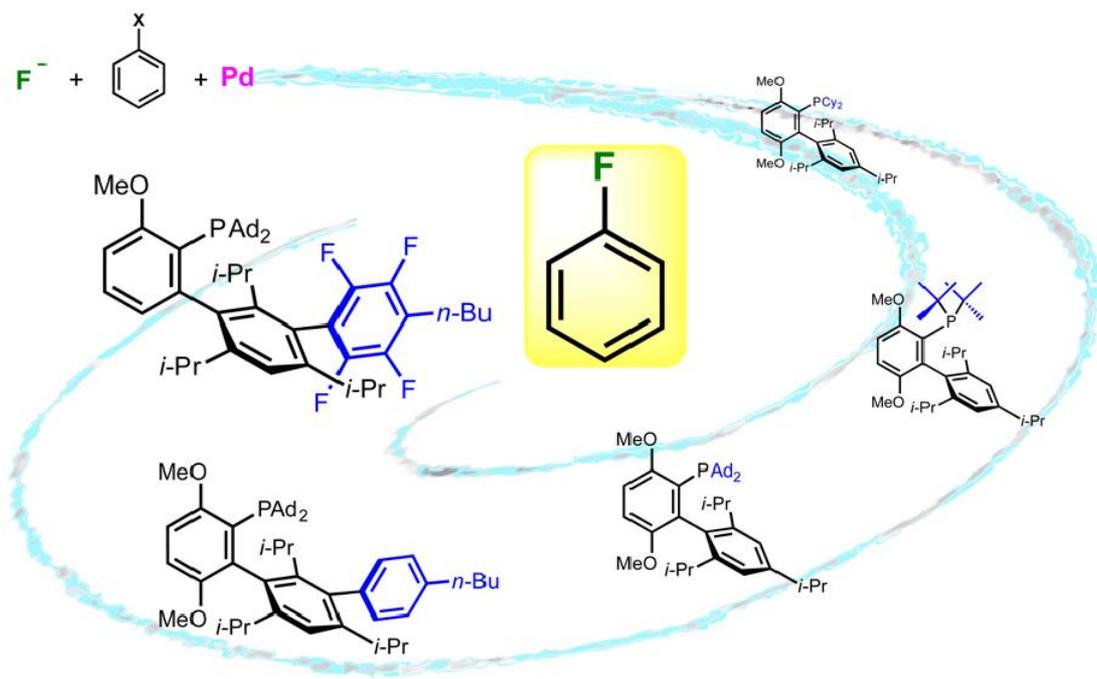


The Evolution of Pd⁰/Pd^{II}-Catalyzed Aromatic Fluorination

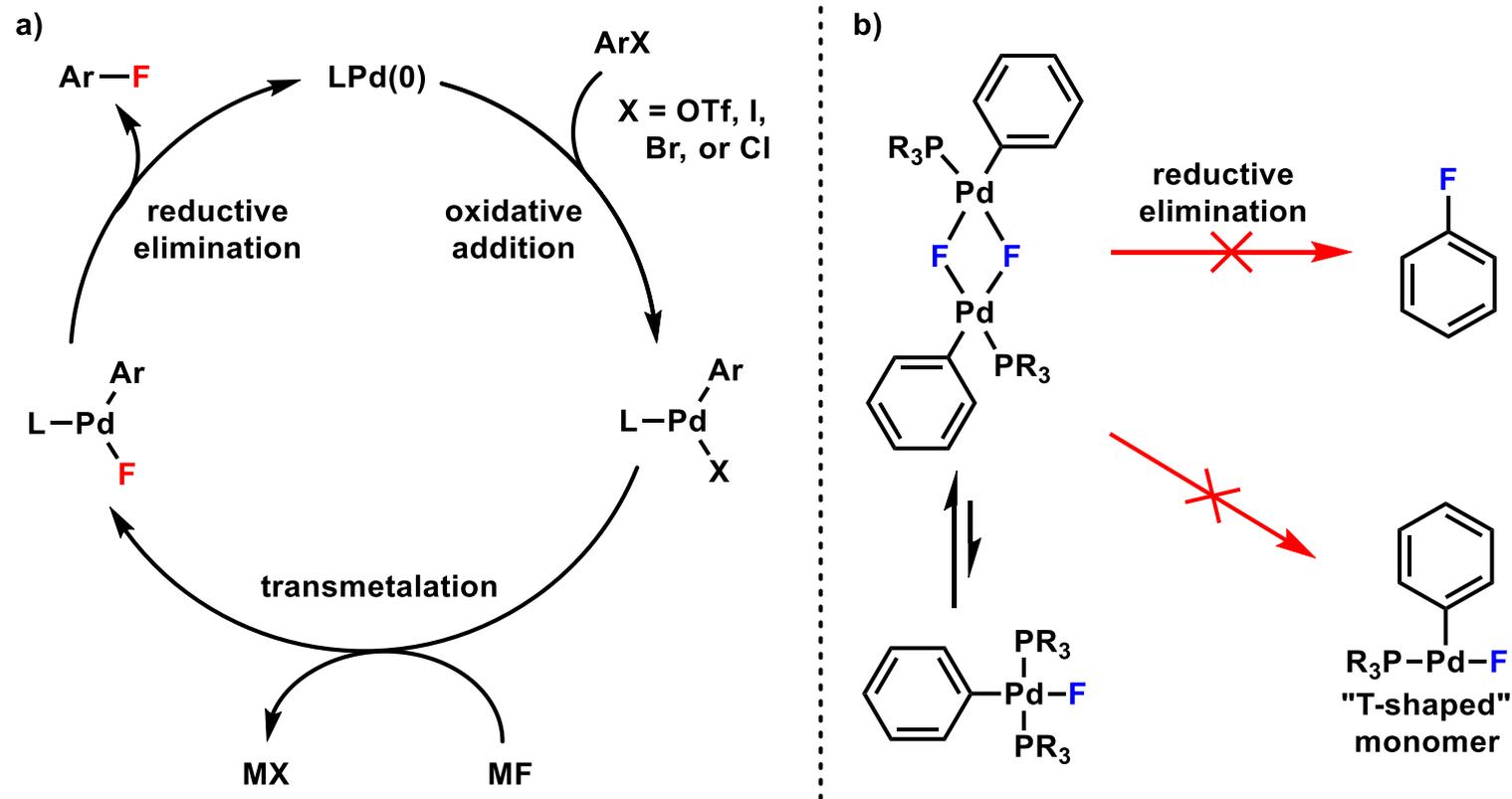


Reporter: Song Feifei
Supervisor: Prof. Yong Huang
2016.10.31

Outline

- **Introduction**
- Pd-catalyzed fluorination: discovery
- In situ catalyst modification
- Formation of regioisomeric aryl fluorides
- Pd-catalyzed fluorination: developments
- Conclusions and future perspectives
- Acknowledgment

Introduction

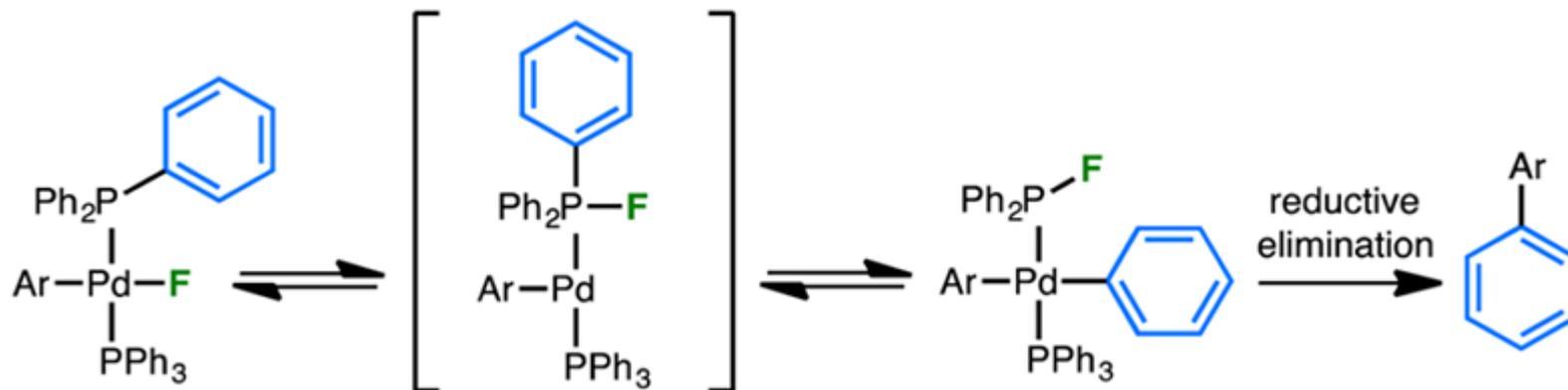


a) Proposed Pd⁰/Pd^{II} catalytic cycle for aryl fluorination.

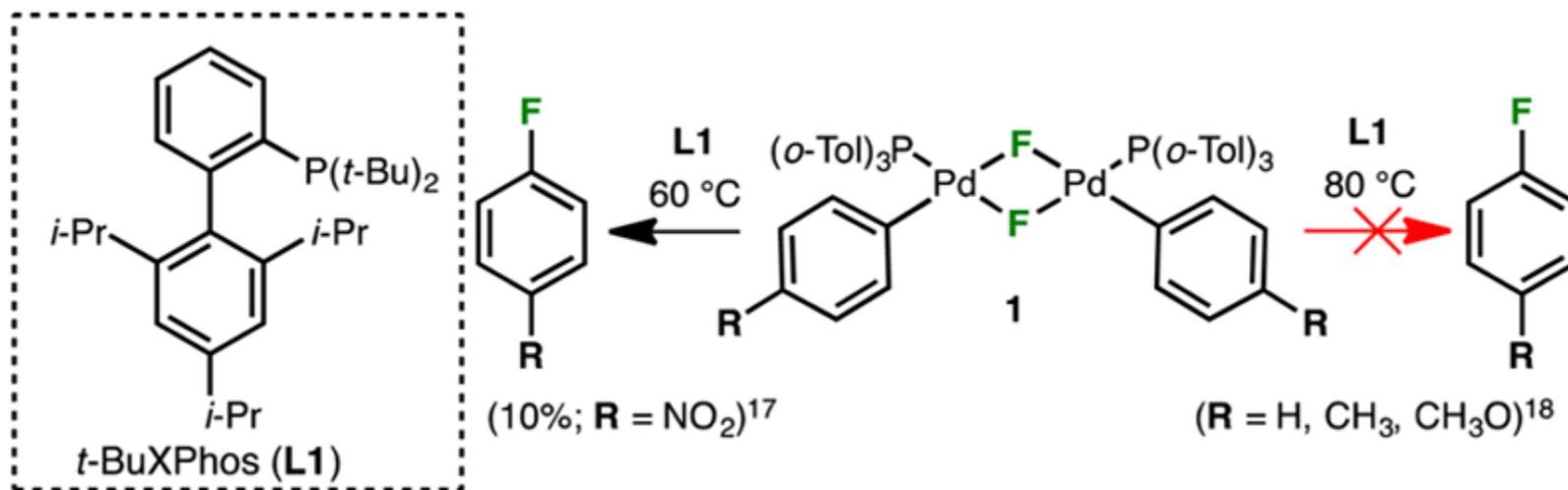
b) Challenges associated with Pd-catalyzed cross-coupling.

Introduction

Decomposition pathway observed in the thermal decomposition of $L_2Pd(Ar)F$ complexes.



