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Simple and expedient metal-free C–H-functionalization of fluoro-arenes by the BHAS method – Scope and limitations

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ABSTRACT

We report here the facile substitution of aromatic iodides with non-activated fluoroarenes through radical-promoted reaction conditions. Applying the recently-popularized BHAS methodology, catalytic 1,10-phenanthroline and KO*t*Bu and the desired fluorobenzene as reactant and solvent, various fluorinated biaryls can be synthesized in moderate to good yields. The method provides a simple access to generate potentially many 'F_nAr'-substituted derivatives from a single haloarene synthetic intermediate, using relatively cheap and non-toxic fluoroarene substrates directly from the bottle, and may therefore be of use for medicinal chemistry campaigns. Although the method has a limitation in that it is not compatible with substrates featuring base-sensitive substituents, especially 1,4-difluorobiaryls are accessible in good yields. These investigations facilitate the exploitation of the potential of this protocol to synthesize biologically active fluorinated biaryls, e.g. WNT-active molecules.

1. Introduction

Fluorinated arenes play a pivotal role in pharmacological applications and material sciences. In particular fluorinated biaryls have shown activity in many different biological systems. Notable examples are the drug diflunisal [1–11], the fungicide fluxapyroxad [12] or the WNT-active molecules **3** and **4** [13,14], shown in Fig. 1.

So far, around 70,000 fluorinated, 45,000 difluorinated and 20,000 trifluorinated biaryls have been reported (according to Scifinder). Besides the classical cross-coupling Suzuki, Stille, Kumada and Ullmann reactions [15] (for references from our labs: [16–19]) (Scheme 1, left), arylation by classical aryl radicals generated from peroxides [20] or other sources like diazonium salts [21], or dimerization reactions [22], selective C–H activation reactions of fluorinated arenes emerged recently (Scheme 1, right) (for references from our labs: [23,24]).

In the latter context, metal-catalyzed reactions in particular with the aid of copper [25–27], palladium [28,29], platinum [30] complexes or with aluminum [31] (for a comparison: [32]) have been used very successfully.

Recently the H-substituting arylation of simple arenes with haloarenes has been shown to proceed in the absence of transition metals. This method, the Base-Promoted Homolytic Aromatic Substitution (BHAS) is a new base-driven form of the long-known homolytic aromatic substitution [33]. The reaction requires excess alkali-metal tertiary-butoxide base (usually KO*t*Bu) alongside an activating additive with chelating heteroatoms, usually phenanthroline [34], or related heterocycles like pyridines [35] or quinolones [36], alternatively phenylhydrazine, porphyrins and even amino acids like proline [37].

The BHAS reaction has been used for the synthesis of fluoro-decorated biaryls on occasion. It should be noted that these examples are scarce and a broad investigation of the scope was still required.

During our exploration of the acetal method for the construction of dibenzo[1,3]dioxepines, 2,2′-biphenols and biaryls more generally [23,24], we found that substrates designed to provide cyclization/coupling cascade reactions can allow the incorporation of a wide range of arenes, including 1,4-difluorobenzene [38]. This finding prompted us to investigate the intermolecular arylation of (poly)fluoroarenes with *functionalized* arenes.

