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ORIGINAL PAPER

Dimeric *ortho*-palladated complex of 2,3-dimethoxybenzaldehyde oxime catalyzed Suzuki–Miyaura cross-coupling reaction under microwave irradiation

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Abstract The catalytic activity of dimeric $[Pd\{C_6H_2(–CH=NOH)–(OMe)_2\text{-}2,3\}(\mu–Cl)]_2$ complex as an efficient, air, and moisture-tolerant catalyst was investigated in Suzuki cross-coupling reactions of various aryl halides. The combination of homogenous metal catalyst, microwave irradiation, and microwave-active polar solvents gave high yields of substituted biaryl products in short reaction times.

Keywords *ortho*-Palladated catalyst · Palladacycle complexes · Oxime · Suzuki reaction · Biaryls

Introduction

Transition metal-catalyzed coupling reactions are among the most potent and convenient tools of modern organic synthesis [1]. Palladium is used as efficient and active catalyst in these reactions [2–4]. Generally, the combination of palladium catalysts with various phosphine ligands [5–8] and also *N*-heterocyclic carbenes [9–11] results in excellent yields and high efficiency in cross-coupling reactions, however, they are usually sensitive to air and moisture or expensive. Palladacycle complexes, with air and moisture stability and high catalytic activity have recently been employed in cross-coupling reactions [12–15]. The high productivity of the palladacycle catalysts is due to the slow generation of low ligated Pd(0) complexes from a stable palladium(II) pre-catalyst [16].

There are various cross-coupling reactions and among them the Suzuki–Miyaura coupling of aryl halides with aryl boronic acids is one of the most versatile and utilized synthetic method for the construction of symmetric and unsymmetric biaryls [17–23]. Biaryls are an important class of organic compounds due to their range of excellent physical and chemical properties. They present significant interest for the synthesis of herbicides [24], pharmaceuticals [25], natural products [26], bioactive products [27], microelectrode array [28], conducting polymers, and liquid crystal materials [29]. The key benefits of the Suzuki–Miyaura coupling are the mild reaction conditions, the tolerance of a broad range of functionalities, commercial availability and easy handling of organoboron reagents, and removal of the nontoxic boron-containing by-products [30].

Transition metal-catalyzed cross-coupling reactions typically need long reaction times and an inert atmosphere to reach completion with traditional heating. Modern techniques are focused on the design of novel methodologies to modify these chemical transformations using simpler, faster, and more efficient processes. The use of microwave irradiation in homogeneous transition metal-catalyzed reactions leads to the reduction of reaction times, production of high yields and higher selectivity, the decrease of discarded by-products from thermal side reactions, and increased lifetime of the catalyst [31–33].

In continuation of our recent investigations on the synthesis of the palladacycle catalysts and application of these complexes in microwave-assisted cross-coupling reactions [34–39], we now wish to report the synthesis and the extension of $[Pd\{C_6H_2(–CH=NOH)–(OMe)_2\text{-}2,3\}(\mu–Cl)]_2$ homogeneous complex, as a thermally stable and oxygen

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insensitive catalyst for the cross-coupling reaction of various aryl halides with aryl boronic acids and sodium tetraphenylborate under microwave irradiation.

Experimental

Reagents and measurements

All melting points were taken on a Gallenkamp melting apparatus. ^{1}H-NMR spectra were recorded using 400 MHz in $CDCl_3$ solutions at room temperature (TMS was used as an internal standard) on a Bruker, Avance 500 instrument (Rheinstetten, Germany) and Varian 400 NMR. FT-IR spectra were recorded on a spectrophotometer (Jasco-680, Japan). Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies were reported in a wave number (cm^{-1}). We used the Milestone microwave (Microwave Labstation-MLS GmbH-ATC-FO 300) for synthesis. Furthermore, we used Gas chromatography (GC) (BEIFIN 3,420 Gas Chromatograph equipped a Varian CP SIL 5 CB column-30 m, 0.32 mm, 0.25 μm) for examination of reaction completion and yields. Palladium chloride, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

General procedure for the synthesis of *ortho*-palladated oxime complex

2,3-Dimethoxybenzaldehyde oxime was synthesized according to our previous work [40]. For the synthesis of *ortho*-palladated oxime complex, to a solution containing $PdCl_2$ (1 mmol) and 2 mmol LiCl in methanol (40 mL), a methanol solution of 2,3-dimethoxybenzaldehyde oxime (1 mmol) and sodium acetate (1 mmol) was added. The mixture was stirred for 48 h at room temperature. Then the mixture was filtered and water (30 mL) was added to the filtrate to give yellow solid. The residue was recrystallized from dichloromethane to give catalyst (**A**) (53 %). Elemental analysis ($C_{18}H_{20}N_2O_6Cl_2Pd_2$); calculated: C, 33.56; H, 3.13; N, 4.35. Found: C, 33.62; H, 3.12; N, 4.30. M.P. 186 °C dec.

