^{DMP}DAB–Pd–MAH: A Versatile Pd(0) Source for Precatalyst Formation, Reaction Screening, and Preparative-Scale Synthesis

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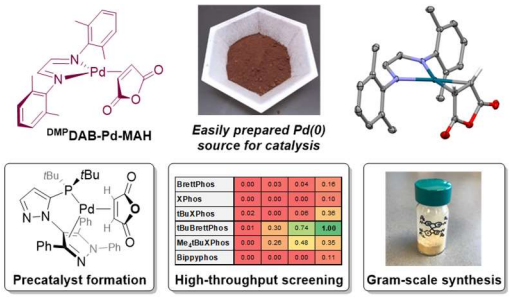
ABSTRACT: We report an easily prepared and bench-stable mononuclear Pd(0) source stabilized by a chelating *N,N'*-diaryldiazabutadiene ligand and maleic anhydride: ^{DMP}DAB–Pd–MAH. Phosphine ligands of all types, including bidentate phosphines and large cone angle biarylphosphines, rapidly and completely displace the diazabutadiene ligand at room temperature to give air-stable Pd(0) phosphine complexes. ^{DMP}DAB–Pd–MAH itself is readily soluble and stable in several organic solvents, making it an ideal Pd source for *in situ* catalyst preparation during reaction screening, as well as solution-dispensing to plate-based reaction arrays for high-throughput experimentation. Evaluation of ^{DMP}DAB–Pd–MAH alongside other common Pd(0) and Pd(II) sources in microscale reaction screens reveals that ^{DMP}DAB–Pd–MAH is superior at identifying hits across six different C–N, C–C, and C–O coupling reactions. ^{DMP}DAB–Pd–MAH, and the phosphine precatalysts derived therefrom, are also effective in preparative-scale cross couplings at low Pd loadings.



INTRODUCTION

Palladium-catalyzed cross-coupling is one of the most powerful tools in modern synthetic chemistry,[1–3] with widespread application in total synthesis,[4] pharmaceutical discovery and process chemistry,[5–7] agrochemistry,[8] and materials synthesis.[9] Given the large number of reaction variables to optimize for every new system, there is a daunting variety of reported reaction conditions for each general transformation. Whether by iterative one-variable-at-a-time optimization or multivariate high-throughput experimentation (HTE),[10–14] rapid reaction screening is critical for successful implementation of cross-coupling methods and development of new reactions. In particular, ligand identity is one of the most important factors in cross-coupling reaction design.[15–20] While screening with single-component precatalysts where the ligand is already metallated can be advantageous in certain cases,[10,21–25] a more general and operationally simple strategy is to combine the free ligand with an appropriate Pd precursor to generate the catalyst *in situ*. This is especially useful when exploring a large ligand library, and when appropriate precatalysts are not available. On the other hand, *in situ* catalyst formation introduces additional variables and uncertainties: what Pd precursor should be used, how robust and reliable is the precursor, and how can one be sure *in situ* metallation/activation is successful?

Since the advent of Pd-catalyzed cross-coupling, simple Pd(II) sources such as halide and carboxylate salts have been the most common choice for *in situ* catalyst formation (Figure 1); however, multiple potential reduction pathways to generate active Pd(0) makes these systems more complex than they appear.[26–31] Other Pd(II) sources exploit the reactivity of allyl ligands to enable formation of metallated Pd(0) complexes *in situ*. CpPd(allyl) and CpPd(cinnamyl) are known to react with phosphines and generate Pd(0) via reductive elimination,[32,33] though this reactivity is ligand-specific.[34] Pd(II) allyl chloride-bridged dimers are frequently used to generate active catalysts *in situ*,[35–42] or are the basis of single-component precatalysts;[22,43] however, comproportionation reactions can result in the formation of inactive Pd(I) μ-allyl dimers depending on the substitution pattern of the allyl ligand.[44,45] An improved indenyl-based precatalyst scaffold has been designed by Hazari and co-workers to avoid this issue.[23,46] Another general drawback of allyl-based Pd(II) sources is the observed difficulty in coordinating very large ligands, including many biaryl phosphines that are highly active for C–N cross-coupling. While chloride abstraction using Ag(I) salts to generate cationic [LPd(allyl)]$^+$ precatalysts is successful where L is large,[22] this strategy is impractical for *in situ* catalyst formation.

