Cu-Catalyzed Desaturation of Carbonyl Compounds

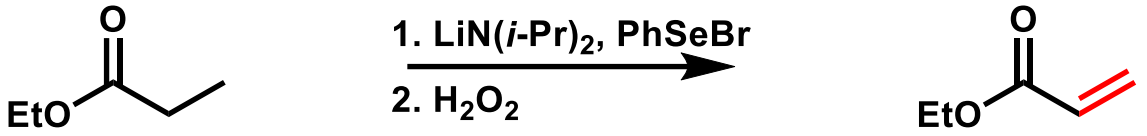
2020.8.29.

Shu Nakamura

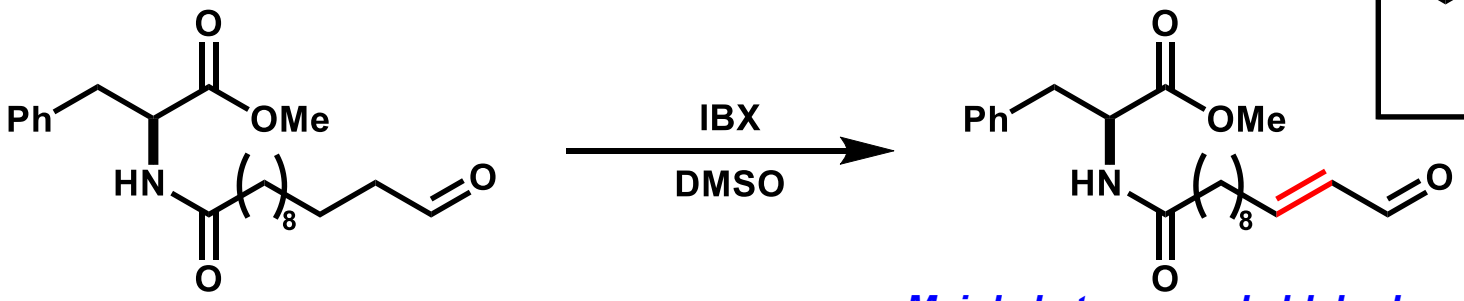
Contents

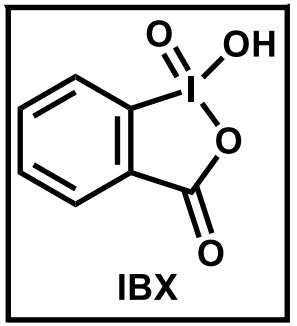
α,β-Unsaturated Carbonyl Compounds

a) Multistep method



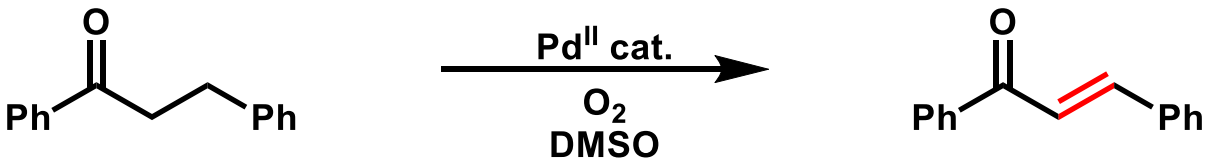
b) Direct dehydrogenation (IBX, DDQ)





Mainly ketones and aldehydes

c) Catalyzed by transition metals (Pd, Ir, …)



1) Turlik, A.; Chen, Y.; Newhouse, T. R. *Synlett* **2016**, *27*, 331.
2) Diao, T.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887.

Prof. Su and Dong

Prof. Weiping Su

1987 B.S. @ Anhui Institute of Education
1999 Ph.D @ Fujian Institute of Research on the Structure of Matter
2000 Postdoctral fellow @ Harvard University
2001 Postdoctral fellow @ Rutgers University (Prof. Jing Li)
2002 Postdoctral fellow @ Iowa State Uniersity (Prof. John G. Verkade)
2006-Professor @ Fujian Institute of Research on the Structure of Matter

Research topic: Selective activation and transformation of inert bonds
Design, synthesis and application of catalysts and ligands

Prof. Guangbin Dong

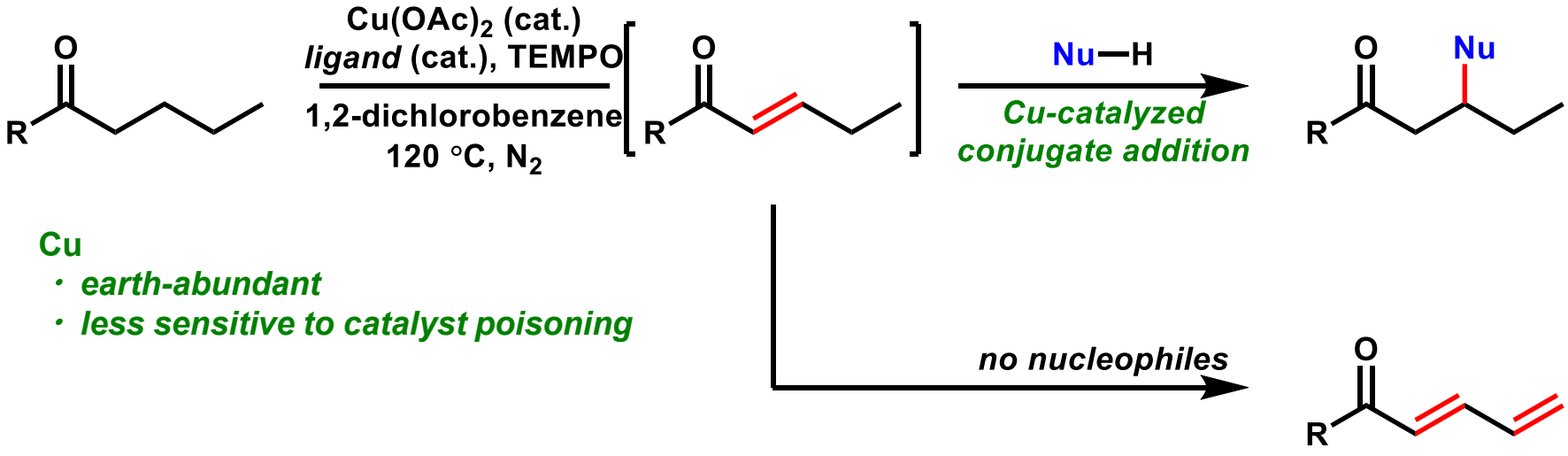
2003 B.S. @ Peking University
2009 Ph.D @ Stanford University (Prof. Barry M. Trost)
2009 Postdoctral fellow @ California Institute of Technology
(Prof. Robert H. Grubbs)
2011 Assistant Professor @ The University of Texas at Austin
2016-Professor @ The University of Chicago

Research topic: C-H, C-C activation
Total synthesis, Polymer chemistry

1) http://english.fjirsm.cas.cn/pe/ge/201303/t20130314_99678
2) http://english.fjirsm.cas.cn/pe/fas/RP/202003/t20200305_230666.html
3) https://chemistry.uchicago.edu/faculty/guangbin-dong

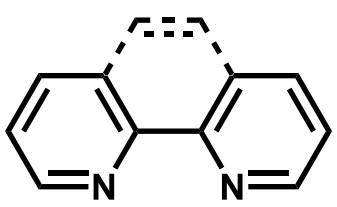
Contents

Desaturation of Ketones by Su's Group

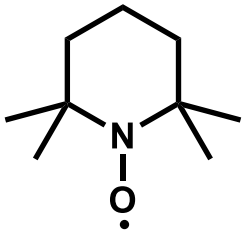


Cu

- *earth-abundant*
- *less sensitive to catalyst poisoning*



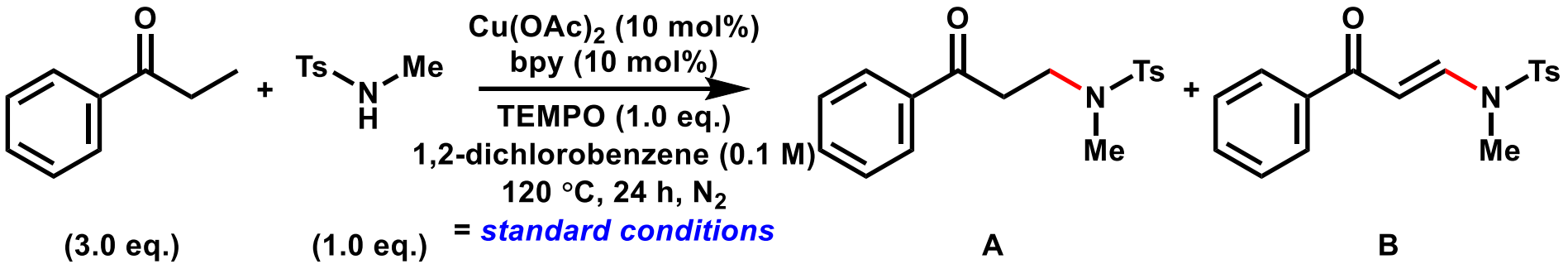
ligand



TEMPO

1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.
2) Shang, Y.; Jie, X.; Jonnada, K.; Zafar, S. N.; Su, W. *Nat. Commun.* **2017**, *8*, 2273.

