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Palladium-Catalyzed C−H Trifluoroethoxylation of *N*-Sulfonylbenzamides

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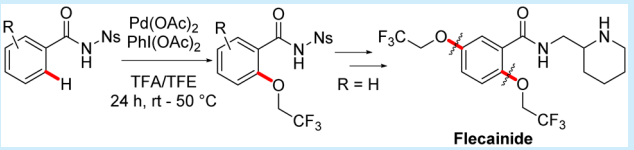
Supporting Information

ABSTRACT: The trifluoroethyl aryl ethers are important motifs in drug molecules. However, a report devoted specifically to the study of transition-metal-catalyzed C−H trifluoroethoxylation has not been reported to date. A protocol of Pd(II)-catalyzed *o*-C−H trifluoroethoxylation of a broad range of benzoic acid derivatives (i.e., *N*-sulfonylbenzamides) has been developed. This method is also applied to the formal synthesis of the drug molecule flecainide, wherein the first *m*-C−H trifluoroethoxylation is also exemplified.



The distinctly important role of fluorinated organic compounds in material sciences, pharmaceuticals, and agrochemicals has induced numerous efforts to develop effective methods for introducing fluorine and fluorinated groups into organic molecules.[1,2] The trifluoroethyl aryl ether motif is widely found in many drugs with enhanced bioavailability resulting from the metabolic stability and distinct physicochemical properties such as a high electron-withdrawing effect and significant lipophilicity of the trifluoroethoxyl (CF_3CH_2O) group (Figure 1).[3] Consequently, the development of an efficient method of

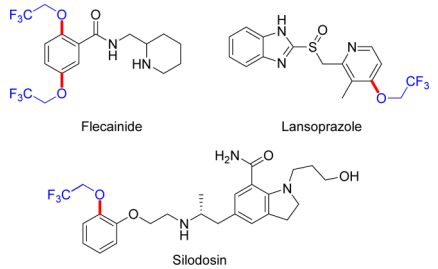
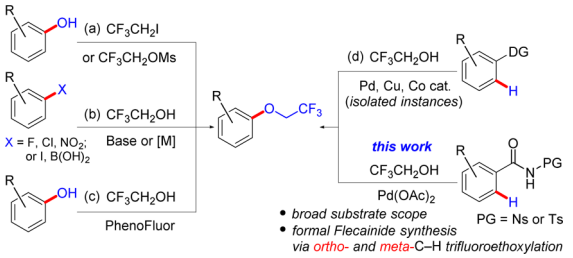


Figure 1. Representative drug molecules with the CF_3CH_2O group.

introducing the CF_3CH_2O group onto arenes is of considerable interest.[4−7] One conventional method is trifluoroethylation of phenols with trifluoroethyl iodide or mesylate via S_N2 reactions (Scheme 1a).[4] However, this method requires elevated temperatures and suffers from competing *β*-fluorine eliminations.[4c] Another method is the trifluoroethoxylation of aromatic halides/nitrobenzenes using 2,2,2-trifluoroethanol (TFE) under basic conditions at high temperatures via direct aromatic nucleophilic substitution, which is limited to activated arenes/heteroarenes (Scheme 1b).[5] Other valuable routes are transition-metal-catalyzed/-mediated cross-coupling reactions of aryl halides or aryl boronic acids with TFE (Scheme 1b).[6] Recently, the Ritter group reported an interesting method of aryl trifluoroethyl ether

Scheme 1. Methods of Introducing the Trifluoroethoxyl Group



formation by the reaction of phenols with TFE mediated by PhenoFluor (Scheme 1c).[7] However, all the present methods require the use of prefunctionalized aryl groups with hydroxyl, halides, or boryl substituents. Herein, we report a method of direct trifluoroethoxylation of benzoic acid derivatives (i.e., *N*-sulfonylbenzamides) via *o*-C−H activation. Moreover, the first *m*-C−H trifluoroethoxylation of a benzoic acid derivative is also exemplified in the formal synthesis of flecainide.

