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An Efficient Class of P,N-Type "PhMezole-phos" Ligands: Applications in Palladium-Catalyzed Suzuki Coupling of Aryl Chlorides

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This study describes an efficient class of hemilabile benzimidazolyl–phosphane ligands that can be easily accessed from commercially available and inexpensive starting materials. The application of this ligand array in the palladium-catalyzed Suzuki–Miyaura coupling reaction of aryl chlorides with arylboronic acids is described. The palladium catalyst generated from this hemilabile phosphane is highly effective in the Suzuki–Miyaura coupling of unactivated aryl chlorides, and catalyst loadings as low as 1 ppm can be achieved.

Introduction

The palladium-catalyzed Suzuki–Miyaura cross-coupling is undoubtedly one of the most versatile and useful tools for the synthesis of diversified biaryls, which have numerous applications in pharmaceutical, materials, and agricultural chemistry.[1] To deal with the coupling reaction of aryl bromides as well as aryl chlorides, many effective supporting ligands have been developed in the past decade. The advancement of some notable ligands such as $t\mathrm{Bu}_3\mathrm{P}$,[2] Bellers's PAP,[3] Buchwald's biaryl–phosphanes,[4] and Hartwig's Q-Phos[5] provide excellent catalytic activity in various cross-coupling reactions with aryl chlorides.[3c] In view of the characteristics of the ligand structure, they are generally electron-rich and sterically hindered monophosphanes. The increase of electron-richness can enhance oxidative addition. Meanwhile, sterically bulky skeletons can assist the catalyst complex to generate unsaturated palladium(0) species, which can facilitate both oxidative addition and reductive elimination steps. Indeed, monophosphane ligands may still give stable palladium catalysts. However, monophosphane ligands have limited coordinative flexibility for stabilizing the unstable low-coordinate and low-valent palladium complex, which is highly active but easily decomposed at high temperature or under prolonged heating. Consequent decomposition of the active catalysts would lead to the formation of inactive palladium black, which limits the maximum turnover, especially at extremely low catalyst-loading conditions. Beller and co-workers suggested that a several-fold dosage increase of monophosphane ligand is an effective means of preventing decomposition of active low-valent palladium complexes, thus enabling the catalyst loading to be lowered and the TON to be maximized.[6,3b] However, the choice between reactivity and the cost of sacrificing ligand becomes a dilemma and is clearly inefficient. The introduction of hemilabile phosphane ligands that have two basic sites with different donating ability provided a new way to address this problem. A hemilabile coordinating group offering both reactivity and stability towards the palladium center is sensitive to dynamic needs of the metal atom at different stages of the catalytic cycle. For instance, the nitrogen donor atom can weakly coordinate to soft metal centers (e.g., Pd and Rh)

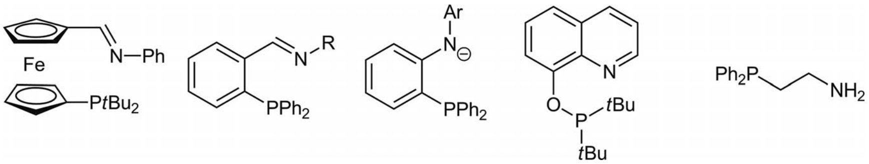

Figure 1. Recent developments on P,N-ligands for the Suzuki coupling reaction.

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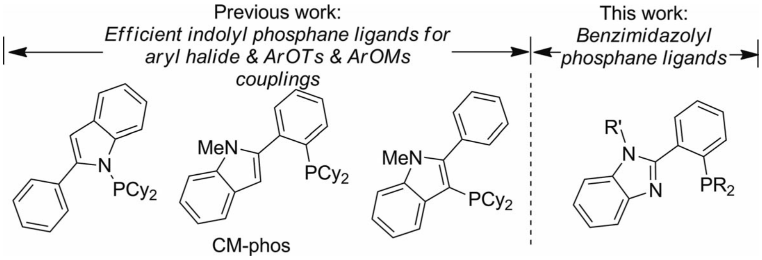


