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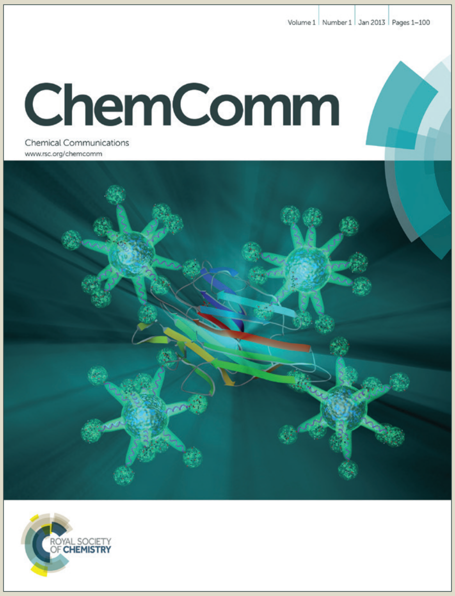

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ARTICLE TYPE

Palladium-catalyzed Aerobic Oxidative Allylic C–H Arylation of Alkenes with Polyfluorobenzenes

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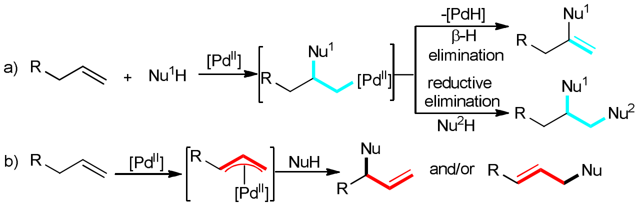
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

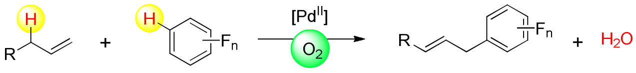
An aerobic oxidative cross-coupling reaction of alkenes with polyfluorobenzenes through palladium-catalyzed allylic C−H activation is reported. The attractive route provides a new way to forge allylic C−C bonds of valuable products in good yields with high regioselectivity.

Palladium-catalyzed oxidation reaction of alkenes continues to be an active area of research. Representative reactions included 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 the traditional palladium-catalyzed oxidation of alkenes, a different reaction selectivity in oxidative allylic C□H bonds functionalzation of alkenes has been significantly developed and plays vital roles 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 palladium catalysts in oxidative alkene functionalization remains challenging and rewarding.



Scheme 1 Pd-catalyzed oxidative alkene functionalization.

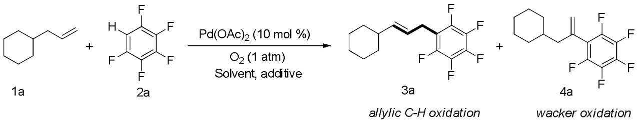
We have recently reported a new regioselective palladium-catalyzed oxidative allylic C□H oxygenation[5d] and carbonylation[8] of alkenes with water and carbon monoxide (CO), respectively, as nucleophiles. On the basis of these preliminary studies, we hypothesized that electron-deficient polyfluoroarenes could be chosen as nucleophiles for allylpalladium species, which would provide straightforward approach for direct allylic C□H arylation of alkenes to the traditional Trost-Tsuji reaction involved protocols[13]. Furthermore, polyfluoroarenes are a key structural motif found in various functional molecules, such as pharmaceuticals, agrochemicals, liquid crystals, and electronic device.[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 sole oxidant, which avoids the environmentally hazardous by-products obtained with other oxidants.[15]



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

At the outset of this study, allylcyclohexane (**1a**) and pentafluorobenzene (**2a**) were used as the 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

Table 1 Optimization of the reaction conditions[a]



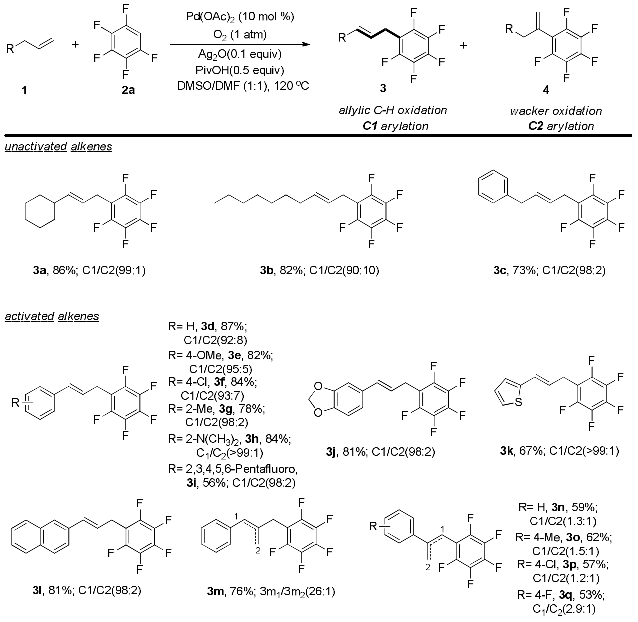
Entry	Solvent	Additive (equiv.)	T/°C	Yield(%) (3a:4a)[b]
1	DMSO	-	100	28(83:17)
2	CH_3CN	-	100	17(30:70)
3	Dioxane	-	100	21(12:88)
4	Toluene	-	100	23(10:90)
5	DMF	-	100	31(60:40)
6	DMSO/DMF(1:1)	-	100	42(85:15)
7	DMSO/DMF(1:1)	Ag_2O (0.1), PivOH (0.5)	100	75(99:1)
8	DMSO/DMF(1:1)	PivOH (0.5)	100	44(95:5)
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 ^1H 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) in DMSO at 100 °C for 24 h, this reaction provided 30% NMR yield of **3a** with observation of Wacker oxidation product of **4a** (Table 1, entry 1). Further screening of solvents indicated that a mixed solvent system of DMSO/DMF (1:1) was found to benefit the reaction (Table 1, entries 2-6). 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 86% 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, 9). The replacement of Ag_2O with other silver salts, such as Ag_2CO_3, AgF and AgOAc, could also furnish **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). The lower yield of **3a** was obtained when replaced O_2 (1 atm) with air (entry 15). Finally, the absence of Pd-catalyst did not give any desired product (Table 1, 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]

