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**PAPER**

# Palladium-catalyzed direct arylation of polyfluoroarenes with aryl tosylates and mesylates†

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This study reports the first general Pd-catalyzed direct arylation of polyfluoroarenes with aryl tosylates/mesylates. A wide range of polyfluoroarenes can be coupled with both aryl tosylates and mesylates under relatively mild reaction conditions (90 °C, in the presence of a weak base KOAc, without any additional acid additives). Moreover, a one-pot sequential C–H bond functionalization/C–N bond coupling has been successfully accomplished by employing one single Pd/CM-phos catalyst system.

## Introduction

Polyfluorobiphenyl motifs are commonly found in numerous pharmaceutically attractive and materially valuable molecules.[1] For instance, the perfluorinated polyphenylene sub-unit in photovoltaic polymer (P5FQ),[2] perfluorosubstituted hydroxycoumarins (2*H*-1-benzopyran-2-one) in rodenticides,[3] and trypanosomal cathepsin TbcatB inhibitors (9*H*-purine-2-carbonitrile)[4] have aroused considerable focus in the polyfluorinated biaryl synthesis (Fig. 1).

Although the traditional cross-coupling repertoire has been successful for connecting two aromatic fragments, multi-step syntheses of organometallic nucleophiles are possible drawbacks. Indeed, in addition to the difficult preparation of highly electron-deficient nucleophiles (*e.g.* $C_6F_5B(OH)_2$), the application of electron-poor nucleophilic partners in aromatic bond-forming reactions remain problematic.[5] Recent notable findings showed a great achievement in cross-coupling by using direct arylation of a C–H bond from electron-deficient polyfluoroarenes.[6] Aryl halides[7] and aryl organometallic reagents[8] such as arylboronic acids[9] can both act as efficient coupling partners with polyfluoroarenes. These new protocols are attractive when compared to conventional coupling methods. However, the substrate scope is mainly limited to aryl halides associating with particular reactivity. Apart from aryl halides, it is worth establishing a method for phenolic electrophiles (pseudo-halides) in these reactions. In fact, aryl sulfonates would have a complementary advantage with respect to aryl halides. They potentially offer different or unique substitution patterns in the aromatic ring, in which the corresponding aryl halides may not be commonly available. Thus, the exploration of less expensive, yet more stable aryl arenesulfonates (when compared to aryl triflates) in coupling reactions is highly favourable. Precedence for palladium-catalyzed direct arylation of polyfluoroarenes using aryl sulfonates remains less explored. In 2006, the Fagnou group reported an example of palladium-catalyzed direct arylation of pentafluorobenzene using phenyl triflate.[7b] Very recently, the coupling of aryl triflates was further improved by Seayad and co-workers employing a Pd/MePhos catalyst system.[10] Additionally, steric encumbered aryl triflates could be coupled with pentafluorobenzene using a Pd/RuPhos complex.[10] Apart from triflates, the coupling of aryl tosylates with polyfluoroarenes was only developed recently. In 2011, Zhang reported the palladium-catalyzed direct coupling of polyfluoroarenes with activated heteroaryl tosylates.[11] Yet, no examples of non-activated tosylates were shown.

Aryl mesylates are more atom economical than the corresponding aryl tosylates due to their significantly lower molecular weight. However, aryl mesylates are relatively more inactive and it is challenging to apply them in C–H bond functionalization

