Metallaphotoredox Fragment Couplings of Alcohols and Carboxylic Acids

2022.09.10. Literature Seminar

M1 Jaejoong Han

Contents

1. Introduction

2. Metallaphotoredox Deoxygenative Alcohol Coupling with Aryl Halide (MacMillan, 2021)

3. Coupling of Alcohols and Carboxylic Acids (MacMillan, 2022)

4. Summary

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4. Summary

Introduction of Prof. MacMillan

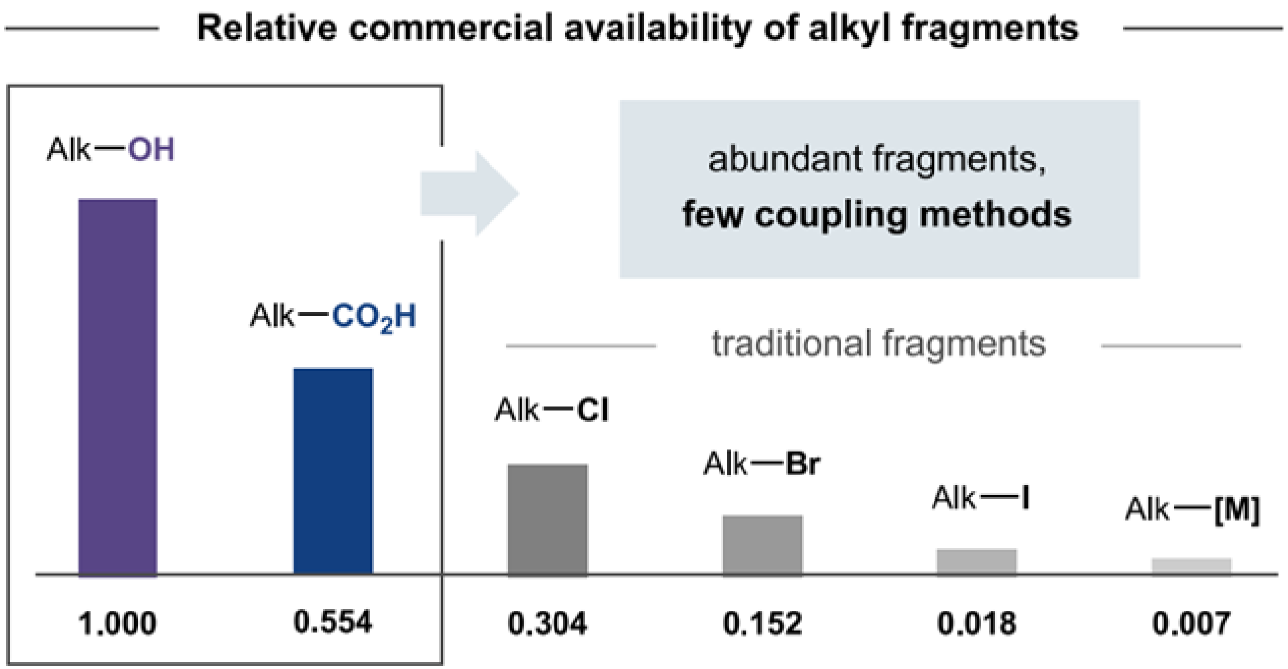
Prof. David W. C. MacMillan (1968 -)

1991 B.S. @ University of Glasgow
1996 Ph.D @ University of California, Irvine
(Prof. Larry E. Overman)
1996- Postdoctral fellow @ 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

Research topics:
Organocatalyst, Photoredox, total synthesis, proximity labeling

1) https://macmillan.princeton.edu/

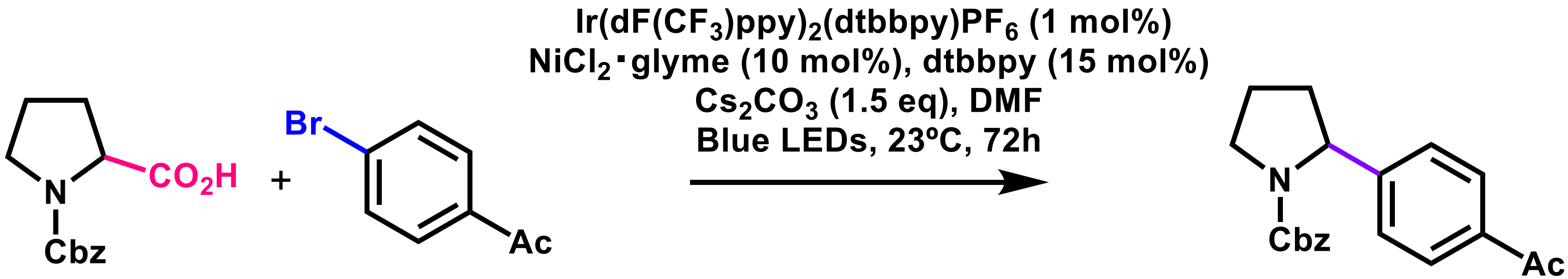
Commercial Availability of Alkyl Fragments

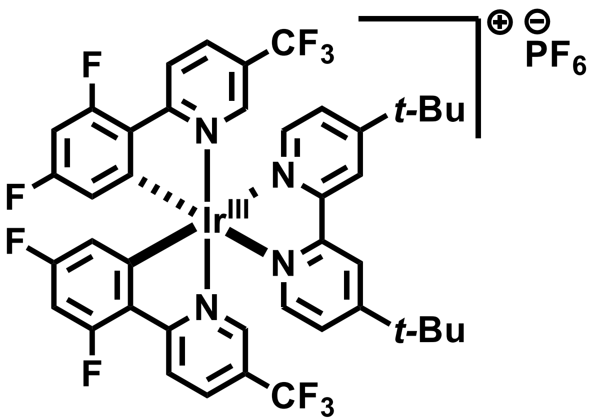


Alcohols and Carboxylic acids are abundant fragments.
However, there is few coupling methods using these fragments.

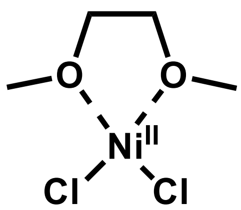
1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

Metallaphotoredox Coupling of Carboxylic Acids and Aryl Halides

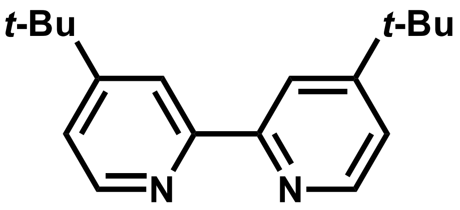




Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$



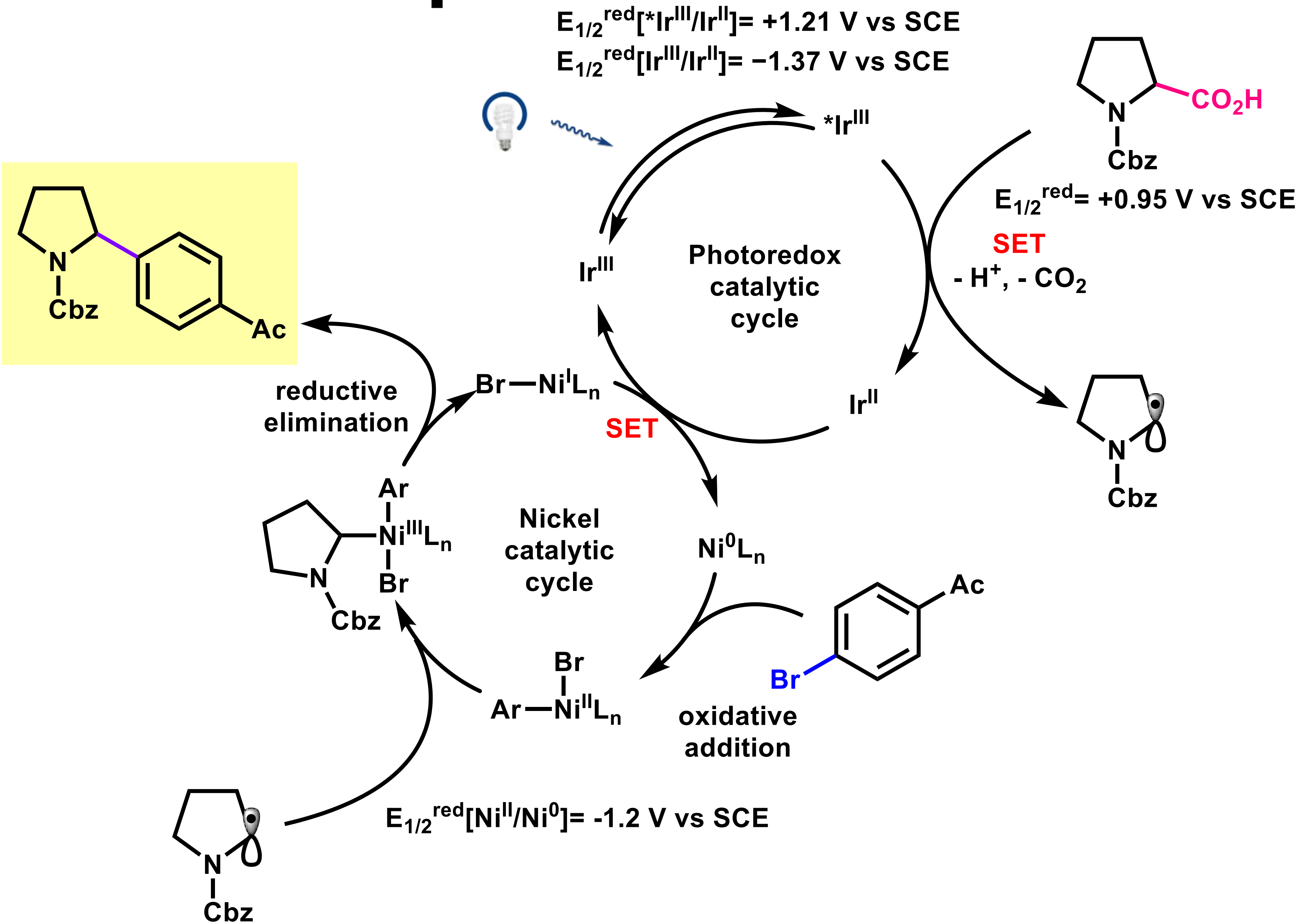
NiCl$_2$·glyme



dtbbpy

1) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science*, **2014**, *345*, 437.

Proposed Mechanism



1) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J, A.; Doyle, A. G.; MacMillan, D. W. C. *Science*, **2014**, *345*, 437.

