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Palladium-Catalyzed Trifluoroethylation of Terminal Alkynes with 1,1,1-Trifluoro-2-iodoethane

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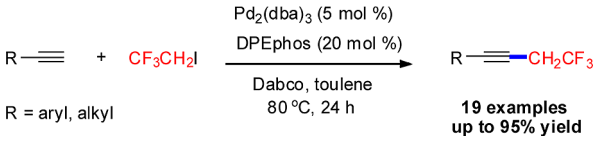
ABSTRACT



An efficient C_{sp}–CH_2CF_3 bond-forming reaction via Pd-catalyzed 2,2,2-trifluoroethylation of aryl and alkyl terminal alkynes has been developed. This protocol proceeds under mild conditions using the readily available and cheap reagent CF_3CH_2I as the source of the CH_2CF_3 group. Various terminal aryl alkynes as well as alkylacetylenes can be transformed into the corresponding trifluoroethylated products in good-to-excellent yields. The method is tolerant of carbonyl, nitro, ester, cyano, and even formyl groups.

The incorporation of fluorine atoms into organic molecules can profoundly influence their chemical and biological activities, such as lipophilicity, metabolic stability, and bioavailability.[1] As a result, much attention has been paid to the development of an appropriate method for the incorporation of fluoroalkyl groups into functional organic structures.[2] In this context, considerable progress has been made in the use of 1,1,1-trifluoro-2-iodoethane (CF_3CH_2I) to form C_{sp^3}–CH_2CF_3 or C_{sp^2}–CH_2CF_3 bonds.[3] For instance, McLoughlin and Thrower groups reported Cu(0)-promoted 2,2,2-trifluoroethylation reactions of iodoaromatic compounds with CF_3CH_2I in 1969.[4] Recently, the Hu[5] and Zou[6] groups respectively reported the palladium-catalyzed

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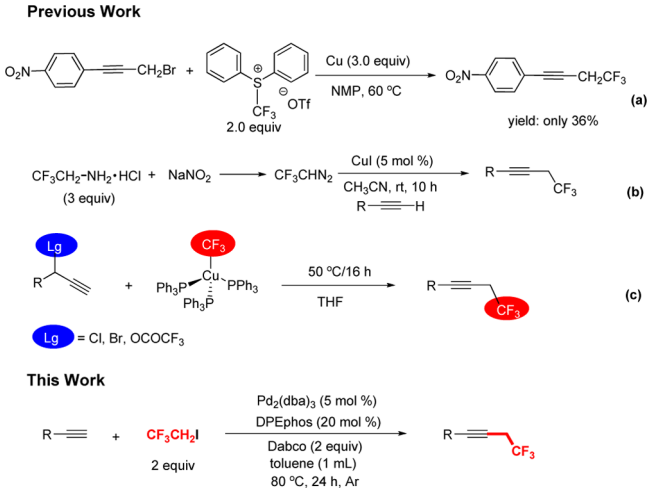
2,2,2-trifluoroethylation of organoboronic acids and esters with readily available 1,1,1-trifluoro-2-iodoethane.

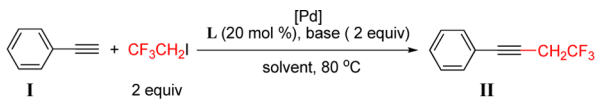
Notably, trifluoroethylated acetylenes are useful organic intermediates. While methods for the construction of C_{sp}-CH_2CF_3 bonds have remained rare, the Shibata group has documented a copper-mediated protocol for the preparation of 1-nitro-4-(4,4,4-trifluorobut-1-ynyl)benzene, but the yield was only 36% (Scheme 1a).[7] In addition, the copper-catalyzed direct 2,2,2-trifluoroethylation of terminal alkynes with pregenerated 2,2,2-trifluorodiazoethane was reported by the Ma group in 2012. The drawback of this method is the need to preprepare the gaseous 2,2,2-trifluorodiazoethane from 2,2,2-trifluoroethylamine hydrochloride and sodium nitrite (Scheme 1b).[8] Meanwhile, the Szabo group developed a copper-mediated trifluoromethylation of propargylic halides and trifluoroacetates, which require prefunctionalization of terminal alkynes (Scheme 1c).[9] Herein, we describe a direct palladium-catalyzed method for 2,2,2-trifluoroethylation of terminal alkynes with readily available 1,1,1-trifluoro-2-iodoethane (CF_3CH_2I). The direct trifluoroethylation of C_{sp}−H bonds represents a straightforward and functional group tolerant protocol applicable for preparation of a broad range of trifluoroethylated acetylenes in moderate-to-excellent yields.

