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Palladium-Catalyzed Benzodifluoroalkylation of Alkynes: A Route to Fluorine-Containing 1,1-Diarylethylenes

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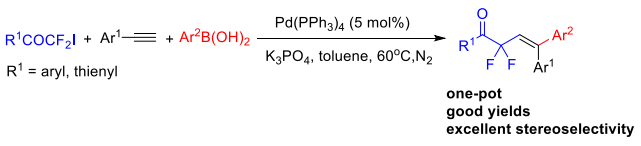
Abstract. A palladium(0)-catalyzed three-component reaction of 2-iodo-2,2-difluoroacetophenones, alkynes and arylboronic acids is introduced for the synthesis of 1-benzoyldifluoromethyl-2,2-diphenylethylenes in good yields and with excellent stereoselectivity. The 1-benzoyldifluoromethyl-2,2-diphenylethylene products synthesized through a radical reaction process are versatile synthons for the construction of various fluorine-containing compounds, which have antiproliferative activity on human tumor cells.

Keywords: multicomponent reactions; 2-iodo-2,2-difluoroacetophenones; 1-benzoyldifluoromethyl-2,2-diphenylethylenes; palladium; antiproliferative activity

The introduction of *gem*-difluoroalkyl motifs into molecules can improve their physicochemical and biological properties.[1] Consequently, the efficient synthesis of *gem*-difluoroalkylated compounds has attracted increasing attention.[2] However, most research has focused on the gem-difluoroalkylation of aromatic compounds,[3] with methods to afford gem-difluoroalkylated alkenes much less explored. Traditionally, the synthesis of *gem*-difluoroalkylated alkenes was achieved by the difluoroalkylation of alkenyl halides,[4] ethyl bromodifluoroacetate through cross-coupling reactions with alkenes or radical addition reaction of alkynes, [5] Copper or iron catalyzed decarboxylative difluoromethylations of alkenes.[6] Our group has reported iododifluoromethyl ketones as alternative difluoroalkylation agents to generate *gem*-difluoroalkylated alkenes *via* radical reactions with terminal and internal alkynes.[7]

Multicomponent reactions have proven to be an efficient and powerful tool in organic synthesis [8] and have been applied to synthesize series of fluoroalkylated unsaturated compounds successfully in recent years.[9] Pd-catalyzed three-component reactions of terminal alkynes or internal alkynes, boronic acids, and perfluoroalkyl iodides for quickly access to trisubstituted or tetrasubstituted alkenes containing perfluoroalkyl groups have been reported by Nevado[9a, 9b] and Chaładaj[9c] groups, respectively. Liang used ethyl difluoroiodoacetate as a difluoroalkylation agent in multicomponent reaction to construct a variety of *gem*-difluoroalkylated alkenes in the present of transition-metal catalysts.[9d-f] However, direct introduction of more complicated CF_2-containing moieties into alkynes *via* multicomponent reaction is still a challenge task.

Spontaneous carbonylation and perfluoroalkylation/difluoroalkylation reactions have been achieved *via* the Pd-catalyzed four-component reactions with iodopolyfluoroalkanes, alkynes, boronic acids and carbon monoxide.[10] We recently focused on the introduction of benzoyldifluoroalkyl groups to different scaffolds by using iododifluoromethyl ketones as difluoroalkylation agents.[7, 11] We have accomplished the synthesis of 1-benzoyldifluoromethyl-2,2-diphenylethylenes through multistep reactions involving iododifluoromethylation of alkyne using 2-iodo-2,2-difluoroacetophenone followed by cross-coupling reaction with phenylboronic acid.[7] On the basis of previous work, we proposed that spontaneous introduction of the benzoyldifluoroalkyl group and an aryl group into alkynes could be achieved in a one-pot operation. Herein, we report a Pd(0)-catalyzed three-component reaction of 2-iodo-2,2-difluoroacetophenones, alkynes and arylboronic acids producing 1-benzoyldifluoromethyl-2,2-diphenylethylenes in a highly stereoselective manner (Scheme 1).



