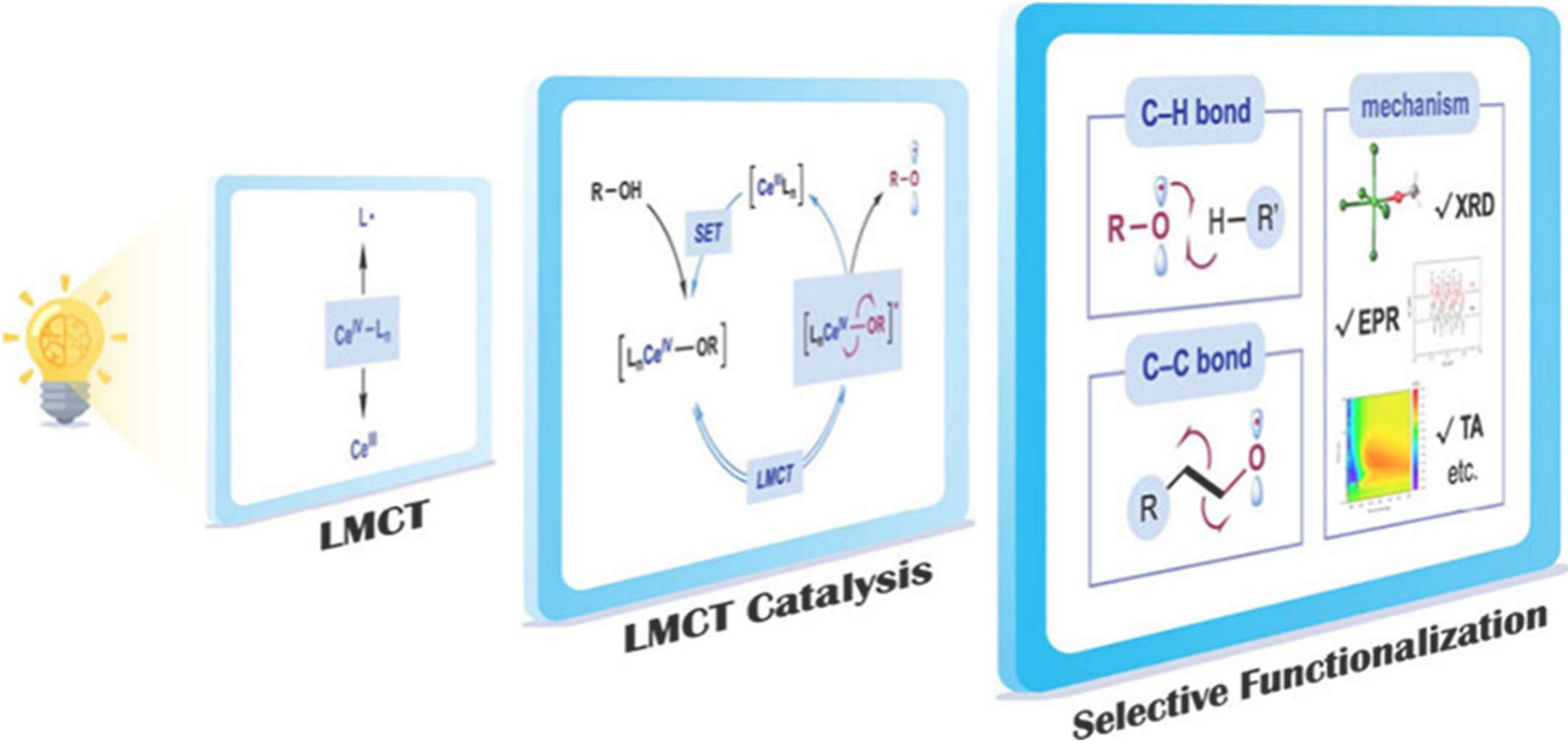


Methylative Cross-Coupling

2025.6.7. Literature Seminar

D3 Kyohei Oga

Contents

1. **Introduction**

2. ORGANIC CHEMISTRY

Alcohol-alcohol cross-coupling enabled by S_H2 radical sorting

Ruizhe Chen[1]†, Nicholas E. Intermaggio[1]†, Jiaxin Xie[1]†, James A. Rossi-Ashton[1]†, Colin A. Gould[1], Robert T. Martin[1], Jesús Alcázar[2], David W. C. MacMillan[1]*

3. JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS Article

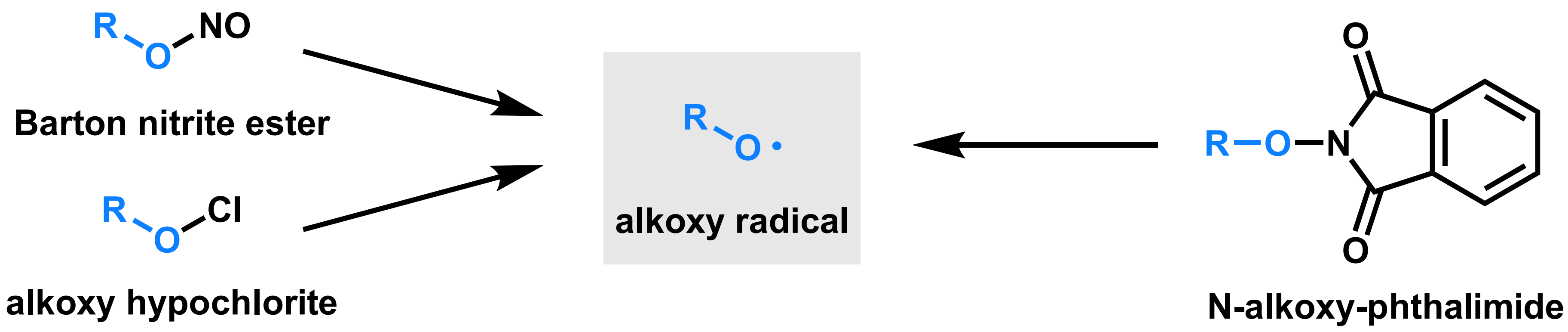
Synergistic LMCT and Ni Catalysis for Methylative Cross-Coupling Using *tert*-Butanol: Modulating Radical Pathways via Selective Bond Homolysis

Lingfei Duan, Yunzhi Lin, Qing An, and Zhiwei Zuo*

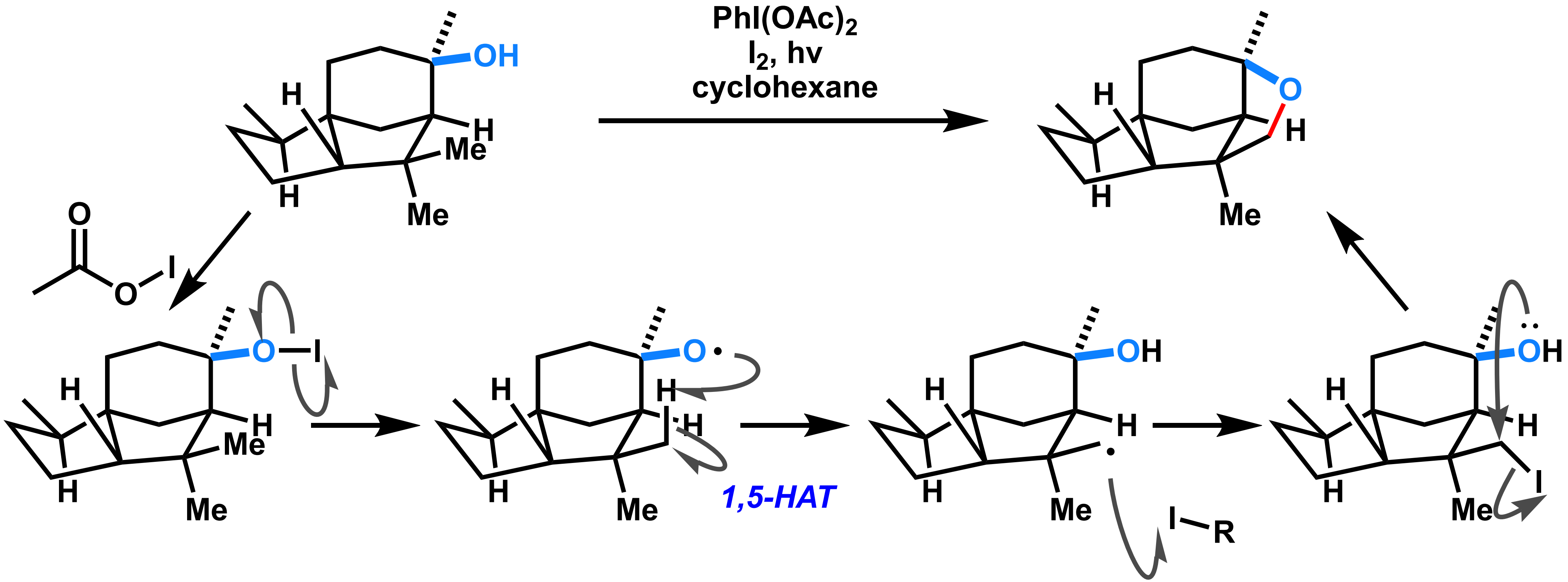
Contents

Alkoxy Radical

Classic precursors for alkoxy radical generation[1]



Total synthesis of Pseudoanisatin[2]



1) Chang, L.; An, Q.; Duan, L.; Feng, K.; Zuo, Z. *Chem. Rev.*, **2022**, *122*, 2429.
2) Hung, K.; Condakes, M.-L.; Morikawa, T.; Maimone, T.-J. *J. Am. Chem. Soc.* **2016**, *138*, 16616.

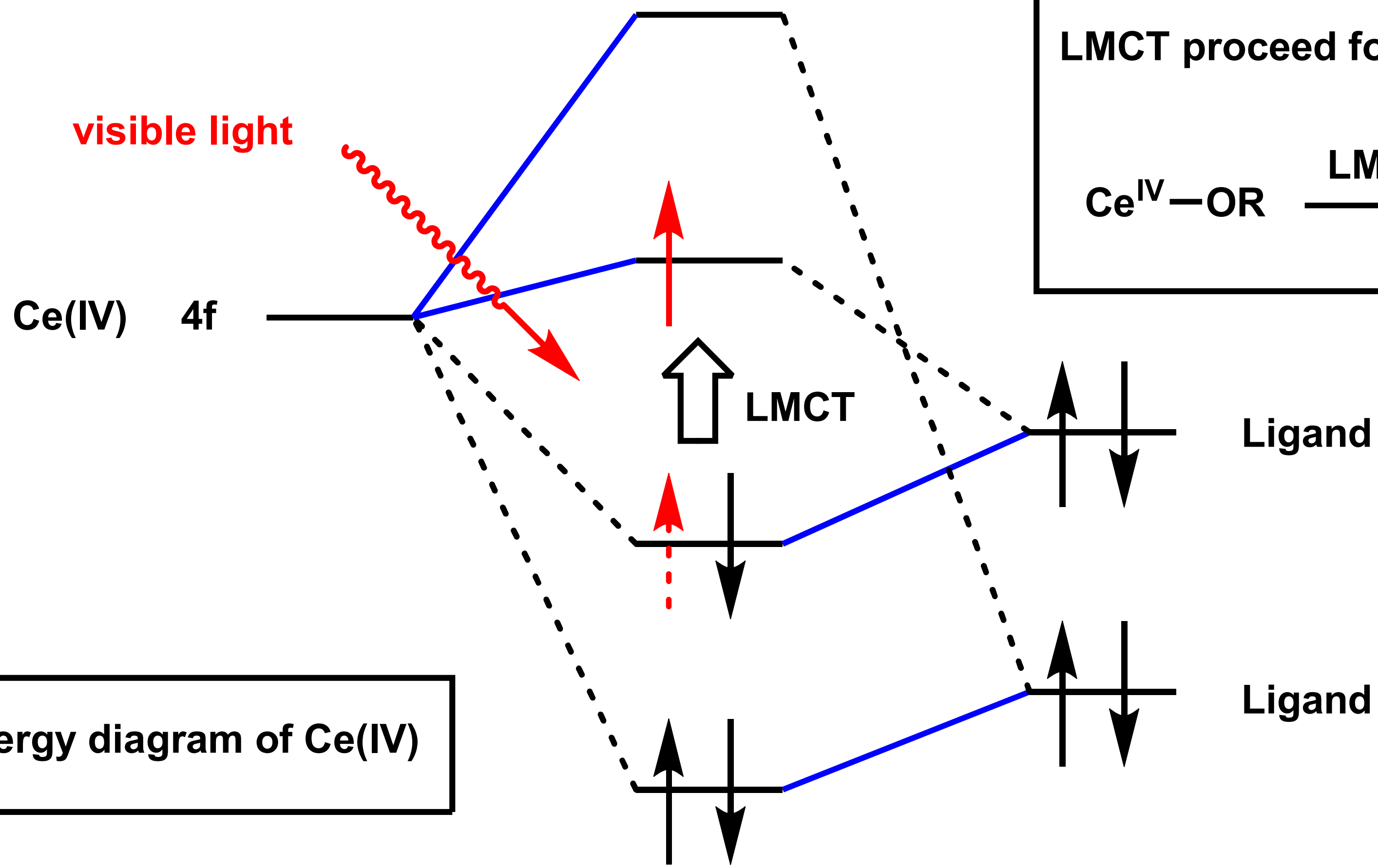
LMCT (Ligand to Metal Charge Transfer) [1) 2)]

LMCT complexes arise from transfer of electrons from MO with ligand-like character to those with metal-like character.
(opposite relationship to MLCT)

*** This type of transfer could occur if complexes have ligands with relatively high-energy lone pairs or if the metal has low-lying empty orbitals.**

LMCT proceed formal reduction of metal

Ce^{IV}–OR —LMCT→ Ce^{III} •OR



energy diagram of Ce(IV)

1) 200418_LS_Shinsuke_Shimizu
2) シュライバー・アトキンス無機化学(下) 第4版

Prof. David W. C. MacMillan / Zhiwei Zuo

Prof. David W. C. MacMillan

-1991 B.S. @The University of Glasgow
-1996 Ph.D. @The University of California, Irvine
(Prof. Larry E. Overman)
-1998 Postdoctoral Fellow @Harvard University
(Prof. David A. Evans)
-2000 (PI) @University of California, Berkeley
-2004 (PI) @California Institute of Technology
-2011 Professor @Princeton University
-Present Distinguished Professor @Princeton University

