Copper in Radical Chemistry

Part 1 : Benzylic Functionnalization

Valentin Soulard
Topic Review

08.06.2017

Presentation Layout

1 – Necessity of Copper

2 – Scope of the method

3 – Investigation on the mechanism

4 – Proposed mechanism

5 – Synthetic Application

Introduction

Copper
29
Cu
63,546

- Copper chemistry is diverse.

- Catalyzed reaction involving one or two electron, sometimes both.

- “Copper-catalyzed synthesis” indicated over 500 papers had been published in 2014

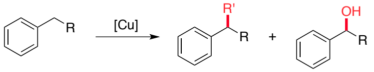
- Copper is an earth-abundant metal :

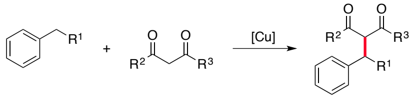
  - Costless and more sustainable compared to precious transition metal catalyst

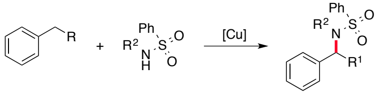
- Low toxicity for a transition metal

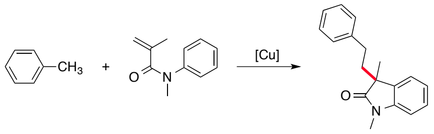
S. R. Chemler, *Beilstein J Org Chem* **2015**, *11*, 2252–2253.

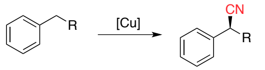
Contents

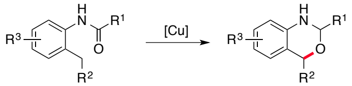

R
[Cu]
R'
R
+
OH
R

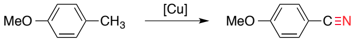

R¹
+
O O
R² R³
[Cu]
O O
R² R³
R¹

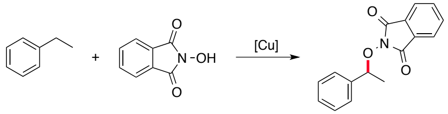

R
+
Ph
R² N S O
H O
[Cu]
Ph
R² N S O
O
R¹

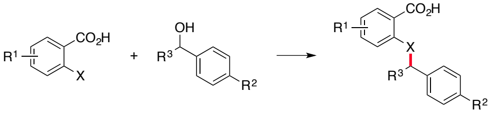

CH₃
+
O N
[Cu]
O
N

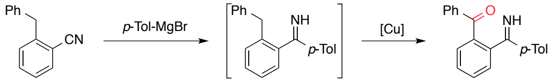

R
[Cu]
CN
R

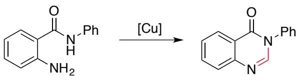

R³
H N R¹
O
R²
[Cu]
R³
H N R¹
O
R²


MeO
CH₃
[Cu]
MeO
C≡N


+
O
N-OH
O
[Cu]
O
O N
O

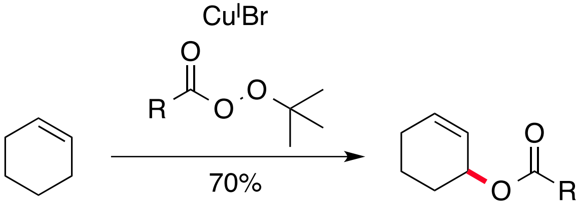

R¹
CO₂H
X
+
OH
R³
R²
R¹
CO₂H
X
R³
R²


Ph
CN
p-Tol-MgBr
Ph
NH
p-Tol
[Cu]
Ph
O
NH
p-Tol

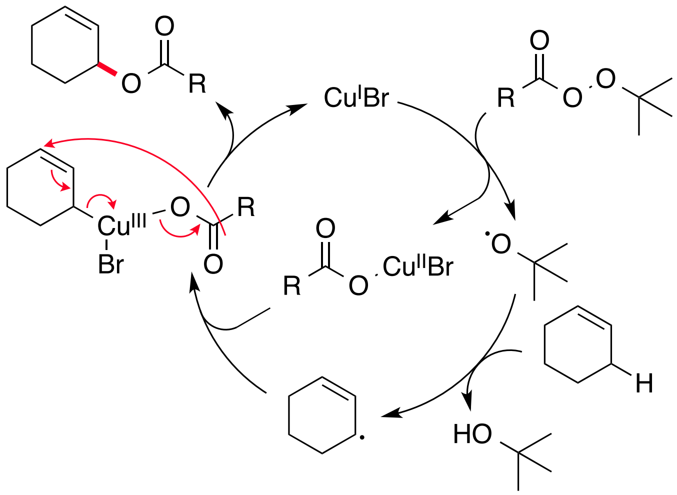

O
N Ph
H
NH₂
[Cu]
O
N Ph
N

1 - Karash-Sosnovsky Type Reaction

Karash-Sosnosky Reaction



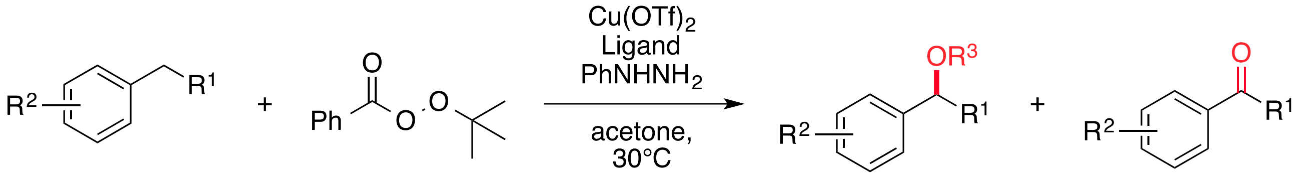
Proposed Mechanism



M. S. Kharasch, G. Sosnovsky, *J. Am. Chem. Soc.* **1958**, *80*, 756–756.
M. Kharasch, A. Fono, *J. Org. Chem.* **1958**, *23*, 324–325.

1 - Kharash-Sosnovsky type reaction

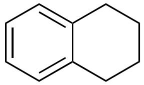
1.2 - Benzylic Oxidation



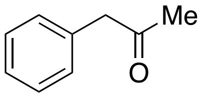
A - R^3 = H
B - R^3 = Bz

C

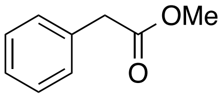
Substrates :



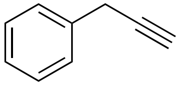
A+B 54% (0.88:1)
C 3.9%



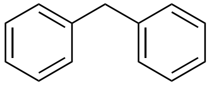
A+B 32% (0.85:1)
C 3.2%



A+B 37% (0.93:1)
C 3.8%



A 43%

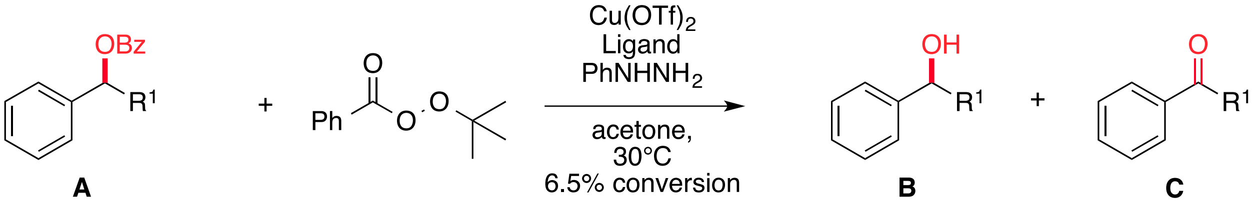


A+B 43% (1.15:1)
C 8.2%

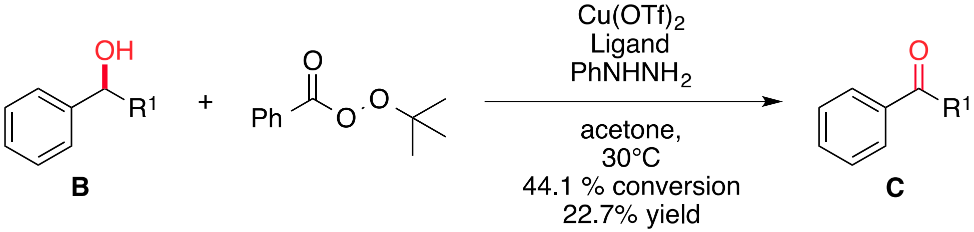
B. Zhang, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron* **2013**, *69*, 2033–2037.

1 - Kharash-Sosnovsky type reaction

1.2 - Benzylic Oxidation



Not observed

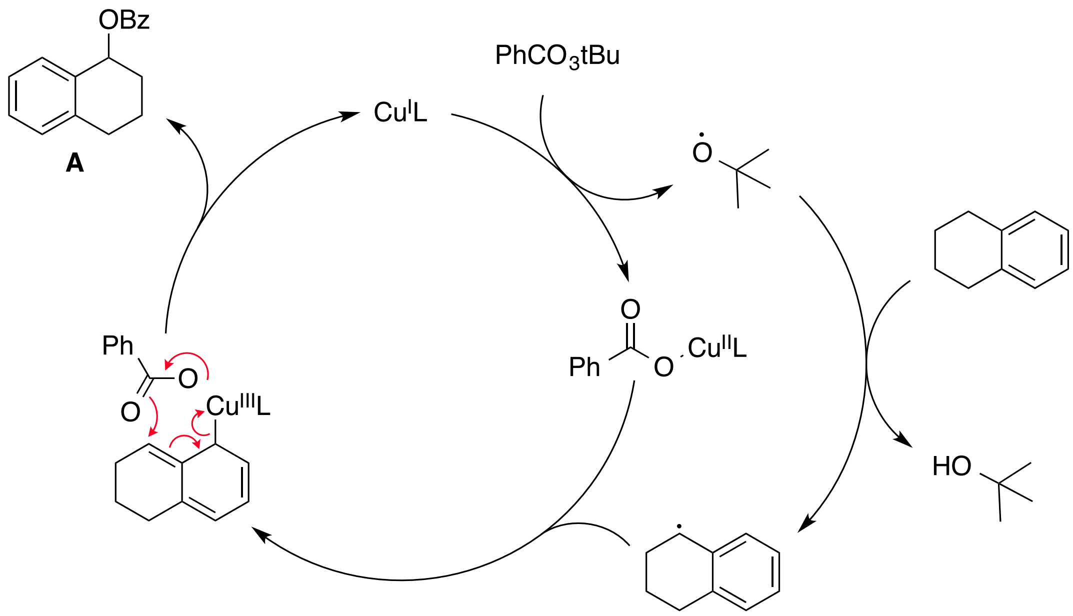


B. Zhang, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron* **2013**, *69*, 2033–2037.

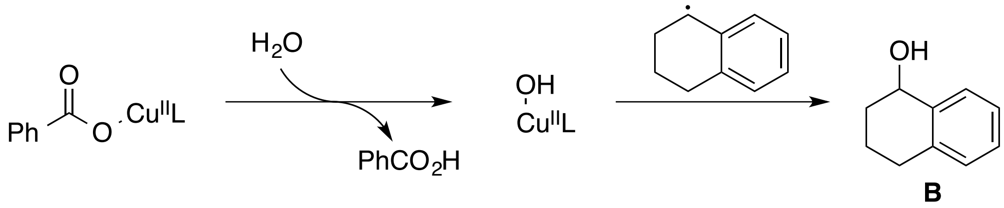
1 - Kharash-Sosnovsky type reaction

1.2 - Benzylic Oxidation

Process A



Process B

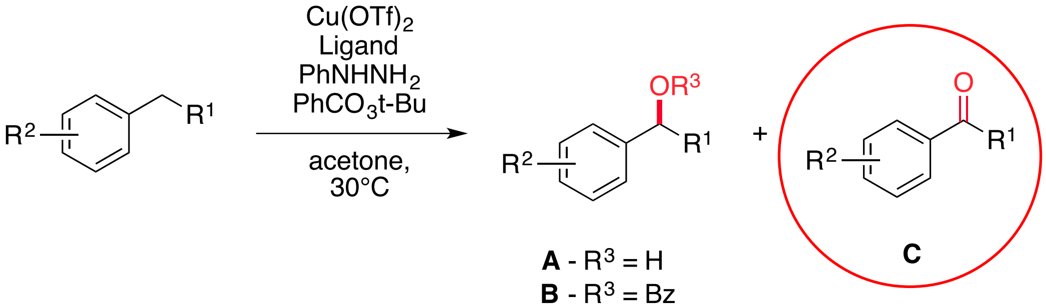


B. Zhang, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron* **2013**, *69*, 2033–2037.

1 - Kharash-Sosnovsky type reaction

1.2 - Benzylic Oxidation

> Mechanism of the Cu^{II}-catalyzed benzylic oxygenation



A - R^3 = H
B - R^3 = Bz

> Benzylic oxygenation of (aryl)heteroaryl)methanes with oxygen

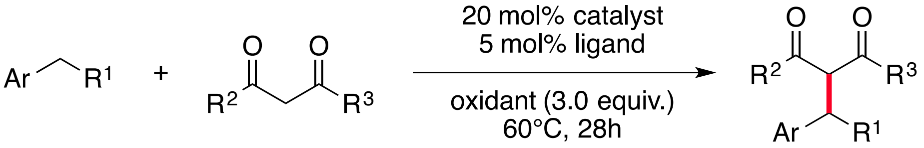
H. Sterckx, J. De Houwer, C. Mensch, I. Caretti, K. A. Tehrani, W. A. Herrebout, S. Van Doorslaer, B. U. W. Maes, *Chem. Sci.* **2015**, *7*, 346–357.

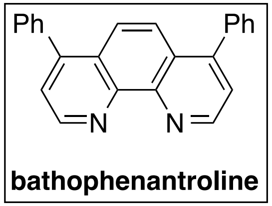
B. Zhang, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron* **2013**, *69*, 2033–2037.

1 - Kharash-Sosnovsky type reaction

1.2 - Benzylic coupling with 1,3-Dicarbonyl compounds

> Catalyzed by Copper ?





