Cross-Coupling Reactions of Alkenylsilanolates. Investigation of the Mechanism and Identification of Key Intermediates through Kinetic Analysis

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Abstract: The mechanism of the fluoride-free, palladium-catalyzed cross-coupling reaction of potassium (*E*)-heptenyldimethylsilanolate, K$^+$(*E*)-**1**$^-$, with 2-iodothiophene has been investigated through kinetic analysis. The order of each component was determined by plotting the initial rates of the reaction against concentration. These data provided a mechanistic picture which involves a fast and irreversible oxidative insertion of palladium into the aryl iodide and a subsequent intramolecular transmetalation step from a complex containing a silicon−oxygen−palladium linkage. First-order behavior at low concentrations of silanolate with excess palladium(0) complex supports the formation of this complex as the turnover-limiting step. The change to zeroth-order dependence on silanolate at high concentrations is consistent with the intramolecular transmetalation becoming the turnover-limiting step.

Introduction

In the preceding paper in this issue, the mechanism of the fluoride-promoted organosilanol cross-coupling reaction[1] was investigated. Derivation of the rate equation combined with spectroscopic studies facilitated the formulation of a mechanistic scheme for the tetrabutylammonium fluoride (TBAF)-promoted organosilicon cross-coupling reaction. Although the basic features of this mechanism are confluent with the current understanding of other cross-coupling processes, the unique role of fluoride in activating the critical transmetalation step provided unexpected dimension. In view of the insights obtained through this study, a similar investigation into the more recently developed fluoride-free variant of this reaction was initiated.

The cross-coupling reaction of organosilicon compounds requires an activating agent that is almost universally a fluoride ion source. Despite the preparative advantages of fluoride activation (rate, generality, stereoselectivity), the cost and corrosiveness of fluoride sources as well as their incompatibility with common protective groups limit the widespread application of this method. These drawbacks provided the impetus behind a recently developed modification that employs in situ generated silanolates that can undergo mild, efficient, and high-yielding cross-coupling reactions with a variety of aryl iodides.[2] Such silanolates can be generated by deprotonation of a silanol with either potassium hydride, sodium hydride, or even with a commercially available inexpensive silanolate, potassium tri-methylsilanolate (TMSOK). Although this method is highly efficient, the mode by which activation of the silicon occurs in this cross-coupling system is not clear. Unlike the TBAF-promoted reaction, the conditions used here are anhydrous, and the reaction exhibits a significant rate dependence on solvent and counterion.[2] In addition, steric and electronic influences at the silicon atom exhibit more pronounced rate effects in this silanolate method than in the TBAF-promoted reaction.[3] Considering these factors, there is little basis to presume that similar mechanisms are operative for these two systems. Therefore, to elucidate the mechanism of the silanolate cross-coupling process, a kinetic analysis of the reaction was undertaken to derive the rate equation and identify the turnover-limiting step.

Background

The success of organosilicon cross-coupling reactions, as witnessed by the number of reports recently published on this topic, relies, in good measure, on the ability of soluble fluoride sources to serve as effective promoters.[4] In contrast to tin and other more electropositive elements, silicon (in its tetracoordinate state) does not undergo facile transmetalation with palladium(0).[4a] However, the high affinity of fluoride for silicon (bond dissociation energy 159 kcal/mol[5]) is believed to enhance the polarization of Si−C bonds to facilitate the transmetalation. Since the first reported use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) as a promoter,[6] other fluoride sources have been used in several systems that employ aryl- and alkenylsilyl fluorides, silyl ethers, silanols, silyl hydrides,

(1) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865 (preceding paper in this issue).
(2) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439.

(3) Denmark, S. E.; Neuville, L.; Christy, M. E. L. Unpublished results from these laboratories.
(4) (a) Hiyama T. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 10. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (c) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (d) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (e) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36* (3), 75.
(5) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246.
(6) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 920.

