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Late-Stage Fluorination: Fancy Novelty or Useful Tool?

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For over a century, fluorine chemistry was dominated by the use of fluorine gas, HF, and alkali-metal halides, and reaction conditions were typically harsh. Fluorine seemed to be forever either too reactive (F_2) or too unreactive (KF) to be used in selective, functional-group-tolerant transformations of even moderately complex small molecules. A number of key fundamental discoveries pertaining largely to fluorination reagents and transition-metal catalysis have allowed the field to break with a tradition of harsh reaction conditions. A few decades ago, the development of a small range of reagents, such as Selectfluor (F-TEDA, see Scheme 1), diethylaminosulfur trifluoride (DAST), *N*-fluoropyridinium salts, and $Et_3N{\cdot}HF$, enabled more selective fluorination chemistry.[1] Over the past decade, another wave of fluorination chemistry has mainly focused on the development of suitable methods for late-stage fluorination, that is, the chemo- and stereoselective fluorination of molecules with higher structural and functional complexity, which could not be achieved with conventional fluorination methods. To date, the relatively recent advances in late-stage fluorination have not yet had a substantial impact on the synthesis of bulk chemicals, ^{18}F positron emission tomography (PET) tracers, or materials. Their synthesis procedures are still dominated by classical fluorination methods. In this Essay, we attempt to provide an unbiased, but select evaluation of the recent advances in late-stage fluorination, and comment on the deficiencies of the current methods as well as their longer-term promise. We have decided to focus on carbon–fluorine bond-forming reactions and not to include related transformations, such as perfluoroalkylation, which have recently undergone a parallel and just as important development. This Essay does not provide a comprehensive review of the most recent developments, but rather aims to take the current pulse of the field through illustrating a few select but representative examples.

What permits us to claim substantial advances in the field of fluorination over the last ten years that go beyond the number of published research papers? Several fundamental discoveries in the field that provide a better fundamental understanding were made within the last few years.[2] For example, the first well-defined reductive elimination reaction to form C–F bonds was reported only in 2008.[3] A substantial part of the recent developments is based on transition-metal chemistry, which may explain why fluorination chemistry is experiencing a rapid development right now: Making C–F bonds with metals often proceeds by reductive elimination reactions, which typically have high free enthalpies of activation. In our opinion, three independent developments substantially contributed to the advent of late-stage fluorination: 1) the progress in effecting challenging reductive elimination reactions from mid-valent transition-metal complexes as pioneered, for example, by the Buchwald group, 2) the exploration of the more facile reductive elimination processes from high-valent transition-metal complexes as pioneered by the Sanford group, for example, and 3) the availability of new fluorination reagents, both nucleophilic and electrophilic, which enabled the development of practical, functional-group-tolerant reactions.[4] Contributions from several research groups have advanced the field of fluorination chemistry substantially over the recent past; we have chosen to summarize some of them in Scheme 1 rather than mentioning them separately as has already been done in recent reviews.[2a,k,5]

Fluorinated products find uses in many different areas of modern society as is highlighted at the beginning of most publications in the field. It is too early to tell which, if any, of the modern late-stage fluorination methods will have a substantial and measurable impact beyond the creation of new fundamental knowledge. It seems prudent, however, to evaluate whether the current shortcomings in the field with respect to their real-life applications are temporary or conceptual. It may be that not enough time has yet passed for modern late-stage fluorination reactions to have an impact on other disciplines, but a more nuanced analysis appears appropriate, especially if it results in the identification of promising research directions.

Even thoughtful analyses as to why C–F bond formation is so challenging rarely go beyond electronegativity arguments, rendering it likely that a lot of fundamental knowledge is still lacking. Carbon–fluorine reductive elimination is more challenging than any other reductive elimination between carbon and the other first-row elements with a partially filled p shell.[2a,c,g,3b,5d,6] The high electronegativity of fluorine results in strong metal–fluorine bonds owing to a strong polar contribution to the bond, and the associated σ-bond orbital is highly contracted and largely localized on the fluorine atom.[7]

