$C(sp^3)$–$C(sp^3)$ Cross-Coupling Using Alcohol and Alkyl Bromide

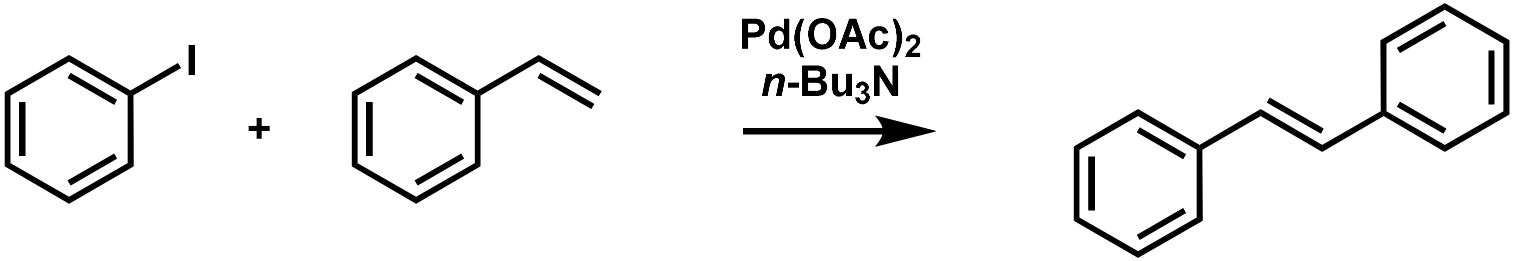
2023.04.15. Literature Seminar

D2 Yuma Komori

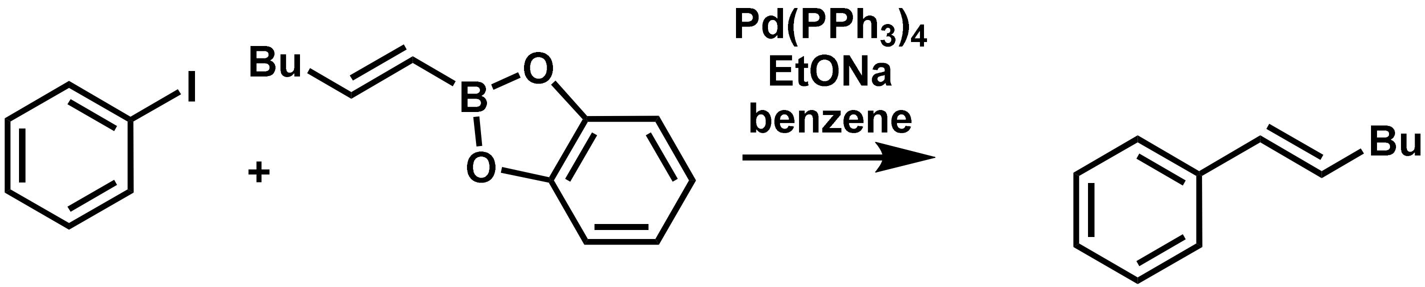
Contents

C(sp²)–C(sp²) Cross-Coupling

1. Heck reaction[1)]



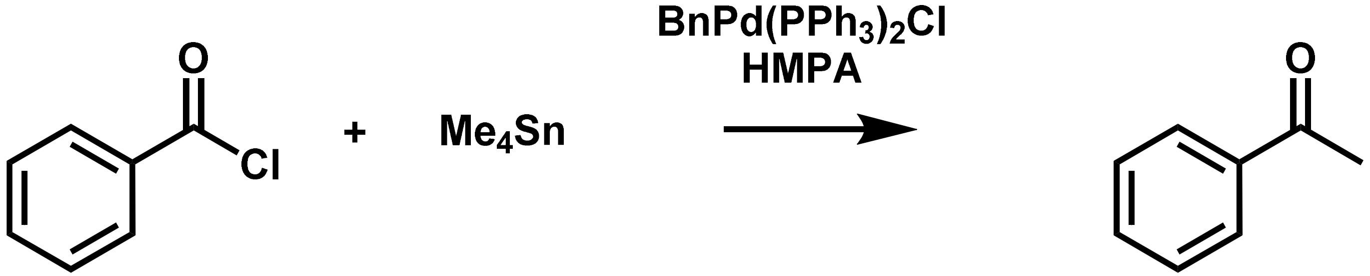
2. Suzuki–Miyaura coupling[2)]



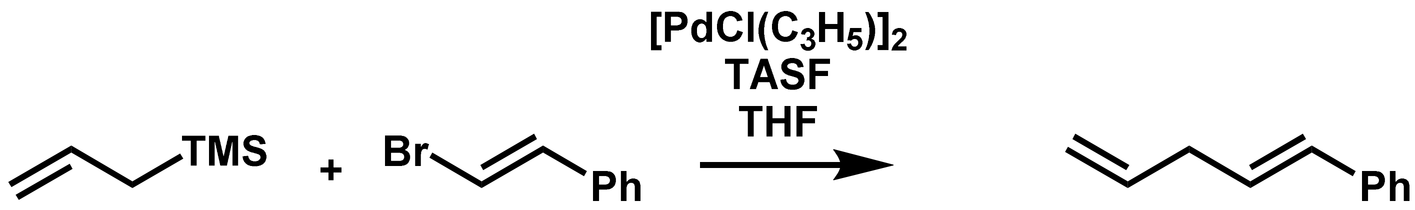
1) Heck, R. F.; Nolley, Jr. K. P. *J. Org. Chem.* **1972**, *37*, 2320.
2) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.

C(sp³)–C(sp²) Cross-Coupling

1. Stille coupling[1)]



2. Hiyama coupling[2)]



1) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.
2) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

Contents

Prof. David W. C. MacMillan

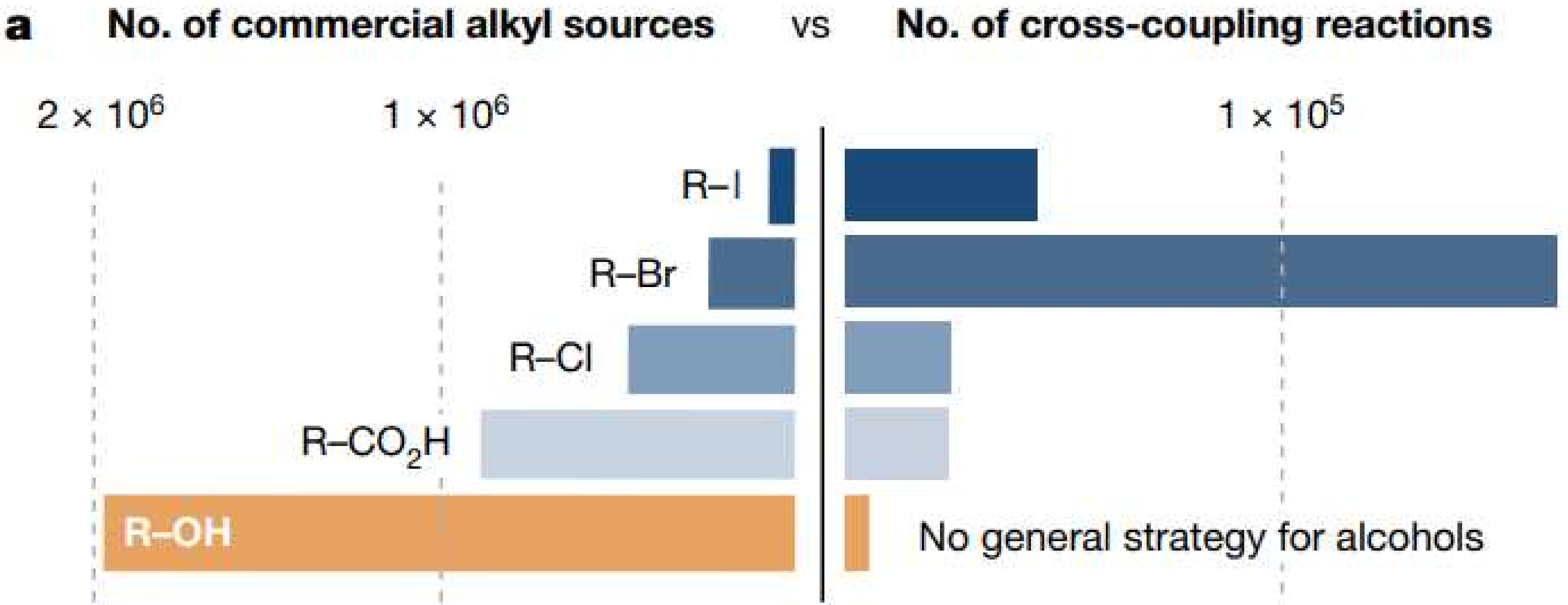
1991 B.S. @The University of Glasgow
1996 Ph.D @The University of California, Irvine (Prof. Larry E. Overman)
1996- Postdoc. @Harvard University (Prof. David A. Evans)
1998- @University of California, Berkeley
2000- @California Institute of Technology
2004- Professor @California Institute of Technology
2006- Professor @Princeton University
2011- Distinguished professor @Princeton University
2021 Nobel Prize in Chemistry

Research topics

- **Organocatalyst**
- **Photoredox**
- **Total synthesis**
- **Proximity labelling**

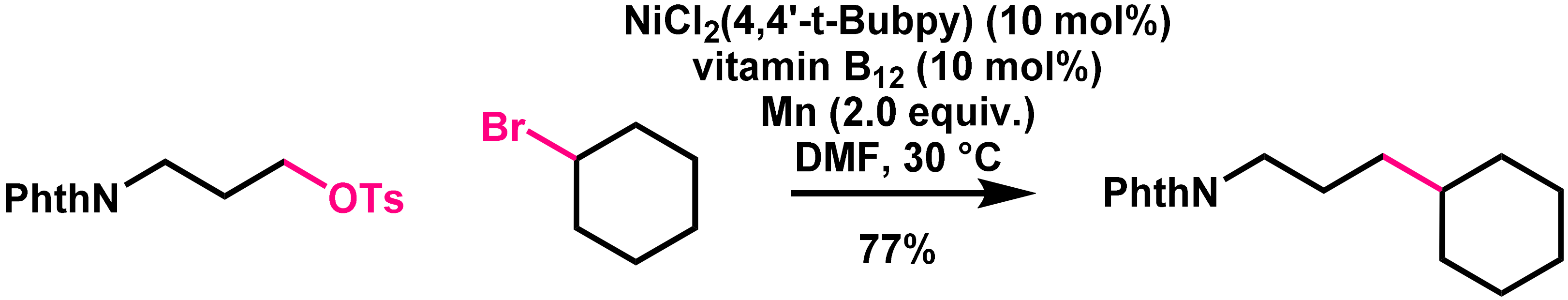
https://macmillan.princeton.edu/dave-macmillan/

