复旦大学化学系

醇作为烷基自由基前体参与的去氧官能团化反应

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汇报时间：2022.11.04

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- 2-3 SCS过程

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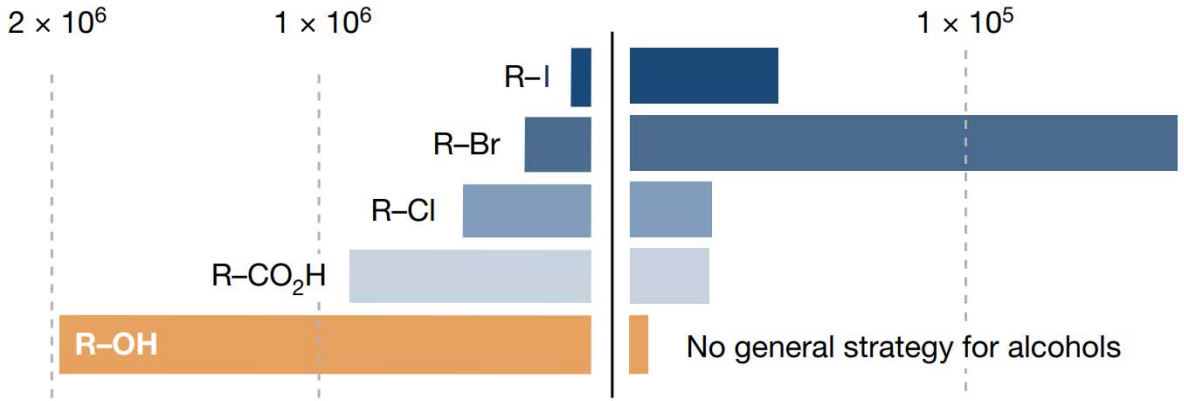
01

研究背景及意义

1 研究背景及意义

Commercial alkyl sources

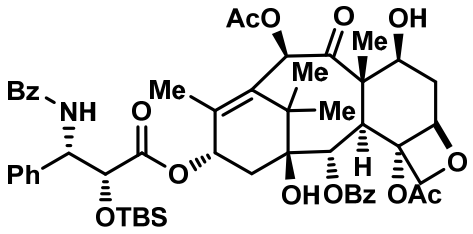


Limitations of Alkyl halides:

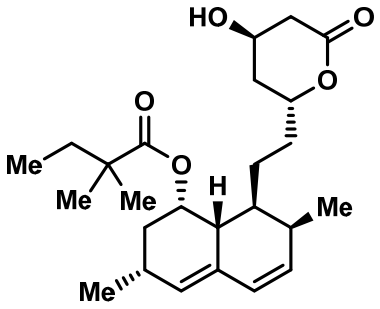
Genotoxicity;

Light-sensitivity;

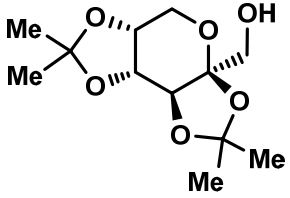
Necessitating care in handling and storing these reagents.



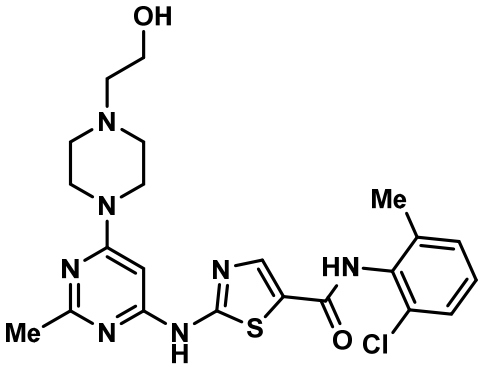
Taxol variant



Simvastatin variant

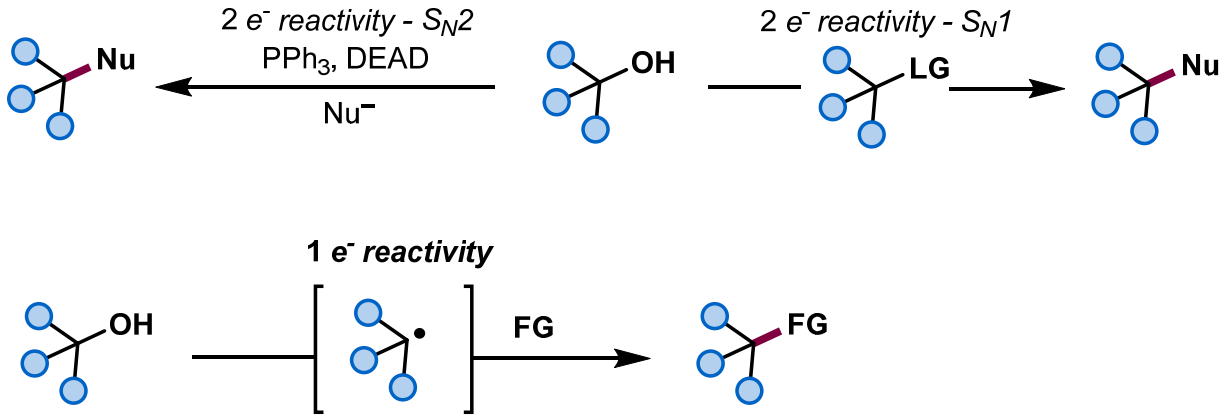


from β-**D-fructopyranose**



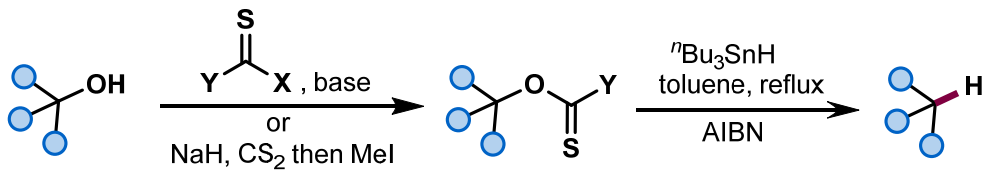
from **dasatinib**

1 研究背景及意义



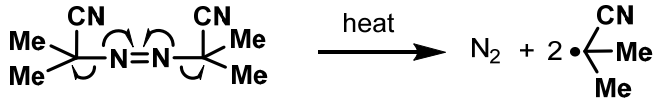
- ***Overcomes steric limitations***
- ***Reduce the possibility of side reactions, e.g. olefination or rearrangement products***
- ***Potential for late-stage functionalization of drug molecules***

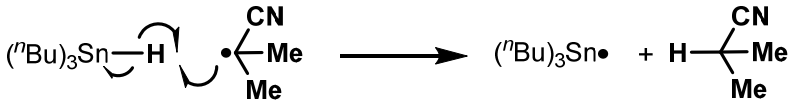
1 研究背景及意义



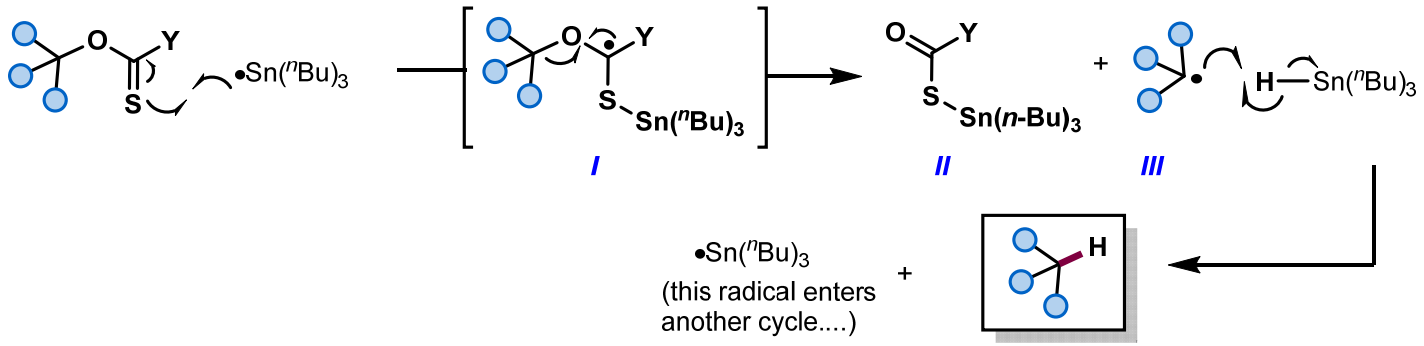
Y = SMe, imidazolyl, OPh, OMe; X = Cl, imidazolyl; base: NaH

Initiation step:





Propagation step:

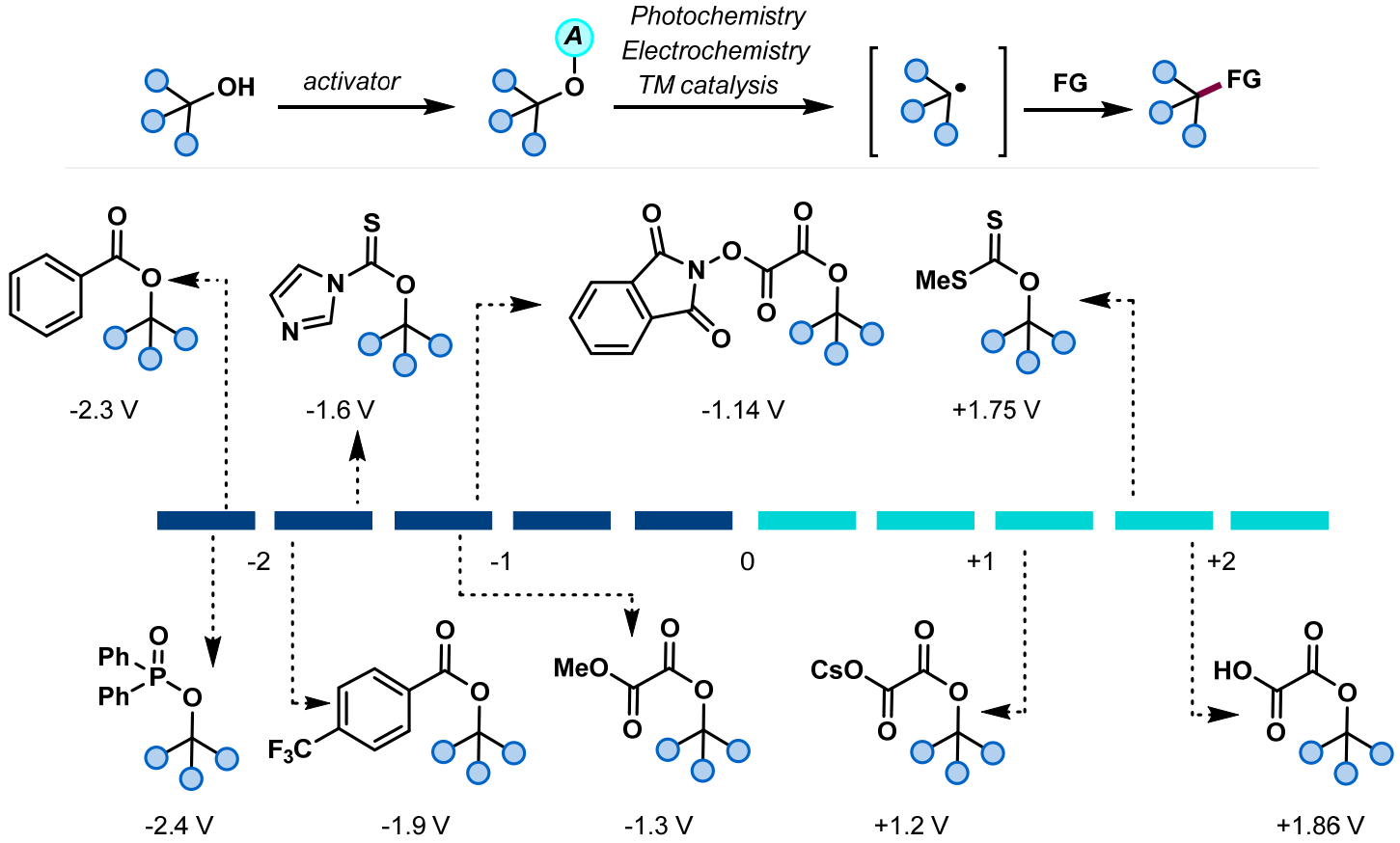


Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.

Barton, D. H. R. et al. *Synthesis* **1981**, 743.

McCombie, S. W. et al. in *Organic Reactions*, *John Wiley & Sons, Inc.* **2012**, 161.

1 研究背景及意义



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.

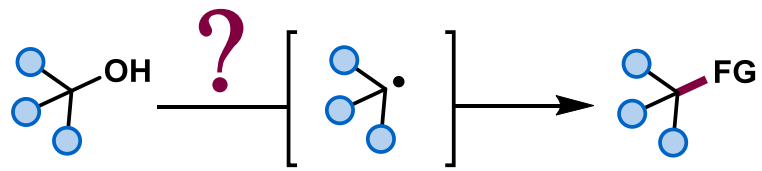
MacMillan, D. W. C. et al. *Chem. Rev.* **2013**, *113*, 5322.

