Microwave-assisted synthesis of 5-arylbenzofuran-2-carboxylates *via* Suzuki coupling using a 2-quinolinealdoxime-Pd(II)-complex

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Abstract

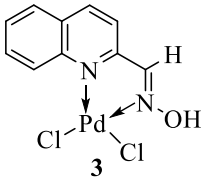
A new quinoline-based Pd(II)-complex was synthesized and its structure was established by single crystal X-ray analysis. Applications of the obtained complex as a precatalyst in Suzuki-Miyaura C-C cross-coupling reactions of 4-bromoacetophenone and 5-bromobenzofuran-2-carboxylate esters with several aryl- and heteroarylboronic acids were investigated. The catalytic activity of the Pd(II)-precatalyst under microwave irradiating conditions was evaluated.

Keywords: Quinolines, benzofurans, palladium catalysis, microwave, Suzuki reactions

Introduction

Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl halides with arylboronic acids,[1-4] is one of the most valuable synthetic routes for the preparation of symmetric and asymmetric biaryls, which are important skeletons in the structures of biologically active compounds,[5] agrochemicals, pharmaceuticals,[6-8] polymers,[9] ligands,[10] and functional materials.[11] The key advantages of the Suzuki-Miyaura cross-coupling are: (i) the mild conditions under which it is conducted, (ii) the high tolerance toward functional groups, (iii) the commercial availability and stability of boronic acids to heat, oxygen and water, and (iv) the ease of handling and separation of boron-containing byproducts from the reaction mixtures.[12] Over the past few decades, water has been reported to be a powerful solvent because of its safe, environmentally benign and cheap properties.[13-17] In addition, there is growing research interest on the use of

microwave irradiation methodology as a heating source, because it assists in achieving rapid incorporation of organic synthesis into broad industrial diversities.[18-22] Benzofuran-2-carboxylic esters have been reported to possess several biological activities including antifungal[23] and potent anti-tumor[24] agents and are inhibitors of human MMP-13 (matrix metalloproteinase-13)[25] and ischemic cell death.[26] In continuation of our recent research work concerned on the use of Pd(II)-complexes as precatalysts in C-C cross coupling reactions in aqueous media under microwave irradiation conditions,[27-36] and on the chemistry of 2- and 3-substituted benzofuran derivatives,[37-39] we report here the synthesis of the new Pd(II)-complex **3** to evaluate its catalytic activity in the Suzuki-Miyaura cross-coupling arylation of 5-bromobenzofuran-2-carboxylate esters **7** and **15**.



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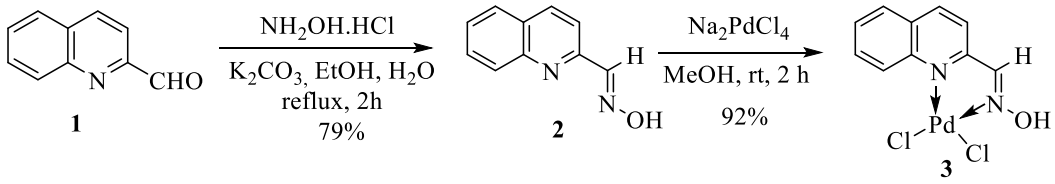
Results and Discussion

Synthesis and X-ray structure of Pd(II)-complex 3

2-Quinolinealdoxime (**2**) was prepared from 2-quinolinealdehyde (**1**) as described in literature.[40] Treatment of 2-quinolinealdoxime (**2**) in methanol with sodium tetrachloropalladate in methanol at room temperature led to the complex **3** (Scheme 1), whose structure was elucidated by elemental and spectral analysis. The structure of the Pd(II)-complex **3** was unequivocally determined by carrying out a single crystal X-ray analysis (Figure 1).



Scheme 1. Preparation of Pd(II)-complex **3**.

The crystal structure of complex **3** revealed a bidentate, chelating binding mode for the *N*,*N*′-ligand. This is the first reported structure of a complex of this ligand. The protonated state of the oxime functionality was established by location of the hydroxyl proton in difference maps and its subsequent positional refinement to a chemically reasonable position implying an intramolecular hydrogen bond with the chloride ligand *cis*- to the oxime. This feature is consistent with findings for various pyridine-2-aldoxime complexes, such as the mixed oxime/oximato-Pd(II) complex [Pd(L-H)L]Cl,[41] featuring N-O-H···O hydrogen bonding to the oximato ligand. Intramolecular

hydrogen bonding is not universally present however, as reported for a cationic square planar Cu(II) complex of *N*,*N*′,*N*″-2,6-diacetylpyridine dioxime[42] or examples where tetrahedral metal coordination precludes this feature.[43]

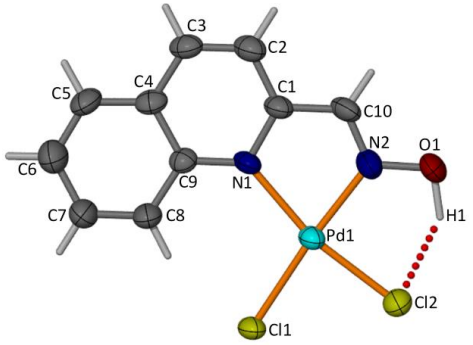


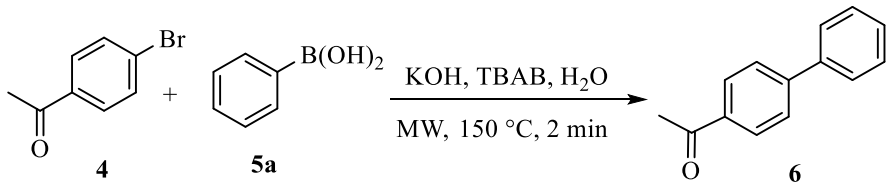
Figure 1. Molecular structure of Pd(II)-complex **3**.

