

Aromatic C–F activation at Ni in the presence of a carbon–chlorine bond: the nickel mediated synthesis of new pyrimidines †

Marianna I. Sladek, Thomas Braun,* Beate Neumann and Hans-Georg Stammler

Fakultät für Chemie, Universität Bielefeld, Postfach 100131, D-33501 Bielefeld, Germany.
E-mail: thomas.braun@uni-bielefeld.de

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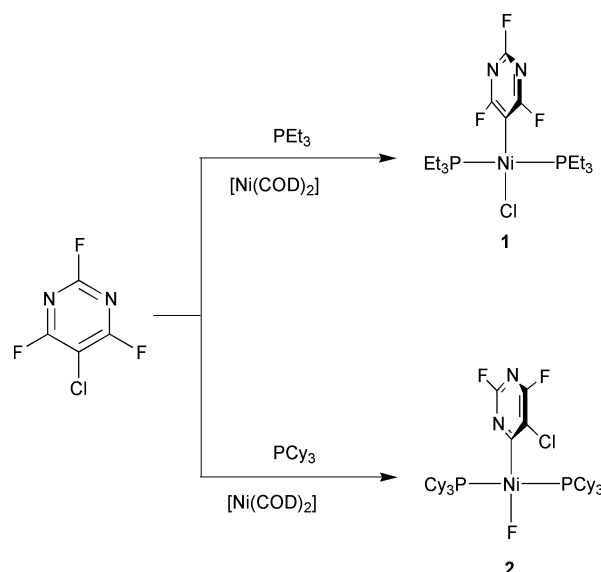
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Treatment of $[\text{Ni}(\text{COD})_2]/\text{PCy}_3$ with 5-chloro-2,4,6-trifluoropyrimidine affords the C–F activation product $\text{trans-}[\text{NiF}(\text{4-C}_4\text{N}_2\text{ClF}_2)(\text{PCy}_3)_2]$ **2**, which reacts with iodine to form 5-chloro-2,6-difluoro-4-iodo-pyrimidine **5**.

Several methods have been described for the activation of carbon–fluorine bonds of fluoroaromatic compounds by reaction at transition metal centres.¹ Catalytic C–F activation has also become a reality.^{2–4} However, the formation of new organofluorine compounds *via* C–F activation, followed by functionalisation within the coordination sphere of the metal is still little developed.^{3–6} Nevertheless, the activation of a C–F bond in pentafluoropyridine, 2,3,5,6-tetrafluoropyridine or 2,4,6-trifluoropyrimidine at a nickel centre can be used as a remarkable approach to obtain fluorinated derivatives which are otherwise inaccessible.^{4,6–8} While C–F activation at nickel is selective over C–H activation,^{2,4,9,10} the activation of a C–F bond in the presence of a C–Cl bond in the same ring has never been observed. Crespo *et al.* reported the C–F activation of the imine $(\text{C}_6\text{F}_5)\text{CH}=\text{NCH}_2(2\text{-ClC}_6\text{H}_4)$ at a Pt(II) centre, but with the C–F and C–Cl bond on different rings.¹¹ In this communication we describe (1) the activation of a C–F bond in the presence of a much weaker C–Cl bond in the same aromatic ring, (2) that the chemospecificity of the activation of a C–X bond (X = F, Cl) in 5-chloro-2,4,6-trifluoropyrimidine by $[\text{Ni}(\text{COD})_2]/\text{PR}_3$ (R = Et, Cy; COD = cycloocta-1,5-diene) is controlled by the size of the phosphine, (3) the nickel-mediated synthesis of new fluorinated pyrimidines by C–F activation.

