

Bulky phosphine ligands promote palladium-catalyzed protodeboronation

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Abstract

The Suzuki-Miyaura cross-coupling reaction is plagued by protodeboronation, an undesirable side reaction with water that consumes the boronic acid derivatives required for the cross-coupling reaction. Meticulous mechanistic studies have previously established protodeboronation to be highly sensitive to the nature of the boronic reagent and reaction conditions. Particularly, the presence of bases, which are essential for the Suzuki-Miyaura coupling, is known to catalyze protodeboronation. However, protodeboronation catalyzed by palladium-phosphine complexes, the benchmark catalyst system for Suzuki-Miyaura cross-coupling, has been understudied compared to its base-catalyzed counterpart. We demonstrate, using automated high-throughput experimentation, comprehensive computational mechanistic analyses and kinetic modeling, that protodeboronation is accelerated by palladium(II) complexes bound to bulky phosphine ligands. While sterically hindered ligands are typically used to facilitate difficult cross-couplings, these ligands can instead paradoxically impede cross-coupling product formation, requiring careful and judicious consideration when choosing ligands for Suzuki-Miyaura cross-couplings.

Introduction

One of the most important uses of organoboron reagents is as a nucleophilic coupling partner in the Nobel-prize winning Suzuki-Miyaura cross-coupling (SMC) reaction, the most popular reaction for C-C bond formations, due to its low toxicity, ease of handling, and robustness.¹⁻⁴ However, organoboron compounds can be unstable in moisture, and undergo protodeboronation (PDB), yielding protoarenes *via* the loss of the boronic moiety. This side reaction has been identified by Kuivila et al. as one of the major degradation pathways of organoboron compounds even before their extensive applications in cross-coupling reactions.⁵⁻⁸ While PDB can either be a useful chemical transformation or leveraged as a means to decompose unreacted substrates during work-up,⁹⁻¹⁴ it is largely considered an undesirable and unproductive side reaction.

As the SMC occurs under basic conditions and is often conducted under at least partially aqueous conditions, the base-catalyzed PDB of arylboronic acid derivatives in aqueous media has received considerable attention.^{5,15-17} In light of this, a wide variety of strategies has been implemented to minimize PDB. One prominent strategy is through ligand design, as it is well-known that the ligand controls the activity of the palladium catalyst.^{18,19} Efforts to facilitate the SMC have been achieved with dialkylbiaryl phosphine ligands, introduced by Buchwald and co-workers, which promotes catalytic turnover by stabilizing reactive monoligated palladium species.^{18,19} Thus, efficient cross-coupling product formation can be achieved *via* ligand design towards faster product formation to outcompete protodeboronative pathways.¹⁸ At the same time, protective groups or reagents like trialkoxy-ligated boronate salts, trifluoroborates, or MIDA boronates that slowly supply their corresponding boronic acids over the course of the reaction further reduces the degree of PDB.²⁰ However, these strategies may not always be effective, particularly for sterically hindered or electron-deficient arylboronic acid derivatives.^{15,16,21}

Amongst other metals,^{6,9,22-25} PDB has also been shown to be catalyzed by Pd(OAc)₂,^{10,11} palladium-ate complexes,²⁶ palladium-phosphine complexes,¹² or environments that promote the formation of Pd black.²⁷⁻²⁹ However, to our surprise, there is a general lack of detailed investigation into how phosphine ligands in promote or suppress palladium-catalyzed PDB under conditions relevant to the SMC in spite of its popular use in the SMC.^{20,30} Instead, the SMC is typically performed with an excess of boronic reagents to compensate for the loss *via* PDB, resulting in extensive downstream purifications, and the wasteful expenditure of expensive boronic reagents. To our knowledge, the only published investigation for the role of the ligand in palladium-catalyzed PDB is that phosphine ligand oxidation can lead to poor ligation and Pd black formation, the latter of which can cause increased protodeboronation.²⁹ However, this was only investigated for a single bidentate ligand (DPEPhos) with a Pd(II) precatalyst and a limited set of reaction conditions, without any attempts to investigate how generally applicable the corresponding conclusions are.

Notably, the main focus of the work was the mechanistic impact of changing the base in the SMC and the corresponding implications from a process perspective.

In this work, we demonstrate, both experimentally and computationally, that sterically hindered phosphine ligands promote palladium-catalyzed PDB of boronic acid derivatives. Our *ab initio* mechanistic investigations reveal that sterically hindered phosphines favor the formation of an unstable post-transmetalation species that leads to facile PDB, while sterically compact phosphines favor the formation of a stable palladium-boron intermediate that prevents PDB. Through detailed kinetic modeling of the competitive rates of each protodeboronative pathway derived from reaction barriers obtained from density functional theory (DFT), we achieve semi-quantitative yield predictions for our ligands. Finally, our statistical analysis reveals a simple steric descriptor for phosphine ligands that correlates well with the degree of palladium-catalyzed PDB, guiding ligand selection for improved SMC yields.

Results and Discussion

Competitive catalytic protodeboronation versus Suzuki-Miyaura cross-coupling

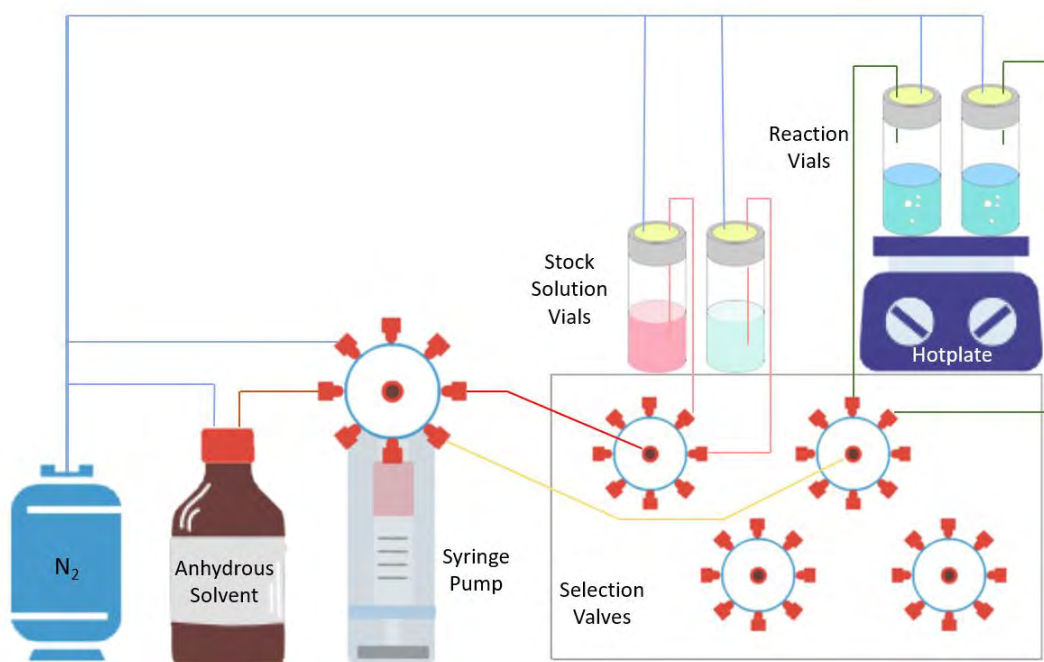


Figure 1: Hardware configuration of the high-throughput reaction screening variant of MEDUSA.

Table 1: Cross-coupled (**CPL**) and protodeboronated (**Naph**) product yields in % of the palladium-catalyzed SMC of 2-naphthalene boronic acid pinacol ester (**2-NaphBpin**) and *para*-bromodimethylaniline (***p*-BrDMA**) with varied ligands and water amounts (**x**). Yields are estimated with HPLC based on duplicate experiments. Inaccuracies in K₃PO₄ equivalents were introduced in rapid manual dosing (see **Experimental Procedures**). See **Supplementary Discussion S2.2** for the full range of conditions assessed.

c1ccc2c(c1)ccc3c2ccc(Bpin)cc3 + BrCc1ccc(NC)cc1
 $\xrightarrow[3-5 \text{ eq K}_3\text{PO}_4, \text{ dioxane, } 60^\circ\text{C, 6 h}]{5 \text{ mol\% [Pd], Ligand, H}_2\text{O}}$
CN(C)c1ccc(cc1)-c2ccc3ccccc3cc2 + c1ccc2c(c1)ccc3c2ccc(B)cc3

2-NaphBpin ***p*-BrDMA** **CPL** **Naph**

$\text{PCy}_3 =$ C1CCCCC1P(C2CCCCC2)(C3CCCCC3)C4CCCCC4
 $\text{P}^t\text{Bu}_3 =$ CC(C)(C)P(C(C)(C)C)(C(C)(C)C)C(C)(C)C
 $\text{CyJohnPhos} =$ C1CCCCC1P(C2CCCCC2)(C3CCCCC3)C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6P7(C8CCCCC8)(C9CCCCC9)C10CCCCC10
 $\text{JohnPhos} =$ CC(C)(C)P(C1=CC=CC=C1)(C2=CC=CC=C2)C3=CC=CC=C3C4=CC=CC=C4P5(C6=CC=CC=C6)(C7=CC=CC=C7)C8=CC=CC=C8

Entry	Ligand mol%	H ₂ O eq	[Pd] source	PCy ₃		P(<i>t</i> -Bu) ₃		CyJohnPhos		JohnPhos	
				CPL	Naph	CPL	Naph	CPL	Naph	CPL	Naph
1a	5	0	no Pd	0	0	0	0	0	0	0	0
1b	5	0	Pd(OAc) ₂	36	2	12	11	9	6	4	3
1c	5	20	Pd(OAc) ₂	41	1	50	11	51	14	30	22
1d	10	0	Pd(OAc) ₂	36	1	15	24	15	9	10	11
1e	10	20	Pd(OAc) ₂	40	2	52	33	52	8	44	15
1f	5	0	Pd ₂ dba ₃	3	0	7	0	3	0	1	0
1g	5	20	Pd ₂ dba ₃	12	0	16	1	4	1	6	1
1h	10	0	Pd ₂ dba ₃	38	0	41	2	28	0	14	1
1i	10	20	Pd ₂ dba ₃	65	0	85	5	68	1	50	1

In the course of our experimental investigations in a prior work, a significant amount of PDB product was observed when preparing extended conjugated systems for organic lasers using the SMC, despite relatively mild conditions being applied (**Supplementary Table S2**).³¹ Noteworthy, base-mediated PDB was not observed, and instead significant amounts of protodeboronated reactants formed with the introduction of

palladium. Thus, to explore this phenomenon further, we evaluated the competitive formation of cross-coupled (**CPL**) and protodeboronated (**Naph**) products using a model reaction, performed under typical SMC reaction conditions with different palladium sources, ligand identities and loadings, water amounts and temperatures (**Table 1, Supplementary Discussion S2.3**). As unprotected electron-deficient and heteroaromatic boronic acid derivatives tend to undergo base-catalyzed PDB very rapidly,^{15,16} we chose the electron-neutral 2-naphthalene boronic acid pinacol ester (**2-NaphBpin**) with a protected boronic ester group which is resistant to base-catalyzed PDB¹⁷ in order to isolate any observed PDB to be palladium-catalyzed PDB. Furthermore, since the SMC is generally rapid and dominant with good coupling partners like aryl iodides which makes it challenging to investigate the reaction details, we selected *para*-bromodimethylaniline (**p-BrDMA**) to modulate the reactivity for our model reaction. Due to the large volume of experiments (>100, each performed in duplicate) and the requirement of precise reagent handling (<±2.5% of 1 mg) under an inert atmosphere, manual operation becomes error prone. As automated high-throughput experiments (HTE) with robotic systems have previously been shown to be effective in cross-coupling reaction optimization campaigns,³² we fully leverage the potential of robotic synthesis and screening by implementing an automated strategy using an automated dosing robot and the HTE variant of our modular robotic synthesis platform MEDUSA (**Figure 1**).^{33,34}

Unsurprisingly, there was negligible formation of **CPL** without the presence of palladium (**Table 1, Entry 1a**). Interestingly, the presence of **Naph** was negligible as well, showing the pinacol esters' resistance to base-catalyzed PDB under our conditions in the absence of metals.^{16,17} When palladium is present, we observed promoted formation of the PDB byproduct **Naph** alongside the expected SMC product **CPL**. In addition to the known ligand effect in the palladium-catalyzed SMC, to our surprise, we also observed a significant effect of phosphine structure on **Naph** yields. Generally, cyclohexyl-substituted (Cy) phosphines show higher reactivity than their *tert*-butyl (*t*-Bu) counterparts in catalyzing productive **CPL** formation over undesirable **Naph** formation. With Pd(OAc)₂ as the palladium source, PCy₃ leads to <1% **Naph** yields and modest to high **CPL** yields in almost all cases (**Table 1, Entries 1b-1e**), while *t*-Bu-substituted phosphines lead to the significant formation of **Naph**, which in several cases have yields comparable to **CPL**. Notably, **Naph** yields can be significant when *t*-Bu substituted phosphines are used under relatively dry conditions commonly used in organic synthesis (bases were stored in desiccators or pre-dried in an oven, and dry N₂ atmosphere was applied by flushing at least 10 vessel volumes to replace O₂ and H₂O in air, see **Experimental Methods**), suggesting that adventitious water is enough to cause PDB. We propose the water comes from adsorbed H₂O on bases and glasswares, which is known to be challenging to remove with "organic dry" protocols.^{35,36}

The yields of **Naph** generally increase across different ligands when 20 eq. of H₂O is added to the reaction. We attribute this to the increased concentration of H₂O, which can provide the hydrogen atom replacing the boronic moiety through PDB (**Entry 1c, 1e vs 1b, 1d**). At the same time, the addition of H₂O promotes **CPL**

yields compared to anhydrous conditions, which was previously observed in reported mechanistic studies of the SMC.^{37–40} Notably, the ratio of **CPL**:**Naph** products generally increases significantly with the addition of 20 eq. of H₂O. This suggests that even though PDB is facilitated with higher H₂O content, performing the SMC under partially aqueous conditions is still beneficial to improve the selectivity for cross-coupled products.⁴¹ Increasing the palladium loading from 5 mol% to 10 mol% does not lead to proportional increases of either **CPL** or **Naph** yields, suggesting the existence of complicated off-cycle equilibria and/or catalyst deactivation processes (**Entry 1d, 1e vs 1b, 1c**).

