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Controlling Pd(IV) reductive-elimination pathways enables Pd(II)-catalyzed enantioselective C(sp³)-H fluorination

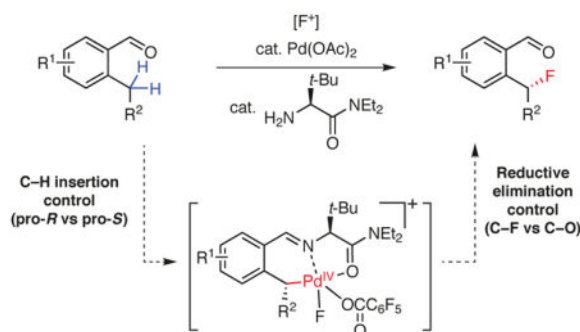
Hojoon Park¹, Pritha Verma¹, Kai Hong¹, and Jin-Quan Yu^{1,*}

¹Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road. La Jolla, California 92037, USA

Abstract

The development of a Pd(II)-catalyzed enantioselective fluorination of C(sp³)-H bonds would offer a new approach to making chiral organofluorines. However, such a strategy is particularly challenging because of the difficulty in differentiating prochiral C(sp³)-H bonds through Pd(II)-insertion, as well as the sluggish reductive elimination involving Pd-F bonds. Here, we report the development of a Pd(II)-catalyzed enantioselective C(sp³)-H fluorination using a chiral transient directing group strategy. In this work, a bulky, amino amide transient directing group was developed to control the stereochemistry of C-H insertion step and selectively promote C(sp³)-F reductive elimination pathway from Pd(IV)-F intermediate. Stereochemical analysis revealed that while the desired C(sp³)-F formation proceeds via an inner-sphere pathway with retention of configuration, the undesired C(sp³)-O formation occurs through an S_N2-type mechanism. The elucidation of the dual mechanism allows us to rationalize the profound ligand effect on controlling reductive elimination selectivity from high-valent Pd species.

Graphical Abstract



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Correspondence and requests for materials should be addressed to J.-Q.Y. (yu200@scripps.edu).

Author Contributions

H.P. developed the enantioselective fluorination reaction. H.P. and K.H. expanded the substrate scope. P.V. conducted the computational studies. J.-Q.Y. conceived and supervised the project.

Readers are welcome to comment on the online version of this article.

Competing financial interests

The authors declare no competing financial interests.

The presence of a C–F bond can uniquely influence the physical and biological properties of a molecule, such as conformation, lipophilicity, and metabolic stability^{1,2}. Therefore, fluorine incorporation has been widely used as a means to tailor the properties of a molecule. The success of this strategy is evidenced by the fact that over 25% of agrochemicals³ and 20% of drug molecules⁴ in the market contain at least one C–F bond in the structure. Accordingly, significant progress has been made in the field of fluorination of organic molecules^{5–7}. Asymmetric methods that directly construct a C(sp³)–F stereocenter have also been achieved through multiple approaches⁸ including α -fluorination of enolate or enolate-equivalents^{9–11}, fluoro-difunctionalization of olefins^{12–14}, and asymmetric addition of nucleophilic fluorides to carbon electrophiles^{15–17}. As an alternative approach, the development of a direct, enantioselective fluorination of a C(sp³)–H bond via metal-insertion would be highly appealing. Although a number of C(sp³)–H fluorination methods using palladium insertion^{18–21} have been reported, an asymmetric version remains to be developed. Radical-mediated processes^{22–26} have been shown to be an effective strategy for direct C(sp³)–H fluorination, however, only a single example of enantioselective benzylic C–H fluorination with low enantioselectivity (25% enantiomeric excess) has been reported²⁷. Such limitations of asymmetric C(sp³)–H fluorination encouraged us to devise a new, highly enantioselective C(sp³)–H fluorination using Pd(II)-insertion chemistry.

