

Pd(OAc)₂ Catalyzed Olefination of Highly Electron-Deficient Perfluoroarenes

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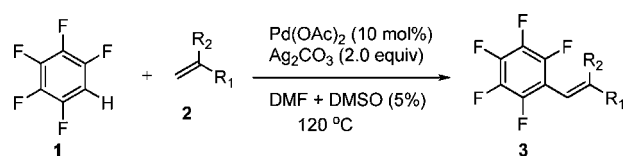
Perfluoroarenes constitute a distinct class of fluorinated compounds due to their importance in materials and life science.¹ Usually, they can be prepared from perfluoroaryl metals, halides, or aldehydes.^{1d,2} However, this “prefunctionalization” process has intrinsic drawbacks in terms of atom and step economy. Recently, the direct arylation, alkenylation and alkylation of perfluoroarenes were reported by Fagnou,³ Daugulis,⁴ and Nakao and Hiyama,⁵ respectively. While, these approaches are attractive, new methods for the direct alkenylation of perfluoroarenes remain highly desirable in view of the requirement of alkenyl halides as substrates⁴ or employment of an air-sensitive Ni(0) catalyst that is only suitable for internal alkynes in this process⁵ in these prior studies. However, unlike the direct olefination of electron-rich arenes,^{6–8} reactions of electron-deficient arenes are still a great challenge, and only rare examples have been reported.⁹ The reason is that the electron-deficient arenes are nonreactive due to their poor coordination with Pd(OAc)₂.^{9a,d} In addition, the σ -bonds between transition metals and perfluorinated groups, such as the highly electron-deficient pentafluorophenyl group (M–C₆F₅), are particularly strong and reluctant to reaction.^{2c,d,10} Pioneering work on insertion of alkenes into the M–C₆F₅ bond using catalytic (NBu₄)₂[Pd₂-(*μ*-Br)₂(C₆F₅)₂Br₂] has been reported by Espinet and Milstein and co-workers.^{2c,d} This work represents an impressive example of transition metal catalysis to access organofluorine compounds, but fluorinated arylhalides were required and nonactivated alkenes such as aliphatic and electron-rich alkenes were less promising substrates. Herein, we report a first example of Pd(OAc)₂ catalyzed direct olefination of highly electron-deficient perfluoroarenes with a broad range of substrates in moderate to high yields and with moderate to high stereo- and regioselectivities.

Initially, a highly electron-deficient pentafluorobenzene **1** and ethyl acrylate **2a** were chosen as model substrates for this study. After a survey of reaction conditions we found that the solvent, oxidants, and Pd catalysts are critical for the reaction efficiency (see Supporting Information). A mixed solvent system of 5% DMSO in DMF was found to be the optimum reaction medium. The reaction carried out with **1** (1 equiv), **2a** (2 equiv), and Ag₂CO₃ (2 equiv) which functions as both a base and oxidant in the presence of Pd(OAc)₂ (10 mol %) at 120 °C provided **3a** in good yield (78%, mixture of *E/Z* isomers, *E/Z* = 14:1). Other oxidants such as Cu(OAc)₂, oxone, BQ, PhI(OAc)₂, and O₂ or other Pd catalysts (PdCl₂, Pd(TFA)₂, and Pd₂(dba)₃) showed less or no activity.

A great variety of pentafluorophenyl substituted alkenes can be generated via this method (Table 1). The alkenylation of **1** worked well for electron-deficient olefins bearing ester, amide, phosphonate, or ketone groups, and moderate to excellent yields and high stereoselectivities were obtained (entries 1–6, 8–10). For some entries, removal of the minor *Z*-isomer required reversed-phase preparative HPLC. Interestingly, in the case of branched olefin **2d**, constitutional isomer **4d** was obtained as the major product (entry

4). Acrylonitrile **2g** was also tolerated, and a 34% yield of a mixture (*E/Z* = 1.4:1) of isomers of **3g** was provided (entry 7). Notably, the nonactivated aliphatic olefins **2k–l** underwent smooth reactions in good yields (entries 11–12), which is in sharp contrast to previous results.^{2c,d} Moreover, electron-rich alkenes were readily reacted with **1** in good yields (entries 13–15). For **2o**, a mixture of constitutional isomers **3o** and **4o** were formed (entry 15).

