

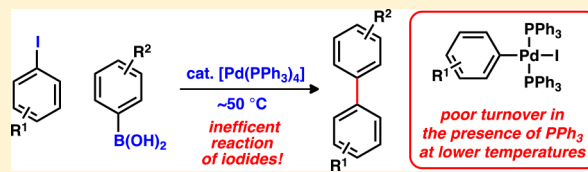
Nuances in Fundamental Suzuki–Miyaura Cross-Couplings Employing $[\text{Pd}(\text{PPh}_3)_4]$: Poor Reactivity of Aryl Iodides at Lower Temperatures

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S Supporting Information

ABSTRACT: We have explored fundamental Pd-catalyzed C_{sp^2} – C_{sp^2} Suzuki–Miyaura cross-couplings of aryl iodides ($\text{Ar}-\text{I}$) employing “classical” Pd/PPh_3 catalyst systems. Surprisingly, we observed particularly inefficient couplings of these ostensibly reactive electrophiles in a range of conventional solvent mixtures at lower temperatures ($\sim 50^\circ\text{C}$), which was in stark contrast to analogous reactions featuring the equivalent aryl bromides. This feature of well-established Pd/PPh_3 -mediated Suzuki–Miyaura reactions has received scant attention in the literature. Most significantly, our studies suggest that the inefficient coupling of aryl iodides at lower temperatures derives from the unexpectedly poor turnover of the key on-cycle intermediate $\text{trans}-[\text{Pd}(\text{PPh}_3)_2(\text{Ar})(\text{I})]$ (or related $\text{Pd}^{\text{II}}-\text{I}$ species) in the presence of PPh_3 .

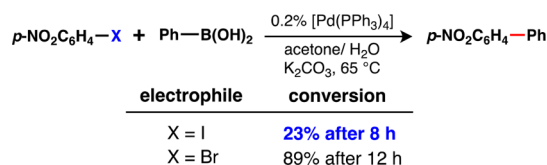


INTRODUCTION

The Suzuki–Miyaura reaction is arguably one of the most important transition-metal-catalyzed C–C coupling processes in organic synthesis.^{1,2} Underscoring this, the 2010 Nobel Prize was awarded to Heck, Negishi, and Suzuki “for palladium-catalyzed cross-couplings in organic synthesis”.³ The identification and development of various alkylphosphine ligands have contributed to enhancing the scope, efficiency, and utility of a range of Pd-catalyzed C_{sp^2} – C_{sp^2} couplings, including the Suzuki–Miyaura reaction.⁴ Nevertheless, more traditional catalyst systems featuring arylphosphine ligands, including the venerable precatalyst $[\text{Pd}(\text{PPh}_3)_4]$, still feature heavily in these pivotal transformations.^{1b} The oxidative addition of aryl halides to phosphine-ligated $\text{Pd}(0)$ complexes has been studied extensively,⁵ and it is generally accepted that the relative rates for the oxidative addition of aryl halides ($\text{Ar}-\text{X}$) to these $\text{Pd}(0)$ species typically follow the trend $\text{Ar}-\text{I} > \text{Ar}-\text{Br} > \text{Ar}-\text{Cl}$.^{5b,6}

While we were in the process of developing a new undergraduate laboratory experiment focused on exploring key features of the Suzuki–Miyaura reactions utilizing a Pd/PPh_3 catalyst system,⁷ we were intrigued by results that counterintuitively suggested the very poor reactivity of aryl iodides at $\sim 50^\circ\text{C}$. This was in stark contrast to efficient couplings of the equivalent aryl bromides at the same temperatures. After searching the literature, we could only identify one published report of similar behavior in Suzuki–Miyaura reactions, which was disclosed by Novak and Wallow over 20 years ago (Scheme 1).^{8,9} These two data points, which were not directly discussed in their work, also tentatively suggested the inefficient coupling of 1-iodo-4-nitrobenzene under these conditions. To our knowledge, the specific reasons for this surprising behavior has not been investigated further: hence, the study reported herein.

