

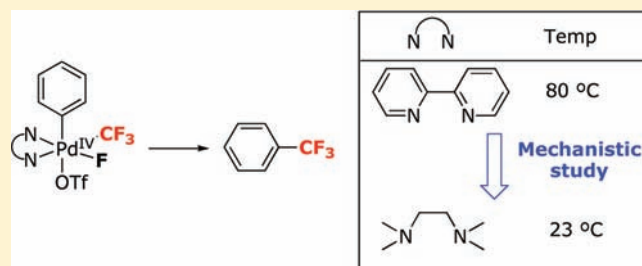
# Mechanistic and Computational Studies of Oxidatively-Induced Aryl–CF<sub>3</sub> Bond-Formation at Pd: Rational Design of Room Temperature Aryl Trifluoromethylation

Nicholas D. Ball, J. Brannon Gary, Yingda Ye, and Melanie S. Sanford\*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

Supporting Information

**ABSTRACT:** This article describes the rational design of first generation systems for oxidatively induced Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>II</sup>. Treatment of (dtbpy)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) (dtbpy = di-*tert*-butylbipyridine) with NFTPPT (*N*-fluoro-1,3,5-trimethylpyridinium triflate) afforded the isolable Pd<sup>IV</sup> intermediate (dtbpy)Pd<sup>IV</sup>(Aryl)(CF<sub>3</sub>)(F)(OTf). Thermolysis of this complex at 80 °C resulted in Aryl–CF<sub>3</sub> bond-formation. Detailed experimental and computational mechanistic studies have been conducted to gain insights into the key reductive elimination step. Reductive elimination from this Pd<sup>IV</sup> species proceeds via pre-equilibrium dissociation of TfO<sup>−</sup> followed by Aryl–CF<sub>3</sub> coupling. DFT calculations reveal that the transition state for Aryl–CF<sub>3</sub> bond formation involves the CF<sub>3</sub> acting as an electrophile with the Aryl ligand serving as a nucleophilic coupling partner. These mechanistic considerations along with DFT calculations have facilitated the design of a second generation system utilizing the tmeda (*N,N,N',N'*-tetramethylethylenediamine) ligand in place of dtbpy. The tmeda complexes undergo oxidative trifluoromethylation at room temperature.



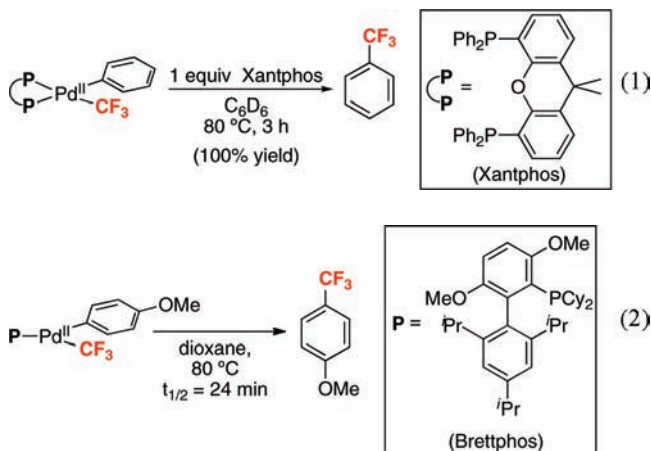
## INTRODUCTION

The formation of C–CF<sub>3</sub> bonds is an important transformation for the construction of pharmaceuticals and agrochemicals.<sup>1</sup> Replacing a methyl group with a trifluoromethyl substituent can have a profound effect on the physical and biological properties of a molecule.<sup>2</sup> As a result, there is high demand for versatile synthetic methods for generating carbon–CF<sub>3</sub> bonds.<sup>3</sup> While there has been significant progress in the construction of sp<sup>3</sup>-carbon–CF<sub>3</sub> linkages,<sup>3</sup> there are comparatively fewer methods for Aryl–CF<sub>3</sub> bond-formation.<sup>4–7</sup>

Transition metal-catalyzed cross-coupling between Aryl–X and CF<sub>3</sub>–Y would serve as an attractive method for the synthesis of benzotrifluorides.<sup>8–11</sup> The use of Pd-based catalysts for such transformations is of particular interest because they serve as versatile and widely used catalysts for a variety of other carbon–carbon bond-forming reactions.<sup>12</sup> However, developments in this area have been limited by the challenges associated with a key step of the cross-coupling catalytic cycle, namely Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>II</sup> centers.<sup>4,13</sup> The vast majority of known Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) complexes are inert to Aryl–CF<sub>3</sub> coupling at temperatures as high as 150 °C.<sup>24,21</sup>

Two strategies have been utilized in the literature to address this challenge. The first has focused on achieving Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>II</sup> via steric and electronic modification of the ancillary ligands (L) at (L)<sub>n</sub>Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>). For example, pioneering work by Grushin demonstrated that the Xantphos ligand (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) facilitates high yielding formation of trifluorotoluene from (Xantphos)-Pd<sup>II</sup>(Ph)(CF<sub>3</sub>) at 80 °C (eq 1).<sup>14</sup> More recently, Buchwald has

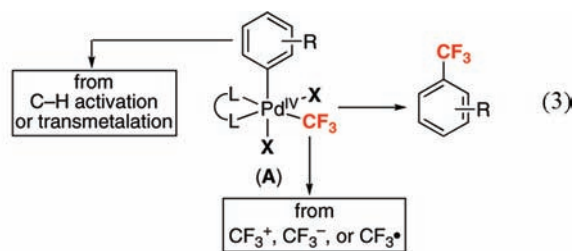
elegantly demonstrated that the sterically large monodentate phosphine ligand Brettphos (Brettphos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl) promotes stoichiometric Aryl–CF<sub>3</sub> coupling from (Brettphos)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) at 80 °C (eq 2).<sup>15</sup> Remarkably, this latter system was successfully applied to the catalytic trifluoromethylation of aryl chlorides with Et<sub>3</sub>SiCF<sub>3</sub> at 130–140 °C.<sup>15</sup>