Sequential Desaturation-Conjugate Addition

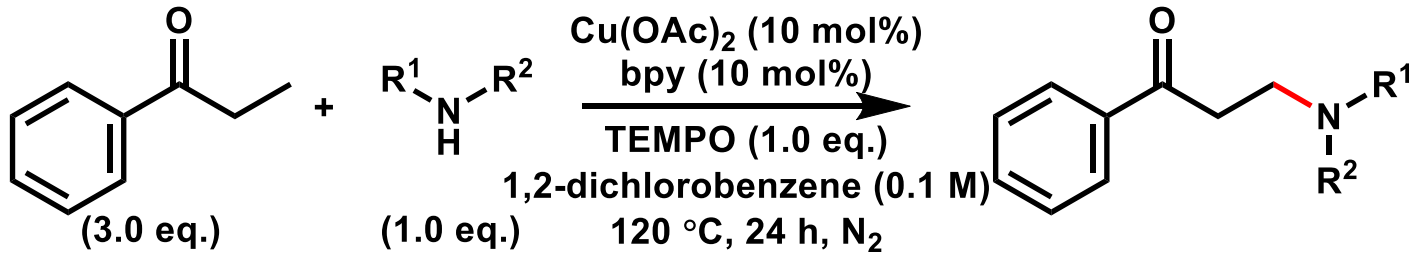


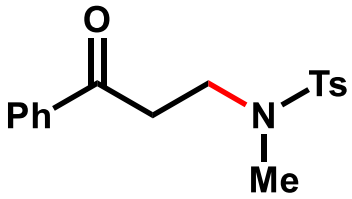
(3.0 eq.) (1.0 eq.) A B

entry	*conditions*	A	B
1	standard conditions	95%	<5%
2	ketone: 1.5 eq.	72%	<5%
3	without $Cu(OAc)_2$	0%	0%
4	without TEMPO	0%	0%
5	without bpy	62%	<5%
6	TEMPO (20 mol%), O_2 (1 atm)	0%	0%
7	(*t*-BuO)$_2$ (2.0 eq.) instead of TEMPO	0%	0%
8	$CuSO_4$ instead of $Cu(OAc)_2$	0%	0%
9	1,10-phenanthroline instead of bpy	94%	<5%
10	1,4-dioxane as solvent	49%	0%

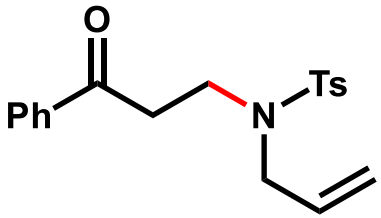
1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.

Substrate Scope (1)

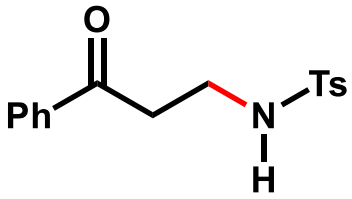




95%



83%



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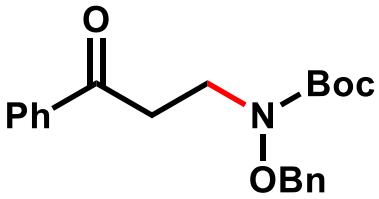

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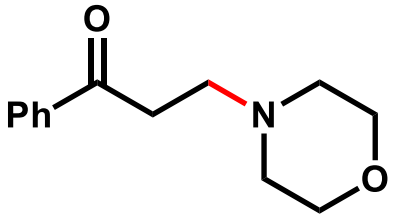
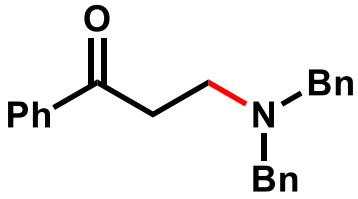


73%



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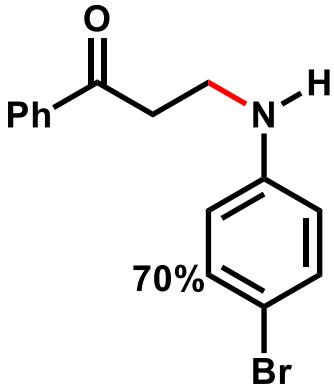

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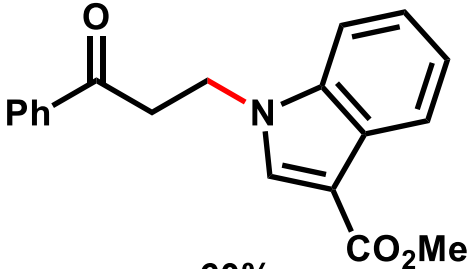
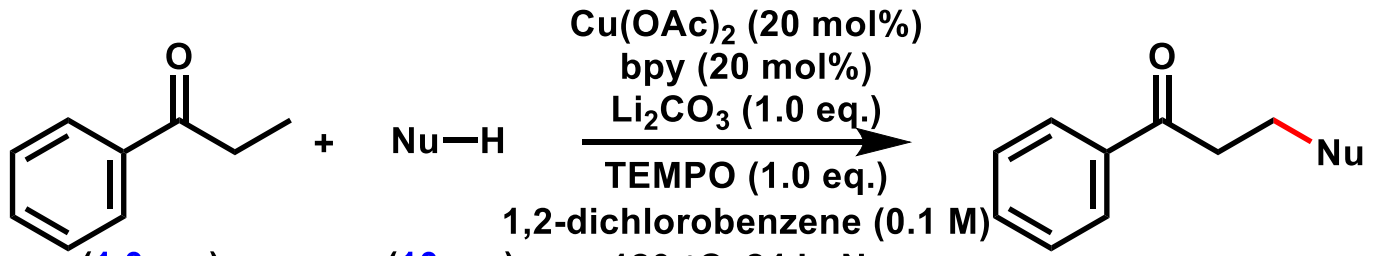
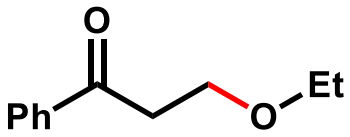


60%

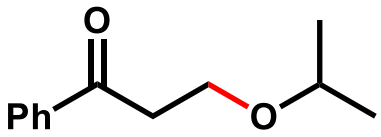
1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.

Substrate Scope (2)

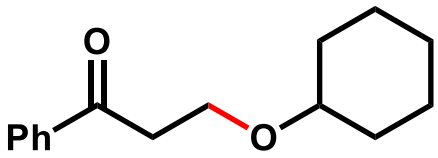




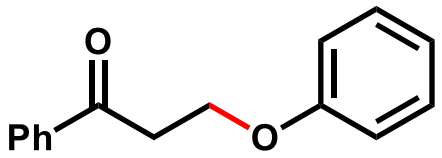
37%



36%

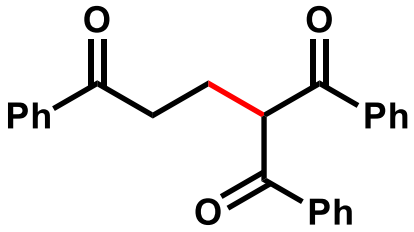


32%

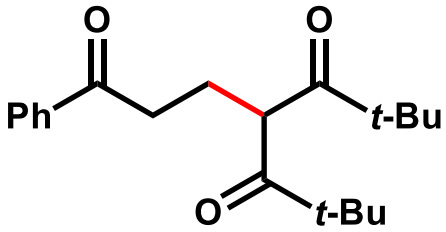


44%*

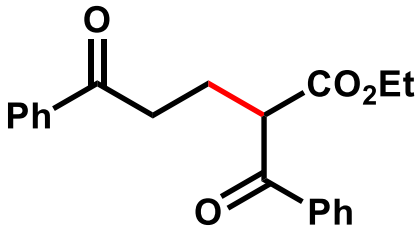
* PhOH: 5.0 eq., $Cu(OAc)_2$: 10 mol%, bpy: 10 mol%, Li_2CO_3: 0 eq., TEMPO: 1.0 eq.



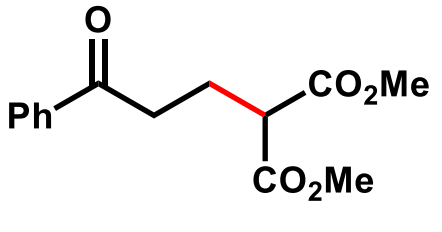
91%[a)]



96%[a)]



70%[a)]

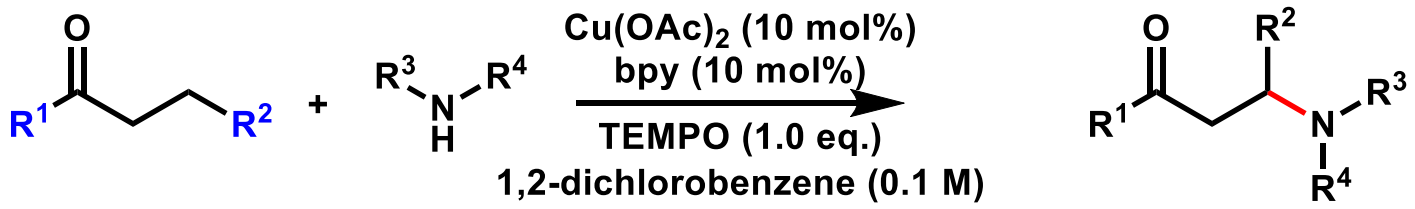


51%[a)]

a) without Li_2CO_3

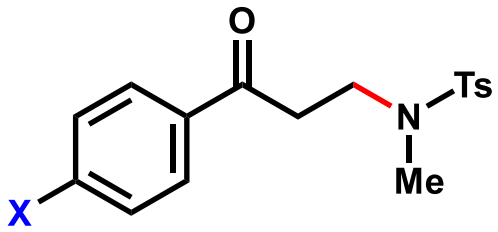
1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.

