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Mechanistic Duality in Palladium-Catalyzed Cross-Coupling Reactions of Aryldimethylsilanolates. Intermediacy of an 8-Si-4 Arylpalladium(II) Silanolate

Scott E. Denmark* and Russell C. Smith

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received August 20, 2009; E-mail: sdenmark@illinois.edu

Palladium (and nickel)-catalyzed cross-coupling reactions have emerged as the premier methods for construction of carbon−carbon (and carbon−heteroatom) bonds between unsaturated organic moieties. The historical development, diversification, and applications of the myriad variants of this process are amply chronicled in recent monographs and authoritative volumes.[1] The generally accepted mechanism for these transition-metal-catalyzed cross-coupling reactions involves (1) oxidative addition to an electrophilic halide or pseudohalide, (2) transmetalation from an organometallic donor, and (3) reductive elimination to generate a new C−X bond. Although the oxidative addition of an organic halide to a Pd(0) complex is common among most coupling reactions, the transmetalation step is distinctive to the organometallic donor employed. The transmetalation of organostannanes has been extensively studied but is still a matter of some debate.[2] These transfers have been suggested to follow an intermolecular S_E2 mechanism by means of stereochemical models. Similarly, organosilane transmetalations can proceed via either a four-centered, closed transition structure (retentive) or an acyclic, open process (invertive).[3] Cross-coupling reactions of organoboranes are highly base dependent, and a pre-coordination of the transferring agent with the transition metal followed by delivery has been proposed for the transmetalation step.[4] Although kinetic studies have provided independent evidence for these pathways, the ability to isolate and characterize pre-transmetalation precursors is needed to unambiguously establish the course of palladium-catalyzed cross-coupling reactions.[5,6]

Recent kinetic investigations from these laboratories on the mechanism of palladium-catalyzed cross-coupling reactions with alkenyl(dimethyl)silanols[7] revealed that the transmetalation step is dependent on the reaction conditions. Cross-coupling of (*E*)-dimethyl(1-heptenyl)silanol under “classical activation” [8] by tetrabutylammonium fluoride proceeds via a pentacoordinate siliconate complex that engages in a bimolecular transmetalation with the organoPd(II)−X acceptor.[9a] However, in a second mechanistic study, the observation of saturation kinetics suggested that, upon silanol deprotonation, the resulting silanolate (**iia**) forms an adduct (**iiia**) with the organoPd(II)−X intermediate (**i**) from which (turnover-limiting) transmetalation occurs spontaneously (Figure 1.1).[9b] Because this latter conclusion violated the reigning dogma that transmetalation from silicon to palladium required an anionic siliconate species,[8] we sought to independently document this new pathway through the isolation and characterization of the palladium silanolate complex and establish the mechanistic relevance of this intermediate.

The unexpectedly facile transmetalation from the putative alkenyl(dimethyl)Si−O−Pd(aryl) species **iiia** precluded its isolation and demonstration of its kinetic behavior. However, we hypothesized that such an intermediate might be isolable by employing an *aryl*silanolate as the nucleophilic partner because cross-coupling reactions of these species require elevated temperatures and proceed via a slower transmetalation step.[10] Moreover, the use of strongly coordinating phosphine ligands might also stabilize the intermediate **iiib** and allow for its isolation. Fortunately, both of these requirements are met in a recent disclosure from these laboratories which reported the cross-coupling of arylsilanolates with aryl halides using bis(tri-*tert*-butyl)phosphine palladium(0).[11] The isolation of stable, T-shaped complexes of arylpalladium halides and alkoxides ligated with (t-Bu)$_3$P[12] suggested that the arylsilanolate complexes could also be sufficiently stable for isolation. We report herein the isolation and characterization of a stable (8-Si-4) complex containing a Pd−O−Si linkage that has allowed the identification of two distinct mechanistic pathways for the cross-coupling of arylsilanolates.

