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One-Pot Formal Carboradiofluorination of Alkenes: A Toolkit for Positron Emission Tomography Imaging Probe Development

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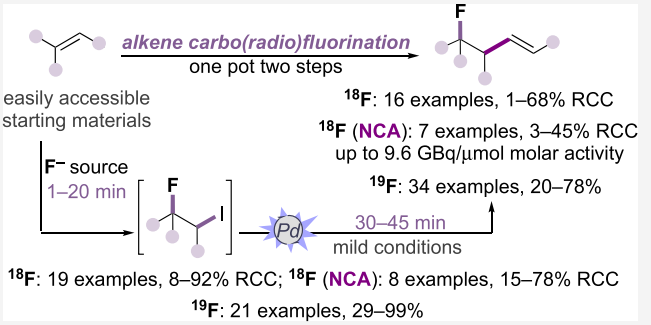
ABSTRACT: We report the first one-pot formal alkene carboradiofluorination reaction employing easily accessible alkenes as both prosthetic group precursors and coupling partners. The methodology features rapid sequential Markovnikov-selective iodofluorination and photoinduced Pd(0/I/II)-catalyzed alkyl Heck reaction as a mild and robust fluorine-18 (^{18}F) radiochemical approach for positron emission tomography (PET) imaging probe development. A new class of prosthetic groups for PET imaging probe synthesis was isolated as iodofluorinated intermediates in moderate to excellent yields. The one-pot formal alkenylfluorination reaction was carried out to produce over 30 analogues of a wide range of bioactive molecules. Further application of the Pd(0/I/II) manifold in PET probe development was illustrated by the direct carbo(radio)fluorination of electron-rich alkenes. The methods were successfully translated to radiolabel a broad scope of medicinally relevant small molecules in generally good radiochemical conversion. The protocol was further optimized to accommodate no-carrier-added conditions with similar efficiency for future (pre)clinical translation. Moreover, the radiosynthesis of prosthetic groups was automated in a radiochemistry module to facilitate its practical use in multistep radiochemical reactions.



1. INTRODUCTION

Methods for construction of carbon−fluorine bonds are in increasingly high demand as the number of drug candidates possessing fluorine atoms has considerably expanded over the past several years. This is in part due to the enhanced physical, chemical, and biological features of these compounds compared to their hydrogen-containing bioisosteres.[1] The incorporation of fluorine into a bioactive molecule may favorably change its lipophilicity, cell membrane permeability, and pharmacokinetic profile.[2] Another reason for the prevalence of fluorine-containing molecules in the biomedical sciences is their use as imaging probes for positron emission tomography (PET). Fluorine-18 (^{18}F) is the most commonly used positron-emitting radionuclide for PET because of its favorable decay characteristics, including a moderately long half-life ($t_{1/2}$ ∼ 110 min), a high positron (β^+) decay ratio of 97% compared to other radionuclides (i.e., ^{64}Cu 18%, ^{68}Ga 89%, and ^{86}Y 33%), and a low β^+ energy ($E_{\beta^+\,max}$: 0.635 MeV).[3] Not surprisingly, a vast number of methods have been developed to construct these valuable C−^{18}F bonds in response to the necessity for target-specific ^{18}F-PET imaging probes.

Incorporation of ^{18}F into a molecule of interest is done by either direct or prosthetic group approaches (Scheme 1a). Direct approaches, such as electrophilic or nucleophilic fluorination or halogen exchange, mainly rely on the synthesis of precursors containing reactive groups like metal salts, boronic esters, iodonium-based, or other charged leaving groups, which can be substituted by the employment of a suitable ^{18}F reagent.[3g] These methods have greatly advanced the synthetic tools available in the past decades, but their application to complex molecules for PET imaging still remains challenging.[2b]

On the other hand, the direct C−H activation approach, though highly appealing for its step and atom economy as it obviates the requisite precursor synthesis, is inherently substrate-controlled and often not selective.[4] Moreover, methods toward the synthesis of C(sp^3)−F bonds have become highly sought-after, in a departure from the broadly applicable but limited S_N2 reactivity, which only applies to primary or secondary C−F bond formation generally under harsh conditions.[5]

A powerful alternative to direct ^{18}F incorporation is the prosthetic group (PG) approach, which involves the rapid and selective synthesis of a typically small building block containing the desired ^{18}F and a synthetic handle. This PG is subsequently

