C-F Bond Formation Mediated by High-Valent Palladium

Nitya Sai Reddy Satyavolu Literature Seminar October 14, 2014

Introduction:

The carbon fluorine bond plays an integral role in pharmaceuticals[1], materials (teflon), perfluorinated solvents and tracers for positron emission tomography (PET).[2] Fluorine when present in organic molecules uniquely affects their properties through strong polar interactions owing to the atom's high electronegativity and small size. Despite the importance of this bond, the installation of fluorine into complex organic molecules has remained a challenging task. During the past few years, chemists have developed new methods to incorporate fluorine into organic molecules by making carbon–fluorine (C–F) bonds on both aromatic rings and aliphatic chains.[2]

Why High-Valent Palladium for C-F bond formation?:

Palladium catalyzed cross coupling reactions have become an indispensable part of organic synthesis in forming carbon–carbon or carbon-heteroatom bonds. The Pd^0 and Pd^{II} intermediates involved in these catalytic cycles have been well characterized. This has led to the domination of low-valent palladium chemistry for many years.[3] The most important step in forming a carbon halogen bond is reductive elimination from the metal centre and it is known that this process is thermodynamically unfavorable and kinetically slow from most Pd^{II} complexes.[4] Over the past decade the reactivity of Pd^{III} and Pd^{IV} intermediates has increasingly been recognized and exploited in catalysis. Preliminary studies involving these intermediates were reported by Sanford[5] and Ritter[6]. Ease of reductive elimination from these high oxidation state Pd complexes to form carbon-halogen (C–X) bond makes them promising candidates for the C–F bond formation. High-valent palladium mediated incorporation of fluorine into complex aromatic organic molecules has seen several important advancements.

Formation of the Ar-F bond:

Sanford and coworkers first demonstrated the formation of aromatic C–F bonds under oxidizing conditions, using electrophilic fluorinating reagents such as Selectfluor (Figure 1).[7] They proposed the formation of Pd^{IV} as an intermediate after the oxidation of a Pd^{II} complex. They, however, did not show any evidence of such an intermediate. Moreover only the carbon-hydrogen bonds proximal to the pyridine directing group were fluorinated.

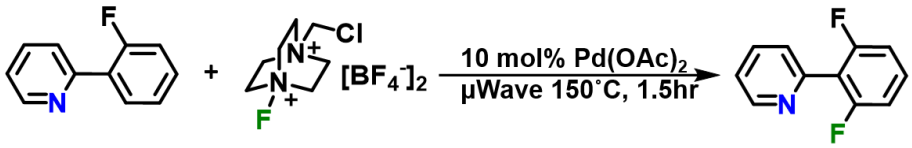

Figure 1: Schematic representing the formation of *ortho*-fluorinated aromatic product under oxidizing conditions.

Soon after Ritter and coworkers established a reaction sequence to convert a boronic acid into the corresponding arylfluoride. Pyridyl-sulfonamide ligands served as ancillary ligands to

support arylpalladium complexes (formed after the transmetalation reaction of the arylboronic acid) that subsequently affords arylfluorides regiospecifically upon treatment with Selectfluor.[8] Further studies on similar but more stable complexes revealed that the pyridyl-sulfonamide ligand plays a crucial role for facile and efficient C–F bond formation. The ability of this ligand to function as a bidentate or tridentate coordinating ligand during oxidation and reductive elimination may be the reason for facile C–F bond formation (Figure2).[9]

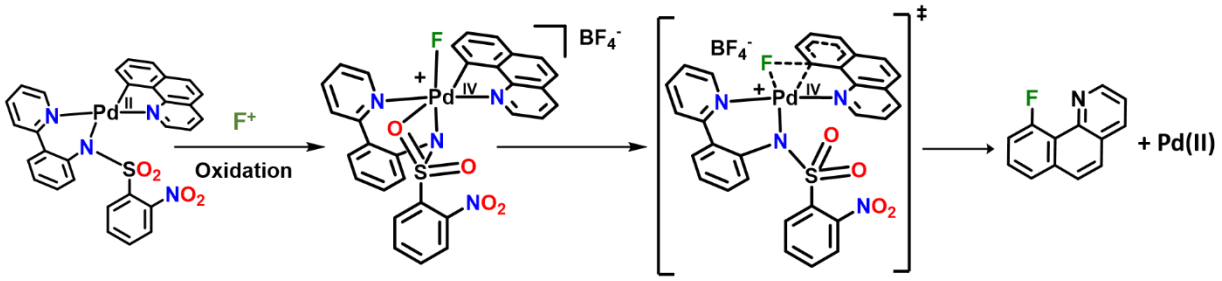

Figure 2: Proposed mechanism for the reductive elimination of C-F bond

Late Stage Fluorination:

Applying the above mentioned chemistry to radiolabel complex organic molecules with ^{18}F would be a useful step in synthesizing PET contrast agents. Using an $^{18}F^{+}$ source would allow the conversion of Pd^{II} to Pd^{IV} and would reductively eliminate the desired product from the high oxidation complex. However almost all the $^{18}F^{+}$ reagents are derived from fluorine gas and $^{18}F[F_2]$ which has low specific activity and is difficult to handle when compared to the $^{18}F^{-}$. Another major challenge is the short half-life time of ^{18}F (110mins). The installation of ^{18}F into a molecule thus requires that the C–F bond formation occur at a late stage in the synthesis to avoid unproductive radioactive decay before injection *in vivo*. In 2011 Ritter and coworkers designed a Pd^{IV} complex that can be synthesized from $^{18}F^{-}$ and can subsequently transfer its fluorine content in an electrophilic fluorination reaction.[10] The transferred fluorine converts a Pd^{II} complex to Pd^{IV} complex and reductively eliminates the ^{18}F fluorinated product at a late stage. The same group also demonstrated that the Pd^{IV} electrophilic fluorination agent can also adopt substrates other than Pd^{II} complexes. Aryl silver complexes and organic molecules with activated double bonds were successfully fluorinated with this reagent.[11]

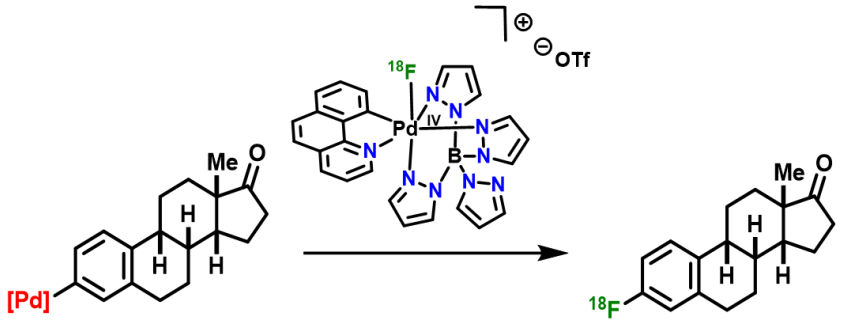

Figure3: Late stage fluorination of deoxyestrone by a Pd^{IV} complex

Conclusions:

High-valent palladium chemistry has a bright and rapidly expanding future with respect to C–F bond formation.[12] Recent years have also seen the formation of sp^3-C–F bonds[13] as well as operationally simple and multigram-scale synthesis of Ar–F bonds[14] via high oxidation state intermediates. It is critical to increase our understanding of catalytic processes involving high-valent palladium intermediates. The ability to control the bond-forming event is of importance in achieving efficient catalytic transformations. Understanding the chemistry behind these high-valent intermediates has indeed allowed scientists to design complexes that have uncovered important applications such as late stage fluorination for PET.

References:

1. Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.
2. Furuya, T.; Kamlet, A. S.; Ritter T. *Nature* **2011**, *473*, 470-477.
3. Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177-185.
4. Roy, A. H.; Hartwig, J. *J. Am. Chem. Soc.* **2003**, *125*, 13944–13945.
5. Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 15142-15143.
6. Powers, D. C.; Ritter, T. *Nature Chem.* **2009**, 1, 302-309.
7. Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134-7135.
8. Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060-10061.
9. Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard III, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793-3807.
10. Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker; J. M.; Ritter, T. *Science* **2011**, *334*, 639-642.
11. Brandt, J. R.; Lee, E.; Boursalian, G.; Ritter, T. *Chem. Sci.* **2014**, *5*, 169-179.
12. Lyons, T. W.; Sanford, M. S.; *Chem. Soc. Rev*. **2010**, *39*, 712-733**.**
13. Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3414–3417.
14. Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012-14015.