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Silver-Catalyzed Decarboxylative Alkynylation of α,α-Difluoroarylacetic Acids with Ethynylbenziodoxolone Reagents

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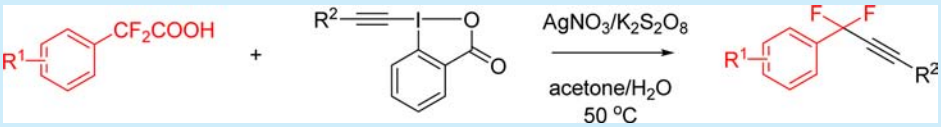
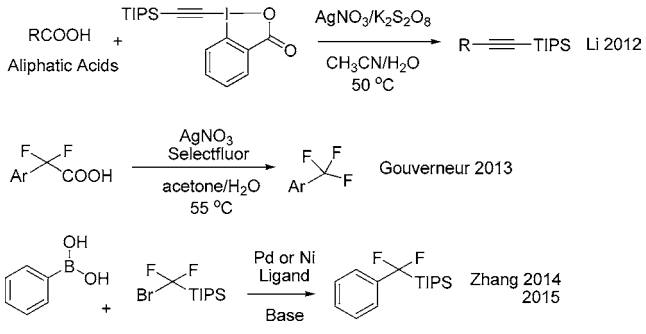
Supporting Information



ABSTRACT: A decarboxylating alkynylation of α,α-difluoroarylacetic acids with ethynylbenziodoxolone reagents is reported. $AgNO_3$ serves as the catalyst and $K_2S_2O_8$ as the oxidant. A series of functional groups were tolerated, and moderate to good yields were obtained.

Compounds containing a difluoromethylene subunit are synthetically useful as intermediates en route to pharmaceuticals, agrochemicals, and materials. The effect of the fluorine atom to remarkably enhance the lipophilicity, stability, and bioavailability of the parent compounds attributes to this development.[1] Traditionally, difluoromethylene groups are introduced via deoxyfluorination of aldehydes or ketones with aminosulfur trifluorides, XeF_2, or F_2.[2] However, the drawbacks of these methodologies include the use of expensive and toxic reagents, harsh conditions, and incompatibility with a range of functional groups. Hence, transition-metal-catalyzed difluoromethylation offers an attractive alternative. Recently, various methods were reported for the cross-coupling of a CF_2-moiety with sp^2-carbon atoms.[3] For example, Zhang et al. reported on copper-, palladium-, and nickel-catalyzed difluoroalkylations of arylboronic acids, haloarenes, alkenes, isocyanides, and heteroarylborons (Scheme 1).[4] Although these efficient methods employ commercially available or easily accessible bromodifluoromethylated building blocks, a direct cross-coupling of a CF_2 unit and an sp-carbon has not been reported so far. On one hand, Li reported a silver-catalyzed decarboxylative alkynylation[5] of aliphatic carboxylic acids with air stable and nontoxic ethynylbenziodoxolone (EBX)[6] reagents. On the other hand, Gouverneur[7] published a decarboxylative fluorination of α,α-difluoroarylacetic acids. This method demonstrated that α,α-difluoroarylacetic acids are stable and easily accessible compounds that can be used as building blocks in difluoromethylations. Very recently, Hao[8] reported silver-catalyzed difluoroalkylation of isocyanides with α,α-difluoroarylacetates. By combining these pioneering works, we report herein a new silver-catalyzed decarboxylative alkynylation of α,α-difluoroarylacetic acids with EBX reagents.

Scheme 1. Previous Work



Initially, we chose commercially available 2,2-difluoro-2-phenylacetic acid (**1a**) and Ph-EBX (**2a**) as a model system to optimize the reaction conditions. Indeed, under the optimized reaction conditions of Li (Table 1, entry 1), 72% of **3a** were generated. However, GC−MS analysis of the product revealed that at least two byproducts were formed (see Scheme 2). One of the two products could be isolated. It turned out to be the product of a radical/radical recombination. The other product was only detected in traces by GC−MS. The fragmentation indicates that this product results from radical addition to the product **3a**. Among various solvents that were tested (entries 2−5), only acetone/H_2O delivered a good yield with perfect selectivity. Other oxidants were tested as well (entries 6 and 7) but without success. $K_2S_2O_8$ is crucial for the reaction,[9] and no products were obtained without it (entry 8). Other EBX derivatives (entry 9) or lower temperature (entry 10) were tested as well, but no desired product was generated.

