LETTER

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Palladium-catalysed electrophilic aromatic C–H fluorination

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Aryl fluorides are widely used in the pharmaceutical and agrochemical industries[1,2], and recent advances have enabled their synthesis through the conversion of various functional groups. However, there is a lack of general methods for direct aromatic carbon–hydrogen (C–H) fluorination[3]. Conventional methods require the use of either strong fluorinating reagents, which are often unselective and difficult to handle, such as elemental fluorine, or less reactive reagents that attack only the most activated arenes, which reduces the substrate scope. A method for the direct fluorination of aromatic C–H bonds could facilitate access to fluorinated derivatives of functional molecules that would otherwise be difficult to produce. For example, drug candidates with improved properties, such as increased metabolic stability or better blood–brain-barrier penetration, may become available. Here we describe an approach to catalysis and the resulting development of an undirected, palladium-catalysed method for aromatic C–H fluorination using mild electrophilic fluorinating reagents. The reaction involves a mode of catalysis that is unusual in aromatic C–H functionalization because no organometallic intermediate is formed; instead, a reactive transition-metal-fluoride electrophile is generated catalytically for the fluorination of arenes that do not otherwise react with mild fluorinating reagents. The scope and functional-group tolerance of this reaction could provide access to functional fluorinated molecules in pharmaceutical and agrochemical development that would otherwise not be readily accessible.

Conventional methods for aromatic fluorination require elemental fluorine or similarly reactive reagents, which are unselective and require specialized equipment to handle safely[4]. Bench-stable electrophilic fluorinating reagents—such as *N*-fluoropyridinium salts, *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor—are easier to handle but less reactive, and require either very electron-rich arenes or multiple equivalents of the arene to accomplish direct C–H fluorination[5,6]. Catalysis of aromatic C–H fluorination reactions has been reported using coordination-assistance to promote fluorination proximal to Lewis-basic functional groups, but such approaches are limited in scope to those substrates containing the required directing groups[7–10]. Advances in aliphatic C–H fluorination have been made[11], but currently there is no method for direct aromatic C–H fluorination with broad scope.

In our investigation into the catalysis of aromatic C–H fluorination reactions, we sought an approach that was distinct from the common C–H activation sequence in which C–H metalation precedes functionalization; with few exceptions[12–14], the conventional approach[15] requires multiple equivalents of the arene substrate to promote C–H metalation in the absence of a coordinating directing group. Instead, we sought to design catalysts with ancillary ligands that would favour the oxidation of the complex before any interaction with the substrate, giving rise to a reactive, high-valent metal-fluoride intermediate that is electrophilic at fluorine and capable of oxidative fluorine transfer to arenes. We designed the Pd(II) complex **1**, ligated simultaneously by a tridentate (terpyridine, terpy) and a bidentate (2-chloro-1,10-phenanthroline, 2-Cl-phen) ligand, which would be oxidized by electrophilic fluorinating reagents to yield the desired Pd(IV)–F complex **2** (Fig. 1b). The oxidation of doubly cationic **1** is promoted by a destabilizing interaction between the lone pair of the apical donor atom and the filled d_{z^2} orbital on Pd(II), which is readily apparent in the highest occupied molecular orbital of **1** as calculated by density functional theory (DFT) (Fig. 1c). X-ray diffraction corroborates the apical interaction: the

