Pd–PEPPSI N-Heterocyclic Carbene Complexes from Caffeine: Application in Suzuki, Heck and Sonogashira Reactions

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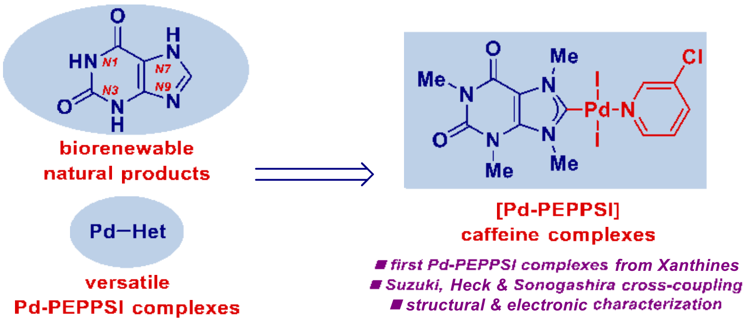


ABSTRACT: The first synthesis of Pd–PEPPSI N-heterocyclic carbene complexes derived from the abundant and renewable natural product caffeine is reported. The catalysts bearing 3-chloro-pyridine, pyridine and N-methylimidazole ancillary ligands were readily prepared from the corresponding N9-Me caffeine imidazolium salt by direct deprotonation and coordination to PdX_2 in the presence of N-heterocycles or by ligand displacement of $PdX_2(Het)_2$. The model Pd–PEPPSI–caffeine complex has been characterized by x-ray crystallography. The complexes were successfully employed in the Suzuki cross-coupling of aryl bromides, Suzuki cross-coupling of amides, Heck cross-coupling and Sonogashira cross-coupling. Computational studies were employed to determine frontier molecular orbitals and bond order analysis of caffeine derived Pd–PEPPSI complexes. This class of catalysts offers an entry to utilize benign and sustainable biomass-derived Xanthine NHC ligands in the popular Pd–PEPPSI systems in organic synthesis and catalysis.

Introduction

The development of N-heterocyclic carbene (NHC) ligands has attracted major attention during the last two decades owing to the unique electronic and steric properties of NHCs that render efficient applications for transition-metal-catalysis.[1–5] At present, the design of new NHC ligands is focused on three major avenues: (1) N-wingtip modification, (2) backbone modification, (3) NHC class alteration.[1–5] In this context, the utilization of renewable and benign resources that are readily available from biomass is a major strategy to establish a sustainable and green research effort in NHC ligand design.[6]

Xanthines, such as caffeine and theophylline (Figure 1), are widely abundant and inexpensive natural products.[7] The presence of the imidazole ring in Xanthines makes them attractive precursors to N-heterocyclic carbenes with modified backbone from the classical imidazol-2-ylidenes.[8] N-Heterocyclic carbenes derived from Xanthines play important functions in medicinal chemistry as antimicrobial and antiproliferative agents as amply demonstrated by the groups of Youngs,[9] Casini,[10] Willans,[11] and others.[12,13] In sharp contrast, very few examples of Xanthines as NHC ligands for transition-metal-catalysis have been reported.[14–16] In particular, the development of Pd complexes of NHC ligands derived from Xanthines is only in its infancy and remains unexplored.[17–20] Despite the importance of Pd–PEPPSI systems bearing N-heterocycles as ancillary ligands,[4c,21] which are increasingly more popular as Pd(II)–NHC complexes in organic synthesis due to rapid access, versatility, air- and moisture-stability,[21] surprisingly, Pd–PEPPSI complexes derived from Xanthines have not been reported.

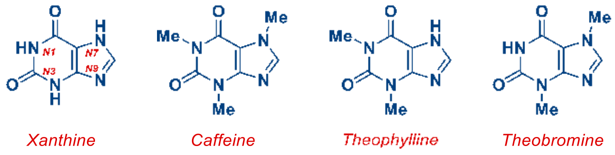


Figure 1. Xanthine and Xanthine natural products.

As part of our program in NHC ligand development[22] and sustainable synthesis,[23] herein, we report the first synthesis of Pd–PEPPSI N-heterocyclic carbene complexes derived from the abundant and renewable natural product caffeine. We present modular synthesis of catalysts bearing 3-chloro-pyridine, pyridine and N-methylimidazole ancillary ligands by direct deprotonation and coordination to PdX_2 in the presence of N-heterocycles or by ligand displacement of $PdX_2(Het)_2$. The model Pd–PEPPSI caffeine complex has been characterized by x-ray crystallography. The complexes were successfully employed in the Suzuki cross-coupling of aryl bromides, Suzuki cross-coupling of amides, Heck cross-coupling and Sonogashira cross-coupling. Computational studies were employed to determine frontier molecular orbitals and bond order analysis of caffeine derived Pd–PEPPSI complexes. The study offers an entry to the increasingly important Pd–PEPPSI complexes bearing heterocycles as ancillary ligands derived from benign, sustainable and biomass-derived Xanthine NHC ligands.

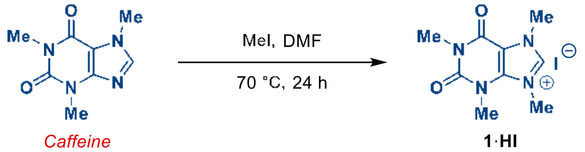
Results and Discussion

Synthesis. Imidazolium salt **1·HI** was prepared by N9-methylation of caffeine with MeI in DMF (Scheme 1).[24]

In terms of ancillary PEPPSI ligands, for this study we selected the classical 3-chloropyridine[25] ligand as well as pyridine[26] since this ligand is often employed as an electronically-modified and inexpensive alternative to 3-chloropyridine as well as N-methylimidazole ligand as a representative of 5-membered heterocycles.[27] The synthesis of well-defined Pd–PEPPSI complexes bearing 3-chloropyridine (**2**), pyridine (**3**) and N-methylimidazole (**4**) throw-away ligands is summarized on Scheme 2.