We have recently developed a Pd(II)-catalyzed enantioselective C(sp³)–H arylation using a chiral amino acid transient directing group²⁸. This finding led us to investigate the feasibility of developing a new chiral transient directing group to enable an enantioselective C(sp³)–H fluorination. The major pitfall of C(sp³)–H fluorination using Pd(II/IV) catalysis is the relatively sluggish C–F reductive elimination from Pd(IV) species, which renders [F⁺] a broadly useful bystander oxidant that favors the reductive elimination of other C(sp³)–C(sp³) or C(sp³)–heteroatom bonds (Figure 1a)^{29–31}. In addition, C(sp³)–[Pd(IV)(L_n)]–F species have been proposed to undergo S_N2-type reactions with various oxygen- and nitrogen-nucleophiles, forming C(sp³)–O and C(sp³)–N bonds instead of C(sp³)–F bond^{32–34}. These observations call into the question whether such reductive elimination selectivity could be biased towards fluorination by modifying the ligand environment of a Pd(IV)–F intermediate. Herein, we report the first Pd(II)-catalyzed enantioselective C(sp³)–H fluorination via metal-insertion. We achieved this goal using a transient directing group strategy (Figure 1b), in which the transient directing group serves as a chiral ligand that controls the stereochemistry in the C–H insertion step and promotes C(sp³)–F formation over the undesired C(sp³)–O formation during the reductive elimination step. Stereochemical analysis of the products suggests the reductive elimination proceeds via two distinct reaction pathways to provide the C(sp³)–F and C(sp³)–O products respectively. The identification of the dual pathways of Pd(IV) reductive elimination provides a rationale for the profound ligand effect observed on the reductive elimination selectivity (Figure 1c).

Results and discussion

Our initial efforts were focused on evaluating oxidants that can avoid the undesired oxidation of aldehyde (**1a**) and yet are capable of oxidizing Pd(II) to Pd(IV) species. After extensive screening (Supplementary Table 1), we were able to observe a mixture of fluorinated and acetoxyated aldehyde products when *N*-Fluoro-2,4,6-trimethylpyridinium

salt ($[F^+]$) was used in AcOH solvent (Table 1). With simple glycine (**TDG1**) as the transient directing group (entry 1), $[F^+]$ mainly served as a bystander oxidant, providing the acetoxylation product **2a** as the major product over the fluorination product **3a** with a ratio of 9.7:1. As sterics on the amino acid transient directing groups increases, we began to observe the formation of more **3a** (16%) and less **2a** (47%) (entries 2, 3). It is noteworthy that chiral **TDG3** (entry 3) gave **2a** with 88% enantiomeric excess (e.e.) and **3a** with 90% e.e., which implies that C–H insertion is highly stereoselective. Considering the previously observed beneficial effect of tertiary amides such as DMF and NMP in Pd(II)-catalyzed C–H fluorination reactions^{35,36}, we prepared the amino acid-derived diethyl amide **TDG4** for our reaction. Importantly, **TDG4** switched the preference of the reaction pathways to afford **3a** as the major product for the first time with high enantioselectivity, albeit still low chemoselectivity (entry 4). To further enhance the chemoselectivity in favor of fluorination over acetoxylation, we evaluated various solvents that could replace the solvent quantity of AcOH. We found the use of benzene as solvent with 10% AcOH improved the selectivity to 1:6.7 in favor of fluorination (entry 5). The lower ee value of the acetoxylation product **2a** in this case is likely to originate from the competing inner-sphere C–O reductive elimination. Indeed, systematically lowering the concentration of AcOH slows down the bimolecular outer-sphere pathway and further decreases the ee values (Supplementary Fig. 3). Through further screening of acid additives (Supplementary Table 4), we identified $C_6F_5CO_2H$ as the most effective carboxylic acid which allows the fluorination to proceed with moderate efficiency, good chemoselectivity, and high enantioselectivity (entry 6). Notably, the control of reductive elimination selectivity from Pd(IV) intermediates during catalysis has only been demonstrated with C(sp²)–O vs. C(sp²)–N bond formation³⁷. The loss of both reactivity and selectivity with amino acid directing group **TDG3** (entry 7) and the less hindered amide directing groups **TDG5-7** (entry 8–10) indicates the importance of the amide moiety and the bulky quaternary substituent of the transient directing group (Supplementary Table 5).

The high enantioselectivities observed in both C(sp³)–O and C(sp³)–F forming processes allow us to probe the mechanism of the reductive elimination pathway through the lens of stereochemistry. Thus, the absolute stereochemistry of both **2a** and **3a** were identified by X-ray crystallography (Figure 2a). Interestingly, the opposite absolute configuration of these two products was observed, indicating the involvement of two distinct reaction pathways. The configuration of **3a** is consistent with our previous arylation reaction²⁸, suggesting that fluorination proceeds through a classic inner-sphere reductive elimination process with retention of stereochemistry, while **2a** is formed through an S_N2-type mechanism to achieve inversion of stereochemistry. To further support this mechanistic hypothesis, we conducted a series of experiments to rule out the possibility of **2a** and **3a** forming through an identical mechanism from two different diastereomeric palladacycles. First, we showed that C(sp³)–H insertion process is irreversible via deuterium incorporation experiments, because no deuterium incorporation was observed in substrate and products in either absence or presence of $[F^+]$ with both **TDG3** and **TDG4** (Figure 2b). Second, stoichiometric reaction between the pre-formed imine **7** and Pd(OAc)₂ with AcOD-*d*4 at 70 °C allowed us to isolate the palladacycle intermediate **8**, which bears the same stereochemistry with **3a** as expected (Figure 2c). When intermediate **8** was treated with $[F^+]$ in AcOH, **2a** and **3a** with opposite configuration were formed, consistent with the catalytic reaction (Table 1, entry 4), although