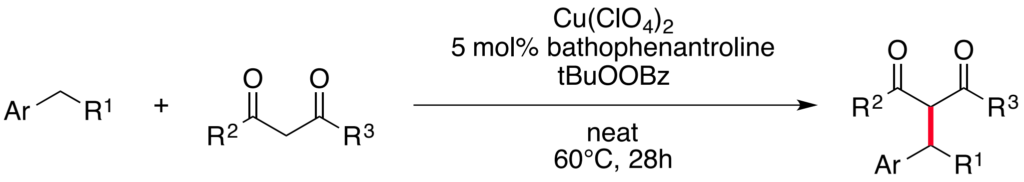
Entry	Reaction conditions	Yield
1	no catalyst, t-BuOOBz, neat	< 5%
2	$Cu(ClO_4)_2$, no ligand, tBuOOBz, neat	57%
3	$Cu(ClO_4)_2$, tBuOOBz, neat	71%

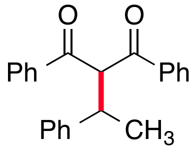
N. Borduas, D. A. Powell, *J. Org. Chem.* **2008**, *73*, 7822–7825.

1 - Kharash-Sosnovsky type reaction

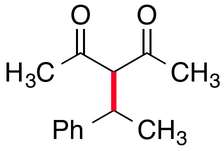
1.2 - Benzylic coupling with 1,3-Dicarbonyl compounds

> Scope

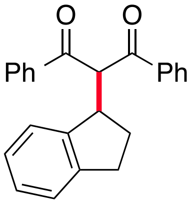




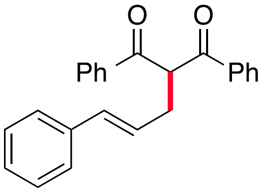
66%



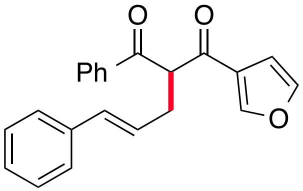
62%



66%



71%



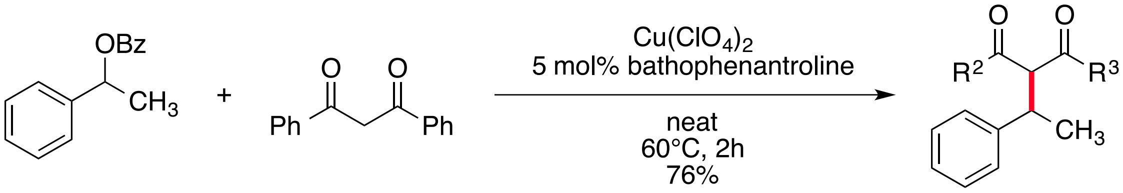
51%

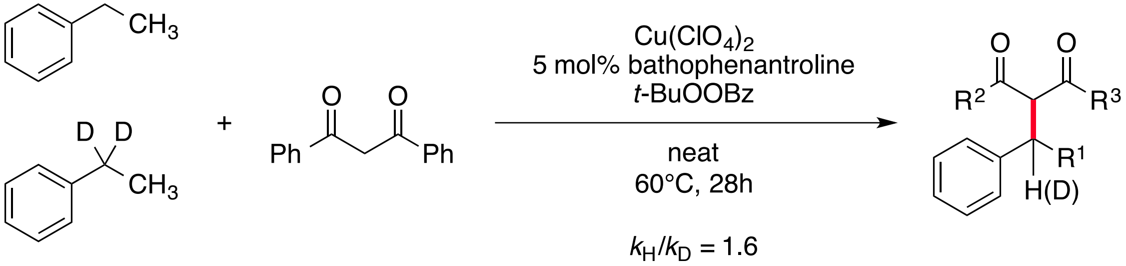
N. Borduas, D. A. Powell, *J. Org. Chem.* **2008**, *73*, 7822–7825.

1 - Kharash-Sosnovsky type reaction

1.2 - Benzylic coupling with 1,3-Dicarbonyl compounds

> Mechanistic Studies



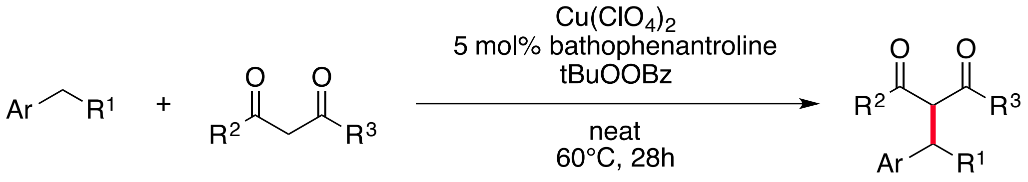


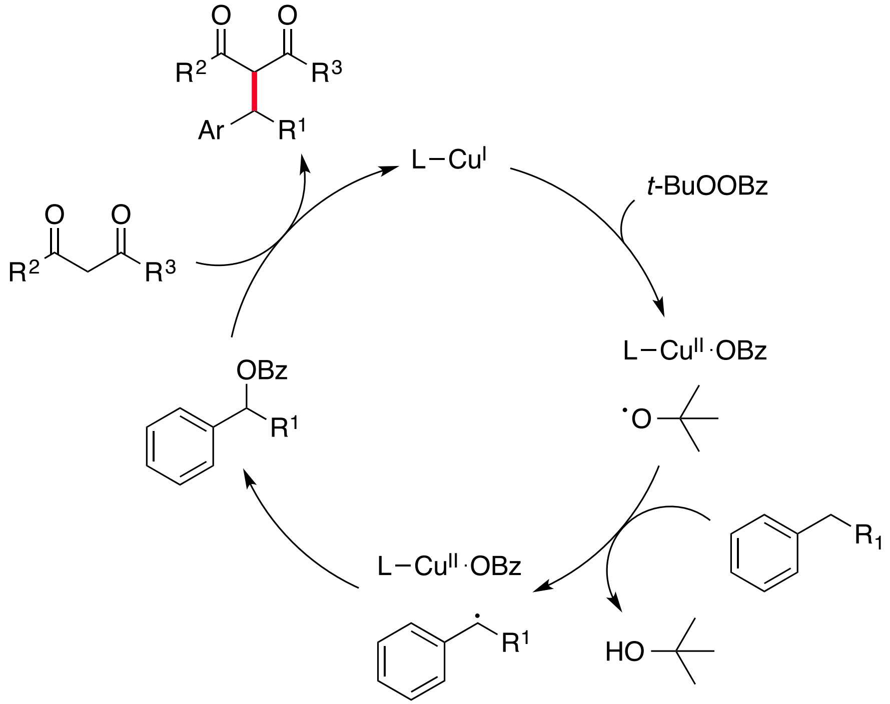
N. Borduas, D. A. Powell, *J. Org. Chem.* **2008**, *73*, 7822–7825.

1 - Kharash-Sosnovsky type reaction

1.2 - Benzylic coupling with 1,3-Dicarbonyl compounds

> Proposed Mechanism

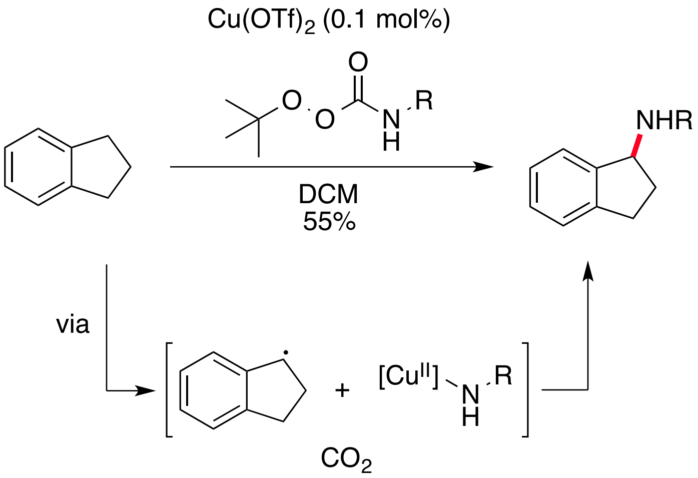


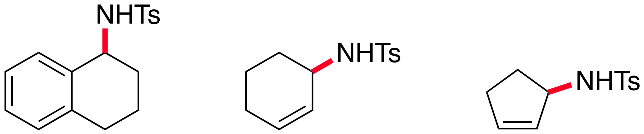


N. Borduas, D. A. Powell, *J. Org. Chem.* **2008**, *73*, 7822–7825.

1 - Kharash-Sosnovsky type reaction

1.3 - Benzylic Amination

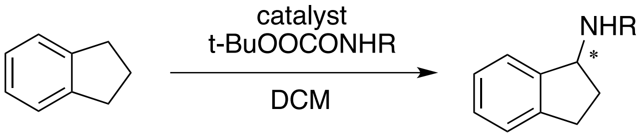




45%

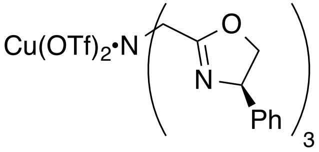
27%

53%



4%, 28% ee

Catalyst



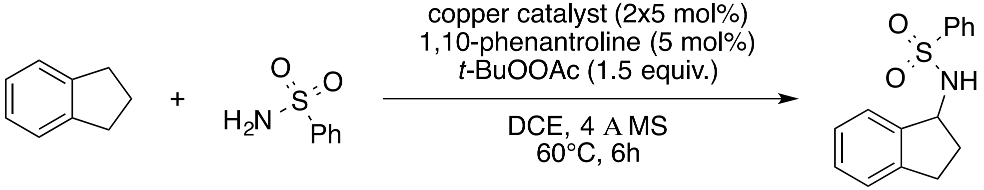
> The mechanism of the formation of p-toluenesulfonamide (major side product, up to 54%) is unclear.

Y. Kohmura, K.-I. Kawasaki, T. Katsuki, *Synlett* **1997**, *1997*, 1456–1458.

1 - Kharash-Sosnovsky type reaction

1.3 - Benzylic Amination

> Catalyzed by Copper ?



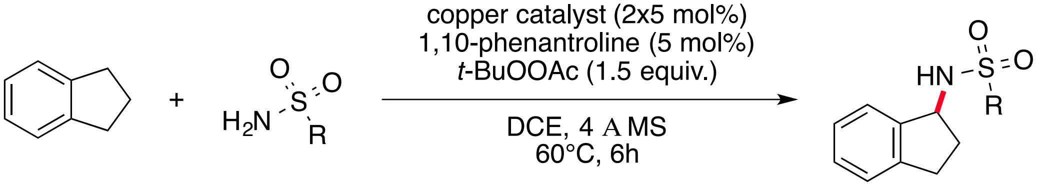
Entry	Catalyst	Yield
1	none	0%
2	$Cu(OTf)_2$	73%

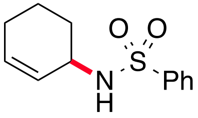
G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031–6034.

1 - Kharash-Sosnovsky type reaction

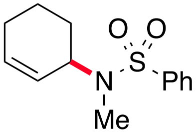
1.3 - Benzylic Amination

> Scope

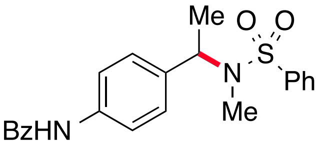




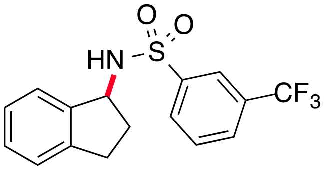
75%



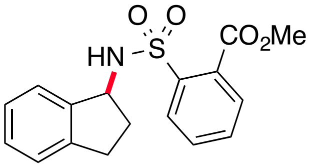
61%



64%



70%



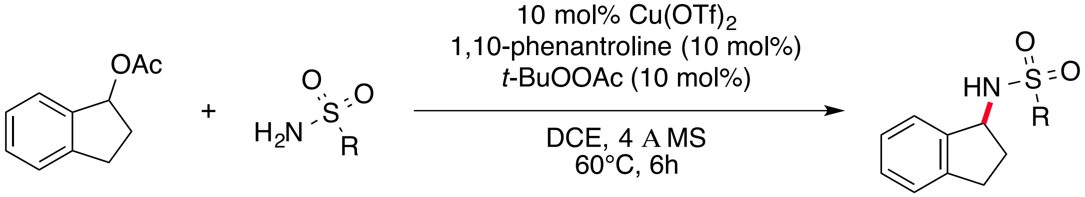
76%

G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031–6034.

1 - Kharash-Sosnovsky type reaction

1.3 - Benzylic Amination

> Mechanistic Studies



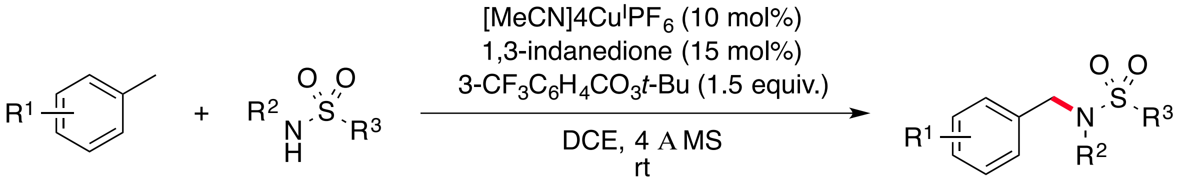
no $Cu(OTf)_2$ catalyst, 16h : <5% yield
no t-BuOOAc oxidant, 16h: <5% yield
30 min : 56% yield
25°C, 2h: 83% yield

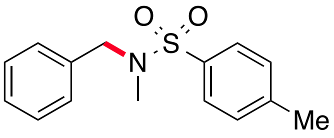
G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031–6034.

1 - Kharash-Sosnovsky type reaction

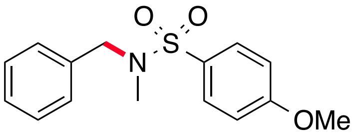
1.3 - Benzylic Amination

> Scope





72%



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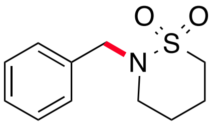

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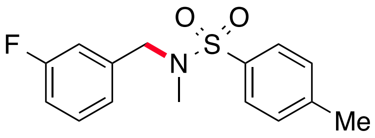
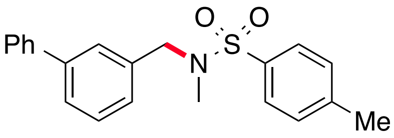


63%



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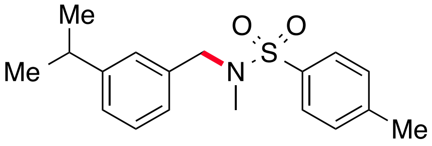


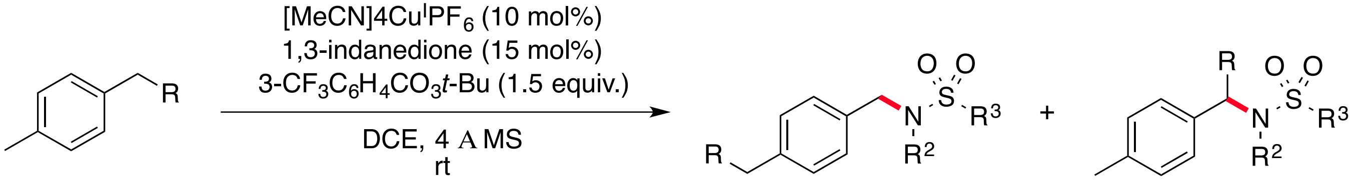
39%

D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726–2729.

