Communication

Pd-Catalyzed Stereoselective Carboperfluoroalkylation of Alkynes

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Pd-Catalyzed Stereoselective Carboperfluoroalkylation of Alkynes

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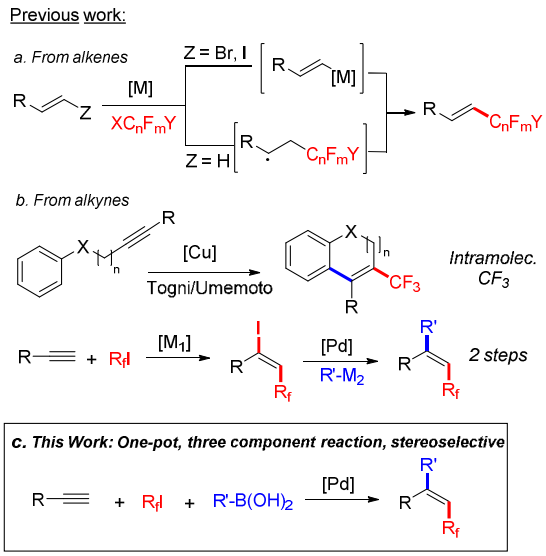
Supporting Information Placeholder

ABSTRACT: A Pd-catalyzed three component reaction involving terminal alkynes, boronic acids and perfluoroalkyl iodides is presented here. Trisubstituted perfluoroalkenes can be obtained in a highly regio- and stereocontrolled manner by the simultaneous addition of both aryl and C_nF_m groups across the triple bond in a radical-mediated process. The reaction is operationally simple offering a broad scope and functional group tolerance.

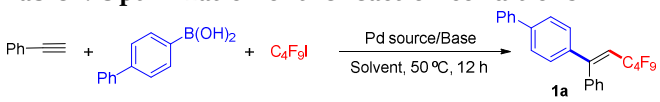
As a result of the unique solubility, cell permeability and metabolic stability observed for organofluorine compounds,[1] the efficient introduction of fluoroalkyl motifs in commonly used building blocks has attracted increasing attention.[2] In contrast to the recent significant progress in the fluoroalkylation of aromatic compounds,[3] efficient methods to access fluoroalkylated alkenes are less abundant. Common strategies include transition metal mediated cross-coupling reactions of fluoroalkyl species with alkenyl halides as well as fluoroalkyl radical addition and elimination reactions on alkenes (Scheme 1, a).[4] More straightforward approaches enabling additional functionalization have been explored with alkynes as starting materials and thus the hydro-,[5] oxy-,[6] amino-trifluoromethylation[7] as well as the iodoperfluoroalkylation[8] of alkynes have been recently reported.[9] Carbotrifluoromethylations to simultaneously construct C-C and C(sp^2)-C_nF_m bonds across the C≡C bond have also been explored, but the portfolio of these reactions is still limited to intramolecular settings.[10,11] Alternatively, multistep-processes involving first an alkyne iodoperfluoroalkylation followed by classical Pd-catalyzed cross couplings have also been described to produce trisubstituted perfluoroalkenes (Scheme 1, b).[8a-c] Most of the above-mentioned processes either require the preparation of alkenyl halides and/or fluoroalkyl radical precursors, which can be time-consuming and tedious, or rely on the use of electrophilic CF_3 sources such as Togni or Umemoto reagents,[12] which are expensive or require multistep synthesis. Furthermore, functionalization of alkynes via transition metal catalysed multicomponent reactions has been studied extensively although, with few exceptions,[13] multi-step protocols using sensitive, highly reactive metal species are required and thus competitive homo- and/or cross-coupling reactions are present in these transformations.[14] Thus, driven by our interest in radical reactions and fluorine chemistry,[15] we decided to explore the possibility of a one-pot intermolecular carboperfluoroalkylation reaction with alkynes as starting materials. Herein, we disclose a novel Pd-catalyzed three component reaction in which two new C-C bonds are simultaneously formed by addition of perfluoroalkyl halides and boronic acids to alkynes producing trisubstituted perfluoroalkylated alkenes in a highly regio- and stereoselective manner (Scheme 1, c).