Alcohol as Abundant Alkyl Source

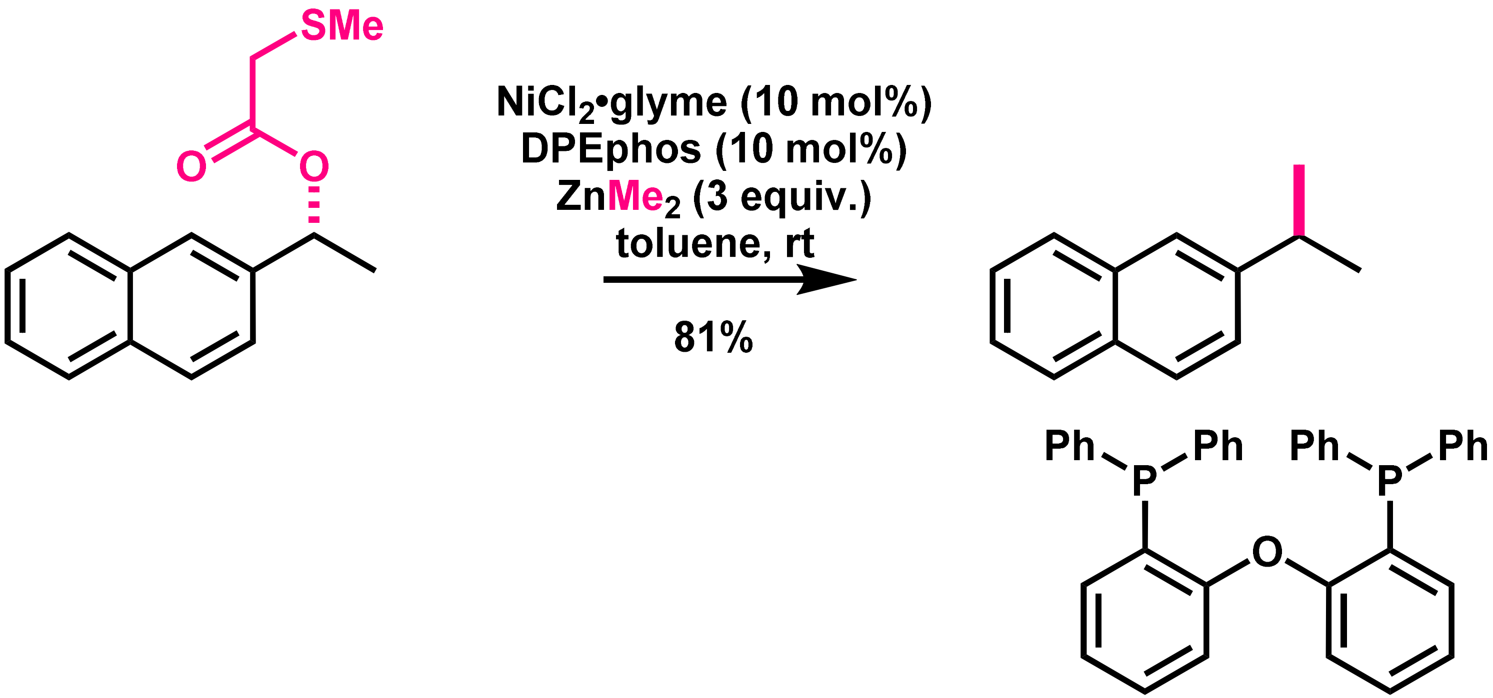


$C(sp^3)$–$C(sp^3)$ Cross-Coupling Using Alcohol Derivative

1. coupling using tosylate[1)]



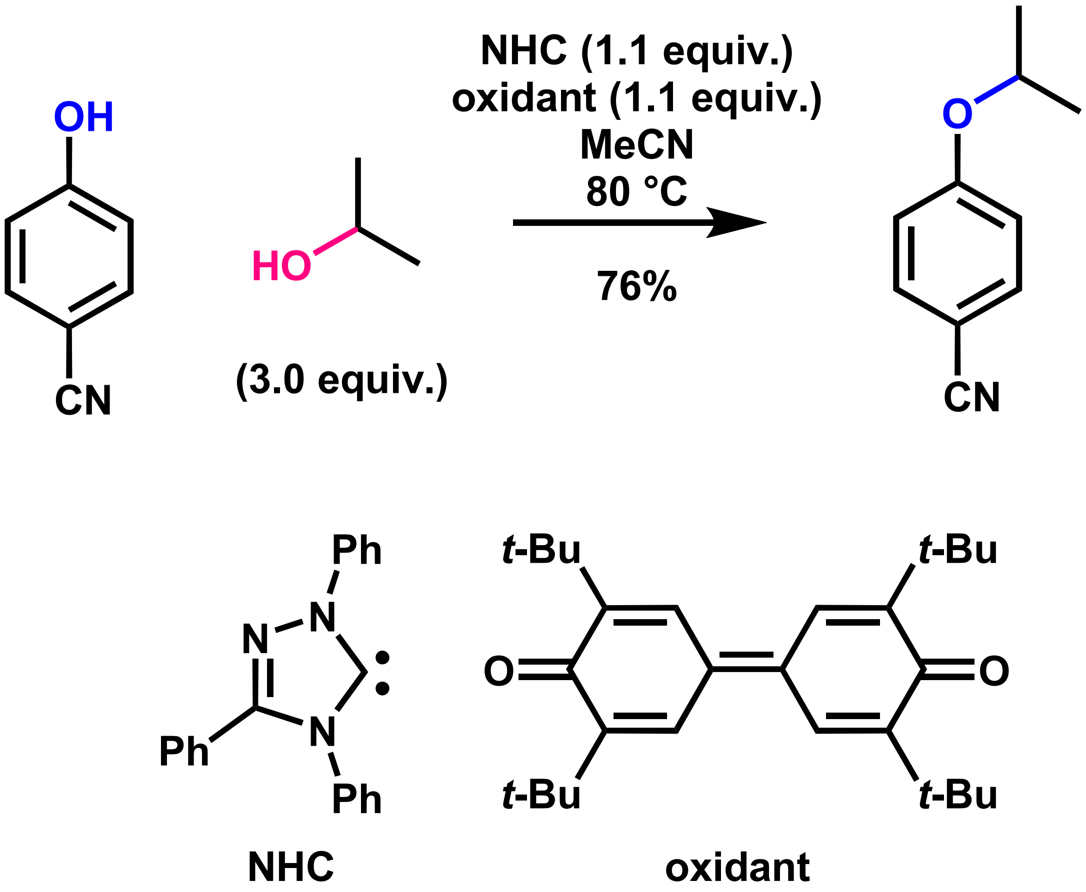
2. coupling using benzylic ester[2)]



DPEphos

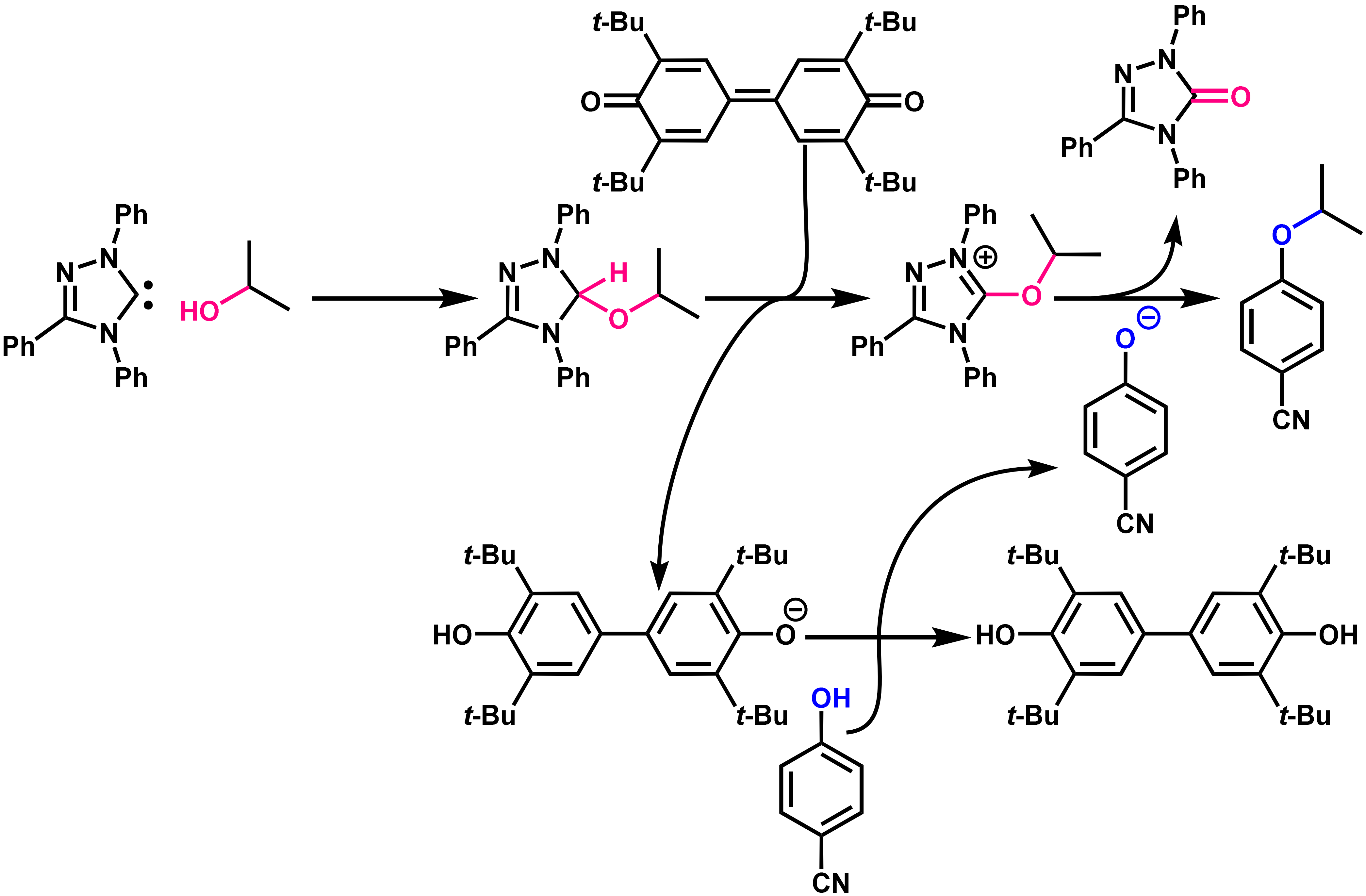
1) Komeyama, K.; Michiyuki, T.; Osaka, I. *ACS Catal.* **2019**, *9*, 9285.
2) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083.

