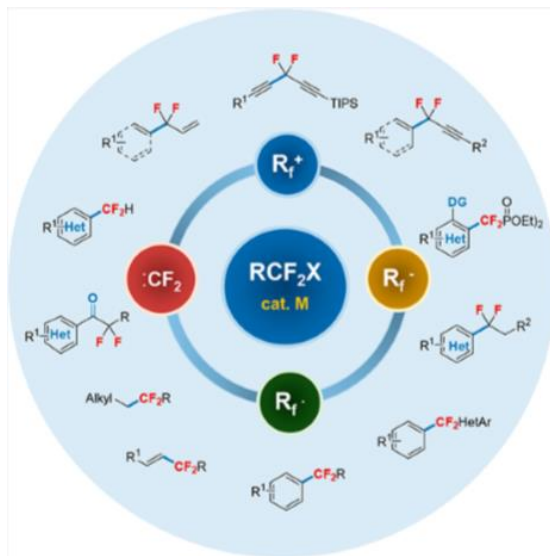


Transition-Metal (Cu, Pd, Ni)-Catalyzed Difluoroalkylation via Cross-Coupling with Difluoroalkyl Halides



Reporter: Ke Liao

Supervisor: Prof. Yong Huang

2018-12-10

Outline

1. Introduction

2. Catalytic nucleophilic difluoroalkylation

3. Catalytic electrophilic difluoroalkylation

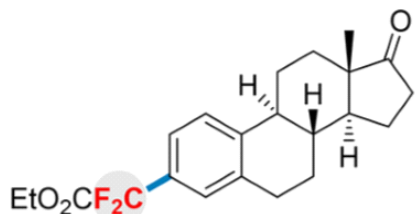
4. Catalytic radical difluoroalkylation

5. Catalytic difluoromethylation by metal-difluorocarbene coupling

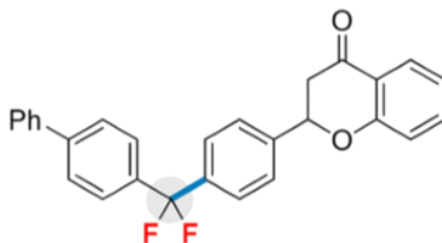
6. Conclusion

Introduction

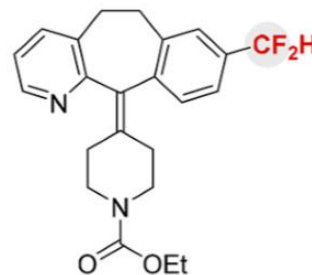
Applications in pharmaceuticals



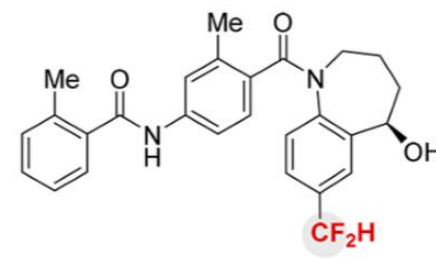
Estrone derivative



Flavanone derivatives



from Loratadine



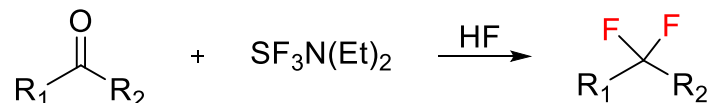
from Tolvaptan

Difluoromethylene (CF_2) group at the benzylic position can dramatically improve the metabolic stability and oral bioavailability of biologically active molecules.

Introduction

Conventional methodology

(1). Deoxyfluorination of a carbonyl moiety



Middleton, W. J. New Fluorinating Reagents. *J. Org. Chem.* **1975**, 40, 574–578

Modest functional group compatibility

High cost

(2). Copper-mediated cross-couplings based on Ullmann reaction



Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, 27, 6103–6106.

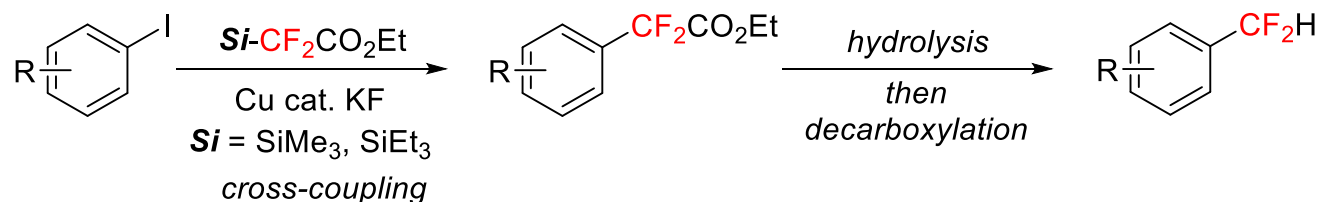
Facilitate the reaction under mild condition

Require excess copper

Limitation of substrate scope (activated hetero or aryl electrophiles)

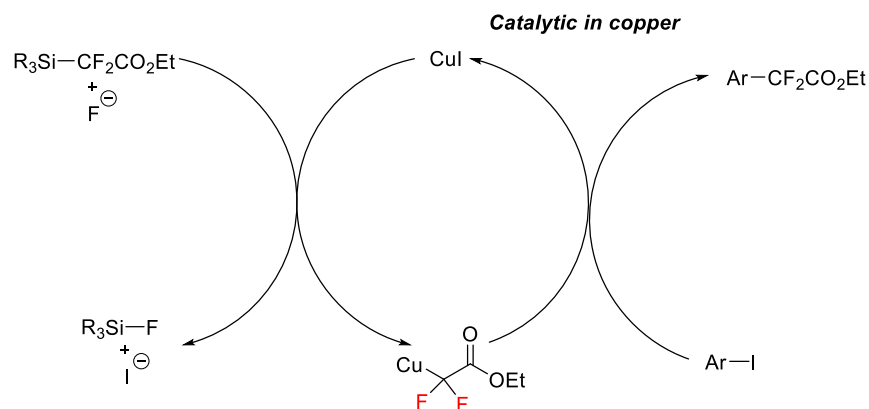
Introduction

(3). Classical copper-catalyzed cross-coupling



Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, 13, 5560–5563.

Mechanism



Difluoroalkylated metal species are unstable and prone to protonation, dimerization, and/or generation of unknown byproducts

Outline

1. Introduction

2. Catalytic nucleophilic difluoroalkylation

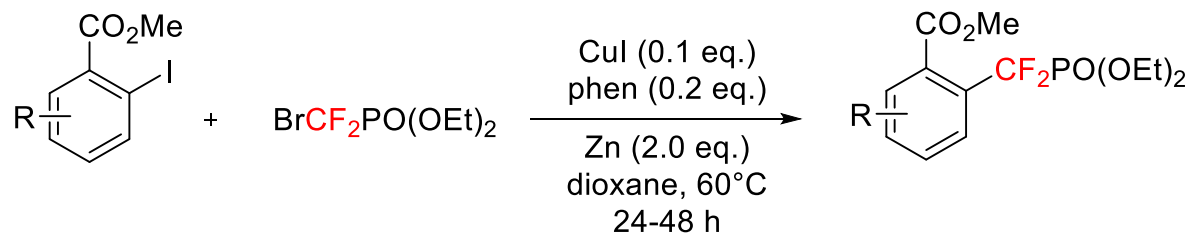
3. Catalytic electrophilic difluoroalkylation

4. Catalytic radical difluoroalkylation

5. Catalytic difluoromethylation by metal-difluorocarbene coupling

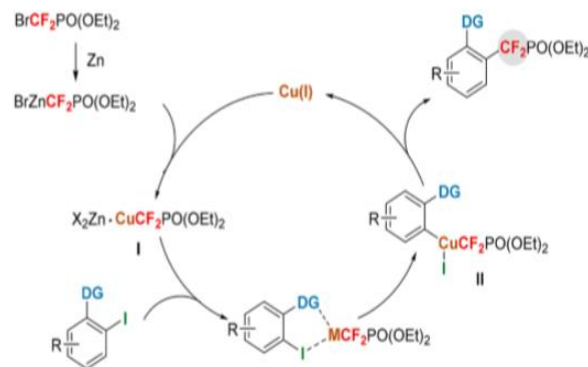
6. Conclusion

Catalytic nucleophilic difluoroalkylation



Feng, Z.; Chen, F.; Zhang, X. *Org. Lett.* **2012**, *14*, 1938–1941.

