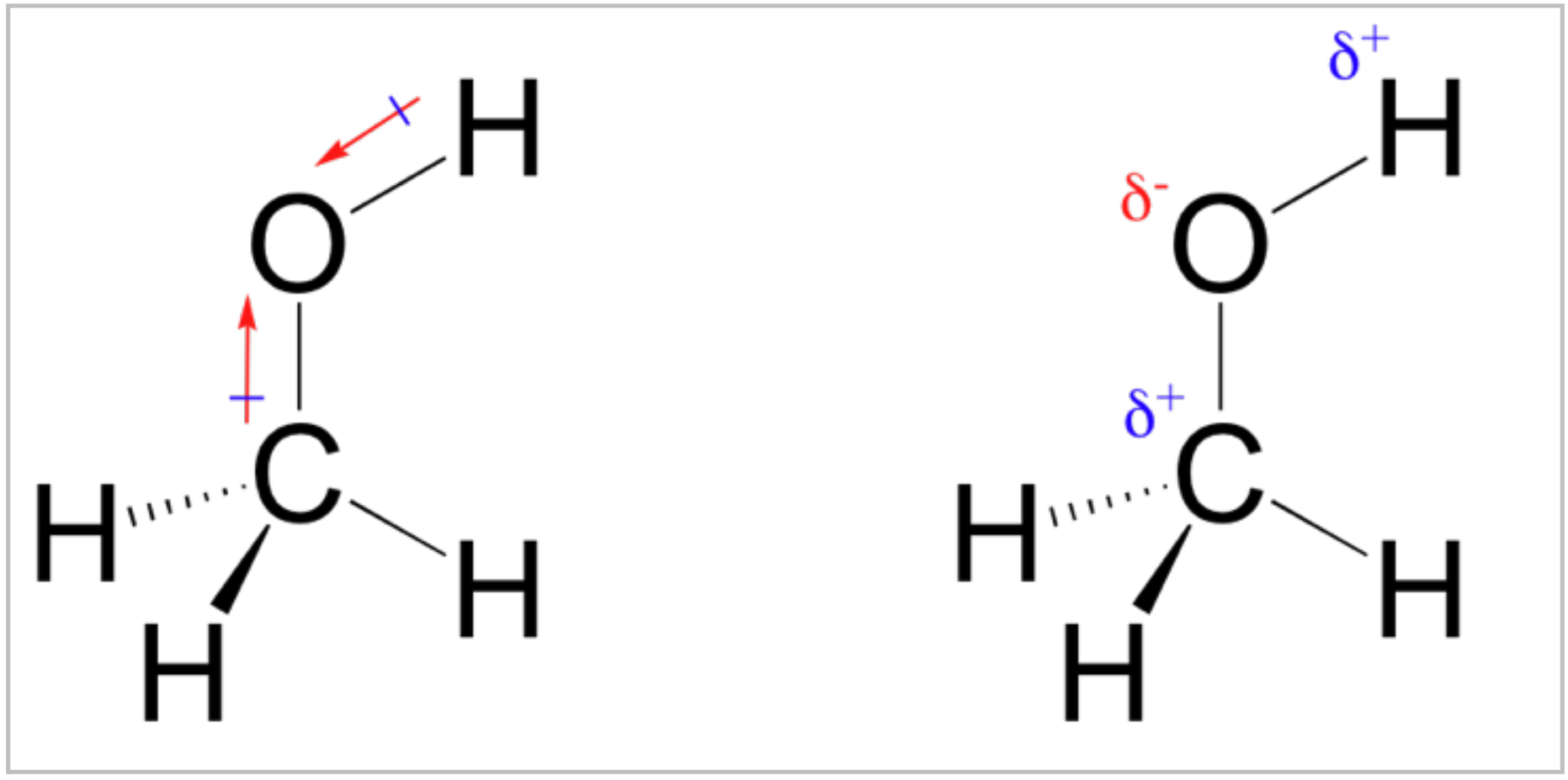
Functionalization of C–O Bonds

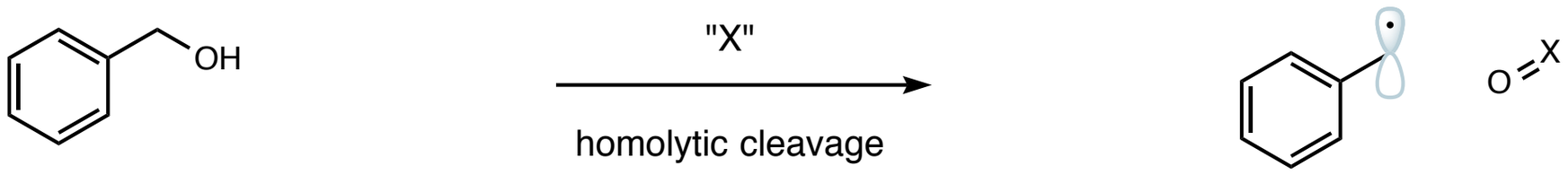


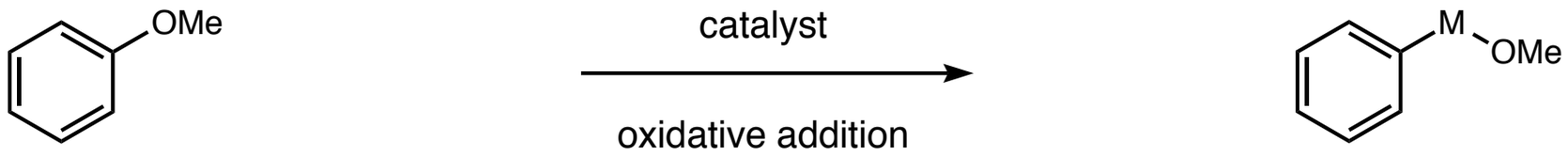
Stefan McCarver

MacMillan Lab Group Meeting

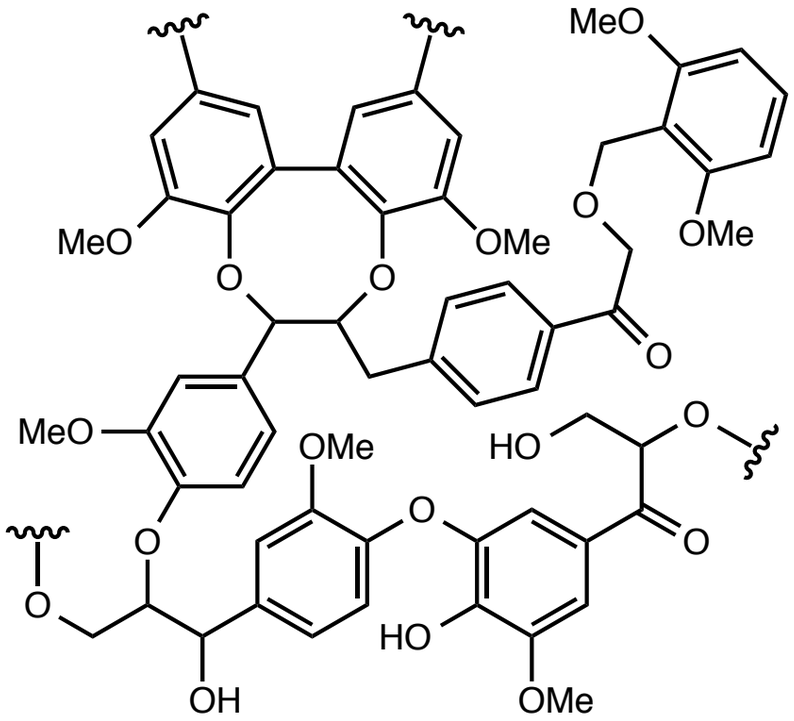
November 23rd, 2016

Functionalization of C–O Bonds



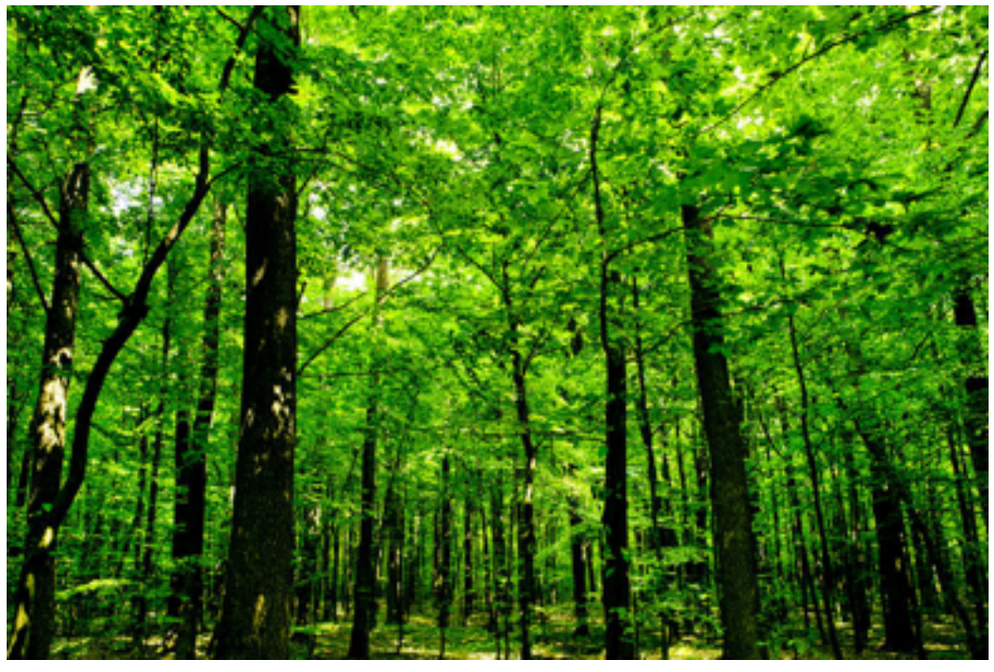


Why is C–O Bond Manipulation Important?

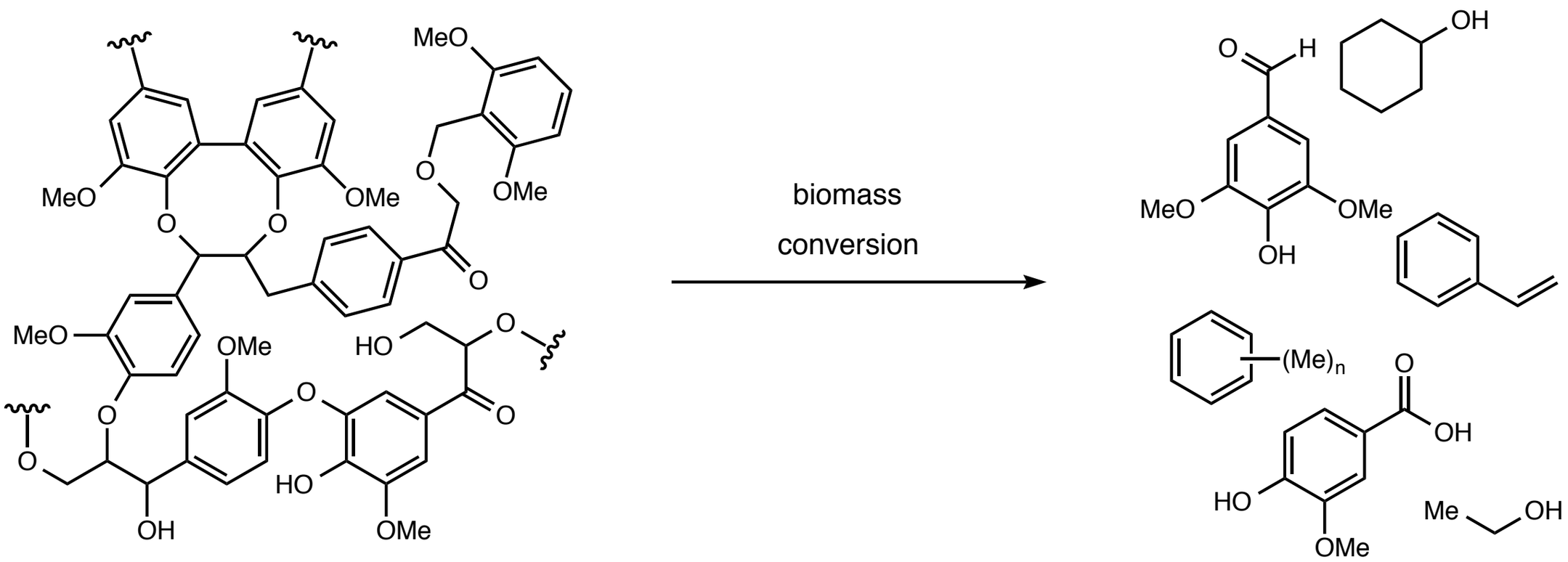


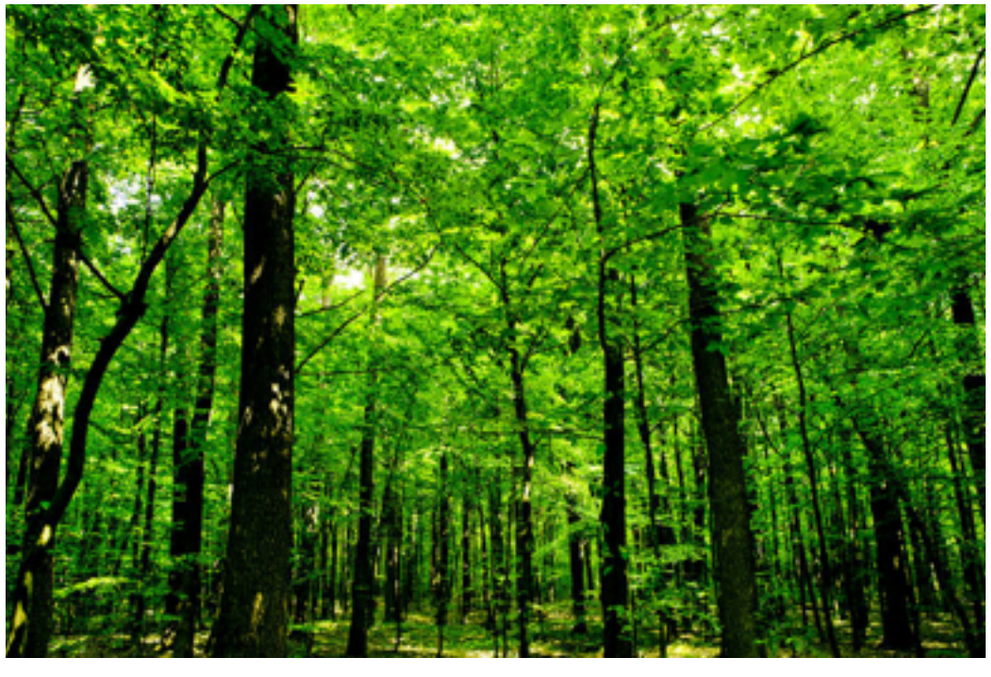
Lignin

- **Second most abundant biopolymer**
- **About 30% of organic carbon on earth**
- **Byproduct of paper production**
- **Potential fine chemical feedstock**

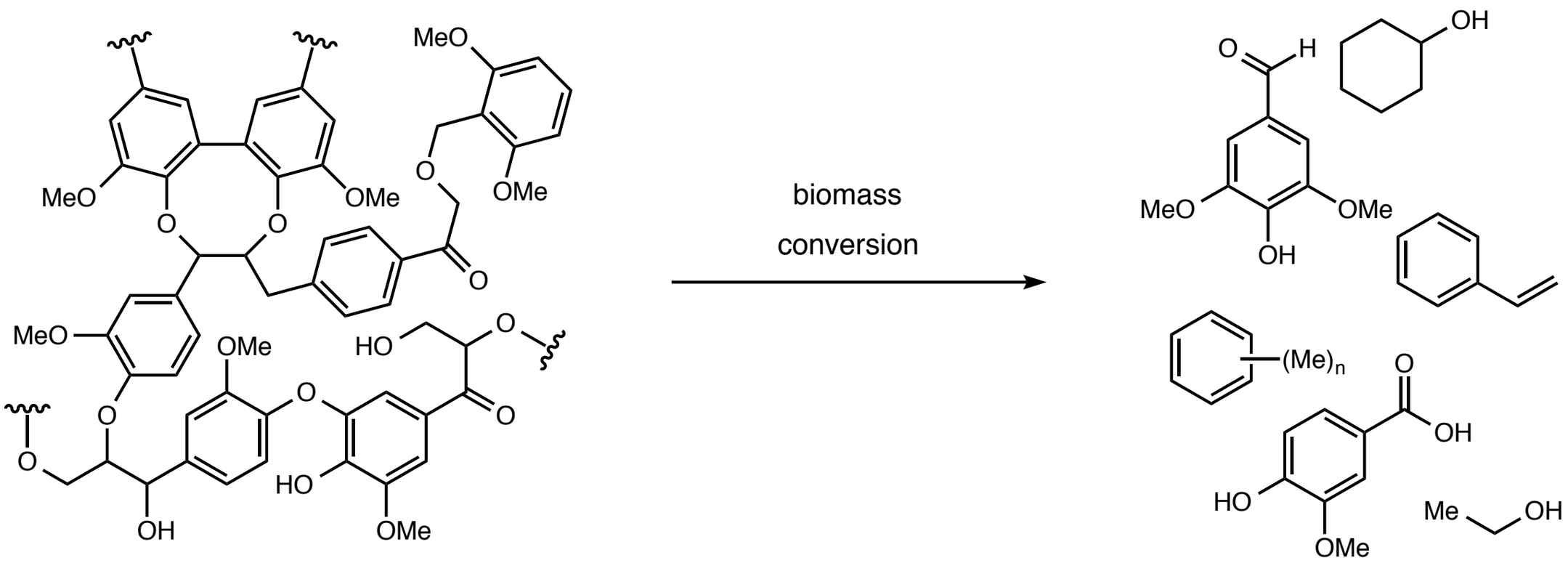


Why is C–O Bond Manipulation Important?





Why is C–O Bond Manipulation Important?

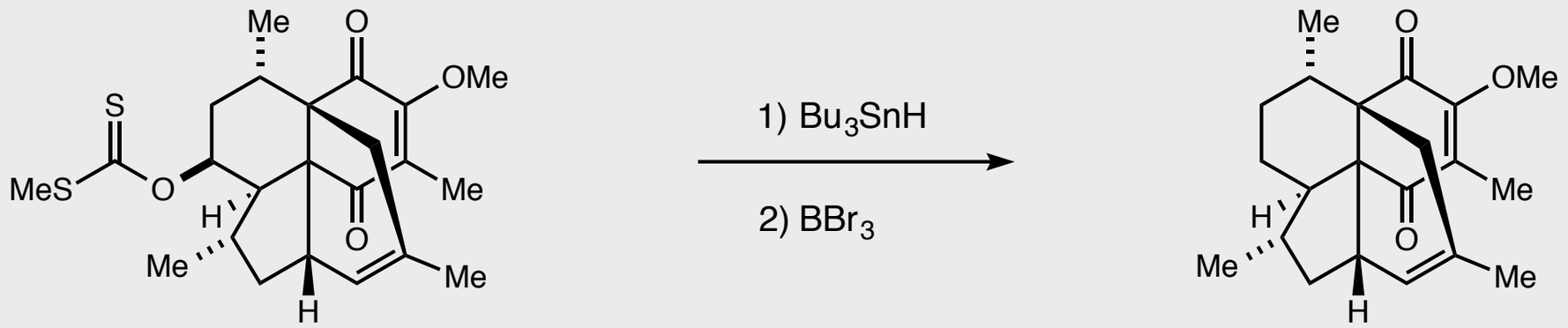


Spero™
Pioneering a greener future

startup company (founded 2014) based on one step removal of lignin from biological feedstocks and upgrading to valuable commodity chemicals

Why is C–O Bond Manipulation Important?

complex molecule total synthesis



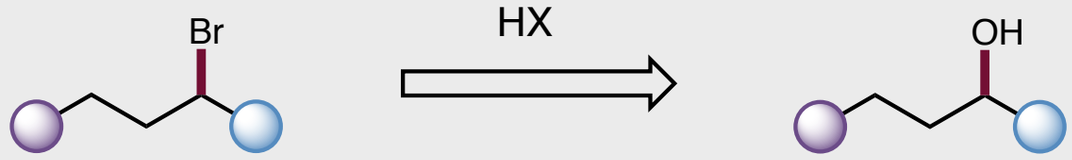
(–)-colombiasin A

most alkyl halides are derived from the corresponding alcohol

versatile for

cross coupling

or derivatization



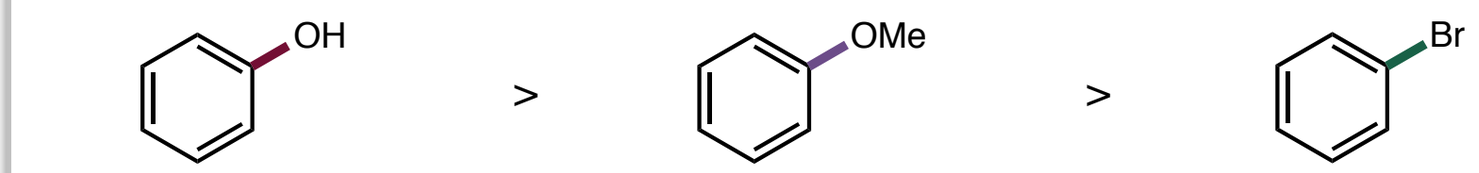
stable and

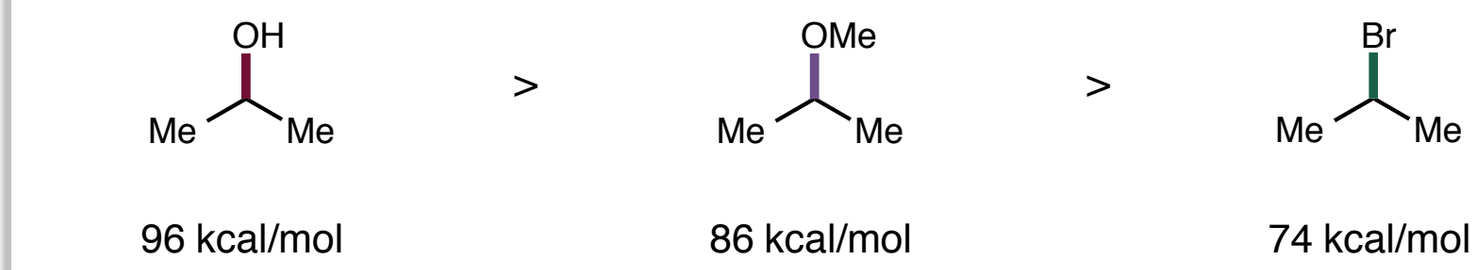
widely

available

Nicolau, K. C.; Vassilikogiannakis, W.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2482

