Mechanism of the Stille Reaction. 1. The Transmetalation Step.

Coupling of R¹I and R²SnBu₃ Catalyzed by trans-[PdR¹IL₂] (R¹ = C₆Cl₂F₃; R² = Vinyl, 4-Methoxyphenyl; L = AsPh₃)

Arturo L. Casado and Pablo Espinet*
Contribution from the Departamento de Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, E-47005 Valladolid, Spain
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Abstract: The so far accepted mechanism of the Stille reaction (palladium-catalyzed cross-coupling of organotin reagents with organic electrophiles) is criticized. Based on kinetic studies on catalytic reactions, and on reactions with isolated intermediates, a corrected mechanism is proposed. The couplings between R¹I (R¹ = C₆Cl₂F₃ = 3,5-dichlorotrifluorophenyl) and R²SnBu₃ (R² = CH=CH₂, 2a; C₆H₄-4-OCH₃, 2b), catalyzed by trans-[PdR¹II(AsPh₃)₂] (3a), give R¹−R² and obey a first-order law, r = a[3a][2a]/(b + [AsPh₃]), with a = (2.31 ± 0.09) × 10⁻⁵ s⁻¹ and b = (6.9 ± 0.3) × 10⁻⁴ mol L⁻¹, for [I] = [2a] = 0−0.2 mol L⁻¹, [3a] = 0−0.02 mol L⁻¹, and [AsPh₃] = 0−0.07 mol L⁻¹, at 322.6 K in THF. The only organopalladium(II) intermediate detected under catalytic conditions is 3a. The apparent activation parameters found for the coupling of I with 2a support an associative transmetalation step (ΔH°obs = 50 ± 2 kJ mol⁻¹, ΔS°obs = −155 ± 7 J K⁻¹ mol⁻¹ in THF; and ΔH°obs = 70.0 ± 1.7 kJ mol⁻¹, ΔS°obs = −104 ± 6 J K⁻¹ mol⁻¹ in chlorobenzene, with [I]₀ = [2a] = 0.2 mol L⁻¹, [3a] = 0.01 mol L⁻¹). The reactions of 2a with isolated trans-[PdR¹X(AsPh₃)₂] (X = halide) show rates Cl > Br > I. From these observations, the following mechanism is proposed: Oxidative addition of R¹X to Pd₃ gives cis-[PdR¹X₂L₂], which isomerizes rapidly to trans-[PdR¹X₂L₂]. This trans complex reacts with the organotin compound following a Se²(2cyclic) mechanism, with release of AsPh₃ (which explains the retarding effect of the addition of L), to give a bridged intermediate [PdR¹L(μ-X)(μ-R²)SnBu₃]. In other words, an L-for-R² substitution on the palladium leads R² and R¹ to mutually cis positions. From there the elimination of XSnBu₃ yields a three-coordinate species cis-[PdR¹R²L], which readily gives the coupling product R¹−R².

Introduction

The palladium-catalyzed cross-coupling of organotin reagents with organic electrophiles (Stille reaction) has become an attractive method in modern organic synthesis, mainly due to the advantages of using trialkylorganotin species. They are readily available and quite air and moisture stable and tolerate many functional groups. The broadly accepted mechanism is the catalytic cycle in Scheme 1, both the oxidative addition and the reductive elimination steps are supposed to be fast, compared to the Sn/Pd transmetalation, which is the rate-determining step. This proposal fits the observations that the reaction rate is zeroth order in electrophile (the oxidative addition must be fast) and first order in stannane.

Scheme 1

We have proved recently that the oxidative addition of R¹I to PdL₂ is not as simple as it appears in Scheme 1. It gives first cis-[PdR¹IL₂] (I), which then isomerizes to trans-[PdR¹IL₂] (II) in a reaction autocatalyzed by both isomers (Scheme 2).

Scheme 2

* R¹ = C₆Cl₂F₃, L = PPh₃.


Also, the transmetalation step (framed in Scheme 1) is still not well understood. Although there is no evidence, it is generally thought to preserve the trans configuration of complex II,48 which is the more coordinatively unsaturated species and will be fast. In addition, the rate-determining step likely is the dissociation of L,49,50 which occurs not only in cis-R2L2 complexes but also in trans-R2L2. Since the dissociation of L is rate-determining, it is often assumed to give a trans-[PdR2L2] complex. Thus, the mechanism in Scheme 3, involving a dissociative X-for-R2 substitution (X = L, Br) with preservation of the stereochemistry at the Pd, has been proposed for vinyl- and arylstannanes. It is assumed that this mechanism cannot undergo transmetalation, probably because it is too electron rich, and a ligand dissociation occurs previous to the transmetalation; it is the more coordinatively unsaturated complex. This proposal is qualitatively consistent with the observations: the existence of a (fast) preequilibrium explains the first-order dependence on the stannane. However, attempts at gaining insight into the transmetalation step have shown that the addition of neutral ligand L retards the coupling.10,11,14 This has been taken as an indication that L dissociation from II is a key step in the transmetalation. Thus, the mechanism in Scheme 3, involving a dissociative X-for-R2 substitution (X = L, Br) with preservation of the stereochemistry at the Pd, has been proposed for vinyl- and arylstannanes. It is assumed that this mechanism cannot undergo transmetalation, probably because it is too electron rich, and a ligand dissociation occurs previous to the transmetalation; it is the more coordinatively unsaturated species (most likely having a coordinated solvent molecule, S) that is involved in the electrophilic substitution at tin. This proposal is qualitatively consistent with the observations: the existence of a (fast) preequilibrium explains the retarding effect of L, whereas the (slow) transmetalation on C explains the first-order dependence on the stannane. However, it is stated in the literature10 that the equilibrium constant for the dissociation of II in Scheme 3 (for R1 = C6H5, L = AsPh3, THF at 323 K) is Kdiss = (k′/k−1) = 8.6 × 10−4 mol L−1. From this we calculate 40% dissociation in the experimental conditions,12 a value impossible to accept.13 Thus this mechanism is inconsistent with the quantitative results. Alternatively, if the L dependence was attributed to the dissociation step in Scheme 3 being slow and rate determining, one would expect the process to be independent of the concentration and nature of the stannane, against what is observed.

