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Palladium-Catalyzed Coupling of Polyfluorinated Arenes with Heteroarenes via C–F/C–H Activation

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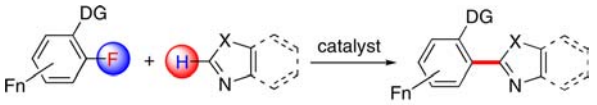
ABSTRACT



DG = Directing group; X = O, S, NR

The first palladium-catalyzed coupling of 2-pyridyl-polyfluoroarenes and benzoxazole, thiazole, benzothiazole, benzoimidazole, oxazole or oxadiazole via a concurrent C–F/C–H activation is described. Initial mechanistic studies showed that C–F activation of perfluoroarene is likely the rate-limiting step of the catalytic cycle. This protocol provides a useful and operationally simple process to functionalized polyfluoroarenes.

Compared to the well-developed cross-coupling reactions of aryl chlorides, bromides and iodides,[1] analogous reactions that involve the selective activation of a C–F bond in polyfluoroarenes are rare,[2] mainly due to not only the fundamental challenges in activating one of the strongest single bonds to carbon[3] but also the difficulties in controlling the site selectivity of the multiple C–F bonds in polyfluoroarenes.[2,4] In the past 10 years, a few methods[5–8] that proceeded through transition metal-catalyzed activation of the C–F bond in polyfluorinated arenes have been reported. These methods typically coupled polyfluorinated arenes with aryl nucleophiles such as aryl-magnesium halides (Grignard reagents), zinc, boronic acids or tin reagents. While these methods are quite effective for the preparation of partially fluorinated arenes, we envisioned that if a concurrent selective C–F bond activation of polyfluoroarenes and C–H bond activation of the second coupling partner can be realized, a more efficient and straightforward strategy could be developed for the preparation of partially fluorinated arenes that are important structural motifs in many compounds that are useful for pharmaceuticals, argochemicals and material sciences.[9] Such a process represents an intriguing synthetic challenge because of the difficulties in activating both a C–F bond and a C–H bond at the same time and in suppressing the

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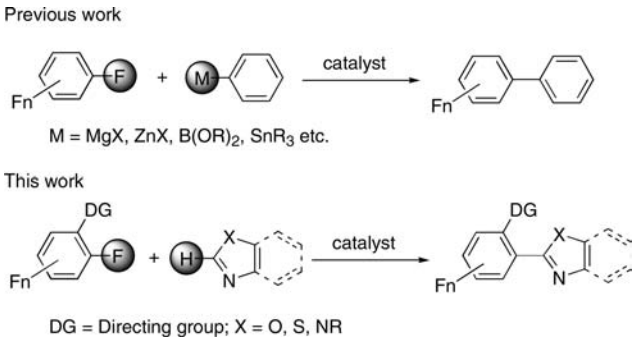
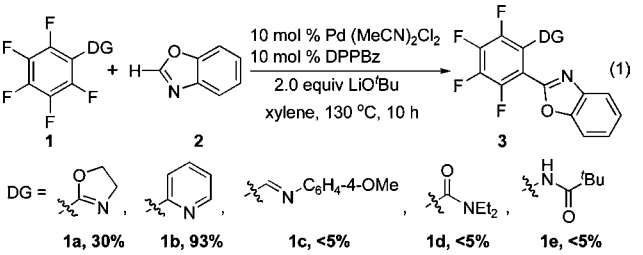
Scheme 1. Strategies for Transition Metal-catalyzed C−F Bond Activation



activation of the undesired but kinetically more favorable C−H bond of the polyfluoroarene substrates. We now report a direct palladium-catalyzed cross-coupling reaction of polyfluoroarenes with heteroarenes. Our report is the first example of a transition metal-catalyzed carbon−carbon bond formation via a concurrent C−F/C−H bond activation process (Scheme 1).[10,11]

