Carbonylation

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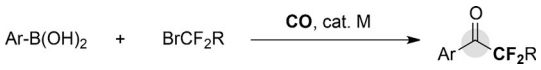
Carbonylation of Difluoroalkyl Bromides Catalyzed by Palladium

*Hai-Yang Zhao, Zhang Feng, Zhiji Luo, and Xingang Zhang**

Abstract: *Although important progress has been made in the fluoroalkylation reactions, the transition-metal-catalyzed carbonylative fluoroalkylation reaction remains challenging so far. Herein, we report the first example of a Pd-catalyzed carbonylation of difluoroalkyl bromides with (hetero)arylboronic acids under one atmosphere pressure of CO. The reaction can also be extended to the aryl potassium trifluoroborate salts. The advantages of this protocol are synthetic simplicity, broad substrate scope, and excellent functional group compatibility. The resulting difluoroalkyl ketones can serve as versatile building blocks for the synthesis of various useful fluorinated compounds.*

The past several decades have witnessed the development of transition-metal-catalyzed cross-coupling reactions and their wide application in the pharmaceuticals, fine chemicals, and functional materials. These cross-coupling strategies, however, are generally not ready to be adapted to the construction of a carbon-fluorocarbon (C-R_f) bond with high predictability and generality,[1] because the unique properties of fluorine atom(s) can dramatically influence the stability and reactivity of fluoroalkyl transition-metal complexes, leading to some unexpected reactions.[2] Given the importance of fluorinated compounds in medicinal chemistry and material sciences,[3] introduction of fluorinated substituents into organic molecules through transition-metal catalysis of the cross-coupling/fluoroalkylations has emerged as one of the most attractive, efficient, and environmentally benign strategies to access fluorinated compounds.[1] One of the challenges belonging to this theme is the transition-metal catalyzed carbonylative fluoroalkylation reaction. Although numerous of carbonylation reactions have been developed since Heck and coworkers reported their pioneering work of the Pd-catalyzed carbonylation of aryl halides in the 1970s,[4,5] no example of transition-metal-catalyzed carbonylative fluoroalkylation reaction has been reported yet. The reason is that compared with their hydrocarbon counterparts the stronger σ-bonds between fluoroalkyl groups and transition metals (R_f-M) are less prone to undergo carbonyl insertion.[6] To date, only few examples of carbon monoxide (CO) inserting into a M-R_f bond to produce a fluoroacyl complex (M-C(O)R_f) have been documented.[7] In addition, once the M-C(O)R_f complexes are formed, their decarbonylation to generate the (CO)M-R_f will probably occur, which is a classic technique to prepare fluoroalkyl metal complexes.[8] As a result, it is very difficult to control the catalytic cycle to obtain the desired fluorinated products. Nevertheless, herein, we describe the discovery and development of the reaction that can meet these challenges.

We began this study by examining the feasibility of palladium-catalyzed carbonylation of difluoroalkyl bromides with arylboronic acids (Scheme 1). The choice of difluoroalkyl bromides, a type of inexpensive and widely available compounds, as the model substrate is because the unique properties of difluoromethylene group (CF_2) often lead to profound changes in physical, chemical, and biological properties of organic molecules.[9] Although the targeting difluoroalkyl ketones are valuable intermediates and building blocks in the synthesis of various useful fluorinated compounds, the existing methods to prepare difluoroalkyl ketones are limited to substrate scope, functional group compatibility, and requirement of a stepwise procedure thus lowering the reaction efficacy. Therefore, it is also highly demanding to develop new, efficient and green methods to prepare such a valuable structural motif with high functional group tolerance.



Scheme 1. Pd-catalyzed carbonylation of difluoroalkyl bromides with arylboronic acids.

Inspired by our recent work on palladium-catalyzed difluoroalkylation of arylboronic acids with bromodifluoroacetate **2a**,[10a] we focused our initial study on the Pd-catalyzed carbonylation reaction of **2a** with arylboronic acid **1a** under 1 atmosphere pressure of CO (Table 1). In addition, **2a** is low-cost and widely available and can provide a good platform for downstream transformations. After carefully examining the catalytic system, we found that 14% of carbonylation product **3a** could be obtained with utilization of $PdCl_2(PPh_3)_3$ (5 mol%), Xantphos (10 mol%), Cs_2CO_3 (2.0 equiv) and 1 atm of CO in dioxane at 80°C (entry 1). Surprisingly, compound **3a** could also be produced in 6% yield in the absence of CO (entry 2). This unusual finding is noteworthy as no carbonylation reaction has been previously reported through such a mode. The decomposition of **2a** is likely to occur under the current reaction conditions and generate CO as the carbonyl source for the following carbonylation reaction. Stimulated by this unprecedented result, a survey of reaction parameters, such as palladium sources, ligands, bases, and solvents, with **2a** as a self-serve CO source was conducted (for details see the Supporting Information). The combination of $PdCl_2(PPh_3)_2$, Xantphos, and dioxane

