

Literature Report VI

Dinuclear Gold-Catalyzed *para*-Selective C-H Arylation of Undirected Arenes by Noncovalent Interactions

Reporter: Shan-Shan Xun

Checker: Han Wang

Date: 2023-11-20

Liu, D.-Y.; Xie, J*. *et al. Angew. Chem. Int. Ed.* **2023**, e202313122

CV of Prof. Xie Jin (谢劲)



Research Interest:

- ❑ Organic Synthetic Methodology
- ❑ Mechanistic Studies

Background:

- ❑ **2004-2008** B.S., Northeast Forestry University
- ❑ **2008-2013** Ph.D., Nanjing University
- ❑ **2013-2014** Research Associate, Nanjing University
- ❑ **2014-2017** Postdoc., Heidelberg University
- ❑ **2017-2019** Associate Professor, Nanjing University
- ❑ **2019-now** Professor, Nanjing University

Contents

1 Introduction

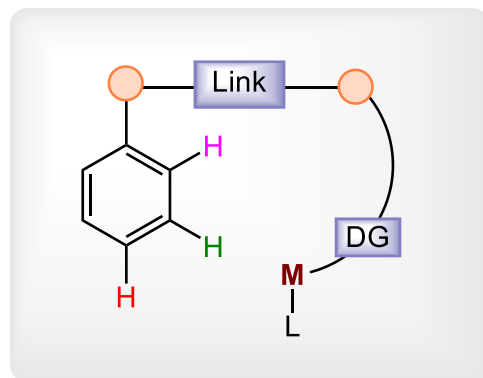
2 Dinuclear Gold-Catalyzed *para*-C-H Arylation of Fluoroarenes

3 Summary

Introduction

Strategies for Selective Aromatic C-H Bond Activation

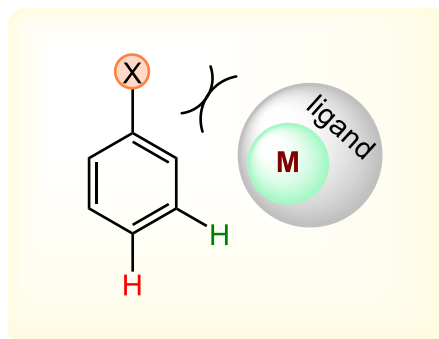
directing group



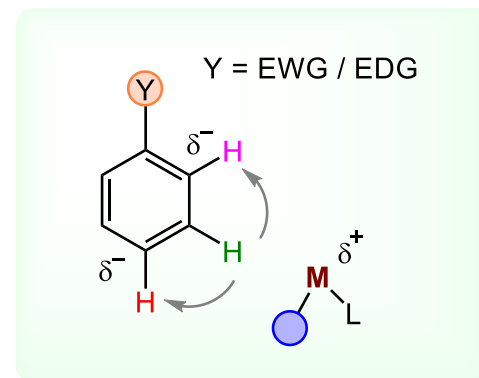
☹️ Require additional steps to install directing groups or sterically bulky groups