Scheme 1. Results of Pd-Catalyzed Suzuki–Miyaura Couplings Reported by Novak and Wallow in 1994⁸



RESULTS AND DISCUSSION

In order to explore these observations in more detail, we employed standard Suzuki–Miyaura reaction conditions that would allow us to conduct experiments across a broad temperature range.¹⁰ Thus, reactions of phenylboronic acid with *p*-iodo- and *p*-bromotoluene, respectively, in the presence of $[\text{Pd}(\text{PPh}_3)_4]$ at 100 and 80°C , provided efficient couplings (Table 1, entries 1 and 2). When the analogous Suzuki–Miyaura couplings were conducted at 70 and 60°C , the efficiency of reactions featuring *p*-iodotoluene (**1**) decreased significantly; especially in comparison to equivalent reactions using bromide **2** (entries 3 and 4). Most notably, in reactions with iodide **1** at 50°C , limited cross-coupling occurred and the results clearly suggested that reaction with bromide **2** was much more efficient in comparison (Table 1, entry 5, and Figure 1).^{11,12} Analogous results were observed in THF/ H_2O or acetone/ H_2O solvent mixtures, while employing DMF/ H_2O provided a notable difference in the relative efficiencies of electrophiles **1** and **2** (entries 6–8). The substitution of Na_2CO_3 for either K_2CO_3 or NaOH did not provide significant differences (entries 9 and 10).¹³ In general, the substitution of

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Table 1. Respective Suzuki–Miyaura Couplings of Iodide 1 and Bromide 2 with PhB(OH)₂: Influence of Reaction Parameters

$$p\text{-tol-X} + \text{Ph-B(OH)}_2 \xrightarrow[\substack{4:1 \text{ } n\text{-PrOH}/\text{H}_2\text{O} \\ \Delta, 0.5 \text{ h}}]{\substack{1\% [\text{Pd}] \\ 4 \text{ equiv Na}_2\text{CO}_3}} p\text{-tol-Ph} \quad \mathbf{3}$$

1: X = I
2: X = Br

entry	[Pd]	temp. (°C)	yield (%) ^a	
			using 1	using 2
1	[Pd(PPh ₃) ₄]	100	94 (91)	94 (81)
2	[Pd(PPh ₃) ₄]	80	77 (69)	77 (78)
3	[Pd(PPh ₃) ₄]	70	26 (20)	67 (65)
4	[Pd(PPh ₃) ₄]	60	15 (13)	67 (57)
5	[Pd(PPh ₃) ₄]	50	8 (7)	61 (29)
6 ^b	[Pd(PPh ₃) ₄]	50	4 (3)	19 (14)
7 ^c	[Pd(PPh ₃) ₄]	50	10 (7)	39 (30)
8 ^d	[Pd(PPh ₃) ₄]	50	37 (23)	14 (6)
9 ^e	[Pd(PPh ₃) ₄]	50	4 (4)	51 (57)
10 ^f	[Pd(PPh ₃) ₄]	50	<2 (<2)	48 (27)
11	Pd(OAc) ₂ , 4% PPh ₃	100	89 (83)	90 (77)
12	Pd(OAc) ₂ , 4% PPh ₃	80	76 (47)	74 (73)
13	Pd(OAc) ₂ , 4% PPh ₃	50	5 (4)	67 (54)
14	Pd(OAc) ₂ , 2% PPh ₃	100	96 (88)	92 (87)
15	Pd(OAc) ₂ , 2% PPh ₃	80	78 (71)	80 (80)
16	Pd(OAc) ₂ , 2% PPh ₃	50	11 (9)	68 (57)
17	Pd(OAc) ₂ , 1% PPh ₃	50	55 (47)	63 (56)
18	Pd(OAc) ₂	50	70 (53)	65 (59)

^aDetermined via gas chromatography (GC) with the aid of a calibrated internal standard (average of two experiments). Yields after 0.25 h are given in parentheses. ^bTHF used instead of *n*-PrOH. ^cAcetone used instead of *n*-PrOH. ^dDMF used instead of *n*-PrOH. ^eK₂CO₃ used instead of Na₂CO₃. ^fNaOH used instead of Na₂CO₃.

