A New Family of Tunable Indolylphosphine Ligands by One-Pot Assembly and Their Applications in Suzuki−Miyaura Coupling of Aryl Chlorides

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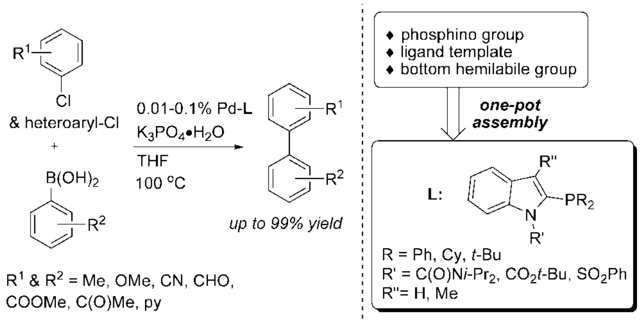

This study describes a new class of indolylphosphine ligands, which can be easily accessed by a simple one-pot assembly from commercially available indoles, acid chlorides, and chlorophosphines. A combination of these three starting materials provides a high diversification of the ligand structure. The application of this ligand array in palladium-catalyzed Suzuki−Miyaura coupling reaction of aryl chlorides with arylboronic acids is described. A catalyst loading down to 0.01 mol % of Pd can be achieved.

Palladium-catalyzed cross-coupling reactions have received significant attention in the past decades and have become extremely versatile protocols in organic synthesis for the connection of electrophilic and organometallic fragments in the formation of either carbon−carbon or carbon−heteroatom bonds.[1] In particular, the Suzuki−Miyaura cross-coupling reaction of arylboronic acids and aryl halides is useful for the construction of diversified biaryls, which have numerous applications in pharmaceutical, material, and agricultural chemistry.[2]

The structure of the ligand has been recognized to significantly influence the efficiency of cross-coupling processes. Therefore, a strategic ligand modification with appropriate steric and electronic diversity is crucial in dealing with problematic and specific substrates in this area. The lore in the field is that the effective palladium catalysts for C−C bond coupling processes from aryl chlorides generally contain electron-rich (enhancement of oxidative addition) and sterically bulky (improvement of reductive elimination) phosphine ligands. Novel ligand design was found to be important for a number of considerable advancements. During the past decade, Beller,[3] Buchwald,[4] Fu,[5] Hartwig,[6] and other groups[7] have contributed a huge amount of work to the area of phosphine ligand design and synthesis. Although significant progress has been made, the scope of these reactions and ligand syntheses can still be improved.

Phosphine ligands that possess a potential hemilabile coordinating group have been studied in the past decade.[8] In 1999, Guram/Bei et al. reported active benzenoid *P*,*O*-type ligands with an acetyl group for Suzuki−Miyaura cross-coupling reactions of aryl chloride.[9] A simlar ligand using ferrocenyl

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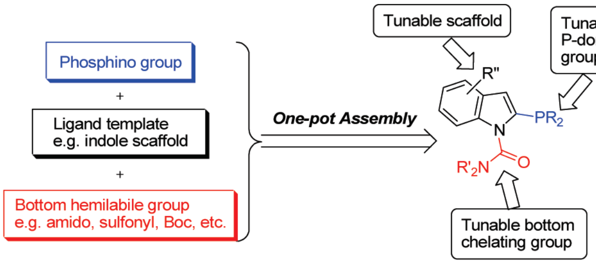
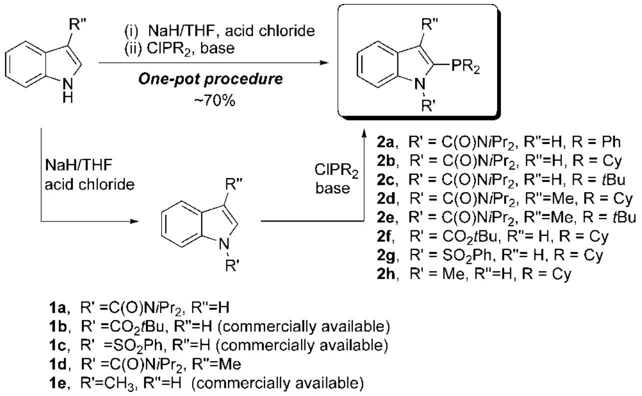
SCHEME 1. Strategic Design and Exploration of a Simple and Easily Diversified Phosphine Ligand Family



