Palladium catalysed Suzuki reactions of fluoroarenes†

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A novel palladium catalysed cleavage of C–F bonds in a series of Suzuki reactions of aryl fluorides is described together with a discussion of the mechanistic implications.

Palladium catalysed cross-coupling reactions have found an important place in modern synthetic protocols.[1] The first step of these reactions is the insertion of a palladium(0) species into a carbon–halogen or in special cases, a carbon–oxygen bond.[1] Although aryl iodides, bromides and triflates are most commonly used, recently aryl chlorides, hitherto regarded as inert to palladium catalysed cross-coupling reactions, have been shown to be effective participants provided there is an electron withdrawing group on the aryl ring[2] (including the η^6-tricarbonylchromium(0) group)[3] and/or a basic phosphine ligand[4–8] on the palladium. In contrast, fluoroarenes in palladium cross-coupling reactions were not described in the literature prior to our work on fluoroarenechromium(0) complexes[9,10] despite the fact that cross-coupling reactions of fluoroarenes present a particular academic challenge.

The C–F bond is the strongest of the C-halide bonds,[11] cleavage of which is only described for multifluorinated compounds,[12] in nickel assisted C–F bond activations[13,14] or by nucleophilic aromatic substitution of electron deficient fluoroarenes[11] and fluoroarenechromium(0) complexes.[15,16] Very recently, subsequent to our reported palladium catalysed coupling with fluoroarenetricarbonylchromium(0) complexes,[9,10] two examples of a Kumada–Corriu reaction of fluoroarenes catalysed with nickel were published.[17,18] We now report here the first successful palladium catalysed Suzuki reaction of an uncomplexed fluoroarene.

† Electronic supplementary information (ESI) available: full experimental procedures and data. See http://www.rsc.org/suppdata/cc/b2/b212138g/

Following the Suzuki and Stille couplings of fluoroarenetricarbonylchromium(0) complexes,[9,10] the question arose as to whether fluoroarenes themselves could undergo such couplings. When the defined conditions‡ for the Suzuki coupling were applied to electron deficient 2,4-dinitrofluorobenzene **1a** (Sanger's reagent), with phenylboronic acid **2a**, the expected coupled product was isolated in 85% yield (Scheme 1) (Table 1, Run 1).

Since Sanger's reagent is known to undergo ready nucleophilic aromatic substitution reactions,[19] control experiments were carried out in order to define more precisely the reaction pathways as discussed previously.[9,10] The reaction did not occur in the absence of palladium. Reflux of **1a** with 1 equiv. of trimethylphosphine for 16 h in DME led to no sign of the formation of a phosphonium species and starting material was recovered unchanged. Reflux in DME for 16 h of **1a** with caesium carbonate and phenylboronic acid **2a**, but without any palladium catalyst, led to the decomposition of the starting material, but no trace of a borate substituted species or coupled product was detectable. These observations established that palladium catalysis was involved and that the fluoro-species and not a phosphonium or borate analogue was a reactant.

The scope for the boronic acid partner in the process was explored by reacting Sanger's reagent **1a** with a range of boronic acids under the defined conditions. All examples (Table 1, Run 1–8), including the heterocyclic analogue 2-furylboronic
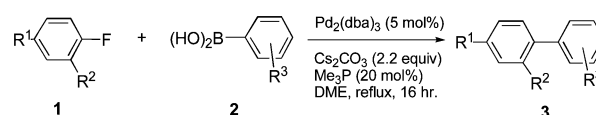
Scheme 1

Table 1 Suzuki coupling of fluoroarenes[a]

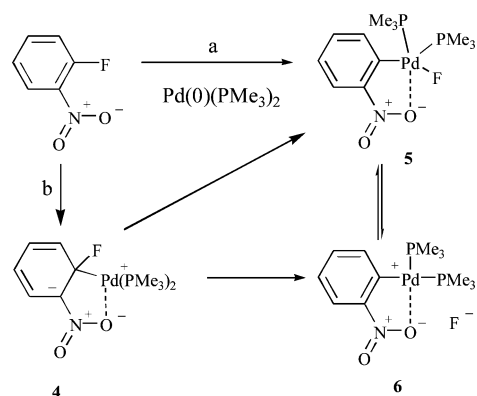| Run	Fluoroarene			Boronic Acid		Biaryl	Yield [%]
		R¹	R²		R³		
1	**1a**	NO₂	NO₂	**2a**	H	**3a**	85
2	**1a**	NO₂	NO₂	**2b**	2-MeS	**3b**	84
3	**1a**	NO₂	NO₂	**2c**	4-MeO	**3c**	81
4	**1a**	NO₂	NO₂	**2d**	2-MeO	**3d**	83
5	**1a**	NO₂	NO₂	2-Furylboronic acid		**3e**	83
6	**1a**	NO₂	NO₂	**2e**	4-Cl	**3f**	66
7	**1a**	NO₂	NO₂	**2f**[b]	3-NH₂	**3g**	50[c]
8	**1a**	NO₂	NO₂	**2g**	4-*t*-Bu	**3h**	79
9	**1b**	H	NO₂	**2a**	H	**3i**	26
10	**1b**	H	NO₂	**2c**	4-MeO	**3j**	37
11	**1c**	CF₃	NO₂	**2a**	H	**3k**	67
12	**1c**	CF₃	NO₂	**2h**	2-Me	**3l**	30
13	**1d**	Me	NO₂	**2a**	H	**3m**	22
14	**1e**[d]	MeO	NO₂	**2a**	H	**3n**	25
15	**1f**	NO₂	H	**2a**	H	**3o**	0
16	**1g**	H	CF₃	**2a**	H	**3p**	0
17	**1h**[d]	CF₃	COOMe	**2a**	H	**3q**	0
18	Hexafluorobenzene			**2a**	H	**3r**	0
19	2-Fluoropyridine			**2a**	H	**3s**	0

