含氟C-1烷烃在氟烷基化反应中的应用

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导师：施章杰 教授

2021-11-05

1. 背景介绍

1.1 氟化学背景

1.2 氟烷基化反应简介

1.3 四类含氟C-1烷烃分子简介

2. 含氟C-1分子在氟烷基化反应中的应用

2.1 三氟甲烷 (CF_3H)

2.2 三氟碘甲烷 (CF_3I)

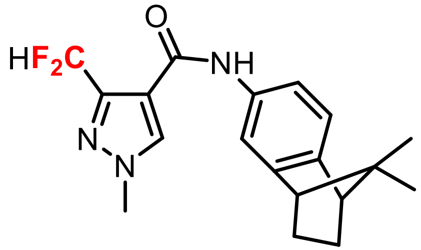
2.3 一氯二氟甲烷 ($ClCF_2H$)

2.4 一溴二氟甲烷 ($BrCF_2H$)

3. 总结与展望

1.1 氟化学背景

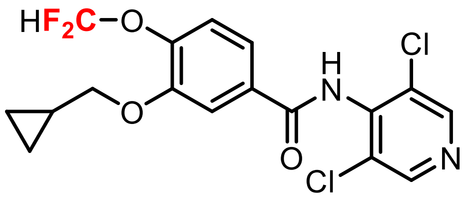
农药



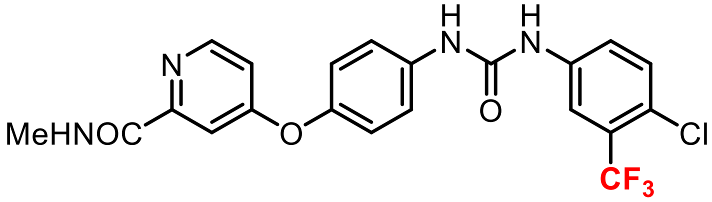
吡唑萘菌胺
（杀菌剂）

- 高选择性
- 化学稳定性

医药



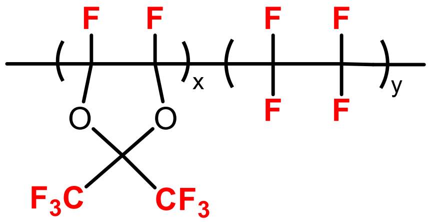
罗氟司特
（治疗慢性阻塞性肺疾病）



索拉非尼
（第一个治疗肿瘤的口服药物）

- 代谢稳定性
- 亲脂性
- 生物利用度

材料



聚四氟乙烯

- 稳定
- 耐腐蚀

Wang, M. and Li, Q. et al. *Chem. Rev*. **2015**, *115*, 683.
Song, Q. et al. *Chem. Soc. Rev*. **2020**, *49*, 9197.

1.1 氟化学背景

9 F
18.998
$1s^2 2s^2 2p^5$

电负性：3.98

范德华半径：F 135 pm
H 120 pm

C-F 键　490 kJ/mol
$C-CF_3$键　431 kJ/mol

热稳定性
化学稳定性
抗氧化性

冰晶石 (Na_3AlF_6)

萤石 (CaF_2)

萤石是唯一一种可以提炼大量氟元素矿物

氟磷灰石 ($Ca_{10}(PO_4)_6F_2$)

水温为18 ℃时，$CaF_2$100 g水中只溶解0.0016 g

质子性溶剂亲核性：

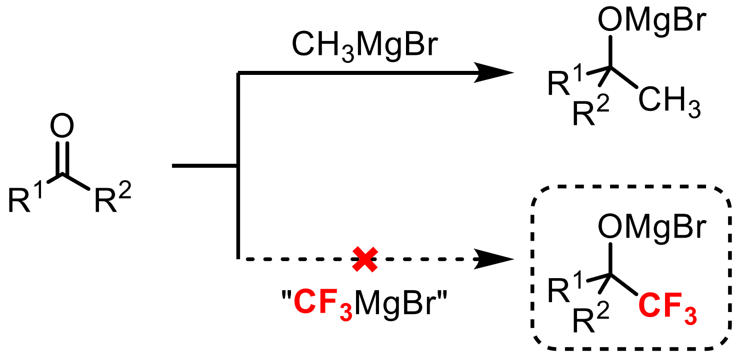
I^- > $NH_3(RNH_2)$ > RO^- > Br^- > Cl^- >> H_2O > F^-

→ 天然含氟有机化合物稀少

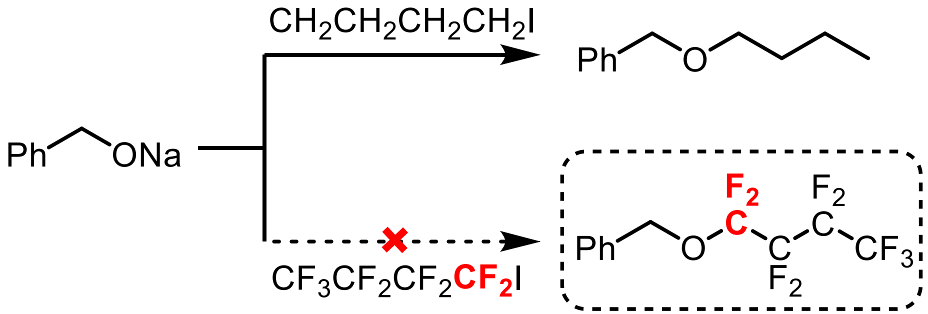
Wang, M. and Li, Q. et al. *Chem. Rev*. **2015**, *115*, 683.　　Hu, J. et al. *Chem. Soc. Rev*. **2016**, *45*, 5441.

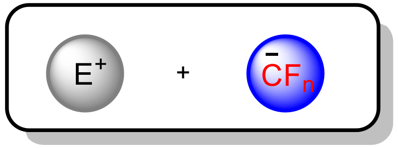
1.1 氟烷基化反应简介

氟烷基化反应的特殊性

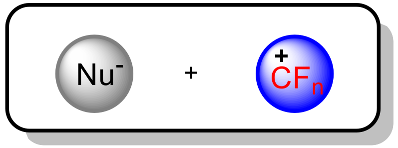


Negative Fluorine Effect (NFE)

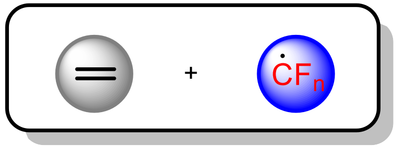




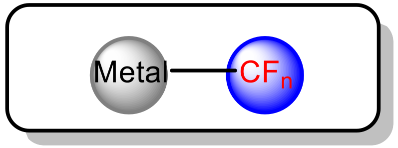
- 亲核氟烷基化反应



- 亲电氟烷基化反应



- 自由基氟烷基化反应

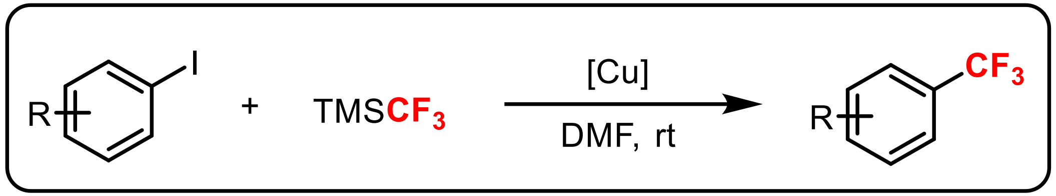


- 过渡金属参与的氟烷基化反应

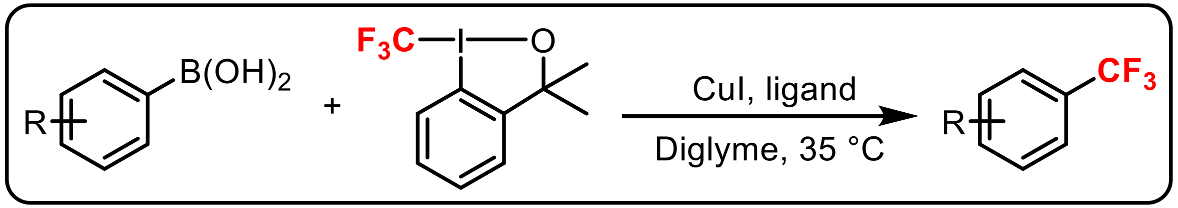
Hu, J. et al. *Chem. Soc. Rev*. **2016**, *45*, 5441.

Zhang, X. et al. *Acc. Chem. Res*. **2018**, *51*, 2264.

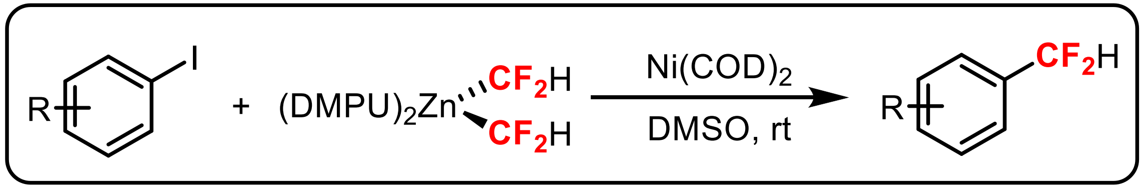
1.2 氟烷基化反应简介



Vicic, D. A. *J. Am. Chem. Soc*. **2008**, *130*, 8600.



Shen, Q. et al. *Org. Lett*. **2011**, *13*, 2342.



Vicic, D. A. et al. *J. Am. Chem. Soc*. **2016**, *138*, 2536.

三氟甲基化试剂

CF_3CO_2X (X = Na, K, Me, etc)

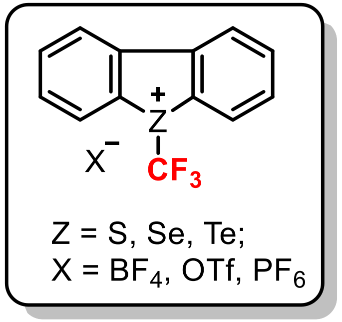
1981, Kondo

$TMSCF_3$

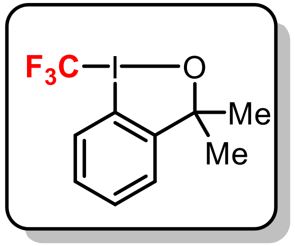
1984, Ruppert-Prakash

$FSO_2CF_2CO_2Me$

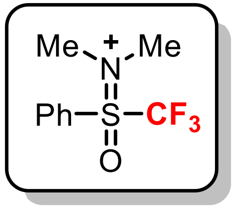
1989, Chen



1990, Umemoto



2006, Togni



2008, Shibata

二氟甲基化试剂

$(DMPU)_2Zn(CF_2H)_2$

2016, Vicic

$TMSCF_2Br$

$TMSCF_2CO_2Et$

$[Zn](SO_2CF_2H)_2$

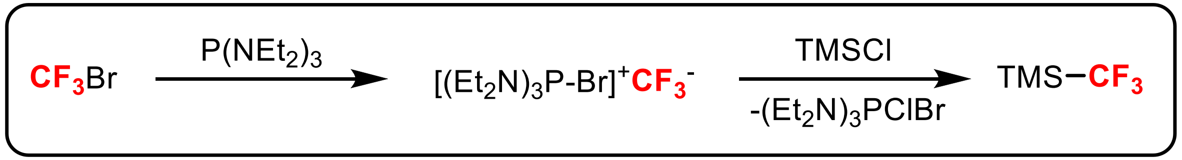
2012, Baran

$BrCF_2CO_2Et$

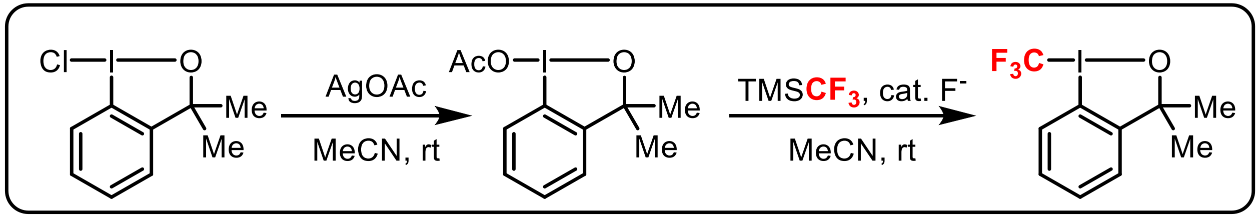
$[PPh_3PCF_2Br]^+Br^-$

Postigo, A. et al. *Chem. Eur. J*. **2017**, *23*, 14676.   Li, C. et al. *Chem. Soc. Rev*. **2021**, *50*, 6308.

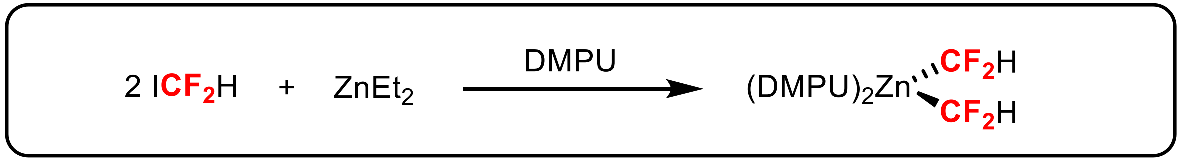
1.2 氟烷基化反应简介



Ruppert, I. et al. *Tetrahedron* **1984**, *25*, 2159.



Togni, A. et al. *Chem. Eur. J*. **2006**, *12*, 2579.



Vicic, D. A. et al. *J. Am. Chem. Soc*. **2016**, *138*, 2536.

CF_3I	300 RMB/kg
CF_3H	90 RMB/kg
$ClCF_2H$	293 RMB/kg
$BrCF_2H$	

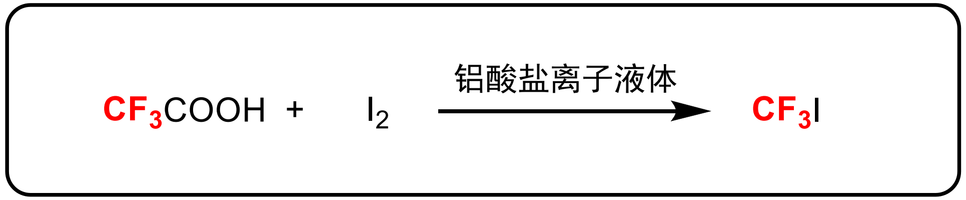
Postigo, A. et al. *Chem. Eur. J.* **2017**, *23*, 14676.

Li, C. et al. *Chem. Soc. Rev*. **2021**, *50*, 6308.

1.2 四类含氟C-1烷烃分子简介

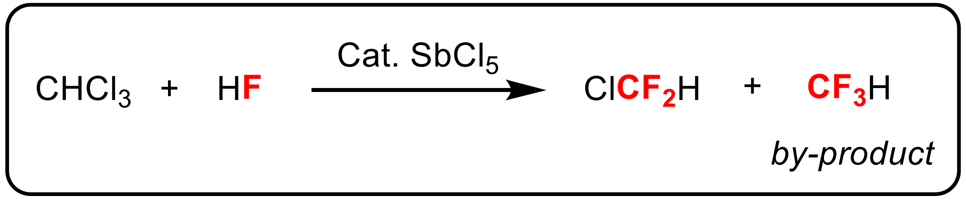
CF_3I

- 沸点：-22.5 ℃; 主要用于灭火剂和制冷剂
- 低毒，无色，无味



CF_3H

- 沸点：-82 ℃; 溶于大多有机溶剂
- 无毒，无色，无味

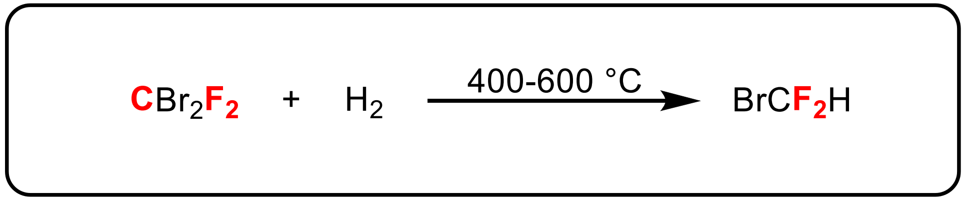


$ClCF_2H$

- 沸点：-40.8 ℃；溶于大多数有机溶剂
- 低毒，无色，轻微的甜气味
- 氟利昂-22；是合成聚四氟乙烯的原料

$BrCF_2H$

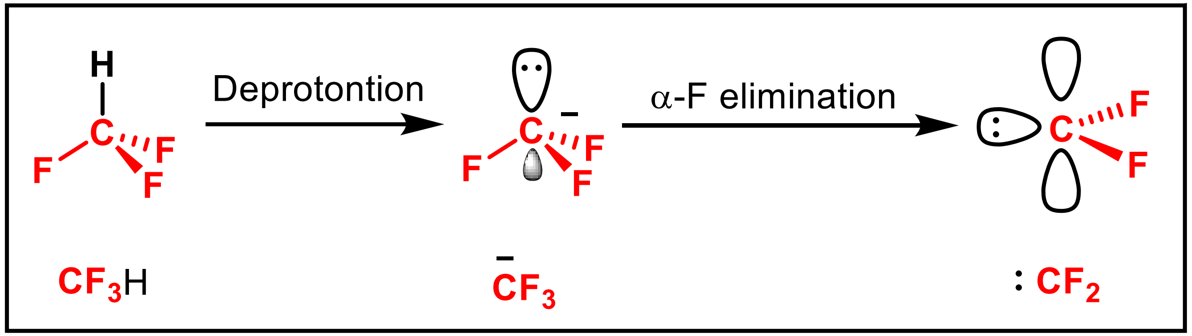
- 沸点：-14.5 ℃
- 有毒，无色，无味

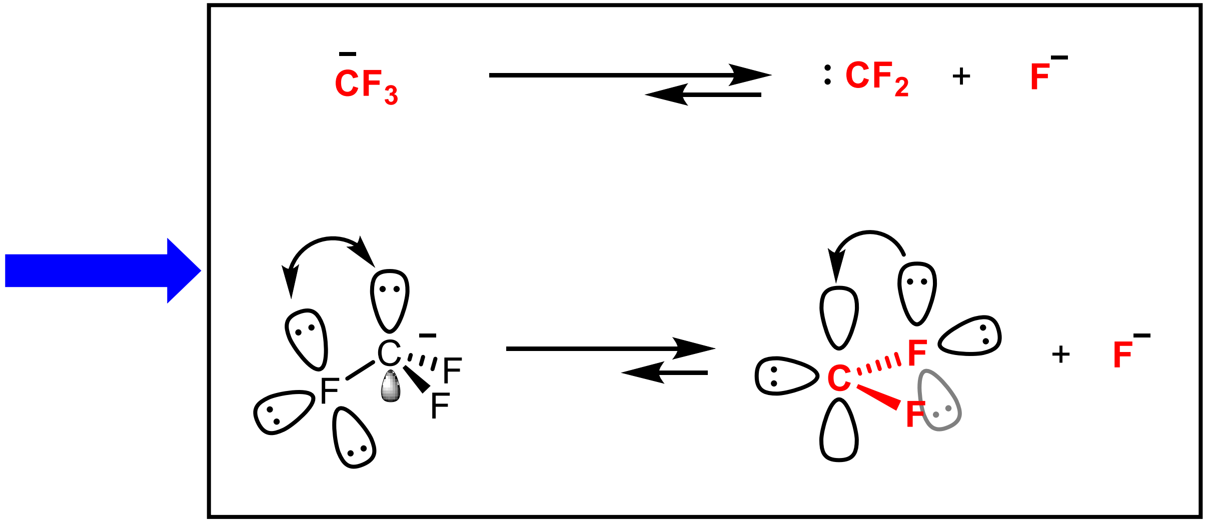


Lindley, A. A. et al. *J. Fluorine Chem*. **2005**, *126*, 1457.

1.2 四类含氟C-1烷烃分子简介

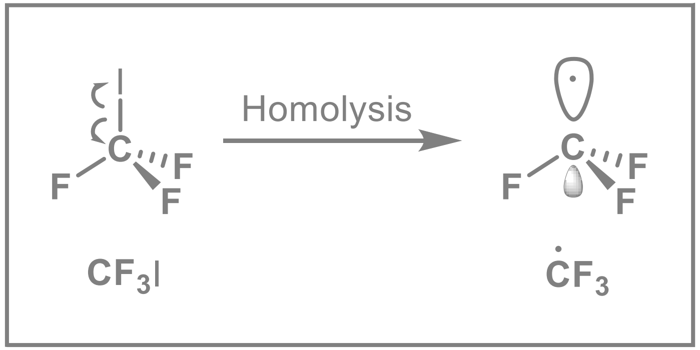
CF_3H





- C-H键酸性较弱 (pK_a = 27 in water)

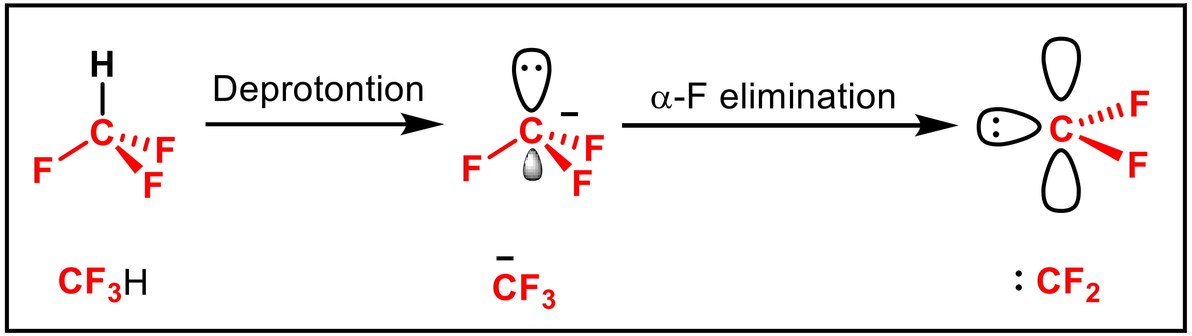
CF_3I



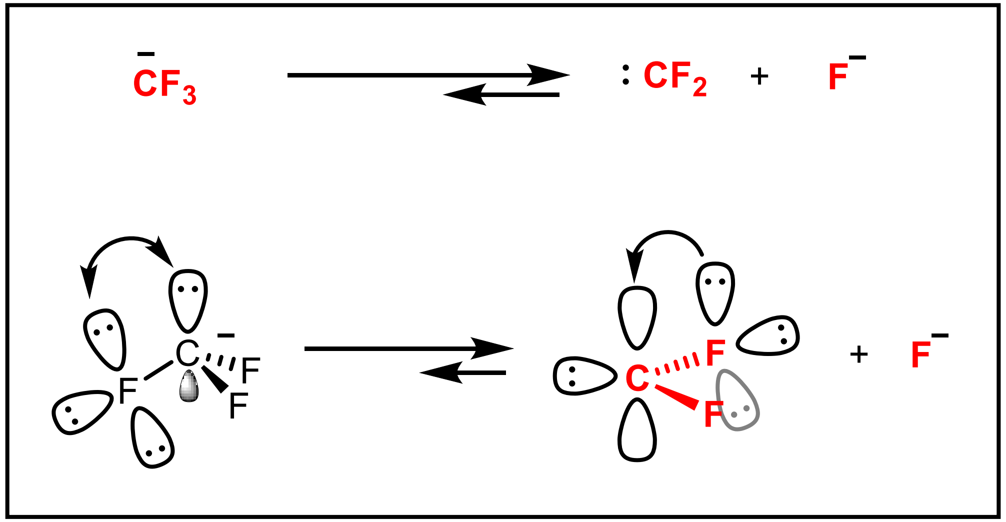
Dailey, W. P. et al. *Chem. Rev*. **1996**, *96*, 1585.

