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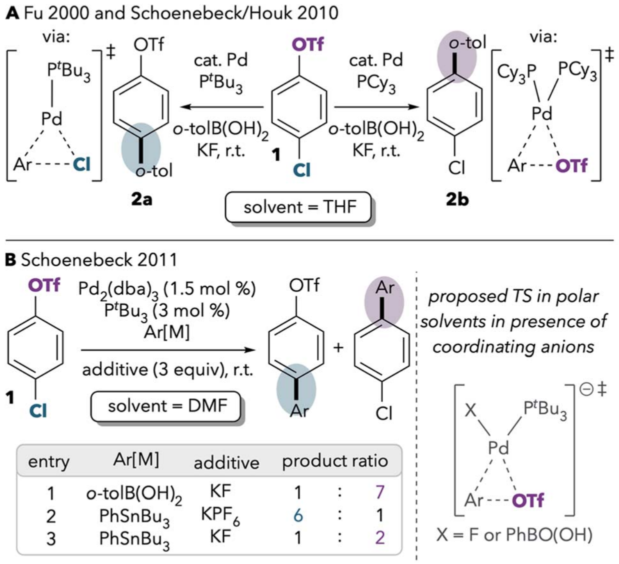
Solvent coordination to palladium can invert the selectivity of oxidative addition†

Emily K. Elias, ‡ Steven M. Rehbein ‡ and Sharon R. Neufeldt *

Reaction solvent was previously shown to influence the selectivity of Pd/P^{t}Bu$_3$-catalyzed Suzuki–Miyaura cross-couplings of chloroaryl triflates. The role of solvents has been hypothesized to relate to their polarity, whereby polar solvents stabilize anionic transition states involving [Pd(P^{t}Bu$_3$)(X)]$^-$ (X = anionic ligand) and nonpolar solvents do not. However, here we report detailed studies that reveal a more complicated mechanistic picture. In particular, these results suggest that the selectivity change observed in certain solvents is primarily due to solvent coordination to palladium. Polar coordinating and polar noncoordinating solvents lead to dramatically different selectivity. In coordinating solvents, preferential reaction at triflate is likely catalyzed by Pd(P^{t}Bu$_3$)(solv), whereas noncoordinating solvents lead to reaction at chloride through monoligated Pd(P^{t}Bu$_3$). The role of solvent coordination is supported by stoichiometric oxidative addition experiments, density functional theory (DFT) calculations, and catalytic cross-coupling studies. Additional results suggest that anionic [Pd(P^{t}Bu$_3$)(X)]$^-$ is also relevant to triflate selectivity in certain scenarios, particularly when halide anions are available in high concentrations.

Oxidative addition is a key elementary step in diverse transformations catalyzed by transition metals.[1] For instance, this step is common to traditional cross-coupling reactions, which are among the most widely used methods for small molecule synthesis. During the oxidative addition step of cross-coupling reactions, a low valent metal [usually Pd(0)] inserts into a C–X bond with concomitant oxidation of the metal by two electrons. The "X" group of the C–X bond is commonly a halogen or triflate. Despite a wealth of research into this step,[2–5] uncertainties remain about its mechanistic nuances. The mechanistic details are especially pertinent to issues of selectivity that arise when substrates contain more than one potentially reactive C–X bond.[6]

One of the best-studied examples of divergent selectivity at the oxidative addition step is the case of Pd-catalyzed Suzuki couplings of chloroaryl triflates. In 2000, Fu reported that a combination of Pd(0) and P^{t}Bu$_3$ in tetrahydrofuran (THF) effects selective coupling of **1** with *o*-tolylB(OH)$_2$ *via* C–Cl cleavage, resulting in retention of the triflate substituent in the final product **2a** (Scheme 1A).[7] In contrast, the use of PCy$_3$ (ref. 7) or most other phosphines[8] provides complementary selectivity (product **2b**) under similar conditions. The unique selectivity imparted by P^{t}Bu$_3$ was later attributed to this ligand's ability to promote a monoligated oxidative addition transition state on account of its bulkiness.[5,8] Smaller ligands, on the other hand, favor bisligated palladium, which prefers to react at triflate. The relationship between palladium's ligation state and chemoselectivity has been rationalized by Schoenebeck and Houk through a distortion/interaction analysis.[5] In brief, the selectivity preference of PdL$_2$ is dominated by a strong



entry	Ar[M]	additive	product ratio
1	o-tolB(OH)$_2$	KF	1 : 7
2	PhSnBu$_3$	KPF$_6$	6 : 1
3	PhSnBu$_3$	KF	1 : 2

Scheme 1 Seminal reports on the effects of (A) ligands and (B) solvents on the selectivity of cross-coupling of a chloroaryl triflate.[5,7,9]

Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717, USA. E-mail: sharon.neufeldt@montana.edu

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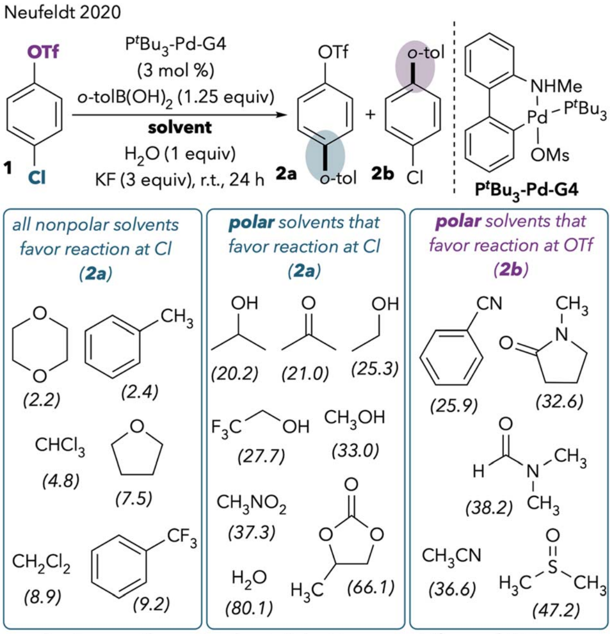
‡ These authors contributed equally.

interaction between the electron-rich Pd and the more electrophilic site (C–OTf). On the other hand, PdL is less electron-rich and its selectivity preference mainly relates to minimizing unfavorable distortion energy by reacting at the more easily-distorted C–Cl bond.