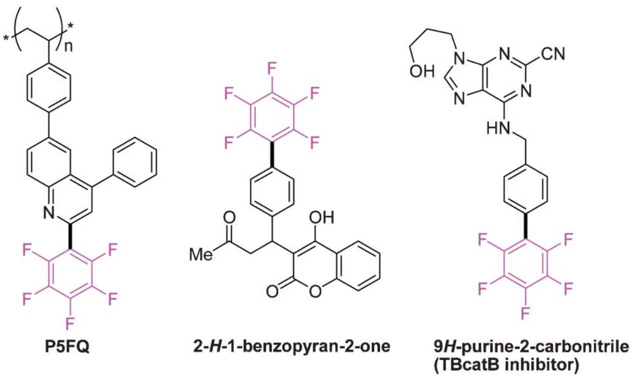

**Fig. 1** Examples of useful perfluoroarene containing molecules.

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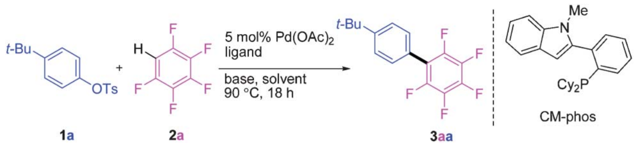
under palladium catalysis. In 2012, Seayad showed the first palladium-catalyzed coupling of aryl mesylates with polyfluoroarenes.[10] Only activated aryl mesylates were successfully applied in this transformation under the conditions of high Pd loading (10 mol%) and at high temperature (120 °C). To the best of our knowledge, a general procedure for non-activated (hetero)aryl mesylates and aryl tosylates has been sporadically reported to date. Herein, we report our efforts in developing a general and efficient catalyst system for handling aryl tosylates/mesylates in the direct arylation of perfluoroarenes.

## Results and discussion

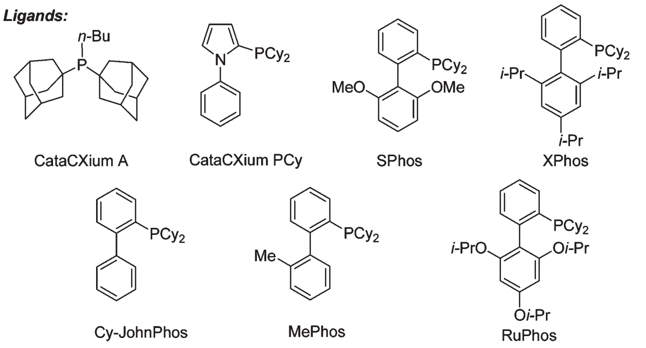
We initially embarked on the coupling of aryl tosylates with polyfluoroarenes by using non-activated 4-*tert*-butylphenyl tosylate and pentafluorobenzene as the benchmark substrates (Table 1). A series of reaction parameter screenings were then deployed. Commercially available and well-recognized phosphine ligands[12] such as CataCXium®A, CataCXium®PCy, SPhos, Xphos, Cy-JohnPhos, MePhos and RuPhos were initially screened (entries 1–7). Moderate substrate conversions and fair product yields were afforded by using biaryl-type monodentate phosphines (entries 3–7). A catalyst system comprising $Pd(OAc)_2$ and CM-phos[13] was found superior for this tosylate coupling (entry 8). Of the commonly used organic solvents examined, the alcoholic solvent *t*-BuOH was found to be the best solvent of choice whereas DMF and dioxane gave moderate and poor conversions, respectively (entries 8, 11, 13). *t*-BuOH/DMF solvent mixture also afforded a good yield for this direct arylation (entries 12). The addition of pivalic acid (to the $K_2CO_3$ system) greatly improved the conversion (entries 8 *vs.* 10). Surprisingly, weak bases such as KOAc or $Na_2CO_3$ were equally efficient and gave excellent yields even without the employment of additional PivOH (entries 14–15).

