Oxidation of a Cyclometalated Pd(II) Dimer with "CF₃⁺": Formation and Reactivity of a Catalytically Competent Monomeric Pd(IV) Aquo Complex

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Abstract

The reaction of [(bzq)Pd(OAc)]₂ (bzq = benzo[*h*]quinoline) with "CF₃⁺" reagents to afford the monomeric Pd^{IV} aquo complex (bzq)Pd(CF₃)(OAc)₂(OH₂) is demonstrated. Heating this Pd^{IV} adduct at 60 °C for 12 h leads to highly chemoselective Aryl–CF₃ bond-forming reductive elimination. The rate and yield of this transformation are both significantly enhanced by the addition of Brønsted and Lewis acidic additives. The mechanism of C–CF₃ bond-formation from (bzq)Pd(CF₃)(OAc)₂(OH₂) has been studied, and the major pathway is proposed to involve pre-equilibrium acetate dissociation followed by C–CF₃ coupling. Finally, this monomeric Pd^{IV} complex is shown to be a kinetically competent intermediate for C–H trifluoromethylation with "CF₃⁺" reagents. Collectively, these studies provide valuable insights about the speciation, nuclearity, and reactivity of Pd intermediates in catalytic C–H trifluoromethylation reactions.

Introduction

Over the past 6 years, the field of Pd-catalyzed ligand-directed C–H functionalization has grown exponentially.[1] Much of the work in this area has focused on using Pd catalysts in conjunction with strong oxidants (e.g., hypervalent iodine reagents, electrophilic halogenating reagents) to convert C–H bonds into C–C or C–heteroatom linkages.[1] Despite great progress in new reaction development, the nature of the catalytically active high oxidation state Pd intermediates in these transformations remains the subject of intense study and discussion.[2,3] For example, monomeric,[4,5] dimeric,[6,7] and trimeric[8] Pd complexes in oxidation states ranging from +2 to +4 have all been proposed as catalytically active species.[2] Furthermore, while co-solvents and additives are frequently employed to promote these transformations, their effects are generally empirically derived and poorly understood.[1,2] Studies that provide further mechanistic insights should facilitate the optimization and rational design of new reactions in this area.

Several recent reports have focused on the role of cyclometallated Pd^{II} dimers like **1** and **3** (eqs 1 and 2) as intermediates in Pd-catalyzed C–H functionalization.[6,7] For example, the oxidation of **1** to generate acetate-bridged Pd dimer **2** has been kinetically implicated as the turnover-limiting step in C–H arylation reactions (eq. 1).[6] Similar dimeric Pd^{III} adducts (**4**) have been isolated from the stoichiometric reaction of complex **3** (and analogues) with PhICl₂ and PhI(OAc)₂ (eq. 2).[7] While monomeric Pd^{IV} species have also been proposed as

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possible intermediates in catalytic C–H functionalization,[1–4] to date such complexes have not been detected from the oxidation of catalytically relevant dimers like **1** and **3**.[5]

(1)

(2)

We demonstrate herein that the reaction between **3** and various electrophilic trifluoromethylating reagents in the presence of AcOH produces an isolable monomeric Pd^{IV} product. This Pd^{IV} complex undergoes C–CF$_3$ bond-forming reductive elimination, and both the rate and yield of this transformation can be tuned with Lewis/Brønsted acids. Mechanistic investigations of the C–CF$_3$ bond forming process are described and provide new insights into the potential role of acidic promoters in Pd-catalyzed C–H functionalization.[9,10] Finally, we demonstrate that this Pd^{IV} species is a catalytically competent intermediate in C–H trifluoromethylation reactions.

Results and Discussion

Synthesis and Characterization of Pd^{IV} Complex 6

Our initial investigations focused on the reaction of Pd^{II} dimer **3** with the CF$_3^+$ reagents **5a–e**[11] in AcOH. In all cases, ^{19}F NMR spectroscopic analysis after 1 h at 40 °C showed the formation of a new Pd–CF$_3$ product (**6**) in yields ranging from 2–60% (Table 1, entries 1–5).[12] When the solvent was changed to 1,2-dichloroethane (which has been used as a solvent for Pd-catalyzed C–H trifluoromethylation with similar oxidants),[9] the reaction of **3** with **5b** afforded <2% of **6**. However, interestingly, when this same reaction was conducted in the presence of 1–20 equiv AcOH (which is present during catalytic C–H trifluoromethylation, *vide infra*),[9] **6** was formed in modest to good yield (Table 1, entries 7–9). Complex **6** was isolated in 60% yield as a pale yellow solid from the reaction of **3** with 3 equiv of **5b** in AcOH at room temperature.[12,13]

^{1}H and ^{19}F NMR spectroscopic analysis of complex **6** at room temperature showed that this molecule contains a cyclometalated benzo[*h*]quinoline, a CF$_3$ group, and two different acetate ligands. In addition, when samples of **6** were cooled to −40 °C, a broad ^{1}H NMR resonance integrating to 2 protons was observed at 10.45 ppm, implicating the presence of a coordinated water molecule.

