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C(sp^3)–O Bond-Forming Reductive Elimination from Pd^{IV} with Diverse Oxygen Nucleophiles

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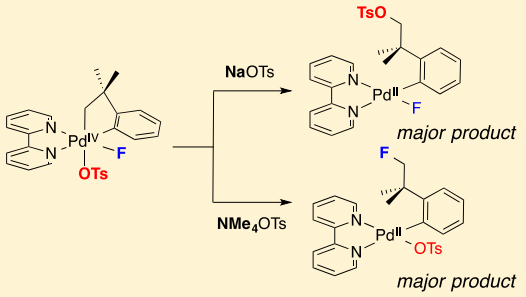
Supporting Information

ABSTRACT: This article describes an investigation of C(sp^3)–O bond-forming reductive elimination reactions from Pd^{IV} complexes. Phenoxide, acetate, difluoroacetate, dimethylphosphate, tosylate, and nitrate nucleophiles are shown to participate in this reaction. In all cases, C(sp^3)–O bond formation occurs with high selectivity over potentially competing C(sp^2)–O coupling. Additives have a profound impact on the chemoselectivity of these reductive elimination reactions. An excess of RO$^-$ was found to limit competing C(sp^3)–C(sp^2) bond-forming reductive elimination, while the presence of Lewis acidic cations was found to suppress competing C(sp^3)–F coupling. Mechanistic investigations were conducted, and the available data are consistent with a sequence involving pre-equilibrium dissociation of the oxyanion ligand (RO$^-$) followed by nucleophilic attack of RO$^-$ on a cationic Pd^{IV}–alkyl intermediate.



INTRODUCTION

Carbon–oxygen bond-forming reductive elimination from Pd^{IV} centers is believed to serve as the product release step of numerous important catalytic transformations,[1] including ligand-directed C–H bond oxygenation,[2] allylic acetoxylation,[3] and alkene difunctionalization.[4] Previous work by our group[5,6] and others[7−10] has probed the mechanism of C(sp^2)–O bond-forming reductive elimination reactions from high-valent Pd complexes. These studies have informed the design and development of new catalytic processes.[2−4] In marked contrast, much less is known about the corresponding C(sp^3)–O coupling reactions at high-valent Pd.[11,12] Previous attempts to investigate these transformations have been plagued by the low stability of high-valent Pd intermediates[1] and by side reactions such as competing methyl group transfer from Pd^{IV} intermediates to Pd^{II} reactants as well as C–C coupling at Pd^{IV}.[13] As a result, the mechanisms of these transformations remain opaque, and the scope of oxygen nucleophiles that can participate in this fundamental organometallic transformation has not been well-studied. In addition, the chemoselectivity of C–heteroatom bond-forming reductive elimination is poorly understood in systems where multiple competing reductive elimination reactions could take place.

In this report, we describe the design of a model system that has enabled the first detailed exploration of the scope, chemoselectivity, and mechanism of C(sp^3)–O bond-forming reductive elimination from Pd^{IV}. We have found that these transformations can proceed even with very weak oxygen nucleophiles such as nitrate and tosylate. To our knowledge, the direct observation of reductive elimination reactions that form C(sp^3)–ONO$_2$ and C(sp^3)–OTs linkages has no precedent in the literature.[14] In addition, we demonstrate that cationic additives (i.e., Li$^+$ vs NBu$_4^+$) can play a previously unappreciated role in the chemoselectivity of competing C(sp^3)–O and C(sp^3)–F couplings at Pd^{IV} centers.

