

An efficient catalyst for Suzuki–Miyaura coupling reaction in aqueous medium under aerobic conditions

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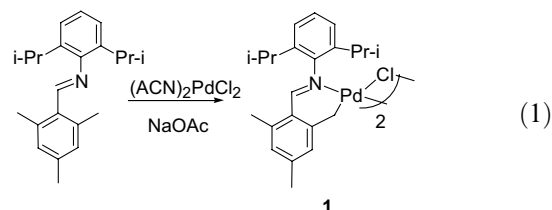
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Abstract—A cyclopalladated complex, $[\text{Pd}(\text{Cl})(k^2N, C\text{-CH}_2\text{C}_6\text{H}_2(\text{Me})_2\text{CH=NC}_6\text{H}_3(\text{Pr}^i)_2)]_2$ was found to be an excellent catalyst for Suzuki–Miyaura coupling of aryl halides with arylboronic acid in aqueous medium under aerobic conditions.

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Among various palladium-catalyzed carbon–carbon formation reactions, the Suzuki–Miyaura coupling provides a powerful tool for preparation of unsymmetrical biaryls.^{1–5} In recent years, developments in this catalysis have been focused on the syntheses of new transition metal complexes as catalysts for the use of aryl chlorides,^{1,4,5} under aerobic conditions^{2,4,5} or even in aqueous solutions.^{3,5} Accordingly, palladacycles were found to be the most promising catalysts in this regard. Recently, Bedford et al.⁴ and Nájera and co-workers⁵ have demonstrated that the coupling reaction of aryl chlorides can be achieved efficiently by using the cyclopalladated imino-complexes. Here, we would like to report the preparation of benzylic palladacycles and its catalytic activity toward Suzuki–Miyaura coupling in aqueous solution under aerobic atmosphere.

Condensation of 2,4,6-trimethylbenzaldehyde with the 2,6-diisopropylaniline yielded the desired imine ligand, which was subsequently reacted with $(\text{CH}_3\text{CN})_2\text{PdCl}_2$ in the presence of sodium acetate in tetrahydrofuran at ambient temperature for 38 h to give the palladacycle product **1**⁷ (Eq. 1). This complex was isolated as air stable solid upon crystallization. The C–H activation at benzylic position⁶ was established by its ¹H NMR and X-ray single-crystal determination. The appearance of signal at 3.24 ppm with the integration of 2H in the ¹H NMR spectra was assigned to the methylene protons of Pd–CH₂—resulted from the C–H activation with the palladium complex.



X-ray diffraction study on the single crystal confirmed the detail of the structure proposed. Figure 1 displays the ORTEP plot of the palladacycle. The palladium metal displays a slightly distorted square-planar geometry with nitrogen and carbon donors in *cis*-fashion. All bond distances and bond angles lie within normal ranges for **1**.⁸ The length of C(8)–N(1) [1.280(5) Å] is

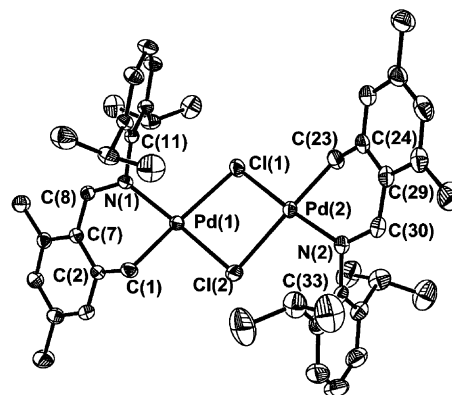


Figure 1. ORTEP drawing of **1** (drawn with 30% probability ellipsoids); Pd(1)–N(1) 2.043(3) Å, Pd(1)–C(1) 2.003(4) Å, N(1)–Pd(1)–C(1) 86.2(1)°.

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characteristic for C=N double bond. The small bite angle N(1)–Pd(1)–C(1) [86.1°] is similar to those benzylic type palladacycles reported by Sales and coworkers.⁹ It is noticed that the angle of Pd(1)–C(1)–C(2) [116.0(3)°] deviating from the angle for a tetrahedral geometry is presumably due to the constraints imposed by the chelating rings. The distances of Pd–C(1) trans to the carbon donor are slightly longer (ca. 0.17 Å) than those *trans* to the imine donor, as expected, because of the trans influence. Examination of those dihedral angles along Pd(1)–N(1)–C(8)–C(7)–C(2)–C(1) of **1** reveals this chelate ring adopting to a twist half-chair conformation, which is due to the presence of two double bonds of N(1)–C(8) and C(2)–C(7) in the ring. The isopropyl groups on the aromatic ring readily force that phenyl ring perpendicular to the coordination plane.