In the past decade, transition-metal-catalyzed direct C−H bond functionalization has emerged as a powerful tool for step- and atom-economical synthesis of complex organic molecules.[8,9] In particular, formation of C−O bonds through directed C−H bond activation has been extensively investigated since Sanford's pioneering work of palladium-catalyzed directed C−H alkoxylation and acetoxylation of arenes employing $PhI(OAc)_2$ as the terminal oxidant.[10] As one of the valuable C−O formation methods, C−H alkoxylation has also been developed rapidly with $C(sp^2)$−H as well as $C(sp^3)$−H bonds.[10−12] However, only a few isolated instances of C−H trifluoroethoxylation have been reported to date (Scheme 1d).[10a,13] In this work, we focus on the

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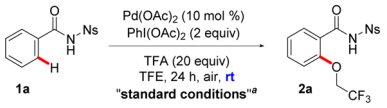
investigation of alkoxylation using electron-deficient TFE with various *N*-sulfonylbenzamides.

Our study began with extensive directing group optimization, which led to *N*-nosylbenzamide **1a** as the best substrate and *N*-tosylbenzamides[11d,14] as comparable candidates (Table 1). After

Table 1. Optimization of Reaction Conditions



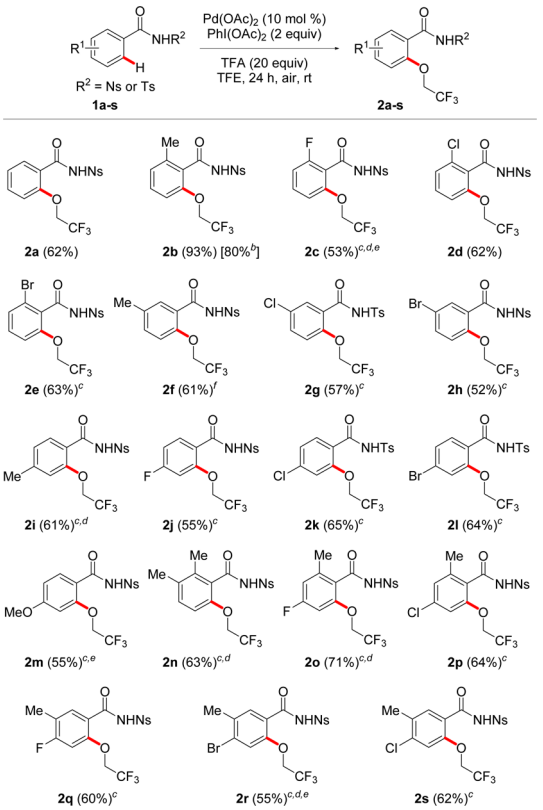
entry	variation from the standard condition	yield[b] (%)
1	none	70 (62)[c]
2	under argon instead of air	57
3	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	70 (60)[c]
4	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	9[d]
5	$PdCl_2$ instead of $Pd(OAc)_2$	0
6	AgOAc (3 equiv) instead of $PhI(OAc)_2$	0
7	$K_2S_2O_8$ instead of $PhI(OAc)_2$	0
8	NFSI instead of $PhI(OAc)_2$	40
9	add 20 mol % of Ac-Gly-OH	58
10	add 60 mol % of Ac-Gly-OH	58
11	add 60 mol % of Ac-Ile-OH	37
12	at 50 °C	60
13	at 90 °C	49
14	add 10 equiv of HFIP	31
15	no TFA	2
16	10 equiv of TFA	48
17	30 equiv of TFA	64
18	1.85 mL of TFE (0.05 M)	50
19	0.35 mL of TFE (0.2 M)	52