N-Heterocyclic Carbene as Activator of Alcohol



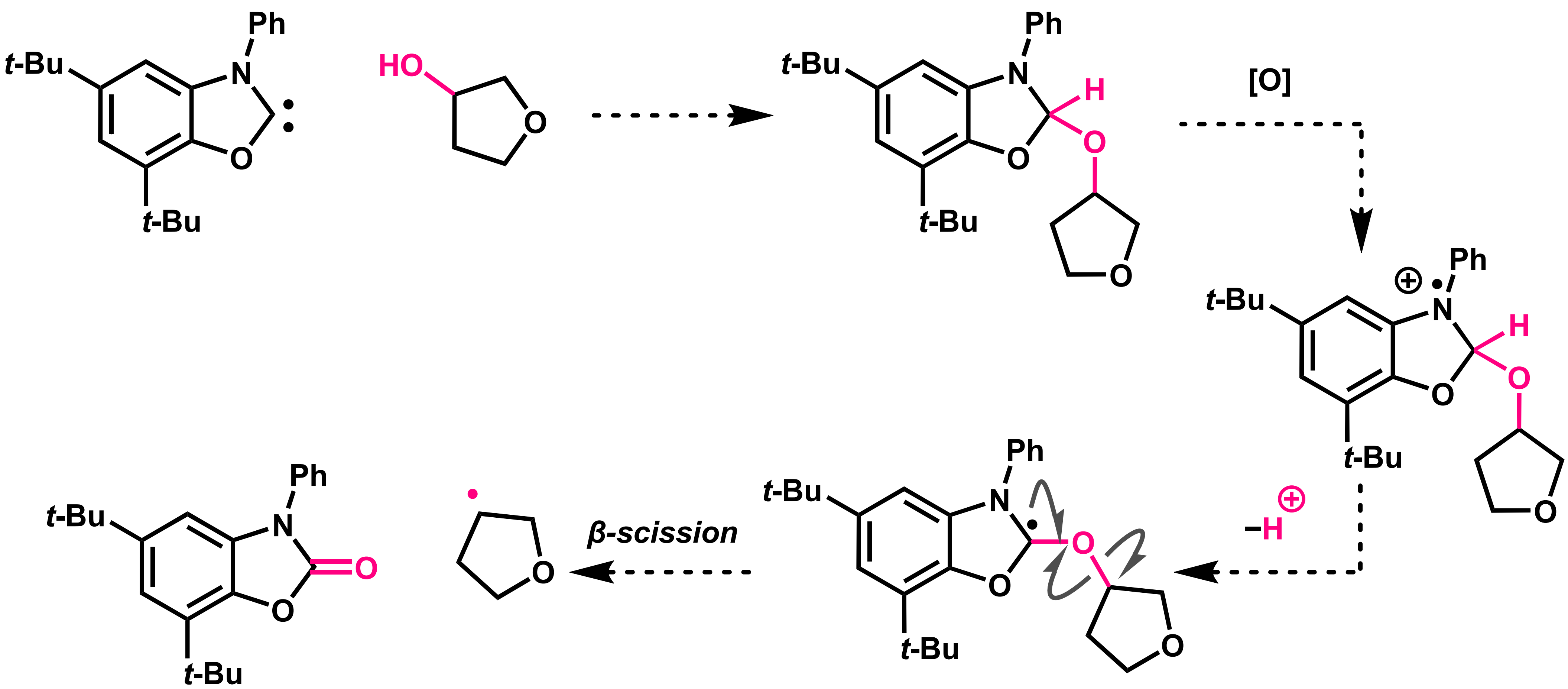
Kato, T.; Matsuoka, S.; Suzuki, M. *Chem. Commun.* **2016**, *52*, 8569.

Reaction Mechanism



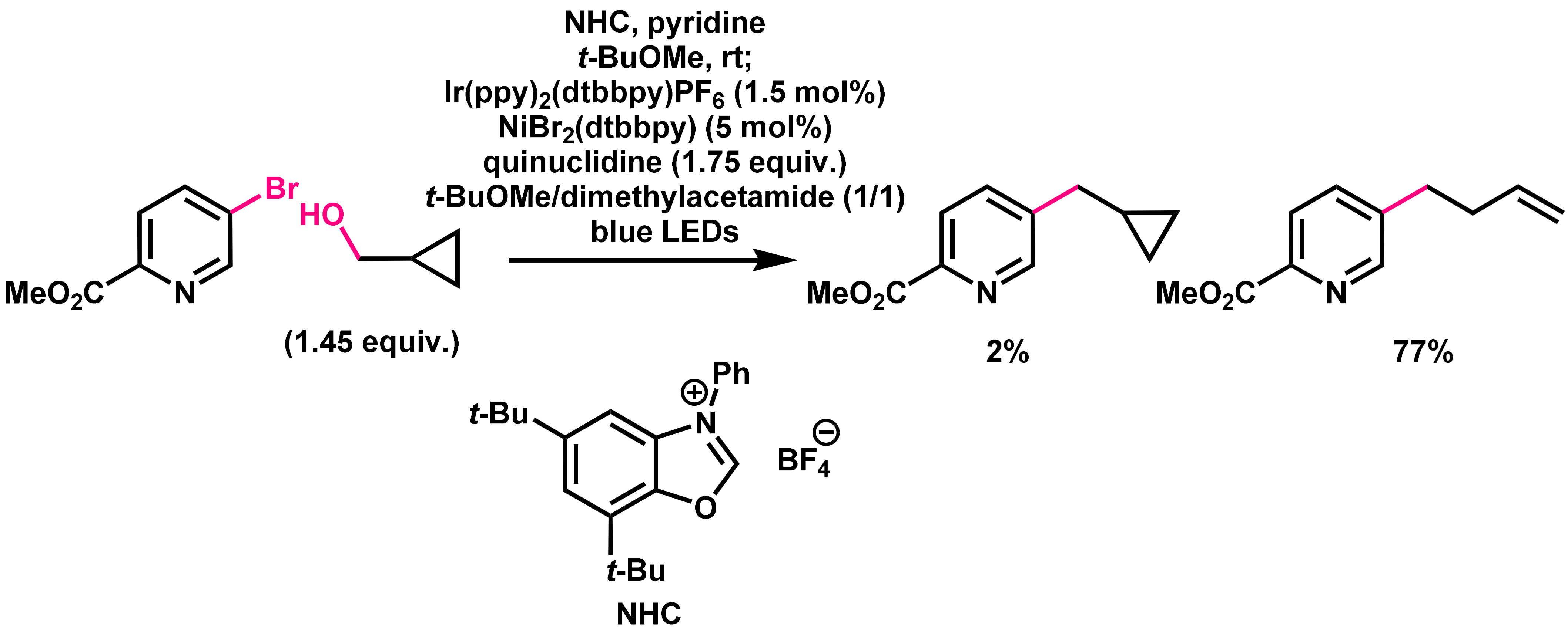
Kato, T.; Matsuoka, S.; Suzuki, M. *Chem. Commun.* **2016**, *52*, 8569.

Strategy of Activation of Alcohol



Dong, Z.; MacMillan, D. W. C. *Nature* **2021**, *598*, 451.

Study of Reaction Mechanism



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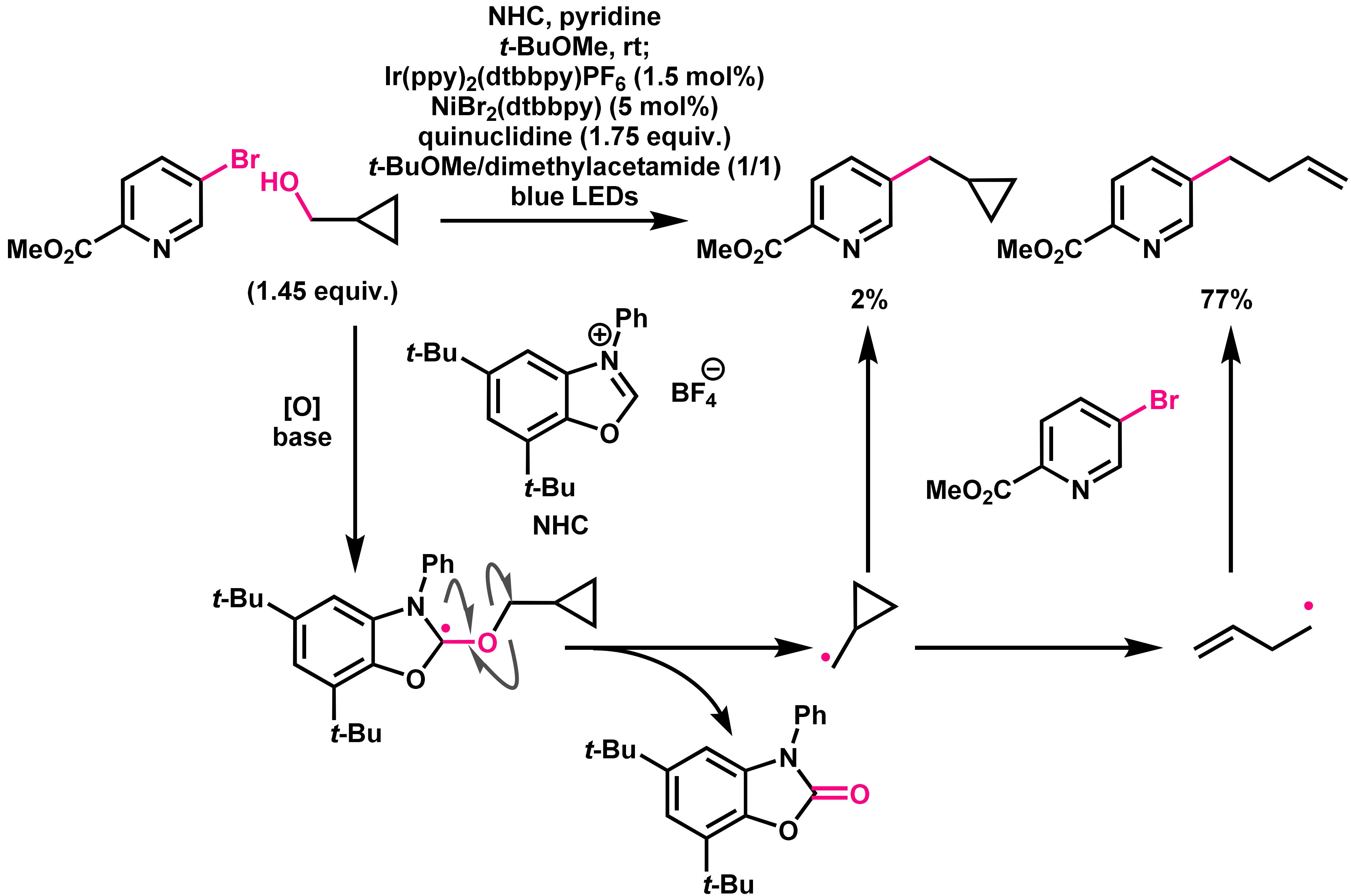
Study of Reaction Mechanism



