

Microwave-assisted C-C cross-coupling reactions of aryl and heteroaryl halides in water

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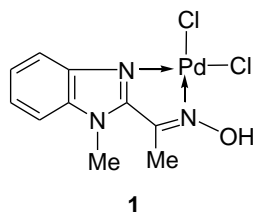
Abstract

The catalytic activity of a benzimidazole-oxime Pd(II)-complex towards Suzuki and Heck C-C cross-coupling reactions of activated and deactivated aryl- and heteroaryl bromides under microwave irradiation as well as thermal heating using water as a green solvent was evaluated. The turnover frequency reached 420,000 under microwave condition.

Keywords: Palladium complex, catalysis, microwave, C-C cross-coupling, water solvent

Introduction

Transition metal-mediated cross-coupling reactions, particularly those based on palladium, have become key transformations in organic synthesis.¹ Therefore, there has been considerable interest in the development of new, highly-active palladium catalysts that can be used in C-C cross-coupling reactions. In addition, microwave-assisted organic synthesis is advantageous for enabling rapid, reproducible, and scalable chemistry development in research laboratories and industrial processes.² The first microwave-assisted Suzuki cross-coupling reaction was reported in 1996.³ Our recent research work is directed to the use of palladium(II) complexes in Suzuki-Miyaura and Heck-Mizoroki cross-coupling reactions under microwave heating conditions in aqueous media.⁴ Very recently, we examined the catalytic activity of the Pd(II)-complex **1** in cross-coupling reactions of 4-halophenylthiazoles,⁵ herein we report general applications of the Pd(II)-complex **1** as a precatalyst in Suzuki and Heck cross-coupling reactions of aryl- and heteroaryl halides assisted with microwave irradiation using water as a green solvent.



Results and Discussion

Effect of concentration of the Pd-complex **1** on the Suzuki coupling of 4-bromoacetophenone with phenylboronic acid in water under μw irradiation

The effect of concentration of palladium(II) complex **1** on the Suzuki-Miyaura cross-coupling reaction between 4-bromoacetophenone **2a** and phenylboronic acid **3a** in water under microwave irradiation was examined. At first, the reaction was conducted using 1 mol% of the precatalyst **1** with 1 mmol 4-bromoacetophenone, 1.2 mmol phenylboronic acid, 0.6 mmol tetrabutylammonium bromide, 2 mmol potassium hydroxide under microwave irradiation (at 160 °C, 250 Watt) in water (3 mL) as solvent. TLC showed complete consumption of the starting bromide **2a** after 2 min of irradiation. The product 4-acetyl-1,1'-biphenyl (**4**) was isolated in 97% yield. Next, the same experiment was repeated using 0.5 mol% then with 0.1 mol% of the catalyst **1** under identical reaction conditions as above where complete consumption of the bromide **2a** was observed after 2 min of irradiation with 93 and 95% isolated yields, respectively. Furthermore, the same reaction was repeated with 0.05 mol% of the precatalyst **1** for 2 min of μw heating to give full conversion in 96% isolated yield of compound **4** as shown in Table 1, run 4. Interestingly, when the cross coupling of **2a** with **3a** was conducted under the same reaction condition using 0.01 and 0.005 mol% of complex **1** it resulted in their conversion into compound **4** in 76 and 70% isolated yields, respectively (Table 1, runs 5 and 6). The high catalytic activity of the Pd-complex **1** can be observed with the very high turnover number (TON) 14000 (TON: the number of mole of product per mole of Pd-complex) and the very high turnover frequency (TOF) 420000 h⁻¹ (TOF: mole of product per mole of Pd-complex per hour) as shown in Table 1, run 6.

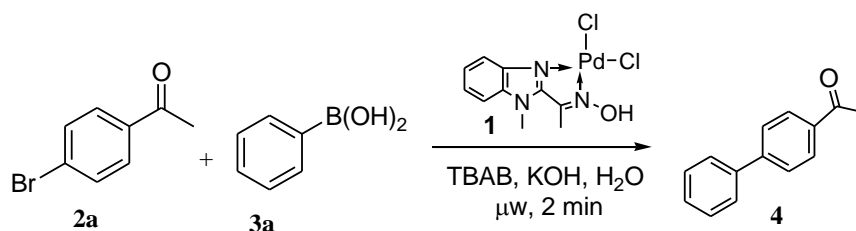


Table 1. Effect of concentration of catalyst **1** on Suzuki coupling of 4-bromoacetophenone with phenylboronic acid in water under microwave heating

Entry	mol% of Pd-Cat. 1	Yield % ^{a,b}	TON	TOF [h ⁻¹]
1	1	100 (97)	97	2910
2	0.5	100 (93)	186	5580
3	0.1	100 (95)	950	28500
4	0.05	100 (96)	1920	57600
5	0.01	88 (76)	7600	228000
6	0.005	86 (70)	14000	420000

^aConditions: **2a** (1.0 mmol), **3a** (1.2 mmol), KOH (2.0 mmol), TBAB (0.6 mmol), water (3 mL) at 160 °C, 250 Watt.

