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The air-stable and highly efficient P, N-chelated palladium(II) complexes as catalysts for the Suzuki cross-coupling reaction at room temperature

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Abstract—Two air-stable P, N-chelated palladium(II) complexes have been evaluated as highly efficient and simple catalysts for Suzuki cross-coupling reaction between aryl bromides and arylboronic acids. They exhibit high activity and selectivity at room temperature.

Biaryls are versatile intermediates in organic synthesis and are recurring functional groups in many natural products, bioactive compounds and liquid crystal materials.[1,2] As a result, considerable effort has been directed towards the development of efficient and selective methods for the synthesis of biaryls.[3–5] The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction represents one of the most widely used processes for the synthesis of biaryls.[6–9] There has recently been considerable interest in the synthesis of new, highly active palladium-based catalysts that can be used in the Suzuki reaction since such catalysts have the potential to be used in industrial systems.[10,11] One of the highlighted works in this area is Fu's publication on the usage of Pd-based *t*-Bu_3P complexes, which is taken as the cover page of a recent issue of the *Journal of Organic Chemistry*.[12] Fu's work showed that *t*-Bu_3P, in conjunction with a Pd catalyst precursor, is a very good system for aryl chloride coupling chemistry.[13] Although *t*-Bu_3P is a very active ligand for challenging coupling reactions, this pyrophoric, low melting solid requires special careful handling techniques. In addition, the in situ conditions often result in the formation of the active species and this will sometimes cause formation of byproducts, leading to relatively lower yields and irreproducible results.[14,15] The utilization of fully formed Pd complexes of *t*-Bu_3P such as Pd(*t*-$Bu_3P)_2$ and [*t*-$Bu_3P(\mu$-Br)Pd]$_2$ to circumvent some of these problems was recently demonstrated.[13d,e,14] However, the above two catalysts have not been developed in economical and commercial routes because they undergo decomposition within hours if not stored properly.[7d] Bearing this in mind, it is worth noticing that bis(aminephosphine) palladium chelated complexes, $[Ph_2P(CH_2)_nNH_2]_2PdCl_2 (n = 2, 3)$, are thermally stable and not sensitive to oxygen and moisture. These complexes were conveniently prepared according to the report by Habtemariam.[15] Moreover, their catalytic activity for C–C bond formation was not evaluated. Habtemariam et al.[16] reported that bis(aminophosphine) complexes of the type $\{Pd(Ph_2P(CH_2)_nNH_2)_2\}^{2+}$ exist in chelate ring-closed and ring-opened forms both in the solid state and in aqueous solution. Based on the behaviours of bis(aminophosphine) palladium complexes, the opening of the chelate bite may be initiated under catalytic conditions, thus generating free coordination sites for catalysis,[17] which encouraged us to synthesize these P and N coordinated palladium chelated complexes and evaluate them in the Suzuki reactions. Herein we report the preliminary results of our research.

We began our study by preparing bis(aminephosphine) palladium complexes, $[Ph_2P(CH_2)_2NH_2]_2PdCl_2$ **1** and

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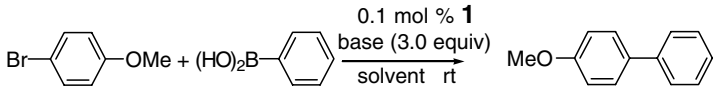
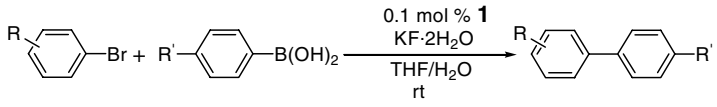
Table 1. Screening of solvents and bases for Suzuki cross-coupling of 4-bromoanisole with phenylboronic acid using catalyst **1**[a]