Scheme 1. Comparison of methods to produce perfluoroalkyl alkenes

The addition of *n*-perfluorobutyl iodide and 4-biphenylboronic acid to phenyl acetylene was selected as benchmark reaction (Table 1).[16] In the presence of 4 mol% of $PdCl_2(PPh_3)_2$ and 2 equiv. of K_2CO_3 in THF, CH_3CN, 1,4-dioxane or acetone, only traces of the desired product were formed (Table 1, entry 1). Using dichloromethane as solvent, in the absence as well as in the presence of water, **1a** was obtained in moderate yields (Table 1, entries 2-3). Increasing the amount of the *n*-perfluorobutyl iodide resulted in an optimized 81% isolated yield for **1a**, which was obtained as a single regio- and stereoisomer (Table 1, entry 4). The replacement of water by other protic solvents as well as the change of base to Cs_2CO_3 or catalyst to $Pd(PPh_3)_4$ did not increase the yield of product **1a** either (Table 1, entries 5-8).
With the optimized reaction conditions in hand (Table 1, entry 4), we set out to explore the scope of this transformation.

Table 1. Optimization of the reaction conditions



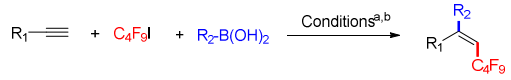
Entry[a]	Catalyst (4 mol%)	Solvent	Base (2 equiv)	Yield of **1a** (%)[d]
1[a]	$PdCl_2(PPh_3)_2$	THF, CH_3CN, 1,4-dioxane, Me_2CO	K_2CO_3	trace
2[a]	$PdCl_2(PPh_3)_2$	DCM	K_2CO_3	57
3[a]	$PdCl_2(PPh_3)_2$	DCM/H_2O	K_2CO_3	62
4[b]	**$PdCl_2(PPh_3)_2$**	**DCM/H_2O**	**K_2CO_3**	**85(81)**
5[b]	$PdCl_2(PPh_3)_2$	DCM/EtOH	K_2CO_3	50
6[b]	$PdCl_2(PPh_3)_2$	DCM/H_2O	Cs_2CO_3	73
7[b,c]	$PdCl_2(PPh_3)_2$	DCM/H_2O	K_2CO_3	70
8[b]	$Pd(PPh_3)_4$	DCM/H_2O	K_2CO_3	70

[a]Conditions: phenyl acetylene (1 equiv), boronic acid (1.3 equiv), *n*-perfluorobutyl iodide (2 equiv), 0.2 M. Solvent:H_2O (5:1) if applied. [b] *n*-Perfluorobutyl iodide (3 equiv). [c] 1 equiv of base. [d] Yield determined by ^1H NMR with *p*-nitroacetophenone as internal standard. In brackets: isolated yield after column chromatography.

First, different aryl boronic acids were investigated in combination with phenyl acetylene (Table 2, top). Oxygen-based electron-donating groups in the aromatic ring were well tolerated and produced the corresponding difunctionalized products in excellent yields and complete regio- and stereoselectivity (**1a-d**). The presence of alkyl groups had also a positive influence in the reaction outcome, even in the case of sterically-demanding ortho-substituted substrates, as demonstrated by the high yields obtained for products **1e-g**. Not only phenyl boronic acid, but also the corresponding pinacol ester and the potassium trifluoroborate proved to be amenable substrates under these conditions (**1h**). Naphthyl, cinnamyl, octenyl as well as heteroaryl boronic acid could be coupled in moderate to high yields (**1i-m**). Halogen groups (**1n-p**) were also well tolerated, whereas the presence of electron-withdrawing groups seems to limit the reaction efficiency as demonstrated in **1q-s**. More elaborated boronic acids could also be successfully involved as shown by compounds **1t** and **1u**, respectively. In all studied cases, the products were obtained with perfect regio- and stereocontrol as single isomers.

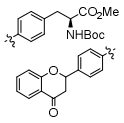
The substitution pattern on the alkyne was explored next (Table 2, bottom). Using *p-tert*butyl-phenyl boronic acid as partner, aryl alkynes bearing both electron-donating as well as electron-withdrawing groups were submitted to the standard reaction conditions providing the corresponding trisubstituted olefins in high yields and complete stereocontrol in favor of the *E* isomer (**2a-k**). The structure of **2h** could be confirmed by X-Ray diffraction analysis.[17] The presence of a 2-thiophene or a bulky triisopropylsilyl group seemed to compromise the reaction efficiency (**2j, 2k**). Alkyl substituted alkynes proved to be suitable partners for the present difunctionalization reaction. Different boronic acids could be incorporated across a set of unactivated olefins providing the corresponding trisubstituted alkenes in excellent yields and good levels of sterecontrol in favour of the thermodynamically favoured *E*-olefin (**2l-s**).