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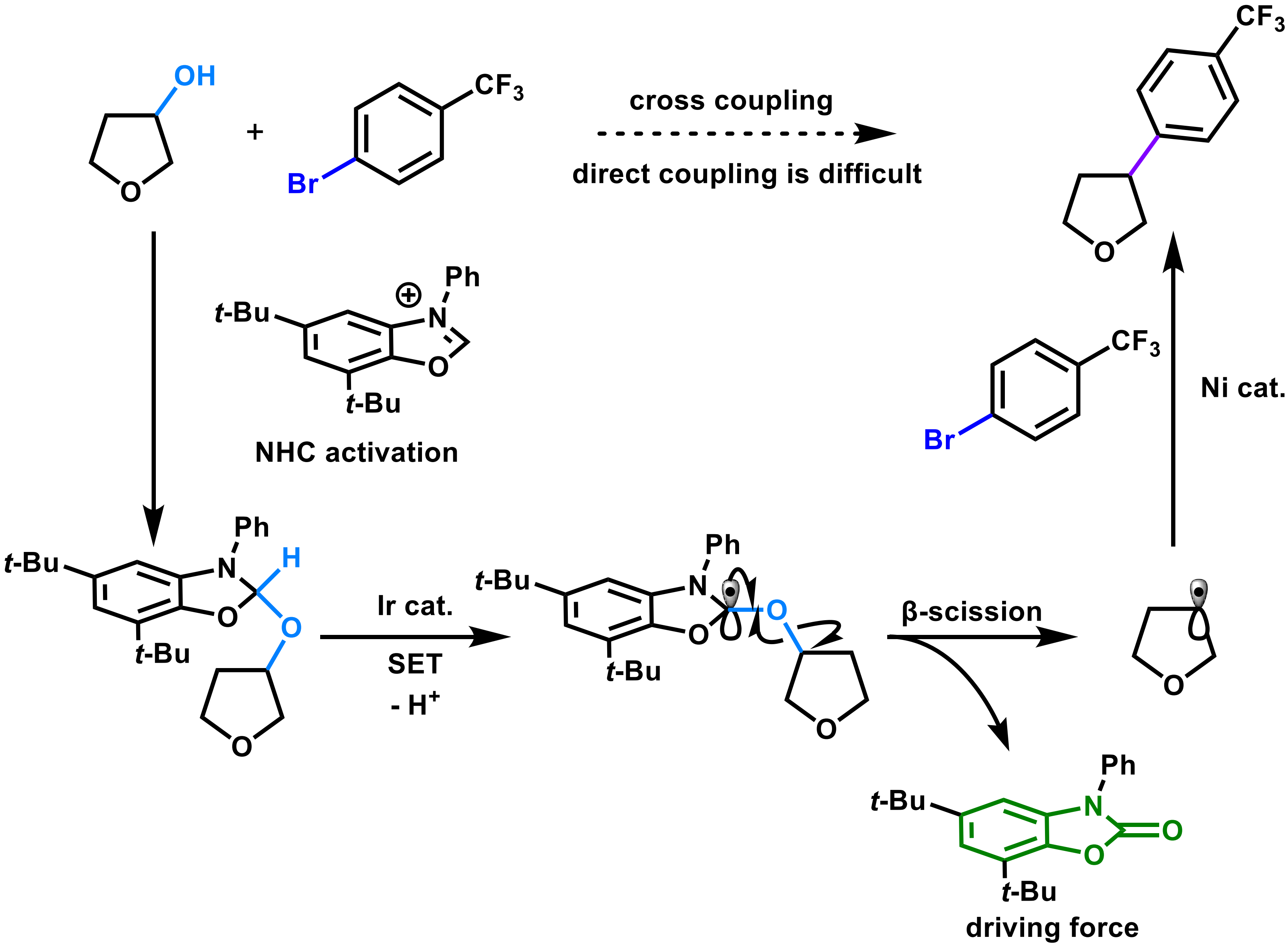
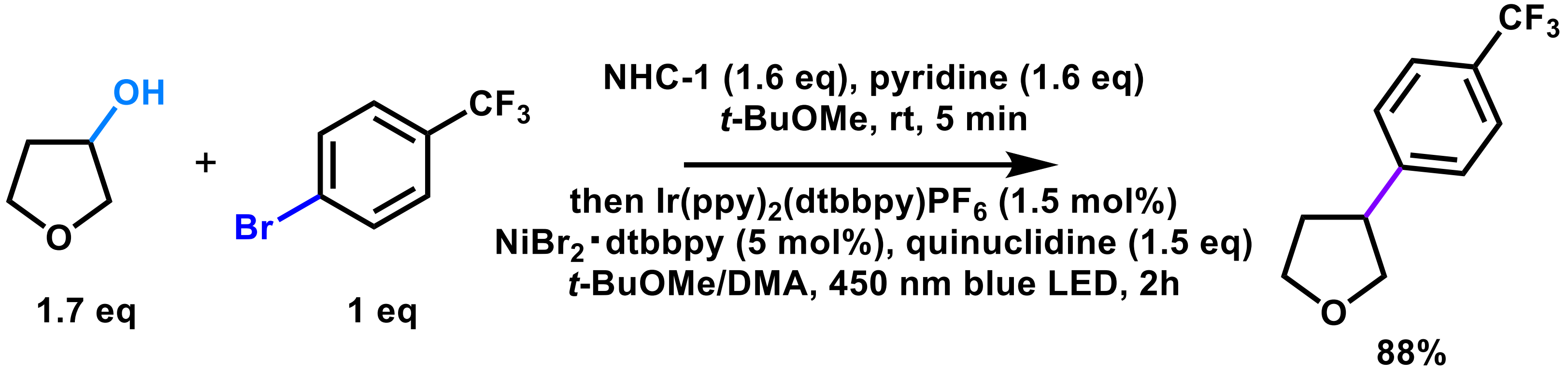
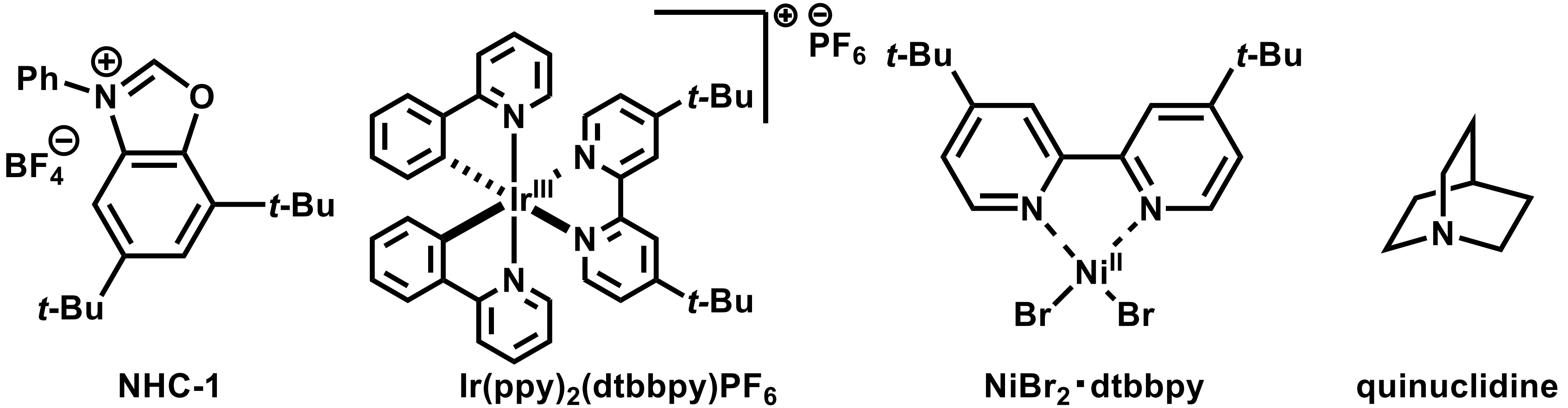
Outline for Deoxygenative Cross Coupling