^bConversion% based on ¹H NMR of the crude reaction product and values between parentheses refer to the isolated yields.

Suzuki-Miyaura cross-coupling of aryl halides with phenylboronic acid using pre-catalyst **1** in water under microwave irradiation

A general utility of complex **1** in Suzuki-Miyaura cross-coupling reactions was investigated as illustrated in Table 2. The Suzuki coupling reactions of the activated aryl bromides **2a-d** with phenylboronic acid **3a** were carried out under microwave irradiation conditions resulting in the formation of the corresponding biaryl derivatives **4-7** with full conversions in high isolated yields. Under similar reaction conditions as above, the Suzuki coupling between phenylboronic acid **3a** with deactivated aryl bromides **2e-g** was performed to give excellent yields of the cross-coupled products **8-10** after 2-5 min of microwave heating (Table 2, runs 5-7). 4-Iodobenzoic acid cross-coupled smoothly with phenylboronic acid after one min of microwave heating using 0.5 mol% of complex **1** to give 85% isolated yield of 4-phenylbenzoic acid (**6**) (Table 2, runs 8).

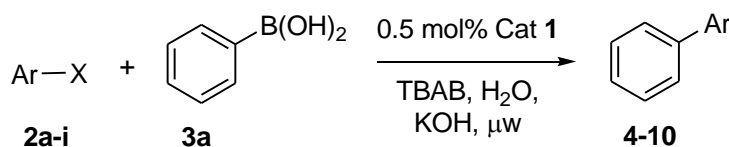
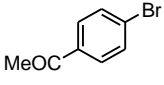
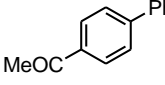
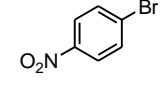
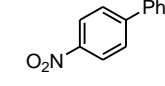
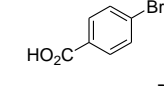
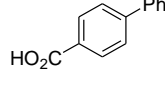
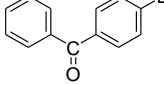
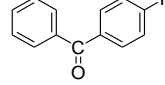
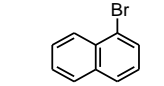
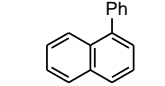
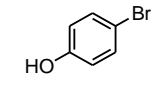
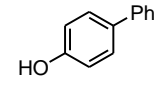
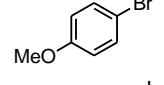
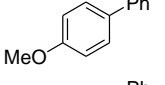
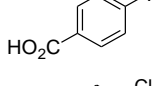
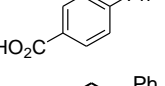
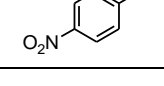
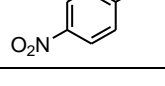


Table 2. Suzuki-Miyaura cross-coupling of aryl halides with phenylboronic acid using pre-catalyst **1** in water under microwave irradiation

Entry	Ar-X	Product	Time (min)	Yield % ^a
1	 2a	 4	2	93
2	 2b	 5	3	90
3	 2c	 6	2 ^c	83
4	 2d	 7	4	92
5	 2e	 8	2	89 ^b
6	 2f	 9^b	4	88
7	 2g	 10	5	91
8	 2h	 6	1 ^c	85
9	 2i	 5	3 ^d	90

^aConditions: Halides **2a-i** (1.0 mmol), boronic acid **3a** (1.2 mmol), KOH (2.0 mmol), TBAB (0.6 mmol), water (3 mL) at 160 °C, 250 Watt.

^bTraces of the starting bromide **2e** were detected by TLC.

^cThe reaction product was treated with few drops of acetic acid.

^d1.0 mmol of TBAB was used. In all runs above, traces of the homo-coupling product (biphenyl) were detected by TLC and mass spectrum.⁶

4-Nitrochlorobenzene **2i**, as an example of activated aryl chlorides, was subjected for cross-coupling with phenylboronic acid **3a** under microwave heating conditions (Table 2, run 9). Under this condition, the coupled product **5** was obtained in 90% isolated yield after 3 min of μ wave irradiation.

As shown in Table 2, the Pd(II)-complex **1** was found to efficiently catalyze the coupling of a wide range of aryl bromides in excellent yields regardless their activating or deactivating substituents.