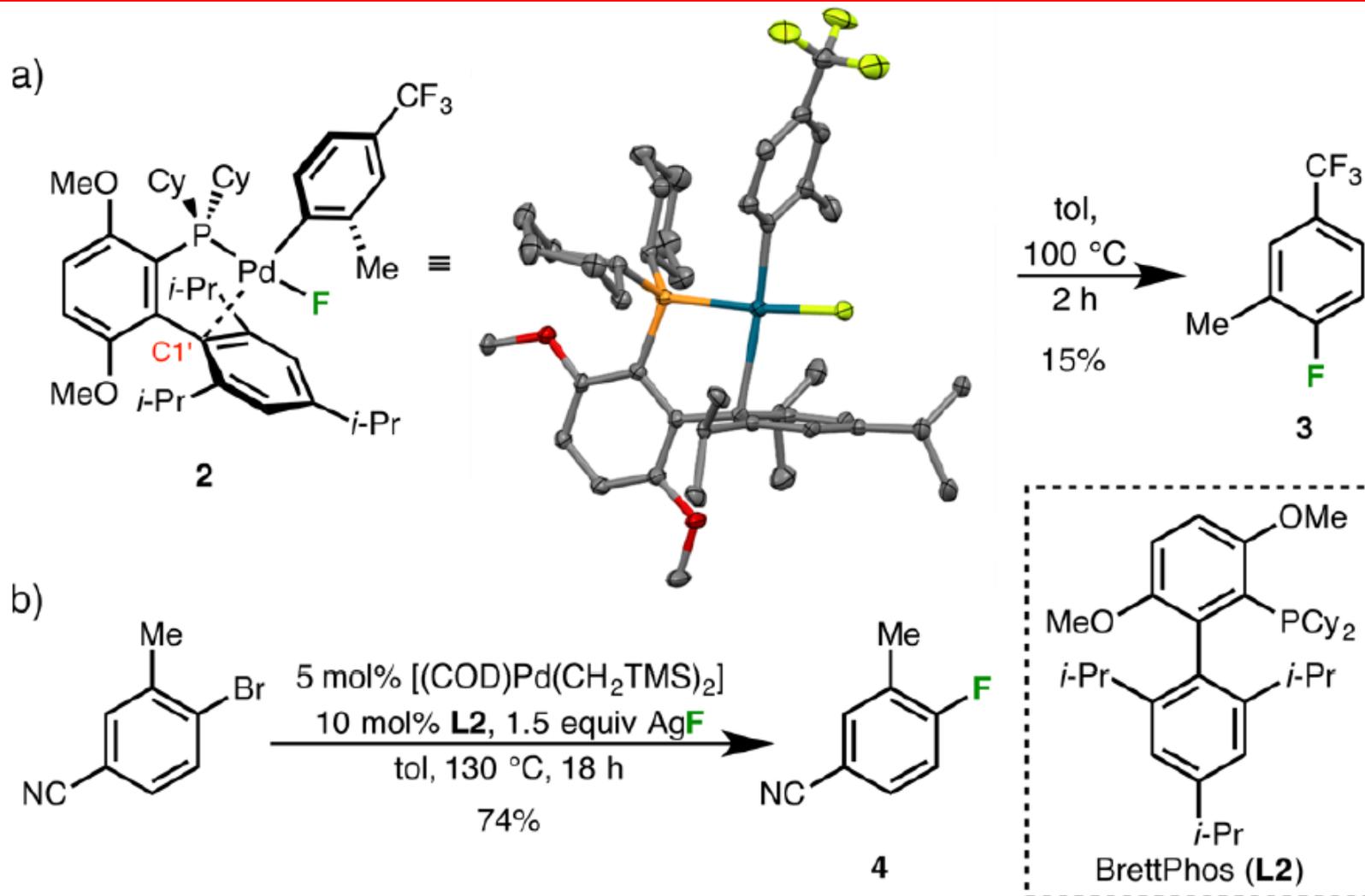
Thermal decomposition of **1** in the presence of L1.



Outline

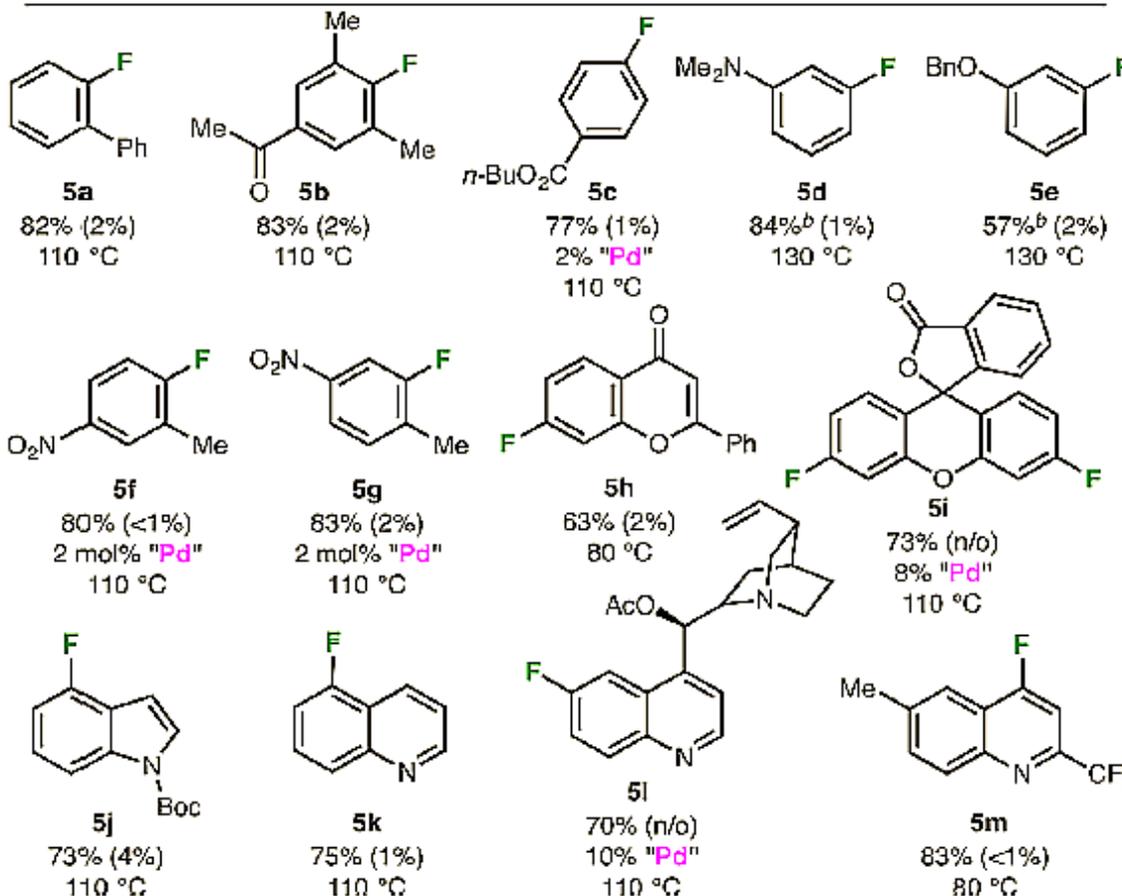
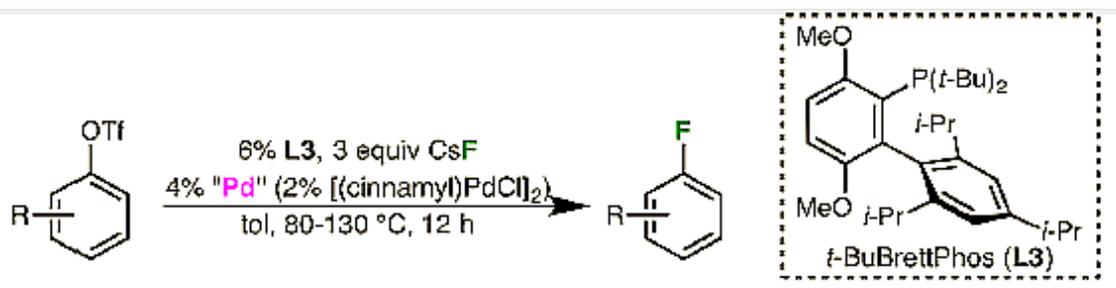
- Introduction
- **Pd-catalyzed fluorination: discovery**
- In situ catalyst modification
- Formation of regioisomeric aryl fluorides
- Pd-catalyzed fluorination: developments
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Pd-catalyzed fluorination: discovery



- (a) X-ray crystal structure of 2 and C-F reductive elimination from 2.
(b) Catalytic fluorination using L2.

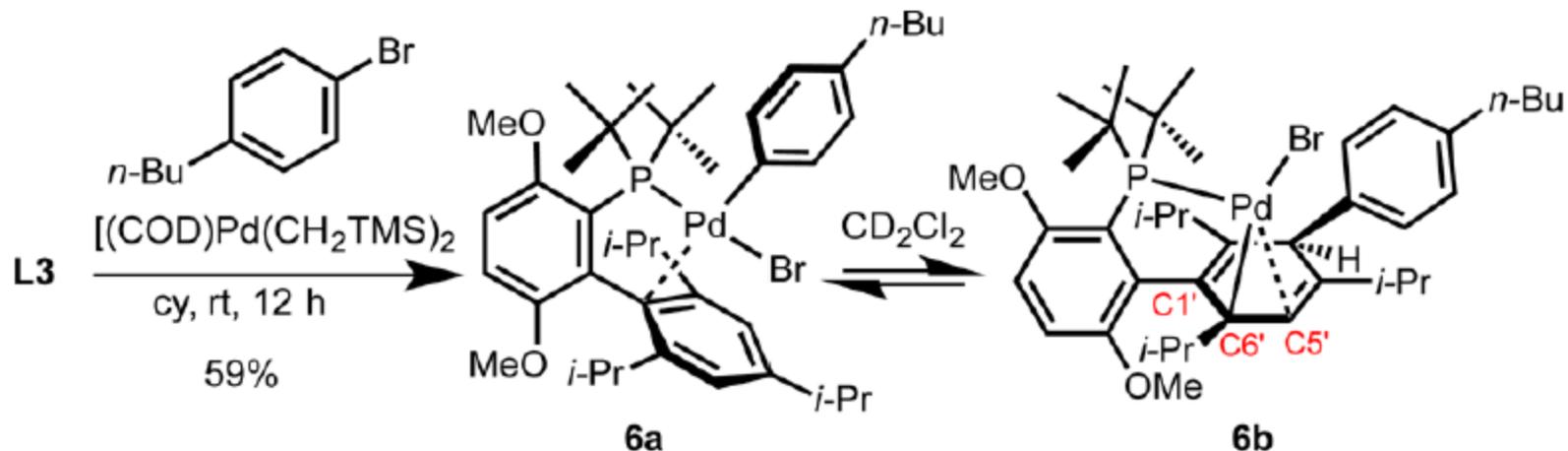
Pd-catalyzed fluorination of aryl triflates^a



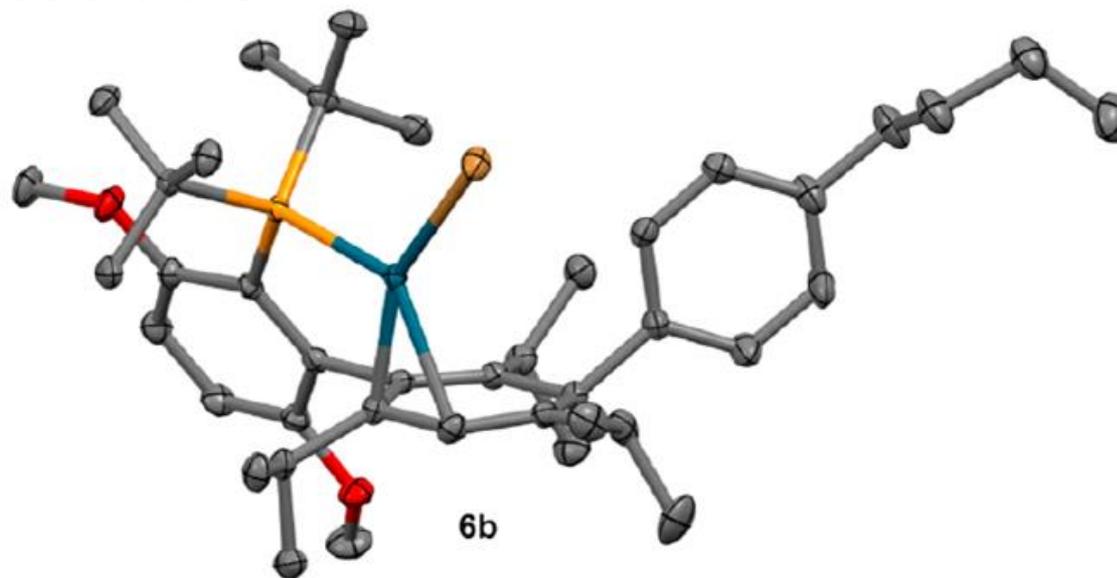
^aIsolated yields are shown. Values in parentheses indicate the amounts of reduction products (ArH) formed (n/o = not observed). ^bCyclohexane was used as the reaction solvents.