Proutiere and Schoenebeck later discovered that replacing THF with dimethylformamide (DMF, Scheme 1B, entry 1) or acetonitrile caused a change in selectivity for the Pd/P^{t}Bu$_3$ system.[9,10] In these two polar solvents, preferential reaction at triflate was observed, and P^{t}Bu$_3$ no longer displayed its unique chloride selectivity. The possibility of solvent coordination to Pd was considered, as bisligated Pd(P^{t}Bu$_3$)(solv) would be expected to favor reaction at triflate. However, solvent coordination was ruled out on the basis of two intriguing studies. First, DFT calculations using the functional B3LYP suggested that solvent-coordinated transition states are prohibitively high in free energy (about 16 kcal mol^{-1} higher than the lowest-energy monoligated transition structure). Second, the same solvent effect was not observed in a Pd/P^{t}Bu$_3$-catalyzed base-free Stille coupling in DMF (Scheme 1B, entry 2). Instead, the Stille coupling was reported to favor reaction at chloride despite the use of a polar solvent. This result appears inconsistent with the possibility that solvent coordination induces triflate-selectivity, as coordination of DMF to Pd should be possible in both the Stille and Suzuki conditions, if it happens at all. Instead, it was proposed that the key difference between the Suzuki and Stille conditions was the absence of coordinating anions in the latter (unlike traditional Suzuki couplings, Stille couplings do not necessarily require basic additives such as KF to promote transmetalation). Indeed, when KF or CsF was added to the Stille reaction in DMF, selectivity shifted to favor reaction at triflate (Scheme 1B, entry 3), thereby displaying the same behavior as the Suzuki coupling in this solvent. On the basis of this and the DFT studies, it was proposed that polar solvents induce a switch in chemoselectivity if coordinating anions like fluoride are available by stabilizing anionic bisligated transition structures (Scheme 1B, right).

However, our recent extended solvent effect studies produced confounding results.[11] In a Pd/P^{t}Bu$_3$-catalyzed Suzuki cross-coupling of chloroaryl triflate **1**, we observed no correlation between solvent polarity and chemoselectivity (Scheme 2). Although some polar solvents such as MeCN, DMF, and dimethylsulfoxide (DMSO) favor reaction at triflate, a number of other polar solvents provide the same results as nonpolar solvents by favoring reaction at chloride. For example, cross-coupling primarily takes place through C–Cl cleavage when the reaction is conducted in highly polar solvents like methanol, water, acetone, and propylene carbonate. In fact, the only solvents that promote reaction at triflate are ones that are commonly thought of as "coordinating" in the context of late transition metal chemistry.[12] These are solvents containing nitrogen, sulfur, or electron-rich oxygen lone pairs (nitriles, DMSO, and amides). The observed solvent effects were upheld for a variety of chloroaryl triflates and aryl boronic acids.[11]

We have sought to reconcile these observations with the earlier evidence[9] against solvent coordination. Herein we report detailed mechanistic studies indicating that coordinating solvents alone are sufficient to induce the observed selectivity switch. In solvents like DMF and MeCN, stoichiometric oxidative addition is favored at C–OTf even in the absence of anionic additives. The apparent contradiction between our observations and the previously-reported DFT calculations and base-free Stille couplings is reconciled by a reevaluation of those studies. In particular, when dispersion is considered in DFT calculations, neutral solvent-coordinated transition structures involving Pd(P^{t}Bu$_3$)(solv) become energetically feasible. Furthermore, we find that the selectivity analysis in the Stille couplings is convoluted by low yields, the formation of side products, and temperature effects. When these factors are disentangled, the Stille coupling in DMF displays selectivity similar to the Suzuki coupling in the same coordinating solvent. In light of these new results, anionic bisligated [Pd(P^{t}Bu$_3$)(X)]$^-$ does not appear to be the dominant active catalyst in nonpolar or polar solvents unless special measures are taken to increase the concentration of free halide, such as adding tetraalkylammonium halide salts or crown ethers.



number in parentheses is solvent dielectric constant (from ref. 18)

Scheme 2 Expanded solvent effect studies in the Pd/P^{t}Bu$_3$-catalyzed Suzuki coupling.[11]

Results and discussion

Based on the observed solvent trends in Scheme 2, we hypothesized that selectivity depends on the solvent's ability to coordinate to palladium during oxidative addition. In this scenario, oxidative addition of triflate in solvents such as DMF would not necessarily involve anionic [Pd(P^{t}Bu$_3$)(X)]$^-$, but rather would involve neutral solvent-bound palladium such as Pd(P^{t}Bu$_3$)(DMF). The experiments described below support this hypothesis. We also considered the hypothesis that selectivity could relate to the solvent's ability to solubilize the base (KF). In solvents in which

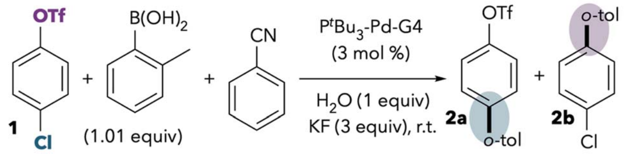
KF is more soluble, a higher concentration of anions [F^-, HO^-, or $ArBO(OH)^-$] would be available to promote formation of anionic palladium. However, we found no correlation between KF solubility and selectivity (see ESI† for details on this and other alternative hypotheses).

