Steric Crowding Makes Challenging C_sp3–F Reductive Eliminations Feasible

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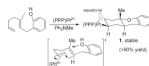
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Abstract

A high-yielding fluorination of (triphos)Pt-R$^+$ has been achieved using an array of F$^+$ sources, with XeF$_2$ yielding R–F in minutes. The C–F coupling proved to be a stereoretentive process that proceeds via a concerted reductive elimination from a putative dicationic Pt(IV) center. The larger the steric congestion of the (triphos)Pt–C$_{sp3}$$^+$ complexes, the more efficient the fluorination, seemingly a result of sterically accelerated C–F reductive elimination along with simultaneous deceleration of its competing processes (β-H elimination).

Organofluorine compounds are pervasive in pharmaceuticals, agrochemicals, biomedical imaging agents and materials.[1] This has led to significant interest in developing metal-catalyzed C–F bond forming reactions.[1–7] While transition metal mediated C–F couplings with F$^-$ are underdeveloped,[1d,3] methods based on "F$^+$" reagents have proven more tractable,[4–6] in part due to their propensity to generate high valent organometallic M–F intermediates (e.g. Pd(IV), Ag(III), Au(III)), which may be more prone to C–F coupling.[1f, 8]

Electrophilic Pt(II) dications catalyze C–C bond forming reactions that propagate via cation-olefin sequences which parallel sterol biosynthesis[9,10] and proceed through Pt–C$_{sp3}$ intermediates. It would be desirable to convert such Pt–C bonds into F–C bonds, as C3-fluoro steroids are bioactive and fluoro-carbocycles in general are difficult to synthesize.[1] Despite the ease of accessing the tetra-valent oxidation state with Pt-organometallics (e.g. the Shilov reaction),[11] Pt analogs of the above C–F couplings are rare. For example, adding F$^+$ to P$_2$PtR$_2$ complexes only afford the product of C–C (R–R, R = Me, Ph) and not C–F coupling.[7] As the transformation of a Pt–C bond into an F–C bond was unknown, we initiated a study aimed at rectifying this situation.

(1)

As illustrated in eq. 1, wherein PPP = bis(2-diphenylphosphinoethyl)phenylphosphine (i.e., triphos), pincer ligands inhibit β-H elimination and enable the isolation of relevant cyclization intermediates.[10,12] With the eventual goal of a catalytic cyclization/fluorination reaction,[13] we utilized compounds like **1** to study key issues retarding progress on the Pt–C

fluorination step. We report, herein, a Pt–C_{sp3} bond fluorination reaction that is stereoretentive and provide evidence suggesting that it is steric congestion in a putative Pt(IV)-fluoride that advantages the critical C–F reductive elimination over competing reactions.
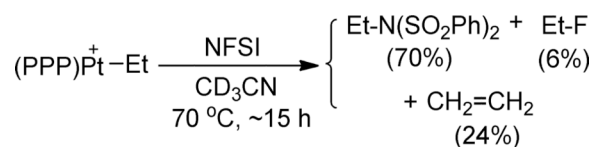
We began by examining the electrophilic fluorination of **1**,[10e] which generated **2** in >80% yields with an array of F$^+$ reagents (Table 1);[14] the mass balance being the known β-H elimination product **3**.[10c] Electron rich *N*-fluoropyridinium tetrafluoroborates were unreactive or required elevated temperatures while the more aggressive 2,6-dichloro derivative and Selectfluor® provided **2** at room temperature. Most remarkable was XeF$_2$, which gave complete conversion within 3 min at 0 °C. *N*-fluorobenzenesulfonimide (NFSI, entry 6) was also effective and in contrast to the C–N bond formations reported by Michael[15] and Liu[6b,6c] for Pd$^{II/IV}$ chemistry, it provided **2** in good yields.