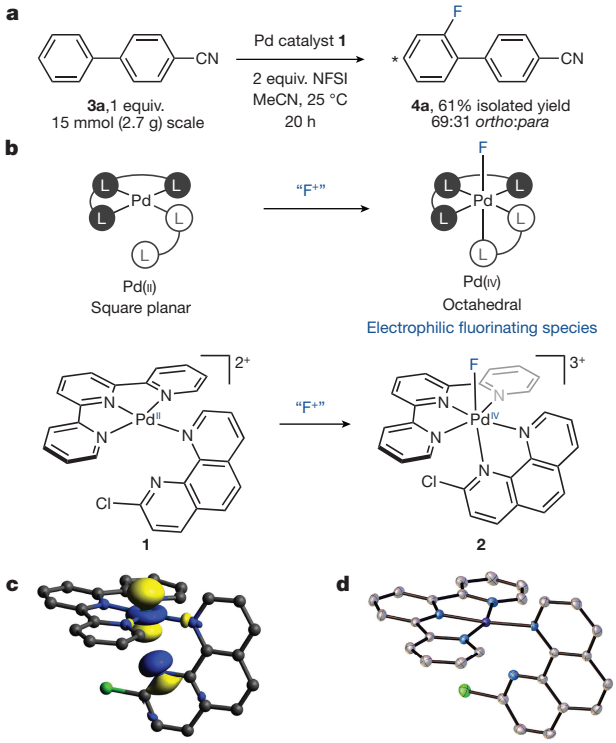

Figure 1 | Aromatic fluorination catalysed by 1. a, Palladium catalyst **1** enables the direct, non-chelation-assisted fluorination of 4-cyanobiphenyl. **b**, Oxidation of Pd(II) complex **1**, assisted by the ligand combination of terpy and 2-Cl-phen, yields the triply cationic Pd(IV)–F electrophile **2**. **c**, The highest occupied molecular orbital of **1**, as calculated by DFT, showing destabilizing orbital interaction. Hydrogen atoms are omitted for clarity. Calculations at the CPCM(MeCN)TPSS0 D3/def2-QZVP//PBE0 D3/def2-TZVP level of theory; iso = 0.05. **d**, X-ray crystal structure of **1**, shown with 50%-probability ellipsoids. Hydrogen atoms and solvent molecules are omitted for clarity.

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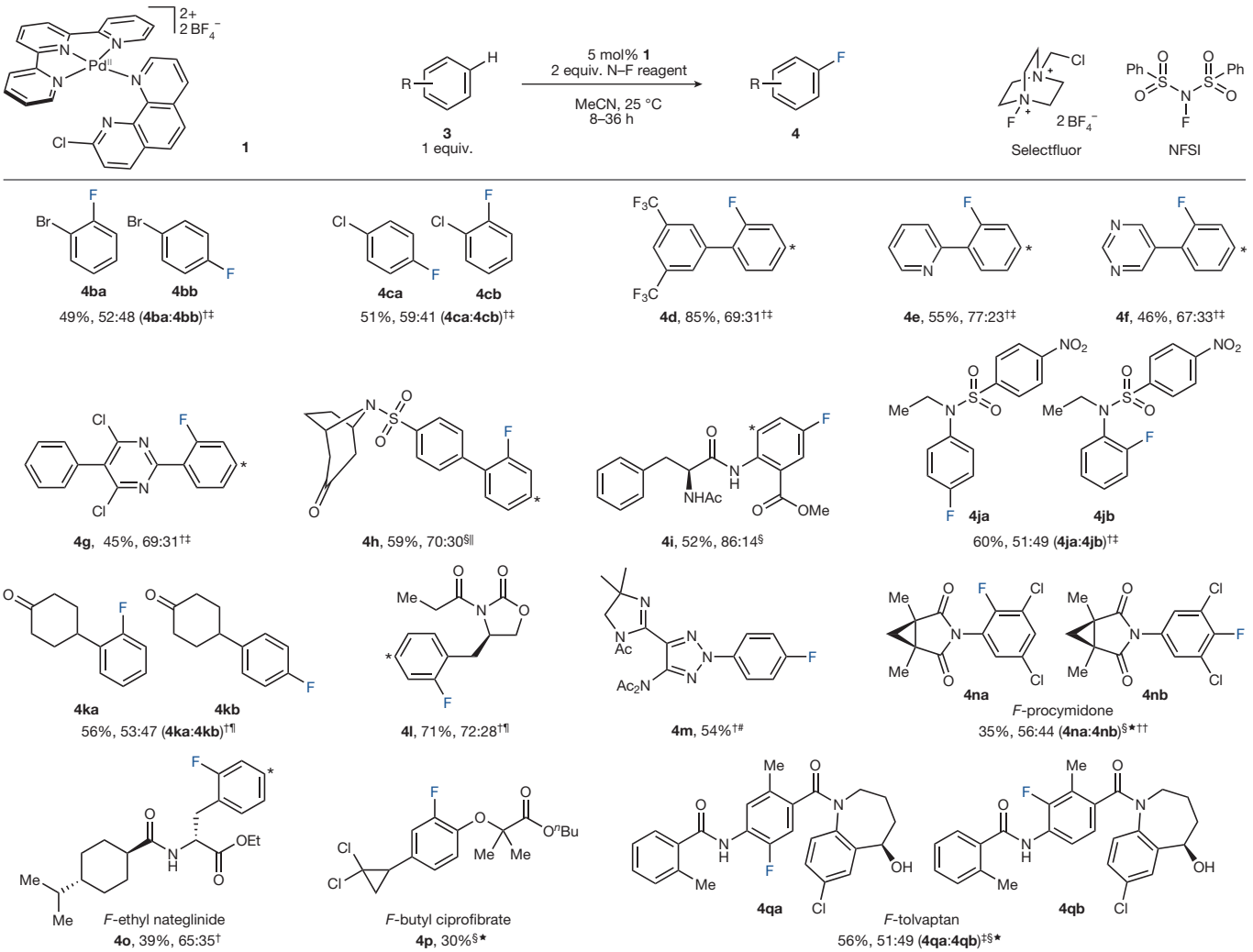