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The transition state for reductive elimination requires electron reorganization, with electron density shifting away from the fluorine atom towards the forming C–F bond, which results in a high kinetic barrier even in systems where reductive elimination is thermodynamically highly favorable. The development of ligands tailored to facilitate the C–F bond-formation step as well as an improved understanding of how to access high-valent transition-metal intermediates has enabled a substantial reduction of the activation energy for C–F reductive elimination. Nonetheless, reductive elimination is still generally the rate-limiting step in metal-mediated C–F bond formation and thus dictates the selection of metals and ligands for a particular transformation. New insights into how the kinetic barrier could be further reduced, possibly through a better understanding of the bonding interactions as a function of the transition metal, its oxidation state, and the nature of the ancillary ligands, would enable to shift the focus of research towards the identification of appropriate starting materials and inexpensive reagents.

The selection of the ideal starting materials for a C–F bond-forming reaction defies a simple answer. Currently, functional-group-tolerant transformations frequently rely on starting materials disproportionately complex for the introduction of a simple monoatomic substituent: Starting from aryl metal species, such as those of tin or boron, leads to a transformation that displaces a heavy fragment, such as $SnBu_3$ or BOR_2, which is commonly accessed from the corresponding halide, by a single atom. The direct fluorination of carbon–halide bonds can suffer from a complicated purification of the final fluorinated compound if the reaction does not proceed to completion, unless purification by distillation is possible. Alcohols, phenols, and carboxylic acids are convenient starting materials in many respects, but suffer from a lack of general reactions to access them directly from C–H bonds. The direct fluorination of C–H bonds appears to be the obvious solution and would clearly be desirable for the synthesis of a number of fluorinated materials with various applications. However, compared to other C–H functionalization reactions, such as oxygenation reactions, fluorination poses a set of special challenges: The fluorinated reaction products often exhibit a similar reactivity to the starting materials, which can hamper selective monofunctionalization. Aryl fluorides, for example, are only marginally less electron-rich than the corresponding arenes, and a fluorine substituent provides almost no steric deactivation. If selective reactions can be achieved, the separation of the fluorinated products from the starting materials is often complicated by their similar physical properties. Therefore, C–H fluorination reactions that require excess starting material or do not proceed to complete conversion may not be as practical as they seem. Exceptions exist, however, such as the AgF_2 mediated fluorination of pyridines, in which the physical properties of the fluorinated product differ sufficiently from those of the starting material to permit facile isolation.[111,m] A good indication that a reaction meets certain criteria for practicality are yields that correspond to the purified, isolated material rather than yields determined by ^{19}F NMR spectroscopy. Given the current challenges for enabling direct transformations of C–H into C–F bonds, it may also be advisable to invest in research directed towards the better purification of fluorinated molecules and towards developing slightly more circuitous pathways for C–H to C–F transformations, for example, the formation of C–OH moieties (or another polar functional group) from a C–H bond, coupled with a deoxyfluorination reaction, which might yield more practical routes to pure fluorinated products.

The potential application of modern late-stage fluorination methods to the synthesis of ^{18}F PET tracers is often listed as a motivation for the development of novel fluorination reactions. But despite the adoption of several modern fluorination methods to ^{18}F radiosynthesis, the projected dramatic increase in the number of available PET tracers has not yet occurred.[8] More hurdles need to be crossed for a reaction to show promise in practical PET tracer synthesis than a short reaction time and the use of fluoride as a limiting reagent. Purification, for example, is an issue commonly addressed when a reaction has been successfully developed; in the context of ^{18}F chemistry, appropriate product purification should enter the reaction design at the outset to ensure that the pure radiofluorinated product can be obtained from a reaction mixture containing thousands of equivalents of starting material and reagents. Several modern methods that have been applied to ^{18}F radiolabeling are transition-metal-catalyzed or -mediated, which can make hydrodefunctionalization, a common side reaction observed in many cross-coupling reactions, of concern.

