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Nucleophile-Catalyzed, Facile, and Highly Selective C–H Activation of Fluoroform with Pd(II)

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Supporting Information

ABSTRACT: Exceedingly facile (23 °C) and chemoselective H-CF_3 activation with [(dppp)Pd(Ph)(OH)] in the presence of a Lewis base promoter such as *n*-Bu_3P leads to Pd-CF_3 bond formation in nearly quantitative yield. A combined experimental and computational study points to a new mechanism that involves H-bonding Pd-O(H)···H-CF_3 and nucleophilic attack of the promoter on the metal, followed by a push-pull-type collapse of the resultant five-coordinate Pd(II) intermediate via a polar transition state.

Trifluoromethane (CHF_3, fluoroform, HFC-23), a side product of the fluoropolymer industry, is a nontoxic and ozone-friendly gas that nonetheless must be destroyed because of its high greenhouse effect (>10^4 that of CO_2) and >250-year atmospheric lifetime.[1] Releasing CHF_3 waste streams into the atmosphere may lead to an ecological disaster. The risk of the so-called "climate bomb" is increasingly high now that the carbon credit trading program has recently come to an end.[2]

Incineration of CHF_3, a flame retardant, consumes much energy and results in large amounts of inorganic waste.[1] A clearly preferred alternative to the destruction of CHF_3 would be its use as a feedstock in the production of valuable fluorinated organic compounds. Fluoroform has long been recognized[3,4] as the cheapest, readily available, and most atom-economical CF_3 source for the needs of the pharmaceutical, agrochemical, and specialty materials industries.[5,6] However, chemoselective H-CF_3 activation for the synthesis of trifluoromethylated building blocks and intermediates is highly challenging.

Until very recently, only one way to activate fluoroform, a weak acid (pK_a = 27 in H_2O),[7] was known, i.e., deprotonation with strong bases.[4] The thus generated CF_3^- carbanionic species are notorious for their facile decomposition to difluorocarbene via fluoride elimination. In 2011, the first reactions of selective fluoroform activation with transition metal complexes were reported.[8−10] Daugulis et al.[8] demonstrated the first zincation of fluoroform to give Zn-CF_3 derivatives in one step. Goldman and co-workers[9] found the first H-CF_3 oxidative addition to an Ir(I) pincer complex. Our group discovered the first direct cupration of fluoroform[10] and demonstrated its synthetic utility.[10−14]

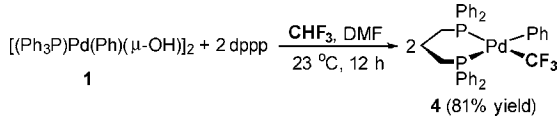
In spite of the progress made, the highly promising area of CHF_3 activation with transition metals is still in its toddler years. Finding new transition metal-based systems for selective fluoroform activation reactions and understanding their mechanisms is key to further developments in this important field. Herein we report the first example of H-CF_3 activation at a Pd(II) center, which readily and cleanly occurs at room temperature and atmospheric pressure to furnish Pd-CF_3 complexes in high yield. A combined experimental and computational study of this new transformation reveals a striking mechanism that is unprecedented[9,15,16] in the chemistry of fluoroform activation.

For initial studies, we selected $[(Ph_3P)_2Pd_2(Ph)_2(\mu\text{-}OH)_2]$ (**1**),[17] an easily accessible dinuclear complex that readily reacts with a variety of acids.[18] Although even such weak acids as cyclopentadiene[18a] and primary amines[18d,i] are activated by **1**, chloroform only forms a hydrogen bond to the oxygen atoms of **1** without full ionization.[17] Therefore, we did not expect **1** to cleave the C-H bond of CHF_3 that is orders of magnitude less acidic than $CHCl_3$.[7] The lack of reaction between **1** and CHF_3 in benzene, THF, and DMF was confirmed. We reasoned that the reactivity toward fluoroform could be enhanced by adding to **1** a tertiary phosphine PR_3 that would lead to the formation of mononuclear species[19] $[(Ph_3P)_n(R_3P)_mPd(Ph)OH]$ ($m + n = 2$) bearing a more basic terminal OH ligand.