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While this first approach has provided important breakthroughs, Pd<sup>II</sup>-mediated Aryl–CF<sub>3</sub> bond-forming reactions remain limited by the requirement for specialized and expensive phosphine ligands<sup>16,17</sup> relatively high reaction temperatures (80–140 °C), and the need for expensive Et<sub>3</sub>SiCF<sub>3</sub><sup>18</sup> in catalytic processes. As a result, several groups have focused on a second, complementary strategy for achieving Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd.<sup>19–21</sup> This approach hinges on changing the oxidation state, rather than the ancillary ligand environment, at the metal center. As shown in eq 3, it was expected that palladium(IV) complexes of general structure (L)<sub>2</sub>(X)<sub>2</sub>Pd<sup>IV</sup>(Aryl)(CF<sub>3</sub>) (A) would be highly kinetically and thermodynamically reactive toward Aryl–CF<sub>3</sub> coupling. This hypothesis is predicated on literature reports showing that Pd<sup>IV</sup> complexes participate in numerous carbon-heteroatom bond-forming reductive elimination reactions that remain challenging at Pd<sup>II</sup> centers.<sup>22,23</sup> A key advantage of this approach would be that Pd<sup>IV</sup> intermediate A could potentially be accessed using nucleophilic (CF<sub>3</sub><sup>−</sup>),<sup>24</sup> electrophilic (CF<sub>3</sub><sup>+</sup>),<sup>25</sup> or free-radical (CF<sub>3</sub>•)<sup>26</sup> based trifluoromethylating reagents.



Two preliminary examples have shown the viability of this approach. First, Yu and co-workers have elegantly demonstrated the Pd<sup>II/IV</sup>-catalyzed ligand-directed C–H trifluoromethylation with electrophilic trifluoromethylating reagents (CF<sub>3</sub><sup>+</sup> reagents).<sup>19</sup> Subsequent stoichiometric studies implicated a mechanism involving: (a) C–H activation to form a cyclometalated Pd<sup>II</sup>–Aryl intermediate, (b) oxidation with CF<sub>3</sub><sup>+</sup> to generate Pd<sup>IV</sup>(Aryl)(CF<sub>3</sub>), and (c) Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>IV</sup> to release the product.<sup>20</sup>

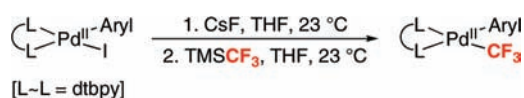
In a second example, our group has shown the viability of stoichiometric Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>IV</sup> centers bearing  $\sigma$ -aryl ligands that do not contain chelate directing groups.<sup>21</sup> In this system, the key Pd<sup>IV</sup> intermediate is generated via oxidation of a preassembled Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) species with an *N*-fluoropyridinium reagent. We report herein a detailed mechanistic study of Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>IV</sup> in this latter system. This work provides valuable insights into the influence of ancillary ligands, the role of each coupling partner, and the nature of the transition state for this transformation. These mechanistic studies have also allowed us to rationally design the first examples of room temperature Aryl–CF<sub>3</sub> bond-formation from palladium.

## RESULTS AND DISCUSSION

### Development and Scope of Aryl–CF<sub>3</sub> Coupling at Pd<sup>IV</sup>.

Our studies began with the synthesis of a series of Pd<sup>II</sup>–CF<sub>3</sub> complexes of general structure (dtbpy)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) (1a–i, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine). These compounds were prepared by the treatment of (dtbpy)Pd<sup>II</sup>(Aryl)(I) with CsF followed by TMSCF<sub>3</sub> in THF at 23 °C (Table 1). The products were isolated as yellow solids in 32–70% yield.<sup>21</sup> X-ray quality crystals of 1a were obtained by vapor diffusion of pentanes into a dichloromethane

Table 1. Synthesis of Complexes 1a–i



entry	aryl	compound	isolated yield
1	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	1a	70%
2	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	1b	54%
3	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1c	63%
4	<i>p</i> -PhC(O)C <sub>6</sub> H <sub>4</sub>	1d	51%
5	<i>p</i> -PhC <sub>6</sub> H <sub>4</sub>	1e	58%
6	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	1f	32%
7	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	1g	49%
8	C <sub>6</sub> H <sub>5</sub>	1h	47%
9	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	1i	42%

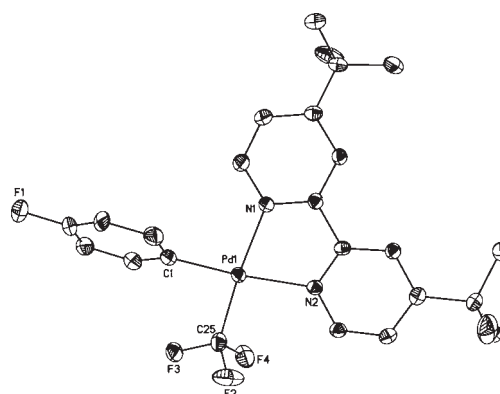
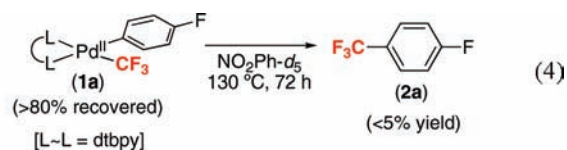


Figure 1. ORTEP drawing of complex 1a. Thermal ellipsoids are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Pd–C(1) 2.005(3), Pd–C(25) 2.007(4), Pd–N(1) 2.107(2), Pd–N(2) 2.143(3). Selected bond angles (deg): C(1)–Pd–C(25) 89.99(13), C(1)–Pd–N(1) 95.58(11), C(1)–Pd–N(2) 169.99(11), C(25)–Pd–N(1) 173.92(12), C(25)–Pd–N(2) 96.67(11).