Figure 2. Efficient indolyl–phosphane ligands for coupling reactions.

to stabilize low-valent metal complexes, yet can easily dissociate in solution to provide a vacant site whenever demanded.[7] In fact, phosphane ligands that possess potential hemilabile ability have been studied in the past decade (Figure 1).[8]

In respect to P,N-type ligands,[9] in 2004, Hor et al. reported active ferrocenyl-derived P,N-type ligands with an imino group for the Suzuki coupling reaction.[9f] The X-ray crystal structures showed that the ferrocenyl hemilabile ligands provided both P- and N-coordination to the palladium center. In 2005, a similar ligand with an aryl scaffold was also found to be effective in coupling processes.[10] Liang et al. reported an amido–phosphanyl complex as an effective catalyst for the Suzuki coupling of aryl chlorides.[11] He et al. reported the use of bis(aminophosphane)-palladium chelated complexes for the Suzuki coupling of aryl bromides.[9e] Scrivanti et al. reported a P,N-type coordination ({8-[(di-*tert*-butylphosphanyl)oxy]quinoline}-$PdCl_2$) complex for low-catalyst-loading Suzuki coupling of aryl bromides.[12] Palladium complexes supported by these ligands demonstrated excellent catalytic activities towards the Suzuki coupling of aryl bromides and/or activated aryl chlorides at extremely low catalyst loadings (down to 1 ppm). However, currently developed hemilabile phosphane ligands, especially, P,N-type phosphane ligands, still have much room for improvement, particularly for the Suzuki coupling of neutral and deactivated aryl chlorides in systems with extremely low catalyst loadings. This challenge has still not been met.

Our group previously developed a series of indolyl–phosphane ligands that show good to excellent catalytic activity in palladium-catalyzed coupling reactions of aryl sulfonates and halides (Figure 2).[13]

To retain the advantage of an effective skeleton and further introduce beneficial hemilability to the ligand, we were inspired to use 2-phenylbenzimidazole as the main ligand scaffold. This framework features the same advantages as the 2-phenylindole scaffold and allows high potential diversification from the rapid assembly of two starting components through the application of simple synthetic methods. Moreover, the additional nitrogen atom provides a weak coordinating site for potential dynamic interaction that could increase catalyst longevity (Figure 3). Recently, we have successfully applied this class of benzimidazolyl–phosphane ligands in the Suzuki coupling of aryl mesylates with arylboronic acids.[14] Herein, we disclose an extension to this class of ligands in the Suzuki coupling of aryl chlorides.

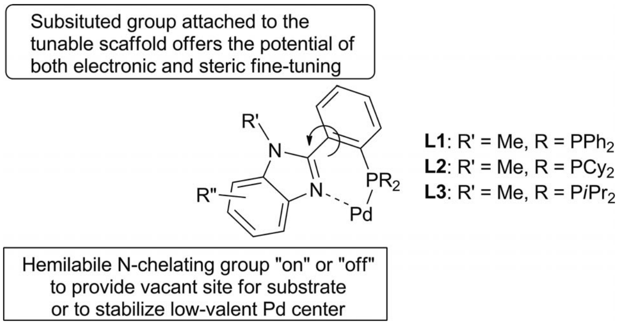


Figure 3. Strategic design and exploration of a simple and easily diversified phosphane ligand family.