The stepwise treatment of $[\text{Ni}(\text{COD})_2]$ with PEt_3 and 5-chloro-2,4,6-trifluoropyrimidine in hexane solution at room temperature results in the formation of $\text{trans-}[\text{NiCl}(\text{5-C}_4\text{N}_2\text{F}_3)(\text{PEt}_3)_2]$ **1**, which was crystallised at -20°C (Scheme 1).[‡] The isolated yield of 20% was limited principally by the extreme solubility of the product. However, there was a minor amount (5%) of a yellow solid, insoluble in all common solvents, which could not, as yet, be identified. The ^{19}F NMR spectrum of **1** shows two resonances at $\delta -37.77$ and -55.72 with a ratio of 2 : 1 revealing the presence of the trifluoropyrimidyl group. The observed preference for C–Cl activation is fully consistent with comparable reactions of chloropentafluorobenzene and 3,5-dichlorotetrafluoropyridine, which are described in the literature.⁹

On using PCy_3 instead of PEt_3 exclusive activation of the C–F bond takes place. Treatment of $[\text{Ni}(\text{COD})_2]$ with PCy_3 in the presence of 5-chloro-2,4,6-trifluoropyrimidine results in the formation of $\text{trans-}[\text{NiF}(\text{4-C}_4\text{N}_2\text{ClF}_2)(\text{PCy}_3)_2]$ **2**.[‡] The ^{31}P and ^{19}F NMR spectrum of the reaction solution reveals the presence of a minor product (18%), which was assigned as $\text{trans-}[\text{NiCl}(\text{4-C}_4\text{N}_2\text{ClF}_2)(\text{PCy}_3)_2]$ **3**.[‡] However, after recrystallisation we obtained a pure sample of **2** in moderate yield (34%). The ^{19}F NMR spectrum of **2** exhibits a triplet at $\delta -377.56$ (J_{PF} 40 Hz) characteristic of the metal fluoride and two further resonances at $\delta -49.86$ and -73.67 with a 1 : 1 ratio revealing



Scheme 1 Reactivity of $[\text{Ni}(\text{COD})_2]$ towards 5-chloro-2,4,6-trifluoropyrimidine.

the presence of a difluoropyrimidyl group.^{4,8–10} The ^{31}P NMR spectrum displays a doublet resonance at $\delta 19.65$ (J_{PF} 39 Hz) for the two equivalent phosphorus nuclei coupled to the metal-bound fluorine.

The formation of compound **3** can be explained by a reaction of **2** with free 5-chloro-2,4,6-trifluoropyrimidine. Indeed, treatment of a solution of **2** with the organic substrate affords complex **3**. A comparable substitution of a metal-bound fluoride by a chloro ligand using chloropentafluorobenzene has been described at a rhodium centre.¹² Complex **3** can also be synthesised by reaction of **2** with NaCl (Scheme 2).

Complex **2** was crystallised at -20°C from hexane. The structure was determined by X-ray diffraction at low temperature (Fig. 1).[§] Despite a rotational disorder of the aromatic ring in **2** (62 : 38) the structure provides useful data. The Ni–F bond of 1.845(2) Å is comparable to the distance found in $\text{trans-}[\text{NiF}(\text{2-C}_3\text{NF}_3\text{H})(\text{PEt}_3)_2]$ [1.856(2) Å].⁹ The distance found for the Ni–C bond in **2** [1.828(8) Å, 1.863(12) Å] is in the same range as the values found in **1** [1.8849(13) Å] and $\text{trans-}[\text{NiF}(\text{2-C}_3\text{NF}_3\text{H})(\text{PEt}_3)_2]$ [1.869(4) Å].^{†9}

We believe that a precoordination of the aromatic system at the nickel centre, *via* a nitrogen atom or in an η^2 mode, is a crucial step in the activation of a C–X bond in 5-chloro-2,4,6-trifluoropyrimidine. Similar intermediates have been discussed in the C–F activation of hexafluorobenzene, octafluoronaphthalene and pentafluoropyridine at $\text{Ni}(\text{PEt}_3)_2$.^{4,9,10,13} It has been proposed that these reactions proceed by a concerted oxidative addition mechanism. The observed chemospecificity in the formation of **1** and **2** might therefore be attributed to different intermediates or, more likely, different transition states.^{13,14} Although there is a small difference in the electronic properties of PEt_3 and PCy_3 at nickel, we believe that the chemospecificity is determined by steric factors.¹⁵ However,

† Electronic supplementary information (ESI) available: synthesis details for compounds **1–3** and crystal data for **1**. See <http://www.rsc.org/suppdata/dt/b1/b110128e/>

