OL Organic Letters

pubs.acs.org/OrgLett

Letter

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

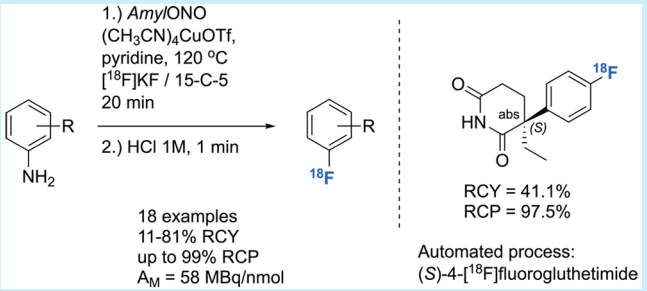
R. Manuel Pérez-García, Gaute Grønnevik, and Patrick J. Riss*

Cite This: *Org. Lett.* 2021, 23, 1011−1015

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

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[^{18}F]fluorogluthetimide on a radiosynthesis module.

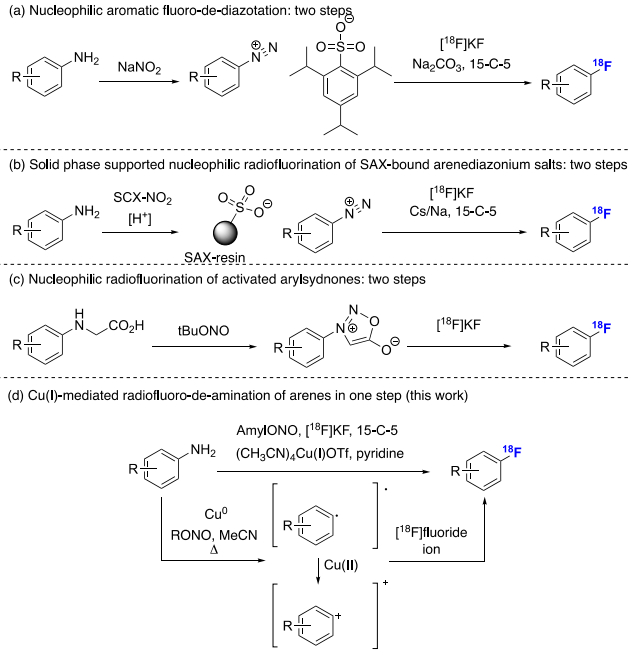


The availability of methods for introduction of fluorine-18 into a scaffold of interest is regarded as a critical bottleneck in the development of radiopharmaceuticals for positron emission tomography (PET). In recent years, methods for late-stage radiolabeling of drug scaffolds with short-lived nuclides (>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 [^{18}F]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] boronates,[4−6,9−12] and main group metal organyls[7] 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 NH_2−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 convert anilines to aryl 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[^{18}F]F, [^{18}F]fluoride, or [^{18}F]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 NH_2-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.[13−19] Unfortunately, disproportionation of Cu(I) by the fluoride ion into Cu and insoluble CuF_2 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-[^{18}F]fluorotoluene was made from 4-toluenediazonium 2,4,6-tri-isopropylbenzenesulfonate (Scheme 1a).[18] This was refined by using ion-exchange resin-bound aryldiazionium salts to obtain ^{18}F-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 S_NAr 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).

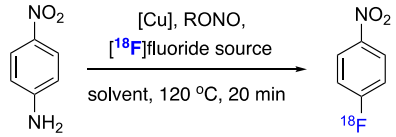
Received: December 20, 2020
Published: January 25, 2021

Scheme 1. Modern Methods for Fluoro-deamination Reactions (SAX, Strong Anion Exchanger; SCX, Strong Cation Exchanger)



The starting point for this investigation was the attempt to employ the Cu(II)-mediated fluorination conditions in a direct conversion of anilines.[3−6] We surmised that radicals formed by reaction of alkyl nitrites 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.[15,21−24] Table 1 summarizes the key steps of method development.