☹️ Compromising the reaction economy

steric hindrance

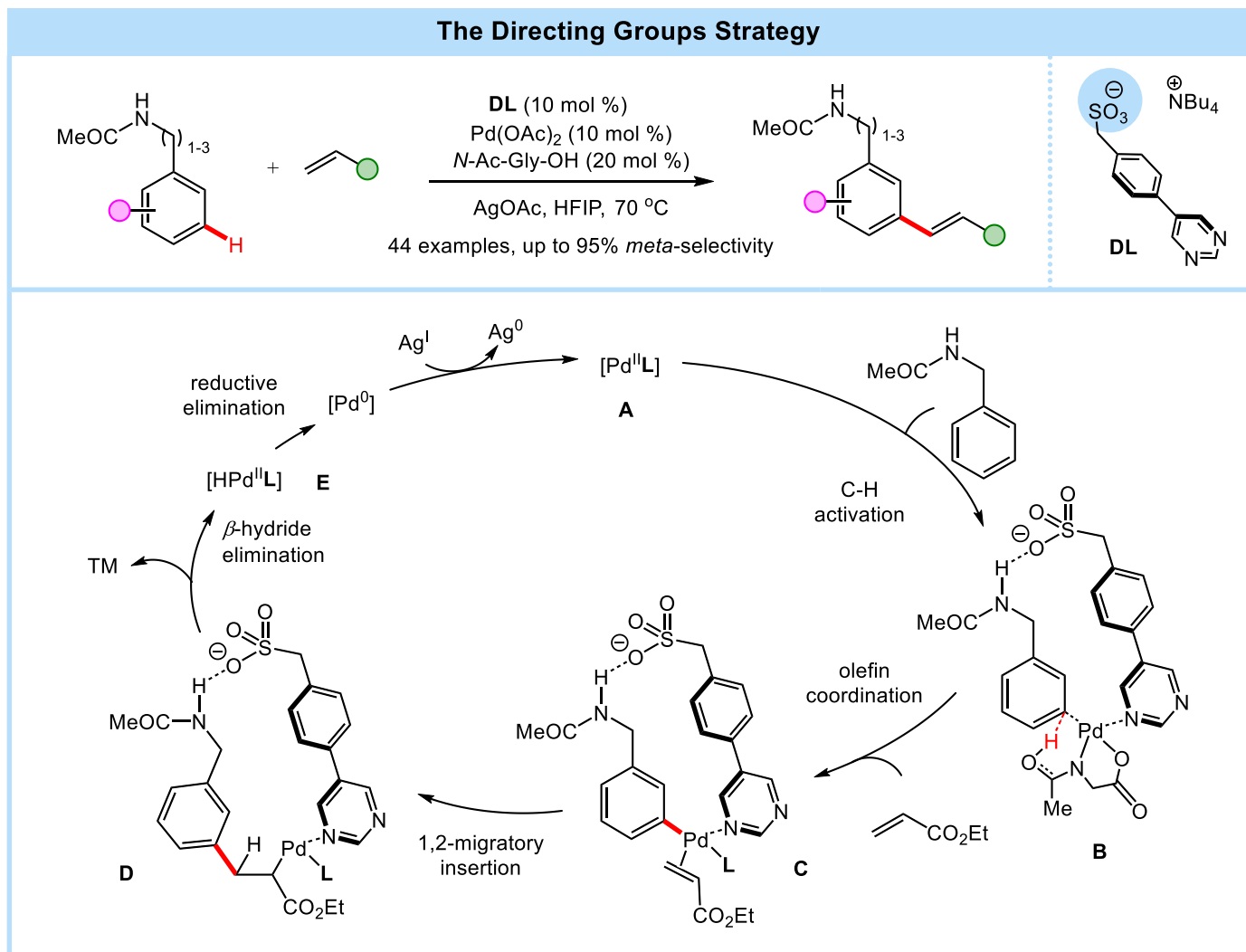


electronic effect



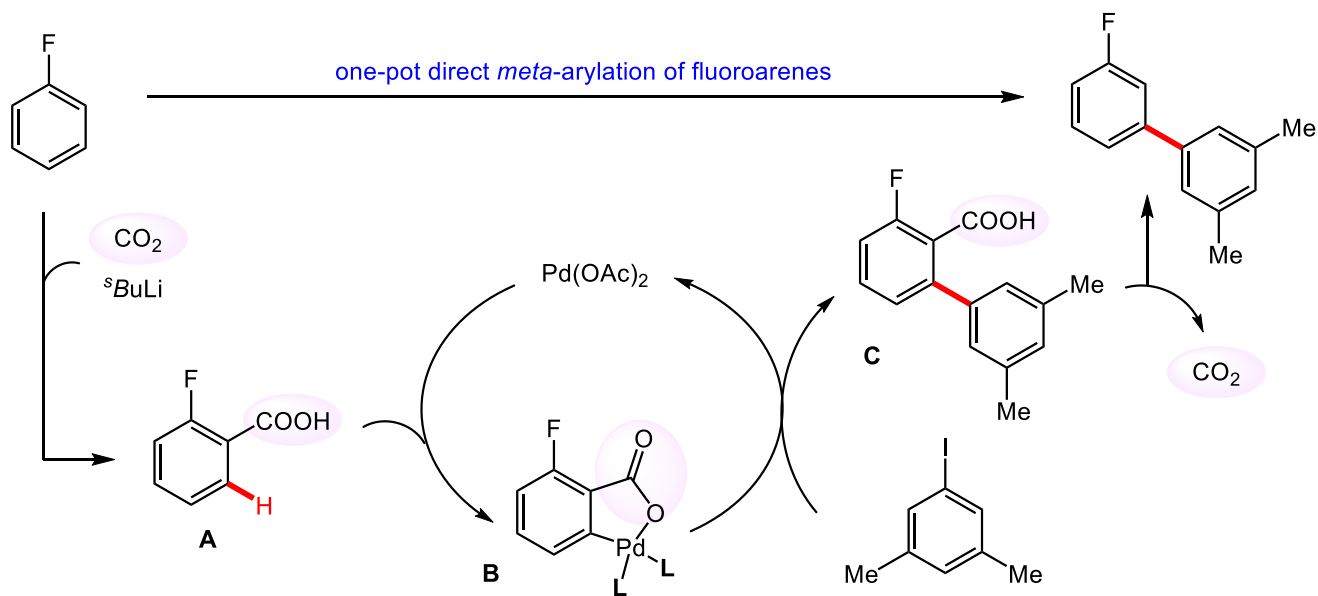
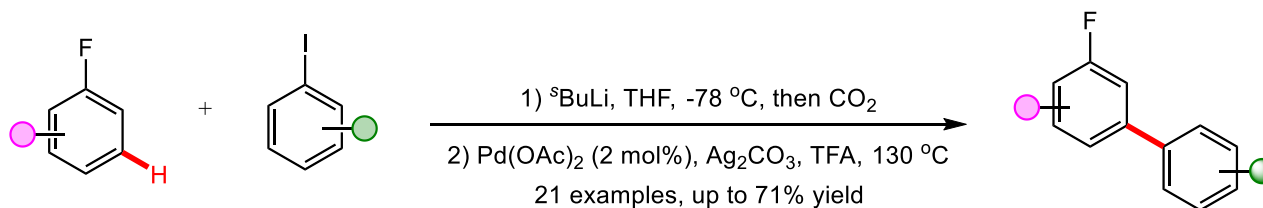
☹️ EWG / EDG substituent in most cases gives rise to poor *ortho*-, *meta*- and *para*-regioselectivity

Introduction



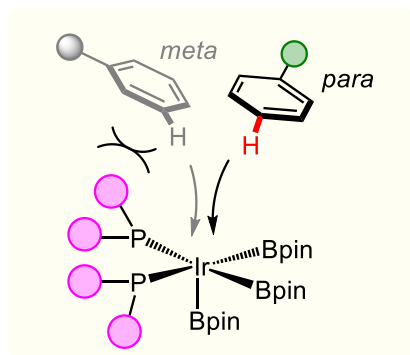
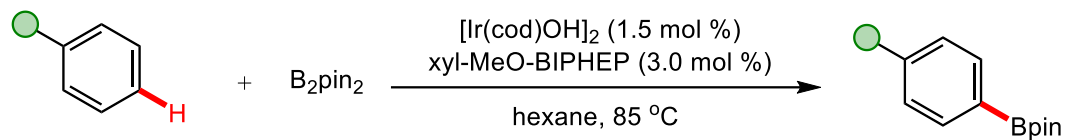
Introduction

The Transient Directing Groups Strategy



Introduction

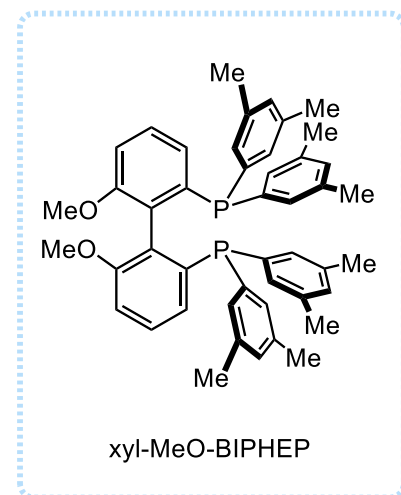
The Steric Hindrance Strategy



22 examples
up to 91% *para*-selectivity

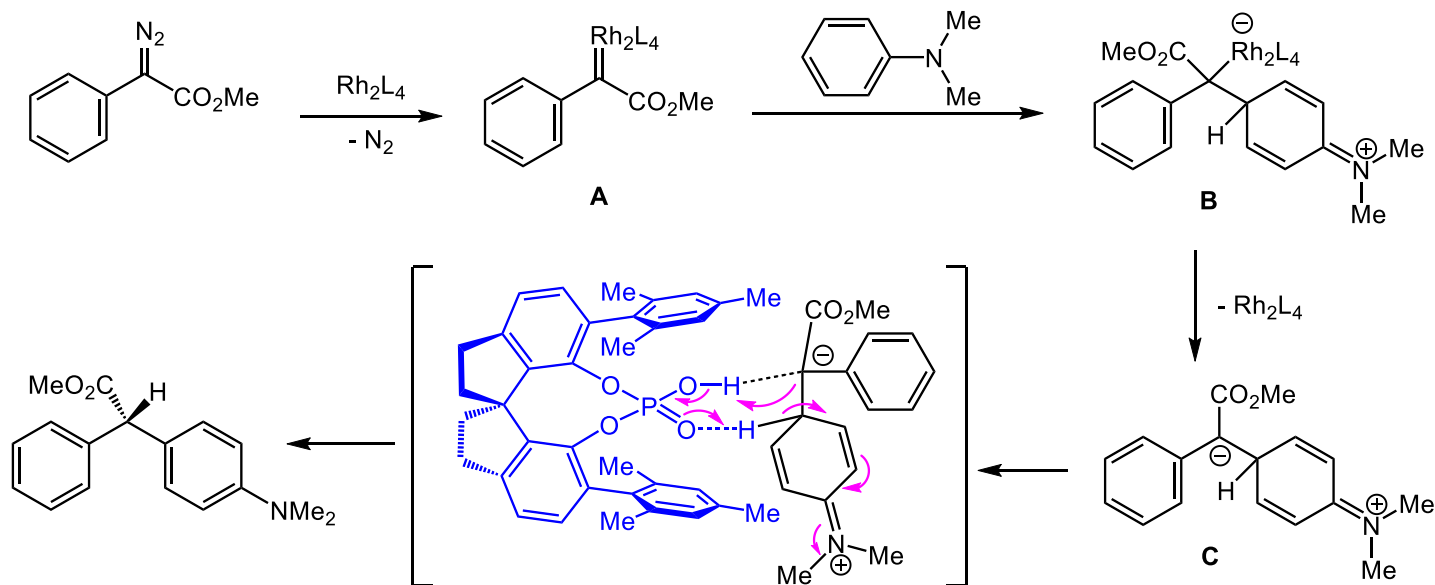
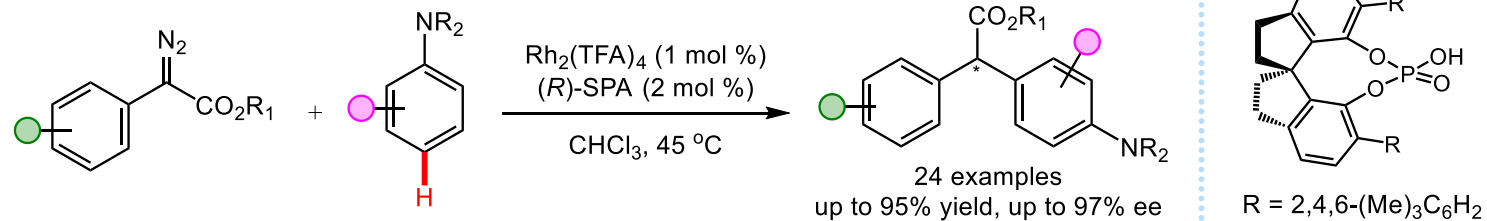
Bulky ligand blocking *meta* approach

Achieve *para*-selective C-H borylation



Introduction

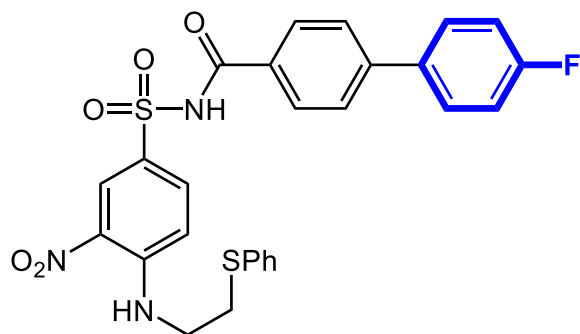
The Electronic Effect Strategy



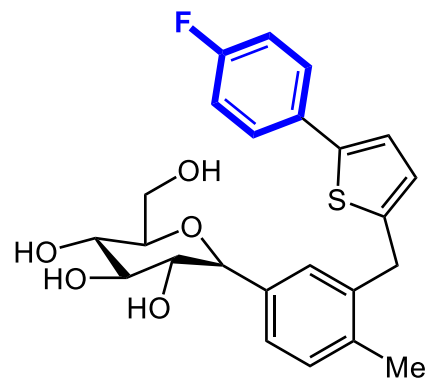
Xu, B.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700

