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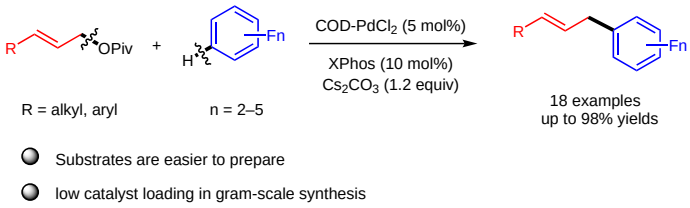
Palladium-Catalyzed Allylation of Polyfluoroarenes with Allylic Pivalates

Xinpeng Jiang[a]
Yong Liu[a]
Lei Zhang[a]
Jinkang Chen[a]
Kang Cheng[a]
Chuanming Yu*[a,b]

[a] College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. of China
[b] Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P. R. of China
ycm@zjut.edu.cn



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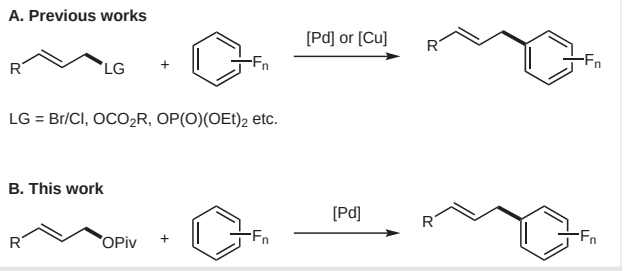
Abstract An efficient 1,5-cyclooctadiene–$PdCl_2$/dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (XPhos) catalytic system was developed for C–H allylation of polyfluoroarenes with allylic pivalates. The reactions showed excellent functional-group tolerance, good yields, and high regioselectivities. Mechanistic investigations supported a (π-allyl)palladium complex pathway through a directed oxidative addition of the allylic pivalate to palladium, followed by sequential nucleophilic attack by the polyfluorobenzene and reductive elimination. In a gram-scale reaction, a palladium loading of 0.5 mol% was enough to afford the required product in good yield.

Key words polyfluoroarenes, allylation, palladium catalysis, C–H functionalization, fluoro compounds

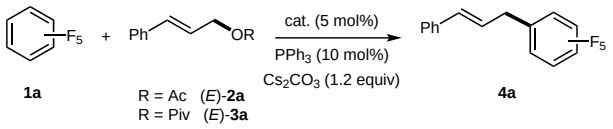
Owing to their unique physicochemical and biological properties, polyfluoroarenes have been widely used in life science,[1] agrochemicals,[2] and materials science.[3] Because the conventional Friedel–Crafts reaction is limited to electron-rich substrates,[4] the development of efficient methods to functionalize these important structural motifs is therefore highly valuable.[5] Although the allyl group is synthetically useful due to its diverse functional-group transformations through simple treatments,[6] few examples have been reported of direct transition-metal-catalyzed allylations of electron-deficient polyfluoroarenes (Scheme 1a). As an alternative, stoichiometric amounts of aryl metal reagents have been used to generate allylic polyfluoroarenes.[7] Only a few groups have reported direct allylations of polyfluoroarenes. For instance, Zhang and co-workers reported palladium-catalyzed allylations of polyfluorobenzenes with allylic carbonates[8] or allylic halides.[9] Similarly, Miura and co-workers employed allyl phosphates in the presence of a [$Cu(acac)_2$]/1,10-phenanthroline catalyst system,[10] and Xie and Chang developed a copper/N-heterocyclic carbene catalyzed C–H allylation under mild conditions.[11] Nevertheless, most of these methods require either substrates containing specific leaving groups that are difficult to install or relatively high catalyst loadings. Consequently, it would be highly desirable to develop a method to synthesize allylated polyfluoroarenes that would overcome these limitations. We recently developed a series of methods to synthesize functionalized polyfluoroarenes[12] and polyfluoroheterocycles.[13] In a continuation of this work, we report a simple palladium-catalyzed allylation reaction with allylic pivalates for the synthesis of allyl-substituted polyfluorobenzenes (Scheme 1b).



