Sequential C–F activation and borylation of fluoropyridines *via* intermediate Rh(I) fluoropyridyl complexes: a multinuclear NMR investigation†

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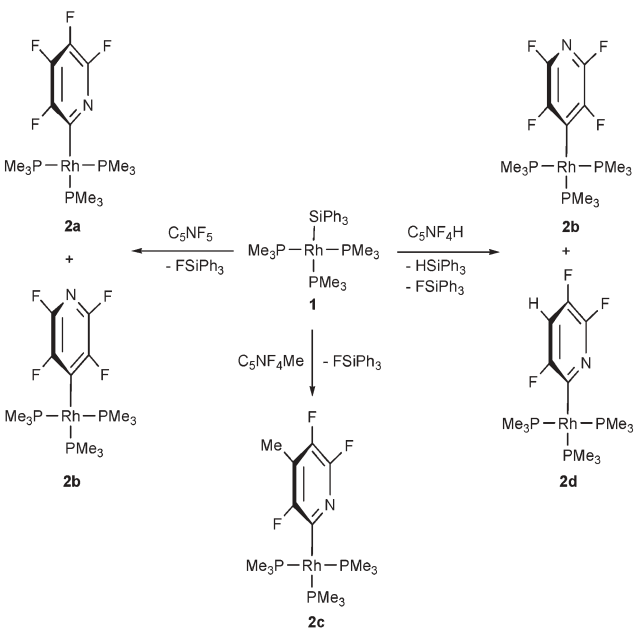
The C–F bond activation of fluoropyridines by $[Rh(SiPh_3)(PMe_3)_3]$ afforded Rh(I) fluoropyridyl complexes of the type $[Rh(Ar^F)(PMe_3)_3]$ with concomitant formation of fluorotriphenylsilane; subsequent treatment with bis-catecholatodiboron yielded *fac*-$[Rh(Bcat)_3(PMe_3)_3]$ and the free fluoropyridyl boronate esters (Ar^FBcat).

Aryl boronate esters, $ArB(OR)_2$, have a wide variety of applications in boron neutron capture therapy, in sugar receptors and as versatile reagents in organic chemistry. In particular, they are used as precursors to alcohols and as synthetic intermediates in Suzuki–Miyaura couplings.[1,2] The importance and variety of compounds with metal–boron bonds is growing rapidly.[3–5] C–H bond borylation as a route to $ArB(OR)_2$ was first demonstrated by Marder *et al.* in 1993, when the borylation of toluene was observed during the room temperature reaction of $[Ir(\eta^5\text{-}C_9H_7)(cod)]$ with HBcat (cat = $1,2\text{-}O_2C_6H_4$).[6] Since 1999, transition metal boryl complexes of groups 6–9 have been found to be active for the direct catalytic borylation of unreactive, saturated and unsaturated hydrocarbons by C–H activation. In particular, iridium systems such as $[Ir(Bpin)_3(dtbpy)]$ catalyse selective C–H bond borylation at room temperature.[7–13] In contrast, no definitive examples of C–F bond borylation reactions have been reported, despite the developments in metal-mediated C–F bond activation.‡[14,15] One well-established system for C–F oxidative addition is $[Ni(COD)_2]$ which reacts with a variety of fluoropyridines (Ar^F–F) in the presence of excess PR_3 (R = Et, Cy, PPh_3) to yield complexes of the type *trans*-$[NiF(Ar^F)(PR_3)_2]$.[16] In a different type of C–F activation process, $[RhH(PEt_3)_3]$ reacts with pentafluoropyridine to afford $[Rh(4\text{-}C_5NF_4)(PEt_3)_3]$ with loss of HF. The same product is obtained *via* C–H activation of 2,3,5,6-tetrafluoropyridine, with loss of H_2.[17] Only a few examples of C–F bond functionalisation have been reported, where a fluorine in an organic molecule is replaced by a new group through metal-mediated reaction.[18–22] Furthermore, many of these reactions are limited to hydrodefluorination, *i.e.* conversion to C–H bonds.[14,23,24] Milstein demonstrated that the catalytic hydrodefluorination of C_6F_6 to C_6F_5H is achieved in the presence of $[Rh(C_6F_5)(PMe_3)_3]$ and $HSiR_3$ (R = Ph or OEt). In this case, the active species for C–F bond activation is the Rh(I) silyl complex $[Rh(SiR_3)(PMe_3)_3]$.[25,26] On the basis of these reports, we investigated the reactivity of $[Rh(SiPh_3)(PMe_3)_3]$ towards fluoropyridines and sought to establish whether C–F bond borylation could be achieved by reaction with a diborane. Here we show that rhodium complexes can be used for the borylation of fluoroaromatics.

