光参与的甲基化反应研究进展

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指导教师： 麻生明 教授
2022年4月29日

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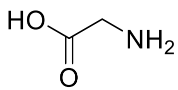
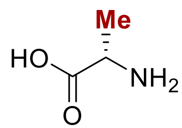
1 背景介绍

increasing methylation

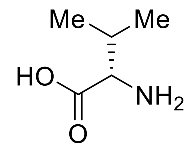


glycine

vs

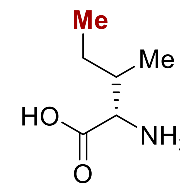


alanine

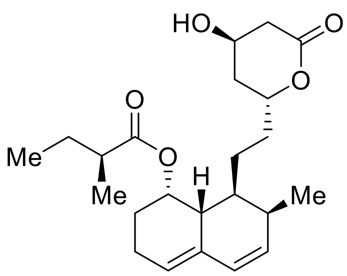


valine

vs



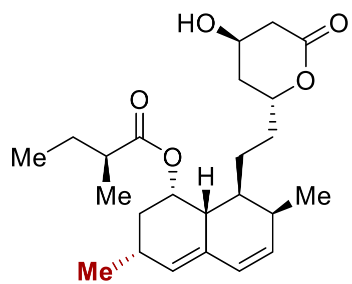
isoleucine



Mevastatin

never marketed

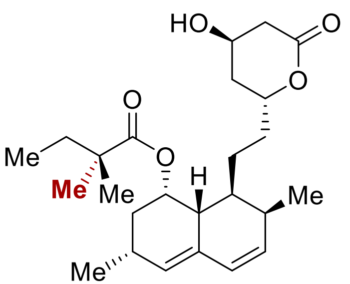
vs



Lovastatin

first marketed statin drug

vs



Simvastatin

second-generation statin drug

Chen, Y. *Chem. Eur. J.* **2019**, *25*, 3405-3439.

Cernak, T. et al., *Angew. Chem. Int. Ed. 2013*, **52**, 12256-12267.

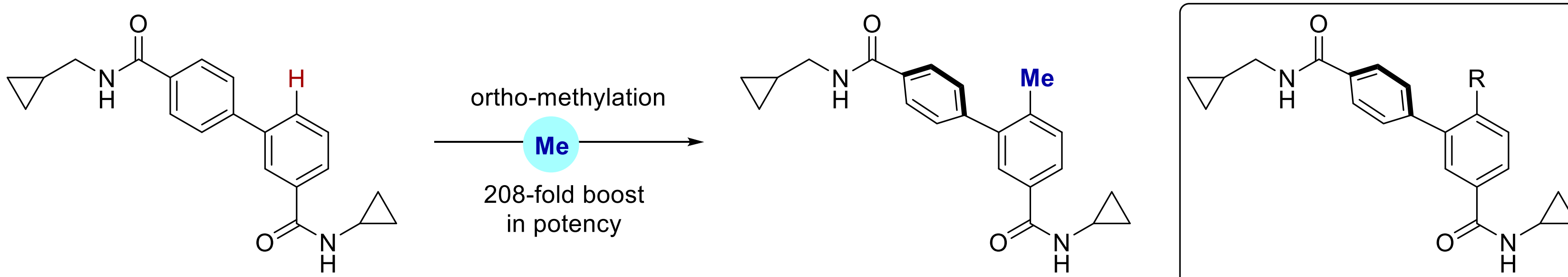
1 背景介绍

Magic Methyl Effect

Conformational preorganization

low-energy conformers (unbound)

low-energy conformers (bound)



1, p38α, IC_{50} > 2500 nM

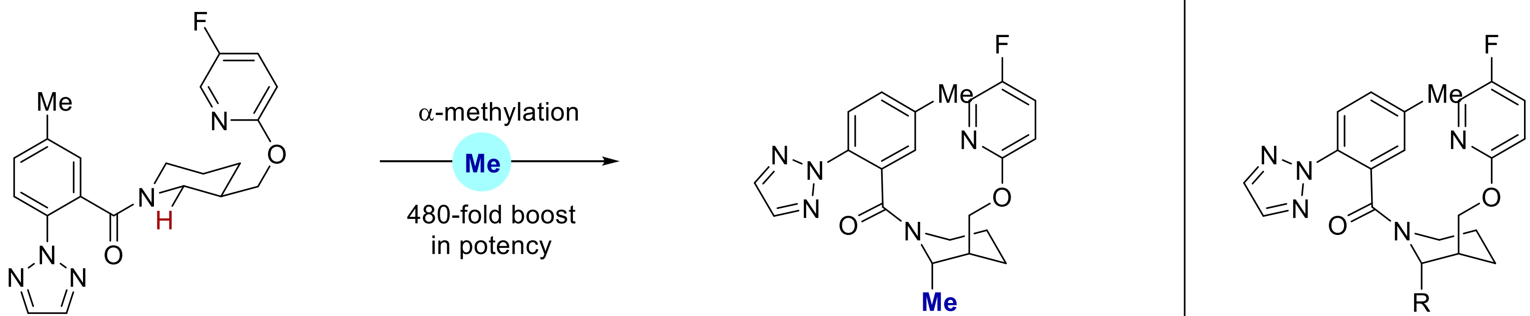
biaryl dihedral angle 50°

2, p38α, IC_{50} 12 nM

biaryl dihedral angle 65°

3 (R = H or Me)

biaryl dihedral angle 85°



U-shaped

U-shaped (unbound)

4, OX_1R, IC_{50} 96 nM

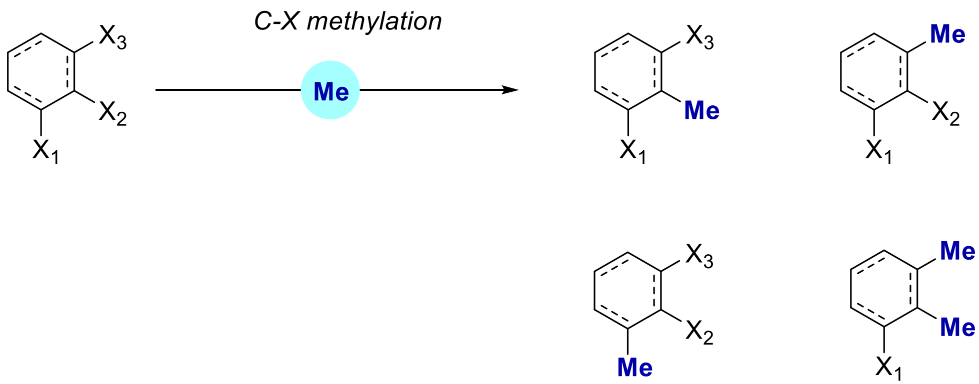
5, OX_1R, IC_{50} 0.2 nM

6 (R = H or Me)

Cernak, T. et al., *Angew. Chem. Int. Ed. 2013*, **52**, 12256-12267.

1 背景介绍

Traditional methods for methylation

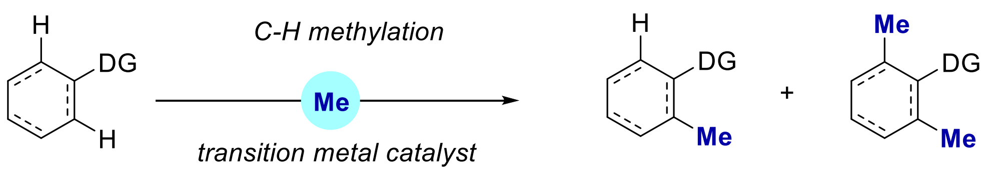


etc.

Limimtations

- *C-X differentiation*
- *functional group tolerance*
- *multiple methylation*

C-H activation based methylation



TM: Pd, Co, Fe, Rh, Ni, etc.

Methylation reagents: MeI, $SnMe_4$, $MeB(OH)_2$, $MeBF_3K$, MeMgCl, $AlMe_3$, etc.

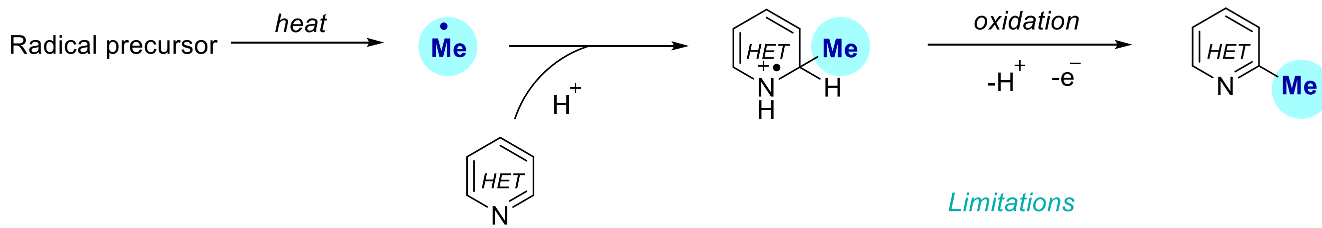
Limitations

- *pre-installation of directing groups*
- *stoichiometric amounts of oxidants*
- *harsh conditions*
- *sensitive methylation reagents*
- *multiple methylation*
- *less feasible for heteroarenes*

[1] Yu, J-Q. et al., *J. Am. Chem. Soc*. **2006**, *128*, 78-79. [2] Li, C-J. et al., *J. Am. Chem. Soc*. **2008**, *130*, 2900-2901. [3] Carretero, J. C. et al., *J. Org. Chem*. **2011**, *76*, 9525-9530. [4] Yu, J-Q. et al., *J. Am. Chem. Soc*. **2007**, *129*, 3510-3511. [5] Nakamura, E. et al., *Org. Lett*. **2011**, *13*, 3232-3234. [6] Shi, Z-J. et al., *Angew. Chem. Int. Ed*. **2013**, *52*, 2063-2067. [7] Liao, X. et al., *Angew. Chem. Int. Ed*. **2016**, *55*, 9743-9747. [8] Dixon, D. J. et al., *Chem. Soc. Rev*., **2021**, *50*, 5517-5563.

1 背景介绍

Classic Minisci protocols for methylation

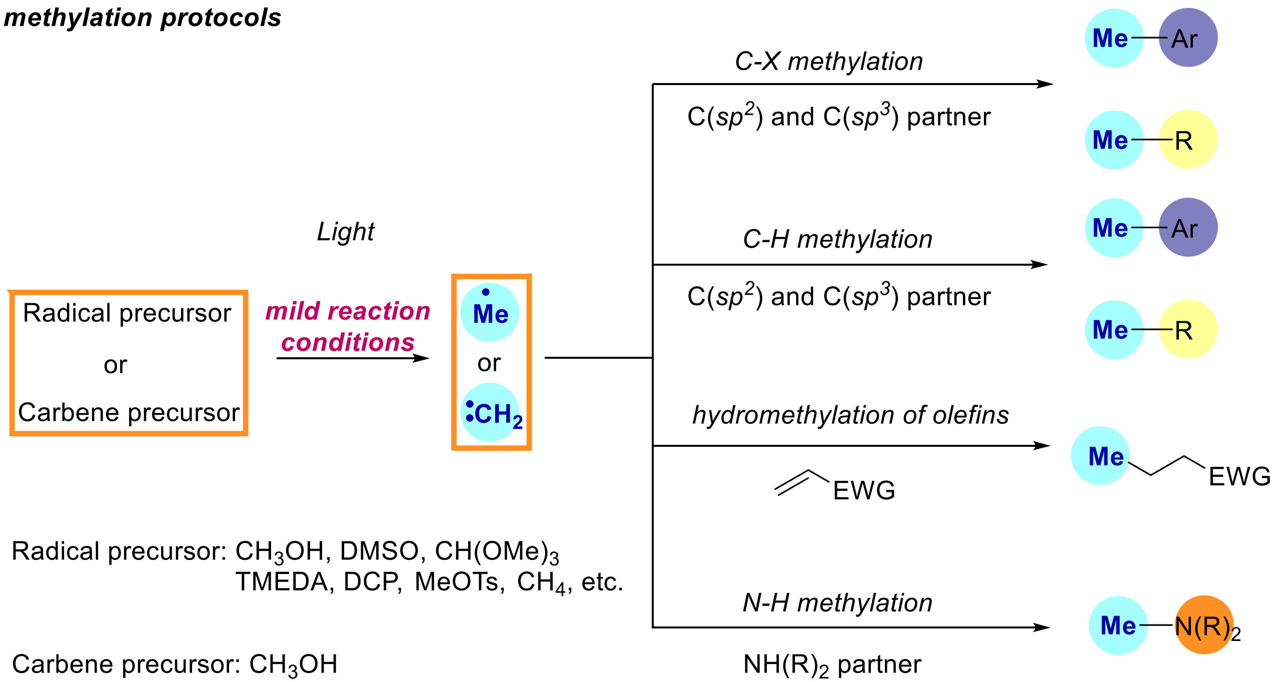


Radical precursor: CH_3COOH, DMSO, TBHP, etc.

Limitations

- *high temperature*
- *strong oxidants*
- *limited substrate scope*

Light promoted methylation protocols



Radical precursor: CH_3OH, DMSO, $CH(OMe)_3$
TMEDA, DCP, MeOTs, CH_4, etc.

Carbene precursor: CH_3OH

[1] Minisci,F. et al., *Tetrahedron Lett*. **1968**, *9*, 5609-5612. [2] Minisci, F. et al., *Tetrahedron Lett*. **1970**, *11*, 15-16. [3] Minisci, F. et al., *Tetrahedron* **1971**, *27*, 3575-3579. [4] Shafirovich, V. et al., *J. Phys. Chem. B*. **2009**, *113*, 12773-12781. [5] Kasai, H. et al., *Bioorg, Med. Chem. Lett*. **2010**, *20*, 260-265. [6] Li, C-J. et al., *ACS Catal*. **2020**, *10*, 6248-6253. [7] Wu, X. et al., *Nat Commun*. **2021**, *12*, 5365-5374.

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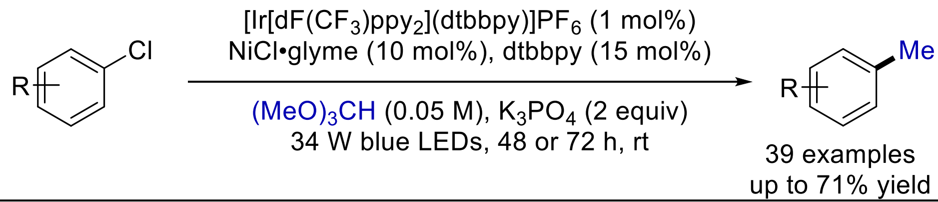
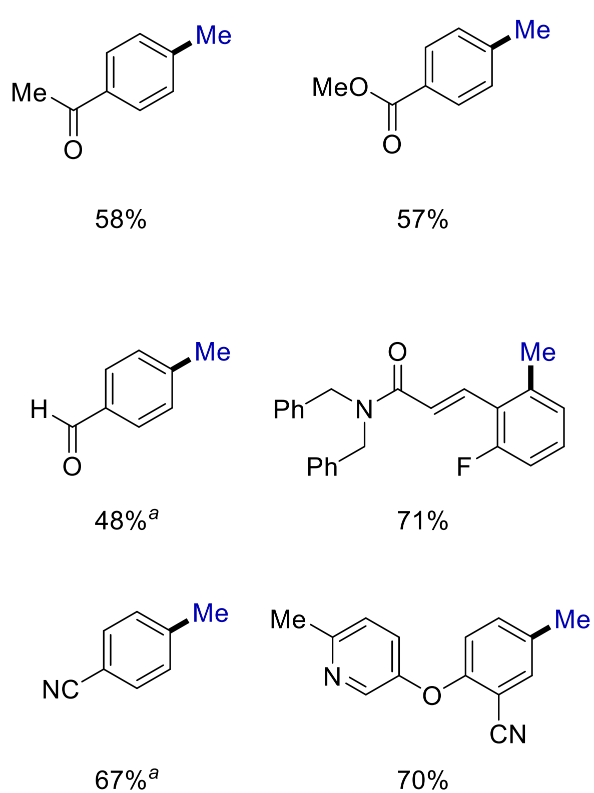
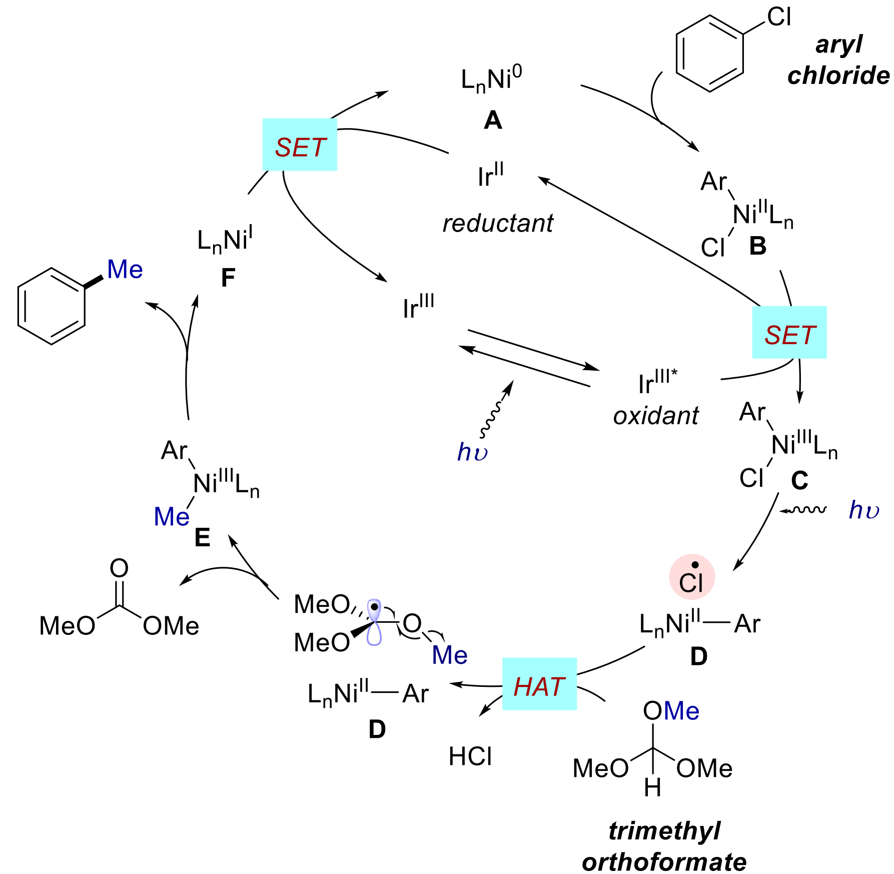
2.1 C-X键甲基化反应