Substrate Scope (3)

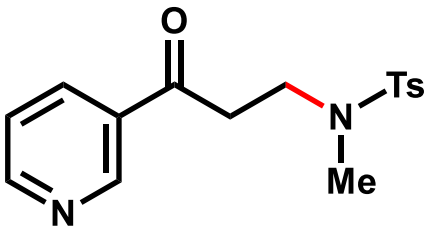


(3.0 eq.) (1.0 eq.)

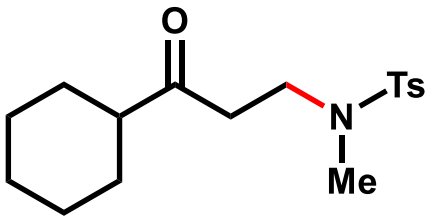
for a) (1.0 eq.) (3.0 eq.)



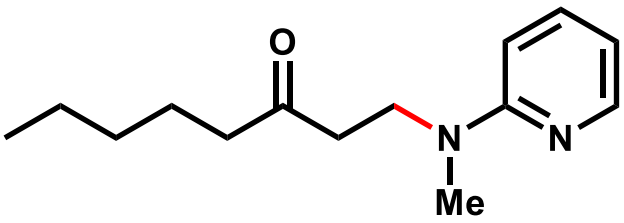
X = Me: 89%
OMe: 90%
F: 94%
Cl: 93%
Br: 94%
CF_3: 79%*
OH: 85%



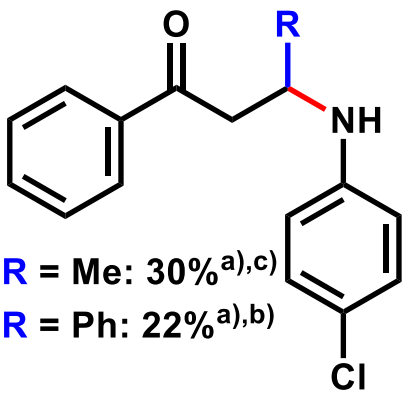
81% (without bpy)



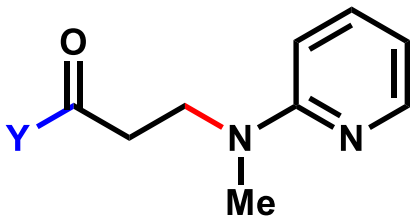
57%[b)]



60%[b)]



R = Me: 30%[a),c)]
R = Ph: 22%[a),b)]

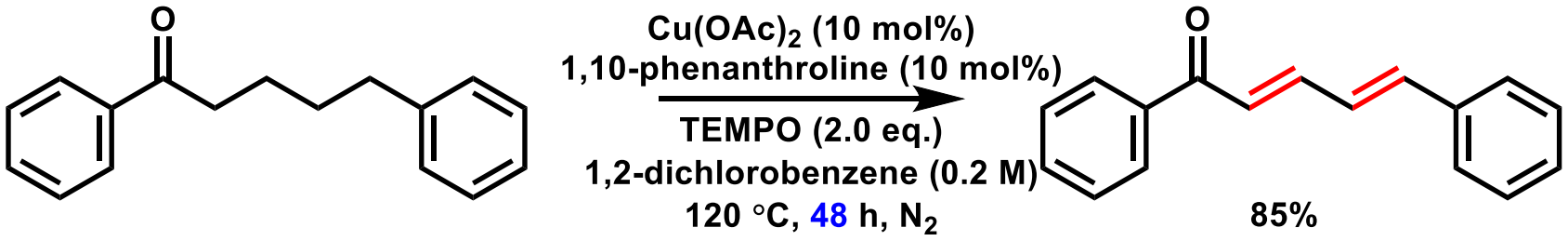


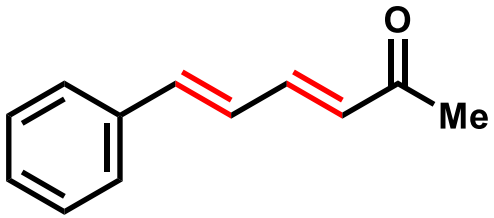
Y = OEt: 0%
Y = NMe_2: 0%

* conducted at 100 °C
b) $Cu(OAc)_2$ (30 mol%), bpy (30 mol%)
c) bpy (20 mol%), Na_2CO_3 (0.5 eq.)

1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.

Desaturation-Relay





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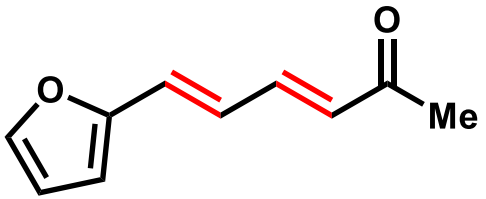
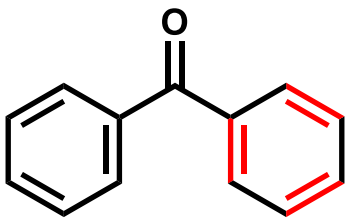
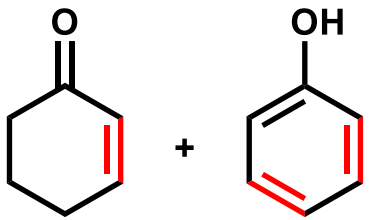


62%



81%[a)]

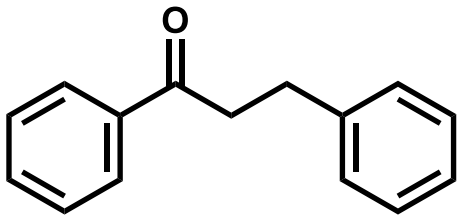


68%[b)] + 16%[b)]

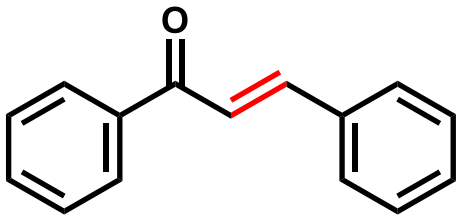
a) $Cu(OAc)_2$ (20 mol%), 1,10-phenanthroline (20 mol%), TEMPO (3.0 eq.), 130 °C
b) TsOH (10 mol%), solvent = *tert*-amyl alcohol (0.4 M)

1) Shang, Y.; Jie, X.; Jonnada, K.; Zafar, S. N.; Su, W. *Nat. Commun.* **2017**, *8*, 2273.