These fluorination reactions worked equally well in a variety of solvents including MeCN, CH_2Cl_2, and $MeNO_2$. Monitoring reactions with ^{1}H and ^{19}F NMR spectroscopy revealed that **2** was produced as a single diastereomer (^{19}F: δ = –170.4 ppm; ^{1}H for the geminal H: δ = 4.67 ppm, $^2J_{F-H}$ = 48 Hz). NOESY analysis and X-ray diffraction showed the F atom in **2** to be equatorial,[14] indicating that the fluorination was *stereoretentive* (Figure 1). Several representative C3-platinated carbocycles generated by cation-olefin cyclizations[10e,f] were tested; *N*-fluoropyridinium salts, Selectfluor®, XeF$_2$ and NFSI all led to the expected stereoretentive C–F couplings, with XeF$_2$ again being particularly effective (Table 2, entry 1–4). Such organofluorine compounds would otherwise be difficult to access.[1a]

These initial data suggested a Pt–C fluorination that was general and uniformly high yielding, however, simple acyclic (triphos)Pt-R$^+$ complexes were unexpectedly complex. While R = cyclohexyl was only slightly diminished compared to entries 1–4 (Table 2), the isopropyl and ethyl complexes underwent preferential β-H elimination, producing only 14 and 41% of the fluorocarbon product, respectively. The benzyl complex, which lacks β-hydrogens, gave exclusively benzyl fluoride, while the methyl complex reacted with XeF$_2$ to yield a complex mixture of methyl Pt(IV) fluoro complexes but no CH_3–F (entry 9). Fluorinations using NFSI (70 °C, CD_3CN) were comparable to XeF$_2$ (fluorocyclohexane: 76%; 2-fluoropropane: <5%; benzyl fluoride: >94%), except for the R= Me and Et complexes which *preferentially formed C–N products* (eqs. 2 and 3).[14]

$$(PPP)\overset{+}{Pt}-Me \xrightarrow[\substack{CD_3CN \\ 70\ °C,\ \sim12\ h}]{NFSI} Me\text{-}N(SO_2Ph)_2\ (100\%)$$

(2)

$$(PPP)\overset{+}{Pt}-Et \xrightarrow[\substack{CD_3CN \\ 70\ °C,\ \sim15\ h}]{NFSI} \begin{cases} Et\text{-}N(SO_2Ph)_2\ +\ Et\text{-}F \\ \qquad (70\%) \qquad\quad (6\%) \\ \qquad +\ CH_2{=}CH_2 \\ \qquad\quad (24\%) \end{cases}$$

(3)

The reactivity of Pt-R complexes therefore depends on both the identity of the R group and (partially) on the F$^+$ source. From data analysis emerge several generalizations: 1) XeF$_2$ fluorinates bulky alkyls (with retention) more efficiently than less bulky ligands; 2) the NSFI reagent fluorinates (with retention) bulky alkyls with similar fluorocarbon:alkene ratios as XeF$_2$, however, Me and Et ligands are preferentially amidated by the [N(SO$_2$Ph)$_2^-$] counterion; 3) fluorination conditions make otherwise stable (triphos)Pt-R$^+$ complexes

susceptible to β-H elimination; and 4) the reaction of (triphos)Pt-Me$^+$ with XeF$_2$ yields Pt(IV) fluoro complexes.

Several mechanisms have been considered, with reaction pathways involving direct backside S$_E$2 attack of F$^+$ onto the Pt–C σ bond being ruled out as these processes would be invertive C–F couplings. While direct attack of F$^+$ onto the Pt–C bond would be retentive, this later mechanism does not explain the increased rates of β-H elimination and the C–N bond forming products for R = Me and Et. The mechanism, based in large part on precedence established by Ritter,[4d] Sanford,[4e] Vigalok,[7b] and mechanistic commodities of Shilov type reactions,[11] and best able to explain the observations is outlined in Scheme 1.[16] Initiating F$^+$ attack generates the common intermediate **A**, a dicationic Pt(IV) fluoride. When the steric demand of the alkyl is high, rapid (concerted) C–F reductive elimination follows;[17,18] when lessened, β-H elimination becomes competitive, or even favorable.[19] Finally, when the alkyl (Me, Et) is sterically susceptible to nucleophilic attack by the counterion, the S$_N$2-type amidation can become dominant.[11,18] Overall, these data suggest that **A** can be coaxed away from β-H elimination and C–N coupling by *enhancing* the size of the R group, the consequence of which is to apparently accelerate C–F reductive elimination and slow β-H elimination and C–N bond formation (for NFSI).[20]

