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Application of *ortho*-palladated homoveratrylamine complex containing mixed phosphorus–nitrogen donors in the Suzuki reaction

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The catalytic activity of [Pd{$C_6H_2(CH_2CH_2NH_2)$-$(OMe)_2$,3,4}Br(PPh_3)] monomeric *ortho*-palladated complex of homoveratrylamine and triphenylphosphine was investigated in the Suzuki cross-coupling reaction of various aryl halides with aryl boronic acids. The substituted biaryls were produced in excellent yields using a catalytic amount of this complex in ethanol at 60°C. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Suzuki reaction; catalyst; *ortho*-palladated complex; triphenylphosphine

Introduction

The palladium-catalyzed cross-coupling of nucleophilic organborans with electrophilic organic halides and triflates, known as the Suzuki reaction, has emerged as a powerful and versatile tool for the synthesis of substituted biaryls.[1–5] Biaryls are applied as the building block for a wide range of herbicides,[6] pharmaceuticals,[7] natural and bioactive products,[8] microelectrode arrays,[9] conducting polymers, and liquid crystal materials.[10] The key benefits of the Suzuki–Miyaura coupling are the mild reaction conditions, tolerance of a broad range of functionalities, commercial availability and easy handling of organoboron reagents, and removal of the nontoxic boron-containing byproducts.[11,12] In view of the importance of biaryls, a number of effective palladium catalytic systems have been developed for the Suzuki cross-coupling reaction. Among the new methods the palladacycle catalysts are the most important classes, used very efficiently in catalysis at very low concentration in organic synthesis,[13–16] material science,[17] biologically active compounds[18] and macromolecular chemistry.[19–21] 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.[22,23]

In continuation of our recent investigations on the synthesis and application of palladacycle complexes in cross-coupling reactions,[24–34] we now wish to report the extension of the [Pd{C_6H_2 $(CH_2CH_2NH_2)$–$(OMe)_2$,3,4}Br(PPh_3)] monomeric *ortho*-palladate complex for the cross-coupling reaction of various aryl halides with aryl boronic acids.

Results and Discussion

A suitable chemical production process via palladium catalysis requires high catalyst productivity and activity. Also the availability and cost of catalysts and the price of the organic starting materials are of great importance for industrial processes. Monomeric *ortho*-palladated complex [Pd{$C_6H_2(CH_2CH_2NH_2)$–$(OMe)_2$,3,4}Br(PPh_3)] was prepared according to our previous work.[25] The acetate-bridged *ortho*-palladated complex was obtained from homoveratrylamine by addition of $Pd(OAc)_2$ in acetonitrile as a binuclear complex. The halogen-bridged *ortho*-palladated complex was prepared by the addition of NaBr to a solution of the acetate-bridged complex in acetone. Addition of triphenylphosphine to this dimeric *ortho*-palladated complex [Pd{$C_6H_2(CH_2CH_2NH_2)$–$(OMe)_2$,3,4}(μ-Br)]$_2$ in dichloromethane gave the monomeric *ortho*-palladated complex [Pd{$C_6H_2(CH_2CH_2NH_2)$-$(OMe)_2$,3,4}Br(PPh_3)]. Homoveratrylamine as an *N*-donor ligand is an available and inexpensive amine. The *ortho*-palladation reaction of this substrate is simple and leads to an efficient catalyst for coupling reactions. Homoveratrylamine in combination with triphenylphosphine ligand gave monomeric complex. The monomeric complex containing mixed phosphorus–nitrogen (P–N) donors was found to be more active than the corresponding dimeric one, which contains only a single nitrogen donor especially for unreactive aryl halides or even aryl chlorides, which are available and cheap substrates. The monomeric complexes are easier to reduce to the active Pd(0) species compared with the dimeric catalyst.[35] Herein, the efficiency of monomeric complex is evaluated in the Suzuki cross-coupling reaction (Scheme 1).

Initially, to determine the optimal conditions, Suzuki cross-coupling reaction was carried out between 4-iodoanisole and phenylboronic acid using monomeric *ortho*-palladated complex in different solvents and bases as shown in Table 1.