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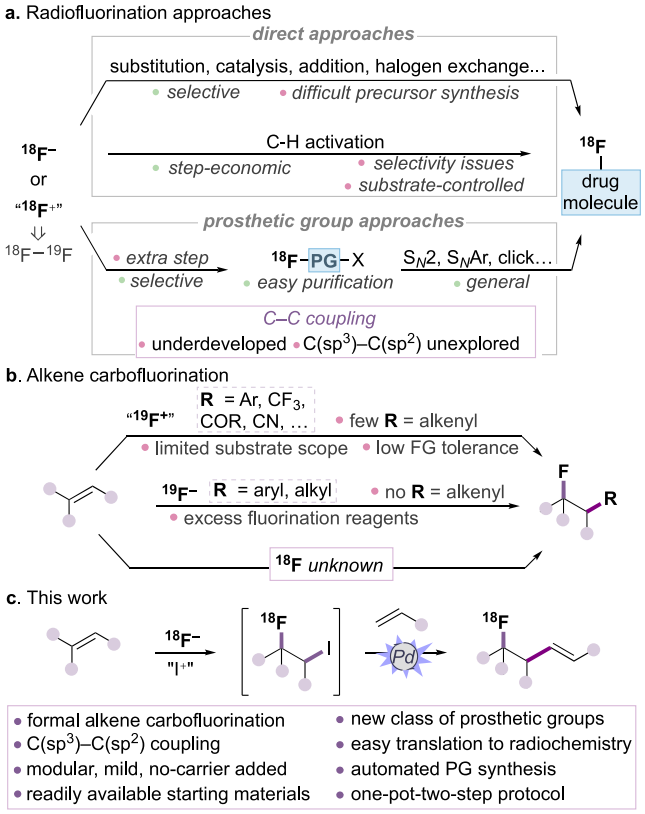
Scheme 1. (a) Radiofluorination Approaches; (b) Alkene Carbofluorination; (c) This Work



attached to a target molecule at the late stage of the synthetic route.[6] This approach offers great opportunities for diversification in terms of imaging probe development that are unavailable by direct methods requiring dedicated precursor syntheses. The implication of a synthetic handle enables the at-will incorporation of PGs, in contrast to C−H activation methods.[4] However, the two-step nature of the PG approach adds urgency to its installation due to ^{18}F decay. Consequently, available protocols are limited to the most robust methods, including click reaction, substitution, carbonyl condensation, or reductive amination, with rare examples of aryl−aryl or aryl−vinyl C−C coupling.[6,7]

Although one of the most potent methods to build molecular scaffolds is by C−C bond formation, this tool has yet to find a foothold in the scale- and time-restricted synthesis of ^{18}F-labeled PET imaging probes. Certainly, expanding the toolkit for PG incorporation to include an operationally simple C−C cross-coupling methodology would significantly expand the catalog of PET imaging probes. Moreover, given the abundance of aliphatic olefins in bioactive molecules, the development of a C(sp^3)−C(sp^2) technology for this purpose would allow unprecedented access to abundant and valuable alkylvinyl C−C coupled products bearing the desired ^{18}F label.

The most straightforward approach to address this radiosynthetic problem would be the carbofluorination of alkenes, where new C−C and C−F bonds are assembled onto simple alkenes in a single operation (Scheme 1b). Although some methods for direct alkene carbofluorination exist,[8] most require the use of electrophilic fluorine sources, which do not feasibly translate to radiochemistry as they can generally only be accessed from ^{18}F−^{19}F gas.[2a,9] Furthermore, current carbofluorination methods are limited in alkene scope and generally employ aryl, with only a handful of examples of alkenyl carbon sources.[10] Recent reports featuring fluoride, though as an excess reagent, do not have such an alkene scope limitation.[8i,j] However, they are restricted to aryl and alkyl carbon sources, while alkenylfluorination remains elusive. To the best of our knowledge, no general methods for alkene alkenylfluorination or alkene carboradiofluorination exist.

Accordingly, we aimed at the development of a modular prosthetic group approach to enable a formal alkene carbofluorination while employing easily accessible and commercially available alkenes as both the PG precursor and cross-coupling partner (Scheme 1c). We hypothesized that the Mizoroki−Heck reaction between alkyl halides and alkenes would be the most promising cross-coupling candidate to achieve this transformation. In recent years, our group and others[11] developed a visible-light-induced Pd(0/I/II) manifold to enable the mild, exogenous photosensitizer- and oxidant-free C−C coupling of primary, secondary, and tertiary alkyl halides with electronically diverse alkenes,[12] dienes,[13] oximes,[14] and hydrazones.[15] This robust technology thus fits the profile for translation into a PG installation approach.

Here, we report the development of the first one-pot formal alkene carboradiofluorination reaction as a blueprint for PET imaging probe development. This general and modular method features the photoinduced palladium-catalyzed alkyl Heck reaction between a new class of ^{18}F-PGs and easily accessible alkenes.

2. RESULTS AND DISCUSSION

We began our efforts by examining the Markovnikov-selective alkene iodofluorination reaction as a known rapid protocol for PG synthesis, which innately requires the use of a nucleophilic fluorine source instead of its less practical electrophilic counterpart.[16] We carried out a substrate mapping study, normally employed in-house, to assess the functional group compatibility of protocols under development.[17] Expectedly, this method is tolerant of a range of functionalities, from aliphatic chains to drug-like fragments and heteroatom-containing molecules (Schemes S1 and S2). To our surprise, despite the long history of this reaction,[18] it was scarcely used to synthesize this class of iodofluorinated products.[19] Consequently, several new aliphatic PGs (**2**) were isolated and characterized (Scheme 2). Employment of electronically different styrene derivatives afforded benzylic fluorides (**2a−j**) in good to excellent yields. Valuable fluorine- and nitrogen-containing arenes (**2k−2m**) were also highly efficient. Aliphatic alkenes containing moieties such as bromide (**2n**), ester (**2o**), and phosphonate (**2p**) worked well in this reaction. Lastly, diversely substituted acyclic (**2q−r**) and cyclic (**2s−u**) alkenes were shown to work in a regioselective manner.

