Current Trends in Practical Fluorination Chemistry

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Introduction
This white paper briefly discusses some of the recent advances in chemical methods used to install fluorine and fluorinated functional groups, with special focus on practical methods related to fluorinated arene synthesis. The role of commercially available reagents in fluorinated arene synthesis is also described in this paper.

Current Trends in Practical Fluorination Chemistry
The importance of fluorinated organic molecules and in particular fluorinated arenes, has become well-appreciated in modern society, in applications such as pharmaceuticals, agrochemicals, and \( ^{18} \text{F} \) positron emission tomography (PET).\(^1\)-\(^3\) Developing practical chemistry for the synthesis of functionalized and structurally complex fluorinated small molecules remains challenging; however, modern fluorination research has led to the development of new methods and reagents that provide greatly improved access to fluorinated compounds.\(^4\)-\(^7\) In this piece, we briefly highlight some of the recent chemical advances that allow for the installation of fluorine and fluorinated functional groups. Here we focus primarily on practical developments in the field pertaining to fluorinated arene synthesis, including commercially available reagents; we therefore exclude a number of other fundamentally important developments such as direct C–H fluorination reactions that have not yet achieved practicality for broad and routine use, as well as fluorination methods that have been developed specifically for \(^{18} \text{F} \) PET applications. We refer the interested reader to several recent reviews that cover the field in greater depth.\(^5\)-\(^8\)

Nucleophilic fluoride is the most practical and economical source of fluorine and as a result significant effort has been devoted to developing nucleophilic arene fluorination reactions. A key challenge, however, has been the reactivity of fluoride anion: fluoride has a propensity to form strong hydrogen bonds, which diminishes its nucleophilicity;\(^9\),\(^10\) but, in the absence of hydrogen bond donors, “naked” fluoride anion is strongly basic, which can lead to undesired side reactions and a lack of tolerance to protic functional groups.\(^11\),\(^12\) Recent work has been able to overcome these challenges, through the development of new reagents as well as metal-mediated and -catalyzed nucleophilic fluorination reactions (Figure 1).

In our opinion, one of the most practical methods for nucleophilic arene fluorination is the deoxyfluorination of phenols using the commercially available PhenoFluorMix™ reagent.\(^13\)-\(^15\) A variety of electron-rich and -poor (hetero)aryl fluorides can be synthesized from the corresponding phenol starting material using this method.

![Figure 1: Examples of modern reagents and methods for nucleophilic arene fluorination.](image-url)
The use of transition metals as mediators or catalysts has also been a successful strategy to tame the reactivity of fluoride anion and allow for selective fluorination reactions. Along with phenols, aryl halides and pseudo-halides are attractive and readily-available substrates, and allow for fluorination via a cross-coupling approach. A key breakthrough in this area of research was the development of palladium-catalyzed fluorination of aryl (pseudo)halides, using simple fluoride salts such as CsF, KF, and AgF.\(^{16}\) Aryl triflates, iodides, and bromides can be fluorinated and studies on the effect of the supporting phosphine ligand led to efficient conditions for fluorination of heterocyclic aryl bromides.\(^{17,18}\) While this method is among the most promising general strategies for nucleophilic fluorination, a key remaining challenge is that the basicity of the dried fluoride salts can lead to side reactions that produce mixtures of constitutional isomers in some cases.

Aryl iodides can also undergo nucleophilic fluorination using super-stoichiometric Cu(I) reagents and AgF as the fluoride source.\(^{19}\) This method is generally effective for electron-rich and -poor arenes as well as sterically hindered substrates, but the formation of hydrodehalogenated side products renders purification of the aryl fluoride products challenging. Aryl bromide substrates can also be fluorinated using catalytic Cu(I) and AgF, but this method is limited to substrates that feature a coordinating directing group.\(^{20}\) A more general and selective copper-catalyzed nucleophilic fluorination reaction was reported for unsymmetrical diaryliodonium salts using KF, which allows for synthesis of aryl as well as some heteroaryl fluorides.\(^{21}\) While this reaction is attractive due to the use of catalytic amounts of copper and significantly milder reaction conditions than for aryl halide substrates (60 °C vs. ≥120 °C), a drawback is the need for synthesis of the functionalized diaryliodonium substrates.

The development of bench-stable fluorination reagents — including Selectfluor\textsuperscript{®}, N-fluoropyridinium salts, and N-fluorobenzenesulfonimide (NFBS or NFSI) — has enabled the fluorination of aryl nucleophiles via an electrophilic approach,\(^{22}\) which is complimentary to nucleophilic fluorination and avoids many of the problems of fluoride anion (Figure 2). However, the aryl nucleophile substrates (typically aryl–metal reagents) are not as readily available as aryl halides and phenols. Most of the practical electrophilic arene fluorination reactions reported to date are also mediated or catalyzed by late transition metals.