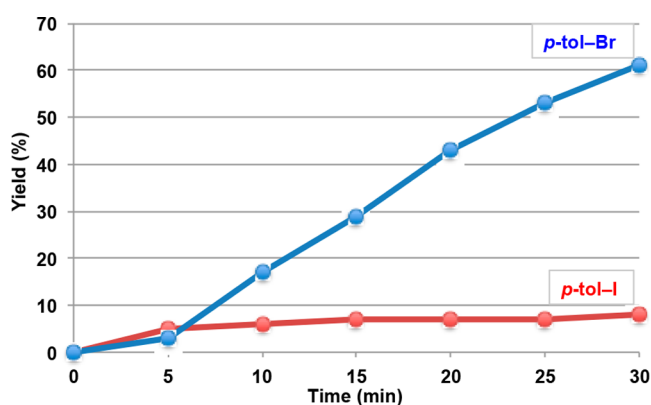


Figure 1. Formation of biaryl **3** in respective Suzuki–Miyaura couplings employing iodide **1** (red) and bromide **2** (blue) at 50 °C (conditions: Table 1, entry 5). Each data point represents the average of two experiments with yields determined via GC with the aid of a calibrated internal standard.

1% [Pd(PPh₃)₄] for 1% Pd(OAc)₂/PPh₃ (2 or 4%) provided similar results (entries 11–16).^{14–16} Notably, employing either 1% Pd(OAc)₂/1% PPh₃ or “ligandless” conditions (no PPh₃) provided efficient iodide couplings at 50 °C (entries 17 and 18). This demonstrates the adverse effect that the presence of PPh₃ has on the efficiency of the coupling of aryl iodides relative to bromides at ~50 °C, which is consistent with Novak and Wallow’s observations (Scheme 1) and other pioneering studies highlighting the acceleration of Suzuki–Miyaura couplings under “ligandless” conditions.^{8,17}

Next, we investigated the role of electronic and steric effects on reactions using various pairs of electrophiles and nucleophiles. In this way, we demonstrated more generally that iodides were less efficient coupling partners relative to the

equivalent bromides, and this uniform trend was observed across a range of sterically and electronically varied aryl halides and boronic acids (Table 2). In reactions at 50 °C, featuring

Table 2. Investigating Electronic and Steric Effects in Suzuki–Miyaura Couplings

$$\text{Ar}'\text{-X} + \text{Ar}''\text{-B(OH)}_2 \xrightarrow[\substack{4:1 \text{ } n\text{-PrOH}/\text{H}_2\text{O} \\ 50 \text{ } ^\circ\text{C}, 0.5 \text{ h}}]{\substack{1\% [\text{Pd(PPh}_3)_4] \\ 4 \text{ equiv Na}_2\text{CO}_3}} \text{Ar}'\text{-Ar}''$$

X = I, Br

entry	Ar'	Ar''	yield (%) ^a	
			using Ar–I	using Ar–Br
1	<i>o</i> -tol	Ph	8 (6)	59 (40)
2	<i>m</i> -tol	Ph	5 (3)	52 (35)
3	<i>p</i> -OMeC ₆ H ₄	Ph	10 (8)	55 (38)
4	<i>p</i> -NO ₂ C ₆ H ₄	Ph	17 (11)	74 (53)
5	Ph	<i>p</i> -tol	12 (10)	59 (49)
6	Ph	<i>p</i> -OMeC ₆ H ₄	15 (14)	52 (41)
7 ^b	Ph	<i>p</i> -NO ₂ C ₆ H ₄	16 (13)	50 (39)

^aDetermined via GC with the aid of a calibrated internal standard (average of two experiments). Yields after 0.25 h are given in parentheses. ^bReaction performed at 70 °C.

sodium phenyltrihydroxyborate as the nucleophile, couplings were also more efficient employing bromide **2** in comparison to iodide **1** (Table 3, entry 1). We then explored whether

Table 3. Respective Suzuki–Miyaura Couplings of Iodide 1 and Bromide 2: Influence of Nucleophiles

$$p\text{-tol-X} + \text{Ph-R} \xrightarrow[\substack{4:1 \text{ } n\text{-PrOH}/\text{H}_2\text{O} \\ \Delta, 0.5 \text{ h}}]{\substack{1\% [\text{Pd(PPh}_3)_4] \\ 4 \text{ equiv Na}_2\text{CO}_3}} p\text{-tol-Ph} \quad \mathbf{3}$$

