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Unexpected Intermediates and Products in the C#F Bond Activation of Tetrafluorobenzenes with a Bis(triethylphosphine)Nickel Synthon: Direct Evidence of a Rapid and Reversible C#H Bond Activation by Ni(0)

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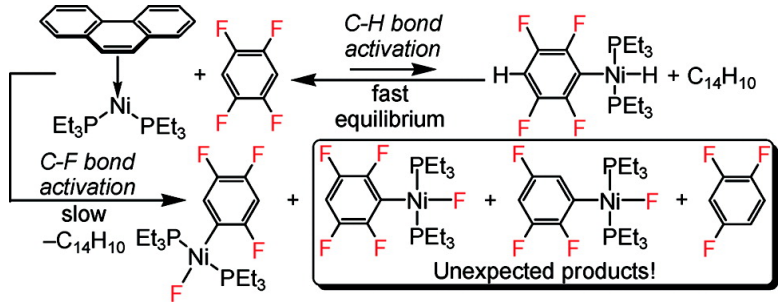

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Unexpected Intermediates and Products in the C−F Bond Activation of Tetrafluorobenzenes with a Bis(triethylphosphine)Nickel Synthon: Direct Evidence of a Rapid and Reversible C−H Bond Activation by Ni(0)

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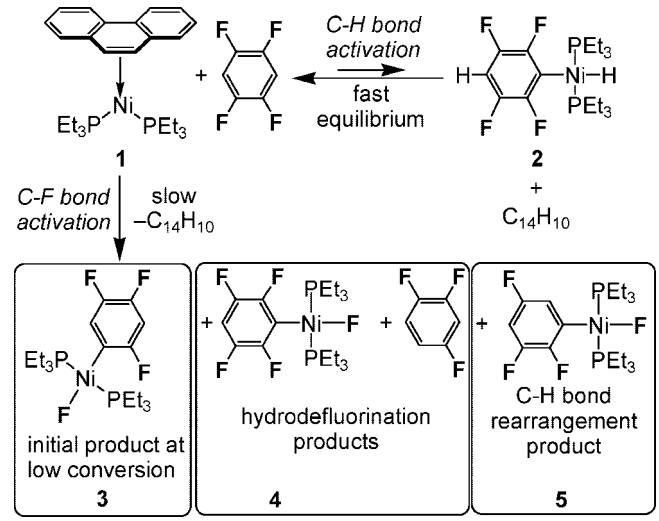
The selective activation and functionalization of C−F bonds in the commercially available polyfluorobenzenes is an attractive goal because of potential use of these compounds as starting materials for pharmaceuticals and agrochemicals containing partially fluorinated aromatic groups.[1,2] The difficulties associated with the oxidative addition of C−F bonds is similar to those encountered with C−H bond activation,[3] due in large part to the strength of the C−F bond. However, the selective activation of C−F bonds in the presence of C−H bonds generates additional issues, because many second and third row late transition metal complexes that are capable of the oxidative addition of C−F bonds display lower activation barriers for C−H bond oxidative addition.[4,5] Thus, despite the efficacy of these heavier metals in the activation of perfluorinated aromatic substrates, they are of no utility with more synthetically useful substrates such as penta-, tetra-, tri- and difluorobenzene. Although this difficulty has been bypassed in a few cases by utilizing metal complexes that react with aromatic substrates via electron transfer or nucleophilic mechanisms,[6] these complexes produce activation products which cannot be conveniently incorporated into catalytic cycles.

The relatively low cost of nickel provides an impetus for its use in lieu of its heavier congeners, and the potential of nickel(0) complexes in C−F bond activation and catalytic functionalization have been investigated extensively.[7,8] It has been shown via calculation that the oxidative addition of C−H bonds in C_6H_6 to a bis(phosphine)nickel(0) moiety is thermodynamically disfavored by ~18 kcal·mol^{-1}, whereas C−F bond activation in C_6F_6 is favored.[9] In principle, this should allow for selective activation in a range of polyfluoroaromatics, but to date the selective activation of C−F bonds using nickel complexes has been limited to perfluorinated aromatics and nitrogen containing heterocycles. The reaction of $(PEt_3)_4Ni$ with pentafluorobenzene is reported to produce a mixture of products,[8] while no reactions with the tetrafluorobenzenes have been described.

