

Article

# A Highly Efficient and Reusable Palladium(II)/Cationic 2,2'-Bipyridyl-Catalyzed Stille Coupling in Water

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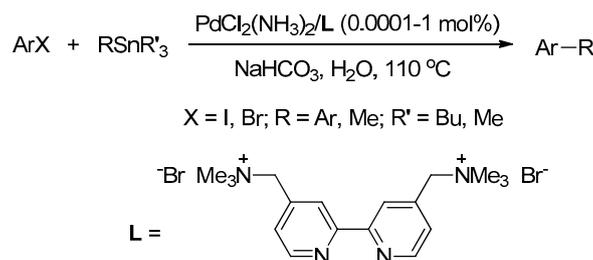
**Abstract:** A water-soluble PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>/cationic 2,2'-bipyridyl system was found to be a highly efficient catalyst for Stille coupling of aryl iodides and bromides with organostannanes. The coupling reaction was conducted at 110 °C in water, under aerobic conditions, in the presence of NaHCO<sub>3</sub> as a base to afford corresponding Stille coupling products in good to high yields. When aryltributylstannanes were employed, the reactions proceeded smoothly under a very low catalyst loading (as little as 0.0001 mol %). After simple extraction, the residual aqueous phase could be reused in subsequent runs, making this Stille coupling economical. In the case of tetramethylstannane, however, a greater catalyst loading (1 mol %) and the use of tetraethylammonium iodide as a phase-transfer agent were required in order to obtain satisfactory yields.

**Keywords:** stille coupling; water-soluble catalyst; reusable; aryl halides; organostannane

## 1. Introduction

The palladium-catalyzed cross-coupling of aryl halides or pseudo-halides with organo-stannanes, known as the Stille coupling, is one of the most powerful methods for the straightforward construction of carbon–carbon bonds in synthetic chemistry [1–3]. The main advantages of the Stille coupling reaction include the stability and functional group tolerance of stannanes, the broad reaction scope of aryl halides and pseudo-halides, and its chemoselectivity; therefore, this reaction has been widely applied in natural product synthesis [4–10], biological research [11], and for pharmaceutical purposes [12]. Stille coupling reactions are generally carried out in organic solvents under homogeneous catalysis, and, hence, it is difficult to separate the catalyst from the reaction mixture and then recycle it at the end of the reaction, leading to wastage of precious metals. Therefore, the development of a recyclable and reusable catalytic system is highly attractive and valuable from the viewpoints of green chemistry and practical application. To circumvent this problem, several new strategies involving heterogenized homogeneous catalysts have been developed for recycling and reusing catalysts, including the use of Pd complexes supported by silica gel [13,14], polymers [15,16], nanoparticles [17,18], porous metal–organic frameworks [19], bulky proazaphosphatane ligands [20], mesoporous silica [21–26], and metal nanoparticles [27–42]. Alternatively, combinations of palladium complexes with several green solvents, such as ionic liquids [43–45], polyethylene glycol [46–50], H<sub>2</sub>O [51–54], or H<sub>2</sub>O in the presence of surfactants [55–57], have also been applied as reusable catalytic systems.

We recently reported that cationic 2,2'-bipyridyl is an excellent ligand to bring PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub> into the aqueous phase, in order to efficiently perform several carbon–carbon bond-formation reactions, and the residual aqueous solution can be reused for the next run [58–63]. As part of our continuing efforts in the development of water-soluble and reusable catalytic systems for carbon–carbon bond-forming reactions, we report, herein, on a reusable PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>/cationic 2,2'-bipyridyl catalytic system, which can be applied for Stille coupling of aryl halides with organostannanes in water under aerobic conditions, in the presence of NaHCO<sub>3</sub> as a base. The loading amount of the catalyst in a single batch reaction could be reduced to as little as 0.0001 mol % (1 ppm), still affording products in high yields (Scheme 1).