Mechanism



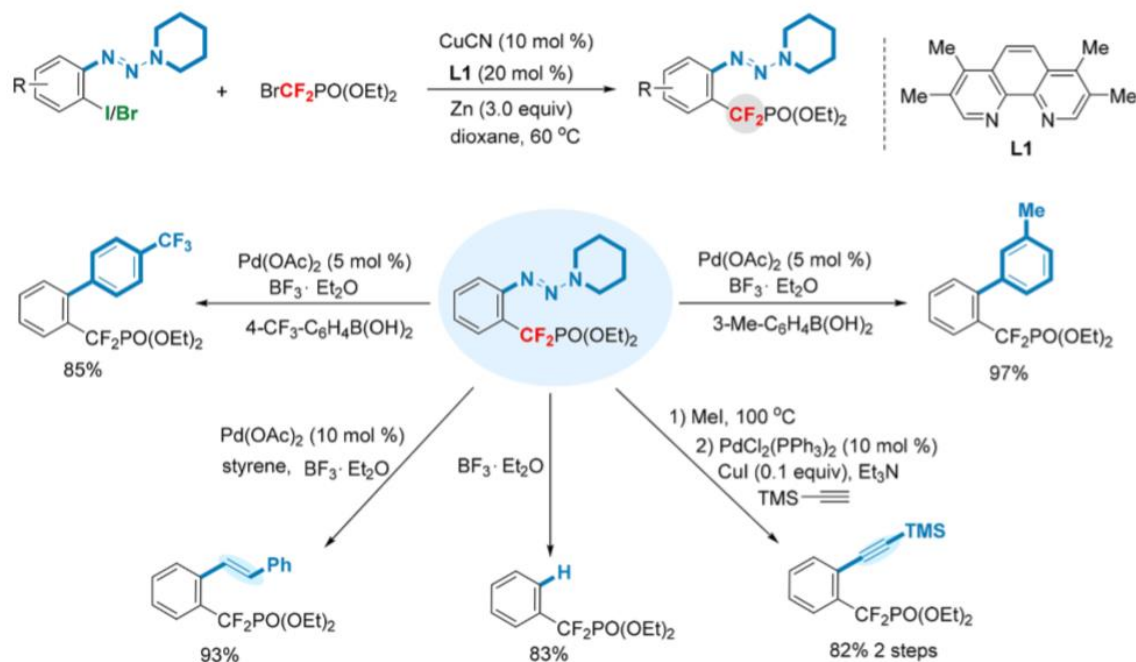
Zn(II) salt: as a linker to attach both catalyst and DG

DG: facilitate the oxidative addition of copper to the Ar-I bond

Aryldifluoromethylphosphonates ($\text{Ar-CF}_2\text{PO(OEt)}_2$) can exhibit significant bioactivity as protein phosphotyrosine phosphatase (**PTPase**) inhibitors

Catalytic nucleophilic difluoroalkylation

Triazene-directed cross-coupling



Feng, Z.; Xiao, Y.-L.; Zhang, X. *Org. Chem. Front.* **2014**, 1, 113–116.

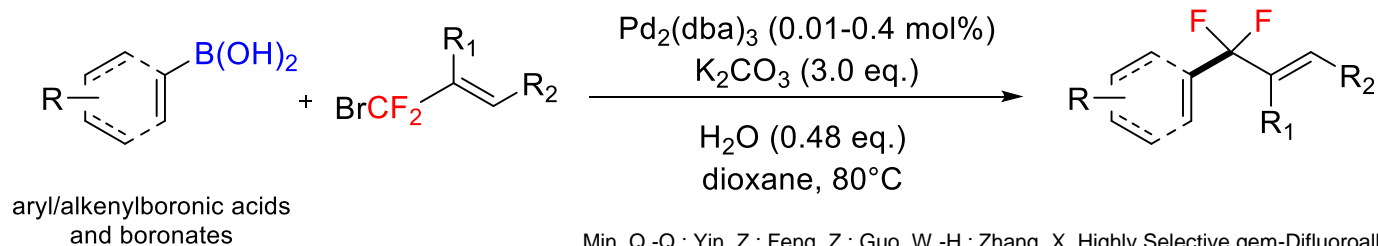
A diverse range of aryldifluoromethylphosphonates difficult to synthesize by conventional methods were synthesized

Outline

1. Introduction
2. Catalytic nucleophilic difluoroalkylation
- 3. Catalytic electrophilic difluoroalkylation**
4. Catalytic radical difluoroalkylation
5. Catalytic difluoromethylation by metal-difluorocarbene coupling
6. Conclusion

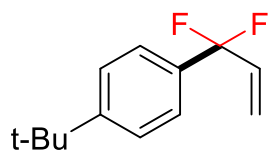
Catalytic electrophilic difluoroalkylation

(1) Palladium-catalyzed gem-difluoroallylation

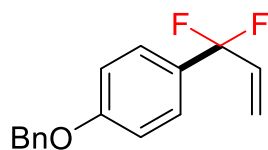


Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. Highly Selective gem-Difluoroallylation of Organoborons with Bromodifluoromethylated Alkenes Catalyzed by Palladium. *J. Am. Chem. Soc.* **2014**, 136, 1230–1233.

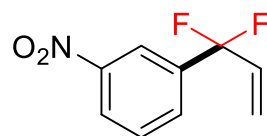
Substrates:



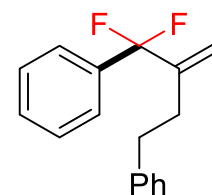
80% (10:1)



87% (28:1)



70% (13:1)

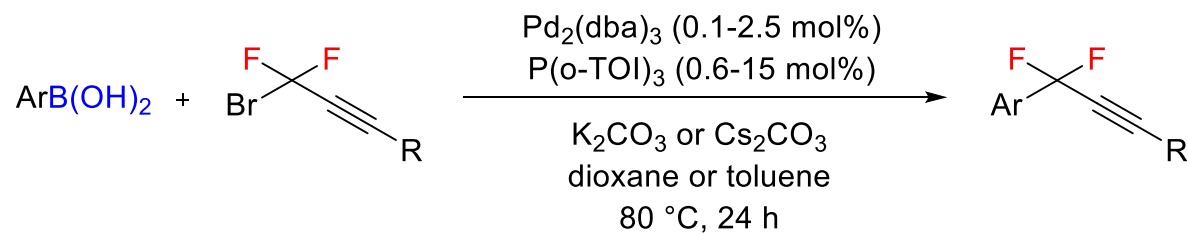


70% (13:1)

(α/γ up to >37:1) : probably due to the strong electron-withdrawing effect of the CF₂ group, which strengthens the Pd–CF₂R bond

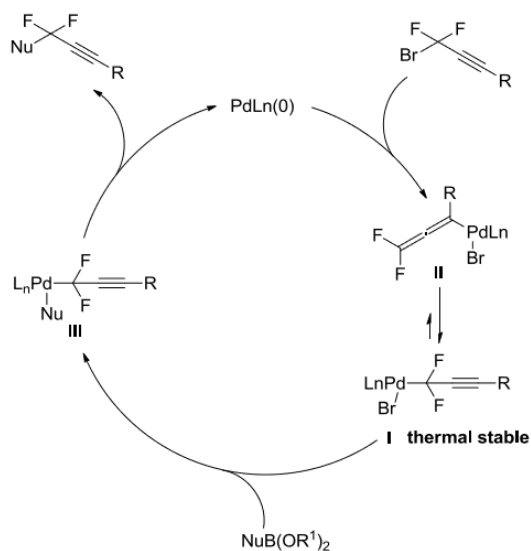
Catalytic electrophilic difluoroalkylation

(2) Palladium-catalyzed gem-difluoropropargylation



Yu, Y.-B.; He, G.-Z.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, 53, 10457–10461.

