Fluorination

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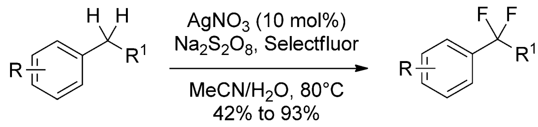
Silver-Catalyzed Oxidative Activation of Benzylic C–H Bonds for the Synthesis of Difluoromethylated Arenes**

*Peng Xu, Shuo Guo, Liyan Wang, and Pingping Tang**

Abstract: *A mild and catalytic method to form difluoromethylated arenes through the activation of benzylic C–H bonds has been developed. Utilizing $AgNO_3$ as the catalyst, various arenes with diverse functional groups undergo activation/fluorination of benzylic C–H bonds with commercially available Selectfluor reagent as a source of fluorine in aqueous solution. The reaction is operationally simple and amenable to gram-scale synthesis.*

Fluorinated compounds are important in pharmaceuticals, agrochemicals, and materials.[1] The introduction of fluorine atoms into small molecules often improves their lipophilicity and metabolic stability. In addition, ^{18}F-labeled organic compounds are clinically used as radiotracers for positron emission tomography (PET).[2] The difluoromethyl group (CF_2) is of interest in medicinal chemistry because it is isosteric with the hydroxy group, and is found in various biologically active compounds.[3] However, methods for the synthesis of difluoromethylated arenes are limited.[4] Herein, we present a mild and catalytic method to form difluoromethylated arenes through activation/fluorination of benzylic C–H bonds with the commercially available Selectfluor reagent as the source of fluorine. This is the first example of the use of silver catalysis for the activation of benzylic C–H bonds to prepare difluoromethylated arenes (Scheme 1).



Scheme 1. Synthesis of difluoromethylated arenes.

Traditional methods for the synthesis of difluoromethylated arenes through deoxyfluorination of aldehydes or ketones with SF_4, *N*,*N*-diethylaminosulfur trifluoride (DAST), and derivatives of DAST suffer from poor functional-group compatibility.[5] Recently, Amii and co-workers reported a copper-catalyzed three-step route to difluoromethylarenes, however, the final step was limited to electron-deficient aryl iodides and required high temperature (> 170 °C).[6] The groups of Hartwig[7] and Surya Prakash[8] presented a one-step copper-mediated transformation of iodoarenes into difluoromethylarenes, respectively. Gouverneurs and co-workers recently reported a silver-catalyzed fluorodecarboxylation to prepare difluoromethylarenes from α-fluoroarylacetic acids.[9] Baran and co-workers reported the direct difluoromethylation of heteroarenes with zinc difluoromethanesulfinate (DFMS), however, reactions with arenes were not reported.[10] Zhang and co-workers reported a palladium-catalyzed difluoroalkylation of aryl boronic acids to form difluoromethylated arenes.[11] In addition to the recent success in using cross-coupling reactions to prepare fluoroalkyl compounds,[12] methods for the transformation of C(sp^3)–H bonds to C(sp^3)–F bonds were also developed.[13–16] In 2006, Sanford reported a palladium-catalyzed benzylic fluorination.[13] Recently, Groves and co-workers reported manganese-catalyzed fluorination of unactivated C(sp^3)–H and benzylic C–H bonds.[14] Lectka and co-workers reported a copper-catalyzed fluorination of unactivated C(sp^3)–H, an iron-catalyzed fluorination of benzylic C–H, and a photocatalyzed fluorination of aliphatic groups.[15] Inoue reported a metal-free fluorination of C(sp^3)–H bonds using a catalytic *N*-oxyl radical generated from *N*,*N*-dihydroxypyromellitimide.[16] During the preparation of our manuscript, Chen and co-workers reported a diarylketone-catalyzed selective activation of benzylic C–H bonds for the synthesis of mono- and difluoromethylated arenes using visible light.[17] This was the first report of a selective activation of a benzylic C–H bond to form difluoromethylated arenes. In the course of a research program toward the synthesis of difluoromethylated arenes, we were inspired by Groves' finding of difluoromethylated arenes in 5% yield during the manganese-catalyzed monofluorination of benzylic C–H bonds.[14b] Thus, we reasoned that difluoromethylated arenes could be obtained through transition-metal-catalyzed oxidative activation of benzylic C–H bonds based on Groves' previous report.