the C(sp³)-O/C(sp³)-F ratio and the enantioselectivity slightly vary. These combined experimental data renders the alternative hypothesis that two diastereomeric palladacycles undergo different bond-formations unlikely. Lastly, we verified the linear relationship between the e.e. of **3a** and **TDG4** in order to exclude the possibility of an external Pd-bound fluoride undergoing S_N2 pathway for C(sp³)-F formation (Supplementary Fig. 2). It has been shown by Doyle and coworkers that Pd-bound fluoride species can act as nucleophile in Pd-catalyzed allylic fluorination³⁸. Indeed, our mechanistic hypothesis of the competitive nature of C(sp³)-Pd(IV) reductive elimination mechanism (S_N2 vs. inner-sphere) is supported by a number of previous kinetic and computational studies^{32,33,39-41}. It is intriguing that under our system the ratio of C(sp³)-O vs. C(sp³)-F can serve as a measurement for the competition between the inner-sphere reductive elimination and S_N2 pathway from Pd(IV) intermediate during catalysis. It is noteworthy that a related study of controlling the stereochemical course of reductive elimination has been conducted using stoichiometric Pt(IV) complexes⁴².

Based on these mechanistic investigations, we propose a rationale for the switch of chemoselectivity of the C(sp³)-F and C(sp³)-O bond forming processes as depicted in Figure 3. A number of literature precedents propose that the formation of a cationic, five-coordinate Pd(IV) species must precede both C(sp²)-F and C(sp³)-F reductive elimination⁴³⁻⁴⁵. However, using an amino acid-type transient directing group (**TDG1-3**) will lead to a neutral, five-coordinate Pd(IV) intermediate (Figure 3, **I-III**) and render the desired C(sp³)-F reductive elimination slower than competing pathways, which is the S_N2 C(sp³)-O formation in our case. Among the amino acid-type transient directing groups, we clearly observed a steric effect (Figure 3, **I-III**) which complies with the study of Gagné and coworkers on C(sp³)-F reductive elimination from high-valent Pt and Pd species⁴⁶. When the carboxylic acid moiety of the transient directing group is replaced with a neutral diethyl amide group, a cationic, five-coordinate Pd(IV) intermediate suitable for C(sp³)-F reductive elimination can be formed (Figure 3, **IV**), which shifts the selectivity towards C(sp³)-F formation without affecting the overall yield. While it was previously proposed that tertiary amide additives such as NMP promote fluorination via accelerating the Pd(II)/(IV) oxidation step^{35,36}, our result suggests that the role of tertiary amide motif is more likely to promote the C(sp³)-F reductive elimination step. Indeed, computational analysis showed that the switch from **TDG3** to **TDG4** reduces the barrier for inner-sphere C(sp³)-F and S_N2-type C(sp³)-O reductive elimination by 4.5 kcal/mol and 2.8 kcal/mol, respectively, which is qualitatively in accordance with the observed higher fluorination selectivity with **TDG4**. Our hypothesis is that the switch from neutral to cationic Pd(IV) not only reduces the energy level of σ*(Pd-C), which would accelerate both reductive elimination pathways, but also affect the property of Pd-F bonding, which would have a larger influence on the inner-sphere C(sp³)-F reductive elimination. To support this hypothesis, we performed frontier molecular orbital (FMO) and natural bond orbital (NBO) analysis to show that the switch from **TDG3** to **TDG4** leads to 1) a decrease in the energy level of LUMO (σ*(Pd-C)), and 2) increases in the resonance stabilization energy in both σ(Pd-C)→σ*(Pd-F) and σ(Pd-F)→σ*(Pd-C) interactions (See Supplementary Information). Finally, the selectivity and efficiency of fluorination is further promoted when AcOH is replaced with C₆F₅CO₂H (Figure 3, **V**). Extensive screening of benzoic acids shows that 2,3,5,6-tetrafluoro-

substitution is essential for obtaining satisfactory yield of the fluorination product (Supplementary Table 4). The use of electron-deficient benzoic acid not only reduces the C(sp³)-O bond formation due to poor nucleophilicity, but also promotes C(sp³)-F reductive elimination as would be expected from an electron-withdrawing anionic ligand bound to Pd(IV).