2.1.1 芳香环C(sp^2)-X键的甲基化







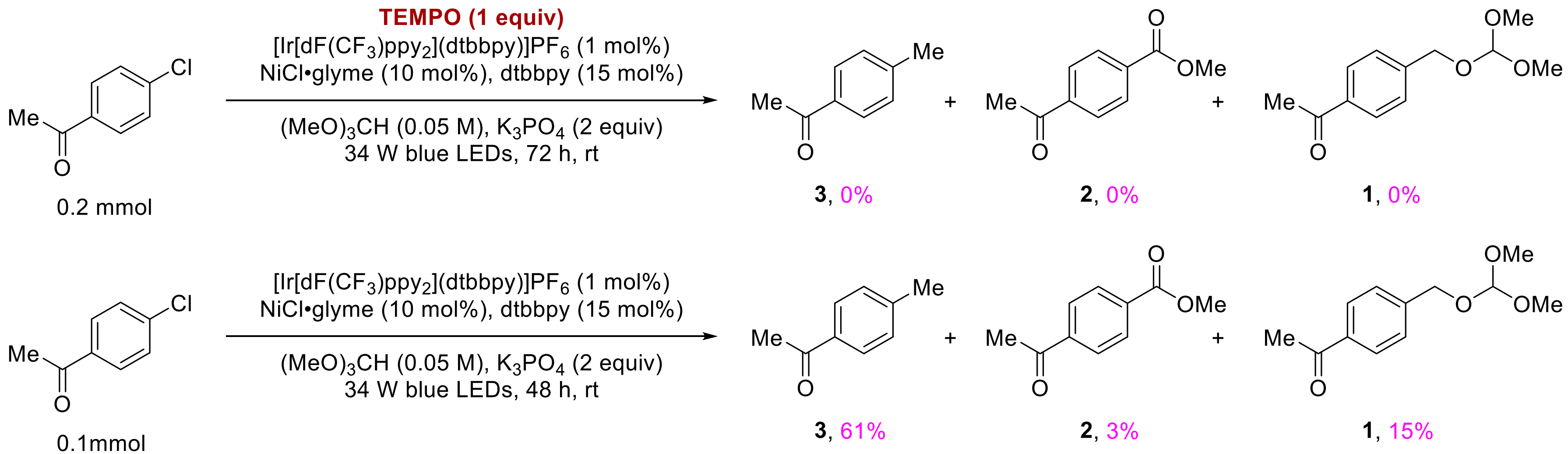
[a] ^{19}F NMR yield.

Doyle, A. G. et al., *J. Am. Chem. Soc.* **2020**, *142*, 7683-7689.

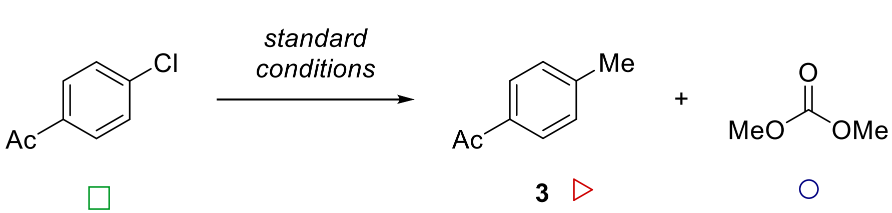
2.1 C-X键甲基化反应

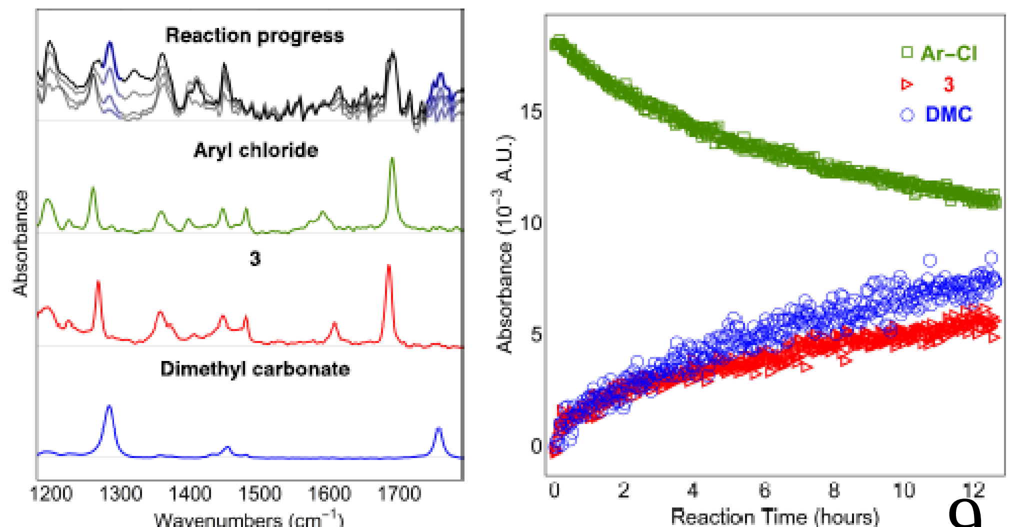
机理研究

A. Radical trapping experiment



B. ReactIR monitoring



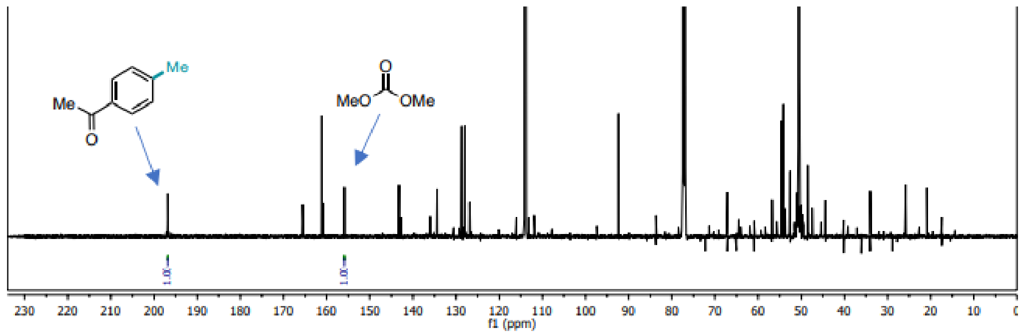


Doyle, A. G. et al., *J. Am. Chem. Soc.* **2020**, *142*, 7683-7689.

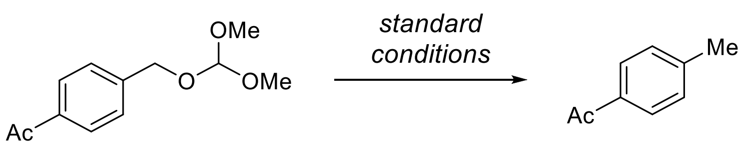
2.1 C-X键甲基化反应

机理研究

C. Quantitative ^{13}C NMR experiment

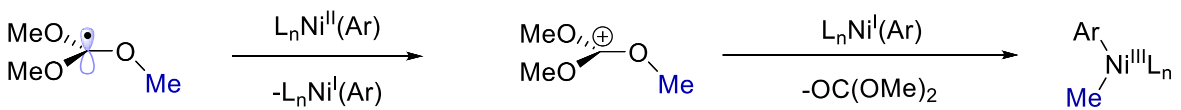


D. Hydrodealkoxylation experiment



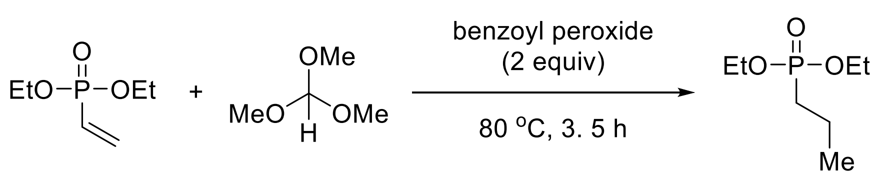
1 **3**, 0%

E. Alternative mechanistic pathway



E

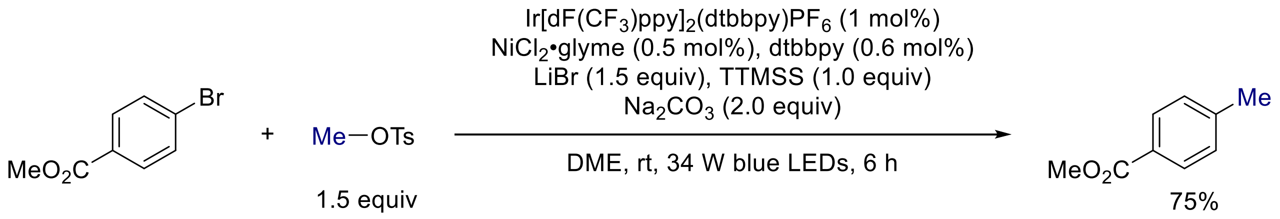
F. Methyl radical generation and trapping in the absence of Ni



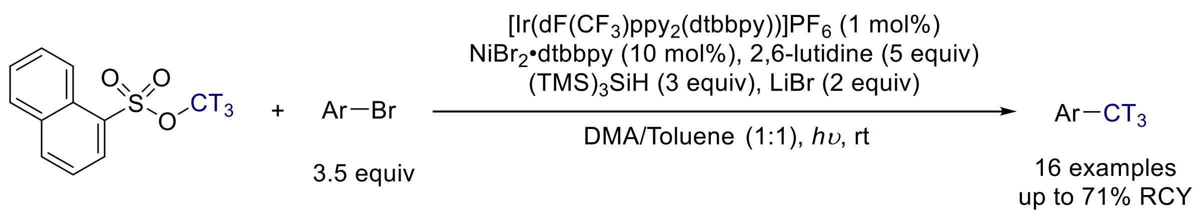
0.05 M 22%

Doyle, A. G. et al., *J. Am. Chem. Soc.* **2020**, *142*, 7683-7689.

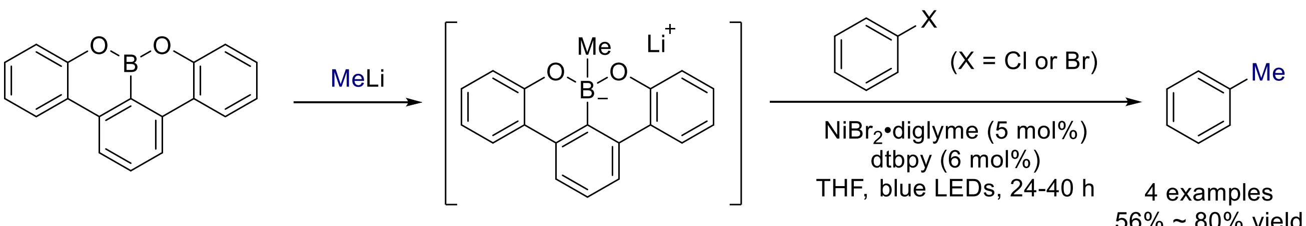
2.1 C-X键甲基化反应



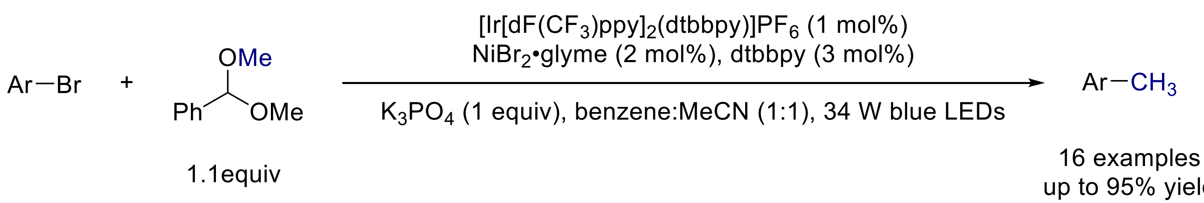
MacMillan, D. W. C. et al., *J. Am. Chem. Soc*. **2016**, *138*, 8084-8087.



MacMillan, D. W. C. et al., *Nature* **2020**, *589*, 542-547.



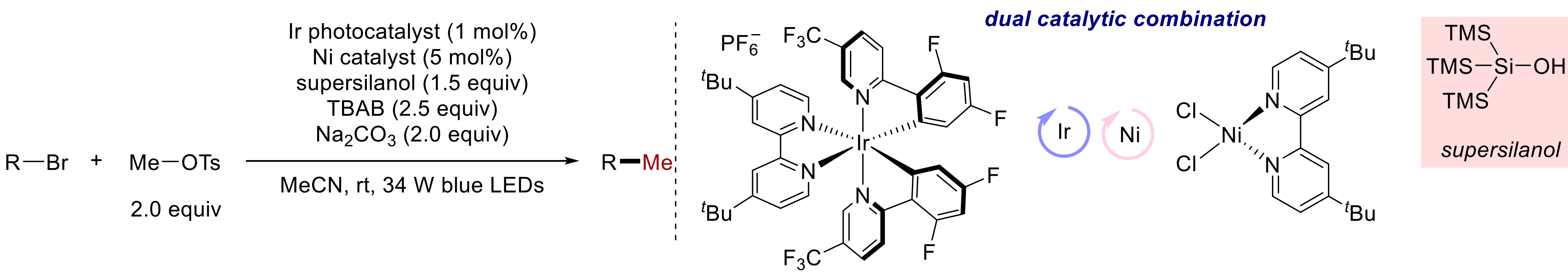
Ohmiya, H. et al., *J. Am. Chem. Soc*. **2020**, *142*, 9938-9943.

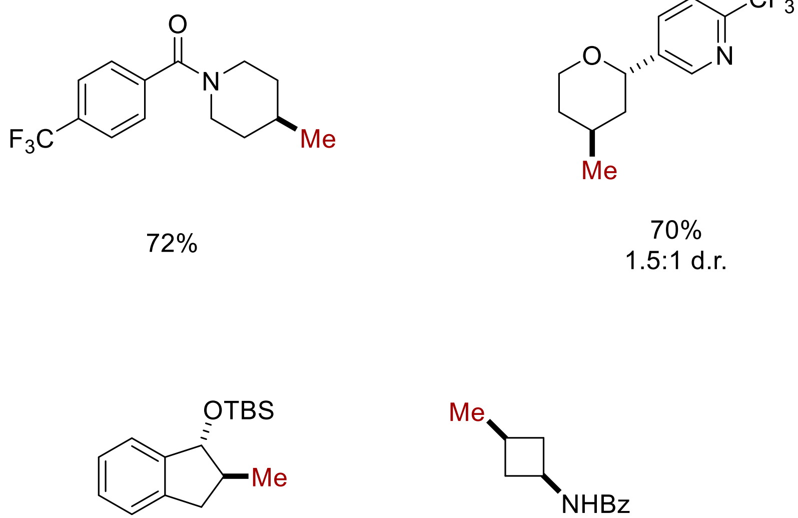


Doyle, A. G. et al., *J. Am. Chem. Soc*. **2022**, *144*, 1045-1055.