scaffold was also found be effective in coupling processes.[10] Moreover, the X-ray crystal structures showed that the ferrocenyl hemilabile ligands provided both P and O (from either acetyl[10] or methoxy group)[11] coordination to the palladium center. In 2004, Singer/Tom et al. reported a new sulfone type ligand containing a hemilabile sulfonyl oxygen and a dialkylphosphino group.[12] Meanwhile, it has been reported that *P*,*O*-type ligands with amido group are highly effective for the Suzuki–Miyaura coupling of aryl chlorides and amination of aryl halides.[13] Although a variety of ligands have been introduced, a rapid assembly of structurally diverse ligand systems via simple synthetic methods is still important for the development of versatile catalysts for widespread applications in coupling reactions. We speculate that a versatile ligand contains three components: a main ligand skeleton, a phosphino group, and a tunable frame. A combination of these three elements would likely generate multifunctional ligand entities. In addition, the target ligand will be even more attractive to the industry, if the ligand synthesis is particularly straightforward. With these rationales, we herein report our exploration and development of a new class of indolylphosphine ligand (Scheme 1). The beneficial features of this ligand family can be highlighted by their one-pot synthesis and the ease of diversification. Upon application of this key synthetic pathway, a library of ligands (by cross-matching between the three principal components) could be easily prepared by a simple one-pot assembly (Scheme 1).

We propose designing this new class of ligand based on several strategic points: (1) the ligand synthetic route should be straightforward; (2) the starting materials should be inexpensive and readily available; (3) the ligand synthesis should eliminate the metal/halogen exchange (from either ArBr or ArI) to have a better scope of atom economy;[14] (4) the ligand diversity and tuning should be easily accessible; (5) the potential

SCHEME 2. Synthetic Pathways for the Indolyl Phosphine Ligands



of the hemilabile property[15] of the bottom group should be applicable toward stabilizing the metal center whenever needed.[16]

To fulfill the above criteria, we chose the commercially available and inexpensive indole as the basic scaffold (Scheme 2). The indole nitrogen was directly deprotonated by NaH, and the sodium salt was subsequently reacted with different acid chlorides giving a series of *N*-substituted indoles. The 2-H on the indole ring is relatively acidic that could be effectively abstracted by directed *ortho*-metalation (DoM)[17] using *n*-BuLi. Trapping the lithiated intermediate by a variety of $ClPR_2$ generated a series of the corresponding indolylphosphines **2** in good yields (Scheme 2). Notably, the above cascaded synthetic steps can be performed as a one-pot procedure. The solid-state crude product was simply purified by washing with methanol/ethanol mixture without crystallization or tedious chromatographic purification process. Particularly noteworthy is that this class of ligand exhibits high air stability in both solid and solution states.[18]

To test the effectiveness of the new ligands, the sterically hindered 2-chloro-*m*-xylene was used as the benchmark substrate. The indolylphosphine ligands **2a**–**e** bearing the carbamoyl group were first examined in the Suzuki–Miyaura reaction (Table 1). A catalyst loading of 0.05 mol % of $Pd(OAc)_2$ was initially applied in probing the ligand efficacy (Table 1). The metal to ligand ratio, metal source and the catalytic activity of ligand **2a**–**e** were subsequently investigated using toluene as the solvent and $K_3PO_4 \cdot H_2O$ as the base. Ligand **2a** with a diphenylphosphino moiety provided no conversion, while the dicyclohexylphosphino analogue, **2b**, gave better catalytic activity (entries 1 and 2). Ligand **2c** bearing a sterically congested and electron-donating di-*tert*-butylphosphino moiety showed a lower catalytic activity toward the coupling reaction. Increasing the bulkiness of **2b** and **2c** (giving **2d** and **2e**, respectively) by the addition of a methyl group to the indole 3-position decreased the catalytic activity of the ligands. Since **2b** provided the highest catalytic activity in the coupling reaction, it was selected to further optimize the reaction

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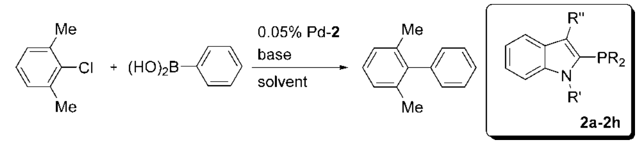
(18) There were no detectable phosphine oxide signal of this class of indolylphosphine ligands from ^{31}P NMR when the solid form ligand was stored under air for a month or in a solution for at least 7 days. In contrast, P-*t*-Bu_3 has been shown to be oxidized in air within 2 h; see ref 4a.

