



Novel bulky pyrazolyolphosphine ligands for the Suzuki coupling of aryl chlorides

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ABSTRACT

Bulky 1-(3,5-di-*tert*-butyl)pyrazolyl-dicyclohexylphosphine and 1-(3,5-di-*tert*-butyl)pyrazolyl-di-*tert*-butylphosphine were prepared from the reactions of 3,5-di-*tert*-butylpyrazolide and corresponding chlorodialkylphosphines. They were successfully employed as ligands in the Suzuki coupling reactions of phenylboronic acid and various aryl bromides and chlorides.

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Palladium-catalyzed cross-coupling reactions,^{1,2} such as the Suzuki coupling of arylboronic acid and aryl halides,³ are powerful and versatile tools for carbon–carbon bond formation in organic synthesis. The efficiency of the catalysts depends largely on the ancillary ligands. Among the most commonly used ligands are electron-rich and sterically hindered tertiary phosphines. Functionalized phosphines, such as N-substituted aminophosphines, have attracted considerable interest as potential ligands and have demonstrated high activities.⁴ Recently, unsymmetrical pyrazole-tethered tridentate PCN-type and bidentate PN-type phosphine ligands have been successfully employed in cross-coupling reactions.^{5,6} Pyrazolyolphosphines (Fig. 1), with a single P–N bond between one phosphino group and one pyrazolyl group (R = Me or H), have been known for over thirty years.⁷ However, due to air- and moisture-sensitivity, their use as ancillary ligands was limited to metal complexes containing electron-withdrawing groups such as CO.^{8,9} We recently reported a pyrazolyolphosphine ligand, 1-(3,5-di-*tert*-butyl)pyrazolyldiphenylphosphine (**1**), and its stable Au(I) complex that did not contain an electron-withdrawing group.¹⁰ The ligand contained sterically hindered *tert*-butyl groups on the pyrazolyl moiety and showed improved stability over its smaller methyl analogues. Here we wish to report the synthesis and catalytic applications of novel bulky pyrazolyldialkylphosphines based on 3,5-di-*tert*-butylpyrazole.¹¹

Deprotonation of 3,5-di-*tert*-butylpyrazole with potassium hydride, followed by treatment of the potassium pyrazolide with chlorodialkylphosphines, afforded the corresponding compounds

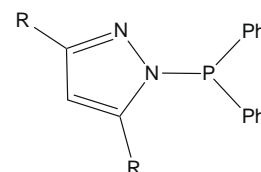
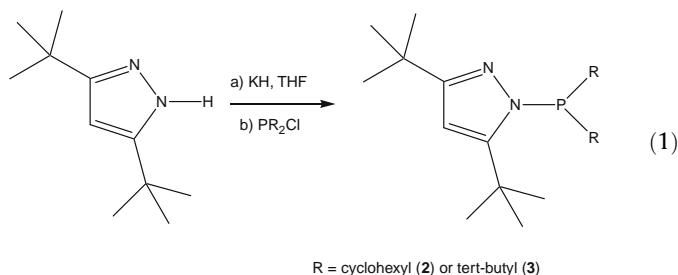


Figure 1. Pyrazolyolphosphines.

2¹² and **3**¹³ (Eq. 1). The compounds showed improved stability over their smaller methyl analogues⁷ as both can be handled in air. In GC/MS analysis, the compounds showed peaks of 376 and 324 which corresponded to the molecular ions of **2** and **3**, indicative of their thermal stability. The results of elemental analysis were in good agreement with calculated values. Their IR spectra showed the P–N stretches at 796 and 800 cm⁻¹, within the range of reported values for ν(P–N) in N-substituted aminophosphines.¹⁴ The ¹H spectra of both compounds showed a doublet (⁴J_{P,H} = 2.0 and 2.4 Hz) at 6.0 ppm for the hydrogen on the pyrazolyl moiety, reflecting the long range interaction between hydrogen and phosphorus nuclei. Similar interaction was also observed for the hydrogen atoms in the di-*tert*-butylphosphino group, P^tBu₂ (³J_{P,H} = 12.2 Hz) in **3**. The ³¹P{¹H} NMR resonances for **2** and **3** were observed at 68.45 and 89.23 ppm, respectively. The chemical shifts are significantly different from those of pyrazole-tethered phosphine compounds without a direct P–N bond, in which the ³¹P shifts are often in the upfield region with negative values.⁶ The downfield chemical shifts in **2** and **3** suggested that the electronegative nitrogen atom decreased the electron density on the phosphorus atom.