and disiloxanes (Figure 1).[4] The need for nucleophilic fluoride activation spurred the development of new fluoride sources as alternatives to the widely employed, yet expensive and hygroscopic TBAF. Deshong, for example, developed tetrabutylammonium difluorotriphenylsilicate (TBAT) as an air-stable nucleophilic fluoride source.[7]
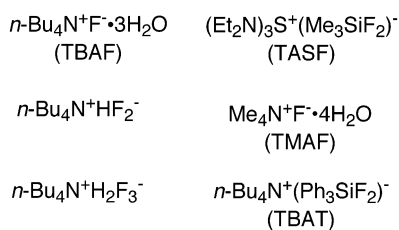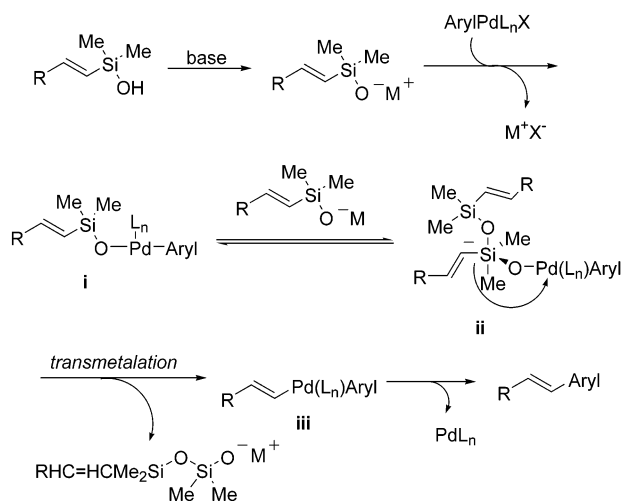
$$n\text{-Bu}_4\text{N}^+\text{F}^-\cdot 3\text{H}_2\text{O} \qquad (\text{Et}_2\text{N})_3\text{S}^+(\text{Me}_3\text{SiF}_2)^-$$
$$(\text{TBAF}) \qquad\qquad (\text{TASF})$$

$$n\text{-Bu}_4\text{N}^+\text{HF}_2^- \qquad \text{Me}_4\text{N}^+\text{F}^-\cdot 4\text{H}_2\text{O}$$
$$(\text{TMAF})$$

$$n\text{-Bu}_4\text{N}^+\text{H}_2\text{F}_3^- \qquad n\text{-Bu}_4\text{N}^+(\text{Ph}_3\text{SiF}_2)^-$$
$$(\text{TBAT})$$

Figure 1. Commonly used nucleophilic fluoride sources for organosilicon cross-coupling reactions.

Unfortunately, despite the wide spectrum of organosilicon nucleophiles, palladium sources, ligands, and electrophiles, the range of promoters for this reaction has been surprisingly narrow. With few exceptions, all of the promoters employed are simply different fluoride sources.[8] An alternative activator developed by Mori[9] is a stoichiometric amount of silver(I) oxide, which is proposed to promote the cross-coupling by ionization of the palladium halide and generation of a pentacoordinate siliconate species. In developments from these laboratories, the conjugate bases of alkenylsilanols[2] and arylsilanols[10] (silanolates) were shown to be effective cross-coupling partners. We hypothesized that the silanol moiety served not only as a director for the coupling, but also as the activator as well (Scheme 1). This is reflected in the proposed mechanism whereby one silanolate unit is believed to displace the halide on palladium in the aryl−PdL$_n$−X species to form complex **i**. A second molecule of silanolate is then proposed to function as a nucleophilic activator, generating a pentacoordinate siliconate, **ii**, which is then capable of transmetalation. The interesting

Scheme 1

feature of this proposal is the ability of the silanolate to render the key transmetalation step *intra*molecular by directly bonding to the palladium through a Si−O−Pd linkage.

Under the reaction conditions, it is not unlikely that a complex such as **i** could be formed. Indeed, several transition-metal−silanolate complexes are known and can be synthesized by halide displacement on the palladium by an alkaline silanolate.[11] In addition, palladium−oxygen−boron linkages have also been proposed as intermediates in Suzuki coupling reactions (Figure 2).[12] Also noteworthy is the enhanced rate of alkenylborane coupling reactions when an alkoxypalladium species is employed in place of the corresponding halopalladium complex (Figure 2).[13]
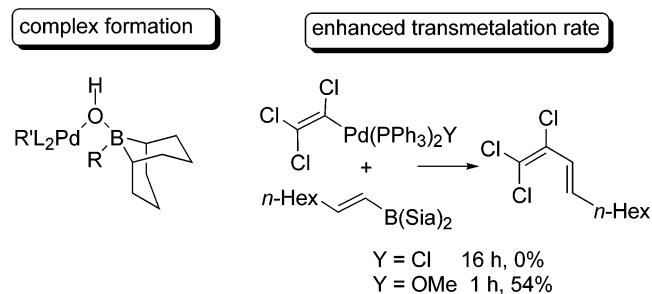
Figure 2. Proposed role of oxygen in palladium-catalyzed cross-coupling reactions.

The objectives of the study described below are to identify the intermediates in the silanolate cross-coupling reaction and to formulate a mechanistic picture of this fluoride-free process. The rate equation for this cross-coupling reaction can be derived by determining the order of each component of the reaction shown in Scheme 2. The order in silanolate should provide the most useful information. Even though several possibilities exist for the turnover-limiting step (TLS), most can be differentiated by determining the silanolate order as outlined in Table 1 following the mechanistic proposal in Scheme 2.