Suzuki cross-coupling of aryl(heteroaryl) bromides **2a,j,k** with arylboronic acids **3a-d** under thermal heating and μ w irradiation

The catalytically active Pd(II)-complex **1** was next applied for Suzuki-Miyaura reaction of aryl- and heteroaryl bromides **2a,j,k** with variety of activated and deactivated arylboronic acids **3a-d**. Thus, thermal heating of 4-bromoacetophenone **2a** with arylboronic acid **3a-d** using 0.5 mol% of Pd-complex **1** in the presence of KOH as a base, water as a solvent and TBAB as phase transfer agent for 2 hours gave excellent isolated yields of the corresponding biaryls **4, 11-13** (Table 3). Similarly, when the same reactions were repeated under microwave irradiation at 160 °C and 250 Watt, they gave very high isolated yields of the same biaryls after 2-6 min as shown in Table 3. Interestingly, the chlorine atom in compound **11** was survived under both thermal and microwave heating modes and there was no evidence for the formation of 4-(4'-chlorobiphenyl)acetophenone in the crude reaction mixture from the cross coupling of **2a** with 4-chlorophenylboronic acid **3b**.

Subsequently, the cross-couplings between 4-bromoisoquinoline **2j** and phenylboronic acid **3a** was conducted in water using KOH as a base and TBAB as a phase transfer agent in the presence of 0.5 mol% of the Pd(II)-complex **1** to give 4-phenylisoquinoline **14** in 90% yield after 9 min of microwave irradiation. Three further examples of arylboronic acids **3b-d** (activated and deactivated) were similarly allowed to cross-couple with 4-bromoisoquinoline **2j** under the same optimized reaction conditions to afford the corresponding 4-arylisoquinolines **15-17** in excellent yields as listed in Table 3, column 3.

Suzuki-Miyaura couplings of 3-bromoquinoline **2k** with the arylboronic acids **3a-d** were similarly conducted in water under microwave heating conditions using the same molar ratios of the precatalyst **1** and the reactants as shown above to give the corresponding 3-arylquinolines **18-21** in high yields as illustrated in Table 3, column 4.

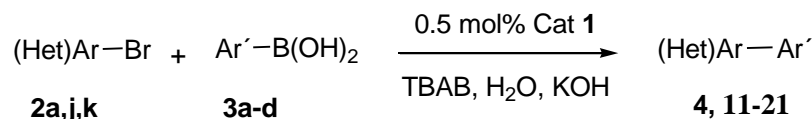
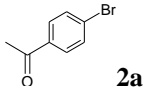
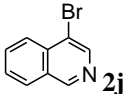
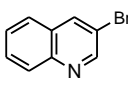
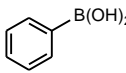
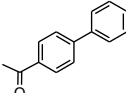
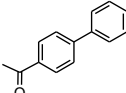

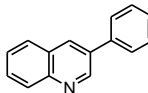
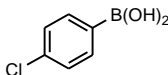
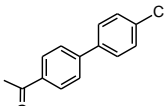
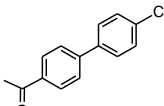
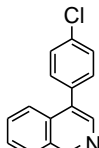
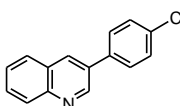
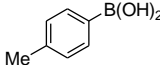
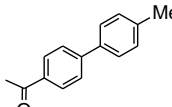
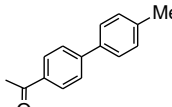
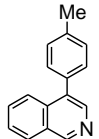
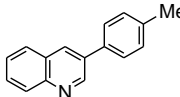
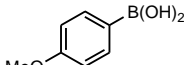
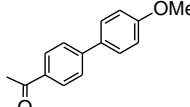
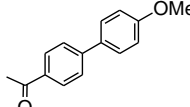
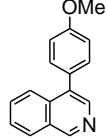
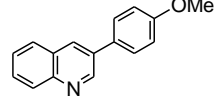


Table 3. Suzuki cross-coupling of aryl (heteroaryl) bromides **2a,j,k** with arylboronic acids **3a-d** in water under thermal and microwave heating

Ar-B(OH) ₂				
	Thermal	Microwave	Microwave	Microwave
Ar (Het)-Br	2h/ yield% ^a	time(min)/Yield% ^a	time(min) Yield% ^a	time(min) Yield% ^a
 3a	 4 97	 4 2 / 95	 14 9 90 ^{b,d}	 18 8 93 ^{c,d}
 3b	 11 98	 11 2 / 93	 15 9 95	 19 10 94
 3c	 12 97	 12 4 / 96	 16 12 80 ^d	 20 10 90
 3d	 13 90	 13 6 / 93	 17 12 86 ^d	 21 11 80

^aConditions: Bromides **2a,j,k** (1.0 mmol), boronic acids **3a-d** (1.2 mmol), KOH (2.0 mmol), TBAB (0.6 mmol), water (3 mL) at 100 °C for thermal heating and at 160 °C (250 Watt) for μ w irradiation. All values refer to the isolated yields.

