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Direct Decarboxylative Alkynylation of α,α-Difluoroarylacetic Acids under Transition Metal-Free Conditions

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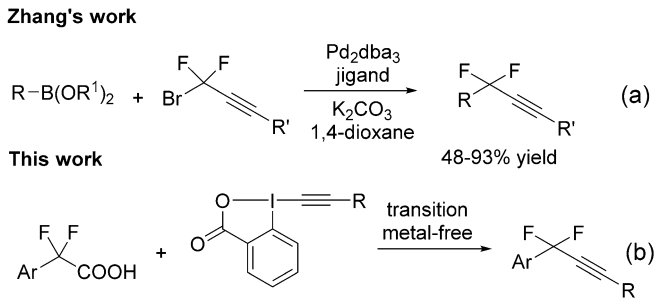
Abstract: An efficient and generally applicable protocol for decarboxylative coupling of α,α-difluoroarylacetic acids with ethynylbenziodoxolone (EBX) reagents has been developed, affording α,α-difluoromethylated alkynes bearing various functional groups in moderate to excellent yields. Remarkably, this potassium persulfate ($K_2S_2O_8$)-promoted reaction employs water as solvent under transition metal-free conditions, thus providing a green synthetic approach to α,α-difluoromethylated alkynes.

Keywords: alkynylation; decarboxylation; α,α-difluoroarylacetic acids; α,α-difluoromethylated alkynes; transition metal-free conditions

Fluorine-containing compounds are of great importance in pharmaceuticals, agrochemicals and material science.[1] Specifically, the difluoromethylene group (CF_2) plays an important role in medicinal chemistry because the incorporation of a difluoromethylene group into an organic molecule not only leads to profound changes of the compound's physical, chemical, and biological properties,[2] but also acts as a bioisostere of an oxygen atom or carbonyl group.[3] In particular, α,α-difluoromethylated alkynes have wide applications in organic synthesis, especially for the preparation of CF_2-containing compounds because the alkyne moiety could be easily functionalized by oxidation, reduction, addition or click reactions,[4] thus providing potential opportunities for new discoveries in medicinal chemistry.

Due to the their unique structure and properties, developing a simple and facile route to α,α-difluoromethylated alkynes is highly desirable. Traditional procedures for the preparation of α,α-difluoromethylated alkynes mainly rely on two synthetic approaches.[5–7] One is the direct difluoropropargylation of electrophiles (aldehydes or imines) with diverse *gem*-difluoropropargyl synthons, such as *gem*-difluoropropargylmetal or difluoropropargylindium complexes, but this approach is still suffering from the harsh reaction conditions and narrow substrate scope.[5] Another route to α,α-difluoromethylated alkynes is the direct transformation from *gem*-difluoropropargyl bromide or γ-bromodifluoroallenes and nucleophiles, affording the corresponding α,α-difluoromethylated alkynes in good yields. However, the multistep preparation and the unstable character of γ-bromodifluoroallenes restrict the wide application of these synthetic routes.[6] To resolve these limitations, just recently, Zhang and co-workers developed a palladium-catalyzed Suzuki-type reaction of *gem*-difluoropropargyl bromide with organoboron compounds, generating α,α-difluoromethylated alkynes as the products in high yields (Scheme 1a).[8] However, this pioneering work employed a water- and air-sensitive reagent, *gem*-difluoropropargyl bromide, as a difluoromethyl and alkyne source.

α,α-Difluoroarylacetic acids are easy to prepare, usually stable, and insensitive to moisture or air, and should serve as promising difluoromethylating reagents. Recently, Gouverneur and co-workers reported the preparation of difluoromethylarenes *via* a silver-catalyzed decarboxylative fluorination of α-fluoroarylacetic acid under mild conditions.[9] On the other hand, the reagent ethynylbenziodoxolone



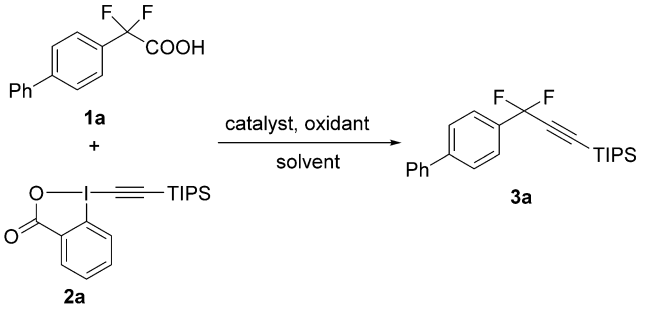
Scheme 1. Synthesis of α,α-difluoromethylated alkynes.