The sodium reduction of $Br_2Ni(PEt_3)_2$ in the presence of phenanthrene provides a synthon for the unisolable $Ni(PEt_3)_2$ moiety, $(PEt_3)_2Ni(\eta^2\text{-}C_{14}H_{10})$ (**1**).[10] Complex **1** has been characterized by X-ray crystallography and NMR spectroscopy; details are provided in the Supporting Information. Mixtures of **1** and 1−10 equiv 1,2,4,5-tetrafluorobenzene in pentane, d_8-toluene, C_6D_6 or THF all react over weeks to provide C−F bond activation products; however, immediate characterization of these solutions revealed an initial equilibrium producing the unexpected C−H bond activation product, $(PEt_3)_2NiH\text{-}2,3,5,6\text{-}F_4C_6H$, **2**, as shown on the top of Scheme 1. As expected for an equilibrium, the addition of phenanthrene decreased the concentration of **2** and the addition of 1,2,4,5-tetrafluorobenzene increased the concentration of **2**, as monitored by ^{19}F NMR spectroscopy.

Scheme 1



A representative reaction between **1** and 2 equiv 1,2,4,5-tetrafluorobenzene in d_8-toluene is described; similar results were obtained irrespective of solvent or equivalents of 1,2,4,5-tetrafluorobenzene utilized. The ^{19}F NMR spectrum of this mixture featured second order multiplets at δ −117.8 and −143.7 for the small equilibrium amount of complex **2**. In the 298 K ^1H NMR spectrum a broad triplet was observed at δ −14.3, as anticipated for a nickel hydride complex.[11,12] Upon cooling to 233 K this broad resonance sharpened and could be modeled as a multiplet with couplings to two ^{31}P nuclei, two *o*-fluorine, and two *m*-fluorine substituents. The relatively large $^2J_{PH}$ value of 67.7 Hz is diagnostic of a bis(phosphine)nickel hydride fragment,[11] and the remaining couplings identify the complex as **2**. The 298 K $^{31}P\{^1H\}$ NMR spectrum featured broad resonances for **1** and **2** at δ 18.1 and 23.5, respectively. Cooling the solution to 233 K resulted in the sharpening of these resonances in the $^{31}P\{^1H\}$ NMR spectrum, and in the ^1H coupled ^{31}P NMR spectrum the peak at δ 23.5 was a doublet with a 68 Hz coupling to the hydride.

The broad ^1H hydride and $^{31}P\{^1H\}$ NMR resonances at 298 K are indicative of a fluxional exchange, and a ^{19}F EXSY spectrum with a mixing time of 0.5 s revealed positively phased cross peaks between the 1,2,4,5-tetrafluorobenzene peak and the ^{19}F resonances of **2**. Further evidence for the reversible nature of this C−H bond activation over a range of temperatures was obtained by the reaction a d^8-toluene solution of **1** and 2 equiv of monodeuterated 1,2,4,5-tetrafluorobenzene, which was analyzed by ^1H and ^{19}F and $^{31}P\{^1H\}$ NMR spectroscopy. Signals were observed for equilibrium amounts of the C−H and C−D

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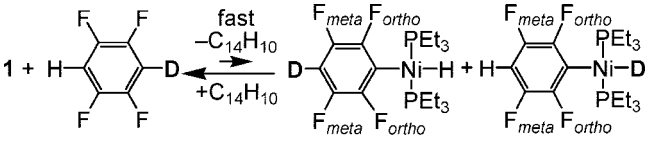
activation products **2a** and **2b**, shown in Scheme 2. An expansion of the hydride region at 233 K is shown on the left side of Figure 1 and displays couplings and shifts identical to **2**. Expansions of the AA′MM′ spin system signals of this equilibrium species in the 273 K ^{19}F and ^{19}F{^{1}H} NMR spectra are shown on the right side of Figure 1. These appear at δ −118.0 for the overlapping *o*-fluorine resonances of **2a** and **2b**, whereas the resolved resonances for the *m*-fluorines of **2a** and **2b** appear at δ −144.1 and −143.8, respectively. This shift of ∼0.3 ppm for fluorine nuclei adjacent to H versus D is typical for fluorinated aromatics. The ^{19}F NMR spectrum also exhibits the appropriate couplings to the hydridic ^{1}H; the F_{ortho} resonance associated with **2a** exhibits a $^{4}J_{FH}$ of 9.5 Hz and the F_{meta} resonance associated with **2a** exhibits a $^{5}J_{FH}$ of 4.2 Hz, consistent with the ^{1}H NMR spectral data. Additionally, a $^{3}J_{FH}$ of 9.3 Hz is observed between the aromatic hydrogen and the F_{meta} resonance associated with **2b**. The temperature dependence of the integration of *m*-fluorine resonances for **2a** and **2b** reveals that this C−H bond oxidative addition is in kinetic equilibrium near room temperature. The oxidative addition shown in Scheme 2 favors **2a** over **2b**, due to the zero-point energy difference between carbon-H/D and nickel-H/D bonds. At 298 K, the ratio of the integrals of these peaks is 2.1:1. Cooling to 233 K gradually changes this ratio to 3.4:1. At temperatures lower than 233 K this reaction is slowed sufficiently that the ratio of **2a** to **2b** does not change noticeably within an hour. The ^{31}P {^{1}H} NMR spectrum at 233 K featured a broad 1:1:1 triplet at 23.8 with a $^{2}J_{PD}$ of ∼10 Hz for **2b** and a singlet at 23.5 for **2a**.