Table 1. Influence of the Cu- and F-Source on RCY of [^{18}F]1[a]



no.	[Cu]	solvent	F-source	RONO	RCY[b]
1	$Cu(OTf)_2$	DMF	[^{18}F]TBAF	tBuONO	0.75%
2	$Cu(OTf)_2$	MeCN	[^{18}F]TBAF	tBuONO	22.5%
3	$Cu(OTf)_2$	MeCN	[^{18}F]KF	tBuONO	39.9%
4	CuOTf	MeCN	[^{18}F]KF	tBuONO	44.0%
5	CuOTf	MeCN	[^{18}F]KF	AmylONO	61.9%
6	CuOTf	MeCN	[^{18}F]KF[c]	AmylONO	73.9%
7	$Cu(OTf)_2$	MeCN	[^{18}F]KF[c]	tBuONO	56.1%

[a]Conditions: Aniline (30 mmol), RONO (45 mmol), [Cu] 4 equiv, KOTf or TBAOTf (36 mmol), n.c.a. [^{18}F]fluoride ion, 1 mL volume. [b]Isolated RCY, averages of two duplicate experiments. [c]With 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 [^{18}F]**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.[21−24] Fortunately, a negative control experiment conducted while exploring oxidation of Cu(I) to Cu(II) in solution provided new insight.[25] While oxidation practically extinguished the reactivity (6% ([^{18}F]**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).[25] Substitution of tBuONO for AmylONO further increased the yield, in particular when combined with degassing of the reaction mixtures (Table 1 entry 5).[25b] Furthermore, successful elution of the [^{18}F]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 $Cu(II)OTf_2$ 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 N_2−CuF binding has been described which suggests the involvement of a direct N−CuF interaction in the reaction mechanism;[32] however, we consider a collaborative mechanism between Cu and Cu(II), formed by disproportionation from Cu(I) by fluoride, more plausible.[25d,26] 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 $1:1.2 \times 10^5$) disfavors formation of insoluble CuF_2, 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 [^{18}F]**3** and [^{18}F]**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

https://dx.doi.org/10.1021/acs.orglett.0c04209
Org. Lett. 2021, 23, 1011−1015

Table 2. Substrate Scope of the Reaction[a]

Compound		RCP/%	RCY/%
[^{18}F]**1**	n.c.a.	97.4±2	56.0 ±5
	c.a.	99.8	73.9
[^{18}F]**2**	n.c.a.	90.1±1	40.2±2
	c.a.	93.1	68.2
[^{18}F]**3**	n.c.a.	97.2±1	40.7±4
	c.a.	97.6	57.2
[^{18}F]**4**	n.c.a.	90.9±0.4	37.7±6
	c.a.	99.7	56.1
[^{18}F]**5**	n.c.a.	28.6±10	11.2±5
	c.a.	70.7	38.5
[^{18}F]**6**	n.c.a.	47.7±14	19.7±5
	c.a.	98.7	76.9
[^{18}F]**7**	n.c.a.	98.8±0.6	53.1±3
	c.a.	94.6	68.4
[^{18}F]**8**	n.c.a.	99.2±0.2	81.6±4
	c.a.	98.8	74.2
[^{18}F]**9**	n.c.a.	97.7±0.6	31.1±5
	c.a.	87.2	41.5
[^{18}F]**10**	n.c.a.	N/A	N/A
	c.a.	Trace	Trace
[^{18}F]**11**	n.c.a.	92.5±1	39.6±2
	c.a.	98.0	75.9
[^{18}F]**12**	n.c.a.	27.1±10	20.1±6
	c.a.	Trace	Trace
[^{18}F]**13**	n.c.a.	87.1±3	43.9±8
	c.a.	37.8	32.2
[^{18}F]**14**	n.c.a.	97.7±0.3	45.9±12
	c.a.	98.5	72.2
[^{18}F]**15**	n.c.a.	9.6±1	3.7±1
	c.a.	10.6	4.0
[^{18}F]**16**	n.c.a.	92.7±3	41.0±2
	c.a.	99.8	71.8
[^{18}F]**17**	n.c.a.	N/A	21.6±5%
	c.a.	N/A	N/A
[^{18}F]**18**	n.c.a.	97.4±2	41.4±5
	c.a.	95.1	65.1

[a]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.