Herein we report the first example of a silver-catalyzed oxidative activation of a benzylic C–H bond to prepare difluoromethylated arenes with Selectfluor under mild conditions. Initial investigations focused on the silver-catalyzed activation of the benzylic C–H bond of 4-fluoro-2-methylbenzoic acid (**1i**). This substrate was selected because it could generate the acyloxy radical in the presence of silver(I) and peroxydisulfate, which may facilitate an intramolecular

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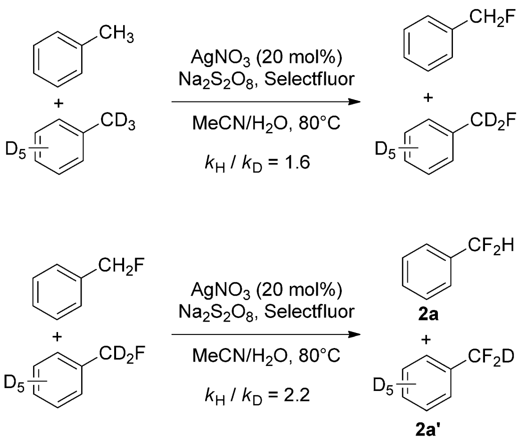
abstraction of a benzylic C–H through 1,5-hydrogen transfer from the benzylic position to the acyloxy radical.[18] After extensive screening with $AgNO_3$ as the catalyst, the reaction of 4-fluoro-2-methylbenzoic acid (**1i**) with Selectfluor and $Na_2S_2O_8$ in acetonitrile/H_2O (v:v = 1:1) at 80 °C for 3 h under N_2 atmosphere led to the formation of difluoromethylated arenes (**2i**) in 89 % yield, determined by ^{19}F NMR analysis of the crude product. The control experiment was performed in the absence of a silver salt and the difluoromethylated product was obtained in only 20 % yield. In addition, no desired product was generated when the reaction was performed without both $AgNO_3$ and $Na_2S_2O_8$. Several silver salts catalyzed the activation of benzylic C–H bonds with equal efficiency, but $AgNO_3$ was ultimately chosen as the catalyst because it formed difluoromethylated arenes in the same yield range of yields and is less expensive than other silver salts (see the Supporting Information for more details). Also, water proved to be essential for the reaction, as no difluoromethylated products resulted when the reaction was performed in anhydrous acetonitrile. The role of water has not yet been established. The reaction was found to be sensitive to the amounts of $Na_2S_2O_8$ and Selectfluor. The difluorination yield increased in the presence of $Na_2S_2O_8$, and switching the fluorine source from Selectfluor to *N*-fluorobenzenesulfonimide (NFSI) led to no reaction at all. $Na_2S_2O_8$ is believed to oxidize the silver(I) salt to a silver(II) species and to facilitate the formation of difluoromethylated arenes (see Scheme 3). After thorough optimization of the reaction conditions, reactions with 10 mol % of $AgNO_3$, 0.5 equivalents of $Na_2S_2O_8$, and 3.0 equivalents of Selectfluor produced the desired products in high yields.

Using the optimized conditions, the substrate scope was subsequently investigated. A variety of methylated arenes (**1**) were smoothly transformed into the corresponding difluoromethylated arenes (**2**) with yields of isolated products ranging from 42 % to 93 % (Table 1). A variety of functionalities, such as a ketone, ester, carboxylic acid, amide, sulfonamide, aromatic fluoride, chloride, or bromide, were well tolerated under the reaction conditions. In general, methylated arenes without *ortho* substituents (**1a, 1c** to **1h**) reacted more slowly, and required high catalyst loadings and a higher amount of Selectfluor. For example, the transformation of toluene to the difluoromethylbenzene (**2a**) proceeded under standard reaction conditions in 60 % yield. When 20 mol % of $AgNO_3$ and 4.0 equivalents of Selectfluor were used in the reaction, the yield increased to 85 %. Notably, heteroaromatic substrates (**1x**, **1y**, and **1z**) were also successfully employed to provide the corresponding difluoromethylated arenes (**2x**, **2y**, and **2z**). Some substrates (**1j**, **1m**, **1w**, **1y**, **1z**) were poorly soluble in MeCN/H_2O and thus gave the corresponding products in moderate yields. The reaction also worked with ethyl benzene derivatives (**1aa**, **1bb**, and **1cc**) and heteroatom-substituted alkyl-chain derivative (**1ee**). No selectivity was observed for a substrate with competitive benzylic positions (**1dd**) and 2,5-bis(difluoromethyl)benzamide (**2dd**) was obtained. The total yield of mono- and trifluoromethylarene by-products was limited to less than 10 % in all cases. For some substrates, this required additional optimization of the reaction conditions. For example, the transformation of a heteroaromatic substrate (**1x**) to the difluoromethylated product (**2x**) proceeded under standard reaction conditions in 11 % yield with 71 % monofluorination by-product. When 20 mol % of $AgNO_3$, 5.0 equivalents of $Na_2S_2O_8$, and 4.0 equivalents of Selectfluor were used in the reaction, the yield of difluoromethylated product increased to 82 % and no monofluorination by-product was observed. To prove both the practicality and effectiveness of this method for large-scale synthesis, **2o** was prepared on a gram scale under the reaction conditions with 2.5 equivalents of Selectfluor in 86 % yield of isolated product.