As typical SMC conditions involve Pd(0)-Pd(II) cycles, we further evaluated Pd₂dba₃ as the Pd(0) source (**Entries 1f-1i**). We note that various other oxidation states have been shown to be relevant for the SMC, but it is unlikely that palladium exists under those oxidation states under our conditions.^{42–46} The yields of **Naph** are generally negligible and yields of **CPL** are generally much higher, revealing more efficient SMC over PDB. Therefore, Pd(0) species likely play a minor role in palladium-catalyzed PDB, unlike their dominant role in the SMC catalytic cycle. Similar to previous observations, adding 20 eq. H₂O promotes the yield of **CPL** (**Entry 1g, 1i vs 1f, 1h**), but **CPL** yields are affected more significantly when ligand equivalents are increased to 2 eq., as excess phosphines are required to replace the dba ligand and generate mononuclear Pd(0) active species (**Entry 1h, 1i vs 1f, 1g**).

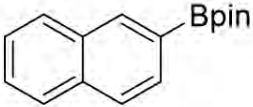
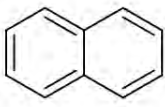
Screening conditions for palladium-catalyzed protodeboronation

Having established that PDB can be promoted by phosphine-ligated palladium complexes, we focused on understanding the key factors of PDB without the presence of a coupling partner. Such a simplified system avoids the complicated equilibria in the SMC reaction mixture, and allows us to dive deeper into how the palladium source, ligand identity and loading, base identity, and water content directly affect palladium-catalyzed PDB.

We first performed experiments to investigate the impact of the palladium source on PDB under conditions typically used in the SMC with K₃PO₄ as the base (**Table 2, Supplementary Discussion S3.1**). Similar to the observations in the competitive reactions, no PDB happens without palladium (**Entry 2a**). This is consistent with the fact that electron-neutral boronic reagents are not prone to base-catalyzed PDB (**Supplementary Discussion S6.1**) and our earlier results in the competitive cross-coupling experiments (**Table 1**). Interestingly, PDB does not happen with palladium alone without ligands, regardless of the palladium source (**Entries 2b, 2h, 2m**). As a significant amount of Pd black forms in these reactions (**Supplementary Figure S19**), we suspect that the lack of stabilizing ligands leads to catalyst poisoning under basic conditions, and therefore a lack of palladium-catalyzed PDB. As prior work has reported that Pd black and Pd nanoparticles can catalyze PDB,^{27–29} we perform two control studies where we intentionally form Pd black to observe its effect on PDB in our system. Our observations affirm that neither Pd black nor Pd nanoparticles are major contributing factors to PDB under the experiment conditions we evaluated

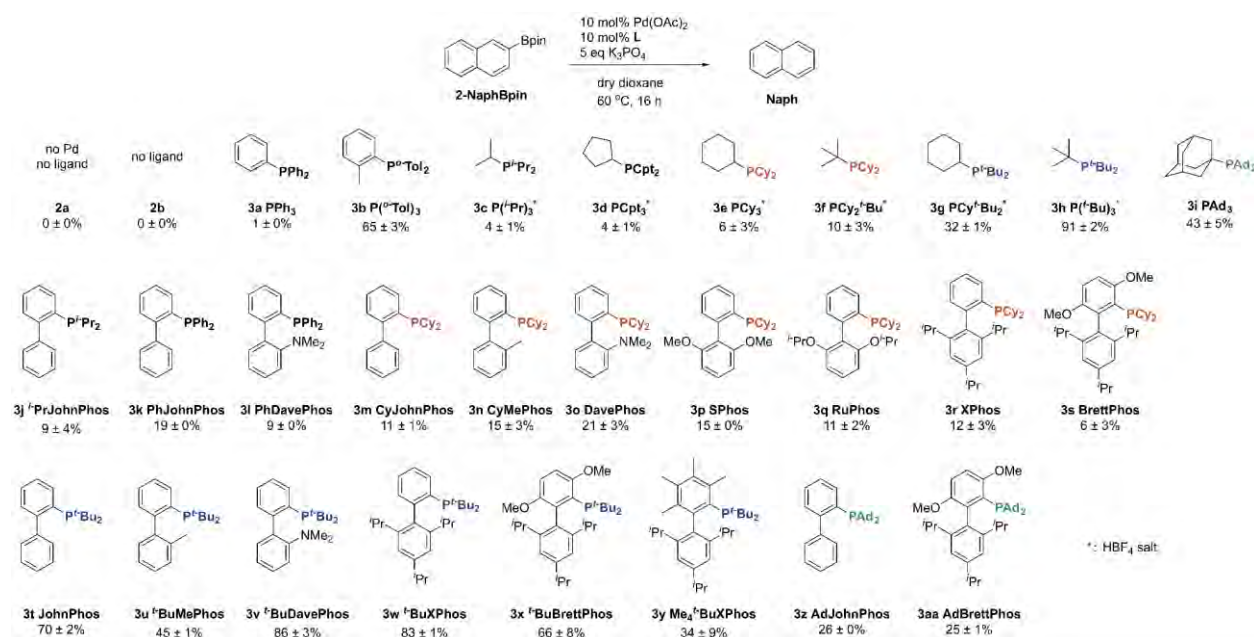
(**Supplementary Discussion S3.6**). This is in line with previous reports on homogeneously-catalyzed Pd-catalyzed PDB,^{10–12,26} and is also consistent with Kuivila et al.'s seminal work on metal-catalyzed PDB, where they were not able to obtain kinetic data for PdCl₂ in an aqueous buffer solution.⁶ This is also consistent with our proposed mechanism and computational results for palladium-catalyzed PDB by palladium without phosphines, where no PDB is observed (**Supplementary Discussion S6.2**).

Table 2 Yields and errors of palladium-catalyzed protodeboronation (**Naph**) with different palladium sources using K₃PO₄ as base at 60 °C. *: in the form of HBF₄ salt. **: errors were not included for yields <0.1%.

 2-NaphBpin 10 mol% [Pd] 3-5 eq K₃PO₄ 0.43 eq o-terphenyl dry dioxane 60 °C, 16 h  Naph		
Entry	Palladium source	Naph / %
2a	No Pd	0**
2b	Pd(OAc) ₂	0**
2c	Pd(OAc) ₂ + P(t-Bu) ₃ *	91 ± 2
2d	Pd(OAc) ₂ + JohnPhos	70 ± 3
2e	Pd(OAc) ₂ + PCy ₃ *	6 ± 3
2f	Pd(OAc) ₂ + CyJohnPhos	11 ± 1
2g	Pd(OAc) ₂ + XPhos	12 ± 3
2h	PdCl ₂	0**
2i	PdCl ₂ + P(t-Bu) ₃ *	68 ± 4
2j	PdCl ₂ + JohnPhos	22 ± 1
2k	PdCl ₂ + PCy ₃ *	0**
2l	PdCl ₂ + CyJohnPhos	1 ± 0
2m	Pd ₂ dba ₃	0**
2n	Pd ₂ dba ₃ + P(t-Bu) ₃ *	26 ± 3
2o	Pd ₂ dba ₃ + JohnPhos	4 ± 1
2p	Pd ₂ dba ₃ + PCy ₃ *	3 ± 0
2q	Pd ₂ dba ₃ + CyJohnPhos	3 ± 0
2r	P(t-Bu) ₃ Pd G4	72 ± 6
2s	JohnPhos Pd G4	6 ± 0
2t	XPhos Pd G2	16 ± 3

With Pd(OAc)₂ as the palladium source, the *t*-Bu-substituted ligands P(*t*-Bu)₃ and JohnPhos lead to >70% **Naph** yields, while the Cy-substituted ligands PCy₃, CyJohnPhos and XPhos lead to <15% **Naph** yields (**Entries 2c-2g**). As these results align well with the observations in the competitive reactions (**Table 1**), we believe that the reactivities obtained here without the coupling partner are representative of the palladium-catalyzed PDB in the presence of the aryl halide coupling reagent. Using PdCl₂ as a Pd(II) source reproduces the ligand-dependent trend with slightly less **Naph** yields (**Entries 2h-2l**), while significantly reduced **Naph** yields are observed when switching to Pd₂dba₃ as a Pd(0) source (**Entries 2m-2q**). However, we note that moderate protodeboronation is still observed when Pd₂dba₃ is used with a bulky ligand like P(*t*-Bu)₃, suggesting that Pd(II) intermediates in the Suzuki-Miyaura catalytic cycle are also capable of PDB (**Entry 2n**). As AcO⁻ is known to promote the reduction of Pd(II) to Pd(0),^{47,48} while halides other than F⁻ cannot,⁴⁹ the similar observed PDB yields when Pd(OAc)₂ is used compared to PdCl₂ suggests that the role of the counterion is minimal in palladium-catalyzed PDB. Using preformed palladacycles which generate Pd(0) rapidly in contact with base leads to highly ligand dependent reactivity (**Entries 2r-2t**). These results further strengthen the major role of Pd(II) species in palladium-catalyzed PDB over Pd(0) species, which reiterates findings in the competitive cross-coupling reactions (**Table 1**).

Figure 3: Yields of protodeboronated product (**Naph**) from the palladium-catalyzed protodeboronation of 2-naphthalene boronic acid pinacol ester (**2-NaphBpin**) with various phosphine ligands. Inaccuracies in K₃PO₄ equivalents were introduced in rapid manual dosing (see **Experimental Procedures**). Yields and errors are estimated with HPLC based on duplicate experiments.



