

Synthesis of Fluorinated Alkyl Aryl Ethers by Palladium-Catalyzed C–O Cross-Coupling

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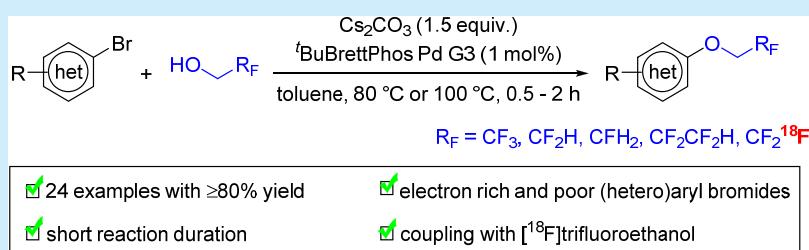
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ABSTRACT: Herein, we report a highly effective protocol for the cross-coupling of (hetero)aryl bromides with fluorinated alcohols using the commercially available precatalyst $^t\text{BuBrettPhos Pd G3}$ and Cs_2CO_3 in toluene. This Pd-catalyzed coupling features a short reaction time, excellent functional group tolerance, and compatibility with electron-rich and -poor (hetero)arenes. The method provides access to ^{18}F -labeled trifluoroethyl ethers by cross-coupling with ^{18}F trifluoroethanol.

Fluorinated alkyl aryl ethers are encountered in medicinal chemistry and agrochemistry, due to the ability of fluorine to modulate molecular properties including lipophilicity and metabolic stability.¹ Prominent molecules featuring these motifs include the multibillion-dollar proton pump inhibitor lansoprazole, the antiarrhythmic flecainide, and idalopirdine (Figure 1). Approaches for fluoroalkyl aryl ether preparation

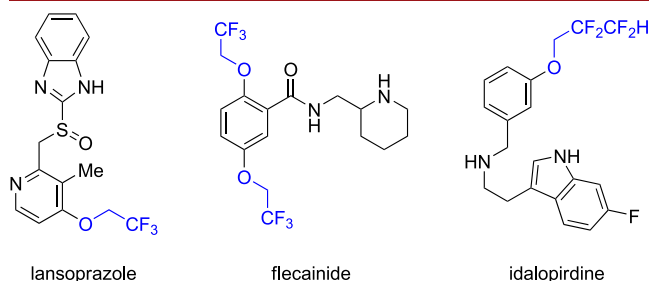


Figure 1. Drugs containing fluorinated alkyl aryl ethers.

include Chan–Lam coupling of aryl boronic acids,^{2,3} Williamson ether synthesis,⁴ and transition metal mediated cross-coupling of aryl halides with fluorinated alcohols.^{5–8} Copper mediated approaches include coupling of fluorinated alcohols with aryl iodides under copper catalysis reported by Bonnet-Delpon and co-workers⁵ and reaction of aryl bromides with a copper(I) fluoroalkoxide complex reported by the Weng group.⁸ The Singh group has reported palladium-catalyzed coupling of fluorinated alcohols with aryl bromides bearing *para*-electron-withdrawing groups.^{6,7} Limitations of these

protocols include the use of stoichiometric transition metals (Cu(I) fluoroalkoxide procedure),⁸ limited substrate scope (Pd-catalyzed procedure), long reaction times, and/or the requirement of neat fluorinated alcohols (Cu-catalyzed procedure).⁵

Shekhar and co-workers reported novel biaryl phosphorinane ligands for Pd-catalyzed C–O cross-coupling with electron-rich and heteroaryl halides, but these ligands are currently not commercially available.⁹ In this field of research, the contribution of Buchwald and co-workers stands out by providing an excellent procedure for C–O cross-coupling of alcohols and aryl halides in the presence of NaO^tBu in dioxane and using commercially available precatalysts $^t\text{BuBrettPhos Pd G3}$ and $\text{AdCyBrettPhos Pd G3}$.¹⁰ For alcohols of reduced nucleophilicity including 2,2,2-trifluoroethanol and 2,2,3,3,3-pentafluoropropanol, superior yields were obtained using $\text{AdCyBrettPhos Pd G3}$.