Reaction of $[Rh(SiPh_3)(PMe_3)_3]$ **1** with a number of fluoropyridines yielded new square-planar Rh(I) fluoropyridyl complexes of the type $[Rh(Ar^F)(PMe_3)_3]$ (Scheme 1). The new rhodium fluoropyridyl complexes formed at room temperature and were identified by multinuclear NMR spectroscopy. According to these spectra, the consumption of starting material was complete after 1–4 days. The extreme sensitivity of the complexes towards air and moisture prevented isolation of pure samples. In all cases, the C–F activation reactions generated fluorotriphenylsilane as the fluorine containing by-product. Treatment of **1** with 1 equiv. of C_5NF_5 produced $[Rh(2\text{-}C_5NF_4)(PMe_3)_3]$ **2a** and $[Rh(4\text{-}C_5NF_4)(PMe_3)_3]$ **2b** in a 3 : 1 ratio (determined by integration of the ^{19}F NMR spectrum).§ The ^{19}F NMR spectrum displays seven new resonances due to the three products. **2a** exhibits ^{19}F resonances at δ −87.0 (td, J_{FF} = 31, 15 Hz), −128.4 (tm, J_{FF} = 33 Hz), −154.0 (m) and −175.8 (dd, J_{FF} = 31, 15 Hz) corresponding to the F atoms at the 6, 3, 4 and 5 positions of the ring, respectively.¶



Scheme 1 Reactions of **1** with fluoropyridines.

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† For CIF file of **2b** (CCDC 648397) see DOI: 10.1039/b707840d

These assignments are consistent with those for [NiF(2-C_5NF_4)(PEt_3)$_2$] and are characteristic of tetrafluoropyridyl coordinated to a metal *ortho* to nitrogen.[27] The ^{19}F NMR resonances for **2b** are at δ −100.7 (m) and δ −117.3 (m) for the atoms *ortho* and *meta* to nitrogen, respectively. These resonances are consistent with other transition metal complexes with a tetrafluoropyridyl ligand coordinated *para* to nitrogen. The ^{19}F NMR spectrum also displays a singlet at δ −169.0 with silicon satellites (J_{SiF} = 280 Hz) for Ph_3SiF, which is formed in a 1 : 1 ratio with respect to the total amount of **2a** and **2b**. The $^{31}P\{^1H\}$ NMR spectrum of the product mixture reveals a complex second order pattern in the region δ −13 to −16. This chemical shift region is characteristic of PMe_3 ligands in Rh(I) aryl complexes including [RhPh(PMe_3)$_3$] and [Rh(C_6F_5)(PMe_3)$_3$].[25,28]

Complex **2b** was synthesised and characterised independently by treatment of [Rh(PMe_3)$_4$]Cl with 2,3,5,6-tetrafluoropyridyl magnesium bromide.[29] Extractions with toluene and heptane allowed isolation of pure yellow crystals of **2b**. The structure of **2b** was confirmed by X-ray crystallography (Fig. 1).‖ The pyridyl ligand lies approximately perpendicular to the coordination plane, with an 88.75(5)° angle between the planes. The sum of the angles at Rh is 359.89°, as expected for a square-planar complex. For the plane defined by C(1), P(1), P(2) and P(3), the deviations from the plane are: P(1) 0.041(1) Å, P(2) 0.040(1) Å, P(3) −0.035(1) Å, C(1) −0.046(1) Å and Rh(1) 0.064(1) Å. The Rh–C bond length C(1)–Rh(1) is 2.0700(13) Å, which compares with 2.078(8) Å for [Rh(C_6F_5)(PMe_3)$_3$] and 2.0623(14) Å for [Rh(4-C_5NF_4)-(PEt_3)$_3$].[17,25] The $^{31}P\{^1H\}$ NMR spectrum of isolated **2b** exhibits an approximate doublet of doublets at δ −16.0 (J_{PP} = 44, J_{RhP} = 136 Hz) for the two mutually *trans* PMe_3 ligands, and a broad doublet of triplets of multiplets at δ −13.9 (J_{PP} = 44, J_{RhP} = 127 Hz) for the unique phosphorus (second order distortion is observed as before). This spectrum is comparable to the PEt_3 analogue of **2b**, which has been described by Braun *et al.*[17]