Evidence supporting the intermediacy of **A** was sought through low temperature trapping studies in acetonitrile.[21] Only in the case of R = Et were spectroscopic data consistent with solvated (triphos)Pt(Et)(F)$^{2+}$ observable (XeF$_2$, −20 °C); ^{31}P and ^{19}F NMR spectroscopic data established its similarity to the unreactive methyl analogue (entry 9, Table 2).[14] Additionally, it undergoes a slow β-H elimination and competing C–F coupling at −20 °C. Similarly informative were reactions of (triphos)Pt-CH$_2$Ph$^+$ and XeF$_2$ in melting acetonitrile. In addition to the expected PhCH$_2$F and (triphos)Pt^{2+} species,[22] ~10% of a cyclometallated benzyl Pt(IV) fluoride complex was spectroscopically identified (**4**, Scheme 2);[23,24] a seemingly related cyclometallated benzyl Pt(IV) fluoro species was invoked by Vigalok and co-workers to account for their fluorination of a ligand benzyl C–*H* bond.[7b] While stable for a time at RT, **4** could not be isolated and its structure was deduced by ^{1}H, ^{31}P, and ^{19}F NMR spectroscopy as well as HRMS.[14]

These in situ experiments together support the notion that Pt(IV) fluoro intermediates (i.e. **A**) are involved. Moreover, they demonstrate that steric effects significantly affect the rate of C– F reductive elimination in **A**, with R = Me being negligible, R = Et being observable at −20°C, and R larger than Et being too rapid to observe the intermediate.

To investigate the role of supporting ligation on C–F coupling, the fluorination (XeF$_2$, RT, CH$_3$CN) of several additional Pt-cyclohexyl complexes was investigated.[14] Variable quantities of fluorocyclohexane was observed for the different ligand sets, with the yield steadily improving as the steric congestion around the Pt center increased.[25]

NMR yield: ~20%   47%   79%
(F-Cy)
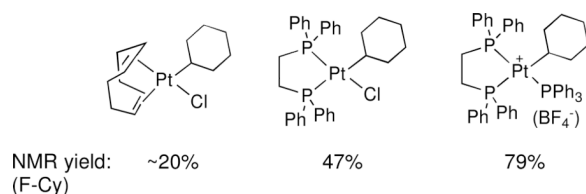
Also illuminating were experiments to investigate the possibility that the preferential C–N formation observed by Michael[15] and Liu[6b,6c] using NSFI was a metal effect (i.e. Pd vs. Pt). In a direct parallel to **1**, fluorination of palladium alkyl **5**[10e] with NFSI gave a 76% yield of

2 (XeF$_2$ gave 82% yield in min at 0 °C), with **3** again providing the mass balance (eq. 4). These experiments demonstrate that C–F vs. C–N bond formation is not a consequence of metal choice, but the overall steric encumbrance of the putative tetravalent organometallic intermediate.
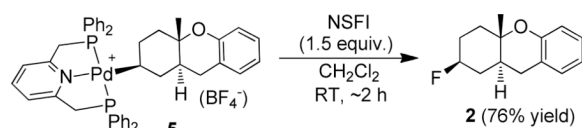
(4)

In summary, Pt^{II}–C$_{sp3}$ bonds can be efficiently fluorinated by electrophilic F$^+$ reagents when the coordination environment of the putative Pt(IV) intermediate is congested. These data suggest that C–F reductive elimination is sterically accelerated over the competing processes of β-H elimination and/or nucleophilic attack of the F$^+$'s counterion. Taken together these studies suggest strategies for optimizing the propensity of high valent Pd and Pt reactive intermediates to undergo desirable C–F coupling reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. see Supporting Information.

