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Mechanistic Origin of Ligand Effects on Exhaustive Functionalization During Pd-Catalyzed Cross-Coupling of Dihaloarenes

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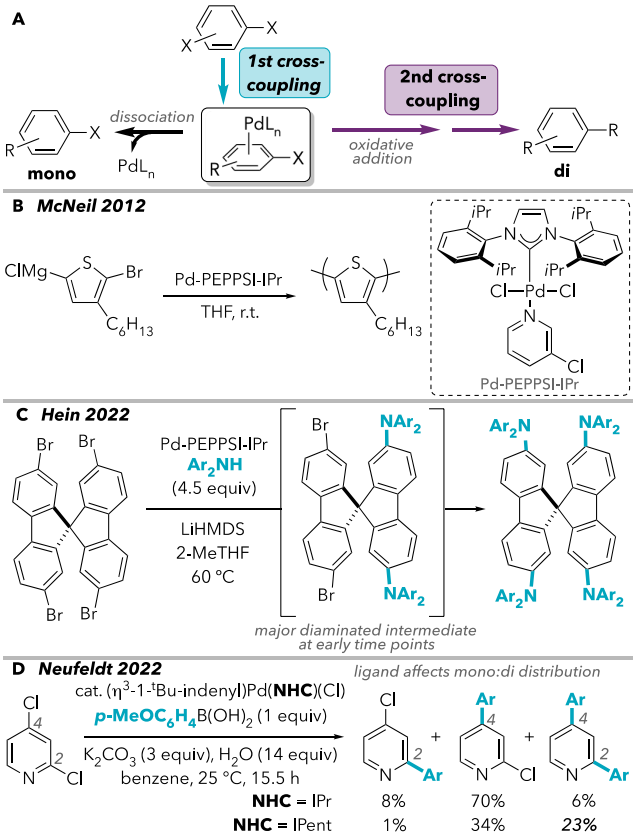
ABSTRACT: We describe a detailed investigation into why bulky ligands—those that enable catalysis at "12*e*⁻" Pd^0—tend to promote overfunctionalization during Pd-catalyzed cross-couplings of dihalogenated substrates. After one cross-coupling event takes place, PdL initially remains coordinated to the π system of the nascent product. Selectivity for mono- vs. difunctionalization arises from the relative rates of π-decomplexation versus a second oxidative addition. Under the Suzuki coupling conditions in this work, direct dissociation of 12*e*⁻ PdL from the π-complex cannot outcompete oxidative addition. Instead, Pd must be displaced from the π-complex as 14*e*⁻ PdL(L') by a second incoming ligand L'. The incoming ligand is another molecule of dichloroarene if the reaction conditions do not include π-coordinating solvents or additives. More overfunctionalization tends to result when increased ligand or substrate sterics raises the energy of the bimolecular transition state for separating 14*e*⁻ PdL(L') from the mono-cross-coupled product. This work has practical implications for optimizing selectivity in cross-couplings involving multiple halogens. For example, we demonstrate that small coordinating additives like DMSO can largely suppress overfunctionalization and that precatalyst structure can also impact selectivity.

INTRODUCTION

Di- and polyhalogenated (hetero)arenes are readily accessible substrates for iterative cross-couplings and other halide substitution reactions to prepare bioactive small molecules and functional materials.[1,2,3] However, in Pd-catalyzed cross-couplings of polyhalogenated substrates, controlling the degree of functionalization can be challenging. For example, a high preference for exhaustive functionalization is seen with some ligands,[4-14] even when the nucleophilic coupling partner is not used in excess. A mechanistic understanding of how ligands affect this type of selectivity could enable better control of reaction outcomes.

Exhaustive cross-coupling has been attributed to a fast intramolecular oxidative addition relative to the rate of dissociation of Pd^0 from the mono-cross-coupled intermediate.[10,15,16] If dissociation is slow, Pd can "ring-walk" around the π system to initiate a second oxidative addition that leads to a difunctionalized product (Scheme 1A). This ring-walking ability has been exploited in catalyst-transfer cross-coupling polymerization using bulky ligands for Pd[17,18] such as IPr19 (Scheme 1B) and P^tBu_3.[20] Ring-walking also enabled desymmetrization of tetrabromospirobifluorenes by selective diamination using Pd-PEPPSI-IPr (Scheme 1C).[10] However, when monosubstitution of a dihaloarene is desired, ring-walking behavior is detrimental. For example, we recently evaluated *N*-heterocyclic carbene (NHC) ligands for inverting site-selectivity in the cross-coupling of 2,4-dichloropyridines (Scheme 1D).[7,8] We found that the amount of undesired diarylation increases with more hindered NHC ligands like IPent, which is unfortunate because only hindered NHCs promote selective cross-coupling at C4 over the more conventional C2 site.

Scheme 1. Cross-Coupling Examples in Which Pd Ring-Walking is Implicated in Product Distribution.



A survey of the literature suggests that ligand sterics influence the extent to which Pd ring-walking occurs. The ancillary ligands reported to promote high amounts of polyfunctionalization are those that also promote catalysis at 12e^- Pd^0,[21,22] such as P^tBu_3, RuPhos, SIPr, IPr, and IPent.[4–14,17,19–23] These ligands are all larger than the reported threshold for promoting oxidative addition at monoligated PdL,[22] yet there is still considerable variability in their effects on selectivity. Despite an apparent steric trend, *the mechanistic basis for the relationship between ligand sterics and ring-walking behavior has not been demonstrated*. Here we answer this question by investigating how PdL (L = bulky ligand) is released from the mono-cross-coupled product. We provide evidence that 12e^- Pd(NHC) does not directly dissociate from the intermediate π-complex. Instead, another smaller ligand displaces Pd^0 as a 14e^- species. Thus, bulkier ancillary ligands promote exhaustive functionalization by inhibiting a bimolecular mechanism for displacement of Pd^0 from the initial cross-coupled product.