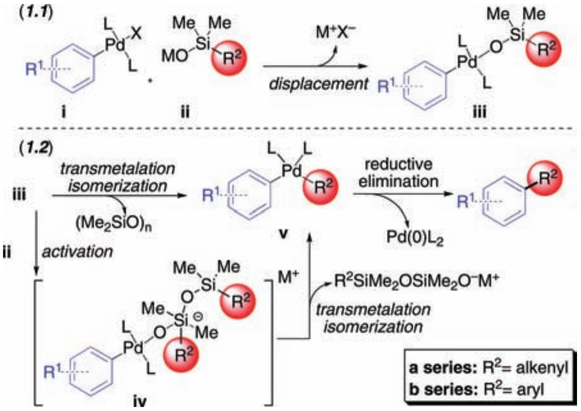
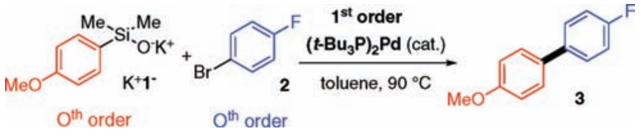


Figure 1. Mechanistic proposal for the coupling of alkenyl- and aryldimethylsilanolates.

First, to vouchsafe that the arylsilanolate cross-coupling was proceeding in a transmetalation-limiting regime, we determined the rate equation for the cross-coupling of potassium (4-methoxyphenyl)dimethyl silanolate ($K^+\mathbf{1}^-$) with 1-bromo-4-fluorobenzene (**2**) catalyzed by (t-Bu$_3$P)$_2$Pd. The partial order in each component in the reaction was determined individually at 95 °C in toluene (Scheme 1) using ^{19}F NMR analysis. Kinetic rates were determined from the slope of the plot of the loss of aryl bromide over time as determined through >3 half-lives.[13]

Scheme 1



The partial order in silanolate was obtained by comparison of the initial rates of consumption of aryl bromide versus 75, 150, and 300 mM concentrations of $K^+\mathbf{1}^-$. An overlay of the linear plots of the kinetic data clearly shows no effect on the concentration of $K^+\mathbf{1}^-$ and establishes zeroth-order behavior for this component. Next, the rate dependence on [**2**] was similarly established to be zeroth order using concentrations of 100, 200, and 400 mM for this component. Finally, the rate dependence on the amount of the palladium catalyst was determined by comparison of the rate constant (k_{obs}) versus 0.05, 0.10, 0.15, and 0.20 equiv of (t-Bu$_3$P)$_2$Pd at 100 mM in **2**. A positive slope of 0.979, obtained from a log plot of k_{obs} versus [Pd], is consistent with a first-order dependence of the

10.1021/ja907049y

observed rate constant on the concentration of palladium. Thus, the overall rate equation for the reaction of $\mathrm{K}^+\mathbf{1}^-$ with **2** catalyzed by $(t\text{-Bu}_3\mathrm{P})_2\mathrm{Pd}$ is shown in eq 1 (with a rate of 1.06×10^{-2} mM s^{-1}). This rate equation matches that of the alkenylsilanolates reported previously,[9b] and we thus conclude that here, as well, a turnover-limiting transmetalation from an arylpalladium(II) intermediate is taking place. However, this rate equation cannot differentiate between direct transmetalation via **iiib** or activated transmetalation via **ivb** (Figure 1.2).[14] Accordingly, if transmetalation is indeed the turnover-limiting step, then either arylpalladium(II) silanolate complex **iiib** or **ivb** should be detectable. However, ^{31}P NMR analysis of the reaction mixtures showed that the predominant phosphine-containing species was the PdL_2 catalyst (δ ^{31}P, 85.4 ppm).[15] A plausible explanation for this behavior is that the signal for the palladium silanolate complex is broadened at elevated temperatures and is not visible. Thus, to gain insight into the individual steps in the catalytic cycle, our attention shifted to investigating these events under stoichiometric conditions.

$$-\mathrm{d}[\mathbf{2}]/\mathrm{d}t = k_{\mathrm{obs}}[\mathrm{K}^+\mathbf{1}^-]^0[\mathbf{2}]^0 \qquad \text{with } k_{\mathrm{obs}} = k[\mathrm{Pd}]^{0.98} \tag{1}$$

