CHEMICAL REVIEWS

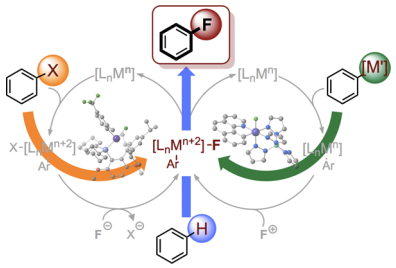
Review

pubs.acs.org/CR

Modern Carbon–Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis

Michael G. Campbell and Tobias Ritter*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States



CONTENTS

1. INTRODUCTION: FUNDAMENTAL CHALLENGES OF ARENE C–F BOND FORMATION

In recent years, there has been a dramatic increase in available methods for the installation of fluorine and fluorine-containing functional groups in organic molecules,[1−4] and the importance of fluorinated organic molecules to a variety of applications in modern society has become well-appreciated.[5−12] However, an unintended side effect of the recent increase in fluorination methods has been to obscure the fact that C–F bond formation remains a challenging problem, particularly for the synthesis of aryl fluorides. While a variety of reactions now exist for aryl fluoride synthesis, there is still a lack of practical, broadly useful reactions that afford access to functionalized aryl fluorides. This problem is due in large part to the reactivity of fluorine sources: electrophilic sources such as fluorine gas (F_2) are highly reactive but often unselective and intolerant of many common functional groups; in contrast, fluoride anion is only weakly nucleophilic unless hydrogen bond donors are rigorously excluded, in which case fluoride's basicity often results in unproductive side reactions. As a result, the harsh reaction conditions of many conventional fluorination reactions (using either electrophilic F_2 or nucleophilic fluoride) typically limit their substrate scope and selectivity. Fluorination reactions that are well-established on an industrial scale are often conducted on simple substrates that are subsequently used as building blocks for elaboration.[13,14] For many applications, however, it is necessary to perform fluorination on advanced intermediates that already bear complex functionality. Therefore, the

Special Issue: 2015 Fluorine Chemistry

Received: July 10, 2014
Published: December 4, 2014

   dx.doi.org/10.1021/cr500366b | Chem. Rev. 2015, 115, 612–633

synthesis of fluoroarenes via C−F bond formation has received considerable attention.

In this review, we survey modern methods for synthesis of functionalized aryl fluorides by C−F bond formation, highlighting both key advances and conceptual hurdles that have yet to be overcome. While the adjective "modern" is necessarily subjective, for the purposes of this review we have loosely defined the term to cover advances within the past decade. Additionally, we have included select results that are "outside" the scope of arene fluorination: results that have not been applied to aryl fluoride synthesis, but which seem conceptually poised to impact future advances. In this way, we hope to aid in defining a clearer path forward for the highly active field of fluorination research.

1.1. Challenges Associated with Using Nucleophilic Fluoride

A fundamental challenge of any C−F bond forming reaction, regardless of the approach, is the nature of fluorine itself. Fluorine is the most oxidizing and most electronegative element (Pauling electronegativity 4.0). The fluoride anion, due to its electronegativity and small ionic radius (1.33 Å),[15] can form strong hydrogen bonds with a variety of hydrogen bond donors such as water, alcohols, amines, and amides.[16] The high solvation energy of the fluoride ion in aqueous media results in a tightly bound hydration shell of water molecules around the ion. Therefore, fluoride is typically only weakly nucleophilic in the presence of hydrogen bond donors, and this attenuated nucleophilicity of fluoride limits access to C−F bonds via nucleophilic substitution reactions.[17] The challenge of nucleophilic fluoride's low reactivity is in direct contrast to electrophilic fluorine sources (e.g., F_2 gas), which typically display much higher reactivity but with poor selectivity (vide infra, section 4). Fluoride is a better nucleophile when hydrogen bond donors are meticulously excluded, but also a strong base, which can lead to undesired side reactions. Basic fluoride reacts readily with even weak hydrogen bond donors to form bifluoride (HF_2^-), a stable anion with the strongest known hydrogen-bonding interaction.[16] The first recognized natural fluorinating enzyme, 5′-fluoro-5′-deoxyadenosine synthase, likely dehydrates solvated fluoride in its active site and thereby increases fluoride's nucleophilicity for the ensuing substitution reaction.[18,19]

1.2. Traditional Nucleophilic Arene Fluorination Reactions

Despite the potential problems associated with using fluoride anion, many conventional nucleophilic arene fluorination reactions that were developed in the early 20th century are still commonly used for the synthesis of fluoroarenes on the industrial scale.[14] We do not aim to comprehensively survey traditional, established methods for aryl fluoride synthesis, but only to provide a few representative examples that establish a sufficient backdrop to contrast the "modern" reactivity reviewed herein. A primary challenge associated with traditional nucleophilic arene fluorination reactions is the limitation to relatively simple substrates, resulting from harsh reaction conditions and the strong bacisity of nucleophilic fluoride.

In 1927, Balz and Schiemann developed a nucleophilic fluorination of arenes via thermal decomposition of aryl diazonium tetrafluoroborate salts (Figure 1).[20,21] Later work showed that yields can often be improved when hexafluorophosphates (PF_6^-) or hexafluoroantimonates (SbF_6^-) are used instead of tetrafluoroborates.[22,23] Alternative approaches include a one-pot diazotization/fluorodediazoniation of anilines

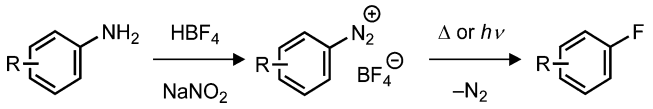


Figure 1. Nucleophilic fluorination of aryl diazonium salts (the Balz−Schiemann reaction).

with $NOBF_4$, which provided improved yields and a broader substrate scope.[24] Other variations involve fluorodediazoniation in HF/pyridine and in $BF_3{\cdot}Et_2O$,[25,26] the use of triazenes,[27−30] and fluorodediazoniation in ionic liquids.[28,31]

Displacement of the chloride in electron-poor aryl chlorides under forcing conditions with anhydrous potassium fluoride (the halogen exchange, or "Halex" process) was developed in 1936,[32] followed by the fluorodenitration of arenes by *ipso* attack at the carbon atom bearing the nitro group (Figure 2).[33]

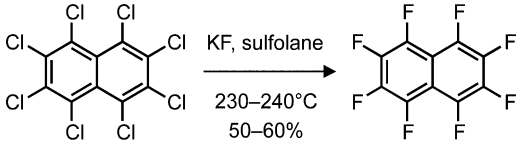


Figure 2. Nucleophlic aromatic substitution of electron-poor arenes (the Halex process).

Increased efficiency for arene fluorodenitration has also been reported by performing the reaction in a molten salt as solvent.[34] Aryl chlorides and nitroarenes are more suitable substrates for nucleophilic fluorination reactions than aryl bromides and iodides because the rate-limiting step in S_NAr fluorination reactions is the addition of fluoride to form a Meisenheimer complex; therefore, more electron-withdrawing leaving groups accelerate the substitution by fluoride. Trimethylammonium groups are also highly electron-withdrawing and have been used as leaving groups for nucleophilic aromatic fluorination, especially in the context of ^{18}F-radiofluorination for positron emission tomography (PET) (vide infra, section 6.4).

Aryl fluorides can also be accessed from the reaction of aryl bromides with anhydrous tetramethylammonium fluoride (TMAF).[35] However, this reaction serves to highlight one of the key challenges of nucleophilic fluorination: the process actually occurs through fluoride trapping of aryne intermediates generated from elimination of the bromide with the strongly basic anhydrous fluoride and, therefore, provides a mixture of constitutional isomers (Figure 3).

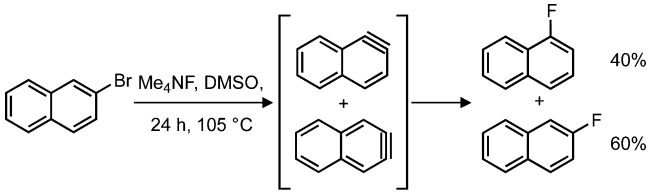


Figure 3. Fluorination of aryl bromides via aryne intermediates.

1.3. Challenges of Metal-Mediated C−F Bond Formation

It has long been recognized that the harsh reaction conditions required for nucleophilic arene fluorination, such as the high temperatures used in the Halex process, are the consequence of a substantial kinetic barrier to C−F bond formation:[36] however, the C−F bond is the strongest of all C−X single bonds,[37] so

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

nucleophilic fluorination of aryl halides is typically a thermodynamically favorable process. Therefore, improving nucleophilic arene fluorination can ideally be approached by catalysis, and finding appropriate transition-metal catalysts for aryl fluoride formation has been the subject of intense study in recent years. Conceptually, metal-catalyzed arene fluorination could proceed via a mechanism analogous to a typical C−X cross-coupling reaction,[38−42] and a general catalysis cycle is shown in Figure 4. Overcoming the activation barrier to C−F

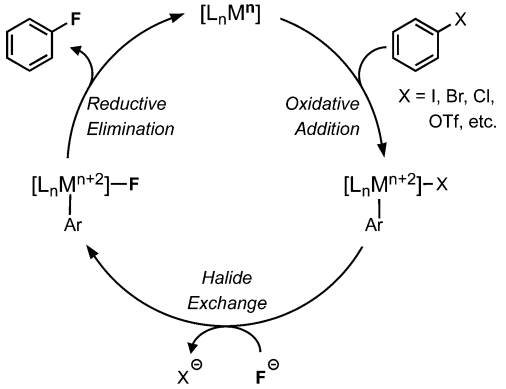


Figure 4. General catalysis cycle for metal-catalyzed nucleophilic fluorination.

bond formation from aryl−metal fluoride complexes is also challenging, however, because metal−fluorine bonds are also strong and highly polarized, and thus, the design of appropriate catalysts is more difficult than for conventional C−C or C−N cross-coupling reactions.[2,42]

In large part due to the success of palladium-catalyzed cross-coupling reactions between carbon and a wide variety of other atoms—in particular B,[43,44] C,[38,45] N,[46−49] and O[50,51]—Pd-mediated and -catalyzed arene fluorination has been targeted as a promising approach. Early work in this field was primarily led by Grushin, who began exploring the synthesis and reactivity of the first mononuclear arylpalladium(II) fluoride complexes (Figure 5).[52−54] It was quickly discovered, however, that such

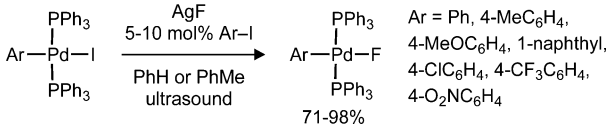


Figure 5. Synthesis of the first molecular arylpalladium(II) fluoride complexes, which do not undergo C−F reductive elimination.

complexes did not undergo the desired C−F reductive elimination under any conditions investigated.[42,55] Rather it was found that the phosphine ligands took part in competing side reactions such as P−F bond formation, giving Ph_3PF_2 among other side products. Early attempts at synthesis and C−F bond formation from phosphine-free arylpalladium(II) fluoride complexes were also reported to be unsuccessful.[35,42]

In general, C−F reductive elimination from a transition metal such as Pd is kinetically challenging because metal−fluorine bonds are significantly polarized toward fluorine. For reductive elimination to occur, there must be sufficient orbital overlap between the metal−carbon and the metal−fluorine σ-bonds; due to fluorine's high electronegativity and small size, electron density is lacking in the region where it is required for C−F bond formation.[2] The high polarization of the metal−fluorine bond results in a significant ionic contribution to the bond,[56] which strengthens it and increases the energy barrier to C−F reductive elimination. An additional challenge resulting from such polarization of the metal−fluorine bond is that the fluoride ligands on palladium(II) fluoride complexes have been observed to be strongly basic: even when bridging two Pd centers in a μ^2 fashion, short F···H hydrogen bonds with solvent molecules have been crystallographically observed (Figure 6).[57] The basicity of fluoride ligands can lead to

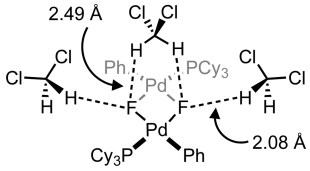


Figure 6. Solid-state structure of $[(Cy_3P)_2Pd_2(Ph)_2(\mu\text{-}F)_2][CH_2Cl_2]_3$ showing hydrogen-bonding interactions with CH_2Cl_2 solvent due to the basicity of the fluoride ligands.

unproductive hydrolysis of metal−fluorine bonds.[58] Solution-state ^{19}F and ^{31}P NMR studies demonstrated that trace amounts of hydrogen bond donors, such as water, can facilitate rapid Pd−F ionization and fluoride ligand exchange for mononuclear palladium(II) fluoride complexes such as those shown in Figure 5.[52,53] These consequences of Pd−F bond polarization and fluoride's basicity present further hurdles to productive C−F reductive elimination. Only after more than a decade of development were such obstacles overcome, using carefully designed Pd complexes as well as other metals such as Ag and Cu (vide infra).

A promising early result, reported by Yandulov, demonstrated C−F bond formation from an arylpalladium(II) fluoride dimer in the presence of the bulky monodentate phosphine ligand *t*-BuXPhos (Figure 7).[59] While a C−F reductive

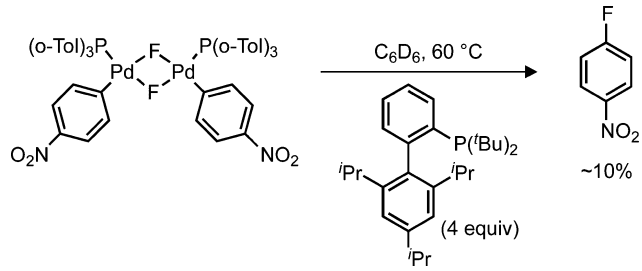


Figure 7. First reported aryl C−F bond formation from an arylpalladium(II) fluoride complex.

elimination mechanism for aryl fluoride formation was not rigorously established, and an S_NAr pathway is also feasible,[60] use of the *t*-BuXPhos ligand reflects the need for reductive elimination from a mononuclear, three-coordinate, "T"-shaped palladium complex.[59,61]

Carbon−fluorine reductive elimination was also targeted from Rh(III) via the reaction of aryl halides with rhodium(I) fluoride complexes, and the synthesis of $(Ph_3P)_3RhF$ was reported.[62] However, as for the early arylpalladium(II) fluoride complexes, $(Ph_3P)_3RhF$ was observed to undergo competitive side reactions in the presence or absence of aryl halide substrates involving P−F bond formation via metallophosphorane intermediates (Figure 8).[63] These results helped to

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

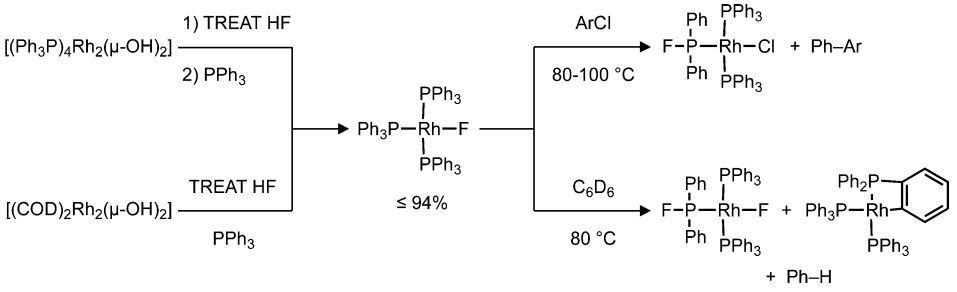


Figure 8. Synthesis and unexpected reactivity of $(Ph_3P)_3RhF$.

rationalize the zero-order kinetic dependence of additional phosphine ligands on the rate of P–F bond formation in both the Rh(I) and Pd(II) systems.[42]

2. NUCLEOPHILIC ARENE FLUORINATION

While synthesis of aryl fluorides via nucleophilic fluorination is challenging for the reasons outlined above, this approach is still highly desirable, in part due to the low cost of alkali-metal fluoride salts, especially compared to electrophilic fluorinating reagents (vide infra, section 4).[64] Moreover, the arene substrates themselves are typically readily accessible aryl halides or pseudohalides, adding to the overall appeal of nucleophilic arene fluorination. Recent years have seen significant advances in two general areas: the development of "naked" fluoride sources with high nucleophilicity and improved catalyst systems that can overcome the high kinetic barrier to C–F bond formation. A key challenge that remains in the nucleophilic fluorination approach is the suppression of undesired side reactions resulting from the high basicity of fluoride ion.