Research topics:
Photoredox catalysis, Organocatalysis, Labeling biomolecules, Total synthesis

Prof. Zhiwei Zuo

-2007 B.S. @Nanjing University
(Prof. Yixiang Chen)
-2012 Ph.D. @ Shanghai Institute of Organic Chemistry
(Prof. Dawei Ma)
-2015 Postdoctoral Fellow @Princeton University
(Prof. David W. C. MacMillan)
-2020 Assistant Professor @ShanghaiTech University
-Present Professor @Shanghai Institute of Organic Chemistry

Research topics:
Photoinduced LMCT catalysis for C-H functionalization, C-C bond Formation/cleavage, and efficient synthetic process

1) https://macmillan.princeton.edu/
2) http://zuogroup.sioc.ac.cn/zuo_group/

Contents

1. Introduction

2. ORGANIC CHEMISTRY

Alcohol-alcohol cross-coupling enabled by S_H2 radical sorting

Ruizhe Chen[1]†, Nicholas E. Intermaggio[1]†, Jiaxin Xie[1]†, James A. Rossi-Ashton[1]†, Colin A. Gould[1], Robert T. Martin[1], Jesús Alcázar[2], David W. C. MacMillan[1]*

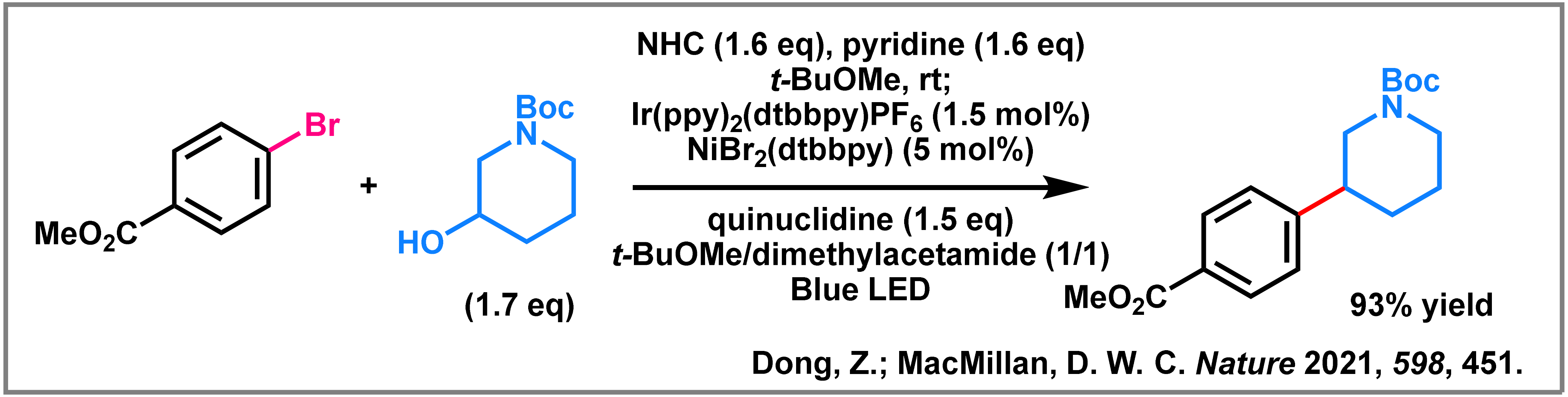
3. JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

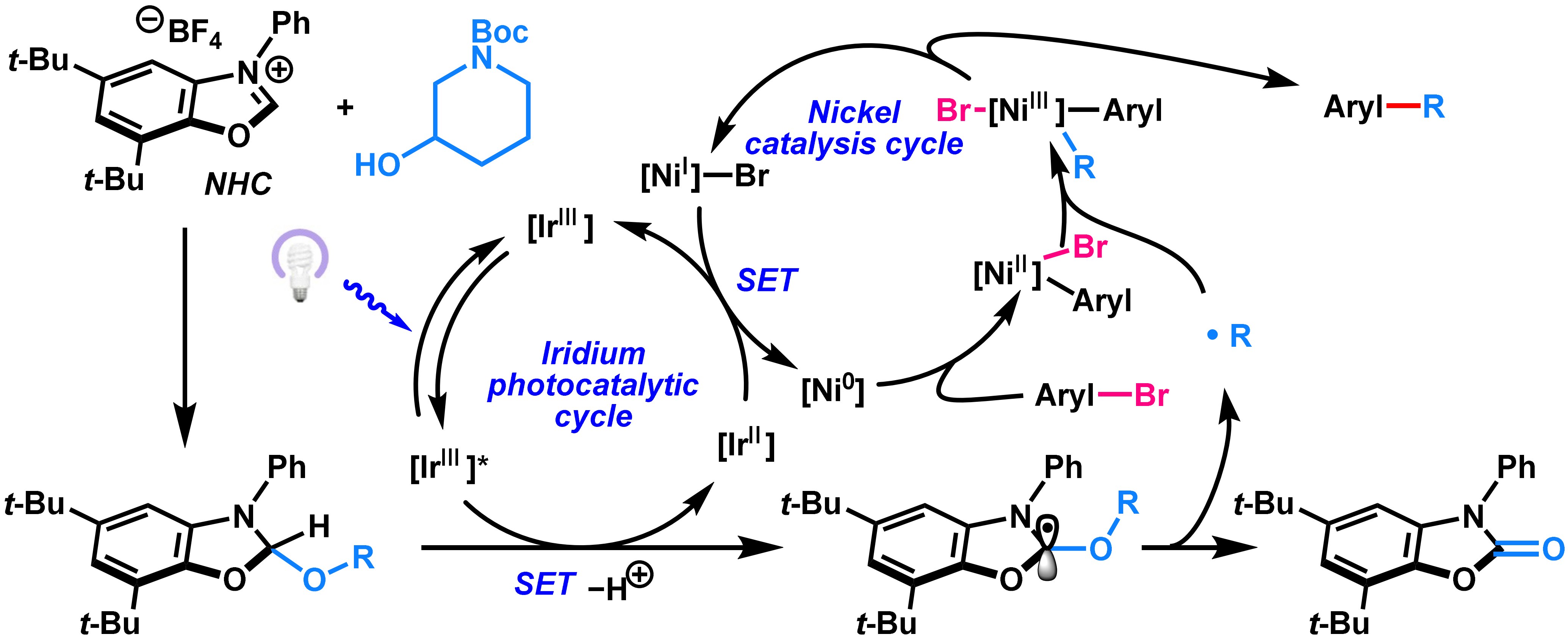
pubs.acs.org/JACS Article

Synergistic LMCT and Ni Catalysis for Methylative Cross-Coupling Using *tert*-Butanol: Modulating Radical Pathways via Selective Bond Homolysis

Lingfei Duan, Yunzhi Lin, Qing An, and Zhiwei Zuo*

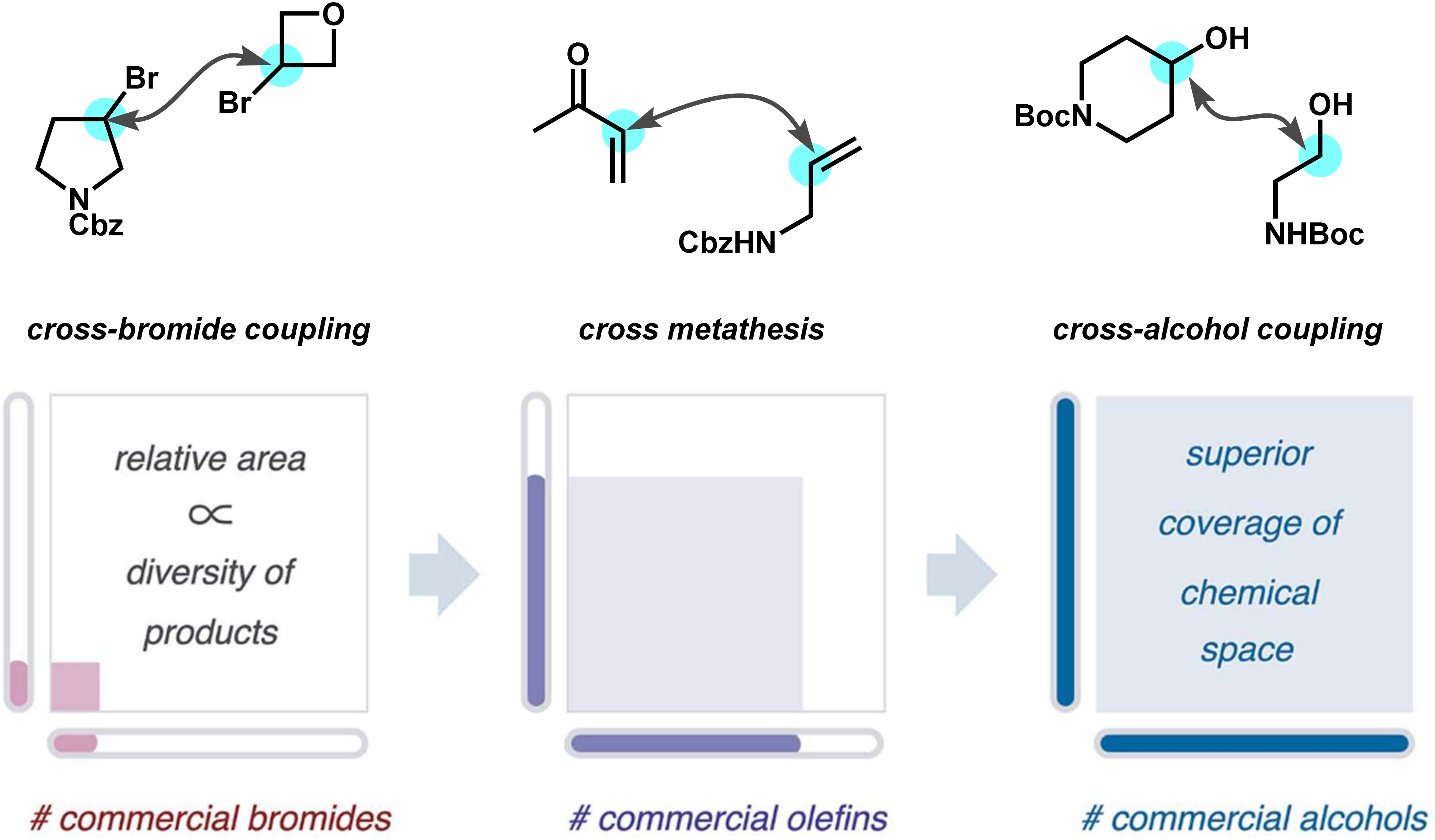
Previous Work in MacMillan Lab





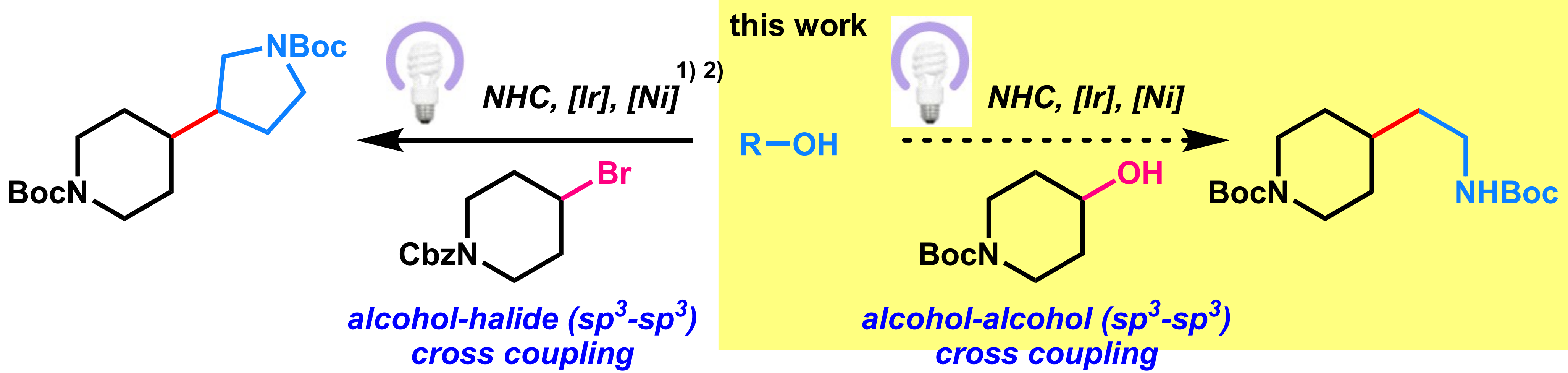
1) Dong, Z.; MacMillan, D. W. C. *Nature* **2021**, *598*, 451.
2) Nicholas, A.; Seokjoon Oh, T.; MacMillan, D. W. C.; Bird, M. J. *J. Am. Chem. Soc.* **2021**, *143*, 9332.