Mechanistic Study (1) – Kinetics

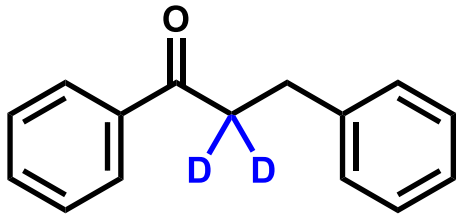


standard conditions

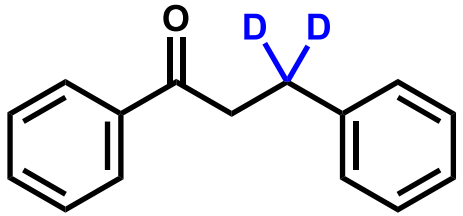


90%

SM	1st order
$Cu(OAc)_2$/bpy	1st order
TEMPO	0th order



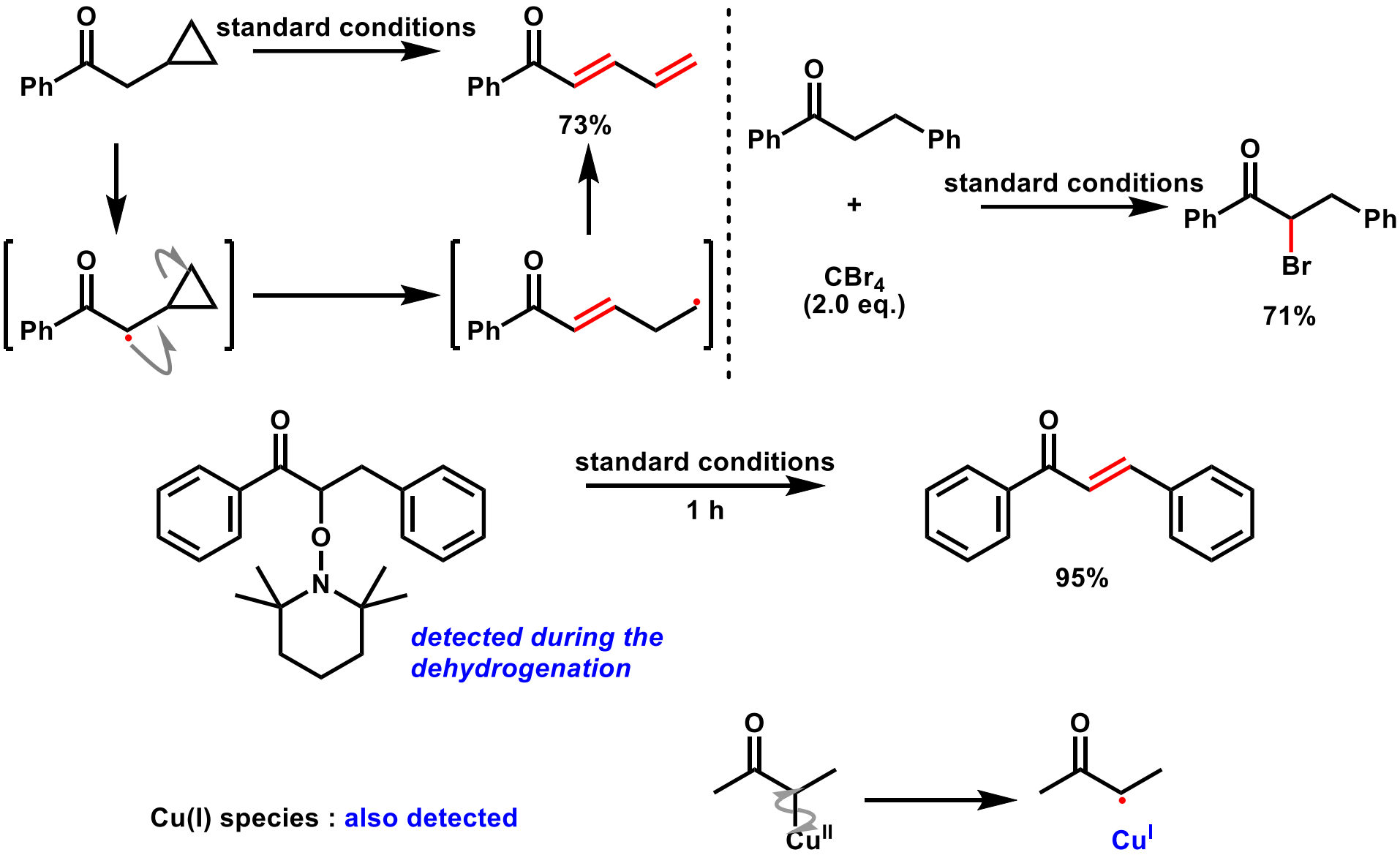
k_H/k_D = 5.32



k_H/k_D = 1.02

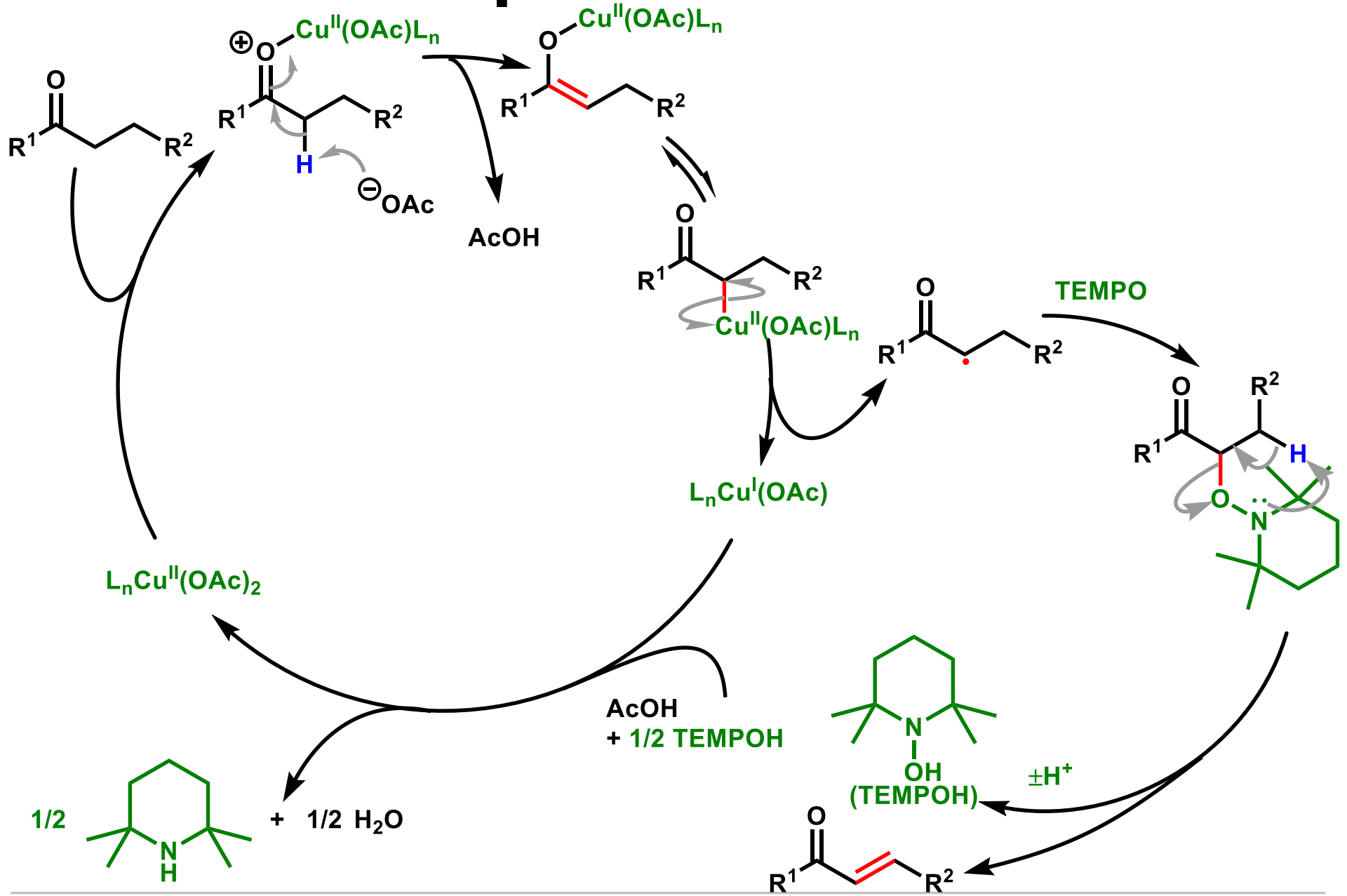
1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.

Mechanistic Study (2) - Intermediate



1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.

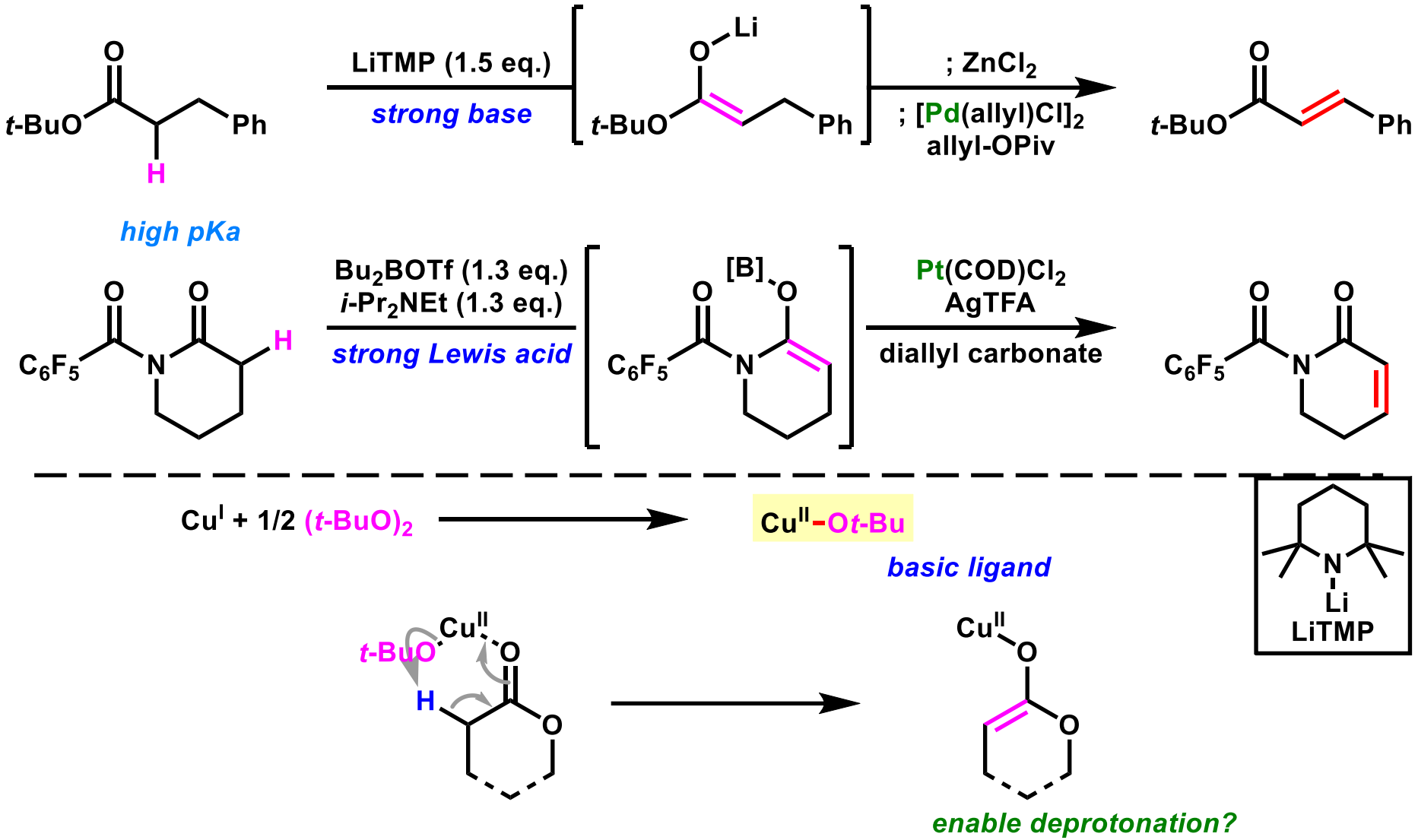
Proposed Mechanism



1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.
2) Qian, P.; Deng, Y.; Mei, H.; Han, J.; Pan, Y. *Chem. Commun.* **2017**, *53*, 2958.