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 研究背景及意义



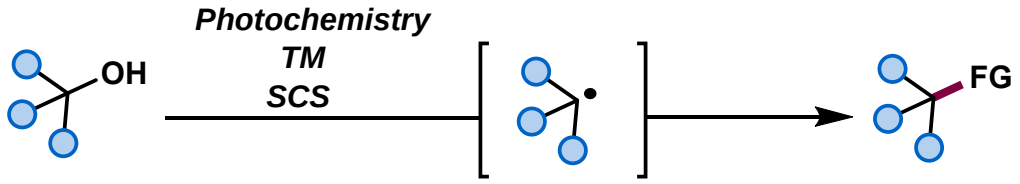
Overcome several challenges,
most notably the in situ cleavage of strong C–O bonds

(1) require no separate alcohol pre-activation step

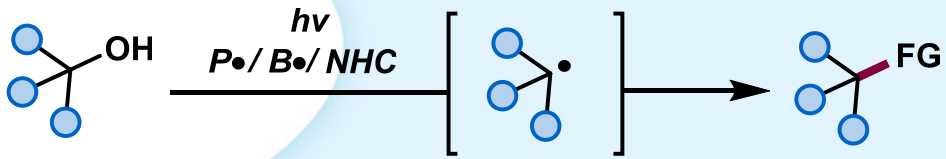
(2) be amenable to all classes of alkyl alcohol substrates

(3) exhibit exceptional levels of functional group tolerance

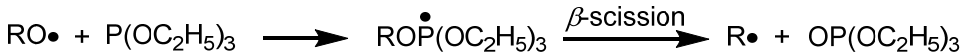
(4) be readily adaptable across diverse connections



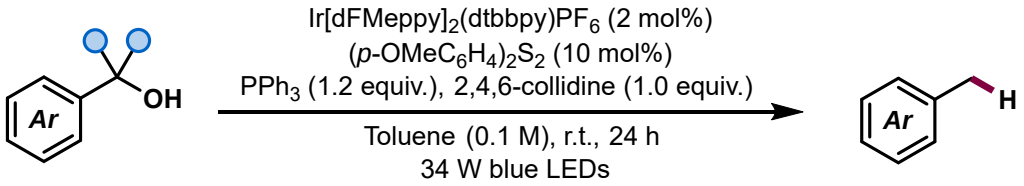
2-1 醇通过光化学活化去氧产生烷基自由基



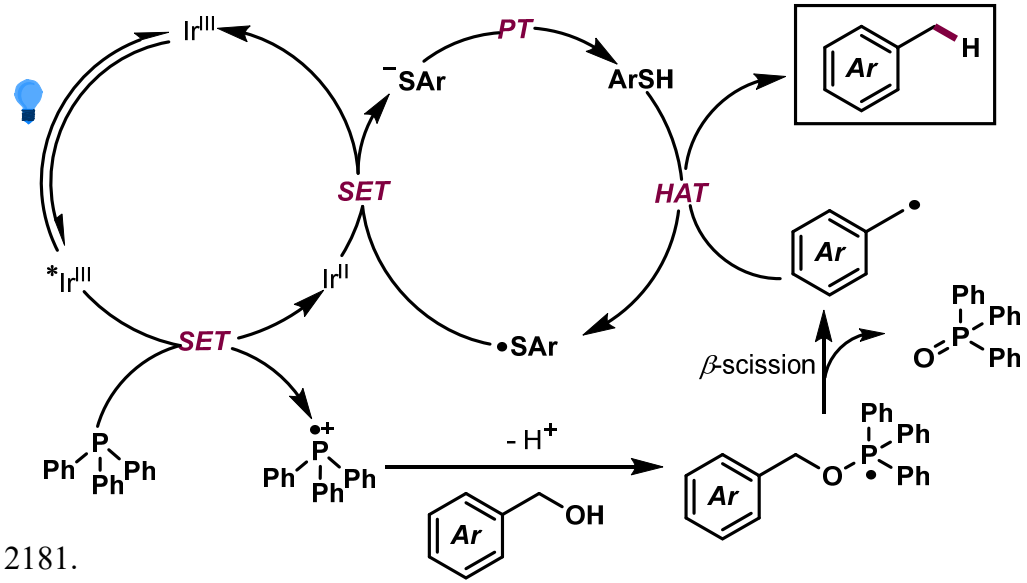
2-1-1 通过P自由基活化的醇的去氧-氢化反应



(Savas, 1960)



Proposed mechanism

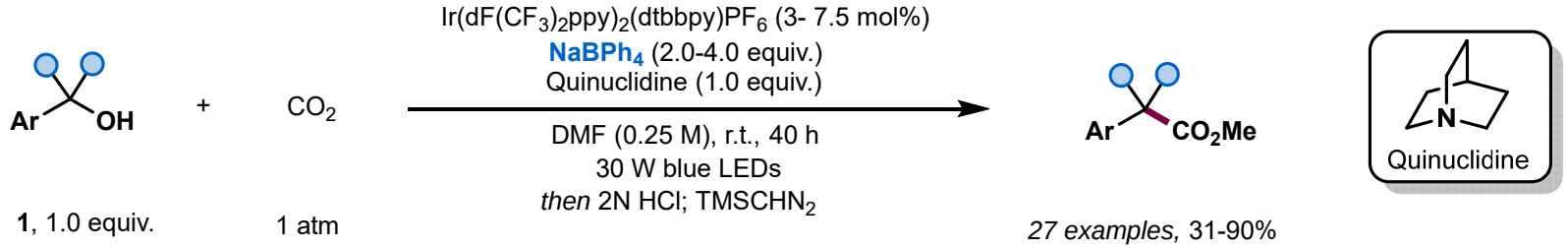


Savas, E. S. et al. *J. Am. Chem. Soc.* **1960**, *82*, 2181.

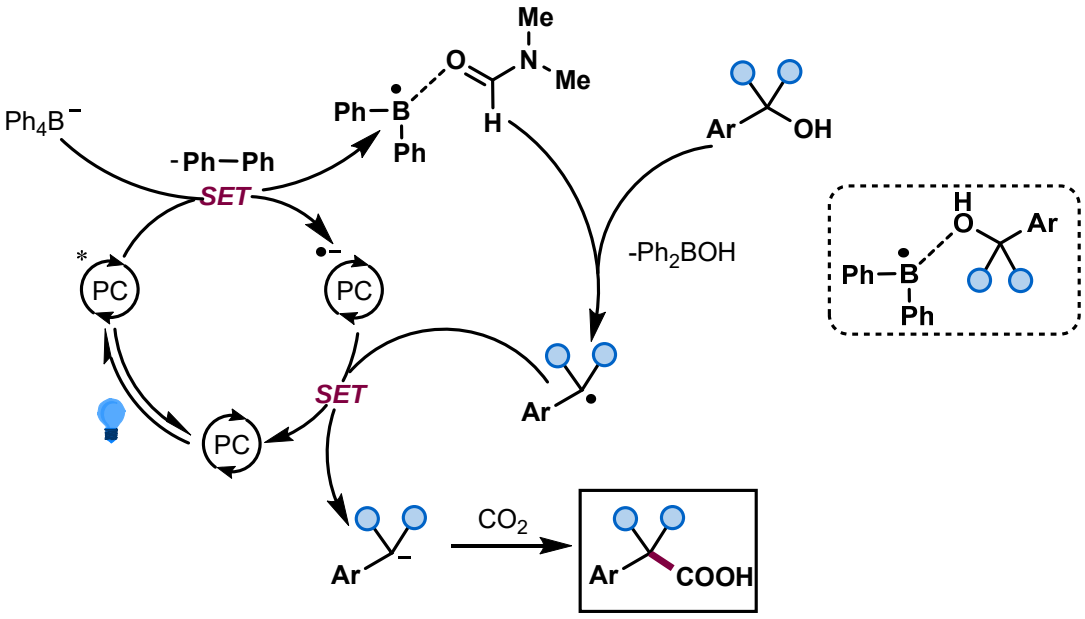
Bentrude, W. G. et al. *Acc. Chem. Res.* **1982**, *15*, 117.

Doyle, A. G. et al. *ACS Catal.* **2018**, *8*, 11134.

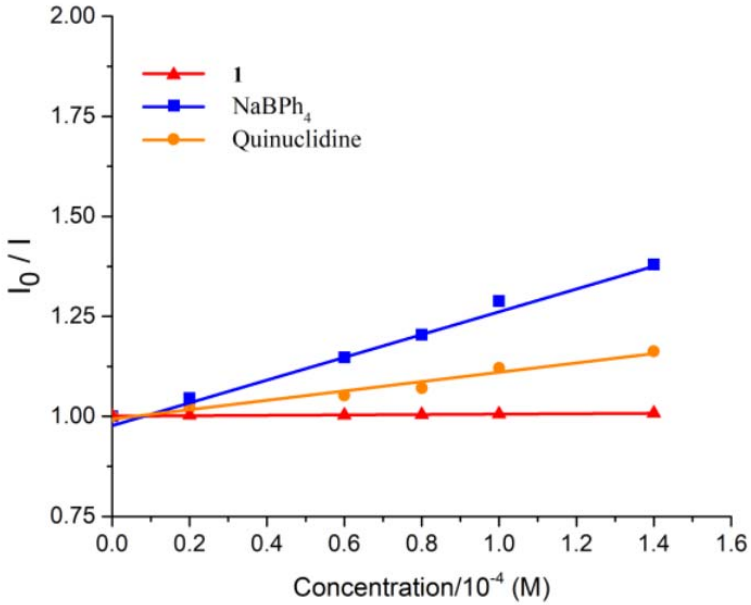
2-1-2 通过B自由基活化的醇的去氧-羧基化反应



Proposed mechanism



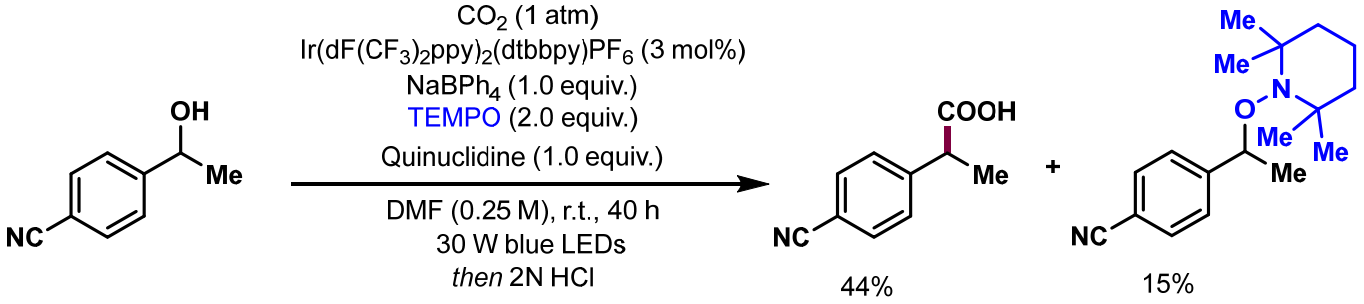
Stern-Volmer Analysis



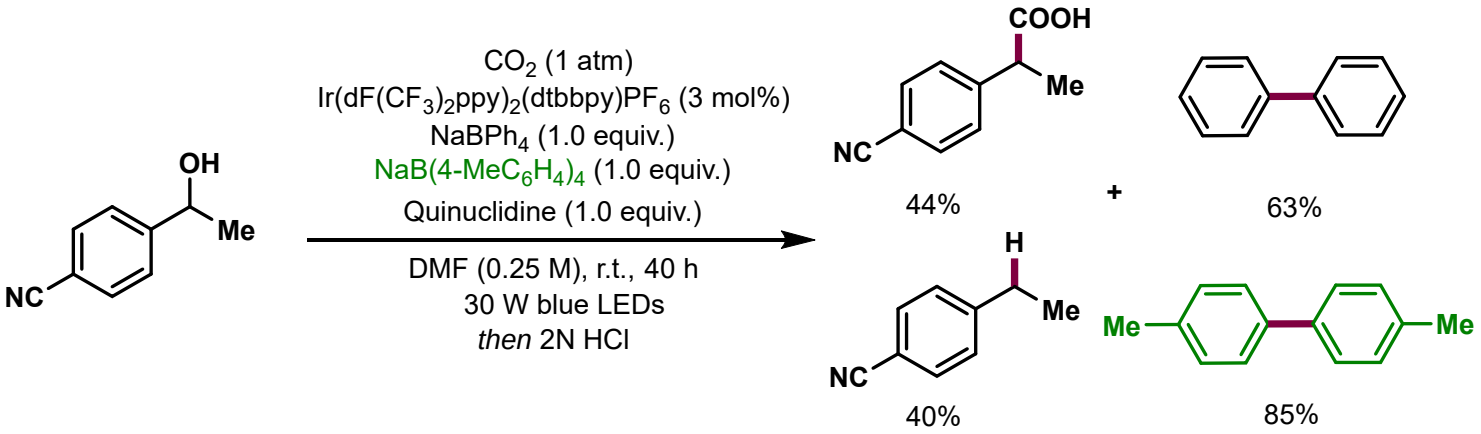
Xia, J. B. et al. *J. Am. Chem. Soc.* **2022**, *144*, 8551.