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R = cyclohexyl (2) or tert-butyl (3)

Next we evaluated the efficiency of the ligands in the Suzuki coupling reactions of aryl halides and phenylboronic acid. As the solvent and base may have profound effects on the catalytic efficiency,¹ we examined several solvents and bases commonly used in the Suzuki reactions. 4-Bromoanisole, a deactivated bromide and a fairly inert halide, was chosen as the aryl halide substrate.¹⁵ Compound **1** was used as the ligand for screening purposes. At 100 °C in 1,4-dioxane, with 1 mol % Pd(OAc)₂ and ligand loading, the yield was excellent (91%) when cesium carbonate was used as the base (Table 1, entry 3). Under similar conditions, the yield was only 48% without any ligand (entry 9) and 61% when triphenylphosphine was employed as the ligand (entry 10). Thus ligand **1** is essential for the high yield. The yield was also good (81%) in tetrahydrofuran (THF) (entry 4). We chose to use dioxane as the solvent and Cs₂CO₃ as the base for subsequent investigation.

We then investigated the efficiency of the catalysts in the coupling reactions of aryl chlorides, which are more abundant and economically desirable yet less reactive than aryl bromides. A variety of aryl chlorides were examined, including activated aryl chlorides such as 1-chloro-4-nitrobenzene, a neutral aryl chloride, 4-chlorotoluene, and a deactivated aryl chloride, 4-chloroanisole. At 1 mol % catalyst loading, the pyrazolyldiphenylphosphine ligand **1** was largely inefficient in the coupling of aryl chlorides (Table 2, entries 1, 4, 7, and 10). However, the more electron-rich and sterically hindered dialkylphosphines **2** and **3** gave good to excellent yields (entries 2, 3, and 5). The coupling of neutral and deactivated aryl chlorides required a higher catalyst loading (3 mol %). Ligand **2** was the most efficient in the coupling of activated aryl chlorides (entries 5, 6, 8, 9, 13, and 14), whereas the most sterically hindered ligand **3** was the most efficient in the coupling of neutral and deactivated aryl chlorides (entries 15–18). For example, a yield of 85% was obtained for the coupling of 4-chlorotoluene with **3** at 3 mol % catalyst loading. Even though directly P–N-bonded pyrazolyldiphosphine ligands are not as electron-rich as the pyrazole-tethered phosphines,⁶ the electron-rich *tert*-butyl groups on the phosphorus atom and the pyrazolyl moiety can improve the phosphines' donating ability and enhance the oxidative addition of aryl chloride to the palladium center. Furthermore, the bulky *tert*-butyl groups will facilitate the reductive elimination of the biphenyl product in the catalytic cycle. These factors rendered the bulky pyrazolyldiphosphines efficient ligands in the Suzuki coupling of aryl chlorides.

Table 1
Screening of base and solvent^a

Entry	Solvent	Base	Yield ^b (%)
1	Toluene	Cs ₂ CO ₃	29
2	DMF	Cs ₂ CO ₃	19
3	1,4-Dioxane	Cs ₂ CO ₃	91
4	THF	Cs ₂ CO ₃	82
5	1,4-Dioxane	KOH	75
6	1,4-Dioxane	K ₃ PO ₄	77
7	1,4-Dioxane	K ₂ CO ₃	63
8	1,4-Dioxane	NaOAc	27
9	1,4-Dioxane	Cs ₂ CO ₃	48 ^c
10	1,4-Dioxane	Cs ₂ CO ₃	61 ^d

^a 1.0 mmol bromoanisole, 1.5 mmol phenylboronic acid, 2.0 mmol base, 0.010 mmol Pd(OAc)₂, 0.010 mmol ligand, 3 mL 1,4-dioxane, 100 °C, 21 h.

^b GC yields based on 4-bromoanisole.

^c Without any ligand.

^d PPh₃ used as a ligand.

Table 2
Suzuki coupling of aryl chlorides^a

Entry	R	Ligand	Yield ^b (%)
1	NO ₂	1	26
2	NO ₂	2	93 (86) ^c
3	NO ₂	3	89
4	CH ₃ CO	1	5
5	CH ₃ CO	2	78 (70) ^c
6	CH ₃ CO	3	43
7	CHO	1	6
8	CHO	2	44
9	CHO	3	30
10	Me	1	Trace
11	Me	2	12
12	Me	3	50
13	CHO	2	93 ^d
14	CHO	3	57 ^d
15	Me	2	27 ^d
16	Me	3	85 ^d
17	MeO	2	10 ^d
18	MeO	3	54 ^d

^a 1.0 mmol aryl halide, 1.5 mmol phenylboronic acid, 2.0 mmol Cs₂CO₃, 0.010 mmol Pd(OAc)₂, 0.010 mmol ligand, 3 mL 1,4-dioxane, refluxing, 21 h.

^b GC yields based on aryl chlorides.

