Literature Report

Chlorodifluoromethane-triggered formation of difluoromethylated arenes catalysed by palladium

Reporter: Mu-Wang Chen
Checker: Fan-Jie Meng
Date: 2017-07-10

Zhang Feng, Qiao-Qiao Min, Xia-Ping Fu, Lun An and Xingang Zhang
Nature Chem. **2017**, doi:10.1038/nchem.2746. (3.14)

CV of Xingang Zhang

Education:

- 1994-1998 B.S., Sichuan University
- 1998-2003 Ph.D., Shanghai Institute of Organic Chemistry
- 2003–2008 Postdoc., University of Illinois at Urbana-Champaign

Research:

- 过渡金属催化下的氟芳基化反应及其在有机光电材料中的应用.
- 过渡金属催化下选择性氟烷基化及相关反应.
- C-F键的选择性构筑与断裂.
- 利用所发展方法高效合成具有潜在应用前景的含氟生物活性化合物，并借助于化学生物学手段研究具有抗菌、抗肿瘤生物活性化合物的作用机制，探索发现新型抗生素和抗肿瘤药物.

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2 Metal-catalyzed difluoromethylation of arenes

3 Summary

Introduction

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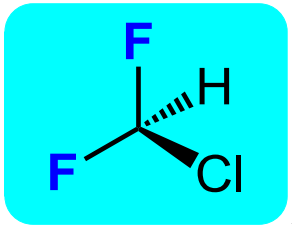
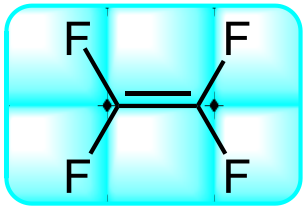
氟利昂22 (R22)

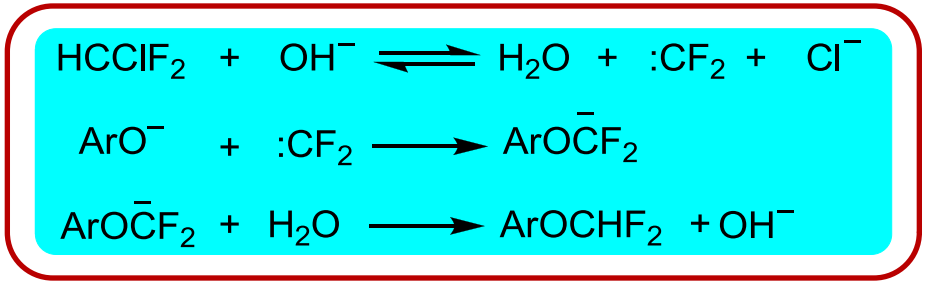
制冷剂
(8-10元/千克)



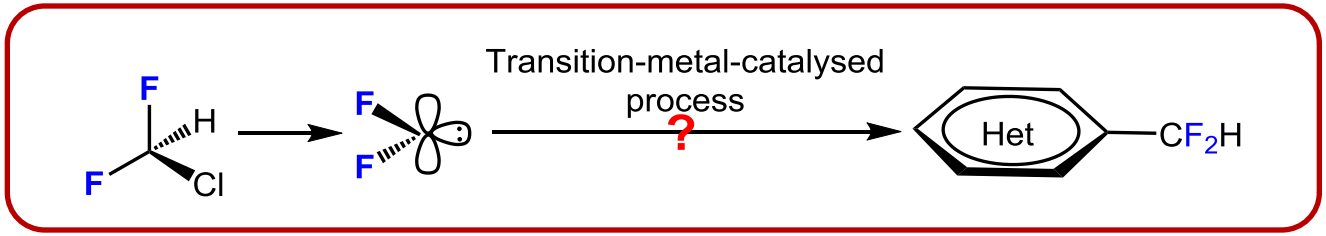


RO-CF_2H, RS-CF_2H
R_2N-CF_2H, etc

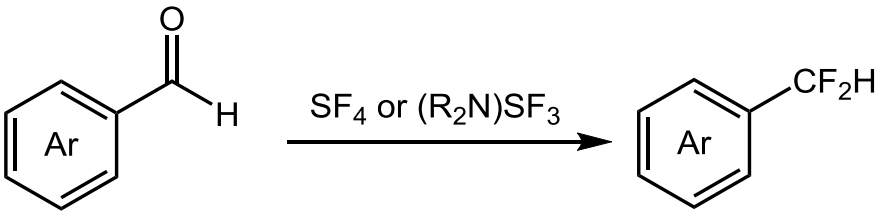
Activation of $ClCF_2H$ in organic synthesis



Miller, T. G.; Thanassi, J. W. *J. Org. Chem.* **1966**, *25*, 2009.



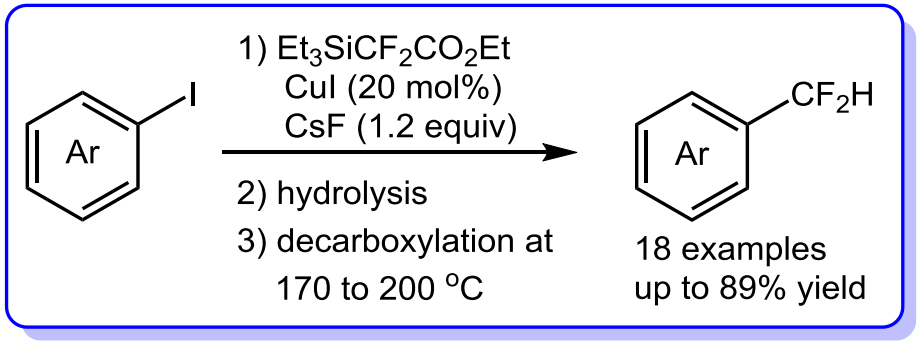
Preparation of difluoromethylarenes

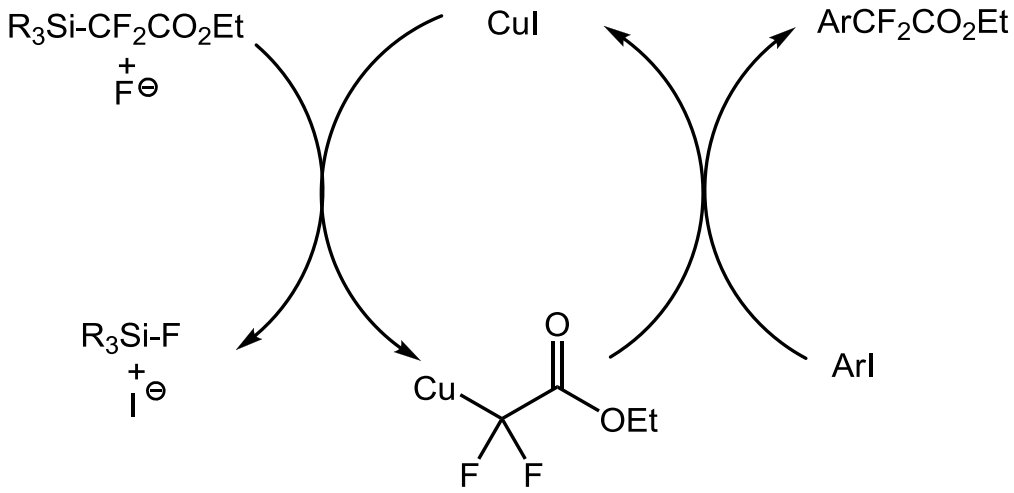


hydrogen fluoride
explosive decomposition when heated

(a) Markovski, L. N.; Pahinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787;
(b) Middleton, W. J. *J. Org. Chem*. **1975**, *40*, 574.