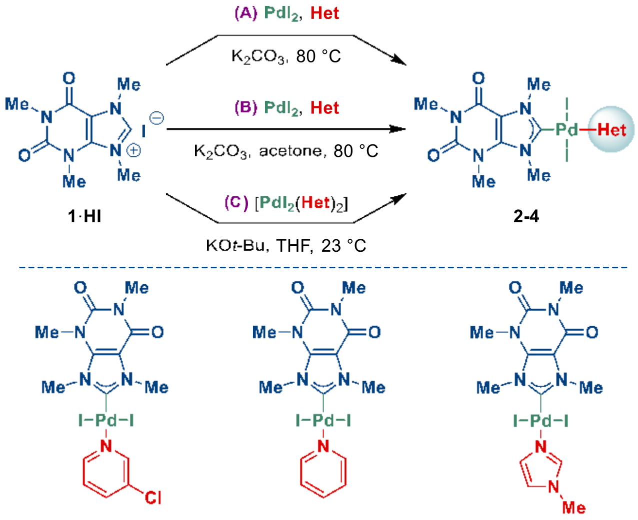
At the outset, we prepared [Pd(**1**)(3-Cl-py)Cl_2] by the reaction of imidazolium salt (**1·HI**) with $PdCl_2$ in the presence of K_2CO_3 in 3-chloro-pyridine as solvent at 80 °C,[25–27] which afforded [Pd(**1**)(3-Cl-py)I_2] (**2**) as the major product (not shown); however, this approach was complicated by the halogen exchange of the [Pd(**1**)(3-Cl-py)X_2] complex (X = I, Cl). Similar substitution of chloride by iodide ligand indicated better thermodynamic stability of [Pd(**1**)(Het)I_2] (**2–4**) compared to their chloro congeners.

Scheme 1. Synthesis of Imidazolium Salt 1·HI[a]



[a]Conditions: Caffeine (1.0 equiv), MeI (8.6 equiv), DMF (3.0 M), 70 °C, 24 h, 81%.

Scheme 2. Synthesis of Pd–PEPPSI Complexes 2–4[a]



2	**3**	**4**
Method A: 97%	*Method A: 98%*	*Method A: 92%*
Method B: 95%	*Method B: 93%*	*Method B: 96%*
Method C: 76%	*Method C: 77%*	*Method C: 72%*

[a]Conditions: **(A)** **1·HI** (1.1 equiv), PdI_2 (1.0 equiv), K_2CO_4 (3.0 equiv), Heterocycles (0.25 M), 80 °C, 15 h. **(B)** **1·HI** (1.1 equiv), PdI_2 (1.0 equiv), K_2CO_4 (3.0 equiv), Heterocycles (3.0 equiv), Acetone (0.1 M), 80 °C, 15 h. **(C)** **1·HI** (1.1 equiv), [$PdI_2(Het)_2$] (1.0 equiv), KO*t*Bu (1.5 equiv), THF (0.1 M), 23 °C, 15 h.

Accordingly, we employed PdI_2, which delivered [Pd(**1**)(Het)I_2] (**2–4**) complexes (Het = 3-chloro-pyridine, pyridine, 1-methylimidazole) in quantitative yields as single products (Scheme 2A). We further determined that [Pd(**1**)(Het)I_2] (**2–4**) complexes can also be prepared by reacting of PdI_2 and **1·HI** with 3 equivalents of heterocycles in acetone at 80 °C (Scheme 2B). Furthermore, the Pd–PEPPSI complexes [Pd(**1**)(Het)I_2] (**2–4**) complexes can also be synthesized at room temperature by using KO*t*-Bu base to deprotonate the **1·HI** salt, followed by the reaction with [Pd(Het)$_2I_2$] (Scheme 2C). Importantly, the Pd–PEPPSI complexes [Pd(**1**)(Het)I_2] (**2–4**) were readily isolated by trituration with cold ether. All complexes were found to be stable to air and moisture.

Crystallographic Analysis. The model Pd–PEPPSI complex [Pd(**1**)(3-Cl-py)I_2] (**2**) was characterized by X-ray crystallography (Figure 2). Sample for crystallographic analysis was obtained by slow evaporation from dichloromethane. The complex [Pd(**1**)(3-Cl-py)I_2] (**2**) crystallized as two molecules in the unit cell. The complex features square planar geometry of Pd (Figure 2A-B). Bond angles of complex **2** (C–Pd–I, 85.3°, 90.1°; I–Pd–N, 91.4°, 93.2°, and C–Pd–I, 84.7°, 89.6°; I–Pd–N, 91.5°, 94.1°) are consistent with square planer geometry and in the range for Pd–PEPPSI complexes bearing imidazol-2-ylidene ligands (e.g., [Pd(**IMes**)(3-Cl-py)Cl_2], C–Pd–Cl, 90.2°, 89.6°; Cl–Pd–N, 89.72°, 90.56°).[26] The bond lengths of complex **2** (Pd–C, 1.958 Å; Pd–I, 2.5933 Å, 2.6241 Å; Pd–N, 2.106 Å, and Pd–C, 1.949 Å; Pd–I, 2.6077 Å, 2.6230 Å; Pd–N, 2.105 Å) can be compared with the bond lengths of imidazol-2-ylidene Pd–PEPPSI complex [Pd(**IMes**)(3-Cl-py)Cl_2] (Pd–C, 1.962 Å; Pd–Cl, 2.298 Å, 2.290 Å; Pd–N, 2.117 Å).[26]

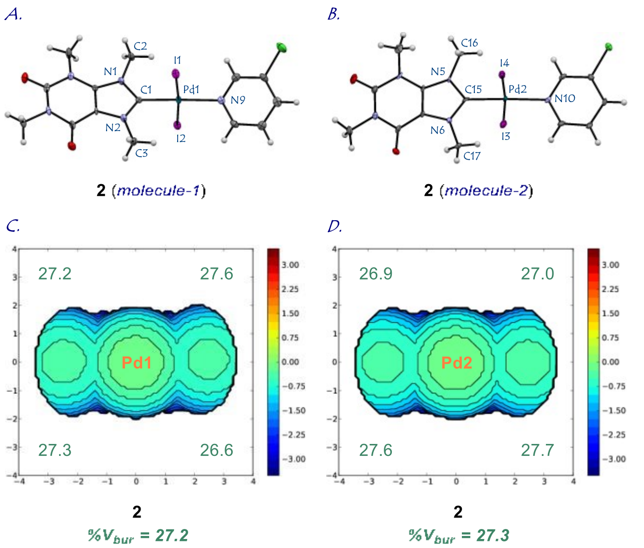
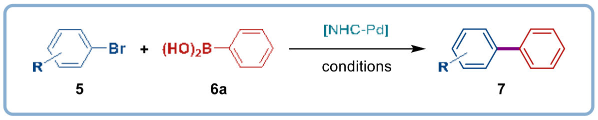


