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# $Pd(OAc)_2$-catalyzed cross-coupling of polyfluoroarenes with simple aromatics in imidazolium ionic liquids (ILs) without oxidant and additive and with recycling/reuse of the IL

Rajesh G. Kalkhambkar, Kenneth K. Laali *

*Department of Chemistry, University of North Florida, 1, UNF Drive, Jacksonville, FL 32224, USA*

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## ABSTRACT

Polyfluoroarenes can be cross-coupled with simple aromatics (benzene, toluene, and anisole), in good isolated yields, by using $Pd(OAc)_2$ dissolved in imidazolium ILs [(bmim)$PF_6$ and (bmim)$BF_4$] as solvent, without the need for an oxidant and an additive. The reaction is catalyzed by HOAc and it is subject to a primary isotope effect ($K_H/K_D = 4.87$). Competitive cross-coupling reactions of 1,2,4,5-tetrafluorobenzene with benzene/toluene, benzene/anisole, and anisole/toluene gave $K_B/K_T = 5.1$, $K_B/K_A = 5.7$, and $K_A/K_T = 5.0$, respectively, indicative of a remote substituent effect on Pd insertion into the phenyl C–H bond. Mild reaction conditions, simple product isolation and recycling/reuse of the IL are additional advantages of this method.

There are notable earlier studies in the literature on fluorinated biaryl synthesis via the transition metal catalyzed cross-coupling reactions, whereby electron-deficient polyfluorobenzenes are coupled to arylboronic acids,[1] or pentafluorophenylboronic acid is coupled to aryl halides (iodide and bromide) via a Suzuki–Miyaura reaction.[2] The Pd-catalyzed decarboxylative cross-coupling in which polyfluorobenzoate salts are coupled to aryl halides (bromide, chloride, or triflate) constitutes another approach to unsymmetrical biaryl synthesis.[3,4] A further development in this area was the finding that perfluoroarenes can be directly coupled to aryl halides by using an in situ generated Pd-catalyst in conjunction with $K_2CO_3$ in dimethyl acetamide (DMA) as solvent.[5]

Recent studies reported by Wei and Su,[6] and by Shi and associates,[7] in which polyfluoroarens are coupled with nonactivated 'simple' arenes under $Pd(OAc)_2$ catalysis to form fluorinated biaryls constitute a noteworthy new development. In the Wei and Su method,[6] an oxidant and a base are required and the reactions are carried out in DMA as solvent. In the method developed by Shi et al.[7] an oxidant (typically $AgCO_3$) and an acid (HOAc, TFA, TFE, or tBuCOOH) along with an additive are required. Among various such additives that were surveyed, di-isopropyl sulfide was quite effective. In both methods high temperatures must be employed (110–120 °C).

In continuation of our studies on electrophilic and onium ion chemistry in ionic liquids (ILs),[8] and as a follow up to our recent work on $Pd(OAc)_2$-catalyzed Matsuda–Heck reaction in ILs,[9] we report here on the facile cross-coupling of polyfluoroarenes with simple arenes (benzene, toluene, and anisole) under $Pd(OAc)_2$ catalysis in (bmim)$BF_4$ or (bmim)$PF_6$ in the presence of catalytic amounts of HOAc, without an oxidant or an additive, under mild reaction conditions with recycling/reuse of the IL. Other studies are also presented in an effort to define the scope and to gather mechanistic insights.

As summarized in Scheme 1, pentafluorobenzene, 1,2,4,5-tetrafluorobenzene, tetrafluoropyridine, and 2,3,5,6-tetrafluorobenzotrifluoride reacted smoothly with benzene, toluene, and with anisole in the presence of 10 mol % $Pd(OAc)_2$ in imidazolium ILs as solvent and with catalytic amounts of HOAc, to furnish the corresponding unsymmetrical biaryls in isolated yields ranging from 56% to 72%.[10] The results are gathered in Table 1.

It is instructive to compare and contrast chemo- and regioselectivities observed in the present study in ILs with those reported in Ref. 7 under a very different set of conditions. In cross-coupling of tetrafluorobenzene with benzene a mixture of mono- and bis-coupling products were obtained by Shi et al.[7] whereas no bis-coupling product was detected in the present study. The isomer distribution observed in cross-coupling of pentafluorobenzene with toluene (*meta*:*para* 1 to 1) is close to that reported by Shi et al.[7] (*meta*:*para* 1.2 to 1), but that for coupling to anisole (*meta*:*para* 1 to 0.15) is substantially different (*meta*:*para* 2.1 to 1).