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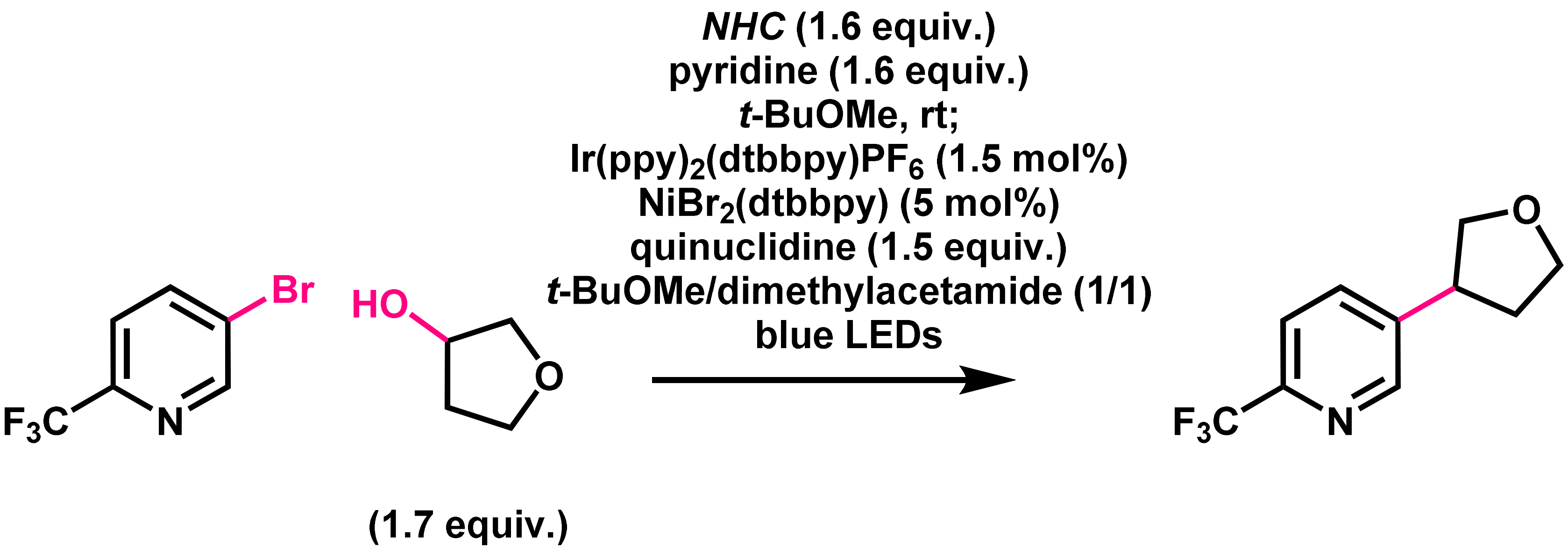
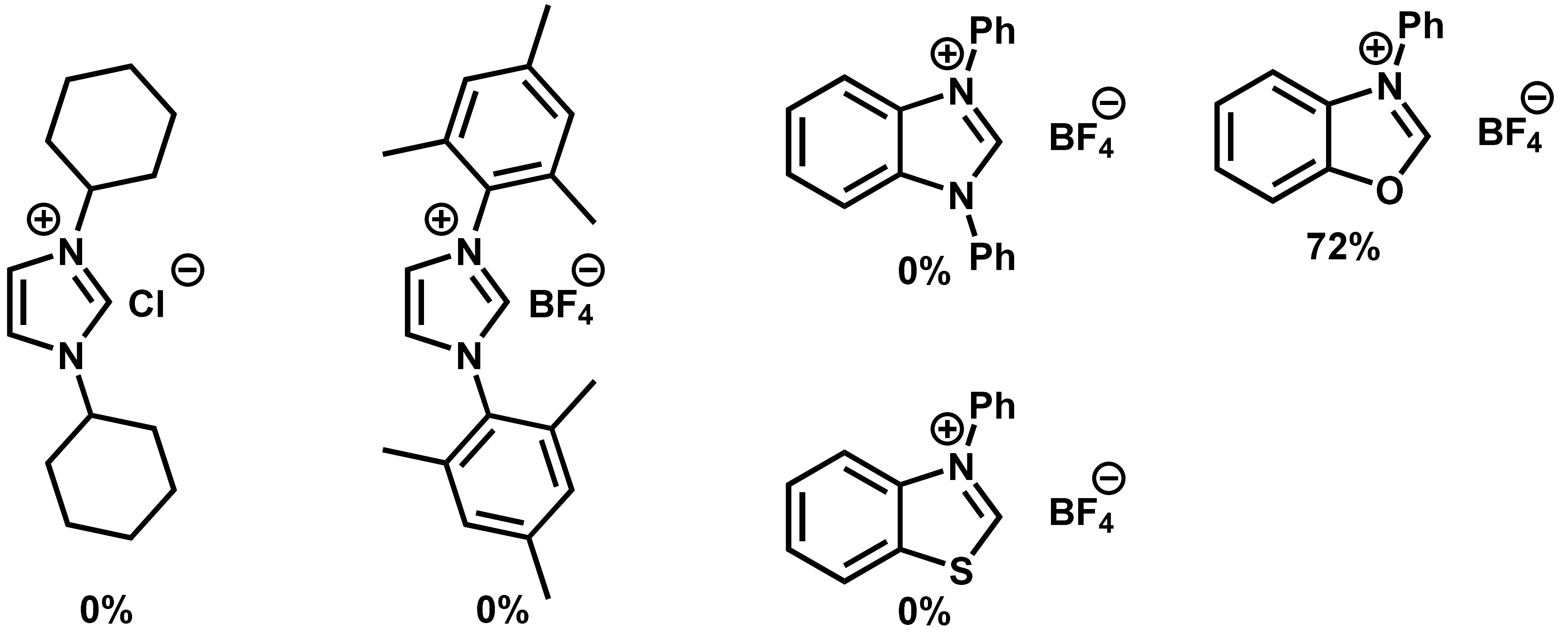
Investigation of NHC Precursor





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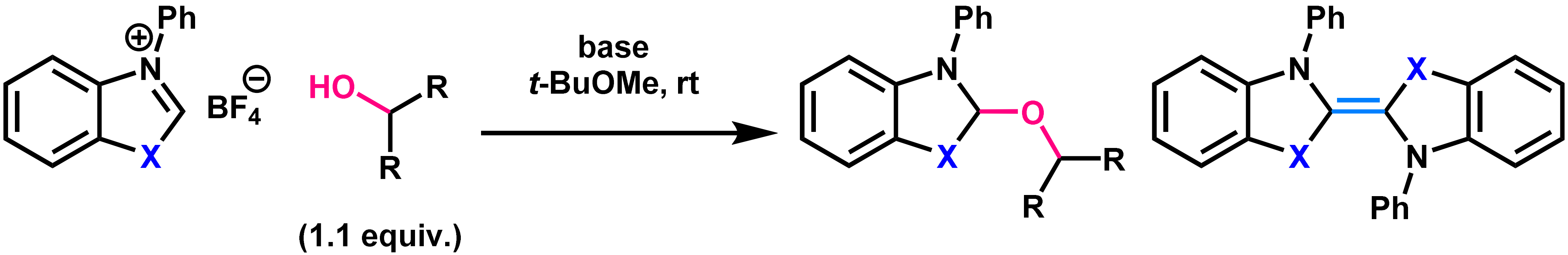
Side Reaction of NHC



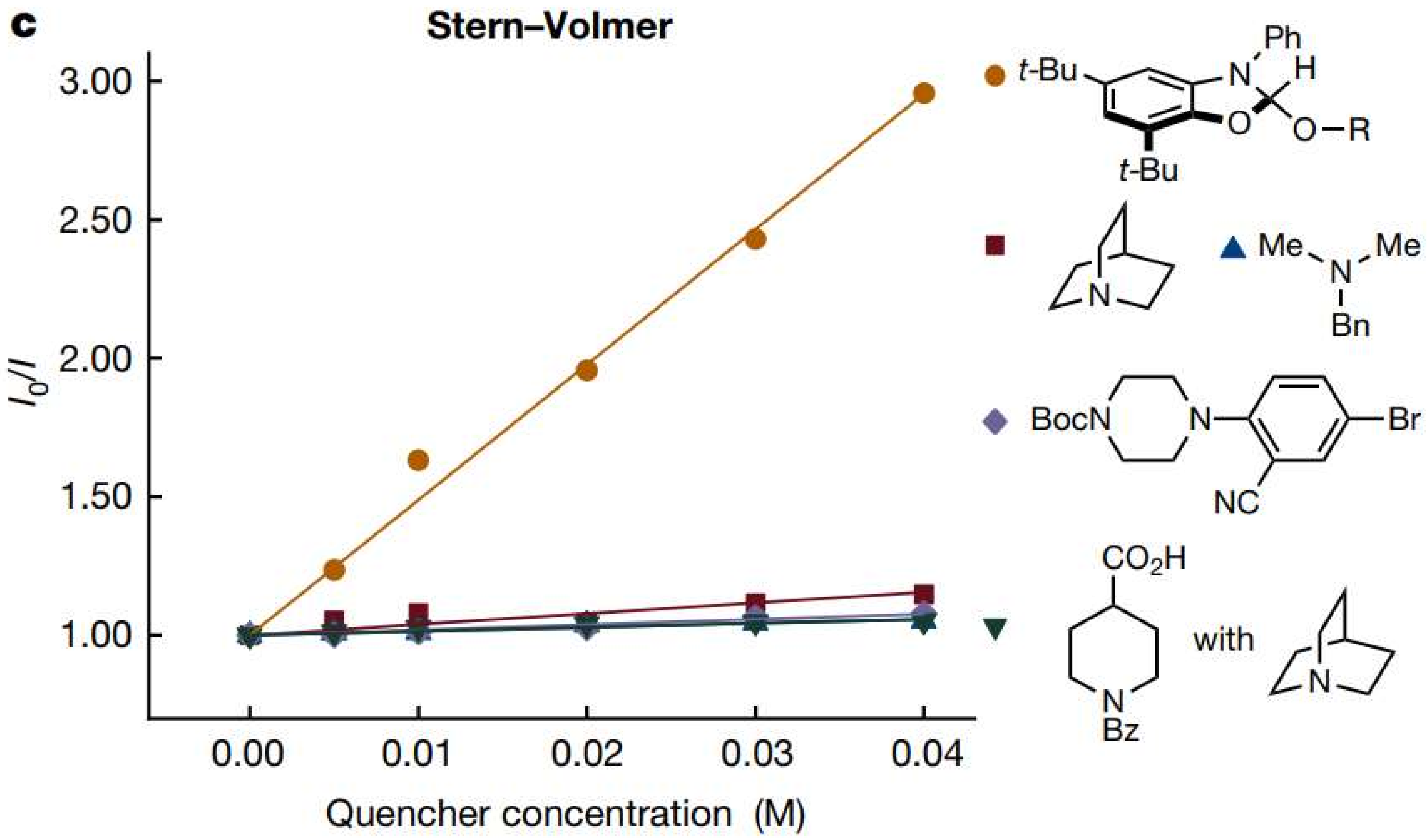
X = S and NPh	50% to 70%	>30%
X = O	85% to 96%	<5%

Dimer is easily oxidazed, which inhibits oxidation of NHC-alcohol adduct.

Dong, Z.; MacMillan, D. W. C. *Nature* **2021**, *598*, 451.