We recently developed a palladium catalyzed Suzuki-Miyaura coupling reaction of polyfluorophenyl oxazolines, in which the selective ortho-C−F activation was directed by the oxazoline group.[12] In light of these preliminary studies, we initially chose to examine the reaction of pentafluorophenyl oxazoline and benzoxazole as the second coupling partner, in an effort to achieve the concurrent C−F/C−H bond activation. After careful investigation, we were excited to find that the desired carbon−carbon bond forming product could be obtained in 30% yield when pentafluorophenyl oxazoline and 2.0 equiv of benzoxazole were heated in xylene at 130 °C for 10 h with lithium *tert*-butoxide as the base and a catalyst generated in situ from $Pd(MeCN)_2Cl_2$ and DPPBz (1,2-bis(diphenylphosphino)benzene). The major side product was identified as 2-(2-*tert*-butoxy-3,4,5,6-tetrafluorophenyl)-4,5-dihydrooxazole. We reasoned that the side product was generated by substitution of *tert*-butoxide of the ortho-C−F bond because of the electron-withdrawing oxazoline group. In agreement with our assumption, switching the directing group from oxazoline to 2-pyridinyl resulted in significant improvement of the yield to 93%. Interestingly, other directing groups such as an imine or amide were ineffective under these conditions (eq 1).



Encouraged by these initial results, we further optimized the reaction parameters such as the palladium precursors, ligands, bases and solvents (See Supporting Information for details). It was found that ligand is critical for the reaction efficiency. For example, electron-rich, sterically hindered monodentate trialkyl ligands such as P^tBu_3, PCy_3 and RuPhos that have been widely used for the coupling of aryl chlorides were ineffective. Bidentate ligands with large bite angles such as Xantphos or DPEPhos were also not effective. In contrast, reactions using bidentate ligands such as DPPF, DPPE, DPPP, BINAP and DPPBz occurred to full conversion after 10 h at 130 °C. It was found that the reaction using DPPBz as the ligand afforded the desired product in higher yield than those using other ligands as determined by ^{19}F NMR spectroscopy. The reaction was sensitive to the base. Reactions using weak base K_3PO_4 or Cs_2CO_3 led to lower yields. Using bases such as NaO^{t}Bu or KO^{t}Bu led to much lower yield while reaction with LiO^{t}Bu as the base gave comparable yield under the same conditions. Next, the effect of the solvent was further evaluated. No product was observed when the reaction was conducted in polar, aprotic solvent such as dimethylacetamide. Reactions in less polar solvents such as dioxane, diethoxy ethane or 1,2-dichloroethane occurred slowly to afford the product in lower yields. Finally, to our delight, the catalyst loading can reduce to 5.0 mol % without significant loss of the yield. With the optimized conditions now in hand, we investigated the scope of the palladium-catalyzed C−F/C−H bond activation/carbon−carbon bond formation reaction of polyfluoroaryl pyridines, and the results are summarized in Scheme 2. A variety of 4-, 5- or 6-subsittuted benzoxazoles were subjected to the reaction conditions to afford the desired coupled products in good yields. It is worth noting that the carbon-chloride bond of 5-chlorobenzoxazole remained intact under these conditions, indicating that the directing group favors the cleavage of the strong C−F bond (Scheme 2, entry **3c**). The presence of Cl in the products is very useful for further synthetic manipulations via numerous cross-coupling reactions. When 6-fluorobenzoxazole was used, the desired product **3j** was

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(11) For selected examples on C−X/C−H activation, see: (a) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090. (b) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044. (c) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K.-H.; He, C.; Wang, H.; Kwong, F.-Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (e) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (d) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (e) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (f) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (g) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (h) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (i) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (j) Zanardi, A.; Novikov, M. A.; Martin, E.; BEnet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901.