Given our interest in narrowing the gap between ^{19}F - and ^{18}F -chemistry,^{11–14} we considered applying this C–O cross-coupling as a radiosynthetic route to install ^{18}F -labeled fluorinated alkyl aryl ethers motifs. For this purpose, it was necessary to adapt the protocol to accommodate short reaction

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times (^{18}F half-life = 109.7). In addition, it is important that no large excess of fluorinated alcohol is required for effective coupling considering that cyclotron-produced ^{18}F -fluoride is available in the picomolar range. Herein, we report the Pd-catalyzed C–O coupling of fluorinated alcohols using ^tBu -BrettPhos Pd G3 with the mild base Cs_2CO_3 in toluene. This protocol accommodates an extensive range of (hetero)aryl bromide and fluorinated alcohols and was adapted for cross-coupling with [^{18}F]trifluoroethanol.

We investigated the Pd-catalyzed cross-coupling reaction between trifluoroethanol and **1a**, a demanding aryl bromide considering the lack of an activating electron-withdrawing group attached directly to the aromatic ring, and the presence of mildly acidic protons α to the ketone (Table 1). We

Table 1. Reaction Optimization

XPhos: R = Cy
 $^t\text{BuXPhos}$: R = ^tBu

BrettPhos: R = Cy
 $^t\text{BuBrettPhos}$: R = ^tBu

$^t\text{BuBrettPhos Pd G3}$
L = $^t\text{BuBrettPhos}$

Entry	Catalyst	Solvent	Base	Yield (%) ^a
1	BrettPhos, $\text{Pd}_2(\text{dba})_3$	toluene	Cs_2CO_3	0
2	XPhos, $\text{Pd}_2(\text{dba})_3$	toluene	Cs_2CO_3	0
3	$^t\text{BuXPhos}$, $\text{Pd}_2(\text{dba})_3$	toluene	Cs_2CO_3	0
4	$^t\text{BuBrettPhos}$, $\text{Pd}_2(\text{dba})_3$	toluene	Cs_2CO_3	51
5	$^t\text{BuBrettPhos Pd G3}^*$	toluene	Cs_2CO_3	70
6	$^t\text{BuBrettPhos Pd G3}^*$	toluene	Na_2CO_3	0
7	$^t\text{BuBrettPhos Pd G3}^*$	toluene	K_2CO_3	8
8	$^t\text{BuBrettPhos Pd G3}^*$	toluene	K_3PO_4	70
9	$^t\text{BuBrettPhos Pd G3}^*$	1,4-dioxane (80 °C, 16 h)	NaO^tBu	48
10	$^t\text{BuBrettPhos Pd G3}^*$	1,4-dioxane	Cs_2CO_3	61
11	$^t\text{BuBrettPhos Pd G3}^*$	<i>tert</i> -amyl alcohol	Cs_2CO_3	33
12	$^t\text{BuBrettPhos Pd G3}^*$	toluene (80 °C)	Cs_2CO_3	34
13	$^t\text{BuBrettPhos Pd G3}^*$	toluene (30 mins)	Cs_2CO_3	48

^aYields determined by ^{19}F qNMR with PhCF_3 as internal standard. For entries 1–4, 0.5 mol % of $\text{Pd}_2(\text{dba})_3$ and 1.25 mol % of ligand were used. For entries 6–13, 1 mol % of the precatalyst was used.

screened short reaction durations with the foresight of applying the coupling for introducing ^{18}F -labeled motifs. Under conditions similar to those reported by Singh, using BrettPhos, $\text{Pd}_2(\text{dba})_3$, and Cs_2CO_3 in toluene, no coupled product was formed after 1 h (entry 1).⁶ Switching the ligand to either XPhos or $^t\text{BuXPhos}$ also resulted in no product formation (entries 2 and 3).^{15,16} Using $^t\text{BuBrettPhos}$ as ligand, the