2.1 C-X键甲基化反应

2.1.2 烷烃C(*sp*³)-X键甲基化反应



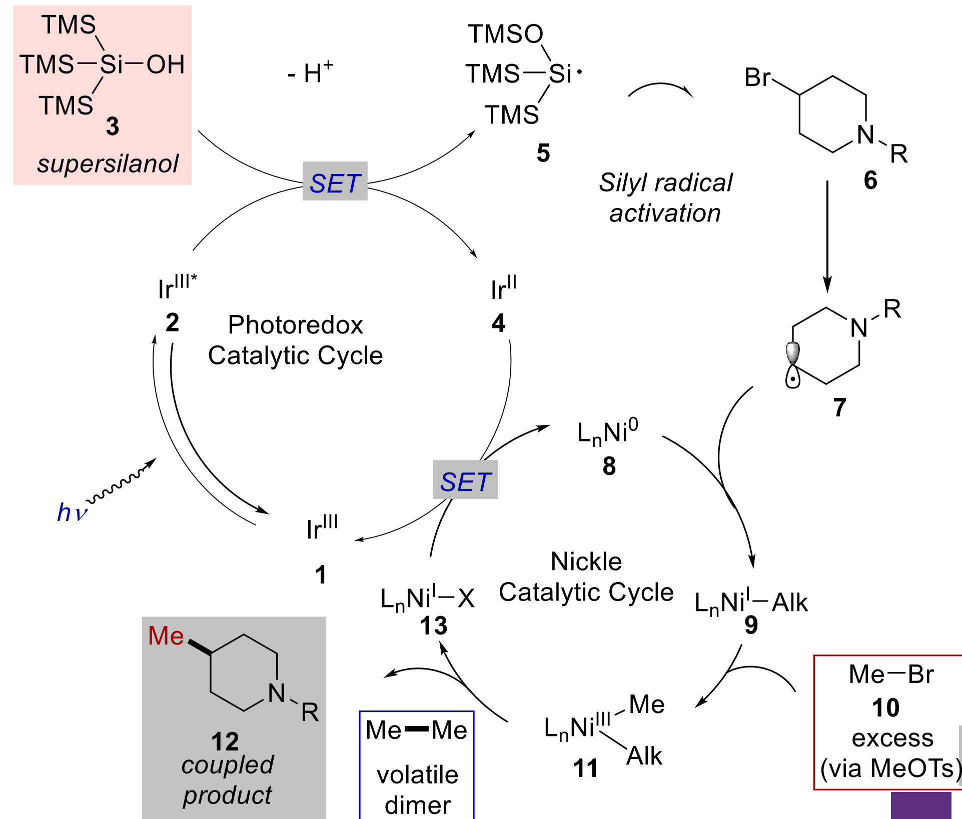


72%

70%
1.5:1 d.r.

42%
>20:1 d.r.

68%
1.2:1 d.r.



MacMillan, D. W. C. et al., *J. Am. Chem. Soc.* **2018**, *140*, 17433-17438.

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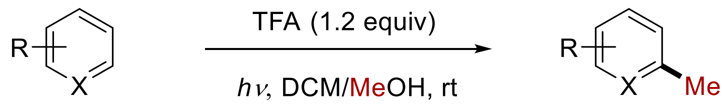
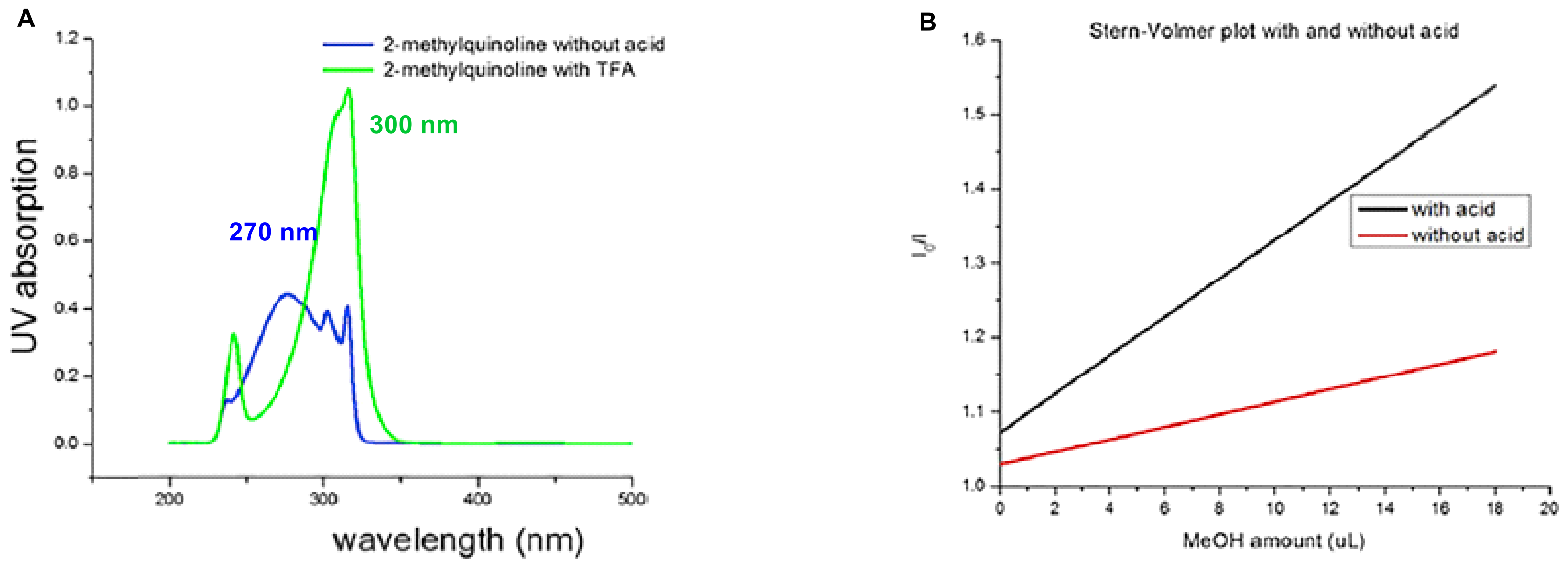
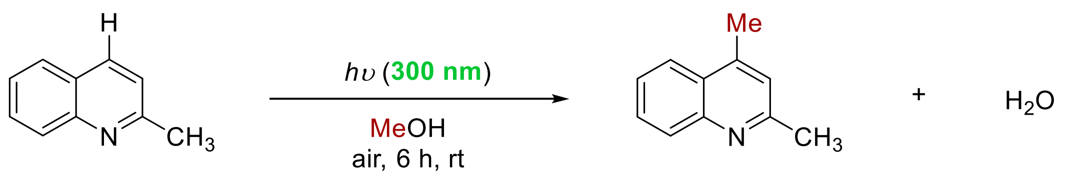
2.2 C-H键甲基化反应

2.2.1 杂芳环C(sp^2)-H键甲基化







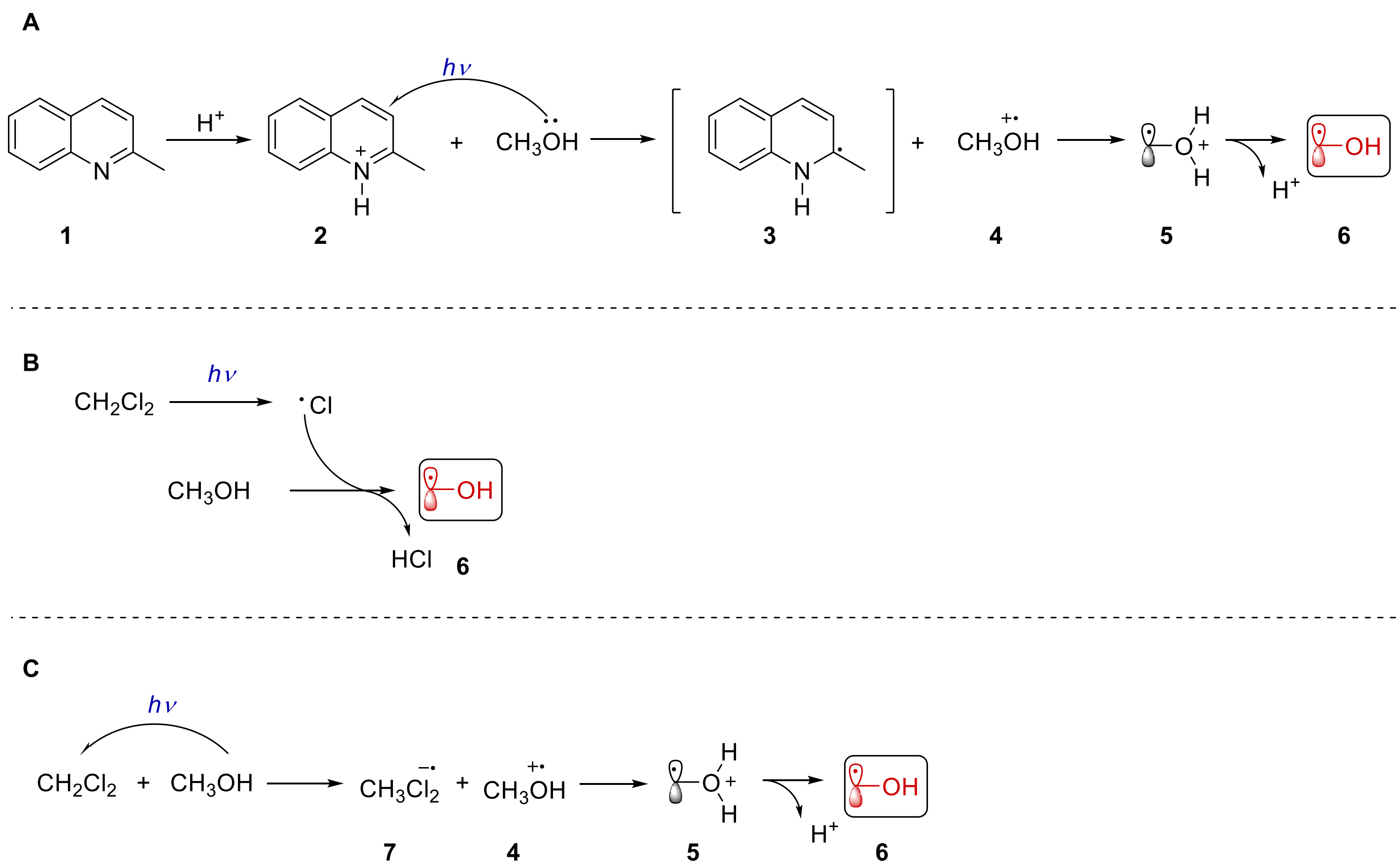
with TFA (1.2 equiv)	29% yield
without TFA	trace

Li, C-J. et al., *Chem* **2017**, *2*, 688-702.

2.2 C-H键甲基化反应

反应机理

1 Generation of hydroxymethyl radical

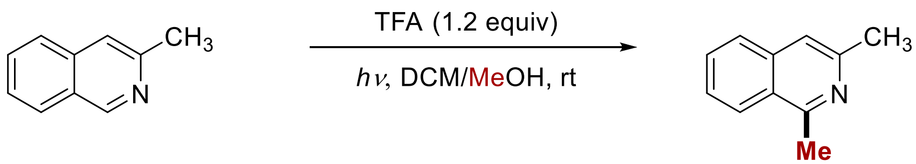


Li, C-J. et al., *Chem* **2017**, *2*, 688-702.

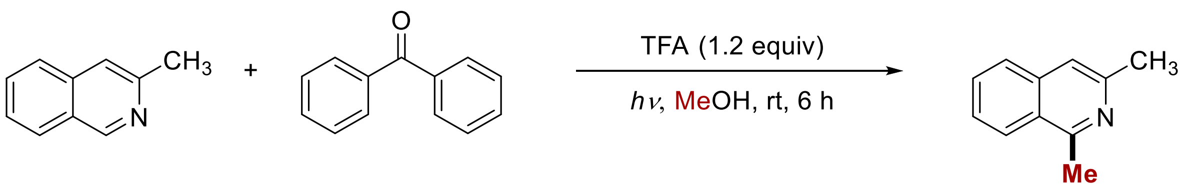
2.2 C-H键甲基化反应

反应机理

The substrates which involve benzophenone as additive of CH_2Cl_2

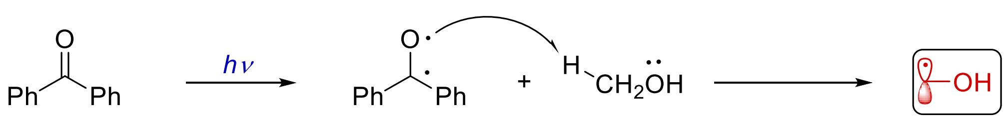


0.1 mmol　　0%



0.1 mmol　　2 equiv　　60%

D

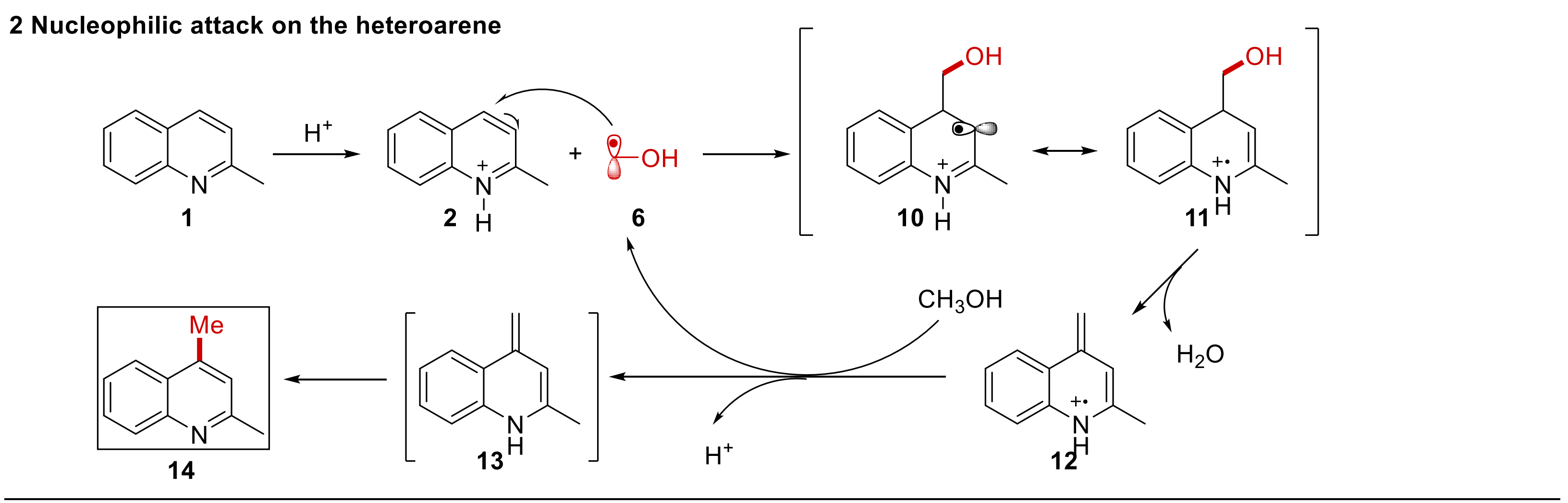


8　　**9**　　**6**

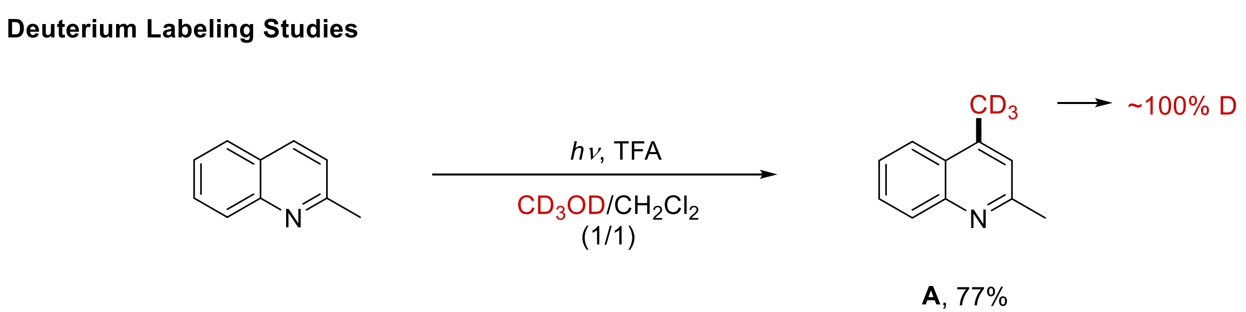
Li, C-J. et al., *Chem* **2017**, *2*, 688-702.

