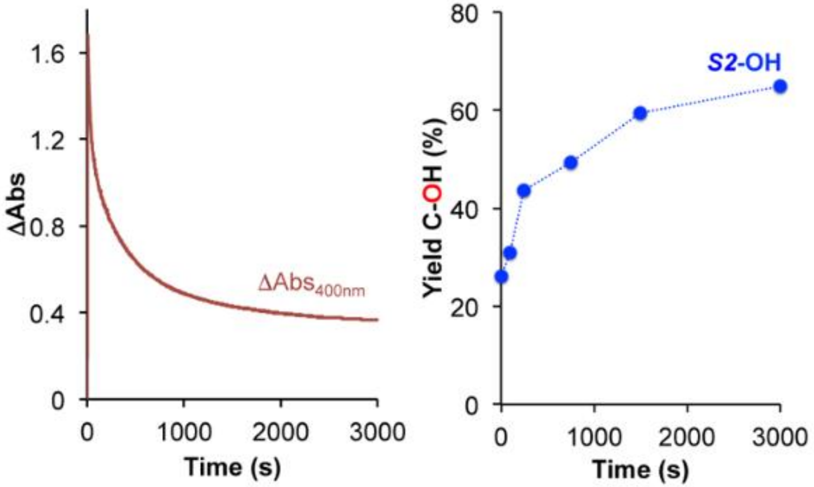
The ***'harder'*** **S1**: reacted **at 0℃**





The ***'easier'*** **S2**: reacted **at -40℃**

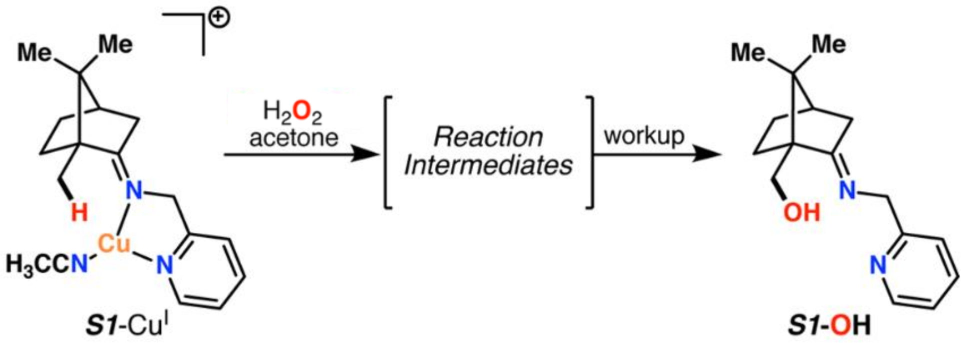


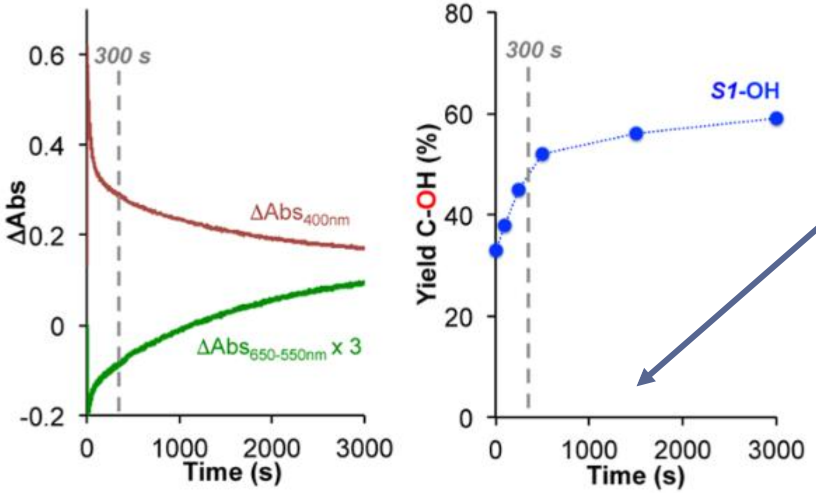


Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

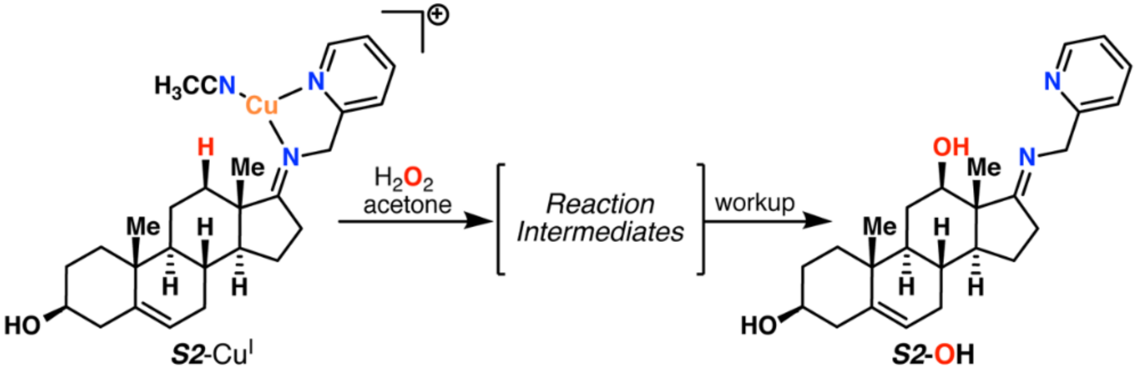
Or is it the whole picture?