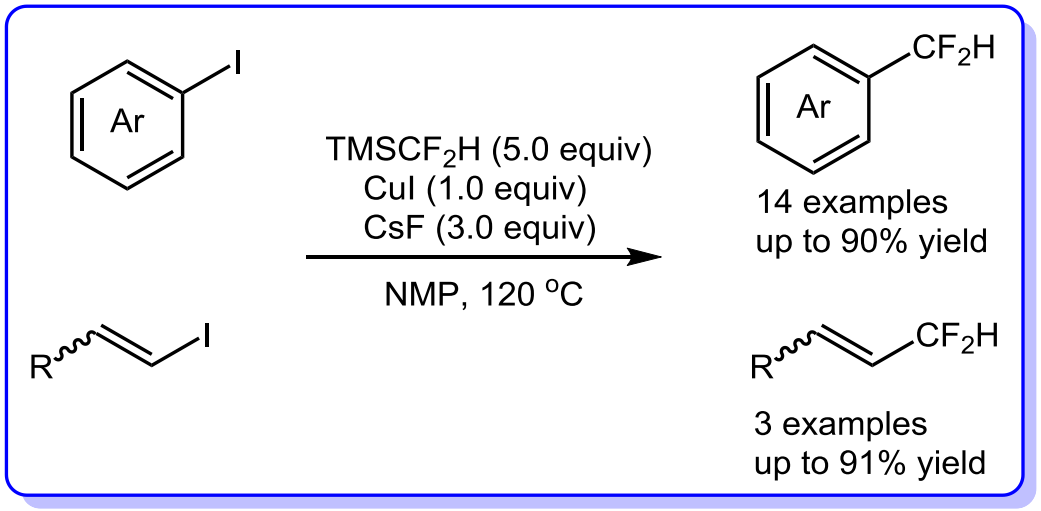
Copper-catalyzed difluoromethylation





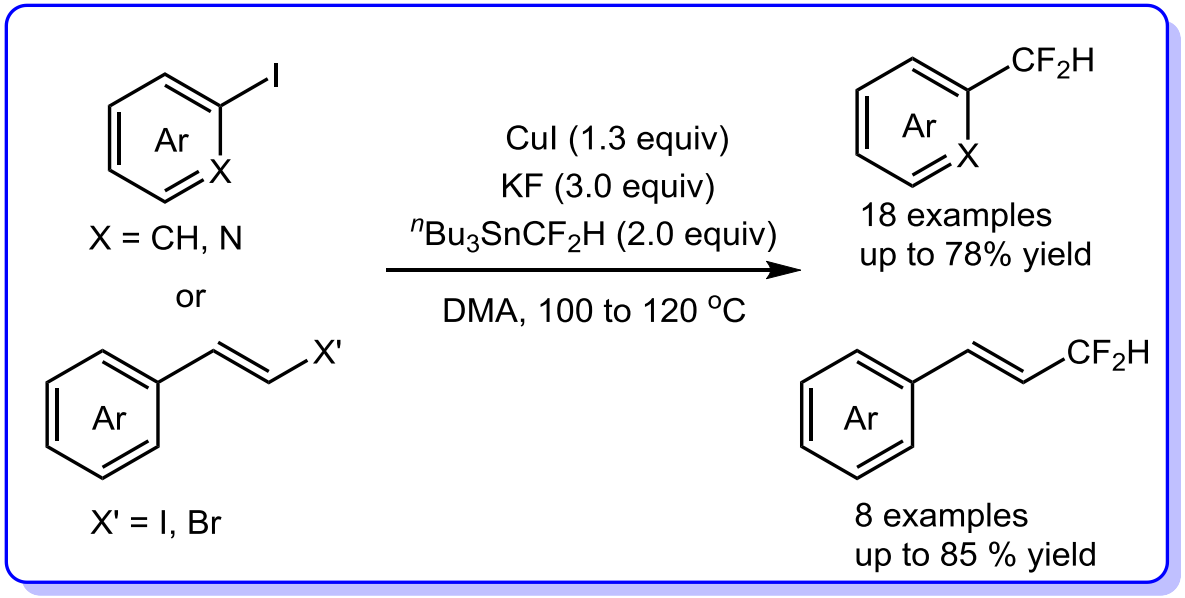
Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett*. **2011**, *13*, 5560.

Copper-mediated difluoromethylation



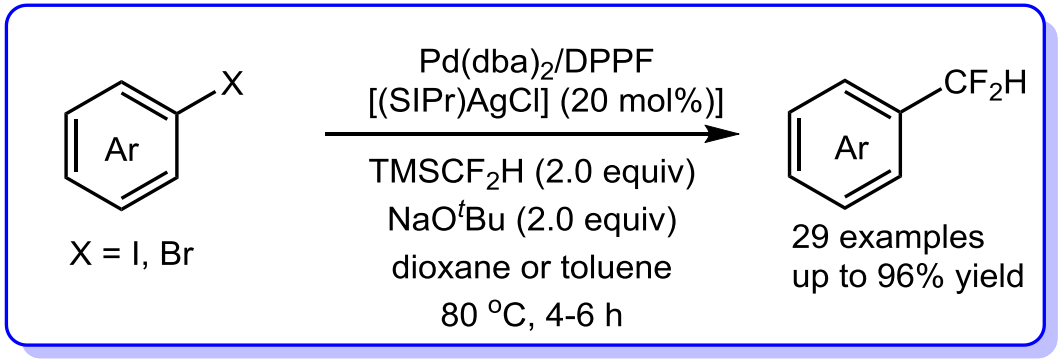
Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524.

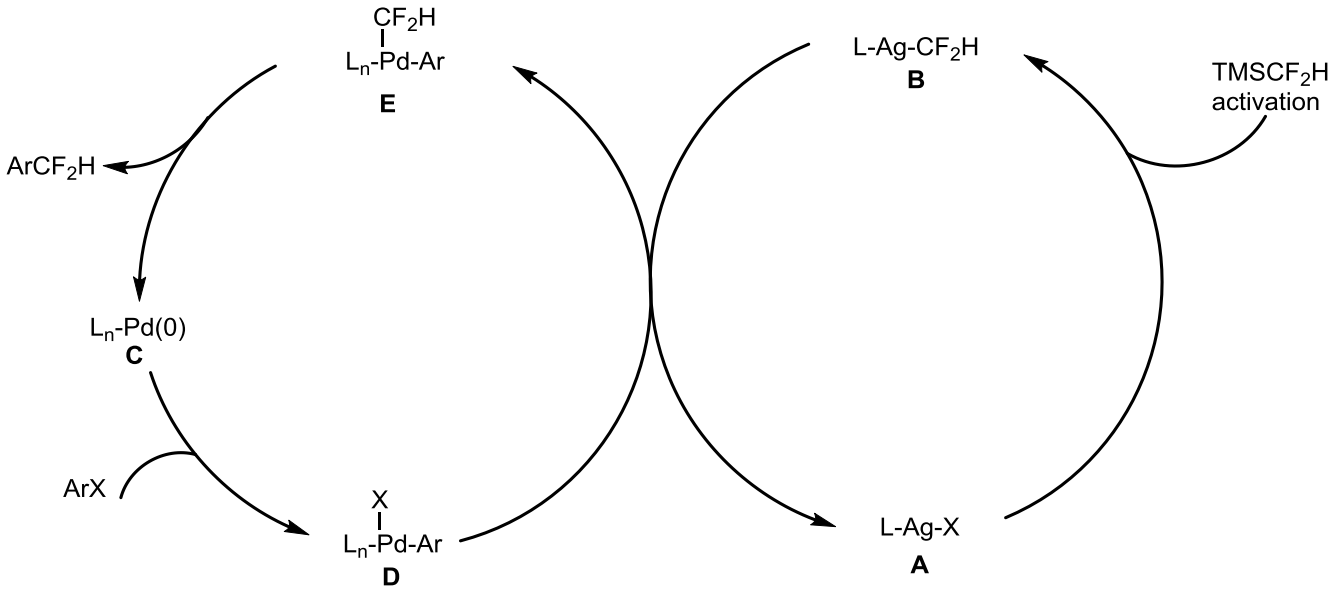
Copper-mediated difluoromethylation



Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem. Int. Ed*. **2012**, *51*, 12090.

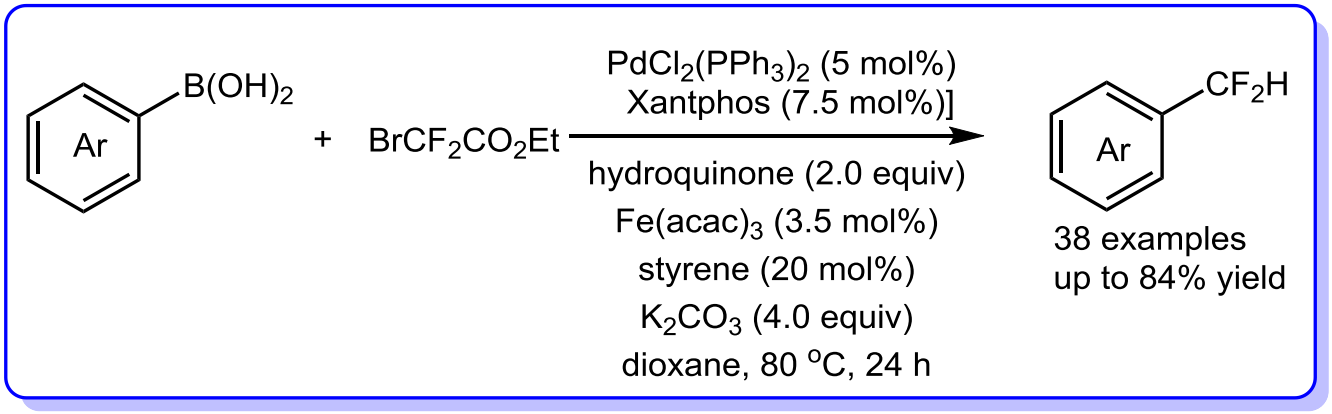
Palladium/silver catalyzed difluoromethylation



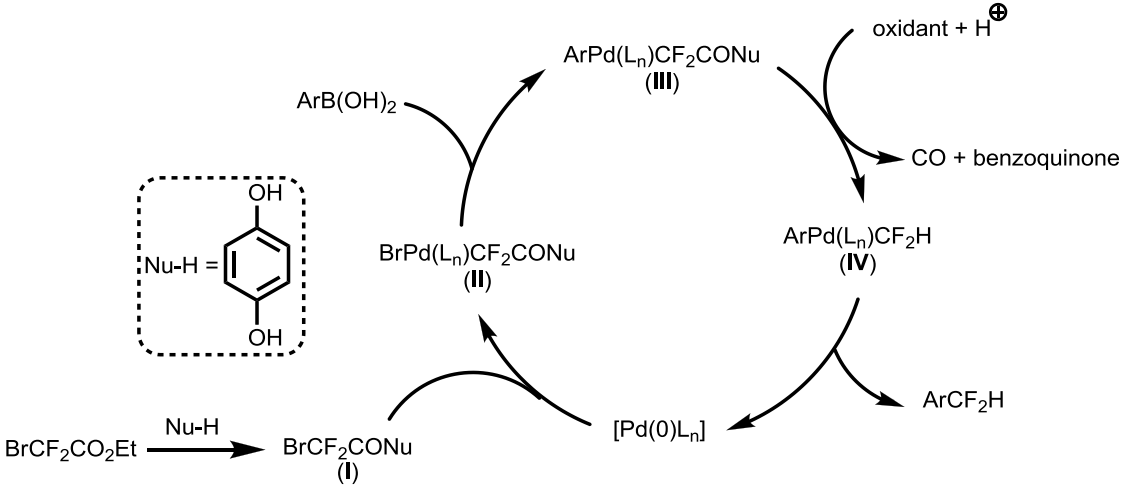


Gu, Y.; Leng, X.; Shen, Q. *Nat. Commun*. **2014**, *5*, 5405.