Effect of benzonitriles on selectivity

Nitriles, including acetonitrile and benzonitrile, were observed to promote reaction at triflate (Scheme 2). Because nitriles are common σ-donor ligands for Pd, we were interested in whether the use of nitriles as substoichiometric additives rather than solvents would still provoke a change in selectivity. To answer this question, the Suzuki reaction was conducted under our standard optimized conditions with THF as solvent in the presence or absence of 0.5 equiv. of benzonitrile (Table 1). This small amount of benzonitrile, corresponding to <3% of the solvent volume, should have a minimal effect on the polarity of the reaction medium. Our optimized conditions use Buchwald's air-stable P^tBu_3-Pd-G4 precatalyst (see Scheme 2) for convenience of handling. Importantly, the use of the Buchwald precatalyst does not impact selectivity when compared to Fu's original system using $Pd_2(dba)_3$ (see ref. 11 and ESI†).[7,13] One equivalent of water was routinely added to the Suzuki couplings because this leads to better reproducibility. Small amounts of water are needed to promote transmetallation, and our lab is located in a particularly dry climate where adventitious water can be negligible. However, the addition of 1 equiv. of water does not impact observed selectivities (see ESI†). All results reported herein are the average of at least 2 trials (see ESI† for results of individual replicates). The estimated uncertainty in total mass balance for each catalytic trial is about ±3% due to measurement and instrument error (see ESI†).

Consistent with the hypothesis that benzonitrile can coordinate to palladium and influence selectivity, even a substoichiometric amount of PhCN (0.5 equiv.) in THF leads to erosion of chloride-selectivity when compared to the reaction without PhCN. Although the reaction gives >70 : 1 selectivity for **2a** in the absence of PhCN (Table 1, entry 1), the addition of 0.5 equiv. of PhCN leads to a lower selectivity of 14 : 1 (**2a** : **2b**, entry 2). For comparison, the use of PhCN as solvent provides a complete reversal of selectivity, affording **2a** and **2b** in a ratio of 1 : 8 (entry 3). Analysis of other ratios of PhCN : THF reveals that selectivity inverts when PhCN comprises 10–25% of the total solvent volume, and that small amounts of PhCN lead to lower conversion than observed in either neat THF or PhCN (see ESI† for details and discussion).

Table 1 Effect of benzonitrile on selectivity[a]



Entry	Solvent	PhCN (equiv.)	1 (%)	2a (%)	2b (%)	2a : 2b
1	THF	0	20	74	<1	>74 : 1
2	THF	0.5	39	55	4	14 : 1
3	PhCN	(Solvent)	27	7	53	1 : 8

[a] GC yields calibrated against undecane as the internal standard. Average of at least three trials. ≤4% yield of the diarylated product was detected in all trials.

We next repeated this experiment using a series of substituted benzonitriles, inspired by a similar experiment performed by Watson and coworkers.[14] This study led to a linear free energy relationship plot that revealed a positive correlation between Hammett σ^+ values and preference for reaction at chloride (Fig. 1).[15] Benzonitriles bearing more electron-donating groups in the *para* position are expected to be better σ-donors (better ligands) for palladium. Indeed, more reaction at triflate is observed with more electron-rich benzonitriles, consistent with the hypothesis that σ-donation of the nitrile to palladium during oxidative addition promotes reaction at triflate. However, even the most electron-deficient benzonitriles lead to more reaction at triflate compared to the results in the absence of benzonitrile additives (horizontal dashed line in Fig. 1).

Solvent variants with modified coordinating ability

Like benzonitrile, acetonitrile also promotes reaction at triflate. We hypothesized that a more electron-deficient derivative of acetonitrile would coordinate more poorly to palladium, and thereby display less of a preference for triflate selectivity than acetonitrile itself. Indeed, the use of fluoroacetonitrile leads to poor selectivity (**2a** : **2b** = 1 : 2; Table 2, entry 2), whereas MeCN strongly favors reaction at triflate (entry 1). This observation is consistent with weaker coordination of fluoroacetonitrile to

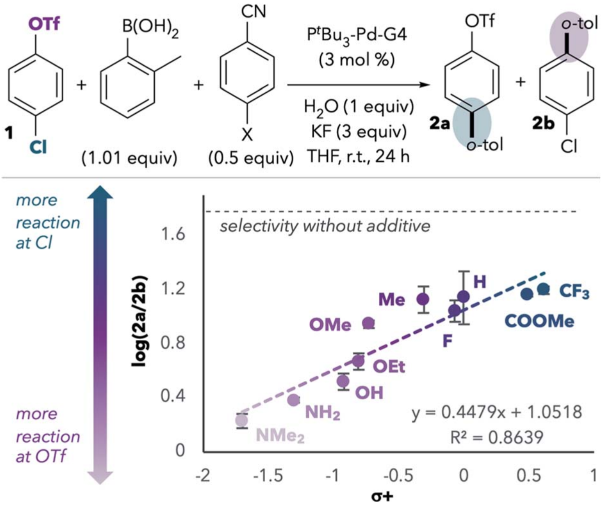
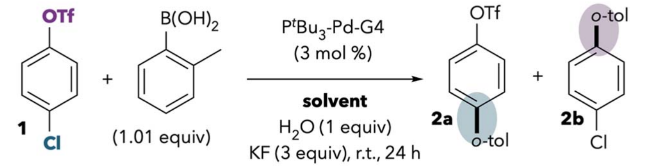
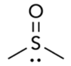


Fig. 1 Hammett-type plot shows a correlation between benzonitrile donor ability and increasing reaction at triflate. Each data point represents the average of three trials, and the error bars represent standard deviation.