X-ray quality crystals of **6** were obtained by vapor diffusion of pentanes into a concentrated dichloroethane solution. As shown in Figure 1, the crystal structure shows the monomeric

Pd^{IV} complex (bzq)Pd(CF$_3$)(OAc)$_2$(OH$_2$). In the solid state, the aquo ligand is trans to the σ-aryl group, and it participates in two intramolecular hydrogen bonds with the carbonyl oxygens of the acetate ligands.[14] The O$_{Ac}$---H bond distances 1.69(5) and 1.82(2) Å are similar to hydrogen bonds reported in I^{i}PrPd^{II}(OAc)$_2$(OH$_2$) (1.73 and 1.82 Å, I^{i}Pr =1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene).[15] The H-bonding interaction in **6** is also apparent by IR spectroscopy (ν$_{OH}$(KBr) = 3414 cm^{-1}).

Complex **6** is remarkable for several reasons. First, this mono-σ-aryl Pd complex is unusually stable at room temperature.[2] In the solid state, **6** can be stored for at least 1 month without noticeable decomposition; furthermore, the t$_{1/2}$ for decomposition in CD$_3$CO$_2$D solution is 16 h at 25 °C. Second, **6** is formed under conditions analogous to those reported for catalytic C–H trifluoromethylation (using CF$_3$$^+$ reagents in DCE containing 1–20 equiv of exogenous AcOH),[9] suggesting the possibility that it is a catalytic intermediate (*vide infra*). Finally, the formation of **6** shows that dimer **3** can be oxidized to afford monomeric Pd^{IV} complexes.[13] This is particularly notable in light of recent work by Ritter, who demonstrated that the reaction of **3** with PhIX$_2$ (X = Cl, OAc) in dry CH$_2$Cl$_2$ at −35 °C produces Pd^{III} dimers (eq. 2).[7] On the basis of these studies, he concluded that "bimetallic Pd^{III} complexes are responsible for a large class of C–H oxidations previously proposed to proceed via Pd$^{II/IV}$ redox cycles."[7b] In contrast, the current work suggests that factors such as reaction solvent, oxidant structure, ancillary ligands, and temperature are all likely critical in determining the structure(s) of high oxidation state intermediates in such transformations.[3]

C–CF$_3$ Bond-Forming Reductive Elimination from 6

Complex **6** could undergo reductive elimination to produce at least three products: bzq–CF$_3$ (**7**), bzq–OAc (**8a**), or bzq–OH (**8b**) (Table 2). Thus, this system provides an opportunity to assess the relative rates of these different C–CF$_3$ and C–O bond-forming processes. While C–O bond-forming reductive elimination is well-precedented from palladium(IV)[5b,17] and many other metal centers/oxidation states,[18] C–CF$_3$ coupling reactions remain extremely rare in organometallic chemistry.[19,20,21]

Heating **6** at 60 °C for 12 h in a variety of solvents (AcOH, CHCl$_3$, DCE, and nitrobenzene) produced trifluoromethylated product **7** in 54–62% yield along with <2% of **8a** and **8b** (Table 2, entries 1–4). We propose that the remarkably high chemoselectivity for C–CF$_3$ bond formation may be due to hydrogen bonding between the coordinated H$_2$O and OAc ligands, which slows competing C–O bond coupling. Although no other organic products could be identified in these reactions, we could only account for approximately 60% of the benzo[*h*]quinoline ligand. The only other recognizable benzo[*h*]quinoline-containing product was [(bzq)Pd(OAc)]$_2$ (**3**), which was formed in <3% yield.[22]

Literature reports have described similarly modest mass balance in other oxidatively-induced reductive elimination reactions from Pd.[23] In many of these cases, the addition of pyridine (which can bind to highly reactive, coordinatively unsaturated Pd intermediates) led to improved results.[23] Thus, we also examined the thermolysis of **6** in DCE in the presence of 50 equiv of pyridine. As anticipated, the mass balance improved significantly under these conditions (with 84% of the benzo[*h*]quinoline ligand accounted for). However, intriguingly, the chemoselectivity of the reaction was reversed, and only the C–O coupled product **8b** was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Table 2, entry 5). We hypothesize that this dramatic change in selectivity may result from disruption of the H-bonding in **6** (by either deprotonation or displacement of the H$_2$O ligand by pyridine), which then lowers the barrier for C–O bond formation.