Treatment of **1** with 1 equiv. of 2,3,5,6-tetrafluoro-4-methylpyridine produced [Rh(2-C_5NF_3Me)(PMe_3)$_3$] **2c** exclusively because neither C–F or C–H activation at the 4-position are possible. Reaction of 2,3,5,6-tetrafluoropyridine with **1** resulted in competitive C–H and C–F activation to yield **2b** and [Rh(2-C_5NF_3H)(PMe_3)$_3$] **2d** as the initial products in a 1 : 1.3 ratio, along with Ph_3SiF and Ph_3SiH. A secondary reaction then occurs between **2d** and Ph_3SiH to yield 2,3,5-trifluoropyrdine and an unidentified Rh complex. Overall, this product corresponds to hydrodefluorination of 2,3,5,6-tetrafluoropyridine at the 2-position. As a test of this reaction sequence, we added Ph_3SiH to a mixture of **2a** and **2b**, which afforded 2,3,4,5-tetrafluoropyridine from the reaction of silane with **2a** (Scheme 2). Complex **2b** did not react with Ph_3SiH.

Prior to attempting the borylation reactions of **2a–d**, the known complexes [Rh(C_6F_5)(PMe_3)$_3$] **2e** and [RhPh(PMe_3)$_3$] **2f** were treated with the diborane B_2cat_2 (Bcat = B{1,2-$O_2C_6H_4$}) in order to produce the free boronate esters (Ar–Bcat).[25,28] We found that 2 equiv. of B_2cat_2 was required to produce stable products. Addition of 2 equiv. of B_2cat_2 to solutions of **2e** and **2f** in d_8-toluene afforded *fac*-[Rh(Bcat)$_3$(PMe_3)$_3$] **4** and the corresponding free aryl boronate ester C_6F_5Bcat and PhBcat, respectively. The formation of the boronate esters was confirmed by GC-MS. The tris-boryl complex **4** has been described in the literature following the reaction of [RhMe(PMe_3)$_4$] with B_2cat_2.[30] At room temperature, the $^{31}P\{^1H\}$ NMR spectrum of **4** displays a broad signal at δ −26.2 as a result of the quadrupolar boron nuclei coordinated *trans* to the PMe_3 ligands. We have now discovered that this signal resolves to a doublet (J_{RhP} = 72.4 Hz) at δ −24.9 on cooling to 210 K, indicative of the *fac* geometry. This coupling constant is remarkably low for a Rh(III) species and is a measure of the exceptionally strong *trans* influence of Bcat which is a very strong σ-donor ligand.[31]

Treatment of the C–F activation product mixture of **2a** and **2b** (generated *in-situ*) with 2 equiv. of B_2cat_2 resulted in complete conversion to C_5N-2-(Bcat)-3,4,5,6-F_4 **3a**, C_5N-4-(Bcat)-2,3,5,6-F_4 **3b** together with **4** (Scheme 3).** The ^{19}F NMR spectrum of the product mixture shows complete consumption of the **2a** and **2b**, and six new resonances for the boronate ester reductive elimination products. **3a** exhibits four signals at δ −81.7 (td, J_{FF} = 27, 19 Hz) −135.3 (m), −141.5 (m) and −152.4 (m), while **3b** displays two multiplet resonances at δ −92.1 (m) and −131.0 (m).†† The ^{11}B NMR spectrum shows overlapping resonances at δ 29 for **3a** and **3b**, which is consistent with other aryl boronate esters.[32]

