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Sequential Ir/Cu-Mediated Method for the *meta*-Selective C—H Radiofluorination of (Hetero)Arenes

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Abstract

This Article describes a sequential Ir/Cu-mediated process for the *meta*-selective C—H radiofluorination of (hetero)arene substrates. In the first step, Ir-catalyzed C(sp^2)—H borylation affords (hetero)aryl pinacolboronate (BPin) esters. The intermediate organoboronates are then directly subjected to copper-mediated radiofluorination with [^{18}F]tetrabutylammonium fluoride to afford fluorine-18 labeled (hetero)arenes in high radiochemical yield and radiochemical purity. This entire process is performed on a bench-top without Schlenk or glovebox techniques and circumvents the need to isolate (hetero)aryl boronate esters. The reaction was automated on a TracerLab FX_{FN} module with 1,3-dimethoxybenzene and a *meta*-tyrosine derivative. The products, [^{18}F]1-fluoro-3,5-dimethoxybenzene and an ^{18}F-labeled *meta*-tyrosine derivative, were obtained in 37 ± 5% isolated radiochemical yield and >99% radiochemical purity and 25% isolated radiochemical yield and 99% radiochemical purity, and 0.52 Ci/μmol (19.24 GBq/μmol) molar activity (A_m), respectively.

Graphical Abstract

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.

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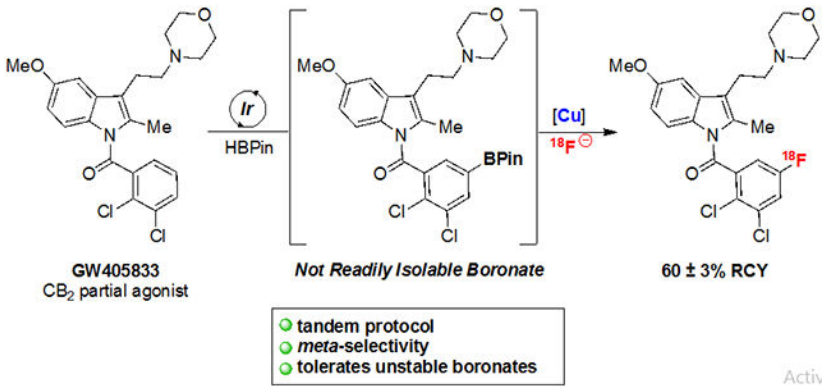
Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

- Materials and methods; preparation of precursors and reference standards; radiofluorination details; screening information; NMR spectra; HPLC traces.



Introduction

Positron emission tomography (PET) with ^{18}F-labeled radiotracers is widely used for the detection, staging, and study of disease.[1,2] While numerous ^{18}F-containing molecules have been deployed in PET, those containing aromatic C—^{18}F bonds are particularly desirable due to their resistance to metabolic defluorination. As such, there is a pressing need for synthetic methods for the late-stage radiofluorination of (hetero)arenes, particularly those that are fast (due to the short ~110 min half-life of ^{18}F), use nucleophilic [^{18}F]fluoride (which has high molar activity and is readily available from small medical cyclotrons), and are translatable to automated clinical production laboratories.

Most existing protocols for the nucleophilic radiofluorination of (hetero)arenes are limited in scope and/or utilize precursors that require multi-step syntheses (Scheme 1A). For instance, classical S_NAr radiofluorination reactions require highly electron deficient (hetero)aryl halide/pseudohalide substrates.[3] This electronic limitation has been overcome by moving to alternative mechanistic pathways and/or precursors, including those involving diazonium salts,[4] triazenes,[5] organo-nickel[6] or -palladium complexes,[7] phenols,[8-10] hypervalent iodine derivatives,[11-13] organoboron or stannane reagents,[14-17] or sulfur-substituted aromatics.[18-19] However, challenges with the synthesis, handling, isolation, scalability, and/or long-term storage of these precursors continue to limit widespread application of many of these methods in clinical settings.[20-23] The Cu-mediated radiofluorination (CMRF) of organoboron precursors is a general (in terms of substrate scope) and practical (in terms of precursor availability and translation to automated syntheses) radiofluorination strategy that has been widely adopted for clinical use.[24] Although many simple aryl boron reagents exhibit high bench-top stability, the purification, storage, and/or handling of highly functionalized (hetero)arylboron compounds (for example those derived from the late-stage borylation of bioactive scaffolds) as well as of 2-azaaryl and polyfluorinated aryl boron derivatives can be quite challenging.[25]

