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Aerobic and Efficient Direct Arylation of Five-Membered Heteroarenes and Their Benzocondensed Derivatives with Aryl Bromides by Bulky α-Hydroxyimine Palladium Complexes

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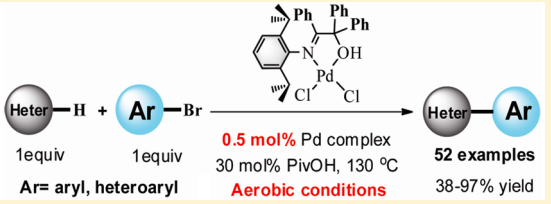
Supporting Information

ABSTRACT: In the present work, a series of α-hydroxyimine palladium complexes with bulky substituents (i.e., {[Ar-N=C(R)−C(R)$_2$−OH]PdCl$_2$} (**C1**, R = Me, Ar = 2-diphenylmethyl-4,6-dimethylphenyl; **C2**, R = Me, Ar = 2,6-bis(diphenylmethyl)-4-methylphenyl; **C3**, R = Me, Ar = 2,6-bis(diphenylmethyl)-4-methyoxylphenyl; **C4**, R = Me, Ar = 2,6-bis(diphenylmethyl)-4-chlorophenyl; **C5**, R = Ph, Ar = 2,6-dimethylphenyl; **C6**, R = Ph, Ar = 2,6-diisopropylphenyl)) were synthesized and characterized. The structures of palladium complexes **C1** and **C2** were determined by X-ray diffraction. These bidentate N,O-palladium complexes were applied for direct arylation under aerobic conditions. The effects of the reaction conditions and ligand substitution on the catalytic activity were evaluated. Upon a low palladium loading of 0.5 mol %, the bulky palladium complex **C6** was successfully used to catalyze the cross-coupling of a variety of five-membered heteroarenes and their benzo-condensed derivatives with (hetero)aryl bromides. The mechanistic investigation on the direct arylation supported the involvement of a Pd(0)/Pd(II) CMD process.



INTRODUCTION

Since the initial work by Ohta and co-workers, the palladium-catalyzed direct arylation reactions of heteroaromatics with aryl halides have received much attention and are promising prospects in pharmaceuticals, functional materials, and polymer science.[1,2] These reactions exploit the direct C−H bonds of substrates, which are atom economical and environmentally friendly and exclude the need for prefunctionalization of organometallic derivatives, such as in traditional palladium-catalyzed Suzuki, Stille, Kumada, Hiyama, and Negishi cross-couplings.[3] Although Pd(OAc)$_2$ with phosphine ligands has been investigated as the most efficient catalyst system for the preparation of arylated heteroaromatics via direct arylations,[4] it is important to note that phosphine-free ligands, especially nitrogen-based ligands, have generated interest due to their many favorable characteristics, such as being cost-effective and easily available as well as exhibiting relatively high palladium complex stability.[5] Yu, Ozawa, Itami, and Guillaumet have shown that 1,10-phenanthroline (phen)/Pd(OAc)$_2$ efficiently catalyzed the direct C−H arylation of heteroarenes with aryl iodides and aryl bromides to yield regioselective products.[6] In addition, 2,2′-bipyridyl ligands developed by Mori and Itami[7] as well as other phosphine-free catalytic systems have also exhibited moderate to good catalytic activities.[8]

Despite the impressive progress in phosphine-free palladium-catalyzed cross-coupling reactions, some drawbacks still exist in these studies. In most cases, the substrate scope is limited, and aryl iodides were used as substrates. However, cheaper and more available aryl bromides or aryl chlorides have only been rarely used, which may be due to oxidative addition of the C−Br or C−Cl bonds to the palladium center being unfavorable.[2b] Generally, a relatively high palladium loading of 5−10 mol % is required, and in some cases, a stoichiometric amount of Ag additive was required as a halide scavenger.[6−8] Moreover, the reported phosphine-free palladium precursors are generally stable; nevertheless, their catalytic species are often sensitive in the presence of oxygen, forming the unreactive peroxo species LPd(O$_2$) rapidly, which requires an air- and moisture-free environment in the catalytic process.[9] To date, the C−H activation of direct arylation has been successfully achieved in rare instances under aerobic conditions.[10] Therefore, the development of a phosphine-free catalytic system to overcome these difficulties is considered to be the most challenging area of direct arylation.

Recently, we have developed types of nitrogen-based α-hydroxyimine palladium complexes which were highly efficient

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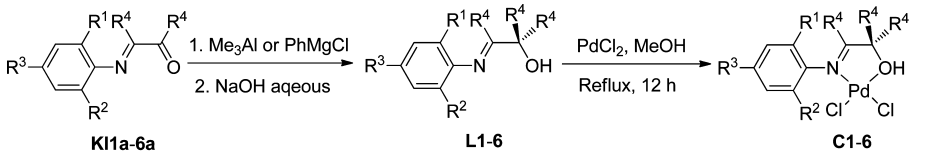
Scheme 1. Synthetic Route of the α-Hydroxyimine Palladium Complexes



C1: R^1=$CHPh_2$, R^2=R^3=Me, R^4=Me;
C2: R^1=R^2=$CHPh_2$, R^3=Me, R^4=Me;
C3: R^1=R^2=$CHPh_2$, R^3=OMe, R^4=Me;
C4: R^1=R^2=$CHPh_2$, R^3=Cl, R^4=Me;
C5: R^1=R^2=Me, R^3=H, R^4=Ph;
C6: R^1=R^2=*i*Pr, R^3=H, R^4=Ph;

for Suzuki−Miyaura cross-couplings under aerobic conditions at a temperature of 60 °C.[11] Because a higher reaction temperature is employed in C−H activation, we envisioned that strong binding of the electron-rich and bulky N,O-based ligands will help the palladium retain its ligand and retard the decomposition of the catalyst. Therefore, a longer catalyst lifetime and consistently excellent reactivity throughout the course of direct arylations is achieved without any protection by a nitrogen/argon atmosphere. Herein, we describe a series of generally applicable bulky α-hydroxyimine palladium complexes (Scheme 1) for efficient direct arylation of five-membered heteroarenes and their benzo-condensed derivatives, such as thiophenes, furan-2-carbaldehyde, thiazole, imidazo[1,2-*a*]-pyridine, and 1,2,3-triazole.

RESULTS AND DISCUSSION

Synthesis and Characterization of the α-Hydroxyimine Ligand and Its Palladium Complexes. The α-hydroxyimine compounds were prepared in a two-step sequence using a slightly modified literature procedure that was previously reported by our group.[11] First, commercially available biacetyl was reacted with aniline in the presence of a catalytic amount of acid (i.e., HOAc or HCOOH) to obtain α-ketoimines. Then, treatment of the α-ketoimines with trimethylaluminum or a phenyl Grignard reagent followed by hydrolysis afforded the ligands in good yield (Scheme 1). These compounds were characterized using spectroscopic methods. For example, a ^{1}H NMR resonance at 1.20 ppm was observed for **L1**, which can be assigned to the proton of methyl on imine (CH_3C═N). However, the expected singlet signal of the *gem*-methyl group disappeared and was split into two separate signals at resonances of 1.35 and 1.11 ppm, indicating the diastereotopic nature of the *gem*-methyl at room temperature. Probably, the slow isomerization of **L1** within the NMR time scale can result from the rotation of the aniline moiety,[12] even bearing a bulky benzhydryl group. This assignment of the resonance signals to *gem*-methyl was further investigated by variable-temperature ^{1}H NMR experiments (seen in Figure S1 in the Supporting Information). By heating the solution of **L1**, it was found that the split signals merged with each other and finally become one singlet at a temperature of 80 °C. The investigation indicated that the rapid aryl rotation can make the protons of *gem*-methyl chemically equivalent at high temperature. In addition, the hydroxy (−O*H*) resonance appears at 5.41 ppm, which confirmed the addition of the organometallic reagents to the α-ketoimine. Moreover, the ^{13}C NMR exhibited tertiary carbon bonded on hydroxyl and imine carbon (C═N) resonances at 73.4 and 179.5 ppm, respectively. For **L6**, the ^{1}H NMR spectra individually showed restricted configuration with only a single isomer (seen in Figure S14 in the Supporting Information). The obvious difference between **L1** and **L6** could be a result of the more bulky triphenyl backbone and aniline moiety on **L6**, which could effectively prohibit the rotation of the C_{Ar}−N bonds. To further confirm the structure of the desired ligands, suitable crystals for X-ray diffraction analysis were obtained from a methanol solution for **L5** and **L6**. The X-ray data collection parameters are provided in the Supporting Information. As shown in Figures 1 and 2, the tertiary carbon is

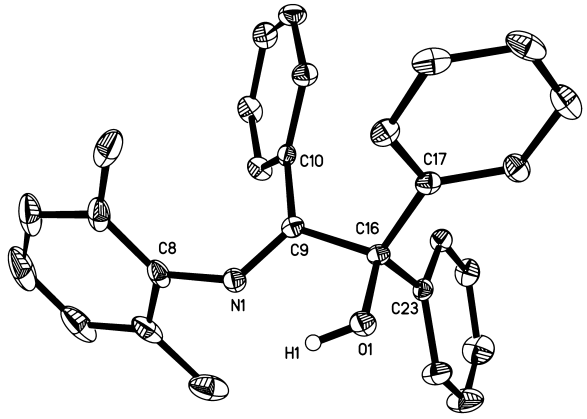


Figure 1. Molecular structure of **L5** depicted with 30% thermal ellipsoids. Hydrogen atoms, except on the hydroxyl, have been omitted for clarity. Selected bond distances (Å): N(1)−C(8) 1.426(1), N(1)−C(9) 1.274(2), C(9)−C(16) 1.516(1), O(1)−C(16) 1.422(1).

indeed attached to O(1) rather than N(1), which further confirms that the reductive addition was carried out at the ketone position. Moreover, within the crystal lattice of **L5** and **L6**, a hydrogen bonding between OH and N was observed, with distances of 2.005 and 1.957 Å (N−H), respectively.