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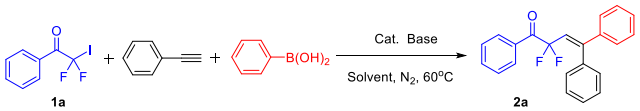
Scheme 1. The synthesis of benzoyldifluoro-1,1-diarylethylene

We began the optimization of reaction conditions by selecting the addition of 2,2-difluoro-2-iodo-1-phenylethanone **1a** and phenylboronic acid to ethynylbenzene as a model reaction. Gratifyingly, the reaction proceeded smoothly in toluene with K_2CO_3 as a base catalyzed by either Pd(0) or Pd(II) at 60°C under nitrogen, leading to the desired product 2,2-difluoro-1,4,4-triphenylbut-3-en-1-one **2a** in moderate yields (Table 1, entries 1 and 2). Since $Pd(PPh_3)_4$ is cheaper and more available than $PdCl_2(PPh_3)_2$, we chose $Pd(PPh_3)_4$ as optimized catalyst. Control reaction demonstrated that no reaction occurred in the absence of base (Table 1, entries 3). Screening of base and solvents (Table 1, entries 4-8) indicated that K_3PO_4 and toluene were the most suitable base and solvent (Table 1, entry 5). Increasing or decreasing the temperature failed to improve the yield of product **2a** (Table 1, entries 9-10). When the catalyst loading was reduced to 4 mol%, desired product **4a** was observed in a decreased yield (Table 1, entry 11). Consequently, the optimized reaction conditions were confirmed by using $Pd(PPh_3)_4$ as catalyst in the presence of K_3PO_4 in toluene at 60°C under nitrogen (Table 1, entry 5).

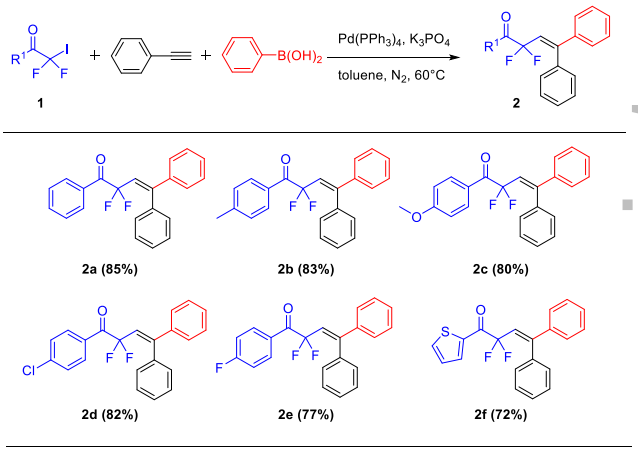
Table 1. Optimization of the reaction conditions for difluoroalkylation of alkynes.[a]



Entry	Catalyst (mol%)	base	solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$ (5)	K_2CO_3	toluene	63
2	$PdCl_2(PPh_3)_2$ (5)	K_2CO_3	toluene	50
3	$Pd(PPh_3)_4$ (5)	-	toluene	0
4	$Pd(PPh_3)_4$ (5)	$CsCO_3$	toluene	60
5	$Pd(PPh_3)_4$ (5)	K_3PO_4	toluene	89
6	$Pd(PPh_3)_4$ (5)	K_3PO_4	1,4-dioxane	25
7	$Pd(PPh_3)_4$ (5)	K_3PO_4	THF	14
8	$Pd(PPh_3)_4$ (5)	K_3PO_4	CH_3CN	0
9[c]	$Pd(PPh_3)_4$ (5)	K_3PO_4	toluene	57
10[d]	$Pd(PPh_3)_4$ (5)	K_3PO_4	toluene	70
11	$Pd(PPh_3)_4$ (4)	K_3PO_4	toluene	60

[a] Reaction conditions: **1a** (1.0 mmol), ethynylbenzene (1.2 mmol), phenylboronic acid (1.0 mmol), toluene (2.0 ml), 12h, under N_2.
[b] GC yield.
[c] Performed at 40 °C.
[d] Performed at 80 °C.