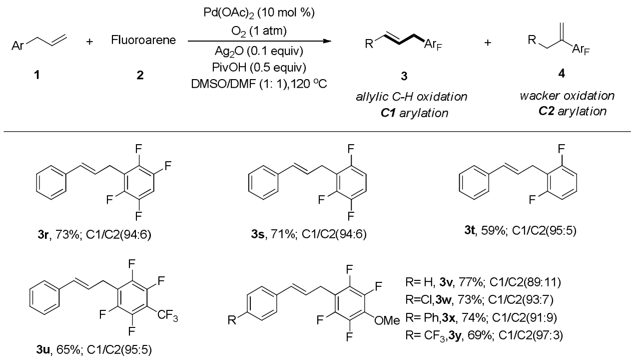


[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (0.1 equiv.) and PivOH (0.5 equiv.) in DMSO/DMF (2 mL, 1:1) under O_2 (1 atm) at 120 °C for 24 h; Isolated yield; Ratio of two isomers were determined by ^{1}H NMR.

Heteroaryl-substituted propene such as 5-allylbenzo[d][1,3]dioxole and 2-allylthiophene also provided desired products in good yields (**3k**, **3j**). Interestingly, 2-naphthylpropene gave the corresponding product in 77% yield (**3l**). It is noteworthy that 2,3-disubstituted propene performed well in this transformation, leading to the corresponding trisubstituted product in good yields (**3m**). Unexceptedly, *α*-methyl styrene and its derivatives proceeded efficiently under the optimized conditions but affording double bond isomerization products as major products (**3n-3q).**

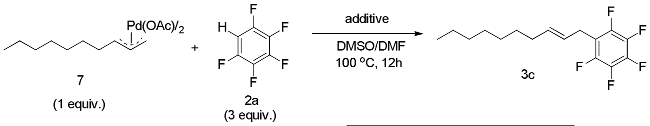
Next, the scope of polyfluoroarenes was examined in this reaction (Table 3). Variations of fluoroarenes containing 2-4 fluorines were investigated, comparable yields of compounds **3r**, **3s** and **3t** were provided at 120 °C with use of 3.0 equiv of fluoroarenes. Furthermore, another fluoroarene,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

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 (2mL, 1:1) under O_2(1 atm) at 120 °C for 24 h; Isolated yield; Ratio of two isomers were determined by ^{1}H NMR.

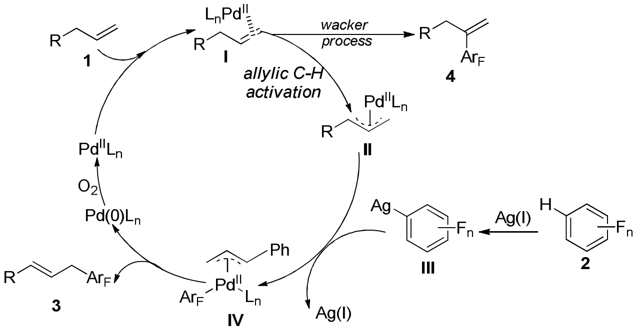
Experimental support for an allylic C□H activation mechanism was obtained by preparing π-allylpalladium complex 7 and investigating its reactivity with fluorobenzene **2a** (Scheme 3). When the reaction was performed in the presence of PivOH (1.5 equiv) and Ag_2O (1.2 equiv), product **3c** was formed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



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.

According to the experimental results and by referring to the leading references,[12,13b,16] the mechanism was proposed in Scheme 4. First, intermediate **I** is formed through the coordination of the olefin to palladium. Then, there is a competition between allylic C-H activation and Wacker process in the following step. The addition of PivOH affected the selectivity and facilitate 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 Pd-(polyfluoroaryl) complex **IV**. Finally, reductive elimination and reoxidation by O_2 regenerate active Pd(II)L_n species.



Scheme 4 Plausible reaction mechanism.

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 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 gave the expected allylated polyfluoroarenes. Undoubtedly, this method is a valuable complementary to the well-known Trost-Tsuji reaction from an atom-economic and environmental perspective. Further investigations are focused on expanding the scope of this transformation and elucidating the detailed mechanism.

We are grateful to the National Natural Science Foundation of China (21172076 and 21202046), the National Basic Research Program of China (973 Program) (2011CB808600), the Guangdong Natural Science Foundation (10351064101000000 and S2012040007088), and the Fundamental Research Funds for the Central Universities (2014ZP0004 and 2014ZZ0046).

Notes and references

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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/b000000x/

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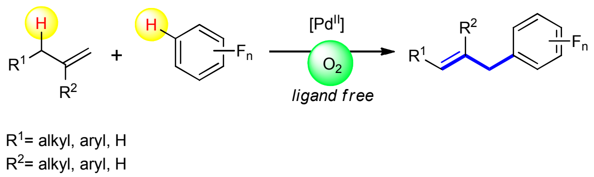

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