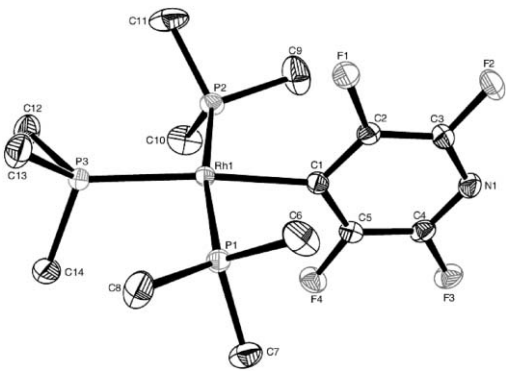
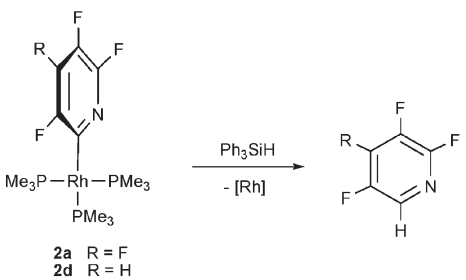
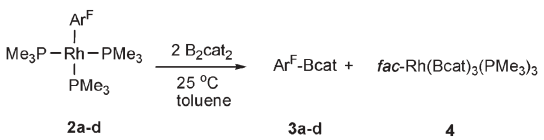


Fig. 1 A view of the molecular structure of **2b**. Ellipsoids are drawn at the 50% probability level and hydrogens are omitted for clarity. Selected bond lengths [Å] and angles [°]: Rh(1)–C(1) 2.0700(13), Rh(1)–P(1) 2.3094(4), Rh(1)–P(2) 2.2838(4), Rh(1)–P(3) 2.2821(4); Rh(1)–C(1)–C(2) 124.22(10), Rh(1)–C(1)–C(5) 124.59(10), C(2)–C(1)–C(5) 111.07(12), C(1)–Rh(1)–P(1) 84.64(4), P(2)–Rh(1)–P(3) 95.043(14), P(2)–Rh(1)–C(1) 86.21(4), P(1)–Rh(1)–P(3) 174.29(4).



Scheme 2 Reactions of **2a** and **2d** with Ph_3SiH.



Scheme 3 Reactions of **2a–d** with B_2cat_2.

Formation of the pyridyl boronate esters was confirmed by high-resolution mass spectrometry. Corresponding reactivity was found for the other fluoropyridyl complexes described above. Compound **2c** reacted with the diborane to yield C_5NMe-2-(Bcat)-3,5,6-F_3 **3c** and **4**, exclusively. When the mixture of **2b** and **2d** was treated with 2 equiv. of B_2cat_2 the products were **3b**, C_5NH-2-(Bcat)-3,5,6-F_3 **3d** and **4**.

To conclude, we have demonstrated the first definitive examples of C–F bond borylation, *via* intermediate Rh(I) fluoroaryl or fluoropyridyl species. Furthermore, both the C–F activation and C–B bond formation steps are achieved at room temperature. The borylation step generates *fac*-[Rh(Bcat)$_3$(PMe$_3$)$_3$] which acts as a thermodynamic sink. It should be possible to develop catalytic versions of this process in the future.

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Notes and references

‡ Smith *et al.* observed formation of small quantities of C_6HF_4(Bpin) and $C_6H_3F_2$(Bpin) during the borylation reactions of C_6HF_5 and 1,3,5-$C_6H_3F_3$, respectively, catalysed by [Rh(η^5-C_5Me_5)(η^4-C_6Me_6)] or [Ir(η^5-C_5Me_5)(H)(Bpin)(PMe$_3$)]. However, the authors state that the fluoroaromatic starting materials contained impurities ($C_6H_4F_2$ isomers in 1,3,5-$C_6H_3F_3$) and that the borylation products were not rigorously quantified. Therefore, they conclude that it is unclear whether these products arose from C–F borylation of the principal fluoroaromatic or from C–H borylation of the impurities.[32]

§ In a typical experiment, **1** (10 mg, 0.017 mmol) was dissolved in d_8-toluene (500 μL) in a dried Young's tap NMR tube. A stock solution of fluoropyridine (1 mmol dm^{-3}) in d_8-toluene was prepared and 17 μL (0.017 mmol) was added to the NMR tube by microsyringe, followed by mixing. The solution changed colour from red to yellow after 1–4 days at 25 °C, with quantitative formation of the C–F/C–H activation products and silane by-product. The products were analysed by NMR spectroscopy.