In situ catalyst modification

Synthesis of 6a and the dearomative rearrangement of 6a to 6b

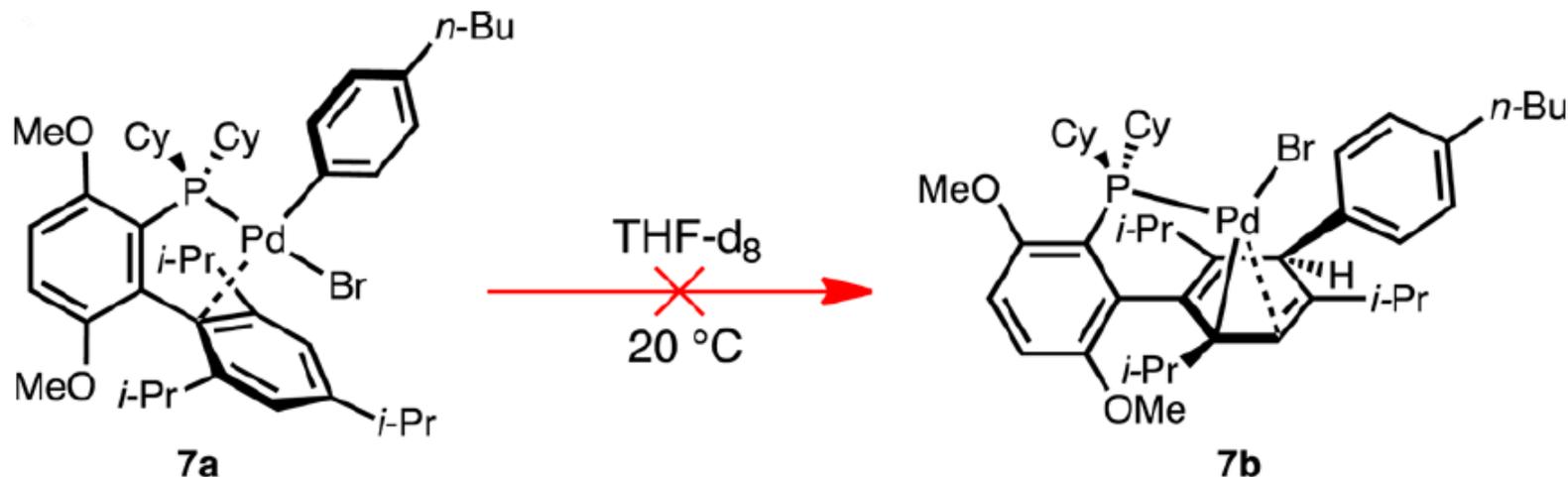


X-ray crystal structure of 6b

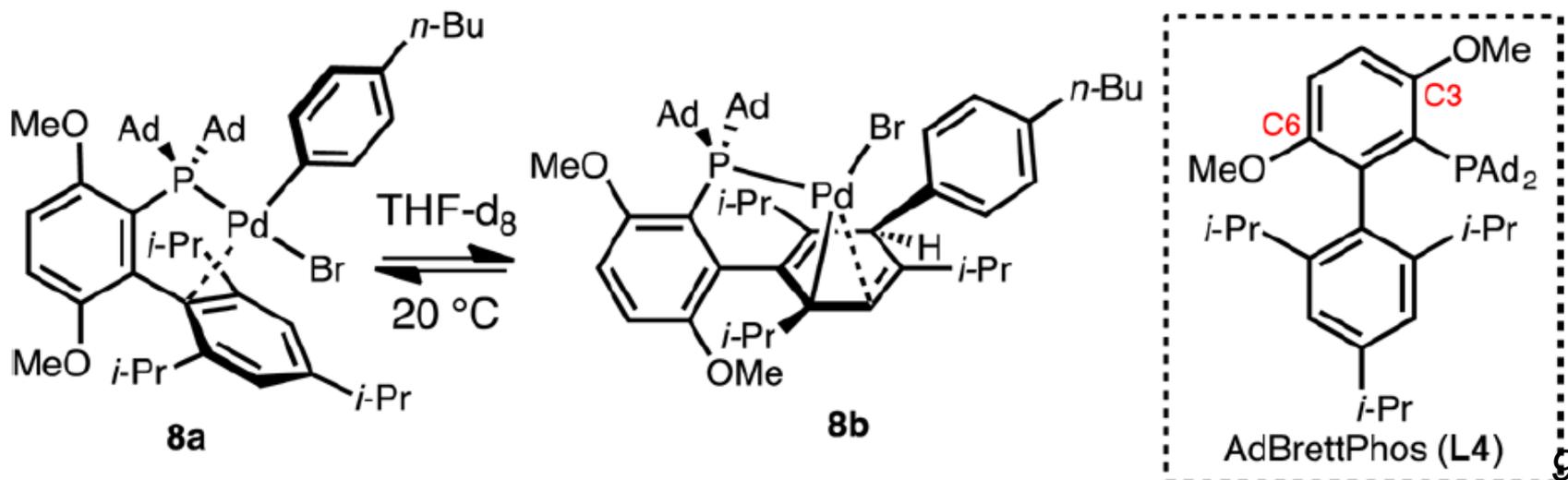


In situ catalyst modification

L2-supported oxidative addition complex 7a does not undergo rearrangement to 7b.

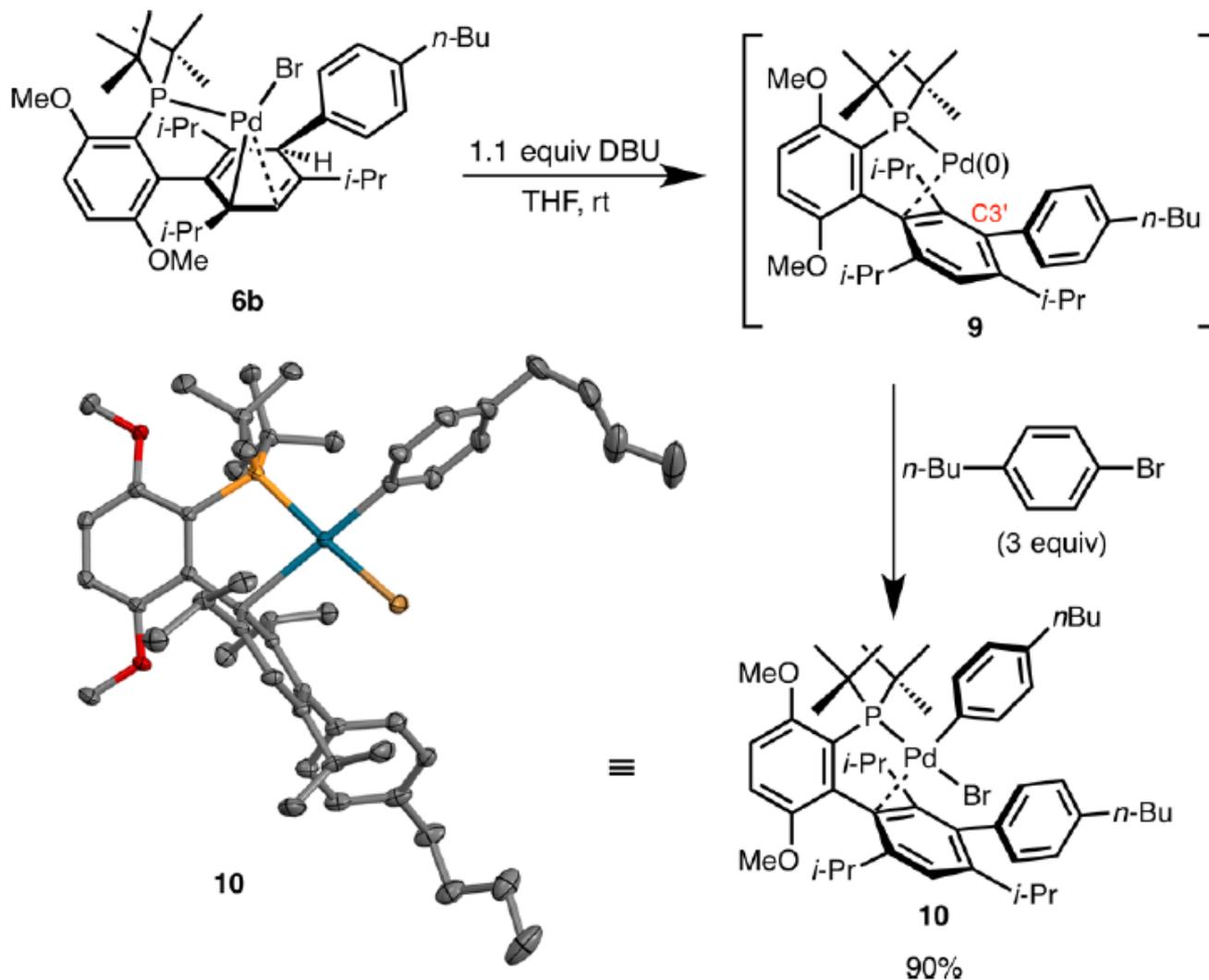


Dearomative rearrangement of 8a to 8b



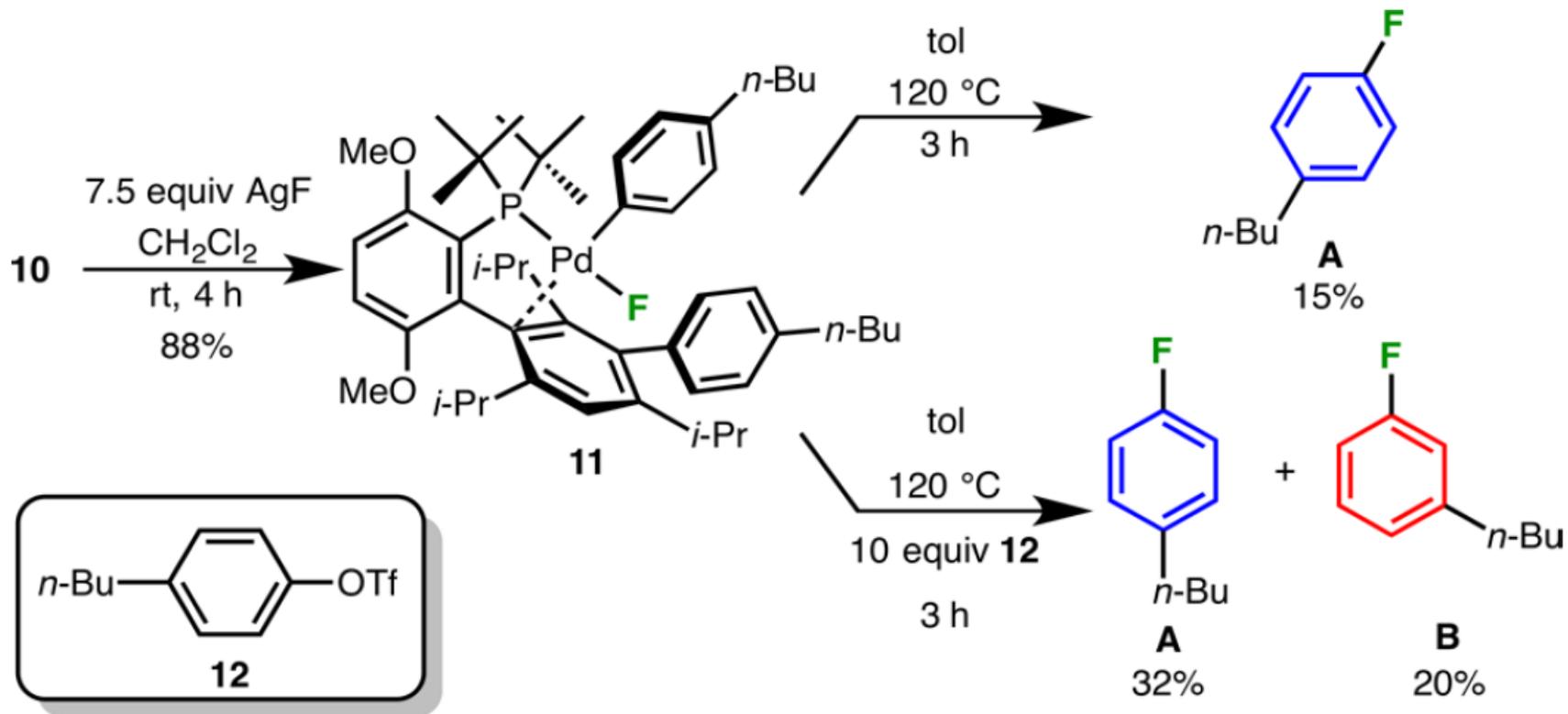
In situ catalyst modification

Rearomatization of **6b** followed by trapping with 4-(*n*-Bu)PhBr to complex **10**. The X-ray crystal structure of **10** is also shown.