Next, the translatability of the interhalogenation reaction was explored for the development of new PET imaging probes.[9] The most recent guidelines for radiosynthetic methodology development were employed as benchmarks. Here, radiochemical conversion (RCC) represents reaction efficiency as determined by HPLC analysis of a reaction aliquot, similar to analytical crude yields in organic chemistry.[20]

At the bench, screening of various commonly used nucleophilic fluorine sources resulted in poor to moderate efficiency, up to a 43% yield (Table S1). Since H^{19}F-pyridine was the best working reagent but is not yet available as a radiofluorination reagent, employment of [^{18}F]-tetraethylam-

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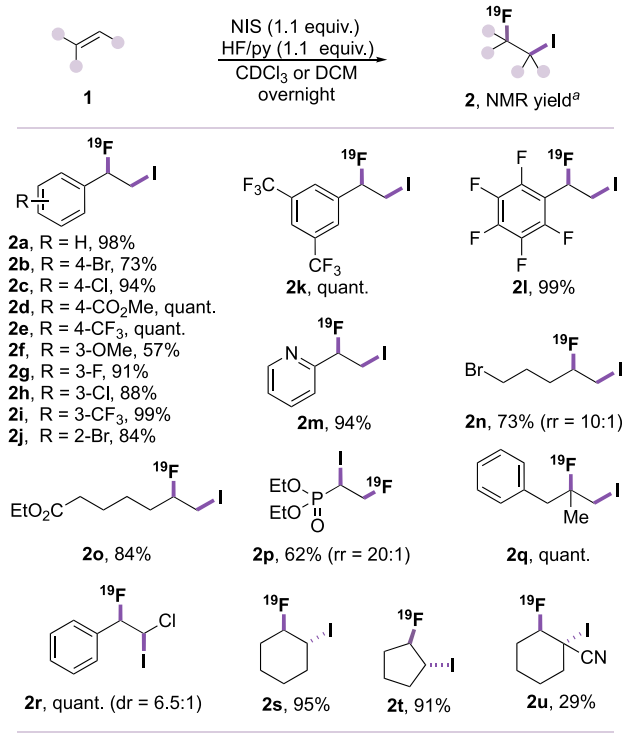
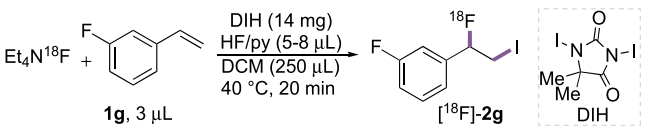
Scheme 2. PG Synthesis



[a]Due to the instability of pure products **2**, NMR yields were reported, and an analytical sample was characterized.

monium fluoride ($Et_4N^{18}F$) with charged organic additives was chosen as a starting point for radiochemical translation (Table 1, entries 1−3). Excitingly, the reaction was most efficient

Table 1. Selected Screening Results for Prosthetic Group Radiosynthesis



entry	Change	[^{18}F]-**2g** RCC (%)
1[b]	Py-HOTf	86
2[b]	Py-HOTs	79
3[b]	TBAI	0
4[a]	no additive	100
5	3 min	56
6	5 min	69
7	no carrier added	100

[a]Average of two reactions. [b]42 μmol additive was used.

without additives (entry 4). Furthermore, control and time experiments showed that PG synthesis was fast and efficient (entries 5−6), even without carrier added (entry 7).[17]

With the PG radiosynthesis method successfully developed, the scope of the reaction was examined (Scheme 3). In anticipation of the subsequent C−C coupling, H^{19}F-pyridine was employed to quench excess alkene starting material, as the difference in scale between the ^{18}F reagent and substrate leaves a huge (several orders of magnitude) excess of alkene that could lead to undesired cross-coupling side products in the next step. Notably, this reaction occurred with an efficiency similar to that of its ^{19}F-isotopologue. Electronically diverse styrenes ([^{18}F]-**2a**−**2y**), even those possessing free carboxylic acid and nitro groups ([^{18}F]-**2z** and [^{18}F]-**2a^1**), worked well in this reaction. Disubstituted alkenes [^{18}F]-**2b^1** and [^{18}F]-**2r** were also efficient. Aliphatic alkenes bearing drug-like fragments ([^{18}F]-**2c^1**−**2e^1**) and those vicinal to heteroatoms ([^{18}F]-**2f^1**, [^{18}F]-**2g^1**) afforded PGs in good radiochemical conversions. Furthermore, we demonstrated the automated radiosynthesis of compound [^{18}F]-**2a** in an 11% activity yield, which is a measure of the amount of a radioactive product obtained from a starting amount of activity, indicating the efficiency of a production process.[36] Simple filtration of the crude mixture with a C18-light cartridge afforded product in >99% radiochemical purity, which further illustrates the utility of the [^{18}F]-PGs for automated multistep reaction settings (Figure S5). The remarkable functional group tolerance of this iodoradiofluorination protocol validates the use of the ^{18}F-PG framework for PET imaging probe development for radiolabeling of small organic drug molecules and potentially theranostic drug conjugates,[3i,21] macromolecules, and peptide-based tumor-targeting ligands.[22]