Mechanism of C–CF$_3$ Bond-Forming Reductive Elimination

The most likely mechanisms for C–CF$_3$ bond-forming reductive elimination from complex **6** are paths **A**, **B**, and **C** in Figure 2. Path **A** involves dissociation of an acetate ligand to afford a five-coordinate cationic intermediate (**I**) followed by C–CF$_3$ bond-forming reductive elimination to afford **7**. Path **B** proceeds via dissociation of H$_2$O to generate a neutral 5-coordinate Pd^{IV} species **II** and subsequent C–CF$_3$ coupling. Finally, path **C** involves direct reductive elimination from octahedral complex **6**. Notably, ionic dissociative mechanisms (like path **A**),[24,25] neutral dissociative mechanisms (like path **B**),[26] and concerted processes (like path **C**)[27] have significant precedent in reductive elimination reactions from octahedral Pd^{IV} and Pt^{IV} complexes.

Our first mechanistic studies probed the viability of carboxylate dissociation/exchange (step i of path **A**). The addition of 20 equiv of AcOH-d_4 or 20 equiv of NMe$_4$OAc-d_3 to complex **6** in DCE-d_4 led to complete exchange of both acetate ligands within minutes at room temperature (as determined by ^{1}H NMR spectroscopic analysis) (eq. 3). These results demonstrate that carboxylate ligand substitution is significantly faster than C–CF$_3$ coupling.

(3)

We next investigated the influence of exogenous NBu$_4$OAc on C–CF$_3$ bond-forming reductive elimination from **6**. Interestingly, the addition of 1 equiv of NBu$_4$OAc almost completely shut down the formation of bzq–CF$_3$ (**7**); under these conditions, the major identifiable organic products were oxygenated compounds **8a** and **8b** (Table 3, entry 3). In the presence of smaller amounts of NBu$_4$OAc (0.2 equiv), **7** was formed, but in significantly lower yield than without this additive (26% versus 54% yield, Table 3, entries 1 and 2, respectively).

Quantitative kinetic analysis of these transformations was complicated by the presence of an induction period. Nonetheless, it was instructive to compare the reaction profile (yield versus time) in the presence and absence of NBu$_4$OAc. As shown in Figure 3, the addition of NBu$_4$OAc significantly increased the induction period and slowed the rate of bzq–CF$_3$ coupling. In notable contrast, the addition of NBu$_4$PF$_6$ had minimal impact on the yield (Table 3, entry 4) or reaction profile (Figure S16) compared to the analogous reaction without additive. This indicates that the dramatic effect of NBu$_4$OAc is specifically due to the acetate anion.

Finally, we examined the influence of H$_2$O on reductive elimination from **6**. The addition of 1–10 equiv of H$_2$O had minimal impact on the overall yield of **7** after 12 h at 60 °C (Table 3, entries 5 and 6). The presence of 1 equiv of H$_2$O did slow the rate and increase the induction period for this transformation (Figure 3); however, this effect was much smaller than that observed with 0.2 equiv NBu$_4$OAc.

Summary of Mechanistic Data—On the basis of all of this data, we propose that mechanism **A** (involving pre-equilibrium acetate dissociation followed by rate-determining C–CF$_3$ coupling) is a major pathway for C–CF$_3$ bond formation from **6**. The AcOH-d_4 and NMe$_4$OAc-d_3 exchange experiments indicate that step i of path **A** is fast relative to C–CF$_3$ bond-formation. The inhibition of this reaction by exogenous NBu$_4$OAc (but not by NBu$_4$PF$_6$) is consistent with the expected inverse 1st order dependence on [AcO$^-$] (see

Figure S10 for derivation of the rate expression). Importantly, the current data do not definitively rule out mechanisms **B** or **C** as competing pathways. However, the comparatively small influence of added H_2O on the product distribution, yield, and reaction profile is consistent with mechanism **A** as the most significant contributor to this transformation.