Scheme 1 Approaches to allylation of electron-deficient arenes

We commenced our study by choosing cinnamyl acetate [(*E*)-**2a**] and pentafluorobenzene (**1a**) as substrates. Initially, the reaction of pentafluorobenzene (**1a**) with cinnamyl acetate [(*E*)-**2a**] was investigated in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) in toluene at 120 °C. We were please to observe the formation of coupling product **4a** in 68% yield (Table 1, entry 1). When the leaving group was changed to OPiv, the yield of **4a** reached 87% (entry 2). Other transition-metal catalysts, such as $Cu(OAC)_2$ and $NiCl_2$, proved to be ineffective with these substrates (entries 3 and 4).

Table 1 Screening of Substrate Leaving Groups and Transition-Metal Catalysts[a]



1a R = Ac (*E*)-**2a**; R = Piv (*E*)-**3a** **4a**

Entry	R	Catalyst	Yield[b] (%)
1	Ac	$Pd(OAc)_2$	68
2	Piv	$Pd(OAc)_2$	87
3	Piv	$NiCl_2$	NR[c]
4	Piv	$Cu(OAc)_2$	trace

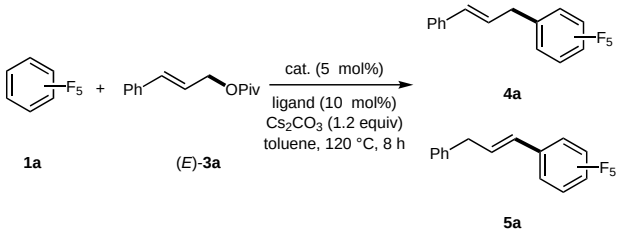
[a] Reaction conditions: (*E*)-**2a** or (*E*)-**3a** (1.0 mmol), **1a** (2.0 equiv), Cs_2CO_3 (1.2 equiv), catalyst (5 mol%), PPh_3 (10 mol%), PhMe (3.0 mL), 120 °C, 8 h, under argon.
[b] Yield of the isolated product.
[c] NR = no reaction.

Encouraged by these results, we chose pentafluorobenzene (**1a**) and allylic pivalate [(*E*)-**3a**] for further optimization of the reaction conditions (Table 2). In the absence of a ligand,[9] the reaction in the presence of $Pd_2(dba)_3$ (dba = dibenzylideneacetone) or $Pd(OAc)_2$ afforded **4a** in 17 and 18% yield, respectively (Table 2, entries 2 and 3). Various ligands were then evaluated in the presence of 5 mol% of $Pd(OAc)_2$. The nitrogen ligand 2,2′-bipyridine gave a trace of the product (entry 4); consequently, we screened various phosphine ligands. The bidentate ligands 1,1′-bis(diphenylphosphino)ferrocene (dppf), bis(diphenylphosphino)propane (dppp), and (*R*)-BINAP were less effective than PPh_3 (entries 5–7), possibly due to hampered formation of the (π-allyl)palladium pivalate, which is important for the efficiency of the reaction.[9] It's worth noting that (*R*)-BINAP produced a small amount of isomer **5a** along with required product **4a** (**4a/5a** = 10:1). Fortunately, the monodentate ligand dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (XPhos) gave a higher yield under similar conditions (entry 8). Further investigation of the palladium catalyst showed that $Pd(PPh_3)_4$ gave a lower yield and selectivity (entry 9). The Pd(II) catalysts $Pd(TFA)_2$, $PdCl_2$, and $Pd(PPh_3)_2Cl_2$ afforded the corresponding products in 83, 68, and 85% yield, respectively (entries 10–12). When $Pd(acac)_2$ was used, a 91% yield of **4a** was obtained with lower regioselectivity (**4a/5a** = 15:1) (entry 13). The best palladium catalyst was found to be COD–$PdCl_2$, giving 98% of **4a** with high regioselectivity (**4a/5a** > 33:1) (entry 14). With respect to the base, K_2CO_3 gave a lower yield, suggesting that strong basic conditions are essential for this reaction (entry 15).