An attractive alternative would be to directly use C(sp^2)—H substrates as precursors for nucleophilic radiofluorination. The (hetero)arene substrates of these transformations are exceptionally stable and readily available. However, there are major challenges to realizing this approach, including (1) developing strategies for the rapid activation/radiofluorination of traditionally inert C(sp^2)—H bonds and (2) controlling the selectivity of ^{18}F incorporation

when there are multiple C(sp^2)—H sites. Several recent reports have shown the feasibility of C(sp^2)—H radiofluorination in limited contexts (Scheme 1B). For instance, aminoquinoline directing groups were used to control reactivity and selectivity in *ortho*-selective C(sp^2)—H CMRF of (hetero)arenes.[26] Additionally, *para*-selective electrophilic aromatic substitution (EAS) on electron rich (hetero)arenes was employed for the *in situ* generation of hypervalent iodine precursors for CMRF.[27] A related *para*-selective EAS reaction was leveraged to access aryl sulfonium salts, which then undergo uncatalyzed nucleophilic radiofluorination.[28] Finally, an organic photoredox approach was utilized to achieve *para*-selective nucleophilic radiofluorination of electron rich (hetero)arenes.[29] In this report, we demonstrate a sequential Ir/Cu-mediated C(sp^2)—H radiofluorination with a wide substrate scope, complementary site selectivity, and high operational simplicity compared to existing methods (Scheme 1C). This transformation merges the Ir-catalyzed C(sp^2)—H borylation of (hetero)arenes[30,31] with Cu-mediated radiofluorination to achieve *meta*-selective ^{18}F-labeling of electronically diverse (hetero)arene substrates.

Results and Discussion

Although other tandem Ir C—H borylation sequences have been reported,[32] we anticipated three major challenges for combining Ir-catalyzed C(sp^2)—H borylation and Cu-mediated radiofluorination of the resulting (hetero)aryl boronate esters. First, CMRF reactions are well-known to be highly sensitive to conditions (e.g., solvent, ligands, additives),[33,34] thus creating potential compatibility issues with the Ir catalysis. Second, due to the sensitivity of the active Ir catalyst, the Ir-catalyzed reaction is most commonly conducted with rigorous exclusion of air and moisture, which is not feasible in standard radiochemistry labs. Third, Ir-catalyzed C(sp^2)—H borylation proceeds with modest site selectivity for certain classes of substrates, which could ultimately result in mixtures of radiofluorinated products.

We first probed the anticipated compatibility issues by conducting the CMRF of **1-BPin** in the presence of different components of the Ir-catalyzed C—H borylation reaction (Table 1). Under standard radiofluorination conditions (20 μmol **1-BPin**, 0.25 equiv of $Cu(py)_4(OTf)_2$, [^{18}F]tetrabutylammonium fluoride ([^{18}F]TBAF) in DMA at 120 °C for 20 min), **1-^{18}F** is formed in 80% radiochemical yield (RCY; entry 1), which was measured by multiplying radiochemical conversion (RCC) values obtained via radio-thin-layer chromatography (rTLC) analysis by radiochemical purity (RCP) values obtained via radio-high-performance liquid chromatography (rHPLC) analysis. However, as predicted, the addition of various C—H borylation reaction components significantly lowers the yield of **1-^{18}F**. Iridium sources containing chloride ligands (e.g., $[Ir(COD)Cl]_2$, entry 2), are particularly problematic, likely due to competing reactions of the Cl^- ion. Consistent with this proposal, the addition of 5 μmol of tetrabutylammonium chloride (TBACl, entry 6) completely shuts down the CMRF reaction. Moving to the halide-free Ir precursor $[Ir(COD)OMe]_2$ restores the yield to ~80% (entry 3).

Common ligands for Ir-catalyzed C—H borylation, 4,4’-di-*tert*-butylbipyridine (dtbpy) and 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen), also impede radiofluorination (entries 4, 5). We hypothesize that these ligate the Cu and render it less reactive. To mitigate this issue, the Cu loading was increased from 5 μmol (equimolar with the added ligands) to 20

μmol (>3-fold excess relative to the dtbpy/tmphen). This change in stoichiometry restores the radiofluorination yield to >80% (entries 7-9). Finally, B_2Pin_2 and HBPin inhibit the radiofluorination step (entries 10, 11). We hypothesized that this could be addressed by using an alcohol additive to quench reactive boron species.[35,36] Indeed, the addition of 30 equiv of *n*-BuOH[37,38] renders the radiofluorination reaction insensitive to boron additives (entries 13, 14).[39]

The C—H borylation step was next evaluated using the most compatible precatalyst and ligand, $[Ir(COD)OMe]_2$/tmphen. Initial studies focused on identifying an operationally simple bench-top procedure, since most radiochemistry laboratories lack specialized equipment for air-free reactions. These studies revealed that the ligand, catalyst, and solvent for C—H borylation can be dispensed into a vial under ambient conditions followed by a 2 min argon sparge of the resulting solution. Subsequent addition of HBPin and **1-H** followed by heating at 80 °C for 16 h results in the formation of **1-BPin** in 82% NMR yield and 16 : 1 *meta* : *ortho* selectivity. This is comparable to the 92% NMR yield and identical regioselectivity obtained under rigorously dry/air-free conditions.