1 - Kharash-Sosnovsky type reaction

1.3 - Benzylic Amination

> Selectivity Experiment



1° amination product

2° amination product

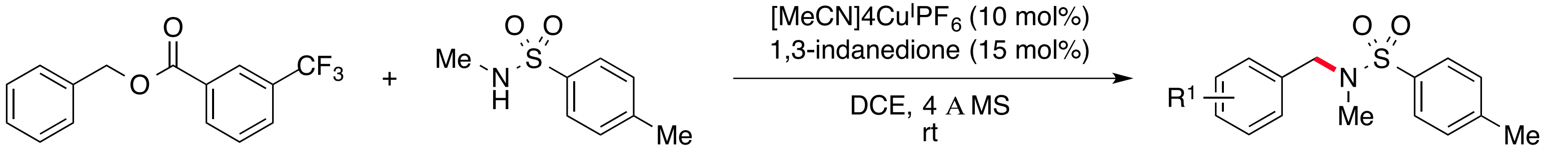
R = Me	84% combined yield	2°/1° ratio = 4 : 1
R = Et	68% combined yield	2°/1° ratio = 2 : 1

D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726–2729.

1 - Kharash-Sosnovsky type reaction

1.3 - Benzylic Amination

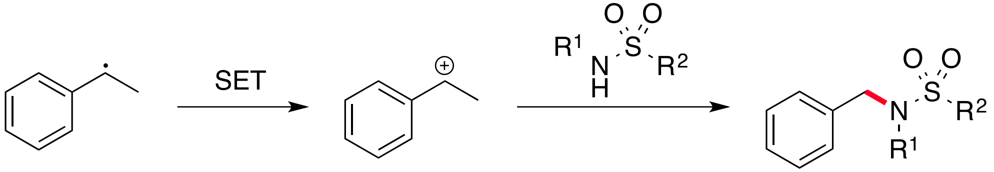
> Mechanistic Studies



Conditions :		
	as above	<5% yield
	+20 mol% oxidant	<5% yield

> Different conclusion than the previous case.

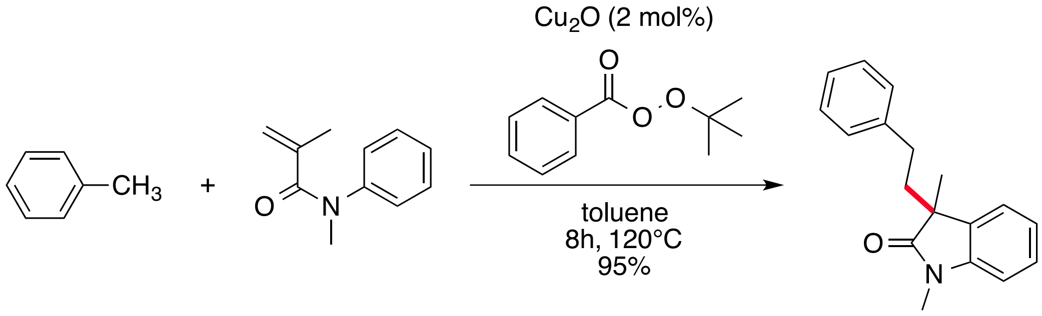
> Proposal



D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726–2729.

1 - Kharash-Sosnovsky type reaction

1.4 - Benzylic arylation of activated alkenes



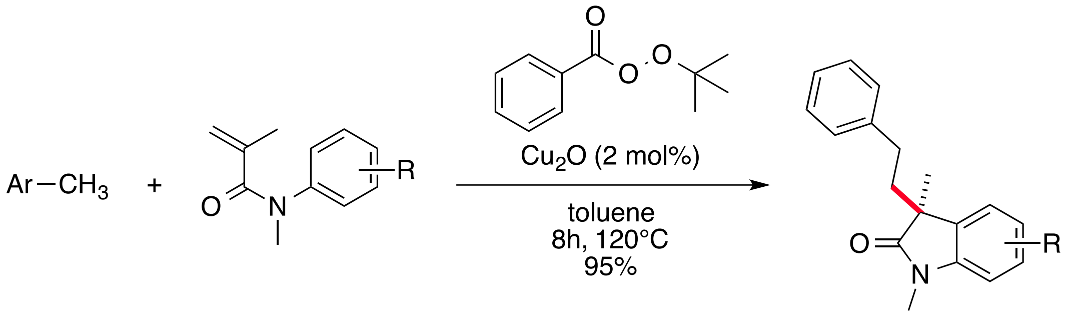
Entry	Catalyst	Yield
1	/	65%
2	CuCl (5 mol%)	89%
3	Cu_2O (5 mol%)	96%
4	Cu_2O (2 mol%)	95%

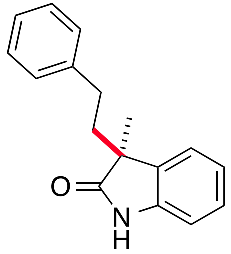
N. Borduas, D. A. Powell, *J. Org. Chem.* **2008**, *73*, 7822–7825.

1 - Kharash-Sosnovsky type reaction

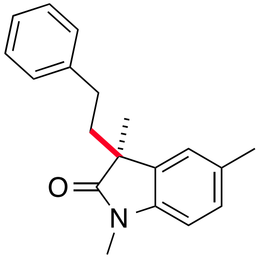
1.4 - Benzylic arylation of activated alkenes

> Scope

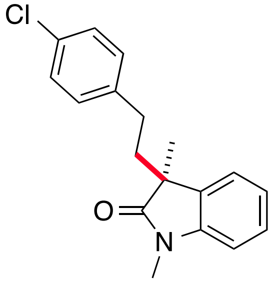




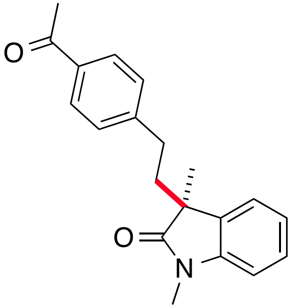
0%



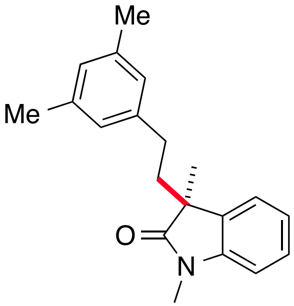
75%



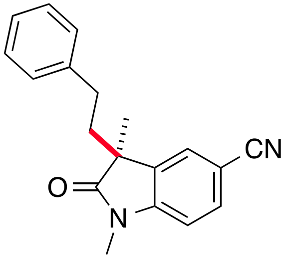
77%



63%



95%



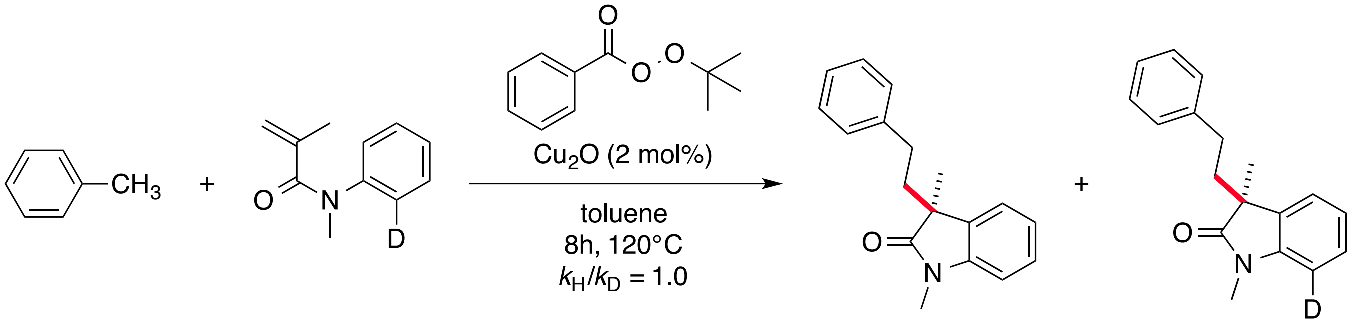
80%

S.-L. Zhou, L.-N. Guo, H. Wang, X.-H. Duan, *Chem. Eur. J.* **2013**, *19*, 12970–12973.

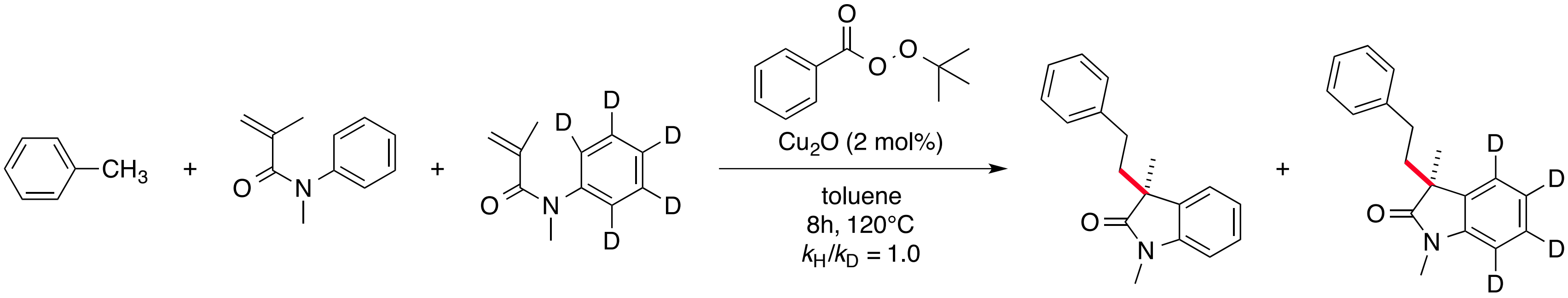
1 - Kharash-Sosnovsky type reaction

1.4 - Benzylic arylation of activated alkenes

> Mechanistic Studies



82% yield



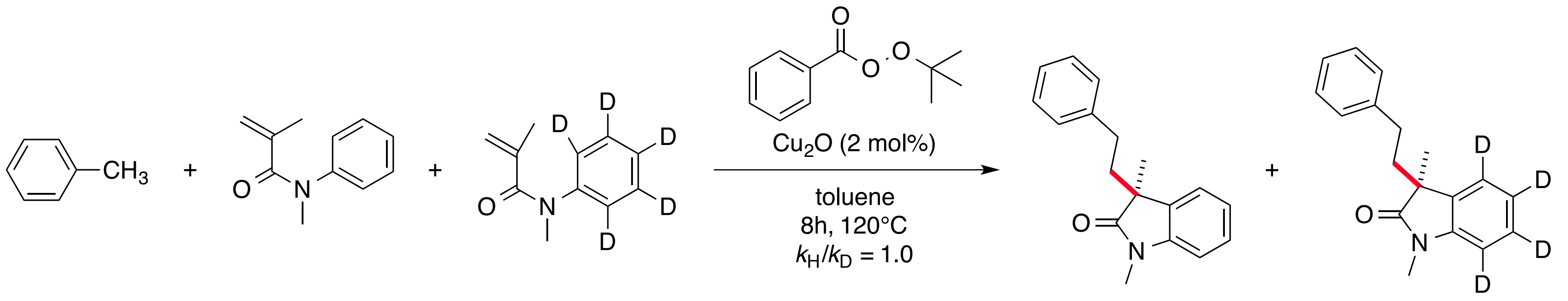
87% yield

S.-L. Zhou, L.-N. Guo, H. Wang, X.-H. Duan, *Chem. Eur. J.* **2013**, *19*, 12970–12973.