[*] H.-Y. Zhao, Z. Feng, Z. Luo, Prof. Dr. X. Zhang
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: xgzhang@mail.sioc.ac.cn

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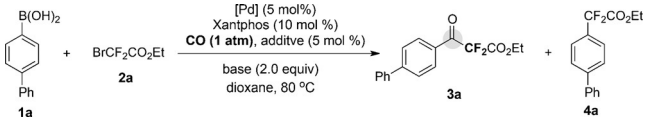
Table 1: Representative results for optimization of Pd-catalyzed carbonylation of **2a** with **1a**.[a]



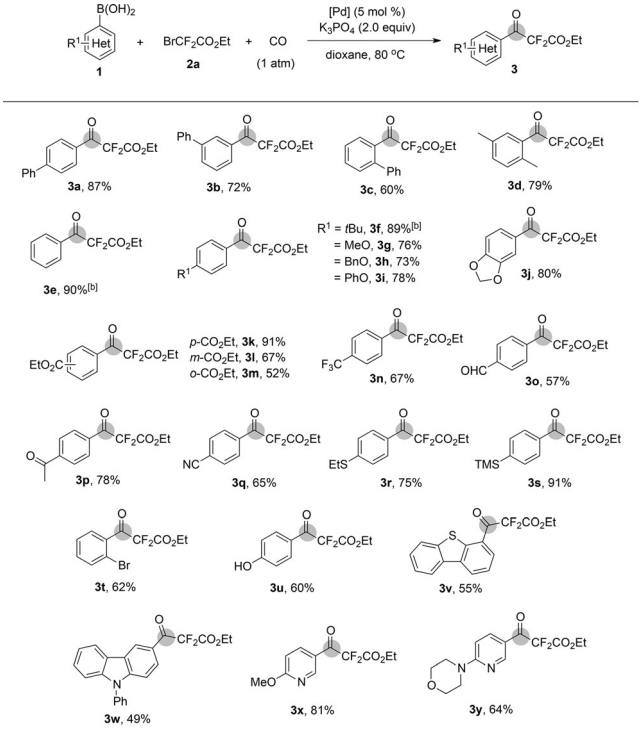
Entry	[Pd]	Base	Additive	**3a**/**4a** Yield [%][b]
1	$PdCl_2(PPh_3)_2$	Cs_2CO_3	–	14/<1
2[c]	$PdCl_2(PPh_3)_2$	Cs_2CO_3	–	6/6
3[c]	$PdCl_2(PPh_3)_2$	K_3PO_4	–	16/31
4[c]	$PdCl_2(PPh_3)_2$	K_3PO_4	$Cu(hfac)_2$	35/64
5	$PdCl_2(PPh_3)_2$	K_3PO_4	$Cu(hfac)_2$	81/trace
6[d]	$PdCl_2(PPh_3)_2$	K_3PO_4	$Cu(hfac)_2$	92 (87)/6

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol, 1.0 equiv), **2a** (2.0 equiv), dioxane (2 mL), 24 h. [b] Determined by ^{19}F NMR using fluorobenzene as internal standard and number in parenthesis is isolated yield. [c] Reaction ran in the absence of CO. [d] Molecular sieves (3 Å) were added.

remained the optimal choice and K_3PO_4 afforded **3a** in a slightly higher yield (16%) along with 31% yield of byproduct difluoroacetylated arene **4a** (entry 3). Taking into account the fact that the copper salt can facilitate the transmetalation step thus benefiting the reaction efficiency,[11] a variety of copper salts were examined (for details see the Supporting Information). When $Cu(hfac)_2$ [hfac = hexafluoroacetylacetone monoanion] was employed, an increased yield of **3a** (35%) was provided, accompanied by a significantly increased amount of byproduct **4a** (64%) (entry 4). The facile production of **4a** appears to compete with the desired carbonylation reaction, which is limited by the relatively slow release of CO from **2a**. Accordingly, additional CO (1 atm) was used to suppress this competitive reaction and afforded **3a** in a high yield (81%; entry 5). Finally, the optimal reaction conditions were identified by addition of 3 Å molecular sieves (MS), providing **3a** in 87% yield upon isolation (entry 6). No product or poor yield of **3a** was obtained without palladium catalyst or Xantphos,[12] thus demonstrating the critical role of $PdCl_2(PPh_3)_2$/Xantphos in promotion of the reaction (for details see the Supporting Information).

