Tertiary dialkyl ether synthesis

2021. 11. 13. Literature Seminar

M2 Risa Yoshinaga

Contents

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1. Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; Bel, M. D.; Gallego, G. M.; Spangler, J. E.; Starr, J.; Yang, S.; Blackmond, D. G.; Baran, P. S., *Nature*, **2019**, *573*, 398.
2. Shibutani, S.;Kodo, T.; Takeda, M.; Nagao, K.; Tokunaga, N.; Sasaki, Y.; Ohmiya, H., *J. Am. Chem. Soc.*, **2020**, *142*, 1211.

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2. Shibutani, S.;Kodo, T.; Takeda, M.; Nagao, K.; Tokunaga, N.; Sasaki, Y.; Ohmiya, H., *J. Am. Chem. Soc.*, **2020**, *142*, 1211.

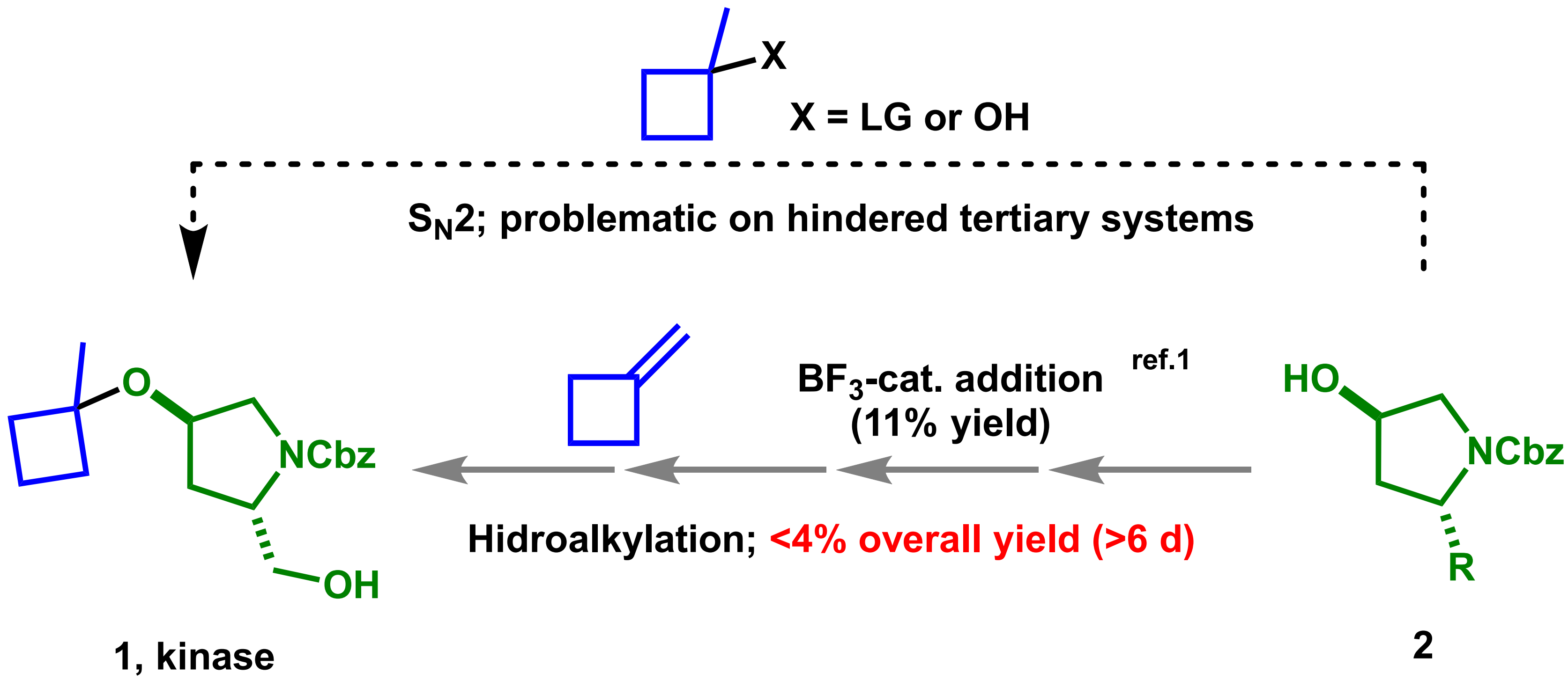
Previous ether synthesis

William ether synthesis[ref.1]

Hydroalkylation

1. Williamson, W., *Justus Liebigs Ann. Chem.*, **1851**, *77*, 37.

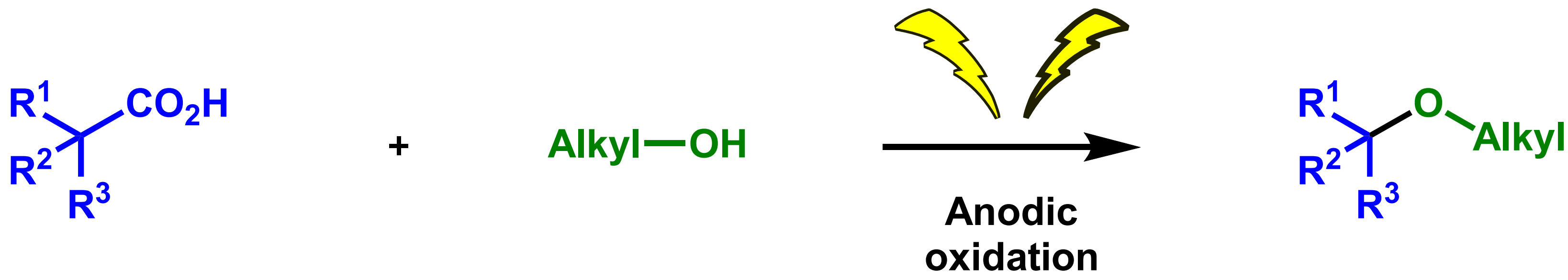
Pathways to hinderd dialkyl ethers



1. Abraham, S.; Bhagwat, S. S.; Hadd, M. J.; Holladay, M. W.; Liu, G.; Milanov, Z. V.; Patel, H. K.; Setti, E.; Sindac, J. A. WO2011088045, **2011**, A1.

Previous decarboxylation etherications

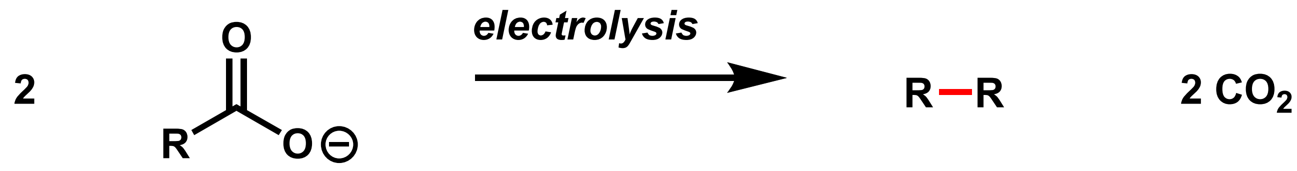
Electrochemistry

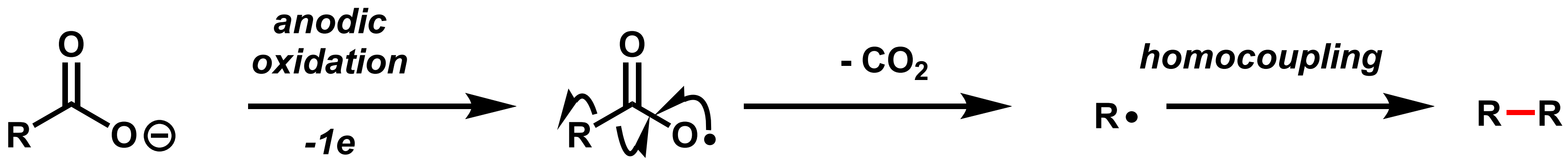


Photochemistry

Alkyl NHPI esters | Phenols | Alkyl aryl ethers

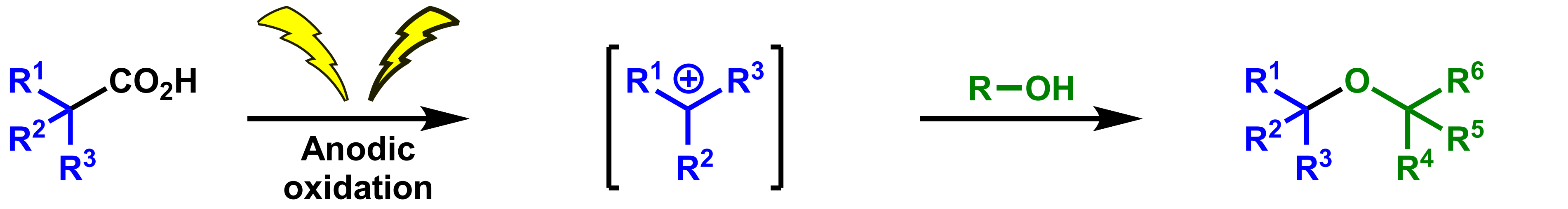
Kolbe Electrolysis





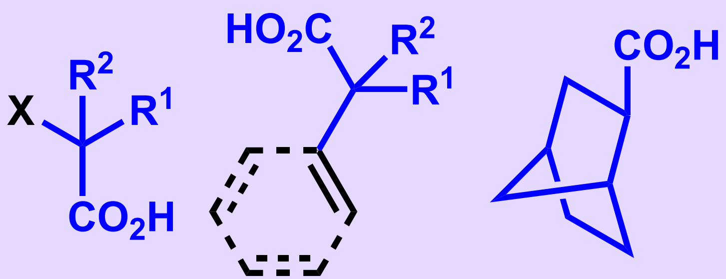
Kolbe, H., *J. Prakt. Chem.,* **1847**, *41*, 137.

Hofer-Moest reaction



Alkyl acid	Carbocation	Hindered ethers
• Ubiquitous	• Reactive	• Difficult to acsess
• Inexpensive	• Non-acidic generation	• Medicinally important

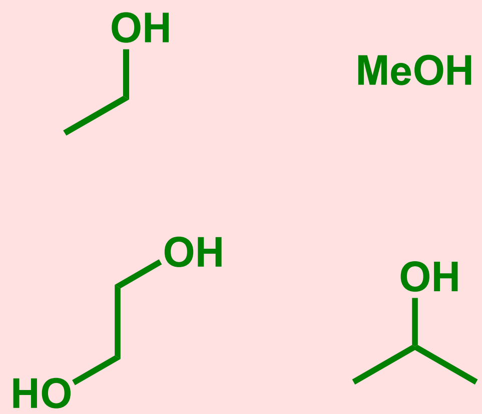
Typical acid scope



X = N, O, Si

Alkyl-CO_2H (Me, ^{n}Ph, etc.)

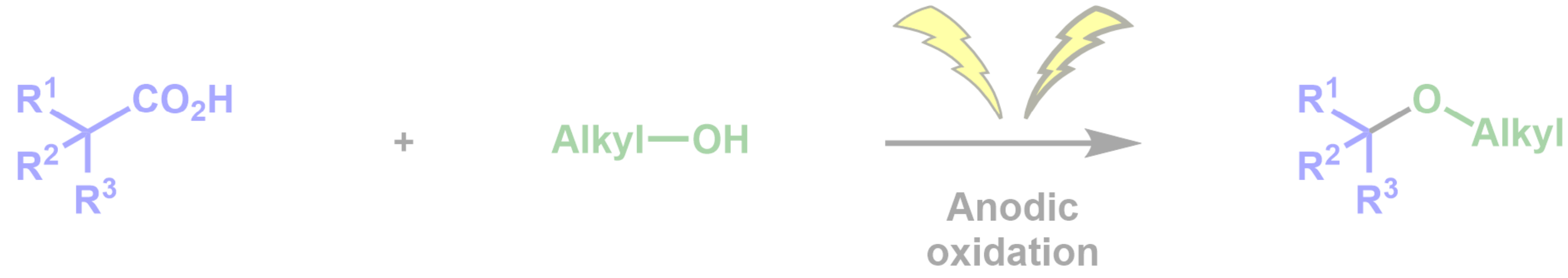
Alcohol scope (solvent)



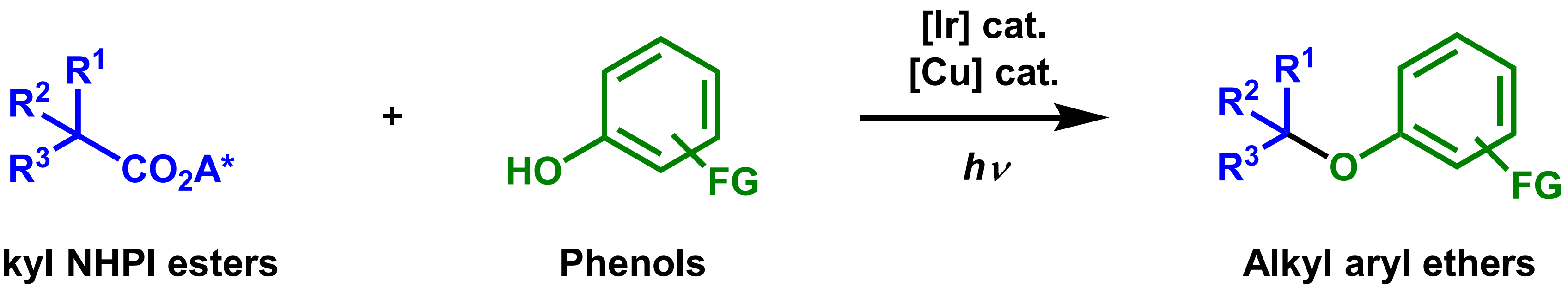
Hofer, H.; Moest, M. *Ann. Chem.*, **1902**, *323*, 28.