Activation of C–O Bonds is Challenging



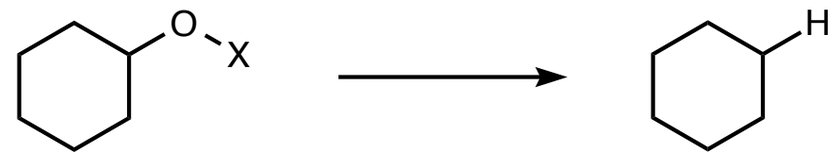


carbon–oxygen bonds are much stronger than the corresponding carbon–halide bonds

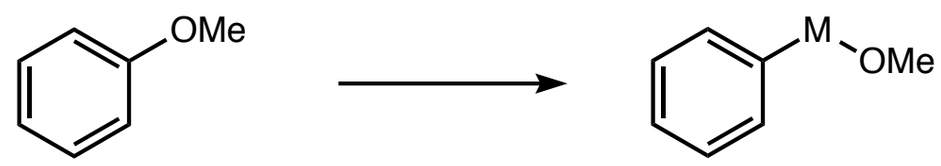
Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255

Functionalization of C–O Bonds

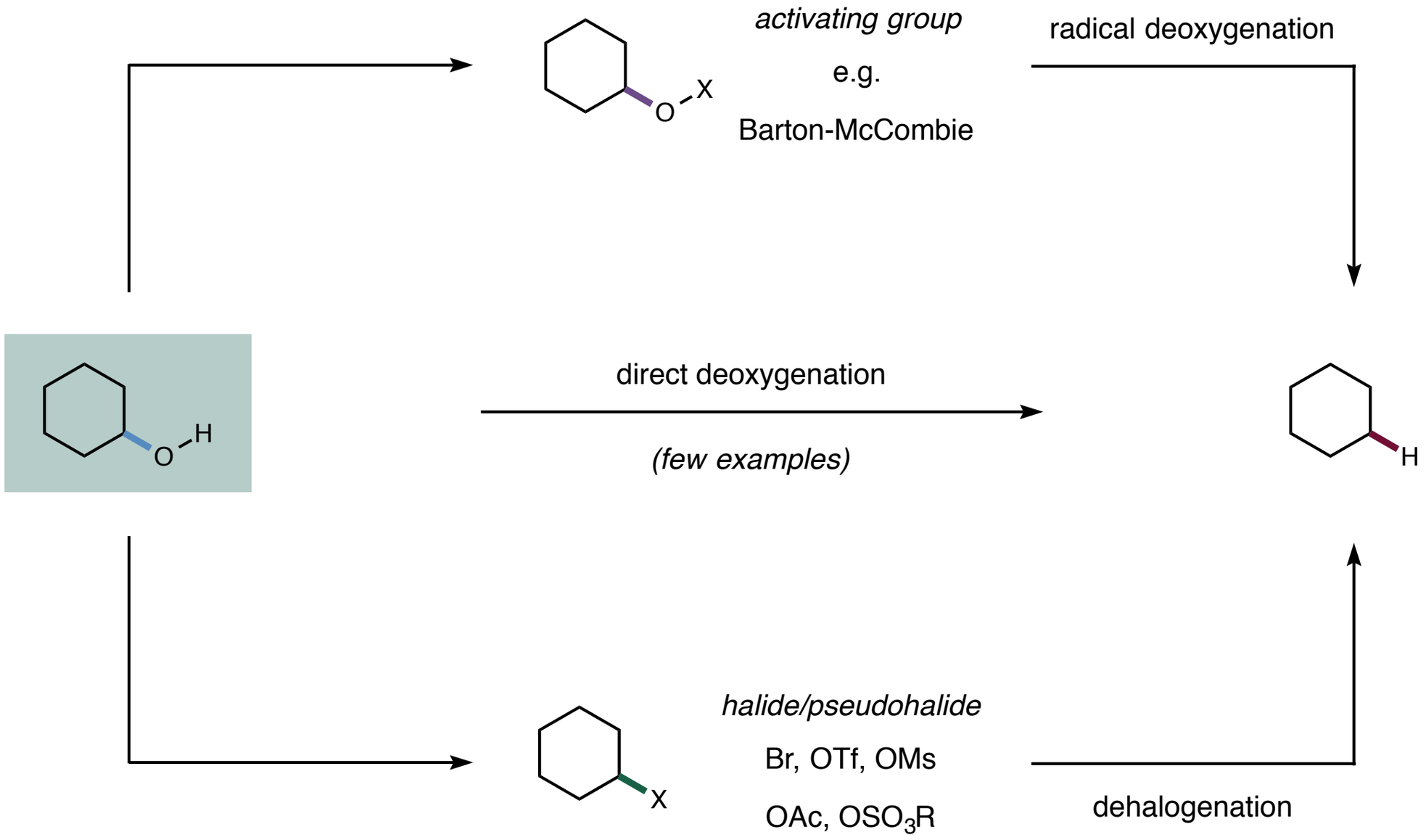
- **Radical alcohol deoxygenation**
  - **Thiocarbonyl methods**
  - **Phosphite activation**
  - **Thiol catalysis**
  - **Titanium-mediated deoxygenation**



- **Transition metal C–O bond insertion**
  - **Aryl methyl ether electrophiles**
  - **Ru directed C–O bond insertion**
  - **Phenol cross-coupling**

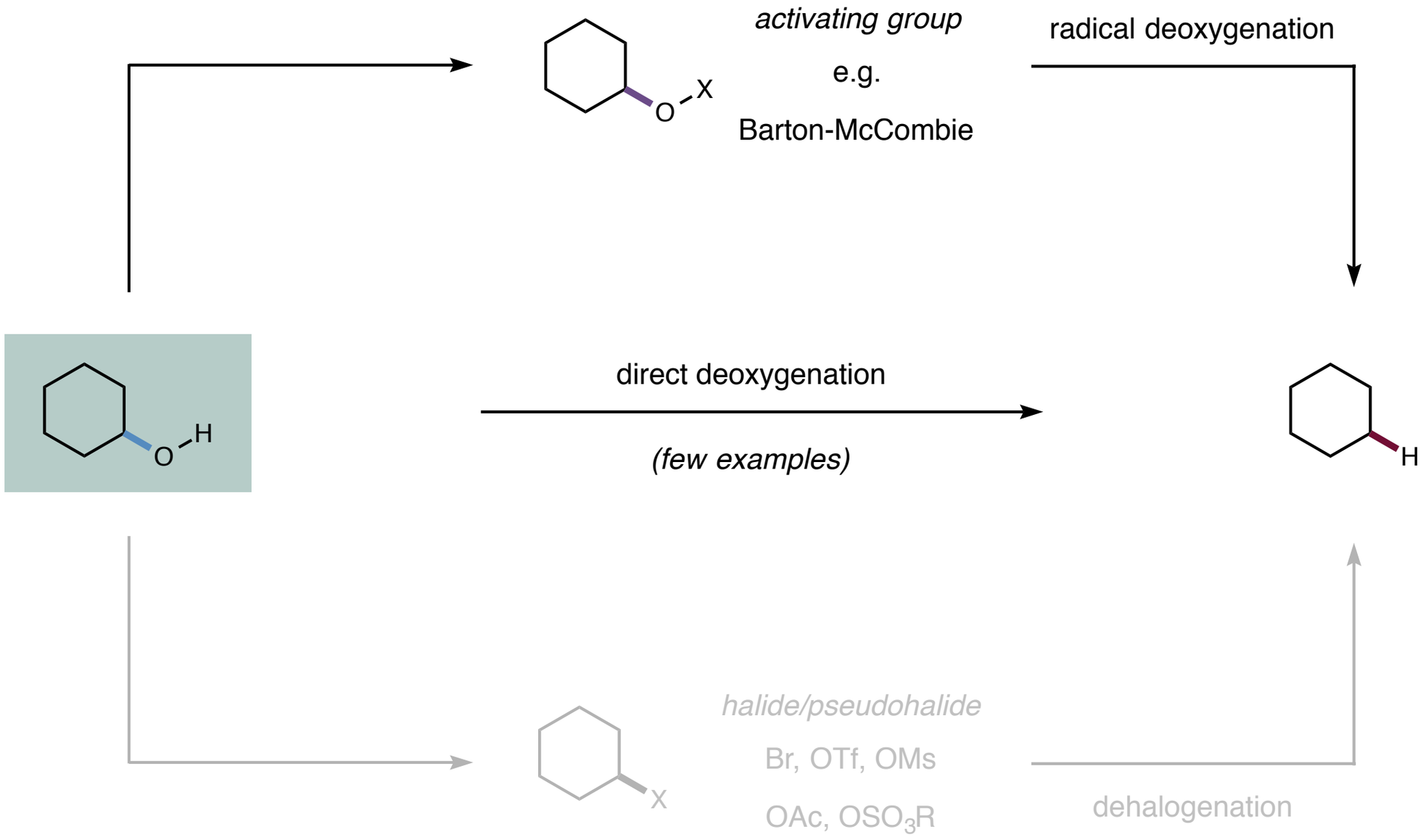


Reduction of C–O Bonds



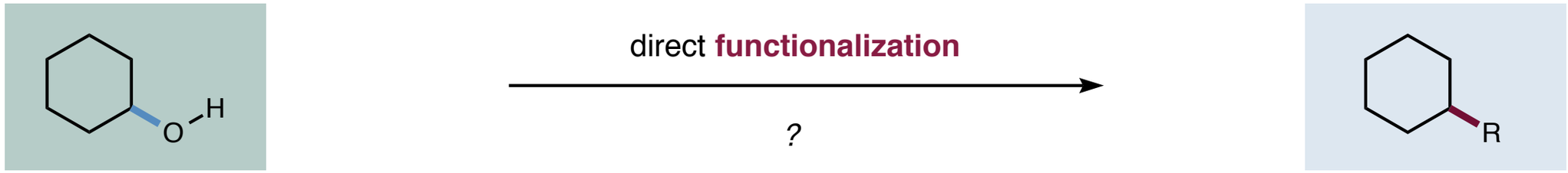
Herrmann, J. F.; König, B. *Eur. J. Org. Chem.* **2013**, 7017

Reduction of C–O Bonds



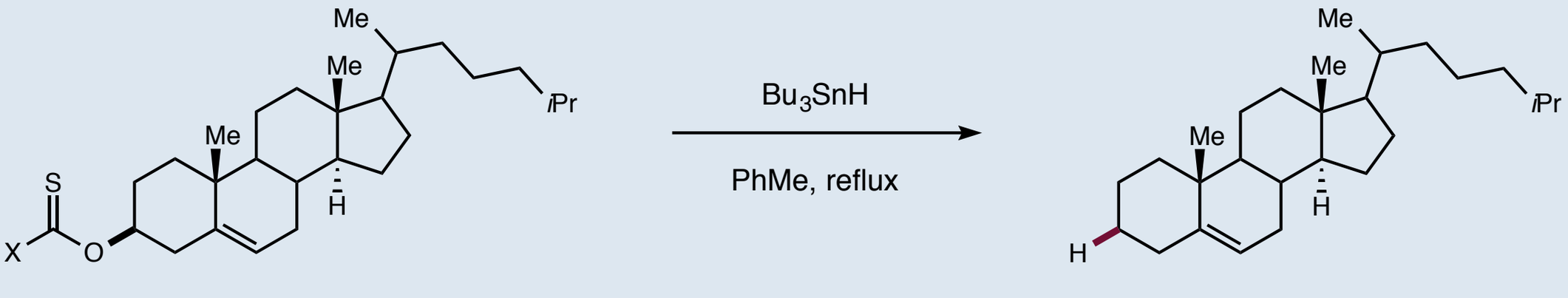
Herrmann, J. F.; König, B. *Eur. J. Org. Chem.* **2013**, 7017

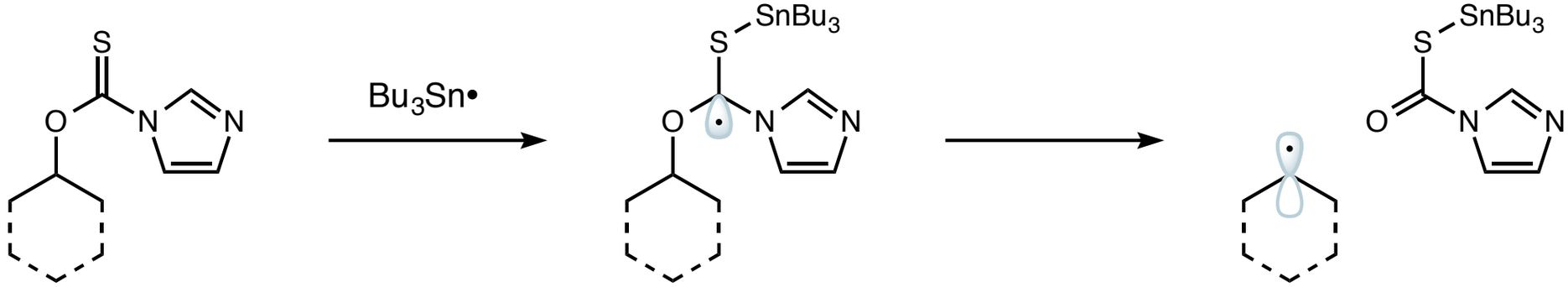
General Functionalization Methods are Not Yet Available



Herrmann, J. F.; König, B. *Eur. J. Org. Chem.* **2013**, 7017

The Barton-McCombie Alcohol Deoxygenation

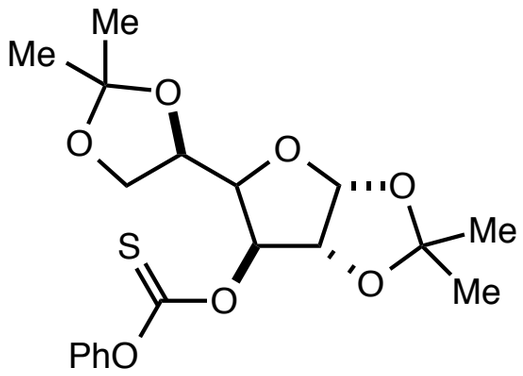




conversion from C=S to C=O provides thermodynamic driving force

Barton, D. H. R.; McCombie, S. W. *Perkin Trans. I.* **1975**, 1574

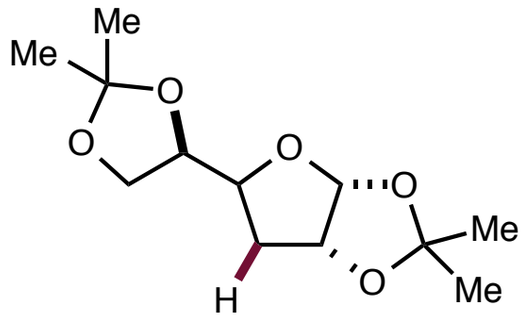
Catalytic Barton-McCombie Deoxygenation



15 mol% Bu_3SnH

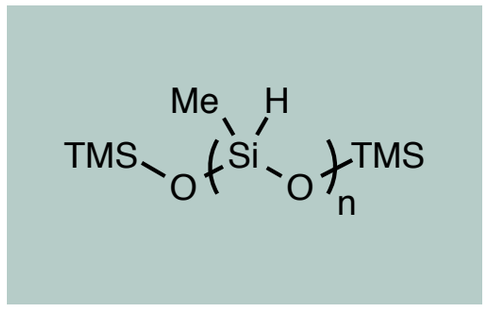
PMHS, AIBN

PhMe, reflux

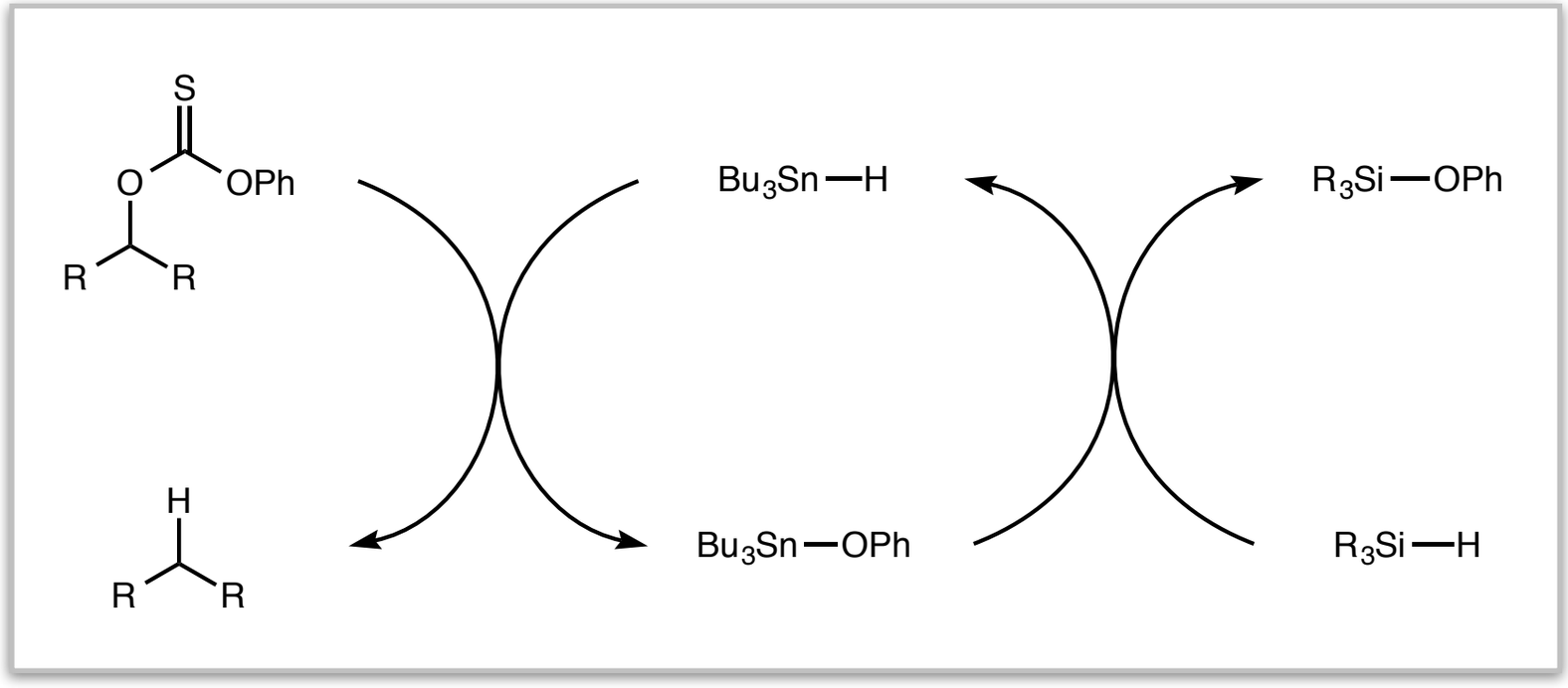


75% yield (catalytic)

79% (stoichiometric)