Screening experiments were performed by adding CHF_3 in excess to a mixture of **1** and a PR_3 ligand in DMF and monitoring the reaction by ^{19}F NMR. Over a dozen of various tertiary phosphines were tested. In most instances (Ph_3P, Cy_3P, *n*-Bu_3P, (*o*-anisyl)$_3P$, dppm, Xantphos, dippf, and dcypf),[20] no reaction was observed. It was encouraging to find that a few other ligands (dppb, dpppent, and dppf) did promote CHF_3 activation to give Pd-CF_3 species, albeit in only 1−7% yield.[20a,21] A slightly higher yield (15%) was observed with dppe that brought about the formation of [(dppe)Pd(Ph)(CF_3)] (**3**).[22] To our delight, [(dppp)Pd(Ph)(CF_3)] (**4**)[22] was produced in 81% yield from **1** and CHF_3 in the presence of dppp (2 equiv per Pd; Scheme 1).

The formation of **4** was also observed in other aprotic dipolar solvents (DMAC and NMP) but not in media of low polarity (benzene and THF). The lack of formation of 1,1-difluoro-2-phenylcyclopropane in a repeat of the reaction in DMF (Scheme 1) in the presence of deliberately added styrene (20 equiv) suggested that the H-CF_3 activation is unlikely mediated by difluorocarbene and, therefore, by CF_3^-.

Scheme 1. Activation of CHF_3 with 1/dppp



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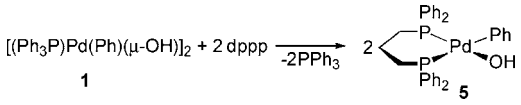
It was reasonable to propose that the reactive species in the **1**/dppp system was [(dppp)Pd(Ph)(OH)] (**5**) that would be formed upon dppp coordination to Pd, followed by chelation and PPh_3 loss. Indeed, it was found that **1** readily underwent ligand exchange with dppp to give **5** in nearly quantitative yield (Scheme 2). In a preparative experiment, **5** was isolated in 88% yield and fully characterized in solution and in the solid state.[21] The X-ray structure of **5** (Figure 1) shows the anticipated square-planar geometry around Pd, with the P-Pd-P angle of 95.2(1)° being in the expected range, e.g., 93.4(1)° found in **4**.[22] The Pd-P bond trans to the OH (2.251(1) Å) is nearly 0.1 Å shorter than that trans to the Ph ligand (2.344(1) Å), attesting to the immense difference in the trans influence of these two ligands.

Scheme 2. Synthesis of 5 from 1 and dppp



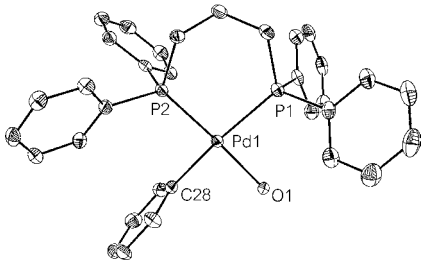
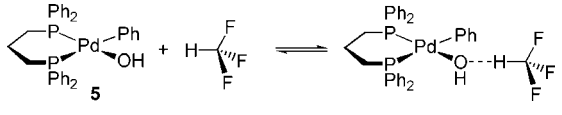


Figure 1. ORTEP drawing of [(dppp)Pd(Ph)(OH)] (**5**) with thermal ellipsoids drawn at the 50% probability level and all hydrogen atoms omitted for clarity.

It came as a total surprise when adding fluoroform to a solution of preisolated pure **5** in DMF resulted in no reaction. Not even traces of **4** were produced (^{19}F NMR). Importantly, however, upon addition of CF_3H the OH signal (dd, J = 6.7 and 5.3 Hz) in the ^{1}H NMR spectrum of **5** in THF-d_8 shifted upfield by ca. 0.1 ppm. Simultaneously, the upfield doublet (−14.2 ppm $J_{P\text{-}P}$ = 47.3 Hz) in the ^{31}P NMR spectrum shifted downfiled by ca. 1.5 ppm, whereas the other doublet stayed at its position (17.0 ppm). Furthermore, **5** was found to promote H/D exchange between CHF_3 and D_2O (ca. 8% conversion).[21] Evidently, **5** formed a hydrogen bond to CHF_3 in a reversible process (Scheme 3) that manifested itself in the evolution of the NMR signals from the hydroxo proton and the P nucleus trans to the OH. The ability of CHF_3 to hydrogen-bond to O-donors has long been established.[23]