Then, the coordination reactions were conducted by treatment of the ligands with $PdCl_2$ in refluxing methanol for 12 h, which afforded the mononuclear complexes as brown solids. After workup, α-hydroxyimine palladium complexes **C1**−**C6** were isolated from the CH_2Cl_2/hexane solution in high yields. It is important to note that the coordination process was carried out under aerobic conditions due to the excellent thermal stability of both the ligands and the corresponding palladium complexes. To further confirm the solution stability of the palladium complex under the reaction conditions, the DMAc solution of **C6** was heated at a temperature of 130 °C for 4 h, and the palladium complex was recovered in more than 92% yield. Therefore, this palladium complex is a highly thermally stable precatalyst for direct cross-coupling reactions. All of the new palladium compounds were characterized using

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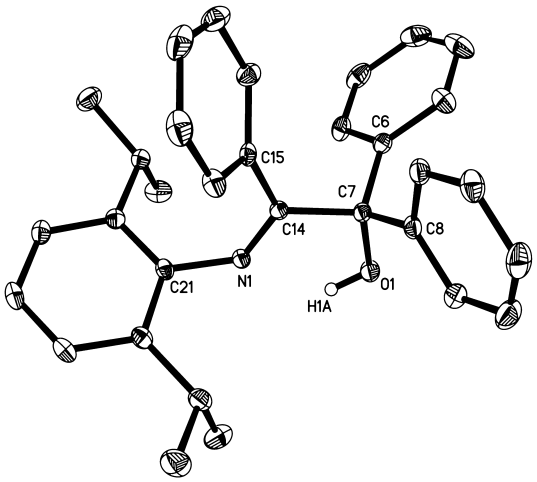

Figure 2. Molecular structure of **L6** depicted with 30% thermal ellipsoids. Hydrogen atoms, except on the hydroxyl, have been omitted for clarity. Selected bond distances (Å): N(1)−C(21) 1.429(1), N(1)−C(14) 1.276(2), C(7)−C(14) 1.561(1), O(1)−C(7) 1.417(1).

spectroscopic methods and elemental analysis. In addition, the molecular structures of **C1** and **C2** were determined via X-ray single-crystal diffraction. As shown in Figures 3 and 4, the solid-

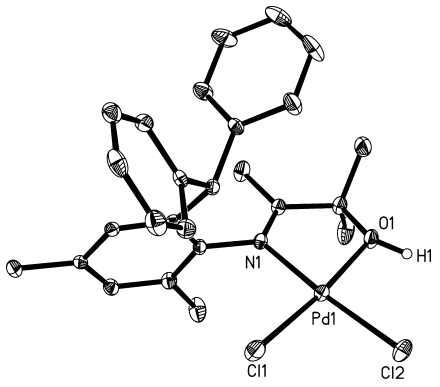

Figure 3. Molecular structure of **C1**·2MeOH depicted with 30% thermal ellipsoids. Hydrogen atoms, except on the hydroxyl, and two uncoordinated methanol molecules have been omitted for clarity. Selected bond distances (Å) and angles (deg): Pd(1)−O(1) 2.038(2), Pd(1)−N(1) 2.013(2), Pd(1)−Cl(1) 2.255(1), Pd(1)−Cl(2) 2.285(1); N(1)−Pd(1)−O(1) 80.20(9), N(1)−Pd(1)−Cl(1) 94.33(7), O(1)−Pd(1)−Cl(1) 174.33(6), N(1)−Pd(1)−Cl(2) 174.28(7), O(1)−Pd(1)−Cl(2) 94.12(6), Cl(1)−Pd(1)−Cl(2) 91.36(3).

state structure revealed that the geometry around the palladium is square planar, where each palladium exhibits nearly the same coordination angle (ca. 80.0°). The Pd(1)−N(1) bond length was determined to be 2.013 Å in **C1**, which is shorter than that in **C2** (2.031 Å). The Pd(1)−O(1) distance in **C1** (2.038 Å) was longer than that in **C2** (2.027 Å). These structural features imply that the aniline moiety played an important role in the palladium coordination environment, where **C2** with a 2,6-diphenylmethyl on the aniline yields more hindrance and electron density to the palladium in comparison to those of the monosubstituted diphenylmethyl in **C1**. In addition, the aryl ring on the aniline moiety is approximately perpendicular to the chelate ring in **C1** and **C2**, which results in dihedral angles of 82.7 and 87.8°, respectively. This result is reasonable because

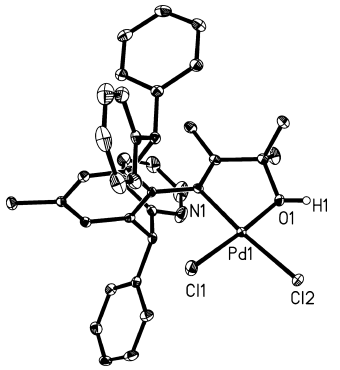

Figure 4. Molecular structure of **C2**·2EtOH depicted with 30% thermal ellipsoids. Hydrogen atoms, except on the hydroxyl, and two uncoordinated ethanol molecules have been omitted for clarity. Selected bond distances (Å) and angles (deg): Pd(1)−O(1) 2.027 (1), Pd(1)−N(1) 2.031(2), Pd(1)−Cl(1) 2.245(1), Pd(1)−Cl(2) 2.281(1); N(1)−Pd(1)−O(1) 80.00(7), N(1)−Pd(1)−Cl(1) 95.70(6), O(1)−Pd(1)−Cl(1) 175.19(6), N(1)−Pd(1)−Cl(2) 173.52(6), O(1)−Pd(1)−Cl(2) 93.52(5), Cl(1)−Pd(1)−Cl(2) 90.76(3).

more steric repulsion of the bulkier substitution causes more axial shielding on the palladium, which provides protection for the metal center in the direct arylation cross-coupling.

Direct Arylation Catalyzed by α-Hydroxyimine Palladium Complexes. To evaluate the effects of the activities of the palladium complexes, the direct arylation of benzo[*b*]-thiophene (**1a**) with 4-bromotoluene (**2a**) employed in equimolar quantities was conducted at 130 °C for 4 h as a model reaction. The cross-coupling reactions were carried out utilizing K_2CO_3 as a base in DMAc at a 0.5 mol % palladium loading. In addition, 30 mol % of pivalic acid (PivOH) was used as an additive.[4f,13] Then, the role of the steric and electronic substituents on the catalytic ability was investigated. Initially, we studied precatalysts **C1**−**C4**, which possess the same 1,1,2-trimethyl backbone. As reported in Table 1, the catalytic efficiency of precatalyst **C1** with 2-benzhydryl-4,6-dimethylaniline was similar to that of **C2** with 2,6-benzhydryl-4-dimethylaniline, which gives the coupling product **3aa** in 74 and 72% yields, respectively. However, the introduction of an electron-rich group on the para aniline resulted in positive effects. For example, **C3** with a para anisole group was determined to be more active and afforded the coupling product (**3aa**) in 81% yield. In addition to the aniline moiety, the effect of substituents on the backbone had a profound effect. For example, **C5**, which had a 1,1,2-triphenyl group on the backbone and 2,6-dimethyl groups on the aniline, gave the corresponding product (**3aa**) in 68% yield. To our delight, with the bulkier 2,6-diisopropylaniline, **C6** was formed in almost quantitative conversion, and a satisfying yield of 90% was obtained, which indicates that this catalyst is the most active and general palladium catalyst to date. In contrast, the replacement of one of the phenyl groups with a methyl substituent on the backbone resulted in the less bulky **C7** and **C8** affording lower productivity. Although the solid-state structure of **C6** is not available, the structure of **L6** was obtained (Figure 2). The bulky 1,1,2-triphenyl backbone is tilted toward the chelate ring. Therefore, additional axial steric bulk behind the metal center has been introduced, which can suppress rotation of the aniline group around the C_{Aryl}−N bond, leading to increased stability of the palladium species.[14]

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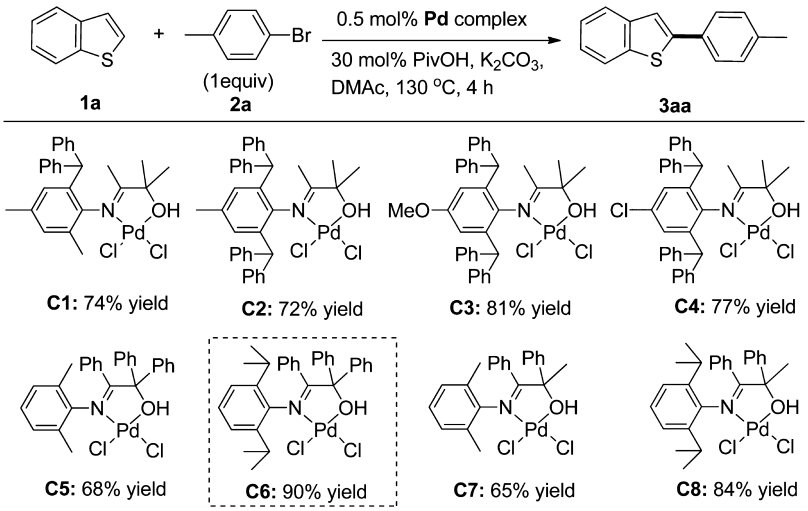
Table 1. Screening of α-Hydroxyimine Palladium Complexes on Direct Arylation Reaction of Benzo[*b*]thiophene with 4-Bromotoluene



In addition, the steric bulk is thought to facilitate reductive elimination and promote the catalytic cycle.[15] As electron-rich groups, the 1,1,2-triphenyl groups on the backbone can further enhance the interaction of the N,O-coordinated atoms that are bonded to the metal center, and the σ-donating character can increase the nucleophilicity of the Pd center, which lowers the activation energy for oxidative addition.[16] Therefore, excellent catalytic efficiency was observed. Moreover, it is worth noting that this cross-coupling showed less sensitivity toward air and moisture, and the reaction could be carried out under aerobic conditions without using an anhydrous solvent.

On the basis of these promising results, optimization of the conditions, such as the PivOH and palladium loadings, reaction temperature, organic solvents, and the bases used, were screened using **C6** as the precatalyst. As observed in Table 2, without the palladium source, no cross-coupling product was detected (run 1, Table 2). Moreover, a profound effect of the acid additives was observed. For example, in the absence of PivOH, minimal conversion (6%) was observed (run 2, Table 2). However, the addition of 10 mol % of PivOH resulted in a dramatic increase in activity, giving **3aa** in 72% conversion. A higher yield was obtained by increasing the amount of PivOH to 30 mol %, which generated a higher conversion of 94% (run 4, Table 2). A further increase in the amount of PivOH above 30 mol % did not improve the results. In addition, a decrease in the catalyst loading (0.1 mol %) or reaction temperature (110 °C) slowed the reaction (runs 6−11, Table 2). In the direct arylation, a change in solvent or base strongly influenced the activity. The best results were obtained with DMAc as the solvent and K_2CO_3 as the base, and neither other polar solvents nor strong bases yielded better results. It is important to note that KOAc,[17] which is frequently used to promote direct arylation reactions, was effective, resulting in a promising conversion of 85%.

Under the optimal conditions, benzo[*b*]thiophene (**1a**) was coupled with a variety of aryl bromides, affording the corresponding products in synthetically good to excellent yields (Table 3). The electronic effect of the substituents did not have a substantial effect on the overall performance of the reaction. For example, 4-bromoanisole afforded **3ad** in a yield of 79%, and 4-bromobenzonitrile afforded **3ah** in a comparable yield of 73%. Substrates with ortho substituents, which impede the oxidative addition and transmetalation processes, tend to be less active in other catalytic systems.[18] It is noteworthy that the reaction between **1a** and sterically hindered substrates such as 1-bromo-2-methylbenzene, 1-bromonaphthalene, and 1-bromo-2-methylnaphthalene also furnished the heterocyclic biaryl products **3ac**, **3ae**, and **3af** under the optimal conditions.

