**Nucleophilic Fluoride as a Source for C(sp3-H) Fluorination**

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**Introduction**

Fluorine has been used in medicinal chemistry for decades now with nearly 300 fluorine containing FDA approved drugs last reported in 2022 (1). This begs the question, why is fluorine so prevalent in medicinal chemistry. At a quick glance in the fluorine literature, it can be seen that installing fluorine onto a bio-active molecule can influence potency, cell permeability, clearance, and metabolic stability. These effects are seen by even the addition of a single fluorine atom onto a small molecule drug due to its ability to impart conformational biases, pKa changes, act as a hydrogen bond acceptor, and due to the strength of the carbon fluorine bond (2). With the growing importance of the carbon fluorine bond in medicinal chemistry there has been an insurgence in method development to allow ease of access to fluorinated small molecules. In this paper I will focus on recent developments in the field of nucleophilic fluoride as a source for C(sp3-H) fluorination. The field is underexplored compared to electrophilic fluorine chemistry, but its use could allow for orthogonal functional group compatibility, cheaper source of fluorine, and is better suited for synthesis of 18F labeled Positron-Emission-Tomography (PET) tracers for in vivo imaging (3).

**Sp3 C-H Fluorination Catalyzed by Manganese Porphyrin**

In 2012 the Groves lab developed the first method utilizing nucleophilic fluoride as a source for unactivated sp3 C-H fluorination (4). The Mnv species generates a carbon centered radical followed by fluorine atom transfer from the difluorinated (Mn(TMP)F2). Using a bulky manganese catalyst biased C-H activation to occur at more readily available unhindered methylene positions. This method was later expanded on in 2018 to include the use of [18F]-F- for PET tracer synthesis (4). The catalyst was changed to MnIII(TPFPP)OTs a more electron deficient manganese catalyst which was found to impart faster reaction times of 10 minutes which is desirable for 18F labeling due to a short half-life time of 109 minutes (2).

**Scheme 1. Sp3 C-H fluorination catalyzed by Mn(TMP)Cl**

Groves and coworkers then published a paper on benzylic sp3 C-H 18F fluorination catalyzed by Mn(salen)OTs in 2014 (5). The catalyst was originally Mn(salen)Cl (Jacobsen catalyst), but the Chloride was exchanged for a tosylate group as to allow for quicker exchange with the 18F- ligand to impart quicker reaction times. Optimization of reaction times led to 65% radio chemical conversion of their test substrate in 10 minutes. This reaction was tested on several substrates including bioactive molecules showing great selectivity for the benzylic position and with conditions mild enough to tolerate electrophilic function groups.

**Doyle Lab Pd-Catalyzed Allylic C-H Fluorination**

Doyle and coworkers in 2013 developed a method for fluorination of allylic C-H bonds, specifically branched over linear selectivity (6). The method took inspiration from the White group paper published in 2004 that showed with the addition of a Pd-sulfoxide catalyst and benzoquinone the nucleophilic acetate would selectively acetylate the branched position (7). This selectivity was imparted by the π-acidity of the benzoquinone which could coordinate with the Pd and generate a more electron deficient substrate. The system showed great regioselectivity for allylic over benzylic and propargylic and was mild enough to work with various electrophilic function groups. The method did however have limitation in that yields were diminished with internal olefins, β-branched olefins, and conjugated systems.



**Scheme 2. Doyle Lab Pd-Catalyzed Allylic C-H Fluorination**

**Doyle Lab HAT Followed by Radical Polar Crossover for Benzylic Fluorination**

Hydrogen atom transfer to generate a carbon centered radical intermediate followed by functionalization is generally mediated by electrophilic reagents, but it would be ideal if nucleophilic reagents could also be used for functionalization. In 2021 the Doyle group developed a method that would utilize an Iridium photocatalyst to do a single electron transfer (SET) to a phthalimide ester ultimately generating a methyl radical that would undergo HAT with a benzylic C-H bond (8). The iridium photocatalyst then oxidizes the benzylic carbon center radical to generate a carbocation that can be trapped by various nucleophiles, including fluoride. The method has yet to be extended to the use of [18F]-F- fluorination but showed great success in their 2020 paper that utilized pre-functionalized substrates with phthalimide esters (9).



**Scheme 3. Methyl radical HAT followed by oxidation to a carbocation for nucleophilic trapping.**

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