With the optimized reaction conditions in hand, we examined the substrate scope of our enantioselective fluorination (Table 2). Substrates with longer alkyl chains on the 2-position of benzaldehyde were tolerated with reduced efficiency and higher enantioselectivity (**3b-c**). With these bulkier substrates, only trace amount of C(sp³)-O products were observed, which is in accordance with our mechanistic hypothesis. Next, substrates bearing electron-withdrawing groups were tested. Carbonyl substituents, such as ester (**3d**) and ketone (**3e**), gave the fluorinated products in synthetically useful yields and excellent enantioselectivities. Nitro-substituted benzaldehyde (**3f**) also provided the fluorinated product in moderate yield. Unfortunately, substrates solely bearing electron-donating functional groups did not afford fluorination products under our current reaction conditions. Thus, we tested substrates that contain both a -NO₂ group and an additional functional group. To our delight, these proved to be suitable substrates for our enantioselective fluorination (**3g-i**). Interestingly, a tetralin scaffold could also be fluorinated with excellent enantioselectivity albeit low yield (**3j**). Benzaldehydes containing *ortho*-F also underwent C(sp³)-H fluorination with moderate yields and excellent enantioselectivity (**3l-m**). Lastly, a heterocyclic substrate was also fluorinated with high enantioselectivity as well (**3o**). When a non-substituted 2-ethylbenzaldehyde (**1p**) was subjected to the reaction conditions, the reaction suffered not only from low efficiency, but also from the undesired C(sp²)-H activation (**3p**). With a substrate bearing an electron-donating -OMe group (**1q**), both C(sp²)-O and C(sp³)-O formations were favored over C-F formation, affording **2q** as the major product with very low e.e. values. It is possible that **2q** is formed through a distinct mechanism, most likely through a quinone methide-type intermediate which undergoes a nucleophilic addition of C₆F₅CO₂H. Such drastic effect of a *para*-OMe group on reductive elimination of benzylic site has been reported by Sanford and coworkers⁴⁷. We also observed that substrate **1r** with primary C(sp³)-H bond gives **2r** as the sole product which is expected from the S_N2 reaction at a less hindered primary carbon center.

The incompatibility of our reaction with substrates bearing electron-donating groups prompted us to employ the well-known S_NAr reactions of the fluorinated products bearing an *ortho*-F group (**3k-3n**) to install a wide range of functional groups. To test this approach, we subjected our *ortho*-F-benzaldehyde product **3k** into various S_NAr reaction conditions (Figure 4). To our delight, the -F group can be smoothly substituted to form C-N (**4a, 4b**), C-O (**4c**), and C-S (**4d**) bonds without eroding the enantiopurity of the compound. Furthermore, we demonstrated that **3k** can serve as a precursor for heterocyclic scaffolds that bear a stereogenic 1-fluoroethyl moiety. We were able to obtain benzothiophene (**4e**), anthranil (**4f**), and quinazoline⁴⁸ (**4g**) compounds without eroding the enantiopurity. While a 1,2,4-triazoloquinoxaline scaffold⁴⁹ (**4h**) can also be accessed, partial racemization was observed.

In summary, we have developed a Pd(II)-catalyzed enantioselective C(sp³)-H fluorination method using a chiral transient directing group. The choice of anionic or neutral transient directing groups to favor the formation of neutral or cationic Pd(IV) intermediates offers an effective method for controlling the dual reductive elimination pathways. The use of a bulky amino amide transient DG was critical in achieving high enantioselectivity and promoting C-F reductive elimination. We are currently applying this design principle to achieve Pd-catalyzed enantioselective fluorination of other alkyl C-H bonds.

Methods

General procedure for the enantioselective fluorination

A sealed tube with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 2.2 mg), NBu₄PF₆ (0.05 mol, 19.4 mg), [F⁺]BF₄⁻ (0.15 mmol, 34.0 mg), C₆F₅CO₂H (0.5 mmol, 106.0 mg), substrate (0.1 mmol), and **TDG4** (20 mol%, 3.7 mg) in air. Then, benzene (0.4 mL) or DCM (0.4 mL) was added as solvent. The reaction mixture was stirred at room temperature for 10 minutes, then at 70 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with DCM. The organic layer was washed with sat. NaHCO₃ (aq) solution for 2 times. The organic layer was dried with Na₂SO₄, filtered through a silica plug with ethyl acetate, and concentrated *in vacuo*. The crude reaction mixture was purified on silica gel using hexanes/ethyl acetate as eluent to afford the desired product as a mixture with the corresponding substrate. Isolated yield were calculated based on the isolated mass and the ratio of substrate and product determined by analysis of ¹H NMR spectrum. Pure analytical samples for characterization were isolated by multiple preparative TLC. Full experimental details and characterization of compounds can be found in the Supplementary Information.

