The Yang Research Group
Precise Synthesis Lab at Tongji University

借助NHC活化策略进行的脱氧官能化研究进展及展望

汇报人：张利利
导师：杨泽鹏 教授
汇报时间：2024. 6. 7

The Yang Research Group
Precise Synthesis Lab at Tongji University

目 录

◆ 背景介绍

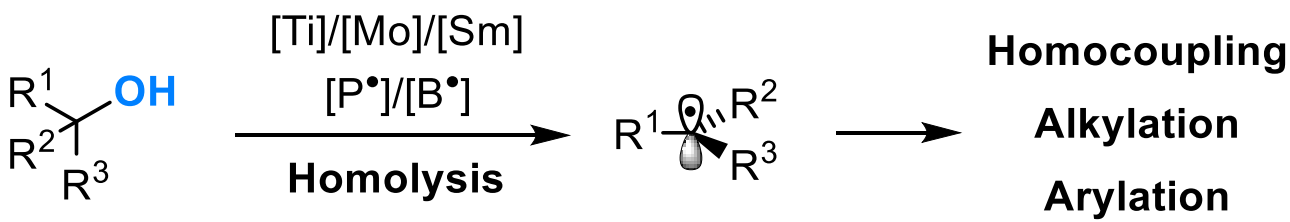
◆ NHC策略脱氧形成碳-碳键

◆ NHC策略脱氧形成碳-杂键（N, S, P, Se）

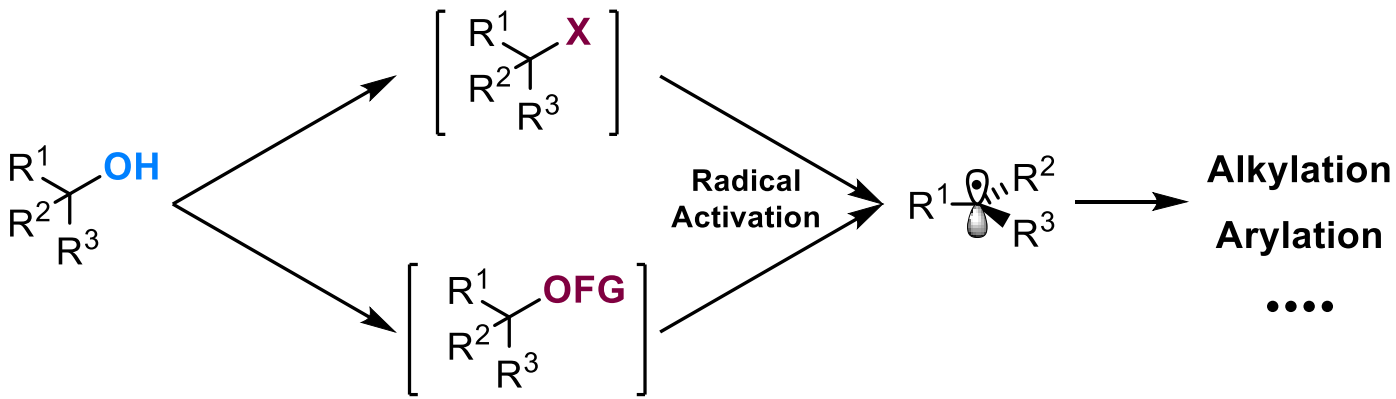
◆ 总结与展望

1. 背景介绍

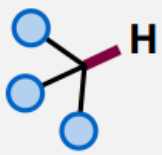
➢ 直接活化烷基醇碳氧键



➢ 间接活化烷基醇碳氧键

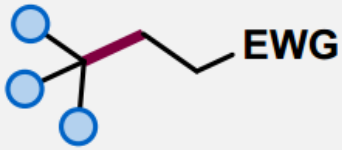


1. 背景介绍--直接活化烷基醇碳氧键



Deoxy-hydrogenation

Ti, Young, **1979**

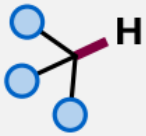


Deoxy-Giese type reaction

Ti, Ukaji, **2018**

Deoxy-alkenylation

Ti, Ukaji, **2020**



Deoxy-hydrogenation

P•, Doyle, **2018**

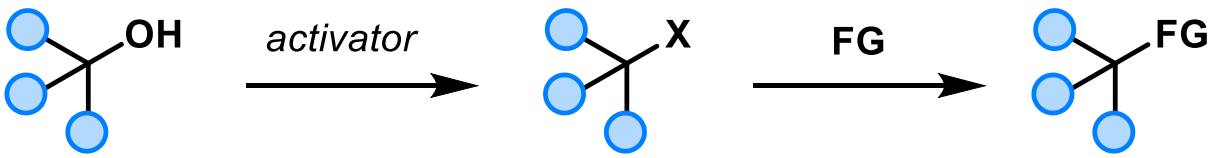
Deoxy-carboxylation

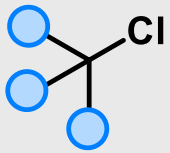
B•, Xia, **2022**

✓ 步骤经济性高

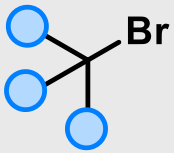
× 反应条件苛刻，底物范围窄

1. 背景介绍--间接活化烷基醇碳氧键





Huang, **2013**

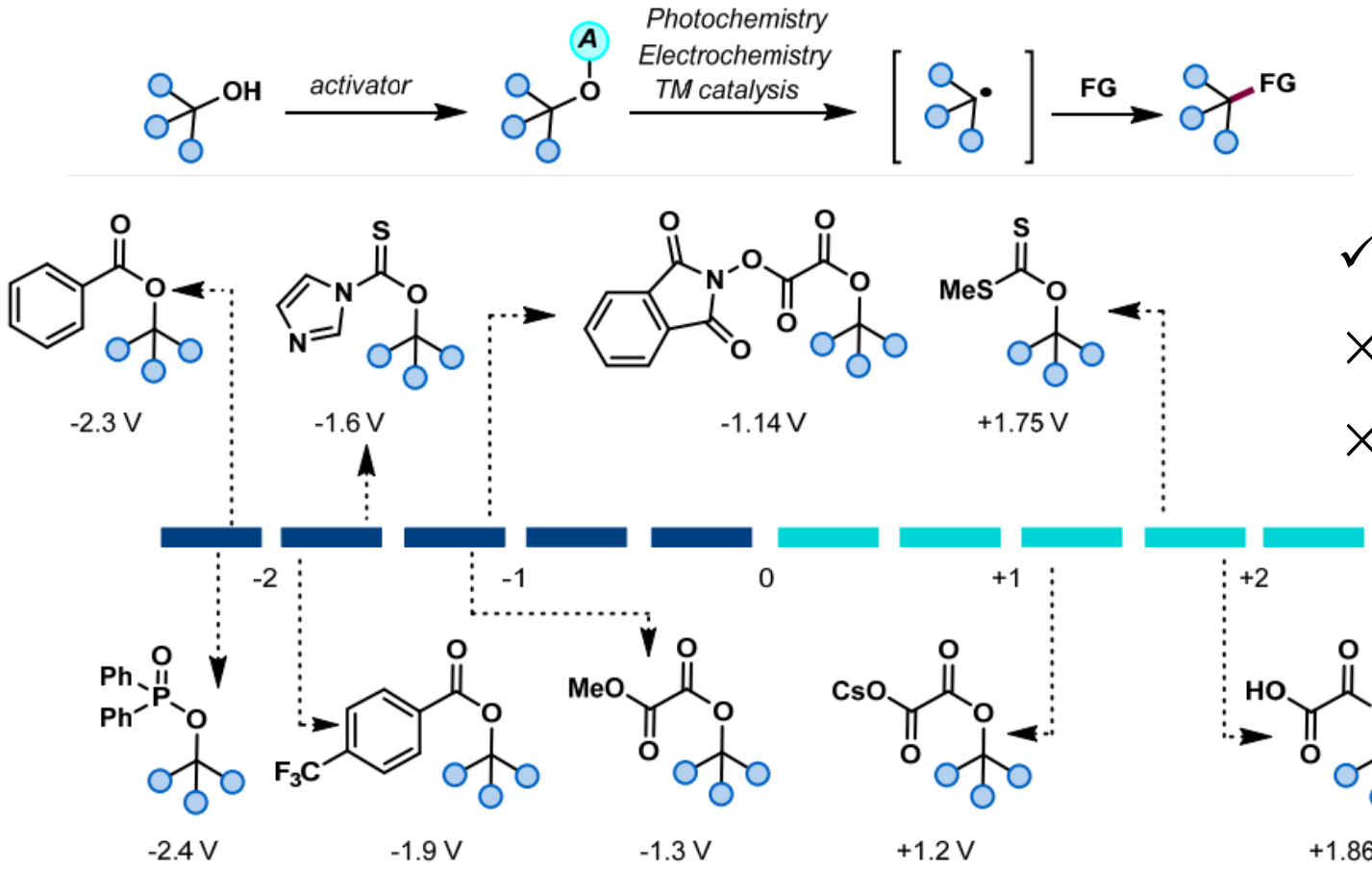


Li, **2021**
Gong, **2021**
Weix, **2022**

Fu, **2013**

Huang. *Angew. Chem. Int. Ed*. **2013**, *52*, 3494–3498
Li. *J. Am. Chem. Soc*. **2021**, *143*, 3536-3543
Gong. *ACS Catal*. **2021**, 11, 14102−14109
Weix. *ACS Catal*. **2022**, 12, 580−586
Fu. *J. Am. Chem. Soc*. **2013**, *135*, 16288-16291

1. 背景介绍--间接活化烷基醇碳氧键



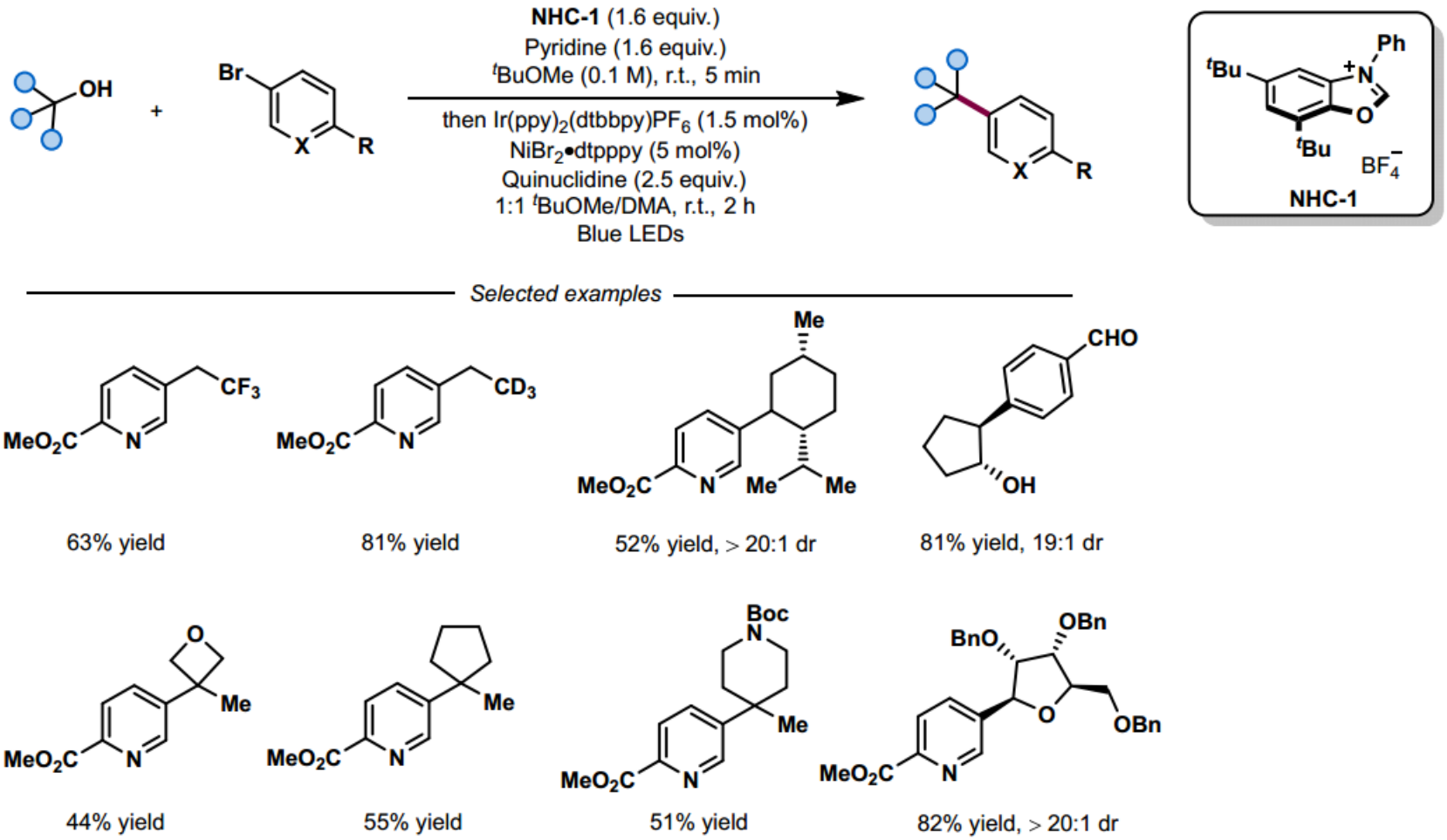
✓ 条件温和

× 步骤经济性差

× 底物范围窄

MacMillan, D. W. C. et al. *J. Org. Chem.* **2016**, *81*, 6898.
Nicewicz, D. A. et al. *Chem. Rev.* **2016**, *116*, 10075.
Konig, B. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 10034.
MacMillan, D. W. C. et al. *Chem. Rev.* **2013**, *113*, 5322.
Malins, L. R. et al. *J. Am. Chem. Soc.* **2022**, *144*, 23.
Waldvogel, S. R. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 5594.
Waldvogel, S. R. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 6018.

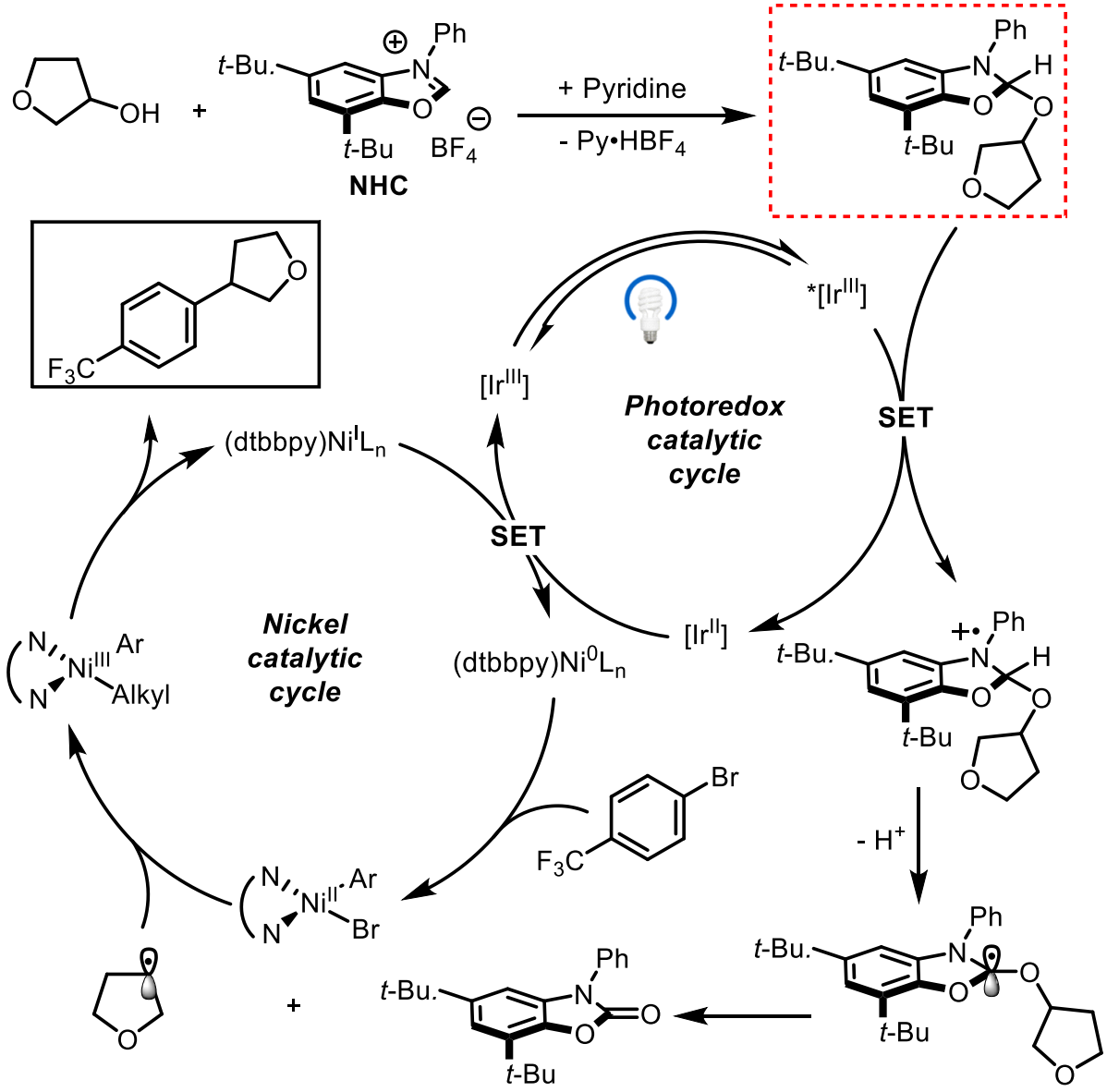
1. 背景介绍



- 非活化的烷基醇活化
- 底物范围广泛
- 反应条件温和
- 光催化与金属催化相结合
- 廉价金属催化
- 反应高效快速

David W. C. MacMillan. *Nature.* **2021**, *598*, 451–456.