2.1. Advances in Nucleophilic Aromatic Substitution

A simple but effective approach to improving nucleophilic arene fluorination has been to develop soluble fluoride sources that exclude water and other hydrogen bond donors that would attenuate fluoride's nucleophilicity.[65] The use of tetraalkylammonium ions as counterions for fluoride reduces the ionic bond strength and increases solubility in organic solvents.[66] Tetrabutylammonium fluoride (TBAF) is a common soluble fluoride source that is available as a trihydrate. The presence of water reduces the nucleophilicity of fluoride by hydrogen bonding and is responsible for side reactions, such as alcohol formation, by serving as a hydroxide source. The drying of most quaternary ammonium fluorides is difficult because of competing Hofmann elimination with fluoride serving as a strong base under anhydrous conditions.[67] Hofmann elimination can be avoided by using tetramethylammmonium fluoride (TMAF), which lacks β-hydrogen atoms for elimination and can be obtained as an anhydrous salt.[68] Additionally, the use of tertiary alcohol additives such as *tert*-butyl alcohol has been shown to maintain the nucleophilicity of the fluoride while diminishing its basicity, thereby reducing the formation of undesired byproducts in aliphatic substitution reactions with fluoride.[69,70]

In 2005, the synthesis of anhydrous TBAF via the nucleophilic aromatic substitution of hexafluorobenzene with cyanide was reported by Sun and DiMagno (Figure 9, top).[71] TBAF produced by this procedure is highly nucleophilic and allows for the fluorination of electron-poor chloroarenes, nitroarenes, or trimethylammonium arenes at room temperature in up to >95% yield (Figure 10).[72,73] The group of Schwesinger has described the preparation of a variety of

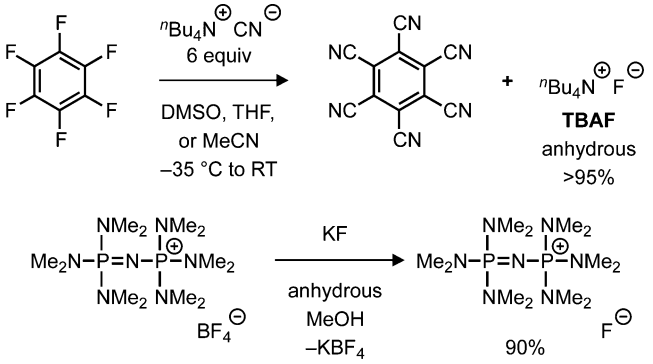


Figure 9. Synthesis of anhydrous "naked" fluoride sources.

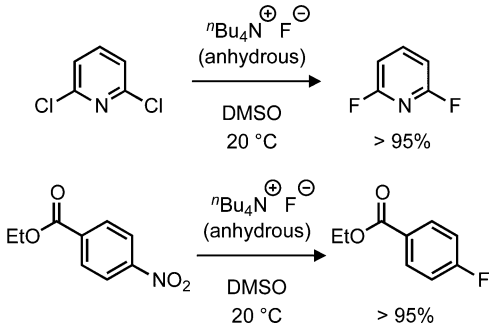


Figure 10. Room temperature nucleophilic arene fluorination using anhydrous TBAF. Yields were determined by ^{19}F NMR spectroscopy.

anhydrous phosphazenium fluoride salts which provide soluble, "naked" fluoride sources (Figure 9, bottom).[74] However, the phosphazaneium fluorides typically favor elimination over nucleophilic substitution in reactions with alkyl halides and pseudohalides[75] and to date have not been reported as reagents for practical aryl fluoride synthesis.

2.2. Palladium-Catalyzed Nucleophilic Fluorination

As described in section 1.3, a significant amount of early work in metal-catalyzed nucleophilic arene fluorination focused on palladium fluoride complexes. While a number of arylpalladium(II) fluoride complexes were synthesized and characterized, the desired C–F reductive elimination remained elusive for many years. A breakthrough in the field was reported in 2009 when the Buchwald group described the Pd-catalyzed nucleophilic fluorination of aryl triflates (Figure 11).[76,77] Crucial to the success of the Pd catalyst system is use of the bulky monodentate phosphine ligand *t*-BuBrettPhos, which promotes C–F reductive elimination from a three-coordinate, T-shaped Pd(II) intermediate.[59] The fluorination of aryl triflates displays a broad substrate scope and tolerates nucleophilic functional groups not often tolerated in electro-

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612–633

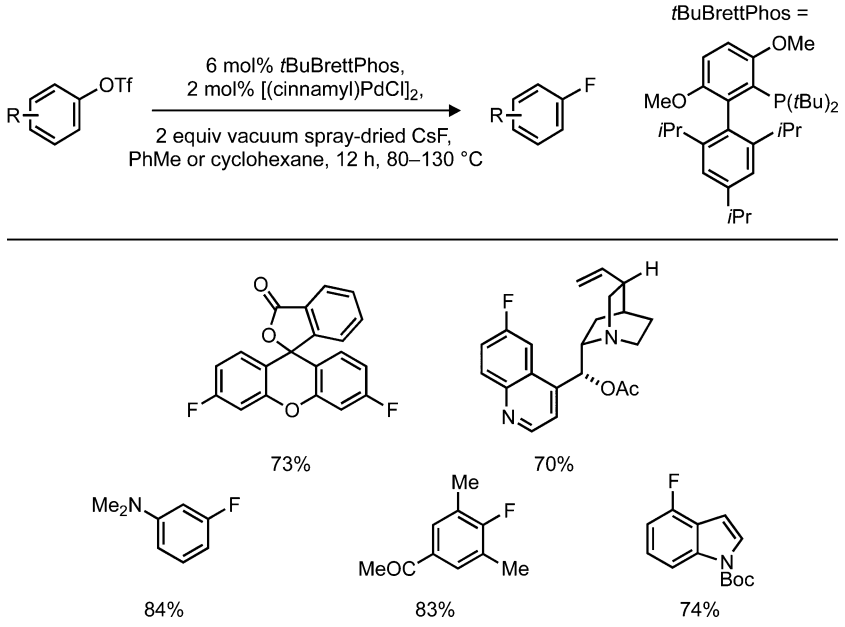


Figure 11. First reported Pd-catalyzed nucleophilic arene fluorination using aryl triflates. Yields given are for isolated products.

philic fluorination reactions because of competing side reactions (vide infra). Reduction of the aryl triflate substrates to form C−H (rather than C−F) bonds was sometimes observed as an undesired minor side reaction; separation of fluoroarenes from reduced arene side products is typically challenging using standard chromatographic methods. Protic functional groups are not tolerated due to the strongly basic anhydrous fluoride used. Furthermore, the strongly basic reaction conditions result in the formation of a mixture of aryl fluoride constitutional isomers for some substrates, potentially via aryne intermediates (see Figure 3). In general, substrates that feature an electron-donating group in the *para* position were found to give higher amounts of constitutional isomers, unless an *ortho* substituent is also present.

In the course of mechanistic investigations of Pd-catalyzed (pseudo)halide fluorination, it was observed that the active palladium catalyst in the fluorination reaction contained a ligand that was modified from the originally used *t*-BuBrettPhos ligand.[78] A side reaction was discovered in which C−H arylation of *t*-BuBrettPhos by the aryl halide substrate occurred, and the product of this reaction was a competent fluorination catalyst. Stoichiometric reactivity studies showed that the arylpalladium(II) fluoride complex featuring the arylated phosphine ligand underwent C−F reductive elimination under conditions relevant to catalysis, which was not true for the analogous *t*-BuBrettPhos complex (Figure 12).

Subsequently, several variations of Pd-catalyzed (pseudo)-halide fluorination have been reported, including a one-pot procedure from phenols,[79] and a fluorination of aryl bromides in which a reverse micellar reaction medium formed from sodium dodecyl sulfate (SDS) is proposed.[80] The Buchwald group has developed an improved Pd catalyst system that allows for a general and efficient nucleophilic fluorination of (hetero)aryl bromides and iodides (Figure 13).[81,82] The new Pd(0) precatalyst features a monodentate triarylphosphine ligand, derived from arylation of adamantyl-BrettPhos, and 1,5-cyclooctadiene (COD) as a stabilizing "dummy" ligand. The improved reaction conditions provide better suppression of reduced arene side products, which makes isolation of the aryl

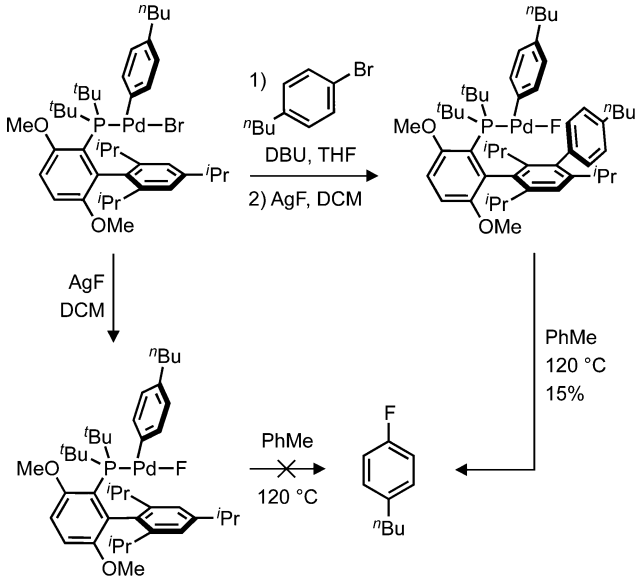


Figure 12. Evidence for in situ ligand modification during Pd-catalyzed fluorination of aryl halides.

fluoride products easier. However, formation of aryl fluoride constitutional isomers is still observed for some substrates, such as 3-bromopyridine.

2.3. Copper-Mediated and -Catalyzed Nucleophilic Fluorination

Along with palladium, copper-based catalysts have shown the most promise in recent years as catalysts for nucleophilic arene fluorination.[83] The viability of an oxidative addition/reductive elimination sequence for fluorination of aryl halides via a Cu(I)/Cu(III) cycle was established by the Ribas group using a designed macrocyclic substrate that allowed for isolation of key Cu(III) intermediates (Figure 14).[84] Halide exchange took place at an arylcopper(III) halide complex, followed by C−F reductive elimination from Cu(III). The Wang group subsequently reported a related C−H fluorination of azacalix[1]arene[3]pyridines via Cu(III) using KF or CsF.[85]

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

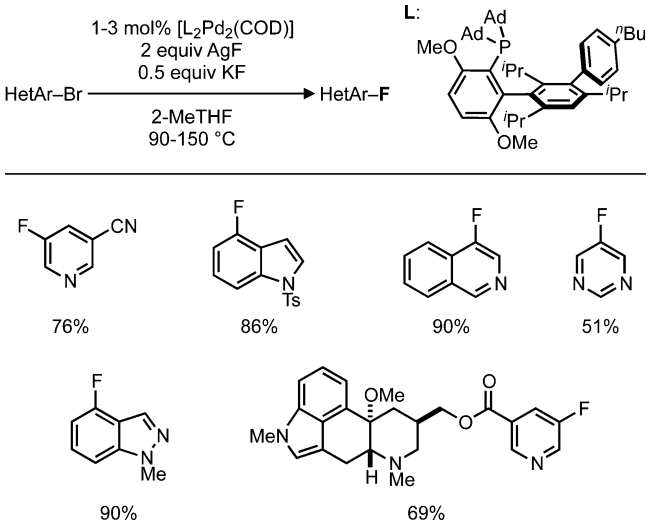


Figure 13. Pd-catalyzed nucleophilic fluorination of heterocyclic aryl bromides. Yields given are for isolated products.

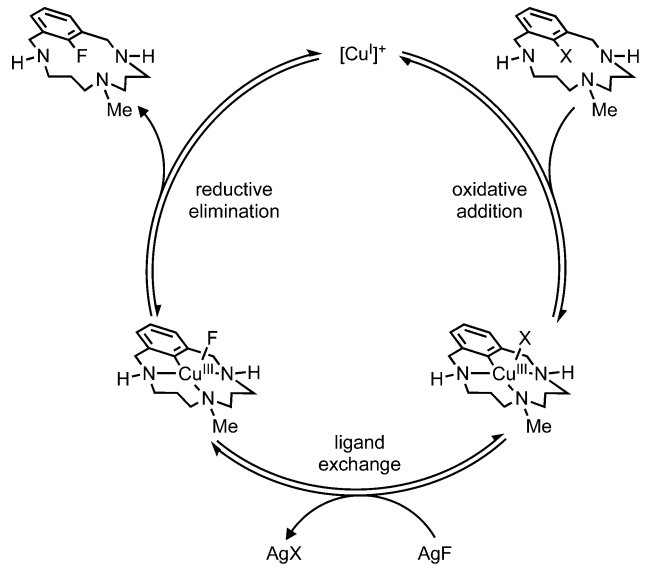


Figure 14. Cu-catalyzed halide exchange on arenes via a Cu(I)/Cu(III) cycle.

A more general copper-mediated fluorination of aryl iodides was reported by Hartwig using 3 equiv of a Cu(I) complex and AgF (Figure 15).[86] The reaction is 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. Liu and co-workers have demonstrated that catalytic Cu(I) can be used for aryl bromide fluorination with AgF, but coordinating directing groups such as pyridine are required (Figure 16).[87] Mechanistic studies and XANES/EXAFS analysis indicate that the coordinating pyridyl group accelerates C−Br oxidative addition by the Cu(I) catalyst and alleviates unproductive oxidation of the Cu(I) catalyst by AgF.

Copper catalysis has also been used for an S_NAr-type nucleophilic fluorination of diaryliodonium salts. Nucleophilic fluorination of diaryliodonium salts has been known since the early 1980s using KF as the fluoride source (Figure 17).[88] The aryl fluoride products can be formed in up to 85% yield, though typically as a mixture with the corresponding aryl iodide and

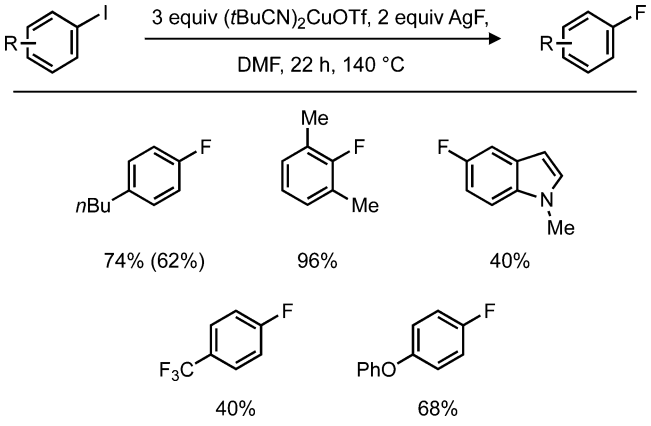


Figure 15. Cu-mediated fluorination of aryl iodides with AgF. Yields were determined by ^{19}F NMR spectroscopy (isolated yields given in parentheses).

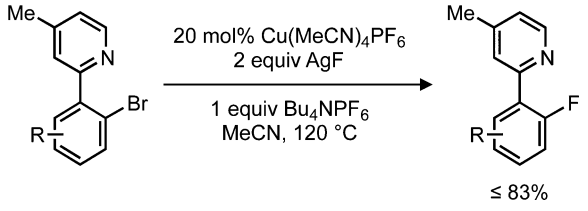


Figure 16. Cu-catalyzed fluorination of 2-pyridylaryl bromides. Yields given are for isolated products.

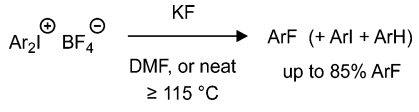


Figure 17. Nucleophilic fluorination of diaryliodonium salts with KF.

reduced arene side products. A drawback is the need for preparation of the diaryliodonium substrates, as compared to more readily available aryl halides and pseudohalides. The additional necessity of a symmetric diaryliodonium salt, to prevent formation of a mixture of different aryl fluorides, presents a further synthetic challenge when targeting functionalized aryl fluorides. In 2013 Sanford reported the Cu-catalyzed fluorination of unsymmetrical diaryliodonium salts at 60 °C using KF (Figure 18).[89] It was found that fluorination of the less sterically hindered arene was preferred, allowing for use of a bulky mesityl group as an "innocent" aryl group on iodine(III). On the basis of DFT calculations, a Cu(I)/Cu(III) cycle was proposed for catalysis.