Previous decarboxylation etherications

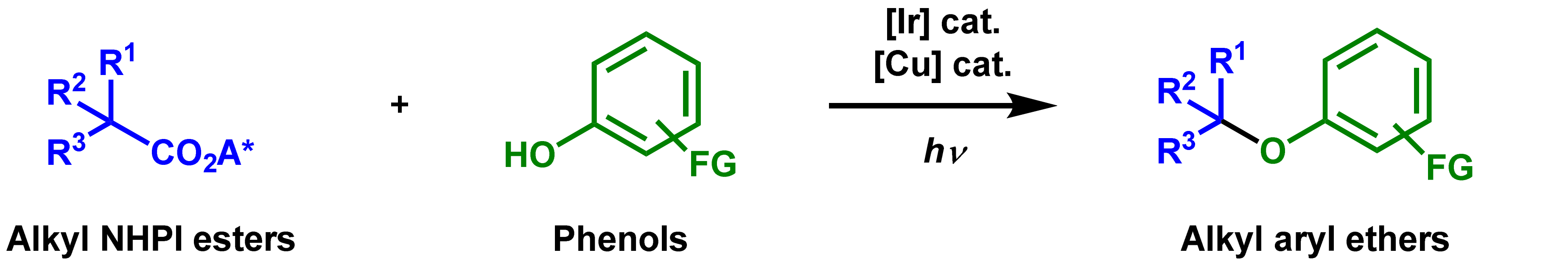
Electrochemistry

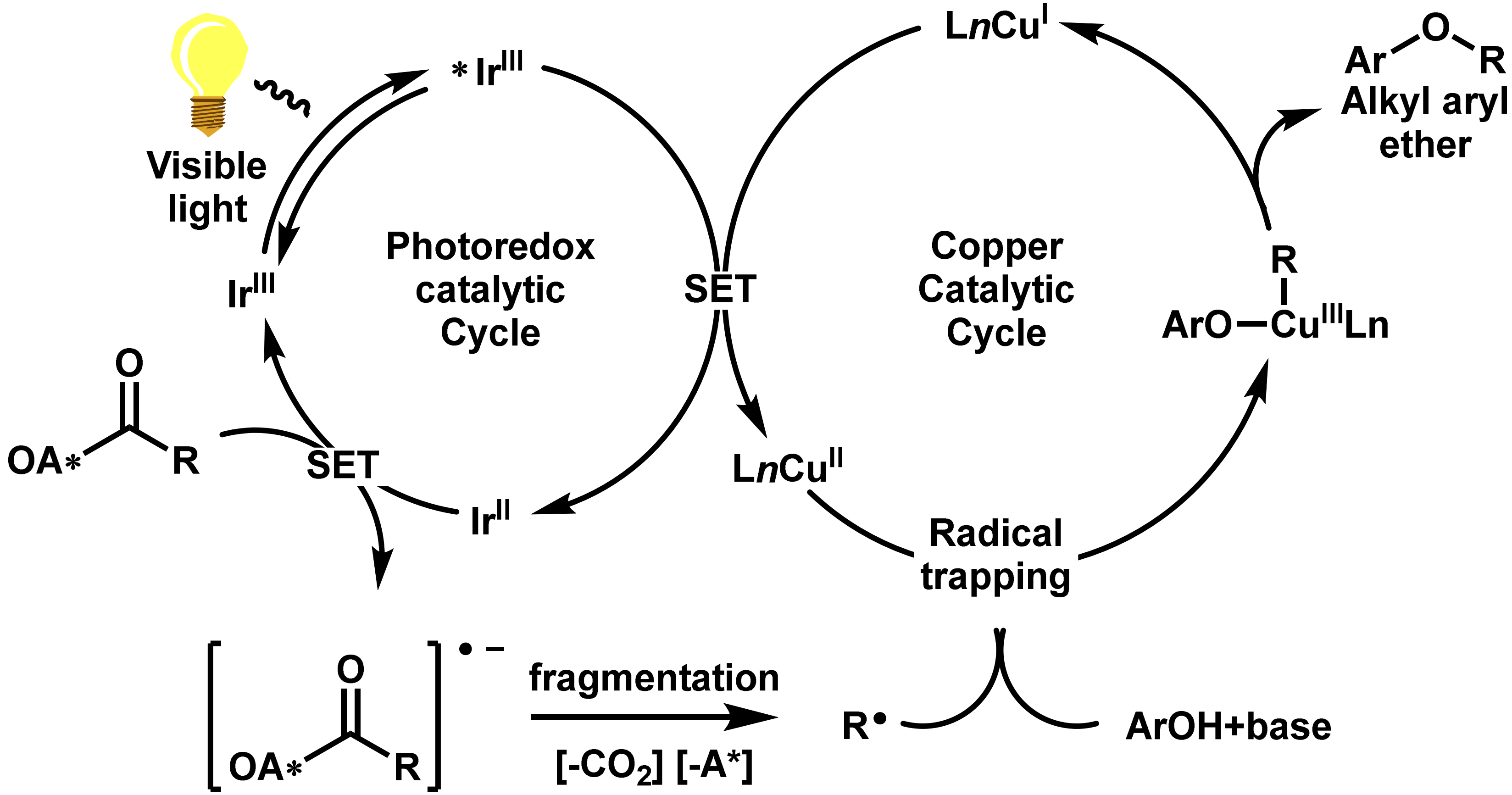


Photochemistry



Photochemistry





Mao, R.; Balon, J.; Hu, X. *Angew. Chem. Int. Ed.* **2018**, *57*, 13624.

Prof. Phil S. Baran and Prof. Hirohisa Ohmiya

Phil S. Baran

Education
Ph.D. (Chemistry), Scripps Research, 2001
B.S. (Chemistry), New York University, 1997

Professional Experience
2006-2008 Associate Professor (with tenure), Chemistry, Scripps Research
2003-2006 Assistant Professor, Chemistry, Scripps Research
2001-2003 NIH Postdoctoral Fellow with Dr. E. J. Corey, Harvard University

Hirohisa Ohmiya

Education
2007 Dr degree in Engineering, Kyoto University (Prof. Koichiro Oshima)
2004 M.S., Kyoto Pharmaceutical University (Prof. Jun'ichi Uenishi)
2002 B.S., Kyoto Pharmaceutical University

Professional Experience
2019 JST PRESTO Researcher
2017 Professor, Kanazawa University
2010 Associate Professor, Hokkaido University (Prof. Masaya Sawamura)
2008 Assistant Professor, Hokkaido University (Prof. Masaya Sawamura)
2007 Postdoctoral fellow, Massachusetts Institute of Technology（Prof. Timothy F. Jamison）

Contents

1. **Introductuion**

2. **Hindered dialkyl ether synthesis with electrogenerated carbocations**
   (ref.1: *Nature*, **2019**, *573*, 398.)

3. **Organophotoredox-Catalyzed Decarboxylative C(sp3)−O Bond Formation**
   (ref.2: *J. Am. Chem. Soc.,* **2020**, *142*, 1211.)

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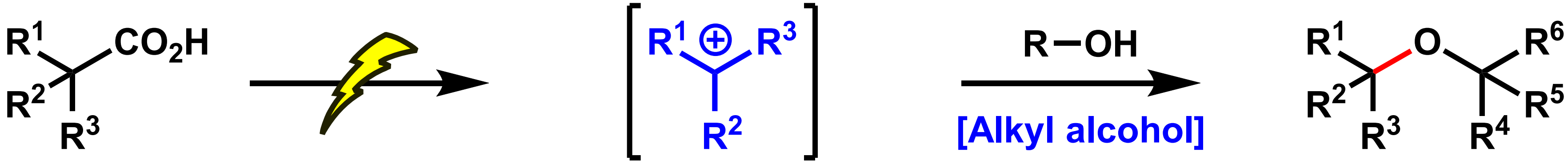
Direct decarboxylative etherification



[Alkyl acid]

▪Ubiquious
▪Inexpensive

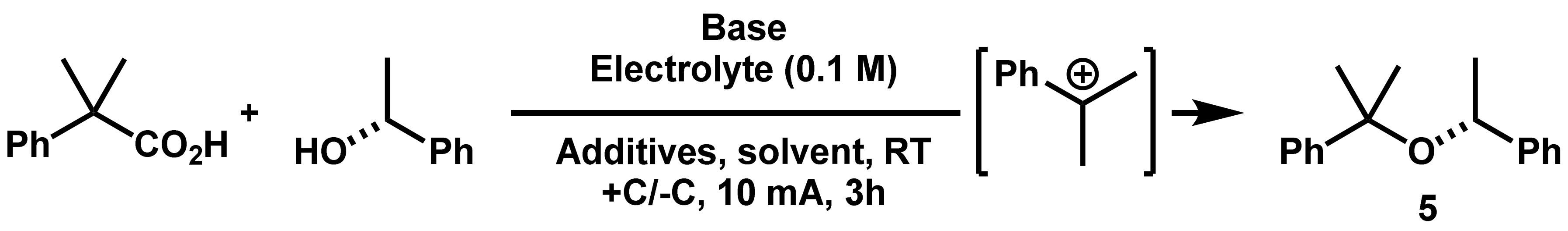
[Carbocation]

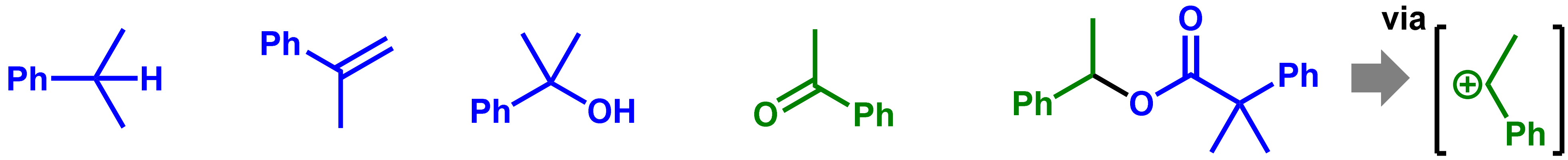
• Reactive
• Non-acidic generation

[Hindered ethers]