The two steps of the sequence were next combined by adding *n*-BuOH to the crude C—H borylation mixture and then directly subjecting this solution to radiofluorination with $Cu(py)_4(OTf)_2$ and [^{18}F]TBAF in DMA at 120 ºC for 20 min. As shown in Scheme 2, this sequence affords **1-^{18}F** in 88 ± 6% non-isolated RCY and 16 : 1 *meta* : *ortho* selectivity, as confirmed by rHPLC. Importantly, the RCY is based on ^{18}F as the limiting reagent.[40] This sequence was directly translated to automated radiosynthesis by loading the crude C—H borylation mixture into a TracerLab FX_{FN} synthesis module. Under automated conditions, **1-^{18}F** is produced in 37 ± 5% isolated RCY and >99% radiochemical purity (RCP, n=3), illustrating the potential for clinical translation (Scheme 2, see SI for full details).

This optimized sequence is effective for the ^{18}F-labeling of electronically diverse 1,3-disubstituted arenes, affording **1-^{18}F** to **11-^{18}F** in RCYs ranging from 8 to 88% (Scheme 3).[41,42] In these examples, the ^{18}F-labeled product is formed with high *meta*-selectivity, and regioisomers could be separated and quantified using analytical or semi-preparative HPLC (see SI). The C—H borylation site-selectivity is lowest for substrates bearing relatively small cyano and fluoro substituents (**9-11**), as expected for the sterically-controlled C—H functionalization step.[43,44] However, the isomer ratio in the ^{18}F-labeled products is typically higher than that observed in the C—H borylation step. For instance, the Ir-catalyzed C—H borylation of **9-H** proceeds *ortho*- and *meta*- to the nitrile substituent with 5 : 1 selectivity favoring the less sterically congested *meta*boronate. However, the radiolabeling reaction affords **9-^{18}F** in 10 : 1 selectivity favoring the same position.[45] Even more strikingly, C—H borylation of methyl 3-fluorobenzoate **11** affords a 2.5 : 1 mixture of isomers ArBPin **a** and **b** (Scheme 4A); however, after radiofluorination, **11-^{18}F** is formed as a 41 : 1 mixture favoring the *meta*-isomer **b**.

NMR studies show that the selectivity enhancement in both **9** and **11** is due to facile decomposition of the *ortho*-borylated intermediates under CMRF conditions. This decomposition occurs via a combination of protodeboronation and oxidation pathways (see

SI for complete details).[46,47] Notably, it is well documented that *ortho*-fluorine substituents accelerate protodeboronation in various media, supporting these conclusions.[48,25a]

Arenes with other substitution patterns are similarly effective substrates for this sequence. For instance, veratrole **13-H** undergoes selective C—H borylation/radiofluorination to afford **13-^{18}F** in 83% RCY. The C—H borylation of 1-(2-methoxyphenyl)ethan-1-one **14-H** is slow at room temperature but proceeds efficiently at 80 ºC to afford 2: 1 selectivity for the site *para*- to the acetyl substituent. The isomer ratio is enhanced in the CMRF step, resulting in **14-^{18}F** as a 3.4 : 1 mixture of isomers.[49] Anisole **15-H** undergoes C—H borylation to generate a 3.3 : 1 : trace mixture of the *meta : para : ortho* boronate esters. Here again, the *meta*-selectivity is modestly enhanced in the CMRF step (**15-^{18}F** is generated in a 12 : 3 : 1 mixture). Notably, this *meta*-selectivity with **15-H** is complementary to that obtained in C—H radiofluorination reactions involving EAS or radical cation pathways (where the *para*-isomer is strongly favored, Scheme 1B).[27,28a,50] This protocol is also compatible with modified C—H borylation systems that override intrinsic substrate regiochemistry.[51] For example, indole **16-H** undergoes selective C—H borylation at C-6 through the *in situ* installation of a traceless BPin directing group at the N-H bond prior to the C—H borylation to form adduct **c** (Scheme 4B, see SI for protocol).