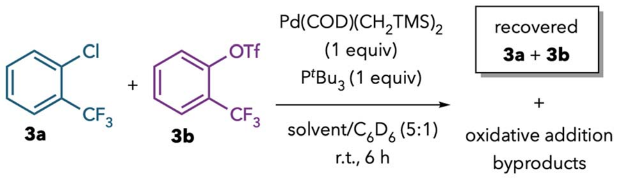
Table 2 Modifying the coordinating ability of common solvents leads to changes in selectivity[a]



Entry	Solvent	ε^b	2a (%)	2b (%)	2a : 2b
1	CH_3CN	36.6	2	77	1 : 39
2	CH_2FCN	~36	4	10	1 : 2
3		47.2	1	45	1 : 45
4		42.2	44	11	4 : 1

[a] GC yields calibrated against undecane as the internal standard. Average of two trials. ≤3% yield of the diarylated product was detected in all trials. [b] Dielectric constants from ref. 18 (entries 1–4) and ref. 19 (entry 2).

Table 3 Solvent effect on selectivity of stoichiometric oxidative addition



		Recovered[a] (%)		Reacted
Entry	Solvent	3a	3b	3a : 3b
1	Toluene	89	≥99	≥11 : 1
2[b]	Toluene	52	98	24 : 1
3	THF	55	97	15 : 1
4	Acetone	71	98	15 : 1
5	MeOH	70	≥99	≥30 : 1
6	MeCN	97	1	1 : 33
7	DMF	78	44	1 : 3
8	Sulfolane	86	95	3 : 1
9	PC[c]	83	94	3 : 1
10[d]	MeCN	≥99	≥99	—
11[d]	DMF	≥99	≥99	—
12[e]	MeCN	n.a.	3	—
13[e]	DMF	n.a.	28	—

[a] ^{19}F NMR yields calibrated against C_6H_5F as an internal standard. Average of two trials. [b] Heated to 80 °C for 2 h. [c] PC = propylene carbonate. [d] $Pd(COD)(CH_2TMS)_2$ was omitted from the reaction mixture. [e] **3a** was omitted from the reaction mixture (n.a. = not applicable).

palladium, resulting in a lower concentration of $Pd(P^tBu_3)(solv)$ and less reaction at triflate.

We also compared DMSO to sulfolane. DMSO, a highly polar sulfoxide, can coordinate to soft metals through sulfur's lone electron pair.[16] The use of DMSO as solvent strongly favors reaction at triflate (Table 2, entry 3). Sulfolane has a similar polarity to DMSO, but because it is a sulfone (no lone pair on sulfur) it cannot coordinate to metals in the same manner as DMSO. Consistent with coordinating ability being a critical solvent feature, the use of sulfolane as solvent provides the opposite selectivity as DMSO (entry 4).[17]

Stoichiometric oxidative addition studies

The observed solvent trends in the Suzuki coupling support the hypothesis that solvent coordination to Pd during oxidative addition can lead to a switch in chemoselectivity. To eliminate confounding factors, we next sought to study the oxidative addition step in isolation. We conducted NMR studies on the reaction of $Pd(P^tBu_3)$ with competing aryl chloride and aryl triflate electrophiles, **3a** and **3b**.[20] These fluorinated substrates were chosen so that their consumption could be monitored by ^{19}F NMR. The putative Pd^0 complex $Pd(P^tBu_3)$ was generated *in situ* from a 1 : 1 mixture of $Pd(COD)(CH_2TMS)_2$ and P^tBu_3.[21,22] C_6D_6 was added to the reactions to facilitate locking the NMR samples.

The reaction in the noncoordinating solvents toluene, THF, acetone, sulfolane, and propylene carbonate leads to consumption of **3a** (Table 3, entries 1–5, 8 and 9), and the known complex $(P^tBu_3)Pd(2\text{-}CF_3C_6H_4)(Cl)$ is detected by ^{19}F and ^{31}P NMR in most of these solvents.[23] In contrast, nearly all of the aryl triflate **3b** remains unreacted. This result is consistent with the high selectivity for C–Cl activation observed in the catalytic Suzuki coupling of **1** in these solvents. The lower reactivity in toluene at room temperature (entry 1) is ascribed to the formation of $Pd(P^tBu_3)_2$, which can be detected by ^{31}P NMR and has been shown previously to react sluggishly with aryl chlorides.[2a,b]

In contrast to the results in non-coordinating solvents, the use of MeCN or DMF leads to preferential consumption of **3b** *via* C–OTf activation. In MeCN, **3b** is nearly fully consumed after 6 h at room temperature (entry 6), with concomitant formation of palladium black,[24–26] an intractable mixture of trifluoromethyl-containing by-products, and a new ^{19}F signal at −77.5 ppm assigned to "free" triflate anion by comparison to the chemical shift of NBu_4OTf in the same solvent mixture. Similar results are observed in DMF (entry 7), albeit with lower conversion and lower selectivity compared to MeCN.[27]

Interestingly, the ^{31}P NMR spectrum of the reaction in DMF reveals a signal at ~75 ppm that is not detected in any of the other solvents. This signal is also observed when **3a** is omitted from the reaction mixture (entry 13). Monitoring the reaction over time reveals that a signal at ~64 ppm is also present at early time points, but is completely replaced by the ~75 ppm signal within 3 h (see ESI†). The ~64 ppm signal can also be detected at 6 h when the reaction is run at 0 °C (see ESI†). We hypothesize that these two signals, which are unique to the reaction in DMF, represent DMF-coordinated species such as

$[ArPd(P^tBu_3)(DMF)_2]OTf$, resulting from oxidative addition of the triflate. Analogous signals are not observed in MeCN, despite its strong coordinating ability. MeCN-bound oxidative addition adducts may decompose more readily due to the smaller sterics of MeCN. For example, NMR and GCMS data indicate that one decomposition pathway under these conditions involves Heck coupling with COD (see ESI†), and coordination of COD to Pd(II) may be less favored in the presence of bulkier DMF ligands compared to MeCN ligands.