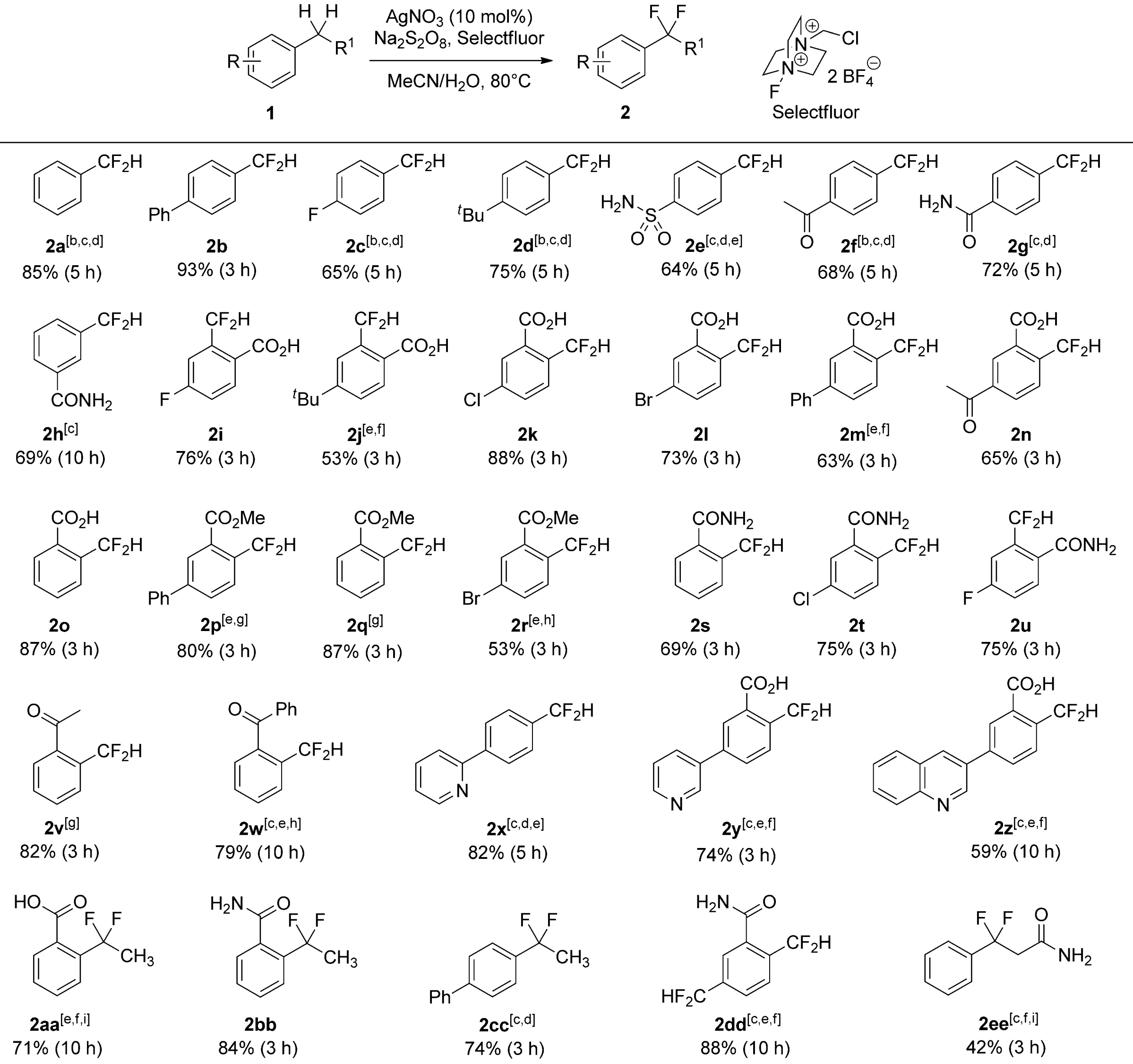
Although the detailed mechanism of this reaction is currently unclear, some preliminary studies indicate that a radial-chain mechanism or single-electron transfer (SET) may be involved in this transformation. No difluoromethylated arene was formed when 2.0 equivalents of the radical inhibitor butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added to the reaction. In addition, yields were much higher in the strict absence of O_2 than in its presence.[20] Together, these observations suggest the involvement of a free radical in the reaction. To gain further insights into the reaction mechanism, the intermolecular kinetic isotope effect (KIE) was measured (Scheme 2). The modest primary KIE values were observed from competition experiments of monofluorination using a 1:1 mixture of toluene and $[D_8]$toluene ($k_H/k_D = 1.6$) and a 1:1 mixture of benzyl fluoride and $[D_7]$benzyl fluoride ($k_H/k_D = 2.2$) in excess under the reaction conditions, which indicated that the C–H bond cleavage step might be involved in the rate-limiting step of this transformation.[21]