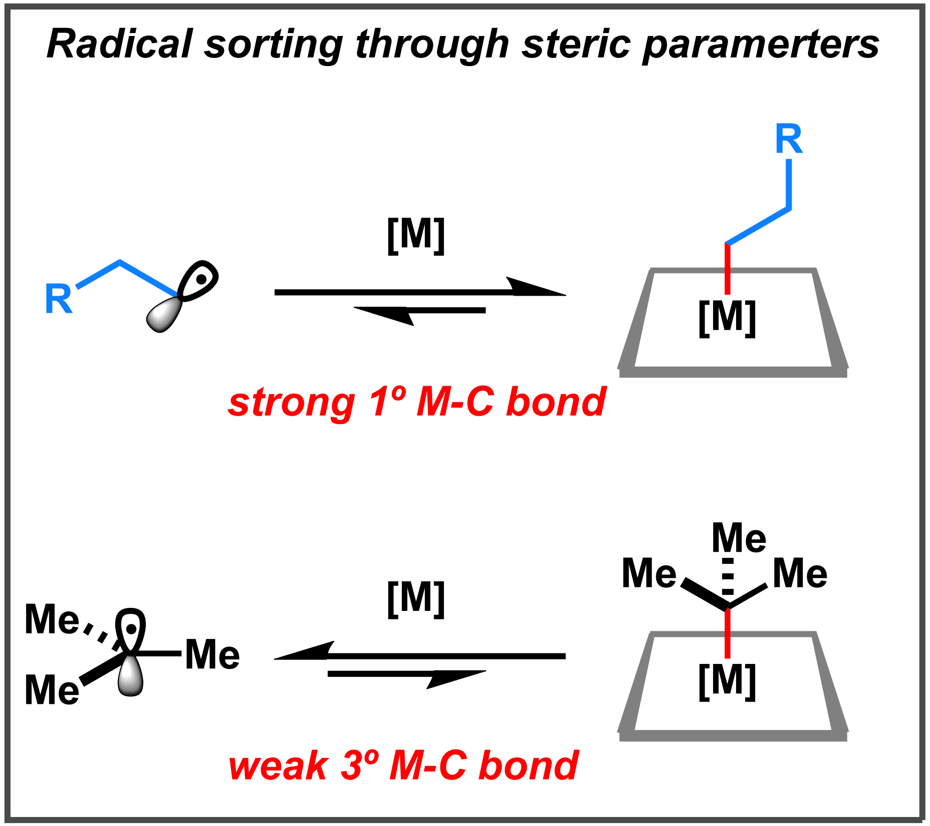
Single Functional Group Coupling

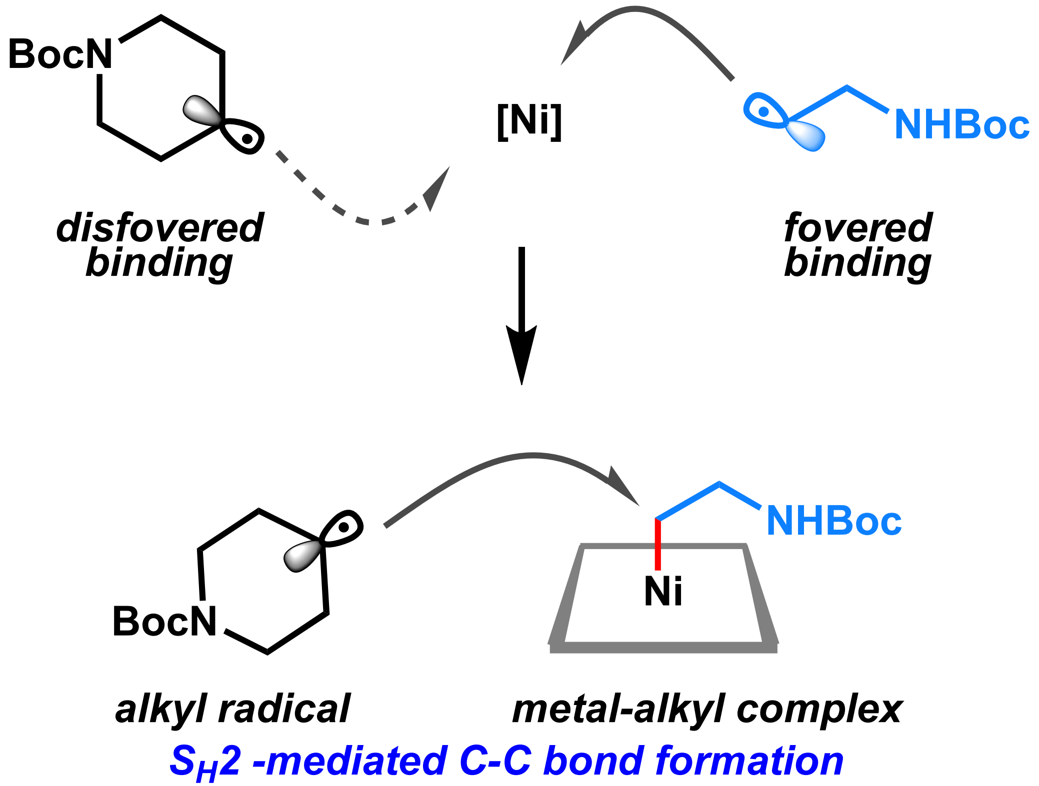


1) Chen, R.; Intermaggio, N. E.; Xie, J.; Rossi-Ashton, J. A.; Goulg, C. A.; Martin, R. T.; Alcazar, J.; MacMillan, D. W. C. *Science* **2024**, *383*, 1350.

Working Hypothesis

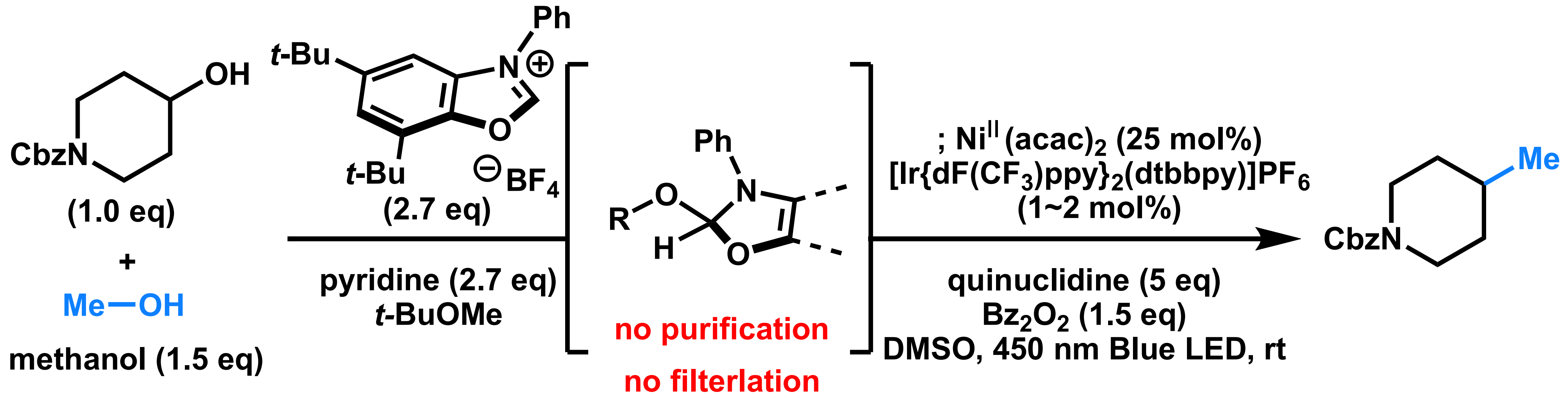


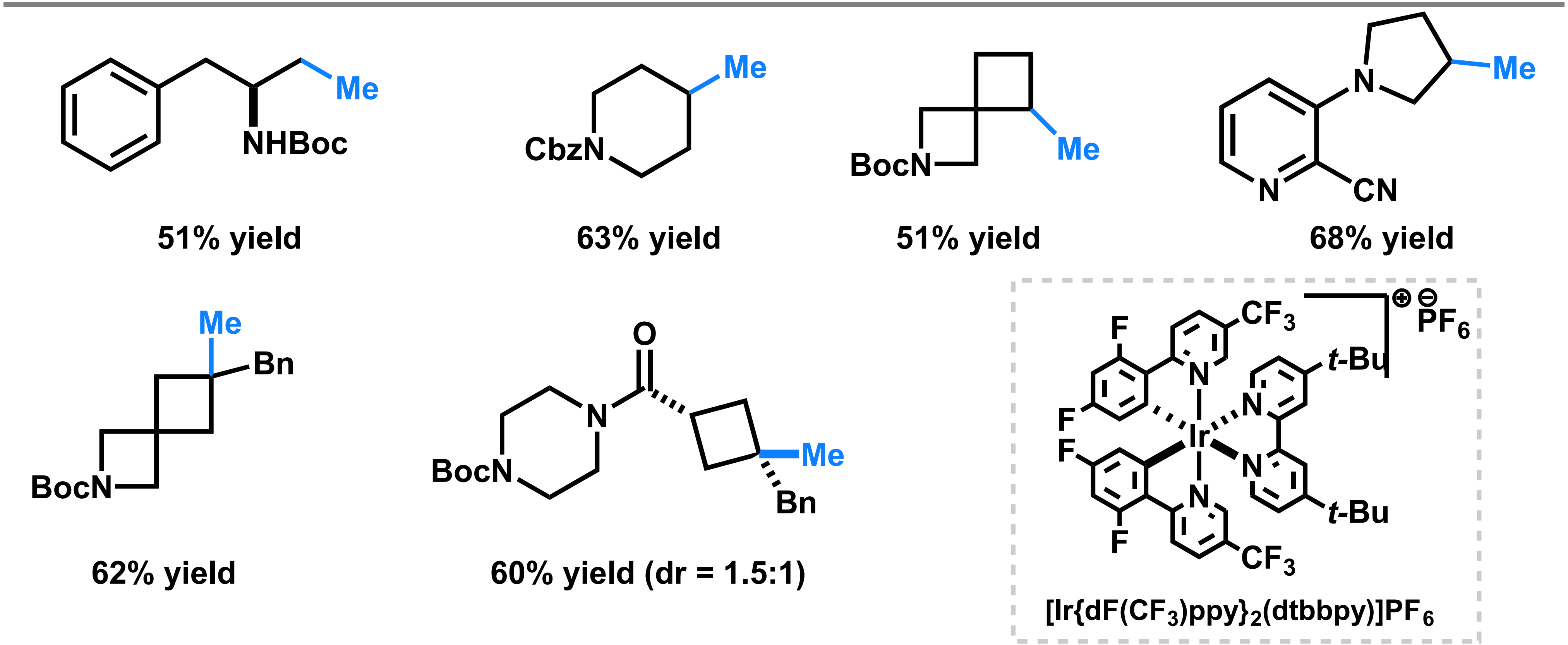




1) Lyon, W. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2023**, *145*, 7736.
2) 230415_LS_Yuki_Komori

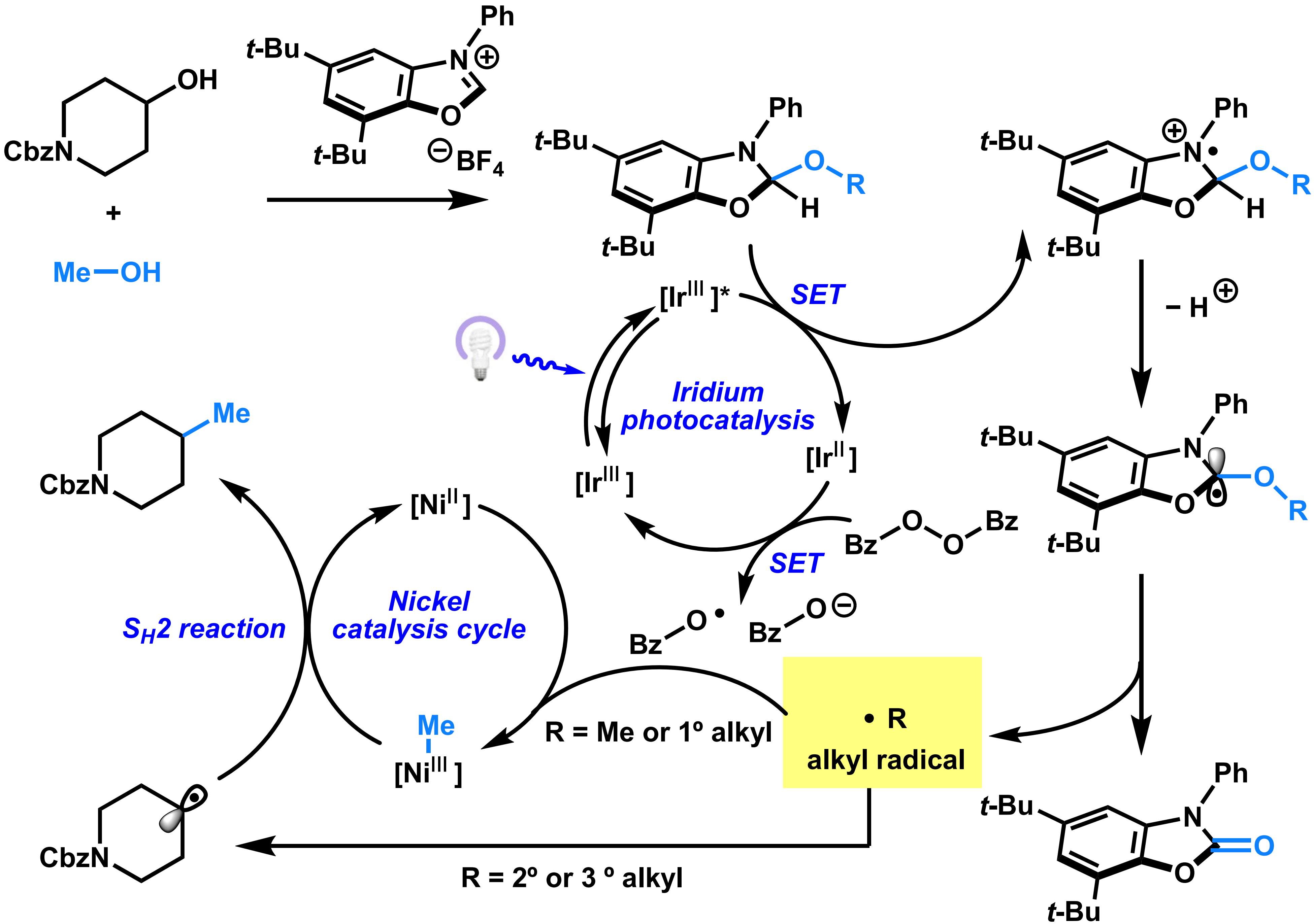
Substrate Scope





1) Chen, R.; Intermaggio, N. E.; Xie, J.; Rossi-Ashton, J. A.; Goulg, C. A.; Martin, R. T.; Alcazar, J.; MacMillan, D. W. C. *Science* **2024**, *383*, 1350.

Proposed Reaction Mechanism



1) Chen, R.; Intermaggio, N. E.; Xie, J.; Rossi-Ashton, J. A.; Goulg, C. A.; Martin, R. T.; Alcazar, J.; MacMillan, D. W. C. *Science* **2024**, *383*, 1350.