Importantly, palladium-free control studies demonstrate that the substrates do not decompose in the absence of Pd (entries 10 and 11). Furthermore, the presence of **3a** is not necessary for reaction of **3b** to take place in coordinating solvents, suggesting that formation of an anionic species like $[Pd(P^tBu_3)(Cl)]^-$ *via* initial C–Cl activation of **3a**, is not a prerequisite for C–OTf activation in these experiments (entries 12 and 13).[28]

The results of these stoichiometric studies provide strong evidence that coordinating solvents alone—in the absence of anionic ligands for Pd—can promote a switch in the chemoselectivity of oxidative addition compared to the use of non-coordinating solvents. Based on the known preference for bisligated Pd to react at triflate over chloride, the most likely explanation for the observed selectivity in coordinating solvents is involvement of $Pd(P^tBu_3)$(solv) during oxidative addition. We next turned to computational studies to further evaluate the feasibility of solvent-bound species.

DFT studies

In the earlier report by Proutiere and Schoenebeck, solvent coordination to Pd during oxidative addition at C–OTf was tentatively ruled out, in part on the basis of the high energy values that were calculated for such transition structures.[9] The prior DFT results had indicated that solvent-coordinated transition structures involving $Pd(P^tBu_3)$(solv) were prohibitively high-energy compared to monoligated transition structures with $Pd(P^tBu_3)$. However, those calculations were conducted with a DFT method (B3LYP)[33] that does not take dispersion into account. Schoenebeck and others have since demonstrated that, in general, the computed energies of crowded structures are significantly lower when dispersion is considered.[34,35]

Therefore, we reevaluated the energetics of solvent coordination to Pd using methods that include dispersion. Fig. 2 compares the results of calculations performed with B3LYP (no dispersion) and with MN15L[36] (accounts for dispersion) using the CPCM solvation model for DMF. When dispersion is not considered (Fig. 2A), the DMF-coordinated transition structure for oxidative addition at triflate (**TS5b-dmf**) is about 16 kcal mol^{-1} higher in energy than the lowest-energy monoligated transition structure (**TS5a**), suggesting that **TS5b-dmf** is unfeasible. However, use of MN15L leads to very different results: **TS5b-dmf** is now predicted to be favored over **TS5a** (Fig. 2B).[37] At minimum, these results demonstrate that solvent coordination should not be ruled out on the basis of DFT calculations. Instead, solvent coordination to palladium is likely to be energetically feasible during oxidative addition, especially under experimental conditions in which solvent is in large excess relative to Pd and substrate.

Stille cross-couplings

Although the Pd/P^tBu_3-catalyzed Suzuki coupling of 1 in DMF favors reaction at triflate, the analogous base-free Stille coupling was reported to favor reaction at chloride in this solvent (see Scheme 1B, entry 2). This result is perplexing, because Suzuki and Stille couplings are thought to proceed through the same oxidative addition step, and our stoichiometric NMR studies indicate that oxidative addition of triflate is preferred in DMF even in the absence of anionic additives.

To understand this contradiction, we examined the Stille coupling between **1** and $PhSnMe_3$ in DMF (Scheme 3).[38,39] Poor conversion is observed at room temperature,[40] but **7b** is slightly favored over **7a**. Methylated products **7e** and **7f** were also detected in the reaction mixture.[41] Overall, the ratio of chloride : triflate activation under these conditions is approximately 4 : 7 [(**7a** + **7e**) : (**7b** + **7f**)], which is qualitatively consistent with the triflate selectivity observed in the Suzuki coupling and in the stoichiometric oxidative addition studies. These results suggest that there may not be a discrepancy between the behavior of Pd/P^tBu_3 in the catalytic Suzuki *vs.* Stille couplings in DMF. However, the low conversion in the Stille coupling calls into question the accuracy of selectivity analysis for at least two reasons. First, measurement errors may be introduced when integrating small product peaks on a GC chromatogram or when isolating small quantities of materials. More importantly, the low conversion suggests a very sluggish rate of cross-coupling. If cross-coupling is slow, it is possible for undesired processes like catalyst decomposition to compete with coupling, which could lead to different catalyst speciation compared to the much faster Suzuki coupling system.[42]

In an effort to increase the conversion of the Stille coupling, the reaction was heated to 100 °C. Slightly higher yields were observed at this temperature, and, interestingly, reaction at chloride becomes preferred. The ratio of chloride : triflate activation under these conditions is approximately 59 : 7 [(**7a** + **7e**) : (**7b** + **7f**)]. The chloride preference under these conditions is consistent with the prior report.[9] However, further examination suggests that the selectivity at 100 °C should not be compared to the selectivity at room temperature. We observe an analogous change in selectivity upon heating the Suzuki coupling of **1** in DMF. At 100 °C, selectivity is eroded when using Buchwald's P^tBu_3-Pd-G4 catalyst (Table 4, compare entries 1 and 2). Furthermore, selectivity actually inverts at 100 °C when using a mixture of $Pd_2(dba)_3$ and $Pd(P^tBu_3)_2$ (entries 3 and 4).[43] High temperatures are expected to disfavor bisligated Pd (*i.e.*, reaction at triflate) for entropic reasons. However, the observation that precatalyst influences the selectivity at 100 °C indicates that the increased formation of **2a** may reflect more than simply an entropic penalty. We hypothesize that the palladium catalyst is transformed at high temperature into a species that displays different selectivity than the active catalyst at room temperature.[44,45] As such, a high-temperature Stille coupling is