Having the preliminary optimized reaction conditions in hand, we examined a range of aryl tosylates in this reaction (Table 2). To the best of our knowledge, there has been no successful example of non-activated aryl tosylates reported to date in direct

**Table 1** Initial screenings of Pd-catalyzed arylation of polyfluoroarenes with aryl tosylate and mesylate[a]

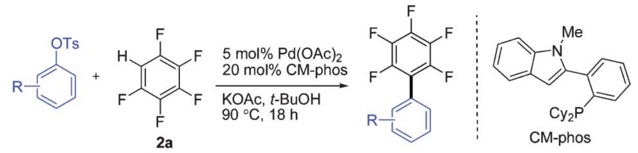


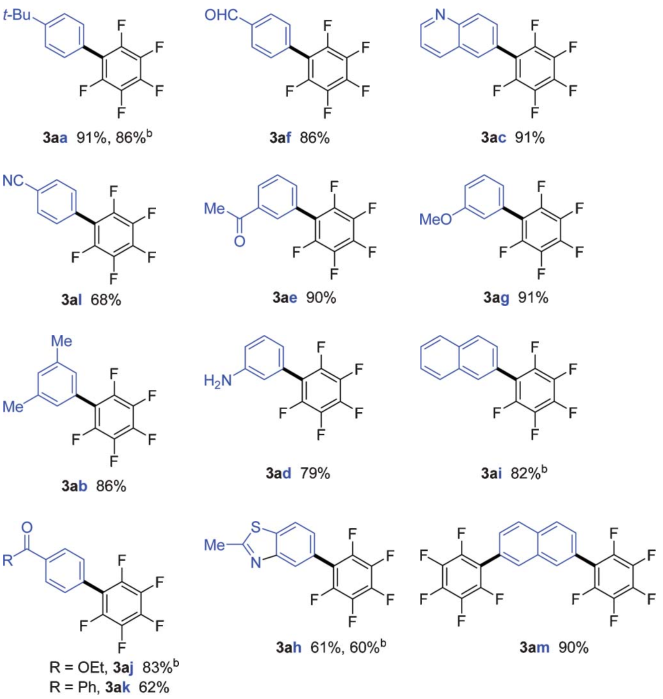
| Entry | Ligand | Solvent | Base | Yield (%)[b] |
|---|---|---|---|---|
| 1 | CataCXium® A | *t*-BuOH | $K_2CO_3$ | 0 |
| 2 | CataCXium® PCy | *t*-BuOH | $K_2CO_3$ | 0 |
| 3 | SPhos | *t*-BuOH | $K_2CO_3$ | 47 |
| 4 | XPhos | *t*-BuOH | $K_2CO_3$ | 37 |
| 5 | Cy-JohnPhos | *t*-BuOH | $K_2CO_3$ | 4 |
| 6 | MePhos | *t*-BuOH | $K_2CO_3$ | 12 |
| 7 | RuPhos | *t*-BuOH | $K_2CO_3$ | 43 |
| 8 | CM-phos | *t*-BuOH | $K_2CO_3$ | 76 |
| 9[c] | CM-phos | *t*-BuOH | $K_2CO_3$ | 43 |
| 10[d] | CM-phos | *t*-BuOH | $K_2CO_3$ | 87 |
| 11 | CM-phos | DMF | $K_2CO_3$ | 51 |
| 12 | CM-phos | *t*-BuOH/DMF (1 : 1) | $K_2CO_3$ | 77 |
| 13 | CM-phos | Dioxane | $K_2CO_3$ | 32 |
| 14 | CM-phos | *t*-BuOH | $Na_2CO_3$ | 90 |
| 15 | CM-phos | *t*-BuOH | KOAc | 90 |
| 16[d] | CM-phos | *t*-BuOH | KOAc | 92 |
| 17 | CM-phos | *t*-BuOH | NaOAc | 73 |



[a] Reaction conditions: ArOTs 1a (0.3 mmol), $C_6F_5H$ (0.6 mmol), $Pd(OAc)_2$ (5.0 mol%), (Pd : ligand = 1 : 4), base (0.45 mmol) and *t*-BuOH (1.0 mL) under $N_2$ at 90 °C for 18 h. [b] GC yields were reported. [c] 2.0 mol% of $Pd(OAc)_2$ was used. [d] 10 mol% of PivOH was added.

