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Stoichiometric and Catalytic Aryl–Perfluoroalkyl Coupling at Tri-*tert*-butylphosphine Palladium(II) Complexes

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Supporting Information

ABSTRACT: This Communication describes studies of Ph–R_F (R_F = CF_3 or CF_2CF_3) coupling at Pd complexes of general structure (P^tBu_3)Pd^{II}(Ph)(R_F). The CF_3 analogue participates in fast Ph-CF_3 coupling (<5 min at 80 °C). However, the formation of side products limits the yield of this transformation as well as its translation to catalysis. DFT and experimental studies suggest that the side products derive from facile α-fluoride elimination at the 3-coordinate Pd^{II} complex. Furthermore, they show that this undesired pathway can be circumvented by changing from a CF_3 to a CF_2CF_3 ligand. Ultimately, the insights gained from stoichiometric studies enabled the identification of Pd(P^tBu_3)$_2$ as a catalyst for the Pd-catalyzed cross-coupling of aryl bromides with $TMSCF_2CF_3$ to afford pentafluoroethylated arenes.

Fluoroalkyl (R_F) groups, such as CF_3 and CF_2CF_3, appear in a variety of pharmaceuticals[1] and agrochemicals.[2] These substituents are commonly appended to aromatic rings to enhance the lipophilicity and oxidative stability of bioactive molecules. A variety of synthetic methods have been developed to form aryl–R_F bonds.[3] Among these, $Pd^{0/II}$-catalysis is the least developed, despite the widespread utility of other $Pd^{0/II}$-catalyzed C–C coupling processes.[4] This has largely been attributed to challenges associated with the product-release step of the catalytic cycle, which involves aryl–R_F coupling from L_nPd^{II}(Aryl)(R_F) intermediates (Figure 1a).[4a,5] To date, only three ligands, Xantphos,[5c] dfmpe,[5d] and BrettPhos,[4a] have been shown to enable high-yielding aryl–R_F coupling from isolated Pd^{II} complexes (Figure 1b).[6] Furthermore, only BrettPhos and related RuPhos have been successfully translated to $Pd^{0/II}$-catalyzed aryl-fluoroalkylation processes.[4a]

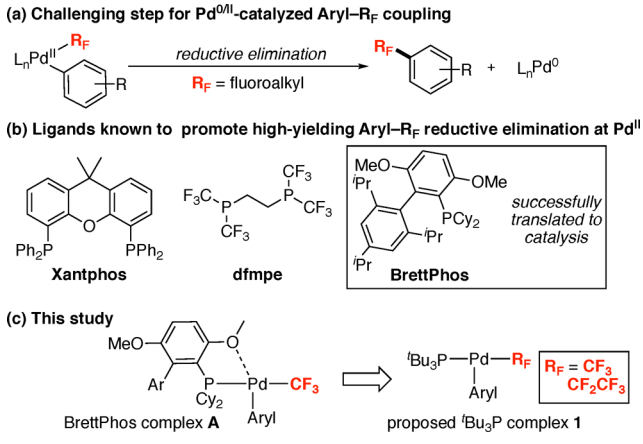

Figure 1. (a) Challenging aryl–R_F coupling step; (b) ligands known to promote aryl–R_F coupling; (c) this study.

We sought to identify new ligands that promote aryl–R_F coupling at Pd^{II} centers. Additionally, we aimed to identify key obstacles to the translation of stoichiometric aryl–R_F coupling reactions to catalysis. We noted that BrettPhos forms monophosphine Pd^{II} complexes of general structure **A** (Figure 1c), which are stabilized by a hemilabile Pd^{II}–O interaction.[4a,7] Inspired by the work of Hartwig,[8] we hypothesized that P^tBu_3 would form related 3-coordinate monophosphine complexes (**1**) that might be even more reactive toward aryl–R_F coupling.[8−11] Herein, we describe DFT and experimental studies of (P^tBu_3)Pd^{II}(Ph)(R_F) (R_F = CF_3 or CF_2CF_3). We show that both complexes undergo Ph–R_F coupling under mild conditions (within 15 min at 80 °C). However, studies of the CF_3 analogue reveal that an α-fluoride elimination pathway limits the selectivity and efficiency of both stoichiometric and catalytic transformations. We demonstrate that this pathway can be circumvented by moving from R_F = CF_3 to R_F = CF_2CF_3. Ultimately, these stoichiometric studies enabled the development of the Pd(P^tBu_3)$_2$-catalyzed pentafluoroethylation of aryl bromides.