Having established that bulky phosphines tend to promote PDB with Pd(II) sources, we expanded the screening scope to 27 phosphines to comprehensively study the ligand dependency of palladium-catalyzed PDB, using Pd(OAc)₂ as the palladium source (**Table 3, Supplementary Discussion S3.2**). Similar to results in the competitive cross-coupling experiments (**Table 1**), both palladium and phosphine ligands are required for PDB (**Table 2, Table 3, 2a-b**), and a wide range of **Naph** yields are observed across different phosphines, with bulky phosphines having higher **Naph** yields than their less sterically-congested counterparts. We specifically highlight that the use of Cy-containing and tBu-containing ligands on average result in 12% and 63% **Naph** respectively. This is most apparent when comparing PPh₃ (**Table 3, 3a**) and P(*o*-tol)₃ (**Table 3, 3b**), and in the increased **Naph** yields of the P(*t*-Bu)_x(Cy)_{3-x} series with increasing *x* (**Table 3, 3e-3h**). We observe similar trends with Buchwald ligands, where bulky *t*-Bu (**Table 3, 3t-3y**) groups lead to increased **Naph** yields compared to their less bulky isopropyl and phenyl (**Table 3, 3j-3l**) or cyclohexyl (**Table 3, 3m-3s**) counterparts. However, elevating the steric congestion around the phosphorus atom by replacing phenyl with biphenyl (**Table 3, 3a vs 3j**) or by increasing biphenyl bulkiness of the dicyclohexyl Buchwald ligands (**Table 3, 3m vs 3n-s**) does not significantly promote PDB, suggesting that steric bulk further away from the phosphorus atom is less effective at promoting PDB. While the extra-bulky 1-adamantyl phosphines (**Table 3, 3i, 3z, 3aa**) show increased PDB compared to their cyclohexyl variants (**Table 3, 3e, 3m, 3s**), they show inferior PDB compared to their *t*-Bu analogs (**Table 3, 3h, 3t, 3x**). Small amounts of binaphthalene from homocoupling were observed as a minor by-product (**Supplementary Discussion S3.3**). However, the yields of binaphthalene were generally below 5%, precluding the elucidation of any significant trends. We propose that binaphthalene forms through oxidative coupling with either Pd(II) as an oxidant or trace amounts of residual oxygen, despite the extensive degassing in our workflow.^{39,50}

Increasing the palladium and phosphine loadings simultaneously does not lead to an observable increase of **Naph** yields, and instead inconsistent trends were observed (**Supplementary Discussion S3.3**). While for most phosphines the **Naph** yields either increased slightly or did not change, for JohnPhos the **Naph** yields decreased with higher palladium-phosphine loadings (**Supplementary Discussion S3.4**). Considering the prolonged reaction time of 16 h, we propose the overall end-point **Naph** yields are determined by catalyst deactivation and/or reaction equilibrium, which we confirmed by reaction kinetic monitoring (*vide infra*). Interestingly, since phosphines are known to reduce Pd(II) to Pd(0) in the presence of base,^{47,51} we expected that an increase in phosphine equivalents would inhibit PDB by promoting palladium reduction. However, while phosphines are essential for palladium-catalyzed PDB, increasing L:Pd ratios does not result in decreased **Naph** yields as expected, and using up to four equivalents of phosphine slightly promoted PDB instead (**Supplementary Discussion S3.4**).

We performed experiments under the same conditions on 6-MeO and 6-CN functionalized versions of **2-NaphBpin** as electron-rich and electron-poor model compounds, which provide comparable steric but distinct electronic effects compared to **2-NaphBpin** (**Supplementary Discussion S3.7**). In both cases,

negligible PDB is observed without Pd, or when Pd(OAc)₂ is used without phosphines (**Supplementary Table S10, Entries 10a-b, 10g-h, 10m-n**), in line with our previous observations. When Pd(OAc)₂ is used with ligands, we do not see significant differences for PCy₃ (**Entries 10c, 10i, 10o**) and P(*t*-Bu)₃ (**Entries 10d, 10j, 10p**), likely because the performance of the palladium-phosphine complex at catalyzing PDB is too weak or strong, respectively. However, CyJohnPhos and JohnPhos, which previously gave intermediate PDB yields for Naph-2-BPin, showed increased and decreased PDB for the electron-withdrawing -CN and electron-donating -OMe groups, respectively. Given the long reaction times, we posit that the reduced yields are not a result of reduced reaction rates, but rather that electron-withdrawing groups on the aryl substituent shift selectivity towards a Pd-catalyzed protodeboronation pathway, while electron-donating substituents disfavor the same pathway.

We additionally investigated the base dependency of palladium-catalyzed PDB across 16 inorganic and organic bases, using Pd(OAc)₂ as the palladium source and JohnPhos as the ligand (**Supplementary Discussion S3.5**). In summary, oxo-bases are essential for PDB, which is consistent with the oxophilicity of the boron moiety as a major driving force for the cleavage of B-R bonds, while weakly/non-coordinating bases (e.g. pyridine, DBU) are unable to drive the B-R bond cleavage, resulting in low PDB. Generally, stronger and more soluble bases promote PDB (**Supplementary Table S8**).^{47,51,52} Despite the base choice having an effect on **Naph** yields, we note that the choice of ligand is still the dominating factor, as base screening experiments conducted with CyJohnPhos or Pd(OAc)₂ without phosphines show little variance in **Naph** yields, and in some cases even show zero PDB (**Supplementary Table S8, Entries 7b-l, 8b-l**). These results emphasize the fact that, under SMC conditions, substrates resistant to base-catalyzed PDB can still undergo Pd-catalyzed PDB.^{15–17} However, NaH, KO(*t*-Bu), and NaO(*t*-Bu) cause significant PDB regardless of the choice of ligand or even under ligand-free conditions, suggesting that caution should be exercised when using these bases with boronic reagents (**Supplementary Table S8, Entries 6-8e, 6-8g, 6-8k**).

We further investigated the source of H atom in the **Naph** product that replaces the boron moiety of **2-NaphBpin**. By intentionally introducing 20 eq. H₂O or D₂O, PDB reactions catalyzed by Pd(OAc)₂ and JohnPhos reach full conversion regardless of whether the reactions were performed in vials or in NMR tubes. Importantly, we recovered both 2-¹H-naphthalene and 2-²D-naphthalene in a 1:4 ratio based on ¹H-NMR integration for reaction with 20 eq. D₂O, suggesting that up to five equivalents of H₂O (0.025 mmol, ~0.06% V/V) exists in our reaction conditions (**Supplementary Discussion S5.1**), likely from the “organic dry” conditions used in our reaction protocols (see **Experimental Methods**). This suggests that the origin of the H atom is a protic hydrogen in H₂O, which aligns well with the established mechanism of base-catalyzed PDB (**Supplementary Discussion S6.1**).^{15–17}

Online monitoring and reaction kinetics

During the end-point analysis of reaction screening, we found that competing catalyst deactivation or off-cycle equilibria may happen along with the palladium-catalyzed PDB major pathway as established by the formation of Pd black after reaction (**Supplementary Figure S19**). Therefore, we performed kinetic experiments with the Pd(OAc)₂-JohnPhos-K₃PO₄ system to gain more insight into the reaction mechanism of palladium-catalyzed PDB. The modularity of the MEDUSA platform allowed us to set up automatic online monitoring *via* HPLC under an inert atmosphere, a capability which is not routinely available to common automated synthetic platforms (see **Figure 2a**, **Experimental Methods** and **Supplementary Discussion S4**). With **2-NaphBpin**, we identified a short induction period which we attribute to the heating up of the reaction mixture (**Supplementary Discussion S4.2, S4.3**). Afterwards, the formation of **Naph** increased roughly linearly. Based on the dependence of the corresponding initial rates on temperature, we derived an enthalpic activation barrier of 18.1 kcal/mol for JohnPhos (**Figure 2b, 2c**), and the reaction order of the Pd(OAc)₂-JohnPhos complex was found to be 0.58 based on the initial rate fitting method (**Supplementary Table S21 and S23, Supplementary Figure S39**). The Pd-CyJohnPhos system has an estimated barrier of >20 kcal/mol based on comparing initial rates with respect to Pd-JohnPhos experiments (**Supplementary Table S22 and S24**), though inconsistencies were observed across monitoring experiments and no conclusive reaction partial order can be determined for the Pd-CyJohnPhos system. Additionally, half-lives of less than three hours were identified with P(*t*-Bu)₃ and JohnPhos as ligands, while no effective PDB was observed in the base-only experiments even in the 16 h end-point analysis experiments (**Supplementary Table S9**), emphasizing the catalytic activity of palladium-phosphine complexes compared to base for electron-neutral boronic reagents (**Figure 2d, Supplementary Figure S27-S28**). Finally, while the reaction yield increased linearly over 3 h for JohnPhos, the yield for CyJohnPhos significantly slowed down within 1 h, suggesting that the Pd(OAc)₂/CyJohnPhos system is sluggish in catalyzing PDB, possibly due to catalyst deactivation (**Supplementary Figure S28c**).

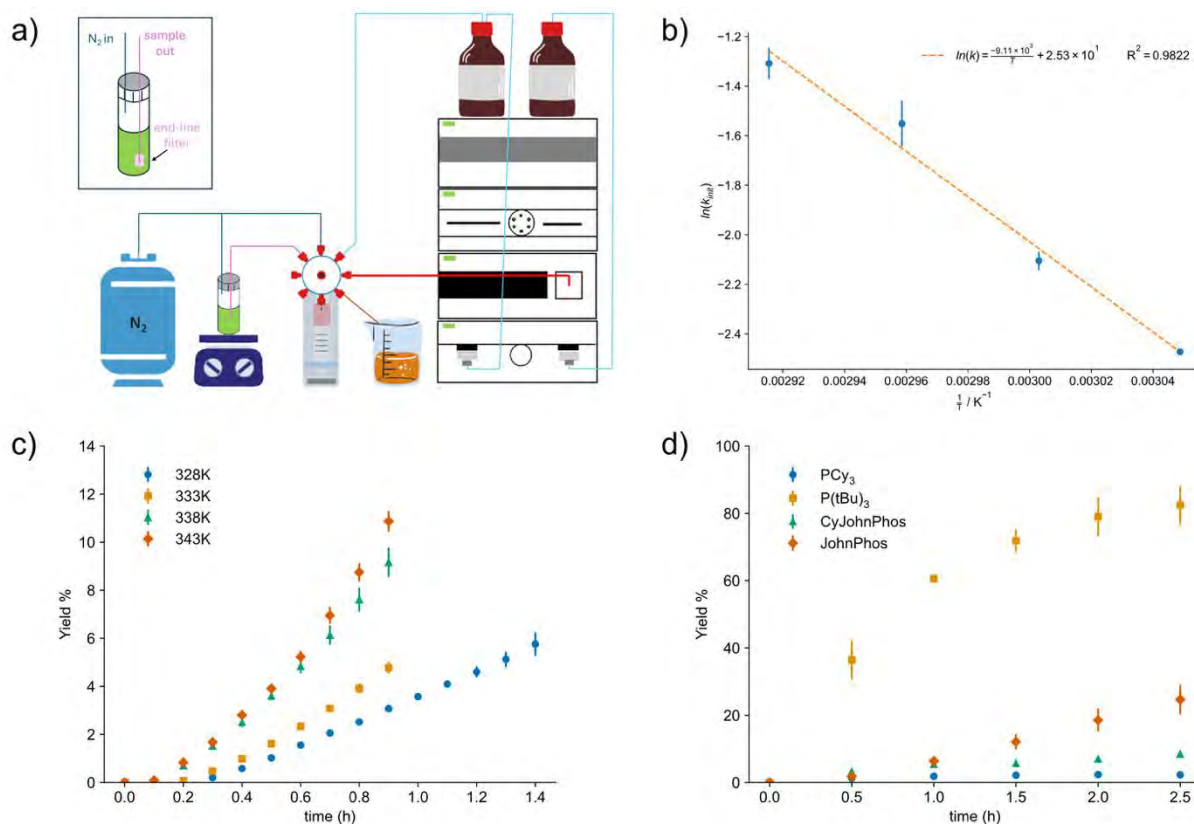


Figure 2: **a)** Hardware configuration of the continuous reaction monitoring variant of MEDUSA. **b)** $\ln(\text{initial rate})$ vs $1/T$ of **Naph** via palladium-catalyzed PDB of **2-NaphBpin** using $\text{Pd}(\text{OAc})_2$, JohnPhos and K_3PO_4 in dry dioxane. **c)** Monitoring of **Naph** formation via palladium-catalyzed PDB of **2-NaphBpin** over time using $\text{Pd}(\text{OAc})_2$, JohnPhos and K_3PO_4 in dry dioxane. **d)** Ligand dependent palladium-catalyzed PDB reactivity as demonstrated by **Naph** formation via palladium-catalyzed PDB of **2-NaphBpin** over time using $\text{Pd}(\text{OAc})_2$ and K_3PO_4 in dry dioxane at 333 K.

Computational mechanistic investigations

To further elucidate the underlying reasons for the difference in palladium-catalyzed PDB between ligands, we computationally investigated the mechanism of palladium-catalyzed PDB using DFT (**Figure 3**, see **Computational Methods**). While both boronic esters and boronic acids are capable of directly transmetalating onto palladium without hydrolysis,^{52–54} we chose to model the boronic reagent as a boronic acid, as boronic esters have been demonstrated to undergo facile hydrolysis under basic aqueous conditions,¹⁷ and that we had also experimentally identified trace amounts of 2-naphthalene boronic acid under our reaction conditions consistently. We note that it is possible for both the boronic acid and ester to exist simultaneously in the reaction mixture, but the proposed mechanism does not change between the two forms and the conclusion remains the same (see **Supplementary Discussion S7.9** for a computational evaluation of Pd-catalyzed PDB via the boronic ester).