Next, the scope of the substituted allylic pivalates was examined under the optimal reaction conditions (Scheme 2). Generally, substrates bearing an electron-donating group afforded the required products **4a–e** in good yields (81–98%), whereas pivalates substituted with electron-withdrawing groups gave lower yields (68–83%) (Scheme 2; **4f** and **4g**). Interestingly, when (*E*)-3-(4-chlorophenyl)allyl pivalate was used, the three-component coupling product **4h** was obtained in good yield (76%) due to a sequential C(sp^2)–Cl bond activation. Sterically hindered and less-reactive aliphatic allylic pivalates gave products **4i** and **4j** in 71% and 60% yield, respectively. Furthermore, heterocyclic-substituted allylic pivalates also give products **4j** and **4k** in 58 and 63% yield, respectively.

To further extend the scope of this method, various fluoroarenes **1** containing two to four fluorine atoms were tested. In general, the yields increased with increasing number of fluorine atoms (Scheme 3). Substrates containing four fluorine atoms gave products **6a–d** in 73–84% yield, regardless of the electronic properties of the substituent groups. Furthermore, those substrates possessing more than one reaction site afforded the corresponding monoallylated products **6c** and **6d** in good yields. For 1,3,5-trifluorobenzene, a moderate yield of **6e** was obtained under the standard conditions. We also detected trace amounts (<2%)

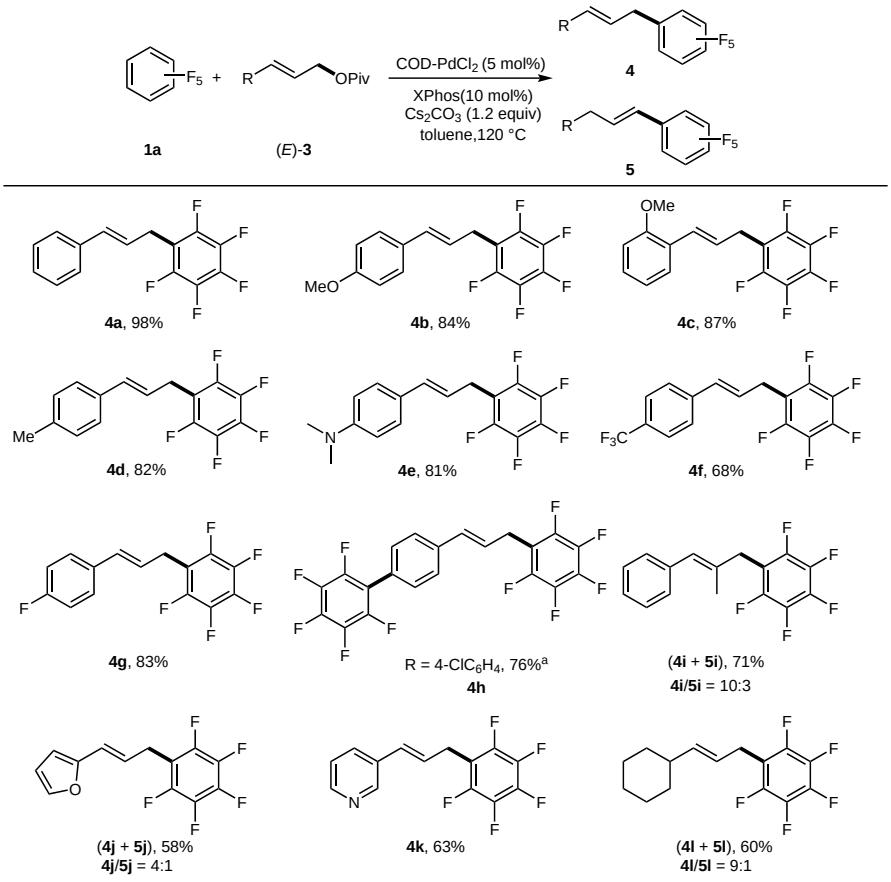
Table 2 Optimization of the Reaction Conditions[a]