RESULTS AND DISCUSSION

Design of the Model System. Several considerations went into the design of a model system for studying C(sp^3)–O bond-forming reductive elimination from Pd^{IV}. First, a Pd^{IV}–alkyl complex that does not contain β-hydrogens was selected in order to avoid competing β-hydride elimination. Second, a ligand environment was targeted that would render the Pd^{IV} intermediates isolable (or at minimum detectable) and still be highly modular to allow for the introduction of diverse oxyanion nucleophiles. Finally, a system that would enable the investigation of competing C(sp^3)–O and C(sp^3)–F bond-forming reductive eliminations was sought in order to mimic important considerations in catalytic methodologies. For instance, prior work by our group has shown that competing C(sp^3)–O and C(sp^3)–F bond formation occurs during the fluorination of 8-methylquinoline with AgF/PhI(OPiv)$_2$ catalyzed by high-valent Pd.[15] Achieving the selective formation of a single product remains a major challenge in this and related Pd$^{II/IV}$-catalyzed methods.

Previous studies by our group have demonstrated that Pd^{IV} derivatives of general structure (bpy)Pd(CH$_2$CMe$_2$-*o*-C$_6$H$_4$)(F)(X) can be stable and often isolable complexes.[16] When X = OTf, this ligand can be readily displaced by other anions or Lewis bases (e.g., TsNH$^-$, pyridine). Some of these complexes have been shown to participate in selective reductive elimination at the C(sp^3) ligand. Furthermore, depending on the conditions, competing C(sp^3)–X and C(sp^3)–F reductive eliminations can

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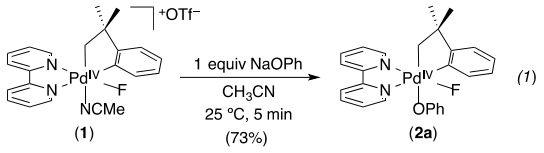
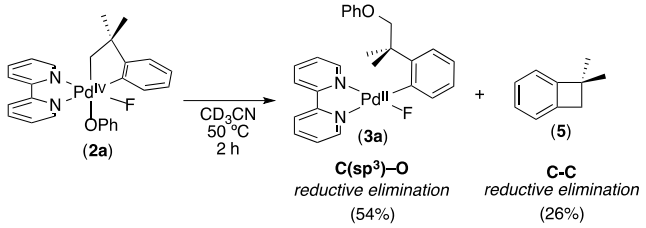
be observed.[16b] Thus, this system was selected to probe the scope, mechanism, and selectivity of C(sp^3)−O bond-forming reductive elimination at Pd^{IV}.

Initial Studies with Phenoxide as the Nucleophile. Phenoxide ligands are known to serve as coupling partners in a number of reductive elimination reactions, including C(sp^2)−O coupling at Pd^{II} centers,[17] C(sp^3)−O coupling at Pd^{II},[12] and C(sp^3)−O bond formation at Pt^{IV}.[11b] On the basis of these precedents, we targeted Pd^{IV} phenoxide complex **2a** for our initial investigations. Complex **2a** was obtained in 73% isolated yield by the treatment of Pd^{IV} triflate complex **1** (which exists predominantly as the cationic solvento complex in CH_3CN solution) with 1 equiv of sodium phenoxide in CH_3CN at room temperature (eq 1).[18] Complex **2a** was characterized by one- and two-dimensional ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy (see the Supporting Information for full details of the spectral assignments).



When **2a** was heated at 50 °C for 2 h in CD_3CN, it underwent C(sp^3)−O bond-forming reductive elimination to form **3a** in 54% yield as determined by ^{1}H NMR spectroscopic analysis (Scheme 1). The main side product in this reaction was

