ARTICLES
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Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes

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Difluorocarbene has important applications in pharmaceuticals, agrochemicals and materials, but all these applications proceed using just a few types of reaction by taking advantage of its intrinsic electrophilicity. Here, we report a palladium-catalysed strategy that confers the formed palladium difluorocarbene (Pd=CF_2) species with both nucleophilicity and electrophilicity by switching the valence state of the palladium centre (Pd(0) and Pd(II), respectively). Controllable catalytic difluorocarbene transfer occurs between readily available arylboronic acids and the difluorocarbene precursor diethyl bromodifluoromethylphosphonate ($BrCF_2PO(OEt)_2$). From just this simple fluorine source, difluorocarbene transfer enables access to four types of product: difluoromethylated and tetrafluoroethylated arenes and their corresponding fluoroalkylated ketones. The transfer can also be applied to the modification of pharmaceuticals and agrochemicals as well as the one-pot diversified synthesis of fluorinated compounds. Mechanistic and computational studies consistently reveal that competition between nucleophilic and electrophilic palladium difluorocarbene ([Pd]=CF_2) is the key factor controlling the catalytic difluorocarbene transfer.

Difluorocarbene (:CF_2) is an electrophilic ground-state singlet carbene[1] that has important applications in various fields[2,3]. In industry, difluorocarbene undergoes homocoupling to synthesize tetrafluoroethene for the production of Teflon (DuPont), a widely used polymer (Fig. 1a)[4]. In drug production and medicinal chemistry, difluorocarbene serves to construct different fluorinated moieties (Fig. 1b–e), such as difluoromethyl ethers[5,6], *gem*-difluorocyclopropanes[7,8] and *gem*-difluoroalkenes[9]. Difluorocarbene can also be used for the preparation of diverse ^{18}F-labelled trifluoromethylation compounds as radioisotopes for positron emission tomography studies (Fig. 1e)[10–13]. Despite the range of applications, difluorocarbene has limited reaction types (Fig. 1a–d)[2–14], which mainly take advantage of its electrophilic nature[1,2]. To overcome this limitation, there have been attempts over 40 years to tune the reactivity of difluorocarbene by coordination to transition metals[15]. Although various metal difluorocarbene ([M]=CF_2) complexes based on groups 6 to 10 have been synthesized and isolated, their inherently low reactivity compared to their non-fluorinated counterparts has hindered further transformation and posed challenges for catalysis cycling[16–20]. Only recently has catalytic difluorocarbene transfer been realized to install a difluoromethyl (CF_2H) group onto aromatic rings[21–23]. However, these methods do not involve controllable manipulation of the reactivity of metal difluorocarbene between nucleophilicity and electrophilicity, and can only access one type of fluorinated compound. Controllable catalytic difluorocarbene transfer remains an elusive goal and has not yet been reported, mainly due to the lack of mechanistic insight into the metal difluorocarbene chemistry.

A few examples have demonstrated that [M]=CF_2 species of groups 8 and 9 with formal d^8 electron configurations (Ru^0, Os^0, Ir^I, Co^I) exhibit nucleophilic character[16,17,24–26], providing the opportunity to develop a new paradigm for difluorocarbene transfer reactions. We speculated that the reactivity of [M]=CF_2 could be modulated by altering the oxidation state of the central transition metal. Because palladium is a normal transition metal for the catalysis process, and the transition between Pd(0) and Pd(II) is common[27], the reactivity of [Pd]=CF_2 might be modulated between Pd^0 (with d^{10}) and Pd^{II} (with d^8). [Pd^0]=CF_2 (with d^{10}) is expected to possess unusual nucleophilic reactivity as a result of electron donation from the more electron-rich Pd^0, while [Pd^{II}]=CF_2 (with d^8) should maintain the electrophilic behaviour of difluorocarbene due to the relative electron deficiency of Pd^{II} (Fig. 1f). In this way, [Pd]=CF_2 can present either electrophilicity or nucleophilicity in a controllable manner, acting as catalytic species in a catalytic cycle.

We sought to control the reactivity of difluorocarbene to be nucleophilic or electrophilic, and to diversify the difluorocarbene transfer reactions to produce a variety of different compounds. The proposed mechanism comprises the following steps (Fig. 1f): (1) a nucleophilic [Pd^0]=CF_2 species reacts with an electrophile (E) to afford the key fluoroalkyl palladium intermediate [Pd^{II}]–CF_2E; (2) electrophilic difluorocarbene(s) are inserted into [Pd^{II}]–CF_2E to elongate the fluoroalkylated chain[28]. From these steps, it is possible to provide an array of products containing different units of difluoromethylene (CF_2) by varying the concentration of difluorocarbene in the presence of the nucleophilic Pd carbenoid. These catalytic steps enable a straightforward strategy to install CF_2 units into organic molecules in a controllable manner, which has not been achieved with other methods. The challenge of this strategy is to selectively produce the fluoroalkylated compound at each step as a major product. We now report the achievement of controllable palladium-catalysed difluorocarbene transfer reactions between arylboronic acids and a readily available difluorocarbene precursor $BrCF_2PO(OEt)_2$ (ref. [29] and Fig. 1f). Manipulation of the oxidation states of palladium leads to two different types of [Pd]=CF_2 species

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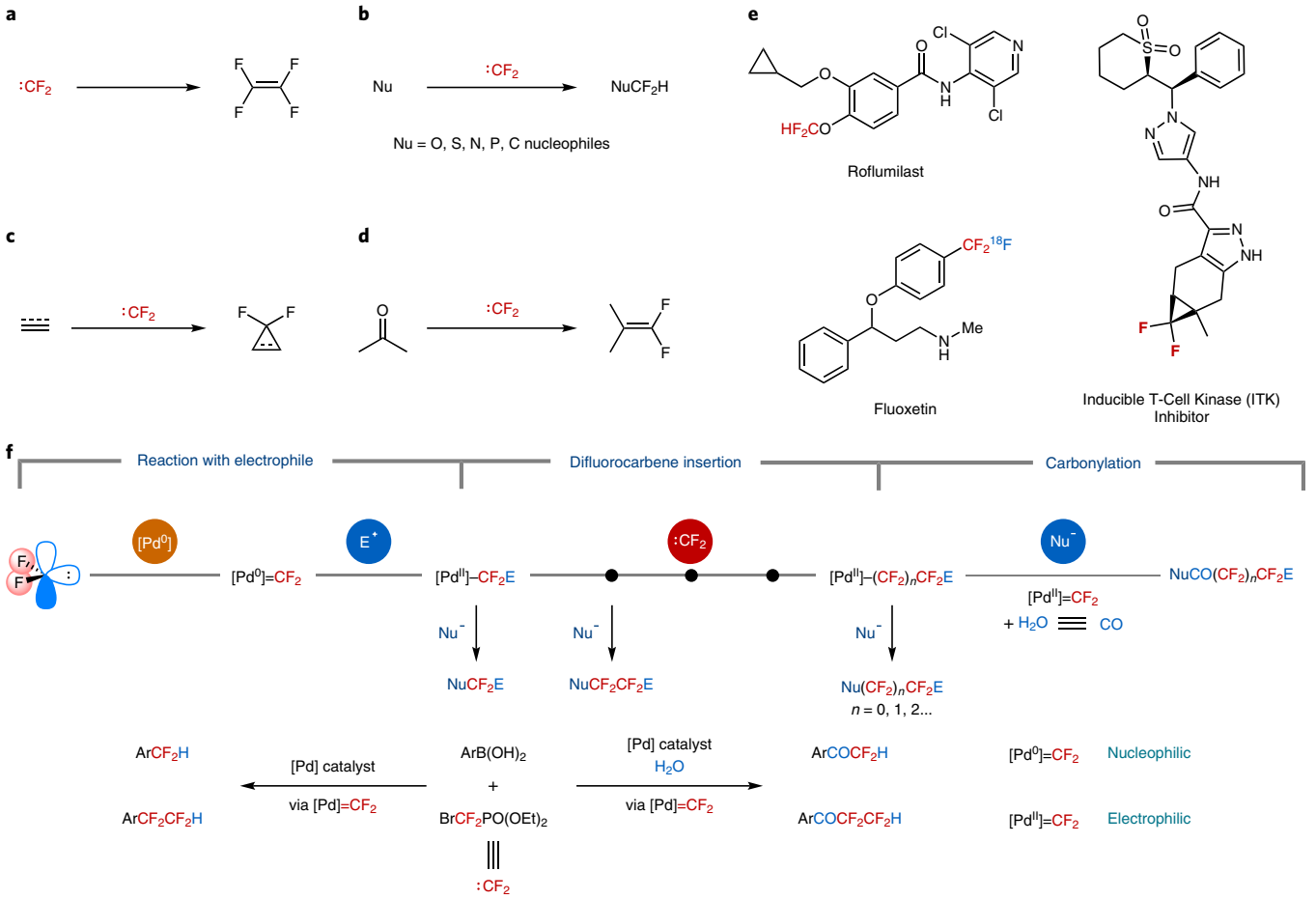