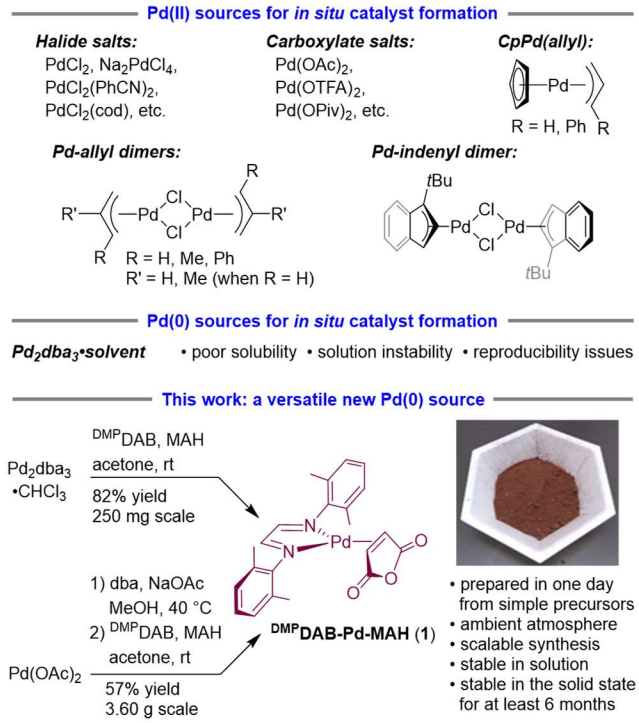


Figure 1. Common Pd(II) and Pd(0) sources for *in situ* catalyst formation, and synthesis of new Pd(0) source ^{DMP}DAB-Pd-MAH (**1**).

In stark contrast to the prevalence of Pd(II) sources for *in situ* catalyst formation, there is a paucity of Pd(0) sources available for the same purpose. Using a Pd(0) source has the advantage of not requiring a reduction step during catalyst formation/activation; however, Pd_2dba_3 and its various solvates are effectively the only option for a Pd(0) source in catalyst screening. While used extensively in organopalladium catalysis, there are well-documented issues with Pd_2dba_3: it has relatively poor solubility (problematic from a solution-dosing standpoint in high-throughput screening); suffers from batch-to-batch inconsistency in performance;[47] exhibits differential reactivity based on the specific solvate used;[48] and decomposes to palladium nanoparticles during storage either in solution or in the solid-state.[47] Phosphine metallation rates also vary by ligand structure, sometimes significantly.[49,50]

Herein, we report a new and versatile Pd(0) precursor: ^{DMP}DAB–Pd–MAH (**1**, Figure 1). This Pd(0) complex offers several specific advantages over other Pd sources, including good solubility, solution stability, and rapid/complete substitution of the *N,N'*-diaryldiazabutadiene ligand with many catalytically-relevant phosphines. We also report the preparation of 13 air-stable [phosphine]–Pd–MAH precatalysts by using **1** as a precursor. Through a series of microscale high-throughput screening experiments for C–N, C–O, and C–C coupling reactions, we demonstrate that ^{DMP}DAB–Pd–MAH is superior at identifying ligand hits when evaluated alongside other common Pd sources. Finally, we demonstrate that catalysts derived from **1** (*in situ* or preformed) are able to catalyze preparative-scale reactions at low Pd loadings, including a high-yielding synthesis of the hole-transport material *spiro*-OMeTAD.[51]

RESULTS AND DISCUSSION

^{DMP}DAB–Pd–MAH synthesis and properties. Inspired by prior work from Vrieze and co-workers on fundamental studies of related complexes,[52] we designed our Pd(0) source to be stabilized by a chelating diazabutadiene (DAB) ligand and maleic anhydride (MAH) as an electron-deficient alkene. We incorporated sterically-demanding 2,6-dimethylphenyl substituents at nitrogen (^{DMP}DAB) to favor rapid and complete phosphine displacement during *in situ* catalyst formation. By treating an acetone suspension of Pd_2dba_3•$CHCl_3$ with ^{DMP}DAB and MAH at room temperature (open-flask, benchtop), ^{DMP}DAB–Pd–MAH (**1**) can be isolated in 82% yield (Figure 1). We have also developed a telescoped synthesis of **1** from $Pd(OAc)_2$ (proceeding via crude "$Pd(dba)_2$") that can be conducted in one day with 57% isolated yield on multigram scale. Using either method, **1** is isolated *via* simple precipitation in high purity (determined by NMR spectroscopy), with no need for recrystallization. Compound **1** is an air and moisture stable mononuclear Pd(0) complex that is soluble in a variety of organic solvents (*vide infra*). Analysis by NMR spectroscopy generates simple and easy to interpret spectra that are consistent with the given structure, providing an excellent method to quickly assess purity. This is in contrast to the solution behavior of Pd_2dba_3, where the presence of multiple species and extensive magnetic inequivalence leads to complex NMR spectra,[47] and poor solubility leads to a low signal-to-noise ratio. We have also obtained the solid-state molecular structure of **1** *via* X-ray diffraction (Figure 2).

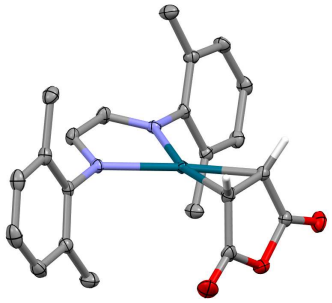


Figure 2. Solid-state molecular structure of complex **1**. Atom colors: C: grey; N: light blue; O: red; Pd: green/blue. Thermal ellipsoids plotted at 50% probability. Hydrogen atoms omitted for clarity, except those on the maleic anhydride ligand. See the Supporting Information for metrical parameters and data collection details.