Figure 2 | Substrate scope of the Pd-catalysed fluorination of arenes. Reaction conditions: arene, 1 mmol; catalyst **1,** 5 mol%; Selectfluor or NFSI, 2 equiv.; MeCN, 0.1 M. All isomers of non-volatile products have been isolated and characterized as analytically pure samples. The asterisk denotes the site of fluorination of the constitutional isomer that is not shown. Overall yields and the ratio of the constitutional isomers are based on ^{19}F NMR integration of reaction mixtures with internal standard. †Reaction performed with Selectfluor. ‡Reaction performed at 50 °C. §Reaction performed with NFSI. ‖Reaction performed with 1,2-dichloroethane and MeCN (1:1, 0.1 M). ¶Reaction performed at 0 °C. #10 mol% catalyst **1** was used. ⋆7.5 mol% catalyst **1** was used. ††Reaction performed at 80 °C.

Pd–N distance in the X-ray structure of **1** (Fig. 1d) is 2.6 Å, which is 1.2 Å shorter than the sum of the van der Waals radii of Pd and N (ref. 16).

Complex **1** is a competent catalyst for the fluorination of various arenes by either Selectfluor or NFSI. The substrates shown in Fig. 2 underwent fluorination in the presence of **1** at room temperature or at 50 °C, but little background reactivity was observed in the absence of **1** under otherwise identical conditions (maximum <1% yield) or even under reflux in acetonitrile (maximum 21% yield). In our studies, catalyst **1** was formed *in situ* from $[Pd(terpy)(MeCN)](BF_4)_2$ and 2-Cl-phen, but it can also be generated by combining the commercially available palladium source $[Pd(MeCN)_4](BF_4)_2$ and the ligands before the addition of the reactants. Compatible functional groups include nitriles (**3a**), aryl bromides (**3b**), chlorides (**3c**, **3g**, **3n**, **3p**, **3q**), certain heterocycles (**3e**–**3g**, **3m**), sulfonamides (**3h**, **3j**), ketones (**3h**, **3k**), amides (**3i**, **3l**–**3o**, **3q**), esters (**3i**, **3o**, **3p**), carbamates (**3l**), ethers (**3p**) and free hydroxy groups (**3q**). Five-membered heteroarenes containing nitrogen (**3m**) can be tolerated, but oxidatively labile functional groups such as amines and thiols cannot, owing to their general incompatibility with electrophilic fluorinating reagents. Electron-deficient arenes such as **3b**–**3d** are not successfully fluorinated through conventional methodologies, but are suitable substrates for fluorination via catalysis with **1**. However, more electron-deficient arenes, such as methyl benzoate, are insufficiently reactive and undergo little or no conversion.

Structurally complex substrates—such the pesticide procymidone (**3n**), the type-2 diabetes drug nateglinide (**3o**), the lipid-lowering agent ciprofibrate (**3p**) and the hyponatremia drug tolvaptan (**3q**)—were fluorinated directly via catalysis with **1**. Although fluorine can impart desirable properties on pharmaceuticals and agrochemicals, fluorinated analogues of structurally complex molecules can currently be difficult to access; conventional fluorination methods failed to provide the fluorinated products shown in Fig. 2.