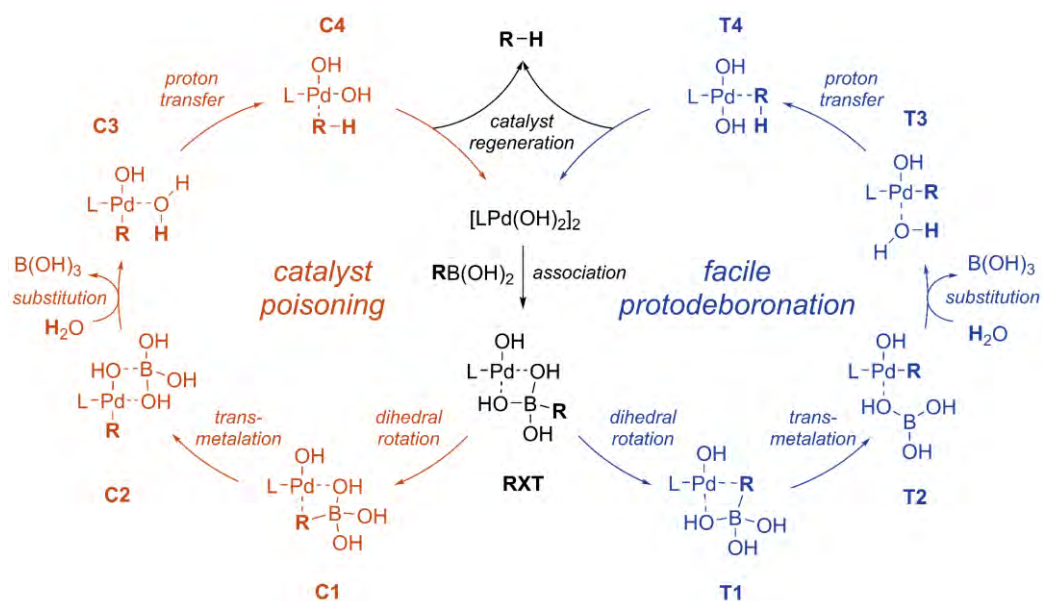


Figure 3: Proposed mechanism for palladium-catalyzed protodeboronation.

We note that mononuclear palladium-boron complexes have been previously isolated and shown to be the key species that undergoes transmetalation.^{52–54} Thus, in our proposed mechanism for palladium-catalyzed PDB, we propose that this mononuclear square-planar palladium-boron complex (**RXT**) is formed from our starting Pd(II) catalyst. As Pd(II) forms a complex equilibrium of structures under PDB and SMC conditions,⁴⁷ the structures of the major components of phosphine-supported palladium species in basic conditions have not yet been confirmed. In order to find an appropriate Pd(II) catalyst reference state for our computations, we performed a systematic computational analysis by considering the coordination of palladium to various Lewis bases within our experimental conditions. We found that, in general, the mononuclear palladium-phosphine species $LPd(OH)_2$, when either uncoordinated or coordinated to various Lewis bases (H_2O , dioxane, phosphine), showed large differences in computed energies compared to the proposed mononuclear square-planar palladium-boron complex **RXT**. Additionally, there was a large variation in stability of the investigated reference states between phosphine ligands. Our analysis reveals that representing the reference state as the dinuclear Pd(II) catalyst $[LPd(OH)_2]_2$ offered consistency in relative stability to **RXT** and between ligands, which is why we chose this as the reference state for the analysis below (see **Supplementary Discussion S7.2** for a detailed analysis on other mononuclear or oligomeric reference states). We also note that while the choice of the reference state is necessary to define a state the catalyst returns to after one turnover cycle for our computational microkinetic analysis, it has no impact on the selectivity between the different pathways, which is represented by the yield of **Naph** at the end of the kinetic campaign.

After the association of the boronic acid to the dinuclear Pd(II) catalyst $[LPd(OH)_2]_2$ to form **RXT** by breaking the dinuclear computational reference state up into a mononuclear complex, subsequent rotations around

Pd-O-B-C_{aryl} dihedrals result in two different pre-transmetalation intermediates where the ligand and aryl moiety are *cis* (**C**-prefixed structures) or *trans* (**T**-prefixed structures) to each other, respectively (**C1/T1**). The aryl group undergoes transmetalation onto the palladium center (**C2/T2**, see **Supplementary Discussion S7.3** for details on the forms of **C2**), and H₂O subsequently displaces the B(OH)₃ ligand *via* nucleophilic substitution to form palladium-aqua complexes (**C3/T3**). Finally, intramolecular proton transfer from the coordinated water to the transmetalated *ipso*-carbon forms η^2 -protoarene products (**C4/T4**), and facile protoarene dissociation regenerates the Pd(II) catalyst. Notably, the proton transfer and arene dissociation steps are formally the microscopic reverse of a concerted metalation deprotonation step in C-H activation.⁴⁸ In the following discussions, we broadly define “transmetalation” as the two steps involving intermediates **RXT**, **C1/T1** and **C2/T2**, and “proton transfer” as the two steps involving **C2/T2**, **C3/T3**, and **C4/T4**. We note that it is conceivable that a general base mechanism is operable instead, A base can increase the nucleophilicity of H₂O via deprotonation and catalyze the **T2-T3** nucleophilic substitution, after which the proton is transferred directly to the aryl moiety – or the base can serve as a proton shuttle to facilitate the **T3-T4** proton transfer. We do not consider these processes as under our reaction conditions, there is no prime candidate for such a base that is dissolved and present in sufficiently high amounts, and due to the difficulty of modeling such processes using static DFT simulations.⁵⁵

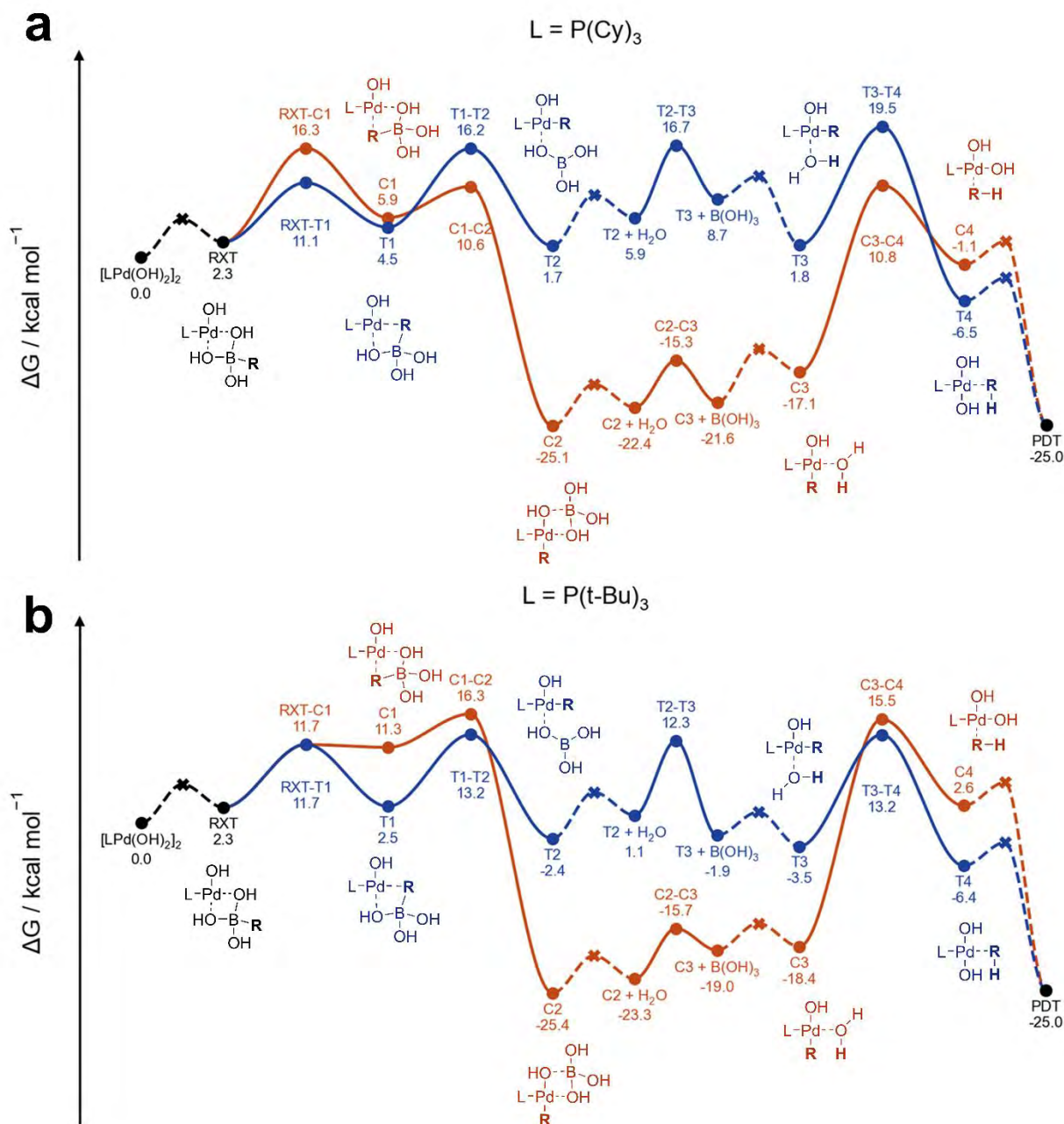


Figure 4: Computed reaction profiles for **a**) PCy_3 and **b**) $P(t-Bu)_3$ for the proposed mechanism. ●: computed structures. ✕: Estimated transition state energies based on a 3.5 kcal/mol diffusion barrier at $T = 333.15\text{K}$ (see **Computational Methods**).

We note that the general form of the reaction profile is preserved across all 27 computed ligands (see **Supplementary Figures S151-S177**). Thus, we exemplify the analysis of the steric dependence of palladium-catalyzed PDB with PCy_3 (**Figure 4a**) and $P(t-Bu)_3$ (**Figure 4b**), which experimentally showed negligible and significant PDB, respectively. The key difference in observed reactivity between ligands

stems from the competition between the formation of catalytically inactive species in **C**-transmetalation versus the facile transmetalation and proton transfer processes in the **T**-pathway. This difference arises from the unstable **T**-transmetalation products **T2** and **T3**, as the ligands around the palladium center in these structures are arranged in a mutually *trans* soft-soft (phosphine and aryl) and hard-hard (-OH and OH_2 or BOH_3) fashion. In this arrangement, the soft ligands are unable to fully donate their electron densities to the palladium center as they compete to donate to the same metal d-orbital. This effect has previously been described as antisymbiotic destabilization.^{56,57} Comparatively, **C2** and **C3** possess mutually *trans* soft-hard arrangements, allowing both soft ligands to fully contribute their electron density to the palladium center, making them very stable compared to their reference states.

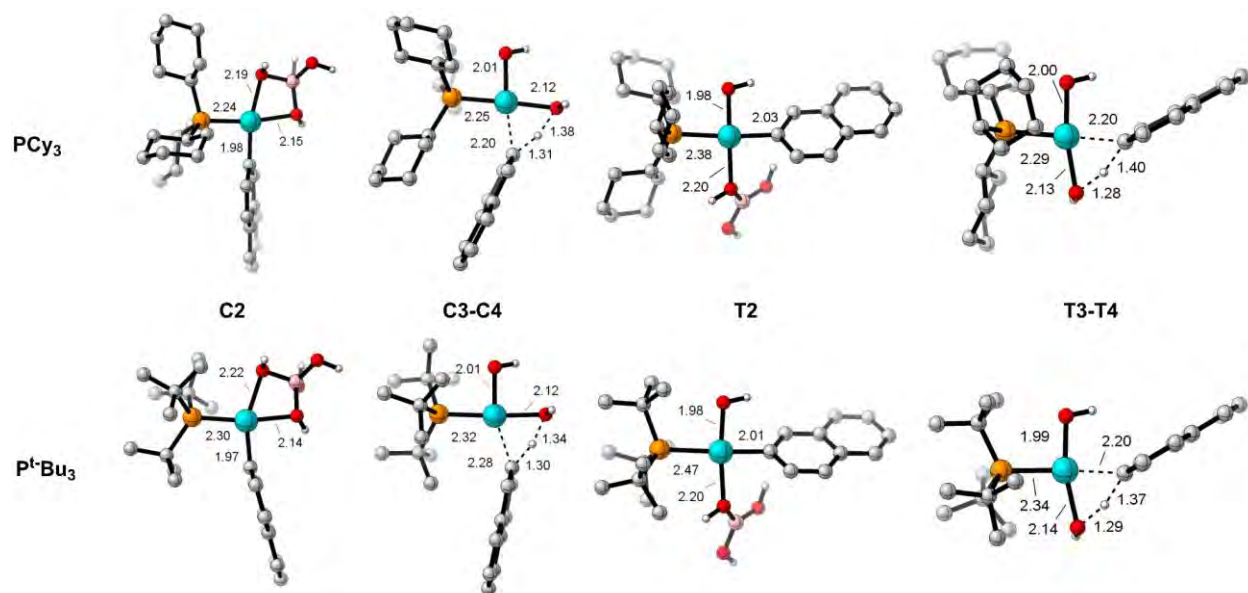


Figure 5: Key intermediates **C2** and **T2**, and transition states **C3-C4** and **T3-T4** for PCy_3 (top row) and $\text{P}(t\text{-Bu})_3$ (bottom row) with key bond lengths labeled in Angstroms (Å).