Data Availability

All characterization data, computational data, and experimental protocols are provided in the Supplementary Information or are available from the authors upon request. Metrical parameters for the structure of compound **5a**, **6**, and **8** are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC 1556389, CCDC 1556390, and CCDC 1577327 respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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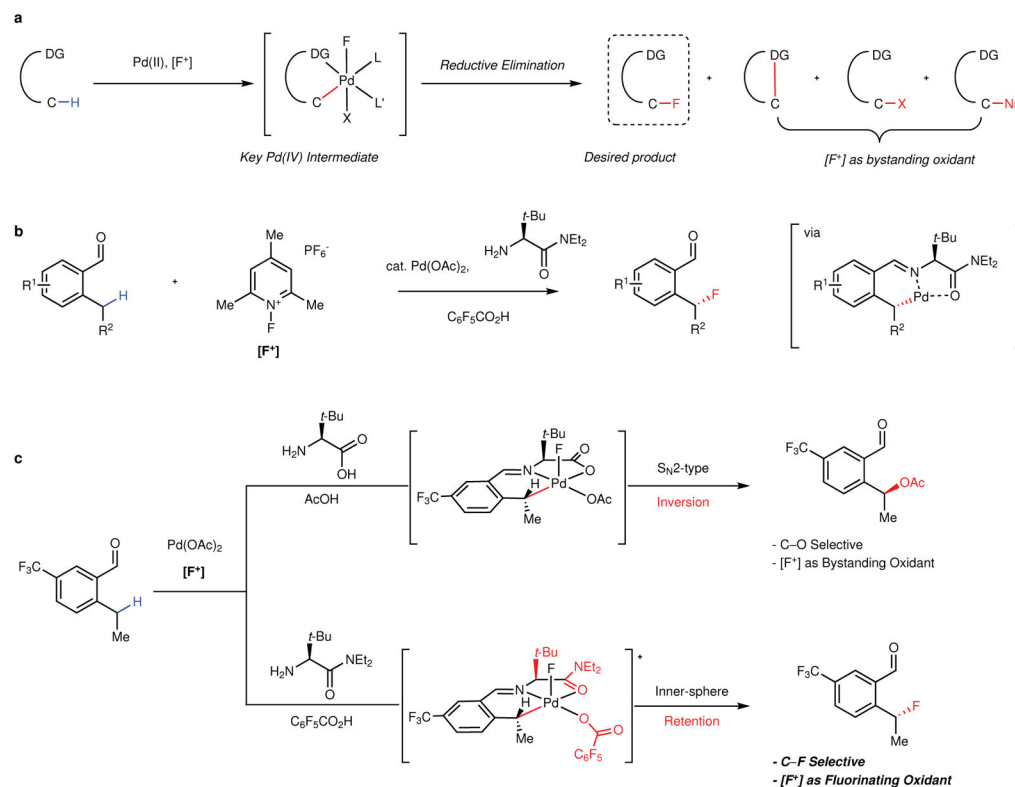


Figure 1. Enantioselective C(sp³)-H Fluorination

a, The possibility of multiple reductive elimination pathways from Pd(IV) species generated with [F⁺] as oxidant presents a challenging selectivity issue. **b**, This work: Pd(II)-catalyzed enantioselective C(sp³)-H fluorination using chiral transient directing group strategy. **c**, Profound ligand effect was observed on reductive elimination selectivity (C(sp³)-O vs. C(sp³)-F). Stereochemical analysis of products suggests that such ligand effect originates from the dual mechanism of Pd(IV) reductive elimination step.

