Mechanistic Studies on the Aryl−Aryl Interchange Reaction of $ArPdL_2I$ (L = Triarylphosphine) Complexes

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Abstract: The aryl−aryl interchange reaction of $ArPdL_2I$ complex **1m** was found to follow pseudo-first-order kinetics. A marked inhibition in the presence of excess phosphine and/or excess iodide was observed, suggesting that a dissociative pathway was involved, contrary to the analogous alkyl−aryl interchange reaction studied previously. Phosphine flooding experiments could not be performed due to a competing phosphonium salt formation reaction that occurred in the presence of excess phosphine. A deuterium labeling experiment indicated that the interchange reaction proceeded via the reductive elimination to form the phosphonium salt, suggesting that excess phosphine was acting as a trap for intermediate palladium(0) species preventing the generation of the interchanged palladium-(II) complex. Substituent effect studies of the interchange reaction indicated that it was inhibited by electron-withdrawing groups on both the phosphine and palladium-bound aryl groups and by increased steric bulk on both the phosphine and palladium-bound aryl groups. Under catalytic conditions, the distribution of phosphines formed from the aryl−aryl interchange during palladium-mediated cross-coupling reactions could be modeled by statistics. Various strategies for eliminating the formation of byproducts caused by the interchange during cross-coupling reactions were screened and optimized.

Introduction

Palladium-mediated cross-coupling reactions, such as the coupling of an organic electrophile with an organoboron (Suzuki coupling),[1] -tin (Stille coupling),[2] -aluminum,[3] -silicon,[4] -zinc,[5] -zirconium,[6] or -magnesium[7] reagent; the coupling of an aryl halide with an alkene (Heck coupling)[8] or alkyne (Hagihara coupling);[9] or more recently the coupling of an aryl halide with anionic amides,[10] thiolates,[11] or alkoxides,[12] are very useful tools in the arsenal of the synthetic chemist. In addition to their obvious importance as a method for the formation of carbon−carbon or carbon−heteroatom bonds, these reactions possess the added benefits of proceeding through readily accessible substrates, being tolerant of most functionalities, and preserving the regiochemistry of the reactants involved. Under the appropriate conditions, the yields of these reactions can be close to quantitative, which makes them useful for condensation polymerization reactions. Indeed, a large variety of polymeric materials have been synthesized using the methodologies provided by these reactions.[13]

One unfortunate drawback to these methodologies is the occurrence of an interchange between phosphorus-bound aryl moieties and palladium-bound aryl[14] or alkyl[15] groups in the

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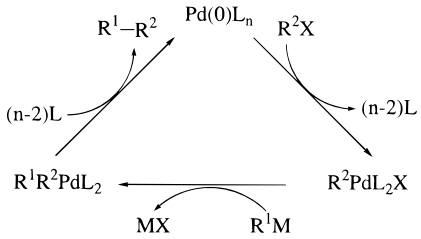
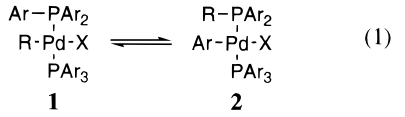
Scheme 1. Simplified Mechanism for Palladium-Catalyzed Cross-Coupling Reactions



$RPdL_2X$ intermediates (where L = triarylphosphine, X = Br or I, and R = aryl or alkyl) of these reactions (eq 1). A



simplified catalytic coupling cycle is depicted in Scheme 1.[1i] The $RPdL_2X$ species is usually believed to be the resting state of the catalyst in the cycle,[16] and the occurrence of this interchange would allow the ligand-bound aryl groups to enter the cross-coupling *in lieu* of the aryl or alkyl halide derived organic moieties. In fact, several recent investigations have attributed the formation of phosphine-derived byproducts in catalytic[17] and stoichiometric[18] cross-coupling reactions to this exchange. Furthermore, our own work on water-soluble poly(*p*-phenylenes)[19] suggests that incorporation of phosphine ligands into cross-coupling polymerizations can not only result in production of monofunctional aryl endcaps but also produce branched network structures by inadvertent generation of multifunctional phosphine monomers.[20] Given these consequences, it would be useful to gain a more detailed understanding of the interchange process, with the end goal of eliminating it altogether from the coupling reactions, thus improving the efficiency of small-molecule couplings as well as providing a means for synthesizing polymers with the intended linear architecture.

In this paper, we present kinetics experiments performed on the aryl−aryl interchange of $ArPdL_2I$ complexes **1a**−**z**, in an attempt to elucidate the mechanism of this reaction. Recently, Norton and co-workers presented a detailed account on the mechanism of the alkyl−aryl interchange of $RPdL_2I$ complexes.[15] But, as we shall point out, there are a number of interesting and fundamental differences between the two exchange reactions despite their apparent similarity. Secondly, we will present the results of several analytical experiments to quantitatively show the impact of the aryl−aryl interchange on a number of small-molecule Suzuki coupling reactions and, from these, infer the possible consequences upon analogous polymerizations. Finally, we will suggest some possible strategies that might be used by synthetic organic and polymer chemists alike to minimize, if not eliminate, the interchange from palladium-mediated cross-coupling reactions.

Results and Discussion

Kinetics Experiments. Complexes **1a**−**z** were synthesized as described elsewhere.[21] Of these, complex **1m** (R = 4-methoxyphenyl, Ar = 4-fluorophenyl) was deemed the most suitable for initial kinetics studies due to its comparative solubility and stability and to the fact that the ^{1}H NMR resonances for the palladium-bound aryl group both before and after exchange were clearly resolvable. The aryl−aryl interchange reaction appeared to follow simple first-order kinetics with an observed rate constant of $(7.30 \pm 0.12) \times 10^{-4}$ s^{-1} at 50 °C and 0.042 M initial concentration in THF-d_8. Kinetics did not deviate from linearity for the almost five half-lives over which the experiments were run, and the observed rate constants were found to be insensitive to the initial concentration of **1m** in the range 0.021−0.164 M. As the interchange is a reversible process ($K_{eq} \approx 20$), the observed rate constant reflects the sum of the rate constants for the forward and reverse reactions.[22] Also, while the interchange reaction is progressing, there is almost certainly a rapid dissociation and association of the phosphine ligands taking place, resulting in a statistical mixture of phosphines with zero, one, two, and three exchanged aryl groups.[14a,15] Consequently, the kinetics observed are the loss of palladium-bound methoxyphenyl groups and the growth of palladium-bound fluorophenyl groups, independent of the specific identity of the phosphine ligands involved. The fact that the kinetics remain linear for the entire process suggests that the individual rate constants for the different possible exchange reactions are not significantly divergent.

To test for a pathway involving the predissociation of a phosphine ligand, kinetics were followed in $CDCl_3$ at 60 °C and 0.042 M in initial concentration of **1m**, in the presence of varying amounts of excess phosphine; the results are presented in Figure 1. As can be seen from this graph, there is a noticeable inhibition of the rate of interchange with increased phosphine concentration, again indicating that the loss of ligand is somehow involved in the mechanism. Another noticeable feature of this graph is the ample curvature of the plots, indicating the presence of additional chemical processes. Indeed, when kinetics were followed with excess phosphine in THF-d_8, a precipitate formed in the NMR tube. This was isolated and characterized by ^{1}H, ^{19}F, and ^{31}P NMR as well as FAB mass spectrometry, which indicated that this solid was an approximately 4:1 mixture of two different phosphonium salts, tris(4-fluorophenyl)(4-methoxyphenyl)phosphonium iodide and bis(4-fluorophenyl)bis(4-methoxyphenyl)phosphonium iodide, as well as a trace of a third, tetrakis(4-fluorophenyl)-

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(16) For aqueous Suzuki couplings with aryl bromides, we have found the rate to be dependent upon concentration of catalyst and boronic acid, suggesting that transmetalation is rate-determining, in agreement with results for other coupling systems: (a) Reference 3d. (b) Brown, J. M. Cooley, N. A. *Organometallics* **1990**, *9*, 353. (c) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. Smith *et al.* similarly found transmetalation to be rate-determining when aryl iodides were used in organic Suzuki coupling systems. However, when aryl bromides were used, oxidative addition was rate-determining, suggesting that this generalization is not universal: (d) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151.

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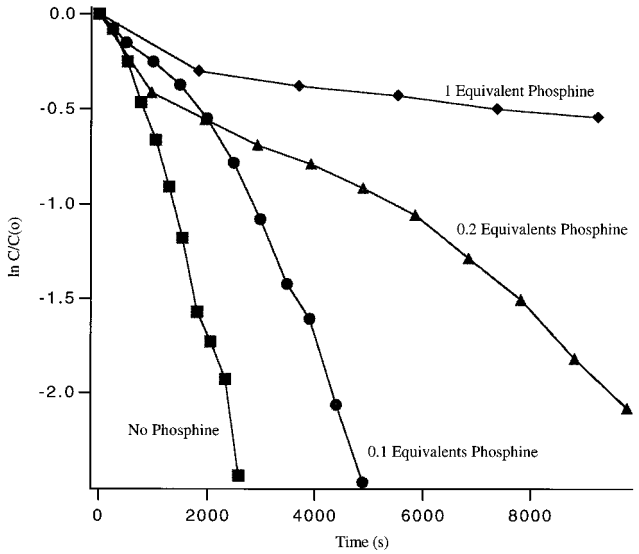


Figure 1. Disappearance of **1m** in the presence of excess tris(*p*-fluorophenyl)phosphine in $CDCl_3$ at 60 °C.

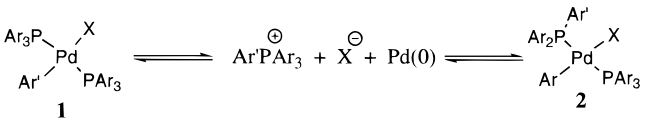
phosphonium iodide. Palladium complexes are known to catalyze the formation of phosphonium salts from aryl halides and triarylphosphines,[23] so it is not surprising that this side reaction occurs here. Unfortunately, the presence of this additional reaction prevents the use of flooding experiments that would be required to obtain absolute rate constants for a multistep chemical pathway. Finally, it should be noted that the disappearance of **1m** in the 1 equiv of additional phosphine plot is almost entirely due to the competing phosphonium salt formation. After 3 h at 60 °C, only about 3% of the exchanged product **2m** had grown in, in agreement with the observations of Kong and Cheng.[14a]

Another aspect worth noting in Figure 1 is the curvature of the plot for the run with no phosphine added. This feature was not present in the experiments performed in THF-d_8, but the curvature was noticeable when kinetics were run in tetrachloroethane-d_2. Furthermore, for the experiments performed in chlorinated solvents, there was as much as 30% less signal for **2m** at the end of the run than there was for **1m** at the beginning. These results indicated a competing decomposition reaction in chlorinated solvents. Upon comparison of the ^{1}H NMR spectrum of the isolated phosphonium salt mixture with spectra obtained from the kinetics runs performed in chlorinated solvents, we noticed that the very distinctive splitting pattern (due to coupling with both ^{19}F and ^{31}P nuclei) at 7.78 ppm in the phosphonium salt spectrum was present in the spectra from the kinetics runs, as well as the methoxy resonance at 3.94 ppm. Unfortunately, the ^{19}F and ^{31}P NMR spectra were not as clear due to the fact that the phosphonium salts and the ArPdL$_2$I complexes have resonances in the same regions. This seems to indicate that the competing decomposition seen in chlorinated solvents is due to the phosphonium salt formation, even without the presence of additional phosphine. Further evidence that this might indeed be occurring was recently provided by Yamamoto and co-workers, who observed that *trans*-[PdPhI(PPh$_3$)$_2$] produced *ca.* 30% PPh$_4$I upon reflux in methylene chloride, again without the presence of additional phosphine.[14d] Why the phosphonium salt formation does not seem to occur in nonhalogenated solvents without the addition of excess phosphine is uncertain.

