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Detailed Study of C−O and C−C Bond-Forming Reductive Elimination from Stable $C_2N_2O_2$−Ligated Palladium(IV) Complexes

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Abstract: This paper describes the synthesis of a series of Pd^{IV} complexes of general structure $(N{\sim}C)_2Pd^{IV}(O_2CR)_2$ ($N{\sim}C$ = a rigid cyclometalated ligand; O_2CR = carboxylate) by reaction of $(N{\sim}C)_2Pd^{II}$ with $PhI(O_2CR)_2$. The majority of these complexes undergo clean C−O bond-forming reductive elimination, and the mechanism of this process has been investigated. A variety of experiments, including Hammett plots, Eyring analysis, crossover studies, and investigations of the influence of solvent and additives, suggest that C−O bond-forming reductive elimination proceeds via initial carboxylate dissociation followed by C−O coupling from a 5-coordinate cationic Pd^{IV} intermediate. The mechanism of competing C−C bond-forming reductive elimination from these complexes has also been investigated and is proposed to involve direct reductive elimination from the octahedral Pd^{IV} centers.

Introduction

Our group has recently reported a Pd-catalyzed reaction for the ligand-directed acetoxylation of carbon−hydrogen bonds using $PhI(OAc)_2$ as the terminal oxidant (Scheme 1).[1−3] The key carbon−oxygen coupling step of this transformation was proposed to involve C−O bond-forming reductive elimination from a rare, high oxidation state Pd^{IV} species of general structure **A**.[1,4] While analogous C−O bond-forming reductive elimination reactions from Ni^{III},[5] Pd^{II},[6] and Pt^{IV} [7] centers have been studied extensively, detailed investigation of such reactions at Pd^{IV} complexes has thus far remained elusive.[8,9]

Studies of C−O bond formation at Pd^{IV} have proven challenging for two major reasons. First, there are relatively few examples of isolable Pd^{IV} complexes containing oxygen donor ligands.[8,9] Second, the available complexes are typically stabilized by the presence of multiple σ-alkyl and/or aryl ligands. As a result, investigations of C−O bond-forming reductive elimination have been hampered by competing C−C coupling processes.[8,9] Hence, we sought to design a new model system that would allow for systematic mechanistic investigations of C−O bond-forming reductive elimination from Pd^{IV} centers.

We reasoned that Pd^{IV} complexes of general structure $(N{\sim}C)_2Pd^{IV}(O_2CR)_2$ (**B**) ($N{\sim}C$ = a rigid cyclometalated ligand) might serve as attractive models for **A** on the basis of several key design features (Scheme 2). First, the N∼C ligands were selected to stabilize the desired Pd^{IV} species, due to their rigid, bidentate structures[8−10] and the fact that they contribute two electron-donating σ-aryl ligands to the high oxidation state Pd

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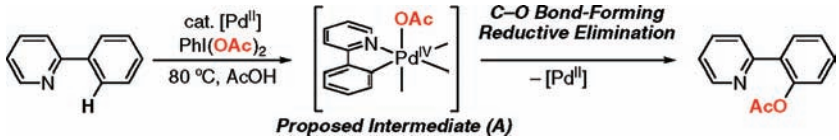
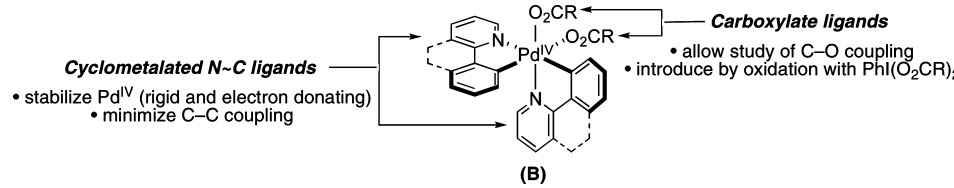
10.1021/ja9014474 CCC: $40.75

Scheme 1. Proposed Mechanism for Pd-Catalyzed Acetoxylation of 2-Phenylpyridine



Scheme 2. Design of Complex **B** for Study of C−O Bond-Forming Reductive Elimination from Pd^{IV}



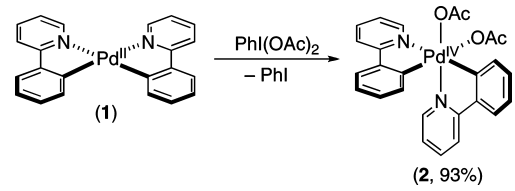
complex.[8–11] Additionally, we hypothesized that the rigid and chelating nature of the two N∼C ligands would limit competing C−C bond-forming processes relative to the desired C−O coupling. Finally, we reasoned that the two carboxylates could be incorporated by oxidation of (N∼C)$_2$Pd^{II} with PhI(O$_2$CR)$_2$, which is the same terminal oxidant used for the catalytic reactions in Scheme 1.

We report herein detailed studies on the synthesis and reactivity of Pd^{IV} complexes of general structure **B**. These complexes are readily prepared by the oxidation of (N∼C)$_2$Pd^{II} with PhI(O$_2$CR)$_2$ and are remarkably stable at room temperature.[12,13] However, at elevated temperatures, most undergo clean C−O bond-forming reductive elimination to afford ester products. This paper describes full mechanistic investigations of this C−O bond-forming process and also provides mechanistic insights into competing C−C coupling reactions.

Results and Discussion

Initial Investigations. 2-Phenylpyridine (Phpy) was selected as the N∼C chelating ligand due to its high reactivity in Pd-catalyzed C−H activation/acetoxylation reactions[1] and the availability of the starting material (Phpy)$_2$Pd^{II} (**1**).[14] Gratifyingly, treatment of **1** with PhI(OAc)$_2$ in CH$_2$Cl$_2$ at 25 °C for 30 min produced a single inorganic product (**2**) (Scheme 3). Complex **2** was isolated in 93% yield as a pale yellow solid by precipitation with diethyl ether. This species was remarkably stable in the solid state and could be stored for 12 months at −35 °C without significant decomposition.

Scheme 3. Oxidation of (Phpy)$_2$Pd^{II} (**1**) with PhI(OAc)$_2$



The ^{1}H NMR spectrum of **2** in acetone-d_6 shows 16 distinct aromatic signals between 6.29 and 9.46 ppm and two different acetate resonances at 1.63 and 1.74 ppm. This spectroscopic data is indicative of an unsymmetrical octahedral Pd^{IV} species with two different Phpy and acetate ligand environments. Further characterization of **2** by X-ray crystallography confirmed that this complex has an octahedral geometry with *cis*-phenylpyridine and acetate ligands (Figure 1). This is a highly unusual example of a room temperature stable Pd^{IV} complex containing a C$_2$N$_2$O$_2$ coordination environment.

We next examined the reactivity of Pd^{IV} complex **2** toward thermally induced reductive elimination. Two possible reductive elimination reactions are possible from **2** - carbon−oxygen bond-forming reductive elimination to generate 2-(2-acetoxyphenyl)pyridine (**3**) and/or C−C bond-forming reductive elimination to afford 2,2′-di(pyridin-2-yl)biphenyl (**4**) (Scheme 4). Literature reports have shown that related Pd^{IV} species [for example, (bipy)Pd^{IV}(Me)$_3$(O$_2$CPh) (bipy = 2,2′-bipyridine)] undergo C−C bond formation at comparable or faster rates than the desired C−O coupling reaction.[8,9]

We were pleased to find that heating a solution of **2** in CH$_3$CN for 30 min at 80 °C resulted in the formation of **3** as the sole

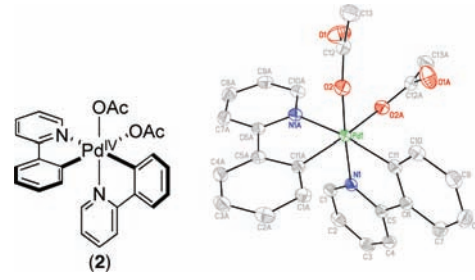


Figure 1. ORTEP structure of (Phpy)$_2$Pd^{IV}(OAc)$_2$ (**2**).