Fig. 1 | Previous and present approaches to difluorocarbene transfer. a, Homocoupling of difluorocarbene is a typical reaction to generate tetrafluoroethene for the production of Teflon. **b**, Reactions of difluorocarbene with heteroatom or carbon nucleophiles are commonly used to prepare difluoromethylated compounds, but those with carbon nucleophiles have limited substrate scope. **c**, [2+1] cyclizations of unsaturated carbon–carbon bonds with difluorocarbene. **d**, Wittig olefinations to prepare *gem*-difluoroalkenes. **e**, Examples of bioactive molecules prepared by using difluorocarbene transfer approaches to introduce fluorinated moieties. **f**, Outline of the present strategy for controllable catalytic difluorocarbene transfer. Manipulation of the oxidation states of palladium leads to two different types of [Pd]=CF_2 species (with nucleophilicity or electrophilicity), which can make controllable catalytic difluorocarbene transfer feasible and produce a variety of different fluorinated compounds.

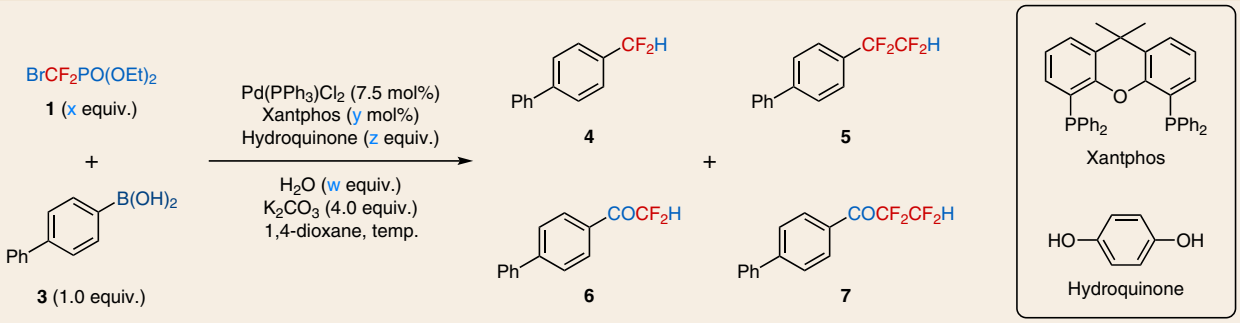
with opposite reactivity (nucleophilicity or electrophilicity). In the study, we also discovered that [Pd^{II}]=CF_2 can serve as a CO surrogate in the presence of H_2O (ref. [16]), leading to a carbonylation reaction that terminates the difluorocarbene insertion and provides fluoroacylated compounds (Fig. 1f). These transformations selectively afford four typical types of difluorocarbene transfer product: difluoromethylated and tetrafluoroethylated arenes and their corresponding fluoroalkylated ketones. By deliberately tuning the reaction conditions, it is possible to manipulate the reaction to selectively produce each of the four products.

Results and discussion

To investigate the advances of such controllable difluorocarbene transfer reactions, we focused on transition-metal catalysis with a suitable difluorocarbene precursor. After extensive efforts, $BrCF_2PO(OEt)_2$ **1** was identified as a suitable difluorocarbene precursor in combination with hydroquinone **2** and a Brønsted base (K_2CO_3); the concentration of difluorocarbene in the reaction can be controlled by adjusting concentrations of **1**, **2** and the base. We investigated a model reaction, using arylboronic acid **3** as a nucleophile to react with **1** in the presence of **2**, K_2CO_3, H_2O, palladium catalyst $PdCl_2(PPh_3)_2$ and a phosphine ligand (Xantphos), in which a proton was proposed to be the electrophile. Unexpectedly, besides the formation of difluoromethylated arene **4** and tetrafluoroethylated arene **5**, two fluoroacylated compounds, difluoromethylaryl ketone **6** and tetrafluoroethylaryl ketone **7**, were also observed. The CO probably originates from the difluorocarbene moiety, implying that an electrophilic [Pd^{II}]=CF_2 is involved in the reaction[16]. The formation of these fluoroalkylated ketones is intriguing, because no transition-metal-catalysed perfluoroalkylation–carbonylation reaction has been reported previously due to the strong σ bond between the transition metal and the perfluoroalkyl group in M–R_f (R_f = perfluoroalkyl)[30]. Additionally, as a versatile functional group, the carbonyl group offers great opportunities for downstream transformations.

Subtle adjustment of the reaction conditions allows the selective production of one of these four types of compound, as shown in Table 1. The reaction temperature and the concentration of **1** are critical factors. Overall, a lower reaction temperature is favourable for the formation of carbonylation products **6** and **7**, while a higher concentration of the difluorocarbene precursor **1** benefits CF_2 elongation to produce **5** and **7**. In this study, the selective formation of difluoromethyl arylketone **6** was the most difficult to achieve among the competitive reactions; another CO source, tungsten

Table 1 | Optimization of the selective formation of fluoroalkylated arenes in a model reaction.



Conditions[a]	4 (%)[b]	5 (%)[b]	6 (%)[b]	7 (%)[b]
Conditions A: $x=2.0$, $y=11.5$, $z=2.0$, $w=1.0$, 100 °C	82 (80)	ND	2	6
Conditions B: $x=3.0$, $y=20$, $z=3.0$, $w=0$, 4 Å MS, 120 °C	16	64 (64)	ND	20
Conditions C: $x=2.0$, $y=11.5$, $z=1.0$, $w=0$, 80 °C, $W(CO)_6$ (25 mol%)	15	ND	56 (54)	ND
Conditions D: $x=4.0$, $y=20$, $z=3.0$, $w=1.0$, 80 °C	9	3	3	73 (70)

[a]The reaction was carried out with **3** (0.3 mmol, 1.0 equiv.) and **1** in 1,4-dioxane (conditions A, 3.0 ml; conditions B, 4.0 ml; conditions C, 2.5 ml; conditions D, 3.0 ml) under suitable reaction conditions (conditions A–D). [b] The yields were determined by ^{19}F NMR using fluorobenzene as the internal standard; numbers given in parentheses are isolated yields. ND, not determined. MS, molecular sieves.

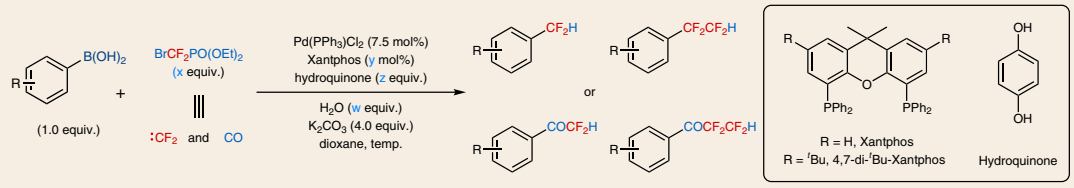
hexacarbonyl ($W(CO)_6$) was added to the reaction to selectively furnish **6** with 56% yield, but a 15% yield of **4** was still obtained (Table 1, conditions C). Control experiments showed that the palladium catalyst, Xantphos ligand and hydroquinone all play essential roles in promoting the reaction (Supplementary Table 5).

