JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Reductive C(sp^2)−N Elimination from Isolated Pd(IV) Amido Aryl Complexes Prepared Using H_2O_2 as Oxidant

Elikplim Abada, Peter Y. Zavalij, and Andrei N. Vedernikov*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States

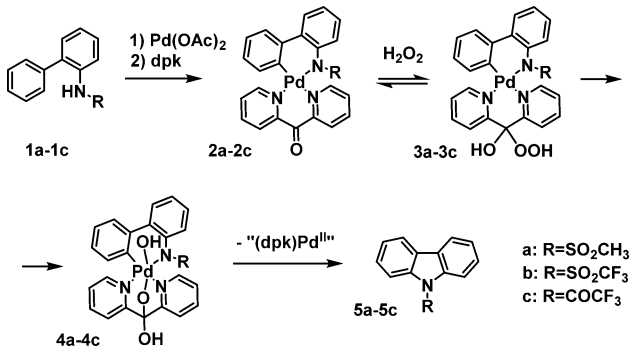
Supporting Information

ABSTRACT: Di-2-pyridyl ketone (dpk)-supported amidoarylpallada(II)cycles derived from various 2-(*N*-R-amino)biphenyls (R = H, Me, CF_3CO, $MeSO_2$, CF_3SO_2) react with hydrogen peroxide in MeOH, THF, MeCN or AcOH to form the corresponding C−N coupled products, *N*-R-substituted carbazoles, in 82−98% yield. For R = $MeSO_2$ and CF_3SO_2, the corresponding reaction intermediates, amidoaryl Pd(IV) complexes were isolated and characterized by single crystal X-ray diffraction and/or NMR spectroscopy. For the first time, the C(sp^2)−N reductive elimination from isolated amidoaryl Pd(IV) complexes has been studied in detail.

Carbon−nitrogen coupling is a key product-forming step in transition-metal-mediated syntheses of organic amines.[1] The most prominent example of this chemistry is the Buchwald−Hartwig amination of electrophilic arene derivatives catalyzed by Pd complexes.[1−3] Palladium-catalyzed oxidative C−H amination of arenes is an alternative approach to the synthesis of aromatic amines which, depending on the nature of the oxidant, can be quite atom-economical, as expected in the case of O_2 or H_2O_2 used as oxidants. In fact, the existing protocols of palladium-catalyzed oxidative C−H amination utilize a range of oxidants. In particular, oxidative C(sp^2)−H amination of 2-aminobiphenyls to form carbazoles was reported using as an oxidant O_2/$Cu(OAc)_2$,[4] PhI(OAc),[5] Oxone[6] or O_2 in a Cp*Ir(III)-photoredox system.[7] Oxidative CH amination of C(sp^2)−H or C(sp^3)−H bonds was also performed using such oxidants as $K_2S_2O_8$,[8] AgOAc,[9] $Ce(SO_4)_2$[10] or *N*-fluoro-2,4,6-trimethylpyridinium triflate.[10] Formation of high-valent Pd amido hydrocarbyl intermediates and their C−N reductive elimination were proposed as important steps in some of these reactions.[5,6] Recently, a selective C(sp^3)−N reductive elimination from an isolated aryl alkyl Pd(IV) complex was reported by Sanford;[11] no C(sp^2)−N elimination was detected. It was concluded that the C(sp^3)−N coupling reaction at the Pd(IV) center operates an S_N2-type mechanism and is reminiscent of C(sp^3)−N coupling of a series of amido methyl Pt(IV) complexes studied by Goldberg.[12] In turn, the formation of amido aryl Pd(IV) complexes and their C(sp^2)−N bond elimination were proposed by Gaunt[5] to occur in Pd-catalyzed oxidative C(sp^2)−H amidation but no Pd(IV) complexes have been observed in those experiments. In this Communication, we report the first isolable amido aryl Pd(IV) complexes **4a** and **4b** (Scheme 1, Figure 1b) that can undergo C(sp^2)−N reductive elimination to form the corresponding N-substituted carbazoles **5** and discuss some factors that affect the oxidative C(sp^2)−N coupling. These results improve our understanding of the key steps of the latter reaction involving high-valent Pd complexes, a synthetic method that has found important applications in modern organic synthesis.[5,6] Our results can also serve to improve our understanding of the reductive elimination reactivity of organotransition metal complexes, one of the fundamental organometallic reactions.[13] Notably, in this work the preparation of the amido aryl Pd(IV)complexes **4a** and **4b** could be achieved by oxidation with H_2O_2 of the corresponding Pd(II) precursors **2** (e.g., **2b** in Figure 1a or a MeOH adduct of **2c**, **2c(MeOH)** in Figure S73) in a range of solvents: MeOH, MeCN, AcOH and THF.