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16. (triphos)Pt-R$^+$ has been shown to be especially prone to electrophilic attack (H$^+$), see: Feducia JA, Campbell AN, Anthis JW, Gagné MR. Organometallics. 2006; 25:3114.

17. Concerted/direct C–heteroatom reductive elimination from Pt(IV) centers are rare, with the only known example being: Khusnutdinova JR, Newman LL, Zavalij PY, Lam Y-F, Vedernikov AN. J. Am. Chem. Soc. 2008; 130:2174. [PubMed: 18220400]

18. S_N2-type C–heteroatom reductive couplings from Pt(IV) centers are overwhelmingly observed. See for example: (a) Pawlikowski AV, Getty AD, Goldberg KI. J. Am. Chem. Soc. 2007; 129:10382. [PubMed: 17672451] (b) Williams BS, Goldberg KI. J. Am. Chem. Soc. 2001; 123:2576. [PubMed: 11456927] (c) Yahav-Levi A, Goldberg I, Vigalok A, Vedernikov AN. J. Am. Chem. Soc. 2008; 130:724. [PubMed: 18081290] (d) One exception is the direct C–O reductive elimination of a Pt[IV]-oxetane, see reference 17.

19. β-H elimination from Pt(IV) centers has been studied. See for example: Smythe NA, Grice KA, Williams BS, Goldberg KI. Organometallics. 2009; 28:277.

20. Additionally contributing to C–F over C–N coupling in the reaction of cycloalkyl compounds with the NFSI reagent is the inaccessibility of the Pt–C bond for backside (S_N2) attack by $^-N(SO_2Ph)_2$ (also a steric effect).

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22. A mixture of (triphos)Pt-(NCCD$_3$)$^{2+}$ and (triphos)Pt-F$^+$ complexes were observed in CD$_3$CN, whereas the latter was generated for reactions in CD$_2$Cl$_2$ or CD$_3$NO$_2$.

23. Complex **4** was not observed when carrying out the fluorination at RT in CD$_2$Cl$_2$ (i.e. Table 2).

24. Cyclometallated benzyl Pt complexes are known, see: Boer, HJRde; Schat, G.; Akkerman, OS.; Bickelhaupt, F. Organometallics. 1989; 8:1288. For other representative analogues, see: (a) Stang PJ, Song L, Lu Q, Halton B. Organometallics. 1990; 9:2149. (b) Begum RA, Chanda N, Ramakrishna TVV, Sharp PR. J. Am. Chem. Soc. 2005; 127:13494. [PubMed: 16190702]