The independent synthesis of the proposed intermediate **iiib** began with the preparation of the oxidative addition complex.[12a] Treating $(t\text{-Bu}_3\mathrm{P})_2\mathrm{Pd}$ with an excess of **2** resulted in the formation of the T-shaped, monomeric complex $(t\text{-Bu}_3\mathrm{P})(4\text{-FC}_6\mathrm{H}_4)\mathrm{PdBr}$ (**4**), which could be isolated and spectroscopically characterized. Next, the displacement step was simulated by adding an equimolar quantity of $\mathrm{K}^+\mathbf{1}^-$ to a solution of **4** in toluene. Inspection of both the ^{31}P and ^{19}F NMR spectra of the mixture revealed no observable changes of the diagnostic resonances. Even after 30 min, only a single species was present that appeared to be the starting complex **4**.[16] However, inspection of the ^{1}H NMR spectrum of this solution revealed that the chemical shift of the methyl groups on silicon had changed and that two new aryl proton signals appeared. This new species was spectroscopically identified as the proposed arylpalladium(II) silanolate complex **5**.

Ultimately, the structure of adduct **5** was confirmed by isolation and single-crystal X-ray analysis (Figure 2).[12c,17a] The Pd(1)−O(1) bond length (2.02 Å) is similar to those previously observed for palladium(II) silanolates.[18] Furthermore, the Si(1)−O(1) bond length is typical for silanolates, which suggests that the ligand effect at the palladium center is not as substantial as in other bisphosphine palladium(II) silanolate complexes.[17b] A weak agostic interaction between one of the H atoms of a *t*-Bu methyl group and the palladium is noted. In addition, the Pd(1)−O(1)−Si(1) angle of 128.5° is considerably more acute compared to those in other known palladium(II)[18] and platinum(II)[6] silanolates, and the nonbonded distance between the silicon-bearing ipso carbon and the palladium atom (3.70 Å) hints to a weak interaction that anticipates the transmetalation event.

With the desired palladium(II) silanolate complex in hand, we were poised to study the transmetalation process. Simply heating complex **5** (formed in situ) in toluene at 50 °C resulted in the formation of the biaryl product in 80−90% yields with concomitant formation of PdL_2 (Scheme 2).[19,20] The thermal transmetalation process followed a first-order decay with $k_{\mathrm{obs}} = 5.0 \times 10^{-4}$ s^{-1}. Because the starting palladium catalyst has a 2:1 ligand/palladium ratio, the stoichiometric transmetalation was performed in the presence of $t\text{-Bu}_3\mathrm{P}$ to establish if a partial order in ligand could be detected as well. Heating a solution of complex **5** in the presence of 1.0 and 5.0 equiv of $t\text{-Bu}_3\mathrm{P}$ led to clean reactions with rate constants of 4.7×10^{-4} and 4.9×10^{-4} s^{-1}, respectively. The similar rate constants for the thermal reaction at varying concentrations of free phosphine clearly indicate a zeroth-order concentration dependence for the ligand. These data suggest that phosphine dissociation *is not required* for transmetalation and that the arene simply transfers to the open coordination site on palladium directly. These experiments provide further evidence of an *unactivated, thermal transmetalation pathway* for silicon-based cross-coupling reactions.

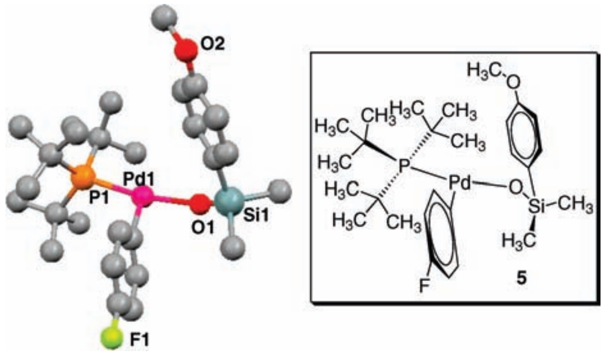
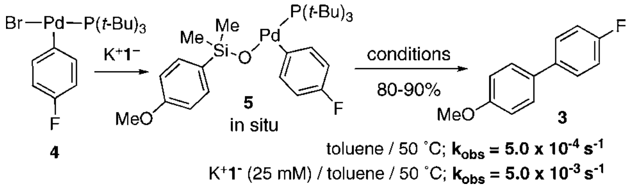


Figure 2. X-ray crystal structure of complex **5**. Hydrogens are removed for clarity.

