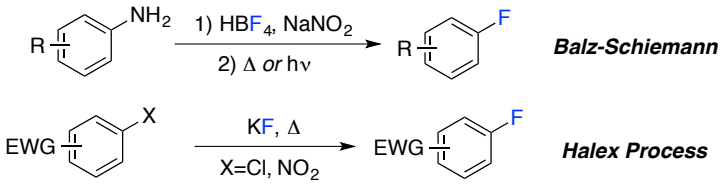
RECENT ADVANCES IN ARYL CARBON-FLUORINE BOND FORMATION

Reported by Zhao Wu March 3rd, 2015

Introduction

Carbon-fluorine bonds are widespread in pharmaceuticals, agrochemicals, materials, and tracers for positron emission tomography.[1] The installation of fluorine into organic molecules uniquely influences their properties due to the high electronegativity and small radius of fluorine. For example, in modern medicinal chemistry, fluorination is routinely applied to tune molecular properties such as metabolic stability, lipophilicity, and functional group acidity/basicity so as to favor bioavailability and target binding affinity.[2] As such, approximately 30% of all agrochemicals[2b] and 20% of all pharmaceuticals[2a] contain fluorine, including drugs such as Lipitor, Prozac, and Ciprobay.[1, 2a] However, owing to harsh reaction conditions, the strong basicity of fluoride sources, and the electronic demands for nucleophilic aromatic substitution reactions, conventional approaches towards the synthesis of arylfluorides, such as the Balz-Schiemann reaction or the Halex (halogen exchange) process (Scheme 1), are limited to relatively simple substrates. A practical, scalable, and regio-selective fluorination of more complex arenes in the presence of various functional groups is a significant synthetic challenge.[1] Over the past decade, chemists have developed new methods to incorporate fluorine into aromatic molecules via transition metal catalysis.[4-8] Many nucleophilic and electrophilic fluorinating reagents have been developed and applied in the synthesis of various fluorine-containing molecules.

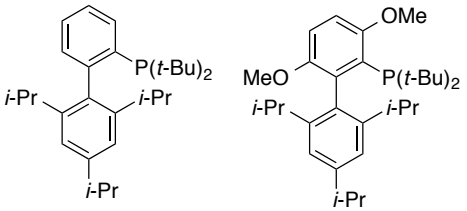
Scheme 1. Conventional Routes to Fluoroarenes



Nucleophilic Fluorination

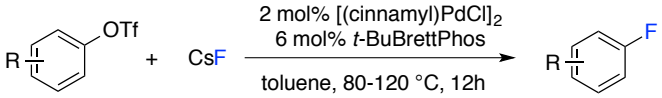
Although palladium-catalyzed cross-coupling reactions to form C-N, C-O, and C-S bonds have advanced significantly since 1990s,[1b] the C-F analogue has been slower coming due to the highly polarized metal-fluoride bond and poor polarizability of the small fluoride anion. These factors significantly slow the rate of concerted reductive elimination from the intermediates in the catalytic coupling to form C-F bonds. Early studies by Grushin[3a] and Yandulov[3b] have demonstrated the challenges associated with the difficult C-F reductive elimination from Pd(II) center: (1) the formation of stable Pd(II) fluoride-bridged dimer, and (2) a myriad fluoride-induced ligand decomposition pathways. An early result reported by Yandulov,[3b] demonstrated that 10% para-fluoronitrobenzene was formed from $[Pd(p\text{-}NO_2C_6H_5)F(P(o\text{-}Tolyl)_3)]_2$ in the presence of an excess of the bulky monodentate phosphine ligand *t*-BuXPhos (Figure 1). A breakthrough in this field was reported in 2009 when Buchwald's group described the palladium-

Figure 1. Bulky Monodentate Phosphine Ligands



catalyzed cross-coupling of aryltriflates and CsF in the presence of *t*-BuBrettPhos (Scheme 2).[4] This catalytic system illustrates that *t*-BuBrettPhos is crucial to facilitate C-F reductive elimination through a three-coordinate, T-shaped Pd(II) intermediate. However, for electron-rich non ortho-substituted aryltriflates, the formation of constitutional isomers complicates isolation of the desired product and limits the method's applicability.[4] More recently, Cu-mediated and -catalyzed fluorination reactions provide promising alternatives towards cost-efficient and scalable fluorination reactions.[5]

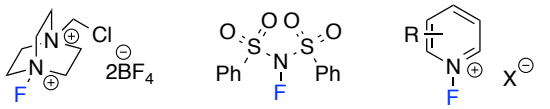
Scheme 2. First Catalytic Nucleophilic Arene Fluorination



Electrophilic Fluorination

Compared to the difficult C-F reductive elimination from a Pd(II) center, an alternative route from a high valent palladium complex would be more feasible due to the high electron deficiency of the metal center. The development of crystalline, benchtop-stable oxidative fluorinating reagents (Figure 2) greatly facilitates electrophilic fluorination. In 2006, the Sanford group reported the first Pd-catalyzed fluorination of 8-methylquinoline and phenylpyridine via C-H activation strategy using N-Fluorpyridium salts as the F^+ source.[6] Beyond directed C-H activation, electrophilic arene fluorination can also be addressed via a transmetalation of aryl stannanes, aryl silanes, and arylboronic acids[7] followed by oxidative fluorination and reductive elimination from high valent palladium,[6] silver,[7] or copper[8] complexes. As a complementary method of nucleophilic fluorination, electrophilic fluorination avoids the formation of constitutional isomers and side reactions caused by strong basicity of the nucleophilic fluoride. However, drawbacks include the high cost and poor atom economy of most electrophilic reagents, and potential side reaction between electrophilic fluorinating reagents and nucleophilic functional groups such as amines.

Figure 2. Electrophilic fluorine (F^+) reagents



Summary

Transition metal-mediated and -catalyzed fluorination provides access to various substituted arenes in the presence of many functionalities. However, current methods still lack practicality and cost efficiency for general use in large-scale manufacturing. Future research in fluorination chemistry will need to focus on selective arene fluorination using readily available and inexpensive substrates, fluorinating reagents, and catalysts.

Reference

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