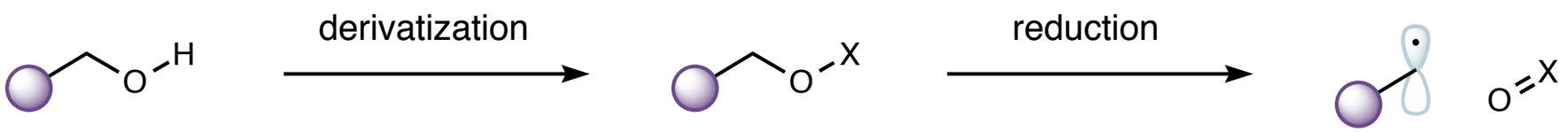
PMHS



Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949

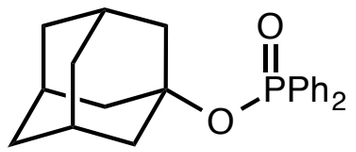
Tin-Free C–O Bond Reductions

general deoxygenation scheme

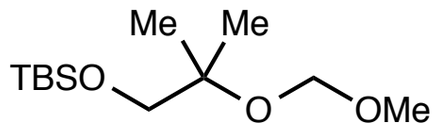


deoxygenation reactions driven by

- ***entropy***
- ***formation of O=X bond***
- ***typically irreversible***

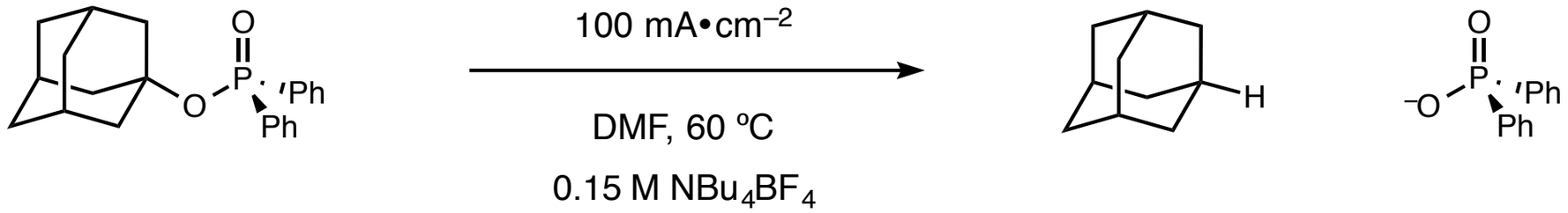


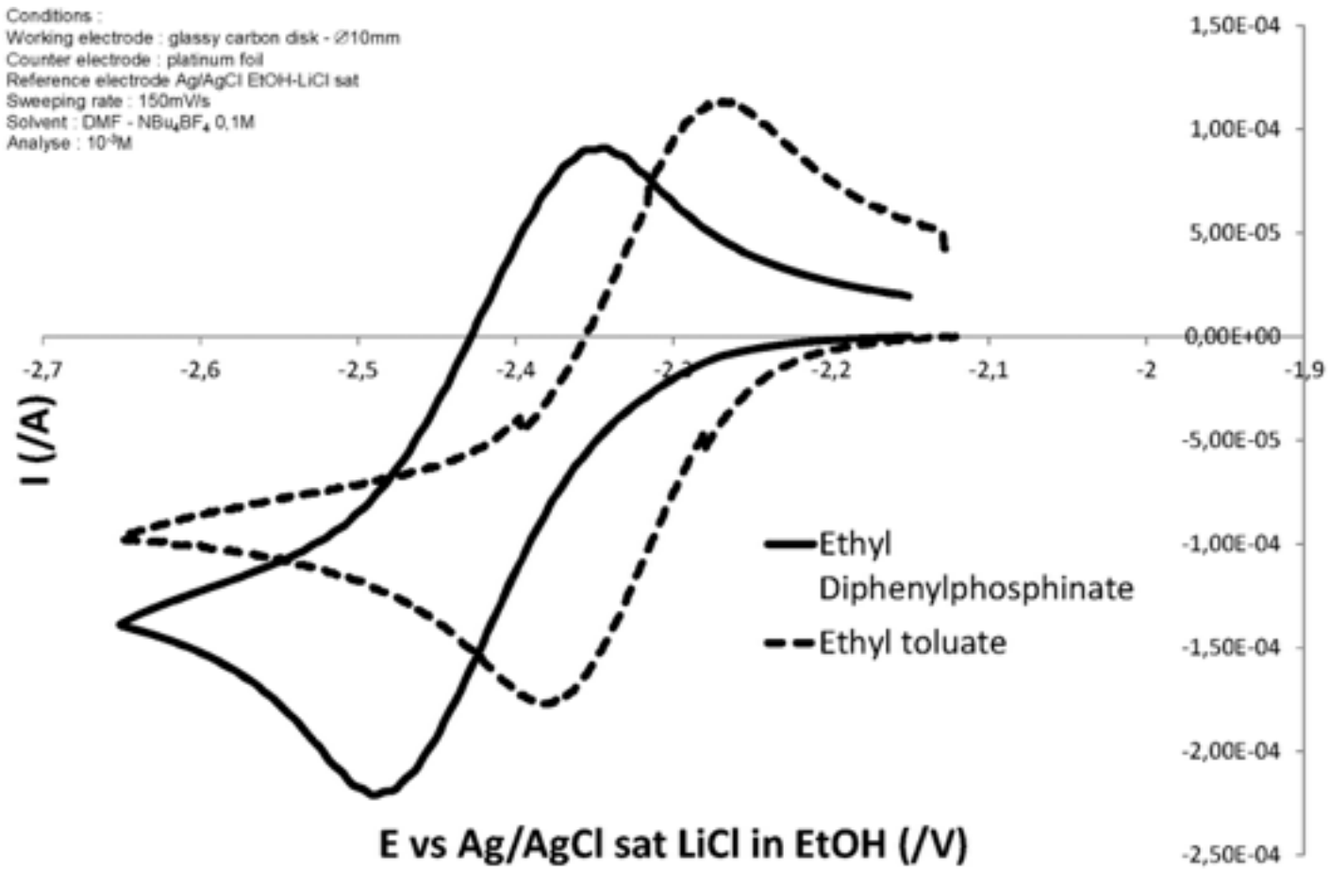
electrochemical reduction



polarity-reversal catalysis

Electrochemical Reduction of Diphenylphosphinate Esters



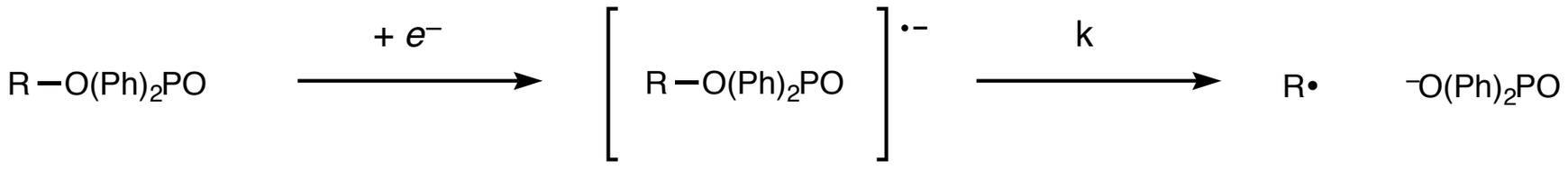


–2.4 V (Ag/AgCl) = –2.1 V (SCE)

electrolysis at –2.4 V (Ag/AgCl)
only provided trace product

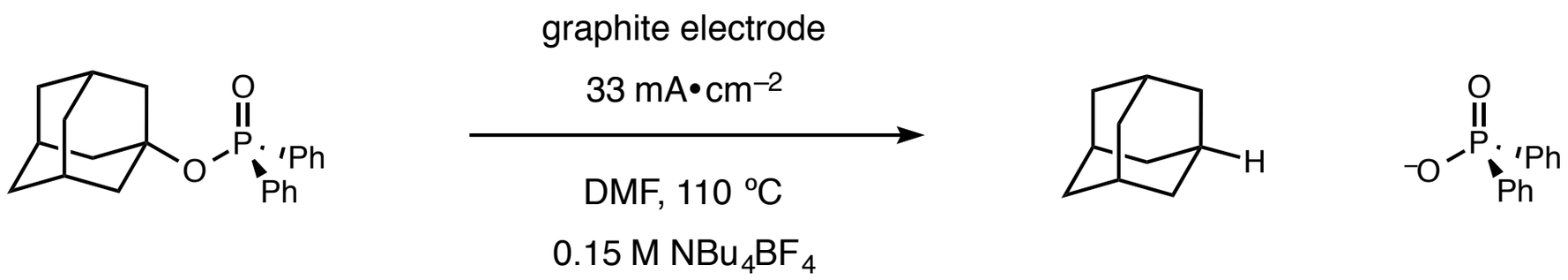
Lam, K.; Marko´, I. E. *Org. Lett.* **2011**, *13*, 406

Electrochemical Reduction of Diphenylphosphinate Esters



Lam, K.; Marko´, I. E. *Org. Lett.* **2011**, *13*, 406

Electrochemical Reduction of Diphenylphosphinate Esters

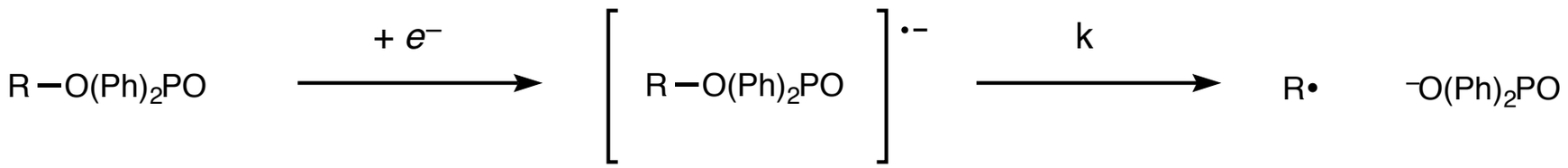


solvent	yield
DMSO	0%
MeCN	0%
NMP	43%
DMF	44%

Lam, K.; Marko´, I. E. *Org. Lett.* **2011**, *13*, 406

Electrochemical Reduction of Diphenylphosphinate Esters

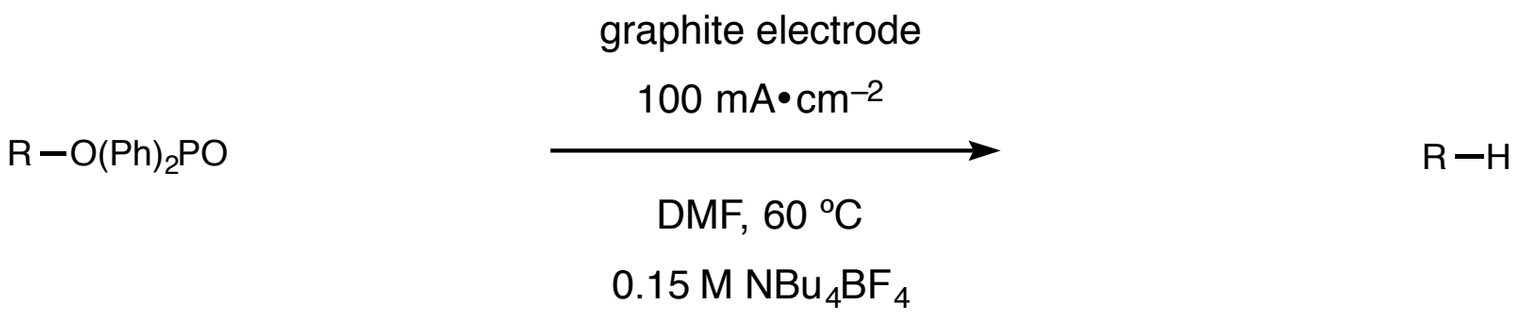
fragmentation rates support a radical mechanism

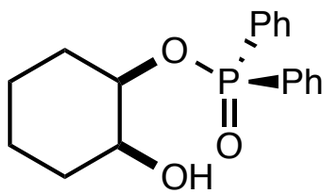


R	k
ethyl	0.19
cyclohexyl	0.33
1-adamantyl	0.70
allyl	too fast to measure

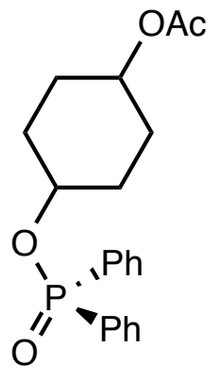
Lam, K.; Marko´, I. E. *Org. Lett.* **2011**, *13*, 406

Electrochemical Reduction of Diphenylphosphinate Esters

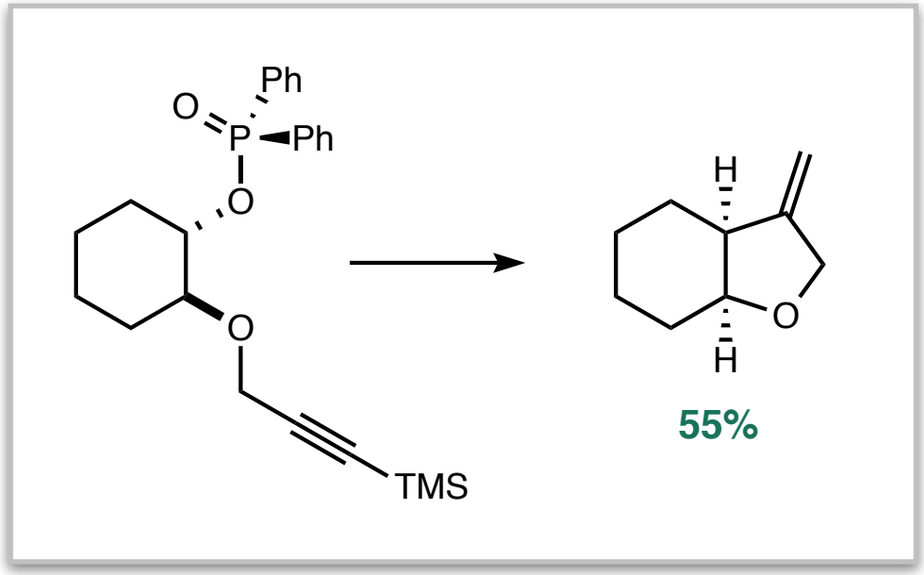




81%

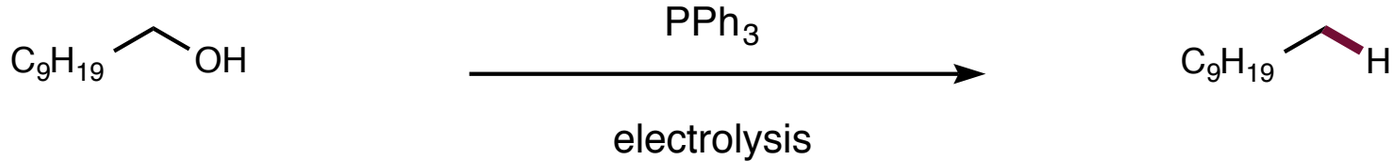


74%



Lam, K.; Marko´, I. E. *Org. Lett.* **2011**, *13*, 406

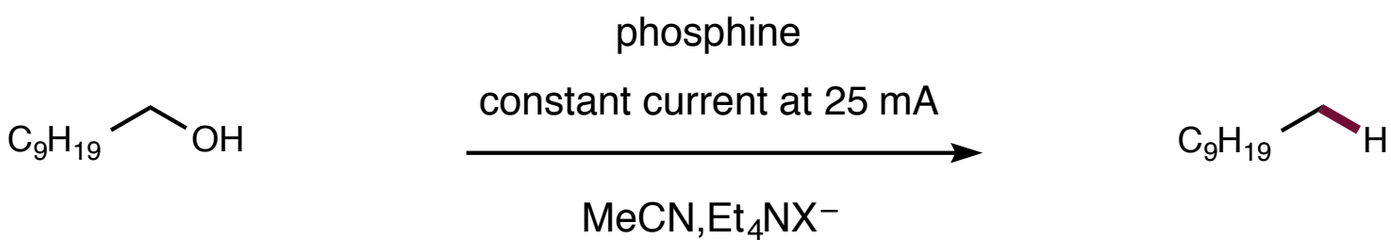
In Situ Phosphine Activation



can the phosphine intermediate be formed in situ?

Maeda, H.; Maki, T.; Eguchi, K.; Koide, T.; Ohmori, H. *Tet. Lett.* **1994**, *35*, 4129

In Situ Phosphine Activation

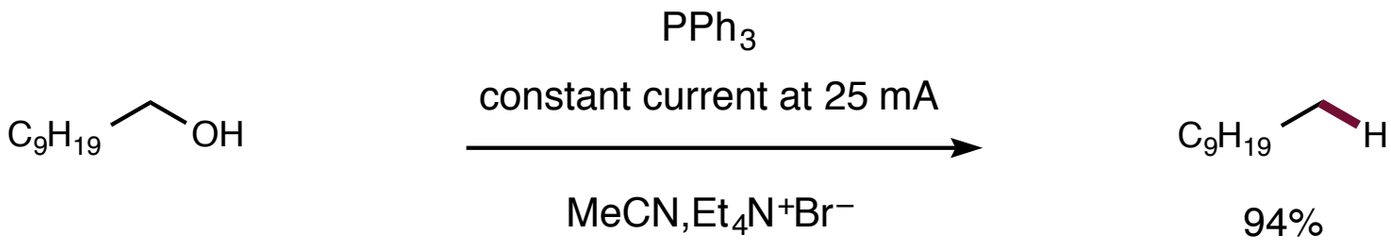


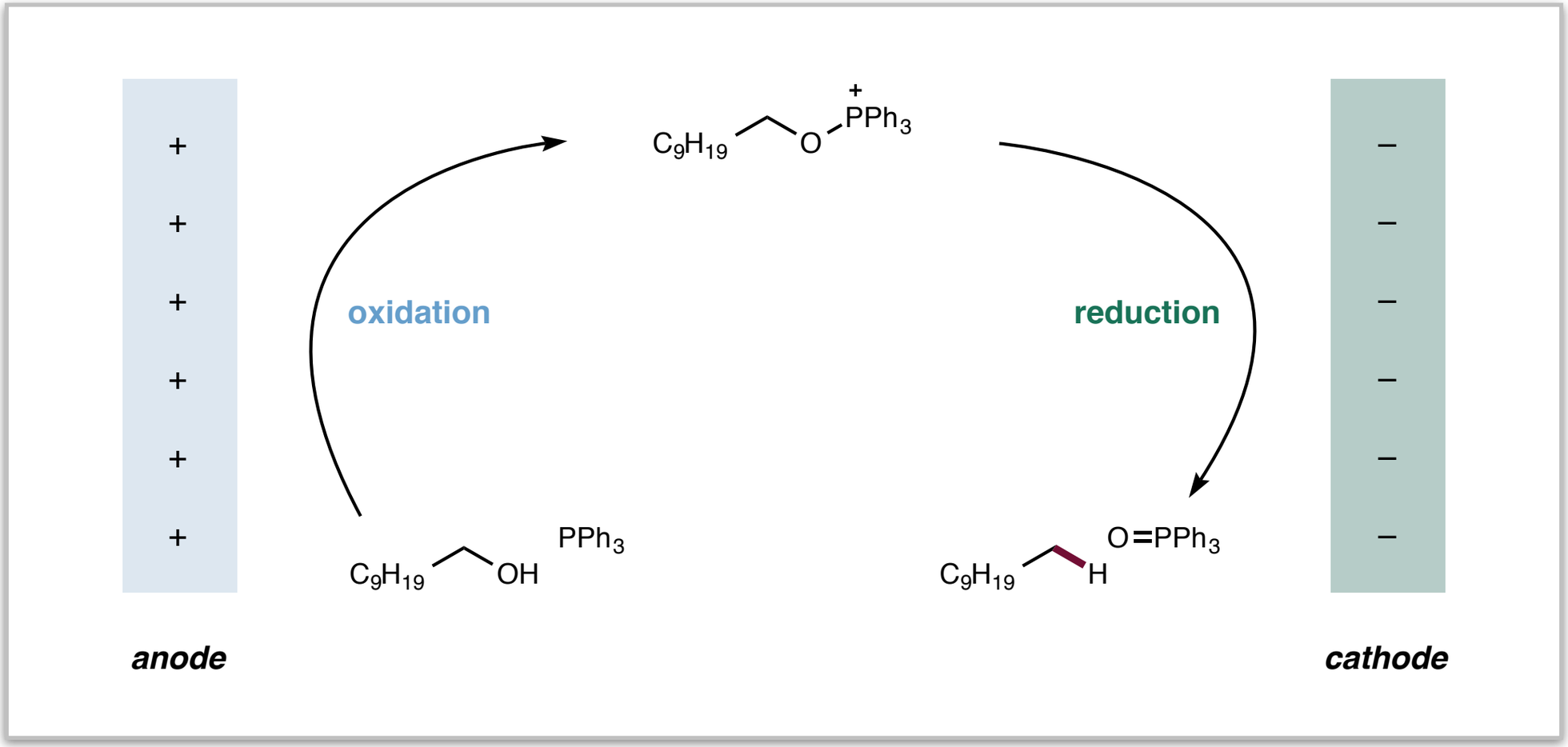
phosphine	triethylammonium salt	total electricity	yield
PPh_3	BF_4^-	5 F/mol	trace
PPh_3	Cl^-	5 F/mol	66%
PPh_3	Br^-	5 F/mol	94%
PPh_3	Br^-	4 F/mol	70%
PBu_3	Br^-	5 F/mol	68%
none	Br^-	5 F/mol	0%

phosphine necessary for reduction to occur

Maeda, H.; Maki, T.; Eguchi, K.; Koide, T.; Ohmori, H. *Tet. Lett.* **1994**, *35*, 4129

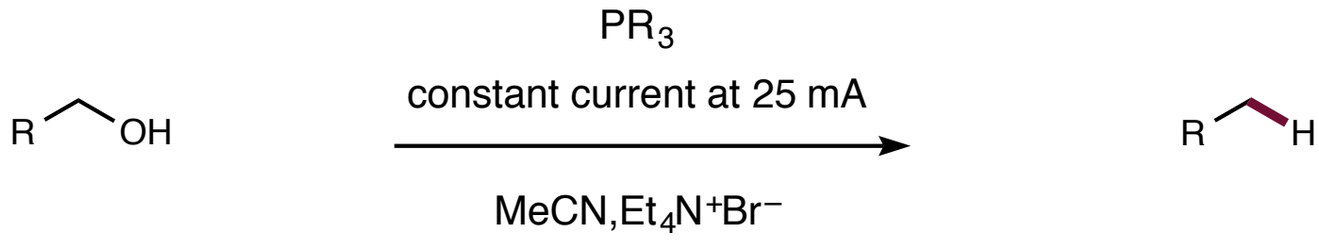
In Situ Phosphine Activation

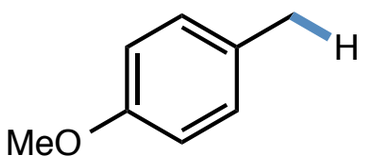




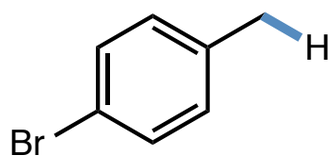
Maeda, H.; Maki, T.; Eguchi, K.; Koide, T.; Ohmori, H. *Tet. Lett.* **1994**, *35*, 4129

