Pyrazole-based P,N-ligand for palladium catalyst : applications in Suzuki coupling and amination reactions

Anuradha Mukherjee and Amitabha Sarkar[¶]*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700 032, India
E-mail: ocas@ iacs.res.in

Abstract

A new pyrazole-tethered phosphine ligand has been used for efficient palladium-catalyzed Suzuki coupling between phenylboronic acids and aryl halides. The same ligand also facilitates palladium-catalyzed amination of aryl bromide or triflate.

Keywords: Suzuki coupling, amination, pyrazole, palladium, catalyst, P, N-ligand

Introduction

Palladium catalyzed coupling reactions are extremely powerful tools to construct new C-C and C-N bonds. The mild reaction conditions of these reactions offer considerable advantages over classical methods, that require either activated molecules or harsh reaction conditions. Recently, significant developments in Suzuki coupling reaction[1] and amination of aryl halide or triflate have been reported by Buchwald[2] and Hartwig[3]. That stereoelectronic effects and the bite angle[4] of the employed ligands are significant factors for efficient coupling reactions, have been illustrated by a recent set of electron-rich and functionalized phosphine ligands displayed in Fig-1. For example, Buchwald has shown that 2-dicyclohexylphosphanyl-2′-dimethylaminobiphenyl, **ii**, is an excellent ligand[2e,2f] for coupling of aryl bromides and chlorides with boronic acids at room temperature.

[¶] Present address: Department of Organic Chemistry, Indian Association for the Cultivation of Science, Kolkata, India.
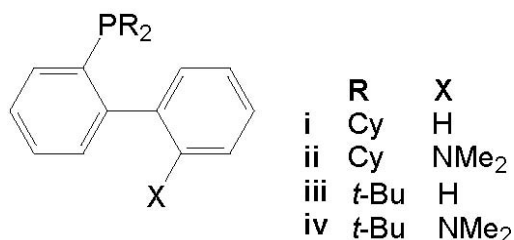e-mail: ocas@mahendra.iacs.res.in

	R	X
i	Cy	H
ii	Cy	NMe$_2$
iii	t-Bu	H
iv	t-Bu	NMe$_2$

Figure 1. Phosphine ligands developed by Buchwald [2d, 2e, 2f] for coupling reaction.

In keeping with our continuing interest in pyrazole-derived ligands[5] we sought to expand the range of ligands used with palladium in such reaction and selected pyrazole based P-N ligands as a basic motif. They are easy to prepare and are amenable to diverse structural modifications. Suitably located substituents in the aryl and pyrazolyl rings would permit tuning of donor ability of phosphorus and nitrogen. Also, steric effect of the ligand can be modulated by incorporating bulky substituents at appropriate positions. Such variations are often crucial for optimizing catalytic activity in several important reactions.

Although pyrazole as a ligand has been extensively used in coordination and organometallic chemistry following the pioneering work of Trofimenko,[6] their catalytic chemistry has not been explored to similar extent. The ligand **1** was expected to provide an interesting variation to the theme of P~N bidentate ligand[7] since pyrazole as a donor is quite different from pyridine, oxazoline or Schiff base.