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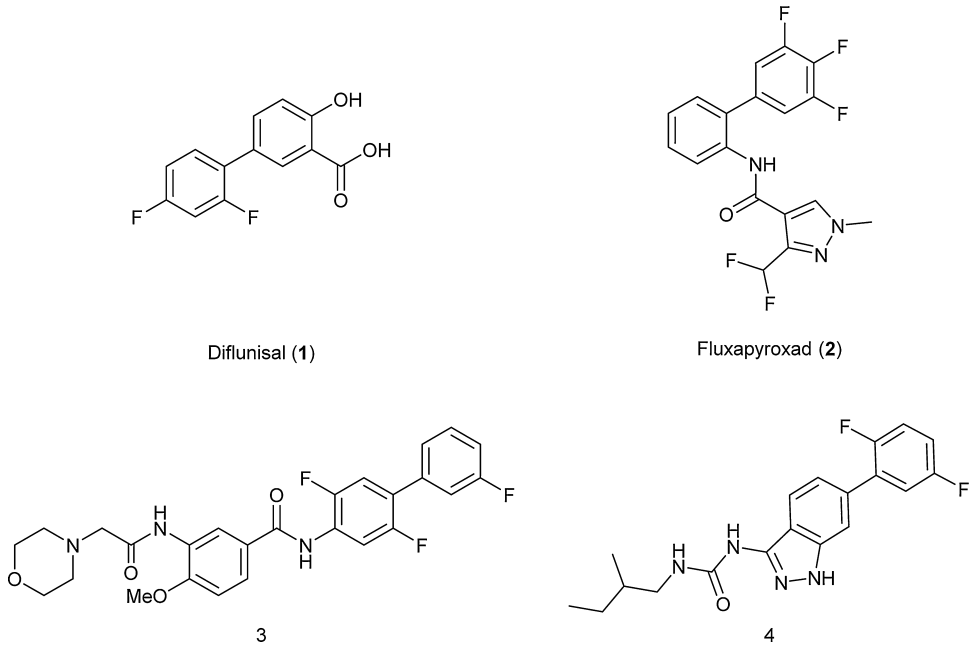
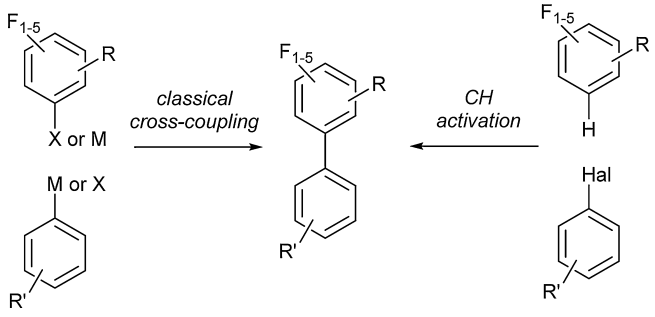


Fig. 1. Fluorinated arenes with pharmacological applications: diflunisal (**1**) [1–11], fluxapyroxad (**2**) [12] and the two WNT-active polyfluorobiaryls **3** [13] and **4** [14].

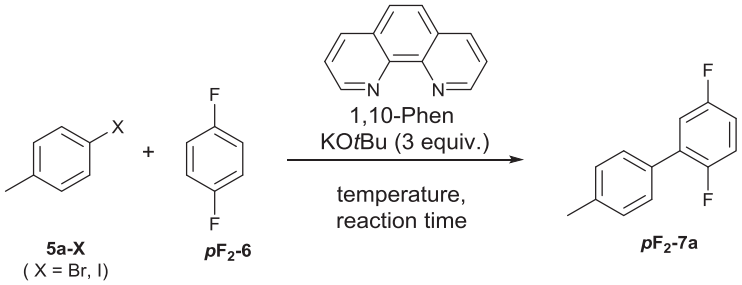


Scheme 1. Strategies for the synthesis of fluorinated biaryls.

2. Results and discussion

Initially, the reaction conditions for the cross-coupling of fluoroarenes were investigated using the conversion of 4-iodotoluene (**5a**) with 1,4-difluorobenzene (**pF_2-6**) as a model reaction (Table 1). All reactions were carried out in vials applying the now well-established conditions of Shi et al. [34] – 1,10-phenanthroline as organocatalyst in combination with KO*t*Bu (3 equiv.) and an excess of the fluorobenzene as both coupling-partner and solvent. Using 10 equiv. of fluorobenzene **pF_2-6** and 30 mol% of 1,10-phenanthroline at 100 °C for 3 h, the biaryl **pF_2-7a** was furnished in 37% (entry 1). The yield was dramatically enhanced by increasing the amount of fluoroarene to 40 equiv. (75%, entry 2) while less catalyst led to poorer yield (entry 3). Changing the reaction time to 1, 2, or 4 h, respectively, had little

Table 1
Optimization of the reaction conditions for the synthesis of 2,5-difluoro-4′-methyl-1,1′-biphenyl (**pF_2-7a**).



Entry	1,4-Difluorobenzene (**pF_2-6**) [equiv.]	1,10-Phenanthroline [equiv.]	Temperature [°C]	Reaction time	Yield[a] [%]
1	10.0	0.300	100	3 h	37
2	**40.0**	**0.300**	**100**	**3 h**	**75** (66)[b]
3	40.0	0.100	100	3 h	64
4	40.0	0.300	100	4 h	71
5	40.0	0.300	100	2 h	75
6	40.0	0.300	100	1 h	73
7	40.0	0.300	120	3 h	61
8	40.0	0.300	80	3 h	69

The best conditions are highlighted.
[a] Isolated yields for X = I.
[b] 4-Bromotoluene was used as starting material.