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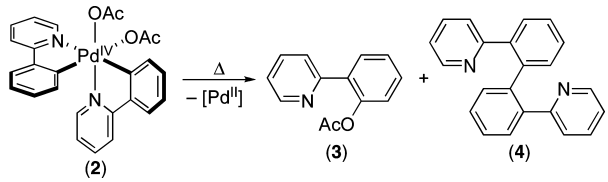
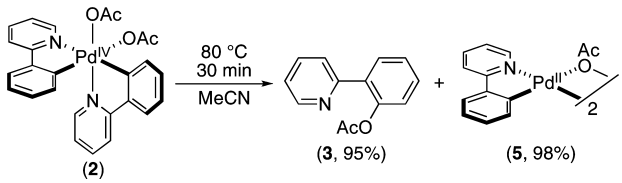
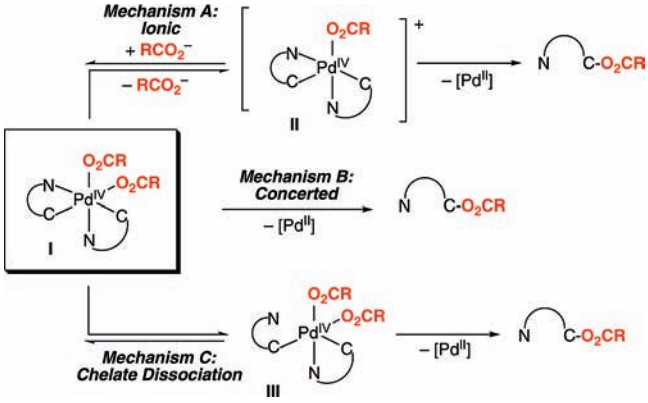
Scheme 4. Possible Organic Products of Reductive Elimination from **2**



Scheme 5. Reductive Elimination from $(Phpy)_2Pd^{IV}(OAc)_2$ (**2**)



Scheme 6. Possible Mechanisms for C−O Bond-Forming Reductive Elimination from **I**



organic product in nearly quantitative yield (95%) as determined by ^{1}H NMR spectroscopy (Scheme 5). The inorganic product of this reaction was the cyclometalated Pd^{II} dimer **5**, which was obtained in 98% yield. To our knowledge, this is the first direct observation of sp^2 C−O bond-forming reductive elimination from an isolated Pd^{IV} center. As a result, this system presented a unique opportunity for mechanistic studies relevant to the proposed product-forming step in Pd-catalyzed C−H bond acetoxylation reactions.[1–4]

Mechanistic Considerations. We considered three mechanisms for C−O bond-forming reductive elimination from complexes of general structure **I** (Scheme 6). The first possibility was an ionic mechanism (**A**), which would proceed via carboxylate dissociation from **I** to form five-coordinate intermediate **II**, followed by reductive elimination from this cationic species. Mechanism **B**, concerted bond formation, would involve direct C−O reductive elimination from the coordinatively saturated octahedral Pd^{IV} complex **I**. Finally, Mechanism **C**, chelate dissociation, would involve dissociation of an N-donor ligand to generate the neutral 5-coordinate species **III**, followed by reductive elimination. Notably, within all three mechanisms, there are two distinct carboxylates that could participate in C−O bond-forming reductive elimination. In mechanism **A**, C−O coupling from intermediate **II** could occur via nucleophilic attack by the dissociated carboxylate or by direct reaction of the coordinated carboxylate. In mechanisms **B** and **C**, reductive elimination could involve C−O coupling with the carboxylate trans to the pyridine nitrogen or with the carboxylate trans to the σ-Ar ligand.

There is literature precedent for each of these mechanisms in reductive elimination reactions at group 10 metal centers. For example, mechanism **A** has been implicated for sp^3 C−O,[7] sp^3 C-halogen,[15] sp^3 C−N,[16] and sp^2 C-halogen[17] bond-forming reductive elimination from Pt^{IV}. A concerted-type mechanism has been proposed for sp^2 C−O,[6] sp^2 C−N,[18] and sp^2 C−S[19] bond-forming reductive elimination from Pd^{II} centers. Finally, mechanism **C** has been reported for some C−C bond-forming reactions from Pt^{IV}.[20]

We aimed to distinguish between these mechanistic possibilities by systematically studying C−O bond-forming reductive elimination from $(Arpy)_2Pd^{IV}(O_2CR)_2$ (Arpy = substituted arylpyridine, O_2CR = substituted carboxylate). These complexes were synthesized by the reaction of **1** with $PhI(O_2CR)_2$ (Scheme 7).[21] Our initial investigations in this area provided preliminary evidence in support of mechanism **C**.[12] More recently, a computational study by Liu and co-workers has suggested that mechanism **B** is operating in these systems.[22] To gain further insights into this transformation, we have carried out numerous additional experiments to probe both C−O and related C−C bond-forming reductive elimination processes from $(Arpy)_2Pd^{IV}(O_2CR)_2$. As detailed below, these new investigations, as well as reevaluation/reinterpretation of our previous data, lead us to conclude that mechanism **A** is, in fact, most likely operating in this system.

Mechanism of C−O Bond-Forming Reductive Elimination: Carboxylate Exchange. Our mechanistic studies first probed the viability of mechanism **A** by investigating whether complex **2** undergoes exchange between free and bound carboxylates at temperatures below those required for reductive elimination (Scheme 8). Because **2** is coordinatively saturated, carboxylate exchange would require dissociation of an acetate ligand via a process analogous to the first step of mechanism **A**. Notably, Goldberg and co-workers have shown that such exchange reactions occur rapidly at the Pt^{IV} complex *fac*-(dppbz)$PtMe_3$(OAr) (dppbz = bis(diphenylphosphino)benzene), which undergoes C−O bond-forming reductive elimination via mechanism **A**.[7b]

Carboxylate exchange was first studied by treating complex **2** with 1 equiv of $NBu_4(O_2CC_9H_{19})$ at 25 °C in acetone-d_6. Importantly, these conditions are far milder than those required to induce C−O bond-forming reductive elimination from **2**. Analysis of the reaction by ^{1}H NMR spectroscopy after 5 min showed formation of one major new Pd^{IV} species with characteristic upfield and downfield ^{1}H NMR resonances at 6.31 and

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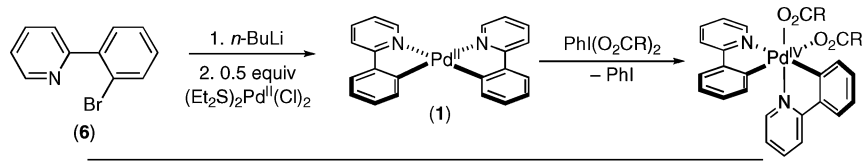
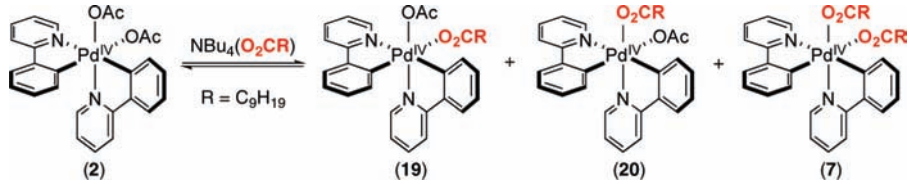
Scheme 7. General Synthetic Route to (Phpy)$_2$Pd^{IV}(O$_2$CR)$_2$