A final noteworthy feature of this sequence is that it does not require either (1) high conversion in the C—H borylation step or (2) the generation of isolable boronate esters. This is exemplified by the formation of product **8-^{18}F**. The Ir-catalyzed C—H borylation of 2-bromo-4-methylpyridine proceeds in low (<10%) yield as determined by ^{1}H NMR spectroscopy. Furthermore, the intermediate 2-pyridyl-substituted boronate ester is notoriously unstable.[25b,c,52] Nonetheless, this substrate was successfully functionalized in 8% RCY, thereby circumventing the need to synthesize, isolate, and store the boronate ester precursor.[53]

The ability to directly and selectively convert bioactive molecules into radiofluorinated analogues offers opportunities to streamline ^{18}F-radiotracer synthesis and development. As such, it is critical to evaluate this method in the context of such scaffolds (Scheme 5). Under the standard C—H borylation/CMRF conditions, the anesthetic lidocaine reacts to furnish **17-^{18}F** in 15 ± 8% RCY. Notably, this radiolabeling approach is complementary to Hooker's synthesis of the ^{18}F-fluoroethyl analogue [^{18}F]radiocaine.[54]

Protected aromatic amino acid derivatives undergo high yielding radiofluorination to afford products such as **18-^{18}F** and **19-^{18}F**. These have potential applications for imaging dopaminergic metabolism and tumor proliferation.[55] Automated labeling was followed by semi-preparative HPLC purification to afford **18-^{18}F** in 25% isolated RCY, 99% RCP, and 0.52 Ci/μmol (19.24 GBq/μmol) A_m (n=2). ICP-MS analysis of **18-^{18}F** obtained from this procedure indicated an Ir content of 13.46 ng, which is below the exposure limits (e.g. parenteral = 10 μg/day) stipulated for human use.[56] This analysis further emphasizes the suitability of this radiolabeling method for use in conjunction with human PET imaging studies. Furthermore, manual labeling of **19-H** to afford phenylalanine derivatives was achieved following acidic deprotection in HCl, and the *meta*- and *para*-regiosomers were separated using analytical rHPLC.[57] Over the C—H radiofluorination protocol and the

subsequent deprotection **19-^{18}F** was obtained in >99% ee as determined via chiral HPLC analysis.

This method is also effective for the *meta*-selective radiofluorination of a protected guanidine. Deprotection of the crude product with trifluoroacetic acid delivered **20-^{18}F**. Notably, previous access to related imaging agents required the multi-step synthesis of iodonium precursors.[58] Finally, the densely functionalized cannabinoid receptor 2 partial agonist GW405833 undergoes C—H radiofluorination to afford **21-^{18}F** in 60 ± 3% RCY. Multiple attempts to chromatographically isolate the boronate ester intermediate of this transformation led to the recovery of protodeboronated GW405833 substrate. Our approach enables high-yielding radiofluorination by circumventing the requirement to isolate/store this boronate. Once again, the incorporation of ^{18}F onto the aromatic ring complements existing radiolabeling strategies for this molecule, which involve the multi-step installation of a [^{18}F]fluoroethyl group.[59] Overall, these examples highlight the broad functional group compatibility of the method, including tolerance of esters, amines, indoles, amides, and protected guanidines.

Conclusions

In summary, this report describes the development of a method for the *meta*-selective borylation/CMRF of aromatic C—H bonds. This approach enables the rapid and selective ^{18}F-labeling of lead compounds for the development of imaging agents. Execution of the tandem procedure is operationally simple and readily translated to automated synthesis on a TracerLab FX_{FN} module. As such, we anticipate that it can be adopted for both exploratory and clinical radiosyntheses of ^{18}F PET imaging agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(40). This explains why the yield for the two step C—H borylation/radiofluorination sequence (88%; determined based on ^{18}F as limiting reagent) is higher than that of the C–H borylation step (82%; determined based on **1-BPin** as the limiting reagent).

(41). Electron deficient substrates afford better yields using $Cu(impy)_4(OTf)_2$ (impy=imidazo[1,2-b]pyridazine) in place of $Cu(py)_4(OTf)_2$ (see ref 17).

(42). A modified C—H borylation procedure was developed to address the inhibitory effect of some functional groups, such as the C—I bond in **6-H** and the basic nitrogen in pyridine **7-H**. This involved heating the solution of [Ir], ligand, and HBPin in order to more efficiently generate the active catalyst prior to substrate addition (see SI for full details).

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(45). Since Ir is known to induce selective protodeboronation, we considered the possibility that residual C—H borylation materials may be responsible for this selectivity enhancement. However, comparable regioselectivities were obtained in the CMRF of purified boronates derived from **14-H** in the presence/absence of the C—H borylation components (see SI). See: Kallepalli VA; Gore KA; Shi F; Sanchez L,; Chotana GA; Miller SL; Maleczka RE; Smith MR Harnessing C—H Borylation/Deborylation for Selective Deuteration, Synthesis of Boronate Esters, and Late Stage Functionalization. Journal of Organic Chemistry, 2015, 80, 8341–8353.**14-H**

(46). (a)Similar selectivity enhancement was observed for **9-^{18}F** and **10-^{18}F**. There was some run-to-run variability in the C—H borylation selectivity. However, only traces of *ortho*-^{18}F-labeled isomers were detected in all runs.(b)Subjecting a 2.5 : 1 mixture of **a : b** to the Cu radiofluorination conditions without added [^{18}F]TBAF led to quantitative consumption of **b**. In contrast, isomer **a** remained after 20 min (see SI for further details).