^c Isolated yields.

^d 0.030 mmol Pd(OAc)₂, 0.030 mmol ligand.

ered phosphines,⁶ the electron-rich *tert*-butyl groups on the phosphorus atom and the pyrazolyl moiety can improve the phosphines' donating ability and enhance the oxidative addition of aryl chloride to the palladium center. Furthermore, the bulky *tert*-butyl groups will facilitate the reductive elimination of the biphenyl product in the catalytic cycle. These factors rendered the bulky pyrazolyldiphosphines efficient ligands in the Suzuki coupling of aryl chlorides.

In conclusion, novel bulky pyrazolyldiphosphines have been prepared and characterized. The ligands showed improved stability over previously reported smaller methyl analogues. They demonstrated good to excellent activity in the Suzuki coupling reactions of various aryl chlorides. The ease of preparation and improved stability make them viable ligands for late transition metal complexes. We are currently exploring the applications of the bulky ligands in other catalytic transformations.

Acknowledgments

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12. **Preparation of 2:** Potassium hydride (0.44 g, 11.0 mmol) was added to a solution of 3,5-di-*tert*-butylpyrazole (1.00 g, 5.55 mmol) in 30 mL of THF. The mixture was stirred at room temperature for three hours and filtered. Chlorodicyclohexylphosphine (1.29 g, 5.55 mmol) was added to the filtrate. After stirring for two days at room temperature, the mixture was filtered. The volatiles were removed under vacuum. Recrystallization of the crude product from hexane afforded crystalline solids. Yield: 1.50 g (72%). Mp: 86–88 °C. Anal. Calcd for C₂₃H₄₁N₂P: C, 73.36; H, 10.97; N, 7.44. Found: C, 73.24; H, 10.71; N, 7.75. GC/MS (EI): 376 (M⁺). IR (KBr, cm⁻¹): 2956 s, 2927 s, 2950 s, 1537 s, 1493 w, 1477 m, 1361 s, 1309 m, 1267 w, 1249 m, 1227 w, 1196 w, 1129 s, 1051 w, 990 m, 889 w, 849 m, 796 m, 712 w, 515 m. ¹H (C₆D₆, 500.13 MHz, ppm): δ 5.98 (d, 1H, ⁴J_{P,H} = 2.0 Hz, CH of pyrazolyl), 2.51 (m, 2H, cyclohexyl), 1.87 (m, 2H, cyclohexyl), 1.67 (m, 4H, cyclohexyl), 1.55 (m, 4H, cyclohexyl), 1.51 (s, 9H, ^tBu), 1.3 (s, 9H, ^tBu), 1.22 (m, 10H, cyclohexyl). ³¹P{¹H} (C₆D₆, 202.47 MHz, 85% H₃PO₄ as external reference, ppm): δ 68.45.
13. **Preparation of 3:** compound **3** was prepared in a similar fashion to that of **2**. However, the mixture was refluxed after the addition of chlorodi-*tert*-butylphosphine. Yield: 56%. Mp: 38–40 °C. Anal. Calcd for C₁₉H₃₇N₂P: C, 70.33; H, 11.49; N, 8.63. Found: C, 70.58; H, 11.33; N, 8.67. GC/MS (EI): 324 (M⁺). IR (KBr, cm⁻¹): 2956 s, 2899 m, 2862 m, 1537 s, 1498 w, 1475 m, 1359 s, 1299 m, 1249 w, 1225 w, 1205 w, 1178 m, 1128 m, 1110 w, 991 m, 934 w, 807 w, 800 m, 648 w, 516 m. ¹H (C₆D₆, 500.13 MHz, ppm): 6.01 (d, 1H, ⁴J_{P,H} = 2.4 Hz, CH of pyrazolyl), 1.49 (s, 9H, ^tBu), 1.40 (s, 9H, ^tBu), 1.29 (d, ³J_{P,H} = 12.2 Hz, 18H, ^tBu₂P). ³¹P{¹H} (C₆D₆, 202.47 MHz, 85% H₃PO₄ as external reference, ppm): δ 89.23.
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15. **General procedures for Suzuki reactions:** A 20-mL reaction tube was charged with an aryl halide, phenylboronic acid, Pd(OAc)₂, a ligand, and a base in 3 mL of solvent under argon and heated to 100 °C for 21 h. The mixture was then cooled to room temperature. The volatiles were removed under a reduced pressure. The organic product was extracted with ether and analyzed on an Agilent 6890 GC-FID instrument. The GC yields were calculated based on the unreacted aryl halide and calibrated relative to standards containing the aryl halide starting material and biphenyl product. Pure products were obtained by flash column chromatography on silica gel using 5% ethyl acetate–hexane as an eluent.