To investigate a possible pathway involving the predissociation of iodide, kinetics of the aryl−aryl interchange were followed at 0.042 M in initial concentration of **1m** in THF-d_8 at 50 °C, first in the presence of 0.206 M LiI, then in the presence 0.206 M LiPF$_6$, and finally in the presence of 0.103 M in each (see the Supporting Information for linearized kinetic plots). There was only a slight inhibition of the rate caused by the addition of LiI with respect to kinetics with no added salt ($(6.05 \pm 0.13) \times 10^{-4}$ s^{-1} vs $(6.76 \pm 0.05) \times 10^{-4}$ s^{-1}, respectively). However, as added salt significantly changes the polarity of the solvent medium, a better comparison is with kinetics followed in the presence of an equimolar amount of added LiPF$_6$. The kinetics followed in the presence of LiI were significantly slower than those followed in the presence of LiPF$_6$ ($(11.5 \pm 0.2) \times 10^{-4}$ s^{-1}) with the kinetics in the presence of one-half the amount of each falling in between. When kinetics were followed in the presence of 0.206 M lithium trifluoromethanesulfonate, the observed rate constant ($(20.3 \pm 0.02) \times 10^{-4}$ s^{-1}) was very close to that for kinetics observed in the presence of 0.206 M LiPF$_6$ ($(19.1 \pm 0.4) \times 10^{-4}$ s^{-1}), suggesting that this salt effect is general. From these results it is apparent that, in addition to a reaction pathway involving the predissociation of phosphine, there is a completely separate pathway involving the predissociation of iodide.

Given these results, it is tempting to propose a mechanism that requires a predissociation of either a phosphine or an iodide. However, this mechanism is inconsistent with the observation that an added equivalent of phosphine completely shuts down the exchange reaction, since the additional phosphine should have no effect on the iodide dissociation pathway.[24] An additional problem with this mechanism is the observation of Hartwig, who found that the aryl−aryl interchange in (bis(diphenylphosphino)ethane)Pd(aryl)(thiolate) complexes was inhibited by the presence of added triphenylphosphine.[11f] The monodentate triphenylphosphine ligand cannot have an effect on the dissociation equilibrium of (diphenylphosphino)ethane due to the strong chelate effect of the latter ligand.

A possible solution to this conundrum was recently provided by Chenard *et al.*, who suggested that the interchange reaction occurred first through a reductive elimination to form the phosphonium salt, followed by an oxidative addition of a different phosphorus−carbon bond to generate **2** (eq 2).[14c]



(2)

Evidence for this was given by the fact that phosphonium salts were successfully coupled with aryl stannanes by a phosphine-free catalyst. Soon afterward, Yamamoto and co-workers showed that quaternary phosphonium salts could oxidatively add to palladium(0) olefin species.[14d] These results would explain the phosphine inhibition effect mentioned above in that added phosphine could trap out the palladium(0) intermediate as PdL$_3$, preventing the subsequent oxidative addition. A precedent for this was provided by Rubinskaya *et al.*, who isolated a zwitterionic palladium(0) compound upon heating an (alkenyl)Pd(PPh$_3$)$_4$ complex.[25] Here the phosphonium salt

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(24) Additional phosphine should have no effect on the iodide dissociation pathway unless the added phosphine was able to trap out the dissociated palladium species as a cationic [ArPdL$_3$]$^+$ complex. However, if this were occurring, a signal for this hypothetical complex should be present in the ^{31}P NMR spectrum of an ArPdL$_2$I compound in the presence of excess phosphine. Garrou and Heck saw no evidence of peak broadening, chemical shift changes, or coalescence when complex **1z** was heated to 45 °C in the presence of added phosphine: Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4113.

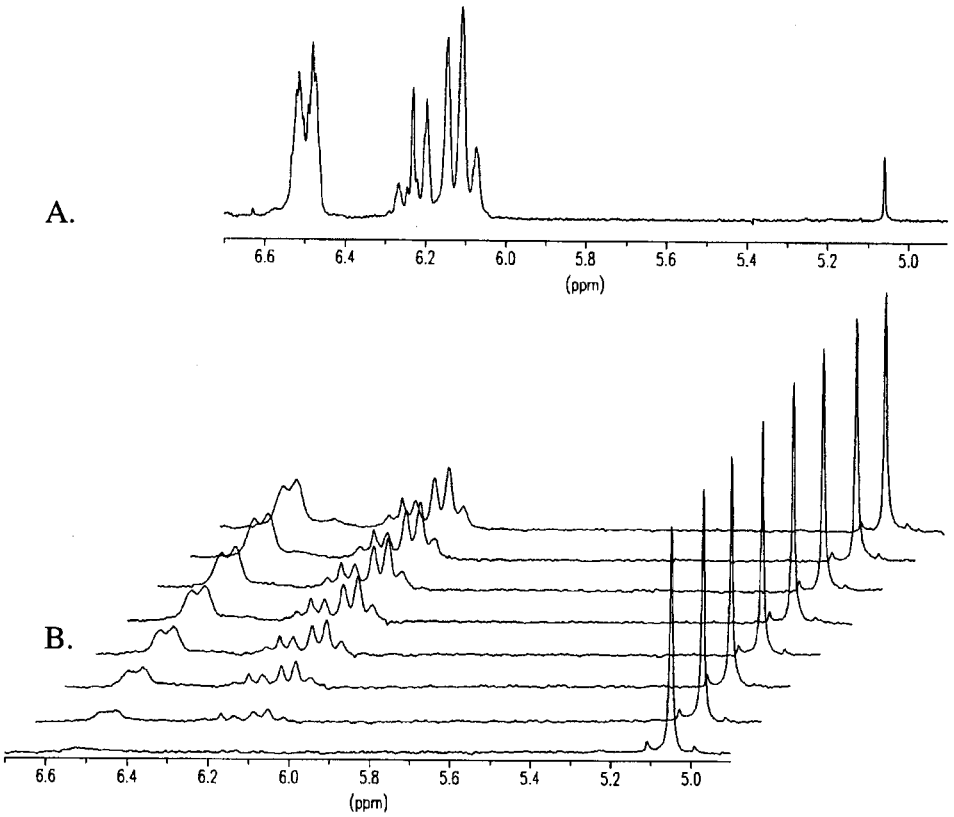
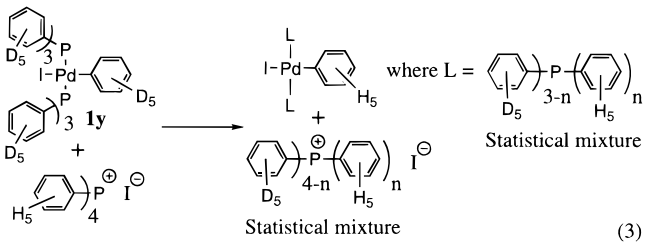


Figure 2. (A) Pd−Aryl region of the ^{1}H NMR spectrum of complex **1z** in $CDCl_3$. (B) Stack plot of the reaction of perdeuterated complex **1y** with 10 equiv of $Ph_4P^+I^-$ in $CDCl_3$. The signal at δ 5.08 ppm is due to the trioxane internal standard.

formed has its own intramolecular Pd(0) trap which prohibits oxidative addition of a P−C bond to form the interchanged Pd(II) species.

To verify the intermediacy of phosphonium salts in the aryl−aryl interchange reaction, the perdeuterated complex **1y** was heated at 50 °C in $CDCl_3$ in the presence of 10 equiv of tetraphenylphosphinium iodide to see if signals due to palladium-bound [$^1H_5$]phenyl groups would appear in the ^{1}H NMR spectrum (eq 3).[26] A stack plot of this experiment is presented



(3)

in Figure 2B. One can clearly see the anticipated signals growing in with time. Figure 2A shows the same region of a spectrum of the nondeuterated derivative, $PhPd(PPh_3)_2I$ (**1z**), for comparison.

If this phosphonium cation intermediate were indeed involved in the aryl interchange reaction, one would expect to see the same effects of excess iodide and phosphine on the observed rate constants of phosphonium salt formation as one sees on the rate constants of aryl−aryl exchange. That the phosphonium salt formation would be facilitated by a predissociation of phosphine might seem contradictory since phosphine is consumed during this reaction. However, Yamamoto noted that the dimeric $[Pd(Ph)(I)(PPh_3)]_2$ with only one phosphine per palladium was more susceptible to the elimination of the phosphonium salt in methylene chloride than the monomeric *trans*-$[PdPhI(PPh_3)_2]$, suggesting that ligand dissociation may indeed play a role in the mechanism.[14d] Furthermore, there is ample literature precedent for the dependence of reductive elimination reactions upon ligand predissociation.[27] To test for this experimentally, the kinetics of phosphonium salt formation for complex **1i** were followed in THF-d_8 at 60 °C in the presence of various concentrations of added LiI, $LiPF_6$, and triphenylphosphine-d_{15} (kinetic plots can be found in the Supporting Information). The derived pseudo-first-order rate constants are listed in Table 1. The disappearance kinetics of **1i** appears to be first order in complex as were the kinetics for the aryl−aryl interchange. At the high phosphine concentrations required for pseudo-first-order conditions, the inhibitory effect

Table 1. Observed Rate Constants for the Disappearance of **1i** in the Presence of Varying Amounts of Added Phosphine, LiI, and $LiPF_6$

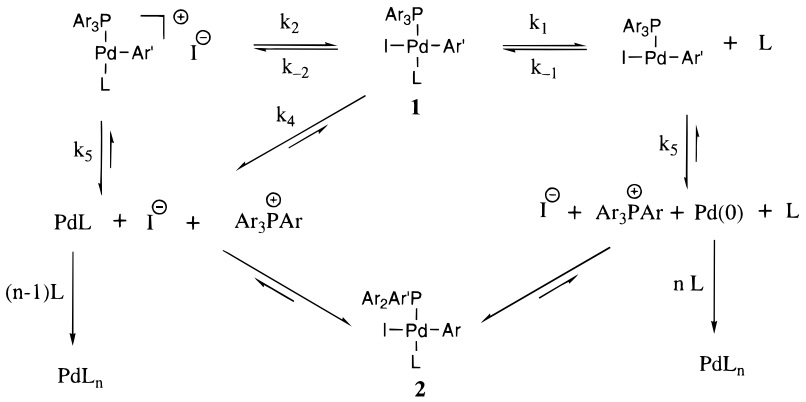
$[PPh_3$-$d_{15}]$	[LiI]	$[LiPF_6]$	k_{obs} ($\times 10^4$ s^{-1})
0.400	0.200	0	1.10 ± 0.02
0.300	0.200	0	1.11 ± 0.02
0.200	0.200	0	1.09 ± 0.02
0.100	0.200	0	1.34 ± 0.02
0.040	0.200	0	curvature
0.020	0.200	0	curvature
0.400	0.160	0.040	1.19 ± 0.02
0.400	0.120	0.080	1.08 ± 0.02
0.400	0.080	0.120	1.22 ± 0.02
0.400	0	0.200	1.48 ± 0.02

(25) Rybin, L. V.; Petrovskaya, E. A.; Rubinskaya, M. I.; Kuz'mina, L. G.; Struchkov, Yu. T.; Kaverin, V. V.; Koneva, N. Yu. *J. Organomet. Chem.* **1985**, *288*, 119.

(26) Norton and co-workers (ref 15) performed a similar experiment to rule out phosphonium salt intermediates in alkyl−aryl interchanges (*vide infra*).

(27) For example, see: (a) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1868. (b) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857. (c) Reference 18d.

