

RECENT ADVANCEMENT IN SILVER MEDIATED C-F BOND FORMATION

Reported by Jiabao Zhang

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Introduction

Carbon-fluorine bond plays an important role in pharmaceuticals, agrochemicals, materials^{1,2}. Fluorine uniquely affects the properties of organic molecules through its high electronegativity (4.0 in Pauling electronegativity) and small size (1.33 Å). The introduction of fluorine into organic compounds can make them more bioavailable, lipophilic and metabolically stable, and can increase the strength of a compound's interactions with a target protein. Approximately 20% of all pharmaceuticals contain fluorine, including drugs such as Lipitor, Lexapro and Prozac. Therefore, it is not a surprise that chemists have given special attention to the introduction of fluorine to molecules^{1,3}.

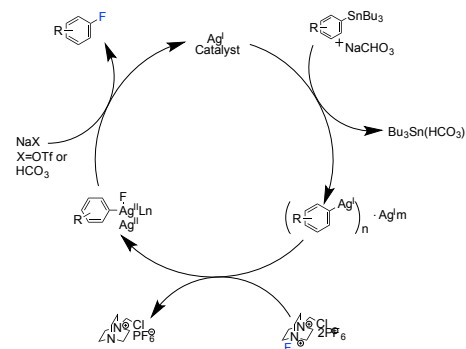
Challenge associated with C-F bond formation

The challenge in C-F bond formation derives from the fact the fluorine is the most electronegative element and its small ionic radius. The fluoride is typically only weak nucleophile in the presence of hydrogen-bond donor due to fluoride's ability to form strong hydrogen bond and therefore limits the access to the C-F bonds via nucleophilic substitution. While when hydrogen bond donors are excluded, fluoride does become a better nucleophile, but the basicity arising from this can also lead to undesired product.

Conventional fluorination methods generally require harsh condition and consequently have limited substrate scope. However, if we think about the fact that most C-F bond forming reaction are thermodynamically favored because of the strong C-F bond energy, in fact, no other element forms stronger single bond to carbon than fluorine does, then the question become how to overcome the kinetic barrier, which can be addressed by using transition metal as a catalyst to lower the barrier. The most challenging step in transition metal catalyzed C-F bond formation is reductive elimination, in which step the fluorine expels the metal it originally bonds, and forms a new C-F bond. The strong metal-fluorine bond makes this step difficult.

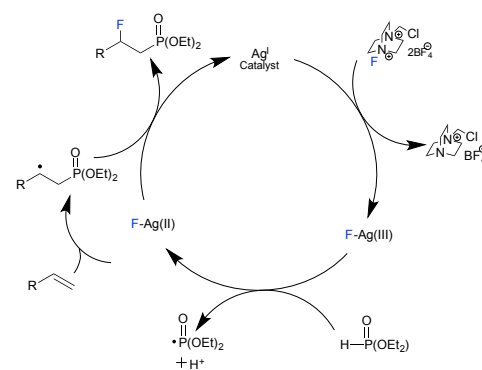
Silver mediated C-F bond formation

One way to address this issue is to rationally design a way to promote reductive elimination and silver aggregates can be utilized as a tool. Metal aggregates are known to enable transformations inaccessible to single metal⁴. Forming a Ag aggregate can create a positive charge near the metal center where reductive elimination happens, making the metal center more electro-deficient and therefore promotes the reductive elimination, and this has been shown by Ritter group when they use silver (I) as the catalyst. Their proposed mechanism is shown on the right⁵.



Scheme 1. Proposed mechanism for Ag catalyzed fluorination.

Another way to facilitate the formation of C-F bond is via single electron process. In this process, the single electron transfer will generate radicals which can easily catch the fluorine and then forms the desired bond. This strategy has been shown extremely successful by Li group in the fluorination of unactivated alkenes. And these reactions can be done in aqueous media. The proposed mechanism is shown on the right⁶.



Scheme 2. Proposed mechanism for Ag catalyzed phosphonofluorination.

Summary

The C-F bonds formation is important in drug discovery and transition metal catalyzed C-F bonds formation has enabled chemists to the access of fluorination at both aromatic rings and aliphatic chains. Silver, by its ability to form aggregates and transfer single electron, has been successfully utilized to achieve the desired C-F bonds formation. And these two features of silver should be studied more for future development of new methods.

Reference

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