Focusing on the catalytic role of the acid, in their yield optimization studies Shi et al.[7] found several acids (HOAc, TFA, TFE, and tBuCOOH) to be effective along with an oxidant (typically $Ag_2CO_3$)

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* Corresponding author. Tel: +1 904 620 1503; fax: +1 904 620 3535.
*E-mail address:* kenneth.laali@UNF.edu (K.K. Laali).

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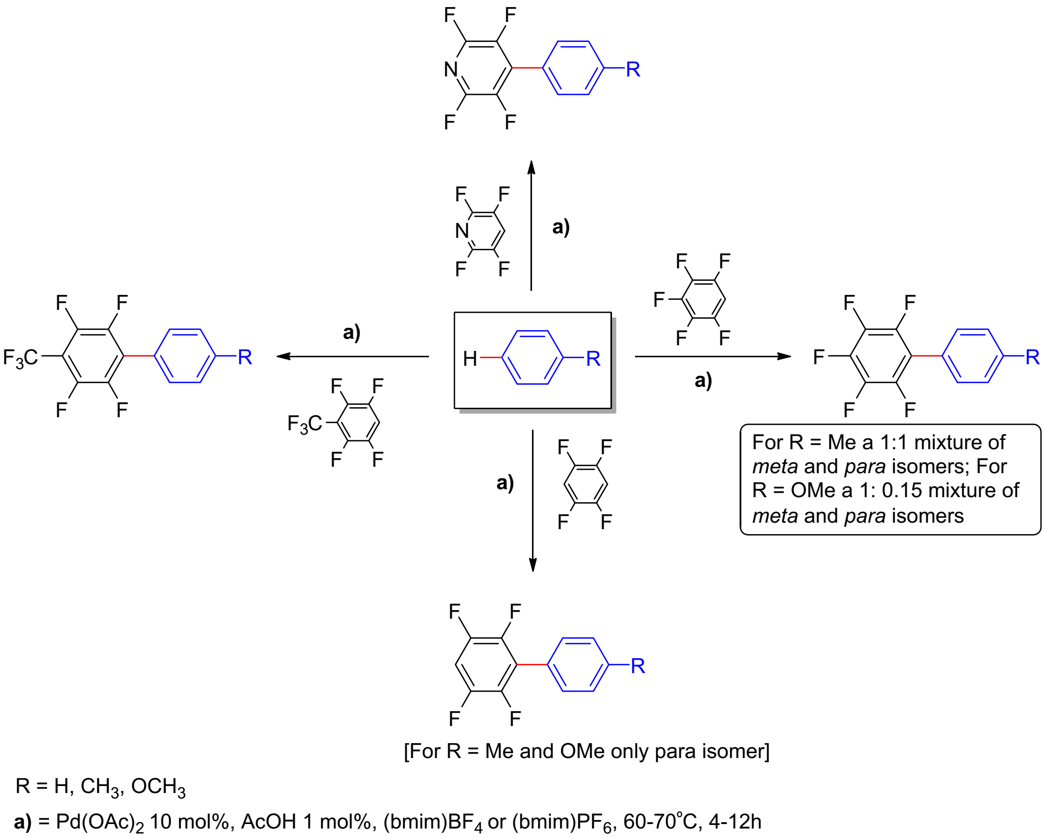


For R = Me a 1:1 mixture of *meta* and *para* isomers; For R = OMe a 1: 0.15 mixture of *meta* and *para* isomers

[For R = Me and OMe only para isomer]