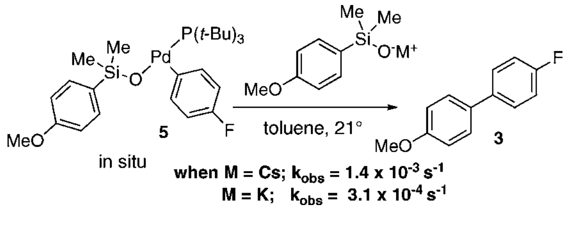
Scheme 2



For the kinetic studies described above, the palladium(II) silanolate complex was generated in situ for ease of manipulation. However, in a few instances the rapid formation of biaryl products was observed at room temperature. To elucidate the origin of these anomalously fast reactions, complex **5** was treated with $\mathrm{K}^+\mathbf{1}^-$ (1.0 equiv), and **3** was formed in excellent yield (>90%) at room temperature! Because the catalytic reaction is necessarily performed with a large excess of silanolate with respect to palladium, a kinetic study was undertaken to compare the rates of transmetalation of these different processes. Therefore, treating **5** with 1.0 equiv of $\mathrm{K}^+\mathbf{1}^-$ at 50 °C afforded the biaryl product with $k_{\mathrm{obs}} = 5.0 \times 10^{-3}$ s^{-1}. *This observed rate constant corresponds to a 10-fold increase compared to the thermal process established above. These data suggest that an activation-type pathway via a 10-Si-5 complex may also be operative.*

If, in fact, the silanolate is opening a pathway for activated transmetalation, then modulating the nucleophilicity of the arylsilanolate should manifest in an observable change in rate. Thus, when the cesium salt of **1** was employed in combination with **5** at 50 °C, *product formation was so fast that the rate could not be measured.* To compare the rates of transmetalation using different silanolates, the reaction was instead performed at room temperature (21 °C). Scheme 3 clearly shows that $\mathrm{Cs}^+\mathbf{1}^-$ leads to a more rapid consumption of **5** to afford the unsymmetrical biaryl product. In fact, the rate constant for the $\mathrm{Cs}^+\mathbf{1}^-$-induced reaction was 4.5 times larger than that for $\mathrm{K}^+\mathbf{1}^-$. These data suggest that the increased nucleophilicity of the arylsilanolate plays a role in the formation of the 10-Si-5 siliconate intermediate. Furthermore, the kinetic dependence on $[\mathrm{Cs}^+\mathbf{1}^-]$ at 6.6, 12.5, and 25 mM was determined by comparing the rate constants for the reaction in Scheme 3. A log plot of k_{obs} versus