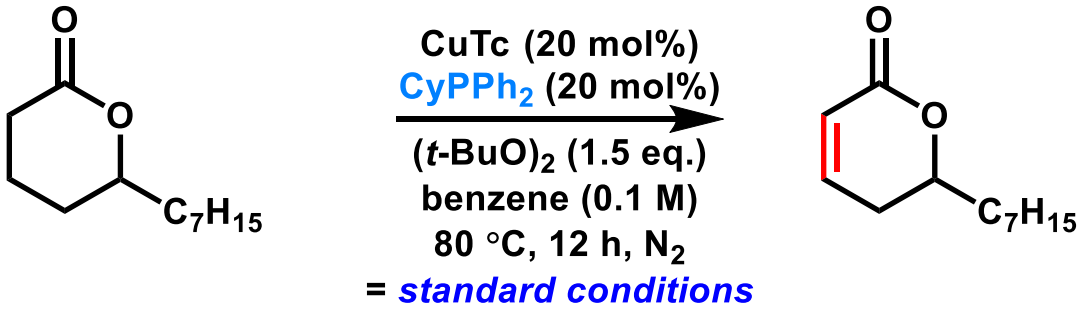
Contents

Concept



1) Turlik, A.; Chen, Y.; Newhouse, T. R. *Synlett* **2016**, *27*, 331.
2) Chen, M.; Rago, A. J.; Dong, G. *Angew. Chem. Int. Ed.* **2018**, *57*, 16205.
3) Gephart, R. T., III; McMullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 1735.
4) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Desaturation of Lactones, Lactams, Ketones

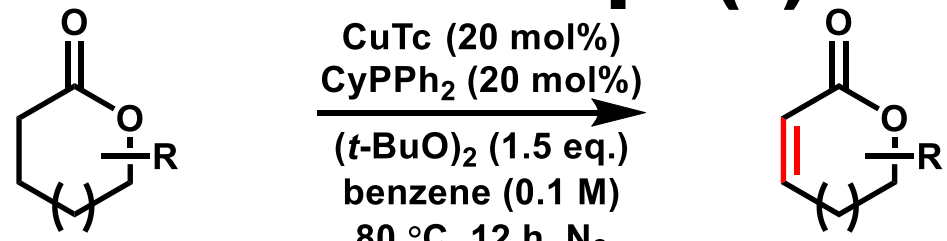


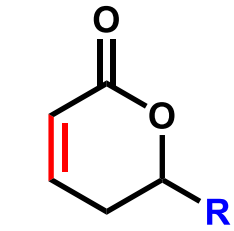
entry	*conditions*	yield
1	standard conditions	82%
2	CuOAc instead of CuTc	78%
3	CuCl instead of CuTc	20%
4	$Cu(MeCN)_4PF_6$ instead of CuTc	0%
5	$Cu(OAc)_2$ instead of CuTc	trace
6	$(PhCMe_2O)_2$ instead of $(t\text{-BuO})_2$	58%
7	*t*-BuOOBz instead of $(t\text{-BuO})_2$	0%
8	1,2-dichloroethane as solvent	20%

entry	*ligand* (instead of $CyPPh_2$)	yield
1	none	trace
2	pyridine	10%
3	bpy	14%
4	PPh_3	64%
5	$P(p\text{-OMe-}C_6H_4)_3$	72%
6	$P(p\text{-}CF_3\text{-}C_6H_4)_3$	48%
7	*i*-$PrPPh_2$	82%
8	Cy_3P	56%

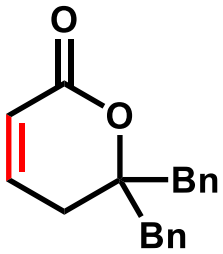
1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Substrate Scope (1)

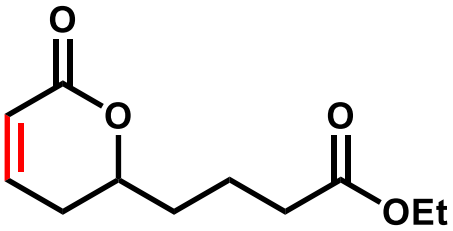




R = H: 73%
Me: 68%
Ph: 71%
t-Bu: 73%

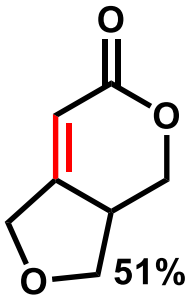


41%

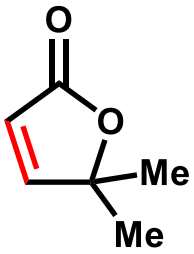


72%*

* *i*-PrPPh$_2$ was used.

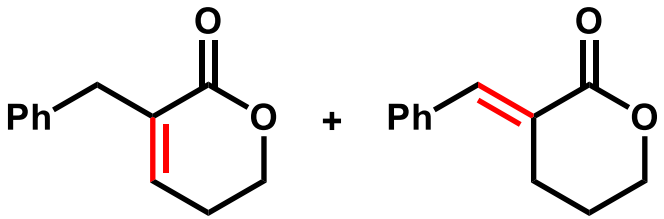


51%

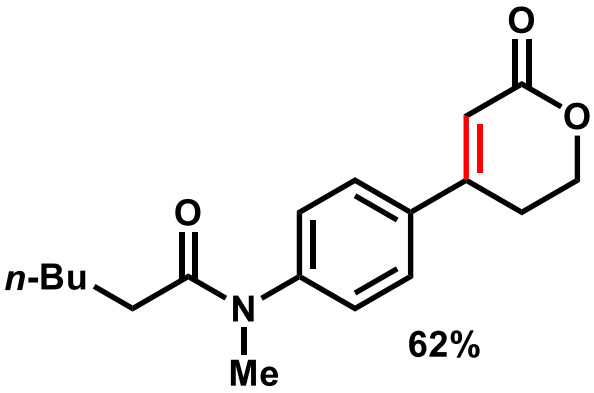


54%**

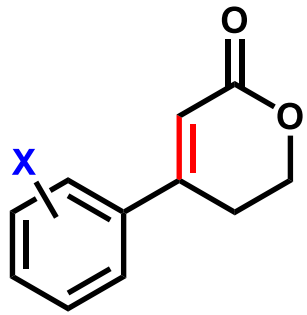
** at 100 °C



25%+9%



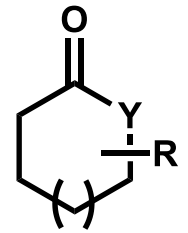
62%



X = H: 60% 2-OPh: 61%
4-Me: 57% 4-OMe: 52%
4-Br: 53% 4-OCF$_3$: 58%
4-I: 49%* 4-TMS: 62%

1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

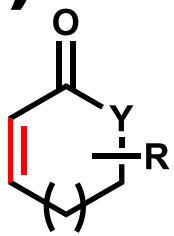
Substrate Scope (2)



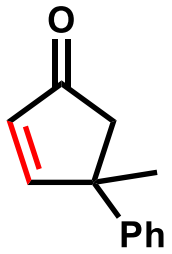
n = 0 or 1

CuTc (20 mol%)
$CyPPh_2$ (20 mol%)

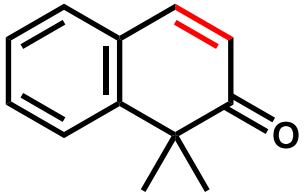
$(t\text{-}BuO)_2$ (1.5 eq.)
benzene (0.1 M)
80 °C, 12 h, N_2
= *standard conditions*



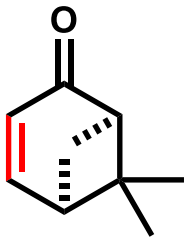
n = 0 or 1



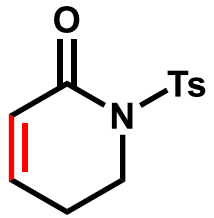
52%



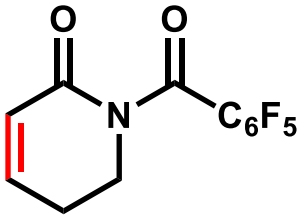
60%



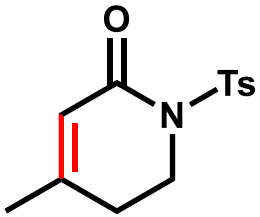
57%



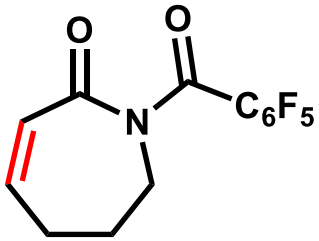
62%[a)]