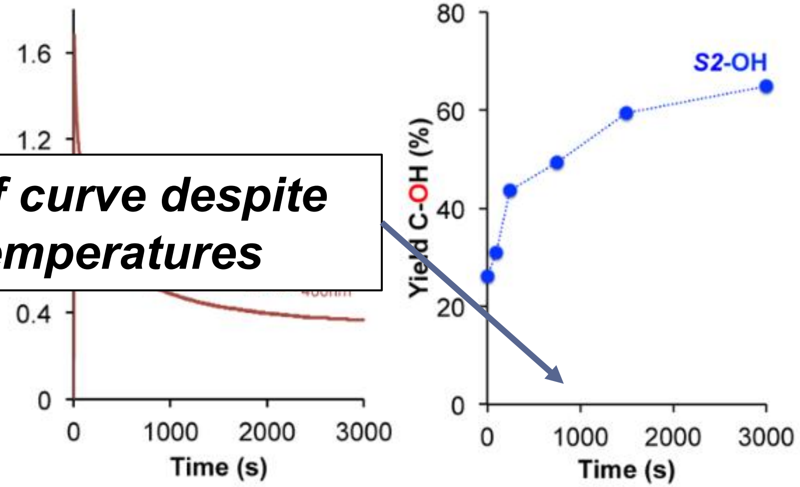
The ***'harder'* S1**: reacted **at 0℃**





The ***'easier'* S2**: reacted **at -40℃**



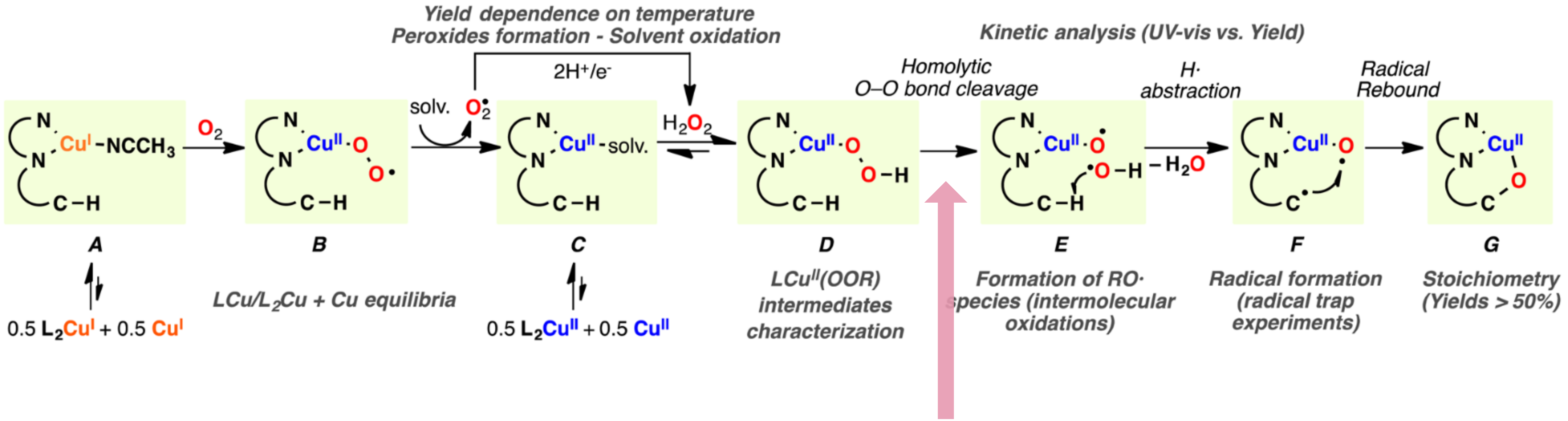


Similar time scale of curve despite vastly different temperatures

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Or is it the whole picture?

However…



It is reasonable to assume that this is the RDS.