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

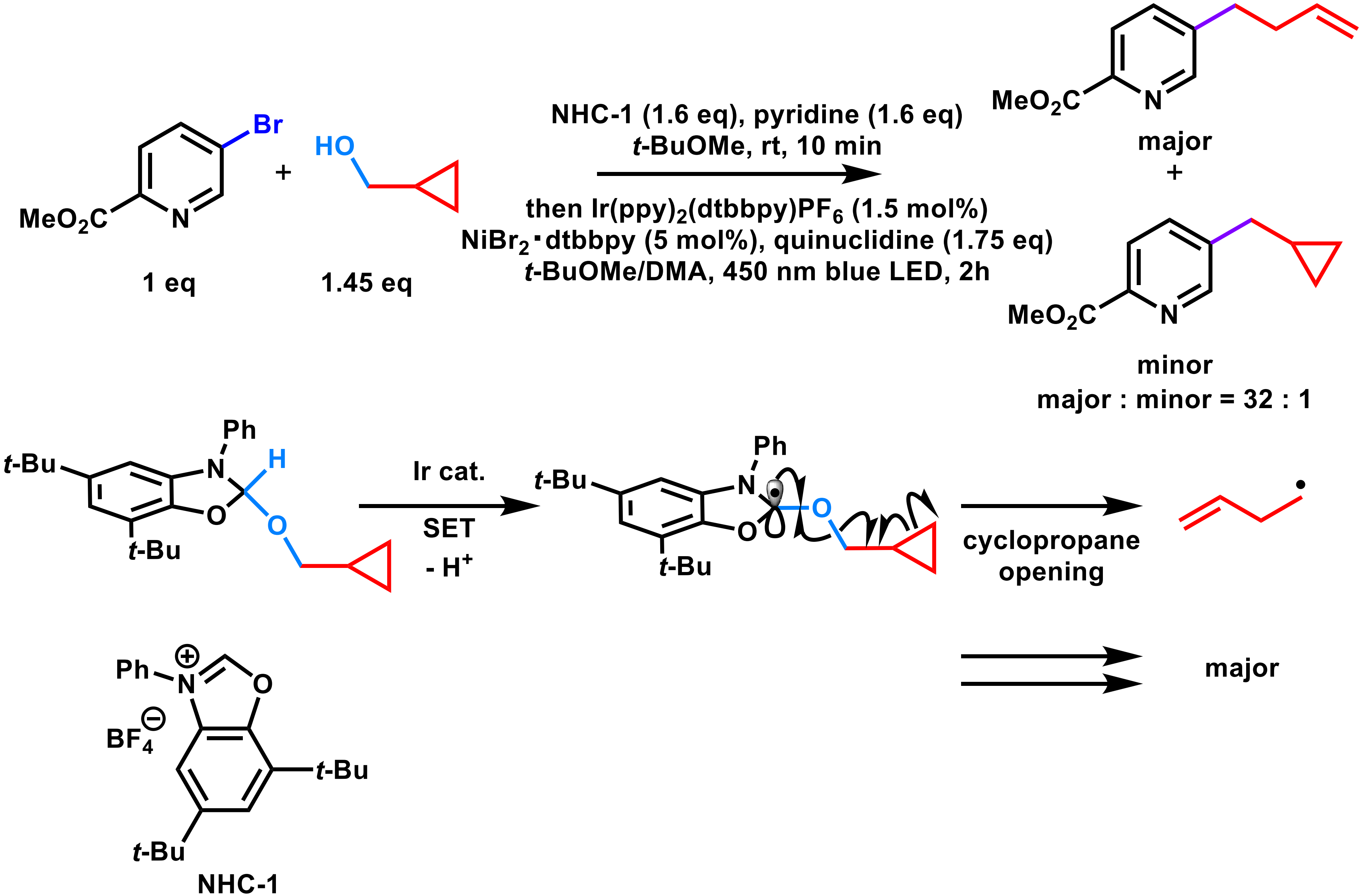
Reaction Conditions





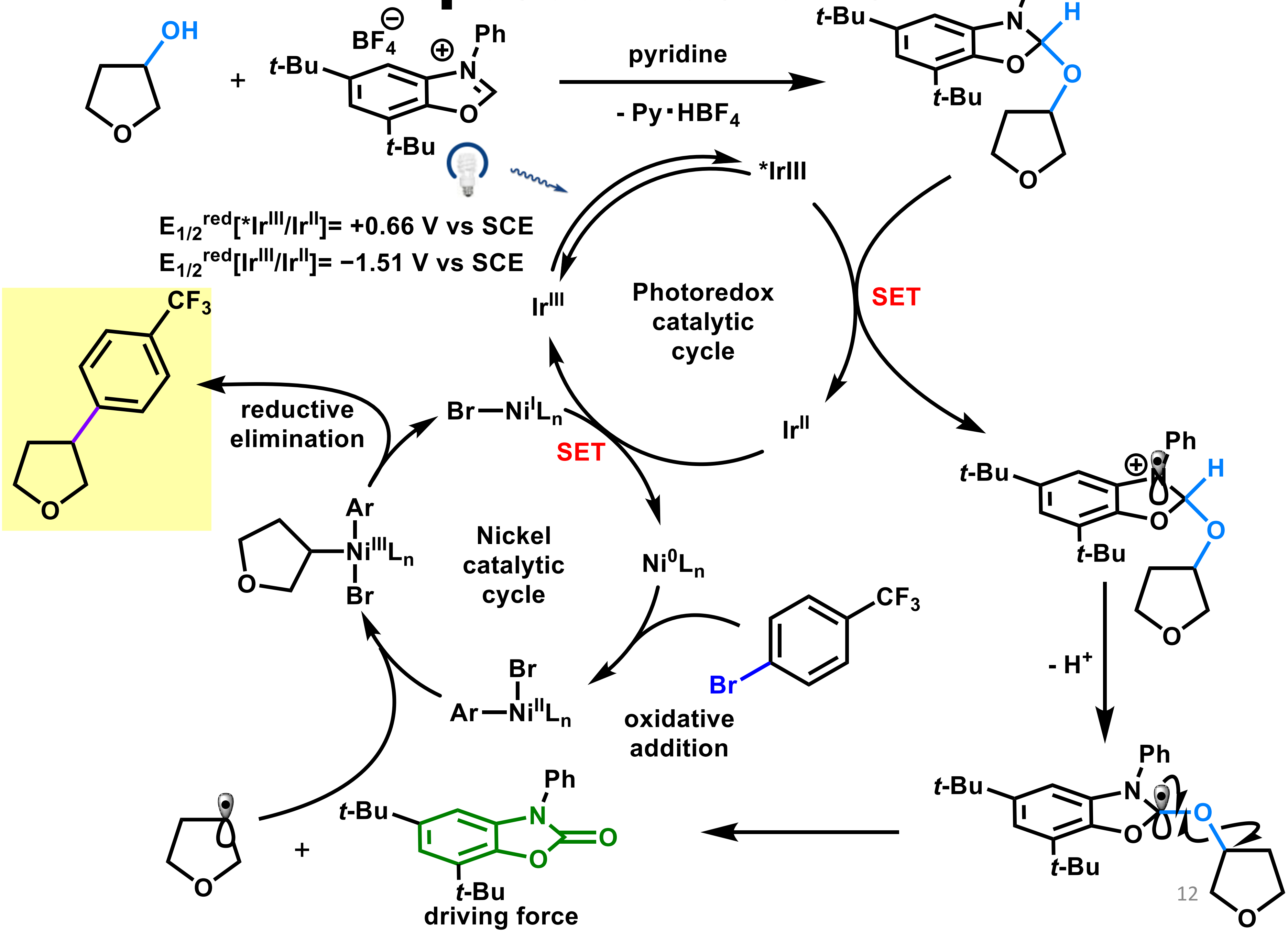
1) Dong, Z.; MacMillan, D. W. C. *Nature*. **2021**, *598*, 451.

Mechanismic Study

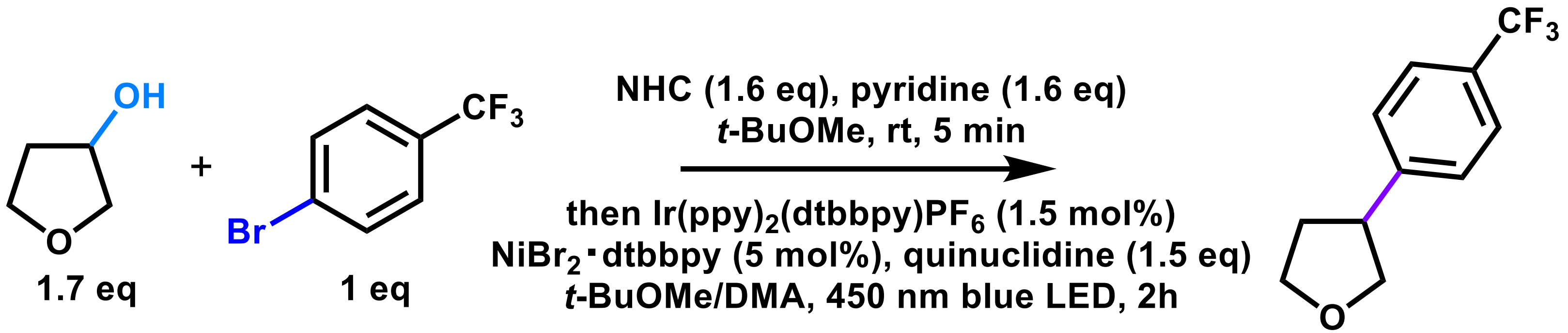


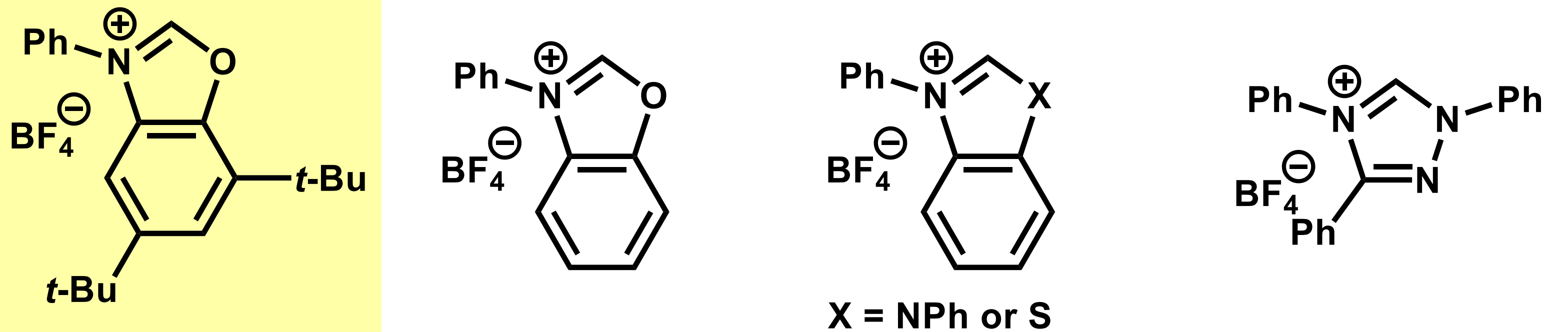
1) Dong, Z.; MacMillan, D. W. C. *Nature*. **2021**, *598*, 451.

Proposed Mechanism



Optimizaztion of NHC

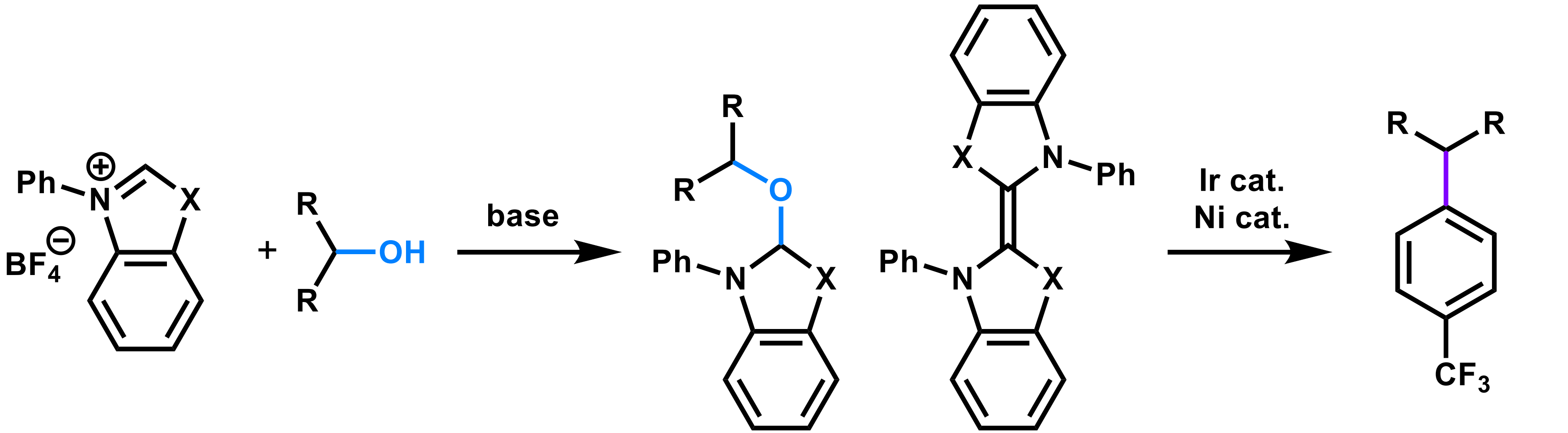




NHC-1	NHC-2	NHC-3	NHC-4
88%	72%	0%	0%

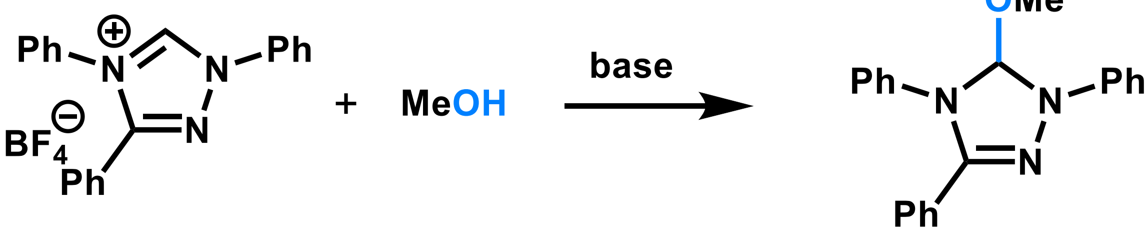
1) Dong, Z.; MacMillan, D. W. C. *Nature*. **2021**, *598*, 451.

Problems with Each NHCs

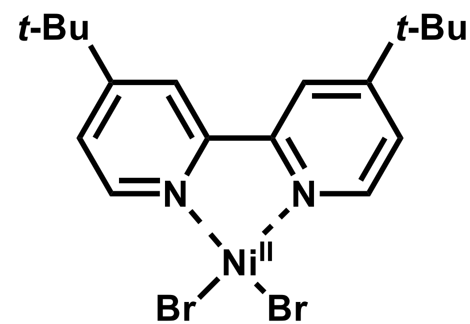


	desired	byproduct	Arylation product
NHC-3 X = S, or NPh	50% to 70%	>30%	0%
NHC-1 X = O	85% to 96%	<5%	>50%

NHC-dimer is a stronger reductant than NHC-alcohol adduct.
When NHC-3 is used, carbon radical couldn't be generated.