We first studied complex **1-CF_3** using DFT calculations involving the dispersion functional B3LYP-D3.[12] The lowest energy ground-state structure is T-shaped, with the fluoroalkyl ligand trans to P^tBu_3 (Figure 2). The isomer with the Ph ligand trans to P^tBu_3 (**1-I-CF_3**) is 5.8 kcal/mol higher in energy, consistent with the stronger trans influence of Ph versus CF_3.[4a,5a−d] The formation of $PhCF_3$ from **1-CF_3** can occur via two distinct pathways, both of which have been proposed previously for related systems.[7,13] The first involves direct Ph–CF_3 coupling via the concerted transition state **TS-1-CF_3-RE**, with a calculated barrier of 27.0 kcal/mol.[14] The second involves initial α-fluoride elimination to form difluorocarbene intermediate **A**.[5b,15] Subsequent phenyl migration to form difluorobenzyl complex **B**[16] is followed by C–F coupling via **TS-B-CF_3-RE** to yield $PhCF_3$. The highest energy transition state in this latter sequence is for the phenyl migration step (21.8 kcal/mol). Overall, these calculations predict that **1-CF_3** could form $PhCF_3$ via either pathway under relatively mild conditions.

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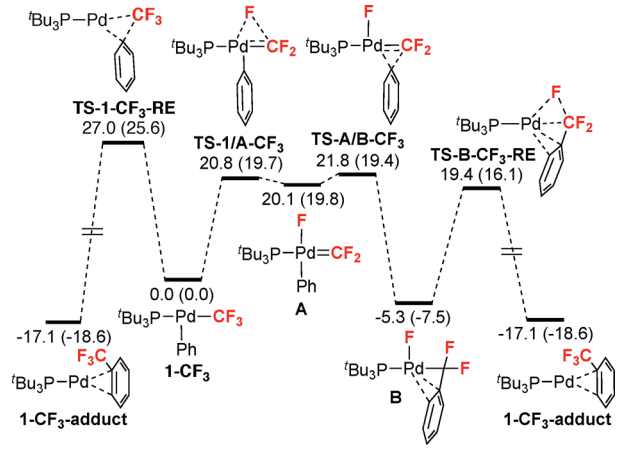
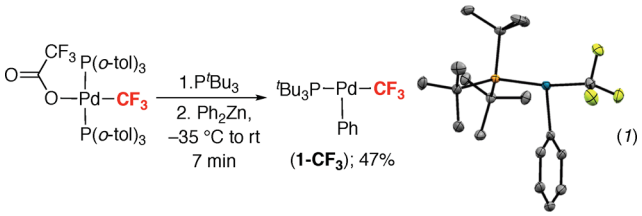


Figure 2. Reaction coordinate from DFT calculations of **1-CF$_3$**. Energies ΔG (ΔH) in kcal/mol.

To test this experimentally, **1-CF$_3$** was synthesized via the treatment of $[P(o\text{-tol})_3]_2Pd^{II}(CF_3)(OC(O)CF_3)$[17] with P^{t}Bu$_3$ followed by Ph_2Zn (eq 1). The X-ray structure of **1-CF$_3$** shows