Optimization of catalytic conditions for Suzuki cross-coupling

Firstly, the effect of concentration of Pd(II)-complex **3** on the cross-coupling reaction between 4-bromoacetophenone (**4**) and phenylboronic acid (**5a**) in water using potassium hydroxide as a base and tetrabutylammonium bromide (TBAB) as an additive under microwave irradiation conditions at 150 ºC for 2 min, was examined as illustrated in Table 1. Thus, the reaction was firstly carried out using 1 mol% of the Pd(II)-complex **3** and the reaction components molar ratios were as follow: 4-bromoacetophenone (**4**) / phenylboronic acid (**5a**) / TBAB / KOH: 1 / 1.2 / 0.6 / 2, to give full conversion into 4-acetylbiphenyl (**6**) in 96% yield. Secondly, we used 0.7 mol% of the precatalyst **3** to give full conversion (97% yield) after 2 min of microwave irradiation. The coupling reaction was repeated with different concentrations (mol%) of Pd(II)-complex **3** as shown in Table 1. In all cases, full conversion was obtained even when 0.001 mol% of the Pd-precatalyst **3** was employed in the cross-coupling reaction. It is noteworthy to mention here that, when Pd-complex **3** was used in 0.001 mol% the number of mmoles of the reacting species were raised to be: 4-bromoacetophenone (**4**) (3 mmoles), phenylboronic acid (**5a**) (3.6 mmoles), TBAB (1.8 mmoles), KOH (6 mmoles) and water (6 mL) to give the 4-acetylbiphenyl (**10**) in full conversion (92% yield) after 2 min of MW irradiation with a turn over number (TON) 92,000 and turnover frequency (TOF) 2,760,000 h^{-1} (entry 7, Table 1). From the data outlined in Table 1, it can be concluded that the Pd-complex **3** shows excellent catalytic activity, giving rise to extremely high TONs and TOFs.

Some further parameters that may necessary to achieve full conversions and hence maximum yield for the cross-coupling reaction were optimized. Solvents and bases are among such parameters where they play important roles for such purpose. The effect of different bases and solvents on the coupling reaction between 4-bromoacetophenone (**4**) and phenylboronic acid (**5a**) were evaluated and the results are outlined in Table 2. In all cases the Pd-precatalyst **3** was used in 0.1 mol% and the reaction was carried out under microwave heating for 2 min in different solvents: water, DMF, toluene and 1,4-dioxane, acetonitrile using several bases; potassium

hydroxide, potassium carbonate, cesium carbonate and triethylamine. Full conversions with high isolated yields were obtained when water/TBAB in the presence of the inorganic bases KOH, K_2CO_3, and Cs_2CO_3 were employed as catalytic systems. The use of the organic base: Et_3N was not suitable at all regardless the solvent used. Solvents other than water, such as DMF, toluene, 1,4-dioxane and acetonitrile are not proper for this coupling reaction in KOH or K_2CO_3, however the use of cesium carbonate was effective (full conversion with high isolated yields) when toluene or 1,4-dioxane were applied under microwave irradiation. Therefore, water, toluene and 1,4-dioxane are effective solvents for carrying out the coupling reactions especially in the presence of Cs_2CO_3.**Table 1.** Effect of concentration of Pd(II)-complex **3** on Suzuki coupling of 4-bromoacetophenone (**4**) with phenylboronic acid (**5a**) under microwave irradiation



4 5a 6

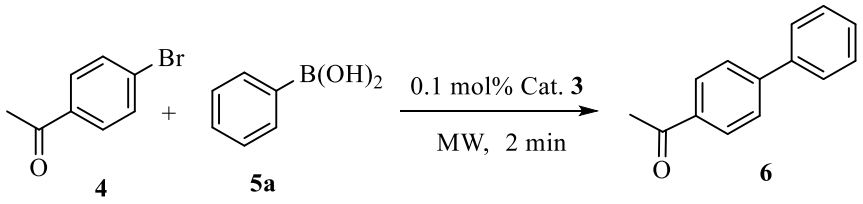
Entry	Cat. **3**, mol%	Yield%[a,b]	TON	TOF (h^{-1})
1	1	96	96	2880
2	0.7	97	139	4170
3	0.5	95	190	5700
4	0.1	94	960	28800
5	0.05	96	1960	58800
6	0.01	95	9500	285000
7	0.001[c]	92	92000	2760000

[a] Reaction Conditions: Bromide/ boronic acid/ KOH/ TBAB /water (3 mL): 1/ 1.2/ 2/ 0.6, under microwave irradiation at 150 °C (200 Watt). TON: turnover number, TOF: turnover frequency. [b] The % values refer to the isolated yields. [c] Bromide/ boronic acid/ KOH/ TBAB /water (6 mL): 3/ 3.6/ 6/ 1.8.