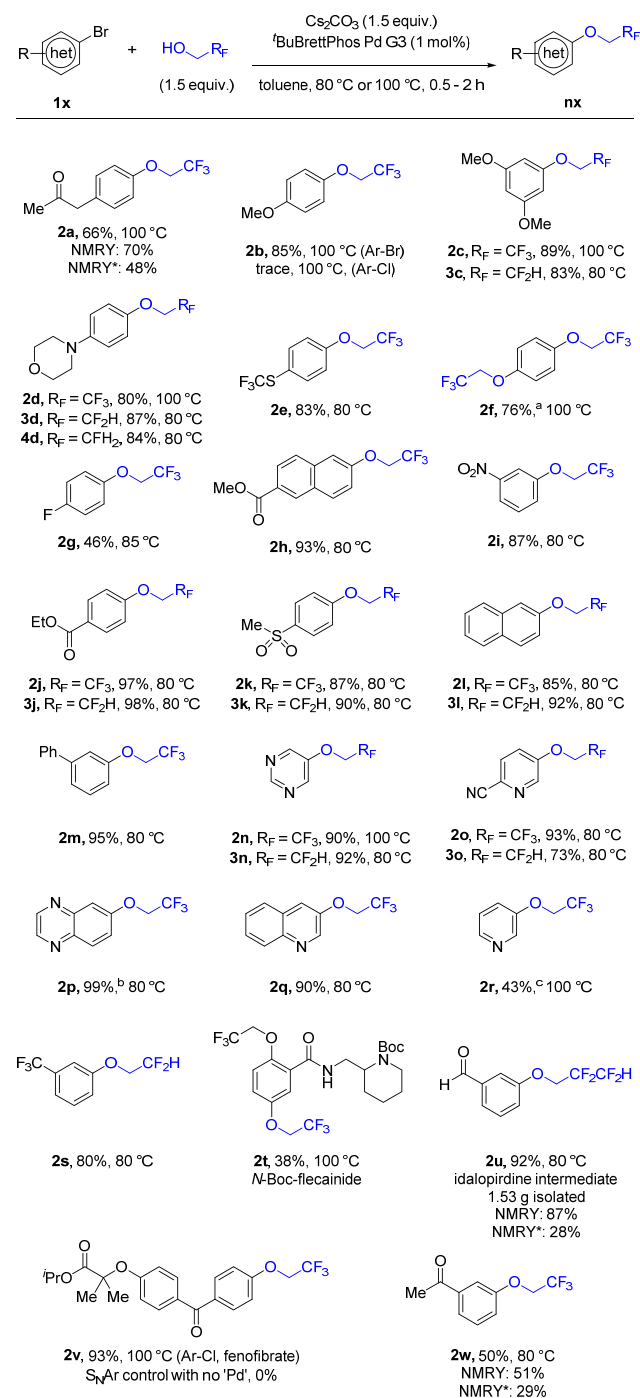
coupled product was observed in 51% yield (entry 4). An increase to 70% yield was observed using Buchwald's ^tBu -BrettPhos Pd G3 precatalyst (entry 5). Buchwald's precatalysts are air and moisture stable Pd(II)-palladacycles, which allow for quantitative formation of the catalytically active LPd(0) species *in situ* following base induced C–N reductive elimination.¹⁷ Cs_2CO_3 gave superior results compared to both sodium and potassium carbonate (entries 6 and 7). K_3PO_4 was an effective base, affording the product in 70% yield (entry 8). While Cs_2CO_3 was used for this study, use of K_3PO_4 may be advantageous on a larger scale, as it is significantly cheaper than Cs_2CO_3 . The use of NaO^tBu as base with 1,4-dioxane as solvent¹⁰ resulted in a reduced yield (entry 9). While stronger bases such as NaO^tBu can promote C–O cross-couplings at lower temperatures than weaker inorganic bases such as Cs_2CO_3 , they can also lead to reduced yields for base-sensitive substrates.^{18,19} Toluene afforded a higher yield than 1,4-dioxane (entry 10) and *tert*-amyl alcohol (entry 11). Reducing the reaction duration to 30 min or the temperature to 80 °C resulted in lower yields (entries 12 and 13).