[a]All reactions were carried out on a 0.1 mmol scale in 1 mL of solvents (solvents include TFA and TFE) for 24 h, TFA (0.15 mL, 20 equiv). [b]The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard. [c]Isolated yield in parentheses. [d]No TFA added. TFA, trifluoroacetic acid; TFE, 2,2,2-trifluoroethanol; Ns, 4-nitrobenzensulfonyl (nosyl); NFSI, *N*-fluorobenzenesulfonimide; Gly, glycine; Ile, isoleucine; HFIP, hexafluoro-2-propanol.

the reaction conditions were extensively optimized, we were delighted to find that the desired trifluoroethoxylated product **2a** was obtained in 62% isolated yield at room temperature; no substrate or other product such as acetoxylated benzamide was observed, which may imply that partial decomposition of substrate might occur in this challenging C−H trifluoroethoxylation (entry 1). Running the reaction under argon atmosphere instead of air did not promote the reaction (entry 2). Use of $Pd(TFA)_2$ as the catalyst was also feasible and gave similar isolated product (entry 3), but this reaction was almost shutdown without TFA (entry 4). However, $PdCl_2$ was not an effective alternative catalyst (entry 5). Other oxidants were also investigated. Weak oxidant AgOAc was not a viable oxidant (entry 6). Strong oxidant potassium persulfate ($K_2S_2O_8$) did not afford any product either (entry 7), although NFSI was capable of generating 40% of desired product (entry 8). Monoprotected amino acid ligands that might promote C−H oxidation in the literature and our previous study were also tested.[15,16b] However, no improved yield was observed using such ligands with different loadings (entries 9−11). Surprisingly, inferior reaction performance was observed when the reaction temperature was increased to 50 or 90 °C possibly due to more decomposition of the substrate at higher temperature (entries 12 and 13). The addition of potential promoter hexafluoro-2-propanol only led to a significant reduction of the yield (entry 14).[16] Notably, addition of TFA proved to be crucial as only a trace of product was produced without TFA, while changing the loading of TFA did not further increase the yield (entries 15−17). Finally, control of the reaction concentration seemed to be important (entries 18 and 19), since the yields were diminished at lower or higher reaction concentration (see the Supporting Information for more substrate and condition screenings).

With the optimized standard conditions in hand, we examined the scope of this *ortho*-selective C−H trifluoroethoxylation protocol with *N*-nosylbenzamides or *N*-tosylbenzamides (Scheme 2). To our delight, *ortho* substituents such as

Scheme 2. Substrate Scope of *o*-C−H Trifluoroethoxylation[a]



[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), $PhI(OAc)_2$ (0.2 mmol), TFA (2.0 mmol, 0.15 mL), TFE (0.85 mL), 24 h, rt, under air. Isolated yields were reported. [b]Isolated yield in a 1.0 mmol scale. [c]50 °C. [d]Ac-Gly-OH (60 mol %). [e]TFA (15 equiv). [f]TFA (5 equiv).

electron-donating methyl groups and electron-withdrawing halides were tolerated, producing good yields of *o*-trifluoroethoxylated products (**2b−e**). It should be noted that a higher temperature of 50 °C was required for some substrates during expantion of the substrate scope (**2c**, **2e**, and **2g−s**). Satisfactory results were also obtained with *meta*-substituted substrates, affording the desired products in moderate yields (**2f−h**). Pleasingly, the reaction was also compatible with various *para*-substituted compounds (**2i−m**). Notably, multiple disubstituted substrates reacted smoothly to give desired products in moderate to good yields (**2n−s**). Importantly, the chloro and bromo substituents are tolerated in the reaction for several substrates, enabling further elaboration of the trifluoroethoxylated products at the respective halogenated sites.

