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# (*N*-Heterocyclic carbene) ion-pair palladium complexes: Suzuki–Miyaura cross-coupling studies in neat water under mild conditions

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Ministry of Science and Technology, Taiwan, Grant/Award Number: MOST 107-2113-M-126-001-MY2 The synthesis and characterization of a series of (*N*-heterocyclic carbene)  $PdCl_3^{-}(NMe_3H)^+$  ion-pair complexes are presented. Applying the quaternary ammonium salt as the function with NHC–Pd(II) complexes yields the new ion-pair complexes. The NHC–Pd(II) ion-pair complexes work well by undergoing the Suzuki–Miyaura reaction with aryl chloride substrates in water under mild conditions in air at room temperature. Twenty products resulting from Suzuki–Miyaura coupling reactions carried out in the presence of the new NHC–Pd(II) ion-pair complex under mild optimal conditions were examined to determine the optimum yields.

#### **KEYWORDS**

*N*-donor, neat water reaction, NHC-palladium complexes, quaternary ammonium salts, Suzuki–Miyaura reaction

# **1** | INTRODUCTION

In cross-coupling reactions, among transition metal catalysts, palladium catalysts are extremely powerful and important for the construction of carbon-carbon as well as carbon-heteroatom bonds in the synthesis of bioactive, natural, conductive, and fluorescent compounds, which have wide applications in pharmaceutical and materials sciences.<sup>[1]</sup> Now, the Suzuki-Miyaura reaction is believed to be widely used in both laboratory and industry because of the great functional group tolerance of this transformation and the innocuous nature and properties of boronic acids, which are nontoxic and stable in heat, air, and moisture.<sup>[2]</sup> Earlier studies focused on the rich variety of organometallic nucleophiles that could be used for these reactions.<sup>[3]</sup> However, recent studies have focused on the activation of more challenging and varied electrophiles such as aryl chlorides under mild conditions.<sup>[4]</sup> This change in focus has resulted not only in increasing number of studies gaining hands-on experiences with

catalysts designed but also in increasing more insights and clear information of mechanistic studies explored by research groups.<sup>[1b,d,e,5]</sup>

Currently, chemists are most interested in developing green processes, as sustainability has become an important factor in every area of human activity.<sup>[6]</sup> Using safe solvents is one of the 12 principles of green chemistry, which aims to minimize hazardous effects such as toxicity, pollution, and waste treatment issues, among others.<sup>[6,7]</sup> In general, 80% of chemical wastes resulting from most reactions are attributed to the solvent. Moreover, solvents are expensive and are highly toxic, which limits their large-scale industrial applications. According to a recent survey, many pharmaceutical companies lay emphasis on green chemistry and consider water as a potentially useful and safe solvent because of its environmentally friendly and economically favorable properties, such as being nontoxic, nonflammable, economical, abundant, and noncorrosive. Water, an alternative to organic solvents, plays a critical role in research dealing with synthetic chemistry and catalysis.<sup>[8]</sup> Thus, using water as the only reaction medium is one of the challenges for modern chemists.

Water has been used as a medium of the Suzuki-Miyaura reaction in homogeneous and heterogeneous systems by Polshettiwar<sup>[9]</sup> and Ward groups,<sup>[10]</sup> respectively. However, they did not address the issues that follow: (i) the reactivity of low-cost aryl chlorides, (ii) low catalyst loading, (iii) the tolerance of functional groups, and (iv) mild reaction conditions.<sup>[8,10]</sup> In the past decade, the notable *N*-heterocyclic carbenes (NHCs) with catalytically useful ligands have been developed widely. Because the properties of nitrogen atoms in NHCs comprise the adjacent electron-withdrawing as well as *p*-electrondonating stabilize this structure both inductively by lowering the energy of the occupied  $\sigma$ -orbital and mesomerically by donating electron density into the empty *p*-orbital.<sup>[11]</sup>

Therefore, the development of efficient and air-stable systems using water as a solvent for the Suzuki–Miyaura reaction under mild conditions is of current interest. Figure 1 shows the effective NHC–Pd catalysts used in the Suzuki–Miyaura reaction in water or solvents mixed with water.<sup>[12]</sup>