Entry	Base	Solvent	Time[b] (h)	Yield[c] (%)
1	$K_3PO_4·3H_2O$	THF/H_2O	14	86
2	$KF·2H_2O$	THF/H_2O	10	97
3	Na_2CO_3	THF/H_2O	10	93
4	KOH	THF/H_2O	12	79
5	NaOAc	THF/H_2O	12	76
6	Et_3N	THF/H_2O	12	60
7	$KF·2H_2O$	CH_3CN/H_2O	10	73
8	$KF·2H_2O$	$EtOH/H_2O/PhMe$	10	90
9	$KF·2H_2O$	THF	6	0
10	$KF·2H_2O$	H_2O	6	0

[a] 4-Bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), base (3.0 mmol, dissolved in 2.0 mL of H_2O), catalyst **1** (0.001 mmol), solvent (2.0 mL).
[b] Reaction time not optimized.
[c] Isolated yield.

Table 2. Suzuki reaction of aryl bromides catalyzed by **1**[a]



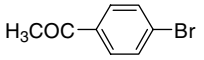
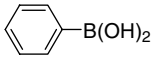
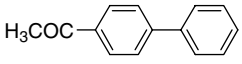
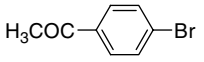
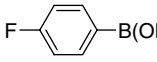
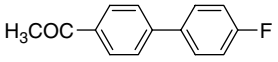
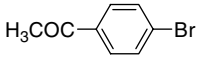
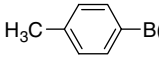
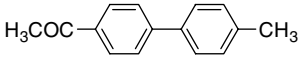
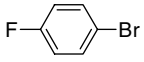
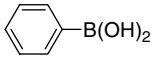
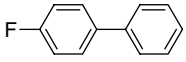
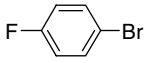
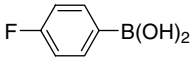
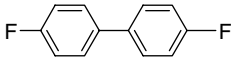
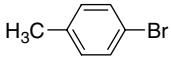
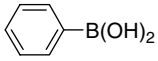
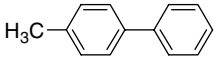
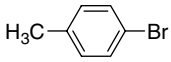
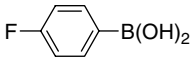
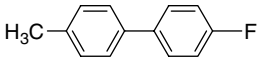
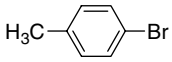
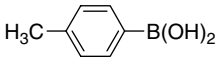
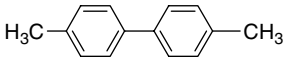
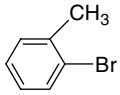
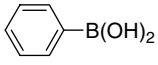
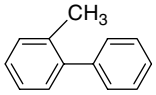
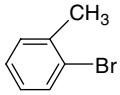
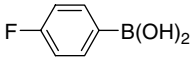
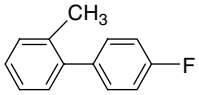
Entry	ArBr	$Ar'B(OH)_2$	Product[a]	Time[b] (h)	Yield[c] (%)
1				6	99
2				6	98
3				8	99
4				7	96
5				7	99
6				10	99
7				6	99
8				5	99
9				10	86
10				9	93

Table 2 (*continued*)

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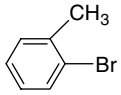
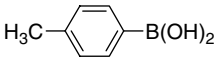
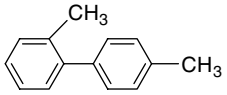
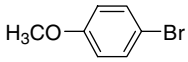
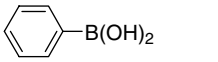
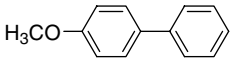
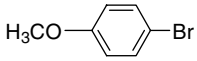
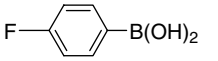
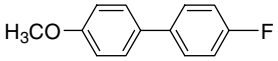
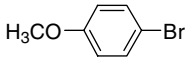
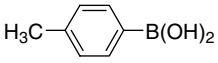
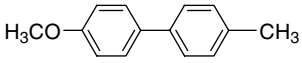
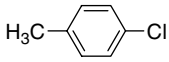
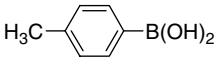
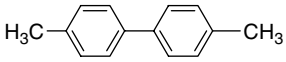
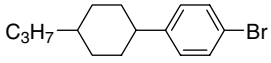
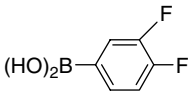
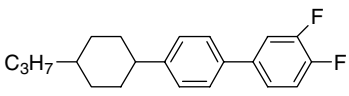
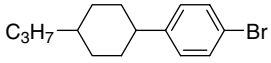
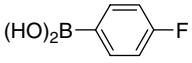
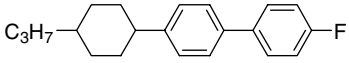
11				9	95
12				14	97
13				12	99
14				14	96
15				12	16[d]
16				5	96
17				4	94