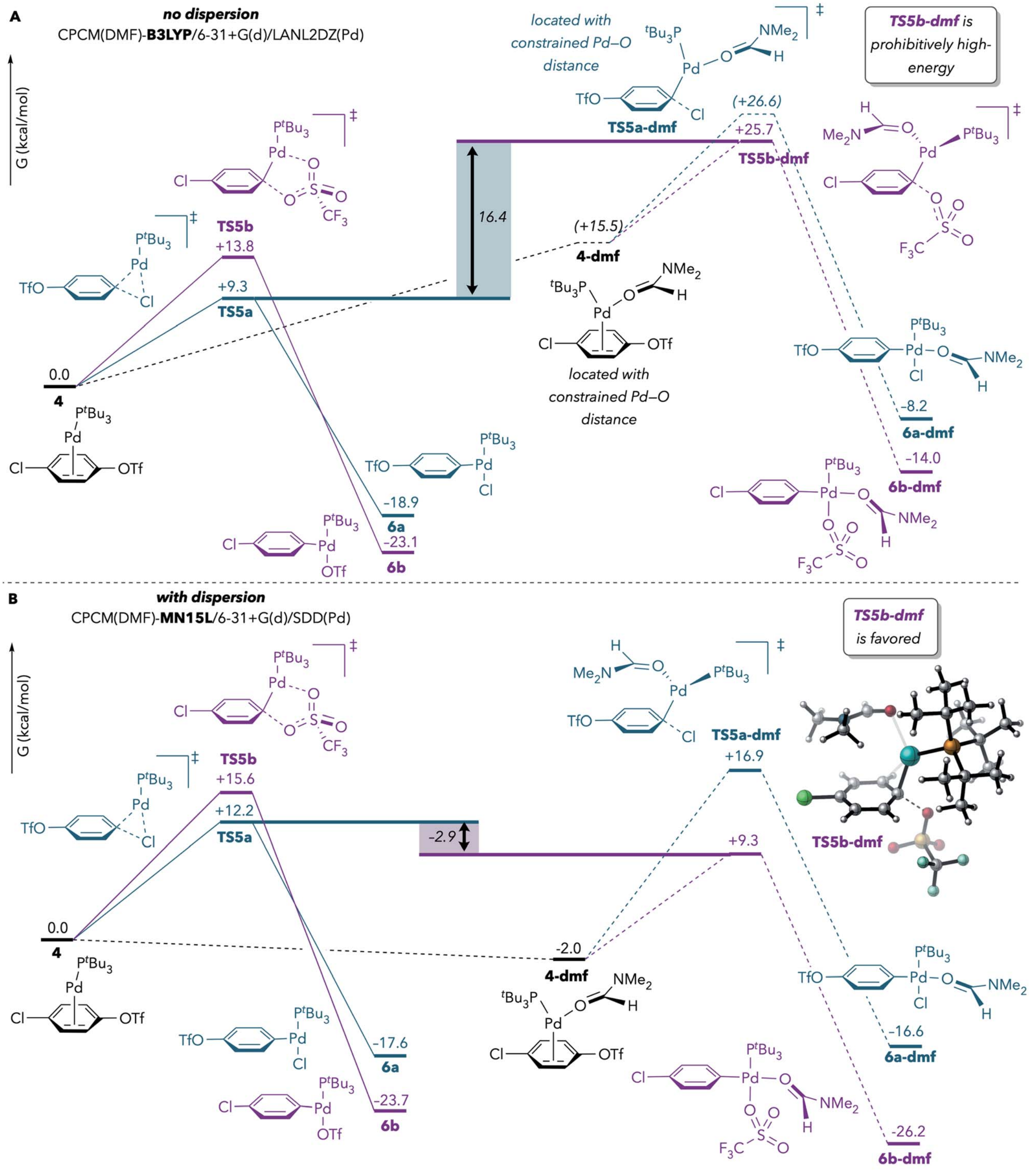
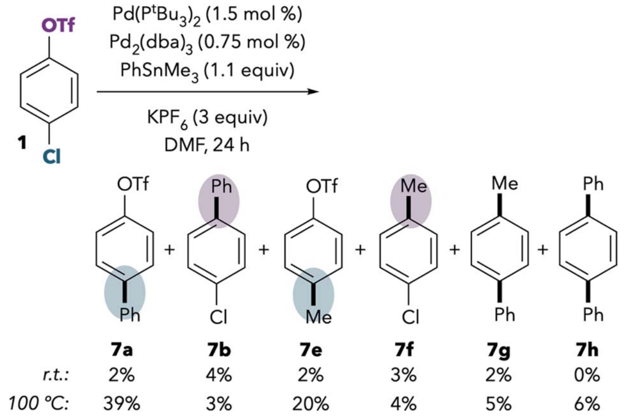


Fig. 2 Effect of dispersion on the stability of DMF-coordinated oxidative addition transition structures. Calculations were performed (A) without dispersion or (B) with dispersion. Free energy values are corrected for concentration (DMF : Pd = 765 : 1) and are reported after applying Cramer and Truhlar's[29] and Head-Gordon's[30] quasi-harmonic approximations to vibrational entropy and enthalpy, respectively.[31,32]

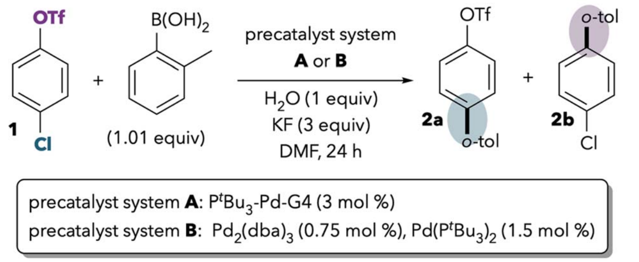
not comparable to a room-temperature Suzuki coupling or to the room-temperature oxidative addition studies. For these reasons, and in order to achieve a faster rate for the room temperature Stille coupling, we next examined the use of a more reactive substrate, **8**.[46]

The room-temperature Stille coupling between $PhSnMe_3$ and chloronaphthol derivative **8** proceeds to higher conversion compared to the reaction of 1 (Table 5, entry 1). After 24 h, only 24% of **8** remained unreacted, and numerous products were detected by GCMS. The two major products are **9b** and **9d**,



Scheme 3 Base-free stille coupling of **1** Catalyzed by Pd/P^{t}Bu$_3$. GC yields calibrated against dodecane as an internal standard. Results are the average of two trials. Leftover **1**: 83% at r.t., 4% at 100 °C.