With the optimized reaction conditions in hand, we examined the scope of these transformations (Table 2). A wide range of difluoromethylated arenes can be selectively obtained under conditions A with good yields[31–34]. Many functionalities (for example, thioether, trimethylsilyl (TMS), esters and ketones) showed good tolerance to the reaction (**12**–**18**). In the case of substrates bearing electron-withdrawing groups, the addition of 1.0 equiv. of LiCl benefitted the reaction (**15**–**18**). Good yields were also obtained under conditions B for the selective formation of tetrafluoroethylated arenes; even the alkene-containing substrate reacts without formation of *gem*-difluorocyclopropane side product (**30**)[7]. Although the selective formation of difluoromethyl ketones appears relatively difficult, moderate yields were still obtained under conditions C. In contrast, a variety of arylboronic acids reacted smoothly with **1** under conditions D to selectively produce tetrafluoroethylaryl ketones. These reactions are readily scalable, as demonstrated by the gram-scale synthesis of fluoroalkylated arenes **14** and **42**. The promising selective formation of these fluorinated products encourages evaluation of these controllable difluorocarbene transfer reactions with complex molecules. Commercially available drugs, such as clofibrate, ezetimibe and δ-vitamin E, were viable in the reactions from their corresponding arylboronic acid derivatives (**23**, **24**, **31**, **48**–**50**). In particular, the selective difluoromethylation and tetrafluoropropanoylation of ezetimibe (**24** and **49**) with the free hydroxyl group intact provides a convenient synthetic method for modulation of bioactive molecules without the need for a multistep protection–deprotection procedure. CF_2H is a bioisostere of hydroxyl and thiol groups[35] and can serve as a lipophilic hydrogen bond donor[36]; the 1,1,2,2-tetrafluoroethyl (CF_2CF_2H) group is a structural mimic of the trifluoromethyl group and can improve the lipophilicity of the molecules[37]. Consequently, these transformations provide useful tools for modification of pharmaceuticals and other bioactive molecules.

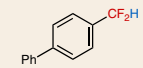
To demonstrate the utility of these catalytic controllable difluorocarbene transfer reactions, the direct fluoroalkylation of *N*-Boc-mexiletine, an anti-arrhythmic drug, was conducted by sequential C–H bond boroylation[38] and fluoroalkylation (Fig. 2a). Three mexiletine analogues (**52**–**54**) were selectively obtained in good yields, providing a straightforward and versatile route for applications in medicinal chemistry without parallel de novo synthesis. In addition, three diversified fluoroalkylated products can be accessed from one simple starting material in a one-pot reaction, as demonstrated in the modification of herbicide nitrofen (Fig. 2b). This one-pot, diversity-oriented synthetic strategy provides a facile and step-economic route for applications in the discovery of different interesting new bioactive molecules, which would otherwise be difficult to realize by conventional methods.

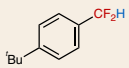
To gain mechanistic insight into these processes, we conducted several stoichiometric experiments (Fig. 3). The preparation and isolation of unstable $[Pd^0]{=}CF_2$ monomer complexes is difficult and has not yet been reported. In our study, complexes (^{t}Bu-Xantphos)$Pd^0{=}CF_2$ (**A1-1**) and [4,7-di-^{t}Bu(^{t}Bu-Xantphos)]$Pd^0{=}CF_2$ (**A1-2**) were prepared in good yields (70%) by defluorination from their corresponding trifluoromethyl palladium(II) salts ($Pd^{II}{-}CF_3$) (**B1-1** and **B1-2**, respectively) with potassium graphite (KC_8) (Fig. 3a)[18]. Here, the use of bulkier ^{t}Bu-Xantphos and 4,7-di-^{t}Bu(^{t}Bu-Xantphos) ligands sterically stabilizes the vulnerable $[Pd^0]{=}CF_2$. The ^{13}C NMR spectra of complexes **A1-1** and **A1-2** showed a characteristic positive chemical shift for metal difluorocarbene carbon ($[Pd^0]{=}\mathbf{C}F_2$, **A1-1**: δ 231.5 ppm, triplet of triplet, $^1J_{CF}=519.9$ Hz, $^2J_{CP}=68.0$ Hz; **A1-2**: δ 231.0 ppm, triplet of triplet, $^1J_{CF}=519.5$ Hz, $^2J_{CP}=67.6$ Hz). A single-crystal X-ray diffraction study of complex **A1-2** further confirmed that the $[Pd^0]{=}CF_2$ complexes involved in the reaction are monomers. **A1-2** has a Pd–C(carbene) bond length of 1.78(2) Å, ~0.23 Å shorter than the $[Pd^{II}]{-}CF_2H$ bond in difluoromethyl complex **C1** (Fig. 3b). The sum of the bond angles around the carbene carbon atom in **A1-2** is very close to 360° (≤359.8°), featuring the sp^2 carbon in the $[Pd^0]{=}CF_2$ structure. Complexes **A1** show unique nucleophilicity and are readily protonated with arylboronic acid or H_2O at room temperature to produce complexes $[Pd^{II}]{-}CF_2H$ (**C1**) with full conversion (Fig. 3b and Supplementary

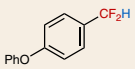
Table 2 | Substrate scope of the controllable palladium-catalysed difluorocarbene transfer.

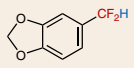


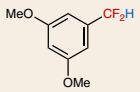
Conditions A[a]

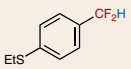

4, 80%

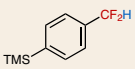

8, 80%

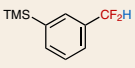

9, 60%

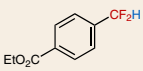

10, 55%[e]

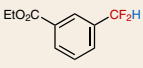

11, 70%

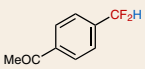

12, 70%[e]

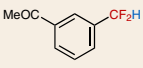

13, 76%

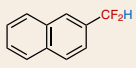

14, 73%, 60%[k]

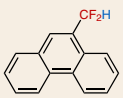

15, 70%[f]

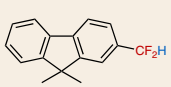

16, 70%[f]

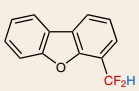

17, 65%[f]

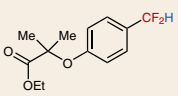

18, 60%[f]

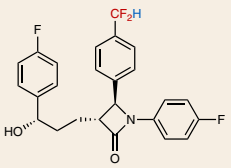

19, 63%


20, 74%[e]

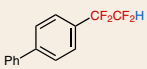

21, 65%

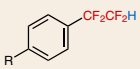

22, 75%

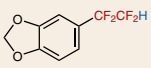

23, 50%[g]
(from clofibrate,
against cardiovascular disease)

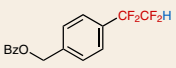

24, 65%[g]
(from ezetimibe, antiatherosclerosics)

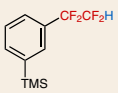
Conditions B[b]

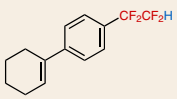

5, 64%

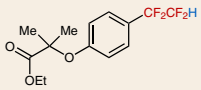

25, R = tBu, 74%
26, R = EtS, 50%


27, 63%

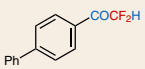

28, 50%[h]

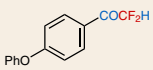

29, 65%

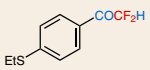

30, 61%

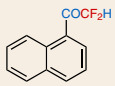

31, 70%
(from clofibrate,
against cardiovascular disease)

Conditions C[c]

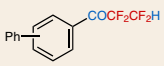

6, 54%

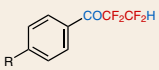

32, 55%[i]

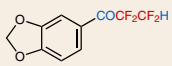

33, 60%[i]

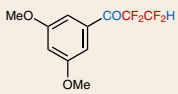

34, 41%

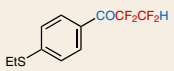
Conditions D[d]