RESULTS AND DISCUSSION

Systematic Evaluation of Steric Trends. We first examined a series of NHC and phosphine ligands for the Suzuki cross-coupling of dichloroarene **1** with 1 equiv of $PhB(OH)_2$ in THF at room temperature (Figure 1A). Pre-formed Hazari-type Pd^{II}-ligand precatalysts supported by 1-*tert*-butylindenyl were used.[24] The reactions were monitored over time because the proportion of diarylated product is expected to increase even in the absence of ring-walking as **1a-mono** becomes more abundant. The bulkiest ligand in this NHC series is IPent. This ligand displays a remarkably strong preference for **1a-di**.[14] In fact, **1a-mono** was never observed with this ligand, even at early time points. The slightly smaller ligand IPr also favors diarylation, but **1a-mono** is seen as a significant minor product. In stark contrast, the still smaller ligand IMes gives **1a-mono** as the major product and the diarylated product **1a-di** only slowly accumulates over time. Of the phosphines in this study, SPhos promotes the most diarylation, although **1a-mono** is overall favored.[25] The other phosphines (P^tBu_3, PCy_3, $PhPCy_2$, and CyJohnPhos) give a similar product distribution to IMes, favoring monoarylation. The product ratio with these smaller ligands (around mono:di = 8:1 at the end of the reaction) may reflect the statistical distribution of products when diarylation results not from ring-walking, but rather from intermolecular encounters between Pd and **1a-mono**. Of the phosphines evaluated, SPhos is the bulkiest based on having the largest Boltzmann averaged percent buried volume (%V_{bur}),[26,22] which is consistent with a relationship between ligand sterics and ring-walking. However, it appears that the NHC ligands IPr and especially IPent[13] are unique in promoting a high degree of diarylation for this cross-coupling system involving dichloroarene **1**. Overall, selectivity spans a wide range even when comparing ligands that are all expected to facilitate catalysis at 12e^- Pd^0 such as the NHCs, P^tBu_3, and the biarylphosphines.

Relevance of Ringwalking to Diarylation. We expected that the exclusive selectivity for diarylation with IPent was due to ring-walking, but an alternate explanation could be that **1a-mono** is much more reactive than **1** toward an intermolecular reaction with Pd-IPent.[27] To evaluate this possibility, a competition between **1** and its monoarylated analog **3** was conducted (Figure 1B). With Pd/IPent, the dichloride **1** was found to react at a similar rate to **3**. This outcome indicates that the Pd/IPent-catalyzed formation of **1a-di** results from intramolecular oxidative addition due to slow release of Pd from the intermediate π-complex, rather than exceptional reactivity between the monoarylated intermediate and Pd/IPent in an *inter*molecular fashion.

Mechanistic Possibilities to Explain Ligand Trends. The selectivity for di- versus monoarylation can be understood by the mechanistic scenarios in Figure 1C. If Pd is monoligated during reductive elimination, as expected with bulky ligands, PdL initially remains coordinated to the π system of the nascent product (**π-complex**). PdL can then ring-walk and undergo intramolecular oxidative addition leading to the diarylated product (Path I). If Path I is slow enough, the monoarylated product could instead be released through either Path II or Path III. In Path II, Pd dissociates directly as a 12e^- species, while in Path III, an incoming ligand displaces Pd as a 14e^- complex. Understanding ligand effects on selectivity requires addressing the following key mechanistic question: *is monoarylated product released by direct dissociation of 12e^- PdL (Path II) or by bimolecular displacement of 14e^- PdL(L') (Path III)?*

