Fluorination

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Copper-Mediated Aminoquinoline-Directed Radiofluorination of Aromatic C–H Bonds with $K^{18}F$

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Abstract: *A Cu-mediated ortho-C–H radiofluorination of aromatic carboxylic acids that are protected as 8-aminoquinoline benzamides is described. The method uses $K^{18}F$ and is compatible with a wide range of functional groups. The reaction is showcased in the high specific activity automated synthesis of the RARβ2 agonist [^{18}F]AC261066.*

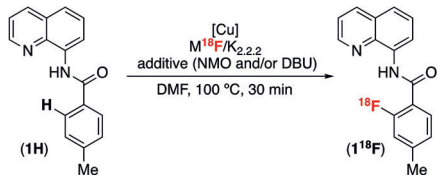
Aryl fluorides are widely prevalent in pharmaceuticals,[1,2] and their ^{18}F isotopologs are important for positron emission tomography (PET) imaging.[3,4] As such, there is significant interest in methods for the late-stage ^{18}F-fluorination of aromatic scaffolds.[5,6] The majority of existing methods for arene radiofluorination require a prefunctionalized starting material. For instance, hypervalent iodine reagents,[6c] organoborons,[6d–f,j,k] organostannanes,[6g] Ni/Pd complexes,[6a,b] and phenols[6h,i] have recently been introduced as precursors for nucleophilic radiofluorination reactions. However, this requirement for pre-installed functionality at the target site can be a roadblock for the application of these methods to complex radiotracer targets.

A complementary approach would involve the direct radiofluorination of a C–H bond of an arene substrate. Several strategies have been developed for the radiofluorination of aliphatic[7] and benzylic[8] C–H bonds. However, analogous transformations of C(sp^2)–H substrates have proven considerably more challenging. While C(sp^2)–H radiofluorination can be accomplished via electrophilic aromatic substitution (S_EAr) with [^{18}F]F_2 or [^{18}F]Selectfluor,[9] the generation and handling of these reagents requires specialized equipment that is not widely accessible. Additionally, the site- and chemoselectivities of S_EAr reactions are typically modest, and the final products generally have low specific activity.[10] In principle, these limitations could be addressed through the development of nucleophilic ($^{18}F^-$) C(sp^2)–H radiofluorination methods. However, in practice, realization of this approach has remained elusive due to the inertness of C(sp^2)–H bonds and the electronic mismatch between nucleophilic $^{18}F^-$ and most arene substrates.[11]

An attractive strategy to address these challenges would be to leverage modern advances in transition-metal catalyzed C(sp^2)–H functionalization. For example, recent work by Daugulis demonstrated that 8-aminoquinoline directing groups enable Cu-catalyzed *ortho*-C(sp^2)–H activation/nucleophilic fluorination reactions with AgF.[12] The directing group is easily cleaved, thus providing access to *ortho*-fluorinated carboxylic acids. This communication describes translation of this method to a radiofluorination process. While AgF was required in Daugulis' original transformation, our studies reveal that $K^{18}F$ is optimal for radiofluorination. This nucleophilic radiofluorination of aromatic C–H bonds is applied to a variety of carboxylic acid derivatives and automated to access high specific activity radiotracers.

We initially examined the Cu-catalyzed radiofluorination of aminoquinoline substrate **1H** with $Ag^{18}F$[13] under conditions closely analogous to those reported by Daugulis[12] (**1H** (20 μmol), CuI (5 μmol), *N*-methylmorpholine *N*-oxide (NMO, 90 μmol), $K_{2.2.2}$ (1.33 μmol), $Ag^{18}F$ (2500–3500 μCi) in DMF). However, these conditions did not afford detectable quantities of **1-^{18}F** as determined by radio-TLC and radio-HPLC analysis (Table 1, entry 1). Notably, the $Ag^{19}F$ likely serves two roles in the original Daugulis reaction. First, it acts as the nucleophile to install the C(sp^2)–F bond. Second, it serves as a base to sequester the proton that is generated during C–H activation. Since $Ag^{19}F$ is present in 3- to 4-fold excess relative to **1H,** there is sufficient fluoride available for

Table 1: Optimization of C–H radiofluorination.[a]