Scheme 2



T (K)	2a	2b
298	67.8 %	32.2 %
273	70.6	29.4
253	73.7	26.3
233	77.7	22.3

Over the course of 2 weeks these mixtures gradually convert to C−F bond activation products and the concentration of **2** decreases as **1** is consumed. Despite the presence of a single fluorine chemical environment in 1,2,4,5-tetrafluorobenzene, these reactions provide a mixture of three C−F bond activation products and 1,2,4-trifluorobenzene, as shown in Scheme 1. Monitoring the reaction by ^{19}F{^{1}H} NMR spectroscopy, $(PEt_3)_2$NiF-2,4,5-$F_3C_6H_2$ (**3**) is the only C−F activation product observed at low conversion, typically within the first 8 h, with three

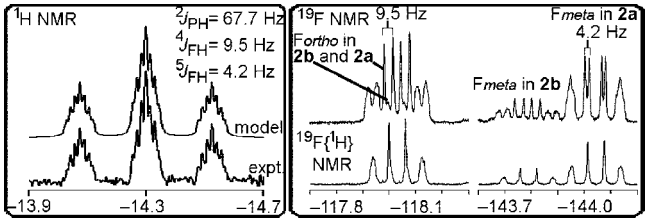
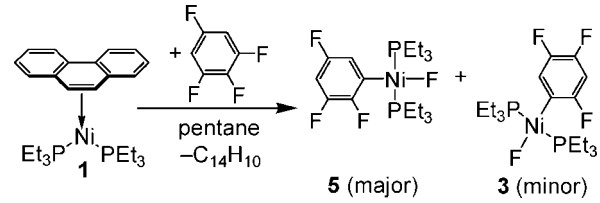


Figure 1. Hydridic signal in the 233 K ^{1}H NMR spectrum with modeled spectrum shown above (left) and selected peaks in the 273 K ^{19}F and ^{19}F{^{1}H} NMR spectra for an equilibrium amount of **2a** and **2b** prepared from a mixture of **1** and 1,2,4,5-F_4C_6HD. Chemical shifts are in ppm and ^{19}F shifts are with respect to $CFCl_3$.

aromatic multiplets at δ −93.4, −145.4, and −146.6, as well as a Ni−F environment at δ −378.5, which is a triplet of doublets due to coupling to two equivalent ^{31}P environments ($^{2}J_{PF}$ = 48.8 Hz) and a single *o*-F ($^{2}J_{FF}$ = 10 Hz). Complex **3** displays a doublet ^{31}P{^{1}H} resonance at δ 12.1. As the reaction proceeds, two other unanticipated C−F bond activation products are observed. One product, which has ^{19}F resonances at δ −119.2, −143.2, and −390.1, the latter of which is a triplet of triplets due to coupling to two ^{31}P environments and two *o*-fluorine substituents, can be identified as $(PEt_3)_2$NiF-2,3,5,6-F_4C_6H (**4**). Complex **4** features a doublet in the ^{31}P{^{1}H} NMR at δ 13.6 with a $^{2}J_{PF}$ value of 46.5 Hz. This assignment was verified by an alternate synthesis of **4** via the oxidative addition of 1-bromo-2,3,5,6-tetrafluorobenzene to $Ni(COD)_2$ in the presence of PEt_3 to generate $(PEt_3)_2$NiBr-2,3,5,6-F_4C_6H, followed by reaction with tetrabutylammonium fluoride hydrate. The second unexpected product is $(PEt_3)_2$NiF-2,3,5-$F_3C_6H_2$ (**5**), with ^{19}F resonances at δ −119.9, −121.3, −137.6, and −379.6, the latter of which features coupling to two ^{31}P nuclei and a single *o*-fluorine. The ^{31}P{^{1}H} NMR signal appears at δ 12.6 with a $^{2}J_{PF}$ value of 48.0 Hz. This assignment was verified by the reaction of 1,2,3,5-tetrafluorobenzene with **1**, shown in Scheme 3, which produces **5** as an isolable major product, but also features **3** as ∼3% of the C−F bond activation products, by integration of the aromatic ^{19}F resonances. Complex **5** was characterized by X-ray crystallography and details are presented in the Supporting Information. DFT calculations predict that isomer **5** is only slightly lower in energy than **3**, thus the conversion of **5** to small amounts of **3** is thermodynamically viable, despite the observation of the microscopic reverse reaction with 1,2,4,5-tetrafluorobenzene.