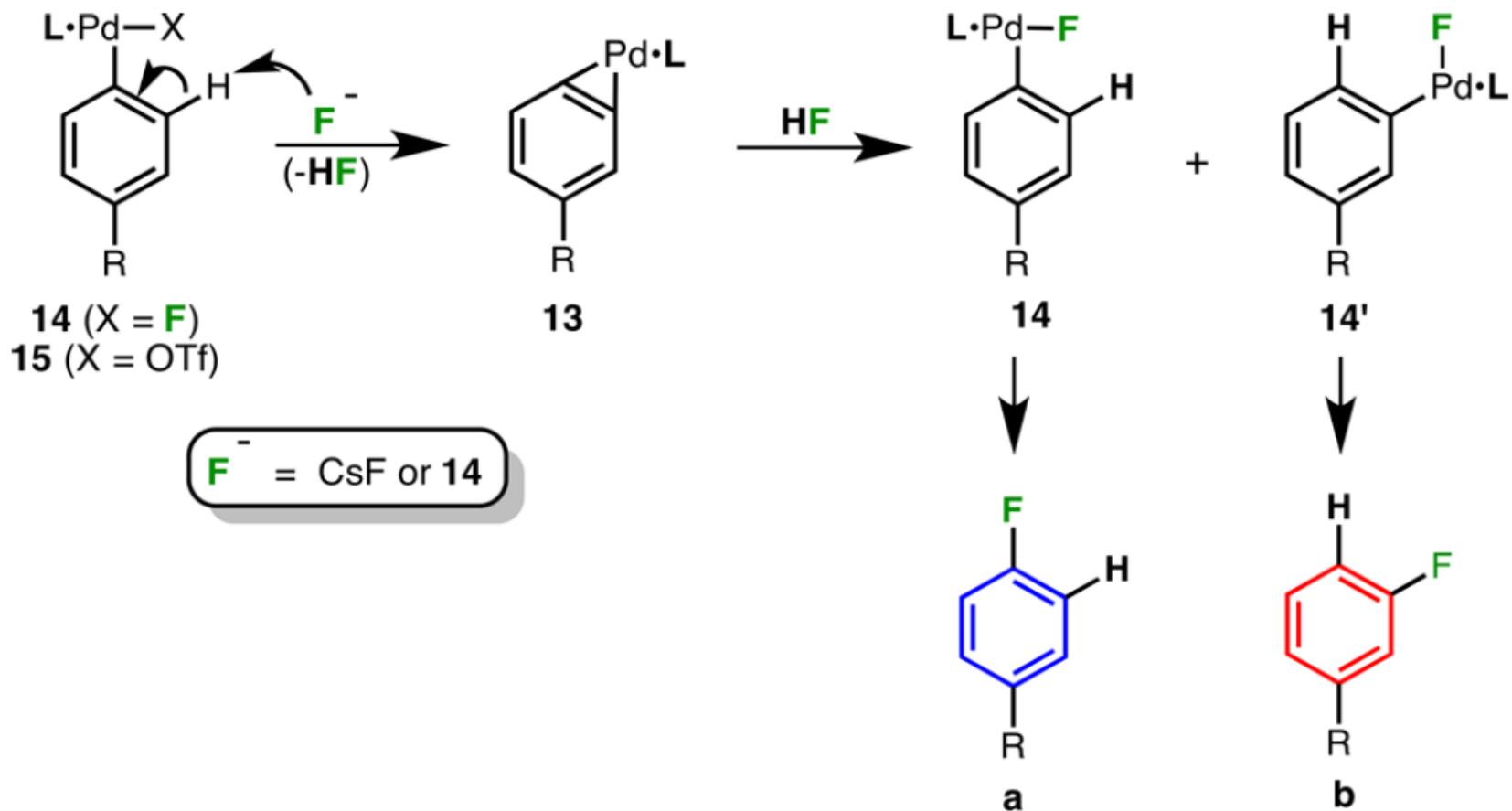
In situ catalyst modification

Synthesis and reactivity of LPd(Ar)F complex 11



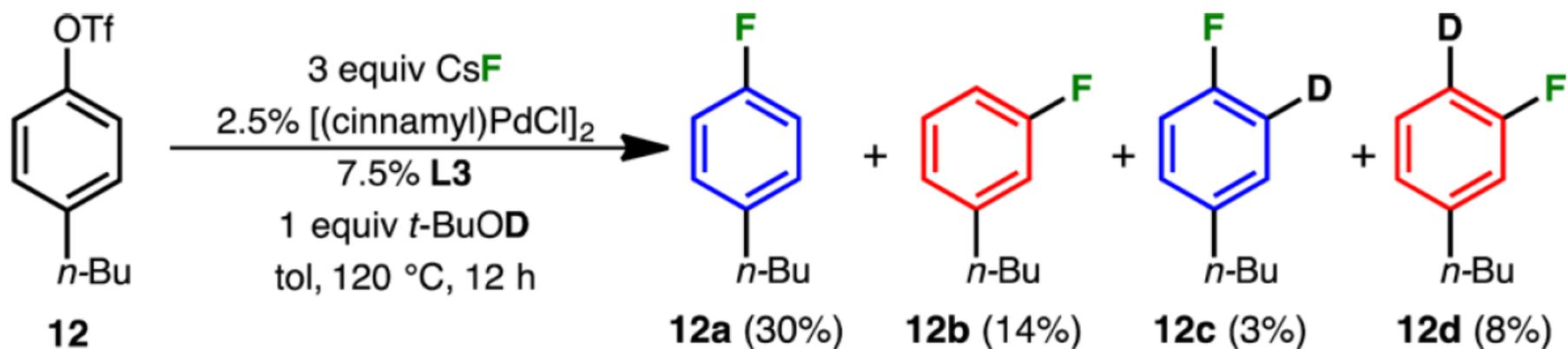
Formation of regioisomeric aryl fluorides

Proposed mechanism for the formation of regioisomeric aryl fluorides from para-substituted aryl triflates.



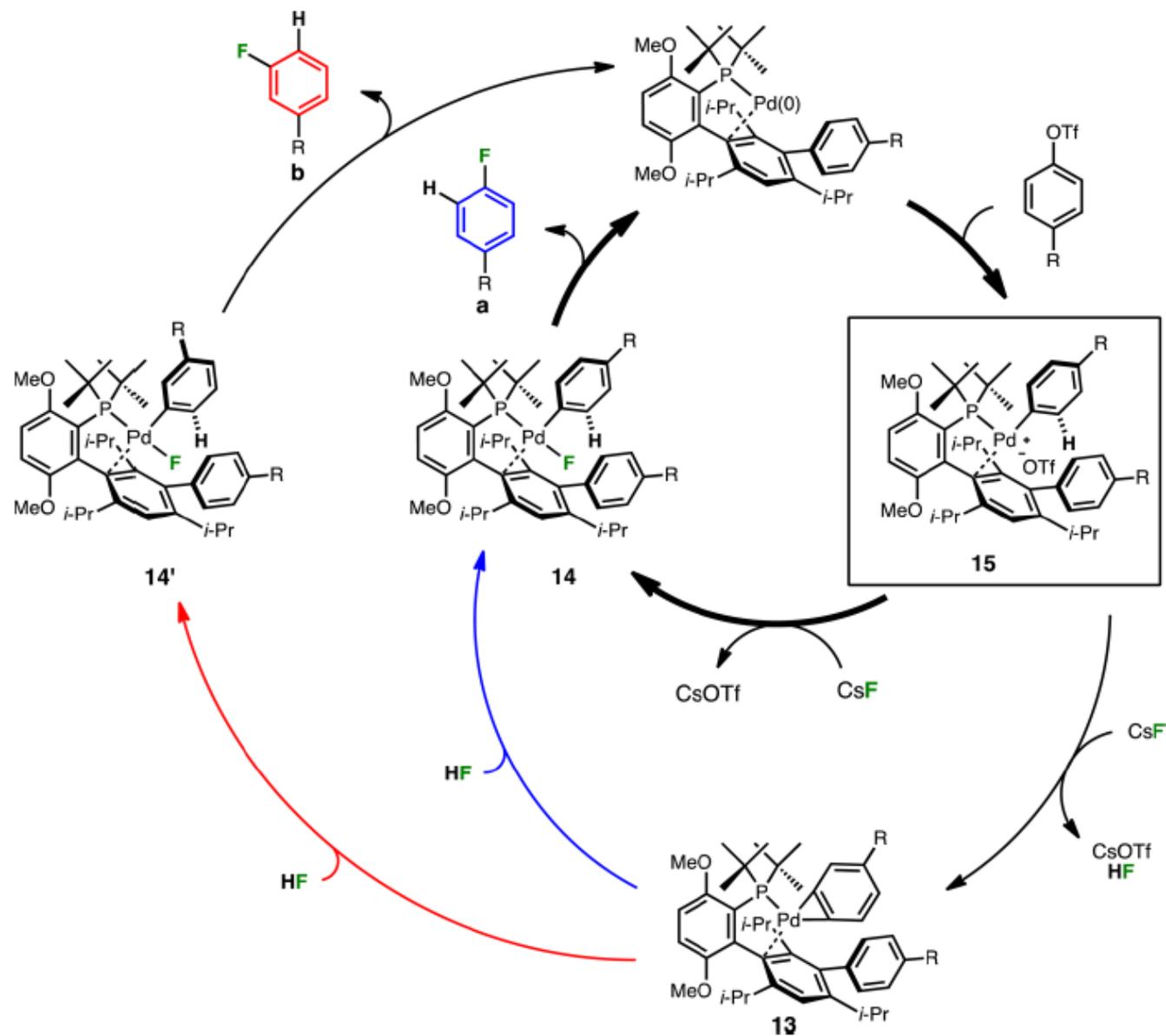
Formation of regioisomeric aryl fluorides

Addition of *t*-BuOD to the Pd-catalyzed fluorination of **12** gives a mixture of aryl fluorides (**12a-d**).