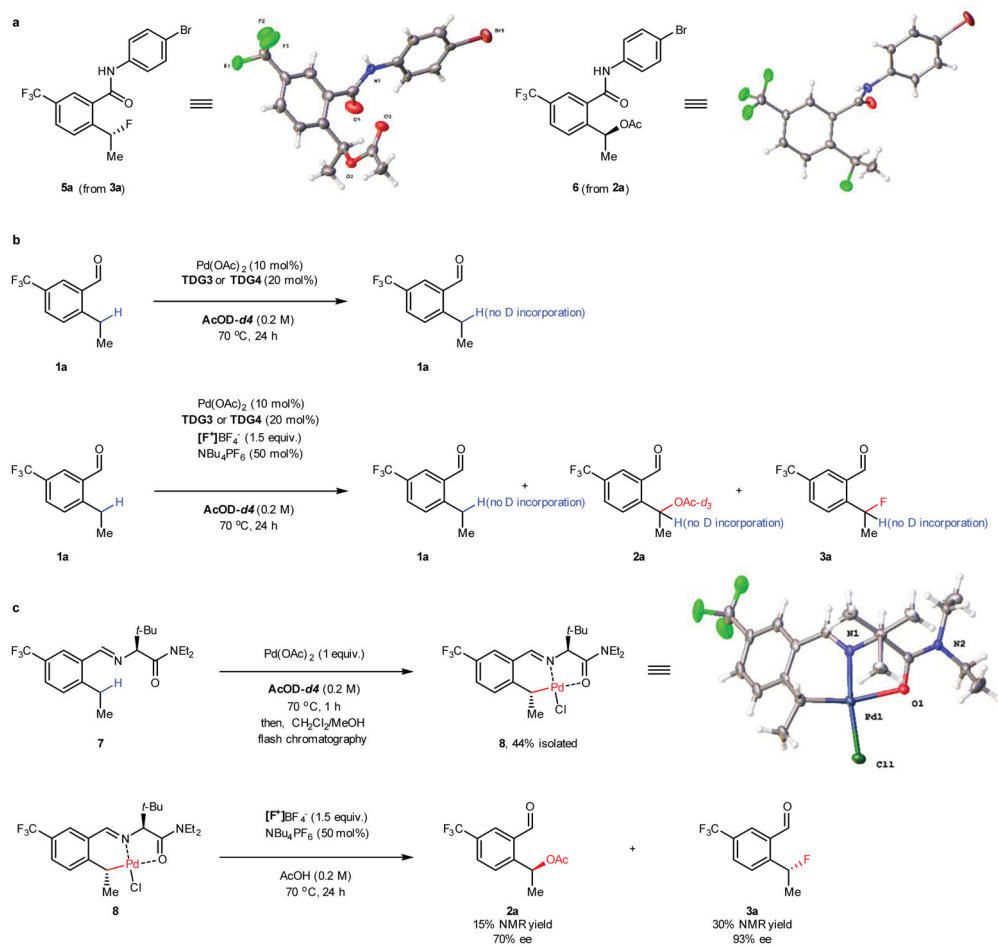


Figure 2. Experimental evidence for the dual mechanism of Pd(IV) reductive elimination
a, Stereochemical analysis of acetoxylation & fluorination reveals opposite configuration. **b**, Deuterium incorporation experiments show that C(sp³)-H insertion process is irreversible under our catalytic conditions. **c**, Bicyclic palladacycle **8** was synthesized and characterized via X-ray crystallography. Identical stereochemical outcome was observed with the catalytic conditions when **8** was reacted with [F⁺].

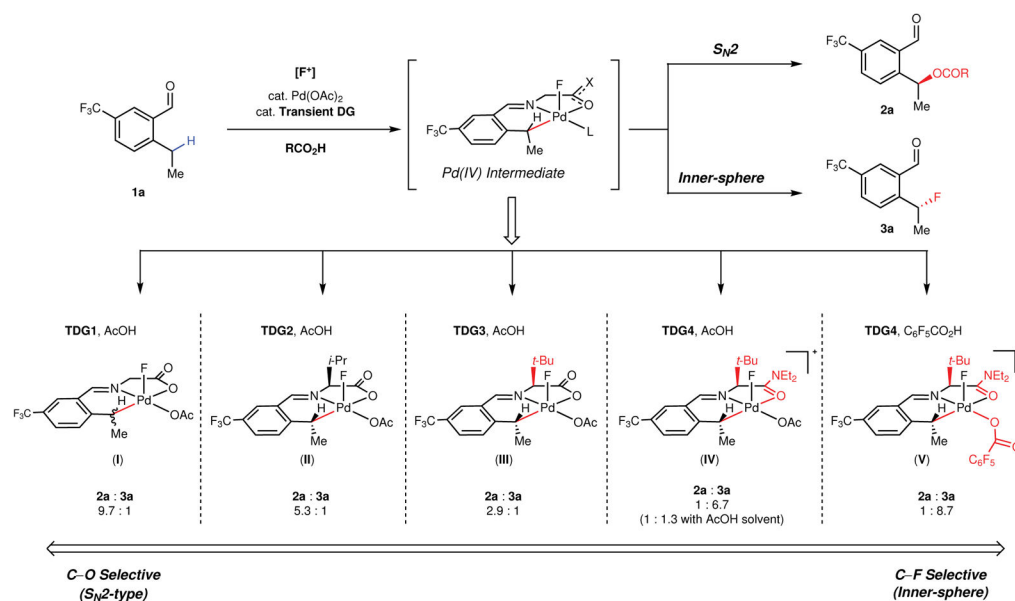


Figure 3. Controlling reductive elimination pathways from putative Pd(IV) intermediates
Trends of reductive elimination selectivity observed with anionic and neutral transient directing groups.