^{1}H-NMR (500 MHz): δ 8.72 (s, 1H), 8.46 (s, 1H), 6.91 (d, ^3J = 8.8 Hz, 1H), 6.85 (d, ^3J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H). IR (cm^{-1}): 3,400, 3,000, 1,650, 1,600, 1,560, 1,510, 1,450.

General procedure for Suzuki reaction of aryl halides

A mixture of the aryl halide (1 mmol), phenylboronic acid (1.2 mmol) or Ph_4BNa (0.25 mmol), K_2CO_3 (2 mmol), *ortho*-palladated oxime catalyst (**A**) (0.05 mmol %) was added to ethanol (2 mL) in round-bottom flask equipped with condenser and placed into the Milestone microwave. Initially the microwave irradiation of was set at 400 W, the temperature was ramped from room temperature to the desired temperature of 60 °C. Once this was reached, the reaction mixture was held at this temperature until the reaction was completed. The direct control of reaction mixture temperature carried out with the IR sensors, and software enables on-line temperature–pressure control by regulation of microwave power output. The mixture was stirred continuously during the reaction and monitored by both TLC and GC. After the reaction was completed, the mixture was cooled to room temperature and was diluted with *n*-hexane and water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure using rotary evaporator. The residue was purified by silica gel column chromatography. The products were characterized by comparing their m.p., IR, ^{1}H, ^{13}C NMR spectra with those found in the literature [39].

Results and discussion

In this paper, dimeric *ortho*-palladated complex $[Pd\{C_6H_2(–CH=NOH)–(OMe)_2\text{-}2,3\}(\mu–Cl)]_2$ (**A**) was synthesized (Scheme 1) and the efficiency of this catalyst was investigated in Suzuki reaction of various aryl halides under microwave irradiation.

Scheme 1 Preparation of *ortho*-palladated catalyst (**A**)

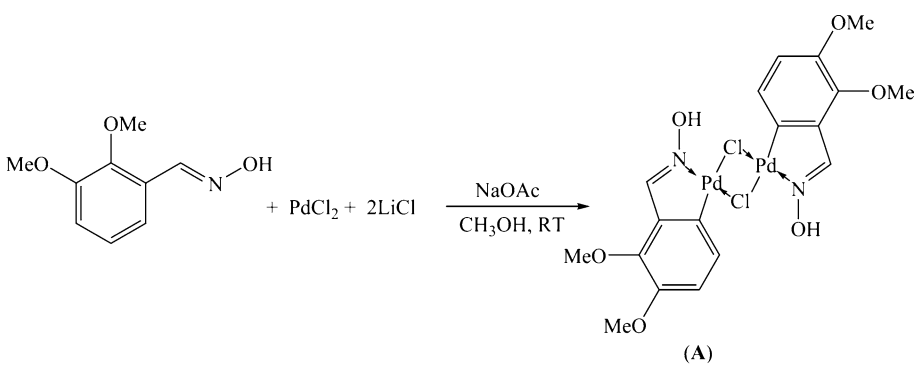

Table 1 Optimization of reaction conditions in Suzuki cross-coupling of aryl halides under microwave irradiation

Entry	Base	Solvent	Catalyst (mmol %)	Temperature (°C)	Conversion (%)[a]
1	K_2CO_3	DMF	0.1	120	68
2	K_2CO_3	DMF	0.2	120	72
3	Na_2CO_3	DMF	0.2	120	60
4	NaOAc	DMF	0.2	120	57
5	Cs_2CO_3	DMF	0.2	120	80
6	K_2CO_3	NMP	0.3	130	63
7	K_2CO_3	Dioxane	0.3	90	22
8	K_2CO_3	THF	0.3	80	29
9	K_2CO_3	CH_3CN	0.4	80	48
10	K_2CO_3	EtOH	0.05	60	100
11	K_2CO_3	EtOH	0.04	60	91
12	K_2CO_3	EtOH	0.1	60	100
13	–	EtOH	0.05	60	–

Reaction conditions: 4-bromoanisole (1 mmol), phenylboronic acid (1.2 mmol) K_2CO_3 (2 mmol), solvent (2 ml), *ortho*-palladated catalyst (**A**), 400 W, 3 min

[a] Determined by GC

To optimize the reaction conditions, we employed the coupling reaction of 4-bromoanisole with phenylboronic acid using catalytic amounts of the *ortho*-palladated complex (**A**) to evaluate the effects of the various bases and solvents under microwave irradiation, as shown in Table 1.