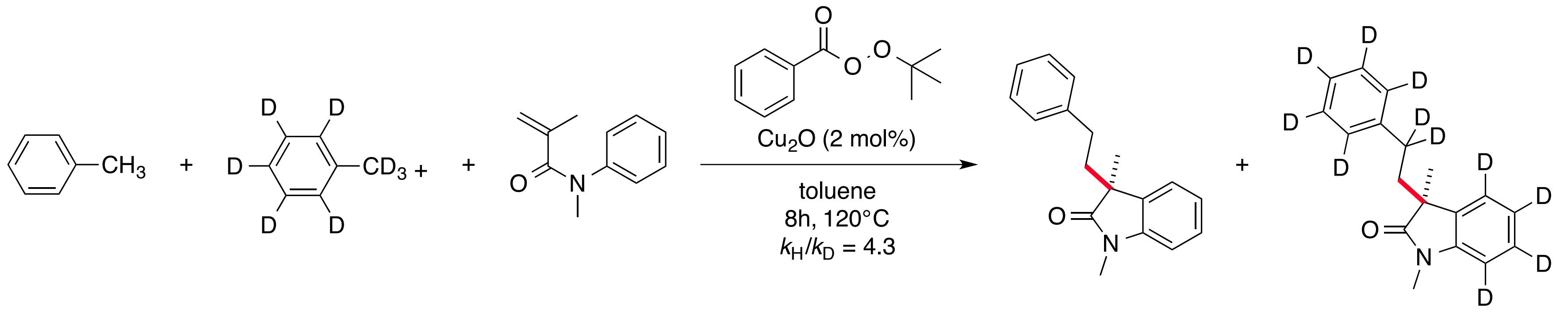
1 - Kharash-Sosnovsky type reaction

1.4 - Benzylic arylation of activated alkenes

> Mechanistic Studies



87% yield



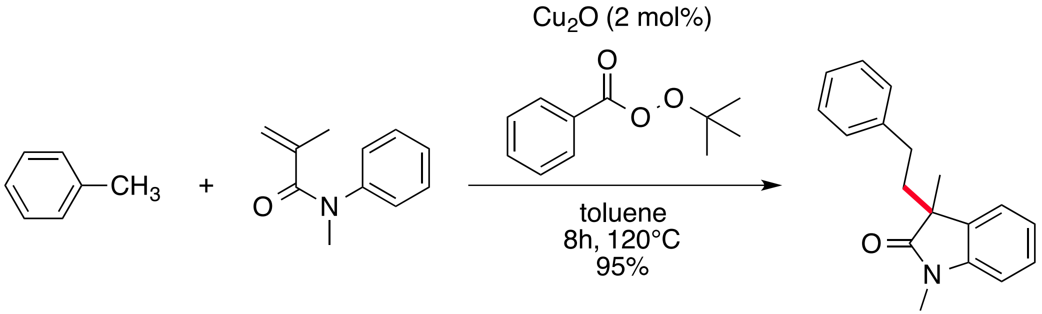
66% yield

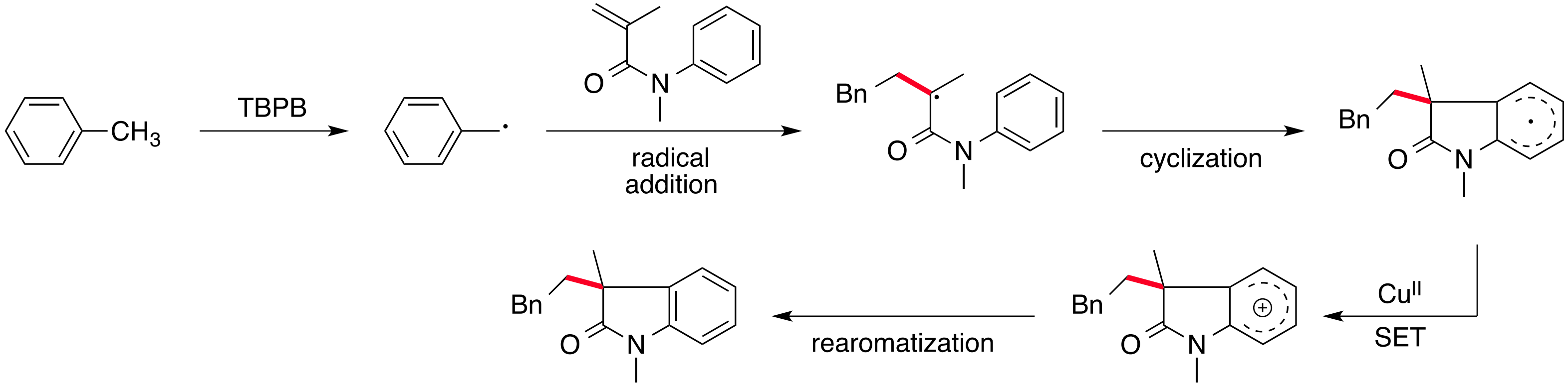
S.-L. Zhou, L.-N. Guo, H. Wang, X.-H. Duan, *Chem. Eur. J.* **2013**, *19*, 12970–12973.

1 - Kharash-Sosnovsky type reaction

1.4 - Benzylic arylation of activated alkenes

> Proposed Mechanism

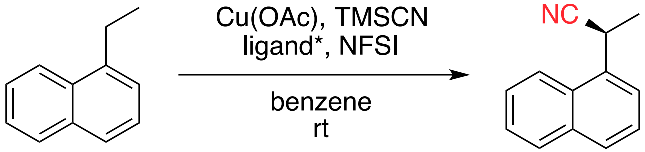


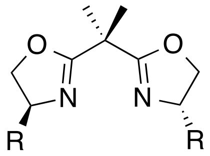


S.-L. Zhou, L.-N. Guo, H. Wang, X.-H. Duan, *Chem. Eur. J.* **2013**, *19*, 12970–12973.

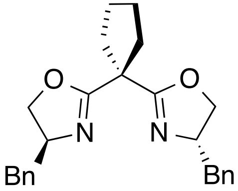
2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

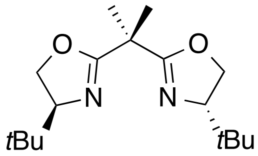




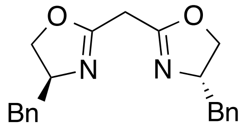
L1 : R = H : 25% (ee N/A)
L2 : R = Bn 91% (ee 96%)



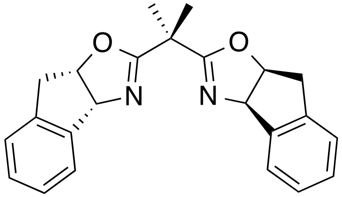
L3 : 84% (ee 95%)



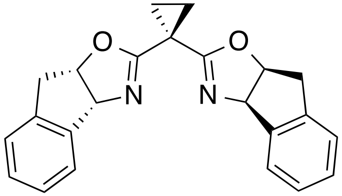
L4 : 6% (ee 15%)



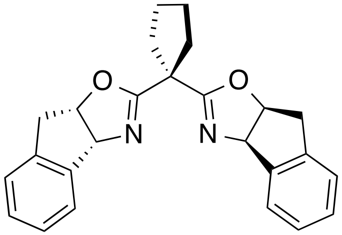
L5 : traces



L6 : 53% (ee -97%)



L7 : 37% (ee -88%)



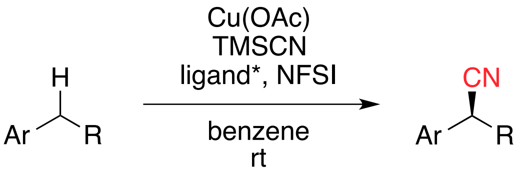
L8 : 71% (ee -97%)

W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

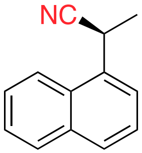
> Scope



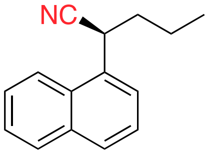
Cu(OAc)
TMSCN
ligand*, NFSI

benzene
rt

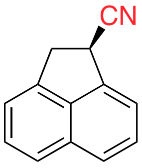
> Alkyl naphtalenes



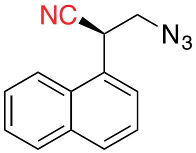
91%
ee 96%



80%
ee 96%

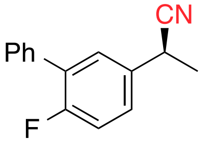


55%
ee 72%

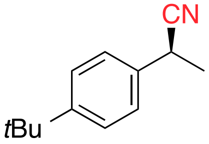


73%
ee 97%

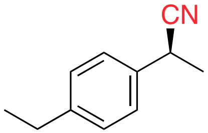
> Alkyl arenes



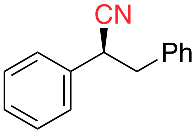
67%
ee 90%



93%
ee 85%

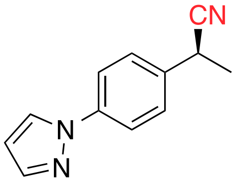


76%
ee 84%

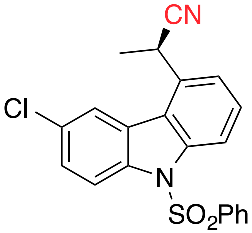


62%
ee 94%

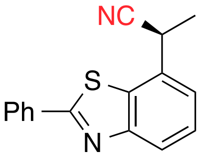
> Heterocycles-containing arenes



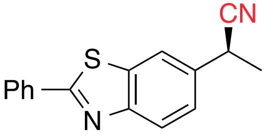
59%
ee 90%



76%
ee 98%



80%
96% ee



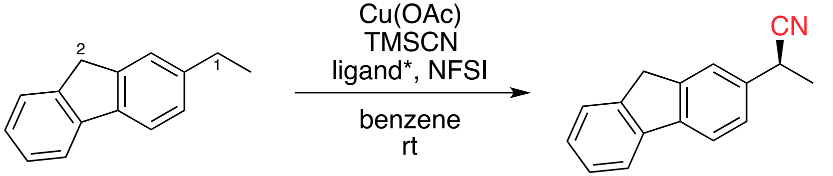
89%
ee 83%

W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

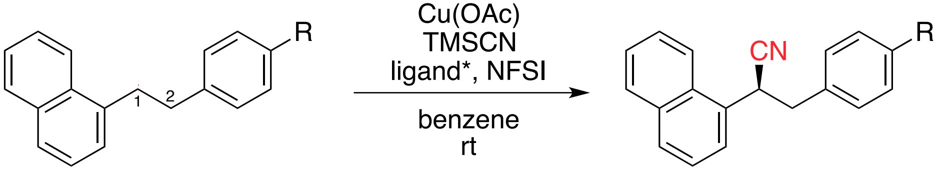
2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

> Selectivity Experiments



58%
ee 88%
ee 96% after recryst.

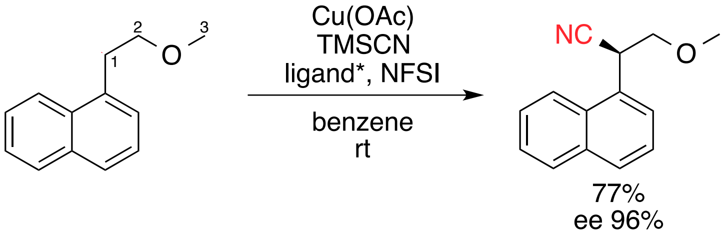


W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

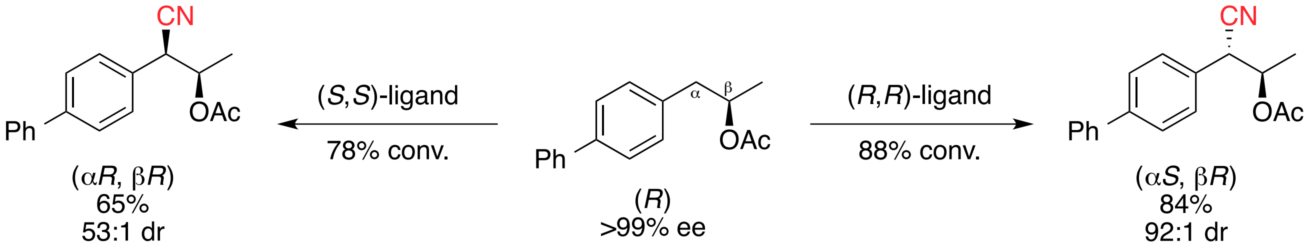
> Selectivity Experiments



Cu(OAc)
TMSCN
ligand*, NFSI

benzene
rt

77%
ee 96%



(*S*,*S*)-ligand
78% conv.

(αR, βR)
65%
53:1 dr

(*R*)
>99% ee

(*R*,*R*)-ligand
88% conv.

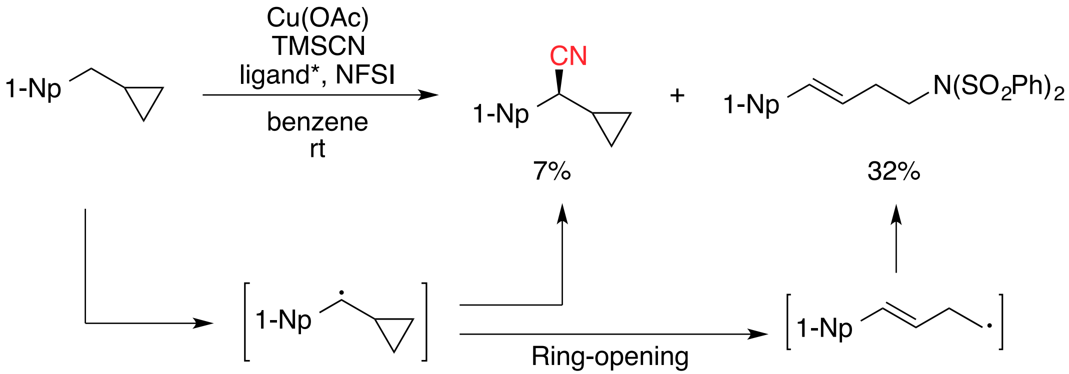
(αS, βR)
84%
92:1 dr

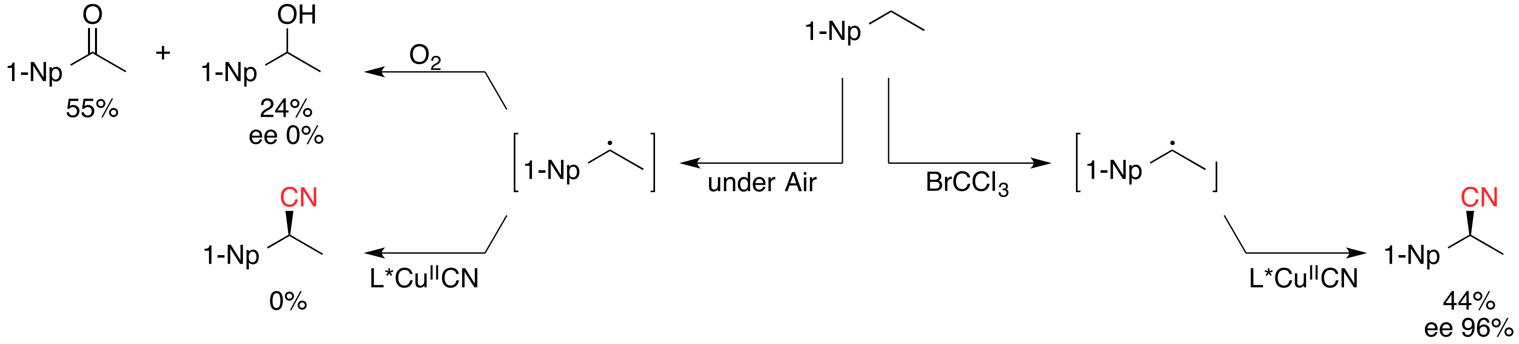
W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