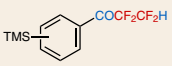

7, *p*-Ph, 70%
35, *m*-Ph, 73%

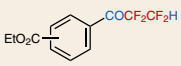

36, R = tBu, 60%
37, R = PhO, 67%

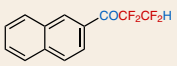

38, 50%

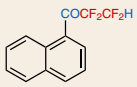

39, 65%

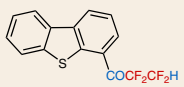

40, 62%


41, *p*-TMS, 60%
42, *m*-TMS, 64%, 55%[k]


43, *p*-CO_2Et, 61%[j]
44, *m*-CO_2Et, 61%[j]


45, 56%


46, 52%


47, 62%

48, 50%
(from clofibrate,
against cardiovascular disease)

49, 70%
(from ezetimibe, antiatherosclerosics)

50, 50%
(from δ-vitamin E, antioxidants)

Isolated yields are shown. [a]Conditions A: $x = 2.0$, $y = 11.5$, $z = 2.0$, $w = 1.0$, 100 °C. [b]Conditions B: $x = 3.0$, $y = 20$, $z = 3.0$, $w = 0$, 4 Å MS, 120 °C. [c]Conditions C: $x = 2.0$, $y = 11.5$, $z = 1.0$, $w = 0$, 80 °C, $W(CO)_6$ (25 mol%). [d]Conditions D: $x = 4.0$, $y = 20$, $z = 3.0$, $w = 1.0$, 80 °C. [e]Reaction run at 80 °C. [f]Using 1.0 equiv. of LiCl. [g]Using 2.0 equiv. of K_2CO_3. [h]Using 2.5 mol% $Pd_2(dba)_3$. [i]4,7-di-tBu-Xantphos was used. [j]Using 20 mol% 4,7-di-tBu-Xantphos and 70 mg of 4 Å MS without addition of H_2O. [k]Gram-scale synthesis.

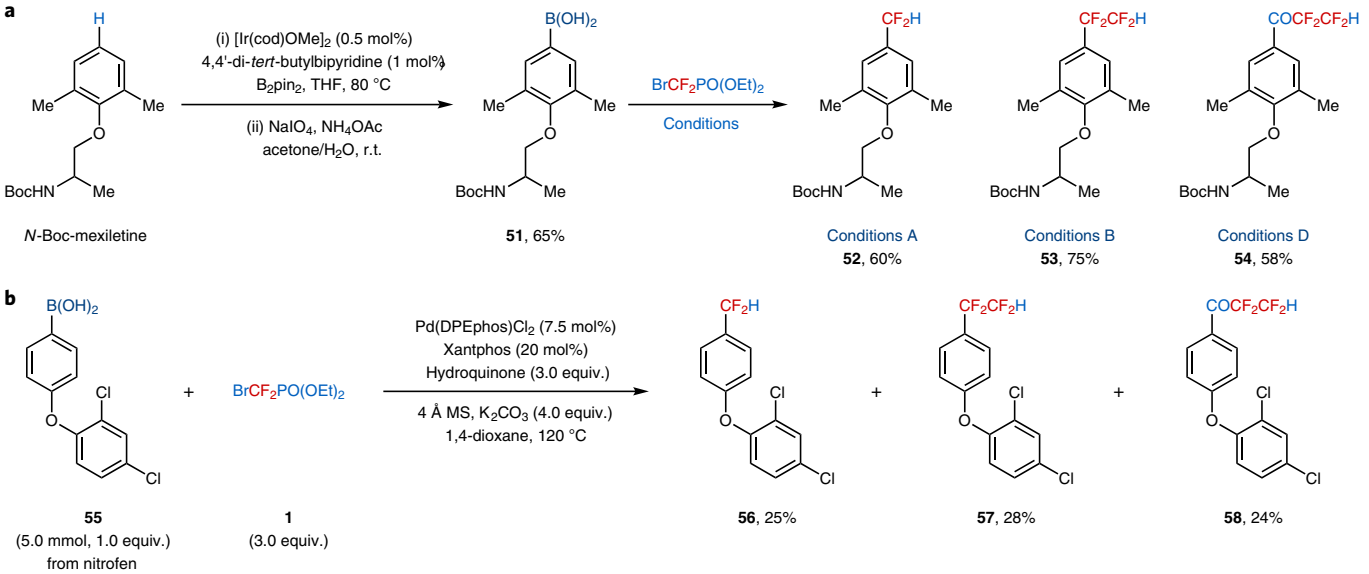


Fig. 2 | Diversified synthesis of fluoroalkylated arenes. a, Selective C–H bond borylation and fluoroalkylation of pharmaceuticals. Mexiletine, an anti-arrhythmic drug, can be readily modified to selectively provide three mexiletine analogues through the presented late-stage strategy. **b**, One-pot diversity-oriented modification of agrochemicals. Nitrofen, a herbicide, can be readily modified from one simple starting material to provide three diversified fluoroalkylated nitrofen analogues. Isolated yields are shown. B_2pin_2, 4,4,4′,4′,5,5,5,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane). DPEphos, (oxybis(2,1-phenylene))bis(diphenylphosphane).

Fig. 1). So far, metal difluorocarbene protonated by H_2O has not been reported[16,17,24–26]. This extreme nucleophilicity seems unique to the [Pd⁰]=CF_2 monomer, because the previously isolated palladium difluorocarbene trimer cannot react with H_2O (ref. [23]).

Density functional theory (DFT) calculations shed light on the nucleophilicity of [Pd⁰]=CF_2 (Fig. 4a). As shown in the calculated charge distributions (Fig. 4b), the electron density on the carbon of difluorocarbene increases substantially from the free difluorocarbene to complex **A** (0.07 atomic units (a.u.) versus −0.03 a.u.). This is possibly a result of electron donation from the occupied *d* orbital of palladium to the vacant *p* orbital of difluorocarbene[39], which is responsible for the property reversal of the difluorocarbene carbon from electrophilicity to nucleophilicity, and the carbene carbon can be attacked by a proton or other electrophiles. Indeed, the protonation of [Pd⁰]=CF_2 at the carbon site by arylboronic acid, via a four-membered ring transition state ($\mathbf{TS_{A\text{-}C'}}$), is ~20 kcal mol^{-1} more favourable over protonation at the palladium centre ($\mathbf{TS_{A\text{-}C'''}}$) (Fig. 4a), ruling out the pathway where a proton attacks at the metal centre, as observed with other nucleophilic M=CF_2 (refs. [16,24–26]). The barriers for the protonation of [Pd⁰]=CF_2 by hydroquinone or water are higher than that by phenylboronic acid. The prediction that the more strongly acidic arylboronic acid serves as a more favourable electrophile confirms the nature of the reaction. The more weakly acidic water and hydroquinone can also serve as proton donors under the current reaction conditions, as shown in Supplementary Fig. 2. The catalytic reactions of arylboronic acid **3** with $BrCF_2PO(OEt)_2$ can occur in the presence of deuterated hydroquinone or water, suggesting the highly nucleophilic activity of [Pd⁰]=CF_2.

The introduction of multiple CF_2 units was confirmed by the reaction of the *trans*-[(Xantphos)Pd^{II}(CF_2H)(Cl)] complex **C2** with difluorocarbene precursor $TMSCF_2Br$ (ref. [40] and Fig. 3c). On the basis of the DFT calculation (Fig. 4c), we assumed that [(HCF_2)(Xantphos)Pd^{II}=CF_2(OH)] complex **A′** is formed by the complexation of *trans*-[(Xantphos)Pd^{II}(CF_2H)(OH)] (***trans*-C**) with a difluorocarbene ligand[41], which is a thermodynamically favourable process (ΔG = −9.5 kcal mol^{-1} without barrier). Subsequently, **A′** overcomes a small barrier (6.8 kcal mol^{-1}) via $\mathbf{TS_{A'\text{-}E}}$ to afford the much more stable *trans*-[(Xantphos)Pd^{II}(CF_2CF_2H)(OH)] (**E**), which is −41.2 kcal mol^{-1} downhill from **A′**, providing the driving force for the CF_2 elongation. This CF_2 elongation shows a lower barrier than that for the transmetallation of arylboronic acid with difluoromethyl palladium complex **C** ($\mathbf{TS_{A'\text{-}E}}$ versus $\mathbf{TS_{\textit{trans}\text{-}C\text{-}\textit{cis}\text{-}D1}}$, Fig. 4c), thus enabling the difluorocarbene insertion to occur before transmetallation.