(EBX), which is prepared from commercially available 2-iodobenzoic acid and corresponding alkynylsilane,[10] is a safe and air-stable alkyne source that has found wide applications in decarboxylation, C–H bond activation and many other types of reactions in recent years.[11–14] Inspired by these reports, we envisioned a simple and facile construction of the difluoropropargyl moiety under transition metal-free conditions by using the above-mentioned α,α-difluoroarylacetic acids and ethynylbenziodoxolone (EBX) reagents as difluoromethyl and alkyne source, respectively, which would establish a new synthetic strategy for difluoropropargyl derivatives (Scheme 1b).

Initially, biphenyl-4-yl(difluoro)acetic acid (**1a**) and 1-[(triisopropylsilyl)-ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **2a**) were used as model substrates to optimize the reaction conditions. Using the typical $AgNO_3/K_2S_2O_8$ catalytic decarboxylative system,[15] the desired product **3a** could be obtained in 47% yield in aqueous media CH_3CN/H_2O (1 mL/1 mL) at 55 °C under air (Table 1, entry 1). To our delight, when the reaction was conducted under a nitrogen atmosphere, the yield was improved to 91% (Table 1, entry 2). Subsequently, other solvents such as CH_2Cl_2/H_2O (1 mL/1 mL), acetone/H_2O (1 mL/1 mL) or neat water were tested, and the CH_3CN/H_2O (1 mL/1 mL) was the best choice (Table 1, entries 3–5). Surprisingly, the reaction proceeded smoothly in the absence of silver catalyst, affording the desired product in a higher yield of 93%, while the reaction did not occur without the oxidant, indicating that the oxidant was essential for this reaction (Table 1, entries 6 and 7). Then, some other oxidants were checked, and among them, only $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ gave lower yields (Table 1, entries 8–12). Finally, some control experiments were also performed (Table 1, entries 13 and 14). For example, when the amount of oxidant was changed to 1.0 equiv., the yield decreased sharply to 30%, and the reaction did not occur at all at room temperature.

With the optimized conditions in hand, we next explored the substrate scope and the result was summarized in Table 2. First, the electronic effect of *gem*-di-

Table 1. Optimizing the reaction conditions.[a]