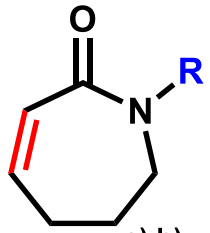
48%[a)]



59%[a)]



48%[a),b)]



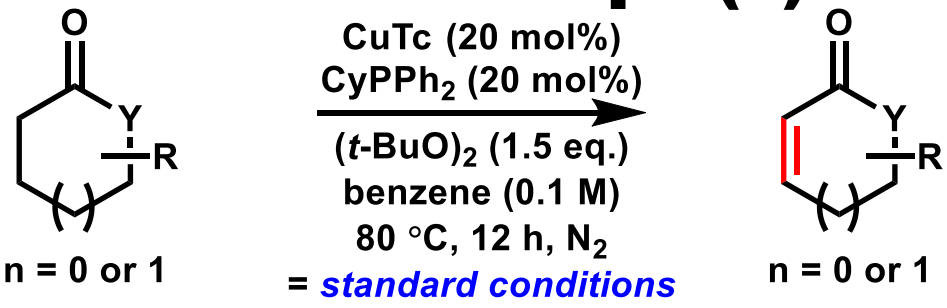
R = Ts: 42%[a),b)]

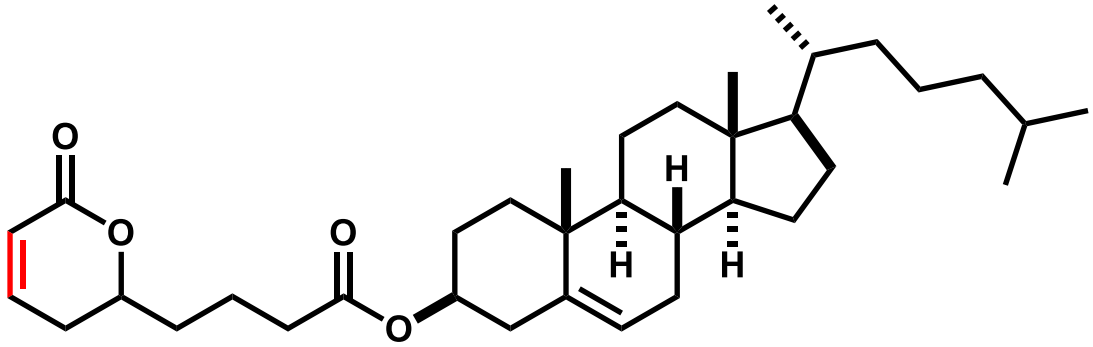
R = H: SM remained

a) *i*-$PrPPh_2$ was used. b) at 100 °C

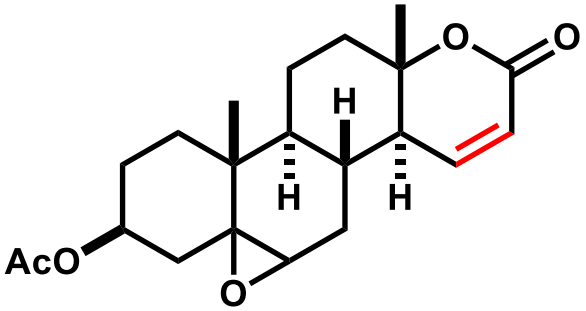
1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Substrate Scope (3)



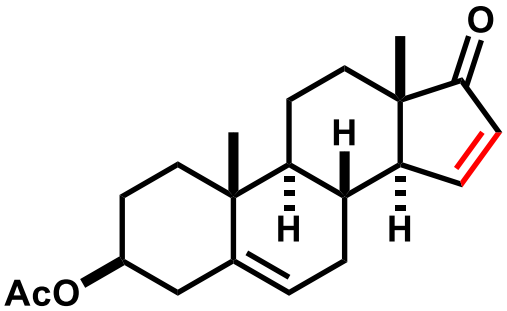


56%

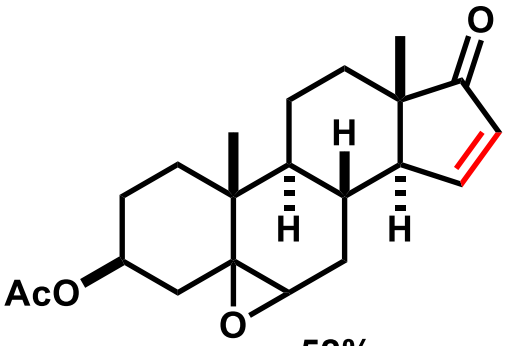


64%*

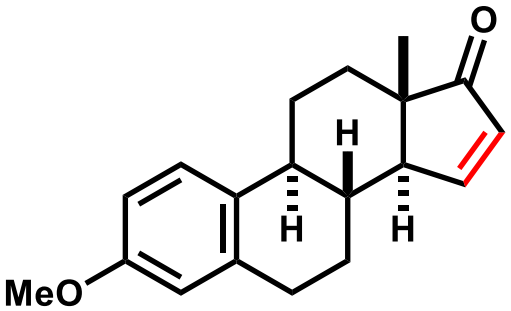
* *i*-PrPPh$_2$ was used.



55%



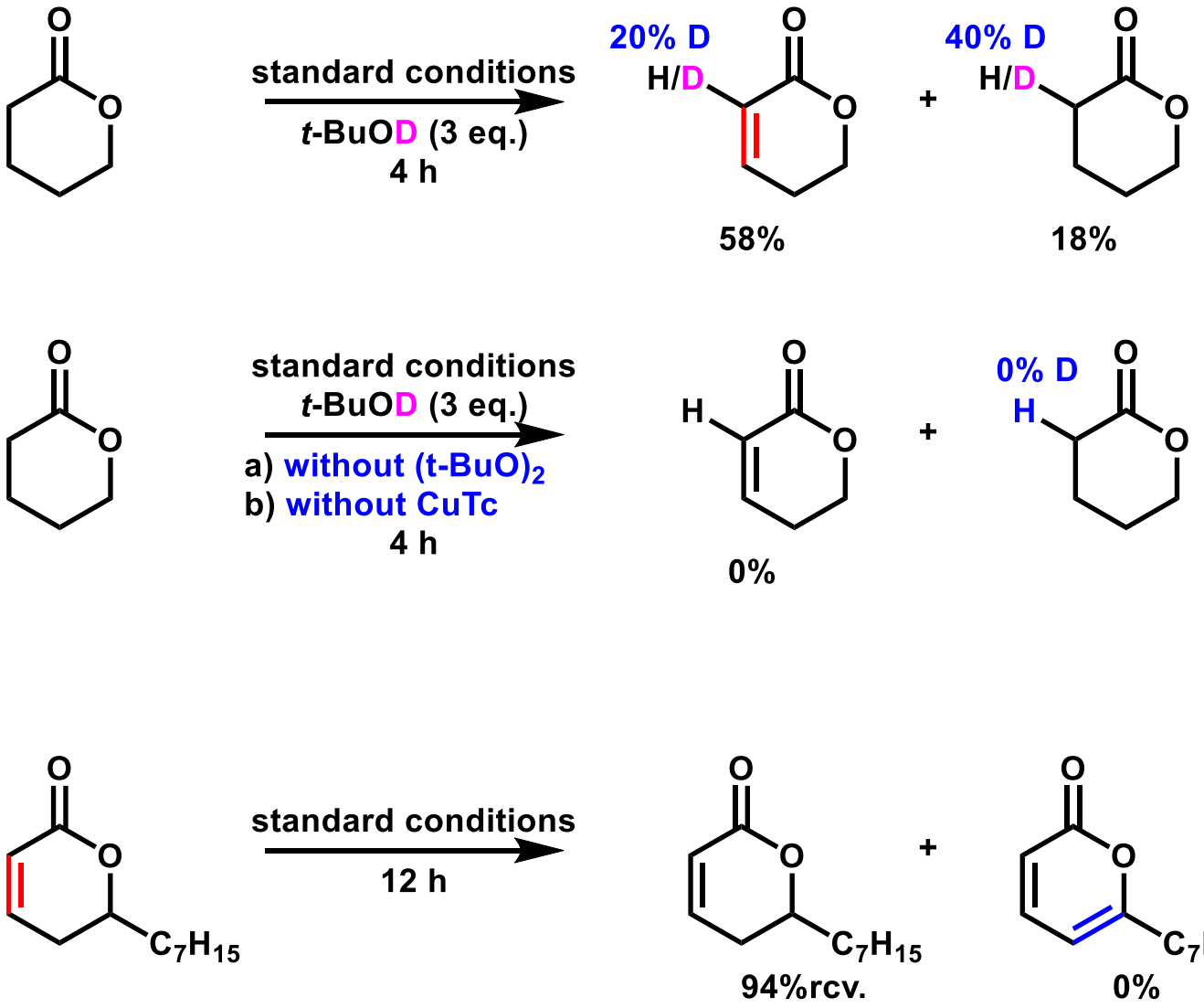
52%



41%

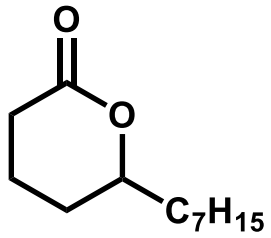
1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Mechanistic Study (1) – Deprotonation