Thus, the two plausible mechanisms initiated by a dissociation of L (whether fast or slow) are inconsistent with the data in the literature and must be discarded.

Other obscure points reveal that further studies are needed. In effect, it is not clear that the trans-to-cis isomerizations in [PdR2L2] complexes are fast. On the contrary, the theoretical paper usually cited to support this assumption states literally, “T-shaped trans-[PdR2L2], arising from dissociation of L in [PdR2L2], will encounter a substantial barrier to polytopic rearrangement to cis-[PdR2L2].”56 Actually, the isomerizations studied in isolated [PdR2L2] complexes are slow56 or extremely slow.14 Thus, intermediates of the type trans-[PdR2L2] (A) might be expected to be quite long-lived, but they have never been detected under catalytic conditions.58

This warns, in our opinion, against a cursory acceptance of an I-for-R2 substitution with preservation of the configuration at the palladium.

Finally, substitution reactions in palladium involving initial L dissociation are a rarity.15 Since associative models are perfectly compatible with an eventual neutral ligand dissociation, they should not be discarded a priori on the basis of the observed L retarding effect. On the contrary, measurements of activation parameters, not available so far, seem convenient in order to better decide which mechanism is more consistent with the observations.

In the same paper where they proposed the formation of a three-coordinate intermediate as the general mechanism for the transmetalation with organotin compounds, Louie and Hartwig remarked, “Moreover, dissociative ligand substitution typically occurs by initial loss of the covalent ligand that is being replaced. It is striking that transmetalation reactions involving organotin reagents are dissociative and even more unusual that it is a dative spectator ligand that undergoes dissociation”.10 These puzzling questions disappear in the light of an associative ligand substitution of L (which is not a spectator ligand anymore) as the rate-determining step. Thus, we have considered the alternative cycle proposed in Scheme 4, which in our opinion solves all the inconsistencies just analyzed. Differently from the proposals in the literature, the transmetalation involves an associative L-for-R2 substitution, which gives directly a cis R1/R2 rather than a trans R1/R2 arrangement in IV, and therefore the cis T-shaped V, from which the coupled product will immediately be eliminated.

Our proposal is consistent with the observations in the literature and is supported by a detailed kinetic study of the Stille coupling between 1-iodo-3,5-dichlorotrifluorobenzene (C6Cl2F3I) and vinyl- or 4-methoxyphenyltributyltin, catalyzed by trans-[Pd(C6Cl2F3)2(AsPh3)2]. Furthermore, it offers a plausible picture of the kind of bonding interactions leading from the reagents to the products (see later) and eliminates the need for unlikely fast trans-to-cis isomerization after the transmetalation step.


12. Reference 1b, p 10, gives a dissociation constant at 50 °C in THF: Kdiss = 8.6 × 10−4 mol L−1. The catalyst concentration was [Pd(0)]cat = 3.2 × 10−3 mol L−1. The concentration of three-coordinate trans-[PdPh2(AsPh3)] can be calculated from Kdiss = [PdPh2(AsPh3)]/[PdPh2(AsPh3)] [PdPh2(AsPh3)] = 8.6 × 10−4 mol L−1. This gives [PdPh2(AsPh3)] = x = 1.3 × 10−4 mol L−1, corresponding to 40% dissociation.

13. For instance, complexes cis-[PdR2L2] (R = C6F5, C6F5L = tetrahydroxiphene, an easily dissociable ligand), we have estimated the dissociation of L as 0.13% for a solution 8 × 10−4 mol L−1 in the complex. See ref 14b.

The use of information of the latter necessarily obey a first-order law as well. The catalyst was replaced by addition of AsPh₃. The catalyst was the only organopalladium(II) species detected under catalytic conditions.¹⁸

Results

Preparation of the Catalyst. The catalyst trans-[Pd(C₆Cl₃F₃)I(AsPh₃)₂] (3a) was prepared in quantitative yield as shown in Scheme 5.¹⁶ Under the standard conditions used in catalytic couplings (10⁻² mol L⁻¹ in THF at 323 K), no detectable dissociation was found by ¹⁹F NMR.¹⁷

Catalytic Studies. The couplings of C₆Cl₃F₃(I) with R₂SnBu₃ (R² = CH=CH₂, 2a; or C₆H₄-OCH₃, 2b) catalyzed by 3a were monitored by ¹⁹F NMR (eq 1, Figure 1). The products R²C₆Cl₂F₃ were followed by monitoring the disappearance of 2a as a function of time (eq 2).