Table 4 Effect of temperature on the selectivity of the Pd/P^{t}Bu$_3$-catalyzed Suzuki coupling of **1**[a]



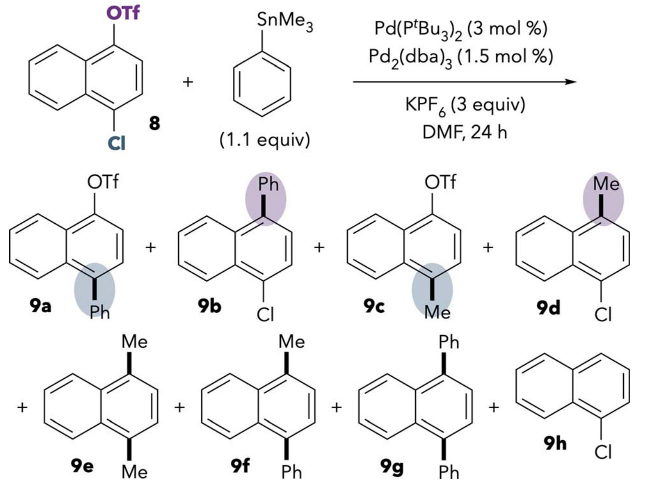
Entry	Cat.	Temp (°C)	**1** (%)	**2a** (%)	**2b** (%)	Ratio **2a** : **2b**
1	A	r.t.	23	10	60	1 : 6.0
2	A	100	2	21	30	1 : 1.4
3	B	r.t.	17	11	67	1 : 6.1
4	B	100	7	33	23	1.4 : 1

[a] GC yields calibrated against undecane as an internal standard. Results are the average of at least two trials. ≤2% yield of the diarylated product was detected in all trials.

resulting from triflate activation. Overall, the ratio of chloride : triflate activation is ~4 : 52 [(**9a** + **9c**) : (**9b** + **9d** + **9h**)]. Again, these results show that the Stille coupling displays the same oxidative addition preference as the Suzuki coupling in DMF. Consistent with earlier observations, more reaction at chloride is observed upon heating (entry 2). At 100 °C, the ratio of chloride : triflate activation is ~46 : 17 [(**9a** + **9c**) : (**9b** + **9d** + **9h**)]. Similar selectivity trends are observed when using PhSn^{n}Bu$_3$ instead of PhSnMe$_3$ (see ESI†).

Taken together, our studies indicate that the selectivity of oxidative addition is similar under stoichiometric, catalytic Suzuki, and base-free Stille conditions at room temperature in DMF. This conclusion is consistent with the hypothesis that DMF coordinates to palladium and promotes C–OTf oxidative addition at a bisligated Pd(P^{t}Bu$_3$)(DMF) complex.

Table 5 Base-free Stille coupling of **8** catalyzed by Pd/P^{t}Bu$_3$[a]



Entry	Temp	8	9a	9b	9c	9d	9e	9f	9g	9h
1	r.t.	24	1	**9**	3	**42**	1	1	1	1
2	100 °C	1	**13**	4	**33**	12	1	8	9	1

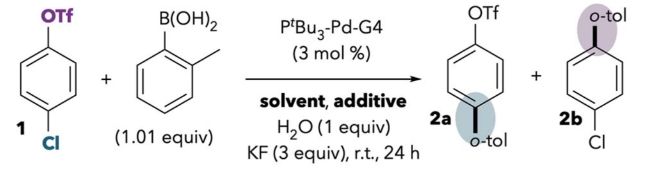
[a] GC yields calibrated against undecane as an internal standard. Results are the average of two trials. No other products derived from **8** could be identified by GCMS.

Role of anions on selectivity

The evidence presented thus far strongly suggests that coordinating solvents can promote oxidative addition at triflate through solvent-ligated transition states. As such, it is not necessary to invoke anionic [Pd(P^{t}Bu$_3$)(X)]$^-$ to explain the selectivity of Suzuki couplings of chloroaryl triflates in coordinating solvents. However, oxidative addition of PhOTf at [PdL(X)]$^-$ in the presence of quaternary ammonium chloride and bromide salts has been described by Hartwig [L = (P(*o*-tolyl)$_3$)].[47] Oxidative addition at anionic palladium complexes bearing electron-deficient phosphines or in the absence of phosphines or other strong ancillary ligands has also been proposed.[48] Furthermore, DFT calculations suggest that if [Pd(P^{t}Bu$_3$)(X)]$^-$ participates in oxidative addition, it would preferentially react at triflate as seen for other PdL$_2$ complexes.[5,9,11] We speculated that transition states involving [Pd(P^{t}Bu$_3$)(X)]$^-$ might be primarily responsible for triflate selectivity under some conditions.