1: X = I
2: X = Br

entry	nucleophile	temp (°C)	yield (%) ^a	
			using 1	using 2
1 ^b	Ph-B(OH) ₃ Na	50	15 (13)	57 (57)
2	Ph-Bpin	100	89 (89)	95 (81)
3	Ph-Bpin	80	87 (62)	85 (79)
4	Ph-Bpin	50	7 (7)	61 (43)
5	Ph-BF ₃ K	100	77 (72)	67 (43)
6	Ph-BF ₃ K	80	47 (34)	50 (25)
7	Ph-BF ₃ K	50	<2 (<2)	12 (2)

^aDetermined via GC with the aid of a calibrated internal standard (average of two experiments). Yields after 0.25 h are provided in parentheses. ^bNa₂CO₃ not added.

substituting phenylboronic acid with either phenylboronic acid pinacol ester or potassium phenyltrifluoroborate would also provide similar results. In general, analogous trends were observed using phenylboronic acid pinacol ester (Table 3, entries 2–4). Less discernible trends were evident in coupling reactions using potassium phenyltrifluoroborate (Table 3, entries 5–7).^{18,19}

We then investigated the effects of other ligands in Pd-catalyzed Suzuki–Miyaura couplings. Employing monodentate ligands that are bulkier than PPh₃ provided both efficient (*P*(*o*-tol)₃) and inefficient (TTMPP) couplings of iodides (Table 4, entries 1–3). Ligands with cone angles similar to that of PPh₃ (AsPh₃ and *P*(*p*-tol)₃) facilitated cross-couplings of iodides effectively (entries 4 and 5). The presence of monodentate ligands that are electronically similar to PPh₃ (AsPh₃, *P*(*o*-tol)₃, *P*(*p*-tol)₃, and PBN₃) and more electron deficient (*P*(2-furyl)₃,

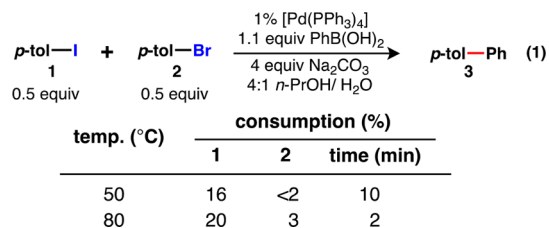
Table 4. Respective Suzuki–Miyaura Couplings of Iodide 1 and Bromide 2: Influence of Ligands

$p\text{-tol-X} + \text{Ph-B(OH)}_2 \xrightarrow[4:1 \text{ } n\text{-PrOH/H}_2\text{O}, 50^\circ\text{C}, 0.5 \text{ h}]{1\% \text{ Pd(OAc)}_2, 2\% \text{ ligand}, 4 \text{ equiv Na}_2\text{CO}_3}$ $p\text{-tol-Ph} \quad \mathbf{3}$				
entry	ligand ^c	θ (deg) ^b	ν (cm ⁻¹) ^c	yield (%) ^a
				using 1 using 2
1	PPh ₃	145	2068.9	11 (9) 68 (57)
2	P(<i>o</i> -tol) ₃	194	2066.6	66 (50) 61 (56)
3	TTMPP	184		6 (5) 47 (27)
4	AsPh ₃	142	2067.9	57 (50) 22 (18)
5	P(<i>p</i> -tol) ₃	145	2066.7	43 (35) 51 (39)
6	P(2-furyl) ₃	133	2078.4	51 (44) 9 (9)
7	P(OPh) ₃	130	2075.9	66 (53) 54 (49)
8	PBn ₃	139.5	2066.1	39 (26) 42 (34)
9	dppf			42 (20) 28 (9)
10 ^d	dppf			47 (31) 25 (9)
11	dppe			3 (3) <2 (<2)
12 ^d	dppe			<2 (<2) <2 (<2)

^aDetermined via gas chromatography (GC) with the aid of a calibrated internal standard (average of two experiments). Yields after 0.25 h are given in parentheses. ^bTolman cone angle.^{9,20} ^cTolman electronic parameter (IR frequency of Ni(CO)₃L).^{9,20a,21} ^d1% ligand used. ^eAbbreviations: TTMPP, tris(2,4,6-trimethoxyphenyl)phosphine; dppf, 1,1'-ferrocenediylbis(diphenylphosphine); dppe, bis(diphenylphosphino)ethane.