In most cases, the fluorination reaction affords mixtures of at least two constitutional isomers, resulting from similar rates of fluorination at the positions *ortho* and *para* to the aromatic substituents. Purification of aryl fluoride products from mixtures of their constitutional isomers and the starting material is often challenging[17,18]. However, the isolation and characterization of all the non-volatile products obtained here has been achieved, although optimization of the separation protocol was required for each substrate. For example, the *ortho*- and *para*-fluorinated products of the gram-scale fluorination of 4-cyanobiphenyl have been separated in 61% isolated yield (Fig. 1a). Although high positional selectivity is generally desired in C–H functionalization reactions, mixtures of constitutional isomers can be advantageous for some applications. For example, in the late-stage derivatization of drug candidates, each product isomer is an additional derivative that can be obtained without the need for costly and laborious *de novo* synthesis[19,20]. Fluorinated tolvaptan

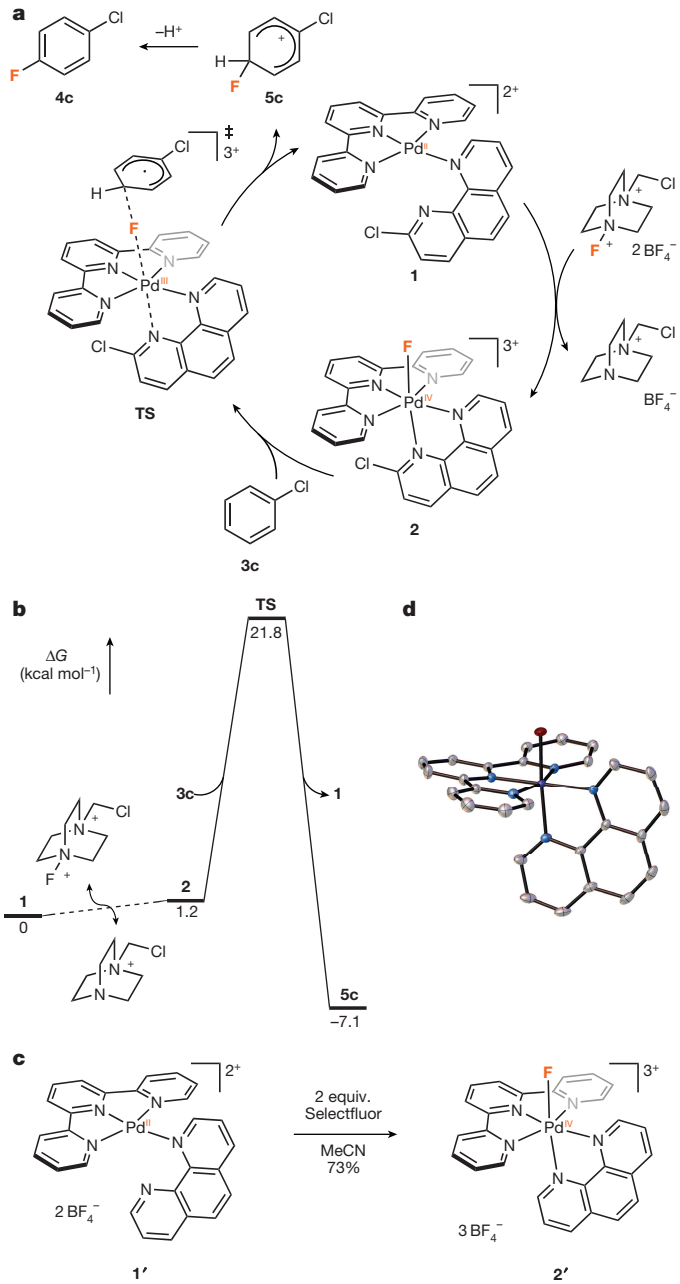

Figure 3 | Mechanism of fluorination catalysed by 1. a, The proposed catalytic cycle for the fluorination of chlorobenzene (**3c**). **b**, Energy-level diagram of the proposed catalytic cycle with chlorobenzene (**3c**); energies calculated by DFT. **c**, Synthesis of Pd(IV)–F complex **2′** via the oxidation of **1′** by Selectfluor. **d**, X-ray crystal structure of **2′**, shown with 50%-probability ellipsoids. Pd–F bond length: measured, 1.9120(7) Å; calculated, 1.89 Å.

(**4q**), for example, would be challenging and time-consuming to prepare with conventional chemistry through *de novo* syntheses. Late-stage fluorination, even with the requirement for a custom-made separation protocol, can conveniently produce promising new candidates that may have never been evaluated otherwise.