• Difficult to acsess
• Medicinally important

Reaction optimization



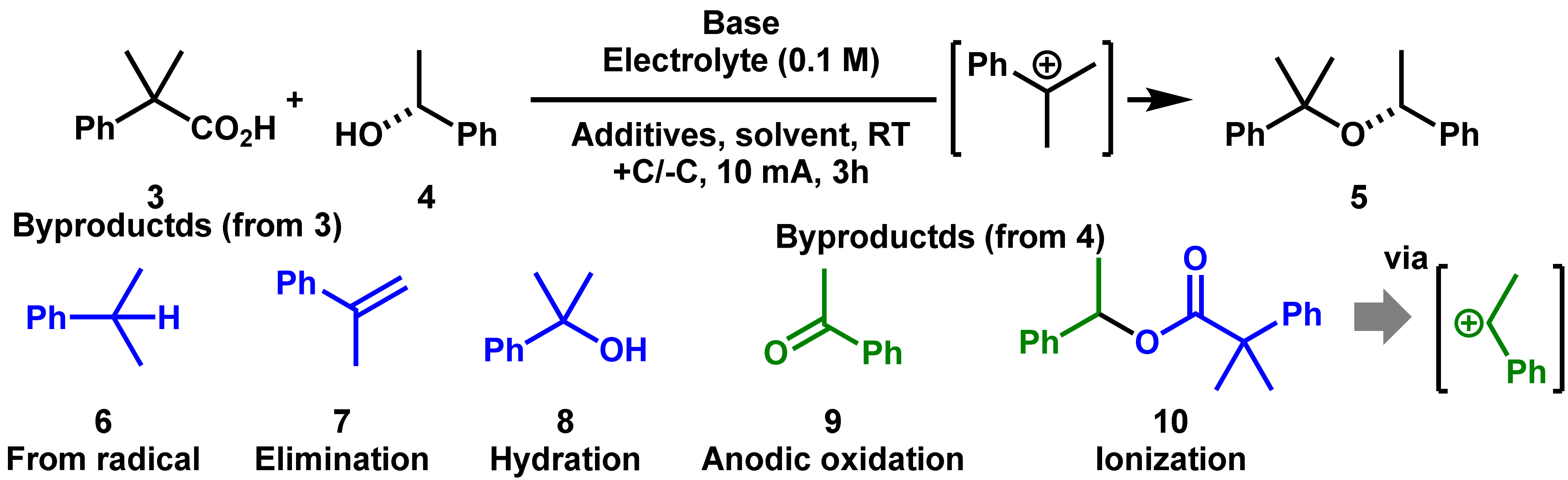


6 From radical | 7 Elimination | 8 Hydration | 9 Anodic oxidation | 10 Ionization

Entry	Conditions	Yield (%) 5	6	7	8	9	10
1	Et_3N, $^nBu_4NClO_4$, DMF or acetone	<1	-	-	<1	<1	-
2	K_2CO_3, $^nBu_4NClO_4$, DMF	<1	15	<1	40	<1	-
3	2,4,6-collidine, $^nBu_4NPF_6$, DMF	6	3	28	14	<1	-
4	2,4,6-collidine, $^nBu_4NPF_6$, CH_2Cl_2	40	4	-	14	6	-
5	2,4,6-collidine, $^nBu_4NPF_6$, 3Å MS, CH_2Cl_2	43	5	2	<1	3	-
6	$AgPF_6$, 2,4,6-collidine, $^nBu_4NPF_6$, 3Å MS, CH_2Cl_2	79 (77)	-	-	-	7	-

(continued to the next page)

Reaction optimization

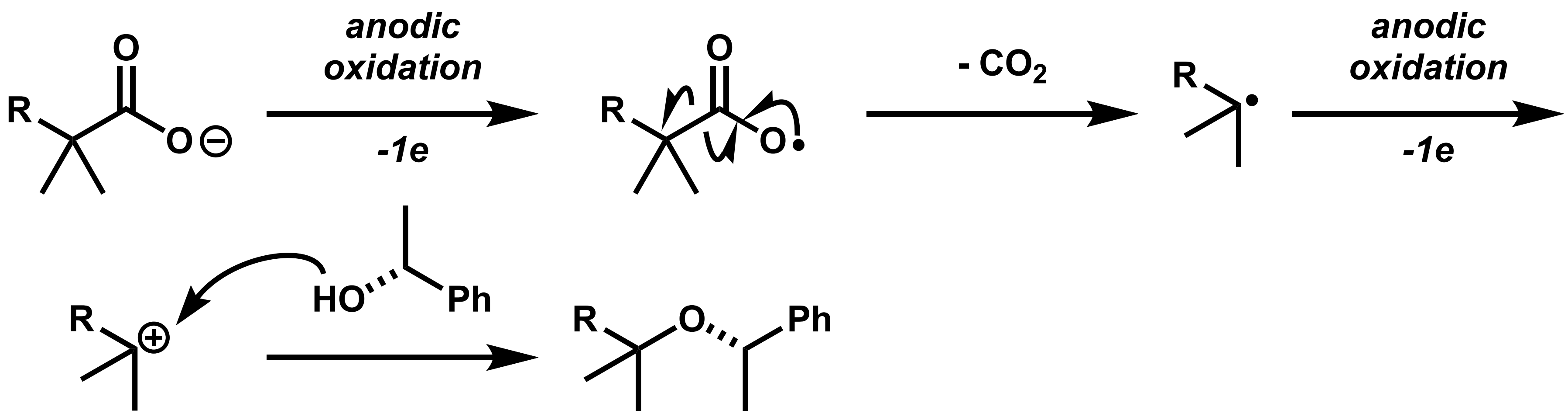


(continued)

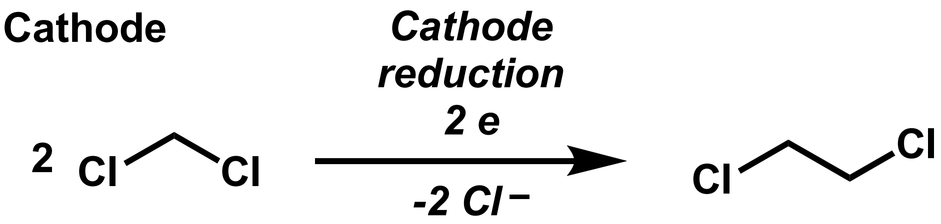
Entry	Conditions	Yield (%)	5	6	7	8	9	10
7	AS in entry 6, 1 equiv. alcohol		34	<1	<1	<1	6	<1
8	AgPF6, nBu_4^NPF, 3Å MS, CH_2Cl_2		-	<1	<1	-	22	54

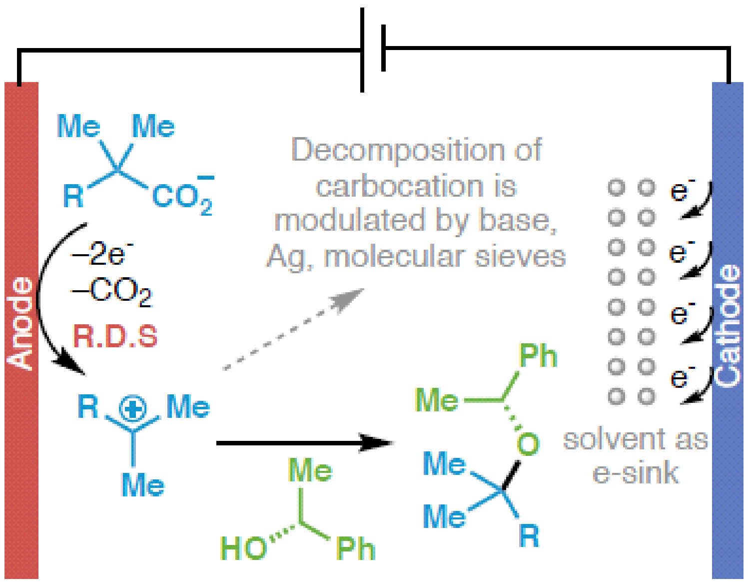
Reaction mechanism

Anode



Cathode

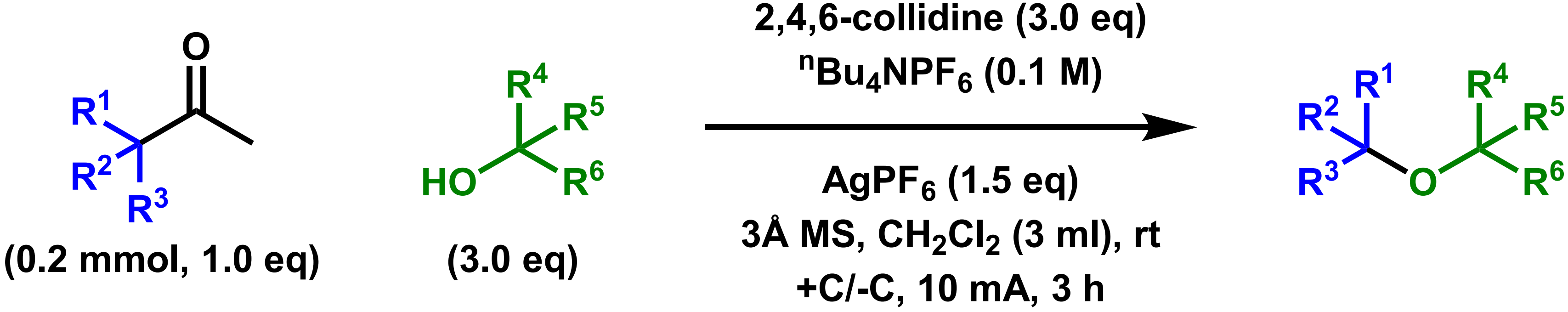


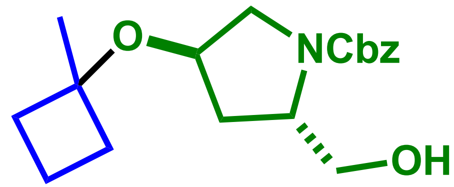


1. the rate-limiting oxidation of a carboxylate on the anode to generate a carbocation

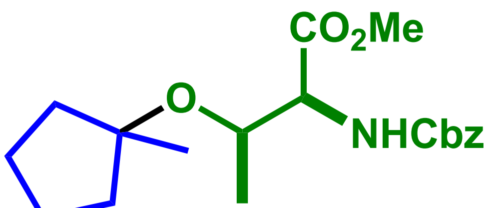
2. nucleophilic attack by an alcohol to afford the ether product

Substrate scope (applications)

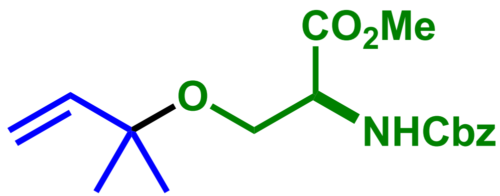




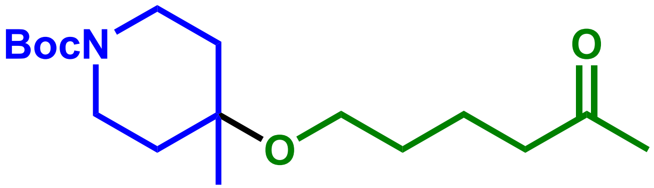
Current route: 2 steps
(51%, 15 h)
Previous route: 3 steps
(<4% over all, >6 d)



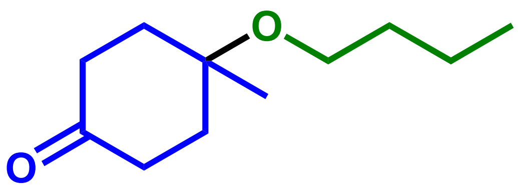
1 steps
(32%, 3 h)
5 steps
(31% over all, 2.5 d)



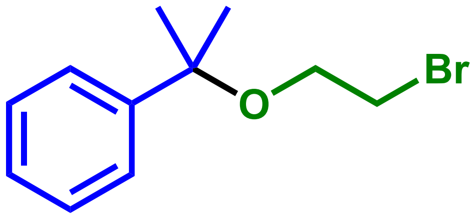
1 steps
(40%, 3 h)
7 steps
(37% over all, >3 d)



1 steps
(21%, 3 h)
6 steps
(24% over all, 2 d)

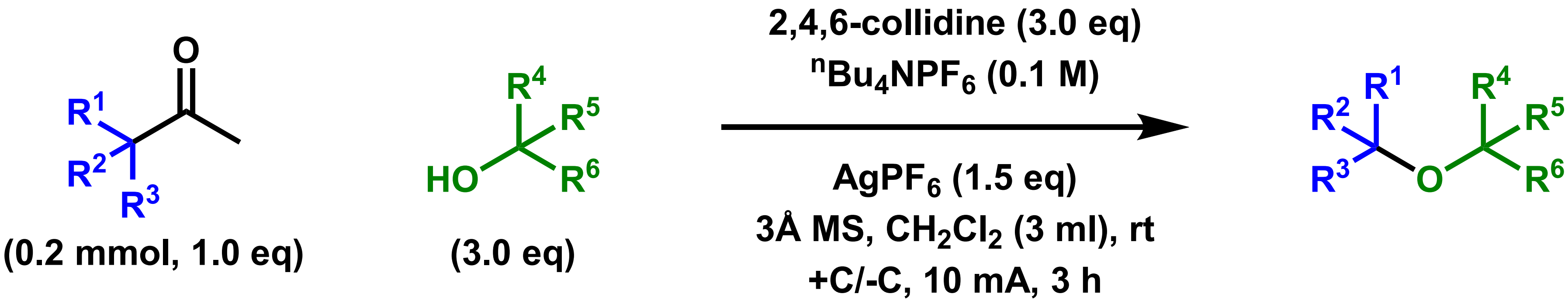


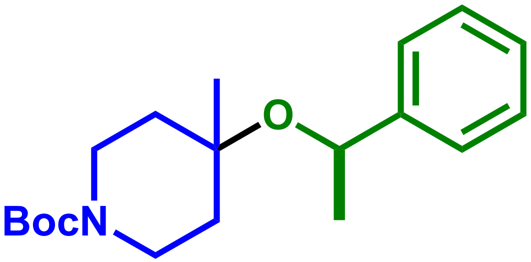
1 steps
(42%, 3 h)
4 steps
(47% over all, >2 d)