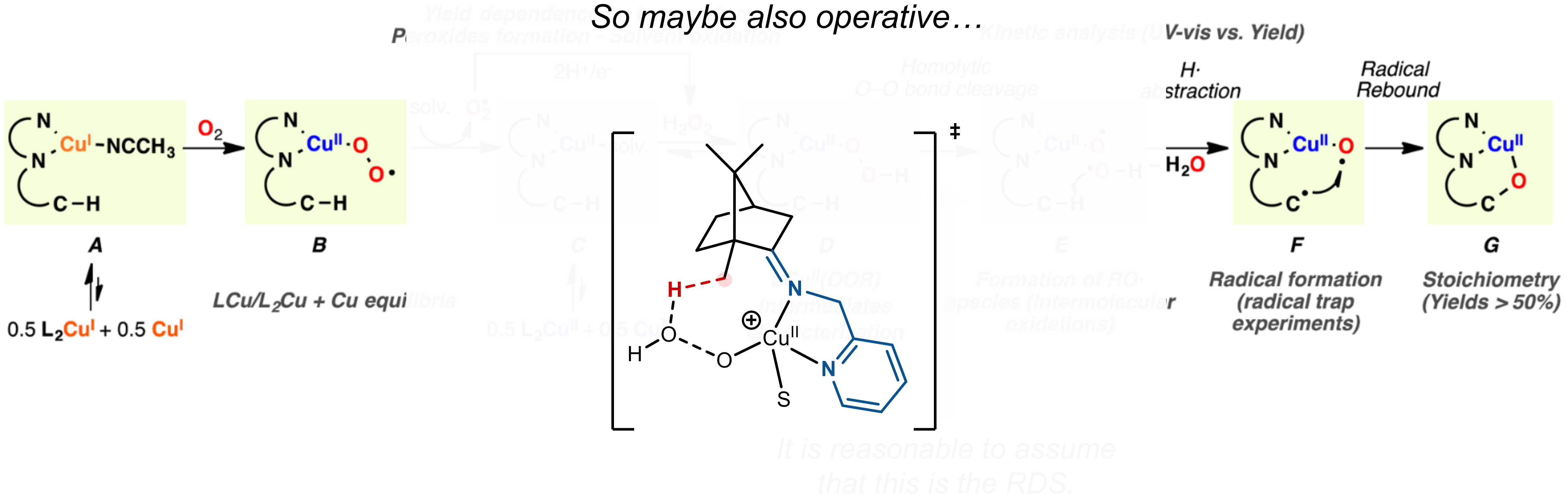
But the decomposition of LCu^{II}–OOH should not be so dramatically influenced by some ligand C–H bond

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Or is it the whole picture?

However…

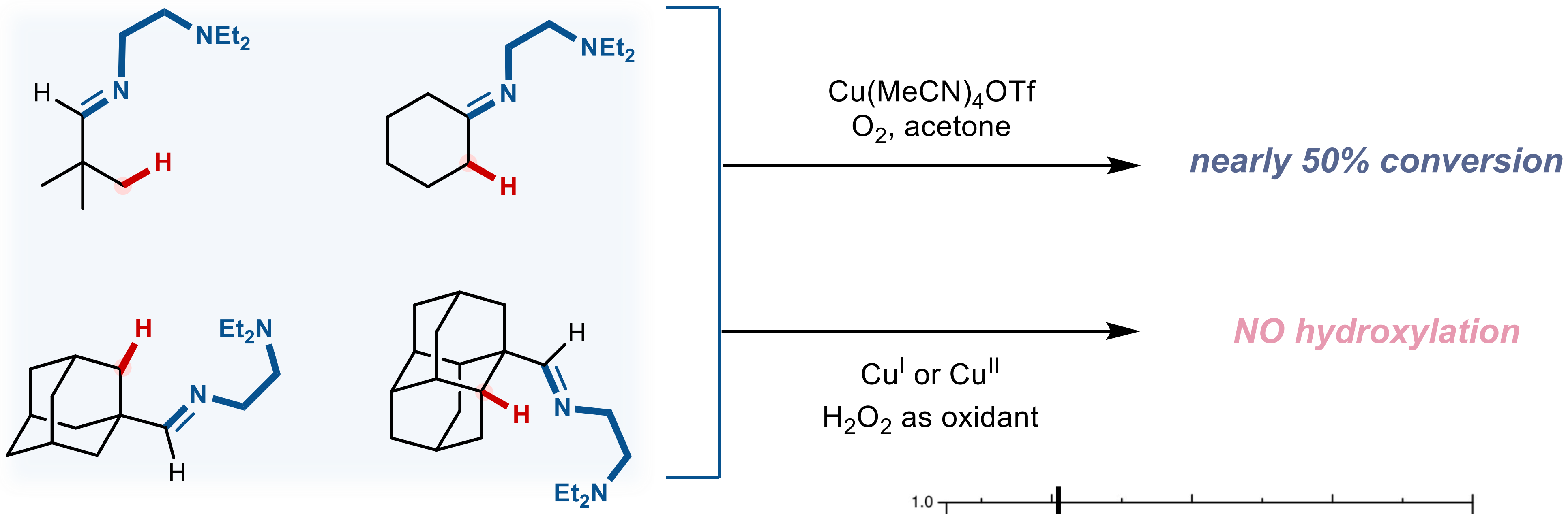
So maybe also operative…



But the decomposition of LCu^{II}–OOH should not be so dramatically influenced by some ligand C-H bond

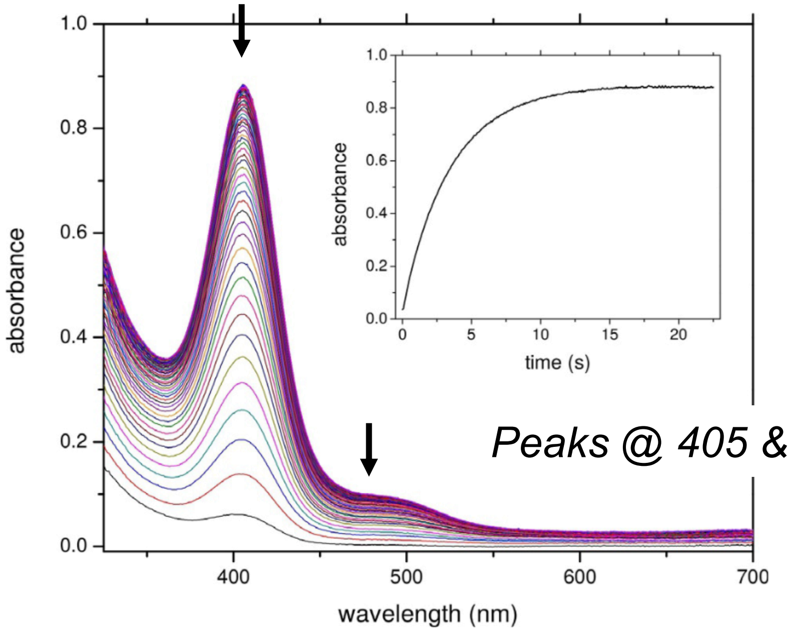
Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

