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Palladium-Catalyzed Direct C−H Allylation of Electron-Deficient Polyfluoroarenes with Alkynes

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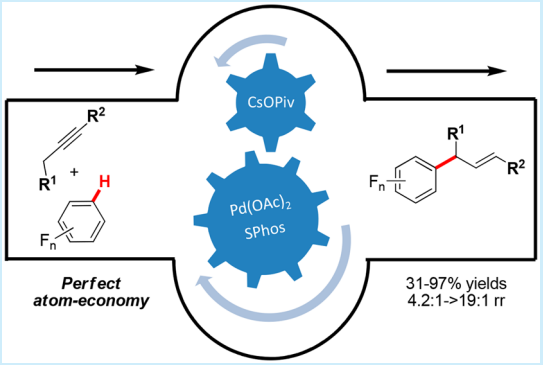
Supporting Information

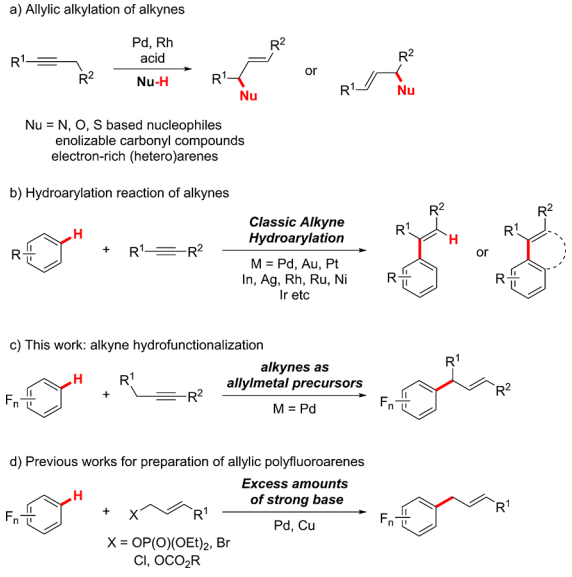
ABSTRACT: A palladium-catalyzed intermolecular direct C−H allylation of polyfluoroarenes with alkynes is reported. Unlike classic hydroarylation reactions, alkynes are used as allylic electrophile surrogates in this direct aromatic C−H allylation. As an atom-economic and efficient method, various linear allylated fluoroarenes were synthesized from two simple and easy-to-access feedstocks in good to excellent yields, as well as regio- and stereoselectivity.



Transition-metal-catalyzed allylation reactions are among the most fundamental and powerful approaches to construct C−C and C−heteroatom bonds in organic synthesis.[1] Of those, in particular, the allylic substitution reactions[2] and allylic C−H oxidation reactions[3] have found widespread application. Although valuable, the preinstallation of a leaving group to the allylic electrophile or the requirement for stoichiometric amounts of an oxidant, respectively, diminishes the atom-efficiency of this chemistry.[4] In pioneering studies by Trost and Yamamoto in the late 1990s and early 2000s, an alternative strategy to synthesize allylic alkylated products was proposed by using allenes or alkynes as atom-economic and redox-neutral allyl precursors in Pd-catalyzed allylation reactions.[5] Inparticular, alkynes have drawn increasing interest in the field of allylation reactions due to their versatile, readily available and bench-stable character.[6] Over the past decades, the use of nitrogen-, oxygen-, and sulfur-based nucleophiles in this area has witnessed enormous progress; however, carbon nucleophiles are so far limited to enolizable carbonyl compounds or electron-rich arenes (Scheme 1a).[7] However, electron-deficient arenes, which are less reactive in an electrophilic aromatic substitution, have been far less explored.[8]

Polyfluoroarenes are important fluorinated aromatic cores that widely occur in pharmaceuticals, organic materials, and electronic devices.[9] Therefore, the development of efficient access to functionalized fluoroarenes has been the subject of intensive research. Although the direct functionalization of aromatic C−H bonds with alkynes has been proven to be an effective way to generate the corresponding alkenylated products[10] (Scheme 1b), we hypothesized that the direct C−H allylation reaction of polyfluoroarenes with alkynes could be achieved, if the corresponding metal hydride species is capable of transforming alkynes into π-allylmetal species (Scheme 1c).[11]

Scheme 1. Transition-Metal Catalyzed Alkyne Hydrofunctionalizations



Although many elegant works have been reported to prepare allylic polyfluoroarenes, these protocols require stoichiometric amounts of bases to promote the required deprotonation (Scheme 1d).[11a−d,g,h,12] On the contrary, adding a Brønsted