(47). We thank a reviewer for offering alternative explanations for the regioselectivity enhancements observed in the fluoroarene substrates. These have been examined using *meta*- and *ortho*-substituted BPin precursors **11-BPin**, which do not afford appreciable quantities of the *ortho*-labeled radiofluorine under the CMRF conditions, ruling out other pathways. These controls demonstrate that isomerization of the radiofluorine products via a benzyne mediated by an IrH species does not operate (see SI for details).

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(49). CMRF of the independently synthesized boronate regioisomers corresponding to **14-H** employed as mixtures in various ratios gave regiochemical outcomes consistent with regioselectivity observed in the tandem protocol, see the SI for details. For a prior investigation of this substrate under a different Ir C—H borylation system, see: Tajuddin H; Harrisson P; Bitterlich B; Collings JC; Sim N; Batsanov AS; Cheung MS; Kawamorita S; Maxwell AC; Shukla L; Morris J; Lin Z.; Marder TB; Steel PG Iridium-Catalyzed C—H Borylation of Quinolines and Unsymmetrical 1,2-Disubstituted Benzenes: Insights into Steric and Electronic Effects on Selectivity Chem. Sci 2012, 3, 3505–3515.**14-H**

(50). Coenen HH; Franken K; Kling P; Stöcklin KG Direct Electrophilic Radiofluorination of Phenylalanine, Tyrosine and Dopa. Int. J. Radiat. Appl. Instrumentation 1988, 39, 1243–1250.

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(53). No competing S_NAr labeling was observed during this CMRF reaction, which was confirmed by subjecting **8-H** to the labeling conditions.

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(57). In the case of monosubstituted **19-H**, the isomeric mixture could be resolved with HPLC following acidic deprotection in HCl. This analysis showed a 1.7:1 regioisomeric ratio favoring the meta-functionalized isomer.

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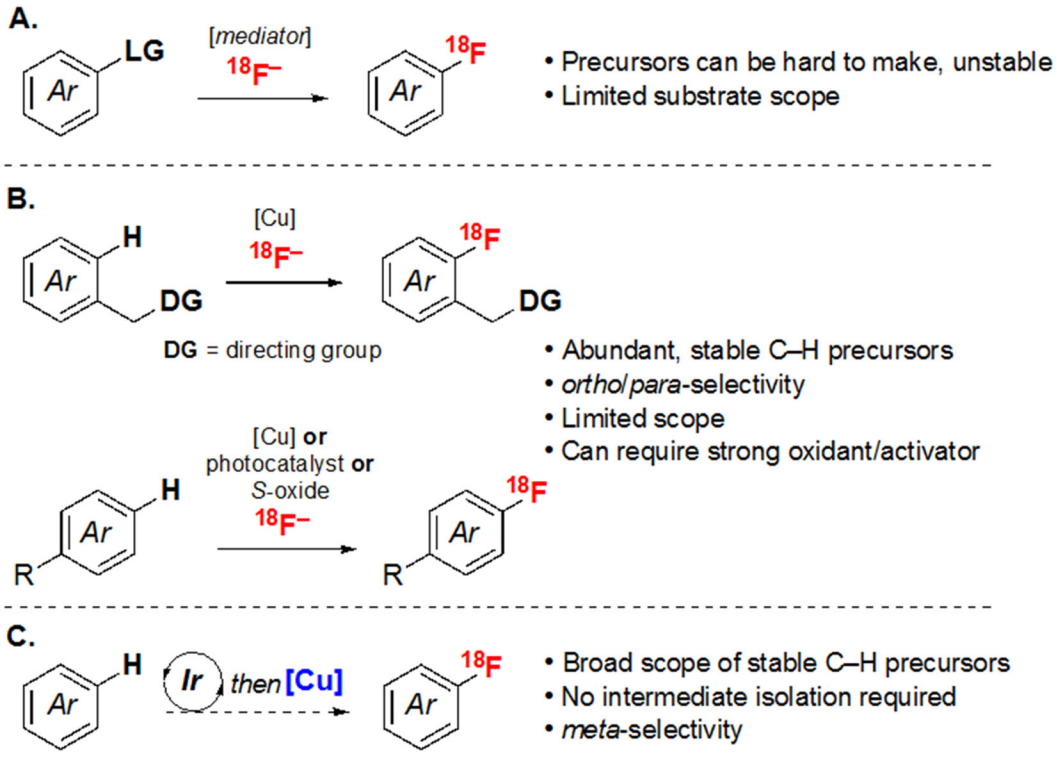
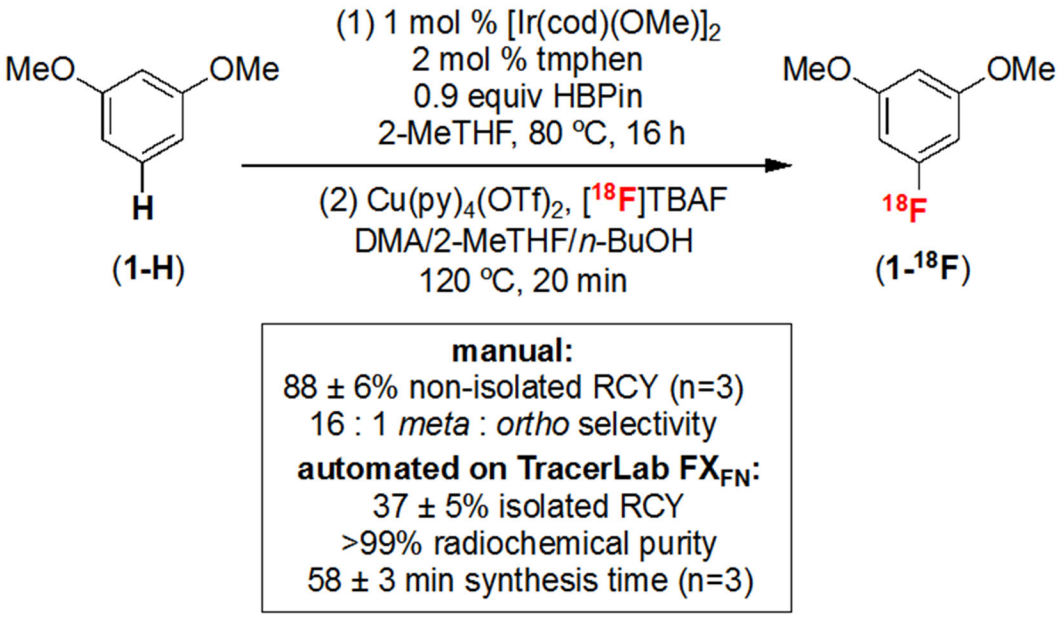