¶ *Selected NMR spectroscopic data for* **2a–d** (d_8-toluene, 300 K): **2a** ^{1}H (500.1 MHz) δ 1.0 to 0.8 (br m). ^{31}P{^{1}H} (202.46 MHz) δ −13.0 to −16.0 (complex 2nd order pattern). ^{19}F (470.59 MHz) δ −87.0 (td, J_{FF} = 15, 31 Hz, 1 F), −128.4 (tm, J_{FF} = 33 Hz, 1 F), −154.0 (m, 1 F), −175.8 (dd, J_{FF} = 15, 31 Hz, 1 F). **2b** ^{1}H (500.1 MHz) δ 0.95 (br d, J_{PH} = 6 Hz, 9 H), 0.81 (d vt, J_{RhH} = 1 Hz, J_{PH} = 3 Hz, 18 H). ^{31}P{^{1}H} (202.46 MHz) δ −16.0 (dd, J_{PP} = 44 Hz, J_{RhP} = 136 Hz, 2 P), −13.9 (br dtm, J_{PP} = 44 Hz, J_{RhP} = 127 Hz, 1 P). ^{19}F (470.59 MHz) δ −100.5 (m, 2 F), −117.2 (m, 2 F). **2c** ^{1}H (500.1 MHz) δ 2.04 (s, 3 H), 1.06 (br s, 9 H), 0.90 (br s, 18 H). ^{31}P{^{1}H} (202.46 MHz) δ −12.9 to −15.3 (complex 2nd order pattern). ^{19}F (470.59 MHz) δ −92.3 (t, J_{FF} = 34 Hz, 1 F), −111.3 (d, J_{FF} = 34 Hz, 1 F), −158.4 (d, J_{FF} = 34 Hz, 1 F). **2d** ^{1}H (500.1 MHz) δ 6.52 (m), 1.0 to 0.8 (br m). ^{31}P{^{1}H} (202.46 MHz) δ −13.0 to −15.0 (complex 2nd order pattern). ^{19}F (470.59 MHz) δ −92.5 (td, J_{FF} = 32 Hz, J_{HF} = 8 Hz, 1 F), −106.5 (dt, J_{FF} = 32 Hz, J_{HF} = 6 Hz, J_{PF} = 6 Hz, 1 F), −152.9 (dd, J_{FF} = 32 Hz, J_{HF} = 10 Hz, 1 F).

‖ *Crystal data for* **2b**: $C_{14}H_{27}F_4NP_3Rh$, M = 481.19, monoclinic, space group $P2_1/c$ (no. 14), a = 12.1172(6) Å, b = 9.2891(5) Å, c = 20.422(3) Å, β = 102.8010(10)°, U = 2012.48(18) Å^3, Z = 4, D_c = 1.588 Mg m^{-3}, λ = 0.71073 Å, μ = 1.118 mm^{-1}, F(000) = 976, T = 120(2) K. Data were collected on a Bruker SMART Apex X-ray diffractometer for $1.72 < \theta < 29.99°$. The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least squares using SHELXL-97.[33,34]

** Compounds **2a–d** were generated by C–F/C–H activation, as described above. B_2cat_2 (8 mg, 0.034 mmol) was added to the solution and the sample was mixed. After several minutes, the solution changed from yellow to colourless due to quantitative formation of **4** and **3a–d**. The products were analysed by NMR spectroscopy and mass spectrometry.

†† *Selected spectroscopic data for* **3a–d** (d_8-toluene, 300 K): **3a** ^{19}F (470.59 MHz) δ −81.7 (td, 1 F, J_{FF} = 27, 19 Hz), −135.3 (m, 1 F), −141.5 (m, 1 F), −152.4 (m, 1 F). ^{11}B (160.46 MHz) δ 29. **3b** ^{19}F (470.59 MHz) δ −92.1 (m, 2 F), −131.0 (m, 2 F). ^{11}B (160.46 MHz) δ 29. High-resolution mass spectrum (EI) **3a/3b** *m/z* 269.027496 (269.027122 calcd. for $C_{11}H_4BNO_2F_4$, Δ = 0. 374 mDa). **3c** ^{19}F (470.59 MHz) δ −87.9 (t, J_{FF} = 28 Hz, 1 F), −118.0 (dd, J_{FF} = 9, 30 Hz, 1 F), −134.3 (dd, J_{FF} = 9, 29 Hz, 1 F). ^{11}B (160.46 MHz) δ 28. High-resolution mass spectrum (EI) **3c** *m/z* 265.052453 (265.052194 calcd. for $C_{12}H_7BNO_2F_3$, Δ = 0.259 mDa). **3d** ^{19}F (470.59 MHz) δ −87.4 (m, 1 F), −113.1 (m, 1 F), −128.5 (m, 1 F). ^{11}B (160.46 MHz) δ 28.

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