To evaluate the potential breadth of the substrate scope, a survey of thiophenes bearing C-2 electron-donating and electron-withdrawing functional groups, such as 2-methylthiophene (**1b**), 2-chlorothiophene (**1c**), and thiophene-2-carbaldehyde (**1d**), was applied for the direct arylation reaction (Table 3). Under the standard conditions developed herein, all of these candidates participated in the reaction with numerous aryl bromides, resulting in moderate to high yields of the products **3ba**−**3df**. Nevertheless, the substrate 2-chlorothiophene (**1c**) was found to be somewhat problematic in the case of coupling with phenyl bromide, giving **3cb** in a much lower yield of 56% in comparison with other similar cross-coupling products such as **3ab**, **3bb**, and **3db**. To our delight, the yield was found to be greatly improved to 90% when an excess of phenyl bromide was employed (2 equiv). On the other hand, the presence of double or multiple arylation as side reactions was not determined.

Motivated by the reactivity of the N,O-palladium complex in thiophenes, we explored the generality of the reaction with other heteroaryl substrates under the optimized conditions (Table 4). Various heteroaryls, such as furan-2-carbaldehyde, thiazole, imidazo[1,2-*a*]pyridine, and 1,2,3-triazole, were employed for coupling with aryl bromides. It was found that palladium precatalyst **C6** accommodated variations in the aryl bromide coupling partner, with moderate to excellent cross-coupling yields being obtained for aryl bromides containing electron-withdrawing (e.g., 4-Cl, 4-CN, 4-CHO) or electron-donating (e.g., 4-CH_3, 2-CH_3) groups under aerobic conditions. In addition, the high regioselectivity on the C-5 arylation of 4-methylthiazole was investigated. The electronic nature and steric hindrance of the aryl bromides, such as *p*-cyano, methyl, chloride, and *o*-methyl, were well tolerated, leading to excellent yields.

The synthesis of biheteroarenes via direct arylation remains an important but challenging task, because the ligation of the heteroarene partner can poison the catalyst.[19] Inspired by the

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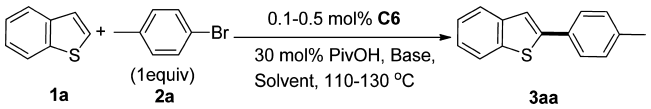
Table 2. Optimization of Conditions in Direct Palladium-Catalyzed Cross-Coupling Reactions[a]



run	solvent	Pd loading (%)	base	T (°C)	t (h)	conversn (%)[b]
1	DMAc		K_2CO_3	130	4	[g]
2[c]	DMAc	0.5	K_2CO_3	130	4	6
3[d]	DMAc	0.5	K_2CO_3	130	4	72
4	**DMAc**	**0.5**	**K_2CO_3**	**130**	**4**	**94 (90)**[f]
5[e]	DMAc	0.5	K_2CO_3	130	4	83
6	DMAc	0.1	K_2CO_3	130	4	48
7	DMAc	0.1	K_2CO_3	130	8	57
8	DMAc	0.1	K_2CO_3	130	12	61
9	DMAc	0.5	K_2CO_3	110	4	10
10	DMAc	0.5	K_2CO_3	110	8	18
11	DMAc	0.5	K_2CO_3	110	12	22
12	DMAc	0.5	KOAc	130	4	85
13	DMAc	0.5	KF	130	4	26
14	DMAc	0.5	K_3PO_4	130	4	88
15	DMAc	0.5	Na_2CO_3	130	4	37
16	DMAc	0.5	$NaHCO_3$	130	4	38
17	DMAc	0.5	$C_6H_5CO_2Na$	130	4	4
18	DMAc	0.5	Cs_2CO_3	130	4	[g]
19	DMAc	0.5	NaOAc	130	4	20
20	DMAc	0.5	KOH	130	4	11
21	DMAc	0.5	NaOH	130	4	11
22	DMAc	0.5	LiOH	130	4	[g]
23	DMAc	0.5	*t*-BuOK	130	4	5
24	DMAc	0.5	*t*-BuONa	130	4	8
25	DMF	0.5	K_2CO_3	130	4	57
26	xylene	0.5	K_2CO_3	130	4	[g]
27	NMP	0.5	K_2CO_3	130	4	79
28	dioxane	0.5	K_2CO_3	110	4	[g]
29	DMSO	0.5	K_2CO_3	130	4	[g]
30	toluene	0.5	K_2CO_3	110	4	[g]

[a]Reaction conditions unless specified otherwise: benzo[*b*]thiophene (1 mmol), 4-bromotoluene (1 mmol), **C6** (0.005 mmol), PivOH (0.3 mmol), base (1.5 mmol), solvent (3 mL) in an aerobic environment. Unless otherwise specified, commercial solvent was used as received and anhydrous technology was avoided. [b]Cross-coupling product determined by GC. [c]In the absence of PivOH. [d]10 mol % PivOH added. [e]100 mol % PivOH added. [f]Isolated yields in parentheses. [g]Not determined.

excellent performance of the α-hydroxyimine palladium complex of **C6**, we carried out further catalytic studies on the cross-coupling of heteroarenes and heteroaryl bromides. As shown in Table 5, a variety of heteroarenes, such as thiophenes, thiazole, imidazo[1,2-*a*]pyridine, and 1,2,3-triazole, undergo reactions with 3-pyridyl, 5-bromopyrimidine, and 2-bromo-5-methylthiophene to give the respective products **7ba**−**7ga** with high efficiency. An array of functionalities on the heteroarenes was tolerated.

Mechanism of the Direct Arylation Reaction. An understanding of the mechanism of the palladium-catalyzed direct C−H arylation could provide important insight into the design of more efficient catalytic systems for cross-coupling reactions.[20] In the optimization experiments, we noticed that PivOH and base (K_2CO_3 or KOAc) was crucial for the success of this cross-coupling (runs 2 and 3, Table 1). Therefore, it is reasonable that the catalysts bonded with halide (Cl or Br) would react with these additives under the reaction conditions. To simplify the reaction, initially, we conducted the reaction of PivOH/K_2CO_3 or PivOH/KOAc with precatalyst **C6** in a DMAc solution at a temperature of 130 °C. The preliminary investigation involved tracing any catalytic species with ESI-MS, which indicated the existence of ligand exchange.[21] A similar phenomenon was also investigated using **C8**. However, a further attempt to obtain the purified product of the carboxylate palladium compounds was unsuccessful due to the complicated nature of the mixtures. Fortunately, one crystal suitable for X-ray diffraction was grown in the reaction flask. As shown in Figure 5, **C9**, which has one acetate ion bound to the palladium, was confirmed.[22] Although the actual catalytic intermediates require further study, the observed behavior of the additives may be due to carboxylate-assisted ligand exchange, which may be involved in the direct arylation.[20d]

In order to provide further information on the mechanism, we carried out kinetic experiments on the direct arylation of phenyl bromide (**2b**) and thiophene-2-carbaldehyde (**1d**). Initially, **2b** (0.01 M) was treated with a large excess of **1d** at 130 °C in DMAc. However, this gave a rapid conversion of **2b** within a very short reaction time. To avoid large errors, the reaction was then conducted at a lower temperature of 110 °C. As shown in Table 6, the rate constants observed at different concentrations of **2b** and **1d** obeyed pseudo-first-order kinetics with respect to substrate **2b**, when **C6** was used as the precatalyst (Figure S2 in the Supporting Information). Moreover, the observed rate constant (k_{obsd}) values exhibited a roughly linear correlation with the concentrations of **1d**. The rate equation can be depicted as $d[\mathbf{2b}]/dt = k_{obsd}[\mathbf{2b}] = k[\mathbf{2b}][\mathbf{1d}]$ ($k = [4.47(57)] \times 10^{-4}$ s^{-1} M^{-1}). The results demonstrated the involvement of both reactants in the rate-determining step in the direct arylation, implying that the reaction may follow the commonly proposed catalytic cycle, involving oxidative addition, C−H bond cleavage, and reductive elimination.[2g] The direct arylation reaction was also examined using **C1** as the precatalyst. Like the behavior of **C6**, the formation of **3db** was found to obey pseudo-first-order kinetics, giving a lower value for the rate constant (k_{obsd}) of 0.95×10^{-4} s^{-1} (Table 6, run 6). Subsequently, other solvents such as DMF and NMP were examined. It was found that the solvent played a crucial role in the reactions and these solvents were less efficient than DMAc, which is consistent with the screening conditions.

Kinetic experiments on direct arylation of thiophene substrates with different electronic effects were then investigated under the standard reaction conditions (130 °C) to gain more information. As illustrated in Figure 6, it is noteworthy that no distinct induction period was observed in these reactions, which suggested that the active center was generated simultaneously. Moreover, the experiments revealed significantly different catalytic behaviors of these four substrates. For instance, at an initial reaction time of 5 min, **1a**,**b** permitted 22% and 29% yields of **3ab**,**bb**, respectively. On the other hand, **1c**,**d** showed a significantly higher reaction rate and led to high conversions after 5 min (ca. 50%). This result clearly showed the greater efficiency of electron-deficient substrates, excluding a competitive S_EAr pathway[23] but supporting the CMD mechanism.[4c,i,10b,e]

To provide additional evidence for this process or not, a one-pot competition experiment performed with an equimolar mixture of 2-chlorothiophene and 2-methylthiophene was

