Synthesis of [^{18}F]-Aryl fluoride tracers using Pd(IV)-based electrophilic fluorination: critical design considerations

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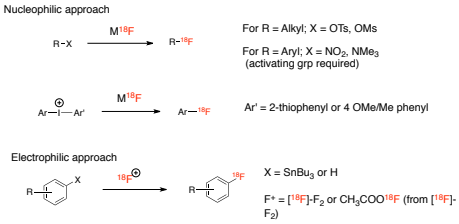
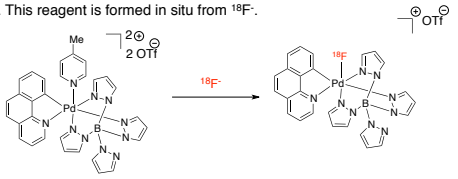
Introduction

Synthesis of ^{18}F compounds is typically accomplished either via S_n2 type nucleophilic substitution chemistry or by using electrophilic fluorination. These methods are reviewed in the schemes below:



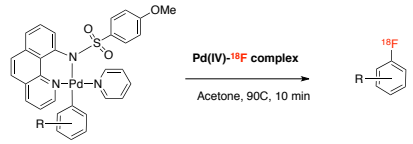
Though widely used and useful there remains a need for new fluorination methods using ^{18}F.

Recently a new Pd based electrophilic fluorination method[1] that uses Pd(IV)-^{18}F as the electrophilic fluorine source was described by Ritter et. al. This reagent is formed in situ from ^{18}F$^-$.



Pd(IV)-Picoline complex **Pd(IV)-^{18}F complex**

When treated with a Pd(II)Aryl complex such as the one shown below, Ar-^{18}F compounds can be formed that are typically difficult to make via nucleophilic or electrophilic fluorination:

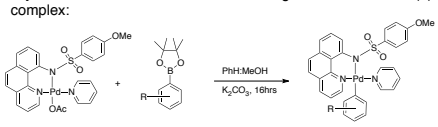


This poster will outline the scope of this new transformation including structural limitations and its application towards synthesis of new ^{18}F-Aryl compounds.

Synthesis of Pd Complexes

Pd(II)Aryl Complex

Synthesis of Pd(II)Aryl complexes is as shown below. A bench top transmetallation reaction between the Pd(II)Acetate complex and Aryl boronate ester under mild conditions gives the desired Pd(II)Aryl complex:

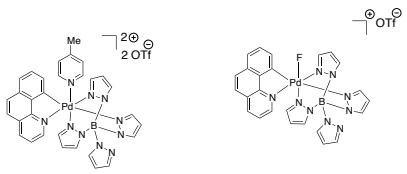


Pd(II)OAc complex **Arylboronate** **Pd(II)Ar Complex**

The synthesis of the **Pd(II)OAc** complex in turn can be accomplished by a 4 step sequence from commercially available reagents. All steps are high yielding and do not require a glove box.

Pd(IV)Picoline and Pd(IV)-F complex

The synthesis of Pd(IV)Picoline complex is accomplished from commercially available reagents via a 6 step sequence but does requires a glove box as it is air & moisture sensitive. The Pd(IV)F complex is made in one step from Pd(IV)Picoline complex.



Pd(IV)-Picoline complex **Pd(IV)-F complex**

Air & moisture sensitive; Handling in N_2 atmosphere necessary

Air and moisture stable

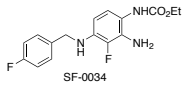
Structural design features

The table below shows the functional group tolerance for this transformation. While a number of functional groups are tolerated, basic amines are problematic.

Tolerated	Not Tolerated
Boc protected amines	Basic amines
Furans	Thiols, Thioethers
Electron rich aromatics	Unprotected protic functional groups
Ketones	*Ortho* substitution
Amides	
Cyclopropanes & Ethers	

Application of Pd(IV) electrophilic fluorination: Synthesis of [^{18}F]-Fluoroezogabine, SF0034, a KCNQ2/3 channel opener

SF0034 or Fluoroezogabine is a internally discovered KCNQ 2/3 channel opener, for the treatment of epilepsy .



SF0034 has a very favorable pharmacological profile compared to the currently approved drug, Ezogabine (Potiga, ; Valeant Pharma/ GlaxoSmithKline):

- >5 fold more potentiation vs. Ezogabine in a patch clamp assay
- Negative Ames test
- >4 higher IC_{50} values for hERG inhibition vs. Ezogabine
- Increased hepatic clearance vs. Ezogabine
- ED_{50} >3 lower than Ezogabine in a in vivo efficacy study (anti convulsant activity)
- Better therapeutic index vs. Ezogabine in mice

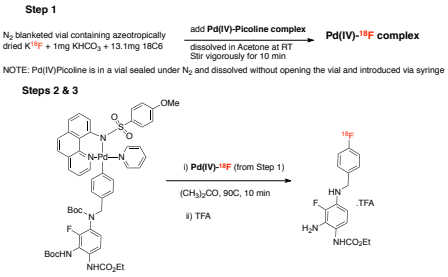
SF0034 therefore has the potential to be a next generation anti-epileptic drug.

In an effort to understand this drug better, we have synthesized the corresponding ^{18}F analog, using the electrophilic Pd technology for biological studies.

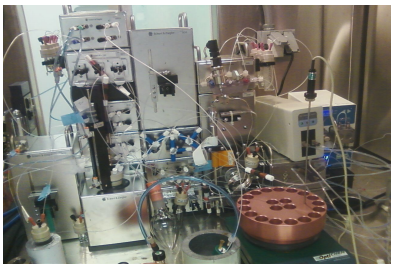
Synthesis of [^{18}F]-SF0034: From bench scale to large scale

^{19}F-SF0034 was first synthesized from the corresponding Pd(II) Aryl precursor directly using Pd(IV)F to understand how this reaction will work on an ^{18}F scale. Yields of 40% (NMR) were achieved for this transformation.

^{18}F-SF0034 was then synthesized on the bench scale using 0.5-1 mCi ^{18}F via a three step sequence. Radio-TLC conversions of 37% were observed for this transformation.



After successful bench scale synthesis, the process was transferred on to two radiosynthesis modules (Explora RN & Eckert & Ziegler). 1-2 mCi of ^{18}F-SF0034 has been successfully made on these modules post HPLC purification and further optimization is ongoing for imaging studies



E&Z radiosynthesis module used for Pd chemistry

Conclusions

Pd(IV) based electrophilic fluorination is a powerful new transformation that is applicable for synthesis of both ^{19}F & ^{18}F compounds. It extends the scope of existing electrophilic fluorination methods by allowing the synthesis of previously difficult ^{18}F aryl fluorides. However, the presence of certain functional groups as well as the synthesis of Pd(II)/Pd(IV) starting materials make this chemistry challenging to implement.

At SciFluor, we are further developing this transformation as exemplified by the successful synthesis of ^{18}F-SF0034 using this technology. Several other ^{18}F aryl compounds are also being developed using this technology.

References:

1: Lee, E. *et al., Science* **334,** 639 (2011)

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