With the optimized reaction conditions in hand, we set out to explore the scope and generality of the three-component reaction. First, idifferent 2-iodo-2,2-difluoroacetophenones were investigated in combination with ethynylbenzene and phenylboroaaaanic acid (Scheme 2). Electron-donating groups in the aromatic ring were well tolerated and gave the expected trisubstituted benzoyldifluoro alkenes **2a**–**2c** in high yield as well as halogen atoms (**2d** and **2e**). Whereas, the presence of electron-withdrawing group, such as trifluoromethyl, brought negative influence in the reaction efficiency, resulting in no corresponding product but the recovery of starting materials. When 2,2-difluoro-2-iodo-1-(thiophen-2-yl)ethan-1-one **1f** was employed in the three-component reaction, the expected product **2f** was obtained in moderate yield.



Scheme 2. Scope of 2-iodo-2,2-difluoroacetophenones.

The scope of alkynes and arylboronic acids were explored next (Scheme 3). Aryl alkynes bearing both electron-donating as well as electron-withdrawing groups were tested in combination with **1a** and phenylboronic acid providing the corresponding 1-benzoyldifluoromethyl-2,2-diphenylethylenes (**3a**–**3i**) in good yields with perfect stereocontrol as single isomers. X-ray diffraction analysis of compound **3f** confirmed the structural assignment of the reaction products (Figure 1).[12] 2-Ethynyl-6-methoxynaphthalene was found to undergo the reaction smoothly to give the corresponding product **3i** in 64% yield. However, alkyl-substituted alkynes were not suitable substrates. To our delight, the internal alkyne prop-1-yn-1-ylbenzene is also a competent substrate, providing the corresponding product **3j** in low yield. A number of arylboronic acids were investigated next. In general, electronic properties of substituents on the phenyl group of boronic acids did not have significant effect on the reaction efficiency. The corresponding products **3k**–**3t** were obtained in moderate to good yields with excellent stereoselectivity. Also, the naphthyl and thienyl substrates worked well and gave the corresponding products **3s** and **3t** in moderate yields. It is worth mentioning that the alkyne with a 3,4,5-trimethoxy substituent on the aryl group participated efficiently in the reaction to give the corresponding product **3u** in 69% yield.

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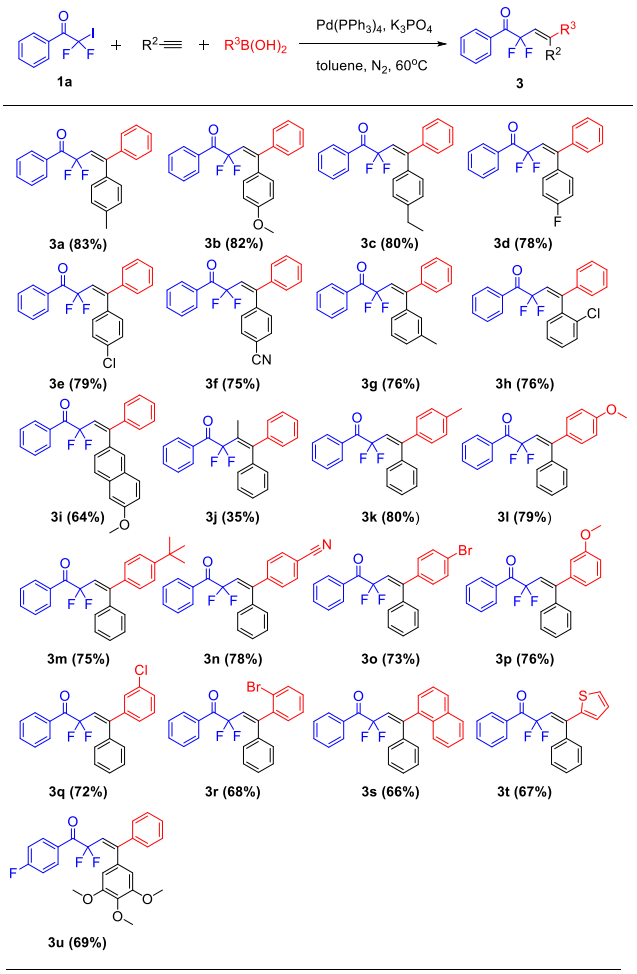