(Amine, Imine) directing systems



Catalytically relevant species: $Cu^{III}{}_2O_2$

in a real [Cu_2O_2] case, extra reductant (ascorbate) or Cu^{II}/H_2O_2 systems stop working



Peaks @ 405 & 490 nm

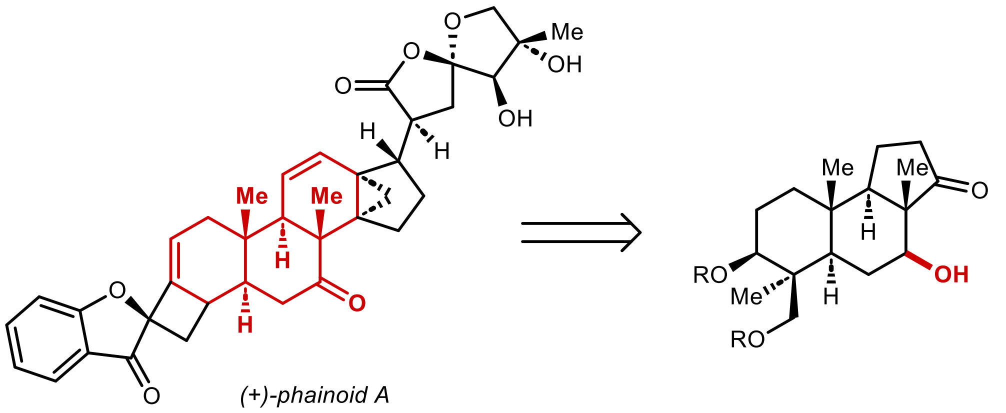
Schindler, S. *et al.* *Chem Eur J* **2018**, *24* (58), 15543–15549; *Eur J Inorg Chem* **2021**, *2021* (20), 1961–1970.

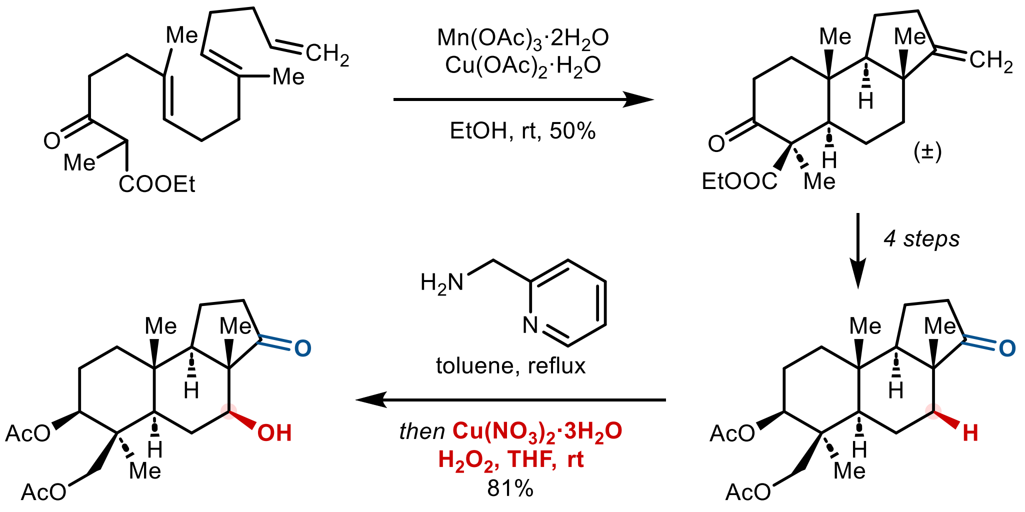
Outline

- Introduction: Cu in biology
- Copper-dependent monooxygenases: case studies on two enzymes
- Small molecule emulation
- Application

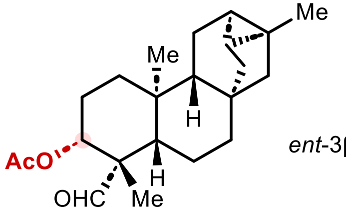
Selected Applications in TotSyn

- (+) phainoid A (*Dong, 2023*)