Scheme 1. Synthetic Protocols of Trifluoroethylated Acetylenes

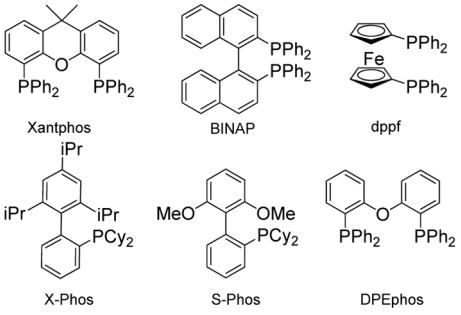


Our study began with the cross-coupling of phenylacetylene (**I**) with the CF_3CH_2I. Initially we examined direct 2,2,2-trifluoroethylation in the presence of $Pd_2(dba)_3$ (5 mol %), Xantphos (20 mol %), and Cs_2CO_3 (2.0 equiv) in 1,4-dioxane at 80 °C, which is similar to previously reported reaction conditions.[5] Fortunately, the desired product was detected, although the yield was very low (Table 1, entry 1). With the aim of improving the desired product yield, different organic solvents were examined, and $PhCH_3$ gave the best yield compared with other solvents (Table 1, entries 2−6). To our surprise, screening different monodentate and bidentate phosphine ligands (Table 1, entries 7−11) led to the discovery that DPEphos was an effective ligand, forming the product in 72% yield (Table 1, entry 11). Reasoning that a base might play an important role in this reaction, we tested several inorganic (Table1, entries 12−15) and organic bases (Table1, entries 16 and 17). It was found that 1,4-diazabicyclo[2.2.2]octane (Dabco) could provide the most efficient yield of 86% (Table 1, entry 17), while other organic and inorganic bases

Table 1. Optimization of the Reaction Conditions[a]



entry	Pd source	ligand	base	solvent	^{19}F NMR yield of **II** (%)
1	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	1,4-dioxane	11
2	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	DMF	5
3	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	DMSO	20
4	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	DCE	9
5	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	CH_3CN	trace
6	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	$PhCH_3$	60
7	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	$PhCH_3$	15
8	$Pd_2(dba)_3$	dppf	Cs_2CO_3	$PhCH_3$	33
9	$Pd_2(dba)_3$	X-Phos	Cs_2CO_3	$PhCH_3$	12
10	$Pd_2(dba)_3$	S-Phos	Cs_2CO_3	$PhCH_3$	16
11	$Pd_2(dba)_3$	DPEphos	Cs_2CO_3	$PhCH_3$	72
12	$Pd_2(dba)_3$	DPEphos	t-BuOK	$PhCH_3$	4
13	$Pd_2(dba)_3$	DPEphos	t-BuONa	$PhCH_3$	2
14	$Pd_2(dba)_3$	DPEphos	t-BuOLi	$PhCH_3$	trace
15	$Pd_2(dba)_3$	DPEphos	K_2CO_3	$PhCH_3$	34
16	$Pd_2(dba)_3$	DPEphos	Et_3N	$PhCH_3$	42
17	$Pd_2(dba)_3$	DPEphos	Dabco	$PhCH_3$	86
18[b]	$Pd(OAc)_2$	DPEphos	Dabco	$PhCH_3$	35
19[b]	$PdCl_2$	DPEphos	Dabco	$PhCH_3$	77
20[b]	$Pd(PPh_3)_4$	DPEphos	Dabco	$PhCH_3$	3
21	---	DPEphos	Dabco	$PhCH_3$	NR
22	$Pd_2(dba)_3$	---	Dabco	$PhCH_3$	<1
23[c]	$Pd_2(dba)_3$	DPEphos	Dabco	$PhCH_3$	trace



[a] Unless otherwise noted, the reactions were carried out with **I** (0.5 mmol), CF_3CH_2I (2 equiv), base (2 equiv), $Pd_2(dba)_3$ (5 mol %), ligand (20 mol %), and toulene (1 mL) under Ar, 80 °C, 24 h. [b] 10 mol % of $Pd(OAc)_2$, $PdCl_2$, and $Pd(PPh_3)_4$ were used. [c] Under air.