Mechanism

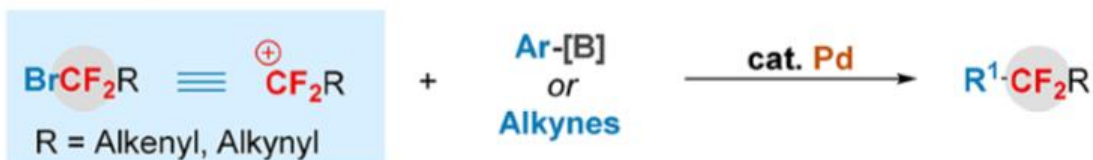


Differences between electrophilic and nucleophilic

a. Nucleophilic Difluoroalkylation



b. Electrophilic Difluoroalkylation

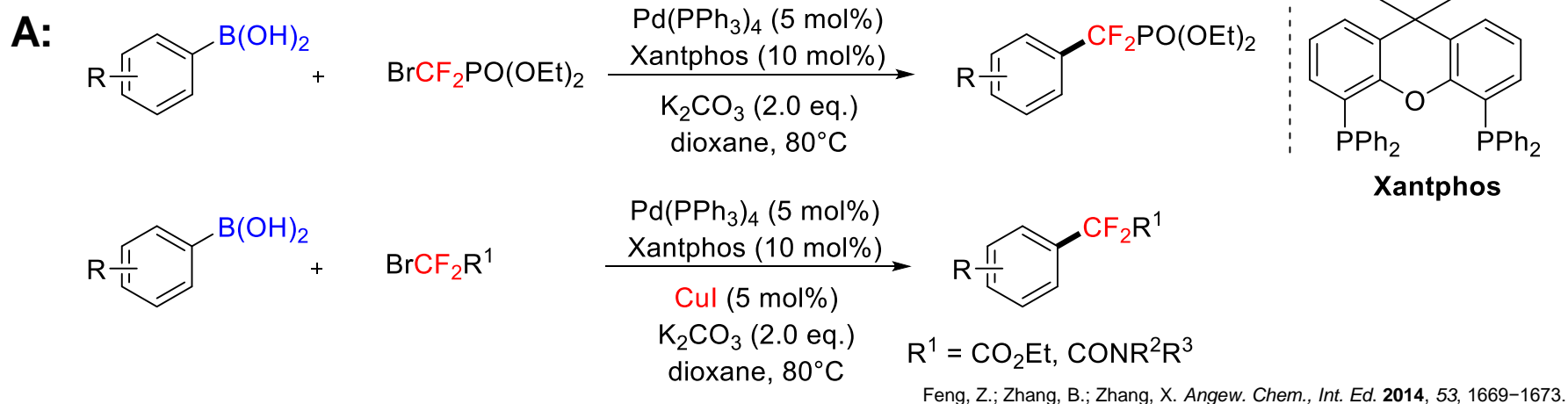


Outline

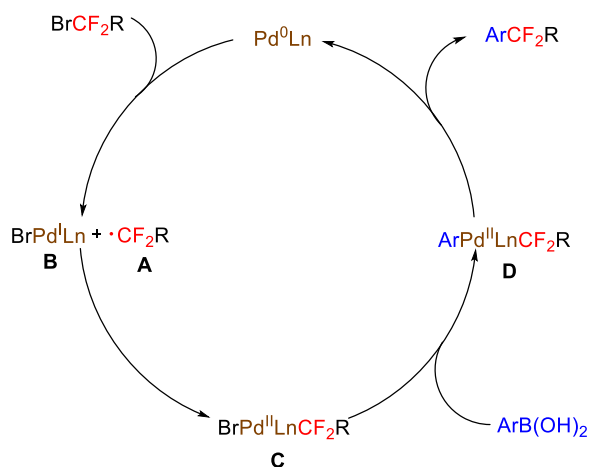
1. Introduction
2. Catalytic nucleophilic difluoroalkylation
3. Catalytic electrophilic difluoroalkylation
- 4. Catalytic radical difluoroalkylation**
5. Catalytic difluoromethylation by metal-difluorocarbene coupling
6. Conclusion

Catalytic radical difluoroalkylation

(1) Palladium-catalyzed radical difluoroalkylation

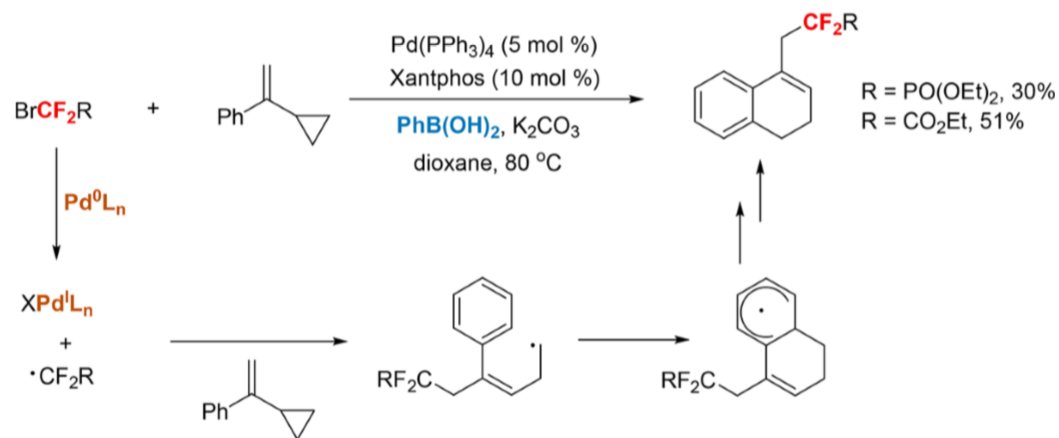


Proposed mechanism

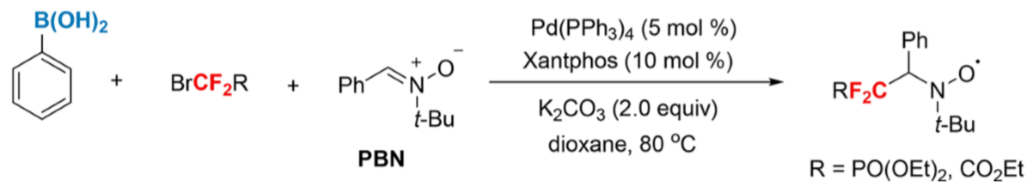


Difluoroalkyl Radical Trapping Experiments

a. Radical Clock Experiments

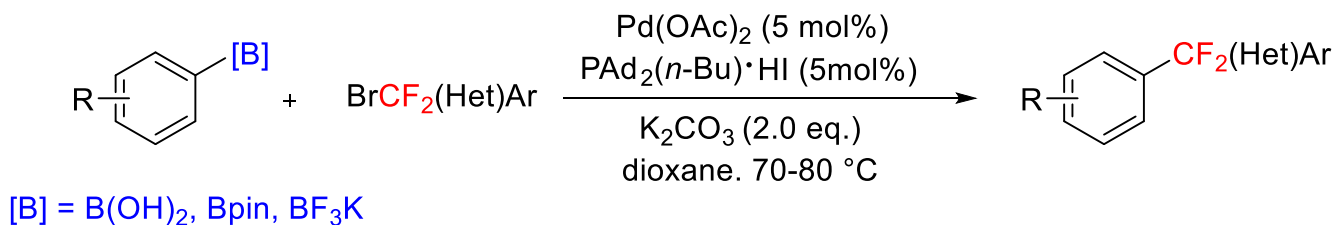


b. EPR Studies



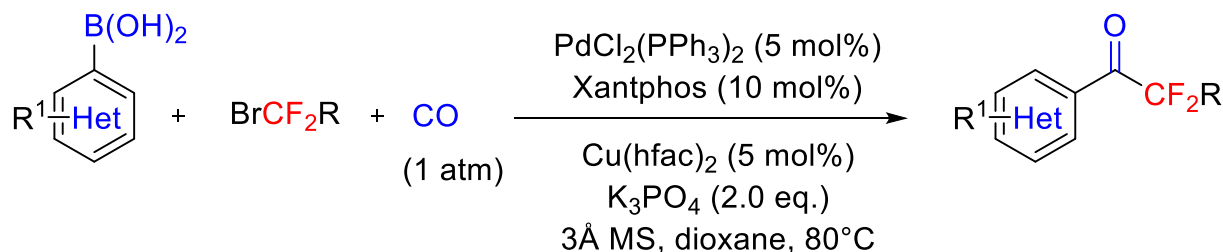
Catalytic radical difluoroalkylation

B: cross-coupling of arylboron with $\text{BrCF}_2(\text{Het})\text{Ar}$



Xiao, Y.-L.; Zhang, B.; Feng, Z.; Zhang, X. *Org. Lett.* **2014**, 16, 4822–4825.
Gu, J.-W.; Guo, W.-H.; Zhang, X. *Org. Chem. Front.* **2015**, 2, 38–41