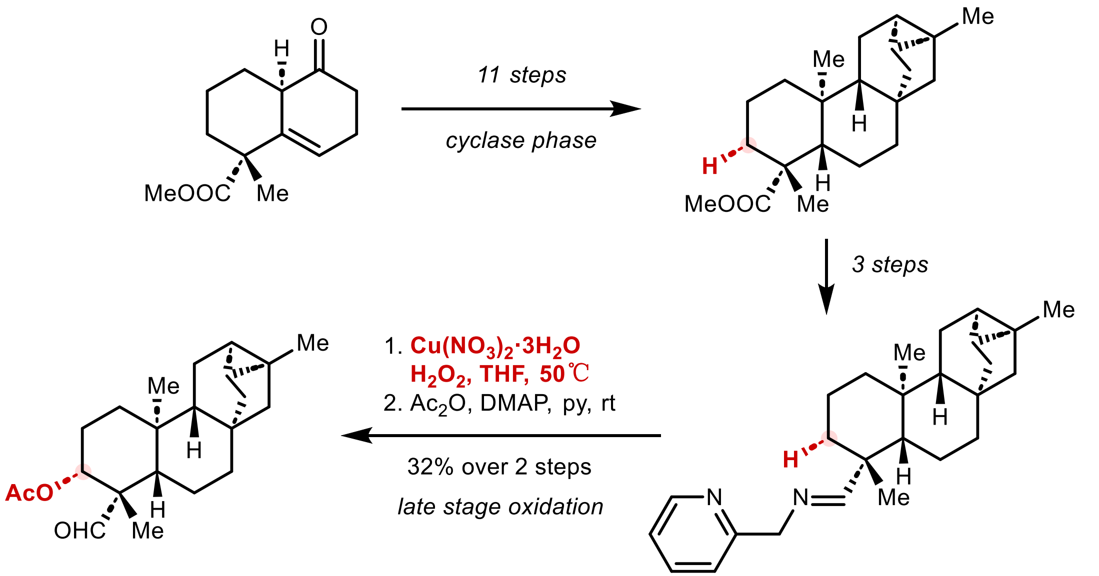




- *ent*-trachylobane diterpenoids (*Magauer, 2022*)



ent-3β-acetoxy-trachyloban-19-al



Dong, G. *et al. J. Am. Chem. Soc.* **2023**, *145* (8), 4828–4852.
Magauer, T. *et al. Angew. Chem. Int. Ed.* **2022**, *61* (3), e202113829.

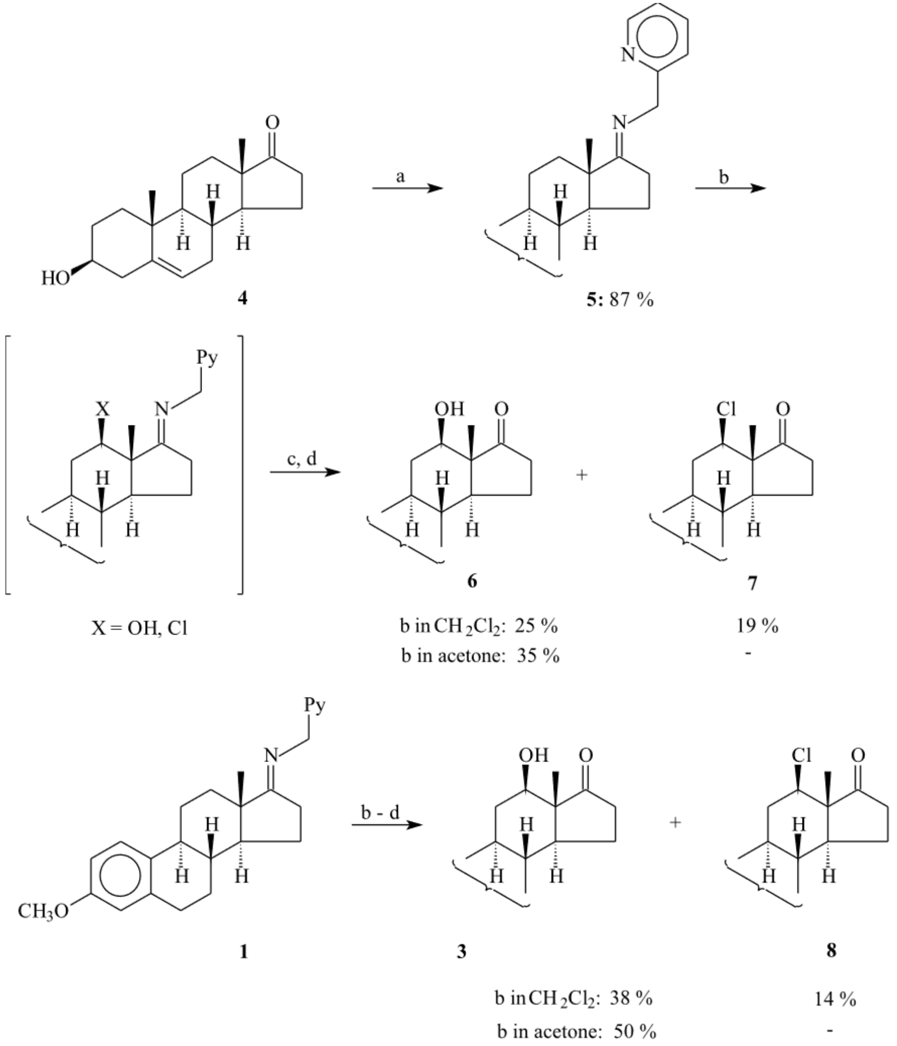
Thank you for your attention!

