Palladium catalysed cross-coupling of (fluoroarene)tricarbonylchromium(0) complexes

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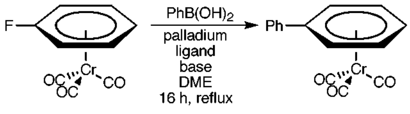
Fluoroarenetricarbonylchromium(0) complexes were found to undergo Suzuki reactions with arylboronic acids to form biaryltricarbonylchromium(0) complexes in the presence of trimethylphosphine/palladium dibenzylideneacetone and caesium carbonate or caesium fluoride.

The Suzuki reaction is one of the most widely used and successful processes for the synthesis of biaryls and styrenes.[1] Although aryl iodides and bromides are the most commonly used halide partners in the reaction, in some remarkable recent developments, aryl chlorides, hitherto regarded as inert to palladium coupling, have been shown to be effective participants provided that an electron-withdrawing group on the aryl ring[2] (including an η^6-tricarbonylchromium group[3]) or a basic phosphine ligand for palladium[4–9] is present. In the latter case, it has been shown that tricyclohexylphosphine and tri-*tert*-butylphosphine ligands on the palladium catalyst are particularly effective, even with electron rich aryl chlorides.[4] We have previously demonstrated the unique synthetic potential of monofluoroarene complexes in the synthesis of polyfunctionalised aromatics[10,11] and given the ease and efficiency with which chloroarenetricarbonylchromium complexes undergo cross-coupling reactions,[3] we were prompted to attempt the Suzuki reaction of the fluoro complexes as a route to highly functionalised biaryls. We now report the first step towards that objective, the palladium catalysed cross-coupling of aryl fluorides.

Using standard conditions for Suzuki coupling,[1] tetrakis(triphenylphosphine)palladium catalyst, fluorobenzenetricarbonylchromium(0) and phenylboronic acid gave the coupled complex but only in trace amounts (Table 1, run 1). When the reaction was repeated with tris(dibenzylidenacetone)dipalladium/tricyclohexylphosphine and caesium fluoride as the base (Fu conditions[4]), no coupled product was detectable (run 2) but tris(dibenzylidenacetone)dipalladium/trimethylphosphine (run 3) did produce the biphenyltricarbonylchromium(0) complex in 52% yield.

Table 1 Suzuki coupling reactions of fluorobenzenetricarbonylchromium(0) and phenylboronic acid



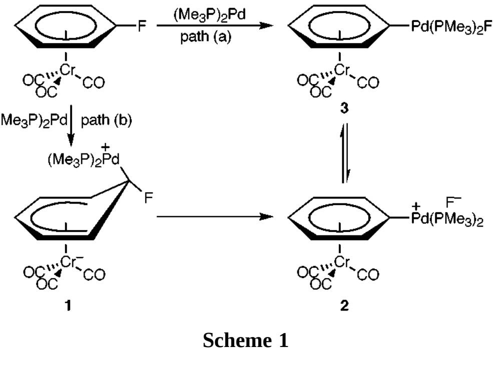
Run	Ligand	Palladium	Base (equiv.)	Yield (%)
1[a]	—	$Pd(PPh_3)_4$	Na_2CO_3 (2.2)	Trace
2	PCy_3	$Pd_2(dba)_3$	CsF (4)	0
3	PMe_3	$Pd_2(dba)_3$	CsF (4)	52
4	—	$Pd_2(dba)_3$	CsF (4)	0
5[b]	PMe_3	$Pd_2(dba)_3$	—	0
6	PMe_3	$Pd_2(dba)_3$	Cs_2CO_3 (2.2)	61
7	PMe_3	—	Cs_2CO_3 (2.2)	0

[a] Toluene as solvent. [b] 4-Methoxyphenylboronic acid replaced phenylboronic acid.

The participation of a fluoroarene, albeit as its tricarbonylchromium complex, in a palladium catalysed cross coupling is unprecedented[12] and required careful evaluation. Control experiments covering the more obvious factors were carried out and the results are summarised in Table 1. Firstly, the ready displacement of fluoride in these complexes by other nucleophiles,[13–16] particularly higher halides, which could then undergo cross-coupling, required that the system be free of any source of such nucleophiles. Thus no solvent/additive which might release higher halide was used and initially, high purity (99.9%) caesium fluoride was used as the base. In principle fluoride should be catalytic but attempts to demonstrate this failed.

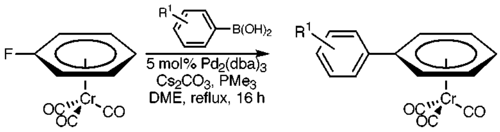
The ineffectiveness of tricyclohexylphosphine as ligand (run 3) could be a consequence of steric hindrance between the bulky tricarbonylchromium unit and the bulky phosphine, and the smaller trimethylphosphine was used in all subsequent experiments. In the absence of any phosphine, the coupling failed (run 4). Reaction without a base (run 5) also failed but the use of caesium carbonate (run 6) increased the yield to 61%. A reaction in the presence of base and phosphine but without palladium (run 7) gave no coupling. The presence of unchanged starting material from this reaction removed the possibility that a borate anion was displacing the fluoride group from the complex and that the resultant arylborate was the active cross coupling partner. This result also demonstrated the unreactivity of neutral phosphine to the fluoro complex, but to reinforce this conclusion a reaction between trimethylphosphine and fluorobenzene complex under cross-coupling conditions was attempted. The complex was recovered unchanged in 98% yield. This precludes a process of phosphonium salt formation and participation of this in cross-coupling[17,18] as the reaction sequence.