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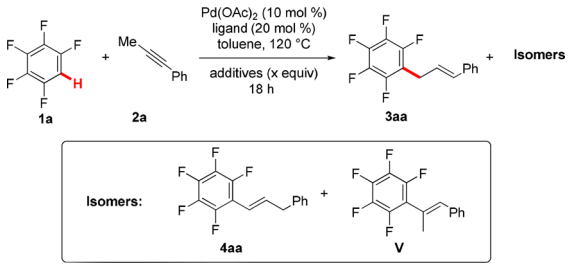
acid cocatalyst is crucial to promote the alkyne-to-allene isomerization for subsequent allylation reactions.[6,7] Thus, the main challenge in achieving this goal is the introduction of a proper acid under the basic reaction conditions.[12] We envisioned that a weak base might be sufficient for the deprotonation of polyfluoroarenes. The thus-generated acid could promote the formation of a Pd hydride species, which consequently could isomerize the alkyne to the allene and ultimately to the desired π-allylpalladium intermediate. Herein, we report on a Pd-catalyzed C−H allylation reaction of alkynes and polyfluoroarenes.

We initiated the investigation with pentafluorobenzene (**1a**) and 1-phenyl-1-propyne (**2a**) serving as model substrates (Table 1). In the presence of 10 mol % of $Pd(OAc)_2$, 20 mol %

Table 1. Optimization of the Reaction Conditions[a]



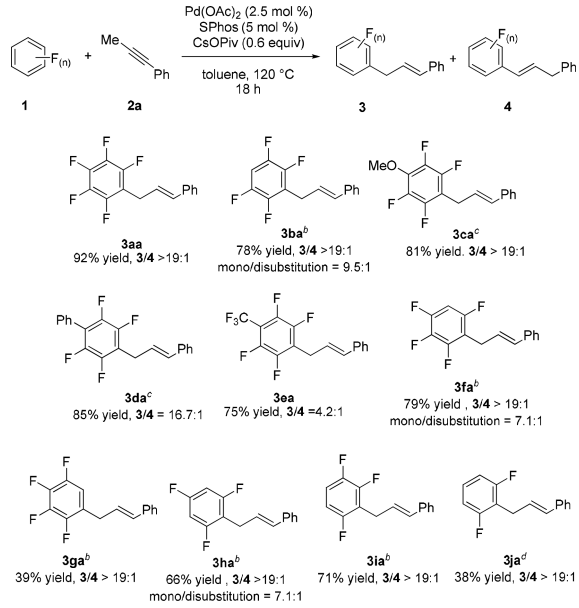
entry	ligand	additives (x)	yield[b] (%)	3aa/4aa/V[c]
1	PCy_3	CsOPiv (1.2)	55	16.7/2/1
2	SPhos	CsOPiv (1.2)	88 (81)	14.3/1/0
3	SPhos	CsOPiv (0.6)	91 (83)	16.7/1/0
4	SPhos	CsOPiv (0.2)	88 (82)	18.3/1/0
5	SPhos	*d*	80 (73)	9.1/1/0
6	SPhos	HOPiv (0.6)	43	16.7/1/0
7	SPhos	Cs_2CO_3 (0.6)	66	16.7/1/0
8	SPhos	CsOAc (0.6)	72	7.8/1/0
9[e]	SPhos	CsOPiv (0.6)	92 (86)	16.7/1/0
10[f]	SPhos	CsOPiv (0.6)	(92)	>19:1:0

[a]Reaction conditions (unless otherwise specified): **1a** (2.0 equiv), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), monodentate ligands (20 mol %) or bidentate ligands (10 mol %), additive (x equiv), toluene (0.2 mL), 18 h, 120 °C. [b]Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are reported in parentheses. [c]Ratio was determined by ^{19}F NMR spectroscopy. [d]Without additive. [e]$Pd(OAc)_2$ (5 mol %) was used. [f]Reaction conditions: **1a** (2.0 equiv), **2a** (0.4 mmol), $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), CsOPiv (0.6 equiv), toluene (0.4 mL), 18 h, 120 °C. Ratio of E/Z > 19:1 determined by ^{1}H NMR spectroscopy.