**Scheme 1.** Palladium-catalyzed Stille coupling in water.

## 2. Results and Discussion

### 2.1. Optimization of Stille Coupling Conditions

Water-soluble cationic 2,2'-bipyridyl ligand **L** was synthesized according to our previously-published method [58,59]. The catalytic system was prepared by mixing equimolar amounts of PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub> and **L** in water, and then it was stored under air. Stock solutions of this catalytic system were prepared at different concentrations to obtain various catalyst loadings. In order to discover the optimal conditions, the coupling of 4'-iodoacetophenone (**1a**, 1 mmol) and PhSnBu<sub>3</sub> (**2a**, 1.2 mmol) in the presence of PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>/L (1 mol %) in water (3 mL), at 110 °C for 0.5 h, was first investigated, and the results are summarized in Table 1.

**Table 1.** Optimization studies for the Pd(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/L-catalyzed Stille coupling of 4'-iodoacetophenone (**1a**) and PhSnBu<sub>3</sub> (**2a**) in water <sup>a</sup>.

Entry	Base	Yield (%) <sup>b</sup>
1	KOH	70
2	K <sub>3</sub> PO <sub>4</sub>	75
3	K <sub>2</sub> CO <sub>3</sub>	85
4	KF	60
5	KOAc	74
6	NaHCO <sub>3</sub>	95
7 <sup>c</sup>	NaHCO <sub>3</sub>	32
8 <sup>d</sup>	NaHCO <sub>3</sub>	35
9 <sup>e</sup>	NaHCO <sub>3</sub>	0
10 <sup>f</sup>	NaHCO <sub>3</sub>	90
11 <sup>g</sup>	NaHCO <sub>3</sub>	95

<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), base (2 mmol), PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>/L (1 mol %), H<sub>2</sub>O (3 mL) at 110 °C for 0.5 h; <sup>b</sup> Isolated yields; <sup>c</sup> In the absence of **L**; <sup>d</sup> 2,2'-Bipyridyl was used as the ligand; <sup>e</sup> 2,2'-Bipyridine-4,4'-dicarboxylic acid was used as the ligand; <sup>f</sup> PhSnCl<sub>3</sub> (1.2 mmol) was used; <sup>g</sup> PhSnMe<sub>3</sub> (1.2 mmol) was used.

Initially, several commonly-used bases were screened, and it was found that the use of NaHCO<sub>3</sub> provided the Stille coupling product in a 95% yield, which was higher than the yields obtained using other inorganic bases (Entries 1–6). Then, two additional experiments were performed to demonstrate



**Table 2.** Pd-catalyzed Stille coupling of aryl iodides (**1**) and aryltributylstannane (**2**) in water <sup>a</sup>.

Entry	Aryl Iodide	ArSnBu <sub>3</sub>	[Pd] (mol %)	Duration (h)	Yield (%) <sup>b</sup>
1	4-IC <sub>6</sub> H <sub>4</sub> COMe <b>1a</b>	C <sub>6</sub> H <sub>5</sub> SnBu <sub>3</sub> <b>2a</b>	0.01	3	<b>3aa</b> (98)
2 <sup>c</sup>	<b>1a</b>	<b>2a</b>	0.0001	48	<b>3aa</b> (82)
3	<b>1a</b>	4-FC <sub>6</sub> H <sub>5</sub> SnBu <sub>3</sub> <b>2b</b>	0.01	3	<b>3ab</b> (97)
4	<b>1a</b>	4-MeOC <sub>6</sub> H <sub>5</sub> SnBu <sub>3</sub> <b>2c</b>	0.01	3	<b>3ac</b> (93)
5 <sup>c</sup>	<b>1a</b>	<b>2c</b>	0.0001	48	<b>3ac</b> (72)
6	4-IC <sub>6</sub> H <sub>4</sub> CN <b>1b</b>	<b>2a</b>	0.01	3	<b>3ba</b> (91)
7 <sup>c</sup>	<b>1b</b>	<b>2a</b>	0.0001	48	<b>3ba</b> (75)
8	<b>1b</b>	<b>2b</b>	0.01	3	<b>3bb</b> (93)
9	<b>1b</b>	<b>2c</b>	0.01	3	<b>3bc</b> (90)
10	C <sub>6</sub> H <sub>5</sub> I <b>1c</b>	<b>2a</b>	0.01	6	<b>3ca</b> (95)
11	<b>1c</b>	<b>2b</b>	0.01	6	<b>3cb</b> (95)
12	<b>1c</b>	<b>2c</b>	0.01	6	<b>3cc</b> (90)
13	4-IC <sub>6</sub> H <sub>4</sub> Me <b>1d</b>	<b>2a</b>	0.01	6	<b>3da</b> (89)
14 <sup>c</sup>	<b>1d</b>	<b>2a</b>	0.0001	48	<b>3da</b> (59)
15	<b>1d</b>	<b>2b</b>	0.01	6	<b>3db</b> (82)
16	<b>1d</b>	<b>2c</b>	0.01	6	<b>3dc</b> (88)
17	4-IC <sub>6</sub> H <sub>4</sub> OMe <b>1e</b>	<b>2a</b>	0.01	6	<b>3cc</b> (94)
18 <sup>c</sup>	<b>1e</b>	<b>2a</b>	0.0001	48	<b>3cc</b> (66)
19	<b>1e</b>	<b>2b</b>	0.01	6	<b>3eb</b> (84)
20	<b>1e</b>	<b>2c</b>	0.01	6	<b>3ec</b> (80)

