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Palladium-Catalysed Carbon–Fluorine and Carbon–Hydrogen Bond Alumination of Fluoroarenes and Heteroarenes

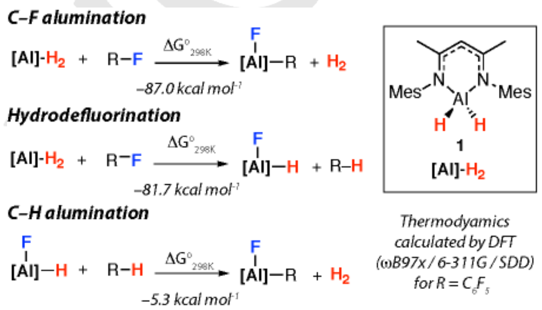
Wenyi Chen,‡ Thomas N. Hooper,‡ Jamues Ng, Andrew J. P. White, Mark R. Crimmin*

Abstract: *Through serendipitous discovery, a palladium bis(phosphine) complex was identified as a catalyst for the selective transformation of sp^2C–F and sp^2C–H bonds of fluoroarenes and heteroarenes to sp^2C–Al bonds (19 examples, 1 mol% Pd loading). The carbon–fluorine bond functionalization reaction is highly selective for the formation of organoaluminum products in preference to hydrodefluorination products (selectivity = 4.4:1 to 27:1). Evidence is presented for a tandem catalytic process in which hydrodefluorination is followed by sp^2C–H alumination.*

Due to the large number of pharmaceuticals, agrochemicals and organic materials that contain at least one fluorine atom,[1-3] the selective functionalization of carbon–fluorine bonds remains an important challenge in contemporary catalysis.[4,5] Perfluorinated hydrocarbons are readily available at low cost through the Fowler process.[6] Many groups have promoted the idea of the selective defluorination of heavily fluorinated building blocks as a synthetic entry point to fluorine contain molecules.[7] The vast majority of studies, however, have focused on hydrodefluorination (HDF) and cross-coupling protocols.[8-13] These reactions have their limitations as the newly formed C–H and C–C bonds have narrow reactivity. Only in the past few years have methods emerged to form reactive building blocks from unreactive fluorocarbons. [14-18] For example, Rh- and Ni-based catalysts have been reported for the C–F borylation of fluoroarenes using diboranes as stoichiometric reagents.[19-21] We, and others, have shown that low-valent main group reagents, including Al(I),[22,23] Si(II),[24] Ge(II),[25] and Mg(I)–Mg(I) species,[26] can achieve C–F activation of both sp^2C–F and sp^3C–F bonds under mild conditions in the absence of catalyst.

As a complementary approach to the low-valent, chemistry we have been interested in reactions of the β-diketiminate stabilized aluminium dihydride **1** with fluoroarenes (Figure 1).[27,28] The advantage of using **1** over Al(I) precursors is its ease of preparation on scale from $LiAlH_4$.[27] In the presence of a catalyst, this reagent effects the competitive hydrodefluorination and C–F alumination of fluoroarenes. In all cases reported to date, however, the selectivity for the more desirable C–F alumination reaction over hydrodefluorination is low (<2:1).[27,28]

Figure 1. Alumination of fluoroarenes.



One strategy to circumvent the formation of hydrodefluorination products would be to develop a catalyst that was capable of sp^2C–H alumination. This catalyst could cycle hydrofluoroarenes back to the desired organometallic products and correct the undesired hydrodefluorination pathway (Figure 1). There is limited precedent for this approach with boron reagents. Braun and coworkers have demonstrated stepwise hydrodefluorination and C–H borylation as a means to achieve a net C–F borylation of pentafluoropyridine with HBpin catalyzed by $[Rh(PEt_3)_3(H)]$ (HBpin = pinacolborane). This reaction is extremely slow and proceeds over 21 days ultimately reaching a TON of 18.[29]

In this communication, we report commercially available $[Pd(PCy_3)_2]$ as a catalyst for selective sp^2C–F and sp^2C–H alumination of fluoroarenes and heteroarenes with **1**. Reactions proceed at low catalyst loadings and, depending on the substitution pattern of the fluoroarene, with both *para*- and *meta*-regioselectivity.