Next, optimization of the catalytic activity of complex **3** in Suzuki cross-coupling reaction of methyl 5-bromobenzofuran-2-carboxylate (**7**) with phenylboronic acid (**5a**) in Cs_2CO_3 using different concentrations of **3** under microwave condition was investigated as described in Table 3. At first, when water/TBAB/Cs_2CO_3 as catalytic system was applied using 1 mol% of the Pd(II)-complex **3**, the reaction was completed after 10 min of microwave irradiation. However, the main product, in this case, was found to be 5-bromobenzofuran-2-carboxylic acid due to the hydrolysis of the ester **7** under the aqueous basic hot reaction condition.[44] Therefore, conduction of the Suzuki coupling of **5a** with **7** was performed in toluene/Cs_2CO_3 using 1 mol% of the Pd(II)-complex **3** and the reaction components molar ratios were as follow: 5-bromobenzofuran ester **7** / phenylboronic acid (**5a**) / Cs_2CO_3: 1 / 1.2 / 2, in toluene (3 mL) for 15 min the starting

substrate **7** was still available as examined by TLC and the product **8** was isolated in 67% yield. Full conversion of **7** into methyl 5-phenylbenzofuran-2-carboxylate (**8**) was ascertained after 23 min of MW irradiation with 94% isolated yield (Table 3, run 1). Secondly, the use of 0.7 mol% of the precatalyst **3** led also to full conversion (97% yield) after 23 min of microwave irradiation. Furthermore, the coupling reaction was repeated using 0.5 and 0.1 mol% of Pd(II)-complex **3** as shown in Table 3 (runs 3 and 4), where the coupling reaction was completed after 23 min of heating giving the coupled product **8** in 95 and 93% yields, respectively. The maximum TON and TOF values were 930 and 2426, respectively (Table 3, run 4), reflected the moderate activity of the precatalyst **3** towards the Suzuki coupling of **7**.

Table 2. Base and solvent effects on the Suzuki coupling of 4-bromoacetophenone (**4**) with phenylboronic acid (**5a**) under microwave irradiation

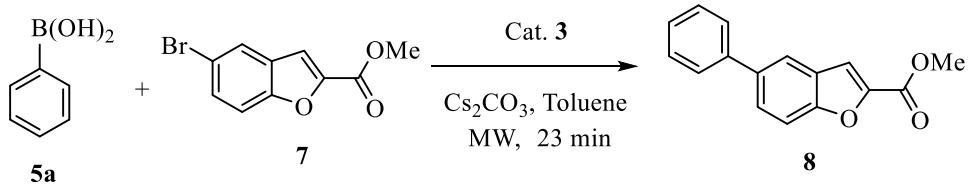


4 **5a** **6**

Entry	Solvent	Yield%[a,b]			
		Base: KOH	K_2CO_3	Cs_2CO_3	Et_3N
1	Water/TBAB	100 (97)	100 (96)	100 (89)	54 (35)
2	DMF	80 (71)	80 (63)	65 (50)	30
3	Toluene	87 (75)	80 (73)	100 (92)	30
4	1,4-Dioxane	90 (75)	70 (55)	100 (95)	25
5	Acetonitrile	60 (40)	30	40 (26)	15

[a] Reaction conditions: Bromide/ boronic acid/ base/ TBAB/ solvent (3 mL): 1/1.2/2/0.6, microwave irradiation (200 Watt) at 150 °C for 2 min. [b] Conversions were based on ^{1}H NMR spectra of the crude product and the values in parentheses refer to the isolated yields.

Table 3. Catalytic activity of Pd(II)-complex **3** in Suzuki coupling of phenylboronic acid (**5a**) with methyl 5-bromobenzofuran-2-carboxylate (**7**) under microwave irradiation



5a **7** **8**

Entry	Cat. **3**, mol%	Yield%[a]	TON	TOF (h^{-1})
1	1	94	94	245
2	0.7	90	128	334
3	0.5	95	190	496
4	0.1	93	930	2426

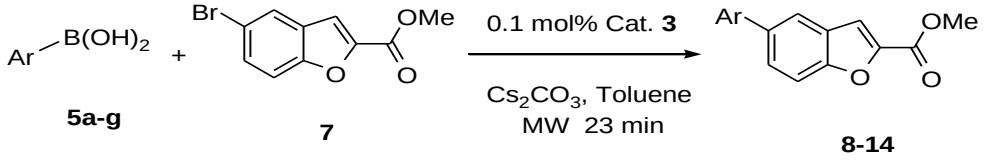
[a]Reaction conditions: Bromide **7**: 1 mmol; phenylboronic acid (**5a**): 1.2 mmol; Cs_2CO_3: 2 mmol; toluene: 3 mL, Pd-complex **3**, microwave heating (200 Watt) at 150 ºC.

Suzuki cross-coupling of methyl 5-bromobenzofuran-2-carboxylate (7)

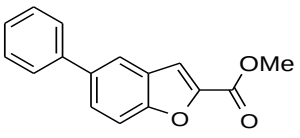
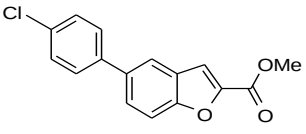
Next, the application of the Pd(II)-complex **3** was extended to Suzuki cross-coupling reactions between methyl 5-bromobenzofuran-2-carboxylate (**7**) and further arylboronic acids **5b-g** (Table 4). Thus, employing 0.1 mol% of the complex **3** in the coupling of the bromide **7** with 4-chlorophenylboronic acid **5b** in toluene/Cs_2CO_3 resulted in full conversion of **7,** after 25 min of microwave irradiation, into methyl 5-(4-chlorophenyl)benzofuran-2-carboxylate (**9**) in 96% isolated yield (Table 4, run 2).

