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Synthesis, crystal structures, and catalytic activities of palladium imidazole complexes formed by 2-hydroxyethyl group cleavage

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Abstract *N*-4,6-dimethyl-2-pyrimidinylimidazole **1** and its hydroxyethyl derivative 1-(2-hydroxyethyl)-3-(4,6-dimethyl-2-pyrimidinyl)imidazolium chloride **2** have been synthesized and characterized. The attempted synthesis of bis(*N*-heterocyclic carbene)palladium complexes via the direct reaction of **2** with $Pd(OAc)_2$ results in the unexpected formation of a bis(*N*-arylimidazole) palladium complex **3**. Additionally, the analogous bis(*N*-methylimidazole) palladium complex **4** has also been synthesized by the above method. Compounds **1**–**4** were characterized by elemental analysis, IR, and ^{1}H NMR. Additionally, their crystal structures have been determined by X-ray diffraction. Complexes **3** and **4** were found to be efficient catalysts for the Suzuki reaction.

Introduction

Palladium-catalyzed coupling reactions such as the Suzuki coupling have become an extremely powerful method in organic synthesis for the formation of carbon–carbon bonds [1–3]. Thus, the design and development of new palladium catalysts is an important research topic. In the past decade, *N*-heterocyclic carbenes (NHCs) have been developed as a new generation of strong σ-donor ligands and widely used in organometallic chemistry and homogeneous catalysis [4, 5]. Most significantly, NHC-palladium complexes derived from imidazolium precursors have been successfully developed as highly active precatalysts for such coupling reactions [6–8]. Synthetic procedures leading to the precursor imidazolium salts have been elucidated [9], and NHC ligands have been shown not merely to be innocent spectators, but reactive intermediates in themselves, with a number of new products being formed [10, 11]. In recent years, part of our research effort has focused on the synthesis and application of palladium complexes [12–14]. In the course of our research into NHC-palladium complexes [15], we sought to synthesize such complexes via the direct reaction of imidazolium salts with $Pd(OAc)_2$. In this work, we have prepared a new *N*-arylimidazole ligand **1** and its imidazolium salt **2**, and we also observed the two unexpected formation of palladium imidazole complexes **3** and **4** from the imidazolium salt **2** (Scheme 1). The ability of complexes **3** and **4** to catalyze the Suzuki reaction was also investigated. The results are presented in this paper.

Experimental

Solvents were dried and freshly distilled prior to use. All other chemicals were commercially available expect for 1-(2-hydroxyethyl)-3-methylimidazolium chloride [16] and 4,6-dimethyl-2-iodopyrimidine [17], which were prepared according to the published procedures. Elemental analyses were determined with a Thermo Flash EA 1112 elemental analyzer. IR spectra were collected on a Bruker VECTOR22 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as an internal standard.

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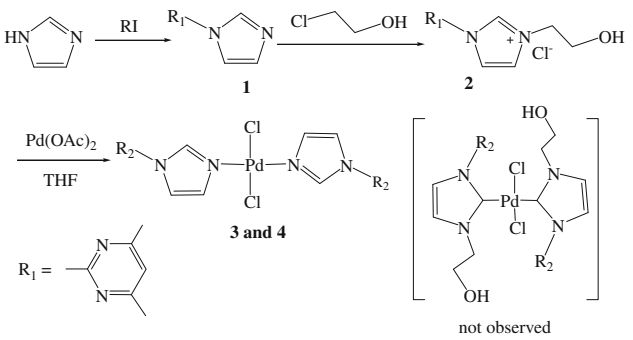