2-1-2 通过B自由基活化的醇的去氧-羧基化反应

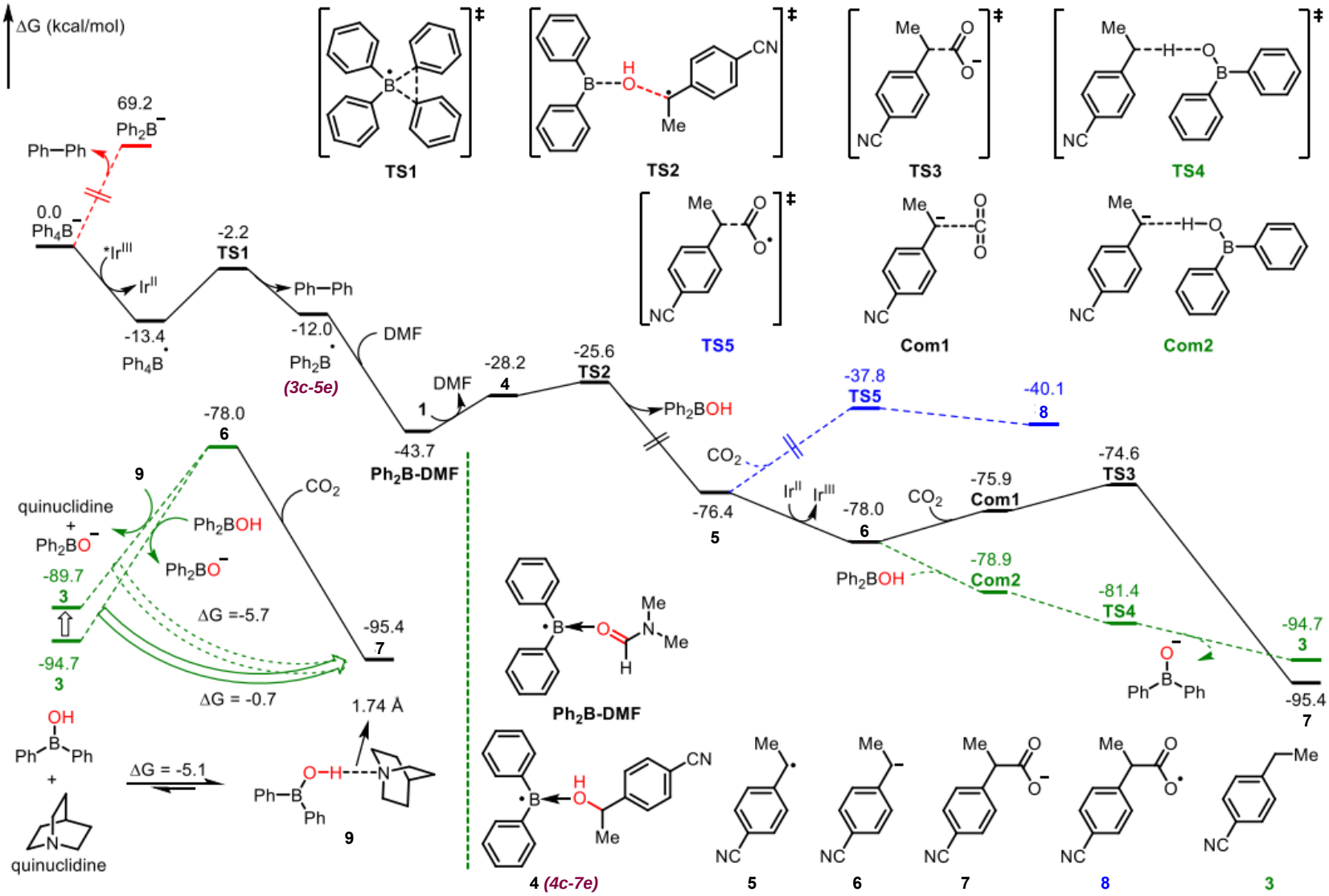
Radical Inhibition Studies



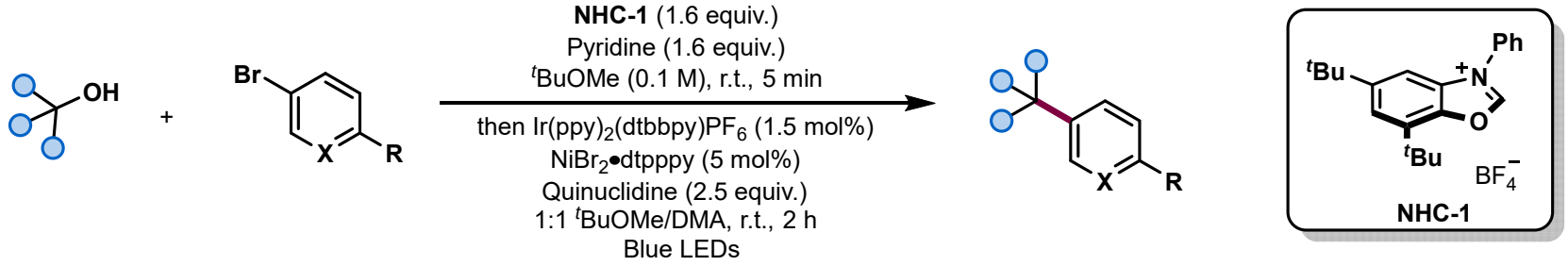
Crossover experiment using $NaBPh_4$ and $NaB(4\text{-}Me\text{-}C_6H_4)_4$



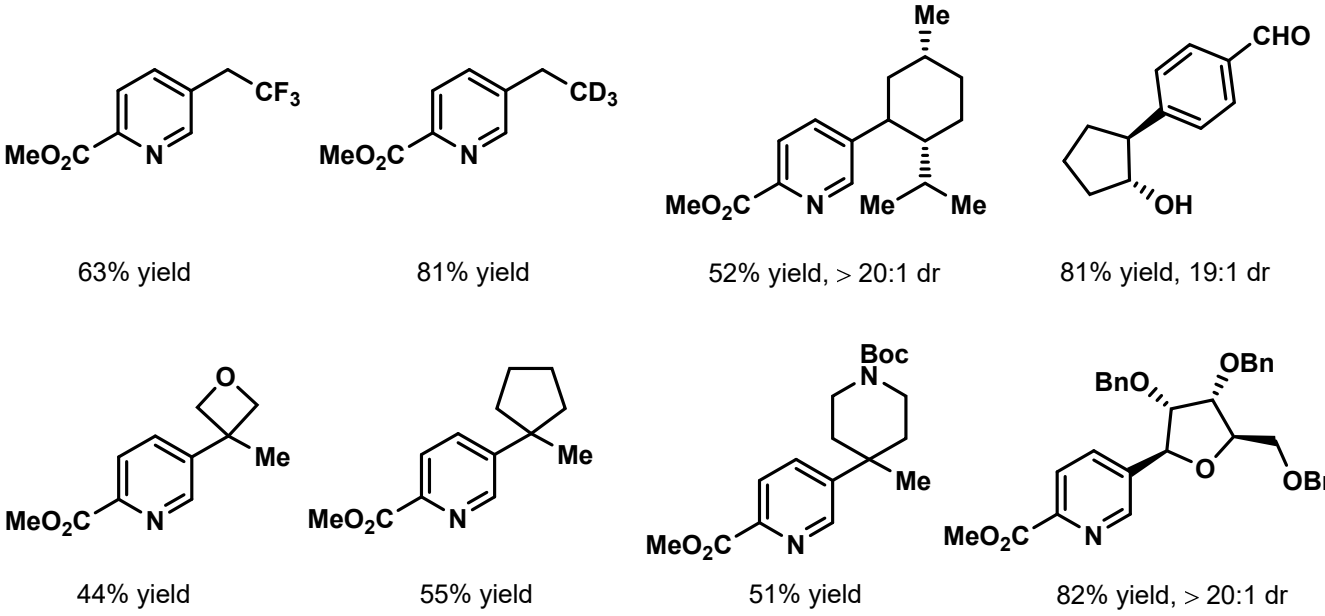
2-1-2 通过B自由基活化的醇的去氧-羧基化反应



2-1-3 醇通过NHC活化参与的去氧-杂芳基化反应



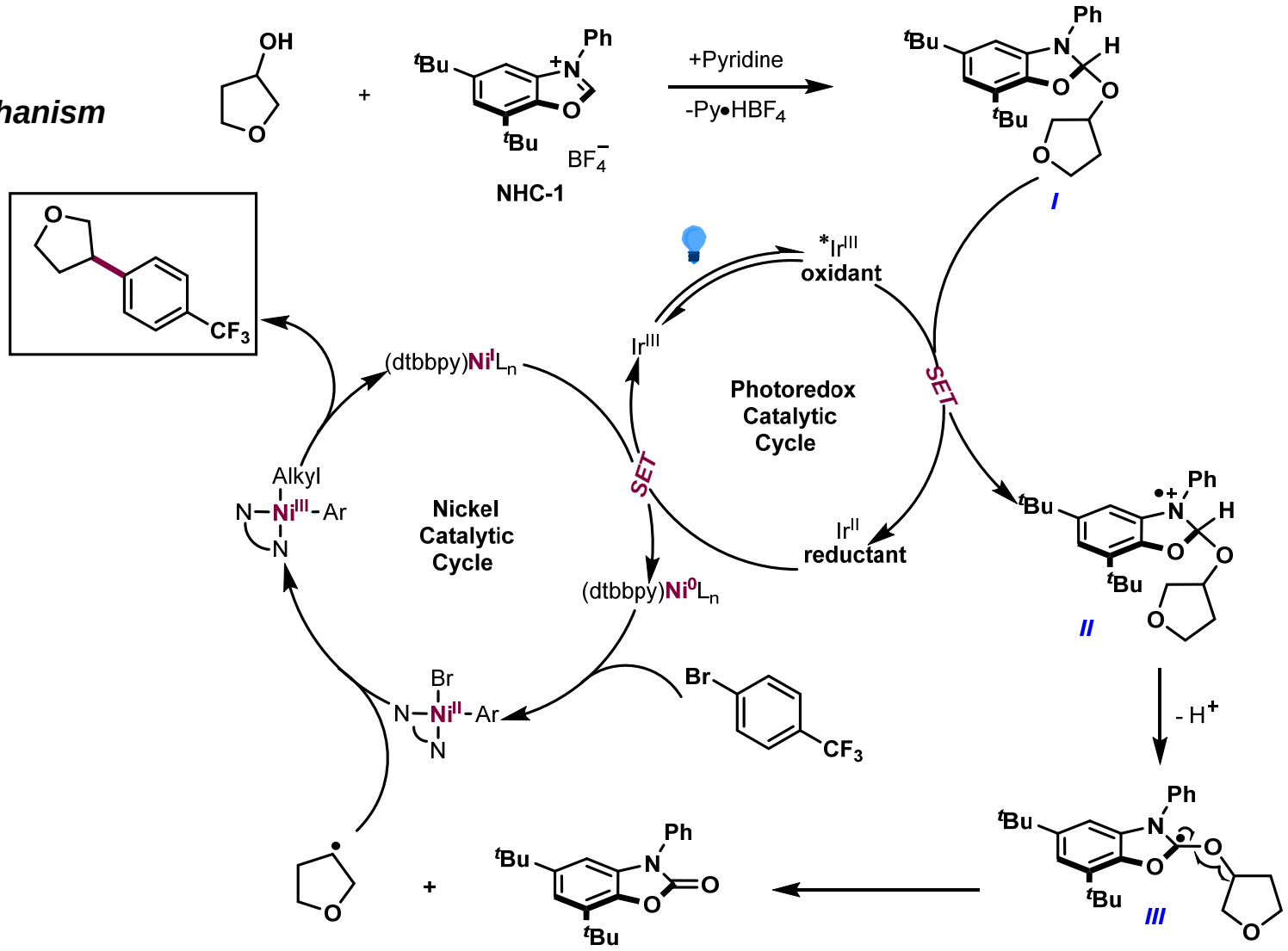
Selected examples



MacMillan, D. W. C. et al. *Nature* **2021**, *598*, 451.

