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Highly efficient Suzuki coupling using moderately bulky tolylphosphine ligands

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Abstract

Tolylphosphines, P(*o*-tolyl)$_n$Ph$_{3-n}$ have been used in the palladium catalyzed Suzuki cross-coupling reactions of a series of aryl-bromides, chlorides and also two bromoarylphosphine oxides and a bromoarylphosphine with arylboronic acids. The effects of the phosphine, palladium source, base, solvent and promoter salt were investigated. In all studied phosphines, particularly P(*o*-tolyl)$_2$Ph high conversions and turnovers were seen compared to ortho-unsubstituted phosphines which indicates that other factors such as cyclometallation in addition to steric and electronic effects may be responsible.

Keywords: Suzuki coupling reaction; Tolylphosphine; Palladium catalyst

1. Introduction

Palladium-catalyzed Suzuki cross-coupling reactions of aryl halides with arylboronic acids have emerged as an extremely efficient and important tool in organic synthesis, as well as in a variety of industrial processes [1–20]. Commercially available PPh_3 has been used extensively for these reactions; however, it requires elevated reaction temperatures, tends to be inactive towards aryl chloride substrates, and produces phenyl-aryl by-products [21–23]. On the other hand, opposite activities have been reported using P(*o*-tolyl)$_3$ in the Suzuki cross-coupling reactions. Although many authors have reported P(*o*-tolyl)$_3$ to be a very active phosphine, Fu and co-worker have reported this ligand to be a relatively inactive phosphine [6]. In addition, Richards and co-workers have demonstrated a relationship between the steric and electronic effects of the phosphines as a plot where P(*o*-tolyl)$_3$ was placed in a lower activity zone [24]. This difference in activity results from the presence of many reaction steps, each of which may contribute in the rate of reaction (Scheme 1). The main components of the mechanism for the Suzuki coupling are believed to be an pre-dissociation and or reduction step in which the Pd(II) source is converted to the more active and coordinatively unsaturated Pd(O) catalyst. Sterically demanding and more electron-rich phosphines enforce this step (e.g., Wilkinson hydrogenation process) [23,25–27]. The next steps are an oxidative addition of aryl halide to the Pd(O) active catalyst followed by a transmetallation step in which the aryl group is transferred from boron to palladium, and finally a reductive elimination to release the product. More electron-rich and less bulky phosphines facilitate the oxidative addition step while more bulky and less electron-rich phosphines facilitate the reductive elimination step [28,29]. Therefore, the relative contribution of steric and electronic effects is very important, particularly for less reactive aryl chlorides [30–32]. Since the type and the number of substituents have an important effect on the bulkiness and electron density of the phosphines, and in continuation of our previous investigations on the

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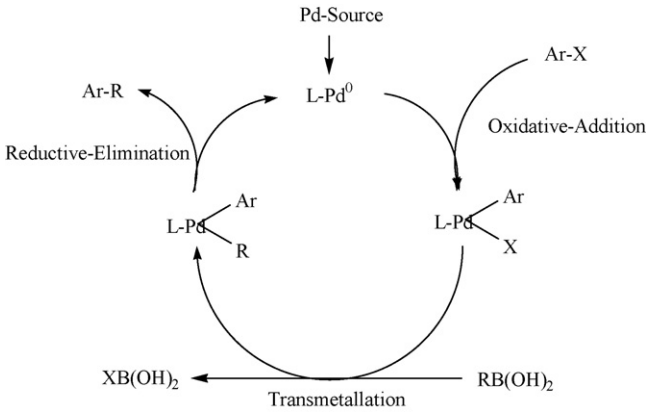
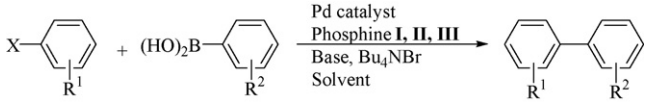


Scheme 1. General mechanism for the Suzuki cross-coupling reactions.



I: P(o-toly)Ph_2, **II**: P(o-toly)$_2$Ph, **III**: P(o-toly)$_3$

Scheme 2. Screening the reaction of aryl halides with arylboronic acid.

application of mixed arylphosphines in the Suzuki coupling [33], we were encouraged to synthesize mixed phenyltolylphosphines, P(*o*-tolyl)$_n$Ph$_{3-n}$ **I–III** and investigate their activity in Suzuki cross-coupling (Scheme 2).