In sum, quaternary ammonium salts not only perform well in C–C coupling reactions,<sup>[13]</sup> but they also serve as a phase-transfer cocatalyst,<sup>[14]</sup> with electrosteric properties to stabilize palladium active species by preventing the premature deactivation of Pd black.<sup>[15]</sup> In our previous studies, we have successfully demonstrated that alkylamines as auxiliary ligands in NHC–Pd(II) complexes showed good catalytic activities in cross-coupling reactions under mild conditions.<sup>[4e,16]</sup> Herein, ion-pair palladium complexes have shown remarkable catalytic activities toward the Suzuki–Miyaura reaction in IPA (Isopropanol)/water<sup>[,12d]</sup> and now we use the quaternary ammonium salt as the functional role instead of the sodium sulfonate salt on the NHC ligand to create new NHC-Pd(II) ion-pair complexes as in Figure 2.

#### 2 | EXPERIMENTAL

### 2.1 | Reagents and methods

Unless otherwise noted, all reactions were carried out in air at ambient temperature. All solvents and reagents were used as received. The reagents were purchased from



**FIGURE 1** Effective NHC-Pd complexes used in water for the Suzuki-Miyaura reaction

**FIGURE 2** Idea of designing active catalysts

Sigma-Aldrich, Acros, Merck, TEDIA, and Alfa-Aesar of USA. The imidazolium salts IPr·HCl and SIPr·HCl and NHC-palladium complexes were prepared following literature procedures, and their identity and purity were confirmed using <sup>1</sup>H NMR spectroscopy.<sup>[17]</sup>

All aryl halides and boronic acids were used as received. Technical-grade ethyl alcohol was used to carry out the Suzuki–Miyaura cross-coupling reactions. Flash chromatography was performed on silica gel 60 (230–400 mesh) using mixtures of hexane/ethyl acetate (10:1) unless otherwise noted.

<sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded either on Bruker-AV-300 or Bruker-AV-400 spectrometers in chloroform-*d* at ambient temperature unless stated otherwise and referenced internally to the residual solvent peak and reported as parts per million relative to tetramethylsilane. Elemental analyses were performed using a Heraeus CHN-O rapid analyzer or a FLASH 2000 Series Nitrogen and Carbon Analyzer instrument (Thermo). The Suzuki–Miyaura cross-coupling reactions were analyzed using gas chromatography–mass spectrometry (GC–MS) on a Bruker SCION 436 SQ instrument equipped with a Bruker BR-5 ms column. The MS detector was configured with an electronic impact ionization source.

## 2.1.1 | Synthesis of 1a

A vial was charged with [Pd(µ-Cl)Cl(IPr)]<sub>2</sub> (340 mg, 0.3 mmol) and trimethylamine hydrochloride (57 mg, 0.6 mmol) and chloroform (2 ml) as solvents. The solution was heated at 50°C, stirred for 15 h. It was then filtered through a pad of celite, and the filtrate was removed from the solvent to produce a pale yellow solid, to obtain the desired compound in 98% yield (389 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.07(d, 12H, J = 8 Hz,  $CH(CH_3)_2$ , 1.43(d, 12H, J = 4 Hz,  $CH(CH_3)_2$ ), 2.66(s, 9H,  $NH(CH_3)_3$ , 3.11(sep, 4H, J = 6.7 Hz,  $CH(CH_3)_2$ ), 7.06(s, 2H, CH=CH), 7.32(d, 4H, J = 8 Hz, ArH), 7.47(t, 2H, J = 8 Hz, ArH), 10.60(s, 1H, NH). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz) δ 23.3(s, CH(CH<sub>3</sub>)<sub>2</sub>), 26.2(s, CH(CH<sub>3</sub>)<sub>2</sub>), 28.7(s, CHiPr), 45.1(s, N (CH<sub>3</sub>)<sub>3</sub>), 124.0(s, CH), 124.9(s, CH aromatic), 130.0(s, C aromatic), 135.5(s, C aromatic), 147.2(s, C aromatic), 154.3(s, C<sub>carbene</sub>). Anal. Calcd for C<sub>30</sub>H<sub>46</sub>Cl<sub>3</sub>N<sub>3</sub>Pd: C, 54.47; H, 7.01; N, 6.35. Found: C, 54.02; H, 6.95; N, 6.85.