Results and Discussion

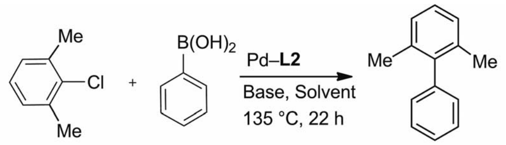
In this study, we used ligands **L1**–**L3** to examine the catalytic activity of this new class of ligands in the Suzuki coupling reaction. To evaluate the effectiveness of the hemilabile ligands, sterically hindered 2-chloro-*m*-xylene was used as the benchmark substrate (Table 1). A range of inorganic bases were first surveyed in the presence of ligand **L2** (Table 1, Entries 1–7). $K_3PO_4 \cdot H_2O$ was found to be the best base in this catalytic system. For commonly used organic solvents [tetrahydrofuran (THF), dioxane, *N*,*N*-dimethylformamide (DMF), toluene, mesitylene and *t*BuOH], dioxane was the best single solvent (Table 1, Entries 1 and 8–12).

Upon investigating the metal/ligand ratio from 1:2 to 1:4, a ratio of 1:2 provided the highest yield (Table 1, Entries 13–15). The use of a metal/ligand ratio of 1:2 was then chosen for the further screening trials. Mixing dioxane with mesitylene gave the best result (Table 1, Entry 18). Ligand **L1** with a diphenylphosphanyl moiety provided only trace amounts of substrate conversion, whereas the dicyclohexylphosphanyl analogue **L2** gave the best catalytic activity. Ligand **L3**, bearing a diisopropylphosphanyl moiety, showed a lower catalytic activity in the Suzuki coupling reaction (Table 1, Entries 20).

A range of aryl chlorides were examined under the preliminary optimized reaction conditions (Table 2). It was immediately clear that the palladium catalyst supported by the hemilabile benzimidazolyl–phosphane ligand was highly active towards the Suzuki coupling reaction.

The catalyst loading and turnover number for the electron-neutral and deactivated aryl chloride could be reduced to 0.001 mol-% Pd (80000 TON) and 0.002 mol-% Pd

Table 1. Optimization of the reaction conditions.



Entry	Pd [mol-%]	M/L	Solvent	Base	Yield[b] [%]
1	0.2	1:2	dioxane	$K_3PO_4 \cdot H_2O$	99
2	0.2	1:2	dioxane	K_3PO_4	58
3	0.2	1:2	dioxane	K_2CO_3	44
4	0.2	1:2	dioxane	Na_2CO_3	22
5	0.2	1:2	dioxane	Cs_2CO_3	25
6	0.2	1:2	dioxane	CsF	38
7	0.2	1:2	dioxane	*t*BuONa	36
8	0.2	1:2	THF	$K_3PO_4 \cdot H_2O$	24
9	0.2	1:2	toluene	$K_3PO_4 \cdot H_2O$	34
10	0.2	1:2	DMF	$K_3PO_4 \cdot H_2O$	11
11	0.2	1:2	*t*BuOH	$K_3PO_4 \cdot H_2O$	23
12	0.05	1:2	mesitylene	$K_3PO_4 \cdot H_2O$	42
13	0.05	1:2	dioxane	$K_3PO_4 \cdot H_2O$	74
14	0.05	1:3	dioxane	$K_3PO_4 \cdot H_2O$	71
15	0.05	1:4	dioxane	$K_3PO_4 \cdot H_2O$	65
16	0.05	1:2	dioxane/ toluene	$K_3PO_4 \cdot H_2O$	51
17	0.05	1:2	dioxane/ xylene	$K_3PO_4 \cdot H_2O$	52
18	0.05	1:2	dioxane/ mesitylene	$K_3PO_4 \cdot H_2O$	99
19[c]	0.05	1:2	dioxane/ mesitylene	$K_3PO_4 \cdot H_2O$	1
20[d]	0.05	1:2	dioxane/ mesitylene	$K_3PO_4 \cdot H_2O$	81

[a] Reaction conditions: [Pd(OAc)$_2$], M/L = 1:2, 1-chloro-2,6-dimethylbenzene (1.0 mmol), phenylboronic acid (1.5 mmol), base (3.0 mmol), solvent (3 mL), 135 °C, N_2, 22 h. [b] Calibrated GC yields are reported (dodecane as internal standard). [c] Ligand = **L1**. [d] Ligand = **L3**.