Scheme 2. Proposed Mechanism for Aryl−Aryl Interchange and Phosphonium Salt Formation



appears to be saturated. Kinetics were also monitored with lower concentrations of added phosphine, and the effect was found to be much more pronounced. The curvature of the plots (due to the fact that the phosphine concentration was not constant during the course of the reaction), however, prevented accurate determination of the pseudo-first-order rate constants. The dependence of observed rate constant on flooded iodide concentration is not nearly as significant as it was for the aryl−aryl interchange. Rate constants with 0.2 M LiI and 0.04 M LiI/0.16 M $LiPF_6$ are essentially identical, and the constant for 0.2 M $LiPF_6$ is only marginally faster. This discrepancy may be due to the fact that different phosphines were used in the two different kinetics studies.

One unfortunate drawback to the use of the deuterated phosphine is that any aryl−aryl interchange that is occurring, possibly via a pathway that does not involve intermediate phosphonium salts, is masked since the growth of phenyl-d_5 fragments bound to palladium would not be visible by ^{1}H NMR. Furthermore, since it is only the disappearance of **1i** that is being measured, other first-order chemical phenomena may be present that would similarly not be visible in the observed kinetics. To investigate these possibilities, a THF solution 0.02 M in **1i** and 0.4 M in triphenylphosphine was monitored by ^{31}P NMR before and after submersion in a 50 °C bath for 10 h. The resonance at 22.6 ppm due to **1i** had diminished considerably after the thermal treatment to be replaced predominantly by a signal at 21.9 ppm assigned as (4-methoxyphenyl)triphenylphosphonium iodide by comparison with an authentic sample ($\delta = 22.0$ ppm). However, smaller (but not negligible) resonances at 23.2, 23.4, and 25.3 were also noticeable, indicating that other chemical pathways, possibly including aryl−aryl interchange, were occurring despite the presence of a large excess of triphenylphosphine. Because of this, the observed rate constants obtained reflect the sum of all first-order processes occurring, and consequently, quantitative absolute rate constant data again could not be obtained.

One aspect that is apparent from these kinetics experiments is that in addition to mechanistic pathways involving loss of ligand, there is another route, which does not involve predissociation, by which phosphonium salt formation (and presumably thereby aryl−aryl exchange) can occur. This latter pathway was masked in studies of the interchange reaction by the trapping of Pd(0) intermediates in the presence of excess phosphine. There is precedent for such multipathway behavior in similar stoichiometric reactions involving palladium(II)[28] and palladium(IV).[29]

With these results in mind, we can append the mechanism depicted in Scheme 1 to incorporate the reversible phosphonium salt formation reaction as well as the apparent trapping of the Pd(0) intermediates in the presence of excess phosphine. This new proposed mechanism is presented in Scheme 2. The exact nature of the extremely coordinatively unsaturated intermediates is uncertain, but with the presence of flooded phosphine and their apparent activity towards oxidative addition, their lifetime is almost certainly very short. Furthermore, such exposed palladium species with as few as one phosphine have been cited as intermediates in other reaction pathways,[30] and a number of palladium(0) compounds with only two phosphines for ligands have been isolated.[31] In addition, halides, as well as phosphines, are known to stabilize coordinatively unsaturated palladium(0)[32] and palladium(II)[33] complexes. Unfortunately, due to the presence of a non-zero k_4, plots of $\log(k_{obs})$ vs $\log([L])$ (or $\log[I^-]$) or $1/(k_{obs})$ vs [L] (or $[I^-]$) would not provide useful information. Similarly, due to the curvature in the kinetics plots for phosphine concentration less than 0.1 M and to the apparent insensitivity of k_{obs} on phosphine or iodide concentrations under less dilute conditions, plots of k_{obs} vs $1/[L]$ (or $1/[I^-]$) do not provide much meaning. Furthermore, with the apparent presence of additional first-order reactions, even k_4, the rate constant for when iodide and phosphine effects are both saturated, cannot be quantitatively determined. As a result, this mechanism cannot be proven beyond doubt from the data presented here, although it is consistent with the deuterated labeling experiment described earlier as well as the qualitative trends observed in the kinetics for both the aryl−aryl interchange and the disappearance of **1i** in the presence of excess phosphine.

(28) For example, see: (a) Reference 24. (b) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457. (c) Sustman, R.; Lau, J. *Chem. Ber.* **1986**, *119*, 2531.

(29) For example, see: (a) Byers, P. K.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D. *Organometallics* **1988**, *7*, 1363. (b) Aye, K.-T.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D.; Watson, A. A. *Organometallics* **1989**, *8*, 1518.

(30) (a) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (c) Grushin, V. V.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4035. (d) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.

(31) (a) van der Linde, R.; de Jongh, R. O. *J. Chem. Soc., Chem. Commun.* **1971**, 563. (b) Musco, A.; Kuran, W.; Silvani, A.; Anker, M. W. *J. Chem. Soc., Chem. Commun.* **1973**, 938. (c) Immirzi, A.; Musco, A. *J. Chem. Soc., Chem. Commun.* **1974**, 400. (d) Matsumoto, M.; Yoshioka, H.; Nakatsu, K.; Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1974**, *96*, 3322. (e) Mann, B. E.; Musco, A. *J. Chem. Soc. Dalton Trans.* **1975**, 1673. (f) Kuran, W.; Musco, A. *Inorg. Chim. Acta* **1975**, *12*, 187. (g) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134. (h) Urata, H.; Suzuki, H.; Yoshihiko, M.; Ikawa, T. *J. Organomet. Chem.* **1989**, *364*, 235. (i) ref. 32b. (j) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

(32) (a) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Organomet. Chem.* **1989**, *363*, C41. (c) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375. (d) Amatore, C.; Jutand, A.; Khalil, F.; Nielsen, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 7076. (e) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

(33) (a) Klabunde, K. J.; Low, J. Y. F. *J. Am. Chem. Soc.* **1974**, *96*, 7674. (b) Kavaliunas, A. V.; Taylor, A.; Reike, R. D. *Organometallics* **1983**, *2*, 377.

It is very interesting to note that the observations presented here are in stark contrast to those reported by Norton on the related alkyl−aryl interchange reaction (eq 1, R = alkyl).[15] This reaction was completely unaffected by the addition of excess phosphine. Furthermore, the authors were able to eliminate the possibility of phosphonium salt intermediates by monitoring the exchange of the perdeuterated complex, $Pd(P(C_6D_5)_3)_2CH_3I$, in the presence of methyltriphenylphosphonium triflate. The fact that no undeuterated phenyl groups were incorporated into the palladium phosphine complexes eliminated the possibility of phosphonium cation intermediates. This disparity would seem to suggest that, despite the apparent similarity of the two interchange reactions, they proceed *via* entirely different mechanisms. The novelty of this discrepancy can perhaps be mollified if one considers that, although the aryl−aryl interchange reaction has generated a lot of recent interest due to Kong and Cheng's report,[14a] the problem of P−C cleavage,[34−40] mediated by a variety of transition metals in both stoichiometric[34−39] and catalytic[34,40] reactions, is not a new one. In these examples, authors have provided evidence for P−C cleavage mechanisms involving oxidative addition of the P−C bond,[35f,h−j,l,o;37c;40a,c,e] *ortho*-metalation of the phosphorus-bound aryl group,[35p,38a,b] radicals,[35n] benzyne,[38c] and nucleophilic attack at phosphorus,[35b,d−e,k,39e] as well as the afore-mentioned reductive elimination to form intermediate phosphonium salts.[41] *ortho*-Metalation and benzyne intermediates can be ruled out for the aryl−aryl interchange since the *para* regiochemistry on the aryl groups is maintained throughout. Hartwig has found byproduct formation due to aryl−aryl interchange to be unaffected by the presence of radical traps, suggesting that radical mechanisms are not involved.[11f] The phosphonium salt formation does bear a striking resemblance to the cleavage of triphenylphosphine by $Pd(OAc)_2$ studied by Matsuda.[35b,d−e,k] However, this reaction is retarded by electron-donating groups on the phosphine (supporting the nucleophilic attack at phosphorus mechanism) while aryl−aryl interchange (*vide infra*) and phosphonium salt formation are facilitated by electron-donating groups on the phosphine.[23a] An additional aryl interchange pathway via oxidative addition to form Pd(IV) intermediates (as suggested by Kong and Cheng[14a]), however, cannot be ruled out. (Indeed, it is possible that the additional first-order processes indirectly observed by ^{31}P NMR as described above may be due to an alternative pathway for aryl−aryl interchange.) Considering that there is convincing evidence for the intermediacy of Pd(IV) species in the reductive elimination of $(alkyl)_2PdL_2$ compounds[42] and that there is also strong evidence against Pd(IV) intermediates in the reductive elimination of $RR'PdL_2$ (R,R′ = aryl, alkenyl) complexes,[43] it does not seem too unreasonable to suggest that aryl−aryl interchange may proceed predominately via a reductive elimination pathway involving predissociation of phosphine or iodide, while alkyl−aryl interchange may proceed via an oxidative addition pathway in which predissociation is not involved. This interesting disparity warrants further study.

Substituent effects of the aryl−aryl interchange reaction were investigated by monitoring 0.021 M solutions of complexes **1a**−**x** in $CDCl_3$ before and after exposure to ambient and then elevated temperatures for specified amounts of time. The results of this experiment are listed in Tables 2 and 3. For complexes of the same phosphine, it is clear that electron-donating groups on the palladium-bound aryl group accelerate the interchange reaction while electron-withdrawing groups appear to inhibit it completely. This agrees well with the trends observed by Migita on the substituent effects of phosphonium salt formation.[23a] Similarly, for complexes with the same palladium-bound aryl moiety, the exchange reaction is accelerated for complexes with phosphines having electron-donating groups relative to those having electron-withdrawing groups. Since a positive charge is formed on the reductively eliminated phosphonium species, a rate enhancement due to electron-donating substituents on the phosphine is not surprising. Unfortunately, the equilibrium effects are somewhat clouded by the competing decomposition reaction (particularly with electron-rich species), but Kong and Cheng found that electron-donating substituents on the palladium-bound aryl group drive the equilibrium to the right,[14a] and our work, as well as that of others,[14b−c,15,17c] corroborates this. One interesting comparison is with complexes **e**, **i**, and **m**; although **e** approaches equilibrium the fastest (due to its more electron-donating phosphine), the final equilibrium values of percent **2** for **i** and **m** are higher. We believe that this is due to the greater discrepancy between the electronics of the phosphine-bound aryl groups and those bound to the metal; the larger the difference between the free energies of **1** and **2**, the larger the value of K_{eq}. In this table, complex **q** had not been allowed to come to full equilibrium. Upon heating this sample for 24 h at

(34) For a review, see: Garrou, P. E. *Chem. Rev.* **1985**, *85*, 171.

(35) For examples of P−C cleavage in palladium compounds, see: (a) Coulson, R. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1530. (b) Kikukawa, K.; Yamane, T.; Takagi, M.; Matsuda, T. *J. Chem. Soc., Chem. Commun.* **1972**, 695. (c) Asano, R.; Moritani, I.; Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2910. (d) Yamane, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Tetrahedron* **1973**, *29*, 955. (e) Kawamura, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2021. (f) Kikukawa, K.; Yamane, T.; Ohbe, Y.; Takagi, M.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1187. (g) Kikukawa, K.; Takagi, M.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1493. (h) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981. (i) Nishiguchi, T.; Tanaka, K.; Fukuzumi, K. *J. Organomet. Chem.* **1980**, *193*, 37. (j) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. (k) Kikukawa, K.; Matsuda, T. *J. Organomet. Chem.* **1982**, *235*, 243. (l) Abatjoglou, A. G.; Bryant, D. R. *Organometallics* **1984**, *3*, 932. (m) Goel, A. B. *Tetrahedron Lett.* **1984**, *25*, 4599. (n) Goel, A. B. *Inorg. Chim. Acta* **1984**, *84*, L25. (o) Ortiz, J. V.; Havlas, Z.; Hoffman, R. *Helv. Chim. Acta* **1984**, *67*, 1. (p) Bumagin, N. A.; Bumagina, I. G.; Beletskaya, I. P. *Zh. Org. Khim.* **1984**, *20*, 457. (q) Reference 14.