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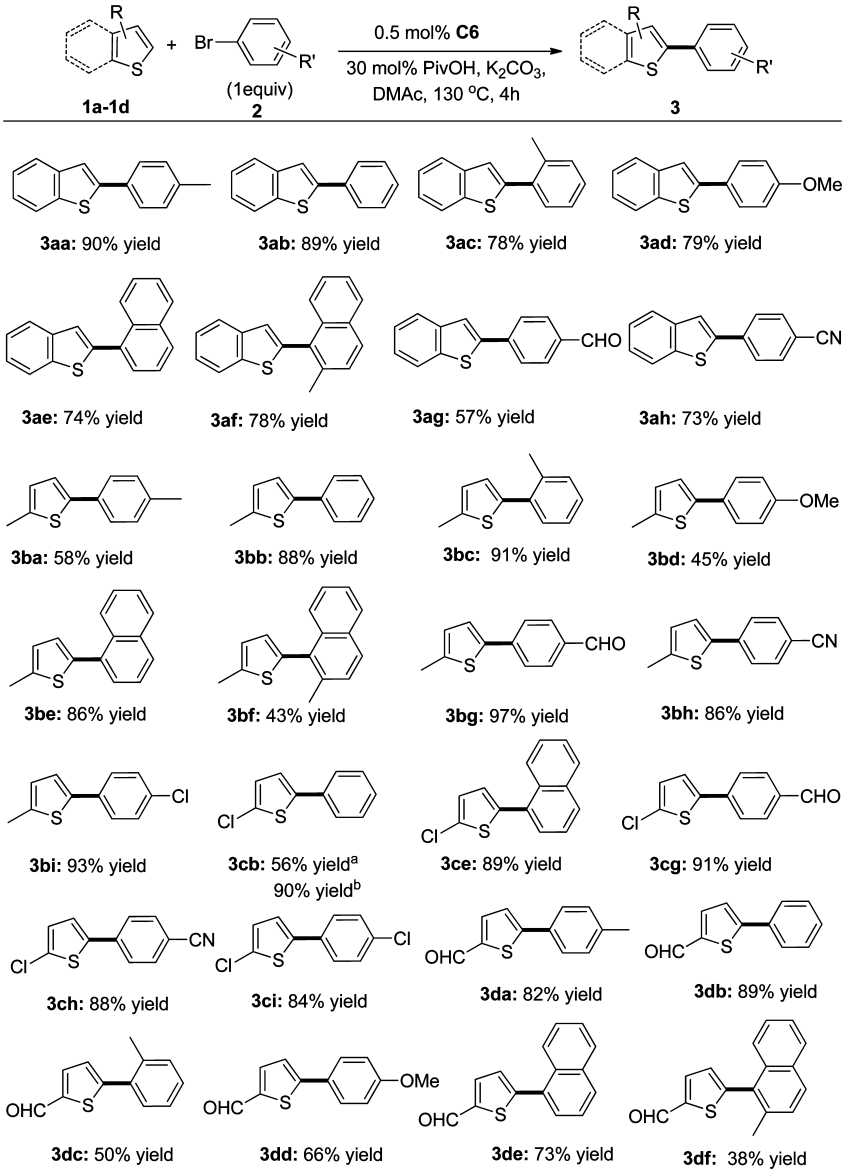
Table 3. Direct Arylation Reactions of Thiophenes with Aryl Bromides under Aerobic Conditions[a]



[a]Reaction conditions unless specified otherwise: thiophene (1 mmol), aryl bromide (1 mmol), **C6** (0.005 mmol), PivOH (0.3 mmol), base (1.5 mmol), solvent (3 mL) in an aerobic environment. [b]In this case, 2-chlorothiophene (1 mmol) and phenyl bromide (2 mmol) were used.

conducted. The experiment showed that arylation of the more electron deficient 2-chlorothiophene was favored over that of the more nucleophilic 2-methylthiophene in a 3.4:1 ratio (Scheme 2). This outcome is in line with the CMD mechanism, for which arylation of the electron-deficient substrate was favored.[4i]

To gain more insight into the C−H bond cleaving process, anisole was utilized as a substrate for the direct arylation (Scheme 3). Although a low yield of 7% was obtained, the reaction of anisole with phenyl bromide afforded the ortho-, meta-, and para-arylated anisoles in a 26:45:29 molar ratio, which is consistent with the CMD mechanism, as is the case for $Pd(OAc)_2$/DavePhos system.[13]

Next, kinetic isotope effect (KIE) studies were employed to examine the C−H bond cleavage step. As shown in Scheme 4, a primary KIE of 1.64 was observed between benzo[*b*]thiophene-*d* with 4-methylphenyl bromide when two parallel reactions were conducted. Another set of reactions between benzo[*b*]-thiophene-*d* and phenyl bromide exhibited a KIE value of 1.58 (seen in Scheme S1 in the Supporting Information). Furthermore, a one-pot intermolecular competitive reaction was performed and gave a KIE value of 1.56 (seen in Scheme S2 in the Supporting Information). These deuterium-labeling experiments with lack of a significant but nonnegligible KIE effect implied that the C−H bond cleavage occurs as part of the mechanism of the reaction; however, the involvement of the rate-determining step cannot be definitely determined.[24] Although the KIE results disagreed with the common CMD type mechanism proposed by Fagnou and Lee,[25] we noticed that a recent work involving a CMD pathway in the palladium-catalyzed direct arylation of 2-methylthiophene also exhibited no notable KIE effect.[19]

In recent years, other direct arylation mechanisms, such as radical[10b] and Heck[26] pathways, for palladium-catalyzed cross-coupling have also been proposed. First, we performed the catalytic reaction between benzo[*b*]thiophene and phenyl

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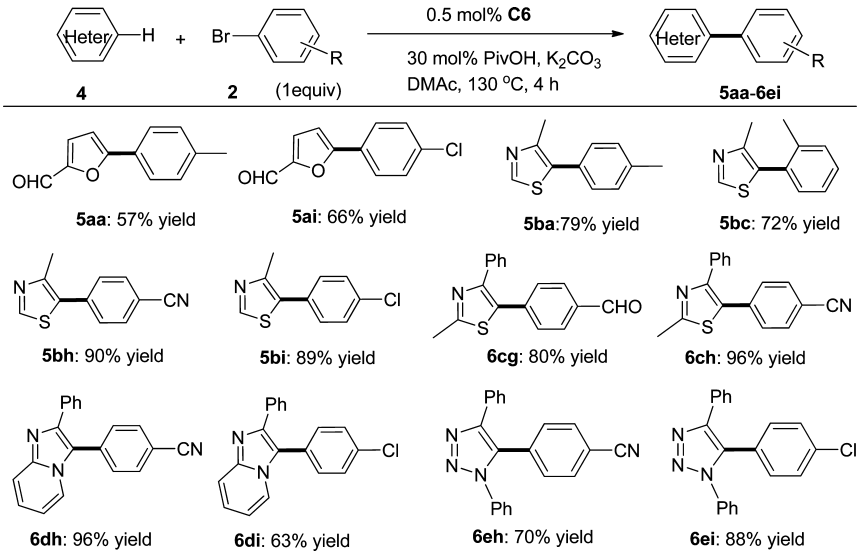
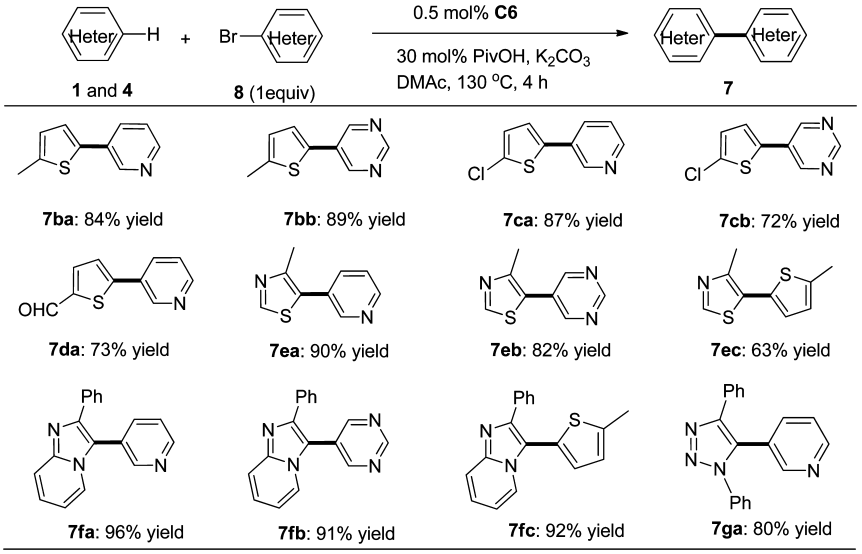
Table 4. Direct Arylation Reactions of Heteroarenes with Aryl Bromides under Aerobic Conditions[a]



[a]Reaction conditions: heteroarene (1 mmol), aryl bromide (1 mmol), **C6** (0.005 mmol), PivOH (0.3 mmol), base (1.5 mmol), solvent (3 mL) in an aerobic environment.

Table 5. Direct Arylation Reaction of Heteroarenes with Heteroaryl Bromides under Aerobic Conditions[a]



[a]Reaction conditions: heteroarene (1 mmol), heteroaryl bromide (1 mmol), **C6** (0.005 mmol), PivOH (0.3 mmol), base (1.5 mmol), solvent (3 mL) in an aerobic environment.

bromide in the presence of 1 atm of oxygen or with 2 equiv of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as oxidant and radical scavenger. Unexpectedly, the product yields were 63% and 54%, respectively, which confirmed the insensitivity of the oxidant to the palladium center. In addition, the free radical scavenger of TEMPO did not quench the catalytic reaction, indicating that the involvement of a free radical path in the reaction mechanism can be excluded.[27] In comparison with the control run, the reaction run under a nitrogen atmosphere also gave a satisfactory yield of 92%, which suggests that the oxidant is not necessary in this protocol. Moreover, we also investigated the possibility of a Heck-type (insertion and β-H elimination) pathway. It is known that arylboronic acid can accelerate the Heck reaction, especially in the presence of a nitrogen-based palladium, to generate the Ar-LPd−X intermediate via a transmetalation reaction rather than the oxidative addition of aryl bromides.[28] When phenylboronic acid was employed under our standard reaction conditions (Scheme 5), however, a sharp decrease in the activity (ca. 5% conversion) was observed. Moreover, a mixture of C-4 and C-5 arylated products was obtained in a ratio of 62:38, which deviates from the result obtained with aryl bromides. Therefore, Pd-catalyzed direct arylation via a Heck mechanism is not plausible.

Pd-catalyzed direct arylation can be promoted by either a Pd(0)/Pd(II)[4,7,8] or Pd(II)/Pd(IV) catalytic cycle.[29,30] To probe the possible catalytic species responsible for this reaction, we tested the homocoupling of the benzyl chloride under our reaction conditions, as the benzyl chloride is known to induce clean and fast electron transfer from Pd(0) complexes to form the dibenzyl.[31] When anexcess of benzyl chloride (200 equiv) was used, the corresponding amount of dibenzyl was detected, offering the possibility of the involvement of Pd(0) complexes

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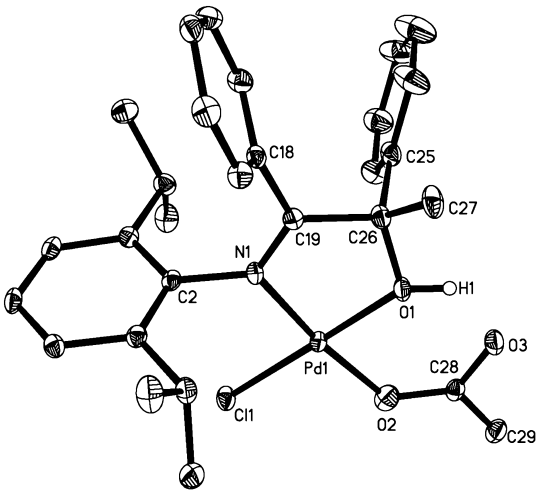


Figure 5. Molecular structure of **C9** depicted with 30% thermal ellipsoids. Hydrogen atoms, except on the hydroxyl, and one uncoordinated water molecule have been omitted for clarity. Selected bond distances (Å) and angles (deg): Pd(1)−O(1) 1.978(2), Pd(1)−N(1) 2.017(3), Pd(1)−Cl(1) 2.2829(10), Pd(1)−O(2) 2.017(3); N(1)−Pd(1)−O(1) 80.94(11), N(1)−Pd(1)−Cl(1) 97.84(8), Cl(1)−Pd(1)−O(2) 88.25(9), O(1)−Pd(1)−O(2) 93.00(11), O(1)−Pd(1)−Cl(1) 178.52(8), N(1)−Pd(1)−O(2) 173.60(11).