Operational simplicity is another important criterion for PET chemistry. Our palladium-mediated late-stage fluorination, for example, is an example of a conceptually remarkable, but operationally flawed ^{18}F reaction: The transformation consists of two reaction steps, separated by a filtration, and necessitates the use of a moisture-sensitive precursor mole-

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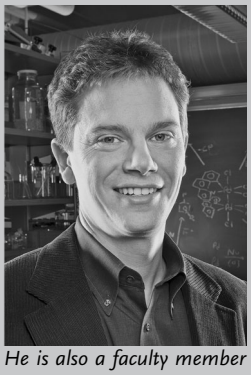

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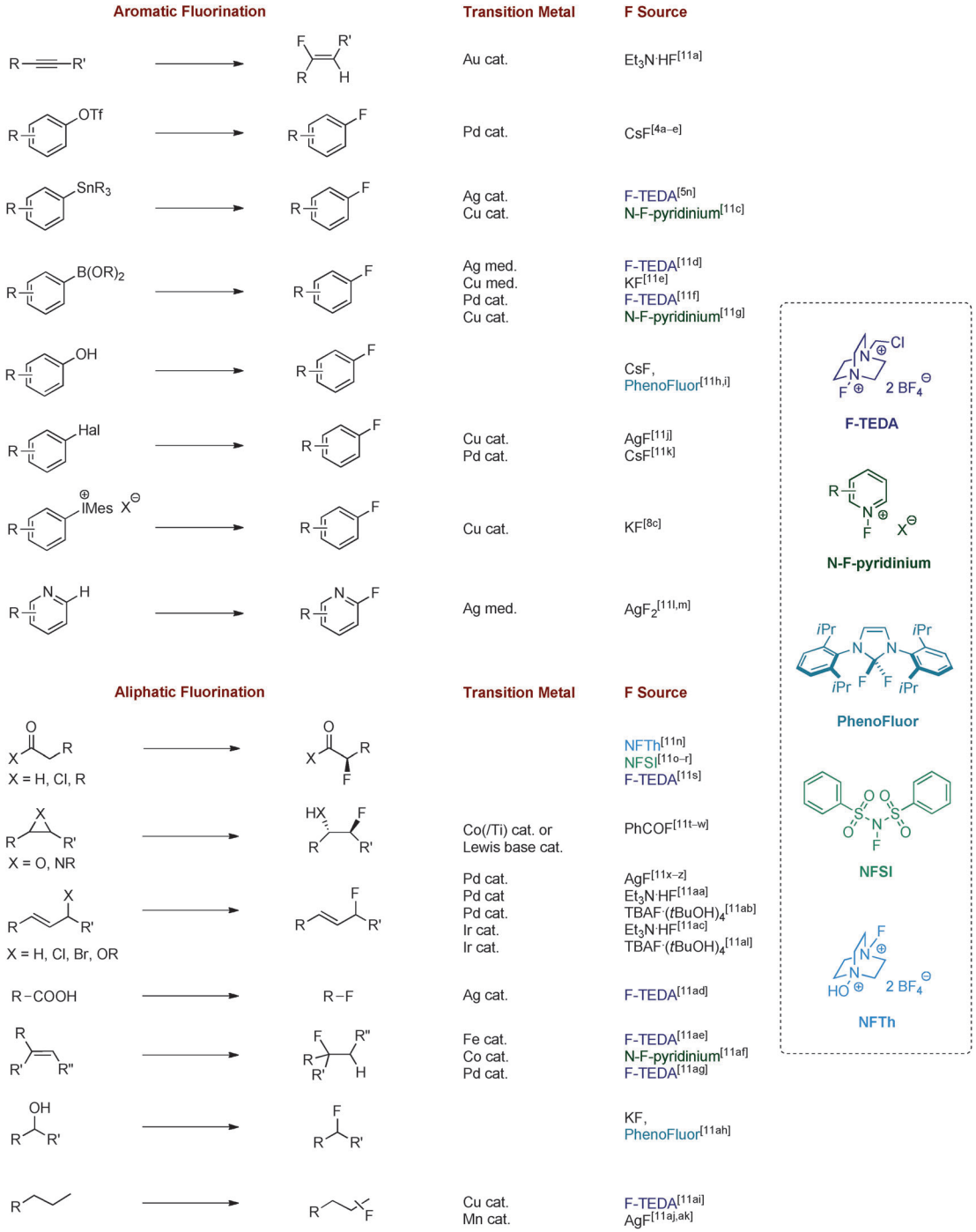