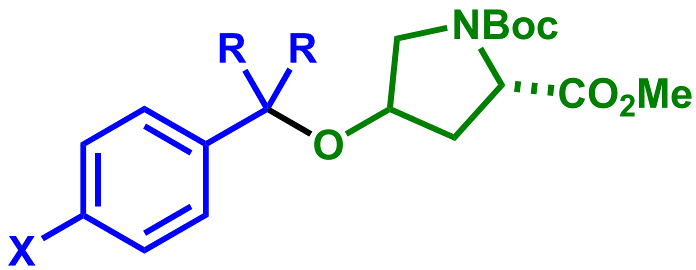
1 steps
(81%, 3 h)
2 steps
(<2% over all, >5 d)

Substrate scope (carboxylic acids)

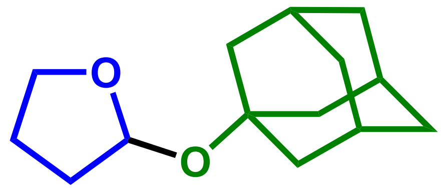




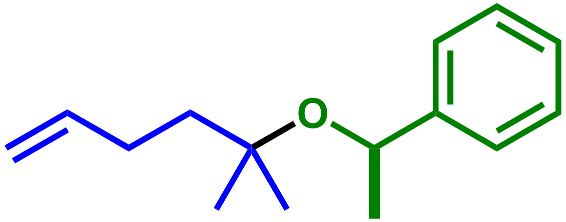
45%
95% ee



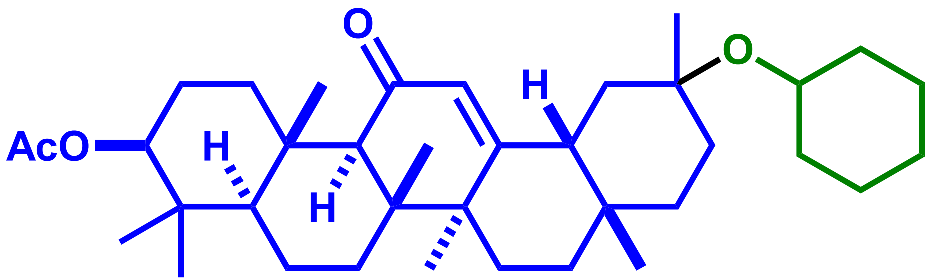
R = R = $-(CH_2)_5-$, X = F, 46%
R = R = Me, X = BPin, 54%



58%

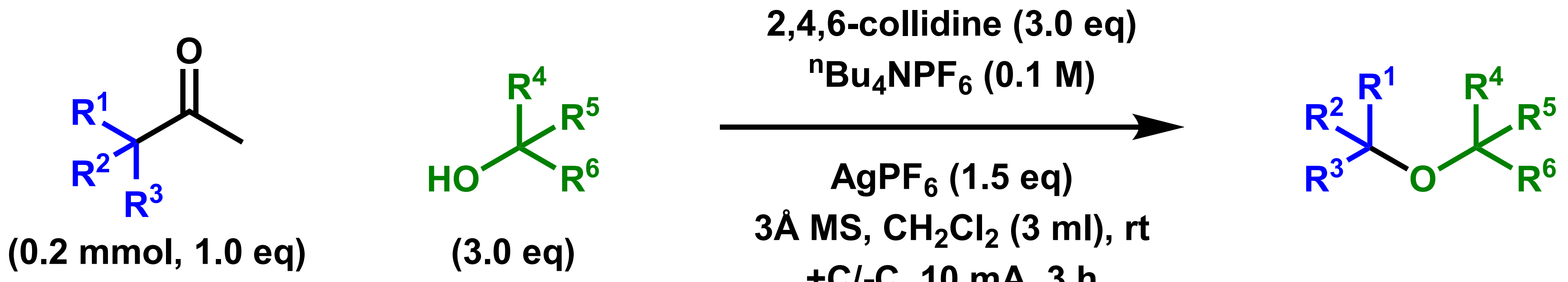


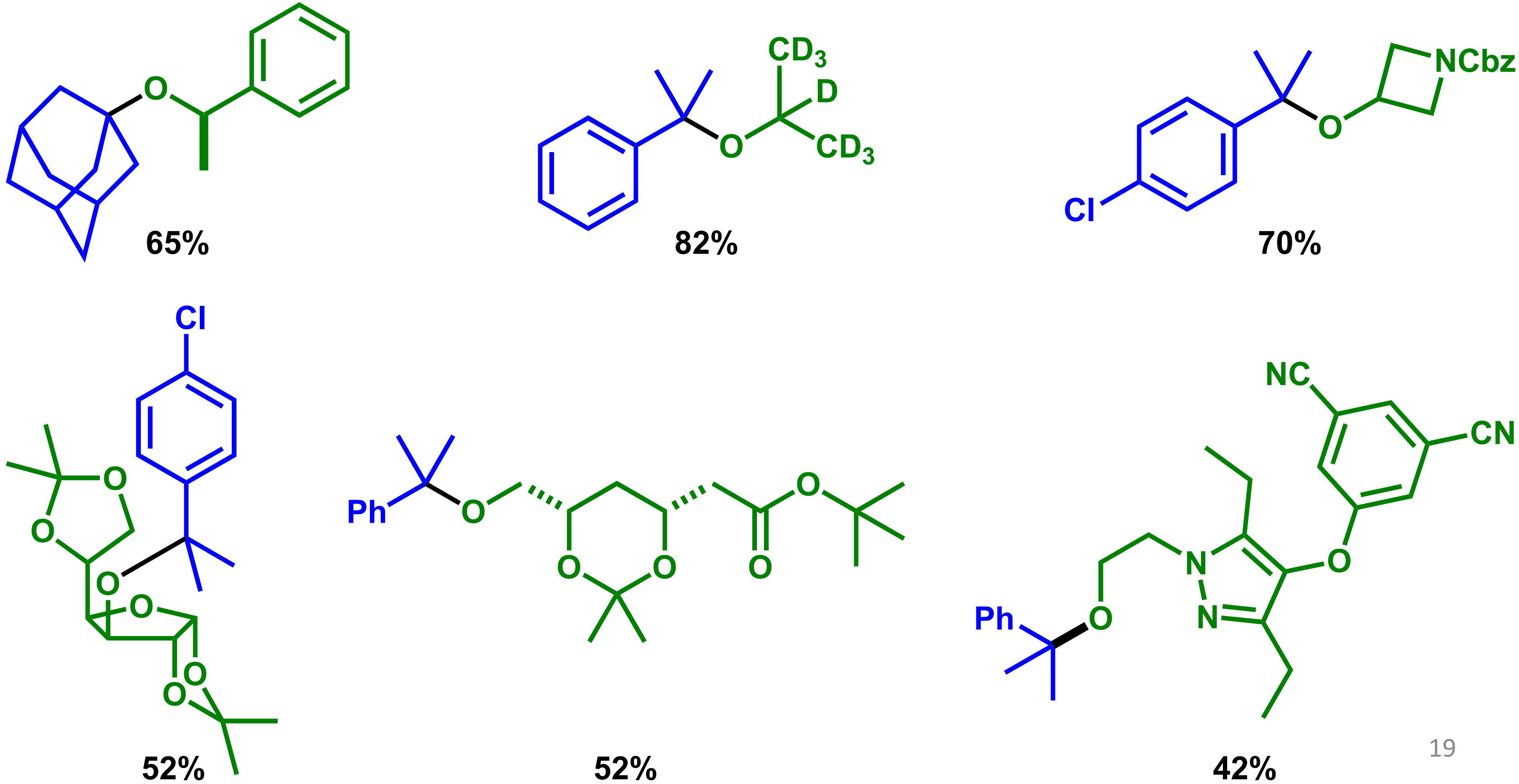
42%



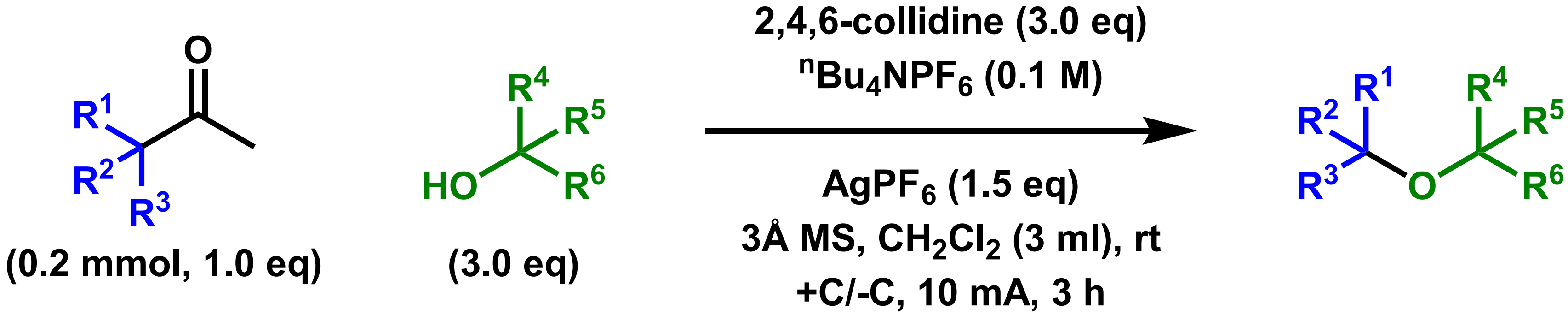
35%, dr = 1:1

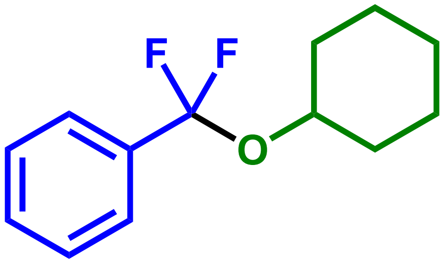
Substrate scope (alcohol)



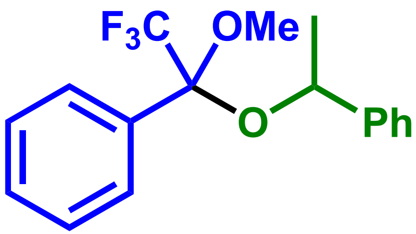


Substrate scope (fluoride, ether)