^bYield was 75% after 9 min of μ w irradiation when catalyst **1** was used in 0.1 mol%.

^cYield was 73% after 9 min of μ w irradiation when catalyst **1** was used in 0.1 mol%.

^dTraces of the starting bromides were detected by TLC.

Mizoroki-Heck cross-coupling of aryl (heteroaryl) bromides in water under microwave irradiation

The Pd(II) complex-catalyzed cross-coupling reaction of aryl (heteroaryl) bromides **2a,j,k** with styrene (Heck reaction) under microwave condition was also investigated. Firstly, the reaction was performed using 0.5 mol% of the precatalyst **1** for the coupling of 4-bromoacetophenone **2a** with styrene **22** in the presence of TBAB and potassium hydroxide in water as solvent under microwave irradiation at 160 °C for 5 min to give 4-acetylstilbene **23** in 94% yield (Table 4). The same reaction was repeated for 4-bromoquinoline **2j** and 3-bromoquinoline **2k** with styrene.

The starting bromides **2j,k** were completely consumed after 15 min of microwave irradiation to give the corresponding styryl derivatives **24** and **25** in 86 and 87% yields, respectively, as outlined in Table 4.

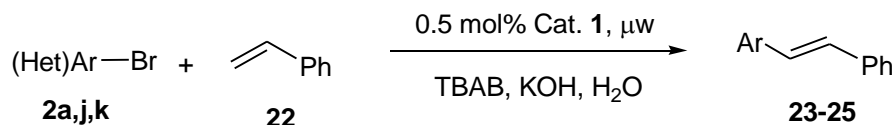
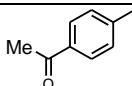




Table 4. Heck cross coupling of aryl (heteroaryl) bromides in water under μW heating

Run	Ar	Product	Time (min)	Yield % ^a
1		23	5	94
2		24	15	86
3		25	15	87

^aConditions: Bromides **2a,j,k** (1 mmol); styrene **22** (1.5 mmol); TBAB (0.6 mmol); KOH (2 mmol); water (3 mL), at 160 °C (250 Watt). All values refer to the isolated yields.

In conclusion, the Pd(II)-complex **1** was found to be an efficient and highly active precatalyst for Suzuki–Miyaura and Heck–Miyoroki cross-coupling reactions of activated and deactivated aryl halides as well as heterocyclic bromides. The extremely high turnover number (TON) and turnover frequency (TOF) under microwave irradiation conditions represents the importance of conducting such reactions for mass production on an industrial scale.

Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (¹H NMR) and at 75 MHz (¹³C NMR) using CDCl₃ as solvent and internal standard (δ 7.27 and 77.36 ppm, for ¹H NMR and ¹³C NMR, respectively). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. TON (turnover number) was calculated as: (a catalyst displaying TON 1000 means that the catalyst leads to 100% conversion of starting materials at a load of 0.1% mol). Microwave irradiation was carried out using a CEM Discover Labmate™ microwave apparatus (300 W with ChemDriver™ Software). Aryl- and heteroaryl halides as well as arylboronic acids were used as purchased without further purification.

Effect of concentration of Pd(II)-complex 1 on the Suzuki cross-coupling of 4-bromoacetophenone with phenylboronic acid in water under microwave irradiation

A mixture of 4-bromoacetophenone **2a** (199 mg, 1 mmol) and phenylboronic acid **3a** (146 mg, 1.2 mmol), tetrabutylammonium bromide (TBAB) (194 mg, 0.6 mmol), palladium complex **1** (3.66 mg, 1 mol%), KOH (112 mg, 2 mmol) and water (3 mL) was heated under microwave condition at 160 °C and 250 watt for 2 minutes to give 4-acetyl-1,1'-biphenyl **4**. The same experiment was repeated using of palladium precatalyst **1** in different mol% *e.g.* 0.5, 0.1, 0.05, 0.01 and 0.005 mol% with respect to 4-bromoacetophenone. The molar ratio of the reaction components were in all cases as follows; 4-bromoacetophenone, phenylboronic acid, TBAB, KOH, water: 1 / 1.2 / 0.6 / 2 / 3 mL water. The product was purified with flash column chromatography using hexane/EtOAc (10:1) as eluent to give 4-acetyl-1,1'-biphenyl **4**. The yield % versus concentration of palladium precatalyst **1** is outlined in Table 1.