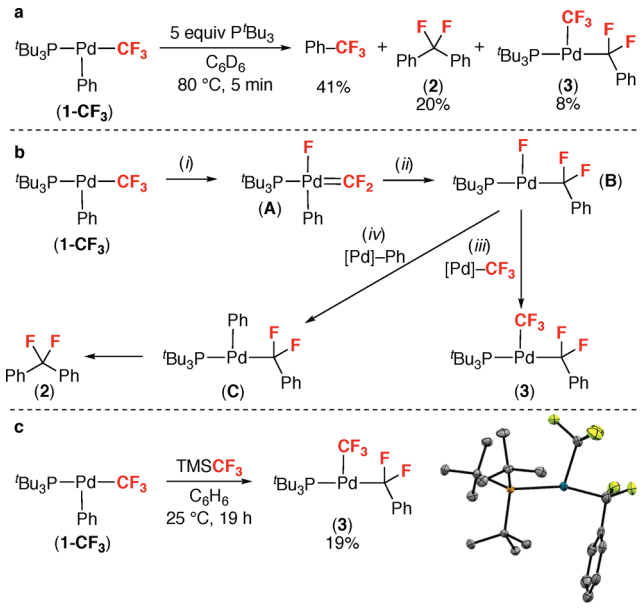


a T-shaped complex with the CF_3 ligand trans to P^{t}Bu$_3$ (eq 1). A Pd–H–C agostic interaction is predicted from placing the H atoms in idealized positions (Pd–H = 2.18 Å).[8c] The P–Pd bond distance (2.372 Å) is significantly longer than that in $(P^tBu_3)Pd^{II}(Ph)(Br)$ (2.285 Å),[8c] reflecting the greater trans influence of CF_3 versus Br. In solution, **1-CF$_3$** shows a ^{19}F NMR resonance at −28 ppm (d) and a ^{31}P NMR resonance at 55 ppm (q). No agostic interaction is detected by ^{1}H NMR spectroscopy down to −70 °C in CD_2Cl_2.

Heating a benzene solution of **1-CF$_3$** in the presence of 5 equiv of P^{t}Bu$_3$ at 80 °C for 5 min resulted in the complete consumption of the starting material and the formation of $PhCF_3$ in 41% yield (Scheme 1a).[18−20] Notably, these conditions are similarly mild to those required for aryl–CF_3 coupling from $(BrettPhos)Pd^{II}(aryl)(CF_3)$ ($t_{1/2}$ = 22–24 min at 80 °C).[4a] The high conversion of **1-CF$_3$** but modest yield of $PhCF_3$ in our system suggests that there are competing decomposition pathways. Indeed, ^{19}F NMR spectroscopic analysis shows the presence of two major side products: difluorodiphenylmethane (**2**, 20% yield) and Pd^{II} difluorobenzyl complex **3** (8% yield).[21,22]

We hypothesize that **2** and **3** are formed from the α-fluoride elimination/phenyl migration intermediate **B**. As shown in Scheme 1b, transmetalation between **B** and $L_nPd(CF_3)$ would form side product **3**. Analogous exchange with $L_nPd(Ph)$ would yield **C**, and subsequent C–C coupling from **C** would release **2**. Notably, the Pd-fluoride intermediate **B** was not detected by ^{19}F NMR spectroscopy during this reaction. However, we hypothesized that **B** could be trapped *in situ* with $TMSCF_3$ to generate **3**.[5c] Indeed, allowing **1-CF$_3$** to stand at 25 °C in the presence of excess $TMSCF_3$ afforded **3** in 19% isolated yield (Scheme 1c). Overall, the formation of **2** and **3** provides strong evidence that α-fluoride elimination pathways are accessible

Scheme 1. (a) Thermolysis of 1-CF$_3$; (b) Proposed pathway to 2 and 3; (c) Independent synthesis of 3



from **1-CF$_3$**[23] and, further, that these could be problematic in catalysis.[24]

Literature reports suggest that CF_2CF_3 ligands are less susceptible to α-fluoride elimination relative to their CF_3 counterparts.[25] Indeed, DFT studies of **1-CF$_2$CF$_3$** predict a 34.7 kcal/mol barrier for α-fluoride elimination/phenyl migration (Figure 3).[26] This is almost 14 kcal/mol higher than the

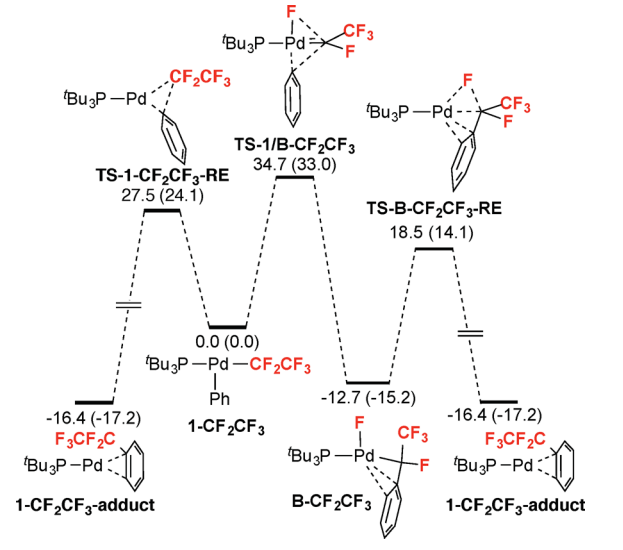


Figure 3. Reaction coordinate from DFT calculations of **1-CF$_2$CF$_3$**. Energies ΔG (ΔH) in kcal/mol.