3. NUCLEOPHILIC DEOXYFLUORINATION OF PHENOLS

Along with aryl halides, phenols are attractive, readily available substrates for aryl fluoride synthesis. Catechols can be monodeoxyfluorinated by oxidation of the catechol to the *o*-quinone followed by nucleophilic deoxofluorination with Deoxo-Fluor and then reduction with sodium borohydride (Figure 19).[90] This one-pot oxidation/fluorination/reduction method affords a mixture of *ortho*-fluorinated phenol constitutional isomers. One of the first examples of the deoxyfluorination of nitro-substituted phenol was accomplished with *N,N′*-dimethyl-2,2-difluoroimidazolidine (DFI; Figure 20).[91]

A general method for nucleophilic deoxyfluorination of phenols has been described by our research group. The *ipso*-

dx.doi.org/10.1021/cr500366b | Chem. Rev. 2015, 115, 612−633

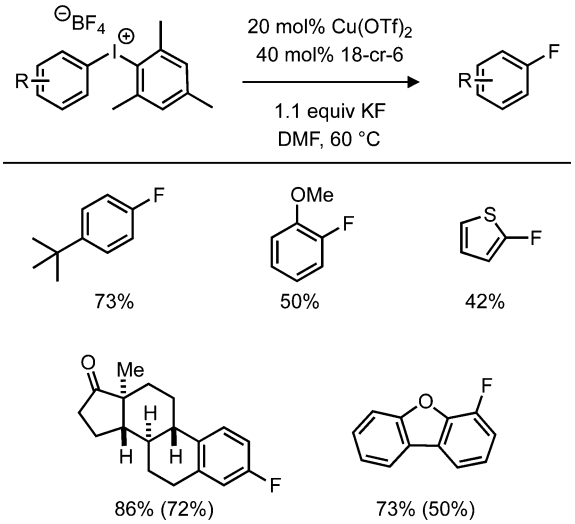


Figure 18. Selective Cu-catalyzed nucleophilic fluorination of unsymmetrical diaryliodonium salts with KF. Yields were determined by ^{19}F NMR spectroscopy (isolated yields given in parentheses).

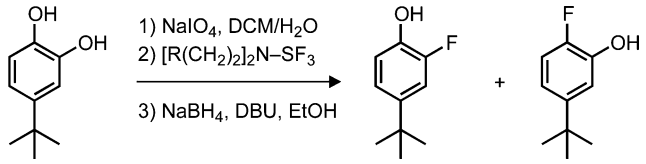


Figure 19. Deoxyfluorination of catechols via a one-pot oxidation/fluorination/reduction sequence.

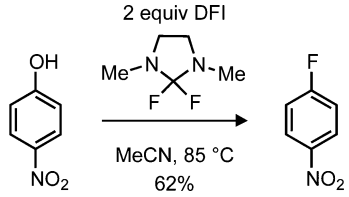


Figure 20. Deoxyfluorination of nitrophenols using DFI.

deoxyfluorination of phenols was accomplished with the now commercially available difluoroimidazoline reagent PhenoFluor and cesium fluoride (Figure 21a).[92] Electron-poor, -neutral, and -rich aryl fluorides in addition to heteroaromatic fluorides can be synthesized from the corresponding phenol precursors using this method.[93] The proposed mechanism for fluorination with PhenoFluor involves formation of a 2-phenoxyimidazolium bifluoride salt, which affords fluorinated arene and the urea byproduct upon nucleophilic attack by fluoride. When 4-methoxyphenol was mixed with Phenofluor, salt **1** was isolated, and heating **1** in the presence of CsF gave the aryl fluoride product (Figure 21b).

4. ELECTROPHILIC ARENE FLUORINATION

A complementary approach toward arene fluorination is to use aryl nucleophiles and an electrophilic fluorinating reagent.[94] Potential benefits of electrophilic fluorination are that problematic side reactions caused by the strong basicity of nucleophilic fluoride may be avoided and substrates bearing protic functional groups may be tolerated. Drawbacks include the need for arylmetal substrates that are less readily available than aryl (pseudo)halides or arylphenols, the potential for side reactions between electrophilic fluorinating reagents and nucleophilic functional groups such as amines, and the high cost and poor atom economy of most electrophilic fluorinating reagents. Electrophilic arene fluorination can also be addressed via a transition-metal cross-coupling approach, and a general catalysis cycle for metal-catalyzed electrophilic arene fluorination is shown in Figure 22. We note, however, that transmetalation of the arene substrate to the transition-metal catalyst can potentially occur at either a low- or high-valent metal center (before or after the oxidation step).

4.1. Electrophilic Fluorinating Reagents

The archetypal electrophilic fluorinating reagent is elemental fluorine (F_2), and the majority of other electrophilic fluorinating reagents are ultimately derived from fluorine gas.[95] Xenon difluoride was developed as a more stable electrophilic fluorination source, but its high reduction potential and need for handling under inert atmosphere conditions still limit its functional group tolerance and practical utility.[96] The development of crystalline, benchtop-stable fluorinating reagents was critical to the development of selective, functional-group-tolerant fluorination methods, and a selection of commonly used electrophilic fluorinating reagents is shown in Figure 23: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, F-TEDA-BF_4),[97] *N*-fluorobenzenesulfonimide (NFBS) and related analogues,[98−102] and *N*-fluoropyridinium salts.[103−108]

We do not aim here to examine the reactivity of electrophilic fluorinating reagents in detail, as this topic has been covered elsewhere.[109,110] However, for the purpose of the mechanistic discussions that follow in this review, it will be important to briefly discuss the nature of fluorination with these "*N*-fluoro" reagents. Even though *N*-fluoro reagents can formally behave as a source of fluoronium cations ("F^{+}"), the N−F bonds are polarized toward fluorine, with a partial negative charge on fluorine. Reactions may occur through S_N2 displacement with nucleophilic attack at fluorine;[111] for steric reasons, the σ^*_{N-F} orbital is only accessible for nucleophilic attack at the fluorine atom. Possibly as a consequence of the small orbital coefficient of the σ^*_{N-F} orbital on the fluorine atom and the low energy level of the σ^*_{N-F} orbital, other mechanism pathways, such as single-electron transfer (SET), can compete. For each class of *N*-fluoro reagents shown in Figure 23, clear experimental evidence for fluorination via an SET pathway has been obtained (Figure 24).[106,112−115] Often the process by which an overall two-electron oxidation proceeds for a given electrophilic fluorination reaction is a matter of debate in the literature: pathways involving both two single-electron transfers and concerted two-electron transfer for fluorination have been proposed.[109,111,116]

4.2. Arene C−H Fluorination Using Transition Metals

Currently, the development of functional-group-tolerant, direct conversion of arene C−H bonds to the corresponding C−F bonds with predictable regioselectivity is a frontier in the field of fluorination. The fluorination of arenes by electrophilic aromatic substitution (C−H → C−F) is challenging compared to other halogenations, possibly because the electronegativity of fluorine disfavors the rate-limiting formation of the halocyclohexadienyl cation. However, as with nucleophilic aromatic substitution of aryl halides with fluoride, this problem is kinetic in nature and can be addressed by catalysis. Fluorination with redox-active transition-metal catalysts can potentially proceed

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

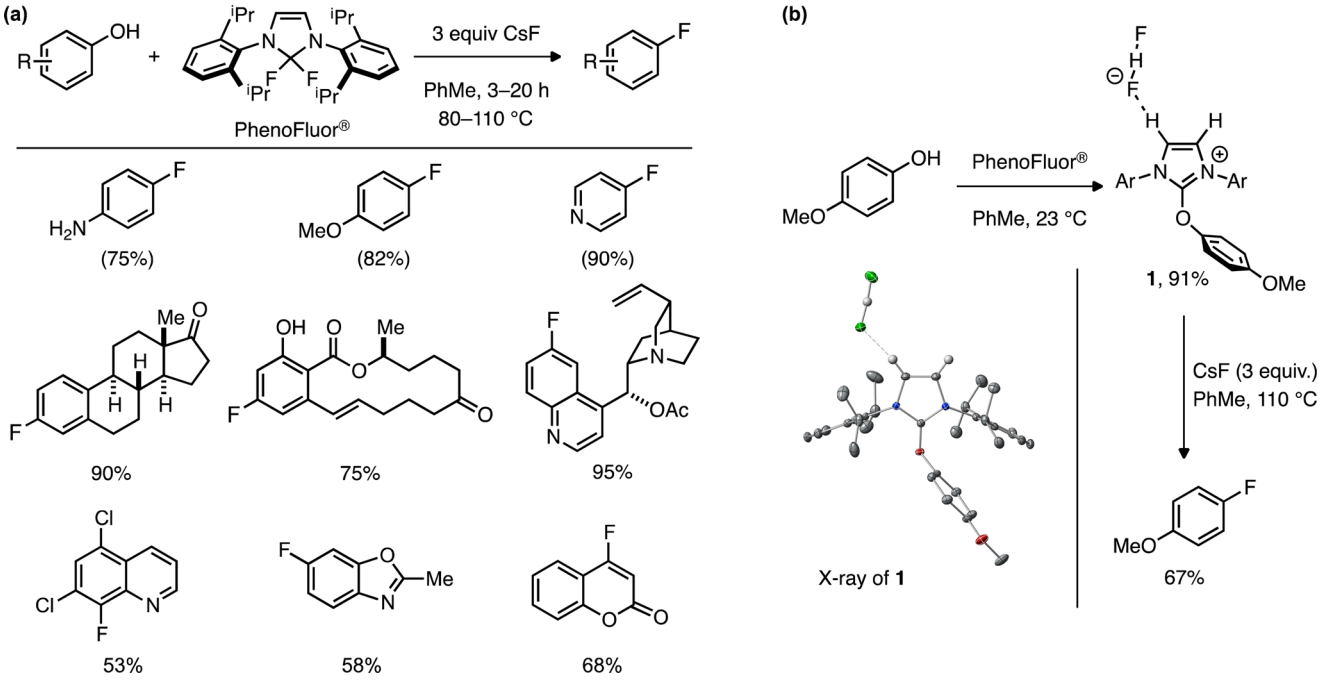


Figure 21. (a) Synthesis of (hetero)aryl fluorides via deoxyfluorination with PhenoFluor. Yields given are for isolated products (^{19}F NMR yields for volatile products given in parentheses). (b) 2-Phenoxyimidazolium bifluoride intermediate **1** observed upon treatment of phenols with PhenoFluor.

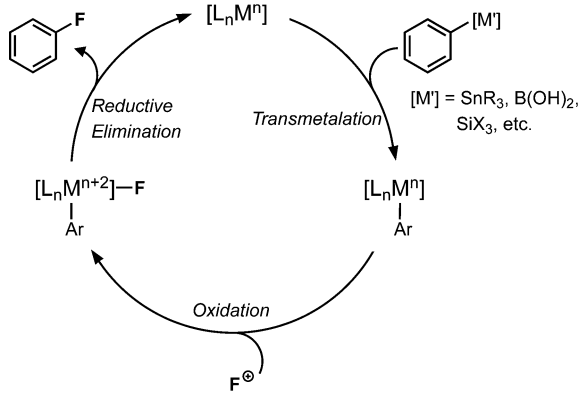


Figure 22. General catalysis cycle for metal-catalyzed electrophilic fluorination.

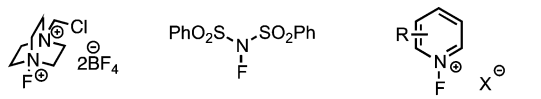


Figure 23. Commonly used, commercially available electrophilic fluorinating reagents.

through the intermediacy of high-valent organo-transition-metal fluorides.[3] In the case of arene C−H fluorination, the metal−carbon bond can proceed via direct C−H metalation, followed by oxidation of the metal center with an electrophilic fluorinating reagent. Depending on the reaction conditions, oxidation can result in the formation of a monometallic high-valent intermediate[117,118] or a high-valent multimetallic complex.[119,120]

A remarkable early result was reported in 2002 in which the electrophilic fluorinating reagent CuF_2 was used to synthesize fluorobenzene from benzene at 450−550 °C.[121] The resulting Cu(0) byproduct could be converted back to CuF_2 using HF and O_2, thereby rendering the overall process catalytic in copper, and regeneration of the fluorinating reagent could be improved by using modified copper fluoride salts.[122] While such an approach has high potential for an industrial synthesis of simple fluoroarenes, poor regioselectivity is observed for substituted arenes.

In 2006, the Sanford group reported that arene substrates bearing coordinating directing groups, such as 2-phenylpyridine, can undergo Pd-catalyzed C−H fluorination using an *N*-fluoropyridinium reagent (Figure 25, top).[123] The Yu group subsequently reported a related C−H fluorination of *N*-benzyltriflamide derivatives (Figure 25, bottom).[124] These Pd-catalyzed fluorination reactions were the first examples of transition-metal-catalyzed aromatic fluorination, and extension of this methodology to arene substrates with a variety of coordinating directing groups has since been reported.[125−127] Double fluorination through two subsequent *ortho* fluorinations is a problematic side reaction for the reactions shown in Figure 25: this problem can be addressed by using the weakly coordinating anionic *ortho*-directing group *N*-perfluorotoluamide, which allows for rapid displacement of the monofluorinated product by the substrate, thus affording high selectivity for monofluorination.[128] While direct C−H fluorination is desirable, the necessity of coordinating groups currently limits the scope of the substrates that can be fluorinated; a general selective C−H fluorination of arenes that do not bear coordinating directing groups has not yet been reported.

A practical C−H fluorination of pyridines and diazines with AgF_2 was reported by the Hartwig group (Figure 26).[129] The reaction proceeds at room temperature in 1 h and affords 2-fluoropyridines with high selectivity. Electron-donating and -withdrawing groups are tolerated, along with carbonyl-containing functional groups and base-sensitive functional groups such as alkyl tosylates; unprotected alcohols and amines are not tolerated. A mechanism analogous to amination of

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

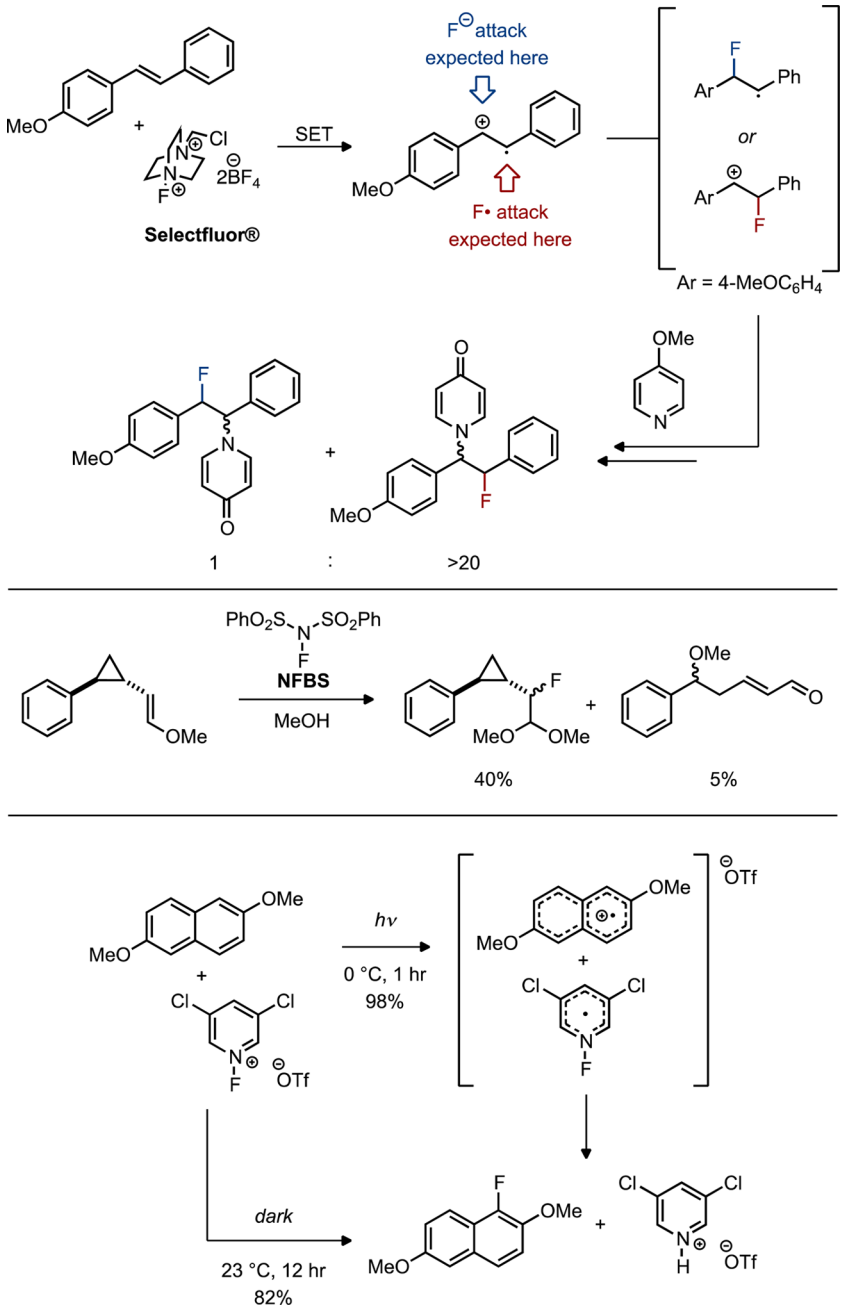


Figure 24. Experimental evidence for SET mechanisms in fluorination reactions with Selectfluor, NFBS, and *N*-fluoropyridinium reagents.

pyridines with $NaNH_2$ (the Chichibabin reaction) was proposed in which nitrogen coordination of the pyridine substrate to AgF_2 is followed by $F^{\bullet}$ transfer and subsequent H atom abstraction by a second equivalent of AgF_2 to afford the 2-fluoropyridine product and 2 equiv of AgF. The silver-mediated reaction was used to prepare a variety of fluorinated derivatives of medicinally relevant compounds, including fluoropioglitazone and a fluorinated Prilosec (omeprazole) precursor. While product isolation and purification is often a challenge for arene C−H fluorination reactions (due to similar polarities of the arene starting materials and fluoroarene products), the 2-fluoropyridine products differ sufficiently in basicity from the pyridine starting materials that product isolation is readily accomplished by standard silica gel chromatography.