# 2.1.2 | Synthesis of 1b

The procedure for the preparation of 1b was similar to that used for 1a, but here a vial was charged with  $[Pd(\mu\text{-}Cl)Cl(SIPr)]_2$  (341 mg, 0.3 mmol) and trimethylamine hydrochloride (57 mg, 0.6 mmol) and

2 ml chloroform as solvents. The desired compound was obtained as a pale yellow solid in 93% yield (372 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.23(d, 12H, J = 4 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 1.52(d, 12H, J = 4 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 2.62(s, 9H, NH(CH<sub>3</sub>)<sub>3</sub>), 3.51(sep, 4H, J = 6.67 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 4.00(s, 4H, CH<sub>2</sub>), 7.28(d, 4H, J = 4 Hz, ArH), 7.39(t, 2H, J = 8 Hz, ArH), 10.40(s, 1H, NH). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  24.3(s, CH(CH<sub>3</sub>)<sub>2</sub>), 26.7(s, CH(CH<sub>3</sub>)<sub>2</sub>), 28.7(s, CHiPr), 45.1(s, N (CH<sub>3</sub>)<sub>3</sub>), 53.6(s, CH<sub>2</sub>), 124.4(s, CH aromatic), 129.2(s, *C* aromatic), 135.7(s, *C* aromatic), 148.1(s, *C* aromatic), 185.7(s, *C*<sub>carbene</sub>). Anal. Calcd for C<sub>30</sub>H<sub>48</sub>Cl<sub>3</sub>N<sub>3</sub>Pd: C, 54.31; H, 7.29; N, 6.33. Found: C, 54.14; H, 7.45; N, 6.47.

# 2.1.3 | Synthesis of 2a

The procedure for the preparation of 2a was similar to that used for 1a, but here a vial was charged with  $[Pd(\mu-Cl)Cl(IMes)]_2$  (289 mg, 0.3 mmol) and trimethylamine hydrochloride (57 mg, 0.6 mmol) and 2 ml chloroform as solvents. The desired compound was obtained as a pale yellow solid in 84% yield (290 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.31(s, 12H, CH<sub>3</sub>), 2.35(s, 6H,  $CH_3$ ), 2.66(s, 9H, NH( $CH_3$ )<sub>3</sub>), 7.00(d, 2H, J = 8 Hz, CH=CH + ArH, 9.92(s, 1H, NH). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz) δ 19.1(s, CH<sub>3</sub>), 21.1(s, CH<sub>3</sub>), 45.3(s, NH(CH<sub>3</sub>)<sub>3</sub>), 124.0(s, CH), 129.0(s, CH aromatic), 135.4(s, C aromatic), 136.8(s, C aromatic), 139.0(s, C aromatic), 150.5(s, Ccarbene). Anal. Calcd for C24H34Cl3N3Pd: C, 49.93; H, 5.94; N, 7.28. Found: C, 50.03; H, 6.03; N, 7.06.

# 2.1.4 | Synthesis of 2b

The procedure for the preparation of **2b** was similar to that used for **1a**, but here a vial was charged with  $[Pd(\mu-Cl)Cl(SIMes)]_2$  (288 mg, 0.3 mmol) and trimethylamine hydrochloride (57 mg, 0.6 mmol) and 2 ml chloroform as solvents. The desired compound was obtained as a pale yellow solid in 87% yield (304 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.30(s, 12H, CH<sub>3</sub>), 2.52(s, 12H, CH<sub>3</sub>), 2.65(s, 9H, NH(CH<sub>3</sub>)<sub>3</sub>), 3.97(s, 4H, CH<sub>2</sub>), 6.94(s, 4H, ArH), 10.20(s, 1, NH). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  19.4(s, CH<sub>3</sub>), 21.0(s, CH<sub>3</sub>), 45.2(s, N (CH<sub>3</sub>)<sub>3</sub>), 50.9(s, CH<sub>2</sub>), 129.3(s, CH aromatic), 135.2(s, C aromatic), 137.6(s, *C* aromatic), 138.2(s, *C* aromatic), 183.9(s, *C*<sub>carbene</sub>). Anal. Calcd for C<sub>24</sub>H<sub>36</sub>Cl<sub>3</sub>N<sub>3</sub>Pd: C, 49.76; H, 6.26; N, 7.25. Found: C, 49.85; H, 6.39; N, 7.14.