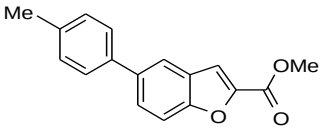
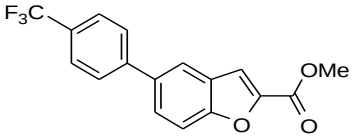
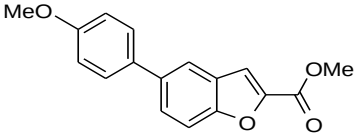
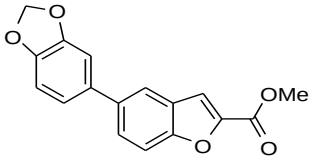
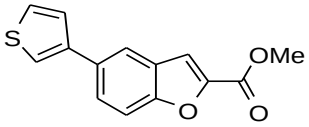
Similarly, the arylboronic acids **5c-g** coupled smoothly with the 5-bromobenzofuran ester (**7**) under the same experimental conditions to give the corresponding cross-coupled products methyl 5-arylbenzofuran-2-carboxylates **10-14** in high isolated yields as postulated in Table 4. It is notable to mention that, coupling of the arylboronic acids **5e-g** with **7** (Table 4, runs 5-7) took longer reaction times and the isolated yields were lower than the other derivatives. The structures of the coupling products were confirmed by their ^{1}H and ^{13}C NMR, MS spectra and elemental analyses. The ^{1}H NMR spectrum of methyl 5-(4-methylphenyl)benzofuran-2-carboxylate (**10**), as an example of the series prepared, revealed characteristic singlet signals at δ 2.42 and 4.0 due to 4-methylphenyl and the Me-ester protons, respectively. The ^{13}C NMR spectrum of **10** showed two aliphatic carbons at δ 21 and 52.3. The mass spectrum of compound **10** showed a peak (M^+) at *m/z* 266 due to its molecular ion.

Table 4. Suzuki cross-coupling of methyl 5-bromobenzofuran-2-carboxylate (**7**) with arylboronic acids **5a-g**



5a-g **7** **8-14**

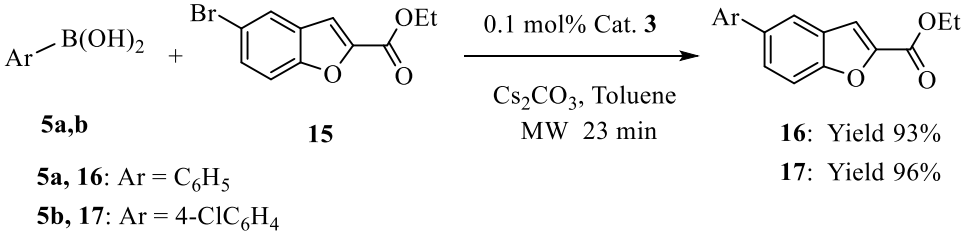
Entry	Ar-B(OH)$_2$	Product	MW heating[a] time (min)	yield%[b]
1	**5a**	 **8**	23	93
2	**5b**	 **9**	25	96

3	**5c**	 **10**	10	87
4	**5d**	 **11**	13	94
5	**5e**	 **12**	45[c,d]	85
6	**5f**	 **13**	35[d]	88
7	**5g**	 **14**	35[d]	75

[a]Reaction conditions: Bromide **7** (1 mmol); arylboronic acids **5a-g** (1.2 mmol); Cs_2CO_3 (2 mmol); toluene: 3 mL, Pd-complex **3**: 0.1 mol%, microwave heating (200 Watt) at 150 ºC. [b]The % values refer to isolated yields. [c]When the irradiation was stopped after 30 min, the starting material **7** was still present and the product **12** was isolated in 53% yield. [d]In all cases, traces of the starting material **7** were detected by TLC and the yield did not change when the reaction was repeated using 0.5 mol% of the Pd-complex **3**.

Suzuki cross-coupling of ethyl 5-bromobenzofuran-2-carboxylate (15)

The catalytic activity of the Pd(II)-precatalyst **3** in the Suzuki cross-coupling of ethyl 5-bromobenzofuran-2-carboxylate (**15**) with arylboronic acids **5a,b** under typical reaction condition above was also evaluated. Therefore, carrying out the coupling reaction of **15** with **5a,b** in Cs_2CO_3 as base and toluene as solvent using 0.1 mol% of the complex **3** under microwave condition for 23 min led to full conversion into the corresponding ethyl 5-arylbenzofuran-2-carboxylates **16** and **17** in 93 and 96% isolated yields, respectively (Scheme 2).



Scheme 2. Suzuki cross-coupling of ethyl 5-bromobenzofuran-2-carboxylate (**15**).

Conclusions

The 2-quinolinealdoxime-Pd(II)-complex **3** was found to be extremely active precatalyst for Suzuki cross-coupling reaction of 4-bromoacetophenone with phenylboronic acid, under eco-friendly green condition (water and microwave irradiation), with very high TON and TOF values. Complex **3** was also found as an effective precatalyst for the coupling of 5-bromobenzofuran-2-carboxylate esters **7** and **15** for the synthesis of new 5-arylbenzofran-2-carboxylates. These high catalytic findings of **3** are important for forthcoming industrial applications.