1.2 四类含氟C-1烷烃分子简介

CF_3H

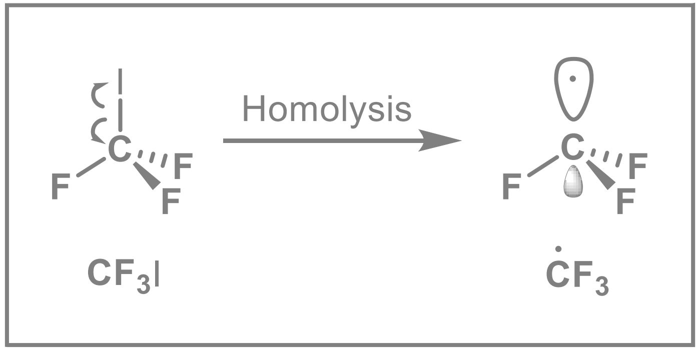


- C-H键酸性较弱 (pK_a = 27 in water)



1. DMF 用强的亲电试剂捕获
2. $CuCF_3$ 将电荷分散到金属的空轨道
3. $TMSCF_3$ 形成容易断裂的 σ 键

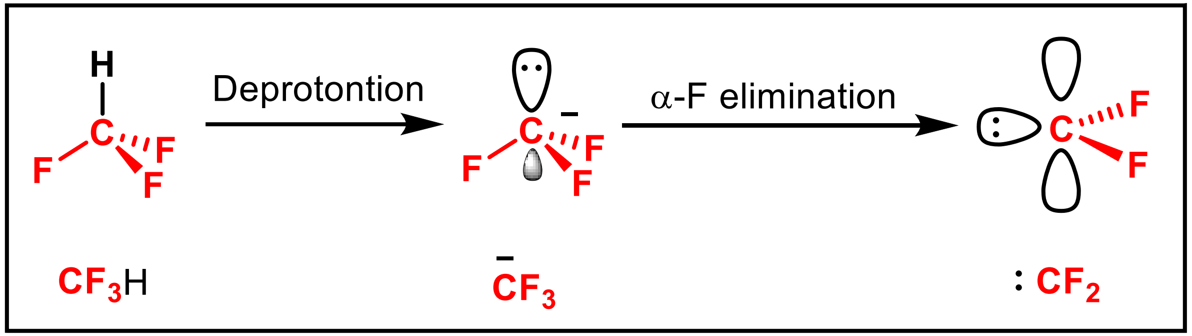
CF_3I

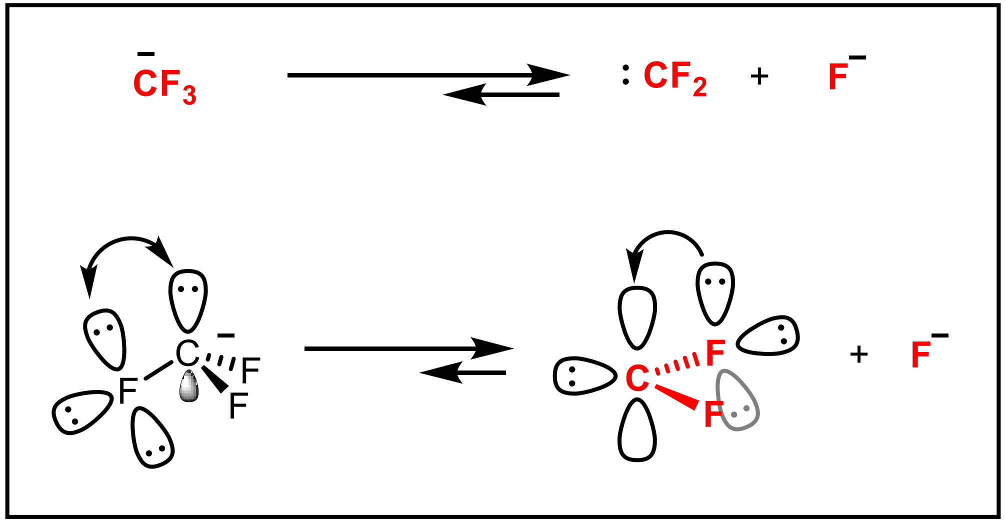


Dailey, W. P. et al. *Chem. Rev*. **1996**, *96*, 1585.

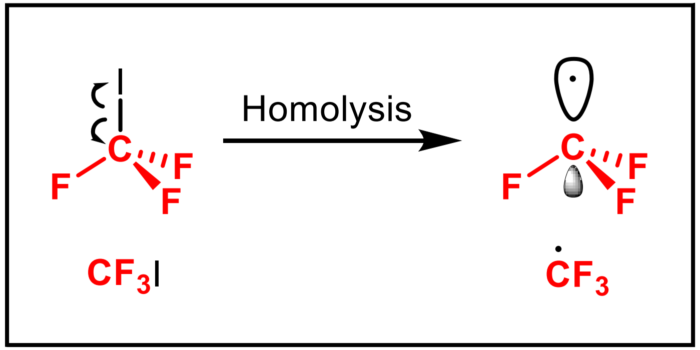
1.2 四类含氟C-1烷烃分子简介

CF_3H





CF_3I



热力学稳定性

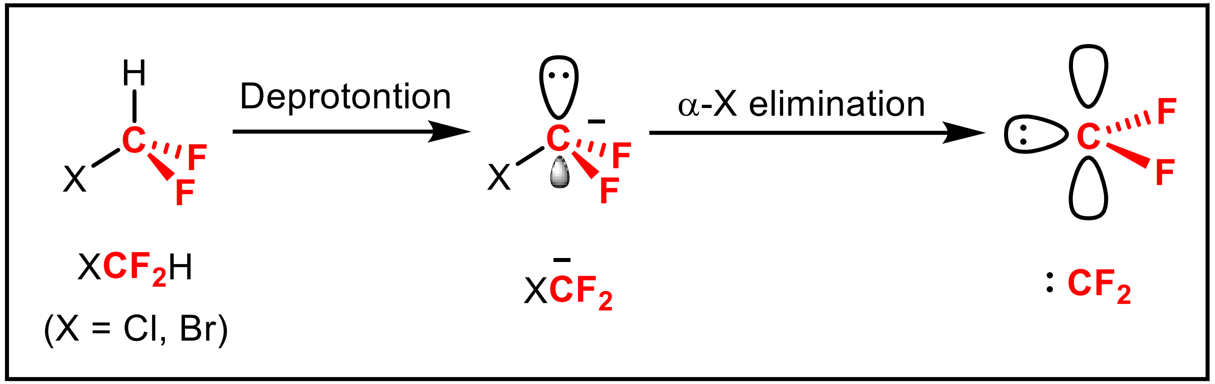
$\dot{C}H_3$ > $\dot{C}F_3$

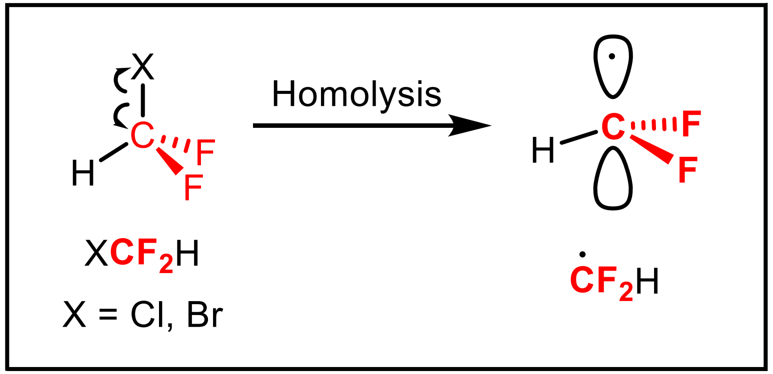
Hu, J. et al. *Chem. Soc. Rev.* **2016**, *45*, 5441.

1.2 四类含氟C-1烷烃分子简介

$ClCF_2H$

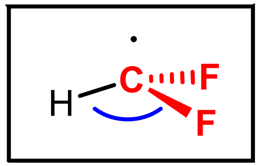
$BrCF_2H$





热力学稳定性

$\dot{C}FH_2 > \dot{C}F_2H > \dot{C}H_3 > \dot{C}F_3$



Hu, J. et al. *Chem. Soc. Rev.* **2016**, *45*, 5441.

1. 背景介绍

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1.3 四类含氟C-1烷烃分子简介

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2.2 三氟碘甲烷 (CF_3I)

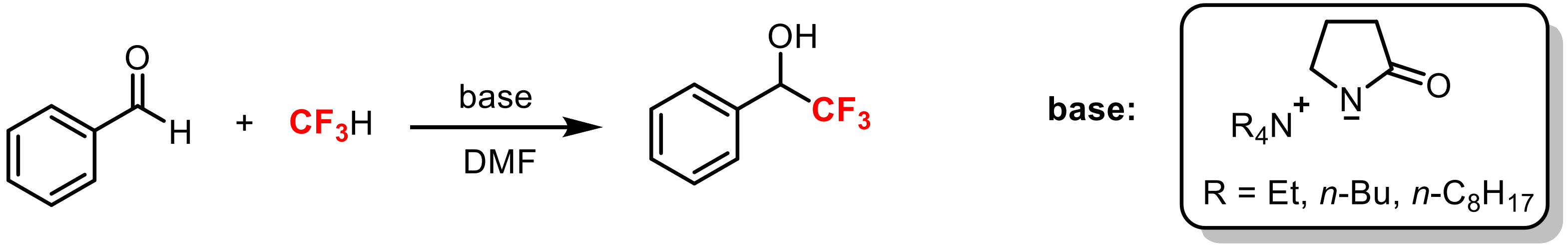
2.3 一氯二氟甲烷 ($ClCF_2H$)

2.4 一溴二氟甲烷 ($BrCF_2H$)

3. 总结与展望

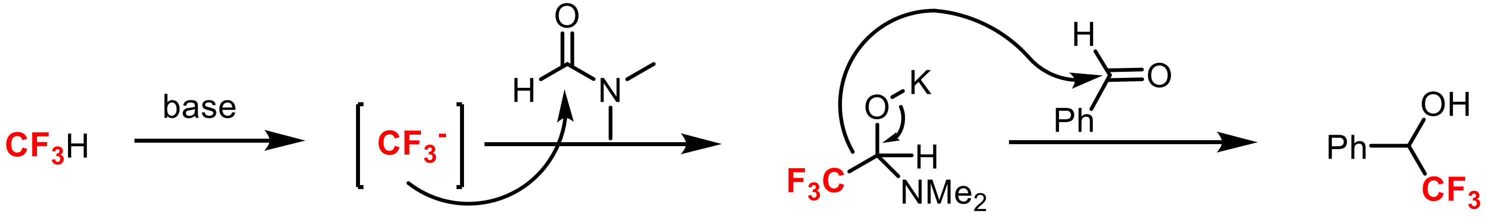
2.1 三氟甲烷 (CF_3H)

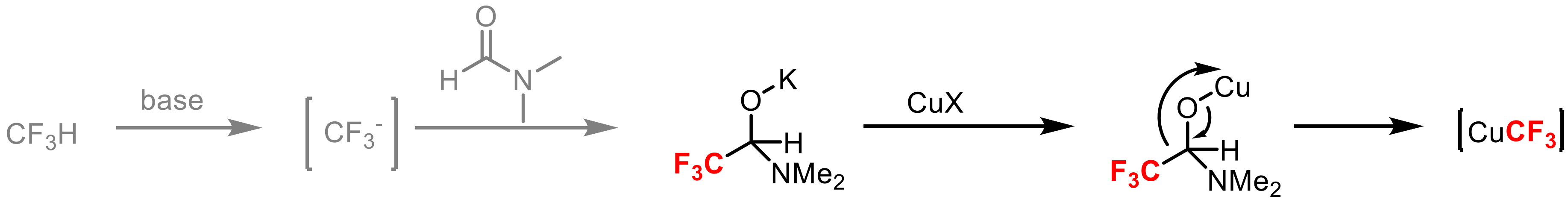
2.1.1 首例使用CF_3H进行的亲核三氟甲基反应



Shono, T. et al. *J. Org. Chem.* **1991**, *56*, 2.

2.1.2 溶剂DMF作为亲电试剂的关键作用

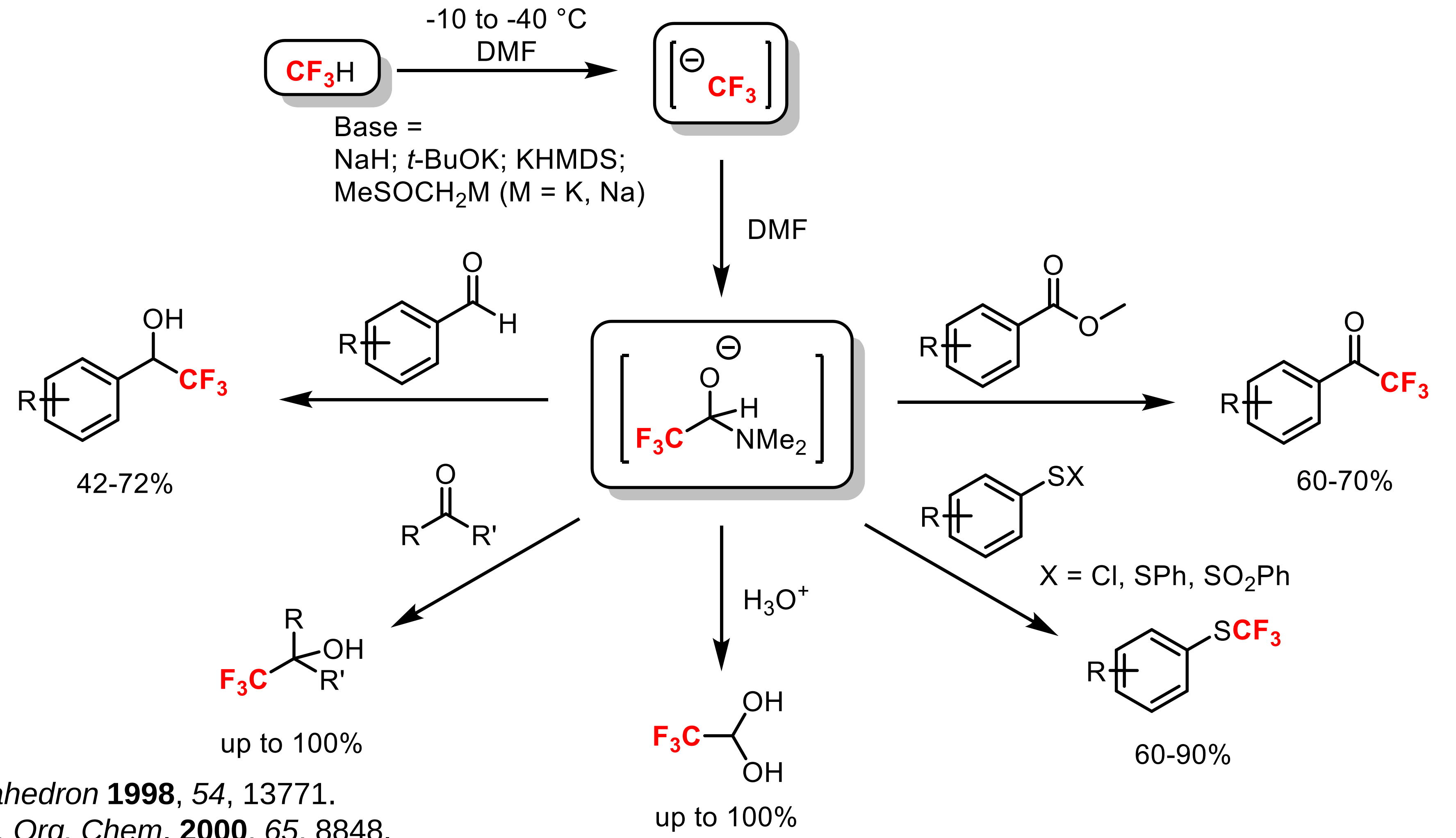




Roques, N. et al. *Tetrahedron* **1998**, *54*, 13771.
Normant, J. F. et al. *Tetrahedron* **2000**, *56*, 275.

2.1 三氟甲烷 (CF_3H)

2.1.3 用CF_3H对不同底物的三氟甲基化反应

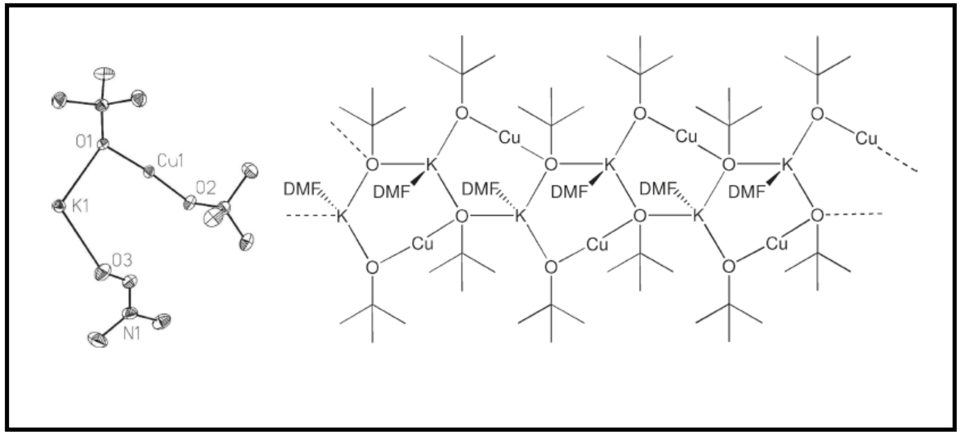


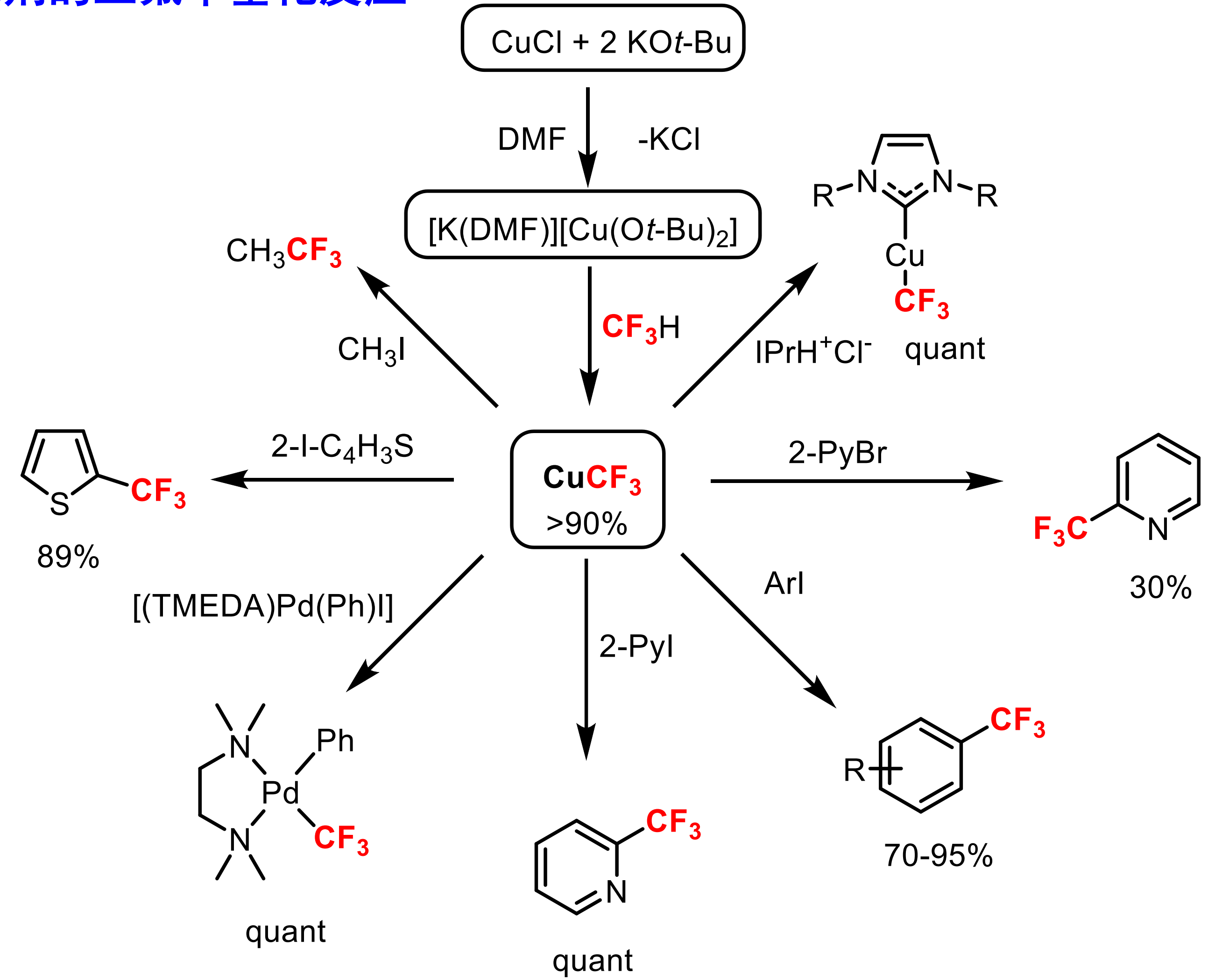
Roques, N. et al. *Tetrahedron* **1998**, *54*, 13771.
Langlois, B. R. et al. *J. Org. Chem*. **2000**, *65*, 8848.
Normant, J. F. et al. *Tetrahedron* **2000**, *56*, 275.