If a first-order rate dependence on silanolate concentration is observed, then formation of either complex **i** or complex **ii** could be turnover-limiting. The latter would imply that the palladium catalyst is saturated in the form of **i** (under catalytic conditions). Otherwise, second-order rate dependence on silanolate concentration would be observed. If transmetalation from either **i** or **ii** is turnover-limiting, then a zeroth-order rate dependence on silanolate concentration would be expected since such an event would be an intramolecular process. However, if there is a preequilibrium in the formation of **ii**, then this preequilibrium would be manifest in a first-order rate dependence on silanolate concentration for a turnover-limiting transmetalation from **ii**.

Two other possibilities must be considered: (1) turnover-limiting oxidative insertion of palladium into the aryl iodide or (2) turnover-limiting reductive elimination in the product-

(7) (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166. (b) Handy, C. J.; Lam, Y.-F.; DeShong, P. *J. Org. Chem.* **2000**, *65*, 3542.

(8) Hiyama has also reported the use of 6 equiv of NaOH to activate chlorosilanes in cross-coupling reactions: (a) Hagiwara, E.; Gouda, K.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439. Tetrabutylammonium hydroxide has also served as an effective promoter for certain silane couplings: (b) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221.

(9) (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342.

(10) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357.

(11) Formation of siloxoplatinum complexes through similar pathways has been reported: (a) Mintcheva, N.; Nishihara, Y.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *629*, 61. For a review on siloxy-transition-metal complexes, see: (b) Marciniec, B.; Maciejewski, H. *Coord. Chem. Rev.* **2001**, *223*, 301.

(12) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

(13) Miyaura. N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.
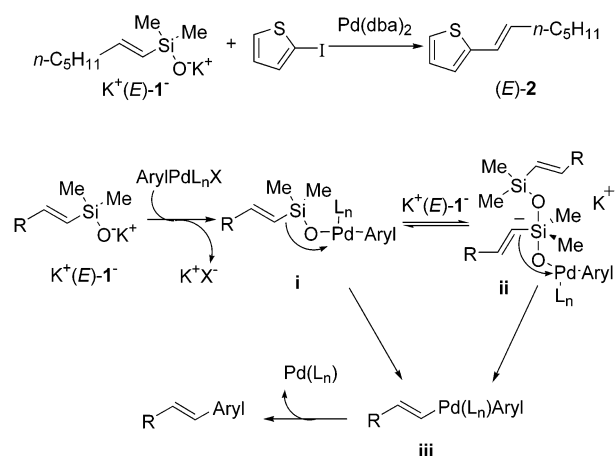
Scheme 2

Table 1. Correlation of Possible Turnover-Limiting Steps of Silanolate Cross-Coupling Reaction with the Expected Order in Silanolate (See Scheme 2)

scenario	turnover-limiting step	kinetic consequence
1	formation of **i**	first-order in silanolate
2	transmetalation from **i**	zeroth-order in silanolate
3	formation of **ii**	first-order in silanolate with Pd/R$_3$SiOK ratio <1 (palladium saturated in form of **i**)
		second-order in silanolate with Pd/R$_3$SiOK ratio >1 (palladium is saturated as aryl−PdL$_n$−X)
4	transmetalation from **ii**	zeroth-order in silanolate if palladium is saturated as **ii**
		first-order if palladium is saturated as **i** (preequilibrium exists for association)

forming step. However, in prior studies of palladium-catalyzed cross-coupling reactions, it has been observed that, under the conditions of the catalytic cross-coupling reaction, oxidative insertion into aryl iodides and reductive elimination from a dialkylpalladium(II) are fast and irreversible.[14,15] Thus, it is highly unlikely that these steps are turnover-limiting here either.[16]

Because there is more than one mechanistic interpretation for both first- and zeroth-order in silanolate, the dependence was determined both with a catalytic amount of palladium and with palladium in excess of silanolate. The objective of this latter experiment was to ensure that palladium could not be saturated in the form of **i**. This would clarify interpretation of a process proceeding through **ii**. The kinetic results from both experiments, combined with the order obtained for the iodide and palladium, should eliminate a number of hypotheses and simplify this picture significantly.

