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Easily Accessible and Highly Tunable Indolyl Phosphine Ligands for Suzuki–Miyaura Coupling of Aryl Chlorides

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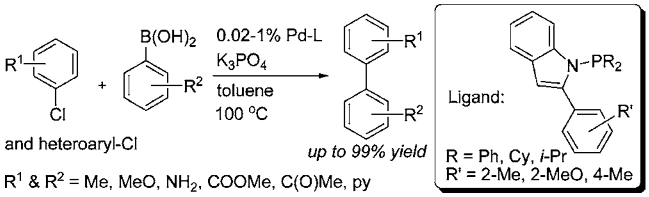
ABSTRACT



This study describes a new class of easily accessible indolyl phosphine ligands, prepared via an efficient protocol involving Fischer indolization from readily available phenylhydrazine and substituted acetophenones. This versatile ligand scaffold provides beneficial features, including high potential of steric and electronic tunability. The air-stable indolyl phosphines in combination with a palladium metal precursor provide highly effective catalysts for Suzuki–Miyaura coupling of unactivated aryl chlorides, and the catalyst loading down to 0.02 mol % can be achieved.

Transition-metal-catalyzed cross-coupling reactions have become an extremely versatile protocol in organic synthesis for the connection of two different fragments via the formation of either carbon−carbon and/or carbon−heteroatom bonds.[1] More specifically, the Suzuki−Miyaura reaction represents one of the most powerful methods for the construction of diversified biaryls, and they have a myriad of applications in pharmaceutical, material, and agricultural chemistry.[2] It has been recognized that the ligand employed in these processes has significant impact on the outcome of the reactions. Hence, the strategic design of ligands with appropriate steric/electronic natures and great diversity is crucial in dealing with challenging and problematic substrates in this area.

Recently, various observations and comments have been made that palladium complexes derived from sterically bulky and electron-rich phosphines are effective catalysts for C−C bond coupling processes from aryl chlorides.[3] In particular, the Pt-Bu$_3$ by Fu[4] and Koie,[5] the ferrocenyl-based dialkylphosphines by Hartwig,[6] the elegantly designed biphenyl-based dialkylphosphines by Buchwald,[7] and the heteroaromatic dialkylphosphines by Beller[8] are highly versatile

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10.1021/ol070898y CCC: $37.00

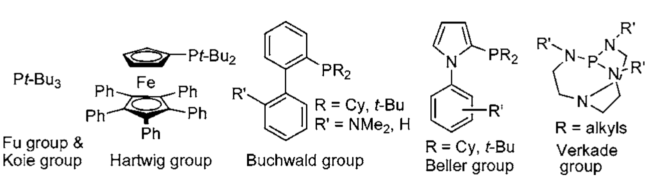


Figure 1. Recent developments on phosphorus ligands.

(Figure 1). Moreover, phosphine ligands with hemilabile coordinating ability have been reported to be effective in coupling reactions with low catalyst loading.[9]

Among various supporting ligands reported, phosphorus donor ligands that possess N−P bonds in the ligand scaffold remain sporadically studied.[10] In fact, aminophosphines can be conveniently prepared from the deprotonation of amine followed by quenching with chlorophosphine. The unique electron-donating capability of these ligands reported by Woollins and co-workers[11] showed that phosphine containing N−P bound amino groups could provide an unusually electron-rich σ-donor character on the phosphorus atom. Recently, Verkade reported the triaminophosphine, proazaphosphatranes (Figure 1), which were synthesized by the reaction of triamine with $P(NMe_2)_3$ at 175 °C for 48 h to give a colorless liquid.[12] These conceptually interesting ligands are effective in cross-coupling reactions.[13]

Although a variety of ligands have been introduced, the rapid assembly of structurally diverse ligand systems via simple synthetic methods is still important for the development of versatile catalysts for widespread applications of coupling reactions. Herein, we report a new class of indolyl-type phosphine ligands (Figure 2), which can be directly prepared from commercially available 2-phenylindole (**1a**). Further derivatization of this ligand can be easily achieved by Fischer indole synthesis. This diversified ligand scaffold offers remarkably high tunability in both steric and electronic properties.