The monitoring system for reaction times, temperature, pressure, and power in microwave reactor allow for an excellent control of reaction parameters which generally leads to rapid optimization and more reproducible reaction conditions. The direct control of reaction mixture temperature; carry out with the IR sensors. At high temperature in DMF and NMP as solvent, biphenyl was obtained due to homocoupling of phenylboronic acid and also 4,4′-dimethoxybiphenyl was formed due to homocoupling of 4-bromoanisole as by-products. The best results were obtained in ethanol as the high microwave absorbing solvent and K_2CO_3 as base by employing 0.05 mol % of *ortho*-palladated complex (**A**) as the catalyst at 60 °C and 400 W (Table 1, entry 10). As this catalyst is not sensitive to oxygen, the reactions were carried out under air atmosphere. These optimize reaction conditions were applied in the Suzuki cross-coupling reaction of various aryl halides under microwave irradiation (Scheme 2).

As is demonstrated in Table 2, the catalyst can be used for coupling reaction of aryl iodides, bromides and even less reactive aryl chlorides with aryl boronic acids and sodium tetraphenylborate in good to excellent yields (Table 2). Sodium tetraphenylborate, unlike boronic acid reagents can react with four equivalents of electrophilic reagents. This phenylating agent is a cheap and easily available starting material in place of phenylboronic acid. Therefore, from both economical concerns and increased environmental awareness, this is an atom economical reaction.

We examined the electronic and steric effects on the resulted yields and conversion times of the reactions. Aryl bromides and iodides substituted with electron-withdrawing groups are the most suitable substrates for the Suzuki–Miyaura cross-coupling reaction. Aryl chlorides are, however, more attractive as starting materials because of their lower cost and more widely available than their bromide or iodide counterparts. Due to the strength of the C–Cl bond compared with C–Br and C–I bonds and their reluctance towards oxidative addition to Pd(0), required times for conversion of aryl chlorides to biaryls are longer (Table 2, entries 21–24). Aryl halides with electron-withdrawing substituent transformed to the corresponding coupled products rather than electron-donating substituent with better conversions and shorter reaction times. The steric hindrance of the procedure was examined using 2-,

Scheme 2 Suzuki reaction of aryl halides using *ortho*-palladated catalyst (**A**)

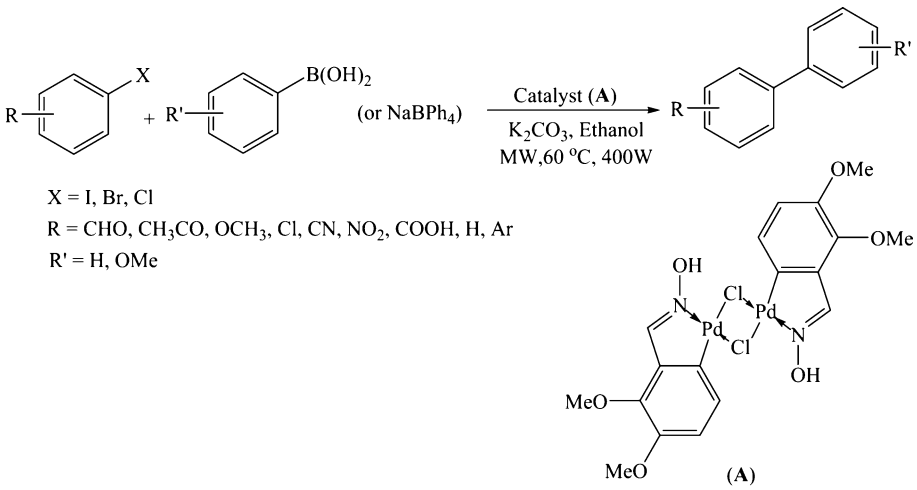

Table 2 Suzuki cross-coupling reaction of various aryl halides under microwave irradiation