Scheme 2. Mechanism study.

A mechanism can be proposed based on our findings (Scheme 3). It is known[18] that in the presence of silver(I) salts, a peroxydisulfate anion disproportionates into a sulfate dianion and a sulfate radical anion [Eq. (1)]. The silver(I) salt is oxidized to a silver(II) species by peroxydisulfate [Eq. (1)], a sulfate radical anion [Eq. (2)], or an aminium radical cation [Eq. (3)]. The silver(II) species oxidizes the benzylic C–H bond (**A**) in turn to a benzylic radical (**B**). The substrates that contain a carbonyl group in the *ortho* position might have

Table 1: Scope of the silver-catalyzed activation of benzylic C—H bonds for the synthesis of difluoromethylated arenes.[a]



[a] Reaction conditions: substrate **1** (1.0 equiv), $AgNO_3$ (10 mol%), $Na_2S_2O_8$ (0.5 equiv), Selectfluor (3.0 equiv), 80°C, N_2. Yields refer to isolated product with a purity of more than 98%, unless otherwise noted. [b] Yields were determined by integration of the ^{19}F NMR spectrum using fluorobenzene as an internal standard. [c] 20 mol% of $AgNO_3$ was used. [d] 4.0 equiv of Selectfluor was used. [e] 5.0 equiv of $Na_2S_2O_8$ was used. [f] 5.0 equiv of Selectfluor was used. [g] 3.0 equiv of F-TEDA-PF_6[19] was used. [h] 5.0 equiv of F-TEDA-PF_6 was used. [i] 60°C was used. F-TEDA-PF_6 = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate).

a weak coordination between the carbonyl group and the silver(II) species, which may facilitate an intramolecular abstraction of a benzylic C—H to form a benzylic radical. Selectfluor is known to react through a radical mechanism,[22] and thus reacts with the benzylic radical (**B**) to form a monofluorinated intermediate (**C**), which can generate a benzylic radical (**D**) again with the silver(II) species, and then form difluoromethylated products (**E**) with Selectfluor.

In summary, we presented the first example of a silver-catalyzed oxidative activation of a benzylic C—H bond with the commercially available Selectfluor reagent for the preparation of difluoromethylated arenes. The reaction proceeds under mild conditions, tolerates various functionalities, and is amenable to the gram-scale synthesis of functionalized difluoromethylated arenes. Excess reagents and, in some cases, a higher catalyst loading are required to obtain high yields, which is a current limitation of this method. On the other hand, the commercial availability and air/moisture stability of both the fluorine reagent and the silver catalyst render this new radical fluorination a safe method of practical value in the synthesis of difluoromethylarenes.

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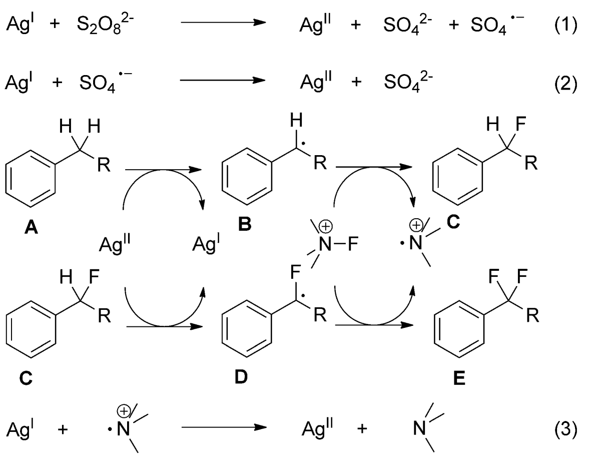

Scheme 3. Proposed mechanism for the silver-catalyzed activation of benzylic C–H bonds for the synthesis of difluoromethylated arenes.

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