**Table 2** Palladium-catalyzed arylation of pentafluorobenzene with aryl and heteroaryl tosylates[a]





**3aa** 91%, 86%[b]
**3af** 86%
**3ac** 91%
**3al** 68%
**3ae** 90%
**3ag** 91%
**3ab** 86%
**3ad** 79%
**3ai** 82%[b]
R = OEt, **3aj** 83%[b]
R = Ph, **3ak** 62%
**3ah** 61%, 60%[b]
**3am** 90%

[a] Reaction conditions: ArOTs (0.3 mmol), $C_6F_5H$ (0.6 mmol), $Pd(OAc)_2$ (5.0 mol%), (Pd : CM-phos = 1 : 4), KOAc (0.45 mmol) and *t*-BuOH (1.0 mL) under $N_2$ at 90 °C for 18 h (reaction time for each substrate was not optimized). Isolated yields are reported. [b] $Na_2CO_3$ was used as base.

arylation of perfluoroarenes. Electronically neutral aryl tosylates were effective and gave the corresponding products in good to excellent yields. Functional groups such as methoxy, keto, cyano, ester and aldehyde were compatible under these reaction conditions. Heterocyclic benzothiazoyl and quinolinyl tosylates gave the corresponding coupling products smoothly.

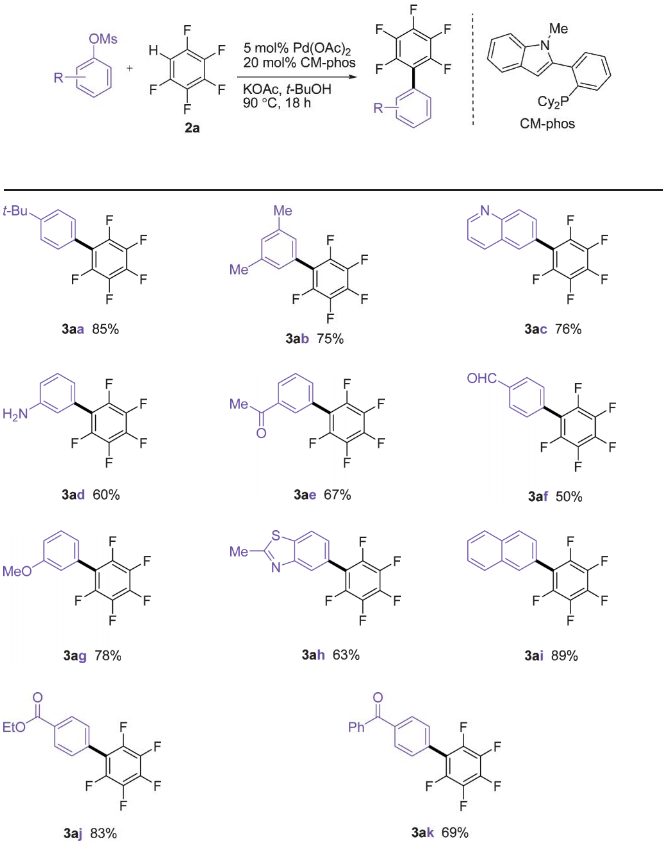
The Pd/CM-phos catalytic system was also found to be effective in promoting the coupling of aryl mesylates (Table 3). An array of aryl mesylates were tested in this coupling reaction. Heteroaryl mesylates were found to be applicable in this system.

To further expand the substrate scope, we next investigated the feasibility of using other polyfluoroarenes as the coupling partners (Table 4). Moderate to excellent yields resulted.

To further show the potential application of this coupling process in synthesizing related cathepsin TbcatB inhibitors (consisting of –$C_6F_5$, N-Ar and –CN moieties),[4] a tandem reaction was attempted. To our delight, the one-pot synthesis of an *N*-aryl aminobenzonitrile (65% yield in two steps) was successful from direct coupling of aryl tosylate with pentafluorobenzene and subsequent *N*-arylation of the amino moiety (Scheme 1).