Contents

1. Introduction

2. ORGANIC CHEMISTRY

Alcohol-alcohol cross-coupling enabled by S_H2 radical sorting

Ruizhe Chen[1]†, Nicholas E. Intermaggio[1]†, Jiaxin Xie[1]†, James A. Rossi-Ashton[1]†, Colin A. Gould[1], Robert T. Martin[1], Jesús Alcázar[2], David W. C. MacMillan[1]*

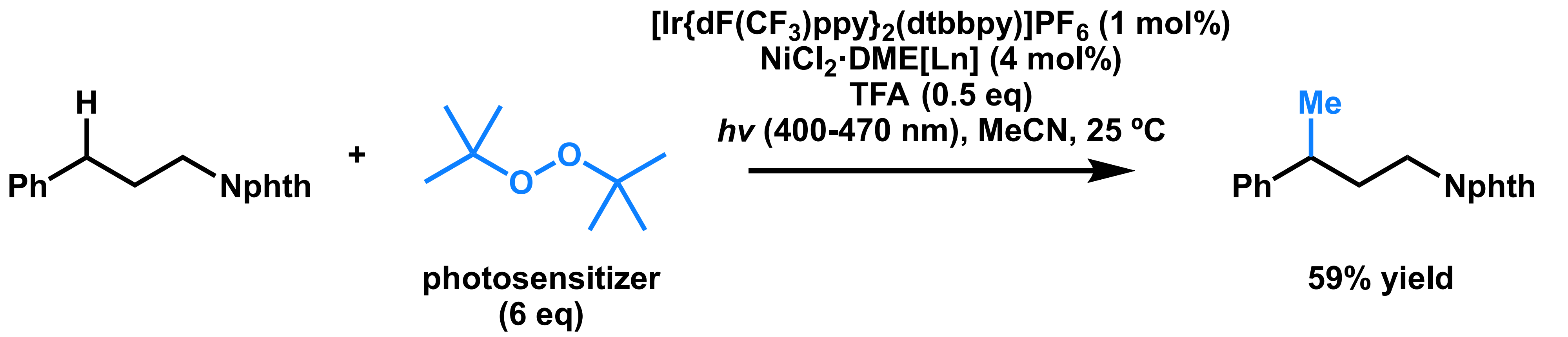
3. JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JACS Article

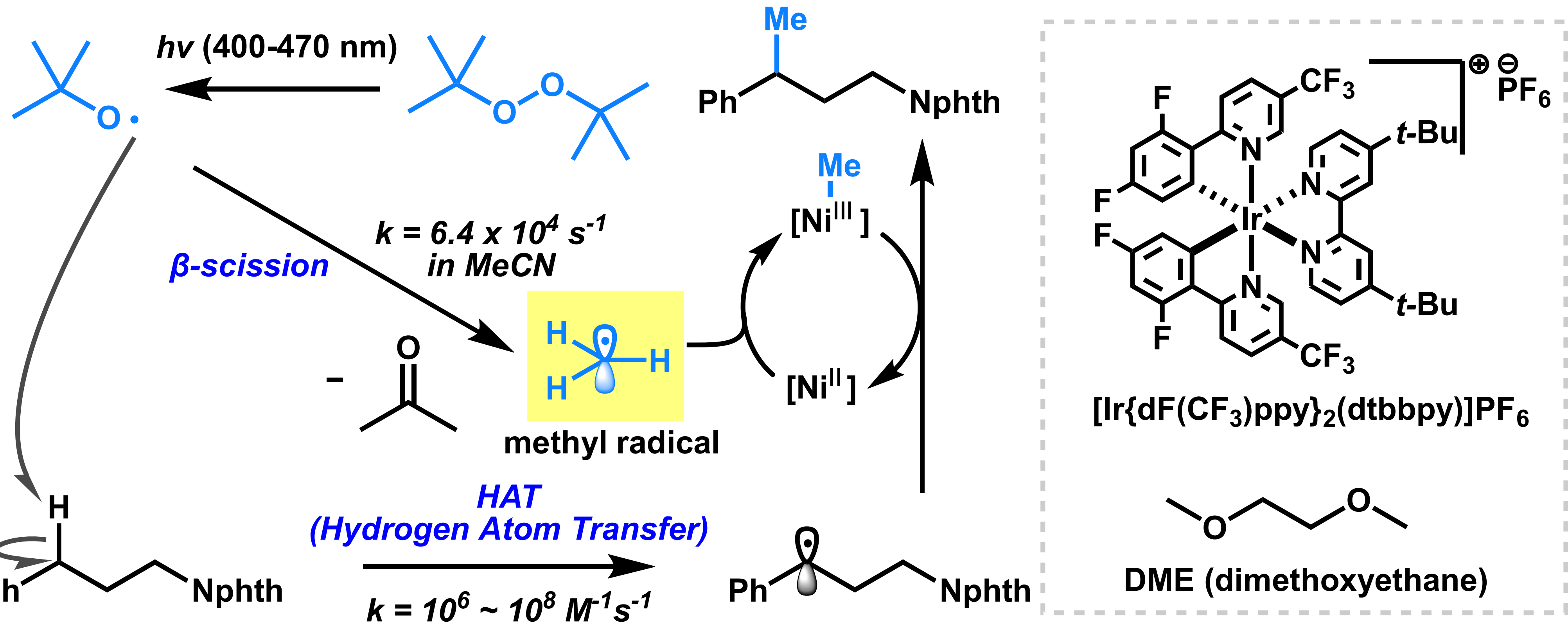
Synergistic LMCT and Ni Catalysis for Methylative Cross-Coupling Using *tert*-Butanol: Modulating Radical Pathways via Selective Bond Homolysis

Lingfei Duan, Yunzhi Lin, Qing An, and Zhiwei Zuo*

Use of tert-Butoxy Radical as Methyl Source

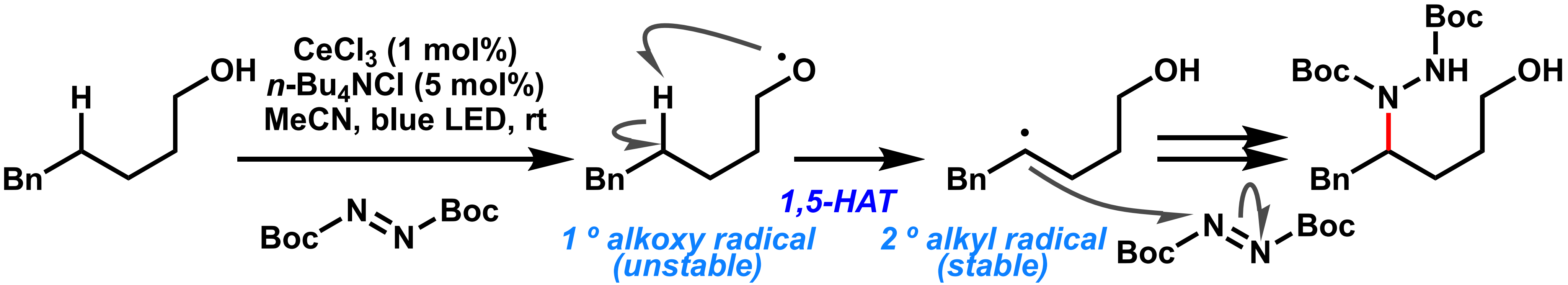


Vasilopoulos, A.; Krska, S. W.; Stahl, S. S. *Science* 2021, *372*, 398.

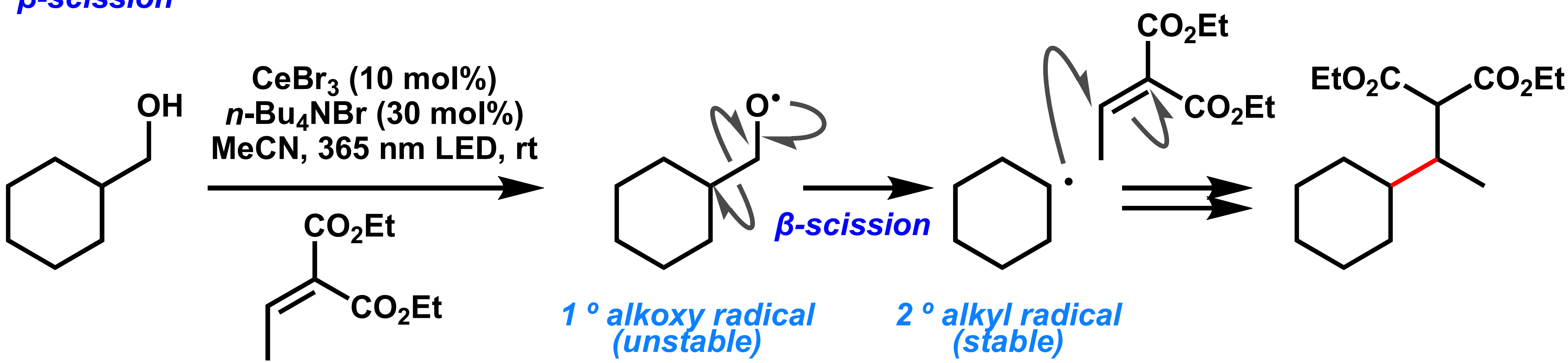


Previous Work by Zuo group

Hydrogen Atom Transfer (HAT) [1)]

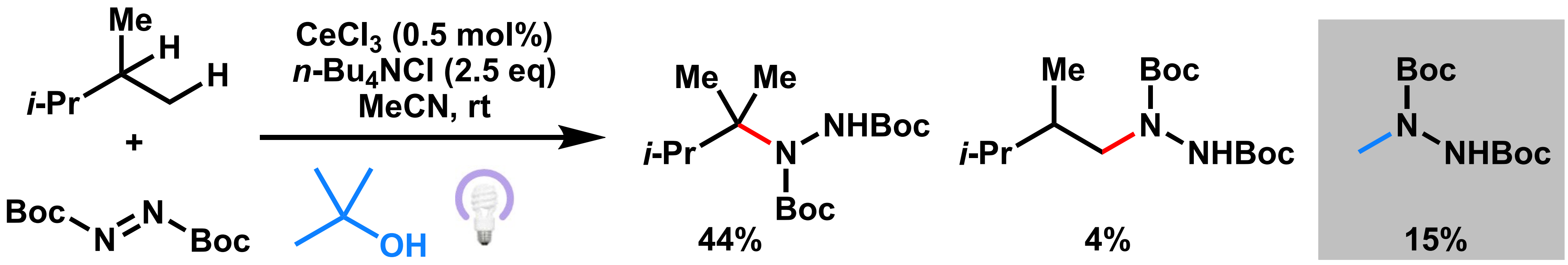


β-scission [2)]

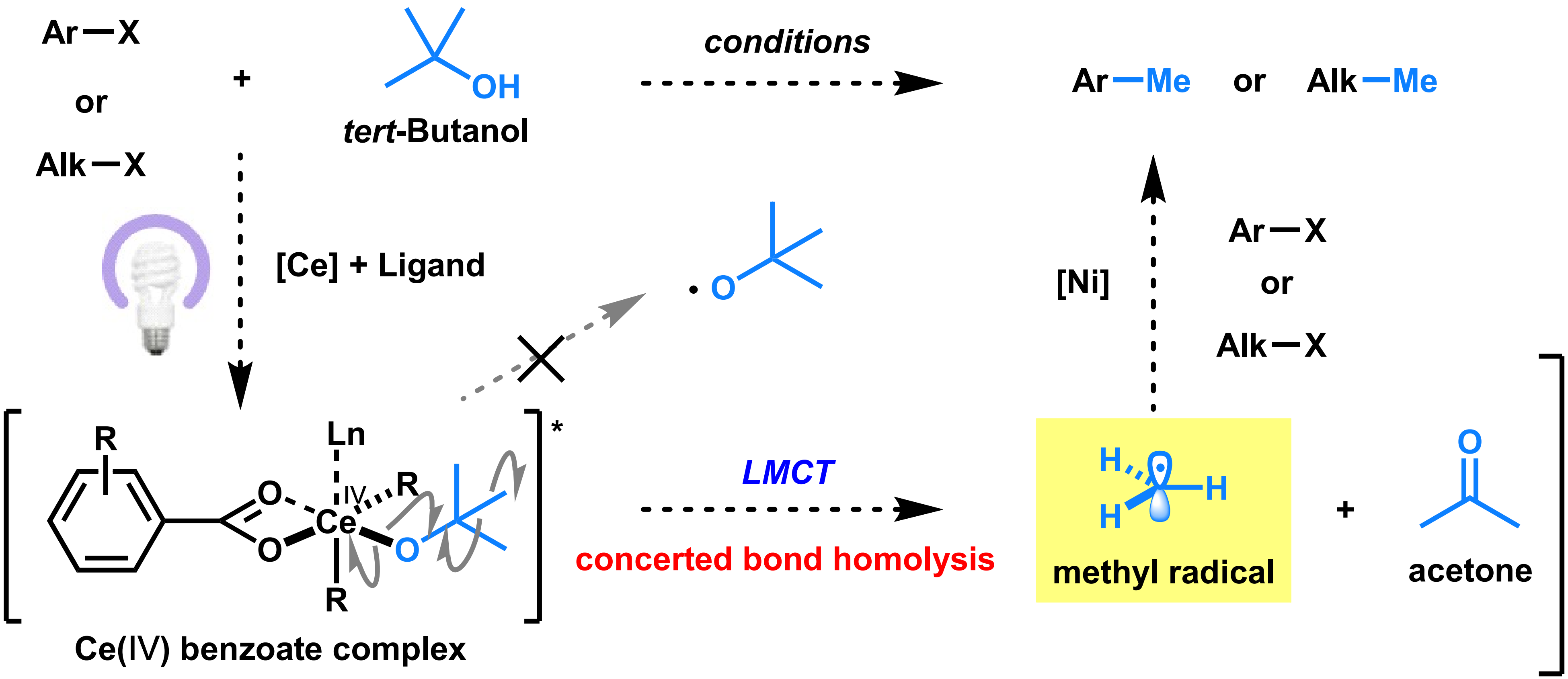


1) Hu, Anhua.; Guo, J.-J.; Pan, H.; Tang, H.; Gao, Z.; Zuo, Z. *J. Am. Chem. Soc.* **2018**, *140*, 1612.
2) Zhang, K.; Chang, L.; An, Q.; Wang, X.; Zuo, Z. *J. Am. Chem. Soc.* **2019**, *141*, 10556.