Both proton transfer transition states (**C3-C4** and **T3-T4**) transiently form unstable $[\text{LPd}(\text{II})\text{OH}]^+$ structures as the R^- ligand dissociates in the proton transfer step, causing the electron density at the palladium center to decrease (**Figure 5**, see NBO⁵⁸ charges in **Supplementary Table S30**). In **T3-T4**, the electron density loss is less detrimental (**Supplementary Table S30**) as it is mitigated by the soft phosphine ligand *trans* to the partially dissociated R^- , and, thus, accessing the **T3-T4** transition state from **T2** or **T3** is feasible, allowing for catalyst regeneration (19.4 and 16.8 kcal/mol for PCy_3 and $\text{P}(t\text{-Bu})_3$, respectively, **Figure 4a, 4b**). However, in **C3-C4**, the hard hydroxyl ligand *trans* to the partially dissociated R^- ligand is unable to compensate for the loss in electron density, resulting in a large energetic barrier to access this transition state — PCy_3 and $\text{P}(t\text{-Bu})_3$ require 35.9 and 39.8 kcal/mol, respectively, to surmount proton transfer barriers **C3-C4** (**Figure 4a, 4b**). Consequently, catalytic turnover only happens through the **T**-pathway.

In our proposed mechanism, ligands like PCy₃, which favor **C**-transmetalation over the **T**-pathway, will lead to the rapid population of stable species (**C2** or **C3**) and reduced **Naph** yields due to catalyst inactivity. In support of our proposed mechanism, we detected traces of a **C2** derivative for PCy₃ as a cation that is part of the boron"ate" complex [(2-Naph)Pd(PCy₃)]⁺ = [R-Pd-L]⁺ using HR-MS (**Supplementary Discussion S5.2**) collected from a reaction mixture one hour after the start of the reaction. As we observe binaphthalene in our final reaction mixture, we further propose that **C2** may also transmetalate with another molecule of a boronic acid derivative and, subsequently, undergo reductive elimination to yield binaphthalene, and Pd(0), which is inactive in PDB but essential for the SMC cycle (**Supplementary Discussion S7.8**).

In general, the nucleophilic substitution of B(OH)₃ by H₂O (**T2-T3**) is difficult as it requires a nucleophilic attack from a weak nucleophile (H₂O). The subsequent proton transfer to the coordinated naphthalene (**T3-T4**) is also difficult as palladium-aqua complexes are weak acids. We further note that the direct proton transfer from H₂O (**Supplementary Discussion S7.4**) or BOH₃ (**Supplementary Discussion S7.7.4**) onto the aryl moiety without nucleophilic substitution via **T2-T3** are both less energetically feasible than our proposed pathway. Hence, for significant PDB to occur, sufficient steric hindrance must be present to disfavor **C**-transmetalation and, in turn, favor the difficult post-transmetalation **T**-pathway steps. This preference can be described by an overall $\Delta\Delta G^\ddagger$ that accounts for the relative feasibility of catalyst trapping (**C**-transmetalation) versus catalytic PDB (**T**-pathway), computed as the difference between the maximum transition state Gibbs free energy of **C**-transmetalation ($C_{\max TM}$) and that of the entire **T**-pathway ($T_{\max}$). In agreement with experimental observations, sterically compact ligands (phenyl, cyclohexyl) have relatively facile **RXT-C1** and **C1-C2** barriers that lead to quick catalyst poisoning and low **Naph** yields (brown and purple points, **Figure 6**). Phosphines with local steric bulk around the phosphorus atom (*t*-Bu or 1-adamantyl moieties) generally experience significant steric hindrance in *cis*-transmetalation **C1-C2** when the naphthalene moiety is forced closer to the phosphine ligand (orange points, **Figure 6**). This disfavors catalyst poisoning, leading to higher **Naph** yields. Finally, Buchwald ligands with compact alkyl substituents generally have elevated **RXT-C1** barriers, where the increased remote steric bulk from its biaryl moiety interferes with the dihedral rotation. However, such steric interference is less effective than for ligands with local steric bulk, ultimately leading to moderate **Naph** yields (blue points, **Figure 6**). The results of this analysis are consistent with the ligand-dependence identified in the experimental results (**Table 3**). Finally, the observed electronic dependence for both 6-MeO and 6-CN substituted Naph is manifested in the relative stability of **T2**. The degree of antisymbiotic destabilization is decreased for 6-MeO due to its electron-donating nature.

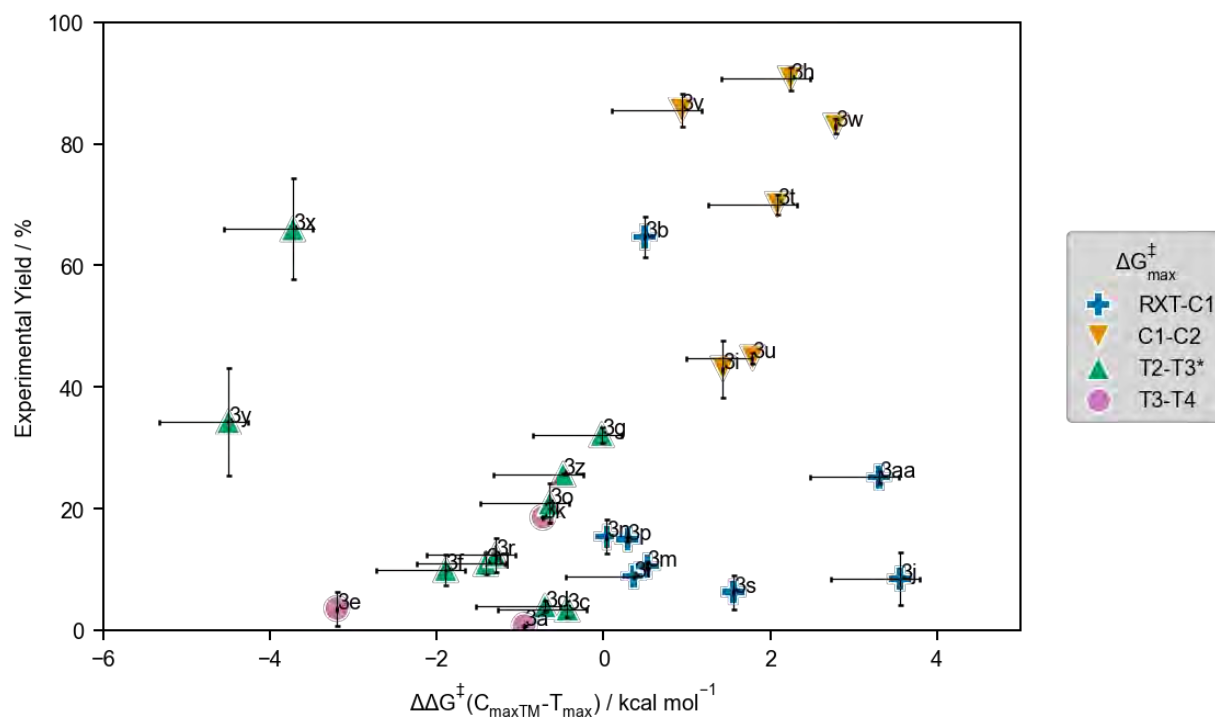


Figure 6: Experimental yield versus the free energy difference ($\Delta\Delta G^\ddagger$) between **C**-transmetalation ($C_{\max TM}$) and the entire **T**-pathway ($T_{\max}$) for all 27 ligands at 3.5 eq $[\text{H}_2\text{O}]$. The vertical error bars denote the error in experimental yield (**Table 2**). The horizontal error bars denote how $\Delta\Delta G^\ddagger(C_{\max TM} - T_{\max})$ is affected by changes to $[\text{H}_2\text{O}]$ between 1.0 eq. (left bound) to 5.0 eq. (right bound). **T2-T3** barriers have a +2.59, +1.76, and +1.52 kcal/mol correction to account for the effects of $[\text{H}_2\text{O}]$ at 1.0, 3.5 and 5.0 eq. respectively (**Supplementary Discussion S7.7.1**).

Kinetic modeling

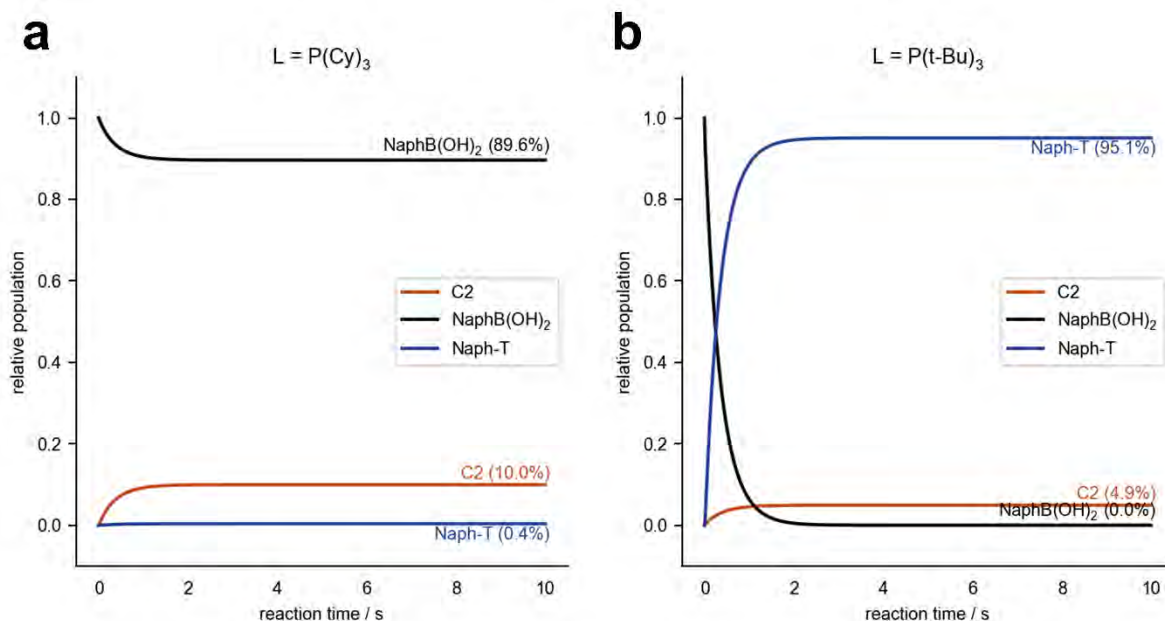


Figure 7: Relative population of key intermediates in the proposed mechanism from the kinetic model (Supplementary Table S31) for a) PCy₃ and b) P(*t*-Bu)₃.

To further validate our proposed mechanism, we constructed a kinetic model using *pykinetic*⁵⁹ and tracked the evolution of the intermediates and **Naph** over time (see **Supplementary Table S31** for the list of transformations in the kinetic model). We further distinguish between the two ways **Naph** can be made with a **-C** or **-T** suffix corresponding to the pathway that **Naph** is generated from. The kinetic campaign starts with the initial concentrations of [LPd(OH)₂]₂ = 0.001M and [NaphBOH₂] = 0.020M, following the experimental conditions used (see **Experimental Methods**), and 3.5 eq of H₂O ([H₂O] = 0.070M), an estimate obtained from the deuterium incorporation experiment. Across all ligands computed, we observe that there is no formation of **Naph-C** due to the formation of the thermodynamic trap **C2**, and thus the **T**-pathway is the only pathway that forms **Naph**. Ligands that have low **Naph-T** populations stem from the faster consumption of palladium to form **C2** (exemplified by PCy₃ in **Figure 7a**), limiting the extent of palladium-catalyzed PDB. Ligands that have high **Naph-T** populations also show significant populations of **C2** as the formation of **C2** is in general competitive with the formation of **Naph-T**. However, the extent of palladium-catalyzed PDB is not constrained by the energetically disfavored **C**-pathway, resulting in significant PDB (exemplified by P(*t*-Bu)₃ in **Figure 7b**).

Assessing the validity of the proposed mechanism

We note that some ligands depart from the general trend observed for the relationship between experimental yield and $\Delta\Delta G^\ddagger$ (**Figure 6**), suggesting that it is possible that the ligand choice can affect the mechanism of palladium-catalyzed PDB. However, as the density functionals approximations contain

intrinsic errors due to the approximations used to make computations tractable, and that the adventitious amounts of H₂O present may vary between experimental points, the selectivities between the **C**- and **T**-pathways are also subject to error, ultimately affecting the computational yields of **Naph-T**.