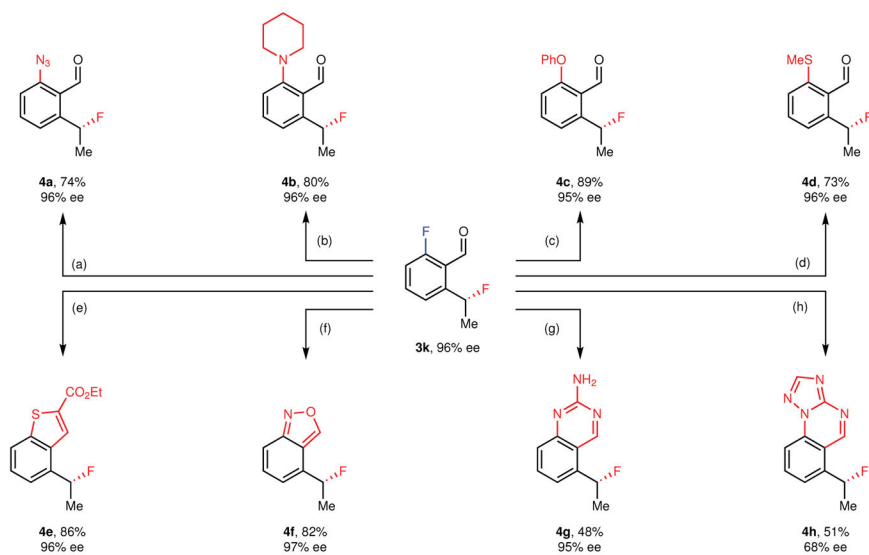


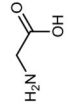
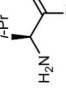
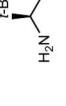
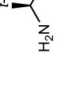

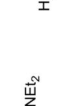

Figure 4. Access to diverse chiral organofluorines

a, NaN₃ (4.0 equiv.), HMPA (0.2 M), r.t., 36 h. **b**, piperidine (3.0 equiv.), K₂CO₃ (3.0 equiv.), DMF (0.2 M), 100 °C, 12 h. **c**, PhOH (3 equiv.), K₂CO₃ (3.0 equiv.), DMF (0.2 M), 100 °C, 2 h. **d**, NaSMe (3.0 equiv.), DMF (0.2 M), 60 °C, 4 h. **e**, Ethyl thioglycolate (3.0 equiv.), K₂CO₃ (3.0 equiv.), DMF (0.2 M), 60 °C, 3 h. **f**, NaN₃ (3.0 equiv.), DMF (0.2 M), 100 °C, 12 h. **g**, guanidine carbonate (2.5 equiv.), DMA (0.2 M), 150 °C, 1 h. **h**, 3-amino-1,2,4-triazole (2.0 equiv.), Cs₂CO₃ (3.0 equiv.), DMF (0.2 M), 100 °C, 2 h.

Table 1

Optimization of Reaction Conditions.^{a, b}

entry	Transient DG	Solvent	RCO ₂ H	Yield 2a	ee 2a	Yield 3a	ee 3a	2a : 3a
1	TDG1	AcOH	--	58%	--	6%	--	9.7 : 1
2	TDG2	AcOH	--	48%	72%	9%	--	5.3 : 1
3	TDG3	AcOH	--	47%	88%	16%	90%	2.9 : 1
4	TDG4	AcOH	--	29%	79%	37%	92%	1 : 1.3
5	TDG4	Benzene	AcOH (10% cosolvent)	6%	68%	40%	90%	1 : 6.7
6	TDG4	Benzene	C₆F₅CO₂H^c	7% ^d	--	61%	91%	1 : 8.7
7	TDG3	Benzene	C ₆ F ₅ CO ₂ H ^c	8%d	--	7%	--	1.1 : 1
8	TDG5	Benzene	C ₆ F ₅ CO ₂ H ^c	17%d	--	10%	--	1.7 : 1
9	TDG6	Benzene	C ₆ F ₅ CO ₂ H ^c	12%d	--	7%	--	1.7 : 1
10	TDG7	Benzene	C ₆ F ₅ CO ₂ H ^c	6%d	--	3%	--	2 : 1