<sup>a</sup> Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), NaHCO<sub>3</sub> (2 mmol), H<sub>2</sub>O (3 mL) at 110 °C; <sup>b</sup> Isolated yields;

<sup>c</sup> **1** (10 mmol), **2** (12 mmol), NaHCO<sub>3</sub> (20 mmol), H<sub>2</sub>O (30 mL) at 110 °C.

Analogous reactions of cheaper aryl bromides were also investigated (Table 3). Activated aryl bromides **4a** and **4b**, were efficiently coupled with **2a–c** under conditions identical to those used for aryl iodides; however, a longer reaction time was required (Entries 1–9).

**Table 3.** Pd-catalyzed Stille coupling of aryl bromides (**4**) and aryltributylstannane (**2**) in water <sup>a</sup>.

Entry	Aryl Bromide	ArSnBu <sub>3</sub>	[Pd] (mol %)	Duration (h)	Yield (%) <sup>b</sup>
1	4-BrC <sub>6</sub> H <sub>4</sub> COMe <b>4a</b>	C <sub>6</sub> H <sub>5</sub> SnBu <sub>3</sub> <b>2a</b>	0.01	6	<b>3aa</b> (96)
2 <sup>c</sup>	<b>4a</b>	<b>2a</b>	0.0001	48	<b>3aa</b> (70)
3	<b>4a</b>	4-FC <sub>6</sub> H <sub>5</sub> SnBu <sub>3</sub> <b>2b</b>	0.01	6	<b>3ab</b> (96)
4	<b>4a</b>	<b>2b</b>	0.001	12	<b>3ab</b> (91)
5	<b>4a</b>	4-MeOC <sub>6</sub> H <sub>5</sub> SnBu <sub>3</sub> <b>2c</b>	0.01	6	<b>3ac</b> (92)
6	<b>4a</b>	<b>2c</b>	0.001	12	<b>3ac</b> (95)
7	4-BrC <sub>6</sub> H <sub>4</sub> CN <b>4b</b>	<b>2a</b>	0.01	6	<b>3ba</b> (93)
8	<b>4b</b>	<b>2b</b>	0.01	8	<b>3bb</b> (90)
9	<b>4b</b>	<b>2c</b>	0.01	8	<b>3bc</b> (88)
10	C <sub>6</sub> H <sub>5</sub> Br <b>4c</b>	<b>2a</b>	1	24	<b>3ca</b> (92)
11	<b>4c</b>	<b>2b</b>	1	36	<b>3cb</b> (96)
12	<b>4c</b>	<b>2c</b>	1	36	<b>3cc</b> (94)
13	4-BrC <sub>6</sub> H <sub>4</sub> OMe <b>4e</b>	<b>2a</b>	1	24	<b>3cc</b> (84)
14	<b>4e</b>	<b>2b</b>	1	24	<b>3eb</b> (83)
15	<b>4e</b>	<b>2c</b>	1	36	<b>3ec</b> (97)
16 <sup>d</sup>	4-BrC <sub>6</sub> H <sub>4</sub> OH <b>4f</b>	<b>2a</b>	1	3	<b>3fa</b> (90)
17 <sup>d</sup>	<b>4f</b>	<b>2a</b>	0.01	12	<b>3fa</b> (96)
18 <sup>c,d</sup>	<b>4f</b>	<b>2a</b>	0.0001	48	<b>3fa</b> (56)
19 <sup>d</sup>	<b>4f</b>	<b>2b</b>	0.01	12	<b>3fb</b> (94)
20 <sup>d</sup>	<b>4f</b>	<b>2c</b>	0.01	12	<b>3fc</b> (88)