Figure 2. (A-B) X-ray structure of [Pd(**1**)(3Cl-py)I_2] (**2**) (50% ellipsoids), two molecules in the unit cell. Selected bond lengths [Å], bond angles [°], dihedral angles [°] (**2**): molecule-1, Pd1–C1, 1.958(5); Pd1–I1, 2.5933(5); Pd1–I2, 2.6241(5); Pd1–N9, 2.106(4); C1–N1, 1.386(7); C1–N2, 1.333(6); C1–Pd1–I1, 85.3(2); C1–Pd1–I2, 90.1(2); I1–Pd1–N9, 91.4(1); I2–Pd1–N9, 93.2(1); I1–Pd1–C1–N1, 92.1(4); I1–Pd1–C1–N2, 85.3(4); I2–Pd1–C1–N1, 87.1(4); I2–Pd1–C1–N2, 95.6(4). molecule-2, Pd2–C15, 1.949(5); Pd2–I3, 2.6077(6); Pd2–I4, 2.6230(6); Pd2–N10, 2.105(4); C15–N5, 1.382(6); C15–N6, 1.345(6); C15–Pd2–I3, 84.7(2); C15–Pd2–I4, 89.6(2); I3–Pd2–N10, 91.5(1); I4–Pd2–N10, 94.1(1); I3–Pd2–C15–N5, 92.1(5); I3–Pd2–C15–N6, 82.5(5); I4–Pd2–C15–N5, 89.3(5); I4–Pd2–C15–N6, 96.1(5). (C-D) Topographical steric maps of [Pd(**1**)(3Cl-py)I_2] (**2**) showing $\%V_{bur}$ per quadrant. **2**: CCDC 2165221.

To further evaluate the steric impact of Xanthine-derived ligand, the percent buried volume ($\%V_{bur}$) of [Pd(**1**)(3-Cl-py)I_2] (**2**) was calculated using the method by Cavallo (Figure 2C-D).[3] The $\%V_{bur}$ of complex **2** is 27.2% (SW, 27.3%; NW, 27.2%; NE, 27.6%; SE, 26.6%) and 27.3% (SW, 27.6%; NW, 26.9%; NE, 27.0%; SE, 27.7%). These values can be compared with the $\%V_{bur}$ of 26.7% (SW, 27.2%; NW, 26.4%; NE, 27.0%; SE, 26.2%) for the linear [Au(**1**)Cl] complex reported earlier by Casini.[10]

Catalysis. With access to Pd–PEPPSI precatalysts **2–4**, we next evaluated their reactivity in the Suzuki cross-coupling of unactivated aryl bromides (Table 1). First, we tested the activity of precatalysts **2–4** in the Suzuki cross-coupling of 4-bromotoluene with phenylboronic acid under the aqueous KOH/H_2O conditions reported by Luo (Table 1, entries 1-3).[18] We found that all three catalyst **2– 4** promoted the reaction with the imidazole-based catalyst **4** as the most effective under these conditions. The use of other bases (KO*t*-Bu, NaO*t*-Bu) was ineffective (<10% yield) (not shown). The catalysts were ineffective at room temperature (not shown). Next, we tested the activity of precatalysts **2–4** in the Suzuki cross-coupling using mild carbonate base (Table 1, entries 4-6). Pleasingly, we found that all three precatalysts promoted the cross-coupling using K_2CO_3 in *i*-PrOH at 80 °C, albeit the yields were modest. Finally, we established that the Suzuki cross-coupling of electronically-deactivated 4-bromoanisole is possible using a combination of K_2CO_3 and MeOH at 80 °C (Table 1, entries 7-9). Interestingly, all three precatalysts **2–4** promoted the reaction with high efficiency. The use of 1-chloro-4-methoxybenzene was ineffective under these conditions (not shown).

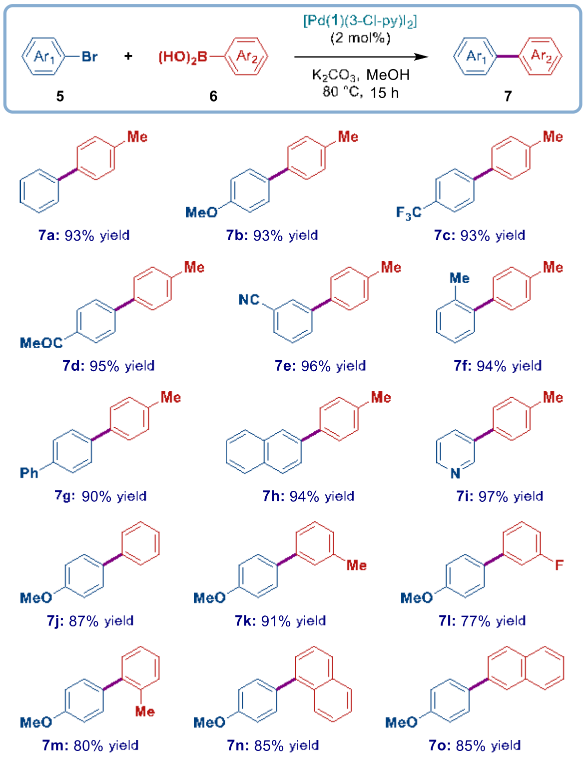
Table 1. Suzuki–Miyaura Cross-Coupling using Pd–PEPPSI Complexes 2–4[a]



entry	catalyst	R-C_6H_4-Br	solvent	base	*T* (°C)	yield (%)
1	**4**	4-Me-C_6H_4-Br	H_2O	KOH	65	78
2	**3**	4-Me-C_6H_4-Br	H_2O	KOH	65	67
3	**2**	4-Me-C_6H_4-Br	H_2O	KOH	65	50
4	**4**	4-Me-C_6H_4-Br	*i*-PrOH	K_2CO_3	80	42
5	**3**	4-Me-C_6H_4-Br	*i*-PrOH	K_2CO_3	80	28
6	**2**	4-Me-C_6H_4-Br	*i*-PrOH	K_2CO_3	80	34
7	**4**	4-MeO-C_6H_4-Br	MeOH	K_2CO_3	80	92
8	**3**	4-MeO-C_6H_4-Br	MeOH	K_2CO_3	80	90
9	**2**	4-MeO-C_6H_4-Br	MeOH	K_2CO_3	80	93

[a]Conditions: R-C_6H_4-X (1.0 equiv), Ph-B$(OH)_2$ (2.0 equiv), catalyst (2 mol%), base (3.0 equiv), solvent (0.2 M), *T*, 15 h.