Given the importance of reliability in reaction screening, whether standard or high-throughput, we assessed the stability of compound **1** over time in both the solid-state (for long term storage) and in solution (for manual or automated solution dispensing). The compound is stable in the solid-state for at least 6 months at room temperature under ambient atmosphere, with no discernable change to the NMR spectra over this time. Prior studies of Pd(0) complexes of this type describe rapid solution decomposition to metallic Pd,[52] which would severely hamper its use in solution-based dispensing. We therefore monitored the concentration of **1** over time (initially 20 mg/mL) at room temperature by ^{1}H NMR spectroscopy (Figure 3).

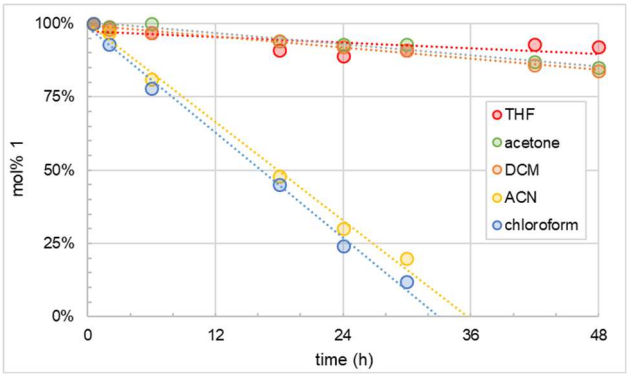


Figure 3. Solution stability of complex **1** at 20 mg/mL (0.043 M) initial concentration in five deuterated solvents (48 h, room temp.). Concentration determined by relative integration versus internal standard (1,3,5-trimethoxybenzene).

In both acetonitrile and chloroform, we observe rapid decomposition (3% **1** consumed per hour), with only 25-30% remaining after 24 hours. Fortunately, complex **1** is 10-20 times more stable in THF, acetone, and DCM (decomposition rates 0.15-0.3% h^{-1}). After 6 hours, a typical length of time needed to dispense solutions to a screening plate, the amount of **1** remaining in these solvents is 97-100%. After 24 hours, the length of an automated solution dispense protocol to multiple reaction plates, 89-93% of complex **1** remains; notably, no discernable byproducts or formation of solids is observed. Based on these data, we recommend working with **1** in freshly-prepared THF or acetone solutions for dispensing to HTE plates. Because **1** is air and moisture stable, solution preparation and dispensing can be performed using regular lab-grade solvents without the need for an inert-atmosphere glovebox.

Phosphine metallation and precatalyst synthesis. Given the simple synthesis and stability of **1**, we further studied its suitability as a precursor for *in situ* catalyst formation during reaction screening by HTE. Our key criteria is that phosphine metallation to Pd(0) must be rapid at room temperature to give a single, well-defined Pd species. This will ensure self-consistent results across a screening plate that do not depend on secondary factors such as catalyst activation. In a series of preliminary experiments, we mixed **1** with 2 molar equivalents of a variety of mono and bidentate phosphines in d_6-acetone and monitored the rate and extent of ligand substitution by ^{1}H and ^{31}P NMR spectroscopy. In every case, we observed rapid and complete conversion to a single new ^{31}P-containing species.

Based on these results, we prepared and isolated a series of 13 [phosphine]–Pd–MAH precatalysts (**2-14**) using a set of ligands commonly used in cross-coupling catalysis. All of these syntheses are carried out at room temperature in THF, and the products isolated by simple precipitation under ambient atmosphere. The prepared compounds range from the known complex dppp–Pd–MAH (**2**) to those with large biaryl and bispyrazolyl ligands including *t*BuBrettPhos (**11**), *t*BuBippyPhos (**12**), Me_4*t*BuXPhos (**13**), and JackiePhos (**14**). Figure 5 contains solid-state molecular structures of five of these complexes, determined by single crystal X-ray diffraction.

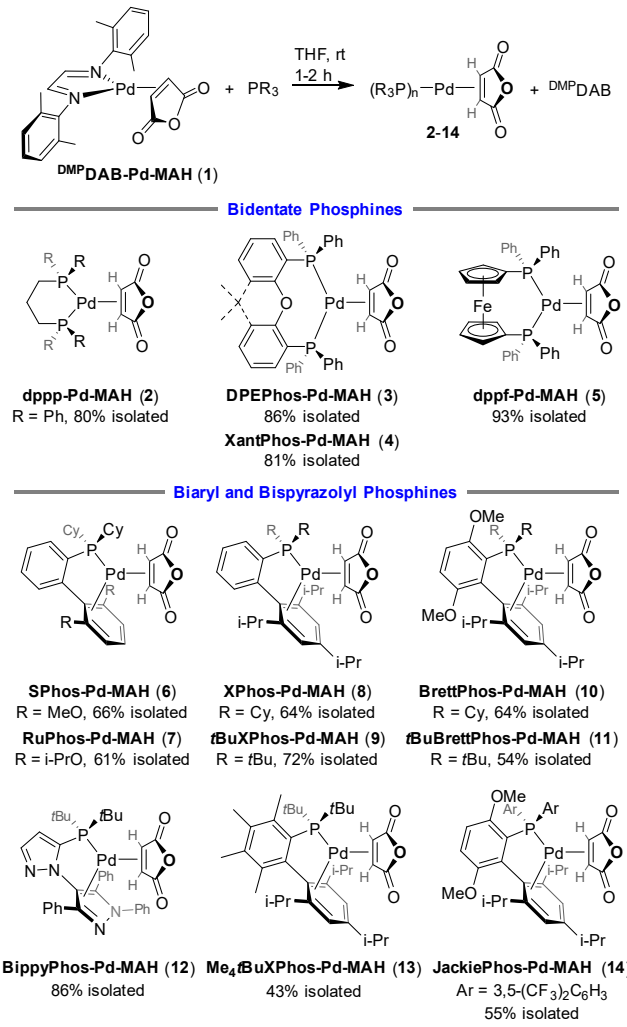


Figure 4. Synthesis and isolation of [phosphine]–Pd–MAH complexes **2-14** via ligand substitution at complex **1**.