The scope of the reaction with respect to the aryl bromide was explored next (Scheme 1). Various electron-rich aryl bromides underwent coupling with trifluoroethanol in high yield after 0.5 to 2 h, with morpholinyl and methoxy substitution well tolerated (**2b** to **2d**). Product **2c** was isolated in 89% yield, while it has been reported to form in 69% NMR yield using NaO^tBu and 1,4-dioxane.¹⁰ The reaction conditions were applied to the double C–O cross-coupling of 1,4-dibromobenzene to yield **2f** in a single step. Electron-deficient aryl bromides also underwent coupling in excellent yields (substrates **2h** to **2k**). A wide range of functional groups were well tolerated including sulfone, ester, ketone, aldehyde, and nitro groups, some bearing acidic α -protons. For many substrates, the reaction temperature could be decreased to 80 °C without detrimental impact on reactivity. In contrast, when electron-rich aryl bromides such as **1d** were reacted with trifluoroethanol at 80 °C, starting material was recovered almost quantitatively. Heteroaryl bromides also underwent coupling (**2n**–**2r**), with 80 °C being adequate for some substrates. Pyridines, pyrimidine, quinoline, and quinoxaline substrates all coupled effectively. This cross-coupling method was applied to prepare the drug precursor *N*-Boc-flecainide (**2t**).

Aryl chlorides were also investigated as substrates. The activated aryl chloride fenofibrate **1v** underwent C–O cross-coupling in excellent yield. A control experiment excluding $^t\text{BuBrettPhos Pd G3}$ afforded no product, ruling out a nucleophilic aromatic substitution mechanism. Contrarily, electron-rich aryl chloride **1b(Cl)** afforded only traces of the coupled product. For preparing compounds **2a**, **2u**, and **2w**, the conditions reported herein were compared directly to use of NaO^tBu with 1,4-dioxane (NMRY for conditions herein vs NMRY* for NaO^tBu conditions, Scheme 1).¹⁰ In these cases, higher yields were observed using Cs_2CO_3 and toluene.

Various other fluorinated alcohols were successfully coupled to aryl bromides under our optimized conditions. Notably, in contrast to 2,2,2-trifluoroethanol, coupling reactions of electron-rich aryl bromides with 2,2-difluoroethanol could be carried out at 80 °C. Furthermore, electron-poor aryl bromides and heteroaryl bromides successfully coupled with 2,2-difluoroethanol. 2-Fluoroethanol also reacted in high yield (**4d**). In a competition experiment in which equimolar quantities of 2,2,2-trifluoroethanol, 2,2-difluoroethanol, and 2-

Scheme 1. Pd-Catalyzed C–O Cross-Coupling of Fluorinated Alcohols with Aryl Bromides (Yields of Isolated Products Are Quoted)