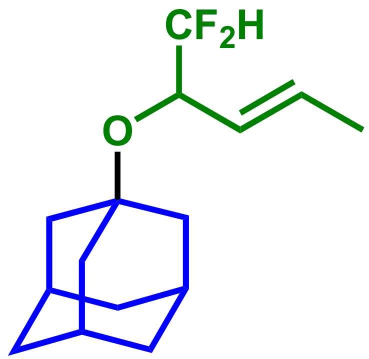




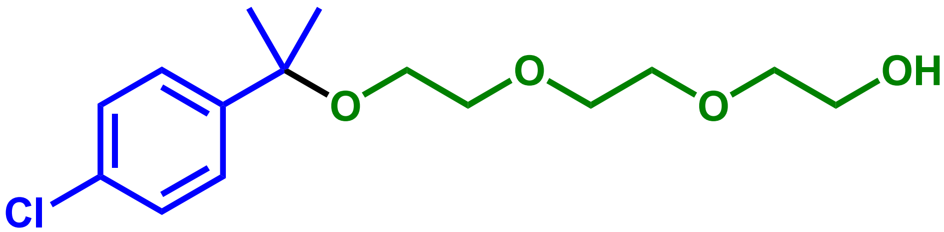
46%



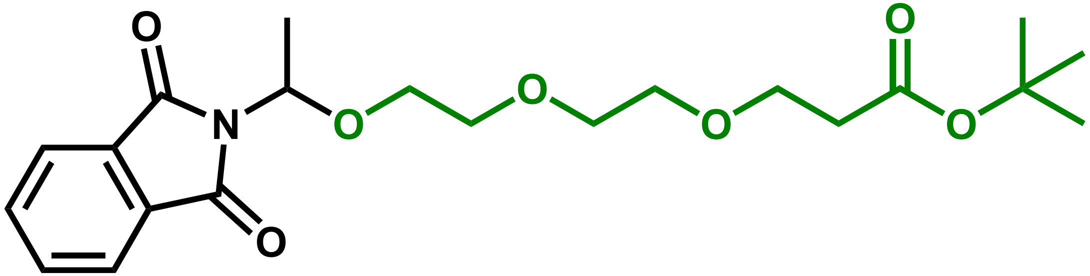
88%, dr = 1:1



51%

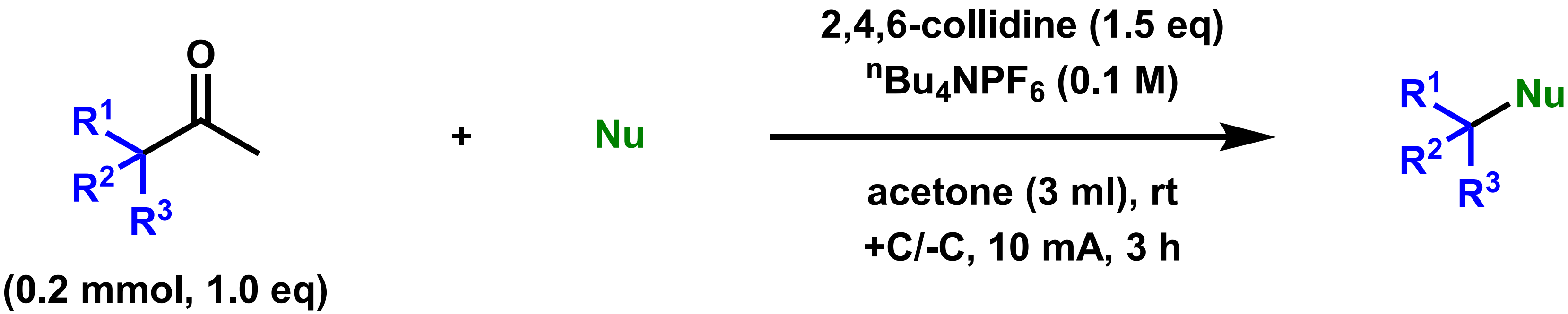


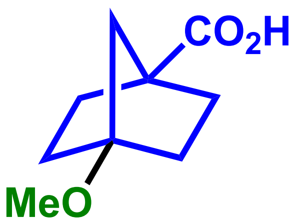
59%



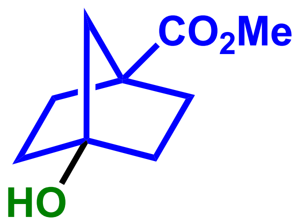
57%

Substrate scope (applications)

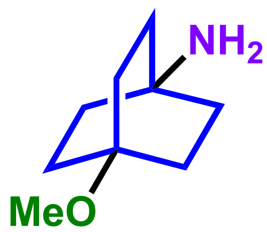




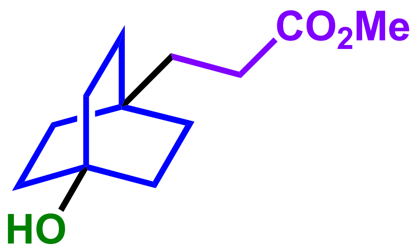
Current route: 2 steps
(56%, 9 h)
Previous route: 7 steps
(21% over all, >4 d)



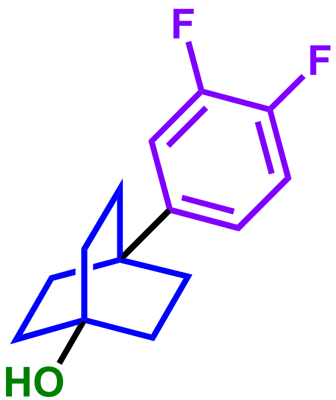
1 steps
(66%, 3 h)
5 steps
(15% over all, >5 d)



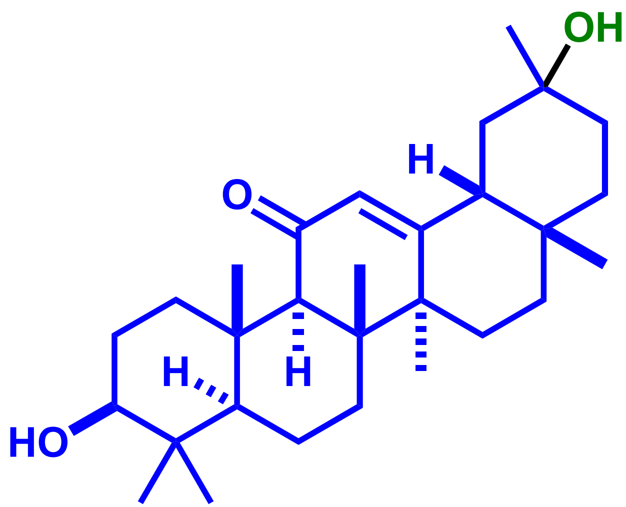
2 steps
(31%, 24 h)
7 steps
(12% over all, 3 d)



2 steps
(22%, 27 h)
14 steps
(5% over all, >9 d)

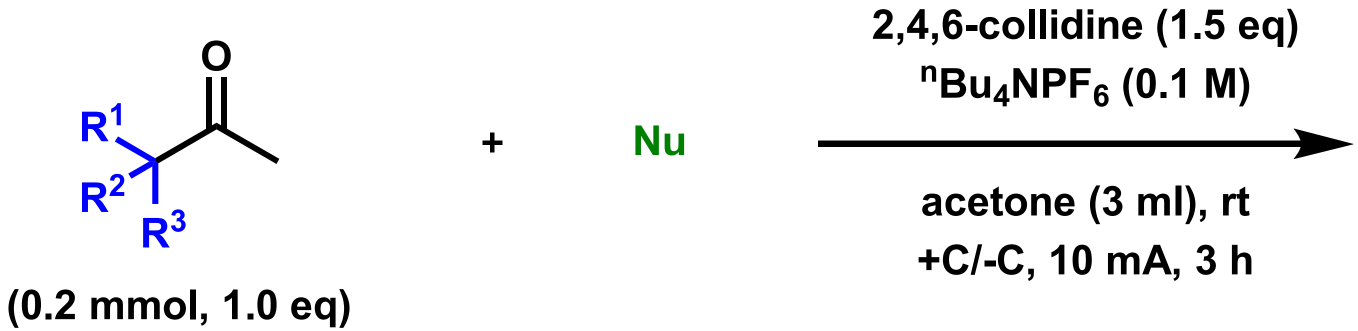


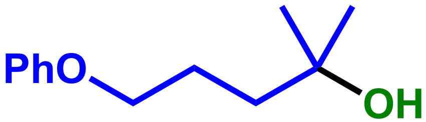
3 steps
(17%, 21 h)
7 steps
(8% over all, 62 h)



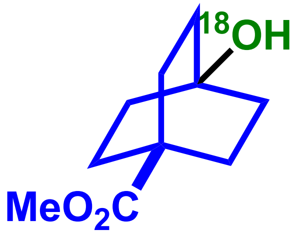
1 steps
(61%, dr = 1.1:1, 3 h)
5 steps
(yield not reported)

Substrate scope

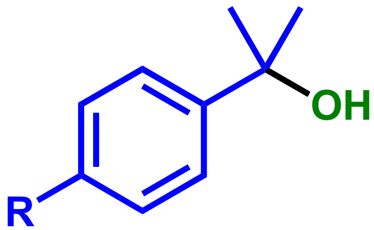




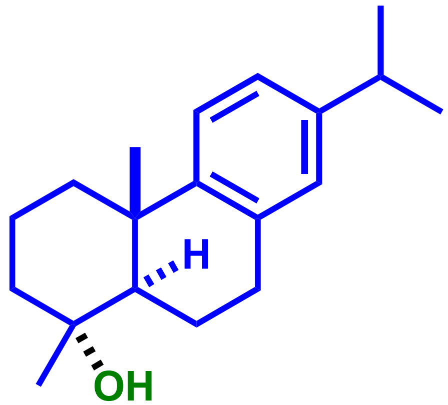
66%



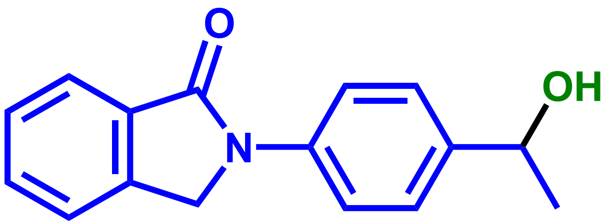
51% yield
(67.1% ^{18}O labelled)



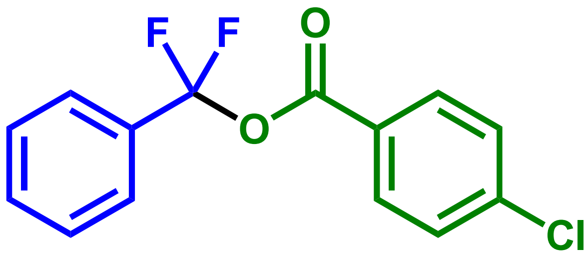
R = Br, 67%
R = Bpin, 55%



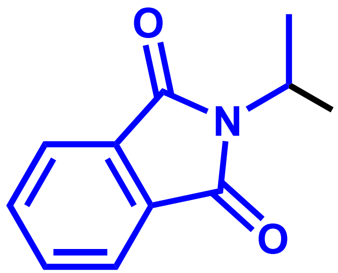
32% (dr = 3:1)
from dehydroabietic acid



40%
from indoprofen



36%



62%

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2. Hindered dialkyl ether synthesis with electrogenerated carbocations
(ref.1: *Nature*, **2019**, *573*, 398.)

3. **Organophotoredox-Catalyzed Decarboxylative C(sp3)−O Bond Formation**
(ref.2: *J. Am. Chem. Soc.,* **2020**, *142*, 1211.)