C: catalytic carbonylation of difluoroalkyl bromides

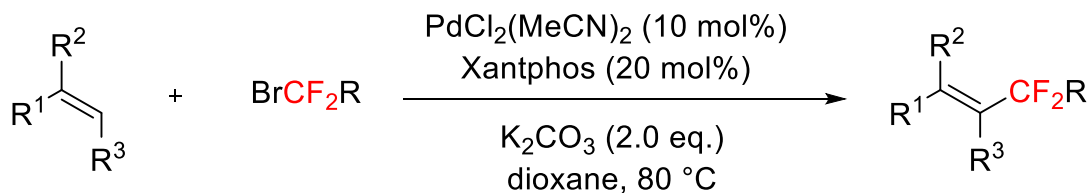


Zhao, H.-Y.; Feng, Z.; Luo, Z.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, 55, 10401–10405.

Overcome the reluctant insertion of CO into the σ bonds between fluoroalkyl groups and transition metals
Provide a new and efficient route for the preparation of fluoroalkylcarbonylated compounds

Catalytic radical difluoroalkylation

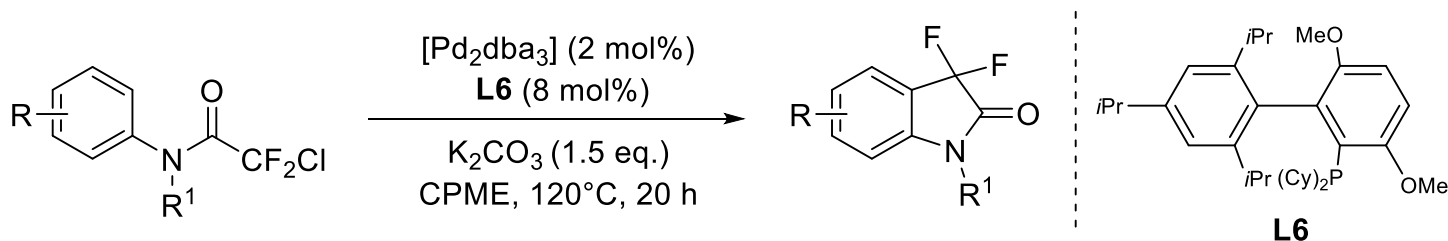
D: Heck-type reaction to prepare difluoroalkylated alkenes



enable olefination of a wide range of difluoroalkyl bromides and perfluoroalkyl bromides

Feng, Z.; Min, Q.-Q.; Zhao, H.-Y.; Gu, J.-W.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1270–1274.

E: intramolecular C-H difluoroalkylation from chlorodifluoroacetamides

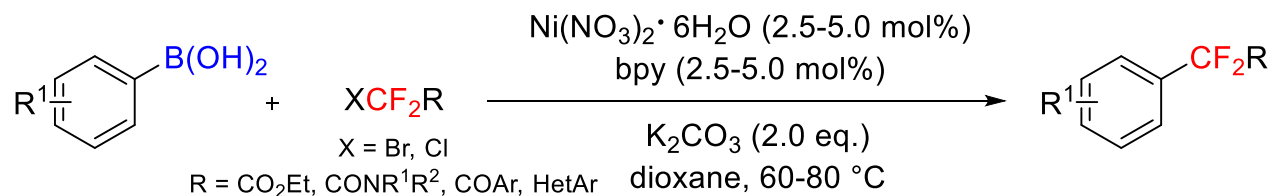


Shi, S.-L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1646–1650.

Catalytic radical difluoroalkylation

(2) Nickel-catalyzed radical difluoroalkylation

A:

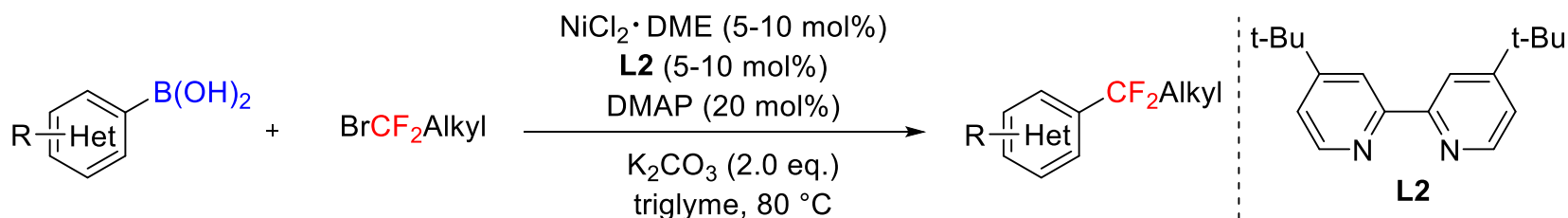


Xiao, Y.-L.; Guo, W.-H.; He, G.-Z.; Pan, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, 53, 9909– 9913.

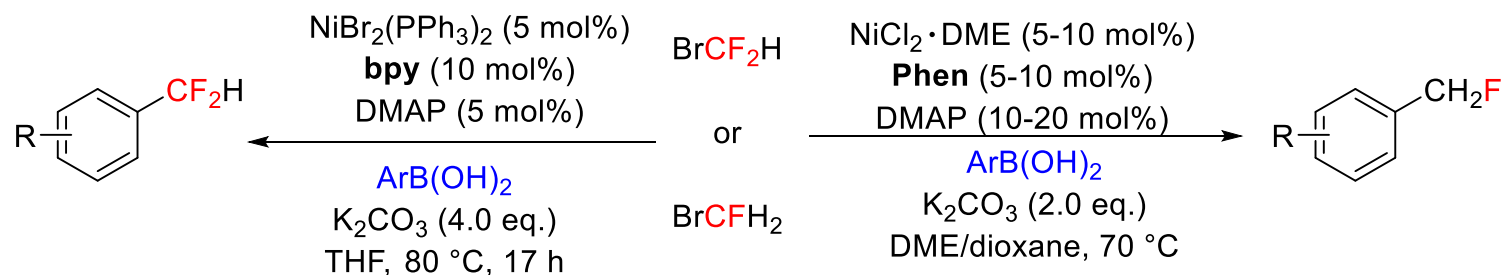
First example of a nickel-catalyzed cross coupling to access difluoroalkylated arenes

Catalytic radical difluoroalkylation

B: Cross-coupling using unactivated $\text{BrCF}_2\text{-alkyl}$ even BrCF_2H and BrCFH_2



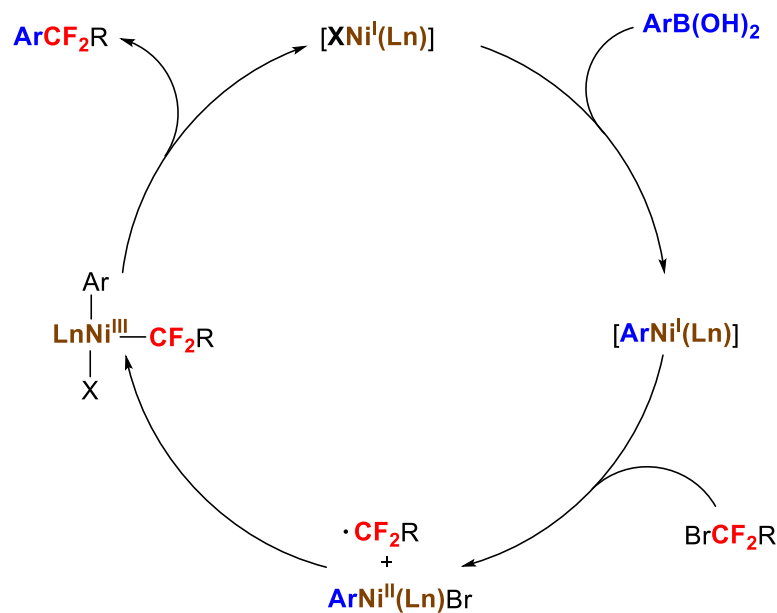
Xiao, Y.-L.; Min, Q.-Q.; Xu, C.; Wang, R.-W.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, 55, 5837–5841.
 An, L.; Xiao, Y.-L.; Zhang, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2018**, 57, 6921–6925.