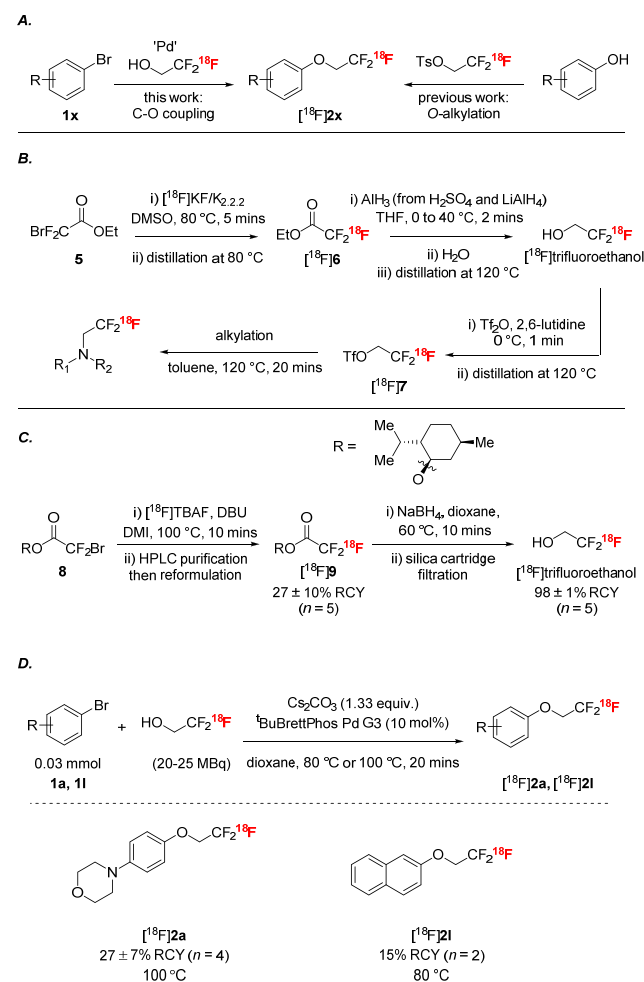
^a2 mol % ^tBuBrettPhos Pd G3, 3 equiv of Cs₂CO₃ and trifluoroethanol used. ^bYield determined by ¹⁹F qNMR. ^cReaction duration of 4 h. NMRY = NMR yield under the conditions reported herein. NMRY* = NMR yield using NaO^tBu in 1,4-dioxane at 40 to 80 °C.

fluoroethanol were reacted with substrate 1d at 100 °C for 2 h under the conditions reported herein, the trifluoroethyl, difluoroethyl, and fluoroethyl ethers were formed in an ~1:3:2 ratio, respectively. This supports decreased reactivity of 2,2,2-trifluoroethanol relative to 2,2-difluoroethanol and 2-fluoroethanol.

The scalability of the C–O cross-coupling reaction was demonstrated by the gram-scale coupling of 2,2,3,3-tetrafluoropropanol and 3-bromobenzaldehyde for the preparation of 2u, an intermediate in the synthesis of the drug idalopirdine (Figure 1).²⁰ For this scale-up, the catalyst loading was reduced to 0.5 mol % without impacting the yield of isolated product. On a larger scale, use of Pd₂(dba)₃ with ^tBuBrettPhos rather than ^tBuBrettPhos Pd G3, and K₃PO₄ rather than Cs₂CO₃, may be preferable to reduce costs.

The short reaction time and high efficiency of incorporation of the fluorinated alcohol encouraged the use of this cross-coupling reaction for the introduction of ¹⁸F-labeled motifs, specifically [¹⁸F]trifluoroethanol (Scheme 2A). Preparation of

Scheme 2. (A) Approaches to [¹⁸F]Trifluoroethyl Ethers; (B) Previously Reported Synthesis of [¹⁸F]Trifluoroethanol Requiring Multiple Distillations and AlH₃; (C) Our Approach for the Synthesis of [¹⁸F]Trifluoroethanol; (D) Coupling of Aryl Bromides with [¹⁸F]Trifluoroethanol



^aRCY = radiochemical yield, determined by integration of the radio-HPLC trace (prior to HPLC for compound 9).

an ¹⁸F-trifluoroethyl ether has been reported by the Riss group via alkylation of the corresponding phenol with [¹⁸F]-trifluoroethyl tosylate (Scheme 2A).^{21–24} Here, we propose a complementary approach that utilizes a C–O cross-coupling event to prepare ¹⁸F-trifluoroethyl ethers [¹⁸F]2 from aryl bromides and [¹⁸F]trifluoroethanol. [¹⁸F]Trifluoroethanol has

previously been synthesized by nucleophilic radiofluorination of ethyl bromodifluoroacetate **5** with $[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$, followed by reduction with AlH_3 prepared *in situ* from LiAlH_4 and H_2SO_4 (Scheme 2B).²⁵ The $[^{18}\text{F}]$ trifluoroethanol was not used directly and required an additional step to generate $[^{18}\text{F}]$ -trifluoroethyl triflate, which was then applied for amine alkylation. Multiple distillations were used to purify ethyl $[^{18}\text{F}]$ trifluoroacetate **7** and $[^{18}\text{F}]$ trifluoroethanol.

