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Anion-Dependent Switch in C–X Reductive Elimination Diastereoselectivity

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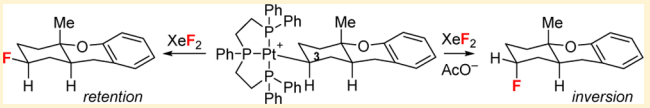
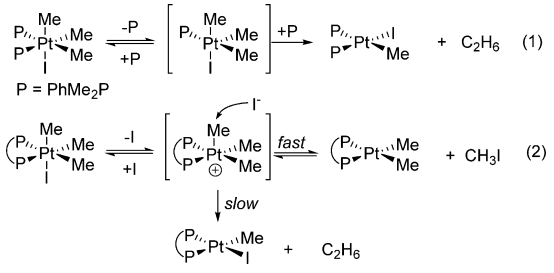
Supporting Information

ABSTRACT: Reaction of a complex Pt organometallic species with electrophilic halogen sources in the presence of X^- ligands changes the mechanism of reductive elimination from a concerted reductive coupling type to an S_N2 type reductive elimination. In the absence of the added X^- ligand the reductive elimination is stereoretentive; in its presence, the process is stereoinvertive. This selectivity hinges on the reactivity of a key five-coordinate Pt(IV) intermediate with the X^- ligand.

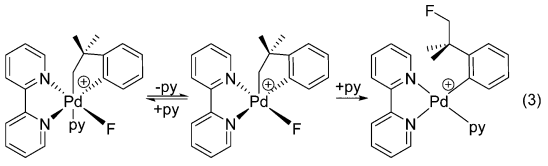


The oxidative addition of carbon–halogen bonds to transition-metal centers is one of the most fundamental transformations in organometallic chemistry. Its microscopic reverse, reductive elimination, has received considerably less attention. Carbon–halogen bond forming reductive elimination from Pt(IV), commonly observed as a byproduct in Shilov chemistry in the form of CH_3Cl,[1] has been the focus of several important studies. Seminal works by Puddephatt[2] and Goldberg[3] on tetravalent P_2PtMe_3I complexes have revealed the dominant mechanism to be dissociative and proceed through key five-coordinate intermediates accessed through ligand loss from the ground-state octahedral structure. In the case of monodentate phosphines,[2] phosphine dissociation precedes the reductive elimination of ethane (eq 1). Chelating diphosphines, on the



other hand, make iodide dissociation more favorable, which enables a kinetically preferred but reversible S_N2 type reductive elimination of iodomethane (eq 2).[3]

Fluorinated organic compounds are of considerable interest, due in part to their pervasiveness in drugs and drug candidates,[4] their utility in ^{18}F PET,[5] and the inertness of the C–F bond. Electrophilic fluorinating reagents have been especially useful in the context of group 10 organometallic catalysts, as their ability to oxidatively generate tetravalent Pd (mostly) intermediates has led to new oxidative synthesis methods that may[6] or may not[6a,d,e,7] include the generation of C–F bonds.[8] Important in the divergence of methods where in some cases "F^+" only acts as the oxidant and others where F–C couplings take place are the kinetics of C–F reductive elimination, which are typically sluggish and can shift the preference to C–C or C–N bond forming reductive elimination.[9] In cases where C–F bond formation does occur from octahedral complexes, several studies reinforce the dissociative nature of such eliminations.[10] Ritter has demonstrated that the C_{aryl}–F bond forming reductive elimination from Pd(IV) precursors occurs subsequent to ligand dissociation from a 6-coordinate complex.[11] Sanford has also reported that C_{alkyl}–F reductive elimination from a cyclometalated Pd(IV) precursor is also preceded by pyridine dissociation (eq 3).[12] While the authors could not differentiate between direct and S_N2 type reductive elimination, a direct mechanism was favored.