Scheme 3. Substrate Scope of Suzuki–Miyaura Cross-Coupling using [Pd(1)(3-Cl-py)I_2] 2[a]



[a]Conditions: Ar-Br (1.0 equiv), Ar-B$(OH)_2$ (2.0 equiv), catalyst (2 mol%), K_2CO_3 (3.0 equiv), MeOH (0.2 M), 80 °C, 15 h.

With the optimized conditions in hand, the scope of the Suzuki–Miyaura cross-coupling using [Pd(**1**)(3-Cl-py)I_2] (**2**) precatalyst was investigated (Scheme 3). As shown, complex **2** is effective in promoting Suzuki cross-coupling of a range of aryl bromides, including electron-neutral (**7a**), electron-rich (**7b**) and electron-deficient (**7c–7e**) substrates. Importantly, sensitive electrophilic functional groups, such as ketone (**7d**) and cyano (**7e**) are readily tolerated under these conditions. The challenging orthosterically-hindered substrates can also be used under these conditions (**7f**). Furthermore, polyaromatic bromides, such as 4-phenylaryl (**7g**) and 2-napthyl (**7h**) are compatible with this cross-coupling. Finally, heterocyclic aryl halides are compatible as exemplified by the cross-coupling of 3-Br-pyridine (**7i**). The scope of boronic acids was investigated using electronically-deactivated 4-bromoanisole as a representative substrate. As shown, electron-neutral (**7j–7k**) and electron-deficient (**7l**) aryl boronic acids are competent substrates for the reaction. Furthermore, we were pleased to find that sterically-hindered boronic acids (**7m**) and polyaromatic boronic acids (**7n–7o**) are also well-tolerated.

Next, we evaluated the activity of Pd–PEPPSI precatalysts **2–4** in the Suzuki cross-coupling of amides by N–C(O) activation. Recently, there has been a major surge in the development of unconventional cross-coupling reactions of amides by selective amide N–C bond cleavage, however, comparatively few ligands for Pd catalysis have been developed for this reactivity manifold.[28] We were pleased to find that all three Pd–PEPPSI precatalysts **2–4** promoted the challenging acyl Suzuki cross-coupling of a model N-benzoyl-glutarimide under mild carbonate base conditions (K_2CO_3, dioxane, 120 °C) in good yields (Table 2, entries 1-3). The imidazole-based precatalyst **4** showed the highest reactivity in this N–C cross-coupling.

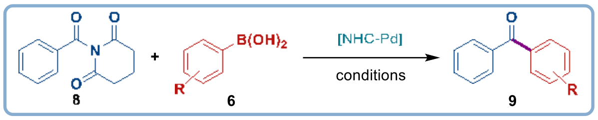
Next, we were intrigued to evaluate the activity of Pd–PEPPSI precatalysts **2–4** in Heck and Sonogashira cross-couplings. Pleasingly, we found that all three catalysts promote the model Heck cross-coupling of 4-acetyl-1-bromobenzene using K_2CO_3 in DMA at 90 °C (Table 3, entries 1-3) with the pyridine catalyst **3** as the most effective under these conditions. The use of aqueous conditions was ineffective.[18] Furthermore, we were pleased to find that Pd–PEPPSI precatalysts **2–4** promote the model Sonogashira cross-coupling of 4-acetyl-1-bromobenzene in the presence of CuI (5 mol%) (Table 4, entries 1-3). In this coupling, the combination of K_2CO_3 as a base and DMF as a solvent was most effective (82-98%) with the imidazole catalyst **4** giving the best results. Interestingly, the use of aqueous conditions is also possible in this coupling [**4** (2 mol%), CuI (5 mol%), K_2CO_3 (3 equiv), H_2O (0.25 M), 90 °C, 88% yield] (not shown).[18]

We conducted mercury poisoning studies to probe for the presence of heterogeneous palladium. We found that the model reaction between 4-MeO-C_6H_4-Br and 4-Tol-B$(OH)_2$ catalyzed by [Pd(**1**)(3-Cl-py)I_2] for 15 min and 15 h gave 81% and 93% yield under the standard conditions, and 68% and 92% yield in the presence of a large excess of mercury. This suggests that homogenous Pd is the active catalyst, in agreement with the ligand effect observed in the coupling (*vide infra*).

There is a clear ligand effect in these cross-couplings promoted by caffeine derived Pd–PEPPSI complexes (Tables 1-4). We have performed control reactions using PdI_2 under the standard conditions, which gave 42%, <5%, <5% and <5% yield under the standard conditions in Suzuki, amide Suzuki, Heck and Sonogashira cross-coupling, respectively. It is worth noting that there is no product formation without ligand in the amide bond N–C cross-coupling. We have also tested the activity of the catalysts in Buchwald-Hartwig amination. As expected, the reactions resulted in no conversion. Steric hindrance of N-wingtips is required for Buchwald-Hartwig amination.[3,4] Future studies will focus on expanding this family of Xanthine-derived ligands to N-sterically demanding analogues. It is further important to point out that the present Xanthine ligands represent a sustainable alternative to ITMe (1,3,4,5-tetramethylimidazol-2-ylidene) and related ligands.[3,4]