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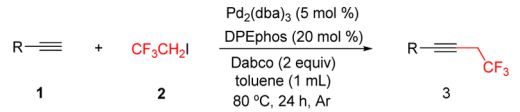
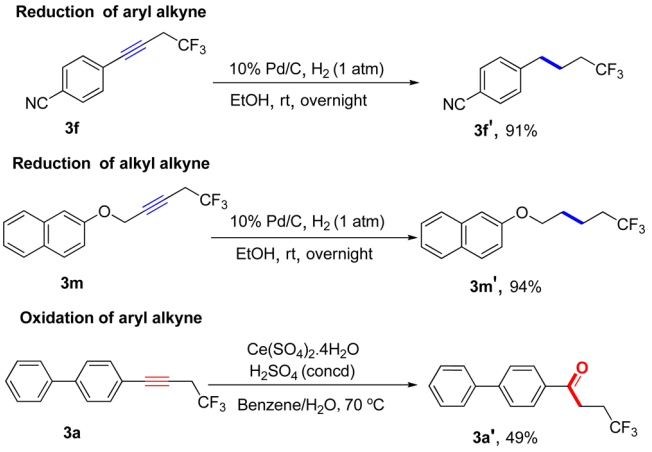
Table 2. Pd-Catalyzed Trifluoroethylation of Terminal Alkynes to 1,1,1-Trifluoro-2-iodoethane[a]



entry	substrates	products	yield(%)[b]
1	1a	3a	57
2	1b	3b	84
3[c]	1c	3c	81
4[c]	1d	3d	73
5	1e	3e	45
6	1f	3f	60
7	1g	3g	57
8	1h	3h	43
9	1i	3i	82
10	1j	3j	82
11	1k	3k	80
12	1l	3l	76
13	1m	3m	90
14	1n	3n	90
15	1o	3o	89
16	1p	3p	81
17	1q	3q	95
18	1r	3r	56
19	1s	3s	94

[a] Reaction conditions: **1** (0.5 mmol), CF_3CH_2I (2 equiv), $Pd_2(dba)_3$ (5 mol %), DPEphos (20 mol %), and Dabco (2 equiv) in toluene (1 mL), 80 °C, Ar, 24 h. [b] Isolated yields. [c] Yields were determined by ^{19}F NMR with an internal standard (benzotrifluoride).

Scheme 2. Reduction and Oxidation Reaction of Aryl and Alkyl 2,2,2,-Trifluoroethylation Product



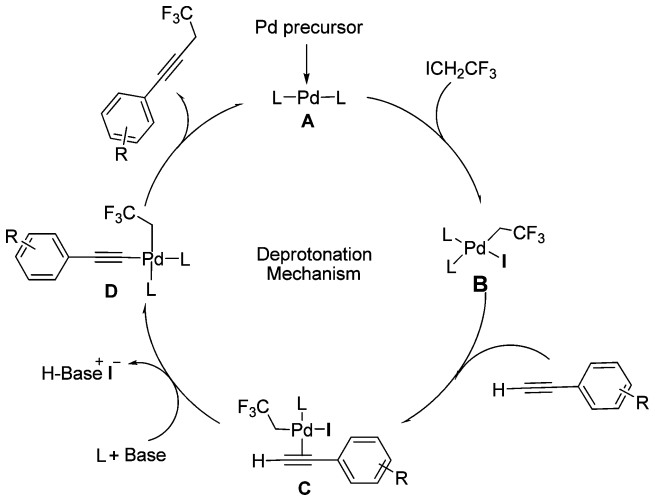
were less effective. Finally, an examination of different palladium sources revealed that palladium(II) catalysts were less effective compared to the $Pd_2(dba)_3$ catalyst (Table 1, entries 18 and 19). However, other palladium(0) catalysts, such as $Pd(PPh_3)_4$, gave only a low yield (Table 1, entry 20). Obviously, both palladium catalyst and ligand were essential for reaction efficiency, as hardly any detectable product was observed in the absence of $Pd_2(dba)_3$ or DPEphos (Table 1, entries 21 and 22). Only a trace amount of the target product was obtained when the reaction was carried out under aerobic conditions (Table 1, entry 23).