Questions are welcome

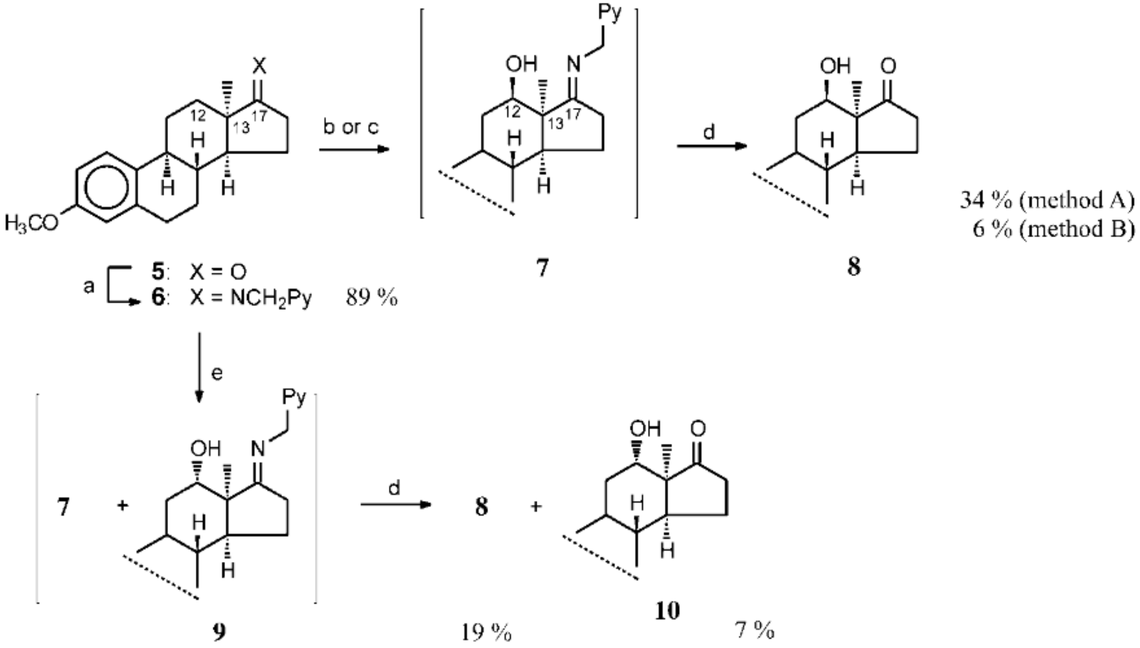
Backup Slides

Discovery

- ***SP***: chlorination;
- require Cl^- (from basic DCM or added chloride)



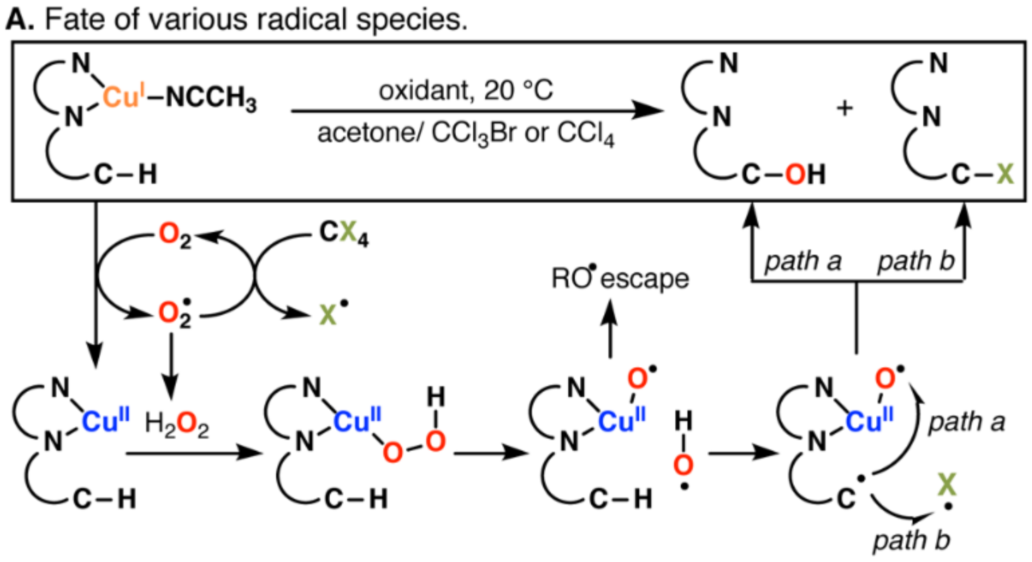
- ***Additional Stereochem***
- e: using Cu(OTf)(toluene) instead of $Cu(MeCN)_4PF_6$