Proposed mechanism



2. NHC策略脱氧烷基化反应

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

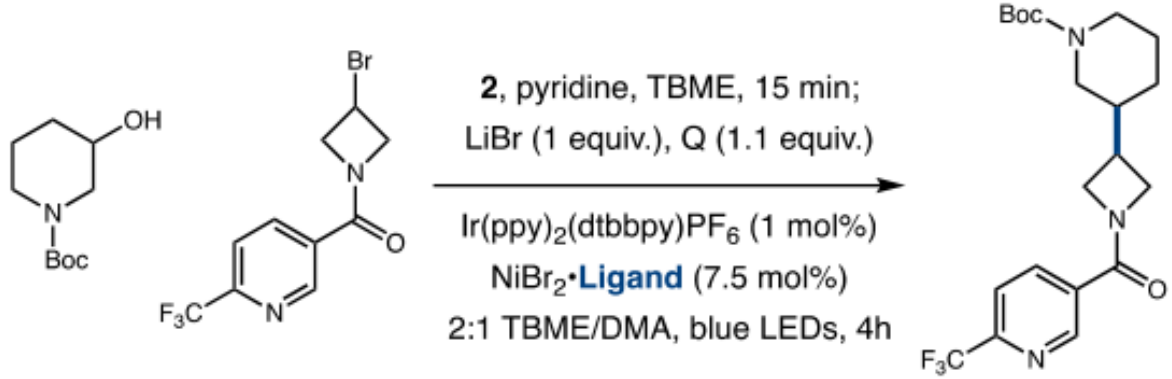
Expedient Access to Underexplored Chemical Space: Deoxygenative C(sp^3)–C(sp^3) Cross-Coupling

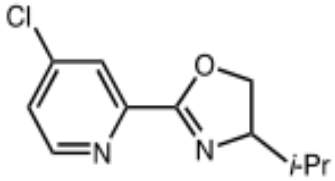
William L. Lyon and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2023, 145, 7736–7742
Read Online

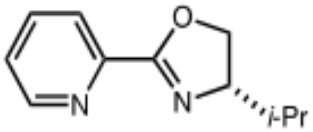
2. NHC策略脱氧烷基化反应

➢ 配体筛选

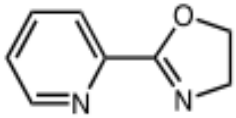




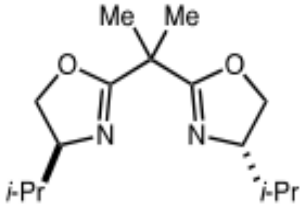
(±)-18
82% yield



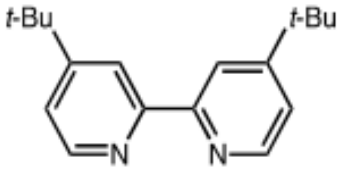
19
78% yield



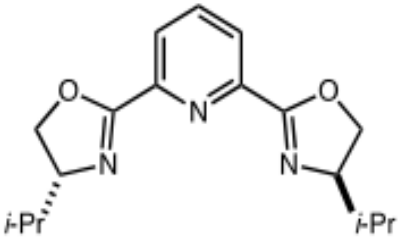
20
52% yield



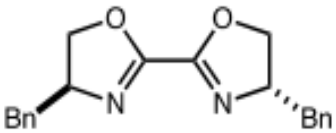
24
33% yield



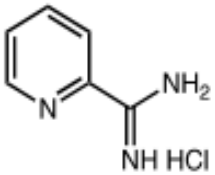
21
59% yield



22
10% yield

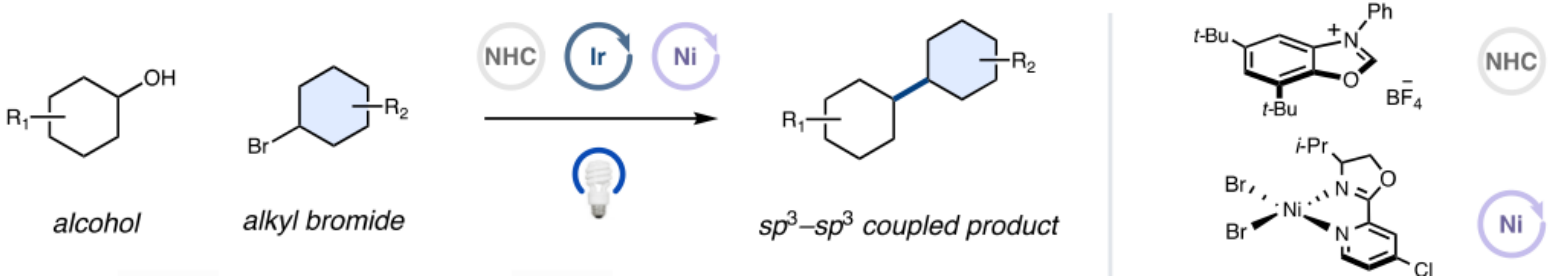


23
22% yield



25
13% yield

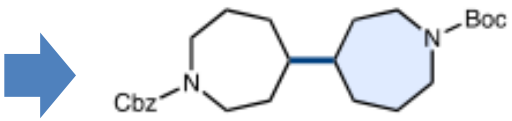
2. NHC策略脱氧烷基化反应



4–4

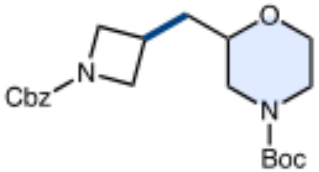
58, 50% yield[b]

7–7



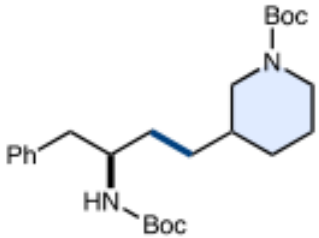
(±)-**71**, 29% yield[d,g,j]

1°–2°



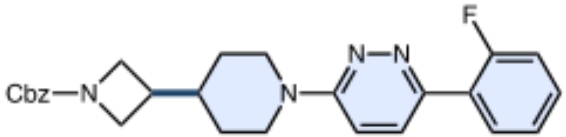
(±)-**72**, 50% yield[d]

1°–1°



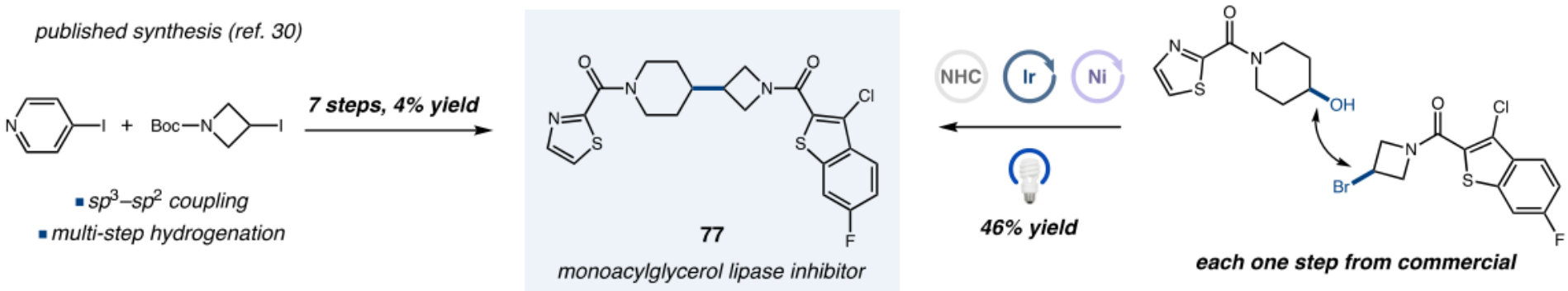
(±)-**74**, 42% yield[d,i]

oxidizable substrates

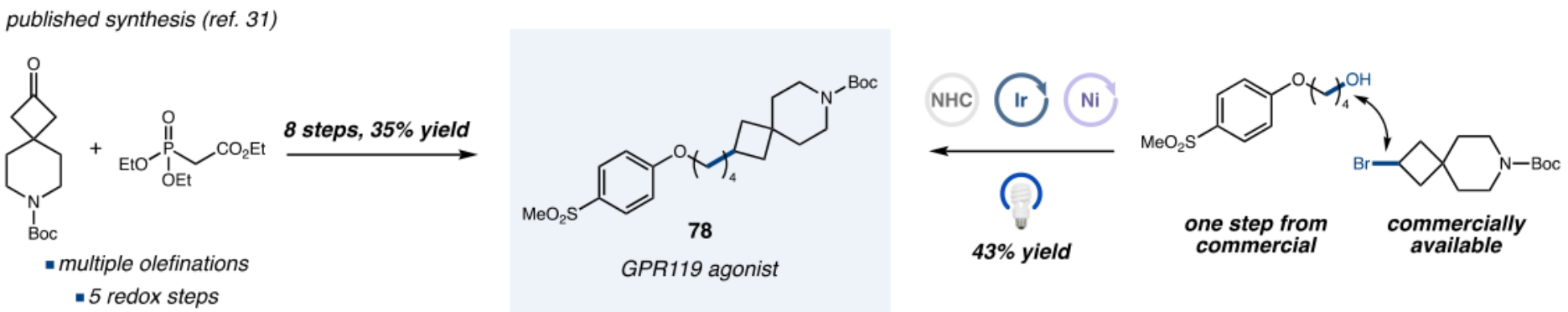


75, 36% yield[l]

2. NHC策略脱氧烷基化反应



单酰基甘油脂肪酶抑制剂



GPR119受体拮抗剂

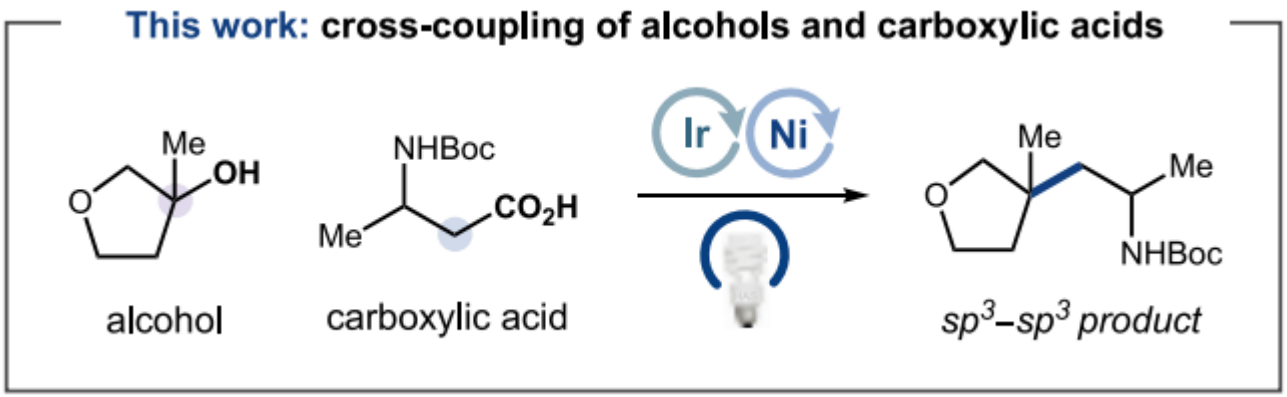
2. NHC策略脱氧形成碳-碳键

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

Nontraditional Fragment Couplings of Alcohols and Carboxylic Acids: C(sp^3)–C(sp^3) Cross-Coupling via Radical Sorting

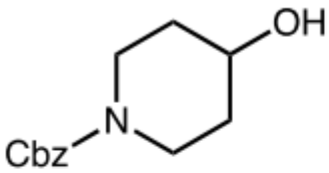
Holt A. Sakai and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2022, 144, 6185–6192
Read Online



首次提出“Radical Sorting”策略

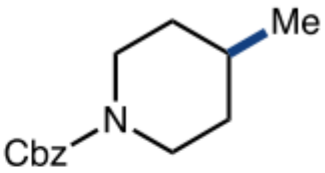
2. NHC策略脱氧形成碳-碳键



aliphatic alcohol

NHC-1, pyridine
MTBE (0.10 M), rt, 15 min;
MesI(OAc)$_2$ (2 equiv)