Previously, we reported oxidation with H_2O_2 in water[14,15] of a series of di(2-pyridyl)ketone (dpk)-supported cationic aryl Pd(II) complexes that could be cleanly converted to their

Scheme 1. Synthesis of Neutral Amido Aryl Palladium(IV) Complexes 4a−4c and Their C(sp^2)−N Reductive Elimination To Form Carbazoles 5a−5c



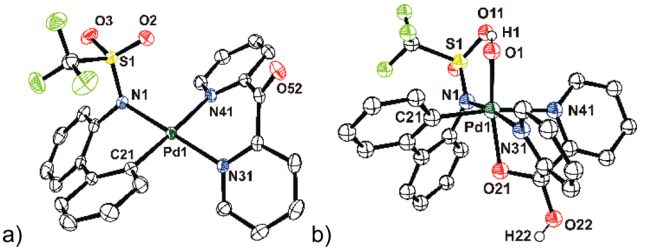


Figure 1. ORTEP plot (50% probability ellipsoids) for the amido aryl Pd(II) complex **2b** (a) and its Pd(IV) derivative **4b** (b). Hydrogen atoms except those of the OH groups are omitted for clarity.

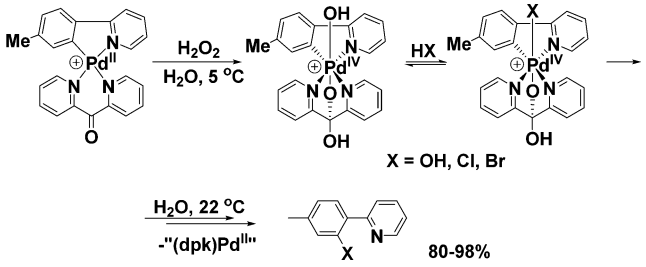
Received: December 8, 2016
Published: January 3, 2017

© 2017 American Chemical Society

DOI: 10.1021/jacs.6b12648
J. Am. Chem. Soc. 2017, 139, 643−646

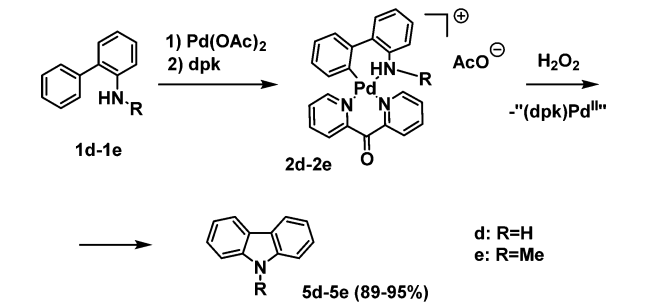
isolable Pd(IV) derivatives.[16] The latter could be involved in various reductive C(sp^2)–X elimination reactions (X = OH, Cl, Br; Scheme 2).

Scheme 2. Previous Preparation of Cationic Isolable Aryl Pd^{IV}(X) Complexes and Their C(sp^2)–X (X = OH, Cl, Br) Reductive Elimination Reactivity[14]



Our attempts to extend the scope of this reaction to oxidative C(sp^2)–N coupling and the preparation of amido aryl Pd(IV) complexes met initially with only partial success. Oxidation with H_2O_2 (3 equiv) of the cationic κ^2-C,*N*-aminoaryl complex **2d** and its *N*-methyl derivative **2e** (Scheme 3) in methanolic

Scheme 3. Oxidation of Ionic Amine Aryl Palladium(II) Complexes 2d and 2e to the Corresponding Carbazoles 5d and 5e



solutions at 22 °C produced rapidly the corresponding carbazoles **5** in high 89–95% yields. This result confirmed the synthetic utility of the dpk-enabled oxidative Pd(II)–C(sp^2) bond functionalization of amidoaryl Pd(II) complexes with H_2O_2 as oxidant. At the same time, no noticeable accumulation of the anticipated amido aryl Pd(IV) intermediates was observed when the reactions were monitored at 5–20 °C. Hence, our experiments with the substrates **2d** and **2e** furnished no direct evidence for the existence of the derived amidoaryl Pd(IV) intermediates, most likely because of the high reactivity of the anticipated Pd(IV) species.