(37000 TON), respectively (Table 2, Entries 4 and 6). Common functional groups such as ketone, aldehyde, ester, and nitrile were compatible with these mild reaction conditions, and the catalyst loading could generally be reduced to 0.01 mol-% Pd (Table 2, Entries 8–15). The maximum catalytic activity of this new system was also probed (Table 2, Entries 16–19). When the catalyst loading was reduced to 0.0005 and 0.0002 mol-% Pd, this system was still effectively able to convert the substrate into the corresponding product in excellent yields. Although incomplete conversion of substrate was observed when 1 ppm of palladium catalyst was applied, turnover numbers as high as 720000 (TON) were achieved.

We then applied 2-[2-(dicyclohexylphosphanyl)phenyl]-*N*-methyl-1*H*-indole (CM-phos, Figure 2),[13] in which the nitrogen group is replaced by a C–H group, in the low-catalyst-loading coupling reaction (Table 2, Entries 4 and 5). The result showed that the hemilabile nitrogen coordinating group plays an important role in sustaining the high catalytic activity of the catalyst.

Generally, heteroaryl chlorides are classified as electron-deficient aryl chlorides due to the electron-withdrawing property of the heteroatom. However, under very-low-catalyst-loading conditions, the coordinating property of the heteroatom to the metal complex becomes significant and may be problematic for coupling reactions. Indeed, the high concentration of coordinating substrates may displace the phosphane ligands to generate inactive complexes and lead to a reduction in the catalytic activity of the original active species.

This newly developed system can effectively deal with pyridyl and the quinolyl substrates when the metal/ligand ratio is 1:2 at a catalyst loading of 0.01 mol-% Pd. The isolated yield can be as high as 99% (Table 2, Entries 20–23). Actually, the deleterious coordinating effect becomes serious when the catalyst loading was reduced to 0.002 mol-% Pd (Table 2, Entry 24). A slight increase of the metal/ligand ratio from 1:2 to 1:4 was required to compensate for the coordinating substrates under the extremely low-catalyst-loading conditions. The catalyst loading could be further decreased to 0.001 mol-% Pd, and the isolated yield remained as high as 99% (Table 2, entry 25). This finding showed that the hemilabile group reduces the dependence of the reaction on the ligand concentration and can maintain the catalyst activity. Our previous X-ray crystallographic studies confirmed that the benzimidazolyl–phosphane ligand **L2** is coordinated in a κ^2-*P*,*N* fashion to the palladium center.[14]

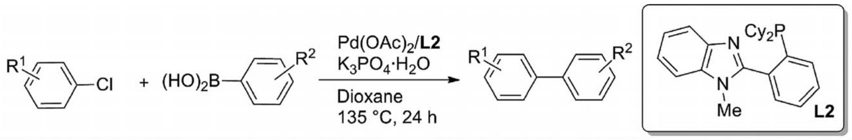
Conclusions

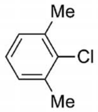
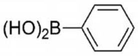
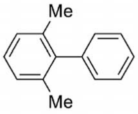
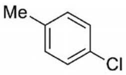
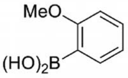
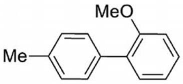
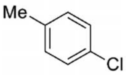
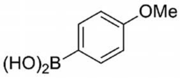
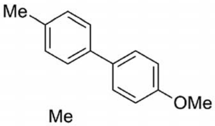
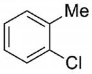
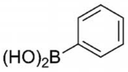
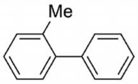
We have developed a series of efficient hemilabile benzimidazolyl–phosphane ligands that can be easily synthesized from inexpensive and commercially available starting materials. Palladium complexes derived from these ligands showed excellent catalytic activities for the Suzuki–Miyaura coupling of aryl chlorides with arylboronic acids, especially under very-low-catalyst-loading conditions. Benefiting from the hemilabile benzimidazolyl group, the catalyst loading for the Suzuki coupling of functionalized aryl chlorides can be reduced to 1 ppm Pd; the palladium levels in neutral, deactivated and coordinating aryl chloride systems can be reduced to 0.001 mol-% Pd. To the best of our knowledge, this is the lowest catalyst loading achieved by P,N-type phosphane ligands. In view of the simplicity of the ligand synthesis as well as the ease with which the ligand skeleton can be modified, we anticipate that further enhancements in reactivity and versatility of the ligand series will be attainable.