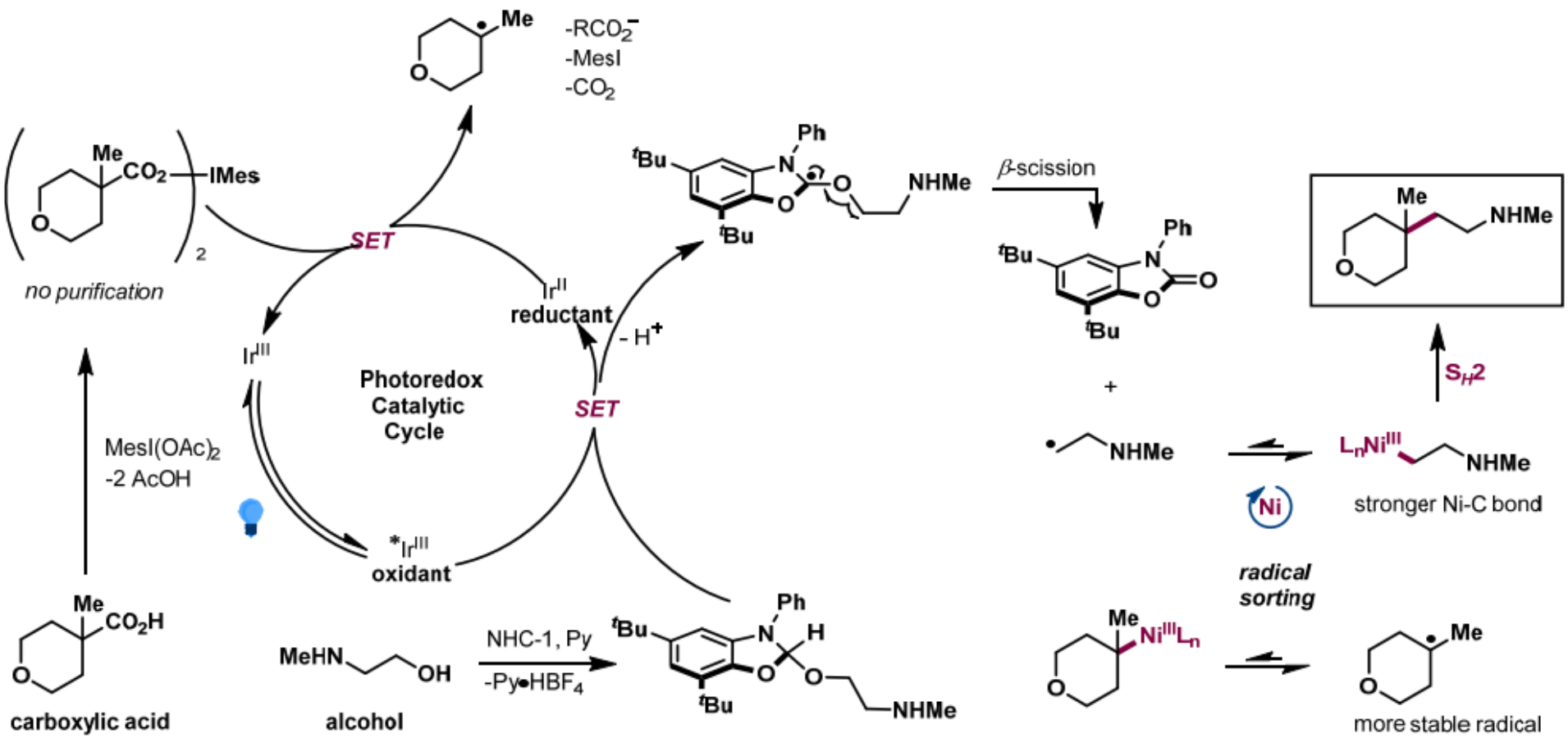
10 mol% **12**, 1 mol% **5**,
MTBE/DMSO (1:1, 0.02 M)
blue LEDs, 1 h, rt



C(sp^3)–C(sp^3)
coupled product

entry	deviation from above	yield[b]
1	none	76%
2	Ni(acac)$_2$ instead of **12**	73%
3	NiCl$_2$·dtbbpy instead of **12**	24%
4	PhI(OAc)$_2$ instead of MesI(OAc)$_2$	71%
5	1 equiv of MesI(OAc)$_2$	67%
6	irradiation for 5 min	67%
7	no Ir catalyst	<5%
8	no Ni catalyst	12%

2. NHC策略脱氧形成碳-碳键

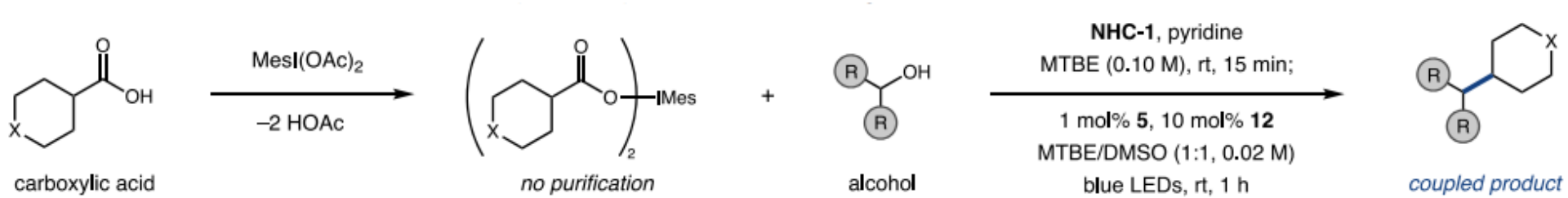


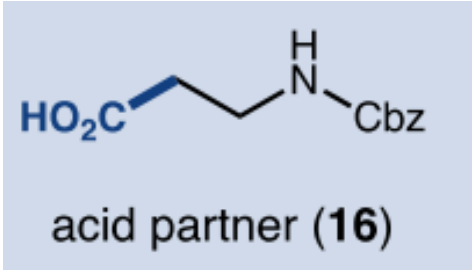
i）烷基具有不同的稳定性（位阻+电性）

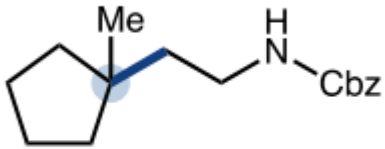
ii）镍-碳键强度存在差异

iii）自由基捕获的可逆性

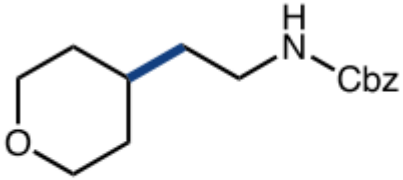
2. NHC策略脱氧形成碳-碳键



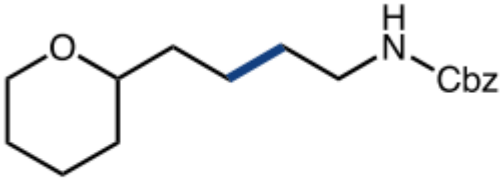




31 75% yield



18 62% yield[b]



(±)-29 52% yield[b,f]

两个一级自由基也可以偶联，产率较低

2. NHC策略脱氧形成碳-碳键

ORGANIC CHEMISTRY

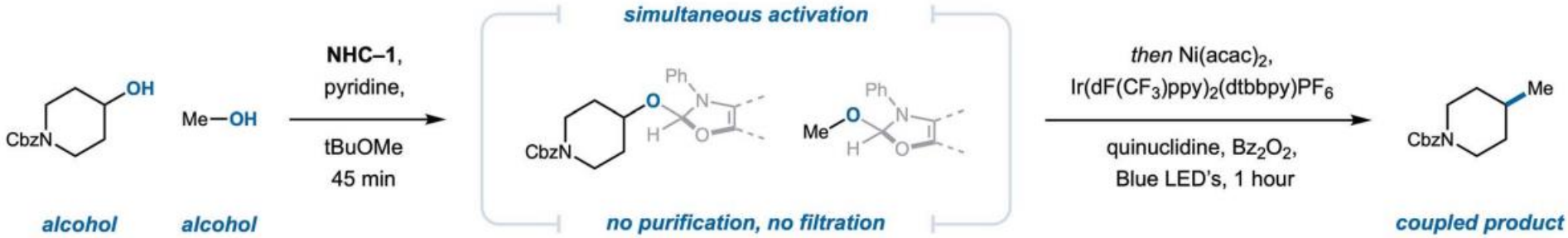
Alcohol-alcohol cross-coupling enabled by S_H2 radical sorting

Science 383, 1350–1357 (2024)

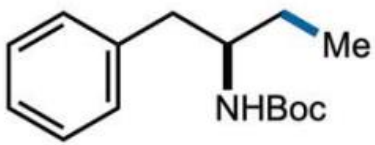
Ruizhe Chen[1]†, Nicholas E. Intermaggio[1]†, Jiaxin Xie[1]†, James A. Rossi-Ashton[1]†, Colin A. Gould[1], Robert T. Martin[1], Jesús Alcázar[2], David W. C. MacMillan[1]*

- 醇与醇偶联
- 空气中即可进行
- 加合物无需过滤

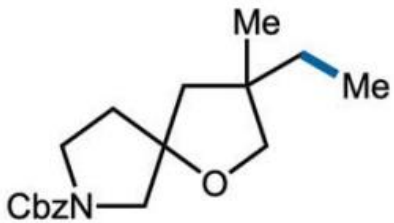
2. NHC策略脱氧形成碳-碳键



Primary Methylation

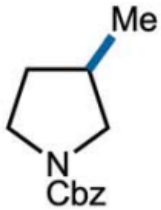


2, 51% yield

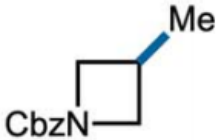


(±)-**3**, 55% yield§†

Secondary Methylation



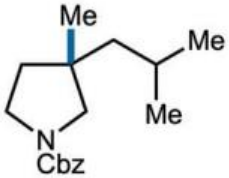
(±)-**5**, 70% yield



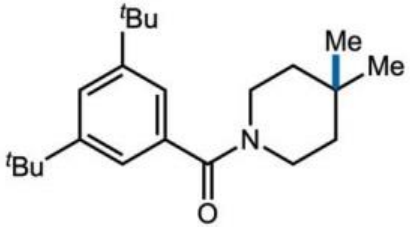
6, 71% yield

Quaternary Methyl Formation†

21, 71% yield



(±)-**22**, 50% yield



23, 63% yield

"magic methyl effect"

2. NHC策略脱氧形成碳-碳键

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

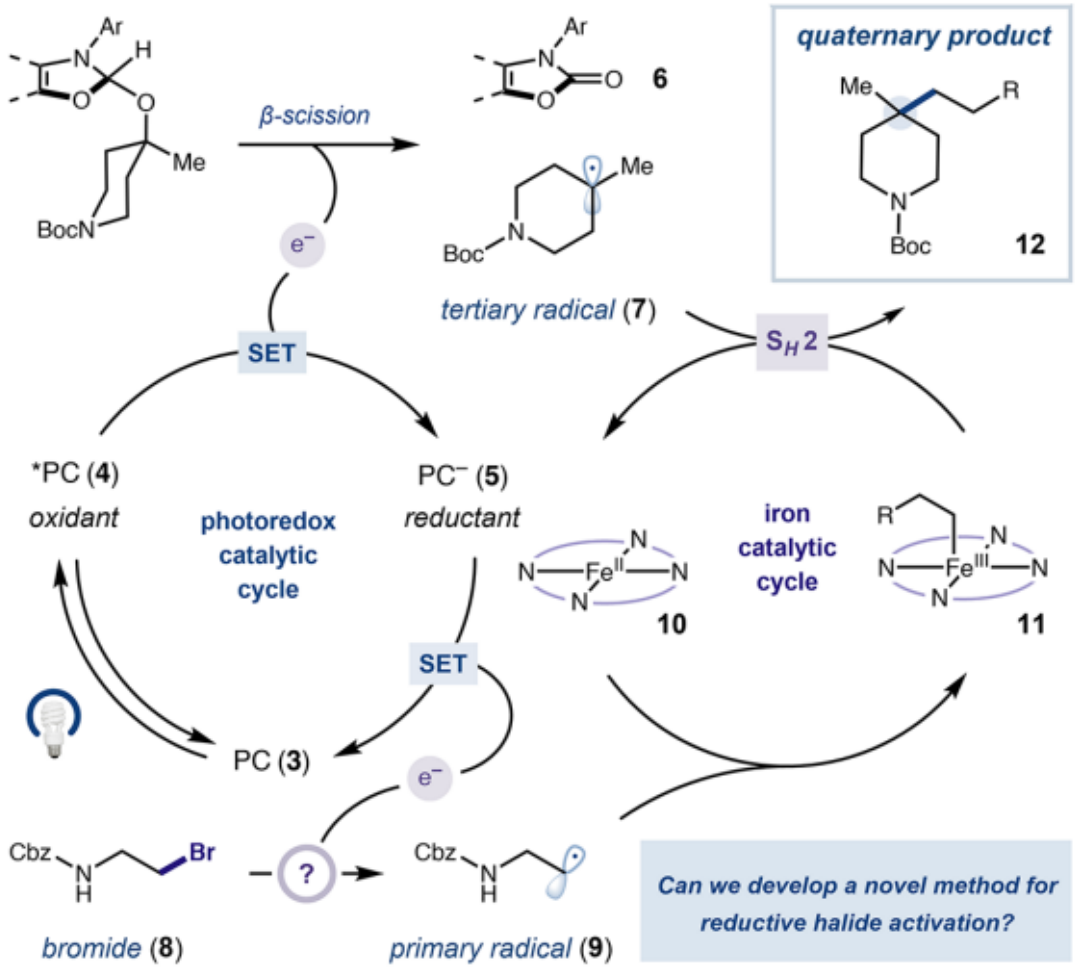
Rapid and Modular Access to Quaternary Carbons from Tertiary Alcohols via Bimolecular Homolytic Substitution

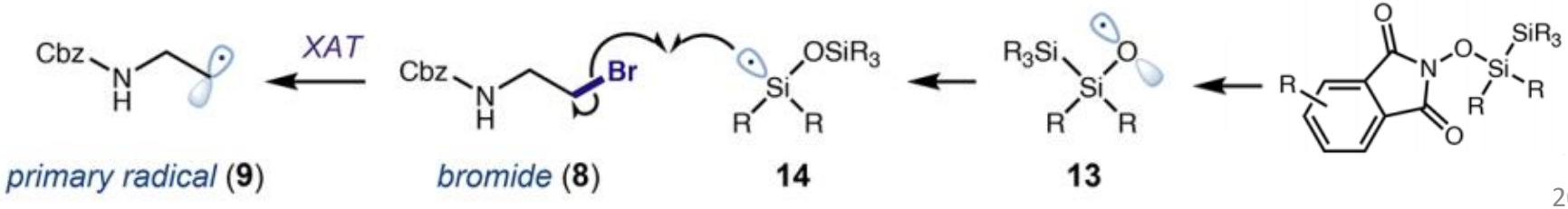
Colin A. Gould, Andria L. Pace, and David. W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2023, 145, 16330−16336
Read Online

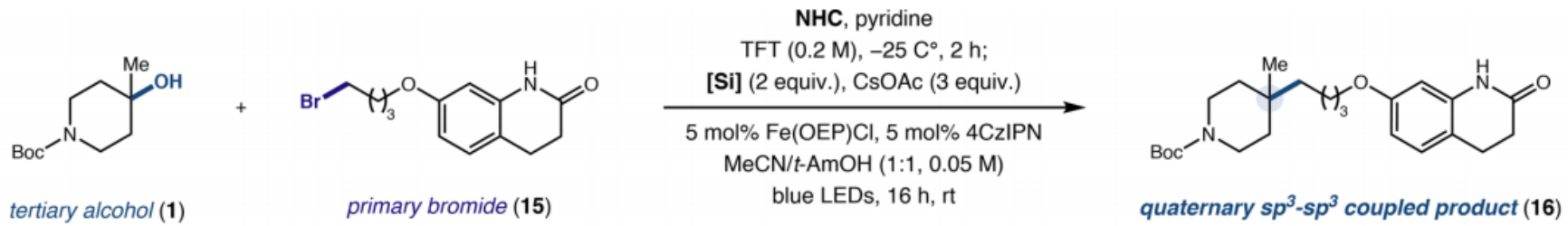
铁催化SH2模式形成季碳中心

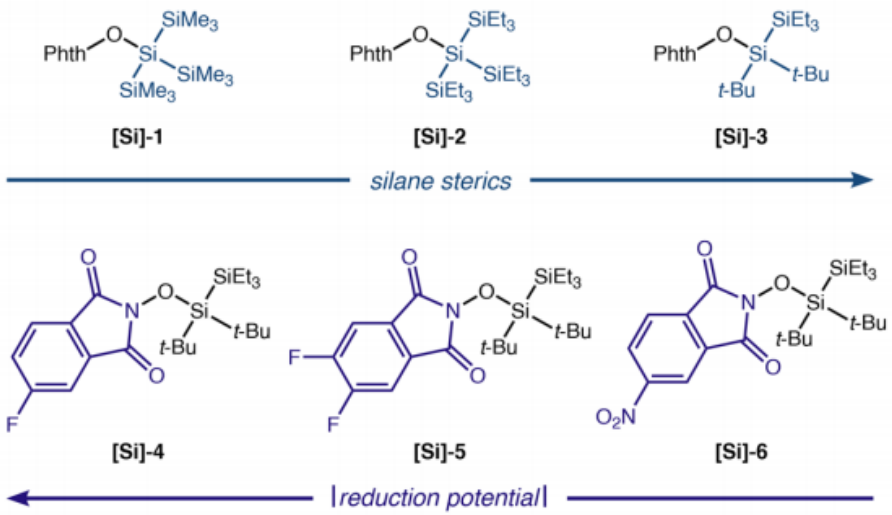
2. NHC策略脱氧形成碳-碳键



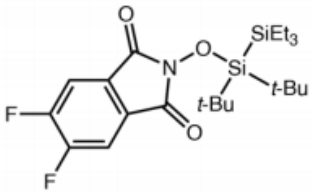


2. NHC策略脱氧形成碳-碳键





entry	silane reagent	yield
1	none	6%
2	[Si]-1	17%
3	[Si]-2	12%
4	[Si]-3	60%
5	[Si]-4	67%
6	**[Si]-5**	**71%**
7	[Si]-6	0%