Next, the operationally practical semi-one-pot and one-pot strategies to access the homoallylic fluoride products were examined, which required new reoptimization milestones from previously reported protocols. This was not trivial, as the task to reduce the total alkyl Heck reaction time from 6 to 24 h into the benchmark 30−45 min (due to ^{18}F decay) had to be done without compromising its functional group tolerance (i.e., by subjecting prosthetic groups to harsh conditions). Moreover, the merger of polar iodofluorination and radical transition-metal-catalyzed cross-coupling, which was challenging by itself, had to be done under conditions that could be reproduced in a radiochemical setting. Therefore, success had to be achieved without rigorously degassed solvents or operationally complicated processes, and under much more dilute or very scaled-down conditions, to accommodate the pico−femtomolar scale of ^{18}F-fluoride in typical production.

After substantial optimization, the translatability of the protocol to a semi-one-pot and one-pot reaction was demonstrated.[17] In the case of the interhalogenation reaction, changing the solvent to dioxane and increasing the reaction temperature to 80 °C resulted in a decrease in reaction time to 1−3 min (Table S9). The reaction profiles of the subsequent alkyl Heck-type reaction were monitored for benchmark compounds **4a** and **4j** under two 427 nm lamps without a fan attached, with the temperature reaching up to 70 °C (Figure S1). Full conversion of prosthetic groups **2a** and **2g** into corresponding products **4a** and **4j** was observed within 30 and 20 min, respectively.[17] The reaction was also efficiently scaled down from 100 to 4 μmol scale and diluted to 20 mM concentrations, which were positive indicators for radiosynthetic translation (**4a** and **4j**, Scheme 4).[9,17]

Substantial work has been carried out on earlier generations of the alkyl Heck-type reaction, validating its application to a broad range of functional groups.[12] Nevertheless, its adaptation to the one-pot, two-step formal alkenylfluorination reaction for privileged PG substrates under reoptimized conditions was examined next. Despite the scarce examples of homoallylic fluorides in the literature,[23] we found that even the benchmark reaction to make product **4a** from simple styrene resulted in the fluorine-tagged analogue of a retinoic acid receptor (RARγ) agonist,[24] which is in line with the ubiquity of alkenes and homoallylic C−H bonds in drug-like molecules. Thus, the

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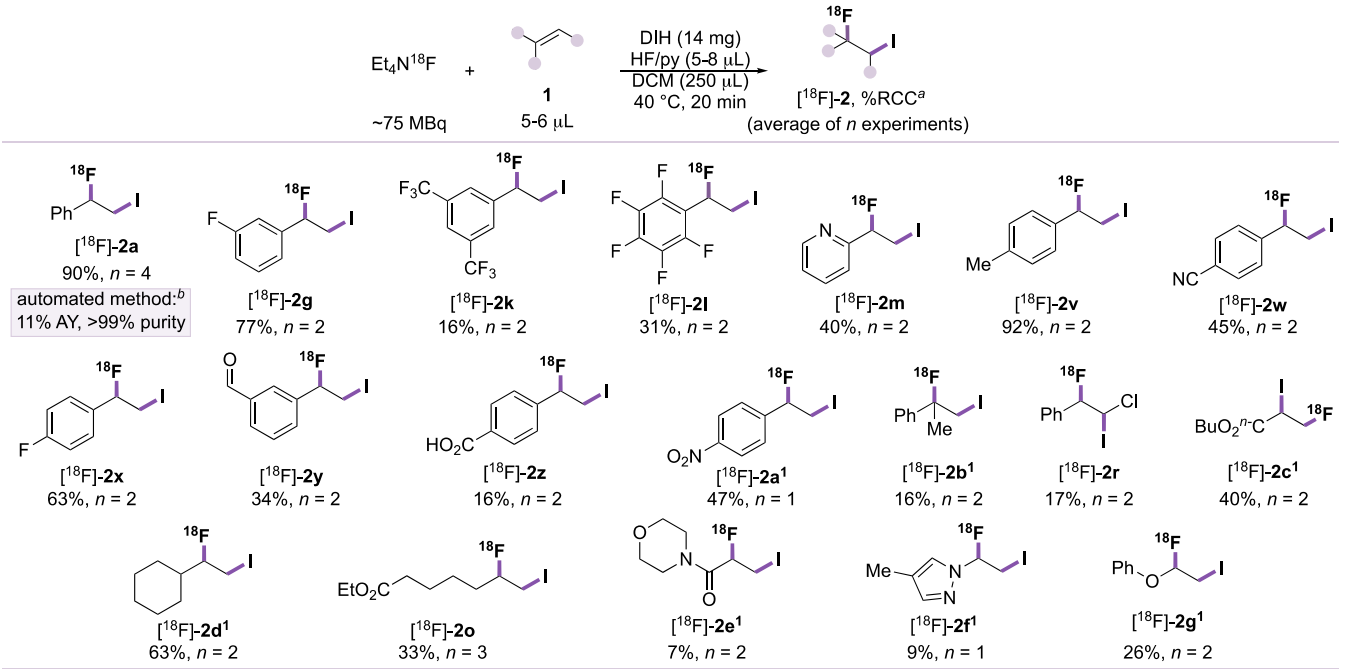
Scheme 3. Carrier-Added PG Radiosynthesis