An, L.; Xiao, Y.-L.; Min, Q.-Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, 54, 9079–9083.

Even gaseous BrCF_2H and BrCFH_2 are competent coupling partners

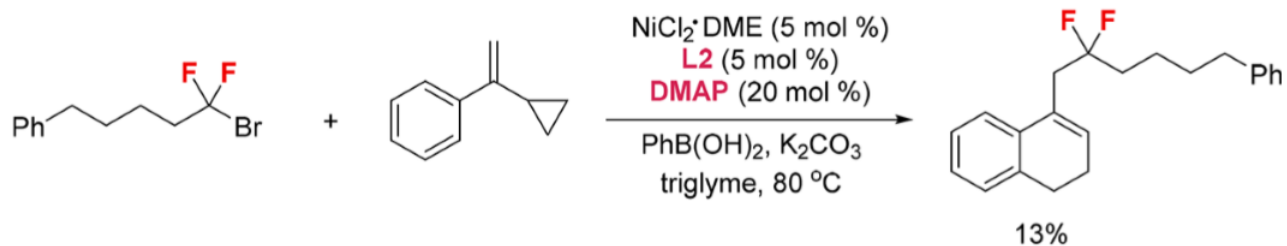
Catalytic radical difluoroalkylation



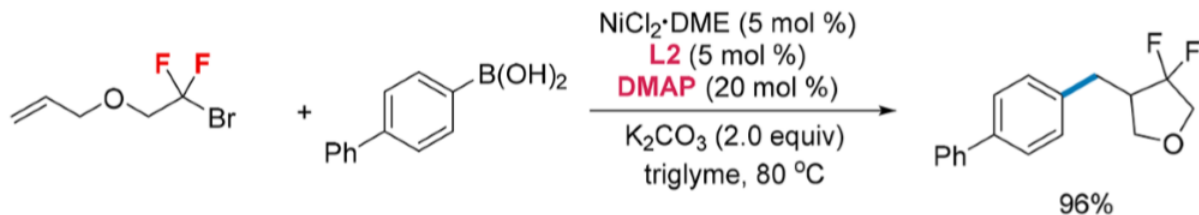
Proposed mechanism for Nickel-Catalyzed Cross-coupling of arylboronic Acids with difluoroalkyl halides

Difluoroalkyl Radical Trapping Experiments

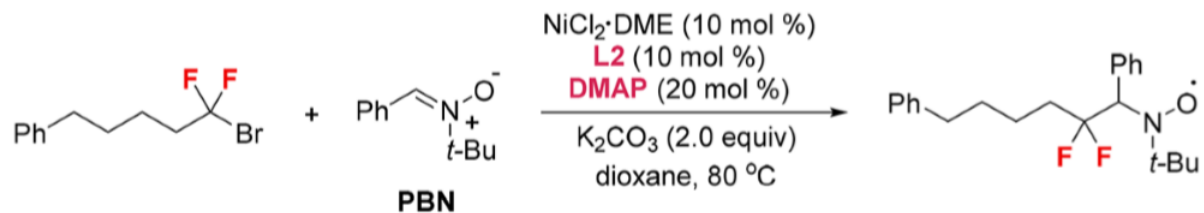
a. Radical Clock Experiment



b. Tandem Radical Cyclization/Cross-Coupling

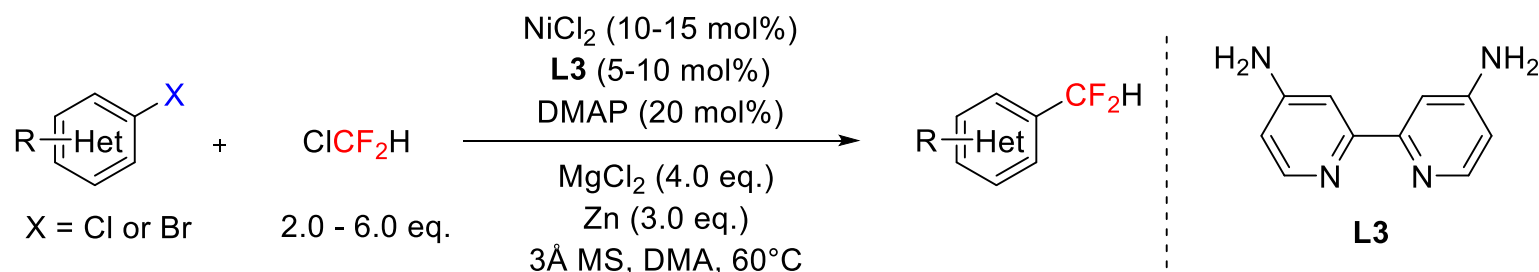


c. EPR Study



Catalytic radical difluoroalkylation

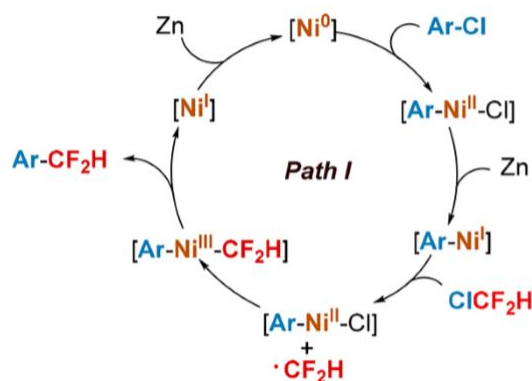
C: Cross-coupling of (hetero)aryl chlorides/bromides with ClCF_2H



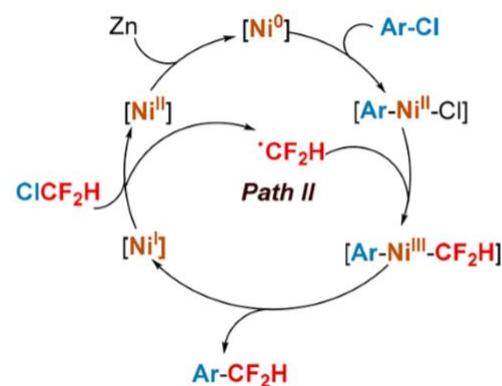
Xu, C.; Guo, W.-H.; He, X.; Guo, Y.-L.; Zhang, X.-Y.; Zhang, X. *Nat. Commun.* **2018**, 9, 1170

Proposed mechanism

a. Radical-Cage Rebound Process



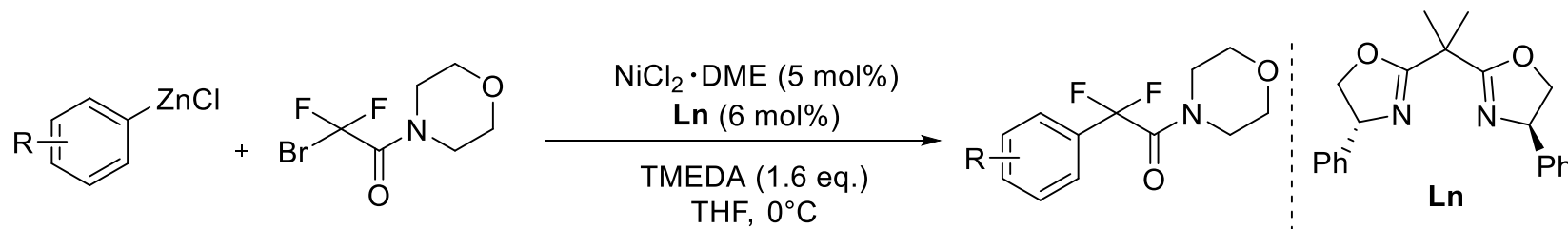
b. Radical Chain Mechanism



start from the oxidative addition of the aryl chloride/bromide to $[\text{Ni}^0]$, and a radical-cage rebound process and/or a radical chain mechanism are/is involved in the catalytic cycle