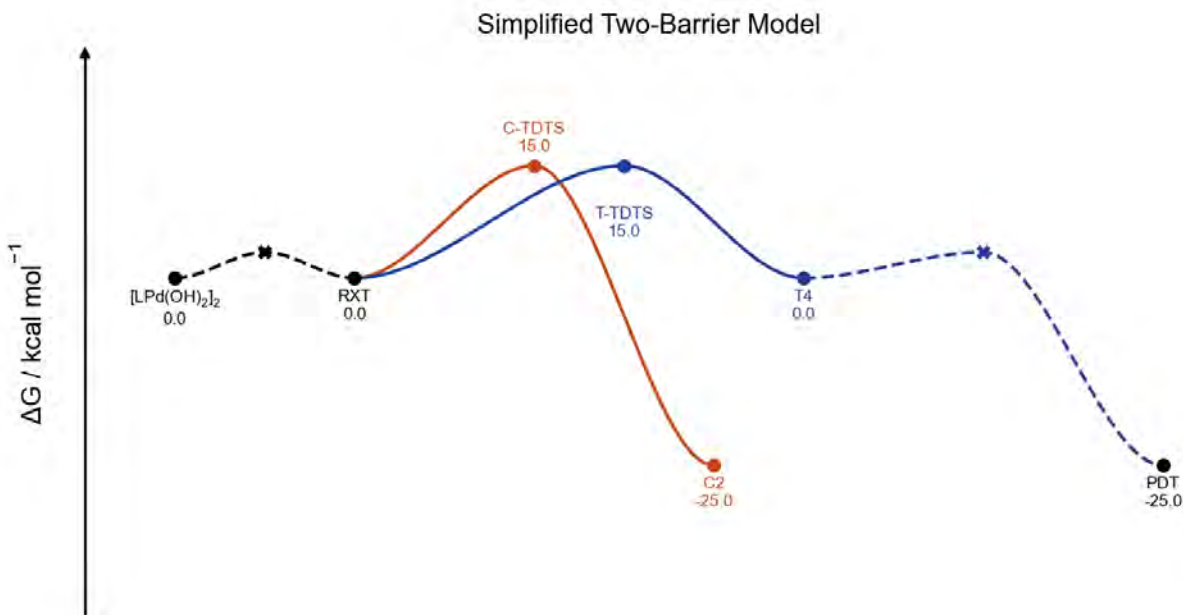


Figure 8: Reaction profile diagram for a simplified two-barrier model that aims to reproduce the full proposed mechanism by only considering the turnover-frequency determining transition states (TDTS) in the C- and T- pathways as **C-TDTS** and **T-TDTS** respectively.

In order to differentiate between the effects mentioned above, it is first necessary to determine the impact of the errors in each $\Delta G^\ddagger$ on the computed yield. However, evaluating the full mechanism requires the consideration of the errors of six transition state energies, leading to a large family of solutions that ultimately return the same $\Delta G^\ddagger$ and computed yield. Thus, we devise a simplified two-barrier model (**Figure 8**) defined by a single $\Delta\Delta G^\ddagger$ that is representative of our proposed mechanism. As the identity of the highest barrier changes between the ligands, this model replaces the **C**- and **T**-pathways each with a single turnover-frequency determining transition state (TDTS), defined as **C-TDTS** and **T-TDTS** respectively, that ultimately leads to catalyst trapping or protodeboronation respectively. Since catalyst trapping involves only transmetalation, **C-TDTS** is modelled as first-order, while **T-TDTS** is modelled as H₂O-dependent and thus second-order to capture the effects of H₂O consumption as the reaction progresses (**Supplementary Table S32**). We then compare the computed yields from the full proposed mechanism to this simplified model, and record the $\Delta\Delta G^\ddagger$ required (presented as $\Delta\Delta G^\ddagger_{(\text{RXT-C2-RXT-T4})}$ in **Figure 9**) for the simplified model to reproduce the yield from the full mechanism. We also record the $\Delta\Delta G^\ddagger$ required to reproduce the experimental yield, and plot that as the central sigmoidal line in **Figure 9**. In essence, the horizontal distance

from a ligand's point in **Figure 9** to the central sigmoidal line signifies the amount $\Delta\Delta G^\ddagger$ needs to change by in order for the computational yield in the simplified model to achieve parity with the experimental yield.

With no prior assumption for the distribution of errors in the transition states, we calculate the change to $\Delta\Delta G^\ddagger$ by assuming that both $\Delta G^\ddagger_{\text{C-TDTS}}$ and $\Delta G^\ddagger_{\text{T-TDTS}}$ must shift to the same extent and in opposite directions of each other, and that only the absolute energies of **C-TDTS** and **T-TDTS** shift. We denote this value as the *barrier tuning to parity prediction* metric. If the *barrier tuning to parity* prediction metric is below 1.0 kcal/mol (chemical accuracy, and the upper bound of performance of our method on benchmark reaction barrier height tasks),⁶⁰ denoted by the green shaded region in **Figure 9**, the mechanism is considered valid for the ligand considered. If the metric is larger than 1.0 kcal/mol (red shaded region in **Figure 9**), the proposed mechanism cannot reproduce the experimental yields within our defined bounds, suggesting that the proposed mechanism may not be correct for the ligand considered. We note that the bounds for computational yield for determining if the yields are well-predicted are variable as slight errors in $\Delta\Delta G^\ddagger$ make it more difficult to correctly predict intermediate yields compared to extreme yields. We further note that the conclusions based on this simplified model does not significantly affect the analysis below when compared to analyzing the full mechanism (**Supplementary Discussion S7.7.3**).

The above analysis based on the *barrier tuning to parity prediction* metric affords us the ability to identify ligands that may follow a separate mechanism. Gratifyingly, we observe that a majority (22 out of 27) of our ligands studied are able to reproduce the experimental yield within computational error bounds -- which is to have *barrier tuning to parity* prediction metrics of $<\pm 1.0$ kcal/mol (**Figure 9**). In addition, we also plotted how computational yields are affected when $[\text{H}_2\text{O}]$ is either 1.0 or 5.0 eq given that our estimates for $[\text{H}_2\text{O}]$ could be subject to error. A minority of ligands (**3j**, **3s**, **3aa**) can reproduce the experimental yields within error bounds if $[\text{H}_2\text{O}]$ is closer to 1.0 eq as opposed to the 3.5 eq estimate from our deuterium-incorporation experiments. Other ligands (**3x**, **3y**) cannot reproduce the experimental yields even with higher $[\text{H}_2\text{O}]$ equivalents, due to the fact that these ligands are characterized by an extremely high **T2-T3** barrier. We observe that conformationally-locked ligands (either with $-\text{OCH}_3$ or $-\text{Me}$ groups on the aryl ring connected to the phosphorus atom) with immense remote steric bulk from the 2,4,6-tri-isopropylbenzene moiety (**3s**, **3x**, **3y**, **3aa**) are poorly described by our mechanism.

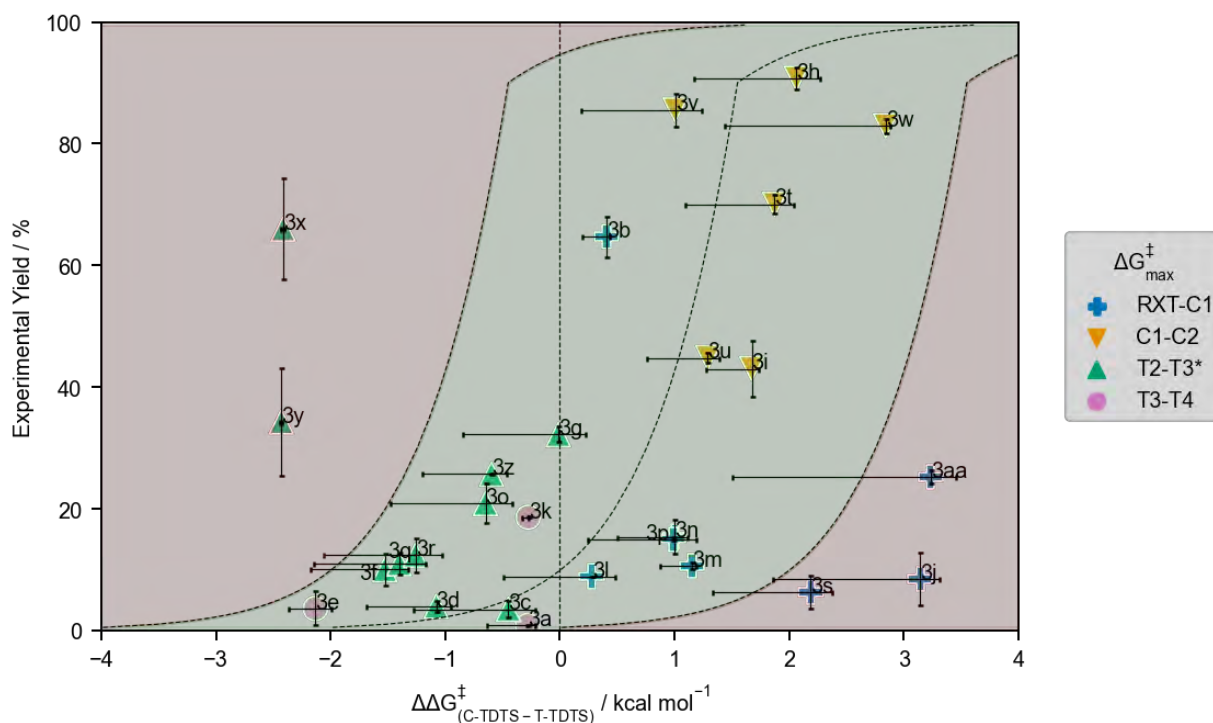


Figure 9: Experimental yield versus the free energy difference ($\Delta\Delta G^\ddagger$) in the simplified two-barrier model (**Figure 8**) that reproduces the computational yield at 3.5 eq $[\text{H}_2\text{O}]$ of the full proposed mechanism for all 27 ligands. The vertical error bars denote the error in experimental yield (**Supplementary Discussion S3.1**), while the horizontal error bars denote the values of $\Delta\Delta G^\ddagger$ of the simplified model that reproduces the experimental yield when $[\text{H}_2\text{O}]$ is 1.0 eq (left bound) and 5.0 eq (right bound). The central sigmoidal black dotted line denotes predicted computational yield for a given $\Delta\Delta G^\ddagger$ barrier for a simplified two-barrier model (**Supplementary Discussion S7.7.1**). Peripheral black dotted lines denote an error bound of ± 2.0 kcal/mol for the simplified model's $\Delta\Delta G^\ddagger$, which corresponds to a *barrier tuning to parity prediction* metric of ± 1.0 kcal/mol. Green and red shaded regions denote that the computed yields reproduce the experimental yields within, or outside the defined error bounds, respectively. The highest overall barrier amongst C-transmetalation and the T-pathway ($\Delta G^\ddagger_{\text{max}}$) in the full proposed mechanism computed for each ligand is color-coded with different markers in the legend, and T2-T3 barriers have a +1.76 kcal/mol correction to account for the effects of $[\text{H}_2\text{O}]$ (**Supplementary Discussion S7.7.1**).

Alternative mechanisms

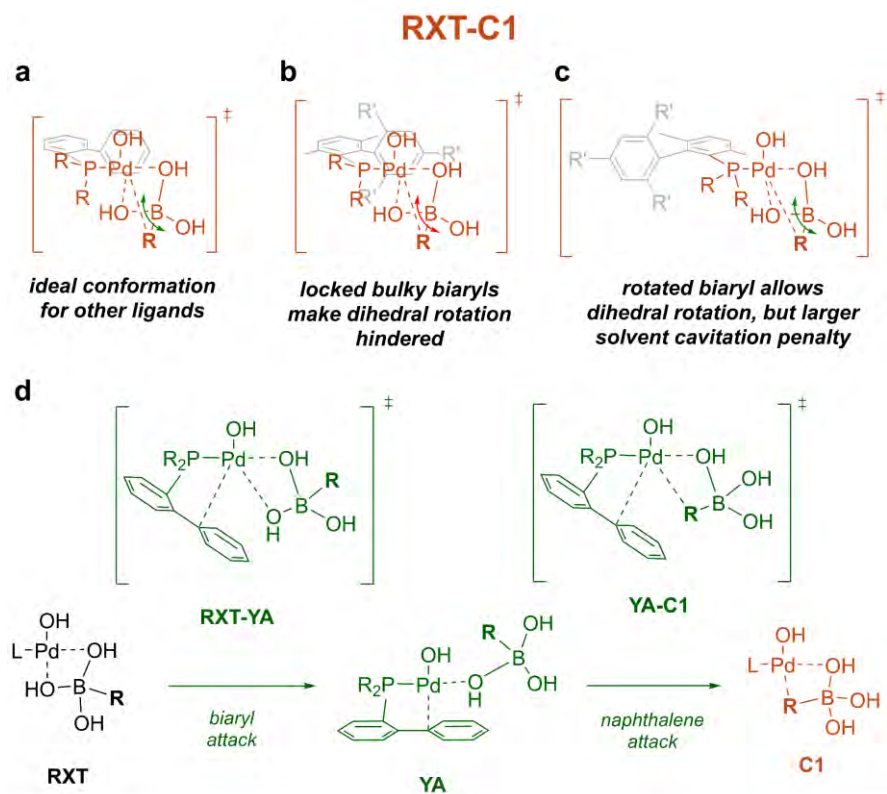


Figure 10: Conformations for the **RXT-C1** transition states, and proposed alternative mechanism for the conversion of **RXT** to **C1** via **RXT-YA** and **YA-C1**.

