



Dichlorobis(dibenzyl diisopropylphosphoramidite)palladium-Catalyzed Suzuki Coupling of Aryl Chlorides in N-Methyl Pyrrolidone Under Aerobic Conditions

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The air and moisture stable dichlorobis(dibenzyl diisopropylphosphoramidite)-palladium $\{[(\text{PhCH}_2\text{O})_2\text{P}(\text{CH}_3)_2\text{CHNCH}(\text{CH}_3)_2]_2\text{PdCl}_2\}$ (**2**) containing electron-rich, sterically bulky phosphane (**1**) has been successfully used in palladium-catalyzed Suzuki cross-coupling of aryl chlorides in N-methyl pyrrolidone under aerobic conditions. The corresponding coupling products were obtained in satisfactory to excellent yields.

Key Words: Palladium complex, Suzuki cross-coupling, Aryl chlorides.

INTRODUCTION

Suzuki cross-coupling reactions which produce biaryls are an important class of compounds for many applications including pharmaceuticals, conducting polymers, advanced materials, liquid crystals and natural products, are currently among the most highly prized processes in synthetic chemistry. The 2010 Nobel prize in chemistry was awarded to Suzuki for his discovery and development of the Suzuki reaction for biaryls¹⁻⁹. Since Suzuki and co-workers reported the preparation of biaryls in 1981¹⁰, various catalytic systems have been described, such as phosphine ligand palladium catalysts¹¹⁻¹³, phosphine-free palladium catalysts¹⁴⁻¹⁹, ligand-free palladium catalysts²⁰⁻²⁴. However, until late 1990s, many catalytic systems are limited to the coupling of aromatic iodides and bromides because the comparatively inexpensive and readily available aryl chlorides, which represent the most attractive candidates for industrial applications of these reactions, are reluctant toward oxidative addition in the Suzuki cross-coupling reactions process²⁵. As a result, significant research effort has been focused on the design, preparation and use of catalysts capable of activating aryl chloride substrates^{9,26}. During the past few years, the use of sterically hindered and electron-rich ligand played crucial roles in the cross coupling of these challenging substrates, such as trialkylphosphine^{27,28}, heterocyclic carbene²⁹⁻³¹, palladacycle^{32,33}, etc. Therefore, the development of new ligands or the application of existing ligands in this reaction involving

aryl chlorides as substrates is still of considerable importance³⁴. Recently, we have reported that the air and moisture stable dichlorobis(dibenzyl diisopropylphosphoramidite)palladium (**2**) containing electron-rich, sterically bulky phosphane (**1**) (Fig. 1) is a highly efficient catalyst for Suzuki cross-coupling reaction of aryl bromides at room temperature in aqueous media under ambient atmosphere³⁵. Thus, as a part of our ongoing efforts to develop efficient methods for the coupling of aryl chlorides, we investigated the catalytic property of this complex (**2**) in the Suzuki cross-coupling reaction of aryl chlorides in N-methyl pyrrolidone.

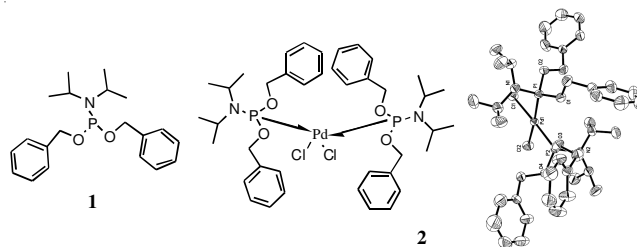


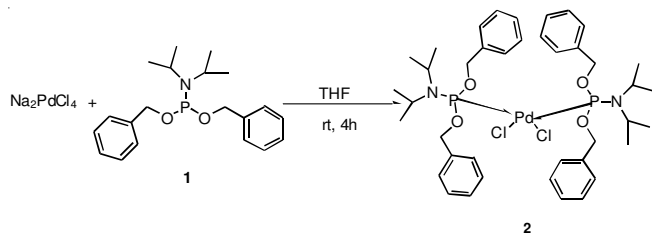
Fig. 1. Dichlorobis(dibenzyl diisopropylphosphoramidite)palladium (**2**) containing electron-rich, sterically bulky phosphane (**1**)

EXPERIMENTAL

All reagents were supplied commercially from Aldrich or Alfa Aesar and used without any prior purification. Silica

gel 60 GF₂₅₄ was used for analytical TLC. ¹H and ¹³C NMR spectra were recorded on a Bruker-400 spectrometer using tetramethylsilane as the internal standard and CDCl₃ as the solvent.

The complex $\{[(\text{PhCH}_2\text{O})_2\text{P}(\text{CH}_3)_2\text{CHNCH}(\text{CH}_3)_2]\text{PdCl}_2\}$ (**2**) used in this work was prepared according to recently reported literature procedures summarized in **Scheme-I**³⁵.



Scheme-I: Synthesis of dichlorobis(dibenzyl diisopropylphosphoramidite) palladium (**2**)

Typical experimental procedure for the Suzuki cross-coupling reaction: A mixture of aryl chloride (1.0 mmol), aryl boronic acid (1.2 mmol), NaOAc·3H₂O (2 mmol), $\{[(\text{PhCH}_2\text{O})_2\text{P}(\text{CH}_3)_2\text{CHNCH}(\text{CH}_3)_2]\text{PdCl}_2\}$ (0.03 mmol) in N-methyl pyrrolidone (NMP) (4 mL) was heated at 140 °C under air atmosphere until complete consumption of starting material as monitored by TLC analysis. Upon cooling to the room temperature, water (100 mL) was added. The mixture was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate solution was washed with saturated NaCl solution (3 × 25 mL). The combined organic phase was dried with MgSO₄, filtered, solvent was removed on a rotary evaporator and the product was isolated by preparative thin layer chromatography on silica gel. The purified products were identified by ¹H and ¹³C NMR spectroscopy and melting points with the literature data.