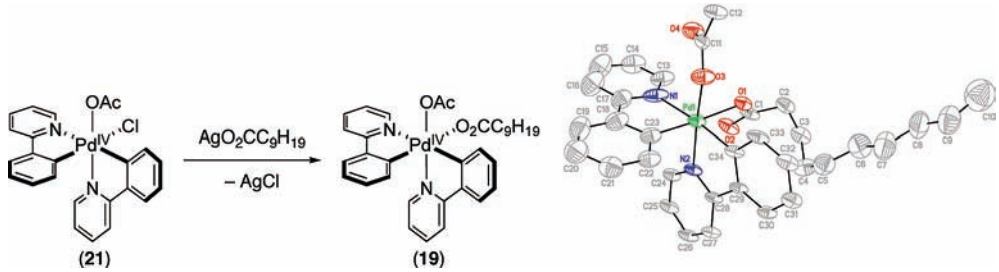


R	complex	yield	R	complex	yield
C_9H_{19}	**7**	78%	*p*-ClC_6H_4	**13**	78%
p-$MeOC_6H_4$	**8**	83%	*p*-BrC_6H_4	**14**	82%
p-MeC_6H_4	**9**	88%	*p*-AcC_6H_4	**15**	80%
C_6H_5	**10**	90%	*p*-$CF_3C_6H_4$	**16**	74%
p-$PhOC_6H_4$	**11**	83%	*p*-CNC_6H_4	**17**	94%
p-FC_6H_4	**12**	93%	*p*-$NO_2C_6H_4$	**18**	85%

Scheme 8. Potential Products of Carboxylate Exchange Reaction



Scheme 9. Independent Synthesis of Complex **19** and ORTEP Picture of **19**



9.49 ppm. These are slightly shifted relative to the starting material, which has signals at 6.29 and 9.44 ppm. We hypothesized that this new complex was the monoacetate adduct **19** where the acetate ligand trans to C was replaced with $O_2CC_9H_{19}$. The selective replacement of this OAc can be rationalized on the basis of the larger trans influence of the σ-aryl ligand versus the pyridine nitrogen.[23]

The isolation of **19** from the reaction mixture proved challenging, as this species was not readily separable from tetrabutylammonium-containing byproducts. Thus, an authentic sample of **19** was synthesized independently by reaction of (Phpy)$_2$Pd^{IV}(Cl)(OAc)[24] (**21**) with 1 equiv of $AgO_2CC_9H_{19}$ (Scheme 9). This product showed identical ^{1}H NMR resonances to those observed in the exchange reaction. In addition, its structure was unambiguously established by X-ray crystallography (Scheme 9).

While ^{1}H NMR spectroscopic analysis was consistent with **19** as the major product of the exchange process, we were unable to definitively establish whether small quantities of **20** and **7** were also formed, since these have closely overlapping ^{1}H NMR resonances. As such, electrospray mass spectrometry was used to analyze the products of a related reaction [the thermoneutral exchange between (Phpy)$_2$Pd^{IV}(OAc)$_2$ and NBu$_4$(OAc-d_3) (Scheme 10)]. Electrospray MS of all of the possible products (which were each synthesized independently)[25] showed major peaks consistent with loss of the acetate ligand trans to the σ-aryl group. For example, the peak for (Phpy)$_2$Pd^{IV}(OAc-d_3)(OAc) (**2a-*d*$_3$**) was [(Phpy)$_2$Pd^{IV}(OAc)]$^+$ (MW = 473.0) while that for (Phpy)$_2$Pd^{IV}(OAc)(OAc-d_3) (**2b-*d*$_3$**) was [(Phpy)$_2$Pd^{IV}(O$_2$CCD$_3$)]$^+$ (MW = 476.0). Furthermore, coinjection of a 1: 1 mixture of **2**: **2-*d*$_6$** showed peaks of equal intensity, demonstrating that peak intensities can be used to determine the relative concentrations of these species.

When a 1: 1 mixture of (Phpy)$_2$Pd^{IV}(OAc)$_2$ and NBu$_4$(OAc-d_3) was combined in CH_2Cl_2, stirred for 20 min, and then analyzed by electrospray MS, a single peak for [(Phpy)$_2$Pd^{IV}(OAc)]$^+$ (MW = 473.0) was observed (Scheme 10). This result indicates that neither **2b-*d*$_3$** nor **2-*d*$_6$** is formed, thereby providing further evidence that carboxylate exchange occurs solely at the site trans to the σ-aryl ligand.

As discussed above, carboxylate exchange cannot occur by an associative mechanism, since the starting complex is coordinatively saturated. Thus, the observation of rapid exchange suggests strongly that carboxylate dissociation (the first step of mechanism **A**) can occur at temperatures below those required for reductive elimination. However, more experiments were

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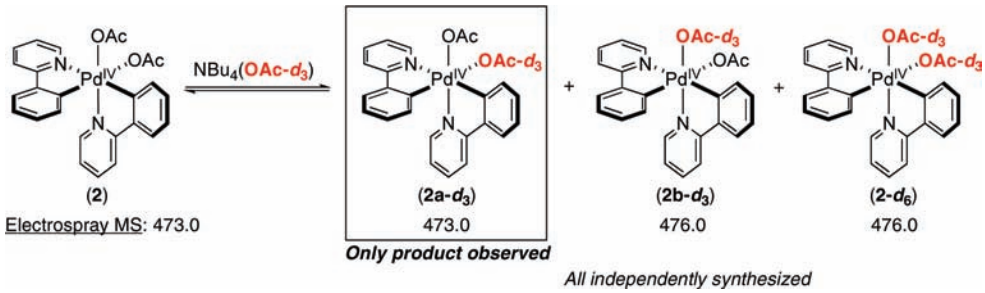
(24) Whitfield, S. R. Ph.D. Thesis, University of Michigan, 2008.
(25) These complexes were synthesized by reaction of (Phpy)$_2$Pd^{IV}(Cl)(OAc) or (Phpy)$_2$Pd^{IV}(Cl)(OAc-d_3) with the corresponding silver carboxylate. See the Supporting Information for full details.

Scheme 10. Electrospray MS Data for Reaction between **2** and $NBu_4(OAc\text{-}d_3)$



Scheme 11. Original Crossover Experiment from Ref 12

Scheme 12. AcO/AcO-d_3 Crossover Experiment

required to determine whether this exchange was mechanistically relevant to C−O bond-forming reductive elimination.

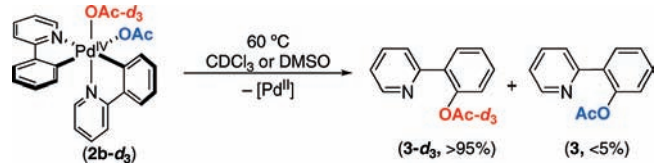
Mechanism of C−O Bond-Forming Reductive Elimination: Crossover Studies. We next investigated whether crossover between free and bound carboxylate occurred during the course of the reductive elimination reaction. A first crossover study involved thermolysis of the bis-benzoate complex **8** in the presence of 5 equiv of NBu_4OAc in either $CDCl_3$ or DMSO (Scheme 11).[12] Analysis of the reaction mixture by GC and GCMS showed that the predominant organic product was **22**, and that <5% of the crossover product **3** was formed.