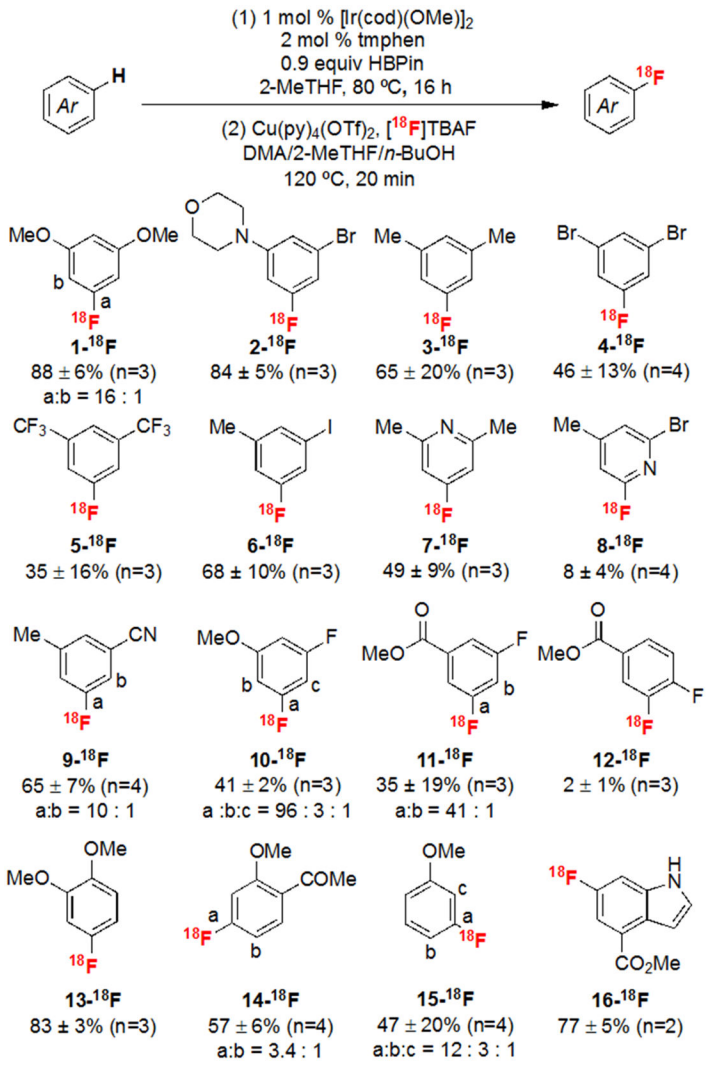
Scheme 1.