[a]RCC = radiochemical conversion as determined by radio-HPLC analysis of an aliquot of the reaction mixture; [b]4070 MBq activity was used.

scope of the investigation was designed to include fragments or analogues of several classes of bioactive molecules, illustrating the (radio)synthetic utility of the strategy for PET imaging probe development given the well-established use of fluorine as a bioisostere of hydrogen (Scheme 4).[1]

Primary homobenzylic iodide PG **2a** underwent the Heck reaction efficiently with electronically diverse styrene derivatives to form compounds **4a**−**4i**. Styrene-derived prosthetic groups reacted analogously in good yields (**4j**−**4o**). The modularity of the approach for the synthesis of RARγ analogues was demonstrated by varying the prosthetic groups to include "magic methyls"[25] in the benzylic (**4p**) and allylic (**4q**) positions, inserting a carboxylate moiety vicinal to the fluorine atom (**4r**), and by replacing the arene entirely with cyclobutyl (**4s**) and linear (**4t**) aliphatic systems in moderate to good yields, each of which would otherwise require a dedicated synthetic route.

N-Methyl-D-aspartate receptor allosteric modulator[26] analogues **4u** and **4v** were synthesized in reasonable yields from cyclohexene- and styrene-derived PGs, respectively. Piperidine-containing prosthetic groups were well tolerated in this reaction to produce GABA inhibitor analogue[27] with medicinally relevant azobenzene styrene derivative **4w** and fluorine-tagged GPCR agonist[28] **4x** and its analogue **4y** in good yields. Free and protected vinyl resorcinols reacted smoothly with cyclohexene-derived PG to produce compounds **4z**−**b**^{1}, which are analogues of TRPA1 desensitizer[29] and TEAD modulator.[30] The free catechol motif is present in other important radiopharmaceuticals, like F-DOPA,[31] which generally requires a global protection and deprotection step before and after radiofluorination.[32] This example nicely illustrates the utility of this methodology with respect to functional group tolerance. Related DYRK1A inhibitor[33] analogues **4c**^{1}−**4e**^{1} were also synthesized in good yields. Autotaxin inhibitor[34] analogue **4f**^{1}, bearing a benzylic phosphonate, reacted efficiently. Lastly, Janus kinase inhibitor[35] fragment **4g**^{1} and analogue **4h**^{1}, synthesized from pyrazole and imidazole PGs, respectively, were produced in good yields.

With this diverse catalog of fluorine-labeled bioactive molecules in hand, we proceeded to investigate the radiocarbofluorination reaction of alkenes. Gratifyingly, the methodology developed at the bench only had to be minimally revised to yield the desired radiolabeled molecules in generally good radiochemical yields (Scheme 5). We were excited to see the great efficiency of the one-pot, two-step reaction using a small amount of activity. Indeed, electronically diverse styrenes readily underwent formal carboradiofluorination to afford ^{18}F-homoallylic fluorides [^{18}F]-**4a**−**4m** and [^{18}F]-**4v**. ^{18}F at a quaternary center ([^{18}F]-**4q** and [^{18}F]-**4s**), as well as bearing ^{18}F-α-to-heteroatom ([^{18}F]-**4r** and [^{18}F]-**4h**^{1}), proceeded with a similar efficiency. Cyclic and secondary PGs reacted well with good RCCs ([^{18}F]-**4e**^{1} and [^{18}F]-**4p**).

As mentioned earlier, the employment of carrier H^{19}F-pyridine in the one-pot, two-step protocol was rationalized by the need to quench excess alkenyl starting material from PG synthesis to prevent undesired side reactions in the following step. However, this usually translates to low molar activity (A_m), which is defined as the measured radioactivity per mole of the compound at the end of synthesis.[20,36] In most cases, low molar activity is a negative indicator of (pre)clinical translation.[36] Aiming to further improve our protocol to enable its potential use in a (pre)clinical setting, a no-carrier-added (NCA) method was developed to avoid diluting the ^{18}F label with the H^{19}F-pyridine carrier. First, the conditions for the PG synthesis were modified. Expectedly, it was found that the NCA reactions showed similar efficiency as before and accommodated electronically diverse styrenyl ([^{18}F]-**2a**−**2w**), alkyl multisubstituted ([^{18}F]-**2za**−**2q**), and cyclic [^{18}F]-**2s** alkene starting materials (Scheme 6).