\[ \text{Scheme 5} \]

\[ \text{Scheme 4} \]

\[ \text{(1)} \]

products R²C₆Cl₂F₃ (R² = CH=CH₂, 4a; or C₆H₄-OCH₃, 4b) were formed in up to 95% yield (~1% of (C₆Cl₃F₃)SnBu₃ (2c) was also detected after long reaction periods). Vinyltributyltin 2a reacts much faster than 4-methoxytributyltin, 2b. Both couplings are retarded by addition of AsPh₃. The catalyst 3a was the only organopalladium(II) species detected under catalytic conditions.¹⁸

Kinetic Studies. The couplings of C₆Cl₃F₃(I) with 2a or 2b were followed by monitoring the disappearance of I by ¹⁹F NMR. The reactions followed first-order kinetics, providing straight lines ln[1/1₀] = [-kₜ₁) resulted in [2a] = 0.092 mol L⁻¹ (other conditions the same as before) resulted in rₜ₀ = 3.2 × 10⁻⁵ mol L⁻¹ s⁻¹ (kₜ₀ = 3.5 × 10⁻⁴ s⁻¹).

2. Retardation by Addition of Free Neutral Ligand. The reaction rate is minus first order with respect to [AsPh₃] (the slope of ln(kₜ₀) vs ln[AsPh₃] is −1.1). Then, a good linear dependence kₜ₀⁻¹ vs [AsPh₃] is observed, with a slope (4.31 ± 0.17) × 10⁵ mol⁻¹ L s⁻¹ in THF at 322.6 K (Figure 2).

3. Catalyst Activity. The kinetic order with respect to the catalyst concentration [3a] was determined in the presence of added AsPh₃ (0.02 mol L⁻¹). The slope of ln(kₜ₀) vs ln[3a] is 1.0, indicating a first-order dependence with respect to [3a]. Accordingly, the experimental values fit very well a straight line kₜ₀ vs [3a], the slope being (1.16 ± 0.05) × 10⁻³ mol⁻¹ L s⁻¹ (Figure 3a).

Numerical analysis of the kinetic data leads to the rate law given in eq 2, with \( a = (2.32 ± 0.09) \times 10^{-3} \) s⁻¹ and \( b = 6.9 \).

obtained from Figure 2 and from Figure 3a, supporting the
result that the imprecision in the intercept in Figure 2, (3.37 ± 0.04) 
× 10⁻¹⁴ s⁻¹ measured in the absence of added AsPh₃.

Although it is not relevant to the catalytic conditions, where ratios 
L/Pd > 2:1 are used, it can be noted that in absence of 
added AsPh₃ (L/Pd = 2:1) the increase of rate with the catalyst 
concentration is not linear (Figure 3b).

4. Activation Parameters. The temperature dependence of 
the rate was examined within the range 295–328 K (lower 
temperatures gave very low rates, difficult to measure; the upper 
limit is imposed by the boiling point of the solvent). Eyring 
plots (Figure 4) provided the apparent activation parameters 
given in Table 1. The apparent activation entropy S°app is very 
(negative ranging from −56 to −155 J K⁻¹ mol⁻¹) 
gariables regardless of the presence or not of added neutral ligand AsPh₃,
the type of organotributyltin reagent, or the solvent used. This result 
suggests an associative rate-controlling step.

(20) Note that the precision in the intercept in Figure 2, (−2 ± 6) 
× 10⁻¹⁴ s, is higher than the value measured (in fact a negative intercept makes 
no physical sense). Thus the b coefficient has been calculated from those of 
a and kobs = (3.37 ± 0.04) × 10⁻¹⁴ s⁻¹ measured in the absence of added AsPh₃.

(21) Under these conditions (L/Pd = 2:1), the kinetic order in respect to 
[3a] is 0.27 (Figure 3b). This order is only apparent. The nonlinear behavior 
probably comes from the fact that in the absence of added AsPh₃ the 
concentration of AsPh₃ arising from dissociation (otherwise negligible) must 
be considered and is not fixed but varies with the concentration of 3a (we 
have studied a similar phenomenon before in ref 14b). Moreover, this 
dissociation must lead to the formation of other catalytic species (such as 
ido-bridged dimers; see ref 10), contributing to the catalysis. This effect 
having never been noticed before, probably because generally an excess of 
nearby ligand is used in catalytic coupling (see ref 1). However, Scott 
and Stille ⁶ already noticed that the reaction rate did not increase linearly 
with the amount of palladium added for higher concentrations of Pd and 
attributed this to “increased concentration of free phosphine in solution, 
catalyst aggregation, or change in the catalytic species in solution”.

(22) The activation parameters given in the Table 1 cannot be assigned to
any elemental step at this point (see Discussion). For this reason we
refer to them as “apparent”.

Figure 2. Retarding effect of the addition of AsPh₃ on the coupling of 
C₆Cl₂F₃I (1, 0.2 mol L⁻¹) and (CH₂=CH)SnBu₃ (2a, 0.2 mol L⁻¹) 
catalyzed by trans-[Pd(C₆Cl₂F₃)I(AsPh₃)₂] (3a, 0.01 mol L⁻¹) in THF 
at 322.6 K.

Figure 3. kobs vs [3a] plot for the coupling of C₆Cl₂F₃I (1, 0.2 mol L⁻¹) and 
(CH₂=CH)SnBu₃ (2a, 0.2 mol L⁻¹) catalyzed by trans-[Pd(C₆-
Cl₂F₃)I(AsPh₃)₂] (3a) in THF at 322.6 K: (a) with AsPh₃ (0.02 mol L⁻¹); 
(b) without AsPh₃.