Table 6. Rate Constants for Direct Arylation of 1d with 2b under Various Reaction Conditions[a]

run	preatalyst	solvent	**1d** (M)	**2b** (M)	k_{obsd} (10^{-4} s^{-1})
1	**C6**	DMAc	0.20	0.01	1.26
2	**C6**	DMAc	0.30	0.01	1.62
3	**C6**	DMAc	0.35	0.01	1.82
4	**C6**	DMAc	0.40	0.01	2.19
5	**C6**	DMAc	0.40	0.02	2.02
6	**C1**	DMAc	0.20	0.01	0.95
7	**C6**	DMF	0.20	0.01	0.58
8	**C6**	NMP	0.20	0.01	0.83

[a]The reaction was performed at a temperature of 110 °C, using a catalyst loading of 2 mol %.

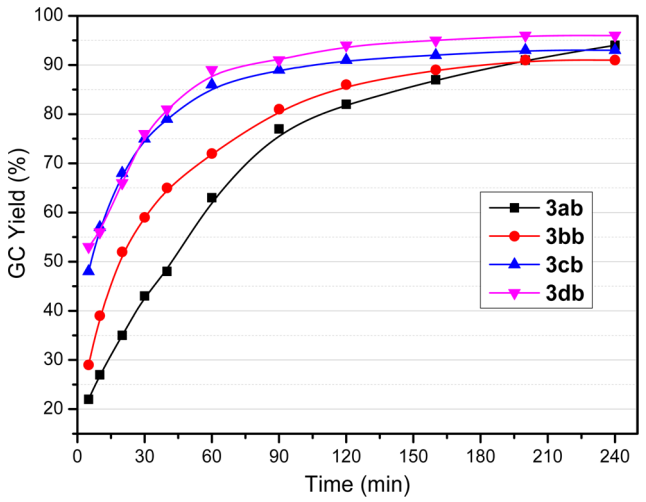
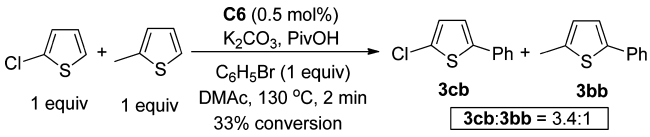
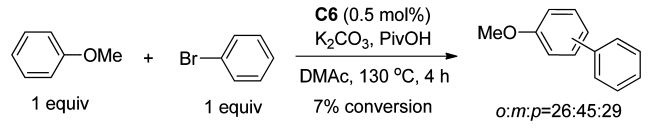


Figure 6. Kinetic profiles for the arylation of thiphenes with phenyl bromide. Reactions were performed under conditions [a] as given in Table 3, except that 2-chlorothiophene was performed under conditions [b].

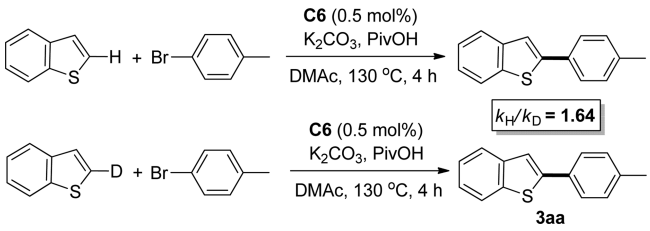
Scheme 2. One-Pot Competition Study



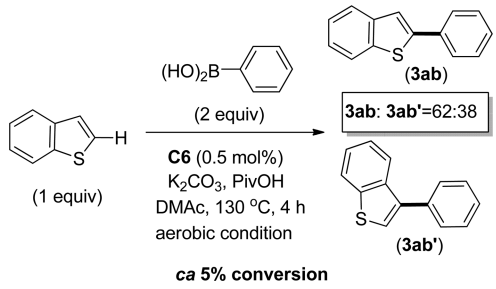
Scheme 3. Pd-Catalyzed Direct Arylation of Anisole with Phenyl Bromide



Scheme 4. Kinetic Isotope Effect Studies

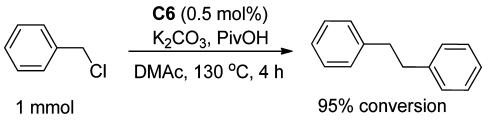


Scheme 5. Pd-Catalyzed Direct Arylation of Benzo[*b*]thiophene with Phenylboronic Acid



as the active form of the catalysis (Scheme 6). We also carried out Hg and PPh_3 poisoning experiments to determine the

Scheme 6. Pd-Catalyzed Homocoupling of the Benzyl Chloride



possibility of the existence of heterogeneous Pd(0) species. However, the reaction was not quenched with use of these poisoning agents (seen in Figure S3 in the Supporting Information), which suggested a homogeneous nature of the active palladium center. On the other hand, the Pd(II)/Pd(IV) catalytic cycle was also ruled out, because the stoichiometric reaction of **C6** and phenyl bromide in the catalytic reaction gave biphenyl quantitatively, whereas the halide exchange product of phenyl chloride via a Pd(II)/Pd(IV) process was not observed (Scheme 7).[31b] In addition, the generation of biphenyl also indicated a Pd(0)Pd/(II)-catalyzed Ullmann reaction.[32]

DFT Study on the CMD Reaction Mechanism. To provide deeper insights into our proposed CMD reaction

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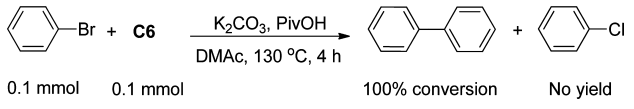
Scheme 7. Stoichiometric Reaction of Palladium Complex and Phenyl Bromide



mechanism for this palladium-catalyzed direct arylation of thiophenes with aryl bromides, DFT calculations were carried out using catalyst **C6** as the full model. The obtained free energy profile and key structures for the catalytic cycle are depicted in Figures 7 and 8, respectively.

Oxidative Addition. The oxidative addition of the aryl bromide to the Pd(0) center was found to be highly feasible under the standard reaction conditions, with a calculated activation free energy of 2.6 kcal/mol (**TS1**). This strongly supports the possibility of the involvement of the Pd(0) complex as the active form to activate aryl bromide in our catalytic systems. This exergonic oxidative addition step leads to the relatively stable aryl Pd(II) intermediate **IM1** (downhill by 23.7 kcal/mol).

C−H Bond Cleavage. After a ligand exchange, the benzo[*b*]thiophene coordinates to the Pd(II) center (**IM2**). Then, the C−H bond of benzo[*b*]thiophene is activated by the Pd(II) center via formation of a C−H agostic interaction (**IM3**), As shown in Figure 8, in **IM3**, the Pd···C distance is 2.332 Å and the C−H bond is elongated to 1.088 Å, in comparison to the former C−H bond in **IM2** (1.081 Å). This C−H agostic interaction leads to the C−H bond cleavage via the typical CMD transition state **TS2**, where the forming Pd−C bond length is 2.121 Å, the breaking C−H bond length is 1.317 Å, and the forming O−H bond length is 1.327 Å. The structure of **TS2** is very close to those computed in similar systems.[33] The NPA charge of the migrating hydrogen evolves from 0.313 in **IM3**, through 0.414 in **TS2**, to 0.525 in **IM4**, which clearly suggests a proton transfer for the CMD mechanism. In **TS2**, the concerted deprotonation is assisted by the $PivO^-$ anion, supporting the involvement of PivOH as an important additive. The activation free energy of C−H bond cleavage is 21.5 kcal/mol relative to aryl-Pd(II) intermediate **IM1**. It should be noted that this C−H bond cleavage is not the rate-determining step ($\Delta G^{\ddagger}$ = 32.9 kcal/mol for reductive elimination; see discussion below). This is in good agreement with our experimental KIE observations (KIE = 1.64, 1.58, 1.56). It was also reported in similar systems that C−H bond cleavage is not the rate-determining step and no notable KIE effect was found.[19]

Reductive Elimination. The reductive elimination (**TS3**) to give the arylation product is the rate-determining step along the CMD pathway, with a calculated activation free energy of 32.9 kcal/mol relative to **IM1**, which is higher than the C−H cleavage transition state (**TS2**) by 11.4 kcal/mol. Therefore, it is not surprising to see an insignificant KIE effect in our experimental studies (Scheme 3). The reductive elimination was also suggested to be the rate-determining step of the CMD mechanism by computational and KIE studies in arylpalladium acetate systems.[19] A reductive elimination as the rate-determining step implies that the direct arylation reactivity should be affected by both reaction components, the thiophenes and the aryl bromides. Furthermore, our calculated activation free energy of 32.9 kcal/mol is consistent with the experimental condition that the reaction occurs at high temperature. Nevertheless, it is noteworthy that the excellent catalytic efficiency of the α-hydroxyimine palladium complexes proved their superiority relative to the most conventional catalysts. Reasonably, the efficiency can be ascribed to the bulky steric ligand bonded to the palladium, which can retard the decomposition of the active species and favor the reductive elimination pathway, thus enhancing the catalytic activity under aerobic conditions.