4.3. Palladium-Mediated and -Catalyzed Electrophilic Arene Fluorination

Regioselective electrophilic arene fluorination can be addressed through the use of prefunctionalized aryl nucleophiles, which can broaden the potential substrate scope as compared to currently available C−H fluorination reactions that require coordinating directing groups. A variety of arylmetal nucleophiles—including arylboron,[130−132] -germanium,[133] -lead,[134−136] -mercury,[137−140] -platinum,[141] -silicon,[142−147] and -tin[133,134,137,148−153]—can react with fluorine gas, xenon difluoride, hypofluorites, and fluoroxysulfates to afford fluorinated arenes; however, the substrate scope is limited due to the high reactivity of the reagents and often results in unselective fluorination. Transmetalation of the arylmetal reagent to a redox-active transition-metal catalyst can enable a more selective fluorination reaction using milder conditions

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

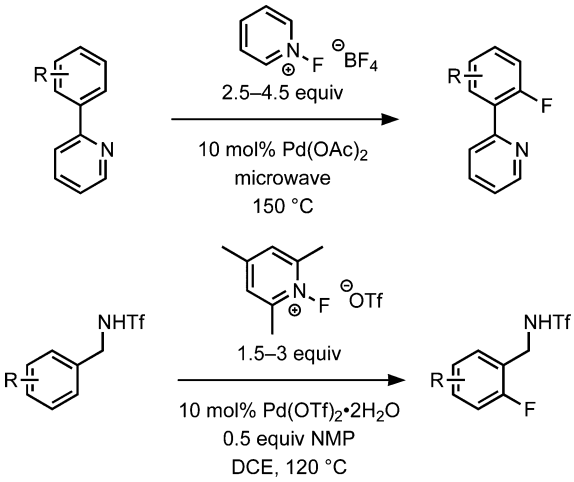


Figure 25. Pd-catalyzed C–H fluorination for arene substrates containing coordinating directing groups.

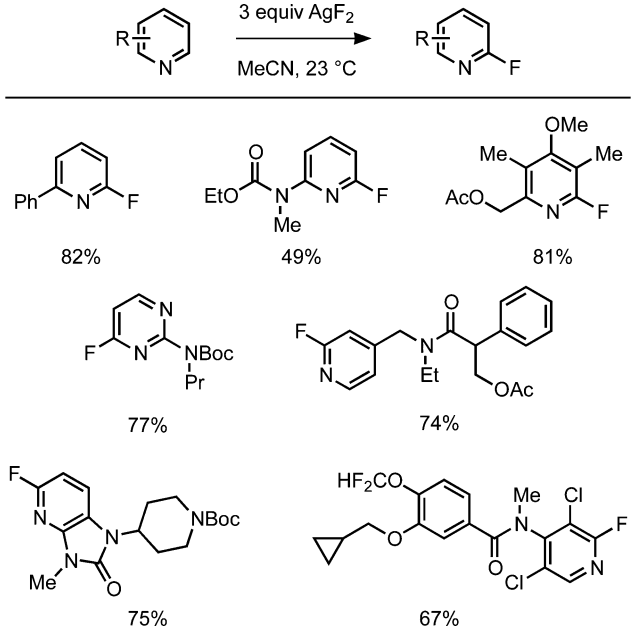


Figure 26. Synthesis of 2-fluoropyridines using AgF_2. Yields given are for isolated products.

and less reactive electrophilic fluorinating reagents (vide supra, Figure 22). Transition-metal catalysts can also afford aryl fluorides through a wider spectrum of mechanisms as compared to main group organometallics, which contributes to their successful use for arene C–F bond formation. As in nucleophilic fluorination, the use of palladium as a mediator or catalyst for electrophilic fluorination has been widely explored; additionally, the viability of multiple mechanisms for electrophilic arene fluorination from palladium has been demonstrated.

4.3.1. C–F Reductive Elimination from Pd(IV). In 2008, our group reported a regioselective fluorination of arylboronic acids using Selectfluor and a stoichiometric palladium complex (Figure 27).[154] The two-step reaction sequence proceeded by transmetalation of the arene substrate from boron to palladium, followed by oxidation to afford the aryl fluoride product. Experimental and computational investigations supported a concerted C–F reductive elimination mechanism in which

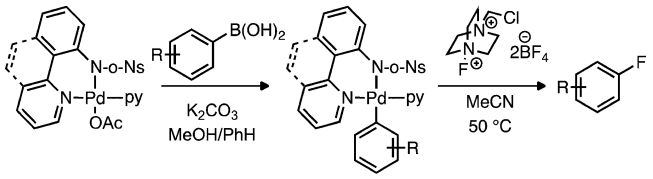


Figure 27. Pd-mediated fluorination of arylboronic acids.

dissociation of one oxygen atom of the tridenate pyridylsulfonamide ligand gives a five-coordinate Pd(IV) complex that readily undergoes C–F reductive elimination (Figure 28).[155,156] While this work established the viability of arene

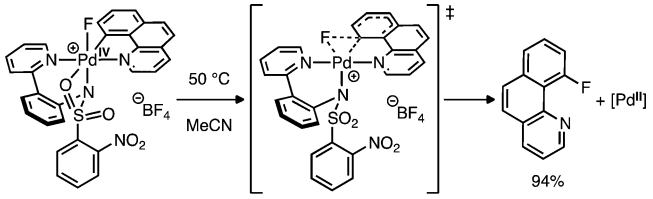


Figure 28. First reported concerted C–F reductive elimination from a palladium(IV) fluoride complex.

fluorination via high-valent palladium complexes, stoichiometric amounts of palladium are needed. The incompatibility of reaction conditions for the transmetalation and fluorination steps prevented the application of this reactivity to a Pd-catalyzed fluorination reaction; however, the Pd-mediated reaction has successfully been applied to synthesis of ^{18}F-labeled arenes for radiotracer synthesis in which stoichiometric Pd is not necessarily of concern (vide infra, section 6.4.2).

The Sanford group has also reported the isolation and reactivity of an arylpalladium(IV) fluoride complex, synthesized by oxidation of an arylpalladium(II) fluoride complex with XeF_2 (Figure 29).[157] Interestingly, the palladium(IV) fluoride

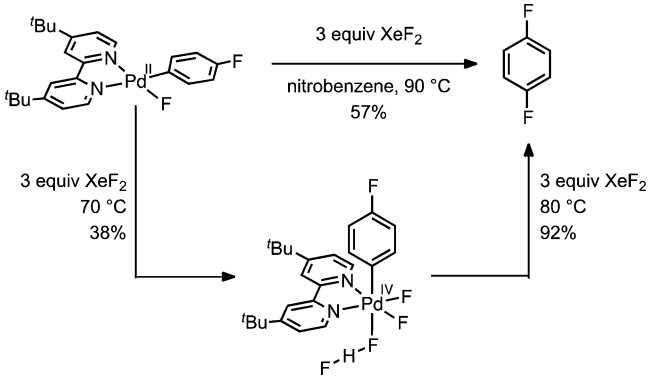


Figure 29. Oxidatively induced C–F bond formation from a palladium(IV) bifluoride complex.

complex did not undergo C–F reductive elimination upon heating, and the aryl fluoride product was only formed when the Pd(IV) complex was treated with an additional excess of XeF_2. Therefore, the mechanism of C–F bond formation in this case is unclear, and both electrophilic C–Pd bond cleavage and C–F reductive elimination are feasible. The presence of multiple fluoride ligands may contribute to the stability of the palladium(IV) fluoride complex: similarly, the arylpalladium(IV) monofluoride complex shown in Figure 28 was observed to be less thermally stable toward C–F reductive elimination

dx.doi.org/10.1021/cr500366b | Chem. Rev. 2015, 115, 612–633

than a related arylpalladium(IV) difluoride complex.[155] These observations may reflect the need for ligand dissociation to form a five-coordinate Pd(IV) complex prior to C−F reductive elimination, which is unfavorable for anionic fluoride ligands that form strong bonds to palladium.

4.3.2. Single-Electron Transfer Pathway via Pd(III). Extension of Pd-mediated fluorination of arylboronic acid derivatives to a Pd-catalyzed reaction was reported in 2013.[158] The Pd-catalyzed fluorination reaction proceeds in an open flask at 4−40 °C using Selectfluor and a terpyridylpalladium(II) catalyst (Figure 30). Aryl trifluoroborates featuring both

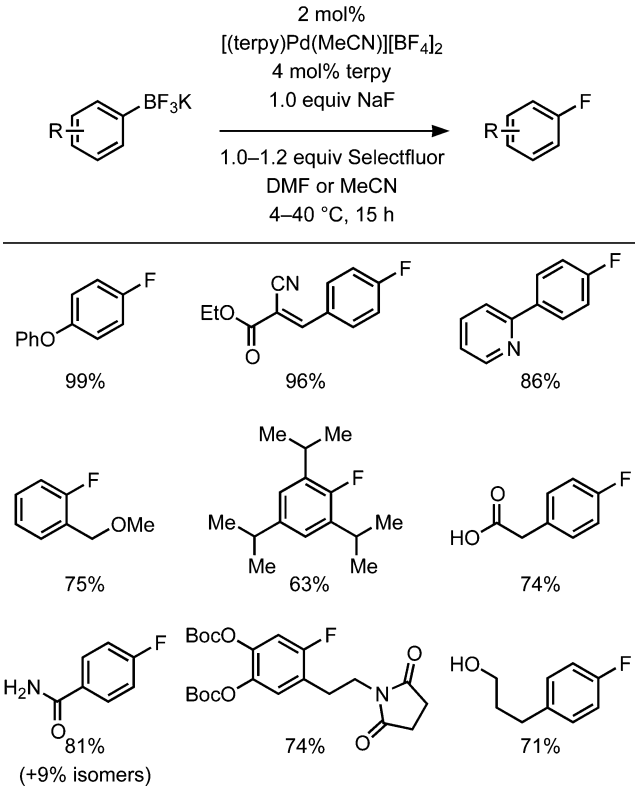


Figure 30. Pd-catalyzed fluorination of aryl trifluoroborates. Yields given are for isolated products.

electron-donating and -withdrawing groups are efficiently fluorinated, as well as very sterically hindered, substrates, and protic functional groups such as alcohols, carboxylic acids, and primary amides are tolerated. Some substrates with electron-withdrawing substituents were found to give constitutional isomers and difluorinated products along with the expected aryl fluoride product (typically ≤10%), and the Pd-catalyzed reaction is ineffective for fluorination of heterocycles. Modified conditions were also reported for fluorination of pinacol boronic esters, arylboronic acids, and MIDA (*N*-methyliminodiacetic acid) boronates.

As described above, a key challenge for metal-catalyzed fluorination of arylboronic acid derivatives is the slow transmetalation of the arene from boron to the transition-metal catalyst under conditions that are suitable for fluorination (section 4.3.1).[154] For the Pd-catalyzed fluorination of arylboronic acid derivatives, mechanistic studies indicate a catalysis cycle that does not involve transmetalation to form an arylpalladium intermediate. Instead, the data suggest an SET mechanism involving a Pd(III) intermediate and C−F bond formation via F• transfer from a partially reduced Selectfluor radical cation (Figure 31). The putative Pd(III) intermediate **3**

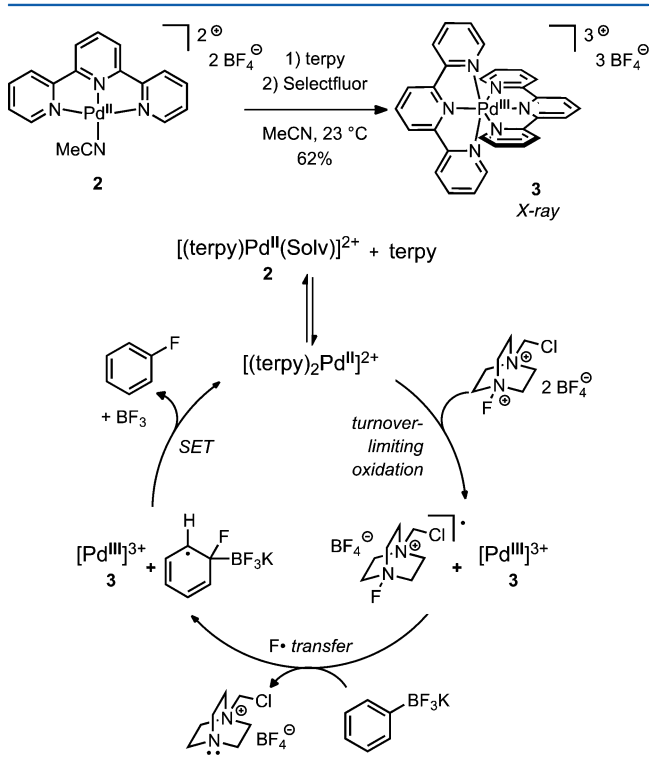


Figure 31. Proposed SET mechanism for Pd-catalyzed fluorination of arylboronic acid derivatives.

was synthesized under conditions relevant to catalysis and was characterized spectroscopically and by X-ray crystallography. The palladium-catalyzed fluorination reaction is unusual in that it seems to proceed without the formation of organopalladium intermediates, yet provides high levels of selectivity.

4.4. Silver-Mediated and -Catalyzed Fluorination

Silver-mediated fluorination was first investigated by Tius using XeF_2.[153,159,160] Silver-catalyzed intramolecular aminofluorination of alkynes with NFBS has also been used to synthesize heteroaryl fluorides such as 4-fluoroisoquinolines.[161] Silver-mediated fluorination of arylboronic acids,[162] arylsilanes,[163] and arylstannanes[164] has been reported using Selectfluor (Figure 32), and further development resulted in a silver-catalyzed fluorination of arylstannanes using F-TEDA-PF_6 (Figure 33).[165] While the silver-catalyzed reaction requires the preparation and use of toxic arylstannanes, this method displays the broadest substrate scope and functional group tolerance in the field so

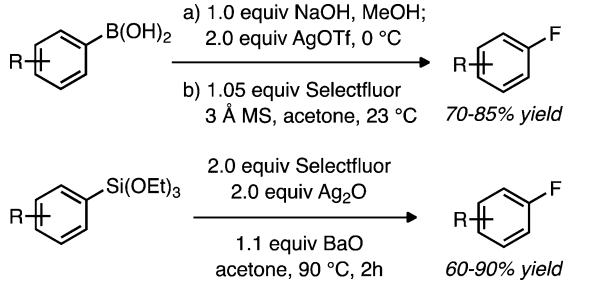


Figure 32. Ag-mediated fluorination of arylboronic acids and arylsilanes.

