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A Novel, Air-Stable Phosphine Ligand for the Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reaction of Chloro Arenes

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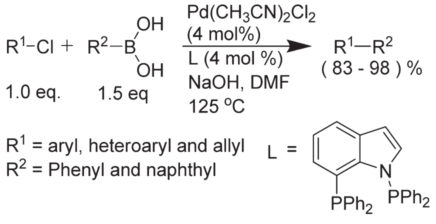
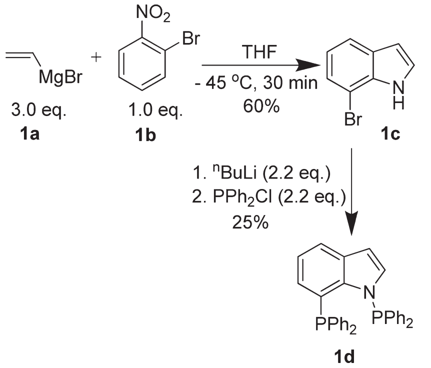


A novel, air-stable phosphine ligand, prepared from readily available 2-bromonitrobenzene and vinylmagnesium bromide, combines with $\text{Pd(CH}_3\text{CN)}_2\text{Cl}_2$ to afford an effective catalyst for Suzuki−Miyaura cross-coupling of aryl, heteroaryl, and allyl chlorides with phenylboronic acid.

The transition metal-catalyzed cross-coupling reaction of aryl and vinyl halides/sulfonates is one of the most efficient methods for carbon−carbon bond formation.[1] In this class, the Suzuki−Miyaura coupling reaction stands out as a powerful, convenient, and versatile method for cross-coupling of aryl bromides, iodides, or triflates with arylboronic acids.[2] It has several practical advantages: excellent functional group tolerance, wide substrate scope, and ready separation of nontoxic boron-containing byproduct.[3] A benchmark for catalytic activity in such a reaction is the ability of the catalyst to activate inexpensive aryl or vinyl chlorides, rather than expensive bromides or iodides.[4] The challenge essentially lies in the fact that the aryl chlorides are less reactive due to their relatively high C−Cl bond strength and their reluctance to undergo oxidative addition.[5]

SCHEME 1. Synthesis of Ligand



Recently significant progress has been made toward activation of aryl chlorides in the Suzuki coupling reaction through the use of alkylphosphine ligands, e.g., $^{t}\text{Bu}_3\text{P}$ by Fu,[6] biphenyl based aryldialkylphosphines by Buchwald,[7] heteroaromatic phosphines by Beller,[8] and ferrocene-based dialkylphosphine by Hartwig.[9] Trialkyl- or dialkylarylphosphines make the metal center electron rich, which facilitates oxidative addition by less active C−Cl bonds. It is known that various palladium-[10] and nickel-based[11] catalysts and nano-sized palladium[12] are also very effective with aryl chlorides. Phosphine ligands containing amino phosphine donor have been successfully used in cross-coupling reactions.[13] It was explained that an alkyl amino group provides an electron-rich σ-donor character to the phosphorus atom[14a] whereas a pyrrolyl nitrogen attached to phosphorus makes it a poorer σ-donor but better π-acceptor.[14b] In this report, we describe the synthesis and molecular structure of a novel bidentate

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SCHEME 2. Synthesis of Palladium Complex

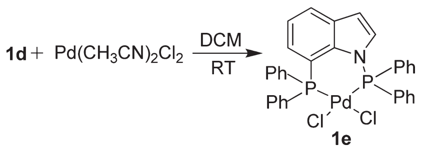
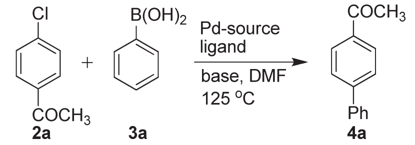