We performed further DFT calculations to evaluate a carboxylatopalladium(II) complex as the active species. The results suggest that a carboxylatopalladium(II)-promoted direct arylation is less likely to occur. The rate-determining step has

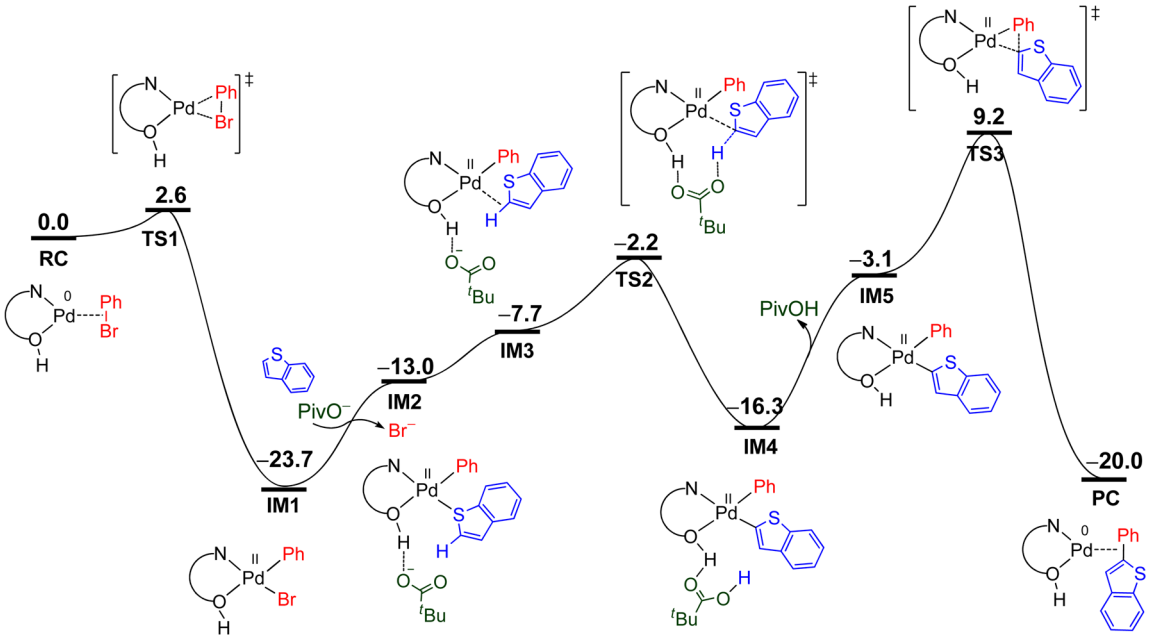


Figure 7. Free energy profile for the palladium (**C6**)-catalyzed direct arylation of benzo[*b*]thiophene and phenyl bromide. Free energies are given in kcal/mol.

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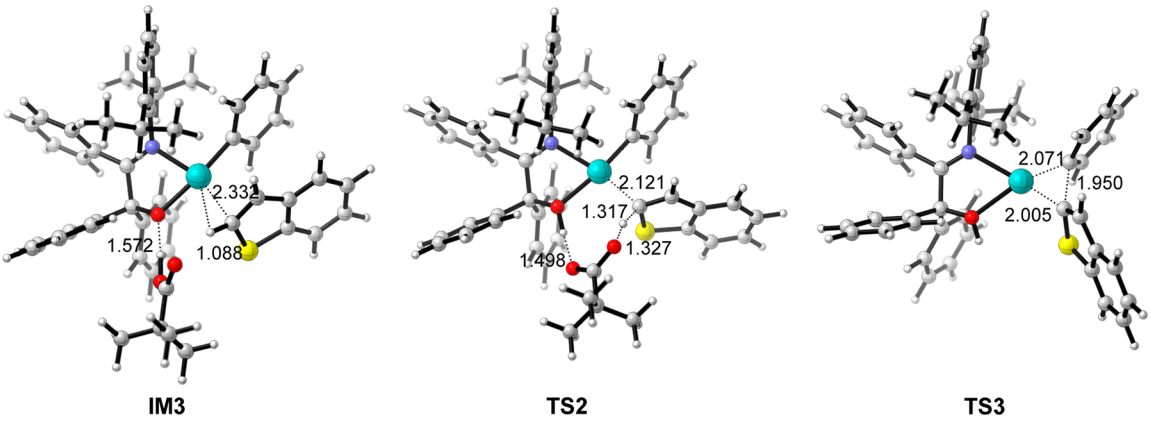
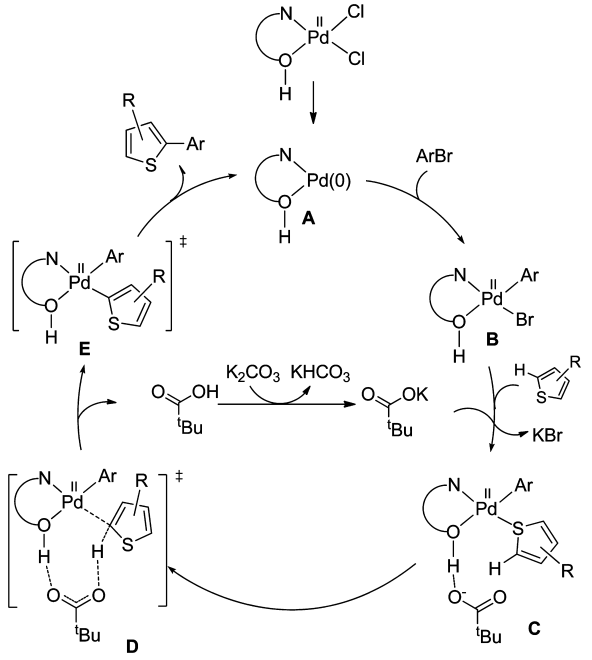


Figure 8. Key structures for the palladium (**C6**)-catalyzed direct arylation of benzo[*b*]thiophene with phenyl bromide. Bond lengths are given in angstroms.

an activation free energy as high as 46.3 kcal/mol (Figure S4 in the Supporting Information). Our experimental study (Scheme 7) also rules out the Pd(II)/Pd(IV) catalytic cycle. Therefore, a carboxylatopalladium(II) species is a resting state instead of an active species in our system. The palladium(II) species will most likely transform into a Pd(0) species as the active site for the direct arylation. The possibility of the involvement of Pd(0) complexes as the active form is also well supported by our experimental study (Scheme 6).

On the basis of our experimental and computational results, as well as the results reported by other groups, a plausible Pd(0)/Pd(II) CMD pathway is depicted in Scheme 8. First, in the presence of base and substrates, the Pd(II) complex was reduced to the Pd(0) catalyst (**A**). Then, the oxidation of Ar-Br with Pd(0) species is envisioned to occur, affording an aryl-Pd(II) intermediate (**B**). After a ligand exchange, the coordination of thiophene would lead to the Pd intermediate (**C**). This species subsequently undergoes C−H bond cleavage, via a CMD type transition state (**D**), to form the diaryl-Pd(II) intermiediate (**E**), along with the liberation of PivOH. Finally, the catalytic cycle is completed via reductive elimination, the rate-determining step, to produce the arylated product and the Pd(0) catalyst is regenerated.

Scheme 8. Proposed Catalytic Cycle for Pd-Catalyzed Direct Arylation of Heteroaromatics with Aryl Halides



CONCLUSIONS

In summary, we have developed a type of α-hydroxyimine palladium complex with bulky subsituents. The steric effects of the bulk on the catalytic efficiency are understood on the basis of the ligand design. In the presence of both heteroarenes and aryl bromides employed in equimolar quantities, **C6** with a bulky steric group gave a versatile, regioselective direct arylation of heteroarenes with aryl or heteroaryl bromides. This easy manipulation is highlighted by the low palladium loading (0.5 mol %) and aerobic conditions. In addition, the mechanism was proposed to proceed via a Pd(0)/Pd(II) CMD pathway in the direct arylation.

EXPERIMENTAL SECTION

Physical Measurements and Materials. 2,6-Dimethylaniline and 2,6-diisopropylaniline were purchased from Aldrich Chemical and were distilled under reduced pressure before being used. Palladium chloride and trimethylaluminum (1 M, hexane) were purchased from Aldrich Chemical. 2,3-Butanedione and benzil were purchased from Guangzhou Chemical Reagent Factory and were used as received. 2,6-Diphenylmethyl-4-methylaniline, 2,6-diphenylmethyl-4-chloroaniline, and 2,6-diphenylmethyl-4-methoxylaniline,[34] 2,6-$(CH_3)_2C_6H_3$-N═C-(Ph)-C(Ph)═O (**KI5a**) and 2,6-$(iPr)_2C_6H_3$-N═C(Ph)-C(Ph)═O (**KI6a**),[35] **C7** and **C8**,[11] and benzo[*b*]thiophene-d[28b] were prepared according to literature methods.

The NMR data of compounds were obtained on a Varian Mercury-Plus 400 MHz spectrometer at ambient temperature with the decoupled nucleus, using $CDCl_3$ as solvent and referenced versus TMS as standard. Elemental analyses were determined with a Vario EL Series Elemental Analyzer from Elementar. The X-ray diffraction data of single crystals were obtained with the $\omega-2\theta$ scan mode on a Bruker SMART 1000 CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 173 K. The structure was solved using direct methods, and further refinement with full-matrix least squares on F^2 was obtained with the SHELXTL program package.[36] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced in calculated positions with the displacement factors of the host carbon atoms.

General Procedures for the Synthesis of α-Ketoimine (Ar-N═C(CH_3)C(CH_3)═O) Compounds. A solution of 2,3-butanedione (0.48 mL, 5.5 mmol) and formic acid (0.08 mL) in dichloromethylene (15 mL) was placed in a flask and stirred. Substituted aniline (5 mmol)

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in 5 mL of dichloromethylene was added dropwise to the flask over 1 h, and the mixture was then refluxed. After a reaction time of 12 h, all of the volatiles were removed in vacuo. The crude product was crystallized from ethanol as a light yellow powder.

2-(CHPh$_2$)-4,6-(CH$_3$)$_2$C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)=O (**KI1a**): obtained in 89% yield. Mp: 115.6−116.3 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30−7.01 (m, Ar-H, 10H), 6.93 (s, Ar-H, 1H), 6.61 (s, Ar-H, 1H), 5.34 (s, CH(Ph)$_2$, 1H), 2.53 (s, CH$_3$, 3H), 2.23 (s, CH$_3$, 3H), 1.89 (s, CH$_3$, 3H), 1.10 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 199.4 (C=N), 167.7(C=O), 144.3 (C$_{Ar}$), 143.0 (C$_{Ar}$), 142.2 (C$_{Ar}$), 132.8 (C$_{Ar}$), 132.1 (C$_{Ar}$), 129.4 (C$_{Ar}$), 129.2 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.7 (C$_{Ar}$), 126.3 (C$_{Ar}$), 126.2 (C$_{Ar}$), 123.6 (C$_{Ar}$), 52.5 (CHPh$_2$), 25.0 (CH$_3$), 21.1 (CH$_3$), 17.6 (CH$_3$), 14.2 (CH$_3$). Anal. Calcd for C$_{25}$H$_{25}$NO: C, 84.47; H, 7.09; N, 3.94. Found: C,84.33; H, 7.12; N, 3.89.