Results

The order of each component in the reaction of potassium (*E*)-1-heptenyldimethylsilanol (K$^+$(*E*)-**1**$^-$) with 2-iodothiophene, catalyzed by bis(dibenzylideneacetone)palladium(0) (Pd(dba)$_2$),

(14) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(15) (a) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. (b) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10488.
(16) At this point, we cannot rigorously rule out the possibility that transmetalation does not involve the formation of a diorganopalladium(II) species as is assumed for cross-coupling in general. If so, a different late-appearing step that depends on silanolate may be turnover-limiting.

was determined by varying the concentration of each reactant individually and monitoring the progress of the reaction at room temperature. Silanolate K$^+$(*E*)-**1**$^-$ was prepared from the corresponding silanol (*E*)-**1** and potassium hydride in DME. The salt was stored as a solution in DME under argon, and the concentration of silanolate in this solution was checked by determining the amount of silanol formed (by GC analysis relative to that of biphenyl as an internal standard) upon exposure of a known volume of this solution to acetic acid.[17] The initial time (*t*$_o$) of each kinetic run corresponded to the addition of the catalyst to the mixture.

Throughout the course of the reaction, aliquots were removed and quenched by injection into a 20% aqueous solution of 2-diethylaminoethanethiol. This reagent was shown to instantaneously quench the reaction by sequestering the palladium catalyst. The samples were then filtered through a small prepacked pipet of silica gel which was then eluted with diethyl ether, and the eluent was then analyzed by gas chromatography.[18] The chromatograms were analyzed for the formation of the product as a function of time. The progress of the reaction was determined by integrating the product peak relative to that of an internal standard, biphenyl, after correction for their predetermined relative response factors. 2-Iodothiophene was chosen as the electrophile because its lower rate of reaction allowed for a convenient manual kinetic analysis. Employing this set of coupling substrates enabled a larger number of data points to be taken at the onset of the reaction so that accurate initial-rate fits could be obtained.

First, the order in 2-iodothiophene was determined by plotting the initial rate versus concentration (Figure 3). A slope of −0.07 clearly reveals no effect on the rate of reaction by varying the aryl iodide concentration from 25 to 100 mM, and therefore establishes zeroth-order behavior in this system.
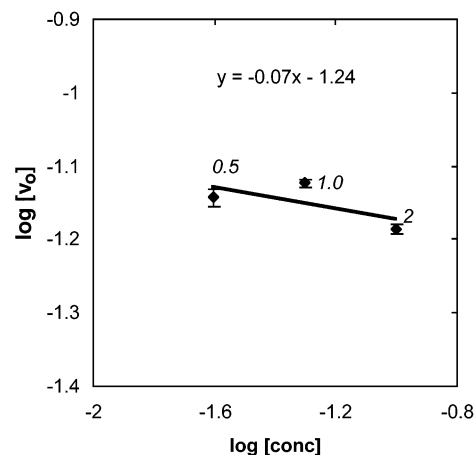

Figure 3. Log plot of the initial-rate dependence on the concentration of 2-iodothiophene.

As mentioned above, the order of K$^+$(*E*)-**1**$^-$ was determined under two separate conditions. In the first analysis with a catalytic amount of palladium (0.05 equiv with respect to iodide), the dependence of rate on the amount of the silanolate

(17) (a) Disiloxane was not formed under these conditions. If this were not the case, calculation of the silanolate concentration would be determined from the amounts of both silanol and disiloxane formed. (b) This check was necessary due to the slow deterioration of silanolate in the stock solution over several weeks.
(18) Details of the procedure and analysis are provided in the Supporting Information.

showed two distinct regimes. Below 1.0 equiv (relative to iodide), a slope of 0.94 (based on four data points at 0.5, 0.625, 0.75, and 1.00 equiv of silanolate) is consistent with first-order behavior (Figure 4). Beyond 1.0 equiv, however, no further increase in rate is observed as the slope for 1.00, 1.50, 2.00, and 3.00 equiv of silanolate is only 0.08.
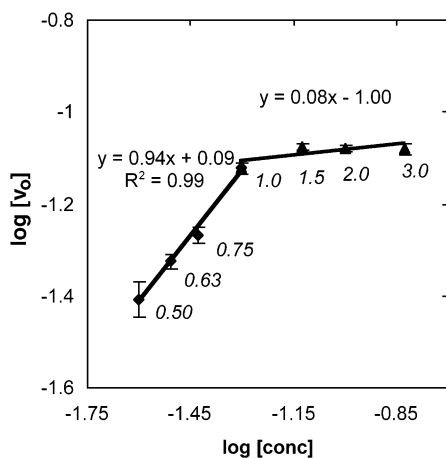

Figure 4. Log plot of the initial-rate dependence on the concentration of $K^+(E)$-**1**$^-$ with 0.05 equiv of Pd(dba)$_2$.