air-stable, crystalline solid

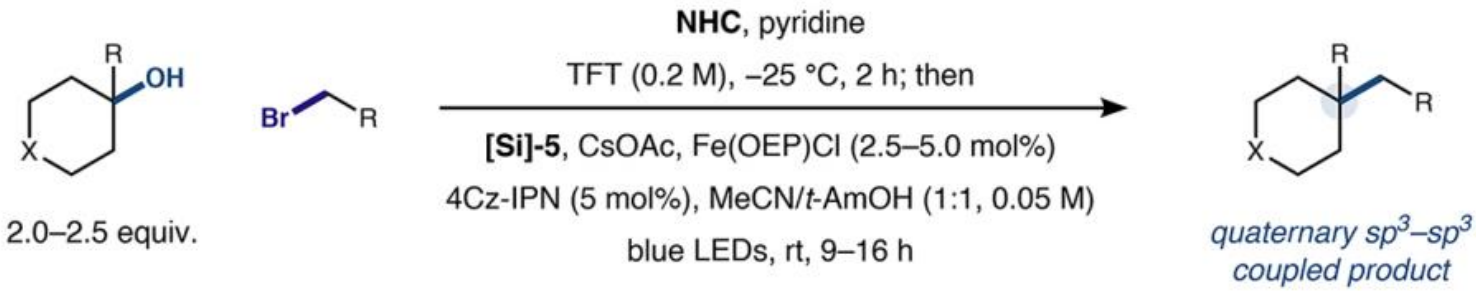
decagram-scale synthesis

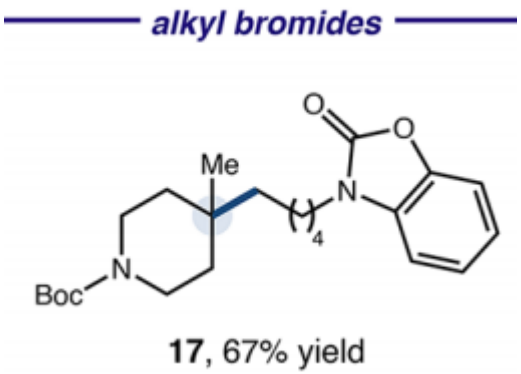
alkyl or aryl bromide activation

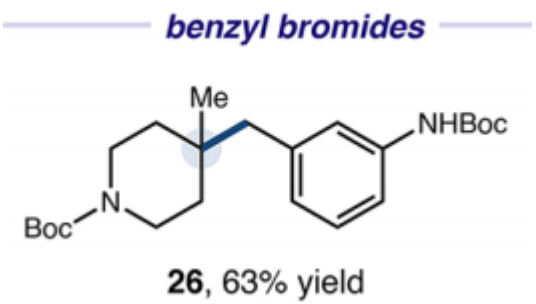
[a]Performed with bromide (0.05 mmol, 1.0 equiv), alcohol (2.5 equiv), **NHC** (2.8 equiv), pyridine (2.8 equiv), silane reagent ([**Si**], 2.0 equiv), and CsOAc (3.0 equiv). Yields determined by HPLC analysis with 1,3,5-trimethoxybenzene as an internal standard. See Supporting Information for experimental details.

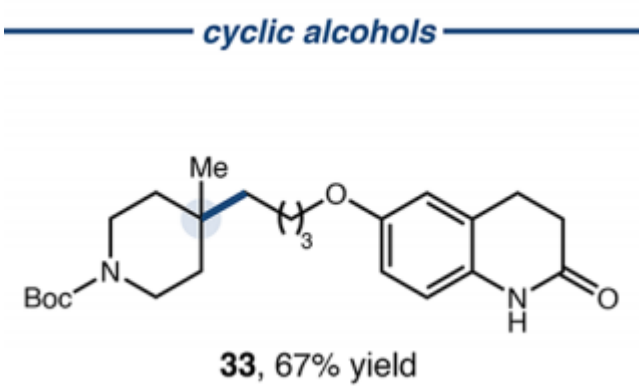
硅试剂：位阻+还原性

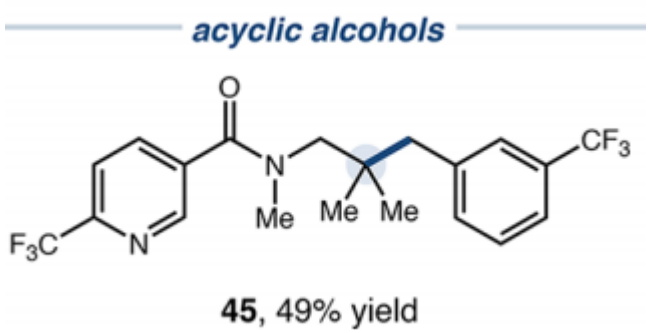
2. NHC策略脱氧形成碳-碳键











2. NHC策略脱氧Giese型加成反应

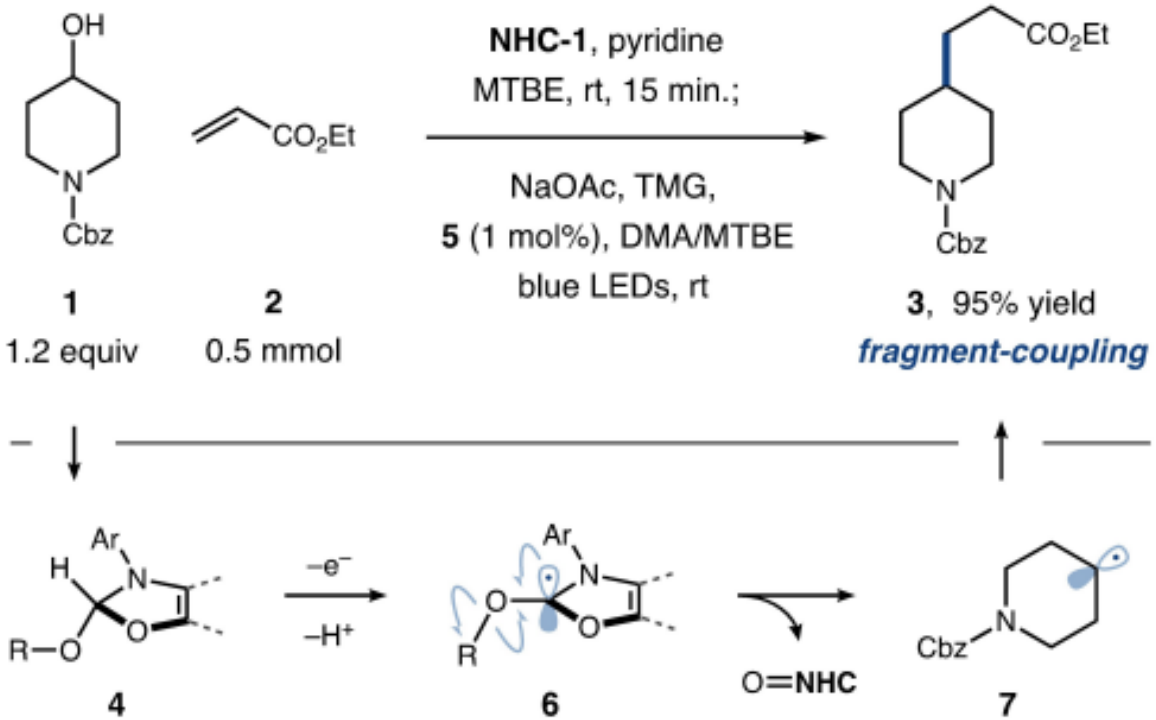
GDCh Communications Angewandte International Edition Chemie www.angewandte.org

Photochemistry Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2022**, *61*, e202207150
International Edition: doi.org/10.1002/anie.202207150
German Edition: doi.org/10.1002/ange.202207150

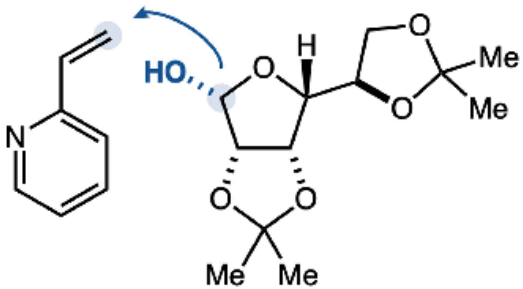
Alcohols as Alkylating Agents: Photoredox-Catalyzed Conjugate Alkylation via In Situ Deoxygenation

*Johnny Z. Wang, Holt A. Sakai, and David W. C. MacMillan**

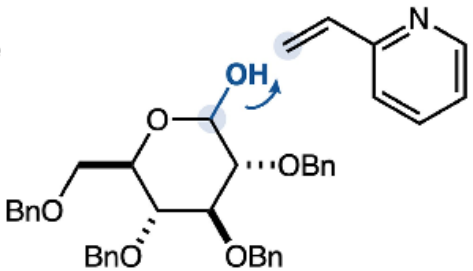


2. NHC策略脱氧Giese型加成反应

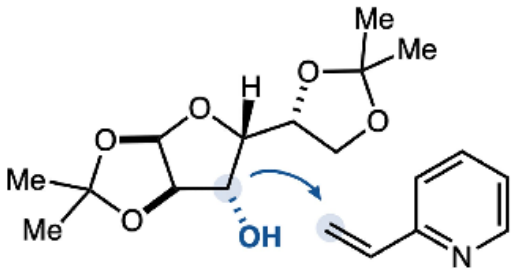
biomolecules



47, 84% yield (>20:1 d.r.)
from α-D-mannofuranose

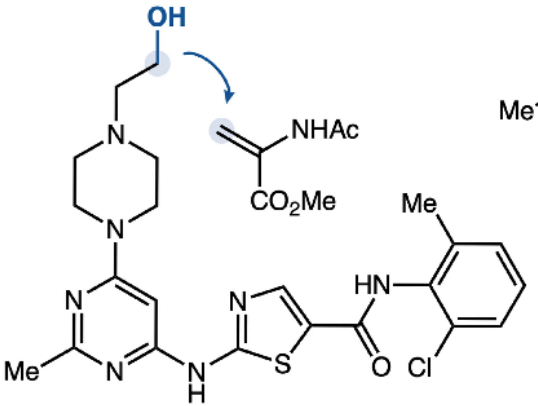


48, 79% yield (5:1 d.r.)
from D-glucopyranose

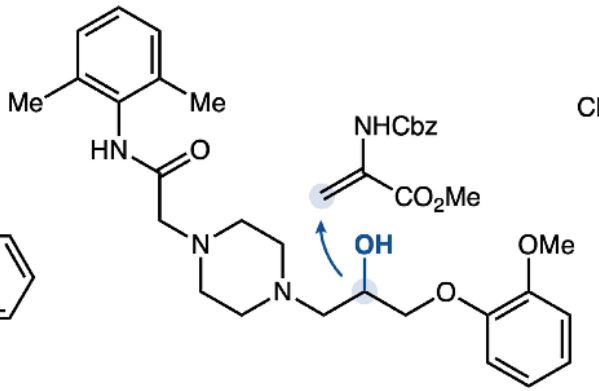


49, 77% yield (6:1 d.r.)
from α-D-glucofuranose

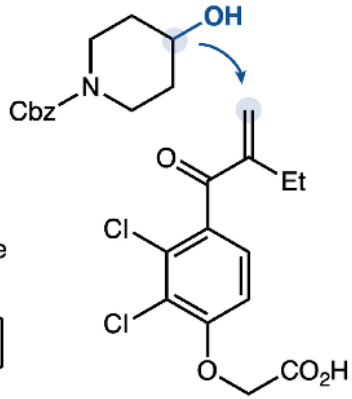
pharmaceutical agents



(±)-**52**, 52% yield
from dasatinib



(±)-**53**, 65% yield
from ranolazine



(±)-**54**, 85% yield
from ethacrynic acid

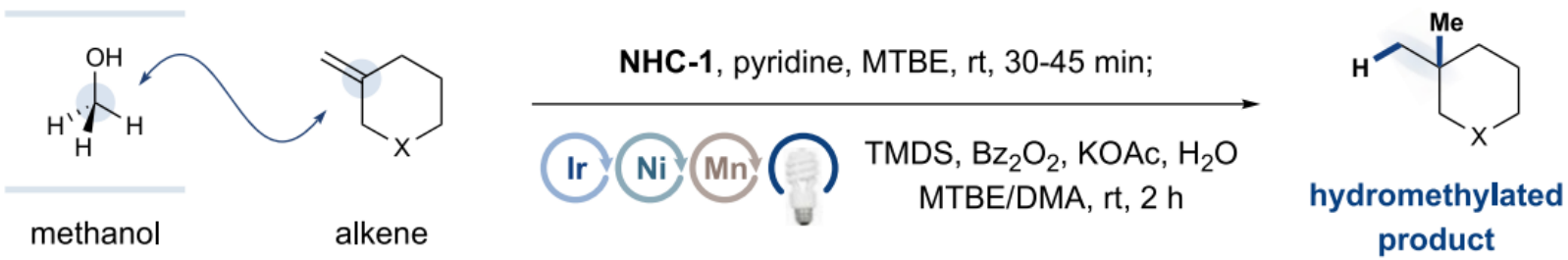
2. NHC策略脱氧形成碳-碳键

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

Engaging Alkenes in Metallaphotoredox: A Triple Catalytic, Radical Sorting Approach to Olefin-Alcohol Cross-Coupling

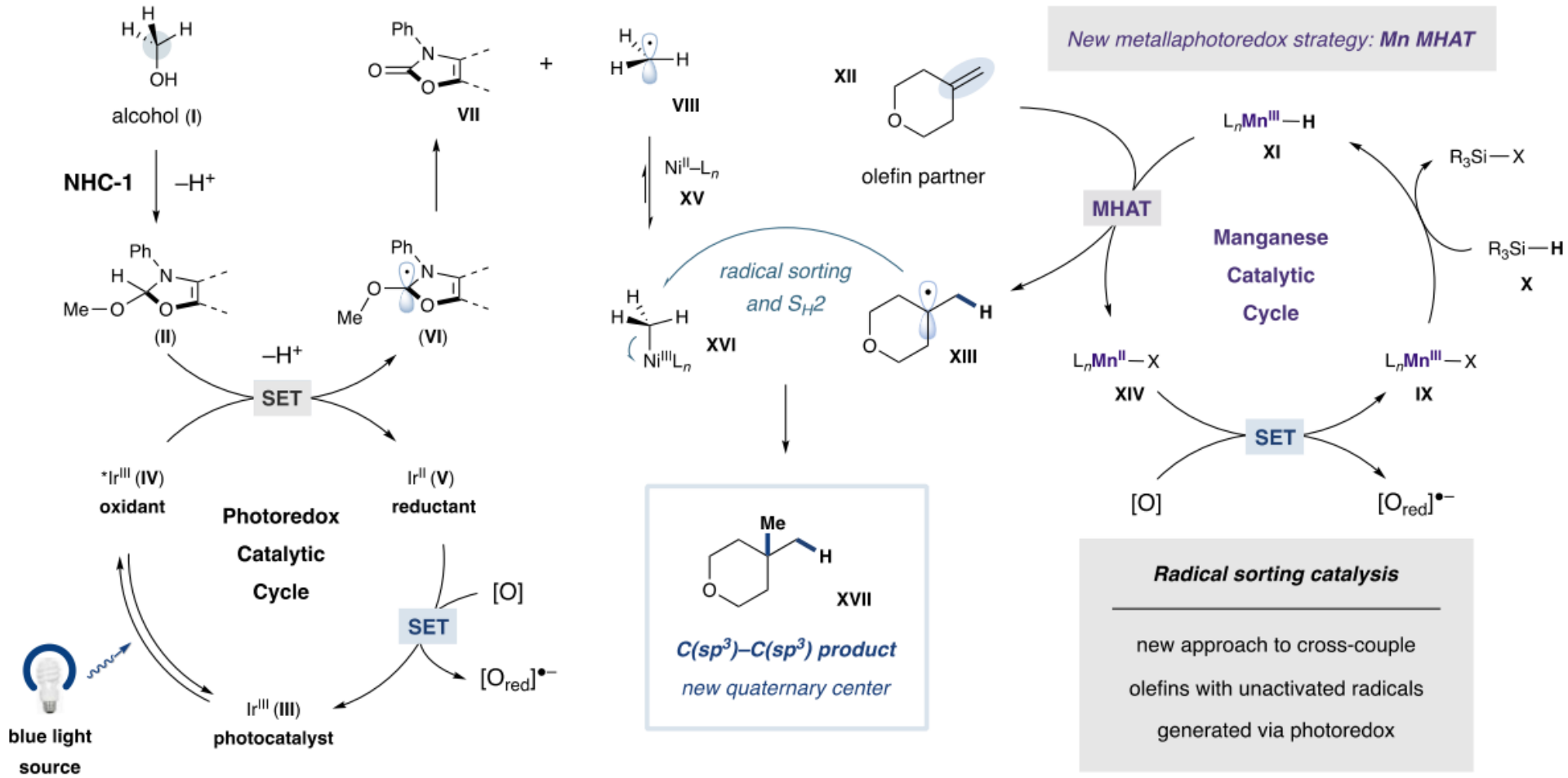
Qinyan Cai,[‡] Iona M. McWhinnie,[‡] Nathan W. Dow,[‡] Amy Y. Chan, and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2024, 146, 12300−12309
Read Online

