A Superior Non-Symmetrical NCP Pincer Type Palladacycle Catalyst Precursor for the Coupling of Aryl Boronic Acids with Aryl Chlorides

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Abstract: The air and water stable non-symmetrical pincer palladacycle [$Me_2NCH_2(Cl)C{=}C(CH_2)_2OP(i\text{-}Pr)_2$-*k*N*k*C*k*P]PdCl **5**, easily prepared from the chloropalladation of the hetero-substituted alkyne $Me_2NCH_2C{\equiv}C(CH_2)_2OP(i\text{-}Pr)_2$, is a highly efficient catalyst precursor for the coupling of aryl boronic acids and aryl chlorides. Both electron-rich and electron-poor aryl chlorides are efficiently coupled in the presence of **5** to furnish the corresponding cross-coupled products in excellent yields, and a wide variety of functional groups are tolerated in both aryl chloride and aryl boronic acid.

Key words: palladacycles, cross-coupling, boronic acids, aryl chlorides, Suzuki coupling

The palladium-catalysed cross coupling of aryl halides with boronic acids (Suzuki reaction) is one of the most efficient methods for the construction of C_{aryl}–C_{aryl} bonds and has found widespread use in organic and polymer syntheses.[1] Although several other cross-coupling reactions are available to produce biaryls, the Suzuki reaction has been the most used over the course of the last few years, since it has several advantages compared with other available methods. One of the advantages of the Suzuki reaction is the innocuous nature of boronic acids, which are generally non-toxic and thermally, air-, and moisture stable. In addition to being environmentally safer, the handling and removal of boron-containing by-products is easy when compared with other organometallic reagents, especially in large-scale synthesis. Another key advantage is that the Suzuki reaction can be carried out under mild conditions and tolerates a variety of functional groups in the starting aryl halides and aryl boronic acids. It is now well established that almost any palladium catalyst precursor promotes the coupling of aryl iodides and bromides with organoboron compounds, under mild reaction conditions.[2] Moreover, significant advances have been recently achieved in catalyst design for the coupling of the less reactive and cheaper aryl chlorides.[3] For example, the replacement of the commonly used triarylphosphines ligands with bulky electron-rich phosphines or carbenes, generates very active catalysts for the coupling of aryl chlorides.[4] Moreover, CN and CS palladacycles[5] are now emerging as an alternative class of phosphine-free catalyst precursors for coupling reactions of aryl chlorides with aryl boronic acids (Figure 1). In this respect, the oxime-containing palladacycle **1** catalyses the coupling of a range of aryl and hetero-aryl chlorides including electron-rich substrates, in the presence of water and tetrabutylammonium bromide in variable yields.[6] The cyclopalladated compounds derived from the *ortho*-metallation of benzyl *tert*-butyl thioether **2** is also able to perform the coupling of electron-poor aryl chlorides at room temperature in excellent yields (90–95%).[7] However, only low conversions were obtained with reactions involving electron-neutral and electron-rich aryl chlorides (up to 46%).

It has been recently reported that phosphine adducts of CN or CP palladacycles such as **3** and **4** (Figure 1) efficiently promote the Suzuki coupling of both activated and non-activated aryl chlorides.[8] These adducts combine the thermal stability of a palladacyclic fragment with the electronic and steric effects of the phosphorus ligands. We have recently reported that the chloropalladation of hetero-substituted alkynes is a simple and efficient method for the construction of non-symmetrical NCP, NCS pincer type palladacycles.[9] Of note is that the NCP-pincer type palladacycle such as **5** (Scheme 1) is structurally and electronically similar to adducts **3** and **4**, and consequently they are potential catalyst precursors for the Suzuki coupling of aryl chlorides. We wish to report herein that indeed the palladacycle **5**, obtained from the chloropalladation of (5-dimethylamino-pent-3-ynyl) di-

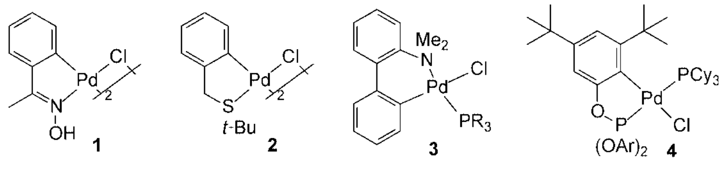

Figure 1 Examples of palladacycles used as catalyst precursors for the Suzuki coupling of aryl chlorides.