A similar study that employed exactly 1.00 equiv of Pd(dba)$_2$ relative to the aryl iodide, with silanolate loadings from 0.5 to 1.25 equiv was then undertaken. This series was intended to evaluate the rate dependence of concentration under conditions where $K^+(E)$-**1**$^-$/Pd < 1 so that the mechanistic possibilities could be further clarified. A slope of 0.93 was obtained, reflecting once again first-order behavior (Figure 5). This outcome, combined with the data in Figure 4, indicates that, below a $K^+(E)$-**1**$^-$/Pd ratio of 20/1 (i.e., (a) below 1.00 equiv of the silanolate with 0.05 equiv of Pd(dba)$_2$, Figure 4, or (b) all data points taken with 1 equiv of Pd(dba)$_2$, Figure 5), first-order behavior is consistently observed. At ratios greater than 20/1, Figure 4 indicates that a switch to zeroth order is observed.
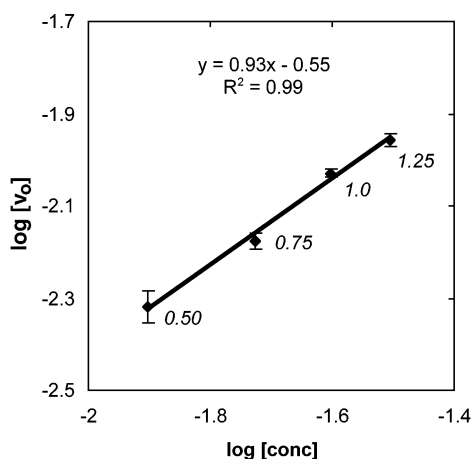

Figure 5. Log plot of the initial-rate dependence on the concentration of $K^+(E)$-**1**$^-$ with 1.00 equiv of Pd(dba)$_2$.

Next, with the overall order in reactants obtained, the rate-constant dependence on catalyst loading was determined by plotting the calculated first-order rate constant versus the concentration of Pd(dba)$_2$ (Figure 6).[19] A slope of 1.07 was obtained for palladium loadings of 5, 10, and 20 mol %, which

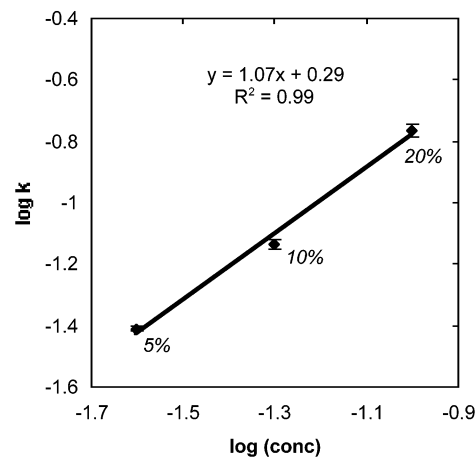is consistent was a first-order dependence of the observed rate constant on the concentration of palladium.

Figure 6. Log plot of the first-order rate constant dependence on the concentration of Pd(dba)$_2$.

Finally, because potassium iodide is a byproduct of the cross-coupling reaction, it was important to determine if the addition of KI (or a soluble iodide source, n-Bu$_4$N$^+$I$^-$) affected the rate of the reaction. With 1.00 equiv of either salt, no change in rate was noted (Figure 7). The implications of these results for the existence of certain intermediates are discussed below.
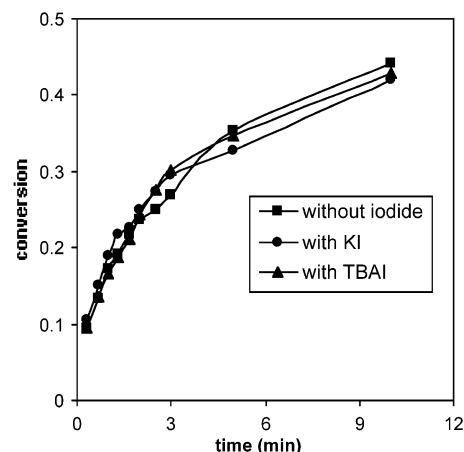

Figure 7. Kinetic plot of conversion vs time with and without added iodide sources.

Discussion

One of the primary objectives of this kinetic study was to investigate the intermediacy of a species containing a silicon−oxygen−palladium linkage. This complex, which brings together the nucleophile, electrophile, and palladium moiety in a single unit, constitutes the basis of the mechanism proposed in Scheme 1. All the kinetic data collected and described above were evaluated in the context of this objective. The correlation of kinetic results with hypothetical scenarios (see Table 1) provided a framework to distinguish among limiting possibilities. To assist the analysis, the following outline provides the interpretation of the reaction order in each component and how every subsequent experiment further reduced the number of consistent mechanistic scenarios.