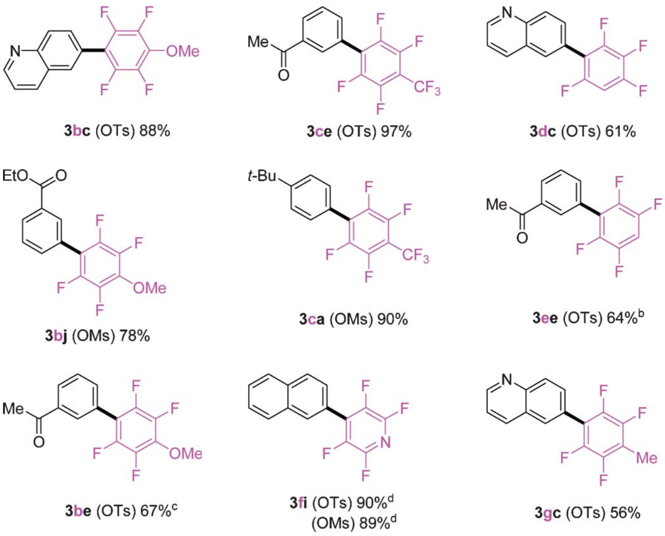
In order to investigate the dependence of the C–H bond cleavage, a kinetic isotope effect (KIE) experiment was carried out. A KIE of 1.2 was observed from the competitive experiment of deuteropentafluorobenzene and pentafluorobenzene. This result indicated that the C–H bond cleavage is likely to be not the kinetically rate-determining step in this catalysis.

**Table 3** Palladium-catalyzed arylation of pentafluorobenzene with aryl and heteroaryl mesylates[a]

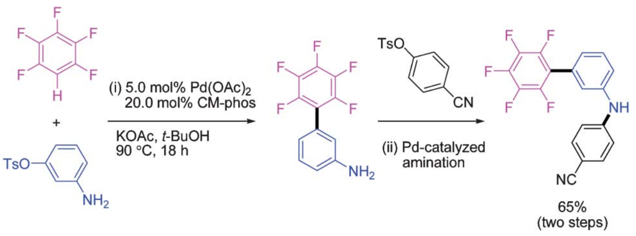


[a] Reaction conditions: ArOMs (0.3 mmol), $C_6F_5H$ (0.6 mmol), $Pd(OAc)_2$ (5.0 mol%), (Pd:CM-phos = 1 : 4), KOAc (0.45 mmol) and *t*-BuOH (1.0 mL) under $N_2$ at 90 °C for 18 h (reaction time for each substrate was not optimized). Isolated yields are reported.

**Table 4** Palladium-catalyzed arylation of polyfluoroarenes with (hetero)aryl tosylates and aryl mesylates[a]



[a] Reaction conditions: ArOTs/OMs (0.3 mmol), polyfluoroarene (0.9 mmol), $Pd(OAc)_2$ (5.0 mol%), (Pd : CM-phos = 1 : 4), KOAc (0.45 mmol) and *t*-BuOH (1.0 mL) under $N_2$ at 90 °C for 18 h (reaction time for each substrate was not optimized). Isolated yields are reported. [b] 1.2 mmol of polyfluoroarene was used. [c] 0.6 mmol of polyfluoroarene was used. [d] 24 h was used.



**Scheme 1** One pot sequential reaction (see ESI† for detailed procedures).

## Conclusions

In summary, we reported the first general palladium-catalyzed direct arylation of polyfluoroarenes with aryl tosylates and mesylates. This protocol offers a convenient access to polyfluorobiaryl scaffolds from phenolic derivatives. Particularly noteworthy is that the reaction conditions are relatively mild (weak base, KOAc; at 90 °C, without acid additives). Moreover, the cascade direct arylation/C–N bond-coupling sequence could be carried out by using one Pd/CM-phos catalyst system. We believe this direct arylation protocol using sulfonate coupling partners is versatile for diversified functional materials and pharmaceuticals.

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