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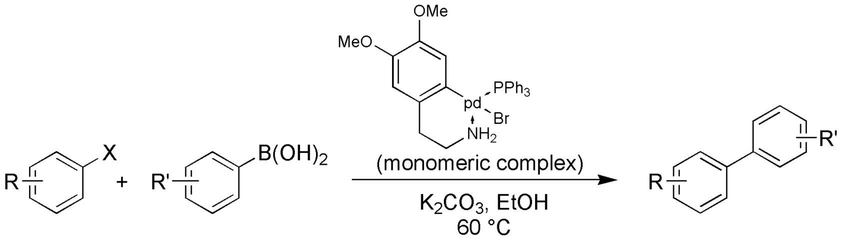

Scheme 1. The Suzuki cross-coupling reaction by monomeric *ortho*-palladated complex

Table 1. Optimization of reaction conditions on Suzuki reaction of 4-iodooanisole with phenylboronic acid[a]

Entry	Solvent	Base	Catalyst concn (mol%)	Temperature (°C)	Time (h)	Conversion (%)[b]
1	DMF	K_2CO_3	1	130	1.5	97
2[c]	EtOH	K_2CO_3	1	60	0.7	93
3[c]	EtOH	K_2CO_3	1	r.t	3.5	89
4[c]	EtOH	K_2CO_3	0.5	60	1	89
5	EtOH	—	0.5	60	1	0
6	EtOH	K_2CO_3	0.5	60	0.5	98
7	NMP	K_2CO_3	1	130	7.5	44
8	Dioxane	K_2CO_3	1	85	6	20
9	THF	K_2CO_3	1	60	12	40
10	CH_3CN	K_2CO_3	1	75	5	70
11	Toluene	K_2CO_3	1	100	6	25
12	EtOH	Cs_2CO_3	1	60	0.6	94
13	EtOH	Na_2CO_3	1	60	3.5	66
14	EtOH	NaOAc	1	60	3	43
15	EtOH	$NaHCO_3$	1	60	14	65
16	EtOH	Et_3N	1	60	3	10

[a] Reaction conditions: 4-iodooanisole (1 mmol), phenylboronic acid (1.2 mmol), base (2 mmol), monomeric *ortho*-palladated complex.

[b] GC yield.

[c] base (1 mmol).

Table 2. Optimization of catalyst concentration on the Suzuki reaction of 4-bromobenzonitrile with phenylboronic acid[a]

Entry	Catalyst concn (mol%)	Time (h)	Conversion (%)[b]
1	None	3	0
2	0.1	0.8	91
3	0.2	0.6	100
4	0.3	1.3	92
5	0.4	1	91
6	0.5	1	94
7	1	0.5	90

[a] Reaction conditions: 4-bromobenzonitrile (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2 mmol), monomeric *ortho*-palladated complex, EtOH (2 ml), 60°C.

[b] GC yield.

As demonstrated in Table 1 (entry 6), K_2CO_3 as base and ethanol as solvent gave the best results. Various catalyst concentrations were also tested and 0.2 mol% (Table 2, entry 3) gave the best result. As this catalyst is not sensitive to oxygen, the reactions were carried out under air atmosphere.

We applied the optimized conditions to the Suzuki cross-coupling reaction of different types of aryl halides with phenylboronic acids, as shown in Table 3.

As is demonstrated in Table 3, the monomeric *ortho*-palladated catalyst can be used for cross-coupling reactions of aryl iodides, bromides and even less reactive aryl chlorides with aryl boronic acids in good to excellent yields. We examined the electronic and steric effects of various aryl halides bearing electron-donating and electron-withdrawing groups on the resulting yields and conversion times of the reactions. The substituent effects in the aryl iodides emerged to be less significant than in the aryl bromides, and the reactivity of aryl bromides with electron-withdrawing substituent was higher than that of aryl bromides with electron-donating substituent. The steric hindrance of the procedure was examined using 2-, 3- and 4-bromoacetophenone as hindered substituted aryls. Increased hindrance in the vicinity of the leaving group can cause a decrease in the reaction conversion (Table 3, entries 10–12). The chemo-selectivity of the procedure was examined using chlorobromobenzene derivatives (Table 3, entries 13–16 and 25–27). In these reactions Br acted as a better leaving group. This catalytic complex was compatible with a wide range of functional groups such as nitro, cyano, methoxy, halogen, and carbonyl on aryl halides. As demonstrated in Table 4 for some of the aryl halides, the monomeric complex (A) was more active than the dimeric complex (B). In the literature has been ascribed that difference in the catalytic activity shown by the monomeric complexes and the dimeric ones resulted from the triphenylphosphine part. As a result, the monomeric complexes are easier to be reduced to the active Pd(0) species compared with the corresponding dimeric ones under the same conditions.[35]