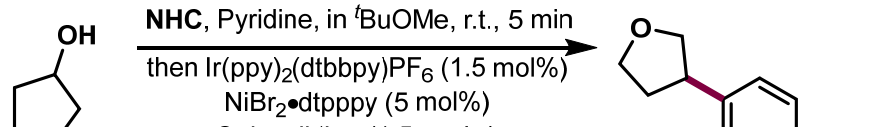
2-1-3 醇通过NHC活化参与的去氧-杂芳基化反应

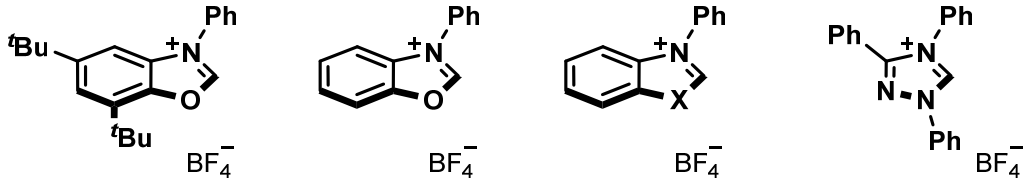
Proposed mechanism



2-1-3 醇通过NHC活化参与的去氧-杂芳基化反应

NHC evaluation





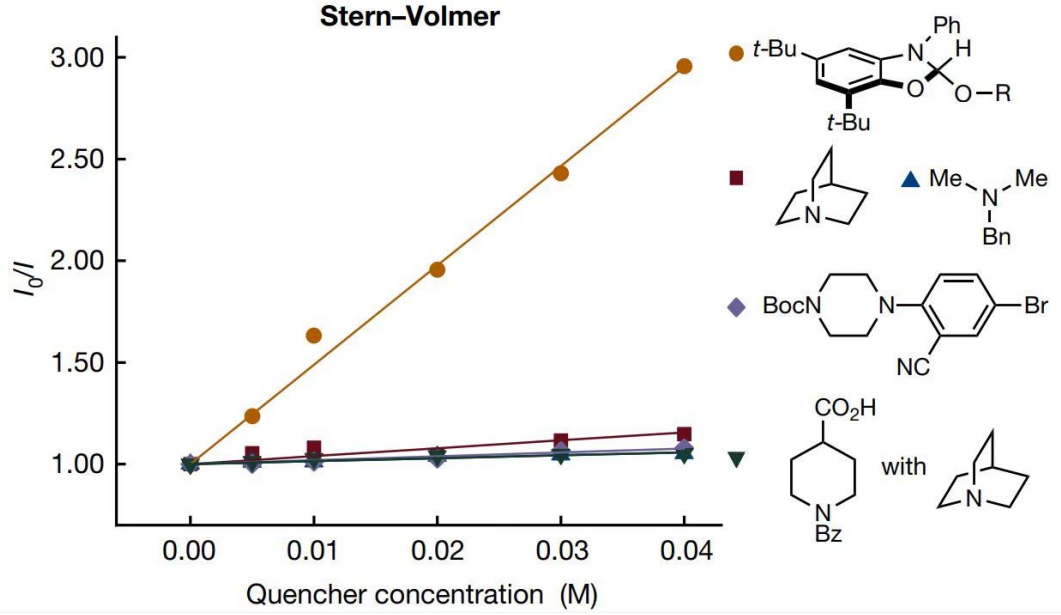
NHC-1 88% yield

NHC-2 72% yield

NHC-3, X = NPh
NHC-4, X = S
0% yield

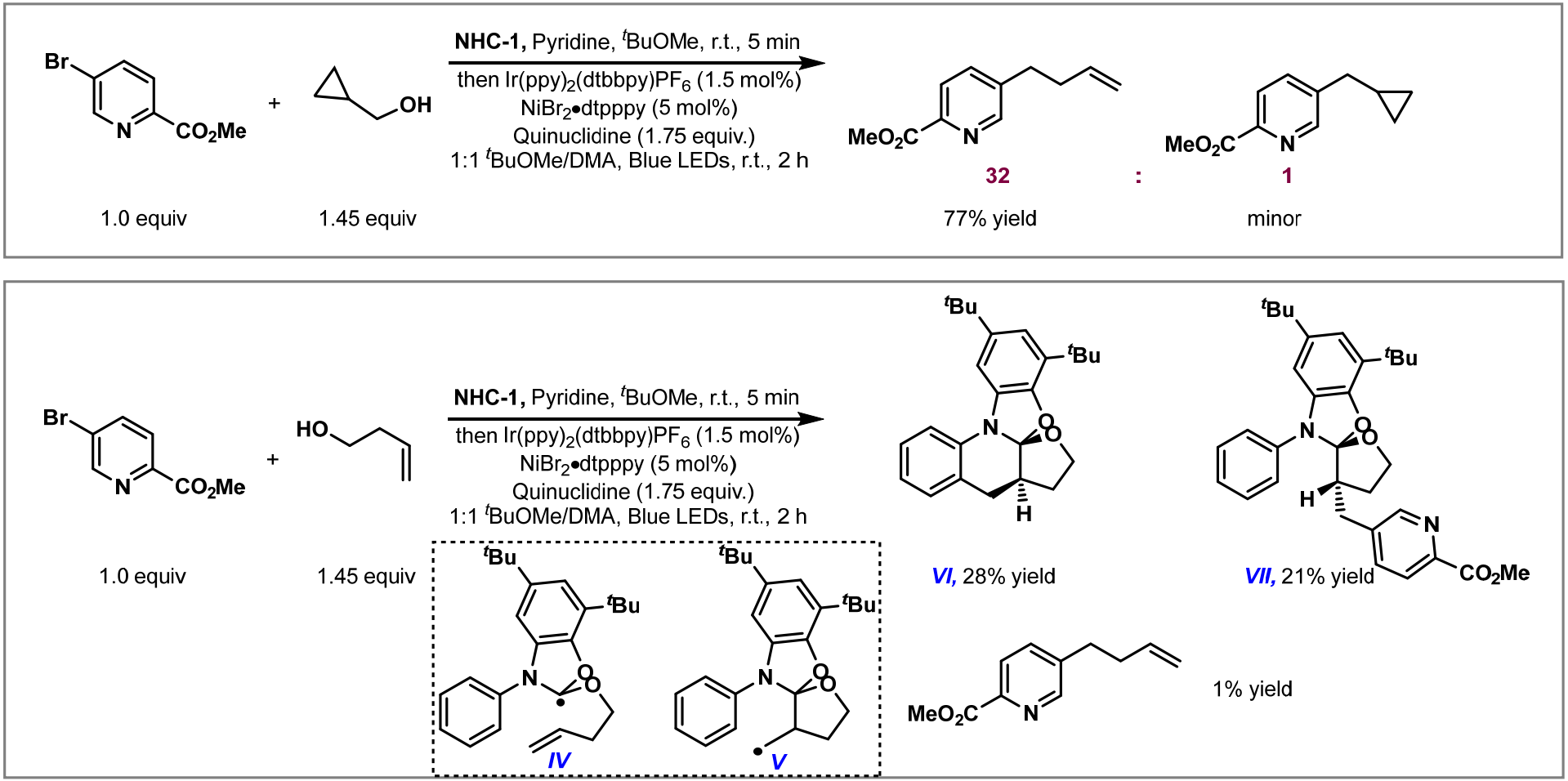
NHC-5 0% yield

Preliminary investigation



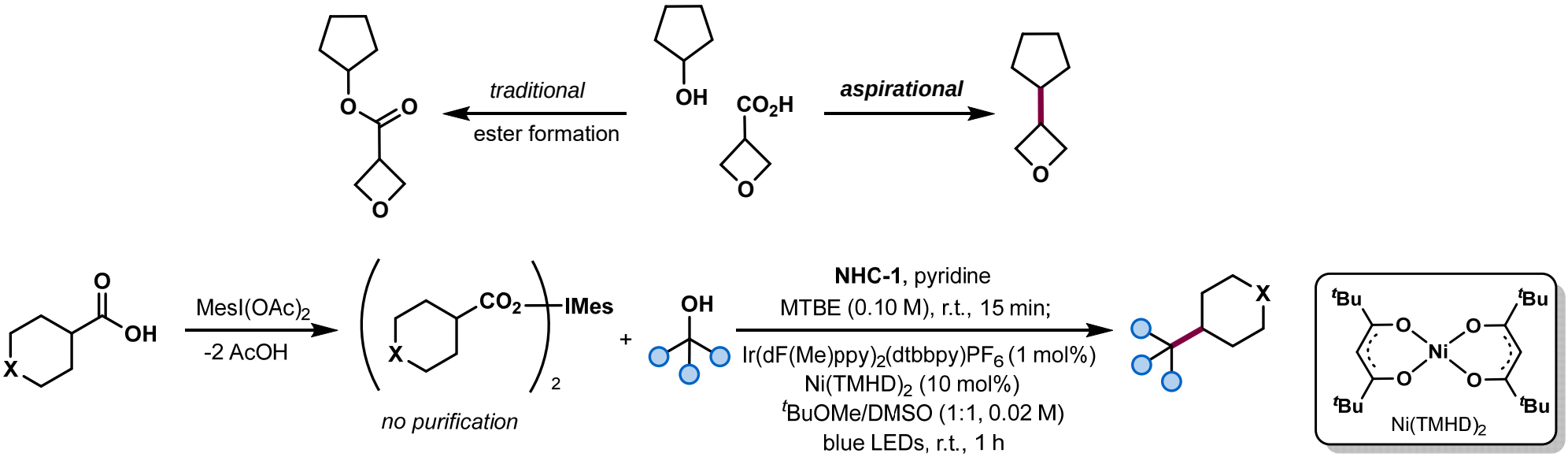
2-1-3 醇通过NHC活化参与的去氧-杂芳基化反应

Investigation of the reaction mechanism



2-1-4 NHC活化的醇与脂肪族羧酸的非传统偶联反应

Fragment coupling of alcohols & carboxylic acids



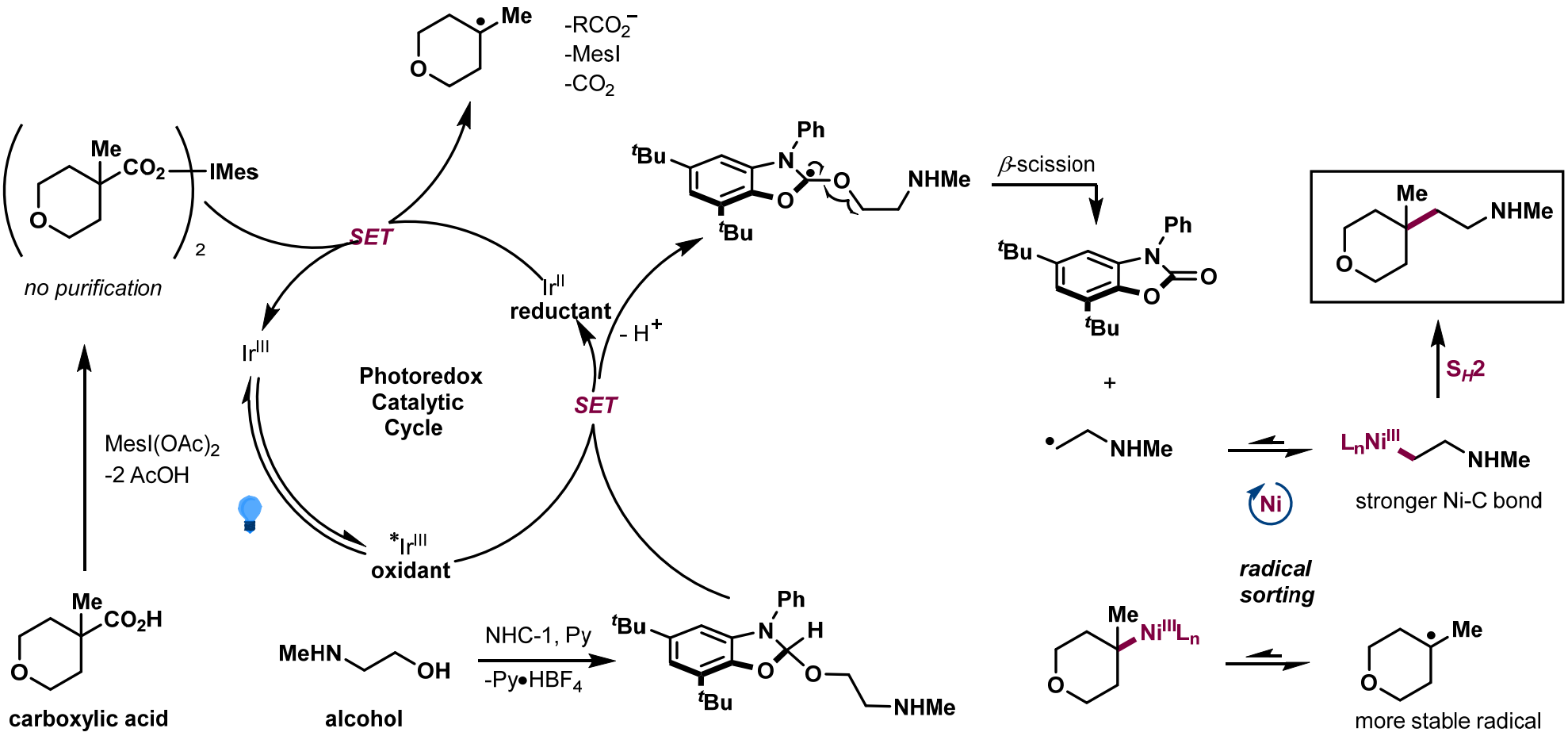
Selected examples

75% yield | 57% yield | 50% yield | 50% yield

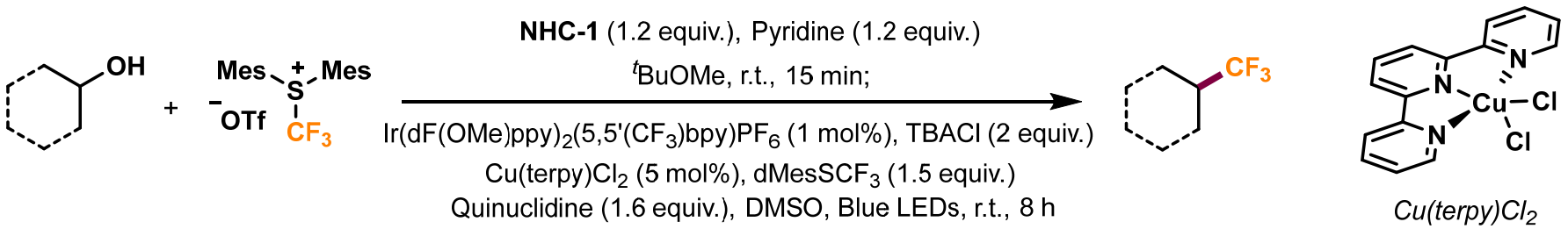
MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