Palladium based catalysts for C–F alumination were developed following identification of catalytically active metal impurity. During a substrate screen with Zr-based catalysts, improved selectivity for sp^2C–Al bond formation was observed with the non-volatile biaryl **2a** (Figure 2) compared to reactions employing pentafluorobenzene. The data, however, were not reproducible across different batches of **2a**. Control reactions revealed that not only was the Zr-catalyst unnecessary but the reaction was dependent upon the impurity profile of **2a** (Figure 2, substrate A). The biaryl **2a** was synthesised by a Pd-catalysed cross-coupling, ICP-OES analysis of samples purified by hot filtration and recrystallization revealed contamination with 0.4% Pd. Trace metal contamination (below the detection limit of the

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Supporting information for this article is given via a link at the end of the document. Experimental procedures, details of the DFT studies, single crystal X-ray data and multinuclear NMR spectra (PDF). X-ray crystallographic data (.cif). Editable NMR data are available as .mnova and .mnpub via a repository DOI: 10.14469/hpc/2663

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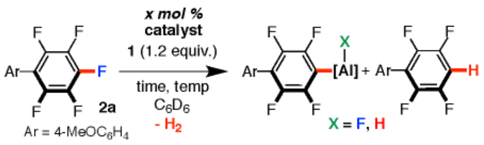
ICP-OES experiment) could be removed by adding at least one chromatography step.

The data suggest that residual Pd-contaminants are responsible for the selective sp^{2}C–F alumination reaction. The hypothesis was confirmed by directly exposing the crude samples of **2a** to the catalytic conditions (Figure 2, substrate B). Ultimately [Pd(PCy$_3$)$_2$] was identified as a convenient commercially available precatalyst for the reaction (Figure 2, substrate C). Employing palladium on charcoal, [PdCl$_2$(PPh$_3$)$_2$], or [Pd(PPh$_3$)$_4$] as precatalysts failed to give the desired products (see supporting information, Table S2). A negative Hg(0) drop experiment suggested that heterogeneous catalysis does not play a role in the chemical transformation.

Figure 2. Identification of an impurity Pd catalyst.

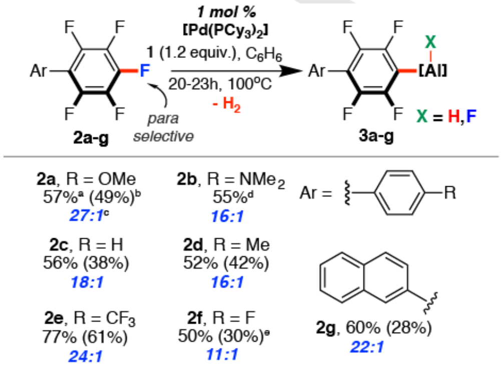


substrate^a	catalyst (mol%)	time (h)	temp (°C)	C–[Al]^b	C–H^b	Selectivity
A	[Cp$_2$ZrCl$_2$] (5)	22	80	61	31	*2:1*
	–	46	80	9	1	*9:1*
B	–	43	80	66	4	*18:1*
C	–	43	80	0	0	–
	[Pd(PCy$_3$)$_2$] (0.1)	19	80	20	<1	*>20:1*
	(1)	19	80	41	<1	*>41:1*
	(1)	19	100	47	<1	*>47:1*

^{a}Prepared by Pd-catalysed cross-coupling follow by: **A:** *hot filtration and recrystallisation,* **B:** *crude mixture,* **C**: *column chromatography and at least one recrystallisation.* ^{b}*Conversion measured by ^{19}F NMR spectroscopy.*