Scheme 3. Hydrogen Bond Formation between 5 and CHF_3



The difference between a solution of **5** generated from **1** and dppp (2 equiv per Pd; see above) and that of preisolated **5** is clearly that the former contains free PPh_3 and dppp in addition to **5** (Scheme 2) and cleaves the H-CF_3 bond to give **4**, whereas the latter does not contain any extra phosphine and fails to cleave the H-CF_3 bond. It therefore became apparent that additional phosphine was needed for efficient H-CF_3 activation and CF_3 transfer to the Pd atom in **5**. Indeed, adding PPh_3 to a solution of **5** and fluoroform in DMF triggered instantaneous reaction producing **4**. This observation prompted the question: can PPh_3 be replaced by other promoters for the trifluoromethylation of the Pd center in **5** with fluoroform? As a result of a series of tests, n-Bu_3P was identified as a superior activator. Upon addition of n-Bu_3P (1 equiv) to **5** and CHF_3 in DMF, the reaction was complete within 30 min to give **4** along with a small quantity (15%) of [$(n$-$Bu_3P)_2$Pd(Ph)(CF_3)] (**6**) in overall 99% yield. In the course of time, the ratio of **4** to **6** lowered due to ligand exchange between **4** and the n-Bu_3P present in the reaction solution. However, as the ligand exchange occurred, the total yield of the Pd-CF_3 products (**4**+**6**) remained the same. Like the **1**/PR_3 systems (see above and Scheme 1), the reaction of **5**/n-Bu_3P with CHF_3 is strongly solvent-dependent. The yields of the Pd-CF_3 products (**4** + **6**) after 2 h of reaction of **5**/n-Bu_3P (1:1) with fluoroform (10 equiv) paralleled the polarity of the medium, being 99%, 75%, 58%, 8%, and 2% in DMF, NMP, DMAC, THF, and benzene, respectively.[21]

After the H-CF_3 bond cleavage leading to **4**, the Lewis base activator is released and therefore, in principle, might be used in catalytic rather than stoichiometric quantities. This was confirmed by performing the reaction of **5** with CHF_3 in the presence of 20 and 10 mol % of n-Bu_3P and observing the formation of **4**+**6** in 100% and 80% total yield, respectively, after 12 h. Unsurprisingly, the Pd-CF_3 bond formation was faster in the presence of larger quantities of n-Bu_3P (Figure 2).

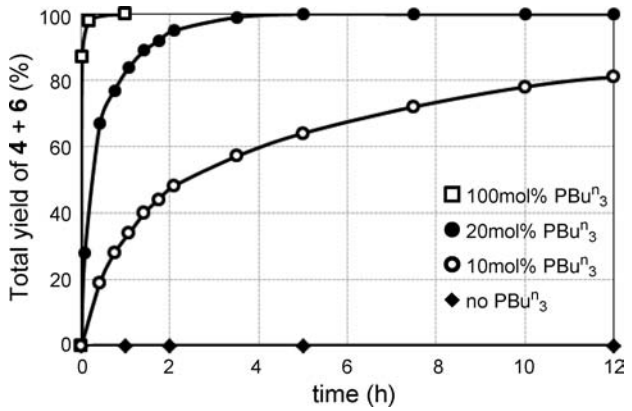


Figure 2. Yield vs time in the n-Bu_3P-catalyzed reaction of **5** with CHF_3 (excess) in DMF at 23 °C.

There are two sites in the H-bond complex **5**···HCF_3 for attack by a Lewis base, the O-H bond and the 16e d^8 Pd(II) center (Figure 3). Deprotonation of the OH (a) would be favored by stronger bases and should be less sensitive to the steric bulk of the base. On the contrary, nucleophilic attack on the more sterically hindered metal center (b) should require a smaller Lewis base with a higher affinity for Pd(II). A study of the promoting effect of various bases (Table 1) provided an unambiguous indication that the role of the promoter is coordination to the Pd center, rather than deprotonation of the OH ligand. The strongest effect was observed for n-Bu_3P (Table 1, entry 2), a much more coordinating yet considerably weaker Brønsted base than Et_3N that did not exhibit any promoting effect (entry 9). More basic than n-Bu_3P yet much bulkier t-Bu_3P was almost inactive (entry 3). Being smaller and less basic than Et_3N, pyridine was nonetheless a better promoter (entries 8 and 9), evidently because of its higher coordinating ability. Finally, poorly basic yet

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coordinating chloride and iodide (entries 10 and 11) promoted the reaction to about the same degree as Ph_3P and p-Tol_3P.