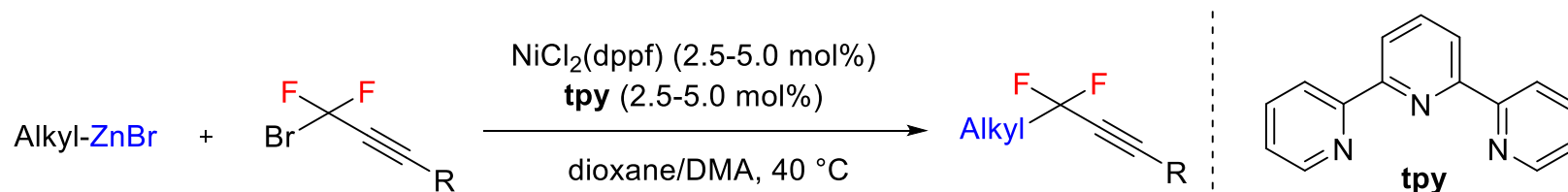
Catalytic radical difluoroalkylation

D: Nickel-Catalyzed Negishi Coupling of Bromodifluoroacetamide with Arylzinc Chlorides



Tarui, A.; Shinohara, S.; Sato, K.; Omote, M.; Ando, A. *Org. Lett.* **2016**, *18*, 1128–1131.

E: Cross-coupling of unactivated alkylzinc with *gem*-difluoropropargyl bromide



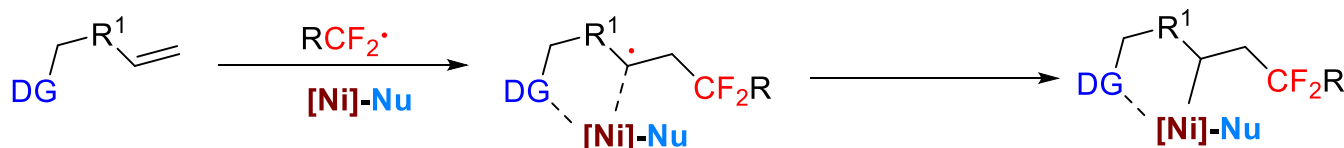
An, L.; Xu, C.; Zhang, X. *Nat. Commun.* **2017**, *8*, 1460

providing a general and straightforward method for site-selective introduction of a CF_2 group into an aliphatic chain

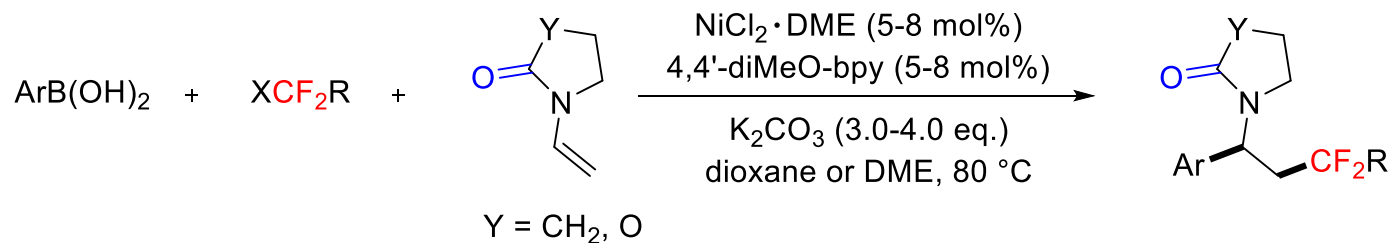
Catalytic radical difluoroalkylation

F: Chelating-group-assisted nickel-catalyzed radical tandem reaction

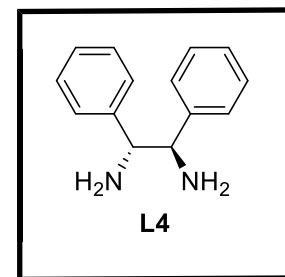
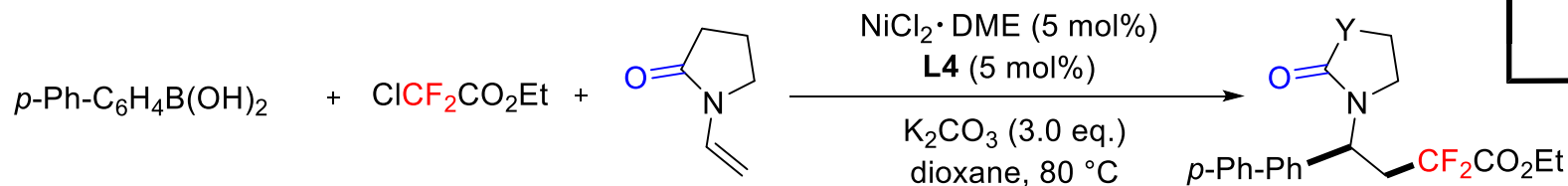
a. Concept for Chelating-Group-Assisted Ni-Catalyzed Tandem Reaction



b. Representative Examples



c. Stereoconvergent Synthesis



The first example of an enantioselective nickel-catalyzed three-component reaction though the low ee.

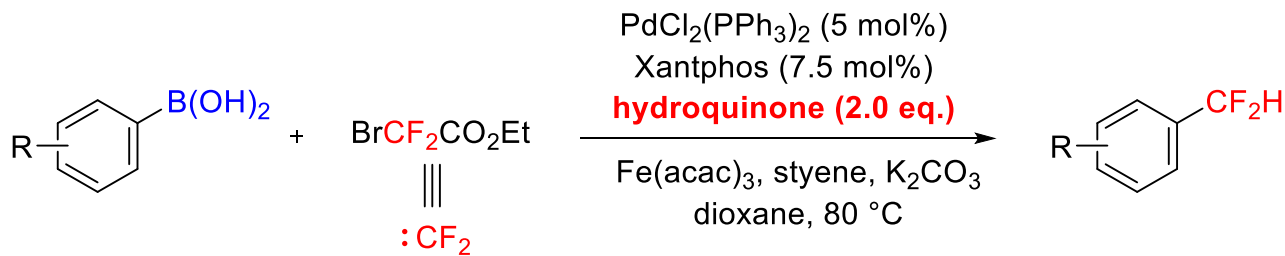
60%, 18% ee

Outline

1. Introduction
2. Catalytic nucleophilic difluoroalkylation
3. Catalytic electrophilic difluoroalkylation
4. Catalytic radical difluoroalkylation
- 5. Catalytic difluoromethylation by metal-difluorocarbene coupling**
6. Conclusion