R = H, $CH_3$, $OCH_3$

**a)** = $Pd(OAc)_2$ 10 mol%, AcOH 1 mol%, $(bmim)BF_4$ or $(bmim)PF_6$, 60-70°C, 4-12h

**Scheme 1.** $Pd(OAc)_2$-catalyzed cross coupling of polyfluoroarenes with simple arenes in ILs.

**Table 1**

$Pd(OAc)_2$-catalyzed cross-coupling of polyfluoroarenes with simple arenes

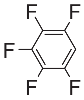
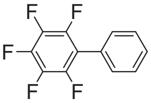
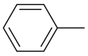
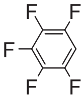
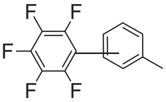
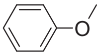
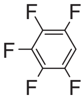
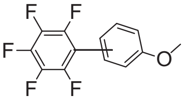
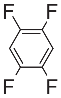
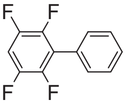
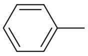
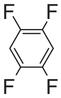
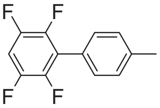
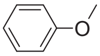
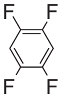
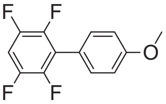
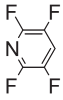
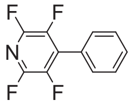
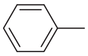
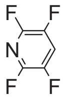
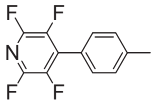
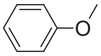
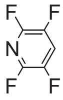
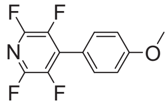
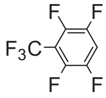
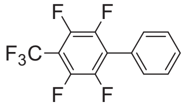
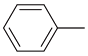
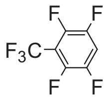
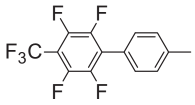
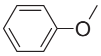
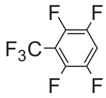
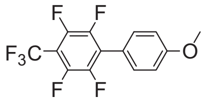
| Entry | Arenes | Polyfluoroarenes | Product | Time (h) | Ionic liquid[a,b] | Isolated yield[c](%) |
|---|---|---|---|---|---|---|
| 1 |  |  |  | 4.5 | $(bmim)BF_4$ | 72 |
| 2 |  |  | <br>meta to para isomer ratio 1:1 | 12[d] | $(bmim)PF_6$ | 68 |
| 3 |  |  | <br>meta to para isomer ratio 1:0.15 | 6[e] | $(bmim)BF_4$ | 70 |
| 4 |  |  |  | 4 | $(bmim)BF_4$ | 64 |
| 5 |  |  |  | 12 | $(bmim)PF_6$ | 56 |
| 6 |  |  |  | 8 | $(bmim)BF_4$ | 62 |

**Table 1** (*continued*)

| Entry | Arenes | Polyfluoroarenes | Product | Time (h) | Ionic liquid[a,b] | Isolated yield[c](%) |
|---|---|---|---|---|---|---|
| 7 |  |  |  | 8 | (bmim)$PF_6$ | 62 |
| 8 |  |  |  | 6 | (bmim)$PF_6$ | 58 |
| 9 |  |  | <br>no other isomer detected | 6.5 | (bmim)$BF_4$ | 66 |
| 10 |  |  |  | 12 | (bmim)$BF_4$ | 64 |
| 11 |  |  | <br>no other isomer detected | 12 | (bmim)$BF_4$ | 58 |
| 12 |  |  | <br>no other isomer detected | 12 | (bmim)$PF_6$ | 70 |

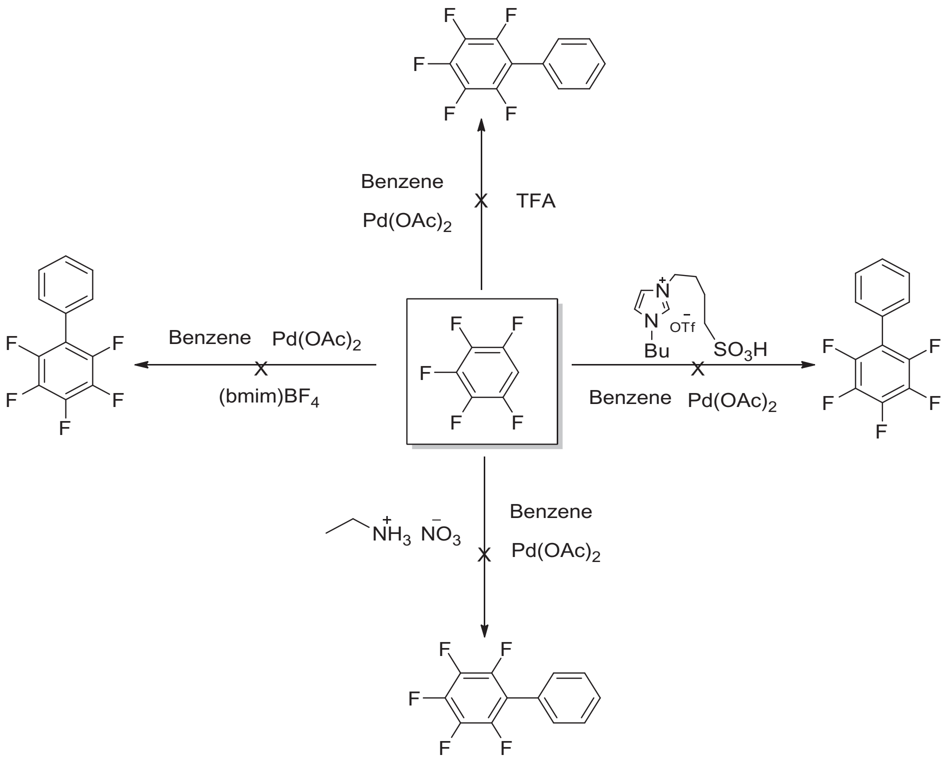
[a] Fresh IL was used in runs 1, 2, 6, 9, and 11, whereas recycled IL was used in others.