> Radical-Probe Experiments



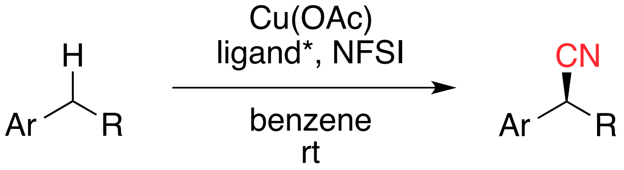


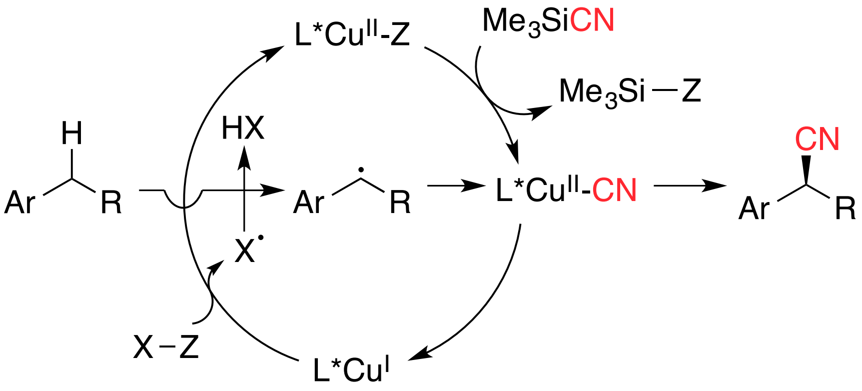
W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

> Proposed Mechanism





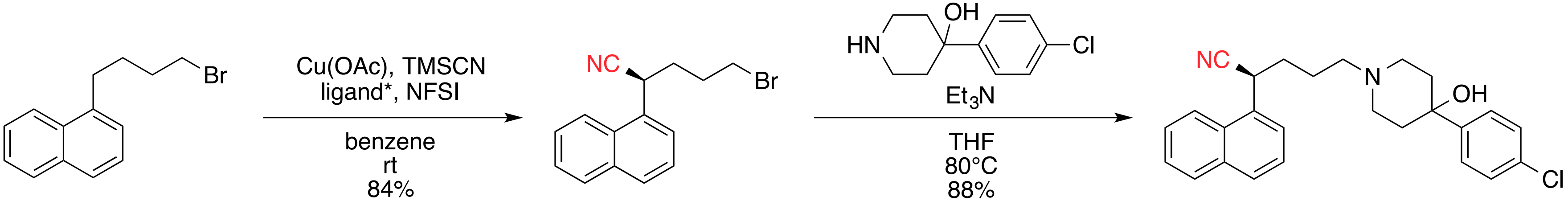
W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

2 - Co-oxidized with fluorine agent

2.1 - Enantioselective benzylic cyanation

> Synthetic Applications

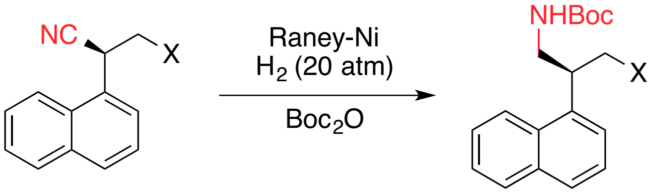
> Mild reaction conditions



ee 97%

ee 95%
biologically active compound

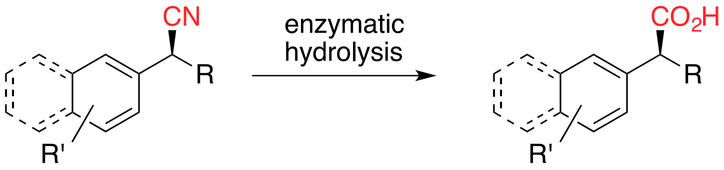
> Nitrile hydrogenation chiral phenethylamine derivatives



X = OH, ee 95%
X = Naphth, ee -98%

X = OH, 65%, ee 96%
X = Naphth, 71%, ee -98%

> Nitrile hydrolysis : chiral arylacetic acid derivatives

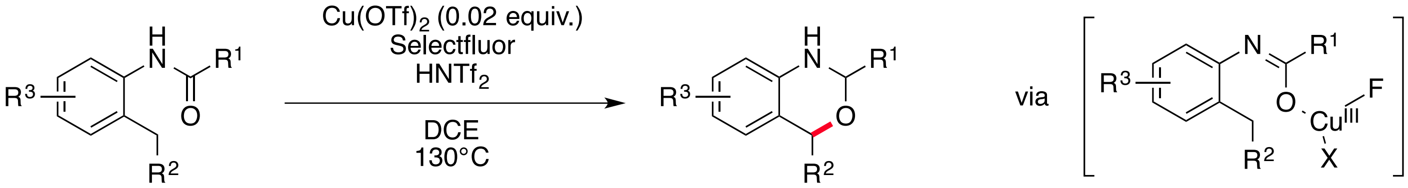


W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018.

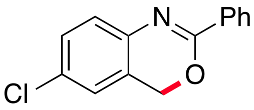
2 - Co-oxidized with fluorine agent

2.2 - Benzylic C-O cyclization

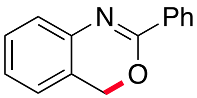
> Summary



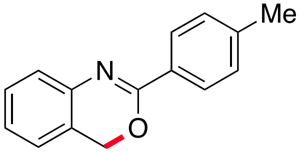
Entry	Catalyst	Oxidant	Additive	Yield
1	$Cu(OTf)_2$	Selectfluor	$HNTf_2$	81%
2	/	Selectfluor	$HNTf_2$	0%
3	$Cu(OTf)_2$	/	$HNTf_2$	0%
4	$Cu(OTf)_2$	Selectfluor	/	0%



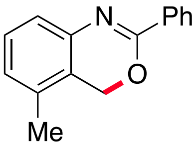
71%



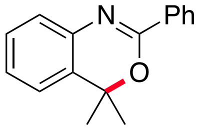
80%



76%



68%



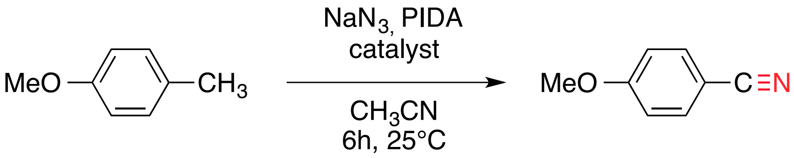
89%

Y. Li, Z. Li, T. Xiong, Q. Zhang, X. Zhang, *Org. Lett.* **2012**, *14*, 3522–3525.

3 - Co-oxidized with hypervalent iodides

3.1 – Direct transformation of Methyl Arenes to Aryl Nitriles

> Catalyzed by Copper ?



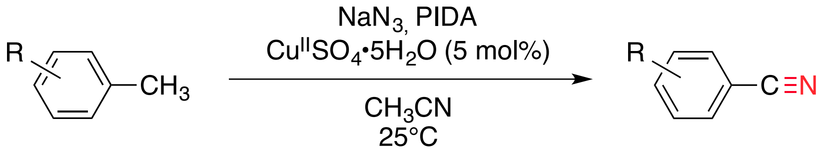
Entry	NaN_3	PIDA	Catalyst	time	Yield
1	0	3.2	/	12h	0%
2	4.0	0	/	12h	0%
3	4.0	3.2	/	3h	42%
4	4.0	3.2	$CuSO_4 \cdot 5H_2O$ (5 mol%)	6h	70%

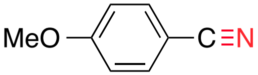
W. Zhou, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097.

3 - Co-oxidized with hypervalent iodides

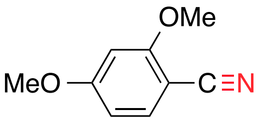
3.1 – Direct transformation of Methyl Arenes to Aryl Nitriles

> Scope





71%



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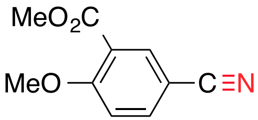

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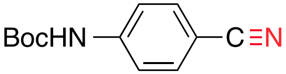

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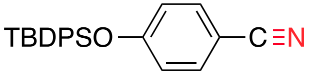

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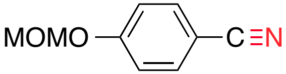


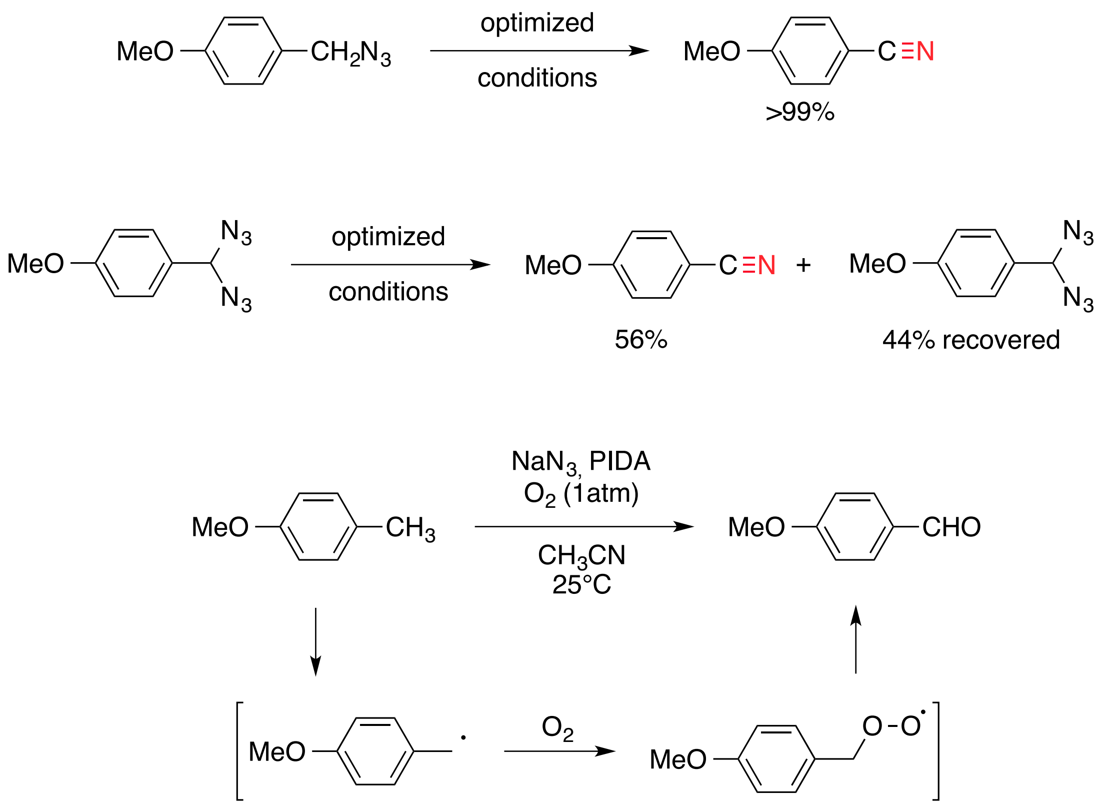
50%

W. Zhou, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097.

3 - Co-oxidized with hypervalent iodides

3.1 – Direct transformation of Methyl Arenes to Aryl Nitriles

> Mechanistic Studies

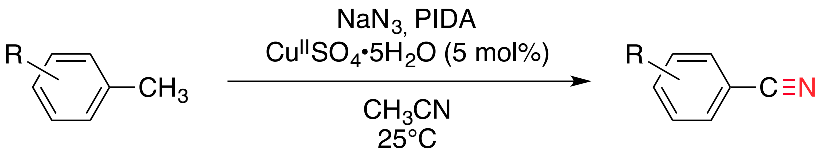


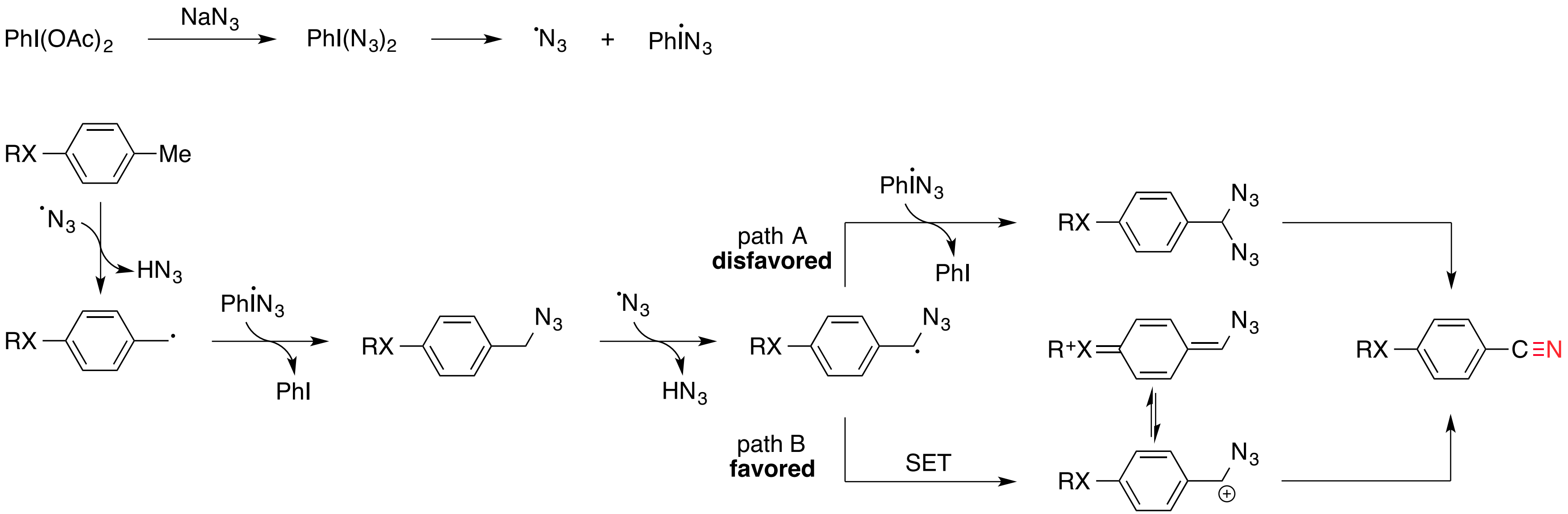
W. Zhou, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097.