2.1 三氟甲烷 (CF_3H)

2.1.4 由CF_3H合成的$CuCF_3$试剂对一系列亲电试剂的三氟甲基化反应

[K(DMF)][Cu(O*t*-Bu)$_2$]

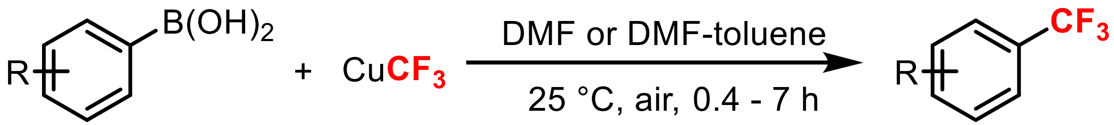


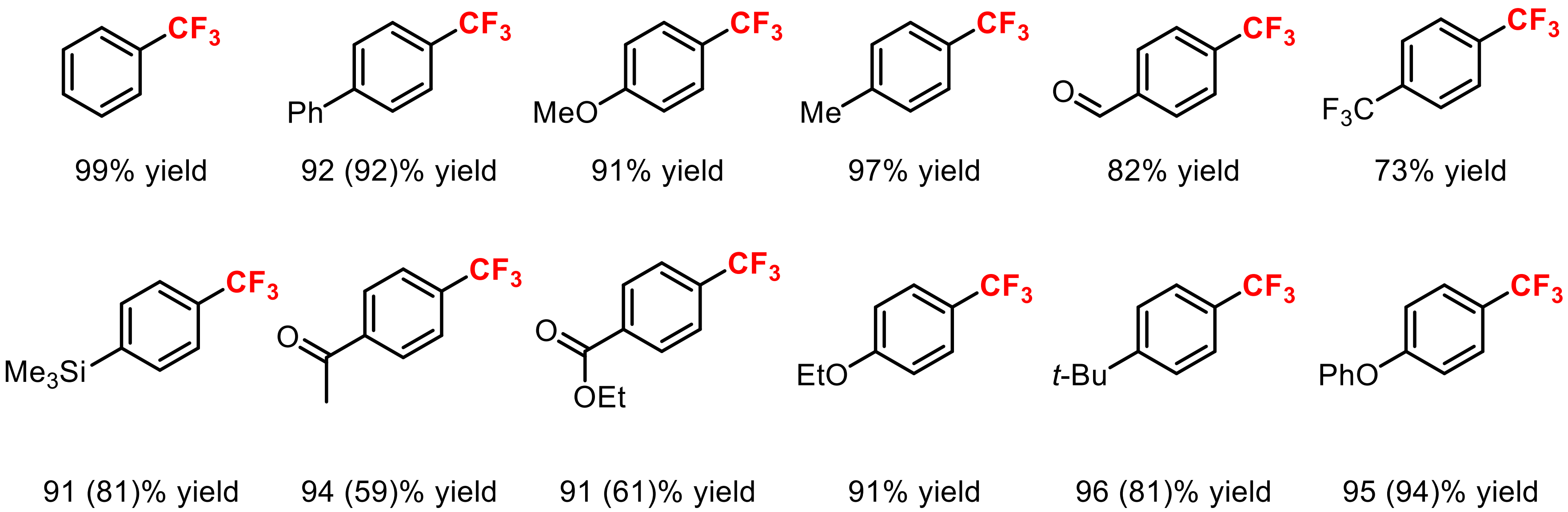


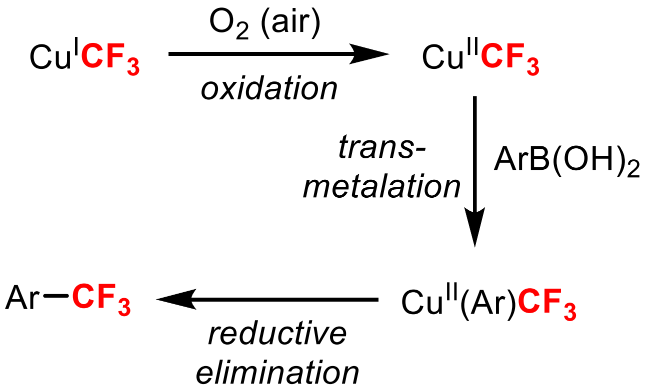
Grushin, V. V. et al. *J. Am. Chem. Soc*. **2011**, *133*, 20901.

2.1 三氟甲烷 (CF_3H)

2.1.5 $CuCF_3$对芳基硼酸的三氟甲基化反应



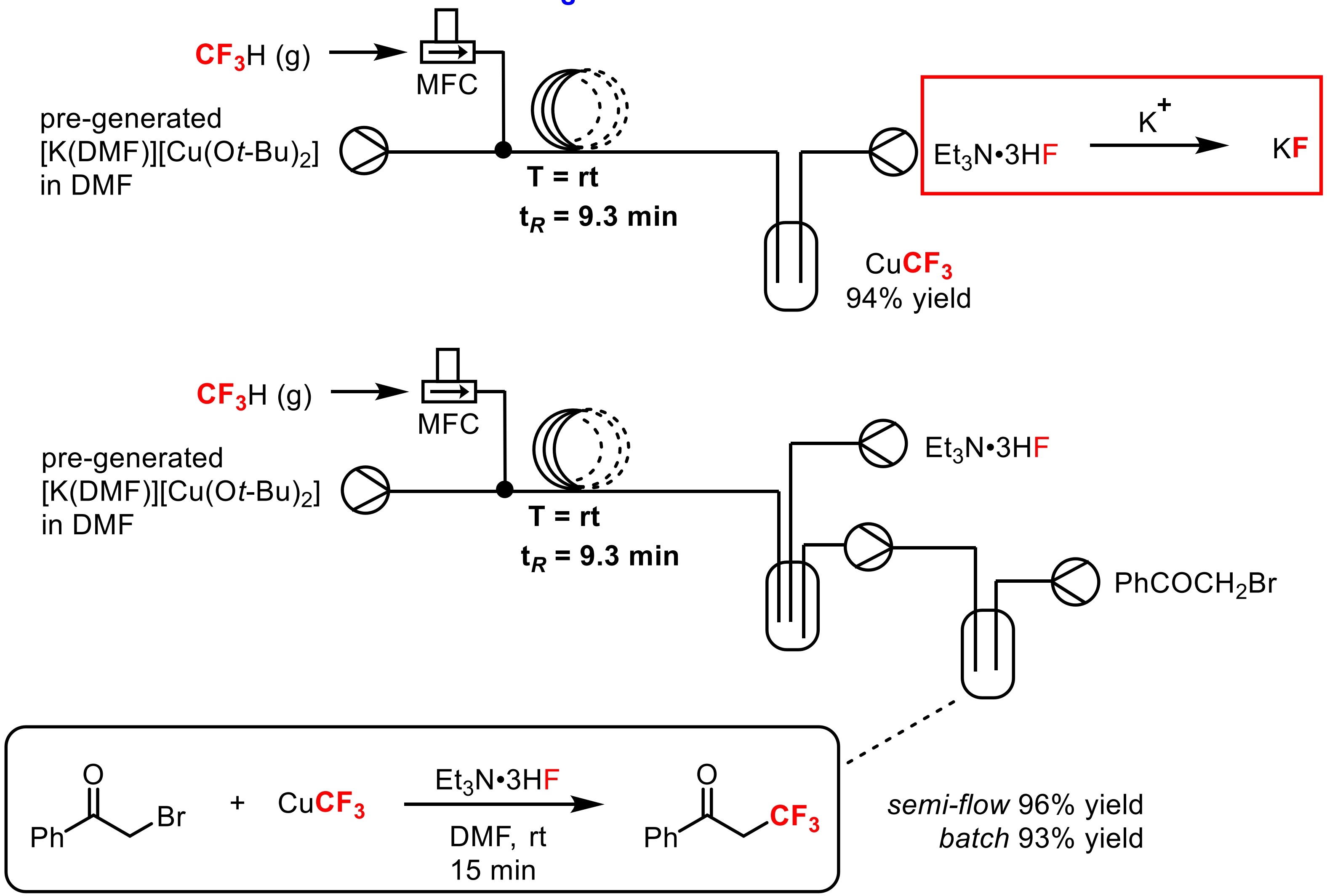




Grushin, V. V. et al. *Angew. Chem. Int. Ed*. **2012**, *51*, 7767.

2.1 三氟甲烷 (CF_3H)

2.1.6 首次使用流动化学技术制备$CuCF_3$

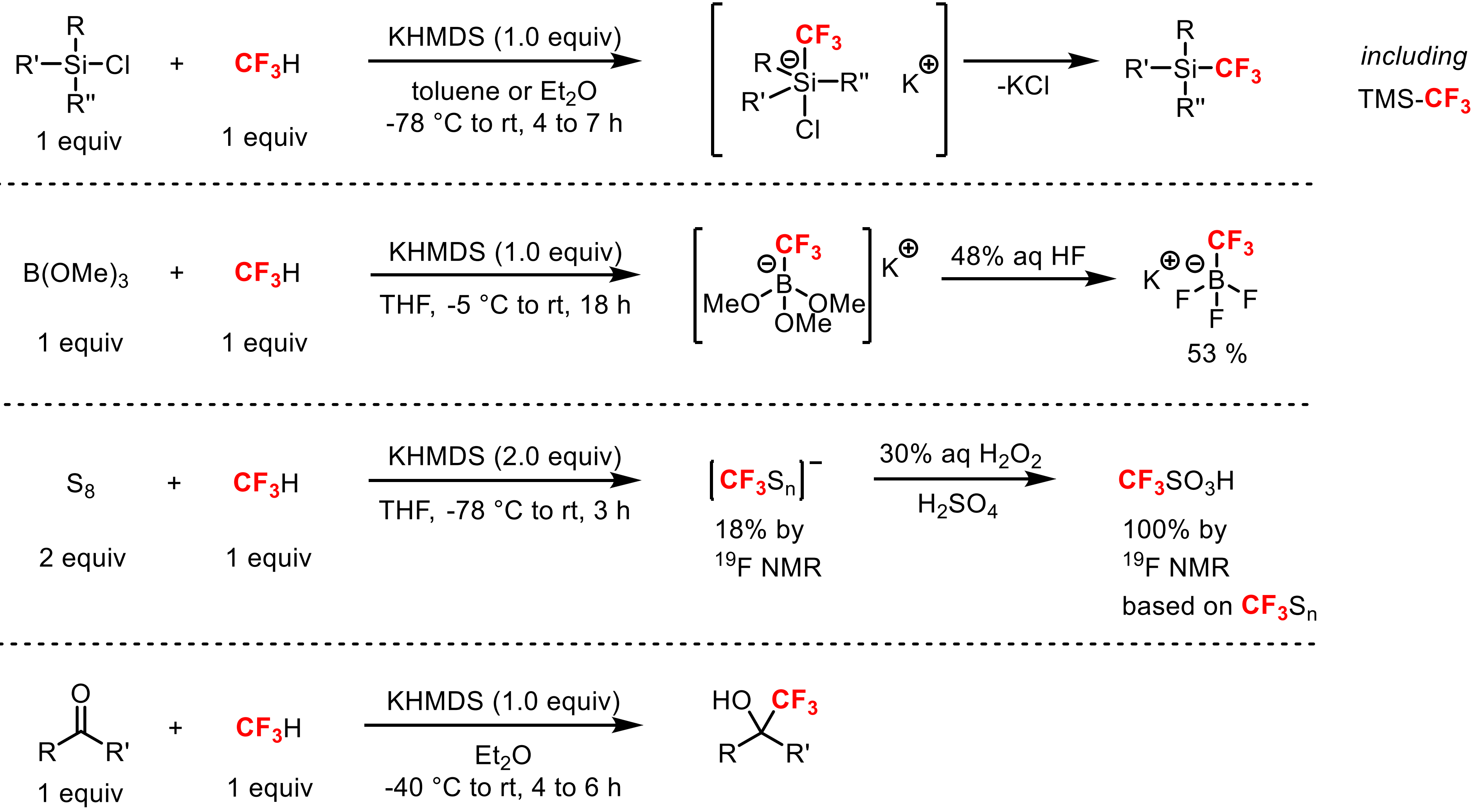


- 精确的温度控制
- 产物完全与反应物分离
- 高效、快速
- 安全使用活性或有毒试剂
- 易于进行多相反应
- 易于自动化、模块化

Grushin, V. V. et al. *Org. Process Res. Dev*. **2014**, *18*, 1020.

2.1 三氟甲烷 (CF_3H)

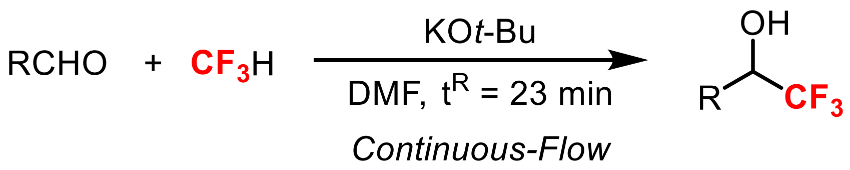
2.1.7 使用CF_3H直接进行亲核三氟甲基化反应



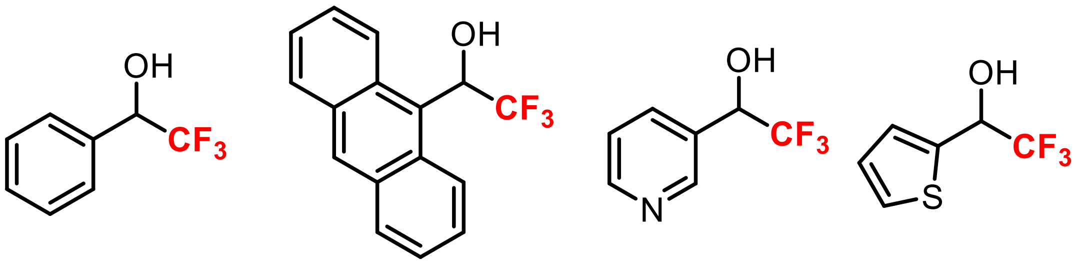
Prakash, G. K. S. et al. *Science* **2012**, *338*, 1324.

2.1 三氟甲烷 (CF_3H)

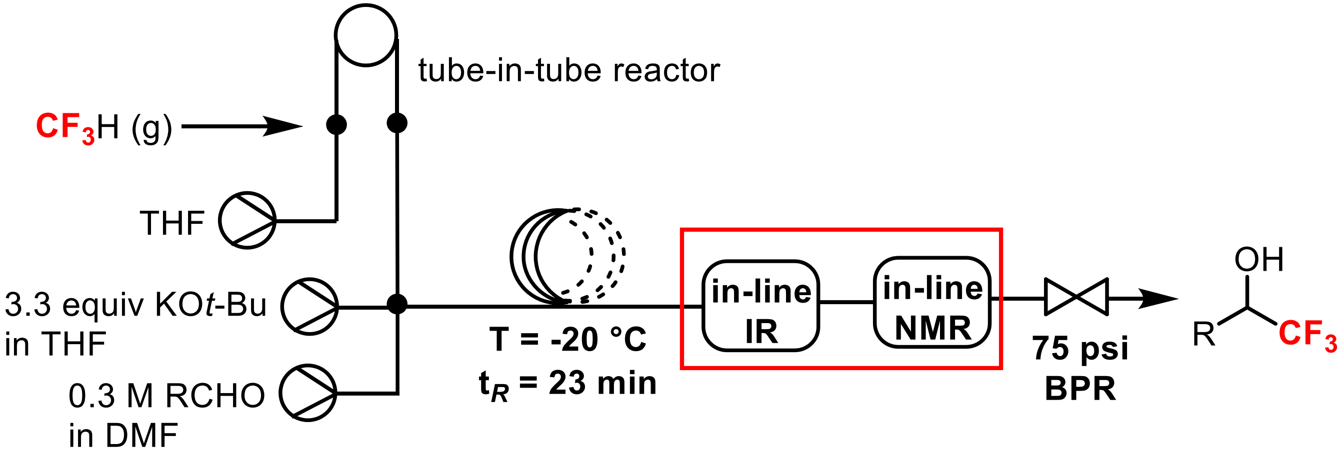
2.1.8 使用流动化学技术合成三氟烷基化合物



Selected examples



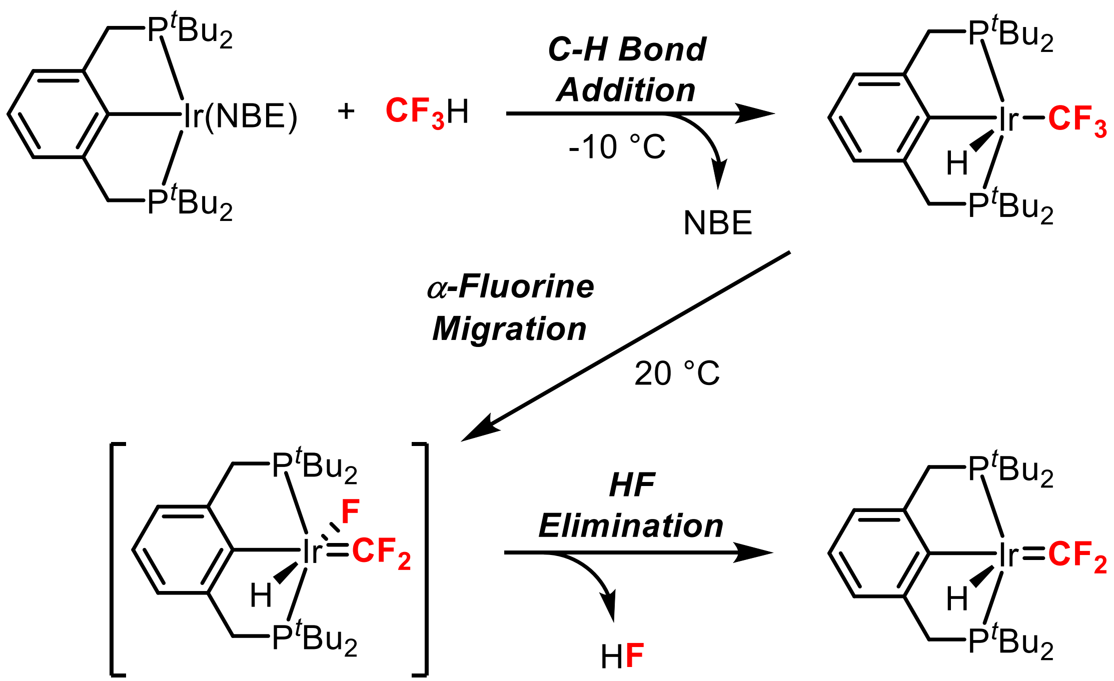
88%	75%	97%	88%

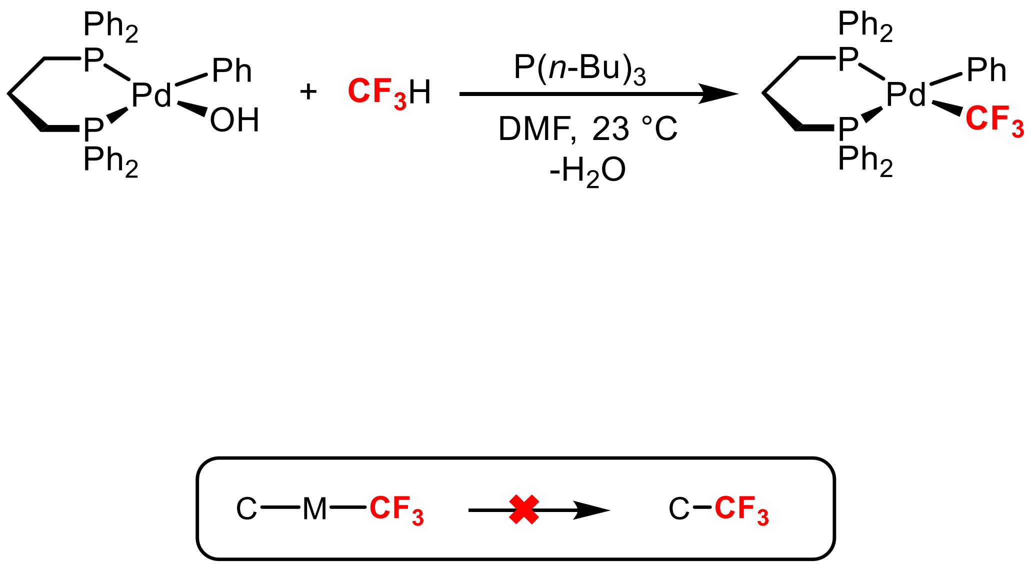


Ley, S. V. et al. *ACS Sustainable Chem*. **2018**, *6*, 1489.

2.1 三氟甲烷 (CF_3H)

2.1.9 过渡金属对三氟甲烷的活化



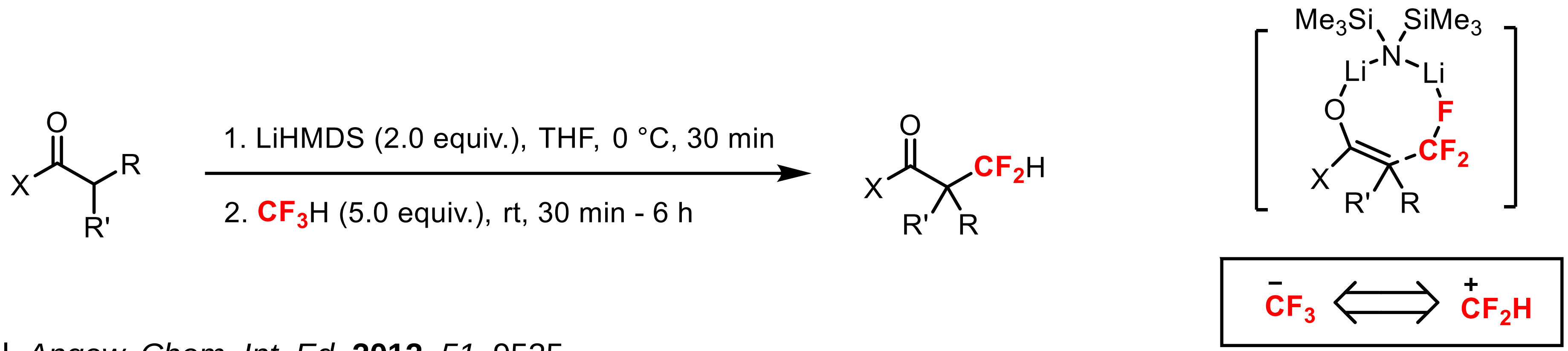


Goldman, A. S. et al. *Science* **2011**, *332*, 1545.