(36) For examples of P-C cleavage in nickel compounds, see: (a) Green, M. L. H.; Simth, M. J.; Felkin, H.; Swierczewski, G. *J. Chem. Soc., Chem. Commun.* **1971**, 158. (b) Nakamura, A.; Otsuka, S. *Tetrahedron Lett.* **1974**, 463. (c) Reference 35f. (d) Reference 35l.

(37) For examples of P−C cleavage in cobalt compounds, see: (a) Reference 35f. (b) Reference 35l. (c) Sakatura, T.; Kobayashi, T.; Hayashi, T.; Kawabata, Y.; Tanaka, M.; Ogata, I. *J. Organomet. Chem.* **1984**, *267*, 171.

(38) For examples of P−C cleavage in osmium compounds, see: (a) Bradford, C. W.; Nyholm, R. S.; Gainsford, G. J.; Guss, J. M.; Ireland, P. R.; Mason, R. *J. Chem. Soc., Chem. Commun.* **1972**, 87. (b) Bradford, C. W.; Nyholm. R. S. *J. Chem. Soc., Dalton Trans.* **1973**, 529. (c) Deeming, A. J.; Kimber, R. E.; Underhill, M. *J. Chem. Soc., Dalton Trans.* **1973**, 2589. (d) Reference 35l.

(39) For examples of P−C cleavage in compounds of other metals, see: (a) Blickensderfer, J. R.; Kaesz, H. D. *J. Am. Chem. Soc.* **1975**, *97*, 2681. (b) Reference 35i. (c) Reference 37c. (d) Reference 35l. (e) Chakravarty, A. R.; Cotton, F. A. *Inorg. Chem.* **1985**, *24*, 3584.

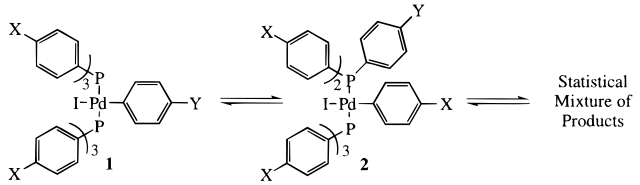
(40) For examples of phosphine-derived byproducts in catalytic reactions, see: (a) Fahey, D. R.; Mahan, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4499. (b) Mitchell, R. H.; Chaudhary, M.; Dingle, T. W.; Williams, R. V. *J. Am. Chem. Soc.* **1984**, *106*, 7776. (c) Dubois, R. A.; Garrou, P. E.; Lavin, K. D.; Allcock, H. R. *Organometallics* **1984**, *3*, 649. (d) Dubois, R. A.; Garrou, P. E.; Lavin, K. D.; Allcock, H. R. *Organometallics* **1986**, *5*, 460. (e) Dubois, R. A.; Garrou, P. E. *Organometallics* **1986**, *5*, 466. (f) Brenda, M.; Greiner, A.; Heitz, W. *Makromol. Chem.* **1990**, *191*, 1083. (g) Reference 17.

(41) (a) Reference 40b. (b) Pietrusiewicz, K. M.; Kuznikowski, M. *Phosphorus, Sulfur, and Silicon* **1993**, *77*, 57. (c) Reference 14c. (d) Reference 14d.

(42) (a) Stille, J. L.; Lau, K. S. Y. *J. Am. Chem. Soc.* **1976**, *98*, 5841. (b) Reference 35h. (c) Reference 35j. (d) Moravskiy, A.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4182. (e) Loar, M. K.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4174. (f) Kurosawa, H.; Emoto, M.; Urabe, A. *J. Chem. Soc., Chem. Commun.* **1984**, 968. (g) Kurosawa, H.; Emoto, M.; Kawasaki, Y. *J. Organomet. Chem.* **1988**, *346*, 137.

(43) (a) Reference 35p. (b) Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1986**, *5*, 2144. (c) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (d) Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* **1989**, *8*, 180. (e) Reference 16b.

Table 2. Substituent Effects of Aryl−Aryl Interchange



			2[a] (%)			
	X	Y	1.5 h, 25 °C	8 h, 25 °C	1 h, 50 °C	3 h, 50 °C
a	OCH_3	CH_3	20	50	71	66
b	OCH_3	H	2	6	28	31
c	OCH_3	F	2	3	12	21
d	OCH_3	CF_3	0	0	0	0
e	CH_3	OCH_3	41	82	93	93
f	CH_3	H	trace	6	31	59
g	CH_3	F	NA[b]	NA[b]	NA[b]	NA[b]
h	CH_3	CF_3	0	0	0	0
i	H	OCH_3	13	52	99	100
j	H	CH_3	6	22	64	95
k	H	F	0	trace	5	13
l	H	CF_3	0	0	0	0
m	F	OCH_3	5	13	64	96
n	F	CH_3	0	8	22	56
o	F	H	trace	trace	2	6
p	F	CF_3	0	0	0	0
q	CF_3	OCH_3	trace	7	27	69
r	CF_3	CH_3	0	trace	6	13
s	CF_3	H	0	trace	4	7
t	CF_3	F	0	trace	3	8

[a] {[**2**]/([**1**] + [**2**])} × 100. **1** refers to complex, regardless of phosphine, where aryl interchange has not yet occurred; **2** refers to complex, regardless of phosphine, where exchange has occurred. [b] Resonances overlapped.

Table 3. Substituent Effects for Aryl−Aryl Interchange

$ArPdL_2I$ ⟷ $Ar'PdLL'I$

1 **2**

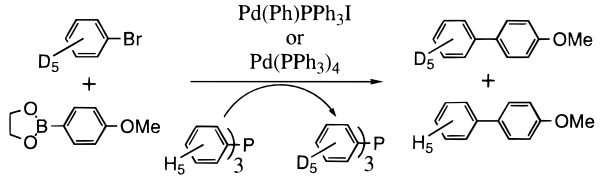
			2[a] (%)			
	Ar	L	1.5 h, 25 °C	8 h, 25 °C	1 h, 50 °C	3 h, 50 °C
u	*p*-tolyl	DPPP	0	0	8	15
v	*p*-tolyl	$EtPPh_2$	0	0	5	20
j	*p*-tolyl	PPh_3	6	22	64	95
w	*o*-tolyl	PPh_3	0	0	0	trace
i	*p*-anisyl	PPh_3	13	52	99	100
x	*o*-anisyl	PPh_3	0	trace	11	19

[a] {[**2**]/([**1**] + [**2**])} × 100. **1** refers to complex, regardless of phosphine, where aryl interchange has not yet occurred; **2** refers to complex, regardless of phosphine, where exchange has occurred. Observations made at 0.021 M in $CDCl_3$.

50 °C, it too had been completely converted to **2**. Comparison of complexes **u** and **v** indicate that chelating ligands have little effect on the interchange reaction. However, the drastic contrast of the results for **j** with **w** and **i** with **x** suggest that *ortho* substituents on the metal-bound aryl group have a strong retardation effect on aryl−aryl exchange. This also agrees with the results of others for both the interchange[14b] and phosphonium salt formation reactions.[23a]

In benzene-d_6, resonances for **1m** and **2m** overlapped. In chlorinated solvents, the competing decomposition prevented the determination of observed rate constants for aryl−aryl exchange. In DMSO-d_6, the exchange was complete in the time it took to shim the NMR and start the automated acquisition program (*ca.* 5 min). However, qualitatively, it appears that the interchange is accelerated by more polar solvents. This trend would support the formation of a charged intermediate in the rate-determining step of the reaction. Polar solvents would also facilitate the iodide-loss pathway since the charged intermediates formed would be stabilized.

Scheme 3. Aryl−Aryl Interchange under Catalytic Conditions



Time-Course Experiments. To evaluate the impact of aryl interchange on both catalysis and polymerization, organic emulsion cross-couplings in conjunction with deuterium labeling and GC−MS analysis yielded time-course data on both cross-coupling and aryl interchange. It is worth noting that the concentration regimes of the kinetics experiments described earlier and the catalytic procedures presented here are drastically different. With this in mind, slight deviations in the results obtained from the two types of experiments are to be expected.[44]

Kong and Cheng used deuterium labeling to confirm that multiple aryl interchanges can occur on a single phosphorus center under stoichiometric conditions, apparently due to rapid intermolecular exchange of phosphines between $ArPdL_2I$ complexes.[14a] The simplest modification of this approach to studying catalytic cross-couplings is outlined in Scheme 3. Bromobenzene-d_5 was used to introduce phenyl-d_5 fragments into the cross-coupling reaction manifold. The fate of these fragments could be determined semi-quantitatively by GC−MS analysis. Catalysts based on nondeuterated phosphines were employed; the evolution of the aryl component of these phosphines could be compared with the incorporation of phosphine-derived [$^1H_5$]phenyl fragments in the 4-methoxybiphenyl cross-coupling byproduct. Results of these studies are compiled in Table 4. Relatively high loadings (1.0 mol %) of catalyst precursors were used to obtain useful signal intensities from the MS detector. Under these conditions, aryl interchange was extensive for $ArPdL_2I$ complexes and less severe for $Pd(PPh_3)_4$ (compare entries 1−2 and 3−5) when bromobenzene-d_5 was the substrate. Different samples of $Pd(PPh_3)_4$ gave different results. Material stored for some months at −30 °C in a drybox underwent significantly greater interchange than a freshly recrystallized sample. These materials were identical by visual inspection and ^1H, ^{13}C, and ^{31}P NMR and possessed very similar catalytic behaviors. This discrepancy remains unexplained.

Quantitation of all phosphines allowed a determination of the exchanged fraction of the initial complement of phosphine-bound aryls. Observed distributions of exchanged phosphines measured using this method could be compared with probabilistic distributions. In general, a set of *n* nonordered independent events with binary outcomes (i.e., heads/tails, true/false, interchange/no interchange, etc.) has $n + 1$ possible outcomes. If the individual events are truly independent, then the most probable distribution of outcomes for a large ensemble of sets of events is given by the binomial frequency function ($B(x)$) (eq 4), where *n* represents the number of independent trials in

$$B(x) = \frac{n!}{x!(n-x)!} p^x(1-p)^{n-x} \qquad (4)$$

a set, *x* represents the number of positive outcomes, and *p* represents the relative frequency of success (i.e., the statistical bias in the ratio of yes:no answers for an individual event).[45]

(44) For a discussion on possible mechanistic differences between catalytic and stoichiometric cross-coupling reactions, see ref 34e.

Table 4. Aryl Exchange During Cross-Coupling[a]

					final composition of triphenylphosphines[c]			
entry	$[C_6D_5Br]$ (mM)	cat.	temp, °C	final exch[b]	d_0	d_5	d_{10}	d_{15}
1	75	10	50	52	7.1 (11.0)	38.9 (35.9)	43.6 (38.9)	10.4 (14.1)
2	75	10	65	65	3.6 (4.2)	24.3 (23.9)	44.7 (44.4)	27.5 (27.5)
3	75	PdL_4[d]	50	23.4	44.0 (44.9)	42.5 (41.2)	12.8 (12.6)	0.8 (1.3)
4	37.5	PdL_4[e]	50	12.0	67.2 (68.0)	29.4 (29.0)	3.4 (3.8	0 (0.2)
5	75	PdL_4[e]	65	5.3	84.0 (84.8)	16.0 (14.6)	0 (0.8)	0 (0)

[a] All reactions went to 95% completion or better, as determined by GC−MS. [b] Percent of all phosphine-bound [$^1H_5$]phenyl moeities replaced by phenyl-d_5 moieties as determined by GC−MS. Values are the average of several measurements. (See the Experimental Section.) [c] Expressed as percentage of total composition. Values in parentheses are expected distributions calculated from the measured percent exchange. [d] L = PPh_3. [e] Results obtained using freshly recrystallized $Pd(PPh_3)_4$.

