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

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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 tBuBrettPhos Pd G3 and Cs2CO3 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 18F-labeled trifluoroethyl ethers by cross-coupling with [18F]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 include Chan–Lam coupling of aryl boronic acids,2 Williamson ether synthesis,4 and transition metal mediated cross-coupling of aryl halides with ﬂuorinated alcohols.3 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.6 The Singh group has reported palladium-catalyzed coupling of ﬂuorinated alcohols with aryl bromides bearing para-electron-withdrawing groups.5,7 Limitations of these protocols include the use of stoichiometric transition metals (Cu(I) ﬂuoroalkoxide procedure),6 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 NaOtBu in dioxane and using commercially available precatalysts tBuBrettPhos Pd G3 and 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 AdCyBrettPhos Pd G3.

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

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Figure 1. Drugs containing fluorinated alkyl aryl ethers.
times (18F 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 18F-fluoride is available in the picomolar range. Herein, we report the Pd-catalyzed C−O coupling of fluorinated alcohols using BuBrettPhos Pd G3 with the mild base Cs2CO3 in toluene. This protocol accommodates an extensive range of (hetero)aryl bromide and fluorinated alcohols and was adapted for cross-coupling with 18F-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 screened short reaction durations with the foresight of applying conditions similar to those reported by Singh, using BrettPhos, a large excess of XPhos or tert-BrettPhos Pd G3 with the mild base Cs2CO3 in toluene. This 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(Bu) and 1,4-dioxiane. The reaction conditions were applied to prepare the drug precursor 1d when electron-rich aryl chlorides such as 1d were reacted with trifluoroethanol at 80 °C, starting material was recovered almost quantitatively. Heteroaryl bromides also underwent coupling in excellent yields (substances 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 (2i).

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 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(Bu) with 1,4-dioxiane (NMRY for conditions herein vs NMRY* for NaO(Bu) conditions, Scheme 1). In these cases, higher yields were observed using Cs2CO3 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-

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**Table 1. Reaction Optimization**

| Entry | Catalyst | Solvent | Base           | Yield (%) |
|-------|----------|---------|----------------|-----------|
| 1     | BrettPhos, Pd2(dba)3 | toluene | Cs2CO3         | 0         |
| 2     | XPhos, Pd2(dba)3 | toluene | Cs2CO3         | 0         |
| 3     | BuXPhos, Pd2(dba)3 | toluene | Cs2CO3         | 0         |
| 4     | BuBrettPhos, Pd2(dba)3 | toluene | Cs2CO3         | 51        |
| 5     | BuBrettPhos Pd G3* | toluene | Cs2CO3         | 70        |
| 6     | BuBrettPhos Pd G3* | toluene | Na2CO3         | 0         |
| 7     | BuBrettPhos Pd G3* | toluene | K2CO3          | 8         |
| 8     | BuBrettPhos Pd G3* | toluene | K3PO4          | 70        |
| 9     | BuBrettPhos Pd G3* | 1,4-dioxane (80 °C, 16 h) | NaO(Bu) | 48        |
| 10    | BuBrettPhos Pd G3* | 1,4-dioxane | 0         | 61        |
| 11    | BuBrettPhos Pd G3* | tert-amyl alcohol | Cs2CO3 | 33        |
| 12    | BuBrettPhos Pd G3* | toluene (80 °C) | Cs2CO3 | 34        |
| 13    | BuBrettPhos Pd G3* | (30 mins) | Cs2CO3 | 48        |

“Yields determined by 19F qNMR with PhCF3 as internal standard. For entries 1−4, 0.5 mol % of Pd2(dba)3, and 1.25 mol % of ligand were used. For entries 6−13, 1 mol % of the precatalyst was used.”
The scalability of the C–O cross-coupling reaction was demonstrated by the gram-scale coupling of 2,2,3,3-tetrafluoroopropanol and 3-bromobenzaldehyde for the preparation of 2u, an intermediate in the synthesis of the drug idalopirdine (Figure 1). 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 K2PO4 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 18F-trifluoroethanol was achieved via alkylation of the corresponding phenol with 18F-trifluoroethanol. [18F]Tri fluoroethyl tosylate (Scheme 2A). Preparation of trifluoroethanol has been reported by the Riss group.9

fluroethanol 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 2,2,3,3-trifluoroethanol relative to 2,2-difluoroethanol and 2-fluoroethanol.

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

an 18F-trifluoroethyl ether has been reported by the Riss group via alkylation of the corresponding phenol with 18F-trifluoroethyl tosylate (Scheme 2A). Here, we propose a complementary approach that utilizes a C–O cross-coupling event to prepare 18F-trifluoroethyl ethers 18F2 from aryl bromides and 18F-trifluoroethanol. 18F-Trifluoroethanol has been reported by the Riss group via alkylation of the corresponding phenol with 18F-trifluoroethyl tosylate (Scheme 2A).9

**RCY = radiochemical yield, determined by integration of the radio-HPLC trace (prior to HPLC for compound 9).
previously been synthesized by nucleophilic radiofluorination of ethyl bromodifluoroacetate $S$ with $[^{18}F]$KF/$K_2$CO$_3$ followed by reduction with AlH$_3$ prepared in situ from LiAlH$_4$ and H$_2$SO$_4$ (Scheme 2B). The $[^{18}F]$trifluoroethanol was not used directly and required an additional step to generate $[^{18}F]$-trifluoroethyl trilate, which was then applied for amine alkylation. Multiple distillations were used to purify ethyl $[^{18}F]$trifluoroacetate 7 and $[^{18}F]$trifluoroethanol.

We sought to develop an $[^{18}F]$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 $[^{18}F]$F was unstable under reversed-phase HPLC conditions. Therefore, we targeted menthol $[^{18}F]$trifluoroacetate $[^{18}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, $[^{18}F]$ synthesis of $[^{18}F]$9 was achieved in 27 ± 10% radiochemical yield (RCY) using $[^{18}F]$TBAF and DBU in 1,3-dimethyl-2-imidazolidinone (DMI). After HPLC purification and reformulation into 1,4-dioxane, reduction using NaBH$_4$ afforded $[^{18}F]$trifluoroethanol in 98 ± 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, $[^{18}F]$trifluoroethanol was coupled with aryl bromide 1a and naphthyl bromide 11 to afford the desired cross-coupled $[^{18}F]$trifluoroethyl ethers (Scheme 2D). Radio-HPLC showed clean reaction profiles, with mainly the $[^{18}F]$-labeled product and unreacted $[^{18}F]$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 $[^{18}F]$trifluoroethanol solution; drying of menthol $[^{18}F]$trifluoroacetate $[^{18}F]$9 under a flow of nitrogen was essential prior to reformulation in 1,4-dioxane. While Pd-mediated C-N and C-C cross-coupling has been used for introduction of $[^{18}F]$-labeled motifs, 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$_2$CO$_3$; the reaction tolerates various electronic patterns on the arene ring, a wide range of functional groups including those with mildly acidic $\alpha$-protons, and proceeds over a short duration. An activated aryl chloride has also been shown to couple effectively. In addition, K$_2$PO$_4$ was found to be a cheaper alternative base to Cs$_2$CO$_3$. 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 $[^{18}F]$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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