While C_{alkyl}–X reductive elimination from Pt(IV) generally proceeds by S_N2 type mechanisms (e.g., eqs 1 and 2),[3b,13] we have previously observed that C_{alkyl}–F,[14] C_{alkyl}–Cl, C_{alkyl}–Br, and C_{alkyl}–I[15] reductive elimination from transient tetravalent (triphos)Pt(R)(X)$^{2+}$ intermediates occur with stereoretention at carbon, by processes most easily explained by *concerted* reductive elimination (Scheme 1).[16] In these cases, reductive elimination is rapid and the putative Pt(IV) intermediates are generated as reactive intermediates.[15,17] The stereochemistry of these transformations shows unambiguously that alkyl C–F, C–Cl, C–Br, and C–I reductive eliminations do not exclusively proceed by invertive processes and can indeed utilize concerted (retentive)

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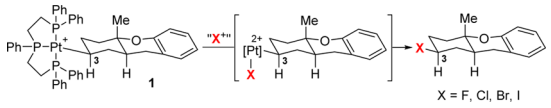
Scheme 1. Stereoretentive C−X Reductive Elimination

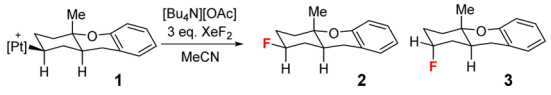


mechanisms. In the case of the complex alkyl structures generated by our cascade cyclization methods,[18] such mechanistic distinctions are important, as they affect the diastereopreference of the R−X product.

Changes in the rate and character of reductive elimination reactions by the addition of competitive nucleophiles is often used to delineate the features of S_N2 type reductive elimination mechanisms. We report herein that similar additions of anionic nucleophiles actually change the mechanism and switch the stereochemistry of C−X reductive elimination from (triphos)-Pt−R(X)$^{2+}$ complexes.

As previously reported, oxidation of compounds such as **1** with electrophilic fluorine sources led to rapid, reductive elimination to a C_3−F fluorinated product that retains the stereochemistry of the Pt−C bond and likely proceeds via a five-coordinate dicationic Pt(IV) fluoride intermediate (X = F; Scheme 1). Since C−F reductive elimination is typically sluggish, we hypothesized that this intermediate could be intercepted by X^- ligands such as OAc^- to access octahedral tetravalent (triphos)-Pt(F)(X)(R)$^+$ intermediates, which might yield new C_3−X products through a selective reductive elimination. To this end, this same reaction was repeated with several added anions. Unexpectedly, however, combining 3 equiv of XeF_2 with $[Bu_4N][OAc]$ did not lead to the hoped-for C_3−OAc product but instead caused a change in the stereochemistry of the C−F reductive elimination. With 1 equiv of $[Bu_4N][OAc]$, a mixture of C−F diastereomers was observed, with a slight preference for the stereoretentive C−F product **2** (50% to 41%) in a total yield of 91% (Table 1). Addition of 5 and 10 equiv of $[Bu_4N][OAc]$ further shifted the preference toward the axial fluoride **3** in a total yields of 63 and 42%, respectively.[19]

Table 1. Fluorination of 1 in the Presence of $[Bu_4N][OAc]$

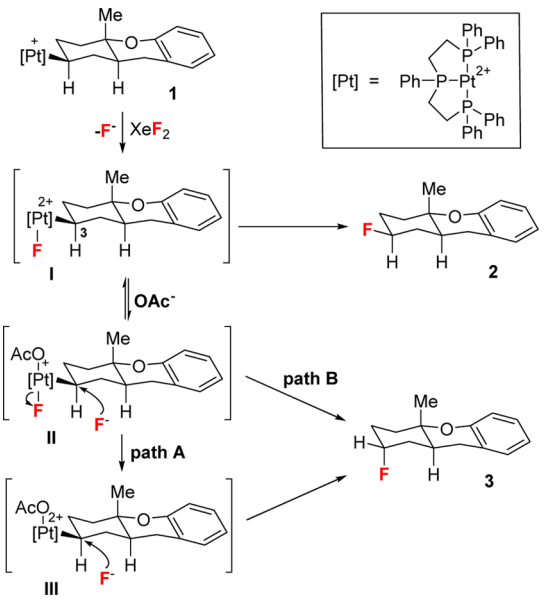


amt of $[Bu_4N][OAc]$, equiv	yield,[a] % total	2	3	ratio 3/2
1	91	41	50	1.2
5	63 (39)[b]	5	58	12
10	42	3	39	13

[a]Yields determined by ^{19}F NMR using 1-fluoro-3,5-dimethoxybenzene as internal standard; the mass balance consists of protodemetalation, β-hydride elimination, and unidentified products. [b]Isolated yield.