Pd-catalyzed difluoromethylation

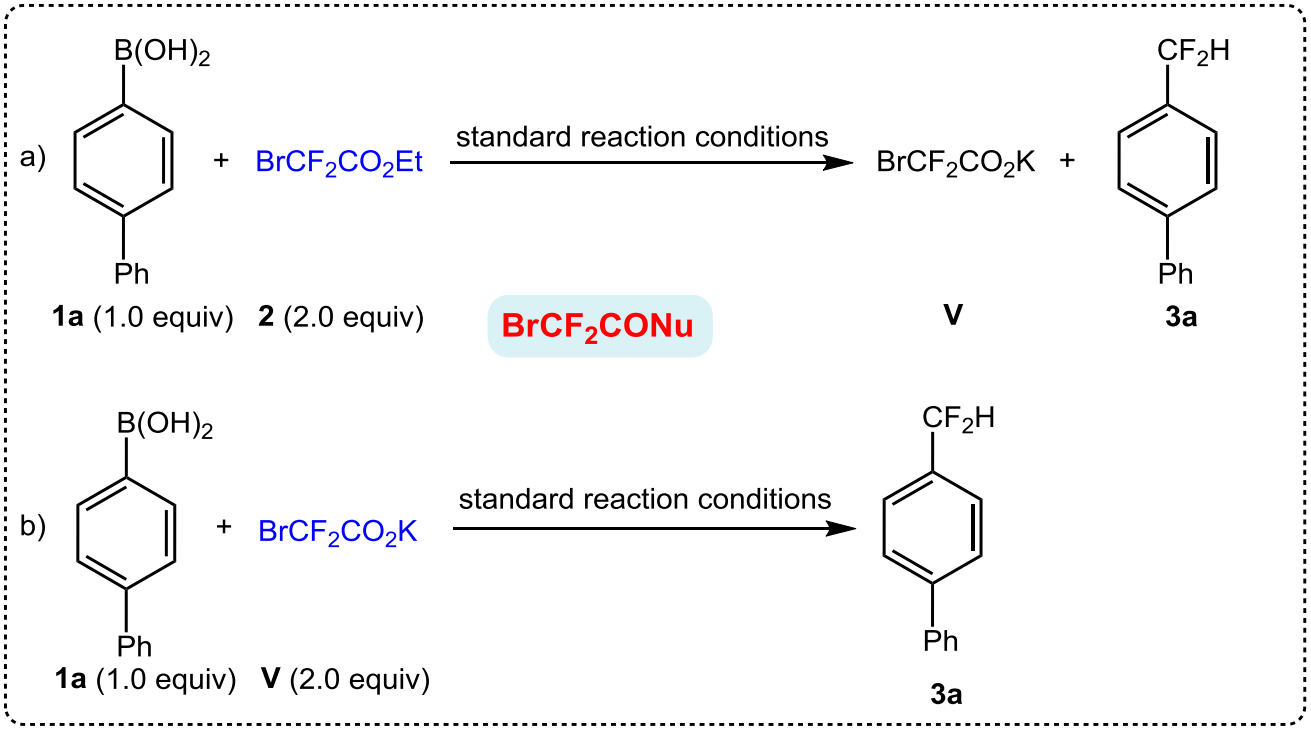


Hypothesis reaction mechanism

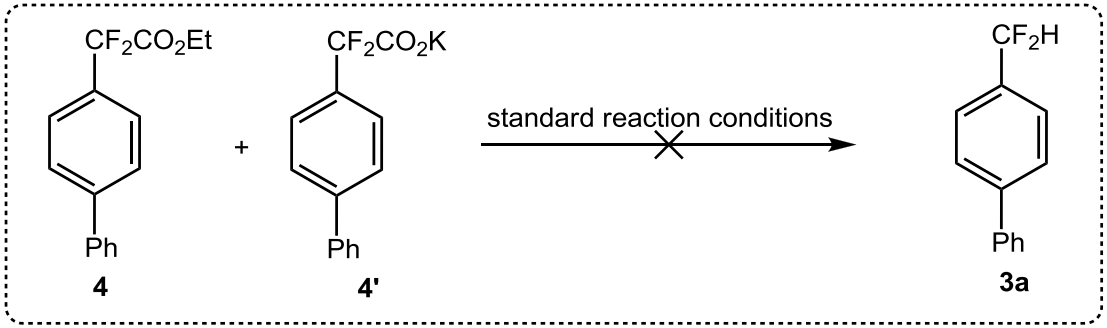


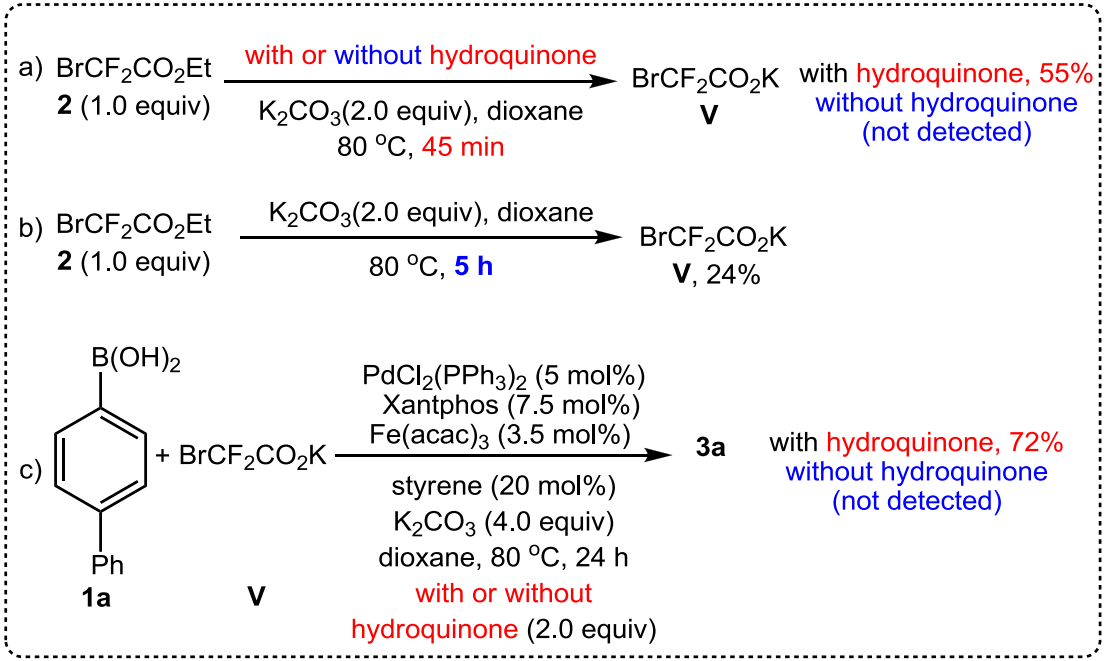
Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44.