# 2.1.5 | Synthesis of 3

A vial was charged with 1a (258 mg, 0.39 mmol) and excess Na<sub>2</sub>CO<sub>3</sub> (0.5 g, 4.72 mmol) and 4 ml deionized

water as solvents. The mixture was stirred at room temperature for 5 h and extracted by dichloromethane and water thrice. The organic layer was dried over MgSO<sub>4</sub>, and the filtrate was pumped off to obtain the desired compound as a pale yellow solid in 89% yield (216 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.09(d, 12H, J = 8 Hz,  $CH_3$ ), 1.46(d, 12H, J = 4 Hz,  $CH_3$ ), 2.17(s, 9H, N( $CH_3$ )<sub>3</sub>), 3.14(seq, 4H, J = 6.7 Hz,  $CH(CH_3)_2$ ), 7.07(s, 2H, CH=CH), 7.34(d, J = 8 Hz, 4H, ArH), 7.50(t, J = 8 Hz, 2H, ArH). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  23.2(s,  $CH_3$ ), 26.2(s,  $CH_3$ ), 28.6(s,  $CH(CH_3)_3$ ), 50.9(s, N( $CH_3$ )<sub>3</sub>), 123.8(s, CH aromatic), 124.8(s, C aromatic), 130.0(s, C aromatic), 135.3(s, C aromatic), 146.7(s, C aromatic), 153.7(s,  $C_{carbene}$ ). Anal. Calcd for C<sub>30</sub>H<sub>45</sub>Cl<sub>2</sub>N<sub>3</sub>Pd: C, 57.65; H, 7.26; N, 6.72. Found: C, 57.33; H, 7.56; N, 6.84.

# 2.2 | X-ray data collection and structure refinement

The crystals of complexes 1a-1b were grown from the concentrated dichloromethane/hexane solution and isolated by filtration. Suitable crystals were mounted on a glass fiber using perfluoropolyether oil (Fomblin Y) and cooled rapidly under a stream of cold nitrogen gas to generate diffraction data at 150 K using a Bruker APEX2 diffractometer. The intensity data were collected in 1350 frames with increasing  $\omega$  (width of 0.5° per frame). Absorption correction was applied using SADABS.<sup>[18]</sup> The structure was determined by direct methods using a SHELXTL package.<sup>[19]</sup> All non-H atoms were located using successive Fourier maps, and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms. Some details of the data collection and refinement are presented in Table S1.

CCDC 1865339 and 1865340 are available in the supporting information of this paper. These crystal data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data\_request/cif.

#### 2.3 | GC-MS/MS conditions

All analyses were performed using a Bruker SCION 436 SQ system equipped with a split/splitless injection port and a CP-8400 autosampler with a 100-vial tray (Varian). The analytes were separated on a Bruker BR-5 ms capillary column (30 m  $\times$  0.25-mm id, and 0.25-µm film thickness, USA). Helium (99.999%) was used as the carrier gas (initial flow rate of 1 ml/min). The oven temperature gradient program was as follows: an initial

temperature of 50°C was held, increased to 250°C at  $10^{\circ}$ C/min and isothermal for 5 min, then ramped up to 280°C at 30°C/min and finally held for 1 min. A solvent delay time of 5 min was used. The column was reconditioned at 300°C for 2 min to eliminate all impurities co-extracted from the matrix and minimize carryover effects. The temperatures of the injection port and the MS transfer line were 250°C and 280°C, respectively. The mass spectrometer operated in the electron ionization positive mode (70 eV). MS spectra were recorded in a total ion current mode.

## 2.4 | Procedure of Suzuki-Miyaura crosscoupling reaction

Complexes 1-2 (1 mol%), base (11 equiv.), and phenylboronic acid (0.6 mmol) were added to a vial equipped with a magnetic bar and sealed with a screw cap. Deionized water (1 ml) was injected into the vial, and the mixture was stirred on a stirring plate at room temperature. Aryl chloride (0.5 mmol, if liquid) was then injected (or charged if solid), and the reaction was monitored using GC–MS. The crude product was extracted by ethyl acetate and  $H_2O$  and dried over MgSO<sub>4</sub>. Then, the organic filtrate was evaporated under vacuum, and the product was isolated using flash chromatography. The amount of product shown is the average of the two runs.