We reasoned that the absence of crossover might be due to an electronic bias for reductive elimination of the benzoate in preference to the acetate ligand. As such, we designed a system to eliminate this electronic bias and differentiate the bound and free carboxylates solely based on isotopic labeling. However, thermolysis of $(Phpy)_2Pd^{IV}(OAc\text{-}d_3)_2$ (**2-*d*$_6$**) in the presence of 5 equiv of NBu_4OAc under otherwise identical conditions to Scheme 11 still afforded <6% of crossover product **3** (Scheme 12).

These results indicate that the nonexchangeable carboxylate ligand participates selectively in the C−O bond-forming reaction. This was confirmed by subjecting complex **2b-*d*$_3$**,[25] which contains two different carboxylate ligands, to the standard reductive elimination conditions. The major product (>95% yield) was **3-*d*$_3$** and <5% of **3** was observed as determined by ^1H and ^2H NMR spectroscopy (Scheme 13).

Mechanism of C−O Bond-Forming Reductive Elimination: Solvent Effects. Polar solvents often accelerate reductive elimination and ligand exchange reactions that proceed via ionic mechanisms.[7,26,27] Thus, we next investigated the effect of solvent on the rates of both C−O bond-forming reductive elimination and carboxylate exchange in a series of solvents with diverse polarities. The bis-decanoate complex $(Phpy)_2Pd^{IV}(O_2CC_9H_{19})_2$ (**7**) was used for these studies due to its high solubility in many different solvents.

Scheme 13. Selectivity of C−O Bond-Forming Reductive Elimination from **2b-*d*$_3$**



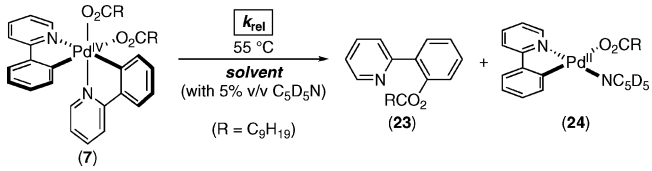
The rate of C−O bond-forming reductive elimination from **7** was examined as a function of solvent under standard conditions (55 °C, 15.2 mM in solvent with 5% v/v pyridine).[28] The disappearance of starting material **7** and concomitant formation of **23** and **24** were monitored by ^1H NMR spectroscopy. Interestingly, changing the solvent had very little influence on the reaction rate, and k_{obs} varied by only ~3-fold over a wide array of solvents (Table 1). In addition, there was no clear correlation between k_{obs} and the solvent polarity. For example, nearly identical rates were observed in benzene and acetone ($k_{rel} = 1$), despite a large difference in dielectric constant ($\varepsilon =$ 2.3 and 21, respectively). Furthermore, comparable and relatively fast rates were observed in nonpolar $CDCl_3$ ($\varepsilon = 4.8$, $k_{rel} = 2.3$) and polar CH_3CN ($\varepsilon = 38$, $k_{rel} = 2.4$).

The rate of carboxylate exchange was also investigated as a function of solvent. In these experiments, 1 equiv of **7** and 1 equiv of $Bu_4N(OAc)$ were dissolved in the appropriate solvent in an NMR tube at −38 °C, and the rate of formation of an equilibrium mixture of **7** and **20** was monitored by ^1H NMR spectroscopy. Intriguingly, k_{obs} for carboxylate exchange also did not show a clear correlation with the polarity of the reaction medium (Table 2). For example, the fastest rate ($k_{kel} = 19$) was observed in $CDCl_3$ ($\varepsilon = 4.8$), while the slowest ($k_{rel} = \sim 0.1$)[29] was in toluene-d_8 ($\varepsilon = 2.4$).

The solvent data for C−O bond-forming reductive elimination (particularly the low correlation between ε and k_{obs}) was initially interpreted as a strong piece of evidence against mechanism

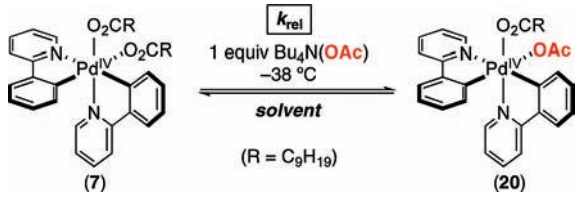
(26) Byers, P. K.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D. *Organometallics* **1988**, *7*, 1363.
(27) Isaacs, N. S. *Physical Organic Chemistry*, 2nd ed.; Pearson Education: New York, 1995.
(28) Initial investigations revealed that clean first order kinetics were not observed in some solvents, and we hypothesized that this might be due to formation of a highly reactive 3-coordinate Pd^{II} intermediate. Closely related challenges have been observed in reductive elimination reactions from Pd^{II} centers (for example, see ref 19a) and have been resolved by the addition of external ancillary ligands, which serve to trap unsaturated intermediates. Similarly, we found that the addition of 5% of pyridine-d_5 to the reductive elimination reactions of **7** in each solvent resulted in clean first order kinetics over greater than three half-lives. Qualitative time studies showed that added pyridine had little effect on the relative rate in each of the solvents studied.

Table 1. Effect of Solvent on the Rate of Reductive Elimination from **7**



entry	solvent	ε	k_{rel}
1	acetone-d_6	21	1.0 ± 0.1
2	C_6D_6	2.3	1.0 ± 0.1
3	chlorobenzene-d_5	5.6	1.0 ± 0.1
4	DMSO-d_6	47	2.0 ± 0.3
5	$CDCl_3$	4.8	2.3 ± 0.2
6	CD_3CN	38	2.4 ± 0.1
7	nitrobenzene-d_5	36	3.1 ± 0.3

Table 2. Effect of Solvent on the Rate of Carboxylate Exchange from **7**



entry	solvent	ε	k_{rel}
1	toluene-d_8	2.4	<0.1
2	acetone-d_6	21	1.0 ± 0.1
3	CD_3CN	38	2.0 ± 0.2
4	$CDCl_3$	4.8	19 ± 1

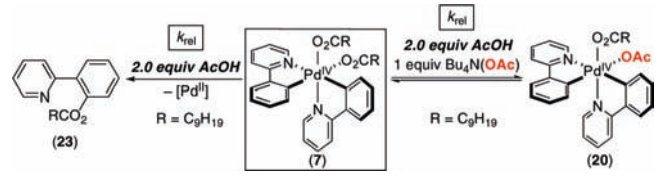
A.[7,9] However, the results from the corresponding solvent study for carboxylate exchange indicate that this interpretation should be reconsidered.

Mechanism of C−O Bond-Forming Reductive Elimination: Entropy of Activation. Previous work has shown that reductive elimination reactions proceeding via mechanism **A** are often characterized by large negative values of $\Delta S^{\ddagger}$. For example, Canty has reported that C−Se bond-forming reductive elimination from Pd^{IV} has $\Delta S^{\ddagger}$ ranging from −40 to −49 eu, depending on the reaction solvent.[9b] This has been rationalized on the basis of significant orientation of solvent molecules around the charged transition state.