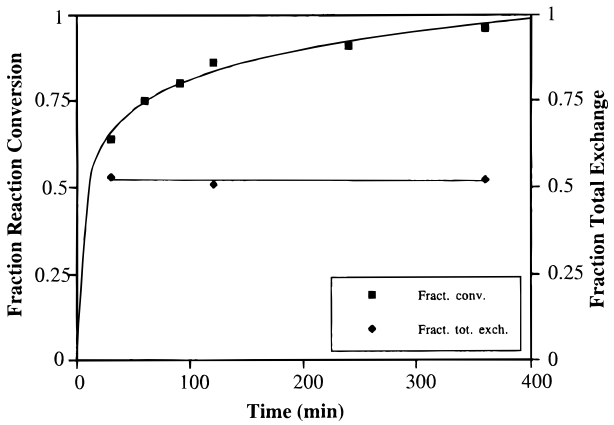


Figure 3. Cross-coupling and aryl interchange in the presence of tris(dibenzylideneacetone)dipalladium(0) at 50 °C (Table 4, entry 1).

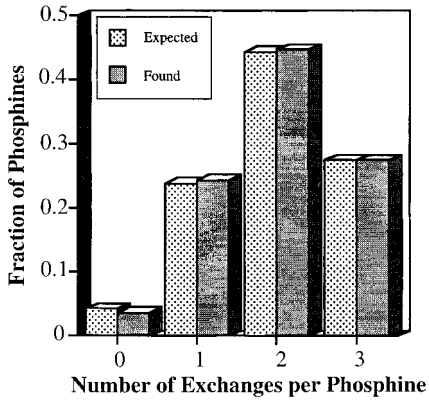


Figure 4. Phosphine distributions for 65% exchange (tris(dibenzylideneacetone)dipalladium(0) at 65 °C, entry 2 in Table 4).

Experimentally measured distributions allowed us to determine the fraction of all phosphine-bound aryl rings interchanged. Predicted distributions for independent exchange processes could then be determined using eq 4 with $n = 3$ (the maximum number of exchanges per phosphine), $x = 0-3$ (the actual number of exchanges per phosphine), and p equal to the experimentally measured fraction of all aryl rings interchanged. Experimental and predicted distributions were generally in excellent agreement. This result provides further evidence of reversibility in the interchange process, since it indicates that interchange of any given aryl moiety bound to a phosphine is statistically independent of any other interchange on the same phosphine.[46] Aryl rings can thus be expected to continue to interchange in catalytic reactions until the equilibration pathway is deactivated by catalyst decomposition, other side reactions that consume phosphines, or completion of the reaction.

Time-course experiments revealed remarkable differences in the behavior of cross-couplings with the two catalyst precursors. In the presence of the $ArPdL_2I$ precursor, cross-coupling occurs very rapidly in early portions of the reaction; the conversion then tapers off. All aryl interchange occurs during the initial burst of catalytic activity; the phosphines become completely decoupled from the interchange process following this initial burst (Figure 3). Nevertheless, the aryl interchange process remains statistically well-behaved (Figure 4). This behavior strongly suggests a change in catalytic mechanism whose specifics require further investigation. The suppression of aryl interchange with concurrent decrease in catalytic activity suggests either that an excess of phosphine relative to homogeneous palladium centers is generated (i.e., through decomposition of the catalyst) or that phosphines are decoupled not only from aryl interchange but from any homogeneous catalytic process. In the latter case, the catalytically active species may be a "poisoned" ligandless colloid analogous to Lindlar's catalyst. Since phosphines are known to produce homogeneous complexes by reacting with supported heterogeneous palladium,[47] the second possibility appears to be the more distant one.

In the presence of $Pd(PPh_3)_4$, cross-coupling occurs in an almost linear manner and aryl interchange is largely suppressed during the initial 75% conversion. As the reaction nears completion, aryl interchange becomes more competitive. One possible explanation is that this behavior is due to the competing phosphonium salt formation. Early in the reaction, the excess phosphine suppresses transfer (*vide supra*) and inhibits cross-coupling relative to the $ArPdL_2I$ species.[48c] However, as the reaction progresses and the excess phosphine is consumed, the catalyst gradually becomes more active (giving rise to the zero-order-like behavior) and the aryl−aryl interchange is allowed to proceed. The evolution of the phosphine distribution can be monitored throughout the reaction; experimental distributions closely mirror the most probable distribution in all cases (Figure 5).

Screening of Possible Strategies for the Elimination of the Aryl-Aryl Interchange Reaction in Palladium-Mediated Cross-Couplings. Given the information gained from the above mechanistic studies, the simplest method to eliminate the aryl−aryl interchange reaction from palladium-mediated cross-couplings would be to eliminate phosphine ligands altogether from the cross-coupling reactions. In an earlier paper,[48c] we

(45) Sokolnikoff, I. S.; Redheffer, R. M. *Mathematics of Physics and Modern Engineering*, 2nd ed.; McGraw-Hill: New York, 1966; pp 617−620.

(46) This argument holds only for electronically and sterically equivalent interchanges. It also assumes that deuterium isotope effects for the interchange of phenyl-d_5 and [$^1H_5$]phenyl rings are negligible. A negligible isotope effect is in fact expected due to the at least two-bond separation between the reaction center and a perturbing isotope, as well as the geometry of the aryl ring, and is strongly confirmed by the fidelity of the experimental interchange distributions to the predicted distributions. For a discussion of secondary isotope effects, see: Carpenter, B. K., *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984; pp 96−100.

(47) De la Rosa, J. M. A.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059.

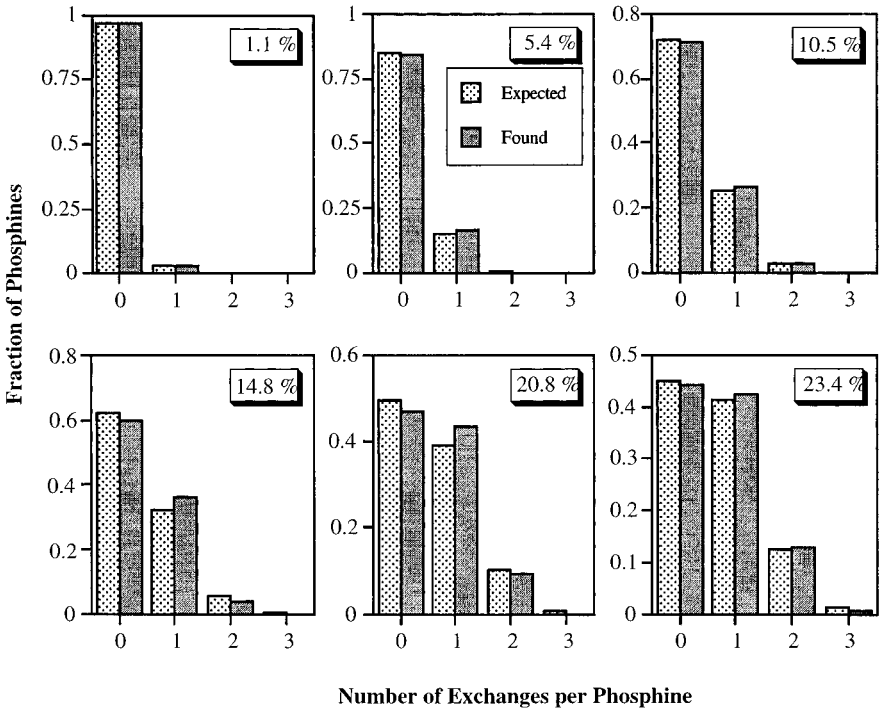


Figure 5. Evolution of phosphine distribution in cross-coupling reactions ($Pd(PPh_3)_4$ at 50 °C; Table 4, entry 3). Boxed numbers indicate total percent exchange.

expanded upon the work of Beletskaya[48b] and showed that simple palladium precursors such as palladium(II) acetate, tris(dibenzylideneacetone)dipalladium(0), and allylpalladium(II) chloride dimer are effective catalysts for the Suzuki coupling reaction with acetone as the organic solvent, *without* the addition of phosphines or other ligands. For most small-molecule applications, we believe that this is the best way to eliminate the formation of undesired side products caused by the incorporation of the ligands into the coupling cycle. However, in the case of our poly(*p*-phenylene) polymerizations, this system was not compatible due to the insolubility of the polymers in the acetone/water solvent medium. Furthermore, for cross-coupling reactions with other organometallic reagents, this medium may not be compatible due to reactivity concerns. Due to these factors, we sought alternative strategies to eliminate the aryl−aryl exchange.

Unfortunately, deviation from the acetone/water solvent system led to almost universal failure. In general, the use of more polar solvents led to more improved results, but the failure of DMSO to promote quantitative coupling suggests that this generalization is not universal. With the failed reactions, a substantial amount of coupling did occur (generally 80% or better), but as condensation polymerizations require quantitative conversion to produce polymers of adequate molecular weight, the results obtained from the "ligandless" systems were unacceptable for our poly(*p*-phenylene) polymerizations.

The next logical strategy was to use non-phosphine-based ligands under typical Suzuki coupling conditions. For example, Elsevier has had excellent success in utilizing acenaphthoquinone-based bidentate imine ligands[49] in palladium-mediated cross-couplings between aryl or benzyl halides and organotin or organomagnesium reagents.[50] Other possibilities were to use phosphite ligands (e.g., triphenyl phosphite), or trialkylphosphines (e.g., tricyclohexylphosphine) under the rationale that, since the alkyl−aryl exchange was found to be irreversible,[15] there should be no migration of alkyl groups from the phosphines to the palladium center under catalytic conditions. In addition to employing the above three ligands, pyridine, 2,2′-bipyridine, triphenylarsine, and 1,2,5-triazaphosphaadamantane were also examined. With the exception of triphenylarsine, which unfortunately is also known to undergo the aryl−aryl interchange reaction in palladium complexes,[14c,15] none of these ligand systems promoted the Suzuki coupling reaction to quantitative conversion.

As increased steric bulk was found to inhibit both the aryl−aryl interchange reaction (*vide supra*) and the phosphonium salt formation reaction,[23] the use of bulky triarylphosphines should minimize the occurrence of these side reactions under catalytic conditions. Indeed, tris(*o*-methoxyphenyl)phosphine has seen use in suppressing byproduct formation in Stille couplings,[14a] and tris(*o*-tolyl)phosphine has been shown to inhibit phosphonium salt formation[8d] and aryl−aryl exchange in Heck and Suzuki couplings.[14c,d] Products derived from the exchange reaction are indeed significantly reduced but not eliminated.[51] Exchange percentages of 0.194 ± 0.023 and 1.80 ± 0.32% were measured using the bulky tris(*o*-methoxyphenyl)phosphine and tris(*o*-tolyl)phosphine ligands, respectively. However, further increase of the steric bulk on the phosphine (i.e., tris(2-trifluorophenyl)phosphine, tris(2,6-dimethylphenyl)phosphine, and tris(2,6-dimethoxyphenyl)phosphine) resulted in the deactivation of the catalyst as evidenced by incomplete conversion of starting materials.