Scheme 1. Reductive Elimination from Complex 2a

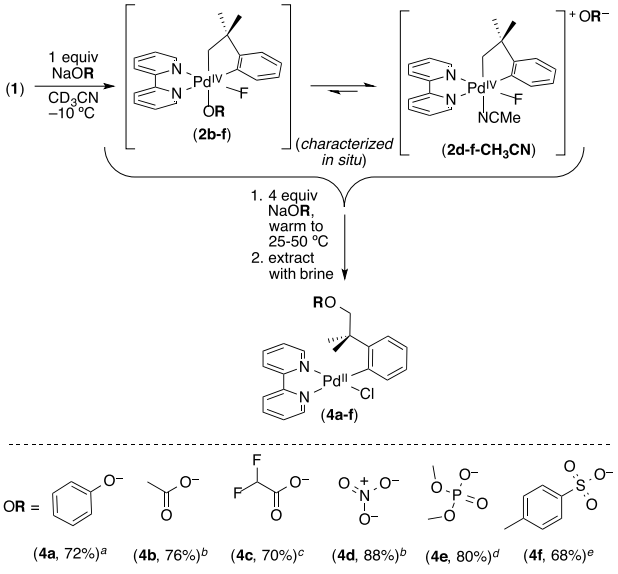


cyclobutane **5** derived from C(sp^3)−C(sp^2) coupling,[16b] which was formed in 26% yield. Importantly, no C(sp^3)−F or C(sp^2)−heteroatom reductive elimination products were observed under these conditions. This is in notable contrast to a recent report by Mirica, who showed that a closely related Pd^{IV}(CH_2CMe_2-*o*-C_6H_4)(OH) complex undergoes clean C(sp^2)−OH coupling upon thermolysis.[9,19]

On the basis of some of our prior work,[16b] we hypothesized that the addition of exogenous PhO$^-$ to reductive elimination reactions from **2a** might enhance the selectivity for C(sp^3)−O coupling. Indeed, the addition of 2−4 equiv of NaOPh resulted in the quantitative formation of **3a** as determined by NMR spectroscopic analysis. This Pd^{II} fluoride product was challenging to isolate because it is highly hygroscopic. However, extraction of CH_2Cl_2 solutions of **3a** with brine resulted in substitution of the fluoride ligand with chloride to form **4a**, which was isolated in 72% yield (Scheme 2).

Scope of Oxygen Nucleophiles. We next explored the scope of oxygen nucleophiles that participate in this transformation, with a particular focus on weakly nucleophilic oxyanions. Treatment of **1** with 1 equiv of NaOR (OR = acetate, difluoroacetate, nitrate, dimethylphosphate, and tosylate) at −10 °C resulted in the formation of new Pd^{IV} complexes, as determined by ^{1}H and ^{19}F NMR spectroscopic analyses.[20]

Scheme 2. Reductive Elimination from 2a−f To Form 4a−f



[a]50 °C, 2 h. [b]25 °C, 5 h. [c]NMe_4DFA, 40 °C, 1 h. [d]DMSO, 50 °C, 1 h. [e]NaOTs/NMe_4OTs, 25 °C, 12 h.

Unlike the phenoxide adduct **2a**, these complexes (**2b−f**) were not sufficiently stable for isolation; however, they were all characterized in situ using one and two-dimensional ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy.[21] Notably, NMR analysis showed that the Pd^{IV} complexes bearing nitrate, dimethylphosphate, and tosylate anions (**2d−f**) were generated as equilibrium mixtures with the corresponding cationic species (likely the acetonitrile adduct, [(bpy)Pd(CH_2CMe_2-*o*-C_6H_4)(F)(CH_3CN)]$^+X^-$). Observation of the solvento complexes in these cases can be attributed to the noncoordinating nature of the oxyanions in **2d−f**.

Warming solutions of **2b−f** to between 25 and 50 °C in the presence of 4 equiv of exogenous NaOR resulted in clean C(sp^3)−O coupling, and the products **4b−e** were isolated in high yield after extraction with brine (Scheme 2).[22,23] The structure of the Pd^{II} nitrate product **4d** was confirmed by X-ray crystallography, and an ORTEP of this structure is shown in Figure 1.

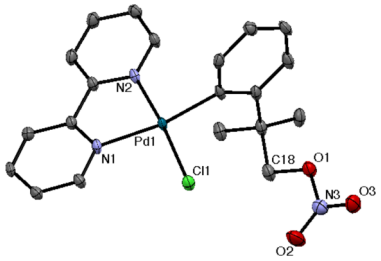


Figure 1. ORTEP of reductive elimination product **4d**.