<sup>a</sup> Reaction conditions: **4** (1 mmol), **2** (1.2 mmol), NaHCO<sub>3</sub> (2 mmol), H<sub>2</sub>O (3 mL) at 110 °C; <sup>b</sup> Isolated yields;

<sup>c</sup> **4** (10 mmol), **2** (12 mmol), NaHCO<sub>3</sub> (20 mmol), H<sub>2</sub>O (30 mL) at 110 °C; <sup>d</sup> 3 equiv. of NaHCO<sub>3</sub> was applied.

A very low catalyst loading could also be applied when employing electron-withdrawing aryl bromides. For example, the coupling of **4a** and **2a** furnished **3aa** in a 70% yield with a 1 ppm catalyst

loading in 48 h (Entry 2). In the cases of **4c** and electron-donating **4e**, the reactions were much slower than those of the iodide analogs. Hence, conduction of the reaction using a 1 mol % catalyst loading and prolongation of the reaction time were necessary in order to obtain satisfactory yields (Entries 10–15). These results indicated that the oxidative addition of a carbon–bromine bond to palladium may be the rate-determining-step in this catalytic cycle. Surprisingly, the reaction rate was dramatically enhanced when deactivated 4-bromophenol (**4f**) was employed (Entries 16–20). Compound **4f** was soluble in basic aqueous solution, producing 4-bromophenoxide. This aryl bromide then underwent oxidative addition to palladium under homogeneous conditions, making this step much faster than for other water-insoluble aryl bromides. Taking advantage of this water-soluble property, **4f** coupled with **2a** very smoothly, providing a 56% yield (TON = 560,000) of **3fa** under a catalyst loading of only 1 ppm at 110 °C for 48 h (Entry 18).

The utility of this reaction protocol for the formation of  $Csp^2$ – $Csp^3$  carbon–carbon bonds was also evaluated. As illustrated in Table 4, the coupling of **1a** and  $SnMe_4$ , **5**, using 1 mol % catalyst loading at 110 °C for 24 h, gave **6a** in only a 51% yield (Entry 1). The use of two equivalents of **5** in the reaction was owing to its low boiling point (74–75 °C). In order to improve upon this outcome, a phase-transfer agent was added into the reaction [55–57]. The use of tetrabutylammonium bromide (TBAB) and tetrabutylammonium hydroxide (TBAOH) led to the formation of **6a** in yields of 63% and 70%, respectively (Entries 2 and 3). It is worth noting that a 91% isolated yield of **6a** could be achieved when tetraethylammonium iodide (TEAI) was applied in the reaction system (Entry 4). Thus, **1b** coupled with **5** under such conditions afforded **6b** in a 78% yield (Entry 5). However, a low product yield was obtained when electron-rich **1e** was utilized (Entry 6). Activated aryl bromides **4a** and **4b** were also coupled with **5**, furnishing **6a** and **6b** in 40% and 31% yields, respectively (Entries 7 and 8).