NHC-4



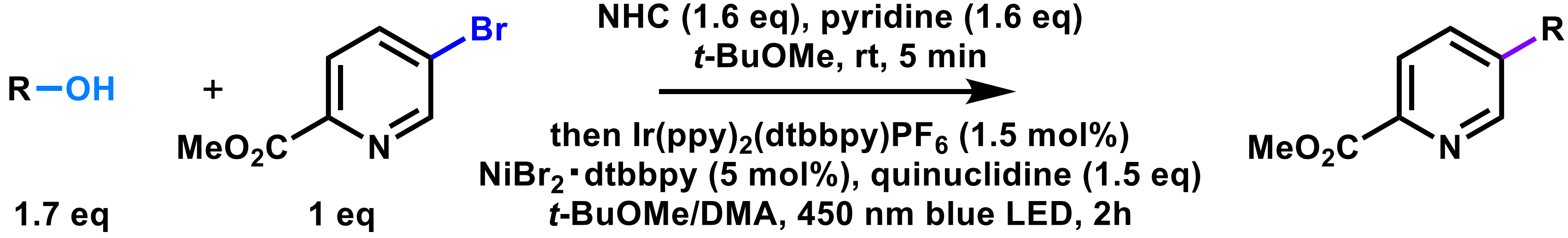
$NiBr_2$·dtbbpy

E_{red} = −0.86 V vs SCE VS E_{red} = ~−1.2 V vs SCE

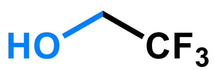
When NHC-4 was used, NHC-alcohol adduct is much easier to be reduced by Ir cat then Ni cat.
Ni-meditated coupling couldn't occur because Ni^{II} isn't reduced to Ni^0.

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

Substrate Scope (1)

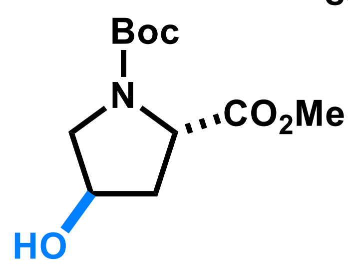


primary alcohol

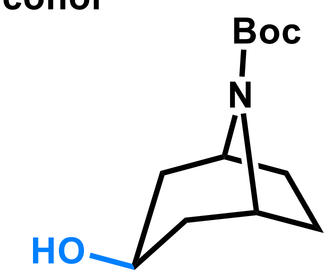


63%
(NHC-1)

secondary alcohol

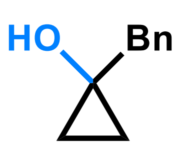


89%, 6.5:1 d.r.
(NHC-1)



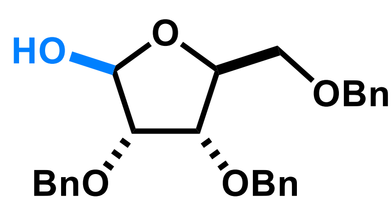
62%, 6:1 d.r.
(NHC-1)

tertiary alcohol

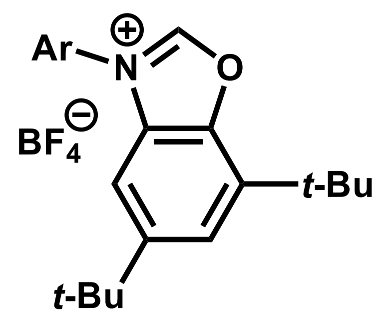


32%
(NHC-5)

Saccharide alcohol



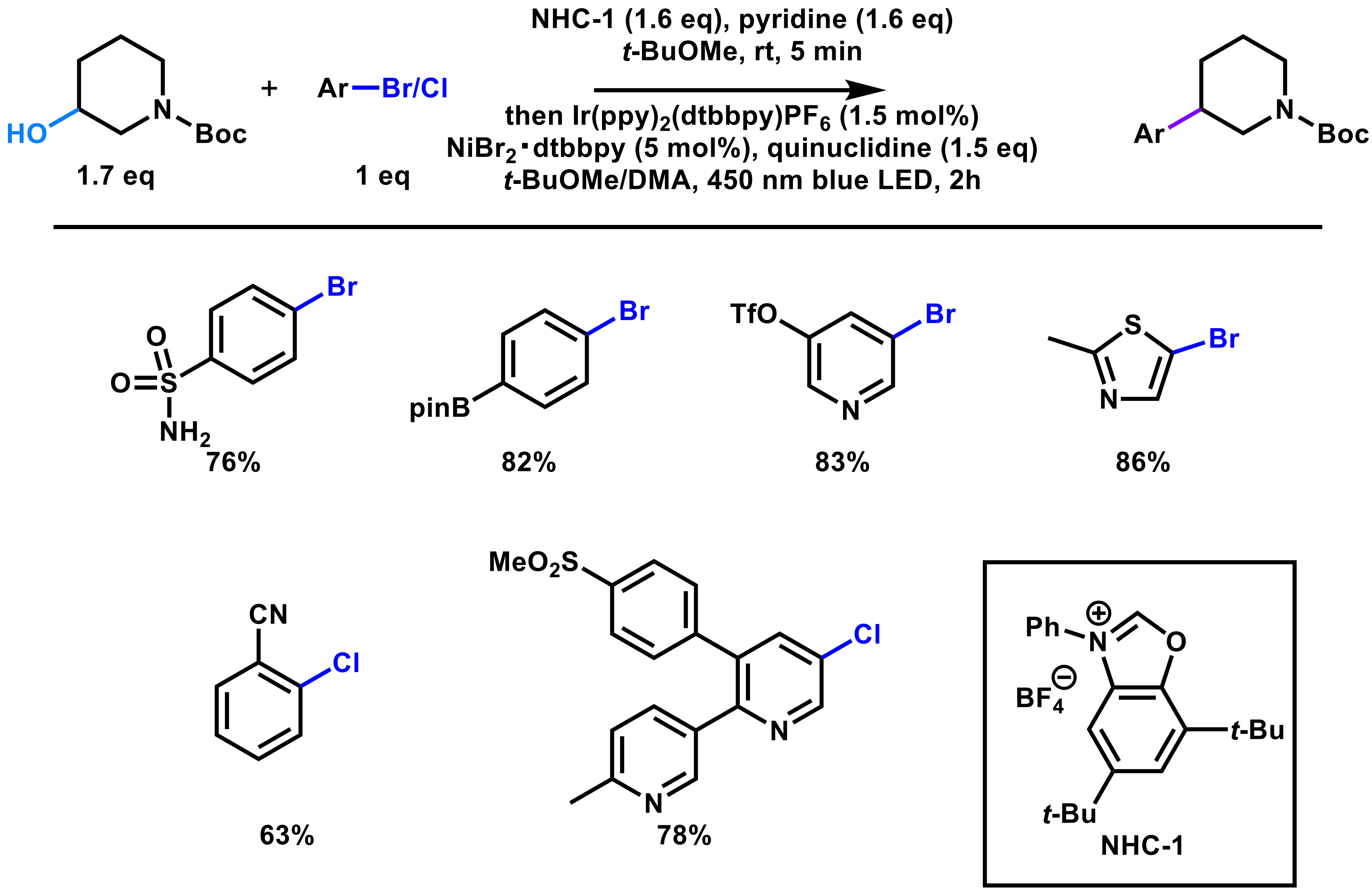
82%, >20:1 d.r.
(NHC-1)



NHC-1, Ar = Ph
NHC-5, Ar = 4-$CF_3C_6H_4$

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

Substrate Scope (2)



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

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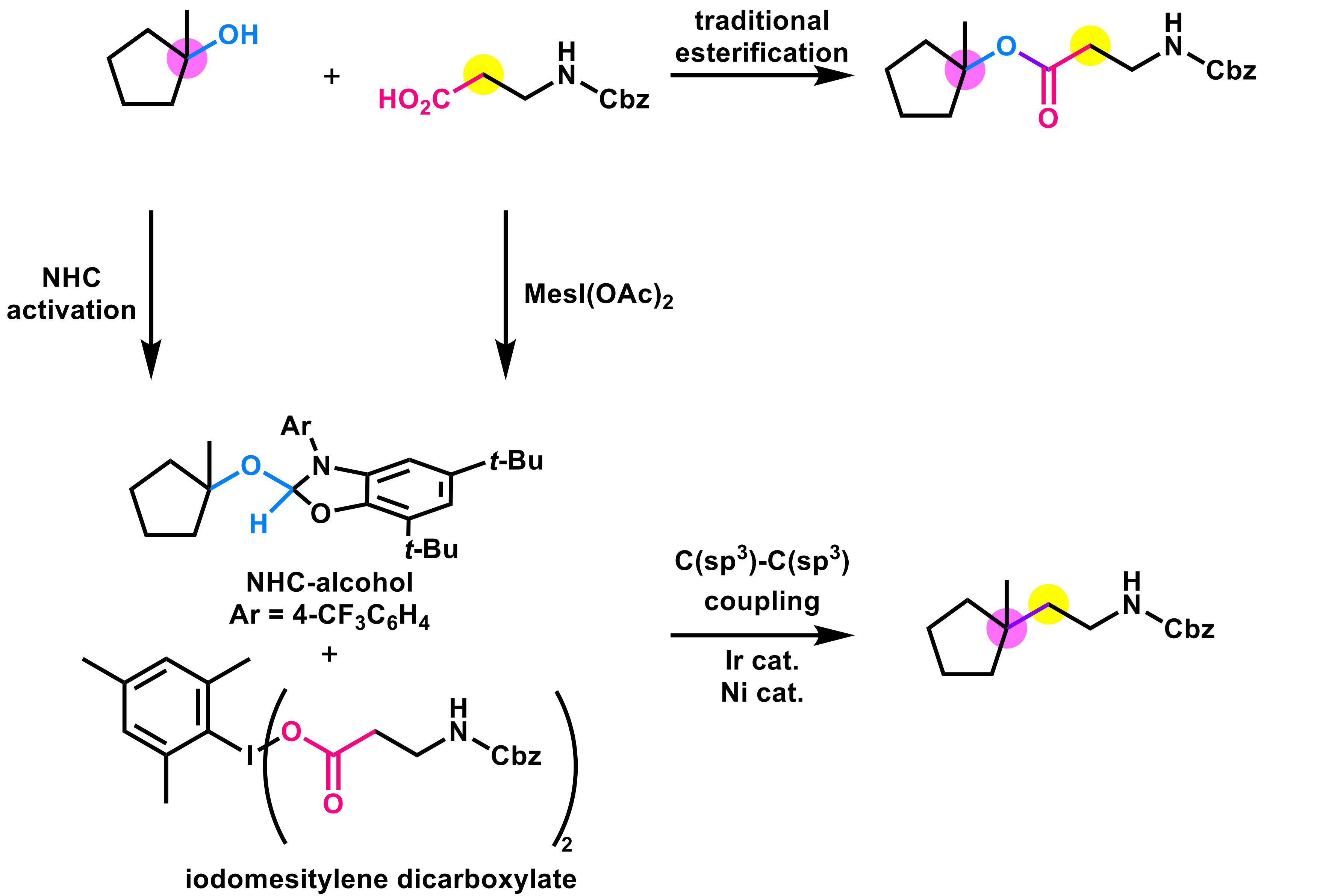
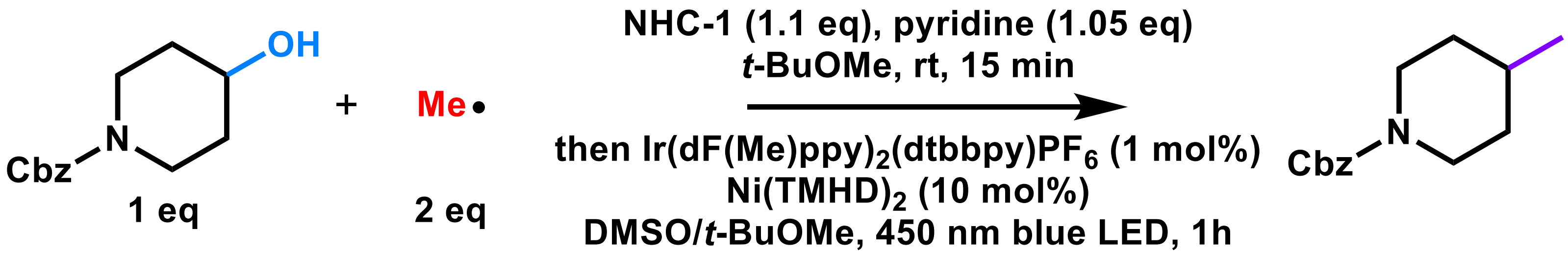
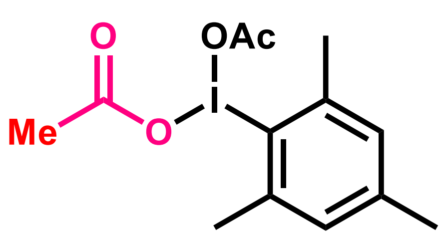
Traditional Esterification and C(sp3) Coupling