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 Shimadzu FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR) using $CDCl_3$ as solvent and internal standard (δ 7.27 and 77.36 ppm, for ^{1}H NMR and ^{13}C NMR, respectively). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography (TLC) was performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Fluka silica gel 60741 (70-230 mesh) was used for flash column chromatography. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Microwave experiments were carried out using a CEM Discover Labmate^{TM} microwave apparatus (300 W with ChemDriver^{TM} Software). Data for the structure of complex **3** was obtained on the MX2 beamline at the Australian Synchrotron, Victoria, Australia. 5-Bromobenzofuran-2-carboxylate esters **7**,[45] and **15**,[46] were prepared following literature procedures. 4-Bromoacetophenone (**4**) and arylboronic acids **5a-g** were used as purchased without further purification.

Synthesis of 2-quinolinealdoxime-Pd(II)-complex 3. A solution of sodium tetrachloropalladate (294 mg, 1 mmol) in methanol (2 mL) was added portionwise to a stirred solution of 2-quinolinealdoxime (**2**) (172 mg, 1 mmol) in methanol (2 mL). After stirring for 2 h a yellow precipitate was formed that was then filtered off, washed with methanol followed by water and again with ethanol and finally dried. The Pd(II)-complex **3** was isolated in a pure state (321 mg, 92%) as yellow powder and was used without further purifications. Mp >300 °C; IR (ν_{max}, cm^{-1}): 3100, 3034, 1460, 1348, 1012, 880. ^{1}H NMR (DMSO-d_6) δ_H 7.29-7.73 (3H$_{arom}$, m, 3CH), 7.78 -8.07 (3H$_{arom}$, m, 3CH), 9.66 (1H, s, CH=N), 11.94 (1H, s, OH); ^{13}C NMR (DMSO-d_6) δ_c 120.4, 127.5, 128.1, 128.4, 128.6, 131.3, 140.3, 142.0, 145.6, 156.5. Anal. Calcd for $C_{10}H_8Cl_2N_2OPd$ (349.51): C, 34.36; H, 2.31; N, 8.02%. Found: C, 34.57; H, 2.42; N, 8.29%.

X-Ray structure determination of Pd(II)-complex 3. Crystals of complex **3** were obtained from a saturated, hot solution of acetonitrile that was allowed to cool slowly to room temperature. Data were collected at -173 °C on a cut, thin pale yellow needle-like crystal mounted on a Hampton Scientific cryoloop at the MX2 beamline of the Australian Synchrotron.[47] Data completeness is limited by the single axis goniometer on the MX beamlines at the Australian Synchrotron, which also prevented absorption correction. The structures were solved by direct methods with SHELXS-97, refined using full-matrix least-squares routines against F^2 with SHELXL-97,[48] and visualized using X-SEED.[49] All non-hydrogen atoms were refined anisotropically. Disordered lattice solvent was apparent, which could not be modeled, requiring the use of SQUEEZE to remove its contribution. Details are provided in the cif file and summarized in the figure caption. The OH proton was located and positionally refined, while all other hydrogen atoms were placed in calculated positions and refined using a riding model with fixed C–H distances of 0.95 Å (sp^2CH). The thermal parameters of all hydrogen atoms were estimated as U_{iso}(H) = 1.2U_{eq}(C). Crystal data for complex **3**: $C_{10}H_8Cl_2N_2OPd$, M = 349.48, trigonal, a = 28.922(5), c = 8.1550(15) Å, U = 5907.6(17) Å^3, T = 100 K, space group R-3 (no. 148), Z = 18, 22437 reflections measured, 2392 unique (R_{int} = 0.1475), 2124 > 4σ(F), R = 0.0638 (observed), R_w = 0.1190 (all data). Thermal ellipsoids are shown at the 50% probability level. Diffuse lattice solvent (NCMe) is omitted for clarity. Selected bond lengths (Å) and angles (°): Pd1-N1,N2,Cl1,Cl2 2.114(6), 1.988(6), 2.3035(17), 2.2860(19), C1-C10 1.433(11), C10-N2 1.268(10), N2-O1 1.372(8), O1-H1 1.05(14), H1···Cl2 2.03(14), N1-Pd1-N2 79.0(2), Cl1-Pd1-Cl2 86.65(7), N-Pd1-$Cl_{cis,trans}$ 88.90(19)-105.51(15), 167.72(15)-175.54(19), N2-O1-H1 101(8), O1-H1···Cl2 145(11). CCDC-893760 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

Effect of concentration of Pd(II)-complex 3 on Suzuki coupling of 4-bromoacetophenone (8) with phenylboronic acid (5a) in water under microwave irradiation. A mixture of 4-bromoacetophenone (**4**) (199 mg, 1 mmol) and phenylboronic acid **5a** (146 mg, 1.2 mmol), TBAB (194 mg, 0.6 mmol), Pd complex **5** (4.59 mg, 1 mol%), KOH (112 mg, 2 mmol) and water (3 mL) were mixed in a process glass vial. The vial was capped properly, and thereafter the mixture was heated under microwave conditions at 150 °C and 200 Watt for 2 min to give 4-acetyl-1,1´-biphenyl (**6**). The same experiment was repeated using different concentrations of the palladium complex **3**. The amount (mol%) of the Pd-complex **3** was changed with respect to 4-bromoacetophenone (0.7, 0.5, 0.1, 0.05 and 0.01 mol% of complex **3** with 1 mmol scale of 4-bromoacetophenone. The same experiment was then repeated using 0.001 mol% of complex **3** and 3 mmol scale of 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 yield % versus concentration of Pd-complex **3** is shown in Table 1.