3 - Co-oxidized with hypervalent iodides

3.1 – Direct transformation of Methyl Arenes to Aryl Nitriles

> Proposed Mechanism



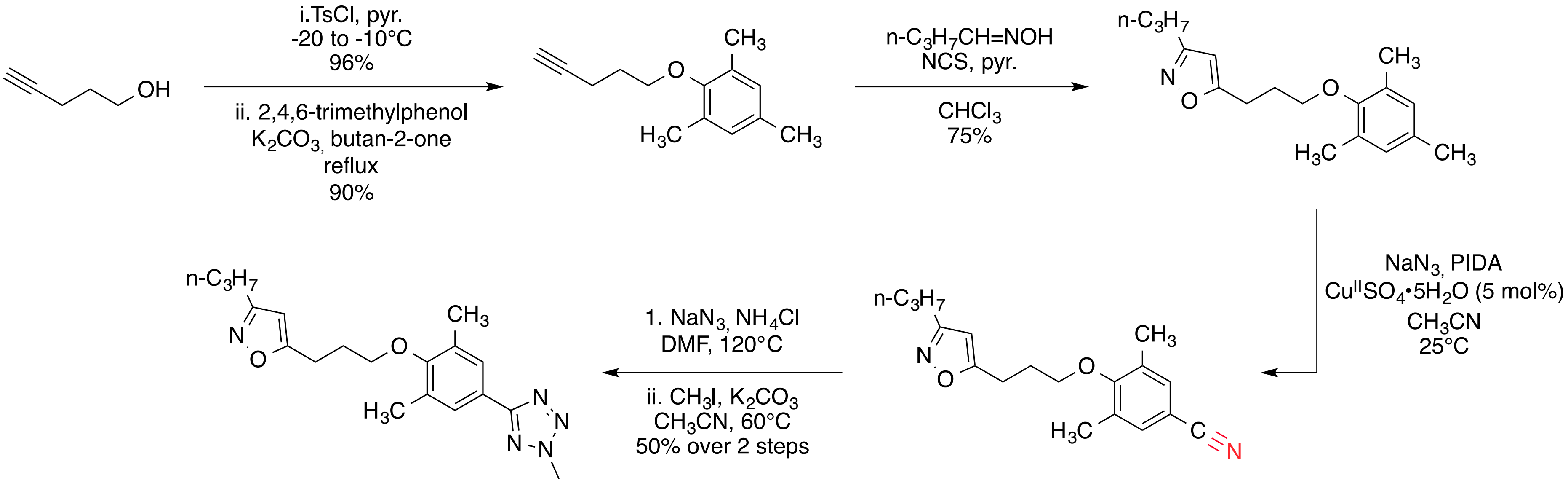


W. Zhou, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097.

3 - Co-oxidized with hypervalent iodides

3.1 – Direct transformation of Methyl Arenes to Aryl Nitriles

> Synthetic Application



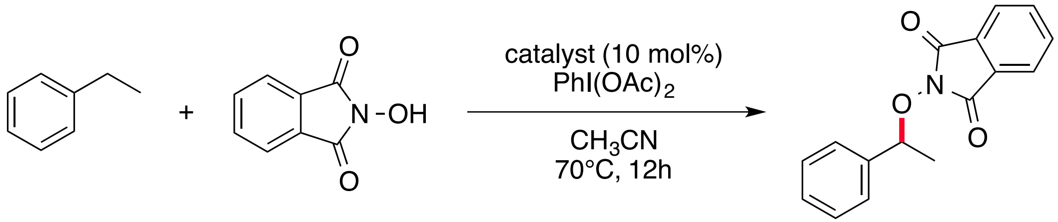
> Tetrazole analogue related to Disoxaril (drug against picornaviruses)

W. Zhou, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097.

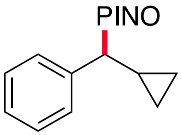
3 - Co-oxidized with hypervalent iodides

3.2 - Benzylic C-O bond formation with NHPI

> Scope



Entry	Catalyst	Yield
1	non	29%
2	CuCl	78%



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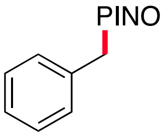

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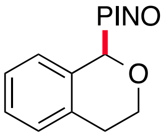

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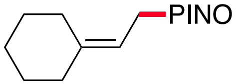
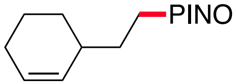


70%



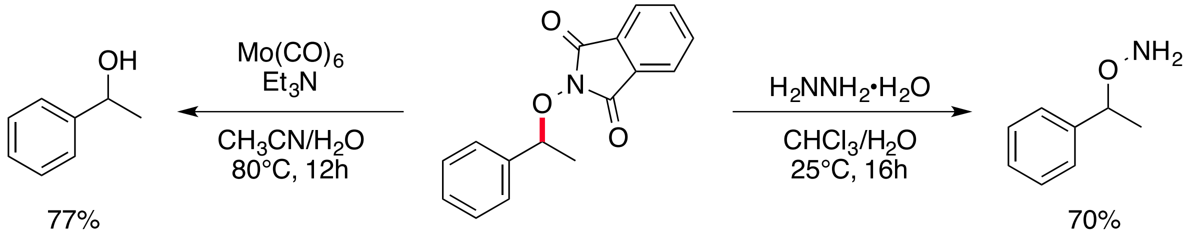
76%

J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

3 - Co-oxidized with hypervalent iodides

3.2 - Benzylic C-O bond formation with NHPI

> Synthetic utility of the method

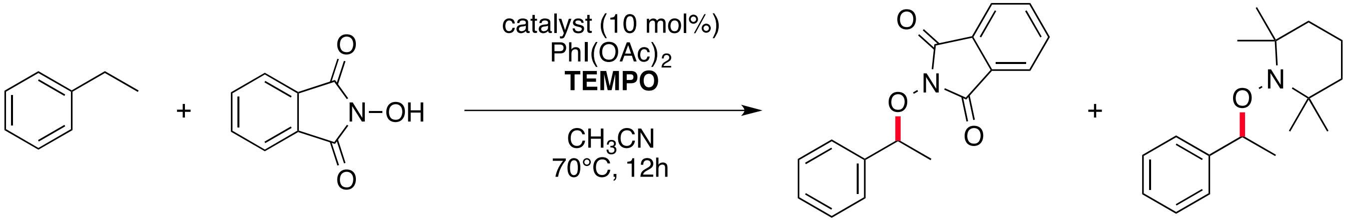


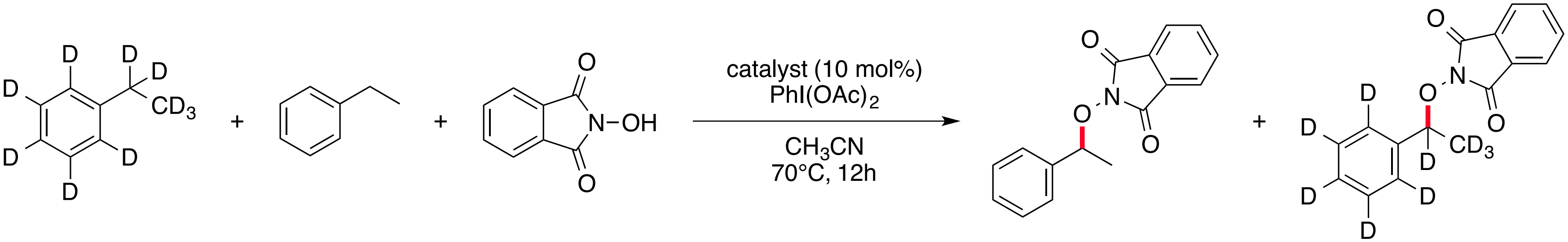
J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

3 - Co-oxidized with hypervalent iodides

3.2 - Benzylic C-O bond formation with NHPI

> Mechanistic Studies

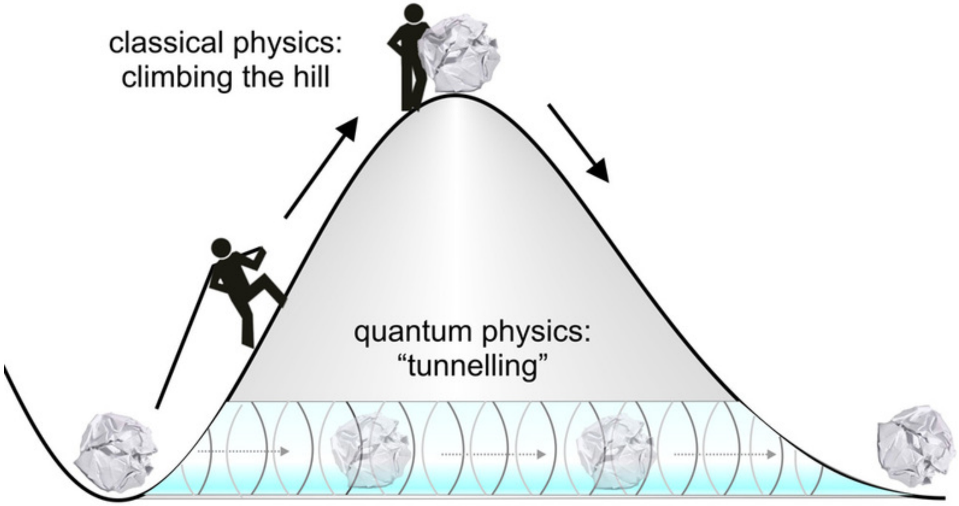


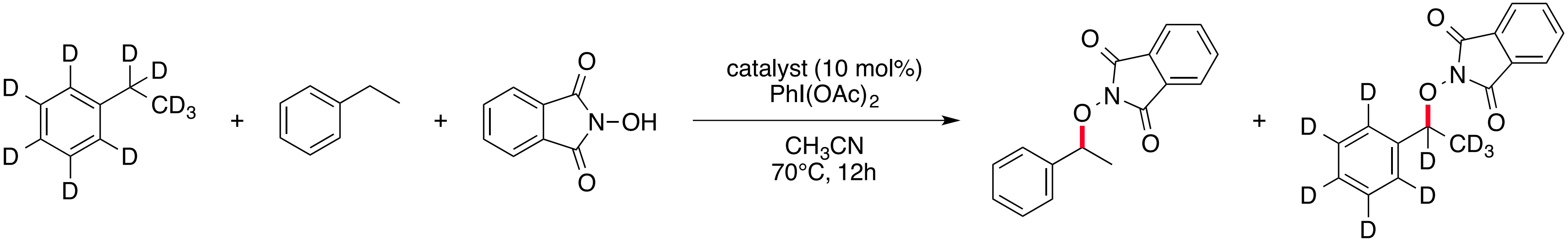


k_H/k_D = 10.8

J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

Quantum Tunneling effect





k_H/k_D = 10.8

J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

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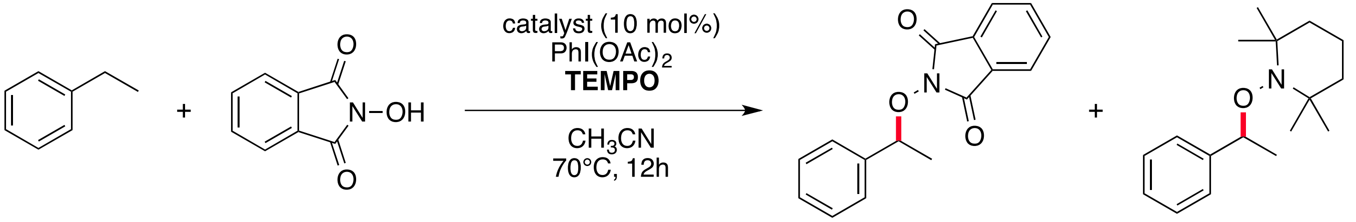
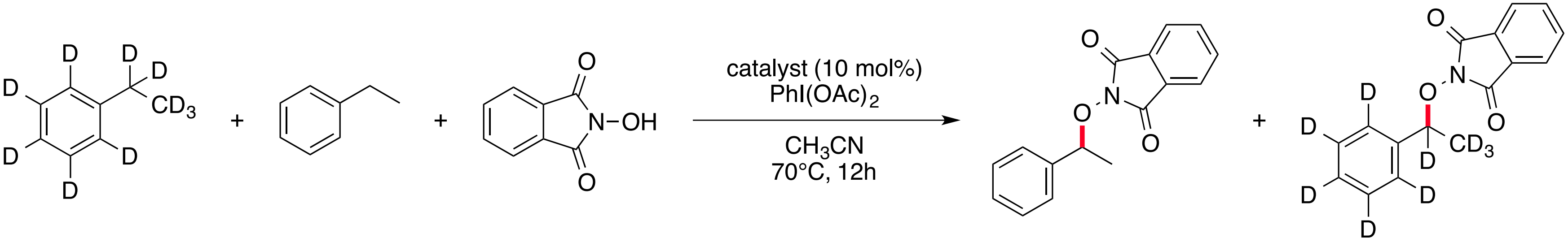
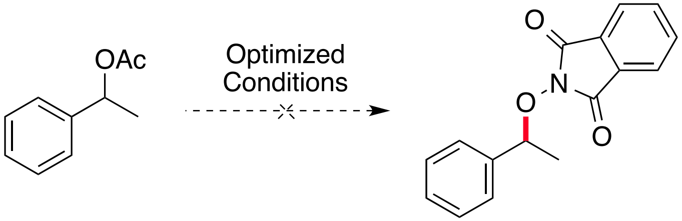
> Mechanistic Studies