Figure 4. Eyring plots for the coupling of C₆Cl₂F₃I (1, 0.2 mol L⁻¹) 
and R²SnBu₃ (2, 0.2 mol L⁻¹) catalyzed by trans-[Pd(C₆Cl₂F₃)I(AsPh₃)₂] 
(3a, 0.01 mol L⁻¹): (a) THF, R² = vinyl; (b) PhCl, R² = vinyl; 
(c) THF, R² = 4-anisyl; (d) THF, R² = vinyl, [AsPh₃] = 0.02 mol L⁻¹.
Cl(CF3)(CH=CH2)L2) could not be detected in transmetalation experiments at moderate temperature (eq 3), suggesting that the reductive elimination occurs fast once the transmetalation has taken place. trans-[Pd(C6Cl2F3)I(AsPh3)] (3a) was the only organopalladium(II) intermediate detected along the catalytic couplings of C6Cl2F3I (1) with R2SnBu3 (R2 = CH=CH2, 2a; C6H4-OCH3, 2b) (eq 1); hence the oxidative addition step and the subsequent cis-to-trans isomerization (Scheme 4) are also faster than the transmetalation.24 The kinetic zeroth order in electrophile 1 agrees with this. Consequently, the kinetic results of the catalytic runs can be properly assigned to the transmetalation step.

The true complexity of the rate law (eq 2) reveals the concurrence at the transmetalation process of a set of elemental steps. The mechanistic interpretation establishes that the elemental composition at the transition state is [2a + 3a - AsPh3].19a In other words, the interaction between 2a and 3a takes place with release of one molecule of AsPh3. We will consider the two general pathways by which AsPh3 can be released from 3a: before or during the interaction with the stannane. We will refer to them as dissociative or associative transmetalation, respectively.

In the so far accepted model, the dissociation of AsPh3 precedes the interaction with the stannane. This has been drawn in Scheme 3 (in our case R1 = C6Cl2F3 and L = AsPh3). If we consider the dissociation to be rate determining, application of the steady-state approximation leads to eq 4.

\[
r_{obs,ss} = k_{obs,ss}[2a] = \frac{k' \left[3a\right]}{k_{-1}^{-1} [AsPh3] + k' \left[2a\right][2a]} (4)
\]

For a very low concentration of AsPh3 (as is the case in the absence of added AsPh3), eq 4 is simplified to \( r_{obs,ss} \approx k' \left[3a\right] \), a rate expression zeroth order with respect to [2a], contrary to the first-order dependence observed experimentally (eq 2). Moreover, the reaction rate becomes mathematically independent of the organotributyltin used, contrary to the marked differences of the organotin compounds. Therefore, the mechanistic assumption leading to eq 4 is to be discarded.

Alternatively, if we consider a fast dissociation,1b,10,11 eq 5 is obtained applying the preequilibrium model,19b with \( K_{dis} = k'/k'-1 \).

\[
r_{obs,pe} = k_{obs,pe}[2a] = \frac{k' \left[K_{dis}[3a]\right]_\text{total}}{[AsPh3][2a]} (5)
\]

Equation 5 agrees with the rate law (eq 2) and data treatment gives \( k'_2 = 1.8 \times 10^{-1} \) s\(^{-1}\) and \( K_{dis} = 1.3 \times 10^{-4} \) mol L\(^{-1}\) at 322.6 K in THF. Since the concentration of catalyst added was \( [3a]_{\text{total}} = 10^{-2} \) mol L\(^{-1}\), the value of \( K_{dis} \) indicates that 12% of catalyst 3a should be dissociated as C (or its corresponding solvated complex) in the absence of added AsPh3. This high dissociation should be detectable by \(^{19}F\) NMR, but the expected effects were not observed.17 Hence the three-coordinate intermediate C is not formed in significant concentration, and the preequilibrium dissociative model is also unsatisfactory.

(24) In fact, the coupling rate of 1 and 2a catalyzed by trans-[Pd(C6Cl2F3)I(PPH3)] (10-2 mol L\(^{-1}\)) in THF at 322.6 K is \( (9.9 \pm 0.4) \times 10^{-6} \) s\(^{-1}\). Casado, A. L., Ph.D. Thesis, Universidad de Valladolid, Spain, March 1998. Under the same conditions, the isomerization rate of cis-[Pd(C6Cl2F3)I(PPH3)] to trans-[Pd(C6Cl2F3)I(PPH3)] is \( (1.49 \pm 0.09) \times 10^{-3} \) s\(^{-1}\), i.e., ~150 times faster (the isomerization limits the formation of trans-[Pd(C6Cl2F3)I(PPH3)], and the oxidative addition is faster; see ref 8).

\[ R^1 = C_6Cl_2F_3, L = AsPh_3, X = halide. \]

Consequently, the two possible models for a dissociative transmetalation, are inconsistent with the observations.