In the absence of acetate, oxidation of **1** with XeF_2 is proposed to generate a five-coordinate Pt(IV) dicationic complex, (**I**; Scheme 2), which then undergoes stereoretentive C−F bond forming reductive elimination. While reaction times both with and without $[Bu_4N][OAc]$ were rapid, the diversion away from the stereoretentive pathway suggests that **I** can be intercepted by acetate to form an unobserved six-coordinate complex such as **II**. The data can therefore be explained by proposing that **II** follows one of two convergent reductive elimination paths: path A, a conventional predissociation of F^- and subsequent attack on the

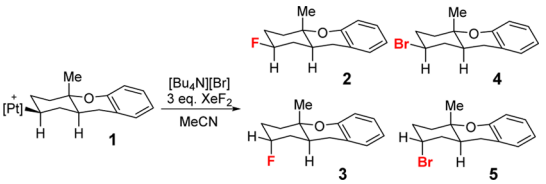
Scheme 2. Proposed Mechanism of C−F Reductive Elimination



five-coordinate intermediate **III**, or direct attack of F^- on **II** without prior ligand loss (path B, Scheme 2). While path B cannot be discounted, significant precedence suggests that path A is more likely. The stepwise process directly generates (triphos)Pt(OAc)$^+$ as the organometallic product (observed), while path B would transiently generate (triphos)Pt(OAc)(F) in a non-square-planar Pt(II) geometry.

Addition of $[Bu_4N][Br]$ in place of $[Bu_4N][OAc]$ resulted in competitive formation of C−F and C−Br products (Table 2).

Table 2. Competitive Fluorination and Bromination of 1 in the Presence of $[Bu_4N][Br]$



amt of $[Bu_4N][Br]$, equiv	yield,[a] % total	2	3	4	5
1	59	51	3		5
2	56	32	1	4	19
5	83	31		21	31

[a]Yields determined by ^1H NMR with 4-methylanisole as internal standard; the mass balance consists of protodemetalation, β-hydride elimination, and unobserved products.

With 1 equiv of $[Bu_4N][Br]$, the stereoretentive fluoride **2** was the main product. Two equivalents of $[Bu_4N][Br]$, however, changes the product distribution such that **2** is generated in 32% yield along with stereoinvertive and stereoretentive bromides **5** and **4** in 19 and 4% yields, respectively. Five equivalents of $[Bu_4N][Br]$ increases the total yield to 83%, with the C−Br products dominating (Table 2).

These data can be rationalized by invoking a mechanism that is related to the acetate effect in Scheme 2, except that bromide can act as a competitive reductive elimination nucleophile. In this

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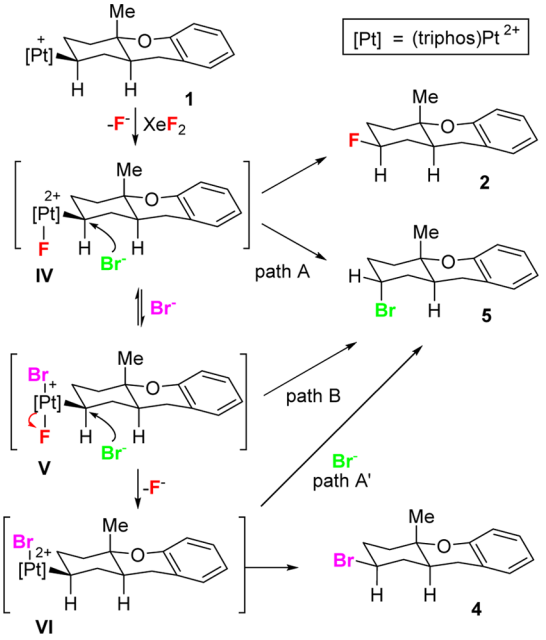
scheme three pathways exist for alkyl bromide formation: (1) invertive attack of bromide on C_3 of the five-coordinate Pt(IV) fluoride **IV** (path A, Scheme 3), (2) trapping of **IV** with bromide