2.2 C-H键甲基化反应

反应机理



机理验证

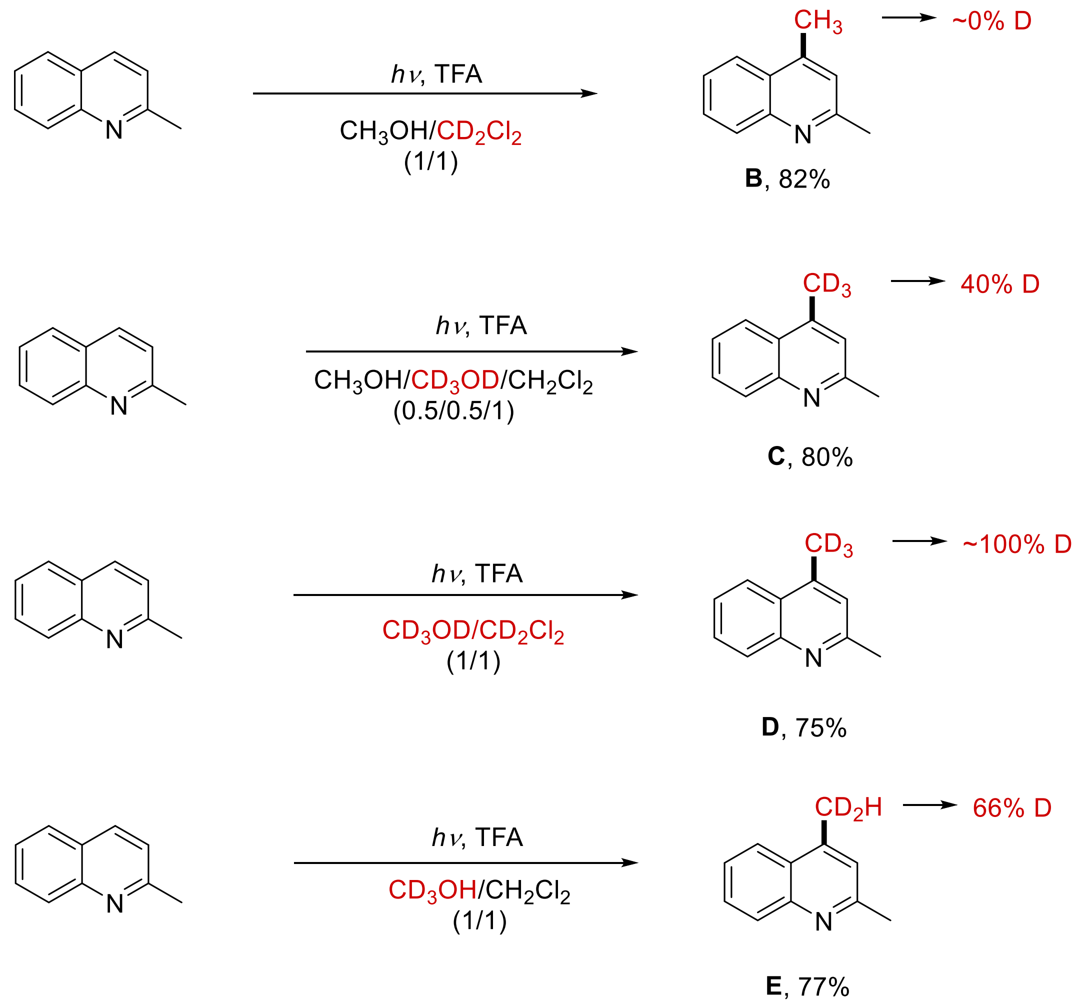


Li, C-J. et al., *Chem* **2017**, *2*, 688-702.

2.2 C-H键甲基化反应

机理验证

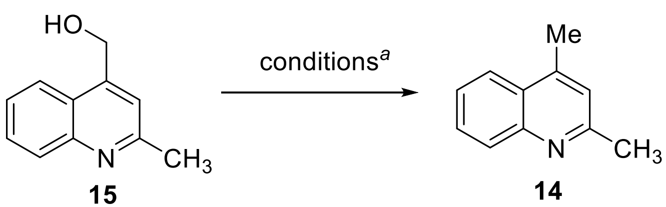
Deuterium Labeling Studies



Li, C-J. et al., *Chem* **2017**, *2*, 688-702.

2.2 C-H键甲基化反应

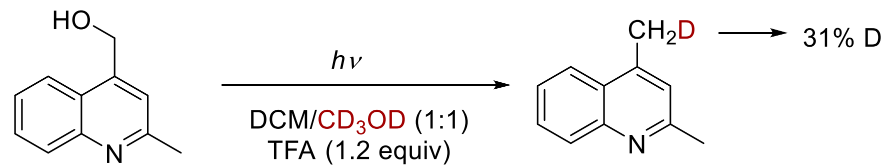
机理验证



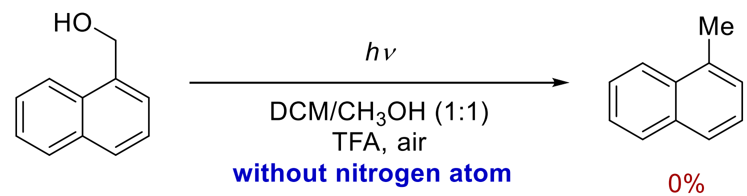
entry	light	TFA	DCM	MeOH	yield
1	**no**	yes	1 mL	1 mL	0%
2	yes	yes	1 mL	1 mL	74%
3	yes	**no**	1 mL	1 mL	28%
4	yes	yes	2 mL	**0 mL**	0%
5	yes	yes	**0 mL**	2 mL	47%

[a] Conditions: **15** (0.1 mmol) and TFA (0.12 mmol) for 6 h in the specified solvent in air unless otherwise specified. The yield was determined by 1H NMR with 1,3,5-trimethoxybenzene as the internal standard.

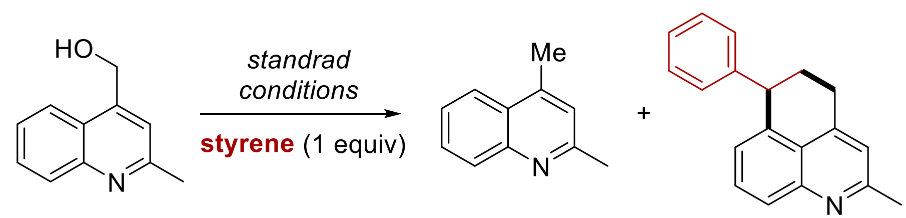
a. deuterium labeling experiment



b. the importance of nitrogen atom



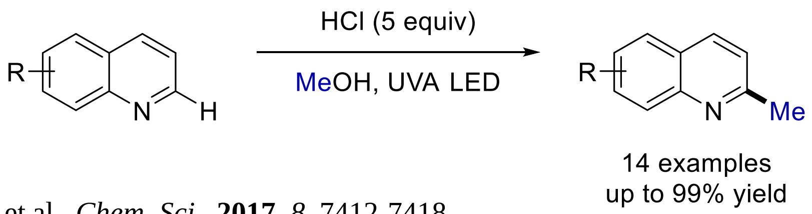
c. radical trapping experiment



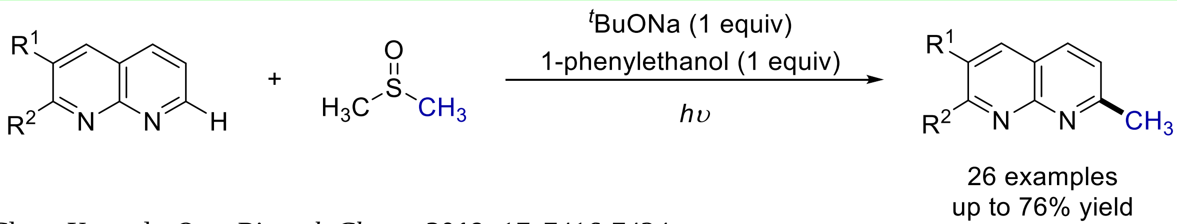
0.1 mmol 1.2 : 1

Li, C-J. et al., *Chem* **2017**, *2*, 688-702.

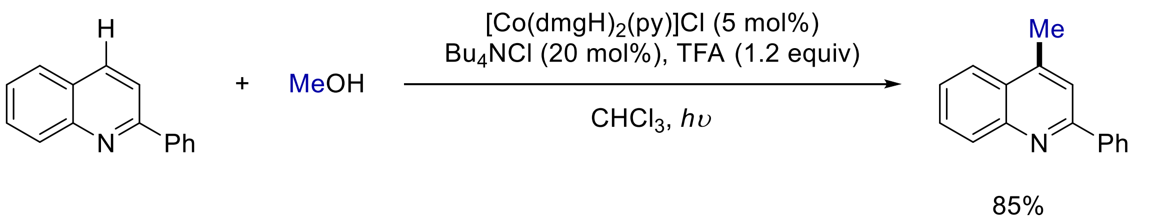
2.2 C-H键甲基化反应



Barriault, L. et al., *Chem. Sci*., **2017**, *8*, 7412-7418.

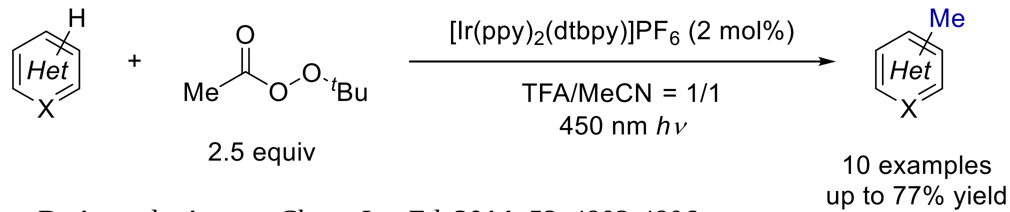


Chen, X. et al., *Org. Biomol. Chem*., **2019**, *17*, 7416-7424.

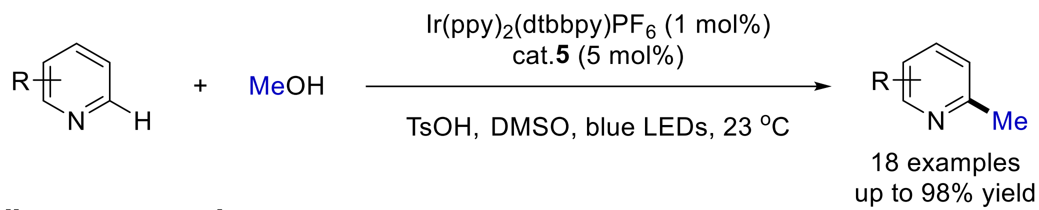


Li, C-J. et al., *Nat. Commun*. **2021**, *12*, 4010-4018.

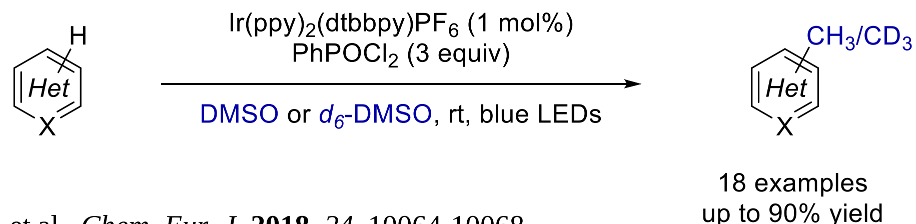
2.2 C-H键甲基化反应



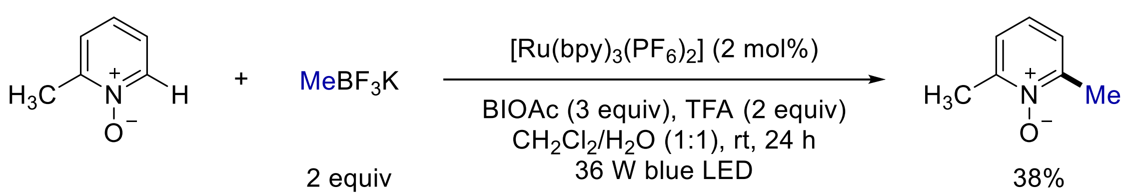
DiRocco, D. A. et al., *Angew. Chem. Int. Ed.* **2014**, *53*, 4802-4806.



MacMillan, D. W. C. et al., *Nature* **2015**, *525*, 87-90.

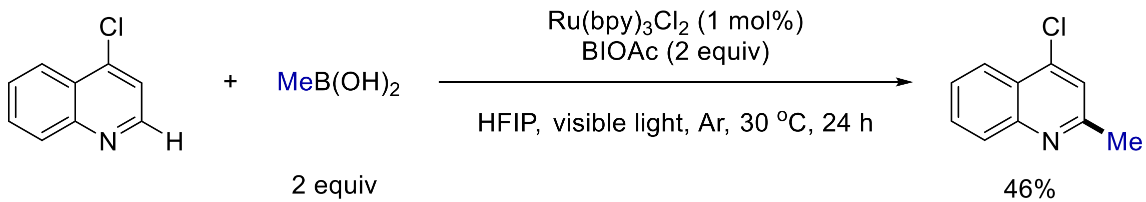


Glorius, F. et al., *Chem. Eur. J.* **2018**, *24*, 10064-10068.

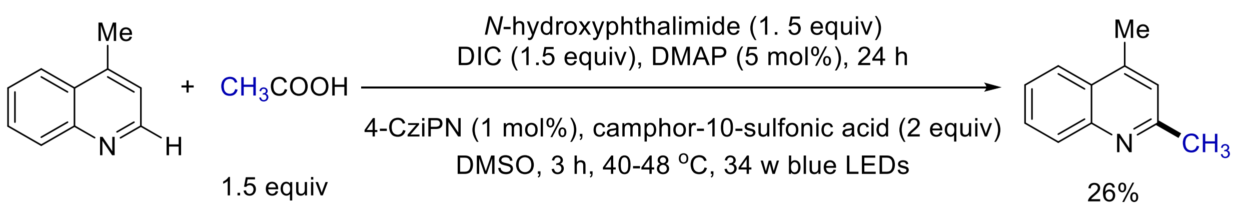


Xu, H. et al., *J. Org. Chem.* **2017**, *82*, 2059-2066.

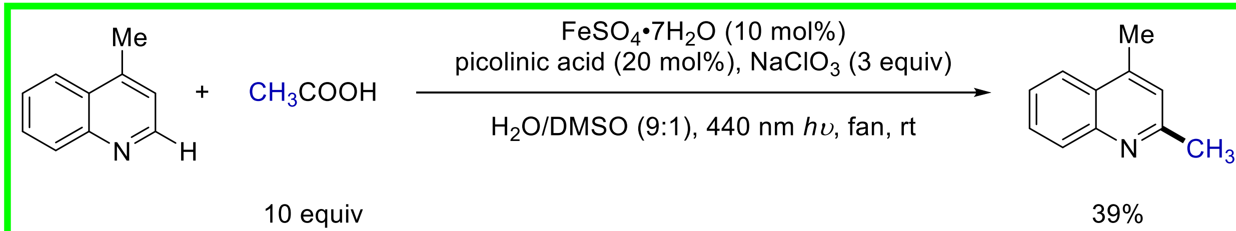
2.2 C-H键甲基化反应



Chen, G. et al., *Chem. Sci.*, **2016**, *7*, 6407-6412.