**Table 4.** Pd-catalyzed Stille coupling of aryl halides (**1** or **4**) and tetramethylstannane (**5**) in water <sup>a</sup>.

Entry	Aryl Halide	Duration (h)	Yield (%) <sup>b</sup>
1 <sup>c</sup>	4-IC <sub>6</sub> H <sub>4</sub> COMe <b>1a</b>	24	<b>6a</b> (51)
2 <sup>d</sup>	<b>1a</b>	24	<b>6a</b> (63)
3 <sup>e</sup>	<b>1a</b>	24	<b>6a</b> (70)
4	<b>1a</b>	24	<b>6a</b> (91)
5	4-IC <sub>6</sub> H <sub>4</sub> CN <b>1b</b>	24	<b>6b</b> (78)
6	4-IC <sub>6</sub> H <sub>4</sub> OMe <b>1e</b>	36	<b>6e</b> (42)
7	4-BrC <sub>6</sub> H <sub>4</sub> COMe <b>4a</b>	48	<b>6a</b> (40)
8	4-BrC <sub>6</sub> H <sub>4</sub> CN <b>4b</b>	48	<b>6b</b> (31)

<sup>a</sup> Reaction conditions: **1** or **4** (1 mmol), **5** (2 mmol), PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>/L (1 mol %), tetraethylammonium iodide (TEAI, 1 mmol), NaHCO<sub>3</sub> (2 mmol), H<sub>2</sub>O (3 mL) at 110 °C; <sup>b</sup> Isolated yields; <sup>c</sup> In the absence of TEAI;

<sup>d</sup> Tetrabutylammonium bromide (TBAB, 1 mmol) was used. <sup>e</sup> Tetrabutylammonium hydroxyl (TBAOH, 1 mmol) was used.

### 3. Experimental Section

#### 3.1. General Information

Chemicals were purchased from commercial suppliers and were used without further purification. Cationic 2,2'-bipyridyl ligand was prepared according to published procedures [58,59]. Aryltributylstannanes were prepared according to known procedures [64]. All <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> at 25 °C on a Bruker Biospin AG 300 NMR spectrometer (Bruker Co., Faellanden, Switzerland), in which chemical shifts (δ in ppm) were determined with respect to the non-deuterated solvent as a reference (<sup>1</sup>H-NMR: CHCl<sub>3</sub> at 7.24, non-deuterated DMSO at 2.49 ppm; <sup>13</sup>C-NMR: CDCl<sub>3</sub> at 77.0, DMSO-*d*<sub>6</sub> at 39.5 ppm). Melting points were recorded using a melting point apparatus, and were uncorrected.

### 3.2. Typical Stille Coupling Procedure

A sealable tube, equipped with a magnetic stirring bar, was charged with aryl halide (1 mmol), organotin (1.2 mmol), NaHCO<sub>3</sub> (2 mmol), and H<sub>2</sub>O (2 mL). In the case of tetramethyltin, the addition of tetraethylammonium iodide (TEAI, 1 mmol) was required. After the addition of PdCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>/L aqueous solution (1 mL H<sub>2</sub>O; different concentrations were required for various substrate/catalyst ratios), the tube was sealed under air using a Teflon-coated screw cap. The reaction vessel was then placed in an oil bath at 110 °C for the indicated reaction duration (see Tables 2–4). After cooling of the reaction mixture to room temperature, the aqueous solution was extracted with hexane or ethyl acetate; the organic phase was dried over MgSO<sub>4</sub>, and the solvent was then removed under vacuum. Column chromatography on silica gel afforded the desired product (see Supplementary Materials for the copies of NMR spectra).

**4-Phenylacetophenone (3aa)**, Table 2, Entries 1 and 2, and Table 3, Entries 1 and 2). CAS: 92-91-1; white solid (m.p. = 119–121 °C, lit. [59] 119–121 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.62 (s, 3H), 7.39–7.41 (m, 1H), 7.44–7.48 (m, 2H), 7.60–7.63 (m, 2H), 7.66–7.68 (m, 2H), 8.01–8.03 (m, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 26.6, 127.1(2C), 127.2 (2C), 128.2, 128.8 (2C), 128.9 (2C), 135.7, 139.8, 145.7, 197.7.