Scheme 3

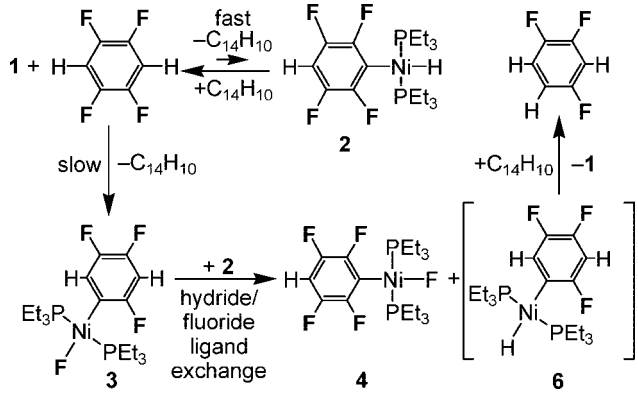


The major product in the reaction of 1,2,4,5-tetrafluorobenzene and **1** depends on reaction conditions, but appears to thermodynamically favor the formation of **4**. For example, the addition of an excess of phenanthrene to the initial reaction mixtures slows the reaction and yields **4** and 1,2,4-trifluorobenzene as the major products. The thermodynamic preference of **4** over **3** can be rationalized by the increased Ni−C bond strength as the number of *o*-F substituents is increased.[4]

Scheme 4 depicts a viable mechanism for the formal hydrodefluorination[2,13] that results in the formation of **4** and 1,2,4-trifluorobenzene. The initial C−H bond activation product **2** is formed rapidly and is present in equilibrium with **1** throughout the reaction. The initial C−F bond activation product **3** is formed at a much slower rate and reacts with the equilibrium amounts of **2** via transmetalation, which exchanges the fluoride and hydride ligands to produce **4** and a new nickel hydride complex, **6**.[14] The exact mechanism for this reaction is unknown due to the paucity of data regarding the reactivity of bis(phosphine)nickel aryl hydrides, but it likely involves a binuclear intermediate.[15] Species **6** was not observed because it can rapidly reductively eliminate a C−H bond to produce 1,2,4-trifluorobenzene. Complex **5** could be formed by a similar C−H bond activation mechanism starting with 1,2,4-trifluorobenzene, al-

though it is impossible to rule out other mechanisms,[16] such as the reversible deprotonation of the ortho hydrogen in **3**, which could convert **3** to **5** via a nickel aryne intermediate.[17]

Scheme 4



These results provide insight into the steps required to utilize these C−F bond activations into catalytic cycles; to generate Ni catalysts for selective C−F bond functionalization in a wide range of polyfluoroaromatics it will be necessary to alter the choice of ancillary ligands to render C−F bond oxidative addition significantly faster than ligand redistribution reactions, thus avoiding unwanted byproducts that result from C−H bond activation. Equally importantly, these low activation barrier C−H bond activations could be exploited to extend the scope of Ni(0) C−H bond activation and catalytic functionalization[18] to include polyfluoroaromatics[19] and other weakly activated substrates,[20] even when C−H bond activation products are thermodynamically disfavored but kinetically accessible. Research toward both these goals is currently underway.[21]

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Supporting Information Available: Coordinates and energies from DFT calculations; full experimental details; CIF files for **1** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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