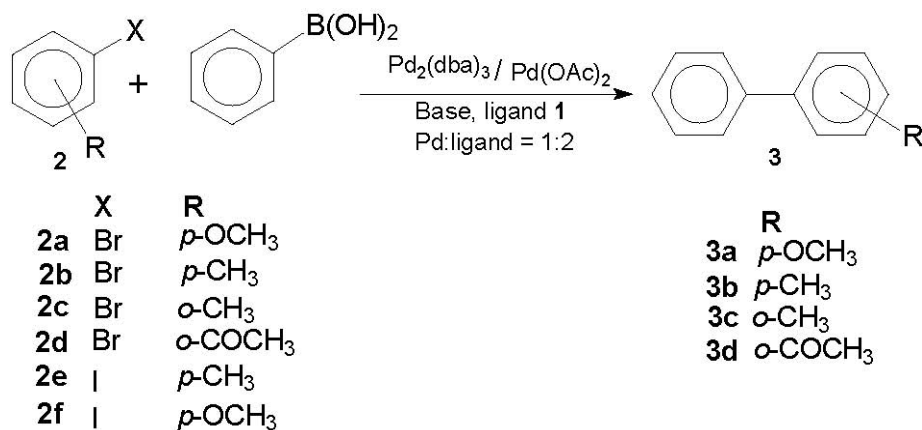## Results and Discussion

1. Synthesis of ligand

Design of ligand **1** has distant yet perceptible resemblance[8] to Buchwald's phosphines shown in Fig 1. The ligand **1** features one aromatic ring joined to a heterocycle that contain the donor atom. The 3-position of pyrazole is ideally suited for studying steric implications of bulky substituents. Electron density on the phosphorus atom and on the pyrazole ring can in principle be tuned by varying substituents at relevant *p*-position on aromatic ring. It was also our interest to find out if a chelate is actually responsible for efficient catalytic cycle. 3, 5-Dimethyl-1-phenylpyrazole was prepared by reaction of acetylacetone and phenylhydrazine as reported.[9] We also followed an alternative route where substituted pyrazoles are coupled with phenylboronic acid by copper acetate in presence of pyridine (Scheme 1).[10] Directed lithiation at 0 °C followed by electrophilic quench with PPh$_2$Cl afforded the product **1**. The compound was purified by crystallization and characterized by its spectral data. In the proton NMR spectrum, the pyrazole-4H appears as a singlet at 5.86 ppm, while two methyl singlets appear at 2.19 and 2.00 ppm. The ^{31}P absorption for the phosphine is observed at -23.89 ppm. A crystal structure determination of compound **1** confirmed the assigned structure (see the supporting information on page 174).
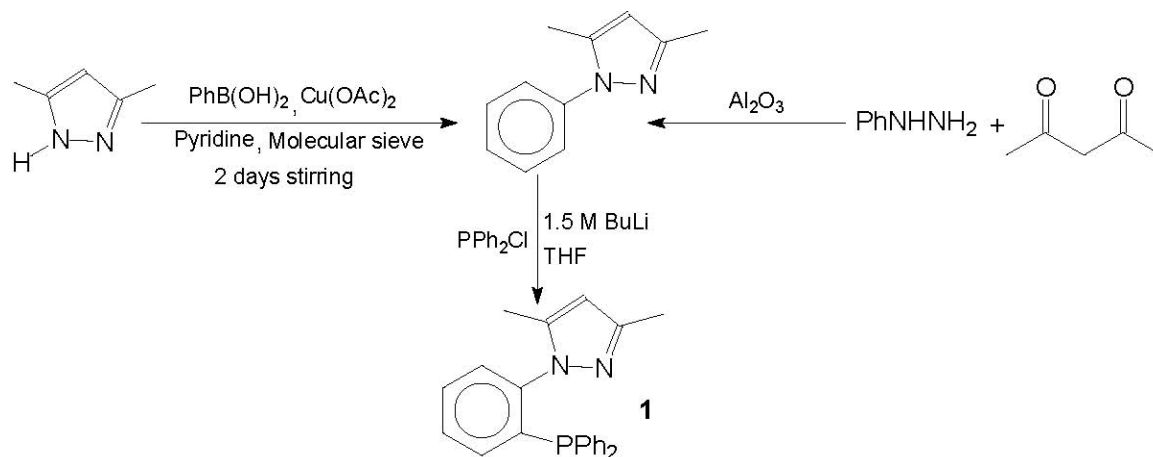
Scheme 1

2. Suzuki Reaction

We initially examined the suitability of the ligand **1** for palladium-catalyzed Suzuki coupling of aryl bromide with phenylboronic acid (Scheme 2). Combination of $Pd_2(dba)_3$ and ligand **1** (Pd : **1** = 1:2) catalyzed the coupling between aryl bromide and phenylboronic acid at 80-85 °C in toluene to produce products in 70-80% yield (Table 1).

	X	R
2a	Br	*p*-OCH$_3$
2b	Br	*p*-CH$_3$
2c	Br	*o*-CH$_3$
2d	Br	*o*-COCH$_3$
2e	I	*p*-CH$_3$
2f	I	*p*-OCH$_3$

	R
3a	*p*-OCH$_3$
3b	*p*-CH$_3$
3c	*o*-CH$_3$
3d	*o*-COCH$_3$

Scheme 2

Table 1. Suzuki cross-coupling of aryl halide with phenylboronic acid using ligand **1**

Entry	Aryl halide (2)	Catalyst Precursor	Base	Cross-coupled Product (3)	Yield (%)
1	**2a**	$Pd_2(dba)_3$	Cs_2CO_3	**3a**	80%
2	**2b**	$Pd_2(dba)_3$	CsF	**3b**	82%
3	**2b**	$Pd_2(dba)_3$	Cs_2CO_3	**3b**	70%
4	**2b**	$Pd_2(dba)_3$	K_3PO_4	**3b**	62%
5	**2c**	$Pd_2(dba)_3$	Cs_2CO_3	**3c**	65%
6	**2d**	$Pd_2(dba)_3$	Cs_2CO_3	**3d**	65%
7	**2e**	$Pd_2(dba)_3$	CsF	**3b**	55%
8	**2f**	$Pd_2(dba)_3$	CsF	**3a**	50%
9	**2b**	$Pd(OAc)_2{}^a$	CsF	**3b**	74%