Table 1. Oxidative Olefination of Pentafluorobenzene with Various Alkenes^a

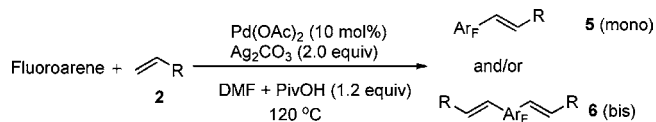


| entry | alkene 2 | product 3 | yield (%) ^b , (<i>E/Z</i>) ^d |
|-----------------|-----------------|-------------------------|------------------------------------------------------------|
| 1 | 2a | 3a | 69 ^c ; (14:1) |
| 2 | 2b | 3b | 69 ^c ; (15:1) |
| 3 | 2c | 3c | 64 ^c ; (13:1) |
| 4 ^e | 2d | 4d | 68 ^c |
| 5 | 2e | 3e | 74, <i>E</i> only |
| 6 | 2f | 3f | 83 ^c ; (12:1) |
| 7 ^f | 2g | 3g | 34, (1.4:1) |
| 8 ^f | 2h | 3h | 44, (60:1) |
| 9 | 2i | 3i | 61, (50:1) |
| 10 | 2j | 3j | 55, (23:1) |
| 11 | 2k | 3k | 85 ^g |
| 12 ^e | 2l | 3l | 83, (50:1) |
| 13 | 2m | 3m | 90, (50:1) |
| 14 | 2n | 3n | 71, <i>E</i> only 80 ^f , <i>E</i> only |
| 15 | 2o | 3o and 4o | 65 ^g 3o (10:1) / 4o = 1.3:1 |

^a Reaction conditions unless otherwise specified: **1** (0.6 mmol), **2** (2.0–3.0 equiv), and DMF (2.4 mL) + DMSO (120 μ L) for 10–12 h. ^b Isolated yield. ^c Yield after purification by reversed-phase preparative HPLC. ^d Determined by ¹⁹F NMR. ^e Using 20 mol % Pd(OAc)₂, 3.0 equiv of Ag₂CO₃ for 12–24 h. ^f Using 20 mol % Pd(OAc)₂, 3.0 equiv of Ag₂CO₃, and 4.0 equiv of alkene. ^g Isolated yield of mixtures of constitutional isomers (see Supporting Information).

The substrate scope with respect to fluoroarenes was also tested, and representative results are summarized in Table 2.¹¹ We found that using 10 mol % of Pd(OAc)₂, 1.2 equiv of PivOH¹² instead of DMSO (5%), and 4.0 equiv of fluoroarenes afforded alkenylated products in moderate yields with moderate to good regioselectivities (for details see Supporting Information). Generally, the reaction with electron-rich alkene **2m** afforded higher yields than that of electron-deficient alkene **2c**. The most acidic C–H bonds located between two fluorines (entries 1–2, 4–5) are primary reaction sites and provided mostly monoalkenylated products in higher yields than substrates with C–H bonds ortho to only one fluorine, such as 1,2,3,4-tetrafluorobenzene (entry 3). However, in the monoalkenylation of 1,2-difluorobenzene to give **5fa** or **5fb**, a decreased regioselectivity between position **a** (**5faa** or **5fba**) and position **b** (**5fab** or **5fbb**) was observed (**5faa/5fab** = 2:1, **5fba/5fbb** = 2:1) (entry 6). It is worth noting that an arylbromide was also tolerated by the reaction conditions (entry 7) providing opportunities for further functionalization. Furthermore, substrates with an electron-donating methoxy group and fluorinated pyridine also furnished the alkenylated products in moderate to good yields (entries 8–9).