In Situ Phosphine Activation

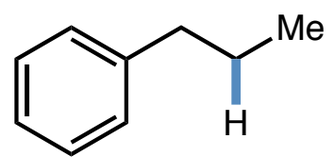




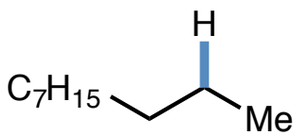
96% (PPh_3)



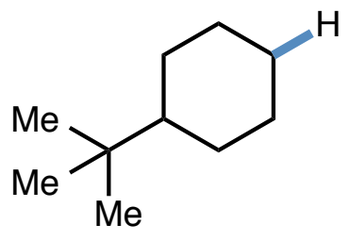
89% (PPh_3)



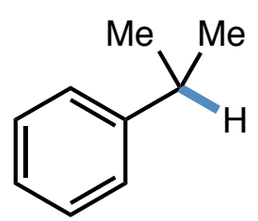
86% (PBu_3)



93% (PBu_3)



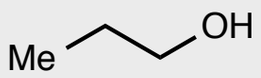
48% (PBu_3)

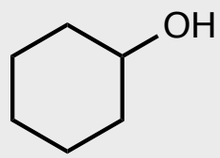


79% ($P(OPh)_3$, 50 mA)

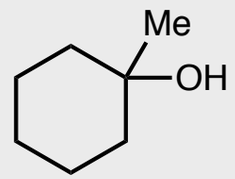
Maeda, H.; Maki, T.; Eguchi, K.; Koide, T.; Ohmori, H. *Tet. Lett.* **1994**, *35*, 4129

Methods for Tertiary Alcohol Deoxygenation are Rare





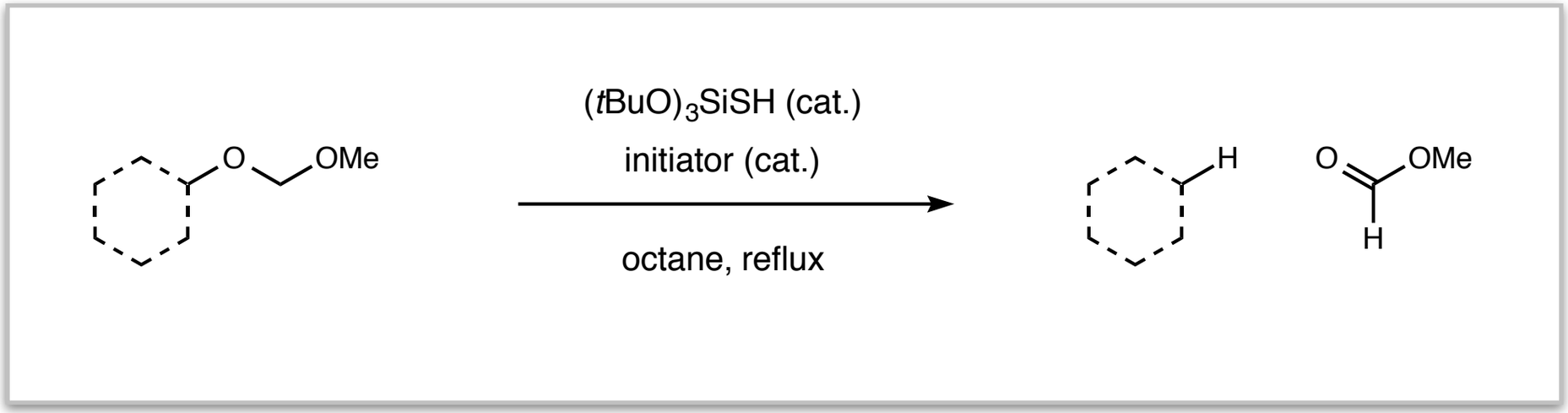
many radical deoxygenation methods exist



activated esters often

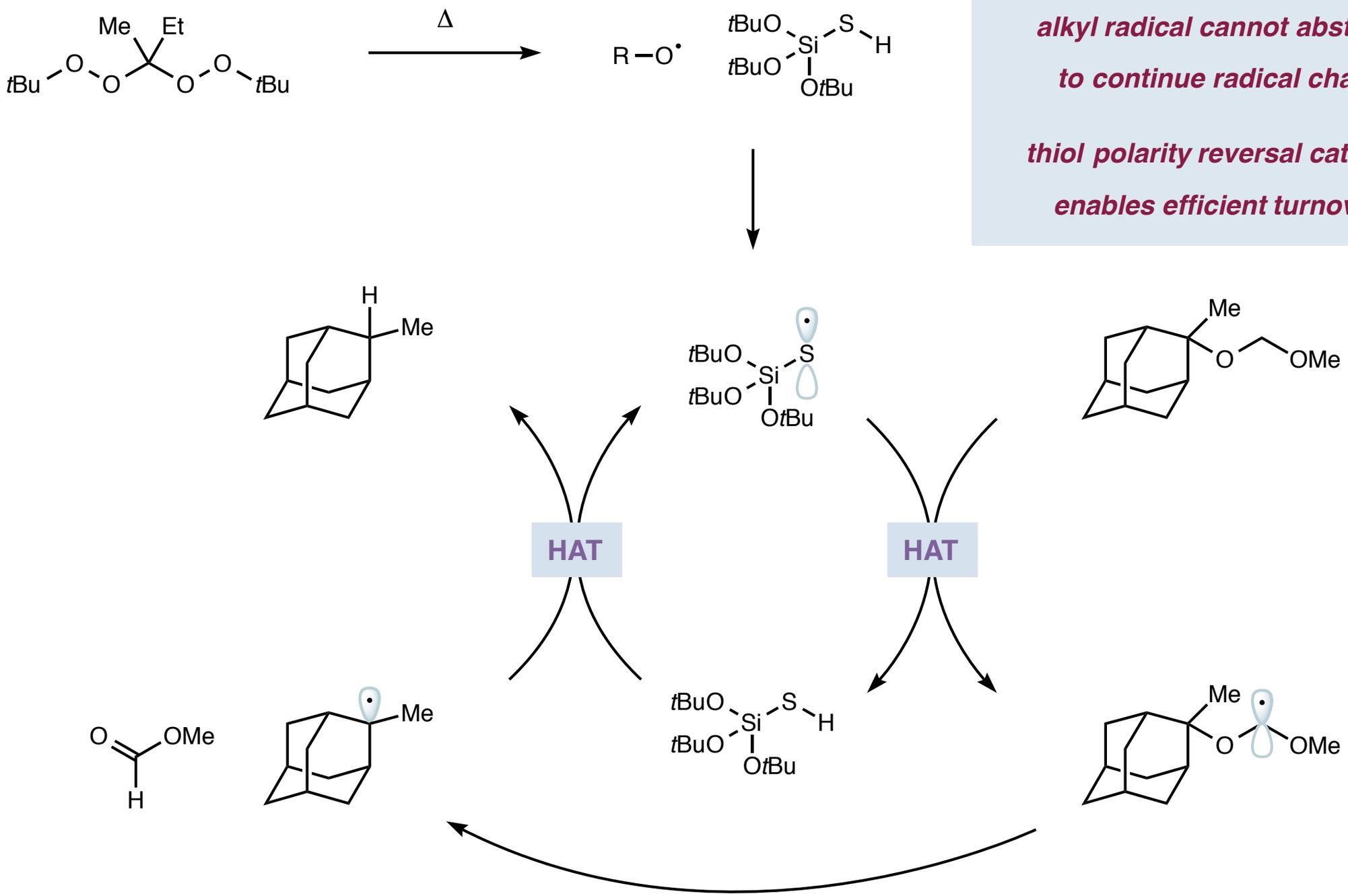
thermally unstable

Polarity Reversal Activation of MOM Ethers



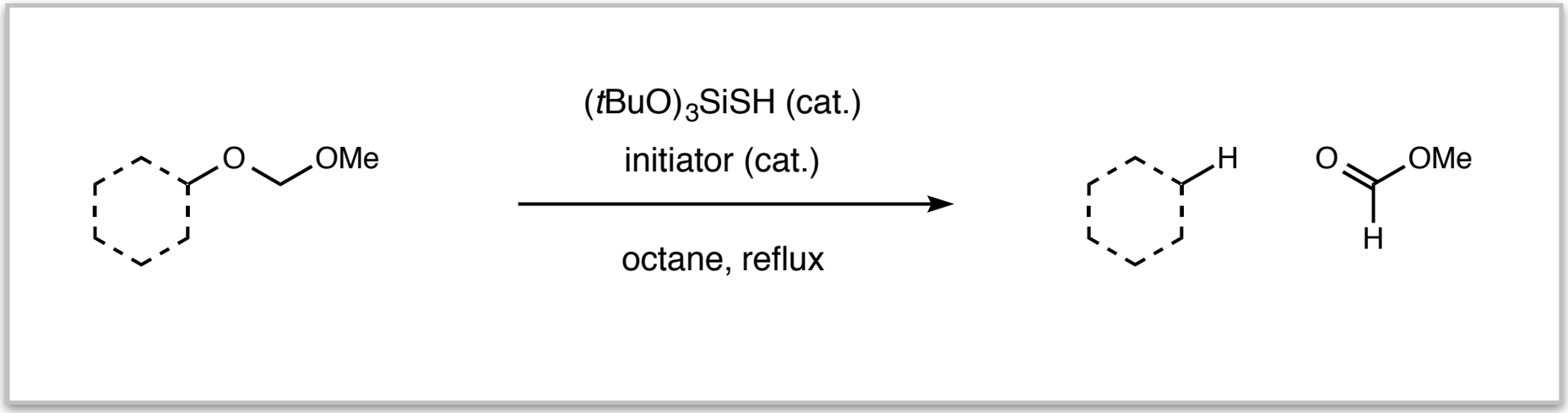
Dang, H.-S.; Franchi, P.; Roberts, B. P. *Chem. Commun.* **2000**, 499

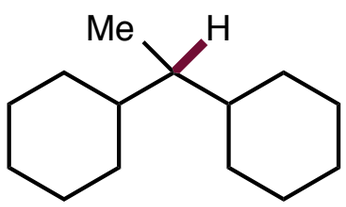
Polarity Reversal Activation of MOM Ethers



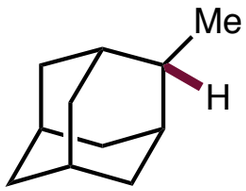
Dang, H.-S.; Franchi, P.; Roberts, B. P. *Chem. Commun.* **2000**, 499

Polarity Reversal Activation of MOM Ethers





88%



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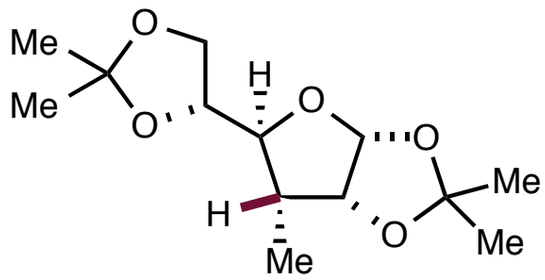
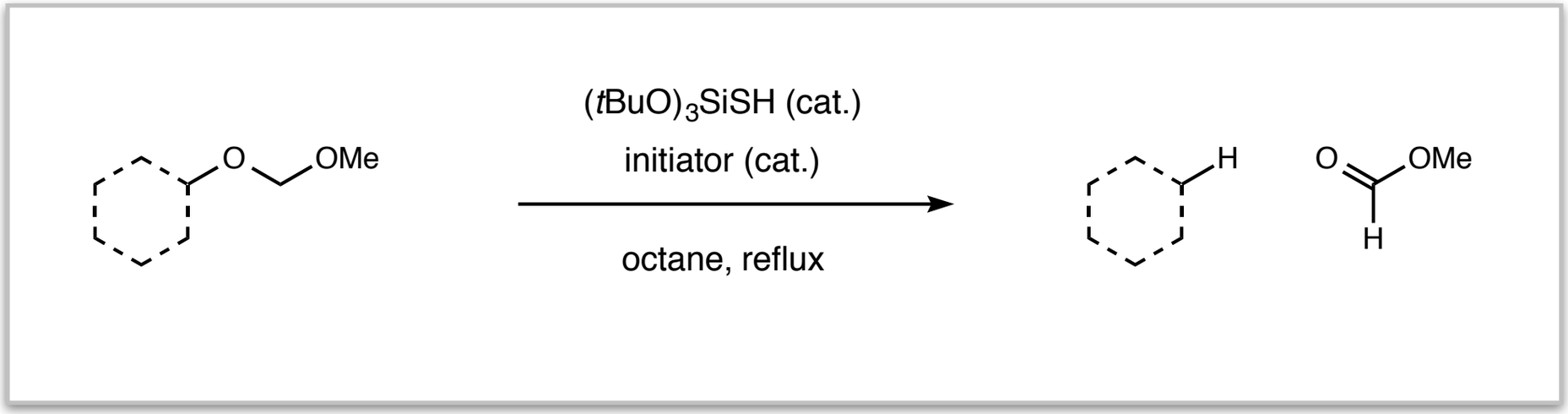
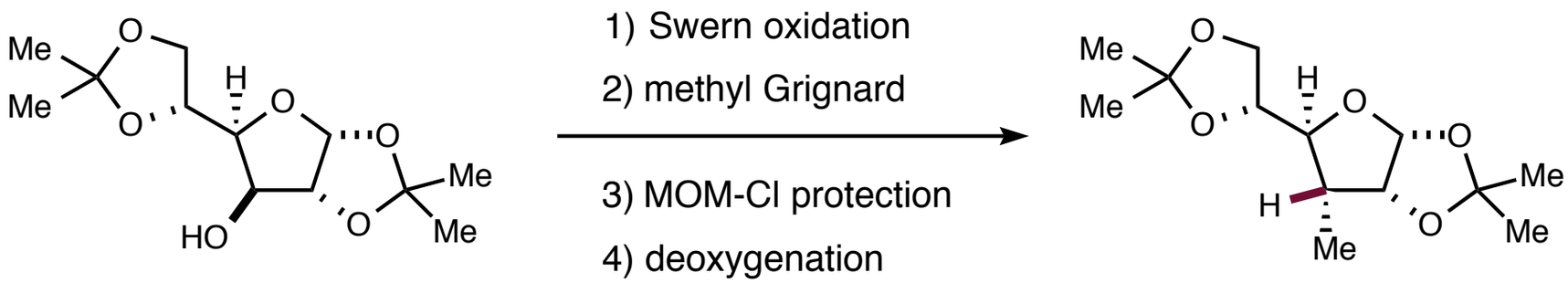


90%, 10:1 dr

Dang, H.-S.; Franchi, P.; Roberts, B. P. *Chem. Commun.* **2000**, 499

Polarity Reversal Activation of MOM Ethers



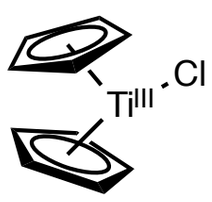


formal O–H to methyl

Dang, H.-S.; Franchi, P.; Roberts, B. P. *Chem. Commun.* **2000**, 499

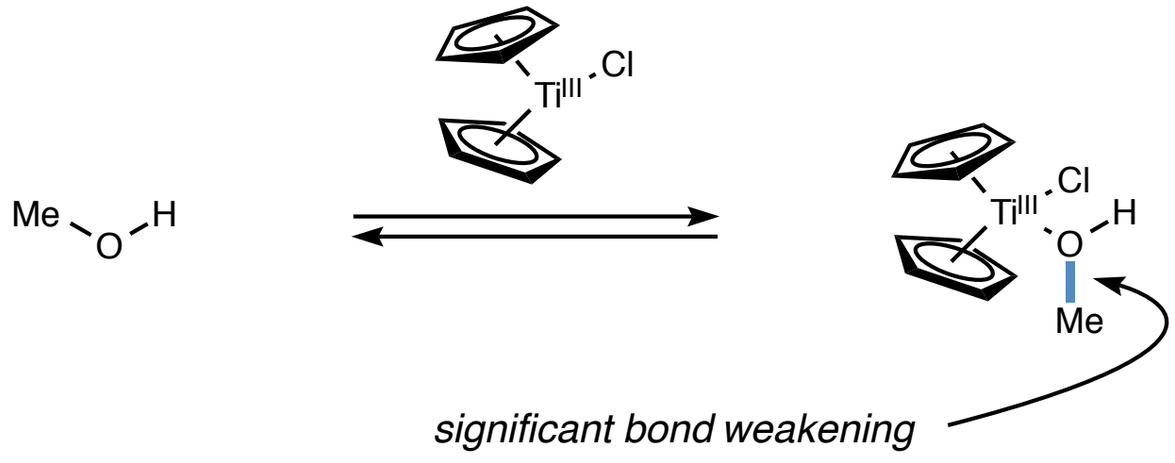
Titanium Mediated Alcohol Reduction

aliphatic alcohol *alkane*



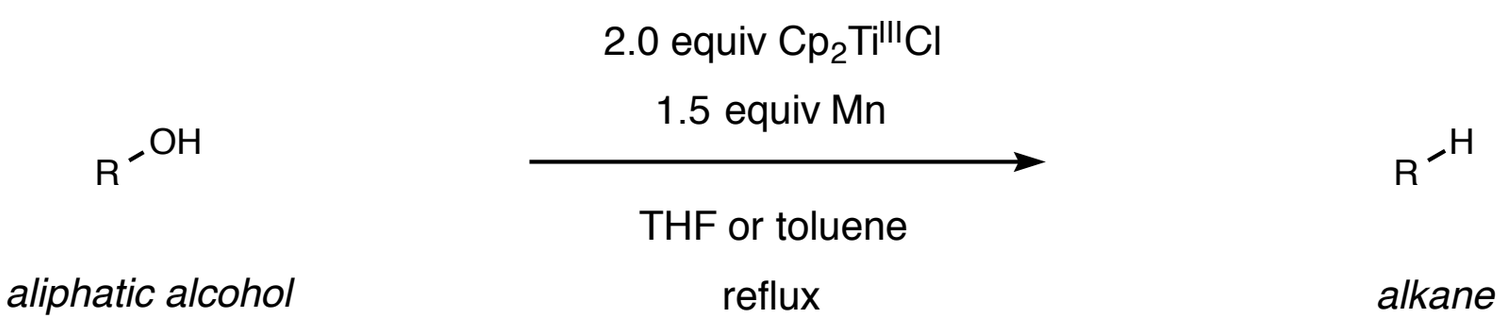
reductant

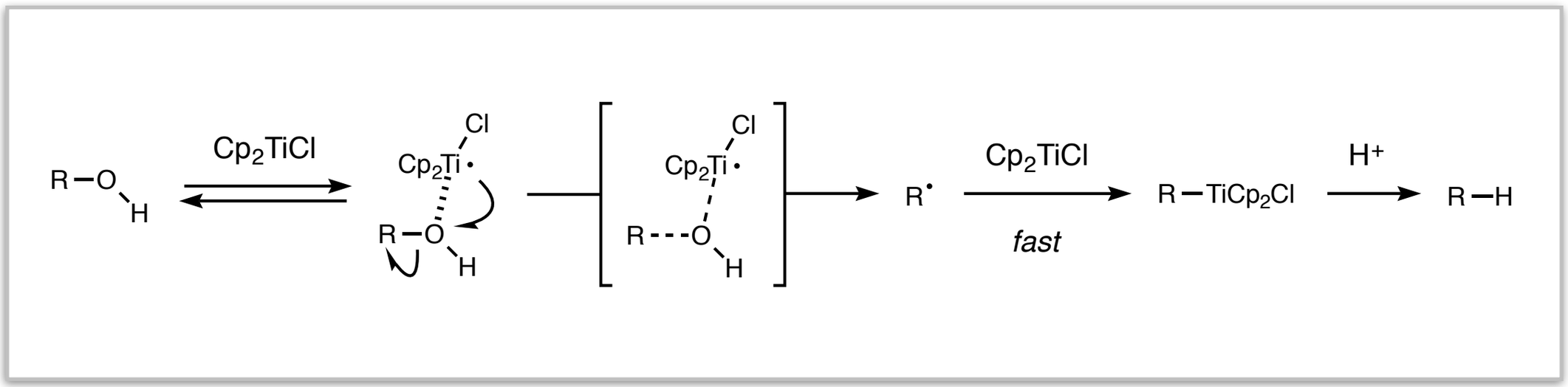
lewis acidic



Barrero, A. F. *et al J. Am. Chem. Soc.* **2010**, *132*, 254

Titanium Mediated Alcohol Reduction





alcohol coordination to Ti(III) ■ **inner sphere reduction** ■ **trapping of radical by Ti(III)**

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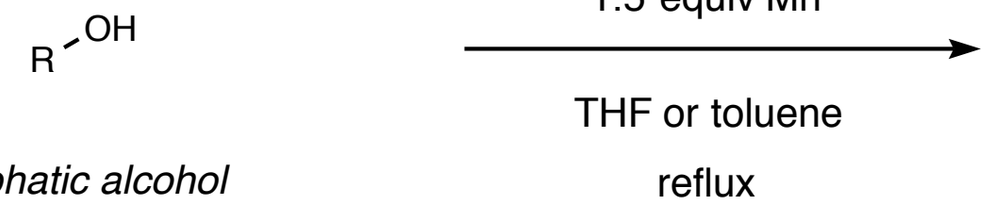
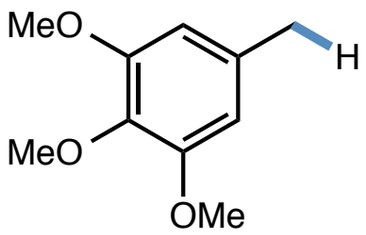
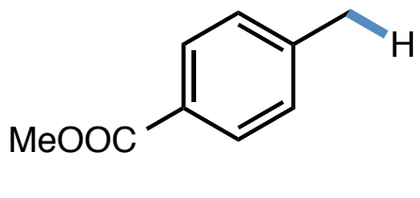
Titanium Mediated Alcohol Reduction