Reaction conditions: $Pd_2(dba)_3$ (1 mol%), ligand **1** (4 mol%), aryl bromide (1 mmol), $PhB(OH)_2$ (1.5 mmol), base (3mmol), solvent (toluene), temp (80-85 °C), time (7-8 hrs). a : 2 mol % $Pd(OAc)_2$ is used (entry no. 9).

A control experiment was run without the addition of ligand **1** to $Pd_2(dba)_3$ when only starting material was recovered after 24 hr. This experiment established that ligand **1** indeed stabilized the catalytic species.

An examination of different bases revealed CsF is effective (entry 2, yield: 82%) compared to Cs_2CO_3 (entry 3, yield: 70%) and K_3PO_4 (entry 4, yield: 62%). Both the catalyst precursor $Pd_2(dba)_3$ (entry 2) and $Pd(OAc)_2$ (entry 9) in presence of ligand **1** and CsF as base in toluene at 80-85 °C gave 82% and 74% of 4-methylbiphenyl. This results suggested the $Pd_2(dba)_3$ is a better catalyst precursor than $Pd(OAc)_2$ in some instances.

Reactions of phenylboronic acid with 4-bromotoluene (entry 3) and 2-bromotoluene (entry 5) afforded 70% yield of 4-methylbiphenyl and 65% of 2-methylbiphenyl, indicating that *ortho*-substitution has minor steric consequence. Electron poor aryl system (entry 6) yielded 65% of the cross-coupled product, while 3-nitrobromobenzene failed to undergo coupling.
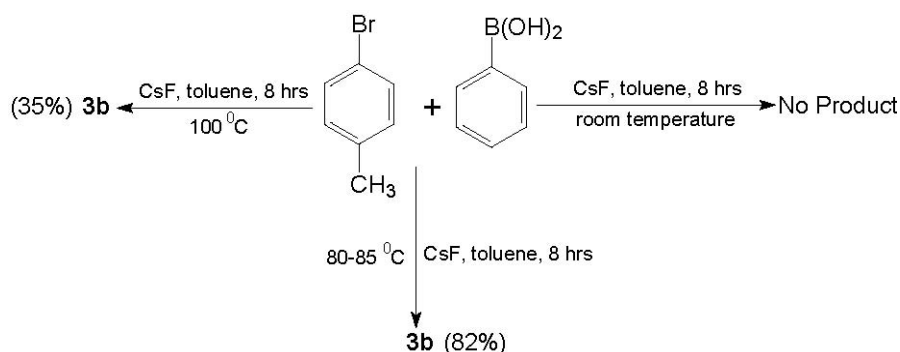
**Figure 2.** Temperature effect on coupling reaction.

The reaction was found to be sensitive to reaction temperature (Fig 2). Instead of enhancing the rate of reaction, elevated temperature (>100 °C) resulted in rapid precipitation of palladium black and yield suffered. The catalyst system does not function at ambient temperature like Buchwald catalysts.

When 4-bromoanisole and phenylboronic acid were treated with N-phenylpyrazole as ligand instead of ligand **1,** below 65 °C, no coupling was observed. Above 65 °C rapid precipitation of Pd-black was observed. These results suggest that presence of phosphine group is crucial for catalysis.

At this part it is unclear whether pyrazole nitrogen indeed stabilizes the palladium intermediate which is coordinatively unsaturated, or whether the heteroaromatic ring serves the purpose by p-participation as in Buchwald's catalysts.
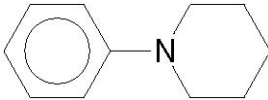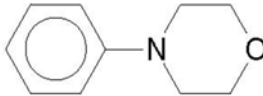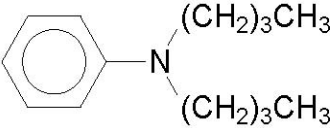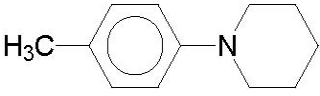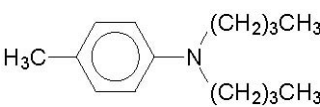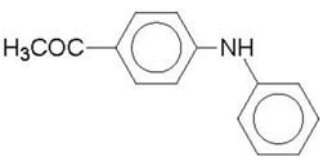
3. Amination reactions