#### **3** | **RESULTS AND DISCUSSION**

# 3.1 | Synthesis of NHC ion-pair palladium (II) complexes

Our aim was to prepare new ion-pair palladium complexes that mimic the sulfonated NHC–Pd complexes. A series of NHC ion-pair palladium complexes **1–2** were obtained by reacting the corresponding [(NHC)PdCl<sub>2</sub>]<sub>2</sub> dimeric complexes with 2 equiv. trimethylamine hydrochloride in chloroform and heating the resultant product at 50°C overnight. Details of the synthetic routes are summarized in Scheme 1. The new ion-pair palladium complexes **1–2** bearing IPr, SIPr, IMes, and SIMes groups were isolated in good yields up to 84%–98% by evaporating the solvent and purifying them with hexane. Complexes **1–2** were all fully characterized using elemental analysis as well as <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. Among these complexes, complexes **1a–1b** solid-state structures were obtained and determined using X-ray diffraction.

Successful complexation of compounds 1-2 was confirmed by the presence of tetraalkylammonium protons at the downfield position ca. 9.92–10.60 ppm (see details



# **SCHEME 1** Synthesis of NHC ion-pair palladium complexes



in Section 2). The <sup>13</sup>C NMR of the carbene carbon finger signals was observed at 154.3 ppm for complex **1a**, 185.7 ppm for complex **1b**, 150.5 ppm for complex **2a**, and 183.9 ppm for complex **2b**, and these signals showed a tendency that was similar to that found in previous studies.<sup>[4e]</sup> Desirably, complexes **1–2** demonstrate high stability toward air and moisture and can be stored in air.

## well as the selected bond lengths and angles are shown in Figures 3 and 4. Crystal structures **1a–1b** were grown from the chloroform–hexane solution and exhibited a distorted square planar geometry with the two chloride ligands perpendicular to the plane of NHC and the third chloride ligand *trans* to it.

Similar to NHC-bearing complexes, the Pd–C<sub>carbene</sub> distance was located in the range of a single bond (1.961(4) and 1.973(4) Å for **1a** and 1.967(2) Å for **1b**), which was longer than that of the sulfonated NHC–Pd complex (1.957(5) Å)<sup>[12d]</sup> or the corresponding parent dimer complexes. The Pd–Cl bond lengths of complexes **1a–1b** fall between the values found for the bond lengths



Molecular structures of the two complexes **1a** and **1b** were identified using X-ray diffraction, and the images as



**FIGURE 3** Crystal structure of **1a** with thermal ellipsoids drawn at the 50% probability level. Selected bond lengths (Å) and angles (°): Pd(1)-C(1) 1.961(4), Pd(1)-Cl(1) 2.3058(12),Pd(1)-Cl(2) 2.2963(12), Pd(1)-Cl(3) 2.3816(11);C(1)-Pd(1)-Cl(1) 91.21(12), C(1)-Pd(1)-Cl(2) 89.05(12), C(1)-Pd(1)-Cl(3) 178.67(14);Cl(1)-Pd(1)-Cl(2) 178.67(14). Solvent and hydrogen atoms are omitted for clarity



**FIGURE 4** Crystal structure of **1b** with thermal ellipsoids drawn at the 50% probability level. Selected bond lengths (Å) and angles (°): Pd(1)-C(1) 1.967(2), Pd(1)-Cl(1) 2.3106(7), Pd(1) -Cl(2) 2.2832(7), Pd(1)-Cl(3) 2.3755(7); C(1)-Pd(1)-Cl(1) 90.89(7), C(1)-Pd(1)-Cl(3) 177.83(8), Cl(2)-Pd(1)-Cl(3) 88.30(3). Solvent and hydrogen atoms are omitted for clarity