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.5 mmol of arylboronic acid, 3.0 mmol of KF·2H$_2$O(dissolved in 2.0 mL of H$_2$O), catalyst 1 (0.001 mmol), 2.0 mL of THF.
[b] Reaction time not optimized.
[c] Isolated yield.
[d] The reaction was performed in DMF at 100 °C 1.0 mol % catalyst **1**.

[Ph$_2$P(CH$_2$)$_3$NH$_2$]$_2$PdCl$_2$ **2**, using the similar procedure described in the literature.[18] For initial studies, 4-bromoanisole was chosen as the main test substrate as it is electronically inactivated and is usually difficult to be activated in cross-coupling reactions. We were delighted to see that complex **1** catalyzes the reaction between 4-bromoanisole and phenylboronic acid smoothly in THF/H$_2$O, K$_3$PO$_4$, and 86% yield based on 4-bromoanisole which was obtained after 14 h at room temperature (Table 1, entry 1). A brief optimization of solvents and bases showed that the widely used solvents and bases, such as THF/H$_2$O, EtOH/H$_2$O/PhMe, CH$_3$CN/H$_2$O, and KF·2H$_2$O, K$_3$PO$_4$·3H$_2$O, Na$_2$CO$_3$, KOH were used in the cross-coupling reaction and the results were that THF/H$_2$O/KF·2H$_2$O mixtures gave the highest activity. The results are summarized in Table 1. Under optimal conditions, the complex **1** gave essentially complete conversion at 0.1 mol % catalyst loading (Table 1, entry 2) and very high turnover numbers (TONs) of up to 8900 towards 0.01 mol % loading.

To evaluate the scope and limitation of this protocol, the reactions of a wide variety of aryl bromides with arylboronic acids were examined under optimal conditions (Table 2). Both electron-rich and electron-deficient aryl bromides were applicable for this reaction. The reactions of aryl bromides with electron-rich groups (such as 4-bromoanisole) gave the coupling products with excellent yield (Table 2, entries 1–3) in the presence of 0.1 mol % 1 at room temperature. Complex **2** also showed good reactivity and gave high yield (93%) with the same protocol. Those reactions involving aryl bromides with electron-deficient groups proceeded smoothly at room temperature to give the coupling product in 99% yield after 6–8 h (Table 2, entries 4–5). Aryl bromides containing ortho-substituents also reacted effectively to afford the desired product in good to excellent yield (Table 2, entries 12–14). No significant difference was observed in yield and in the reaction time when the effect of varying the arylboronic acids in the Suzuki cross-coupling reactions was studied. In addition, we can use this new protocol to synthesize liquid crystal compounds, such as 4-fluoro-(4′-propylcyclohexyl)biphenyl and 3,4-difluoro-(4′-propylcyclohexyl)biphenyl, with excellent yield.[19] Thus, this method provides a highly efficient and mild way to prepare biphenyl derivatives used as liquid crystal compounds (Table 2, entries 16–17).