The most effective electrophilic fluorination reaction currently available for late-stage fluorination of complex small molecules uses arylstannane substrates, Selectfluor\textsuperscript{®} reagent, and catalytic Ag\textsubscript{2}O.\(^{23,24}\) While the functional group tolerance of the silver-catalyzed reaction has not been demonstrated for any other metal-mediated or -catalyzed fluorination reaction, the preparation and use of toxic arylstannane substrates is undesirable. Arylboronic acid derivatives can also undergo electrophilic fluorination, using Selectfluor\textsuperscript{®} and a terpyridyl palladium catalyst.\(^{25}\) The palladium-catalyzed reaction was shown to proceed via an unusual outer-sphere radical fluorination pathway, contrary to a more typical carbon–fluorine reductive elimination mechanism. A drawback of the palladium-catalyzed reaction is that mixtures of constitutional isomers can be produced for some substrates with electron-withdrawing substituents, and heterocycles are not effectively fluorinated. Both arylstannanes and arylboronic acid derivatives can also be fluorinated using N-fluoropyridinium salts and simple copper salts;\(^{26,27}\) however, these reactions require super-stoichiometric copper and typically result in the production of side product resulting from protodemetallation, which complicates product purification.

Modern methods for the electrophilic fluorination of Grignard reagents have been developed; while the basicity and nucleophilicity of Grignard reagents limits substrate scope, an attractive feature is the ability to fluorinate heterocycles, which is a challenging class of substrate for many fluorination reactions.\(^{28-31}\) A practical C–H fluorination of pyridines and diazenes using AgF\textsubscript{2} was reported, in which a radical fluorine-atom transfer pathway was proposed via coordination of the pyridine substrate to AgF\textsubscript{2}.\(^{32}\)
Whereas the products of most C–H fluorination reactions are difficult to isolate, due to similar polarities of the starting materials and fluorinated products, fluorination affects the basicity of the pyridine sufficiently that purification can be accomplished by standard silica gel chromatography.

In addition to aryl fluoride synthesis, functionalization of arenes with fluorinated functional groups has attracted significant interest in recent years. Here, we highlight two of the more important fluorinated arene derivatives: trifluoromethyl arenes and difluoromethyl arenes (Figure 3).

New practical methods and reagents for the synthesis of fluorinated aliphatic compounds have also been developed. While we do not attempt to be comprehensive here, we wish to highlight a few recent advances that we feel are poised for high-impact applications in the near future (Figure 4). Deoxyfluorination reagents for aliphatic alcohols have been widely used for decades, most notably DAST, and related S(IV) reagents including Deoxo-Fluor, XtalFluor, and Fluolead, but this class of reagents frequently suffers from handling issues and a lack of selectivity for fluorination versus competing elimination side reactions. The PhenoFluor™ reagent, originally developed for deoxyfluorination of phenols, has also proven effective for deoxyfluorination of complex aliphatic alcohol substrates. The sulfonyl fluoride-based reagent PyFluor, soon to be commercially available, also displays high selectivity for aliphatic deoxyfluorination and has additionally been demonstrated for 18F radiofluorination.
Synthetically useful metal-catalyzed reactions have also been developed for selective alkyl fluoride synthesis, including allylic fluorination$^{52,53}$ and stereoselective epoxide opening reactions.$^{54-56}$ Decarboxylative fluorination of alkylcarboxylic acids has also been demonstrated as a promising strategy.$^{57,58}$ Remarkable C–H fluorination reactions of alkane substrates are beginning to emerge,$^{59-61}$ but such methods are not yet robust enough for routine synthetic use.

As shown here, key recent advances in fluorination methodology have been enabled by new reaction manifolds, including transition metal-mediated and -catalyzed reactions as well as selective and useful radical-based reactions. Additionally, the development of stable, easily-handled reagents for the installation of fluorine and fluorinated functional groups has been critical to the massive growth of fluorination chemistry in the past decade. We have not attempted to comprehensively review advances in fluorination chemistry in this piece, but rather to highlight practical developments that we feel showcase the huge strides fluorination chemistry has made in recent years and that point toward the kinds of future developments that can have a meaningful impact on the synthetic organic chemistry community.

**Professor Tobias Ritter**

Tobias was born in 1975 in Lübeck, Germany. He received his undergraduate education in Braunschweig, Germany, Bordeaux, France, Lausanne, Switzerland, and Stanford, US, and received a master of science from Braunschweig University in 1999. He has done undergraduate research with Professor Barry M. Trost at Stanford, obtained his PhD working with Professor Erick M. Carreira at ETH Zürich in 2004, and was a postdoc with Professor Robert H. Grubbs at Caltech. In 2006, Tobias was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard, promoted to Associate Professor in 2010 and Professor of Chemistry and Chemical Biology in 2012. In 2015, he accepted a director position at the Max-Planck Institute für Kohlenforschung.

**Michael G. Campbell**

Michael G. Campbell was born in 1986 in Pennsylvania and received his BSc in 2008 from Loyola University Maryland. He earned his PhD in 2014 from Harvard University, where he worked on the chemistry of palladium(III) complexes with Professor Tobias Ritter, including Pd-catalyzed fluorination. He is currently a postdoctoral fellow at the Massachusetts Institute of Technology with Professor Mircea Dincă. In July 2016, Michael will begin his independent career as an Assistant Professor in the Department of Chemistry at Barnard College, Columbia University.
References