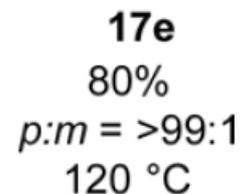
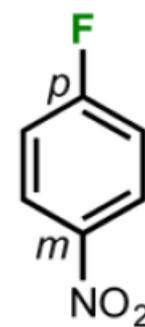
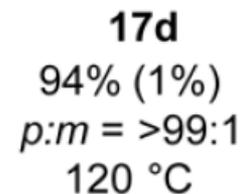
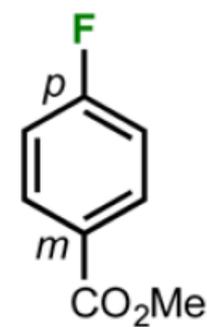
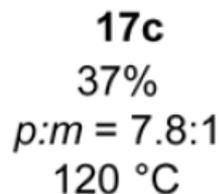
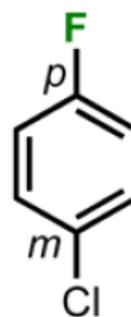
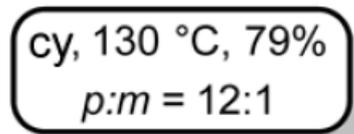
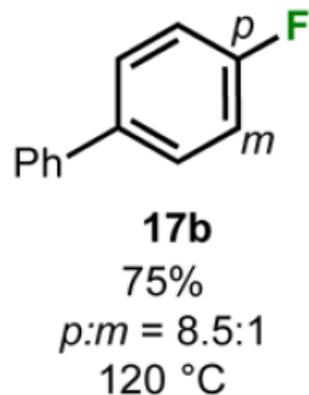
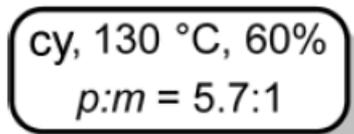
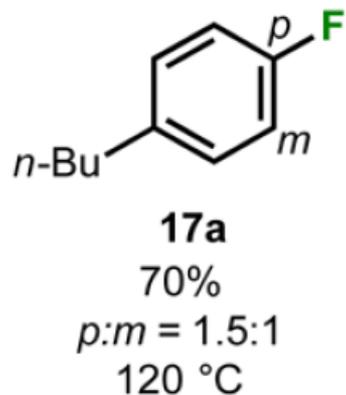
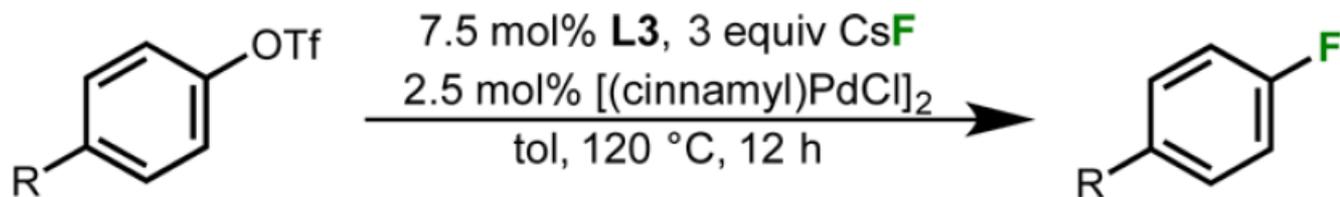
Proposed mechanism

The formation of regioisomeric aryl fluorides **a** and **b**.



Formation of regioisomeric aryl fluorides

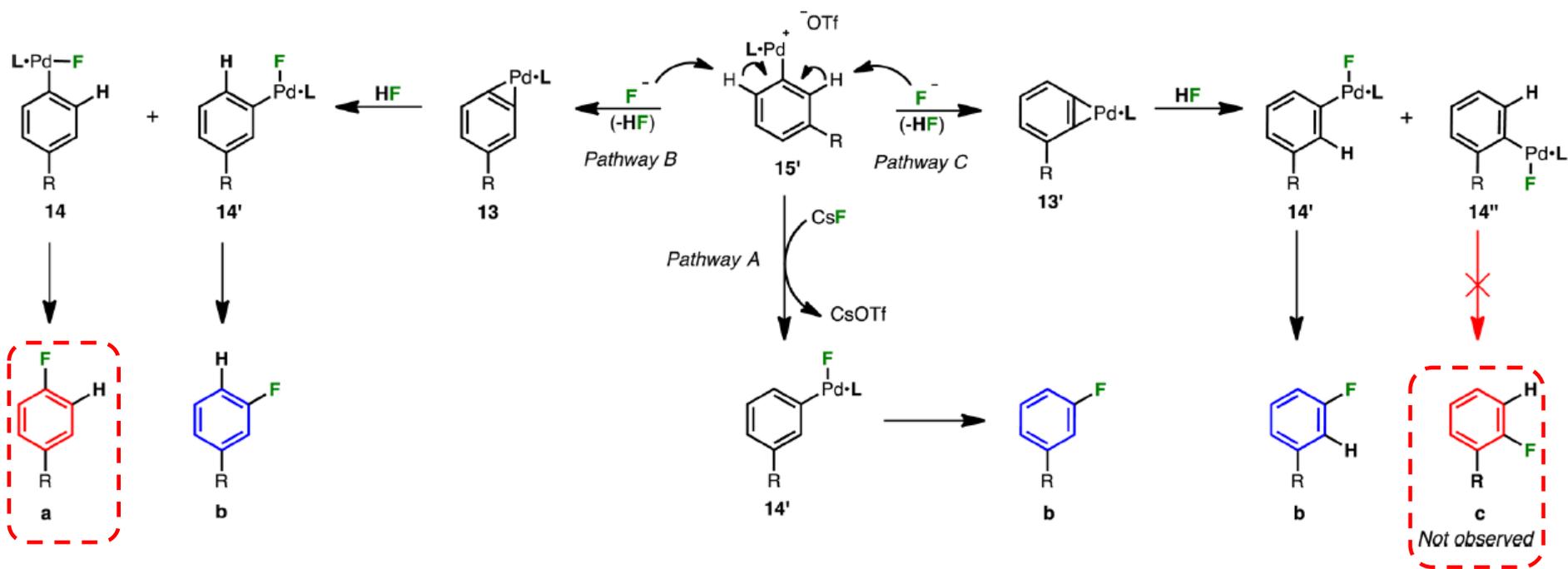
Effect of para substituents on regioisomer formation^a



^aYields were determined by ¹⁹F NMR spectroscopy.

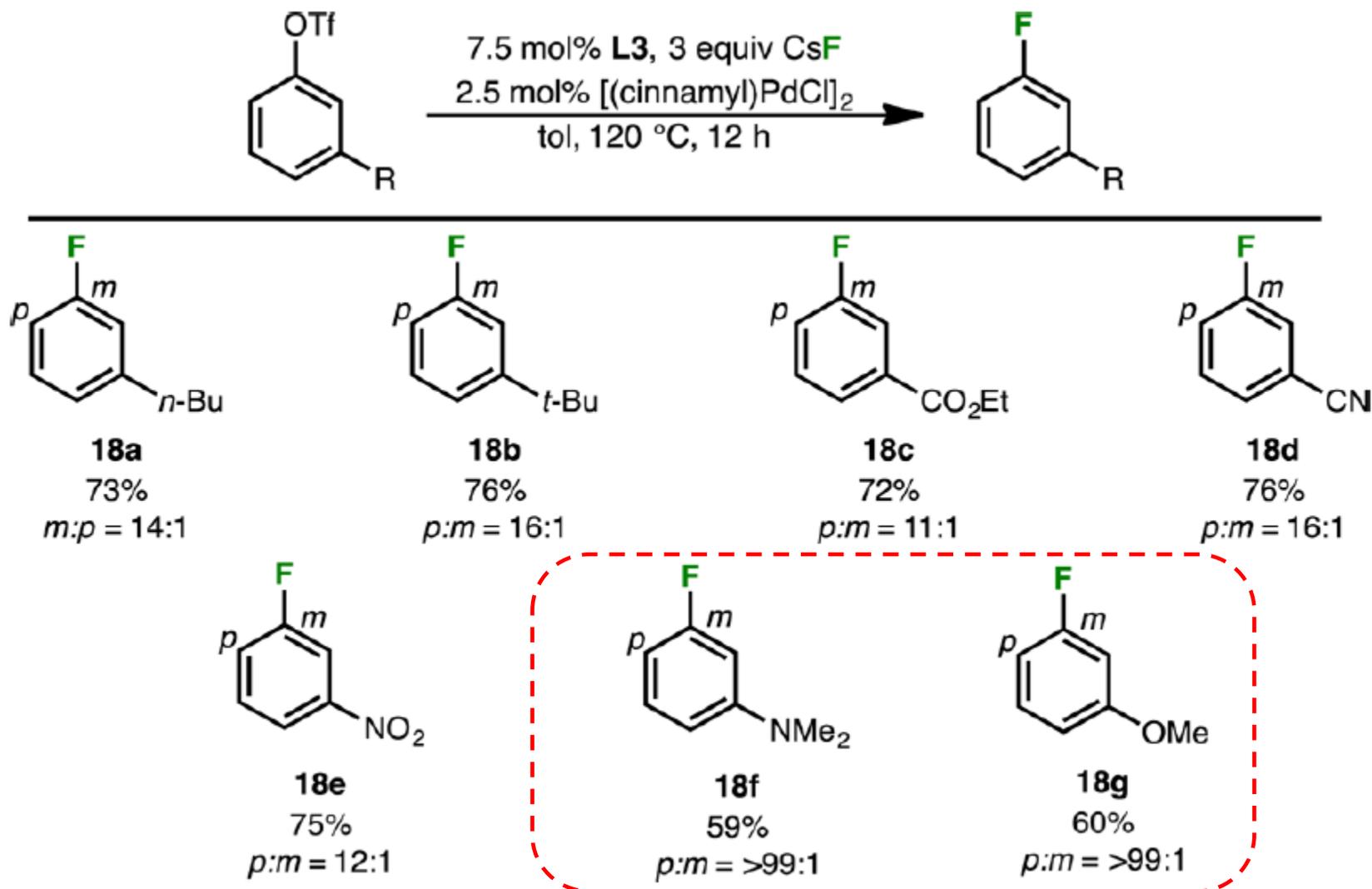
Proposed mechanism

Regioisomer formation from meta-substituted aryl triflates.



Formation of regioisomeric aryl fluorides

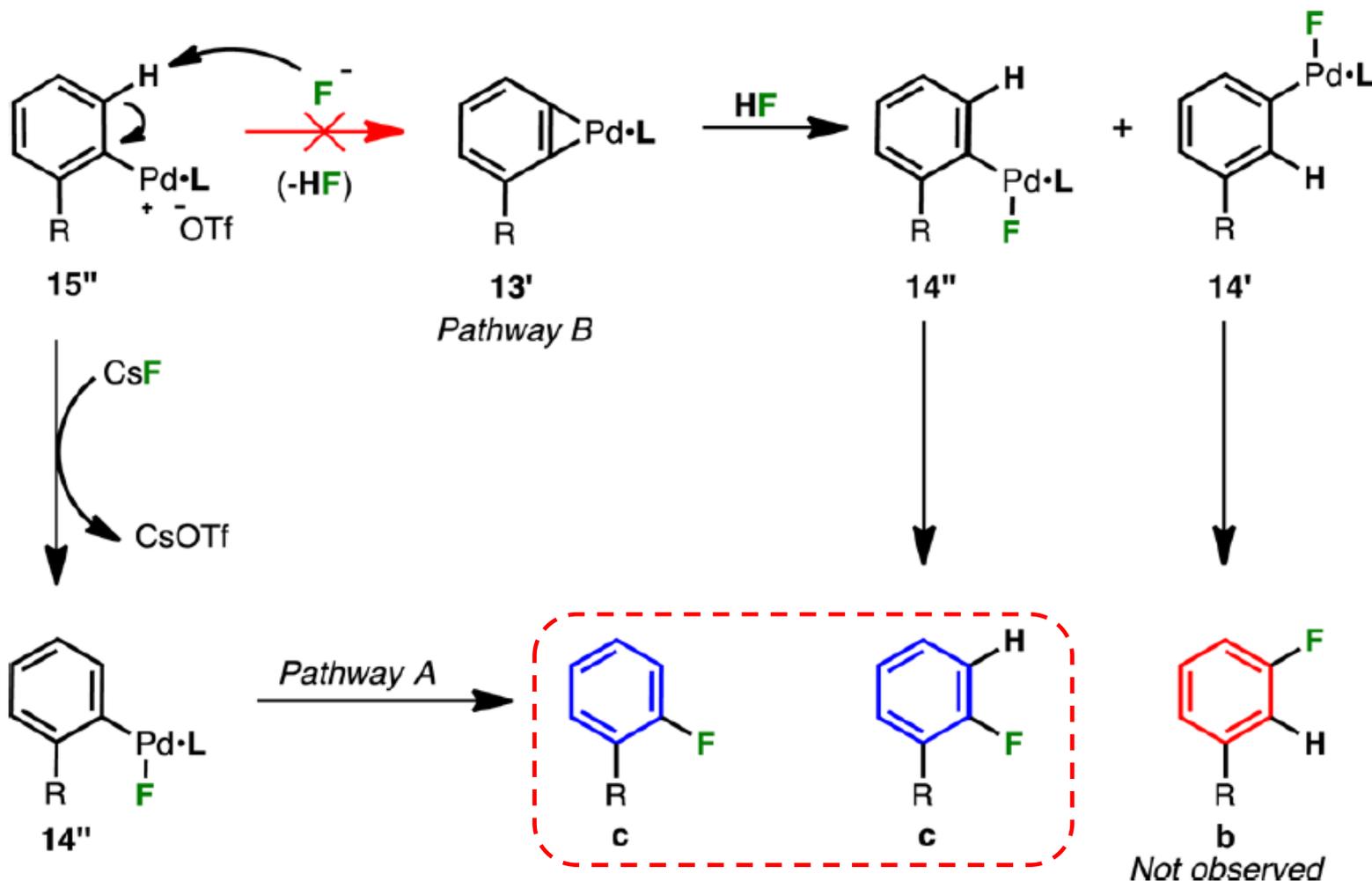
Effect of meta substituents on regioisomer formation^a