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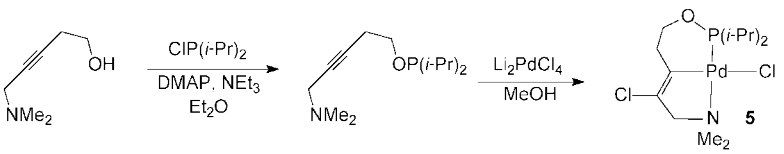
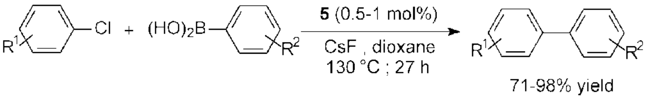


Scheme 1 Synthesis of palladacycle **5** from the chloropalladation of (5-dimethylamino-pent-3-ynyl) diisopropyl phosphinite

isopropyl phosphinite, efficiently promotes the Suzuki cross-coupling reaction of aryl chlorides without the need for the addition of external phosphines.

The phosphinite ligand has been easily obtained in 86% yield from the reaction of 5-dimethylamino-pent-3-yn-1-ol with diisopropylchlorophosphine. The simple addition of (5-dimethylamino-pent-3-ynyl) diisopropyl phosphinite to a methanolic solution of Li_2PdCl_4 at 0 °C generates palladacycle **5** in 58% yield as a light-yellow air and water-stable solid.

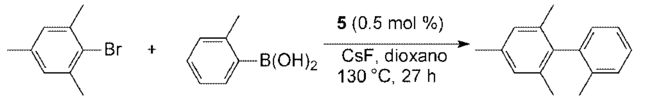
An initial optimisation of the reaction conditions such as solvent (dioxane, THF, DMF, and DMA), base (K_3PO_4, K_2CO_3, KF, $CsCO_3$ and CsF) and temperature showed that dioxane/CsF mixture at 130 °C gave the best results for the coupling of aryl chlorides with aryl boronic acids catalysed by **5** (Equation 1 and Table 1).



Equation 1

For example, the coupling reaction of chlorobenzene and 2-tolylboronic acid in the presence of palladacycle **5** gave the corresponding biphenyl in 98% isolated yield (entry 1). It is clear from Table 1 that both electron-rich and electron-poor aryl chlorides are efficiently coupled in the presence of **5** to furnish the corresponding biaryl products in excellent yields, and a wide variety of functional groups are tolerated in both aryl chloride and aryl boronic acid.

Interestingly, palladacycle **5** is also a highly efficient catalyst precursor for the coupling of sterically demanding substrates such as 1,3,5-trimethyl-2-bromobenzene. Thus, the reaction of 2-tolylboronic acid with 1,3,5-trimethyl-2-bromobenzene under the same reactions employed in Table 1 (using 0.5% of **5**) affords the cross-coupled product in 78% yield (Equation 2).



Equation 2

In conclusion we have prepared a highly efficient catalyst precursor for the coupling of boronic acids with aryl chlorides and, from the standpoint of yields, it ranks amongst the best reported systems in the literature. The applications of non-symmetrical pincer palladacycles such as **5** as catalyst precursors for the Suzuki coupling of sterically demanding substrates and for other coupling reactions are currently under investigation in our Laboratory.

All reactions were carried out under an Ar atmosphere in an oven-dried resealable Schlenk tube. $PdCl_2$ was purchased from Degussa. Aryl chlorides, CsF, and i-Pr_2PCl were purchased from Acros. 4-$NCC_6H_4B(OH)_2$ and 4-$CH_3C(O)C_6H_4B(OH)_2$ were purchased from Combi-Blocks, Inc. $C_6H_5B(OH)_2$, 4-$MeOC_6H_4B(OH)_2$, 4-$MeC_6H_4B(OH)_2$, 2-$MeOC_6H_4B(OH)_2$ and 1-naphthylboronic acid were prepared according to the previously published procedures.[10] Chemicals were used without further purification. Dioxane was dried over metallic Na. NMR spectra were recorded on a Varian Inova 300 spectrometer. IR spectra were measured on a Bomem B-102 spectrometer. Mass spectra were obtained on a GC/MS Shimadzu QP-5050 (EI, 70 eV). GC analyses were performed on a Hewlett-Packard-5890 GC with a FID and 30 meter capillary column with a dimethylpolysiloxane stationary phase.