Suzuki-Miyaura cross-coupling of aryl halides with phenylboronic acid using the precatalyst A in water under microwave irradiation. General procedure

A mixture of the appropriate aryl halide **2a-i** (1 mmol), and phenylboronic acid **3a** (146 mg, 1.2 mmol), TBAB (194 mg, 0.6 mmol), palladium precatalyst **1** (1.83 mg, 0.5 mol %), KOH (112 mg, 2 mmol), and water (3 mL) were mixed in a glass-process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 160 °C and 250 Watt for the appropriate reaction time as listed in Table 2. After the reaction was almost complete as monitored by TLC, the reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous MgSO₄ then filtered and the solvent was evaporated under reduced pressure. The product was purified with flash column chromatography as described above to give the corresponding pure products **4-10**.

4-Acetyl-1,1'-biphenyl (4). White solid, mp. 118-120 °C (Lit.⁷ mp. 119-120 °C); ¹H NMR (CDCl₃): δ 2.65 (s, 3H, COCH₃), 7.46-7.49 (m, 1H), 7.64 (d, 2H, *J* = 7.5 Hz), 7.7 (d, 2H, *J* = 8.4 Hz), 7.83 (d, 2H, *J* = 8.4 Hz), 8.05 (d, 2H, *J* = 8.7 Hz); MS *m/z* (%) 196 (M⁺, 100), 181 (66.7), 144 (83.3), 87 (90).

4-Nitrobiphenyl (5). Yellow needles; mp. 114-116 °C (Lit.⁸ mp. 113-115 °C); ¹H NMR (CDCl₃) δ 7.46-7.54 (m, 3H), 7.64 (d, 2H, *J* = 9.6 Hz), 7.75 (d, 2H, *J* = 9 Hz), 8.62 (d, 2H, *J* = 9 Hz); MS *m/z* (%) 199 (M⁺, 35.6), 169 (28.9), 152 (100), 76 (49.6), 50 (40).

4-Phenylbenzoic acid (6). White crystals; mp. 220-222 °C (Lit.⁹ mp. 220-221 °C); ¹H NMR (CDCl₃) δ 7.44-7.54 (m, 3H), 7.66 (d, 2H, *J* = 9.3 Hz), 7.72 (d, 2H, *J* = 8.1 Hz), 8.21 (d, 2H, *J* = 8.1 Hz); MS *m/z* (%) 198 (M⁺, 100), 181 (44.3), 152 (40.6), 127 (3.8), 76 (5.5).

4-Benzoylbiphenyl (7). Buff crystals, mp. 98-100 °C (Lit.¹⁰ mp. 101-102 °C); ¹H NMR (DMSO-*d*₆) δ 7.41-7.56 (m, 5H), 7.59 (d, 2H, *J* = 7.8 Hz), 7.67-7.71 (m, 1H), 7.77 (d, 2H, *J* = 8.1 Hz), 7.83 (d, 2H, *J* = 8.7 Hz), 7.87 (d, 2H, *J* = 8.7 Hz); MS *m/z* (%) 258 (M⁺, 73.5), 181 (100), 152 (51.3), 105 (21), 77 (28).

1-Phenylnaphthalene (8). Colorless oil;¹¹ ¹H NMR (CDCl₃) δ 7.65 -7.76 (m, 9H), 8.08 (d, 1H, *J* = 7.8 Hz), 8.13 (d, 1H, *J* = 7.8 Hz), 8.25 (d, 1H, *J* = 8.1 Hz); MS *m/z* (%) 204 (M⁺, 100), 189 (10.1), 176 (12.3), 163 (6.7), 150 (8.1), 101 (42), 88 (10.5).

4-Hydroxybiphenyl (9). White crystals, mp. 166-167 °C (Lit.¹² mp. 164-165 °C); ¹H NMR (CDCl₃) δ 5.05 (s, 1H, OH), 6.92 (d, 2H, *J* = 7.8 Hz), 7.30-7.38 (m, 1H), 7.40-7.45 (m, 2H), 7.49 (d, 2H, *J* = 8.1 Hz), 7.56 (d, 2H, *J* = 8.4 Hz); MS *m/z* (%) 170 (M⁺, 100), 141 (32.3), 115 (20.0), 63 (10.3), 51 (12.9).