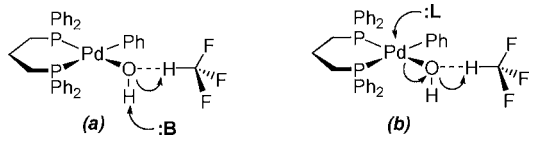
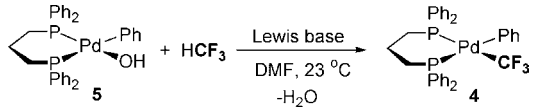


Figure 3. Two sites in **5**···HCF_3 for attack by a base :B (a) and a ligand (nucleophile) :L (b).

Table 1. Lewis Base-Promoted Activation of CHF_3 with 5



entry	Lewis base (equiv)	reaction time, h	yield of **4**, %[21]
1	none	24	<1
2	n-Bu_3P (1)	0.5	99[a]
3	t-Bu_3P (1)	24	4
4	Cy_3P (1)	24	41
5	Ph_3P (1)	24	10
6	p-Tol_3P (1)	24	18
7	dppp (1)	24	76
8	Pyridine (5)	18	17
9	Et_3N (10)	5	0
10	PPN Cl (1)	18	7
11	KI (1)	18	13

[a]Total yield for **4** and **6** in a 5:1 ratio (1:1 after 24 h).

The above-described data pointed to a push-pull-type mechanism of Lewis base-induced CHF_3 activation with **5**. As shown in Figure 3 (b), the electron density pushed by the promoting ligand L through the metal to the oxygen atom is simultaneously pulled from it by the H-bonded CHF_3 molecule. To gain insight into details of this H-CF_3 activation, a density functional theory (DFT) study was performed using [(dpp)Pd(Ph)(OH)] (dpp = $H_2P(CH_2)_3PH_2$) and Me_3P as simplified models of **5** and n-Bu_3P, respectively.[21,24]

The computed reaction profile is shown in Figure 4. The attack of Me_3P on Pd of the H-bonded adduct **S1** gives **S2**, a five-coordinate 18e intermediate with the O(H)···HCF_3 moiety in the apical position of the distorted square pyramid. The Pd-O distance in **S2** (2.496 Å) is 0.42 Å longer than in **S1** (2.076 Å). An increase in electron density on the O atom and substantial polarization of the Pd-OH bond when going from **S1** to **S2** is manifested by considerable changes in the computed group NBO charges for the O(H)···HCF_3 (from −0.52 to −0.72) and OH (from −0.49 to −0.65) units. Intermediate **S2** then collapses with H-CF_3 bond cleavage via the rate-determining transition state **TS2** (Figure S5-4). The computed barrier $\Delta G^{\ddagger}_{298K}$ = 21.4 kcal/mol (in DMF) is consistent with the experimentally observed reaction rates (Figure 2). Furthermore, recomputing $\Delta G^{\ddagger}_{298K}$ for **TS2** in benzene produced the value of 26.7 kcal/mol that accords with no experimentally observable reaction in this and other solvents of low polarity at room temperature (see above). The highly polar nature of **TS2** is apparent from its large dipole moment (19.4 D), as compared to those of **S1** (10.4 D) and **S2** (14.0 D), as well as from the large negative NBO charge on the [HO···H···CF_3] group (−0.84) and the long Pd-O distance (2.749 Å). As the latter is 0.4 Å shorter than the sum of the van der Waals radii of Pd (1.63 Å) and O (1.52 Å), **TS2** may