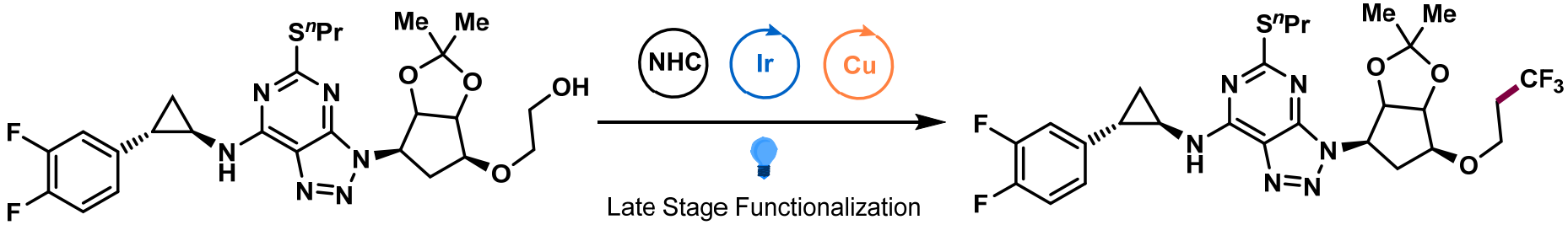
2-1-4 NHC活化的醇与脂肪族羧酸的非传统偶联反应

Proposed mechanism



2-1-5 醇通过NHC活化参与的去氧-三氟甲基化反应





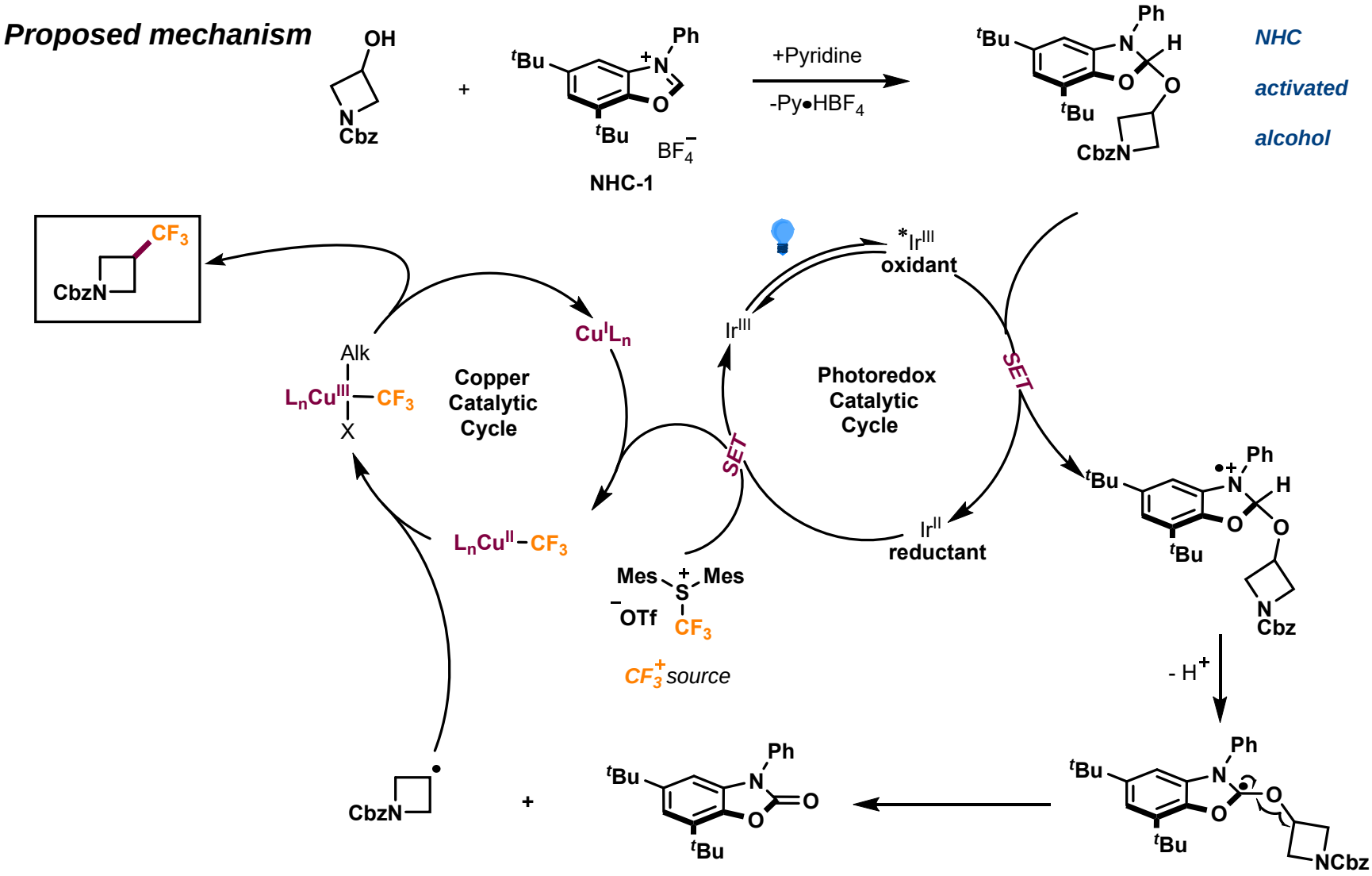
Ticagrelor Acetonide

55% yield

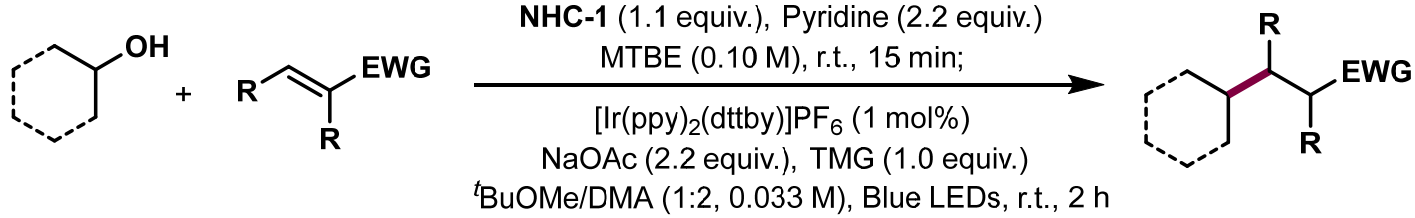
MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2022**, *144*, 11961.

2-1-5 醇通过NHC活化参与的去氧-三氟甲基化反应

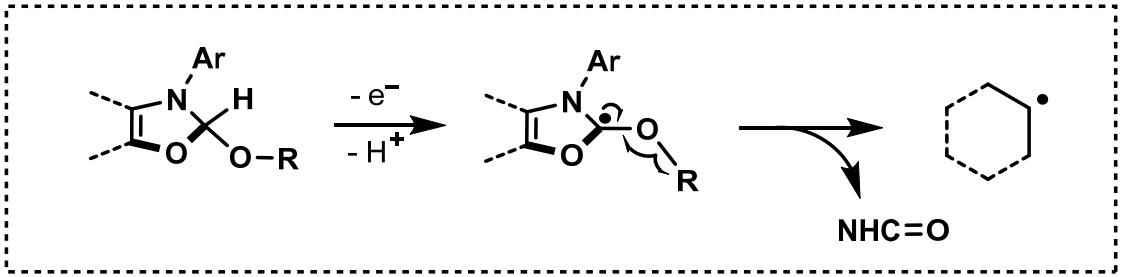
Proposed mechanism



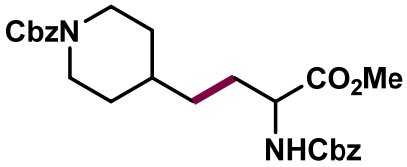
2-1-6 醇通过NHC活化参与的去氧-Giese型反应



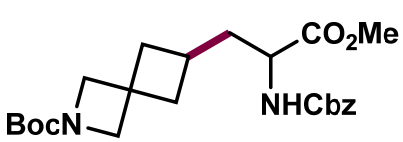
fragment-coupling



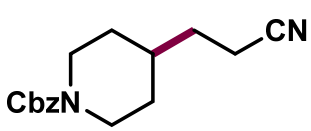
Selected examples



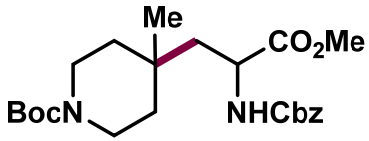
81% yield



88% yield



93% yield

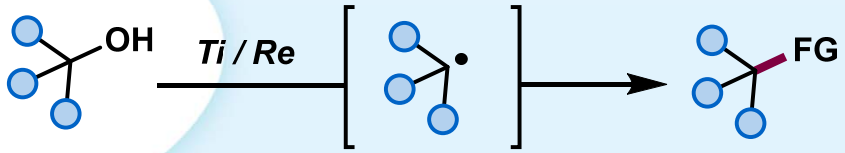


97% yield

MacMillan, D. W. C. et al. *Angew. Chem., Int. Ed.* **2022**, *61*, e202207150.

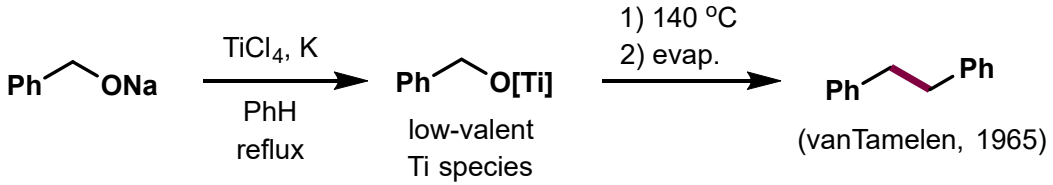
2-2

醇通过过渡金属活化去氧产生烷基自由基

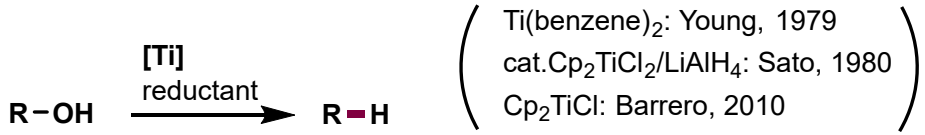


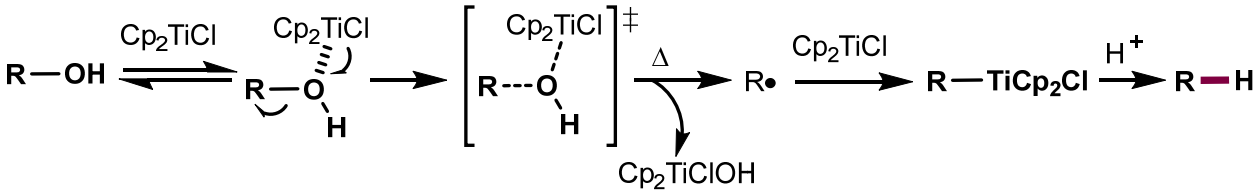
2-2-1 醇通过低价Ti活化参与的去氧-氢化反应

Dimerization (Initial work)



Deoxygenation





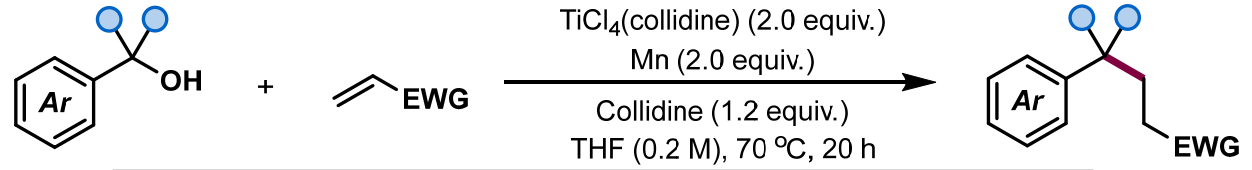
van Tamelen, E. E. et al. *J. Am. Chem. Soc.* **1965**, *87*, 3277.

Young, D. et al. *Tetrahedron Lett.* **1979**, *20*, 173.

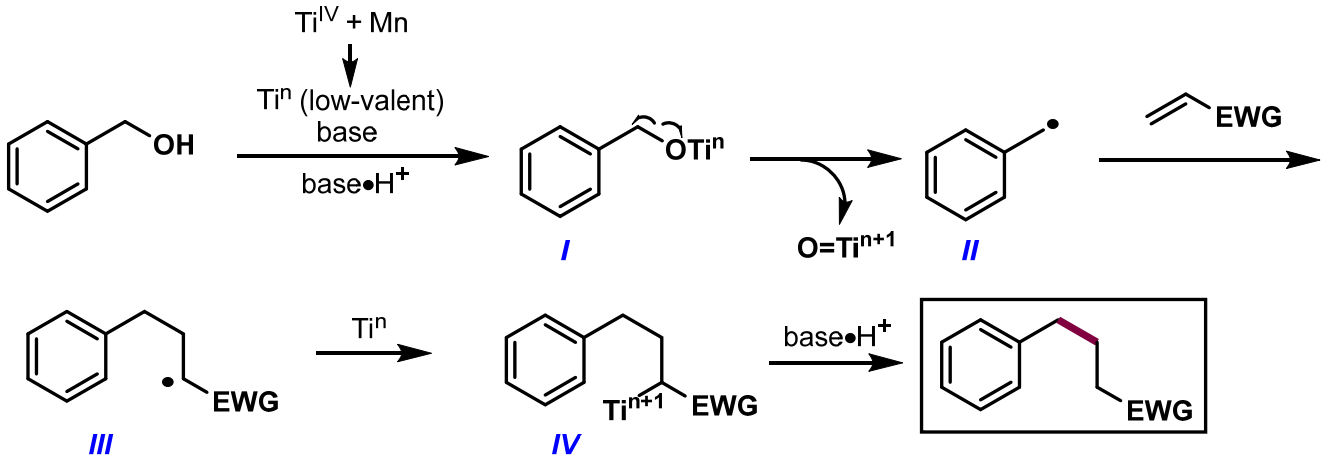
Sato, M. et al. *Chem. Lett.* **1980**, *9*, 103.

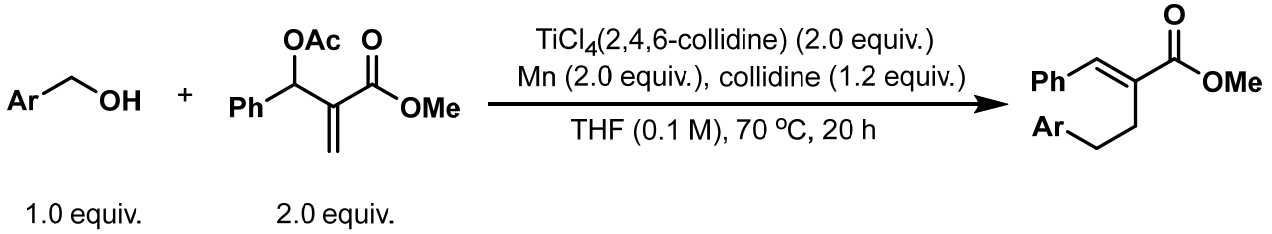
Barrero, A. F. et al. *J. Am. Chem. Soc.* **2010**, *132*, 254.

2-2-2 苄醇通过低价Ti活化参与的去氧-Giese型反应



Proposed mechanism

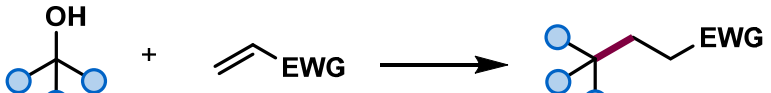




Ukaji, Y. et al. *Org. Lett.* **2018**, *20*, 5389.

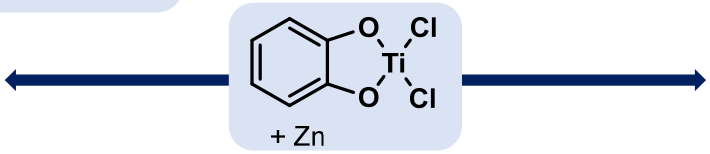
Ukaji, Y. et al. *J. Org. Chem.* **2022**, *87*, 7487.