Encouraged by these results, the feasibility of the one-pot, two-step NCA protocol was tested by removing the excess alkene from the first step via evaporation rather than

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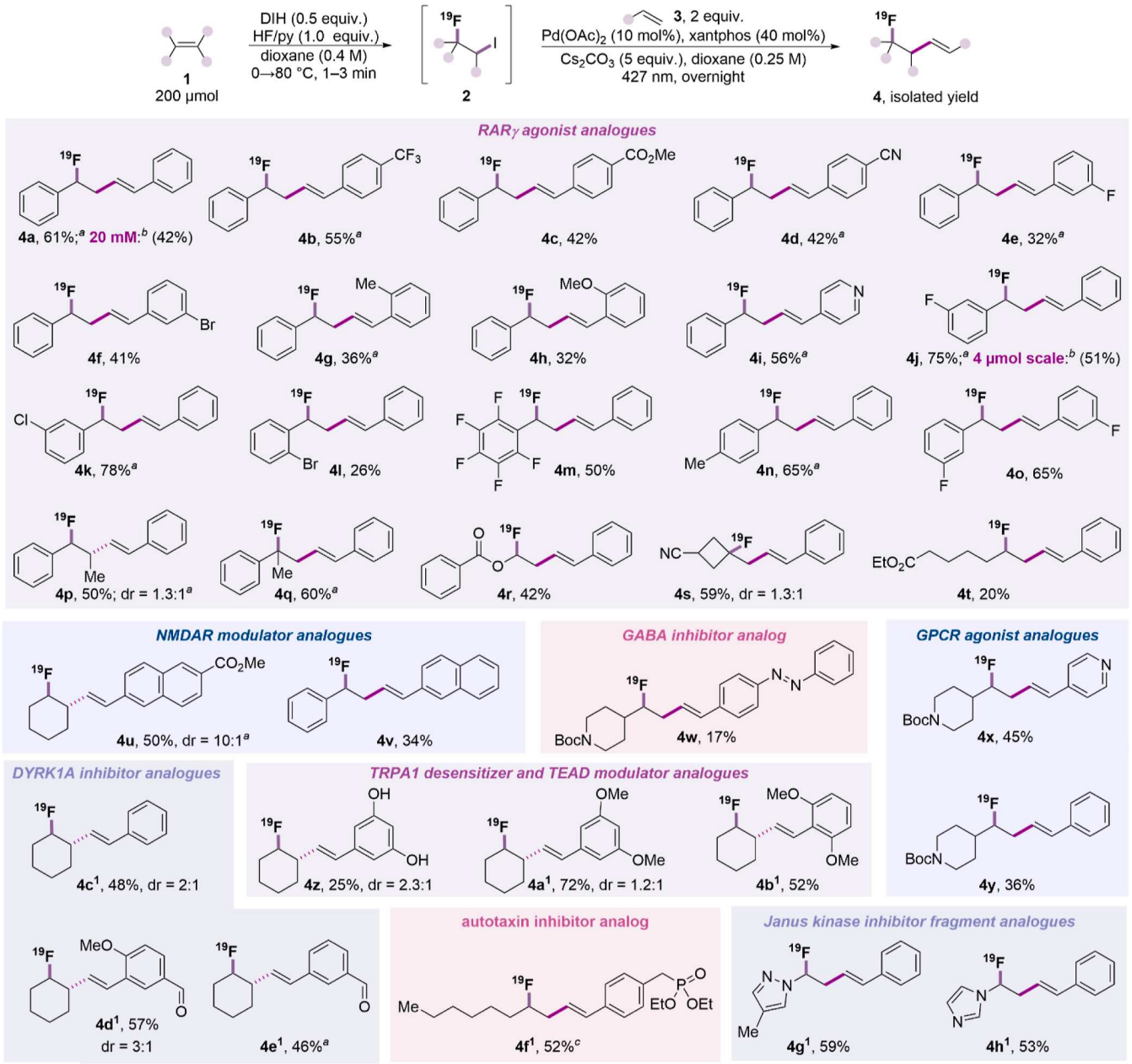
Scheme 4. Synthesis of Homoallylic Fluorides



[a]Reaction was carried out using semi-one-pot conditions (see the Supporting Information for details). [b]Reaction was carried out in a photoreactor at 80 °C. [c]NMR yield using 4-chloro-2-fluorotoluene as an internal standard.

quenching with H[19]F-pyridine. Indeed, it was found that the NCA conditions afforded the corresponding radiofluorinated products [[18]F]-**4a**−**4o** with similar efficiency and moderate to good molar activities (Scheme 7). These results are aligned with our goals to develop a practical and translatable protocol for (pre)clinical use, which would not require carrier addition. The method is mild enough to be translated to a late-stage synthesis, whereby the removal of excess alkene from the PG synthesis step can be carried out by evaporation or other purification methods, like filtration or HPLC.[17]

The C−C-bond forming step of this protocol combines the robustness of transition-metal catalysis with the mildness and high reactivity of radical reactions and is consequently tolerant to a broad range of functional groups.[37] Future development of this transformation toward (pre)clinical uses is expected to include the employment of a suitable photoradiochemical module, as was recently developed and automated for ^{89}Zr[38] or other photoradiochemical setups,[39] which will significantly improve the efficiency of the reaction.