Table 2. Reaction scope on boronic acid and alkynes[a]



Scope Boronic Acid R =

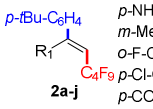
4-Biphe-	**1a**, 81	3-thiophene,	**1m**, 70
p-OMe-C_6H_4-	**1b**, 77	*p*-Cl-C_6H_4-	**1n**, 80
m-OMe-C_6H_4-	**1c**, 78	*o*-F-C_6H_4-	**1o**, 78
3,5-$(OMe)_2$-C_6H_3-	**1d**, 84[c]	2,4-$(F)_2$-C_6H_3-	**1p**, 71
p-*t*Bu-C_6H_4-	**1e**, 75	*p*-CO_2Et-C_6H_4-	**1q**, 57
o-Me-C_6H_4-	**1f**, 79[c]	*p*-CF_3-C_6H_4-	**1r**, 75[c]
2,4-$(Me)_2$-C_6H_3-	**1g**, 80	*p*-Ac-C_6H_4-	**1s**, 50
Ph	**1h**, 67		
Ph	**1h**, 70[d,e]		
Ph	**1h**, 50[d,f]		
2-Napthyl	**1i**, 90		
(E)-cynamyl	**1j**, 48		
(E)-1-octenyl	**1k**, 45		
3-furyl	**1l**, 50		



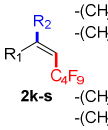
1t, 64

1u, 76[c]

Scope Alkyne



R_1 =		
p-OMe-C_6H_4-	**2a**, 81[g]	
p-*t*Bu-C_6H_4-	**2b**, 76	
4-Biphe-	**2c**, 78	
p-NHAc-C_6H_4-	**2d**, 70	
m-Me-C_6H_4-	**2e**, 83	
o-F-C_6H_4-	**2f**, 70	
p-Cl-C_6H_4-	**2g**, 69	
p-CO_2Me-C_6H_4-	**2h**, 72	
3,5-$(CF_3)_2$-C_6H_3-	**2i**, 40	
2-thiophene	**2j**, 45	

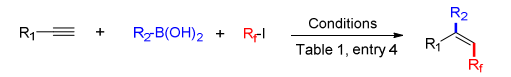


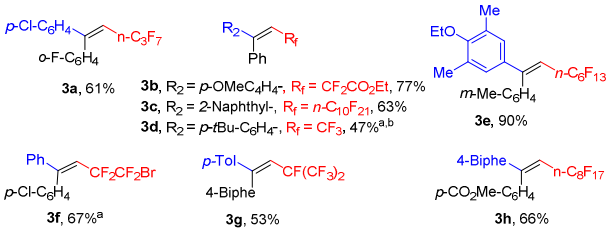
R_1	R_2	
TIPS	4-Biphe-	**2k**, 40
*n*Bu	4-Biphe-	**2l**, 83[h]
-$(CH_2)_3$OBz	4-Biphe-	**2m**, 81[h]
-$(CH_2)_3$OBz	Ph	**2n**, 76[h]
"	*p*-OMe-C_6H_4-	**2o**, 75[h]
"	2,4-$(F)_2$-C_6H_3-	**2p**, 78[h]
-$(CH_2)_3CO_2$-	*p*-*t*Bu-C_6H_4-	**2q**, 70[h]
-$(CH_2)_3$Cl	*p*-*O*iPr-C_6H_4-	**2r**, 82[h]
-$(CH_2)_3$CNPhth	*m*-Me-C_6H_4-	**2s**, 87[i]

[a] Optimized conditions, Table 1, entry 4. [b] Isolated yield after column chromatography. [c] Conditions: alkyne (1.5 equiv), boronic acid (1 equiv), and then as in Table 1, entry 4. [d] ^1H NMR yield with *p*-nitroacetophenone as internal standard. [e] With PhBpin. [f] With $PhBF_3K$. [g] 75% yield in 2 mmol scale. [h] 10:1 E/Z ratio determined by ^{19}F NMR. [i] 6:1 E/Z ratio. 4-Biphe: 4-Biphenyl-.