Catalytic difluoromethylation by metal-difluorocarbene coupling

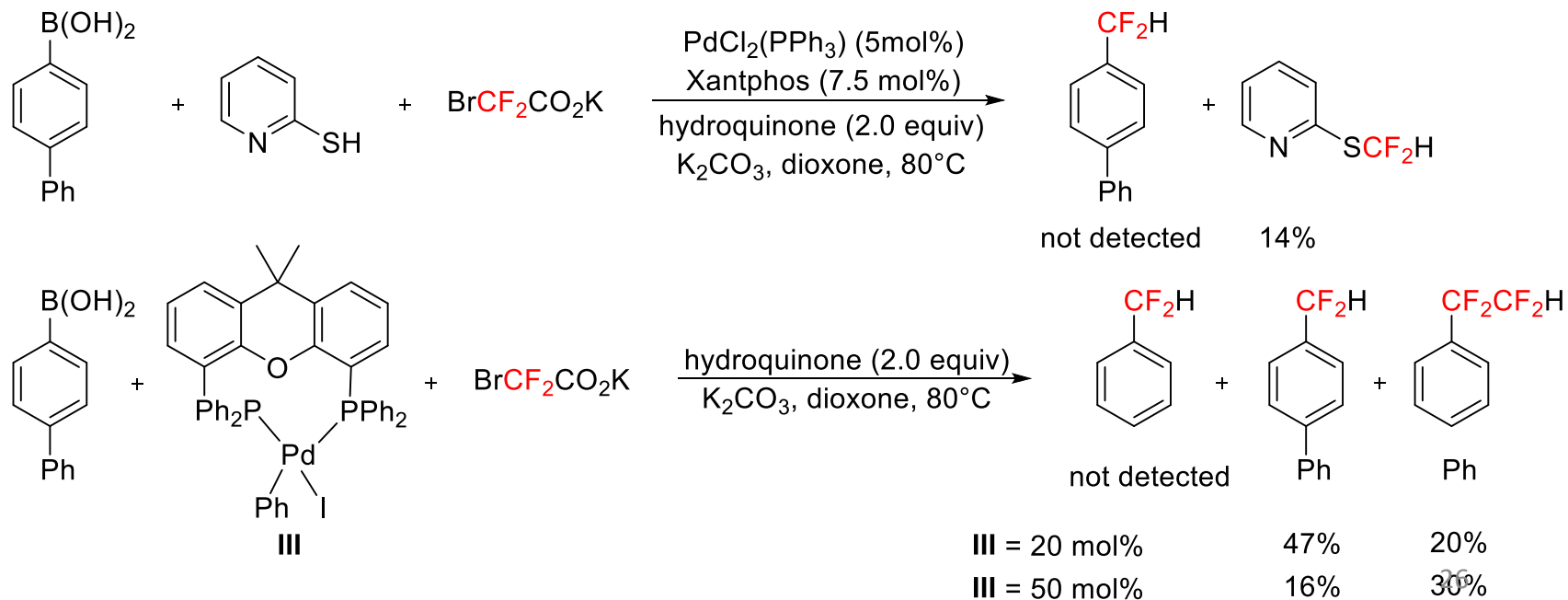
A: Palladium-Catalyzed Difluoromethylation of Arylboronic Acids with $\text{BrCF}_2\text{CO}_2\text{Et}$



Both electron-rich and electron-deficient arylboronic acids undergo the difluoromethylation smoothly

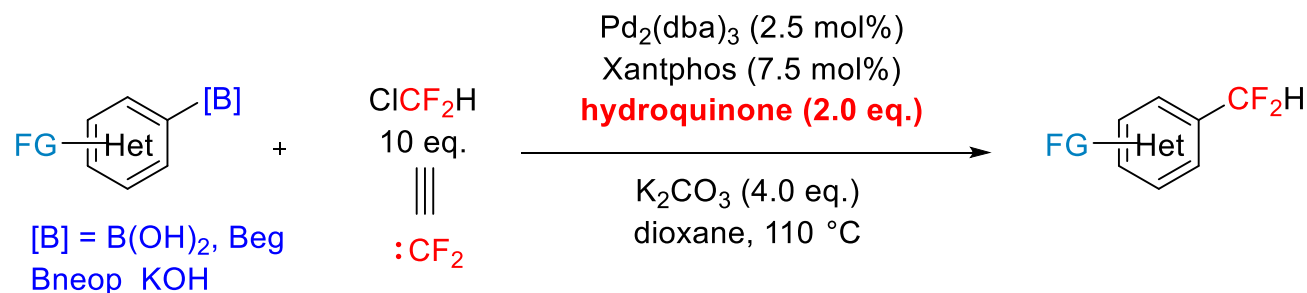
Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44–47.

Difluorocarbene Trapping Experiments



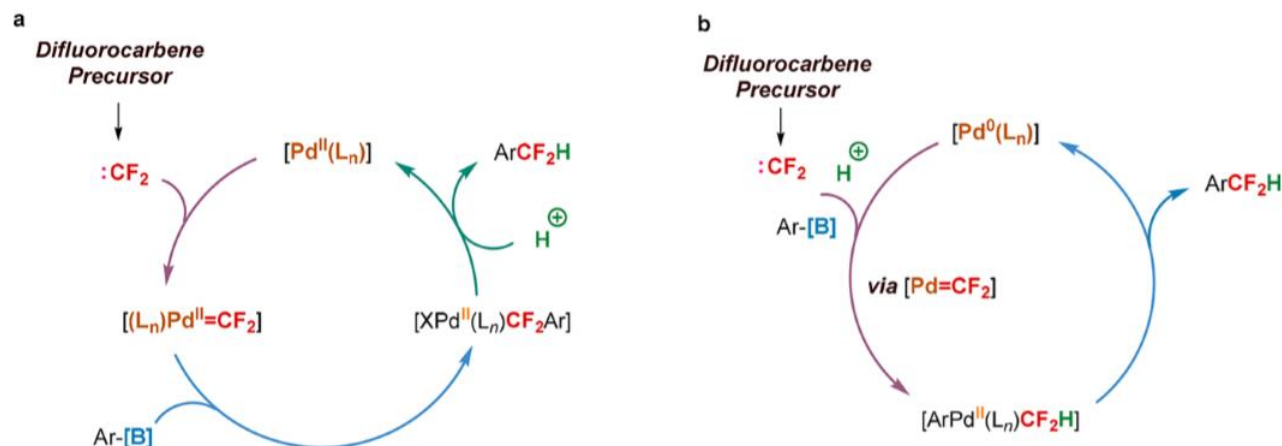
Catalytic difluoromethylation by metal-difluorocarbene coupling

B: Palladium-Catalyzed Difluoromethylation of Arylboronic Acids with ClCF_2H



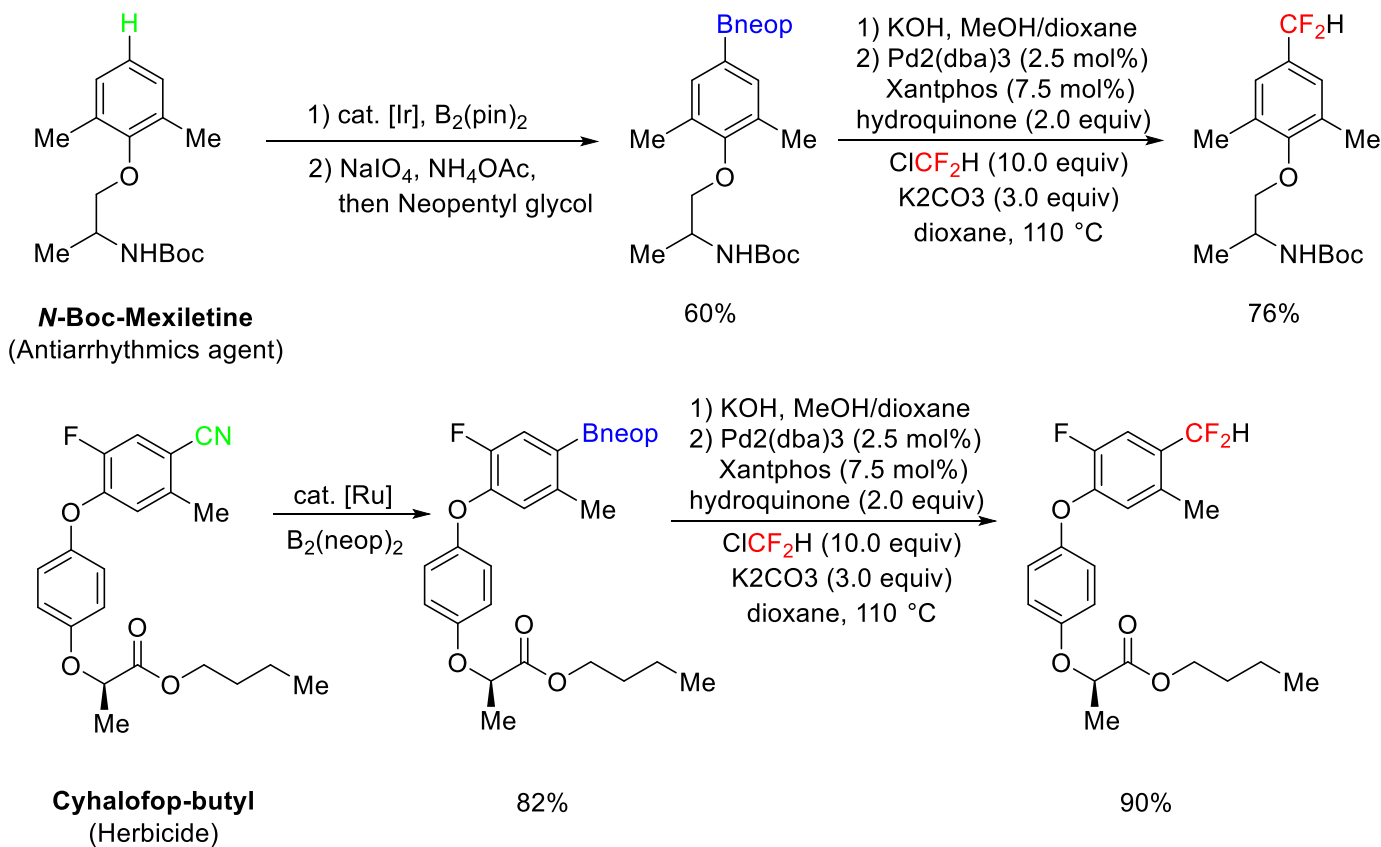
Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, 9, 918–923.