Experimental Section

General Procedure for Suzuki–Miyaura Couplings of Aryl Chlorides: [Pd(OAc)$_2$] (2.3 mg, 0.010 mmol) and ligand **L2** (Pd/L = 1:2) in

Table 2. Palladium-catalyzed Suzuki coupling of aryl chlorides.



Entry	ArCl	Ar'B(OH)$_2$	Product	Pd [mol-%]	Yield[b] [%]	TON
1[c]				0.05	85	1700
2				0.01	72	7200
3				0.01	90	9000
4				0.001	80	80000
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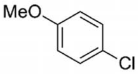
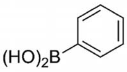
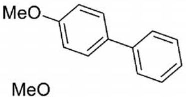
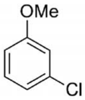
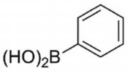
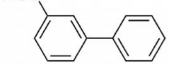
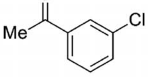
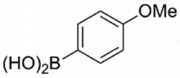
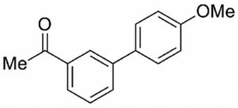
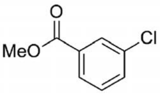
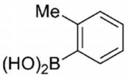
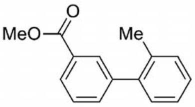
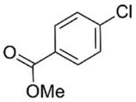
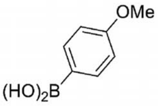
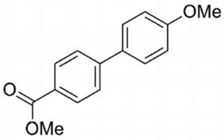
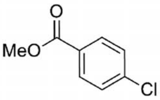
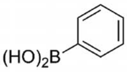
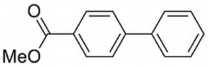
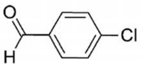
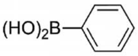
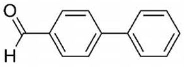
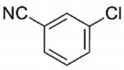
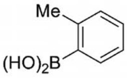
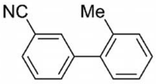
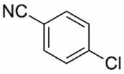
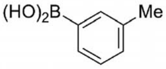
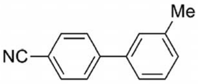
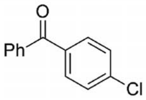
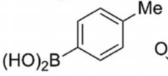
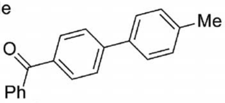
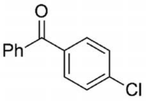
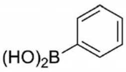
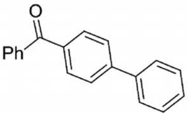
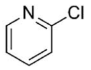
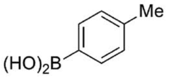
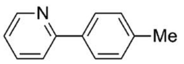
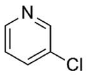
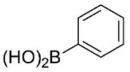
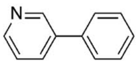
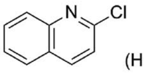
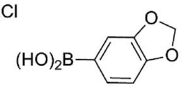
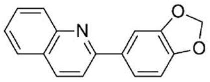
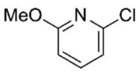
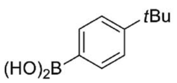
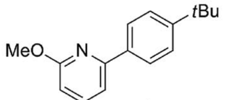
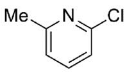
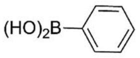
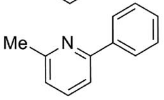
6				0.002	74	37000
7				0.005	90	18000
8[c]				0.01	>99	10000
9[c]				0.025	81	3240
10[c,e]				0.01	94	9400
11[e]				0.001	96	96000
12				0.001	85	85000
13[c]				0.02	81	4050
14[c]				0.01	96	9600
15[c]				0.01	97	9700
16				0.001	>99	100000
17				0.0005	>99	200000
18				0.0002	97	485000
19				0.0001	72	720000

