Single C-F Bond Functionalization of Aryl Trifluoromethyl Groups

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Introduction

Incorporation of fluorine to small molecule drug candidates has become increasingly important in the field of medicinal chemistry. Due to its high electronegativity, carbon-fluorine bonds are highly polarizable, and considerably stronger than carbon-hydrogen bonds. These characteristics are exploited by medicinal chemists to adjust the lipophilicity, pKa, and structural conformation of molecules through incorporation of fluorine[1]. Furthermore, replacement of oxidatively labile carbon-hydrogen bonds with carbon-fluorine bonds can reduce oxidative metabolism in the body, increasing potency and bioavailability[2]. Recently, there has been interest in using aryl trifluoromethyl groups as coupling partners to construct functionalized a,a-difluorobenzylic motifs through monoselective C-F bond functionalization. This class of methodology provides medicinal chemists a facile way to install fluorine while also building molecular complexity, making them an important class of reactions.

Traditional Benzylic Fluorine Installation

Traditional installation of fluorine at a benzylic position proceeds through nucleophilic deoxyfluorination, where a ketone or alcohol is replaced with fluorine[2]. These methods rely on pre-existing functionality and generally are not amenable for complex molecules because of site selectivity issues. Electrophilic fluorinating agents have also seen mild success for constructing benzylic carbon-fluorine bonds[3]. However, these methods usually require excess fluorinating agent and suffer from selectivity issues if multiple benzylic sites are present. Transition metal mediated cross-coupling reactions have also been developed by numerous groups to construct a,a-difluorobenzylic functionality[4]. Unfortunately, these methods require highly specific or synthetically demanding coupling partners, which make them unsuited for effective drug diversification.

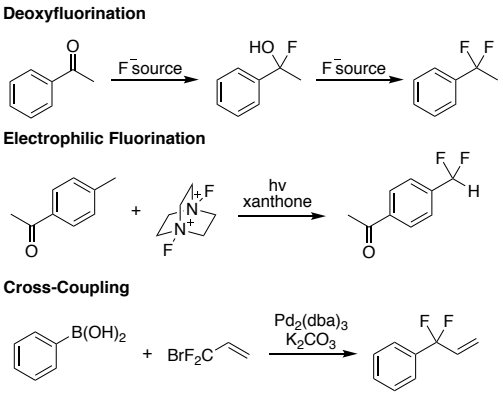

Figure 1. Traditional a,a-difluorobenzylic installation methods

Defluoroalkylation

Photoredox catalysis has been demonstrated by Jui to be effective for

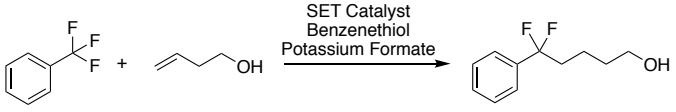

Figure 2. Photoredox catalyzed defluoroalkylation

coupling a variety of terminal olefins with aryl trifluoromethyl groups to synthesize alkylated difulorinated compounds[5]. The system relies on a dual catalytic cycle where single electron transfer (SET) and hydrogen atom transfer (HAT) are used. Impressively, electron rich and poor aryl trifluoromethyl groups can be used as coupling partners, including heteroaromatic trifluoromethyl arene compounds. The methodology can also be utilized to synthesize hydrodefluorinated products, which are important bioisosteres for alcohols and thiols.

Defluoroallylation

Fluorine's unique interactions with silicon were utilized by Bandar to perform a similar transformation as Jui. His methodology allows for the installation of a terminal olefin, which he demonstrated could be further diversified to a wide range of more complex products[6]. This system does not require a transition metal and can be performed with only a fluoride source and a crown ether. Chemoselectivity in molecules with multiple aryl trifluoromethyl groups was also observed, which was attributed to the redox potential of the aromatic rings.

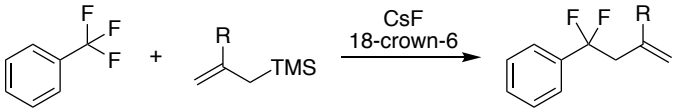

Figure 3. Fluoride catalyzed defluoroallylation

Frustrated-Lewis Pair/Nucleophilic Substitution

Most recently, frustrated lewis pair interactions have been used to functionalize aryl trifluoromethyl groups with a wide variety of nucleophiles[7]. Aryl trifluoromethyl groups with both electron rich and electron poor substituents can be used, and an impressive scope of nucleophiles was demonstrated. Furthermore, trifluoromethoxy groups were also shown to be effective coupling partners, providing further methods for constructing a variety of fluorinated molecules.

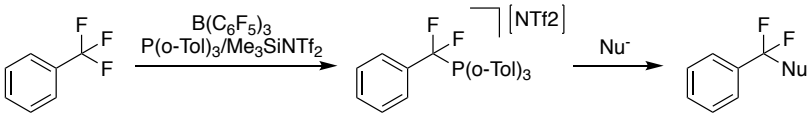

Figure 4. Frustrated Lewis Pair catalysis for nucleophilic functionalization

References

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