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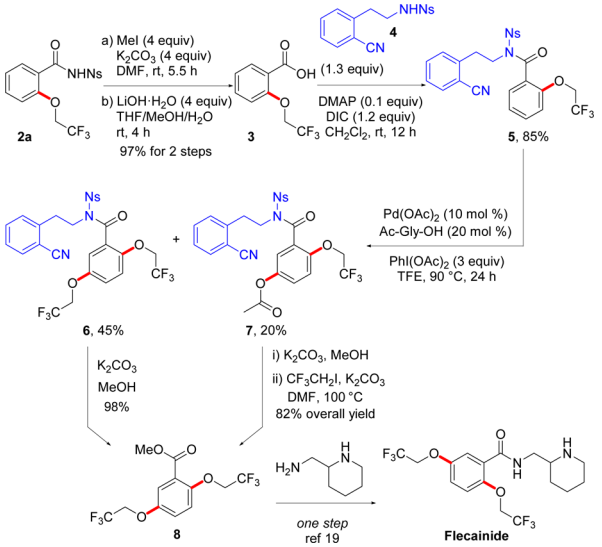
To showcase the utility of this new method, we executed a formal synthesis of flecainide, that is used to prevent and treat tachyarrhythmias (Scheme 3). The synthesis started with

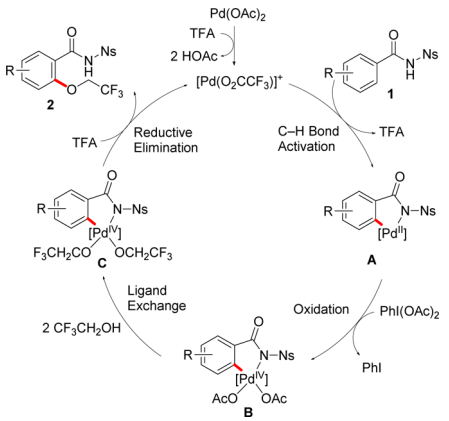
Scheme 3. Formal Synthesis of Flecainide via C−H Activation



conversion of **2a** to 2-(2,2,2-trifluoroethoxy)benzoic acid (**3**) in two steps under mild conventional conditions.[17] Then a *meta*-directing group developed by us for *meta*-C−H functionalization of benzoic acids was attached to acid **3** to afford intermediate **5**.[16b] Much to our delight, substrate **5** underwent *meta*-C−H oxygenation to give desired product **6** as well as acetoxylated product **7** smoothly. Notably, to the best of our knowledge, this is the first direct *meta*-C−H trifluoroethoxylation of an arene.[16b,18] Finally, both **6** and **7** could be transformed to ester **8**, a precursor of flecainide, in high yields, thus providing an alternative synthetic route for felcainide.[19] It should be noted that our method is potentially applicable for the synthesis of flecainide derivatives with other substituents on the arene, which is difficult to achieve in the reported methods but is important in medicinal chemistry and drug discovery.[19]

Based on the above results, a plausible catalytic cycle for this *ortho*-trifluoroethoxylation reaction is proposed in Scheme 4. First, a reactive cationic Pd(II) species is generated from $Pd(OAc)_2$ with TFA.[20] Then the palladacyclic intermediate **A** is generated from benzamide **1** via C−H bond activation catalyzed

Scheme 4. Proposed Reaction Mechanism



with $[Pd(O_2CCF_3)]^+$. Oxidation of palladacycle **A** with $PhI(OAc)_2$ followed by subsequent ligand exchange of the resulting complex **B** produces a Pd(IV) intermediate **C**. Finally, palladacycle **C** undergoes reductive elimination to generate the desired product **2** and $[Pd(O_2CCF_3)]^+$. Alternatively, a Pd(II)/Pd(III) catalytic cycle could not be excluded at the current stage.[21]

In conclusion, we have developed a protocol for Pd(II)-catalyzed *ortho*-C−H trifluoroethoxylation of a broad range of *N*-sulfonylbenzamides. Moreover, the first *meta*-C−H trifluoroethoxylation was also proved to be viable in the formal synthesis of flecainide. Given the importance of the trifluoroethoxyl group in promoting bioavailability of organic molecules in medicinal chemistry, we anticipate that this reaction would be of considerable interest in drug discovery. Studies on site-selective C−H trifluoroethoxylation of other classes of substrates are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01103.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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