Working Hypothesis

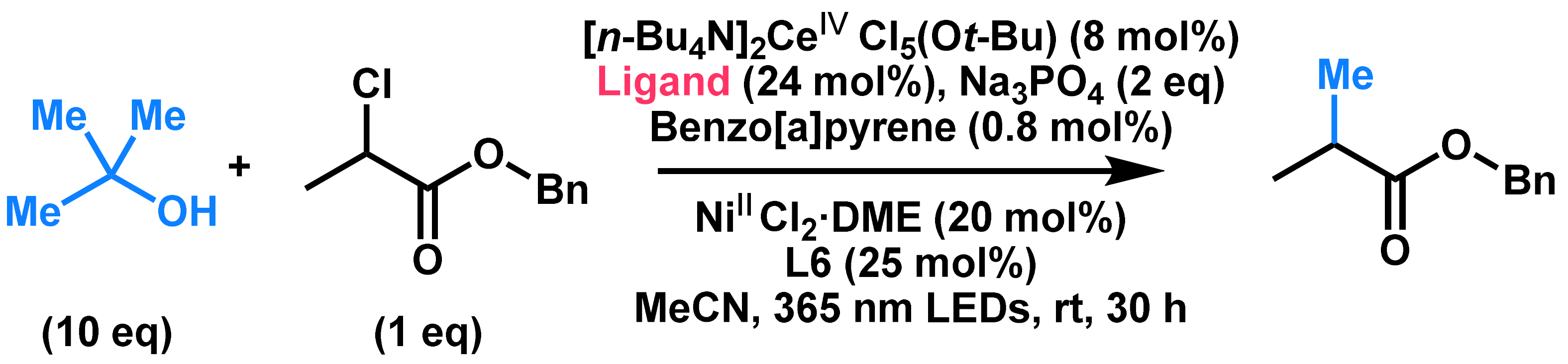


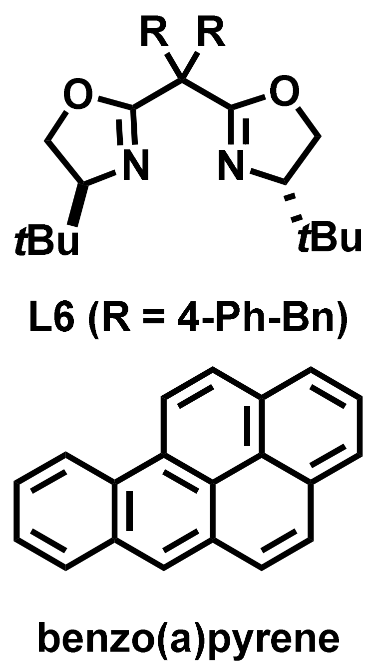
Zuo, Z. et.al. *J. Am. Chem. Soc.* 2023, *145*, 359.



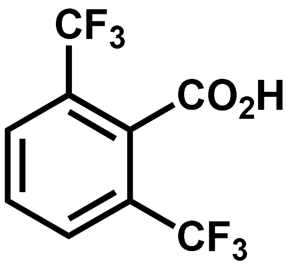
1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

Screening of Benzoate Ligand

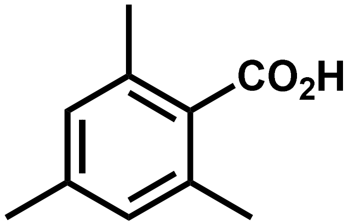




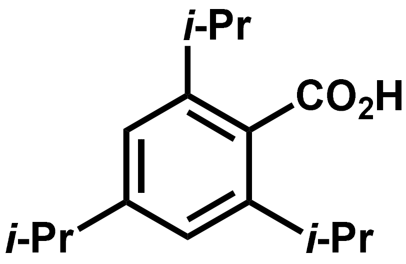
Ligand



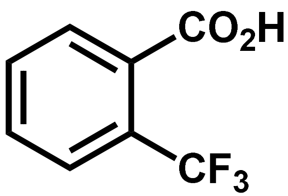
L1: 76%



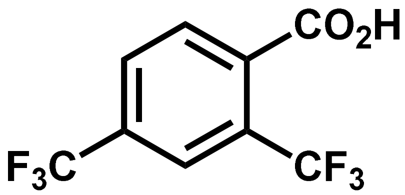
L2: 16%



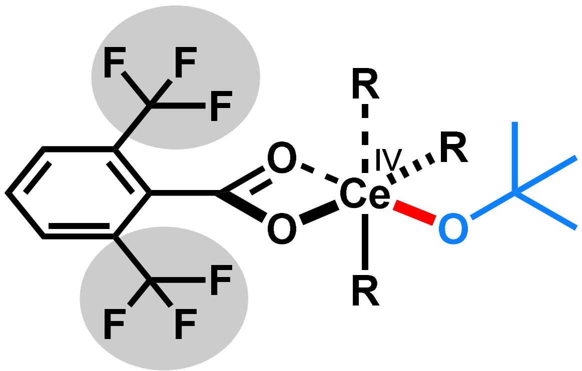
L3: 46%



L4: 43%



L5: 47%

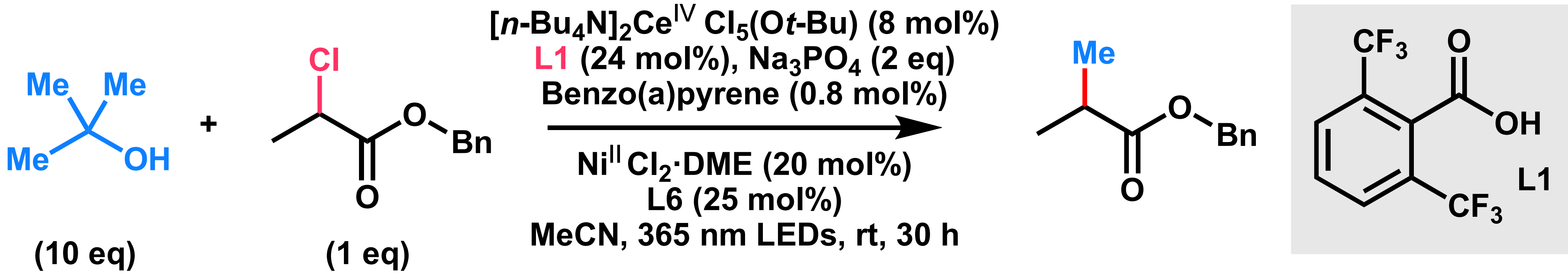


- Steric hindrance of the ligand fixes the coordination to the Ce center.
- Electron-withdrawing substituents on the aromatic ring enhance the binding affinity of tBuO to Ce.

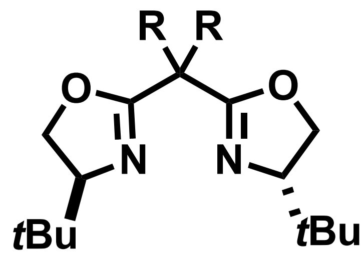
➡ Inhibition of generation of *t*-BuO·

1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

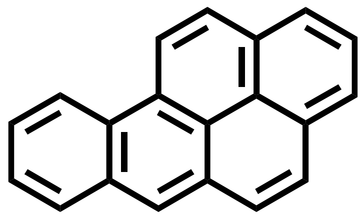
Deviation of Reaction Conditions



entry	variation from the standard conditions	Yield (%)
1	none	76%
2	$[n\text{-}Bu_4N]_2Ce^{IV}Cl_5(Ot\text{-}Bu)$ or $Ni^{II}Cl_2\cdot DME$	0%
3	benzo[a]pyrene	2%
4	no Light	0%



L6 (R = 4-Ph-Bn)

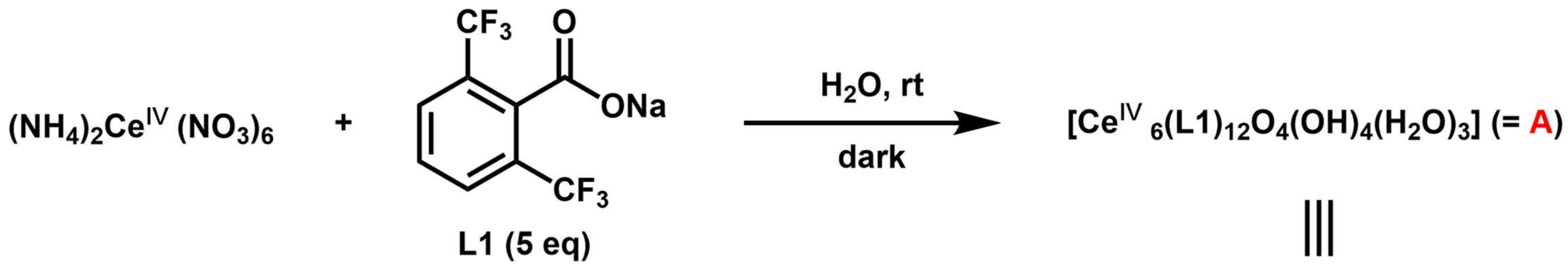


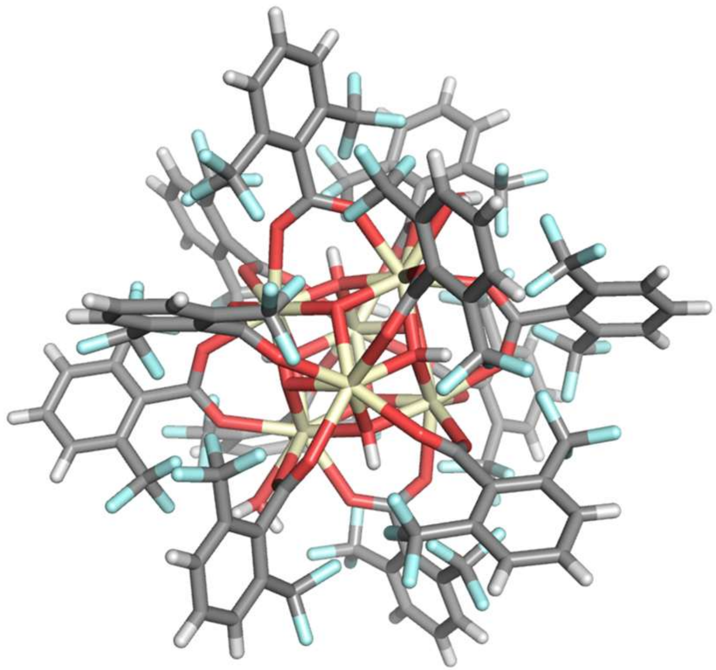
benzo[a]pyrene

1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

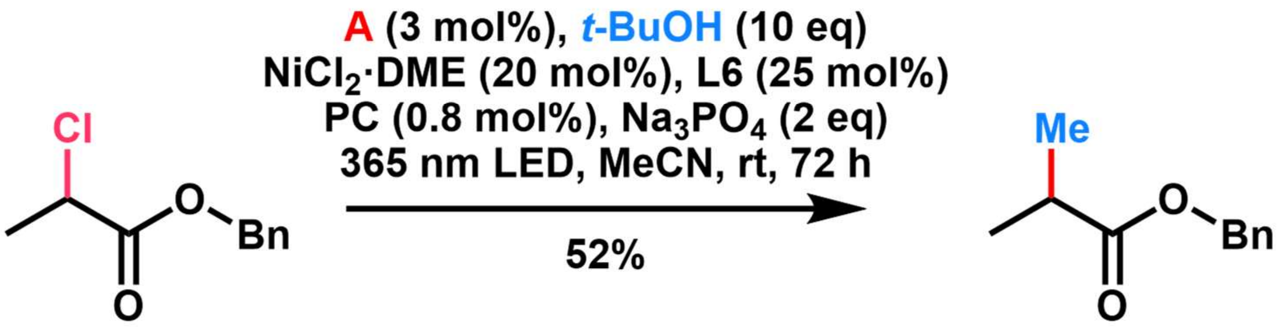
Synthesis and Characterization of Ce(IV) Complex

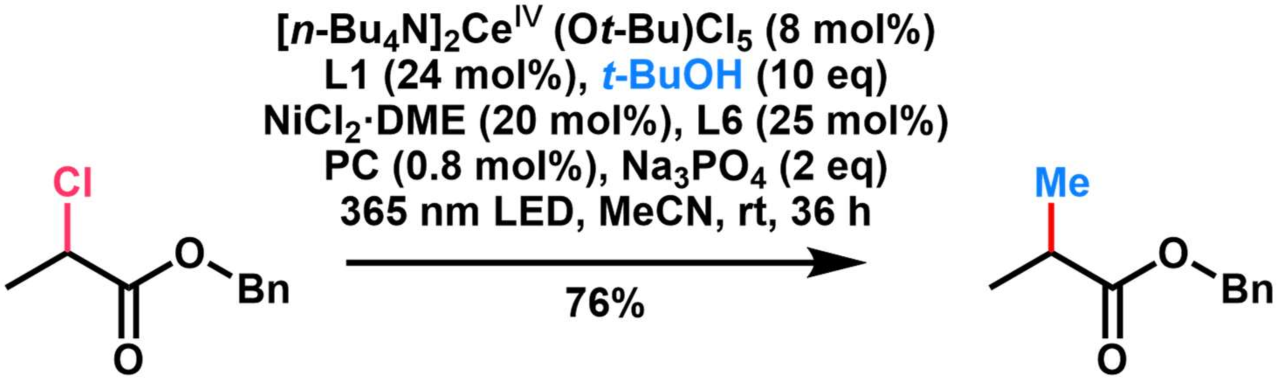
(A) Synthesis of Ce(IV) benzoate complex