We also investigated the mechanism of the carbonylation reaction. We found that the [Pd^{II}]=CF_2 (with d^8) does exhibit electrophilicity and can generate CO easily when reacting with H_2O (Supplementary Fig. 5), suggesting that the CO to form tetrafluoroethylaryl ketones originates from the [Pd^{II}]=CF_2 species. This deduction was further supported by ^{18}O-labelling experiment (Fig. 3d and Supplementary Fig. 6) and DFT studies (Supplementary Fig. 10). Control experiments (Fig. 3e and Supplementary Fig. 7) and DFT calculations further identified that the carbonylation reaction occurs after the transmetallation of Pd^{II} fluoroalkyl species (**E**), and the CO insertion into the Pd–Ar σ bond is preferred over its insertion into the Pd–CF_2CF_2H σ bond by 22.6 kcal mol^{-1} (Fig. 4d).

Collectively, the experimental observations and DFT calculations are consistent with the aforementioned hypothesis (Fig. 1f). Arylboronic acid, H_2O or hydroquinone function as electrophiles for the protonation of nucleophilic [Pd⁰]=CF_2 at the carbene carbon, while H_2O serves as a nucleophile for the hydrolysis of electrophilic [Pd^{II}]=CF_2 to generate CO. Because difluorocarbene and CO insertions are more favourable than the transmetallation of [(Xantphos)Pd^{II}(CF_2H)(OH)] (**C**) ($\mathbf{TS_{A'\text{-}E}}$ versus $\mathbf{TS_{\textit{trans}\text{-}C\text{-}\textit{cis}\text{-}D1}}$) (Fig. 4c) and reductive elimination of [(Ar)(Xantphos)Pd^{II}(CF_2CF_2H)] (**G**) ($\mathbf{TS_{G1\text{-}H1}}$ versus $\mathbf{TS_{G1\text{-}P61}}$) (Fig. 4e), respectively, it makes the selective preparation of fluorinated compounds feasible. An outline of a possible mechanism for this controllable catalytic difluorocarbene transfer is provided in Fig. 5. The reaction begins with the formation of a [(Xantphos)Pd⁰=CF_2] species **A** between Pd⁰ and difluorocarbene, which is generated from the reaction of $BrCF_2PO(OEt)_2$ with hydroquinone in the presence of a base (Supplementary Fig. 9).

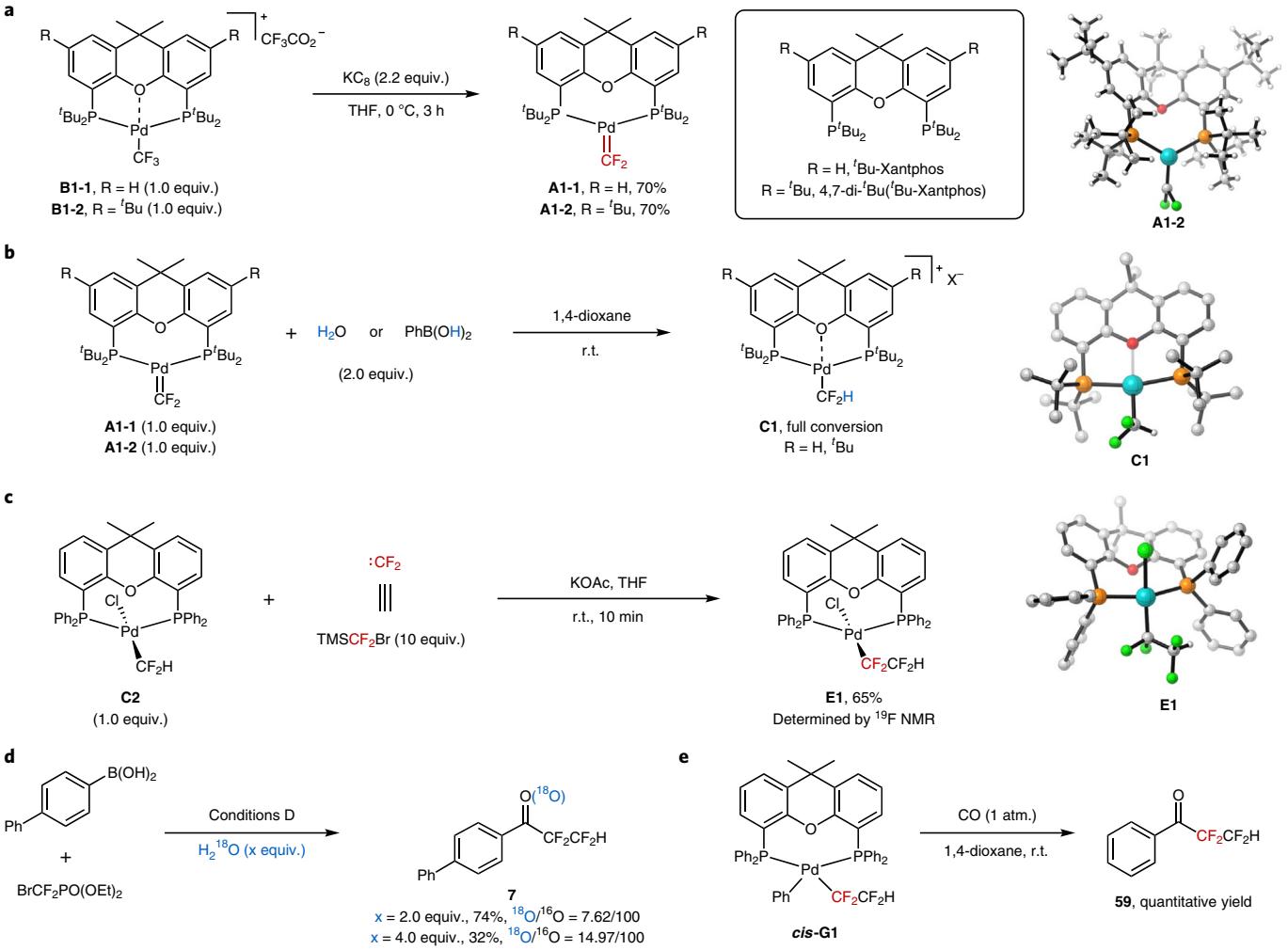


Fig. 3 | Mechanistic studies. a, Preparation of $[Pd^0]{=}CF_2$ complexes **A1** and single-crystal X-ray structure of $[Pd^0]{=}CF_2$ complex **A1-2**. **b**, Protonation of complex **A1** with H_2O or phenylboronic acid and single-crystal X-ray structure of difluoromethyl–palladium complex **C1**. The anions are not shown. **c**, Investigation of CF_2 elongation and the single-crystal X-ray structure of tetrafluoroethyl palladium complex **E1**. **d**, ^{18}O-labelling of compound **7**. A twofold loading amount of $H_2{}^{18}O$ almost doubled the ratio of ^{18}O-labelled **7**, indicating that the CO to form the tetrafluoroethyl aryl ketones is probably derived from the hydrolysis of $[Pd^{II}]{=}CF_2$. **e**, Reaction of *cis*-**G1** with CO. This reaction proceeded smoothly at room temperature to give the carbonylation product in quantitative yield, whereas the reaction of palladium complex **E1** with CO failed to provide the fluoroacyl palladium complex (Supplementary Fig. 7). These results suggest that the carbonylation step occurs after the transmetallation of complex **E1**. X denotes hydroxyl or other oxygen anions. Colour code: grey, carbon; white, hydrogen; blue, palladium; orange, phosphorus; red, oxygen; green, fluorine.