**4-Acetyl-4'-fluorobiphenyl (3ab)**, Table 2, Entry 3, and Table 3, Entries 3 and 4). CAS: 720-74-1; white solid (m.p. = 103–104 °C, lit. [59] 103–104 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.62 (s, 3H), 7.14 (t, *J* = 9.0 Hz, 2H), 7.55–7.63 (m, 4H), 7.99–8.02 (m, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 26.6, 115.9 (d, *J*<sub>C-F</sub> = 22.5 Hz, 2C), 127.0 (2C), 128.8 (d, *J*<sub>C-F</sub> = 7.5 Hz, 2C), 128.9 (2C), 135.8, 136.0 (d, *J*<sub>C-F</sub> = 3.0 Hz), 144.7, 163.0 (d, *J*<sub>C-F</sub> = 247.5 Hz), 197.7.

**4-Acetyl-4'-methoxybiphenyl (3ac)**, Table 2, Entries 4 and 5, and Table 3, Entries 5 and 6). CAS: 13021-18-6; pale yellow solid (m.p. = 153–155 °C, lit. [59] 153–155 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.60 (s, 3H), 3.84 (s, 3H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 26.6, 55.3, 114.3 (2C), 126.5 (2C), 128.3 (2C), 128.9 (2C), 132.1, 135.2, 145.3, 159.8, 197.7.

**4-Phenylbenzotrile (3ba)**, Table 2, Entries 6 and 7, and Table 3, Entry 7). CAS: 2920-38-9; white solid (m.p. = 89–91 °C, lit. [65] 89–90 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.38–7.50 (m, 3H), 7.55–7.59 (m, 2H), 7.65–7.73 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 110.8, 118.9, 127.2 (2C), 127.7 (2C), 128.6, 129.1 (2C), 132.6 (2C), 139.1, 145.6.

**4-(4-Fluorophenyl)benzotrile (3bb)**, Table 2, Entry 8 and Table 3, Entry 8). CAS: 10540-31-5; white solid (m.p. = 115–117 °C, lit. [66] 116–118 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.15 (t, *J* = 9.0 Hz, 2H), 7.52–7.56 (m, 2H), 7.60–7.63 (m, 2H), 7.68–7.61 (m, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 110.9, 115.9 (d, *J*<sub>C-F</sub> = 21.8 Hz, 2C), 118.8, 127.5 (2C), 128.9 (d, *J*<sub>C-F</sub> = 8.3 Hz, 2C), 132.6 (2C), 135.2 (d, *J*<sub>C-F</sub> = 3.0 Hz), 144.6, 163.1 (d, *J*<sub>C-F</sub> = 246.8 Hz).

**4'-Methoxybiphenyl-4-carbonitrile (3bc)**, Table 2, Entry 9 and Table 3, Entry 9). CAS: 58743-77-4; pale yellow solid (m.p. = 104–106 °C, lit. [67] 104–105 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.84 (s, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.60–7.69 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 55.4, 100.4 114.5 (2C), 119.1, 127.1 (2C), 128.3 (2C), 131.4, 132.5 (2C), 145.2, 160.2.

**Biphenyl (3ca)**, Table 2, Entry 10 and Table 3, Entry 10). CAS: 92-52-4; white solid (m.p. = 71–72 °C, lit [68] 71–72 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.34–7.40 (m, 2H), 7.44–7.49 (m, 4H), 7.61–7.64 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 127.1 (4C), 127.2(2C), 128.7 (4C), 141.2 (2C).

**4-Fluorobiphenyl (3cb)**, Table 2, Entry 11 and Table 3, Entry 11). CAS: 324-74-3; white solid (m.p. = 72–73 °C, lit. [69] 72–73 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.10–7.15 (m, 2H), 7.34–7.37 (m, 1H), 7.41–7.46 (m, 2H), 7.52–7.61 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 115.6 (d, *J*<sub>C-F</sub> = 21.0 Hz, 2C), 127.0 (2C), 127.2, 128.7 (d, *J*<sub>C-F</sub> = 8.3 Hz, 2C), 128.8 (2C), 137.3 (d, *J*<sub>C-F</sub> = 3.0 Hz), 140.2, 162.4 (d, *J*<sub>C-F</sub> = 245.3 Hz).