of PCy_3 and 1.2 equiv of CsOPiv as additive in toluene at 120 °C, gratifyingly the desired product **3aa** could be obtained in 55% NMR yield with excellent regioselectivity (16.7:2:1) and stereoselectivity (E/Z > 19:1) (entry 1). Further examination of monodentate and bidentate phosphine ligands revealed that SPhos is the best ligand for this transformation providing **3aa** in 81% isolated yield (entry 2, also see Table S1). Next, the amount of CsOPiv was tested (entries 3−5). CsOPiv (0.6 equiv) was sufficient for this allylation reaction, giving **3aa** in 83% yield, and the reaction could also occur smoothly without CsOPiv, albeit in a lower yield. Further examination of different Pd sources did not show better results (see Table S2). No reaction occurred in the absence of the Pd catalyst (see Table S2). In addition, an investigation of other solvents did not lead to a better outcome (see Table S3). Replacement of CsOPiv by HOPiv, Cs_2CO_3, or CsOAc decreases the efficiency of this reaction (entries 6−8). Finally, the yield of the allylic product **3aa** could be slightly increased by decreasing the amount of $Pd(OAc)_2$, and the highest yield (92%) could be obtained when 2.5 mol % of $Pd(OAc)_2$ was used (entries 9 and 10).

With the optimized reaction conditions in hand, we investigated the scope of various fluoroarenes bearing two to four fluorine atoms for this direct aromatic C(sp^2-H) allylation reaction (Scheme 2). In general, 1,2,4,5-tetrafluorobenzene

Scheme 2. Pd-Catalyzed Allylation of Polyfluoroarenes 1 with 1-Phenyl-1-propyne (2a)[a]



[a]Reaction conditions (unless otherwise specified): **1** (2.0 equiv), **2a** (0.4 mmol), $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), CsOPiv (0.6 equiv), toluene (0.4 mL), 18 h, 120 °C. Isolated yields of the mixture of **3** and **4**. Ratio of *E*-**3**/*Z*-**3** > 19:1. All of the ratios of isomers were determined by ^{1}H NMR or ^{19}F NMR spectroscopy. [b]3.0 equiv of **1** was used. [c]1.2 equiv of **1** was used. [d]Reaction conditions: **1j** (6.0 equiv), **2a** (0.4 mmol), $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), CsOPiv (0.6 equiv), 18 h, 140 °C.

(**1a**) and its analogues whose 3-position contains a methoxy, a phenyl, or a trifluoromethyl substituent behaved well in this reactions, and the corresponding linear allylated polyfluoroarenes (**3ba**−**ea**) could be obtained in good yields (75−85%) with moderate to excellent regioselectivity (4.2:1 → 19:1). Furthermore, 1.2 equiv of methoxy-substituted or phenyl-substituted fluoroarenes were sufficient for obtaining the desired products (**3ca**, **3da**) in good yields (81−85%). For substrates bearing two or three reactive sites, 3 equiv of fluoroarenes were necessary to favor monoallylation products over diallylated scaffolds (**3ba**, **3fa**-**3ia**, mono-/disubstitution = 7.1:1 → 19:1) with good yields (39−79%) and excellent regioselectivity (>19:1). Interestingly, 1,3-difluorobenzene also underwent this transformation smoothly without any solvent affording **3ja** in 38% yield when 6 equiv of 1,3-difluorobenzene was used.

Next, we studied the allylation reactions of **1a** with various alkynes (Scheme 3). Internal aryl alkynes containing electron-donating substituents (methyl and methoxy) were tolerated well, and the corresponding allylic products (**3ab**−**ae**) were obtained in excellent yields (83−97%) and regioselectivities

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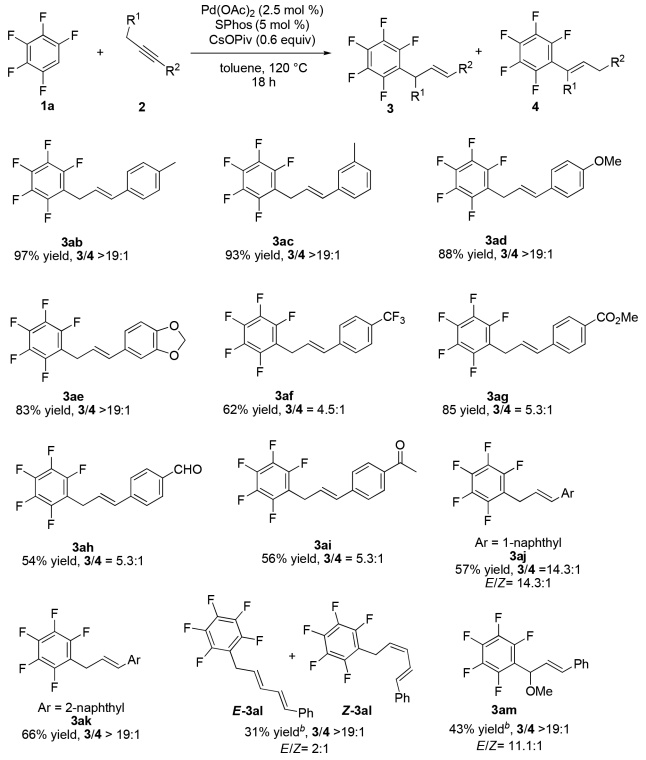
Scheme 3. Pd-Catalyzed Allylation of Pentafluorobenzene (1a) with Various Alkynes 2[a]