Scheme 1 Synthesis of compounds **1**–**4**. $R_2 = R_1$ or Me

Preparation of compounds **1** and **2**

A solution of 4,6-dimethyl-2-iodopyrimidine (1 mol), imidazole (1.1 mol), NaOH (2 mol), and Bu_4NBr (0.1 mol) in benzene/H_2O (50 mL/10 mL) was heated at 100 °C with stirring for 36 h. The solvent was removed on a rotary evaporator. The product **1** was separated by passing through a short silica gel column with dichloromethane as eluent. Then, a mixture of 1-chloroethanol (0.6 mol) and **1** (0.5 mol) was heated at 100 °C with stirring for 24 h. The crude product was recrystallized from MeOH to give a white solid **2**. **1:** Yield 83 %. Found (%): C, 62.3; H, 5.5; N, 32.5. Calc. (%) for $C_9H_{10}N_4$: C, 62.1; H, 5.8; N, 32.2. IR (KBr, cm^{-1}): 3,107, 1,597, 1,545, 1,473, 1,427, 1,385, 1,326, 1,247, 1,181, 1,106, 1,016, 898, 848, 782, 766. ^1H NMR. (400 MHz, $CDCl_3$): δ 8.61 (s, 1H, NCHN), 7.89 (s, 1H, PyH), 7.13 (s, 1H, NCHCHN), 6.89 (s, 1H, NCHCHN), 2.49 (s, 6H, CH_3). **2:** Yield 71 %. Found (%): C, 51.7; H, 5.8; N, 22.3. Calc. (%) for $C_{11}H_{15}ClN_4$: C, 51.9; H, 5.9; N, 22.0. IR (KBr, cm^{-1}): 3,195, 1,582, 1,512, 1,451, 1,370, 1,344, 1,259, 1,061, 1,025, 882, 821, 804, 791. ^1H NMR. (400 MHz, D_2O): δ 8.65 (s, 1H, NCHN), 7.97 (s, 1H, PyH), 7.63 (s, 1H, NCHCHN), 7.45 (s, 1H, NCHCHN), 4.52 (t, 2H, CH_2), 3.98 (t, 2H, CH_2), 2.46 (s, 6H, CH_3).

General method for the synthesis of complexes **3** and **4**

A Schlenk tube was charged with $Pd(OAc)_2$ (1 mmol) and the corresponding imidazolium salt (2.2 mmol) under nitrogen. Dry THF was added via a cannula and the mixture was stirred at 80 °C for 8 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in CH_2Cl_2 and washed three times with water. The crude product was recrystallized from CH_2Cl_2 to give **3** or **4** as yellow solids (complex **4** was obtained in yield 67 %, and its characterization data have been reported in the literature [18]). **3**: Yield 70 %. Found (%): C, 41.4; H, 3.6; N, 21.7. Calc. (%) for $C_{18}H_{20}Cl_2N_8Pd$: C, 41.1; H, 3.8; N, 21.3. IR (KBr, cm^{-1}): 3,152, 1,600, 1,541, 1,484, 1,418, 1,370, 1,322, 1,199, 1,093, 1,065, 1,028, 855, 754. ^1H NMR. (400 MHz, $CDCl_3$): δ 9.13 (s, 1H, NCHN), 7.83 (s, 1H, PyH), 7.53 (s, 1H, NCHCHN), 6.98 (s, 1H, NCHCHN), 2.51 (s, 6H, CH_3).

General procedure for the Suzuki reaction

A prescribed amount of the catalyst, aryl bromide (0.5 mmol), aryl boronic acid (0.75 mmol), base (1.0 mmol), and solvent (3.0 mL) were placed in a Schlenk tube under nitrogen. The reaction mixture was heated at 100 °C for 12 h, then cooled and quenched with water. The mixture was extracted three times with CH_2Cl_2, and then the combined organic layers were washed with water, dried over $MgSO_4$, and evaporated to dryness. The products were isolated by flash chromatography on silica gel using petroleum ether as eluent and identified by comparing melting points or ^1H NMR spectra.

Crystal structure determination

Crystallographic data for compounds **1**–**4** were collected on a Bruker SMART APEX-II CCD diffractometer equipped with a graphite monochromator at 296 K using Mo–Ka radiation ($\lambda = 0.071073$ Å). The data were corrected for Lorentz polarization factors as well as for absorption. The structures were solved by direct methods and refined by full-matrix least-squares methods on F^2 with the SHELX-97 program [19]. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions. The **CCDC** reference numbers are 859298–859301 for **1**–**4**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and discussion

Synthesis and characterization

Imidazolium salts can be obtained from imidazole by stepwise aryl-/alkylation (Scheme 1). Firstly, we prepared **1** by reaction of 4,6-dimethyl-2-iodopyrimidine with imidazole, in the presence of NaOH and Bu_4NBr. The imidazolium salt **2** was synthesized by refluxing **1** with 1-chloroethanol. Both compounds were characterized by elemental analysis, IR, and ^1H NMR. Additionally, their crystal structures have been determined by X-ray diffraction. The structures of the molecules are shown in Figs. 1 and 2. The crystal structure of **1** reveals two molecules in the asymmetric unit with some differences in geometry. Intermolecular C–H···N hydrogen bonds link the molecules