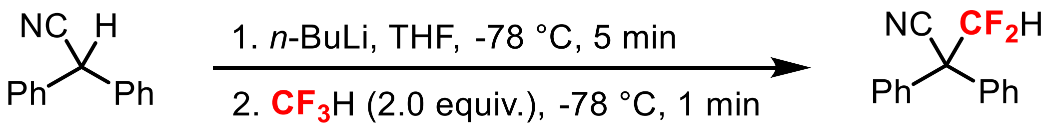
Grushin, V. V. et al. *J. Am. Chem. Soc.* **2013**, *135*, 16837.

2.1 三氟甲烷 (CF_3H)

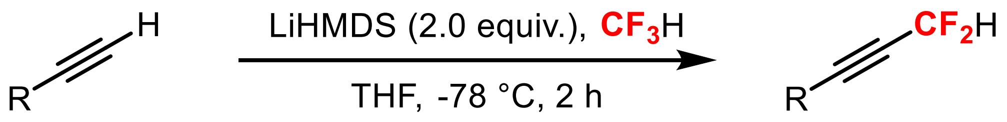
2.1.10 利用C-F键活化策略对羰基α位进行二氟甲基化



Mikami, K. et al. *Angew. Chem. Int. Ed*. **2012**, *51*, 9535.



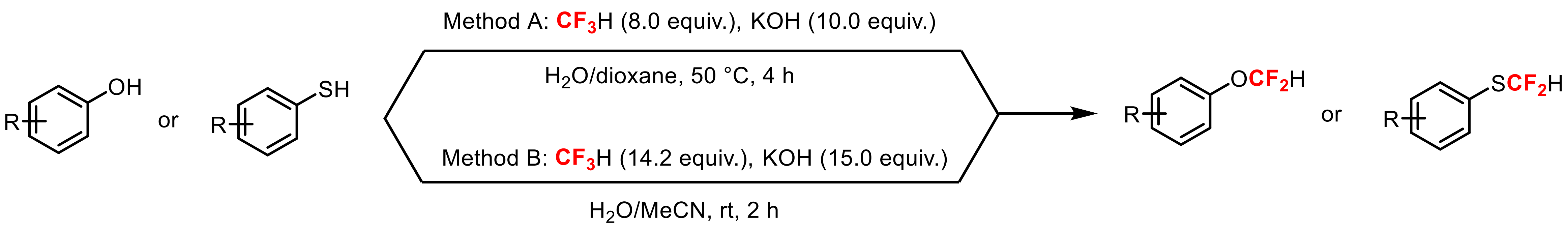
Mikami, K. et al. *Org. Lett*. **2015**, *17*, 4882.



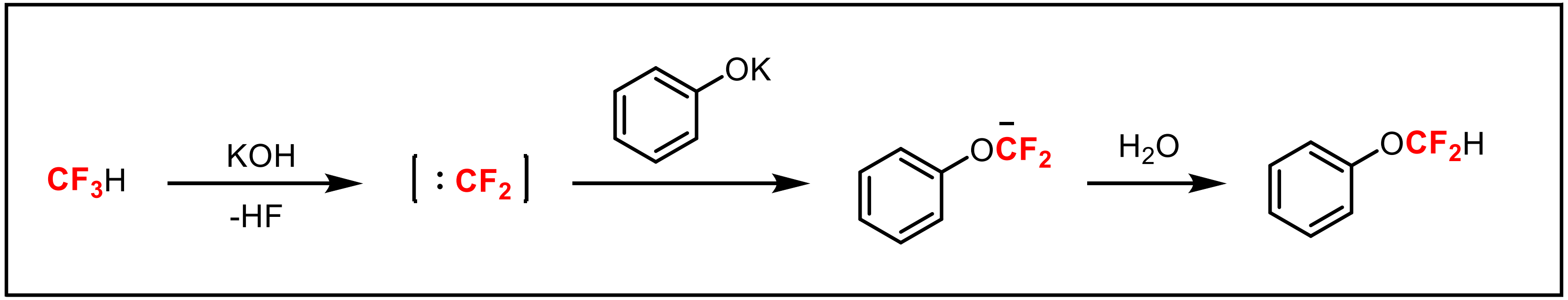
Mikami, K. et al. *Org. Lett*. **2016**, *18*, 3354.

2.1 三氟甲烷 (CF_3H)

2.1.11 CF_3H作为二氟卡宾源合成芳基二氟甲基醚/硫醚



机理



Dolbier, W. R. et al. *J. Org. Chem*. **2013**, *78*, 8904.

1. 背景介绍

1.1 氟化学背景

1.2 氟烷基化反应简介

1.3 四类含氟C-1烷烃分子简介

2. 含氟C-1分子在氟烷基化反应中的应用

2.1 三氟甲烷 (CF_3H)

2.2 三氟碘甲烷 (CF_3I)

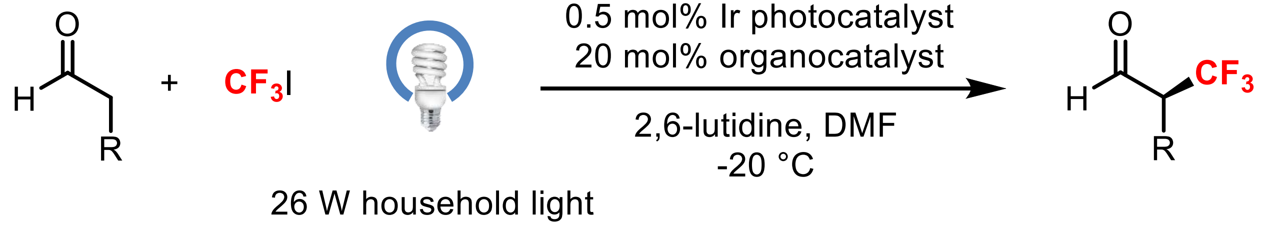
2.3 一氯二氟甲烷 ($ClCF_2H$)

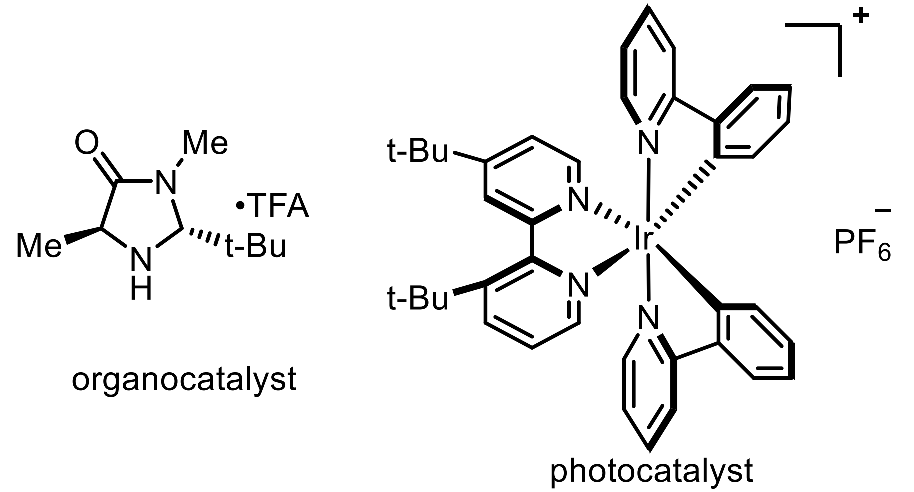
2.4 一溴二氟甲烷 ($BrCF_2H$)

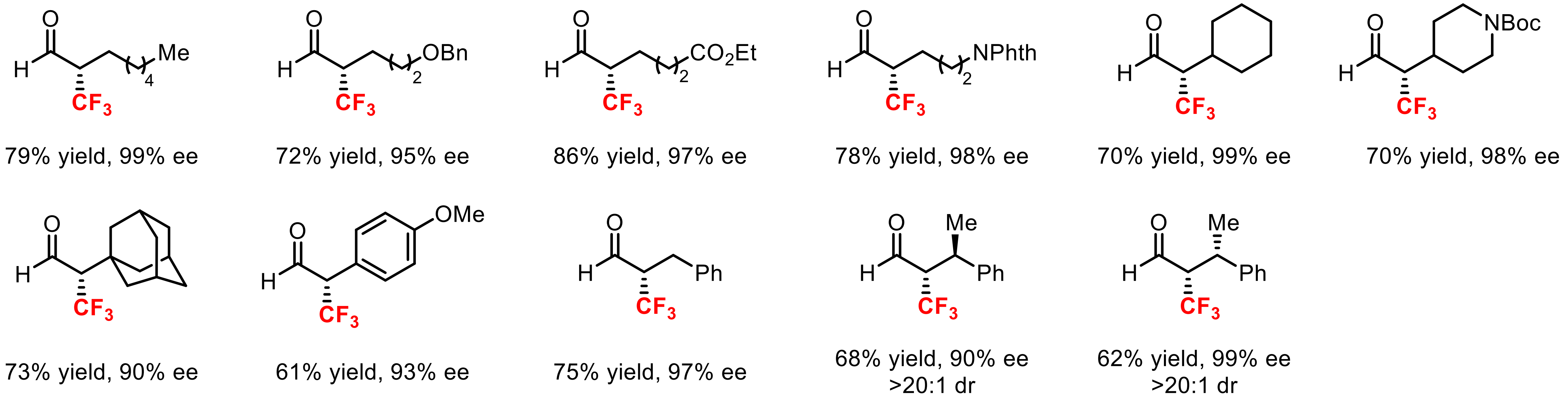
3. 总结与展望

2.2 三氟碘甲烷 (CF_3I)

2.2.1 对映选择性的醛羰基α位三氟甲基化反应



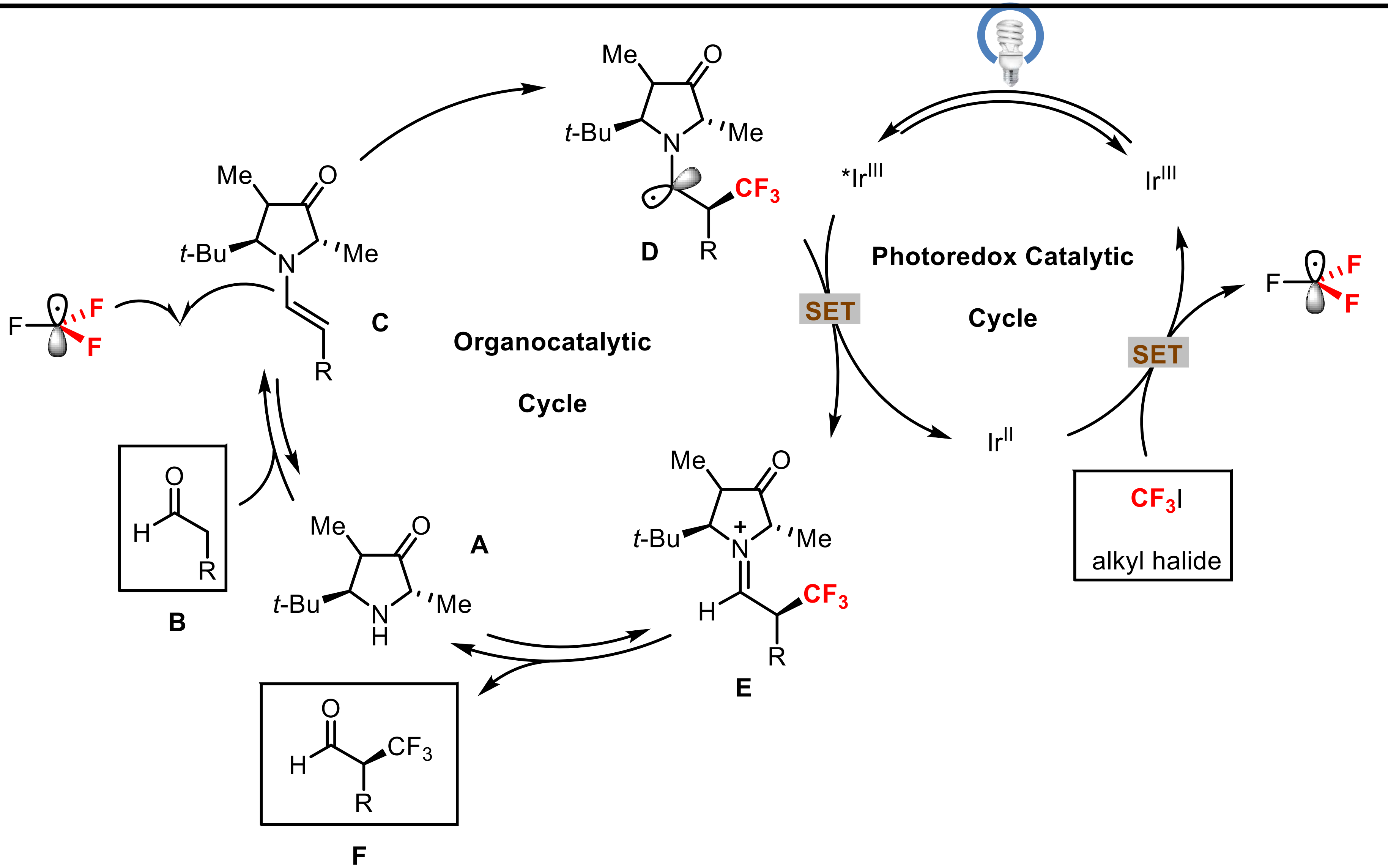




MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

2.2 三氟碘甲烷 (CF_3I)

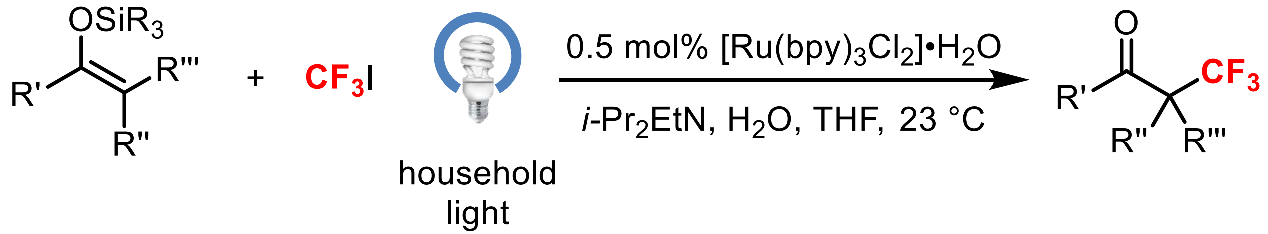
可能的机理



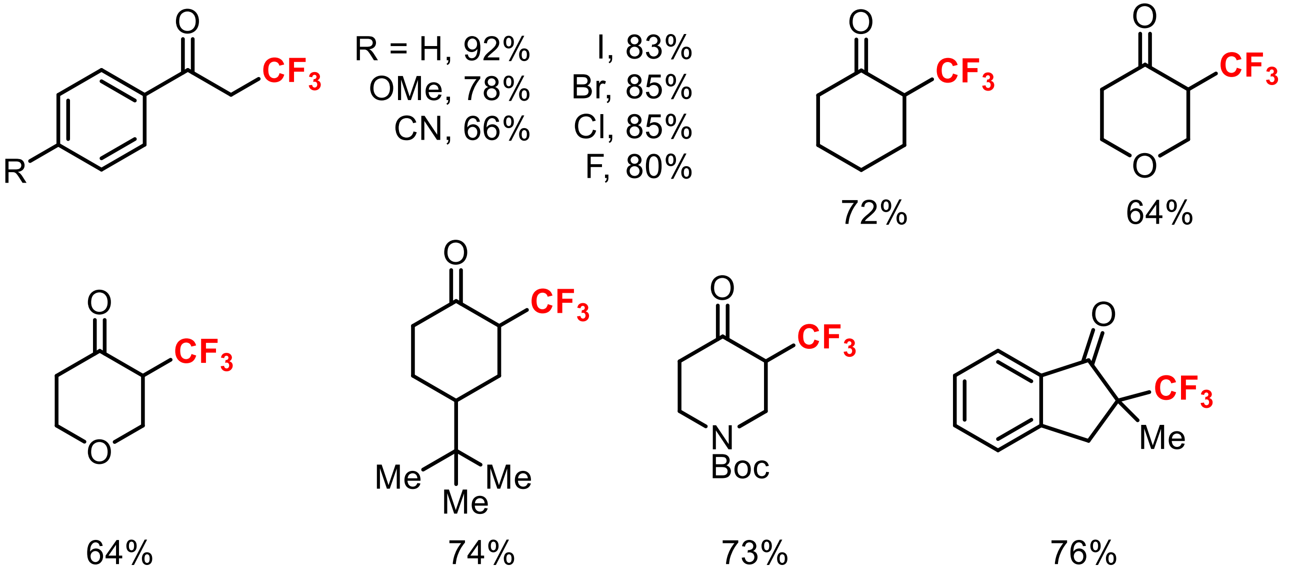
MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

2.2 三氟碘甲烷 (CF_3I)

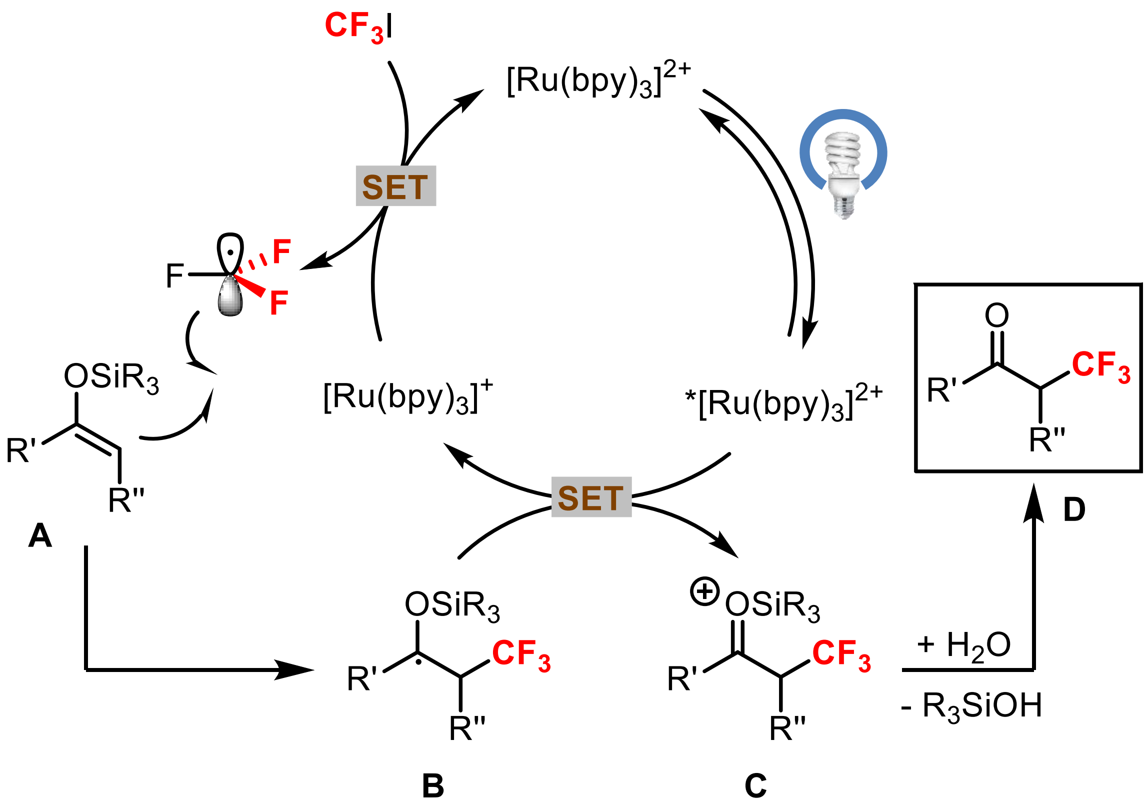
2.2.2 酮羰基α位的三氟甲基化反应



Selected examples



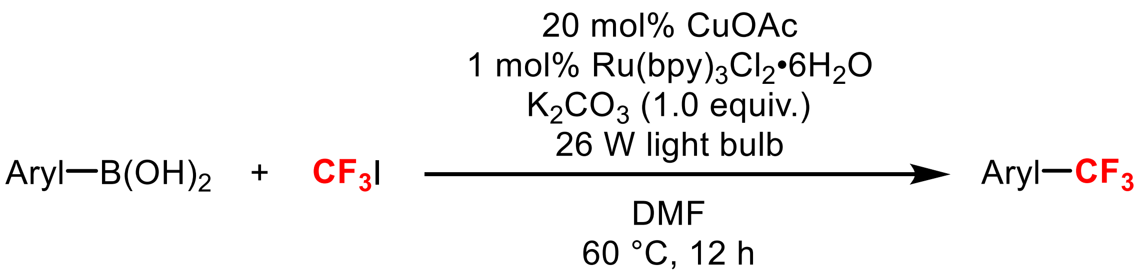
可能的机理



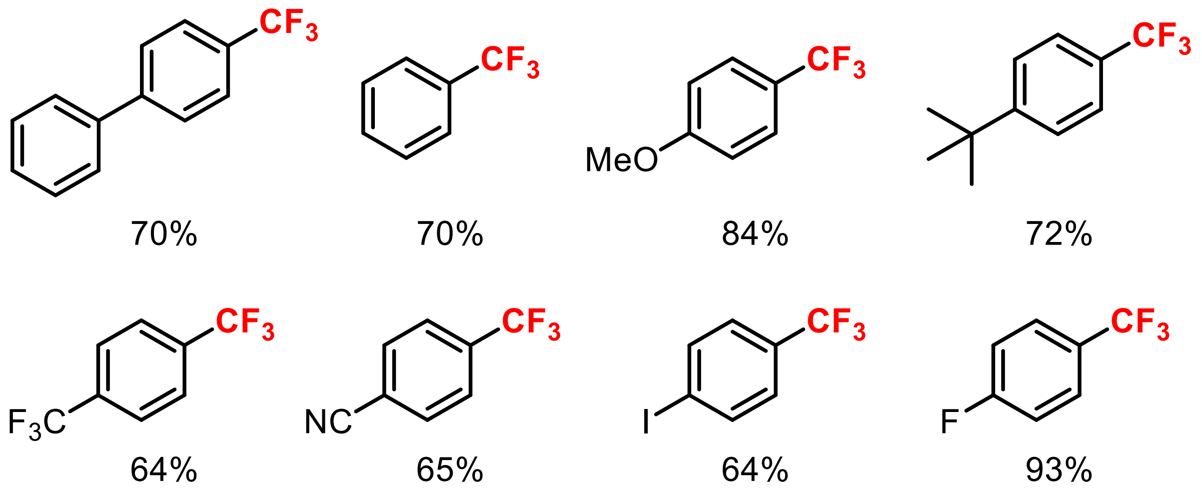
MacMillan, D. W. C. et al. *Angew. Chem. Int. Ed*. **2011**, *50*, 6119.