2,6-(CHPh$_2$)$_2$-4-(CH$_3$)C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)=O (**KI2a**): obtained in 80% yield. Mp: 182.5−183.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29−7.17 (m, Ar-H, 12H), 7.04 (m, Ar-H, 8H), 6.67 (s, Ar-H, 2H), 5.11 (s, CH(Ph)$_2$, 2H), 2.33 (s, CH$_3$, 3H), 2.17 (s, CH$_3$, 3H), 0.69 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 199.3 (C=N), 168.5 (C=O), 144.3 (C$_{Ar}$), 143.0 (C$_{Ar}$), 142.0 (C$_{Ar}$), 132.3 (C$_{Ar}$), 130.8 (C$_{Ar}$), 129.5 (C$_{Ar}$), 129.2 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.0 (C$_{Ar}$), 126.3 (C$_{Ar}$), 126.1 (C$_{Ar}$), 52.3 (CHPh$_2$), 25.0 (CH$_3$), 21.4 (CH$_3$), 14.6 (CH$_3$). Anal. Calcd for C$_{37}$H$_{33}$NO: C, 87.54; H, 6.55; N, 2.76. Found: C, 87.45; H, 6.59; N, 2.71.

2,6-(CHPh$_2$)$_2$-4-(OCH$_3$)C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)=O (**KI3a**): obtained in 85% yield. Mp: 150.6−151.5 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30−7.00 (m, Ar-H, 20H), 6.40 (s, Ar-H, 2H), 5.10 (s, CH(Ph)$_2$, 2H), 3.54 (s, OCH$_3$, 3H), 2.32 (s, CH$_3$, 3H), 0.68 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 199.3, 169.1, 155.4, 142.7, 141.7, 140.4, 132.4, 129.4, 129.2, 128.4, 128.0, 126.4, 126.2, 113.7, 55.1, 52.4, 25.0, 14.7. Anal. Calcd for C$_{37}$H$_{33}$NO$_2$: C, 84.86; H, 6.35; N, 2.67. Found: C, 84.75; H, 6.39; N, 2.63.

2,6-(CHPh$_2$)$_2$-4−Cl-C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)=O (**KI4a**): obtained in 79% yield. Mp: 195.5−196.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30−7.18 (m, Ar-H, 12H), 7.02−6.99 (m, Ar-H, 8H), 6.83 (s, Ar-H, 2H), 5.09 (s, CH(Ph)$_2$, 2H), 2.31 (s, CH$_3$, 3H), 0.66 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 198.8 (C=N), 168.9 (C=O), 145.2 (C$_{Ar}$), 142.0 (C$_{Ar}$), 141.6 (C$_{Ar}$), 141.1 (C$_{Ar}$), 133.1 (C$_{Ar}$), 129.3 (C$_{Ar}$), 129.1 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.2 (C$_{Ar}$), 128.0 (C$_{Ar}$), 126.6 (C$_{Ar}$), 126.5 (C$_{Ar}$), 52.3 (CHPh$_2$), 25.0 (CH$_3$), 14.8 (CH$_3$). Anal. Calcd for C$_{36}$H$_{30}$ClNO: C, 81.88; H, 5.73; N, 2.65. Found: C, 81.74; H, 5.80; N, 2.61.

General Procedures for the Synthesis of α-Hydroxyimine (Ar-N=C(CH$_3$)C(CH$_3$)$_2$−OH) Ligands. α-Ketomine (2 mmol) was dissolved in 10 mL of toluene under a nitrogen atmosphere, trimethylaluminum (3 mL, 1.0 M) or phenyl Grignard reagent was added slowly through a syringe at room temperature, and then the reaction was heated to reflux for 4−6 h. When the determined time was reached, the solution was cooled to 0 °C, and the reaction mixture was carefully hydrolyzed with 5% aqueous NaOH solution. The organic product was extracted with ethyl acetate and dried over MgSO$_4$, and the solvent was evaporated. The crude material was crystallized from ethanol or purified by column chromatography (Hex/EtOAc = 30/1) as white crystals.

2-(CHPh$_2$)-4,6-(CH$_3$)$_2$C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)$_2$OH (**L1**): obtained in 87% yield. Mp: 86.5−87.6 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28−7.03 (m, Ar-H, 10H), 6.91 (s, Ar-H, 1H), 6.59 (s, Ar-H, 1H), 5.54 (s, CH(Ph)$_2$, 1H), 5.41 (br, OH, 1H), 2.22 (s, CH$_3$, 3H), 1.92 (s, CH$_3$, 3H), 1.35 (s, CH$_3$, 3H), 1.20 (s, CH$_3$, 3H), 1.11 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 179.5 (C=N), 144.6 (C$_{Ar}$), 142.9 (C$_{Ar}$), 141.5 (C$_{Ar}$), 134.7 (C$_{Ar}$), 129.6 (C$_{Ar}$), 129.2 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.2 (C$_{Ar}$), 126.5 (C$_{Ar}$), 126.4 (C$_{Ar}$), 73.4 (C-OH), 51.4 (CHPh$_2$), 28.1 (CH$_3$), 15.4 (CH$_3$). Anal. Calcd for C$_{26}$H$_{29}$NO: C, 84.06; H, 7.87; N, 3.77. Found: C, 84.02; H, 7.93; N, 3.75.

2,6-(CHPh$_2$)$_2$-4-(CH$_3$)C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)$_2$OH (**L2**): obtained in 74% yield. Mp: 160.3−161.5 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25−6.98 (m, Ar-H, 20H), 6.65 (s, Ar-H, 2H), 5.31 (br, OH, 1H), 5.26 (s, CH(Ph)$_2$, 2H), 2.15 (s, CH$_3$, 3H), 1.89 (s, CH$_3$, 6H), 0.68 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 178.5 (C=N), 143.9 (C$_{Ar}$), 143.5 (C$_{Ar}$), 142.4 (C$_{Ar}$), 132.5 (C$_{Ar}$), 132.0 (C$_{Ar}$), 129.7 (C$_{Ar}$), 129.3 (C$_{Ar}$), 129.2 (C$_{Ar}$), 128.2 (C$_{Ar}$), 128.0 (C$_{Ar}$), 126.2 (C$_{Ar}$), 126.0 (C$_{Ar}$), 73.2 (C-OH), 51.4 (CHPh$_2$), 28.1 (CH$_3$), 21.4 (CH$_3$), 15.1 (CH$_3$). Anal. Calcd for C$_{38}$H$_{37}$NO: C, 87.15; H, 7.12; N, 2.67. Found: C,87.13; H, 7.16; N, 2.63.

2,6-(CHPh$_2$)$_2$-4-(OCH$_3$)C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)$_2$OH (**L3**): obtained in 85% yield. Mp: 158.9−160.5 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.27−7.00 (m, Ar-H, 20H), 6.44 (s, Ar-H, 2H), 5.31 (br, OH, 1H), 5.28 (s, CH(Ph)$_2$, 2H), 3.54 (s, OCH$_3$, 3H), 1.19 (s, CH$_3$, 6H), 0.71 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 179.2 (C=N), 155.2 (C$_{Ar}$), 143.7 (C$_{Ar}$), 142.3 (C$_{Ar}$), 139.6 (C$_{Ar}$), 134.0 (C$_{Ar}$), 129.7 (C$_{Ar}$), 129.4 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.1 (C$_{Ar}$), 126.4 (C$_{Ar}$), 126.2 (C$_{Ar}$), 114.4 (C$_{Ar}$), 73.2 (C-OH), 55.1 (CHPh$_2$), 51.6 (OCH$_3$), 28.0 (CH$_3$), 14.9 (CH$_3$). Anal. Calcd for C$_{38}$H$_{37}$NO$_2$: C, 84.57; H, 6.91; N, 2.60. Found: C, 84.54; H, 6.96; N, 2.63.

2,6-(CHPh$_2$)$_2$-4−Cl-C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)$_2$OH (**L4**): obtained in 77% yield. Mp: 179.2−180.9 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28 (m, Ar-H, 12H), 7.07 (m, Ar-H, 4H), 6.99 (m, Ar-H, 4H), 6.84 (m, Ar-H, 2H), 5.25 (s, CH(Ph)$_2$, 2H), 5.08 (br, OH, 1H), 1.19 (s, CH$_3$, 6H), 0.66 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 179.9 (C=N), 144.7 (C$_{Ar}$), 143.0 (C$_{Ar}$), 141.7 (C$_{Ar}$), 134.8 (C$_{Ar}$), 129.7 (C$_{Ar}$), 129.3 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.3 (C$_{Ar}$), 126.6 (C$_{Ar}$), 126.5 (C$_{Ar}$), 73.4 (C-OH), 51.4 (CHPh$_2$), 28.0 (CH$_3$), 15.3 (CH$_3$). Anal. Calcd for C$_{37}$H$_{34}$ClNO: C, 81.67; H, 6.30; N, 2.57. Found: C, 81.62; H, 6.34; N, 2.52.

2,6-(CH$_3$)$_2$C$_6$H$_3$N=C(Ph)C(Ph)$_2$OH (**L5**): obtained in 68% yield. Mp: 117.6−119.2 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52 (m, Ar-H, 4H), 7.33 (m, Ar-H, 6H), 7.13 (m, Ar-H, 1H), 6.96 (m, Ar-H, 2H), 6.87 (m, Ar-H, 3H), 6.50 (m, Ar-H, 2H), 2.02 (s, CH$_3$, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.4 (C=N), 145.5 (C$_{Ar}$), 142.1 (C$_{Ar}$), 135.1 (C$_{Ar}$), 128.9 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 127.3 (C$_{Ar}$), 126.5 (C$_{Ar}$), 123.7 (C$_{Ar}$), 82.8 (C-OH), 18.7 (CH$_3$). Anal. Calcd for C$_{28}$H$_{25}$NO: C, 85.90; H, 6.44; N, 3.58. Found: C, 85.88; H, 6.46; N, 3.56.

2,6-(iPr)$_2$C$_6$H$_3$N=C(Ph)C(Ph)$_2$OH (**L6**): obtained in 65% yield. Mp: 113.5−114.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53 (m, Ar-H, 4H), 7.35 (m, Ar-H, 6H), 7.12 (m, Ar-H, 1H), 6.98 (m, Ar-H, 5H), 6.50 (m, Ar-H, 2H), 2.81 (m, C*H*(CH$_3$)$_2$, 2H), 1.21 (d, J_{HH} = 7.2 Hz, CH(C*H*$_3$)$_2$, 6H), 0.89 (d, J = 7.2 Hz, CH(C*H*$_3$)$_2$, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.1 (C=N), 142.5 (C$_{Ar}$), 142.2 (C$_{Ar}$), 136.8 (C$_{Ar}$), 134.6 (C$_{Ar}$), 128.8 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.4 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 127.3 (C$_{Ar}$), 124.4 (C$_{Ar}$), 122.7 (C$_{Ar}$), 82.6 (C-OH), 28.2 (*C*H(CH$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 21.6 (CH(*C*H$_3$)$_2$). Anal. Calcd for C$_{32}$H$_{33}$NO: C, 85.87; H, 7.43; N, 3.13. Found: C, 85.83; H, 7.46; N, 3.15.