For this set of representative ligands, a single set of simple reaction conditions is sufficient to ensure complete metallation at room temperature, even for very large cone-angle phosphines. One specific case illustrates the ability of **1** to undergo ligand substitution with large phosphines: Me_4*t*BuXPhos. This useful and sterically-demanding ligand[53] is known to require elevated temperatures (>100 °C) to react with Pd_2dba_3.[50] While Pd(II) precatalysts based on a palladacycle[54] or allyl[22] framework are reported, *in situ* catalyst generation with this ligand is challenging and potentially unreliable. With 2 equivalents of Me_4*t*BuXPhos and 1 equivalent of **1** in d_6-acetone, we observe >95% conversion to **13** after 60 min at room temperature.[55] Thus, a simple room temperature pre-stir for ~1 h is sufficient to generate **13** *in situ* for screening. Every other [phosphine]–Pd–MAH complex from Figure 4 has similarly rapid formation rates at room temperature.

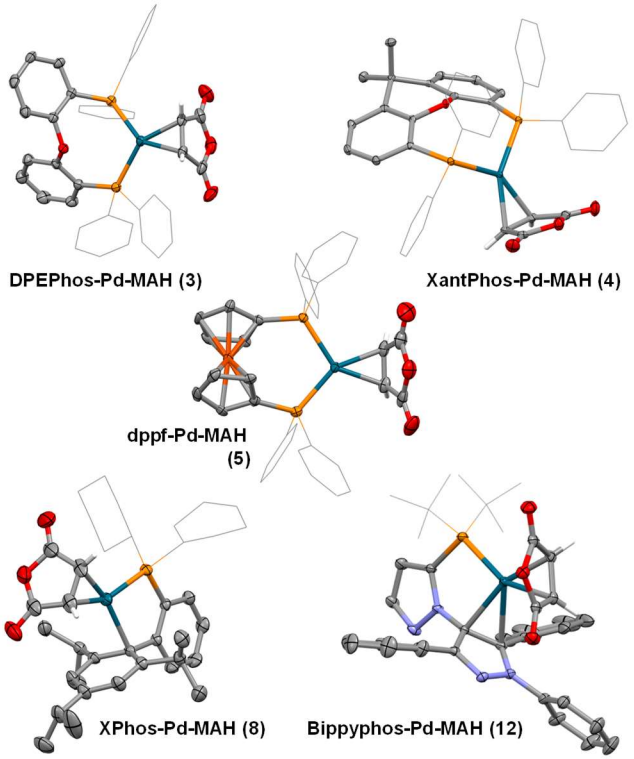


Figure 5. Solid-state molecular structures determined by single crystal XRD of **3**, **4**, **5**, **8**, and **12**. Atom colors: C: grey; N: light blue; O: red; P: orange; Pd: green/blue. Thermal ellipsoids plotted at 30% (**3**, **5**, **8**) or 50% (**4**, **12**) probability. Hydrogen atoms omitted for clarity, except those on the maleic anhydride ligand. Phosphine substituents (Ph, Cy, or *t*Bu) shown in wireframe for clarity; single conformation shown for disordered Cy ring in complex **8**. Solvent molecules in asymmetric unit omitted for clarity. See the Supporting Information for metrical parameters, data collection details, and full structures.

Applications in screening and preparative scale synthesis. To assess the catalytic utility of complex **1**, and the corresponding [phosphine]–Pd–MAH complexes derived therefrom, we have conducted a series of microscale high-throughput screens for several important cross-coupling reactions (Figure 6). Many of the properties of complex **1** – solubility, stability, and rapid ligand substitution – make it attractive as a Pd source for microscale high-throughput screening. We therefore tested **1** alongside three of the most common Pd sources for *in situ* catalyst generation – $Pd(OAc)_2$, $[Pd(allyl)Cl]_2$, and freshly prepared/recrystallized[47] Pd_2dba_3•$CHCl_3$ – in order to make fair comparisons.

Six screens were designed to cover a breadth of C–N, C–C, and C–O coupling reactions. These six reaction classes also do not involve substrates that can easily reduce Pd(II) to Pd(0) (such as arylboronic acids), making appropriate choice of Pd source critical to the success of a screening campaign. Each array was run with 13 mol% Pd (high catalyst loadings are typical in microscale screening), and extent of reaction assessed by normalized HPLC peak area for the desired product (versus internal standard, scaled to a max ratio of 1.00 for values in Figure 6). In each of the six cases, validation of the identified hit(s) was performed on preparative scale (0.42-4.50 mmol of limiting reagent) at lower catalyst loading (0.25-5 mol%) to obtain solution and isolated yields.