Scheme 3. Scope of alkynes and arylboronic acids.

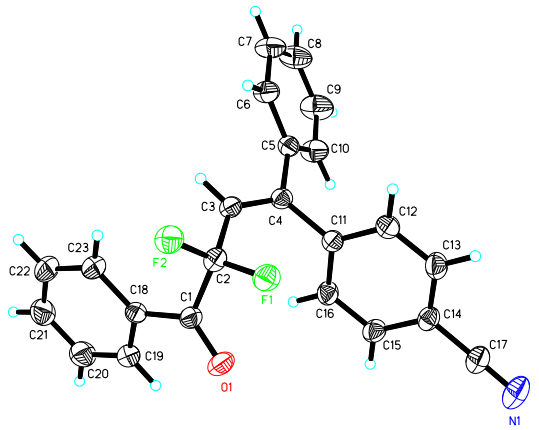
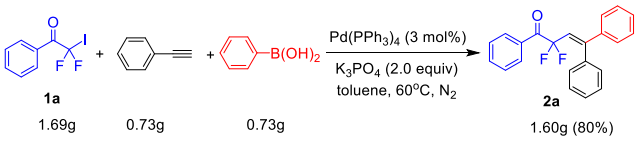


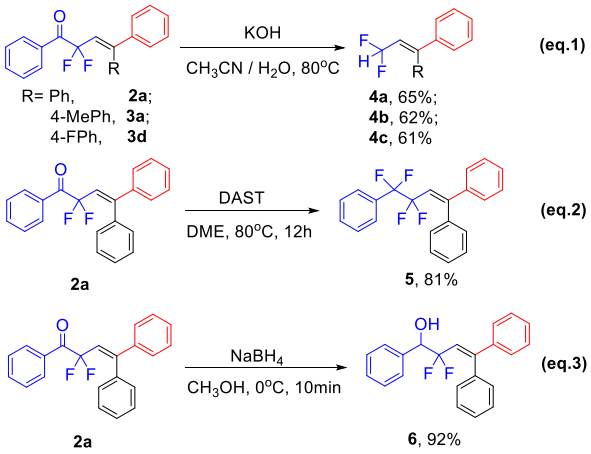
Figure 1. Crystal structure of compound **3f**.

We also carried out a gram-scale reaction which gave product **2a** in high yield of 80%. This result could be achieved by reducing the amount of Pd catalyst to 3 mol% of substrate **1a** (Scheme 4).



Scheme 4. Gram-scale reaction.

The benzoyl group in the products from the three-component reaction is a versatile functional group, which could be readily transformed to a variety of interesting fluorinated moiety. New methods to introduce difluoromethyl ($-CF_2H$) group or tetrafluoroethylene ($-CF_2CF_2-$) group are high demand due to their wide application in pharmaceutical and materials.[13] Hartwig had reported the synthesis of (difluoromethyl)benzene via Haller-Bauer reaction of α-phenyl-α,α-difluoroacetophenone.[14] Hence, in the transformations several 2-difluoromethyl-1,1-diarylethylenes **4** have been readily synthesized from debenzoylation of compounds **2a**, **3a** and **3c** respectively by using Hartwig's procedure (Scheme 5, eq. 1). Moreover, much attention has been paid to the development of new synthetic method for the synthesis of compounds contain $-CF_2CF_2-$ fragment.[15] In this work, we efficiently obtained the $-CF_2CF_2-$ eoxofluorination of carbonyl group in compound **2a** (Scheme 5, eq. 2). These two reactions demonstrate the wide and valuable application of the three-component reaction in synthetic organofluorine chemistry. More transformation was achieved through the conversion of carbonyl group into hydroxyl group (Scheme 5, eq. 3), providing additional evidence for the flexibility of this methodology.