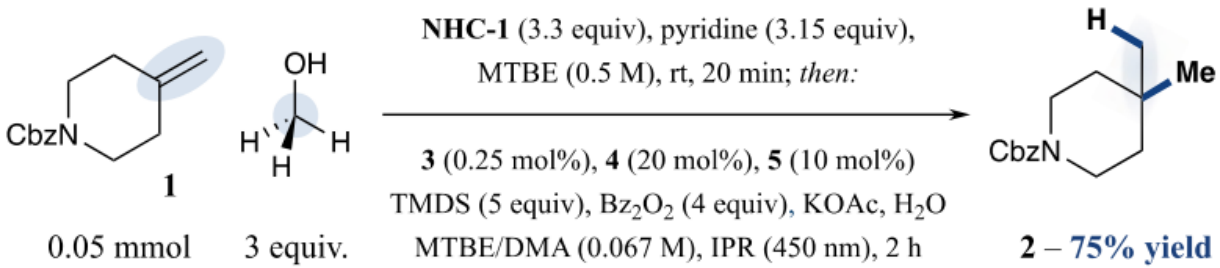


三重催化：Ir photoredox, Mn MHAT, Ni radical sorting

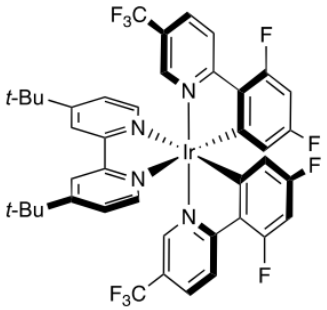
2. NHC策略脱氧形成碳-碳键



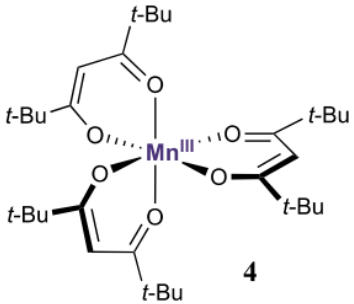
2. NHC策略脱氧形成碳–碳键



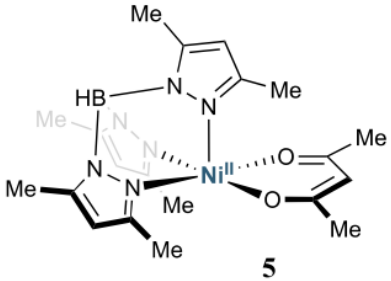
entry	deviation	yield[b]
1	none	75%
2	in absence of base (KOAc)	65%
3	in absence of H_2O additive	65%
4	Fe(OEP)Cl instead of **5**	2%
5	no Ni catalyst **5**	10%
6	$Ni(acac)_2$ instead of **5**	67%
7	$Fe(acac)_3$ instead of **4**	9%
8	$Co(acac)_2$ or Co(salen) instead of **4**	4%
9	no Mn catalyst **4**	0%
10	no light	5%
11	no photocatalyst **3**	19%
12	no TMDS	0%
13	no oxidant	0%



3



4



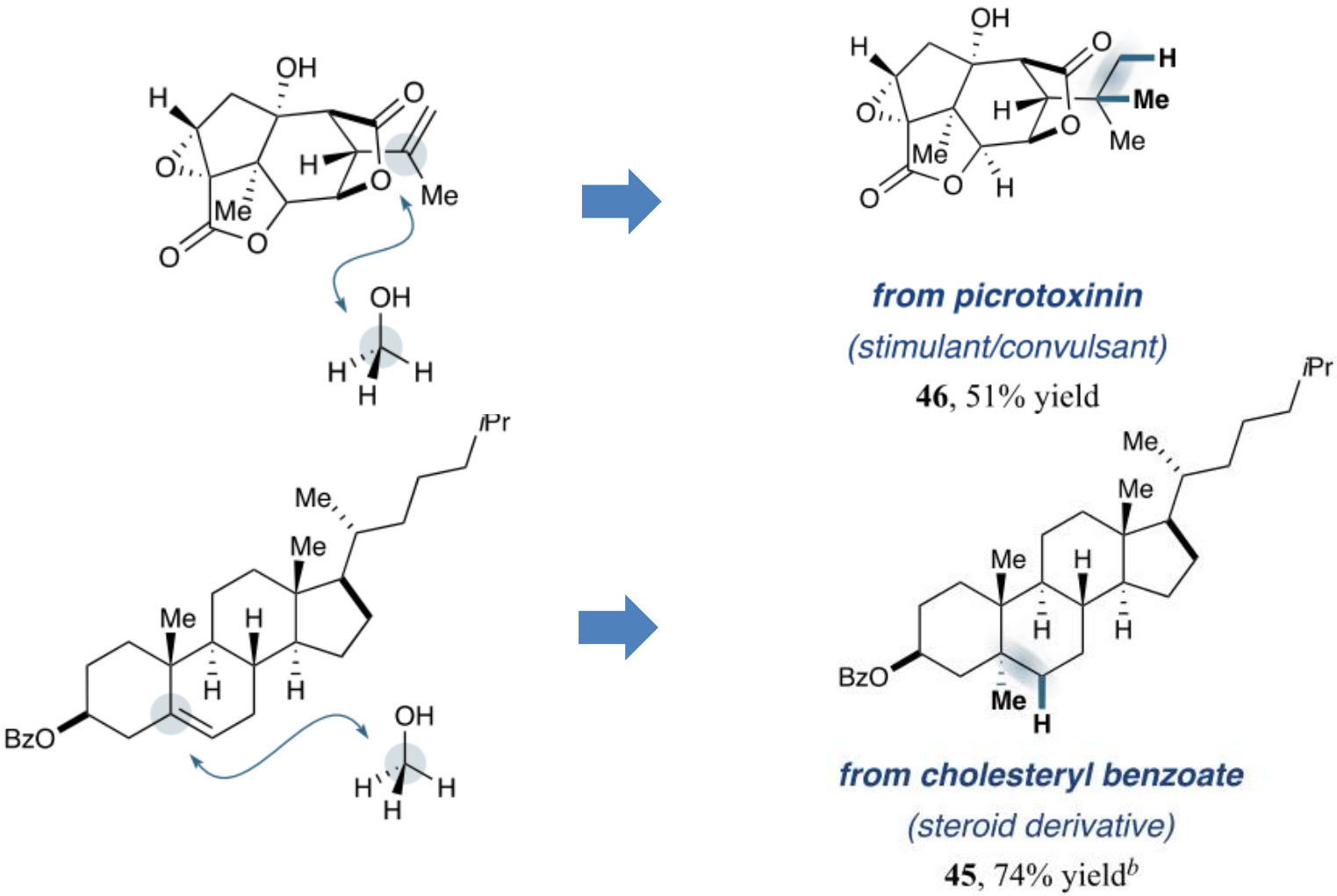
5

催化剂种类及用量的筛选极其重要

2. NHC策略脱氧形成碳-碳键

➢ 后期氢化甲基化

"magic methyl effect"



2. NHC策略脱氧三氟甲基化

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

Deoxytrifluoromethylation of Alcohols

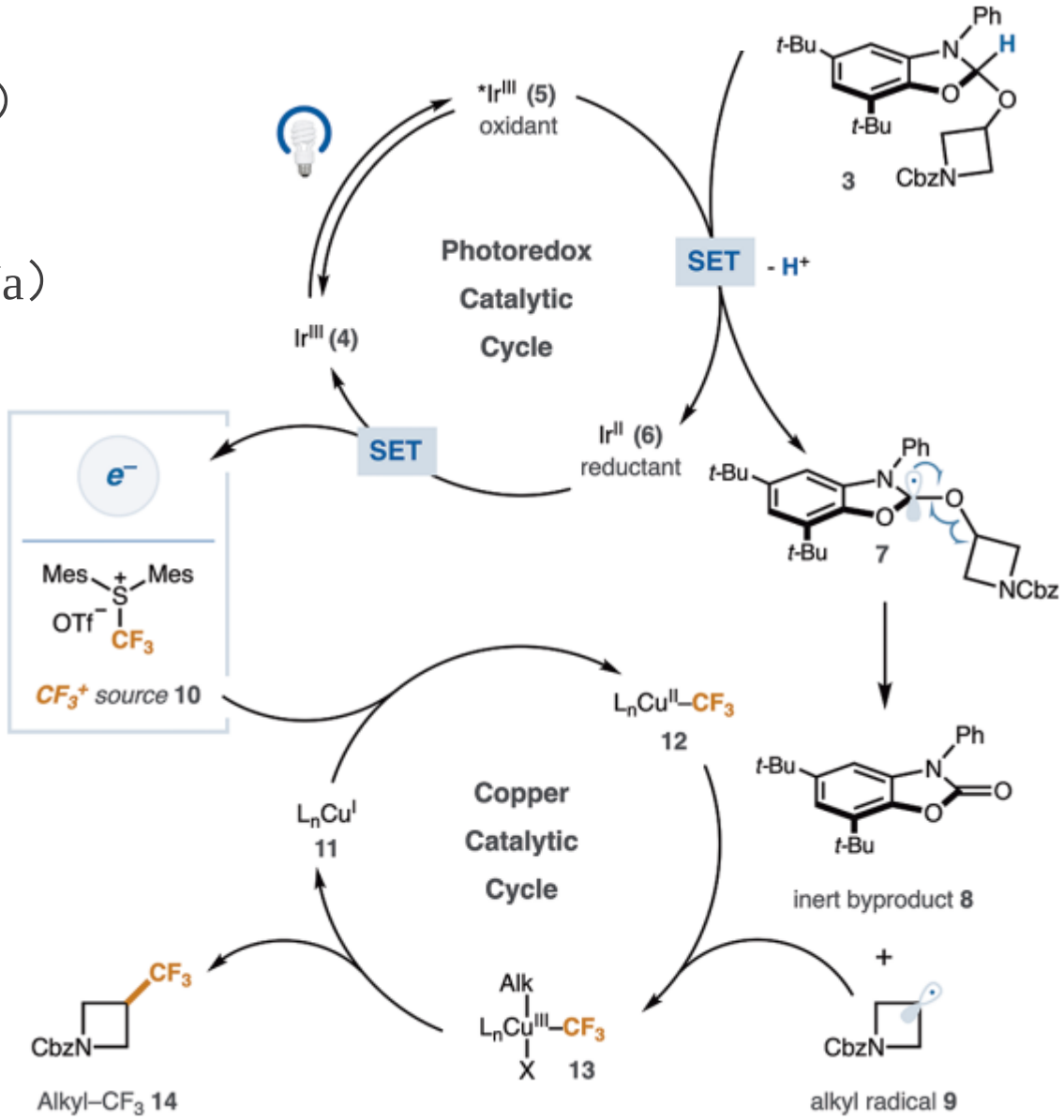
Nicholas E. Intermaggio,† Agustin Millet,† Dali L. Davis, and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2022, 144, 11961−11968
Read Online

三氟甲基基团能够显著改善小分子候选药物的药物性质

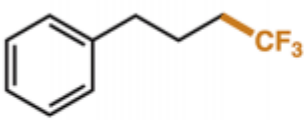
2. NHC策略脱氧形成碳-碳键

- Ruppert试剂（$TMSCF_3$）
- Togni试剂（高价碘）
- Langois试剂（CF_3SO_2Na）
- ✓ Umemoto试剂

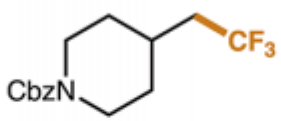


2. NHC策略脱氧形成碳-碳键

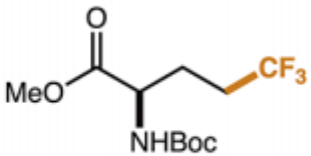
Primary Alcohols



18, 80% (51%) yield[d]

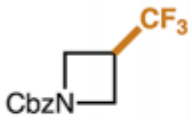


19, 85% (84%) yield[b]



20, 66% (61%) yield[d]

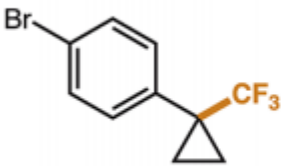
Secondary Alcohols



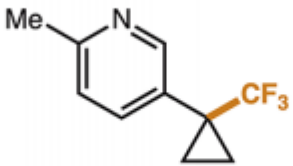
14, 59% (57%) yield[c]

30, 52% yield[d]

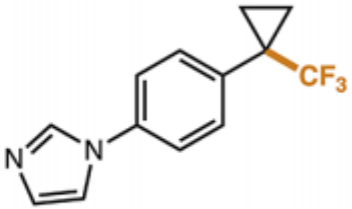
Tertiary Alcohols



43, 74% (58%) yield*



44, 64% (23%) yield*



45, 54% (51%) yield*

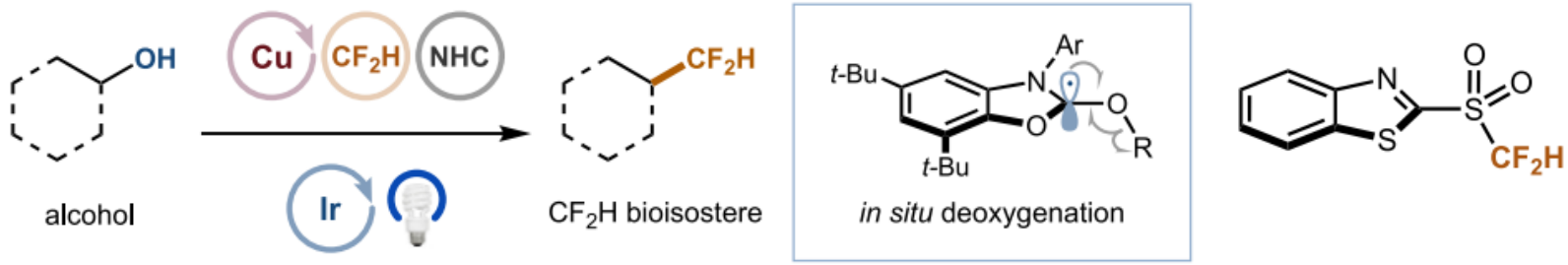
2. NHC策略脱氧形成碳-碳键

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

Direct Bioisostere Replacement Enabled by Metallaphotoredox Deoxydifluoromethylation