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

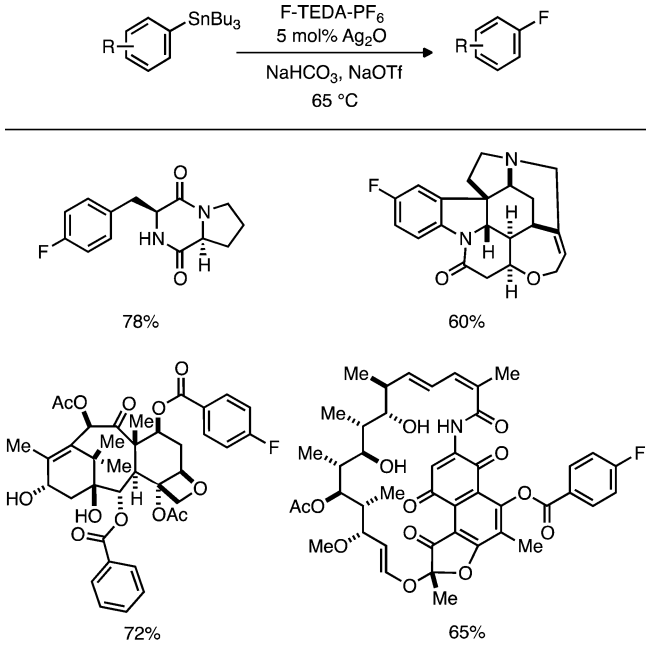


Figure 33. Ag-catalyzed fluorination of functionalized arylstannanes. Yields given are for isolated products.

far, including nitrogenous heteroaryl nucleophiles, nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional groups, and complex natural product derived substrates.

The silver-mediated and -catalyzed arene fluorination reactions are proposed to proceed via the intermediacy of high-valent, multinuclear arylsilver complexes (Figure 34).[164,165] Fluorination of isolated mononuclear arylsilver

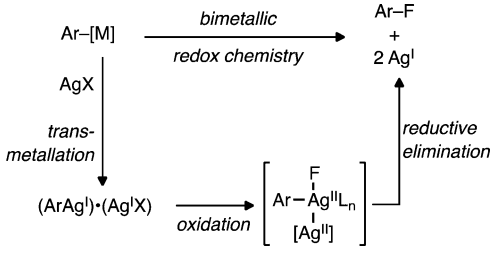


Figure 34. Proposed bimetallic mechanism for Ag-mediated and -catalyzed electrophilic fluorination ([M] = $SnBu_3$, $B(OH)_2$, $Si(OEt)_3$).

complexes was found to proceed in lower yield than when an additional equivalent of AgOTf was added. Redox synergy of the multiple metal centers may help to lower the typically high kinetic barrier to C–F reductive elimination,[120,166] allowing the fluorination of arylstannanes and -boronic acids with silver to occur at temperatures as low as 23 °C.

4.5. Copper-Mediated Fluorination

In 2013, Hartwig and Sanford independently developed a copper-mediated electrophilic fluorination of arylboronic acid derivatives using an *N*-fluoropyridinium oxidant (Figure 35, top), and Sanford also reported a related fluorination of arylstannanes (Figure 35, bottom).[167,168] The copper-mediated fluorination reactions are effective for arenes bearing both electron-donating and -withdrawing substituents, as well as some heterocyclic substrates. However, superstoichiometric

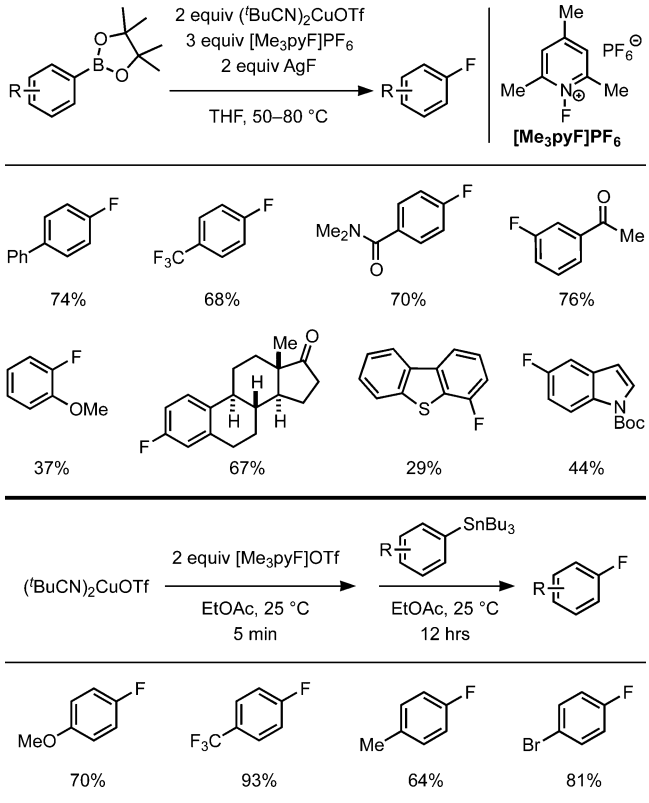


Figure 35. Cu-mediated fluorination of arylboronic acid derivatives and arylstannanes. Yields were determined by ^{19}F NMR spectroscopy.

amounts of both transition metal and oxidant are required, and significant amounts of side products resulting from protodemetalation were observed. Isotopic labeling studies suggested that, in the case of arylboronic acid derivatives, protodemetalation is primarily caused by adventitious water.[167]

In the copper-mediated fluorination of pinacol boronic esters, mechanistic studies suggested that the reaction proceeds via oxidation of Cu(I) to a copper(III) fluoride complex, followed by rate-limiting transmetalation of the arene from boron to Cu(III) (Figure 36).[167] The putative copper(III)

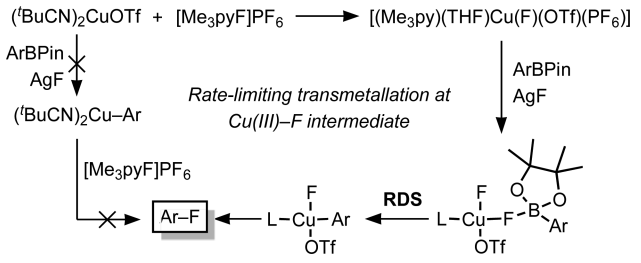


Figure 36. Proposed mechanism for Cu-mediated fluorination of arylboronic acid derivatives involving arene transmetalation at Cu(III) (RDS = rate-determining step).

fluoride complex was characterized by ^{19}F NMR spectroscopy and was observed to undergo reaction with pinacol boronic esters only in the presence of AgF. Transmetalation was not observed to occur at Cu(I), and an independently prepared arylcopper(I) complex did not produce the aryl fluoride product upon reaction with the *N*-fluoropyridinium oxidant. The copper-mediated fluorination reaction is therefore unique compared to the reported palladium- and silver-mediated

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612–633

electrophilic fluorination reactions in that arene transmetalation occurs at the high-valent state of the metal mediator.

4.6. Electrophilic Fluorination of Main Group Organometallic Compounds

The synthetic utility of electrophilic fluorination of non-redox-active arylmetal complexes is generally limited by the high reactivity of the reagents required, such as XeF_2. Use of more electropositive metals, such as aryllithium reagents, can allow reaction with less reactive electrophilic fluorinating reagents, such as *N*-fluorinated reagents (vide supra, Figure 23).[169−171] However, such basic nucleophiles can also undergo unproductive SET processes to give rise to protodemetalated side products. The fluorination of Grignard reagents with electrophilic *N*-fluorinated reagents is currently the most reliable method for simple aryl nucleophiles, but is narrow in scope due to the basicity and nucleophilicity of the arylmagnesium reagents (Figure 37).[169,172−174] An attractive feature of

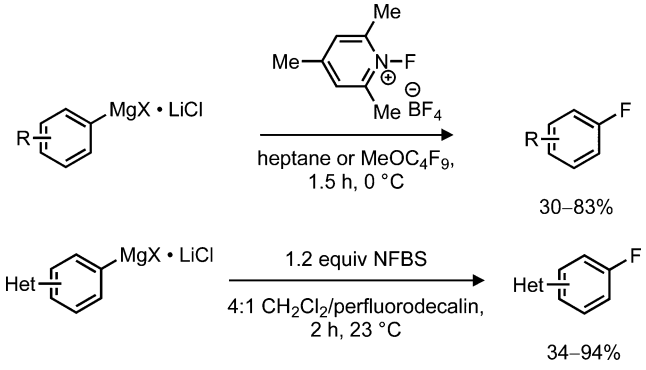


Figure 37. Electrophilic fluorination of aryl Grignard reagents.

Grignard fluorination is the ability to fluorinate heterocycles, which is a challenging class of substrates for many transition-metal-catalyzed fluorination reactions. Undesired side products from protodemetalation can be minimized through appropriate choice of the solvent and reagents.

5. OXIDATIVE FLUORINATION WITH FLUORIDE

As described above, fluorine is the most electronegative and oxidizing element, and therefore, most electrophilic fluorination reactions use reagents that are ultimately derived from fluorine gas (F_2). The development of electrophilic fluorination reactions that utilize fluoride anion and a separate oxidant is therefore conceptually challenging; however, the prospect of merging the benefits of electrophilic fluorination with the use of inexpensive and readily available fluoride salts is highly attractive. Despite the challenge, several groups have reported the first successful examples of oxidative fluorination reactions using fluoride.

5.1. Oxidative Fluorination of C−H Bonds

Oxidative fluorination of C−H bonds has only emerged recently in the literature and to date is less developed for arene C−H bonds as compared to aliphatic C−H bonds. The oxidative C−H fluorination of aliphatic substrates was established by Groves in 2012 using a manganese(III) porphyrin catalyst in the presence of silver fluoride and iodosylbenzene.[175] Sanford and co-workers also reported a Pd-catalyzed oxidative C−H fluorination of functionalized 8-methylquinolinyl substrates.[176] The reaction is postulated to occur through high-valent palladium fluoride intermediates and is enabled by the use of $PhI(OPiv)_2$ and AgF, a reagent combination that was first reported by the Liu group for the oxidative fluorination of aliphatic C−Pd bonds.[177] While the reported reaction conditions for aliphatic C−H bonds have not yet been applied to arene substrates, the conceptual advance is significant and is poised to impact aryl fluoride synthesis in the near future.

Studies by Meng and Li demonstrated the regioselective *para* fluorination of anilides using $PhI(OPiv)_2$ and hydrogen fluoride/pyridine (Figure 38),[178] conditions similar to those

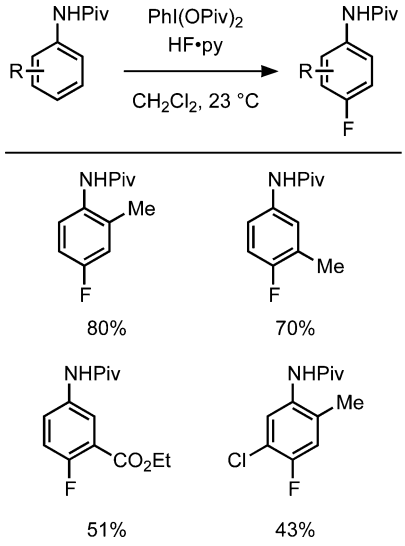


Figure 38. Oxidative C−H fluorination of anilides with *para* selectivity. Yields given are for isolated products.

previously reported by Langlois for oxidative fluorination of 4-*tert*-butylacetanilide and 4-*tert*-butylphenols.[179] While the substrate scope is limited to the use of anilides, a variety of substitution patterns on the arene are tolerated, and the reaction proceeds under mild conditions. Work from the Daugulis group demonstrated that Cu catalysis can be used for oxidative C−H fluorination of benzoic acid derivatives using a coordinating directing group derived from 8-aminoquinoline (Figure 39).[180] A combination of AgF as the fluoride source

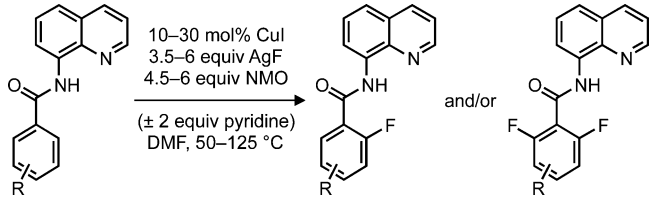


Figure 39. Cu-catalyzed N-directed oxidative fluorination of arene C−H bonds with AgF and NMO.

and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant was used, resulting in mono- or difluorination of the arene substrates.

5.2. Oxidative Fluorination of Arylmetal Complexes

In 2012, our group reported that arylnickel(II) complexes could be used for the regioselective synthesis of aryl fluorides, with a combination of a fluoride source such as tetrabutylammonium triphenyldifluorosilicate (TBAT) and hypervalent iodine oxidant **4** (Figure 40).[181] The nickel-mediated oxidative

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

fluorination reaction was subsequently applied to the synthesis of ^{18}F-labeled arenes for use as PET tracers (vide infra, section 6.4.2).

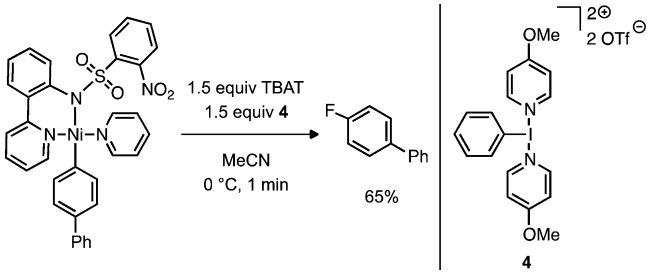


Figure 40. Oxidative fluorination of arylnickel(II) complexes with TBAT and hypervalent iodine oxidant **4**. The yield given is for the isolated product.

The Sanford group has described that their previously reported copper-mediated electrophilic fluorination of aryl trifluoroborates can be performed using KF and an excess of $Cu(OTf)_2$ (4 equiv) in place of an *N*-fluorinated oxidant (Figure 41).[182] In this reaction, copper is hypothesized to play

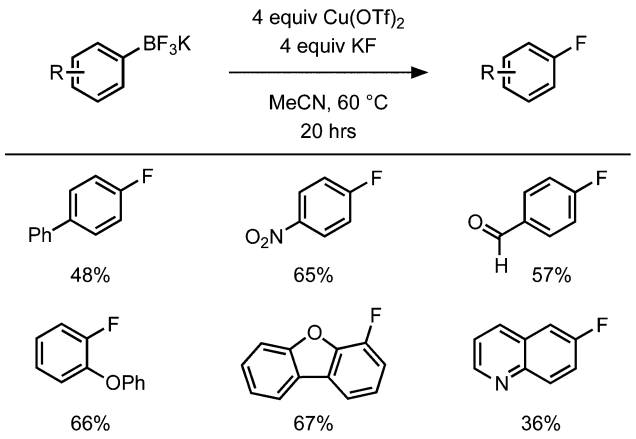


Figure 41. $Cu(OTf)_2$-mediated fluorination of aryl trifluoroborates with KF. Yields given are for isolated products.

dual roles: as a redox-active mediator of C−F bond formation and as a stoichiometric oxidant. Transmetalation is proposed to occur at a copper(II) fluoride complex, followed by oxidation by a second equivalent of $Cu(OTf)_2$ to afford an arylcopper(III) fluoride (as well as a Cu(I) byproduct) and finally C−F reductive elimination from Cu(III) (Figure 42).