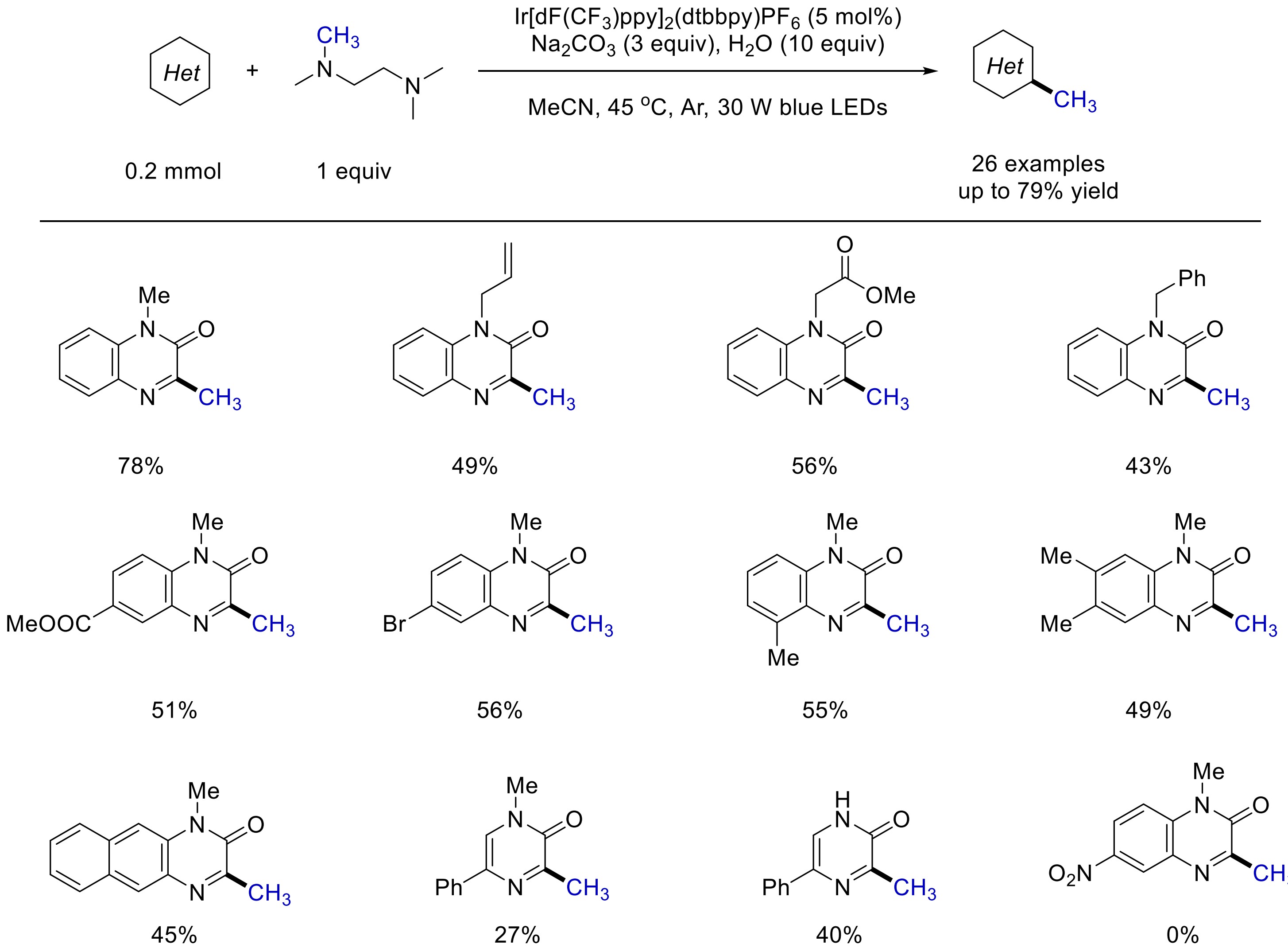


Dhar, T. G. M. et al., *J. Org. Chem.* **2018**, *83*, 3000-3012.



Jin, J. et al., *Org. Lett.* **2019**, *21*, 4259-4265.

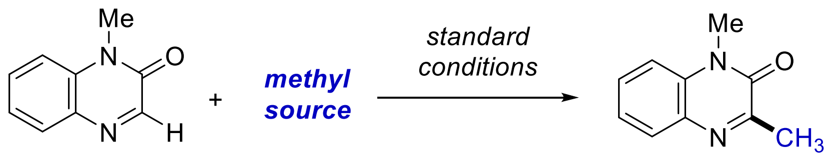
2.2 C-H键甲基化反应



Yang, H. et al., *J. Org. Chem.* **2021**, *86*, 11905-11914.

2.2 C-H键甲基化反应

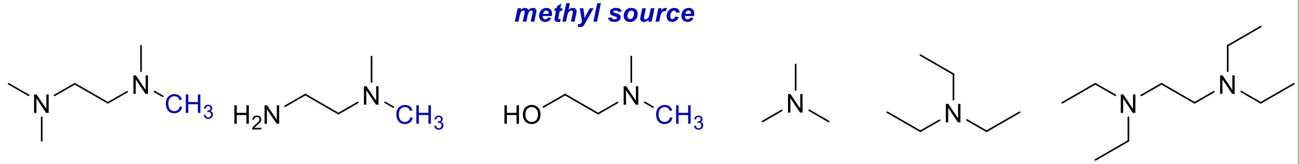
机理研究



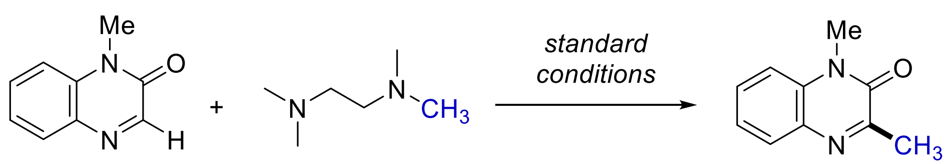
1a 2 3a

Control experiments

methyl source



2	2a	2b	2c	2d	2e	2f
yield of **3a**	78%	38%	26%	nr	nr	nr

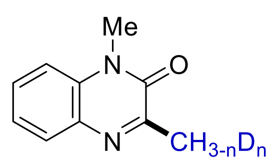


1a 2a 3a

variations

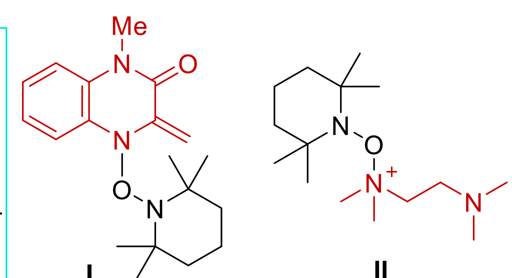
adding **2 equiv. TEMPO**	not detected
in dark	0%
no photocatalyst	0%

adding **10 equiv. D_2O** instead of 10 equiv. H_2O



detected by HRMS and [1]H NMR

(n = 0, 1, 2, 3)



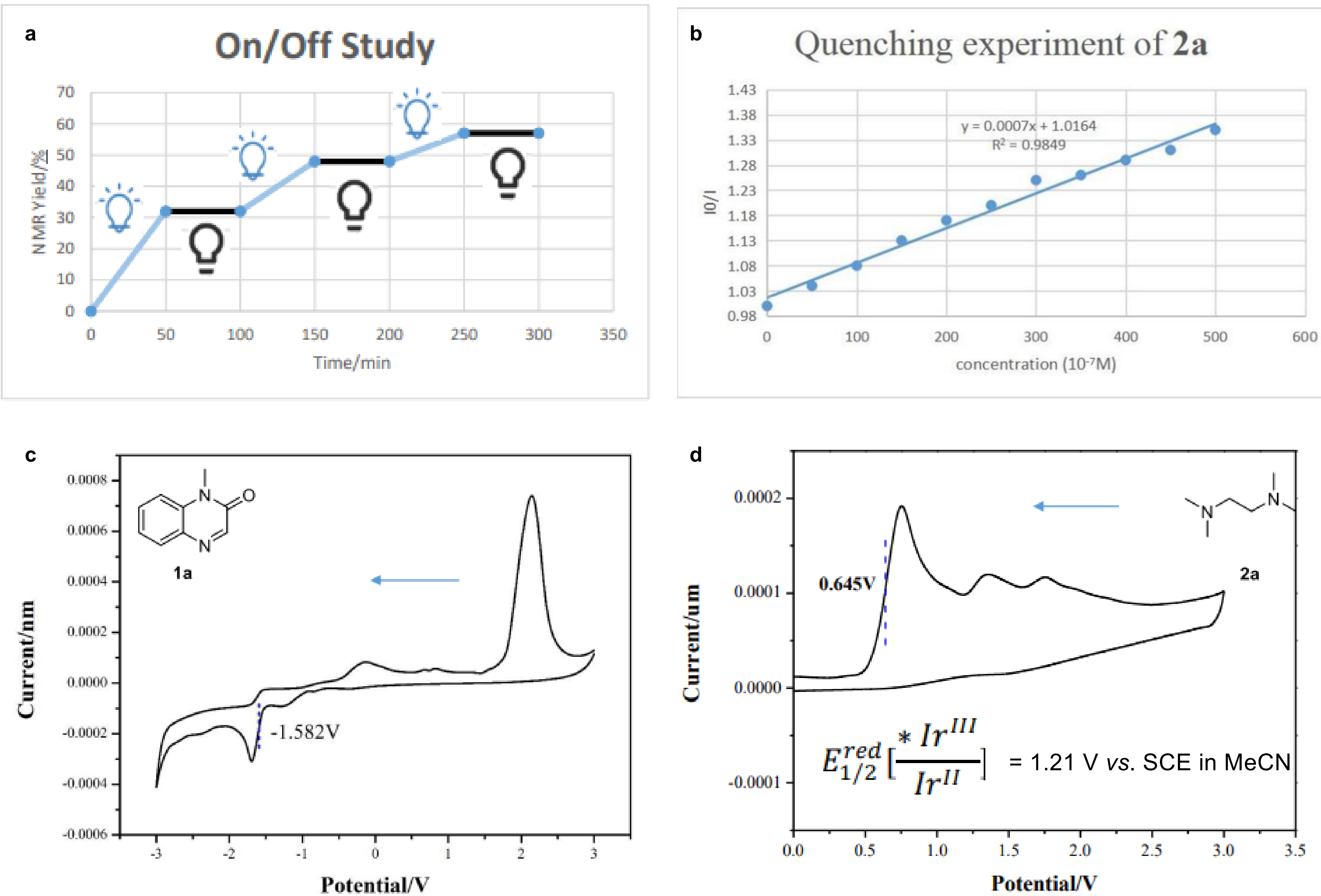
I **II**

detected by HRMS

Yang, H. et al., *J. Org. Chem.* **2021**, *86*, 11905-11914.

2.2 C-H键甲基化反应

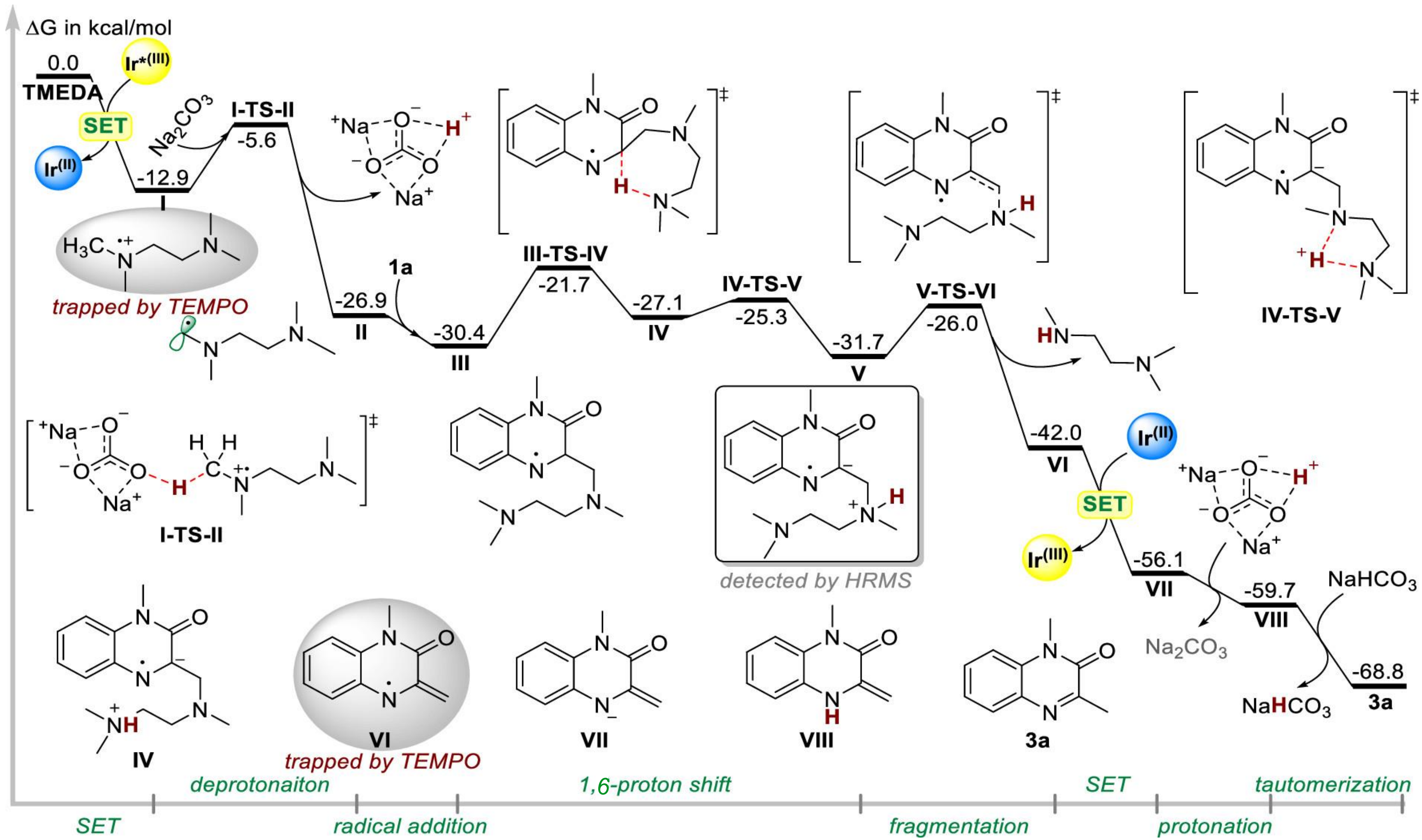
机理研究



Yang, H. et al., *J. Org. Chem.* **2021**, *86*, 11905-11914.

2.2 C-H键甲基化反应

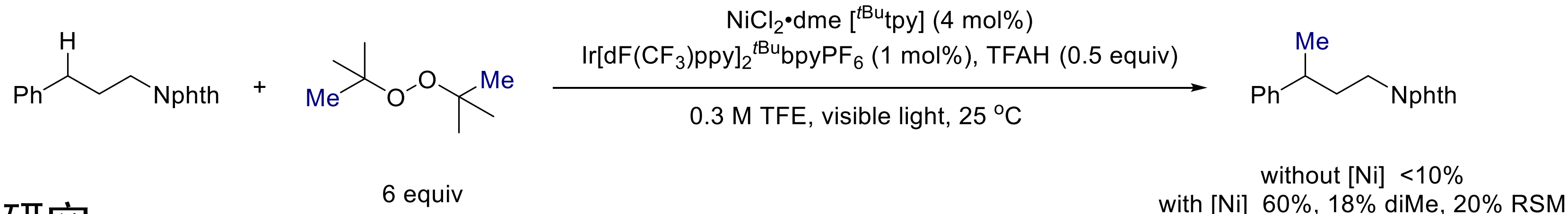
DFT计算



Yang, H. et al., *J. Org. Chem*. **2021**, *86*, 11905-11914.