(B) Characterization of Ce(IV) benzoate complex



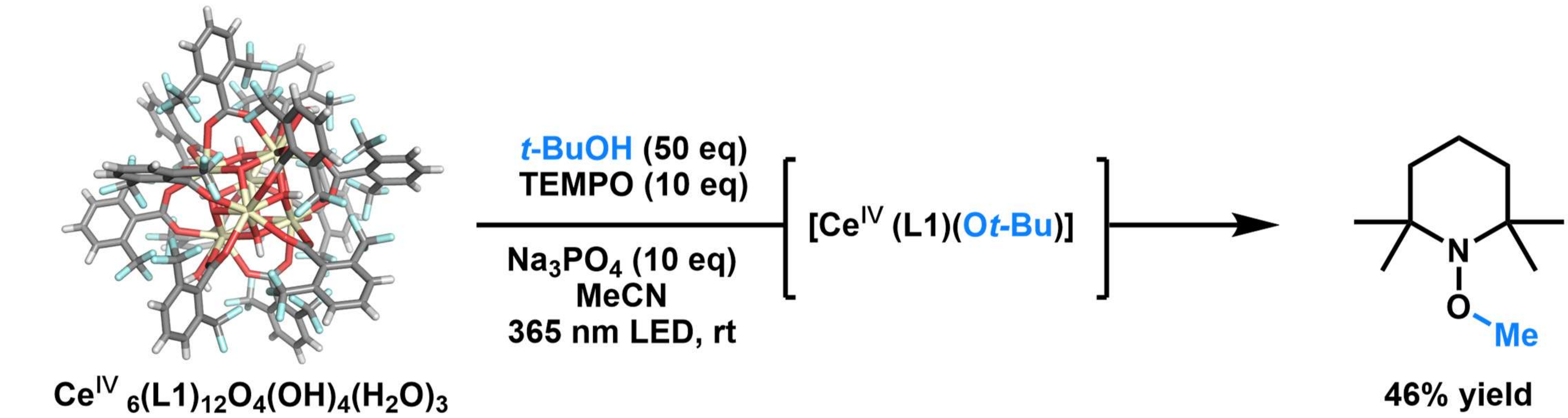


PC = Benzo[a]pyrene

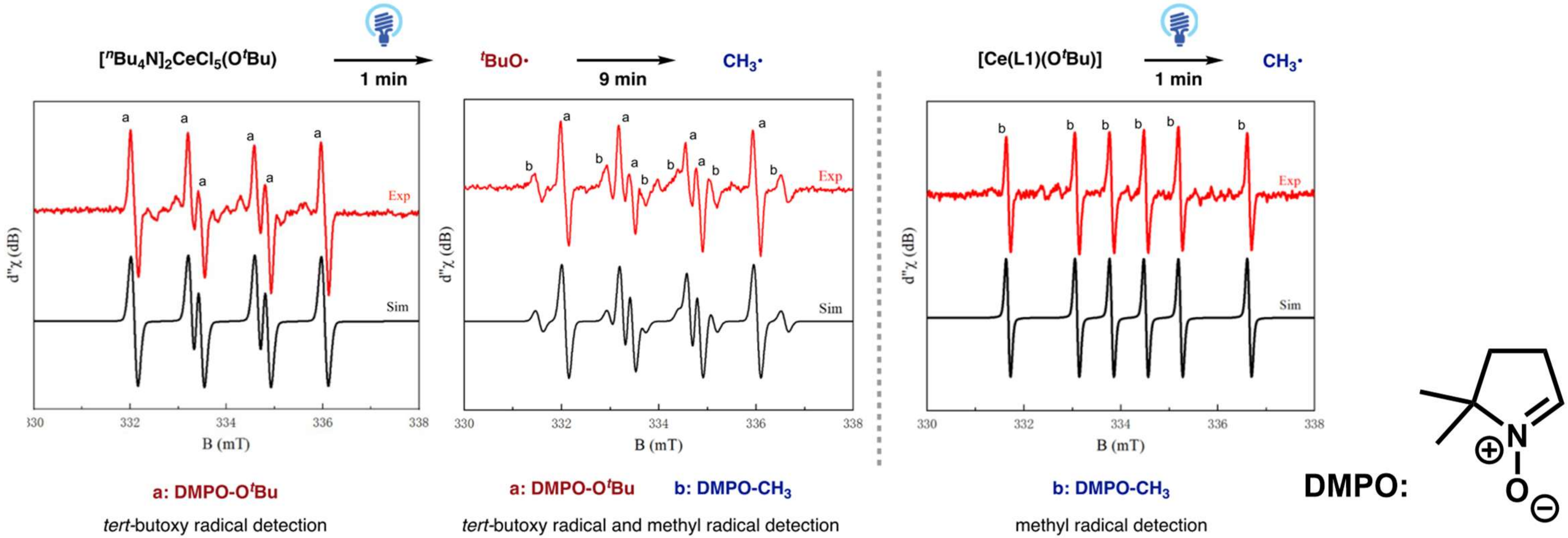
1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

Methyl Radical Trapping and EPR Experiments

(A) Methyl radical trapping by TEMPO

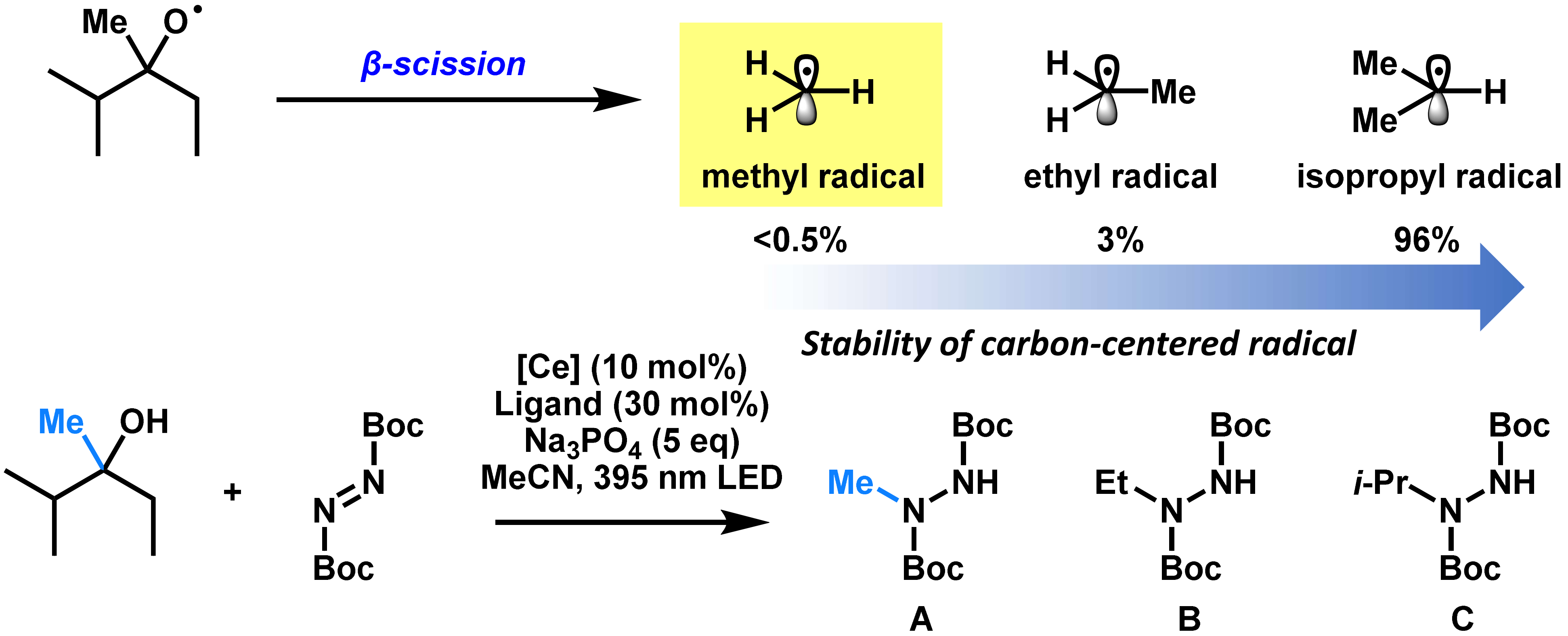


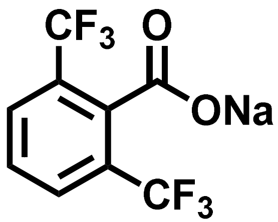
(B) Operando EPR experiments



1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

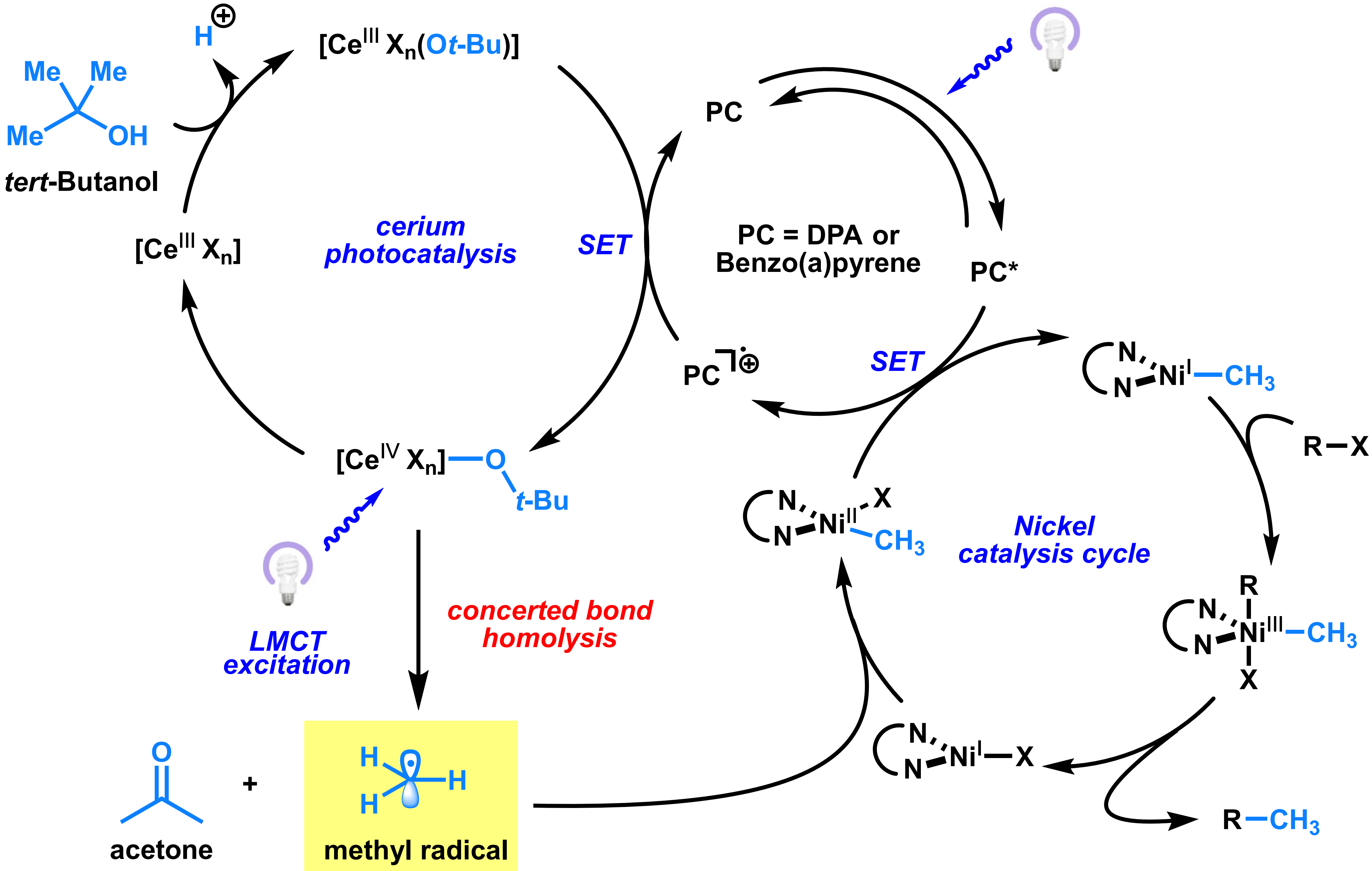
Investigation of Bond Homolysis Selectivity



Ce catalyst	ligand	product distributio scission A	B	C
$Ce^{III}\ Cl_3$	*n*-Bu_4NCl	0.6%	11%	62%
$Ce^{III}\ Cl_3$	 L1	8%	19%	28%
$Ce^{IV}{}_6(L1)_{12}O_4(OH)_4(H_2O)_3$		9%	23%	32%

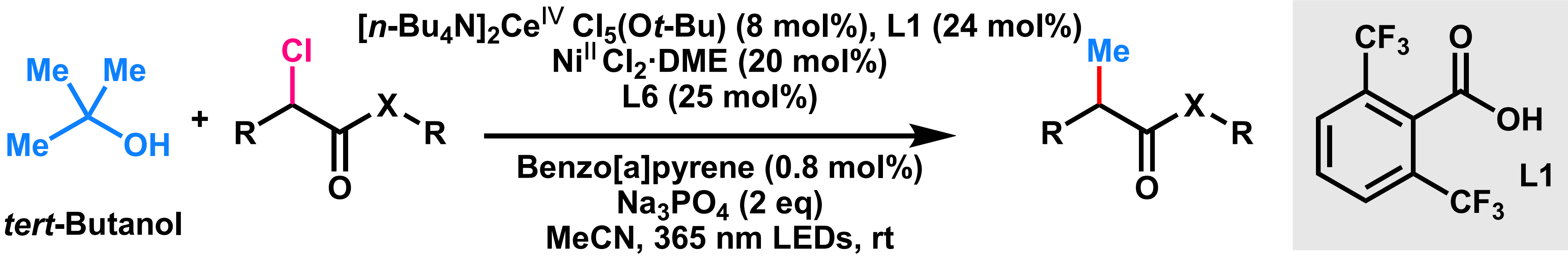
1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

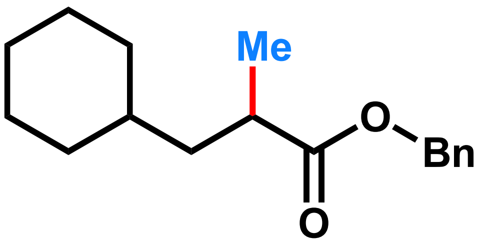
Proposed Reaction Mechanism



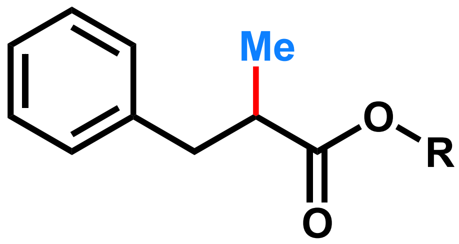
1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