The scope of the reaction was investigated using the optimized conditions (1.2 equiv. of **1**, 1 mol% [Pd(PCy$_3$)$_2$], 100°C in C$_6$H$_6$) and a series of biaryls with electronically distinct substituents and differing fluorine content were investigated. Pentafluorobiaryl substrates yielded *para*-functionalised aluminium complexes as the major product accompanied by minor amounts of hydrodefluorination (Figure 3). The reaction tolerates CF$_3$, OMe and NMe$_2$ groups on the remote aromatic ring and selectivities for C–Al bond formation are high across the series (>11:1). The aluminium products were assigned based on comparison of the ^{19}F NMR data with analogues generated from oxidative addition of substrates to Al(I) (see supporting information). Further evidence for the structural assignment and validation of the *in situ* yields was achieved by protic (methanol) work-up followed by isolation of the hydrofluoroarenes. In addition to the expected major *para*-HDF products, trace amounts of *meta*-HDF and *meta*-*para*-disubstituted di-HDF products were observed. While the parent organoaluminium species that give rise to these minor products could not be assigned due to their low concentration, it was clear from ^{19}F NMR spectroscopic data that the HDF products are not present in significant amounts prior to methanol work up.

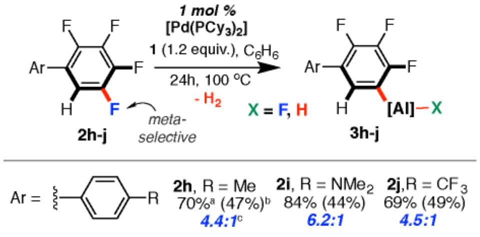
Figure 3. *para*-Selective C–F alumination of fluoroarenes.



^{a}Conversion to **3a-g** measured by ^{19}F NMR spectroscopy, ratio of X H:F = 1:1 to 8:1. ^{b}Isolated yields of HDF products **4a-g** following methanol workup and purification by chromatography (79-93 % purity by HPLC). ^{c}Ratio of C–Al to C–H bond formation from crude measured by ^{19}F NMR. ^{D}HDF product could not be separated from **2b**. ^{E}Trace reaction of the R group observed.

Upon modification of the substrate to a 2,3,4,5-tetrafluorobiaryl, the *meta*-selective C–F alumination pathway became dominant (Figure 4). In these cases, the selectivities for C–Al bond formation were lower (>4.4:1). Similar selectivities have been observed during catalytic C–H borylation and assigned to the steric accessibility of the *para*- and *meta*-C–H bonds of mono-susbtituted arenes.[30]

Figure 4. *meta*-Selective C–F alumination of fluoroarenes.



^{a}Yield of **3h-j** measured by ^{1}H NMR spectroscopy against ferrocene as an internal standard. ^{b}Isolated yields of HDF products **4h-j** following methanol workup and purification by chromatography (80-92% purity by HPLC). ^{c}Ratio of C–Al to C–H bond formation from crude measured by ^{19}F NMR.

To test the hypothesis that C–F functionalization could occur by sequential HDF and C–H activation, we also investigated biaryl substrates with accessible C–H bonds in the *para*- and *meta*-positions of the fluorinated ring. Selective C–H alumination was achieved with 2,3,5,6-tetrafluorobiaryls (Figure 5).[31] Mixtures of **1** and [Pd(PCy$_3$)$_2$] are an extremely active catalyst system for this reaction and the TOF reached ~1000 h^{-1} at 100 °C for the conversion of **2k** to **3k**. Despite keen interest in the functionalization of C–H bonds with boranes,[30] silanes,[32] and stannanes,[33] corresponding alumination pathways are extremely rare. Existing examples rely on the use of specialist aluminium bases.[34-37] To the best of our knowledge, the dehydrocoupling of sp^{2}C–H and Al–H bonds represents a new catalytic transformation.

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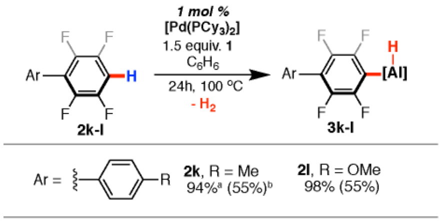
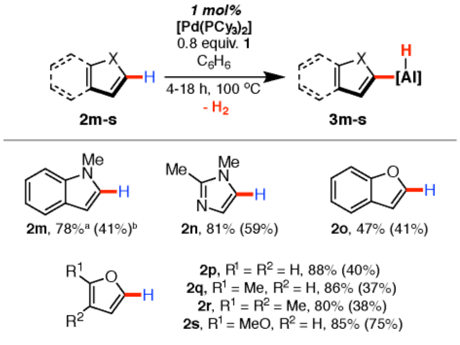
Figure 5. C–H alumination of fluoroarenes.