4-Methoxybiphenyl (10). White solid, mp 87-88 °C (Lit.¹³ mp 87-88 °C); ¹H NMR (CDCl₃) δ 3.87 (s, 3H, OCH₃), 6.99 (d, 2H, *J* = 8.7 Hz), 7.31-7.45 (m, 3H), 7.54 (d, 2H, *J* = 9 Hz), 7.57 (d, 2H, *J* = 7.2 Hz); MS *m/z* (%) 184 (M⁺, 92.5), 169 (77.5), 141 (70), 115 (55), 91 (52.5), 76 (100), 63 (55).

Suzuki-Miyaura cross-coupling of 4-bromoacetophenone 2a with arylboronic acids 3a-d in water under thermal heating. General procedure

A mixture of 4-bromoacetophenone **2a** (199 mg, 1 mmol), and the appropriate arylboronic acid **3a-d** (1.2 mmol), TBAB (194 mg, 0.6 mmol), palladium precatalyst **1** (1.83 mg, 0.5 mol %), KOH (112 mg, 2 mmol), and water (3 mL) was shaken at 100 °C under open air for 2 h (TLC-monitored) as listed in Table 3. The products were extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over anhydrous MgSO₄ then filtered and the solvent was evaporated under reduced pressure. The residue was then subjected to separation via flash column chromatography with petroleum ether/EtOAc (10:1) as an eluent to give the corresponding pure products **4** and **11-13**, respectively.

Suzuki-Miyaura cross-coupling of aryl (heteroaryl) bromides 2a,j,k with arylboronic acids 3a-d in water under microwave irradiation. General procedure

A mixture of the appropriate bromide **2a**, **2j** or **2k** (199 mg, 1 mmol), and the appropriate arylboronic acid **3a-d** (1.2 mmol), TBAB (194 mg, 0.6 mmol), palladium complex **1** (1.83 mg, 0.5 mol %), KOH (112 mg, 2 mmol), and water (3 mL) were mixed in a process vial. The vial was capped properly and the mixture was then heated under microwave irradiating conditions at 160 °C and 250 Watt for the appropriate reaction time as listed in Table 3. After the reaction was almost complete (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over anhydrous MgSO₄ then filtered off and the solvent was evaporated under reduced pressure. The products were purified with flash column chromatography using petroleum ether/EtOAc (5:2 or 10:1) as an eluent to give the corresponding pure cross-coupled products **4** and **11-21** as outlined in Table 3.

4-Chloro-4'-acetyl-1,1'-biphenyl (11). White crystals, mp. 99-100 °C (Lit.¹⁴ mp. 98-100 °C); ¹H NMR (CDCl₃) δ 2.65 (s, 3H, COCH₃), 7.45 (d, 2H, *J* = 8.4 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 7.65 (d, 2H, *J* = 8.1 Hz), 8.04 (d, 2H, *J* = 8.1 Hz); MS *m/z* (%) 232 (M⁺+2, 30.4), 231 (M⁺+1, 11.4), 230 (M⁺, 100), 151 (24.3), 114 (16.4), 75 (14.1), 57 (23.2), 50.1 (20.9).

4-Methyl-4'-acetyl-1,1'-biphenyl (12). White crystals, mp. 122-124 °C (Lit.¹⁵ mp. 121-124 °C); ¹H NMR (CDCl₃) δ 2.42 (s, 3H, CH₃), 2.64 (s, 3H, COCH₃), 7.29 (d, 2H, *J* = 7.8 Hz), 7.54 (d, 2H, *J* = 6.6 Hz), 7.68 (d, 2H, *J* = 8.7 Hz), 8.03 (d, 2H, *J* = 9.6 Hz); MS *m/z* (%) 210 (M⁺, 49.4), 195 (100), 165 (22.1), 152 (32.7), 139 (5.3), 115 (5.9), 63 (5.7), 51 (5.5).

4-Methoxy-4'-acetyl-1,1'-biphenyl (13). White crystals, mp. 152-154 °C (Lit.¹⁶ mp. 152-153 °C); ¹H NMR (CDCl₃) δ 2.64 (s, 3H, COCH₃), 3.88 (s, 3H, OCH₃), 7.01 (d, 2H, *J* = 9 Hz), 7.59 (d, 2H, *J* = 8.7 Hz), 7.66 (d, 2H, *J* = 8.7 Hz), 8.02 (d, 2H, *J* = 8.7 Hz); MS *m/z* (%) 226 (M⁺, 57.9), 211 (100), 183 (18.5), 168 (23), 152 (12.4), 139 (36.3), 105 (5.7), 63 (8.4).

4-Phenylisoquinoline (14). Yellow oil;¹⁷ ¹H NMR (CDCl₃) δ 7.48-7.64 (m, 7H), 7.89-8.02 (m, 2H), 8.48 (s, 1H), 9.24 (s, 1H); MS *m/z* (%) 205 (M⁺, 100), 176 (25.4), 148 (26.9), 102 (25), 88 (17), 77 (27.9).