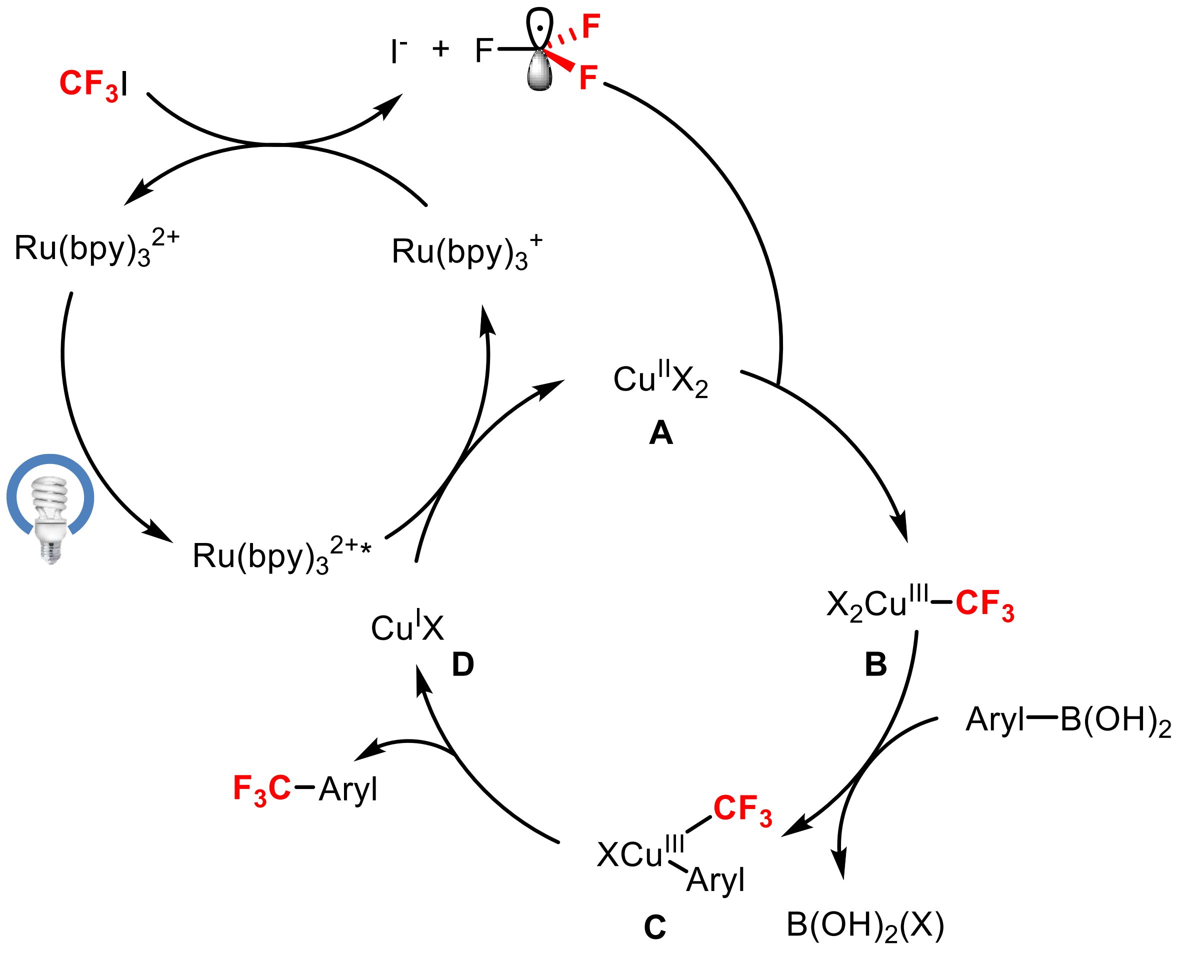
2.2 三氟碘甲烷 (CF_3I)

2.2.3 Cu/光催化的芳基硼酸的三氟甲基化反应



Selected examples

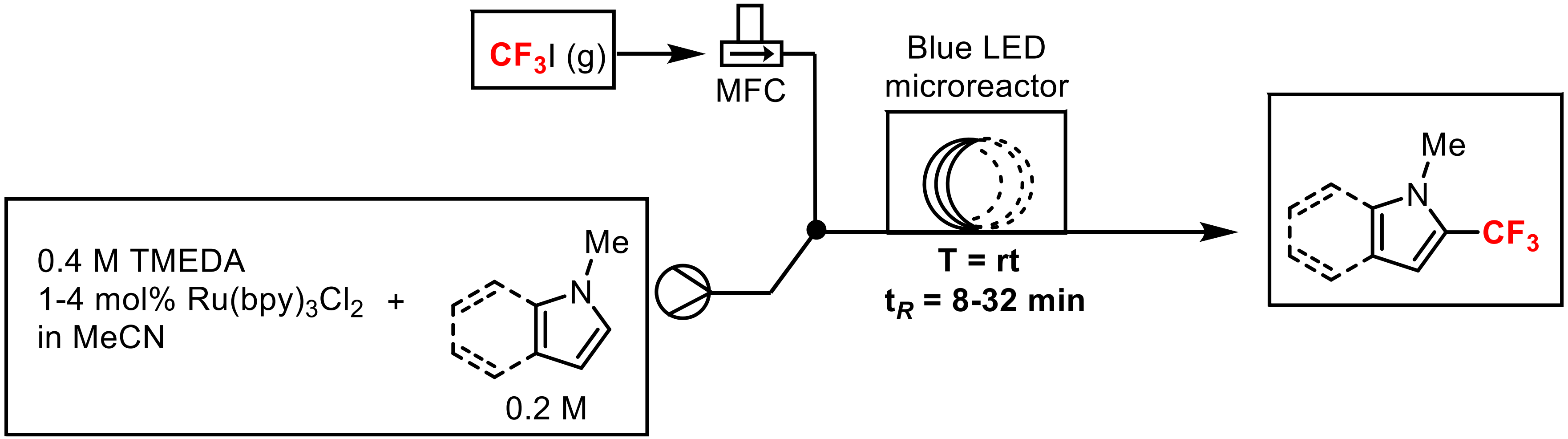




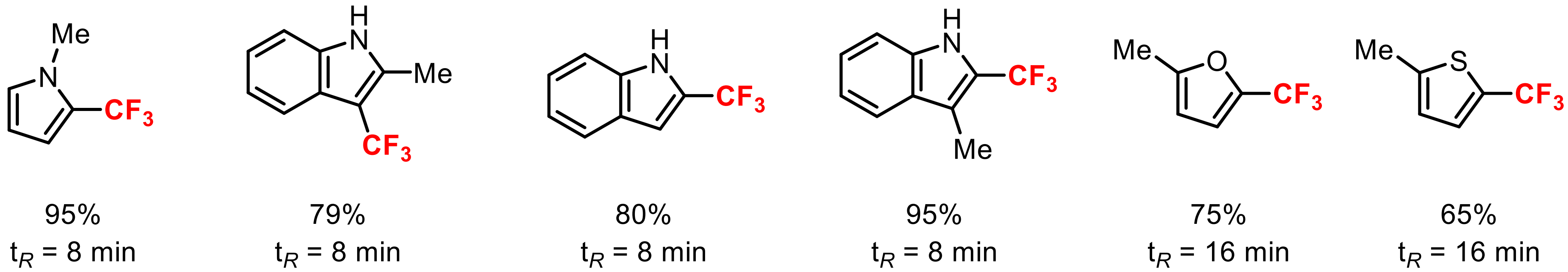
Sanford, M. S. et al. *J. Am. Chem. Soc*. **2012**, *134*, 9034.

2.2 三氟碘甲烷 (CF_3I)

2.2.4 流动化学光催化条件下对五元杂芳环的三氟甲基化反应



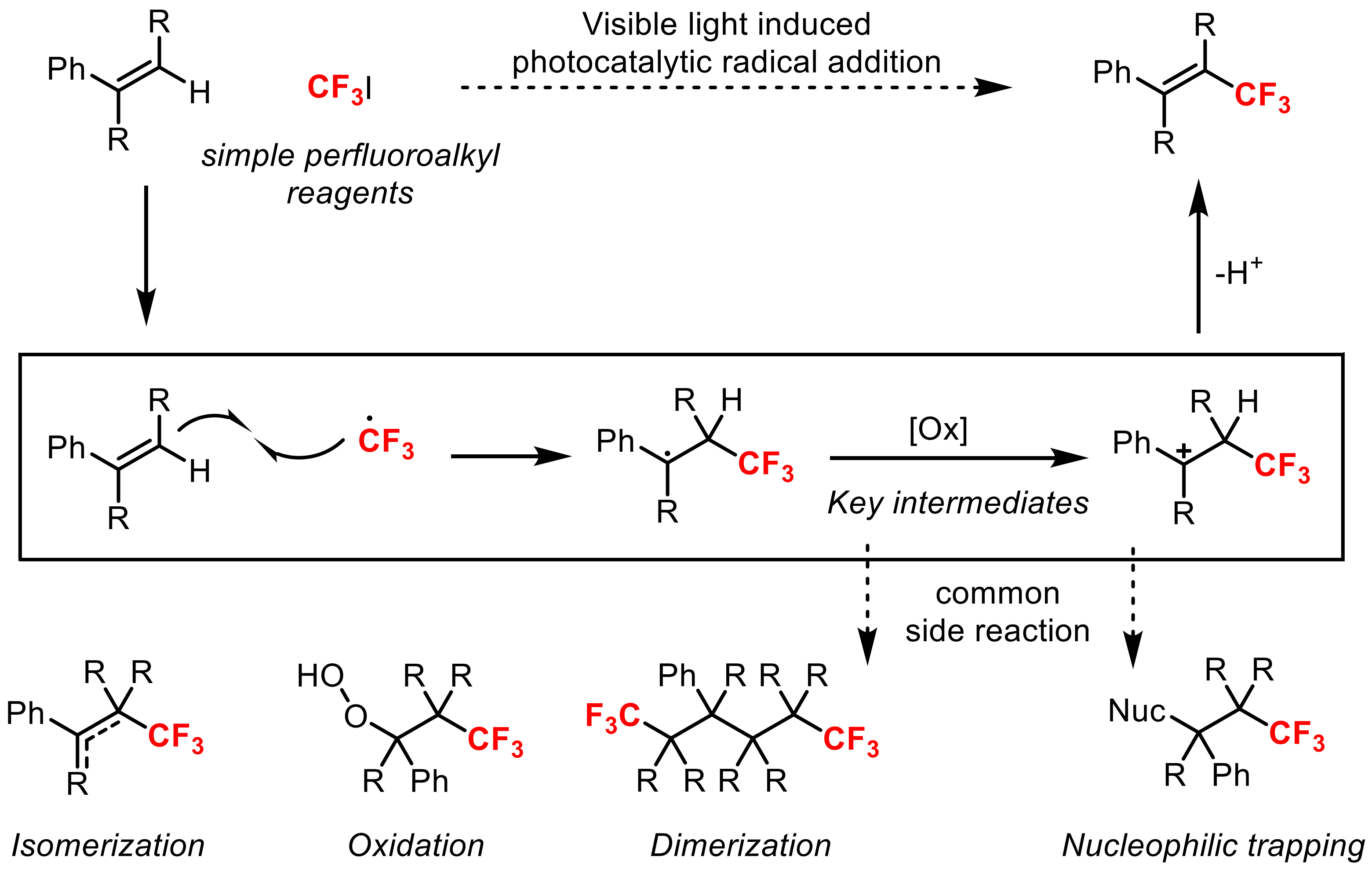
Selected examples



Noël, T. et al. *ChemSusChem* **2014**, *7*, 1612.

2.2 三氟碘甲烷 (CF_3I)

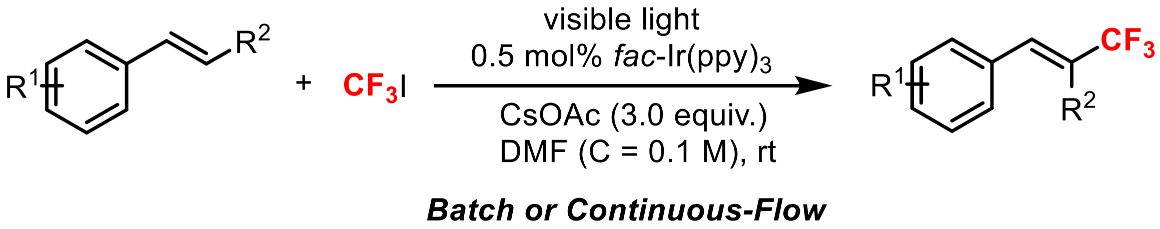
2.2.5 苯乙烯类化合物的三氟甲基化和氢三氟甲基化反应

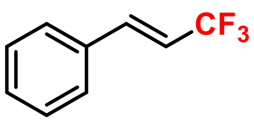


Noël, T. et al. *Angew. Chem. Int. Ed*. **2016**, *55*, 15549.

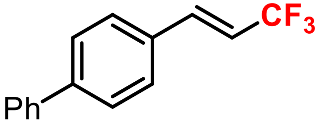
2.2 三氟碘甲烷 (CF_3I)

2.2.6 苯乙烯类化合物的三氟甲基化和氢三氟甲基化反应

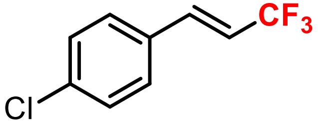




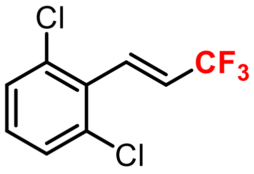
Batch: 75% yield
(72:28 *E/Z*)
Flow: 95% yield
(98:2 *E/Z*)



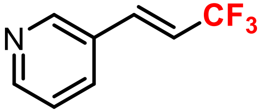
Batch: 89% yield
(83:17 *E/Z*)



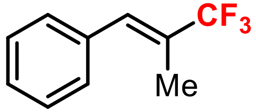
Batch: 88% yield
(54:46 *E/Z*)
Flow: 91% yield
(96:4 *E/Z*)



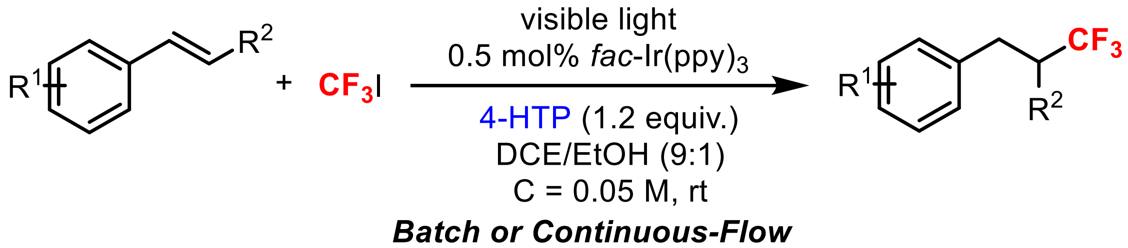
Batch: 75% yield
(68:32 *E/Z*)
Flow: 71% yield
(*E* only)

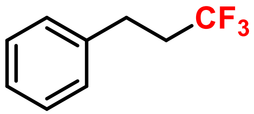


Batch: 75% yield
(75:25 *E/Z*)
Flow: 95% yield
(*E* only)

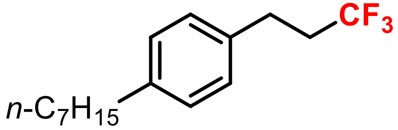


Batch: 75% yield
(69:31 *E/Z*)
Flow: 95% yield
(*E* only)

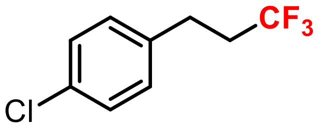




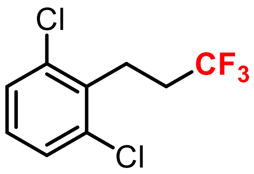
Batch: 79% yield
Flow: 77% (t_R = 50 min)



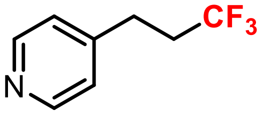
Batch: 88% yield



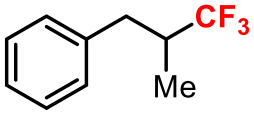
Batch: 71% yield



Batch: 75% yield



Batch: 72% yield

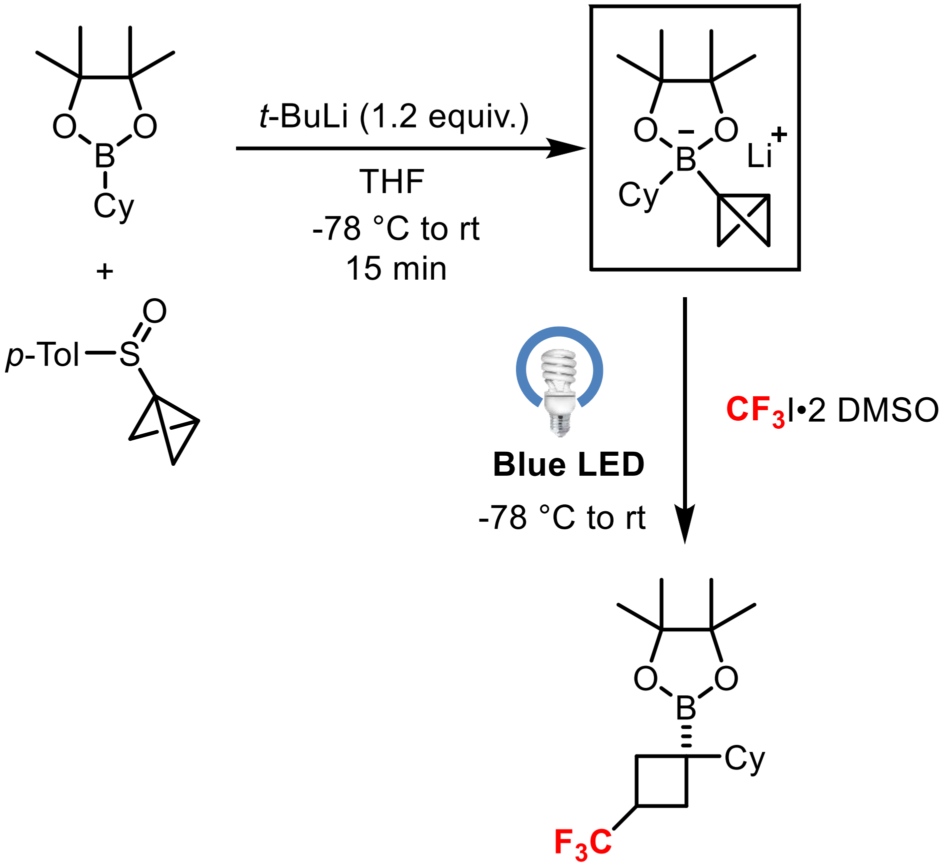


Batch: 82% yield

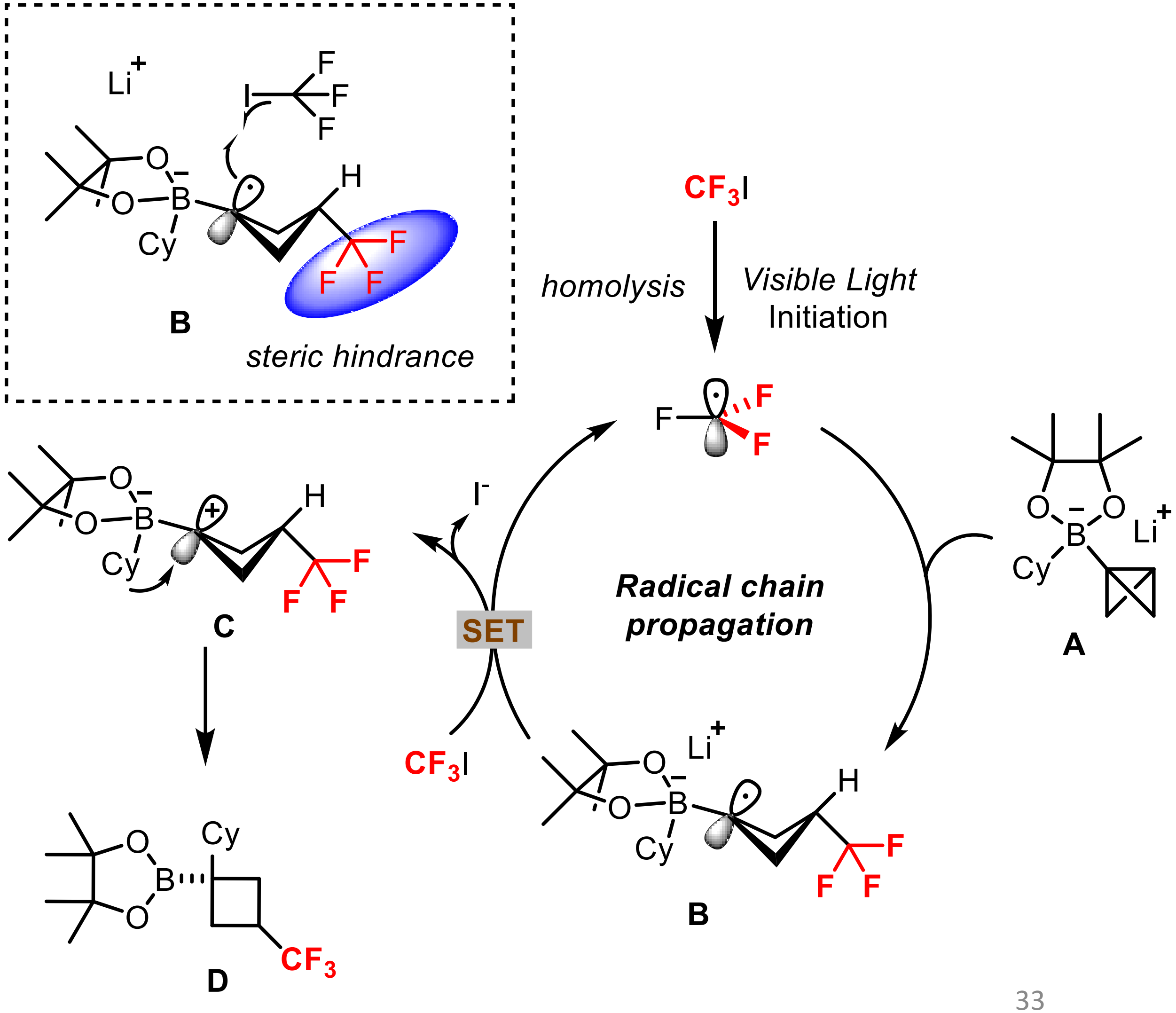
Noël, T. et al. *Angew. Chem. Int. Ed*. **2016**, *55*, 15549.