analogous transformation at **1-CF$_3$**. In contrast, the predicted barrier for concerted Ph–CF_2CF_3 coupling from **1-CF$_2$CF$_3$** is very similar to that from **1-CF$_3$** (27.5 kcal/mol vs 27.0 kcal/mol, respectively).[27]

On this basis, we hypothesized that reductive elimination from **1-CF$_2$CF$_3$** would proceed selectively via this latter pathway to afford $PhCF_2CF_3$ in increased yield and selectivity relative to that of **1-CF$_3$**. Complex **1-CF$_2$CF$_3$** was prepared in 74% yield via an analogous procedure to that for **1-CF$_3$**.

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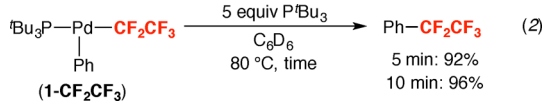
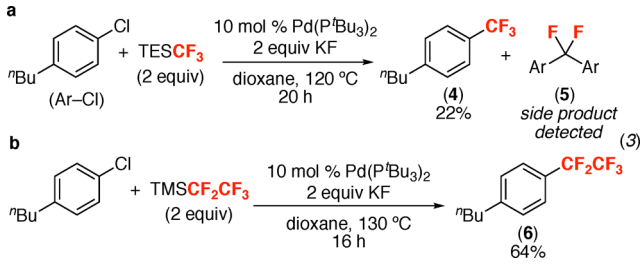
Consistent with our hypothesis, heating **1-CF_2CF_3** for 5 min at 80 °C in C_6D_6 in the presence of 5 equiv of P^tBu_3 afforded $PhCF_2CF_3$ in 92% yield (with 95% conversion of the starting material). Heating for an additional 5 min resulted in 96% yield of $PhCF_2CF_3$ with quantitative conversion (eq 2).[19] No products



derived from α-fluoride elimination were detected by NMR spectroscopy or GC–MS.

To translate these results to catalysis, we first explored the cross-coupling of 1-butyl-4-chlorobenzene with $TESCF_3$ using various P^tBu_3-ligated Pd catalysts (Table S4). The best result was obtained with 10 mol % of $Pd(P^tBu_3)_2$ at 120 °C for 20 h, which afforded **4** in 22% yield (eq 3a).[28] Consistent with the



stoichiometric studies, difluorodiarylmethane **5** was detected as a side product of this reaction. This suggests that α-fluoride elimination intermediate **B** may be formed and undergo undesired side reactions under catalytic conditions.[29,30]

We next explored the catalytic coupling of 1-butyl-4-chlorobenzene with $TMSCF_2CF_3$. Under otherwise identical conditions, this transformation afforded **6** in 64% yield (eq 3b). The increase in yield relative to trifluoromethylation is consistent with the stoichiometric studies. We also note that this is the first reported example of $Pd^{0/II}$-catalyzed pentafluoroethylation of an aryl halide. Additional optimization revealed that aryl bromides afford higher yields than aryl chlorides and that catalysis proceeds at 80 °C. Under the optimized conditions (10 mol % of $Pd(P^tBu_3)_2$, 2 equiv of $TMSCF_2CF_3$, 2 equiv of KF in dioxane at 80 °C for 16 h), **6** was obtained in 73% isolated yield.[31] A preliminary evaluation of substrate scope showed that this transformation proceeds with electronically diverse aryl and heteroaryl bromides to afford **6**-**21** in yields ranging from 53 to 80% (Figure 4).[32]