To illustrate the catalytic activity, complex **1** was used as the catalyst for the Suzuki–Miyaura coupling reaction. In a typical experiment for the reaction, aryl halide, phenylboronic acid and K₂CO₃ in a ratio of 1:1.5:2 were placed in the flask, followed by the addition of the solvent and the catalyst. In all instances the solvent was used as obtained commercially without further purification, while the deionized water was used for aqueous systems. The organic product was isolated by extraction and then analyzed by the ¹H NMR spectroscopy. All results are summarized in Table 1.

In this catalysis, the initial reactions were performed using **1** as the catalyst to study the solvent effect (Table 1, entries 1–5). It appeared that the protic solvents including water gave much better results than any other organic solvents. DMF and toluene are common solvents for the coupling reactions, but providing moderate conversion as compared with alcoholic solvents with palladacycle **1** as the catalyst. It is interesting to note

that the coupling reaction was inhibited in the acetonitrile solution, presumably due to the coordinating nature of this solvent (entry 1).

It was found that the palladacycle **1** remained its catalytic activity in the presence of air (entry 3), indicating that this catalytic precursor is quite stable in air. Therefore, the activities of the catalyst toward various of aryl halides in the Suzuki–Miyaura reaction was screened using water or ethanol as the solvents under aerobic conditions (entries 5–20).

As expected, the catalyst behaves better activity toward the aryl bromides than the chlorides, which is essentially similar to those for such coupling reactions. For the chloride substrates, the addition of tetrabutylammonium bromide (TBAB) in water was required for the better conversion (entry 10), which is consistent with the observation by Bedford et al.⁴ Palladacycle **1** shows an excellent catalytic activity for *p*-acetylphenyl bromide and the catalytic turnover number can reach up to 10⁶ (entry 9). Complex **1** also catalyzed the coupling of a steric bulky aryl bromide with phenylboronic acid in good conversion by increasing the concentration of the catalyst (entry 6).

For the activated chloride substrates, the palladium complex **1** catalyzed the coupling reactions in good yields. An excellent TON of 10³ is seen at 0.1 mol % of Pd (entry 15), suggesting that the conversion is influenced by the lifetime of the catalyst. As can be seen, the coupling of phenylboronic acid with either *p*-acetylphenyl chloride or *p*-nitrophenyl chloride catalyzed by **1** also gave excellent results. However, a poor conversion for the deactivated substrates and phenyl chloride was observed (entries 16–18). For the other arylboronic acids, the palladacycle showed a similar activity on the

Table 1. Coupling reaction of aryl halides with phenylboronic acid catalyzed by palladacycle **1**^a

Entry	ArX	Pd (mmol)	[ArX]/[Pd]	Additive	Solvent	Atm	<i>t</i> (h)	Conv. ^b	Yield (%)	TON
1	<i>p</i> -MeOC ₆ H ₄ Br	1 × 10 ^{−4}	20,000	—	CH ₃ CN	Ar	3	Trace	—	—
2	<i>p</i> -MeOC ₆ H ₄ Br	1 × 10 ^{−4}	20,000	—	Toluene	Ar	3	70%	65	14,000
3	<i>p</i> -MeOC ₆ H ₄ Br	1 × 10 ^{−4}	20,000	—	DMF	Air	3	64%	60	12,800
4	<i>p</i> -MeOC ₆ H ₄ Br	1 × 10 ^{−4}	20,000	—	EtOH	Air	3	100%	99	20,000
5	<i>p</i> -MeOC ₆ H ₄ Br	1 × 10 ^{−4}	20,000	—	H ₂ O	Air	3	100%	99	20,000
6	2,4,6-Me ₃ C ₆ H ₂ Br	1 × 10 ³	2000	—	EtOH	Air	3	74%	72	1480
7	<i>p</i> -MeOC ₆ H ₄ Br	2 × 10 ^{−6}	1,000,000	—	EtOH	Air	20	57%	55	600,000
8	<i>p</i> -MeCOC ₆ H ₄ Br	2 × 10 ^{−6}	1,000,000	—	EtOH	Air	20	100%	97	1,000,000
9	<i>p</i> -MeCOC ₆ H ₄ Cl	2 × 10 ^{−4}	10,000	—	H ₂ O	Air	1	Trace	—	—
10	<i>p</i> -MeCOC ₆ H ₄ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	1	87%	83	8700
11	<i>p</i> -NO ₂ C ₆ H ₄ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	1	88%	87	8800
12	<i>o</i> -NO ₂ C ₆ H ₄ Cl	2 × 10 ^{−3}	1000	TBAB	H ₂ O	Air	2.5	91%	90	910
13	<i>o</i> -NO ₂ C ₆ H ₄ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	4	52%	47	5200
14	2,4-(NO ₂) ₂ C ₆ H ₃ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	4	43%	40	4300
15	2,4-(NO ₂) ₂ C ₆ H ₃ Cl	2 × 10 ^{−3}	1000	TBAB	H ₂ O	Air	3	100%	100	1000
16	C ₆ H ₅ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	2	22% ^c	22	2200
17	C ₆ H ₅ Cl	2 × 10 ^{−3}	1000	TBAB	H ₂ O	Air	2	24%	24	240
18	<i>p</i> -MeOC ₆ H ₄ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	16	10%	8	1000
19 ^c	<i>p</i> -MeOC ₆ H ₄ Br	1 × 10 ^{−4}	20,000	—	EtOH	Air	2	100%	100	20,000
20	<i>p</i> -MeCOC ₆ H ₄ Cl	2 × 10 ^{−4}	10,000	TBAB	H ₂ O	Air	1	85%	82	8500