2.2 三氟碘甲烷 (CF_3I)

2.2.7 CF_3自由基对含张力σ-键的加成反应



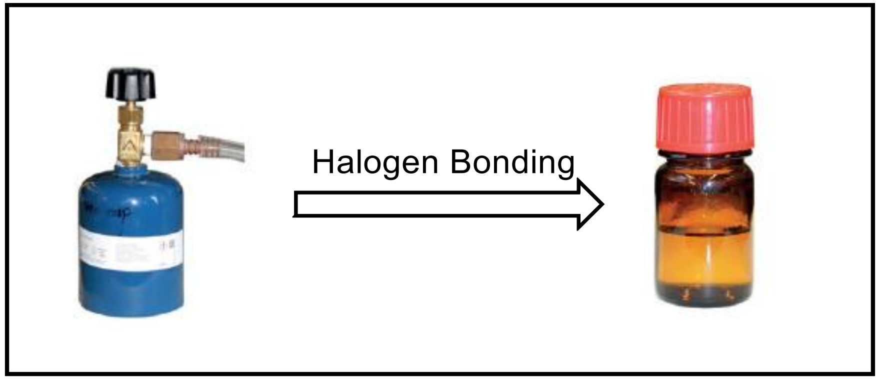
可能的机理

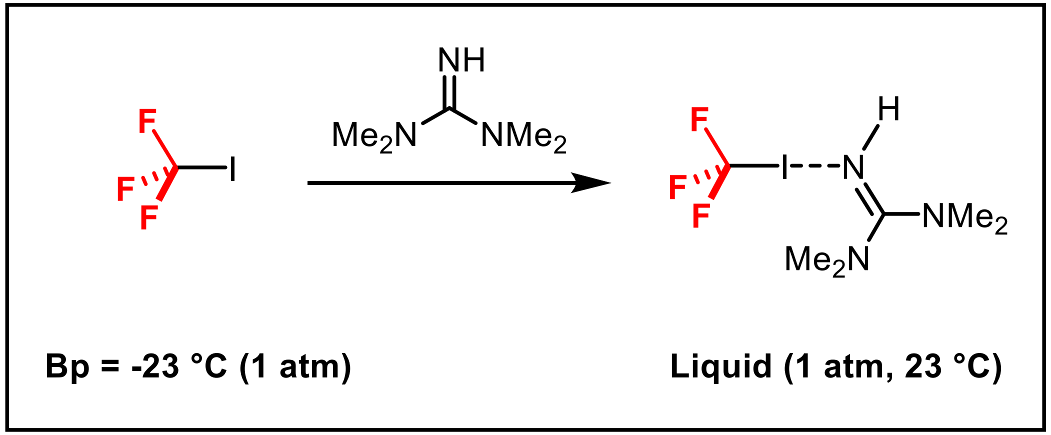


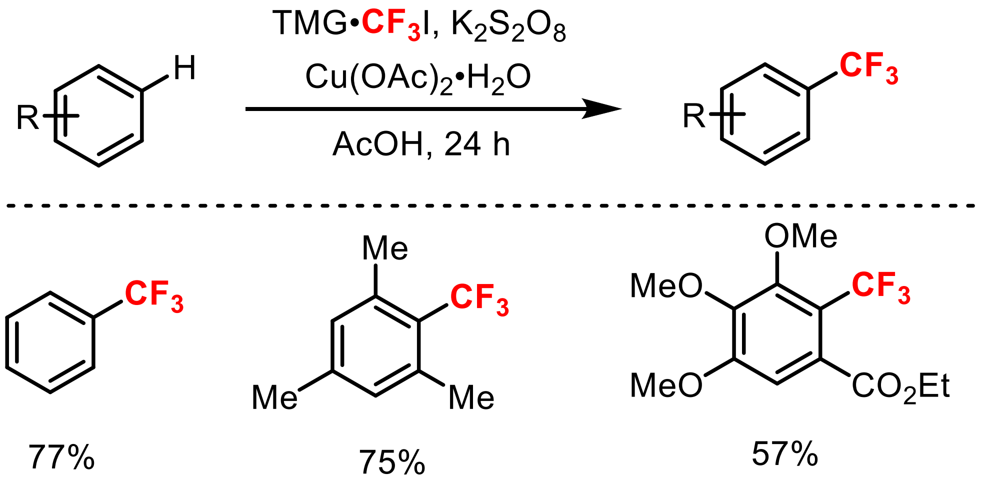
Aggarwal, V. K. et al. *J. Am. Chem. Soc*. **2019**, *141*, 9511.

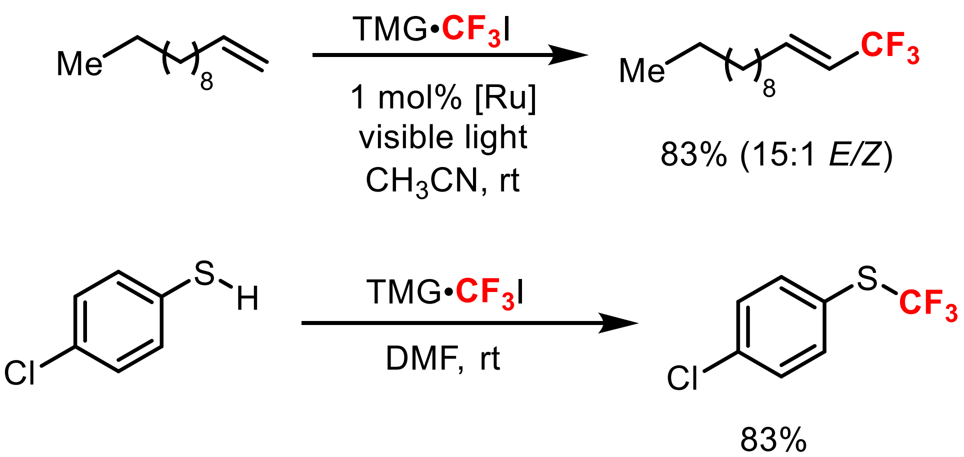
2.2 三氟碘甲烷 (CF_3I)

2.2.8 利用卤键作用制备含CF_3I的商业化溶液





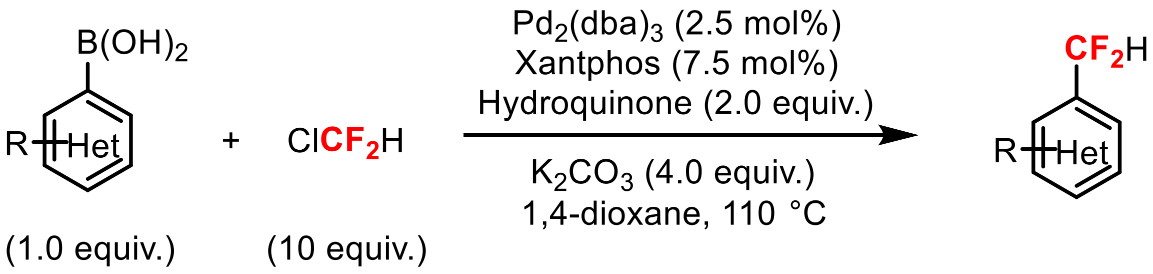


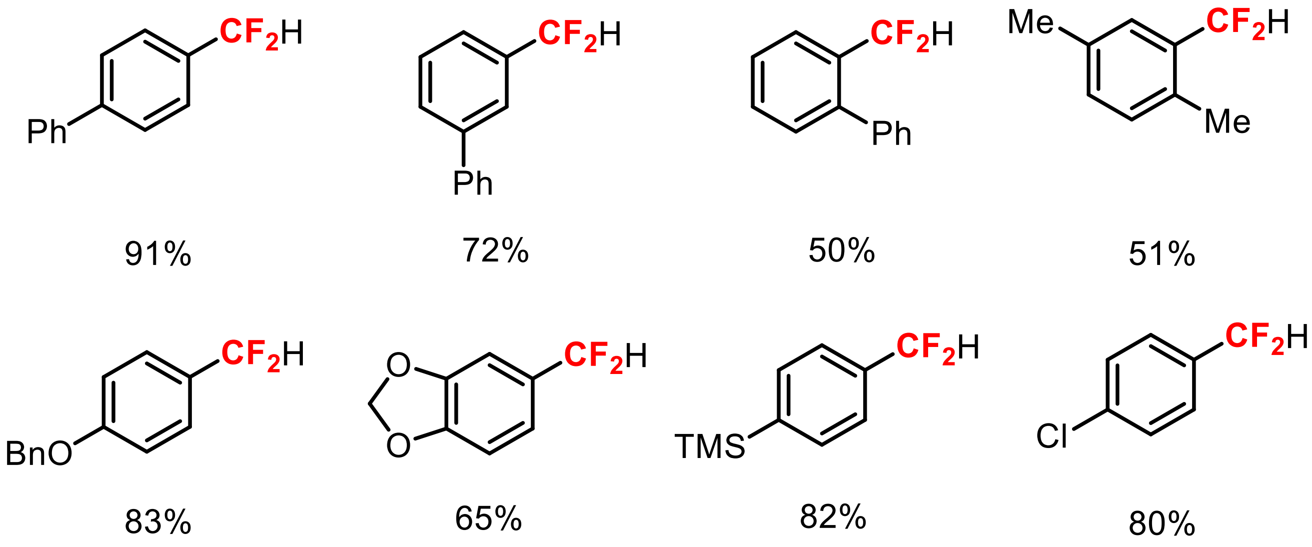


Ritter, T. et al. *Angew. Chem. Int. Ed*. **2015**, *54*, 3712.

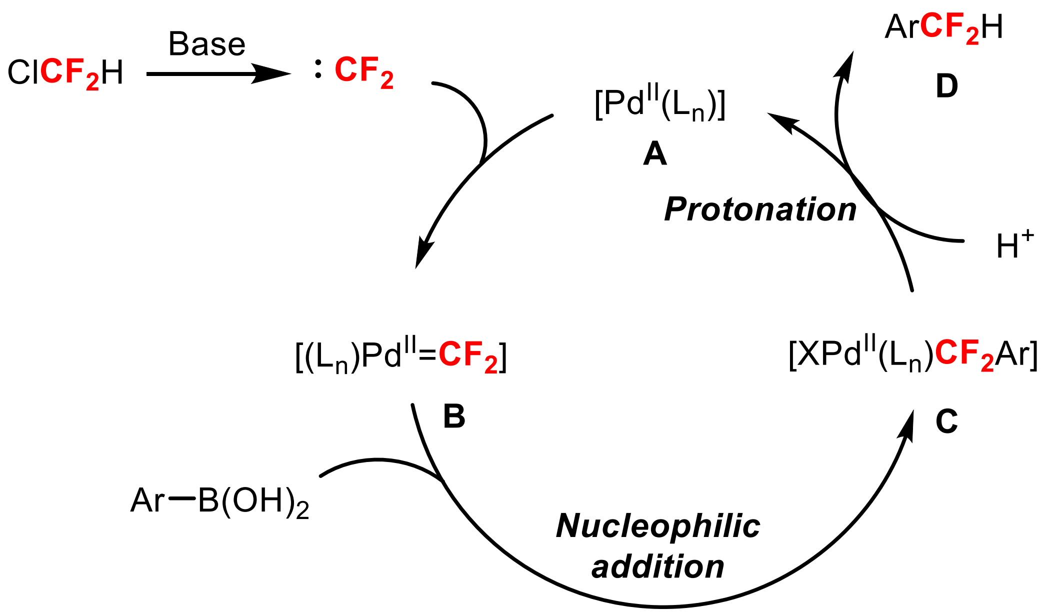
2.3 一氯二氟甲烷 ($ClCF_2H$)

2.3.1 Pd催化的$ClCF_2H$对(杂)芳基硼酸或硼酸酯的二氟甲基化反应





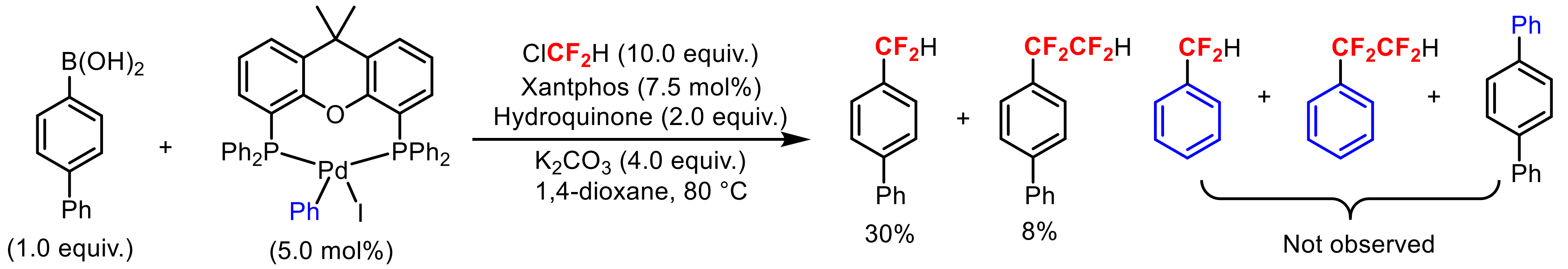
可能的机理

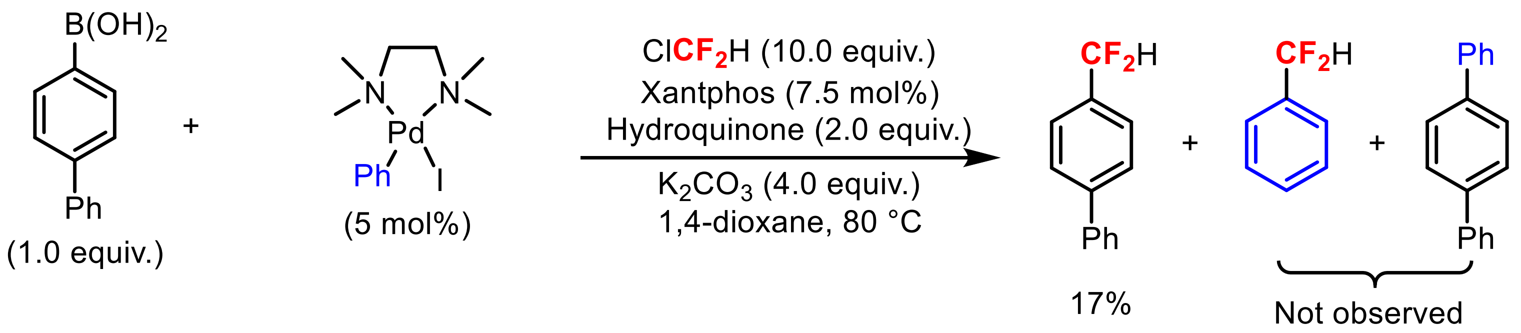


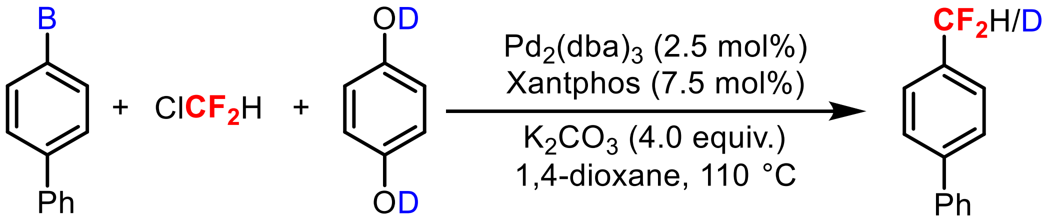
Zhang, X. et al. *Nat. Chem*. **2017**, *9*, 918.

2.3 一氯二氟甲烷 ($ClCF_2H$)

控制实验





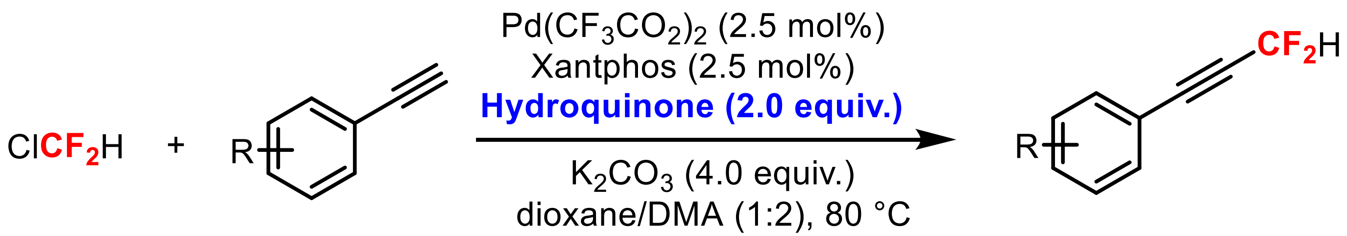


Entry	Reaction conditions	Yield (%), 3-H/3-D
1	B = $B(OH)_2$, $ClCF_2H$	57/22
2	B = Beg, $ClCF_2H$	40/27
3	No hydroquinone	1/-

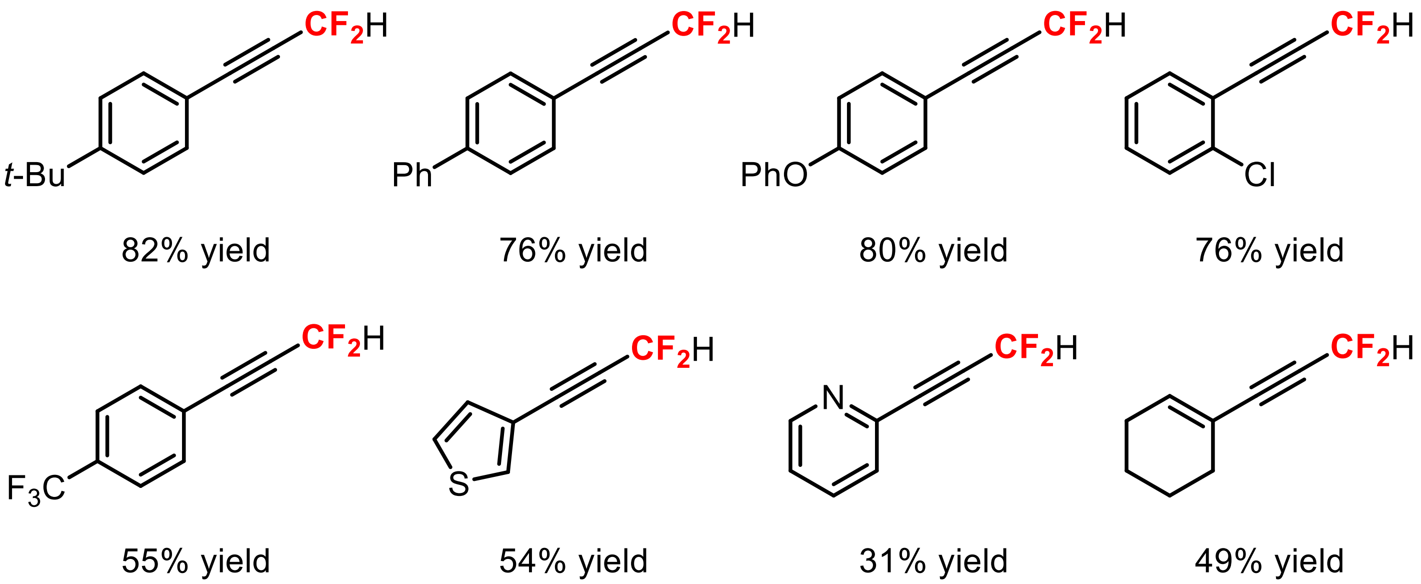
Zhang, X. et al. *Nat. Chem*. **2017**, *9*, 918.