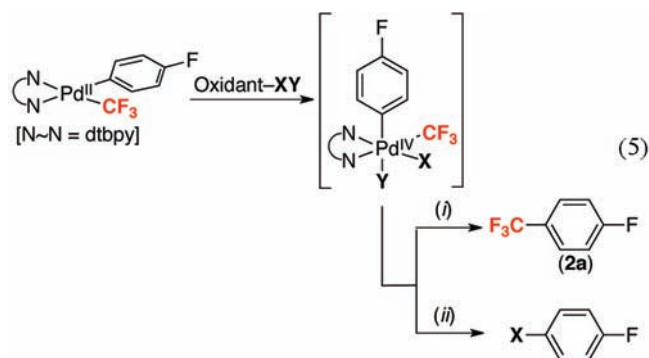
solution of 1a, and the X-ray crystal structure of this complex is shown in Figure 1.

The Pd<sup>II</sup> complexes 1a–i are inert toward direct Aryl–CF<sub>3</sub> bond-forming reductive elimination. For example, heating 1a at 130 °C for 72 h produced <5% of 4-fluorobenzotrifluoride (2a), and the Pd<sup>II</sup> starting material could be recovered in >80% yield (eq 4). Importantly, similarly low reactivity has been reported in the literature for other (L~L)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) complexes (L~L = diphenylphosphinoethane, diphenylphosphinopropane, and diphenylphosphinobenzene).<sup>24a,b</sup> As discussed above, the only demonstrated examples of Aryl–CF<sub>3</sub> bond-forming reductive elimination from Pd<sup>II</sup> require relatively high temperatures (80 °C) and specialized phosphine ligands.<sup>14,15</sup>



We reasoned that the 2e<sup>−</sup> oxidation of (dtbpy)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) would yield a highly reactive Pd<sup>IV</sup> adduct that might undergo more facile Aryl–CF<sub>3</sub> bond-forming reductive elimination (eq 5, i). Thus, we examined the reaction of 1a with *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and PhI(OAc)<sub>2</sub>, which are all

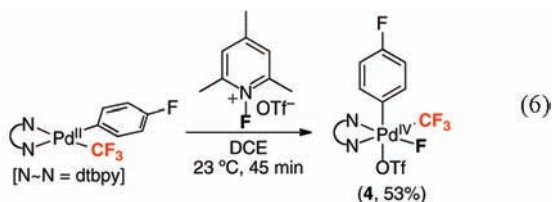
well-known to promote the oxidation of Pd<sup>II</sup> to Pd<sup>IV</sup>.<sup>22</sup> As shown in Table 2, all three oxidants reacted rapidly with **1a** in nitrobenzene-*d*<sub>5</sub> at 80 °C. However, the desired trifluoromethylated product was not obtained; instead, the major organic product contained a nucleophile derived from the oxidant (Br, Cl, or OAc, respectively). These results are consistent with the formation of a Pd<sup>IV</sup> intermediate, from which Aryl–X (X = OAc, Br, and Cl) bond-forming reductive elimination is significantly faster than Aryl–CF<sub>3</sub> coupling (eq 5, ii).<sup>21</sup>



In an effort to avoid competing reductive elimination processes, we next examined the use of electrophilic fluorinating reagents (F<sup>+</sup> sources). These reagents were selected based on the hypothesis that fluoride (the X-type ligand introduced to Pd<sup>IV</sup> by F<sup>+</sup> sources) might undergo slower reductive elimination than CF<sub>3</sub>.<sup>22d,27,28</sup> Gratifyingly, a variety of different F<sup>+</sup> reagents reacted with **1a** to afford modest to excellent yields of the trifluoromethylated product **2a** after 3 h at 80 °C (Table 2, entries 4–10). The optimal electrophilic fluorinating reagent was *N*-fluoro-1,3,5-trimethylpyridinium triflate (NFTPT), which provided **2a** in 70% yield as determined by <sup>19</sup>F NMR spectroscopy.<sup>29</sup> Importantly, <5% of products derived from Aryl–F or Aryl–OTf coupling were observed under these conditions.

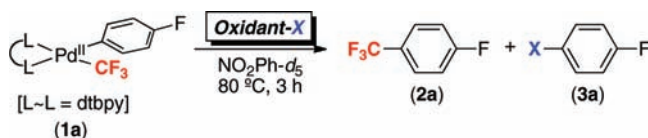
This transformation was next applied to complexes **1b–i**, which contain sterically and electronically diverse aryl groups. As shown in Table 3, the yield of trifluoromethylated product was relatively insensitive to the electronic properties of the arene, and the reaction proceeded with good results in systems containing both electron withdrawing [e.g., CN, C(O)Ph] and electron donating (e.g., CH<sub>3</sub>, OCH<sub>3</sub>) *para*- and *meta*-substituents.<sup>30</sup>

At room temperature, the oxidation of **1a** by NFTPT produced a single major intermediate. This species (**4**) was isolated from dichloroethane as a yellow solid in 53% yield (eq 6). Analysis of **4** by <sup>19</sup>F NMR spectroscopy in MeCN-*d*<sub>3</sub> showed four characteristic resonances: a doublet at –30.9 ppm (Pd–CF<sub>3</sub>), a singlet at –79.4 ppm (Pd–OTf), a multiplet at –117.1 ppm (Pd–ArF), and a quartet at –256.5 ppm (Pd–F) in a 3:3:1:1 ratio. In nitrobenzene-*d*<sub>5</sub>, broad resonances were observed with similar chemical shifts in the same 3:3:1:1 ratio.<sup>31</sup> The <sup>1</sup>H NMR spectrum of **4** showed two diagnostic singlets at 8.47 and 8.40 ppm (3,3' protons of dtbpy) as well as two singlets at 1.49 and 1.41 ppm (<sup>t</sup>Bu groups of dtbpy).