Influence of the Cation on the Chemoselectivity. Selectivity for C−O versus C−F reductive elimination in catalysis is often rationalized on the basis of the relative nucleophilicity of F$^-$ versus RO$^-$, with the more nucleophilic anion dominating the reductive elimination process.[24] Therefore, we were intrigued by the fact that products of C−F coupling were not observed in any of the reactions in Scheme 2, even with the very weakly nucleophilic $NaNO_3$ and NaOTs.

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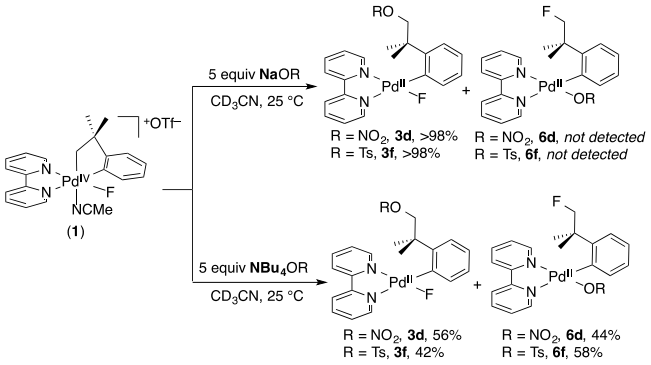
However, changing the nitrate/tosylate source from NaOR to NBu_4OR under otherwise identical conditions resulted in a dramatic change in the product distribution. For instance, as shown in Scheme 3, treatment of **1** with 5 equiv of NBu_4NO_3

Scheme 3. Chemoselectivity of Reductive Elimination as a Function of the Cation[26,27]



resulted in competitive formation of products derived from C(sp^3)−O (**3d**, 56% yield) and C(sp^3)−F (**6d**, 44% yield) bond-forming reductive elimination.[25] Similarly, the use of NMe_4OTs resulted in a 42% yield of C(sp^3)−O-coupled product **3f** and a 58% yield of the corresponding alkyl fluoride **6f**. Notably, similar effects were *not* observed with the more nucleophilic phenoxide, acetate, and difluoroacetate oxyanions; in these systems, exclusive C(sp^3)−O coupling was observed regardless of the cation.

We hypothesize that these counterion effects are due to interactions between the Lewis acidic cation and the Lewis basic fluoride ligand.[28] Consistent with this proposal, the ^{19}F NMR signal for the fluoride ligand in **1** (−336 ppm in CD_3CN) shifts in a concentration dependent manner upon the addition of Lewis acidic cations. For instance, in the presence of 5 equiv of NaOTf (0.11 M) this signal appears at −338 ppm, while with 20 equiv of NaOTf (0.44 M) the resonance appears at −341 ppm. This effect is specific to the cation; for instance, no shift was observed upon the addition of 5 equiv of NBu_4OTf. The stoichiometry of this interaction was assessed by evaluating a series of solutions with a constant total concentration of **1** and NaOTf ([**1**] + [NaOTf] = 36 mM) but with varied mole fraction of **1** (χ). The resulting Job plot (Figure 2) shows a maximum at χ = 0.5, indicative of a 1:1 interaction between **1** and NaOTf.

LiOTf, a stronger Lewis acid than NaOTf,[29] has an even greater impact on the ^{19}F NMR chemical shift of **1** [−343 ppm with 5 equiv of LiOTf (0.11 M)]. In contrast, the weaker Lewis acids KOTf and CsOTf produce negligible changes in the chemical shift (−336 ppm). Treatment of **1** with 5 equiv of KNO_3 and $CsNO_3$ led to 29% and 53% yields of the C−F reductive elimination product, respectively, while the addition of $LiNO_3$ resulted in exclusive formation of the C(sp^3)−O coupling product **3d** (Table 1). Taken together, these data suggest that interactions between the Pd^{IV}−F and the Lewis acidic cation decrease the accessibility of C−F bond-forming pathway(s). These results provide unprecedented new information about the role of cations in reductive elimination reactions from Pd^{IV}; as such, they have numerous potential applications in catalysis.