Our evaluation began with Buchwald-Hartwig amination using two different amines: primary (benzylamine) and secondary (morpholine).[56–58] The same six phosphines – BrettPhos, *t*BuBrettPhos, XPhos, *t*BuXPhos, RuPhos, and $P(tBu)_3$ – were tested in both reactions, and the other reaction conditions were adapted from standard protocols for C–N coupling.[59,60] For the coupling between benzylamine and 2-chloropyridine, HPLC analysis reveals complex **1** as the superior precursor, giving the highest amount of product across several sets of conditions. Among the ligands screened, BrettPhos, *t*BuBrettPhos and *t*BuXPhos were identified as the most active. Based on the known ability of BrettPhos to effectively catalyze arylation of primary amines over secondary amines,[17,61,62] this ligand was chosen for larger-scale validation. Using only 0.25 mol% of complex **10** as a single-component precatalyst gives 85% solution yield of the secondary amine (determined by ^{1}H NMR spectroscopy versus internal standard) on 1.00 mmol scale. By using a combination of **1** (0.25 mol%) and BrettPhos (0.50 mol%), a 91% isolated yield (~750 mg) is obtained on 4.50 mmol scale.

For the coupling between morpholine and 4-bromoanisole, nearly all Pd/ligand combinations result in good amounts of product; however, the catalysts generated from $Pd(OAc)_2$/*t*BuXPhos, $Pd(OAc)_2$/*t*BuBrettPhos, and Pd_2dba_3•$CHCl_3$/*t*BuBrettPhos perform relatively poorly, indicating inefficient catalyst activation. Complex **1** is again comparable or superior to the other Pd sources, with **1**/RuPhos providing the highest amount of product.[17,62] Using complex **8** (2 mol%) with added RuPhos (2 mol%) gives 95% solution yield on 0.42 mmol scale, and the combination of **1** (2 mol%) and RuPhos (4 mol%) gives 92% isolated yield of the coupled product on 1.00 mmol scale.

In addition to C–N couplings with primary and secondary amines, we assessed complex **1** as a precursor for the more challenging arylation of sulfonamides[63–65] and imidazoles.[50] For the synthesis of a representative *N*-arylsulfonamide via Pd-catalyzed coupling, we evaluated several large cone-angle ligands reported to be effective. These include biarylphosphines, such as JackiePhos[66] and *t*BuXPhos,[63] as well as XantPhos[67] and BippyPhos.[15,64,68] Under the conditions used (excess K_2CO_3 and CPME solvent), $Pd(OAc)_2$ is almost completely ineffective, generating only modest amounts of product and yielding no clear hits. The other three Pd sources fare better, with the combination of **1** and *t*BuXPhos giving the largest amount of *N*-arylsulfonamide product. Validation of this hit on 1.00 mmol scale revealed 5 mol% of complex **9** gives a 95% solution yield of the C–N coupled product, and **1** (5 mol%) / *t*BuXPhos (10 mol%) gives a 70% isolated yield after purification.