Scheme 3



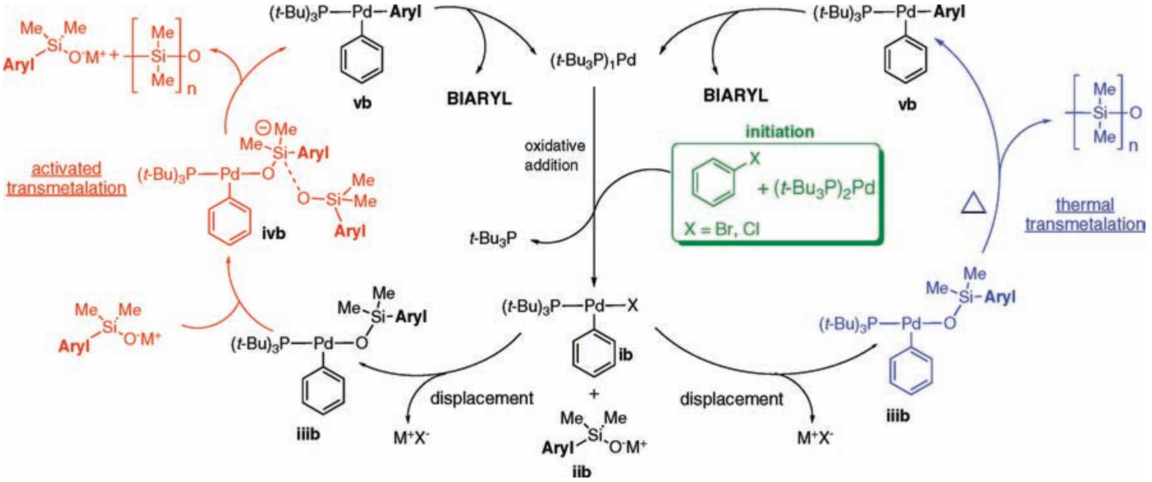


Figure 3. Mechanism for the cross-coupling of arylsilanolates.

concentration clearly shows a first-order dependence and provides additional support for the activated pathway.[21] Once the palladium(II) silanolate is formed from a fast displacement step, a second molecule of $Cs^+\mathbf{1}^-$ is required to activate the silicon atom toward transmetalation.

By combining the results from both the kinetic studies and the stoichiometric experiments, a detailed mechanism for the cross-coupling of arylsilanolates can be formulated that illustrates how both thermal and anionic pathways can operate simultaneously (Figure 3). To initiate the cycle (green), oxidative addition occurs directly from $(t\text{-}Bu_3P)_2Pd$ to generate the monomeric T-shaped complex, **ib**.[22] Rapid displacement of the halide occurs in which the key Pd−O−Si moiety is forged with loss of the M^+X^- salt. Now poised for transmetalation, **iiib** can proceed down two independent pathways that involve either (1) a thermal *intramolecular* transmetalation (8-Si-4, depicted in blue) or (2) an anionically activated pathway involving the formation of a hypervalent siliconate (**ivb**, 10-Si-5, depicted in red). Because under catalytic conditions an excess of silanolate is employed, we conclude that the cross-coupling likely proceeds via the activation pathway.

In conclusion, the mechanistic landscape of the cross-coupling of arylsilanolates with aryl halides has been refined. The isolation and characterization of a palladium silanolate complex allowed for the discovery of both thermal and anionic mechanistic pathways for transmetalation from silicon to palladium. The ability to isolate palladium silanolate intermediates will enable further studies on the molecular details of the transmetalation event.

Acknowledgment. We are grateful to the National Institutes of Health (GM-63167) for financial support and to Johnson Matthey and Strem for gifts of palladium catalysts. Early contributions by Dr. Steven Tymonko are gratefully acknowledged. J. F. Hartwig and B. P. Carrow are thanked for valuable suggestions. R.C.S. thanks the Aldrich Chemical Co. for a Graduate Student Innovation Award and Amgen for a Graduate Fellowship.

Supporting Information Available: Full experimental procedures, kinetic analysis, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) All kinetic data and plots are available as Supporting Information.

(14) (a) The inability to distinguish the pathways results from the likely saturation of either of these intermediates under catalytic conditions. (b) This rate equation is also consistent with turnover-limiting reductive elimination. However, reductive elimination is known to be extremely rapid with palladium; thus, transmetalation remains the only viable turnover-limiting step: Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941.

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(16) Further support for a fast and irreversible displacement was achieved using a systematic titration study. The results of this study are discussed in the Supporting Information.

(17) (a) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 744109. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033 or via www.ccdc.cam.ac.uk/conts/retrieving.html or. (b) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 645666. This palladium(II) silanolate complex and its reactivity will be reported in due course.

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(20) Reactions were performed at a lower temperature than for the catalytic reactions to obtain a reliably measurable rate.

(21) The zeroth-order dependence of the rate on $K^+\mathbf{1}^-$ under catalytic conditions and the increase in rate of the stoichiometric reaction in the presence of $K^+\mathbf{1}^-$ are consistent with the conclusion that anionically activated transmetalation (via **ivb**) is operative. Importantly, this observation is also consistent with the saturation of **ivb** under catalytic conditions. The first-order dependence of k_{obs} on the concentration of $Cs^+\mathbf{1}^-$ shows that saturation has not been reached at 25 mM in $Cs^+\mathbf{1}^-$. We were unable to identify the saturation point because of the solubility of the silanolate salts.

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JA907049Y