With the optimal protocol in hand, we next investigated the substrate scope of this 2,2,2-trifluoroethylation reaction. We found that various terminal aryl alkynes (**1a**–**1l**) and alkyl alkynes (**1m**–**1s**) could be transformed to the corresponding products in good-to-excellent yields (Table 2). Both electron-rich (**1a**–**1e**) and electron-deficient (**1f**–**1l**) aryl alkynes gave the expected trifluoroethylation products in moderate-to-good yields. Many synthetically important functional groups, such as alkoxy, alkyl, nitrile, carbonyl, nitro, ester, amide, and especial formyl groups, were well-tolerated under the optimal conditions (**1b**–**1c**, **1f**, **1g**, **1i**, **1h**, **1j**–**1k**, **1p**, **1n**). Moreover, adjacent heteroatom substituted alkyl alkynes (**1m**–**1q**) reacted with CF_3CH_2I under our conditions to give the products in higher yield, up to 95%. Alkyl alkynes with O,N-heteroatoms at the β-position (**1r**, **1s**) were also tolerated and gave the products in moderate-to-excellent yields.

Application of this new trifluoroethylative method in the synthesis of organofluorine compounds which would otherwise be difficult to access was tested (Scheme 2). We chose 4-(4,4,4-trifluorobut-1-yn-1-yl)benzonitrile (**3f**) and 2-((5,5,5-trifluoropent-2-yn-1-yl)oxy)naphthalene (**3m**) as model substrates, which can be hydrogenated to the fluorinated alkanes **3f′** and **3n′** using a 10% Pd/C catalyst and H_2 at room temperature. Next, the oxidation reaction of 4-(4,4,4-trifluorobut-1-yn-1-yl)-1,1′-biphenyl (**3a**) was investigated with the oxidant $Ce(SO_4)_2 \cdot 4H_2O$ and H_2SO_4 (concd) at 70 °C, producing the corresponding ketone

compound **3a′** in moderate yield. These encouraging results indicated that the present method provides an efficient approach for the preparation of diverse organofluorine compounds.

Scheme 3. A Possible Mechanism for the Catalytic 2,2,2-Trifluoroethylation Reaction



A plausible reaction mechanisim for Pd-catalyzed trifluoroethylation of alkynes with CF_3CH_2I is presented in Scheme 3. Initially, the palladium complex **A**[10−12] would be generated by the reaction of the Pd precursor with ligands. Subsequently, the Pd^{II} intermediate **B**[13] is formed via oxidative addition of complex **A** to CF_3CH_2I. Then, ligand dissociation followed by complexation with the alkyne occurs to form the intermediate complex **C** (η^2-RC≡CH)—Pd(CF_3CH_2)XL.[10,12] The ligated alkyne is then deprotonated by the amine (Dabco), forming a new square planar Pd complex **D**.[10−12] Probably the **C**→**D** process in the catalytic cycle is relatively facile under Cu-free catalytic Sonogashira reaction conditions. A reason for this can be the electron-withdrawing nature of the CF_3 group, which is beneficial for formation of complex **D** from complex **C**. Finally, complex **D** affords the product alkynyl-CH_2CF_3 through reductive elimination.[12,14]

In conclusion, we have successfully developed the palladium-catalyzed 2,2,2-trifluoroethylation reaction of alkyl and aryl terminal alkynes using the readily available reagent CF_3CH_2I. The reaction can be carried out under mild conditions and is compatible with many functional groups, even the formyl group. This reaction provides a straightforward, practically useful way to prepare various trifluoroethylated alkynes.

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Supporting Information Available. Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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