2.3 一氯二氟甲烷 ($ClCF_2H$)

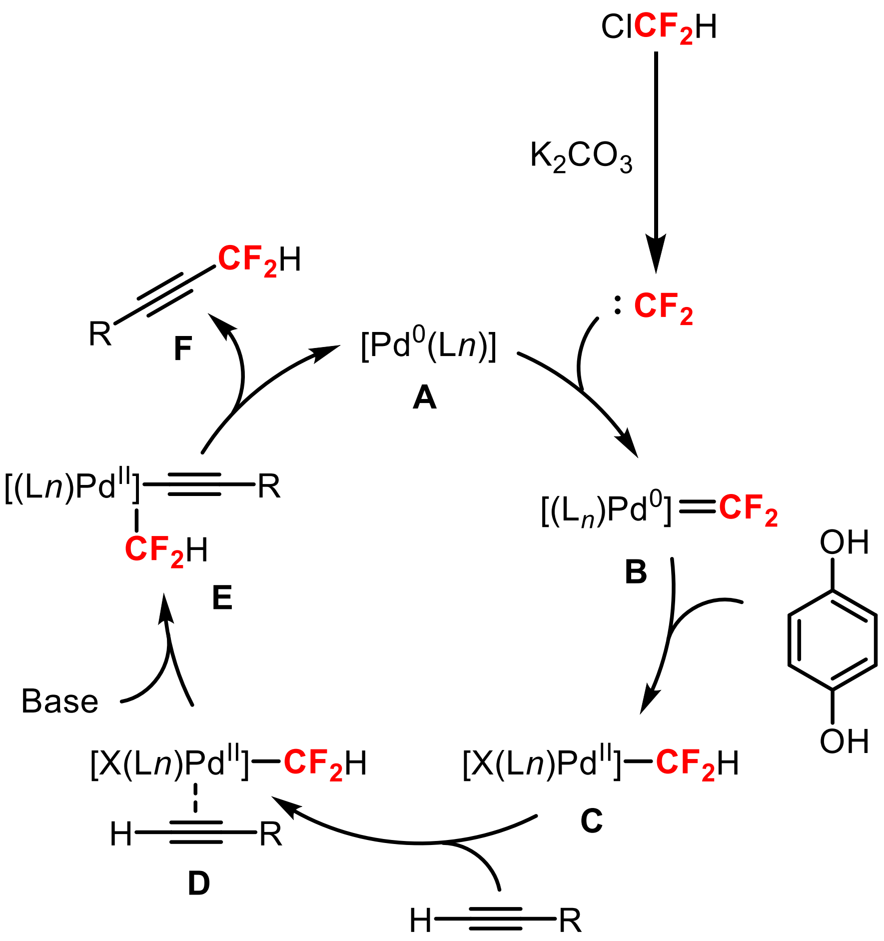
2.3.2 Pd催化的$ClCF_2H$和端炔的交叉偶联反应



Selected examples



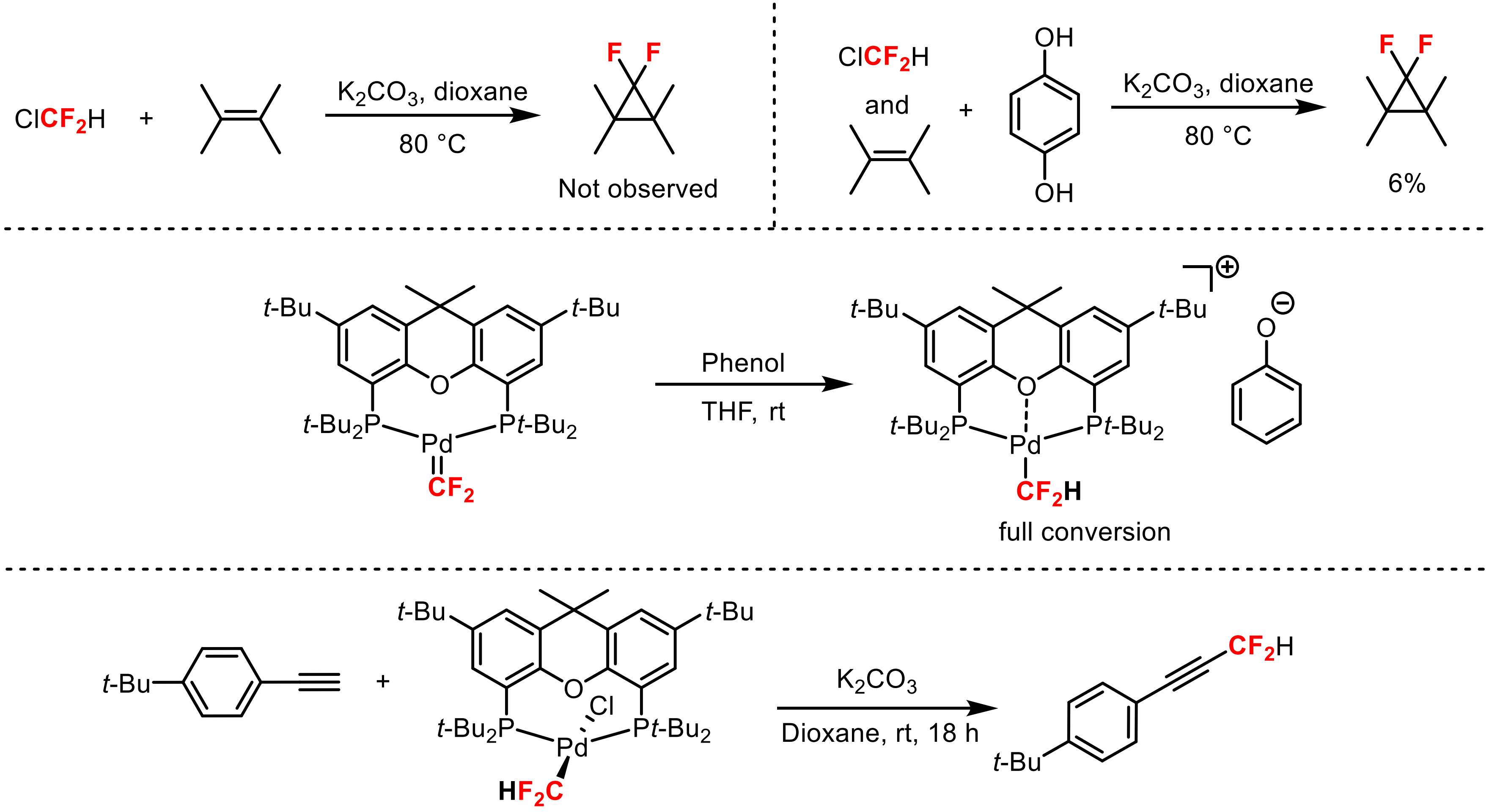
可能的机理



Zhang, X. et al. *CCS Chem.* **2020**, *2*, 293.

2.3 一氯二氟甲烷 ($ClCF_2H$)

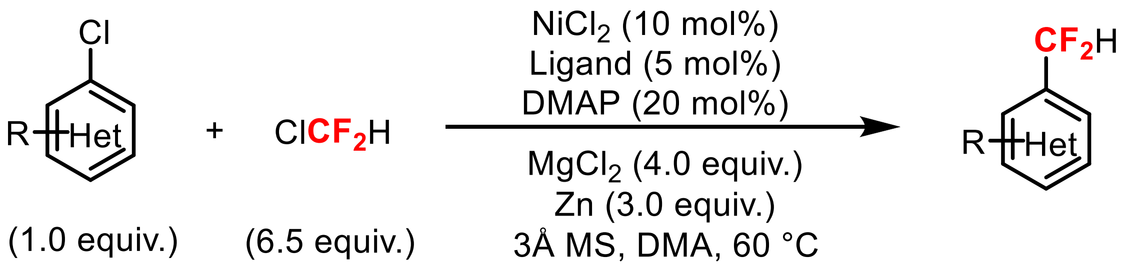
控制实验



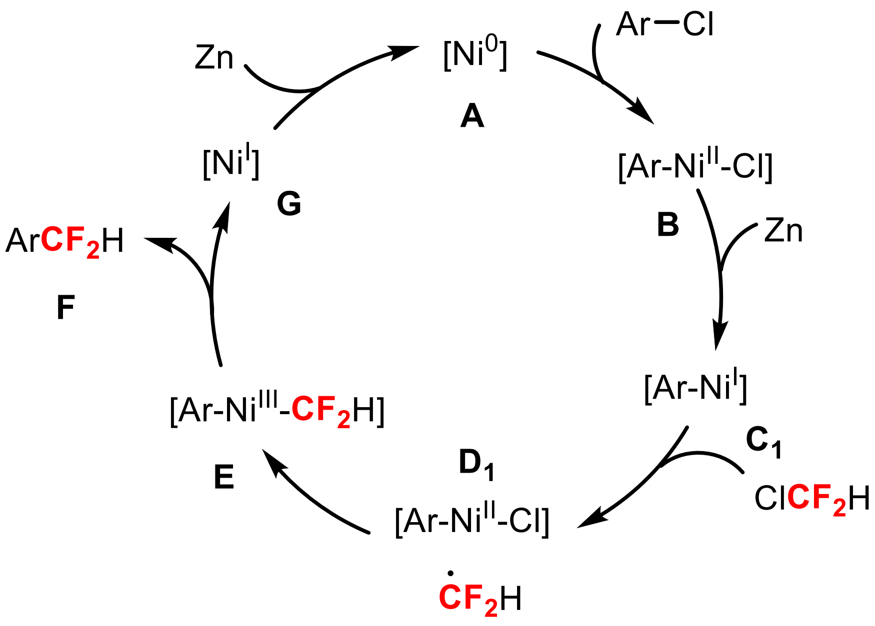
Zhang, X. et al. *CCS Chem.* **2020**, *2*, 293.

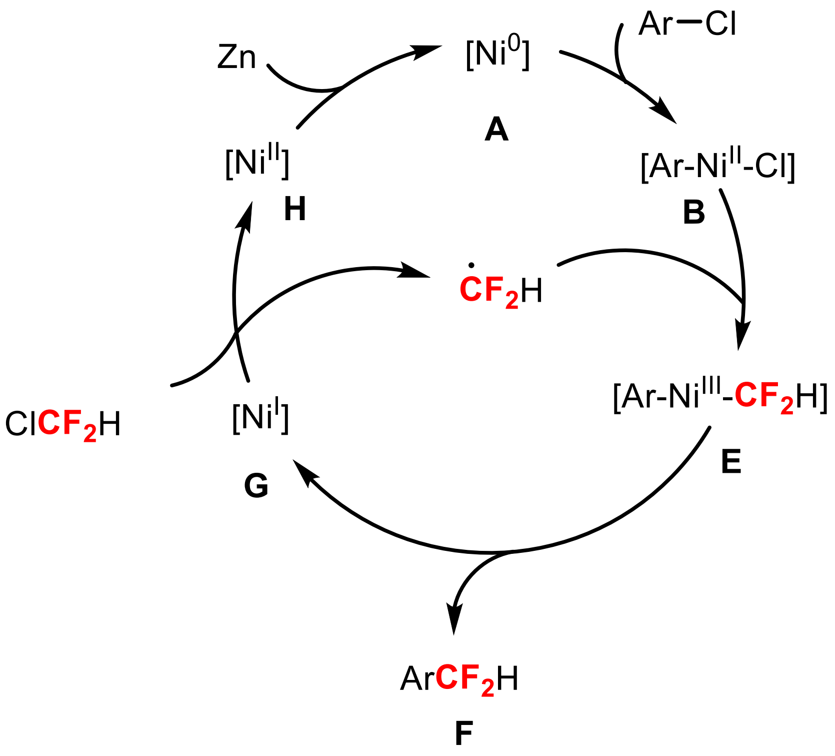
2.3 一氯二氟甲烷 ($ClCF_2H$)

2.3.3 Ni催化(杂)芳基氯化物与$ClCF_2H$的二氟甲基化反应



可能的机理

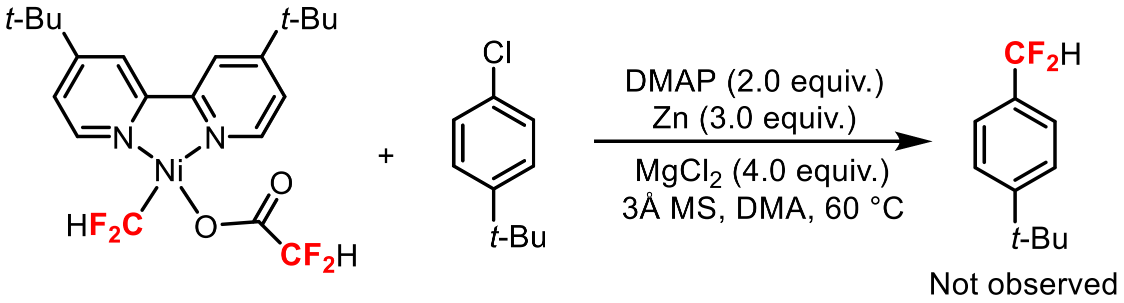


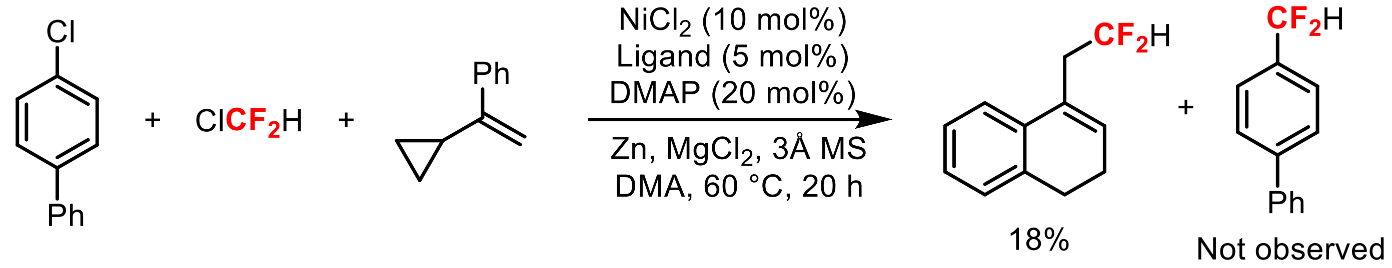


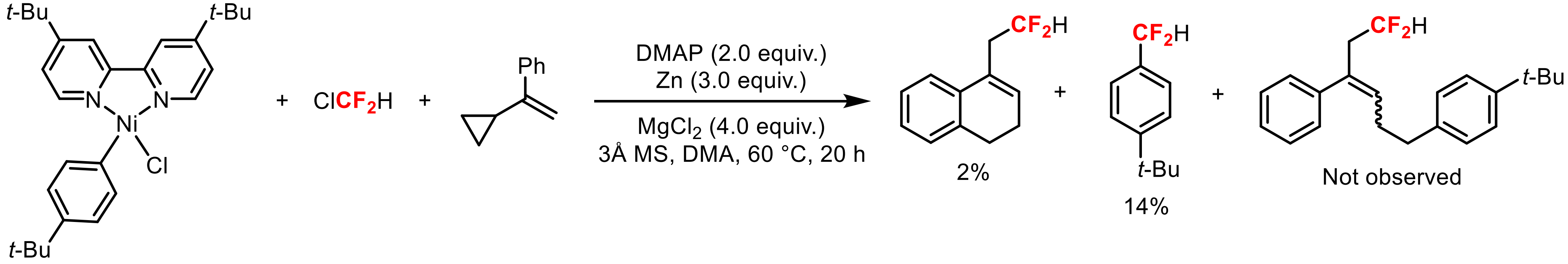
Zhang, X. et al. *Nat. Commun*. **2018**, *9*, 1170.

2.3 一氯二氟甲烷 ($ClCF_2H$)

控制实验



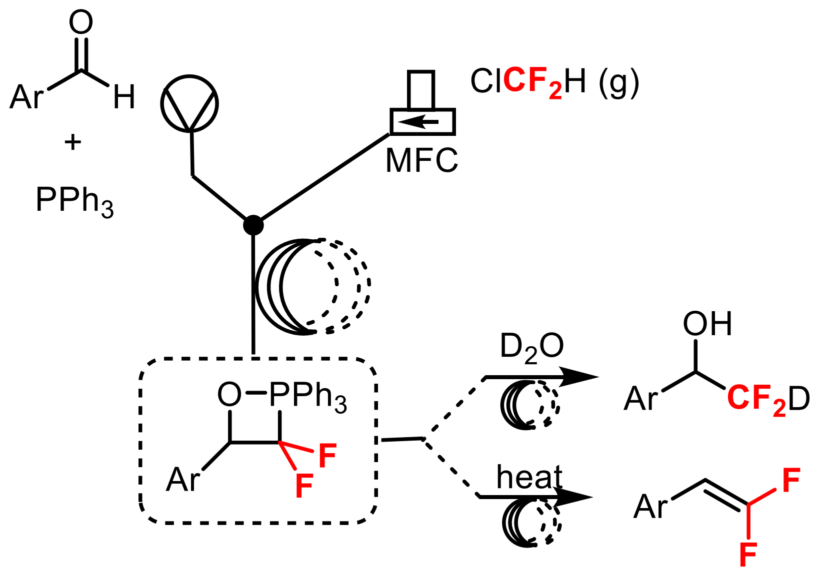


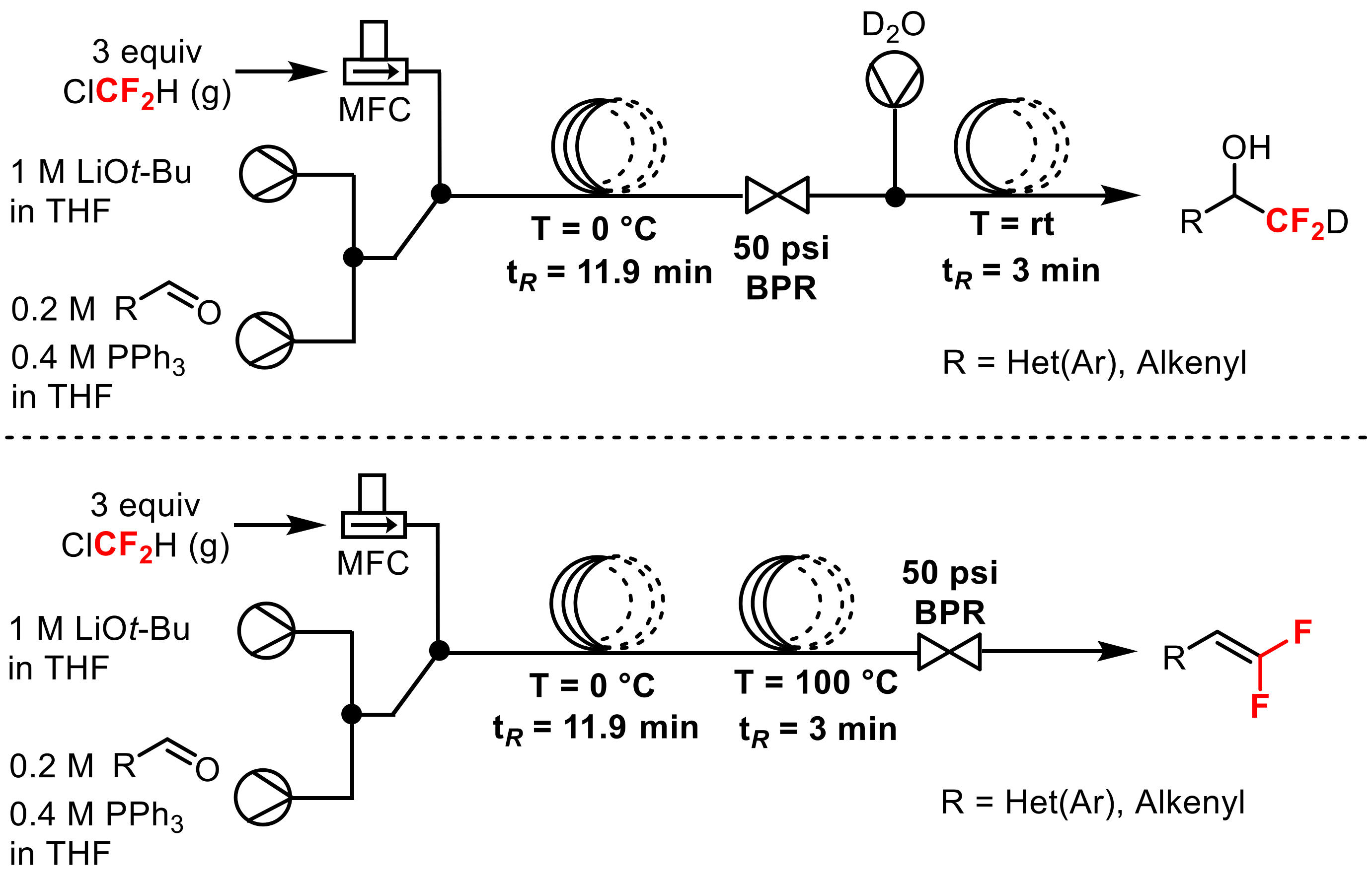


Zhang, X. et al. *Nat. Commun*. **2018**, *9*, 1170.

2.3 一氯二氟甲烷 ($ClCF_2H$)

2.3.4 连续流条件下醛的氘二氟甲基化和偕二氟烯基化反应

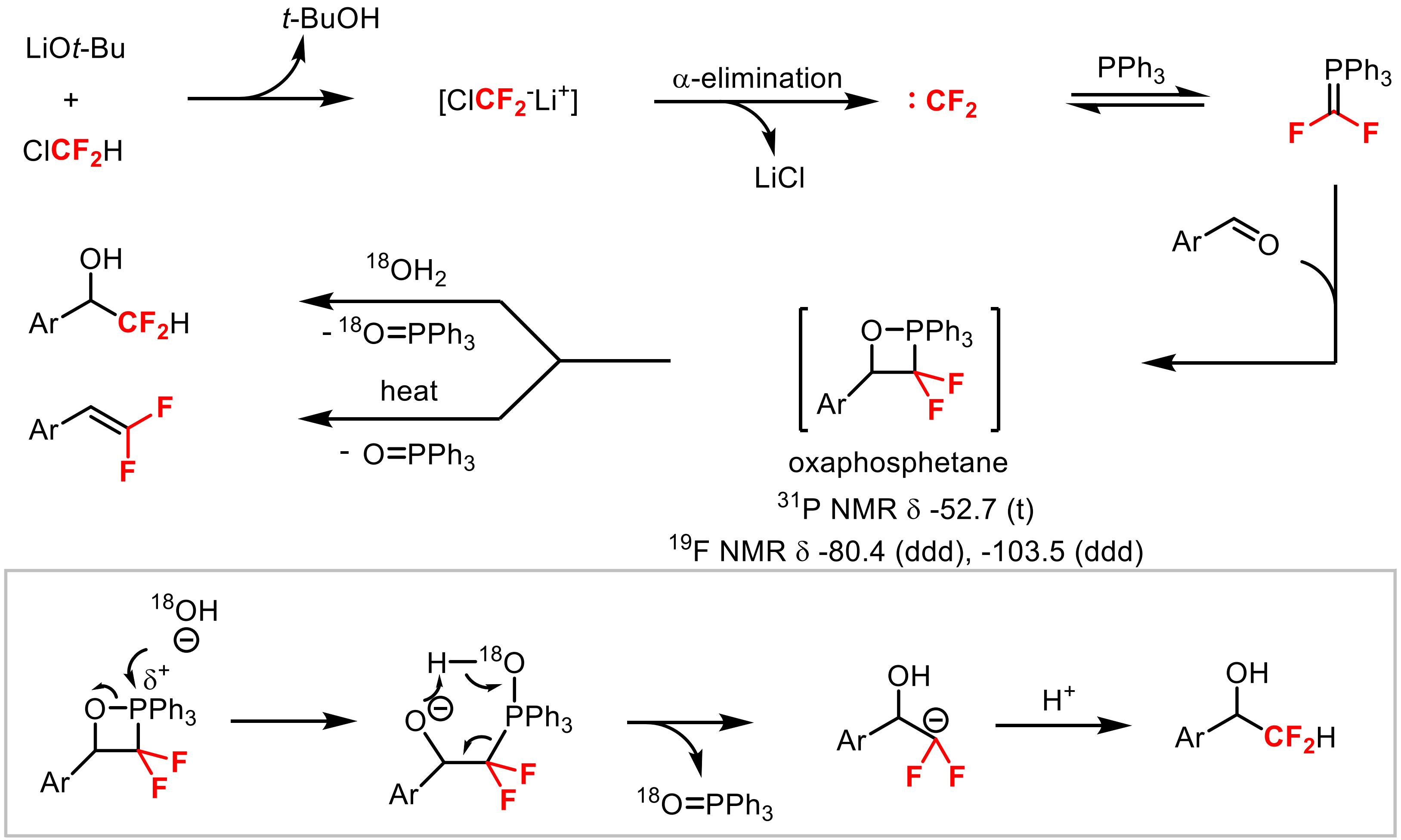




Jamison, T. F. et al. *Angew. Chem. Int. Ed*. **2020**, *59*, 13885. Jamison, T. F. et al. *Chem. Soc. Rev.* **2021**, *50*, 7378.

2.3 一氯二氟甲烷 ($ClCF_2H$)

可能的机理



Jamison, T. F. et al. *Angew. Chem. Int. Ed*. **2020**, *59*, 13885.