Introduction

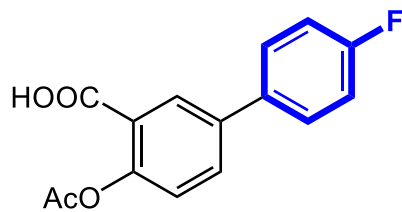
The prevalence of para-arylated fluorobenzene moiety in biologically important compounds



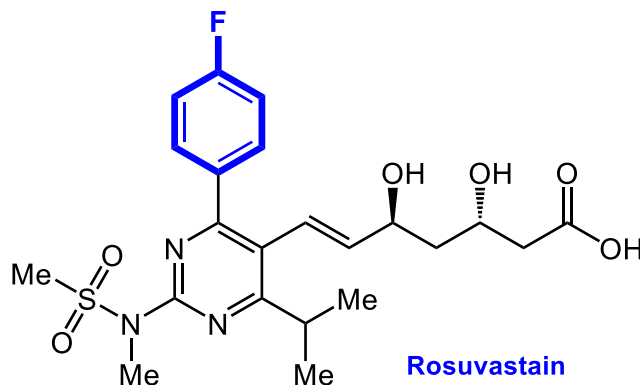
Potent inhibitor of the antiapoptotic protein Bcl-xL



Invokana

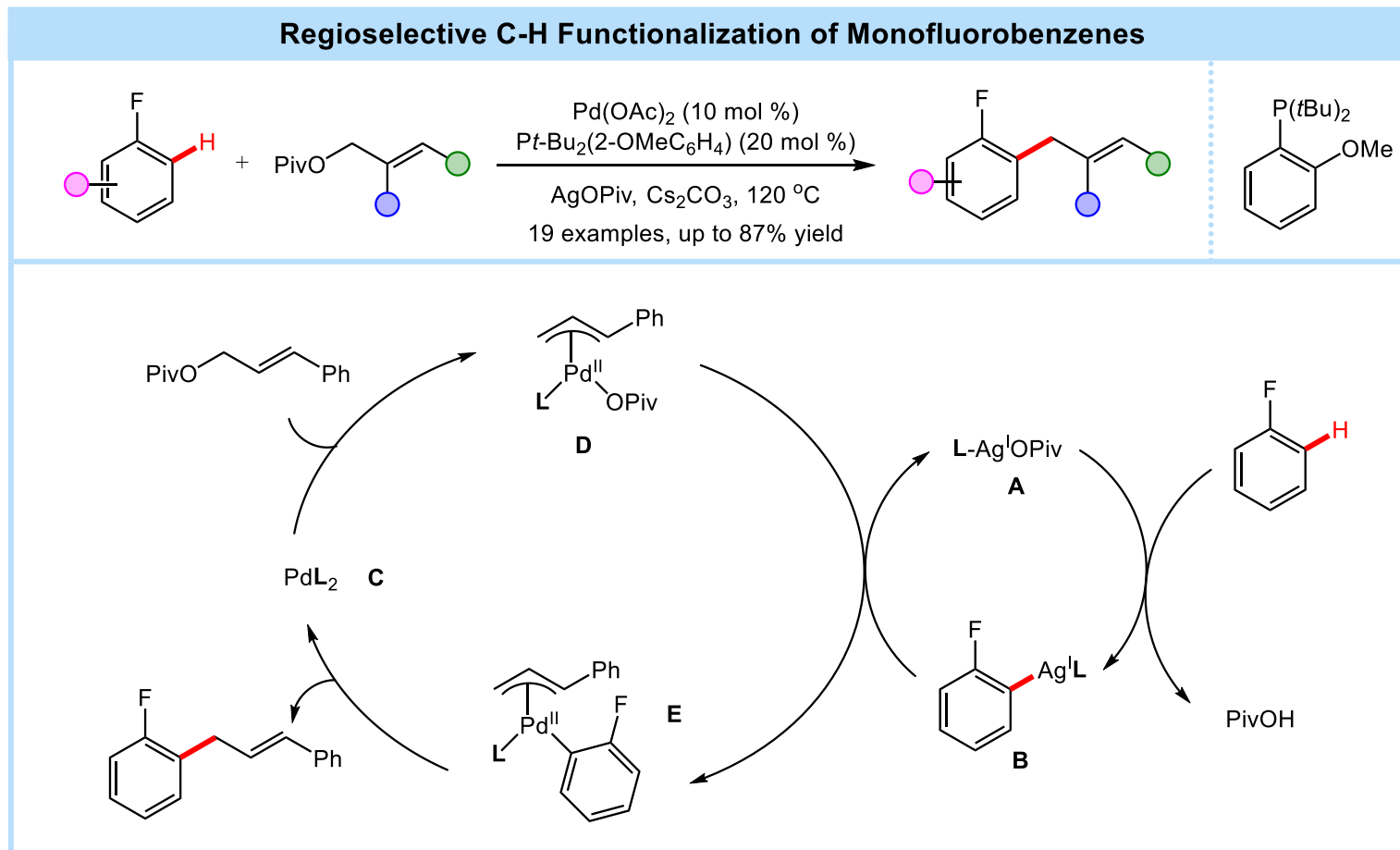


Flufenisal



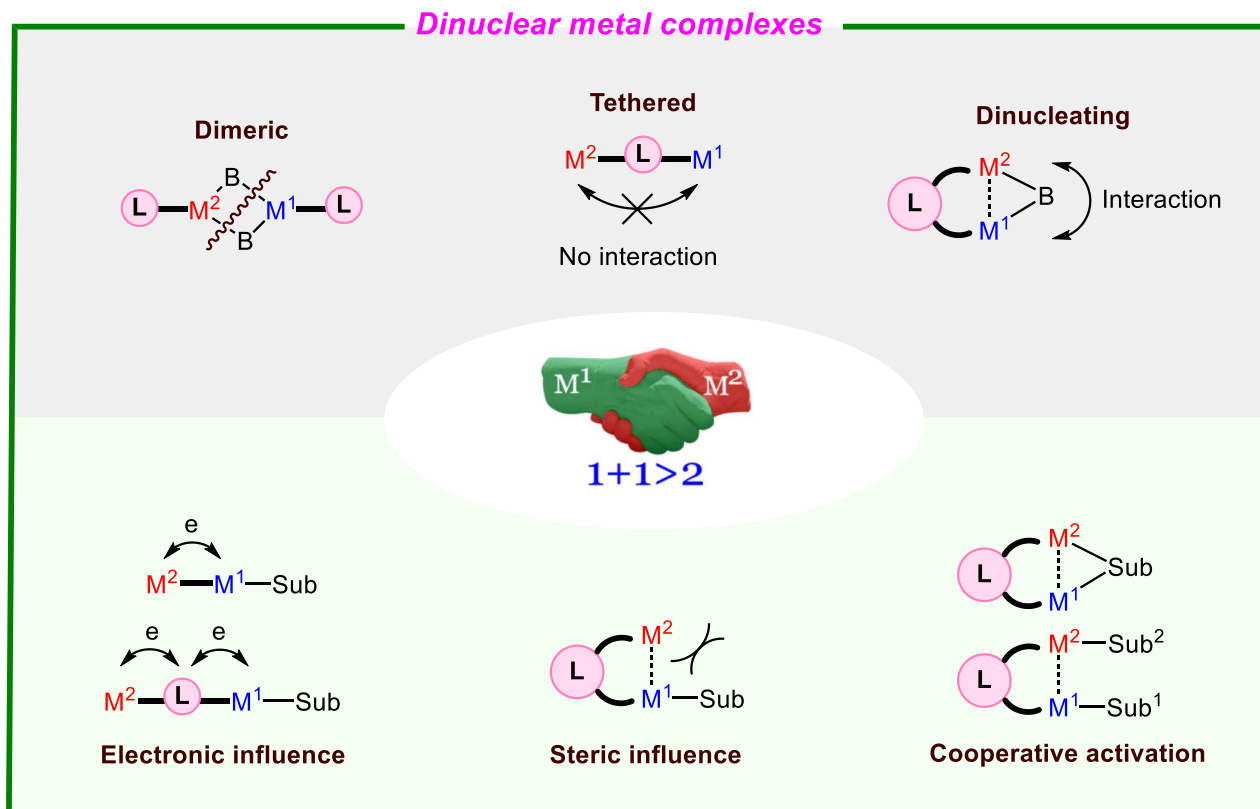
Rosuvastatin

Introduction



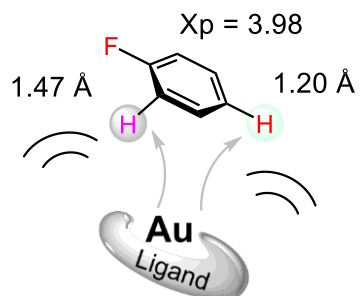
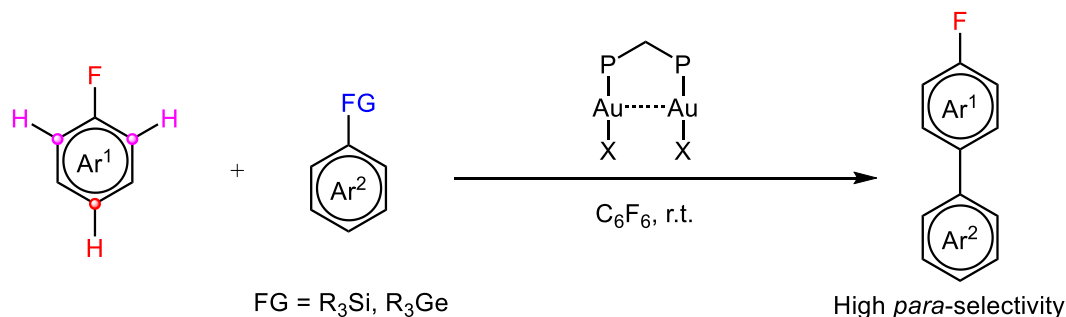
Lee, S. Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 15278

Introduction

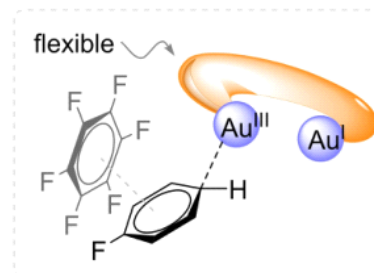


Introduction

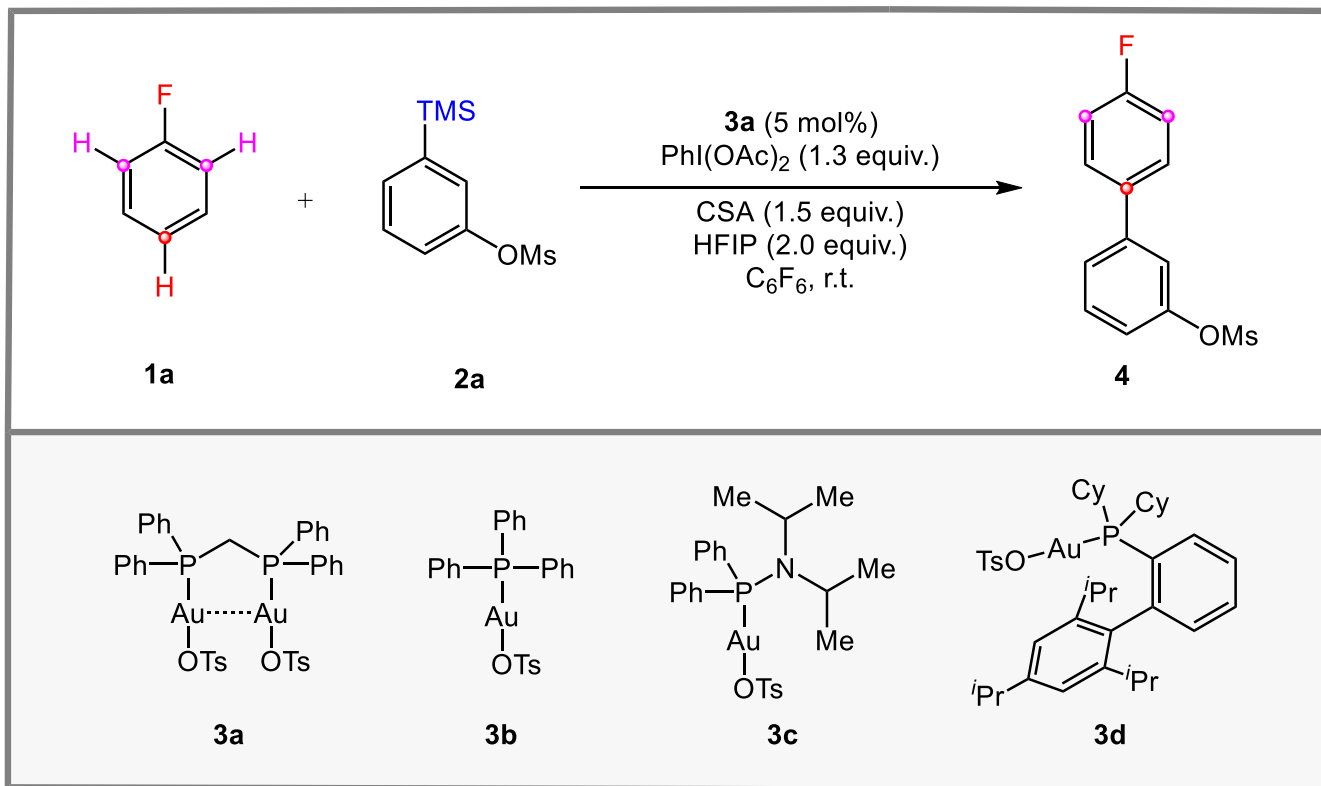
This Work: Dinuclear Gold-Catalyzed *para*-C-H Arylation of Fluoroarenes