2. Experimental

2.1. Materials and techniques

All chemicals were purchased from Fluka and/or Merck companies. ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{31}P (162 MHz) NMR spectra were recorded on a Bruker Avance Spectrometer. Shimadzu GC 14-A and thin layer chromatography on precoated silica gel fluorescent 254 nm (0.2 mm) were used for monitoring the reactions. Conversions were determined by GC, based on bromoacetophenone. Turnovers were defined as mole of product per mole of catalyst. Elemental analysis was performed using CHN Herause rapid model. The cross-coupling biphenyl product was characterized by its ^{1}H NMR spectrum and melting points.

2.2. Preparation of P(o-tolyl)$_3$ (*III*): typical procedure [34]

To a freshly prepared diethyl ether solution of 4-lithiotolyl (33 mmol, 3.23 g) at −78 °C was added freshly distilled PCl_3 (10 mmol, 1.38 g) in 5 mL of anhydrous diethyl ether dropwise with stirring over 20 min. After stirring at −78 °C (at this temperature organolithium reagent has sufficient stability and activity) for 30 min, the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 1.5 h, the reaction mixture was hydrolyzed with HCl (1N, 10 mL), followed by addition of chloroform and then, the organic solution was separated and dried over $MgSO_4$. The solvent was removed at reduced pressure. The residue was washed with methanol (4× 5 mL), to yield the crude product (2.42 g, 79.6%). The crude product was recrystallized from a chloroform/hexane (1/4) to yield desired pure product (2.15 g, 70.7%).

In order to prepare P(*o*-tolyl)$_2$Ph (**II**), and P(*o*-tolyl)Ph_2 (**I**), similar procedures were used using solutions of 4-tolyllithium (22 mmol, 2.16 g and 11 mmol, 1.08 g, respectively) in dry diethyl ether and solutions of PCl_2Ph (10 mmol, 1.78 g) or $PClPh_2$ (10 mmol, 2.25 g) in dry diethyl ether instead of PCl_3. The yields of pure products were 2.25 g (77.6%) for (**II**) and 2.08 g (75.4%) for (**III**), respectively.

Characterization data of phosphines: **I**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 6.7–7.4 (m, 14H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$): δ 21.1, 125.8, 128.0, 128.2, 128.8, 129.5, 132.4, 133.1, 133.5, 135.5, 142.0, 142.5; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −12.35 (s); Anal. calcd. for $C_{19}H_{17}P$, C, 82.60, H, 6.16, Found C, 82.37, H, 6.11. mp = 74–75 °C; **II**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 6H), 7.00–7.30 (m, 13H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$): δ 21.0, 21.5, 126.7, 127.1, 128.0, 128.2, 128.8, 129.2, 134.5, 134.7, 134.9, 135.2, 135.5; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −21.77 (s); Anal. calcd. for $C_{20}H_{19}P$, C, 82.76, H, 6.55, Found C, 82.55, H, 6.48. mp = 85–86 °C; **III**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 9H), 6.60–7.30 (m, 12H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$): δ 21.5, 22.1. 22.5, 126.0, 126.8, 128.4, 128.9, 129.3, 129.8, 132.5, 133.0, 134.0, 134.6, 143.0, 143.4, 144.0; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −31.13 (s); Anal. calcd. for $C_{21}H_{21}P$, C, 82.89, H, 6.90, Found C, 82.69, H, 6.84. mp = 121–123 °C.

2.3. Preparation of n-BuPyBF$_3$Cl: typical procedure

Pyridine (96 g, 1.2 mol) in 10% molar excess was refluxed with *n*-BuCl (105 g, 1.1 mol) for 72 h in dark. The reaction mixture was cooled and the solid obtained was recrystallized from MeCN/EtOAc, filtered under vacuum, washed with EtOAc and quickly transferred to a bottle while still moist with solvent. The excess solvent was then removed under vacuum. Then 1 mol BF_3 was added to *n*-BuPyCl (0.5) mol at room temperature under N_2 to give the desired ionic liquid.

2.4. General procedure for the Suzuki coupling of aryl halides (entry 1, Table 1)

Reaction tube was charged with $PhB(OH)_2$ (1.5 mmol), K_3PO_4 (2 mmol), and **II** (0.4 mol%) under a dry nitrogen atmosphere. A solution of 4-bromoacetophenone (1.0 mmol in 2 mL of freshly dried toluene) along with a solution of palladium acetate (0.1 mol% in 3 mL of dried toluene) was added through a rubber septum. After addition of water (1 mL), the resulting mixture was heated at 100 °C for 1 h. After extraction with ether, the organic phase was dried over $MgSO_4$. The solvent was evaporated and a crude product was obtained. For determination of conversions and yields by GC, a small portion of the crude product was added to a solution of hexadecane as internal standard in CH_2Cl_2 (1 mL). To isolate the product, the crude product was purified by chromatography with hexane/ethyl acetate