***k*$_H$/*k*$_D$ = 10.8**

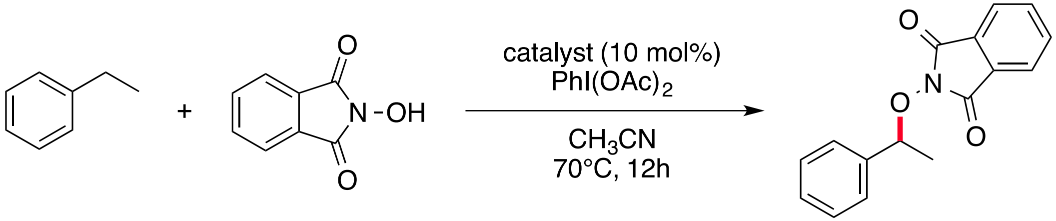


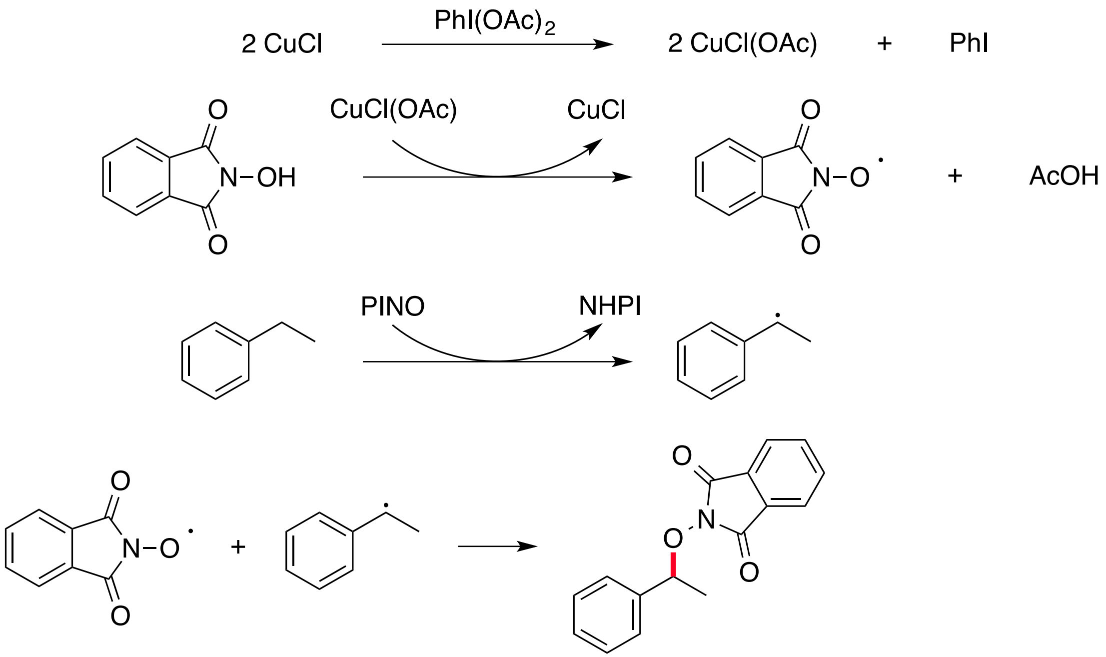
J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

3 - Co-oxidized with hypervalent iodides

3.2 - Benzylic C-O bond formation with NHPI

> Proposed mechanism



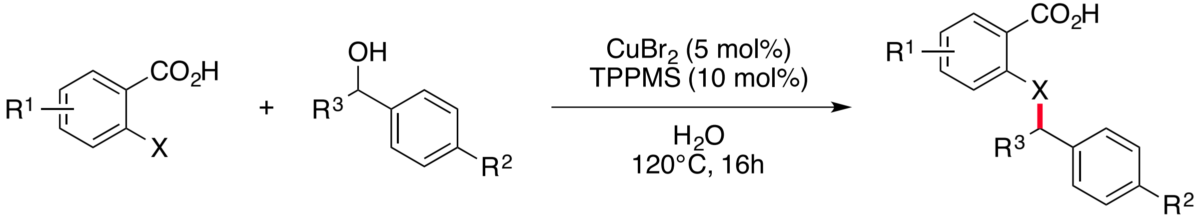


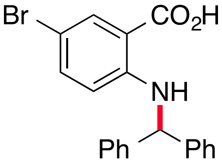
J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

4 – Other Systems

4.1 – Benzylic C-Heteroatomes coupling

> Scope





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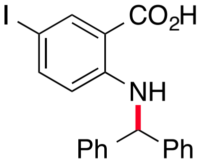

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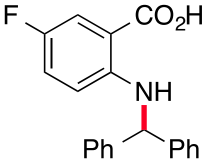

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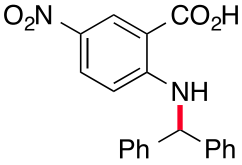

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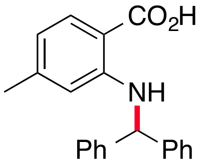

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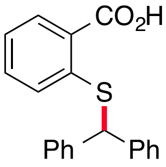

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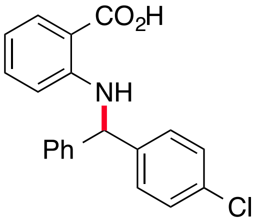

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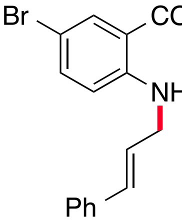


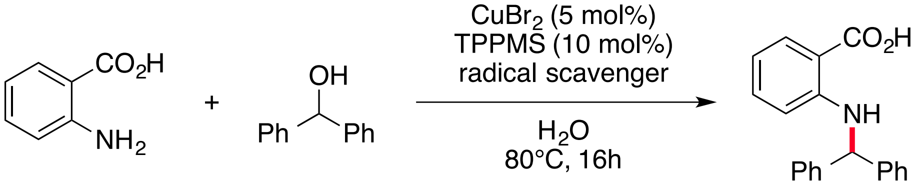
67%

H. Hikawa, Y. Mori, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal.* **2016**, *358*, 765–773.

4 – Other Systems

4.1 – Benzylic C-Heteroatomes coupling

> Mechanistic Studies



Entry	Radical Scavenger	Yield (NMR)
1	BHT (1 equiv.)	13%
2		56%*
3	galvinoxyl (0.5 equiv.)	27%
4	TEMPO (0.5 equiv.)	trace
5	none	69%

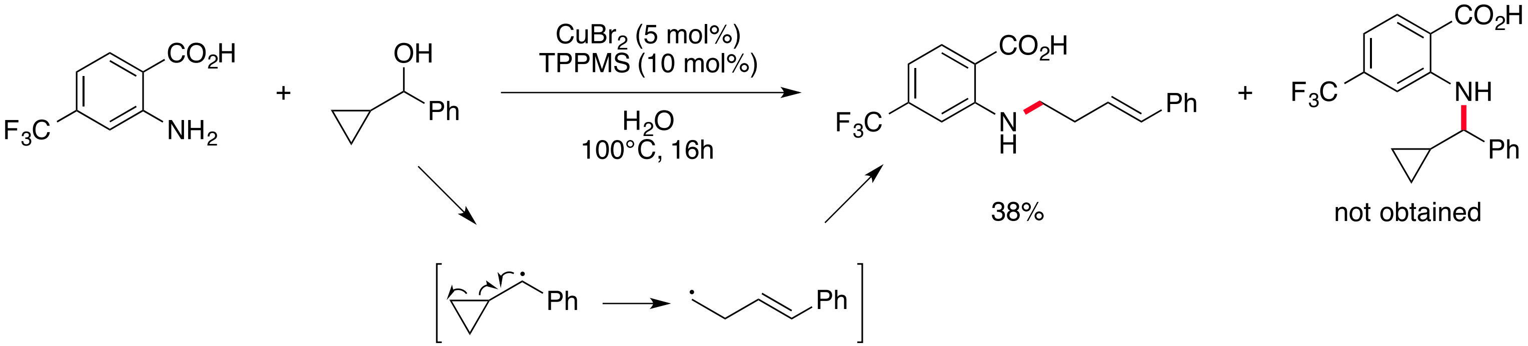
* $AuCl_4Na{\cdot}2\ H_2O$ (5mol%) was used instead of $CuBr_2$

H. Hikawa, Y. Mori, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal.* **2016**, *358*, 765–773.

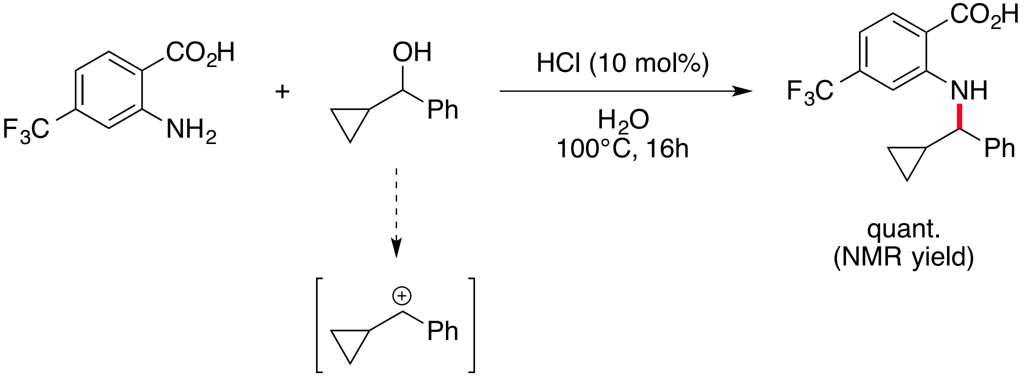
4 – Other Systems

4.1 – Benzylic C-Heteroatomes coupling

> Mechanistic Studies



> Reaction using HCl as catalyst



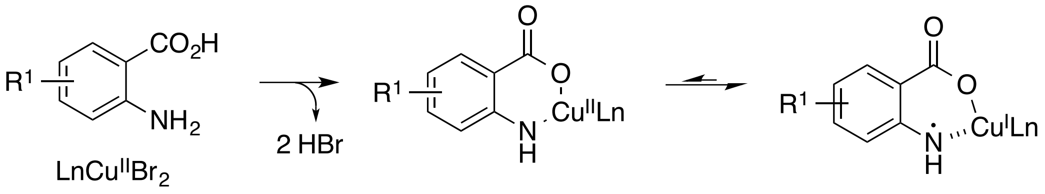
H. Hikawa, Y. Mori, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal.* **2016**, *358*, 765–773.

4 – Other Systems

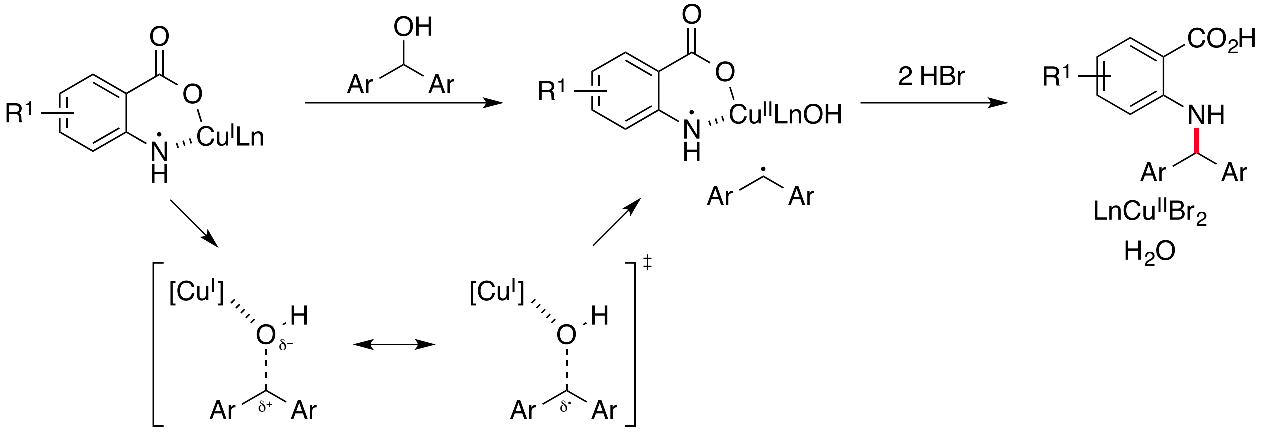
4.1 – Benzylic C-Heteroatomes coupling

> Proposed Mechanism

A: Formation of amine radical with Cu^{I} species



B: Atom-transfer initiated by the Cu^{I}

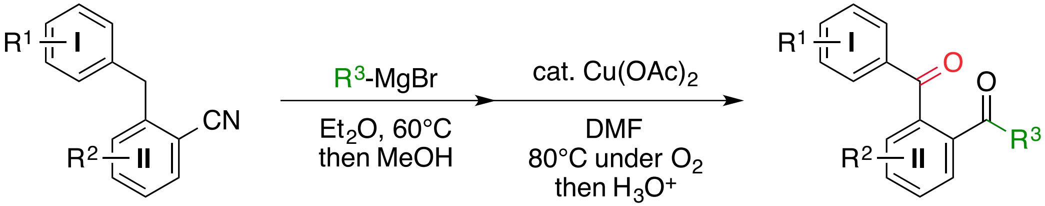


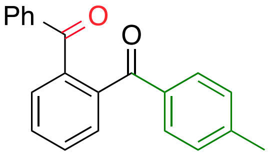
H. Hikawa, Y. Mori, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal.* **2016**, *358*, 765–773.

4 – Other Systems

4.2 - Benzylic C-H Oxygenation under Oxygen Atmosphere

> Scope





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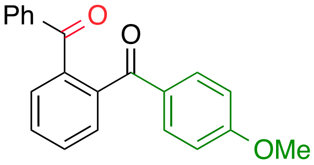

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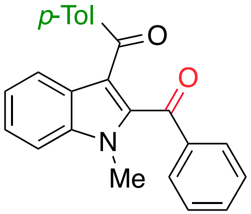

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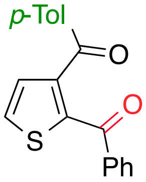

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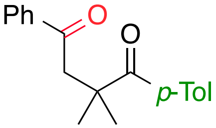