With these results in consideration, the tris(*o*-tolyl)phosphine catalyst system appears to be optimal for minimizing the aryl−aryl interchange during palladium-mediated cross-coupling reactions. We then undertook additional experiments to try and optimize the system further. As can be seen in Table 5, for

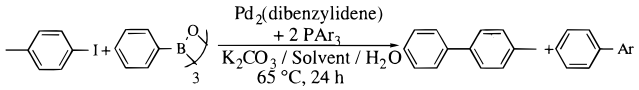
(48) (a) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1977**, *125*, 281. (b) Beletskaya, I. P. *J. Organomet. Chem.* **1982**, *250*, 551 and references therein. (c) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.

(49) van Asselt, R.; Elsevier, C. J.; Smeets, W. J. J.; Spek, A. L.; Benedix, R. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 88.

(50) (a) van Asselt, R.; Elsevier, C. J. *Organometallics* **1992**, *11*, 1999. (b) van Asselt, R.; Elsevier, C. J. *Organometallics* **1994**, *13*, 1972. (c) van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323.

(51) Heitz *et al.* also found a trace amount of tris(*o*-tolyl)phosphine-derived byproducts when this ligand was used in Heck couplings: ref 40f.

Table 5. Analytical Experiments for the Optimization of Conditions for Suzuki Coupling Reactions



Ar	solvent	% cat.	% exch[a]	% possible exch[b]
C_6D_5	THF	0.2	1.10 ± 0.12	91.7 ± 10.0
C_6D_5	THF	0.5	2.76 ± 0.13	92.0 ± 4.3
C_6D_5	THF	1.0	4.94 ± 0.05	82.3 ± 0.8
C_6D_5	THF	2.0	10.57 ± 0.29	88.1 ± 2.3
C_6D_5	THF	5.0	16.76 ± 0.49	55.9 ± 1.7
2-MePh	THF	0.2	0.340 ± 0.035	28.3 ± 2.9
2-MePh	THF	0.5	0.218 ± 0.024	7.27 ± 0.80
2-MePh	THF	1.0	0.311 ± 0.048	5.18 ± 0.80
2-MePh	THF	2.0	0.124 ± 0.034	1.03 ± 0.28
2-MePh	THF	5.0	0.194 ± 0.023	0.647 ± 0.077
2-MePh	CH_2Cl_2	0.2	0.0061 ± 0.0014	0.51 ± 0.12
2-MePh	CH_2Cl_2	0.5	0.00281 ± 0.00014	0.094 ± 0.005
2-MePh	CH_2Cl_2	1.0	0.0081 ± 0.0010	0.14 ± 0.02
2-MePh	CH_2Cl_2	2.0	0.01066 ± 0.00029	0.0889 ± 0.0025
2-MePh	CH_2Cl_2	5.0	0.0276 ± 0.0012	0.092 ± 0.004

[a] (Amount of phosphine-derived biphenyl divided by the total amount of biphenyl) × 100 as determined by GC−MS. [b] (% exchange found divided by theoretical % exchange if all phosphine-bound aryl groups were incorporated into the coupling cycle) × 100. Values given are the average of five trials. The listed errors are the standard deviations for those trials.

couplings carried out in THF, reactions utilizing the tris(*o*-tolyl)-phosphine ligand resulted in the formation of much smaller amounts of phosphine-derived byproducts as compared to those utilizing triphenylphosphine-d_{15}. (The deuterated phosphine was employed to distinguish between biphenyl derived from the phosphine and biphenyl derived from homocoupling of phenylboronic acid, an unrelated side reaction ubiquitous in palladium-mediated cross-couplings.[52]) This difference, however, is less pronounced for the trials utilizing smaller amounts of catalyst (which are more typical conditions for actual synthetic reactions). Byproduct formation can be suppressed further by switching to a less hydrophilic solvent such as methylene chloride. We believe that this is due to a difference in polarity. Although pure methylene chloride has a higher dielectric constant than pure THF, the latter is more water-miscible. Consequently, more water is able to partition into the organic phase of the emulsion, resulting in a more polar environment which is favorable for the aryl−aryl interchange. The optimal conditions appear to be with 0.5% catalyst, tris(*o*-tolyl)-phosphine, and methylene chloride as solvent, resulting in a product that was contaminated by only 0.003% of the phosphine-derived 2-methylbiphenyl byproduct. It is interesting to note that attempts at performing the triphenylphosphine-d_{15} trials in CH_2Cl_2 resulted in incomplete conversions. This was likely due to the decomposition (*via* phosphonium salts) of $ArPdL_2I$ intermediates in chlorinated solvents that was observed earlier. The effect of catalyst concentration on the amount of byproduct formed seems to be a compromise between two competing factors. Larger amounts of catalyst require larger amounts of phosphine, which can in turn supply larger amounts of aryl groups available for the interchange reaction. However, larger amounts of catalyst also lead to faster rates of cross-coupling. As a result, there is less time for the interchange reaction to take place. This effect is evident in the general trend (most visible in the triphenylphosphine-d_{15} entries) that the ratio of percent observed transfer to percent possible transfer decreases with increased amount of catalyst.

In the experiments presented in this section, the catalyst was formed *in situ* by adding 2 equiv of ligand to tris(dibenzylideneacetone)dipalladium(0). Although not apparent from the experiments performed here, some polymerization results that will be presented elsewhere[53] suggest that the dibenzylideneacetone released from the *in situ* catalyst formation may be involved with the catalytic cycle as well. To eliminate this possibility, we suggest the use of bis[tris(*o*-tolyl)phosphine]-palladium(0)[30b,31j] as a catalyst for cross-coupling reactions when the "ligandless" methodology[48] is not suitable. Control experiments analogous to those presented in Table 4 showed comparable results for this catalyst as for that generated *in situ* from tris(dibenzylideneacetone)dipalladium(0) and tris(*o*-tolyl)phosphine.

Conclusions

To summarize, evidence presented in this paper supports the suggestion of Chenard[14c] and Yamamoto[14d] that, unlike the documented alkyl−aryl exchange reaction,[15] the aryl−aryl interchange reaction of $ArPdL_2X$ proceeds first through a reductive elimination to form a phosphonium salt followed by an oxidative addition of a different phosphorusn-carbon bond. The interchange and phosphonium salt formation reactions alike are at least facilitated by predissociation of either phosphine or iodide. Furthermore, like the phosphonium salt reaction,[23] the aryl−aryl interchange is promoted by more polar solvents and inhibited by increased steric bulk. Under catalytic conditions, the distribution of phosphines formed from the aryl−aryl interchange can be modeled by statistics. For most synthetic applications, probably the best strategy to eliminate phosphine-derived byproducts is to use the "ligandless" methodology described elsewhere.[48] However, if this protocol is unsuitable due to reasons of insolubility, reactivity, etc., we suggest the use of bis[tris(*o*-tolyl)phosphine]palladium(0)[30b,31j] as a catalyst and a nonhydrophilic organic solvent such as CH_2Cl_2 to minimize the effects of the aryl−aryl interchange reaction.

Experimental Section

General Procedure. Schlenk-line or drybox techniques were used for all air-sensitive manipulations. ^{1}H NMR spectra were acquired at 200, 300, 400, or 500 MHz using Bruker AC-series, AM-series, MSL series, and AMX-series spectrometers; proton-decoupled ^{13}C, ^{19}F, and ^{31}P spectra were obtained at corresponding frequencies. ^{1}H and ^{13}C chemical shifts are reported relative to internal TMS; ^{31}P chemical shifts are reported relative to an external standard of triphenyl phosphite (δ = 127.0 ppm); ^{19}F chemical shifts are reported relative to an external standard of fluorobenzene (δ = −113.1 ppm). THF, toluene, and hexanes were purified by distillation from sodium/benzophenone and used immediately. CH_2Cl_2, $CDCl_3$, tetrachloroethane, tetrachloroethane-d_2, and dibromomethane were dried over CaH_2 and vacuum-transferred prior to use. THF-d_8 and benzene-d_6 were vacuum-transferred from a sodium/benzophenone ketyl. Triphenylarsine, triphenylphosphine, and triphenylphosphine-d_{15} were purchased from Aldrich, recrystallized from degassed ethanol, and sublimed under vacuum proir to use. Authentic samples of 4-methylbiphenyl, 2-methylbiphenyl, and 2-methoxybiphenyl were obtained from Aldrich and sublimed or distilled prior to use, as were the aryl halides and trioxane. Lithium trifluoromethanesulfonate was purchased from Aldrich and dried for 48 h under vacuum at 100 °C. The benzene adduct of tris(dibenzylideneacetone)di-

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palladium(0),[54] tetrakis(triphenylphosphine)palladium(0),[55] phenylboric anhydride,[48c] 2-(4′-methoxyphenyl)-1,4,3-dioxaborolane,[56] tris(2,6-dimethylphenyl)phosphine,[57] tris[2-(trifluoromethyl)phenyl]phosphine,[58] and bis(*p*-tolylimino)acenaphthene[49] were all prepared via literature procedures. Other chemcals were used as received from commercial suppliers. The preparation of $ArPdL_2I$ complexes except **1y**,**z** is reported elsewhere.[21] FAB Mass spectra were performed by the U.C. Berkeley Mass Spectrometry Laboratory. Analytical data were obtained by the elemental analysis facilities at the University of California at Berkeley and the University of Massachusetts at Amherst. GC−MS measurements were performed on either a Hewlett-Packard 5890A gas chromatograph in line with a 5970 Series mass-selective detector or a Hewlett-Packard 5890 Series II gas chromatograph in line with a 5972 Series mass-selective detector. In either case, the instrument was equipped with a polysiloxane capillary column and helium was used as the carrier gas.

(Phenyl-d_5)Pd[P(C_6D_5)$_3$]$_2$I (1y). A procedure exactly analogous to the syntheses of **1a**−**x**[21] was followed to give **1y** in 82% yield as a pale greenish-yellow powder: IR (neat) 2956 (w), 2856 (w), 1528 (m), 1308 (s), 1046 (m), 1006 (w), 956 (w), 835 (s); ^{13}C NMR (75 MHz, $CDCl_3$) no identifiable resonances due to multiple coupling with deuterium and phosphorus atoms; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.0. Anal. Calcd for $C_{42}D_{35}IP_2Pd$ (assuming 98% D from iodobenzene-d_5, 99% D from triphenylphosphine-d_{15}): C, 58.30; D, 8.05. Found: C, 58.49; D, 8.06.

(Phenyl)Pd[P(C_6H_5)$_3$]$_2$I (1z).[59] A procedure exactly analogous to the syntheses of **1a**−**x**[21] was followed to give **1z** in 85% yield as a pale greenish-yellow powder: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.20 (t, J = 7.0 Hz, 2H), 6.32 (tm, J_t = 7.0 Hz, 1H), 6.59 (dm, J_d = 6.7 Hz, 2H), 7.17−7.35 (m, multiple resonances, 18H), 7.49 (m, 12H) [lit.[34d] (250 MHz, $CDCl_3$) δ 6.25 (d, J = 7.5 Hz, 2H), 6.36 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 7.5 Hz, 2H), 7.3 (m, 18H), 7.54 (m, 12H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.2 (apparent t, J_{app} = 22.5 Hz), 129.1 (apparent t, J_{app} = 22.0 Hz), 132.0 (apparent t, J_{app} = 22.0), 134.4 (apparent t, J_{app} = 19.9 Hz), other resonances not resolved; ^{31}P NMR (202 MHz, 4:1 CH_2Cl_2:$CDCl_3$) δ 22.2 [lit.[24] (solvent and field strength not listed) δ 22.8].