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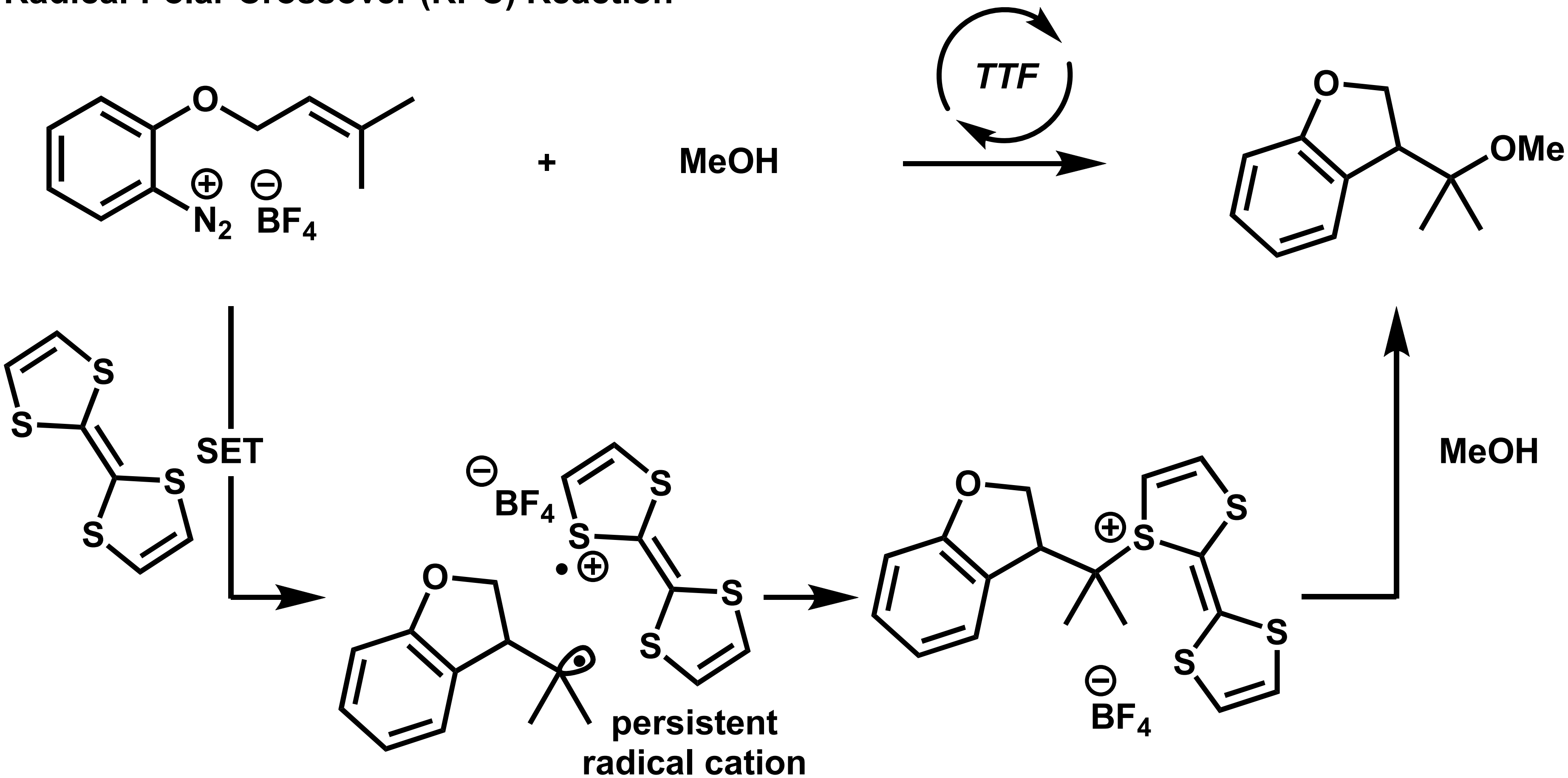
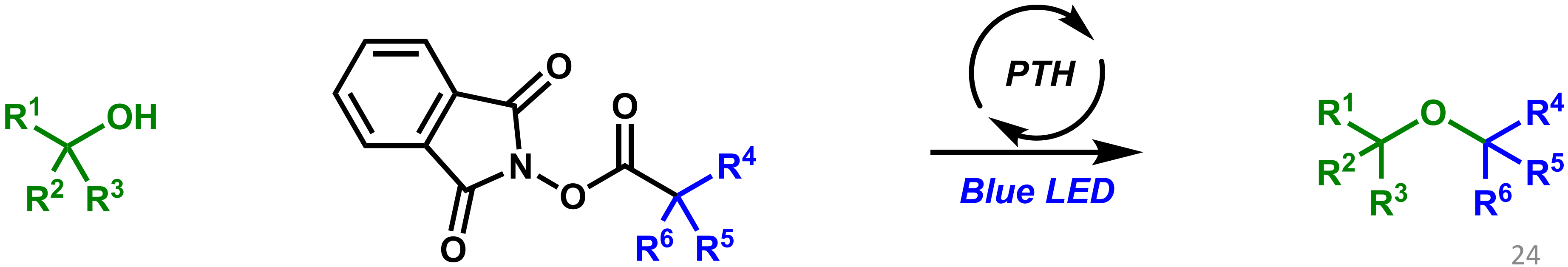
1. Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; Bel, M. D.; Gallego, G. M.; Spangler, J. E.; Starr, J.; Yang, S.; Blackmond, D. G.; Baran, P. S., *Nature*, **2019**, *573*, 398.
2. Shibutani, S.;Kodo, T.; Takeda, M.; Nagao, K.; Tokunaga, N.; Sasaki, Y.; Ohmiya, H., *J. Am. Chem. Soc.*, **2020**, *142*, 1211.

Previous research

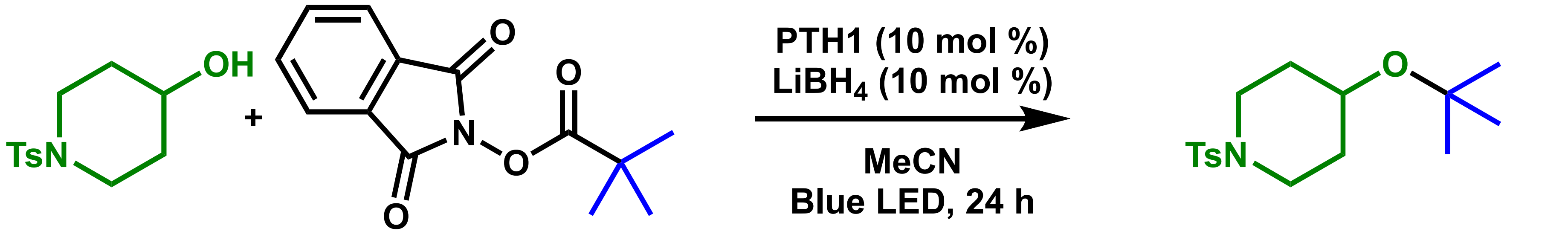
Radical-Polar Crossover (RPC) Reaction

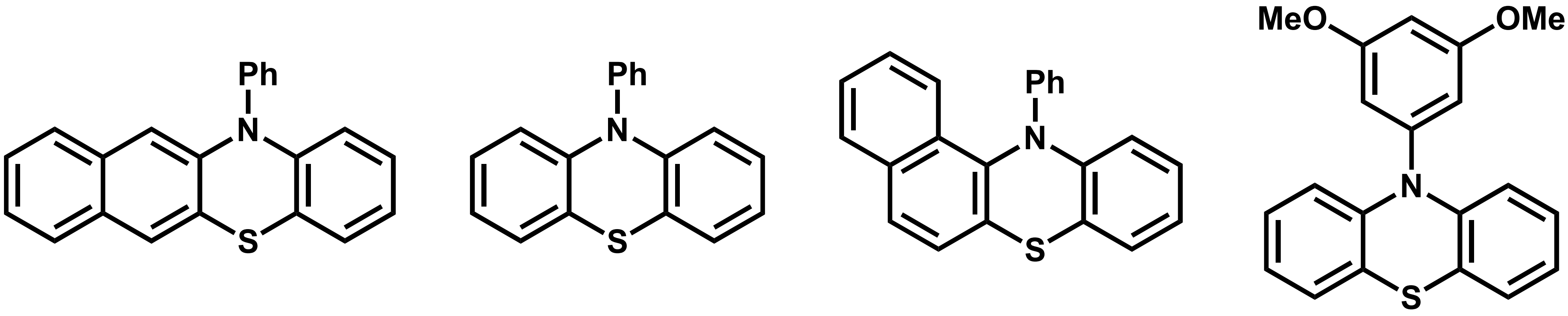


Organophotoredox-Catalyzed C(sp^3)-O Bond Formation



Screening of Catalysts and Bases (1)



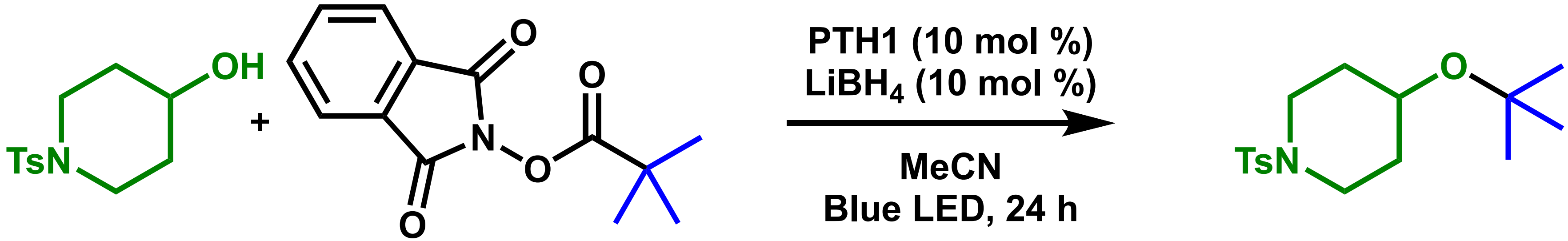


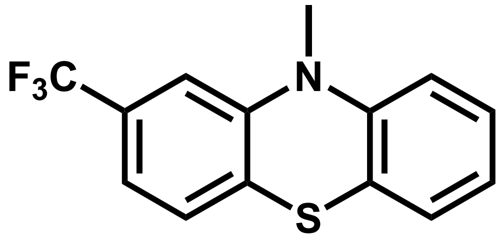
PTH1 PTH2 PTH3 PTH4

Entry	Change from standard condition	Yield (%)
1	none	81
2	PTH2 instead of PTH1	26
3	PTH3 instead of PTH1	54
4	PTH4 instead of PTH1	40

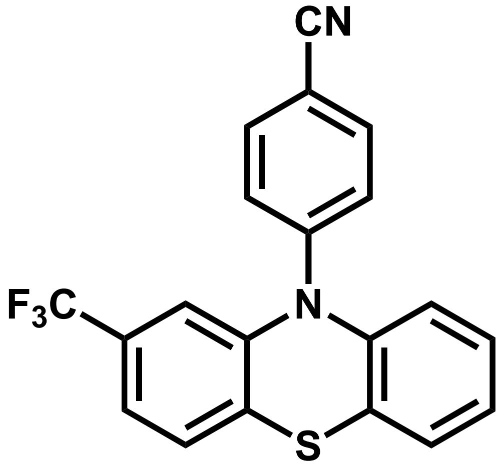
(continued to the next page)

Screening of Catalysts and Bases (2)

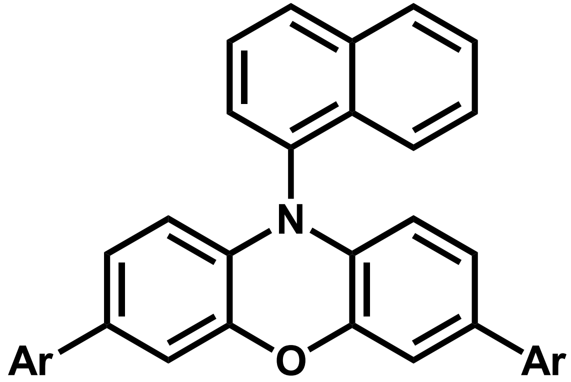




PTH5



PTH6



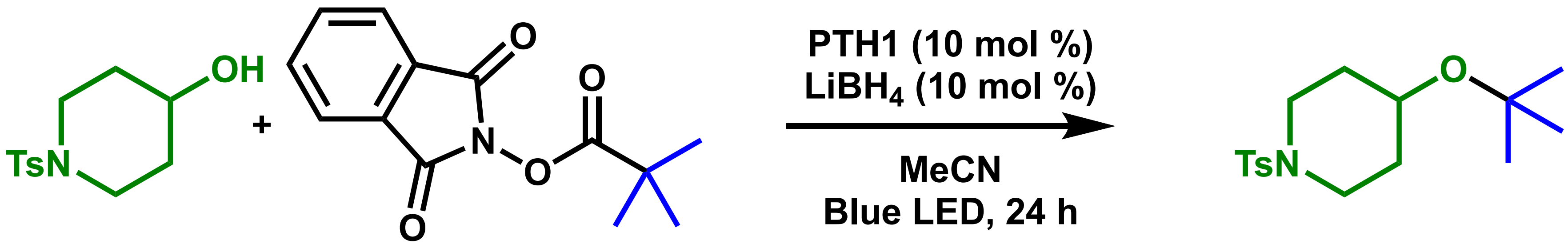
Ar = 4-biphenyl
POX1

(continued)

Entry	Change from standard condition	Yield (%)
5	PTH5 instead of PTH1	86
6	PTH6 instead of PTH1	19
7	POX1 instead of PTH1	40

(continued to the next page)