RESULTS AND DISCUSSION

The complex $\{[(\text{PhCH}_2\text{O})_2\text{P}(\text{CH}_3)_2\text{CHNCH}(\text{CH}_3)_2]\text{PdCl}_2\}$ (**2**) was obtained derived from reactions of dibenzyl diisopropylphosphoramidite and Na₂PdCl₄ in THF at ambient temperature in good yields according to the literature method³⁵. The X-ray crystal structure of **2** is shown in Fig. 1.

Suzuki coupling reaction: In initial experiments, N-methyl pyrrolidone was chosen as the solvent and sodium carbonate as the base for the reaction of electron-withdrawing 4-chloroacetophenone with phenylboronic acid using 3 mol % of complex (**2**) at 140 °C under aerobic conditions. The yield of the target product was enhanced to 85 % for 17 h. We further investigated the influence of the base in the same reaction, examining Et₃N, NaF, NaOAc·3H₂O, Cs₂CO₃, Na₂CO₃, K₃PO₄·3H₂O, NaOH. As shown in Table-1, an investigation of the influence of the base suggested that NaOAc·3H₂O (Table-1, entry 3) was the reagent of choice. Stronger base, Cs₂CO₃, was not necessary in the reaction (Table-1, entry 4).

As illustrated in Table-2, the reaction of a wide variety of aryl chlorides with phenylboronic acids was examined using 3 mol % $\{[(\text{PhCH}_2\text{O})_2\text{P}(\text{CH}_3)_2\text{CHNCH}(\text{CH}_3)_2]\text{PdCl}_2\}$ in N-methyl pyrrolidone and NaOAc·3H₂O as a base at 140 °C. For electron-deficient aryl chlorides such as 4-chloroacetophenone and 4-chloronitrobenzene (Table-2, entries 1-5, 8-9), they could be coupling efficiently leading to relatively high yields,

TABLE-1
SCREENING OF BASES FOR SUZUKI COUPLING REACTION^a

Entry	Base	Yield ^b (%)
1	Et ₃ N	52
2	NaF	61
3	NaOAc·3H ₂ O	92
4	Cs ₂ CO ₃	68
5	Na ₂ CO ₃	85
6	K ₃ PO ₄ ·3H ₂ O	79
7	NaOH	78

^a4-Chloroacetophenone (1.0 mmol), phenylboronic acid (1.2 mmol), base (2 equiv.), NMP (4 mL), Cat. (0.03 mmol), 140 °C, 17 h. ^bIsolated yield.

while electron-donating substituents resulting in relatively low yields (Table-2, entry 13). The sterically hindered 2-substituted substrate could also couple, only moderate yield of 61 % was achieved (Table-2, entry 12). In addition, the effect of varying arylboronic acids containing electron-withdrawing, electron-donating groups for Suzuki cross-coupling reactions was investigated and the yields decreased according to the electronegativity of the arylboronic acids. The higher yields of arylboronic acids containing electron-withdrawing groups were achieved compared to arylboronic acids containing electron-donating groups (Table-2, entries 1-3).

TABLE-2
COMPLEX (**2**) CATALYZED SUZUKI COUPLING OF ARYL CHLORIDES^a

Entry	R ₁	R ₂	Time (h)	Yield ^b
1	4-CH ₃ CO	H	17	92
2	4-CH ₃ CO	4-CH ₃	17	87
3	4-CH ₃ CO	4-CH ₃ O	17	78
4	4-CH ₃ CO	4-F	17	88
5	4-CH ₃ CO	2,4-F	17	82
6	H	4-CH ₃	19	79
7	H	4-CH ₃ O	19	65
8	4-NO ₂	4-CH ₃	17	85
9	4-NO ₂	2,4-F	17	79
10	4-CH ₃	4-CH ₃ O	20	77
11	4-CH ₃	4-F	20	81
12	2-CN	4-CH ₃	21	61
13	4-CH ₃ O	4-CH ₃ CO	24	40

^a4-Chloroacetophenone (1.0 mmol), phenylboronic acid (1.2 mmol), NaOAc·3H₂O (2 equiv.), NMP (4 mL), Cat. (0.03 mmol). ^bIsolated yield.

Conclusion

We have demonstrated that air and moisture stable dichlorobis(dibenzyl diisopropylphosphoramidite)palladium $\{[(\text{PhCH}_2\text{O})_2\text{P}(\text{CH}_3)_2\text{CHNCH}(\text{CH}_3)_2]\text{PdCl}_2\}$ (**2**) is efficient

catalysts for Suzuki cross-coupling of aryl chlorides with phenylboronic acid. This catalytic system conveniently and efficiently gave moderate to excellent yields of corresponding biaryl for aryl chlorides containing electron-withdrawing, electron-donating groups under aerobic conditions. Application of this catalyst in other palladium-catalyzed reactions are currently under investigation in our laboratory.

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