Mechanistic Investigations. A variety of experimental studies were conducted to gain insights into the mechanism of

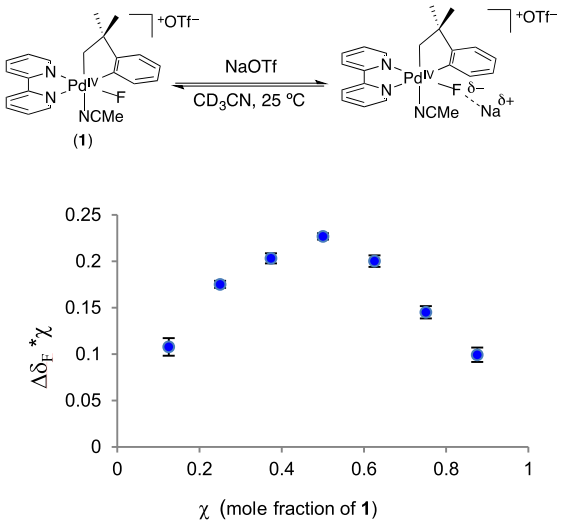
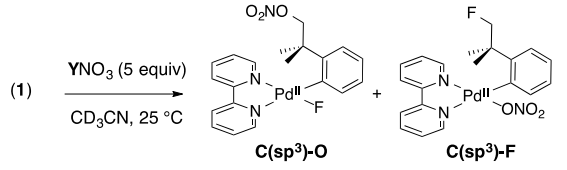


Figure 2. Job plot of $\Delta\delta_F \times \chi$ vs χ at 25 °C, where χ is the mole fraction of substrate **1**.

Table 1. Product Distribution of C−O and C−F Reductive Elimination from 1 as a Function of Cation[a]

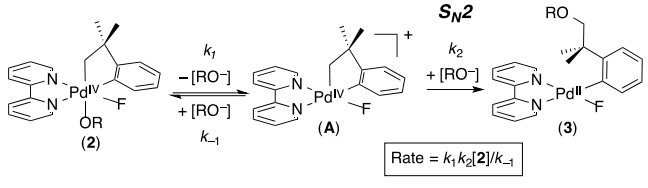


cation (Y^+)	C−O (%)	C−F (%)
Li	>98	nd
Na	>98	nd
K	71	29
Cs	47	53
NBu_4	56	44

[a]Yields were determined by ^1H NMR analysis of the crude reaction mixtures. nd = not detected. Reactions were conducted under ambient conditions with commercial solvents/reagents.

these C(sp^3)−O bond-forming reactions. Complexes **2a−c** were selected for detailed investigation because they all undergo high-yielding C(sp^3)−O bond formation under a standard set of conditions, thereby enabling the direct comparison of reaction rates and additive effects. These studies were conducted using tetramethylammonium salts of the oxyanions in order to render the CH_3CN solutions completely homogeneous for rate measurements. Under these conditions, no competing reductive elimination processes were detected. As described in detail below, these data are consistent with the mechanism presented in Scheme 4. Here, pre-equilibrium dissociation of RO^- is followed by rate-limiting C(sp^3)−O bond formation that

Scheme 4. Proposed Mechanism for C(sp^3)−O Bond Formation from Complexes 2a−c



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proceeds via nucleophilic attack by RO^- on the σ-alkyl ligand. The rate expression for the proposed pathway is shown in Scheme 4.