2,3,4,5-Pentadeuteriobiphenyl. This compound was synthesized by following a known protocol.[48c] A 100 mL Schlenk flask was charged with 1.93 g (11.9 mmol) of bromobenzene-d_5, 1.36 g (13.1 mmol as phenylboric acid) of phenylboronic anhydride, 4.91 g (29.7 mmol) of potassium carbonate sesquihydrate, 25 mL of acetone, 25 mL of HPLC grade water, and a stirbar. This mixture was then degassed via several freeze−pump−thaw cycles, and 0.185 mL (2.39 μmol, 0.02%) of a 0.0129 M (in Pd) solution of **9** was added via syringe. The flask was degassed once more and then heated in a 50 °C bath overnight. The reaction started out as a tan, biphasic mixture and finished as an off-white, triphasic suspension. The reaction was transferred to a separatory funnel, and the water phase was isolated, and washed with 3 × 50 mL of ether. The organic layers were combined and dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to give an orange, greasy solid. This was repeatedly recrystallized from acetone/water until colorless and then sublimed at 50 °C, dynamic 5 mTorr vacuum, to give large, flaky, white crystals of 2,3,4,5-pentadeuteriobiphenyl: 1.53 g (9.62 mmol) recovered, 80.7% yield: mp 69−71 °C (acetone/H_2O) (lit.[60] mp 63−66 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27−7.45 (m, multiple resoncances, 3H), 7.57 (dm, J_d = 6.8 Hz, 2H); MS (*m*/*z*) 159.

Kinetics Experiments for Aryl−Aryl Exchange. (a) Concentration Profile. In a glovebox, 36.0 mg (37.0 μmol), 72.0 mg (74.0 μmol), 144.0 mg (0.1480 mmol), and 288.0 mg (0.2960 mmol) samples of **1m** were weighed into four separate 2 mL volumetric flasks on which the 1.80 mL level (calibrated by weight of toluene) had been marked. These were each dissolved in 1 mL of dry THF-d_8 prechilled to −40 °C and diluted to the 1.80 mL mark, yielding stock solutions of 0.0206, 0.0411, 0.0822, and 0.164 M in concentration. Aliquots (600 μL) of these solutions were then filtered through 0.2 μm syringe filters into 5 mm NMR tubes which were then capped with septa and removed from the glovebox. Dibromomethane (1 μL) was then added to each sample, and the tubes were degassed via three freeze−pump−thaw cycles (or until completely degassed) and sealed under vacuum. The tubes were stored at −40 °C prior to the kinetics experiments.

Kinetics were observed via ^{1}H NMR at 400 MHz on a Bruker AM-400 spectrometer. The temperature of the probe was maintained at 50.0 ± 0.5 °C calibrated with 100% ethylene glycol and monitored with an internal thermocouple. Single scans were then taken at a 90° pulse approximately every 5−6 min. The exact time was monitored via stopwatch. The aryl−aryl exchange reaction was monitored by the decrease of the palladium-bound aryl signals of **1m** and the growth of the corresponding signals for **2m**, integrated relative to the dibromomethane standard. The results were fit to an exponential function via least-squares analysis with Igor, a curve-fitting program for the Apple Macintosh computer. This analysis yielded observed rate constants (k_{obs}) that were equal to the sum of the rate constants for the forward (k_F) and reverse (k_R) exchange reactions.[22] Alternatively, plots of $\ln[(C - C_{inf})/(C_0 - C_{inf})]$ vs time (where C, C_{inf}, and C_0 correspond to integrations ant time = t, infinity, and 0, respectively) yielded straight lines with slopes of k_{obs}. Experimental errors were estimated from the least-squares analyses. The observed rate constant values thus determined were (7.57 ± 0.09) × 10^{-4}, (7.60 ± 0.17) × 10^{-4}, (7.30 ± 0.09) × 10^{-4}, and (7.08 ± 0.09) × 10^{-4} s^{-1} for initial concentrations of **1m** of 0.164, 0.082, 0.041, and 0.021 M, respectively.

(b) Phosphine Inhibition Experiment. In a glovebox, 0.0411, 0.004 11, and 0.008 22 M stock solutions of tris(*p*-fluorophenyl)-phosphine in dry, degassed $CDCl_3$ were prepared in 2.00 mL volumetric flasks. These solutions were chilled to −40 °C, while samples of 72.0 mg (74.0 μmol) of **1m** were weighed into four new vials. Three of these samples were dissolved in 1.80 mL of the respective phosphine stock solutions, while the fourth was dissolved in 1.80 mL of neat $CDCl_3$. In this manner, sample solutions of approximately 0.0411 M in **1m** with 1, 0.2, 0.1, and 0 equiv of added phosphine were obtained. Aliquots (600 μL) of these solutions were then filtered through 0.2 μm syringe filters into 5 mm NMR tubes which were then capped with septa and removed from the glovebox. Tetrachlorethane (1 μL) was added via syringe to each tube, and the samples were sealed as before and stored at −40 °C prior to the kinetics experiments. Kinetics were observed via ^{1}H NMR at 400 MHz on a Bruker AM-400 spectrometer at 60.0 ± 0.5 °C by following the procedure described above. The samples with added phosphine showed a marked inhibition in rate (see Figure 1), but due to the complexity of the kinetics observed, no meaningful rate constants could be derived.

An identical experiment was attempted with 0.4 equiv of added phosphine in THF-d_8. Again, a marked inhibition was observed, but the kinetics were too complex to derive meaningful rate constant data. Also, a small amount white precipitate formed during the kinetics run. Upon analysis by ^{1}H, ^{19}F, and ^{31}P NMR, as well as FAB mass spectrometry, this material was found to be an approximately 4:1 mixture of two major products, as well as a trace of a third, that were not separated. Major product (**3**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.28 (td, J_t = 7.0 Hz, J_d = 2.4 Hz, 2h), 7.47 (m, 6H), 7.62 (dd, J_d = 10.0 Hz, J_d = 7.1 Hz, 2 H), 7.76 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −98.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.2; MS (*m*/*z*) 423. Second product (**4**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J_d = 9.9 Hz, J_d = 7.1 Hz, 2H), 7.71 (m, 2H), three additional resonances not resolved; ^{19}F NMR (376 MHz, $CDCl_3$) δ −99.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.9; MS (*m*/*z*) 435. Third product (**5**): MS(*m*/*z*) 411.

(c) Iodide Inhibition Experiment. In a drybox, 0.206 M stock solutions of LiI and $LiPF_6$ in dry THF-d_8 were prepared in 2.00 mL volumetric flasks. To each of these was added 1 mg of trioxane, and the resulting solutions were chilled to −35 °C. **1m** (48.0 mg, 49.3 μmol) was then weighed into three separate vials. The first of these samples was dissolved in 1.20 mL of the LiI stock solution, the second was dissolved in 1.20 mL of the $LiPF_6$ stock solution, and the third

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was dissolved in 600 μL of each, resulting in solutions of the same overall salt concentration that were approximately 0.041 M in complex with 5, 0, and 2.5 equiv of excess iodide, respectively. Samples were then prepared and stored as described above. Kinetics were observed via ^{1}H NMR at 500 MHz on a Bruker AMX-500 spectrometer at 50.0 $\pm$ 0.5 °C by following the procedure described above. As a check, kinetics were also observed for a solution 0.206 M in lithium trifluoromethanesulfonate and 0.041 M in **1m**. The observed rate constant ($(2.03 \pm 0.02) \times 10^{-3}$ s^{-1}) was almost identical to that observed for the kinetics monitored in the presence of 0.206 M $LiPF_6$ ($(1.91 \pm 0.04) \times 10^{-3}$ s^{-1}), suggesting that the latter salt is not interfering with the aryl−aryl interchange reaction.

(d) Kinetics of Phosphonium Salt Formation. (1) Phosphine Profile. In a drybox, a THF-d_8 stock solution 0.200 M in LiI, 0.500 M in triphenylphosphine-d_{15}, and 6 μM in trioxane in was prepared in a 5.00 mL volumetric flask (stock solution "A"). A second THF-d_8 stock solution that was 0.200 M in LiI, 0.100 M in triphenylphosphine-d_{15}, and 6 μM in trioxane was similarly prepared (stock solution "B"). **1i** (21.2 mg, 0.0244 mmol) was then weighed out into four separate vials. Into the first of these was syringed 0.900 mL of stock solution "A" and 0.300 mL of stock solution "B", resulting in 1.200 mL of a kinetics solution that was 0.200 M in LiI, 0.400 M in phosphine, and approximately 0.020 M in **1i**. Kinetics solutions (all 0.200 M in LiI and 0.020 M in **1i**) that were 0.300, 0.200, and 0.100 M in phosphine were analogously prepared. Samples were prepared and stored at −40 °C as described above. Additional samples that were 0.040 and 0.020 M in phosphine were similarly prepared from two stock solutions, the first 0.0400 M in phosphine and 0.200 M in LiI, the second 0.200 M in LiI with no phosphine. Kinetics were observed via ^{1}H NMR at 200 MHz on a Bruker AC-200 spectrometer at 60.0 $\pm$ 0.5 °C analogous to the protocol described above. The phosphonium salt formation was monitored by the disappearance of palladium-bound aryl signals of **1i** integrated relative to the trioxane internal standard. **(2) Iodide Profile.** Kinetics solutions (all 0.400 M in phosphine and approximately 0.020 M in **1i**) that were 0.160 M in LiI, 0.040 M in $LiPF_6$; 0.120 M in LiI, 0.080 M in $LiPF_6$; and 0.080 M in LiI, 0.120 M in $LiPF_6$ were prepared from stock solution "C" (0.200 M in LiI, 0.400 M in triphenylphosphine-d_{15}, 6 μM in trioxane) and stock solution "D" which was 0.040 M in LiI, 0.160 M in $LiPF_6$, 0.400 M in triphenylphosphine-d_{15}, and 6 μM in trioxane. An additional solution (2.0 mL) that was 0.200 M in $LiPF_6$, 0.400 M in triphenylphosphine-d_{15}, and 6 μM in trioxane was also prepared for the "no iodide" runs. NMR samples were then prepared and kinetics monitored as described above.

(e) Substituent Effect Experiment. In a drybox, 24.7 μmol samples of complexes **1a**−**x** were weighed into separate vials. Into each of these was added 1.20 mL of dry, degassed $CDCl_3$ prechilled to −40 °C, resulting in stock solutions of approximately 0.0201 M in each complex. Samples were then prepared and stored at −40 °C as described above. Eight scan spectra were then taken at −10 °C prior to the experiment, after submerging the samples in a 25 °C oil bath for 1.5 h, after submerging an additional 6.5 h, after heating the samples in a 50 °C bath for 1 h, and after submerging in the 50 °C bath for an additional 2 h. During the time intervals between acquisition of the spectra and submersion in the oil baths, the samples were chilled in ice. The scans were taken on a 90° pulse with a relaxation delay of 2 min between scans to ensure accurate relative intensities. For all complexes except **1g**, the extent of transfer was determined by the loss of signal due to the palladium-bound aryl group for **1** relative to the total signal due to the palladium-bound aryl groups for both **1** and **2**. The resonances for **1g** and **2g** overlapped, preventing the determination of percent exchange for this complex.

Reaction of 1y with Tetraphenylphosphonium Iodide. In a drybox, 186.5 mg (0.400 mmol) of tetraphenylphosphonium iodide and 1 mg of trioxane were weighed into a 2.00 mL volumetric flask which was then diluted to the mark with $CDCl_3$. **1y** (21.3 mg, 0.0245 mmol) was then weighed into a separate vial and then dissolved in 1.2 mL of the above solution, yielding a sample solution that was 0.2 M in tetraphenylphosphonium iodide and approximately 0.02 M in **1y**. NMR samples were prepared and stored at −40 °C as described above. The reaction was monitored at 50.0 $\pm$ 0.5 °C via ^{1}H NMR at 200 MHz with a Bruker AC-200 spectrometer. Four 90° pulse scans were taken every 20 min, and the progress of the reaction was evidenced by the growth of proton signals due to Pd-bound phenyl-h_5 groups as shown in Figure 3.