Table 2. (*Continued*)

Entry	ArCl	Ar'B(OH)$_2$	Product	Pd [mol-%]	Yield[b] [%]	TON
20[c]				0.01	98	9800
21[c]				0.01	>99	10000
22[c]				0.01	72	7200
23[c]				0.01	>99	10000
24				0.002	83	41500
25[f]				0.001	>99	100000

[a] Reaction conditions: [Pd(OAc)$_2$], M/**L2** = 1:2, aryl chloride (1.0 mmol), arylboronic acid (1.5 mmol), $K_3PO_4 \cdot H_2O$ (3.0 mmol), dioxane (3 mL), 135 °C, N_2. [b] Isolated yield. [c] Dioxane/mesitylene (1:1) as solvent (3 mL). [d] CM-Phos as ligand, calibrated GC yield. [e] K_2CO_3 as base. [f] Pd/L = 1:4.

freshly distilled 1,4-dioxane (10 mL; 0.1 mol-% Pd per 1 mL of stock solution) was initially prepared with continuous stirring at room temperature. Arylboronic acid (1.5 mmol), $K_3PO_4 \cdot H_2O$ (3.0 mmol) and a magnetic stirrer bar (3 mm × 8 mm) were charged to an array of Schlenk tubes. Each tube was carefully evacuated and backfilled with nitrogen (3 cycles). Aryl chloride (1.0 mmol) was then added to the Schlenk tubes. The stock solution was further diluted to give different concentrations. The diluted stock solution was then transferred to Schlenk tubes by using syringes. Further solvent was added (final volume 3 mL). This batch of Schlenk tubes were resealed and magnetically stirred in a preheated 135 °C oil bath. After completion of the reaction (judged by GC or TLC analysis), the mixtures were allowed to reach room temperature. Water (ca. 3 mL) and ethyl acetate (ca. 3 × 10 mL) were added. The organic layers were combined and concentrated. The crude products were purified by column chromatography on silica gel (230–400 mesh).

Supporting Information (see footnote on the first page of this article): ^1H, ^{13}C, ^{31}P NMR, mass, HR mass and IR spectra and experimental details.

Acknowledgments

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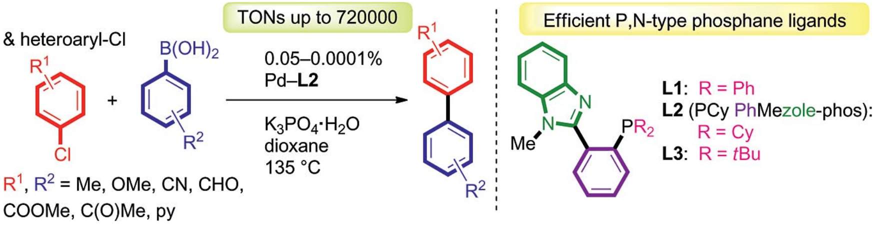
N,P-Ligands in Cross-Coupling



An efficient class of hemilabile benzimidazolyl–phosphane ligands were synthesized. The palladium catalyst generated from this hemilabile phosphane is highly effective in the Suzuki–Miyaura coupling of unactivated aryl chlorides, and catalyst loadings as low as 1 ppm can be achieved.

S. M. Wong, C. M. So,* K. H. Chung, C. P. Lau, F. Y. Kwong* 1–7

An Efficient Class of P,N-Type “PhMezole-phos” Ligands: Applications in Palladium-Catalyzed Suzuki Coupling of Aryl Chlorides

Keywords: Palladium / Ligand design / Cross-coupling / Phosphanes / N,P ligands