of Pd-(µ-Cl) and Pd-Cl of the parent dimer complexes  $[Pd(\mu-Cl)Cl(IPr)]_2$ ,  $[Pd(\mu-Cl)Cl(SIPr)]_2$ : <sup>IPr</sup>Pd-( $\mu$ -Cl) 2.4029(9) Å; <sup>SIPr</sup>Pd-(µ-Cl) 2.4029(9) Å, Pd-Cl: 2.2963(12), 2.3058(12), 2.3816(11);2.2900(13), 2.3183(12), 2.3839(12) Å for **1a** and Pd-Cl: 2.2832(7), 2.3106(7), 2.3755(7) Å for 1b. Compared with the sulfonated NHC-Pd complex in Figure 2, Pd-Cl: 2.297(2), 2.318(2), 2.393(1) Å<sup>[12d]</sup> and both complexes **1a** and **1b** exhibited shorter Pd-Cl bond length that was formed by the strong trans-effect of NHC moiety. Complex 1b showed coordinative behavior similar to complex **1a** but with a disorder phenomenon in amine salt molecule employing C(29) as a reflective atom as shown in Figure 4.

### 3.3 | Catalytic studies

Generally, most of the Suzuki–Miyaura cross-couplings work well in organic solvents. As stated in Section 1, more efforts have been made to carry out the reaction in green solvents or water/organic mixed media under mild conditions. Utilizing the nature, properties, and the function of quaternary ammonium salt(s) of the new ion-pair palladium complexes, we envisioned that the new ionpair Pd complexes may catalyze the Suzuki–Miyaura cross-coupling in an aqueous medium. For initial catalytic studies, the coupling reaction of 2-chloro-*m*-xylene and phenylboronic acid was chosen as the benchmark model reaction (Table 1). The reaction was carried out at  $30^{\circ}$ C in water for 5 h, employing 1 mol% of palladium complex **1a**. Seven inorganic bases and four organic bases were used to screen the optimum conditions. The new complex **1a** performed coupling activities, and the inorganic base–sodium carbonate prevailed over other bases in catalyzing the reaction (entry 2). The screened organic bases did not work under the same condition (entries 8–11). The reason inorganic base–sodium carbonate works well is that Na<sub>2</sub>CO<sub>3</sub> dissolves faster in water and quickly synthesizes boronate species, which in turn reduces free Pd(II) to Pd(0).<sup>[20]</sup>

According to literature, the quantity of base in water will affect the cross-coupling yields; therefore, when an excess of base is used, higher yields are obtained.<sup>[21]</sup> The positive effect of using an excess of base was also investigated for the reaction with 2-chloro-m-xylene by using complex 1a as the catalyst (entries 12-16). With a threshold excess of base, this effect was no longer observed, and coupling yields were better when both 11 and 13 equivalents of base were used (entry 15: 82% vs. entry 16: 85%). The 11 equiv. of base was chosen as the optimal one because 13 equiv. of base loading led to vigorous stirring because of its poor solubility. However, in terms of the eco-friendly claim, this is a small flaw. Fortunately, the presence of an excess or high concentration of base did not lead to the formation of side products in our coupling reactions. When water was used as a solvent, the phenyl boronic acid reacted with water to yield the boronate species (PhB(OH)<sub>2</sub> + H<sub>2</sub>O  $\rightarrow$  PhB (OH)<sub>4</sub> + H<sup>+</sup>), and the pK<sub>a</sub> is the equilibrium constant. Depending on the corresponding law of mass action, [H<sup>+</sup>] could be the corresponding expression derived from the ion product of water at the respective temperature, using the initial concentration of Na<sub>2</sub>CO<sub>3</sub>. The resulting equation showed the concentration of boronate species as a function of the initial concentrations of Na<sub>2</sub>CO<sub>3</sub> and PhB(OH)<sub>2</sub>.<sup>[21]</sup> Therefore, the equivalent of base loading affected the catalytic behavior when water played the role of a solvent. Recently, studies on metal-halogen bond hydrolysis have been reported<sup>[22]</sup> for advanced investigations, by mimicking possible paths in the aqueous medium to yield the active complexes and determine which catalytic species worked in the catalytic cycle. Therefore, spectral studies on the possible hydrolysis of the Pd-Cl bond in pure water solution were carried out under two different conditions (Scheme 2). In the presence of excess Na<sub>2</sub>CO<sub>3</sub>, the reaction of complex 1a in aqueous medium synthesized complex 3 in nearly quantitative yield. Complex 3 was also characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy as well as elemental analysis in Section 2. The blank experiment without the base was also carried out, and the products of  $[Pd(\mu-Cl)Cl(IPr)]_2$  and complex 3 were in the ratio of 76% and 24%, respectively (the spectrum recorded