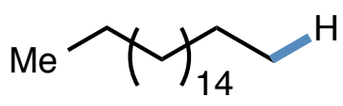
aliphatic alcohol → *alkane*



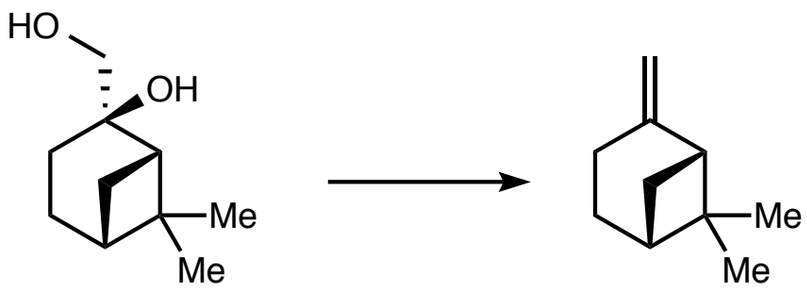
90%



83%



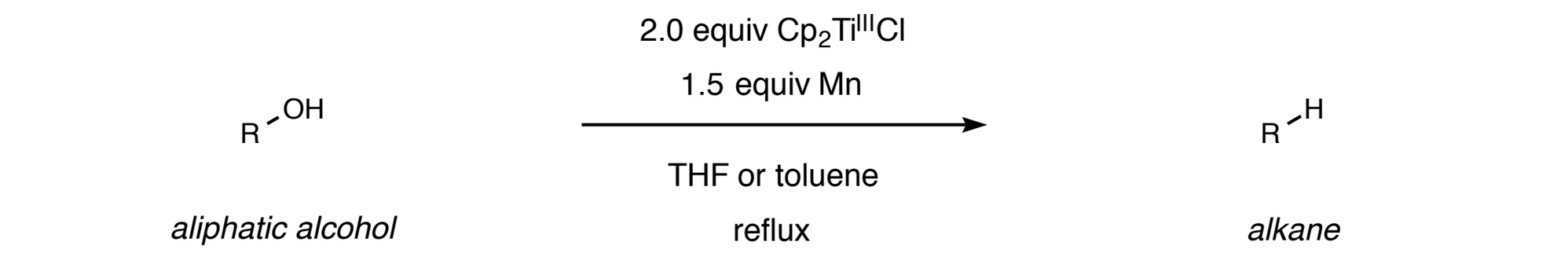
45% (45% elimination)

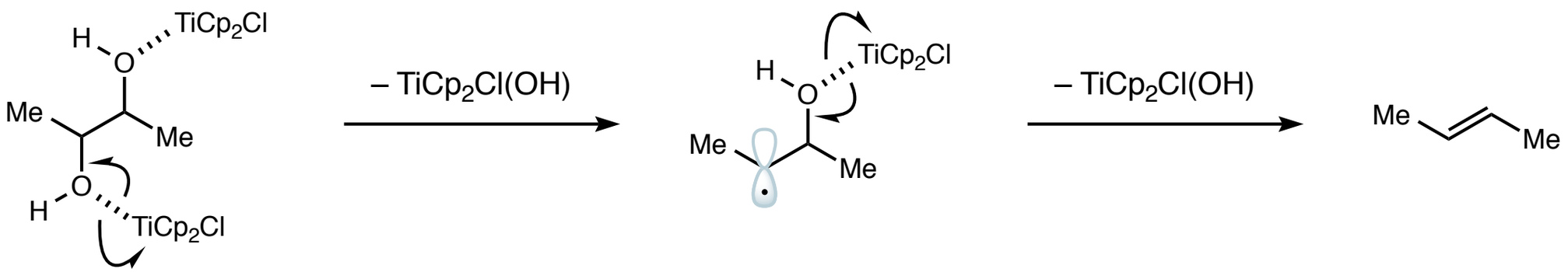


92%

Barrero, A. F. *et al J. Am. Chem. Soc.* **2010**, *132*, 254

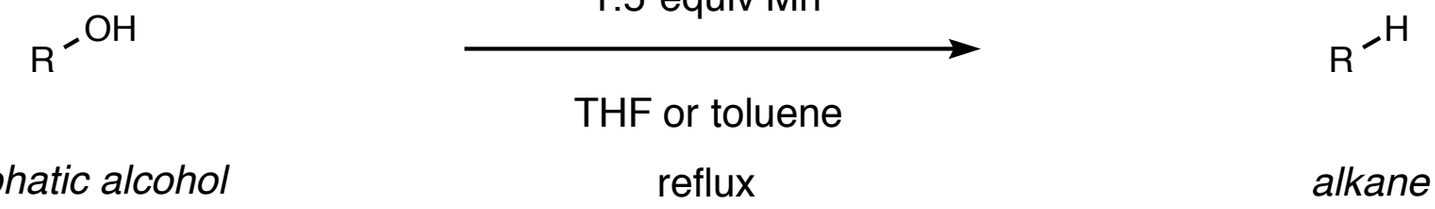
Titanium Mediated Alcohol Reduction



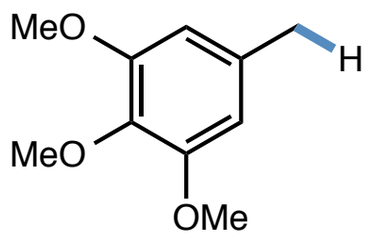


Barrero, A. F. *et al J. Am. Chem. Soc.* **2010**, *132*, 254

Titanium Mediated Alcohol Reduction



aliphatic alcohol *alkane*



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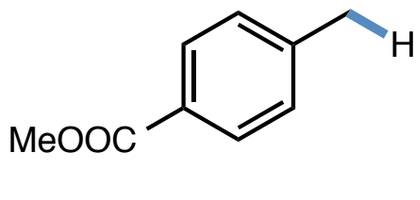

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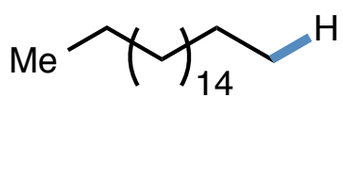
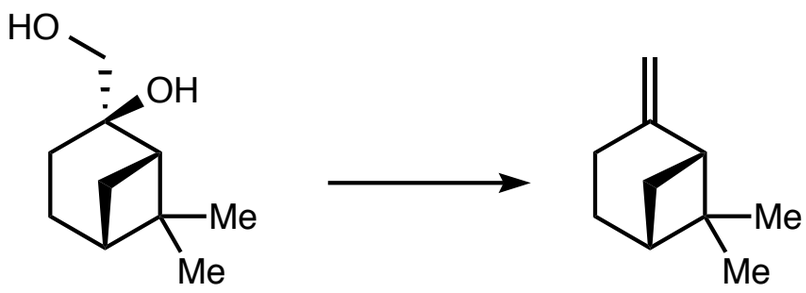
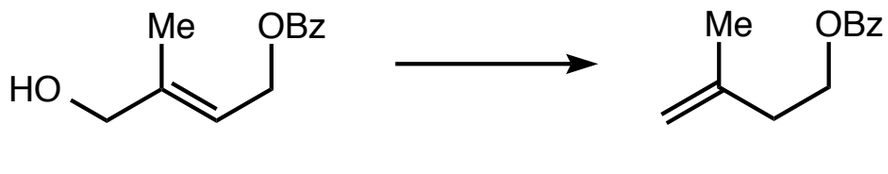


45% (45% elimination)



92%



70%

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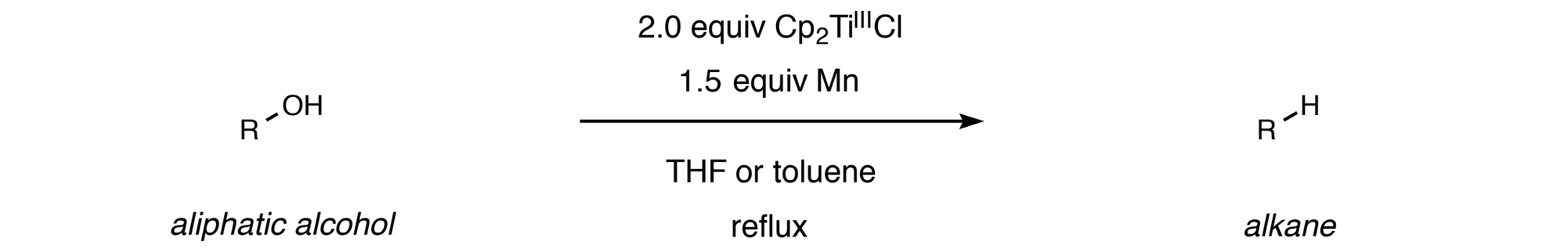
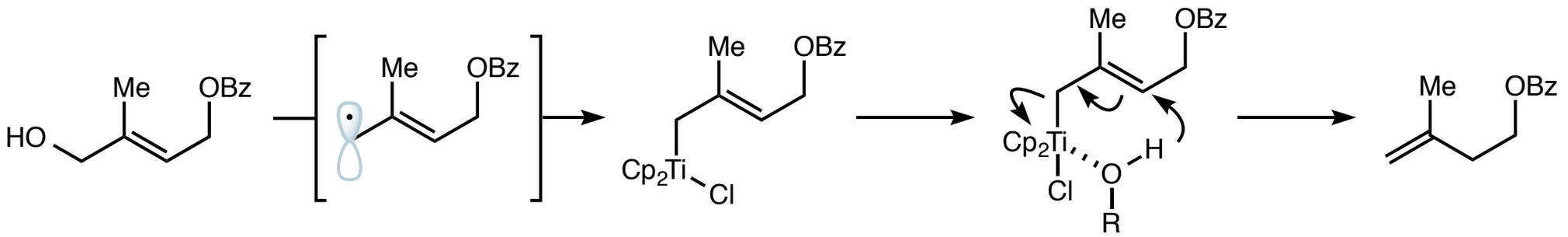
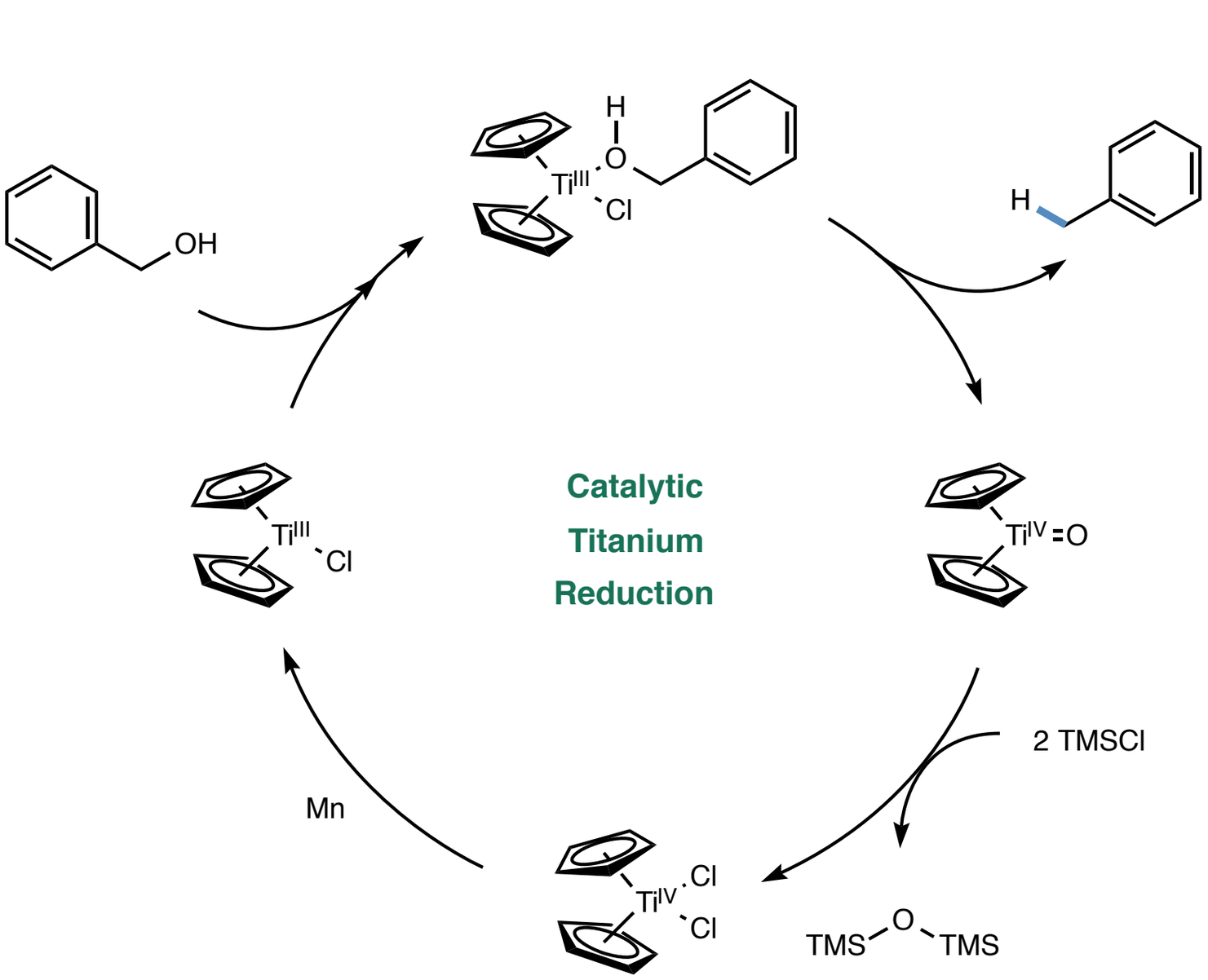
Titanium Mediated Alcohol Reduction

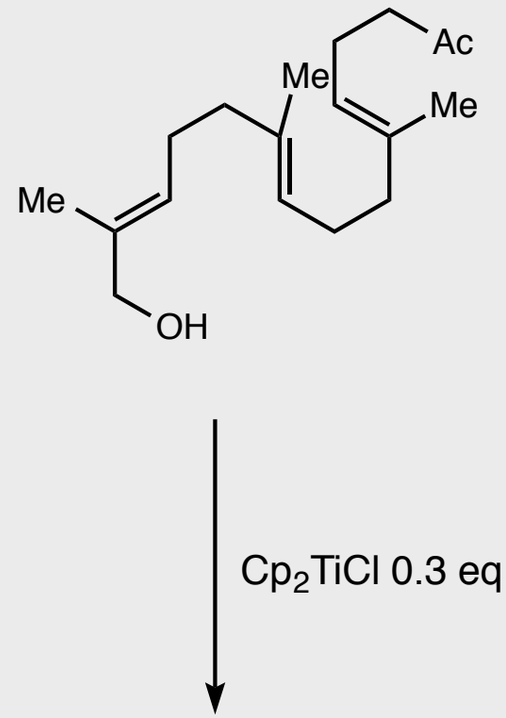


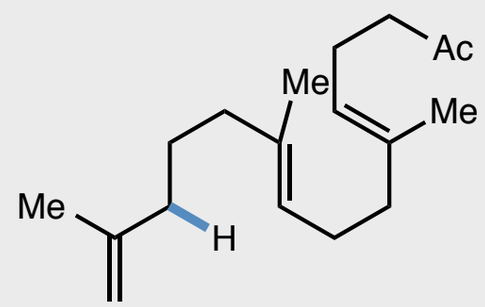


Barrero, A. F. *et al Org. Biomol. Chem.* **2015**, *13*, 3462

Titanium Catalyzed Alcohol Reduction







85% (*38% stoichiometric*)

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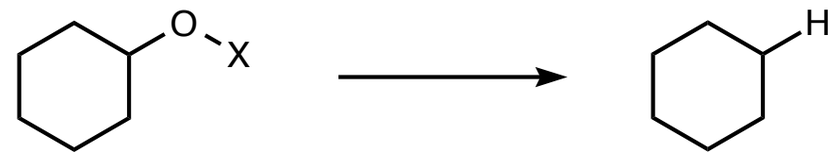
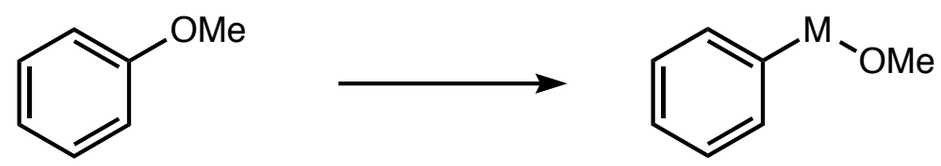
Functionalization of C–O Bonds

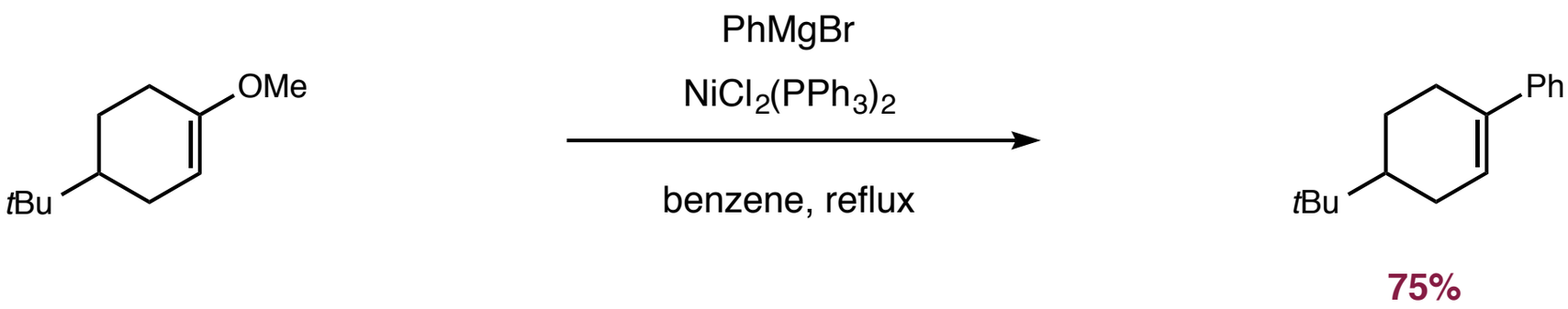
- **Radical alcohol deoxygenation**
  - **Thiocarbonyl methods**
  - **Phosphite activation**
  - **Thiol catalysis**
  - **Titanium-mediated deoxygenation**

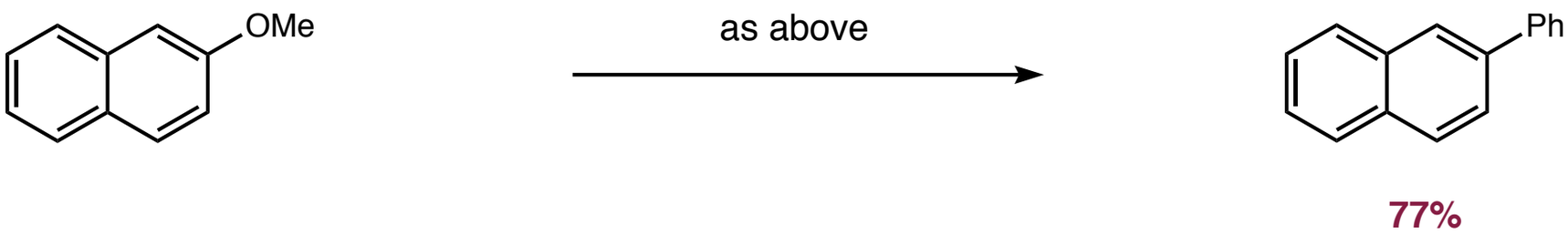


- **Transition metal C–O bond insertion**
  - **Aryl methyl ether electrophiles**
  - **Ru directed C–O bond insertion**
  - **Phenol cross-coupling**



First Report of Aryl Methyl Ether Cross-Coupling

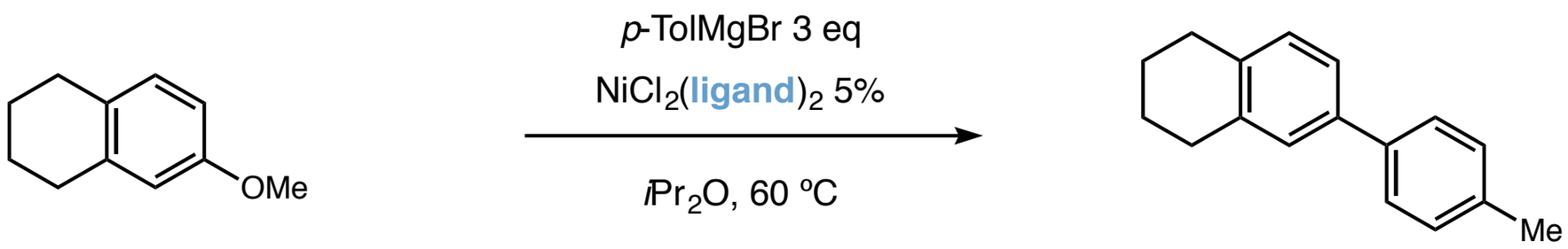




much more efficient for napthyl ethers, although some reactivity observed for anisoles

Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246

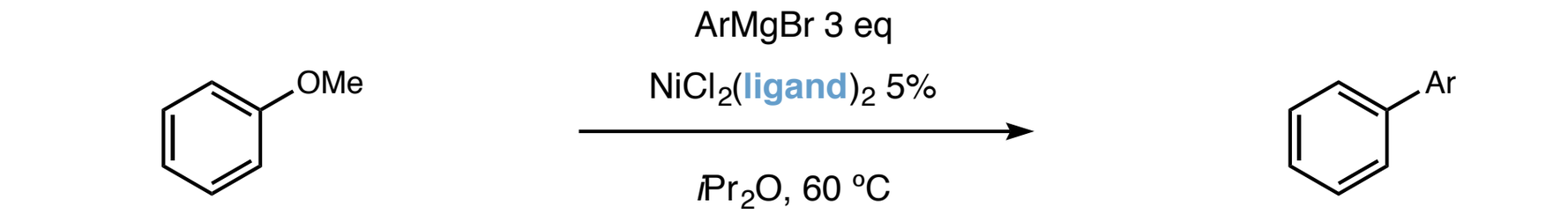
Extension to Anisole Electrophiles

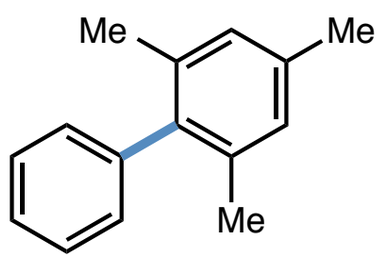


ligand	ArOMe	yield
PEt_3	75%	7%
$P\textit{i}Bu_3$	32%	42%
$P\textit{i}Pr_3$	<1%	82%
PCy_3	0%	93%
PPh_2Cy	7%	81%
PPh_3	74%	15%

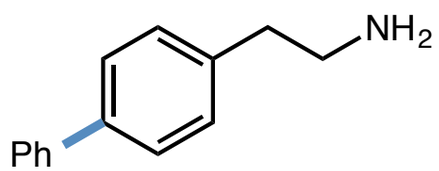
Dankwardt, J. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2428

Extension to Anisole Electrophiles





75%



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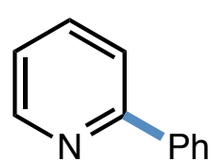
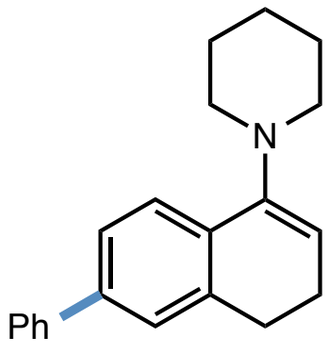
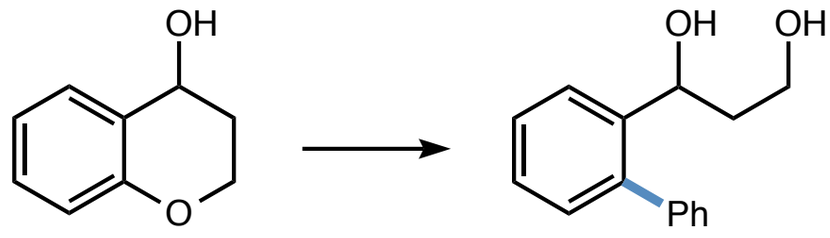


73%



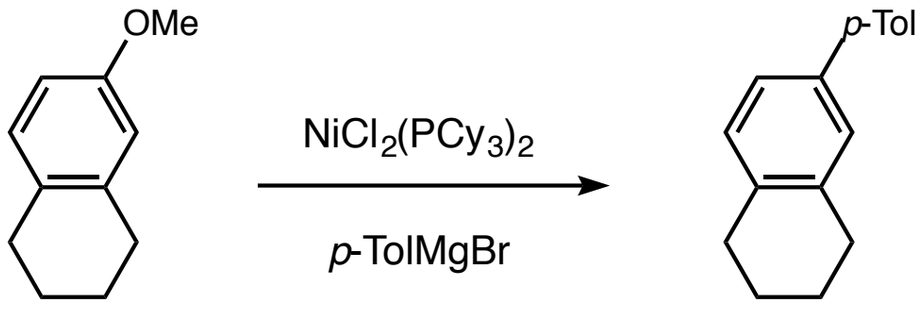
58%



51%

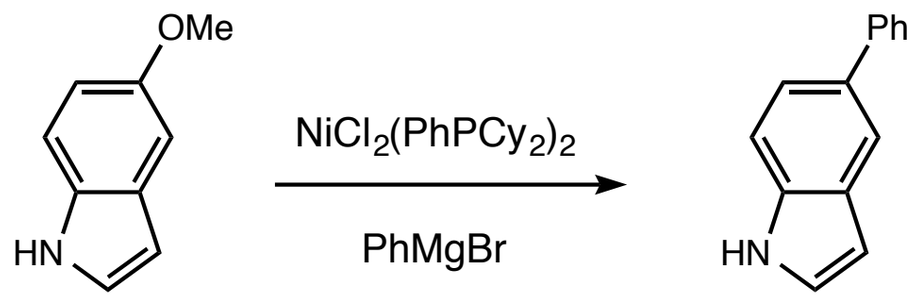
Dankwardt, J. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2428

Methyl Ether Kumada Cross-Couplings



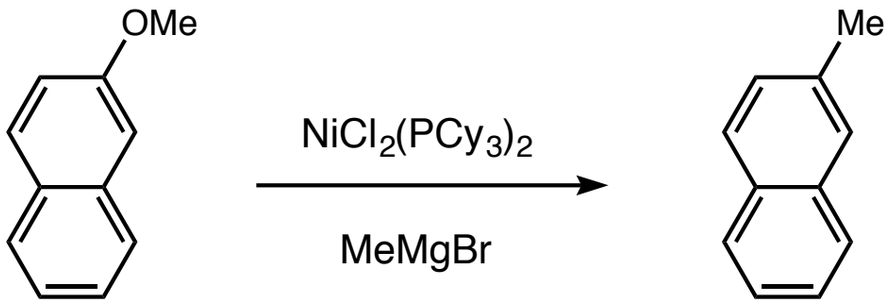
non-extended aromatics

Angew. Chem. Int. Ed. **2004**, *43*, 2428



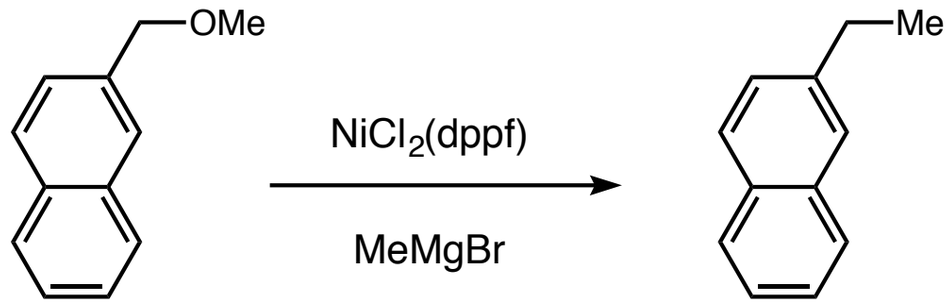
heterocycles

Angew. Chem. Int. Ed. **2004**, *43*, 2428



alkyl Grignards

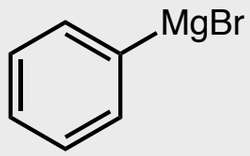
Chem. Commun. **2008**, 1437



benzylic ethers

J. Am. Chem. Soc. **2008**, *130*, 3268

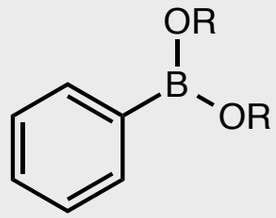
Aryl Methyl Ether Cross-Couplings



poor functional group compatibility

limited availability

challenging to prepare



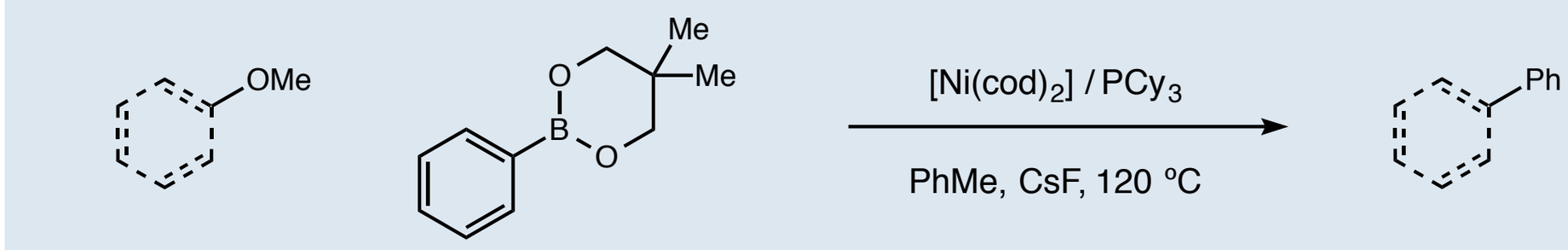
air and moisture stability

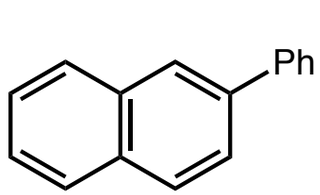
widespread availability

potentially lower reactivity

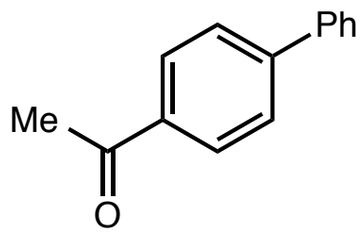
development of an aryl methyl ether Suzuki-Miyaura coupling would be highly advantageous

Aryl Methyl Ether Suzuki-Miyaura





93%



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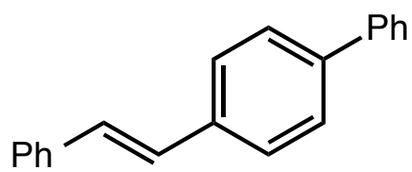

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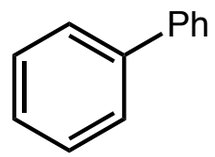

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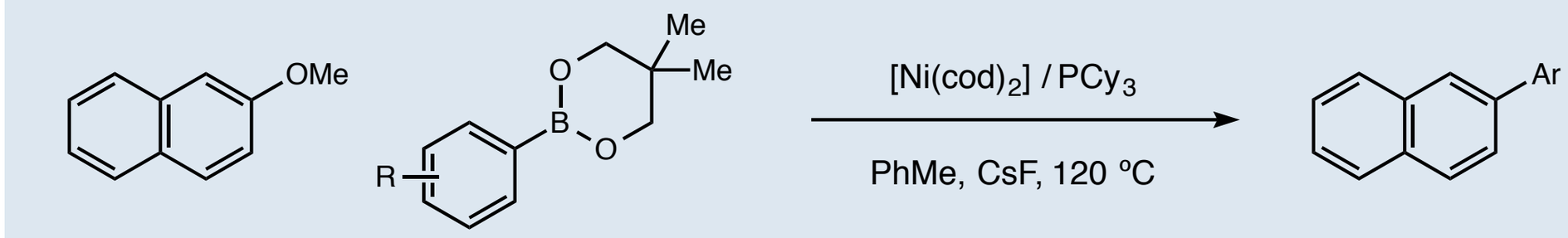
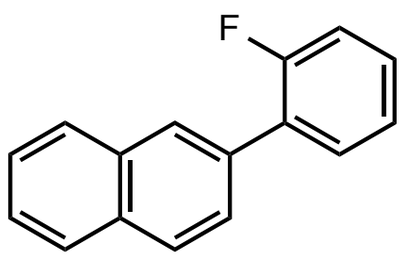
Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866

Aryl Methyl Ether Suzuki-Miyaura





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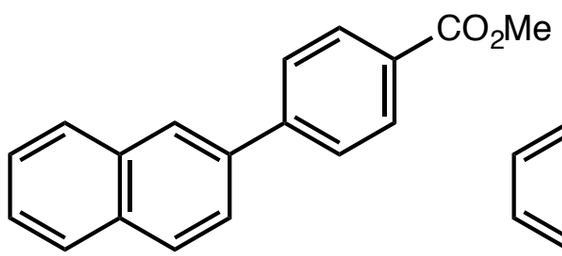

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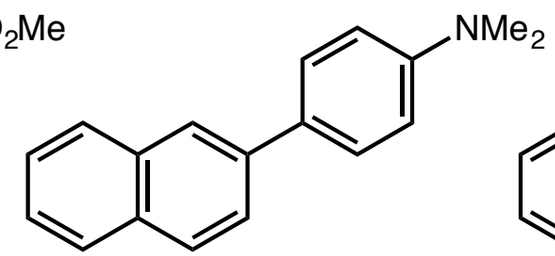

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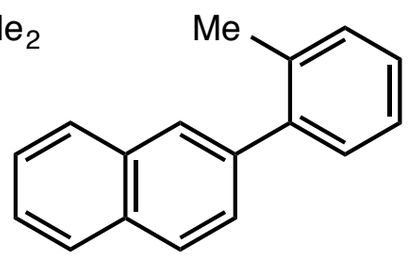

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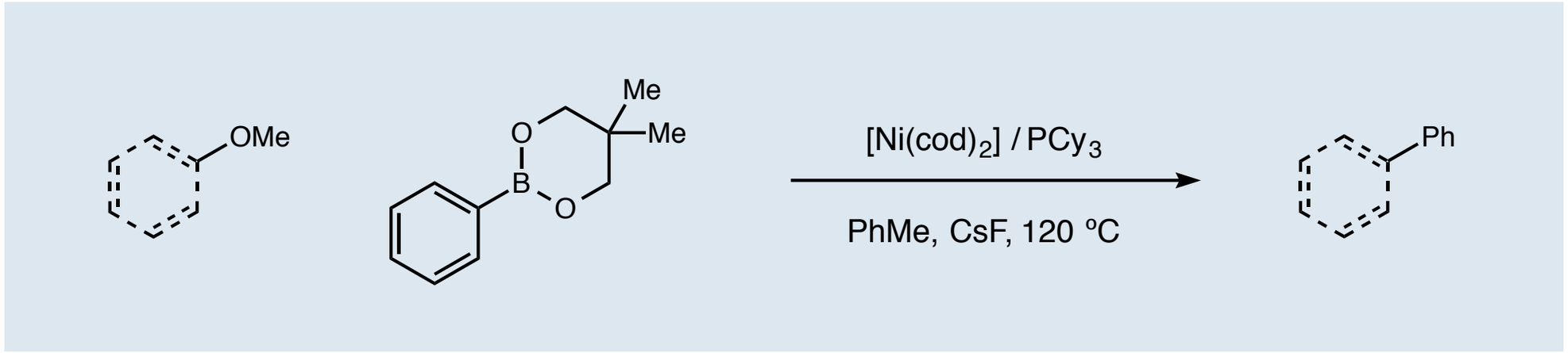
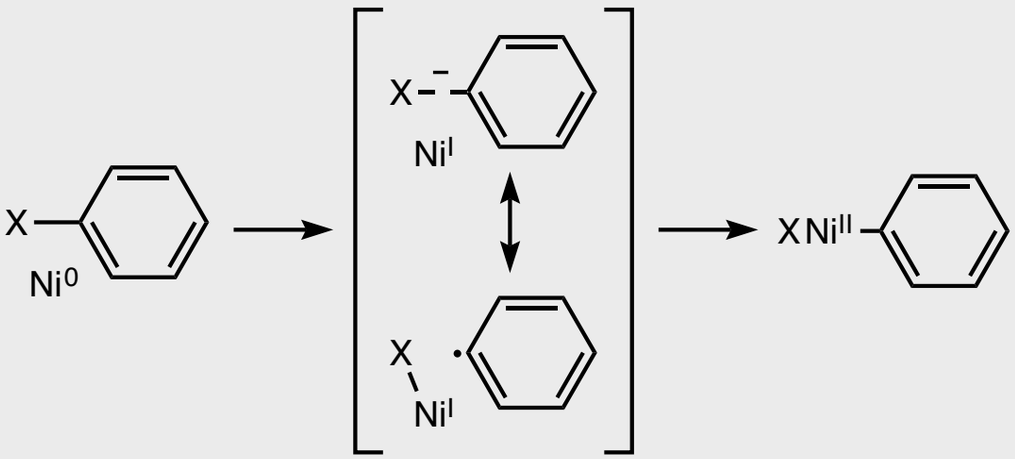
Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866

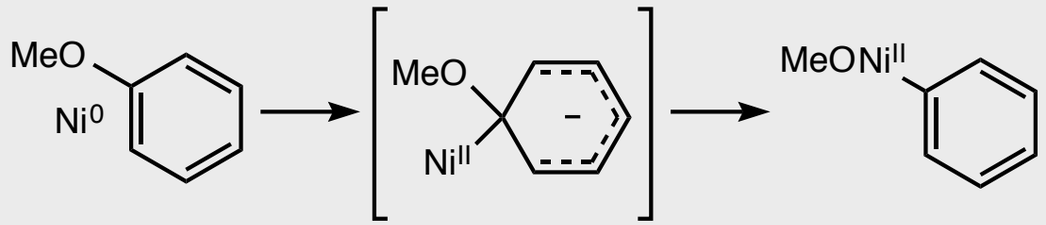
Aryl Methyl Ether Suzuki-Miyaura



requirement for extended conjugation suggests an alternative oxidative addition mechanism



Kochi electron transfer OA

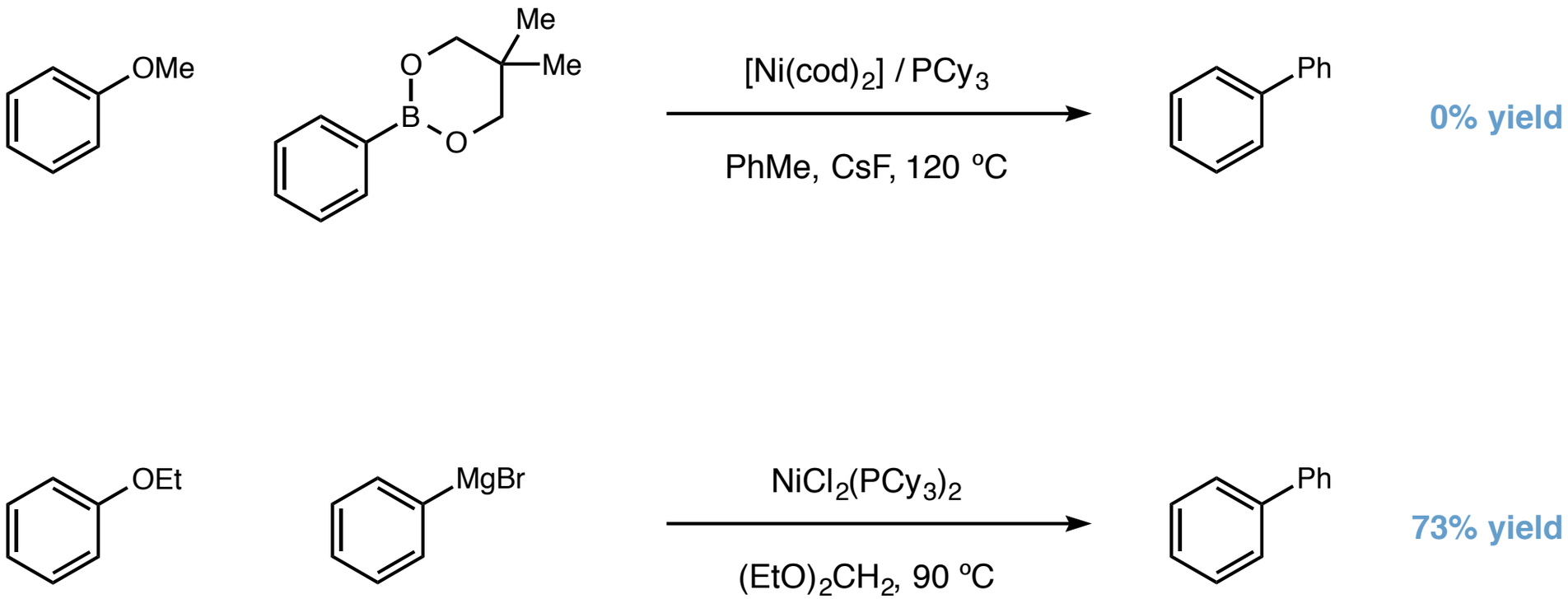


nucleophilic type OA

Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866

Aryl Methyl Ether Suzuki-Miyaura

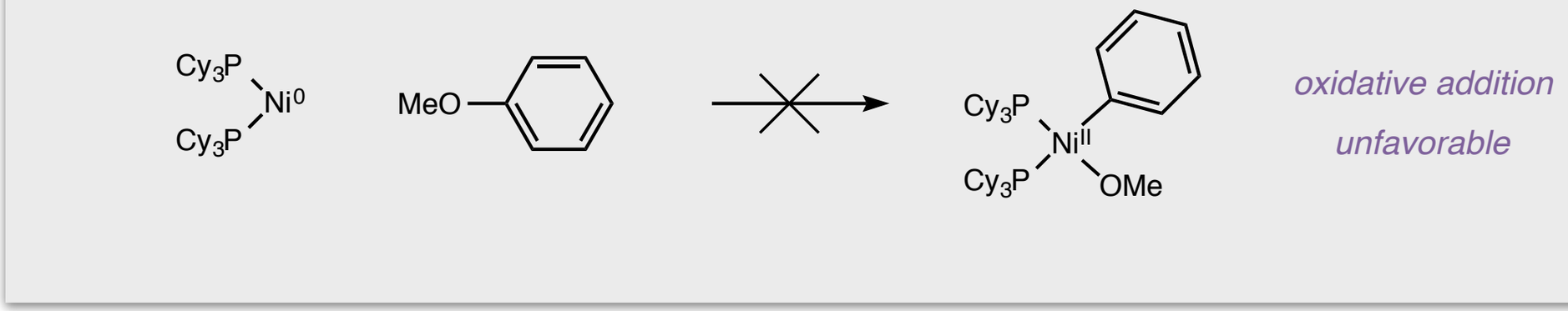
ArOMe effective electrophile in Kumada but not Suzuki-Miyaura coupling