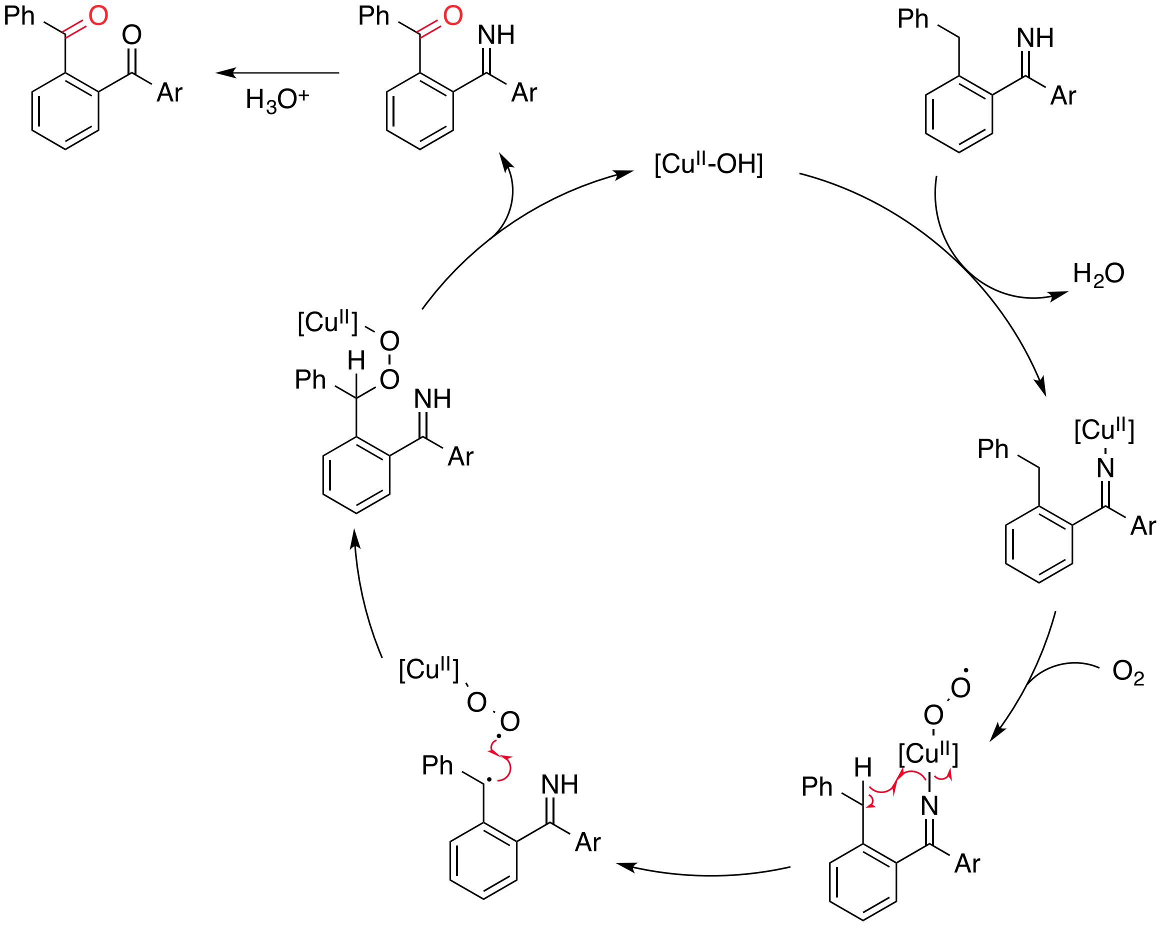
58%

L. Zhang, G. Y. Ang, S. Chiba, *Org. Lett.* **2011**, *13*, 1622–1625.

4 – Other Systems

4.2 - Benzylic C-H Oxygenation under Oxygen Atmosphere

> Proposed Mechanism

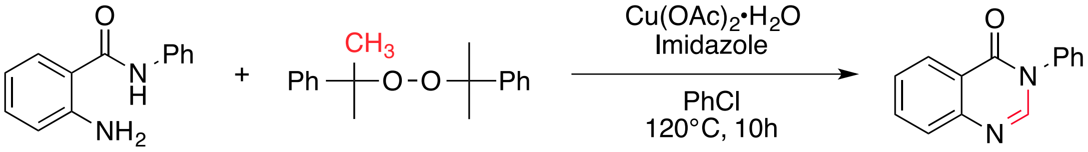


L. Zhang, G. Y. Ang, S. Chiba, *Org. Lett.* **2011**, *13*, 1622–1625.

4 – Other Systems

4.3 - Benzylic N-C Bond formation and generation of Methane Carbocation

> Proposed mechanism



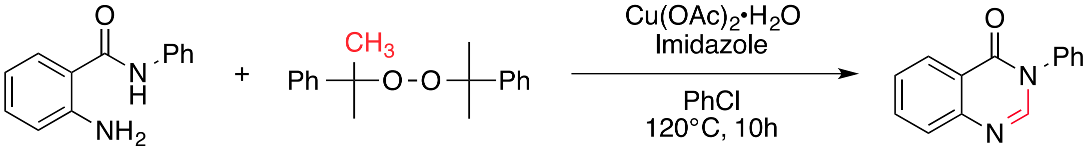
Entry	Catalyst	Base	Yield
1	/	imidazole	20%
2	$Cu(OAc)_2 \cdot H_2O$	/	50%
3	$Cu(OAc)_2 \cdot H_2O$	imidazole	82%

Y. Bao, Y. Yan, K. Xu, J. Su, Z. Zha, Z. Wang, *J. Org. Chem.* **2015**, *80*, 4736–4742.

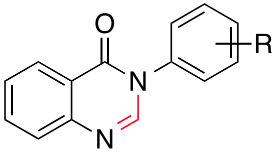
4 – Other Systems

4.3 - Benzylic N-Methylation

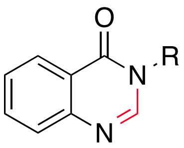
> Generalities and Scope



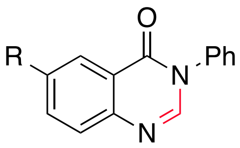
Entry	Catalyst	Base	Yield
1	/	imidazole	20%
2	$Cu(OAc)_2 \cdot H_2O$	/	50%
3	$Cu(OAc)_2 \cdot H_2O$	imidazole	82%



R = 2-CH_3, 75%
R = 4-CF_3, 78%
R = 4-n-butyl, 73%



R = CH_2Ph, 42%
R = isopropyl, 37%
R = cyclohexyl, 35%



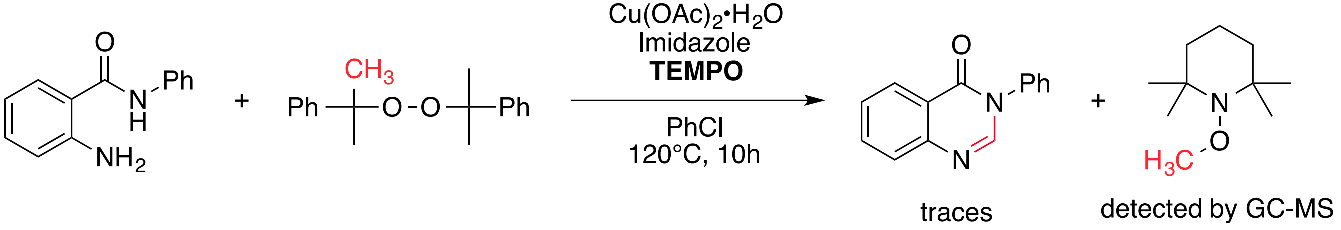
R = CH_3, 72%
R = OCH_3, 52%
R = NO_2, 65%

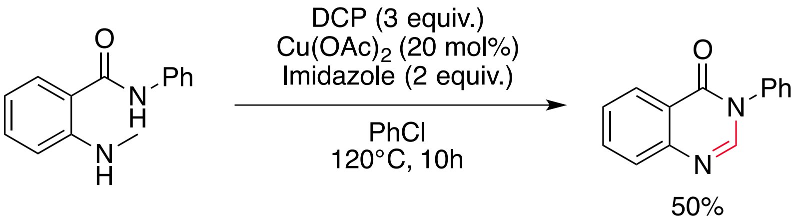
Y. Bao, Y. Yan, K. Xu, J. Su, Z. Zha, Z. Wang, *J. Org. Chem.* **2015**, *80*, 4736–4742.

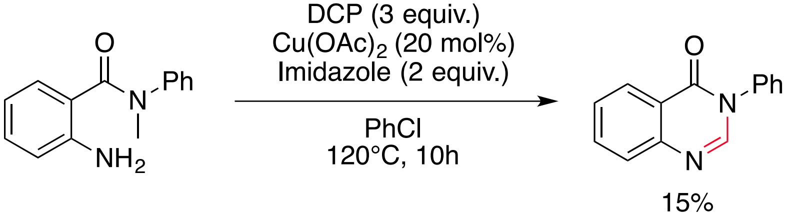
4 – Other Systems

4.3 - Benzylic N-Methylation

> Mechanistic Studies





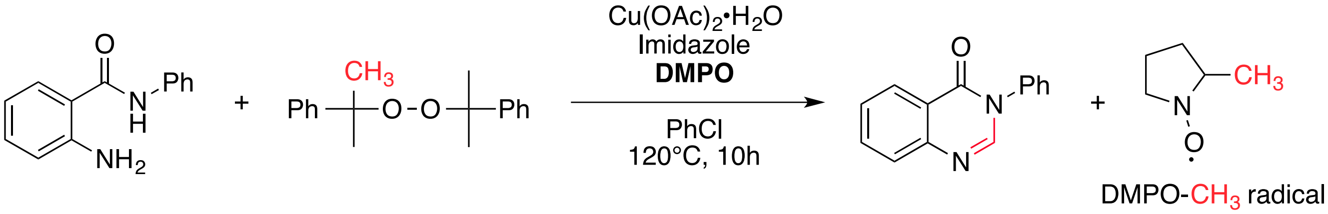


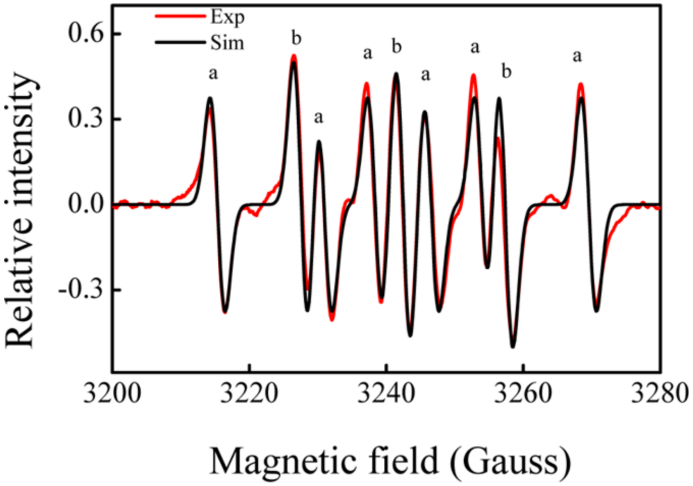
Y. Bao, Y. Yan, K. Xu, J. Su, Z. Zha, Z. Wang, *J. Org. Chem.* **2015**, *80*, 4736–4742.

4 – Other Systems

4.3 - Benzylic N-Methylation

> EPR Study



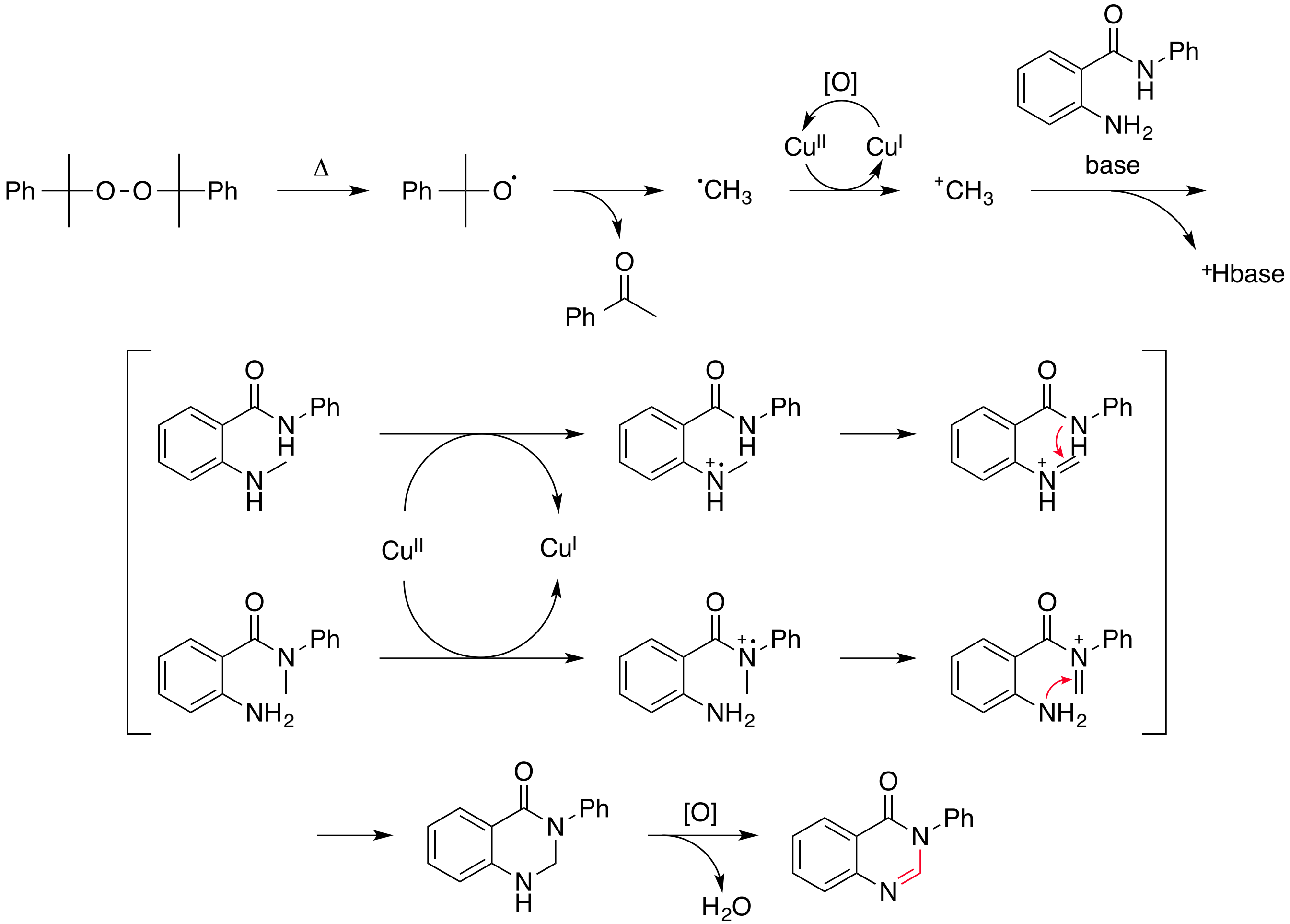


Y. Bao, Y. Yan, K. Xu, J. Su, Z. Zha, Z. Wang, *J. Org. Chem.* **2015**, *80*, 4736–4742.

4 – Other Systems

4.3 - Benzylic N-Methylation

> Proposed mechanism



Y. Bao, Y. Yan, K. Xu, J. Su, Z. Zha, Z. Wang, *J. Org. Chem.* **2015**, *80*, 4736–4742.

Conclusion

> Not always mendatory in some reaction

> Versatiles used of copper

> Able to run enantioselective reaction

> Some mechanisms are still unknown

> Co-oxidation possible with oxygen

A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int.Ed.* **2011**, *50*, 11062–11087.

But that is not the only thing about Copper in Radical Chemistry …

- Alkenes Functionnalization
- Arenes Functionnalization
- Trifluoromethylation reaction
- ATRA reactions
- Various radical chain processes

… and even more.