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 sp²C–F and sp³C–H bonds of fluoroarenes and heteroarenes to sp²C–Al bonds (19 examples, 1 mol% Pd loading). The carbon–fluorine bond functionalization reaction is highly selective for the formation of organoalumination 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 sp²C–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 sp²C–F and sp³C–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-diketiminato stabilized aluminium dihydride 1 with fluoroarenes (Figure 1).[27,28] The advantage of using 1 over Al(II) precursors is its ease of preparation on scale from LiAlH₄.[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]

One strategy to circumvent the formation of hydrodefluorination products would be to develop a catalyst that was capable of sp²C–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(PEt₃)₂(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(PCy₃)₂] as a catalyst for selective sp²C–F and sp³C–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 sp²C–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
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 sp²C–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(PCy₃)₂] was identified as a convenient commercially available precatalyst for the reaction (Figure 2, substrate C). Employing palladium on charcoal, [PdCl₂(PPh₃)₂], or [Pd(PPh₃)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.

The range of the reaction was investigated using the optimized conditions (1.2 equiv. of 1, 1 mol% [Pd(PCy₃)₂], 100°C in C₆H₆) 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 CF₃, OMe and NMe₂ 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 ¹⁹F NMR data with analogues generated from oxidative addition of sp²C–H and Al–H bonds.

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). Mixtures of 1 and [Pd(PCy₃)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 sp²C–H and Al–H bonds represents a new catalytic transformation.
Having observed sp²C–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 sp²C–H bonds over sp³C–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.

A similar reaction of 1 with benzo[b]furan 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. Tetrahydrofuran and 2,5-dimethyfuran 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 $k_{C-H} = 0.002 \text{ h}^{-1}$ and $k_{C-F} = 0.166 \text{ h}^{-1}$ (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(H)(4-C₆F₄N)] 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 i-diketiminate aluminum difluoride, [Al]–F₂. It is possible that oxidative addition of C–F bonds to [Pd(PCy₃)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(PCy₃)₂] [41,43]. Reproducing this reaction allowed clean generation of trans-[Pd(F)(4-C₆F₄N)](PCy₃)₂. Subsequent reaction of trans-[Pd(F)(4-C₆F₄N)](PCy₃)₂ with 1 eq. of 1 at 25 °C resulted in immediate formation of trans-[Pd(H)(4-C₆F₄N)](PCy₃)₂ along with [Al]–HF and [Al]–F₂ which were identified by comparison of the NMR resonances to the known literature values. [27] trans-[Pd(H)(4-C₆F₄N)](PCy₃)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 5. C–H alumination of fluoroarenes.

Figure 6. C–H alumination of heteroarenes.

Figure 7. Selected crystal structures. Bond lengths (Å): 3l, Al–C 1.994(3); 3m, 1.970(3); 3p, Al–C 1.956(2).
Exposing a sample of the 2,3,5,6-tetrafluoropyridine to the catalytic reaction conditions resulted in facile C–H activation yielding 3t as the major product (see supporting information). We propose that C–F alumination process reported herein is a tandem catalytic reaction: hydrodefluorination precedes aluminination 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

We are grateful to the European Research Council (FluoroCat: 655474, FluoroFix:677367) and the Royal Society (UF090149). Johnson Matthey are thanked for generous donation of PdCl₂.

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

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

[31] Reaction of 2l with [Al]–H2F catalyzed by [Pd(PCy₃)₂] also leads to C–H alumination to form 3l (X = F). This latter species could also arise from 3l (X = H) effecting the HDF of a further equivalent of 2l.
[39] Synthesis of 3o by a non-catalytic route (see Si) showed that the Pd(PCy₃)₂ catalyst is required for conversion of the C–H activated to C–O activated product.
[40] While lithium iodide has been shown to promote the oxidative addition of C–F bonds to [Pd(PCy₃)₂], in the current case addition of a Lewis Acid does not promote oxidative addition: M. Ohashi, R. Doi, S. Ogoshi, Chem. Eur. J. 2014, 20, 2040–2048.
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.

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

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