25. 19% Cl-Cy was observed for (dppe)Pt(cy)Cl, hinting that C–F coupling may be slightly more favorable than C–Cl.
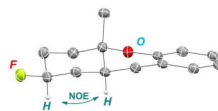
Figure 1.
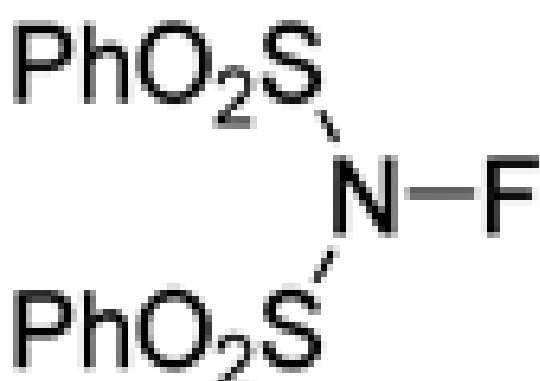X-ray structure of **2**, showing the equatorially disposed C–F bond.
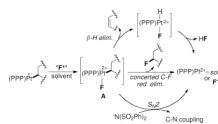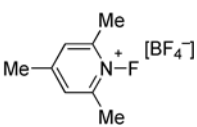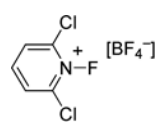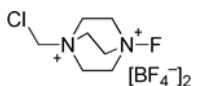
Scheme 1.
Proposed mechanistic pathways for fluorinations of (triphos)Pt-R$^+$.
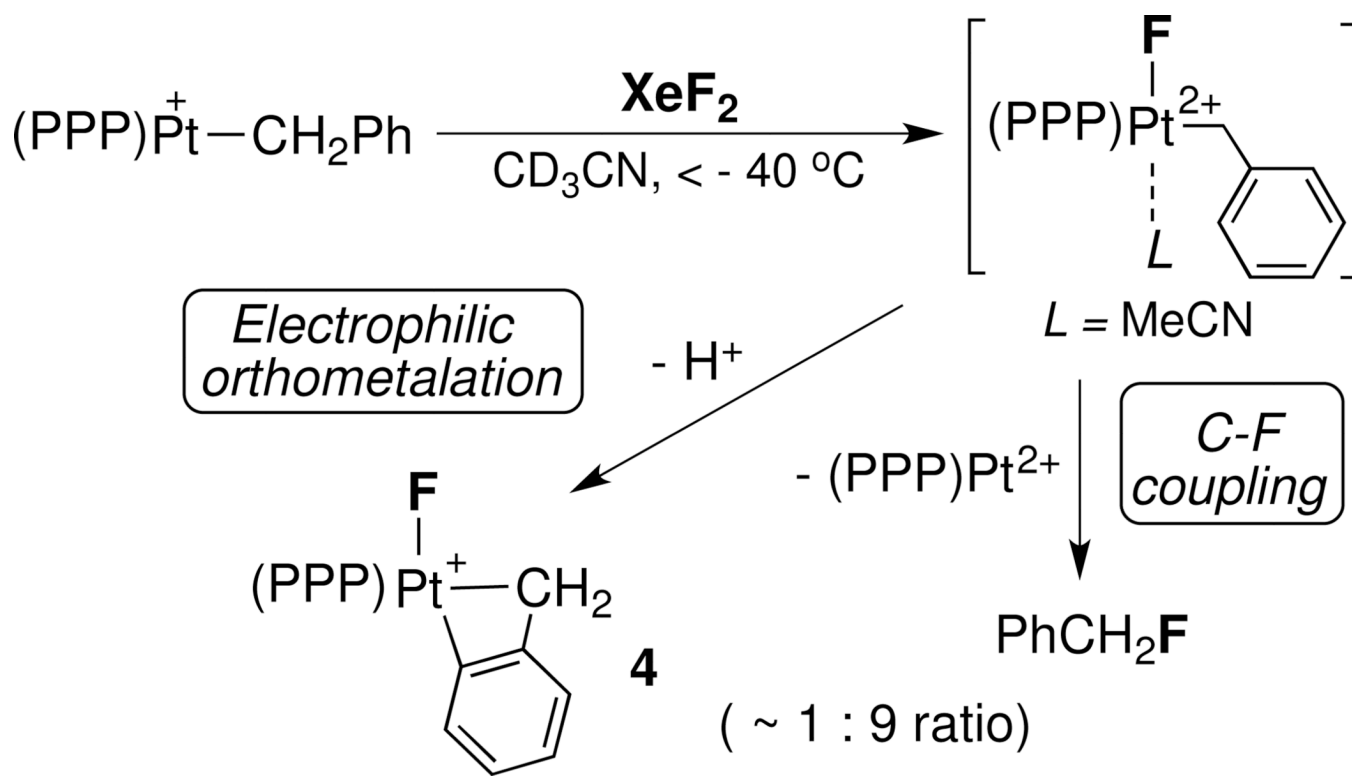
Scheme 2.
Cyclometallation of a putative Pt(IV) fluoride intermediate.