Palladium catalyzed aryl amination is another important reaction developed in recent times. It is believed that a chelated complex is thought to increase the selectivity for reductive elimination over в-hydrogen elimination.[2a, 2c] The ligand **1** was, therefore, expected to provide an efficient and stable catalyst with Pd(0) precursor. Results are summarized in Scheme-3 and Table-2 below. As shown, amination indeed proceed well with aniline or cyclic aliphatic amines. Primary aliphatic amines do not undergo amination readily, while aliphatic acyclic secondary amines give poor results. The catalyst system Pd$_2$(dba)$_3$/**1** was found to be effective at 85-90 °C in toluene while sodium *tert*-butoxide was used as a base.

4a R = H; X = Br
4b R = CH$_3$; X = Br
4c R = COCH$_3$; X = OTf
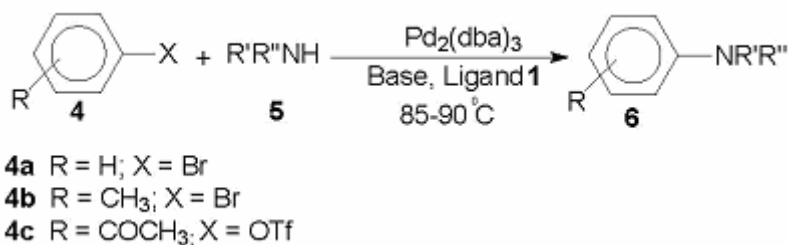
Scheme 3

Table 2. Amination reaction of aryl triflate and aryl bromide with various secondary and primary amines with ligand **1**

Entry	ArX (4)	Amine (5)	Product (6)	Yield of C-N coupled product
1.	**4a**	Piperidine		80%
2.	**4a**	Morpholine		82%
3.	**4a**	Di-*n*-butylamine		20%
4.	**4b**	Piperidine		79%
5.	**4b**	Di-*n*-butylamine		41%
6.	**4c**	Aniline		83%
7.	**4c**	Cyclohexylamine	-	No coupling product

Reaction conditions: aryl bromide (1 mmol), amine (1.5 mmol), $Pd_2(dba)_3$ (1 mol%), Ligand 1 (3 mol%), Base(NaO-tBu, 1.5 mmol) Toluene (3-5 ml), Temperature (80-85 °C), Time (9-10 hrs). a:aryl triflate (1 mmol), amine (1.2 mmol), Cs_2CO_3 (1.4 mmol).

Conclusions

A new, pyrazole-derived P, N-complex, **1**, acts as an effective ligand in palladium-catalysed Suzuki coupling and amination reaction. It was believed that a chelated structure would favor oxidative addition step while sterically crowded non-chelate structure would favor the reductive elimination step of the catalytic cycle.[12b] Although catalysis indeed was observed with this ligand, it is still premature to decide whether the ligand **1** performs as a chelating ligand or not.

Experimental Section

General Procedures. All manipulations were carried out under argon atmosphere. Dried solvents have been used. Reagents and chemicals were used as received from Aldrich and Lancaster. Melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and reported in the Celsius scale. IR spectra were recorded on a Shimadzu FTIR-8400 spectrometer. All spectra (^{1}H NMR, ^{13}C NMR and ^{31}P NMR) were recorded on a Bruker AC200, MSL300 or DRX500 spectrometer.
See page 174