Subsequently, protonation of **A** at the difluorocarbene ligand provides the key intermediate $[(Xantphos)Pd^{II}(CF_2H)(OH)]$ (**C**). As a competitive process to CF_2 elongation, **C** undergoes transmetallation and reductive elimination to afford $ArCF_2H$, depending on the tuning of the reaction conditions (Supplementary Figs. 8, 11 and 12). Difluorocarbene insertion by the reaction of difluorocarbene with **C** affords $[(HCF_2)(Xantphos)Pd^{II}{=}CF_2(OH)]$ complex **A′**. Complex **A′** subsequently undergoes intramolecular difluoromethyl migration to generate the CF_2 elongated complex $[(Xantphos)Pd^{II}(CF_2CF_2H)(OH)]$ (**E**). Complex **E** undergoes transmetallation to deliver the key intermediate $[(Ar)(Xantphos)Pd^{II}(CF_2CF_2H)]$ (**G**). Reductive elimination of **G** affords tetrafluoroethylated arenes. Insertion of CO into the Pd–Ar σ bond of **G**, in which CO is derived from hydrolysis of $[Pd^{II}]{=}CF_2$, followed by reductive elimination, provides tetrafluoroethyl ketones. The key intermediate **C** may also undergo a similar pathway to produce difluoromethyl ketones (Supplementary Figs. 8 and 13). Because the barrier for the formation of $[(Ar)(Xantphos)Pd^{II}(CF_2H)]$ (**D**), a key intermediate for the production of difluoromethyl ketone, is 11.1 kcal mol^{-1} higher than that for the CF_2 elongation step from **C** (Fig. 4c), it is relatively difficult to selectively control the production of the desired difluoromethyl ketone while suppressing the difluorocarbene insertion products in the presence of excessive difluorocarbene. As a result, an additional CO source and lower concentration of difluorocarbene is required to furnish the difluoromethyl ketone (Supplementary Figs. 13 and 14).

In conclusion, a controllable way to synthesize difluoromethyl-, tetrafluoroethyl-, difluoroacetyl- or tetrafluoropropanoyl arenes from arylboronic acids has been developed and explored mechanistically. The ready availability of these compounds is made possible by harnessing metal difluorocarbene chemistry, opening a new chapter in the preparation of fluorinated derivatives of potential value in the pharmaceutical industry.

Methods

All calculations were performed using the Gaussian 09 suite of programs[42]. Geometry optimizations and frequencies were calculated with the B3LYP density functional[43–45] and a mixed basis set of LANL2DZ[46] for Pd and 6–31G(d)[47] for other

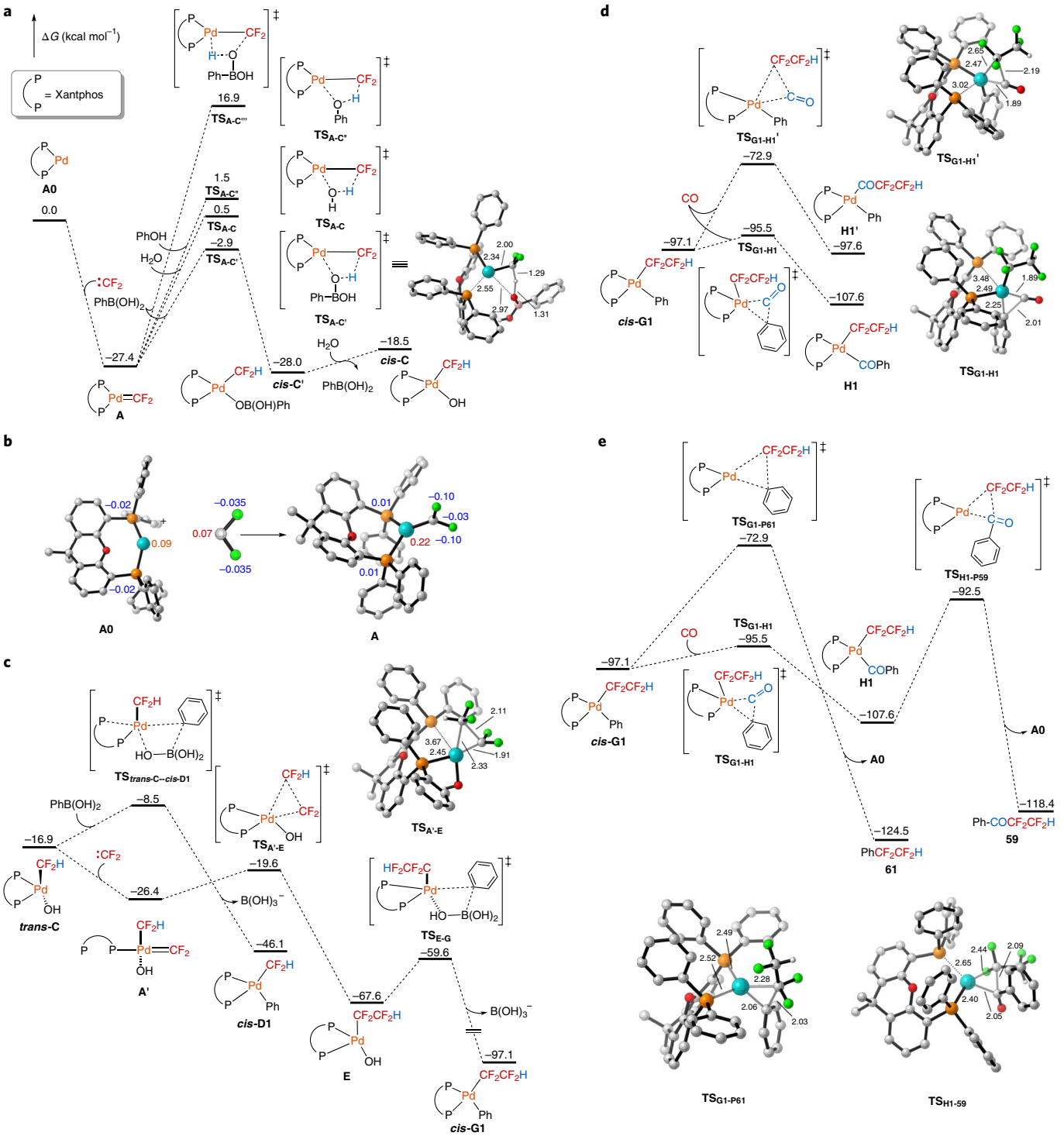


Fig. 4 | Calculated energy profile of the palladium-catalysed difluorocarbene transfer reactions. a, DFT-computed reaction pathways and optimized key transition state structures for protonation of [(Xantphos)Pd^0=CF_2] **A**. Here, we chose *cis*-[(Xantphos)$Pd^{II}(CF_2H)(OH)$] (***cis*-C**) as the protonation intermediate in calculations (also in **c**), because its transmetallation has a lower barrier than the direct transmetallation of [(HCF_2)(Xantphos)Pd^{II}[PhB(OH)O]] (***cis*-C′**) (Supplementary Figs. 11 and 12). **b**, Computed charge model 5 (CM-5) charges of (Xantphos)Pd, difluorocarbene and [(Xantphos)Pd^0=CF_2] **A**. **c**, Free energy barrier differences between difluorocarbene insertion and transmetallation of ***trans*-C**. **d**, DFT-computed reaction pathways and optimized key transition state structures for insertion of CO into complex **G1**. **e**, Free energy barrier differences between reductive elimination and CO insertion of complex **G1**. Colour code: grey, carbon; white, hydrogen; blue, palladium; orange, phosphorus; red, oxygen; green, fluorine; pink, boron. All energies are reference to A0.

atoms, in conjunction with the SMD[48] implicit solvation model to account for the solvation effects of dioxane. Optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) or transition structures (a single imaginary frequency) at the same level of theory. More accurate electronic energies were obtained by single-point energy calculations at the SMD-M06[49,50]/6–311++G(d,p)+SDD(Pd)[51,52] level of theory. All Gibbs energies in solution reported throughout the text are in kcal mol^{-1}, and the bond lengths are in ångstroms (Å). The structures were generated by CYLview[53].