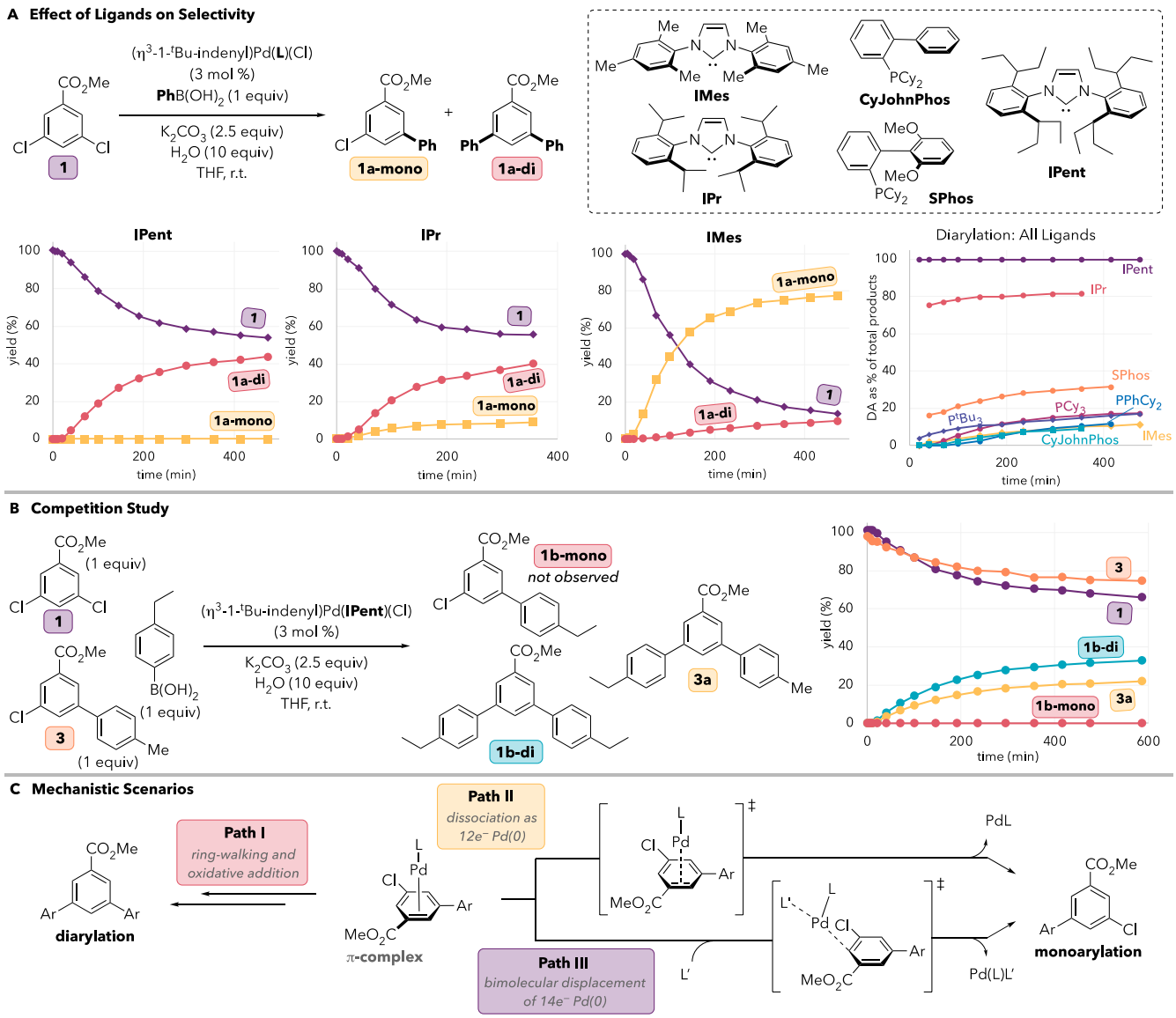
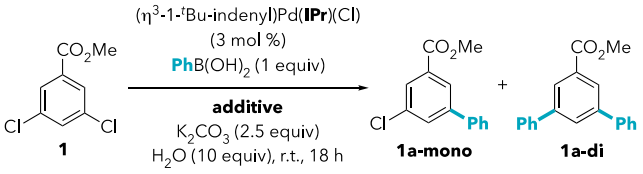


Figure 1. (A) The bulkiest ancillary ligands IPent and IPr favor diarylation, while smaller (yet still bulky) ligands promote monoarylation of a dichloroarene. (B) A competition experiment supports the role of Pd ring-walking in the diarylation of dichloroarenes catalyzed by Pd/IPent. (C) Mechanistic scenarios for generating diarylated versus monoarylated products. For parts A and B, GC yields are calibrated against undecane as an internal standard, and data points typically represent an average of ≥2 trials.

Although low-coordinate Pd^0L has been proposed as an intermediate in cross-coupling catalytic cycles,[21,28,29,30,31,32,33] there is little evidence to support its existence in solution.[34] For example, efforts to engineer an isolable 12*e*⁻ Pd^0 species with exceptionally hindered ligands still provide formally 14*e*⁻ complexes involving a second weaker ligand such as an arene.[35] For this reason, as well as the observed ligand steric trend, Path III initially appeared more intuitive. The bimolecular transition state for Path III would be more crowded than the unimolecular transition state for Path II; thus, Path III should be slowed by ligand steric bulk. Path III has also been proposed as the mechanism for chain transfer in Pd-catalyzed cross-coupling "living" polymerizations.[18] However, a ligand steric trend could also be consistent with Path II if bulkier ligands destabilize the 14*e*⁻ Pd π-complex intermediate. Thus, further studies were undertaken to distinguish between Paths II and III.

Effect of Coordinating Additives (Supports Path III). Release of a monoarylated product by Path III requires a second incoming ligand (L' in Figure 1C). Pd^0 is unlikely to accommodate two bulky ligands like IPr or IPent during the crowded transition structure[8,22,36] for ligand exchange, but L' could be a smaller molecule. We hypothesized that, if Path III is operative, small coordinating additives would increase the proportion of monoarylated product in a cross-coupling reaction. To test this hypothesis, we evaluated the Suzuki coupling of **1** catalyzed by Pd/IPr or Pd/IPent in the presence of several π-accepting additives that should be good ligands for Pd^0 (Table 1).

Table 1. Coordinating Additives and Solvents Increase Selectivity for Mono- versus Diarylation[a]



entry	solvent	additive (equiv)	**1a-mono**	**1a-di**	**mono:di**
1	THF	--	9.7	43.6	1 : 4.5
2	THF	indene (0.1)	58.6	21.3	2.8 : 1
3	THF	1-*t*-Bu-indene (0.1)	23.0	39.4	1 : 1.7
4	THF	pyridine (0.1)	44.0	28.8	1.5 : 1
5	THF	lutidine (0.1)	35.7	33.6	1.1 : 1
6	THF	DMSO (0.1)	62.5	14.7	4.3 : 1
7	THF	DMSO (1)	78.5	10.8	7.3 : 1
8[b]	THF	--	0.0	50.3	1 : >99
9[b]	THF	DMSO (0.1)	1.2	43.6	1 : 38
10[b]	THF	DMSO (10)	31.6	27.7	1.1 : 1
11	MeCN	--	30.9	1.7	19 : 1
12	benzene	--	60.0	16.7	3.6 : 1
13	$PhCF_3$	--	65.8	15.8	4.2 : 1
14	anisole	--	44.9	23.3	1.9 : 1
15	mesitylene	--	25.1	28.0	1 : 1.1

[a]GC yields calibrated against undecane as the internal standard. Average of ≥2 trials. [b]With IPent instead of IPr.