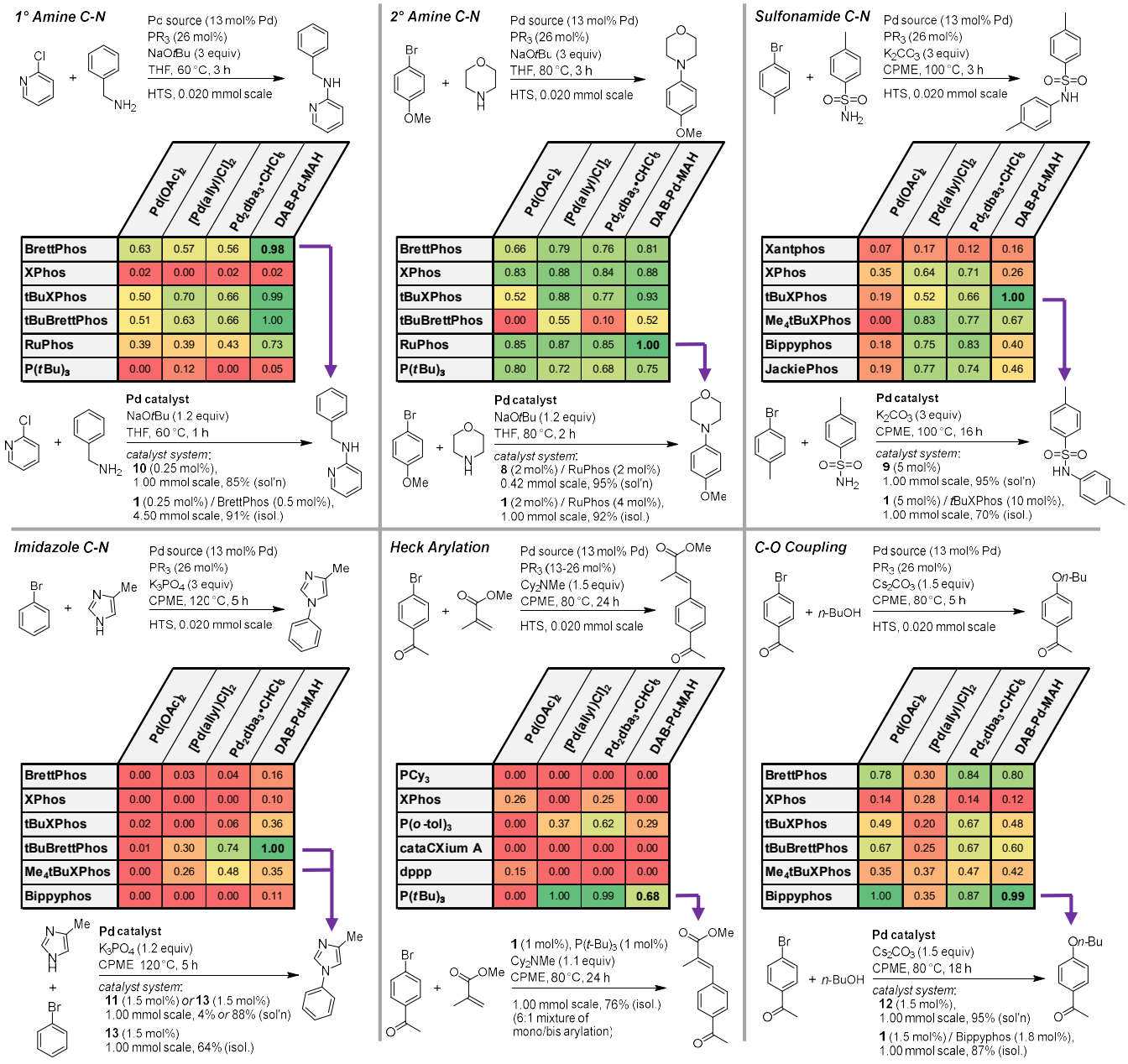


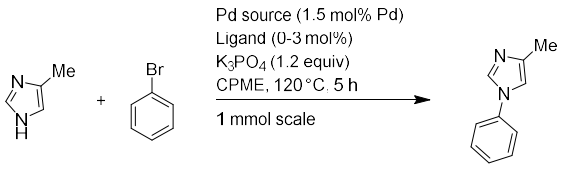
Figure 6. Microscale HTS results comparing four Pd sources for a series of Pd-catalyzed reactions including C–N coupling with several nucleophiles, Heck arylation, and C–O coupling. Color gradient indicates normalized HPLC product peak area / internal standard peak area (red = 0; yellow = 0.50; green = 1.00; largest product/std area ratio normalized to 1.00). Low catalyst loading (≤ 2 mol% Pd) and/or preparative-scale (≥ 1 mmol) examples using either ^{DMP}DAB–Pd–MAH (**1**) or isolated phosphine–Pd–MAH precatalysts shown below each HTS table. Solution yields determined by ^{1}H NMR spectroscopy versus internal standard (1,3,5-trimethoxybenzene).

For the Pd-catalyzed N1-selective arylation of 4-methylimidazole, known to be a challenging reaction,[50] we again evaluated a series of sterically demanding biaryl and bispyrazolyl ligands. Due to the previously observed deleterious effects of imidazole coordination on catalyst activation, we pre-mixed the Pd/ligand components at room temperature for 1 hour before adding the remaining reaction components. In stark contrast to the previously described screens, and consistent with the aforementioned challenges in carrying out this reaction,[50] very few Pd/ligand combinations result in product formation. $Pd(OAc)_2$ and $[Pd(allyl)Cl]_2$ are largely ineffective, though the latter does reveal possible hits with *t*BuBrettPhos or Me_4*t*BuXPhos. The two Pd(0) sources are better, with *t*BuBrettPhos, *t*BuXPhos, and Me_4*t*BuXPhos identified as potentially effective under these conditions. To confirm these hits on 0.020 mmol scale using 13 mol% **1** as the precursor, we determined solution yields by ^{1}H NMR spectroscopy for the reactions with *t*BuXPhos (28%), *t*BuBrettPhos (96%) and Me_4*t*BuXPhos (29%).

Given the apparent superiority of *t*BuBrettPhos from microscale screening experiments, we evaluated precata-

lyst **11** (1.5 mol%) in a 1.00 mmol scale reaction. Unfortunately, only 4% solution yield of the *N*-arylimidazole is observed at this lower catalyst loading. This discrepancy with the screening results prompted a more complete validation study of these catalysts at low Pd loading (Table 1). All of the systems with either *t*BuXPhos or *t*BuBrettPhos failed to generate significant product (entries 1-6). Using Me_4*t*BuXPhos and Pd_2dba_3•$CHCl_3$ – the previously reported system[50] – gives 40% solution yield when a P:Pd ratio of 2:1 is used (entry 7); however, dropping the phosphine loading to 1.8 mol% effectively shuts down the reaction (entry 8). This is likely due to slow metallation of Me_4*t*BuXPhos using Pd_2dba_3•$CHCl_3$, as previously observed by Buchwald and co-workers,[50] leading to formation of inactive imidazolyl–Pd species. In contrast, **1**/Me_4*t*BuXPhos is equally effective at 1.8 mol% and 3 mol% ligand, though solution yields are still modest (36-39%, entries 9-10). By using the single component Me_4*t*BuXPhos-ligated complex **13**, which has a perfect 1:1 Pd-to-ligand ratio, a much higher solution yield is obtained (88%), with a 64% isolated yield after chromatography (entry 11).