Electronic Characterization. To gain insight into the electronic properties of these caffeine derived Pd–PEPPSI complexes, frontier molecular orbitals and bond order analysis of the representative [Pd(**1**)(3-Cl-py)I_2] (**2**) were determined at the B3LYP 6-311++g(d,p) level (Figure 3 and SI).[29] The data show that both HOMO (-5.95 eV) and LUMO (-2.21 eV) of (**2**) are located within Pd–I bond, and LUMO+1 (-2.17 eV) is located on Pd–PEPPSI. These values can be compared with the imidazol-2-ylidene [Pd(**IPr**)(3-Cl-py)Cl_2] (HOMO, -6.06 eV; LUMO, -1.88 eV; LUMO+1, -1.63 eV) and imidazolin-2-ylidene [Pd(**SIPr**)(3-Cl-py)Cl_2]

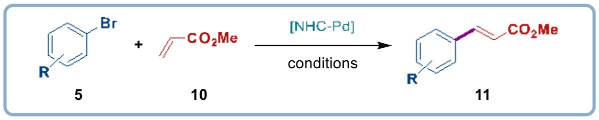
Table 2. Suzuki–Miyaura Cross-Coupling of Amides using Pd–PEPPSI Complexes 2–4[a]



entry	catalyst	R-$C_6H_4B(OH)_2$	solvent	base	*T* (°C)	yield (%)
1	**4**	4-MeO-$C_6H_4B(OH)_2$	dioxane	K_2CO_3	120	81
2	**3**	4-MeO-$C_6H_4B(OH)_2$	dioxane	K_2CO_3	120	76
3	**2**	4-MeO-$C_6H_4B(OH)_2$	dioxane	K_2CO_3	120	75

[a]Conditions: N-benzoyl-glutarimide (1.0 equiv), Ar-B$(OH)_2$ (2.0 equiv), catalyst (2 mol%), K_2CO_3(3.0 equiv), dioxane (0.2 M), 120 °C, 15 h.

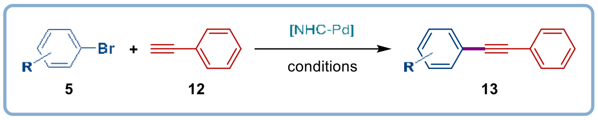
Table 3. Heck Cross-Coupling using Pd–PEPPSI Complexes 2–4[a]



entry	catalyst	R-C_6H_4-Br	solvent	base	*T* (°C)	yield (%)
1	**4**	4-Ac-C_6H_4-Br	DMA	K_2CO_3	90	67
2	**3**	4-Ac-C_6H_4-Br	DMA	K_2CO_3	90	83
3	**2**	4-Ac-C_6H_4-Br	DMA	K_2CO_3	90	69

[a]Conditions: Ar-Br (1.0 equiv), methyl acrylate (5.0 equiv), catalyst (2 mol%), K_2CO_3(3.0 equiv), DMA (0.2 M), 90°C, 15 h.

Table 4. Sonogashira Cross-Coupling using Pd–PEPPSI Complexes 2–4[a]



entry	catalyst	R-C_6H_4-Br	solvent	base	*T* (°C)	yield (%)
1	**4**	4-Ac-C_6H_4-Br	DMF	K_2CO_3	120	98
2	**3**	4-Ac-C_6H_4-Br	DMF	K_2CO_3	120	82
3	**2**	4-Ac-C_6H_4-Br	DMF	K_2CO_3	120	80

[a]Conditions: Ar-Br (1.0 equiv), phenylacetylene (2.0 equiv), catalyst (2 mol%), CuI (5 mol%), K_2CO_3 (3.0 equiv), DMF (0.2 M), 120 °C, 15 h.

(HOMO, -6.05 eV; LUMO, -1.87 eV; LUMO+1, -1.62 eV).[22b] For comparison, we also determined energy levels of [Pd(**1**)(3-Cl-py)Cl_2]. Interestingly, LUMO (-2.08 eV) of [Pd(**1**)(3-Cl-py)Cl_2] is located within Pd–Heterocycle region, while HOMO (-6.38 eV) and LUMO+1 (-1.89 eV) are located within Pd–Cl bond.

To further understand character of the Pd-ligand bonds in caffeine derived Pd–PEPPSI complexes, we performed NBO analysis.[30] The Wiberg bond orders in [Pd(**1**)(3-Cl-py)I_2] (**2**) (Pd–C, 0.6919; Pd–N, 0.3332; Pd–I, 0.7685 and 0.7742) and in [Pd(**1**)(3-Cl-py)Cl_2] (Pd–C, 0.7094; Pd–N, 0.3373; Pd–Cl, 0.6646 and 0.6557) can be compared with the imidazol-2-ylidene [Pd(**IPr**)(3-Cl-py)Cl_2] system (Pd–C, 0.6871; Pd–N, 0.6302; Pd–Cl, 0.6302 and 0.6278).

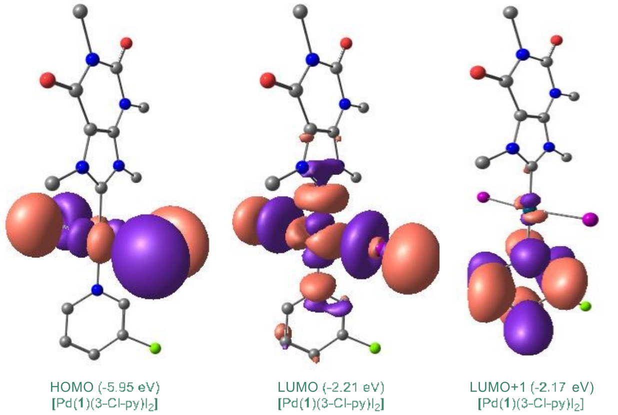


Figure 3. Frontier orbitals and energies (eV) of [Pd(**1**)(3-Cl-py)I_2] (**2**) calculated at B3LYP 6-311++g(d,p). See SI for details.

