A General Protocol for Cu-Mediated Fluoro-deamination: Sandmeyer Fluorination of Diverse Aromatic Substrates

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ABSTRACT: A Cu(I)-mediated fluoro-deamination method for nucleophilic radiofluorination was devised. The method affords fluorinated aromatic products directly from anilines under both no-carrier added and stoichiometric conditions. Isolated radiochemical yields range from 11% to 81% with high radiochemical purities and a molar activity of 58 MBq/nmol. The reaction conditions were implemented successfully in an automated process for production of (S)-4[18F]fluoroglutethimide on a radiosynthesis module.

The availability of methods for introduction of fluorine-18 into a scaffold of interest is regarded as a critical bottleneck in the development of radiopharmaceuticals for positron emission tomography (PET). In recent years, methods for late-stage radiolabeling of drug scaffolds with short-lived nuclides (>2 h half-life) became a focus of research. In this paradigm, existing molecules are subjected to transformations appropriate to incorporate a radionuclide post haste. Metal-mediated reactions with a [18F]fluoride ion are a critical advancement that reshaped the chemical toolkit radiochemists utilize in practice. Transition metal organyls 1,2,8 quasi-metallic main group elements like iodanes,3 boro-nates,4,6,9 12 and main group metal organyls7 have been added to the landscape of suitable precursors for radiochemistry. Radiolabeling of a wide range of substrates, including access to radiopharmaceuticals that were all but impossible to synthesize using established fluorine-18 radiochemistry, has now become possible. Consequently, pushing the limits of late stage fluorination has, nowadays, been directed at functional group transformations that are neither obvious nor without considerable challenge. One such transformation is the direct conversion of amines, specifically aminoarenes, into fluorides to tap the rationale of NH2 → F bioisosterism and a pool of existing bioactive molecules. In light of our research interests in biomedical imaging with PET, the possibility to convert bioactive aminoarenes directly to their fluoroarene bioisosteres is particularly attractive to readily achieve proof-of-principle with potential PET radiotracers. In contrast to heavier halides, fluoro-deamination of anilines in practically useful yields with fluoride ion has been elusive to the synthetic community. The only means to access anilines to ary fluorides are the acidolysis of triazene intermediates as described by Wallach and the Balz–Schiemann reactions, respectively. Both of these reactions do not proceed well with H[18F]F, [18F]fluoride, or [18F]tetrafluoroborate salts and may not be obtained under no-carrier-added (n.c.a.) conditions.13–19 Nonetheless, if achieved such a functional group transformation may provide the means for straightforward exchange of the NH2-group for a fluorine atom in accordance with the concept of late-stage fluorination. Direct fluoro-deamination in analogy to the Sandmeyer reaction could produce fluoroarenes from both activated and nonactivated substrates.15–19 Unfortunately, disproportionation of Cu(I) by the fluoride ion into Cu and insoluble CuF2 impedes Sandmeyer fluorination.

The earliest report to achieve no-carrier-added nucleophilic fluorination of diazonium salts was published in 1995, using two steps via p-toluenediazonium salts. Radiolabeled 4-[18F]fluorotoluene was made from 4-toluenediazonium 2,4,6-tri-isopropylbenzenesulfonate (Scheme 1a).18 This was refined by using ion-exchange resin-bound aryldiazonium salts to obtain 18F-labeled fluoroarenes in 1–8% radiochemical yield (RCY) (Scheme 1b).19 Recently, Murphy et al. reported another indirect method via arylsydnones (Scheme 1c), an exotic leaving group for S2Ar reactions.20 Despite these efforts, there has been a lack of a fluorinating Sandmeyer reaction, wherein diazonium precursors are prepared in situ to produce fluorinated products in one step. Herein, we describe the Cu-mediated direct conversion of anilines into aryl fluorides (Scheme 1d).
Scheme 1. Modern Methods for Fluoro-deamination Reactions (SAX, Strong Anion Exchanger; SCX, Strong Cation Exchanger)

(a) Nucleophilic aromatic fluoro-de-amination: two steps

(b) Solid phase supported nucleophilic fluoro-deamination of SAX-bound arenediazonium salts: two steps

(c) Nucleophilic radfluoro-deamination of activated alkyl nitrites: two steps

(d) Cu-mediated radfluoro-deamination of anilines in one step (this work)

The starting point for this investigation was the attempt to employ the Cu(II)-mediated fluorination conditions in a direct conversion of anilines. We surmised that radicals formed by reaction of alkyl nitrates with anilines in the absence of acid would be readily oxidized in a single electron transfer to Cu(II) allowing for fluoride to capture the aryl cation. Table 1 summarizes the key steps of method development.