(**A**) Radiofluorination of prefunctionalized precursors. (**B**) Existing C—H radiofluorination approaches. (**C**) C—H radiofluorination using sequential Ir/Cu mediated processes (this work).



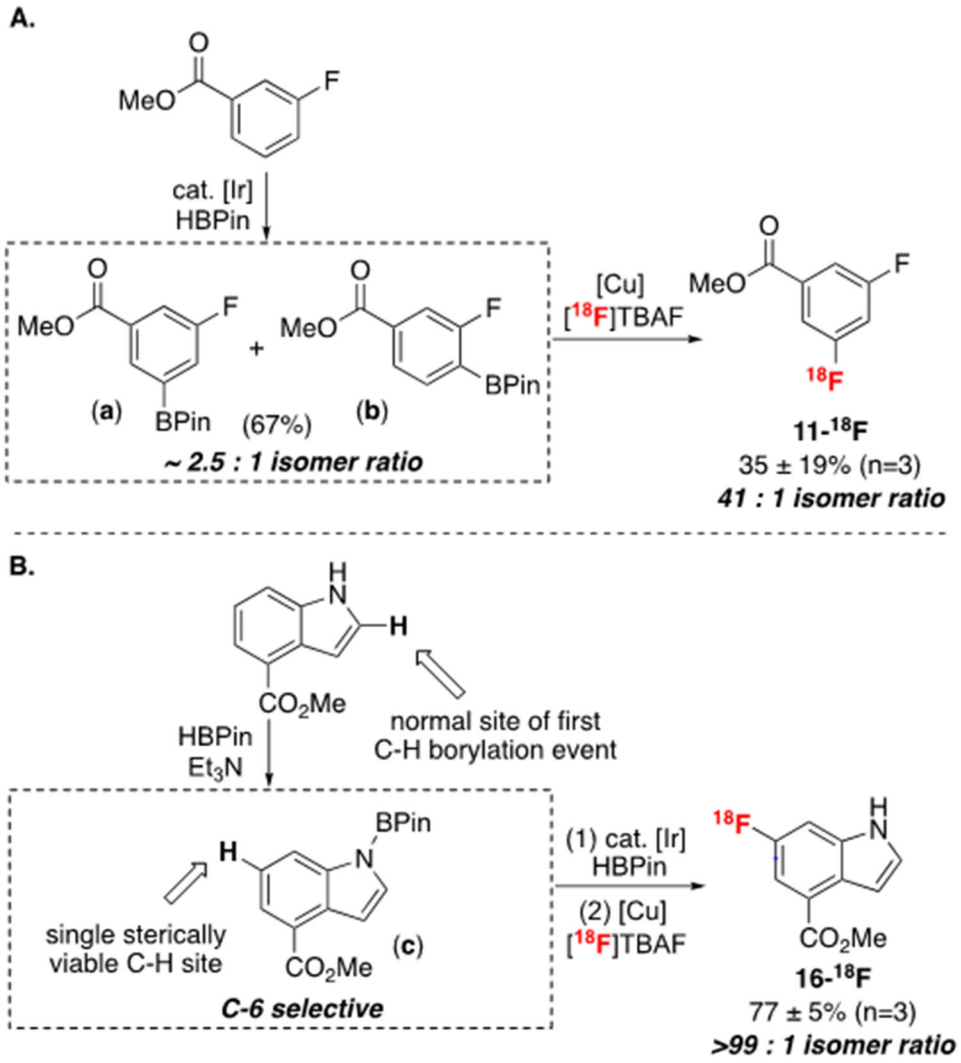
Scheme 2.

Sequence for C—H radiofluorination of **1-H**. See SI for complete experimental details. Non-isolated RCY is calculated by multiplying RCC (measured via radio-TLC) by the RCP (measured via radio-HPLC). Isolated RCY refers to the isolated recovery of the labeled product following semi-preparative HPLC purification.