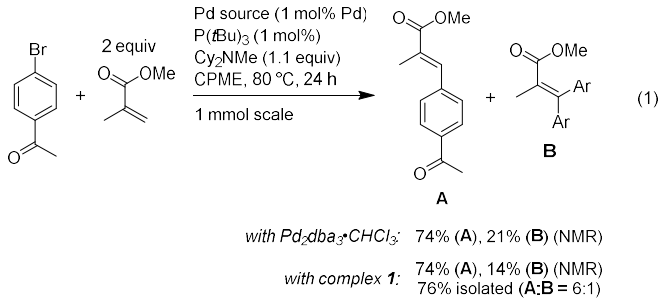
Table 1. Comparison of catalyst systems identified by HTE for imidazole arylation on 1 mmol scale.[a]



Entry	Pd source	Ligand (mol%)	Yield (%)[b]
1	**1**	*t*BuXPhos (3)	1
2	**1**	*t*BuXPhos (1.8)	1
3	**9**	n/a	4
4	Pd_2dba_3•$CHCl_3$	*t*BuBrettPhos (1.8)	6
5	**1**	*t*BuBrettPhos (1.8)	3
6	**11**	n/a	4
7	Pd_2dba_3•$CHCl_3$	Me_4*t*BuXPhos (3)	40
8	Pd_2dba_3•$CHCl_3$	Me_4*t*BuXPhos (1.8)	5
9	**1**	Me_4*t*BuXPhos (3)	39
10	**1**	Me_4*t*BuXPhos (1.8)	36
11	**13**	n/a	88, 64[c]

[a]Pd source and ligand were reacted for 1 h at room temperature before addition of other reaction components. [b]Determined by ^{1}H NMR spectroscopy versus internal standard (1,3,5-trimethoxybenzene). [c]Isolated yield of a separate experiment after chromatography.

In addition to C–N couplings, we have also examined complex **1** as a precursor for Mizoroki-Heck arylation.[4,69,70] We chose to evaluate six sterically-hindered, electron-rich phosphine ligands known to be effective in Mizoroki-Heck couplings.[71,72] For the arylation of methyl methacrylate by *p*-bromoacetophenone, few catalyst/ligand combinations are suitable. $Pd(OAc)_2$ gives very poor conversion for every ligand tested, while the other three Pd sources do generate hits with P(*o*-tol)$_3$ and P(*t*Bu)$_3$.[73] With P(*t*Bu)$_3$ as the ligand, the amount of product observed using **1** as the precursor is somewhat less than for $[Pd(allyl)Cl]_2$, and Pd_2dba_3•$CHCl_3$. To further compare **1** and Pd_2dba_3•$CHCl_3$ under preparative-scale conditions, we tested both sources at 1 mol% Pd for coupling at 80 °C (eq. 1). Analysis of the reaction mixtures by ^{1}H NMR spectroscopy and LCMS revealed the presence of an over-reaction product, resulting from a second Mizoroki-Heck arylation (**B**).[55] While the two Pd sources have roughly equal efficiency to generate the desired product **A** (74% solution yield, determined by ^{1}H NMR spectroscopy versus internal standard), complex **1** gives slightly higher selectivity (**A**:**B** = 5.3:1 versus 3.5:1 with Pd_2dba_3•$CHCl_3$). Performing the reaction with 3 equiv methyl methacrylate and 1 mol% **1**/P(*t*Bu)$_3$ enables isolation of a 6:1 mixture of the two products in 76% combined isolated yield (entry 5).



(1)

The sixth reaction class investigated is C–O coupling, with a representative example using a primary alcohol (*n*BuOH) and an aryl bromide (4-bromoacetophenone). Known to be a challenging transformation, previous work from Beller and co-workers identified AdBippyPhos as a superior ligand.[74] Due to its high cost and restricted availability, we chose to evaluate a set of potential alternative ligands, including the parent BippyPhos.[74–76] While $Pd(OAc)_2$, Pd_2dba_3•$CHCl_3$, and **1** all generate hits for this reaction, with BrettPhos and BippyPhos as the most promising, $[Pd(allyl)Cl]_2$ has poor catalytic activity in combination with every ligand. From these small scale results, $Pd(OAc)_2$/BippyPhos and **1**/BippyPhos are the most active systems. On 1.00 mmol scale with 1.5 mol% Pd, using precatalyst **12** gives 95% solution yield, and the combination of **1** and BippyPhos (1.8 mol%) gives 87% isolated yield.