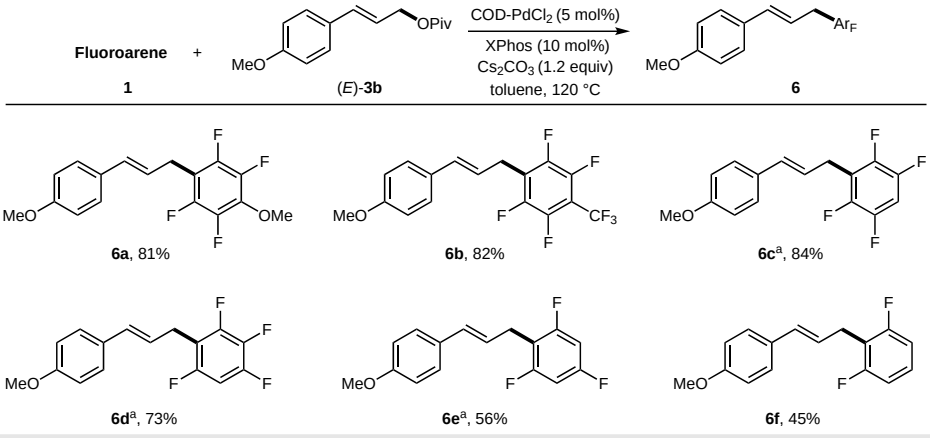
1a (*E*)-**3a** **4a** **5a**

Entry	Catalyst	Ligand	Yield[b] (%)	**4a**/**5a**[c]
1	$Pd(OAc)_2$	PPh_3	87	25:1
2	$Pd_2(dba)_3$	–	17	> 33:1
3	$Pd(OAc)_2$	–	18	20:1
4	$Pd(OAc)_2$	bpy	trace	–
5	$Pd(OAc)_2$	dppf	64	>33:1
6	$Pd(OAc)_2$	dppp	79	33:1
7	$Pd(OAc)_2$	(*R*)-BINAP	75	10:1
8	$Pd(OAc)_2$	XPhos	89	>33:1
9	$Pd(PPh_3)_4$	XPhos	43	15:1
10	$Pd(TFA)_2$	XPhos	83	20:1
11	$PdCl_2$	XPhos	68	20:1
12	$Pd(PPh_3)_2Cl_2$	XPhos	85	25:1
13	$Pd(acac)_2$	XPhos	91	15:1
14	**COD–$PdCl_2$**	**XPhos**	**98**	**>33:1**
15[d]	COD–$PdCl_2$	XPhos	74	>33:1

[a] Reagents and conditions: (*E*)-**3a** (1.0 mmol), **1a** (2.0 equiv), Cs_2CO_3 (1.2 equiv), catalyst (5 mol%), ligand (10 mol%), PhMe (3.0 mL), 120 °C, 8 h, under argon.
[b] Yield of the isolated product.
[c] Determined by ^1H NMR and ^{19}F NMR spectroscopy.
[d] The base was replaced with K_2CO_3 (1.2 equiv).



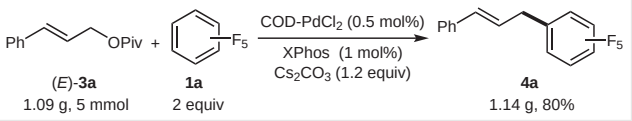
Scheme 2 Reaction of **1a** with various allylic pivalates (*E*)-**3**. *Reaction conditions*: (*E*)-**3** (1 mmol), **1a** (2 equiv), COD–$PdCl_2$ (5 mol%), XPhos (10 mol%), Cs_2CO_3 (1.2 equiv), toluene (3 mL) 120 °C, 8 h, under argon. **4**/**5** > 20:1, unless otherwise specified. [a] Reaction conditions: (*E*)-**3** (1 mmol), **1a** (4 equiv), Cs_2CO_3 (2.4 equiv), COD–PdCl2 (10 mol%), XPhos (20 mol%), toluene (4 mL), 120 °C, 8 h, under argon.