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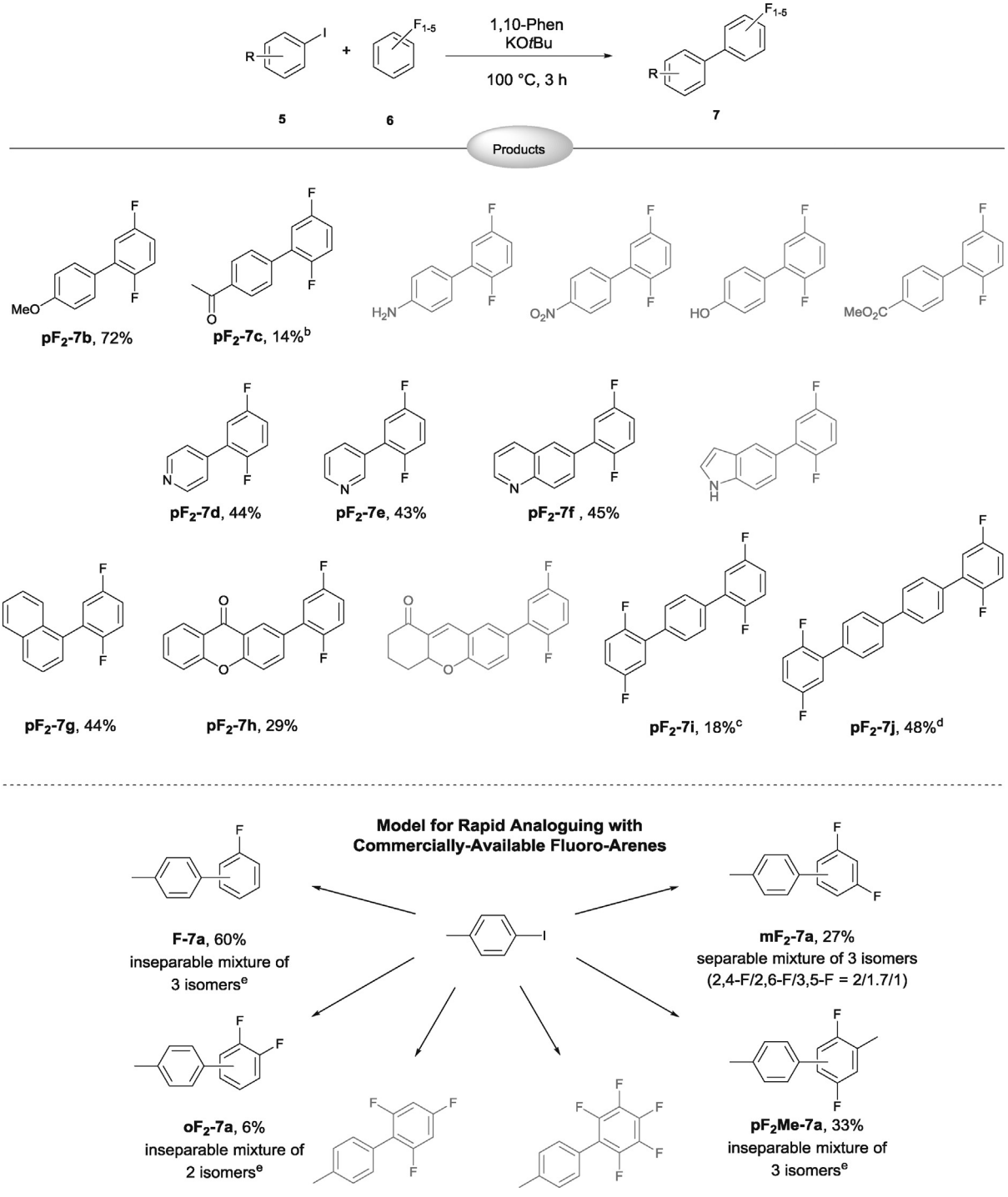
Table 2
Scope and limitation of the cross-coupling of fluoroarenes.[a]