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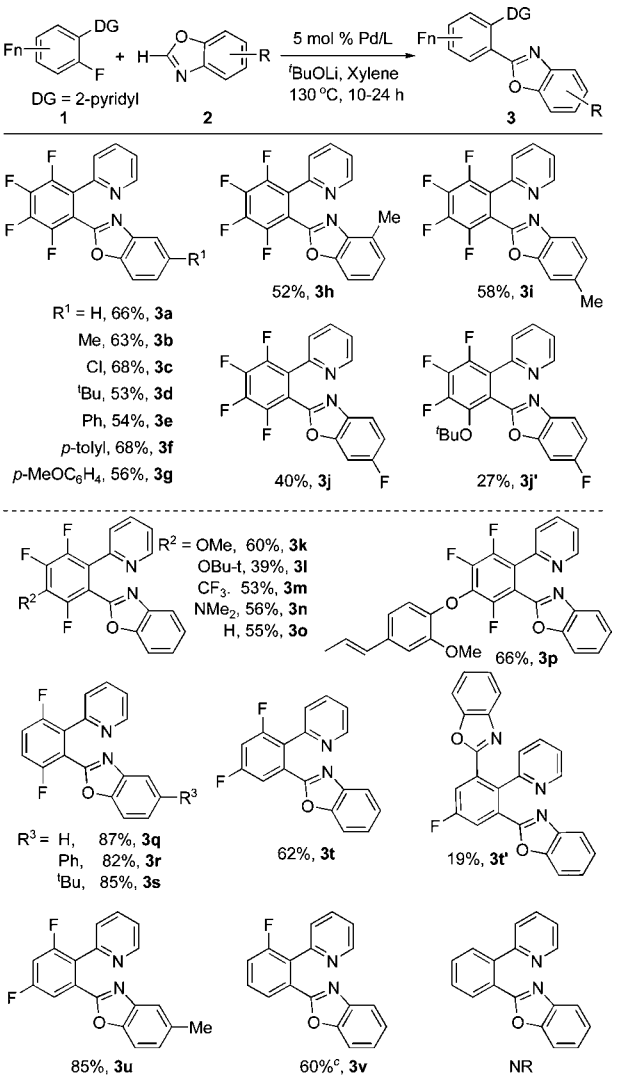
Scheme 2. Palladium-catalyzed Coupling of **1b** with Substituted Benzoxazole via C−F/C−H Bond Activation[a,b]



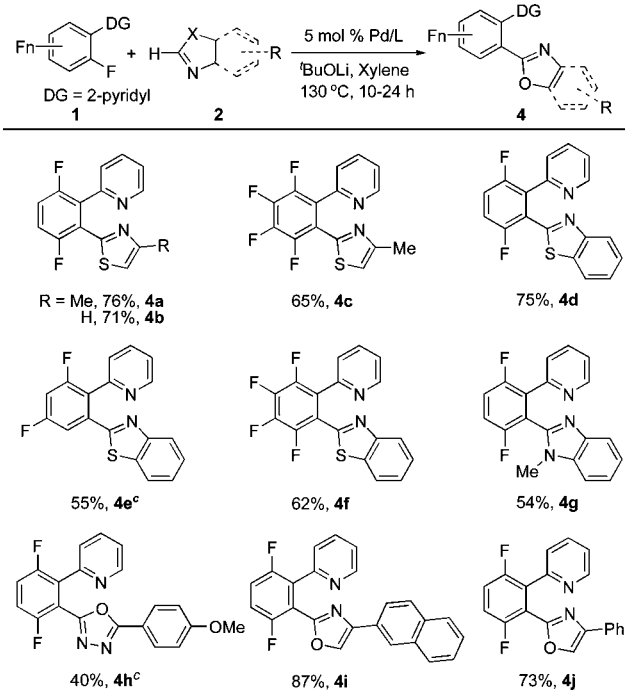
[a] Reaction conditions: 2-(pentafluorophenyl)-pyridine **1b** (1.0 mmol), benzoxazole (2.0 mmol), $Pd(CH_3CN)_2Cl_2$ (5 mol %), DPPBz (5 mol %) and Li*O*^{t}Bu (2.0 mmol) in xylene (20.0 mL) at 130 °C for 10−24 h. [b] Isolated yields. [c] Reaction was conducted at 160 °C for 36 h.

isolated in 40% yield along with a side product **3j′** generated from reaction with the base (Scheme 2, entries **3j** and **3j′**). Interestingly, reactions of benzoxazoles with electron-withdrawing groups such as esters or nitro were more complicated, affording the desired product in much lower yields.