Table 2. Oxidative Olefination of Fluoroarenes with Alkenes^a



| entry | fluoroarene | R | yield (%), ^b 5 | yield (%), ^b 6 |
|----------------|-------------|---------------------------------|------------------------------------------------------|----------------------------------|
| 1 | | CO ₂ Bu ^t | 62 (5aa) | 8 (6aa) |
| | | Ph | 73 (5ab) ^c | 15 (6ab) ^c |
| 2 | | CO ₂ Bu ^t | 66 (5ba) | 8 (6ba) |
| | | Ph | 63 (5bb) | 26 (6bb) |
| 3 | | CO ₂ Bu ^t | 44 (5ca) | --- |
| | | Ph | 48 (5cb) | --- |
| 4 | | CO ₂ Bu ^t | 63 (5da) | 18 (6da) |
| | | Ph | 62 (5db) | 13 (6db) |
| 5 | | CO ₂ Bu ^t | 55 (5ea), (3:1) ^d | --- |
| | | Ph | 54 (5eb), (3.6:1) ^d | trace |
| 6 | | CO ₂ Bu ^t | 61 (5fa), (2:1) ^d | 5 (6fa) |
| | | Ph | 46 (5fb), (2:1) ^d | --- |
| 7 ^e | | CO ₂ Bu ^t | 61 (13:1) ^e , (5ga) ^f | 12 (6ga) |
| | | Ph | 61 (5gb) | --- |
| 8 ^e | | CO ₂ Bu ^t | 38 (10:1) ^e , (5ha) | --- |
| | | Ph | 60, (5hb) | --- |
| 9 ^h | | CO ₂ Bu ^t | 69 (5ia) ⁱ | --- |
| | | Ph | 72 (5ib) | --- |

^a Fluoroarene (4.0 equiv), **2** (0.6 mmol), DMF (2.4 mL) for 18–24 h.

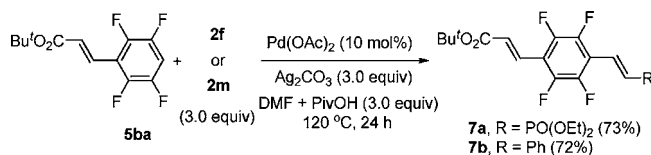
^b Isolated yield. ^c 5% DMSO was used instead of PivOH. ^d Isolated yield of mixtures of regioisomers, number in parentheses is the regioselectivity between position **a** and position (**b+c**) or **b**.

^e Fluoroarene (1.0 equiv), **2** (3.0 equiv), DMF (2.4 mL) + DMSO (5%).

^f Pd(OAc)₂ (15 mol %). ^g Purified by reversed-phase preparative HPLC; number in parentheses is the ratio of E/Z. ^h Fluoroarene (1.0 equiv), **2** (3.0 equiv), DMF (2.4 mL), PivOH (1.2 equiv). ⁱ Pd(OAc)₂ (20 mol %), PivOH (3.0 equiv).

It was also possible to further derivatize the perfluoroarylated alkenes through C–H functionalization. As depicted in Scheme 1, compound **5ba** reacted with **2f** or **2m**, respectively, to form unsymmetrical bis-alkenylated products **7** in good yields. This strategy thus allows the selective installation of substituents at different positions and provides access to highly functionalized perfluoroarenes by catalytic methods. A 2-g-scale synthesis of **3a**

Scheme 1. Formation of Bis(alkenyl)perfluoroarenes



was also performed in good yield (71%), indicating the good reliability of the process (see Supporting Information).

In conclusion, we developed an efficient, Pd(OAc)₂ catalyzed method for direct olefination of highly electron-deficient perfluoroarenes. The reaction scope includes both activated and nonactivated alkenes. Applications of alkenylated perfluoroarenes in design and synthesis of bioactive molecules are under active investigation in our laboratory.

Acknowledgment. NSF of China (20902100, 20852003, 20832008), the Shanghai Rising-Star Program (09QA1406900), and SIOC are greatly acknowledged for funding this work. Professor Wilfred A. van der Donk at UIUC and Professor Feng-Ling Qing at SIOC are greatly acknowledged for their help.

Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA908434E