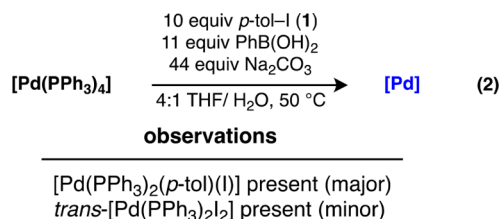
P(OPh)₃ all led to efficient couplings (entries 1, 2, and 4–8). Thus, no clear correlations between the steric or electronic properties of monodentate ligands and reaction efficiency could be identified on the basis of these results. However, in general, these data are consistent with relevant observations reported by Farina and Krishnan in Pd-catalyzed Stille couplings. We also performed reactions with bidentate phosphine ligands dppf and dppe, which provided differing results (entries 9–12).

In competition experiments between *p*-iodo- and *p*-bromotoluene employing [Pd(PPh₃)₄], the catalyst differentiated effectively between these electrophiles at both 50 and 80 °C (eq 1). These data are consistent with oxidative



addition not being the turnover-limiting step of the catalytic cycle in the case of iodide 1 at these temperatures.^{22,31} P NMR spectroscopy indicates that the predominant resting states of the Pd catalyst are *trans*-[Pd(PPh₃)₂(*p*-tol)(I)] and *trans*-[Pd(PPh₃)₂I₂] during the early stages of the reaction (eq 2).^{23–25} When taken together, these results suggest that transmetalation may be the turnover-limiting step in the process featuring iodide 1 at 50 °C.

Indeed, in Pd-catalyzed C_{sp}²–C_{sp}² Suzuki–Miyaura transformations employing aryl iodides, it is often proposed that the turnover-limiting step involves transmetalation.^{22,26} Two fundamental pretransmetalation pathways are postulated to operate.^{27,28} Specifically, pretransmetalation intermediate C^{28a,b}



may be generated either by the reaction of oxidative addition adduct A with a boronate (path A, Figure 2) or via the reaction

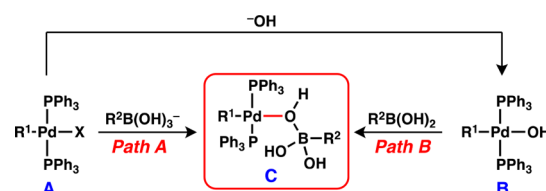


Figure 2. Two fundamental pathways leading to pretransmetalation intermediate C in Suzuki–Miyaura couplings.

of hydroxo-Pd species B with a boronic acid (path B). It is acknowledged that this transmetalation process is particularly complicated, nuanced, and subtly influenced by a range of factors.^{22,26–28} A number of research groups have investigated the kinetics of transmetalation experimentally, and in these particular cases their results indicated that path B was more kinetically favorable than path A (Figure 2).^{22,26,28e,f} Specifically, the results of studies exploring the transmetalation of *trans*-[Pd(PPh₃)₂(Ar)(X)] (X = Br, I) under both stoichiometric and catalytic conditions demonstrate that the respective rates of the Suzuki–Miyaura reactions are consistent with transmetalation likely occurring via the reaction of hydroxo-Pd species with arylboronic acids (Path B).^{22,26,28a,b} This process is orders of magnitude faster than the reaction of *trans*-[Pd(PPh₃)₂(Ar)(X)] with an aryltrihydroxyborate (path A).^{22,26,29}

With the aforementioned issues in mind, we focused on investigating the chemical competence of *trans*-[Pd(PPh₃)₂(*p*-tol)(I)] in both *n*-PrOH/H₂O and DMF/H₂O. We chose to also perform experiments in the latter solvent, as we had previously demonstrated that, in this particular mixture, the relatively efficient coupling of *p*-iodotoluene conspicuously contrasted with results obtained in *n*-PrOH and other organic cosolvents (Table 1, entries 5–8). Reactions in both solvent mixtures clearly demonstrated that *trans*-[Pd(PPh₃)₂(*p*-tol)(I)] is a chemically competent species at 50 °C (Table 5, entry 1). Interestingly, when the equivalent reactions were performed in the presence of 2% PPh₃, very low yields of product 3 were obtained in *n*-PrOH/H₂O while cross-coupling still occurred in DMF/H₂O (Table 5, entry 2). These data indicated that the poor turnover of key on-cycle intermediate *trans*-[Pd(PPh₃)₂(*p*-tol)(I)], in the presence of PPh₃, may be responsible for inefficient Suzuki–Miyaura couplings of aryl iodides in *n*-PrOH cosolvent mixtures at lower temperatures.