*4-Methoxybiphenyl* (**3cc**, Table 2, Entries 12, 17 and 18, and Table 3, Entries 12 and 13). CAS: 613-37-6; white solid (m.p. = 85–87 °C, lit. [59] 85–87 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.85 (s, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.31–7.34 (m, 1H), 7.40–7.45 (m, 2H), 7.52–7.58 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 55.3, 114.2 (2C), 126.6, 126.7 (2C), 128.1 (2C), 128.7 (2C), 133.7, 140.8, 159.1.

*4-Methylbiphenyl* (**3da**, Table 2, Entries 13 and 14). CAS: 644-08-6; white solid (m.p. = 43–45 °C, lit. [59] 43–45 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.41 (s, 3H), 7.24–7.28 (m, 2H), 7.34–7.36 (m, 1H), 7.42–7.47 (m, 2H), 7.50–7.53 (m, 2H), 7.58–7.61 (m, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 21.1, 126.8, 126.9 (4C), 128.7 (2C), 129.5 (2C), 137.0, 138.3, 141.1.

*4-Fluoro-4'-methylbiphenyl* (**3db**, Table 2, Entry 15). CAS: 72093-43-7; white solid (m.p. = 79–81 °C, lit. [70] 78–79 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.39 (s, 3H), 7.11 (t, *J* = 9.0 Hz, 2H), 7.23–7.25 (m, 2H), 7.42–7.45 (m, 2H), 7.50–7.54 (m, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 21.1, 115.6 (d, *J*<sub>C-F</sub> = 21.8 Hz, 2C), 126.8 (2C), 128.5 (d, *J*<sub>C-F</sub> = 8.3 Hz, 2C), 129.5 (2C), 137.0, 137.2 (d, *J*<sub>C-F</sub> = 3.0 Hz), 137.4, 162.3 (d, *J*<sub>C-F</sub> = 247.5 Hz).

*4-Methoxy-4'-methylbiphenyl* (**3dc**, Table 2, Entry 16). CAS: 53040-92-9; white solid (m.p. = 113–114 °C, lit. [59] 113–114 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.42 (s, 3H), 3.87 (s, 3H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 21.0, 55.2, 114.1 (2C), 126.5 (2C), 127.9 (2C), 129.4 (2C), 133.6, 136.3, 137.9, 158.9.

*4-Fluoro-4'-methoxybiphenyl* (**3eb**, Table 2, Entry 19 and Table 3, Entry 14). CAS: 450-39-5; white solid (m.p. = 88–90 °C, lit. [59] 88–90 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.84 (s, 3H), 6.94–6.99 (m, 2H), 7.07–7.13 (m, 2H), 7.44–7.51 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 55.3, 114.2 (2C), 115.5 (d, *J*<sub>C-F</sub> = 21.8 Hz, 2C), 128.0 (2C), 128.2 (d, *J*<sub>C-F</sub> = 7.5 Hz, 2C), 132.8, 136.9 (d, *J*<sub>C-F</sub> = 3.0 Hz), 159.1, 162.0 (d, *J*<sub>C-F</sub> = 243.8 Hz).

*4,4'-Dimethoxybiphenyl* (**3ec**, Table 2, Entry 20 and Table 3, Entry 15). CAS: 2132-80-1; pale yellow solid (m.p. = 178–180 °C, lit. [68] 178–180 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 3.84 (s, 6H), 6.93–6.97 (m, 4H), 7.45–7.49 (m, 4H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 55.3 (2C), 114.1 (4C), 127.7 (4C), 133.4 (2C), 158.6 (2C).