6. ARENE ^{18}F-FLUORINATION FOR POSITRON EMISSION TOMOGRAPHY

One application of C−F bond formation that has received significant attention is radiofluorination using the isotope ^{18}F for the synthesis of tracer molecules used in PET. While a variety of positron-emitting isotopes with short half-lives have been used in PET tracers (such as ^{11}C, ^{13}N, and ^{15}O, all with half-lives ≤20 min), ^{18}F is often preferred due to its half-life of 110 min, which makes the time scale of tracer synthesis and imaging studies more practical.[10] In this section, we will review modern methods for arene ^{18}F-fluorination, as well as highlight key challenges that render radiofluorination a particularly difficult synthetic endeavor. We do not aim to exhaustively review available methods for ^{18}F incorporation into small

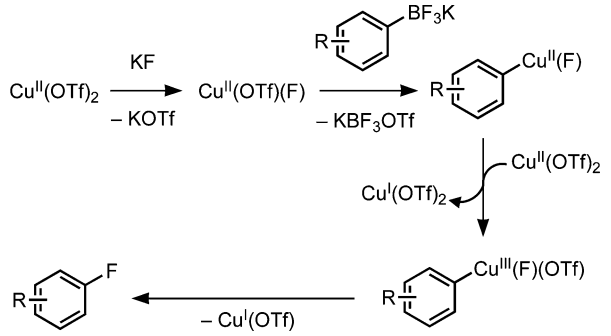


Figure 42. Proposed mechanism for Cu-mediated oxidative fluorination.

molecules, but rather to limit our discussion to fundamental advances in arene C−^{18}F bond formation within the past decade. More comprehensive reviews on ^{18}F-fluorination are available.[10,183−187]

6.1. Challenges of Translation

The development of selective and practical C−F bond forming reactions for the late-stage synthesis of functionalized aryl fluorides is already no easy task; however, formation of the C−F bond is only one challenge associated with the synthesis of ^{18}F PET tracers. Further challenges to the application of fluorination reactions to PET include the need for short reaction times, due to the short half-life of ^{18}F, as well as unique reaction conditions for ^{18}F chemistry. For example, extensive drying of fluoride, as is often required for metal-mediated fluorination reactions using [^{19}F]fluoride, can be impractical when starting from aqueous [^{18}F]fluoride, as ^{18}F PET tracer synthesis is typically executed on a nanomole scale. As a further consequence, the smaller ratio of fluorine to water can be problematic because hydrated fluoride has diminished nucleophilicity. Due to such factors, the translation of promising modern fluorination reactions to radiochemistry is often problematic.[188]

6.2. [^{18}F]Fluoride vs [^{18}F]F_2 and Specific Activity

When transitioning from ^{19}F to ^{18}F chemistry, it is most practical to use nucleophilic [^{18}F]fluoride, which can be produced as an aqueous solution in high specific activity by a cyclotron.[10] Specific activity is defined as the radioactivity of a material divided by the molar amount of the material; in the context of ^{18}F PET tracer synthesis, increased specific activity can be considered as an increase in the ratio of ^{18}F to the natural, PET-inactive isotope ^{19}F. However, while use of [^{18}F]fluoride is desirable, many useful electrophilic arene fluorination reactions require the use of electrophilic fluorinating reagents such as Selectfluor (vide supra, Figure 23). It is important to note that ^{18}F electrophilic fluorinating reagents are generally derived from electrophilic [^{18}F]fluorine gas ([^{18}F]F_2), which requires dilution with [^{19}F]F_2 as a carrier gas.[189] The need for [^{19}F]F_2 as a carrier gas lowers the ^{18}F/^{19}F ratio, resulting in a lower specific activity for [^{18}F]F_2 than for [^{18}F]fluoride. High specific activity is often critical for imaging biological targets with low concentration, such as neurotransmitter receptors in the brain.[10] [^{18}F]F_2 gas is also less practical to handle as compared to [^{18}F]fluoride due to its high reactivity.

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

6.3. Radiofluorination with [^{18}F]F_2-Derived [^{18}F]Electrophilic Fluorinating Reagents

Several ^{18}F-labeled electrophilic fluorinating reagents have been synthesized from [^{18}F]fluorine gas such as acetyl [^{18}F]-hypofluorite,[190,191] [^{18}F]XeF_2,[190,192−196] ^{18}F-labeled *N*-fluoro-sulfonamide or imide reagents,[197,198] and [^{18}F]-*N*-fluoropyridinium salts.[199] Electrophilic radiofluorination by direct fluorination of arenes, such as for the synthesis of [^{18}F]-fluoro-3,4-dihydroxyphenylalanine ([^{18}F]F-DOPA),[200] can lead to multiple fluorinated products and typically is not tolerant of many functional groups. Radiochemical fluorodemetalation has been used for aryl organometallic reagents,[197] arylsilanes,[144,145] and arylstannanes[148,149,191] and can afford selective fluorination.

Gouverneur and co-workers have reported the synthesis of [^{18}F]Selectfluor bis(triflate)[189] using high specific activity [^{18}F]F_2 prepared via the "Solin method"[201] (Figure 43, top).

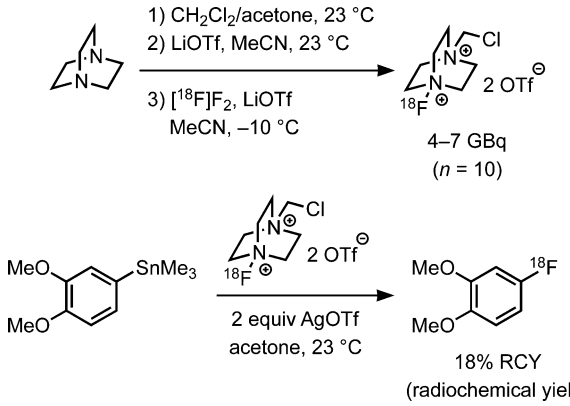


Figure 43. Synthesis and fluorodestannylation reactivity of [^{18}F]-Selectfluor bis(triflate) (*n* = number of experiments).

The electrophilic fluorodestannylation of electron-rich arenes was demonstrated, and the radiofluorination reaction proceeded in 20 min at room temperature in the presence of stoichiometric AgOTf. Under these conditions, a radiochemical yield (RCY) of 18% was reported for [^{18}F]fluoroveratrole, with specific activities of up to 16 GBq·μmol^{-1} (432 mCi·μmol^{-1}; Figure 43, bottom). Subsequently, [^{18}F]Selectfluor bis(triflate) was used in a synthesis of 6-[^{18}F]fluoro-L-DOPA, using a silver-mediated electrophilic fluorination of the corresponding arylboronic ester (vide supra, Figure 32), affording the radiofluorinated product in 19 ± 12% RCY (Figure 44).[202]

6.4. Radiofluorination with Nucleophilic [^{18}F]Fluoride

6.4.1. S_NAr-Type Radiofluorination Reactions. Arene radiofluorination reactions with [^{18}F]fluoride most commonly consist of substitution reactions of aryl electrophiles functionalized with appropriate leaving groups.[203,204] Alkali-metal

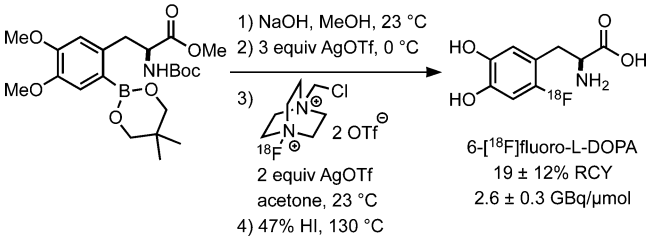


Figure 44. Use of [^{18}F]Selectfluor bis(triflate) in the silver-mediated synthesis of 6-[^{18}F]fluoro-L-DOPA.

[^{18}F]fluoride salts are typically used along with cryptands to increase the fluoride solubility and nucleophilicity.[185] Reaction solvents are chosen such that S_NAr reactions are facilitated, with the most commonly used solvents being polar aprotic solvents such as DMF, DMSO, and acetonitrile. For substrates to undergo S_NAr-type substitution reactions, they generally require at least one electron-withdrawing group on the arene *ortho* or *para* to the leaving group, which can be a nitro, trialkylammonium, halide, or sulfonate group. For example, nicotinic acetylcholine receptor radioligands have been synthesized by nucleophilic aromatic substitution, with a trimethylammonium group as the leaving group.[205]

Diaryliodonium salts can be fluorinated with [^{18}F]fluoride to yield radiolabeled aryl fluorides (see Figure 17 for earlier examples of nucleophilic fluorination of diaryliodonium salts).[206,207] The selectivity for fluorination between the two arenes attached to iodine is based on the electronic structure of the arenes, wherein the more electron-poor arene is fluorinated: electron-rich 2-thiophene has therefore been used successfully as a "dummy" ligand, allowing for selective fluorination of the desired arene (Figure 45). Additionally, the steric bulk near the

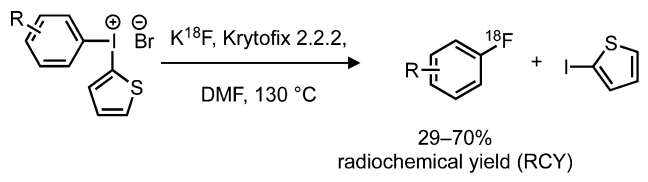


Figure 45. Nucleophilic radiochemical fluorination of aryl(2-thienyl)-iodonium bromides.

iodine atom plays a key role, and *ortho*-substituted arenes are more susceptible to fluorination because of the *ortho* effect.[208] With *ortho*-substituted substrates, radiochemical yields as high as 60% can be achieved. The counterion of the iodonium salts also has a significant effect on the yield of fluorination, with more weakly coordinating and non-nucleophilic counteranions promoting higher radiochemical yields. Sanford and Scott have reported that the copper-catalyzed nucleophilic fluorination of unsymmetrical diaryliodonium salts (vide supra, Figure 18) can be used to achieve selective arene radiofluorination with [^{18}F]fluoride (Figure 46).[209] Using this method, the synthesis of protected versions of the PET tracers 4-[^{18}F]-fluorophenylalanine and 6- [^{18}F]fluoro-L-DOPA was demonstrated.

Further development of nucleophilic radiofluorination of aryliodonium salts has led to an improved protocol using iodonium ylides which allows for a regioselective radiofluorination of unactivated (hetero)arenes (Figure 47).[210−212] Key to this advance was the design of novel spirocyclic iodonium ylides, which provide enhanced stability and prevent common decomposition and disproportionation reactions of the I(III) salts.[212] The iodonium ylide method was used to prepare challenging radiolabeled products, including 4-[^{18}F]-fluorobenzyl azide and 5-[^{18}F]fluorouracil (Figure 47, bottom). An important remaining need is the development of improved methods for the synthesis of complex aryliodonium salts, which would increase the potential utility of aryliodonium salts for the synthesis of PET tracers. Current syntheses of aryliodonium salts often employ strong Lewis or Brønsted acids.[213]

Gouverneur and co-workers have developed an oxidative fluorination of *p*-*tert*-butylphenols in which the *tert*-butyl group

dx.doi.org/10.1021/cr500366b | Chem. Rev. 2015, 115, 612−633

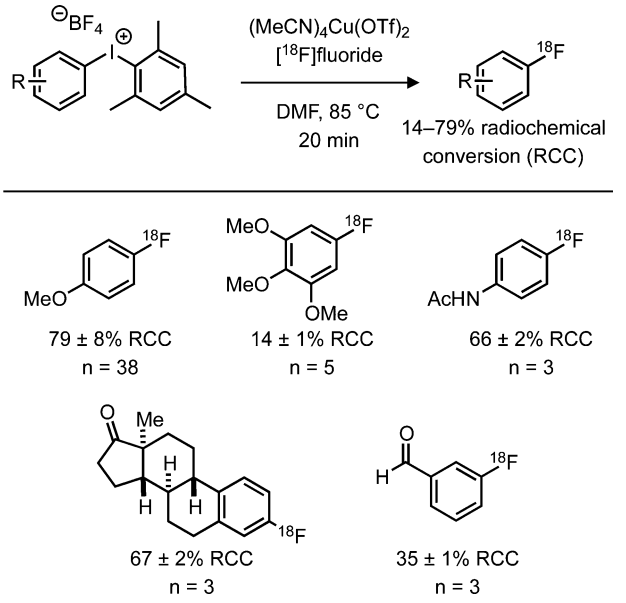


Figure 46. Nucleophilic radiochemical fluorination of diaryliodonium salts catalyzed by copper.

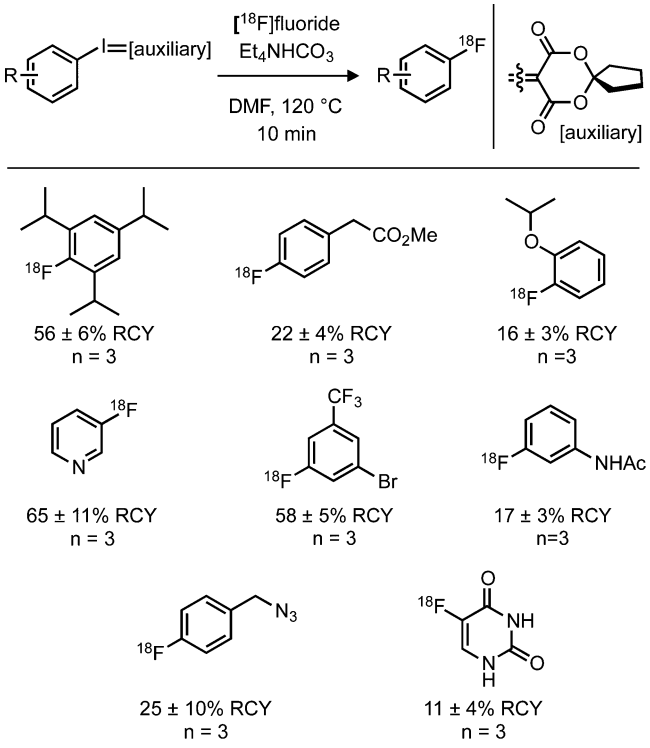


Figure 47. Nucleophilic radiochemical fluorination of spirocyclic iodonium ylides.

is replaced by [^{18}F]fluoride in the presence of iodobenzene diacetate and trifluoroacetic acid (Figure 48).[214] The reaction is based on a two-step procedure previously reported by Langlois using [^{19}F]fluoride and is proposed to occur via oxidative fluorination/dearomatization, followed by rearomatization.[179] The reaction tolerates a wide range of electronically diverse *ortho* substituents, including halides, other *tert*-butyl groups, carbonyl groups, and olefins. Reported radiochemical yields for various *p*-*tert*-butylphenol derivatives range from 7% to 21%.

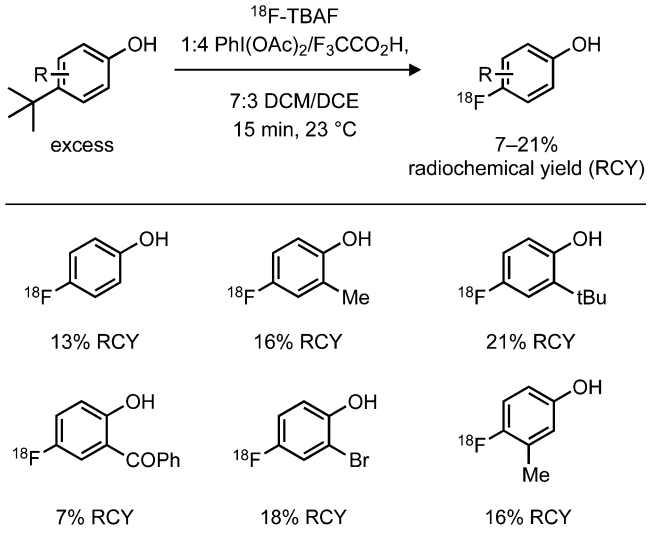


Figure 48. Oxidative radiofluorination of *p*-*tert*-butylphenols.