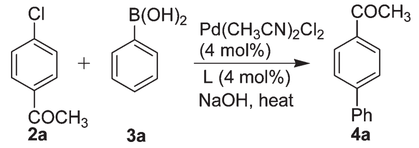
TABLE 1. Optimization of Cross-Coupling Reaction of Aryl Chloride with Boronic Acid[a]



entry	Pd (mol %)	L (mol %)	base	yield (%)[b]
1	$Pd(CH_3CN)_2Cl_2$ (2)	2	NaOH	80
2	$Pd(CH_3CN)_2Cl_2$ (3)	3	NaOH	89
3	$Pd(CH_3CN)_2Cl_2$ (4)	4	NaOH	98
4	$Pd(CH_3CN)_2Cl_2$ (4)	4	NaOH	75[c]
5	$Pd(OAc)_2$ (4)	4	NaOH	80
6	$Pd_2(dba)_3$ (4)	4	NaOH	55
7	$Pd(CH_3CN)_2Cl_2$ (4)	4	Cs_2CO_3	85
8	$Pd(CH_3CN)_2Cl_2$ (4)	4	K_2CO_3	30
9	$Pd(CH_3CN)_2Cl_2$ (4)	4	K_3PO_4	42
10	$Pd(CH_3CN)_2Cl_2$ (4)	4	CsF	80
11	$Pd(CH_3CN)_2Cl_2$ (4)	4	KOH	81
12	$Pd(CH_3CN)_2Cl_2$ (4)	8	NaOH	0

[a] Reaction condition: 4-chloroacetophenone (1 mmol), phenylboronic acid (1.5 mmol), base (2 mmol), DMF (2.5 mL); argon atmosphere. [b] Isolated yield. [c] At 100 °C.

TABLE 2. Screening of Solvents

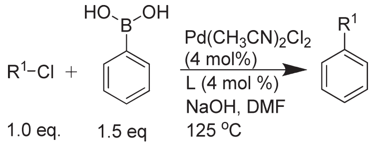


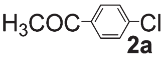
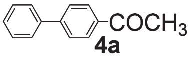
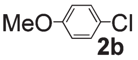
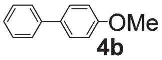
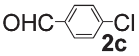
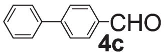
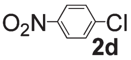
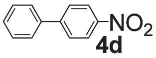
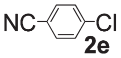
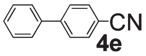
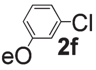
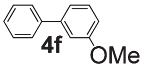
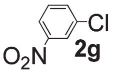
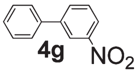
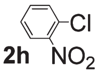
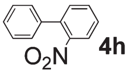
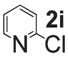
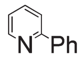
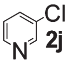
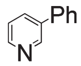
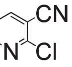
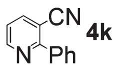
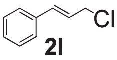
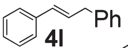
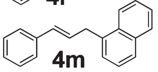
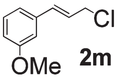
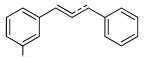
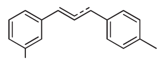
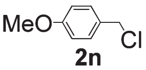
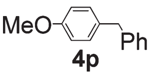
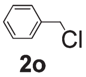
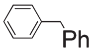
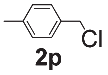
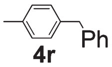
entry	solvent	*T* (°C)	time (h)	yield (%)[b]
1	DMF	125	8	98
2	THF	65	10	2
3	DCM	40	10	0
4	toluene	110	10	25
5	DMSO	125	10	30
6	DMAc	125	8	95

[a] Reaction condition: 4-chloroacetophenene (1 mmol), phenylboronic acid (1.5 mmol), $Pd(CH_3CN)_2Cl_2$ (4 mol %), L (4 mol %), NaOH (2 mmol), solvent (2.5 mL); argon atmosphere [b] Isolated yield of the product.

phosphine ligand (**1d**), its coordination with Pd metal, and its utility in activating aryl, heteroaryl, and allyl chloride for excellent yield in the Suzuki–Miyaura cross-coupling reaction.