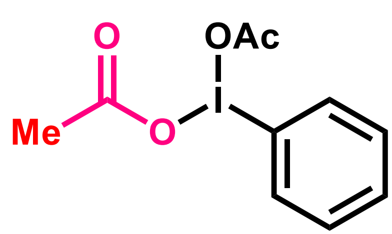
1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

Me Precursor

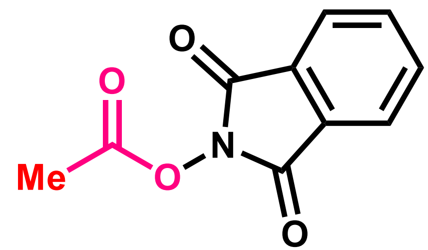




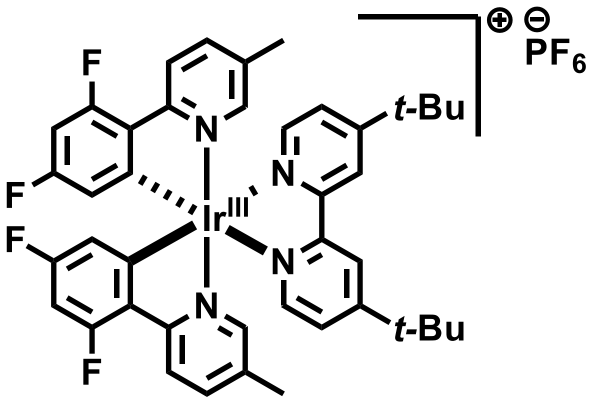
76%



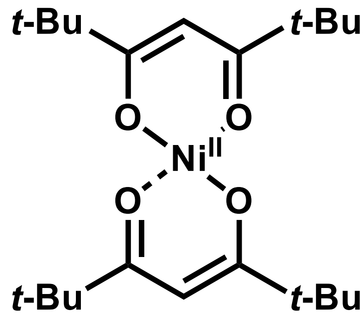
71%



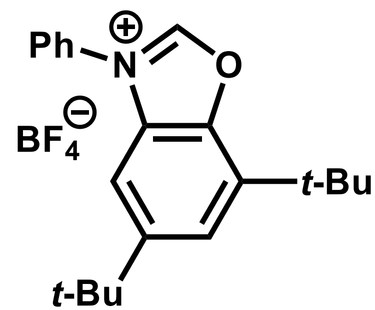
34%



Ir(dF(Me)ppy)$_2$(dtbbpy)PF$_6$



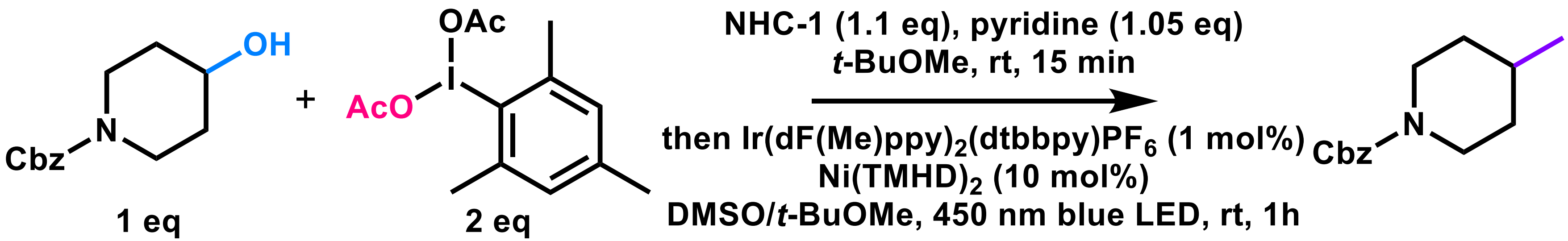
Ni(TMHD)$_2$



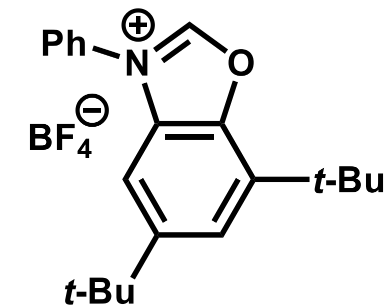
NHC-1

1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

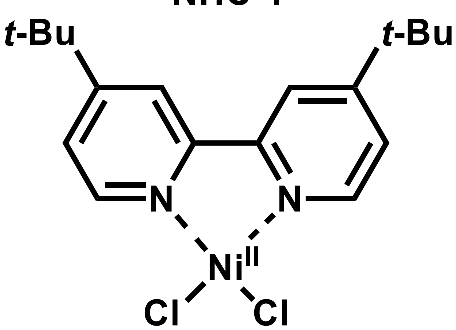
Control Experiments



entry	deviation from above	yield
1	none	76%
2	$NiCl_2$·dtbbpy	24%
3	no Ir cat.	<5%
4	no Ni cat.	12%
5	no Ir cat., no light	0%
6	no Ir cat., no Ni cat.	0%
7	no light, 50 °C	0%