In related experiments, we illustrated the chemical competence of *trans*-[Pd(PPh₃)₂I₂], [Pd(PPh₃)(*p*-tol)(μ-I)]₂, and [Pd(PPh₃)(*p*-tol)(μ-OH)]₂ (Table 5, entries 3–5). The results of equivalent experiments performed in the presence of 2% PPh₃ led to less efficient Suzuki–Miyaura couplings (entries 6–8). It is possible that the inability of these Pd^{II}–I intermediates to efficiently re-enter the catalytic cycle, in the

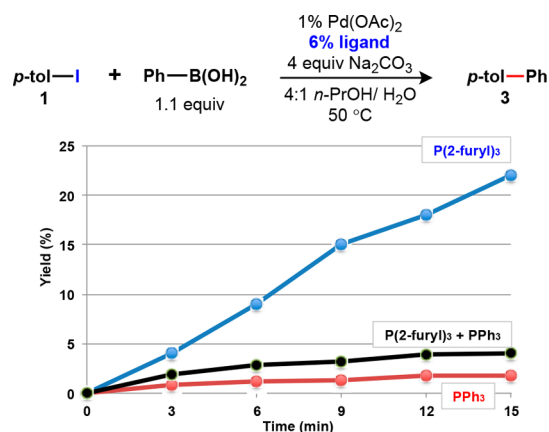
$$\text{p-tol}-\text{I} \quad \text{1} \quad + \quad \text{Ph}-\text{B}(\text{OH})_2 \quad \text{1.1 equiv} \quad \xrightarrow[\text{50 } ^\circ\text{C, 0.5 h}]{\begin{array}{c} \text{1\% [Pd], X\% PPh}_3 \\ \text{4 equiv Na}_2\text{CO}_3 \\ \text{4:1 co-solvent/ H}_2\text{O} \end{array}} \quad \text{p-tol}-\text{Ph} \quad \text{3}$$

entry	[Pd]	PPh ₃ (%)	yield (%) ^a	
			<i>n</i> -PrOH	DMF
1	<i>trans</i> -[Pd(PPh ₃) ₂ (p-tol)(I)]	0	32 (23)	42 (28)
2	<i>trans</i> -[Pd(PPh ₃) ₂ (p-tol)(I)]	2	<2 (<2)	19 (12)
3	<i>trans</i> -[Pd(PPh ₃) ₂ I ₂]	0	43 (26)	49 (34)
4 ^b	[Pd(PPh ₃)(p-tol)(μ-I)] ₂	0	47 (30)	32 (22)
5 ^b	[Pd(PPh ₃)(p-tol)(μ-OH)] ₂	0	43 (27)	49 (37)
6	<i>trans</i> -[Pd(PPh ₃) ₂ I ₂]	2	4 (2)	46 (31)
7 ^b	[Pd(PPh ₃)(p-tol)(μ-I)] ₂	2	<2 (<2)	16 (10)
8 ^b	[Pd(PPh ₃)(p-tol)(μ-OH)] ₂	2	10 (6)	38 (26)

$$\begin{array}{c}
 \text{p-tol-Br} \\
 \text{2}
 \end{array}
 +
 \begin{array}{c}
 \text{Ph-B(OH)}_2 \\
 \text{1.1 equiv}
 \end{array}
 \xrightarrow[50^\circ\text{C, 0.5 h}]{\begin{array}{c} \text{1\% [Pd(PPh}_3)_2(\text{p-tol})(\text{Br})] \\ \text{X\% PPh}_3, \text{ 4 equiv Na}_2\text{CO}_3 \end{array}}
 \begin{array}{c}
 \text{p-tol-Ph} \\
 \text{3}
 \end{array}$$