Monitoring Phosphonium Salt Formation by Phosphorus NMR. In a drybox, 84.8 mg (98.0 μmol) of **1i** and 514.1 mg (1.96 mmol) of triphenylphosphine were dissolved in 4.8 mL of THF. Half of this solution was placed in a scintillation vial and stored overnight in the dark at −35 °C (the "before" sample), while the other half was transferred into a reaction tube with a Teflon stopcock and sidearm. A stirbar was added, and the tube was sealed, removed from the drybox, and placed in a 60 °C oil bath. After the mixture was stirred at 60 °C for 10 h, during which time a precipitate had formed and the reaction had turned from a pale greenish-yellow to a bright yellow, the tube was returned to the drybox. The solution was transferred to a 10 mm NMR tube to which a sealed capillary containing triphenylphosphite (external standard) and 500 μL of $CDCl_3$ (for lock) had been added. An NMR sample of the "before" solution prepared previously was made analogously. The NMR tubes were capped with septa and removed from the drybox. ^{31}P NMR spectra were then acquired at 121 MHz on a Bruker MSL-300 spectrometer.

Time-Course Experiments. (a) Example: $Pd(PPh_3)_4$ as Catalyst. A specially designed reaction flask with an isolable sampling port was flushed with argon and charged with 243 mg of bromobenzene-d_5 (1.50 mmol), 285 mg of 2-(4′-methoxyphenyl)-1,4,3-dioxaborolane (1.60 mmol), 1.322 g of potassium carbonate sesquihydrate (8.0 mmol), and 18.0 mg of 4,4′-dimethylbiphenyl (0.1 mmol). Water (20 mL) and THF (10 mL) were added, and the mixture was degassed with two freeze−pump−thaw cycles. A solution of $Pd(PPh_3)_4$ in degassed THF (1.73 mg/mL; 10 mL gives 1.50×10^{-5} mol, 1% vs bromobenzene-d_5) was introduced, and the mixture was subjected to an additional two freeze−pump−thaw cycles. The flask was immersed in a glycerol bath held at 50 °C and allowed to stir. Aliquots (200 μL) were removed periodically and immediately quenched into prepared Ar-flushed, septum-capped vials containing 200 μL of dilute aqueous KCN (*ca*. 50 mM). Ether (200 μL) was added to the vials, and the aqueous phase was removed via syringe. The organic layer was rinsed twice with 200 μL portions of degassed water, then stored on ice or at −20 °C prior to GC−MS analysis. The data obtained via GC−MS analysis were converted to concentrations (in the case of 4-methoxybiphenyl-d_0 and -d_5) to monitor conversion or used as is (in the case of triphenylphosphine mixtures) to assess the degree of aryl interchange as portrayed in Figures 4 and 5. The example described here corresponds to entry 3 in Table 4 as well. Other runs were conducted in an analogous manner by modifying conditions as specified in Table 4.

(b) Control Experiment: Recovery of Triphenylphosphine from (1l). An argon-flushed round-bottomed flask was charged with 53.6 mg of **1l** and 10 mL degassed DME. KCN (36 mg, 5.5×10^{-4} mol, *ca*. 10 equiv vs Pd) dissolved in 10 mL of degassed water was added to the DME solution, and the mixture was stirred for 5 min. The mixture was extracted into 50 mL of ether; the ethereal layer was washed with 3 × 25 mL of water, then concentrated under vacuum. The residue was sublimed to yield 26.2 mg of triphenylphosphine (1.0×10^{-4} mol, 90% recovery) with ^{1}H and ^{31}P NMR spectra indistinguishable from a commercial sample.

Screening of Possible Strategies for the Elimination of the Aryl-Aryl Interchange Reaction in Palladium-Mediated Cross-Couplings. (a) "Ligandless" Catalyst Systems. A thick-walled glass tube equipped with a sidearm and Teflon stopcock was charged with 1 mmol of aryl halide, 0.106 g of phenylboric anhydride (0.35 mmol, 1.05 equiv as phenylboric acid), 0.450 g of potassium carbonate sesquihydrate (2.72 mmol), 2.5 mL of water, 2.0 mL of organic solvent, and a stirbar. The tube was sealed, and the contents were degassed via several freeze−pump−thaw cycles. Under an argon backflow, the stopcock was replaced with a septum and 0.5 mL of a 4.0 mM catalyst stock solution (0.002 mmol) for the 0.2% catalyst entries, or 0.5 mL of a 20.0 mM catalyst stock solution (0.01 mmol) for the 1.0% catalyst entries was added via syringe. The tube was then resealed, degassed once more, backfilled with argon, and heated in a 65 °C oil bath for the specified amount of time. For the 4-iodotoluene entries, the presence or absence of residual aryl halide was determined by thin layer chromatography (petroleum ether) of the final reaction solutions; the reactions were

not worked up. For the other entries, the crude reactions were extracted into ether (4 × 10 mL), washed with brine, and dried over $MgSO_4$. The solvent was then removed with a rotary evaporator, and the resulting product mixture was analyzed by ^{1}H NMR.

(b) Ligand Screening, 0.2% Catalyst Systems. A thick-walled glass tube equipped with a sidearm and Teflon stopcock was charged with 218.0 mg of 4-iodotoluene (1.00 mmol), 0.106 g of phenylboric anhydride (0.350 mmol, 1.05 equiv as phenylboric acid), 0.450 g of potassium carbonate sesquihydrate (2.72 mmol), 2.5 mL of water, 2.0 mL of THF, and a stirbar. The tube was sealed, and the contents were degassed via several freeze−pump−thaw cycles. Under an argon backflow, the stopcock was replaced with a septum and 0.250 mL of a 16.0 mM ligand stock solution (0.004 mmol) and 0.250 mL of a 4.0 mM solution of the benzene adduct of tris(dibenzylideneacetone)-dipalladium(0) (0.001 mmol, 0.002 equiv of Pd) was added via syringe. The tube was then resealed, degassed once more, backfilled with argon, and heated in a 65 °C oil bath for 12 h. The presence or absence of residual 4-iodotoluene was then determined by thin layer chromatography (petroleum ether). For the 4-iodoanisole entry, the crude reaction was worked up as above, and the resulting product mixture was analyzed by ^{1}H NMR.

(c) Ligand Screening, 5.0% Catalyst Systems. A thick-walled glass tube equipped with a sidearm and Teflon stopcock was charged with 218.0 mg of 4-iodotoluene (1.00 mmol), 0.106 g of phenylboric anhydride (0.350 mmol, 1.05 equiv as phenylboric acid), 0.450 g of potassium carbonate sesquihydrate (2.72 mmol), 0.100 mmol of ligand, 0.05 mmol of palladium species, and a stirbar. The tube was evacuated and backfilled with argon three times, and the stopcock was replaced with a septum. Under an argon backflow, 2.5 mL of degassed THF and 2.5 mL of degassed water were added via syringe. The tube was then resealed, degassed once more, backfilled with argon, and heated in a 65 °C oil bath for 12 h. The two phases were then separated via pipette, and the aqueous phase was washed with 3 × 5 mL of ether. The organic rinsings were combined and shaken vigorously with 10 mL of 10% KCN in a 50 mL separation funnel until the color faded to a pale yellow. The aqueous layer was carefully separated, and the organic phase was washed with 1 × 10 mL of water and then with 1 × 10 mL of brine. The resulting solution was then dried over $MgSO_4$, and the solvent was removed with a rotary evaporator. For the tris-(*o*-tolyl)phosphine entry, the residue was dissolved in $CDCl_3$ and analyzed by ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$). Only signals for residual phosphine ($\delta = -29.9$, authentic sample $\delta = -30.2$) and phosphine oxide ($\delta = 37.1$, authentic sample[61] $\delta = 36.3$) were present. For all the entries, the crude residue was distilled at 100 °C (oven temperature) in a bulb-to-bulb apparatus under a dynamic 5 mTorr vacuum, yielding a clear, solid distillate (150−180 mg), which was then dissolved in 10 mL of ether. This solution (25 μL) was further diluted to 10 mL with ether, and this final solution was analyzed by GC−MS to determine the presence of residual 4-iodotoluene and products resulting from the aryl−aryl exchange reaction. The relative amounts of products formed were determined from integrations of the exact ion chromatograms obtained ($m/z = 184$, 168) from these solutions normalized to predetermined response factors.

(d) Optimization of Cross-Coupling Protocol. In a drybox, stock solutions of phenylboronic anhydride (1.294 M in phenylboric acid), phosphine (0.100 M), and the benzene adduct of tris(dibenzylideneacetone)dipalladium(0) (0.0500 M in Pd) were prepared in the solvent of choice in 10.0, 2.0, and 2.0 mL volumetric flasks, respectively. These solutions were then transferred to glass tubes equipped with sidearms and Teflon stopcocks. A separate, similarly equipped tube (the 5.0% catalyst entry) was then charged with 24.8 mg of tris(dibenzylideneacetone)dipalladium(0) (0.0500 mmol of Pd), 0.100 mmol of phosphine, and a stirbar. The tubes were then sealed, removed from the drybox, and fitted to dual-manifold vacuum lines, along with four additional tubes (the 0.2−2.0% entries) which had been equipped with stirbars, evacuated, and backfilled with argon. On the benchtop, stock solutions of potassium carbonate sesquihydrate (1.089 M, 50 mL, in HPLC grade water) and 4-iodotoluene (1.176 M, 10 mL) were similarly prepared and degassed via three freeze−pump−thaw cycles. The stopcocks were all replaced with septa and to each of the five reaction tubes were added 0.850 mL (1.00 mmol) of the 4-iodotoluene stock, 0.850 mL (1.10 equiv) of the phenylboric anhydride stock, and 2.50 mL (2.72 mmol) of the K_2CO_3 solution, all via syringe. The reaction tubes were then similarly charged with the following amounts of phosphine stock, catalyst stock, and additional degassed organic solvent: 0.2% catalyst entry with 40.0 μL (0.004 mmol) of phosphine stock, 40.0 μL (0.002 mmol) of palladium stock, and 0.720 mL of additional solvent; 0.5% catalyst entry with 100.0 μL (0.010 mmol) of phosphine stock, 100.0 μL (0.005 mmol) of palladium stock, and 0.600 mL of additional solvent; 1.0% catalyst entry with 200.0 μL (0.020 mmol) of phosphine stock, 100.0 μL (0.010 mmol) of palladium stock, and 0.400 mL of additional solvent; 2.0% catalyst entry with 400.0 μL (0.040 mmol) of phosphine stock, 400.0 μL (0.020 mmol) of palladium stock, and no additional solvent; and the 5.0% catalyst entry with 0.800 mL of additional solvent. At this point, each tube contained 2.5 mL of water and 2.5 mL of total organic solvent. The reaction tubes were then all resealed, degassed once more, backfilled with argon, and heated in a 65 °C bath for 24 h.

Each reaction was then worked up as follows. The two phases were separated via pipette, and the aqueous phase was washed with 3 × 5 mL of methylene chloride. The organic washings were combined, dried over molecular sieves, and the solvent was removed with a rotary evaporator. The crude residue was then distilled and analyzed as described above.

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Supporting Information Available: Linearized first-order decay plots for aryl−aryl exchange in the presence and absence of salt and excess phosphine ligands (3 pages). See any current masthead page for ordering and Internet access instructions.

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