Effect of base and solvent on Suzuki coupling of 4-bromoacetophenone with phenylboronic acid under microwave heating. A mixture of 4-bromoacetophenone (**4**) (199 mg, 1 mmol) and phenylboronic acid **5a** (146 mg, 1.2 mmol), TBAB (194 mg, 0.6 mmol), palladium(II)-precatalyst **3** (0.4 mg, 0.1 mol%), KOH (112 mg, 2 mmol) and water (3 mL) was heated under microwave conditions at 150 ^{o}C and 200 Watt for 2 minutes to give 4-acetyl-1,1'-biphenyl (**6**). The same experiment was repeated using different solvents (DMF, toluene and 1,4-dioxane, acetonitrile) and bases (KOH, K_2CO_3, and Cs_2CO_3). The molar ratio of the reaction components were in all cases as follows; 4-bromoacetophenone, phenylboronic acid, TBAB (in case of water), base, solvent: 1 / 1.2 / 0.6 / 2 / 3 mL. The yield % versus different solvents and bases are outlined in Table 2. The cross-coupled product, in each time, was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ then filtered and the solvent was evaporated under reduced pressure. The residue was then subjected to separation via flash column chromatography with petroleum *n*-hexane/EtOAc (9:1) as an eluent to give 4-acetyl-1,1'-biphenyl (**6**) as colourless solid. Mp 118-120 °C (Lit.[50] mp 119-120 °C); ^{1}H NMR ($CDCl_3$) δ_H 2.65 (3H, s, CH_3), 7.41-7.51 ($3H_{arom}$, m, 3CH), 7.62-7.66 ($2H_{arom}$, m, 2CH), 7.70 ($2H_{arom}$, d, $^{3}J_{HH}$ 8.1 Hz, 2CH), 8.04 (2H, d, $^{3}J_{HH}$ 8.1 Hz, 2CH).

Effect of concentration of Pd(II)-complex 3 on Suzuki coupling of methyl 5-bromobenzofuran-2-carboxylate (7) with phenylboronic acid (5a) in toluene under microwave irradiation. A mixture of methyl 5-bromobenzofuran-2-carboxylate (**7**) (255 mg, 1 mmol), phenylboronic acid (**5a**) (146 mg, 1.2 mmol), Cs_2CO_3 (651 mg, 2 mmol) and palladium(II)-precatalyst **3** (1 mol%) in toluene (3 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 150 ^{o}C and 200 Watt. The reaction was complete after 23 minutes (monitored by TLC). The same experiment was repeated using different concentrations of the palladium complex **3**. The amount (mol%) of the Pd-complex **3** was changed with respect to 5-bromobenzofuran ester **7** (0.7, 0.5 and 0.1 mol%) of complex **3** using 1 mmol scale of **7**. The molar ratio of the reaction components were in all cases as follows; 5-bromobenzofuran ester **7**, phenylboronic acid (**5a**), Cs_2CO_3, toluene (mL): 1 / 1.2 / 2 / 3. The yield % versus concentration of Pd-complex **3** is shown in Table 3. In each case, the reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ then filtered off and the solvent was evaporated under reduced pressure. The product was purified with flash column chromatography using *n*-hexane/EtOAc (7:1) as an eluent to give methyl 5-phenylbenzofuran-2-carboxylate (**8**).

Suzuki coupling of methyl 5-bromobenzofuran-2-carboxylate (7) with arylboronic acids 5a-g in toluene under microwave. A mixture of the methyl 5-bromobenzofuran-2-carboxylate **7** (255 mg, 1 mmol), and the appropriate arylboronic acids **5a-g** (1.2 mmol), Pd(II)-complex **3** (0.4 mg, 0.1 mol%), Cs_2CO_3 (651 mg, 2 mmol) in toluene (3 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating

conditions at 150 ºC (200 Watt) for the appropriate reaction times as depicted in Table 4. After the reaction was almost complete (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ then filtered off and the solvent was evaporated under reduced pressure. The products were purified with flash column chromatography using *n*-hexane/EtOAc (7:1) as an eluent to give the corresponding pure 5-arylbenzofuran-2-carboxylates **8-14**.

Methyl 5-phenylbenzofuran-2-carboxylate (8). White powder, mp. 132-134 ºC; IR (ν_{max}, cm^{-1}): 3064, 2957, 2918, 1724, 1564, 1455, 1436, 1215, 1161; ^1H NMR ($CDCl_3$): δ_H 4.0 (3H, s, CO_2CH_3), 7.37-7.49 (3H_{arom}, m, 3CH), 7.57-7.68 (5H_{arom}, m, 5CH), 7.87 (1H_{arom}, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 52.4, 112.4, 114.1, 121.1, 125.7, 127.2, 127.4, 127.5, 128.8, 137.6, 140.8, 145.9, 155.2, 159.8; MS (EI, 70 eV): *m/z* (%) 252 (42.9) [M^+], 184 (23.8), 165 (61.9), 128 (33.3), 110 (61.9), 83 (100), 70 (66.7). Anal. Calcd for $C_{16}H_{12}O_3$ (252.26): C, 76.18; H, 4.79%. Found: C, 76.23; H, 4.86%.

