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Palladium-catalyzed aerobic oxidative allylic C–H arylation of alkenes with polyfluorobenzenes†

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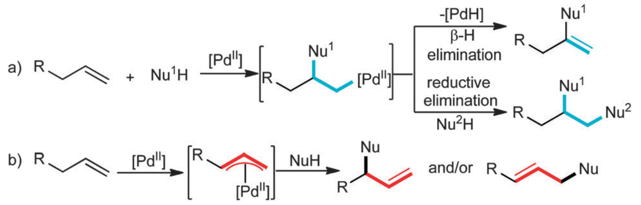
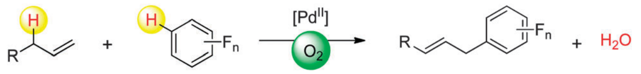
An aerobic oxidative cross-coupling reaction of alkenes with polyfluorobenzenes, through palladium-catalyzed allylic C–H activation, is reported. This attractive route provides a new way to forge allylic C–C bonds of valuable products, in good yields, with high regioselectivity.

Palladium-catalyzed oxidation reactions of alkenes continue to be an active area of research. Representative reactions include Wacker-type oxidation[1] and oxidative difunctionalization.[2,3] These reactions proceed through an alkylpalladium(II) intermediate that forms *via* nucleopalladation (Scheme 1a).[4] In contrast to traditional palladium-catalyzed oxidation of alkenes, a different reaction selectivity involving oxidative allylic C–H bond functionalization of alkenes has been developed and plays a vital role in organic synthesis.[5–11] The reaction is thought to proceed *via* substitution of allylpalladium intermediates generated through allylic C–H cleavage (Scheme 1b).[12] In this case, how to control the selectivity of the palladium catalysts in oxidative alkene functionalization remains challenging and rewarding.

We have recently reported a new regioselective palladium-catalyzed oxidative allylic C–H oxygenation[5d] and carbonylation[8] of alkenes with water and carbon monoxide (CO) as nucleophiles, respectively. On the basis of these preliminary studies, we hypothesized that electron-deficient polyfluoroarenes could be chosen as nucleophiles for the allylpalladium species, which would provide a straightforward approach for direct allylic C–H arylation of alkenes for traditional Tsuji–Trost reaction protocols.[13] Furthermore, polyfluoroarenes are key structural motifs found in various functional molecules, such as pharmaceuticals, agrochemicals, liquid crystals, and electronic devices.[14] Herein we describe the first example of direct palladium-catalyzed aerobic oxidative allylic C–H arylation of alkenes with polyfluorobenzenes *via* twofold C–H functionalization (Scheme 2). Moreover, the reaction proceeds by using molecular oxygen as the sole oxidant, which avoids the environmentally hazardous by-products obtained with other oxidants.[15]



Scheme 1 Pd-catalyzed oxidative alkene functionalization.



Scheme 2 Palladium-catalyzed aerobic oxidative allylic C–H arylation.

At the outset of this study, allylcyclohexane (**1a**) and pentafluorobenzene (**2a**) were used as substrates to optimize the reaction conditions. To our delight, when **1a** and **2a** were treated with $Pd(OAc)_2$ (10 mol%) under a dioxygen atmosphere (1 atm) in DMSO at 100 °C for 24 h, this reaction produced a 28% NMR yield of **3a** and the Wacker oxidation product **4a** was observed (Table 1, entry 1). Further screening of the solvents indicated that a mixed solvent system of DMSO–DMF (1 : 1) was found to benefit the reaction (Table 1, entries 6–16). Encouraged by this result, Ag_2O and pivalic acid (PivOH) were selected as the additive because it was shown to be beneficial for the aerobic dehydrogenative cross-coupling reaction of pentafluorobenzene.[16] Gratifyingly, treatment of **1a** and **2a** with $Pd(OAc)_2$ under a dioxygen atmosphere (1 atm) in the presence of 0.1 equiv. of Ag_2O and 0.5 equiv. of PivOH afforded the desired C1 arylation **3a** in 75% isolated yield with high regioselectivity (Table 1, entry 7), while the absence of either Ag_2O or PivOH gave unsatisfactory results (Table 1, entries 8 and 9). The replacement of Ag_2O with other silver salts, such as Ag_2CO_3, AgF and AgOAc, could also result in **3a**, albeit in lower yields (Table 1, entries 10–12). Furthermore, the reaction temperature was also varied, and 120 °C gave the best yield (entry 13). A lower yield of **3a** was obtained when O_2

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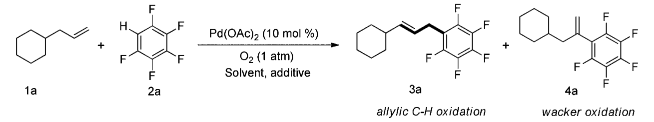
† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H, ^{19}F and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/c4cc02023e

Table 1 Optimization of the reaction conditions[a]