The proposed mode of action of **1** is highly unusual in the catalysis of aromatic oxidation reactions: conceptually, an activated electrophile is generated *in situ* from **1**, in the form of Pd(IV)–F intermediate **2**. The activated Pd(IV)–F electrophile **2** would therefore be capable of electrophilic fluorination of weakly nucleophilic arenes that cannot be fluorinated directly by Selectfluor and NFSI (Fig. 3a)[21,22]. A DFT analysis of the aryl fluorination reaction suggests a mechanism that is accessible to Pd(IV)–F **2** but not to Selectfluor or NFSI. On the basis of these results, we hypothesize that the fluorination mechanism proceeds through a single transition state via fluoride-coupled electron transfer (Fig. 3a, b).

Selectfluor fluorinates only electron-rich arenes such as anisole[23]; complex **1**, conversely, is able to catalyse the fluorination of electron-deficient arenes such as chlorobenzene. DFT calculations suggest that Pd(IV)–F **2** has a higher single-electron reduction potential than that of Selectfluor, although both compounds have a similar thermodynamic driving force for electrophilic fluorination. The transition state **TS** of the fluorination of chlorobenzene with Pd(IV)–F **2** shows high spin-density on the Pd as well as on the aryl carbon atoms. As such, the transition state is most appropriately characterized as a singlet diradical; two subsequent fluoride-coupled electron transfers occur asynchronously as the reaction proceeds through a single transition state. The mechanism is reminiscent of that previously reported for the fluorination of enamines and organometallic reagents with an isolated Pd(IV)–F (ref. 24). The calculated energy barrier for electrophilic fluorination of 21.8 kcal mol^{-1} (Fig. 3b) is in agreement with the observed reaction time and the temperature of the reaction (as discussed below, see Supplementary Information for details).

We sought to produce Pd(IV)–F complex **2**, to verify our design principle as well as to investigate the reactivity of **2** with arenes. Treatment of **1** with XeF_2 in the presence of $LiBF_4$ produced a ^{19}F NMR signal attributable to **2** at $\delta = -258.6$ p.p.m.; however, complex **2** is reduced to **1** in acetonitrile solution, even in the absence of substrate, which hindered our attempts at isolation. Treatment of **1** with Selectfluor over a range of temperatures (−40 °C to 25 °C) resulted in the desired reduction of Selectfluor, but did not produce a ^{19}F NMR signal that could be attributed to a Pd(IV)–F species, presumably because **2** is reduced faster than it is formed under these conditions, and therefore does not accumulate in observable quantities.

Complex **1′**, in which 2-Cl-phen is replaced with unsubstituted phenanthroline (phen), is a competent catalyst for aromatic fluorination, although not as effective as catalyst **1**. When **1′** was treated with Selectfluor in acetonitrile at room temperature and then allowed to stand at −35 °C, the Pd(IV)–F complex **2′** (^{19}F NMR −259.5 p.p.m.) precipitated in 73% yield (Fig. 3c). Complex **2′** is sufficiently stable at low temperature to enable characterization and reactivity studies. The higher stability of **2′** as compared to **2** is understood to result from the greater electron-donating ability of phen relative to that of 2-Cl-phen. Likewise, the greater reactivity of **2** may explain why the 2-Cl-phen-ligated complex **1** outperforms the phen-ligated **1′** in terms of catalytic ability.

Pd(IV)–F complex **2′** reacts with arenes to yield fluorinated products (Fig. 4). For example, 4-cyanobiphenyl (**3a**), when treated with **2′** in acetonitrile, yielded a 66:34 ratio of *ortho*- and *para*-fluoro isomers in 63% overall yield. The positional selectivity of fluorination by **2′** is similar to that observed in fluorination catalysed by **1′** (69:31 *ortho*:*para*), consistent with **2′** being the C–F-bond-forming species in catalysis by **1′**. These selectivity ratios are, in turn, similar to that observed upon fluorination with the optimal 2-Cl-phen-ligated catalyst **1** (71:29 *ortho*:*para*). We cannot rule out the involvement of a different C–F bond-forming pathway in catalysis by **1** (for example, through a Pd(III) species); however, the similar positional selectivities observed in fluorination catalysed by **1**, fluorination catalysed by **1′**, and stoichiometric fluorination by **2′** are consistent with fluorination by similar Pd(IV)–F species in all three cases, corresponding to **2** in the case of catalysis by **1**.