Mechanistic studies: cross-coupling of 1a with 2 or V

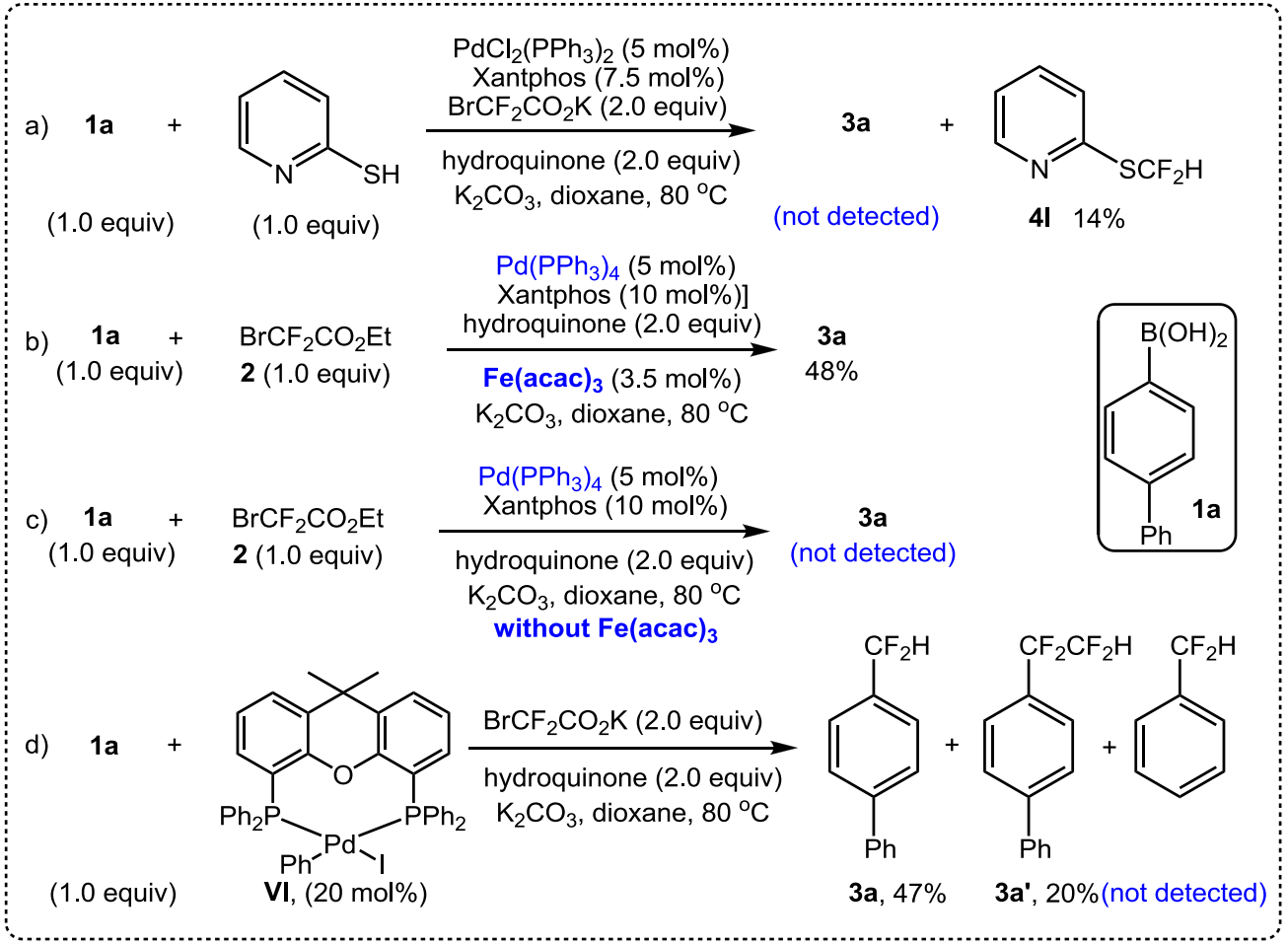


Mechanistic studies: roles of hydoquinone for reaction

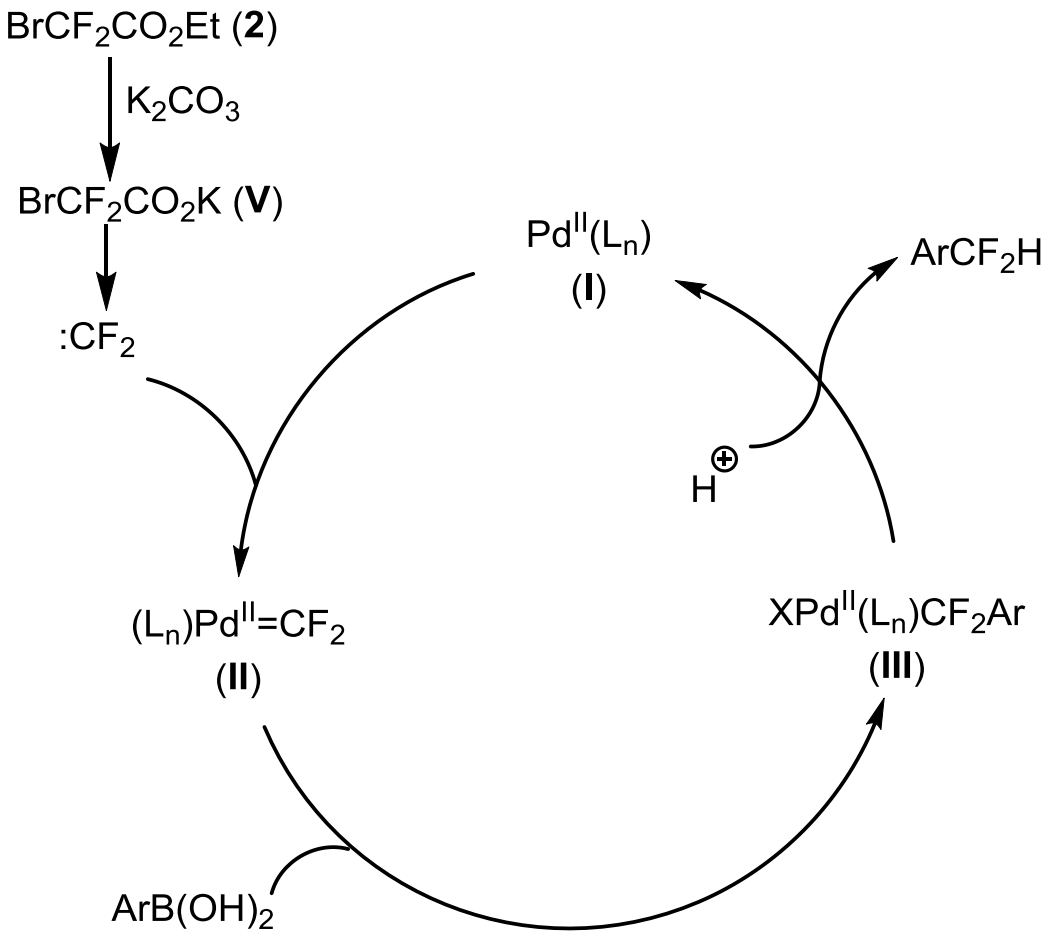




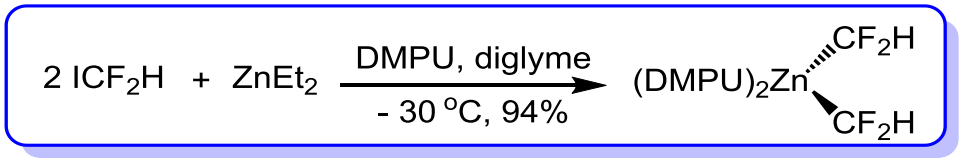
Mechanistic studies

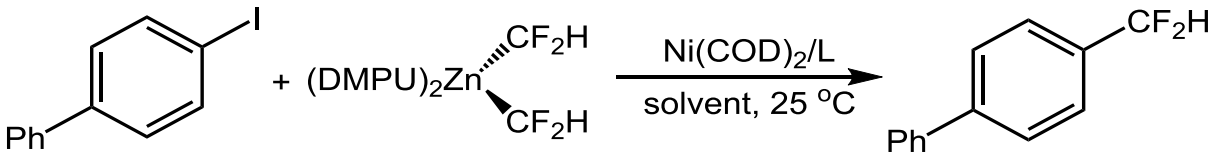


Proposed reaction mechanism



Ni-catalyzed difluoromethylation





entry	$Ni(COD)_2$ (mol%)	L (mol%)	solvent	yield (%)
1	15	dtbpy (15)	DMSO	0
2	15	phen (15)	DMSO	0
3	10	dppf (10)	toluene	trace
4	10	dppf (10)	dioxane	trace
5	10	dppf (10)	DMPU	trace
6	10	dppf (10)	THF	10
7	10	dppf (10)	MeCN	15

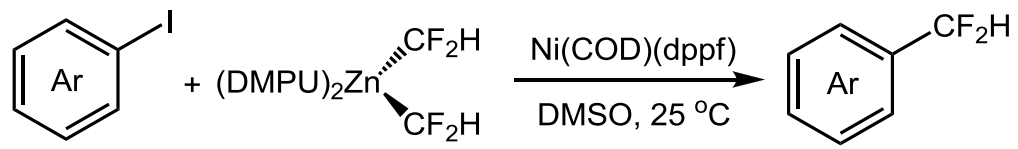
Xu, L.; Vicic, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 2536.

Ni-catalyzed difluoromethylation

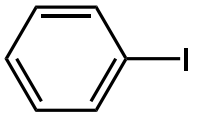
entry	$Ni(COD)_2$ (mol%)	L (mol%)	solvent	yield (%)
8	10	dppf (10)	DMF	16
9	10	dppf (10)	DMSO	51
10	**15**	**dppf (15)**	**DMSO**	**80**
11	15	xantphos (15)	DMSO	10

All of the reactions were run on a 0.1 mmol scale in 0.5 mL of solvent for 24 h; 1.2 equiv of $[(DMPU)_2Zn(CF_2H)_2]$ was used. The yields of $ArCF_2H$ were determined by ^{19}F NMR analysis using *α*,*α*,*α*-trifluorotoluene as an internal standard.

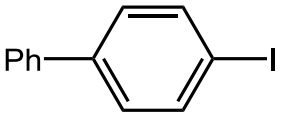
Substrate scope: aryl and heteroaryl iodides



3 1

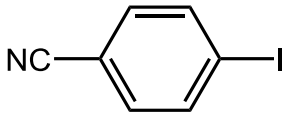


3a, 82%

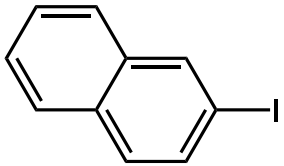


3b, 80%

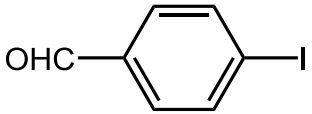
3c, 81%



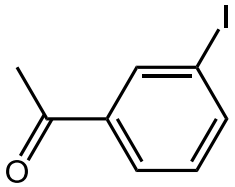
3d, 91%



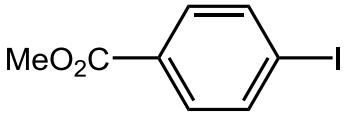
3e, 78%



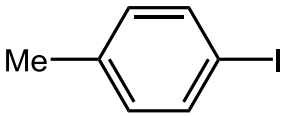
3f, 81%



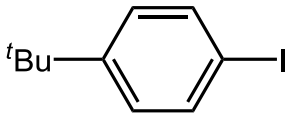
3g, 61%



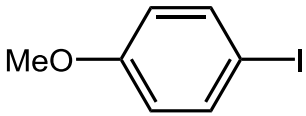
3h, 81%



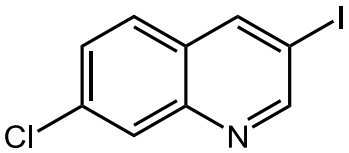
3i, 10%



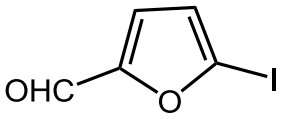
3j, 0%



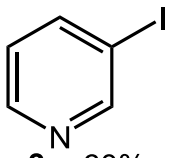
3k, 28%



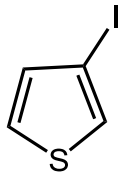
3l, 82%



3m, 78%

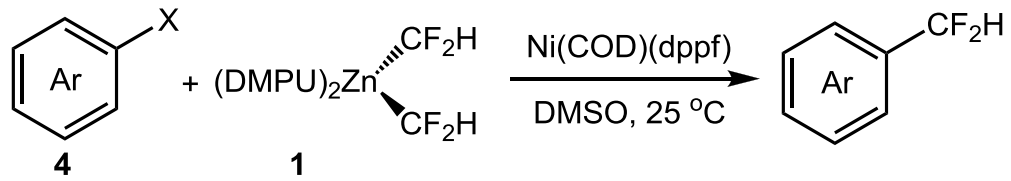


3n, 60%

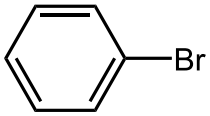


3o, 51%

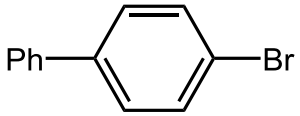
Substrate Scope: aryl bromides and triflates