Synthesis of (5-Dimethylamino-pent-3-ynyl) Diisopropyl Phosphinite; Typical Procedure

Diisopropylchlorophosphine (720 mg, 4.7 mmol) was added slowly, under Ar, to a stirred mixture of 5-dimethylamino-pent-3-yn-1-ol (600 mg, 4.7 mmol), DMAP (10 mg) and Et_3N (480 mg, 4.7 mmol) in anhyd Et_2O (20 mL). After addition, stirring was continued for additional 24 h. The reaction mixture was washed with aq 10% Na_2CO_3 solution (2 × 20 mL), then dried with Na_2CO_3 and the solvent was evaporated, affording the desired amino phosphinite as a pale yellow oil (988 mg, 86% yield), sufficiently pure for further work.

^1H NMR ($CDCl_3$): d = 3.81 (dt, $^3J_{PH}$ = 9.0 Hz, $^3J_{HH}$ = 7.1 Hz, 2 H, CH_2OP), 3.21 (t, $^5J_{HH}$ = 2.2 Hz, 2 H, CH_2N), 2.49 (dtt, $^3J_{HH}$ = 7.1 Hz, $^5J_{HH}$ = 2.2 Hz, $^4J_{PH}$ = 0.7 Hz, 2 H, $CH_2C{\equiv}C$), 2.29 (s, 6 H, NMe_2), 1.71 (dheptet, $^3J_{HH}$ = 7.1 Hz, $^2J_{PH}$ = 1.2 Hz, 2 H, CH), 1.09 (dd, $^3J_{HH}$ = 7.1 Hz, $^3J_{PH}$ = 10.5 Hz, 6 H, CH_3), 1.03 (dd, $^3J_{HH}$ = 7.1 Hz, $^3J_{PH}$ = 15.9 Hz, 6 H, CH_3).

^{13}C {^1H} NMR ($CDCl_3$): d = 81.8, 75.9 ($C{\equiv}C$), 70.5 (d, $^2J_{PC}$ = 20.0 Hz, CH_2OP), 48.0 (CH_2N), 44.0 (NMe_2), 27.9 (d, $^1J_{PC}$ = 16.0 Hz, CH), 21.6 (d, $^3J_{PC}$ = 6.6 Hz, $CH_2C{\equiv}C$); 17.8 (d, $^2J_{PC}$ = 20.0 Hz, CH_3), 16.8 (d, $^2J_{PC}$ = 8.0 Hz, CH_3).

^{31}P {^1H} NMR ($CDCl_3$): d = –93.3.

Synthesis of the Pincer Palladacycle 5; Typical Procedure

A Li_2PdCl_4 solution was prepared by dissolving $PdCl_2$ (720 mg, 4.06 mmol) and LiCl (432 mg, 10.2 mmol) in MeOH (20 mL) with gentle heating. (5-Dimethylamino-pent-3-ynyl) diisopropyl phosphinite (988 mg, 4.06 mmol), dissolved in MeOH (5 mL), was added under stirring to the former solution, which had been cooled to 0 ºC. The stirring was continued at the same temperature for 3 h. The solvent was evaporated under reduced pressure and CH_2Cl_2 (20 mL) was added. The resulting suspension was stirred at r.t. for 3 h. The solvent was evaporated and the residue was extracted with hot hexanes (2 × 20 mL). Drying of the combined extract with $MgSO_4$ and

Table 1 Suzuki Coupling of Aryl Chlorides with Aryl Boronic Acids; Reaction Conditions: ArCl (1 mmol), Ar′B(OH)$_2$ (1.5 mmol), CsF (2 mmol), dioxane (5 mL), 130 °C, 27 h (time not optimised)