Upon the identification of viable reaction conditions, a variety of arylboronic acids were examined in this transformation (Table 2). Generally, arylboronic acids bearing either electron-rich or electron-deficient substituents all undergo the reaction smoothly, providing **3** with high efficiency. The steric effect of the arylboronic acids does not interfere with the reaction. Sterically hindered substrates, such as *ortho*-phenyl substituted phenyl boronic acid and (2,5-dimethylphenyl)boronic acid, afford the corresponding products with good yields (**3c** and **3d**). Meanwhile, this reaction exhibits high tolerance to functional groups: many versatile functional groups, including base or nucleophile sensitive moieties (ester, formyl, enolizable ketone, nitrile, thioether, siyl, and bromide) show excellent compatibility to the reaction (**3k**–**3m**, **3o**–**3t**). It is noteworthy that the phenol derived substrate furnishes the corresponding product **3u** in

Table 2: Pd-catalyzed carbonylation of arylboronic acids **1** with bromodifluoroacetate **2a**.[a]

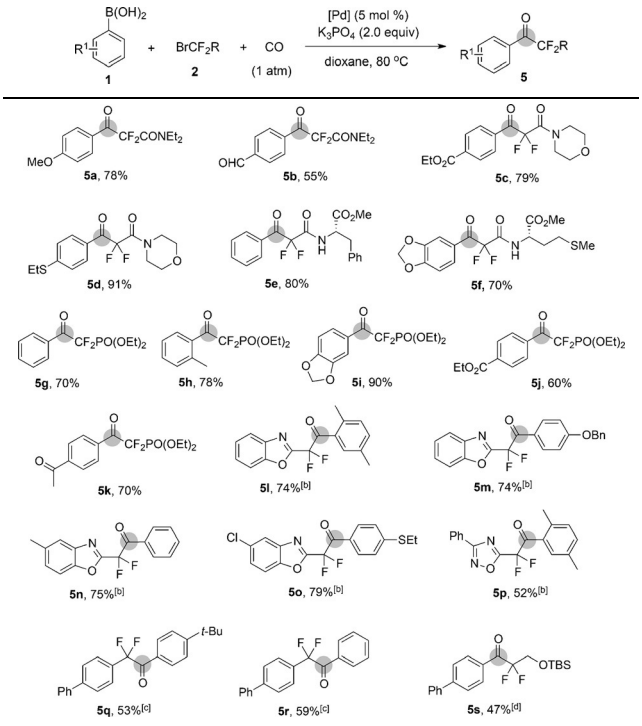


[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol, 1.0 equiv), **2a** (2.0 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), Xantphos (10 mol%), $Cu(hfac)_2$ (5 mol%), 3 Å molecular sieves, dioxane (2 mL), 24 h. [b] Gram-scale synthesis.

good yield without observation of the dicarbonylated side product, which is in sharp contrast to the previously reported results using phenols as nucleophiles for the carbonylation reaction.[5a] The heteroaromatic boronic acids, such as dibenzo[*b*,*d*]thiophene, carbazole, and pyridine containing substrates are also applicable to the reaction (**3v**–**3y**), thus highlighting the advantages of the current process further. It is also possible to prepare compounds **3** on a gram-scale. For examples, yields as high as ~90% were obtained for the gram-scale synthesis of **3e** and **3f**, thus offering a reliable and practical access to the highly functionalized fluorinated molecules.