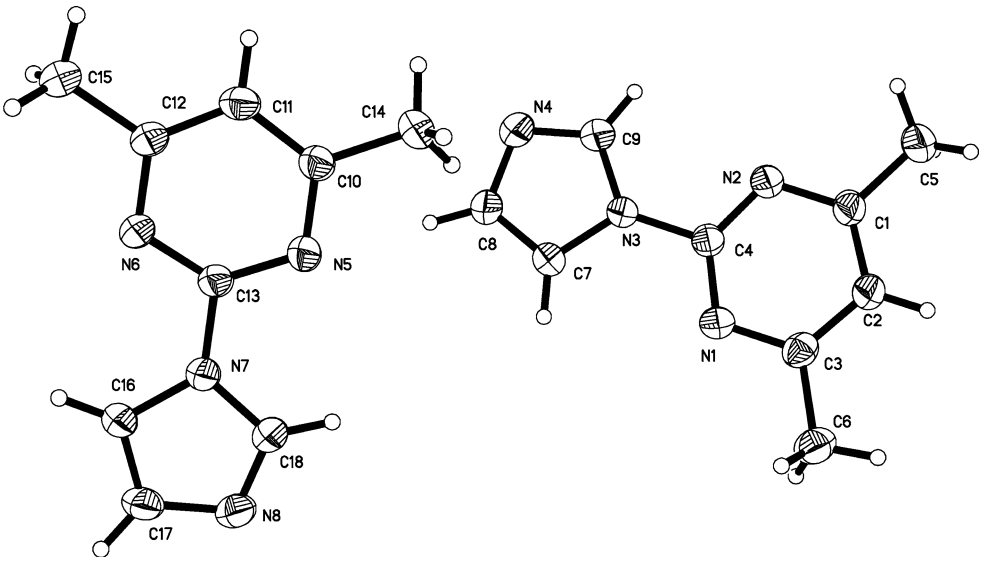

Fig. 1 Molecular structure of **1**

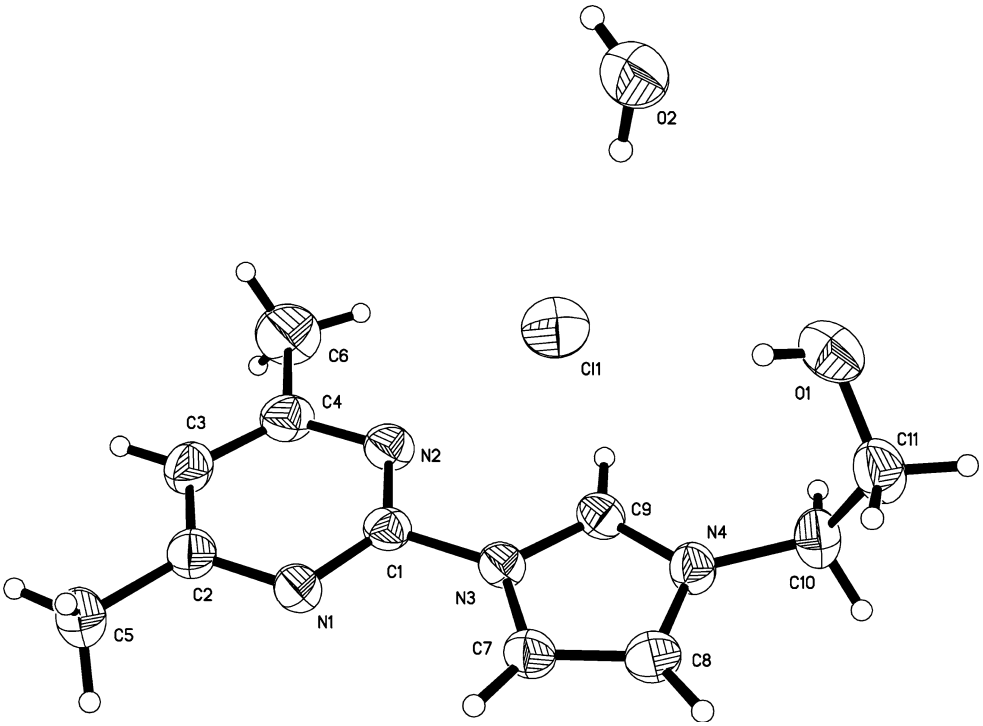

Fig. 2 Molecular structure of **2**·H_2O

into a one-dimensional chain structure. In the crystal of **2**·H_2O, there are many types of intermolecular C(O)–H···Cl and C–H···O hydrogen bonds (Fig. 3); water molecules and chloride anions link to each other to form parallelogram structures.