Effects of Additives on C–CF₃ Bond-Forming Reductive Elimination from 6

On the basis of several literature reports,[5b,18c] we hypothesized that pre-equilibrium dissociation of acetate would be promoted by Brønsted acids [*e.g.,* trifluoroacetic acid (TFA)], Lewis acids (*e.g.,* Yb(OTf)$_3$), and other reagents that react readily with free AcO^- [*e.g.,* trifluoroacetic anhydride (TFAA)]. As such, we next examined the effect of these additives on reductive elimination from **6**. As shown in Figure 4, the addition of 10 equiv of TFA or TFAA or 1 equiv of Yb(OTf)$_3$ eliminated the induction period and provided first order kinetic profiles for bzq–CF$_3$ coupling.

Additionally, these additives led to substantial increases in the yield of C–CF$_3$ coupled product **7** (Table 4). Most notably, with 1 equiv of Yb(OTf)$_3$, nearly quantitative yield of **7** was obtained (compared to 54% in the absence of this additive).

These effects provide further support for mechanism **A** (Figure 2) as a major pathway for C–CF$_3$ coupling in this system. Additionally, the observed enhancements in mass balance suggest that the acidic/electrophilic additives may play a role in sequestering reactive, coordinatively unsaturated Pd intermediates formed during the reductive elimination process.

Catalytic Competence of 6 in Pd-Catalyzed C–H Trifluoromethylation

A recent communication by Yu and coworkers demonstrated the Pd(OAc)$_2$-catalyzed C–H trifluoromethylation of benzo[*h*]quinoline with oxidants **5b**, **5d**, and **5e** in DCE.[9] The addition of 1 equiv of Cu(OAc)$_2$ and 10 equiv of TFA was critical to promote catalytic turnover in these reactions (eq. 4); however, no insights were provided regarding the mechanistic role of these additives. In addition, while the authors speculated that a Pd$^{II/IV}$ pathway was plausible in this system, no mechanistic experiments were reported.

[Pd] = Pd(OAc)$_2$; Initial Rate = 0.08 x 10^{-4} M/s
[Pd] = **6**; Initial Rate = 1.40 x 10^{-4} M/s

(4)

We hypothesized that Pd^{IV} complex **6** might be an intermediate in this catalytic transformation. Using the method of initial rates, we compared the trifluoromethylation of benzo[*h*]quinoline with **5e** using 10 mol % of Pd(OAc)$_2$ to that with 10 mol % of complex **6** under otherwise identical conditions. As shown in eq. 4, the initial rate with **6** was 18-fold faster than that with Pd(OAc)$_2$. Furthermore, both catalysts provided similar yields of product **7** when the reactions were followed to completion. These results clearly demonstrate the kinetic competence of **6** and establish the potential viability of this monomeric Pd^{IV} species as a catalytic intermediate.

Role of Promoters in Catalytic C–H Trifluoromethylation

The demonstration that **6** is a catalytically competent intermediate in C–H trifluoromethylation provided a platform for rationalizing the role that the promoters $Cu(OAc)_2$ and TFA play in the catalytic cycle. All of the studies described above suggest that these additives are important for both the formation of and C–CF_3 reductive elimination from Pd^{IV} complex **6**. As shown in Table 1, the generation of **6** by oxidation of **3** with CF_3^+ requires the presence of at least 1 equiv of AcOH. Under the catalytic conditions, the combination of $Cu(OAc)_2$/TFA would provide an initial source of AcOH through the equilibrium in eq. 5.

$$Cu(OAc)_2 + TFA \rightleftharpoons Cu(TFA)_2 + AcOH \tag{5}$$

The results in Table 4 demonstrate that acidic additives can increase the rate, yield, and mass balance of C–CF_3 bond-forming reductive elimination from **6**. To test whether catalytically relevant quantities of $Cu(OAc)_2$/TFA have a similar effect, we studied the thermolysis of **6** in the presence of 10 equiv of $Cu(OAc)_2$ and 100 equiv of TFA. Under these conditions, reductive elimination occurred extremely rapidly and in nearly quantitative yield (94% compared to 54% in the absence of Cu/TFA) (Figure 5). These results implicate $Cu(OAc)_2$/TFA in: (*i*) accelerating reductive elimination from a Pd^{IV} intermediate like **6** and (*ii*) limiting competing unproductive decomposition pathways of this high oxidation state complex that reduce the yield of bzq–CF_3 (**7**).