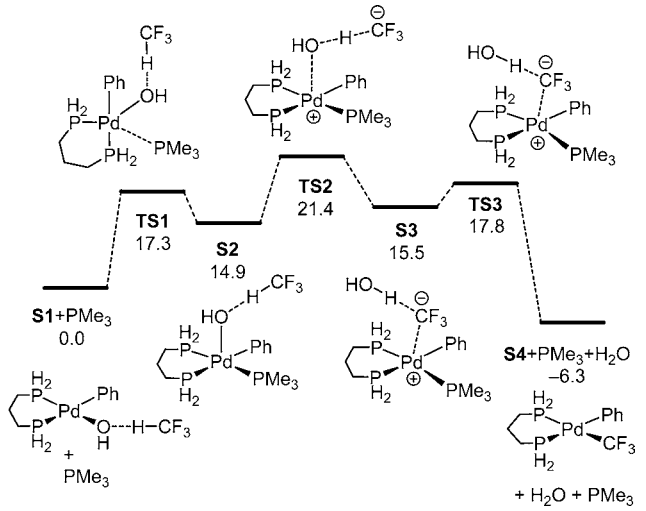


Figure 4. Computed Gibbs free energy (kcal/mol) profile for PMe_3-mediated reaction of [(dpp)Pd(Ph)(OH)] with CHF_3 in DMF.

be viewed as a contact ion pair {[(dpp)Pd(Ph)(Me_3P)][HO···H···CF_3]}. Intrinsic reaction coordinate (IRC) calculations from **TS2** in the forward direction and subsequent optimization established proton migration toward the oxygen atom to yield {[(dpp)Pd(Ph)(Me_3P)][HO-H···CF_3]} (**S3**), an intermediate with an NBO charge of −0.71 on the CF_3 group. The latter is H-bonded to H_2O and has a dative interaction with Pd (Pd···CF_3 = 2.994 Å), which leads to PMe_3 displacement via **TS3** with a low activation barrier of 2.3 kcal/mol to give the final Pd-CF_3 product (**S4**), Me_3P, and H_2O. The computed mechanism (Figure 4) receives further support from the lack of H-CF_3 activation with Cámpora's[25] pincer hydroxides [(PCP)M(OH)] (M = Pd, Ni) even in the presence of n-Bu_3P. Although the terminal OH ligand in these pincer complexes is highly basic, the stereochemical rigidity of the (PCP)M framework precludes conformational changes at the metal center that are required for the reaction to occur (Figure 4).[26]

In conclusion, we have found the first palladation reaction of fluoroform, leading to Pd-CF_3 bond formation in one step. The reaction employs [(dppp)Pd(Ph)(OH)] (**5**), a new monomeric terminal palladium hydroxide, in conjunction with a Lewis base promoter L. The most efficient L found is n-Bu_3P that can be used for the reaction not only in stoichiometric but also in catalytic quantities. Our combined experimental and computational study has identified a remarkable new mechanism of this H-CF_3 activation.[27] The reaction occurs due to the cooperative effect of H-bonding of fluoroform to the OH ligand and coordination of L to the Pd center, facilitating proton transfer within the PdO(H)···H-CF_3 moiety in a polar transition state. This *nucleophile*-assisted push-pull mechanism is distinctly different from the one that operates in the direct cupration of fluoroform and involves *electrophilic* assistance from the alkali metal cation interacting with fluorines on the CHF_3 molecule.[15] Considering the exceptional attractiveness of fluoroform as a CF_3 source and palladium being one of the very few metals that can mediate Ar-CF_3 bond formation,[3,28] the results obtained in the current work will likely lead to further developments in the area of aromatic trifluoromethylation.

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■ ASSOCIATED CONTENT

Supporting Information

Full details of synthetic, computational (PDF), and crystallographic studies (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) Calculations were performed at the M06L/6-31G(d,p)-LANL2DZ level of theory with PCM solvent corrections.[21]

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(26) The low yield of the dppe derivative **3** (see above) might have the same origin, i.e. insufficient flexibility of the (dppe)Pd fragment. An optimal degree of rigidity is apparently needed, however, for the reaction to occur. This is indicated by the poorly efficient H-CF_3 activation or lack thereof with many monodentate and bidentate ligands explored in the current work (see above and Table S1).[21] A detailed study of the influence of conformational, steric, and electronic properties of the supporting ligand on the reaction is the subject of a separate project.

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(28) Although Ar-CF_3 reductive elimination from Pd(II) is highly challenging,[3,29] the formation of $PhCF_3$ from **4** at 145 °C (ca. 60% selectivity) has been reported.[22] Xantphos[20c,29] and subsequently BrettPhos[30] have been found to promote Ar-CF_3 coupling at Pd(II) at as low as 50−80 °C.

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