TABLE 1. Optimization of the Reaction Conditions Using an Array of Indolyl Phosphine Ligand 2[a]



entry	Pd:L	ligand	base	solvent	% yield[b]
1	1:2	**2a**	$K_3PO_4 \cdot H_2O$	toluene	7
2	1:2	**2b**	$K_3PO_4 \cdot H_2O$	toluene	55
3	1:2	**2c**	$K_3PO_4 \cdot H_2O$	toluene	11
4	1:2	**2d**	$K_3PO_4 \cdot H_2O$	toluene	5
5	1:2	**2e**	$K_3PO_4 \cdot H_2O$	toluene	0
6[c]	1:2	**2b**	$K_3PO_4 \cdot H_2O$	toluene	26
7	1:3	**2b**	$K_3PO_4 \cdot H_2O$	toluene	80
8	1:4	**2b**	$K_3PO_4 \cdot H_2O$	toluene	76
9	1:3	**2b**	K_3PO_4	toluene	51
10	1:3	**2b**	Cs_2CO_3	toluene	39
11	1:3	**2b**	Na_2CO_3	toluene	2
12	1:3	**2b**	CsF	toluene	82
13	1:3	**2b**	$K_3PO_4 \cdot H_2O$	THF	>99
14	1:3	**2b**	$K_3PO_4 \cdot H_2O$	dioxane	1
15	1:3	**2b**	$K_3PO_4 \cdot H_2O$	DMF	1
16	1:3	**2f**	$K_3PO_4 \cdot H_2O$	THF	82
17	1:3	**2g**	$K_3PO_4 \cdot H_2O$	THF	10
18	1:3	**2h**	$K_3PO_4 \cdot H_2O$	THF	14

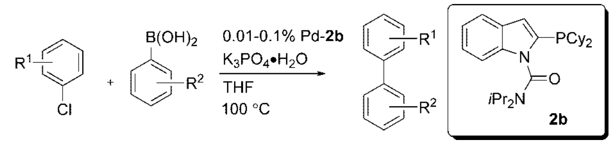
[a] Reaction conditions: $Pd(OAc)_2$ (0.05 mmol, 0.05 mol %), ligand **2** (as indicated), ArCl (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), base (3.0 mmol), and solvent (3.0 mL) were stirred for 24 h at 100 °C under nitrogen. [b] Calibrated GC yields were reported using dodecane as the internal standard. [c] $Pd_2(dba)_3$ as the Pd source.

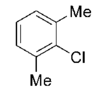
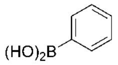
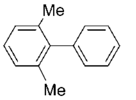
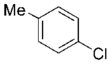
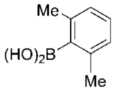
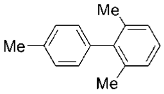
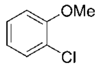
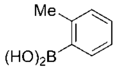
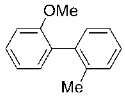
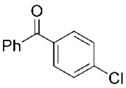
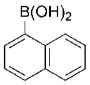
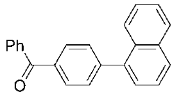
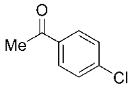
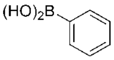
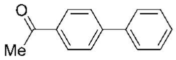
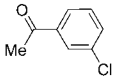
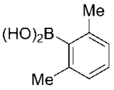
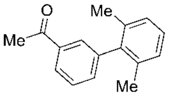
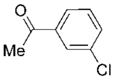
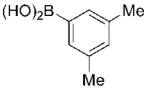
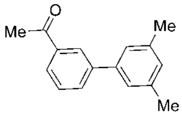
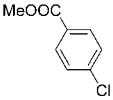
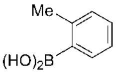
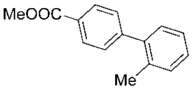
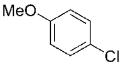
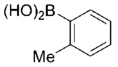
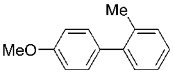
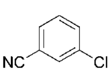
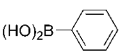
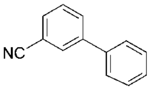
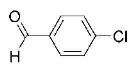
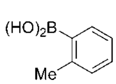
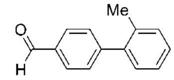
conditions. Upon investigating the metal/ligand ratio from 1:2 to 1:4, the ratio of 1:3 provided the highest yield. Several bases were examined in the presence of ligand **2b**. $K_3PO_4 \cdot H_2O$ and CsF were found to be the best base of choice in this catalytic system. $K_3PO_4 \cdot H_2O$ was finally chosen as the base for further study of the coupling reaction due to economical aspect. Among the commonly used organic solvents examined, THF gave the best result.