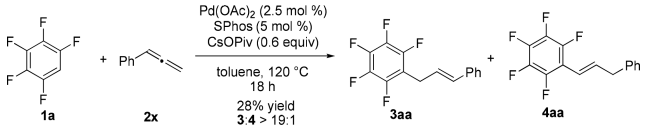


[a]Reaction conditions (unless otherwise specified): **1** (2.0 equiv), **2a** (0.4 mmol), $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), CsOPiv (0.6 equiv), toluene (0.4 mL), 18 h, 120 °C. Isolated yields of the mixture of **3** and **4**. Ratio of *E*-**3**/*Z*-**3** > 19:1. All of the ratios of isomers were determined by ^1H NMR or ^{19}F NMR spectroscopy. [b]$Pd(OAc)_2$ (5 mol %) and SPhos (10 mol %) were used.

(>19:1). Aryl alkynes bearing electron-withdrawing substituents (CF_3, CO_2Me, and CHO) were also suitable for this allylation reaction, providing the linear products (**3af**–**ai**) in good yields (54–85%) with moderate regioselectivities (4.5:1–5.3:1). The decreased regioselectivity in the products bearing electron-withdrawing groups might be due to an easier 1,3-hydrogen shift under the basic reaction conditions.[11b,c,13] Furthermore, alkynes with bulkier 1-naphthyl as well as 2-naphthyl substituents also underwent the reaction smoothly, giving rise to the corresponding coupling products **3aj** and **3ak** in good yield and regioselectivities, respectively (57–66%, 14.3:1 → 19:1). Delightfully, vinylated alkyne could be tolerant in this allylation reaction as well, albeit in a lower yield and regioselectivity. Gratefully, except 1-arylpropynes, (3-methoxyprop-1-ynyl)benzene also worked well in this transformation, providing the allylated product **3am** in 43% yield.

To prove an intermediary allene formation, the reaction of phenyl allene (**2x**) and pentafluorobenzene (**1a**) was carried out (Scheme 4). The desired coupling product **3aa** was obtained in a lower yield with excellent regioselectivity under

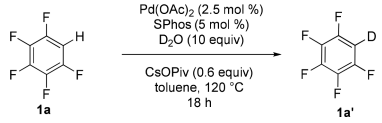
Scheme 4. Control Experiment



the standard reaction conditions, which indicates that an allene intermediate might participate in this reaction. However, due to decomposition of the phenyl allene under these conditions, the yield of **3aa** was severely decreased, which suggests that a low stationary concentration of allene generated in situ from the corresponding alkyne may be essential for this reaction.[7m]

To shed some light on the reaction mechanism, deuterium-labeling experiments were performed. First, the H/D exchange reaction of pentafluorobenzene (**1a**) with 10 equiv of D_2O was studied (Table 2). Under the standard reaction conditions, 62%

Table 2. H/D Exchange Experiments of Pentafluorobenzene[a]



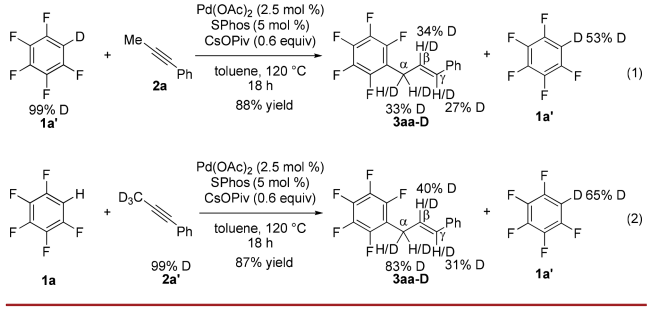
entry	variation from the conditions above	deuteration[b] (%)
1	none	62
2	no CsOPiv	16
3	no $Pd(OAc)_2$, SPhos, CsOPiv	0
4	no $Pd(OAc)_2$, SPhos	95