Entry	Ar–X	Ar′B(OH)$_2$	Biaryl product	Time (min)	Yield (%)[a]
1	Ph–I	PhB(OH)$_2$	Ph–Ph	0.5	97
2	*p*-O_2N–C_6H_4–I	*p*-MeO–C_6H_4–B(OH)$_2$	*p*-O_2N–C_6H_4–C_6H_4–*p*-OMe	1	95
3	*m*-O_2N–C_6H_4–I	*p*-MeO–C_6H_4–B(OH)$_2$	*m*-O_2N–C_6H_4–C_6H_4–*p*-OMe	2	93
4	*p*-MeO–C_6H_4–I	PhB(OH)$_2$	*p*-MeO–C_6H_4–Ph	3	95
5	*p*-MeO–C_6H_4–I	Ph_4BNa	*p*-MeO–C_6H_4–Ph	3	94
6	Ph–Br	*p*-MeO–C_6H_4–B(OH)$_2$	*p*-MeO–C_6H_4–Ph	2	92
7	Ph–Br	Ph_4BNa	Ph–Ph	1	96
8	*p*-MeO–C_6H_4–Br	PhB(OH)$_2$	*p*-MeO–C_6H_4–Ph	4	95
9	*p*-MeO–C_6H_4–Br	*p*-MeO–C_6H_4–B(OH)$_2$	*p*-MeO–C_6H_4–C_6H_4–*p*-OMe	3	93
10	*p*-NC–C_6H_4–Br	PhB(OH)$_2$	*p*-NC–C_6H_4–Ph	3	95
11	*p*-OHC–C_6H_4–Br	PhB(OH)$_2$	*p*-OHC–C_6H_4–Ph	3	92
12	*p*-NC–C_6H_4–Br	Ph_4BNa	*p*-NC–C_6H_4–Ph	4	94
13	*p*-OHC–C_6H_4–Br	Ph_4BNa	*p*-OHC–C_6H_4–Ph	4	90
14	*p*-MeOC–C_6H_4–Br	*p*-MeO–C_6H_4–B(OH)$_2$	*p*-MeOC–C_6H_4–C_6H_4–*p*-OMe	5	93
15	*m*-MeOC–C_6H_4–Br	*p*-MeO–C_6H_4–B(OH)$_2$	*m*-MeOC–C_6H_4–C_6H_4–*p*-OMe	7	90
16	*o*-MeOC–C_6H_4–Br	*p*-MeO–C_6H_4–B(OH)$_2$	*o*-MeOC–C_6H_4–C_6H_4–*p*-OMe	10	87
17	*p*-MeOC–C_6H_4–Br	PhB(OH)$_2$	*p*-MeOC–C_6H_4–Ph	6	91
18	*p*-Cl–C_6H_4–Br	PhB(OH)$_2$	*p*-Cl–C_6H_4–Ph	1	96
19	*m*-Cl–C_6H_4–Br	PhB(OH)$_2$	*m*-Cl–C_6H_4–Ph	1.5	95
20	*o*-Cl–C_6H_4–Br	PhB(OH)$_2$	*o*-Cl–C_6H_4–Ph	3	90
21	Ph–Cl	PhB(OH)$_2$	Ph–Ph	5	94
22	*p*-OHC–C_6H_4–Cl	PhB(OH)$_2$	*p*-OHC–C_6H_4–Ph	6	87
23	*p*-MeOC–C_6H_4–Cl	PhB(OH)$_2$	*p*-MeOC–C_6H_4–Ph	8	73
24	*p*-OHC–C_6H_4–Cl	Ph_4BNa	*p*-OHC–C_6H_4–Ph	6	81

Reaction conditions: aryl halide (1 mmol), phenylboronic acid (1.2 mmol) or Ph_4BNa (0.25 mmol), K_2CO_3 (2 mmol), *ortho*-palladated catalyst (**A**) (0.05 mmol %), ethanol (2 ml), 60 ℃, 400 W

[a] Isolated yield

3- and 4-bromoacetophenone as hindered substituted aryls (Table 2, entries 14–16). Increasing the hindrance in vicinity of leaving group can cause to decrease the reaction conversion. The chemo-selectivity of the procedure was examined using 2-, 3- and 4-choloro-bromobenzene. In these reactions Br acted as better leaving group (Table 2, entries 18–20).

Study on palladacycle catalyst cross-couplings showed that the catalyst role in these reactions probably involve the palladium nanoparticles and palladacycles behave as a mere resource for producing nanoparticles Pd(0) [41–43]. Palladacycles decompose to liberate catalytic Pd(0) species and show a positive Hg(0) test which was assigned as probable evidence for catalysis by Pd nanoparticles [44]. To evaluate the proposed mechanism, the mercury drop test was operated. In the presence of a heterogeneous catalyst, mercury leads to the amalgamation of the surface of it. In contrast, Hg(0) cannot have a poisoning effect on homogeneous palladium complexes, where the Pd(II) metal centre is tightly bound to the ligand. When a drop of Hg(0) was added to the reaction mixture of 4-bromoanisole and phenylboronic acid under mentioned optimized conditions and heated the reaction mixture, no catalytic activity was observed for the catalyst.

Conclusions

In this work, a general protocol was applied for the microwave-promoted Suzuki reaction of various aryl halides with aryl boronic acids and sodium tetraphenylborate using *ortho*-palladated complex of 2,3-dimethoxybenzaldehyde oxime. The catalytic amounts of this dimeric complex as an inherent air and moisture resistant catalyst converted various aryl halides to the corresponding products in excellent yields. The combination of homogenous complex as catalyst, microwave irradiation and also high dipole moment of ethanol as microwave-active polar solvent caused to increase lifetime of the catalyst, improve the yields of the reactions and decrease the reaction times.

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