- ♥ Small steric effect
- ♥ Strong electronegativity
- ♥ Low reactivity



Optimization of Arylation Reaction

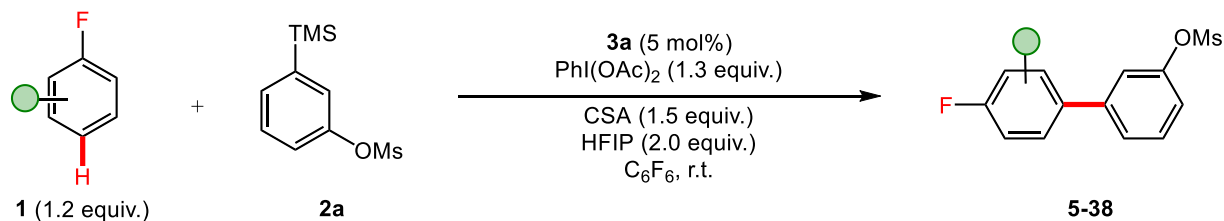


Optimization of Arylation Reaction

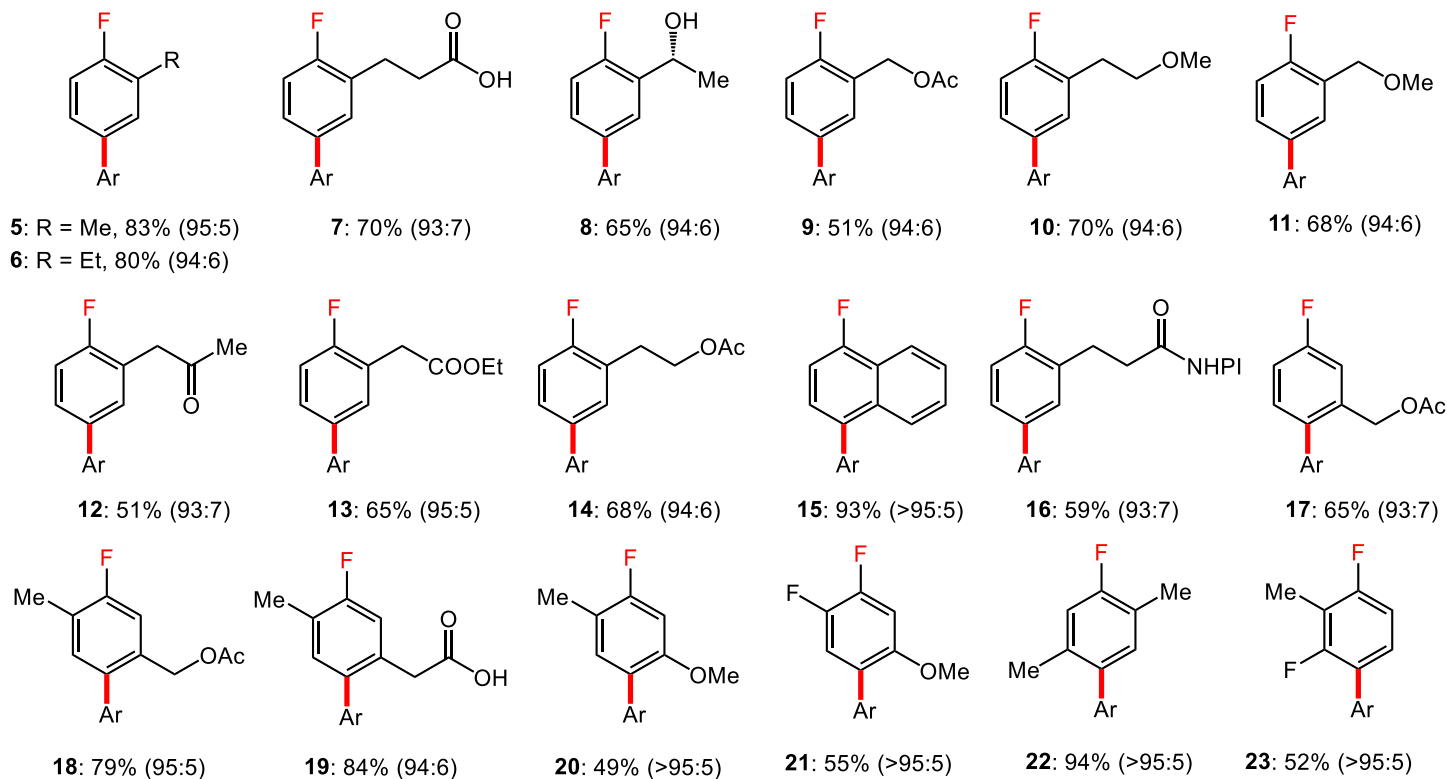
| Entry ^a | Variatuon (s) | Yield ^b | r.r. ^c |
|--------------------|--|--------------------|-------------------|
| 1 | None | 83% | 93 : 7 |
| 2 | DCE instead of C ₆ F ₆ | 88% | 80 : 20 |
| 3 | 3b instead of 3a | 76% | 87 : 13 |
| 4 | 3c instead of 3a | 68% | 86 : 14 |
| 5 | 3d instead of 3a | 67% | 87 : 13 |
| 6 | Without 3a | NR | ND |
| 7 | Without PhI(OAc) ₂ | NR | ND |
| 8 | Without CSA | NR | ND |
| 9 | Without HFIP | NR | ND |

^aReaction conditions: **3a** (5 mol%), **1a** (2 equiv.), **2a** (0.2 mmol, 1.0 equiv.), PhI(OAc)₂ (1.3 equiv.), CSA (1.5 equiv.), HFIP (2 equiv.), C₆F₆ (0.3 mL), rt, 12h. ^bisolated yield. ^cThe regioisomeric ratio (*para* vs. *ortho*) was determined by GC-MS prior to purification.

Substrate Scope

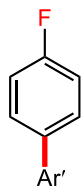


Fluoroaromatics Scope



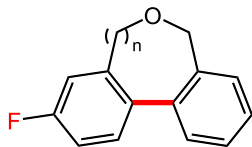
Substrate Scope

Fluoroaromatics Scope



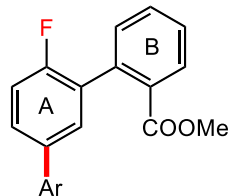
24: Ar' = 4-F-Ph, 72% (93:7)

25: Ar' = 4-Br-Ph, 75% (91:9)



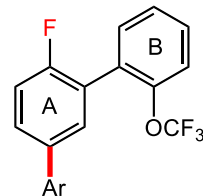
26: n = 0, 71% (>95:5)

27: n = 1, 53% (>95:5)



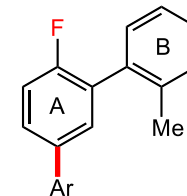
28: 45% (92:8)

R_A:R_B >95:5



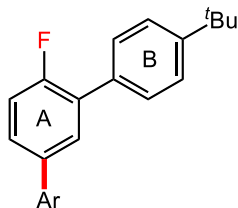
29: 44% (93:7)

R_A:R_B >95:5



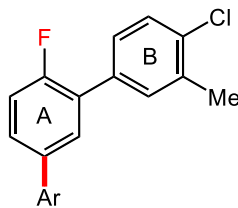
30: 75% (92:8)

R_A:R_B = 90:10



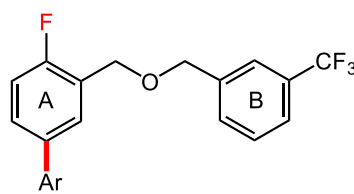
31: 44% (93:7)

R_A:R_B = 95:5



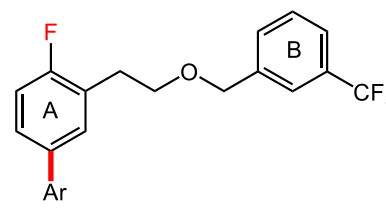
32: 67% (>95:5)

R_A:R_B = 92:8



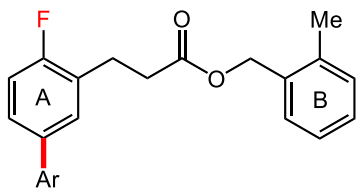
33: 50% (94:6)

R_A:R_B >95:5



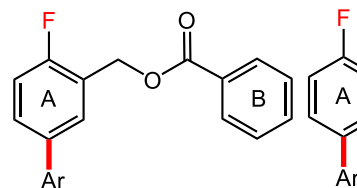
34: 69% (94:6)

R_A:R_B > 95:5



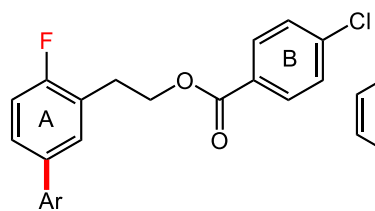
35: 62% (93:7)

R_A:R_B = 92:8



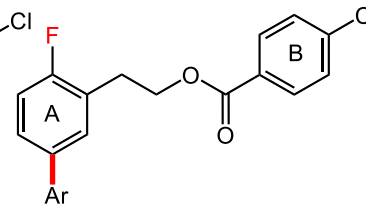
36: 43% (92:8)

R_A:R_B = 95:5



37: 56% (94:6)

R_A:R_B > 95:5

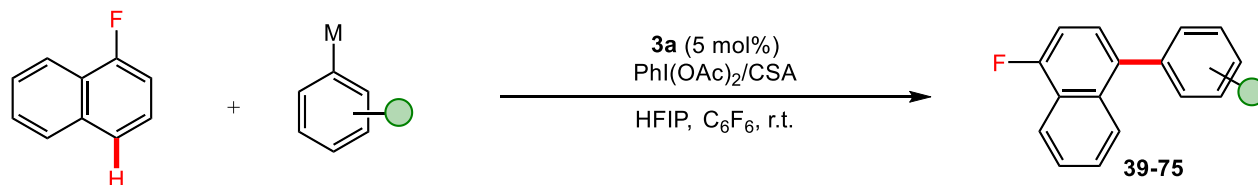


38: 53% (93:7)

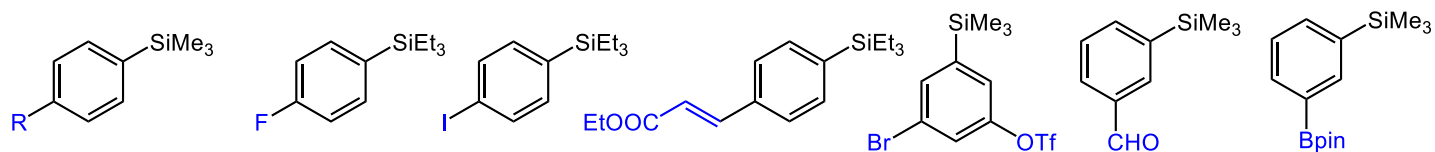
R_A:R_B > 95:5

Isolated yields are given and the regioisomeric ratio (r.r.) of *para*-site of fluorine atoms versus other sites (e.g., *ortho*-site of fluorine atoms and *ortho*, *para*-site of other substituent) is given in parentheses. The regioisomeric ratio between two arenes is given as R_A:R_B.