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol), $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), CsOPiv (0.6 equiv), D_2O (10 equiv), toluene (0.2 mL), 18 h, 120 °C. [b]Determined by ^{19}F NMR spectroscopy of the crude mixture.

deuterium was incorporated at **1a′**. In the absence of CsOPiv, only 16% deuterium incorporation of **1a′** was observed. No deuteration was observed when the reaction was conducted in D_2O and toluene only. Interestingly, the H/D exchange reaction in the presence of CsOPiv in the absence of $Pd(OAc)_2$ and SPhos resulted in 95% deuterium incorporation at **1a′**. These observations suggest that CsOPiv is mainly responsible for the C–H cleavage of the polyfluoroarenes.

The isotope-labeling experiments were conducted with deuterated pentafluorobenzene (**1a′**) and 1-phenyl-1-propyne (**2a**) under standard conditions (Scheme 5, eq 1). Deuterium

Scheme 5. Isotope-Labeling Experiments



incorporation at the α-position of the allylic part of **3aa-D** was found to be 33%, which indicates that the β-hydrogen elimination toward allene formation is reversible. We also found 34% incorporation of deuterium in the β-position of the allylic part of **3aa-D**, which suggests that the intermolecular hydrometalation with a H/D-palladium species occurred after the dissociation of allene from the palladium center. Moreover, only 53% deuterium were detected at the remaining **1a′**, which suggests that the C–H bond cleavage step is reversible. These hypotheses are further supported by deuterium scrambling in

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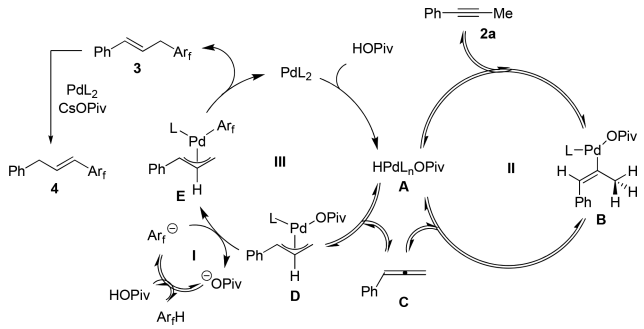
the isotope-labeling study with deutero-alkyne **2a′** (Scheme 5, eq 2). Furthermore, the KIE experiments between pentafluorobenzene (**1a**) and its deuterated derivative (**1a′**) with 1-phenyl-1-propyne (**2a**) were performed. Under standard conditions a primary KIE of 2.1 was observed, which suggests that the C−H bond cleavage of polyfluoroarenes might not be the turnover-limiting step.[14]

Based on these observations and previous investigations,[5g,11b,c] a putative mechanism for the reaction is proposed (Scheme 6). First, pentafluorobenzene was deprotonated by

Scheme 6. Plausible Mechanism



CsOPiv, affording the pentafluorobenzene anion and HOPiv. Then, the oxidation of palladium catalyst with HOPiv generates the hydridopalladium species **A**. *Syn*-migratory insertion of **A** into alkyne **2a** affords the intermediate **B**, which is followed by *β*-hydrogen elimination to afford phenyl allene **C** and regenerates **A**. Migratory insertion of the intermediate **A** to phenyl allene **C** produces the *π*-allylpalladium species **D**. The intermediate **D** reacts with pentafluorobenzene anion to produce intermediate **E**. Finally, the allylic alkylated product is obtained after reductive elimination, and the activated palladium catalyst is regenerated completing the catalytic cycle. The isomer **4** might be formed by the palladium-mediated isomerization of **3**.[11b,c,g,13]

In summary, we have developed an atom-economic and efficient method for the direct C−H allylation of polyfluoroarenes with simple alkynes using a palladium catalyst. This protocol does not need an excess amount of strong base or acid, which greatly enhance the utility of this protocol in terms of synthetic efficiency and atom economy. This process allows the transformation of various simple polyfluoroarenes into linear allylated fluoroarenes in good to excellent yields and regio- and stereoselectivity. Further extensions of our catalyst system toward other electron-deficient arenes are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00393.

Experimental procedures and analytic data for synthesized compounds, including ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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