Entry	[Cu]	$M^{18}F$	NMO	DBU	RCC (%)[b]
1	CuI	$Ag^{18}F$	√	–	nd
2	CuI	$Ag^{18}F$	√	√	26 ± 1
3	$(MeCN)_4CuOTf$	$Ag^{18}F$	√	√	29 ± 0
4	$(MeCN)_4CuOTf$	$K^{18}F$	√	√	33 ± 0
5	$(MeCN)_4CuOTf$	$K^{18}F$	–	√	31 ± 13
6[c]	$(MeCN)_4CuOTf$	$K^{18}F$	–	√	**50 ± 2**

[a] Conditions: **1H** (20 μmol), Cu source (5 μmol), additives [NMO (90 μmol), $K_{2.2.2}$ (1.33 μmol), DBU (20 μmol)], $M^{18}F$ (2500–3500 μCi), DMF (1000 μL). [b] RCC was determined by radio-TLC ($n \geq 3$); nd = not detected. The identity of **1-^{18}F** was confirmed by radio-HPLC. [c] NMM added (90 μmol).

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both of these functions. In contrast, under the radiofluorination conditions, the $Ag^{18}F$ is the limiting reagent. We hypothesized that an exogeneous base might be needed to sequester protons while preserving a reservoir of nucleophilic fluoride for the desired C(sp^2)–F coupling reaction. Consistent with this hypothesis, the addition of 1,8-diazabicyclo-(5.4.0)undec-7-ene (DBU) (20 μmol, 1 equiv relative to **1H)** led to the formation of the desired product **1^{18}F** in 26 ± 1 % RCC as determined by radio-TLC and confirmed by radio-HPLC (Table 1, entry 2).[14] Further optimization revealed that switching from CuI to more soluble $(MeCN)_4CuOTf$ resulted in a slightly improved RCC (29 ± 0 %; Table 1, entry 3). Under these conditions, the [^{18}F]fluoride source could be changed to readily accessible $K^{18}F$[3] to afford 33 ± 0 % RCC of **1^{18}F** (Table 1, entry 4).

We next examined whether NMO is necessary for this transformation. In the $Ag^{19}F$ reaction (which is conducted under inert atmosphere), NMO acts as the terminal oxidant for Cu. However, the radiochemical reactions are conducted under ambient air, which could directly oxidize the Cu. Indeed, excluding NMO from the $Ag^{18}F$ reaction under otherwise identical conditions resulted in a comparable RCC (31 ± 13 %, entry 5),[15] although it did negatively impact the run-to-run reproducibility. We evaluated a number of additives to address this latter issue and found that the use of 90 μmol of *N*-methylmorpholine (NMM), the base counterpart of NMO, resulted in enhanced reproducibility as well as an improved RCC of 50 ± 2 % (Table 1, entry 6).

The scope of this reaction was examined using aminoquinolines derived from a variety of substituted benzoic acids.[16] As shown in Figure 1, electron-neutral (**1^{18}F**–**4^{18}F**), -withdrawing (**5^{18}F**–**10^{18}F**),[17] and -donating (**11^{18}F**) substituents were tolerated on the arene ring. Many functional groups, including benzylic C–H bonds, trifluoromethyl, cyano, nitro, ester, amide, and sulfonamide substituents, were compatible. This C(sp^2)–H radiofluorination was also effective on pyridine- and indole-derived substrates, providing **12^{18}F** and **13^{18}F** in moderate RCC. A substrate containing a fluorine substituent at the activated 4-position on the quinoline reacted to afford the *ortho*-^{18}F-labelled product **14^{18}F** in 50 % RCC.[18] This method was applied to the late-stage radiofluorination of a series of biologically relevant molecules. Four carboxylic acid-containing drugs, probenecid, ataluren, tamibarotene, and AC261066, were converted to the corresponding 8-aminoquinoline benzamides and then subjected to the optimal conditions. The [^{18}F]fluorinated analogues (**15^{18}F**–**18^{18}F**, respectively) were obtained in 13–37 % RCC.[19]