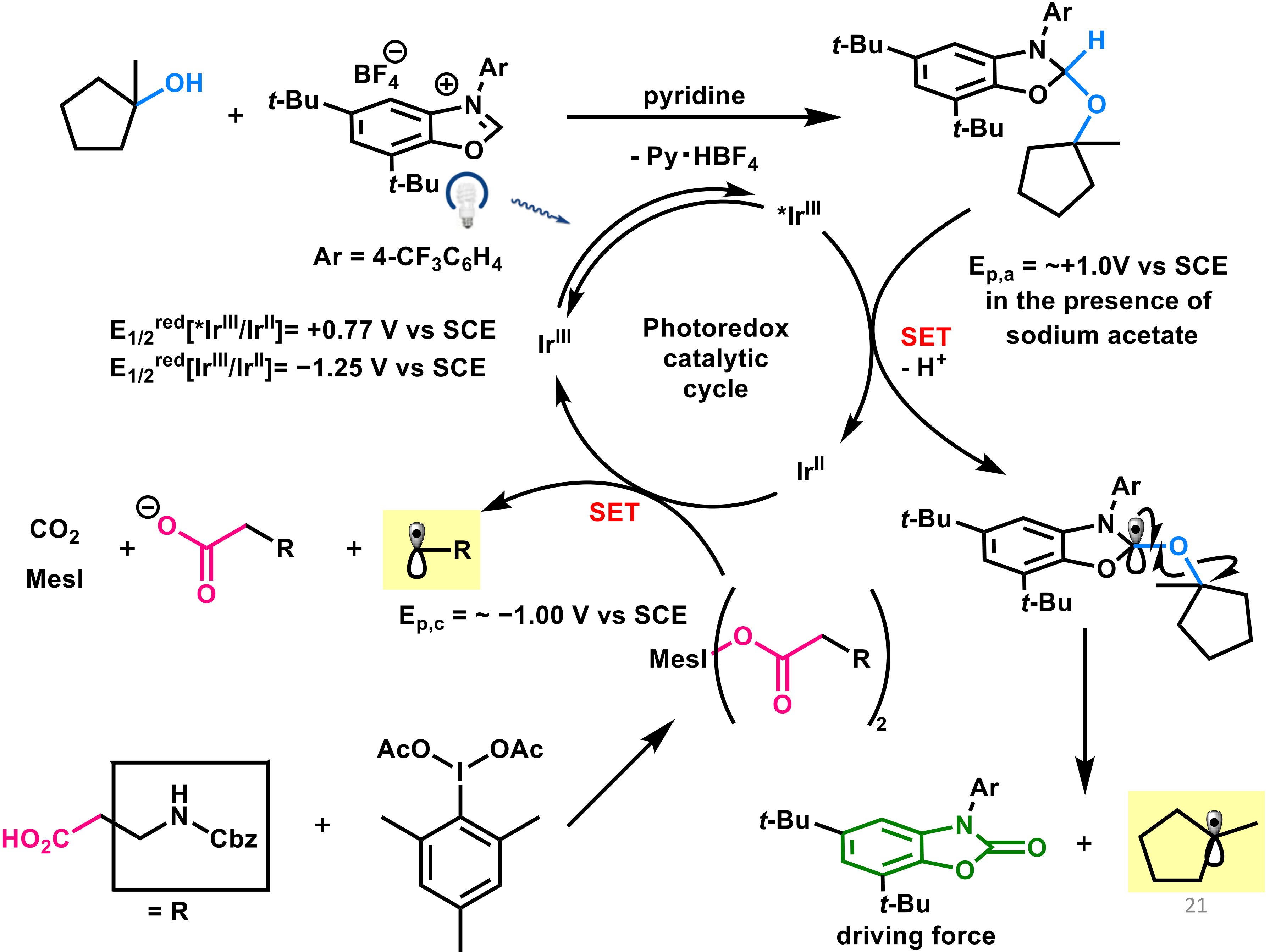


NHC-1



$NiCl_2$·dtbbpy

Proposed Mechanism: Photoredox Cycle

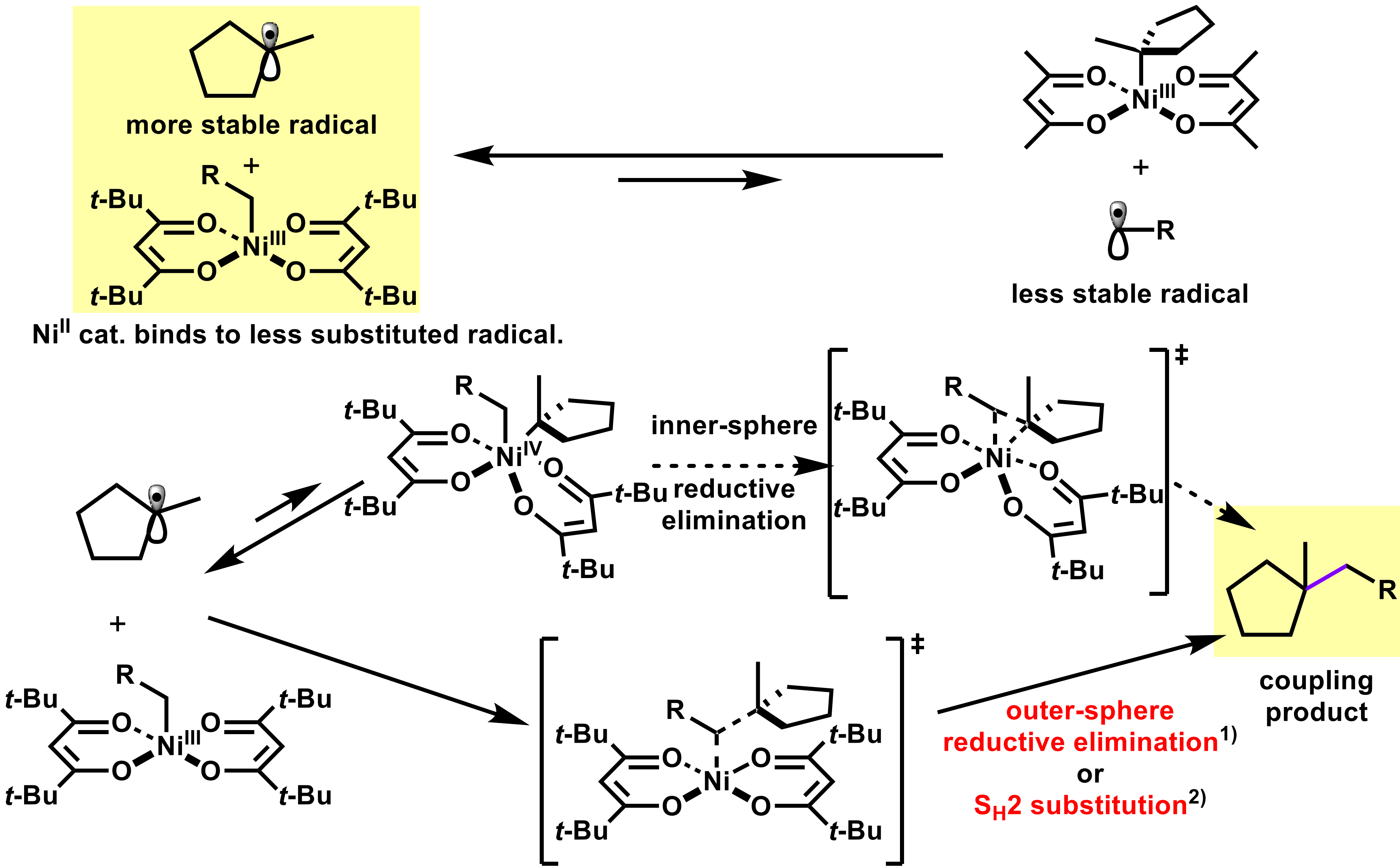


DFT Calculation of Radical Sorting

* acac is used as a model for THMD.
Ni cat. stabilizes less substituted alkyl radical.

1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

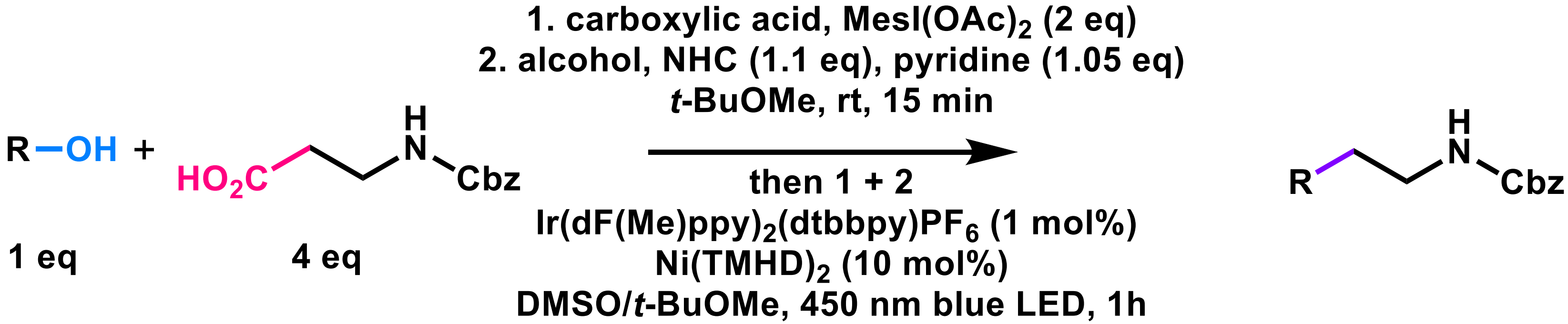
Possible Mechanism: Radical Cross Coupling

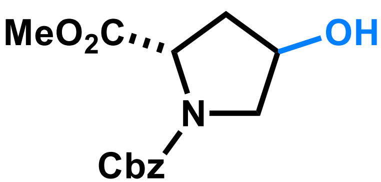


Ni^{II} cat. binds to less substituted radical.

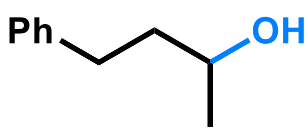
1) Yuan, M.; Song, Z.; Badir, S. O.; Molandar, G. A.; Gutierrez, O. *J. Am .Chem. Soc*. **2020**, *142*, 7225.
2) a) Bour, J. R.; Ferguson, D. M.; McClain, E. J.; Kampf, J. W.; Sanford, M. S. *J. Am .Chem. Soc*. **2019**, *141*, 8914. b) Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcázar, J.; MacMillan, D. W. C. *Science*. **2021**, 374, 1258−1263.

Substrate Scope (1)

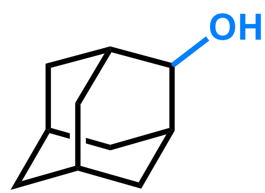




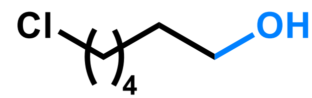
51%
(NHC-1)



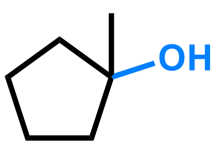
79%
(NHC-1)



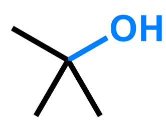
47%
(NHC-1)



50%
(NHC-1)

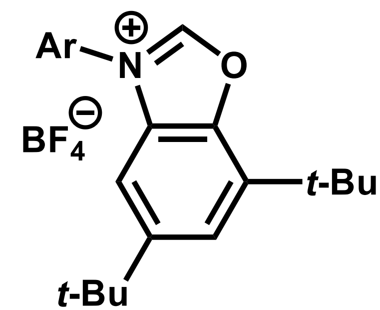


75%
(NHC-5)



74%
(NHC-5)

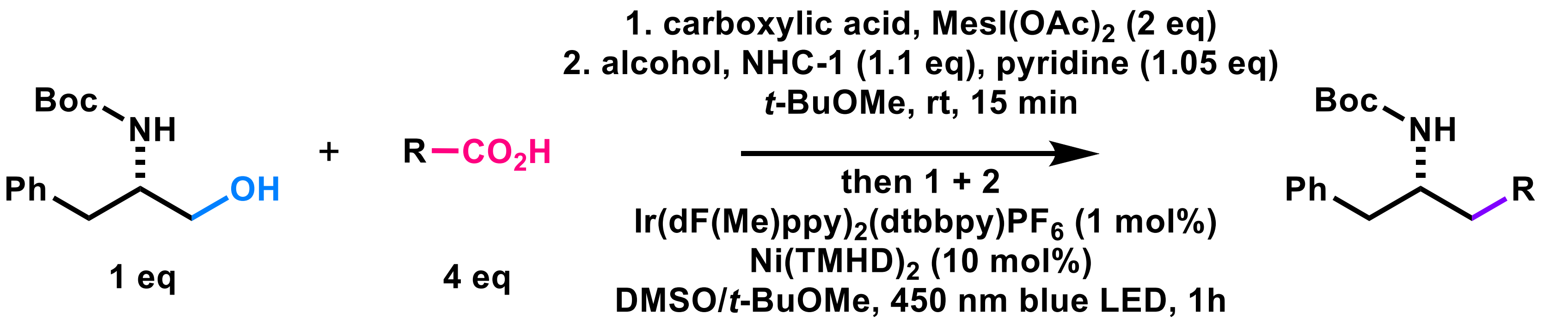
For hindered tertiary alcohol, more electron deficient NHC-5 is used.