The successful translation of this one-pot, two-step NCA formal alkenylfluorination method to radiochemistry toward [[18]F]-homoallylic fluorides also serves as a proof of concept for the potential radiosynthetic utility of this modular PG approach under transition-metal-catalyzed cross-coupling conditions. The radiofluorinated PG can potentially be applied in a variety of cross-coupling reactions like Stille, Sonogashira, and Suzuki coupling, as well as noncatalytic reactions to produce radiolabeled complex scaffolds.

Motivated by the successful radiolabeling of bioactive molecules, we wondered whether the methodology could be

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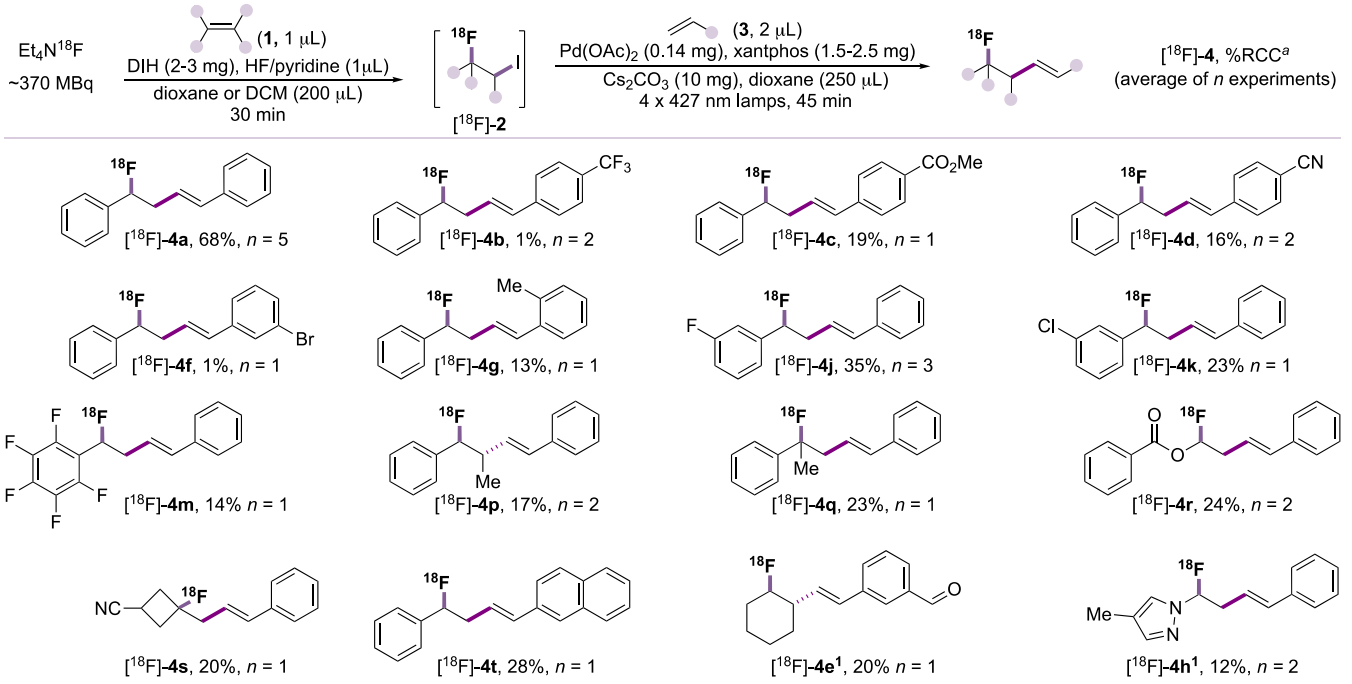
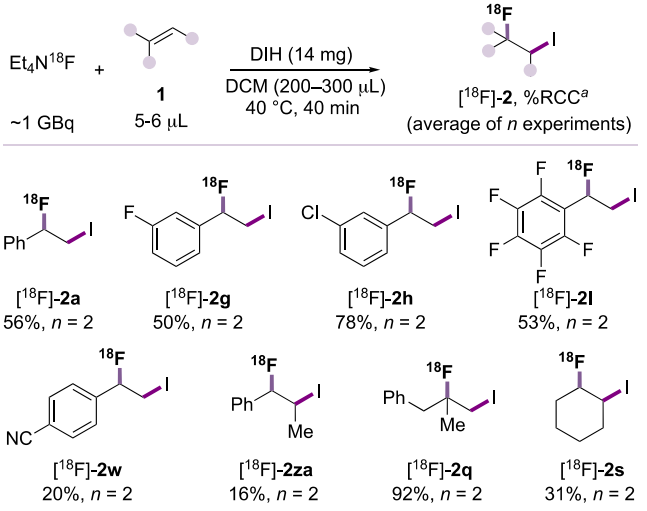
Scheme 5. Carrier-Added Homoallylic [^{18}F]-Fluoride Radiosynthesis