Conclusions

In conclusion, this article describes the oxidation of cyclometalated Pd dimer $[(bzq)Pd(OAc)]_2$ with CF_3^+ reagents to generate monomeric Pd^{IV} trifluoromethyl complex **6**. This complex undergoes highly chemoselective C–CF_3 bond-forming reductive elimination that is accelerated by acidic additives. Complex **6** is also a kinetically competent catalyst for the Pd-catalyzed trifluoromethylation of benzo[*h*]quinoline with CF_3^+ reagents. On the basis of this data, we propose that **6** is a catalytically relevant intermediate in C–H trifluoromethylation reactions. These studies provide new insights into the role of the promoters $Cu(OAc)_2$ and TFA in the catalytic transformations. Specifically, these additives appear to: (1) serve as a source of AcOH (which is critical for the oxidation of dimeric $[(bzq)Pd(OAc)]_2$ **3** to monomeric **6**) and (2) accelerate and enhance mass balance in C–CF_3 coupling from **6**. We anticipate that this (and other related) detailed mechanistic/organometallic investigations of Pd-catalyzed C–H functionalization will facilitate the rational design of new catalysts, promoters, and reagents for these transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Only traces of H_2O are required for the formation of **6**. For example, using AcOH solvent that was dried by distillation over Ac_2O and $KMnO_4$ led to nearly identical yields of **6**.

13. Complex **6** was the major inorganic product regardless of the equiv of `CF_3^+' (from 0.5–3) used in this reaction. Lower equiv of oxidant simply led to lower % conversion of **3**. See Supporting Information (Table S3) for details.

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22. The inorganic by-products of C–CF$_3$ bond-forming reductive elimination in DCE were also characterized. After heating **6** to 60 °C for 12 h, di-*tert*-butylbipyridine (dtbpy) was added to trap the Pd-containing species. Stirring the resulting mixture at room temperature for 1 h afforded (*t*Bu-bpy)(Pd^{II})(CF$_3$)(OAc) and (*t*Bu-bpy)(Pd^{II})(OAc)$_2$ as the major inorganic products. See Supporting Information for full details.

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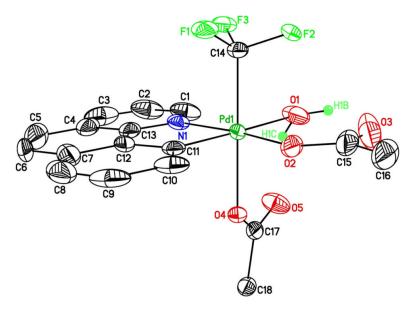
Figure 1.
ORTEP drawing of complex **6**. Thermal ellipsoids are drawn at 50% probability, and hydrogen atoms are omitted for clarity expect for those on the H_2O ligand. The structure was solved as two identical structures in a unit cell (only one is shown, see Supporting Information for more information). Selected bond lengths (Å): Pd–C(14) 2.007(4), Pd–C(11) 2.006 (4), Pd–N(1) 2.042(3), Pd–O(1) 2.168(4), Pd–O(2) 2.012(3), Pd–O(4) 2.105(3), Pd–N 2.042(3), O(1)–H(1B) 1.04(2), O(1)–H(1C) 0.84(4), O(3)–H(1B) 1.69(5), O(5)–H(1C) 1.82(2), O(1)–O(3) 2.624(7), O(1)–O(5) 2.547(5). Selected bond angles (°): C(11)–Pd–C(14) 92.72(17), N(1)–Pd–C(14) 91.31(16), O(3)–H(1B)–O(1) 150(7), O(5)–H(1C)–O(1) 143(7).

Figure 2.
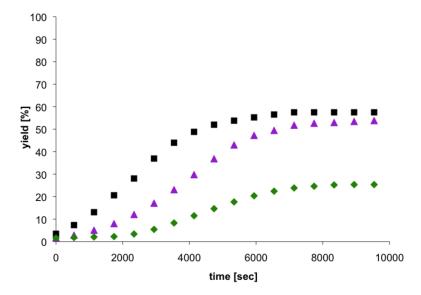Three possible mechanisms for C–CF$_3$ bond-forming reductive elimination from **6**