Stern–Volmer Quenching Experiment

vs Ir[(ppy)$_2$(dtbbpy)]PF$_6$



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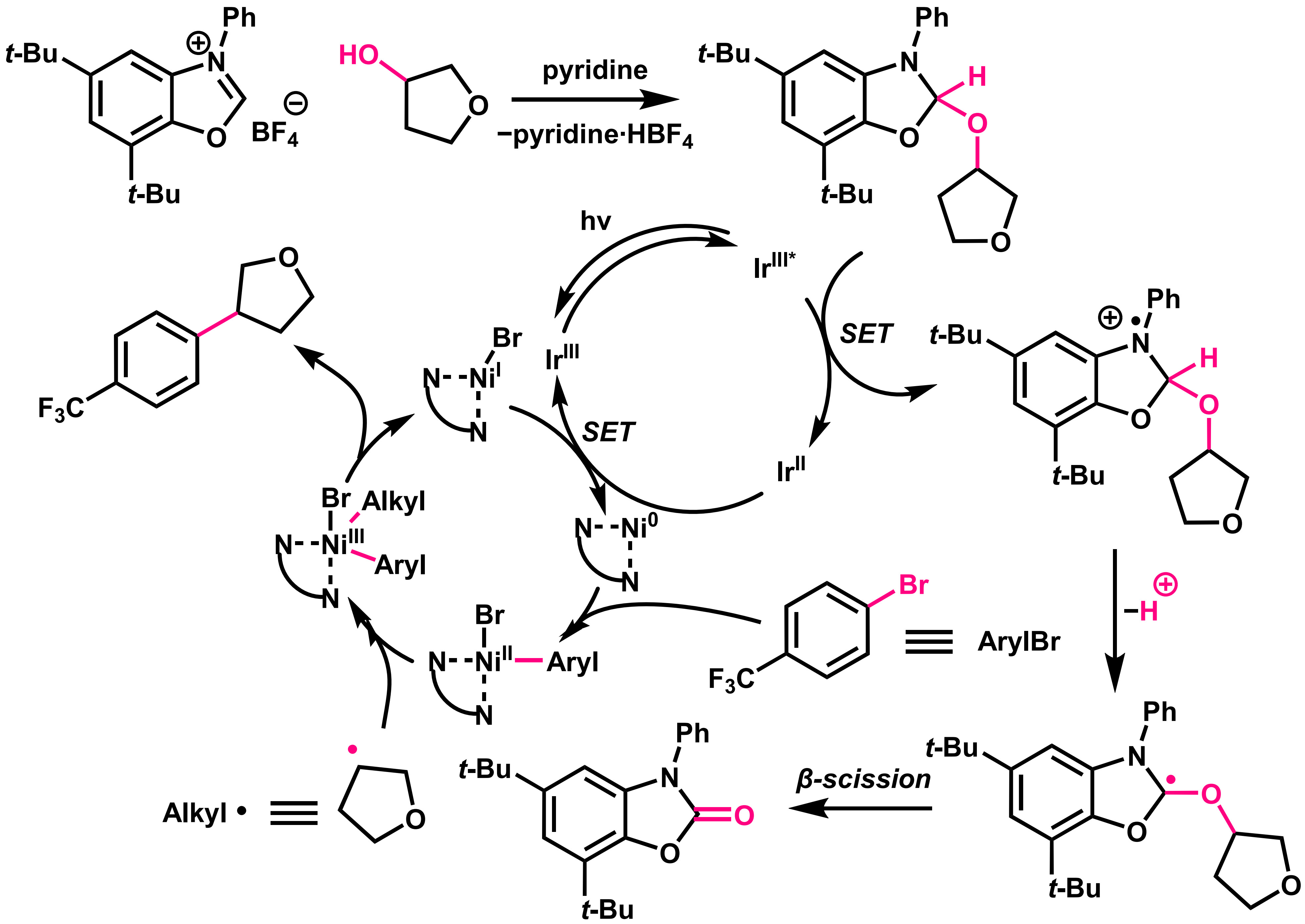
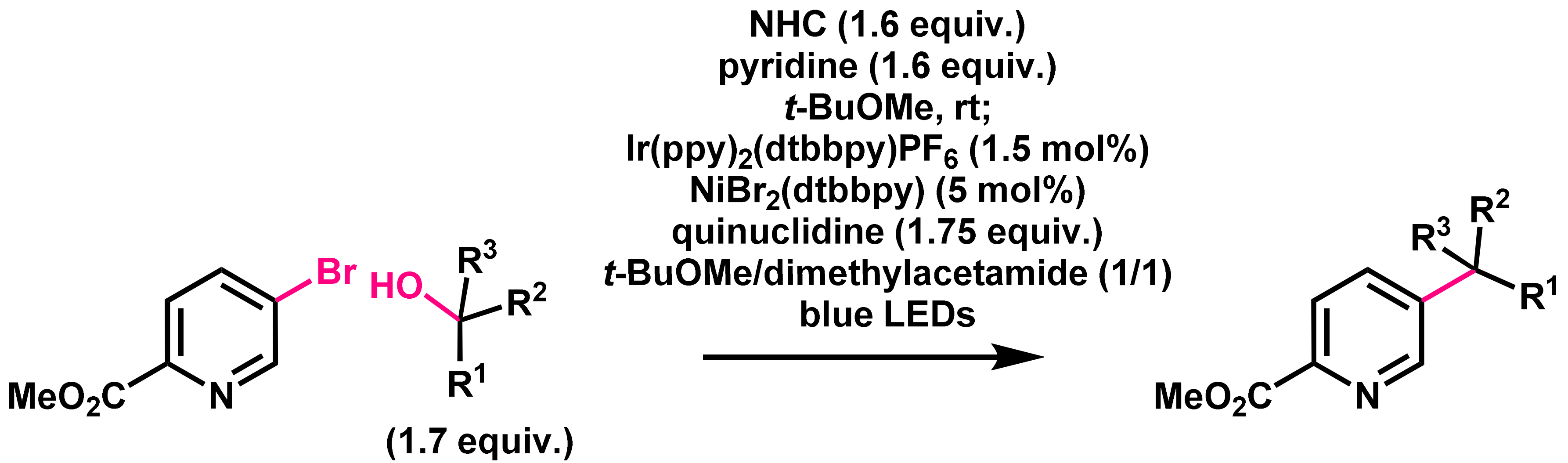
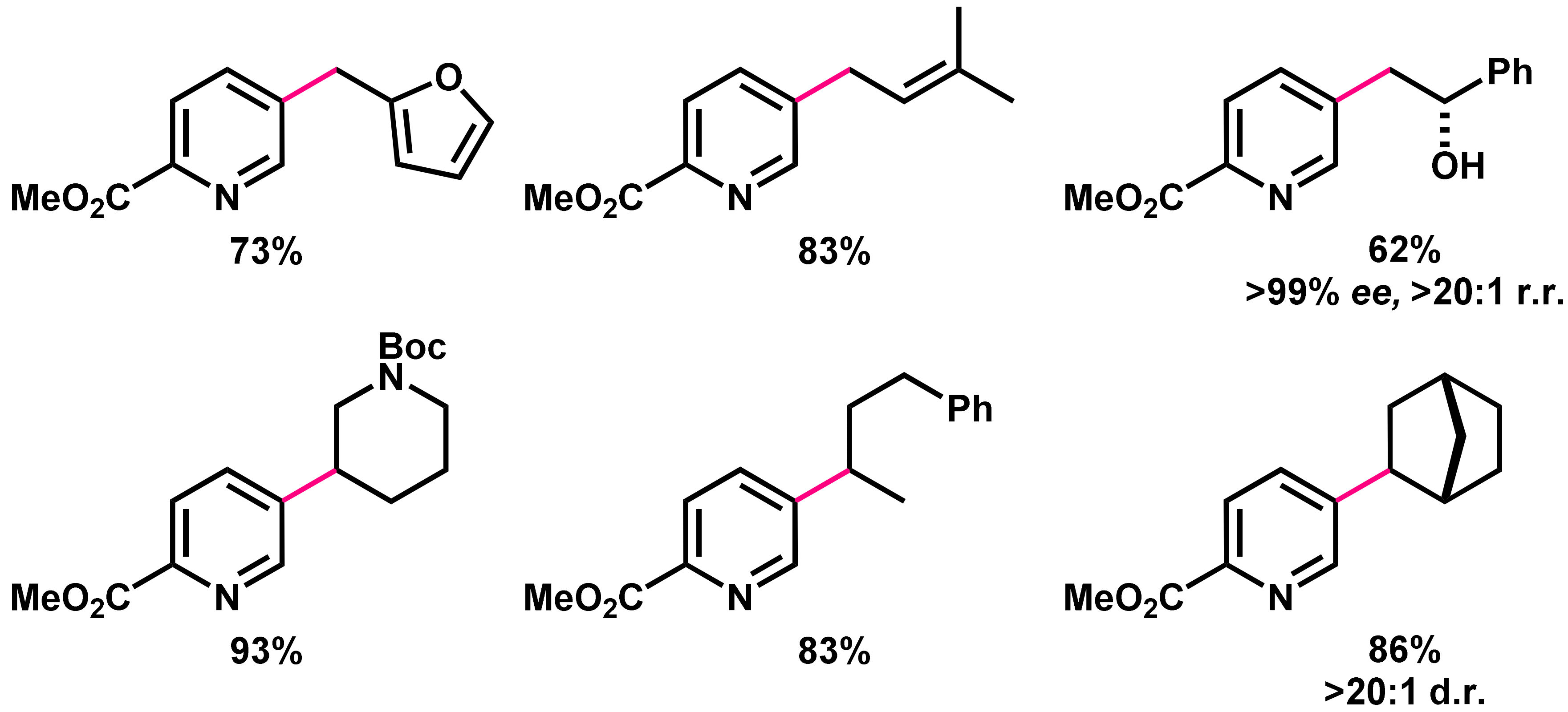
Proposed Mechanism



Dong, Z.; MacMillan, D. W. C. *Nature* **2021**, *598*, 451.

Substrate Scope





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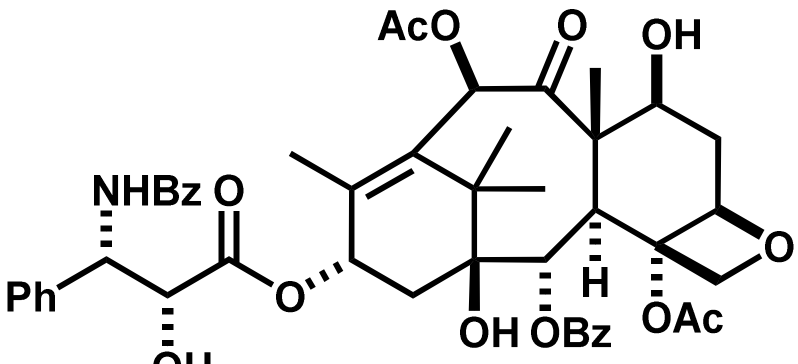
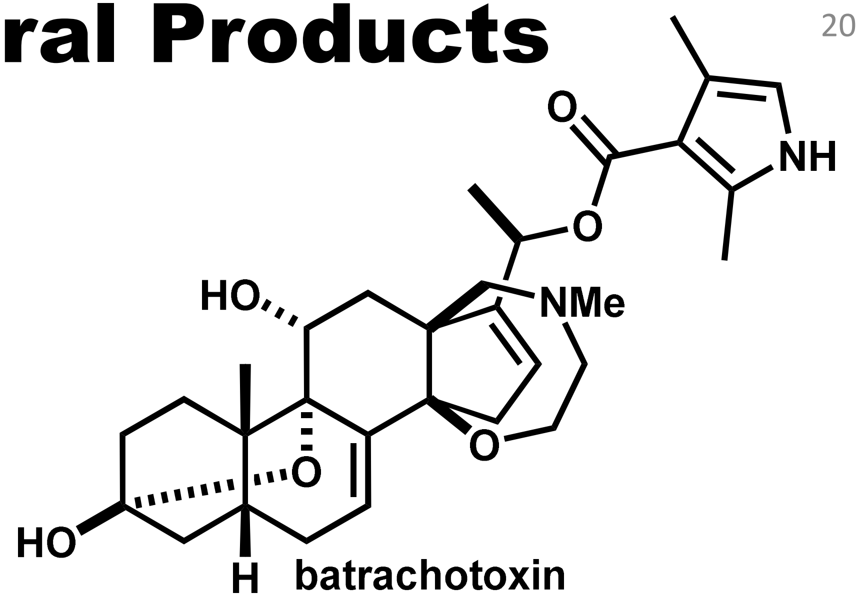
Contents