1. 背景介绍

1.1 氟化学背景

1.2 氟烷基化反应简介

1.3 四类含氟C-1烷烃分子简介

2. 含氟C-1分子在氟烷基化反应中的应用

2.1 三氟甲烷 (CF_3H)

2.2 三氟碘甲烷 (CF_3I)

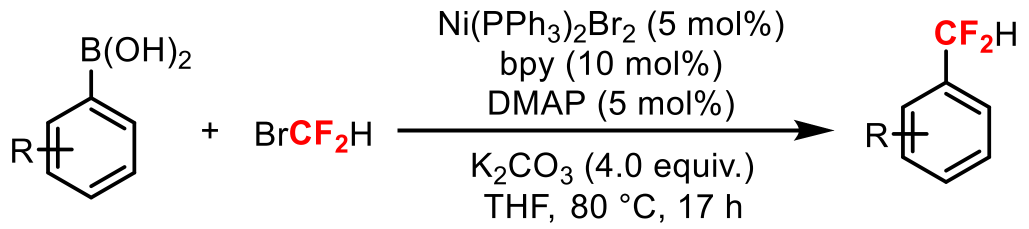
2.3 一氯二氟甲烷 ($ClCF_2H$)

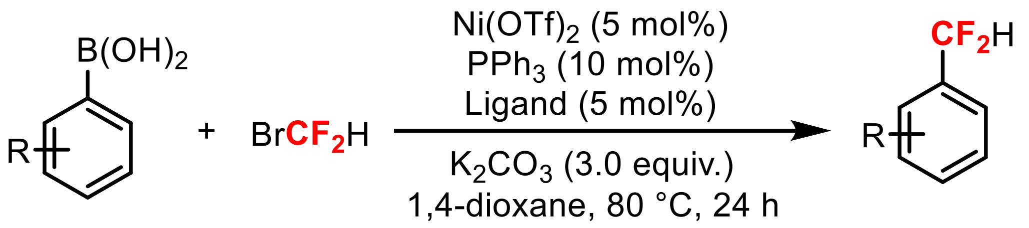
2.4 一溴二氟甲烷 ($BrCF_2H$)

3. 总结与展望

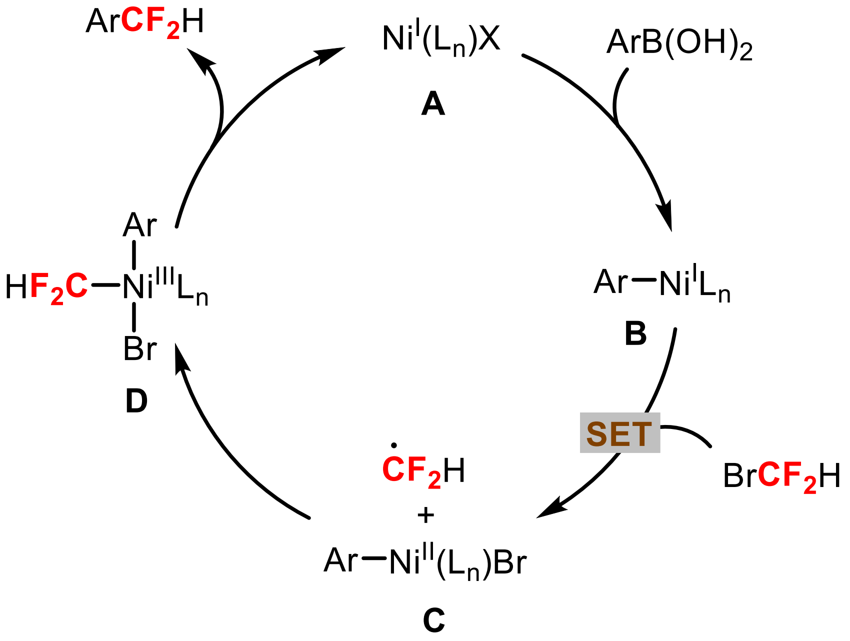
2.4 一溴二氟甲烷 ($BrCF_2H$)

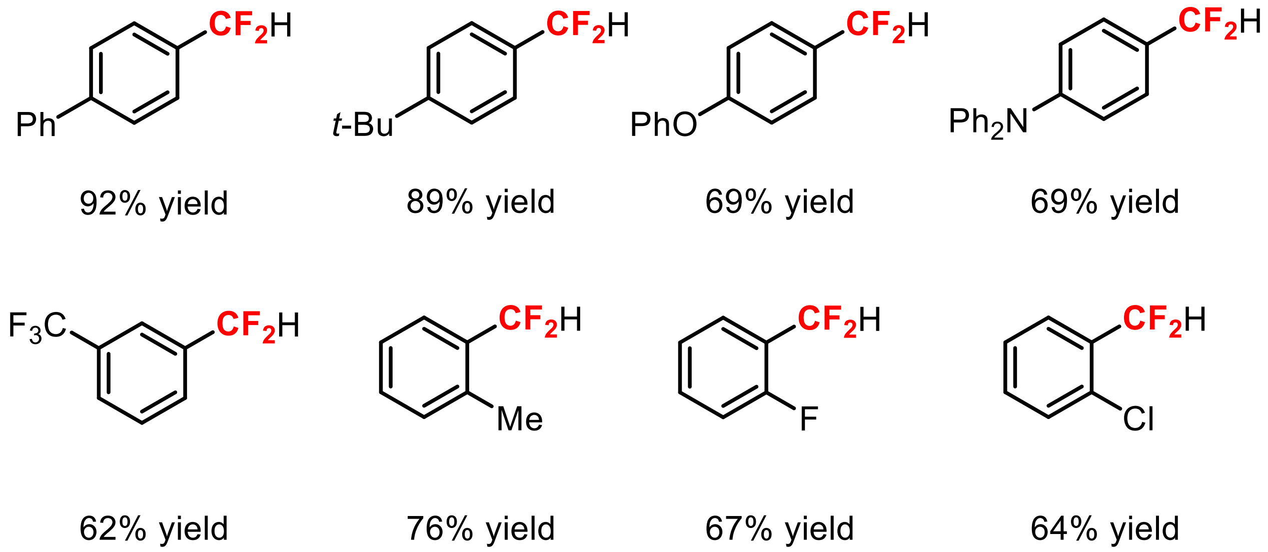
2.4.1 Ni催化的芳基硼酸与$BrCF_2H$的交叉偶联反应





可能的机理



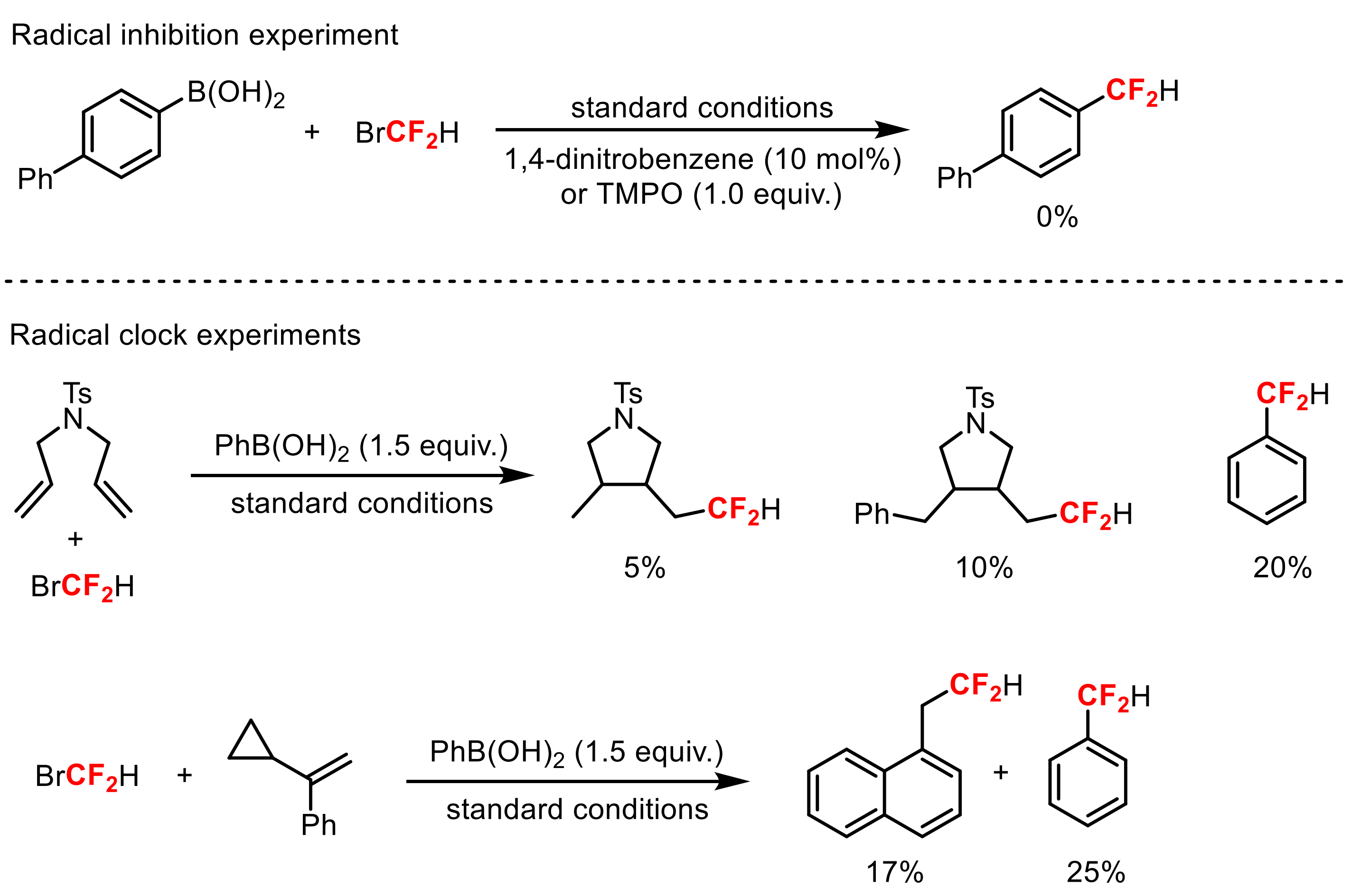


Zhang, X. et al. *Chin. J. Chem.* **2018**, *36*, 143.

Wang, X. S. et al. *Org. Chem. Front.* **2018**, *5*, 606.

2.4 一溴二氟甲烷 ($BrCF_2H$)

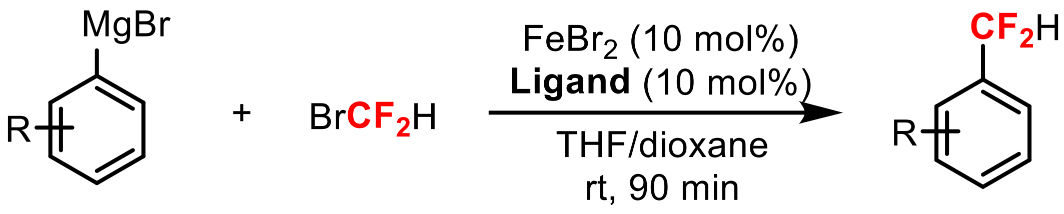
控制实验



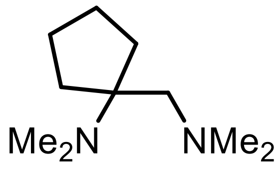
Zhang, X. et al. *Chin. J. Chem.* **2018**, *36*, 143.

2.4 一溴二氟甲烷 ($BrCF_2H$)

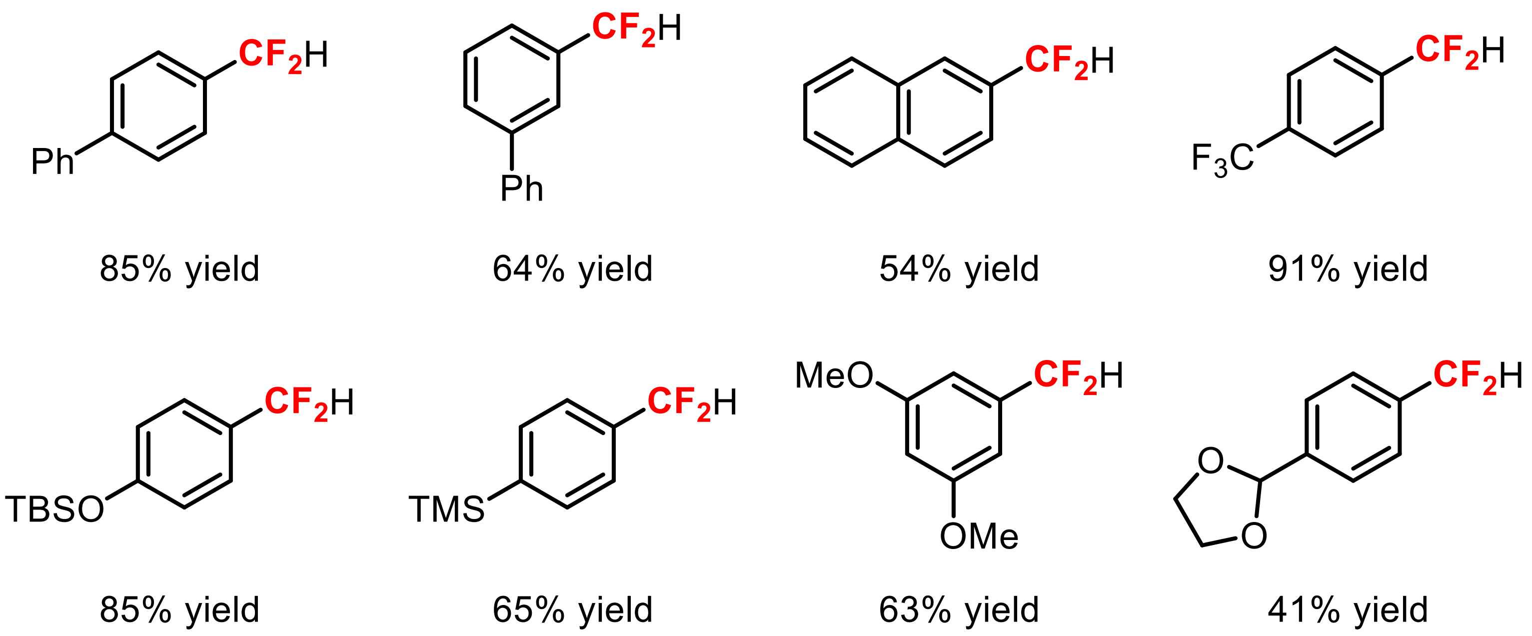
2.4.2 Fe催化的芳基溴化镁和$BrCF_2H$的交叉偶联反应

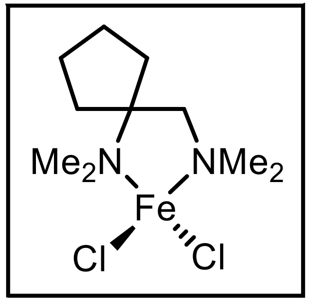


Ligand:

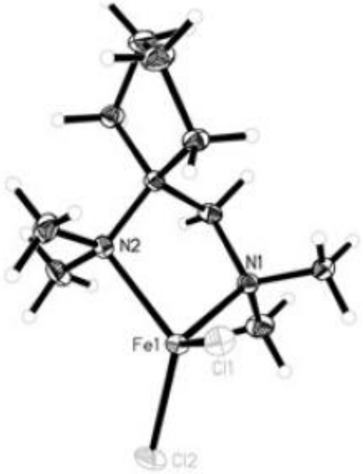


Selected examples





N-Fe-N angle:
82.09(11)°-82.81(10)°

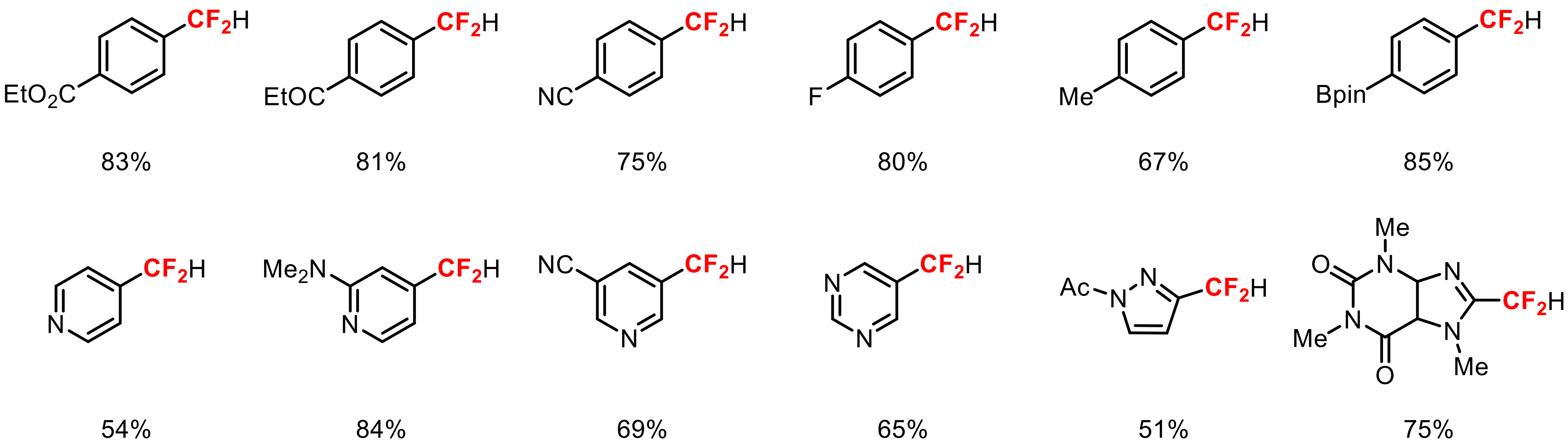


Zhang, X. et al. *Angew. Chem. Int. Ed*. **2018**, *57*, 6921.

2.4 一溴二氟甲烷 ($BrCF_2H$)

2.4.3 Ni/光催化的芳基溴化物的二氟甲基化反应

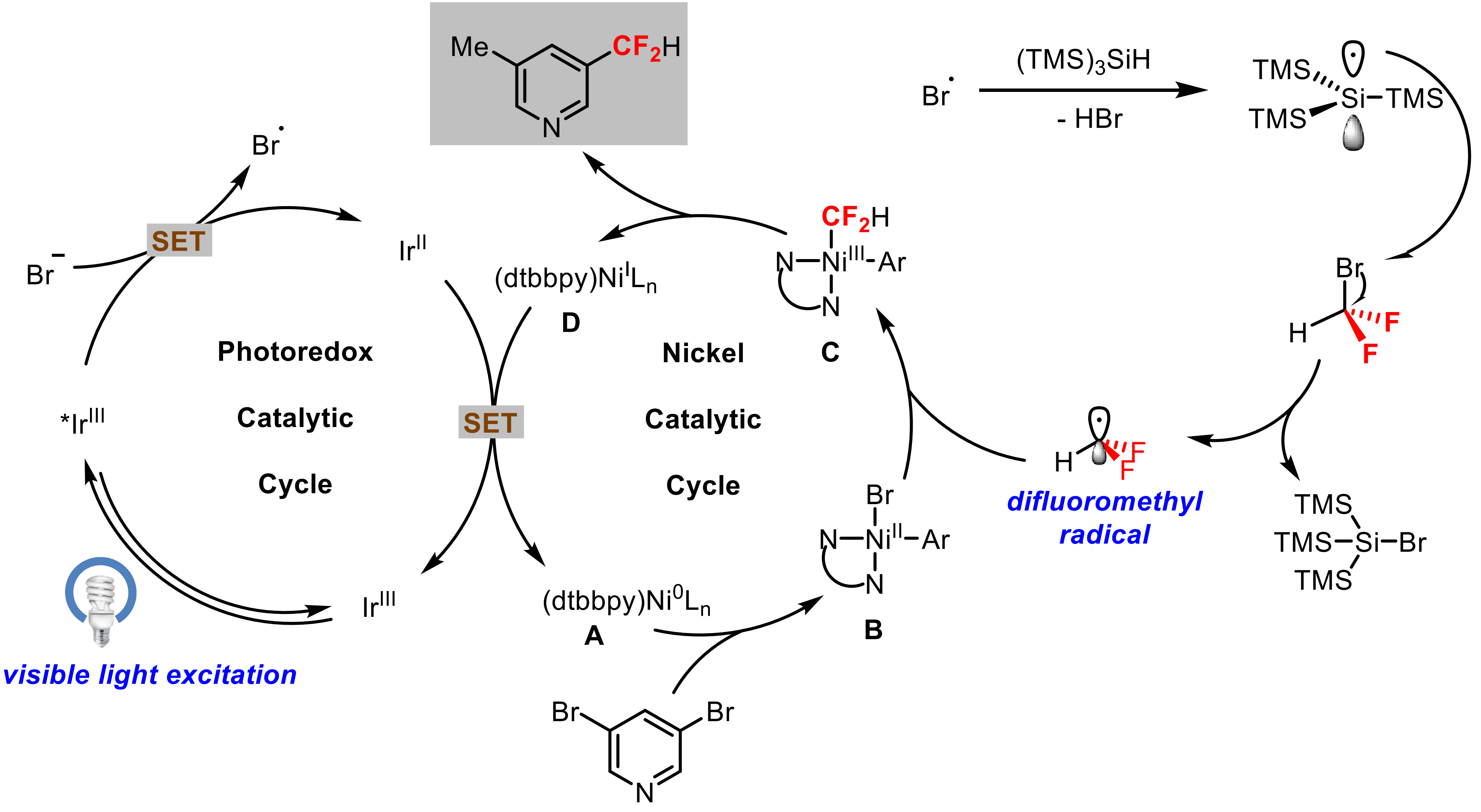
Selected examples



MacMillan, D. W. C. et al. *Angew. Chem. Int. Ed*. **2018**, *57*, 12543.

2.4 一溴二氟甲烷 ($BrCF_2H$)

可能的机理



MacMillan, D. W. C. et al. *Angew. Chem. Int. Ed*. **2018**, *57*, 12543.

3. 总结与展望

CF_3I → $\dot{C}F_3$ → 自由基三氟甲基化

CF_3H → $\bar{C}F_3$ → 亲核三氟甲基化

$ClCF_2H$ → $:CF_2$ → 亲电二氟甲基化

$BrCF_2H$ → $\dot{C}F_2H$ → 亲电二氟甲基化

- 原料廉价，毒性低
- 无需多步合成，原子经济性高

- 气液反应操作起来困难
- 沸点低，安全性问题

→ 流动化学

展 望

- 发展更多的试剂作为含氟气体储存体系。
- 发展新的含氟气体活化模式。
- 各个反应体系可经流动化学提高效率，扩大反应规模。

谢谢大家！

请各位老师同学批评指正！