*4-Phenylphenol* (**3fa**, Table 3, Entries 16–18). CAS: 92-69-3; white solid (m.p. = 148–150 °C, lit. [59] 148–150 °C). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 6.86 (d, *J* = 9.0 Hz, 2H), 7.25–7.28 (m, 1H), 7.36–7.57 (m, 6H), 9.57 (br, 1H); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 115.7 (2C), 126.0 (2C), 126.4, 127.8 (2C), 128.8 (2C), 130.9, 140.2, 157.2.

*4-Hydroxy-4-fluorobiphenyl* (**3fb**, Table 3, Entry 19). CAS: 324-94-7; white solid (m.p. = 168–170 °C, lit. [71] 167–170 °C). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 6.84 (d, *J* = 9.0 Hz, 2H), 7.21 (t, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H), 7.55–7.60 (m, 2H), 9.56 (br, 1H); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 115.5 (d, *J*<sub>C-F</sub> = 21.0 Hz, 2C), 115.7 (2C), 127.7 (2C), 127.8 (d, *J*<sub>C-F</sub> = 9.0 Hz, 2C), 130.0, 136.7 (d, *J*<sub>C-F</sub> = 3.0 Hz), 157.1, 161.2 (d, *J*<sub>C-F</sub> = 240.8 Hz).

*4-Hydroxy-4-methoxybiphenyl* (**3fc**, Table 3, Entry 20). CAS: 16881-71-3; white solid (m.p. = 173–175 °C, lit. [72] 171–173 °C). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 3.75 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 9.46 (br, 1H); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 55.1, 114.2 (2C), 115.7 (2C), 127.0 (2C), 127.2 (2C), 130.7, 132.8, 156.5, 158.1.

*4'-Methylacetophenone* (**6a** [73], Table 4, Entries 1–4 and 7). CAS: 122-00-9; colorless liquid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.38 (s, 3H), 2.55 (s, 3H), 7.23 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 21.6, 26.5, 128.4 (2C), 129.2 (2C), 134.6, 143.8, 197.8.

*p-Tolunitrile* (**6b** [74], Table 4, Entries 5 and 8). CAS: 104-85-8; colorless liquid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.39 (s, 3H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 21.8, 109.2, 119.1, 129.8 (2C), 131.9 (2C), 143.6.

4-Methylanisole (**6e** [26], Table 4, Entry 6). CAS: 104-93-8; colorless liquid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.30 (s, 3H), 3.79 (s, 3H), 6.82 (d,  $J = 9.0$  Hz, 2H), 7.10 (d,  $J = 9.0$  Hz, 2H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  20.4, 55.2, 113.6 (2C), 129.7, 129.8 (2C), 157.4.

### 3.3. Procedure for Reuse of the Catalytic Aqueous Solution

The reaction was conducted following the procedure described in Section 3.2., and under the reaction conditions shown in Table 1, Entry 6. After the initial reaction, the aqueous reaction mixture was extracted with hexane (3 mL  $\times$  3) under vigorous stirring. The organic layer was separated from the aqueous phase by syringe, and the organic product was isolated from the combined organic phase according to a previously-described in Section 3.2. The residual aqueous solution was then charged with **1a**, **2a**, and  $\text{NaHCO}_3$  for the next reaction.

## 4. Conclusions

In conclusion, we have proved that the  $\text{PdCl}_2(\text{NH}_3)_2$ /cationic 2,2'-bipyridyl system is highly efficient and provides a reusable catalyst for Stille couplings. This catalytic system exhibits a high efficiency for the coupling of aryl iodides and activated aryl bromides with various aryltributylstannanes under a very low catalyst loading (1 ppm). This water-compatible catalytic system enables the reaction to be conducted by a very simple procedure, allowing easy separation of the catalytic aqueous solution from the organic products, rendering it very suitable for practical applications.

**Supplementary Materials:** The following are available online at: <http://www.mdpi.com/1420-3049/21/9/1025/s1>: copies of  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra of all Stille coupling products.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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**Sample Availability:** Samples of compounds **3** and **6** are available from the authors.



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