Scheme 5. Further transformation reactions.

Considering that the trisubstituted alkene scaffold is a key structure found in numerous nature products as well as pharmaceuticals,[16] we speculated that the fluorinated trisubstituted alkenes **2** and **3** obtained from this three-component reaction might have potential antitumor activity. The antiproliferative

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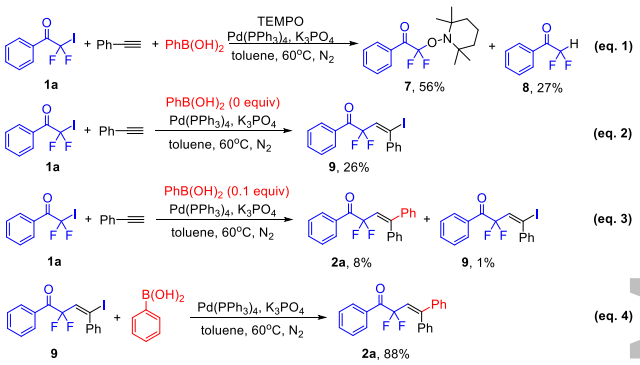
activity of the selected compounds was evaluated on six human tumor cells, namely, HeLa, A549, HTC-116, HepG2, MKN45 and MGC-803 by using Combretastatin A-4 (CA-4) as the positive control. The results are summarized in Table 2 and indicated that compounds with benzoyldifluoro-1,1-diarylethylene scaffold present certain antiproliferative activity on the human tumor cells and could be used for developing potential new antitumor drugs via further structure-activity relationship study.

Table 2 Inhibitory activities of selected compounds on cell proliferation.

Compound	Cellular IC_{50} (μmol/mL)					
	HeLa	A549	HTC-116	HepG2	MKN45	MGC-803
2b	76.23	452.30	79.54	29.99	57.31	84.81
2c	143.10	14.57	22.99	13.49	49.74	39.36
3f	14.32	28.60	23.64	49.49	35.30	34.61
3j	77.42	396.10	73.36	63.06	73.98	79.63
3n	91.63	115.40	126.60	83.75	95.09	86.62
3t	17.56	36.90	18.58	16.68	78.32	19.89
CA-4	11.33	5.99	9.00	16.04	3.42	1.76

Three control experiments were designed to rationalize the reaction pathway. First, we added the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the three-component reaction under standard conditions. No desired product **2a** was obtained; instead, compound **7** and **8** was detected in 56% and 27% yield respectively (^{19}F NMR δ -55.70 for compound **1a**, δ -71.76 for compound **7**, δ -121.79 for compound **8**, see the Supporting Information) (Scheme 6, eq. 1). The result seems to support that a *gem*-difluoroalkyl radical addition pathway might be involved in this process. Then, the reaction of compound **1a** with ethynylbenzene in the absence of phenylboronic acid were carried out to check whether iododifluoroalkylation product **9** could be afforded under our standard condition (Scheme 6, eq. 2). We observed the formation of vinyl iodide **9** in low yield. However, the addition of a catalytic amount of phenylboronic acid (10 mol%) led to the formation of three-component reaction product **2a** with trace amount of vinyl iodide **9** (Scheme 6, eq. 3). Moreover, the vinyl iodide **9** was independently obtained and used to react with phenylboronic acid under standard conditions. The expect Suzuki coupling product **2a** was obtained in high yield (Scheme 6, eq. 4). Additionally, small amount (ca. 19%) of vinyl iodide intermediate **9** was observed at the beginning of the reaction gradually decreases with time. These results indicated that the vinyl iodide **9** might be formed in the one-pot process.