X-ray quality crystals were obtained via vapor diffusion of pentanes into a DCE solution of **4**. As shown in Figure 2, the solid

Table 2. Reaction of **1a** with Diverse Oxidants (Oxidant–X)<sup>a</sup>

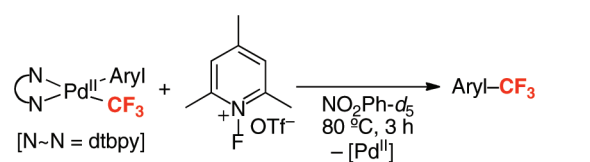


entry	oxidant–X	yield 2a	yield 3a (X)
1		<5%	75% (Br)
2		<5%	70% (Cl)
3		<5%	20% (OAc)
4		<5%	nd (F) <sup>b</sup>
5		60%	<5%
6		53%	<5%
7		69%	<5%
8		55%	<5%
9		68%	<5%
10		70%	<5%
11	XeF <sub>2</sub>	65%	5%

<sup>a</sup> Yields were determined by <sup>19</sup>F NMR spectroscopy and are an average of two runs. nd = not detected. <sup>b</sup> **1a** accounted for the remaining mass balance.

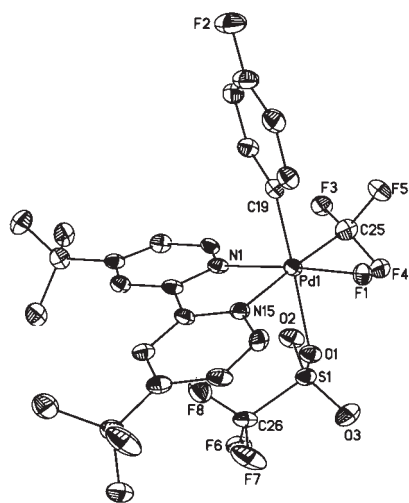
state structure of **4** shows the octahedral Pd<sup>IV</sup> species (dtbpy)-Pd(*p*-FC<sub>6</sub>H<sub>4</sub>)(CF<sub>3</sub>)(F)(OTf). Interestingly, the Pd–CF<sub>3</sub> bond distance in **4** (2.009(4) Å) is nearly identical to that of the Pd<sup>II</sup>–CF<sub>3</sub> starting material **1a** (2.005(3) Å). However, the Pd–N bond lengths of **4** (2.038(4) and 2.082(4) Å) are significantly shorter than those in **1a** (2.107(2) and 2.143(3) Å).

**Mechanistic Study of Aryl–CF<sub>3</sub> Bond-Forming Reductive Elimination from Pd<sup>IV</sup>.** There are at least three possible pathways for Aryl–CF<sub>3</sub> bond-forming reductive elimination from **4**, mechanisms A, B, and C (Figure 3). Mechanism A involves initial triflate dissociation to form a cationic five-coordinate Pd<sup>IV</sup> intermediate I and subsequent Aryl–CF<sub>3</sub> bond formation.

Table 3. NFTPT-Promoted Aryl–CF<sub>3</sub> Coupling at Complexes 1a–i<sup>a</sup>


entry	compound	aryl	yield aryl–CF <sub>3</sub>
1	1a	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	70%
2	1b	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	25%
3	1c	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	55%
4	1d	<i>p</i> -PhC(O)C <sub>6</sub> H <sub>4</sub>	56%
5	1e	<i>p</i> -PhC <sub>6</sub> H <sub>4</sub>	70%
6	1f	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	72%
7	1g	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	66%
8	1h	C <sub>6</sub> H <sub>5</sub>	70%
9	1i	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	64%

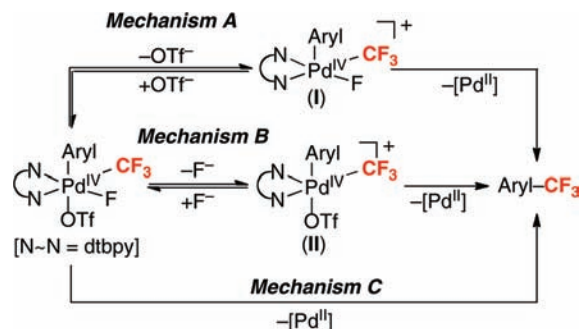
<sup>a</sup> Yields were determined by <sup>19</sup>F NMR spectroscopy and are an average of two runs.



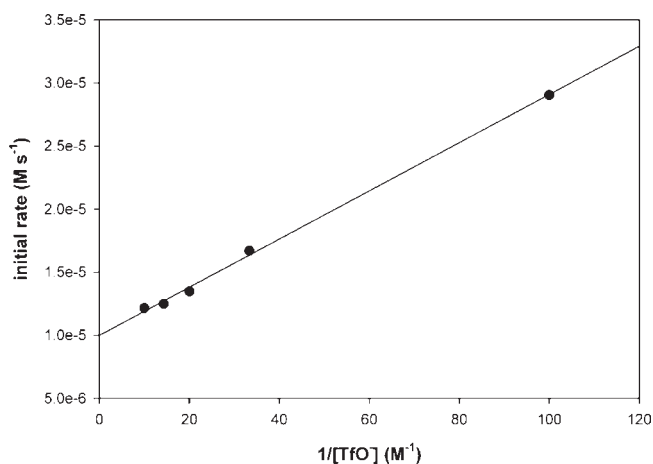
**Figure 2.** ORTEP drawing of complex 4. Thermal ellipsoids are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Pd–C(1) 2.009(5), Pd–C(25) 2.018(5), Pd–N(1) 2.038(4), Pd–N(15) 2.082(4), Pd–O(1) 2.226(3). Selected bond angles (deg): C(19)–Pd–C(25) 91.09(15), C(19)–Pd–N(15) 92.18(16), C(25)–Pd–N(15) 175.68(17), C(19)–Pd–F(1) 91.09(15), C(25)–Pd–F(1) 83.31(16), C(19)–Pd(1)–O(1) 175.74 (16), C(25)–Pd(1)–O(1) 95.15 (16).

Mechanism B involves fluoride dissociation, followed by Aryl–CF<sub>3</sub> coupling from intermediate II. Mechanism C proceeds via concerted C–CF<sub>3</sub> bond-forming reductive elimination. Notably, there is significant literature precedent for both ionic<sup>22e,32,33</sup> and concerted<sup>22e,34</sup> reductive elimination mechanisms from octahedral group 10 metal complexes.