Different perfluoroalkyl halides were also investigated as shown in Scheme 2. Except for trifluoromethyl and bulky perfluoroisopropyliodide (**3d** and **3g**), the corresponding arylperfluoroalkylated products (**3a-c**, **3d-f**, **3h**) could be obtained in comparable yields to those reported in Table 2.

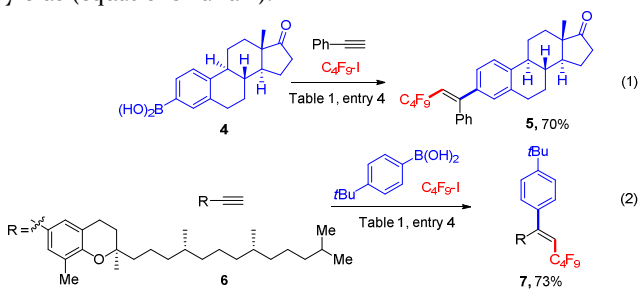
Scheme 2. Reaction scope on perfluoroalkyl iodides





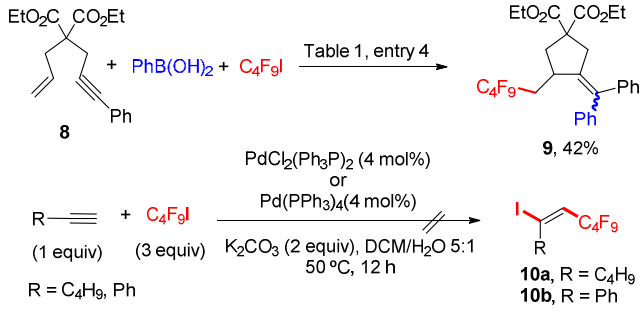
[a] Conditions: alkyne (1.5 equiv), boronic acid (1 equiv), and then as in Table 1, entry 4. [b] All compounds obtained as single isomers except **3d** which was isolated in a 11:1 E/Z ratio (determined by ^{19}F NMR). 4-Biphe: 4-Biphenyl-.

More elaborate substrates such as estrone-derived boronic acid **4** and alkyne γ-tocopherol-containing alkyne **6** could be successfully transformed into the corresponding carboperfluoroalkylated products **5** and **7** respectively in good yields (equations 1 and 2).[18]



Control experiments were also designed to interrogate the reaction mechanism. Addition of TEMPO, BHT or 1,4-dinitrobenzene to the reaction mixture supressed, or substantially compromised, product formation.[16] The reaction of enyne **8** seems to support a radical mediated process, in which addition of C_4F_9 to the more reactive alkene moiety takes place followed by cyclization and trapping of the resulting vinyl radical to give **9** (Scheme 3, top). In this reaction, vinyl iodides could also be detected,[16] prompting us to carry out the reactions of 1-hexyne and phenylacetylene in the absence of boronic acid in order to check whether iodoperfluoroalkylation products **10a-b** could be produced under our standard conditions. As shown in the second half of Scheme 3, neither $PdCl_2(PPh_3)_2$ nor $Pd(PPh_3)_4$ as catalysts managed to produce significant amounts of **10**, thus questioning vinyl iodides as effective intermediates in these transformations.[19]