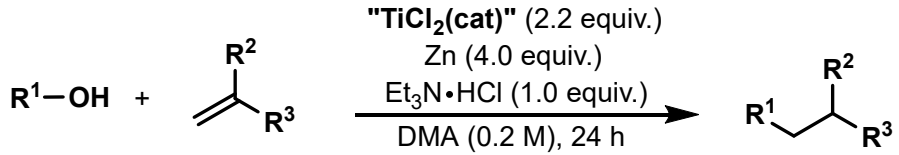
2-2-3 廉价高效的Ti试剂活化的醇的去氧-Giese型反应



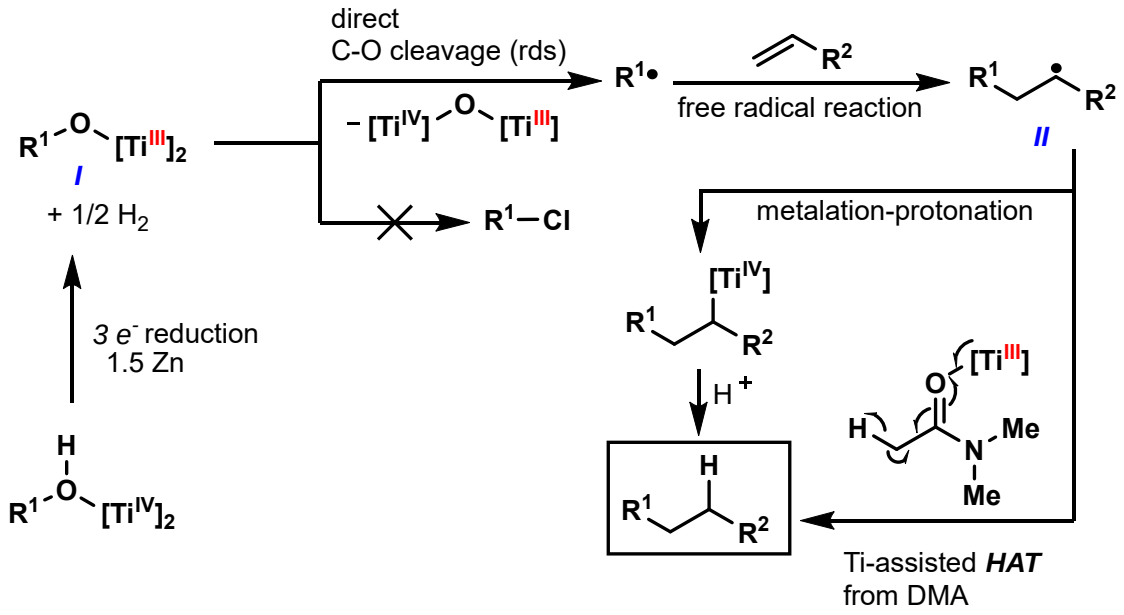
Alcohols	Ph OH	OH	OH	OH
BDE (kcal/mol)	83	96	96	94
Stability of R•	High			Low

$TiCl_4$(collidine)
+ Mn
Ukaji, Y. **2018**





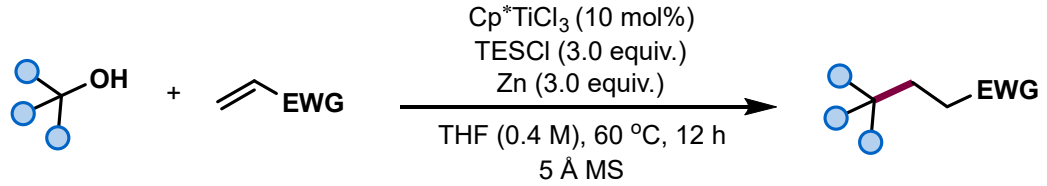
Proposed mechanism



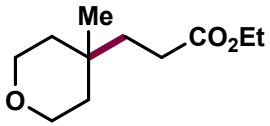
Serrano, R. et al. *J. Organomet. Chem.* **1986**, *315*, 329.

Ukaji, Y. et al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202112533.

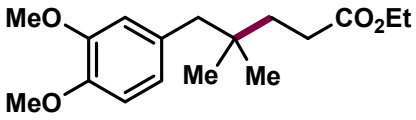
2-2-4 三级醇通过低价Ti活化参与的去氧-Giese型反应



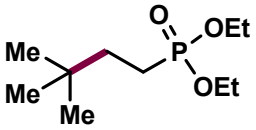
Selected examples



62% yield

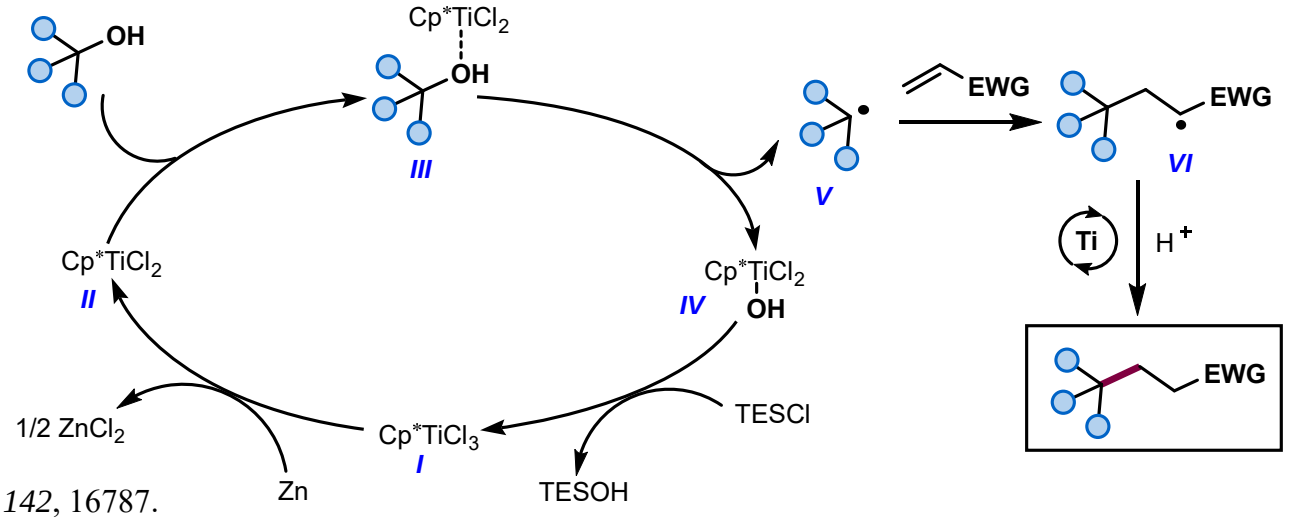


53% yield



64% yield

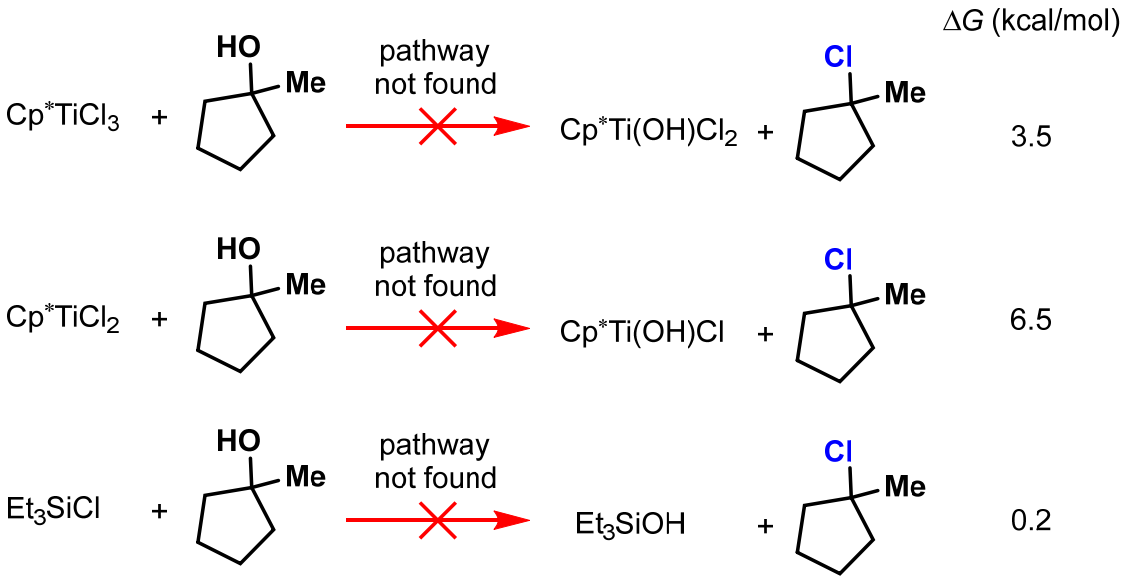
Proposed mechanism



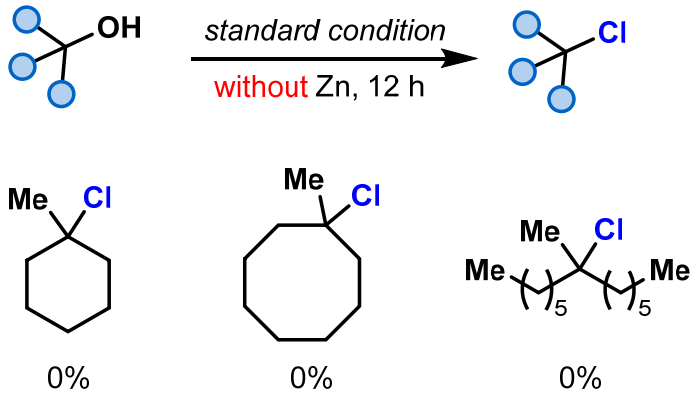
Shu, X. Z. et al. *J. Am. Chem. Soc.* **2020**, *142*, 16787.

2-2-4 三级醇通过低价Ti活化参与的去氧-Giese型反应

DFT calculations:

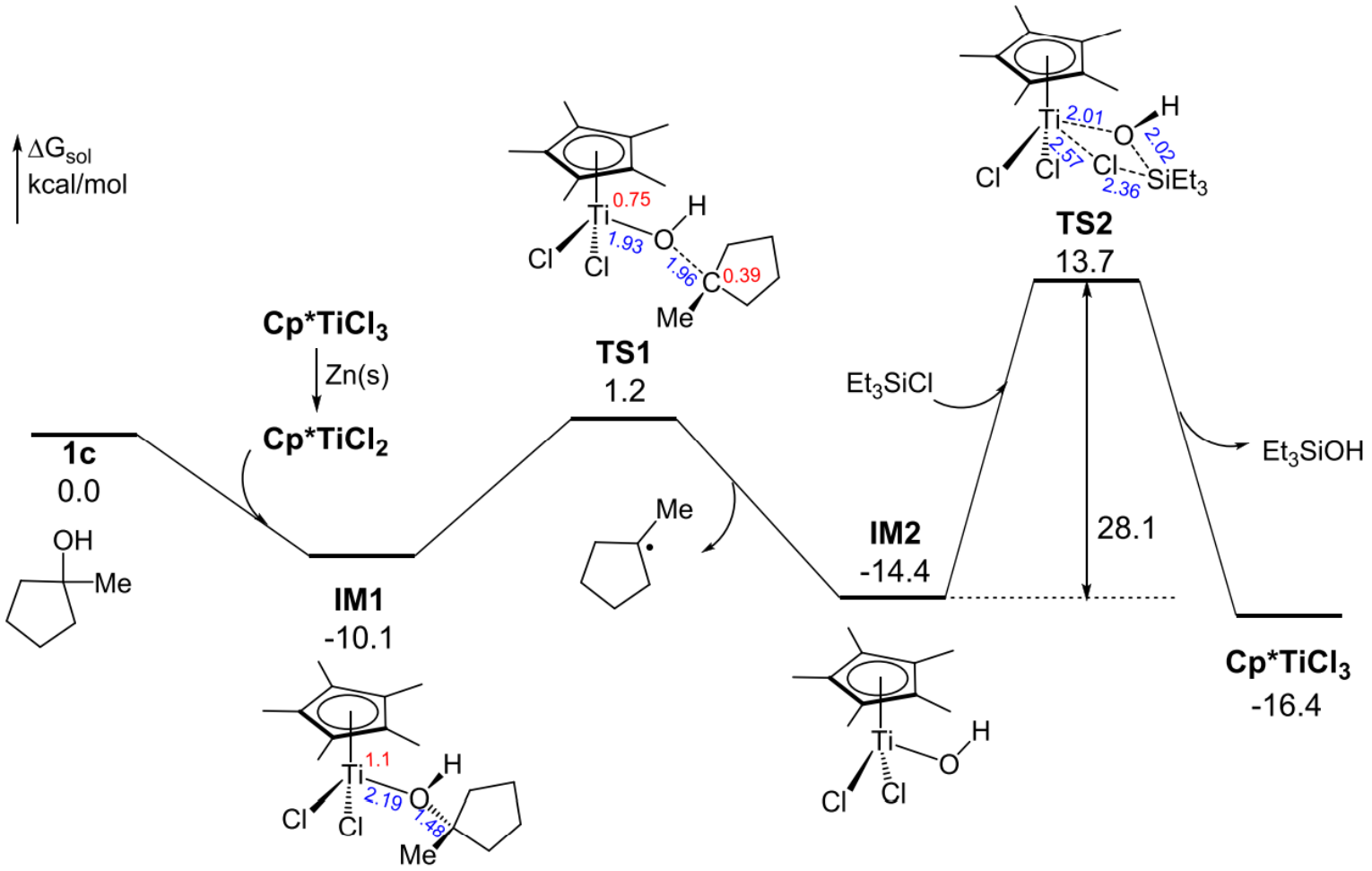


The controlled experiments:

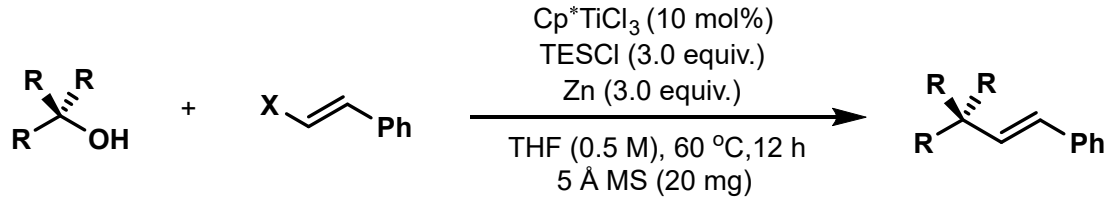


2-2-4 三级醇通过低价Ti活化参与的去氧-Giese型反应

DFT calculations:



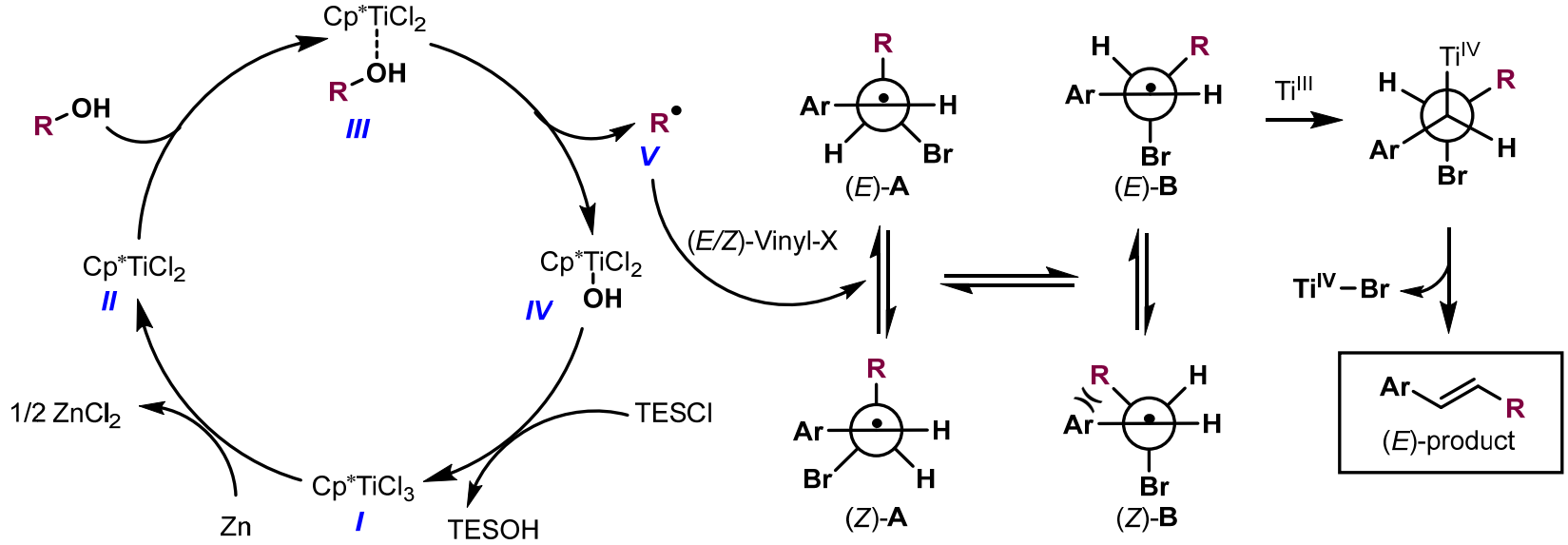
2-2-5 Ti活化的三级醇与烯基卤化物的交叉偶联反应



Reactivity: • Alcohol C-OH homolysis • Vinyl-X (X = F, Cl, Br, I)

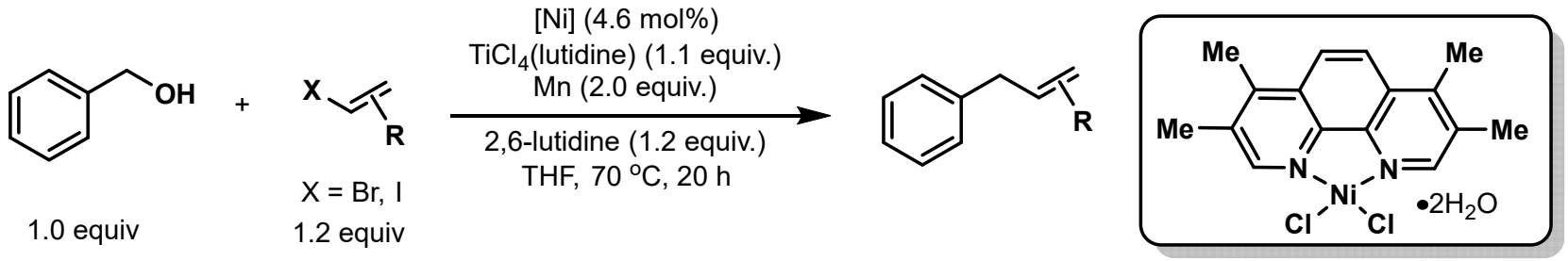
Selectivity: • 3° *over* 1°/2° alcohols • Vinyl-Br *over* Ar-X (X = Br, I, OTf)

Proposed mechanism



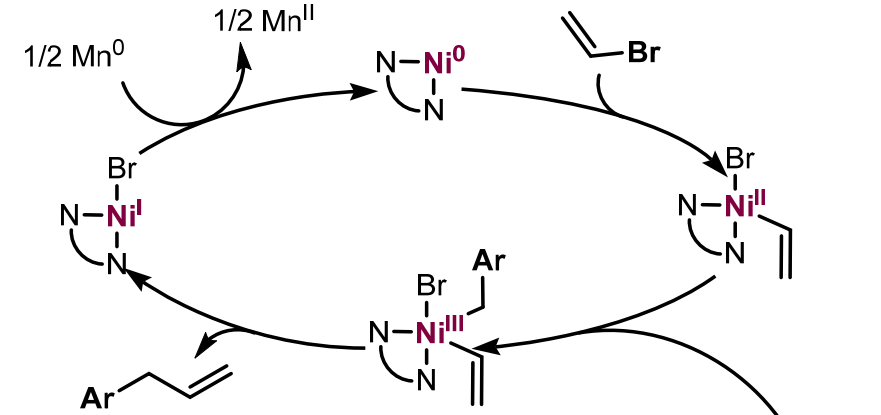
Shu, X. Z. et al. *ACS Catal.* **2022**, *12*, 1018.

2-2-6 Ti活化的苄醇与烯基卤化物的交叉偶联反应



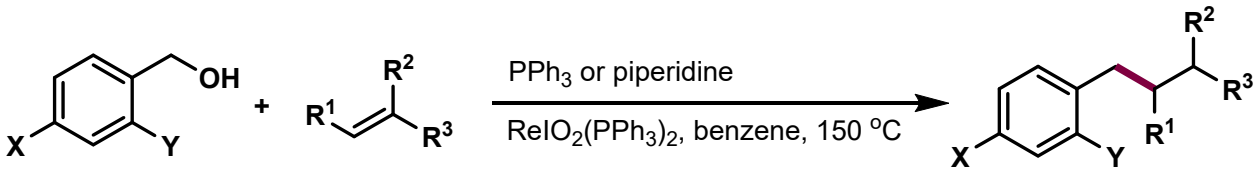
Proposed mechanism

Ni catalysis:

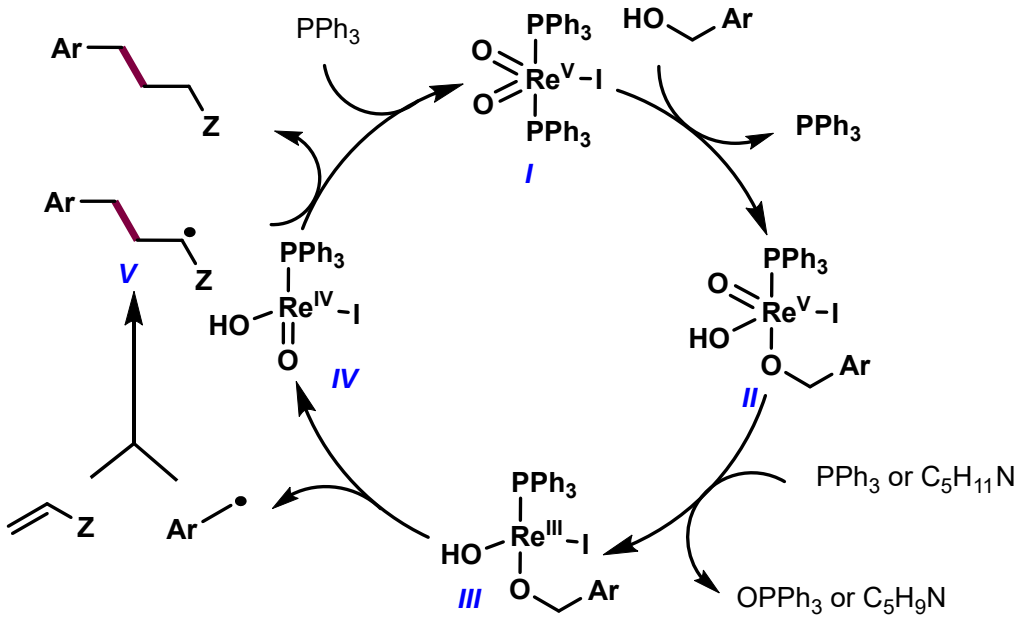


Ukaji, Y. et al. *Adv. Synth. Catal.* **2020**, *362*, 5622.

2-2-7 Re催化的醇的去氧-Giese型反应

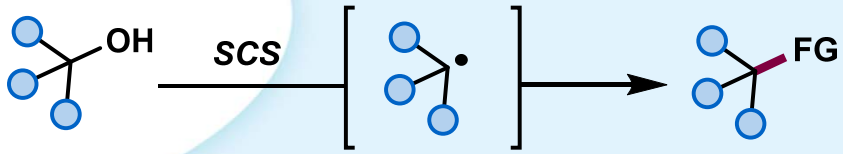


Proposed mechanism



Nicholas, K. M. et al. *J. Org. Chem.* **2020**, *85*, 3320.

2 - 3 醇通过SCS过程去氧产生烷基自由基

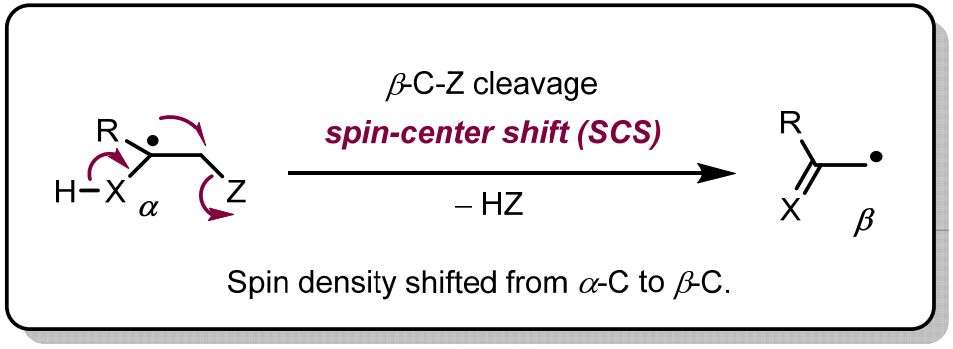


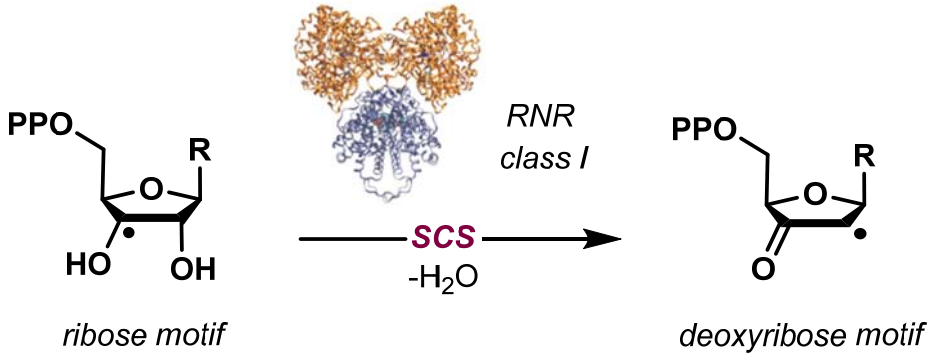
2-3-1 SCS定义

Muehling, O.

"The main feature of this process is the shift of spin density from the former C-O C-atom to the C atom that bears the leaving group. Therefore, we call this overall process ***spin-center shift***."

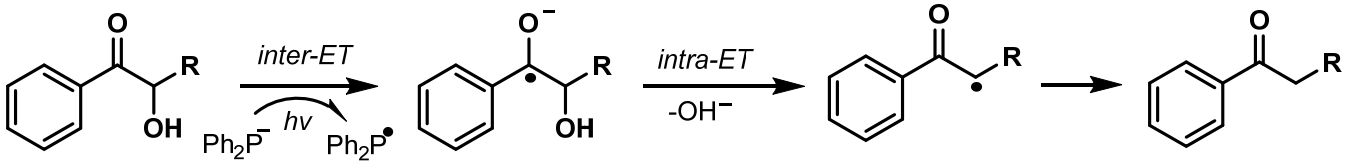
Muehling, O. et al. *Helv. Chim. Acta*. **2003**, *86*, 865.