On the basis of the control experiments and literature data,[9] we proposed a reaction mechanism shown in Scheme 7. As depicted, Pd(0) species reacts with benzoyldifluoroalkylation agent **1** to form benzoyldifluoroalkyl radical and Pd(I) species **A** through an iodine atom transfer process. The benzoyldifluoroalkyl radical adds to the alkyne

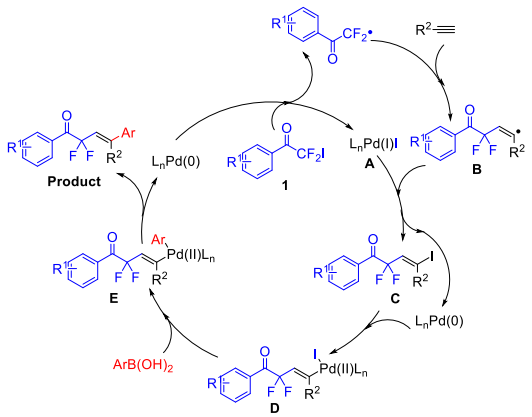


Scheme 6. Control experiments.

moiety to generate the vinyl radical **B**, which could be transferred to the corresponding vinyl iodide **C** *via* atom transfer of iodine from the Pd(I) species **A** accompanied by regenerative Pd(0) species. Then, the vinyl iodide intermediate **C** is capable of coupling with boronic acid through the typical oxidative addition, transmetalation and reductive elimination pathway to form the Suzuki coupling product 1-benzoyldifluoromethyl-2,2-diphenylethyl enes while regenerating Pd(0).

In conclusion, we have successfully developed a Pd(0)-catalyzed three-component difluoroalkylation of alkynes with 2-iodo-2,2-difluoroacetophenones and (hetero)arylboronic acids, generating 1-benzoyldifluoromethyl-2,2-diphenylethyl enes with complete stereocontrol. The reaction provides a general method for the construction of various gem-difluoroalkylated compounds in excellent stereoselectivities. Bioactivity test showed that the compounds with benzoyldifluoro-1,1-diarylethylene scaffold could be developed as potential antitumor drug. Preliminary mechanistic investigation indicated that the formation of the vinyl iodide intermediate was involved in this radical-mediate transformation.

Further synthetic application of the three-component reaction and structure-activity relationship study of the target compounds are currently underway in our laboratory.



Scheme 7. Plausible mechanism.

Experimental Section

General procedure for one-pot Synthesis of Benzoyldifluoro-1,1-Diarylethylenes 2: An oven-dried tube was charged with Phenylboronic acid (1.0 mmol, 1.0 equiv), K_3PO_4 (2.0 mmol, 2.0 equiv), and $Pd(PPh_3)_4$ (0.05 mmol, 5 mol %). The tube was evacuated and backfilled with nitrogen (repeated three times). Then, 2-iodo-2,2-difluoroacetophenones **1** (1.0 mmol, 1.0 equiv) dissolved in toluene (2.0 mL), and Phenylacetylene (1.2 mmol, 1.2equiv) were added into the tube. The reaction mixture was stirring at 60 °C for 6-12 h. After completion of the reaction (as indicated by TLC), the reaction was quenched with water, and the reaction mixture was extracted with ethyl acetate (3*10 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, concentrated in vacuum and the crude residue was purified by silica-gel column chromatography (petroleum ether/EtOAc = 100/1) to afford the desired product **2**.

Acknowledgements

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[12] CCDC 1585704 (**3f**) contains the supplementary crystallographic data for this update. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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Palladium-Catalyzed Benzodifluoroalkylation of Alkynes: A Route to Fluorine-Containing 1,1-Diarylethylenes

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