^a Reaction conditions: ArX (2 mmol), PhB(OH)₂ (3 mmol), K₂CO₃ (4 mmol), solvent (5 mL), at refluxing temperature.

^b Determined by ¹H NMR.

^c *p*-MeOC₆H₄B(OH)₂ was used instead of phenylboronic acid.

coupling reaction (entries 19–20). Thus, complex **1** catalyzed the reaction of *p*-methoxyphenyl bromide with *p*-methoxyphenylboronic acid quantitatively.

In summary, cyclopalladated complex **1** has been successfully prepared in a stable form. This catalyst proves to be an excellent catalyst for Suzuki–Miyaura coupling reaction, which can be carried out in air and in aqueous or protic organic solutions. This result readily offers an environmentally benign preparation of diaryl compounds. Further studies on the reaction mechanism and other applications are currently under investigation.

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- Complex **1**: 75%, orange solid, mp: 270 °C (dec); IR (KBr): 1599 cm⁻¹ (ν_{C=N}); ¹H NMR (CDCl₃, 400 MHz): δ 7.81 (s, 1H, –HC=N), 7.23 (t, *J* = 7.3 Hz, 1H, Ar *H*), 7.14 (d, *J* = 7.3 Hz, 2H, Ar *H*), 6.98 (s, 1H, Ar *H*), 6.82 (s, 1H, Ar *H*), 3.48–3.39 (m, 2H, –CH), 3.24 (s, 2H, –H₂C–Pd), 2.30 (s, 3H, –Me), 2.29 (s, 3H, –Me), 1.47 (d, *J* = 6.7 Hz, 6H, –Me), 1.11 (d, *J* = 6.8 Hz, 6H, –Me); ¹³C NMR: δ 162.7, 148.0, 146.5, 143.7, 140.7, 139.8, 130.6, 127.6, 126.8, 125.4, 123.3, 28.2, 24.8, 23.2, 22.5, 21.4, 19.1; FAB *m/z*: 861 (M⁺–Cl⁻); Anal. Calcd for C₄₄H₅₆Cl₂N₂Pd₂: C, 58.94; H, 6.29; N, 3.12; Found: C, 58.89, H, 6.35, N, 3.08.
- Crystal data for Complex **1**: C₄₄H₅₆Cl₂N₂Pd₂, *F*_w 896.61, Monoclinic, space group *P*2₁/c, *a* = 16.7242(2) Å, *b* = 14.6933(2) Å, *c* = 18.1016(2) Å, *a* = 90°, *b* = 108.931(1)°, *g* = 90°, *V* = 4207.57(9) Å³, *Z* = 4, *D*_{calcd}, 1.415 mg/m³, *F*(000) = 1840, 0.25 × 0.20 × 0.20 mm, 31,332 refln collected with 9636 (*R*_{int} = 0.0567), For [*I* > 2 (*I*)], *R*₁ = 0.0395, *wR*₂ = 0.0896, Goodness-of-fit on *F*²: 1.082. Crystallographic data (excluding structure factors) for **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 240355. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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