We evaluate some alternative mechanistic propositions here, though we highlight in detail other possibilities for the poorly predicted ligands in **Supplementary Discussion S7.7.4** and **S7.7.5**. A full map of all considered mechanistic pathways can be found in **Supplementary Figure S60**. The anomalously high **Naph-T** computational yields for BrettPhos (**3s**) and AdBrettPhos (**3aa**) are due to high **RXT-C1** barriers (**Figure 11a, 11b**). The **RXT-C1** transition states for typical Buchwald ligands have the lowest energy conformer with the biaryl placed near the site of dihedral rotation (**Figure 9a**). However, in this conformation for BrettPhos and AdBrettPhos, the $-\text{OCH}_3$ moieties in the first phenyl of the biaryl force the tri-isopropyl-containing biaryl closer to the palladium center, making dihedral rotations of the naphthalene onto the palladium center extremely sterically hindered (**Figure 10b**). While the lowest energy conformer for BrettPhos was found to take the form in **Figure 10b**, we could not locate such a transition state for AdBrettPhos, and the lowest energy conformer found was one where the bulky biaryls are rotated away from the central palladium reaction core (**Figure 10c**).

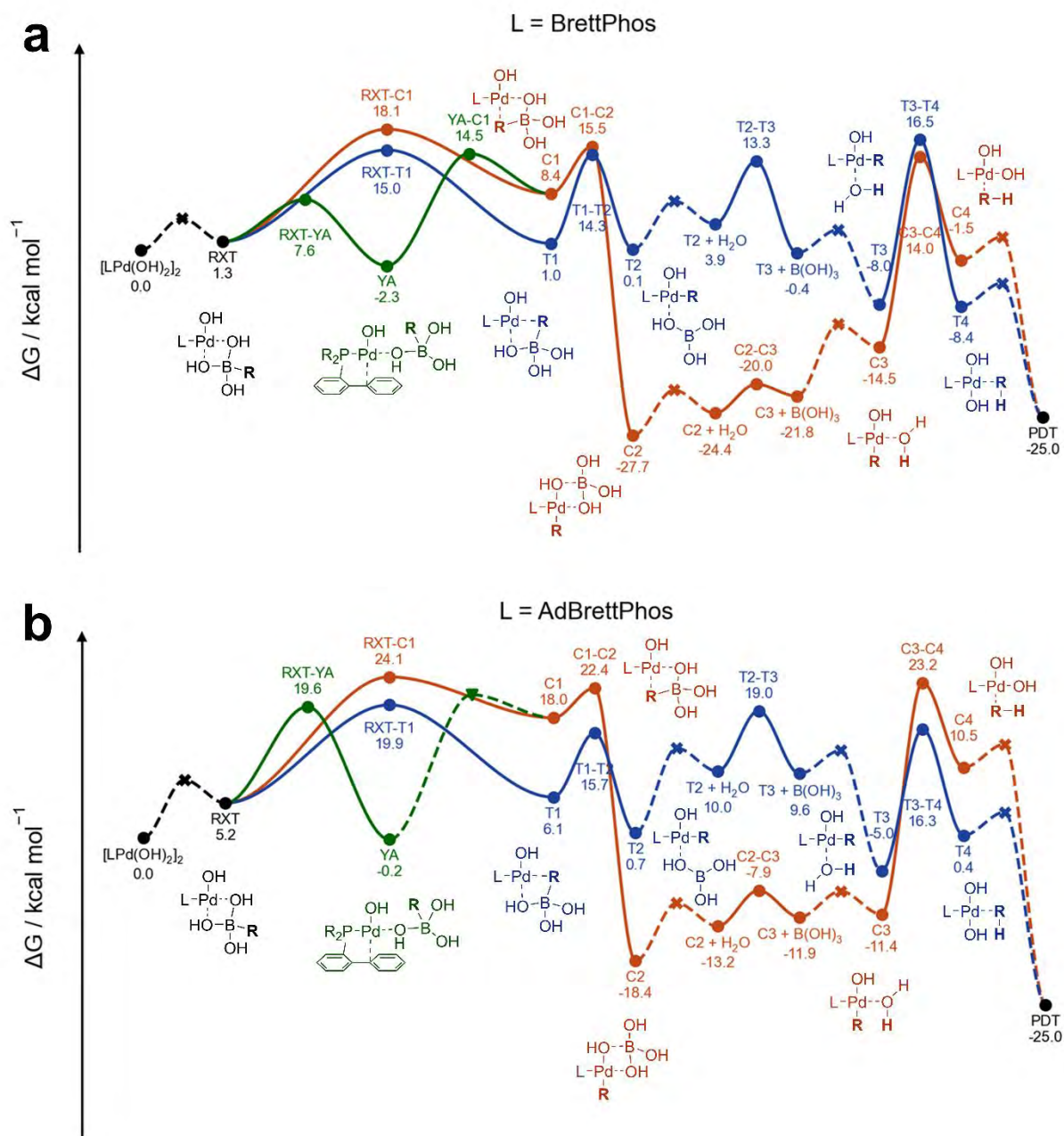


Figure 11: Computed reaction profiles for **a)** BrettPhos and **b)** AdBrettPhos with alternative mechanisms for forming **C1** included. ●: computed structures. ✕: Estimated transition state energies based on a 3.5 kcal/mol diffusion barrier at $T = 333.15\text{K}$ (see **Computational Methods**). ▼: Transition state not found.

In our attempts to locate low-energy conformers for **RXT-C1** with our computational workflow, we found transition states where the tri-isopropyl biaryl attempts to displace either the hydroxyl group (**RXT-YA**) or the naphthalene group in a similar dihedral motion (**YA-C1**) (**Figure 10d**). The intermediate that forms from this process is **YA**, where the biaryl forms a η^2 -coordination to palladium. The inclusion of **RXT-YA** and **YA-**

C1 for BrettPhos suppressed **Naph-T** yields down to 10%, in agreement with experimental yields (**Figure 11a, 12a**), and brings the *barrier tuning to parity* prediction down for BrettPhos down from -1.24 kcal/mol to -0.14 kcal/mol. We note that **RXT-C1** is still favored over the **YA** pathway for a series of other ligands we considered (**Supplementary Discussion S7.7.5**), suggesting that this mechanism may only be appropriate for BrettPhos. However, for AdBrettPhos, due to the steric bulk of the adamantyl moiety and the position assumed by the Buchwald biaryl in **YA**, the naphthalene moiety is not able to attack the palladium atom to form **C1**. As such, we were not able to locate a transition state for **YA-C1** (**Figure 11b**). Even if the **YA** pathway was energetically more feasible than **RXT-C1**, AdBrettPhos still faces immense steric strain in the actual transmetalation event (**C1-C2**) where the 1-adamantyl moieties impede the approach of naphthalene for transmetalation, and, thus, the yields for AdBrettPhos remain poorly predicted (**Figure 12b**).

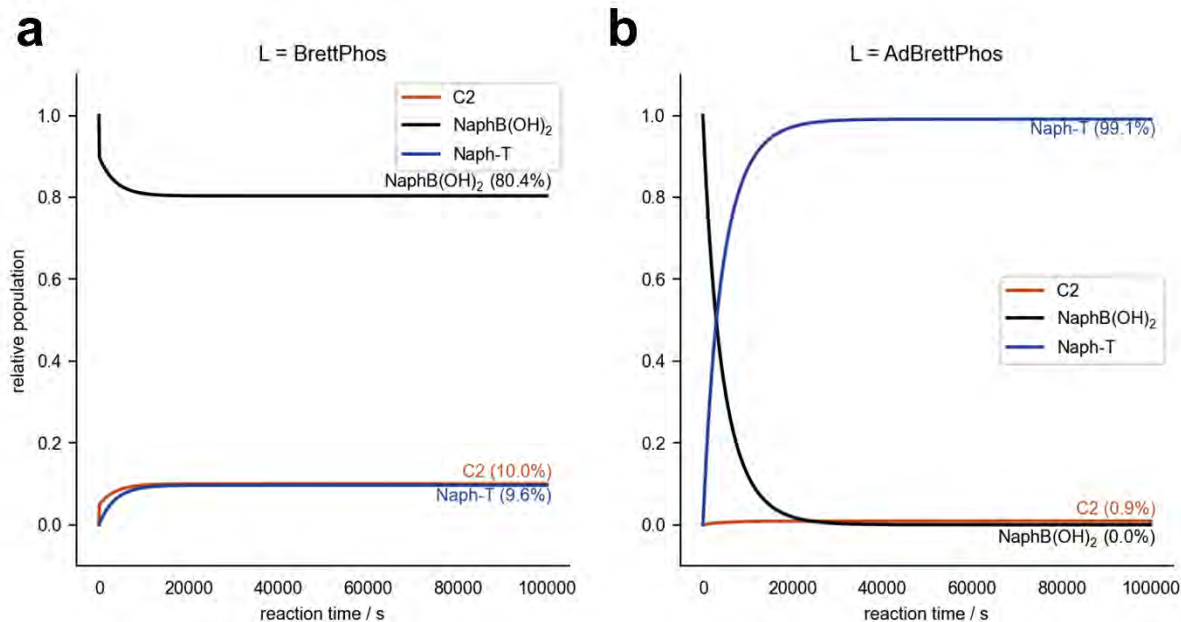


Figure 12: Relative population of key intermediates in the proposed mechanism from the kinetic model (**Supplementary Table S34**) for **a)** BrettPhos and **b)** AdBrettPhos.

Correlation to ligand descriptors

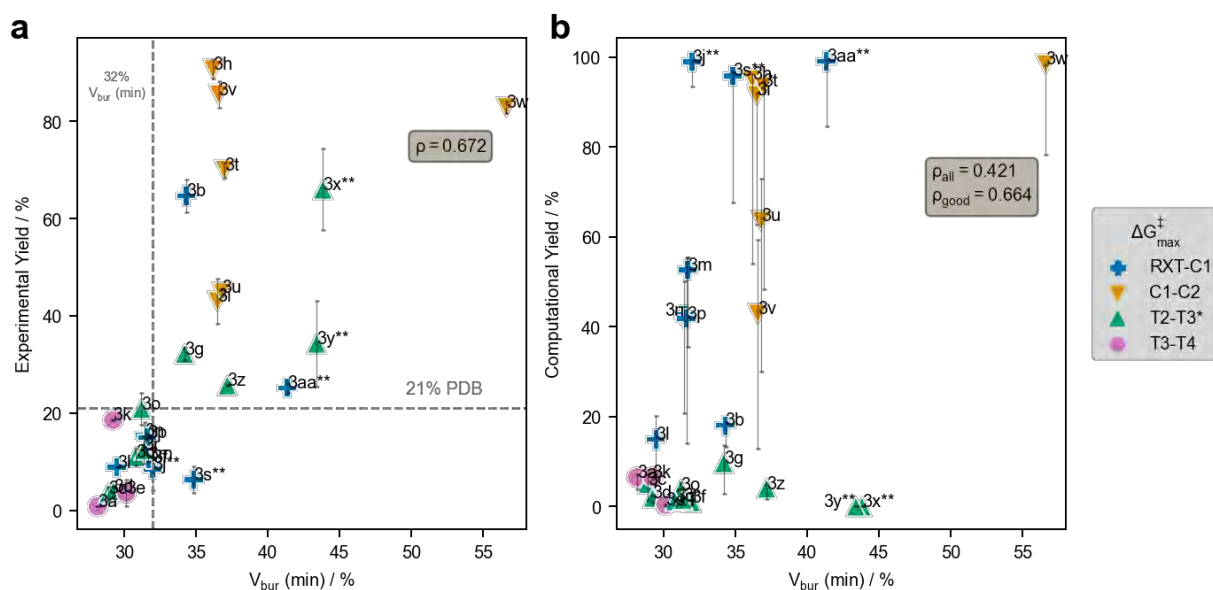


Figure 13: Pearson correlation plots of **a)** experimental yields and **b)** computational yields versus the percent buried volume of the ligand's minimum energy conformer ($V_{bur}(\text{min})$). Prediction quality is considered poor (labels marked with **) if the *barrier tuning to parity prediction* metric is >1.0 kcal/mol (see **Figure 9**). In all figures, a $+1.76$ kcal/mol correction is applied to the bimolecular reaction **T2-T3** to account for $[\text{H}_2\text{O}]$ to compare first-order barriers on equal footing (**Supplementary Discussion S7.7.1**). The highest overall barrier amongst C-transmetalation and the T-pathway ($\Delta G_{\text{max}}^{\ddagger}$) computed for each ligand is color-coded with different markers in the legend. Zoomed-in plot of lower left region provided in **Supplementary Figure S150**. Dotted lines are marked for a suggested 32% $V_{bur}(\text{min})$ threshold for significant experimental protodeboronation yields ($>21\%$ PDB) for the ligands screened in this experiment.