						
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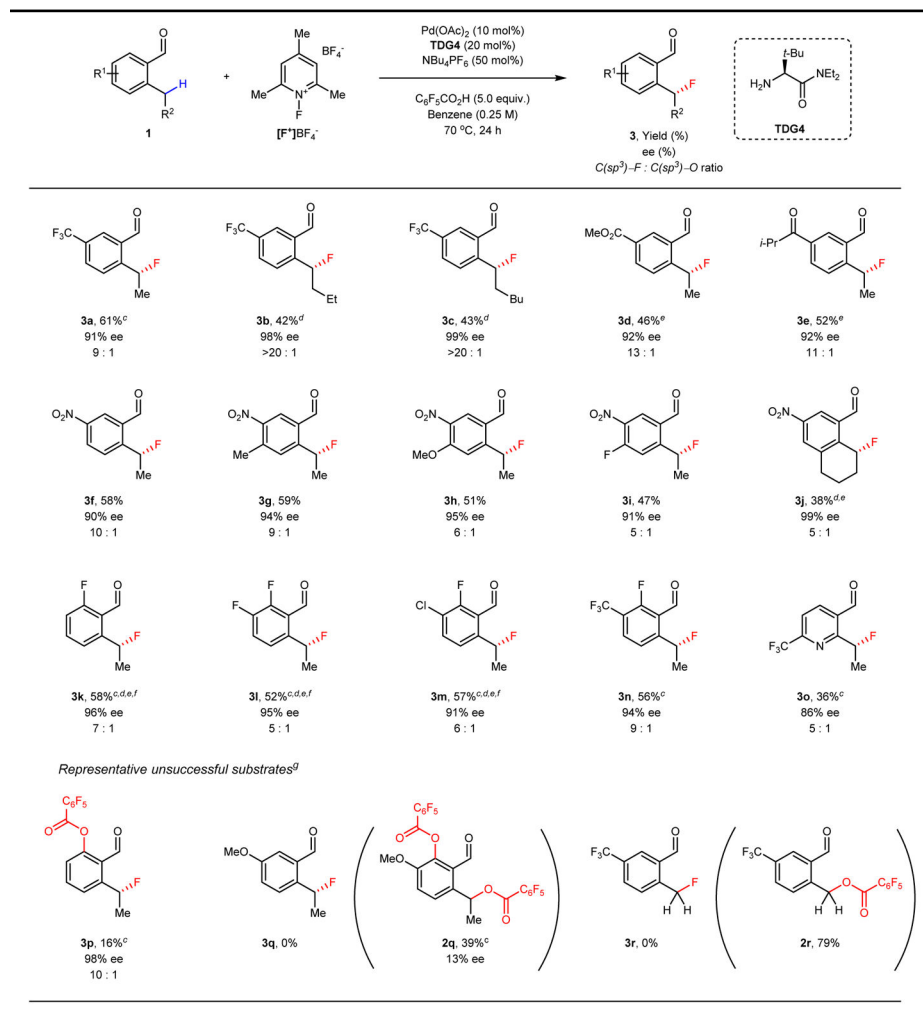
^a Reaction conditions: substrate **1a** (0.10 mmol, 1.0 equiv.), [F⁺][BF₄⁻] (0.15 mmol, 1.5 equiv.), NBu₄PF₆ (0.05 mmol, 0.5 equiv.), Pd(OAc)₂ (10 mol%), Transient DG (20 mol%), Solvent DG (20 mol%), Solvent (entry 1–4): 0.2 M, entry 5–10: 0.25 M), 70 °C, 24 h.

^b The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

^c 5 equiv. of C₆F₅CO₂H was used.

^d R = C₆F₅.

Table 2

Scope of 2-alkylbenzaldehyde substrates for Pd(II)-catalyzed enantioselective C(sp³)-H fluorination.^{a,b}

^aReaction conditions: substrate **1** (0.10 mmol, 1.0 equiv.), [F⁺]BF₄⁻ (0.15 mmol, 1.5 equiv.), NBu₄PF₆ (50 mol%), C₆F₅CO₂H (0.50 mmol, 5.0 equiv.), Pd(OAc)₂ (10 mol%), **TDG4** (20 mol%), Benzene (0.4 mL), 70 °C, 24 h.

^bIsolated yield as a mixture with substrate **1** unless otherwise noted. C(sp³)-F : C(sp³)-O ratio was determined by ¹H NMR analysis.

^cDue to the high volatility of the product, yield was determined by ¹H NMR analysis.

^d[F⁺]PF₆⁻ (0.15 mol, 1.5 equiv.) was used instead of [F⁺]BF₄⁻/NBu₄PF₆.

^eDCM (0.4 mL) was used as solvent.

^f**TDG4** (25 mol%) was used.

^gFull table of unsuccessful substrates are shown in the Supplementary Information.