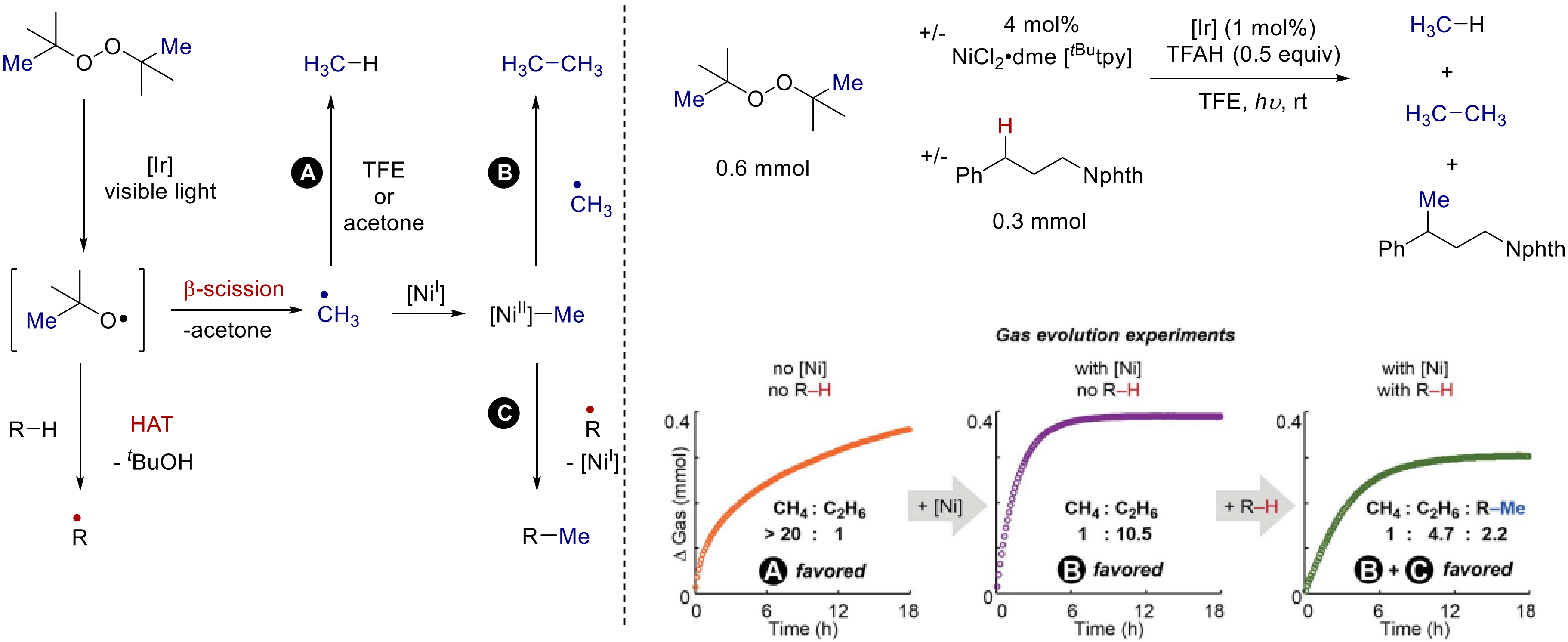
2.2 C-H键甲基化反应

2.2.2 烷烃C(sp^3)-H键甲基化反应



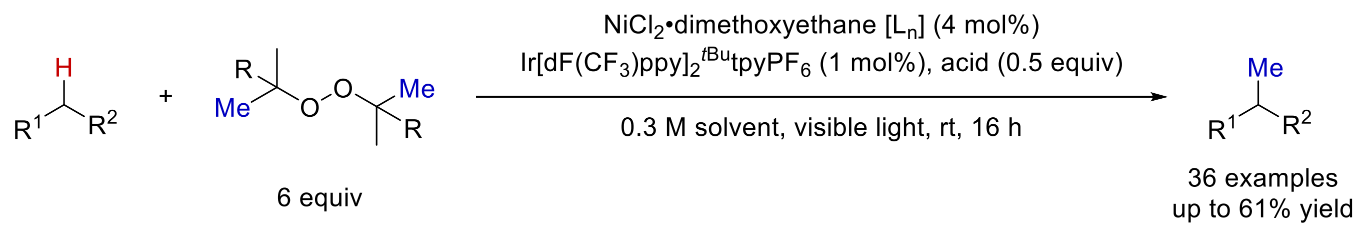
机理研究

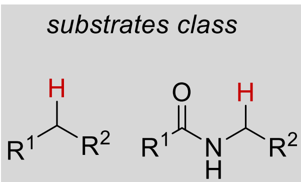
a. Role of nickel catalyst in promoting C-C coupling

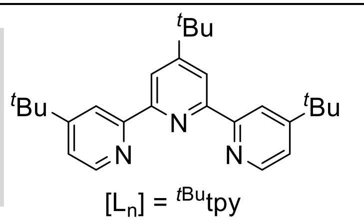


Stahl, S. S. et al., *Science* **2021**, *372*, 398-403.

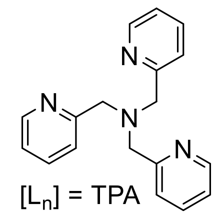
2.2 C-H键甲基化反应

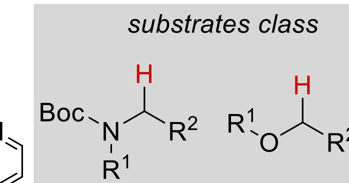




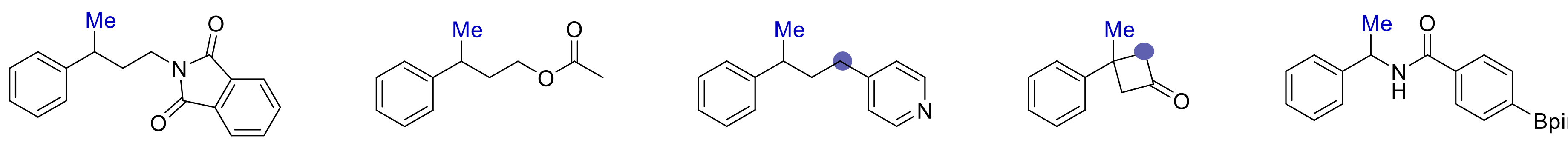


A		**B**	***condition***	**C**		**D**
DTBP	*or*	DCP	*peroxide*	DTBP	*or*	DCP
TFE		MeCN	*solvent*	TFE		MeCN
TFAH		$B(OH)_3$	*acid*	-		$MeB(OH)_2$



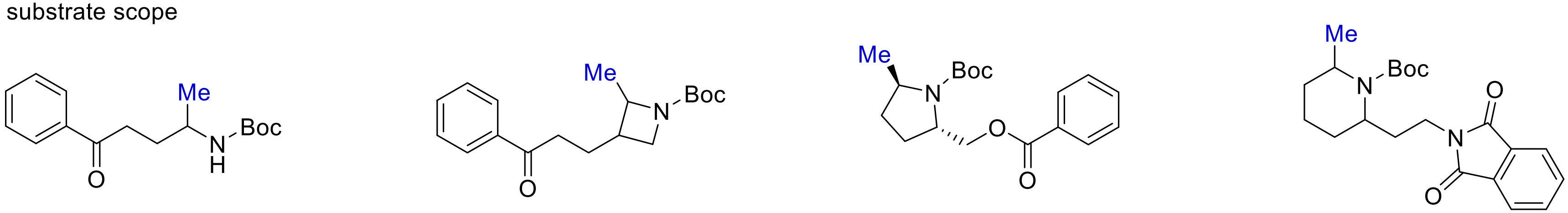


i. Benzylic substrate scopes



59% (**A**) 59% (**A**)[a] 52% (**B**)[b] 28% (**A**)[a] 60% (**B**)[c]

ii. α-Amino substrate scope



40% (**C**)[ab] 31% (**C**)[d] 3.8:1 d.r. 44% (**C**)[bd] 5.4:1 d.r. 55% (**D**)[d] 4.1:1 d.r.

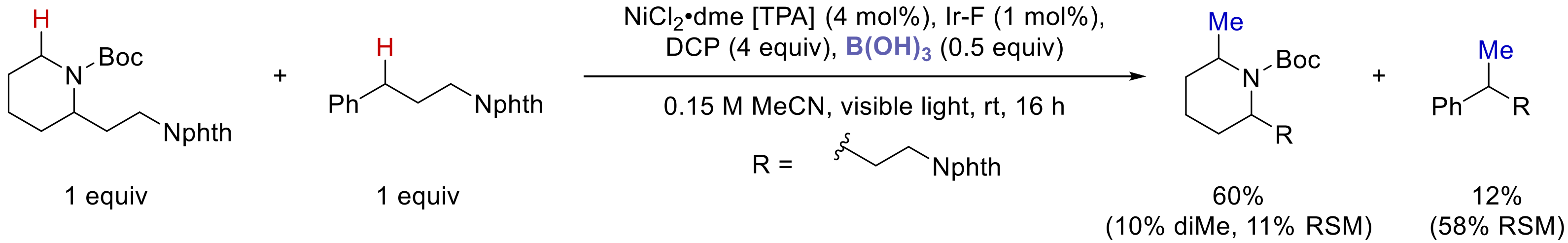
[a] 0.6 M concentration. [b] 0.5 equiv $MeB(OH)_2$ used as acid. [c] 1:1 MeCN:DMSO used as solvent. [d] 0.15 M concentration.

Stahl, S. S. et al., *Science* **2021**, *372*, 398-403.

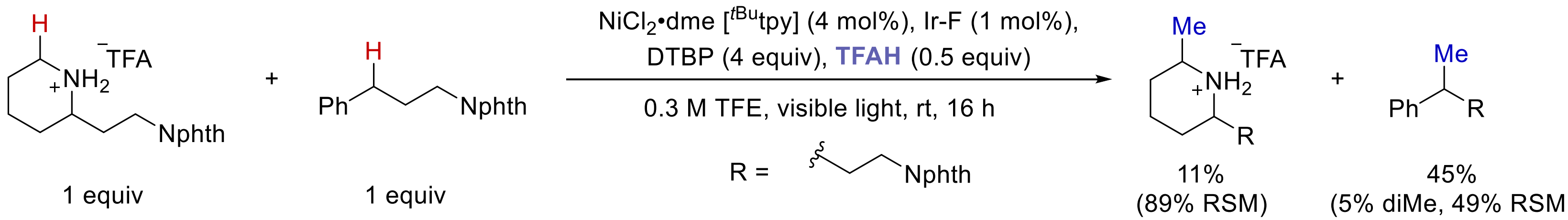
2.2 C-H键甲基化反应

A. Effect of protonation on C(sp^3)-H methylation

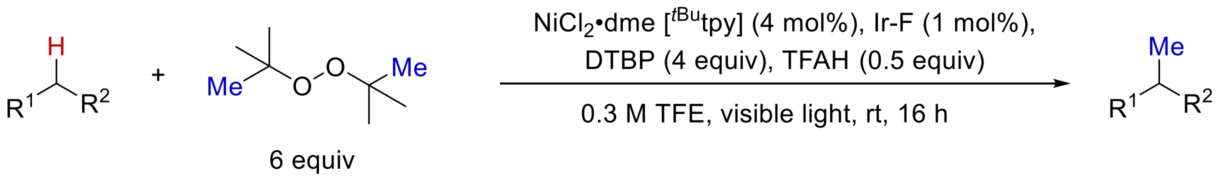
innate selectivity

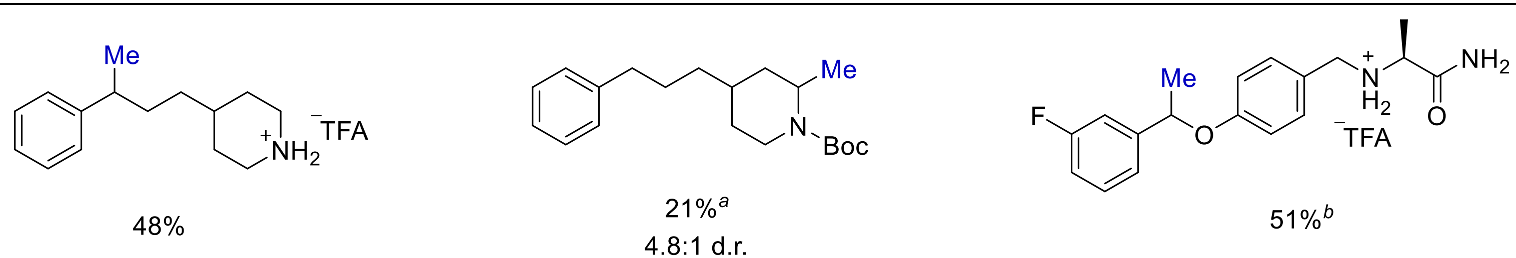


Brønsted acid modification



B. Chemoselective C(sp^3)-H methylation of amine salts

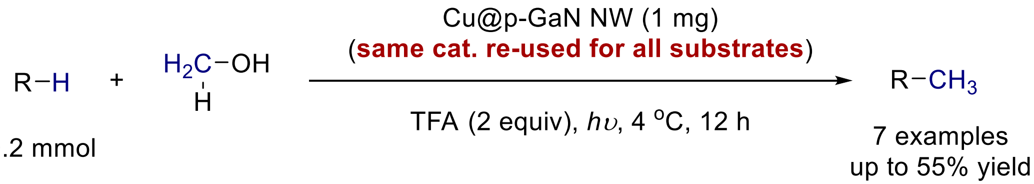


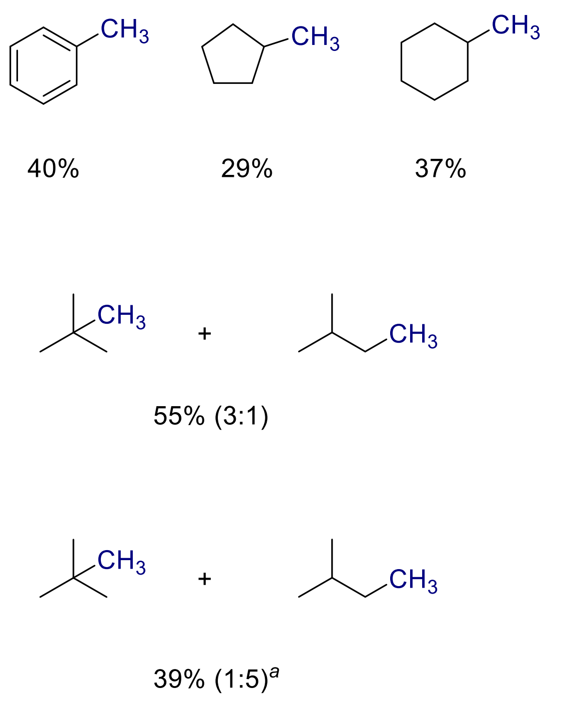


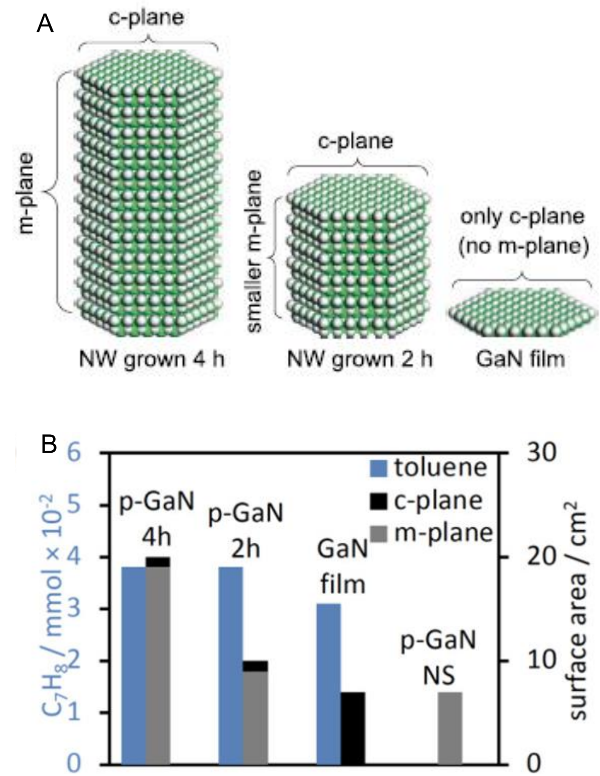
[a] No acid added; used 3 equiv of DCP, TPA as the ligand, and 0.15 M MeCN as the solvent.
[b] 4 equiv of DCP and MeCN used in place of DTBP and TFE.

Stahl, S. S. et al., *Science* **2021**, *372*, 398-403.

2.2 C-H键甲基化反应





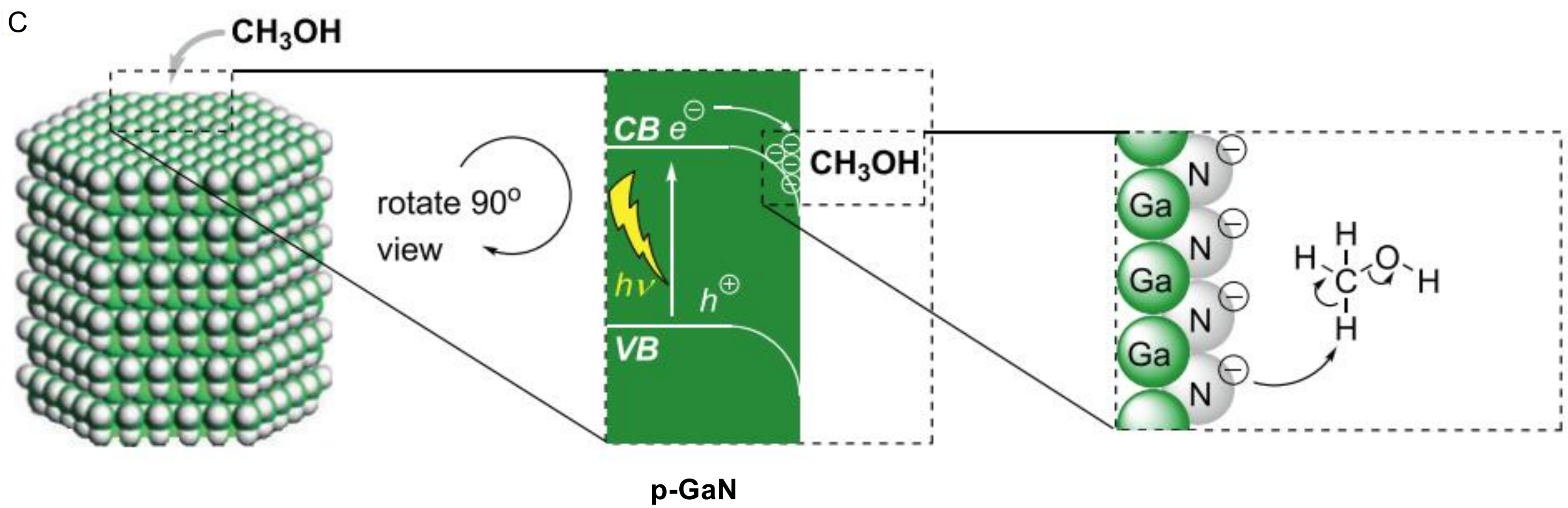


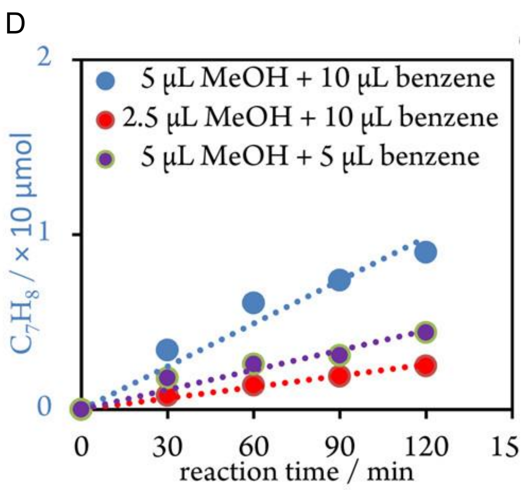
[a] Reaction was conducted at 90 °C.