Scheme 1. Selected modern aromatic and aliphatic fluorination methods arranged by functional group interconversion in order of publication date.[4a–e, 5n, 8c, 11] IMes = 1,3-dimesitylimidazol-2-ylidene.

cule.[9] Whereas neither of these two operational hurdles posed significant challenges in the original development of the reaction nor in small-scale labeling experiments conducted manually, they rendered automation of the procedure for non-human primate imaging challenging and clinical translation prohibitively difficult.[10] Aside from the operational practicality, which is judged by different standards in a general chemistry laboratory and in an imaging context, the selection of substrates is no longer dictated by chemical goals but by real clinical needs. In order to develop ^{18}F fluorination reactions with promise, true late-stage fluorination methods with a level of convenience that can be realized in a clinical-imaging setting are required.

The recent advances in fluorination chemistry have been too numerous to even briefly mention most of them here but with some of the challenges in current late-stage fluorination chemistry identified, we are curious which future directions would significantly advance the field. Beyond the fairly obvious requirements, such as high functional-group tolerance and operational simplicity, we believe that an improved

fundamental understanding of the bonding interactions of fluorine, including ionic and hydrogen bonding and covalent bonding with transition metals, may teach us how to better tackle the problem of improving its reaction chemistry. It has long been understood that fluoride forms exceptionally strong hydrogen bonds to protic solvents, particularly water, which typically reduces the nucleophilicity of the fluoride ion.[12] On the other hand, the high lattice energy of fluoride salts renders them virtually insoluble in all but the most polar solvents.[13] Both facts leave nucleophilic fluoride chemistry with the dilemma of either unfavorable desolvation or a high kinetic barrier owing to low solubility. Given its high electronegativity, fluoride is a hard nucleophile, generally preferring charge-controlled interactions over the desired orbital control leading to C–F bond formation. Rather than exacerbating fluoride's inherent tendency towards charge-controlled interactions through desolvation, new reagents with fluoride biased towards forming bonds to carbon by orbital control could prove advantageous.[6b,14]

The use of TBAF·*t*BuOH and of bifluoride in S^{VI} fluoride exchange as well as the use of ionic liquids and alcohol co-solvents in ^{18}F radiolabeling are notable examples for the enhancement of the effective fluoride nucleophilicity through media that can provide hydrogen bond stabilization.[15] "Soft" fluoride nucleophiles that are suitable for C–F bond formation can also be obtained by binding to transition metals as demonstrated by the synthesis of allylic fluorides by attack of a palladium-bound fluoride on a palladium allyl complex.[11aa] Attempts to achieve attack on palladium allyl complexes by extraneous fluoride ions, on the other hand, led to elimination products rather than fluoride incorporation.[16] A fundamental understanding of the nature of transition-metal fluorides and the ability to predict their reactivity are still lacking: For example, fluoride ligands bound to sulfonamide-supported Pd^{II} or Pd^{IV} complexes persist in wet organic solvents, whereas the fluoride ligand on Pd^{II} BrettPhos complexes shows pronounced basic properties, with likely hydrolysis of the metal–fluorine bond.[3,4] Given our poor fundamental understanding of the properties of metal fluorides, tailoring the properties of the metal fluoride to the desired transformation is hardly possible, and further research is warranted to gain insight into the promising area of metal-bound fluoride chemistry.

Given the dramatic reactivity differences of different fluoride species, it seems advisable to suggest the development of more appropriate reagents. Conventional reagents frequently limit the achievable substrate scope: For example, nucleophilic fluorination reactions are often sensitive to moisture, and the basic nature of dry fluoride can lead to elimination reactions and is commonly incompatible with protic functional groups. The successful use of the TBAF·*t*-BuOH reagent teaches us that nucleophilic fluorination does not categorically need to be free of a hydrogen bond donor.[15b] Electrophilic fluorination reactions are largely executed with only three reagents, namely Selectfluor (F-TEDA), NFSI, and *N*-fluoropyridinium salts. These reagents are comparatively expensive and can lead to side reactions with basic heteroatoms. Generally, electrophilic and nucleophilic fluorinating reagents are largely complimentary in the restrictions that they place on the substrate scope.