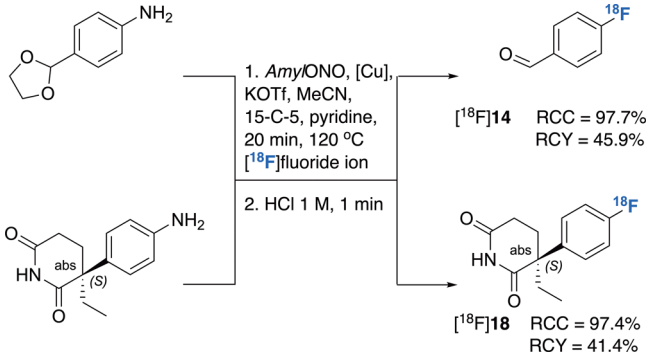
concentration remains low, precipitation of CuF_2 will not withdraw fluoride ions from the liquid phase, and thus the reaction is not impeded. Therefore, the major issue of a Sandmeyer fluorination is circumvented under these reaction conditions. Carrier addition improved yields to a considerable extent 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. [^{18}F]fluoride ion (20−150 MBq). Under these conditions, no-carrier added [^{18}F]**1** was obtained in 61.9% RCY and carrier-added [^{18}F]**1** 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 S_NAr 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 ([^{18}F]**9**). Thus, ortho-substituted nitroaniline was only labeled in 7.3% RCY and benzaldehyde [^{18}F]**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 [^{18}F]**12** in only 20.1% RCY and

https://dx.doi.org/10.1021/acs.orglett.0c04209
Org. Lett. 2021, 23, 1011−1015

[^{18}F]**15** in 4% RCY. Nevertheless, nonactivated substrates ([^{18}F]**2**, 40.2−68.0% RCY) including those with electron donating substituents ([^{18}F]**3**, 40.7−57.2% RCY, [^{18}F]**4**, 37.7−56.0% RCY, [^{18}F]**11** 39.6−75.9% RCY) proved accessible. Notably, freshly opened Cu(MeCN)$_4$OTf produced about 15% higher yields than the material employed in most runs. Although the available aniline was consumed before complete conversion of the [^{18}F]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-[^{18}F]-fluorophenyl iodide ([^{18}F]**3**), [^{18}F]fluorobenzoic acid methyl ester ([^{18}F]**7**), and [^{18}F]fluorobenzaldehyde ([^{18}F]**14**) (Scheme 2) further corroborates the utility of the method.

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



In order to demonstrate the late-stage fluorination on drug molecules as realistic substrates, (−)-4-[^{18}F]fluorogluthetimide [^{18}F]**18** (41.4%−65.1% RCY) (Scheme 2) and the fluorinated carbutamide derivative [^{18}F]**17** (RCY = 21%) were labeled. Product [^{18}F]**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 [^{18}F]fluoride obtained from the cyclotron target without notable loss in reactivity allowing for batch production of [^{18}F]**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-functionalized 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, [^{18}F]**3** was obtained in 58.7 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 $-NH_2$ 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 [^{18}F]**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 radiochemical runs, starting materials and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Patrick J. Riss − *Section of Organic Chemistry, Department of Chemistry, University of Oslo, 0371 Oslo, Norway;* orcid.org/0000-0002-3887-7065; Email: Patrick.Riss@kjemi.uio.no

Authors

R. Manuel Pérez-García − *Section of Organic Chemistry, Department of Chemistry, University of Oslo, 0371 Oslo, Norway*

Gaute Grønnevik − *Section of Organic Chemistry, Department of Chemistry, University of Oslo, 0371 Oslo, Norway*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c04209

Funding

Funding from the research council of Norway (NFR ES 231553 to P.J.R.) is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. A fluoride-derived electrophilic late-stage fluorination reagent for PET imaging. *Science* **2011**, *334*, 639.

(2) Lee, E.; Hooker, J. M.; Ritter, T. Nickel-mediated oxidative fluorination for PET with aqueous [^{18}F]fluoride. *J. Am. Chem. Soc.* **2012**, *134*, 17456.

(3) Ichiishi, N.; Brooks, A. F.; Topczewski, J. J.; Rodnick, M. E.; Sanford, M. E.; Scott, P. J. H. Copper-catalyzed [^{18}F]fluorination of (mesityl)(aryl)iodonium salts. *Org. Lett.* **2014**, *16*, 3224.