Table 1. Influence of the Cu- and F-Source on RCY of [18F]fluorination reactions based on Cu-salts.

| no. | Cu   | solvent | F-source | RONO   | RCY |
|-----|------|---------|----------|--------|-----|
| 1   | Cu(OTf)2 | DMF     | [18F]TBAF | tBuONO | 0.75% |
| 2   | Cu(OTf)2 | MeCN    | [18F]TBAF | tBuONO | 22.5% |
| 3   | Cu(OTf)2 | MeCN    | [18F]KF  | tBuONO | 39.9% |
| 4   | CuOTf  | MeCN    | [18F]KF  | tBuONO | 44.0% |
| 5   | CuOTf  | MeCN    | [18F]KF  | AmylONO | 61.9% |
| 6   | CuOTf  | MeCN    | [18F]KF  | AmylONO | 73.9% |
| 7   | Cu(OTf)3 | MeCN    | [18F]KF  | tBuONO | 56.1% |

*aConditions: Aniline (30 mmol), RONO (45 mmol), [Cu] 4 equiv, KOTf or TBAOTf (36 mmol), n.c.a. [18F]fluoride ion, 1 mL volume.
*bIsolated RCY, averages of two duplicate experiments.
*cWith 0.45 equiv of KF carrier.

Initial trials with Cu(II) in DMF and other polar solvents (Table S1) gave a very low RCY; only MeCN afforded over 20% of 1-fluoro-4-nitrobenzene [18F]1 from model substrate 4-nitroaniline (Table 1, entries 1 and 2). Following a methodological optimization a combination of KOTf and 15-crown-5 was found to form the most active fluoride source in the labeling reaction. A practically useful RCY of nearly 40% was reached (entry 3). When other substrates were employed, it was found that only 2-, 3-, and 4-nitroaniline gave any product. Fortunately, a negative control experiment conducted while exploring oxidation of Cu(I) to Cu(II) in solution provided new insight. While oxidation practically extinguished the reactivity (6% ([18F]1)), an RCY of 46.5% was observed when the Cu(I)OTf acetonitrile complex was used in the absence of the oxidizing agent (Table 1, entry 4). Substitution of tBuONO for AmylONO further increased the yield, in particular when combined with degassing of the reaction mixtures (Table 1 entry 5). Furthermore, successful elution of the [18F]fluoride from ion exchange cartridges with a mixture of alkyl nitrite and aniline in MeCN indicated the presence of diazonium ions rather than smooth production of radicals. Qualitative azocoupling-tests confirmed this and provided a means for optimizing temperature and time by observing degradation of the diazonium intermediate. Combined with the disappointing substrate screen the discovery of a working Cu(I)-mediated reaction gave rise to a new hypothesis. We reasoned that trace Cu(I) formed in situ from Cu(II)OTf2 may have somehow mediated the fluorination reaction. The particular effectiveness of MeCN would then relate to protection of the Cu(I) oxidation state in tetrakis acetonitrile complexes. Indeed, Cu(I) was able to transform a broader spectrum of anilines to fluorides. In the absence of Cu-catalyst, only trace yields were observed and diazonium ions remained stable. A compound formed via N2 fluoride binding has been described which suggests the involvement of a direct N–CuF interaction in the reaction mechanism; however, we consider a collaborative mechanism between Cu and Cu(II), formed by disproportionation from Cu(I) by fluoride, more plausible. Cu is effective for forming aryl radicals from arenediazonium salts, and Cu(II) readily oxidizes aryl radicals to cations to be captured by nucleophilic fluoride. Since the disproportionation is likely to involve a biatomic mechanism requiring two Cu atoms in close proximity, and since the low F concentration in n.c.a. radiochemistry (the n.c.a. F–Cu ratio is about 1:1.2 × 105) disfavors formation of insoluble CuF2, fluoride ions are not removed from the liquid phase but capture aryl carbocations formed from Cu/Cu(II)-couples. Collaborative Cu/Cu(II)-catalysis could even be plausible for other Cu-mediated fluorinations perhaps explaining the large excess of [Cu] employed in these reports. Radical intermediates would also explain the ubiquitous proto analogue formed in all radiofluorination reactions based on Cu-salts.