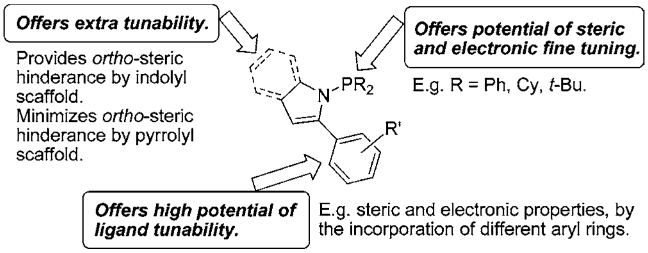
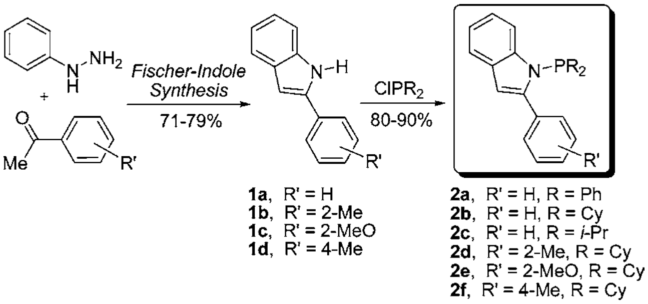


Figure 2. Proposed ligand design with high potential of tunability.

We designed this new class of ligand based on several strategic points: (1) the starting materials should be inexpensive and readily available; (2) the ligand synthesis should be simple and straightforward (an elimination of metal/halogen exchange (from ArBr or ArI) would be even more advantageous); (3) the ligand diversity should be easily accessible and should conveniently provide a high level of steric and electronic fine-tuning.

To fulfill the above criteria, we chose the commercially available and inexpensive phenylhydrazine and acetophenones as the precursors. 2-Arylindole scaffolds were efficiently synthesized by Fischer indole synthesis in good yields (Scheme 1). Notably, the modified Fischer indolization was successful in synthesizing sterically hindered 2′-substituted 2-arylindoles.[14] The straightforward deprotonation

Scheme 1. Synthetic Protocol for Diversified Indolyl Phosphines



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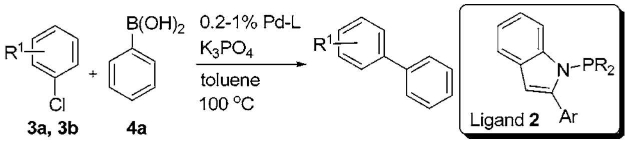
(13) For reviews, see: (a) Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1. (b) Urgaonkar, S.; Verkade, J. G. *Specialty Chem.* **2006**, *26*, 36.

of 2-arylindole **1** by *n*-BuLi and trapping the lithiated intermediate by $ClPR_2$ afforded the corresponding indolyl phosphines **2** in excellent yields (Scheme 1). Essentially complete conversion was observed that highlighted the ease of purification by single crystallization. Particularly noteworthy is that this class of ligand exhibits high air stability in both solid and solution states.[15]

To evaluate the effectiveness of the new ligand series, we chose *p*-chlorotoluene **3a** and phenylboronic acid **4a** as model substrates in the prototypical reaction (Table 1); 0.5 mol % of $Pd_2(dba)_3$ was initially applied in probing the ligand efficiency. Ligand **2a** with a diphenylphosphino moiety apparently provided no conversion, while the dicyclohexylphosphino and diisopropylphosphino analogues, **2b** and **2c**, respectively, showed good to excellent catalytic activity (entries 1−3). However, ligand **2g** without the bottom Ar ring showed significantly lower conversion (entry 4). These comparative results demonstrated the crucial role of the aryl ring directly attached to the 2-position of the indole scaffold. The enhanced catalytic activity of these ligands (**2b** vs **2g**) may due to the effect from the bottom aryl ring, which provides both steric bulkiness to the ligand and the potential metal-arene π-interaction to the metal complex.[16] To investigate the structural/catalytic activity effect of the ligand, we prepared ligand **2d** and **2e**. These ligands, bearing an *ortho*-substituted group on the bottom ring, displayed exceedingly high activity in the Suzuki−Miyaura reaction of aryl chloride (entries 5 and 6). A 93% yield was observed when the catalyst loading was lowered to 0.2 mol % (entry 8). Moreover, ligands with *ortho*-substituents on the aryl ring showed high activity to the sterically congested 2-chlorotoluene (entries 11 and 12).