Substrate Scope (1) : Sp³-Sp³ coupling

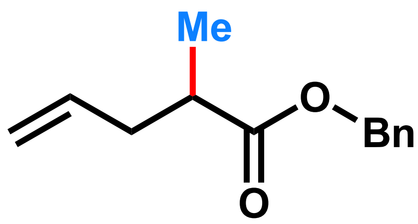




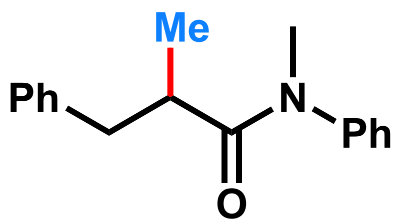
69% yield



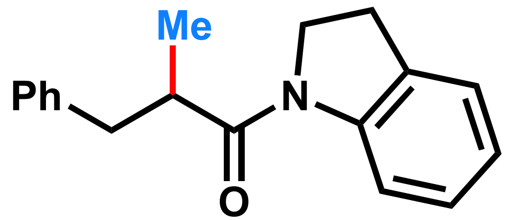
R = Bn: 64% yield
R = Me: 66% yield



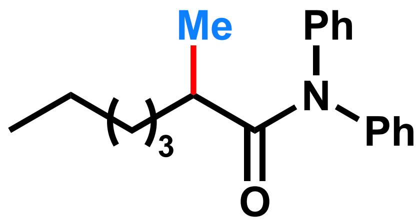
76% yield



55% yield



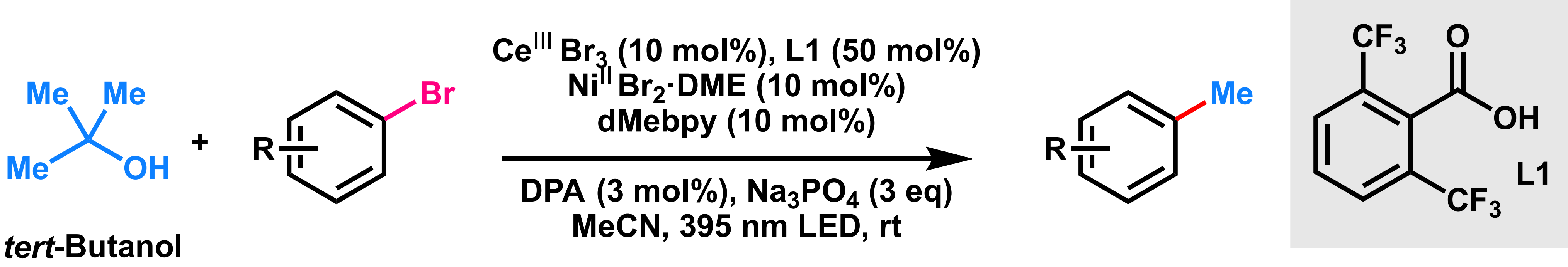
47% yield

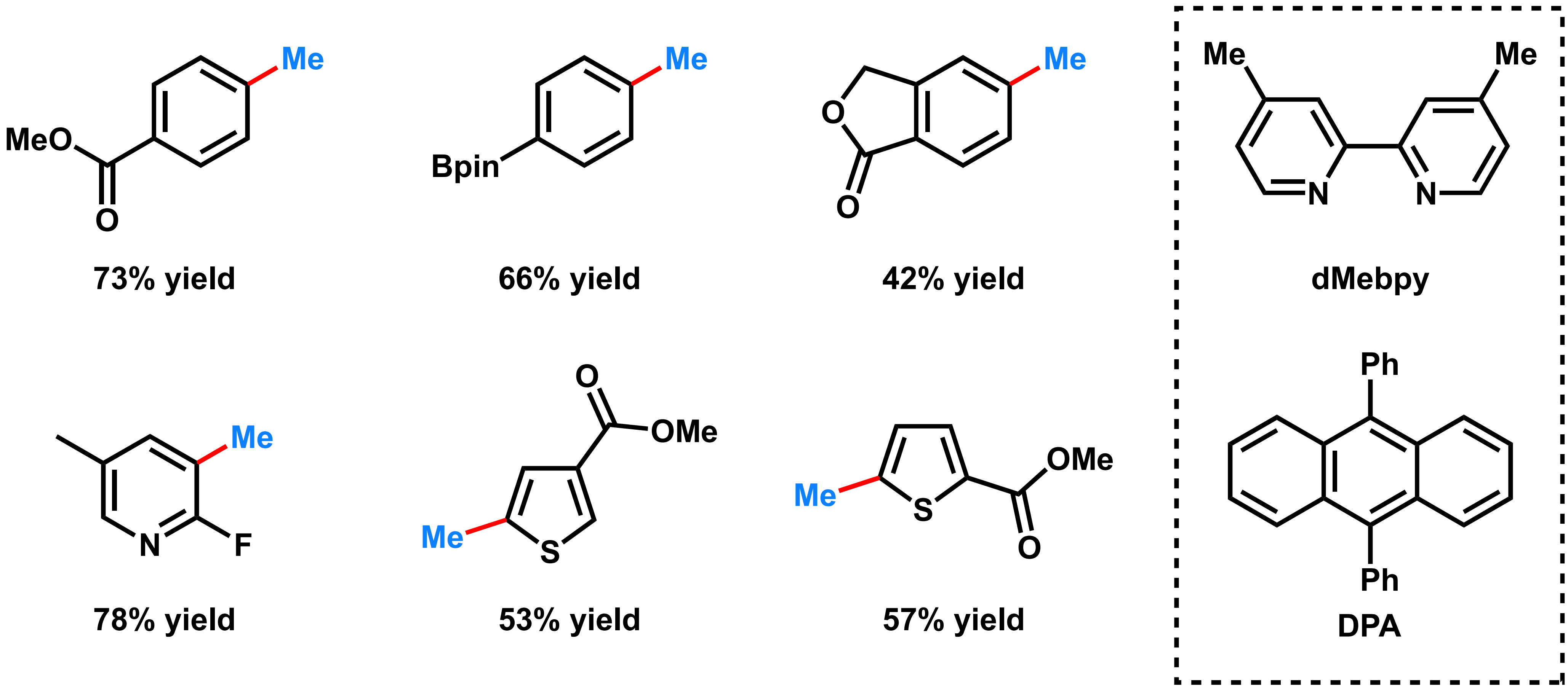


51% yield

1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

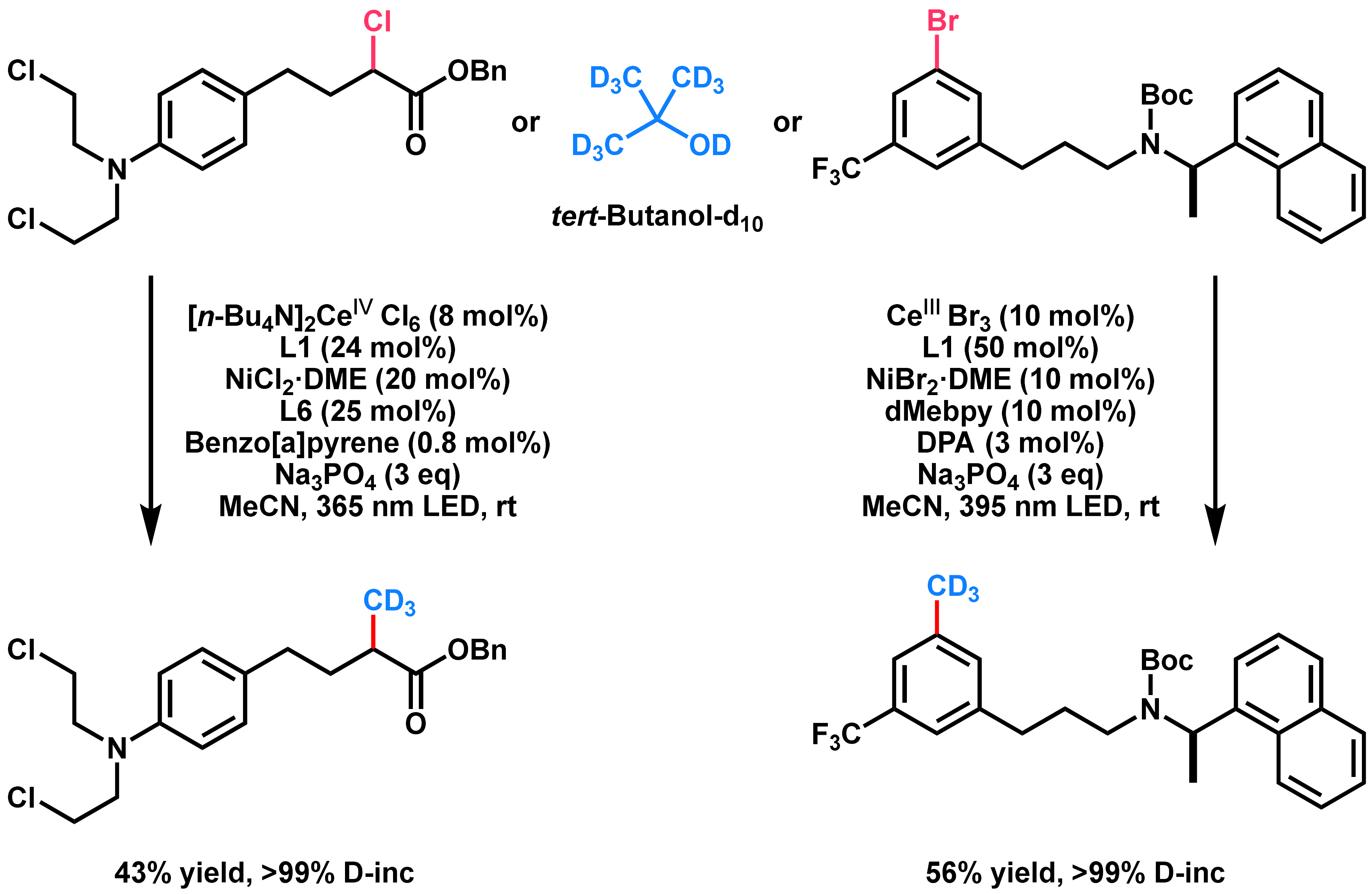
Substrate Scope (2) : Sp^3-Sp^2 coupling





1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

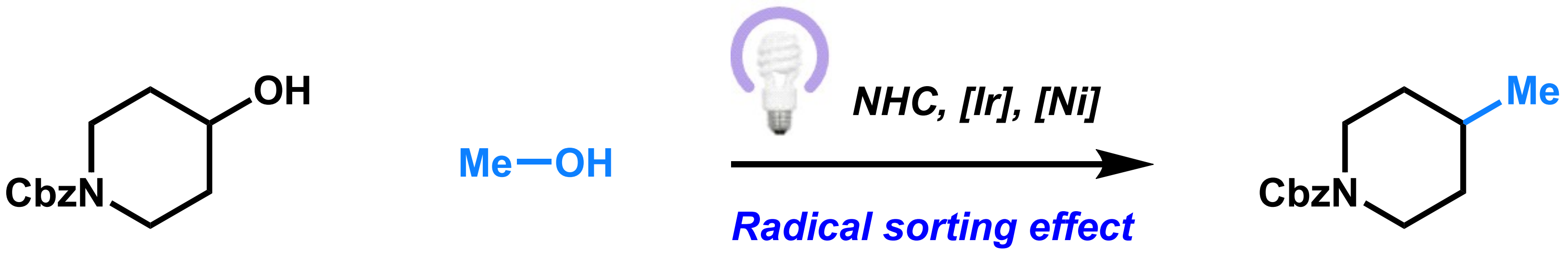
Application for Trideuteromethylation



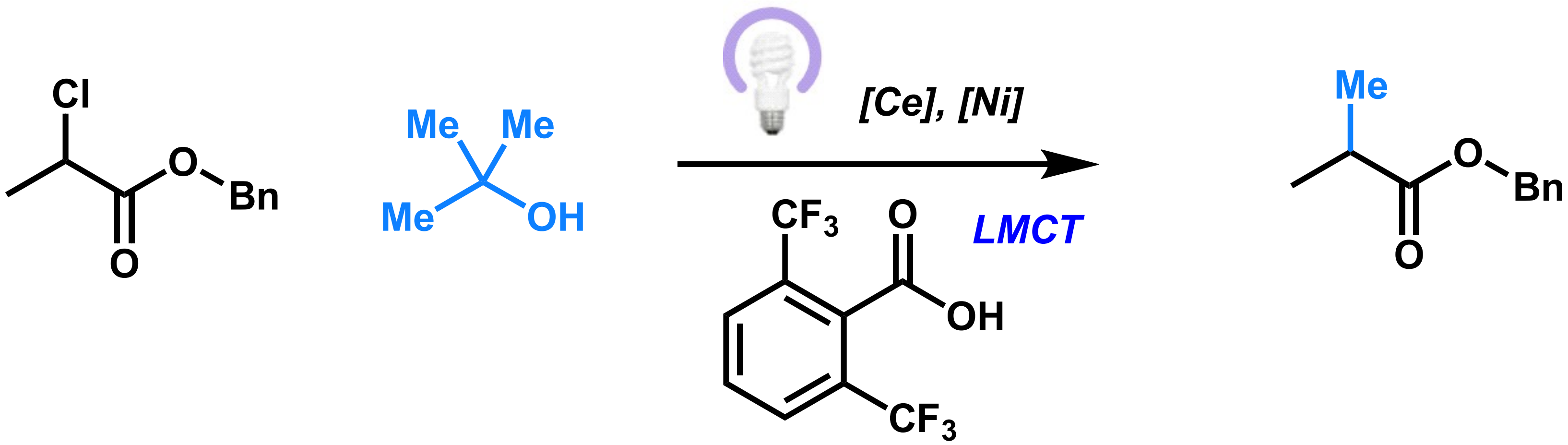
1) Duan, L.; Lin, Y.; An, Q.; Zuo, Z. *J. Am. Chem. Soc.* **2025**, *147*, 14785.