Figure 3.
Reaction profile for reductive elimination from **6** in DCE at 60 °C in the presence of no additive (black squares), 1 equiv of H_2O (purple triangles), and 0.2 equiv of NBu_4OAc (green diamonds).
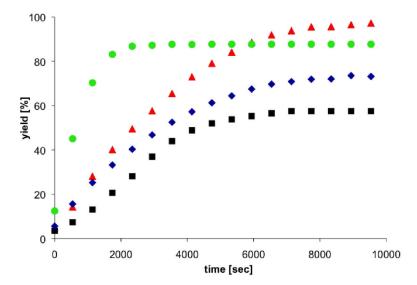
Figure 4.
Reaction profile for reductive elimination from **6** in DCE at 60 °C in the presence of no additive (black squares), 10 equiv of TFA (blue diamonds), 10 equiv of TFAA (green circles), and 1 equiv of $Yb(OTf)_3$ (red triangles).
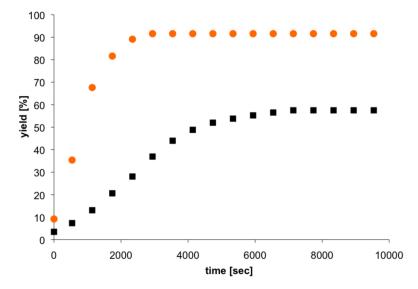
Figure 5.
Reaction profile of reductive elimination from **6** in the presence of no additive (black squares) and 10 equiv Cu(OAc)$_2$/100 equiv TFA (orange circles).

Table 1

Oxidation of **3** with Different ″CF$_3^+$″ Reagents

Entry	Solvent	Oxidant	Yield 6
1	AcOH	5a	45%
2	AcOH	5b	60%
3	AcOH	5c	27%
4	AcOH	5d	2%
5	AcOH	5e	4%
6	DCE	5b	<2%
7	DCE/1 equiv AcOH	5b	48%
8	DCE/5 equiv AcOH	5b	56%
9	DCE/20 equiv AcOH	5b	65%

Conditions: Complex **3** (1 equiv) and ″CF$_3^+$″ reagent (3 equiv) in solvent (0.4 mL) for 1 h at 40 °C. Yields were determined by ^{19}F NMR spectroscopy and represent an average of at least two independent runs.
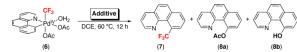
Table 2

Yield and Product Distribution of Reductive Elimination from **6** as a Function of Solvent

Entry	Solvent	Yield 7	Yield 8a	Yield 8b
1	AcOH	56%	<2%	<2%
2	DCE	54%	<2%	<2%
3	CHCl$_3$	62%	<2%	<2%
4	NO$_2$Ph	57%	<2%	<2%
5	DCE/50 equiv pyridine	<2%	<2%	84%

Conditions: Complex **6** (1 equiv) in solvent (0.26 mL) for 12 h at 60 °C. Yields were determined by ^{19}F and ^{1}H NMR spectroscopy and represent an average of at least two independent runs.

Table 3

Effect of Added NBu$_4$OAc, NBu$_4$PF$_6$, and H$_2$O on Reductive Elimination from **6**

Entry	Additive	Yield 7	Yield 8a	Yield 8b
1	None	54%	<2%	<2%
2	0.2 equiv NBu$_4$OAc	26%	<2%	<2%
3	1 equiv NBu$_4$OAc	2%	16%	16%
4	1 equiv NBu$_4$PF$_6$	56%	<2%	<2%
5	1 equiv H$_2$O	50%	<2%	<2%
6	10 equiv H$_2$O	50%	<2%	<2%

Conditions: Complex **6** (1 equiv) and the appropriate additive in DCE (0.26 mL) for 12 h at 60 °C. Yields were determined by ^{19}F and ^{1}H NMR spectroscopy and represent an average of at least two independent runs.

Table 4

Effect of Acidic/Electrophilic Additives on Reductive Elimination from **6**

Entry	Additive	k_{obs} (s^{-1})	Yield 7[a]
1	None	nd[b]	54%
2	10 equiv TFA	$3.31 \pm 0.04 \times 10^{-4}$	73%
3	10 equiv TFAA	$1.43 \pm 0.02 \times 10^{-3}$	84%
4	1 equiv Yb(OTf)$_3$	$2.92 \pm 0.03 \times 10^{-4}$	99%

[a] Conditions: Complex **6** (1 equiv) and the appropriate additive in DCE (0.26 mL) for 12 h at 60 °C. Yields were determined by ^{19}F and ^{1}H NMR spectroscopy and represent an average of at least two independent runs.

[b] k_{obs} could not be determined for this reaction due to an induction period.