The rate of C−O bond-forming reductive elimination from **7** was examined over a range of temperatures from 30 to 70 °C in both $CDCl_3$ and DMSO-d_6. Eyring plots showed that $\Delta S^{\ddagger}$ is close to zero in both solvents ($\Delta S^{\ddagger} = -1.4 \pm 1.9$ eu in $CDCl_3$ and $+4.2 \pm 1.4$ eu in DMSO-d_6). While values of $\Delta S^{\ddagger}$ between 10 and −10 eu are considered difficult to interpret, these values are substantially less negative than those reported by Canty.[27] As such, we initially viewed this data as inconsistent with mechanism **A**.[12]

Similar studies were conducted to obtain an Eyring plot for carboxylate exchange. In these experiments, the reaction of **7** with 1.0 equiv of Bu$_4$N(OAc) in $CDCl_3$ was monitored by ^{1}H NMR spectroscopy over temperatures ranging from −58 to −38 °C, and an Eyring plot provided $\Delta S^{\ddagger} = -7.2 \pm 3$ eu. Again, this value is considerably less negative than those reported by

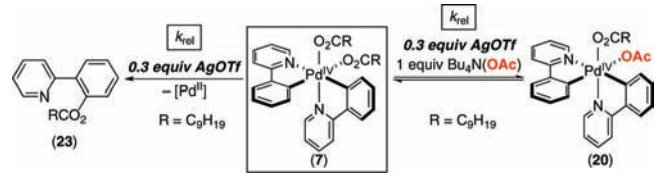
Table 3. Effect of AcOH on C−O Bond-Forming Reductive Elimination and Carboxylate Exchange at **7**



entry	acid	k_{rel} C−O coupling	k_{rel} exchange
1	none	1.0 ± 0.0[a]	1.0 ± 0.0[b]
2	HOAc	3.6 ± 0.2[a]	4.5 ± 0.5[b]

[a] 40 °C in acetone-d_6. [b] −35 °C in acetone-d_6.

Table 4. Effect of AgOTf on C−O Bond-Forming Reductive Elimination and Carboxylate Exchange at **7**



entry	acid	k_{rel} C−O coupling	k_{rel} exchange
1	none	1.0 ± 0.2[a]	1.0 ± 0.1[b]
2	AgOTf	16 ± 0.8[a]	8.7 ± 0.0[b]

[a] 23 °C in $CDCl_3$. [b] −53 °C in $CDCl_3$.

Canty[9b] but is quite similar to that obtained for C−O bond-forming reductive elimination from **7**.[30]

Mechanism of C−O Bond-Forming Reductive Elimination: Acidic Additives. Goldberg has shown that both Brønsted and Lewis acids accelerate C−O and C−C bond-forming reductive elimination from (dppe)Pt^{IV}(OAc)(Me)$_3$ (dppe = diphenylphosphinoethane), which both proceed via mechanism **A**.[7b] For example, the addition of 0.1 equiv of AcOH increased the rate of C−O coupling by a factor of 2, while the use of 0.1 equiv of AgOTf lowered the temperature required for C−C bond-forming reductive elimination from 99 to 25 °C. Both additives were proposed to act by promoting AcO$^-$ dissociation. On the basis of this report, we reasoned that if mechanism **A** were operative in our system, both C−O bond-forming reductive elimination and carboxylate exchange at complex **7** should be accelerated to similar extents by these additives.

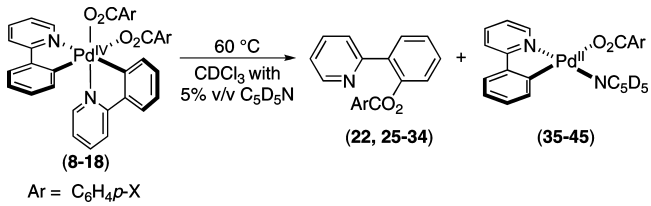
We first studied the rate of C−O bond-forming reductive elimination from (Phpy)$_2$Pd^{IV}(O$_2$CC$_9$H$_{19}$)$_2$ (**7**) in the presence of AcOH or AgOTf. The addition of AcOH (2.0 equiv) resulted in a 3.6-fold acceleration of C−O bond-forming reductive elimination (Table 3, entries 1 and 2), while AgOTf (0.3 equiv) led to a 16-fold increase in k_{obs} for this reaction (Table 4, entries 1 and 2).

The influence of AcOH on the rate of carboxylate exchange was next determined, and, remarkably, a very similar effect was observed. For example, the addition of AcOH (2.0 equiv) resulted in a 4.5-fold increase in the rate (Table 3, entry 2), while AgOTf (0.3 equiv) afforded an 8.7-fold increase in k_{obs} for exchange (Table 4, entry 2). These results are consistent

(29) Carboxylate exchange in toluene progressed too slowly to measure quantitatively at −38 °C (i.e., no observable exchange occurred after 6 h).

(30) More investigation is needed to understand why the entropy of activation is so small in this system. See ref 34 for a possible explanation.

Scheme 14. C−O Bond-Forming Reductive Elimination from **8**−**18**



with the hypothesis that carboxylate exchange and C−O bond-forming reductive elimination are mechanistically linked.

Mechanism of C−O Bond-Forming Reductive Elimination: Carboxylate Electronic Effects. A series of Pd^{IV} complexes (**8**−**18**) were designed to place both σ- and π-electron donating and electron withdrawing substituents on the benzoate ligand. The kinetics of C−O bond-forming reductive elimination from Pd^{IV} complexes **8**−**18** was then studied at 60 °C in a solution of 5% v/v C_5D_5N in $CDCl_3$ (Scheme 14).[28] A Hammett plot of this data showed very good correlation with σ_{para} ($R^2 = 0.95$) and yielded a ρ value of -1.36 ± 0.04 (Figure 2).

A previous report showed that $\rho = +1.44$ for C−O bond-forming reductive elimination from (dppbz)$PtMe_3$(OAr), which proceeds by mechanism **A**.[7b] As such, we initially reasoned that the observed ρ value of -1.36 provided evidence against an ionic mechanism.[12] However, the overall value of ρ (ρ_{obs}) for a reaction proceeding by mechanism **A** is the sum of ρ_{eq} and ρ_2 (Figure 3).[31] The ρ_{obs} of +1.44 in the Pt system was rationalized based on the assumption that $|\rho_{eq}| > |\rho_2|$;[7b] however, since the overall ρ (ρ_{obs}) is a composite, a positive ρ value is not an inherent feature of such mechanisms.[32] Thus, since all of the possible mechanisms (**A**, **B**, and **C**) involve the carboxylate acting as a nucleophilic partner in a rate-determining C−O bond-forming step (Scheme 6), the observed negative ρ value is potentially consistent with any of these pathways.

Mechanism of C−O Bond-Forming Reductive Elimination: Arylpyridine Electronic Effects. A series of complexes containing electronically varied arylpyridine ligands (**15** and **46**−**50**) were designed to place different electron withdrawing and electron donating substituents trans to the Pd-bound carbon atom. The kinetics of C−O bond-forming reductive elimination from **15** and **46**−**50** were studied at 60 °C in a solution of 5% v/v C_5D_5N

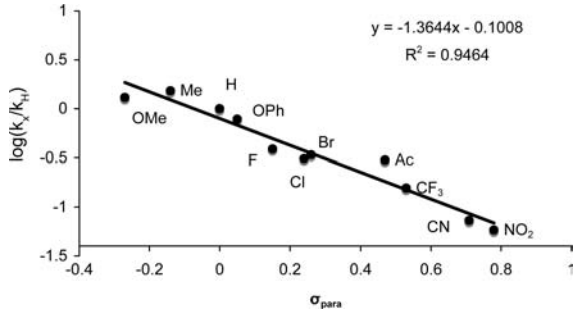


Figure 2. Hammett plot for C−O bond-forming reductive elimination from **8**−**18**.