**Order in Triflate.** The addition of 1 equiv of NBu<sub>4</sub>OTf to the thermolysis of 4 in NO<sub>2</sub>Ph-*d*<sub>5</sub> at 50 °C significantly slowed the initial rate of formation of 2a (from 2.21 × 10<sup>−5</sup> M s<sup>−1</sup> to 1.35 × 10<sup>−5</sup> M s<sup>−1</sup>).<sup>35</sup> Furthermore, an excellent linear fit was observed for a plot of initial rate versus 1/[NBu<sub>4</sub>OTf] (Figure 4).

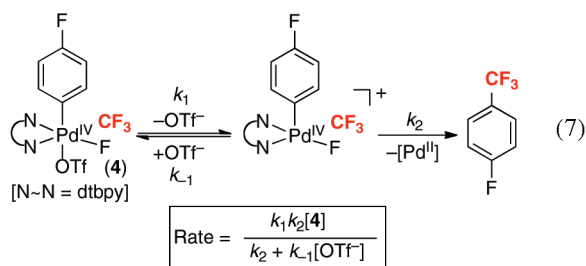


**Figure 3.** Three potential mechanisms for Aryl–CF<sub>3</sub> bond formation from 4.

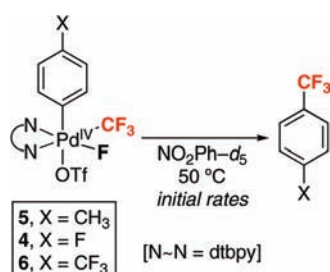


**Figure 4.** Plot of initial rate versus 1/[OTf] for reductive elimination from 4 to form 2a in PhNO<sub>2</sub>-*d*<sub>5</sub> at 50 °C.  $y = (1.91 \times 10^{-7})x + 9.98 \times 10^{-6}$ ;  $R^2 = 0.998$ .

To confirm that the presence of TfO<sup>−</sup> was responsible for the observed effect, this reaction was next examined in the presence of NBu<sub>4</sub>PF<sub>6</sub>, which contains a noncoordinating anion. The use of 1 equiv of NBu<sub>4</sub>PF<sub>6</sub> under otherwise identical conditions resulted in a >2-fold increase in the initial rate of reductive elimination to 5.57 × 10<sup>−5</sup> M s<sup>−1</sup>. This result indicates that inhibition by NBu<sub>4</sub>OTf is specifically due to the TfO<sup>−</sup> anion. Furthermore, it suggests that enhancing the polarity of the medium (by adding noncoordinating ions) accelerates Aryl–CF<sub>3</sub> reductive elimination. Both pieces of data are consistent with ionic mechanism A operating in this system, as reflected by the rate expression in eq 7 (derived using the steady state approximation).<sup>36</sup>



**Activation Parameters.** The initial rate of C–CF<sub>3</sub> bond-forming reductive elimination from 4 in NO<sub>2</sub>Ph-*d*<sub>5</sub> was next examined as a function of temperature. An Eyring plot of the data showed that  $\Delta H^\ddagger$  is +29.1 ± 0.2 kcal/mol, while  $\Delta S^\ddagger$  = +9.48 ± 0.8 eu.

**Table 4. Initial Rates of Aryl–CF<sub>3</sub> Bond-Forming Reductive Elimination from Complexes 4–6<sup>a</sup>**

entry	X	yield aryl–CF <sub>3</sub>	initial rate (M s <sup>-1</sup> ) × 10 <sup>5</sup>
1	CH <sub>3</sub>	93%	45.8
2	F	77%	2.21
3	CF <sub>3</sub>	65% <sup>b</sup>	1.43

<sup>a</sup>Reactions were run in duplicate and yields were determined by <sup>19</sup>F NMR spectroscopy. <sup>b</sup>1,4(bistrifluoromethyl)biphenyl formed in 21% yield.

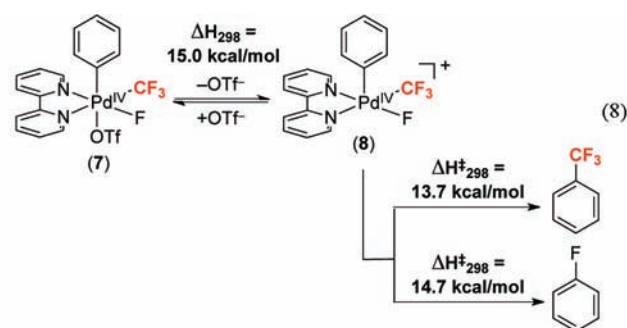
The observed entropy of activation indicates a significant increase in disorder in the transition state for this reductive elimination reaction. Similar values have been observed for carbon-heteroatom bond-forming reductive elimination reactions from Pd<sup>IV</sup> that proceed by ionic mechanisms.<sup>22e,23e,37</sup> For example, C–OAc reductive elimination from Pd<sup>IV</sup> complex (phpy)<sub>2</sub>Pd<sup>IV</sup>(OAc)<sub>2</sub> (phpy = 2-phenylpyridine), which is proposed to involve pre-equilibrium dissociation of an acetate ligand, showed ΔS<sup>‡</sup> of +4.2 ± 1.2 eu.<sup>22e</sup>

**Electronic Effects.** Finally, electronic effects on reductive elimination were evaluated using Pd<sup>IV</sup> complexes containing *p*-fluoro, *p*-methyl, and *p*-trifluoromethyl-substituted aryl groups (complexes 4–6). Thermolysis of 4, 5, and 6 at 80 °C in NO<sub>2</sub>Ph-*d*<sub>5</sub> for 3 h afforded the corresponding benzotrifluorides in 77, 93, and 65% yield, respectively (Table 4). The initial rates of reductive elimination from these complexes at 50 °C in NO<sub>2</sub>Ph-*d*<sub>5</sub> show that electron donating substituents accelerate the reaction. For example, with X = CH<sub>3</sub> (5), the initial rate is more than 20 times greater than with X = F (4). Additionally, when X = CF<sub>3</sub> (6), the initial rate is nearly two times slower than from 4 (Table 4).