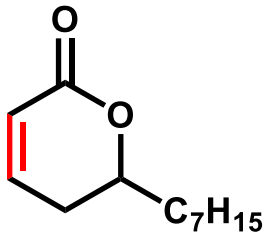
1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Mechanistic Study (2) – Kinetics

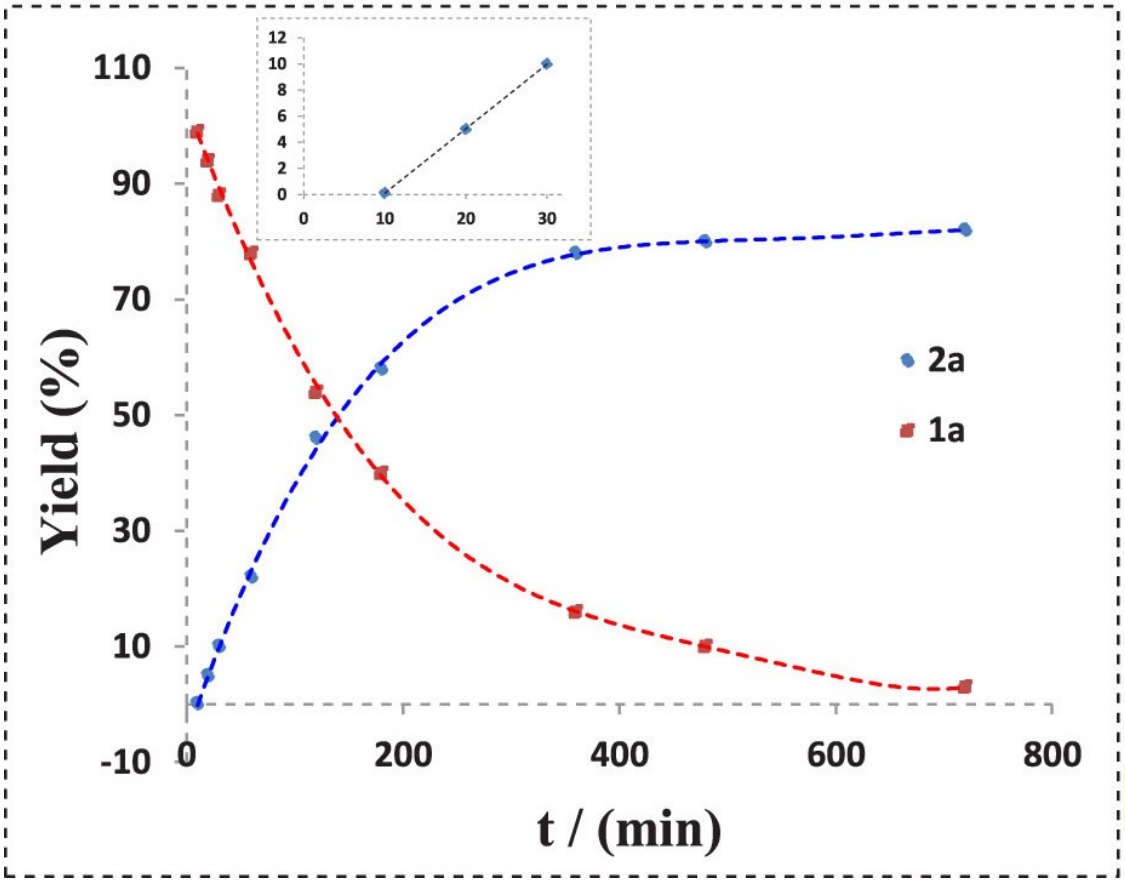


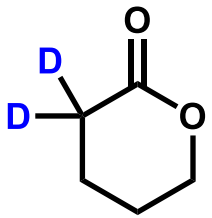
1a

standard conditions

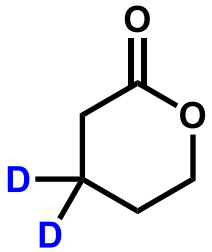


2a





k_H/k_D = 1.2±0.1



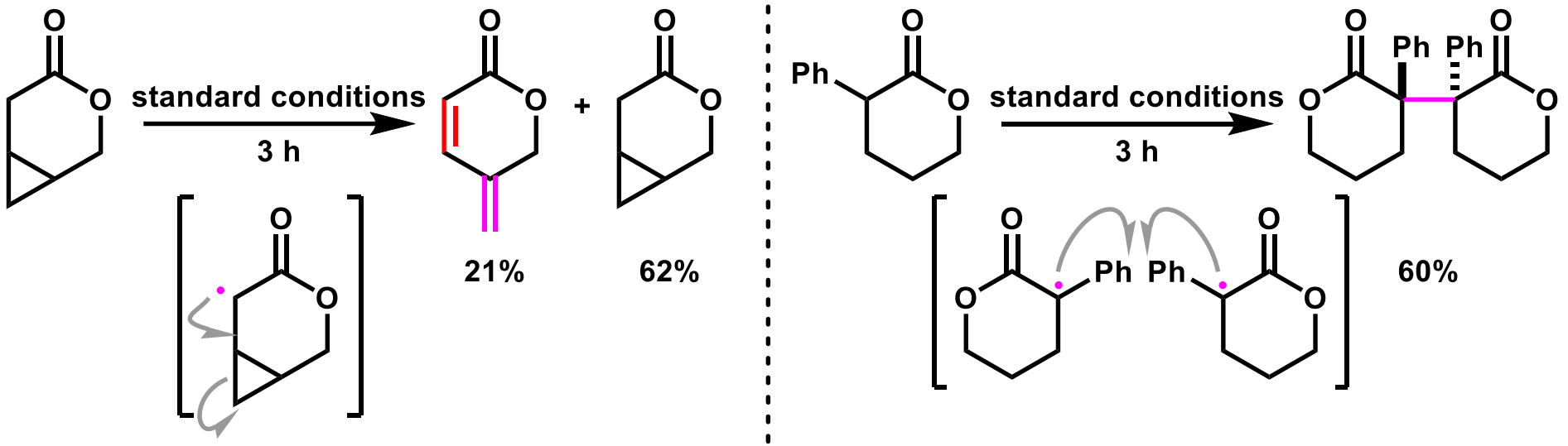
k_H/k_D = 1.0±0.1

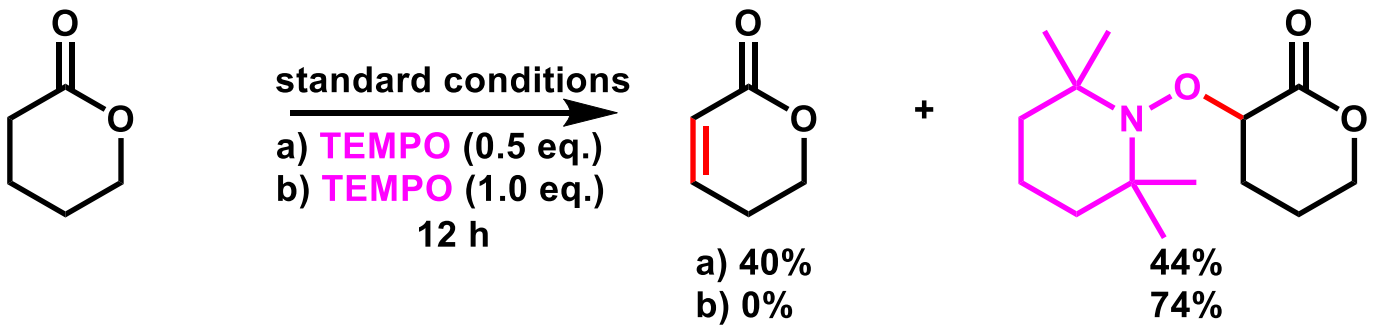
SM	0th order
$CuTc/CyPPh_2$	1st order
$(t\text{-}BuO)_2$	1st order

Cu(II) species : detected during the reaction

1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

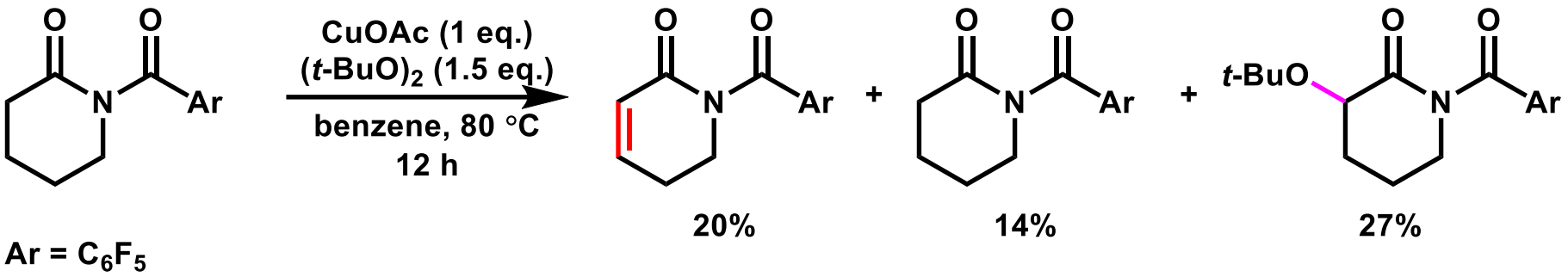
Mechanistic Study (3) – Radical Character