(19) The first-order rate constant was obtained by fitting to the slope of a plot of log[conversion] against time.

Scheme 3

(a) transmetalation from i - TLS
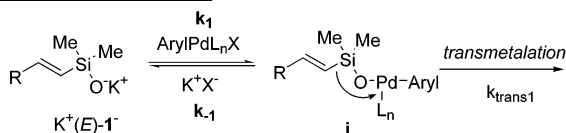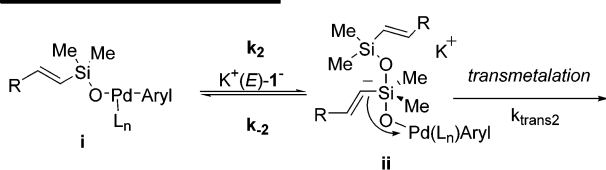
• with pre-equilibrium: rate = $k_{trans}[\mathbf{i}]$

$$[\mathbf{i}] = \frac{[K^+(E)\text{-}\mathbf{1}^-][ArylPdX]k_1}{[K^+X^-]k_{-1}} = \frac{[K^+(E)\text{-}\mathbf{1}^-]}{[K^+X^-]}k_{obs}$$

1st order in $K^+(E)$-$\mathbf{1}^-$

• Pd saturated as **i** (no pre-equilibrium)

rate = $k_{trans1}[\mathbf{i}] = k_{obs}$

0th order in $K^+(E)$-$\mathbf{1}^-$

(b) transmetalation from ii - TLS

• with pre-equilibrium: rate = $k_{trans2}[\mathbf{ii}]$

$$[\mathbf{ii}] = \frac{[K^+(E)\text{-}\mathbf{1}^-][\mathbf{i}]k_{-2}}{k_{-1}} = [K^+(E)\text{-}\mathbf{1}^-]k_{obs}$$

1st order in $K^+(E)$-$\mathbf{1}^-$

• Pd saturated as **ii** (no pre-equilibrium)

rate = $k_{trans1}[\mathbf{ii}] = k_{obs}$

0th order in $K^+(E)$-$\mathbf{1}^-$

The zeroth-order rate dependence on 2-iodothiophene and the first-order dependence of the rate constant on the palladium concentration were quite straightforward to interpret. As in the kinetic analysis in the previous paper in this issue and similar studies on the organotin cross-coupling reaction,[14] these data are consistent with a fast and irreversible oxidative insertion of the palladium catalyst into the aryl–iodide bond. Thus, the oxidative addition step is not interpreted to be the turnover-limiting step (TLS) of this reaction.

The kinetic data from varying the silanolate concentration proved most informative in the elucidation of the mechanism (Figure 4). The results show two regions with distinct slopes that can be interpreted either as a change in mechanism or as a switch in the turnover-limiting step of the same mechanism. In the region below 1.00 equiv of the silanolate (with respect to the aryl iodide) the reaction showed first-order behavior in $K^+(E)$-$\mathbf{1}^-$, which can be interpreted as either turnover-limiting formation of **i** or **ii** or transmetalation from **ii** following a preequilibrium formation. In the region above 1.00 equiv of the silanolate, the slope changes to 0.08, implying a zeroth-order dependence at higher concentrations (Figure 4). This behavior suggests a rate-determining *intra*molecular transmetalation from either **i** or **ii** (with a saturated preequilibrium). The zeroth-order behavior arises because the concentration of palladium catalyst (0.05 equiv) is constant throughout the course of the reaction. Therefore, a turnover-limiting intramolecular process involving this catalyst should exhibit a rate behavior independent of the silanolate concentration.

Scheme 4

(a) formation of i - TLS ($K^+(E)$-$\mathbf{1}^-$ / Pd < 20/1)
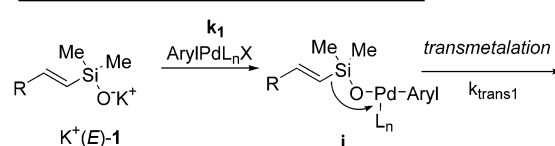
rate = $[K^+(E)\text{-}\mathbf{1}^-][ArylPdL_nX]k_1 = [K^+\text{-}(E)\text{-}\mathbf{1}]k_{obs}$