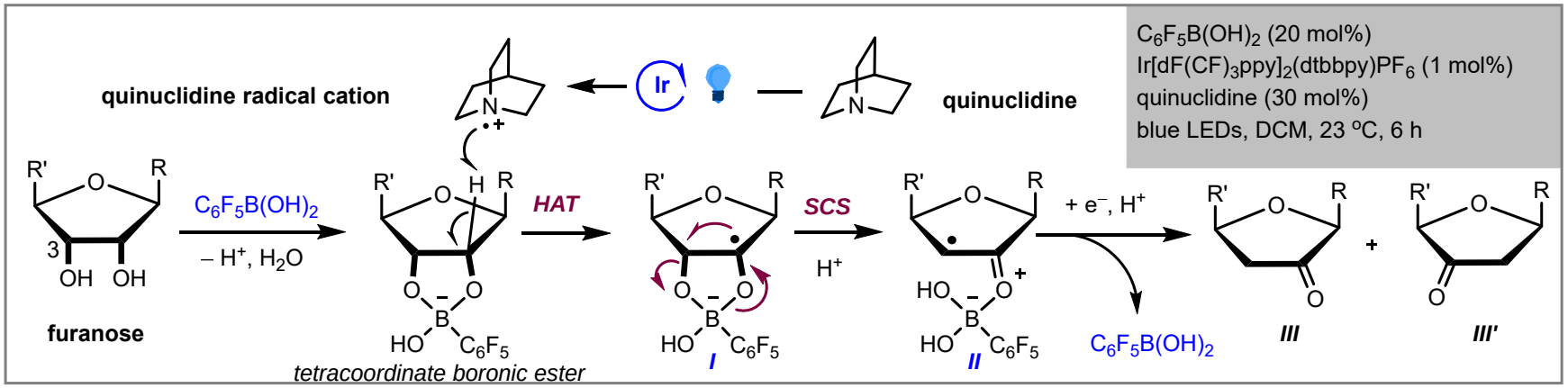


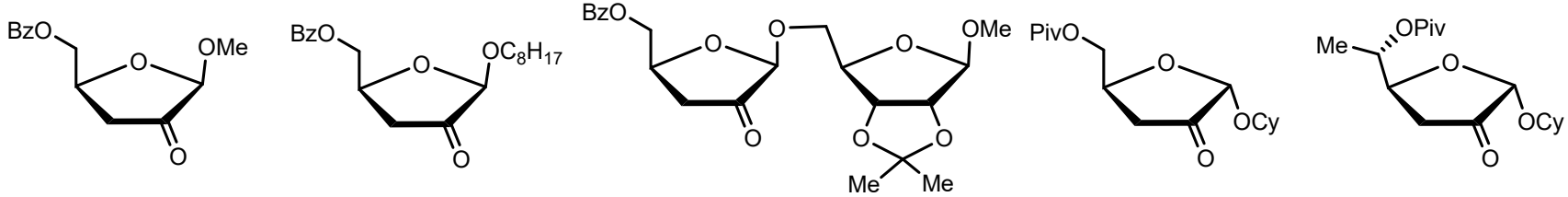


Muehling, O. et al. *Eur. J. Org. Chem.* **2007**, *2007*, 2219.

2-3-2 醇通过SCS过程参与的去氧-氢化反应



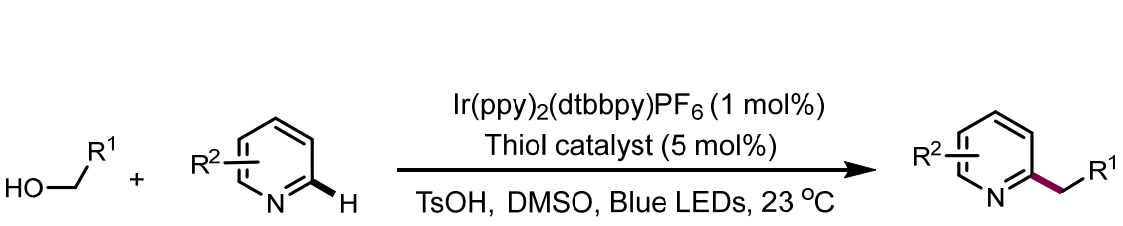


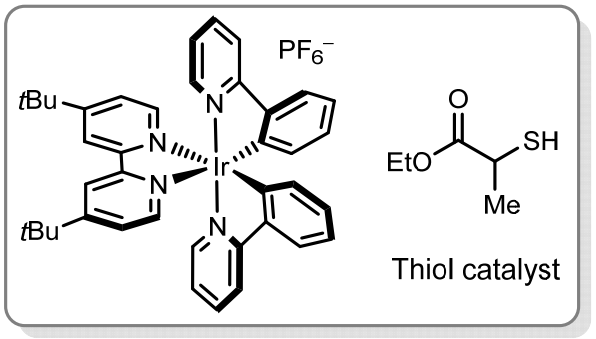


70% yield (9:1) | 73% yield (10:1) | 66% yield (17:1) | 66% yield (10:1) | 68% yield (4.4:1)

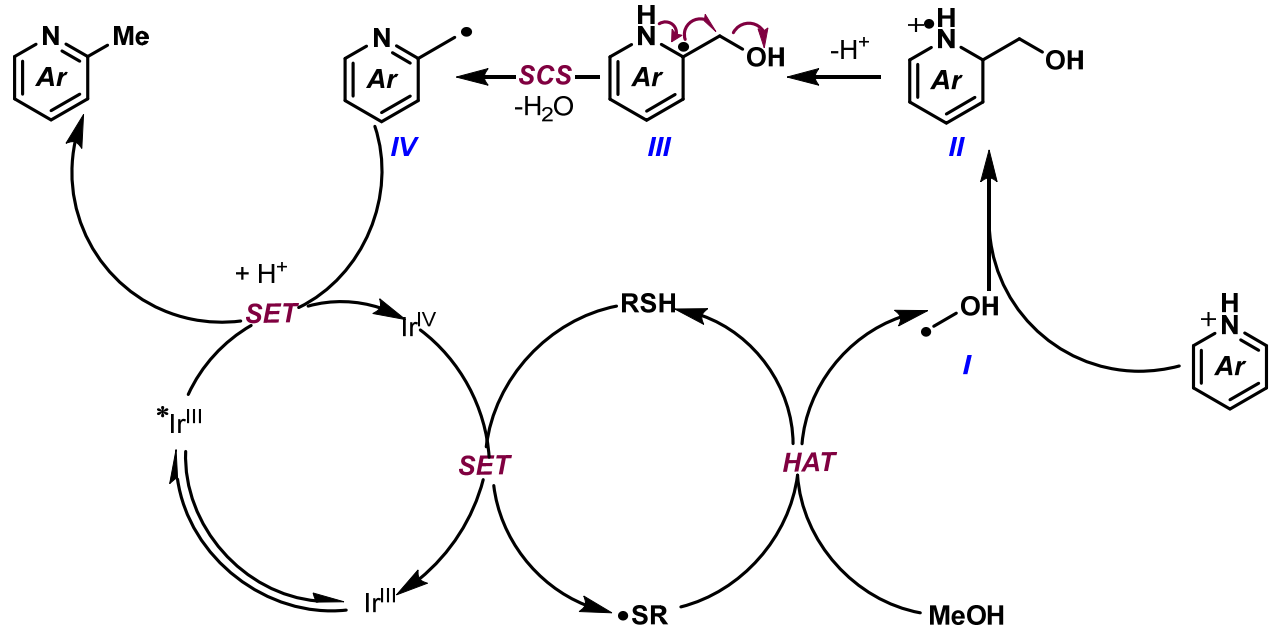
Santiago, A. N. et al. *RSC Adv.* **2013**, *3*, 11493.
Taylor, M. S. et al. *Chem. Sci*. **2020**, *11*, 1531.

2-3-3 醇通过SCS过程参与的去氧杂芳基化反应



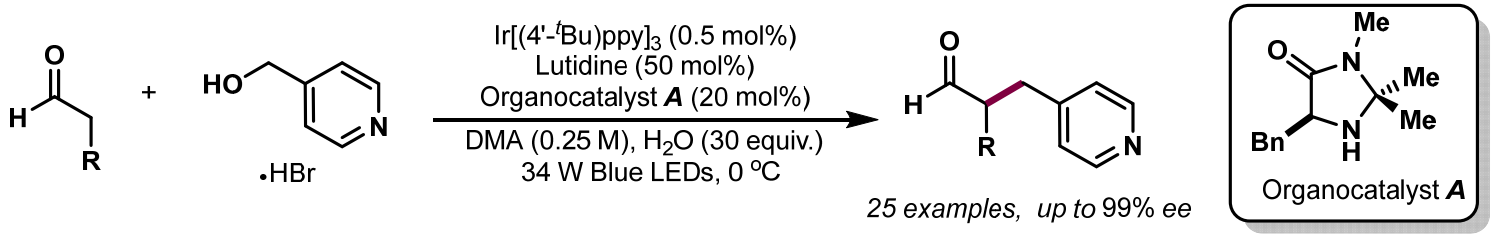


Proposed mechanism

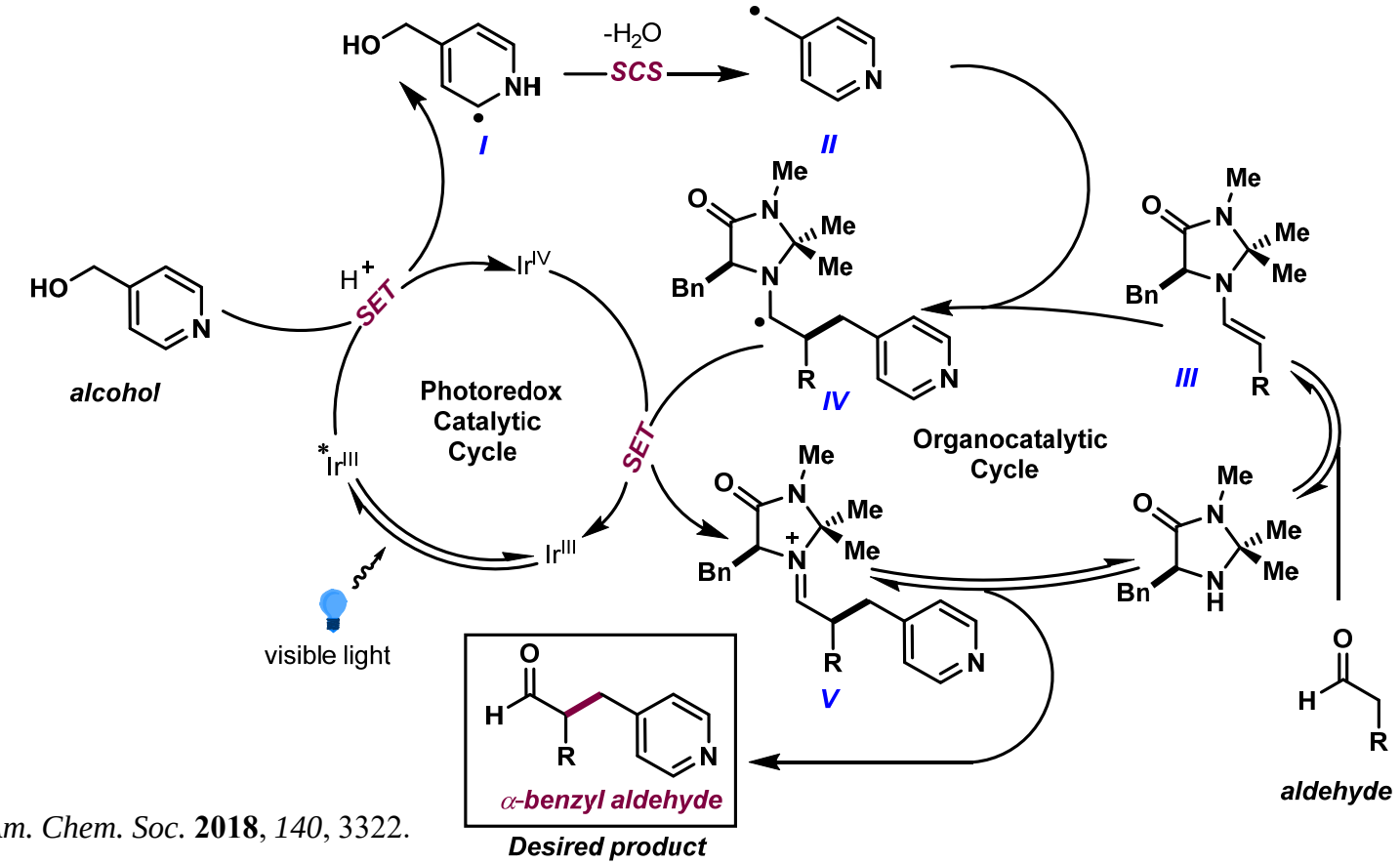


MacMillan, D. W. C. et al. *Nature* **2015**, *525*, 87.

2-3-4 醇通过SCS过程参与的醛α位的对映选择性的苄基化反应



Proposed mechanism



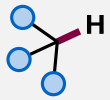
MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2018**, *140*, 3322.

03

总结与展望

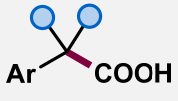
总结与展望

hv



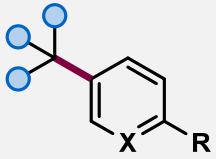
Deoxy-hydrogenation

P•, Doyle, **2018**



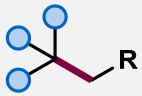
Deoxy-carboxylation

B•, Xia, **2022**



Deoxy-arylation

NHC, MacMillan, **2021**

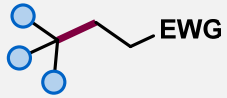


Deoxy-alkylation

NHC, MacMillan, **2022**

Deoxy- trifluoromethylation

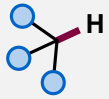
NHC, MacMillan, **2022**



Deoxy-Giese type reaction

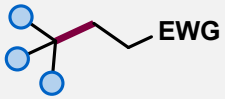
NHC, MacMillan, **2022**

TM



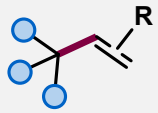
Deoxy-hydrogenation

Ti, Young, **1979**
Ti, Sato, **1980**
Ti, Barerro, **2010**



Deoxy-Giese type reaction

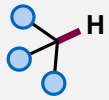
Ti, Ukaji, **2018**
Ti, Shu, **2020**
Ti, Ukaji, **2022**
Re, Nicholas, **2020**



Deoxy-alkenylation

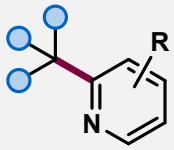
Ti, Ukaji, **2020**
Ti, Shu, **2022**
Ti, Ukaji, **2022**

SCS



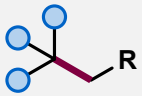
Deoxy-hydrogenation

Santiago, **2013**
Taylor, **2020**



Deoxy-heteroarylation

MacMillan, **2015**



Deoxy-alkylation

MacMillan, **2018**

展 望:

1. 在光化学活化，过渡金属活化，SCS之外，发展醇的其他的活化方式，如电化学活化，酶催化等等

2. 发展更加多样的醇的自由基去氧官能团化反应，实现多种形式的C-C键、C-杂原子键的构建

3. 目前醇的自由基去氧官能团化反应中，不对称例子较少，可以深入研究

4. 过渡金属活化模式中，开发更多的金属种类

复旦大学化学系

感谢各位老师同学
敬请批评指正

汇报人：杜远博　导 师：蔡 泉 青年研究员

汇报时间：2022.11.04