[a] See ESI for details. [b] As the hemisulfate. [c] Crude. [d] **1e** and **1h** were prepared from the phenol and benzoic acid respectively *via* methylation with CH₃I.

acid (Table 1, Run 5), gave good yields of the coupled products and even moderately hindered boronic acids could be used in the reaction (Table 1, Runs 2 and 4) with no significant change of yield.

It is of note that 4-chlorobenzeneboronic acid **2e** gave the coupled product in 66% yield (Table 1, Run 6), which showed, remarkably, that the C–Cl bond of **2e** was less reactive in cross-coupling than the C–F bond of **1a** under these conditions. An even more intriguing result was found with the coupling of 3-aminobenzeneboronic acid hemisulfate **2f** which gave the coupled product in 50% yield. Clearly, in **2f**, the amino-function, whether protonated or not, is insufficiently nucleophilic to compete with the palladium(0) species for the Sanger's reagent. The product **3g**, however, was too labile to allow analytically pure material to be isolated although it was characterized by ^{1}H-NMR, mass spectroscopy and HRMS.

A study of the scope of the fluoroarene partner in coupling with phenylboronic acid **2a** demonstrated a precise requirement. Thus when 2-nitrofluorobenzene **1b** was chosen as the coupling partner with phenylboronic acid **2a** (Table 1, Run 9), the coupled product was obtained in 25% yield. The more electron rich 4-methoxyphenylboronic acid analogue **2c** gave a slightly increased yield of 37% (Table 1, Run 10). On the 2-nitro-fluorobenzene ring, a 4-trifluoromethyl-group **1c** coupled with **2a** in good yield (67%) (Table 1, Run 11). Conversely, coupling of **1c** with the moderately hindered 2-methylbenzeneboronic acid **2h** gave the coupled product in only 30% yield (Table 1, Run 12). When the less electron deficient fluoroarene **1d** was coupled with boronic acid **2a** the yield dropped to 22% (Table 1, Run 13). That the reaction tolerated even a 4-MeO group in the fluoroarene ring was shown by coupling **1e** with **2a** to give the biaryl product in 25% yield (Table 1, Run 14).

In contrast, when 4-nitrofluorobenzene **1f** was reacted with **2a**, no trace of a product could be detected (Table 1, Run 15). When **1g** with the electron withdrawing group CF$_3$ *ortho* to the fluoro- position was applied with boronic acid **1a** again no trace of a product could be detected (Table 1, Run 16). Clearly, a 2-nitro group, which can function not only as an electron withdrawing group, but can also coordinate an incoming palladium atom, is an obligate feature for the coupling process. *Ab initio* calculations[20] of plausible mechanisms (Scheme 2) have shown that such a coordination of palladium has a significant influence on the activation energy of the insertion step.[20] The mechanism could either be a concerted insertion (Scheme 2: path a) or an addition–elimination sequence[16] (Scheme 2: path b) *via* adduct **4** followed by fluoride loss to produce cationic palladium species **5**. Distinction between these cannot be made at this point and both are facilitated by *ortho*-

nitro coordination. The insertion product could be active in the catalytic cycle in either neutral **6** or cationic **5** form.[21] The calculations show that either pathway is energetically feasible under the conditions.[20]

When fluoroarene **1e** with a methyl ester function *ortho* to the fluorine atom was reacted with **2a** no product was detected. The coordinating ability of an ester, in contrast to the nitro group, is apparently too low to facilitate this reaction. Further attempts to couple with hexafluorobenzene and 2-fluoropyridine also failed (Table 1, Run 18 and 19).

In conclusion we have demonstrated for the first time the efficacy of an uncomplexed fluoroarene in a palladium catalysed Suzuki reaction. The reaction tolerates a wide range of boronic acids however a nitro group in the 2-position of the fluoroarene is essential for reaction. The method so developed gives ready access to 2,4-dinitrobiphenyls in good yields from Sanger's reagent.

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Scheme 2