To demonstrate the generality of this catalytic system, bromodifluoroacetamides (**2b**–**2e**) were explored (Table 3). Good yields and high functional group compatibility were still observed. Importantly, the amino acid containing difluoroacetamides undergo the reaction smoothly, leading to the corresponding products with high efficiency (**5e** and **5f**). It should be mentioned that thioethers usually poison the palladium catalyst and inhibit the catalysis reaction,[13] but the methionine residue does not influence the reaction efficiency (**5f**). This transformation is also highly relevant to the drug discovery and development, in light of the importance of α,α-difluoroalkyl ketone based peptide in the medicinal chemistry, for example, α,α–difluoroketone A79285 being an excellent inhibitor of HIV-1 aspartic protease.[14]

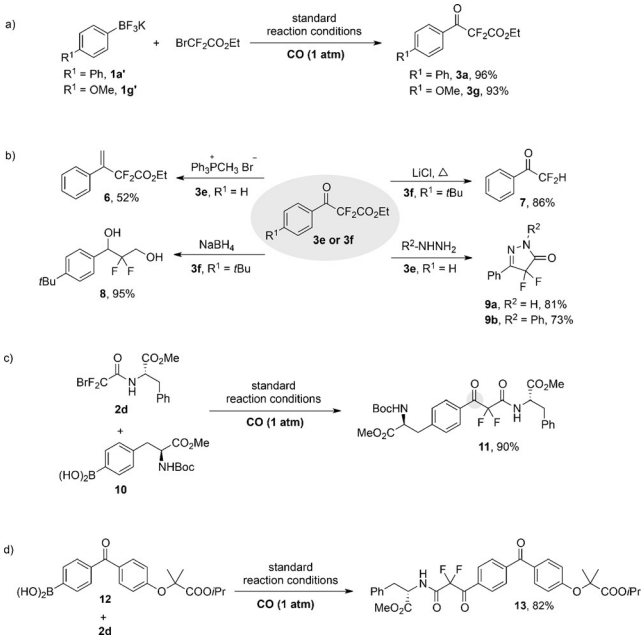
Table 3: Pd-catalyzed carbonylation of arylboronic acids **1** with difluoroalkyl bromides **2**.[a]



[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol, 1.0 equiv), **2a** (2.0 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), Xantphos (10 mol%), $Cu(hfac)_2$ (5 mol%), 3 Å molecular sieves, dioxane (2 mL), 24 h. [b] $Pd(OAc)_2$ (5 mol%), Xantphos (10 mol%), dioxane (2 mL), 24 h. [c] Without 3 Å molecular sieves. [d] 10 mol% of IPr·HCl was used.

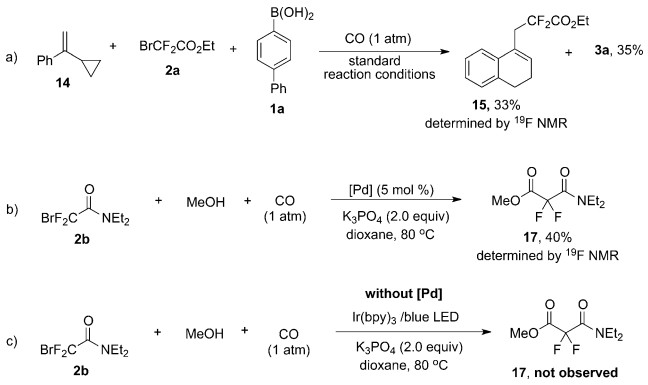
Considering that phosphonyldifluoromethyl group ($CF_2PO(OEt)_2$) is an attractive structural motif in the medicinal chemistry, in which the difluoromethylene group (CF_2) can function as a bioisostere for an oxygen atom,[15] we then extended the substrate scope of the difluoroalkyl bromides to bromodifluoromethylphosphonate **2f** just with minor modification (**5g**–**5k**). The advantages of the current process can also be featured by the carbonylation of bromodifluoromethylbenzoxazole and its derivatives (**5l**–**5p**).[16] But in these cases, $Pd(OAc)_2$ instead of $PdCl_2(PPh_3)_2$ in the absence of copper and molecular sieves additives exhibits good activity. Since benzoxazole and its derivatives are a prominent structural motif present in numerous pharmaceuticals and agrochemicals, this method is a valuable strategy for the discovery of new interesting bioactive compounds. In addition, aryldifluoromethyl bromide is suitable substrate, providing the corresponding products **5q** and **5r** in moderate yields. Remarkably, the unactivated 1-bromo-1,1-difluoroalkane is also viable in the reaction, but a relatively electron-rich *N*-heterocyclic carbene ligand *N*,*N*-bis(2,6-diisopropylphenyl)imidazole-2-ylidene, IPr) is used to promote the reaction (**5s**).