Finally, we assess the correlation of the observed phenomena against pre-computed steric and electronic ligand properties in the monophosphine ligand database *kraken*.⁶¹ We achieve decent Pearson r correlations between the percentage buried volume of the ligand's minimum energy conformer ($V_{bur}(\text{min})$) against both experimental yields ($\rho = 0.672$) and the subset of well-predicted (**Figure 8**, within green bounds) computational yields ($\rho = 0.664$) (**Figure 13**). These results suggest that $V_{bur}(\text{min})$ can appropriately encapsulate both the effects of local and remote steric bulk of our set of phosphine ligands, providing a quick way to estimate the degree of PDB for new ligands. We note that the ligands we considered in our reaction screening can be roughly divided into low and high protodeboronation at the boundary of $V_{bur}(\text{min}) = 32\%$, though it is not a necessary condition for high protodeboronation. We further note that higher correlations can be achieved with bespoke descriptors derived from buried volume (e.g. hemispheric or quadrant buried volumes, see **Supplementary Discussion S8**), but our goal with this model was not to develop a predictive model as the small dataset we used in this study can lead to spurious correlations.

Conclusion

We demonstrated that bulky phosphine ligands can promote palladium-catalyzed protodeboronation under conditions relevant to the SMC. Furthermore, starting from Pd(0) sources like Pd₂dba₃ or Buchwald pre-catalysts that rapidly form Pd(0) instead of using Pd(OAc)₂ could help reduce unwanted protodeboronation in addition to minimizing catalyst initialization periods in SMC. This was observed experimentally under competitive cross-coupling and under conditions without the aryl halide, even when only adventitious water was present. Computational investigations revealed that bulky ligands favor the formation of a reactive post-transmetalation intermediate that, subsequently, undergoes facile proton transfer from water.

Adventitious water is challenging to avoid even with typical anhydrous conditions in organic synthesis, e.g., using anhydrous solvent and storing reagents in desiccators. Our results show that palladium-catalyzed protodeboronation with adventitious water can be a significant source of boronic reagent deactivation in cross-coupling conditions even with the increased resistance of boronic acid pinacol esters. This necessitates careful ligand selection for the SMC, especially in light of the trade-off between the ease of productive oxidative addition, transmetalation, and reductive elimination¹⁸ versus the elevation of unproductive protodeboronation for bulky phosphines. In deciding the ligand for a new SMC synthetic protocol, we recommend consulting the buried volume of the ligand, which can be easily retrieved from the *kraken* database. Based on the ligands we evaluated, buried volumes below 32% show suppressed palladium-catalyzed protodeboronation and should provide greater selectivity for cross-coupled products in the SMC. Where possible, evaluating the full mechanistic pathway for the substrates and ligands of interest may also provide semi-quantitative yield predictions using kinetic modeling. As we have currently only demonstrated the ligand-dependence of palladium-catalyzed protodeboronation for electron-neutral boronic reagents, and how the electronic nature of the boronic reagent affects palladium-catalyzed protodeboronation to a limited extent, comprehensive studies towards the scope of aryl substituents and boronic moieties are required to gain a full understanding of palladium-catalyzed protodeboronation.

Methods

Experimental methods

Synthesis

Screening reactions were prepared by automatic solid weighing (+/- 2.5% limit) using the QUANTOS solid dosing platform for all palladium sources and ligands. Bases were subsequently dosed manually as the last reagent, either using a measuring scoop (K₃PO₄) or on an analytical balance (all bases in base screening, **Supplementary Discussion S3.4**), and the vials were capped immediately to avoid water absorption on the base surface. The reactions were then performed on the high throughput reaction screening variant of the MEDUSA automation platform, including automated inert atmosphere handling, stock solution preparation, liquid dosing and heating/stirring, all controlled by Python code (see **Supplementary Discussion S2.1** for platform design and **Supplementary Discussion S2.2, S3.1-S3.4, S4.1-S4.3** for

reaction details). All reactions were performed under an anhydrous N₂ atmosphere. All bases were stored under an anhydrous atmosphere and dried in an oven when necessary. 1,4-dioxane solvent from *Sure/Seal*TM bottles was used, except for H₂O-loading experiments where a designated amount of H₂O was added to substrate stock solution quantitatively using a microsyringe. All experiments were at least duplicated. HPLC samples were prepared manually from the post-reaction mixtures and analyzed on an Agilent 1200 HPLC equipped with DAD, and the HPLC data (retention time, peak integration) were processed automatically using *python* code. Yield quantifications were performed based on calibration curves using independently synthesized or commercially available materials (see **Supplementary Discussion S1** for details).

Kinetic monitoring

Reagents for the kinetic monitoring procedure were prepared using the QUANTOS platform, and the procedure was performed on the continuous reaction monitoring variant of the MEDUSA automation platform. The automated reaction sampling and vial cleaning were synchronized with the Agilent 1200 HPLC running ChemStation using *python* code (see **Supplementary Discussion S4.1** for platform design, **Supplementary Discussion S4.2-S4.3** for reaction details, and the GitHub repository for platform control code). All experiments were at least duplicated. HPLC data were processed automatically using *python* code.

Computational methods

Density functional theory calculations

Structures were either automatically constructed through replacing phosphine ligands in previously manually-optimized JohnPhos (**3t**) structures *via kallisto*,⁶² which handles post-replacement atomic clashes *via* GFN2-xTB⁶³ constrained optimization, or by manually replacing structural features in cases where the clash handling protocol gave incorrect structures. Conformer searches were subsequently conducted using CREST⁶⁴ with the GFN2-xTB semiempirical level of theory in the gas phase. The distances and angles around the palladium atoms were explicitly constrained to preserve square planar geometries and maintain the groups' relative arrangements around the palladium centers. In evaluating new conformers, transition state structures had key bond lengths additionally constrained based on previously DFT-optimized values. Single-point energy calculations for each optimized conformer were then evaluated at the PBE⁶⁵-D3BJ^{66,67}/def2-SVP⁶⁸ level of theory in the gas phase using Gaussian 16⁶⁹. The lowest energy conformer identified by DFT was subsequently subjected to unconstrained geometry optimization and frequency calculations at the PBE-D3BJ/def2-SVP level of theory in the gas phase, with the W06 auxiliary basis set⁷⁰ for density fitting. Structures were ensured to have zero or one imaginary frequency if they are an intermediate or transition state, respectively. Single points were subsequently calculated using the DSD-PBEB95⁷¹-D3BJ/def2-QZVPP⁶⁸ level of theory with the auxiliary basis sets def2/J,⁷⁰ def2-QZVPP/C,⁷² and def2/JK,⁷³ incorporating implicit solvation in 1,4-dioxane ($\epsilon = 2.2099$) with the SMD⁷⁴ model using ORCA

5.0.3.^{75–79} This level of theory was chosen as it reproduces barrier heights within 1.0 kcal/mol across a variety of reaction benchmarks.⁶⁰ The GoodVibes⁸⁰ package was used to apply quasi-harmonic approximations for frequency calculations *via* the Truhlar scheme⁸¹ at 333.15 K, with solution-phase standard state corrections and entropic corrections concerning symmetry.

Kinetic modeling

The kinetic models were constructed with the *pykinetic* package.⁸² The energies of each reactant and intermediate are provided in one file, while the possible reactions that are allowed in the kinetic model are specified in another file with the energies of the transition state provided for each reaction. All reactions are treated as reversible, and the forward and backward reaction rates are calculated as $(\kappa k_b T/h) \exp(-E_a/RT)$, where k_b is the Boltzmann constant $1.381 \times 10^{-23} \text{ J}\cdot\text{K}^{-1}$, h is the Planck constant $6.626 \times 10^{-34} \text{ kg}\cdot\text{m}^2\cdot\text{s}^{-1}$, E_a is the activation energy specified in J/mol, R is the gas constant $8.314 \text{ J mol}^{-1}\cdot\text{K}^{-1}$, and T is the reaction temperature, specified to be 333.15 K. The transmission coefficient κ is assumed to be 1. The forward and backward activation energies are provided as the differences between the transition state energies and the sum of reactant energies or product energies respectively. The rate of change of each tracked intermediate is expressed as a sum of the rates of reactions that produce and consume the intermediate, and is solved as a system of ordinary differential equations. We used the *scipy* v1.9.⁸³ bindings for the LSODA numerical solver, which is part of the ODEPACK⁸⁴ package. The absolute and relative tolerance parameters for LSODA were defined as 10^{-7} and 10^{-12} , respectively.

Associative and dissociative processes (**Supplementary Table S31**, reactions 1, 2, 7, 12, for example) do not have transition states calculated and are assumed to be diffusion-limited.⁸⁵ The specification of a barrier is necessary to ensure numerical stability in the kinetic model when rates are extremely high due to very small energy differences. The diffusion constant was calculated using the formula proposed by Rush et al.,⁸⁶ incorporating a viscosity constant η with a value of $2.09\cdot 10^{-7} \text{ P}\cdot\text{s}$ for 1,4-dioxane.⁸⁷ Given the temperature of 333.15K, the diffusion barrier is estimated to be 3.46 kcal/mol, and the transition state energies specified for diffusion-limited reactions are calculated from the highest of either the reactant or product energies specified.

The initial concentrations were set to $[\text{LPd}(\text{OH})_2]_2 = 0.001\text{M}$ and $[\text{NaphBOH}_2] = 0.020\text{M}$ following the experimental conditions used (**Supplementary Discussion S2.2**), and $[\text{H}_2\text{O}] = 0.070\text{M}$ (3.5 eq) as an estimate from deuterium incorporation, where 20 equivalents of added D_2O resulted in 83% deuterodeboronated product and 17% of protodeboronated product (**Supplementary Discussion S5.1**). We note that we model the dissociation of $[\text{LPd}(\text{OH})_2]_2$ to form two equivalents of $[\text{LPd}(\text{OH})_2]$ as diffusion-limited, and the initial concentration of $[\text{LPd}(\text{OH})_2]_2$ provided will generate the correct 10 mol% of catalyst in the kinetic model. The products we track are $\text{B}(\text{OH})_3$ and **Naph**, which is split into **Naph-C** and **Naph-T** to illustrate the two ways **Naph** can be formed from the **C**- and **T**-pathways respectively. **Naph-C** is not

depicted in the kinetic model traces as the **C3-C4** transition states are insurmountable in the timescales of the kinetic model. We also track the reaction intermediates **C2**, **T2** and **T3** as they can be more stable than the starting reactant state (depending on the ligand) and build up a significant population. As *pykinetic* requires that the duration of the kinetic modeling be specified before the populations are allowed to evolve, the end time for each ligand was determined to be the point where the populations do not change significantly anymore with time. LSODA adaptively adjusts the time step based on the problem's dynamics, and we have found that the product distributions remain consistent regardless of the solver's step-size adjustments.

Statistical analysis

Pearson correlation analysis between *kraken* descriptors and experimental and computational yields were performed using *scipy* v1.9.3.⁷⁵

Data Availability

All code for experimental hardware manipulation, experimental data extraction, analyze computational output, and plot figures are available on GitHub at <https://github.com/chertianser/pdcatpdb-code> and on Zenodo at <https://doi.org/10.5281/zenodo.13246410>. The raw DAD data is available at <https://doi.org/10.5281/zenodo.15523021>. All code used by and generated by *pykinetic* are also available on GitHub and Zenodo. All computed structures and single points are available on <https://iochem-bd.matter.toronto.edu>.

Author Contributions

C.T.S. and H.H. contributed equally to the work.

Supporting Information

Supplementary Data S1: Raw results for calibration curves and yields and kinetic experiments.

Supplementary Data S2: Computed barriers for all intermediates calculated, computed microkinetic yields and ligand descriptors for each ligand experimentally tested.

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