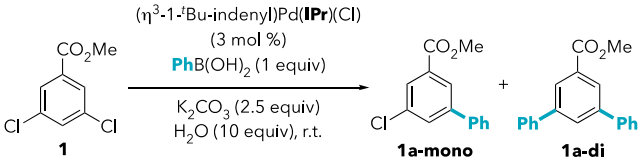
With IPr, the product ratio is about 1:4 (**1a-mono**:**1a-di**) at the end of the reaction in THF in the absence of additives (entry 1). However, just 10 mol % of electron-deficient alkenes (entries 2-3), pyridines (entries 4-5), or DMSO (entry 6) have a dramatic impact on the selectivity, in many cases inverting it to favor **1a-mono**. Unsubstituted indene more strongly promotes monoarylation than the more hindered 1-*tert*-butylindene (entries 2-3), which is consistent with sterics influencing the energy of the crowded transition structure for Path III. Pyridine and 2,6-dimethylpyridine (lutidine) provide similar selectivities (entries 4-5), indicating that coordination of Pd^0 to pyridine's π system may be more significant than coordination through nitrogen. The best selectivity for monoarylation using IPr was achieved with DMSO, reaching a maximum of about 7:1 mono:di selectivity with 1 equiv of this additive (entry 7). This ratio is similar to the selectivity observed with IMes and most of the phosphines in Figure 1A, suggesting that the minor product **1a-di** observed under these conditions may result from intermolecular reaction of **1a-mono**. Remarkably, DMSO also has a strong impact on selectivity in the Pd/IPent-catalyzed cross-coupling. In the absence of additives, IPent promotes exclusive diarylation (entry 8), but monoarylation is slightly favored when 10 equiv DMSO are included as an additive (compare entries 8-10). Larger quantities of DMSO (20 equiv) inhibit the reaction (see Table S10).

Given the profound effect of coordinating additives in promoting monoarylation, we considered that coordinating solvents could play a similar role. Indeed, when THF is replaced with MeCN for the Suzuki coupling catalyzed by Pd/IPr, selectivity inverts to favor **1a-mono**, although the yield is poor (entry 11). The use of a π-coordinating aromatic solvent, benzene, enables higher yield of **1a-mono** (entry 12). Selectivity is modestly affected by the π-accepting ability of aromatic solvents. For example, the more electron-rich anisole is less effective at promoting monoarylation than benzene or trifluorotoluene (compare entries 12-14). Mesitylene promotes less monoarylation than the other aromatic solvents (entry 15), which is consistent with its worse π-coordinating ability due to both electronics and sterics. Taken together, the effect of additives and solvents on selectivity supports the feasibility of Path III for release of monoarylated product from Pd. Additional results with other solvents and additives are available in Table S10.[37]

(How) Does Path III Take Place Without Coordinating Additives? The results above show that π-coordinating additives or solvents can promote release of monoarylated products through Path III. However, we next wanted to determine whether Path III is still operative in the absence of these additives in a solvent like THF, which is not a π-acceptor. To answer this question, we evaluated the effect of reaction concentration on the selectivity of the Suzuki coupling of **1** catalyzed by Pd/IPr. More monoarylation is seen when the reaction is run at higher concentrations in THF (Table 2, entries 1–4), which is consistent with one of the solutes serving as a ligand in the bimolecular transition state for Path III. In contrast, selectivity was independent of concentration in benzene. This outcome is consistent with benzene, whose concentration remains essentially constant, serving as the second ligand for Path III (entries 5-8).

We envisioned that the incoming ligand necessary to promote Path III in non-coordinating THF could be one of three species: (a) a derivative of *tert*-butylindene released upon reduction of the Pd^{II} precatalyst; (b) a dichloroarene substrate molecule; or (c) the arylboronic acid or a related species. Each of these possibilities was evaluated in cross-coupling reactions using IPr as the ligand, as described below. The results suggest that a substrate molecule promotes Path III in THF.

Table 2. Less Diarylation is Observed at Higher Concentrations in THF, but Concentration has no Effect on Selectivity in Benzene[a]

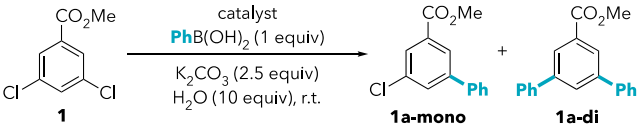


entry	solvent	conc. (*M*)	1a-mono	1a-di	mono:di
1	THF	0.16	6.0	37.2	1 : 6.2
2	THF	0.20	7.7	38.7	1 : 5.0
3	THF	0.25	9.7	43.6	1 : 4.5
4	THF	0.40	14.5	38.4	1 : 2.6
5	benzene	0.16	59.2	16.7	3.5 : 1
6	benzene	0.20	60.0	17.4	3.4 : 1
7	benzene	0.25	60.0	16.7	3.6 : 1
8	benzene	0.40	61.0	17.2	3.5 : 1

[a]GC yields calibrated against undecane as the internal standard. Average of ≥2 trials.

Analysis of the reaction mixture following Suzuki coupling of **1** catalyzed by (η³-1-ᵗBu-indenyl)Pd(IPr)(Cl) revealed 1-*tert*-butyl-3-phenylindene as a byproduct from activation of Pd^{II} to Pd^{0} (see page S21). Because 1-*tert*-butylindene can influence selectivity (Table 1, entry 3), we considered that the electron-deficient alkene 1-*tert*-butyl-3-phenylindene might serve as the ligand to displace Pd in Path III, releasing monoarylated **1a-mono**. However, the reaction catalyzed by $[Pd(IPr)Cl_2]_2$ gives the same selectivity as (η³-1-ᵗBu-indenyl)Pd(IPr)(Cl), suggesting that the indene derivative is not involved in the selectivity-determining step (Scheme 2).

