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# Palladium-catalyzed Heck reaction of *in-situ* generated benzylic iodides and styrenes

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## ABSTRACT

A palladium-catalyzed Heck reaction of *in-situ* generated benzylic iodides and styrenes has been achieved. The reaction proceeds in a one-pot manner through 1) addition perfluoroalkyl iodides to styrenes to give benzylic iodides, 2) followed by a palladium-catalyzed Heck coupling of the resulting benzylic iodides with the same alkenes in high regio- and stereoselectivity. A variety of perfluoroalkylated alkenes were obtained in moderate to excellent yields.

Organo-fluorine compounds play an important role in medicinal chemistry and material science due to their specific biological activity and physicochemical properties.[1] The unique properties of fluorinated compounds[2] usually lead to a profound impact on the design of commonly used building block in pharmaceuticals and agrochemicals. Thus, numerous synthetic methods have been constructed for the introduction of fluorine or fluorine-containing functional groups to organic compounds during the past years.[3] Additionally, among all the fluorine-containing compounds, perfluorinated compounds are widely utilized in industrial and civil field due to their special hydrophobic and strain-resistance properties. Thus, the development of synthetic approach for these perfluorinated compounds preparation has attracted increasing attention in organic synthesis.

Among the developed procedures, the main efforts have been focused on fluoroalkylation of aromatic compounds.[4] Recently, the reaction of perfluoroalkyl radical with alkyne to construct perfluorinated alkenes have also been developed.[5–10] Usually they are based on the usage of transition-metal catalysis such as Pd,[5] Fe,[6] and Ru,[7] or radical initiators.[8] These processes usually involving an initial alkyne iodoperfluoroalkylation, and the resulting vinyl iodide could undergo a typical cross-coupling reaction with various nucleophiles.[9] Most recently, we established a one-pot reaction for the synthesis of perfluoroalkylated enynes from perfluoroalkyl iodides and alkynes.[10] During the process of this work, we found that such type of domino reaction are rarely explored with alkenes.[11] Notably, palladium-catalyzed Heck type coupling of bromodifluoroacetate or [(bromodifluoromethyl)sulfonyl]benzene with alkenes have been achieved.[11d–f] It's important to mentioned that Chen and co-workers reported their study on Pd (0)-catalyzed coupling of fluoroalkyl iodides with alkenes to give the corresponding adducts in high yields in 1988.[11g] Herein, we wish to report our achievement on this idea: a palladium-catalyzed selective domino perfluoroalkylation of alkene.

We started our study with perfluorobutyl iodide and styrene as the model substrates in toluene at 120 °C, with DBU as the base in the presence of $Pd(PPh_3)_4$. To our delight, with a ratio of 2.5:1 between perfluorobutyl iodide and styrene, 73% yield of the desired product can be obtained (Table 1, entry 1). Then various bases, including $K_2CO_3$, $Et_3N$, DiPEA, and DMAP were examined, the yields decreased in all these cases (Table 1, entries 2–5). We next tested the ligand effect, the yields had no improvement with a number of ligands, such as $PCy_3$, $P(o\text{-tolyl})_3$, DPPF, DPEphos, and Xantphos (Table 1, entries 6–10). Subsequently, solvents screening showed that 1,4-dioxane was the optimal media for this transformation (Table 1, entries 11–13). Furthermore, we investigated the catalyst precursors, $Pd(OAc)_2$ and $PdCl_2$ resulted in lower yields (Table 1, entries 14–15), while $Pd(dba)_3$ provided a comparable

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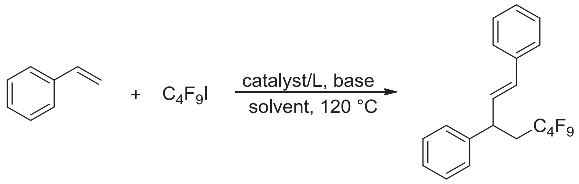
**Table 1**
Screening of the reaction conditions.[a]