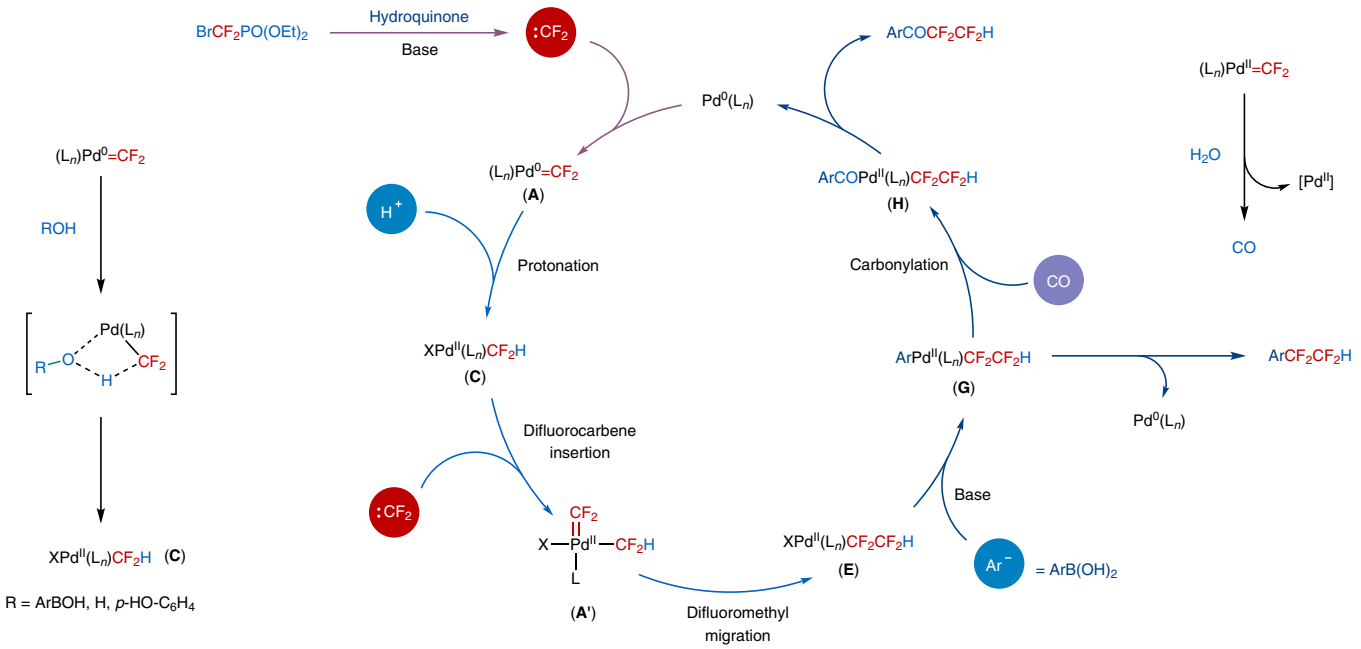


Fig. 5 | Outline of a possible pathway for controllable palladium-catalysed difluorocarbene transfer. The reaction is initiated by the formation of palladium(0) difluorocarbene complex **A**, in which the difluorocarbene is generated by the reaction of $BrCF_2PO(OEt)_2$ with hydroquinone in the presence of base. Subsequent protonation at the difluorocarbene carbon of **A** gives the key intermediate **C**, which is illustrated in more detail at the lower left of the figure. As a process competitive to CF_2 elongation, **C** undergoes transmetallation and reductive elimination to produce $ArCF_2H$, depending on the tuning of the reaction conditions (Supplementary Figs. 8, 11 and 12). Difluorocarbene insertion into **C** forms palladium difluorocarbene complex **A′**, and then intermolecular difluoromethyl migration generates CF_2 elongated complex **E**. Subsequent transmetallation of **E** produces complex **G**, which undergoes reductive elimination to provide tetrafluoroethylated arenes. Alternatively, insertion of CO, which originates from the hydrolysis of $[Pd^{II}]=CF_2$ (as shown in the upper right of the figure), into the Pd–Ar σ bond of **G**, followed by reductive elimination, gives tetrafluoroethyl aryl ketones. In another competitive reaction, the key intermediate **C** may also undergo carbonylation to afford difluoromethyl aryl ketones (Supplementary Figs. 8 and 13). For simplicity, all palladium complexes are illustrated as neutral species, and all processes are depicted as being irreversible. L_n denotes Xantphos coordinated to palladium.

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Center under deposition numbers CCDC 1902891 (**B1-1**), 1916606 (**B1-2**), 1916607 (**A1-2**), 1902894 (**C1-1a**), 1902898 (**C2**), 1902901 (**E1**) and 1902900 (*cis*-**G1**). Copies of the data can be obtained free of charge from https://www.ccdc.cam.ac.uk/strucutres/. All other data supporting the findings of this study are available within the Article and its Supplementary Information, or from the corresponding author upon reasonable request.

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References

1. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications* 2nd edn (Wiley-VCH, 2013).
2. Brahms, D. L. S. & Dailey, W. P. Fluorinated carbenes. *Chem. Rev.* **96**, 1585–1632 (1996).
3. Ni, C. & Hu, J. Recent advances in the synthetic application of difluorocarbene. *Synthesis* **46**, 842–863 (2014).
4. Hudlicky, M. & Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II* (American Chemical Society, 1995).
5. Miller, T. G. & Thanassi, J. W. The preparation of aryl difluoromethyl ethers. *J. Org. Chem.* **25**, 2009–2012 (1960).
6. Hohlfeld, J. M. et al. Roflumilast attenuates pulmonary inflammation upon segmental endotoxin challenge in healthy subjects: a randomized placebo-controlled trial. *Pulm. Pharmacol. Ther.* **21**, 616–623 (2008).
7. Dolbier, W. R. Jr. & Battiste, M. A. Structure, synthesis and chemical reactions of fluorinated cyclopropanes and cyclopropenes. *Chem. Rev.* **103**, 1071–1098 (2003).
8. Burch, J. D. et al. Tetrahydroindazoles as interleukin-2 inducible T-cell kinase inhibitors. Part II. Second-generation analogues with enhanced potency, selectivity and pharmacodynamic modulation in vivo. *J. Med. Chem.* **58**, 3806–3816 (2015).
9. Fuqua, S. A., Duncan, W. G. & Silverstein, R. M. A one-step synthesis of 1,1-difluoroolefins from aldehydes by a modified Wittig synthesis. *Tetrahedron Lett.* **5**, 1461–1463 (1964).
10. MacNeil, J. G.Jr & Burton, D. J. Generation of trifluoromethylcopper from chlorodifluoroacetate. *J. Fluor. Chem.* **55**, 225–227 (1991).
11. Duan, J.-X., Su, D.-B. & Chen, Q.-Y. Trifluoromethylation of organic halides with methyl halodifluoroacetates—a process via difluorocarbene and trifluoromethide intermediates. *J. Fluor. Chem.* **61**, 279–284 (1993).
12. Huiban, M. et al. A broadly applicable [^{18}F]trifluoromethylation of aryl and heteroaryl iodides for PET imaging. *Nat. Chem.* **5**, 941–944 (2013).
13. Levin, M. D. et al. A catalytic fluoride-rebound mechanism for C(sp^3)–CF_3 bond formation. *Science* **356**, 1272–1276 (2017).
14. Dilman, A. D. & Levin, V. V. Difluorocarbene as a building block for consecutive bond-forming reactions. *Acc. Chem. Res.* **51**, 1272–1280 (2018).
15. Reger, D. L. & Dukes, M. D. Molybdenum perfluorocarbene complexes. *J. Organomet. Chem.* **153**, 67–72 (1978).
16. Brothers, P. J. & Roper, W. R. Transition-metal dihalocarbene complexes. *Chem. Rev.* **88**, 1293–1326 (1988).
17. Harrison, D. J., Gorelsky, S. I., Lee, G. M., Korobkov, I. & Baker, R. T. Cobalt fluorocarbene complexes. *Organometallics* **32**, 12–15 (2013).
18. Harrison, D. J., Daniels, A. L., Korobkov, I. & Baker, R. T. d^{10} nickel difluorocarbenes and their cycloaddition reactions with tetrafluoroethylene. *Organometallics* **34**, 5683–5686 (2015).
19. Trnka, T. M., Day, M. W. & Grubbs, R. H. Olefin metathesis with 1,1-difluoroethylene. *Angew. Chem. Int. Ed.* **40**, 3441–3444 (2001).
20. Takahira, Y. & Morizawa, Y. Ruthenium-catalyzed olefin cross-metathesis with tetrafluoroethylene and analogous fluoroolefins. *J. Am. Chem. Soc.* **137**, 7031–7034 (2015).
21. Feng, Z., Min, Q.-Q. & Zhang, X. Access to difluoromethylated arenes by Pd-catalyzed reaction of arylboronic acids with bromodifluoroacetate. *Org. Lett.* **18**, 44–47 (2016).
22. Feng, Z., Min, Q.-Q., Fu, X.-P., An, L. & Zhang, X. Chlorodifluoromethane-triggered formation of difluoromethylated arenes catalysed by palladium. *Nat. Chem.* **9**, 918–923 (2017).
23. Deng, X.-Y., Lin, J.-H. & Xiao, J.-C. Pd-catalyzed transfer of difluorocarbene. *Org. Lett.* **18**, 4384–4387 (2016).
24. Clark, G. R., Hoskins, S. V., Jones, T. C. & Roper, W. R. Oxidation state control of the reactivity of a transition metal–carbon double bond. Synthesis,