The reaction can also be extended to aryl potassium trifluoroborate salts. Even higher yields of **3a** and **3g** were obtained when **1a**′ and **1g**′ were examined (Scheme 2a). The importance and utility of this protocol have also been highlighted by the rapid synthesis of diverse difluoromethylenated molecules from the building blocks **3e** or **3f**. As shown in Scheme 2b, the carbonyl group can be easily converted into vinyl through the Wittig reaction. Decarboxylation of **3f** to difluoromethyl ketone **7**, an important building block for the synthesis of the difluoroalkylated compounds, proceeds smoothly. What is more, excellent yield of diol **8** is also produced through the reduction of both carbonyl and ester moiety of **3f**. Importantly, the condensation of hydrazines with **3e** affords the biologically active compounds 4,4-difluoropyrzaol-5-ones **9a** and **9b** with high efficiency. Finally, application of current process can also efficiently synthesize fluorinated peptiod **11** in only one step with the yield of 90%, which may have potential interest in the discovery of new bioactive molecules (Scheme 2c). The late-stage difluoroalkylation of Fenofibrate®, a drug against cardiovascular disease,[17] is also successfully performed (Scheme 2d), thus featuring the applicability of this protocol in the medicinal chemistry further.



Scheme 2. Transformations of compounds **3** and synthesis of biologically active molecules.

To gain the mechanistic insight into the current reaction, several experiments were conducted, as shown in Scheme 3. Firstly, to identify whether a fluoroalkyl radical pathway is involved in the reaction, α-cyclopropylstyrene **14** was added in the reaction of **2a** with arylboronic acid under the standard reaction conditions (Scheme 3a). A ring-expanded product **15** was obtained in 33% yield, suggesting that a single electron transfer (SET) pathway via a difluoroalkyl radical is involved in the reaction process. The formation of radical intermediate was further confirmed by the ESR study of reaction of **2a** with spin-trapping agent phenyl *tert*-butyl nitrone (PBN) (see the Supporting Information). Thus, both results clearly demonstrate that a free fluoroalkyl radical is involved in the reaction. Secondly, the carbonylation of bromodifluoroacetamide **2b** can also employ methanol as the nucleophile (Scheme 3b), thus suggesting that a fluoroacyl



Scheme 3. Mechanistic studies.

palladium complex may be involved in the catalytic cycle. To rule out the possibility that radical carbonylations without palladium also produce esters, the reaction between **2b** and methanol in the absence of palladium catalyst was conducted (Scheme 3c). However, no ester **17** was observed when the reaction was irradiated by blue LED in the presence of a photocatalyst $Ir(bpy)_3$, but the difluoroalkyl radical [$Et_2NC(O)CF_2$·] was indeed generated.[18] Thus, this result demonstrates that the palladium is essential for the current carbonylation reaction and a fluoroacyl palladium complex may be generated in the reaction process.

On the basis of the present results and previous reports,[5,10] a plausible reaction mechanism was proposed. The reaction was initiated by a Pd^0L_n-promoted single electron transfer (SET) pathway to generate the difluoroalkyl radical [RCF_2·] **A** and [$BrPd(I)L_n$] **B. A** subsequently reacted with **B** to provide [$BrPdL_nCF_2R$] **C**. After insertion of CO into σ bond of palladium species **C** ($BrPdL_n$-CF_2R), the key intermediate difluoroalkylacyl palladium complex [$BrPdL_n$-$(CO)CF_2R$] **D** was provided. **D** underwent transmetalation with arylboronic acids, followed by the reductive elimination to deliver carbonylated products and regenerate Pd^0L_n. However, an alternative pathway through the formation of **D** between [$BrPd(I)L_n$] **B** and difluoroalkylacyl radical that was derived from the reaction of difluoroalkyl radical [RCF_2·] **A** with CO cannot be ruled out.[19]

In conclusion, the first example of transition-metal-catalyzed carbonylative fluoroalkylation reaction has been described. The reaction undergoes smoothly under mild reaction conditions in the presence of 1 atm of CO with high efficiency, broad substrate scope, and excellent functional group compatibility. Applications of the method efficiently lead to diverse fluorinated compounds, thus featuring its importance and usefulness. The remarkable function of Xantphos in the current catalytic system is probably because of its wide bite angle,[12a,b] but it might not always be the key contributing factor.[12d,20] A self-serve CO system for the carbonylation reaction is found, in which $BrCF_2CO_2Et$ can serve as a CO source and a coupling partner. We believe that the current reaction not only provides us a new view to understand transition-metal-catalyzed carbonylative fluoroalkylation reaction but also is useful for the drug discovery and development. Further studies to reveal the detailed mechanism as well as other derivative reactions are now in progress in our laboratory.[21]

Acknowledgements

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