PPh ₃ (%)	yield (%) ^a
0	66 (46)
2	66 (29)

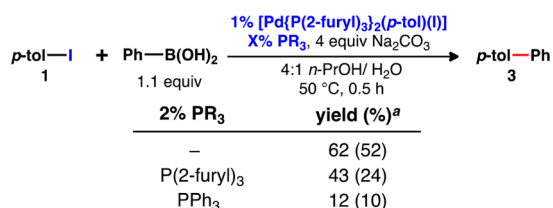
When we monitored Pd-catalyzed Suzuki–Miyaura couplings employing either 6% PPh₃ (Figure 4, red) or 6% P(2-furyl)₃ (blue), we observed results consistent with our aforementioned data (Tables 1 and 4). In an experiment featuring both PPh₃ and P(2-furyl)₃ (Figure 4, black),³³ it appeared that the former


$$\text{Ph-Pd-I} \begin{array}{c} \text{P(2-furyl)}_3 \\ \text{P(2-furyl)}_3 \end{array} \xrightleftharpoons[\text{THF, 24 } ^\circ\text{C}]{\text{P(2-furyl)}_3, \text{PPh}_3} \text{Ph-Pd-I} \begin{array}{c} \text{PPh}_3 \\ \text{PPh}_3 \end{array} \quad (3)$$

$K_{\text{eq}} > 10^2$ (ref. 9)

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Scheme 3. Investigating the Chemical Competence of *trans*-[Pd{P(2-furyl)₃}₂(*p*-tol)(I)] in Suzuki–Miyaura Couplings



^aDetermined via GC with the aid of a calibrated internal standard (average of two experiments). Yields after 0.25 h are given in parentheses.

[Pd(PPh₃)₂(*p*-tol)(I)] (or related Pd^{II}–I species) in the presence of PPh₃ may be responsible for inefficient Suzuki–Miyaura couplings of aryl iodides employing [Pd(PPh₃)₄] at lower temperatures. Throughout, where we have suggested potential reasons for the poor reactivity of aryl iodides in Suzuki–Miyaura cross-couplings at lower temperatures, we have refrained from making direct comparisons to analogous reactions featuring bromide electrophiles as part of this discussion. We have also avoided speculating on the reasons for the differing efficiency of couplings of aryl iodides performed in *n*-PrOH/H₂O in comparison to DMF/H₂O solvent mixtures. In these cases, the differing biphasic natures of these reaction conditions and related issues, such as the common ion effect and boron speciation, complicate these matters and limit our capacity to make such comparisons. Lloyd-Jones and Lennox have provided an erudite overview considering these issues within the context of Suzuki–Miyaura coupling chemistry.²⁷

CONCLUSIONS

Although an array of phosphine-ligated Pd catalyst systems are employed in Suzuki–Miyaura couplings, the use of [Pd(PPh₃)₄] (or related PPh₃-based systems) is still prevalent, particularly in more applied settings. This study, which notably had its origins in the undergraduate laboratory, has revealed the profound (and somewhat surprising) effects that subtle changes in reaction conditions can have on the efficiency of fundamental C_{sp}²–C_{sp}² Suzuki–Miyaura couplings of aryl iodides employing “classical” Pd/PPh₃ catalyst systems. Our data indicate that, in the presence of PPh₃, the poor turnover of *trans*-[Pd(PPh₃)₂(*p*-tol)(I)] (or related Pd^{II}–I species) may be responsible for the inefficient coupling of aryl iodides in various conventional solvent mixtures at lower temperatures. These findings are worth considering, particularly when C_{sp}²–C_{sp}² cross-couplings of aryl iodides are performed at lower temperatures, and can inform the development of optimized reaction conditions in this manifold. We anticipate that our work will contribute to providing a more nuanced understanding of “textbook” Pd-catalyzed Suzuki–Miyaura couplings of fundamental electrophile classes employing the prototypical phosphine ligand PPh₃.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-
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Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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- (11) In general, iodide consumption was comparable to product yield.

(12) Analogous results were obtained in experiments employing higher $[\text{Pd}(\text{PPh}_3)_4]$ loadings (2.5% and 5%) (see the [Supporting Information](#)).