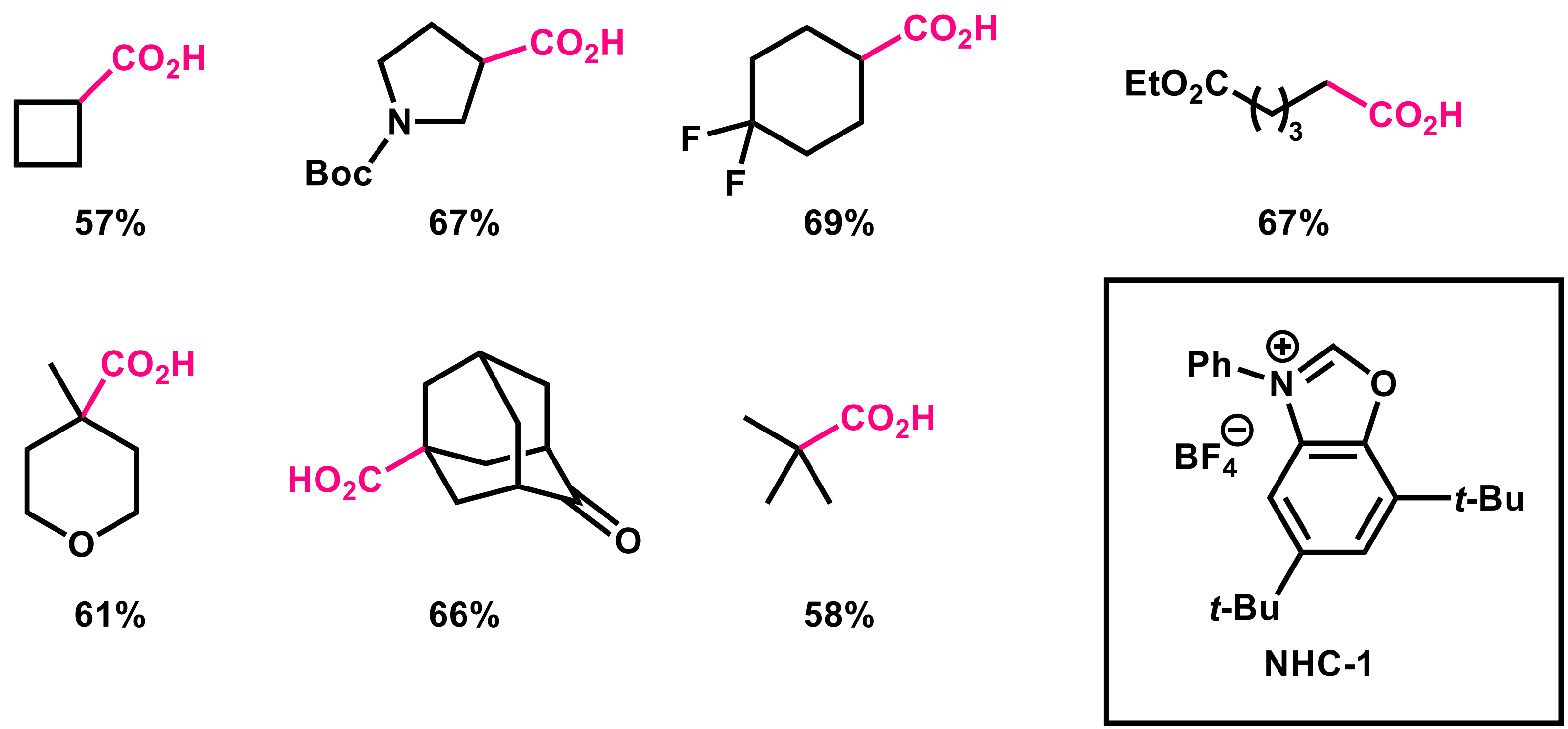


NHC-1, Ar = Ph
NHC-5, Ar = 4-$CF_3C_6H_4$

1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

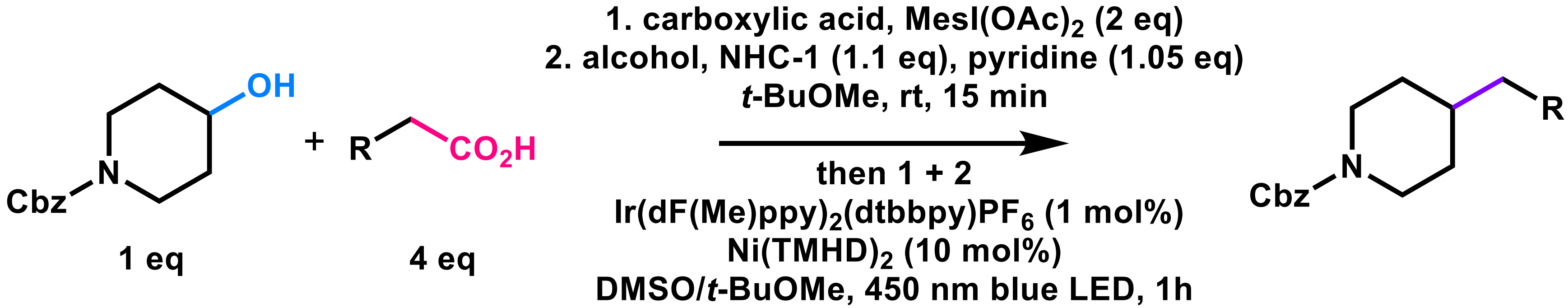
Substrate Scope (2)

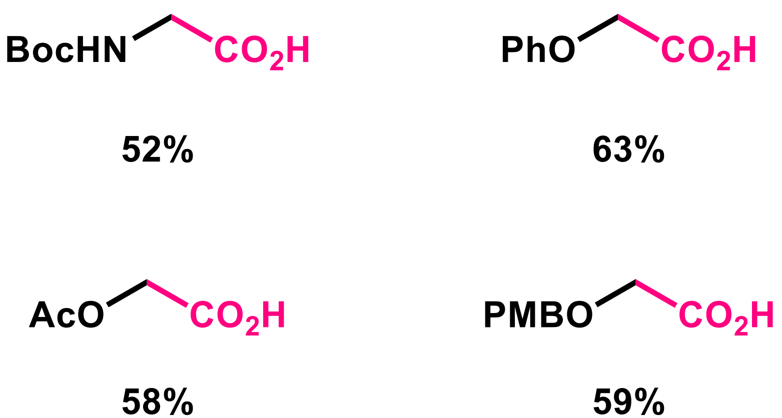


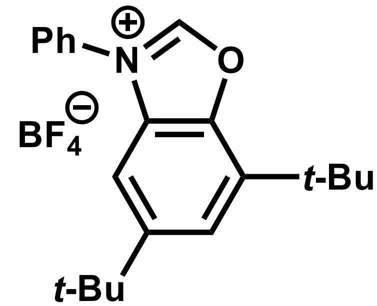


1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

C1 Homologation





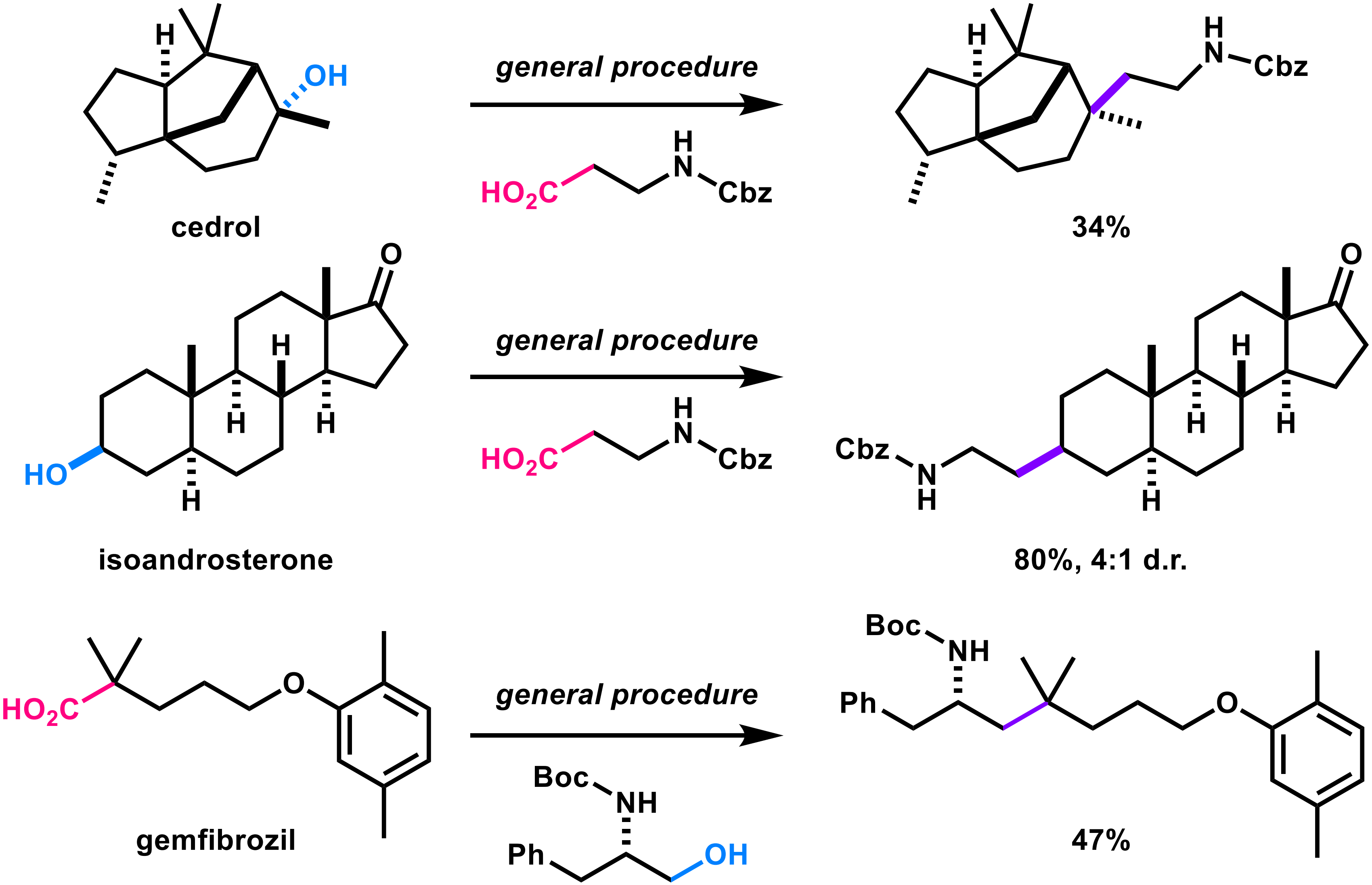


NHC-1

Protected alcohol homologation is possible.

1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

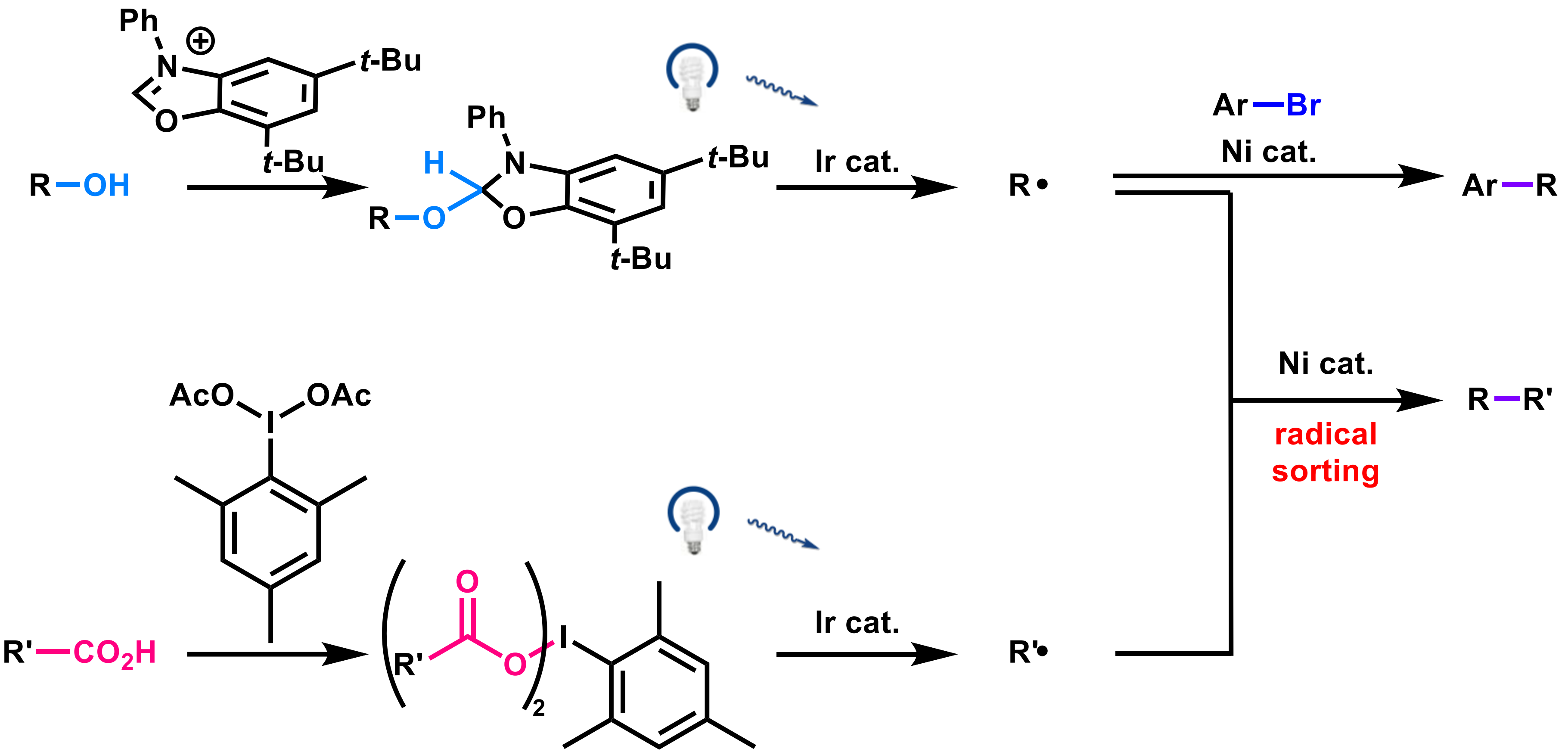
Application to Late Stage Functionalization



This method could be applied to late stage functionalization of natural conpounds.