While Table 4 clearly shows that electron-donating aryl substituents accelerate this reaction, it is challenging to definitively interpret this data in the context of the C–CF<sub>3</sub> bond-forming event. Mechanism A is a two-step process involving triflate dissociation followed by Aryl–CF<sub>3</sub> coupling. Thus, the faster rate with complex 5 may be due to the stronger *trans* effect of a more electron donating σ-aryl ligand and/or from a partial positive charge buildup on the aromatic ring in the transition state for Aryl–CF<sub>3</sub> coupling.

**DFT Calculations.** We next turned to DFT calculations to more fully explore the mechanism of Aryl–CF<sub>3</sub> bond formation. The complex [(bpy)Pd<sup>IV</sup>(Ph)(CF<sub>3</sub>)(F)(OTf)] (7) (bpy = 2,2'-bipyridyl, eq 8) was employed as a model for 5 (Table 4), and the CEP-31G(d)<sup>38,39</sup> basis set and M06<sup>40,41</sup> functional were used along with a single point solvent correction in nitrobenzene (SMD solvation model).<sup>42</sup> As shown in eq 8, the calculated ΔH<sub>298</sub> for loss of TfO<sup>-</sup> from 7 in nitrobenzene to form cationic intermediate [(bpy)Pd<sup>IV</sup>(Ph)(CF<sub>3</sub>)(F)]<sup>+</sup> (8) is 15.0 kcal/mol. Furthermore, the activation enthalpy (ΔH<sup>‡</sup><sub>298</sub>) for Ph–CF<sub>3</sub> bond-forming reductive elimination from 8 is 13.7 kcal/mol. Thus, we calculate that mechanism A has an overall ΔH<sup>‡</sup><sub>298</sub> of 28.7 kcal/mol, which is

in excellent agreement with the experimental value (+29.1 ± 0.2 kcal/mol, *vide supra*).



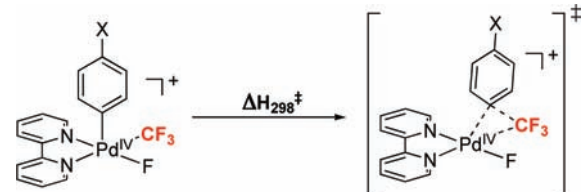
As discussed above, we observe experimentally that trifluoromethylated products are formed selectively over the corresponding fluorinated compounds. To gain further insights into this selectivity, we used DFT to examine the transition state for Ph–F bond-forming reductive elimination from intermediate 8. As shown in eq 8, ΔH<sup>‡</sup><sub>298</sub> (DFT) for Ph–F coupling is 14.7 kcal/mol. As such, this is a higher energy pathway than Ph–CF<sub>3</sub> bond-formation (ΔΔH<sup>‡</sup><sub>298</sub> (DFT) = 1 kcal/mol), consistent with the experimental results.

The calculated charge distribution of intermediate 8 using Natural Bond Order (NBO) analysis<sup>43,44</sup> indicates that the CF<sub>3</sub> carbon carries a significant positive charge (+1.18), while the α-carbon of the phenyl ligand bears a charge of +0.07.<sup>45</sup> This charge difference is amplified in the transition state for C–CF<sub>3</sub> bond-forming reductive elimination, where the CF<sub>3</sub> carbon carries an enhanced positive charge of +1.24, and the charge on the Ph carbon decreases to –0.11. These data imply that the Ph group is acting as the nucleophile during the bond-forming event. This is in sharp contrast to other reports of reductive elimination from Pd<sup>IV</sup> in which the aryl or alkyl ligand typically serves as the electrophilic coupling partner.<sup>22,23</sup>

We next used DFT to determine the transition state enthalpies (ΔH<sup>‡</sup><sub>298</sub>) for Aryl–CF<sub>3</sub> coupling from complexes of general structure [(bpy)Pd<sup>IV</sup>(*p*-XC<sub>6</sub>H<sub>4</sub>)(CF<sub>3</sub>)(F)]<sup>+</sup>. As expected based on the NBO analysis, ΔH<sup>‡</sup><sub>298</sub> was smallest with electron donating *para* substituents (X) on the aromatic ring, consistent with a transition state involving nucleophilic attack by the σ-aryl ligand on the CF<sub>3</sub> moiety (Table 5). Furthermore, the ΔH<sup>‡</sup><sub>298</sub> values showed better correlation with Hammett σ<sup>+</sup> values for X than the corresponding σ or σ<sup>-</sup> parameters. This implicates significant resonance effects in the transition state for Aryl–CF<sub>3</sub> coupling.<sup>46</sup>

Finally, we sought to identify supporting ligands that would lower the energy barrier for Ph–CF<sub>3</sub> bond-forming reductive elimination in this system. Literature studies have shown that (tmeda)Pd<sup>IV</sup>-(CH<sub>3</sub>)<sub>2</sub>(Ph)(I) (tmeda = *N,N,N',N'*-tetramethylethylenediamine) is significantly more reactive toward C–C bond-forming reductive elimination than its bipyridine analogue (bpy)Pd<sup>IV</sup>(CH<sub>3</sub>)<sub>2</sub>(Ph)-(I).<sup>47</sup> Thus, we hypothesized that using tmeda in place of dtbpy in our system might impart a similar effect. Consistent with this hypothesis, DFT calculations show that the nitrobenzene solvent-corrected transition state enthalpy (ΔH<sup>‡</sup><sub>298</sub>) for formation of trifluorotoluene from [(tmeda)Pd<sup>IV</sup>(Ph)(CF<sub>3</sub>)(F)]<sup>+</sup> is 0.8 kcal/mol lower than that for the analogous bpy complex (12.9 versus 13.7 kcal/mol) (eq 9). Furthermore, ΔH<sub>298</sub> for the loss of OTf<sup>-</sup> from [(tmeda)Pd<sup>IV</sup>(Ph)(CF<sub>3</sub>)(F)(OTf)] is >10 kcal/mol lower than that from 7 (4.2 versus 15 kcal/mol). Thus, the calculated