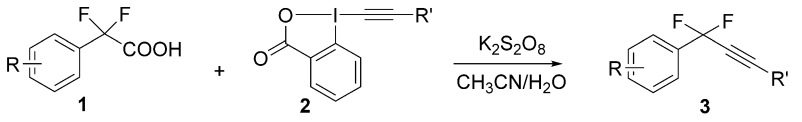


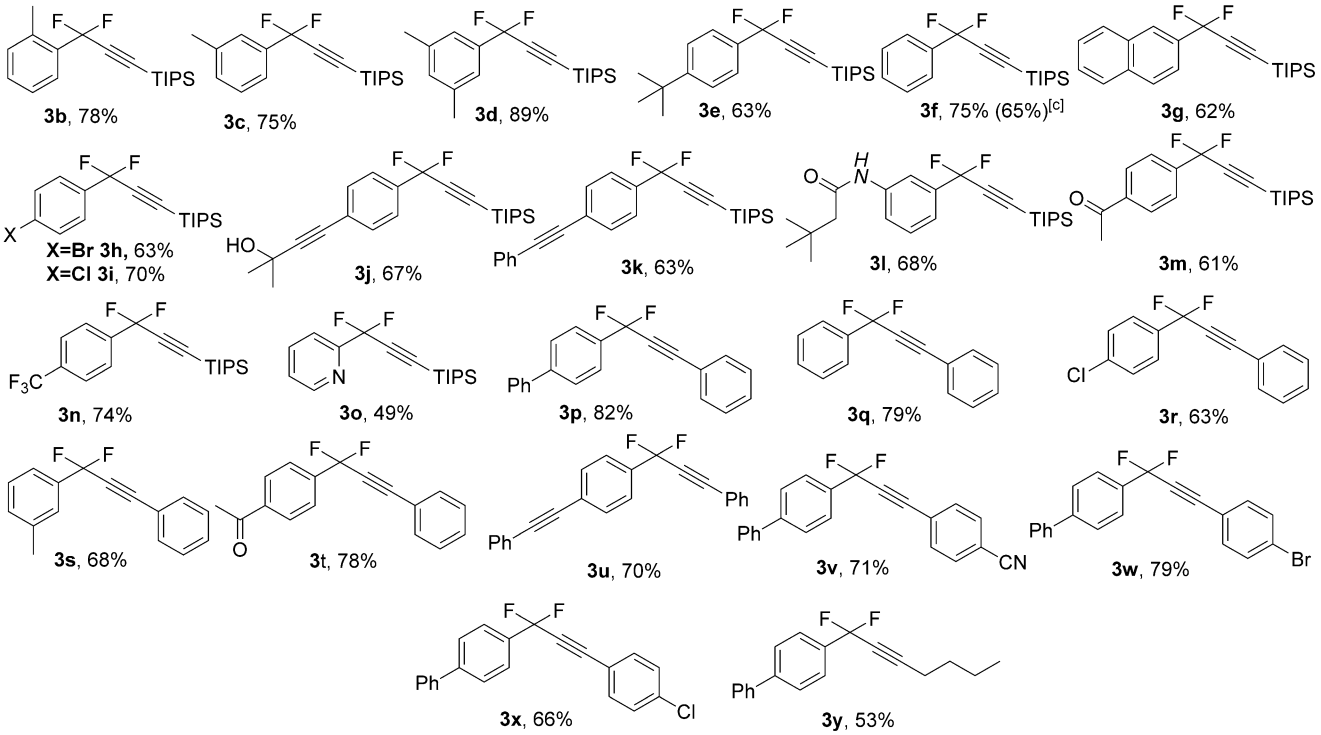
Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1[c]	$AgNO_3$	$K_2S_2O_8$	CH_3CN/H_2O	47
2	$AgNO_3$	$K_2S_2O_8$	CH_3CN/H_2O	91
3	$AgNO_3$	$K_2S_2O_8$	CH_2Cl_2/H_2O	trace
4	$AgNO_3$	$K_2S_2O_8$	acetone/H_2O	65
5	$AgNO_3$	$K_2S_2O_8$	H_2O	trace
6	$AgNO_3$	–	CH_3CN/H_2O	trace
7	**–**	**$K_2S_2O_8$**	**CH_3CN/H_2O**	**93**
8	–	$Na_2S_2O_8$	CH_3CN/H_2O	55
9	–	$(NH_4)_2S_2O_8$	CH_3CN/H_2O	28
10	–	$PhI(OAc)_2$	CH_3CN/H_2O	trace
11	–	TBHP	CH_3CN/H_2O	trace
12	–	BQ	CH_3CN/H_2O	trace
13[d]	–	$K_2S_2O_8$	CH_3CN/H_2O	30
14[e]	–	$K_2S_2O_8$	CH_3CN/H_2O	trace

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (20 mol), oxidant (2.0 equiv.), and solvent (2 mL) at 55 °C under a nitrogen atmosphere for 12 h.
[b] Yield of isolated product.
[c] Under air.
[d] 1.0 equiv. of oxidant was used.
[e] At room temperature.

fluoroarylacetic acids was examined, and the substrates bearing either electron-donating groups[16] or electron-withdrawing groups could be efficiently transformed into the corresponding *gem*-difluoromethylated alkynes in good to high yields (Table 2, **3a**–**3n**). To our delight, the desired product **3f** could be obtained in 65% yield even if the reaction was performed on a 2.0 mmol scale (Table 2, **3f**). The *gem*-difluoroarylacetic acids with a halogen atom at the *para*-position, which could be easily further functionalized, were also well tolerated in this reaction affording the desired products in good yields (Table 2, **3h** and **3i**). It was noteworthy that substrates bearing a synthetically valuable alkyne moiety were also successfully converted into the corresponding products in yields of 67% and 63%, respectively (Table 2, **3j** and **3k**). Moreover, the scope of electron-withdrawing groups could be successfully extended to $NHCOCHC(CH_3)_3$, $COCH_3$ and CF_3 (Table 2, **3l**–**3n**). Furthermore, N-heteroaromatic *gem*-difluoroarylacetic acids were also tolerated in this reaction, affording the desired product in 49% yield (Table 2, **3o**). Next,