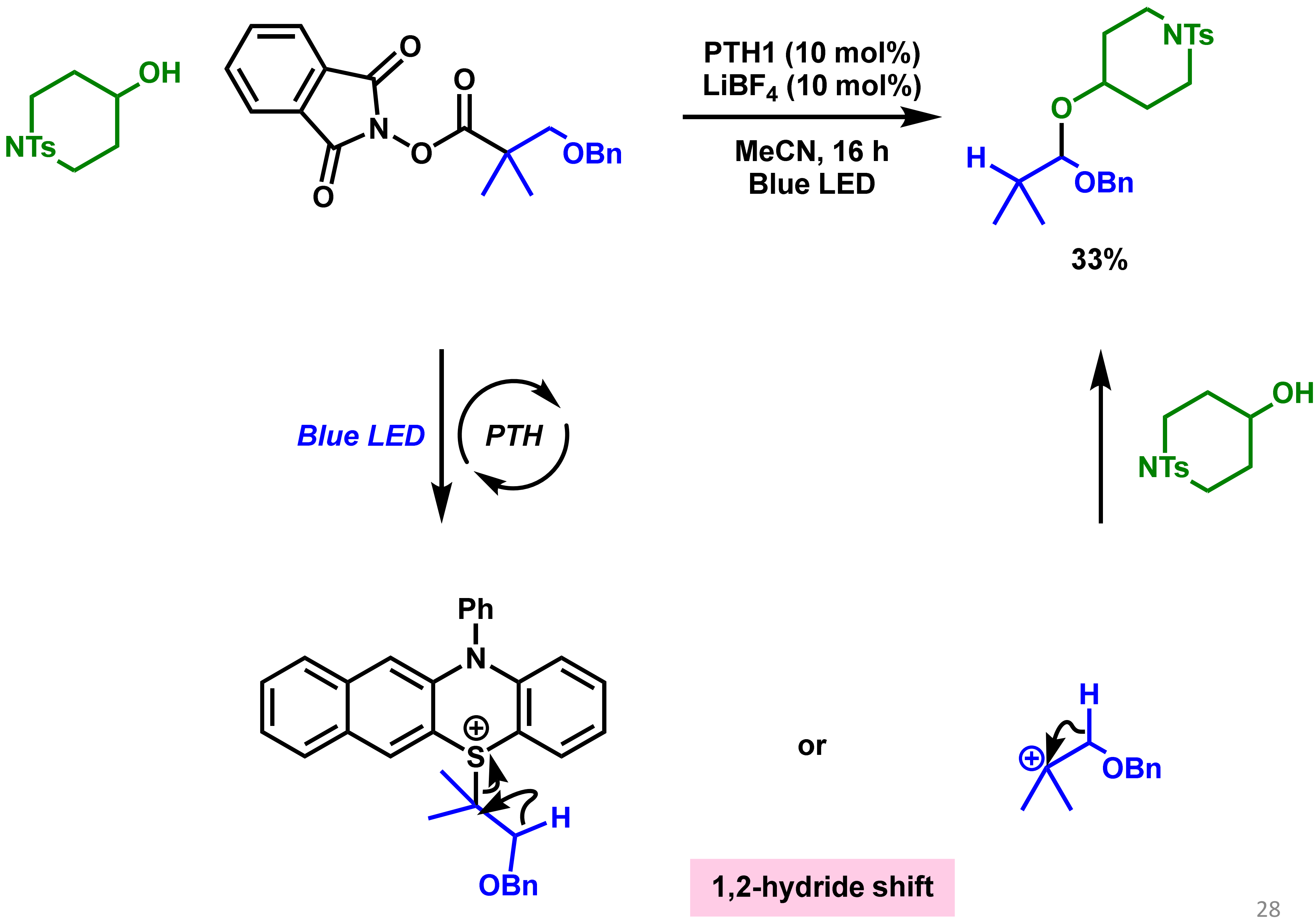
Screening of Catalysts and Bases (3)



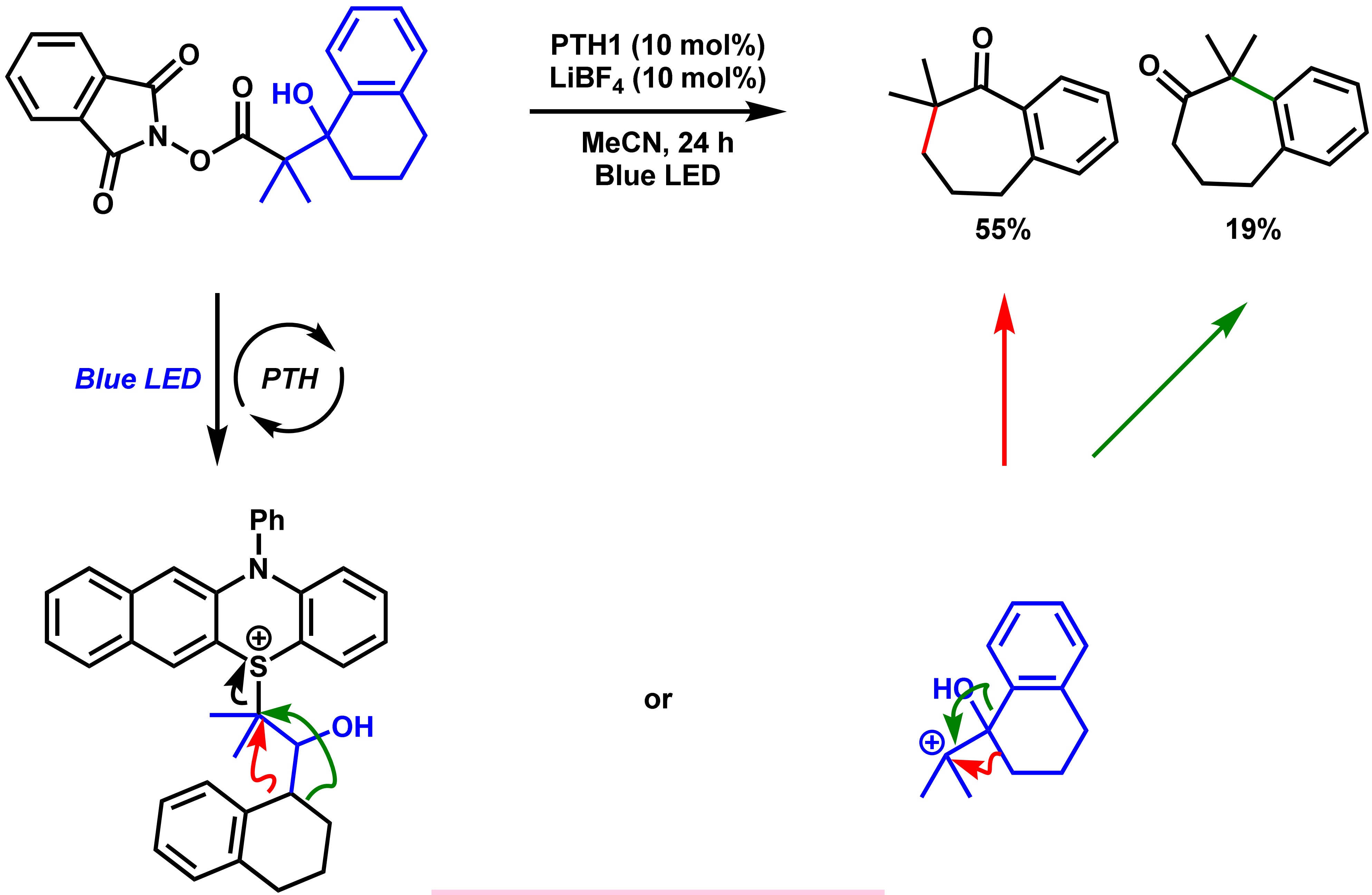
(continued)

Entry	Change from standard condition	Yield (%)
8	$Ir(ppy)_3$ (2 mol%) instead of PTH1	5
9	$Ru(bpy)_3(PF_6)_2$ (2 mol%) instead of PTH1 and $LiBF_4$	8
10	$Ir[sF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol%) instead of PTH1 and $LiBF_4$	1

Mechanitic Studies (A)

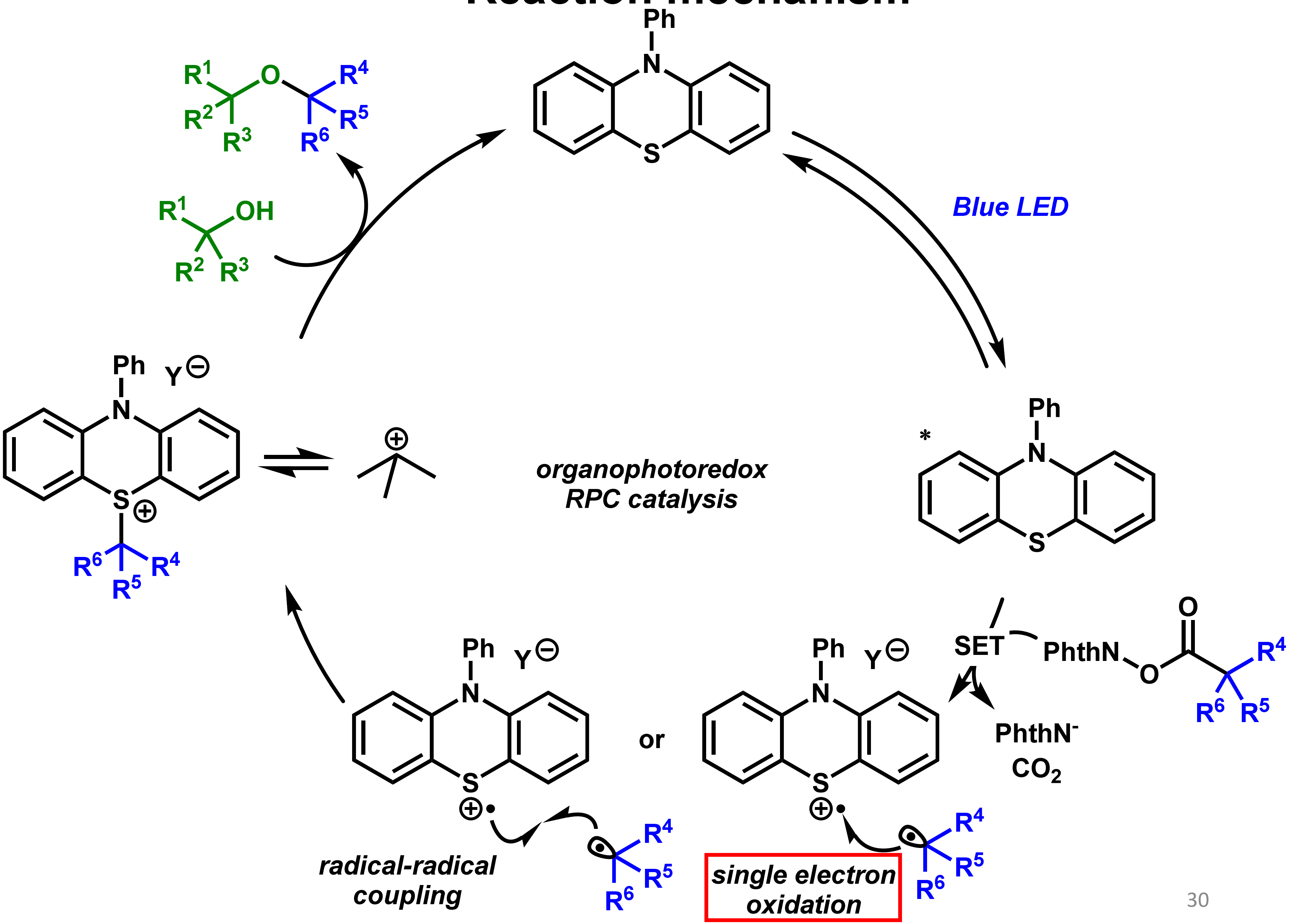


Mechanitic Studies (B)