1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

Summary



C(sp^3)-C(sp^3) cross coupling of alcohol and carboxylic acid was achieved by metallaphotoredox system.
Abundant alcohols and carboxylic acids can be used as homologation unit with this method.

Appendix

Photoreactor

PennOC『Photoreactor m1』

カタログ

最終更新日： 2018/04/19

可視光レドックス反応のための照明・撹拌装置および冷却装置を装備！

『Photoreactor m1』は、450nmの光源、撹拌装置、および温度調節機能を備えたオールインワンシステムです。

遮光インターロックにより、ユーザーが有害な光線にさらされることを防ぎます。

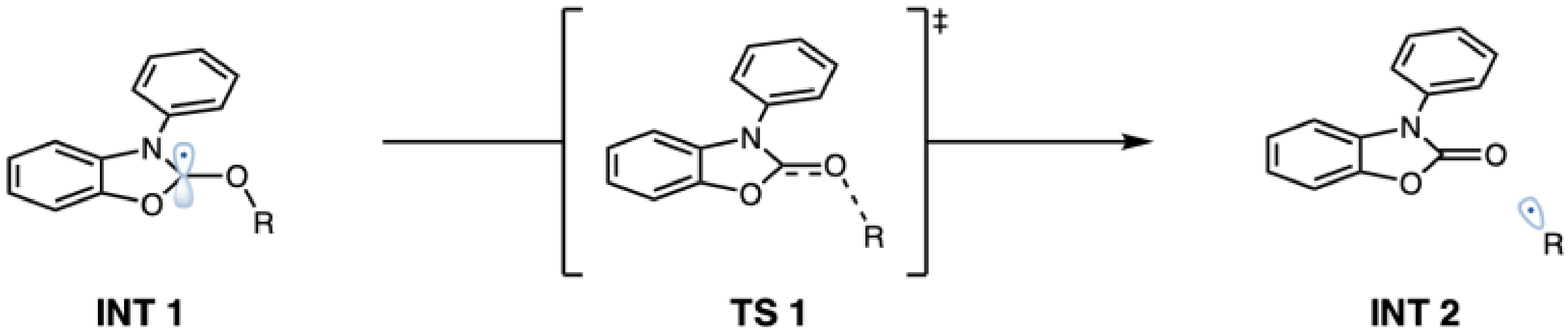
可視光レドックス反応のための照明・撹拌装置および冷却装置を備えています。
更に照明の強度や撹拌の速度、空気の流れなどの反応に関連するパラメータをユーザーが簡便に制御するためのタッチスクリーンが含まれています。

モジュラー設計により様々な波長とバイアルサイズにも対応しています。

【特長】
■450nmの光源、撹拌装置、温度調節機能を備えたオールインワンシステム
■遮光インターロックにより、ユーザーが有害な光線にさらされることを防ぐ
■可視光レドックス反応のための照明・撹拌装置および冷却装置を備えている
■パラメータを簡便に制御するためのタッチスクリーンが含まれている
■モジュラー設計により様々な波長とバイアルサイズにも対応

1) PennOC『Photoreactor m1』 | ライフィクスアナリティカル - Powered by イプロス (ipros.jp)

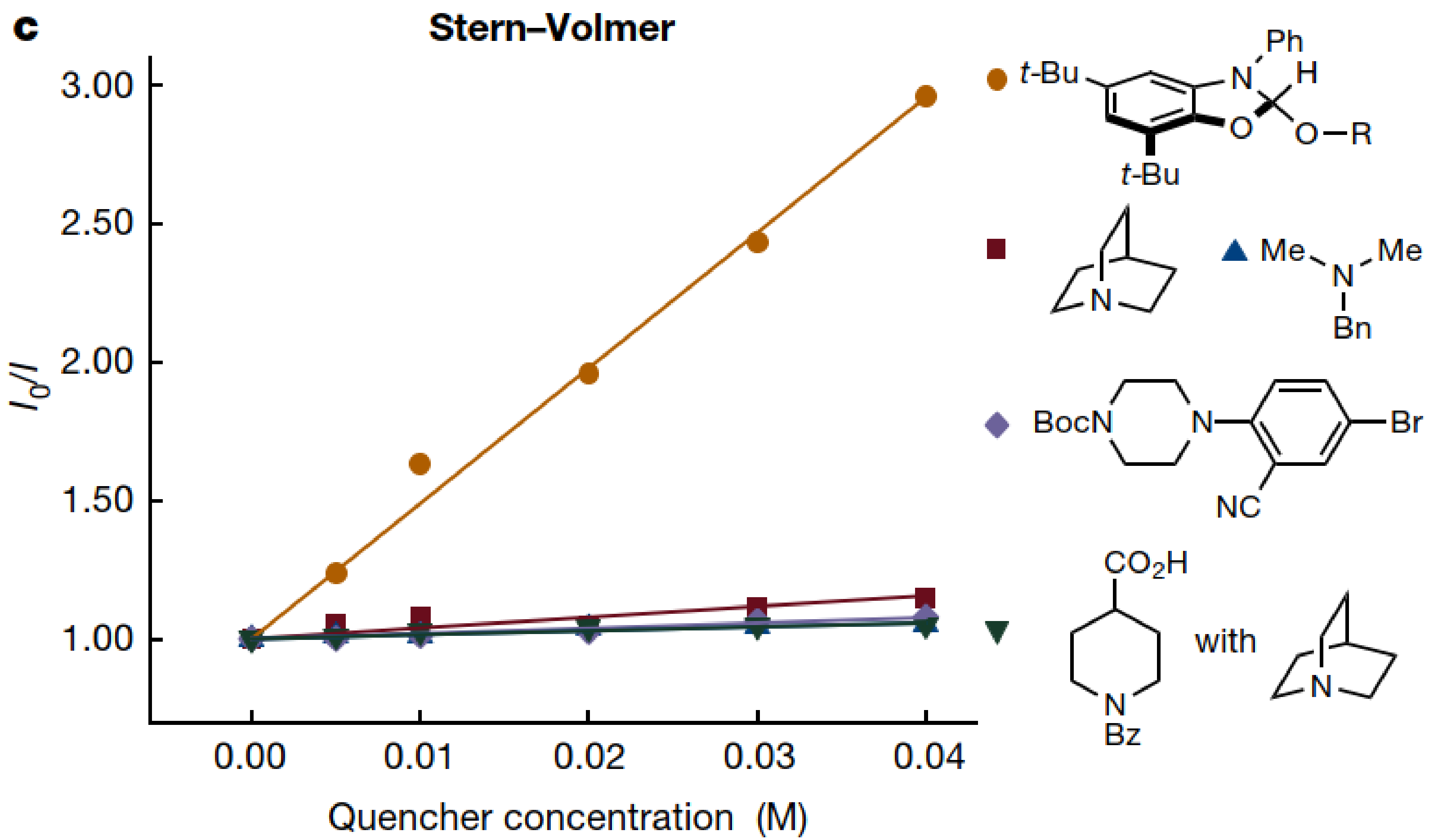
β-scission of Alcohol-NHC adducts



entry	R	ΔG°	ΔG‡	k_{298} (s^{-1})
A	Me	–27.6	11.9	1×10^4
B	Et	–28.6	11.0	5×10^4
C	i-Pr	–29.4	9.9	3×10^5
D	*t*-Bu	–32.3	5.8	4×10^8

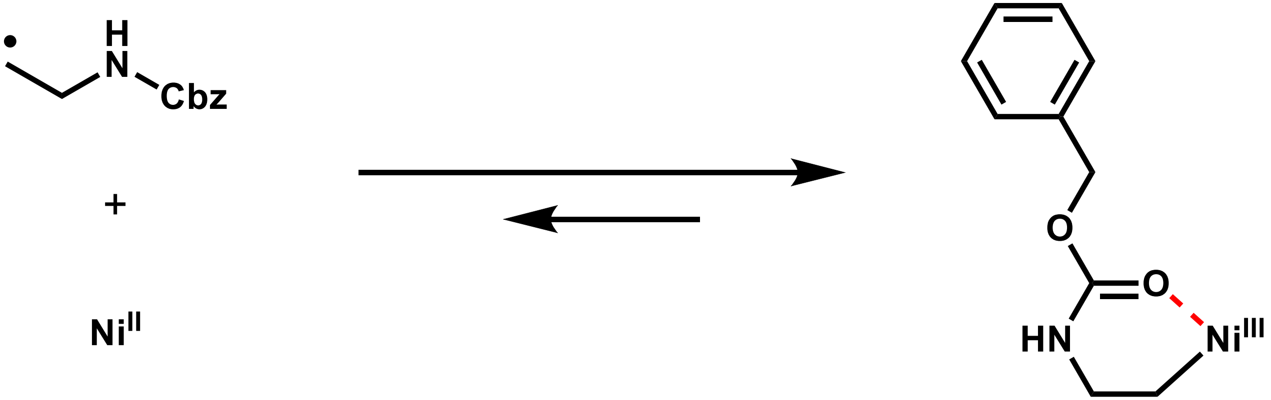
1) Dong, Z.; MacMillan, D. W. C. *Nature*. **2021**, *598*, 451.

Stern-Volmer Quenching Comparison

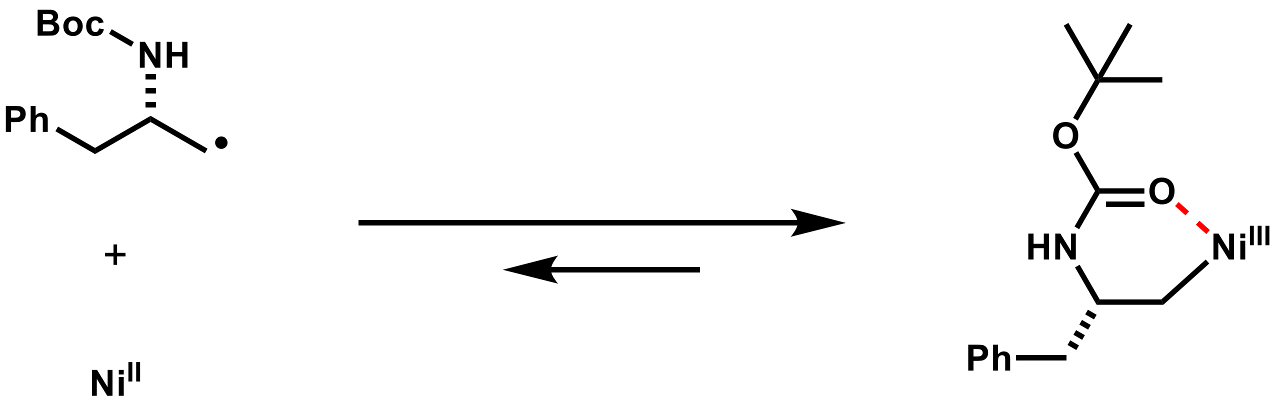


1) Dong, Z.; MacMillan, D. W. C. *Nature*. **2021**, *598*, 451.

Effect of Chelation



chelation stabilizes radical-Ni species



1) Sakai, H, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

SH2 Substitution with Fe