Scheme 3 Cross-coupling reaction of fluoroarenes **1** with allylic pivalates (*E*)-**3b**. *Reaction conditions*: (*E*)-**3b** (1 mmol), **1** (2 equiv), Cs_2CO_3 (1.2 equiv), COD–$PdCl_2$ (5 mol%), XPhos (10 mol%), PhMe (3 mL), 120 ℃, 8 h, under argon.
[a] Minor bisallylic products were also detected by ^{19}F NMR spectroscopy (see Supporting Information).

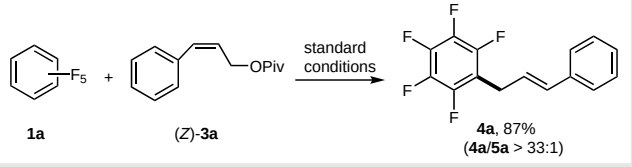
of the corresponding bisallylic products for substrates containing four fluorine atoms. Note that 1,3-difluorobenzene, an unsuitable substrate in previous studies,[8,10] provided the corresponding product **6f** in moderate yield, whereas monofluorobenzenes such as 3-fluorobenzonitrile did not react owing to the low acidity of the C–H bond to be activated.

With these results in hand, we conducted a gram-scale experiment with pivalate **3a** and pentafluorobenzene (**1a**) under the standard conditions (Scheme 4). Because 5 mol% of the palladium catalyst would be expensive if the reaction were scaled up, we reduced the amount of COD–$PdCl_2$ to 0.5 mol%, and the reaction was complete within eight hours, giving the required product **4a** in 80% yield.



Scheme 4 Gram-scale experiment

To investigate the mechanism, we examined the reaction of the (*Z*)-allylic pivalate (*Z*)-**3a** with pentafluorobenzene (**1a**) under the standard conditions (Scheme 5). The linear (*E*)-allylated product **4a** was obtained in 87% yield with no (*Z*)-allylated or branched isomers observed. The high stereo- and regioselectivity indicated that (π-allyl)palladium intermediates are formed in the catalytic reaction.



Scheme 5 Cross-coupling of pentafluorobenzene (**1a**) with (*Z*)-3-phenylallyl pivalate [(*Z*)-**3a**]

On the basis of the above experiment and reports on kinetic isotope effect studies,[8,9] the reaction does not involve a concerted metalation/deprotonation process. A plausible reaction mechanism is therefore proposed in Scheme 6. Initially, Pd^0 is generated from COD–$PdCl_2$ and XPhos. Then, the (π-allyl)palladium complex **I** is formed by oxidative addition of the allylic pivalate to the Pd^0 species. Subsequently, the base-deprotonated polyfluoroaromatic undergoes nucleophilic attack by the (π-allyl)palladium complex **I** to form a (polyfluoroaryl)(allyl)palladium complex **III**. Finally, reductive elimination leads to the expected allylated compound, with regeneration of the Pd^0 species.

In summary, we have developed a highly efficient COD–$PdCl_2$/XPhos-catalyzed allylation of polyfluorobenzenes to synthesize a series of allylfluorobenzenes by means of a C–H bond-functionalization reaction.[14] The new method has excellent functional-group tolerance, competitive yields, and excellent selectivity. Last, but not least, the high reactivity of new catalyst system permits the use of a catalyst loading of as little as 0.5 mol%, making such allylation reactions industrially attractive. Further investigations and applications of this strategy are underway in our laboratory.