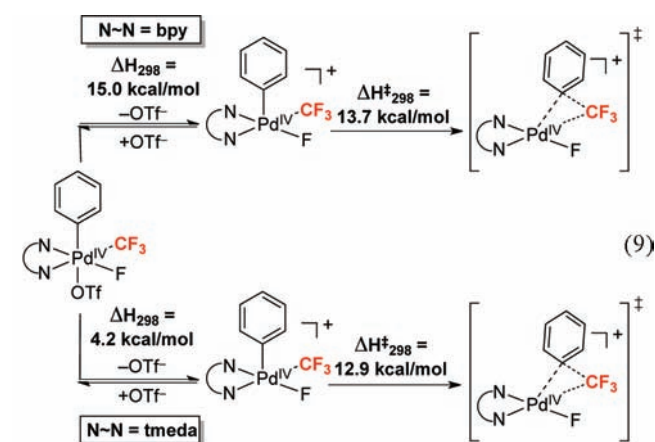
Table 5. Gas Phase Values of  $\Delta H_{298}^\ddagger$  for C–CF<sub>3</sub> Bond-Formation from  $[(\text{N}\sim\text{N})\text{Pd}^{\text{IV}}(\text{p}\text{-XC}_6\text{H}_4)(\text{CF}_3)(\text{F})]^{+\ddagger}$



X	$\Delta H_{298}^\ddagger$ (kcal/mol)	$\sigma^+$
NMe <sub>2</sub>	6.89	-1.70
NH <sub>2</sub>	7.10	-1.30
OH	7.71	-0.92
OMe	7.86	-0.78
SMe	7.79	-0.60
Me	9.19	-0.30
F	8.41	-0.07
H	9.41	0
CF <sub>3</sub>	9.43	0.53
CN	9.23	0.71
NO <sub>2</sub>	9.23	0.78

<sup>a</sup> Complexes are calculated using CEP-31G(d)/M06 level of theory.

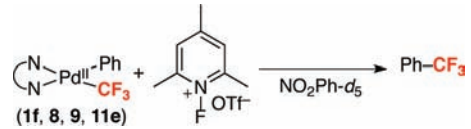
overall  $\Delta H_{298}^\ddagger$  for reductive elimination from the tmeda complex is 17.1 kcal/mol, suggesting that Aryl–CF<sub>3</sub> coupling should proceed at significantly lower temperatures than from 7.



**Room Temperature Arene Trifluoromethylation.** To assess the effect of diamine ligands experimentally, a series of (N~N)Pd<sup>II</sup>(Ph)(CF<sub>3</sub>) complexes (**9**, **10**, and **11e**) were prepared by the reaction of (N~N)Pd<sup>II</sup>(Ph)(I) with CsF followed by TMSCF<sub>3</sub> (see Supporting Information for full details).<sup>48</sup> Treatment of **9**, **10**, and **11e** with NFTPT under our standard conditions (80 °C for 3 h in NO<sub>2</sub>Ph) resulted in clean formation of trifluorotoluene in mode to excellent yield (Table 6). The readily available and inexpensive tmeda ligand was particularly effective. Tmeda complex **11e** afforded 90% yield of trifluorotoluene at 80 °C (entry 4), and, most remarkably, provided 83% yield at room temperature (entry 5). To our knowledge, this is first example of room temperature arene trifluoromethylation at a Pd center.<sup>49</sup>

The scope of room temperature oxidative trifluoromethylation from (tmeda)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) was found to be quite broad.<sup>50</sup> These reactions proceeded efficiently and in high yield with

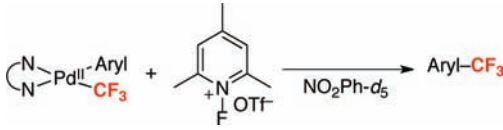
Table 6. NFTPT-Promoted Ph–CF<sub>3</sub> Coupling from Complexes **1f**, **9**, **10**, and **11e**<sup>a</sup>



entry	compound	N~N	temp	yield Ph–CF <sub>3</sub>
<b>1</b>	<b>1f</b>	dtbpy	80 °C	66%
<b>2</b>	<b>9</b>		80 °C	99%
<b>3</b>	<b>10</b>		80 °C	40%
<b>4</b>	<b>11e</b>		80 °C	90%
<b>5</b>	<b>11e</b>		23 °C	83%

<sup>a</sup> Reactions were run in duplicate and yields determined by <sup>19</sup>F NMR spectroscopy.

Table 7. Reactivity of (tmeda)Pd(Aryl)(CF<sub>3</sub>) Complexes<sup>a</sup>



entry	compound	aryl	yield aryl–CF <sub>3</sub> (80 °C)	yield aryl–CF <sub>3</sub> (23 °C)
<b>1</b>	<b>11a</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	81%	78%
<b>2</b>	<b>11b</b>	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	76% <sup>b</sup>	52% <sup>b</sup>
<b>3</b>	<b>11c</b>	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	60%	22%
<b>4</b>	<b>11d</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	92%	95%
<b>5</b>	<b>11e</b>	C <sub>6</sub> H <sub>5</sub>	94%	88%
<b>6</b>	<b>11f</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	90%	83%
<b>7</b>	<b>11g</b>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	95%	95%
<b>8</b>	<b>11h</b>	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	85%	88%
<b>9</b>	<b>11i</b>	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	90%	99%

<sup>a</sup> These reactions were conducted at 80 °C for 3 h and at 23 °C for 1 h. Reactions were run in duplicate and all of the starting material was consumed. Yields were determined by <sup>19</sup>F NMR spectroscopy. <sup>b</sup> At both temperatures, trifluorotoluene was formed in 13% yield.

electron donating and electron neutral substituents on the  $\sigma$ -aryl ligand (for example, Table 7, entries 4–7). The room temperature reactions were lower yielding with arenes bearing highly electron-withdrawing substituents like CF<sub>3</sub> and CN (entries 2 and 3), which is consistent with the proposed transition state (*vide supra*). Finally, tmeda complexes containing *ortho*-substituted aryl groups underwent high yielding room temperature oxidative trifluoromethylation (entries 8 and 9). In contrast, these were poorly effective substrates in the dtbpy system, even at 80 °C.<sup>30</sup>