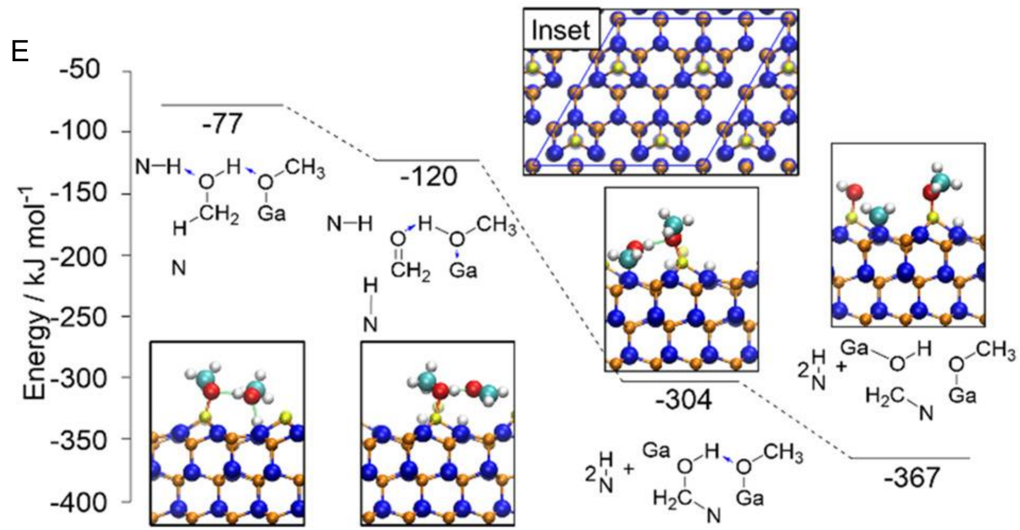
Li, C-J et al., *Chem* **2019**, *5*, 858-867.
Li, C-J. et al., *ACS Catal*. **2020**, *10*, 6248-6253.

2.2 C-H键甲基化反应

机理研究

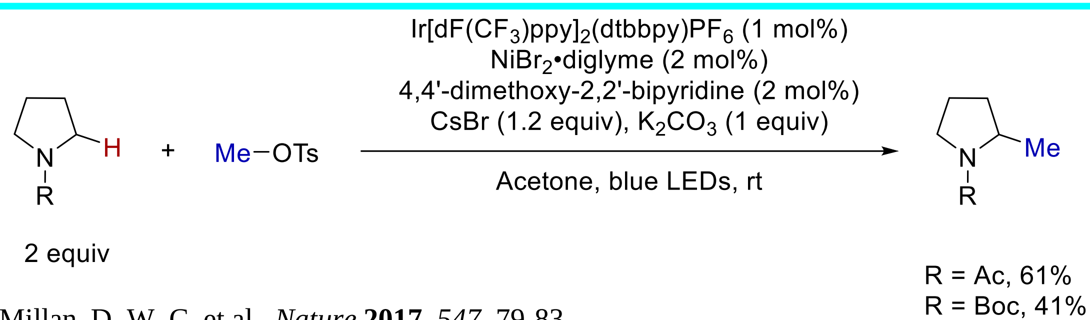




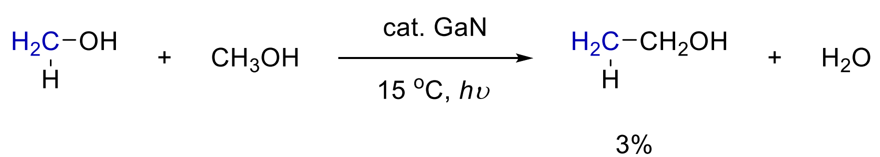


Li, C-J et al., *Chem* **2019**, *5*, 858-867.
Li, C-J. et al., *ACS Catal*. **2020**, *10*, 6248-6253.

2.2 C-H键甲基化反应



MacMillan, D. W. C. et al., *Nature* **2017**, *547*, 79-83.



Li, C-J et al., *Chem* **2019**, *5*, 858-867.

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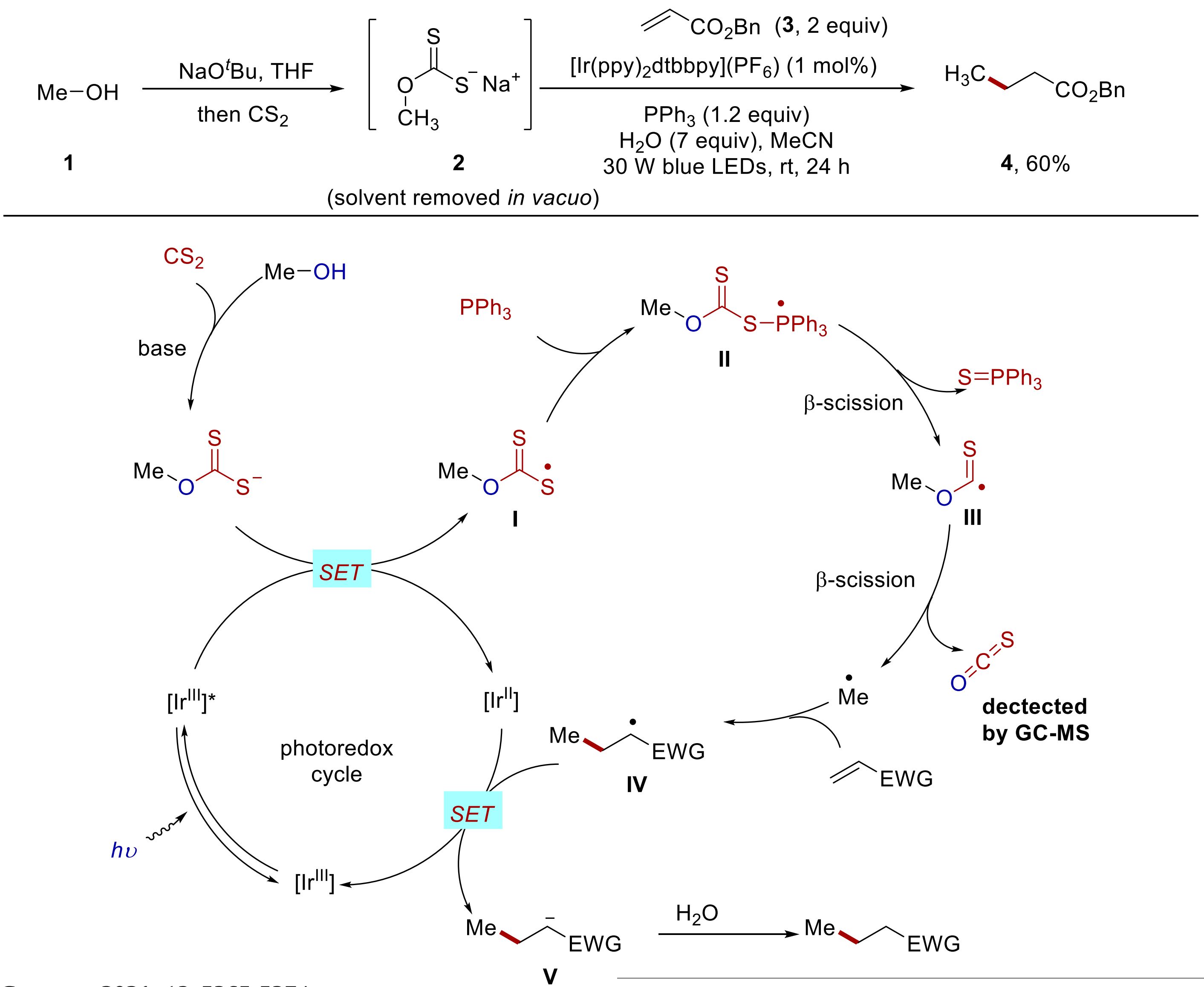
2.3 烯烃的氢甲基化反应

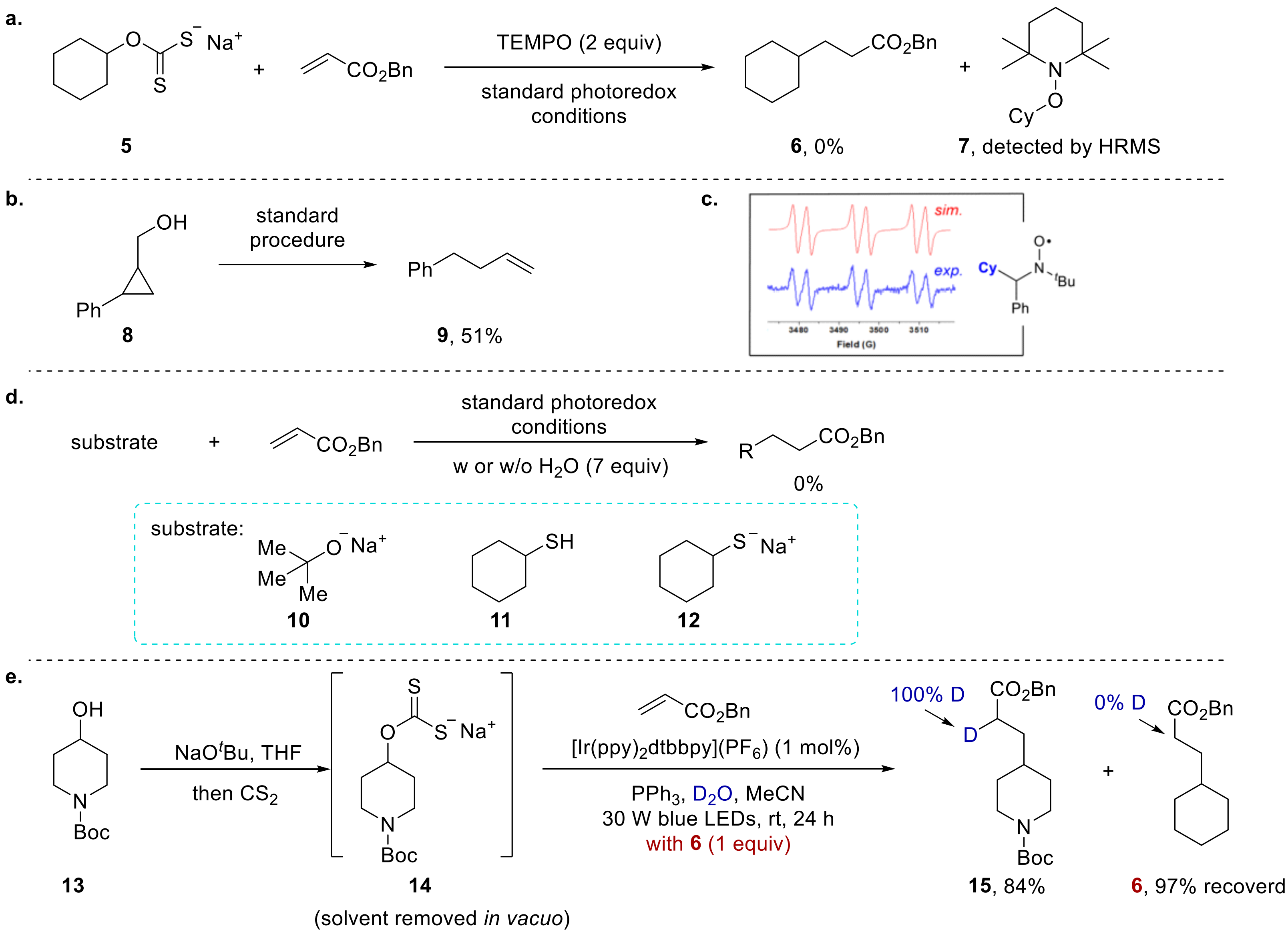
2.3.1 可见光促进烯烃的氢甲基化



Wu, X. et al., *Nat Commun.* **2021**, *12*, 5365-5374.

2.3 烯烃的氢甲基化反应

机理研究

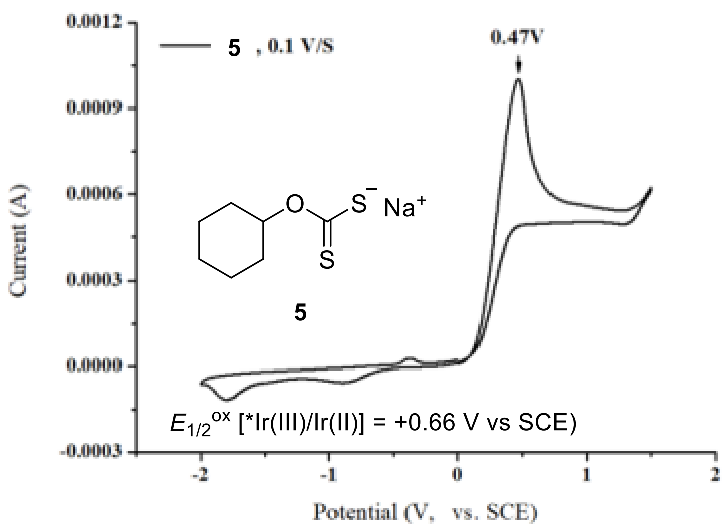


Wu, X. et al., *Nat Commun.* **2021**, *12*, 5365-5374.

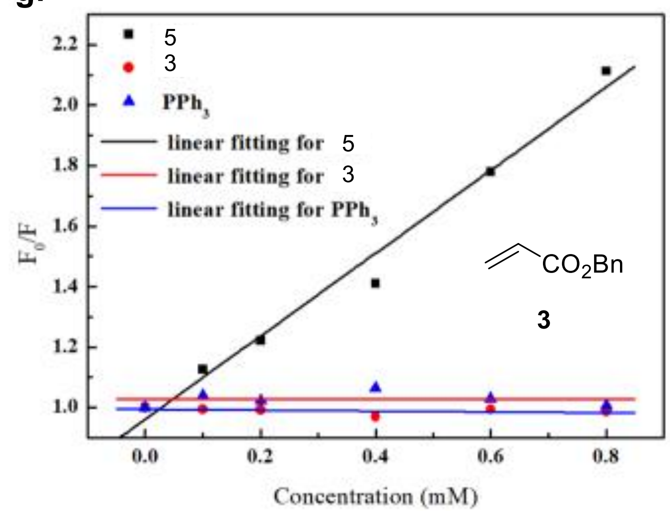
2.3 烯烃的氢甲基化反应

机理研究

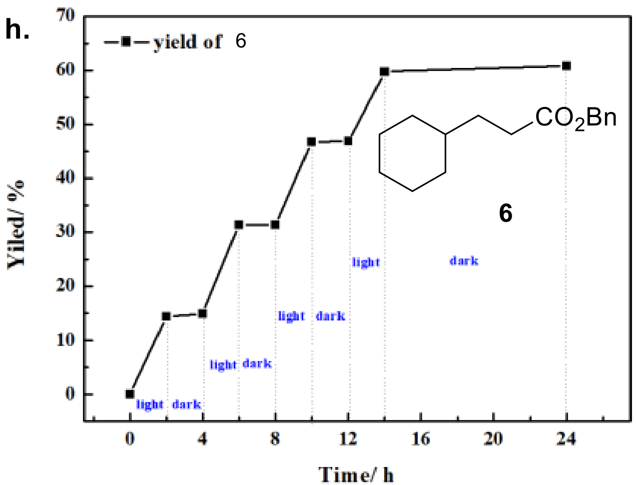
f.



g.