Table 1. Effectiveness of the Indolyl Phosphine Ligand **2**[a]



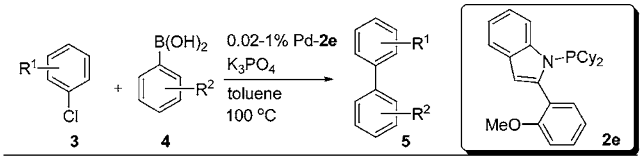
entry	% Pd[b]	ligand **2**, Ar, R	ArCl, R′	% yield[c]
1	1	**2a**, Ph, Ph	4-Me	∼2
2	1	**2b**, Ph, Cy	4-Me	93
3	1	**2c**, Ph, *i*-Pr	4-Me	73
4	1	**2g**, H, Cy	4-Me	55
5	1	**2d**, 2-MeC_6H_4, Cy	4-Me	>99
6	1	**2e**, 2-$MeOC_6H_4$, Cy	4-Me	>99
7	1	**2f**, 4-MeC_6H_4, Cy	4-Me	87
8	0.2	**2e**, 2-$MeOC_6H_4$, Cy	4-Me	93
9[d]	0.2	**2d**, 2-MeC_6H_4, Cy	4-Me	84
10[d]	0.2	**2e**, 2-$MeOC_6H_4$, Cy	4-Me	91
11[d]	0.2	**2d**, 2-MeC_6H_4, Cy	2-Me	96
12[d]	0.2	**2e**, 2-$MeOC_6H_4$, Cy	2-Me	88

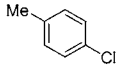
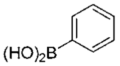
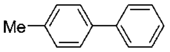
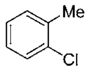
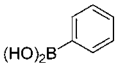
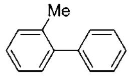
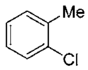
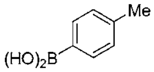
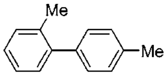
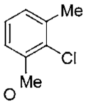
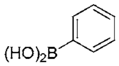
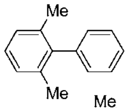
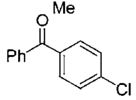
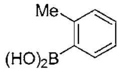
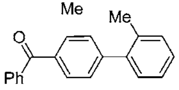
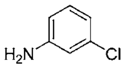
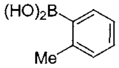
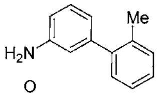
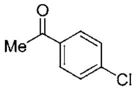
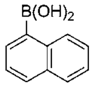
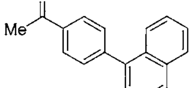
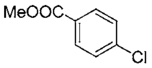
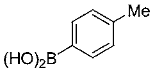
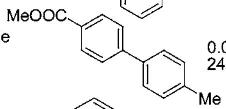
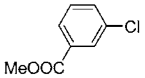
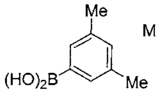
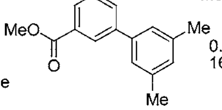
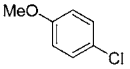
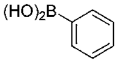
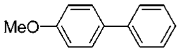
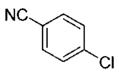
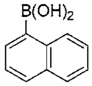
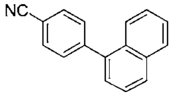
[a] Reaction conditions: ArCl/$PhB(OH)_2$/K_3PO_4 = 1:1.5:3; $Pd(OAc)_2$/L = 1:4; 100 °C for 24 h in toluene (2 mL) under N_2. [b] Mol % of Pd (from $Pd_2(dba)_3$) with respect to ArCl. [c] GC yields. [d] Pd/L = 1:2.

In addition to ligand optimizations, several bases, such as K_3PO_4, Cs_2CO_3, CsF, and KO*t*-Bu, were examined in the presence of ligand **2b**. K_3PO_4 was found to be the base of choice for this catalytic system.

A range of aryl chlorides was examined using the preliminary optimized reaction conditions (Table 2). Sterically hindered aryl chlorides were coupled with arylboronic acid in excellent yields (entries 2−4). Functional groups, such

Table 2. Pd-Catalyzed Suzuki−Miyaura Coupling of ArCl[a]



entry	ArCl	Ar′B(OH)₂	product	mol % Pd	% yield[b]
1				0.2% 24 h	92
2				0.2% 24 h	95
3				1% 24 h	91
4				1% 24 h	94
5				0.05% 16 h	98
6				0.05% 24 h	85
7				0.1% 16 h	93
8				0.02% 24 h	96
9				0.1% 16 h	97
10				0.5% 24 h	95
11				0.05% 16 h	96

[a] Reaction conditions: ArCl/$ArB(OH)_2$/K_3PO_4 = 1:1.5:3; Pd/L = 1:4; toluene (2 mL) under N_2; mol % of Pd (from $Pd_2(dba)_3$) with respect to ArCl. [b] Isolated yields.