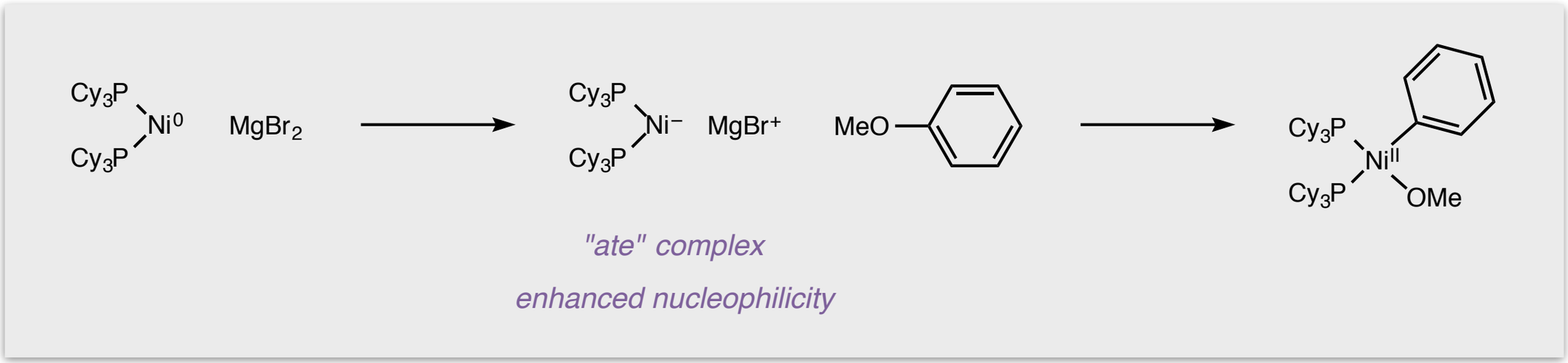


Dankwardt, J. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2428

Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246

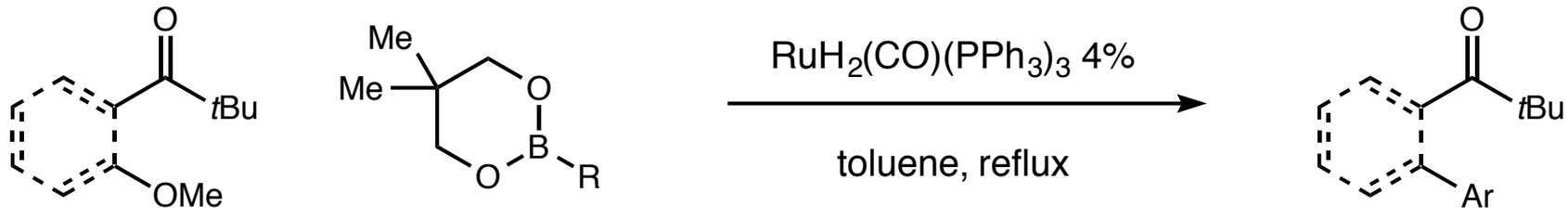
Aryl Methyl Ether Suzuki-Miyaura

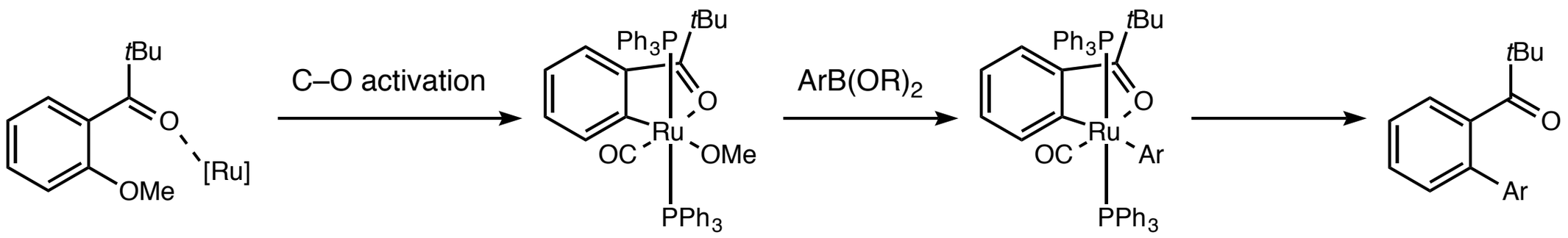




Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246

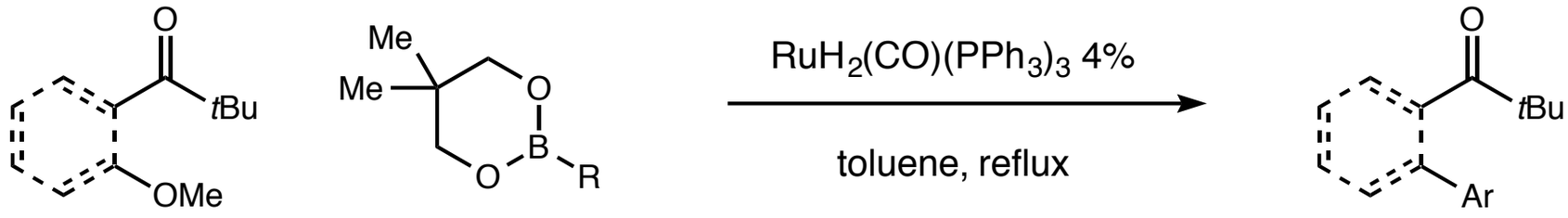
Directed Ru C–O Bond Cross Coupling

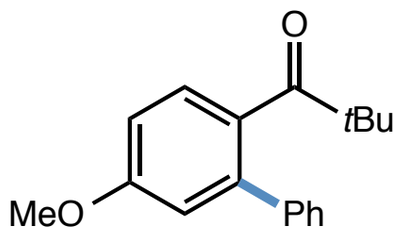




Kakiuchi, F.; Tsui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706

Directed Ru C–O Bond Cross Coupling





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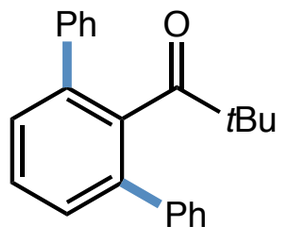

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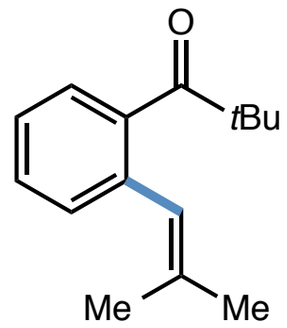

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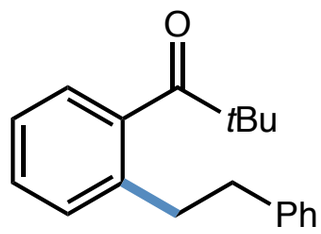

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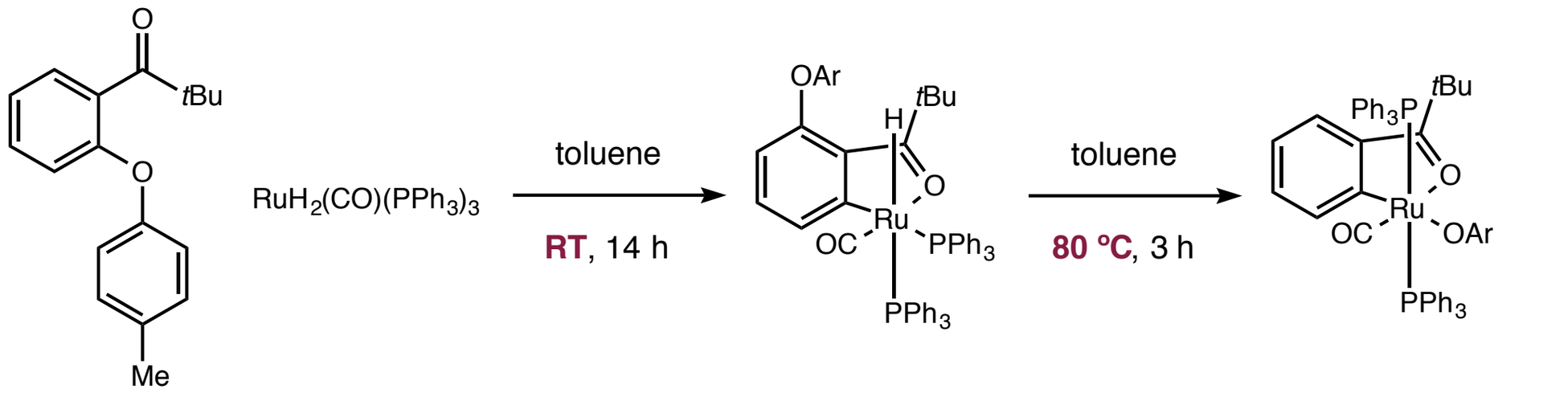
Kakiuchi, F.; Tsui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706

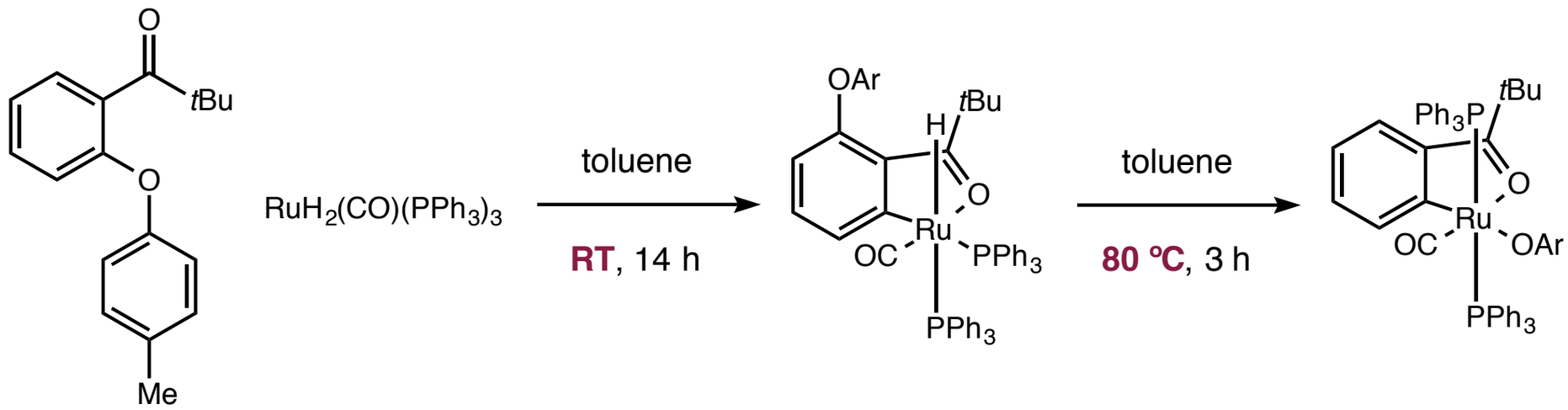
Directed Ru C–O Bond Cross Coupling



kinetic product **thermodynamic product**

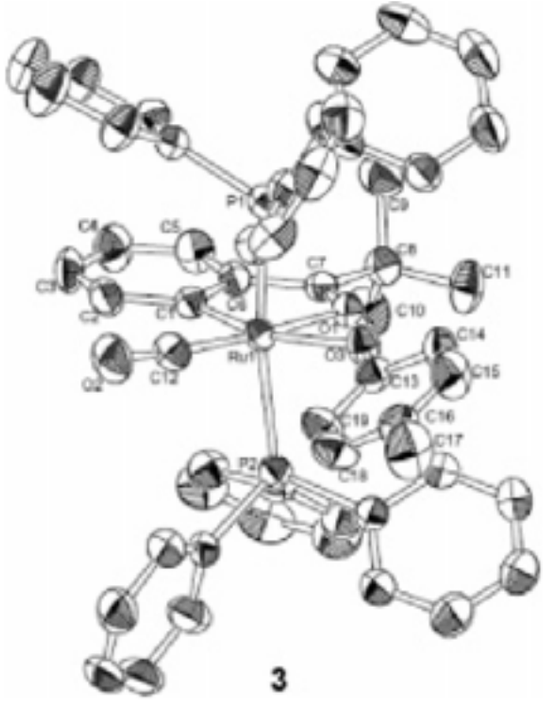
Uno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516

Directed Ru C–O Bond Cross Coupling



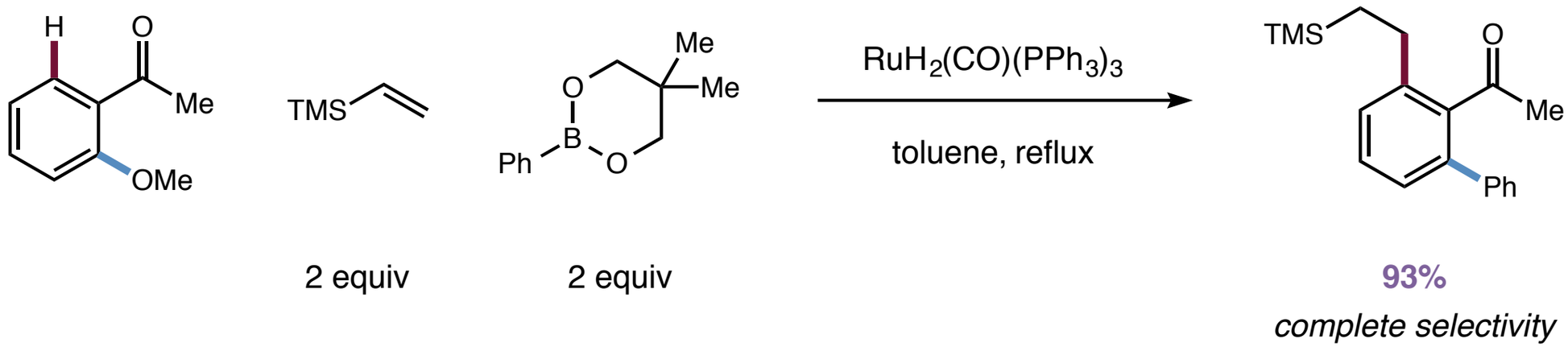
first example of an isolated aryl C–O bond

oxidative addition complex with transition metal



Uno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516

Directed Ru C–O Bond Cross Coupling



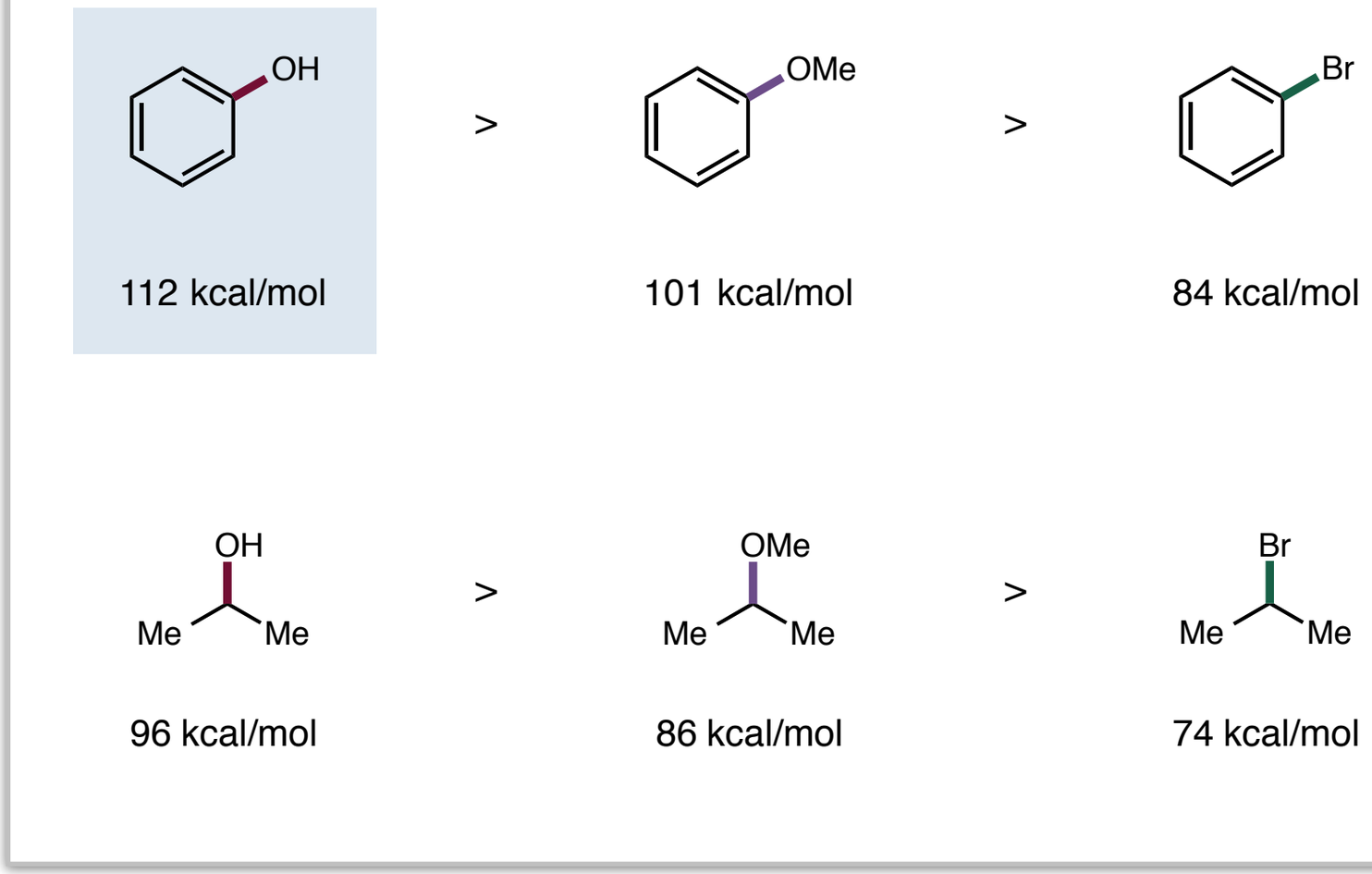
2 equiv 2 equiv

93%

complete selectivity

Uno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516

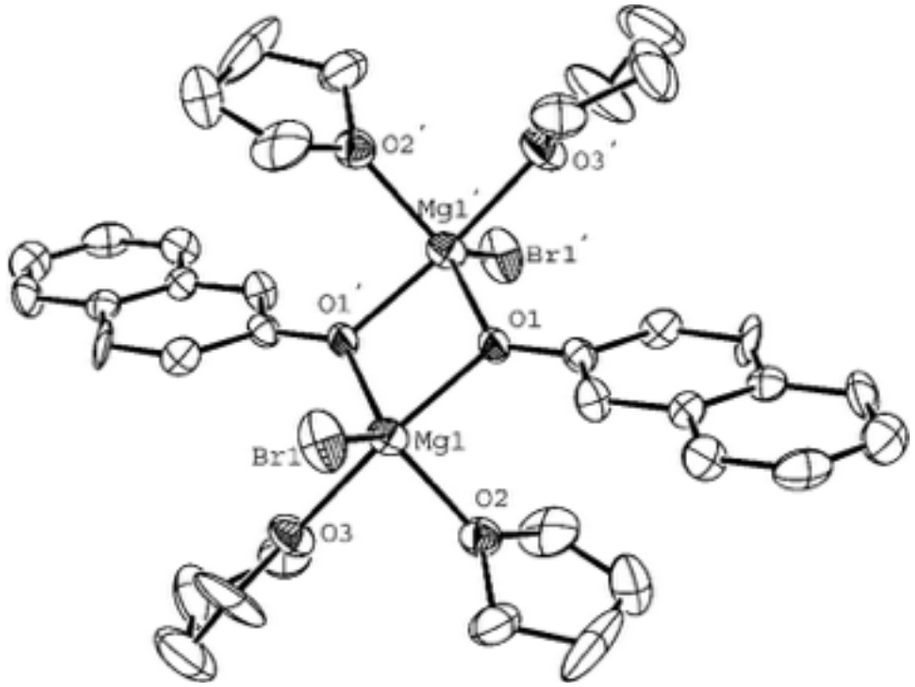
Activation of C–O Bonds is Challenging



carbon–oxygen bonds are much stronger than the corresponding carbon–halide bonds

Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255

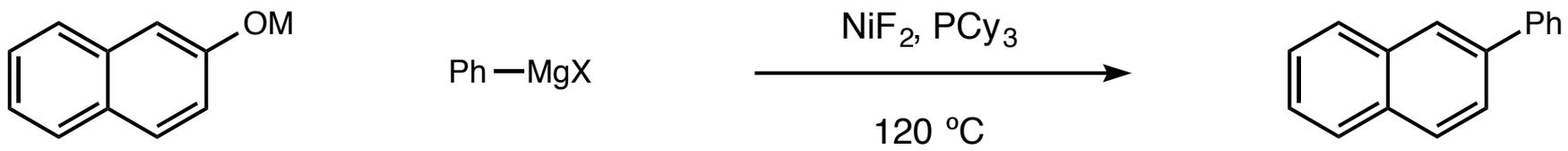
Phenolic C–O Bond Cross-Coupling



[{2-NapOMgBr(THF)$_2$}$_2$]

Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4566

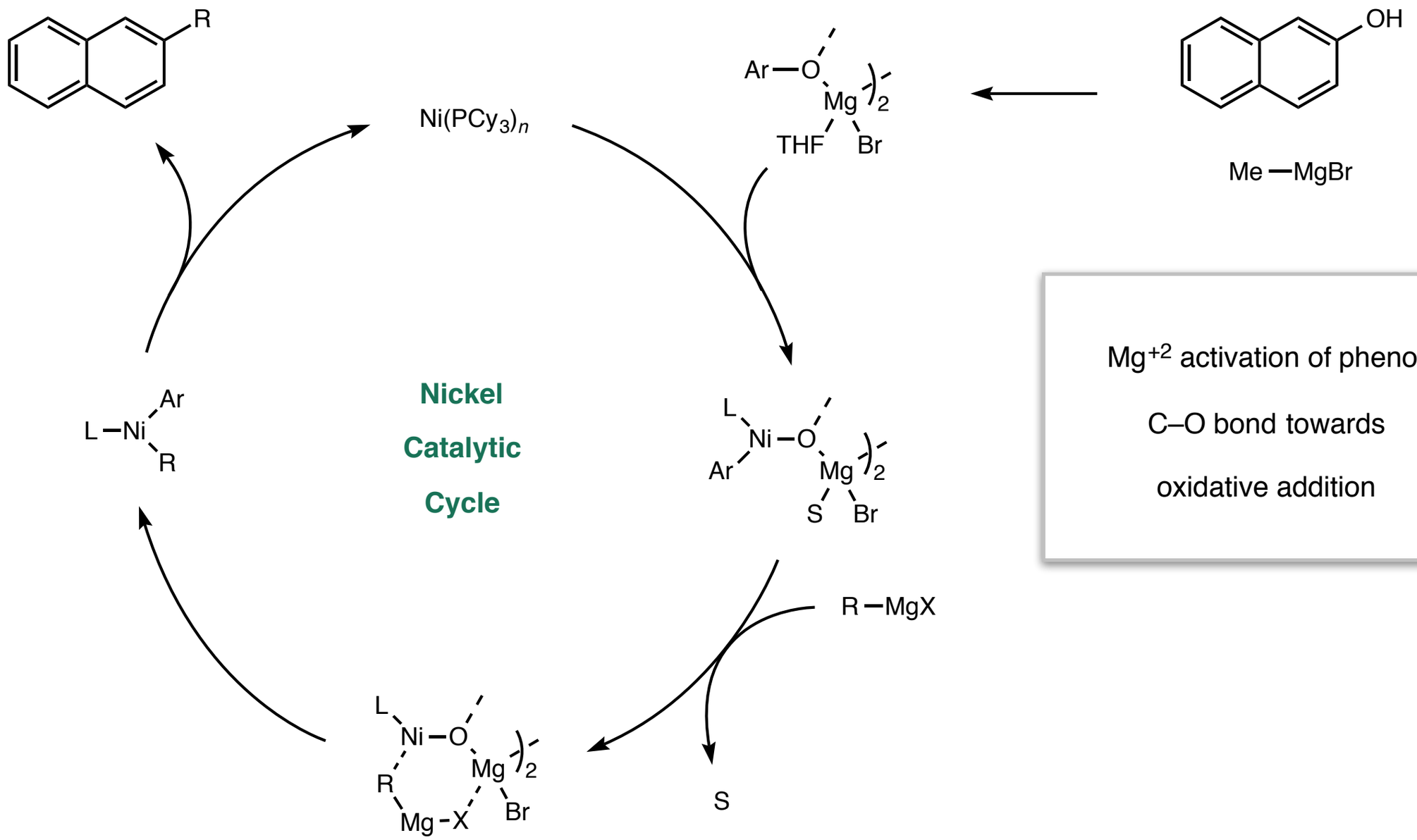
Phenolic C–O Bond Cross-Coupling



metal salt	halide	GC yield
Li^{+}	Br^{-}	8%
K^{+}	Br^{-}	14%
Na^{+}	Br^{-}	81%
Mg^{+2}	Br^{-}	99%
Mg^{+2}	Cl^{-}	64%
Mg^{+2}	I^{-}	87%

Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4566

Phenolic C–O Bond Cross-Coupling



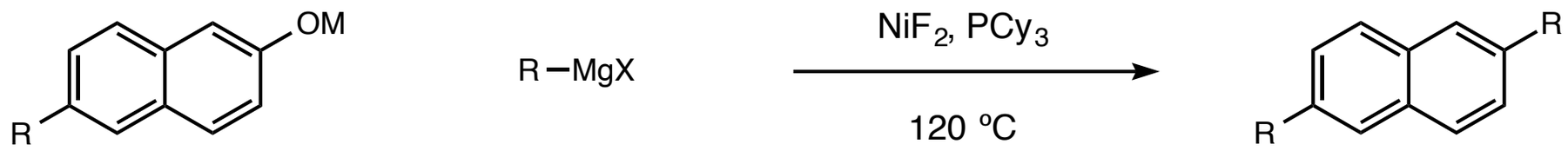
Mg^{+2} activation of phenol

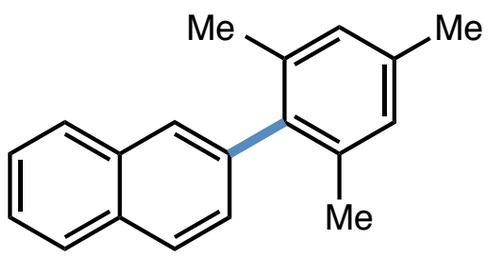
C–O bond towards

oxidative addition

Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4566

Phenolic C–O Bond Cross-Coupling





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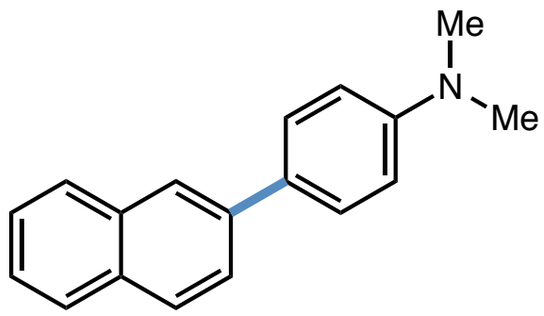

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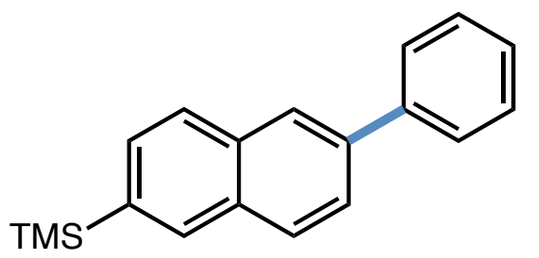

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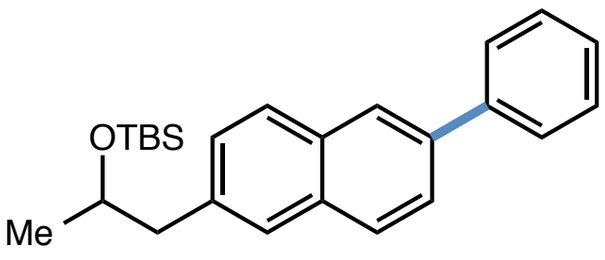

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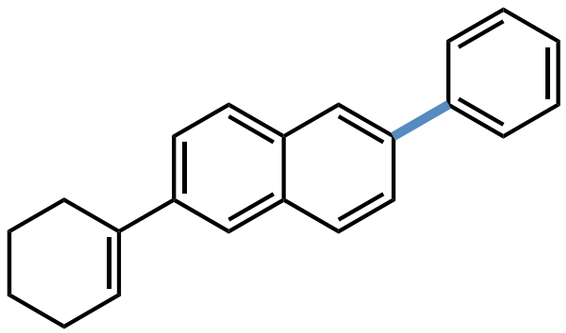

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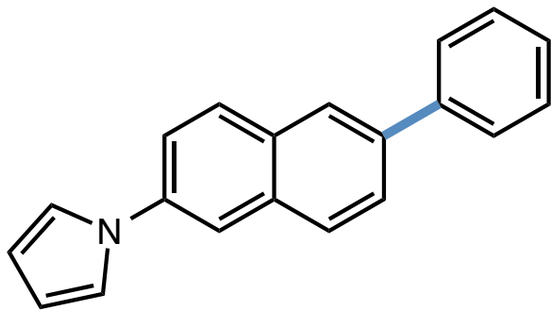

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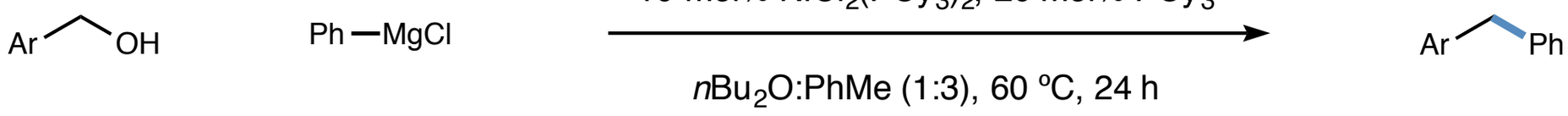
Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4566

Benzylic Alcohol C–O Bond Cross-Coupling

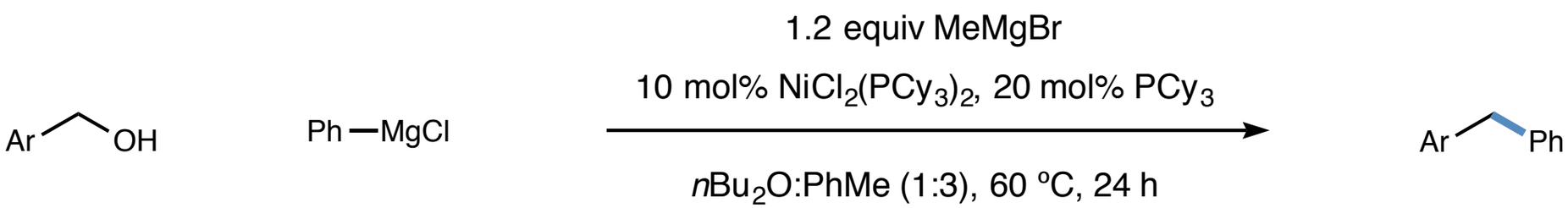


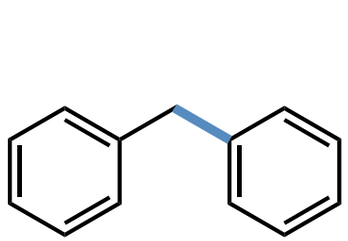
methyl Grignard reagent to form magnesium alkoxide

benzylic alcohol C–O bond weaker than phenol - reflected in lower T required

Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638

Benzylic Alcohol C–O Bond Cross-Coupling





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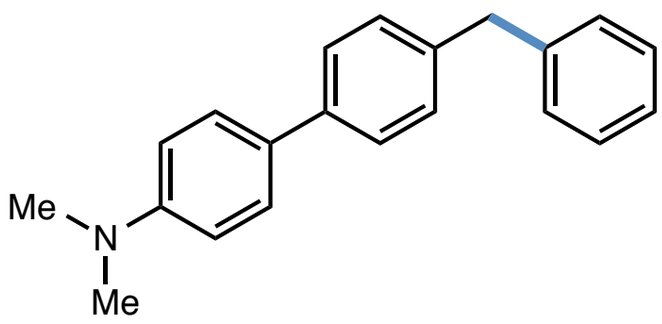

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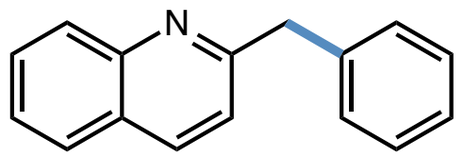

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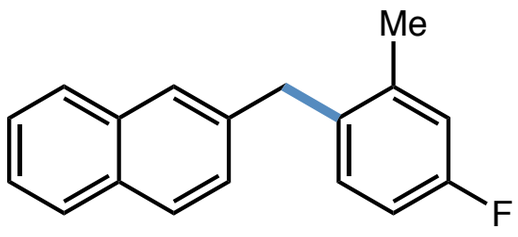

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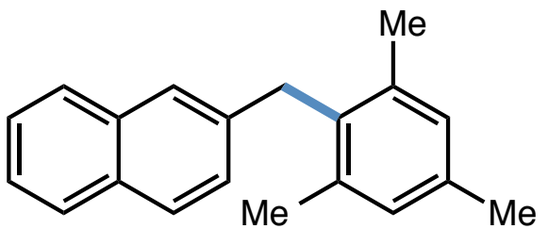

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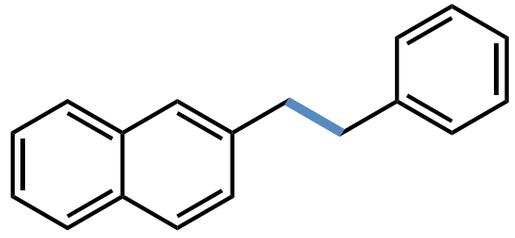
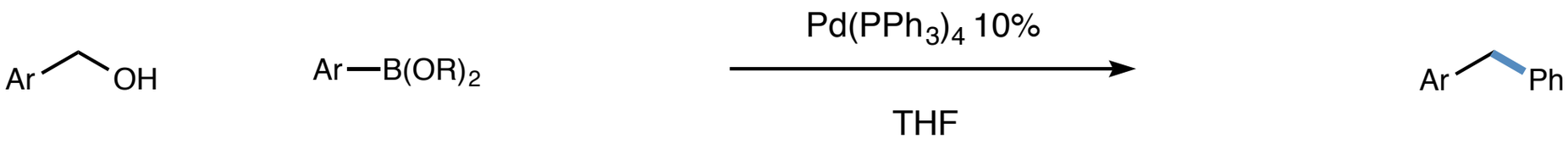


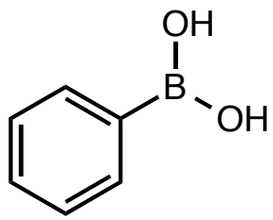
67%

alkyl Grignard reagents were not effective

Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638

Benzylic Alcohol C–O Suzuki-Miyaura





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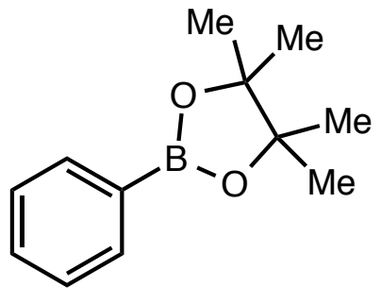

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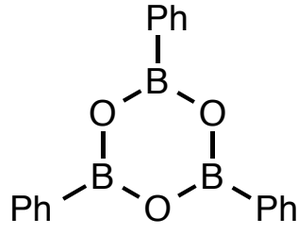

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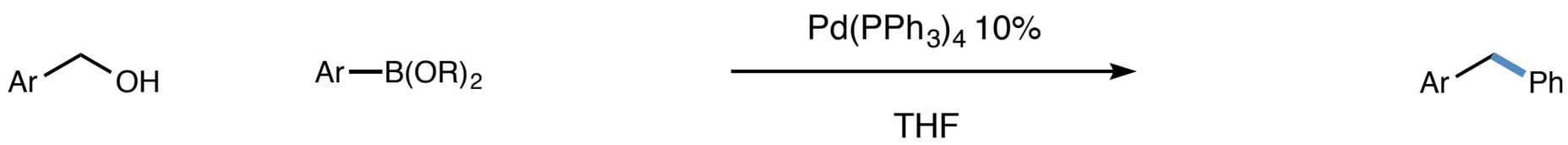
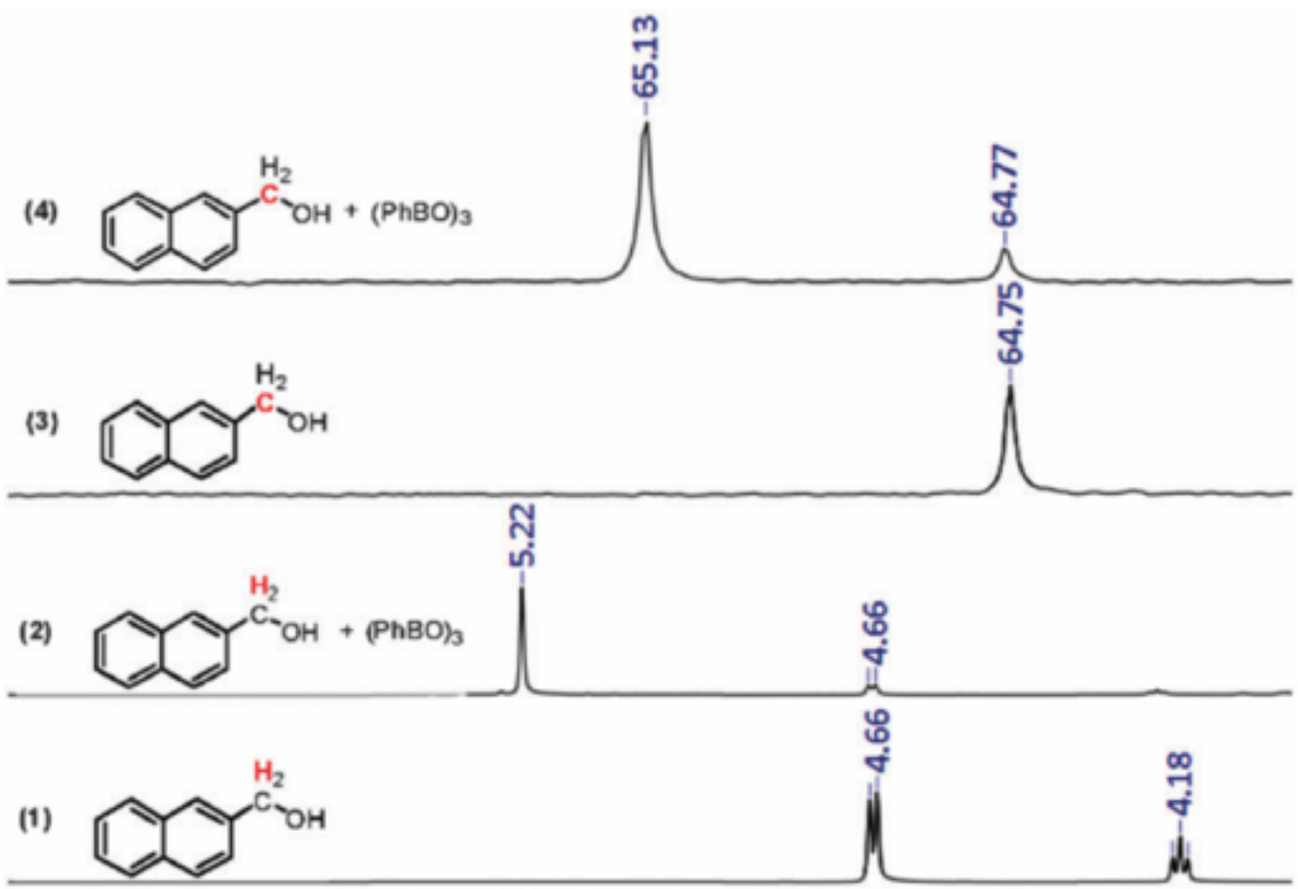
Cao, Z.-C.; Yu, D.-G.; Zhu, R.-Y.; Wei, J.-B.; Shi, Z.-J. *Chem. Commun.* **2015**, *51*, 2683

Benzylic Alcohol C–O Suzuki-Miyaura

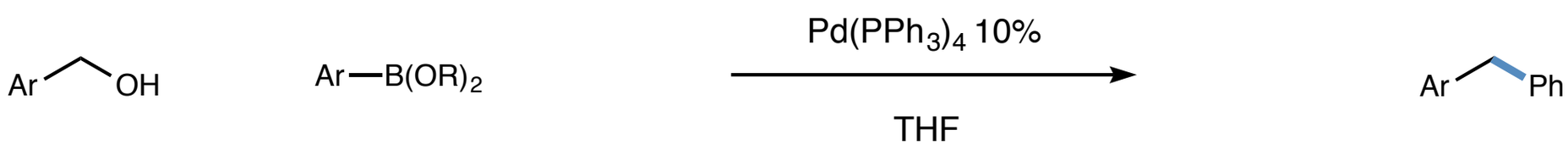


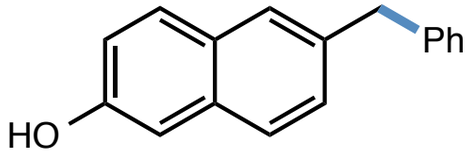


coordination of alcohol to phenylboroxine occurs

Cao, Z.-C.; Yu, D.-G.; Zhu, R.-Y.; Wei, J.-B.; Shi, Z.-J. *Chem. Commun.* **2015**, *51*, 2683

Benzylic Alcohol C–O Suzuki-Miyaura





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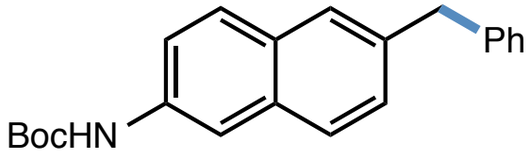
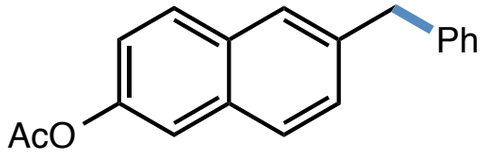


71%



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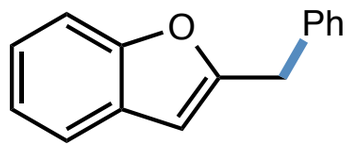

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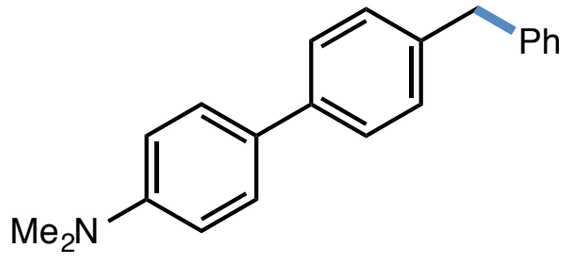

41%

Cao, Z.-C.; Yu, D.-G.; Zhu, R.-Y.; Wei, J.-B.; Shi, Z.-J. *Chem. Commun.* **2015**, *51*, 2683