Preparation of *N*-phenyl-3,5-dimethylpyrazole
Procedure A. *N*-phenyl-3,5-dimethylpyrazole was prepared from acetylacetone (10 g, 98.90 mmol) and phenylhydrazine (10.81 g, 100 mmol) in a manner similar to the procedure[9] reported in literature. Yield: (15 g, 81%).
Procedure B. Distilled pyridine (6.7 ml, 41.66 mmol) was added to a mixture of 3,5-dimethylpyrazole (2 g, 20.83 mmol), phenylboronic acid (5.07 g, 41.66 mmol) and copper acetate (6.23 g, 31.24 mmol) in dichloromethane (20 ml). Activated molecular sieves (4 E) were also added. After stirring for 2 days under dry air, the reaction mixture was filtered through celite and the filtrate was concentrated. The product was purified by flash chromatography. Yield: 2.86 g (80%).
^{1}H NMR (CDCl$_3$, 200 MHz): δ 7.41-7.43 (m, 5H, PhH), 6.00 (s, 1H, 4-PzH), 2.28 (s, 3H, pz-CH$_3$) 2.30 (s, 3H, pz-CH$_3$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 50.32 MHz): δ 147.80, 139.35, 138.32, 128.14, 126.11, 123.58, 106.34,12.72, 11.43 ppm.
Preparation of 3,5-dimethyl-1-(2r-diphenylphosphino)phenylpyrazole (1). To a solution of *N*-phenyl-3.5-dimethylpyrazole (3.44 g, 20 mmol) in 100 ml dry THF n-BuLi (15 ml 1.41M, 21.15 mol) was added dropwise at 0 °C and yellow color of the solution changed successively to blue, yellow, and brown. The reaction mixture was stirred for 4 to 5 h followed by addition of ClPPh$_2$ (3.6 ml, 20 mmol) at 0 °C. Stirring was continued for additional 3 h. The reaction was quenched with water and extracted with ethyl acetate (40 ml Ч 3). Combined organic phase was dried over Na$_2$SO$_4$ and concentrated. The crude semi-solid product was purified by flash chromatography followed by crystallization to obtain **1** as a yellowish white solid (4 g, 56%). Slow evaporation of dichloromethane from a dilute solution of 3 in dichloromethane–pet ether afforded crystals suitable for X-ray analysis. MP: 110 °C. IR (Nujol): 1552 cm^{-1}. ^{1}H NMR

(CDCl$_3$, 200 MHz): δ 7.31 (bs, 14H, PhH), 5.86 (s, 1H, 4-pzH) 2.19 (s, 3H, pz-CH$_3$), 2.00 (s, 3H, pz-CH$_3$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 50.32 MHz): δ 147.72, 143.20, 139.93, 136.14, 135.92, 133.97, 133.86, 133.46, 129.05, 128.39, 128.06, 127.91, 127.73, 105.05, 13.15, 11.39 ppm. ^{31}P {^{1}H} NMR (CDCl$_3$, 81.02 MHz): δ -23.89 ppm. Anal. Calcd for C$_{23}$H$_{21}$N$_2$P (356): C, 77.52; H, 5.89; N, 7.26. Found: C, 76.98; H, 5.34; N, 7.24. Mass (m/z): 356 (M$^+$). Crystal structure of the compound **1** was solved in order to ascertain its identity (see Supporting Information on page 174).

General procedure for Suzuki coupling

An oven dried round bottomed flask was evacuated and flashed with argon and charged with Pd$_2$(dba)$_3$.CHCl$_3$[11] (1 mol%, 0.010g), ligand **1** (4 mol%, 0.014g), the phenylboronic acid (1.5 mmol, 0.181 g) and base (3 mmol) . The flask was evacuated and flashed with argon. Aryl halide (1 mmol) and toluene (3-5 ml) were added by a syringe. The reaction mixture was heated to 80-85 °C with stirring for 7-8 hrs. Completion of reaction was monitored by TLC or GC. The reaction mixture was then cooled to room temperature, filtered through celite and washed with dichloromethane. The crude material was purified by flash chromatography. The product was identified by GC-MS and ^{1}H NMR spectroscopy.[12]

General procedure for amination reaction of bromobenzene

An oven dried round bottomed flask was charged with bromobenzene (1 mmol, 0.11 ml), amine (1.5 mmol), Pd$_2$(dba)$_3$ (1mol%, 0.010 g), ligand **1** (3 mol%, 0.011g) and NaOtBu (1.5 mmol, 0.144 g) and purged with argon. Toluene (5 ml) was added and reaction mixture was heated at 80 °C for 8-9 h. The reaction mixture was filtered through celite and washed with dichloromethane. After removal of solvent desired product was purified by flash chromatography. Reaction was monitored by TLC or GC. The product was identified by their ^{1}H NMR spectra. [12a, 13]

General procedure for amination reaction of triflate

An oven dried round bottomed flask was evacuated and purged with argon and was charged with triflate (1 mmol, 0.3 g), amine (1.2 mmol), Cs$_2$CO$_3$ (1.4 mmol, 0.45 gm), ligand **1** (3 mol%, 0.11 g) and Pd$_2$(dba)$_3$ (1 mol%, 0.010 g). Toluene (5 ml) was added and reaction mixture was heated at 80 °C for 12 h (completion identified by TLC). Reaction mixture was then filtered through celite and washed with dichloromethane. After removal of solvent the crude product was purified by flash chromatography, and identified by 1H NMR spectroscopy.13

Acknowledgements

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