Substrate Scope



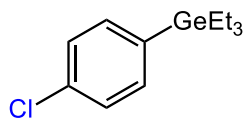
Arylsilanes Scope



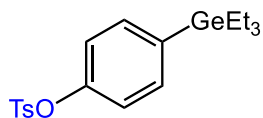
- 2b:** R = H, 62% (98:2) **2d':** 61% (97:3) **2e':** 48% (97:3) **2n:** 71% (>95:5) **2o:** 58% (>95:5) **2p:** 57% (95:5) **2q:** 42% (>95:5)
- 2c:** R = Br, 81% (98:2) **2d:** R = F, 75% (97:3) **2e:** R = I, 65% (98:2) **2f:** R = OTf, 70% (98:2) **2g:** R = CF₃, 83% (97:3)
- 2h:** R = COOMe, 92% (97:3) CO-C6H4-SiMe3 Br-C6H4-SiMe3 CO2Me-C6H4-SiMe3 OTf-C6H3(SiMe3) Ac-C4H2S-TMS MeO2C-C4H2O-TMS
- 2i:** R = Ph, 56% (>95:5) **2j:** R = Bneop, 70% (>95:5) **2k:** R = NO₂, 49% (>95:5) **2l:** R = Ac, 71% (95:5) **2m:** R = CPh, 85% (>95:5) **2r:** 74% (>95:5) **2s:** 88% (97:3) **2t:** 74% (>95:5) **2u:** 40% (90:10) **2v:** 48% (95:5) **2w:** 61% (91:9)

Substrate Scope

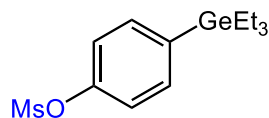
Arylgermanes Scope



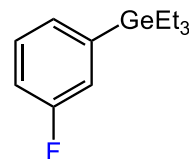
2aa: 74% (98:2)



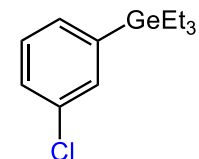
2bb: 91% (>95:5)



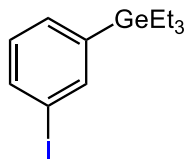
2cc: 93% (>95:5)



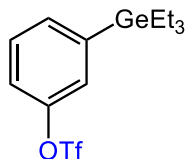
2dd: 79% (97:3)



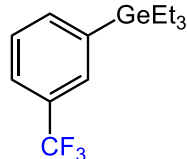
2ee: 92% (97:3)



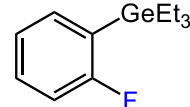
2ff: 89% (>95:5)



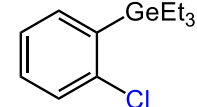
2gg: 92% (>95:5)



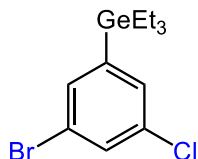
2hh: 88% (>95:5)



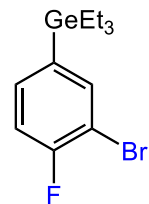
2ii: 33% (91:9)



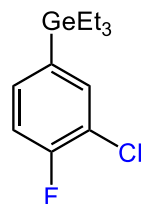
2jj: 37% (89:11)



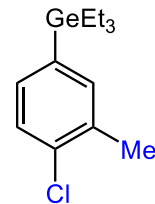
2kk: 85% (98:2)



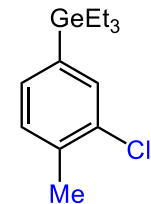
2ll: 89% (98:2)



2mm: 94% (98:2)

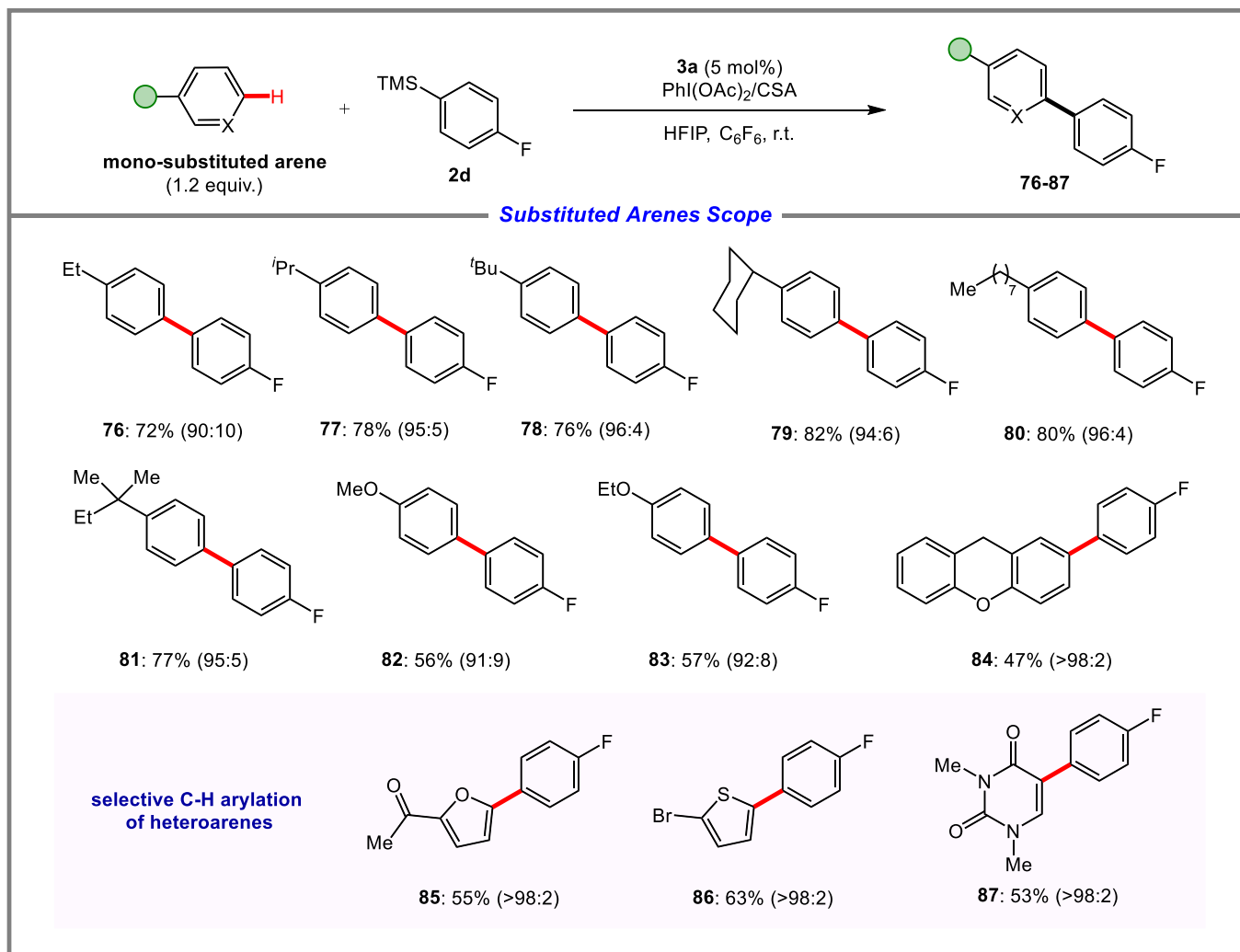


2oo: 85% (93:7)



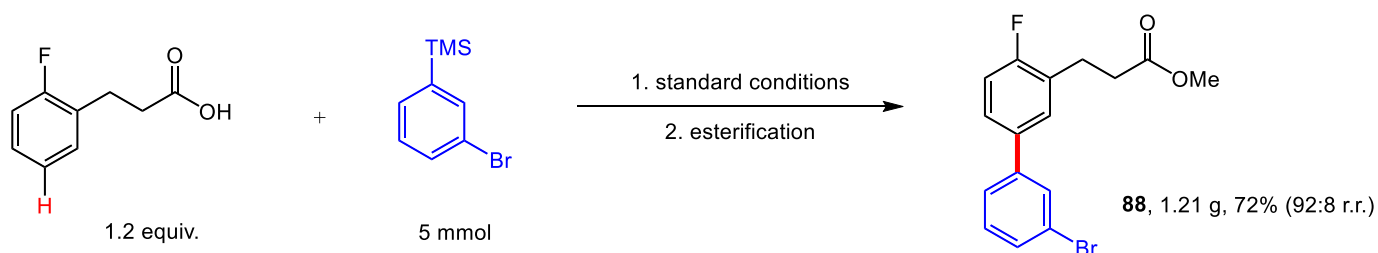
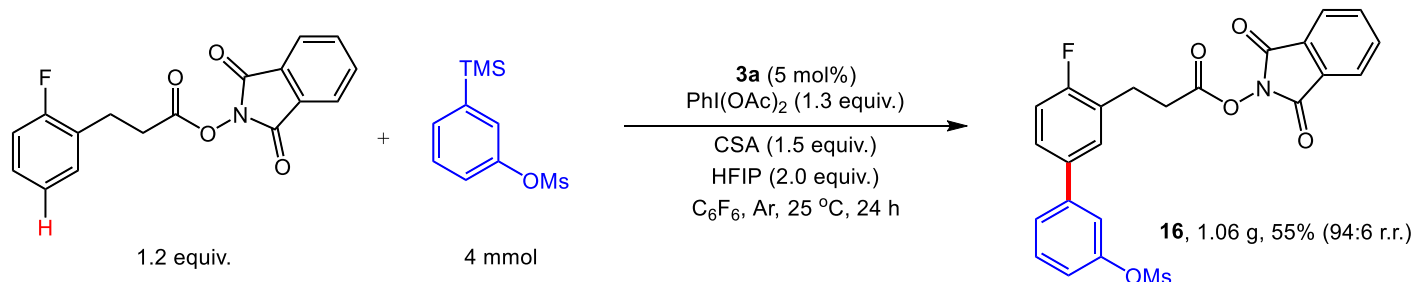
2pp: 67% (96:4)