Table 1

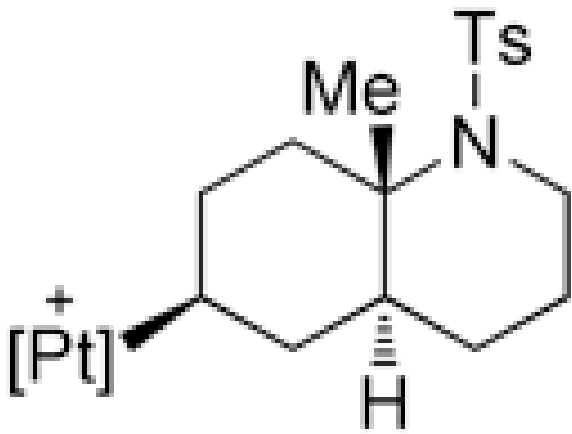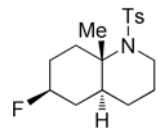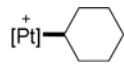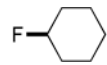Fluorination of **1** with a variety of "F⁺" reagents[a]
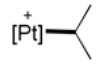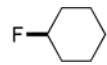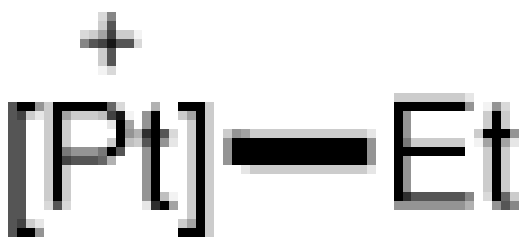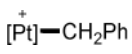
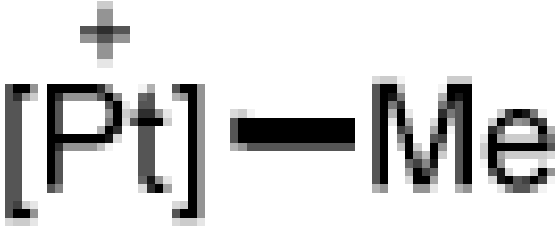| Entry	F⁺ source	Temperature	time	yield of 2[b]
1	[pyridinium N–F] [BF₄⁻]	70 °C	28 h	93%
2	2,4,6-trimethylpyridinium N–F [BF₄⁻]	70 °C	3 d	NR
3	2,6-dichloropyridinium N–F [BF₄⁻]	25 °C	35 h	91%
4	chloromethyl-DABCO N–F [BF₄⁻]₂	25 °C	6 h	88%
5	XeF₂	0 °C	< 3 min	87% (85%)[c]
6	PhO₂S–N(–F)–SO₂Ph	70 °C	17 h	81%

[a]Conditions: **1** (0.02 mmol), 1.2~1.5 equiv of F⁺ source, dry CD₃CN (0.5 mL).

[b]Determined by NMR and GC-MS; average of three trials.

[c]Isolated yield.

Table 2

Fluorination of platinated alkyls with $XeF_2{}^a$

Entry	[(triphos)Pt-alkyl][BF₄]	Product	Isolated yield[b]
1			88%[c]
2			84%
3			87%

Entry	[(triphos)Pt-alkyl][BF4]	Product	Isolated yield[b]
4			91%
5			82%
6			14%[c]
7		Et-**F**	41%[c]
8		PhCH2-**F**	> 95%[c]

Entry	[(triphos)Pt-alkyl][BF$_4$]	Product	Isolated yield[b]
9	[Pt]$^+$—Me	[[Pt^{IV}](**F**)(Me)]$^{2+}$	_d

[a]Conditions: [(triphos)Pt-alkyl][BF$_4$] (0.04 M), 1.2~1.5 equiv of XeF$_2$, dry CD$_2$Cl$_2$, 0 °C, 3 min (entry 1–8), or dry CD$_3$CN, RT, 0–20 min (entry 9).

[b]Average of three trials.

[c]NMR yields, these products are highly volatile.

[d]A mixture with variable product ratios.