Scheme 2. Inclusion of *tert*-Butylindenyl Ligand in Precatalyst Does not Influence Selectivity



	1a-mono	1a-di
(η3-1-tBu-indenyl)Pd(**IPr**)(Cl) (3 mol %):	10%	44%
[Pd(**IPr**)Cl$_2$]$_2$ (1.5 mol %):	10%	40%

GC yields calibrated against undecane. Average of ≥2 trials.

We next considered whether another molecule of dichloroarene displaces Pd^{0} in Path III. More electron-deficient aryl chlorides are known to interact more strongly with Pd^{0} due to back-bonding, so we expected that substrate electronics might affect selectivity.[38] A series of 5-substituted 1,3-dichlorobenzenes were evaluated in the Pd/IPr-catalyzed Suzuki coupling in THF. Remarkably, all substituents at this position promote a large increase in diarylation, regardless of the electronic nature of the group (Figure 2, first six data points **4a**–**8a**). These results indicate that the dichloroarene sterics play an important role in determining selectivity, and are consistent with Path III and prior observations in the polymer literature.[18] Interestingly, a substituent *ortho* to the two chlorides (**6b**) has very little effect on diarylation. In this case, one side of the arene (three contiguous carbons) is completely unsubstituted, leaving the possibility for low steric congestion if a molecule of arene approaches Pd from its unsubstituted edge. Notably, a substituent at the 5-position (*meta* to both chlorides) would introduce steric congestion during the associative displacement in Path III regardless of the nature of the incoming ligand and since the substituent would also be present on the monoarylated intermediate. As such, these results do not clarify whether a second molecule of dichloroarene serves as the displacing ligand.

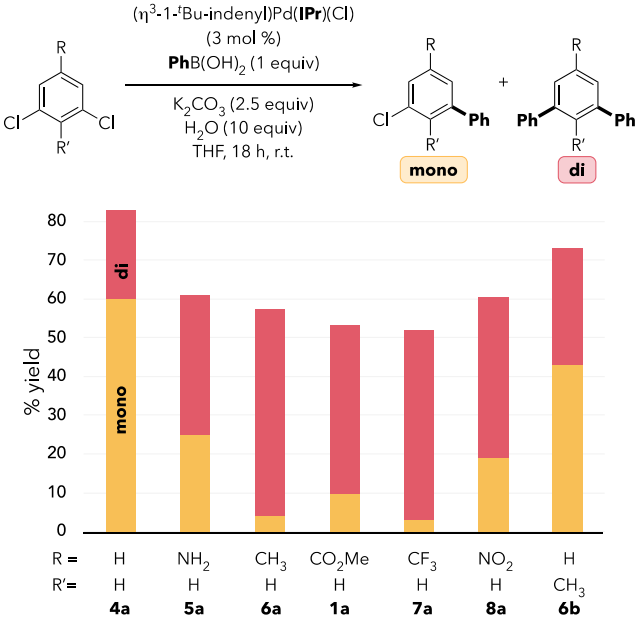


Figure 2. Effect of substrate substituents on ratio of mono- to diarylated products. Sterics appears to be a major factor. GC yields calibrated against undecane as the internal standard. Yields for **6b** assume identical GC response factors to the corresponding isomers **6a**. Average of ≥2 trials.

However, further experiments varying the equivalents of substrate support the role of dichloroarene as the displacing ligand. In particular, significantly more monoarylation is detected when using an excess of dichloroarene (Figure 3). This effect does not appear to be due to a decreased likelihood of intermolecular reaction of **1a-mono**, as the effect remains even when normalizing the data to account for the competition between **1** and **1a-mono** as substrates for Pd (see SI).

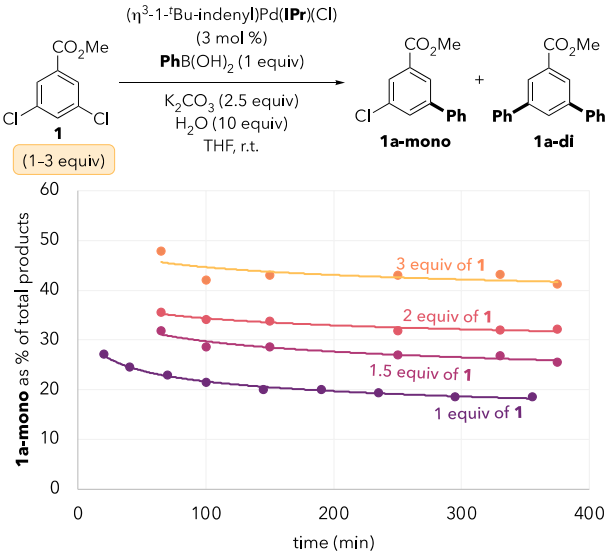


Figure 3. Increasing the concentration of substrate **1** leads to increased monoarylation (y-axis). GC yields calibrated against undecane as the internal standard. Data points for 1 equiv of **1** represent the average of 2 trials. Trendlines do not represent a mathematical fit and are only to guide the eye.

Finally, we considered whether arylboronic acid (or a related byproduct) could serve as a ligand to displace Pd from the nascent mono-cross-coupled product in Path III. However, in stark contrast to the effect of [**1**], increasing the concentration of $PhB(OH)_2$ has a negligible effect on product ratio (Figure 4). The cross-coupling reaction is considerably faster at higher [$PhB(OH)_2$], and the selectivity is known to change slightly over time as dichloroarene **1** is depleted. Thus, to normalize for the changing selectivity as the reactions progress, the data in Figure 4 are plotted against % conversion rather than time. These data do not support involvement of the arylboronic acid in the selectivity-determining step.