#### TABLE 1 Screening conditions of the Suzuki–Miyaura reaction in water<sup>a</sup>



<sup>a</sup>Reaction conditions: 0.5 mmol 2-chloro-*m*-xylene, 0.6 mmol phenylboronic acid, 4 equiv. base, 1 mol% Pd catalyst, 1 ml H<sub>2</sub>O, 30°C, and reaction time of 5 h.

<sup>b</sup>Determined by gas chromatography-mass spectrometry, average of two runs.

°1 mol% Pd loading.





is shown in Figure S1 in supporting information). Both complex 3 and  $[Pd(\mu-Cl)Cl(IPr)]_2$  when tested under the optimized condition to explore their catalytic activity resulted in 72% and 60%, respectively (entry 21 vs. entry 22). This result showed that complex 1a showed better activity and also hinted that the quaternary ammonium salts of complex 1a would possibly help transform complex 1a into the NHC-Pd(0) species in the catalytic cycle

in an aqueous medium. Köhler et al. studied the role of the base and quaternary ammonium salts in coupling reactions. Then, they investigated quaternary ammonium salts in detail by comparing the hydrophilic and hydrophobic precatalysts from the known accelerating effect of water in Suzuki reactions. Importantly, they concluded that an immiscible aryl halide served as an additional organic phase, and Pd(II) precatalyst was reduced to

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TABLE 2 Results of the Suzuki-Miyaura coupling of heterocyclic- and mono-substituted biaryl compounds <sup>a,b</sup>

<sup>a</sup>Reaction conditions: 0.5 mmol aryl chloride, 0.6 mmol arylboronic acid, 11 equiv. Na<sub>2</sub>CO<sub>3</sub>, 1 mol% **1a**,  $T = 30^{\circ}$ C, and 1 ml H<sub>2</sub>O. <sup>b</sup>Determined by gas chromatography–mass spectrometry, average of two runs; values in brackets represent isolated yield after column chromatography.





<sup>a</sup>Reaction conditions: 0.5 mmol aryl chloride, 0.6 mmol arylboronic acid, 11 equiv. Na<sub>2</sub>CO<sub>3</sub>, 1 mol% **1a**, and 1 ml H<sub>2</sub>O. <sup>b</sup>Determined by gas chromatography–mass spectrometry, average of two runs; values in brackets represent isolated yield after column chromatography. Pd(0) by boronate, which was generated in situ from the boronic acid and the base in aqueous systems. The oxidative addition step followed this needed a phase transfer of the reduced palladium in the organic phase species. Then, in the subsequent transmetallation step, the boronate was transferred into the organic phase in the presence of quaternary ammonium salts.<sup>[21]</sup>

In our catalytic studies, among the new ion-pair Pd complexes screened, the optimal complex was found bearing an unsaturated backbone with the substituted group -IPr; complex **1a** generated the best yield of 2,6-dimethylbiphenyl (entry 15 vs. entries 16–19). After the optimization of the most active catalyst (**1a**) and the quantity of base, the scope of the substrate to yield heterocyclic and *mono*-substituted biaryl compounds was investigated (Table 2).

It was highly effective in catalyzing the coupling reaction with nonsubstituted functional group substrates, such as chlorobenzene, 2-chlorothiophene, and 2-chloropyridine, and producing yields of over 70%-90%at 30°C in 0.75–7 h (**5a–5c**, Table 2). Both pyridine and thiophene derivatives did not resist the reaction. The electron-poor substrates, such as 4-chlorobenzaldehyde and 4-chlorobenzotrifluoride, provided yields of over 80%-90% in 1–3 h (**5d–5e**). The electron-rich substrates in both aryl chlorides and phenylboronic acid featuring single *ortho-, meta-*, or *para-*positioned functional groups were also successfully utilized to produce 74%–88% yields in 3–16 h without heating conditions (**5f–5i**).