To evaluate this possibility, we subjected substrate **1** to Suzuki coupling conditions in THF in the presence of a variety of anionic additives (Table 6). As previously reported, reaction at chloride is strongly favored in the absence of extra additives, despite the use of KF (a source of fluoride anion) as a base (entry 1). This suggests that bisligated palladium is not the active catalyst under these conditions. However, addition of 18-crown-6, a chelator for K$^+$, induces a reversal of selectivity (entry 2). Alternatively, replacing potassium with a noncoordinating tetrabutylammonium cation also promotes reaction at triflate, albeit with significant substrate decomposition (entry 3). These

Table 6 Effect of additives on the selectivity of the Suzuki cross-coupling[a]



Entry	Solvent	Additive (equiv.)	1 (%)	2a (%)	2b (%)	Ratio **2a** : **2b**
1	THF	—	20	74	<1	>74 : 1
2	THF	18-Crown-6 (3)	0	1	76	1 : 38
3[b]	THF	NBu_4F (3)	<1	<1	13	<1 : 13
4	THF	NBu_4Cl (1)	20	4	69	1 : 17
5	THF	NBu_4Br (1)	3	2	91	1 : 46
6	THF	NBu_4OTf (1)	26	70	3	23 : 1
7	PC	—	15	71	5	14 : 1
8	PC	18-Crown-6 (3)	5	1	11	1 : 11
7	^{i}PrOH	—	2	87	1	87 : 1
8	^{i}PrOH	18-Crown-6 (3)	0	0	3	<1 : 3
11	DMF	—	20	10	61	1 : 6
12	DMF	18-Crown-6 (3)	0	0	47	<1 : 47

[a] GC yields calibrated against undecane as the internal standard. Average at least of two runs. ≤2% yield of the diarylated product was detected in all trials except entry 2 (8% yield of diarylated product). PC = propylene carbonate. [b] KF was omitted from the reaction mixture.

results suggest that increased availability of free fluoride facilitates reaction at triflate through a mechanism involving $[Pd(P^tBu_3)(X)]^-$. A similar effect is observed with added tetrabutylammonium salts of Cl^- and Br^- (entries 4 and 5). Because chloride and bromide are not basic, their effect on selectivity is unlikely to result from an increase in concentration of hydroxide (from water) or deprotonated boronic acid. Instead, it is reasonable to conclude that these salts promote reaction at triflate through formation of $[Pd(PtBu_3)(Cl)]^-$ or $[Pd(P^tBu_3)(Br)]^-$. The quaternary ammonium salt of a non-coordinating anion (NBu_4OTf) does not have the same effect as the halide salts (entry 6), suggesting that the selectivity change with NBu_4F, NBu_4Cl, and NBu_4Br is not due to a medium effect. In the polar noncoordinating solvents ^{i}PrOH and propylene carbonate, the addition of 18-crown-6 also leads to a reversal of selectivity with an increase in the total yield of **2b** (entries 7–10). However, poor mass balance is observed, likely due to an enhanced rate of triflate hydrolysis under the more basic conditions. The preexisting triflate selectivity appears to be enhanced in DMF upon the addition of 18-crown-6 (compare entries 11 and 12), although the overall quantity of **2b** produced is lower and the poor mass balance complicates interpretation of the selectivity. Taken together, the results in Table 6 show that higher concentrations of "naked" anions promote reaction at triflate. This observation is consistent with the involvement of $[Pd(P^tBu_3)(X)]^-$ under specific conditions that provide free anions in high concentration.

Conclusions

A series of studies were conducted to understand the observed solvent effects in the Pd/P^tBu_3-catalyzed Suzuki coupling of chloroaryl triflates. The results provide strong evidence for solvent coordination to Pd during triflate-selective cross-coupling. A summary of the key results is as follows: the use of coordinating solvents including nitriles, amides, and sulfoxides leads to Suzuki coupling through C–OTf bond cleavage. Conversely, nonpolar solvents as well as polar solvents that are poorly coordinating to palladium, such as propylene carbonate, alcohols, and sulfolane, favor reaction at chloride. Addition of substoichiometric amounts of benzonitrile derivatives to the Suzuki reaction in THF leads to erosion of chloride selectivity, and a correlation is observed between benzonitrile donating ability and increased reaction at triflate. The solvent-dependent selectivity observed in the stoichiometric reaction between Pd/P^tBu_3 and a competing aryl chloride and triflate mirrors that of the catalytic Suzuki coupling. DFT calculations reveal that dispersion dramatically lowers the predicted barrier to oxidative addition at $Pd(P^tBu_3)$(solv). Although previous results suggested that the Pd/P^tBu_3-catalyzed Stille coupling in a coordinating solvent leads to different selectivity than the corresponding Suzuki coupling, we find that the selectivity of these two reactions is approximately identical after controlling for convoluting factors such as low yields, formation of side products, and catalyst decomposition.

To our knowledge, this work represents the first compelling evidence for involvement of a solvent ligand during Ar–X oxidative addition at homogeneous Pd in the presence of a phosphine.[49] Taken together, the studies reported herein are consistent with the following mechanistic paradigm: in the presence of P^tBu_3, preferential reaction of chloride proceeds through an oxidative addition transition state involving monoligated PdL (L = P^tBu_3), as previously established. This selectivity for chloride is observed in non-coordinating solvents in the absence of a high concentration of "naked" halide ions. In coordinating solvents, however, palladium prefers to react at triflate through a transition state involving PdL(solv). Anionic bisligated $[PdL(X)]^-$, where X = halide, also reacts preferentially at triflate. However, this anionic species does not appear to be the dominant active catalyst, even in polar solvents, unless extra measures are taken to increase the concentration of free halide. Such measures include the addition of a crown ether to chelate potassium from KF or the addition of quaternary ammonium halide salts.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

EKE: data curation, formal analysis, investigation, methodology, visualization, writing – original draft; SMR: data curation, formal analysis, investigation, methodology, validation, visualization, writing – original draft; SRN: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, visualization, writing – original draft; writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

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26 The route to formation of Pd black involves clusters and nanoparticles, and the selectivity of such intermediate multinuclear species during oxidative addition is a topic of ongoing study in our group.

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