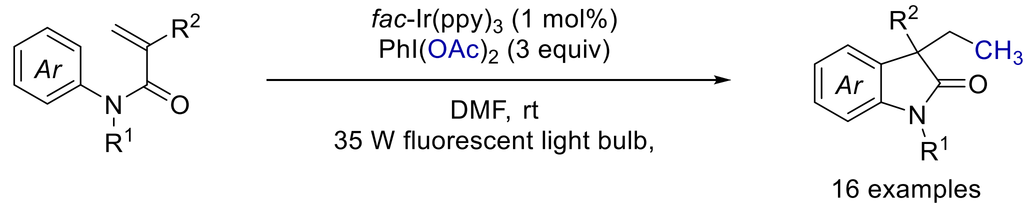


h.

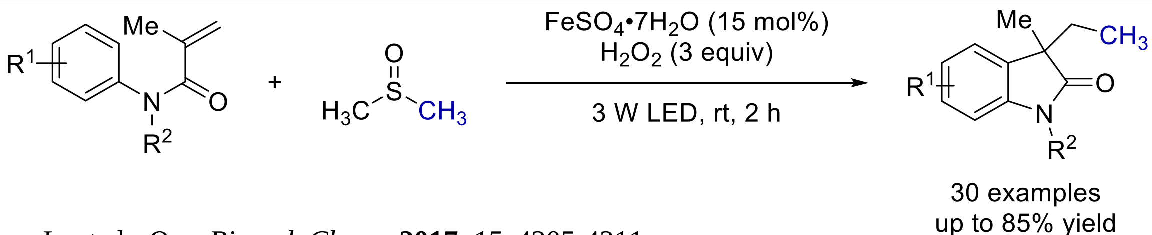


Wu, X. et al., *Nat Commun.* **2021**, *12*, 5365-5374.

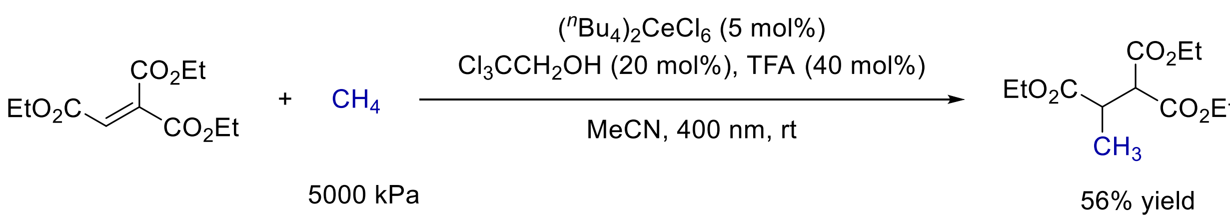
2.3 烯烃的氢甲基化反应



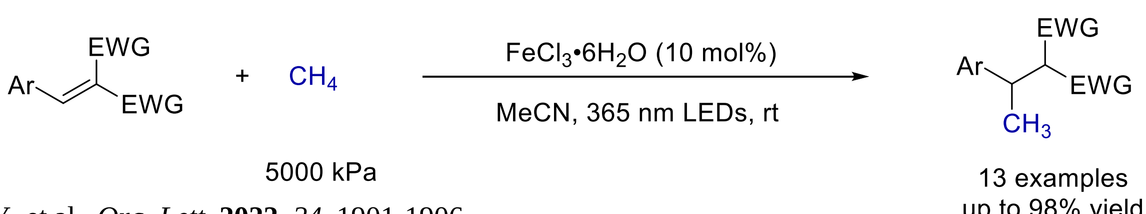
Zhu, C. et al., *Chem. Commun.*, **2013**, *49*, 5672-5674.



Wang, L. et al., *Org. Biomol. Chem.*, **2017**, *15*, 4205-4211.



Zuo, Z. et al., *Science*, **2018**, *361*, 668-672.



Jin, Y. et al., *Org. Lett*. **2022**, *24*, 1901-1906.

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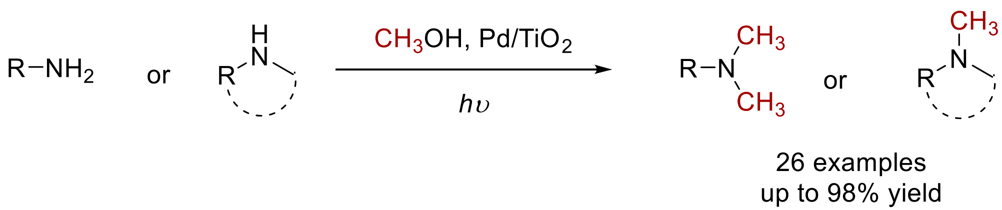
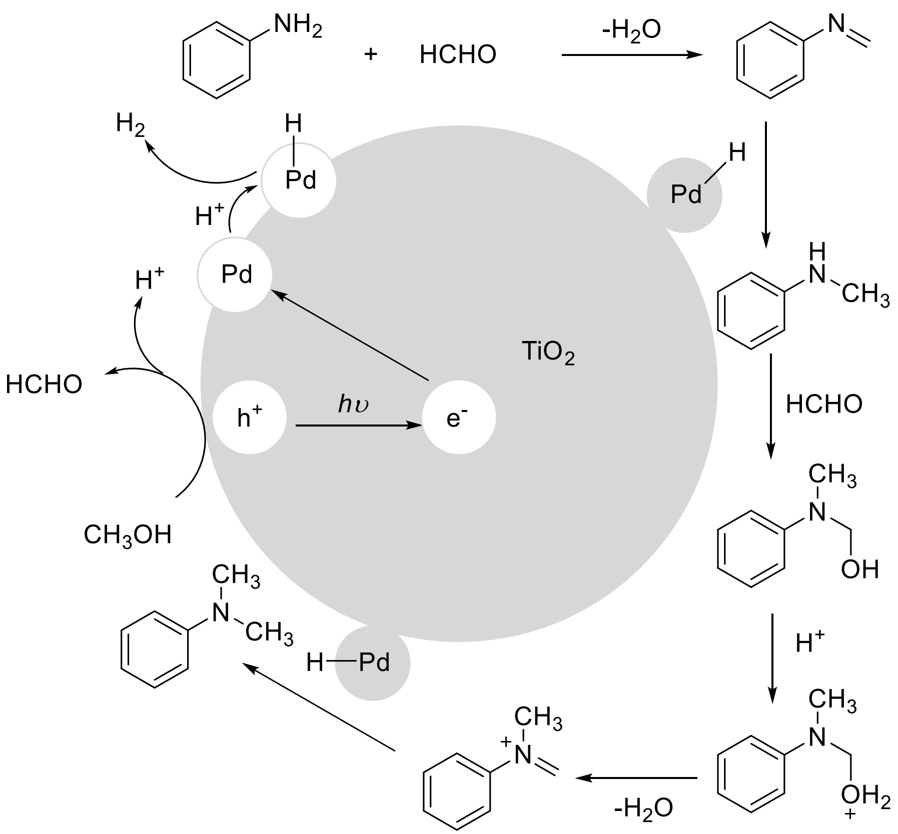
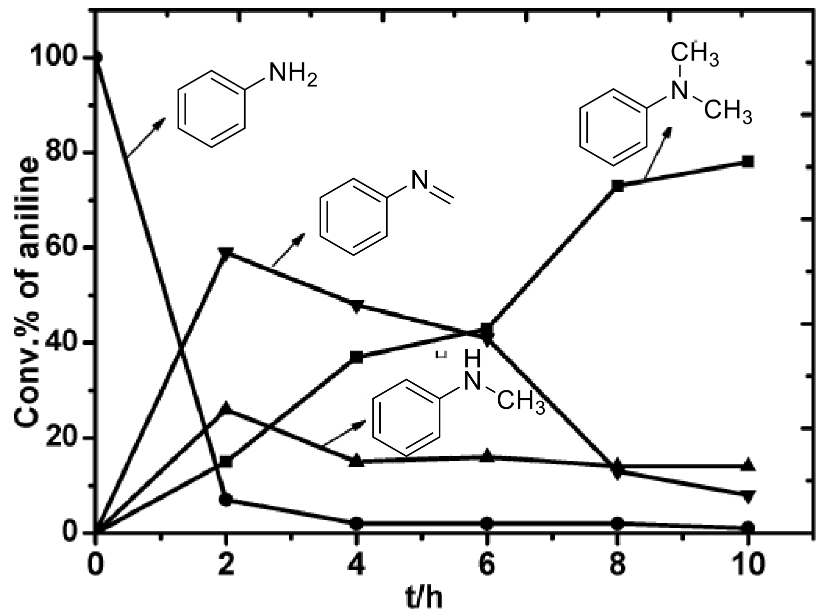
2.5 杂原子甲基化反应

2.5.1 紫外光促进的N原子甲基化反应







Shi, F. et al., *RSC Adv.*, **2015**, *5*, 14514-14521.

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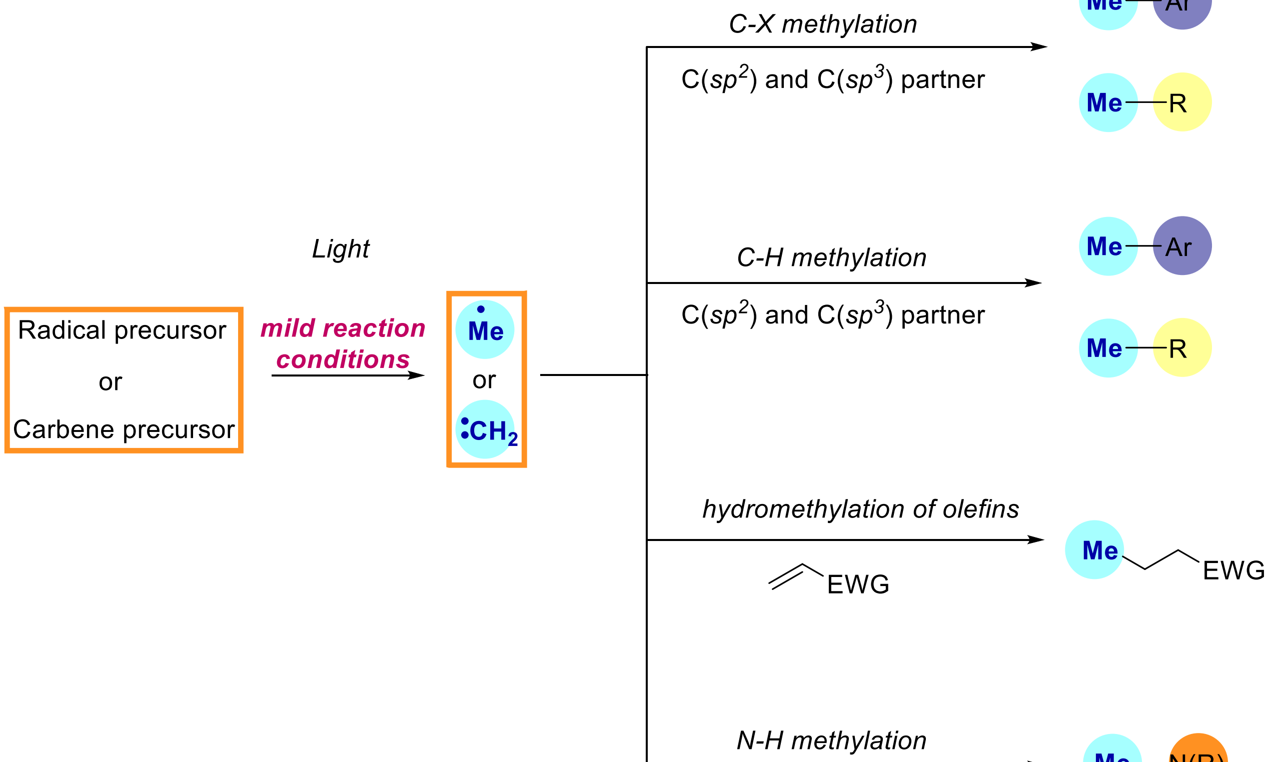
总结

Light promoted methylation



- ***Transition metal catalyst and photoredox-catalyzed methylation***

- ***Light promoted methylation***
- ***Photoredox organocataysis***
- ***Transition metal catalyst and photoredox-catalyzed methylation***

- ***Light promoted hydromethylation***
- ***Transition metal catalyst and photoredox-catalyzed hydromethylation***

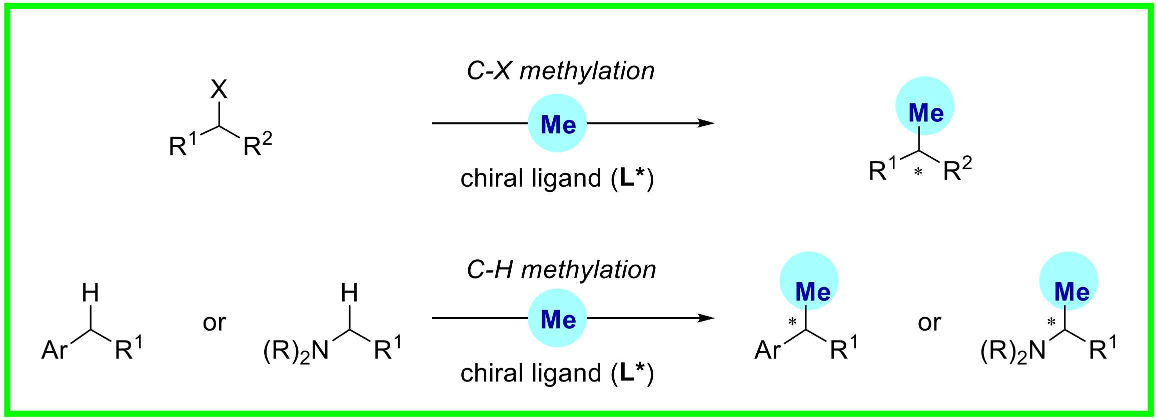
- ***Transition metal catalyst and photoredox-catalyzed methylation***

Radical precursor: CH_3OH, DMSO, $CH(OMe)_3$
TMEDA, DCP, MeOTs, CH_4, etc.

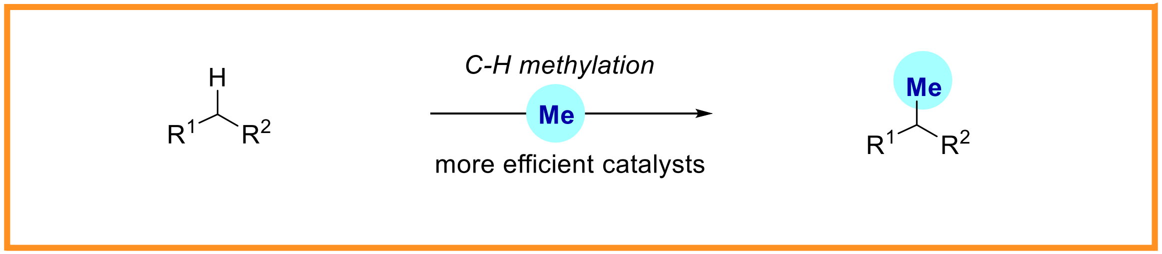
Carbene precursor: CH_3OH

3 总结与展望

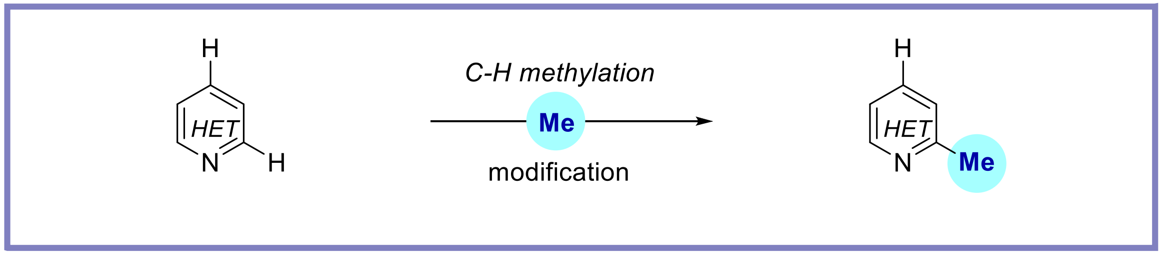
展望



C-X methylation
chiral ligand (L*)
C-H methylation
chiral ligand (L*)
or
or



C-H methylation
more efficient catalysts



C-H methylation
modification
HET
HET

敬请各位老师批评指正！