We propose the associative transmetalation pathway shown in Scheme 6, which leads to the transformation trans-II \( \rightarrow \) cis-V via L-for-R2 substitution at the coordination plane. A nucleophilic attack of the Pd-coordinated halide to the organotin compound makes the palladium center more electrophilic and the C atom of R2 more nucleophilic, assisting the electrophilic attack of Pd to give the activated complex III, from which L is released.14b,25,26 Since associative substitutions via pentacoordinate palladium occur with preservation of the stereochemistry at the palladium,15 intermediate IV, as well as the three-coordinate V, must necessarily have R2 in the position of the leaving AsPh3, i.e., cis to R1. Then, V can readily eliminate the coupling product R1-R2 without the need for further (and comparatively slow) dissociation or isomerization steps that must be proposed in the so far accepted mechanism (Scheme 1).

Applying the steady-state approximation to our associative transmetalation model (Scheme 6), eq 6, with \( k_1 = 0.034 \) mol\(^{-1}\) L s\(^{-1}\) and \( k_2/k_1 = 6.9 \times 10^{-4} \) mol L\(^{-1}\), is obtained (see Appendix; numeric values given hold for X = I, in THF at 322.6 K), which also agrees with the experimental rate law (eq 2).

As \( k_1 \) depends on the nature of the organotin reagent, different coupling rates are to be expected for different organotributyltin, even for \([\text{AsPh}_3] = 0\) (in such case \( k_{\text{obs}} = k_{\text{obs}}^{[2a]} = k_1 \cdot [3a][2a] \)). In fact, the observed rate is vinyl > phenyl.27

Although the interpretation of apparent activation parameters is not simple in such a multistep reaction,28 the very large negative values for the apparent \( \Delta S^\ddagger_{\text{obs}} \) (Table 1, obtained from the composite rate constant \( k_{\text{obs}} \)) found in all cases examined are in agreement with the associative mechanism proposed. This entropy argument also rules out solvent (THF) participation in the AsPh3 replacement (at least as the main pathway), which should produce only a small increase in order in the transition state.19d Moreover, the activation entropy found in chlorobenzene is also negative, although this solvent is much worse ligand than THF.28

Changes of the halogen atom X are expected to produce little effect on the activation entropies of the processes concerned; hence, the variation in rates observed for the transmetalation of trans-[Pd(C6Cl3F3)X(AsPh3)2] (Table 2) must be related to changes in activation enthalpy. These are probably associated with a high activation enthalpy for the pentacoordination of the Pd atom. In fact the II \( \rightarrow \) IV transformation corresponds, with little variation, to the rate-determining step of an associative substitution in Pd complexes.15 The nucleophilic attack of the atom of the R2 group (entering ligand) on the electrophilic Pd complex must be facilitated as the Pd complex becomes more electrophilic and the \( \text{C}_2 \) more nucleophilic (predicting a rate variation Cl > Br > I, as observed).29

The mechanism in Scheme 6 is a variation of the so-called \( \text{S}_2^2\)(cyclic) ligand replacement.15 Thus, for the arylation of [\( \text{PtX}_2\text{L}_2 \)] complexes using aryltrimethylstannanes, four center-activated complexes (Figure 5a) have been suggested.28 Moreover, Hatanaka and Hiyama have proposed similar activated complexes for the palladium-catalyzed coupling of organosilicon compounds with the aid of fluoride ion: This coupling can course with retention or with inversion of configuration, depending on the temperature and the solvent. For the reaction occurring with retention of the configuration, the cyclic transition state (Figure 5b) was proposed, whereas an \( \text{S}_2^2\)(open) mechanism would be operating when the reaction courses with inversion (Figure 5c).30

The \( \text{S}_2^2\)(cyclic) mechanism implies retention of the configuration at \( \text{C}_2 \). Unfortunately, the effect on the stereochemistry of the Pd complex was disregarded, and the effect of added ligand was not studied in refs 7 and 30, where a direct X-for-R2 substitution is implied (Scheme 7). Note that this kind of substitution would lead to a trans arrangement of the two R groups after transmetalation and should be little sensitive to the addition of L, which remains coordinated. On the contrary, our proposal explains the dependence on L observed and produces immediately the cis arrangement needed for fast R1\( \rightarrow \)R2 coupling.31

Finally, some comments about the influence of the neutral ligands, L, can be made in light of our mechanism. It is known from the literature that there is an inverse relationship between ligand donicity and transmetalation rate.11 The Stille reaction runs up to 3 orders of magnitude faster with ligands of modest donicity (AsPh3) than with good donors (PPh3). This seemed to support the dissociative proposal because the former should dissociate more readily. But they will be more easily displaced also in an associative substitution process. Moreover, the electrophilicity of the palladium complex will be higher with L ligands of low donicity, and this will make the activated complex III more accessible. Furthermore, the L ligands must move to equatorial positions in III for the substitution to occur. Hence, if L ligands with similar net donicities are compared, it is reasonable that the transmetalation should be favored by those better \( \pi \) acceptors, as they have a stronger preference for the equatorial sites in \( d^8 \) bpt complexes.32

On the other hand, it seems that there is no clear correlation between rate and the steric parameters of L,15 contrary to the expectations for an initial L dissociation, which should be favored for increasing steric requirement of L. In the mechanism in Scheme 6, the influence of increasing the bulkiness of L is more difficult to predict since this will destabilize the ground and the transition states less differently than when these are four- and three-coordinated (as in the dissociative mechanism). Bulkier ligands will probably make more difficult the access to III, but at the same time they will favor the dissociation to IV. Thus, in a concerted process, a less clear influence can be expected. Note, however, that coming to very bulky ligands, a dramatic change in behavior has been reported. For the transmetalation of the dimeric complex [PdArBrL]2 (Ar = p-Tol, L = P(o-Tol)3) with trialkyltynyl aryls, the rate depends on the square root of the concentration of dimer and is not affected by the addition of L. This is consistent with a dissociative mechanism.10 The scheme proposed in the literature for this mechanism can be accommodated to an \( \text{S}_2^2\)(cyclic) model as shown in Scheme 8.