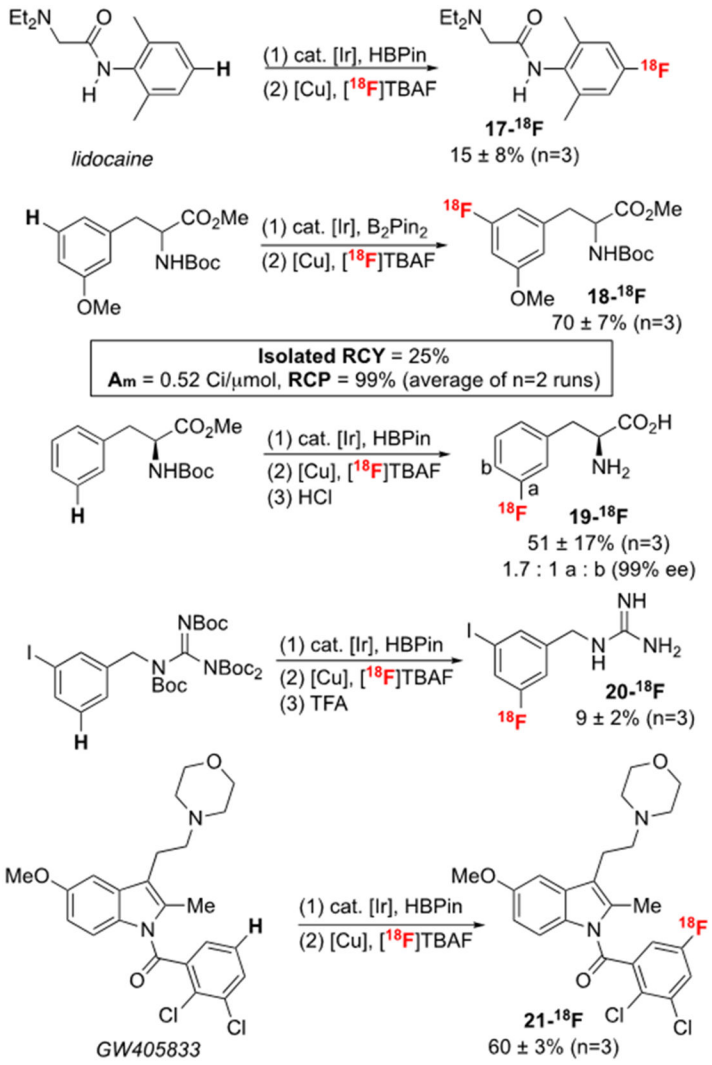
Scheme 3.

Substrate scope. See SI for complete experimental details and minor changes to the Cu mediator structure and temperature for different substrates. Unless otherwise stated, RCYs are non-isolated and are calculated by multiplying RCC (measured via radio-TLC) by the RCP (measured via radio-HPLC).



Scheme 4.

A. Highly meta-selective CMRF preceded by non-selective C—H borylation of fluorinated **12-H**. B. Highly C-6 selective CMRF of indole **16-H** via BPin adduct **c**. Yields are non-isolated RCYs and are calculated by multiplying RCC (measured via radio-thin-layer chromatography) by the RCP (measured via radio-HPLC).

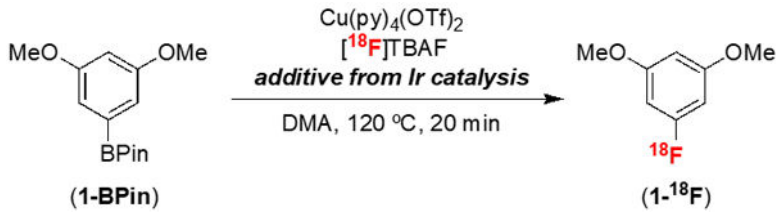


Scheme 5.

Tandem C—H radiofluorination of pharmaceutically relevant scaffolds. See SI for complete experimental details and minor changes to the Cu mediator and temperature for different substrates. Unless otherwise stated, RCYs are non-isolated and are calculated by multiplying RCC (measured via radio-thin-layer chromatography) by the RCP (measured via radio-HPLC). Isolated RCY refers to the isolated recovery of the labeled product following semi-preparative HPLC purification.

Table 1.

Impact of catalysts/ligands/reagents on Ir-catalyzed C—H borylation on CMRF of **1-BPin**. Unless otherwise stated, RCYs are non-isolated and are calculated by multiplying RCC (measured via radio-TLC) by the RCP (measured via radio-HPLC).



(**1-BPin**) (**1-^{18}F**)

entry	[Cu] (μmol)	additive (μmol)	RCY (%)
1	5	none	80 ± 10
2	5	$[Ir(COD)Cl]_2$ (3)	42 ± 10
3	5	$[Ir(COD)OMe]_2$ (3)	80 ± 6
4	5	tmphen (6)	49 ± 13
5	5	dtbpy (6)	58 ± 3
6	5	TBACl (6)	0
7	20	none	92 ± 1
8	20	tmphen (6)	88 ± 3
9	20	dtbpy (6)	91 ± 3
10	20	B_2Pin_2 (10)	36 ± 6
11	20	HBPin (20)	43 ± 9
12	20	*n*-BuOH (550)	96 ± 3
13	20	B_2Pin_2 (10) & *n*-BuOH (550)	83 ± 5
14	20	HBPin (10) & *n*-BuOH (550)	86 ± 2