To further expand the scope of these indolylphosphine ligands, we additionally synthesized **2f** and **2g** by reacting the sodium salt of indole with phenyl *tert*-butyl carbonate and benzenesulfonyl chloride, respectively. The catalytic activity of Pd−**2f** is comparable to that of Pd−**2b** in the coupling reaction, whereas that of Pd−**2g** is significantly lower compared with Pd−**2b**. On the other hand, by comparing the ligands **2b**, **2d**, and **2h**, either increasing the steric bulkiness through the addition of methyl group at the indole 3-position or decreasing the steric bulkiness through the replacement of the carbamoyl group by methyl group would also decrease the catalytic activity of Pd−**2b**. The highest catalytic activity of Pd−**2b** may be explained by the optimum steric effect provided by the ligand skeleton to the Pd metal center during the course of the coupling reaction.

A range of aryl chlorides were examined under the preliminary optimized reaction conditions (Table 2). Sterically hindered aryl chlorides were coupled with arylboronic acid and vice versa in excellent yields (entries 1 and 2). Although 0.05 mol % of Pd was generally applicable for our catalysis, additional efforts were placed to further optimize each entry. Functional groups such as keto, aldehyde, ester, and nitriles were compatible under these reaction conditions, and the catalyst loading ranged from 0.01−0.04 mol % of Pd were achieved (Table 2, entries 4−8, 10, and 11). Deactivated aryl chloride was coupled with boronic acid in excellent yield (Table 2, entry 9).

TABLE 2. Palladium-Catalyzed Suzuki−Miyaura Coupling of ArCl[a]



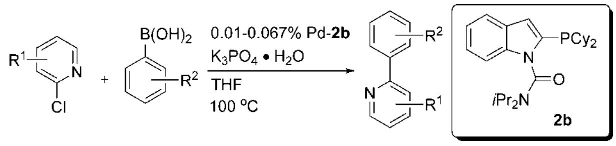
entry	ArCl	Ar'B(OH)2	product	mol% Pd	%yield[b]
1				0.05% 24 h	90
2				0.067% 24 h	81
3				0.067% 24 h	95
4				0.025% 24 h	93
5				0.01% 24 h	99
6				0.04% 24 h	90
7				0.02% 24 h	99
8				0.01% 24 h	86
9				0.067% 24 h	93
10				0.02% 24 h	86
11				0.01% 24 h	90

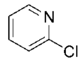
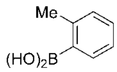
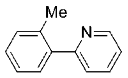
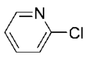
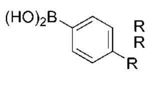
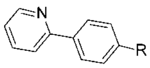
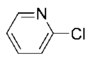
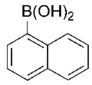
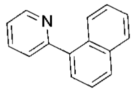
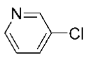
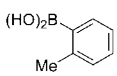
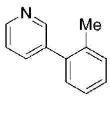
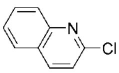
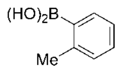
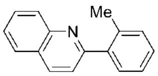
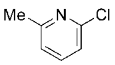
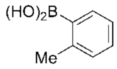
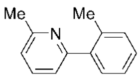
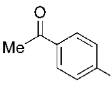
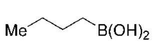
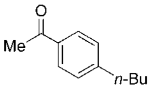
[a] Reaction conditions: ArCl (1.0 mmol), $Ar'B(OH)_2$ (1.5 mmol), $K_3PO_4 \cdot H_2O$ (3.0 mmol), $Pd(OAc)_2/L$ = 1:3, and THF (3.0 mL) were stirred for 24 h at 100 °C under nitrogen. [b] Isolated yields (two or more runs).

Apart from functionalized aryl chlorides, the coupling of heteroaryl chloride was also studied. Under low catalyst loading conditions, 4 equiv of ligand was required to compete with the nitrogen binding to the metal. The results show that the heteroaryl chlorides are also effective substrate for Suzuki−Miyaura coupling (Table 3). In addition, preliminary study on the coupling of alkylboronic acid with aryl chloride was successful (Table 3, entry 8).