Thus, the computational data indicate that Pd–carbene bonds in [Pd(**1**)(3-Cl-py)I_2] (**2**) are relatively stronger than in [Pd(**IPr**)(3-Cl-py)Cl_2], which is an important consideration for catalysis. [22b]

Conclusions

In summary, we have reported the synthesis of Pd–PEPPSI complexes from the abundant Xanthine natural product caffeine. We presented modular synthesis of catalysts bearing 3-chloro-pyridine, pyridine and N-methylimidazole ancillary ligands by direct deprotonation and coordination to PdX_2 in the presence of N-heterocycles or by ligand displacement of $PdX_2(Het)_2$ from the readily available corresponding N9-Me caffeine imidazolium salt. The complexes were successfully employed in the Suzuki cross-coupling of aryl bromides, Suzuki cross-coupling of amides, Heck cross-coupling and Sonogashira cross-coupling. We have further reported structural characterization of the model caffeine-derived Pd–PEPPSI complex and electronic characterization to determine frontier molecular orbitals and bond order analysis in the caffeine derived Pd–PEPPSI complexes.

In a broader sense, this class of Xanthine-derived Pd(II) complexes should be benchmarked against other Xanthine-derived NHCs, which take the advantage of sustainable Xanthines and are fundamentally different in the method of synthesis and sustainability standpoint from imidazol-2-ylidenes. Furthermore, the backbone modification of Xanthines is different than that of imidazol-2-ylidenes, emphasized by electronic properties of the ligands. In particular, the present class of Xanthine-derived complexes represents an attractive entry to sterically-unhindered NHCs, such as analogs of IMe, which have many applications in organic synthesis, organometallic chemistry and catalysis.

Considering the utility of Pd–PEPPSI complexes in organic synthesis and catalysis, this study represents an entry to utilize benign and biomass-derived Xanthine NHC ligands in Pd–PEPPSI systems in organic synthesis.

Experimental Section

General Methods. All compounds reported in the manuscript have been previously described in literature or prepared by the method reported previously unless stated otherwise. All boronic acids are commercially available and have been purchased from Oakwood Chemical. Caffeine is commercially available and has been purchased from Sigma Aldrich. All experiments involving palladium were performed using standard Schlenk techniques under nitrogen or argon unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by distillation from sodium/benzophenone under nitrogen. All solvents were deoxygenated prior to use. All other chemicals were purchased at the highest commercial grade and used as received. All other general methods have been published.[22a] Compounds **1·HI**,[11] **7a**,[31,32] **7b**,[33] **7c**,[31] **7d**,[32] **7e**,[31] **7f**,[31] **7g**,[34] **7h**,[35] **7i**,[33] **7j**,[32] **7k**,[33] **7l**,[33] **7m**,[32] **7n**,[33] **7o**,[33] **9**,[36] **11**,[37] and **13**[38] have been previously reported in the literature. Spectroscopic properties matched literature data.

Procedure for Synthesis of NHC Ligands. 9-Methylcaffeine-ium iodide (1·HI). Caffeine (582 mg, 3.0 mmol) was dissolved in dimethylformamide (1.0 mL) in a pressure tube and iodomethane (1.5 mL, 25.8 mmol) was added. The reaction mixture was then heated at 70 °C for 24 hours. After the indicated time the reaction mixture was cooled down at room temperature, and diethyl ether (20 mL) was added. The resulting precipitation was filtered, washed with diethyl ether, and dried under vacuum to obtain pure product (820 mg, 81.3%). ^{1}H NMR (500 MHz, DMSO) δ 9.34 (s, 1H), 4.16 (s, 3H), 4.05 (s, 3H), 3.74 (s, 3H), 3.26 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 153.8, 150.7, 140.0, 139.8, 108.3, 37.5, 36.2, 31.9, 28.9.

Procedure for Synthesis of [Pd(1)(Het)I_2] Complexes.

Method A. An oven-dried pressure tube equipped with a stir bar was charged with NHC·HI salt (0.11 mmol, 1.1 equiv), PdI_2 (0.1 mmol, 1.0 equiv) and K_2CO_3 (0.3 mmol, 3.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Heterocycle (0.4 mL, 0.25 M) was added, and the reaction mixture was stirred at 80 °C for 15 h. After the indicated time, the solvent was removed under reduced pressure, the solid was dissolved in CH_2Cl_2 (10 mL), the solution was collected by filtration and concentrated. The title product was obtained by trituration from hexanes as a yellow solid.

Method B. An oven-dried pressure tube equipped with a stir bar was charged with NHC·HI salt (0.11 mmol, 1.1 equiv), PdI_2 (0.1 mmol, 1.0 equiv), heterocycle (0.3 mmol, 3.0 equiv), and K_2CO_3 (0.3 mmol, 3.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acetone (1.0 mL, 0.1 M) was added, and the reaction mixture was stirred at 80 °C for 15 h. After the indicated time, the solvent was removed under reduced pressure, the solid was dissolved in CH_2Cl_2 (10 mL), the solution was collected by filtration and concentrated. The title product was obtained by trituration from hexanes as a yellow solid.

Method C. An oven-dried pressure tube equipped with a stir bar was charged with NHC·HI salt (0.11 mmol, 1.1 equiv), and KO*t*Bu (0.2 mmol, 2.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (0.5 mL, 0.2 M) was added, and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was transferred to the solution of [PdI_2(Het)$_2$] (0.1 mmol, 1.0 equiv) in THF (0.5 mL, 0.2 M) under argon atmosphere and stirred at room temperature for 15 h. After the indicated time, the solvent was removed under reduced pressure, the solid was dissolved in CH_2Cl_2 (10 mL), the solution was collected by filtration and concentrated. The title product was obtained by trituration from hexanes as a yellow solid.

[Pd(1)(3-Cl-py)I_2] (2). Method A (66.0 mg, 97%); Method B (64.5 mg, 95%); Method C (52.0 mg, 76%). Decomposed at >250 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.2 Hz, 1H), 8.95 (dd, *J* = 5.5, 1.1 Hz, 1H), 7.77 (ddd, *J* = 8.3, 2.1, 1.4 Hz, 1H), 7.32 (dd, *J* = 8.2, 5.5 Hz, 1H), 4.39 (s, 3H), 4.29 (s, 3H), 3.80 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.13, 152.93, 152.76, 151.94, 150.41, 139.99, 138.19, 132.71, 125.08, 110.96, 40.07, 38.31, 32.16, 28.72. HRMS (ESI) m/z: [M – I]$^+$ Calcd for $C_{14}H_{16}N_5O_2ClPdI$ 553.9069; Found 553.9083.