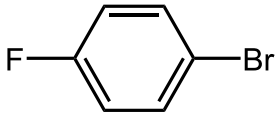
4 **1**



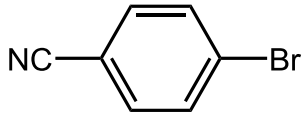
4a, 75%



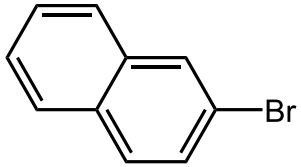
4b, 85%



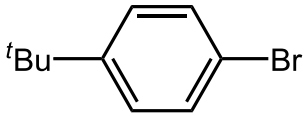
4c, 78%



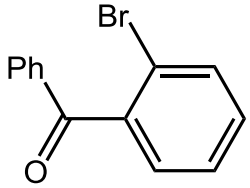
4d, 79%



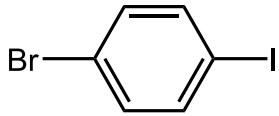
4e, 71%



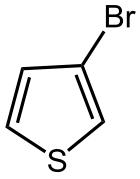
4f, 0%



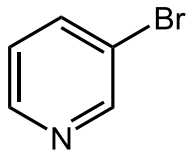
4g, 71%



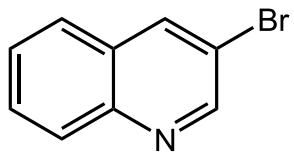
4h, 75% (di)



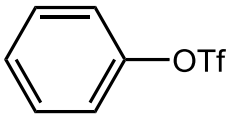
4l, 65%



4j, 60%

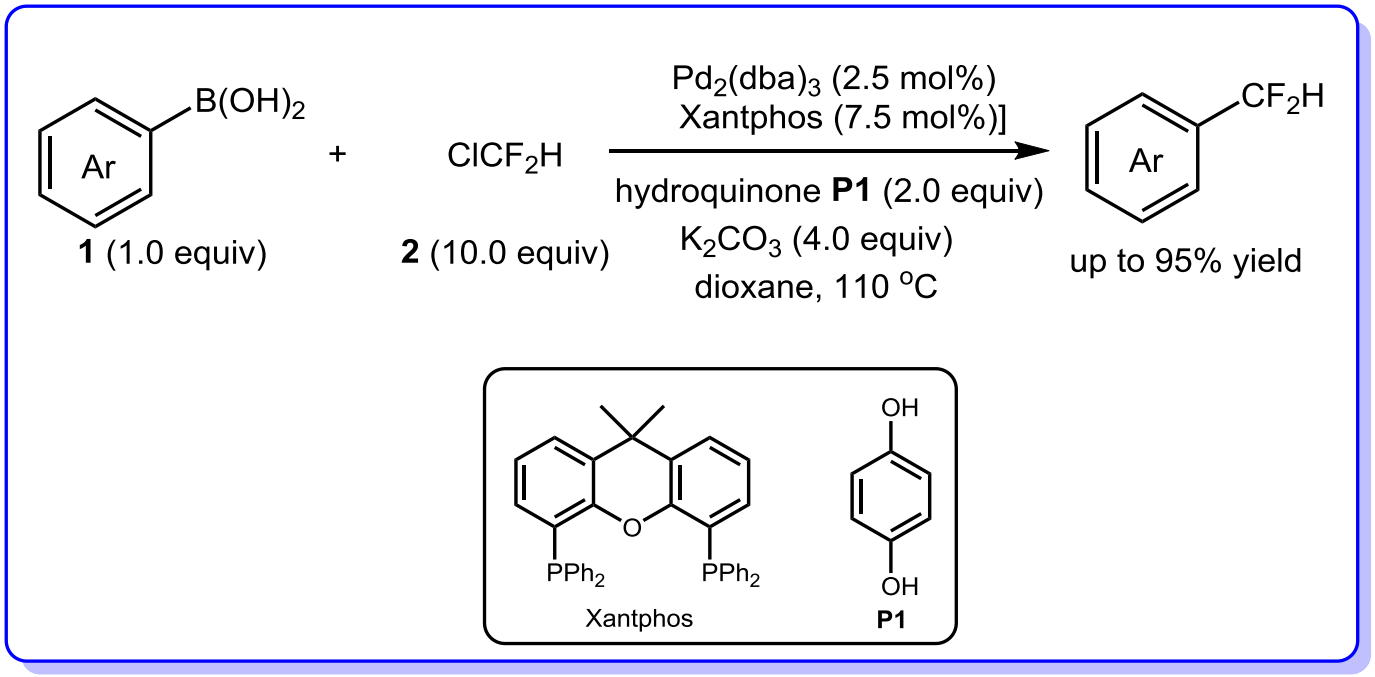


4k 88%



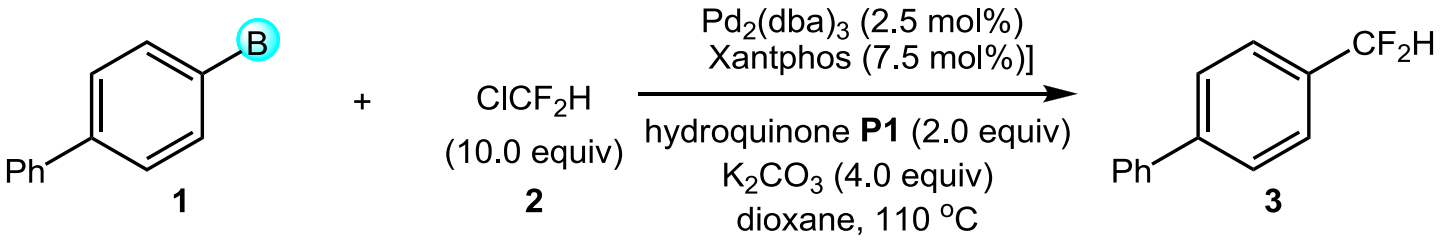
4l, 75%

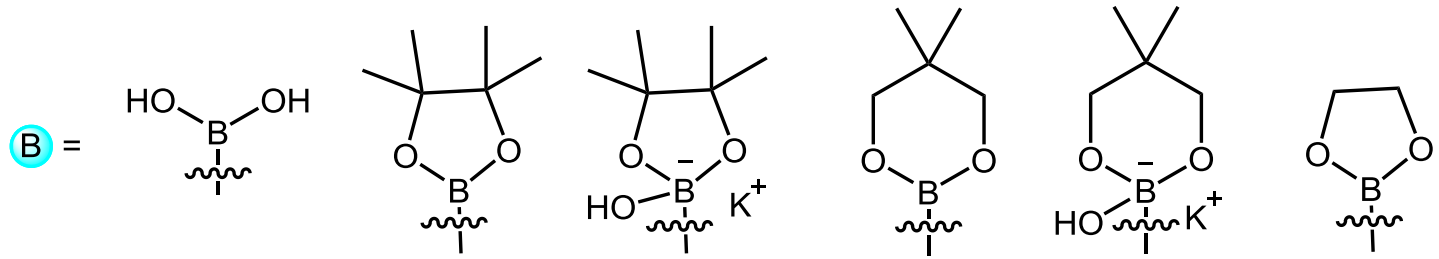
Pd-catalyzed difluoromethylation of arenes with $ClCF_2H$



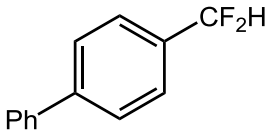
Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nature Chem.* **2017**, doi:10.1038/nchem.2746.