Proposed Mechanism of the Palladium-Catalyzed MeDiC Reaction



Catalytic difluoromethylation by metal-difluorocarbene coupling

C: Sequential C-H/C-CN Bond Borylation and Difluoromethylation



Feng, Z.; Zhang, X. *Acc. Chem. Res.* **2018**, 51, 2264–2278.

Allowed late-stage difluoromethylation, thus offering opportunities for discovering new medicinal agents

Outline

1. Introduction
2. Catalytic nucleophilic difluoroalkylation
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4. Catalytic radical difluoroalkylation
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- 6. Conclusion**

Conclusion

Four modes of catalytic difluoroalkylation

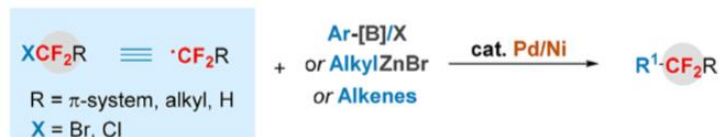
a. Nucleophilic Difluoroalkylation



b. Electrophilic Difluoroalkylation



c. Radical Difluoroalkylation



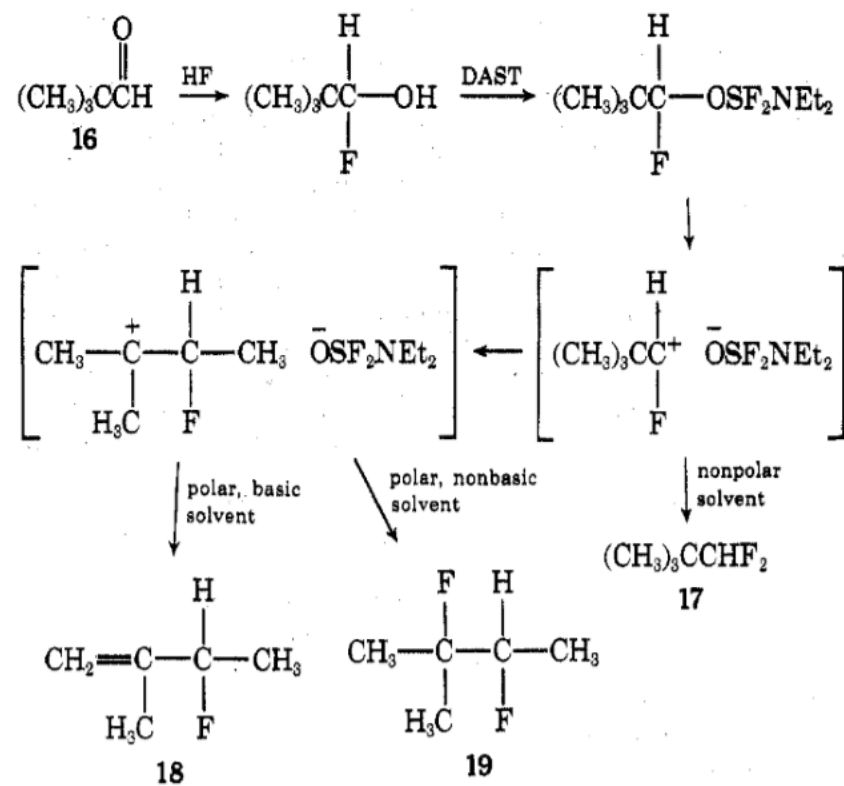
d. Difluoromethylation by Metal-Difluorocarbene Coupling (MeDiC)



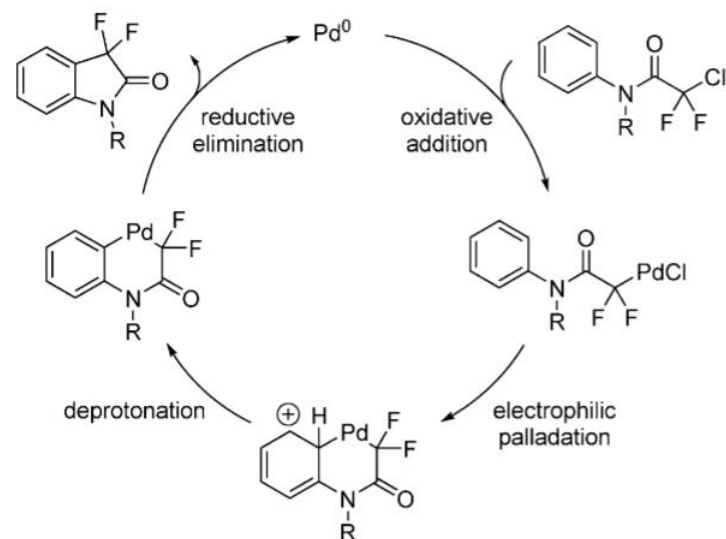
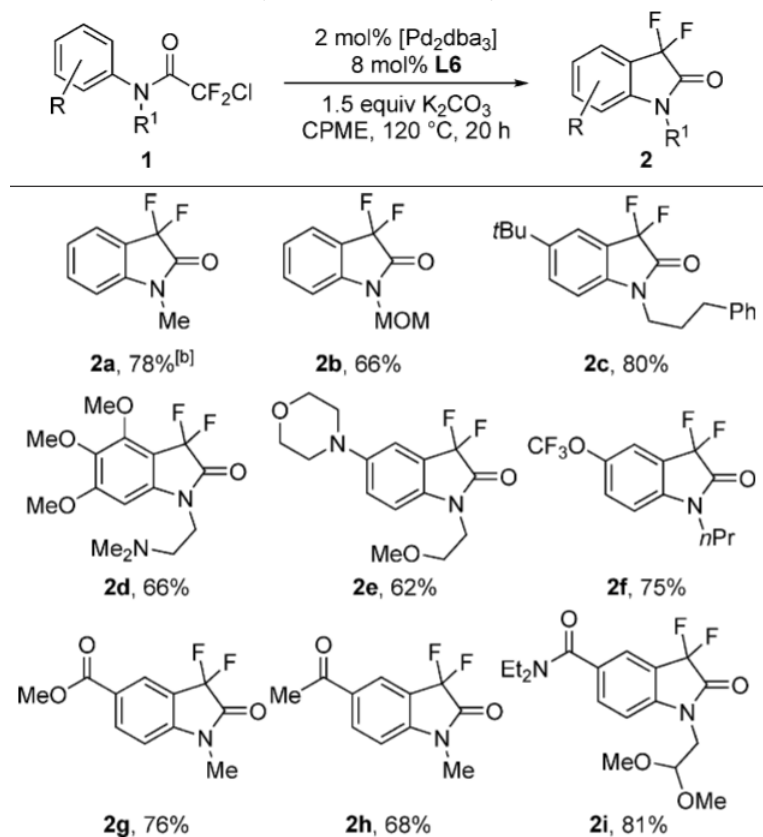
advantages over conventional methods: efficiency, functional group tolerance, structure diversity

The CF₂ group can be site-selectively introduced into organic molecules in a straightforward and highly efficient manner under mild conditions

Thank you



Intramolecular C-H difluoroalkylation from chlorodifluoroacetamides



Scheme 2. Proposed catalytic cycle (the ligand was omitted for clarity).