We first examined the lability of the RO^- ligands in Pd^{IV} complexes **2a−c** using EXSY NMR experiments. In all cases, ^1H and ^{19}F EXSY studies showed exchange between free and bound oxyanions at temperatures where complexes **2a−c** are stable toward reductive elimination (−10 to 15 °C). As shown in Table 2, the minimum temperature for exchange parallels the basicity of the oxyanion, with more basic (and therefore presumably more coordinating) ligands requiring higher temperatures for exchange. These results strongly support the feasibility of rapid pre-equilibrium dissociation of RO^- to form a cationic intermediate prior to C−O bond formation.

Table 2. Experimental Mechanistic Data for Reductive Elimination from 2a−c

complex	RO^-	pK_a (conj acid)	EXSY (minimum temp for exchange)	k_{obs} at 35 °C (10^{-4} s^{-1})
2a		10	15 °C	8.1 ± 1.6
2b		4.7	10 °C	8.1 ± 1.2
2c		1.3	−10 °C	8.0 ± 0.2

We next used rate studies to probe the kinetic order of C(sp^3)−O bond formation from **2a−c** with respect to both [Pd] and [RO^-]. First, reactions of **1** with 5 equiv of NMe_4OR (0.071 M) (RO^- = phenoxide, acetate, difluoroacetate) at 35 °C in CD_3CN were monitored by ^1H NMR spectroscopy. Under these conditions, the decays of in situ-generated **2a−c** proceeded with clean first-order kinetic behavior over 3 half-lives, and a representative kinetics plot is shown in Figure 3. The values of k_{obs} for reductive elimination were determined over a range of concentrations of exogenous [NMe_4OR] (0.021 to 0.13 M, 1.5−9.0 equiv). In all cases, a zeroth-order dependence on [NMe_4OR] was observed. These data rule out a mechanism involving direct attack of an external oxyanion nucleophile on complexes **2a−c**, as such a process would be expected to display a first-order dependence on [NMe_4OR]. The zeroth-order dependence on the nucleophile is fully consistent with the proposed mechanism (see the rate expression in Scheme 4).

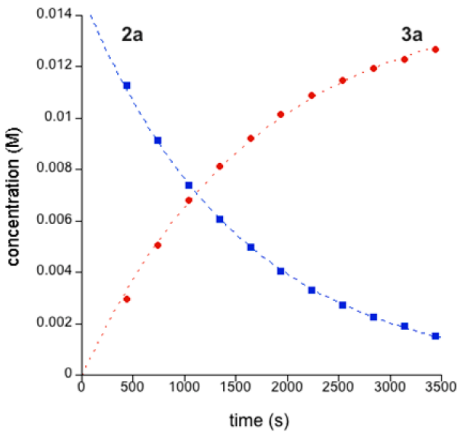

Figure 3. Reaction profile for reductive elimination from in situ-generated **2a** in the presence of 4 equiv of NMe_4OPh at 35 °C.

The values of k_{obs} for this reaction were nearly identical for complexes **2a−c** (Table 2).[30] There is no correlation between the pK_a of the conjugate acid of the oxyanion and the value of k_{obs} for reductive elimination over a pK_a range of >8. Hartwig has reported a similar observation in studies of C(sp^3)−O bond-forming reductive elimination from Pd^{II} centers.[12] These data are consistent with a mechanism involving two sequential steps that have opposing electronic requirements. In our system, the pre-equilibrium RO^- dissociation is accelerated with electron-deficient oxyanions. In contrast, S_N2-type attack of RO^- on the Pd^{IV}−C bond is expected to be fastest with more electron-rich oxyanions. In both our system and Hartwig's, the electronic requirements of these two steps appear to essentially cancel one another.