X-ray crystal structure, and reactions of the zerovalent difluorocarbene complex $[Ru(=CF_2)(CO)_2(PPh_3)_2]$. *J. Chem. Soc. Chem. Commun.* 719–721 (1983).
25. Brothers, P. J., Burrell, A. K., Clark, G. R., Rickard, C. E. F. & Roper, W. R. Trifluoromethyl, difluorocarbene and tetrafluoroethylene complexes of iridium and the crystal structures of $IrI(CH_3)(CF_3)(CO)(PPh_3)_2$, $Ir(CF_3)(C_2F_4)(CO)(PPh_3)_2$ and $Ir(CF_3)(CF_2)(CO)(PPh_3)_2$. *J. Organomet. Chem.* **394**, 615–642 (1990).
26. Hughes, R. P. et al. A simple route to difluorocarbene and perfluoroalkylidene complexes of iridium. *J. Am. Chem. Soc.* **127**, 15020–15021 (2005).
27. Negishi, E. & de Meijere, A. *Handbook of Organopalladium Chemistry for Organic Synthesis* 2nd edn (Wiley, 2002).
28. Yang, Z.-Y., Wiemers, D. M. & Burton, D. J. Trifluoromethylcopper: a useful difluoromethylene transfer reagent: a novel double insertion of difluoromethylene into pentafluorophenylcopper. *J. Am. Chem. Soc.* **114**, 4402–4403 (1992).
29. Zafrani, Y., Sod-Moriah, G. & Segall, Y. Diethyl bromodifluoromethylphosphonate: a highly efficient and environmentally benign difluorocarbene precursor. *Tetrahedron* **65**, 5278–5283 (2009).
30. Cordaro, J. G. & Bergman, R. G. Dissociation of carbanions from acyl iridium compounds: an experimental and computational investigation. *J. Am. Chem. Soc.* **126**, 16912–16929 (2004).
31. Fujiwara, Y. et al. A new reagent for direct difluoromethylation. *J. Am. Chem. Soc.* **134**, 1494–1497 (2012).
32. Fier, P. S. & Hartwig, J. F. Copper-mediated difluoromethylation of aryl and vinyl iodides. *J. Am. Chem. Soc.* **134**, 5524–5527 (2012).
33. Gu, Y., Leng, X. & Shen, Q. Cooperative dual palladium/silver catalyst for direct difluoromethylation of aryl bromides and iodides. *Nat. Commun.* **5**, 5405 (2014).
34. Xu, L. & Vicic, D. A. Direct difluoromethylation of aryl halides via base metal catalysis at room temperature. *J. Am. Chem. Soc.* **138**, 2536–2539 (2016).
35. Meanwell, N. A. Synopsis of some recent tactical application of bioisosteres in drug design. *J. Med. Chem.* **54**, 2529–2591 (2011).
36. Erickson, J. A. & McLoughlin, J. I. Hydrogen bond donor properties of the difluoromethyl group. *J. Org. Chem.* **60**, 1626–1631 (1995).
37. Vaclavik, J., Klimankova, I., Budinska, A. & Beier, P. Advances in the synthesis and application of tetrafluoroethylene- and 1,1,2,2-tetrafluoroethyl-containing compounds. *Eur. J. Org. Chem.* **2018**, 3554–3593 (2018).
38. Ishiyama, T. et al. Mild iridium-catalyzed borylation of arenes. High turnover numbers, room temperature reactions and isolation of a potential intermediate. *J. Am. Chem. Soc.* **124**, 390–391 (2002).
39. Jean, Y. *Molecular Orbitals of Transition Metal Complexes* (Oxford Univ. Press, 2005).
40. Li, L., Wang, F., Ni, C. & Hu, J. Synthesis of *gem*-difluorocyclopropa(e)nes and O-, S-, N- and P-difluoromethylated compounds with $TMSCF_2Br$. *Angew. Chem. Int. Ed.* **52**, 12390–12394 (2013).
41. Pu, M. I., Sanhueza, A., Senol, E. & Schoenebeck, F. Divergent reactivity of stannane and silane in the trifluoromethylation of Pd^{II}: cyclic transition state versus difluorocarbene release. *Angew. Chem. Int. Ed.* **57**, 15081–15085 (2018).
42. Frisch, M. J. et al. Gaussian 09, revision D.01 (Gaussian, 2009).
43. Lee, C., Yang, W. & Parr, R. G. Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B.* **37**, 785–789 (1988).
44. Becke, A. D. Density functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **98**, 5648–5652 (1993).
45. Becke, A. D. A new mixing of Hartree–Fock and local density-functional theories. *J. Chem. Phys.* **98**, 1372–1377 (1993).
46. Hay, P. J. & Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* **82**, 299–310 (1985).
47. Hehre, W. J., Ditchfield, R. & Pople, J. A. Self-consistent molecular orbital methods. XII. Further extensions of Gaussian-type basis sets for use in molecular orbital studies of organic molecules. *J. Chem. Phys.* **56**, 2257–2261 (1972).
48. Marenich, A. V., Cramer, C. J. & Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **113**, 6378–6396 (2009).
49. Zhao, Y. & Truhlar, D. G. Density functionals with broad applicability in chemistry. *Acc. Chem. Res.* **41**, 157–167 (2008).
50. Zhao, Y. & Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **120**, 215–241 (2008).
51. Andrae, D., Haussermann, U., Dolg, M., Stoll, H. & Preuss, H. Energy-adjusted ab initio pseudo potentials for the second and third row transition elements. *Theor. Chim. Acta* **77**, 123–141 (1990).
52. Dolg, M., Wedig, U., Stoll, H. & Preuss, H. Energy-adjusted ab initio pseudo potentials for the first row transition elements. *J. Chem. Phys.* **86**, 866–872 (1987).
53. Legault, C. Y. CYLview, 1.0b (Université de Sherbrooke, 2009); http://www.cylview.org.

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Author contributions

X.Z. and X.-P.F. conceived and designed the experiments. X.Z. directed the project. X.-P.F. performed the experiments and mechanism studies. X.-S.X. conducted the DFT calculations and contributed parts of the mechanism analysis. K.N.H. directed the DFT calculations. X.-Y.Z. conducted parts of the mechanistic studies. Y.-L.G. conducted MS analysis of the palladium complexes. X.L. analysed the X-ray crystal structure of the palladium difluorocarbene complex. X.-P.F., Y.-L.X. and X.Z. analysed the data. X.Z., X.-S.X., S.Z. and K.N.H. co-wrote the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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