Optimization of arylboronic acid and esters

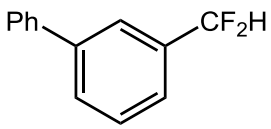




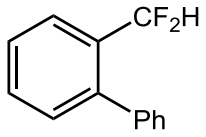
Substrate scope



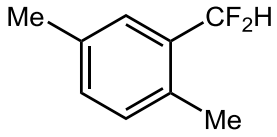
3, 91%



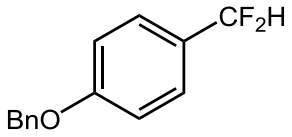
4, 72%



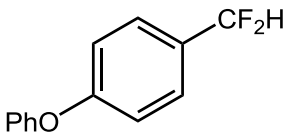
5, 50%



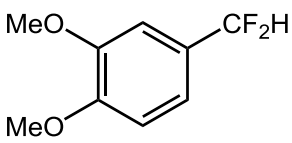
6, 78%



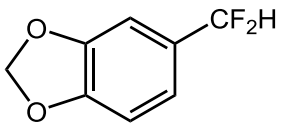
7, 91%



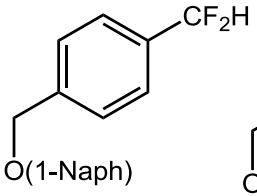
8, 83%



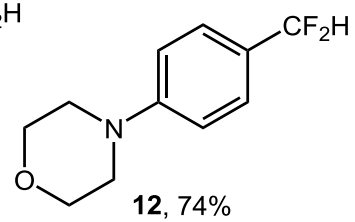
9, 82%



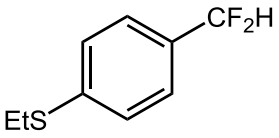
10, 65%



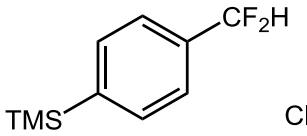
11, 84%



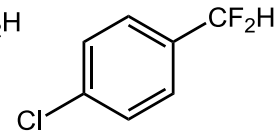
12, 74%



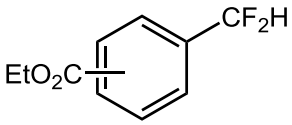
13, 62%



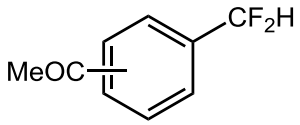
14, 82%



15, 80%

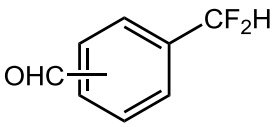


(*p*): **16**, 77%
(*m*): **17**, 78%

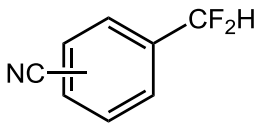


(*p*): **18**, 46%
(*m*): **19**, 55%

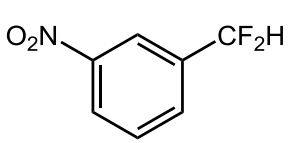
Substrate scope



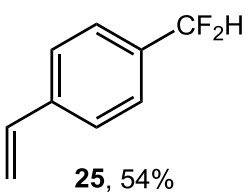
(*p*): **20**, 55%
(*m*): **21**, 50%



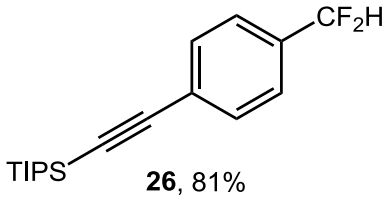
(*p*): **22**, 60%
(*m*): **23**, 85%



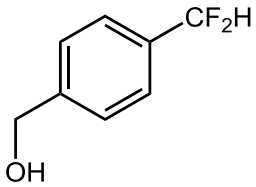
24, 60%



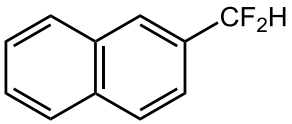
25, 54%



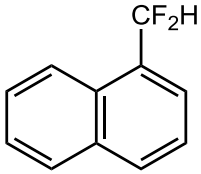
26, 81%



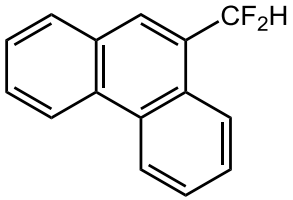
27, 85%



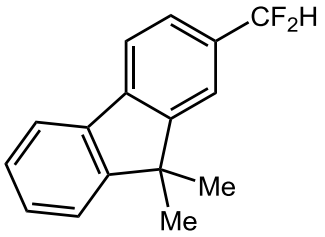
28, 90%



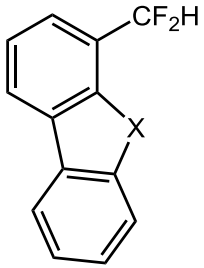
29, 95%



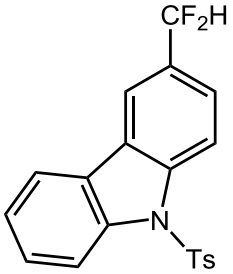
30, 93%



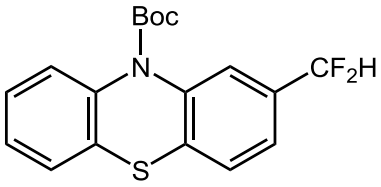
31, 92%



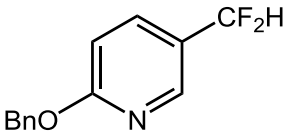
32, X = O, 71%
33, X = S, 73%



34, 72%

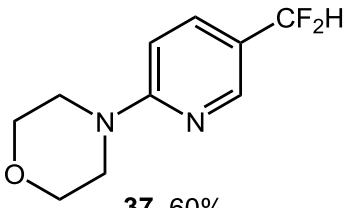


35, 85%

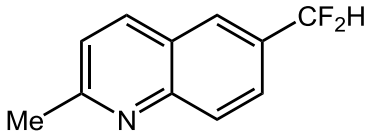


36, 89%

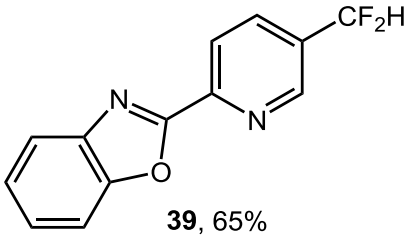
Substrate scope



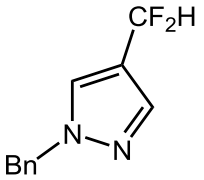
37, 60%



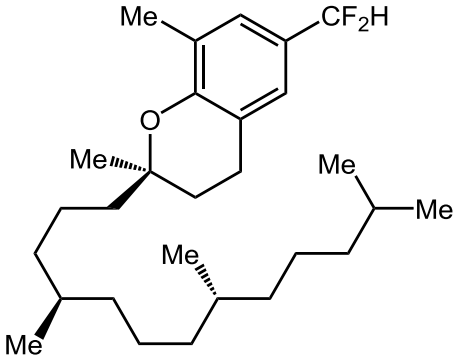
38, 50%



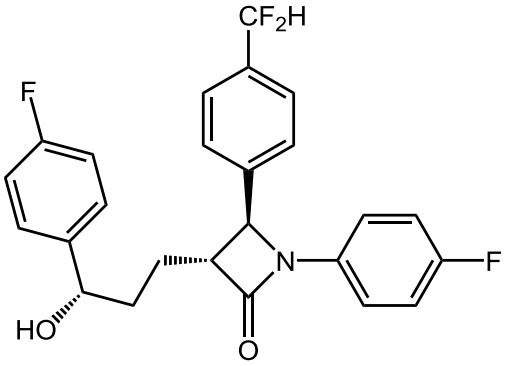
39, 65%



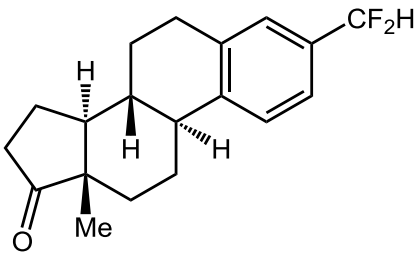
40, 58%



41, 92%
(from δ-vitamin E, antioxidants)

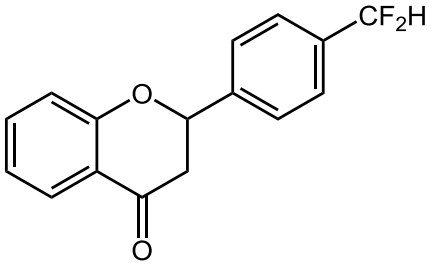


42, 74%
(from ezetimibe, antiatherosclerosics)

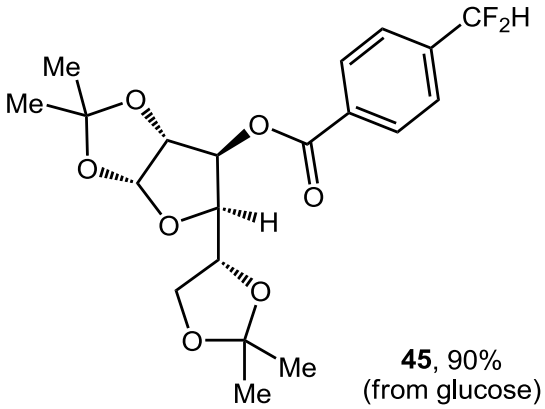


43, 70%
(from estrone, hormone drug)

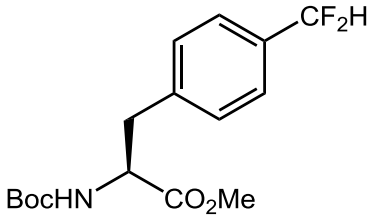
Substrate scope



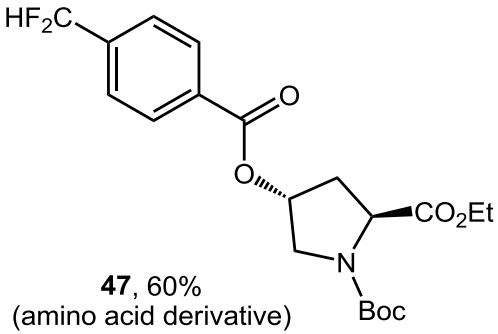
44, 50%
(from flavanone)



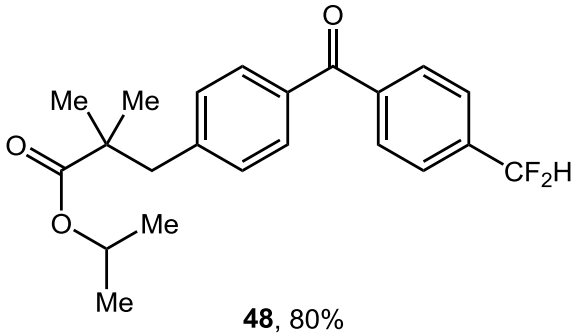
45, 90%
(from glucose)



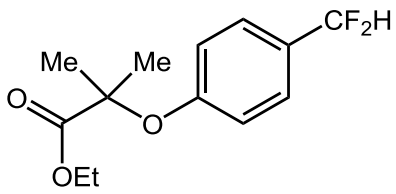
46, 70%
(from tyrosine, amino acid)



47, 60%
(amino acid derivative)

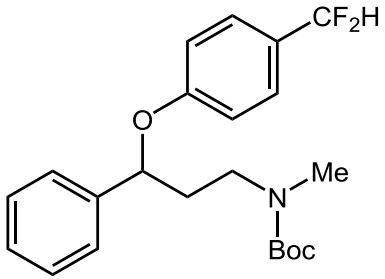


48, 80%
(from fenofibrate, against cardiovascular disease)

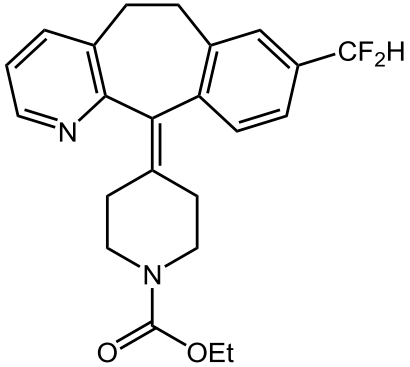


49, 90%; 72% gram-scale
(from clofibrate, against cardiovascular disease)

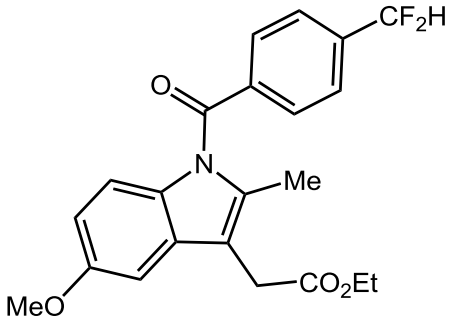
Substrate scope



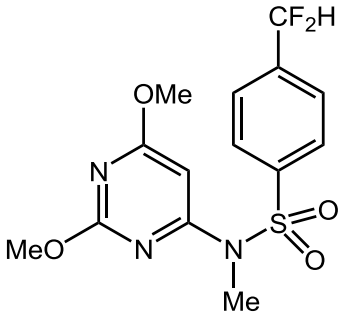
50, 92%
(fluoxetine derivative,
antidepressive drug)