Encouraged by this preliminary result, we explored the scope with respect to the α,α-difluoroarylacetic acids (Table 2). The efficiency of the reaction was independent of a methyl substitution at the arene core and on the attached position

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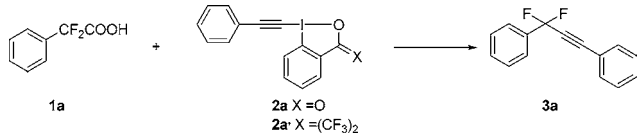
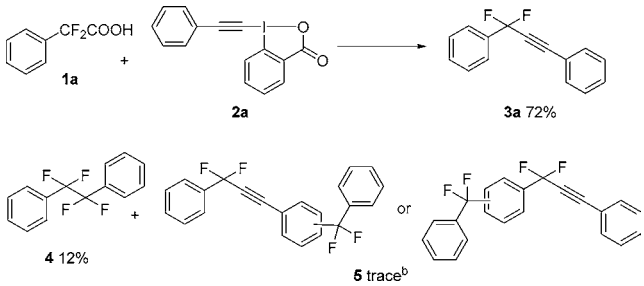
Table 1. Optimization of the Decarboxylative Alkynylation of α,α-Difluoroarylacetic Acid[a]



entry	cat. (equiv)	oxidant (equiv)	solvent	temp (°C)	yield[a] (%)
1	$AgNO_3$(0.25)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:1)	50	72[b]
2	$AgNO_3$(0.25)	$K_2S_2O_8$ (2.0)	THF/H_2O (1:1)	50	nr[c]
3	$AgNO_3$(0.25)	$K_2S_2O_8$ (2.0)	CH_2Cl_2/H_2O (1:1)	50	nr
4	$AgNO_3$(0.25)	$K_2S_2O_8$(2.0)	CH_3CN	50	nr
5	$AgNO_3$(0.25)	$K_2S_2O_8$(2.0)	acetone/H_2O (1:1)	50	76
6	$AgNO_3$(0.25)	$PhI(OAc)_2$ (2.0)	acetone/H_2O (1:1)	50	nr
7	$AgNO_3$(0.25)	tBuOOH (2.0)	acetone/H_2O (1:1)	50	nr
8	$AgNO_3$(0.25)		acetone/H_2O (1:1)	50	nr
9	$AgNO_3$(0.25)	$K_2S_2O_8$ (2.0)	acetone/H_2O (1:1)	50	nr[d]
10	$AgNO_3$(0.25)	$K_2S_2O_8$ (2.0)	acetone/H_2O (1:1)	rt	nr

[a]Reaction conditions: **1a** (0.125 mmol), **2a** (0.125 mmol), catalyst (0.25 equiv), oxidant (2.0 equiv), and solvent (2 mL) at 50 °C for 24 h. [b]See Scheme 2. [c]GC−MS indicated that 2-(phenylethynyl)-tetrahydrofuran was generated; see ref 10. [d]**2a′** was used.

Scheme 2. Byproducts of Entry 1[a]

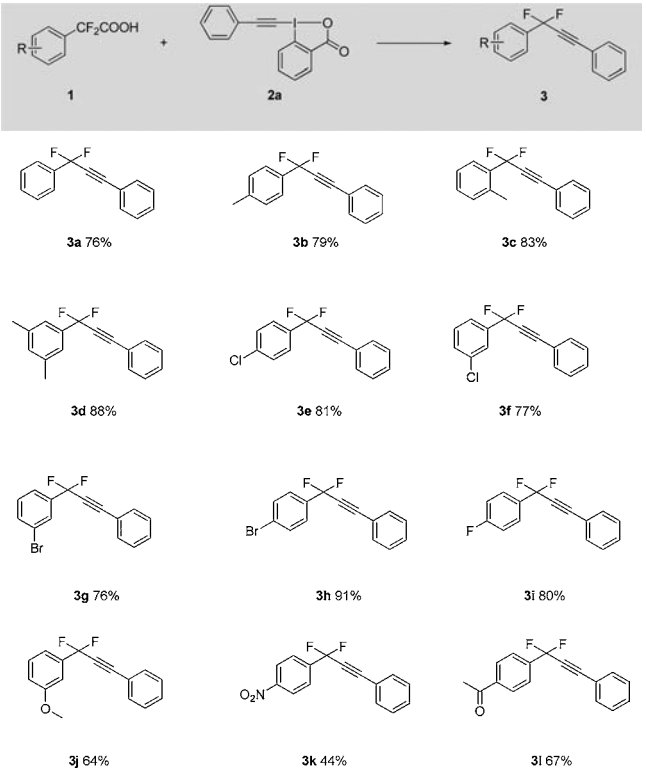


[a]Reaction conditions: **1a** (0.125 mmol), **2a** (0.125 mmol), $AgNO_3$ (0.25equiv), $K_2S_2O_8$ (2.0 equiv), and CH_3CN/H_2O (1:1) (2 mL) at 50 °C for 24 h. [b]Determined by GC-MS, ^1H NMR showed a mixture of several compounds.