In order to validate the disproportionation hypothesis of a Cu/Cu(II) couple in action, we performed a control experiment with Cu(II) in the presence of copper powder. Indeed, these conditions furnished [18F]3 and [18F]8 in radiochemical yields of 24.5% and 38.7%, respectively, strongly supporting the hypothesis. To test the role of disproportionation, we added a carrier in the form of KF to both Cu sources to see if the resultant increase in disproportionation would benefit the outcome. Indeed, addition of substoichiometric amounts of KF carrier (0.45 equiv, 13.5 mM) had a positive effect on the Cu(I) reaction (Table 1 entry 6, 73.9% RCY) but did not have an effect on the Cu(II) reaction (entry 7, 38.8%). This indicates an interaction of Cu(I) and fluoride, such as disproportionation to produce Cu as explained above. Since KF is poorly soluble in MeCN, the fluoride source functions as a phase transfer catalyst, which limits the total amount of fluoride ions in solution at any time. As long as the fluoride...
concentration remains low, precipitation of CuF₂ will not withdraw fluoride ions from the liquid phase, and thus the reaction is not impeded. Therefore, the major issue of a Sandmeyer fluorination is circumvented under these reaction conditions. Carrier addition improved yields to a considerable extent although reaction times for complete consumption of the additional fluoride nucleophile did not increase at all, indicating a higher rate of reaction, i.e. through increase of disproportionation, production of aryl cation captured by fluoride. This may allow for translation of the conditions to stoichiometric fluorination. Tables S1−S7 give an overview of over 200 individual reagent combinations tested during optimization. The following final conditions were developed: Aniline (30 mM), 1.5 equiv of alkyl nitrite, 1.2 equiv of phase transfer catalyst, 4 equiv of [Cu], 120 °C, 20 min, MeCN (1 mL), n.c.a. [18F]fluoride ion (20−150 MBq). Under these conditions, no-carrier added [18F]- was obtained in 61.9% RCY and carrier-added [18F]- in 73.9% yield with stoichiometric KF.33 To elucidate the substrate scope, the method was applied to a diverse selection of anilines (Table 2) with good results.

In general, the substrate scope shows some minor preference of the new protocol on electron-withdrawing groups, although this is not necessarily due to an SNAr mechanism but indicative of the individual stabilities of the corresponding diazonium ions and radical intermediates.31 The method is highly ipso-selective; no ortho-isomers were detected. This suggests that the mechanism follows the proposed single electron transfer mechanism of the Sandmeyer reaction.27 A variety of functional groups are tolerated, including acetals, alkyl chains, amides, aryl halides, cyanides, esters, ethers, ketones, ureas, and others. In all cases, we observed moderate to excellent conversion of the starting material and most products were obtained in high radiochemical purity and good yields (37.7−81.6%) without optimization of the workup. All but one reaction (6 was the major component of a product mixture) afforded a single major labeled product. The major limitations are known intramolecular reactions of diazonium intermediates, e.g. cyclization with ortho-substituents or formation of immines with carbonyl compounds ([18F]-9). Thus, ortho-substituted nitroaniline was only labeled in 7.3% RCY and benzaldehyde [18F]-14 was made from the acetal protected aniline precursor. In some hydroquinone substrates, oxidation by Cu(II) is a prevalent side reaction producing strongly colored quinoneimines and p-quinonediimines. This is illustrated by obtaining [18F]-12 in only 20.1% RCY and

### Table 2. Substrate Scope of the Reaction

| Compound | RCP/% | RCY/% | Compound | RCP/% | RCY/% |
|----------|-------|-------|----------|-------|-------|
| [18F]-1  | n.c.a. | 97.4±2 | 56.0±5  | [18F]-10 | n.c.a. | N/A  | N/A |
| [18F]-2  | n.c.a. | 90.1±1 | 40.2±2  | [18F]-11 | n.c.a. | 92.5±1 | 39.6±3 |
| [18F]-3  | n.c.a. | 97.2±1 | 40.7±4  | [18F]-12 | n.c.a. | 27.1±10 | 20.1±6 |
| [18F]-4  | n.c.a. | 90.9±0.4 | 37.7±6 | [18F]-13 | n.c.a. | 87.1±3 | 43.9±8 |
| [18F]-5  | n.c.a. | 28.6±10 | 11.2±5  | [18F]-14 | n.c.a. | 97.7±0.3 | 45.9±12 |
| [18F]-6  | n.c.a. | 47.7±14 | 19.7±5  | [18F]-15 | n.c.a. | 9.6±1 | 3.7±1 |
| [18F]-7  | n.c.a. | 98.8±0.6 | 53.1±3 | [18F]-16 | n.c.a. | 92.7±3 | 41.0±2 |
| [18F]-8  | n.c.a. | 99.2±0.2 | 81.6±4 | [18F]-17 | n.c.a. | N/A  | 21.6±5% |
| [18F]-9  | n.c.a. | 97.7±0.6 | 31.1±5 | [18F]-18 | n.c.a. | 97.4±2 | 41.4±5 |