To expand the scope of the reaction, we studied the palladium-catalyzed concurrent C−F/C−H bond activation of a variety of polyfluoroarenes, as summarized in Scheme 2. Reactions of 4-substituted-2,3,5,6-tetrafluorophenyl-2-pyridines occurred smoothly to give the desired product in acceptable yields. Interestingly, reactions of 2-(2,3,6-trifluorophenyl)pyridine or 2-(2,4,6-trifluorophenyl)-pyridine occurred in higher yields than those of other polyfluoroarenes (Scheme 2, entries **3q-u**). Reactions of 2-(2,3,6-trifluorophenyl)pyridine occurred preferentially at the 2-position due to the electron-withdrawing effect of the adjacent fluorine atom (Scheme 2, entries **3q-s**). The molecular structure of compound **3q** was characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and was further confirmed by X-ray crystallographic analysis of its single crystals. Reactions of 2-(2,6-difluorophenyl)pyridine was much more difficult than those tri- or tetrafluorosubstituted arenes and required 36 h at 160 °C to only 64% conversion to give the corresponding product in 60% yield (Scheme 2, **3v**). No C−F bond activation was observed for the reaction of 2-(2-fluorophenyl)pyridine as substrate. Several groups have reported that the activation of the C−F bond in less fluorinated arenes were much more difficult than those in pentafluorophenyl substrates.[7,8c,13] Jones and co-workers reported that the strength of the metal−Ar_F bond increases with the increasing of the electronegativity of the aryl group.[14] Consequently, the energy for C−F activation decreased as the number of fluorine increased.

On the basis of these findings, we next explored the use of other heterocycles such as thiazole, benzothiazole,

Scheme 3. Palladium-catalyzed Coupling of 1 with Substituted Thiazole, Benzothiazole, Benzoimidazole, Oxazole and Oxadiazole via C−F/C−H Bond Activation[a,b]



[a] Reaction conditions: 2-(polyfluorophenyl)-pyridine 1 (1.0 mmol), heterocycle (2.0 mmol), $Pd(CH_3CN)_2Cl_2$ (5 mol %), DPPBz (5 mol %), (IPr)CuO^{t}Bu (0.1 mmol) and $LiOCEt_3$ (2.0 mmol) in xylene (20.0 mL) at 130 °C for 10−24 h. [b] Isolated yields. [c] Reaction was conducted at 160 °C for 24 h.

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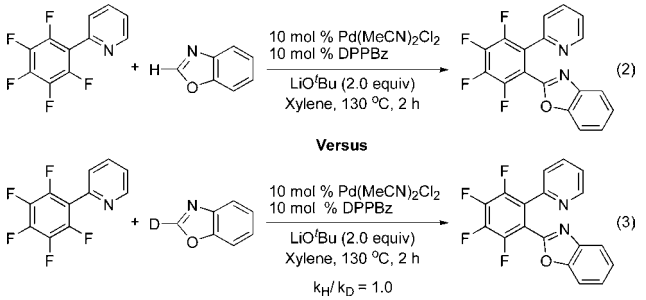
(14) Evans, M. E.; Burke, C. L.; Yalbuathes, S.; Clot, E.; Jones, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 13464.