Edna Mao,[§] Cesar N. Prieto Kullmer,[§] Holt A. Sakai, and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2024, 146, 5067−5073
Read Online



二氟甲基保留了参与氢键相互作用的能力，具有更明显的亲脂性、代谢稳定性和生物相容性。

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

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

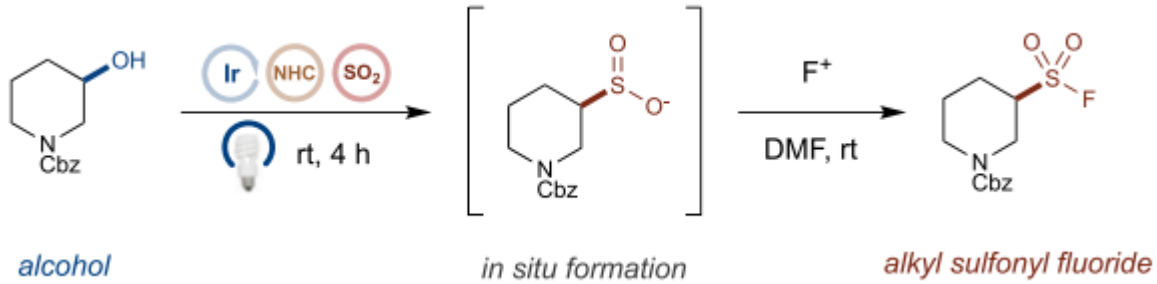
Photoredox Catalysis-Enabled Sulfination of Alcohols and Bromides

William P. Carson II, Patrick J. Sarver, Noelle S. Goudy, and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2023, 145, 20767−20774
Read Online

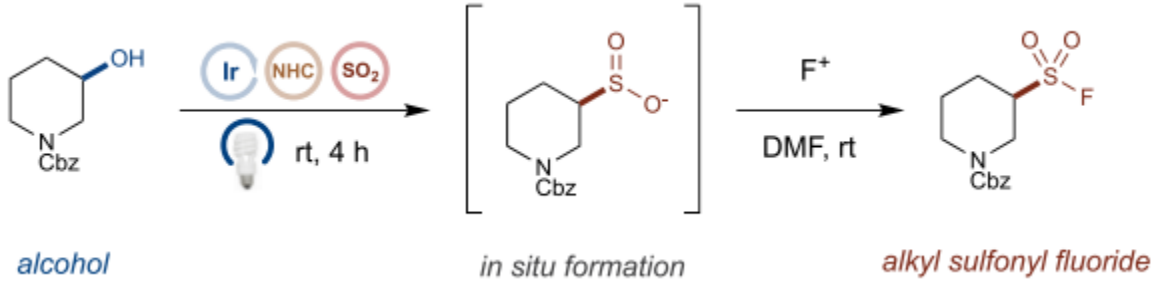
➢ 醇脱氧磺化反应

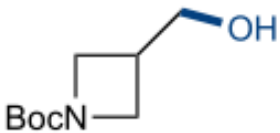
容易被氧化

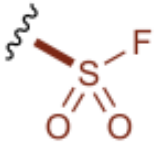


3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

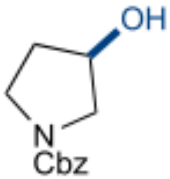
➢ 醇脱氧磺化反应

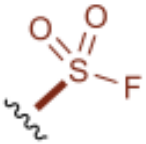




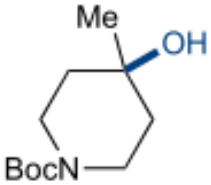


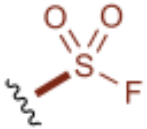
1, 65% yield





(±)-**7**, 65% yield

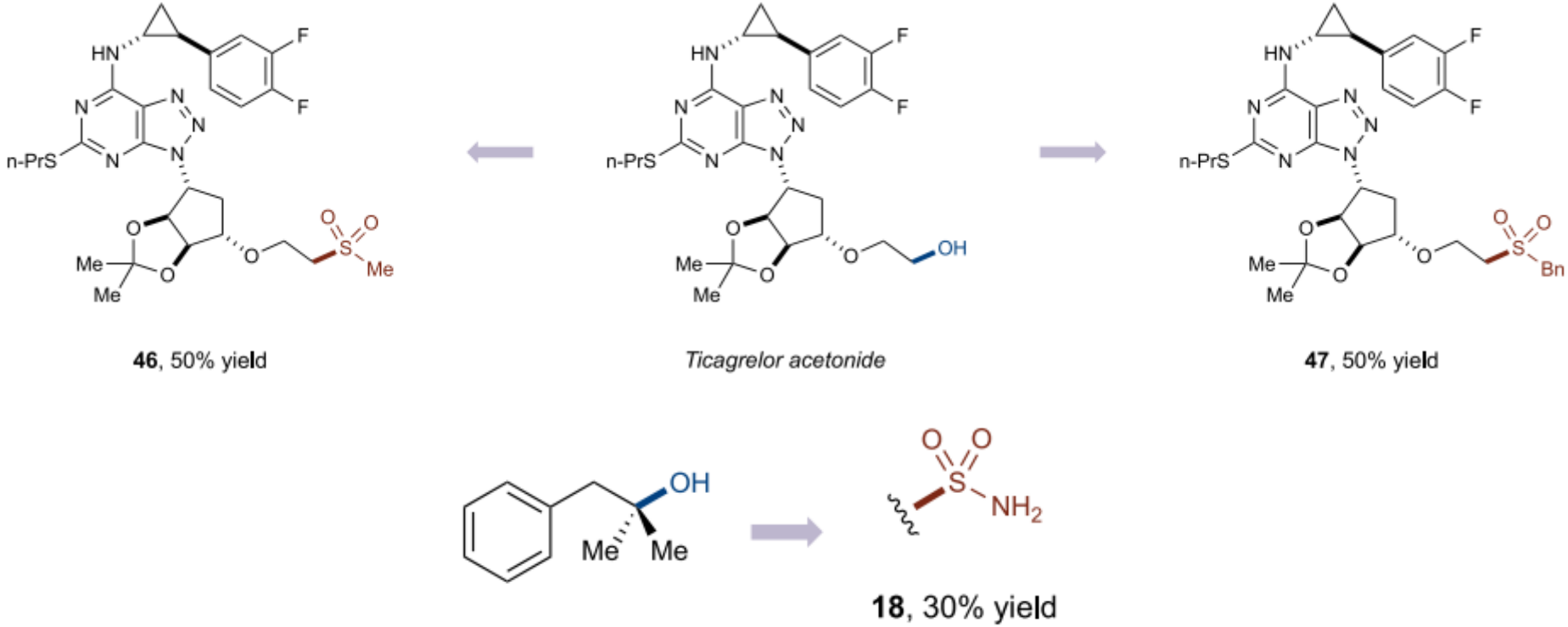




16, 55% yield

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

➢ 醇脱氧磺化反应



最后用不同试剂处理，可分别得到甲基磺酸、苄基磺酸、磺酰胺

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

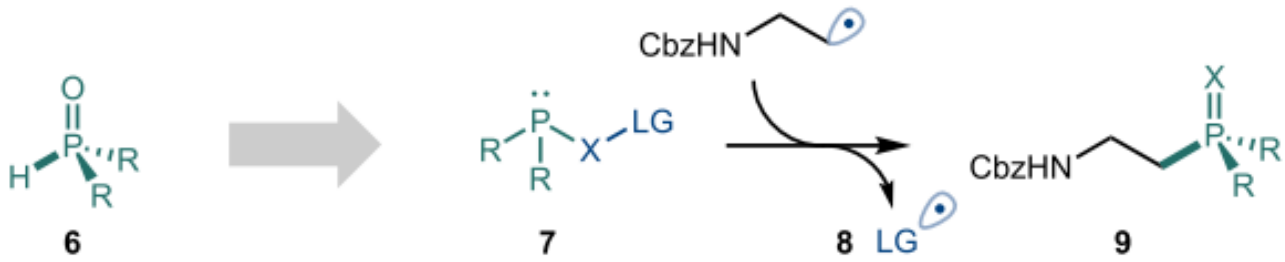
➢ 醇脱氧膦酰化反应

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

Development of a General Organophosphorus Radical Trap: Deoxyphosphonylation of Alcohols

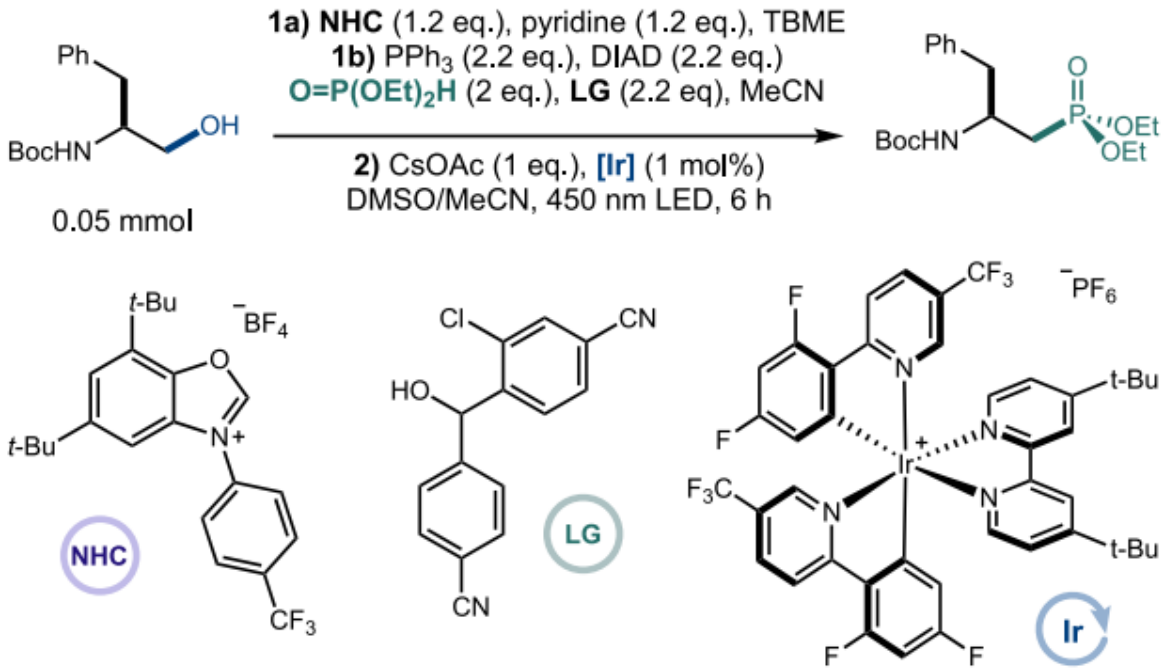
Noah B. Bissonnette, Niels Bisballe, Andrew V. Tran, James A. Rossi-Ashton, and David W. C. MacMillan*

Cite This: *J. Am. Chem. Soc.* 2024, 146, 7942–7949
Read Online



3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

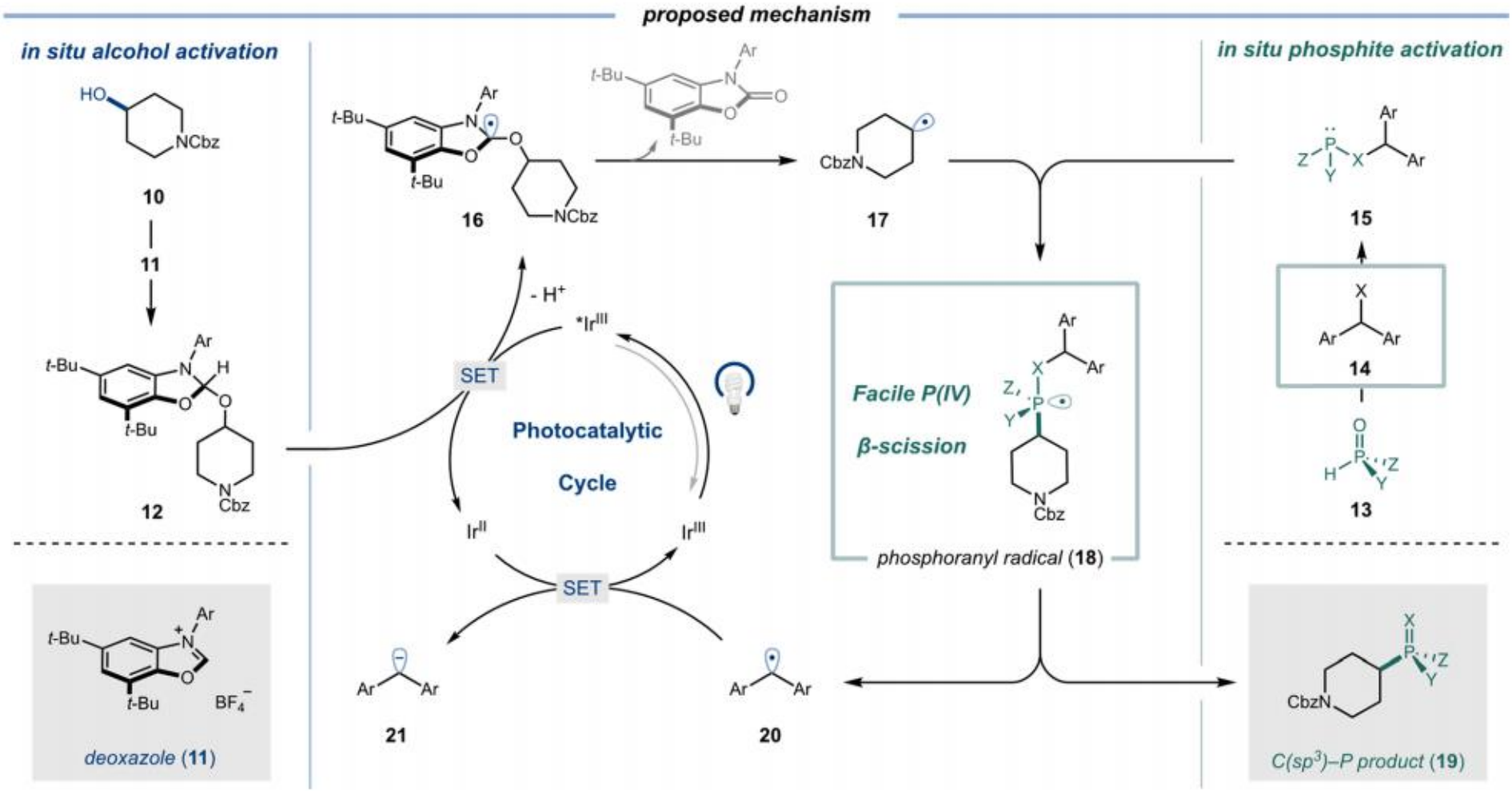
➢ 醇脱氧膦酰化反应



entry	deviation	assay yield (%)
1	none	75
2	no light	0
3	no photocatalyst	<1
4	no leaving group	<1
5	$P(OEt)_3$ or $O{=}P(OEt)_2H$ instead of activated P(III)	0
6	4CzIPN-*t*Bu (2 mol %) instead of Ir	74

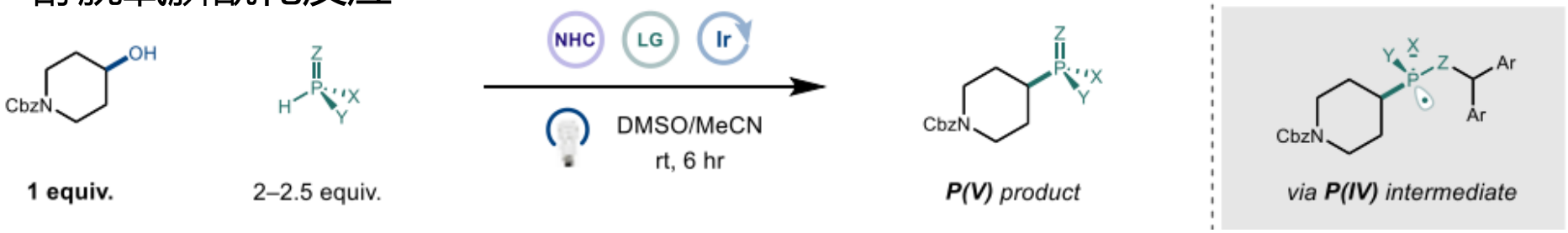
3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