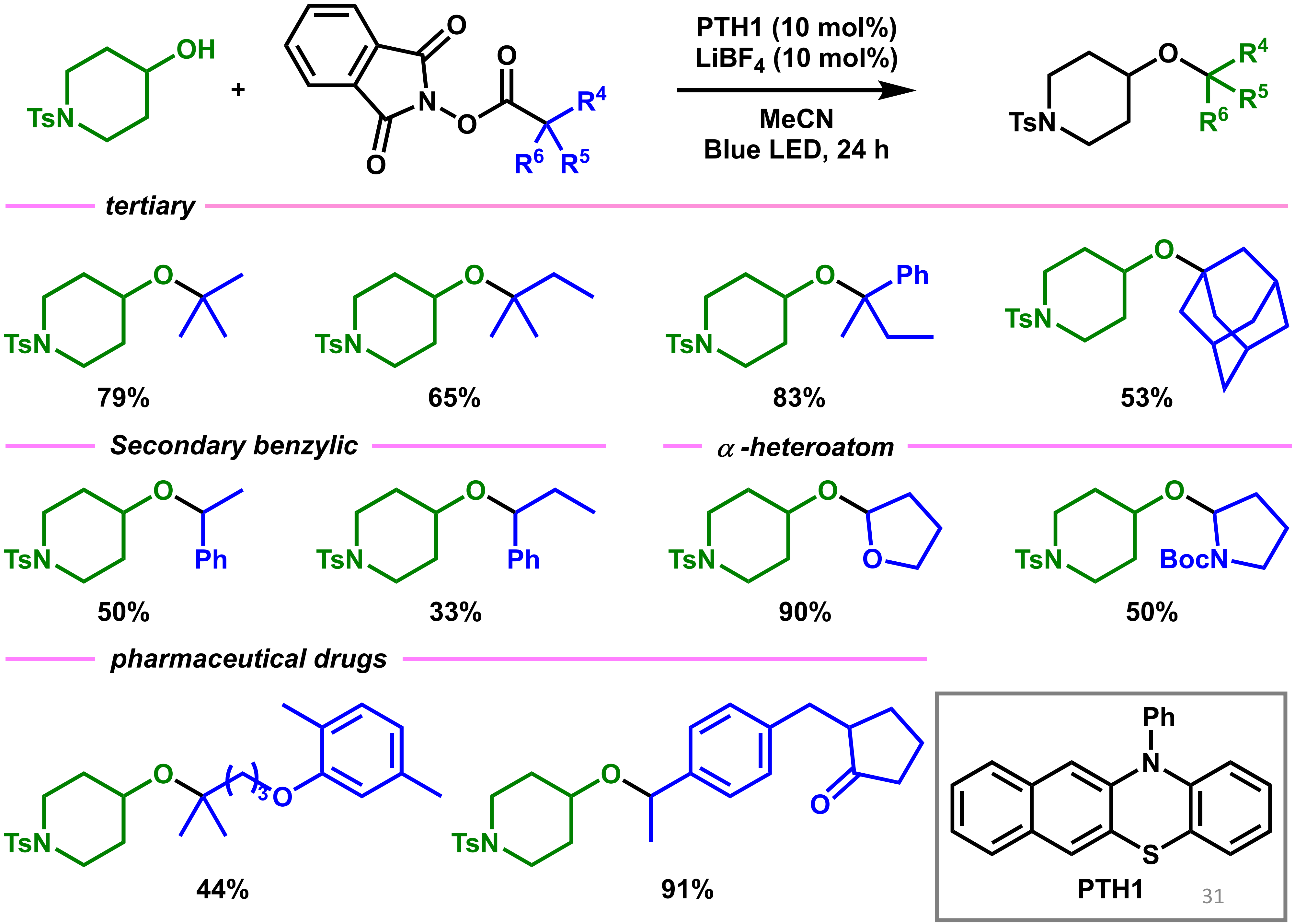


1,2-Carbocation rearrangement

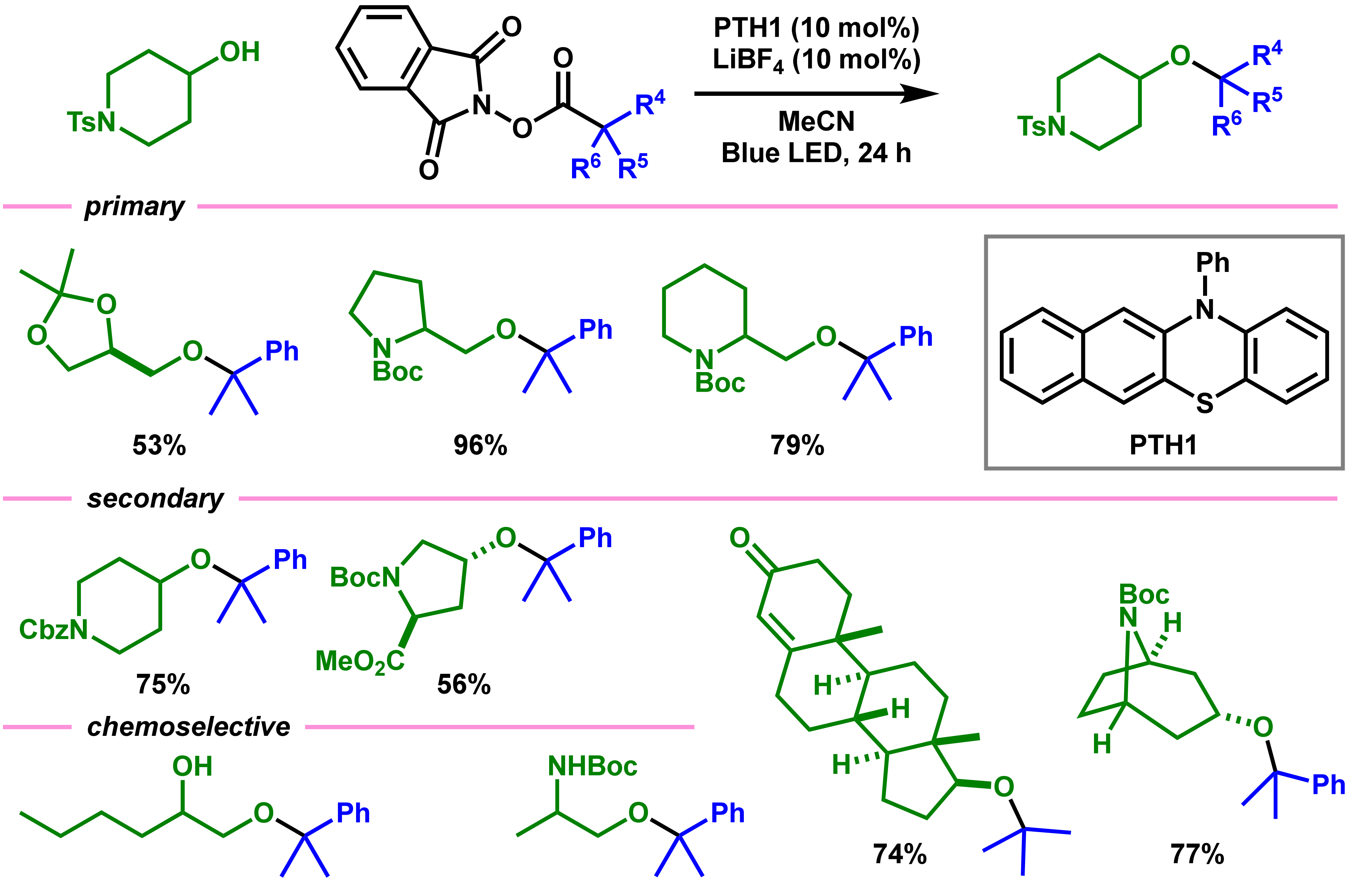
Reaction mechanism



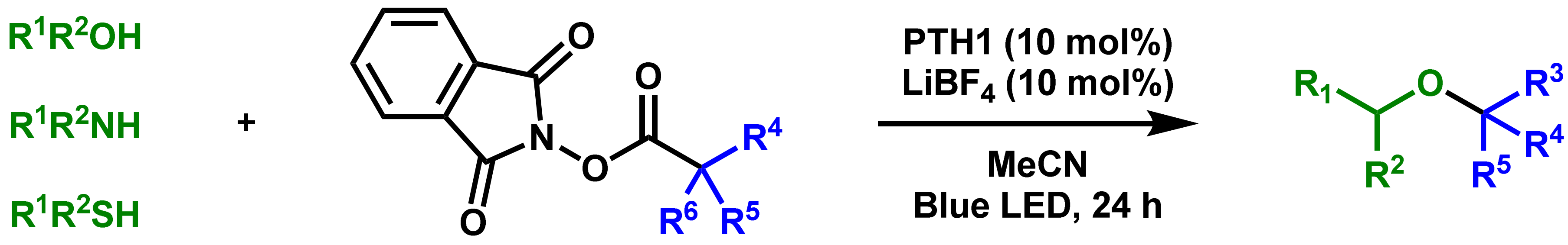
Scope of redox active ester with secondary alcohol

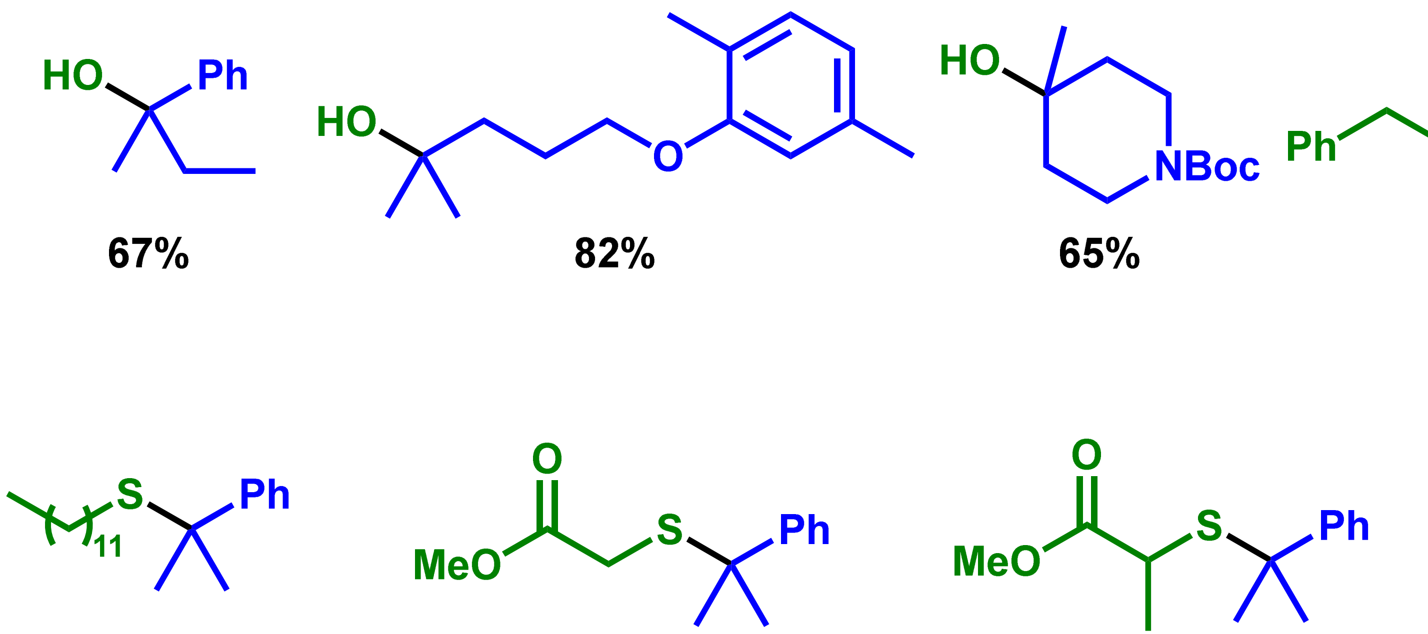


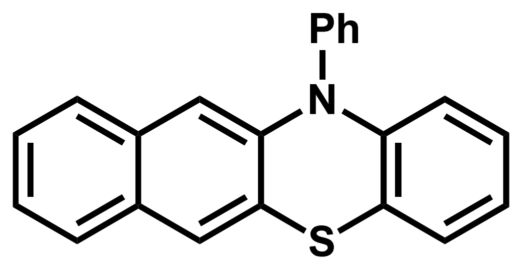
Scope of alcohol with tertiary benzylic redox ester



Scope of water, amine and thiol



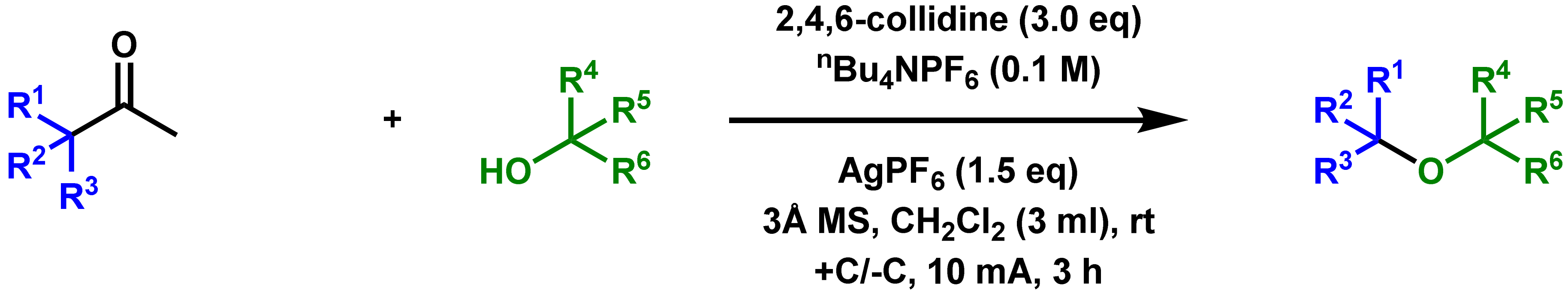




PTH1

Summary

Hindered dialkyl ether synthesis with electrogenerated carbocations



Hindered dialkyl ether synthesis with photoredox catalysis