## CONCLUSION

This article describes the rational design of first generation systems for oxidatively induced Aryl–CF<sub>3</sub> bond forming reductive

elimination from Pd. Experimental mechanistic studies implicate Aryl–CF<sub>3</sub> coupling from a cationic five-coordinate intermediate, and DFT suggests that the CF<sub>3</sub> ligand serves as the electrophilic partner during bond formation. Our investigations into the scope and mechanism of this reaction have facilitated the development of a second generation ligand system that enables Aryl–CF<sub>3</sub> coupling at room temperature. This work provides a basis for the design of novel Pd<sup>II/IV</sup>-catalyzed trifluoromethylation reactions of aryl metal species (metal = B, Sn, Si) or simple arene C–H bonds. Efforts in this area are currently underway in our group and will be reported in due course.

## ■ ASSOCIATED CONTENT

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

## ■ AUTHOR INFORMATION

### Corresponding Author

mssanfor@umich.edu

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(29) The yields in Tables 1 and 2 are ~10% lower than those reported in our original communication (ref 21), due to a minor error associated with the quantity of internal standard used for  $^{19}F$  NMR analysis. The correct yields for these transformations are reported in Table 3.

(30) (dtbpy)Pd<sup>II</sup>(Aryl)(CF<sub>3</sub>) complexes containing *ortho*-substituted aryl ligands reacted with NFTPT to provide very low yields of the corresponding benzotrifluorides. For example (dtbpy)Pd(*o*-CH<sub>3</sub>Ph)(CF<sub>3</sub>) afforded 13% yield of 2-methylbenzotrifluoride. Interestingly, the major product of this reaction was the corresponding fluorinated product (2-fluorotoluene, formed in 62% yield).

(31) In MeCN-*d*<sub>3</sub>, it is likely that the triflate ligand is replaced by a solvent molecule.

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(34) For examples of mechanisms similar to **C** for reductive elimination from Pd<sup>IV</sup> and Pt<sup>IV</sup>, see: (a) Crumpton, D. M.; Goldberg, K. I. *J. Am. Chem. Soc.* **2000**, *122*, 962–963. (b) Crumpton-Bregel, D. M.; Goldberg, K. I. *J. Am. Chem. Soc.* **2003**, *125*, 9442–9456. (c) Arthur, K. L.; Wang, Q. L.; Bregel, D. M.; Smythe, N. A.; O'Neill, B. A.; Goldberg, K. I.; Moloy, K. G. *Organometallics* **2005**, *24*, 4624–4628. (d) Reference 22e.

(35) We initially examined Aryl–CF<sub>3</sub> bond-forming reductive elimination by monitoring the disappearance of **4** and concomitant appearance of **2a** over three half-lives. These studies revealed that the rate of product formation decreases upon higher conversion to product (see Supporting Information for full details). We hypothesize that this is due to a build-up of TfO<sup>−</sup> as the reaction progresses, which then inhibits the first step of Aryl–CF<sub>3</sub> bond-forming reductive elimination from **4**. To avoid this apparent product inhibition, we used the initial rates method (measuring the first 10% conversion) for both the order and activation parameter studies.

(36) The addition of 1 equiv of NMe<sub>4</sub>F to **4** at 23 °C in NO<sub>2</sub>Ph-*d*<sub>3</sub> produced a complex mixture of Pd–F and Pd–CF<sub>3</sub> containing products (as determined by  $^{19}F$  NMR spectroscopy). As a result, it was not possible to definitively assess the effect of F<sup>−</sup> on the rate of reductive elimination from **4**.

(37) The entropy of activation for reductive elimination reactions from M<sup>IV</sup> can be highly dependent on both the structure of the M<sup>IV</sup> complex and the solvent. This is particularly the case in ionic reductive

elimination reactions, where solvent ordering around charged species can have a significant effect. See ref 32a.

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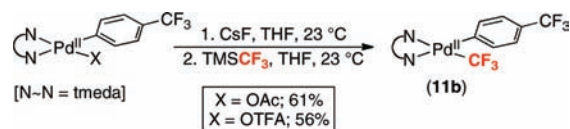
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(45) The ground state structure of the analogous CH<sub>3</sub> complex ((bpy)Pd<sup>IV</sup>(Ph)(CH<sub>3</sub>)(F))<sup>+</sup> has calculated charges of −0.58 and +0.06 on the CH<sub>3</sub> and Ph carbons, respectively.

(46) Assuming a similar entropy component in each transition state, a Hammett plot of log(*k*<sub>X</sub>/*k*<sub>H</sub>) versus  $\sigma^+$  with rate constants calculated based on the electronic energies ( $\Delta H_{298}^\ddagger$ ), provided a reasonably good linear correlation ( $\rho^+ = -0.79$ ;  $R^2 = 0.84$ , Figure S8). Much poorer correlations were observed with  $\sigma$  and  $\sigma^-$  ( $\rho$  value of −1.17 and  $R^2 = 0.57$ ;  $\rho^-$  value of −0.86 and  $R^2 = 0.52$ ).

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(48) Complex **11b** can also be prepared by reacting (tmeda)Pd<sup>II</sup>(*p*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>)(X) (X = acetate or trifluoroacetate) with CsF/TMSCF<sub>3</sub> in THF. This synthetic pathway is potentially useful and relevant for catalytic applications of these transformations. For example, C–H functionalization reactions often use Pd(OAc)<sub>2</sub> or Pd(TFA)<sub>2</sub> as catalysts. For examples, see: Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.



(49) Vicić has reported that the reaction of (NHC)Cu<sup>I</sup>(CF<sub>3</sub>) (NHC = N-heterocyclic carbene) with aryl iodides provides Aryl–CF<sub>3</sub> products at room temperature. The mechanism of the transformation is still under investigation. See refs 8g and 8h.

(50) For the synthesis of these complexes, see Supporting Information.