While the electronic properties of RO^- had a negligible effect on k_{obs}, the addition of a large excess of water did impact the observed rate constant. For instance, in the presence of 100 equiv of water, k_{obs} for reductive elimination from **2b** (18×10^{-4} s^{-1} at 35 °C) was approximately 2-fold faster than that under anhydrous conditions (8.1×10^{-4} s^{-1} at 35 °C).[31] Protic additives have been reported previously to accelerate reductive elimination reactions proceeding through ionic intermediates, presumably by facilitating dissociation of an anionic ligand.[11b,12,32] Consistent with this proposal, EXSY experiments for complex **2b** in the presence of 100 equiv of water showed that exchange of free and bound acetate occurs at a lower temperature (0 °C) than that observed under anhydrous conditions (10 °C) (Table 2). The addition of water, therefore, likely shifts the equilibrium proposed in Scheme 4 toward the cationic intermediate **A**.

SUMMARY AND CONCLUSIONS

In summary, this paper has described the first detailed study of C(sp^3)−O bond-forming reductive elimination from Pd^{IV} complexes. Oxyanions ranging from strongly nucleophilic phenoxide to very weakly nucleophilic tosylate and nitrate participate in this reaction. In all cases, C(sp^3)−O bond formation occurs with high selectivity over C(sp^2)−O coupling. This is in contrast to a recent report by Mirica[9] and may be due to the relative ease of oxyanion dissociation in the two systems. Additives were found to have a profound impact on the chemoselectivity of these reductive elimination reactions. Specifically, the addition of an excess of RO^- was found to limit competing C(sp^3)−C(sp^2) bond-forming reductive elimination, while the presence of Lewis acidic cations was found to suppress competing C(sp^3)−F coupling. Finally, rate studies provide evidence consistent with a pathway involving pre-equilibrium dissociation of RO^- to form a cationic, five-coordinate intermediate followed by S_N2-type C(sp^3)−O coupling. Overall, we anticipate that the detailed studies described herein will prove valuable in the further development, optimization, and mechanistic understanding of C(sp^3)−O coupling reactions catalyzed by high-valent Pd.

ASSOCIATED CONTENT

Supporting Information

Experimental and spectral details for all new compounds and all reactions reported. 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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(18) Unless otherwise noted, all of the Pd^{IV} complexes were formed as a >20:1 ratio of stereoisomers.

(19) In our system, treatment of **1** with NaOH or NMe_4OH led to the formation of a complex mixture of products.

(20) More soluble tetramethyl- or tetrabutylammonium salts were used for low-temperature NMR characterization, except for complex **2e**, which was generated with sodium dimethylphosphate in DMSO.

(21) See the Supporting Information for a full discussion and NMR characterization.

(22) The tosylate reductive elimination product could not be isolated cleanly and was therefore characterized by NMR analysis of the crude reaction mixture.

(23) Reductive elimination from complex **2e** proceeded cleanly only in DMSO.

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(25) There was minimal change in the product ratio or NMR shifts when the reaction was conducted under rigorously dry conditions (i.e., in an inert-atmosphere glovebox with dry solvent and reagents) versus ambient conditions (i.e., with reactions set up on the benchtop with commercial solvents and reagents). Furthermore, the addition of 50 equiv of exogenous H_2O resulted in minimal change in the product ratios. See p S22 in the Supporting Information for complete details.

(26) NMR yields are reported.

(27) A mixture of NMe_4OTs (2.5 equiv) and NaOTs (2.5 equiv) was used for the formation of complex **3f**.

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(30) The rate constants shown in Table 2 were obtained from the average and standard deviation of three separate experiments for each complex, with the reactions conducted under anhydrous conditions.

(31) The values of k_{obs} for reductive elimination from complexes **2a**−**c** under rigorously anhydrous conditions (i.e., in an inert-atmosphere glovebox with dried solvent and reagents) were nearly identical to those obtained under ambient conditions (i.e., on the benchtop with commercial solvents and reagents), where trace amounts of water are expected. Only the addition of exogenous water (10−500 equiv added to reactions set up under ambient conditions) impacted the reductive elimination kinetics. See pp S30−S34 in the Supporting Information for more details.

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