(13) We also investigated the effect of incrementally varying the Na_2CO_3 loading on the outcome of the reaction at 70 °C. Our results suggest that the Na_2CO_3 loading (1–5 equiv) has little effect on the efficiency of reactions employing *p*-iodotoluene (see the [Supporting Information](#)). Substituting either Cs_2CO_3 or NMe_4OH for Na_2CO_3 also provided inefficient couplings of *p*-iodotoluene (see the [Supporting Information](#)).

(14) We also performed experiments employing higher PPh_3 loadings (see the [Supporting Information](#)).

(15) It has been established that PPh_3 can effect the reduction of $\text{Pd}(\text{OAc})_2$ to generate catalytically active $\text{Pd}(0)$ species. See, for example: ref 5c. (a) Carole, W. A.; Colacot, T. J. *Chem. - Eur. J.* **2016**, *22*, 7686–7695. (b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. *Organometallics* **1995**, *14*, 1818–1826. (c) Amatore, C.; Jutand, A.; M'Barki, M. *Organometallics* **1992**, *11*, 3009–3013.

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(17) See, for example: Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1989**, *38*, 2206; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1989**, *38*, 2206.

(18) We also performed experiments investigating the effect of halide additives (20% NH_4I , NH_4Br , NH_4F , NMe_4I , NMe_4Br , NMe_4Cl , LiBr , LiCl , KBr , KCl , CsBr , or CsCl) on Suzuki–Miyaura couplings (see the [Supporting Information](#)).

(19) It is generally acknowledged that defining key transmetalation intermediates is even more complicated with aryltrifluoroborate nucleophiles. See, for example: Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664–674 and references cited therein.

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(24) We were also able to isolate and characterize *trans*- $[\text{Pd}(\text{PPh}_3)_2\text{I}_2]$. The spectroscopic data obtained on this compound were consistent both with equivalent data reported in the literature and also with an authentic sample of *trans*- $[\text{Pd}(\text{PPh}_3)_2\text{I}_2]$ that we prepared via a literature procedure: Hahn, F. E.; Lügger, T.; Beinhoff, M. Z. *Naturforsch. B Chem. Sci.* **2004**, *59*, 196–201.

(25) When the study shown in [eq 2](#) was performed in DMF/ H_2O instead of *n*-PrOH/ H_2O , similar results were obtained. When the experiment shown in [eq 2](#) was performed using *p*-bromotoluene instead of *p*-iodotoluene, ^{31}P NMR spectroscopy indicated that *trans*- $[\text{Pd}(\text{PPh}_3)_2\text{Br}_2]$ was not present in the reaction mixture. *trans*- $[\text{Pd}(\text{PPh}_3)_2\text{Br}_2]$ was also not observed in equivalent experiments performed in DMF/ H_2O .

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(29) Lloyd-Jones and Lennox note that “Elucidation of the dominant pathway to transmetalation is not at all straightforward: one must establish the kinetically active boron and palladium intermediates, and they may not necessarily be the most abundant species present in the medium.”²⁷

(30) Detailed studies exploring the transmetalation of *trans*- $[\text{Pd}(\text{PPh}_3)_2(\text{Ph})(\text{I})]$ with *p*-tol-B(OH)₃K (and 18-crown-6) and $\text{Pd}(\text{PPh}_3)(\text{Ph})(\mu\text{-OH})_2$ with *p*-tol-B(OH)₃ under stoichiometric conditions were performed in THF/ H_2O solvent mixtures.²⁶ Extensive studies employing electrochemical methods to investigate the transmetalation of *trans*- $[\text{Pd}(\text{PPh}_3)_2(\text{Ar})(\text{X})]$ with Ar-B(OH)_2 (*n*-Bu₄NOH as the base) under catalytic conditions were performed in a DMF/MeOH solvent mixture.²²

(31) Germane observations regarding the adverse effect of PPh_3 have also been reported in Pd-catalyzed Stille cross-couplings; see ref 9. (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833–5847. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

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(33) For a study focused on the reactivity of $\text{Pd}(0)$ complexes derived from mixtures of $\text{Pd}(\text{dba})_2$ and PPh_3 and $\text{P}(2\text{-furyl})_3$ ligands, see for example: Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi, F. O. *Organometallics* **1998**, *17*, 2958–2964.

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