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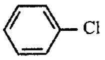
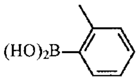
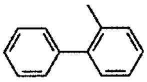
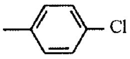
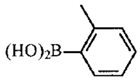
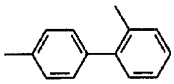
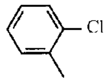
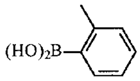
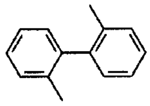
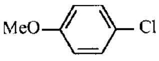
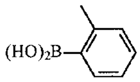
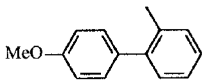
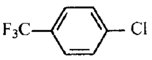
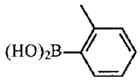
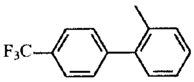
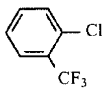
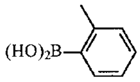
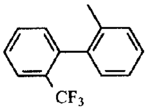
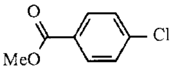
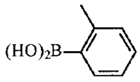
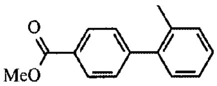
1			1		98
2			1		90
3			1		91
4			1		80
5			0.5		85
6			1		71
7			0.5		89
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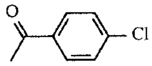
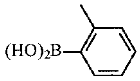
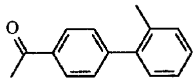
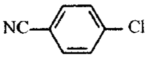
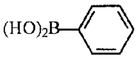
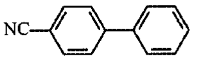
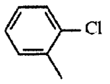
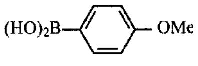
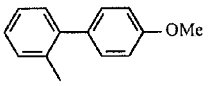
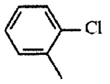
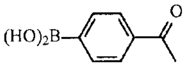
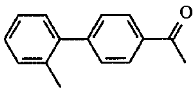
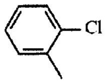
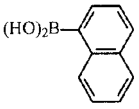
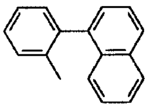
9			1		74
11			1		98
12			1		73
13			1		77
14			1		70

evaporation of the solvent afforded the palladacycle **5**, as a yellow solid (909 mg, 58% yield).

^{1}H NMR (CDCl$_3$): d = 3.91 (dt, $^{3}J_{PH}$ = 15.4 Hz, $^{3}J_{HH}$ = 5.1 Hz, 2 H, CH$_2$OP), 3.49 (dt, $^{5}J_{HH}$ = 2.0 Hz, $^{4}J_{PH}$ = 2.0 Hz, 2 H, CH$_2$N), 2.77 (d, $^{4}J_{PH}$ = 2.4 Hz, 6 H, NMe$_2$), 2.38 (dheptet, $^{3}J_{HH}$ = 7.1 Hz, $^{2}J_{PH}$ = 7.1 Hz, 2 H, CH); 2.25–2.17 (m, 2 H, CH$_2$C=C), 1.37 (dd, $^{3}J_{HH}$ = 7.1 Hz, $^{3}J_{PH}$ = 18.4 Hz, 6 H, CH$_3$), 1.19 (dd, $^{3}J_{HH}$ = 7.1 Hz, $^{3}J_{PH}$ = 15.1 Hz, 6 H, CH$_3$).

^{13}C {^{1}H} NMR (CDCl$_3$): d = 142.6 (C=C), 120.1 (d, $^{2}J_{PC}$ = 5.1 Hz, C=C), 72.2 (d, $^{3}J_{PC}$ = 1.7 Hz, CH$_2$N), 71.7 (d, $^{2}J_{PC}$ = 2.6 Hz, CH$_2$OP), 49.7 (d, $^{3}J_{PC}$ = 2.6 Hz, NMe$_2$), 32.5 (d, $^{3}J_{PC}$ = 9.2 Hz, CH$_2$C=C), 28.9 (d, $^{1}J_{PC}$ = 33.7 Hz, CH), 18.5 (d, $^{2}J_{PC}$ = 4.8 Hz, CH$_3$), 16.8 (d, $^{2}J_{PC}$ = 2.2 Hz, CH$_3$).

^{31}P {^{1}H} NMR (CDCl$_3$): d = –91.5.

Typical Experiment for the Suzuki Coupling of Aryl Chlorides

An oven-dried resealable Schlenk flask was evacuated and back-filled with Ar and charged with CsF (304 mg, 2 mmol), arylboronic acid (1.5 mmol), and palladacycle **1** (4.2 mg, 0.01 mmol). The flask was evacuated, back-filled with Ar and then were added aryl chloride (1 mmol), and dioxane (5 mL). The reaction mixture was stirred at 130 °C for 27 h. The solution was then allowed to cool to r.t., taken up in Et$_2$O (20 mL) and washed with aq NaOH (1 M, 5 mL) and brine (2 × 5 mL). The organic layer was dried over MgSO$_4$, filtered, concentrated in vacuo and then the crude material was purified by flash chromatography on silica gel. The corresponding biaryl products were characterized by ^{1}H and ^{13}C NMR, IR, and GC–MS.

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