^aYields were determined by ¹⁹F NMR spectroscopy.

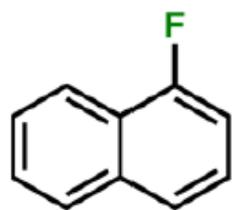
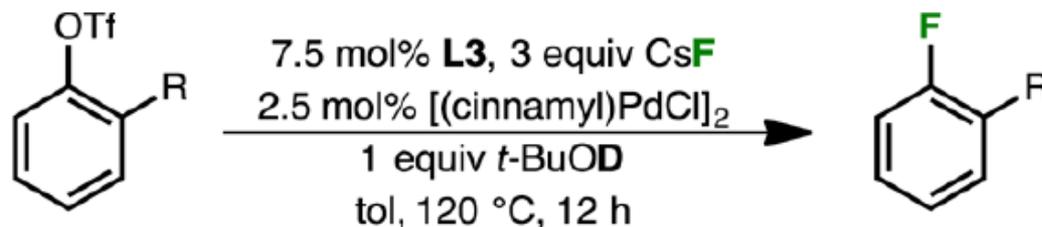
Formation of regioisomeric aryl fluorides

Proposed mechanism for regioisomer formation from ortho-substituted aryl triflates.

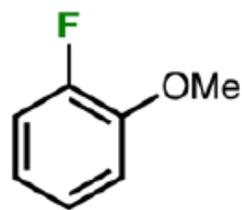


Improved catalyst system

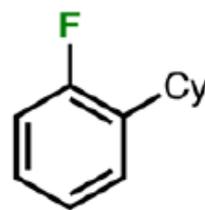
Effect of ortho substituents on regioisomer formation



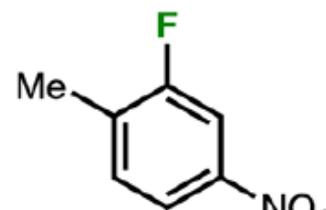
19a
80%



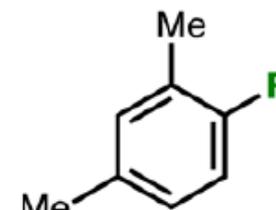
19b
52%



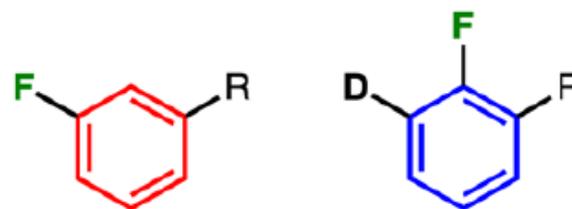
19c
75%



19d
76%



19e
79%



Not observed

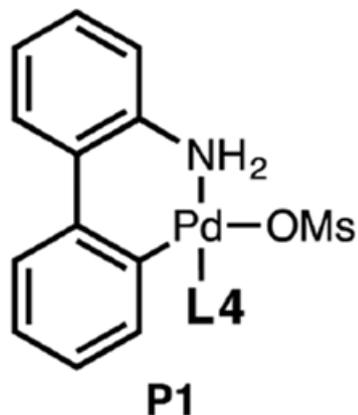
^aYield determined by ¹⁹F NMR.

Outline

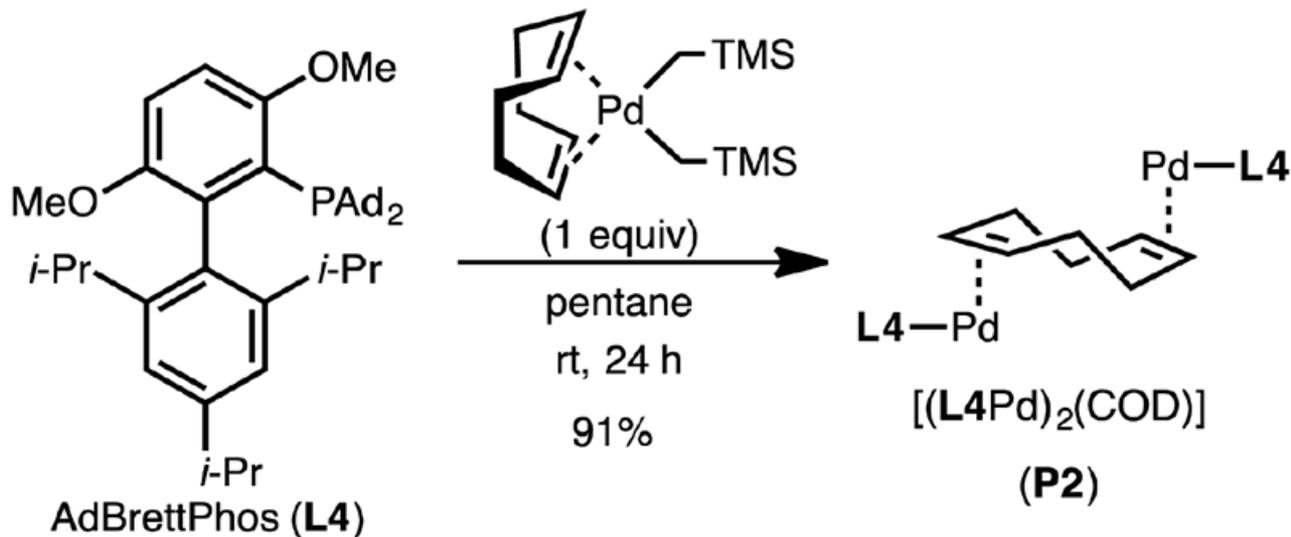
- Introduction
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- Conclusions and future perspectives
- Acknowledgment

Improved catalyst system

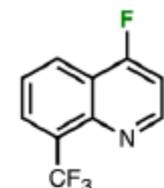
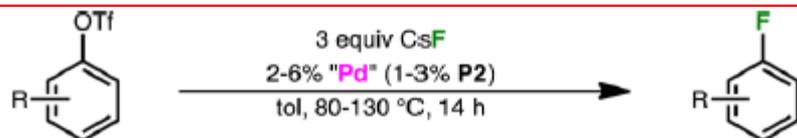
Structure of L4-based precatalyst P1.



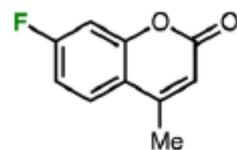
Synthesis of L4-supported Pd(0) precatalyst P2.



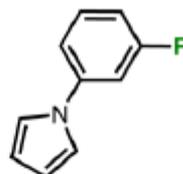
Improved catalyst system



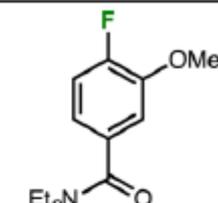
87%
2% "Pd", 90 °C



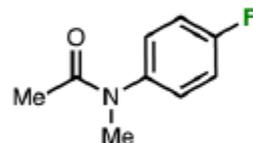
92%
2% "Pd", 110 °C



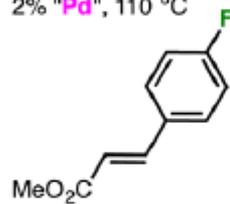
71%
3% "Pd", 120 °C



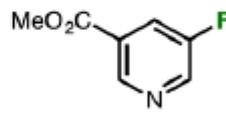
91% (17%)^b
2% "Pd", 110 °C



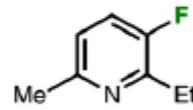
71%^c (58%)^b
4% "Pd", 120 °C



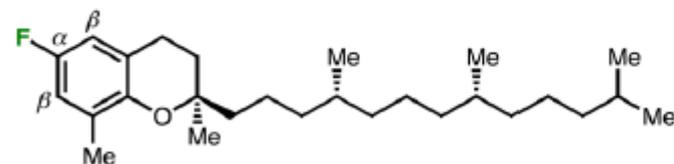
92% (53%)^b
2% "Pd", 80 °C



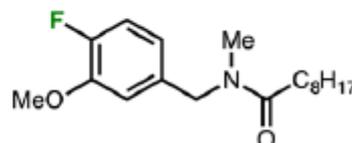
44%
4% "Pd", 130 °C



64% (55%)^b
4% "Pd", 130 °C



88% (>20:1 α : β)^c (28%)^b
3% "Pd", 130 °C



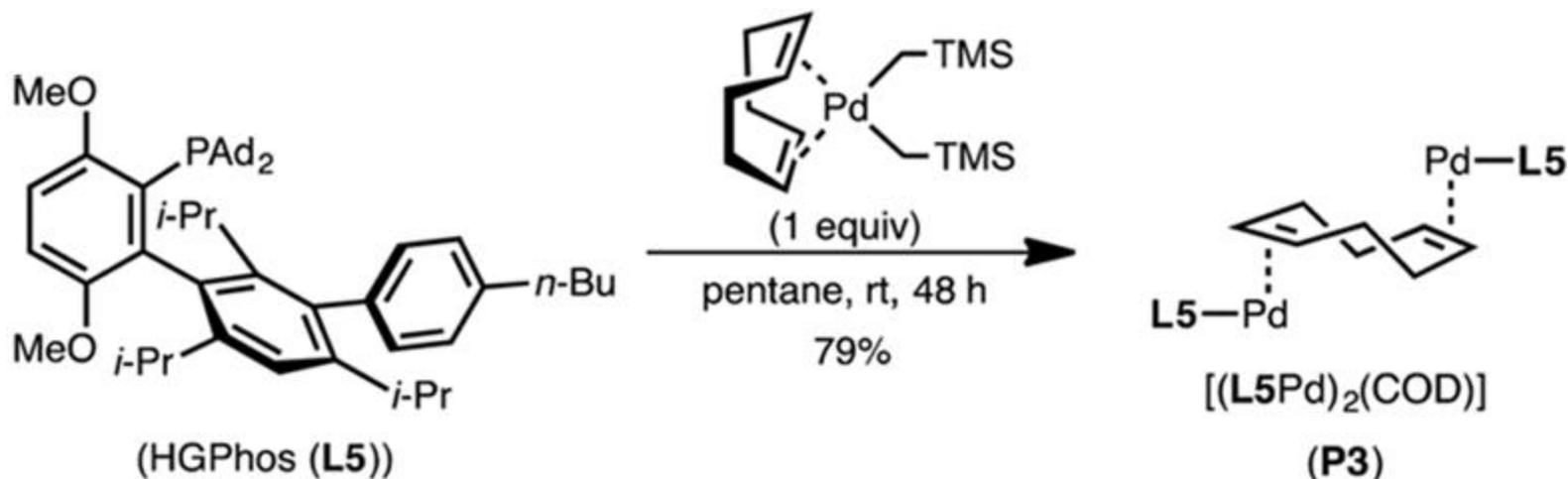
85%
3% "Pd", 130 °C

Fluorination of (hetero) aryl triflates and aryl triflates derived from biologically active phenols

^aIsolated yields are shown. ^bYield when the reaction was conducted under the same conditions using [(cinnamyl)PdCl]₂/L4 (Pd/L4 = 1:1.5) instead of P2. The corresponding ArCl was detected by GC analysis. ^cCyclohexane was used as the reaction solvent.