4-(4-Chlorophenyl)isoquinoline (15). White crystals, mp. 84-86 °C; ¹H NMR (CDCl₃) δ 7.45-7.54 (m, 4H), 7.63-7.72 (m, 2H), 7.87 (d, 1H, *J* = 8.1 Hz), 8.06 (d, 1H, *J* = 8.7 Hz), 8.47 (s, 1H), 9.28 (s, 1H); ¹³C NMR (CDCl₃) δ 124.4, 127.6, 128, 128.8, 130.8, 131.3, 134, 134.2, 135.3, 142.5, 152.1; MS *m/z* (%) 241 (M⁺+2, 34.7), 240 (M⁺+1, 20), 239 (M⁺, 100), 204 (54.2), 176 (28.9), 101 (21.4), 88 (33.3), 75 (16.9). Anal. Calcd for C₁₅H₁₀ClN: C, 75.16; H, 4.21; N, 5.84%. Found: C, 75.12; H, 4.31; N, 5.98%.

4-(4-Methylphenyl)isoquinoline (16). Colorless oil;¹⁸ ¹H NMR (CDCl₃) δ 2.47 (s, 3H, CH₃), 7.34 (d, 2H, *J* = 7.8 Hz), 7.42 (d, 2H, *J* = 6.9 Hz), 7.58-7.67 (m, 2H), 7.94 (d, 1H, *J* = 7.8 Hz), 8.02 (d, 1H, *J* = 8.1 Hz), 8.50 (s, 1H), 9.25 (s, 1H); ¹³C NMR (CDCl₃) δ 21.2, 124.8, 127.0, 127.8, 128.4, 129.3, 129.9, 130.4, 133.2, 134.0, 134.3, 137.7, 142.8, 151.7.

4-(4-Methoxyphenyl)isoquinoline (17). White crystal, mp. 82-84 °C (lit.¹⁸ mp. 82-84 °C); ¹H NMR (CDCl₃) δ 3.91 (s, 3H, OCH₃), 7.07(d, 2H, *J* = 8.1 Hz), 7.46 (d, 2H, *J* = 7.8 Hz), 7.60-7.7 (m, 2H), 7.95 (d, 1H, *J* = 8.1 Hz), 8.04 (d, 1H, *J* = 7.5 Hz), 8.49 (s, 1H), 9.25 (s, 1H); MS *m/z* (%) 235 (M⁺, 100), 220 (60.2), 191 (39.1), 165 (40.7), 95 (8.9), 88 (8.7), 63 (9.1).

3-Phenylquinoline (18). Pale yellow powder, mp. 50-51 °C (lit.¹⁹ mp. 52 °C); ¹H NMR (CDCl₃) δ 7.39-7.45 (m, 4H), 7.48-7.70 (m, 3H), 7.80 (d, 1H, *J* = 8.1 Hz), 8.16 (d, 1H, *J* = 8.7 Hz), 8.21 (s, 1H), 9.18 (s, 1H); MS *m/z* (%) 205 (M⁺, 100), 176 (14.4), 151 (7.8), 102 (14.1), 88 (16.5), 76 (38.4), 63 (16.3).

3-(4-Chlorophenyl)quinoline (19). White crystals, mp. 134-136 °C (Ref.²⁰ mp. 133-134 °C); ¹H NMR (CDCl₃) δ 7.50 (d, 2H, *J* = 8.7 Hz), 7.58-7.66 (m, 3H), 7.73-7.78 (m, 1H), 7.90 (d, 1H, *J* = 8.1 Hz), 8.15 (d, 1H, *J* = 8.4 Hz), 8.28 (d, 1H, *J* = 1.8 Hz), 9.15 (d, 1H, *J* = 2.1 Hz); MS *m/z* (%) 241 (M⁺+2, 37.1), 240 (M⁺+1, 26.6), 239 (M⁺, 100), 204 (37.3), 176 (25.3), 102 (12.2), 88 (45.7), 75 (29.6).

3-(4-Methylphenyl)quinoline (20). White crystal, mp. 72-74 °C (lit.²¹ mp 72-73 °C); ¹H NMR (CDCl₃) δ 2.45 (s, 3H, CH₃), 7.35 (d, 2H, *J* = 8.4 Hz), 7.57-7.67 (m, 3H), 7.72-7.77 (m, 1H), 7.88 (d, 1H, *J* = 8.1 Hz), 8.15 (d, 1H, *J* = 8.4 Hz), 8.29 (s, 1H), 9.2 (s, 1H); MS *m/z* (%) 219 (M⁺, 100), 189 (7.8), 110 (7.6), 109 (11.8), 108 (11.2), 95 (17.4), 94 (8.1).