Our catalyst system made use of ortho-, para-, or diortho-substituted aryl chlorides and ortho-, meta-, para-, or di-ortho-substituted arylboronic acids as coupling partners (Table 3). The electron-poor functional groups on aryl chlorides or phenylboronoic acids demonstrated good yields under milder conditions (30°C) and yields of over 80%-90% in 2-8 h (6a-6h). However, the electronrich substrates bearing di-ortho or one ortho or one metapositioned functional groups on both aryl chlorides and phenylboronics needed long time and heated conditions to produce yields over 80% (6i-6k). Unfortunately, when we tried to use both di-ortho-substituted functional group on aryl chlorides and phenylboronic acid, we obtained a lower yield even when the product was heated at 80°C  $(\geq 60\%)$ . A comparison with the effective catalysts used in the Suzuki-Miyaura reaction (Figure 1) showed that the ion-pair NHC-Pd complex 1a demonstrated better catalytic activities under milder conditions.

To verify if our prepared complexes are useful for the Suzuki reaction, we compared our system with other complexes that used *neat water* as the solvent reported in the literature: Çetinkaya,<sup>[23]</sup> Huynh,<sup>[24]</sup> and Shao<sup>[25]</sup> groups. When 4-chlorobenzaldehyde and phenylboronic acid were used as the starting materials, complex **1a** exhibited better activity under mild conditions (Table 4).

OHC $\leftarrow$ CI + $\bigcirc$ B(OH) <sub>2</sub> $\xrightarrow{1mol\% cat.}$ OHC $\leftarrow$ $\boxed{Ar_1}$ $\leftarrow$ $\boxed{Ar_2}$					
	HOOC	$\begin{bmatrix} & & & & & & \\ $	CI-Pd-CI N N cat. 9 Shao		$ \begin{array}{c}                                     $
Entry	Catalyst	Base	Time (h)	T (°C)	Yield (%) <sup>b</sup>
1	1a	Na <sub>2</sub> CO <sub>3</sub>	1	30	99
2	7	КОН	4	100	92
3	8	K <sub>2</sub> CO <sub>3</sub>	21	80	39
4 <sup>c</sup>	9	KO <sup>t</sup> Bu	24	80	93

**TABLE 4** Comparison of activities of Pd complexes in water<sup>a</sup>

<sup>a</sup>Reaction conditions: 4-chlorobenzaldehyde (0.5 mmol), phenylboronic acid (0.6 mmol), 1 mol% catalyst, and base in neat water. <sup>b</sup>Determined by gas chromatography–mass spectrometry.

°2 mol% catalyst loading.

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Also, it showed better catalytic activities than sulfonated *N*-heterocyclic carbene complexes.<sup>[12d]</sup> Moreover, we tried to understand the reaction mechanism of our catalytic process by carrying out the mercury test of catalysts.<sup>[26]</sup> The test required controlled experimental conditions with 2-chlorotoluene and phenylboronoic acid as starting materials and produced conversion values of 10% and 93% with and without the addition of mercury, respectively (Table S2 in supporting information). This experimental result in Table S2 shows that our system should be concluded as the heterogeneous system or on water catalytic system.

## 4 | CONCLUSIONS

A series of new NHC ion-pair anionic palladium complexes have been successfully prepared and fully characterized. The ion-pair NHC-Pd complex 1a showed robust and highly electron-rich properties, thus demonstrating efficient catalytic activities for the Suzuki-Miyaura crosscoupling reaction at room temperature conducted in single aqueous media-water as a solvent. Sterically hindered aryl chlorides and arylboronic acids were effectively utilized as substrates. We successfully used NHC-Pd(II) complexes equipped quaternary ammonium salts as the function to work well and replaced the original role of "additive reagent". This catalytic system with water as a solvent is attractive as it is cheap and is suitable for green chemistry. Currently, more efforts are being made to synthesize new complexes and investigate their catalytic potentials in cross-coupling reactions in water.

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#### AUTHOR CONTRIBUTIONS

**ming-tsz chen:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Yu-Hsuan Lin:** Data curation; formal analysis; investigation; resources; visualization. **Kun-Han Jian:** Data curation; investigation; resources.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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