6.4.2. Transition-Metal-Mediated Radiofluorination Reactions with [^{18}F]Fluoride. To date, several metal-mediated radiofluorination reactions with [^{18}F]fluoride have been reported. In 2011, our group reported the synthesis of ^{18}F-labeled fluoroarenes with [^{18}F]fluoride using a two-step "fluoride capture/transfer" sequence (Figure 49).[215,216] In the "capture" step, [^{18}F]fluoride binds to a cationic Pd(IV) complex to generate a palladium(IV) [^{18}F]fluoride complex that can behave as an electrophilic fluorinating reagent: reaction with an arylpalladium(II) complex (synthesized by transmetalation from an arylboronic acid derivative) results in oxidative fluorine transfer to give an arylpalladium(IV) [^{18}F]fluoride complex that undergoes C−F reductive elimination to provide the ^{18}F-labeled aryl fluoride. Synthesis of ^{18}F-labeled aryl fluorides with electron-rich arenes and a variety of functional groups was demonstrated. Mechanistic studies indicate that the palladium(IV) [^{18}F]fluoride complex is formed with high rates, even at the nano- to micromolar fluoride concentrations typical for radiosyntheses with ^{18}F, due to fast formation of an outer-sphere complex between fluoride and the cationic Pd(IV) precursor and that the subsequent fluorine transfer to the arylpalladium(II) complex likely proceeds through an unusual SET/fluoride transfer/SET mechanism (Figure 50).[115]

While the palladium-mediated radiofluorination sequence shown in Figure 50 addresses the conceptual challenge of arene fluorination with [^{18}F]fluoride, the need for two separate reaction steps involving two palladium complexes is not ideal. Building on the palladium-mediated procedure, our group subsequently reported a one-step radiofluorination of arylnickel(II) complexes (synthesized by oxidative addition of an aryl halide to a Ni(0) precursor) using aqueous [^{18}F]fluoride and oxidant **4** (Figure 51).[181] The oxidative fluorination reaction proceeds in less than 1 min for a variety of arylnickel(II) complexes and generally provides higher radiochemical yields than the two-step palladium-mediated sequence. The one-pot method involving only the nickel aryl complex, fluoride, and oxidant circumvents the need for preparation of a separate electrophilic fluorinating reagent from [^{18}F]fluoride. Additional steps result in an overall longer preparation time for the final ^{18}F-labeled molecule: due to the 110 min half-life of ^{18}F, the shortest possible preparation time is desirable. The stability of the nickel aryl complexes could

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

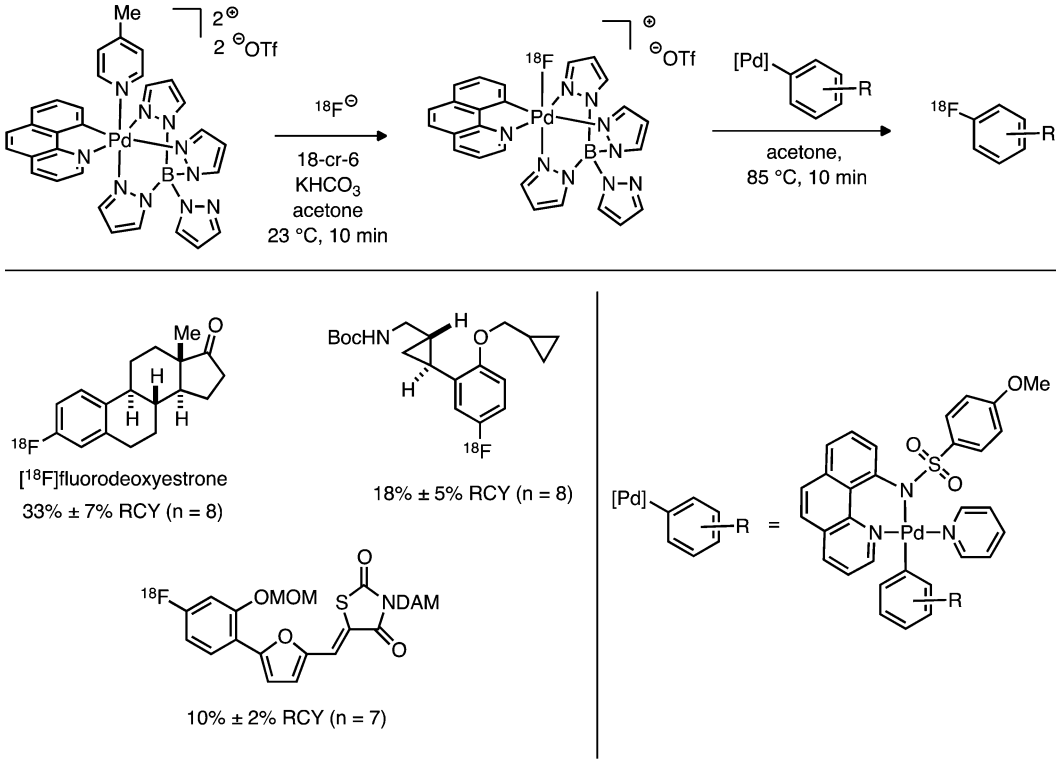


Figure 49. Palladium-mediated radiofluorination using a palladium(IV) [^{18}F]fluoride reagent.

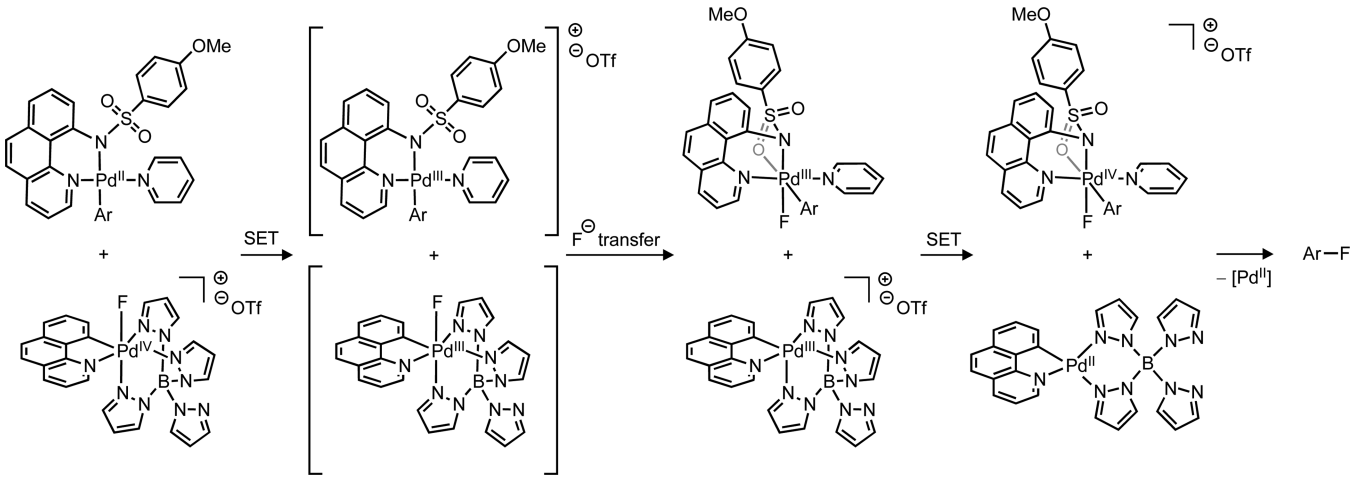


Figure 50. Proposed SET/fluoride transfer/SET mechanism for the Pd-mediated synthesis of ^{18}F-labeled aryl fluorides.

potentially allow for their eventual use in the synthesis of PET tracers;[217] however, oxidant **4** displays limited stability, and replacement of **4** with a suitable, stable oxidant would be a useful advance.

In 2014, Gouverneur and co-workers reported a copper-mediated radiofluorination of (hetero)arylboronic esters with [^{18}F]fluoride using $Cu(OTf)_2(py)_4$ in DMF at 110 °C.[218] Electron-rich, electron-poor, and sterically hindered arenes are effectively fluorinated in 20 min, and radiochemical yields up to 83 ± 2% were reported (Figure 52). The utility of the copper-mediated method was exhibited through efficient synthesis of known radiotracers, including [^{18}F]DAA1106 and 6-[^{18}F]-fluoro-*m*-D,L-tyrosine in 59 ± 5% and 58 ± 9% RCY, respectively (Figure 52, bottom). Production of 6-[^{18}F]fluoro-L-DOPA from the corresponding arylboronic ester on a clinical dose scale was also demonstrated: beginning with 13 GBq (351 mCi) of [^{18}F]fluoride, a dose of 609 MBq (16.5 mCi) of 6-[^{18}F]fluoro-L-DOPA was isolated, corresponding to a 12% decay-corrected RCY. While direct comparison of ^{19}F- and ^{18}F-fluorination reactions is often challenging, we speculate that the mechanism of the copper-mediated radiofluorination reaction may be related to the mechanism of copper-mediated oxidative fluorination of arylboronic acid derivatives previously described by Sanford (vide supra, Figure 44).

7. SUMMARY AND OUTLOOK

The synthesis of functionalized aryl fluorides by C–F bond formation remains a challenging and important problem. The results reviewed here demonstrate that the transition-metal catalysis approach has been the most successful to date, but there is currently a lack of broadly useful transition-metal-

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612–633

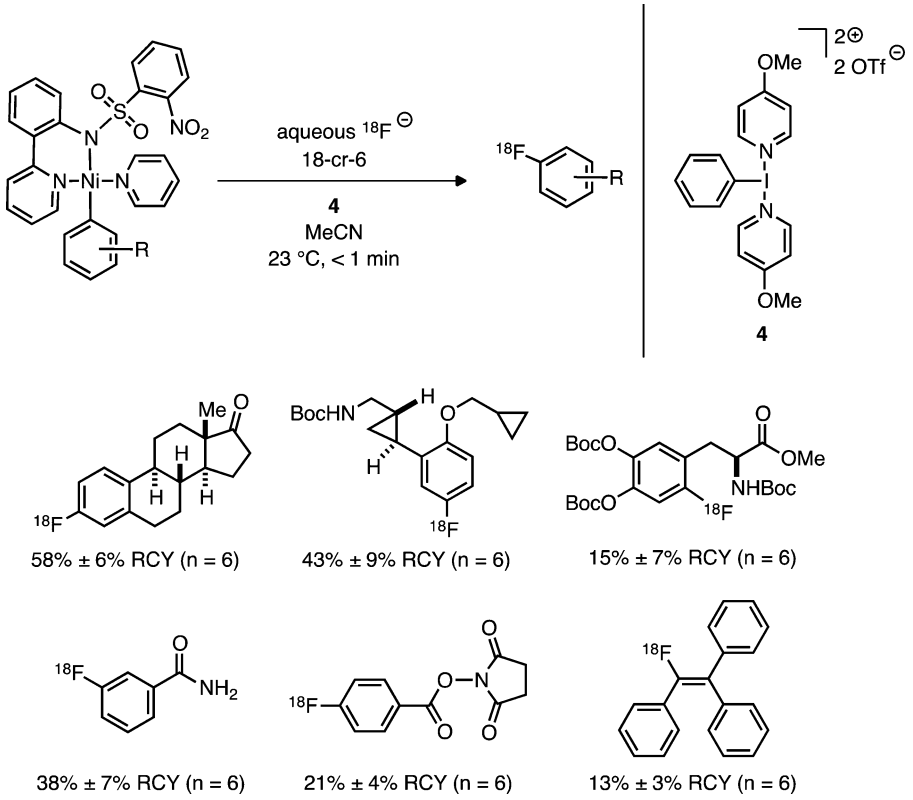


Figure 51. Nickel-mediated arene radiofluorination with aqueous [^{18}F]fluoride.

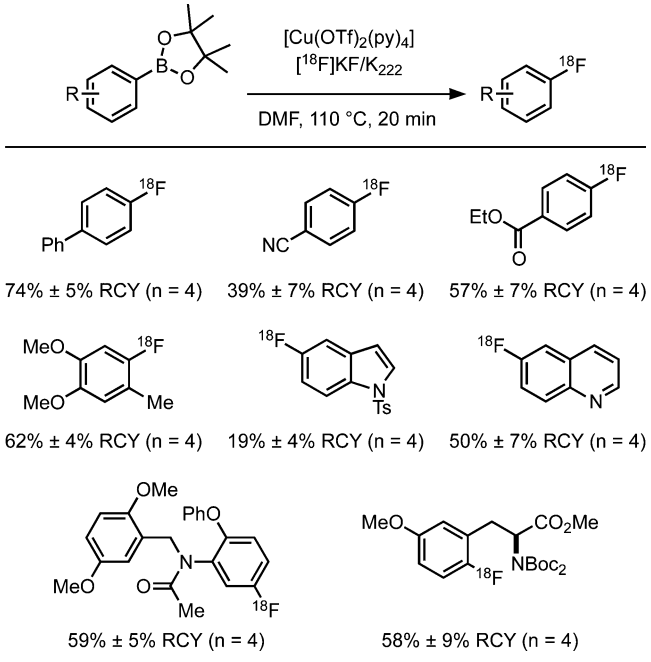


Figure 52. Copper-mediated radiofluorination of (hetero)arylboronic esters with [^{18}F]fluoride.

catalyzed fluorination reactions. Of the currently available methods, metal-catalyzed electrophilic arene fluorination has proven the most effective for highly functionalized substrates, but requires expensive electrophilic fluorinating reagents with poor atom economy, as well as arylmetal substrates that are not always readily available. Metal-catalyzed nucleophilic arene fluorination uses inexpensive fluoride salts and aryl (pseudo)-halide substrates, but a key remaining challenge is the basicity of fluoride under the reaction conditions, which can lead to undesired side reactions. From a perspective of step and atom economy, direct C−H fluorination is ideal, and a handful of metal-catalyzed C−H fluorination reactions have been reported. However, such reactions are thus far limited in their functional group tolerance and substrate scope or require directing groups in the case of aromatic C−H fluorination. Selective C−H functionalization of arenes, without the use of coordinating directing groups, is an area of active research, and a selective C−H fluorination of complex arene substrates would be a powerful advance for the field of fluorination. As an additional conceptual challenge to consider when targeting arene C−H fluorination, the fluorinated product is typically difficult to separate from unreacted starting material by standard chromatographic methods (i.e., C−F vs C−H separation). Such technical issues further complicate the development of practical fluorination reactions, though recent advances in chromatographic separation may help to alleviate fluoroarene purification issues.[219]

Despite the limitations of current methods, modern C−F bond forming reactions have made fluorinated arenes more readily available than ever before. In particular, the methods described herein have begun to impact research areas that do not require large amounts of material, such as drug discovery and PET. Future research in the field will need to focus on the development of practical and selective arene fluorination reactions that also address the needs of large-scale applications. Such reactions will need to be predictable and general and use readily available and inexpensive substrates, fluoride sources, and catalysts.

dx.doi.org/10.1021/cr500366b | *Chem. Rev.* 2015, 115, 612−633

AUTHOR INFORMATION

Corresponding Author

*E-mail: ritter@chemistry.harvard.edu.

Notes

The authors declare no competing financial interest.

Biographies

Michael G. Campbell was born in 1986 in Pennsylvania and received his B.S. in 2008 from Loyola University Maryland. He earned his Ph.D. in 2014 from Harvard University, where he worked on the chemistry of palladium(III) complexes with Prof. Tobias Ritter, including Pd-catalyzed fluorination. He is currently a postdoctoral fellow at the Massachusetts Institute of Technology with Prof. Mircea Dincă.

Tobias Ritter was born in 1975 in Lübeck, Germany. He studied in Braunschweig, Bordeaux, Lausanne, and Stanford. After research with Prof. Barry M. Trost at Stanford, he obtained his Ph.D. working with Prof. Erick M. Carreira at ETH Zurich in 2004. He then carried out postdoctoral research with Prof. Robert H. Grubbs at Caltech. In 2006, he was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard and promoted to Associate Professor in 2010 and to Professor of Chemistry and Chemical Biology in 2012.

ACKNOWLEDGMENTS

M.G.C. thanks the Department of Energy Office of Science Graduate Fellowship program and the Camille and Henry Dreyfus Postdoctoral Program in Environmental Chemistry for graduate and postdoctoral fellowships, respectively.