The field of fluorination is unusual in that late-stage modification processes are more developed in the laboratory than in nature; only a single enzyme that introduces fluorine into organic molecules has been identified. The highly oxidizing conditions required for the formation of an electrophilic fluorination reagent combined with the limited nucleophilicity of the fluoride ion in water are likely causes for the dearth of fluorinated natural products. Despite nature's limited reliance on organofluorine compounds, the synthesis of fluorinated derivatives of salinosporamide A, an anticancer drug candidate, has been achieved through the introduction of the fluorinase gene from *S. cattleya* into a heterologous host.[17] Enzymatic radiolabeling procedures based on the fluorinase enzyme have also been developed; *S*-adenosylmethionine (SAM) was radiolabeled and subsequently subjected to oxidation to yield [^{18}F]fluoroacetate with a radiochemical conversion of 36% in two hours.[18] Another avenue for the rapid construction of complex fluorinated molecules involves a biochemical pathway that consists of two polyketide synthase systems engineered to accept fluoroacetate as a substrate.[19] The combination of synthetic biology approaches with fluorinated building blocks appears to be an attractive and promising strategy to quickly access complex fluorinated molecules that currently cannot be accessed by other means.

The lack of chiral-pool organofluorine compounds makes the development of asymmetric fluorination methods particularly crucial.[20] Halogen functionalization is often accomplished through alkene halogenation, but whereas chlorine, bromine, and iodine readily react with non-activated alkenes via cyclic halonium ions, the corresponding fluoronium ion is not formed.[21] Given the relatively low reactivity of unactivated alkenes towards electrophilic fluorinating reagents, a lot of work has focused on activated alkene derivatives, such as enols, enamines, and allyl silanes.[22] Several methods have been developed that allow highly enantioselective fluorination at the α-position of carbonyl groups.[11o–r,23] Aside from the strategies that build on chiral amine catalysis, anion exchange processes of F-TEDA, which is virtually insoluble in many organic solvents, with chiral anions that increase the solubility of the fluorinating agent have proven very fruitful in the development of synthetic routes towards enantioenriched chiral organofluorine compounds.[24] The fact that fluoride readily engages in hydrogen bonding and dipolar interactions seems to render it uniquely suitable for reactions catalyzed by chiral organocatalysts. Whereas its potential for strong interactions with a catalyst appears promising for achieving substantial levels of catalyst control, the often reduced nucleophilicity of fluoride ions involved in polar interactions limits the potential for bond formation with fluoride. Nevertheless, the use of hydrogen-bonded fluoride reagents is promising owing to the functional-group tolerance of such fluoride sources.

The fluorine substituent has a privileged nature in a diverse range of fields, and synthetic methods for fluorine introduction into complex structures are highly sought after. Modern fluorination methods cannot yet compete with the

Halex process and fluorination with F_2 for the synthesis of bulk chemicals owing to the expensive nature of the majority of the reagents, starting materials, and catalysts used. For applications where the scale permits the use of reagents such as Selectfluor or AgF, however, late-stage fluorination has opened new avenues in terms of functional-group tolerance and substrate scope. In order to advance the field further, fundamental insights into the interplay between nucleophilicity, basicity, hydrogen bonding, and electrostatic interactions of fluoride species may be beneficial. A range of low-cost fluorination reagents with controlled reactivity that are capable of reacting in largely orbital-controlled carbon–fluorine bond-forming transformation while possible side reactions are prevented are needed to create a toolbox of mild and general late-stage fluorination reactions. Direct C–H fluorination reactions have to be held to particularly high standards to achieve general utility owing to potentially challenging purifications. Further developments in ^{18}F fluorination chemistry need to focus on facilitating the translation from small-scale radiolabeling to clinical PET imaging through the use of convenient labeling precursors, easy-to-automate reaction protocols, and efficient purification procedures. With appropriate future developments, late-stage fluorination certainly has the potential to substantially impact several areas of interest. In our opinion, research in the direction of the field akin to what we have proposed in this Essay would accelerate the meaningful development of late-stage fluorination.

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