[Pd(1)(py)I_2] (3). Method A (63.5 mg, 98%); Method B (60.2 mg, 93%); Method C (49.8 mg, 77%). Decomposed at >250 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (dd, *J* = 6.3, 1.4 Hz, 2H), 7.77 (tt, *J* = 7.7, 1.5 Hz, 1H), 7.39 – 7.30 (m, 2H), 4.40 (s, 3H), 4.30 (s, 3H), 3.79 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.49, 153.96, 152.77, 150.43, 139.97, 138.07, 124.81, 110.91, 40.04, 38.25, 32.14, 28.69. HRMS (ESI) m/z: [M – I]$^+$ Calcd for $C_{14}H_{17}N_5O_2PdI$ 519.9462; Found 519.9470. Anal. Calcd for $C_{14}H_{17}I_2N_5O_2Pd$: C, 25.97; H, 2.65; N, 10.82. Found: C, 25.56; H, 2.43; N, 10.22.

[Pd(1)(1-Me-Im)I_2] (4). Method A (60.0 mg, 92%); Method B (62.5 mg, 96%); Method C (47.0 mg, 72%). Decomposed at >250 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.66 (s, 1H), 6.80 (t, *J* = 1.3 Hz, 1H), 4.37 (s, 3H), 4.26 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.42, 152.81, 150.50, 142.83, 140.03, 133.42, 120.43, 110.95, 39.91, 38.10, 34.39, 32.13, 28.69. HRMS (ESI) m/z: [M – I]$^+$ Calcd for $C_{13}H_{18}N_6O_2PdI$ 522.9570; Found 522.9585. Anal. Calcd for $C_{13}H_{18}I_2N_6O_2Pd$: C, 24.00; H, 2.79; N, 12.92. Found: C, 23.98; H, 2.80; N, 12.67.

Procedure for [Pd(1)(Het)I_2] Catalyzed Suzuki Cross-Coupling Reaction.

General Procedure. An oven dried vial with a stir bar was charged with an aryl halide (1.0 equiv), aryl boronic acid (2.0 equiv), K_2CO_3 (3.0 equiv), [Pd(**1**)(3-Cl-py)I_2] catalyst (2.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Methanol (0.2 M) was added and the reaction mixture was stirred at 80 °C for 15 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Procedure. 1.0 Mmol Scale. An oven dried vial equipped with a stir bar was charged with bromobenzene (157.0 mg, 1.0 mmol, 1.0 equiv), *p*-tolylboronic acid (272.0 mg, 2.0 mmol, 2.0 equiv), K_2CO_3 (414.6 mg, 3.0 mmol, 3.0 equiv), [Pd(**1**)(3-Cl-py)I_2] catalyst (2.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Methanol (5.0 mL, 0.2 M) was added and the reaction mixture was stirred at 80 °C for 15 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product. Yield 93% (155.9 mg), white solid.

4-Methyl-1,1'-biphenyl (7a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.30, 138.50, 137.15, 129.62, 128.85, 127.13, 127.11, 126.94, 21.24.

4-Methoxy-4'-methyl-1,1'-biphenyl (7b). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (18.4 mg, 93%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.04 – 6.92 (m, 2H), 3.86 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.07, 138.11, 136.48, 133.88, 129.57, 128.09, 126.72, 114.29, 55.47, 21.19.

4-Methyl-4'-(trifluoromethyl)-1,1'-biphenyl (7c). According to the general procedure, the reaction of 4-bromobenzotrifluoride (22.5 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (22.0 mg, 93%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 4H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.80, 138.30, 137.01, 129.85, 129.18 (q, J^F = 32.4 Hz), 127.31, 127.25, 125.81 (q, J^F = 3.8 Hz), 124.51 (q, J^F = 271.8 Hz), 21.28. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.34 (s).

1-(4'-Methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (7d). According to the general procedure, the reaction of 4’-bromoacetophenone (19.9 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (20.0 mg, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 2H), 7.70 – 7.64 (m, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.64 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.87, 145.85, 138.36, 137.08, 135.73, 129.82, 129.04, 127.23, 127.08, 26.77, 21.30.

4'-Methyl-[1,1'-biphenyl]-3-carbonitrile (7e). According to the general procedure, the reaction of 3-bromobenzonitrile (18.2 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (18.6 mg, 96%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, *J* = 1.4 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.63 – 7.57 (m, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.58, 138.61, 136.19, 131.48, 130.69, 130.60, 130.06, 129.76, 127.11, 119.16, 113.11, 21.36.

2,4'-Dimethyl-1,1'-biphenyl (7f). According to the general procedure, the reaction of 2-bromotoluene (17.1 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (14.6 mg, 94%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 – 7.23 (m, 8H), 2.42 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.01, 139.16, 136.50, 135.53, 130.41, 129.99, 129.21, 128.91, 127.20, 125.87, 21.31, 20.65.

4-Methyl-1,1':4',1''-terphenyl (7g). According to the general procedure, the reaction of 4-bromobiphenyl (23.3 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (22.0 mg, 90%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, *J* = 7.9 Hz, 4H), 7.67 – 7.64 (m, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.92, 140.20, 139.97, 137.95, 137.29, 129.69, 128.94, 127.60, 127.43, 127.42, 127.17, 127.02, 21.27.

2-(*p*-Tolyl)naphthalene (7h). According to the general procedure, the reaction of 2-bromonaphthalene (20.7 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (20.5 mg, 94%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (s, 1H), 7.99 – 7.84 (m, 3H), 7.78 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.47 (m, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 138.71, 138.46, 137.38, 133.96, 132.73, 129.82, 128.58, 128.37, 127.86, 127.48, 126.46, 126.00, 125.79, 125.66, 21.37.

3-(*p*-Tolyl)pyridine (7i). According to the general procedure, the reaction of 3-bromopyridine (15.8 mg, 0.10 mmol) with *p*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (16.4 mg, 97%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.84 (s, 1H), 8.57 (d, *J* = 3.9 Hz, 1H), 7.93 – 7.77 (m, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.35 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.36, 148.34, 138.17, 136.71, 135.09, 134.26, 129.94, 127.12, 123.65, 21.29.