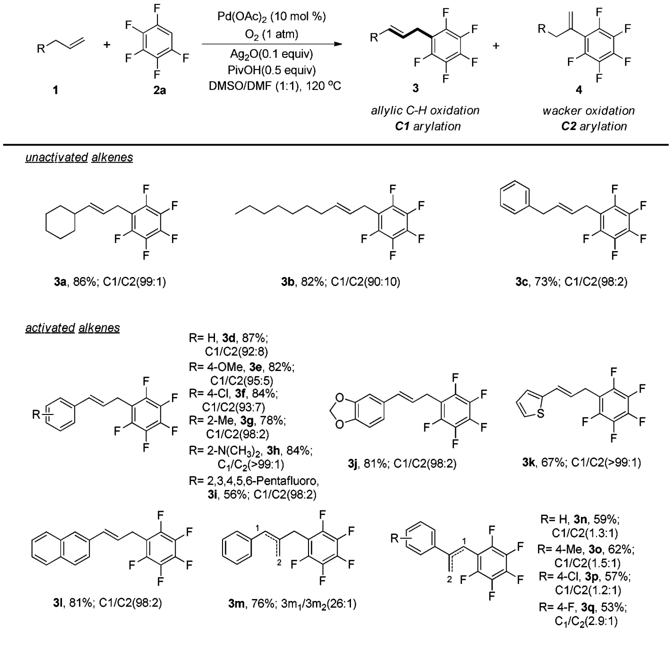
Entry	Solvent	Additive (equiv.)	T (°C)	Yield[b] (%) (**3a** : **4a**)
1	DMSO	—	100	28(83 : 17)
2	CH_3CN	—	100	17(30 : 70)
3	Dioxane	—	100	21(12 : 88)
4	Toluene	—	100	23(10 : 90)
5	DMF	—	100	31(60 : 40)
6	DMSO–DMF (1 : 1)	—	100	42(85 : 15)
7	DMSO–DMF (1 : 1)	Ag_2O (0.1), PivOH (0.5)	100	75(99 : 1)
8	DMSO–DMF (1 : 1)	PivOH (0.5)	100	44(95 : 5)
9	DMSO–DMF (1 : 1)	Ag_2O (0.1)	100	63(84 : 16)
10	DMSO–DMF (1 : 1)	Ag_2CO_3 (0.1), PivOH (0.5)	100	46(92 : 8)
11	DMSO–DMF (1 : 1)	AgF (0.1), PivOH (0.5)	100	28(93 : 7)
12	DMSO–DMF (1 : 1)	AgOAc (0.1), PivOH (0.5)	100	29(95 : 5)
13	**DMSO–DMF (1 : 1)**	**Ag_2O (0.1), PivOH (0.5)**	**120**	**88(99 : 1)**
14	DMSO–DMF (1 : 1)	Ag_2O (0.1), PivOH (0.5)	140	72(98 : 2)[c]
15	DMSO–DMF (1 : 1)	Ag_2O (0.1), PivOH (0.5)	120	21(98 : 2)[d]
16	DMSO–DMF (1 : 1)	Ag_2O (0.1), PivOH (0.5)	120	N.D.[e]

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), **2a** (3.0 equiv.), DMF–DMSO (v/v = 1 : 1, 2 mL, DMSO must be stored with the powder of 4 Å molecular sieves), O_2 (1 atm), 24 h. [b] Determined by ^{1}H NMR or GC analysis of the crude product. [c] Pentafluorobiphenyl was detected. [d] Under air. [e] In the absence of $Pd(OAc)_2$.

(1 atm) was replaced with air (entry 15). Finally, the absence of a Pd-catalyst did not give any desired product (Table 1, entry 16).

With the optimized conditions established, the scope of the terminal alkenes was first examined. As summarized in Table 2, terminal alkyl alkenes such as 4-phenyl-1-butene, allylcyclohexane and 1-dodecene, underwent direct oxidative arylation at the C1 position to generate the corresponding linear (*E*)-allylpentafluorobenzene derivatives in moderate to high yields (**3a–3c**). Moreover, a variety of allyl arenes bearing electron-withdrawing or electron-donating groups afforded the desired products in moderate to good yields with high regioselectivity, and the substituents at the *para* and *ortho* positions of the arene ring did not affect the efficiencies (**3d–3i**).

Table 2 Substrate scope of alkenes[a]



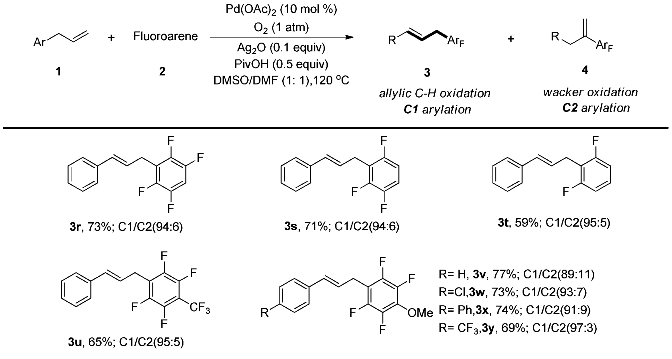
[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (0.1 equiv.) and PivOH (0.5 equiv.) in DMSO–DMF (2 mL, 1 : 1) under O_2 (1 atm) at 120 °C for 24 h; isolated yield; the ratio of the two isomers was determined by ^{1}H NMR.