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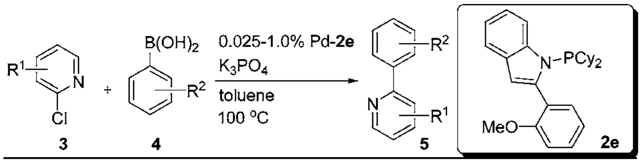
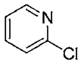
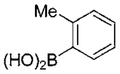
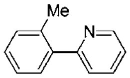
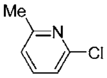
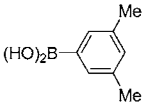
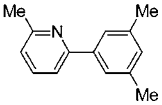
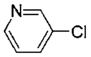
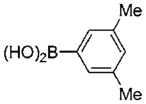
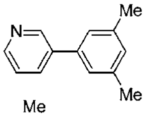
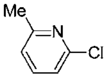
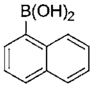
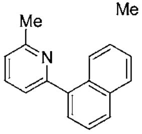
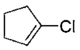
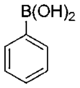
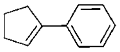
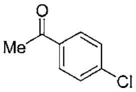
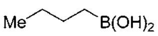
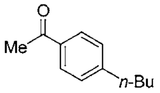
(14) There are no literature reports on the direct Fischer indolization in accessing 2′-substituted 2-arylindoles. Alternatively, these sterically hindered indole templates can be prepared by transition-metal-catalyzed coupling methods, from indole C−H activation (at the 2-position) with aryl halides.

(15) There were no detectable phosphine oxide signals of **2e** from ^{31}P NMR when the solid-form ligand was allowed to stand either under air for 5 days or in solution-form for at least 5 days. In contrast, Pt-Bu_3 has been shown to be destroyed in air within 2 h; see ref 7a.

(16) For metal-arene π-interaction, see: (a) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816. (b) Ref 7d.

Table 3. Pd-Catalyzed Suzuki−Miyaura Coupling of Heteroaryl and Alkenyl Chloride with Aryl or Alkylboronic Acid[a]



entry	Het-ArCl	Ar'B(OH)$_2$	product	mol % Pd	% yield[b]
1				0.025% 16 h	99
2				0.05% 16 h	99
3				0.1% 16 h	90
4				0.05% 16 h	95
5				1.0% 24 h	65
6				0.5% 24h	96

[a] Reaction conditions: ArCl/ArB(OH)$_2$/K$_3$PO$_4$ = 1:1.5:3; Pd/L = 1:4; toluene (2 mL) under N$_2$; mol % of Pd (from Pd$_2$(dba)$_3$) with respect to ArCl. [b] Isolated yields.

as keto, amino, ester, and nitriles, were compatible in these reaction conditions, and the catalyst loading range from 0.02 to 0.1 mol % of Pd was achieved (Table 2, entries 5−9 and 11). Deactivated aryl chloride was coupled with boronic acid in excellent yield (Table 2, entry 10).

Apart from functionalized aryl chlorides, heteroaryl and alkenyl chlorides were effective substrates for Suzuki−Miyaura coupling (Table 3). In addition, preliminary studies on the coupling of alkylboronic acid with aryl chloride were successful (Table 3).

In summary, we have developed a new series of monophosphine ligand **2** bearing a diversified indolyl scaffold with a N−P bound feature. These ligands are readily accessible and could be easily fine-tuned via Fischer indolization from various commercially available phenylhydrazine and substituted acetophenones. Palladium complexes derived from these N−P type ligands provide comparable and sometimes better results (e.g., catalyst loading) than present phosphorus ligands with a N−P moiety for Suzuki−Miyaura coupling of aryl chlorides. In view of the simplicity of the ligand synthesis as well as the easy modification of the ligand skeleton, we anticipate that further enhancements in reactivity and versatility of the N−P type ligand series will be attainable.

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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, MS, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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