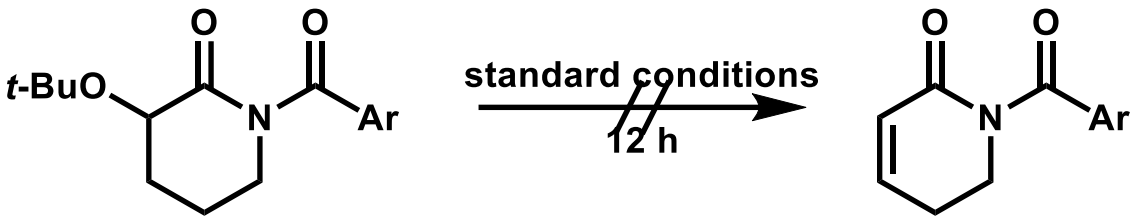




1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Mechanistic Study (4) – Intermediate

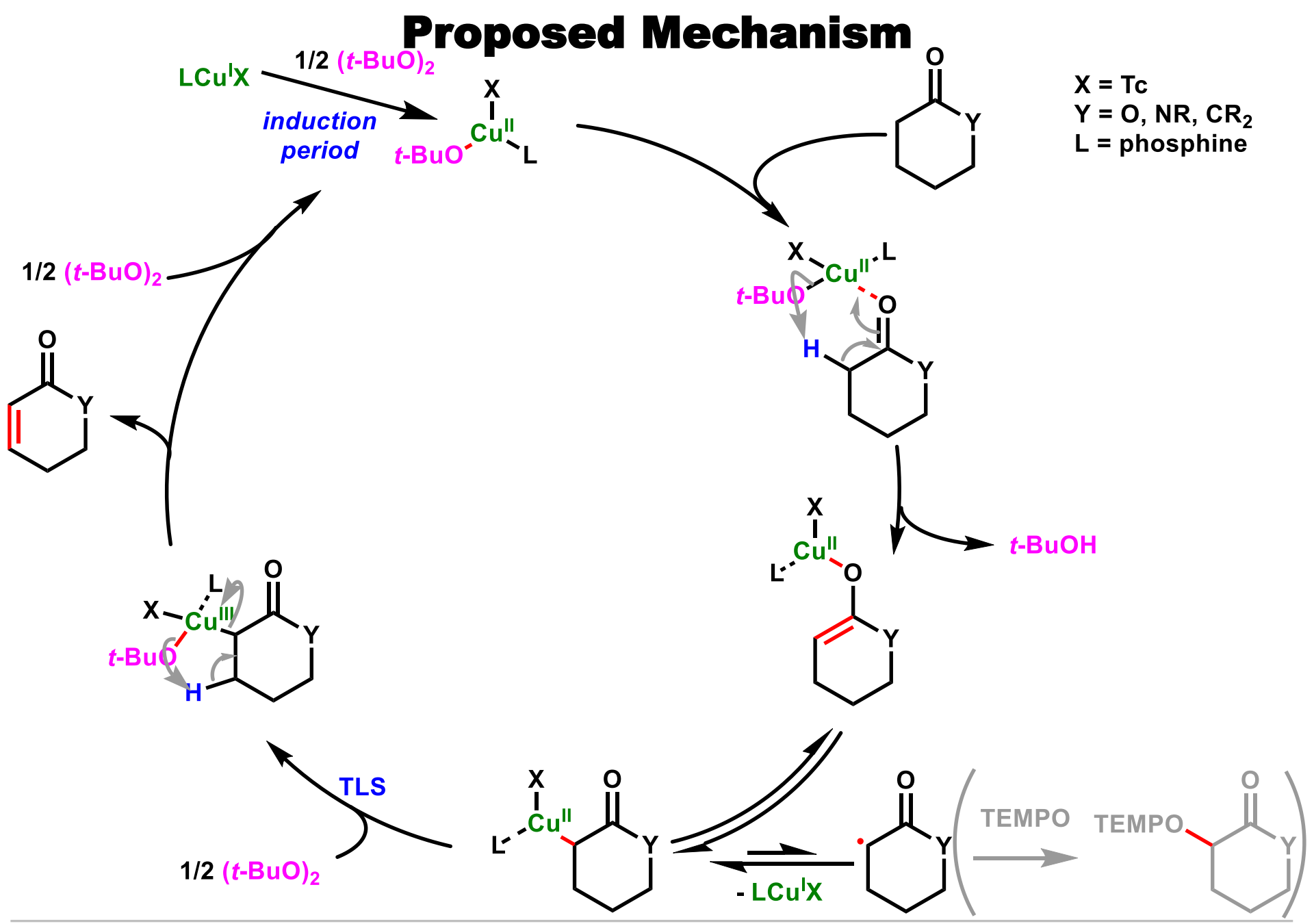




→ α-oxygenated species is not the intermediate of the dehydrogenation.

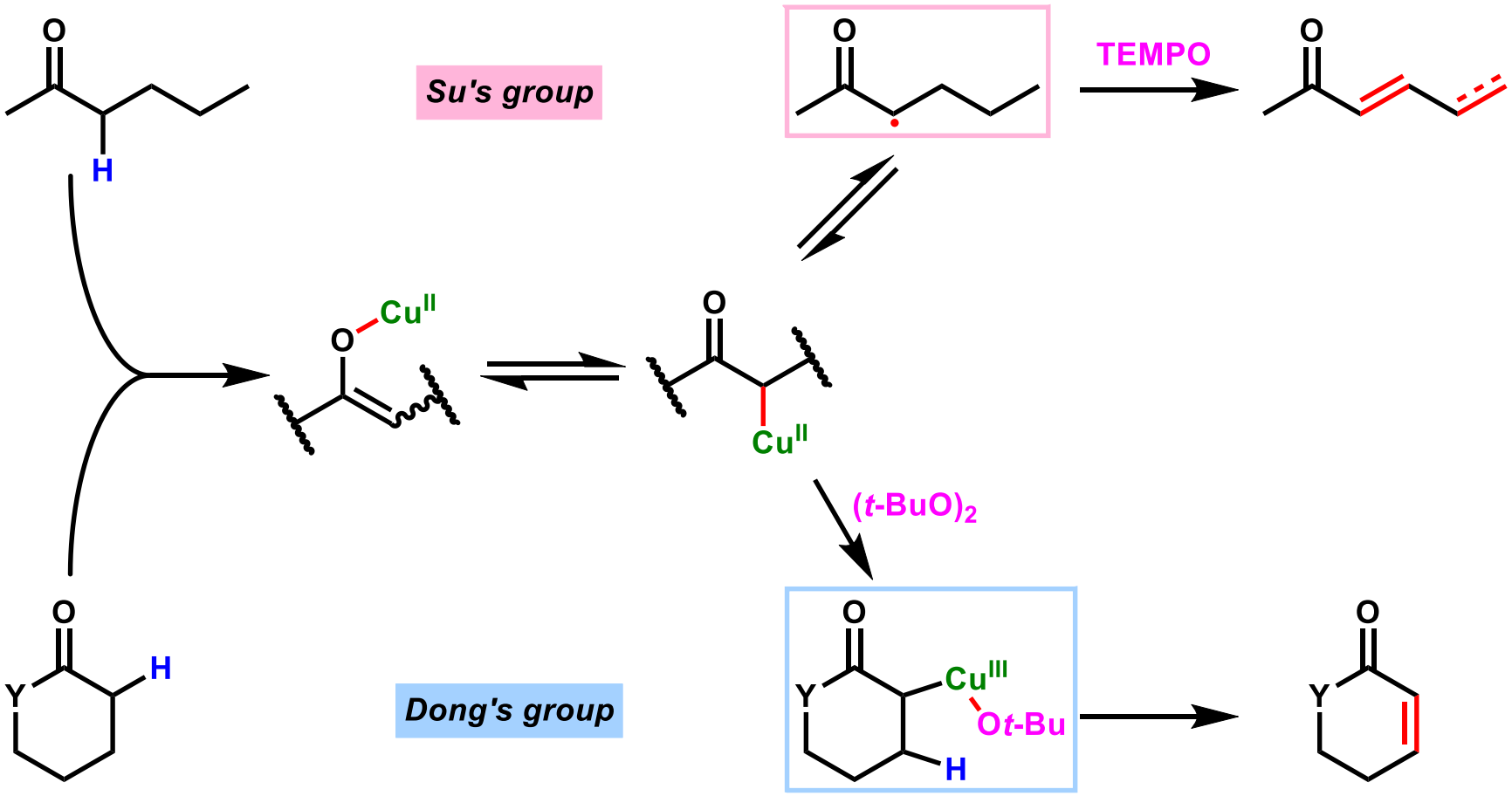
1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Proposed Mechanism



1) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

Summary



1) Jie, X.; Shang, Y.; Zhang, X.; Su, W. *J. Am. Chem. Soc.* **2016**, *138*, 5623.
2) Shang, Y.; Jie, X.; Jonnada, K.; Zafar, S. N.; Su, W. *Nat. Commun.* **2017**, *8*, 2273.
3) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.