➢ 醇脱氧膦酰化反应

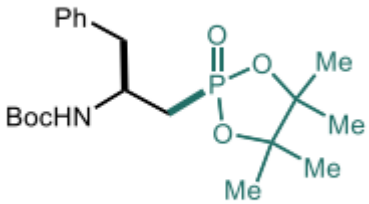


3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

➢ 醇脱氧膦酰化反应

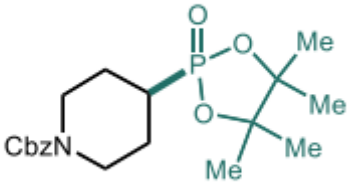


primary alcohols



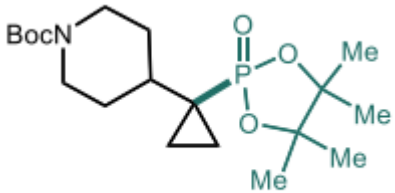
22, 90%
Gram-scale: 94%

secondary alcohols



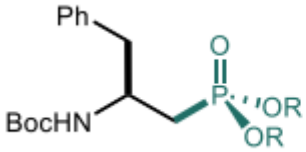
30, 82%

tertiary alcohols

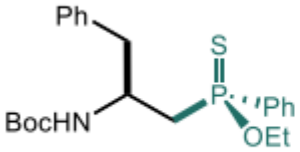


39, 47%

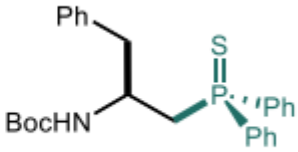
P(V) scope



43, R = Et, 75%
44, R = *i*-Bu, 78%
45, R = *i*-Pr, 62%
46, R = *t*-Bu, 0%[a]



51, 81%[b]



52, 63%

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

nature communications

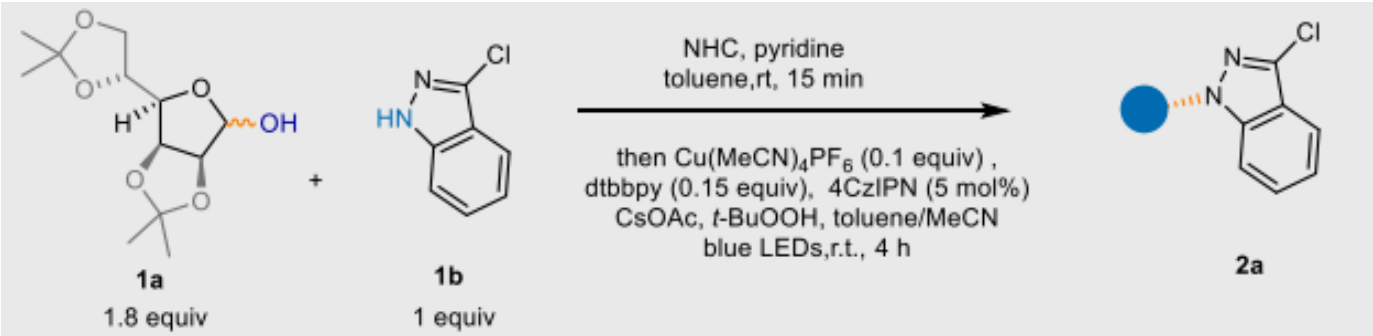
Article

https://doi.org/10.1038/s41467-024-47711-9

Dehydroxylative radical N-glycosylation of heterocycles with 1-hydroxycarbohydrates enabled by copper metallaphotoredox catalysis

Received: 4 February 2024

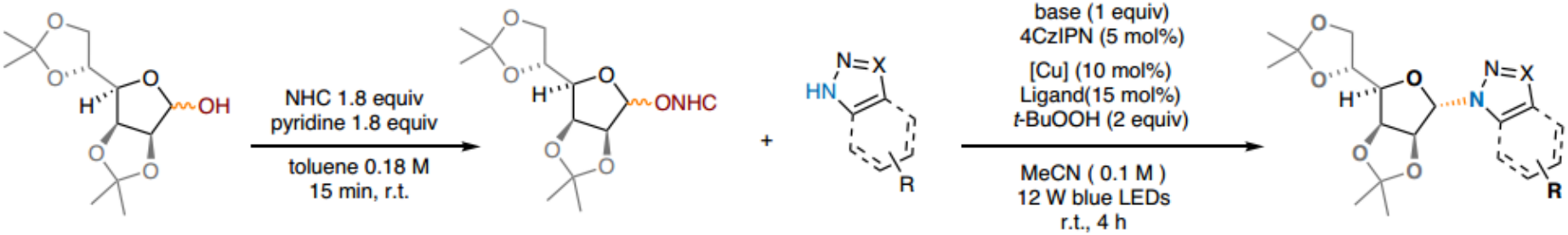
Da-Peng Liu[1], Xiao-Sen Zhang[1], Shuai Liu[1] & Xiang-Guo Hu[1]

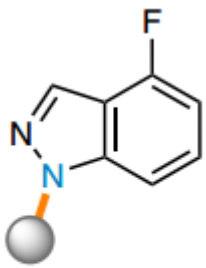


叔丁基过氧酸作为氧化剂

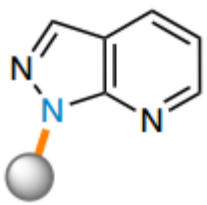
3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

➢ 醇脱氧构筑碳氮键

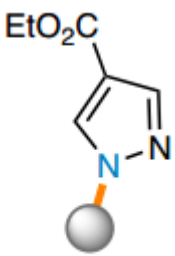




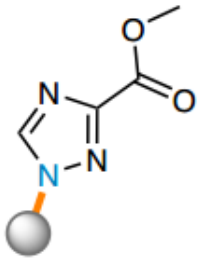
2f, 92%



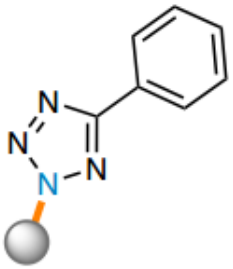
2j, 61%



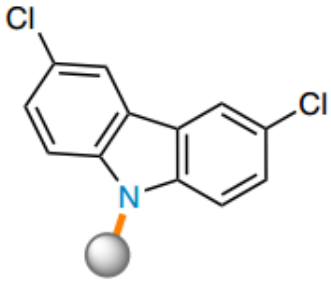
3d, 62%



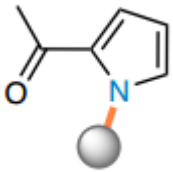
3h, 72%[a,b]



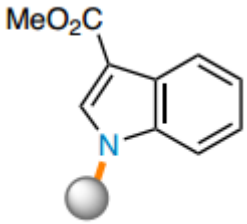
3i, 65%[a,b]



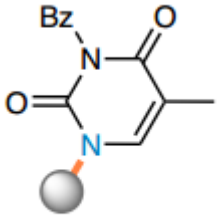
4e, 59%[a,c]



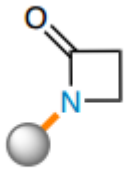
4h, 42%[a,c]



5b, 51%[c]



6c, 46%[a,b]



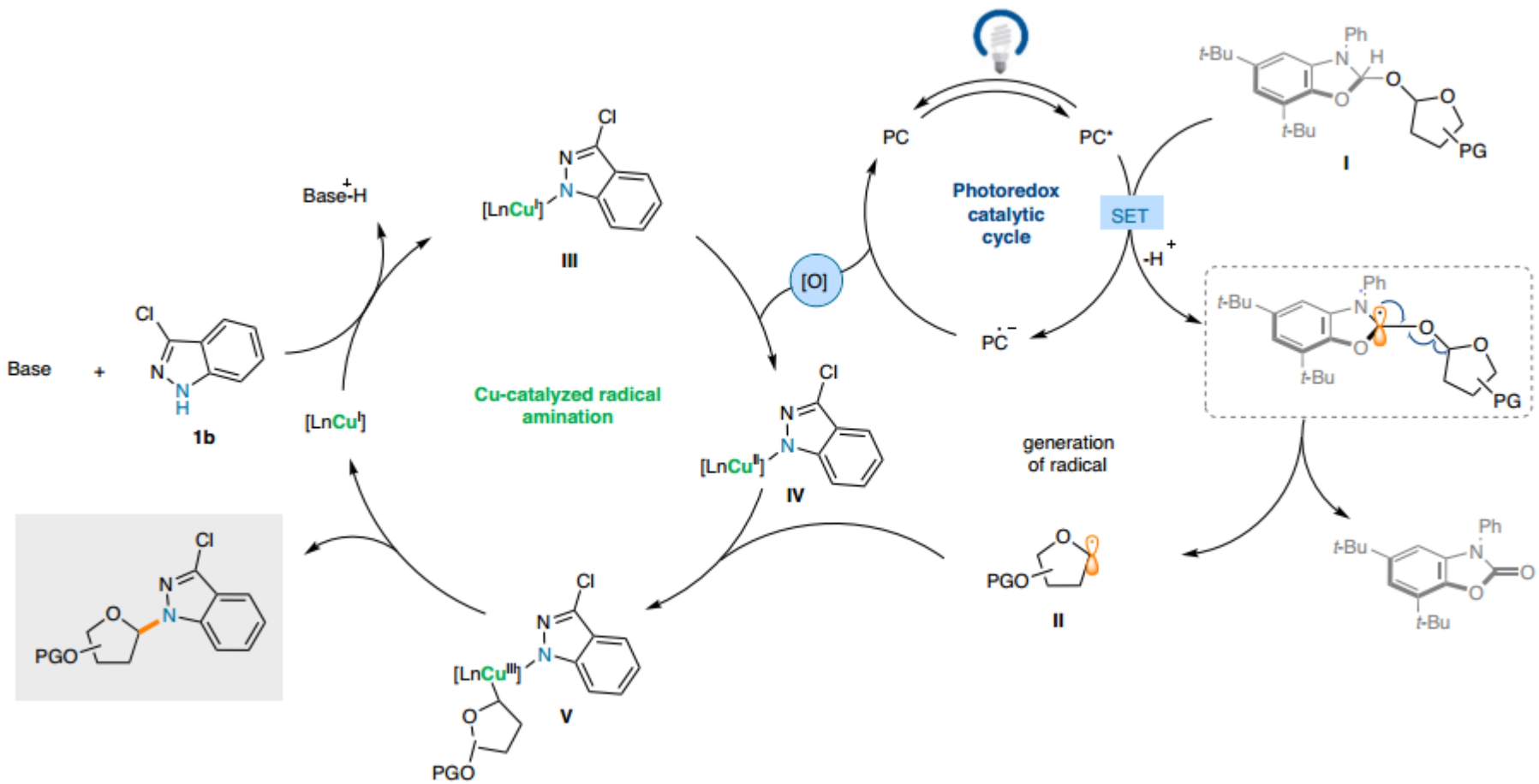
7b, 62%[a,b]

吲唑、氮杂吲唑、吡唑、三唑、四唑、咔唑、吡咯、吲哚、氮杂吲哚、嘧啶、环状酰亚胺、β-内酰胺、异喹啉酮和环状氨基甲酸酯

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

➢ 醇脱氧构筑碳氮键

Proposed Mechanism



3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

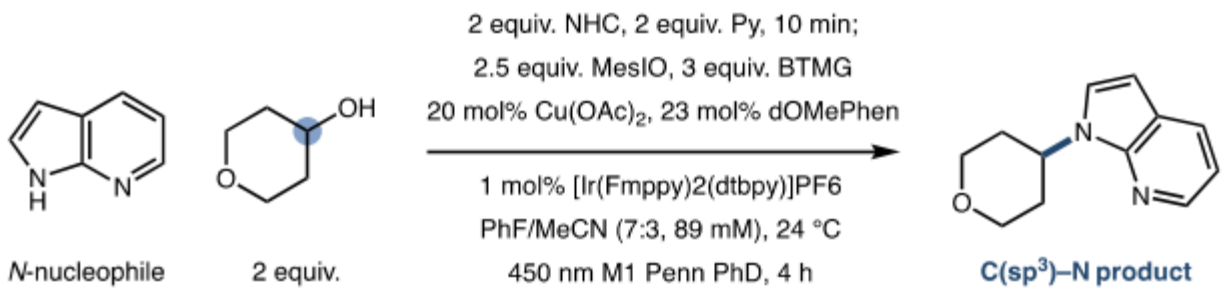
➢ 醇脱氧构筑碳氮键

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

Free-Radical Deoxygenative Amination of Alcohols via Copper Metallaphotoredox Catalysis

William P. Carson II,[†] Artem V. Tsymbal,[†] Robert W. Pipal, Grant A. Edwards, Joseph R. Martinelli, Albert Cabré, and David W. C. MacMillan*