Substrate Scope

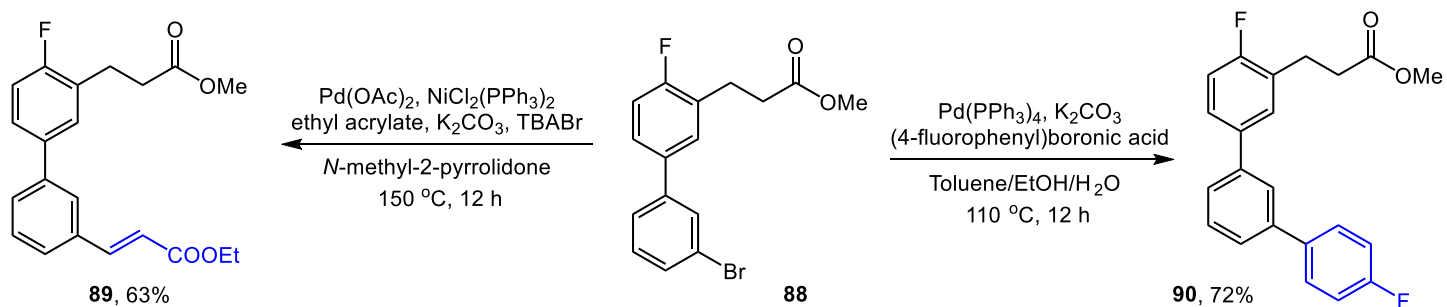


Scale-up Reactions and Synthetic Application

Scale-up Reactions

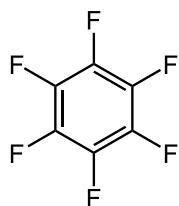


Synthetic Application



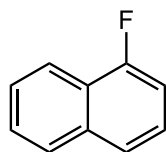
Experimental Mechanistic Studies

1-Fluoronaphthalene-C₆F₆ Complex with New m.p.