Conclusions

The studies presented here concern the conditions most commonly used for the Stille reaction, involving the use of aryl or vinyl halides in solvents of moderate donicity, palladium complexes with monodentate ligands of normal steric bulk, and ratios L:Pd > 2:1. The mechanism proposed in Scheme 4 fits all the observations made on the reaction, either stoichiometric or catalytic. First, it depicts the fact that the oxidative addition

(27) It must be noted that in order to produce the transmetalation, R2 must become bridging ligand using its \( \text{C}_2 \). This does not discount an initial \( \pi \)-coordination of R2 helping the bimolecular interaction, when possible (R2 = vinyl, alkanyl). This kind of coordination has been proposed by Farina et al.11 and would account for two facts observed for vinyl derivatives: (i) A faster reaction rate and (ii) the formation of Heck coupling byproducts in some cases; see: (a) Liao, J.-H.; Kanatzidis, M. G. J. Am. Chem. Soc. 1990, 112, 7399–7400. (b) Kikutkawa, K.; Umekawa, H.; Matsuda, T. J. Organomet. Chem. 1986, 311, C34–C46.


(29) For a dissociative ligand substitution, the converse trend should be expected, as the dissociation of L should be the more difficult (hence \( k_{\text{obs}} \) in eq 8 should be the smaller) the more electronegative the halide.


(31) Pitifully, neglect of the coordination sphere of the metal is quite common in the literature of metal-catalyzed organic transformations. We hope that this paper will serve to draw attention on its mechanistic relevance in some cases.

gives a cis compound, which isomerizes rapidly to the trans isomer. From the latter, an associative ligand substitution produces L-for-R<sub>2</sub> exchange. This leads directly to a T-shaped isomer. From the latter, an associative ligand substitution gives a cis compound, which isomerizes rapidly to the trans course of the mechanism after the transmetalation step. The R<sup>1</sup>-R<sub>2</sub> complex.33 Also, our mechanism predicts retention of configuration at the carbon, which has been observed in some reactions,34 but inversion has been reported in other cases.6 This stresses the idea that other reaction conditions deserve mechanistic studies on their own.

Finally, a unified view seems to be merging for the transmetalations to palladium, whether with Sn (Stille), with silicon fluoride-assisted (Hiyama), and possibly with other transmetalating agents: The reactions occurring with retention of configuration most likely proceed in all cases by an S<sub>a</sub>/2(open) L-for-R replacement at the Pd center. It is plausible that an S<sub>a</sub>/2(cyclic) mechanism (as suggested by Hiyama in Si) can also be operating for the Stille coupling in those cases where inversion has been observed (using the very coordinating solvent mixture HMPA-THF). Further studies are in progress to explore these aspects.

### Experimental Section

The reactions involving organolithium or organomagnesium reagents were carried out under N<sub>2</sub>. Commercial C<sub>6</sub>F<sub>5</sub>SnBu<sub>3</sub>, AsPh<sub>3</sub>, and vinylmagnesium bromide (1 M solution in THF) were used without further purification. The solvents were purified using standard methods. C<sub>6</sub>Cl<sub>2</sub>F<sub>3</sub>I was used without further purification. The solvents were dried over MgSO<sub>4</sub>. To a solution below 0 °C of vinylmagnesium bromide (10 mL) C<sub>6</sub>F<sub>5</sub>SnBu<sub>3</sub> (3.48 mL, 12.8 mmol) was slowly added. The mixture was stirred overnight while it reached room temperature. The resulting white suspension was hydrolyzed with aqueous NaHCO<sub>3</sub>, washed with water (2 × 30 mL), and dried over MgSO<sub>4</sub>. The diethyl ether solution was evaporated to give a pale yellow oil which was vacuum-distilled yielding a colorless liquid 2a (3.45 g, 85%).

119<sup>Sn</sup>NMR (CDCl<sub>3</sub>/THF) δ = 49.96/–49.27 (s, 2b) was similarly prepared from (4-methoxyphenyl)magnesium iodide (3c).

trans-[Pd(C<sub>6</sub>Cl<sub>2</sub>F<sub>3</sub>)Cl(AsPh<sub>3</sub>)<sub>2</sub>]. To a stirred suspension of trans-[Pd(C<sub>6</sub>Cl<sub>2</sub>F<sub>3</sub>)Cl(AsPh<sub>3</sub>)<sub>2</sub>], 100 mg, 0.116 mmol) in acetone (10 mL) was added AsPh<sub>3</sub> (150 mg, 0.488 mmol). After some seconds, white 3c precipitated. The mixture was stirred for 1 h, and the solvent evaporated. The solid was then washed with diethyl ether and air-dried (yield 209 mg, 94%): IR (KBr) 1436 (vs), 1400 (vs), 1046 (m), 777 (s), 739 (vs), 692 (s), 460 (s), 331 (m), 314 (m); 1H NMR (CDCl<sub>3</sub>) δ 7.7–7.6 (m, 2CH<sub>2</sub>) 7.5–7.3 (m, 3CH<sub>2</sub>); 19<sup>F</sup> NMR (CDCl<sub>3</sub>/THF) δ = 91.81/–86.70/–83.72 (m, 2F<sub>2</sub>), –120.02/–116.72/–115.50 (s, F<sub>3</sub>). Anal. Calcd for C<sub>42</sub>H<sub>30</sub>AsCl<sub>2</sub>F<sub>3</sub>Pd: C, 52.86; H, 3.17. Found: C, 52.65; H, 3.35.