Aromatic C–H oxidations catalysed by transition metals generally proceed via C–H metalation followed by oxidation of the resulting organometallic intermediate, with product formation ensuing through reductive elimination. The aromatic fluorination catalysed by **1** presented here is an unusual example of an alternative mode of catalysis for aromatic C–H oxidation, in which a transition-metal catalyst is oxidized to a high-valent intermediate, which in turn oxidizes the substrate by group transfer of a ligand. Such an 'oxidation-first' mechanism is reminiscent of various transition-metal-catalysed aliphatic C–H oxidations, such as hydroxylations[25–27] and halogenations[28] through high-valent metal–oxo complexes, and aminations[29] via metal–nitrenoid

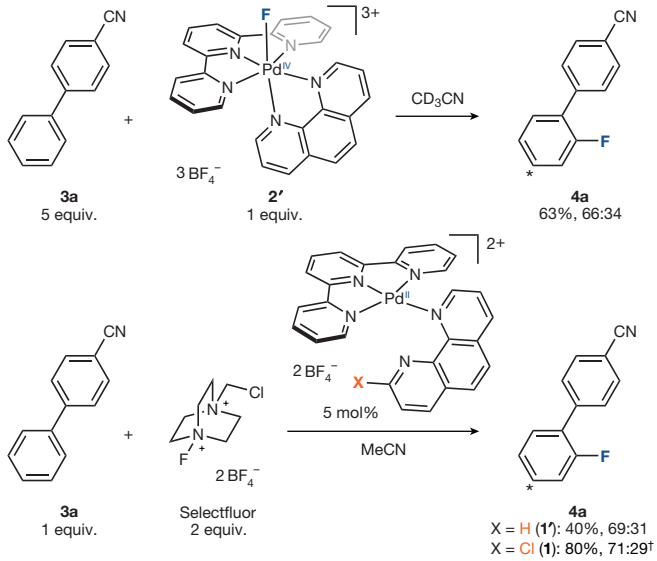

Figure 4 | Comparison of the positional selectivity of stoichiometric and catalytic fluorinations using 2′. Top, stoichiometric fluorination; bottom, catalytic fluorination. †5 equiv. of 4-cyanobiphenyl (**3a**) and 1 equiv. of Selectfluor were used.

species. Reported examples of such a mechanism for aromatic C–H oxidation, however, are rare, and are proposed to involve metal-nitrene or aminyl-radical transfer to the arene, although evidence for the proposed modes of action in these cases is indirect[30,31]. To the best of our knowledge, the aromatic fluorination reaction reported here is the only example so far of a synthetic method for aromatic C–H functionalization in which oxidation reactivity between a high-valent catalytic intermediate and arenes has been directly scrutinized.

The other examples of aromatic and aliphatic C–H oxidation reactions proceeding through 'oxidation-first' mechanisms mentioned above function because the high-valent intermediate provides access to a mechanism of oxidation that is not available to the starting reagents, such as a radical-rebound mechanism in the case of hydroxylation through metal–oxo intermediates. We have shown here data that support the interpretation that catalyst **2** provides access to a fluoride-coupled electron-transfer mechanism that is not accessible to electrophilic fluorinating reagents such as Selectfluor.

We anticipate that the direct electrophilic C–H fluorination of arenes reported here will be a useful tool in medicinal chemistry; indeed, the reaction has already found use in the late-stage derivatization of drug molecules. Furthermore, the unusual mechanism of catalysis by complex **1**, in which a high-valent transition-metal intermediate undergoes group transfer to arenes, may become the basis for a new approach to the catalysis of C–H functionalization reactions.

Data Availability Data are available from the corresponding author on reasonable request.

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Author Contributions K.Y. designed catalyst **1** and optimized the fluorination reaction. K.Y. and J.D.R. conducted mechanistic studies. K.Y. and G.B.B. developed the conceptual approach to the project. J.L., J.A.O.G., J.C.B., K.Y. and J.D.R. explored the substrate scope. J.D.R. performed DFT calculations with input from M.v.G. and F.N. G.B.B. wrote the manuscript with input from all other authors. C.G. and J.J. supported development towards useful examples. K.Y., J.L., J.A.O.G., G.B.B., J.D.R. and T.R. analysed the data. T.R. directed the project.

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