[a]Yield of **3k-I** measured by ^{1}H NMR spectroscopy against ferrocene as an internal standard. [b]Isolated yields following recrystallization.

Having observed sp^{2}C–H bond alumination of fluoroarenes, the substrate scope was expanded to include non-fluorinated aromatics. A range of heteroarenes (**2m-s**) including furans and *N*-methylindole were reacted under similar reaction conditions to produce the aluminated complexes (**3m-s**) in good yield. In all cases, the reactions were selective for sp^{2}C–H bonds over sp^{3}C–H bonds and for the 2-position of the heteroarene. Yields calculated by NMR spectroscopy were found to be >78% and the aluminated products could be isolated by crystallization in modest yields (Figure 6). Control reactions between **2k-p** with **1** in the absence of catalyst did not result in C–H alumination.

Figure 6. C–H alumination of heteroarenes.



[a]Yield of **3m-s** measured by ^{1}H NMR spectroscopy against ferrocene as an internal standard. [b]Isolated yields following recrystallization.

A similar reaction of **1** with benzofuran resulted in initial C–H activation to produce the kinetic reaction product **3o** that could be isolated provided the reaction time was shortened and temperature lowered relative to the standard conditions (1 h, 80 °C). At longer reaction times this species cleanly converted to the previously reported C–O bond activation product.[38-39] Tetrahydrofuran and 2,5-dimethylfuran did not react under the optimised conditions, while benzoxazoles proved susceptible to reduction and ring-opening by hydride attack with **1** in the absence of a catalyst. X-ray crystal structures of several of the products show little distortion of the 5-membered rings upon C–H activation and confirmed the structural assignment (Figure 7).

The independent rates of C–F and C–H bond activation were compared. The reactions of **2d** and **2k** with **1** were monitored as a function of time (1 mol% catalyst, 50 °C). The C–H bond reacts significantly faster than the C–F bond. Initial rate data were fitted to first order kinetics giving rate constants of $k_{C-F} = 0.002$ h^{-1} and $k_{C-H} = 0.166$ h^{-1} (see supporting information). In combination with the observation of small amounts of hydrofluoroarenes in catalytic preparations with **2a-j,** these data suggest that C–F alumination proceeds by slow hydrodefluorination followed by fast C–H alumination.

To probe the mechanism of hydrodefluorination, [Pd(PCy$_3$)$_2$] was added to the fluorobiaryl **2a** but no reaction was observed, even after prolonged heating (18 h, 80 °C) or in the presence of the β-diketiminate aluminum difluoride, **[Al]-F$_2$**.[40] It is possible that oxidative addition of C–F bonds to [Pd(PCy$_3$)$_2$] is reversible and for **2a** the equilibrium lies toward the Pd(0) species. Braun and co-workers have shown that pentafluoropyridine will undergo oxidative addition to [Pd(PCy$_3$)$_2$].[41-43] Reproducing this reaction allowed clean generation of *trans*-[Pd(F)(4-C$_5$F$_4$N)(PCy$_3$)$_2$]. Subsequent reaction of *trans*-[Pd(F)(4-C$_5$F$_4$N)(PCy$_3$)$_2$] with 1 eq. of **1** at 25 °C resulted in immediate formation of *trans*-[Pd(H)(4-C$_5$F$_4$N)(PCy$_3$)$_2$] along with **[Al]-HF** and **[Al]-F$_2$** which were identified by comparison of the NMR resonances to the known literature values.[27] *trans*-[Pd(H)(4-C$_5$F$_4$N)(PCy$_3$)$_2$] undergoes reductive elimination upon heating with a further 5 equiv. of pentafluoropyridine, generating 2,3,5,6-tetrafluoropyridine (Figure 8). Hence, each of the steps of the catalytic cycle for hydrodefluorination has been experimentally verified.