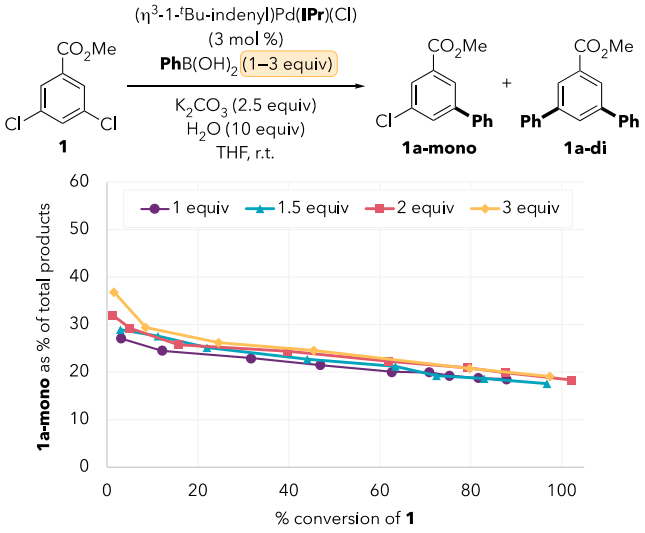


Figure 4. Increasing the concentration of phenylboronic acid has no significant impact on the proportion of monoarylation (y-axis). GC yields calibrated against undecane as the internal standard. Data points for 1, 2, and 3 equiv represent the average of 2 trials.

DFT Calculations (Support Path III). The experiments above support Path III and provide no evidence for release of free 12e^- PdL from the product–PdL π-complex. To better assess the thermodynamic feasibility of 12e^- Pd in our system and to understand the influence of ligand and dichloroarene sterics on Path III, we next undertook DFT calculations. Geometry optimizations were conducted with the MN15L functional in implicit THF solvent (solvent model = CPCM) using the LANL2DZ basis set for Pd and 6-31G(d) for the other atoms. Single point energy calculations on the optimized geometries were conducted at the SMD(THF)-MN15/6-311++G(2d,p)/SDD(Pd) level of theory. These methods were chosen for several reasons: (1) they gave results consistent with experiment in related studies,[8,39] (2) the hybrid MN15[40] and pure MN15L[41] functionals have been benchmarked as among the most accurate for some transition metal complexes,[42] and (3) in our experience MN15L tends to be "well-behaved" toward geometry optimizations of related Pd-containing structures (i.e., giving a relatively high success rate for convergence). Thermodynamic quantities were calculated at room temperature,[43] applying corrections for concentrations consistent with a time point early in the reaction progress (assuming 5% conversion of dichloroarene into monoarylated product).

At the level of theory used, separation of π-complex **9B** into Pd–IPr and **1a-mono** is perhaps just barely thermodynamically accessible at room temperature (ΔG = 20.0 kcal/mol, Figure 5, Path II). However, it was not possible to locate the corresponding transition structure. Importantly, the calculated free energy barriers for either a second oxidative addition (**TS10B**, 17.6 kcal/mol, Path I) or a bimolecular displacement mechanism for release of **1a-mono** via **TS11B** (17.5 kcal/mol, Path III) are substantially lower than the energy of dissociating 12e^- Pd–IPr. Thus, the calculations are consistent with experiment and indicate that **1a-mono** is released through Path III, not Path II. The calculated difference in free energies of activation for Path I vs. Path III is 0.1 kcal/mol (**TS10B** vs. **TS11B**), corresponding to ~1:1 selectivity. This ratio is similar to the experimentally observed selectivity of 1:3 (mono:di) at ~5% conversion (experimental $\Delta\Delta G^{\ddagger}$ = 0.6 kcal/mol).

The bimolecular transition structure for Path II appears more crowded when using IPent instead of IPr (compare **TS11A** to **TS11B**, Figure 5B). In particular, the incoming molecule of dichloroarene **1** cannot approach Pd–IPent as closely due to steric congestion from the ligand's isopentyl groups. Accordingly, the barrier to bimolecular displacement of Pd-IPent is much larger than the barrier to displace Pd-IPr, and about 3 kcal/mol larger than the barrier to oxidative addition of the remaining chloride at Pd-IPent (Figure 5A, 23.0 vs. 19.9 kcal/mol for **TS11A** vs. **TS10A**). Thus, the predicted selectivity for the cross-coupling of **1** catalyzed by Pd/IPent is ~ 1 : 200 (mono:di), which is consistent with the experimentally observed exclusive selectivity for **1a-di** under these conditions. Conversely, calculations using Pd/IMes predict a very facile Path III ($\Delta G^{\ddagger}$ = 9.7 kcal/mol compared to 16.1 kcal/mol for Path I; see page S49), consistent with the strong preference for monoarylation seen with IMes.

Finally, calculations using Pd-IPr in combination with unsubstituted 1,3-dichlorobenzene (**4**) indicate that Path III is much lower-energy in the absence of a 5-substituent. In this case, Path III (leading to **4a-mono**) is predicted to be easier than Path I (leading to **4a-di**) by 3.6 kcal/mol (compare **TS11C** to **TS10C**), which is qualitatively consistent with the preference for monoarylated product in the Pd/IPr-catalyzed cross-coupling of **4**, especially at early time points (see Table S13 for a 1 h time point showing 7:1 selectivity for **4a-mono**). In **TS11C**, the absence of a 5-substituent on either **4a-mono** or **4** allows a closer interaction between Pd and the incoming dichloroarene (Figure 5B).