Methyl 5-(4-chlorophenyl)benzofuran-2-carboxylate (9). Yellowish-white powder, mp. 148-150 ºC; IR (ν_{max}, cm^{-1}): 3055 , 2930, 1725, 1561, 1447, 1306, 1164; ^1H NMR ($CDCl_3$): δ_H 4.01 (3H, s, CO_2CH_3), 7.41-7.58 (6H_{arom}, m, 6CH), 7.65 (1H_{arom}, s, 1CH), 7.83 (1H_{arom}, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 52.4, 112.6, 113.9, 120.9, 125.8, 127.1, 127.5, 128.6, 133.4, 136.3, 139.3, 146.1, 155.3, 159.7; MS (EI, 70 eV): *m/z* (%) 288 (34.7) [M^++2], 287 (24.4) [M^++1], 286 (100) [M^+], 255 (59.2), 199 (34.6), 163 (20.9), 127 (26.1), 100 (16.4), 81 (26.0). Anal. Calcd for $C_{16}H_{11}ClO_3$ (286.71): C, 67.03; H, 3.87%. Found: C, 67.31; H, 3.79%.

Methyl 5-(4-methylphenyl)benzofuran-2-carboxylate (10). Pale grey powder, mp. 138-140 ºC; IR (ν_{max}, cm^{-1}): 3030, 2953, 2923, 2844, 1722, 1560, 1445, 1298, 1161; ^1H NMR ($CDCl_3$): δ_H 2.42 (3H, s, CH_3), 4.0 (3H, s, CO_2CH_3), 7.28 (2H_{arom}, d, $^3J_{HH}$ 7.8 Hz, 2CH), 7.49-7.67 (5H_{arom}, m, 5CH), 7.84 (1H_{arom}, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 21.0, 52.3, 112.4, 114.1, 120.7, 125.7, 127.2, 127.3, 129.5, 136.9, 137.5, 137.9, 145.9, 155.1, 159.9; MS (EI, 70 eV): *m/z* (%) 266 (50) [M^+], 149 (35.3), 105 (29.4), 85 (47.1), 70 (50.0), 57 (100). Anal. Calcd for $C_{17}H_{14}O_3$ (266.29): C, 76.68; H, 5.30%. Found: C, 76.93; H, 5.41%.

Methyl 5-(4-trifluoromethylphenyl)benzofuran-2-carboxylate (11). Pale grey powder, mp. 146-147 ºC; IR (ν_{max}, cm^{-1}): 3110, 3095, 2958, 2843, 1723, 1564, 1432, 1295, 1195; ^1H NMR ($CDCl_3$): δ_H 3.99 (3H, s, CO_2CH_3), 7.56-7.71 (7H_{arom}, m, 7CH), 7.86 (1H_{arom}, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 52.4, 112.7, 113.9, 121.4, 125.6, 125.7, 125.8, 126.0, 127.2, 127.6, 136.0, 144.3, 146.3, 155.5, 159.7; MS (EI, 70 eV): *m/z* (%) 321 (17) [M^++1], 320 (100) [M^+], 319 (82.0), 289 (84.3), 233 (55.0), 183 (15.0), 163 (21.2), 92 (11.2), 63 (23.8). Anal. Calcd for $C_{17}H_{11}F_3O_3$ (320.26): C, 63.75; H, 3.46%. Found: C, 63.88; H, 3.51%.

Methyl 5-(4-methoxyphenyl)benzofuran-2-carboxylate (12). White powder, mp. 142-143 ºC; IR (ν_{max}, cm^{-1}): 3107, 3033, 2957, 2928, 2854, 1722, 1563, 1445, 1296, 1163; ^1H NMR ($CDCl_3$): δ_H 3.86 (3H, s, OCH_3), 3.99 (3H, s, CO_2CH_3), 7.00 (2H_{arom}, d, $^3J_{HH}$ 8.4 Hz, 2CH), 7.52-7.63 (5H_{arom}, m, 5CH), 7.79 (1H_{arom}, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 52.3, 55.3, 112.3, 114.1, 114.3, 120.5, 125.7, 125.8, 127.2, 127.4, 128.4, 133.4, 137.2, 154.9, 159.1; MS (EI, 70 eV): *m/z*

(%) 282 (65.6) [M^+], 281 (50.0), 266 (18.8), 167 (21.9), 149 (40.6), 83 (46.9), 70 (50.0), 57 (100). Anal. Calcd for $C_{17}H_{14}O_4$ (282.29): C, 72.33; H, 5.00%. Found: C, 72.16; H, 5.04%.