4-Methoxy-1,1'-biphenyl (7j). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with phenylboronic acid (24.4 mg, 0.20 mmol) afforded the title compound (16.0 mg, 87%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 (dd, *J* = 11.3, 8.1 Hz, 4H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.28, 140.95, 133.90, 128.85, 128.28, 126.86, 126.79, 114.33, 55.46.

4'-Methoxy-3-methyl-1,1'-biphenyl (7k). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with *m*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (18.0 mg, 91%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 – 7.49 (m, 2H), 7.38 (d, *J* = 11.4 Hz, 2H), 7.33 (dd, *J* = 9.4, 5.6 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.04 – 6.93 (m, 2H), 3.86 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.21, 140.95, 138.40, 134.03, 128.76, 128.29, 127.70, 127.55, 123.99, 114.27, 55.46, 21.69.

3-Fluoro-4'-methoxy-1,1'-biphenyl (7l). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with 3-fluorophenylboronic acid (28.0 mg, 0.20 mmol) afforded the title compound (15.6 mg, 77%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 – 7.47 (m, 2H), 7.43 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 7.06 – 6.93 (m, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 163.36 (d, J^F = 245.2 Hz), 159.69, 143.24 (d, J^F = 7.8 Hz), 132.57 (d, J^F = 2.2 Hz), 130.27 (d, J^F = 8.5 Hz), 128.27, 122.41 (d, J^F = 2.7 Hz), 114.44, 113.66 (d, J^F = 16.3 Hz), 113.49 (d, J^F = 15.6 Hz), 55.48. ^{19}F NMR (471 MHz, CDCl$_3$) δ -113.26.

4'-Methoxy-2-methyl-1,1'-biphenyl (7m). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with *o*-tolylboronic acid (27.2 mg, 0.20 mmol) afforded the title compound (15.8 mg, 80%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32 – 7.21 (m, 6H), 7.03 – 6.92 (m, 2H), 3.88 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.65, 141.68, 135.62, 134.51, 130.43, 130.38, 130.04, 127.10, 125.89, 113.62, 55.42, 20.68.

1-(4-Methoxyphenyl)naphthalene (7n). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with 1-naphthaleneboronic acid (34.4 mg, 0.20 mmol) afforded the title compound (19.9 mg, 85%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (dd, *J* = 15.8, 8.3 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.48 – 7.37 (m, 4H), 7.11 – 7.00 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.08, 140.05, 133.98, 133.26, 131.97, 131.25, 128.40, 127.47, 127.05, 126.21, 126.06, 125.84, 125.54, 113.85, 55.49.

2-(4-Methoxyphenyl)naphthalene (7o). According to the general procedure, the reaction of 4-bromoanisole (18.7 mg, 0.10 mmol) with 2-naphthaleneboronic acid (34.4 mg, 0.20 mmol) afforded the title compound (19.8 mg, 85%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.99 (s, 1H), 7.92 – 7.83 (m, 3H), 7.72 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.53 – 7.43 (m, 2H), 7.07 – 6.99 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.40, 138.30, 133.90, 133.79, 132.46, 128.58, 128.49, 128.19, 127.77, 126.38, 125.79, 125.59, 125.18, 114.47, 55.54.

Procedure for [Pd(1)(Het)I$_2$] Catalyzed Amide Suzuki Cross-Coupling Reaction. An oven dried vial equipped with a stir bar was charged with an N-benzoyl-glutarimide (21.7 mg, 0.1 mmol, 1.0 equiv), 4-methoxybenzeneboronic acid (30.2 mg, 0.2 mmol, 2.0 equiv), K$_2$CO$_3$ (41.4 mg, 0.3 mmol, 3.0 equiv), [Pd(**1**)(Het)I$_2$] catalyst (2.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (0.5 mL, 0.2 M) was added and the reaction mixture was stirred at 120 °C for 15 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.59, 163.29, 138.34, 132.61, 131.96, 130.19, 129.78, 128.25, 113.62, 55.55.

Procedure for [Pd(1)(Het)I_2] Catalyzed Heck Coupling Reaction. An oven dried vial equipped with a stir bar was charged with an 4-bromoacetophenone (19.9 mg, 0.1 mmol, 1.0 equiv), Cs_2CO_3 (97.7 mg, 0.3 mmol, 3.0 equiv), [Pd(1)(Het)I_2] catalyst (2.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Methyl acrylate (43.0 mg, 0.5 mmol, 5.0 equiv) and DMA (0.5 mL, 0.2 M) was added, and the reaction mixture was stirred at 90 °C for 15 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 16.1 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 6.53 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.44, 167.07, 143.44, 138.84, 138.18, 129.00, 128.29, 120.48, 52.05, 26.84.

Procedure for [Pd(1)(Het)I_2] Catalyzed Sonogashira Coupling Reaction. An oven dried pressure tube equipped with a stir bar was charged with an 4-bromoacetophenone (19.9 mg, 0.1 mmol, 1.0 equiv), phenylacetylene (20.4 mg, 0.2 mmol, 2.0 equiv), K_2CO_3 (41.4 mg, 0.3 mmol, 3.0 equiv), [Pd(1)(Het)I_2] catalyst (2.0 mol%), CuI (5.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. DMF (0.5 mL, 0.2 M) was added and the reaction mixture was stirred at 120 °C for 15 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.52 (m, 2H), 7.41 – 7.33 (m, 3H), 2.62 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.47, 136.35, 131.89, 131.85, 128.97, 128.60, 128.43, 128.36, 122.80, 92.86, 88.75, 26.78.

Details of Crystal Structure Analysis of [Pd(1)(3-Cl-py)I_2]. Crystallographic information for all of the compounds is given in Table S1 in the Supporting Information. All compounds were colorless single crystals. Full datasets were collected using graphite-monochromated CuKα radiation (λ = 1.54178 Å) on a Bruker SMART APEX2 single crystal diffractometer. X-rays were provided by a fine-focus sealed X-ray tube operated at 48kV and 30mA. Lattice constants were all determined using the Bruker SAINT software package using all available reflections (after data collection, ORTEP files, see Figures S1-S3).

ASSOCIATED CONTENT

Supporting Information

Crystallographic, computational and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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