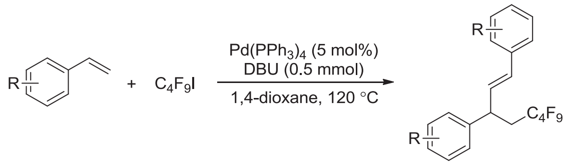
| Entry | Catalyst | Ligand | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | | DBU | Toluene | 73 |
| 2 | $Pd(PPh_3)_4$ | | $K_2CO_3$ | Toluene | 45 |
| 3 | $Pd(PPh_3)_4$ | | $Et_3N$ | Toluene | 59 |
| 4 | $Pd(PPh_3)_4$ | | DiPEA | Toluene | 49 |
| 5 | $Pd(PPh_3)_4$ | | DMAP | Toluene | 45 |
| 6 | $Pd(PPh_3)_4$ | $PCy_3$ | DBU | Toluene | 30 |
| 7 | $Pd(PPh_3)_4$ | P(*o*-tolyl)$_3$ | DBU | Toluene | 25 |
| 8 | $Pd(PPh_3)_4$ | DPPF | DBU | Toluene | 23 |
| 9 | $Pd(PPh_3)_4$ | DPEphos | DBU | Toluene | 28 |
| 10 | $Pd(PPh_3)_4$ | Xantphos | DBU | Toluene | 25 |
| 11 | $Pd(PPh_3)_4$ | | DBU | DMF | 50 |
| 12 | $Pd(PPh_3)_4$ | | DBU | 1,4-Dioxane | 78 |
| 13 | $Pd(PPh_3)_4$ | | DBU | DMSO | 22 |
| 14 | $Pd(OAc)_2$ | | DBU | 1,4-Dioxane | 59 |
| 15 | $PdCl_2$ | | DBU | 1,4-Dioxane | 58 |
| 16 | $Pd(dba)_3$ | | DBU | 1,4-Dioxane | 75 |
| 17[c] | $Pd(PPh_3)_4$ | | DBU | 1,4-Dioxane | 93 |

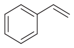
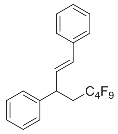
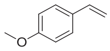
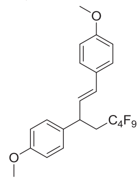
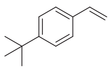
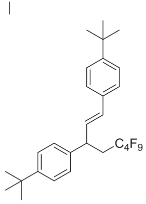
[a] Reaction conditions: perfluorobutyl iodide (1.25 mmol), styrene (0.5 mmol), base (0.5 mmol), catalyst (5 mol%), ligand (10 mol%), solvent (2.5 mL), 120 °C, 12 h.
[b] Yields were determined by GC using dodecane as an internal standard.
[c] 20 h.

yield as $Pd(PPh_3)_4$ (Table 1, entry 16). It was noteworthy that when the reaction time was prolonged to 20 h, the yield of the target product can be increased to 93% (Table 1, entry 17).

With the optimal catalyst system in hand,[12] we then went on our study to the substrates testing. A variety of styrenes were examined under our standard conditions. Substrates with electron-donating groups, such as methoxy, *tert*-butyl, methyl, and acetoxy groups provided the desired products in good to excellent yields (Table 2, entries 2–7). Those substrates with methyl groups substituted at *para*-and *ortho*-position resulted in higher yield than with *meta*-substitution probably due to the electronic effect (Table 2, entries 4–5 *vs.* 6). 2,5-Dimethyl substituted styrene could also afford the

**Table 2**
Pd-catalyzed synthesis of perfluorinated alkenes: testing of alkenes.[a]



| Entry | Styrenes | Products | *E*/*Z* | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | >20:1 | 93 |
| 2 |  |  | >20:1 | 80 |
| 3 |  |  | >20:1 | 75 |

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