Finally, to demonstrate the utility of complex **1** as a precursor in an example screening/optimization workflow, we explored the synthesis of *spiro*-OMeTAD – an important organic hole-transport material used in perovskite-based solar cells[51] – *via* Pd-catalyzed C–N coupling (Figure 7). Six ligands, including several biaryl phosphines and XantPhos, were chosen for microscale screening at high Pd loading and excess diarylamine; XPhos, SPhos, RuPhos, and XantPhos showed good catalytic activity under these conditions. To differentiate between these four ligands, we de-

creased the Pd loading from 13 mol% to 5 mol% and analyzed the reaction mixtures by NMR spectroscopy; SPhos and RuPhos were identified as superior from these experiments, with SPhos giving a 94% solution yield using only 4.1 equiv of the diarylamine substrate. Translating these results into a gram-scale synthetic procedure – using single component precatalyst **6** and CPME as a higher boiling solvent – results in 81% isolated yield of pure *spiro*-OMeTAD after a simple silica plug and recrystallization from THF/MeOH.[55] This procedure is higher yielding and operationally simpler than the reported synthesis,[77] which uses $Pd_2dba_3/P(tBu)_3$ at high catalyst loading (8 mol% Pd, 45% isolated yield).

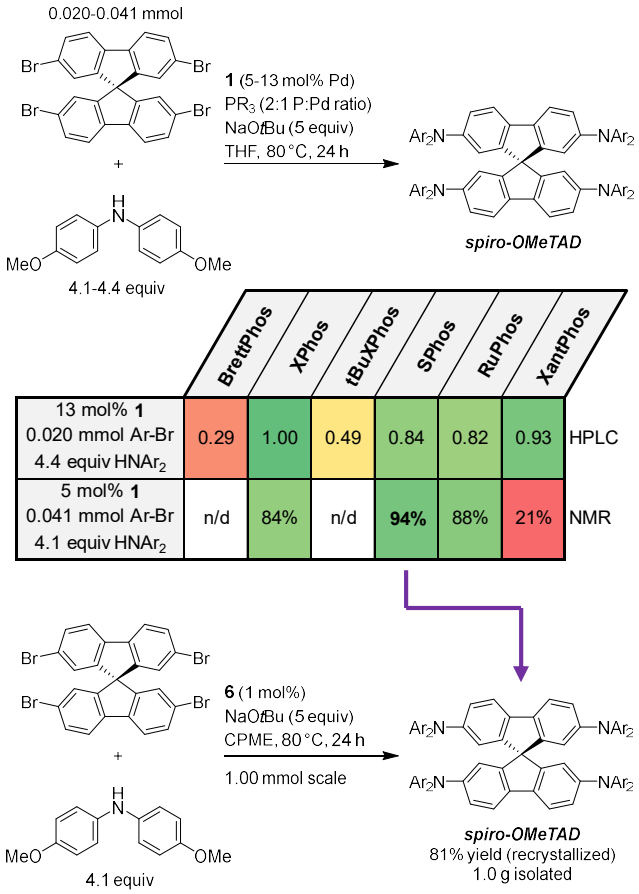


Figure 7. Reaction screening/optimization for the synthesis of *spiro*-OMeTAD via Pd-catalyzed C–N coupling. "HPLC" values indicate normalized HPLC product peak area / internal standard peak area; "NMR" percentages indicate solution yield determined by ^{1}H NMR spectroscopy versus internal standard. Internal standard is 1,3,5-trimethoxybenzene.

CONCLUSIONS

In summary, we have developed a stable, easily prepared, and versatile Pd(0) complex as a reliable precursor for *in situ* cross-coupling catalyst preparation, as well as a platform for single-component precatalyst synthesis. ^{DMP}DAB–Pd–MAH (**1**) has distinct advantages over other Pd sources commonly used for reaction screening, including good solubility in a range of organic solvents, excellent solid-state and solution stability, and rapid ligand substitution of the chelating DAB with a variety of phosphines relevant to cross-coupling, including those with very large cone angles. Furthermore, these phosphine metallation reactions proceed to well-defined Pd(0) products that are easily isolable, providing a method to generate new air-stable single-component Pd(0) precatalysts at-will.

Evaluating complex **1** against three other common Pd sources in microscale high-throughput screens reveals that **1** is excellent at identifying hits across six different reaction classes for C–N, C–C, and C–O coupling. Notably, both $Pd(OAc)_2$ and $[Pd(allyl)Cl]_2$ are markedly inferior in multiple examples, including failure to clearly identify hits for 1° sulfonamide arylation, imidazole arylation, Heck arylation, and C–O coupling with a 1° alcohol. Preparative-scale reactions (≥ 1 mmol substrate) with lower Pd loading (0.25-5 mol%) are feasible using either *in situ* catalyst generation (from **1**/phosphine), or with the [phosphine]–Pd–MAH precatalysts. Thus, complex **1** is a versatile Pd(0) source for cross-coupling reaction screening, optimization, and scale-up, without the problematic aspects of the only other commonly-used Pd(0) source, Pd_2dba_3. Further studies on the catalytic applications of **1** and development of additional Pd(0) systems are underway, and will be reported in due course.

ASSOCIATED CONTENT

Detailed experimental procedures, full tables of screening data, characterization data, and XRD details. This material is available free of charge via the Internet at http://pubs.acs.org. CIFs for complexes **1**, **3-5**, **8** and **12** are deposited with the CCDC with deposition numbers 2056595-2056600.

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Notes

A provisional US patent application has been filed based partly on this work.

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