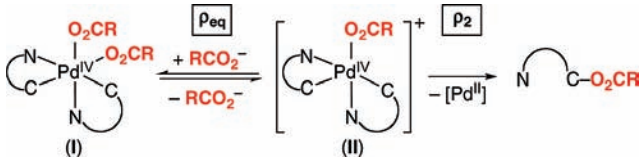
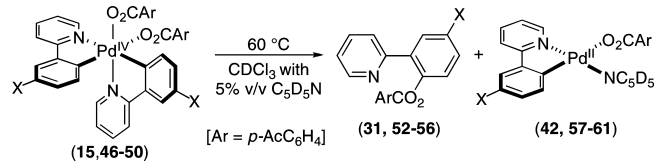


Figure 3. Values of ρ for each step of mechanism **A**.

Table 5. k_{obs} for Reductive Elimination from $(Arpy)_2Pd^{IV}[O_2C(p\text{-}AcC_6H_4)]_2$



Compound	k_{obs} ($s^{-1} \times 10^5$)
*OMe (**46**)	~3[a]
Me (**47**)	4.81
H (**15**)	20.0
F (**48**)	3.64
Cl (**49**)	36.9
*CF_3 (**50**)	~320[a]

[a] These values of k_{obs} are approximate, as samples of **46** and **50** were contaminated with ~10% of inseparable impurities.

in $CDCl_3$. Reductive elimination generally proceeded fastest with electron-withdrawing substituents (Table 5), although Hammett plots showed only modest correlation with σ_{para} ($R^2 = 0.80$), σ^+ ($R^2 = 0.79$), and σ^- ($R^2 = 0.84$). This is consistent with the Ar ring acting as the electrophilic partner in C−O coupling.

Mechanism of C−O Bond-Forming Reductive Elimination: Ligand Rigidity. We originally hypothesized that a decrease in reaction rate with increasing N∼C ligand rigidity would provide support for mechanism **C**.[12] Complexes **62**−**64** were designed to systematically vary the flexibility of the tether between the two pyridine rings (Figure 4). The kinetics of C−O bond-forming reductive elimination from **62**−**64** was studied by ^{1}H NMR spectroscopy at 50 °C in a solution of 5% v/v C_5D_5N in $CDCl_3$. As summarized in Table 6, the rates of reductive elimination did show a correlation with the rigidity of the N∼C ligand. For example, complex **62** reacted twice as fast as **63** and more than 10 times faster than the most rigid **64**.

As discussed above, we originally interpreted these results as being most consistent with the chelate dissociation mechanism (**C**).[12,20] However, a number of literature reports have shown that rigid ancillary ligands stabilize Pd^{IV} complexes toward reductive elimination, even when the ligand plays no direct role in the bond-forming process.[10] Therefore, these results do not definitively establish or rule out any of the three mechanistic manifolds.

Summary of Mechanistic Data for C−O Bond-Forming Reductive Elimination. Mechanisms **A**, **B**, or **C** for C−O bond-forming reductive elimination from $(N\sim C)_2Pd^{IV}(O_2CR)_2$ are kinetically indistinguishable; therefore, we have conducted a series of alternative mechanistic experiments to interrogate this transformation. Our original communication suggested that mechanism **C**, chelate dissociation, was most consistent with initial studies of this process.[12] This conclusion was based on 5 key pieces of data: (i) the absence of a clear correlation between k_{obs} and solvent polarity, (ii) the lack of crossover between free and bound carboxylate, (iii) the small entropy of activation, (iv)

(31) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988.

(32) Reductive elimination reactions from $(Phpy)_2Pd^{IV}(O_2CAr)_2$ have the added complication that these complexes contain two different carboxylate ligands. If mechanism **A** were operating, these two ligands would serve two very different roles in the first step of the reaction - one would dissociate to form an anion (stabilized by electron withdrawing groups), while the other would remain bound to cationic intermediate **II** (stabilized by electron donating groups).

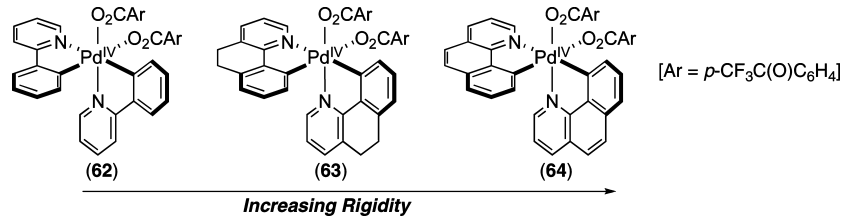
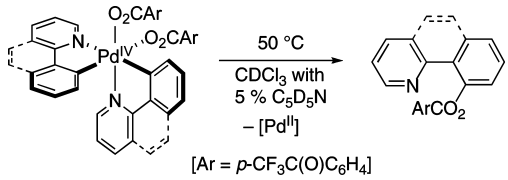


Figure 4. Effect of ligand rigidity on C−O bond-forming reductive elimination.

Table 6. Rate of C−O Bond-Forming Reductive Elimination as a Function of Ligand Rigidity



entry	complex	k_{rel}
1	**62**	1.9
2	**63**	1.0
3	**64**	∼0.1[a]

[a] The slow reaction rate along with competing C−C bond-formation prevented quantitative rate measurement in this system.

the negative ρ value obtained upon substitution of the carboxylate ligand, and (v) the decreased reaction rate with more rigid N∼C ligands.[33]

However, we have conducted a variety of new experiments, and these, along with a re-evaluation of the previous data, have led us to conclude that mechanism **A** is, in fact, most likely operating in this system. These new experiments were particularly focused on the exchange of free and bound carboxylate at $(Phpy)_2Pd^{IV}(O_2CR)_2$, which is expected to proceed by an identical mechanism to the first step of mechanism **A**. This exchange occurs at temperatures far below reductive elimination, and shows similar solvent effects and activation parameters to C−O bond-formation.[34] In addition, the rates of carboxylate exchange and of C−O coupling are increased to very similar extents upon addition of AcOH and AgOTf, additives that have both been reported to promote carboxylate dissociation. The C−C bond-forming reactions discussed below offer further evidence in support of mechanism **A**. In addition, they provide a more complete picture of the reactivity of these Pd^{IV} complexes.

C−C Bond-Forming Reductive Elimination from $(Bzq)_2Pd^{IV}(O_2CR)_2$. In the context of the ligand rigidity studies, we noted that benzo[*h*]quinoline complex **64** reacted to form significant quantities of C−C bond-forming reductive elimination product **66** along with the expected C−O coupled product **65** (Scheme 15). This result was intriguing, since analogous C−C coupling was not observed in any of the phenylpyridine systems. As such, a series of experiments was designed to further interrogate the mechanism of this process.