Conclusion

We employed monomeric *ortho*-palladated complex $[Pd\{C_6H_2(CH_2CH_2NH_2)–(OMe)_2,3,4\}Br(PPh_3)]$ as a highly efficient, stable catalyst that was non-sensitive to air and moisture was and easy to prepare for Suzuki reaction of aryl halides with aryl boronic acids. The Suzuki reaction was carried out under mild conditions for aryl iodides and aryl bromides at 60°C in ethanol as green solvent using a catalytic amount of this catalyst. This catalytic system was also applied for Suzuki cross-coupling of aryl chlorides that led to C&bond;C bond formation in good to excellent yields.

Table 3. Suzuki cross-coupling reaction using monomeric *ortho*-palladated complex of homoveratrylamine and triphenylphosphine

Entry	Ar-X	Boronic agent	Biaryl product	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	Ph-I	PhB(OH)$_2$	Ph-Ph	0.2	100	90
2	*p*-MeO-Ph-I	PhB(OH)$_2$	*p*-MeO-Ph-Ph	1.2	100	92
3	*p*-O$_2$N-Ph-I	PhB(OH)$_2$	*p*-O$_2$N-Ph-Ph	1	100	92
4	*m*-O$_2$N-Ph-I	PhB(OH)$_2$	*m*-O$_2$N-Ph-Ph	1.1	100	89
5	Ph-Br	PhB(OH)$_2$	Ph-Ph	0.25	100	89
6	*p*-MeO-Ph-Br	PhB(OH)$_2$	*p*-MeO-Ph-Ph	1.25	100	93
7	*p*-O$_2$N-Ph-Br	PhB(OH)$_2$	*p*-O$_2$N-Ph-Ph	1.2	100	86
8	*o*-O$_2$N-Ph-Br	PhB(OH)$_2$	*o*-O$_2$N-Ph-Ph	4	92	80
9	*p*-NC-Ph-Br	PhB(OH)$_2$	*p*-NC-Ph-Ph	0.6	100	94
10	*p*-MeOC-Ph-Br	PhB(OH)$_2$	*p*-MeOC-Ph-Ph	1.5	100	90
11	*m*-MeOC-Ph-Br	PhB(OH)$_2$	*m*-MeOC-Ph-Ph	4	90	85
12	*o*-MeOC-Ph-Br	PhB(OH)$_2$	*o*-MeOC-Ph-Ph	5	70	62
13	*p*-Cl-Ph-Br	PhB(OH)$_2$	*p*-Cl-Ph-Ph	0.08	100	93
14	*m*-Cl-Ph-Br	PhB(OH)$_2$	*m*-Cl-Ph-Ph	0.1	100	90
15	*o*-Cl-Ph-Br	PhB(OH)$_2$	*o*-Cl-Ph-Ph	0.25	100	89
16	*p*-OHC-Ph-Br	PhB(OH)$_2$	*p*-OHC-Ph-Ph	1.25	97	88
17	1-Br-Naphthalene	PhB(OH)$_2$	1-Ph-Naphthalene	3	95	85
18	9-Br-Phenanthrene	PhB(OH)$_2$	9-Ph-Phenanthrene	2	100	90
19[d]	*p*-O$_2$NPh-Cl	PhB(OH)$_2$	*p*-O$_2$N-Ph-Ph	17	100	80
20[d]	*p*-OHC-Ph-Cl	PhB(OH)$_2$	*p*-OHC-Ph-Ph	24	100	76
21	Ph-I	*p*-MeO-PhB(OH)$_2$	*p*-MeO-Ph-Ph	0.3	100	92
22	*p*-O$_2$N-Ph-I	*p*-MeO-PhB(OH)$_2$	*p*-O$_2$N-Ph-Ph-*p*-OMe	1.1	100	95
23	*m*-O$_2$N-Ph-I	*p*-MeO-PhB(OH)$_2$	*m*-O$_2$N-Ph-Ph-*p*-OMe	1.25	100	93
24	*p*-Cl-Ph-Br	*p*-MeO-PhB(OH)$_2$	*p*-Cl-Ph-Ph-*p*-OMe	0.17	100	92
25	*m*-Cl-Ph-Br	*p*-MeO-PhB(OH)$_2$	*m*-Cl-Ph-Ph-*p*-OMe	0.25	100	91
26	*o*-Cl-Ph-Br	*p*-MeO-PhB(OH)$_2$	*o*-Cl-Ph-Ph-*p*-OMe	0.4	100	89
27	*p*-NC-Ph-Br	*p*-MeO-PhB(OH)$_2$	*p*-NC-Ph-Ph	1	100	90