The use of the electron-poorer, weakly basic neutral analogs of **2d** and **2e**, the κ^2-C,*N*-amidoaryl complexes **2a**–**2c** (Scheme 1) showed a much more promising but also a more complex behavior that depended on the identity of the complex and solvent used. In the case of the most reactive *N*-methanesylfonylamido Pd(II) derivative **2a**, its reaction with 3 equiv of H_2O_2 in either MeOH or AcOH solution was complete within a few hours at 22 °C to produce **5a** in 88–92% yield; the formation of two or three major intermediates, depending on the solvent, was evident. The oxidation of the electron-poorer *N*-trifluoromethanesylfonyl (**2b**) and *N*-trifluoroacetyl (**2c**) analogs to form the corresponding carbazoles **5** was only possible in AcOH solutions at elevated temperatures; two major intermediates were involved in each case. The reactions required 30 min at 60 °C for completion to produce **5b** and **5c** in 91–98% yield. When a different solvent, MeOH or MeCN, was used, **2c** reacted rapidly with H_2O_2 to form the hydroperoxoketal **3c** that decomposed cleanly back to **2c** after 24 h at 22 °C with apparent evolution of O_2; no carbazole **5c** was observed in these experiments. A low solubility of **2b** in MeOH precluded any ^{1}H NMR monitoring of this system.

Gratifyingly, the reactions of **2a** and **2b** with H_2O_2 could be directed toward selective formation of the respective hydroperoxoketals **3** or amidoaryl Pd(IV) intermediates **4** (Scheme 1) via a correct choice of solvents favoring their crystallization from reaction mixtures. The derived complexes **3** and **4** could be isolated and characterized as described below. The use of THF as a solvent in the reaction of **2a** and H_2O_2 led to a pure colorless crystalline hydroperoxoketal adduct **3a** (Scheme 1, Figure 2) resulting from H_2O_2 addition across the dpk C=O

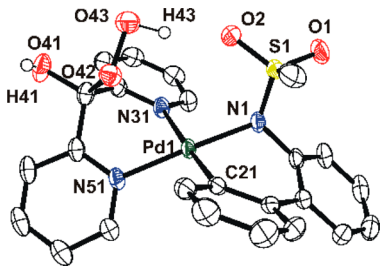


Figure 2. ORTEP plot (50% probability ellipsoids) for the Pd(II) hydroperoxoketal complex **3a**. Hydrogen atoms except those of the OH groups are omitted for clarity. Selected distances, Å: Pd1–O42, 1.888.

bond of **2a** which was characterized by ^{1}H NMR spectroscopy. In THF-d_8, solution **3a** exhibits two prominent singlets of the hydroperoxoketal OOH and OH groups at 11.91 and 8.31 ppm, respectively. Based on crystallographic characterization of **3a**, the oxidizing hydroperoxo group is in the "*endo*" position, close to the reducing Pd(II) center (Pd1–O42, 1.888 Å). In spite of the proximity of these two redox active fragments, the complex is slow to convert to its Pd(IV) isomer **4a** at 22 °C which contributed to the success of its selective crystallization from the reaction mixtures in THF. Interestingly, dissolution of **3a** in MeCN leads to its fast (<15 min) and quantitative (NMR) redox-transformation to the Pd(IV) amido aryl complex **4a** which could be crystallized out of the solution. Alternatively, **4a** could be crystallized from a reaction mixture of **2a** and 3 equiv of H_2O_2 in MeCN directly without isolation of the intermediate **3a**. The ^{1}H NMR spectra of **4a** dissolved in DMSO-d_6 feature two characteristic OH group signals, a sharp singlet of the hydrated dpk ligand at 8.22 ppm,[14] and a broad singlet at 3.74 ppm assigned to the Pd(IV)OH group. As expected, both signals disappear upon addition of two drops of D_2O to the solution.