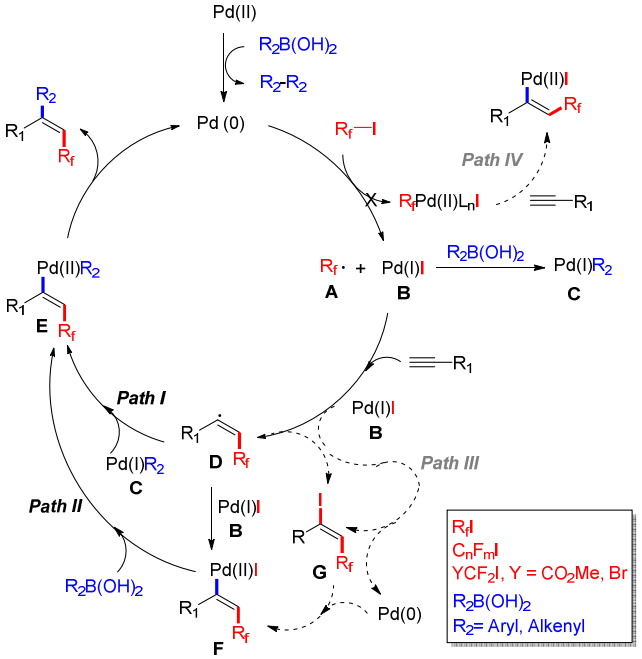
Scheme 3. Control experiments



Although multiple scenarios can be envisaged, based on these and additional control experiments,[16] we propose the following mechanism for these transformations. Palladium not only is a good cross-coupling catalyst,[20] but has also been successfully used as a single electron donor.[21] As depicted in Scheme 4, the electrophilic perfluoroalkyl radical **A** can be formed by reaction of Pd(0) (generated in situ with the aid of boronic acid)[21] with Rf-I.[23,24] The perfluoroalkyl radical could add intermolecularly to the C≡C affording vinyl radical **D**. The subsequent recombination with either $Pd(I)R_2$ (**C**) or Pd(I)I (**B**) (paths I and II respectively) would finally give the key palladium species **E**, which undergoes reductive elimination to produce the corresponding fluoroalkylated alkenes while regenerating Pd(0). Alternatively, a third pathway can be proposed involving the formation of the corresponding iodoperfluoalkyl alkenes **G** as potential reaction intermediates in these transformations (path III). However, the reactions shown at the bottom of Scheme 3 disfavour this hypothesis. The selectivity in favour of the *E* isomer also rules out a reaction mechanism involving the direct perfluoroalkyl palladation of the alkyne via putative Rf-Pd(II)-I intermediate (path IV), in line with the highly unreactive nature towards unsaturated moieties reported for these complexes.[23] As such, the high stereoselectivity can be explained based on the less steric demand of a fast-interconverting *E*/*Z* vinyl radical **D**[25] for recombination with an external radical from the opposite side to that in which the perfluoroalkyl group has been incorporated.

In summary, a simple, functional-group tolerant, Pd-catalyzed three component reaction of terminal alkynes with boronic acids and perfluoroalkyl iodides is reported. This method, involving the simultaneous addition of both aryl/alkenyl and perfluoroalkyl group across the alkyne streamlines the access to perfluroalkylated trisubstituted alkenes in a highly regio- and stereocontrolled manner in what seems to be a radical-mediated process with broad scope and wide synthetic applicability.

Scheme 4. Proposed reaction mechanism



ASSOCIATED CONTENT

Supporting Information

Supplementary information including compound synthesis and characterization, crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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16. For additional experiments, see Supporting Information.
17. X-Ray diffraction analysis data for **2h** are available from the CCDC database: CCDC 1411445.
18. Reaction performed using 1 equiv of boronic acid and 1.5 equiv of alkyne.
19. Independently prepared perfluoroalkyl iodoalkenes **10a** and **10b** could be efficiently engaged in Pd-cross coupling reactions with boronic acids: as already shown in ref. 8a-c. See SI.
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21. See ref. 4j and also: Mazzoti, A.; Campbell, M.; Tang, P.; Murphy J.; Ritter, T. *J. Am. Chem. Soc*. **2013**, *135*, 14012.
22. Traces of biaryls stemming from homocoupling of the boronic acids could be detected in the crude reaction mixtures. See Ref. 16.
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24. Although radical activation of Rf-I by carbonate bases has been recently proposed (see ref. 8c and also: (a) Aihara, Y., Tobisu, M., Fukumoto, Y., Chatani, N. *J. Am. Chem. Soc*. **2014**, *136*, 15509. (b) Zhang, B., Studer, A. *Org. Lett*. **2014**, *16*, 3990), no significant reactivity was observed in the present reactions in the absence of Pd (see ref. 16).
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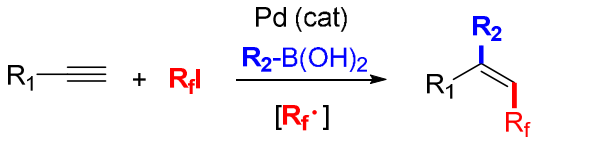
TOC

Pd-catalyzed Alkyne Carboperfluoroalkylation



> 50 examples
Yields 40-94%
Highly stereoselective