To test the suitability of **1** for aryl chloride substrates, we investigated the Suzuki cross-coupling between *para*-chlorotoluene and tolylboronic acid. Unfortunately, this reaction proceeded sluggishly under the catalysis of 1.0 mol % **1**, only biaryls in 16% yield after 12 h in DMF at 100 °C (Table 2, entry 15).

In summary, the bis(aminophosphine) palladium complexes **1** and **2** are active catalysts for Suzuki cross-

coupling reactions. The aryl bromides substituted by *para*-substituent of electron-rich or electron-deficient can react with arylboronic acids under very mild condition. This catalyst **1** has been applied successfully in the synthesis of liquid crystal compounds. These two chelated Pd(II) complexes are air- and moisture-stable, and the reaction can be readily conducted under aerobic conditions. Further studies of their applicability in other synthetic transformation are currently under investigation.

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18. A solution of $H_2NCH_2CH_2PPh_2$ of 0.12 g (0.52 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise to a suspended solution of Na_2PdCl_4 of 0.076 g (0.26 mmol) in CH_2Cl_2 (25.0 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The volume was reduced to ca. 7.0 mL and diethyl ether was added to precipitate a whitish powder which was then filtered off and washed with diethyl ether and recrystallized from acetone–dichloromethane. The complex **1** was obtained in 90% yield which was confirmed as the product by ^{1}H NMR ($CDCl_3$) δ 2.57–2.65 (2H, m, N-CH_2), 2.92–2.97 (2H, m, P-CH_2), 6.18 (NH_2, br, s), 7.25–7.54 (10H, m, Ph); ^{31}P NMR ($CDCl_3$) δ 55.74. and elemental analysis: C 52.36%, H 4.86%, N 4.38% (calcd for $C_{28}H_{32}Cl_2N_2P_2Pd$: C 52.89%, H 5.07%, N 4.40%). Complex **2** was prepared with the same procedure as that described for complex **1**, except that $H_2NCH_2CH_2CH_2PPh_2$ 0.13 g (0.52 mmol) was used to replace the $H_2NCH_2CH_2PPh_2$. yield 87%. ^{1}H NMR ($CDCl_3$) δ 1.62 (2 H, br, m), 2.35 (2 H, br, m), 3.45–3.50 (m, br), 5.62 (NH_2, br), 7.20–7.57 (10H, m, Ph); ^{31}P NMR ($CDCl_3$): δ 19.53.
19. The reaction was carried out in standard Schlenck. THF (2 mL), 4-(4′-propyl-cyclohexyl)bromobenzene (281.2 mg, 1 mmol), 4-fluorophenylboronic acid (209.9 mg, 1.5 mmol), $KF{\cdot}2H_2O$ (282.4 mg, 3 mmol, dissolved in 2 mL of water) and **1** (0.6358 mg, 0.001 mmol) were in the reaction tube. The reaction mixture was stirred at room temperature (25–27 °C) for 5 h. Reaction progress was monitored by TLC and when the reaction was completed, the mixture was quenched with 5 mL of H_2O and extracted by 3×5 mL of ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of crude product by flash chromatography on silica gel afforded 284.6 mg of 4-fluoro-4′-(4-propyl-cyclohexyl)bipheny (96%) as a solid. Anal. Found: C, 85.21; H, 7.49; Calcd for $C_{21}H_{23}F$: C, 85.67; H, 7.87; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.02–1.11 (m, 2H), 1.20–1.39 (m, 5H), 1.44–1.50 (m, 2H), 1.90 (t, $J = 6.4$ Hz, 4H), 2.47–2.53 (m, 1H), 7.07–7.12 (m, 2H), 7.27 (d, $J = 8$ Hz, 2H), 7.46 (d, $J = 8$ Hz, 2H), 7.50–7.54 (m, 2H). ^{13}C NMR: δ 14.61, 20.23, 33.77, 34.54, 37.23, 39.91, 44.47, 115.59, 115.80, 127.07, 127.49, 128.63, 137.47, 137.95, 147.26, 161.23, 163.68.