Scheme 15. Competing C−O and C−C Bond-Forming Reductive Elimination from **64**

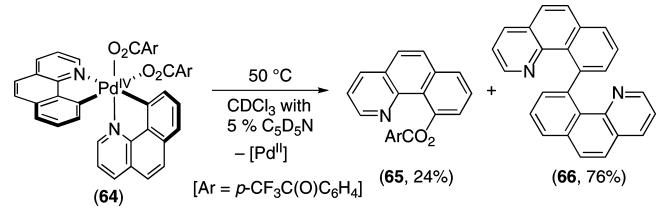
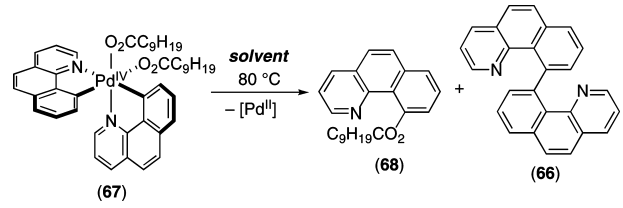


Table 7. Effect of Solvent on the Product Ratio of Reductive Elimination from **67**



entry	solvent	ratio **66**:**68**	k_{rel} for C−O coupling from **7**
1	CH_3CN	0.2:1	2.4
2	$CHCl_3$	0.77:1	2.3
3	nitrobenzene	2.2:1	3.1
4	DMSO	3.3:1	2.0
5	acetone	13:1	1.0
6	benzene	>20:1	1.0

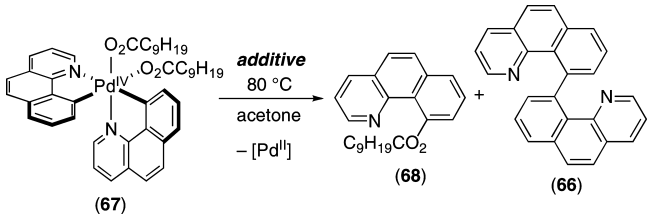
Mechanism of C−C Bond-Forming Reductive Elimination: Solvent Effects. A first study probed the effect of solvent on the relative rates (k_{rel}) of C−C and C−O bond-forming reductive elimination from $(Bzq)_2Pd^{IV}(O_2CC_9H_{19})_2$ (**67**). The values of k_{rel} were determined under a standard set of conditions (80 °C, 4 h, 15.2 mM) on the basis of the ratio of C−C coupled product **66** to C−O coupled product **68** in the crude reaction mixtures. As summarized in Table 7, solvent had a significant influence on the product distribution, with the ratio of **66**:**68** ranging from >20:1 to 0.2:1. While there was no clear relationship between the dielectric constant of the solvent and the product ratio, the largest amounts of **66** were observed in solvents where C−O coupling from the analogous 2-phenylpyridine complex $(Phpy)_2Pd^{IV}(O_2CC_9H_{19})_2$ (**7**) was relatively slow. For example, in benzene and acetone (with $k_{rel} = 1$ for C−O bond-forming reductive elimination from **7**), >10:1 selectivity was observed for **66** (Table 7, entries 5 and 6). Conversely, in CH_3CN and $CHCl_3$, (solvents where C−O bond-forming reductive elimination from **7** was relatively fast), **68** was the major organic reductive elimination product (entries 1 and 2).

Mechanism of C−C Bond-Forming Reductive Elimination: Acidic Additives. Complex **67** was subjected to standard reductive elimination conditions (80 °C, 3 h, 15.2 mM in acetone) in the presence of 5.0 equiv of AcOH or 0.10 equiv AgOTf (additives that accelerate C−O bond-forming reductive elimina-

(33) Calculations on C−O bond-forming reductive elimination reactions from **10** (ref 22) suggested that mechanisms **A** and **B** are relatively close in energy ($\Delta G^{\ddagger}$ = 31.4 and 26.4 kcal/mol, respectively). In contrast, mechanism **C** was calculated to have a much larger activation energy of 44.3 kcal/mol.

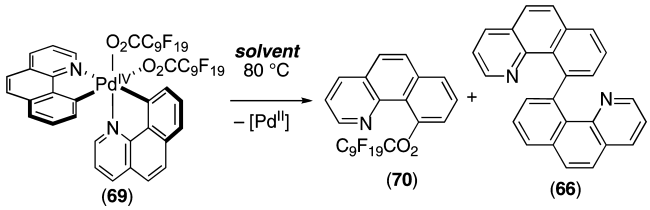
(34) While the observed solvent effects and activation parameters are somewhat unexpected for a system involving ionic intermediates, they may result from an unusually early or late transition state that has relatively little charge buildup.

Table 8. Effect of Acidic Additives on the Product Ratio of Reductive Elimination from **67**



entry	additive	ratio **66**:**68**
1	none	13:1
2	AcOH (5.0 equiv)	3.6:1
3	AgOTf (0.1 equiv)	0.10:1

Table 9. Solvent Effects on Product Distribution of Reductive Elimination from Complex **69**



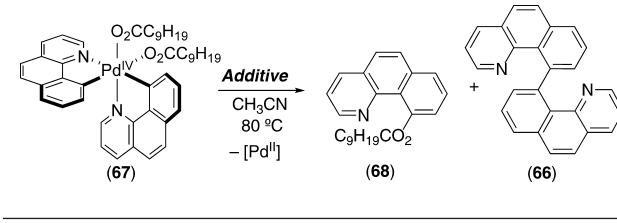
entry	solvent	organic product
1	pyridine-d_5	**66**
2	acetone-d_6	**66**
3	DMSO-d_6	**66**
4	CD_3CN	**66**

tion from $(Phpy)_2Pd^{IV}(O_2CC_9H_{19})_2$ (**7**)), and the ratio of organic products was determined using ^1H NMR spectroscopy. As summarized in Table 8, both additives led to a large increase in the relative amount of the oxygenated product **68**. For example, with AcOH, the ratio of **66** to **68** changed from 13:1 to 3.6: 1. The effect was even more dramatic with AgOTf, where the major organic product was **68** (ratio of **66**:**68** = 0.10:1).

Mechanism of C−C Bond-Forming Reductive Elimination: Carboxylate Electronics. Our earlier studies showed that C−O bond-forming reductive elimination from $(Phpy)_2Pd^{IV}(O_2CAr)_2$ is slowed significantly with electron withdrawing benzoate ligands (cf., Figure 2), and, as such, we first examined complexes of general structure $(Bzq)_2Pd^{IV}(O_2CAr)_2$, where the substituents on the benzoate ligands were systematically varied. However, the low solubility of these compounds precluded quantitative mechanistic studies. Thus, subsequent efforts aimed to compare $(Bzq)_2Pd^{IV}(O_2CC_9H_{19})_2$ (**67**) to $(Bzq)_2Pd^{IV}$-$(O_2CC_9F_{19})_2$ (**69**), which contains sterically similar but highly electron withdrawing perfluorinated carboxylates. In all of the solvents examined (pyridine-d_5, acetone-d_6, DMSO-d_6, and CD_3CN), electron deficient complex **69** was much less reactive than **67**, and it could be recovered quantitatively from the reaction mixtures following our standard reductive elimination conditions (80 °C, 3 h). Complete consumption of $(Bzq)_2Pd^{IV}(O_2CC_9F_{19})_2$ required heating at 80 °C for 3−16 d depending on the solvent. In addition, C−C coupled **66** was the sole organic product in every solvent examined (Table 9).