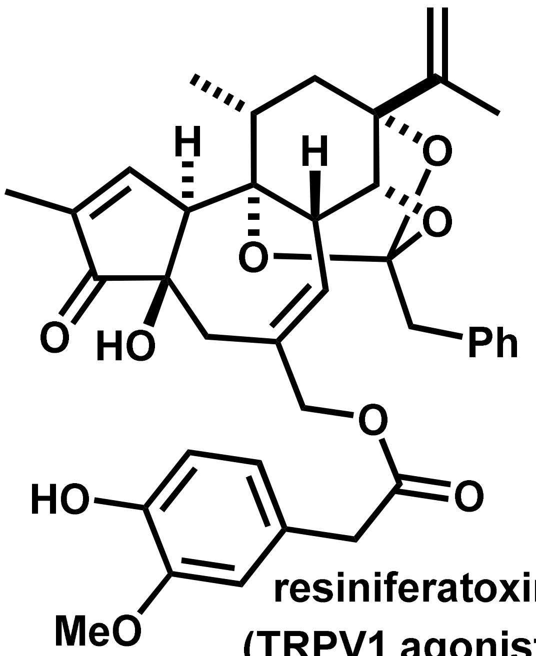
Sp^3-Rich Natural Products



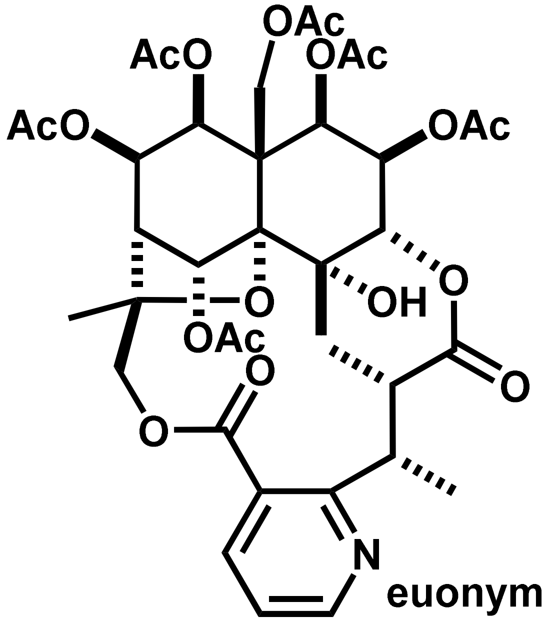
taxol
(antitumor activity[1])



batrachotoxin
(neurotoxicity[2])



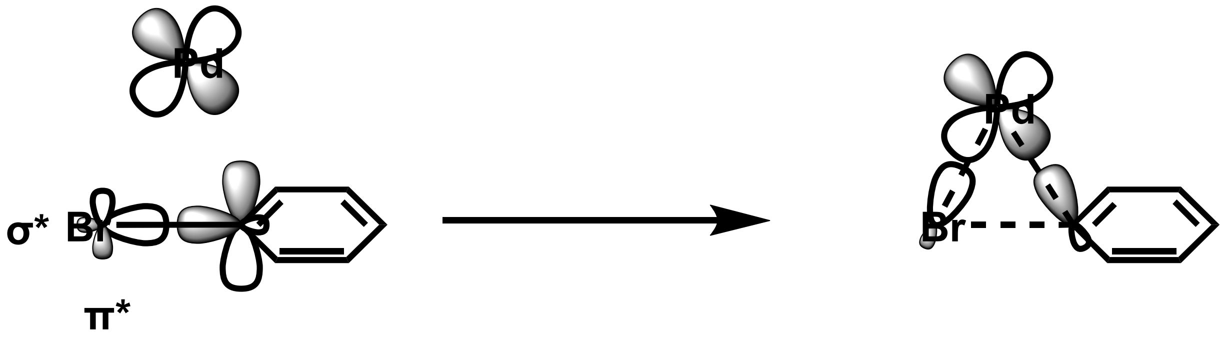
resiniferatoxin
(TRPV1 agonist[3])



euonymine
(anti-HIV activity[4])

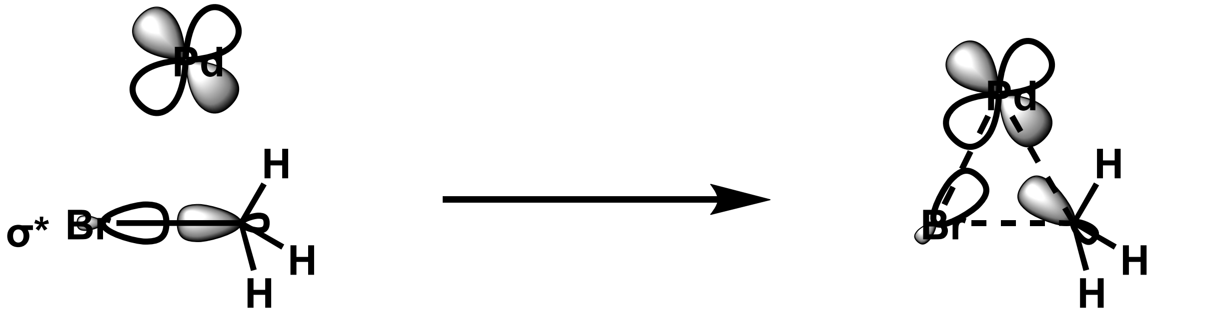
1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
2) Daly, J. W.; Bommer, W. P.; Biemann, K. *J. Am. Chem. Soc.* **1965**, *87*, 124.
3) Szallasi, A.; Blumberg, P. M. *Neuroscience* **1989**, *30*, 515.
4) Duan, H.; Takaishi, Y.; Imakura, Y.; Jia, Y.; Li, D.; Cosentino, L. M.; Lee, K.-H. *J. Nat. Prod.* **2000**, *63*, 357.

Reactivity of Alkyl Bromide



Pd(0) + PhBr

good orbital interaction



Pd(0) + MeBr

poor orbital interaction

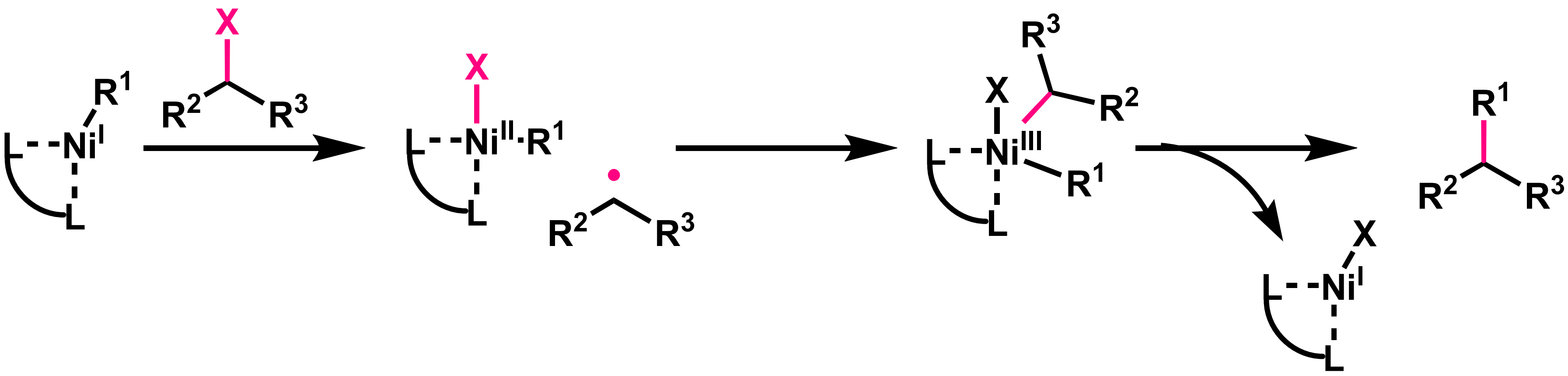
Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030.

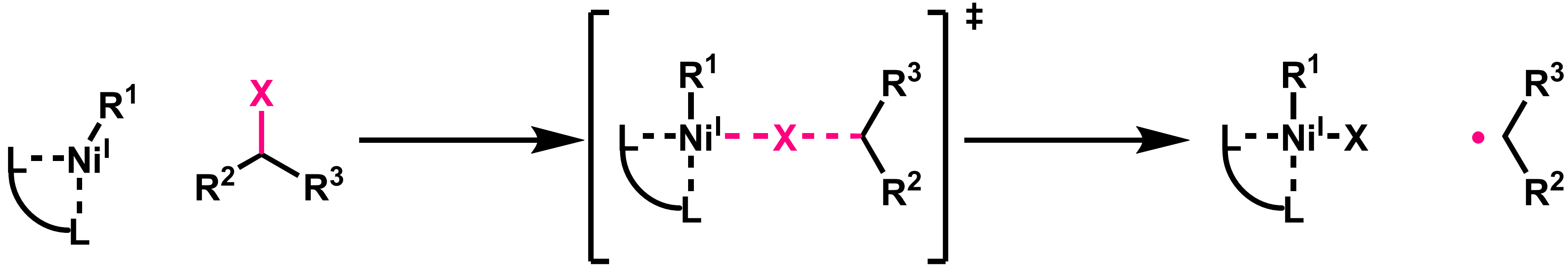
Ni Catalyst vs Pd Catalyst

Nickel		Palladium
Ni^{0}, Ni^{I}, Ni^{II}, Ni^{III}, Ni^{IV}	oxidation state	Pd^{0}, Pd^{II}, Pd^{IV}
smaller	atomic radius	lager
lower	electronegtivity	higher
oxidative addition	preference	reductive elimination
cheaper	cost	more expensive
radical pathway more accessible		

Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

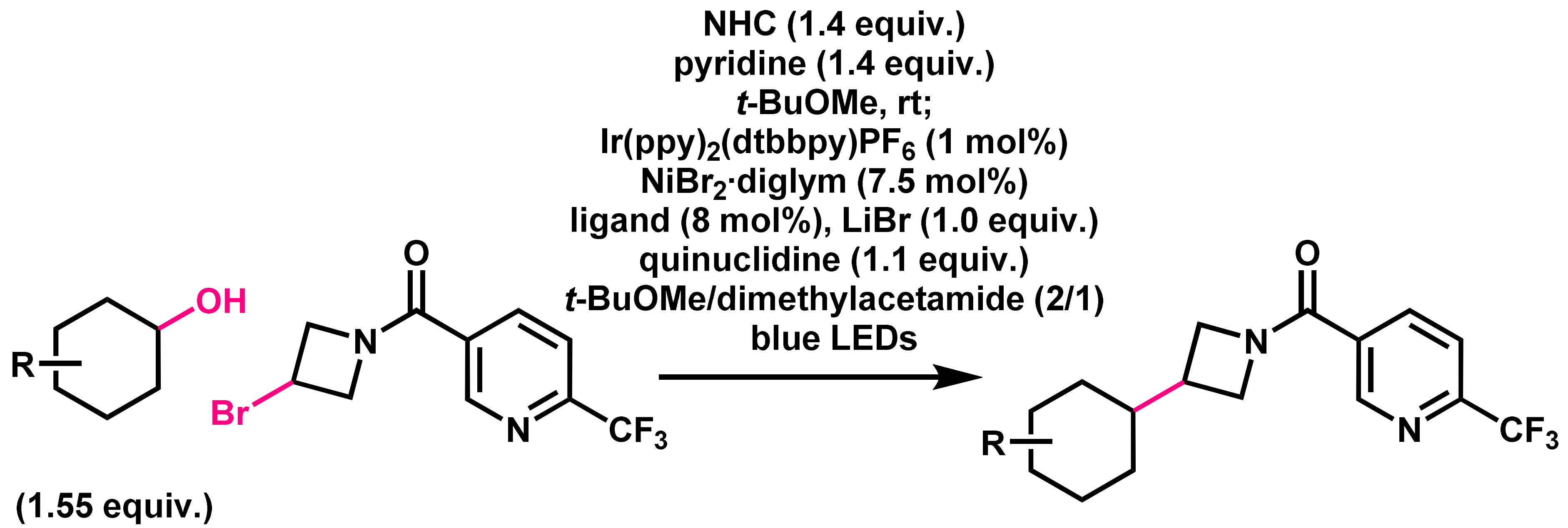
Cross-Coupling Using Ni Catalyst

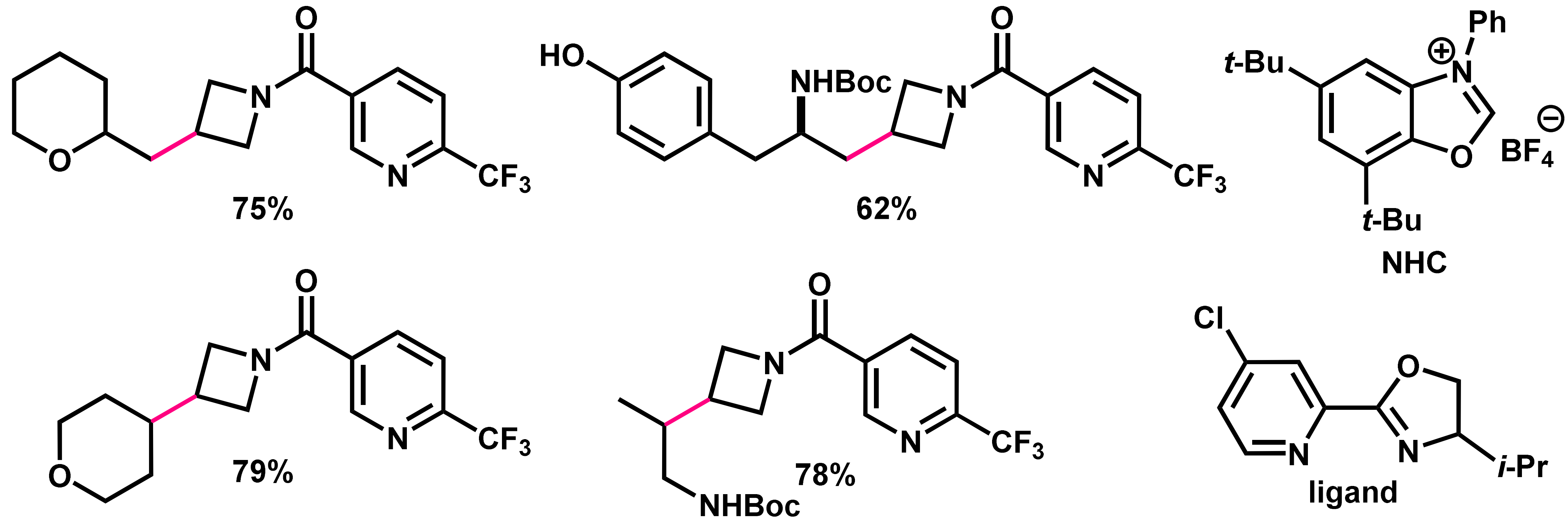




Diccianni, J. B.; Katigbak, J.; Hu, C.; Diao, T. *J. Am. Chem. Soc.* **2019**, *141*, 1788.

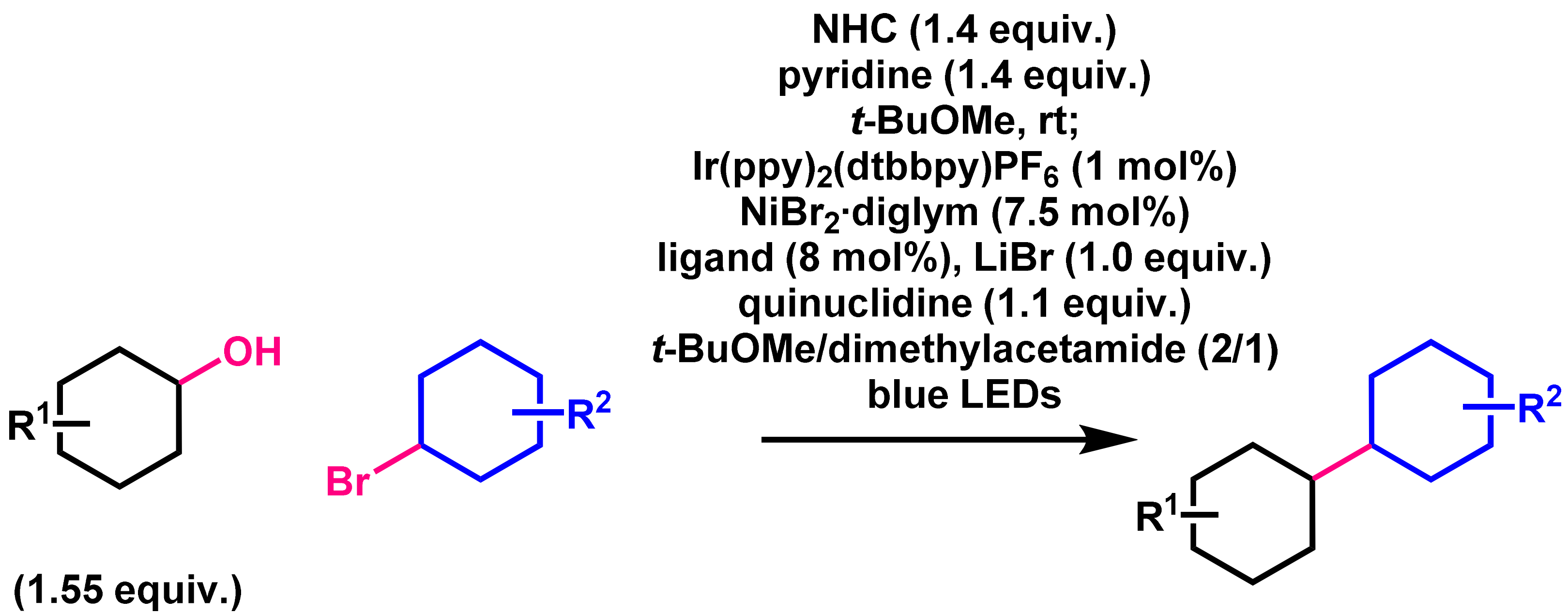
Substrate Scope

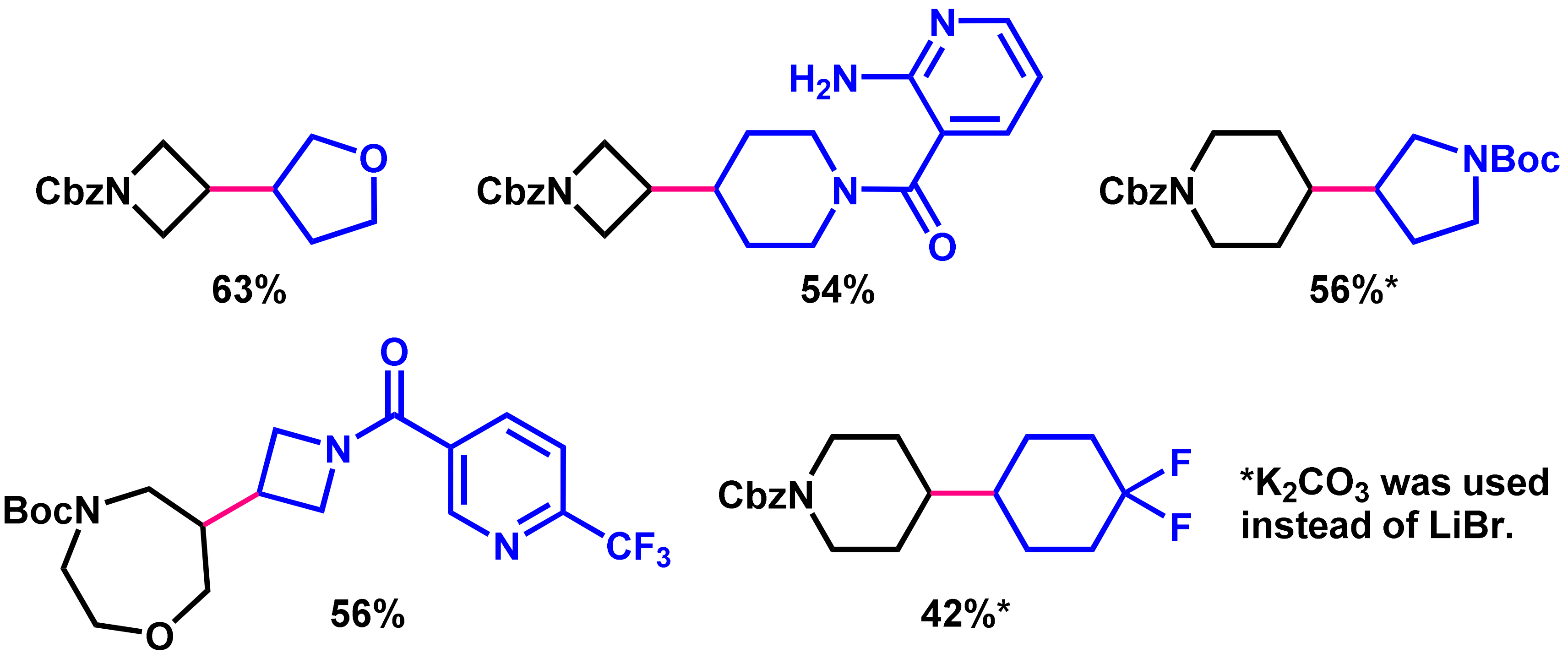




Lyon, W. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2023**, *145*, 7736.