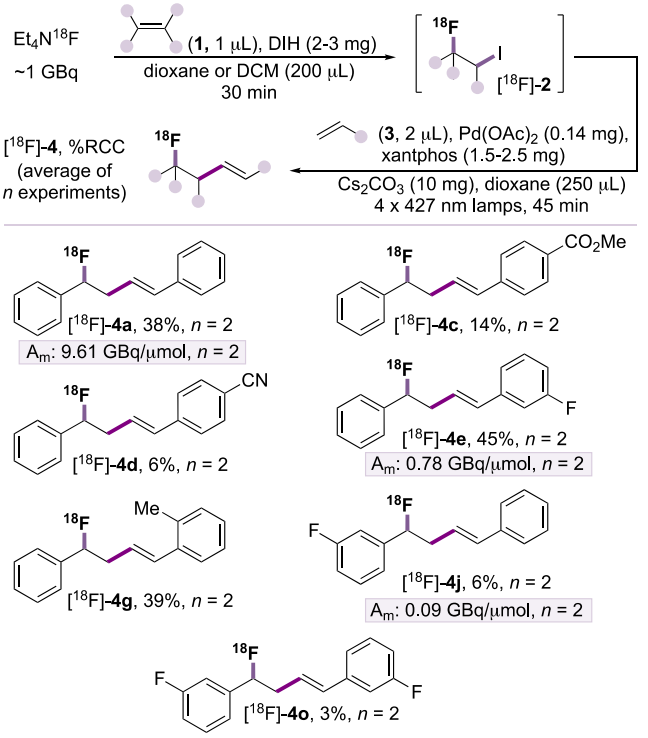
[a]RCC = radiochemical conversion as determined by radioHPLC analysis of an aliquot of the reaction mixture.

Scheme 6. NCA PG Radiosynthesis



[a]RCC = radiochemical conversion as determined by radioHPLC analysis of an aliquot of the reaction mixture.

Scheme 7. NCA Radiosynthesis of Homoallylic [^{18}F]-Fluorides[a]



[a]RCC = radiochemical conversion as determined by radioHPLC analysis of an aliquot of the reaction mixture.

further developed to carry out the direct alkylcarbofluorination of alkenes. Our group previously demonstrated the mechanistic bifurcation of the photoinduced alkyl Heck reaction in the presence of electron-rich substrates capable of stabilizing a radical-polar crossover step to produce an oxocarbenium species that could be trapped by *O*-nucleophiles to yield mixed acetals (Scheme S3).[12b,17]

We were delighted to see that this method could be used in the presence of silver fluoride to produce alkylated α-fluoroethers **8a** and **8b** (Scheme 8)! Furthermore, the method was again easily translated to radiochemistry in a carrier-free protocol that did not require the addition of silver fluoride additive[40] to yield compound [^{18}F]-**8a** in 83% RCC. This represents the first example of palladium-catalyzed direct alkene alkylradiofluorination and a potential extension of this

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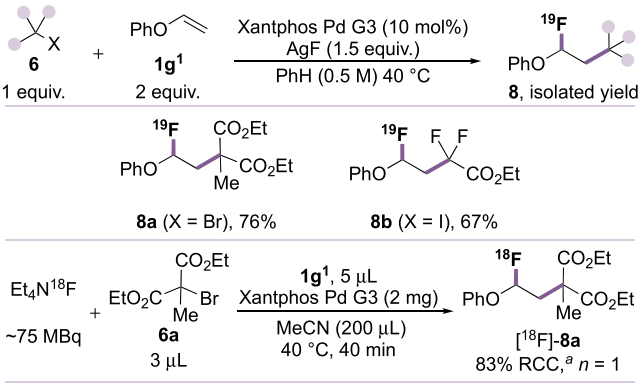
Scheme 8. Direct Alkyl(radio)fluorination of Phenyl Vinyl Ether



[a]RCC = radiochemical conversion as determined by radioHPLC analysis of an aliquot of the reaction mixture.

methodology toward the synthesis of α-alkoxy organofluorine compounds.

3. CONCLUSIONS

We disclose the first formal carboradiofluorination of electronically diverse alkenes under mild one-pot, two-step photoinduced conditions. The methodology was translated from the first formal alkene alkenylfluorination employing a nucleophilic fluorine source and easily accessible starting materials. Furthermore, the direct alkyl(radio)fluorination of electron-rich alkenes under a Pd(0/I/II) manifold was demonstrated for the first time.

The potential (radio)synthetic utility of these approaches was demonstrated by the incorporation of ^{19}F and ^{18}F into several classes of bioactive molecules. In the process, several new PGs were produced, and their radiosynthesis was developed in an automated module for further elaboration in multistep processes. This no-carrier-added methodology toolkit is expected to serve as a prosthetic group blueprint for PET imaging probe development and should find ample application in the radiochemistry community.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c04548.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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