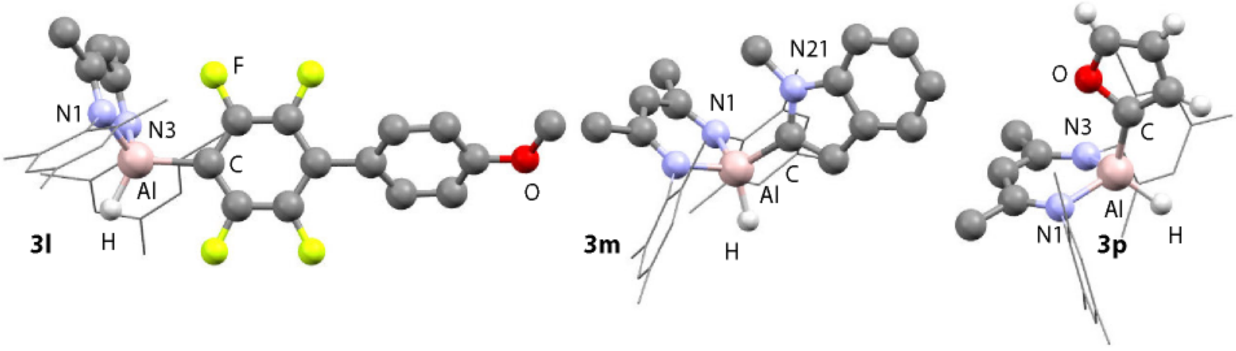


Figure 7. Selected crystal structures. Bond lengths (Å): 3l, Al–C 1.994(3); 3m, 1.970(3); 3p, Al–C 1.956(2).

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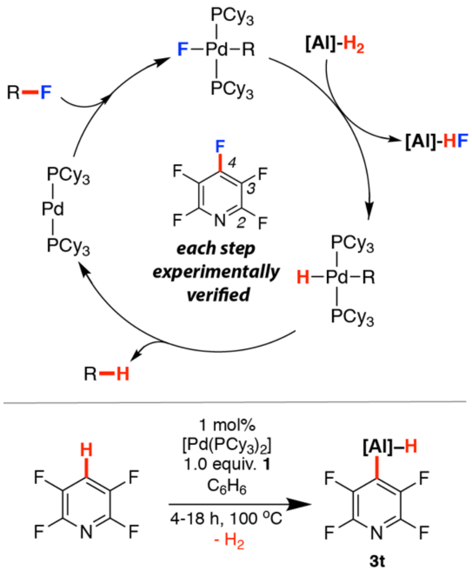
Figure 8. Mechanism of hydrodefluorination and reaction to form aluminated species.



Exposing a sample of the 2,3,5,6-tetrafluoropyridine to the catalytic reaction conditions resulted in facile C–H activation yielding **3**t as the major product (see supporting information). We propose that C–F alumination process reported herein is a tandem catalytic reaction: hydrodefluorination precedes alumination of the resulting C–H bond (Figure 8).

The mechanism of Pd-catalysed hydrodefluorination has been established, but the mechanism for C–H bond functionalization is currently unclear. What is clear is that **1** displays reactivity that is both distinct and complementary to the widely employed borane HBpin. When **1** is replaced with HBpin, only hydrodefluorination of similar substrates is observed with the same Pd-catalyst.[41]

In summary, we report a highly active catalytic protocol for the transformation of C–F and C–H bonds into C–Al bonds. We are continuing to explore the applications of these new reagents in synthesis and the mechanism of C–H bond activation.

Acknowledgements

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Keywords: C–F activation • C–H activation • alumination • fluoroarenes • hydrodefluorination

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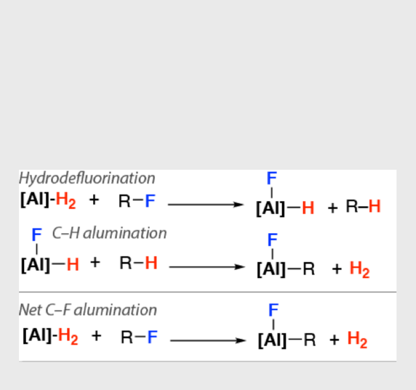
COMMUNICATION

A palladium catalyst is reported for the transformation of sp^{2}C–F and sp^{2}C–H bonds of fluoroarenes and heteroarenes into sp^{2}C–Al bonds



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Carbon–Fluorine and Carbon–Hydrogen Bond Alumination of Fluoroarenes and Heteroarenes: Identification of an Impurity Palladium Catalyst