In summary, we have developed a new series of efficient phosphine ligand **2**. These ligands are easily accessible and could

TABLE 3. Palladium-Catalyzed Suzuki−Miyaura Coupling of Heteroaryl Chlorides with Aryl or Alkylboronic Acid[a]



entry	Het-ArCl	Ar'B(OH)$_2$	product	mol% Pd	%yield[b]
1				0.02% 24 h	95
2		 R = H		0.02% 24 h	99
3		R = Me			99
4				0.02% 24 h	99
5				0.067% 24 h	81
6				0.01% 24 h	94
7				0.01% 24 h	99
8[c]				0.05% 24 h	87

[a] Reaction conditions: Het-ArCl (1.0 mmol), Ar′B(OH)$_2$ (1.5 mmol), $K_3PO_4 \cdot H_2O$ (3.0 mmol), Pd(OAc)$_2$/L = 1:4, and THF (3.0 mL) were stirred for 24 h at 100 °C under nitrogen. [b] Isolated yields (two or more runs). [c] Reaction conditions: ArCl (1.0 mmol), *n*-BuB(OH)$_2$ (2.0 mmol), $K_3PO_4 \cdot H_2O$ (3.0 mmol), Pd(OAc)$_2$/L = 1:3, and toluene (3.0 mL) were stirred for 24 h at 100 °C under nitrogen.

be readily fine-tuned by cross-matching of the three components via simple one-pot assembly of the commercially available starting materials. Palladium complexes derived from these ligands provide highly active catalysts for Suzuki−Miyaura coupling of aryl chlorides. In view of the simplicity of the ligand synthesis as well as the high ability in modifying the ligand skeleton, we anticipate that further enhancements in reactivity and versatility of the ligand series will be attainable.

Experimental Section

One-Pot, Two-Step Synthesis of Indolylphosphine Ligand 2b. Indole (585 mg, 5.0 mmol) was dissolved in anhydrous THF (10 mL) and transferred dropwise to the THF (50 mL) solution containing 1.1 equiv of NaH (60% in mineral oil, 220 mg, 5.5 mmol) at 0 °C. (Note: NaH was prewashed with dry hexane under N_2.) The mixture was stirred for 20 min at rt. After the mixture was recooled to 0 °C, 1.1 equiv of *N*,*N*-diisopropylcarbamoyl chloride (0.896 g, 5.5 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at rt for 2 h. After the completion of the reaction as confirmed by GC−MS analysis, the solution was cooled to −78 °C in dry ice/acetone bath. Titrated *n*-BuLi (5.5 mmol) was added dropwise by a syringe. The reaction mixture was further stirred for 1 h at −78 °C and chlorodicyclohexylphosphine (1.32 mL, 6.0 mmol) was then added dropwise by a syringe. The reaction was allowed to reach rt and stirred overnight. EtOH (~10 mL) was added slowly to quench the reaction. Solvent was removed under reduced pressure. Dichloromethane (~200 mL) and water (~100 mL) were added to the mixture, and the organic phase was separated. The aqueous phase was further extracted with dichloromethane (~100 mL × 2). The combined organic phases was washed with brine, dried over $MgSO_4$, and concentrated. After the solvent was removed under vacuum, the product was successively washed with cold ethanol. The product was then dried under vacuum. The product **2b** was isolated as a white solid (1.54 g, 70%): mp192.1−193.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25−1.92 (m, 34H), 3.43 (m, 2H), 6.74 (s, 1H), 7.12−7.22 (m, 2H), 7.31 (d, $J =$ 7.9 Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 26.2, 27.2, 29.9, 30.0, 33.8, 109.7, 109.8, 110.3, 120.2, 120.4, 122.4, 127.9, 134.6, 134.8, 136.8, 136.9, 151.6 (unresolved C−P couplings were observed); ^{31}P NMR (162 MHz, $CDCl_3$) δ −22.08; IR (cm^{-1}) 2992, 2922, 2848, 1685, 1492, 1431, 1368, 1327, 1206, 1155, 1119, 1060, 1027, 1000, 914, 884, 848, 824, 790, 751, 737, 669, 631, 610, 583, 538, 515, 482, 429; MS (EI) *m/z* (relative intensity) 440 (M^+, 6), 397 (53), 357 (100), 315 (32), 275 (11), 242 (35), 227 (40), 191 (23), 148 (76); HRMS calcd for $C_{27}H_{41}N_2OPH^+$ 441.3035, found 441.3041.

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Supporting Information Available: Detailed experimental procedures, initial screening results, compound characterization data, and copies of ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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