trans-[Pd(C<sub>6</sub>Cl<sub>2</sub>F<sub>3</sub>)X(AsPh<sub>3</sub>)<sub>2</sub>]: X = I (3a), Br (3b). To a colorless solution of 3c (110 mg, 0.115 mmol) in acetone/CH<sub>2</sub>Cl<sub>2</sub> (4/1 mL) was added an excess of NaX (0.20 mmol). The yellow mixture formed was stirred for 1 h and then evaporated to dryness. The residue was extracted in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and evaporated again. The yellow solid was washed with diethyl ether/hexane and vacuum-dried. 3a (93%): IR (KBr) 3073 (m), 1482 (s), 1436 (vs), 1403 (vs), 1047 (m), 775 (m), 735 (vs), 691 (vs), 467 (s), 335 (s), 322 (s); 1H NMR (CDCl<sub>3</sub>) δ 7.58 (m, 2CH<sub>2</sub>) 7.5–7.3 (m, 3CH<sub>2</sub>); 19<sup>F</sup> NMR (CDCl<sub>3</sub>/THF) δ = 91.81/–86.70/–83.72 (m, 2F<sub>2</sub>), –120.02/–116.72/–115.50 (s, F<sub>3</sub>). Anal. Calcd for C<sub>42</sub>H<sub>30</sub>AsCl<sub>2</sub>F<sub>3</sub>Pd: C, 52.84; H, 2.89. Found: C, 52.65; H, 3.35. 3b (89%): IR (KBr) 3055 (m), 1482 (m), 1435 (vs), 1404 (vs), 1047 (m), 777 (m), 737 (vs), 693 (s), 483 (s), 471 (s); 1H NMR (CDCl<sub>3</sub>) δ 7.58 (m, 2CH<sub>2</sub>), 7.5–7.3 (m, 3CH<sub>2</sub>); 19<sup>F</sup> NMR (CDCl<sub>3</sub>/THF) δ = 91.01/–86.82/s, 2F<sub>2</sub>), –120.15/–116.81/–115.89 (s, F<sub>3</sub>). Anal. Calcd for C<sub>39</sub>H<sub>28</sub>AsCl<sub>3</sub>F<sub>3</sub>Pd: C, 50.51; H, 3.03. Found: C, 50.45; H, 3.16.

Isolation of R<sub>2</sub>C<sub>6</sub>Cl<sub>5</sub>F<sub>3</sub> from Catalytic Reaction Mixtures: R<sub>2</sub> = CH=CH<sub>2</sub> (4a), C<sub>6</sub>H<sub>4</sub>-O-CH<sub>3</sub> (4b). After evaporation of the solvent (THF), product 4a was vacuum-distilled (70 °C, 3 mm) as a colorless liquid (98% isolated yield): δ 1.19. IR (NaCl) 2928 (m), 1610 (s), 1463 (vs), 1451 (vs), 1411 (vs), 1219 (s), 1081 (s), 991 (s), 936 (s), 860 (s), 801 (s); 1H NMR (CDCl<sub>3</sub>) δ 6.61 (dd, 3<sub>c</sub>ÅJA = 18.0 Hz, 3<sub>c</sub>ÅJHH = 11.9 Hz, CH<sub>gem</sub>), 6.06 (d, 3<sub>c</sub>ÅJA = 18.0 Hz, CH<sub>trans</sub>), 5.69 (d, 3<sub>c</sub>ÅJHH = 11.9 Hz, CH<sub>trans</sub>); 19<sup>F</sup> NMR (CDCl<sub>3</sub>) δ 154.94 (dd, 1<sub>CF</sub> = 253.9 Hz, 1<sub>c</sub>ÅJCF = 92.8 Hz, 1<sub>c</sub>ÅJCF = 42.2 Hz, CF<sub>2</sub>), 135.77 (dt, 1<sub>CF</sub> = 251.9 Hz, 1<sub>c</sub>ÅJCF = 5.5 Hz, CF<sub>4</sub>, 123.22 (td, 1<sub>CF</sub> = 7.9 Hz, 1<sub>c</sub>ÅJCF = 2.5 Hz, CF<sub>3</sub>), 121.60 (td, 1<sub>CF</sub> = 17.3 Hz, 1<sub>c</sub>ÅJCF = 2.3 Hz, CH<sub>trans</sub>), 112.62 (td, 1<sub>CF</sub> = 16.5 Hz, 1<sub>c</sub>ÅJCF = 4.6 Hz, C- vinyl), 107.29 (dd, 1<sub>CF</sub> = 24.9 Hz, 1<sub>c</sub>ÅJCF = 21.0 Hz, C-H).
Hz. $J_{CF} = 3.9$ Hz, C-CF₃; $^{19}$F NMR (CDCl₃/THF/CIPr) δ $-115.41/-112.21/-111.50$ (d, $J_{FP} = 2.4$ Hz, 2F²), $-113.29/-110.62/-109.57$ (t, $J_{FP} = 2.4$ Hz, F³); MS m/z (%) 226 (50) [M⁺], 191 (41), 156 (100), 105 (25). Anal. Calc'd for $C₃H₇-CI₂F₃: C$, 42.33; H, 1.33. Found: C, 42.27; H, 1.32. 4b: After evaporation of the solvent (THF), the residue was treated with diethyl ether and a saturated aqueous KF solution. After vigorous stirring, FSnBu₃ separated as a white solid. The diethyl ether phase was separated, dried over MgSO₄, and evaporated to dryness. The residue was chromatographed (silica gel/ hexane) giving a white solid, which was recrystallized from pentane at $-28$ °C (white needles, 95%): mp 98–99 °C; IR (KBr) 2941 (m), 2839 (m), 1613 (s), 1522 (s), 1445 (vs), 1408 (vs), 1255 (vs), 1186 (s), 1053 (vs), 1034 (s), 795 (vs), 565 (m), 526 (m); $^1$H NMR (CDCl₃) δ 7.35 (m, 2CH), 7.14 (m, 2CH), 3.87 (s, CH₃); $^{13}$C-$^{1}$H NMR (CDCl₃) δ 160.09 (s, C-Ome), 154.34 (dd, $J_{CF} = 249.7$ Hz), $J_{CF} = 8.3$ Hz, $J_{CF} = 4.4$ Hz, CF₅), 153.80 (dt, $J_{CF} = 250.6$ Hz, $J_{CF} = 5.3$ Hz, CF₄), 131.30 (s, CH), 118.87 (s, C-C₂H₂Cl₂F₃), 114.07 (s, CH), 116.09 (td, $J_{CF} = 20.1$ Hz, $J_{CF} = 4.4$ Hz, C-Ph), 107.34 (dd, $J_{CF} = 25.6$ Hz, $J_{CF} = 21.0$ Hz, $J_{CF} = 3.3$ Hz, CCF), 55.22 (s, CH₃); $^{19}$F NMR (CDCl₃/THF) δ $-115.69/-112.18$ (dt, $J_{FP} = 2.4$ Hz, $J_{FP} = 1.3$ Hz, 2F²), $-113.64/-111.39$ (t, $J_{FP} = 2.4$ Hz, F³); MS m/z (%) 306 (78) [M⁺], 263 (69), 193 (100). Anal. Calc'd for $C₃H₇Cl₂F₃:O: C$, 50.85; H, 2.30. Found: C, 50.84; H, 2.36.