TABLE 3. Cross-Coupling of Aryl, Heteroaryl, and Allyl Chlorides with Phenylboronic Acid[a]



entry	R^1Cl	time(h)	product	yield(%)[b]
1	 **2a**	8	 **4a**	98
2	 **2b**	10	 **4b**	85
3	 **2c**	6	 **4c**	91
4	 **2d**	4	 **4d**	97
5	 **2e**	3.5	 **4e**	96
6	 **2f**	8	 **4f**	83
7	 **2g**	4	 **4g**	95
8	 **2h**	4	 **4h**	95
9	 **2i**	4	 **4i**	95
10	 **2j**	4	 **4j**	96
11	 **2k**	4	 **4k**	93
12	 **2l**	3.5	 **4l**	95
13[c]	**2l**	3.5	 **4m**	93
14[d]	 **2m**	3.5	 **4n**	95
15[e]	**2m**	3.5	 **4o**	94
16	 **2n**	5	 **4p**	65
17	 **2o**	5	 **4q**	67
18	 **2p**	5	 **4r**	63

[a] Reaction condition: Chloro arene (1 mmol), phenylboronic acid (1.5 mmol), $Pd(CH_3CN)_2Cl_2$ (4 mol %), L (4 mol %), NaOH (2 mmol), DMF (2.5 mL); argon atmosphere. In the case of allyl and benzyl chloro arenes Cs_2CO_3 was used as a base. [b] Isolated yield of the product. [c] 1-Naphthaleneboronic acid was used. [d] DMAc as a solvent. [e] *p*-Tolylboronic acid was used.

7-Bromoindole (**1c**) was readily synthesized following a literature procedure.[15a] Condensation of 2-bromonitrobenzene (**1b**)

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and vinylmagnesium bromide solution (**1a**) in THF at −45 °C afforded **1c** in 60% yield (Scheme 1). Treatment of **1c** with 2.2 equiv of ^{n}BuLi at −78 °C followed by trapping the dilithiated intermediate by PPh_2Cl afforded the corresponding bidentate phosphine ligand (**1d**) in 25% yield. The product was purified by flash column chromatography followed by crystallization from petroleum ether. This ligand (**1d**) is stable in air and can be stored in a bottle without any special care for more than a week.[15b]

This novel bidentate phosphine ligand (**1d**) was treated with $Pd(CH_3CN)_2Cl_2$ in dichloromethane to afford[16] a yellow-orange complex (**1e**) (Scheme 2). The molecular structure of the ligand (**1d**) and the palladium complex (**1e**) were determined by single-crystal X-ray analysis. This palladium complex (**1e**) has a distorted square planar geometry around the palladium center with a ligand bite angle of 96.60°.

To examine the usefulness of this new ligand (**1d**), we selected 4-chloroacetophenone (**2a**) and phenylboronic acid (**3a**) as model substrates. Molar ratio of ligand, effect of different base and solvents, and comparison of different Pd-precursors were studied (Table 1). It was found that $Pd(CH_3CN)_2Cl_2$ (entry 3) worked best as the catalyst precursor rather than $Pd(OAc)_2$ and $Pd_2(dba)_3$ (entries 5 and 6). The use of a phosphane:Pd ratio of 1:1 was found to be optimal for this catalytic system. Use of excess ligand was found to be detrimental to catalytic efficiency (entry 12).

We screened several bases, e.g., NaOH, K_2CO_3, CsF, Cs_2CO_3, KOH, and K_3PO_4. Among them, NaOH was found to be the most suitable base (Table 1, entry 3). We found that a polar and coordinating solvent like DMF or DMAC was ideal for this reaction (Table 2, entries 1 and 6).