Next, we studied the direct reaction of **2** with $Pd(OAc)_2$ in THF. We expected that this reaction should produce the NHC-palladium complex $[Pd(NHC)_2Cl_2]$ as the main product. It was surprising that the ^1H NMR spectrum of the main product was very similar to that of **2**. It exhibits similar peaks for the imidazole ring, with a proton ratio of 1:1:1. The downfield NCHN signal is still present, clearly showing that a carbene complex has not been formed. Remarkable downfield chemical shifts were observed for the protons of the imidazole ring in the product compared to those of the free ligand **1**. This effect is common in such complexes, due to the induction of electron density by the metal resulting in effective deshielding the ligand protons in close proximity. These results indicate that the main product is a bis(*N*-arylimidazole) palladium complex. However, the expected NHC-palladium complex was not isolated from the reaction. In order to further investigate

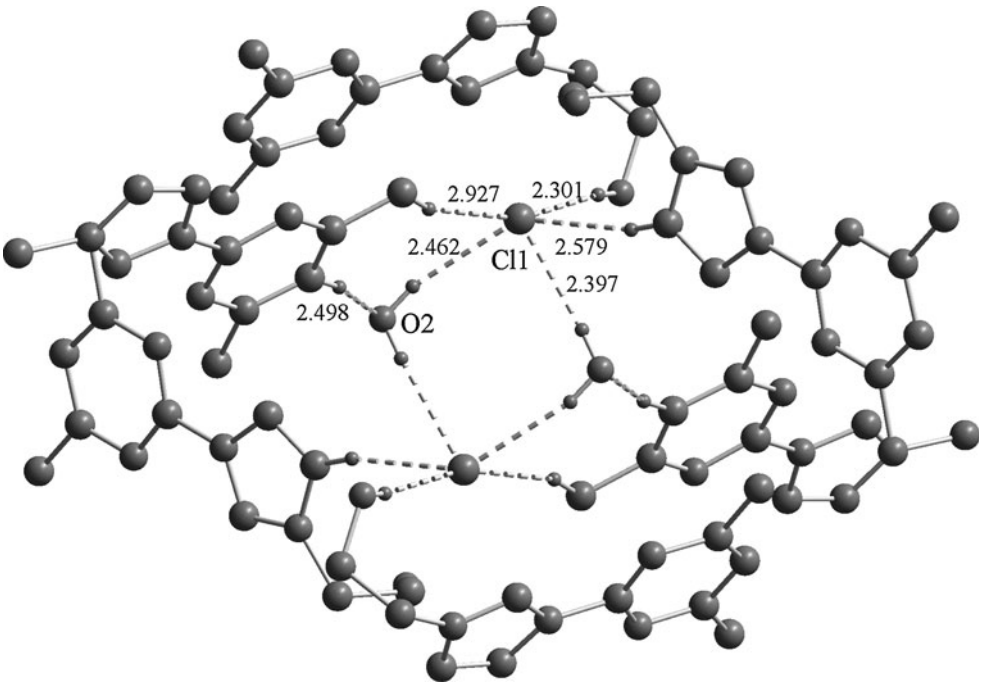

Fig. 3 Packing diagram of **2**·H_2O showing the hydrogen bonds. Non-hydrogen bonding H atoms are omitted for clarity

the nature of the product, its structure has been determined by single crystal X-ray diffraction.

As expected from the spectroscopic analysis, the main product **3** is a bis(*N*-arylimidazole) palladium complex. During the reaction, the 2-hydroxyethyl group from the imidazolium cation was lost, suggesting that the C–N bond can be split with relative ease in the presence of palladium. Although the exact mechanism of nitrogen deprotection is not clear, it is probable that nucleophilic attack of OAc^- on the CH_2 next to the positive charge is the first step of this transformation, and a few similar *N*-substituent cleavage reactions of imidazolium salts have been reported [18, 20–24]. We have observed this type of reaction with the related imidazolium salt [1-(2-hydroxyethyl)-3-methylimidazolium chloride] and $Pd(OAc)_2$. The analogous bis(*N*-methylimidazole) palladium complex **4** has also been synthesized. Even though the base K^{t}OBu was used, the main products of the above reactions were still **3** and **4**, and no NHC-palladium complexes were observed. In addition, an attempt to employ the silver carbene transfer route was unsuccessful. The molecular structures of complexes **3** and **4** are shown in Figs. 4 and 5, respectively. Selected bond lengths (Å) and angles (°) are listed in Table 1. The Pd atom in each complex is coordinated by two *N*-substituted imidazole ligands and two chloride atoms in a square-planar fashion. The two *N*-substituted imidazoles are mutually *trans*. The Pd–N and Pd-Cl bond lengths of complexes **3** and **4** are similar to those of related palladium imidazole complexes [18, 25, 26]. The crystal structure of complex **3** includes π-π stacking interactions between the imidazole and pyrimidine rings, which are used to construct the one-dimensional lamellar structure (Fig. 4).