We sought to develop an $[^{18}\text{F}]$ trifluoroethanol synthesis without distillation, using instead HPLC purification. We also aimed to replace AlH_3 with NaBH_4 , a reducing agent readily available and easy to handle. Our initial experiments showed that ethyl trifluoroacetate $[^{18}\text{F}]$ **6** is unstable under reversed-phase HPLC conditions. Therefore, we targeted menthol $[^{18}\text{F}]$ trifluoroacetate $[^{18}\text{F}]$ **9**, an ester which is more resistant to hydrolysis and therefore amenable to purification by reversed-phase HPLC (Scheme 2C). Under conditions slightly modified from those previously reported by Szabó and Schou,²⁶ synthesis of $[^{18}\text{F}]$ **9** was achieved in $27 \pm 10\%$ radiochemical yield (RCY) using $[^{18}\text{F}]\text{TBAF}$ and DBU in 1,3-dimethyl-2-imidazolidinone (DMI).²⁷ After HPLC purification and reformulation into 1,4-dioxane, reduction using NaBH_4 afforded $[^{18}\text{F}]$ trifluoroethanol in $98 \pm 1\%$ RCY. Menthol, formed during the reduction step, was found to be unreactive under the conditions applied for C–O cross-coupling, and therefore a purification step by filtration to remove salts was sufficient. 1,4-Dioxane was used as the reaction solvent, as it afforded high yields for the reduction (toluene performed poorly) and proved highly suitable for the subsequent C–O cross-coupling (Table 1, entry 10). This modification was advantageous by avoiding a second reformulation step.

Under slightly modified coupling conditions, $[^{18}\text{F}]$ -trifluoroethanol was coupled with aryl bromide **1a** and naphthyl bromide **11** to afford the desired cross-coupled $[^{18}\text{F}]$ trifluoroethyl ethers (Scheme 2D). Radio-HPLC showed clean reaction profiles, with mainly the ^{18}F -labeled product and unreacted $[^{18}\text{F}]$ trifluoroethanol. Extending the reaction duration beyond 20 minutes did not increase the RCY. Our study showed that the coupling was sensitive to the water content in the $[^{18}\text{F}]$ trifluoroethanol solution; drying of menthol $[^{18}\text{F}]$ trifluoroacetate $[^{18}\text{F}]$ **9** under a flow of nitrogen was essential prior to reformulation in 1,4-dioxane.²⁷ While Pd-mediated C–N and C–C cross-coupling has been used for introduction of ^{18}F -labeled motifs,²⁸ this work supports the feasibility of ^{18}F -radiolabeling by Pd-mediated C–O cross-coupling.

In conclusion, we have developed a protocol for Pd-catalyzed cross-coupling between fluorinated alcohols and (hetero)aryl bromides using the mild base Cs_2CO_3 ; the reaction tolerates various electronic patterns on the arene ring, a wide range of functional groups including those with mildly acidic α -protons, and proceeds over a short duration. An activated aryl chloride has also been shown to couple effectively. In addition, K_3PO_4 was found to be a cheaper alternative base to Cs_2CO_3 . The utility of the coupling has been further demonstrated with a new disconnection approach to ^{18}F -labeled trifluoroethyl ethers consisting of C–O cross-coupling of aryl bromides with $[^{18}\text{F}]$ trifluoroethanol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02347>.

Experimental data, characterization data, ^{18}F -radiotracers (PDF)

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Notes

The authors declare no competing financial interest.

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(27) See the [Supporting Information](#) for a full discussion on the radiochemistry, including molar activity.

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