The poor solubility of **4a** in MeCN contributed to the success of its isolation from this solvent but did not permit any quantitative analysis of the kinetics of its C–N reductive elimination to form carbazole **5a**. In contrast, the solubility of **4a** in MeOH is sufficiently high and the C–N reductive elimination of **4a** to produce the carbazole **5a** and a soluble (dpk)Pd(II) complex[17] (Scheme 1) is fast enough to allow the reaction monitoring by means of ^{1}H NMR spectroscopy.[17] The

DOI: 10.1021/jacs.6b12648
J. Am. Chem. Soc. 2017, 139, 643–646

reaction follows clean first-order kinetics with the half-life of 37 ± 1 min at 22 °C ($\Delta G^{\#}$ = 22.0 kcal/mol). Our DFT calculations predict a reasonably close Gibbs activation energy of 20.6 kcal/mol for this reaction in MeOH and point to the realization of a concerted C−N coupling mechanism directly from the 6-coordinate complex **4a**.[14,15,17]

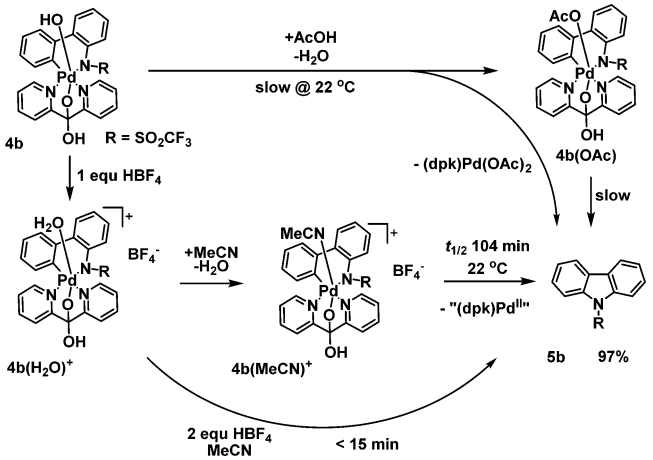
The successful isolation of the *N*-methanesulfonyl derivatives **3a** and **4a** fueled our additional efforts at exploring the reaction of H_2O_2 with an even less reactive *N*-trifluoromethanesulfonyl complex **2b**. The reaction run in MeCN as a solvent produced a poorly soluble colorless crystalline **3b** in high yield. The latter was characterized by ^{1}H NMR in DMSO-d_6 to reveal spectral parameters similar to those of **3a** and **3c**.[18] Remarkably, leaving a suspension of **3b** in MeCN for 3 to 4 days at 22 °C led to its almost complete (>95%) conversion to a poorly soluble orange crystalline amidoaryl Pd(IV) complex **4b** which could be isolated in 83% yield. The transformation of **3b** into **4b** could also be monitored in solutions of **3b** in DMSO-d_6 by means of ^{1}H NMR spectroscopy. This reaction follows clean first-order kinetics with a half-life of 50 ± 1 min at 22 °C ($\Delta G^{\#}$ = 22.2 kcal/mol). The new amidoaryl Pd(IV) complex **4b** was characterized by single crystal X-ray diffraction (Figure 1b) and ^{1}H NMR spectroscopy. Similar to **4a**, in DMSO-d_6 solutions **4b** exhibits characteristic peaks of the hydrated dpk ligand[14,15] and the Pd(IV)OH group at 8.33 and 3.71 ppm, respectively.