[a] Reaction conditions: aryl halide (1 mmol), phenylboronic acid (1.2 mmol), base (2 mmol), monomeric *ortho*-palladated complex (0.2 mol%), EtOH (2 ml), 60°C.

[b] TLC and GC yield.

[c] Isolated yield.

[d] DMF, 120°C.

Experimental

Chemicals

All melting points were taken on a Gallenkamp melting apparatus and are uncorrected. ^{1}H-NMR spectra were recorded using 500 MHz in CDCl$_3$ solutions at room temperature (TMS was used as an internal standard) on a Bruker Avance 500 instrument (Rheinstetten, Germany). FT-IR spectra were recorded on a spectrophotometer (Jasco-680, Japan). Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported as wave number (cm^{-1}). We used a gas chromatograph (BEIFIN 3420 equipped a Varian CP SIL 5CB column, 30 m, 0.32 mm, 0.25 μm) for examination of reaction competition and yields. Palladium acetate, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

General Procedure for the Suzuki Cross-Coupling Reaction

To a round-bottomed flask equipped with a magnetic stirring bar were added aryl halide (1 mmol), phenylboronic acid (1.2 mmol), K$_2$CO$_3$ (2 mmol) and monomeric *ortho*-palladated catalyst (0.2 mol%) in ethanol (2 ml) or DMF (for aryl chlorides). The mixture was heated at 60°C for aryl iodides and bromides or at 120°C for aryl chlorides using an oil bath and the progress was monitored by thin-layer chromatography (TLC) (hexane–EtOAc, 9:1) and gas chromatography (GC). After competition of the reaction, the mixture was cooled to room temperature and diluted with *n*-hexane or ether and water. The organic phase was dried over CaCl$_2$, filtered and concentrated under reduced pressure using a rotary evaporator. The residue was purified by silica gel column chromatography. The products were characterized by comparing their melting points, IR, ^{1}H, ^{13}C NMR spectra with those found in the literature.[29,36]

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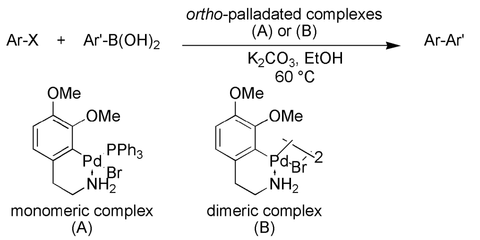
Table 4. Comparison of the monomeric (A) and dimeric (B) *ortho*-palladated complexes in the Suzuki reaction[a]



Entry	Ar-X	Boronic agent	Time (h)	Complex	Conversion (%)[b]
1	9-Br-Phenanthrene	$PhB(OH)_2$	3	A	95
				B	80
2	1-Br-Naphthalene	$PhB(OH)_2$	2	A	100
				B	75
3	*m*-MeOC-Ph-Br	$PhB(OH)_2$	4	A	90
				B	80
4[C]	*p*-O_2NPh-Cl	$PhB(OH)_2$	17	A	100
				B	75
5[C]	*p*-OHC-Ph-Cl	$PhB(OH)_2$	24	A	100
				B	80

[a] Reaction conditions: aryl halide (1 mmol), phenylboronic acid (1.2 mmol), base (2 mmol), *ortho*-palladated complex (0.2 mol%), EtOH (2 ml), 60°C.

[b] GC yield.

[C] DMF, 120°C.

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