1st order in $K^+(E)$-$\mathbf{1}^-$

(b) formation of ii - TLS ($K^+(E)$-$\mathbf{1}$ / Pd < 20/1)
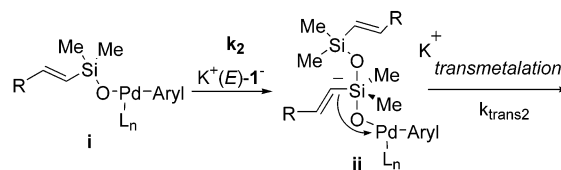
rate = $[K^+(E)\text{-}\mathbf{1}^-][\mathbf{i}]k_2 = [K^+(E)\text{-}\mathbf{1}^-]k_{obs}$

1st order in $K^+(E)$-$\mathbf{1}^-$

at $K^+(E)$-$\mathbf{1}^-$ / Pd > 20/1), transmetalation (without pre-equilbrium) becomes TLS - see Scheme 3

Consideration of both regimes then allows for the formulation of two possibilities. The first possibility proposes a preequilibrium formation of **i** or **ii** followed by a turnover-limiting transmetalation from either species. This equilibrium becomes saturated above a certain $K^+(E)$-$\mathbf{1}^-$/Pd ratio, giving rise to the observed change to zeroth-order dependence (Scheme 3). In the second possibility, complex *formation* (of either **i** or **ii**), rather than transmetalation (from either **i** or **ii**), is turnover-limiting below a certain $K^+(E)$-$\mathbf{1}^-$/Pd ratio (Scheme 4). Above this value, the turnover-limiting step shifts from formation to transmetalation consistent with the change to zeroth-order dependence on the silanolate concentration.

The analysis of order in silanolate with a stoichiometric amount of palladium (Figure 5) allowed for the elimination of one of the possible mechanistic scenarios (Table 1). A first-order dependence of reaction rate on silanolate concentration was observed. This behavior rules out the possibility that activated complex **ii** is involved. Most of the data in this experiment were acquired at concentrations of palladium that were higher than that of $K^+(E)$-$\mathbf{1}^-$ to ensure that the palladium catalyst was not saturated as the silanolate complex **i**. The consequence of increasing the silanolate concentration, therefore, should reveal a second-order rate dependence on silanolate concentration if intermediate **ii** exists. In contrast, when a catalytic amount of palladium was employed in the previous study, first-order rate dependence on the silanolate concentration would not rule out the intermediacy of **ii** because palladium could have been saturated as complex **i**. Hence, the hypothetical pathway involving a subsequent activation to **ii** would have still exhibited first-order, and not second-order, dependence on silanolate. Thus, the combined results from these two experiments support the involvement of only complex **i** in this cross-coupling.

By ruling out the intermediacy of complex **ii**, the landscape of possible mechanistic pathways shown in Schemes 3 and 4 has been greatly simplified. However, there still remained two possibilities for the rate-determining step in the pathway involving complex **i**. In the first case, complex **i** is formed in a reversible preequilibrium (which becomes saturated at high $K^+(E)$-**1**$^-$/Pd ratios) followed by the turnover-limiting transmetalation, Scheme 3a. In the second case, *formation* of **i** is turnover-limiting (Scheme 4a), but above a certain $K^+(E)$-**1**$^-$/Pd ratio, a switch in the rate-determining step to transmetalation occurs. These possibilities could be distinguished by the effect (or lack thereof) of the iodide sources on the reaction rate.[20] The absence of any effect on rate by adding KI or n-Bu$_4$N$^+$I$^-$ refutes the existence of a preequilibrium and supports the conclusion that a change in the rate-determining step from formation to breakdown of **i** is responsible for the change from first- to zeroth-order behavior with increasing concentrations of the silanolate.

Thus, the derived rate equation and its overall interpretation can be summarized as follows (Scheme 5):[21]

$$\text{rate} = k_{\text{obs}}[\text{R}_3\text{SiOK}]^n \tag{1}$$

$$k_{\text{obs}} = k[\text{Pd}]$$

$$n = 1 \text{ when } \text{R}_3\text{SiOK}/\text{Pd} < 20/1$$

$$n = 0 \text{ when } \text{R}_3\text{SiOK}/\text{Pd} > 20/1$$

(1) Support is provided for the existence of an intermediate containing a silicon−oxygen−palladium bond through zeroth-order dependence on silanolate at high concentrations.

(2) The participation of an activated complex, **ii,** is excluded as a result of the first-order dependence on silanolate when R$_3$SiOK/Pd < 1.

(3) The absence of an iodide effect on rate as well as the insolubility of KI disproves a reversible formation of **i**.

(4) Rate-determining formation of **i** at $K^+(E)$-**1**$^-$/Pd < 20, and a rate-determining intramolecular transmetalation from **i** at $K^+(E)$-**1**$^-$/Pd > 20, is supported.