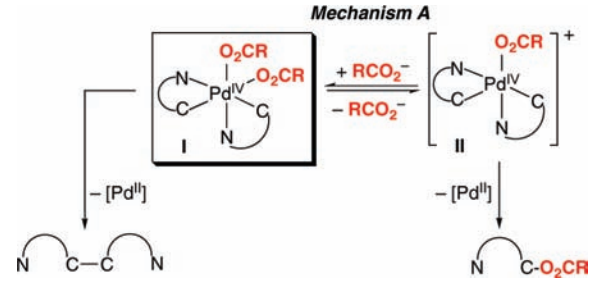
Mechanism of C−C Bond-Forming Reductive Elimination: Added Carboxylate. Under standard reaction conditions (80 °C, 3 h, 15.2 mM in CH_3CN), **68** was the major product, and the **66**:**68** ratio was 0.2:1 as determined by ^1H NMR spectroscopy (Table 10, entry 1). However, when 1 equiv of $NBu_4(O_2CC_9H_{19})$

Table 10. Effect of $NBu_4(O_2CC_9H_{19})$ on the Product Distribution of Reductive Elimination from **67**



entry	additive	ratio **66**:**68**
1	none	0.2:1
2	$NBu_4(O_2CC_9H_{19})$	2:1
3	NBu_4PF_6	0.2:1

Scheme 16. Proposed Mechanisms for C−C and C−O Bond-Forming Reductive Elimination from $(N{\sim}C)_2Pd^{IV}(O_2CR)_2$

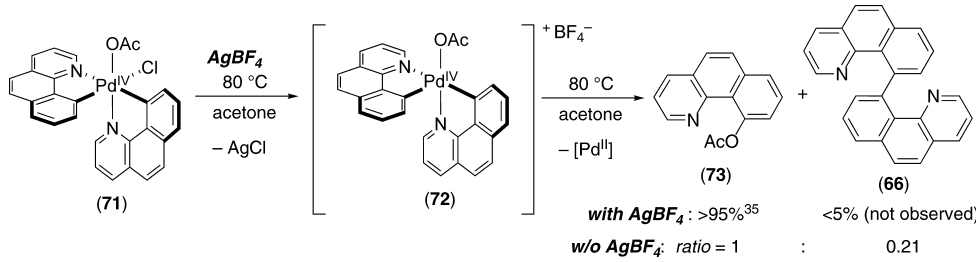


was added, the selectivity completely reversed, and **66** predominated (**66**:**68** ratio = 2:1). To confirm that this effect was not just due to the increased ionic strength of the solution, a control experiment was conducted using 1 equiv of NBu_4PF_6. This experiment provided an identical product ratio to the initial reaction (**66**:**68** = 0.2:1). Therefore, the reversal in product selectivity is clearly specific to the carboxylate ion.

Proposed Mechanism for C−C and C−O Bond-Forming Reductive Elimination from $(N{\sim}C)_2Pd^{IV}(O_2CR)_2$. The solvent, additive, and ligand effect studies, as well as the influence of added carboxylate, all suggest that reductive elimination processes from **67** occur via the pathway outlined in Scheme 16. This proposal is consistent with all of the mechanistic data and also provides a unifying mechanism for C−O and C−C bond-forming reductive elimination for complexes of general structure $(N{\sim}C)_2Pd^{IV}(O_2CR)_2$. In this scenario, C−O bond-forming reductive elimination from **67** proceeds by an analogous mechanism to that proposed for $(Phpy)_2Pd^{IV}(O_2CR)_2$ (via pre-equilibrium carboxylate dissociation followed by C−O coupling, mechanism **A**). In contrast, C−C bond-forming reductive elimination takes place by direct reductive elimination from the 6-coordinate starting material **67**.

The data presented above are all consistent with Scheme 16. In the presence of added carboxylate, the equilibrium for carboxylate dissociation (step *i* of mechanism **A**) should be shifted to the left, thereby leading to increased formation of the C−C coupled product by direct reductive elimination from **I**. Under conditions that accelerate C−O bond-forming reductive elimination by mechanism **A** (i.e., solvents like CH_3CN or $CHCl_3$, additives like HOAc or AgOTf, electron donating carboxylate ligands), the C−O coupled product predominates. In contrast, under conditions shown to slow C−O coupling (e.g., solvents like acetone or benzene, electron withdrawing carboxylate ligands), the C−C coupled product is formed in high yield.

Scheme 17. Effect of $AgBF_4$ on the Product Distribution of Reductive Elimination from **71**



To provide final evidence in support of this mechanistic manifold, we generated $[(Bzq)_2Pd^{IV}(O_2R)]^+$ in situ and examined the distribution of organic products from this species. As shown in Scheme 17, treatment of $(Bzq)_2Pd^{IV}(Cl)(OAc)$ (**71**) with $AgBF_4$ at 80 °C [conditions that are expected to afford $[(Bzq)_2Pd^{IV}(OAc)]BF_4$ (**72**)] resulted in rapid C−O bond-forming reductive elimination to afford **73**, with none of the C−C coupled product **66** observed by ^{1}H NMR spectroscopy.[35] This result is in striking contrast to the reaction of **71** in the absence of $AgBF_4$, which yielded a 1:0.21 ratio of **73**:**66**, as well as to the reaction of $(Bzq)_2Pd^{IV}(OAc)_2$ (**74**) (which gave a 0.5:1 ratio of **73**:**66**). Therefore, it provides a final piece of compelling evidence in support of the proposed mechanism.

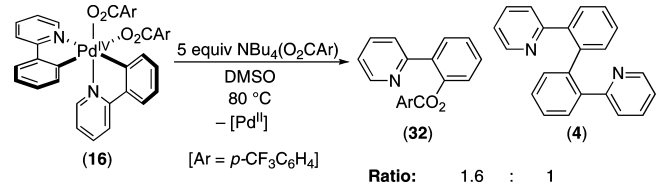
Unified Mechanism: C−C Coupling from Phenylpyridine Complexes. If Scheme 16 does, in fact, represent a unified mechanism for reductive elimination from $(N\sim C)_2Pd^{IV}(O_2CR)_2$, we reasoned that it should be possible to rationally design conditions to achieve C−C coupling from complexes where N∼C = 2-phenylpyridine. Guided by the studies above, we examined conditions under which k_{rel} for C−O bond-forming reductive elimination is predicted to be slow - with a highly electron withdrawing carboxylate ligand and in the presence of an excess of added carboxylate. We were delighted to find that the reaction of $(Phpy)_2Pd^{IV}(O_2CAr)_2$ [Ar = *p*-$CF_3C_6H_4$] in the presence of 5 equiv of $Bu_4N(O_2CAr)$ at 80 °C in DMSO for 5 h resulted in a 1.6:1 mixture of oxygenated product **32** to biaryl product **4** (Scheme 18). This result demonstrates that perturbations of the ancillary ligand set and additives have similar effects in the 2-phenylpyridine and benzoquinoline complexes, providing support for similar mechanisms in both systems.

Conclusions

This paper described the synthesis of a series of unusually stable Pd^{IV} complexes of general structure $(N\sim C)_2Pd^{IV}(O_2CR)_2$.

(35) Only C−O coupled products were formed in this reaction; however, both acetoxylated product **73** and the corresponding phenol (presumably formed by ester hydrolysis under the reaction conditions) were observed.

Scheme 18. Rational Design of Conditions To Achieve C−C Bond-Forming Reductive Elimination from $(Phpy)_2Pd^{IV}(O_2CAr)_2$ Complexes



These complexes have allowed us to conduct the first detailed mechanistic studies of C−O bond-forming reductive elimination from Pd^{IV} centers. In addition, we have studied competing C−C coupling processes. Based on these investigations, we propose that C−O bond-forming reductive elimination proceeds via an ionic mechanism involving initial carboxylate dissociation, followed by C−O coupling from a 5-coordinate cationic intermediate. In contrast, the C−C bond-forming reaction is believed to involve direct reductive elimination from the octahedral Pd^{IV} starting material. Our mechanistic understanding of these processes has facilitated the rational tuning of ancillary ligands and reaction conditions in order to control the ratio of organic products. Current efforts are focused on applying the mechanistic insights obtained from these studies toward the design and optimization of new $Pd^{II/IV}$-catalyzed reactions that form both carbon−oxygen and carbon−carbon bonds.

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Supporting Information Available: Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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