Notably, as compared to the methanesulfonyl analog **4a**, the trifluoromethanesulfonyl compound **4b** is much less reactive with respect to C−N reductive elimination. In particular, in MeOH solutions the corresponding carbazole **5b** formed only in 3.6% yield after 95 h at 22 °C. Based on the pK_a values of related NH acids, *N*-phenylmethanesulfonylamides,[20] the derived amido ligand present in complex **4a** is expected to be more nucleophilic than its fluorinated analog in **4b**. A similar trend, slower C(sp^2)−N reductive elimination from Pd(II) center of amido aryl Pd(II) complexes having electron-poorer amido ligands was recently explored by Buchwald.[19]

Notably, the C−N coupling of **4b** to produce **5b** and (dpk)Pd(OAc)$_2$ was found to be much faster in AcOH solutions. In this case, **5b** formed in 43% yield after 51 h at 22 °C along with 53% of another product which was isolated and identified, based on its ^{1}H NMR spectral pattern and C−N reductive elimination reactivity, as the Pd(IV) acetato complex **4b(OAc)** (Scheme 4, top).[17] The latter compound was also identified as one of the major intermediates previously observed in the reaction of **2b** and H_2O_2 in AcOH, besides **3b** and **4b**.[21]

The accelerating effect of AcOH on the rate of the C−N coupling of **4b** prompted us to probe the effect of stronger acid additives on this reaction. Addition of slightly less than 1 equiv of HBF_4 to a suspension of **4b** in MeCN produced purple solutions of the corresponding cationic MeCN derivative **4b(MeCN)**$^+$, as confirmed by ESI(+)/MS and ^{1}H NMR spectroscopy (Scheme 4). The resulting MeCN solutions react following a clean first-order kinetics to form the carbazole **5b** with half-life of 104 ± 1 min at 22 °C ($\Delta G^{\#}$ = 22.6 kcal/mol). The reaction of **4b(MeCN)**$^+$ isolated in the form of its BF_4^- salt is slightly faster in CH_2Cl_2 with the half-life of 87 ± 2 min at 22 °C ($\Delta G^{\#}$ = 22.5 kcal/mol). Our DFT calculations for the C−N reductive elimination from the ion pairs **4b(MeCN)**$^+$,**BF$_4^-$** predict the reaction Gibbs activation energy of 20.2 kcal/mol in gas phase and 25.2 kcal/mol in CH_2Cl_2.[17] As in the case of complex **4a**, the DFT suggests realization of a concerted C−N coupling from the 6-coordinate cation **4b(MeCN)**$^+$.

Scheme 4. Transformations of 4b and Formation of the Corresponding Carbazole 5b in the Presence of Acid Additives



To probe the reactivity in C−N coupling of **4b**-derived cationic aqua complex, **4b(H$_2$O)**$^+$, the latter was prepared by combining **4a** suspended in CH_2Cl_2 with slightly less than 1 equiv of HBF_4 (Scheme 4). The resulting purple solution was characterized by ESI(+)/MS and ^{1}H NMR spectroscopy. The solution exhibited reactivity that is very similar to that of the MeCN analog in CH_2Cl_2 to produce the carbazole **5b** following first-order kinetics with half-life of 119 ± 4 min at 22 °C ($\Delta G^{\#}$ = 22.7 kcal/mol; compare with the DFT-predicted 21.9 kcal/mol for the reaction involving ion pairs **4a(H$_2$O)**$^+$,**BF$_4^-$** in gas phase and 22.7 kcal/mol in CH_2Cl_2 solution).

Interestingly, the C−N coupling of **4b** can be made even faster when more than 1 equiv of HBF_4 is used. For example, with 3 equiv of HBF_4, the reaction was complete in 15 min at 22 °C in MeCN solution (97% yield of **5b**) but the system exhibited a much more complex kinetics behavior, possibly because of a parallel realization of several competing processes involving different multiply protonated Pd(IV) species.

The results of our studies of reactivity of Pd(II) amido aryl complexes **2a**−**2c** with H_2O_2 can be summarized as follows. In the multistep reaction sequence **2**−**3**−**4**−**5** (Scheme 1) the formation of hydroperoxoketals **3** is facile at 22 °C for all of the substrates and in all the solvents used in this work. The subsequent redox transformation of the hydroperoxoketals **3** to the Pd(IV) amido aryls **4** and the C−N coupling of **4** are both much slower, so that **3** and **4** can be observed in comparable amounts in the reaction mixtures. The Pd(II)-to-Pd(IV) oxidation step (**3**-to-**4**) is faster for the electron-richer *N*-methanesulfonylamido derivative **3a**, as compared to fluorinated compounds **3b** and **3c**; so is the C−N reductive elimination of complex **4a**, as compared to **4b**. Notably, the C−N coupling of **4b** can be accelerated dramatically in the presence of acid additives that produce electron-poorer and much more reactive cationic Pd(IV) species such as **4b(MeCN)**$^+$ and **4b(H$_2$O)**$^+$. Finally, the cationic Pd(II) amino aryl complexes **2d** and **2e** appear to be the most electron rich of all the series of complexes **2** and might also react via the intermediacy of the corresponding highly reactive Pd(IV) species that remained undetected under our reaction conditions.