General Procedures for the Synthesis of Palladium Complexes. α-Hydroxyimine ligand (1.0 mmol) and palladium dichloride (0.177 g, 1.0 mmol) were combined in 10 mL of methanol at room temperature. After the reaction mixture was heated to reflux overnight, the methanol was removed under reduced pressure. The residue was dissolved in 5 mL of dichloromethane, and then 20 mL hexane was added. The precipitate of the palladium complex was collected by filtration, and the brown powder was washed with hexane (2 × 20 mL). Drying in vacuo produced the desired palladium complex.

{[2-(CHPh$_2$)-4,6-(CH$_3$)$_2$C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)$_2$OH]PdCl$_2$} (**C1**): obtained in 89% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.41−7.20 (m, Ar-H, 10 H), 6.86 (s, Ar-H, 1H), 6.65 (s, Ar-H, 1H), 6.58 (br, C*H*(Ph)$_2$, 1H), 2.17 (s, CH$_3$, 3H), 2.08 (s, CH$_3$, 3H), 1.89 (s, CH$_3$, 3H), 1.37 (s, CH$_3$, 3H), 0.84 (s, CH$_3$, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 191.1 (C=N), 142.9 (C$_{Ar}$), 141.0 (C$_{Ar}$), 139.7 (C$_{Ar}$), 137.1 (C$_{Ar}$), 136.8 (C$_{Ar}$), 130.4 (C$_{Ar}$), 129.8 (C$_{Ar}$), 129.6 (C$_{Ar}$), 129.4 (C$_{Ar}$), 129.1 (C$_{Ar}$), 128.1 (C$_{Ar}$), 126.9 (C$_{Ar}$), 126.3 (C$_{Ar}$), 90.6 (C-OH), 52.2 (CHPh$_2$), 28.4 (CH$_3$), 26.0 (CH$_3$), 21.3 (CH$_3$), 18.0 (CH$_3$), 17.7 (CH$_3$). Anal. Calcd for C$_{26}$H$_{29}$Cl$_2$NOPd: C, 56.90; H, 5.33; N, 2.55. Found: C, 56.78; H, 5.36; N, 2.50.

{[2,6-(CHPh$_2$)$_2$-4-(CH$_3$)C$_6$H$_2$N=C(CH$_3$)C(CH$_3$)$_2$OH]PdCl$_2$} (**C2**): obtained in 91% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29−7.14 (m, Ar-H, 20 H), 6.65 (s, Ar-H, 2H), 6.32 (s, C*H*(Ph)$_2$, 2H), 2.12 (s, CH$_3$,

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3H), 1.48 (s, CH_3, 6H), −0.04 (s, CH_3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (C═N), 143.5 (C_{Ar}), 140.4 (C_{Ar}), 139.4 (C_{Ar}), 136.8 (C_{Ar}), 136.4 (C_{Ar}), 130.3 (C_{Ar}), 130.2 (C_{Ar}), 129.8 (C_{Ar}), 128.8 (C_{Ar}), 128.1 (C_{Ar}), 126.9 (C_{Ar}), 126.4 (C_{Ar}), 90.9 (C-OH), 51.8 ($CHPh_2$), 28.1 (CH_3), 21.6 (CH_3), 19.0 (CH_3). Anal. Calcd for $C_{38}H_{37}Cl_2NOPd$: C, 65.10; H, 5.32; N, 2.00. Found: C, 64.89; H, 5.37; N, 1.96.

{[2,6-$(CHPh_2)_2$-4-$(OCH_3)C_6H_2N$═$C(CH_3)C(CH_3)_2OH]PdCl_2} ***(C3)****:* obtained in 85% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.15 (m, Ar-H, 20 H), 6.37 (s, Ar-H, 2H), 6.34 (s, $CH(Ph)_2$, 2H), 3.49 (s, OCH_3, 3H), 1.47 (s, CH_3, 6H), −0.03 (s, CH_3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4 (C═N), 157.8 (C_{Ar}), 143.2 (C_{Ar}), 140.1 (C_{Ar}), 138.2 (C_{Ar}), 135.2 (C_{Ar}), 130.2 (C_{Ar}), 129.8 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 127.0 (C_{Ar}), 126.5 (C_{Ar}), 115.1 (C_{Ar}), 90.8 (C-OH), 54.9 ($CHPh_2$), 52.0 (OCH_3), 28.1 (CH_3), 19.0 (CH_3). Anal. Calcd for $C_{38}H_{37}Cl_2NO_2Pd$: C, 63.65; H, 5.20; N, 1.95. Found: C, 63.52; H, 5.24; N, 1.90.

{[2,6-$(CHPh_2)_2$-4−Cl-C_6H_2N═$C(CH_3)C(CH_3)_2OH]PdCl_2} ***(C4)****:* obtained in 88% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25−7.18 (m, Ar-H, 20 H), 6.83 (s, Ar-H, 2H), 6.33 (s, $CH(Ph)_2$, 2H), 1.43 (s, CH_3, 6H), −0.03 (s, CH_3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4 (C═N), 142.7 (C_{Ar}), 140.2 (C_{Ar}), 139.7 (C_{Ar}), 138.8 (C_{Ar}), 133.2 (C_{Ar}), 130.2 (C_{Ar}), 129.7 (C_{Ar}), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 126.9 (C_{Ar}), 110.0 (C_{Ar}), 90.8 (C-OH), 51.8 ($CHPh_2$), 28.2 (CH_3), 19.2 (CH_3). Anal. Calcd for $C_{37}H_{34}Cl_3NOPd$: C, 61.60; H, 4.75; N, 1.94. Found: C, 61.47; H, 4.79; N, 1.91.

{[2,6-$(CH_3)_2C_6H_3N$═$C(Ph)C(Ph)_2OH]PdCl_2} ***(C5)****:* obtained in 92% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65−7.39 (m, Ar-H, 10H), 7.21−7.12 (m, Ar-H, 2H), 6.86−6.78 (m, Ar-H, 5H), 6.37 (m, Ar-H, 1H), 2.48 (s, CH_3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3 (C═N), 143.3 (C_{Ar}), 136.1 (C_{Ar}), 131.8 (C_{Ar}), 130.3 (C_{Ar}), 130.2 (C_{Ar}), 129.8 (C_{Ar}), 129.1 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.0 (C_{Ar}), 127.3 (C_{Ar}), 126.5 (C_{Ar}), 95.7 (C-OH), 31.6 (CH_3), 19.7 (CH_3). Anal. Calcd for $C_{28}H_{25}Cl_2NOPd$: C, 59.12; H, 4.43; N, 2.46. Found: C, 59.65; H, 4.70.; N, 2.37.

{[2,6-$(iPr)_2C_6H_3N$═$C(Ph)C(Ph)_2OH]PdCl_2} ***(C6)****:* obtained in 94% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76−7.41 (m, Ar-H, 2H), 7.59−7.48 (m, Ar-H, 9H), 7.11−7.05 (m, Ar-H, 3H), 7.00−6.84 (m, Ar-H, 3H), 6.42 (d, J_{HH} = 9.8 Hz, Ar-H, 1H), 3.51 (m, $CH(CH_3)_2$, 2H), 1.71 (d, J_{HH} = 8.0 Hz, $CH(CH_3)_2$, 3H), 1.42 (br, $CH(CH_3)_2$, 3H), 0.90 (d, J_{HH} = 8.0 Hz, $CH(CH_3)_2$, 3H), 0.82 (d, J_{HH} = 8.0 Hz, $CH(CH_3)_2$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 139.9, 131.8, 130.2, 128.9, 128.7, 128.3, 127.6, 127.2, 123.7, 123.5, 110.0, 98.0, 29.0, 24.9, 23.0, 21.8. Anal. Calcd for $C_{32}H_{33}Cl_2NOPd$: C, 61.50; H, 5.32; N, 2.24. Found: C, 62.05; H, 5.53.; N, 2.16.

General Procedure for Direct Arylation Promoted by Palladium Complexes. Unless otherwise noted, the direct arylation reactions were carried out under aerobic conditions. Reaction temperatures are reported as the temperature used to heat the vessel unless otherwise stated. All solvents were not purified and were used as received. A round-bottomed flask containing a stir bar was charged with the palladium complex (0.005 mmol), aryl bromide (1.0 mmol), heteroarene (1.0 mmol), K_2CO_3 (1.5 mmol), PivOH (0.3 mmol), and 3 mL of DMAc. The reaction mixture was carried out at 130 °C for 4 h. After completion of the reaction, the reaction mixture was cooled to room temperature and 20 mL of water was added. The mixture was diluted with Et_2O (5 mL), followed by extraction three times (3 × 5 mL) with Et_2O. The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The crude products were purified by silica gel column chromatography using petroleum ether/ethyl acetate (20/1) as an eluent, and the isolated yield was then calculated on the basis of the feeding of the aryl halide. The isolated corresponding products were characterized by ^1H NMR and ^{13}C NMR, and the spectra are reported in the Supporting Information.

DFT Calculations. DFT calculations were performed using the Gaussian 09 program.[37] The DFT method with B3LYP[38] (Becke's three-parameter hybrid, LYP correlation functional) functional was used in conjunction with effective core potentials (ECPs) with the LANL2DZ basis sets[39] for palladium and the 6-31G(d) basis sets for other elements for the geometry optimizations. At the same level of theory, frequency analysis calculations were performed to characterize the structures to be the minima (no imaginary frequency) or transition states (one imaginary frequency). Transition-state structures were verified by intrinsic reaction coordinate (IRC) calculations. The thermodynamic data were obtained at 403.15 K and 1 atm, according to experimental conditions. Only vibrational entropies in the gas phase were considered to avoid overestimating the entropic contribution due to the ignorance of the suppression effect of solvent on the translation and rotational freedoms of the ideal gas model. To further refine the energetics, the single-point energies of the optimized geometries were obtained with larger basis sets: i.e., the SDD pseudopotential[40] for palladium and 6-311++G(d,p) for other atoms. At the same level of theory, the bulky solvation effect of DMAc (ε = 37.781) was simulated by the SMD continuum solvent mode.[41] The figures of 3D optimized structures in this paper were displayed by the CYLview visualization program.[42]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00181.

Details of experimental procedures and NMR data for all ligands, palladium complexes, and cross-coupling products (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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peaks at m/z 611, 639, and 689, which indicated species such as $[\mathbf{L6}Pd(OAc)]^+$, $[\mathbf{L6}Pd(DMAc)]^+$ and $[\mathbf{L6}PdCl(OAc)]K^+$ were respectively generated. Moreover, the MS analysis of the mixture of **C8** and PivOH/K_2CO_3 showed peaks at m/z of 592 and 627, which could be formed from $[\mathbf{L8}Pd(PivO)]^+$ and $[\mathbf{L8}PdCl(PivO)]^+$. Treatment of **C8** with KOAc also afforded the intermediate $[\mathbf{L8}PdCl(OAc)]^+$ (m/z 551).

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