[a] Isolated yields – the molecules displayed in gray could not be synthesized.
[b] Product could only be isolated as a mixture together with the remaining 4-iodoacetophenone.
[c] 6.00 equiv. of KO*t*Bu was used.
[d] 6.00 equiv. of KO*t*Bu, 0.600 equiv. of 1,10-phenanthroline and 80.0 equiv. of 1,4-difluorobenzene was used.
[e] In case of inseparable mixtures the isomers could not be associated definitely.

influence on the product yield (entry 4–6). According to the obtained yields, the conversion is already completed after 2 h, but slightly longer reaction time did not decline the yield, indicating product stability under the conditions. This is also typical of radical reactions without rate-control, which usually proceed from start to completion very quickly, often after a variable induction period. Therefore a reaction time of 3 h was set for further reactions. Additional experiments were implemented varying the temperature, but only resulting in decreased yields. The optimized conditions were also applied successfully to 4-bromotoluene

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(**5a-Br**) as substrate, yielding biaryl **pF_2-7a** in 66% (entry 2), while the corresponding chlorotoluene (**5a-Cl**) did not react.

With the optimized conditions in hand we first examined the coupling of 1,4-difluorobenzene with other functionalized benzenes (Table 2). While methyl ether-substituted iodobenzene could be converted successfully to the corresponding biaryl **pF_2-7b** in good yields [34], ketone **pF_2-7c** could only be obtained in poor yield. However, base-sensitive substituents like amino or hydroxyl groups as well as nitro and methyl ester functionalities were not tolerated by this procedure. We then proceeded with the cross coupling of heteroaromatic iodides. Here, pyridyl and quinolinyl iodides could be transformed into the biaryls **pF_2-7d**, **pF_2-7e**, **pF_2-7f** in moderate yields whereas indolyl biaryls were not accessible. Furthermore, the procedure also could be applied for the synthesis of naphthalene **pF_2-7g** and xanthone **pF_2-7h**, but not for a base-sensitive tetrahydroxanthone. To our delight diiodides could also be converted via this cross coupling procedure yielding terphenyl **pF_2-7i** in 18% and quaterphenyl **pF_2-7j** in 48%, respectively.

After investigation of the substrate scope for the reaction with 1,4-difluorobenzene (**pF_2-6**), we proceeded to examine the reaction of 4-iodotoluene with other fluorobenzenes. The conversion of fluorobenzene led to an inseparable mixture of three isomers **F-7a** in good yield, whereas other difluorobenzenes (**oF_2-6**, **mF_2-6**, **pF_2Me-6**), only yielded the corresponding coupling products (**oF_2-7a**, **mF_2-7a**, **pF_2Me-7a**) in up to 33%. It should be noted that all possible isomers were formed, which could only be separated in case of 1,3-difluorobenzene. Due to the low regioselectivity this procedure cannot be used for the selective coupling. The trifluoro- and pentafluorobenzene however did not react to the desired coupling product.

3. Conclusions

In summary, we report the investigation of the cross-coupling reaction of fluorobenzenes with aromatic iodides to biaryls through aromatic C–H activation. Using 1,10-phenanthroline in combination with KO*t*Bu and an excess of fluorobenzene, various fluorinated biaryls can be synthesized. These investigations facilitate the exploitation of the potential of this protocol to synthesize biologically active fluorinated biaryls.

4. Experimental part

4.1. General procedure for the synthesis of (poly)fluorobiaryls (GP1)

To a vial (5.0 mL) containing a stirring bar were added sequentially iodobenzene (0.500 mmol, 1.00 equiv.), potassium tert-butoxide (1.50 mmol, 3.00 equiv.) and 1,10-phenanthroline (0.150 mmol, 0.300 equiv.). The vial was capped under an argon shower and the septum was punctured by a needle connected to a Schlenk line and the atmosphere cautiously removed by vacuum whilst stirring, then replaced with argon (repeat three times). Fluorobenzene (40 equiv.) was added to the mixture and the reaction mixture was degassed once more with argon. The vial was then heated at 100 °C for 3 h. After cooling to ambient temperature, the reaction mixture was flushed through a short (3 cm) silica gel plug with ethyl acetate (~150 mL) and the volatiles were removed under reduced pressure. The crude product was then subjected to column chromatography (silica gel, cyclohexane/ethyl acetate).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2015.06.010.

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