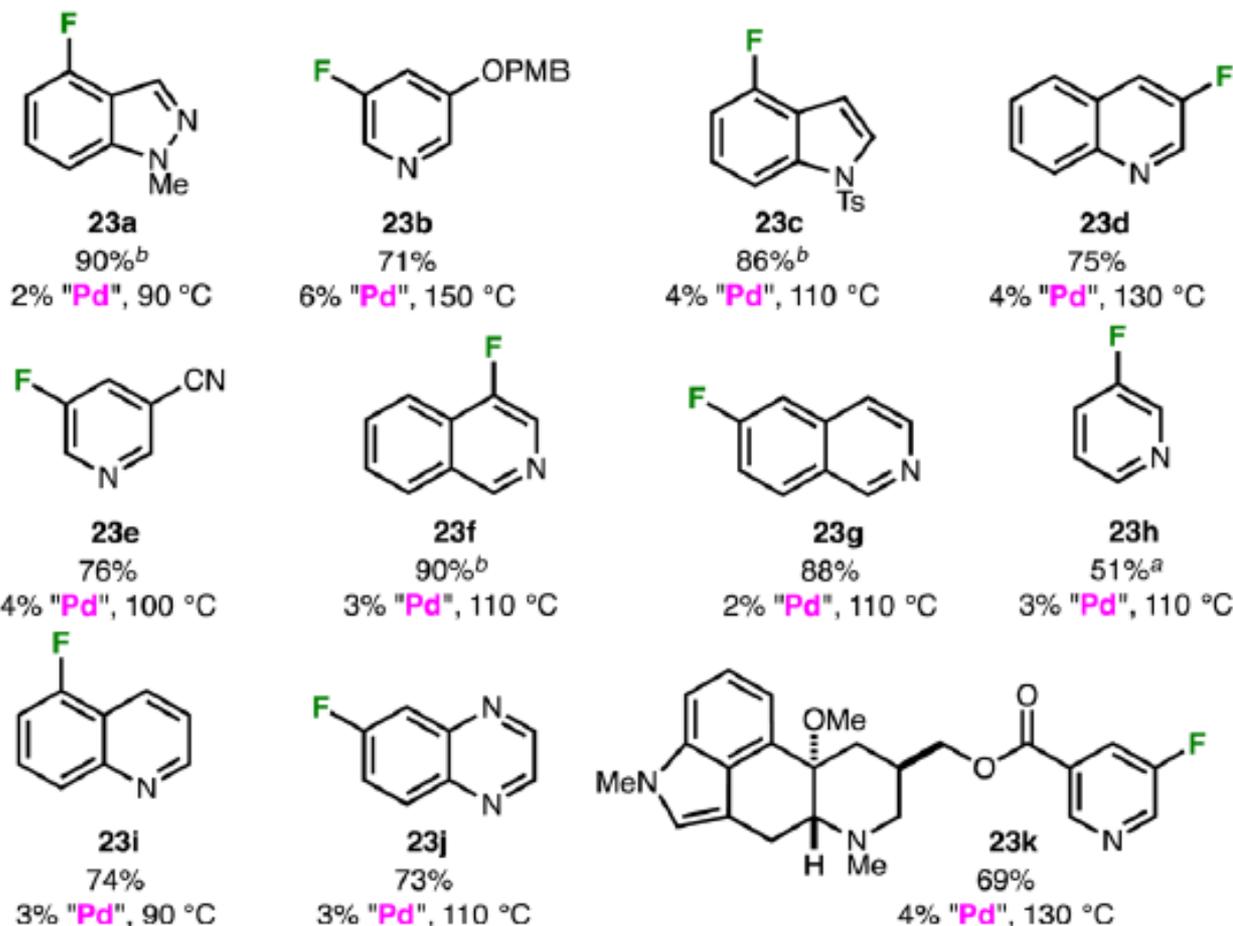
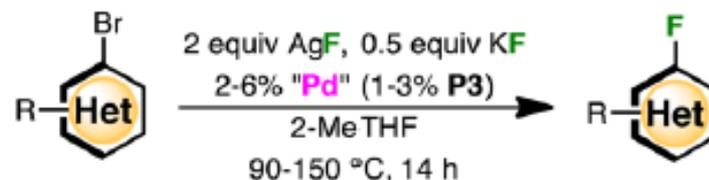
Fluorination of (hetero)aryl bromides

Structure of HGPhos (L5) and the synthesis of P3.



Fluorination of (hetero)aryl bromides

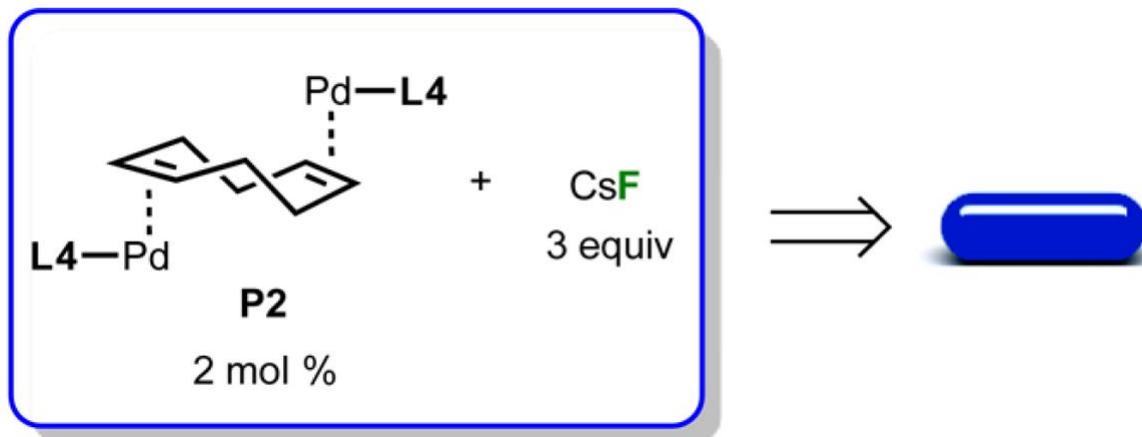
Pd-catalyzed fluorination of heterocyclic aryl bromides using P3^a



^aYields determined by ¹⁹F NMR spectroscopy.

Glove-Box-Free Fluorination

Wax capsules for the Pd-catalyzed fluorination of aryl triflates

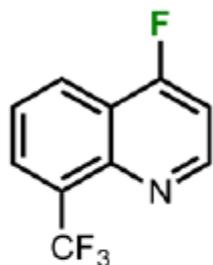
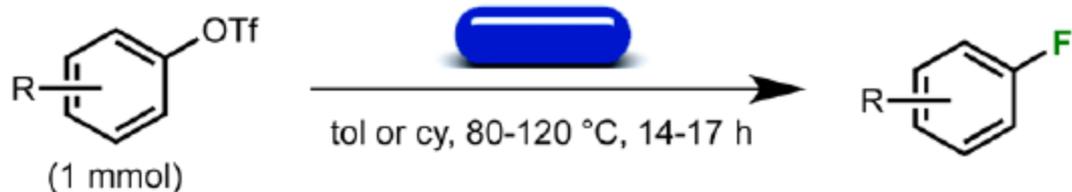


Wax capsules for the Pd-catalyzed fluorination of aryl bromides

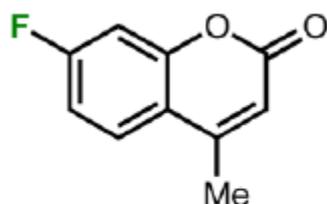


Glove-Box-Free Fluorination

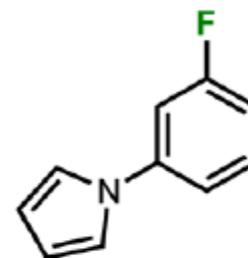
Glove-box-free fluorination of aryl triflates



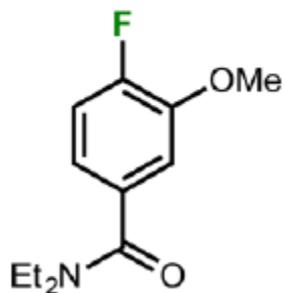
86% (87%)



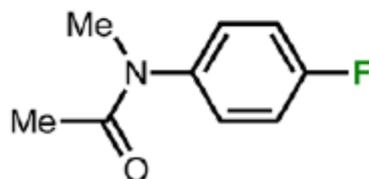
80% (92%)



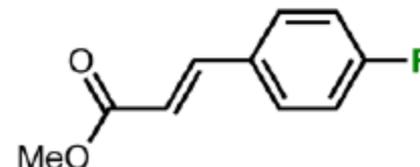
79% (71%)



86% (91%)



74% (71%)



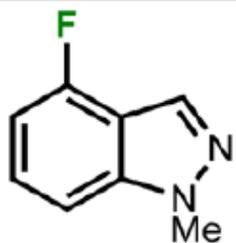
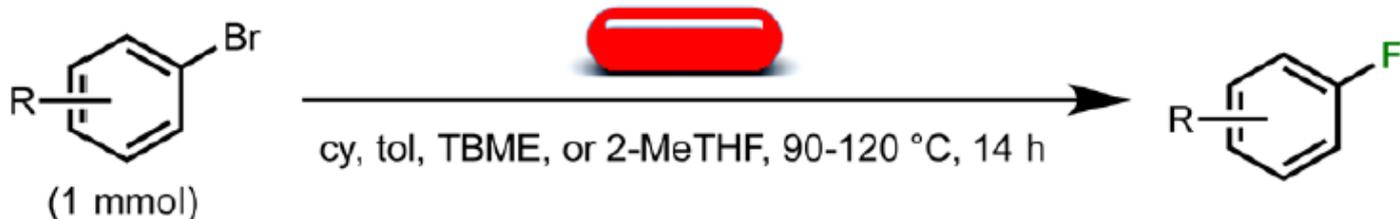
94% (92%)

Isolated yields are reported.

Values in parentheses are isolated yields obtained a glovebox to set up the reaction.