“RCP radiochemical purity of the isolated radioactive product, RCY “radiochemical yield” (product activity counted by dose calibrator and corrected for HPLC purity after quality control). n.c.a.: No-carrier added conditions. c.a.: in the presence of 0.45 equiv of KF. *Cu-mediated oxidation to a quinoide system.
[18F]15 in 4% RCY. Nevertheless, nonactivated substrates ([18F]2, 40.2–68.0% RCY) including those with electron donating substituents ([18F]3, 40.7–57.2% RCY, [18F]4, 37.7–56.0% RCY, [18F]11 39.6–75.9% RCY) proved accessible. Notably, freshly opened Cu(MeCN)4OTf produced about 15% higher yields than the material employed in most runs. Although the available aniline was consumed before complete conversion of the [18F]fluoride was achieved, fluoroarenes were obtained in practically useful yields to facilitate late-stage labeling of existing compounds, which makes this method very useful for initial biological tests. Preparation of the secondary labeling reagents 4-[18F]-fluorophenyl iodide ([18F]3), [18F]fluoro benzonic acid methyl ester ([18F]7), and [18F]fluorobenzaldehyde ([18F]14) (Scheme 2) further corroborates the utility of the method.

Scheme 2. Synthesis of Labelled Aldehyde [18F]14 and the Radiotracer Candidate [18F]18

In order to demonstrate the late-stage fluorination on drug molecules as realistic substrates, (−)-4-[18F]fluorogluthetimide [18F]18 (41.4%–65.1% RCY) (Scheme 2) and the fluorinated carbamate derivative [18F]17 (RCY = 21%) were labeled. Product [18F]18 is under investigation for monitoring mitochondrial CYP2D6 in midbrain dopamine neurons in the context of movement disorders.28–30

The fluoride-mediated disproportionation of soluble Cu(I) provides a way to harness the cooperative activity of a Cu/Cu(II) couple while avoiding solid Cu-powder.25c Heterogeneous mixtures and suspensions, in particular dense, metallic solids, are a notorious challenge for automation of labeling processes. Homogeneous solutions permit rapid liquid transfer in typical automated radiotracer productions. Labeling conditions must be suitable for development of automated processes on a state-of-the-art radiosynthesis platform to be translated into (pre)clinical application. A Synthra RN plus synthesis module was charged with a mixture of aniline and amyl nitrite in MeCN and CuOTf/pyridine in MeCN at room temperature. These mixtures were added to the reaction after processing of the [18F]fluoride obtained from the cyclotron target without notable loss in reactivity allowing for batch production of [18F]18 for preclinical tests. Similar to other transition-metal mediated radiofluorination reactions, a side product formed by protonation instead of fluorination was observed, necessitating the use of pentafluorophenyl-function alized HPLC stationary phases for separation to achieve high chemical purities of radioactive products. Molar activities achieved with the novel protocol were similar to those routinely obtained for nucleophilic aromatic fluorination reactions; e.g., starting with 2.2 GBq, [18F]3 was obtained in 8.7 MBq/nmol, which is an excellent result. The isolated product (>99% RCP) obtained in the automation experiments contained less than 1 nmol radiotracer per mL, which principally bodes well for achieving high molar activities in high activity productions (37 GBq/1 Ci or more).

In conclusion, the fluorinating Sandmeyer reaction, a generally useful Cu-catalyzed deamino-fluorination of anilines, was devised and translated into radiotracer production. This rapid methodology applies to both activated and nonactivated aromatic systems, producing practically useful yields of a single fluorinated product in one step. Given the bioisosterism and hydrogen-bonding tendencies of −NH2 and −F substituents, this new method is an attractive means to conveniently obtain close analogues of drug candidates or even existing drugs for biological tests. Radiosynthesis of fluorine bioisosteres of established drugs demonstrates the potential of this late-stage fluorination method for radiotracer development. Further translation of this methodology with [18F]18 is in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04209.

Supplementary procedures, data tables for individual runs, azocoupling procedures, analytical data for radio-chemical runs, starting materials and products (PDF)

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Notes

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