Application in Suzuki coupling reactions

Although NHCs palladium complexes have been successfully used as highly active catalysts for coupling reactions, *N*-substituted imidazole palladium complexes have not been widely explored in this field [18, 26–29]. Initially, complex **3** was tested as a catalyst in the model coupling reaction of 4-bromotoluene with phenylboronic acid to ascertain the optimum conditions (Table 2). On screening a variety of bases (entries 1–5), Cs_2CO_3 was found to give the best results (98 % yield). A similar survey of solvents indicated that dioxane was much better than other solvents such as THF and DMF (entries 6–7). Toluene also afforded

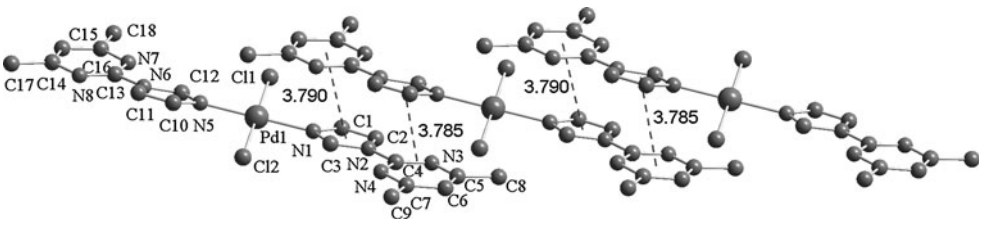

Fig. 4 Packing diagram of **3** showing the π–π stacking interactions. H atoms are omitted for clarity

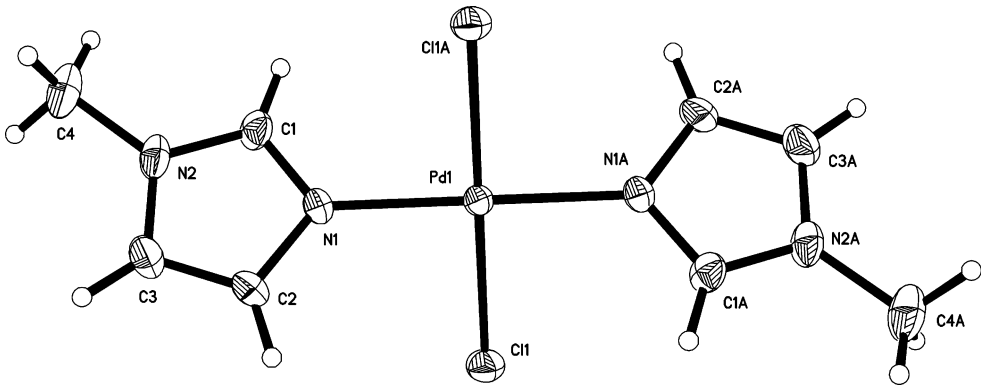

Fig. 5 Molecular structure of **4**. Symmetry code: A 1 − X, 1 − Y, −Z

Table 1 Selected bond lengths (Å) and angles (°) for complexes **3** and **4**

Complex	**3**	**4**
Pd(1)–Cl(1)	2.3023(9)	2.3026(15)
Pd(1)–Cl[(2) or (1A)]	2.2959(9)	2.3027(15)
Pd(1)–N(1)	2.028(3)	2.011(4)
Pd(1)–N[(5) or (1A)]	2.024(3)	2.011(4)
N(1)–Pd(1)–Cl[(2) or (1A)]	89.39(8)	90.06(14)
N(1)–Pd(1)–Cl(1)	91.07(8)	89.94(14)
N[(5) or (1A)]–Pd(1)–Cl(1)	89.61(8)	89.94(14)
N[(5) or (1A)]–Pd(1)–Cl[(2) or (1A)]	89.94(7)	90.06(14)