[b] The IL could be reused without purification for up to three runs, after which it was purified and reused (see Ref. 10)

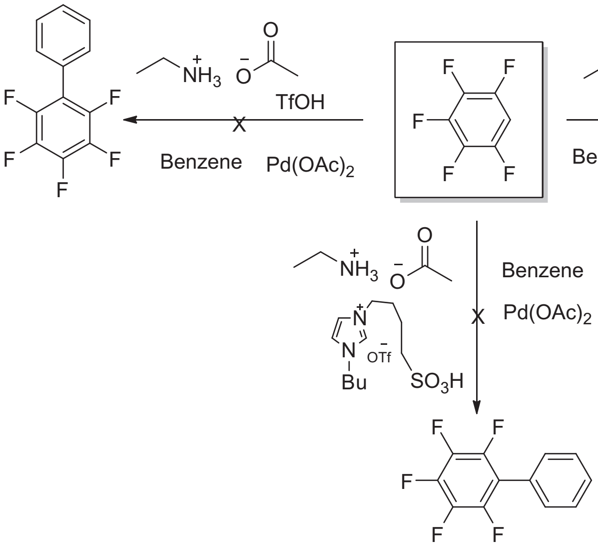
[c] Isolated yield based on quantity of polyfluorinated arenes used.

[d] Isomer ratios determined by $^1$H and $^{19}$F NMR.

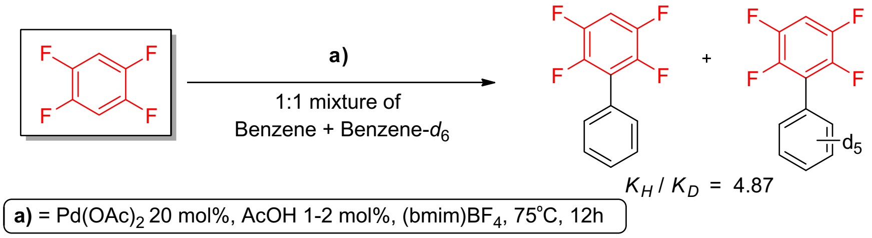
[e] Isomer ratios determined by GC and $^{19}$F NMR.



**Scheme 2.** Control experiments to examine the role of acid catalyst.



**Scheme 3.** Additional control experiments to shed light on the role of acid.



**Scheme 4.** Determination of kinetic isotopic effect (KIE).

and an additive (various sulfides, sulfoxides, or DMSO). Presence of catalytic amounts of HOAc was found to be crucial in the present study in IL. Using the cross-coupling reaction of pentafluorobenzene with benzene as a benchmark, Brønsted acidic ILs $[EtNH_3][NO_3]$ and $[BBIM(SO_3H)][OTf]$ were tested and found to be ineffective, and TFA similarly did not work (see Scheme 2). To check on the possible role of acetate anion in this process, $[EtNH_3][OAc]$ was tested alone and in combination with a Brønsted acidic IL $[BBIM(SO_3H)][OTf]$ or TfOH. However, none of these combinations proved successful (see Scheme 3). These findings imply that cross-coupling in IL is governed by specific acid catalysis and the mechanistic details of the process are yet to be understood.