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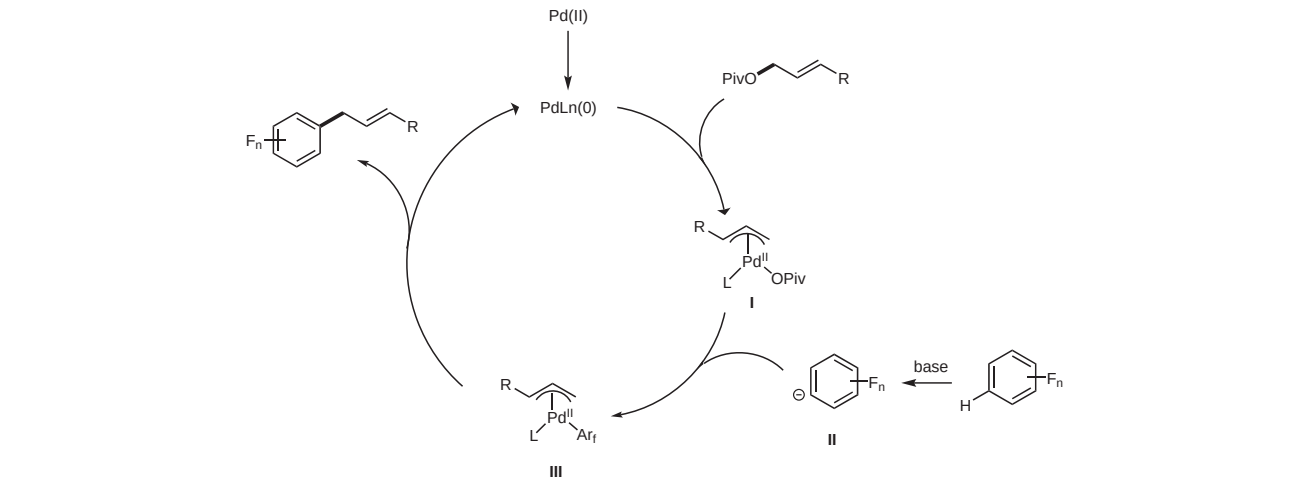
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590914.



Scheme 6 A possible mechanism for the direct palladium-catalyzed allylation of polyfluoroarenes with allylic pivalates. Ar_f = polyfluoroaryl.

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(14) **1,2,3,4,5-Pentafluoro-6-[(2*E*)-3-phenylprop-2-en-1-yl]benzene (4a); Typical Procedure**

COD–$PdCl_2$ (5 mol%), XPhos (10 mol%), Cs_2CO_3 (1.2 mmol, 1.2 equiv), and toluene (3 mL) were added sequentially to a Schlenk tube containing allylic pivalate (*E*)-**3a** (1.0 mmol, 1.0 equiv) and pentafluorobenzene (**1a**; 2.0 mmol, 2.0 equiv) under argon, and the mixture was stirred at 120 °C (oil bath) for 8 h until the reaction was complete (TLC). The mixture was then diluted with EtOAc (40 mL), washed with brine (3 × 20 mL), and dried (Na_2SO_4). After filtration and evaporation of the solvent, the residue was purified by chromatography (silica gel, hexane) to give a white solid; yield: 279 mg (98%); mp 62–64 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 4 H), 7.24–7.20 (m, 1 H), 6.47 (d, *J* = 15.7 Hz, 1 H), 6.21 (dt, *J* = 15.7, 6.7 Hz, 1 H), 3.59 (dd, *J* = 6.7, 1.3 Hz, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 145.00 (dm, *J* = 246.4 Hz), 139.87 (dm, *J* = 252.4 Hz), 137.52 (dm, *J* = 250.4 Hz), 136.57, 132.44, 128.55, 127.64, 126.19, 124.24, 113.23 (t, *J* = 19.1 Hz), 25.60. ^{19}F NMR (565 MHz, $CDCl_3$): δ = –143.90 (dd, *J* = 22.3, 8.4 Hz, 2 F), –157.23 (t, *J* = 22.3 Hz, 1 F), –162.48 (td, *J* = 22.3, 8.4 Hz, 2 F). MS (EI): *m/z* = 284 [M]$^+$.