Substrate Scope

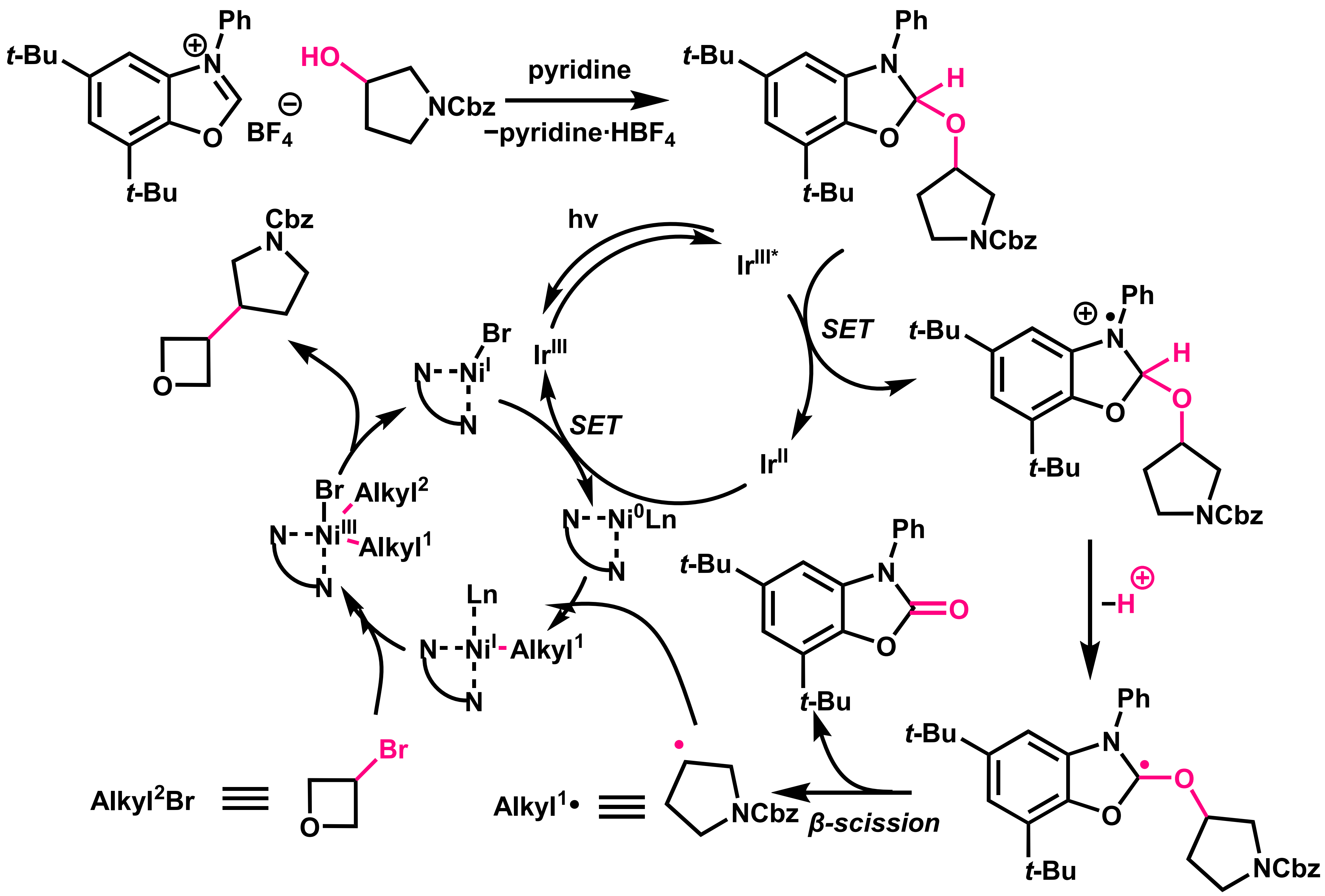




*K_2CO_3 was used instead of LiBr.

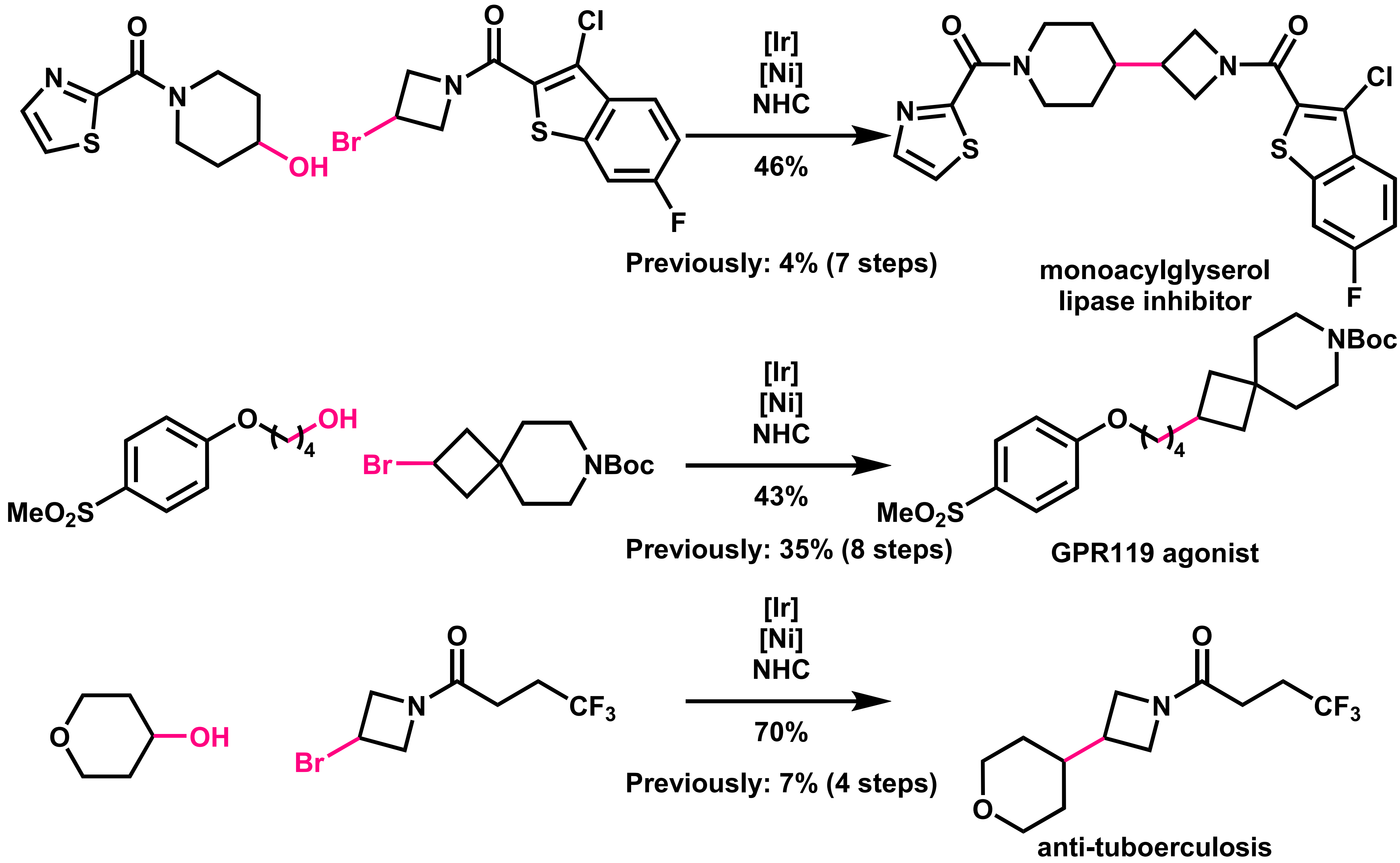
Lyon, W. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2023**, *145*, 7736.

Proposed Mechanism



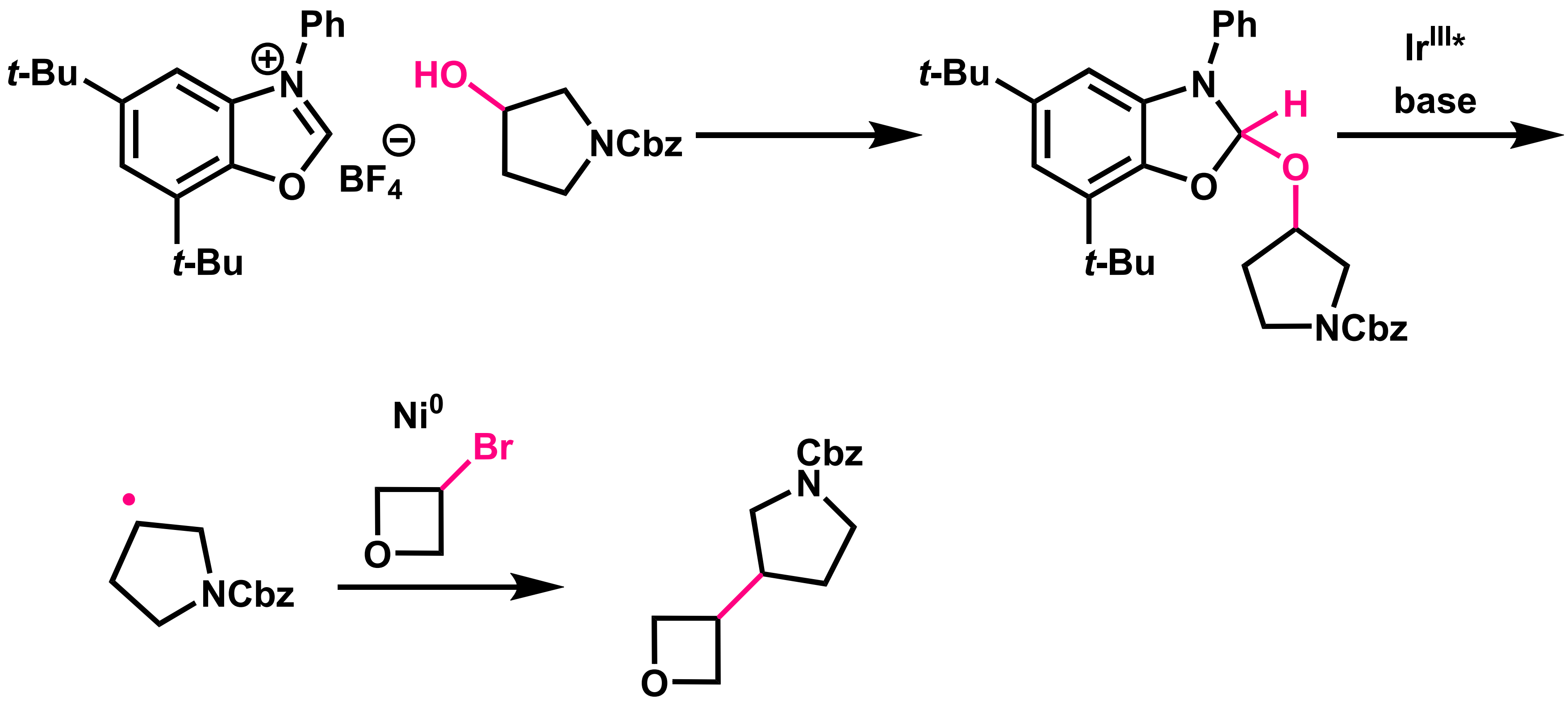
Lyon, W. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2023**, *145*, 7736.

Application to Synthesis of Bioactive Molecules



Lyon, W. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2023**, *145*, 7736.

Summary



Facile and rapid C(sp^3)–C(sp^3) bond formation