A final set of experiments involved automation of this reaction on a TRACERLab FX_{FN} synthesis module and hydrolysis of the aminoquinoline protecting group (Scheme 1). Initial automated studies were conducted with **1H,** and afforded **1^{18}F** in 28 ± 6 % (n = 6) automated RCC or, by incorporating semi-preparative HPLC purification, 9 ± 4 % (n = 6) isolated decay-corrected radiochemical yield (RCY) and > 98 % radiochemical purity (RCP). Starting with 1.7 Ci of [^{18}F]fluoride **1^{18}F** was obtained in 42 ± 3 mCi (n = 3) with high specific activity (6 ± 1 Ci μmol^{-1}). Hydrolysis of the aminoquinoline protecting group was then achieved with 4 M NaOH to afford **19^{18}F** in 90 ± 2 % RCC from **1^{18}F** (n = 3) and 21 ± 2 % RCC based upon starting [^{18}F]fluoride.

An analogous method was applied to the synthesis of [^{18}F]AC261066 (**20^{18}F**), a RARβ2 agonist (Scheme 1).[20] Subjecting **18H** to the C–H radiofluorination conditions afforded **18^{18}F** in 12 ± 2 % automated RCC (n = 3). Starting with 1.7 Ci of [^{18}F]fluoride, **18^{18}F** was obtained in 36 ± 8 mCi (n = 3) after sep-pak purification, corresponding to 3 ± 1 % isolated decay-corrected RCY. Manual hydrolysis of the amide with 4 M NaOH formed [^{18}F]AC261066 (**20^{18}F**) in 98 ± 1 % RCC from **18^{18}F** (n = 5, determined by radio-TLC). Overall, the isolated decay-corrected RCY of **20^{18}F** was 9 ± 7 mCi (2 ± 1 % based upon starting [^{18}F]fluoride, n = 3). The product was obtained in high chemical and radiochemical (> 98 %) purity and high specific activity (0.80 ± 0.25 Ci μmol^{-1}).[21]

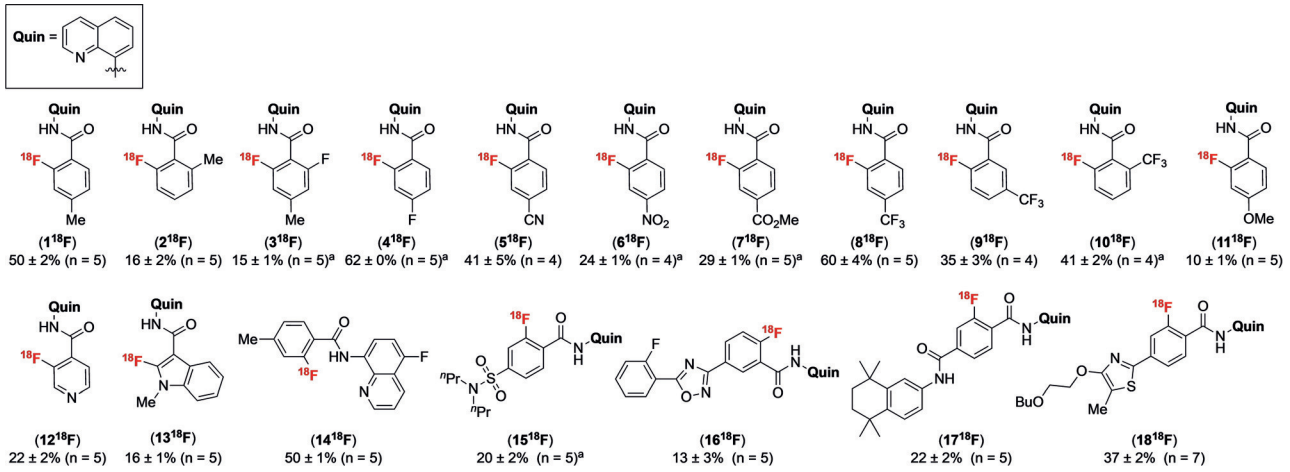
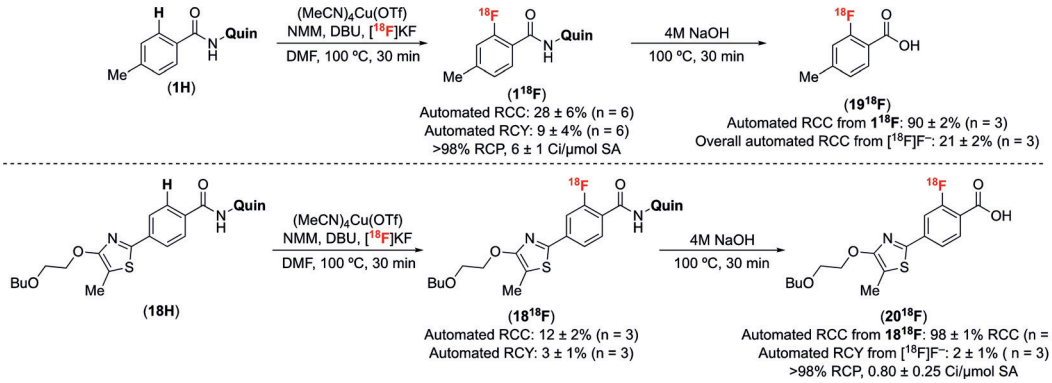