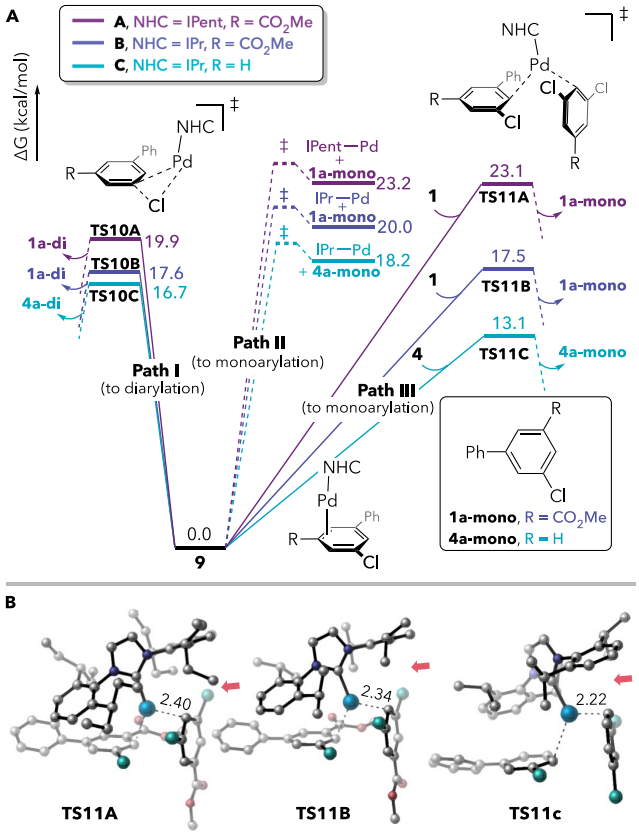
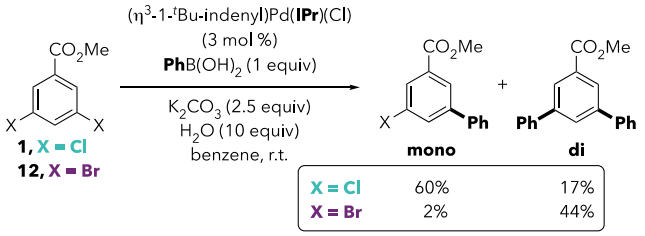


Figure 5. (A) Calculated reaction free energy diagram comparing effect of ligand (IPent vs. IPr) and substrate (**1** vs **4**). (B) Ligand exchange transition structures for Path III. Bond distances in Ångstroms. The red arrows indicate regions of possible crowding between NHC ligand and incoming dichloroarene.

It is worth noting that the calculated thermodynamics of Path II are extremely sensitive to DFT method. For example, single point energy calculations performed with a different dispersion-corrected hybrid functional, B3LYP-D3, suggest that 12e^- Pd-IPr is relatively stable, only about 10.5 kcal/mol higher than π-complex **9B**. On the other hand, single point energy calculations with the pure functional MN15L indicate that 12e^- PdIPr is much higher-energy (26.1 kcal/mol relative to **9B**). Thus, the calculated energy of 12e^- Pd-IPr relative to **9B** ranges from 10.5-26.1 kcal/mol depending on functional. The large differences in the predicted thermodynamic feasibility of Path II illustrate the need for caution when comparing computed energies of metal species with different coordination numbers.[44] Notably, it is unknown whether B3LYP-D3 predicts that Path II involving 12e^- Pd-IPr is actually feasible, since a transition state for that path was not located. Experiments do not support the feasibility of Path II.[18] Overall for our system, the MN15 functional for single point energy calculations leads to predicted product ratios that are closest to experiment compared to B3LYP-D3 or MN15L (see pp S48-S49 for calculated energies using B3LYP-D3 and MN15L).

Implications and Applications. The experimental and computational studies above suggest that the selectivity for mono- vs. diarylation with bulky ligands stems from a competition between a second oxidative addition event (Path I) and bimolecular displacement of Pd from the mono-cross-coupled product (Path III). A possible implication of this work is that substrates with heavier halides may be more prone to overfunctionalization because oxidative addition is generally faster with heavier halides. To test this, we compared the Suzuki coupling reaction of dibromoarene **12** to that of dichloroarene **1** catalyzed by Pd/IPr (Scheme 3). As previously shown, monoarylation of **1** is favored in benzene. However, diarylation dominates when starting from di*bromo*arene **12**. This result is consistent with a faster oxidative addition at C—Br, enabling diarylation to outcompete Path III for release of monoarylated product. Interestingly, less diarylation of **12** was observed in THF, which is the opposite of the solvent trend seen for **1** (see Table S23). Understanding the role of solvents and ligands on cross-coupling selectivity with dibromoarenes is the subject of further investigation.

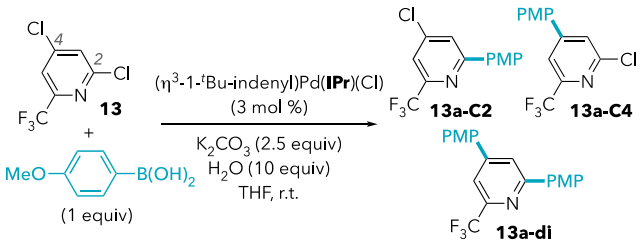
Scheme 3. More Overfunctionalization is Seen with a Dibromoarene Compared to a Dichloroarene



GC yields calibrated against undecane. Average of ≥2 trials.