Table 2. Decarboxylative coupling of *gem*-difluoroarylacetic acids with R-EBX.[a,b]

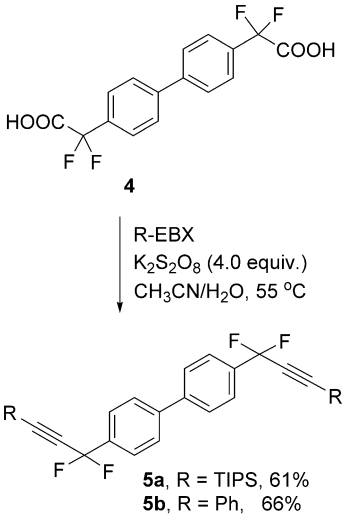




[a] *Reaction conditions:* **1** (0.20 mmol), **2** (0.22 mmol), $K_2S_2O_8$ (2.0 equiv.), CH_3CN (1.0 mL), and H_2O (1.0 mL) at 55 °C under a nitrogen atmosphere.
[b] Yield of isolated product.
[c] Reaction was performed on a 2.0 mmol scale.

different hypervalent alkynyl iodine reagents were also tested, and aryl-substituted EBXs worked well in this process (Table 2, **3p**–**3x**). For example, phenyl-EBX could be coupled with various *gem*-difluoroarylacetic acids efficiently, affording the products in good yields (Table 2, **3p**–**3u**). The reaction could be compatible with the reagents possessing a halogen atom (Cl or Br), thus providing an opportunity for further functionalization (Table 2, **3w**–**3x**). In addition, an alkyl-substituted EBX was also examined, and the desired product could be obtained in 53% yield (Table 2, **3y**).

To further establish the scope of this reaction, we next performed the reaction of 2,2′-([1,1′-biphenyl]-4,4′-diyl)bis(2,2-difluoroacetic acid) (**4a**) with TIP-EBX (**2a**) or Ph-EBX (**2b**) in the presence of 4.0 equiv. of $K_2S_2O_8$, and the corresponding product was obtained in 61% or 66% yields, respectively (Scheme 2). Given the synthetic value of alkynes, these products containing alkyne moieties might have

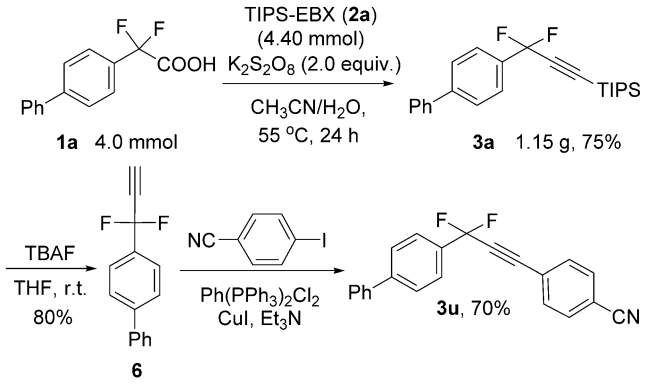


Scheme 2. Decarboxylative reaction of 2,2′-([1,1′-biphenyl]-4,4′-diyl)bis(2,2-difluoroacetic acid).

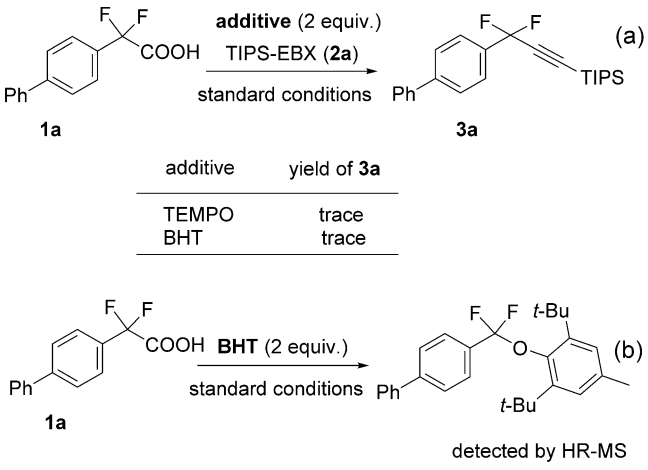
potential synthetic applications in the construction of complicated complexes in medicinal chemistry.