Figure 1. Substrate scope. Reported values indicate radiochemical conversion (RCC) determined by radio-TLC for $n \geq 4$ runs. The identity of all products was confirmed by radio-HPLC. General conditions: Substrate (20 μmol), $(MeCN)_4Cu(OTf)$ (5 μmol), NMM (90 μmol), $K_{2.2.2}$ (1.33 μmol), DBU (20 μmol), $K^{18}F$ (2500–3500 μCi), DMF (1000 μL), 90–110 °C, 30 min. [a] in cases where other products were observed by radio-HPLC analysis, RCCs from radio-TLC analysis were corrected as described in the Supporting Information.[17]



Scheme 1. Automated C(sp^2)–H radiofluorination.

In summary, we describe the Cu-catalyzed, aminoquinoline-directed C(sp^2)–H radiofluorination of arene C(sp^2)–H bonds with $K^{18}F$.[22] The method has been applied to a variety of substrates, including the active pharmaceutical ingredients of probenecid, ataluren, and tamibarotene. In addition, it has been translated to an automated synthesis of high specific activity doses of RARβ2 agonist [^{18}F]AC261066. We note that the automated radiochemical yields and directing group cleavage procedures will require additional optimization before they can be applied in routine radiosyntheses. In addition, future work should target the use of more practical directing groups as well as non-directed approaches to C–H radiofluorination. However, overall this operationally simple procedure demonstrates proof-of-concept that metal-catalyzed nucleophilic C(sp^2)–H radiofluorination is feasible, and that this approach shows promise for the late-stage radiofluorination of bioactive molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H fluorination · C–H functionalization · fluorine-18 · late-stage fluorination · PET radiochemistry

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[14] Other bases were also compatible (e.g. comparable RCCs could be obtained using 1,5-diazabicyclo[4.3.0]non-5-ene; see Supporting Information).
[15] When Table 1, entry 5 was set up in a glovebox and kept under an inert atmosphere the RCC dropped prohibitively (to $6\pm4\%$), further consistent with the role of air as the oxidant.
[16] Product identities were confirmed by radio-HPLC. To further confirm that radiofluorination occurred at the expected *ortho*-site (rather than on the quinoline ring) we conducted control experiments and demonstrated baseline separation of regioisomeric products by HPLC (see Supporting Information).
[17] Some arenes bearing electron-withdrawing substituents give rise to minor side products. We ruled out the formation of side products derived from competing S_NAr reactions (see Supporting Information), but have not been able to positively identity the side products to date.
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[19] Compounds **15**–**18** contain functional groups that could potentially direct C–H fluorination elsewhere in the molecule (e.g. **17H** contains 2 amide groups). Small impurity peaks were detected in the crude radio-HPLC traces of these products; however, $\mathbf{15^{18}F}$–$\mathbf{18^{18}F}$ were the major products in each case, and they appear to be readily separable from the side products formed in the reaction.
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[21] These unoptimized automation results demonstrate that this method can be used to prepare sufficient amounts of radiotracers for pre-clinical evaluation in rodents and non-human primates. We expect that yields can be further improved through careful optimization of the automated method. This work is currently underway, along with qualification of a synthesis and formulation of $\mathbf{20^{18}F}$ for preclinical use.
[22] Radioiodination of this scaffold has been reported. See: L. W. Deady, J. Desneves, L. M. A. Tilley, *J. Labelled Compd. Radiopharm.* **2000**, *43*, 977.

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