Heteroaryl-substituted propenes such as 5-allylbenzo[*d*][1,3]-dioxole and 2-allylthiophene also produced the desired products in good yields (**3k**, **3j**). Interestingly, 2-naphthylpropene gave the corresponding product in 81% yield (**3l**). It is noteworthy that 2,3-disubstituted propene performed well in this transformation, leading to the corresponding trisubstituted product being produced in good yields (**3m**). Unexpectedly, α-methyl styrene and its derivatives proceeded efficiently under the optimized conditions by affording double bond isomerization products as major products (**3n–3q**).

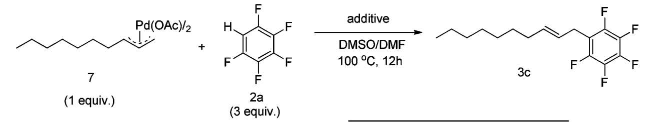
Next, the scope of polyfluoroarenes was examined in this reaction (Table 3). Variations of fluoroarenes containing 2–4 fluorines were investigated, comparable yields of compounds **3r**, **3s** and **3t** were provided at 120 °C with use of 3.0 equiv. of fluoroarenes. Furthermore, other fluoroarenes, such as 1,2,4,5-tetrafluoro-3-(trifluoromethyl)benzene, were also good coupling partners under the present reaction conditions; thus a good yield was obtained as well. Notably, the tetrafluoroarene bearing a –OMe group was tested with several allyl arenes, and comparable yields of the desired products were obtained (**3v–3y**).

Experimental support for an allylic C–H activation mechanism was obtained by preparing π-allylpalladium complex **7** and investigating its reactivity with fluorobenzene **2a** (Scheme 3). When the reaction was performed in the presence of PivOH (1.5 equiv.) and Ag_2O (1.2 equiv.), product **3c** was formed in 53% yield. In the absence of Ag_2O/PivOH or Ag_2O, a trace amount of **3c** was observed, while **3c** was only obtained in 17% yield for the reaction without PivOH. This demonstrates that the silver salt plays a pivotal role in the catalytic cycle. These results are consistent with a mechanism involving π-allylpalladium intermediates and suggest that PivOH facilitates nucleophilic attack on the π-allylpalladium species.[13b]

Table 3 Substrate scope of fluoroarenes[a]

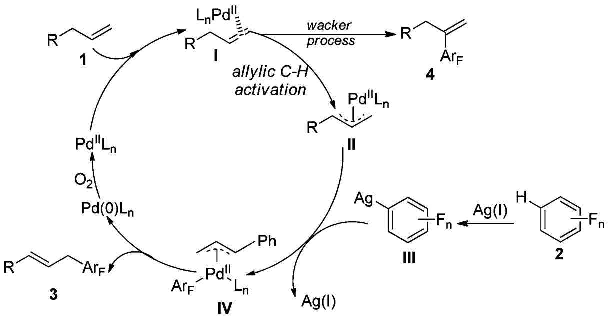


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (0.1 equiv.) and PivOH (0.5 equiv.) in DMSO–DMF (2 mL, 1 : 1) under O_2 (1 atm) at 120 °C for 24 h; isolated yield; the ratio of the two isomers was determined by ^{1}H NMR.



additive	3c
none	trace
Ag_2O(1.2 equiv)	17%
Ag_2O(1.2 equiv)/ PivOH(1.5equiv.)	53%
PivOH(1.2 equiv)	trace

Scheme 3 Experiments for mechanistic studies.



Scheme 4 Plausible reaction mechanism.

According to the experimental results and by referring to the leading references (12,13*b* and 16) the mechanism is proposed in Scheme 4. First, intermediate **I** is formed through the coordination of olefin to palladium. Then, there is a competition between allylic C–H activation and the Wacker process in the following step. The addition of PivOH affects the selectivity and facilitates the allylic C–H activation, leading to π-allylpalladium species **II** *via* an electrophilic allylic C–H cleavage by the Pd(II) catalyst. Then, π-allylpalladium intermediate **II** reacts with intermediate **III**, which was formed by the deprotonation of polyfluoroarene with silver salts, by metal exchange to generate a Pd–(polyfluoroaryl) complex **IV**. Finally, reductive elimination and reoxidation by O_2 regenerate the active Pd(II)L_n species.

In conclusion, we have developed an efficient and straightforward regioselective Pd-catalyzed method for aerobic oxidative allylic C–H direct arylation of alkenes with polyfluorobenzenes, which represents the most atom-efficient approach for the creation of allyl–aryl bonds, and the preparation of allylic polyfluoroarene derivatives of interest in both life and materials science. Various aryl and heteroaryl alkenes, as well as aliphatic alkenes, produced the expected allylated polyfluoroarenes. Undoubtedly, this is a valuable complementary method to the well-known Tsuji–Trost reaction, from an atom-economic and environmental perspective. Further investigations are focused on expanding the scope of this transformation and elucidating the detailed mechanism.

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