3-(4-Methoxyphenyl)quinoline (21). White crystals, mp. 84-86 °C (Lit.²² mp. 83-85 °C); ¹H NMR (CDCl₃) δ 3.89 (s, 3H, OCH₃), 7.07 (d, 2H, *J* = 9 Hz), 7.54-7.74 (m, 4H), 7.86 (d, 1H, *J* =

8.4 Hz), 8.14 (d, 1H, $J = 8.4$ Hz), 8.25 (s, 1H), 9.18 (s, 1H); MS m/z (%) 235 (M^+ , 100), 220 (32.5), 204 (13), 192 (56.3), 177 (15.2), 163 (25.1), 153 (14.7), 132 (13), 117 (19.9), 101 (11.7), 95 (16), 85 (12.1), 76 (12.6), 63 (19).

Mizoroki-Heck cross-coupling of styrene with aryl (heteroaryl) bromides **2a,j,k** in water under microwave heating

A mixture of the appropriate aryl or heteroaryl bromide **2a,j,k** (1 mmol) and styrene **22** (1.5 mmol), TBAB (0.6 mmol), precatalyst **1** (1.83 mg, 0.5 mol%), and potassium hydroxide (112 mg, 2 mmol) in water (3 mL) was mixed in a process vial. The vial was capped properly, and the mixture was then heated under microwave irradiating conditions at 150 °C and 250 Watt for the appropriate reaction time as listed in Table 4. After the reaction was complete as monitored by TLC, the reaction mixture was left to cool to room temperature. The reaction mixture was then extracted three times with EtOAc (3x20 mL) and then the organic fractions were combined together, dried over $MgSO_4$, filtered and then the solvent was removed under vacuum. The residue was then subjected to purification via flash column chromatography with petroleum ether–EtOAc (10:1) as eluent to give the corresponding pure products **23~25**.

(E) 4-Acetylstilbene (23). Colorless crystals, mp 143-144 °C (Lit.^{21,22} mp. 141-142 °C); 1H NMR ($CDCl_3$) δ 2.62 (s, 3H, $COCH_3$), 7.14 (d, 1H, $J = 16.5$ Hz), 7.25 (d, 1H, $J = 15.3$ Hz), 7.31-7.42 (m, 3H), 7.54-7.61 (m, 4H), 7.97 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 26.9, 126.8, 127.1, 127.7, 128.6, 129.1, 129.2, 131.7, 136.2, 136.9, 142.3, 197.7; MS m/z (%) 222 (M^+ , 57.2), 207 (100), 178 (67.2), 152 (10), 104 (11.6), 89 (42.2), 76 (27.7), 63 (14.9), 51 (25.6).

(E) 4-(Styryl)isoquinoline (24). Pale yellow powder, mp. 73-74 °C (Lit.²³ mp. 75 °C); 1H NMR ($CDCl_3$) δ 7.13 (d, 1H, $J = 16.2$ Hz), 7.30-7.41 (m, 3H), 7.52-7.58 (m, 4H), 7.66 (d, 1H, $J = 14.7$ Hz), 7.89 (d, 1H, $J = 8.1$ Hz), 8.06 (d, 1H, $J = 8.7$ Hz), 8.74 (s, 1H), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 122.8, 123.3, 127.2, 127.5, 128.4, 128.5, 128.6, 128.9, 129.1, 130.8, 133.5, 134.1, 137.4, 140.8, 152.2; MS m/z (%) 231 (M^+ , 37), 230 (100), 202 (15.1), 128 (3), 115 (7.8), 101 (10.4), 88 (7), 76 (7.2).

(E) 3-(Styryl)quinoline (25). Yellowish-white crystals, mp. 97-98 °C (Lit.¹⁶ mp. 98-99 °C); 1H NMR ($CDCl_3$) δ 7.24 (d, 1H, $J = 16.5$ Hz), 7.19-7.44 (m, 4H), 7.56-7.60 (m, 3H), 7.69 (d, 1H, $J = 15.3$ Hz), 7.83 (d, 1H, $J = 8.1$ Hz), 8.12 (d, 1H, $J = 8.4$ Hz), 8.19 (s, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 125.5, 127.0, 127.3, 128.1, 128.4, 128.6, 129.1, 129.5, 129.6, 130.6, 131.2, 132.6, 137.1, 147.8, 149.8; MS m/z (%) 231 (M^+ , 73.2), 230 (100), 202 (16.1), 115 (20.4), 101 (24.1), 76 (15.2), 63 (14.3), 51 (13.4).

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