Cite This: https://doi.org/10.1021/jacs.4c04477
Read Online



高碘化合物作为氧化剂

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

ORGANIC CHEMISTRY FRONTIERS

CHINESE CHEMICAL SOCIETY

ROYAL SOCIETY OF CHEMISTRY

RESEARCH ARTICLE

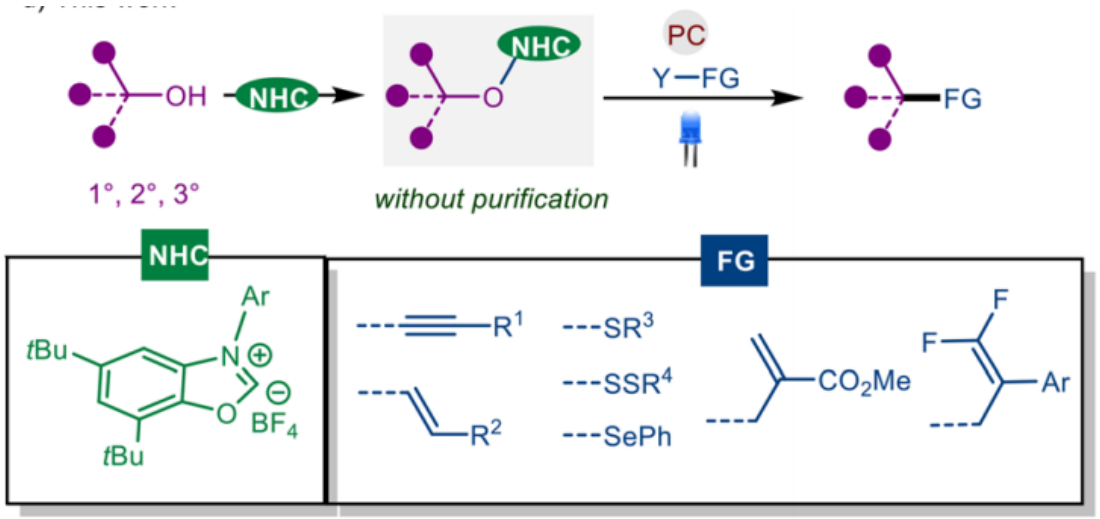
View Article Online
View Journal

Check for updates

Cite this: DOI: 10.1039/d4qo00115j

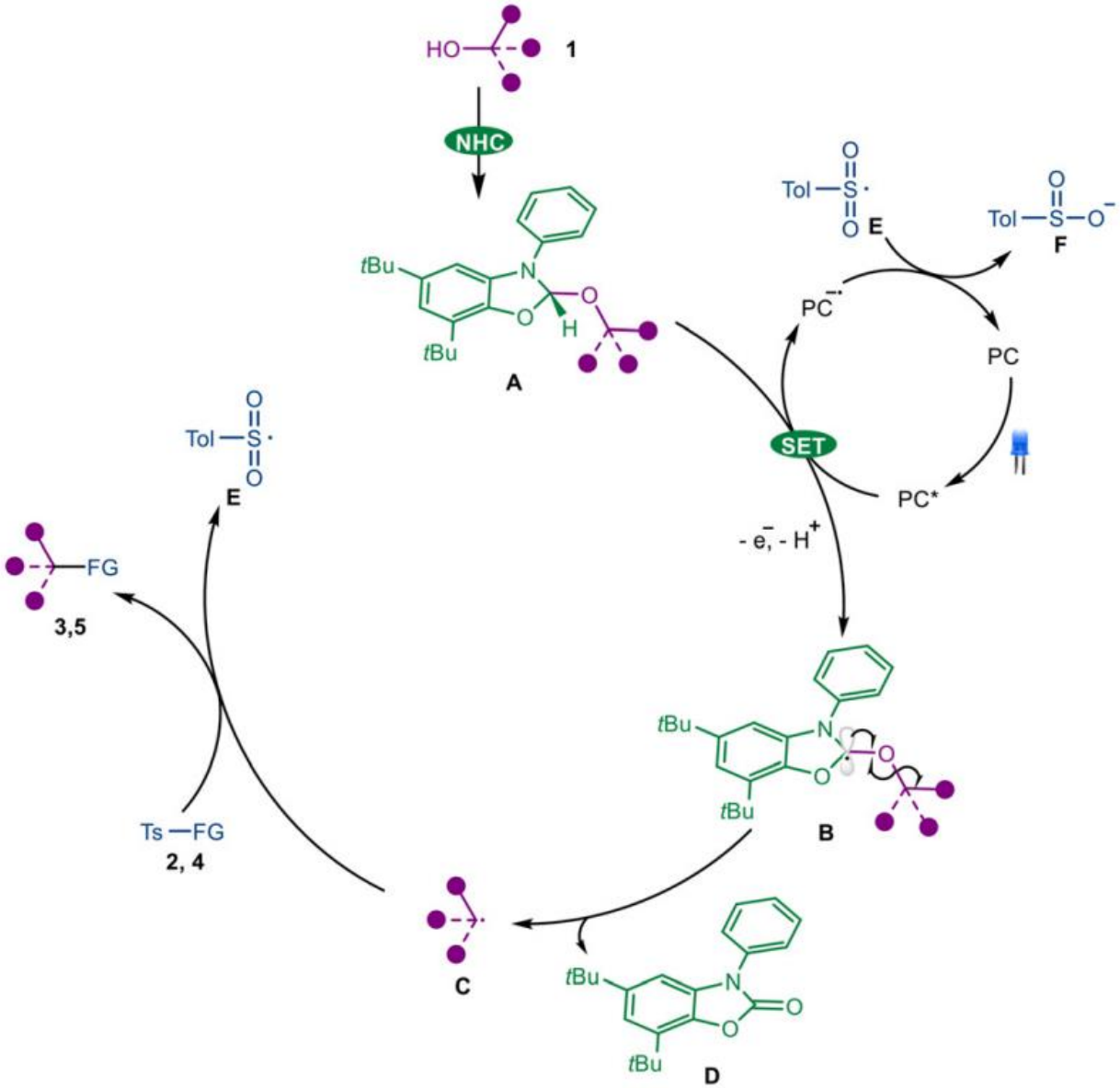
Photoredox catalytic deoxygenative divergent functionalizations of alcohols assisted by N,O-heterocyclic carbenes†

Qiuzhu Wang,[a] Youye Tian,[a] Dan Han,[c] Wenjuan Xiao,[a] Mengtao Ma[a] and Binlin Zhao*[a,b]

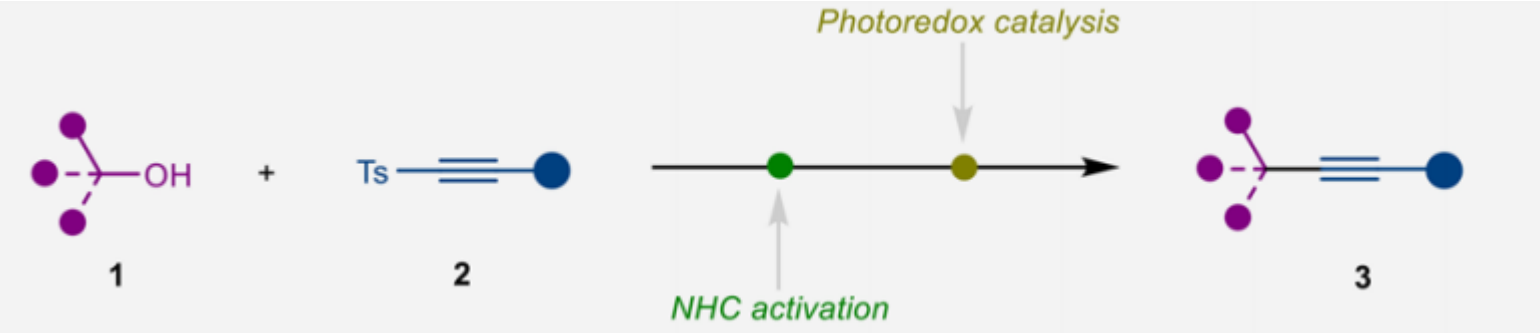


炔化、烯基化、烷基化、硫基化、二硫化、硒基化和偕二氟烷基化

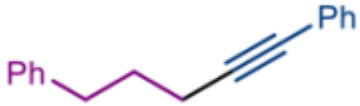
3. NHC策略脱氧形成碳-杂键（N, S, P, Se）



3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

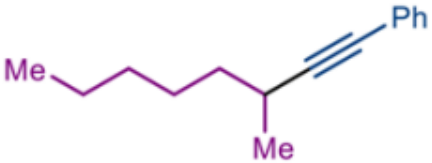


Primary alcohols[a]



3b, 46%

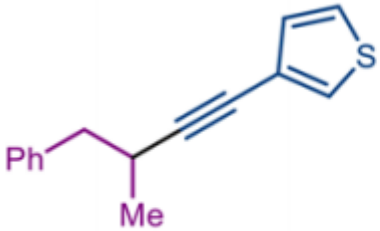
Secondary alcohols[b]



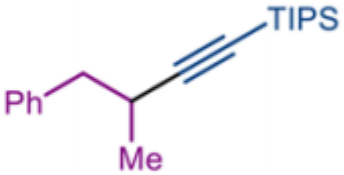
3n, 88%

Tertiary alcohols[c]

3ad, n = 0, 56%
3ae, n = 1, 48%



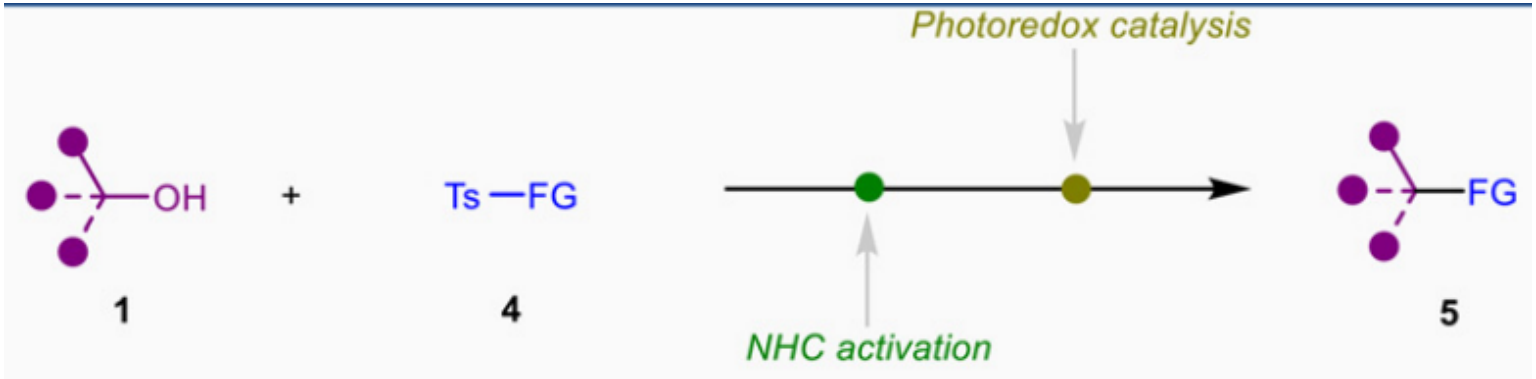
3ar, 59%

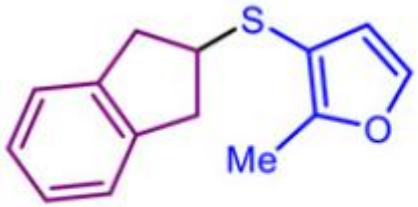


3as, 63%

3at, 42%

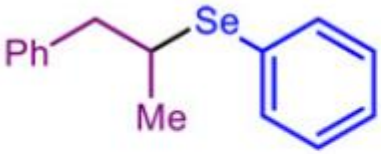
3. NHC策略脱氧形成碳-杂键（N, S, P, Se）



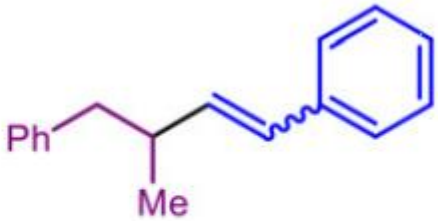


5g, 45%

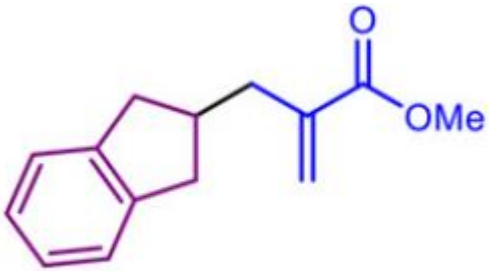
5h, 46% [b]



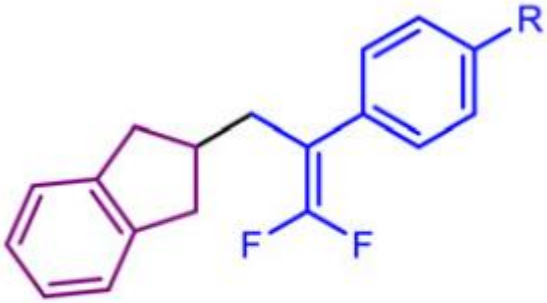
5i, 31%[b]



5j, 77%[a], *E* : *Z* = 1 : 3



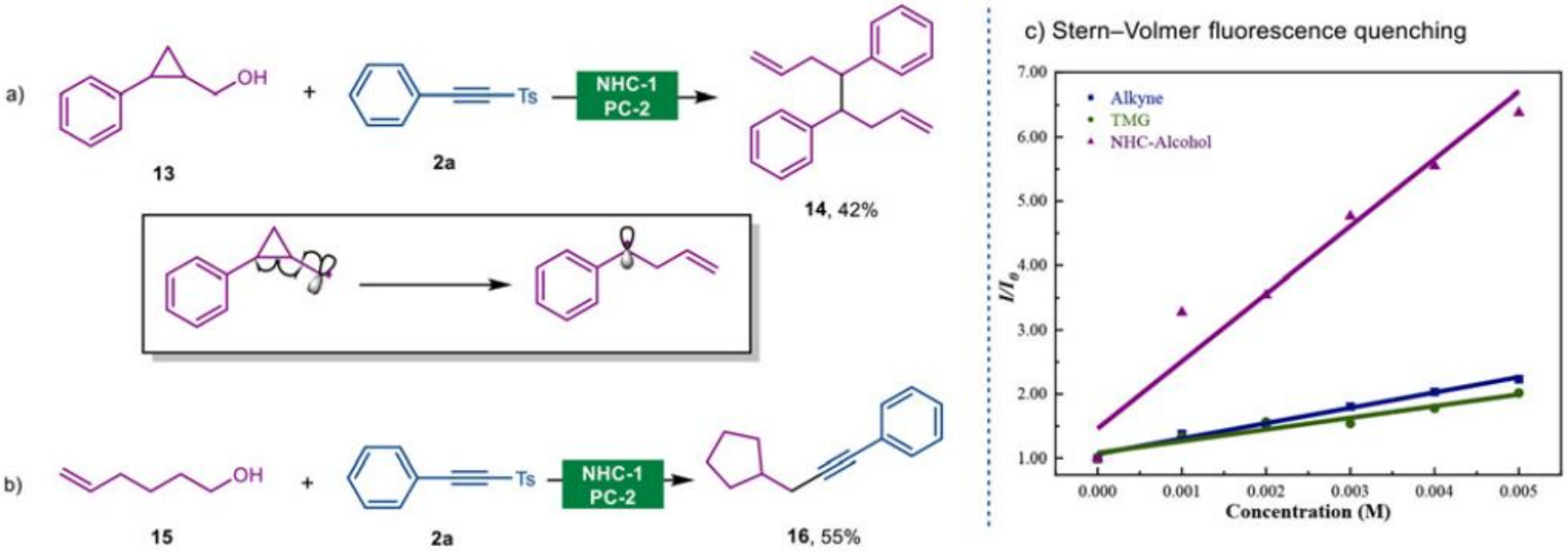
5k, 57%[b]



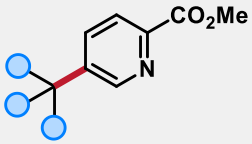
R = OMe, **5p**, 90%[a]
R = OCF_3, **5q**, 49%[a]

硫基化、二硫化、硒基化、烯基化、烷基化、和偕二氟烷基化

3. NHC策略脱氧形成碳-杂键（N, S, P, Se）

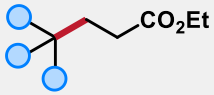


4. 总结与展望



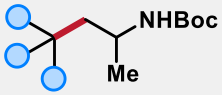
Deoxy-Arylation

Macmillan, ***Nature***, 2021



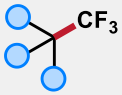
Deoxy-Giese type reaction

Macmillan, ***ACIE***, 2022



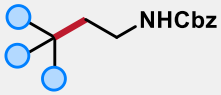
Deoxy-alkylation

Macmillan, ***JACS***, 2022
Macmillan, ***Science***, 2024
Ni: Radical Sorting



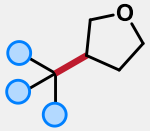
Deoxy-Trifluoromethylation

Macmillan, ***JACS***, 2022



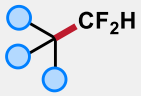
Deoxy-Alkylation

Macmillan, ***JACS***, 2023
Fe: Radical Sorting



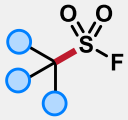
Deoxy-Alkylation

Macmillan, ***JACS***, 2023



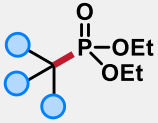
Deoxy-Difluoromethylation

Macmillan, ***JACS***, 2024



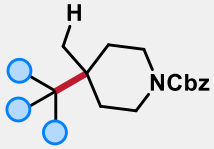
Deoxy-Sulfination

Macmillan, ***JACS***, 2023



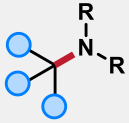
Deoxy-Phosphonylation

Macmillan, ***JACS***, 2024



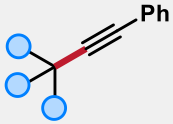
Deoxy-Alkylation

Macmillan, ***JACS***, 2024
Ni: Radical Sorting

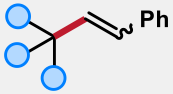


Deoxy-Amination

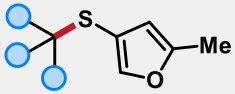
Macmillan, ***JACS***, 2024
Hu, ***Nat. Commun.***, 2024



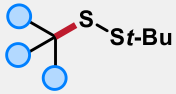
Deoxy-Alkynylation



Deoxy-Alkenylation



Deoxy-Sulfination



Deoxy-Disulfuration

Deoxy-Selenylation

Zhao, ***Org. Chem. Front.***, 2024

- ◆ 各种官能化已迅速发展，不对称官能化发展不足
- ◆ Fe、Ni 介导的“Radical Sorting”为构建大位阻碳中心提供新思路，但机理不够清楚

Thanks!