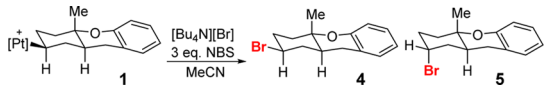
Scheme 3. Proposed Mechanism of C−F and C−Br Reductive Elimination



followed by a subsequent bromide attack onto the six-coordinate **V** (path B, Scheme 3), and (3) a process via five-coordinate intermediate **VI** (path A′, Scheme 3). The minor amounts of stereoretentive bromide would result from direct C−Br reductive elimination from **VI** (Scheme 3), which could also be formed following oxidation of Br^- by "F^+"[20] and direct oxidation of **1** by Br^+, as observed in reactions of **1** with *N*-bromosuccinimide (NBS).[15]

The combination of (NBS) as oxidant and $[Bu_4N][Br]$ as nucleophile was also informative, as it once again showed a diastereoselectivity that was sensitive to the added nucleophile (Table 3). While the reaction of NBS with **1** takes several hours,[15] in the presence of $[Bu_4N][Br]$ full consumption takes minutes.[21] Addition of 1 equiv of $[Bu_4N][Br]$ resulted in a 2:1 ratio of bromide diastereomers (26% to 12%) with a preference for the invertive, while addition of 2 and 5 equiv of $[Bu_4N][Br]$ further shifted the product distribution to the invertive (48% to 12% and 29% to 6%, respectively). These data can be similarly

Table 3. Bromination of 1 with NBS and $[Bu_4N][Br]$

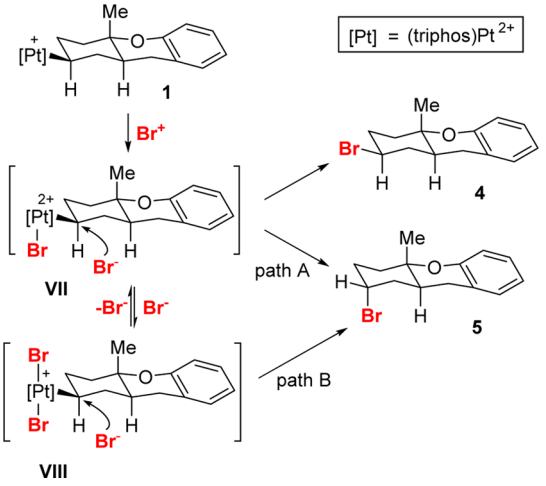


amt of $[Bu_4N][Br]$, equiv	yield, % total[a]	4[b]	5[b]	ratio 5/4
1	38	12	26	2.2
2	60	12	48	4
5	35	6	29	4.8

[a]Yields determined by ^1H NMR with 4-methylanisole as internal standard; mass balance consists of protodemetalation, β-hydride elimination, and unobserved products. [b]Ratios determined by GC/MS.

explained by proposing two pathways for formation of the invertive product: nucleophilic attack upon a five-coordinate (**VII**) or six-coordinate (**VIII**) Pt alkyl complex (Scheme 4).