Methyl 5-(3,4-methylenedioxyphenyl)benzofuran-2-carboxylate (13). Pale grey powder, mp. 119-121 ºC; IR (ν_{max}, cm^{-1}): 3064, 3006 , 2953, 2913, 1725, 1564, 1500, 1429, 1311, 1243, 1229; ^{1}H NMR ($CDCl_3$): δ_H 3.91 (3H, s, CO_2CH_3), 5.93 (2H, s, OCH_2O), 6.80-6.99 ($3H_{arom}$, m, 3CH), 7.47-7.55 ($3H_{arom}$, m, 3CH), 7.69 ($1H_{arom}$, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 52.4, 101.2, 107.9, 108.6, 112.4, 114.1, 120.7, 120.9, 127.3, 127.4, 135.2, 137.3, 145.9, 147.1, 148.1, 155.0, 159.9; MS (EI, 70 eV): *m/z* (%) 297 (19.2) [M^++1], 296 (100) [M^+], 295 (37.2), 265 (7.5), 209 (9.6), 179 (12.8), 150 (14.9), 132 (29.1), 75 (17.8). Anal. Calcd for $C_{17}H_{12}O_5$ (296.27): C, 68.92; H, 4.08%. Found: C, 69.16; H, 4.21%.

Methyl 5-(3-thienyl)benzofuran-2-carboxylate (14). Pale grey powder, mp. 117-118 ºC; IR (ν_{max}, cm^{-1}): 3111, 3018 , 2958, 1723, 1567, 1432, 1295; ^{1}H NMR ($CDCl_3$): δ_H 3.98 (3H, s, CO_2CH_3), 7.38-7.71 ($5H_{arom}$, m, 5CH), 7.81 ($1H_{arom}$, s, 1CH), 7.85 ($1H_{arom}$, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 52.4, 112.5, 113.8, 114.0, 120.3, 125.4, 125.8, 126.5, 127.4, 130.7, 141.9, 146.5, 155.1 159.8; MS (EI, 70 eV): *m/z* (%) 258 (34.5) [M^+], 223 (100), 198 (14.6), 167 (38.6), 149 (16.4), 119 (17.5), 88 (79.5), 62 (90.1). Anal. Calcd for $C_{14}H_{10}O_3S$ (258.29): C, 65.10; H, 3.90; S, 12.41%. Found: C, 65.35; H, 3.99; S, 12.46%.

Suzuki coupling of ethyl 5-bromobenzofuran-2-carboxylate 15 with arylboronic acids 5a,b in toluene under microwave. A mixture of the ethyl 5-bromobenzofuran-2-carboxylate **15** (269 mg, 1 mmol), and the appropriate arylboronic acids **5a,b** (1.2 mmol), Pd(II)-complex **3** (0.4 mg, 0.1 mol%), Cs_2CO_3 (651 mg, 2 mmol) in toluene (3 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 150 ºC (200 Watt) for 23 min as shown in Scheme 2. After the reaction was almost complete (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ then filtered off and the solvent was evaporated under reduced pressure. The products were purified with flash column chromatography using *n*-hexane/EtOAc (7:1) as an eluent to give the corresponding pure ethyl 5-arylbenzofuran-2-carboxylates **16** and **17**.

Ethyl 5-phenylbenzofuran-2-carboxylate (16). White powder, mp 110-111 ºC; IR (ν_{max}, cm^{-1}): 3035 , 2951, 2848, 1731, 1565, 1444, 1165; ^{1}H NMR ($CDCl_3$): δ_H 1.46 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_2CH_3), 4.48 (2H, q, $^3J_{HH}$ 7.2 Hz, CH_2CH_3), 7.38-7.68 ($8H_{arom}$, m, 8CH), 7.86 ($1H_{arom}$, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 14.3, 61.5, 112.4, 113.8, 120.9, 125.7, 127.2, 127.4, 127.6, 128.1, 128.8, 137.5, 140.9, 146.4, 155.2, 159.4; MS (EI, 70 eV): *m/z* (%) 267 (19.9) [M^++1], 266 (100) [M^+], 238 (59.1), 221 (33.6), 194 (22.7), 165 (54.9), 139 (10.8), 115 (12.5), 82 (25.1), 70 (12.7). Anal. Calcd for $C_{17}H_{14}O_3$ (266.29): C, 76.68; H, 5.30. Found: C, 76.89; H, 5.44.

Ethyl 5-(4-chlorophenyl)benzofuran-2-carboxylate (17). Yellowish-white powder, mp 122-124 ºC; IR (ν_{max}, cm^{-1}): 3057 , 2924, 2859, 1733, 1563, 1454, 1305, 1167; ^{1}H NMR ($CDCl_3$): δ_H 1.45 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_2CH_3), 4.47 (2H, q, $^3J_{HH}$ 7.2 Hz, CH_2CH_3), 7.43 ($2H_{arom}$, d, $^3J_{HH}$ 8.7 Hz, 2CH), 7.51-7.65 ($5H_{arom}$, m, 5CH), 7.82 ($1H_{arom}$, s, 1CH); ^{13}C NMR ($CDCl_3$): δ_C 14.3, 61.6, 112.6, 113.7, 120.9, 125.8, 127.0, 127.5, 128.5, 133.4, 136.2, 139.3, 146.5, 155.3, 159.4; MS (EI,

70 eV): *m/z* (%) 302 (34.2) [M^++2], 301 (21.3) [M^++1], 300 (100) [M^+], 272 (59.7), 255 (27.1), 228 (15.8), 199 (28.1), 163 (28.1), 127 (20.3), 99 (16.0), 82 (32.9), 63 (19.0). Anal. Calcd for $C_{17}H_{13}ClO_3$ (300.74): C, 67.89; H, 4.36%. Found: C, 67.77; H, 3.43%.

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