51, 48%
(from loratadine,
antihistaminergic agent)

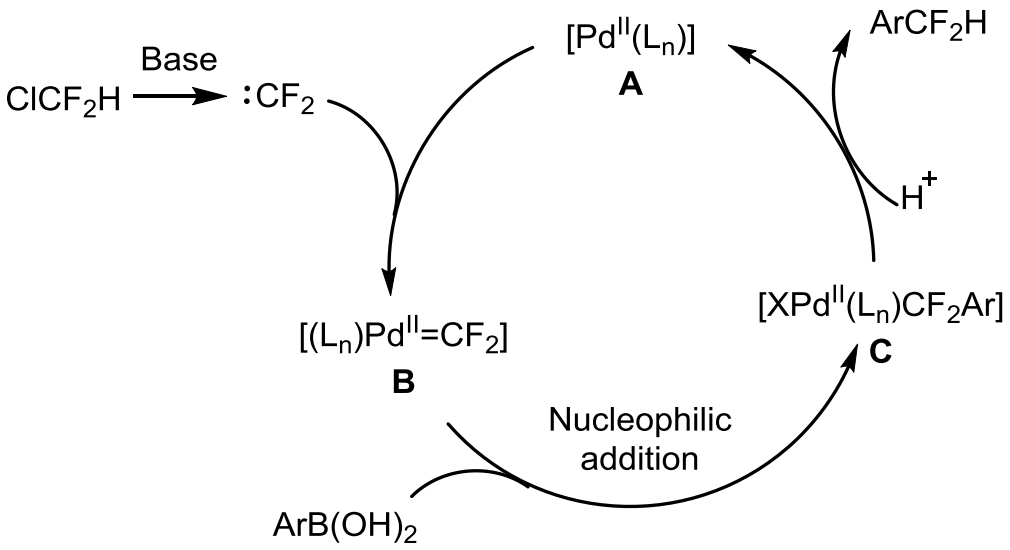


52, 45%
(from indomentacin,
anti-inflammatory drug)

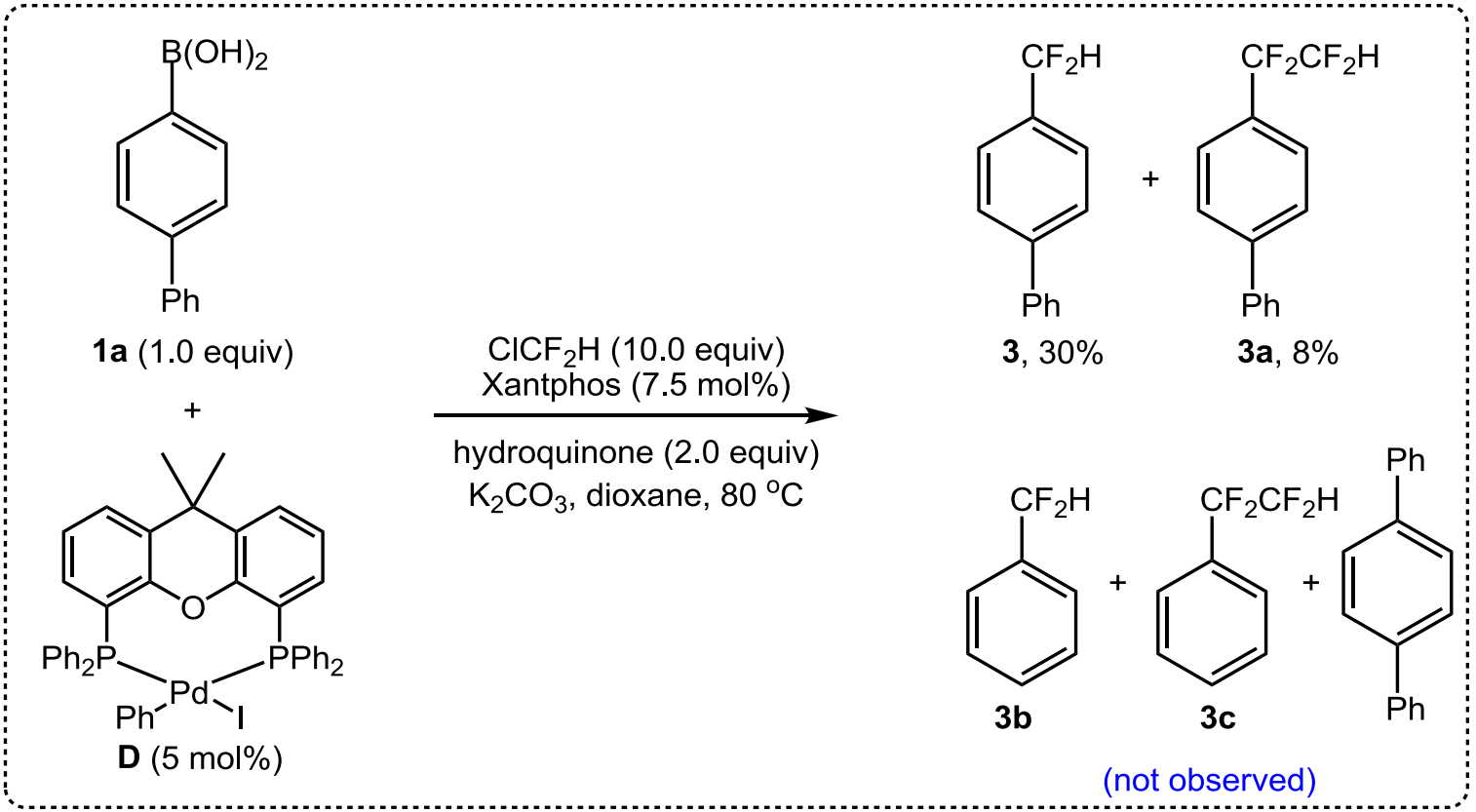


53, 72%
(from sulfadimethoxine,
antibacterial drug)