DOI: 10.1021/jacs.6b12648
J. Am. Chem. Soc. 2017, 139, 643−646

Combined with the ability to generate Pd(IV) amido aryl complexes such as **4a** and **4b** using H_2O_2, these results may be useful for the development of new green protocols for catalytic oxidative C−H amination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12648.

Complete experimental and computational details (PDF)
Crystallographic information for **2b**, **3a**, **4b** and **2c**-(**MeOH**) (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

*avederni@umd.edu

ORCID

Andrei N. Vedernikov: 0000-0002-7371-793X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the U.S. National Science Foundation (CHE-1112019, CHE-1464772) and, in part, the U.S.−Israel Binational Science Foundation (grant 2010119).

■ REFERENCES

(1) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. *1*, pp 1051−1058.

(2) Hartwig, J. F. *Synlett* **2006**, *2006*, 1283−1294.

(3) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23−39.

(4) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561.

(5) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184−16186.

(6) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738−3741.

(7) Choi, S.; Chatterjee, T.; Choi, W. J.; You, Y.; Cho, E. J. *ACS Catal.* **2015**, *5*, 4796−4802.

(8) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049.

(9) Neumann, J. J.; Rakshit, S.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892−6895.

(10) Mei, T. S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806−10807.

(11) (a) Perez-Temprano, M. H.; Racowski, J. M.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 4097−4100. (b) Pendleton, I. M.; Perez-Temprano, M. H.; Sanford, M. S.; Zimmerman, P. M. *J. Am. Chem. Soc.* **2016**, *138*, 6049−6060.

(12) Pawlikowski, A. V.; Getty, A. D.; Goldberg, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 10382−10393.

(13) Hartwig, J. F. Reductive Elimination. In *The Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010; pp 321−348.

(14) Oloo, W. N.; Zavalij, P. Y.; Zhang, J.; Khaskin, E.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2010**, *132*, 14400−14402.

(15) Oloo, W. N.; Zavalij, P. Y.; Vedernikov, A. N. *Organometallics* **2013**, *32*, 5601−5614.

(16) See also a most recent paper presenting the use of H_2O_2 for Pd^{II}−C(sp^2) oxidative functionalization with proposed Pd^{IV} intermediacy: Behnia, A.; Boyle, P. D.; Blacquiere, J. M.; Puddephatt, R. J. *Organometallics* **2016**, *35*, 2645−2654.

(17) See Supporting Information for details.

(18) In particular, ^{1}H NMR spectra of **3b** in THF-d_8 show two singlets at 11.03 and 8.40 ppm integrating as 1H each assigned to the hydroperoxoketal OOH and OH groups, respectively. The correspondign signals observed for **3c** are at 14.12 and 8.76 ppm.

(19) Arrechea, P. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 12486−12493.

(20) The pK_a values for $PhNHSO_2CF_3$ and $PhNHSO_2Me$ determined in 2:1 DMF:H_2O mixture are 4.45 and 8.85, respectively: Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094−1098.

(21) Notably, oxidation with H_2O_2 in AcOH of the *N*-trifluoroacetyl analog **2c** produces two major intermediates that could be assigned, based on their ^{1}H NMR spectral patterns, as **4c** and **4c**(**OAc**), the analogs of the Pd(IV) hydroxo complex **4b** and the Pd(IV) acetoxo complex **4b**(**OAc**), respectively (Scheme 4, R = CF_3CO). See Supporting Information for details.

DOI: 10.1021/jacs.6b12648
J. Am. Chem. Soc. 2017, 139, 643−646