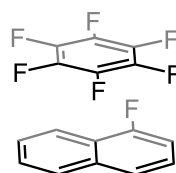


m.p. 4 °C

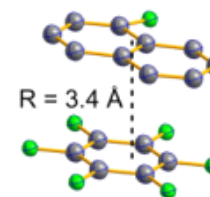
+



m.p. -13 °C

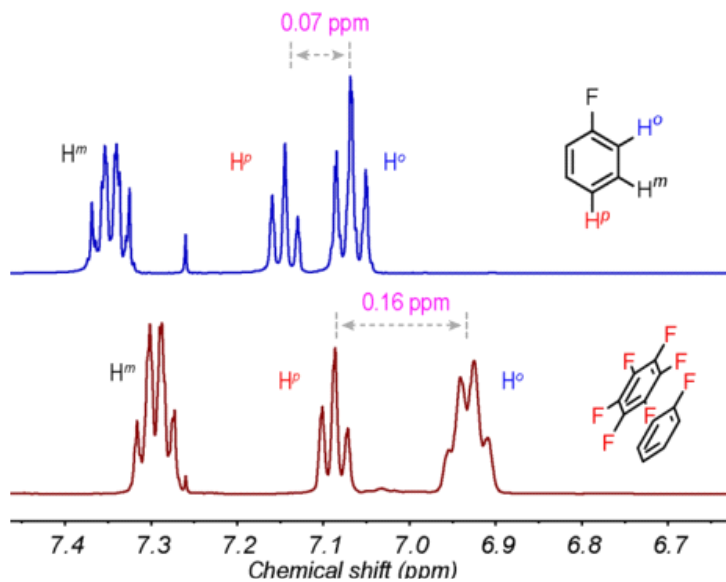


m.p. 49.1-50.5 °C

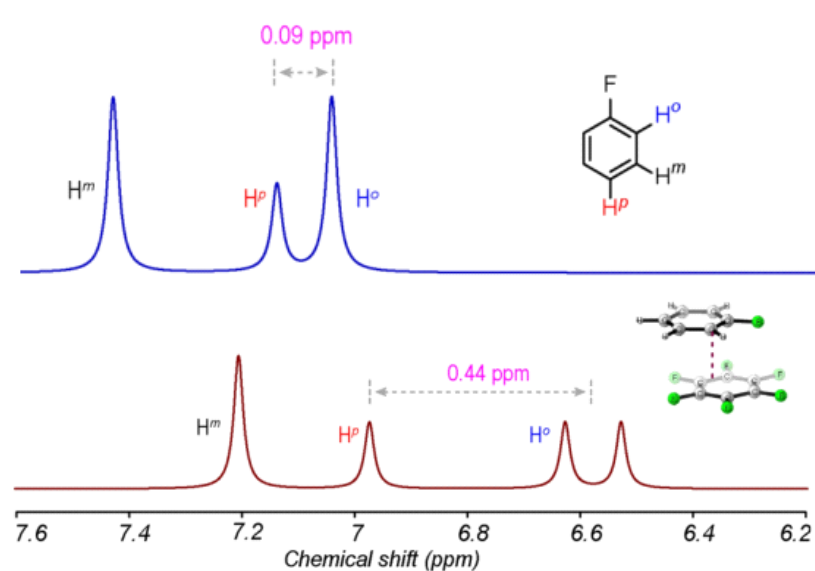


X-ray structure

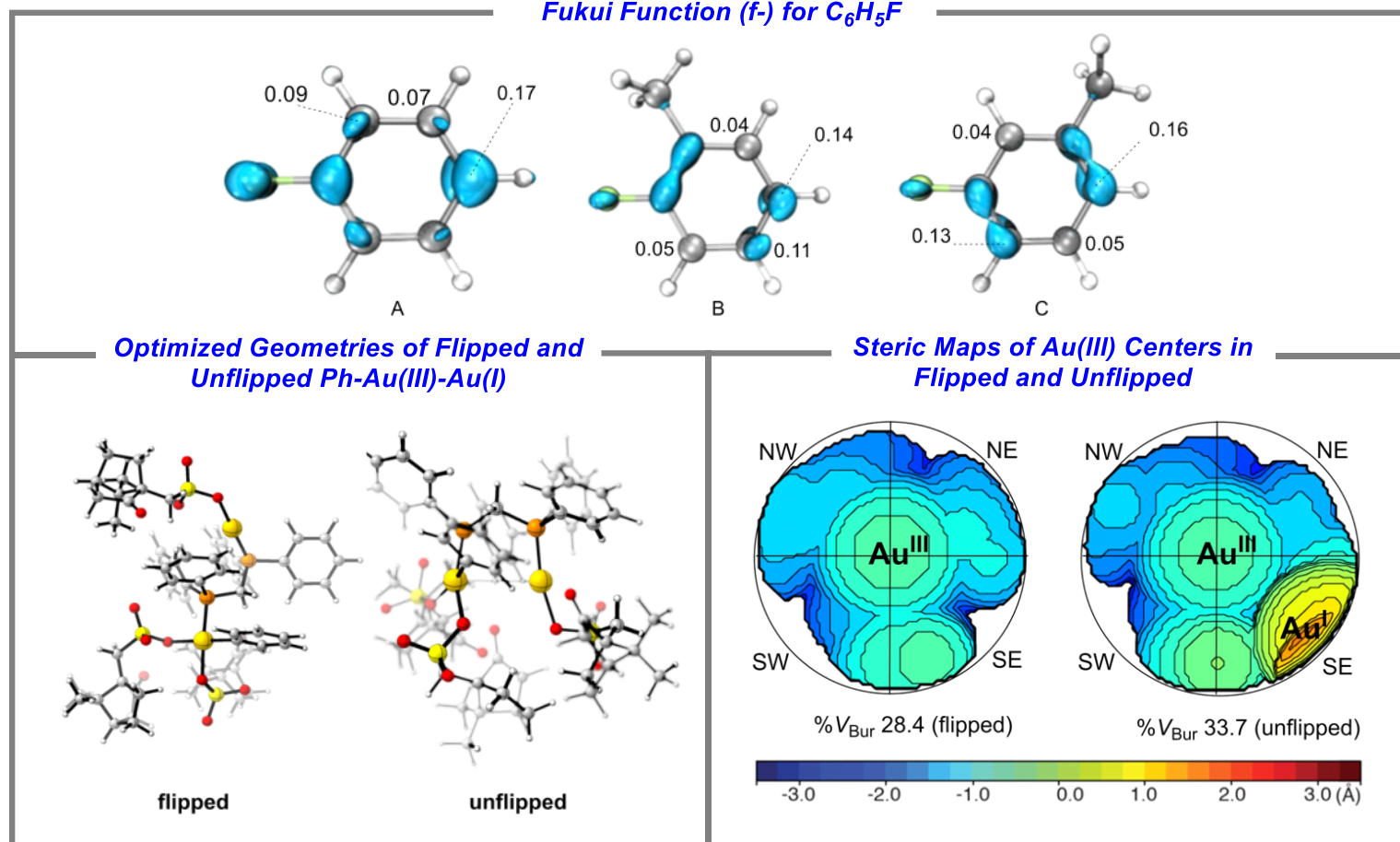
¹H NMR Spectra of PhF-C₆F₆ Mixture



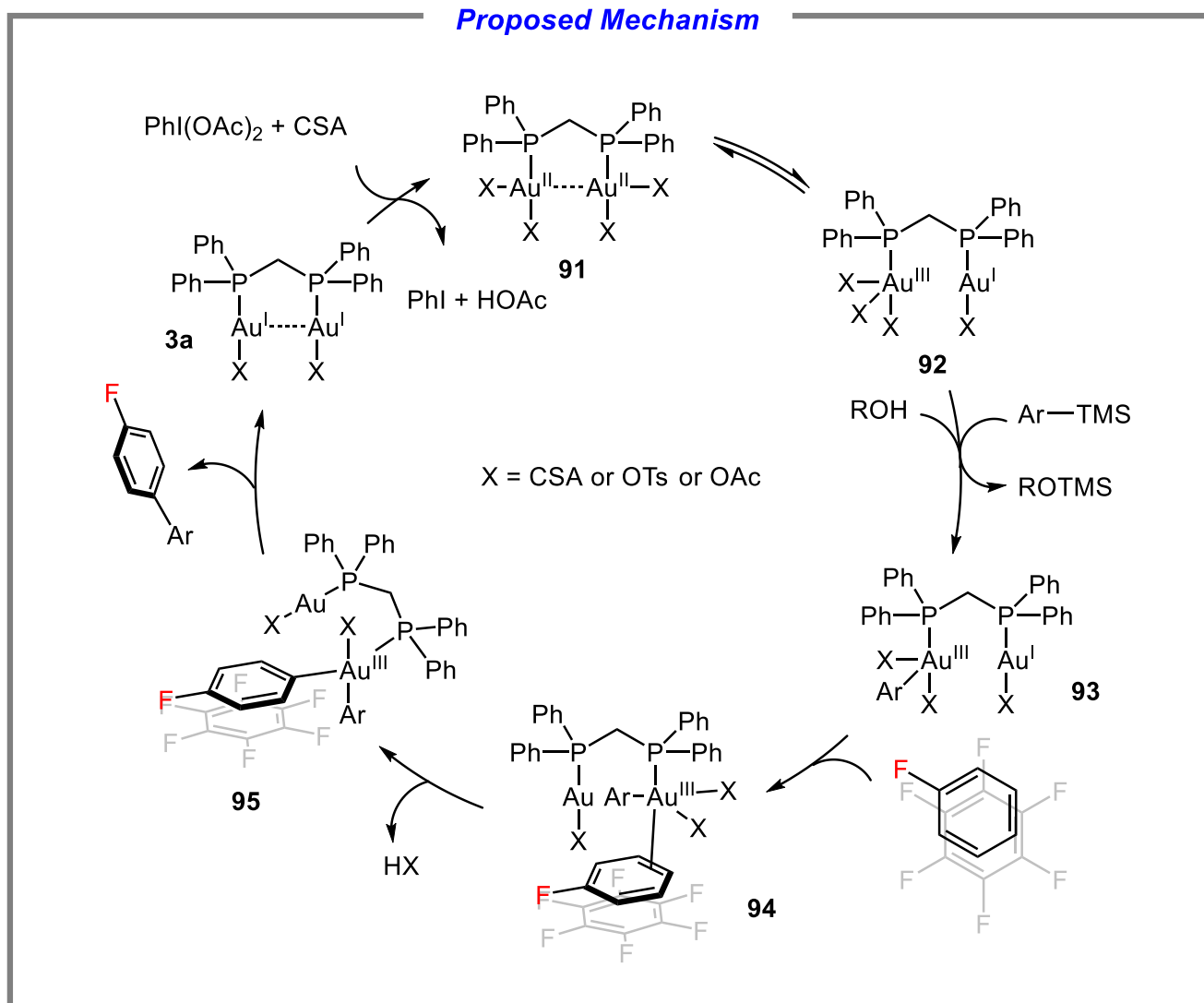
Simulation of the ¹H NMR of PhF-C₆F₆ Complex



Experimental Mechanistic Studies

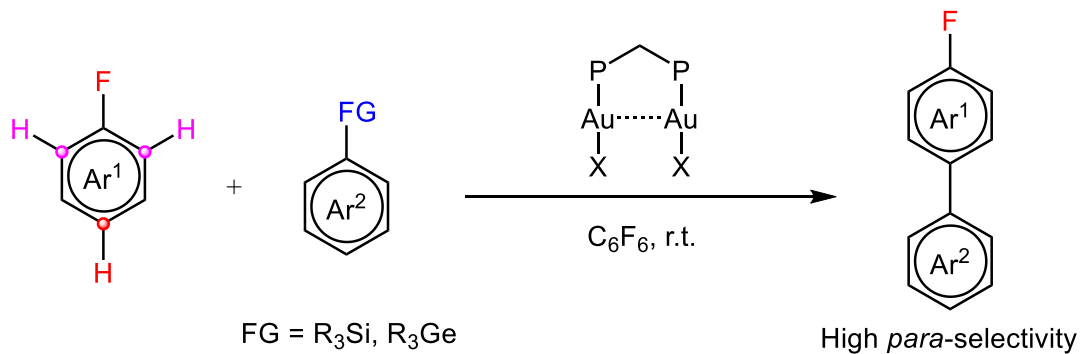


Proposed Mechanism



Summary

Dinuclear Gold-Catalyzed *para*-C-H Arylation of Fluoroarenes



😊 87 Examples, broad substrate scope
😊 Good regioselectivity

😊 Solid mechanistic study
😊 Important to develop di and poly-nuclear transition metal catalysis

Writing Strategy

□ The First Paragraph

Importance of direct activation of C-H bonds



Limitations of current strategies



Challenge

- ✓ **Direct activation of C-H bonds** in aromatic hydrocarbons can result in a powerful C-C bond formation strategy, thus endowing arenes with diversification possibilities for new functions.
- ✓ Although strategies based on directing groups and steric hindrance have been successful, they require additional steps to install directing groups or sterically bulky groups into arene skeletons before C-H activation, thus **compromising the reaction economy**.
- ✓ However, achieving *para*-C-H selective arylation of monofluoroarenes remains **highly challenging** because fluorine atom has a small van der Waals radius (1.47 Å) and high electronegativity (~3.98).

Writing Strategy

□ The Last Paragraph

Summary
of this work



Advantages of
the current method



Outlook
of this work

- ✓ In summary, we have developed a **robust gold-catalyzed *para*-C-H selective arylation strategy** of undirected monofluoroarenes with bench-stable aryl silanes and germanes.
- ✓ Features of this protocol include **broad substrate scope, excellent functional group compatibility, and simple operation under room temperature** ... also competent coupling partners for gold-catalyzed selective arylation.
- ✓ Its success would stimulate more attention to develop di- and poly-nuclear transition metal catalysis to address **the challenging selectivity issues in organic chemistry**.

Representative Examples

In general, the introduction of deactivating groups and weakly activating groups on the aryl rings hardly influence the regioselectivity, and the *para*-C-H site on monofluoroaryl moiety is still the **predominant** reaction site. (主要的)

To our delight, when methanol was used to replace HFIP, this side reaction can be **suppressed** and the desired *para*-arylation products were successfully obtained with high selectivity. (抑制)

This implies a possible noncovalent interaction between 1-fluoronaphthalene and C₆F₆, which **substantially** raises the melting point to 49.1-50.5 °C. (相当多地)

***Thanks
for your attention***