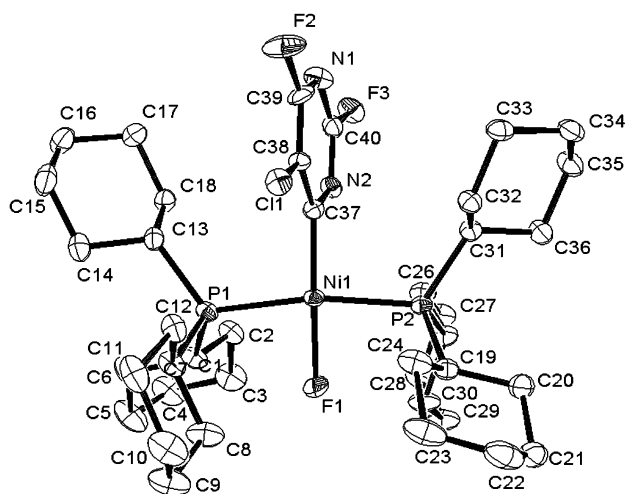
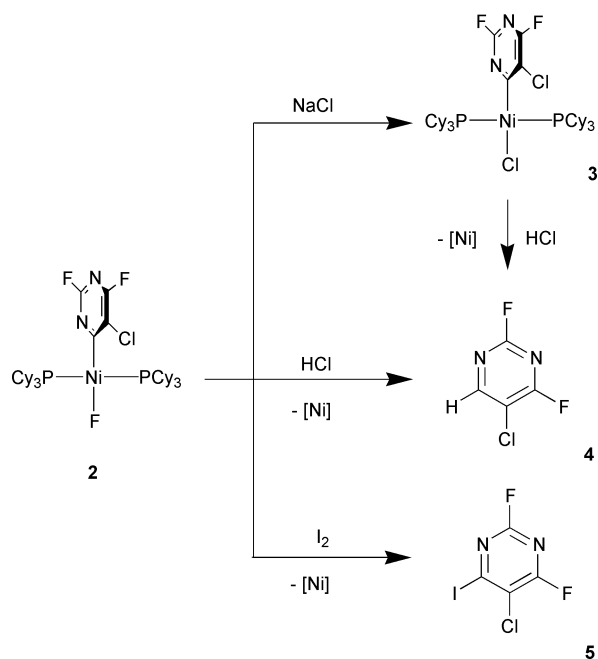


Fig. 1 An ORTEP¹⁸ diagram of **2**. Ellipsoids are drawn at the 50% probability level. Note that the rotational disorder (62 : 38) about Cl(1), N(1), N(2), F(2), F(3) and C(37)–C(40) leads to average locations across the pyrimidyl ring. The two rotamers have identical bond distances within 3 σ . Data for the second rotamer are marked by a #. Selected bond lengths (Å) and angles (°): Ni(1)–F(1) 1.845(2), Ni(1)–C(37) 1.828(8), Ni(1)–C(37)# 1.863(12), N(2)–C(37) 1.362(7), N(2)–C(40) 1.307(6), N(1)–C(40) 1.297(7), N(1)–C(39) 1.30(2), C(37)–C(38) 1.398(7), C(38)–C(39) 1.40(2), Cl(1)–C(38) 1.713(4), F(2)–C(39) 1.31(2), F(3)–C(40) 1.344(5); C(37)–Ni(1)–F(1) 172.98(18), C(37#)–Ni(1)–F(1) 170.4(3), P(1)–Ni(1)–P(2) 168.74(2).

we also cannot exclude that instead of a concerted oxidative addition mechanism an electron transfer process precedes the activation of the C–X bond.¹⁶ Further mechanistic investigations are under way.