Table 2 Optimization of reaction conditions for the Suzuki coupling of 4-bromotoluene with phenyl boronic acid

Entry	Catalyst (mol%)	Base	Solvent	Yield[a] (%)
1	**3**(1)	K_3PO_4	Dioxane	86
2	**3**(1)	Na_2CO_3	Dioxane	72
3	**3**(1)	K_2CO_3	Dioxane	93
4	**3**(1)	Cs_2CO_3	Dioxane	98
5	**3**(1)	Na^tOBu	Dioxane	65
6	**3**(1)	Cs_2CO_3	THF	42
7	**3**(1)	Cs_2CO_3	DMF	27
8	**3**(1)	Cs_2CO_3	Toluene	95
9	**4**(1)	Cs_2CO_3	Dioxane	97

Reaction conditions: 4-bromotoluene (0.5 mmol), $PhB(OH)_2$ (0.75 mmol), base (1.0 mmol), solvent (3 mL), 100 °C, 12 h

[a] Isolated yields

good coupled product yield (95 %, entry 8). Furthermore, complex **4** also showed comparable activity, producing the product in excellent yield (97 %, entry 9).

In contrast to arylboronic acids, the Suzuki coupling reactions of heteroarylboronic acids have been relatively less reported [30–32]. Thus, in the following experiments, we investigated the Suzuki coupling of a variety of electronically and structurally diverse aryl bromides with pyridyl–$B(OH)_2$ catalyzed by complex **3** under the optimized

Table 3 Suzuki coupling of aryl bromides with heteroaryl–$B(OH)_2$ catalyzed by **3**

$$\text{Heteroaryl}-B(OH)_2+Ar_1-Br \xrightarrow[Cs_2CO_3]{\text{Cat 3,dioxane}} \text{Heteroaryl}-Ar_1$$

Entry	Heteroaryl	Ar_1	Yield[a] (%)
1	Pyridin-3-yl	Ph	96
2	Pyridin-3-yl	*p*-MeC_6H_4	94
3	Pyridin-3-yl	*p*-$OMeC_6H_4$	93
4	Pyridin-3-yl	*o*-MeC_6H_4	91
5	Pyridin-3-yl	2,6-$Me_2C_6H_3$	87
6[b]	Pyridin-3-yl	*p*-$NO_2C_6H_4$	90
7	Pyridin-3-yl	Pyridin-2-yl	95
8	Pyridin-4-yl	Ph	94
9	Pyridin-4-yl	*p*-MeC_6H_4	92
10	Pyridin-4-yl	Pyridin-2-yl	97
11	Thiophen-2-yl	Ph	82
12	Furan-2-yl	Ph	86

Reaction conditions: catalyst **3** (1 mol%), Ar_1Br (0.5 mmol), heteroaryl–$B(OH)_2$ (0.75 mmol), Cs_2CO_3 (1.0 mmol), dioxane (3 mL), 100 °C, 12 h

[a] Isolated yields

[b] 0.1 mol% **3**

reaction conditions (Table 3). Reaction of 3-pyridineboronic acid with bromobenzene gave high yield (96 %, entry 1). Good yields were also obtained for 4-bromotoluene and 4-bromoanisole (entries 2–3). *Ortho* substituents were tolerated and even the very sterically hindered 2-bromo-m-xylene provided the product in 87 % yield (entries 4–5). The electron-deficient 4-nitrobromobenzene could be coupled very efficiently with a catalytic loading as low as 0.1 mol% (entry 6). 2-Bromopyridine was found to be an efficient coupling partner in this system, giving 95 % yield (entry 7). Furthermore, the reactions of 4-pyridineboronic acids with aryl bromides proceeded smoothly to provide the desired products in good yields (entries 8–10). Finally, the couplings of thiophen-2-ylboronic acids and furan-2-ylboronic acids with bromobenzene also gave good yields (entries 11–12).

Conclusion

In summary, we have prepared and characterized two new carbene ligand precursors. The attempted synthesis of bis(NHC)palladium complexes via imidazolium salts with $Pd(OAc)_2$ resulted in unexpected palladium imidazole complexes, formed from C–N bond cleavage. These complexes were found to be efficient catalysts for the Suzuki reaction. Further research will focus on the reaction mechanism and the applications involving such complexes in other reactions.

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