Under the optimized condition with $Pd(CH_3CN)_2Cl_2$ (4 mol %), ligand (4 mol %), and NaOH (2 equiv) in DMF, we examined the cross-coupling reaction of a wide range of electronically and structurally diverse aryl chlorides with phenylboronic acid (Table 3). In all cases, the desired products were isolated in good to excellent yield, irrespective of activating and deactivating groups being present on the aryl chlorides. Ortho-substituted chlorides also afforded a high yield of expected products (entry 8 and 11).

Heteroaryl chlorides (entries 9, 10, and 11) afforded almost quantitative yield of products. The reaction proceeded equally well with cinnamyl chloride and its analogues (entries 12−15), sometimes with double-bond isomerization but without any rearrangement. Benzyl chlorides (entry 16−18) on the other hand provided around 65% yield of the product.

In summary, we have developed a novel bidentate phosphine ligand containing an indole scaffold and a N−P bond in the Suzuki−Miyaura coupling cross-coupling reaction of aryl, heteroaryl, and allyl chlorides that provides an excellent yield of desired products. The thermal stability of this novel phosphine ligand in solid as well as in solution phase makes for easer handling. Use of this ligand in related coupling reactions is currently being investigated in our laboratory.

Experimental Section

Preparation of Ligand (1d) from 7-Bromoindole (1c). To a stirred solution of 7-bromoindole (**1c**) (1.57 g, 8 mmol) in THF (30 mL), under argon atmosphere, was added ^{n}BuLi (11 mL, 17.6 mmol, 1.60 M in hexane) dropwise at −78 °C. The mixture was then slowly warmed to rt and then stirred for a further 2 h at rt. After the mixture cooled to −78 °C, chlorodiphenylphosphine (3.25 mL, 17.6 mmol) in THF (10 mL) was added dropwise. The mixture was then warmed to rt and stirred for a further 2 h. It was then quenched with saturated NH_4Cl solution at 0 °C and extracted with diethyl ether (2 × 100 mL). The combined organic layer was washed subsequently with water and brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure gave the crude product. Purification by flash column chromatography (silica gel, 2.2% ethyl acetate/petroleum ether) afforded ligand (**1d**) as white solid (970 mg, 25%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.63 (d, J = 7.73 Hz, 1H), 7.38−7.27 (m, 16H), 7.10−7.04 (m, 5H), 6.90 (d, J = 2.7 Hz, 1H), 6.72 (t, J = 6.21 Hz, 1H), 6.65 (d, J = 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 138.13, 138.00, 137.83, 137.74, 137.58, 137.51, 134.68, 134.66, 134.41, 132.30, 132.03, 131.39, 131.30, 129.61, 129.38, 128.57, 128.49, 121.96, 121.13, 107.23; ^{31}P NMR ($CDCl_3$, 202.44 MHz, ppm) δ 36.70 (d, J = 160 Hz), −16.18 (d, J = 160 Hz). Anal. Calcd for $C_{32}H_{25}NP_2$: C, 79.17; H, 5.19; N, 2.89. Found: C, 79.15; H, 5.20; N, 2.87.

Typical Procedure for the Cross-Coupling Reaction. A solution of ligand (19.4 mg, 0.04 mmol), $Pd(CH_3CN)_2Cl_2$ (10.3 mg, 0.04 mmol), chloro arene (1.0 mmol), arylboronic acid (1.5 mmol), and NaOH (80 mg, 2.0 mmol) in DMF (2.5 mL) was stirred under argon atmosphere at 125 °C for 3.5−10 h (depending on substrate). The reaction mixture was then cooled to rt and diluted with diethyl ether (20 mL). The organic layer was successively washed with cold water (3 × 10 mL) and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (230−400 mesh) with 2−8% acetone in petroleum ether or petroleum ether alone as a eluent.

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Supporting Information Available: Detailed experimental procedures and characterization data for all compounds and CIF file of **1d** and **1e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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