Summary

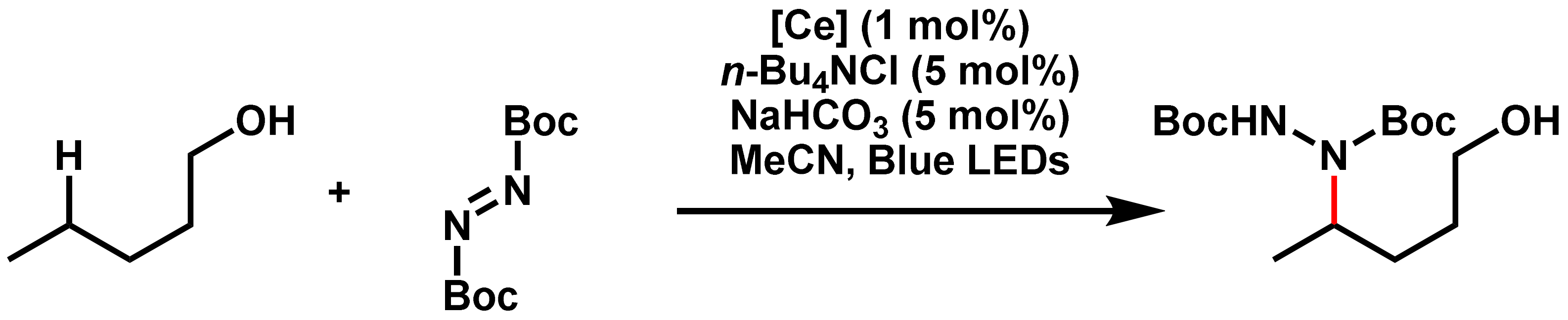
1. Alcohol-Alcohol (sp_3-sp_3) Cross-Coupling (Me-Donor: Methanol)



2. Methylative Cross-Coupling (Me-Donor: *tert*-Buthanol)

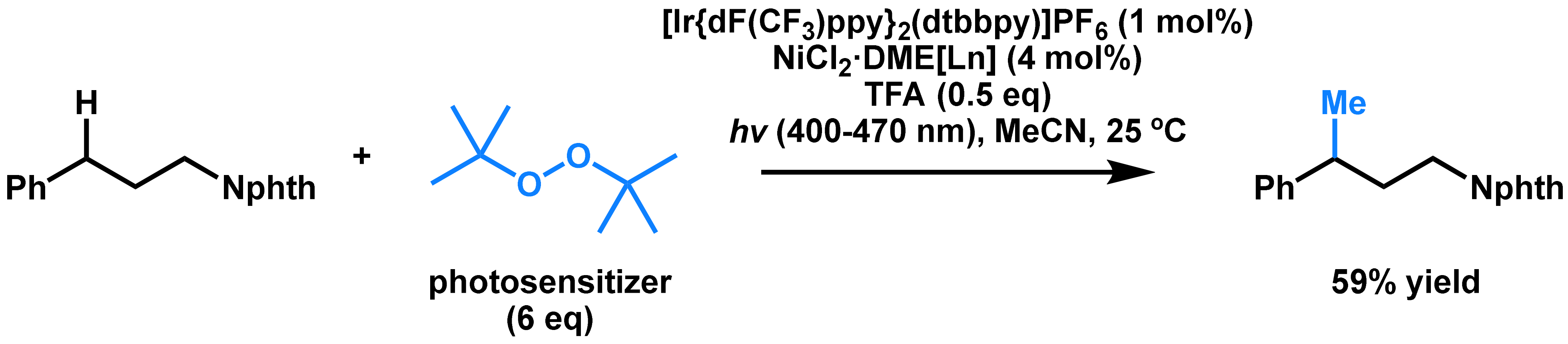


Appendix. Ce(III) and Ce(IV)

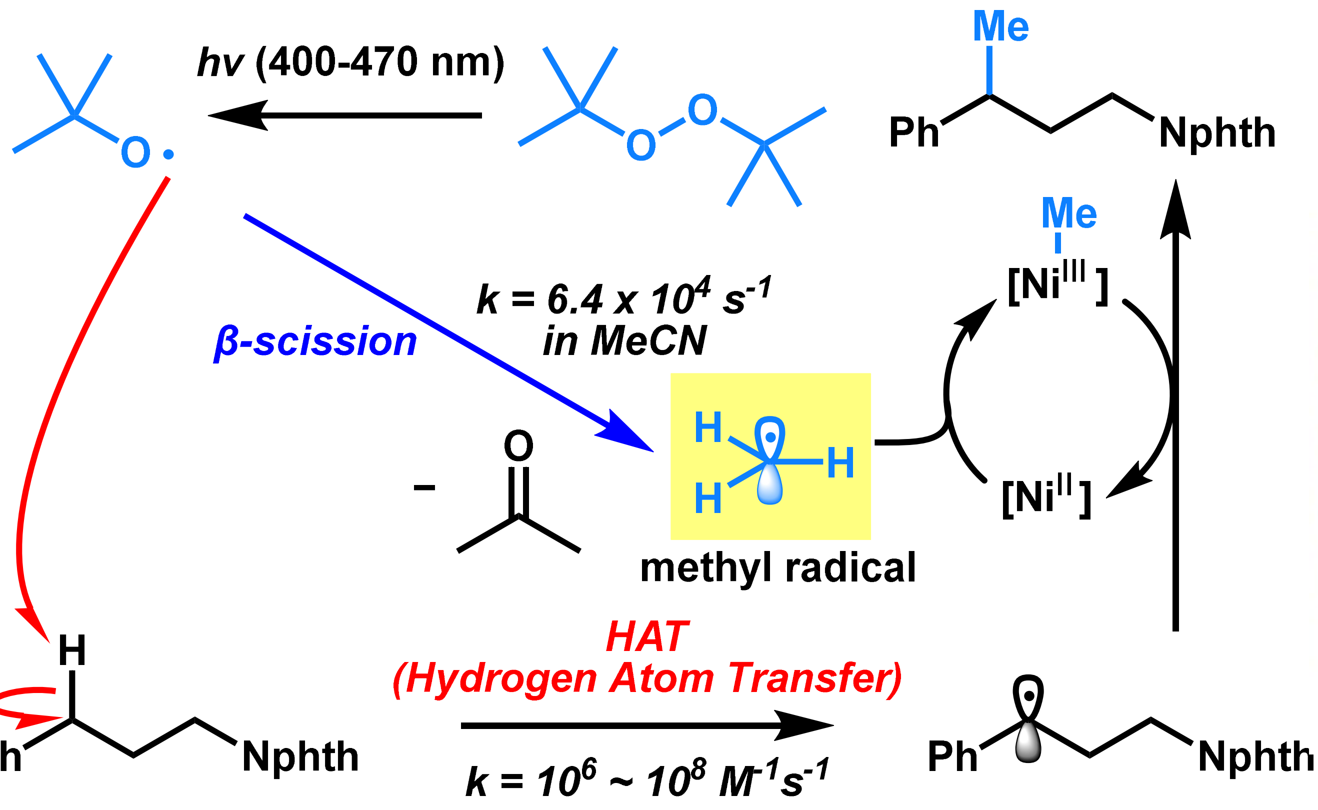


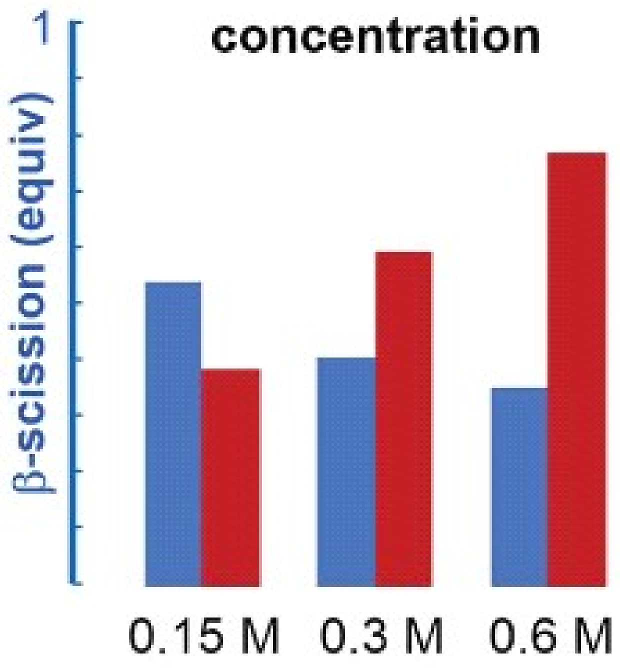
entry	[Ce]	Light	Yield (%)
1	$(n\text{-}Bu_4N)_2[Ce^{IV}Cl_6]$	blue LED	89%
2	$(n\text{-}Bu_4N)_2[Ce^{IV}Cl_6]$	off (60 ºC)	0%
3	$Ce^{III}Cl_3$	blue LED	92%

Concentration of Solvent

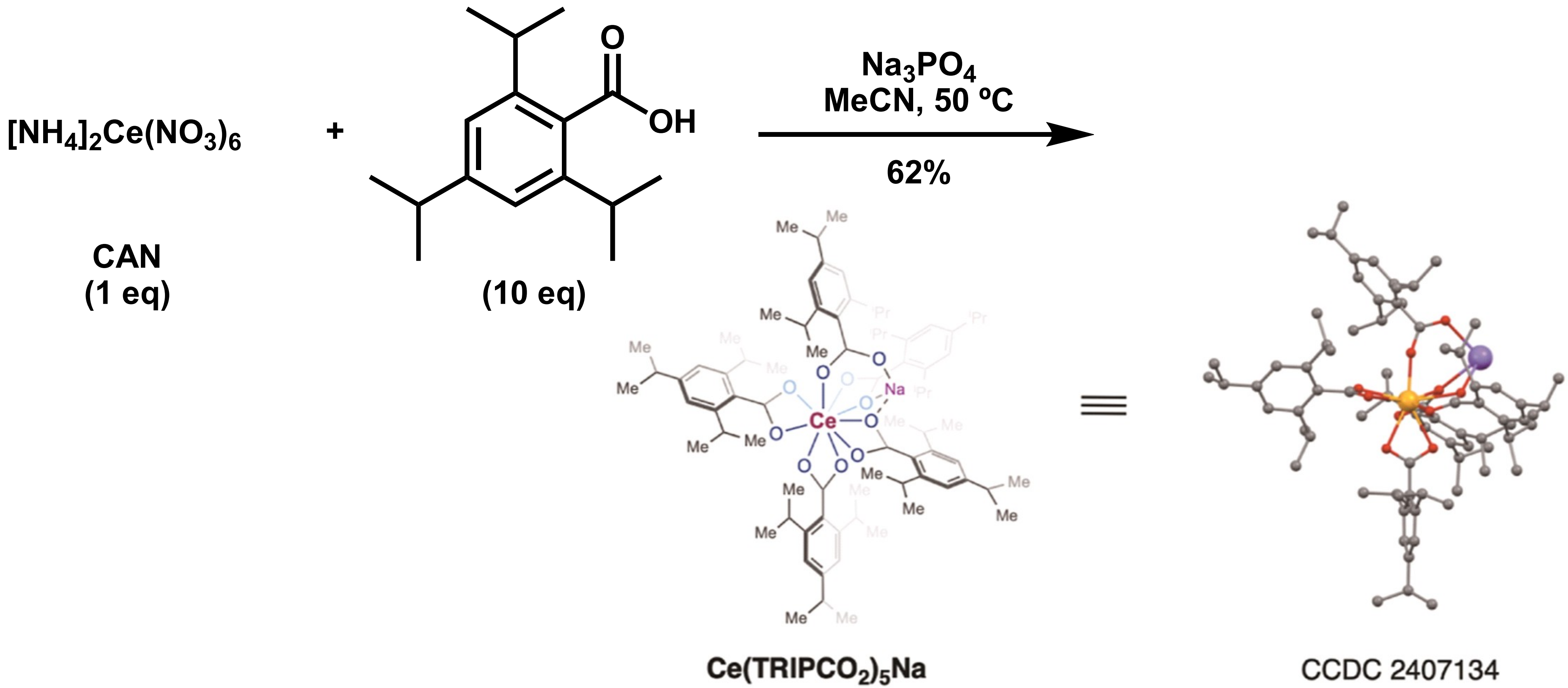


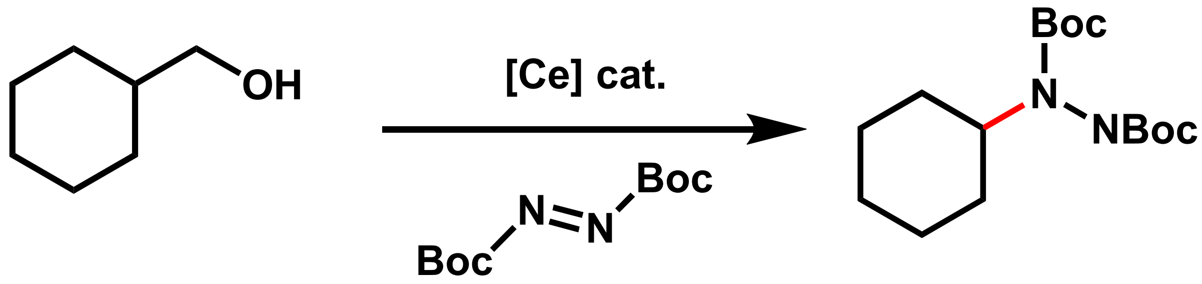
Vasilopoulos, A.; Krska, S. W.; Stahl, S. S. *Science* 2021, *372*, 398.

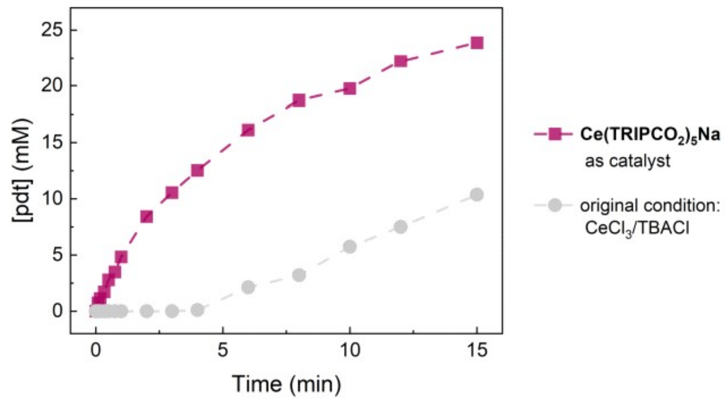




Kinetic Investigation of Ce(IV)-Complex







1) Liang, H.; lai, L.; Zhang, K.; Chen, W.; Mingfeng, C.; Li, M.; Yang, Y.; Li, J.; Zuo, Z. *ACS Catal.* **2025**, *15*, 8069.

UV-bis absorption spectra of in situ formed [Ce]