To highlight the synthetic utility of this protocol, a gram-scale experiment of biphenyl-4-yl(difluoro)-acetic acid (**1a**) with TIPS-EBX (**2a**) was performed under the standard conditions and the desired product could be obtained in 75% yield. Subsequently, the product **3a** was treated with TBAF, affording a terminal alkyne **6** as the product in 80% yield. Further transformation of the terminal alkyne **6** with 4-iodobenzonitrile was also conducted, and the corresponding product **3u** was obtained in 70% yield (Scheme 3).

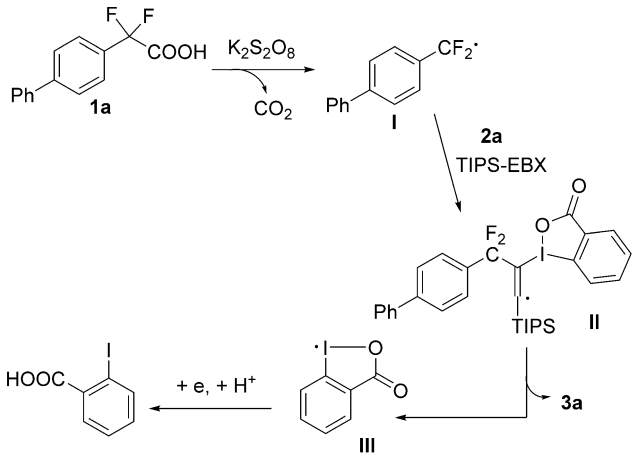
The mechanism was also preliminarily surveyed by adding radical scavengers (TEMPO or BHT) to the reaction system, and only a trace amount of desired product was detected (Scheme 4a). Furthermore, when the reaction of **1a** with BHT was performed under standard conditions, the product **7** could be detected by HR-MS, these results indicated that the reaction pathway probably involved a free radical process (Scheme 4b).



Scheme 3. Late-stage transformations.



Scheme 4. Mechanistic studies.



Scheme 5. Proposed mechanism.

On the basis of these above-mentioned results and previous reports,[12,17] a plausible mechanism is outlined in Scheme 5. First, in the presence of $K_2S_2O_8$, difluoroacetic acid **1a** underwent a decarboxylation process to generate a radical intermediate **I**, releasing a molecular carbon dioxide.[17] Then, the intermediate **I** reacted with TIPS-EBX (**2a**) to produce an adduct radical intermediate **II**, and β-elimination of the intermediate **II** would occur to afford the desired product **3a**, along with the formation of a benziodoxolonyl radical **III**. Finally, the radical **III** may be reduced by the remaining difluoroacetic acid to form 2-iodobenzoic acid through a reduction–protonation process.

In conclusion, we have developed an efficient and facile synthetic protocol for α,α-difluoromethylated alkynes through direct decarboxylative coupling of α,α-difluoroarylacetic acids and ethynylbenziodoxolone (EBX) reagents. Remarkably, this decarboxylative process could proceed smoothly in aqueous solution under transition metal-free conditions and was compatible with various functional groups. Moreover, this simple, mild and transition metal-free protocol could represent a new gateway to difluoromethylated alkynes, which should also belong to the green chemistry process.

Experimental Section

Typical Procedure

An oven-dried, 25-mL Schlenk tube was charged with the biphenyl-4-yl(difluoro)acetic acid **1a** (49.6 mg, 0.2 mmol), TIPS-EBX **2a** (94.0 mg, 0.22 mmol) and $K_2S_2O_8$, then H_2O/CH_3CN (1:1, 2.0 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred at 55 °C for 12 h. After the reaction was complete, the mixture was poured into H_2O (25 mL) and extracted with ethyl acetate three times. The combined organic layer was dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude product

was purified by flash chromatography on silica gel using hexane as the eluent to afford the pure product **3a**; yield: 71.0 mg (93%).

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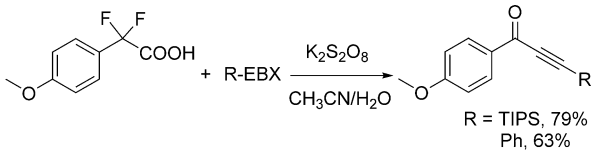
[16] When the substrate 2,2-difluoro-2-(4-methoxyphenyl)-acetic acid was used, the corresponding ynones were obtained as major products instead of the direct decarboxylative products.



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