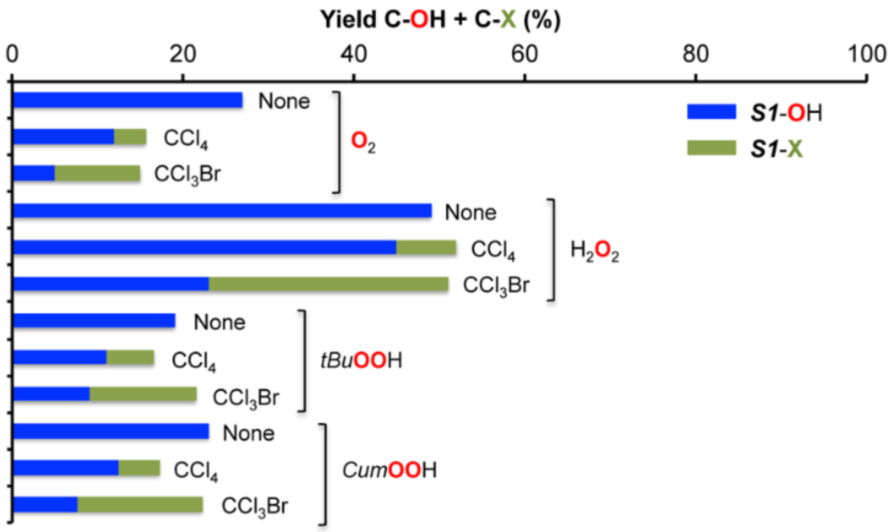


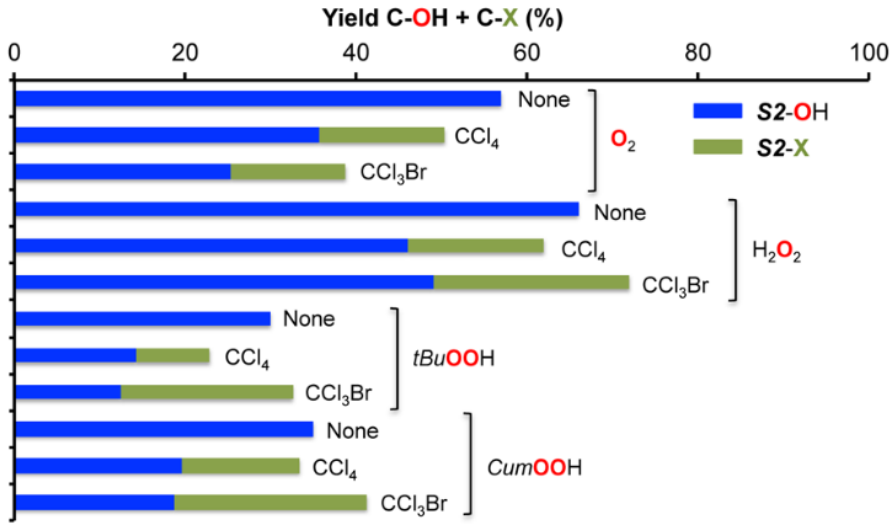
Schönecker, B *et al*. *Angew. Chem. Int. Ed.* **2003**, *42* (28), 3240–3244; *Tetrahedron* **2005**, *61* (1), 103–114; *Chem. Eur. J.* **2004**, *10*, 6029 – 6042

Experimental & spectral validation

Question: prove a radical mechanism



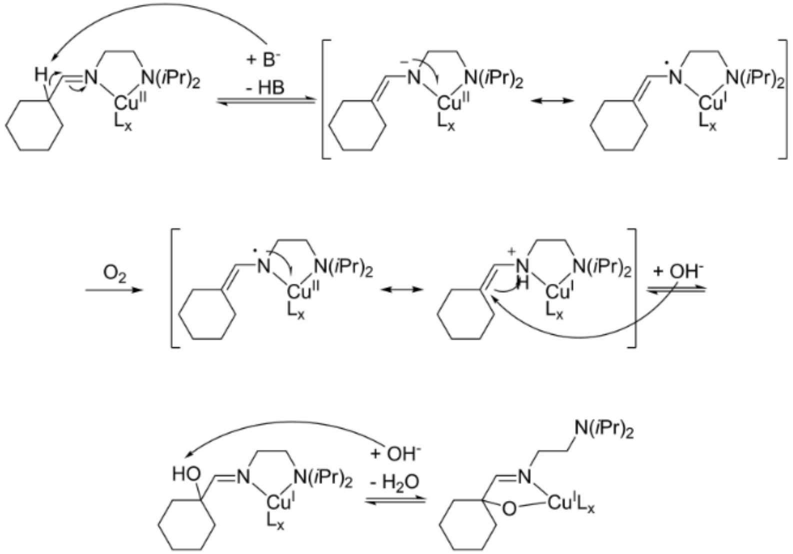




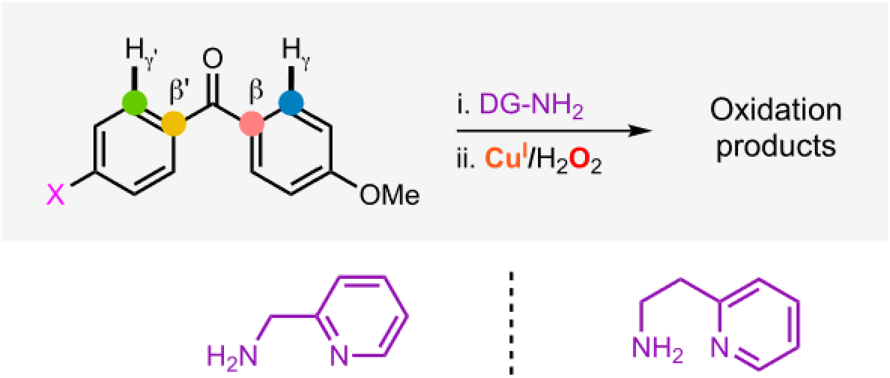
Claim: Extra halogenation w/S1 than S2 due to more peroxide undergoing cage escape and reacting with solvent

Garcia-Bosch, I. *et al. J. Org. Chem.* **2017**, *82* (15), 7887–7904.