In an effort to extend the synthetic scope of this cross-coupling reaction, a number of other substituted arenes were studied for coupling to pentafluorobenzene. Halobenzenes (X = F, Cl, Br), PhCN, and $PhNO_2$ did not undergo cross coupling. Similarly no coupling occurred with the electron rich systems namely ethyl benzene, mesitylene, cumene, and 2,3-dimethoxybenzene.

Focusing on the question whether the C–H cleavage of the nonfluorinated arene is part of the rate determining step in the IL version of this chemistry, coupling of tetrafluorobenzene with a 1:1 mixture of $C_6H_6$ and $C_6D_6$ was studied (Scheme 4).

A primary isotope effect was measured (by $^1H$ and $^{19}F$ NMR; see Supplementary data) with $K_H/K_D = 4.87$. For comparison, a $K_H/K_D = 6.81$ was reported in Ref. 7 for cross-coupling to 2,3,5,6-tetrafluoroanisole.

Whereas competitive experiments to establish relative reactivity of different polyfluorobenzenes have been reported,[5] to our knowledge competitive cross-coupling of a given polyfluorinated arene with two aromatics has not been investigated in an effort to shed light on the electronic effect of the substituent. In the present study, using tetrafluorobenzene, three types of competitive cross-coupling experiments were performed with benzene/toluene (1:1), benzene/anisole (1:1), and toluene/anisole (1:1) and this gave the following substrate selectivities: $K_B/K_T = 5.1$, $K_B/K_A = 5.7$, and $K_A/K_T = 5.0$, respectively. The data indicate that the p-Me and p-OMe groups lower the cross-coupling reactivity relative to p-H by five- to sixfold, and that p-Me lowers the reactivity by fivefold relative to p-OMe.

In summary, cross-coupling reactions of various polyfluorinated aromatic/heteroaromatic compounds to benzene, toluene, and anisole using $Pd(OAc)_2$ dissolved in imidazolium ILs as catalyst have been demonstrated. Whereas catalytic amounts of HOAc are essential for the reaction to proceed, no oxidant or additives are required. The mild reaction conditions employed, facile product isolation, and recycling and reuse of the IL are additional advantages of this method. Whereas the IL version of this chemistry can be applied to a variety of polyfluorinated arenes, its scope relative to the coupling partner seems limited. The chemo- and regioselectivities observed in this study were compared and contrasted with those reported previously under a very different set of reaction conditions. In concert with earlier studies, the reaction is subject to a primary kinetic isotope effect. Competitive cross-coupling reactions imply a relative reactivity sequence p-H > p-OMe > p-Me, but further studies are needed to better understand these remote substituent effects.

## Acknowledgments

Support of this work via research support provided to K.L. by UNF is gratefully acknowledged. We also thank Dr. Nelson Zhao of this department for NMR assistance.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.077.

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10. *General procedure:* The desired polyfluoroarenes (1 mmol) were introduced at rt into an oven-dried Schlenk tube charged with (bmim)$PF_6$ or (bmim)$BF_4$ ionic liquid (~4 mL) under a nitrogen atmosphere. After efficient magnetic stirring (for 10–20 min) $Pd(OAc)_2$ (10–20 mol %) was introduced and was dissolved in the IL by efficient magnetic stirring (for 10–20 min). The reaction mixture was then charged with the arene partner (benzene, toluene, or anisole) (3 mmol). After addition of AcOH (1–2 mol %), the reaction mixture was stirred at 60–75 °C under nitrogen while monitoring the progress of the reaction by TLC and by GC–MS. Upon completion, the brown-colored reaction mass was cooled to rt and the products were extracted with dry diethyl ether (4–5 times). Removal of solvent under vacuum furnished the crude products which were chromatographed with hexane-ethyl acetate mixture (75:25) to afford the pure cross-coupling products which were characterized by GC–MS, $^1H$, $^{13}C$ and $^{19}F$ NMR. The brown-colored IL was dried overnight under vacuum at 50 °C and reused for up to three runs, after which it was set aside for recovery and recycling as outlined below.
    *Procedure for recycling of the ionic liquid:* The combined brown-colored ionic liquids recovered from several set of experiments were dissolved in MeCN and filtered through Celite to remove insoluble black particles. After removal of solvent from the filtrate under vacuum, the recycled IL was dried overnight under vacuum at 50 °C and reused in subsequent runs.