REFERENCES

(1) Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8610.
(2) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804.
(3) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.
(4) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.
(5) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
(6) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(7) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(8) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.
(9) Hung, M.-H.; Farnham, W. B.; Feiring, A. E. In *Fluoropolymers: Synthesis*; Hougham, G., Cassidy, P. E., Johns, K., Davidson, T., Eds.; Plenum: New York, 1999; Vol. *1*, pp 51−66.
(10) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501.
(11) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. *Chem. Soc. Rev.* **2012**, *41*, 31.
(12) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.
(13) Clark, J. H.; Wails, D.; Bastock, T. W. *Aromatic Fluorination*; CRC Press: Boca Raton, FL, 1996.
(14) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley: Weinheim, Germany, 2004.
(15) Shannon, R. D. *Acta Crystallogr., A* **1976**, *32*, 751.
(16) Emsley, J. *Chem. Soc. Rev.* **1980**, *9*, 91.
(17) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225.
(18) O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. *Nature* **2002**, *416*, 279.
(19) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004**, *427*, 561.
(20) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186.
(21) Gribble, G. W. In *Name Reactions for Functional Group Transformations*; Li, J. J., Ed.; Wiley: Hoboken, NJ, 2007; pp 552−563.
(22) Rutherford, K. G.; Redmond, W.; Rigamonti, J. *J. Org. Chem.* **1961**, *26*, 5149.
(23) Sellers, C.; Suschitzky, H. *J. Chem. Soc., C* **1968**, 2317.
(24) Milner, D. J. *Synth. Commun.* **1992**, *22*, 73.
(25) Olah, G. A.; Welch, J. *J. Am. Chem. Soc.* **1975**, *97*, 208.
(26) Shinhama, K.; Aki, S.; Furuta, T.; Minamikawa, J.-I. *Synth. Commun.* **1993**, *23*, 1577.
(27) Rosenfeld, M. N.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, 914.
(28) Chu, C.-K.; Kim, J.-H.; Kim, D. W.; Chung, K.-H.; Katzenellenbogen, J. A.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2005**, *26*, 599.
(29) Döbele, M.; Vanderheiden, S.; Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5986.
(30) Kovac, M.; Anderluh, M.; Vercouillie, J.; Guilloteau, D.; Emond, P.; Mavel, S. *J. Fluorine Chem.* **2013**, *147*, 5.
(31) Laali, K. K.; Gettwert, V. J. *J. Fluorine Chem.* **2001**, *107*, 31.
(32) Gottlieb, H. B. *J. Am. Chem. Soc.* **1936**, *58*, 532.
(33) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034.
(34) Jang, S.-W.; Park, S.-W.; Lee, B.-S.; Chi, D. Y.; Song, C. E.; Lee, S.-Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 881.
(35) Grushin, V. V.; Marshall, W. J. *Organometallics* **2008**, *27*, 4825.
(36) Sheppard, T. D. *Org. Biomol. Chem.* **2009**, *7*, 1043.
(37) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2002.
(38) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9047.
(39) Hartwig, J. F. *Nature* **2008**, *455*, 314.
(40) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.
(41) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
(42) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
(43) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
(44) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701.
(45) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(46) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
(47) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.
(48) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.
(49) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914.
(50) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321.
(51) Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592.
(52) Fraser, S. L.; Antipin, M. Y.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 4769.
(53) Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774.
(54) Marshall, W. J.; Thorn, D. L.; Grushin, V. V. *Organometallics* **1998**, *17*, 5427.
(55) Grushin, V. V. *Chem.—Eur. J.* **2002**, *8*, 1006.
(56) Mezzetti, A.; Becker, C. *Helv. Chim. Acta* **2002**, *85*, 2686.
(57) Grushin, V. V.; Marshall, W. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4476.
(58) Richmond, T. G. *Coord. Chem. Rev.* **1990**, *105*, 221.
(59) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342.
(60) Grushin, V. V.; Marshall, W. J. *Organometallics* **2007**, *26*, 4997.
(61) Cui, L.; Saeys, M. *ChemCatChem* **2011**, *3*, 1060.
(62) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2004**, *126*, 3068.
(63) Macgregor, S. A.; Roe, D. C.; Marshall, W. J.; Bloch, K. M.; Bakhmutov, V. I.; Grushin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 15304.
(64) McPake, C. B.; Sandford, G. *Org. Process Res. Dev.* **2012**, *16*, 844.
(65) Yoshida, Y.; Kimura, Y. *Chem. Lett.* **1988**, *17*, 1355.
(66) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.
(67) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.
(68) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 7619.
(69) Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 16394.
(70) Kim, D. W.; Jeong, H.-J.; Lim, S. T.; Sohn, M.-H.; Katzenellenbogen, J. A.; Chi, D. Y. *J. Org. Chem.* **2008**, *73*, 957.
(71) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.
(72) Sun, H.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720.
(73) Sun, H.; DiMagno, S. G. *Chem. Commun.* **2007**, 528.
(74) Schwesinger, R.; Link, R.; Thiele, G.; Rotter, H.; Honert, D.; Limbach, H.-H.; Männle, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1372.
(75) Schwesinger, R.; Link, R.; Wenzl, P.; Kossek, S. *Chem.—Eur. J.* **2006**, *12*, 438.
(76) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.
(77) Noël, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900.
(78) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.
(79) Wannberg, J.; Wallinder, C.; Ünlüsoy, M.; Sköld, C.; Larhed, M. *J. Org. Chem.* **2013**, *78*, 4184.
(80) Samant, B. S.; Bhagwat, S. S. *Appl. Catal., A* **2011**, *394*, 191.
(81) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 5602.
(82) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 3792.
(83) Mu, X.; Liu, G. *Org. Chem. Front.* **2014**, *1*, 430.
(84) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.
(85) Yao, B.; Wang, Z.-L.; Zhang, H.; Wang, D.-X.; Zhao, L.; Wang, M.-X. *J. Org. Chem.* **2012**, *77*, 3336.
(86) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795.
(87) Mu, X.; Zhang, H.; Chen, P.; Liu, G. *Chem. Sci.* **2014**, *5*, 275.
(88) Van Der Puy, M. *J. Fluorine Chem.* **1982**, *21*, 385.
(89) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134.
(90) Nemoto, H.; Nishiyama, T.; Akai, S. *Org. Lett.* **2011**, *13*, 2714.
(91) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618.
(92) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.
(93) Fujimoto, T.; Bastuck, F.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 1041.
(94) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431.
(95) Villalba, G.; Ayres, R. U.; Schroder, H. *J. Ind. Ecol.* **2007**, *11*, 85.
(96) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605.
(97) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595.
(98) Differding, E.; Ofner, H. *Synlett* **1991**, 187.
(99) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452.
(100) Differding, E.; Lang, R. W. *Helv. Chim. Acta* **1989**, *72*, 1248.
(101) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730.
(102) Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925.
(103) Umemoto, T.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 3271.
(104) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.
(105) Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705.
(106) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
(107) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563.
(108) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379.
(109) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.
(110) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1.
(111) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192.
(112) Lee, K. Y.; Kochi, J. K. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1011.
(113) Bockman, T. M.; Lee, K. Y.; Kochi, J. K. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1581.
(114) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264.
(115) Brandt, J. R.; Lee, E.; Boursalian, G. B.; Ritter, T. *Chem. Sci.* **2014**, *5*, 169.
(116) Borodkin, G. I.; Zaikin, P. A.; Shakirov, M. M.; Shubin, V. G. *Russ. J. Org. Chem.* **2007**, *43*, 1451.
(117) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.
(118) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584.
(119) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302.
(120) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840.
(121) Subramanian, M. A.; Manzer, L. E. *Science* **2002**, *297*, 1665.
(122) Janmanchi, K. M.; Dolbier, W. R., Jr. *Org. Process Res. Dev.* **2008**, *12*, 349.
(123) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
(124) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.
(125) Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun.* **2013**, *49*, 6218.
(126) Ding, Q.; Ye, C.; Pu, S.; Cao, B. *Tetrahedron* **2014**, *70*, 409.
(127) Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2014**, *126*, DOI 10.1002/ange.201483971.
(128) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081.
(129) Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956.
(130) Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073.
(131) Cazorla, C.; Métay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 3936.
(132) Vints, I.; Gatenyo, J.; Rozen, S. *J. Org. Chem.* **2013**, *78*, 11794.
(133) Coenen, H. H.; Moerlein, S. M. *J. Fluorine Chem.* **1987**, *36*, 63.

(134) Adam, M. J.; Berry, J. M.; Hall, L. D.; Pate, B. D.; Ruth, T. J. *Can. J. Chem.* **1983**, *61*, 658.
(135) De Meio, G. V.; Pinhey, J. T. *J. Chem. Soc., Chem. Commun.* **1990**, 1065.
(136) De Meio, G.; Morgan, J.; Pinhey, J. T. *Tetrahedron* **1993**, *49*, 8129.
(137) Bryce, M. R.; Chambers, R. D.; Mullins, S. T.; Parkin, A. *J. Fluorine Chem.* **1984**, *26*, 533.
(138) Visser, G. W. M.; Van Halteren, B. W.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Chem. Soc., Chem. Commun.* **1984**, 655.
(139) Visser, G. W. M.; Bakker, C. N. M.; Van Halteren, B. W.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Org. Chem.* **1986**, *51*, 1886.
(140) Butin, K. P.; Kiselev, Y. M.; Magdesieva, T. V.; Reutov, O. A. *J. Organomet. Chem.* **1982**, *235*, 127.
(141) Zhao, S.-B.; Wang, R.-Y.; Nguyen, H.; Becker, J. J.; Gagné, M. R. *Chem. Commun.* **2011**, *48*, 443.
(142) Lothian, A. P.; Ramsden, C. A. *Synlett* **1993**, 753.
(143) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26.
(144) Di Raddo, P.; Diksic, M.; Jolly, D. *J. Chem. Soc., Chem. Commun.* **1984**, 159.
(145) Speranza, M.; Shiue, C.-Y.; Wolf, A. P.; Wilbur, D. S.; Angelini, G. *J. Fluorine Chem.* **1985**, *30*, 97.
(146) Coe, P. L.; Stuart, A. M.; Moody, D. J. *J. Fluorine Chem.* **1998**, *92*, 27.
(147) Stuart, A. M.; Coe, P. L.; Moody, D. J. *J. Fluorine Chem.* **1998**, *88*, 179.
(148) Adam, M. J.; Pate, B. D.; Ruth, T. J.; Berry, J. M.; Hall, L. D. *J. Chem. Soc., Chem. Commun.* **1981**, 733.
(149) Adam, M. J.; Ruth, T. J.; Jivan, S.; Pate, B. D. *J. Fluorine Chem.* **1984**, *25*, 329.
(150) Bryce, M. R.; Chambers, R. D.; Mullins, S. T.; Parkin, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1623.
(151) Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* **1992**, 831.
(152) Matthews, D. P.; Miller, S. C.; Jarvi, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 3057.
(153) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461.
(154) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993.
(155) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060.
(156) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.
(157) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796.
(158) Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012.
(159) Tius, M. A.; Kawakami, J. K. *Synlett* **1993**, 207.
(160) Tius, M. A.; Kawakami, J. K. *Tetrahedron* **1995**, *51*, 3997.
(161) Xu, T.; Liu, G. *Org. Lett.* **2012**, *14*, 5416.
(162) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.
(163) Tang, P.; Ritter, T. *Tetrahedron* **2011**, *67*, 4449.
(164) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662.
(165) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150.
(166) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092.
(167) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552.
(168) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4648.
(169) Deyoung, J.; Kawa, H.; Lagow, R. J. *J. Chem. Soc., Chem. Commun.* **1992**, 811.
(170) Snieckus, V.; Beaulieu, F.; Mohri, K.; Han, W.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* **1994**, *35*, 3465.
(171) Slocum, D. W.; Shelton, P.; Moran, K. M. *Synthesis* **2005**, 3477.
(172) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219.
(173) Anbarasan, P.; Neumann, H.; Beller, M. *Chem.—Asian J.* **2010**, *5*, 1775.
(174) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215.
(175) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322.
(176) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094.
(177) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.
(178) Tian, T.; Zhong, W.-H.; Meng, S.; Meng, X.-B.; Li, Z.-J. *J. Org. Chem.* **2013**, *78*, 728.
(179) Bienvenu, A.; Barthelemy, A.; Boichut, S.; Marquet, B.; Billard, T.; Langlois, B. R. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1467.
(180) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342.
(181) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456.
(182) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292.
(183) Phelps, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226.
(184) Bolton, R. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 485.
(185) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, 2853.
(186) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998.
(187) Tredwell, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 11426.
(188) Cardinale, J.; Ermert, J.; Kügler, F.; Helfer, A.; Brandt, M. R.; Coenen, H. H. *J. Labelled Compd. Radiopharm.* **2012**, *55*, 450.
(189) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6821.
(190) Chirakal, R.; Firnau, G.; Couse, J.; Garnett, E. S. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 651−653.
(191) Namavari, M.; Bishop, A.; Satyamurthy, N.; Bida, G.; Barrio, J. R. *Int. J. Radiat. Appl. Instrum., A* **1992**, *43*, 989.
(192) Frame, H. D.; Huston, J. L.; Sheft, I. *Inorg. Chem.* **1969**, *8*, 1549.
(193) Firnau, G.; Chirakal, R.; Sood, S.; Garnett, E. S. *J. Labelled Compd. Radiopharm.* **1981**, *18*, 7.
(194) Shiue, C.-Y.; To, K.-C.; Wolf, A. P. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 157−162.
(195) Constantinou, M.; Aigbirhio, F. I.; Smith, R. G.; Ramsden, C. A.; Pike, V. W. *J. Am. Chem. Soc.* **2001**, *123*, 1780.
(196) Vasdev, N.; Pointner, B. E.; Chirakal, R.; Schrobilgen, G. J. *J. Am. Chem. Soc.* **2002**, *124*, 12863.
(197) Satyamurthy, N.; Bida, G. T.; Phelps, M. E.; Barrio, J. R. *Int. J. Radiat. Appl. Instrum., A* **1990**, *41*, 733.
(198) Teare, H.; Robins, E. G.; rstad, E.; Luthra, S. K.; Gouverneur, V. R. *Chem. Commun.* **2007**, 2330.
(199) Oberdorfer, F.; Hofmann, E.; Maier-Borst, W. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 999.
(200) Firnau, G.; Garnett, E. S.; Chirakal, R.; Sood, S.; Nahmias, C.; Schrobilgen, G. *Int. J. Radiat. Appl. Instrum., A* **1986**, *37*, 669.
(201) Bergman, J.; Solin, O. *Nucl. Med. Biol.* **1997**, *24*, 677.
(202) Stenhagen, I. S. R.; Kirjavainen, A. K.; Forsback, S. J.; Jørgensen, C. G.; Robins, E. G.; Luthra, S. K.; Solin, O.; Gouverneur, V. *Chem. Commun.* **2013**, *49*, 1386.
(203) Attiná, M.; Cacace, F.; Wolf, A. P. *J. Chem. Soc., Chem. Commun.* **1983**, 108.
(204) Angelini, G.; Speranza, M.; Wolf, A. P.; Shiue, C.-Y. *J. Fluorine Chem.* **1985**, *27*, 177.
(205) Ding, Y.-S.; Gatley, S. J.; Fowler, J. S.; Volkow, N. D.; Aggarwal, D.; Logan, J.; Dewey, S. L.; Liang, F.; Carroll, F. I.; Kuhar, M. J. *Synapse* **1996**, *24*, 403.
(206) Pike, V. W.; Aigbirhio, F. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2215.
(207) Ross, T. L.; Ermert, J.; Hocke, C.; Coenen, H. H. *J. Am. Chem. Soc.* **2007**, *129*, 8018.
(208) Yamada, Y.; Okawara, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1860.

(209) Ichiishi, N.; Brooks, A. F.; Topczewski, J. J.; Rodnick, M. E.; Sanford, M. S.; Scott, P. J. H. *Org. Lett.* **2014**, *16*, 3224.
(210) Satyamurthy, N.; Barrio, J. R. No-carrier-added nucleophilic [F-18] fluorination of aromatic compounds. WO2010/117435 A2.
(211) Yusubov, M. S.; Svitich, D. Y.; Larkina, M. S.; Zhdankin, V. V. *ARKIVOC* **2013**, *2013*, 364.
(212) Rotstein, B. H.; Stephenson, N. A.; Vasdev, N.; Liang, S. H. *Nat. Commun.* **2014**, *5*, 4365.
(213) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052.
(214) Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 6733.
(215) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.
(216) Kamlet, A. S.; Neumann, C. N.; Lee, E.; Carlin, S. M.; Moseley, C. K.; Stephenson, N.; Hooker, J. M.; Ritter, T. *PLoS One* **2013**, *8*, e59187.
(217) Ren, H.; Wey, H.-Y.; Strebl, M.; Neelamegam, R.; Ritter, T.; Hooker, J. M. *ACS Chem. Neurosci.* **2014**, *5*, 611.
(218) Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 7751.
(219) Regalado, E. L.; Kozlowski, M. C.; Curto, J. M.; Ritter, T.; Campbell, M. G.; Mazzotti, A. R.; Hamper, B. C.; Spilling, C. D.; Mannino, M. P.; Wan, L.; Yu, J.-Q.; Liu, J.; Welch, C. J. *Org. Biomol. Chem.* **2014**, *12*, 2161.