Other reactivities



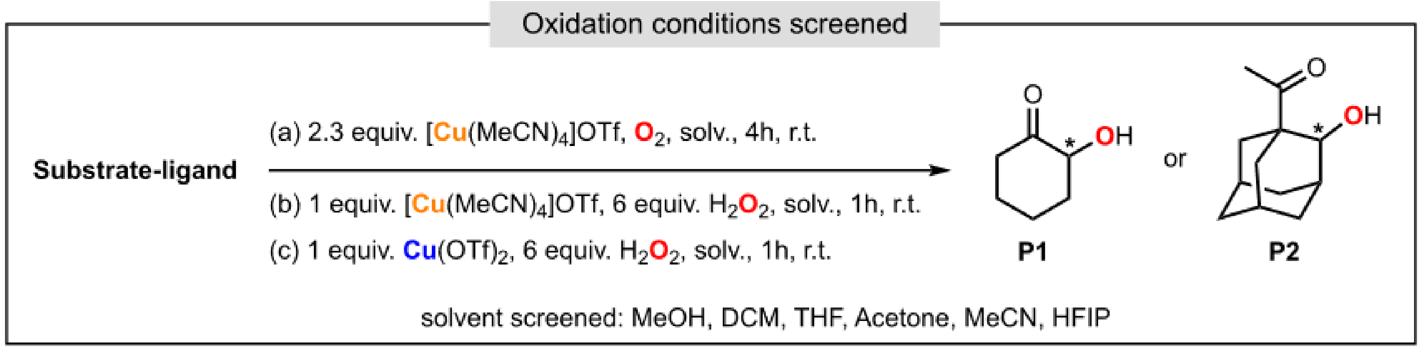
Scheme 5. Proposed mechanism for *β*-hydroxylation of **9** with copper(II).

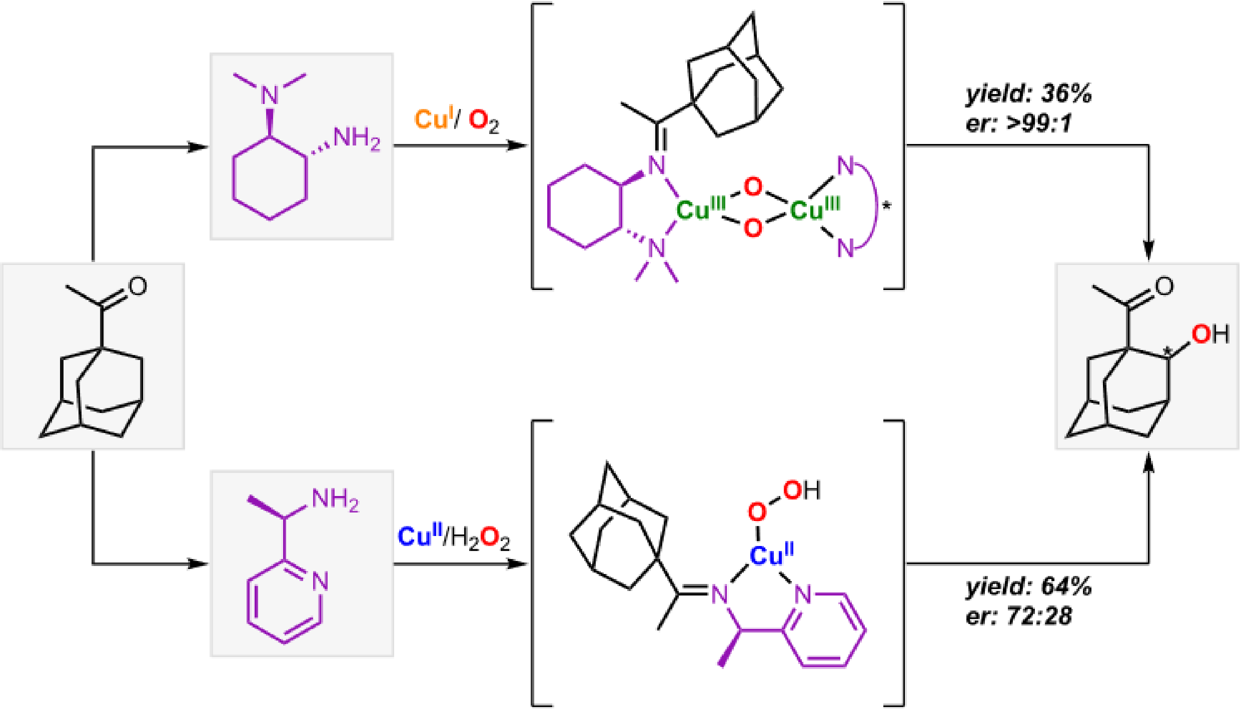


	2-picolylamine β	γ	β'	γ'	2-(2-aminoethyl)pyridine β	γ	β'	γ'
X= Me	0	53	0	47	72	9	0	19
X= F	0	76	0	24	81	7	0	12
X= CF_3	0	86	0	14	80	9	0	11

Figure 9. Comparison of the regioselectivity observed in the Cu-directed hydroxylation of unsymmetrical benzophenones using 2-picolylamine or 2-(2-aminoethyl)pyridine as directing groups.

Chirality





amine-imine: good er, inherently limited yield

pyridine-imine: poor er, potentially higher yield