(4) Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. A general copper-mediated nucleophilic ^{18}F fluorination of arenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 7751.
(5) Mossine, A. V.; Brooks, A. F.; Makaravage, K. J.; Miller, J. M.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. Synthesis of [^{18}F]arenes via the copper-mediated [^{18}F]fluorination of boronic acids. *Org. Lett.* **2015**, *17*, 5780.
(6) Zlatopolskiy, B. D.; Zischler, J.; Krapf, P.; Zarrad, F.; Urusova, E. A.; Kordys, E.; Endepols, H.; Neumaier, B. Copper-mediated aromatic radiofluorination revisited: Efficient production of PET tracers on a preparative scale. *Chem. - Eur. J.* **2015**, *21*, 5972.
(7) Makaravage, K. J.; Brooks, A. F.; Mossine, A. V.; Sanford, M. S.; Scott, P. J. H. Copper-mediated radiofluorination of arylstannanes with [^{18}F]KF. *Org. Lett.* **2016**, *18*, 5440.
(8) Hoover, A. J.; Lazari, M.; Ren, H.; Narayanam, M. K.; Murphy, J. M.; van Dam, R. M.; Hooker, J. M.; Ritter, T. A transmetalation reaction enables the synthesis of [^{18}F]5-fluorouracil from [^{18}F]-fluoride for human PET imaging. *Organometallics* **2016**, *35*, 1008.
(9) Preshlock, S.; Calderwood, S.; Verhoog, S.; Tredwell, M.; Huiban, M.; Hienzsch, A.; Gruber, S.; Wilson, T. C.; Taylor, N. J.; Cailly, T.; Schedler, M.; Collier, T. L.; Passchier, J.; Smits, R.; Mollitor, J.; Hoepping, A.; Mueller, M.; Genicot, C.; Mercier, J.; Gouverneur, V. Enhanced copper-mediated ^{18}F-fluorination of aryl boronic esters provides eight radiotracers for PET applications. *Chem. Commun.* **2016**, *52*, 8361.
(10) Rühl, T.; Rafique, W.; Lien, V. T.; Riss, P. J. Cu(I)-mediated ^{18}F-trifluoromethylation of arenes: rapid synthesis of ^{18}F-labeled trifluoromethyl arenes. *Chem. Commun.* **2014**, *50*, 6056.
(11) Riss, P. J.; Lu, S.; Telu, S.; Aigbirhio, F. I.; Pike, V. W. Cu^{I}-catalyzed ^{11}C carboxylation of boronic acid esters: a rapid convenient entry to ^{11}C-labeled carboxylic acids, esters and amides. *Angew. Chem., Int. Ed.* **2012**, *51*, 2698.
(12) Taylor, N. J.; Emer, E.; Preshlock, S.; Schedler, M.; Tredwell, M.; Verhoog, S.; Mercier, J.; Genicot, C.; Gouverneur, V. Derisking the Cu-mediated ^{18}F-fluorination of heterocyclic positron emission tomography radioligands. *J. Am. Chem. Soc.* **2017**, *139*, 8267.
(13) Balz, G.; Schiemann, G. Über aromatische Fluorverbindungen, I.: Ein neues Verfahren zu ihrer Darstellung. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 1186.
(14) Dai, J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.; Lu, X.; Liu, L.; Fu, Y. Copper-promoted sandmeyer trifluoromethylation reaction. *J. Am. Chem. Soc.* **2013**, *135*, 8436.
(15) Smith, W. B.; Ho, O. C. Application of the isoamyl nitrite-diiodomethaneroute to aryl iodides. *J. Org. Chem.* **1990**, *55*, 2543.
(16) Sandmeyer, T. Ueber die Ersetzung der Amid-Gruppe durch Chlor, Brom und Cyan in den aromatichen substanzen. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633.
(17) Sandmeyer, T. Ueber die Ersetzung der Amid-Gruppe durch Chlor, Brom und Cyan in den aromatichen Substanzen. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2650.
(18) Knöchel, A.; Zwernemann, O. Development of a no-carrier-added method for ^{18}F-labeling of aromatic compounds by fluorodediazonation. *J. Labelled Compd. Radiopharm.* **1995**, *38*, 4.
(19) Riss, P. J.; Kuschel, S.; Aigbirhio, F. I. No carrier-added nucleophilic aromatic radiofluorination using solid phase supported arenediazonium sulfonates and 1-(aryldiazenyl)piperazines. *Tetrahedron Lett.* **2012**, *53*, 1717.
(20) Narayanam, M. K.; Ma, G.; Champagne, P. A.; Houk, K. N.; Murphy, J. M. Synthesis of [^{18}F]fluoroarenes via nucleophilic radiofluorination of *N*-arylsydnones. *Angew. Chem., Int. Ed.* **2017**, *56*, 13006.
(21) Beletskaya, P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. Catalytic sandmeyer bromination. *Synthesis* **2007**, *2007*, 2534.