**Kinetics of Palladium-Catalyzed Coupling of $C₃Cl₂F₃I (1)$ with Organotributyltin (2a,b).** NMR tubes (5 mm) were charged with 1 (5.2 ± 0.1 mg, 19.0 ± 0.3 mmol) and suitable amounts of palladium catalyst 3a, AsPh₃, and organotributyltin 2a,b. The samples were dissolved under N₂ at room temperature (293 K) in THF or PhCl) to a fixed volume of 600 ± 5 μL, charged with an acetone-d₆ capillary for NMR lock, and placed into a thermostated probe (±0.2 K; the temperature was measured by an ethylene glycol standard method). Concentration—time data were then acquired from $^{19}$F NMR signal areas of 1 and the products (4a-b), and fitted to equation ln([1]₀ – [1]) = $k_{obs}$t to get first-order constants $k_{obs}$ (standard deviations are also given). Alternatively, when no good first-order rates were achieved (couplings with 2a in absence of added AsPh₃), first data points (up to 10% of conversion) were fitted to the following second-degree Taylor equation $[1] = a₀ + a₁t + a₂t²$, where $a₁$ gives the initial reaction rate in mol L⁻¹ s⁻¹ ($a₁ = r₀ = -d[1]/dt = -d[2a]/dt$). Since the reaction rate $r$ is first order in 2a and zeroth order in 1 (eq 2), the first-order constants can be estimated in these cases as $k_{obs} = r₀/[2a]₀$.

**Reactions of Organopalladium(II) Complexes and Organotributyltin.** Samples containing 0.01 mol L⁻¹ in palladium complex and 0.2 mol L⁻¹ in the corresponding organotributyltin, prepared as above-described, were allowed to react at 20 °C (thermostated bath). The reaction products were analyzed by $^{19}$F NMR at the reported intervals of time.

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**Supporting Information Available:** Values of the first-order rate constant $k_{obs}$ for the coupling of $C₃Cl₂F₃I (1, 0.2 mol L⁻¹) with R²SnBu₃ (2a,b, 0.2 mol L⁻¹) catalyzed by trans-[Pd(C₆Cl₂F₃)₂(AsPh₃)₂] (3a) under different experimental conditions (1 page, print/PDF). See any current masthead page for ordering information and Web access instructions.

**Appendix: Derivation of the Kinetic Eq 6.** The steady-state concentration of intermediate IV (Scheme 6, $X = 1$), and the reaction rate, are given in eqs 7–9.

$$d[IV]/dt = k_{obs}[2a][3a] - k_{-1}[IV][AsPh₃] - k_2[IV] = 0$$

$$[IV] = \frac{k_{obs}[2a][3a]}{k_{-1}[AsPh₃] + k_2}$$

$$r_{obs,ss} = k_2[IV]$$

$$r_{obs,ss} = k_{obs,ss}[2a] = \frac{k_1 k_2[3a]}{k_{-1}[AsPh₃] + k_2[2a]}$$

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