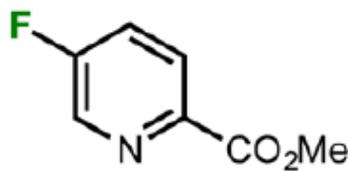
Glove-Box-Free Fluorination

Glove-box-free fluorination of aryl bromides



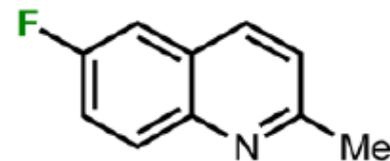
23a

77% (**90%**)



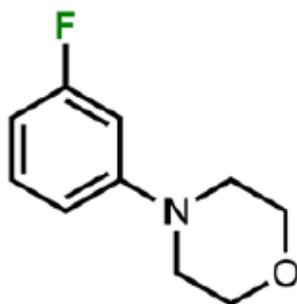
24a

75% (**89%**)



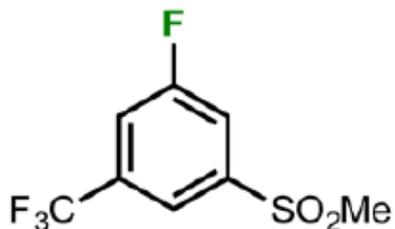
24b

90% (**96%**)



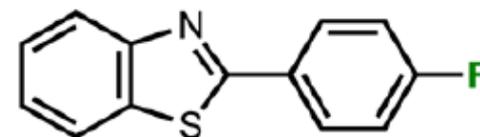
24c

81% (**86%**)



24d

91% (**75%**)



24e

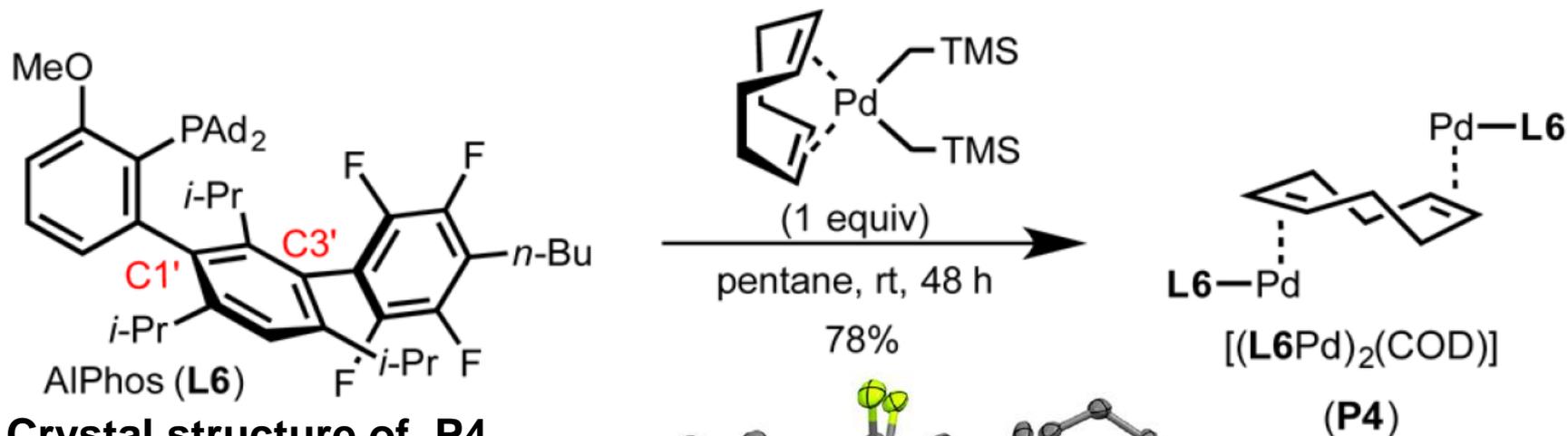
97% (**96%**)

Isolated yields are reported.

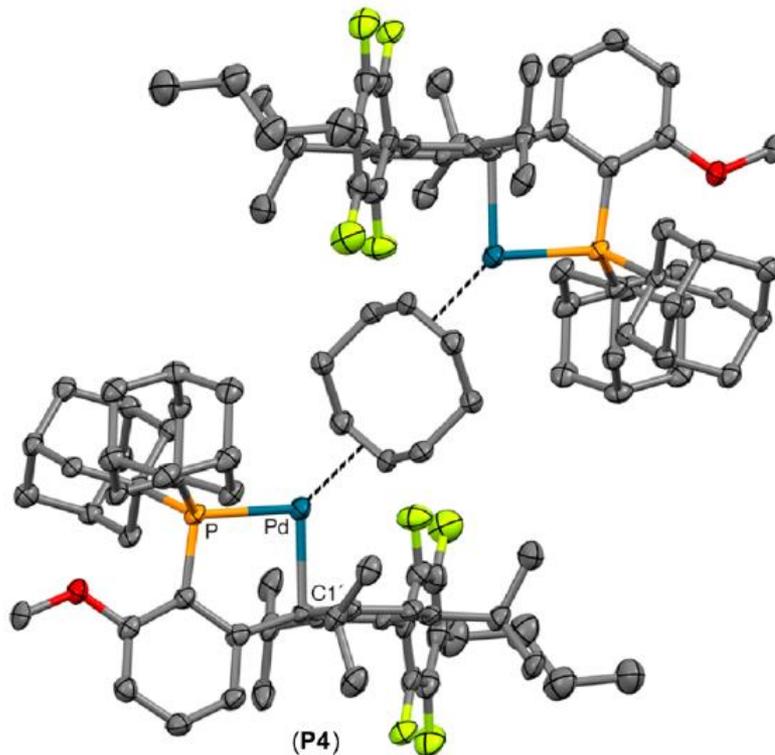
Values in parentheses are isolated yields obtained a glovebox to set up the reaction.

Regioselective and room-temperature fluorination

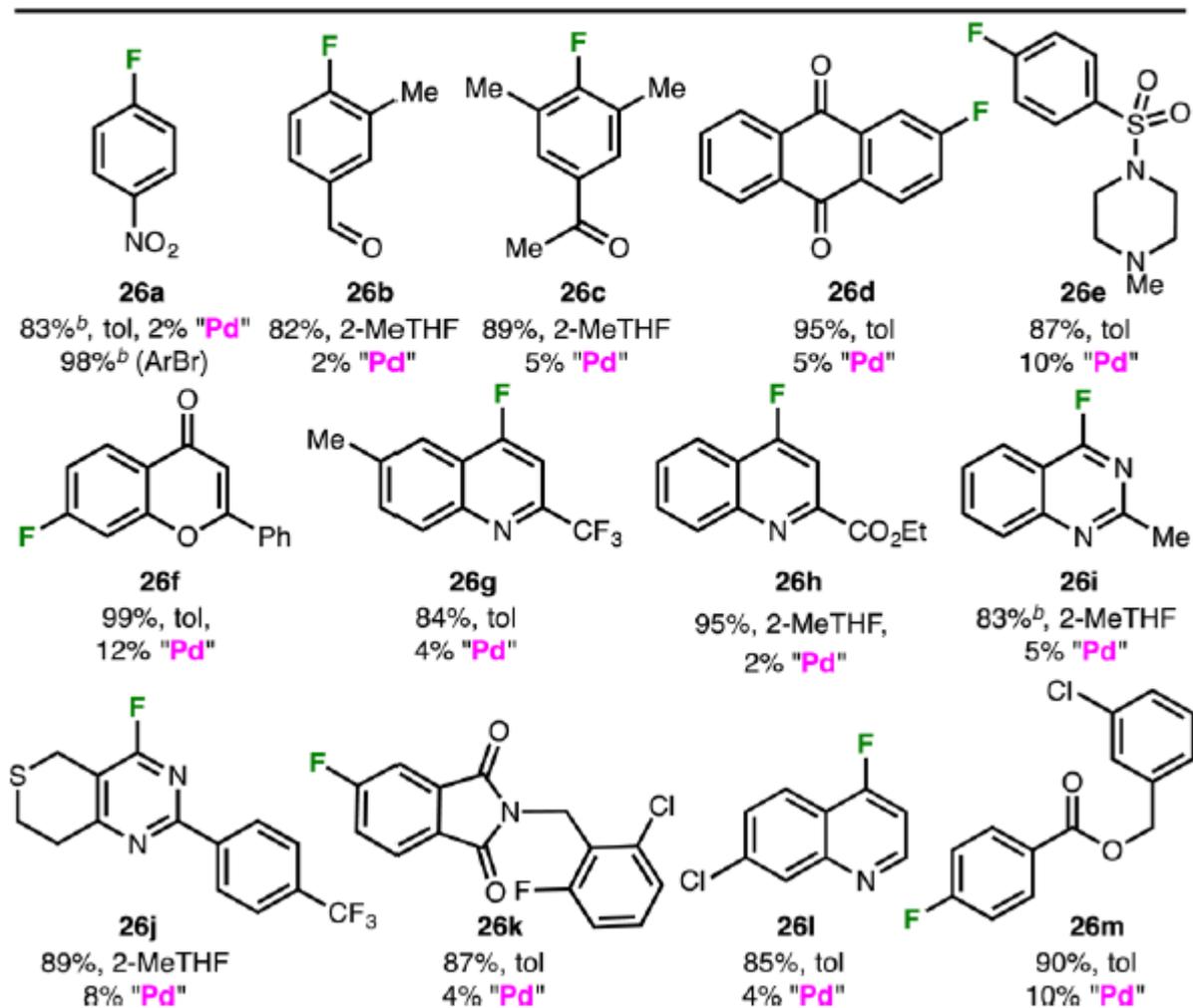
Structure of AlPhos (L6) and the synthesis of [(L6Pd)₂(COD)] (P4).



Crystal structure of P4.



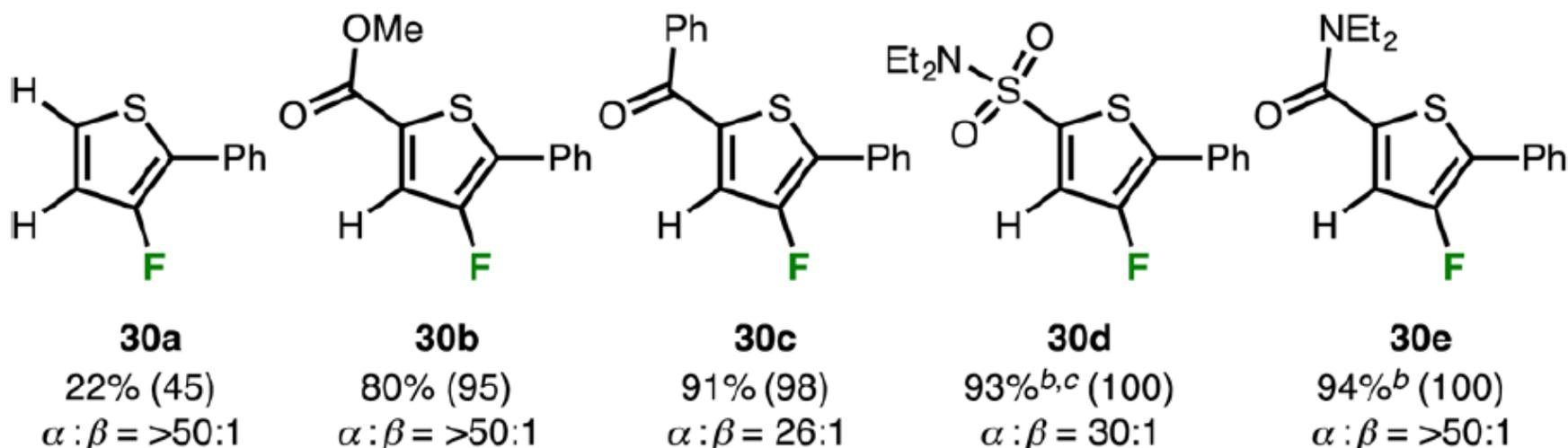
Room-temperature fluorination of aryl triflate^a



^aIsolated yields are shown. ^bYields determined by ¹⁹F NMR spectroscopy.

Fluorination of five-membered heterocycles

Pd-catalyzed fluorination of 2-substituted 3-bromothiophenes^a.



^aYields determined by ¹⁹F NMR spectroscopy are shown. Values in parentheses indicate % conversion of the starting material. ^bIsolated yield. ^cToluene was used as the reaction solvent.

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- Introduction
- Pd-catalyzed fluorination: discovery
- In situ catalyst modification
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- Pd-catalyzed fluorination: developments
- **Conclusions and future perspectives**
- Acknowledgment



Conclusions and future perspectives

- Pd-catalyzed aromatic fluorination.
 - Designed and developed a new biaryl monophosphine ligands to facilitating C-F reductive elimination.
 - Realized glove-box-free or room temperature fluorination
-
- (Hetero)Aryl chlorides, and five-membered heteroaryl (pseudo)halides are not viable substrates



Acknowledgment

Thanks for your attention!