Another implication of the reported work is that small coordinating additives can facilitate access to monoarylated products in cases where overfunctionalization is otherwise problematic. As an example, in 2022 we reported that the bulky ligand IPr uniquely enables unconventional C4-selectivity in cross-couplings of 2,4-dichloropyridine.[7,8] With smaller ligands (e.g., traditional phosphines like PPh_3 or moderately smaller NHCs like IMes), cross-coupling at C2 tends to dominate instead. We found that some 6-substituted-2,4-dichloropyridines represent a limitation to the substrate scope of the optimized C4-selective coupling because of overfunctionalization. For example, the major product of the Pd/IPr-catalyzed Suzuki coupling of **13** with *p*-methoxyphenyl$B(OH)_2$ is **13a-di** (Table 3, entry 1). In light of the results in the current report, we hypothesized that monoarylation could be rescued in situations like these by adding small quantities of DMSO to the reaction mixture. Gratifyingly, diarylation was mostly suppressed with 0.1-5 equiv DMSO (entries 2-3), enabling the desired monoarylated product **13a-C4** to be isolated for the first time in 73% yield.

Table 3. DMSO Additive Enables Pd/IPr-catalyzed Monoarylation at the Unconventional C4 Site of a 6-Substituted 2,4-Dichloropyridine[a]

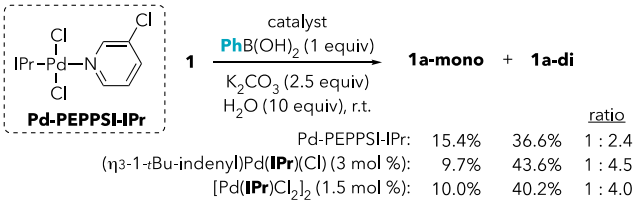


entry	additive (equiv)	13a-C2 (%)	13a-C4 (%)	13a-di (%)	mono: di
1	--	0.8	3.8	39.4	1 : 8.6
2	DMSO (0.1)	1.6	68.7	11.6	6.1 : 1
3	DMSO (5)	7.1	79.8 (73)	3.7	23 : 1

[a]GC yields calibrated against undecane as the internal standard, assuming the same response factor for **13a-C2** and **13a-C4**. Average of three trials. Isolated yield in parentheses. PMP = *para*-methoxyphenyl.

Finally, a third implication of this work is that coordinating additives should be avoided in catalyst-transfer polymerizations.[45] The chain-growth mechanism relies on Pd remaining coordinated to the π-system of the growing polymer chain after each cross-coupling iteration. Pd-PEPPSI-NHC complexes have been studied for catalyst-transfer polymerization to synthesize conjugated polymers.[20] Our data indicate that small quantities of pyridines can displace Pd from the π-system of a cross-coupled product (Table 1, entries 4-5). To determine whether 3-chloropyridine, the "throwaway" ligand of these PEPPSI catalysts, could influence selectivity, we evaluated Pd-PEPPSI-IPr for the Suzuki cross-coupling of **1** (Scheme 4). Indeed, the PEPPSI catalyst results in somewhat lower selectivity for diarylation compared to the Hazari-type Pd-IPr precatalyst or $[Pd(IPr)Cl_2]_2$. This suggests that chain-growth behavior in cross-coupling polymerization might be modestly improved by choosing a Pd-NHC precatalyst supported by a ligand that is less coordinating than 3-chloropyridine, as predicted by McNeil.[19,46]

Scheme 4. 3-Chloropyridine Ligand from Pd-PEPPSI-IPr Influences Selectivity for Monoarylation versus Diarylation



CONCLUSIONS

This work explores the mechanistic origin of mono- and diarylation in Pd-catalyzed Suzuki cross-couplings of dihalogenated arenes in the presence of bulky ligands. The results indicate that monoarylated products are released from Pd by a concerted ligand exchange step. In the absence of other coordinating additives or solvents, a second molecule of dichloroarene serves as the incoming ligand to displace Pd from the mono-cross-coupled product. Because this mechanism involves a bimolecular transition state, its rate is heavily influenced by sterics. Thus, displacement of Pd from the mono-cross-coupled product becomes disfavored with extremely bulky ligands or with additional substituents on the substrate, leading to an increase in diarylation due to competing oxidative addition at the remaining halide. We find no evidence for release of mono-cross-coupled product by direct dissociation of Pd as 12*e*⁻ PdL.

This work suggests several guidelines for minimizing overfunctionalization in cross-couplings of polyhalogenated substrates. First, less hindered ligands should be considered when possible. However, bulky ligands have been critical to many recent advances in cross-coupling catalysis, and should not necessarily be avoided.[21] In these cases, addition of small coordinating additives such as DMSO may be able to suppress overfunctionalization. Furthermore, overfunctionalization is more likely for more highly substituted substrates, due to slower displacement of Pd from the mono-cross-coupled product, and for substrates bearing heavier halides due to faster oxidative addition. If ringwalking is desired for exhaustive cross-coupling or catalyst-transfer polymerization, avoiding coordinating additives or "throwaway" ligands may be beneficial.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental and computational details, NMR spectra, and calculated energies (PDF)

Cartesian coordinates of minimum-energy calculated structures (XYZ)

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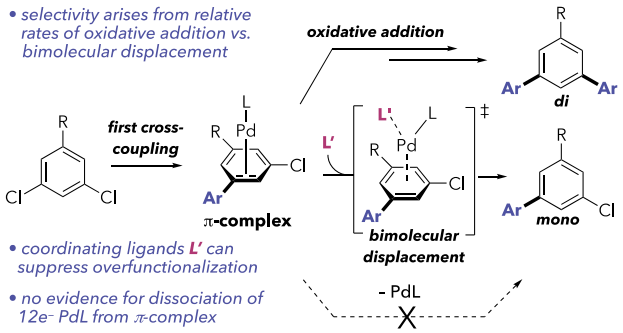
• selectivity arises from relative rates of oxidative addition vs. bimolecular displacement
oxidative addition
first cross-coupling
π-complex
bimolecular displacement
di
mono
- PdL
• coordinating ligands L' can suppress overfunctionalization
• no evidence for dissociation of 12e⁻ PdL from π-complex