Treatment of **2** or **3** with an excess HCl in C₆D₆–diethyl ether affords, after distillation under vacuum, a solution of 5-chloro-2,4-difluoropyrimidine **4** (Scheme 2).[¶] The reaction of **2** with iodine in C₆D₆ yields a solution of 5-chloro-2,6-difluoro-4-iodopyrimidine **5**.^{¶¶} The reactions are quantitative according to the NMR spectra. We have found no previous description of compound **4** or **5**. Fluorinated pyrimidines are of general interest as building blocks in agrochemicals, dyes and because of their antitumor activity.^{6,17}

In conclusion, we have shown the first activation of an aromatic carbon–fluorine bond at a metal centre in the presence of a C–Cl bond in the same ring. Comparable C–F activation

reactions at nickel with a unique regioselectivity and a preference for C–F over C–H activation have been studied before.^{8–10} We have now demonstrated that the scope of these reactions can be expanded to the activation of a carbon–fluorine bond in 5-chloro-2,4,6-trifluoropyrimidine using a sterically more hindered phosphine. The described reaction provides an unusual entry to new fluoropyrimidines bearing three different substituents by selective replacement of one fluorine atom at the already functionalised heterocycle.

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Notes and references

‡ Selected data for **1**, **2** and **3**. **1**: (Found: C, 40.84; H, 6.53; N, 5.99%. C₁₆H₃₀ClF₃N₂NiP₂ requires: C, 41.46; H, 6.52; N, 6.04%). ³¹P NMR (202.5 MHz, C₆D₆, 300 K): δ 15.83 (s). ¹⁹F NMR (470.4 MHz, C₆D₆, 300 K): δ –37.77 (s, br, 2 F), –55.72 (s, br, 1 F). **2**: (Found: C, 60.50; H, 8.35; N, 3.59%. C₄₀H₆₆ClF₃N₂NiP₂ requires: C, 60.97; H, 8.44; N, 3.55%). ³¹P NMR (202.5 MHz, C₆D₆, 300 K): δ 19.65 (d, J_{PF} 39 Hz). ¹⁹F NMR (470.4 MHz, C₆D₆, 300 K): δ –49.86 (s, 1 F), –73.67 (s, 1 F), –377.56 (t, J_{PF} 40 Hz, 1 F). **3**: (Found: C, 59.92; H, 8.70; N, 3.10%. C₄₀H₆₆Cl₂F₃N₂NiP₂ requires: C, 59.72; H, 8.27; N, 3.48%). ³¹P NMR (202.4 MHz, C₆D₆, 300 K): δ 15.67 (s). ¹⁹F NMR (470.4 MHz, C₆D₆, 300 K): δ –48.91 (s, 1 F), –73.77 (s, 1 F).

§ Crystal data for **2**: C₄₀H₆₆ClF₃N₂NiP₂, $M = 788.05$, monoclinic, space group $P2_1/n$, $a = 13.8320(10)$, $b = 20.2110(15)$, $c = 14.5510(10)$ Å, $\beta = 90.459(6)^\circ$, $U = 4067.7(5)$ Å³, $T = 100$ K, $\mu(\text{Mo-K}\alpha) = 0.665$ mm^{–1}, $Z = 4$, $D_c = 1.287$ g cm^{–3}, 28171 reflections measured, 9114 unique ($R_{\text{int}} = 0.0409$). The disorder of the pyrimidyl ligand on two positions was refined to an occupancy of 62 : 38. Final R_1 , wR_2 values on all data 0.06457, 0.0942. R_1 , wR_2 values on [$I_o > 2\sigma(I_o)$, 7325 reflections] data 0.0449, 0.0890. CCDC reference number 173741. See <http://www.rsc.org/suppdata/dt/b1/b110128e/> for crystallographic data in CIF or other electronic format.

¶ Selected spectroscopic data for **4** and **5**. **4**: NMR (C₆D₆, 300 K): ¹H (500.1 MHz): δ 7.37 (d, br, J_{FH} 11 Hz, CH), ¹⁹F (470.4 MHz): δ –45.69 (s, br, 1 F), –59.15 (s, br, 1 F). Mass spectrum (EI) m/z 152 (M⁺, 33%), 150 (M⁺, 100). Accurate mass spectrum (EI) m/z calcd. for C₄HN₂F₂Cl, 149.9796; found, 149.9814. **5**: NMR (C₆D₆, 300 K): ¹⁹F (470.4 MHz): δ –45.64 (s, 1 F), –55.36 (s, 1 F). Mass spectrum (EI) m/z 278 (M⁺, 30%), 276 (M⁺, 100).

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