These experiments provide strong evidence for direct participation of the fluorobenzene complex in the coupling process with the implication of an unprecedented oxidative addition of the C–F bond to the palladium(0) intermediate.[19] Whether this is a concerted insertion [Scheme 1, path (a)] or an addition–elimination sequence [Scheme 1, path (b)] *via* an *exo*-addition[20] of palladium to form **1** followed by fluoride loss to produce **2** cannot be determined at this point. The insertion product could be active in the catalytic cycle in either neutral (**3**) or cationic (**2**) form.[12]



Scheme 1

Table 2 Suzuki coupling reactions of η^6-(fluorobenzene)tricarbonylchromium(0)



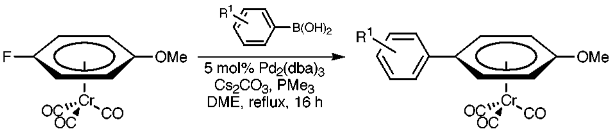
Run	R^1	Yields (%)
1	H	61
2	4-MeO	87
3	2-MeO	78
4	4-Me	81
5	2-Me	79
6	4-Br	0[a]

[a] An intractable oligomeric/polymeric material containing no chromium(0) was produced.

With suitable conditions established, the fluorobenzenechromium complex was coupled with a series of electron-rich arylboronic acids (Table 2).[21] Both moderately hindered (runs 3, 5) and unhindered boronic acids (runs 1, 2, 4) gave good yields. The polymerisation of 4-bromophenylboronic acid under the reaction conditions can be attributed to the greater reactivity of the C–Br bond over the C–F bond.

To further investigate the scope of this process, the more electron-rich 4-methoxyfluorobenzenetricarbonylchromium complex was studied.[21] The yields (Table 3), with both the moderately hindered and the unhindered boronic acids, were comparable to those of the parent complex despite the expected reduction in reactivity of the alkoxy analogue.

Table 3 Suzuki coupling reactions of η^6-(4-fluoromethoxybenzene)-tricarbonylchromium(0)



Run	R^1	Yield (%)
1	H	76
2	2-Me	77
3	4-Me	74

These results clearly raise intriguing mechanistic questions, which we continue to address. The couplings demonstrate the versatility of the arenetricarbonylchromium(0) complexes and add further possibilities to the exploitation of their already widely established role in synthesis.

Notes and references

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21 *Typical procedure*: A solution of η^6-(fluorobenzene)tricarbonylchromium(0) (0.300 g, 1.29 mmol), 4-methoxyphenylboronic acid (0.392 g, 2.58 mmol), caesium carbonate (0.925 g, 2.84 mmol), $Pd_2(dba)_3$ (5 mol%, 0.060 g, 0.06 mmol) and PMe_3 (20 mol%, 0.26 ml, 1 M solution in toluene) in deoxygenated DME (9 ml) was stirred under reflux for 16 h. Et_2O (50 ml) was added and the solution was washed with 10% aq. NaOH (15 ml), water (15 ml) and brine (15 ml) and dried over $MgSO_4$. Concentration *in vacuo* followed by column chromatography (eluent: 5% Et_2O–hexane) gave η^6-(4′-methoxybiphenyl)tricarbonylchromium(0) as a yellow crystalline solid (0.360 g, 87%), mp 58–61 °C (Found: C, 59.99; H, 3.69. $C_{16}H_{12}CrO_4$ requires C, 60.01; H, 3.78%); ν_{max}(KBr)/cm^{-1} 2986w, 2838w, 1977s, 1961s, 1887s, 1868s, 1609m, 1508m, 1454m, 1279m, 1249m, 1176m, 1020m, 840m, 819m, 661m, 629s, 535m; δ_H(270 MHz; $CDCl_3$) 7.43 (2H, d, *J* 8.9), 6.93 (2H, d, *J* 8.9), 5.64 (2H, dd, *J* 6.7, 1.0), 5.49 (2H, t, *J* 6.4), 5.28 (1H, tt, *J* 6.2, 1.0), 3.83 (3H, s); δ_C(68 MHz) 233.0, 160.4, 128.6, 128.3, 114.3, 111.2, 93.2, 91.6, 90.9, 55.4; *m/z* (EI) 320 (M$^+$, 43%), 264 (39), 236 (93), 221 (11), 205 (5), 184 (9), 169 (4), 52 (100) (Observed: M$^+$ 320.0141; $C_{16}H_{12}CrO_4$ requires 320.0130).

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