(22) Cohen, T.; Dietz, A. G.; Miser, J. R., Jr. A simple preparation of phenols from diazonium ions via the generation and oxidation of aryl radicals by copper salts. *J. Org. Chem.* **1977**, *42*, 2053.
(23) LaBarbera, D. V.; Bugni, T. S.; Ireland, C. M. The total synthesis of neoamphimedine. *J. Org. Chem.* **2007**, *72*, 8501.
(24) Doyle, M. P.; Siegfried, B.; Dellaria, J. F. Alkyl nitrite-metal halide deamination reactions. 2. Substitutive deamination of arylamines by alkyl nitrites and copper(II)halides. A direct and remarkably efficient conversion of arylamines to aryl halides. *J. Org. Chem.* **1977**, *42*, 2426.
(25) (a) In contrast to Cu(OTf)$_2$, all Cu(I) salts we used readily dissolved in the reaction mixture and stock solutions, which eased handling significantly; therefore, we attempted to oxidize Cu(I) to Cu(II) in situ. (b) Oxygen in air is an efficient oxidant for Cu(I). (c) Solids and precipitates block valves and tubing, which may cause processes to fail. Fine metal powders tend to block frits and cannot be handled well on synthesisers. In our experiments, a SPE cartridge step was necessary to protect the preparative HPLC from fine solids (putatively copper powder). Screening runs were facilitated by extraction of the organic product prior to analysis. (d) A fine suspension was obtained at the end of reaction on the synthesiser including a dark, dense Cu-precipitate.
(26) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. Mechanistic investigations of Cu-catalyzed fluorination of diaryliodonium salts: elaborating the Cu^{I}/Cu^{III} manifold in copper catalysis. *Organometallics* **2014**, *33*, 5525.
(27) Kochi, J. K. The mechanism of the sandmeyer and meerwein reactions. *J. Am. Chem. Soc.* **1957**, *79*, 2942.
(28) Hammond, G. B.; Plevey, R. G.; Sampson, P.; Tatlow, J. C. Synthesis of fluorinated derivatives of glutethimide and aminoglutethidmide. *J. Fluorine Chem.* **1988**, *40*, 81.
(29) Anwarullah, A. M.; Badshah, M.; Abbasi, R.; Sultan, A.; Khan, K.; Ahmad, N.; von Engelhardt, J. Further evidence for the association of CYP2D6*4 gene polymorphism with parkinson's disease: a case control study. *Genes Environ* **2017**, *39*, 18.
(30) Chattopadhyay, M.; Chowdhury, A. R.; Feng, T.; Assenmacher, C.-A.; Radaelli, E.; Guengerich, F. P.; Avadhani, N. G. Mitochondrially targeted cytochrome P420 2D6 is involved in monomethylamine-induced neuronal damage in mouse models. *J. Biol. Chem.* **2019**, *294*, 10336.
(31) Zollinger, H. Reactivity and stability of arenediazonium ions. *Acc. Chem. Res.* **1973**, *6* (10), 335.
(32) Francis, S. G.; Matthews, S. L.; Poleshchuk, O. Kh; Walker, N. R.; Legon, A. C. N_2-Cu-F: a complex of dinitrogen and cuprous fluoride characterized by rotational spectroscopy. *Angew. Chem., Int. Ed.* **2006**, *45*, 6341.
(33) Standard procedure for Cu-mediated radiofluoro-deaminations: Cyclotron produced a [^{18}F]fluoride ion solution containing 20−150 MBq that was loaded onto a Supel^{TM}-Select SAX SPE (30 mg) cartridge which was preconditioned with K_2CO_3 solution (1 M, 5 mL) and type I water (10 mL). The [^{18}F]fluoride was eluted with a 9:1 acetonitrile−H_2O solution (1 mL) containing KOTf (36 mM) and 15-C-5 (36 mM) into a 5 mL reaction vessel. The mixture was concentrated before residual water was azeotropically distilled off by successive cycles of addition and evaporation of acetonitrile (1 mL × 3). A freshly made solution of Cu(MeCN)$_4$OTf (45 mg, 120 μmol) and pyridine (40 μL, 480 μmol) in MeCN (0.5 mL) was added prior to addition of the aniline (30 μmol) and AmylONO (6 μL, 45 μmol) in MeCN (0.5 mL). The vial is carefully sealed with a screwcap to avoid evaporation of MeCN, and the reaction mixture is heated on the hot plate at 120 °C for 20 min. The reaction is cooled on an ice bath and quenched by the addition of 1 M HCl (1 mL). The labelled product is extracted by SPE (Waters Oasis cartridge) or Et_2O prior to analysis or purification using reversed phase HPLC.

https://dx.doi.org/10.1021/acs.orglett.0c04209
Org. Lett. 2021, 23, 1011−1015