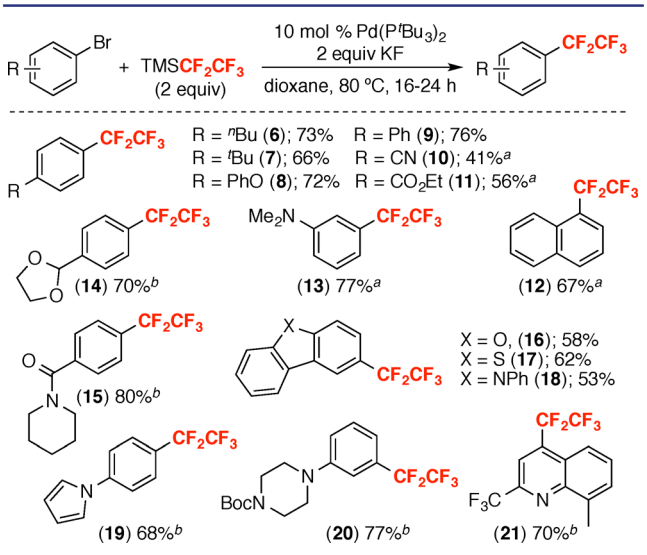


Figure 4. Scope of $Pd(P^tBu_3)_2$-catalyzed pentafluoroethylation of aryl bromides. [a] ^{19}F NMR yield. [b] 24 h.

In summary, this Communication describes aryl–R_F coupling reactions at Pd^{II} complexes of general structure (P^tBu_3)-$Pd^{II}(Ph)(R_F)$. With R_F = CF_3, the complex is susceptible to α-fluoride elimination. DFT calculations suggest that this pathway provides a kinetically viable route to $PhCF_3$. However, experimental studies show that competitive side reactions preclude selective Ph-CF_3 coupling. In contrast, an α-fluoride elimination pathway is not accessible with the CF_2CF_3 derivative. As such, this system can be leveraged to achieve the first example of $Pd^{0/II}$-catalyzed pentafluoroethylation of aryl bromides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05216.

Experimental details, characterization data for new compounds, and DFT calculations(PDF)

Data for C**1**-CF_3(CIF)

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Notes

The authors declare no competing financial interest.

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(18) The addition of P^tBu_3 improved the reaction yield (Table S1). A previous report on the reductive elimination of triarylamines from Pd^{II} P^tBu_3 complexes also used 5 equiv of P^tBu_3 (ref 8d).

(19) The major Pd^0 product of this reaction is $Pd(P^tBu_3)_2$ (as determined by ^{31}P NMR spectroscopy). No Pd black is observed.

(20) Attempts to increase the yield of $PhCF_3$ by variation of the temperature, solvent, and/or concentration were unsuccessful.

(21) Another possible competing side reaction would be exchange between the substituents on phosphorus and the phenyl or CF_3 ligands of Pd. However, GC−MS analysis of the reaction mixtures showed no products consistent with this reaction.

(22) The reported products account for 66% of the fluorine mass balance. The crude reaction mixtures were analyzed by ^{19}F NMR spectroscopy and GC−MS; however, the rest of the fluorine could not be accounted for (see p. S12 for details).

(23) Efforts to probe the operating mechanism of $PhCF_3$ formation from **1-CF_3** were inconclusive. See p. S17 for details.

(24) This side reaction may be limited with BrettPhos based on its hemilabile nature.

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(26) Notably in this system the α-fluoride elimination/phenyl migration is concerted, and no fluorocarbene intermediate could be located.

(27) Rotation of the CF_2CF_3 ligand was found to occur prior to reductive elimination via **TS-1-CF_2CF_3-RE**.

(28) No $TESCF_3$ remains after 20 h. However, after 11 h the yield of $ArCF_3$ is nearly identical (22%), whereas 52% of $TESCF_3$ remains. This suggests that the reaction yield is not limited by the decomposition of $TESCF_3$.

(29) Difluorobenzyl complex **3** is catalytically inactive for the Pd-catalyzed aryl trifluoromethylation of Ar-Cl. As such, the formation of this side product appears to be a dead-end for catalysis. See p. S22 for details.

(30) For a discussion of other potential issues that might limit catalytic turnover, see p. S28.

(31) Translating these conditions to the trifluoromethylation of 1-butyl-4-bromobenzene with $TMSCF_3$ afforded 3% of the trifluoromethylated arene as determined by ^{19}F NMR.

(32) For a comparison with literature methods for arene pentafluoroethylation, see p. S40.

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