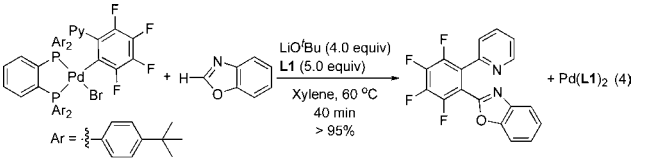
benzoimidazole, oxazole and oxadiazole in the C−F/C-H activation reactions. Surprisingly, it was found that reactions of these heterocycles occurred to low conversions under the current catalyst using $Pd(CH_3CN)Cl_2$/DPPBz. After a brief screening of the effect of different additives, we discovered an acceptable solution in which the reaction of 2-(2,3,5-trifluorophenyl)pyridine with benzothiazole was conducted with 0.1 equiv of (IPr)CuO^{t}Bu[15] to furnish the corresponding product **4d** in 75% yield (Scheme 3, entry **4d**). Under these optimized conditions, various heterocycles such as thiazole, benzothiazole, benzimidazole, oxazole and oxadiazole reacted smoothly to furnish the corresponding coupled products in moderate to good yields (Scheme 3, entries **4a**−**j**). The reactivity trend is similar to that observed with benzoxazole as the substrates. Reaction of 3-(4-anisyl)-oxadiazole with 2-(2,3,5-trifluorophenyl)pyridine was much slower than those of other heterocycles. The reaction required 160 °C for 24 h to occur to full conversion to give the coupled product in 40% isolated yield (Scheme 3, entry **4h**).

To determine if the C−H activation of benzoxazole was the rate-limiting step of the catalytic cycle, we studied the kinetic isotope effects (KIEs) of the catalytic reaction. Two parallel reactions of 2-(pentafluorophenyl)pyridine with benzoxazole and its 2-deuterated derivative were conducted and the reactions were monitored by ^{19}F NMR spectroscopy. No kinetic isotopic effects (KIEs) were observed.



To probe the transmetalation and reductive-elimination steps of the catalytic cycle further, we prepared bis-di-(4-*tert*-butylphenyl)phosphinobenzene (**L1**) ligated palladium complex [(**L1**)Pd(Ar)(Br)] (Ar = 2-pyridyl-3,4,5,6-tetrafluorophenyl) and studied its stoichiometric reaction with benzoxazole. Heating of the complex with benzoxazole and LiO^{t}Bu in the presence of 5.0 equiv of **L1** to trap the Pd(0) product at 60 °C for 40 min formed the reductive-elimination product in almost quantitative yield. In addition, no kinetic isotopic effects were observed for the stoichiometric reaction. These results indicating that the transmetalation and reductive-elimination steps are not the rate-limiting step of the catalytic cycle.

(15) LCu(O^{t}Bu) wea known to accelerate the C-H activation of heteroarenes. (a) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674. (b) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670.



On the basis of these preliminary mechanistic studies, we tentatively postulated that the catalytic cycle involved an initial rate-limiting C−F bond activation, followed by fast C−H activation of benzoxazole and transmetalation and finally reductive-elimination to form the new carbon−carbon bond (Figure 1).

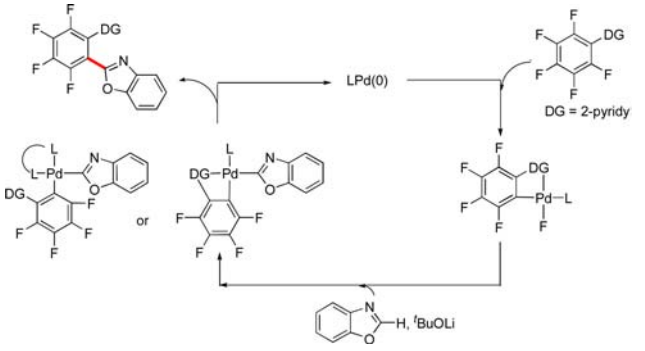


Figure 1. Proposed mechanism for Pd-catalyzed concurrent C−F/C−H activation.

In summary, we have discovered the first palladium-catalyzed coupling of 2-pyridyl-polyfluoroarenes and benzoxazoles via a concurrent C−F/C−H activation. This method thus provides a new strategy for the preparation of partially fluorinated arenes. Further studies to elucidate the mechanism of the C−F/C−H activation and to develop a second-generation catalyst with mild conditions and much broader scope are now the focus of our ongoing study.

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Supporting Information Available. All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.