Scheme 5
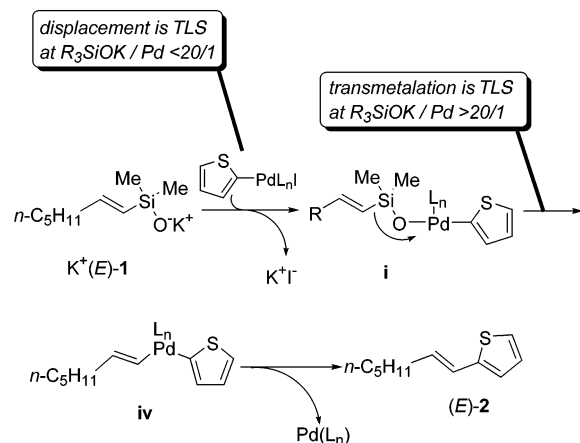
These conclusions were indeed surprising and clearly contradict the reigning view of why activators are needed for

silicon-based cross-coupling reactions. It was not expected that an alkenyl group bonded to silicon could migrate to an arylpalladium unit without prior activation as a pentacoordinate siliconate. The use of nucleophilic activators in all known organosilicon cross-coupling systems is predicated on the assumption that such activation is required for transmetalation.[4] From all empirical experimentation as well as the kinetic analysis provided in the preceding paper in this issue, the intermediacy of pentacoordinate siliconates in cross-coupling reactions is dogma. Indeed, the demonstration that isolable preformed siliconates undergo cross-coupling whereas neutral tetracoordinate silanes do not further supports this assertion.[22,23]

The demonstration that transmetalation can take place from intermediate **i** illustrates the importance of the silicon−oxygen−palladium linkage because it allows an otherwise unfavorable transformation to occur. Moreover, the formation of **i** distinguishes this mechanism from that involving fluoride activation in which an *intermolecular* transmetalation from a fluoride-complexed disiloxane was found to be turnover-limiting. It is remarkable that two entirely different mechanisms can be operative for both fluoride and fluoride-free silanolate couplings, and that both are highly efficient room temperature reactions.

Conclusions

The mechanism of the non-fluoride-activated, palladium-catalyzed coupling between $K^+(E)$-**1**$^-$ and 2-iodothiophene has been examined through kinetic analysis. By independently obtaining the order of the aryl iodide, the catalyst, and the silanolate, the overall rate equation has been composed. Analysis of the implications of this equation allowed for a clear mechanistic picture to evolve which invokes the formation of a complex, **i** (Scheme 5), containing a silicon−oxygen−palladium bond. Furthermore, a change in the turnover-limiting step from formation of **i** to transmetalation from **i** has been identified that is dependent on the amounts of silanolate $K^+(E)$-**1**$^-$ and the palladium catalyst.

Despite the strength of the conclusions drawn from the kinetic studies, many important questions remain unanswered. In particular, the detailed molecular process by which transmetalation proceeds in this and the TBAF-promoted cross-coupling reactions needs to be clarified. The ultimate goal of our study is a comprehensive mechanistic scheme encompassing all transformations associated with each step in the catalytic cycle of palladium (i.e., both before and after the turnover-limiting step). Future studies involving the isolation of reactive intermediates will be conducted pursuant to this goal. In addition, the implications of this study (both in the identity of reactive intermediates and in the results of further kinetic analysis) for the mechanism of organoboron and organostannane cross-coupling reactions are considerable. Studies to identify differences and similarities in the mode of transmetalation among

(20) The lack of solubility of KI in this reaction mixture suggested that formation of **i** cannot be reversible.

(21) For completeness, Arrhenius activation parameters were calculated by studying the reaction over a 40 °C temperature range. $E_a = 9.52$ kcal/mol, $A = 13.55$ mol^{-1} s^{-1}, $\Delta H = 8.94$ kcal/mol, $\Delta S = -6.12$ eu, and $\Delta G = 10.74$ kcal/mol.

(22) (a) Hosomi, A.; Kohra, S.; Tominaga, Y. *Chem. Pharm. Bull. Jpn.* **1988**, *36*, 4622. (b) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542. (c) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266.

(23) The kinetic equation cannot rigorously exclude the possibility that silanolate activation is necessary for the breakdown of an intermediate after the turnover-limiting step. This would be a kinetically silent event and becomes reasonable if the mechanism of transmetalation is different from the current view.

these efficient and versatile cross-coupling methods are under way.

Supporting Information Available: Procedures for the kinetic analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0372356