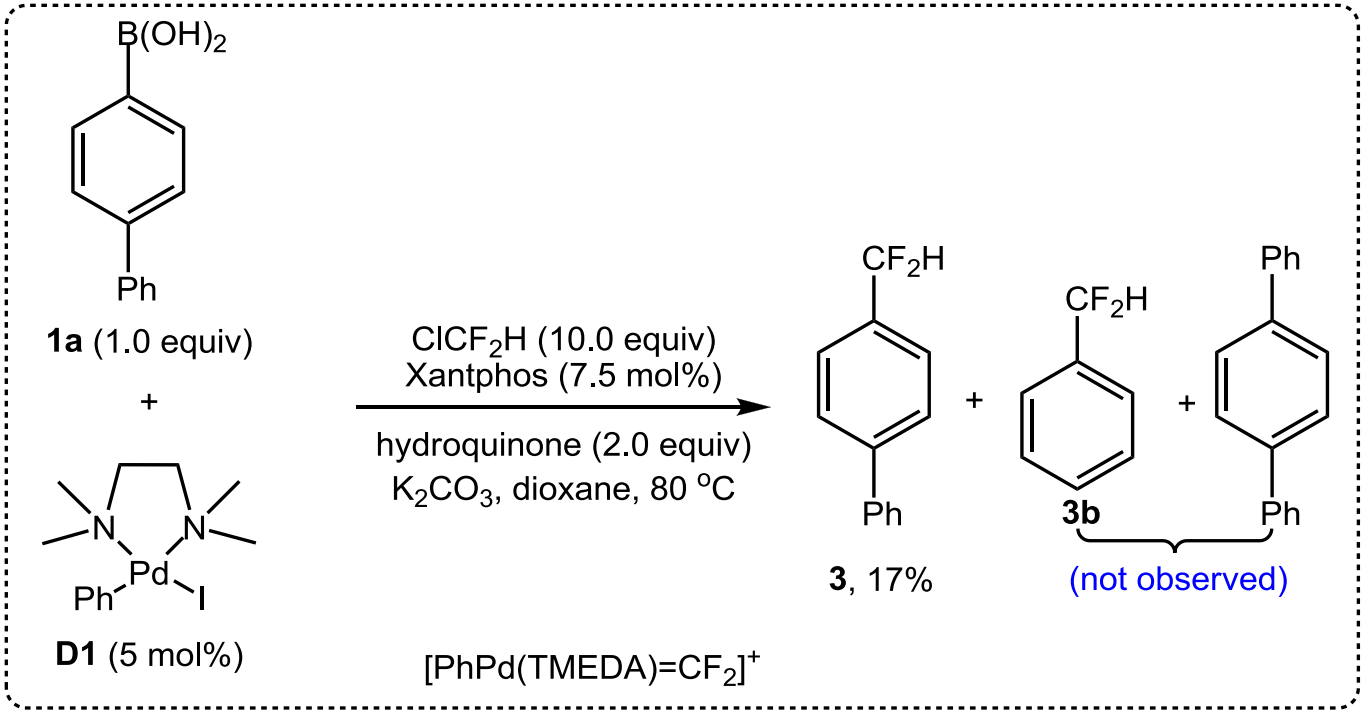
Proposed reaction mechanism



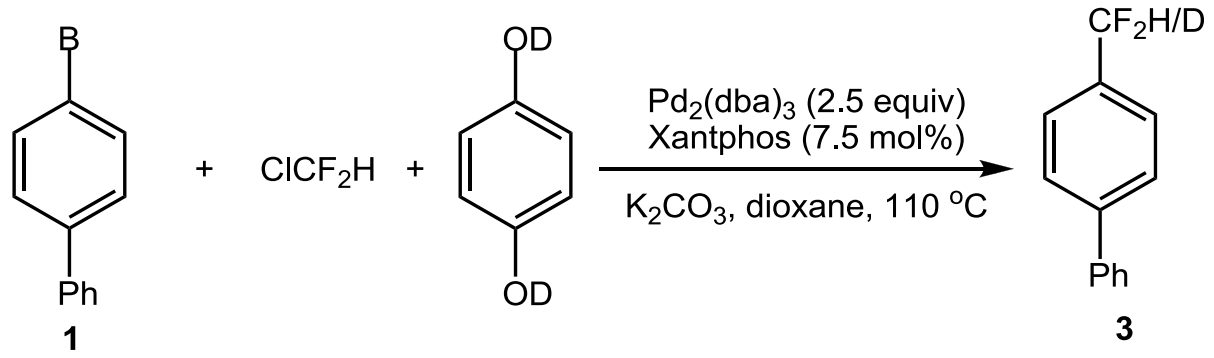
Mechanistic studies



Mechanistic studies

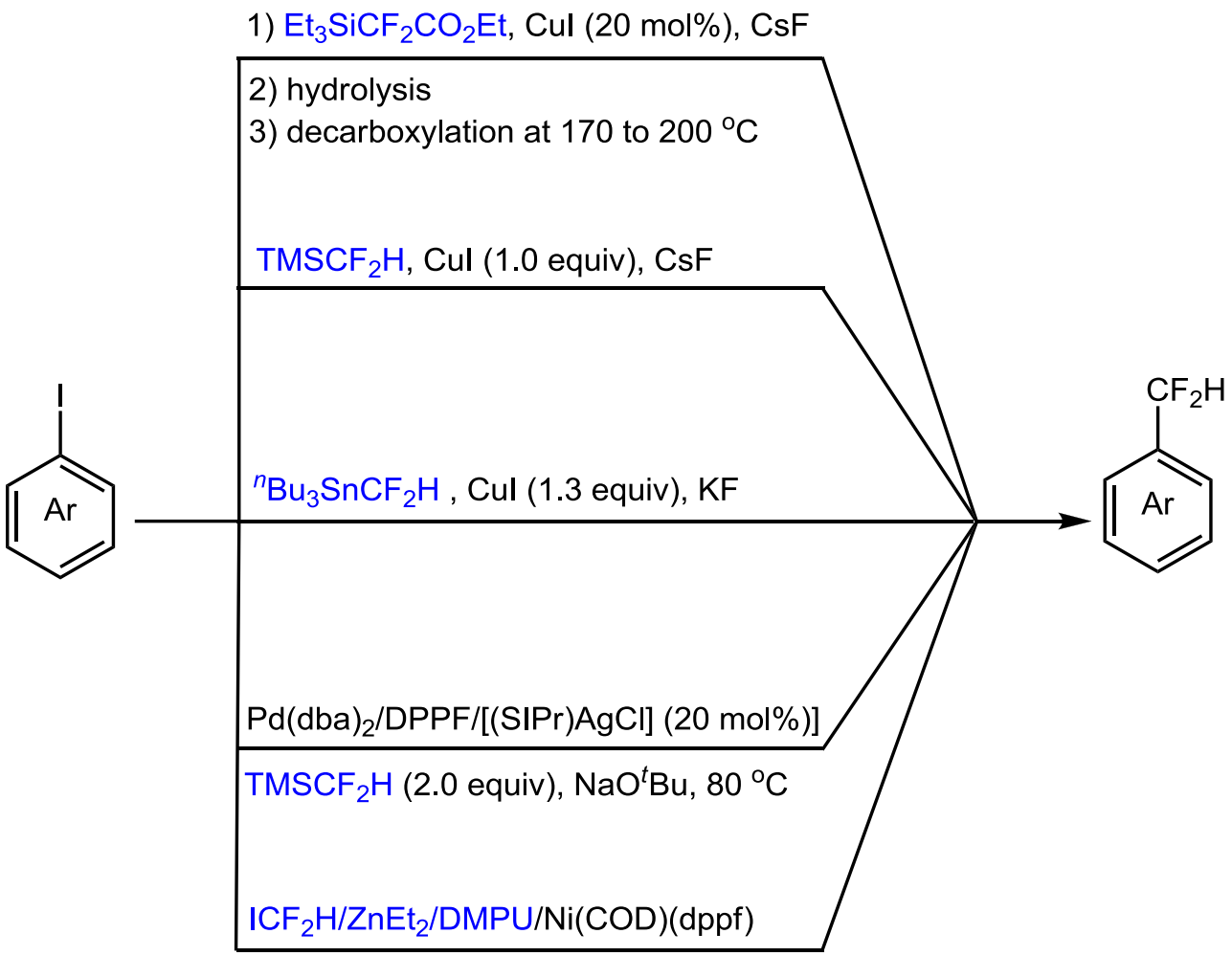


Mechanistic studies

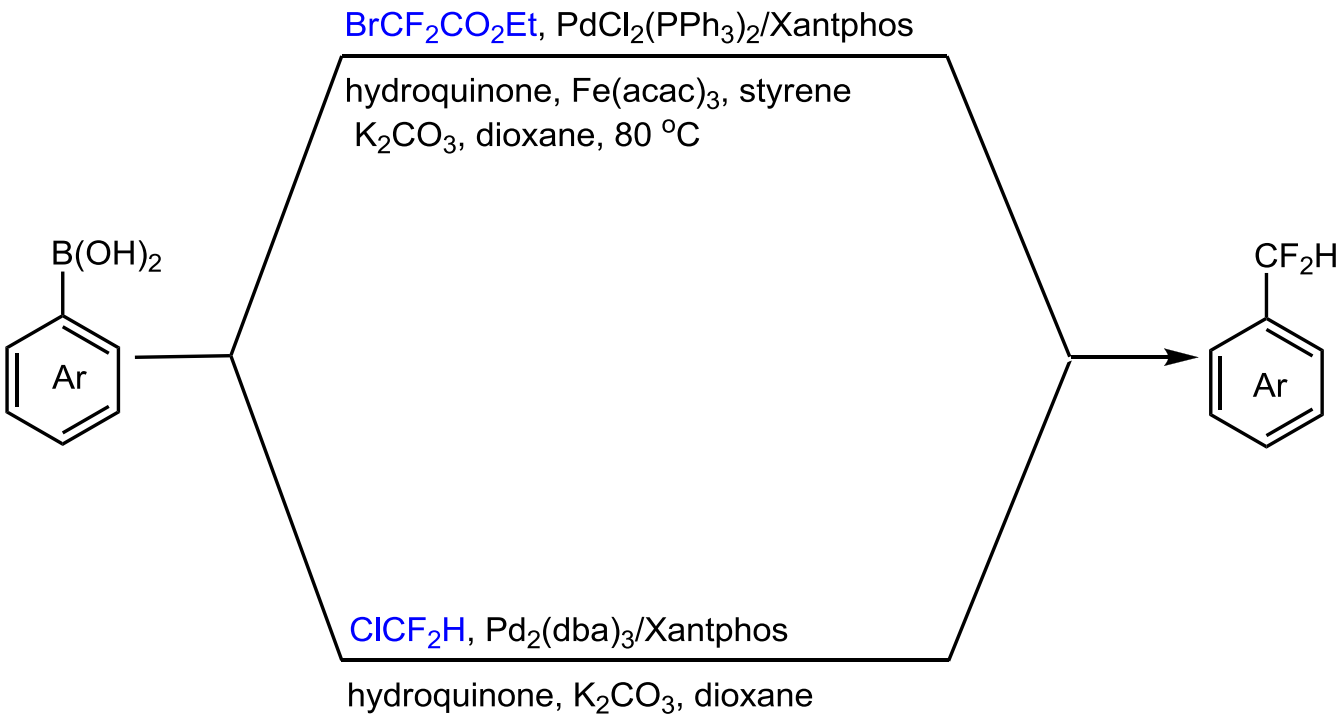


entry	reaction conditions	yield (%), **3-H/3-D**
1	B = $B(OH)_2$, $ClCF_2H$	57/22
2	B = Beg, $ClCF_2H$	40/27
3	No hydroquinone	1/-

Summary


1) $Et_3SiCF_2CO_2Et$, CuI (20 mol%), CsF
2) hydrolysis
3) decarboxylation at 170 to 200 °C
$TMSCF_2H$, CuI (1.0 equiv), CsF
$^nBu_3SnCF_2H$, CuI (1.3 equiv), KF
$Pd(dba)_2$/DPPF/[(SIPr)AgCl] (20 mol%)]
$TMSCF_2H$ (2.0 equiv), NaO^{t}Bu, 80 °C
$ICF_2H/ZnEt_2$/DMPU/Ni(COD)(dppf)
I
Ar
CF_2H
Ar

Summary


BrCF2CO2Et, PdCl2(PPh3)2/Xantphos
hydroquinone, Fe(acac)3, styrene
K2CO3, dioxane, 80 °C
B(OH)2
Ar
CF2H
Ar
ClCF2H, Pd2(dba)3/Xantphos
hydroquinone, K2CO3, dioxane

The first paragraph

The wide application of fluorinated compounds in agrochemicals, pharmaceuticals and materials science has triggered many efforts to develop general and efficient methods for selective introduction of fluorinated groups into organic molecules. Particularly owing to the unique properties of CF_2H, which can serve as a bioisostere of hydroxyl and thiol groups, and also as a lipophilic hydrogen bond donor, the selective introduction of this motif onto aromatic rings can remarkably improve their metabolic stability, oral bioavailability and solubility compared with their non-fluorinated counterparts. Thus, difluoromethylation has become a useful strategy for the modification of biologically active compounds.

The last paragraph

In summary, we have established that the palladium-catalysed difluoromethylation of (hetero)arylboronic acids and esters with the cheap and simple $ClCF_2H$ can efficiently access a variety of difluoromethylated aromatics and that the conditions are compatible with a range of functional groups, including heteroarenes. The ability to directly introduce a difluoromethyl group at metabolic positions of pharmaceuticals provides good opportunities to use $ClCF_2H$ for the synthesis and development new medicinal agents. Preliminary mechanistic studies reveal that a palladium difluorocarbene pathway is involved in the reaction. Current efforts are devoted to elucidating the detailed mechanism and to lower the loading amount of catalyst and $ClCF_2H$.