Scheme 4. Proposed Mechanism for Bromination of 1 using NBS and Added Br^-



This study provides clear evidence for competing mechanisms of reductive elimination from unobserved dicationic Pt(IV) complexes.[22] While a stereoretentive process is favored when no strongly coordinating ligands can occupy the vacant coordination site, acetate or bromide can competitively trap the five-coordinate complex and promote invertive mechanisms. Since the buildup of F^- [23] during the course of fluorination reactions with XeF_2 does not erode the diastereoselectivity of C−F reductive eliminations, F^- itself is not an effective X^- ligand for **I**. The poor ligand qualities of F^- [8] are consistent with catalytic cyclization/fluorination reactions with P_2Pt^{2+} catalysts, which are not inhibited by the buildup of F^-.[14b] An additional corollary to the results observed with OAc^- is that while it can function as a good X^- ligand for intercepting an intermediate such as **I**, it is a poor ligand for both concerted and S_N2-type reductive elimination, being outcompeted by F^- in both mechanisms.

Studies by Goldberg on P_2PtMe_3OAc complexes have shown that, when the electrophilic carbon is CH_3, stepwise C−O reductive eliminations are possible.[13d,24] The divergent activity between CH_3 in the Goldberg case and cycloalkyl in the present case may thus be steric in nature. Consistent with this notion is the reactivity of (triphos)Pt−Me^+ and **1** with F−$N(SO_2Ph)_2$.[14a] In the former case CH_3−$N(SO_2Ph)_2$ is formed from counterion attack on (triphos)$PtF(Me)^{2+}$; this pathway is disfavored for the cycloalkyl **1**, which preferentially undergoes C−F reductive elimination. The small size of CH_3 is thus enabling of classic S_N2 reductive elimination pathways.

The preference for a stereoretentive reductive elimination in the absence of a suitable X^- ligand is likely a result of the aversion of five-coordinate complexes such as **I** and **VII** to generate nucleophilic X^- (F^-, Cl^-, Br^-, I^-) through dissociative ligand loss, as this would form the electronically and sterically unsaturated tricationic, 14-electron reactive intermediate **IX** (Scheme 5). The prohibitive cost of generating such a species en route to an S_N2 type reductive elimination thus shifts the kinetic preference toward the observed stereoretentive pathways. When suitable X^- ligands can trap the five-coordinate complex, however, the oxidizing X^+ ligand can dissociate (as X^-) from the six-coordinate complex and return to participate in S_N2 type

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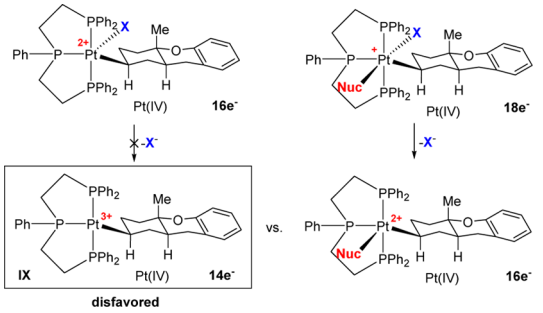
Scheme 5. Comparison of X^- Dissociation Properties from Five- and Six-Coordinate (triphos)Pt^{IV} Complexes



reductive elimination if no competing nucleophilic ligands are present (e.g., "F^+"/OAc^-), or make way for more reactive nucleophiles when present (e.g., "F^+"/Br^-).

In summary, these studies delineate the subtle and not so subtle features controlling the diastereopreference for reductive elimination in (triphos)$PtR(X)^{2+}$ complexes. Key determinants include the availability and nucleophilicity of anionic ligands along with the reluctance of (triphos)$PtR(X)^{2+}$ intermediates to undergo X^- loss (X = F^-, Br^-) as a precursor to a conventional invertive reductive elimination. These studies, coupled with a previous examination of the propensity of (triphos)$PtR(F)^{2+}$ complexes to undergo C–F reductive elimination or β-hydride elimination as a function of R group size,[14a] provides a significantly improved vision of how one can exercise stereochemical control over fundamental transformations such as reductive elimination in complex organometallics.

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental procedures as well as spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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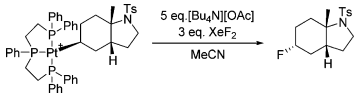
(19) Repeating the reaction conditions with 5 equiv of tetrabutylammonium acetate allowed for isolation of the invertive product in 36% yield with a dr of 12:1 in the reaction



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