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Digest paper

Site selectivities in fluorination

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ABSTRACT

In the synthesis of bio-active compounds, fluorinated compounds play a prominent role. However, the site-selective fluorination of organic molecules is often challenging, because activation of a reaction site using a fluorinating reagent can be difficult in a substrate possessing many functional groups. This digest introduces recent examples of site-selective fluorination reactions.

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Introduction

Organic molecules containing one or more fluorine atoms are undoubtedly useful and important. According to the literature,[1] approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain a fluorine atom. For example, the antidepressant fluoxetine (Prozac),[2] the cholesterol-lowering drug atorvastatin (Lipitor),[3] and the antibacterial ciprofloxacin (Ciprobay)[4] are well-known fluorinated pharmaceuticals.

To synthesize complex fluorinated molecules, the development of highly selective fluorination reactions is required. The main fluorination methods are electrophilic and nucleophilic reactions,[5,6] but more recently reports of radical fluorination reactions have emerged[7–9] (Scheme 1). Judging from those three reaction patterns, the fundamental theory of fluorinations has already been established, and there are already many well-established fluorinating reagents e.g. SelectFluor[10] and DAST (diethylaminosulfur trifluoride).[11]

Although various types of fluorination reactions including C—H fluorination and enantioselective reactions with designer fluorinating reagents have been reported,[10–12] the core issue is to develop more efficient reactions for C—F bond formation addressing the problem of site selectivity with a substrate possessing multiple reaction sites (Scheme 2). In this digest, we attempt to provide an overview of selected recent reports of site-selective fluorination,

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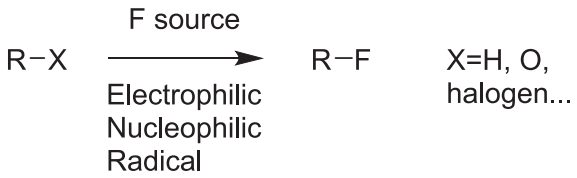


Scheme 1. Fluorination reaction.

together with our insights. We have decided to focus on fluorination reactions which lead to incorporation of a single fluorine atom alone, and not to include related transformations such as fluorofunctionalization where both a fluorine atom and another element are introduced simultaneously. This digest is not intended to be a comprehensive review of recent developments, but simply to introduce a selection of key methods for achieving site selective fluorination reactions.

Site-selective fluorination of hydroxy groups

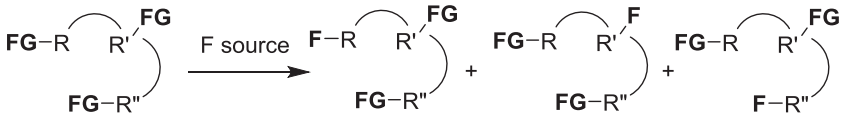
The direct substitution of a hydroxy group with a fluorine atom provides aryl- or alkyl fluorides from phenols or alcohols, a so-called deoxyfluorination reaction. Ritter's group has invented a new deoxyfluorinating reagent, PhenoFluor (**1**).[13] This reagent enables direct substitution of the hydroxy group of both electron-poor and –rich phenols in the presence of CsF (Scheme 3). Although the reaction conditions are not mild (reaction temperature 110 °C), site-selective fluorination was observed when **2** possessing two hydroxy groups was used as a substrate. Fluorine substitution at the hydroxy *para* to the carbonyl in **2** is much faster than that of the *ortho*-hydroxy, probably due to hydrogen bonding between the *ortho*-OH and the ester group.[14]

They also investigated the structure of the intermediate in this reaction. When *para*-anisol (**4**) reacted with **1**, a condensation reaction took place to give salt **5** in 91% yield (Scheme 4). Salt **5** reacted with CsF to produce the fluoride **6** in 67% yield. According to the X-ray structure of **5**, there is a hydrogen bond between one hydrogen atom on the heterocycle and the bifluoride counterion. They speculated that this hydrogen bonding increases the reactivity for fluorinations.

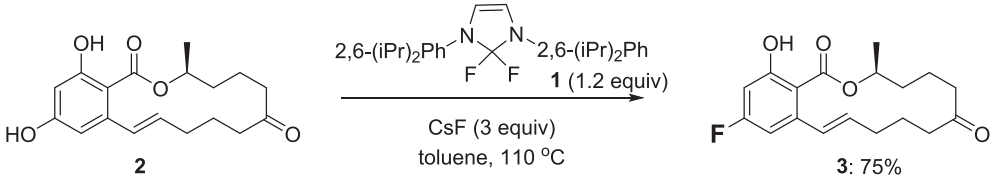
A disadvantage of this deoxyfluorination reaction is the use of a stoichiometric amount of PhenoFluor, which generates a lot of waste. However, the operationally simple protocol and high site-selectivity outweighs this drawback. Ritter's group further demonstrated the advantage of PhenoFluor methodology in late-stage deoxyfluorination of alcohols.[14a] In bio-active molecules such as oligomycin A, ivermectin B_{1a} and everolimus, alcohol groups are located at many positions. Therefore, the late-stage fluorination of such molecules is very difficult without loss of untargeted alcohol groups. The reaction of alcohol, **1**, amine and KF enabled accurate site-selective fluorination (Scheme 5). Under the conditions, PhenoFluor **1** can discriminate between different carbinols, despite the presence of multi hydroxy groups in the compounds shown in Scheme 5. Ritter described the selectivity as follows: "(1) primary alcohols are selectively deoxyfluorinated in the presence of secondary and tertiary alcohols. (2) secondary alcohols react significantly slower or not at all when they are β,β′-dibranched, unless the secondary alcohol is allylic. (3) tertiary alcohols do not react, unless they are allylic. (4) hydroxy groups engaged in hydrogen bonding are not reactive"(cited from Ref. 14a). Hu's group also reported site-selective deoxyfluorinations by using 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors).[14b]

Site-selective fluorination of alkyl halides

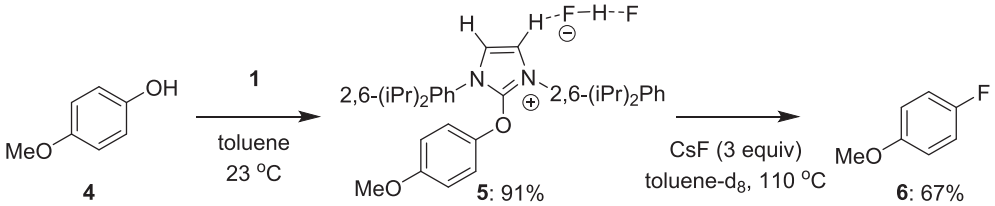
Primary- and secondary-alkyl fluorides can be accessed by conventional nucleophilic fluorination reactions, such as the Finkelstein reaction (Scheme 6).[5,15] Alkyl chlorides, bromides, iodides or triflates can react with fluoride ions to produce alkyl fluorides via nucleophilic substitution. The Finkelstein reaction using an alkali metal fluoride is very convenient and economical, but a major drawback of the reaction is its sensitivity to water. Fluoride ions have a strong tendency to form hydrogen bonds with water



Scheme 2. Fluorination of a substrate possessing multiple reaction sites.



Scheme 3. Deoxyfluorination with PhenoFluor.



Scheme 4. The key intermediate.