(**3b−d**). Even a meta,meta disubstitution of the aromatic ring did not affect the reactivity (**3d**). To our delight, para halogen-substituted substrates (F, Br, Cl) gave the desired products in up to 91% yield (**3e**, **3h**, **3i**). However, halogens in the meta position led to a slight drop in yields (**3f**, **3g**). A nitro-substituted product (**3k**) was isolated in only 44% yield, which might originate from the ability of the nitro group to act as a radical inhibitor.[11] An acetyl-substituted product (**3j**) and a methoxy-substituted product (**3l**) were isolated in 64% and 67% yield, respectively. A hexyl substituent as representative for an alkylalkyne only delivered a complex mixture.

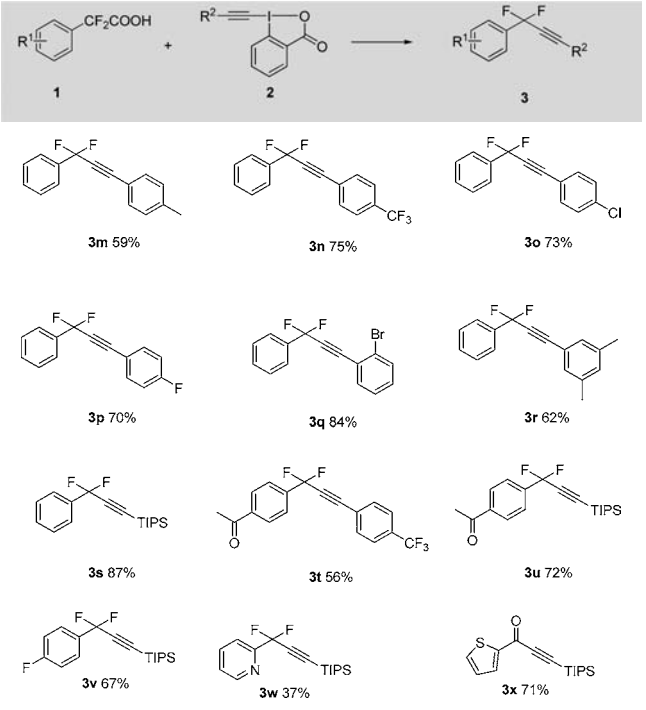
We then studied the reactivity of various EBX reagents (Table 3). A CF_3 group (**3n**) and halogen-substituted (**3o**, **3p**, **3q**) substrates gave yields comparable to those of the model reaction, while methyl substituents on the aryl motif

Table 2. Scope with Respect to the α,α-Difluoroarylacetic Acids[a]



[a]Reaction conditions: **1** (0.125 mmol), **2a** (0.125 mmol), $AgNO_3$ (0.25 equiv), $K_2S_2O_8$ (2.0 equiv), and acetone/H_2O (1:1) (2 mL) at 50 °C for 24 h.

Table 3. Scope with Regard to the EBX Derivatives[a]



[a]Reaction conditions: **1** (0.125 mmol), **2** (0.125 mmol), $AgNO_3$ (0.25 equiv), $K_2S_2O_8$ (2.0 equiv), and acetone/H_2O (1:1) (2 mL) at 50 °C for 24 h.

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reduced the yield (**3m**, **3r**). TIPS−EBX was tolerated as well (**3s**, **3u**, **3v**). Electron-withdrawing groups at the α,α-difluoroarylacetic acid and the EBX reagent just slightly lowered the yield (**3t**). Next, we studied electron-poor and electron-rich heterocyclic substrates as well. While the pyridine substituted substrate gave a low yield of the desired product (**3w**), only a byproduct was obtained in the case of a thiophene substituent (**3x**); this might be rationalized by the weakened C−F bond bearing an electron-rich group nearby.

In conclusion, we describe an efficient and direct decarboxylative cross-coupling of α,α-difluoroarylacetic acids and EBX regents. This method is easily operational under mild conditions. In addition, this system shows a good compatibility with a wide range of functional groups an important feature for further applications in more complex systems.

■ ASSOCIATED CONTENT

Supporting Information

TThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01188.

Detailed experimental procedures, characterization data, and copies of ^{1}H- and ^{13}C NMR spectra for all previously unknown products (PDF)

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Notes

The authors declare no competing financial interest.

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